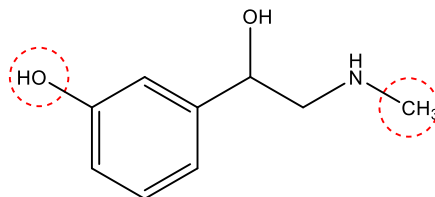


## $\alpha$ -ADRENERGIC RECEPTOR AGONISTS

All selective  $\alpha_1$ -agonists have therapeutic activity as vasoconstrictors. Structurally, they include (a) phenylethanolamines, (b) 2-arylimidazolines.

1. **Phenylephrine**. (Neo-Synephrine<sup>®</sup>, a prototypical selective direct-acting  $\alpha_1$ -agonist) differs from E only in lacking a p-OH group.



phenylephrine

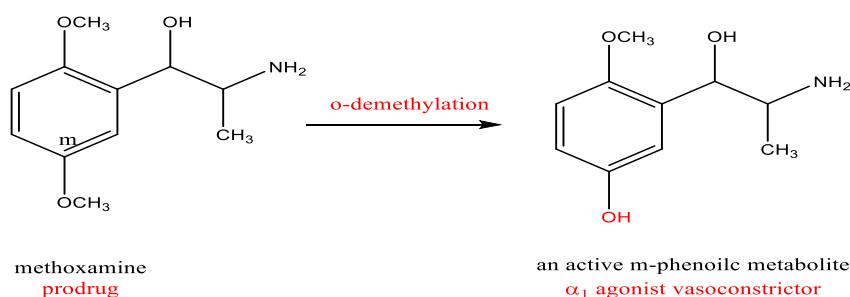
- It is orally active, and its DOA is about twice that of E because it lacks the catechol moiety and thus is not metabolized by COMT
- Its oral bioavailability is less than 10% because of its hydrophilic properties (logP= -0.3), intestinal 3-O-glucuronidation/sulfation and metabolism by MAO.
- Lacking the p-OH group, it is less potent than E and NE but it is a selective  $\alpha_1$ -agonist and thus a potent vasoconstrictor.

### Uses

- In severe hypotension resulting from either shock or drug administration.
- It also has widespread use as a nonprescription nasal decongestant in both oral and topical preparations.
- Treat open-angle glaucoma
- Used in spinal anesthesia to prolong the anesthesia and to prevent a drop in blood pressure during the procedure.

2. **Methoxamine (Vasoxyl)**

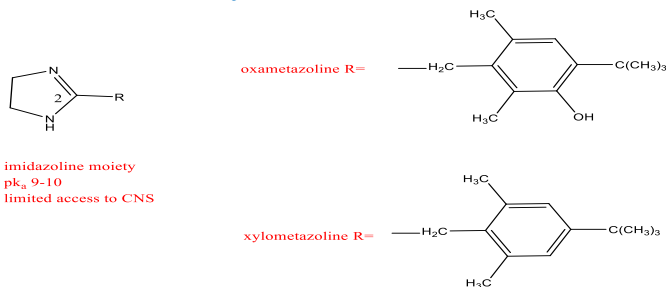
Is another  $\alpha_1$ -agonist and parenteral vasopressor used therapeutically and so have few cardiac stimulatory properties. It is bioactivated by O-demethylation to an active m-phenolic metabolite. Because it is not a substrate for COMT, its DOA is significantly longer than NE.



### Uses

Methoxamine is used primarily during surgery to maintain adequate arterial blood pressure.

### 3. Naphazoline (Privine), tetrahydrozoline (Tyzine, Visine), xylometazoline (Otrivin), and oxymetazoline (Afrin)

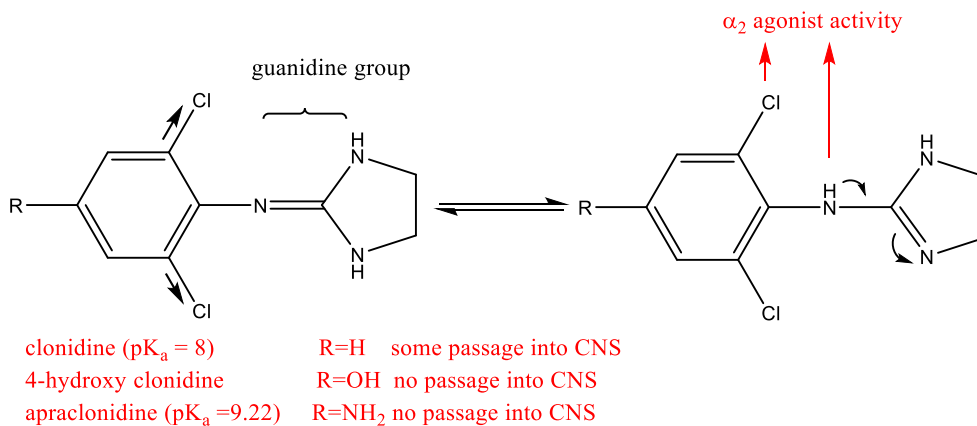


- They are 2-aralkylimidazolines  $\alpha_1$ -agonists.
- All 2-aralkylimidazoline  $\alpha_1$ -agonists contain a one-carbon bridge between C-2 of the imidazoline ring and a phenyl ring, and thus a phenylethylamine structure feature is there.
- Ortho-lipophilic groups on the phenyl ring are important for  $\alpha$ -activity. However, meta or para-bulky lipophilic substituents on the phenyl ring may be important for the  $\alpha_1$ -selectivity.
- They have limited access to the CNS, because they essentially exist in an ionized form at physiological pH caused by the very basic nature of the imidazoline ring (pK<sub>a</sub> = 10–11).
- Oxymetazoline also has significant affinity for  $\alpha_{2A}$ -receptors.

### Uses

Used for their vasoconstrictive effects as nasal and ophthalmic decongestants.

### 4. Clonidine (Catapres)



- It is (phenylimino) imidazolidine derivative that possesses central  $\alpha_2$ -selectivity. The  $\alpha_2:\alpha_1$  ratio is 300:1.
- The o-chlorine groups afford better activity than o-methyl groups at 2 sites. Importantly, clonidine contains a NH bridge (aminoimidazolines) instead of CH<sub>2</sub> bridge in 2-arylimidazoline.
- It has vasoconstrictive activity as a result of stimulation of peripheral  $\alpha$ -receptors. This effect is followed by a much longer-lasting hypotensive effect as a result of the ability of clonidine to enter into the CNS and stimulate  $\alpha_2$ -receptors located in regions of the brain.

### Uses

- ✓ Clonidine quite useful in the **treatment of hypertension**.
- ✓ The ability of clonidine and its analogs to exert an antihypertensive effect depends on the ability of these compounds not only to interact with the  $\alpha_2$ -receptor in the brain but also to gain entry into the CNS

### Example

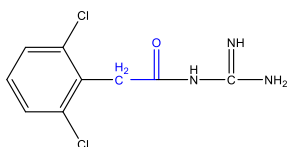
In the case of clonidine, the basicity of the guanidine group (typically  $pK_a = 13.6$ ) is decreased to 8.0 (the  $pK_a$  of clonidine) because of the inductive and resonance effects of the dichlorophenyl ring. Thus, at physiological pH, clonidine will exist to a significant extent in the **nonionized form** required for passage into the CNS. It has an oral bioavailability of more than 90%.

Halogen and alkyl substitutions can be placed at the two ortho positions of the (phenylimino) imidazolidine nucleus without affecting the affinity of the derivatives for  $\alpha_2$ -receptors, methyl analogs are much more readily metabolized to the corresponding acids (inactive) and thus have short DOA. Halogen substituents such as chlorine seem to provide the optimal characteristics in this regard.

Evidence that the hypotensive response of the  $\alpha_2$ -receptor agonists such as clonidine primarily involves the  $\alpha_{2A}$ -receptor subtype.

### 5. Guanfacine (Tenex) (Open-Ring Imidazolidines).

Studies on SAR of central  $\alpha_2$ -agonists showed that the imidazoline ring was not necessary for  $\alpha_2$ -activity.



guanfacine  
pK<sub>a</sub> = 7 → mainly nonionized  
→ penetrate the CNS  
oral bioavailability => 80%

- Guanfacine (pK<sub>a</sub>=7), which are closely related chemically and pharmacologically, are also used as antihypertensive drugs.
- In this compound, the 2,6- dichlorophenyl moiety found in clonidine is connected to a guanidino group by a —CH<sub>2</sub>CO— moiety.
- Conjugation of the guanidino moiety with the bridging moiety helps to decrease the pK<sub>a</sub> of the basic group, so that at physiological pH a significant portion of each drug exists in its **nonionized form**.
- This accounts for their CNS penetration and high oral bioavailability and 80% for guanfacine).