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

Sympathomimetic Agents

- Sympathomimetic agents produce effects resembling those produced by stimulation of the sympathetic nervous system.
- They may be classified as agents that produce effects by:
  1. Direct mechanism of action,
  2. Indirect mechanism of action, or
  3. Mixed mechanism of action.

Direct-Acting Sympathomimetics

Structure–activity Relationships

- **H.W1**

- Retype the general structure of Sympathomimetics and reveal the structure–activity relationships of it.

α -Adrenergic Receptor Agonists

- All selective α 1-agonists have therapeutic activity as vasoconstrictors.
- Structurally, they include:

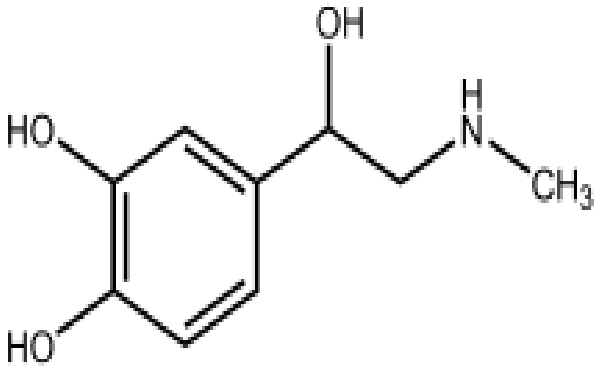
  (a) Phenylethanolamines such as phenylephrine, metaraminol, and methoxamine and

  (b) 2-arylimidazolines such as xylometazoline, oxymetazoline, tetrahydrozoline, and naphazoline.

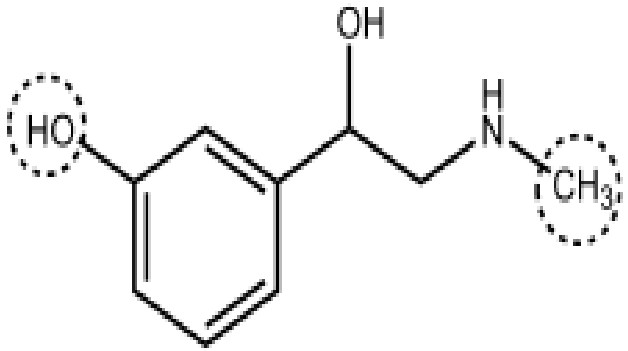
Products

Phenylephrine

- differs from E only in lacking a p -OH group.
- 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.
- Phenylephrine has low *F* (<10%). explain why?



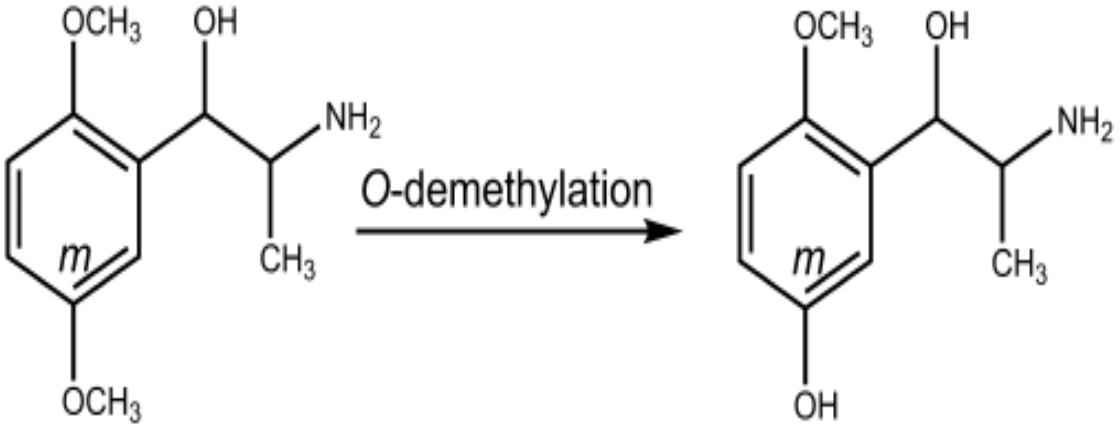
Epinephrine (E)



Phenylephrine

Methoxamine

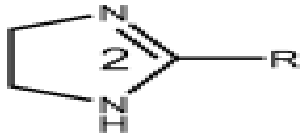
- It is bioactivated by O- demethylation to an active *m*-phenolic metabolite.
- Because it is not a substrate for COMT, its DOA is significantly longer than NE.



Methoxamine
Prodrug

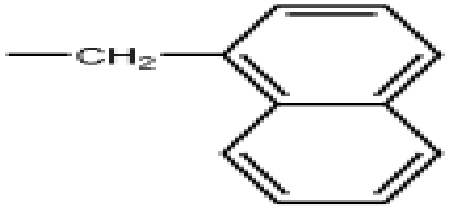
An active *m*-phenolic metabolite
α_1 agonist and vasoconstrictor

Naphazoline, Tetrahydrozoline, Oxymetazoline and, Xylometazoline

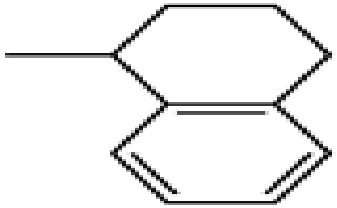


Imidazoline moity
pKa 9-10
Limited access to the CNS

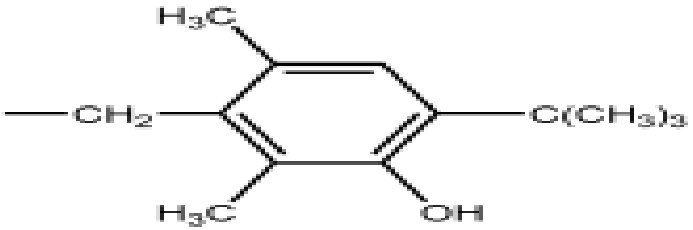
Naphazoline R =



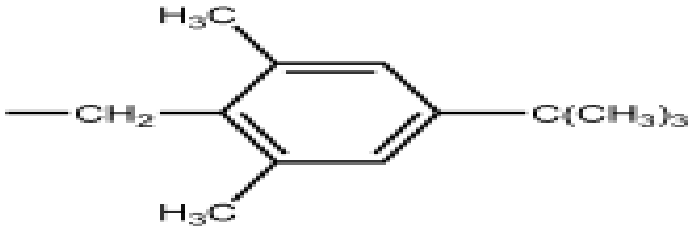
Tetrahydrozoline R =



Oxymetazoline R =



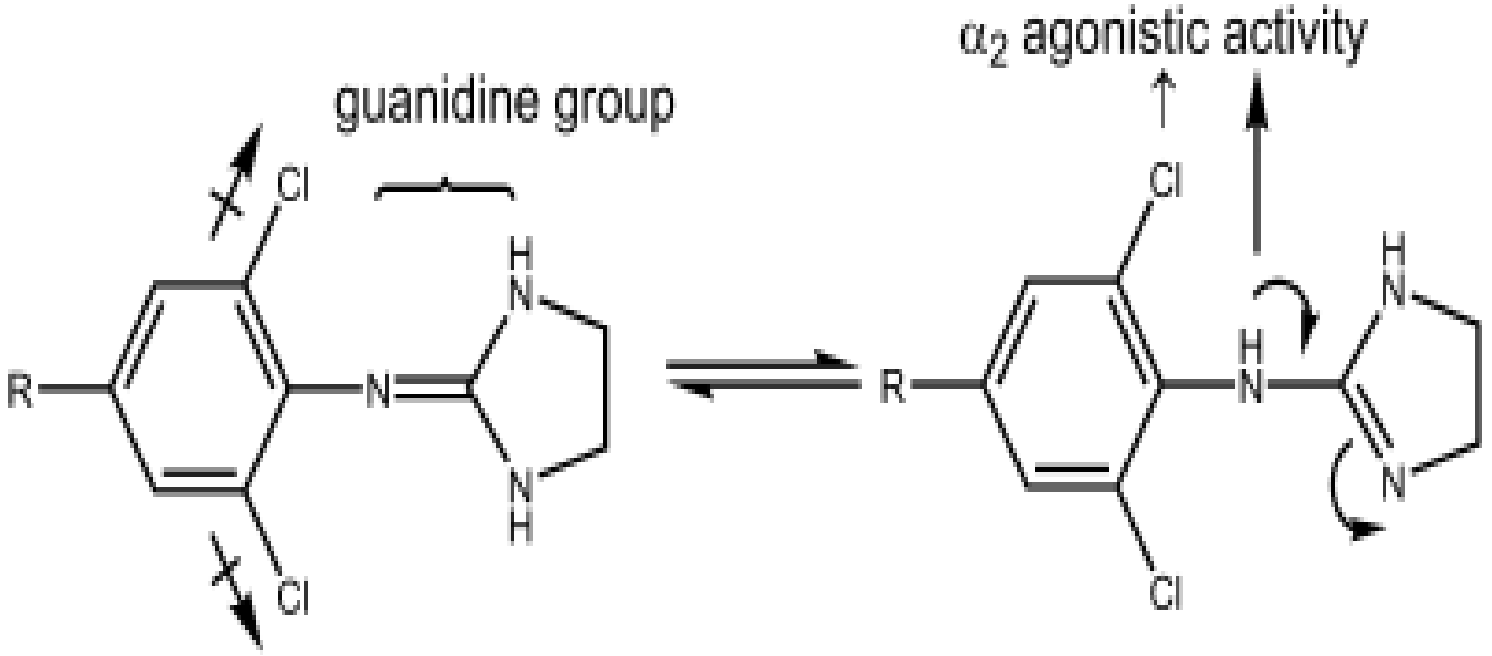
Xylometazoline R =



Clonidine

- Clonidine is an example of a (phenylimino) imidazolidine derivative that possesses central α 2-selectivity.
- The α1 : α2 ratio is 300:1.
- Under certain conditions, such as intravenous infusion, clonidine can briefly exhibit vasoconstrictive activity as a result of stimulation of peripheral α -receptors.
- However, this hypertensive effect, if it occurs, is followed by a much longer-lasting hypotensive effect as a result of the ability of clonidine to enter into the CNS and stimulate α2-receptors

Clonidine



Clonidine (pKa = 8.0) : R = H some passage into the CNS

4-Hydroxyclonidine : R = OH no passage into the CNS

Apraclonidine (pKa = 9.22) : R = NH_2 no passage into the CNS

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