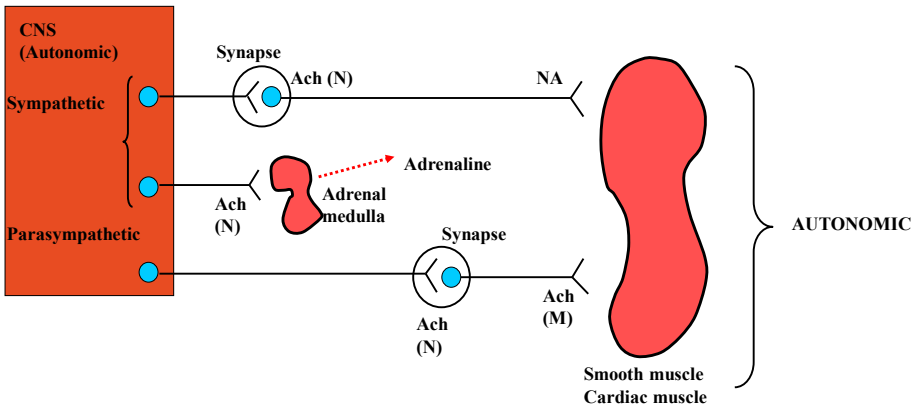
# Adrenergic Drugs

## Peripheral Motor Nervous system

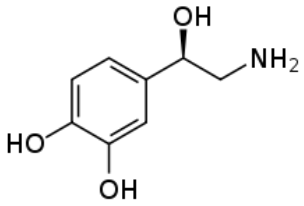


# Sympathetic Nervous System

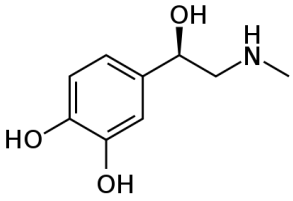
## Functions

- Noradrenaline is released at target organs and leads to
  - Contraction of cardiac muscle and increase in heart rate.
  - Contraction of the peripheral blood vessels.
  - Relaxation of smooth muscle and reduction in the contractions of the GIT and urinary tracts.
  - Reduces secretions such as salivation
  - Glycogen to glucose
- In general, the sympathetic nervous system promotes the 'fight or flight' response by shutting down the body's housekeeping roles (digestion, defecation, urination, etc.), and stimulating the heart.

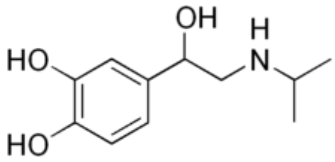
# Neurotransmitters – Catechol amines




Norepinephrine

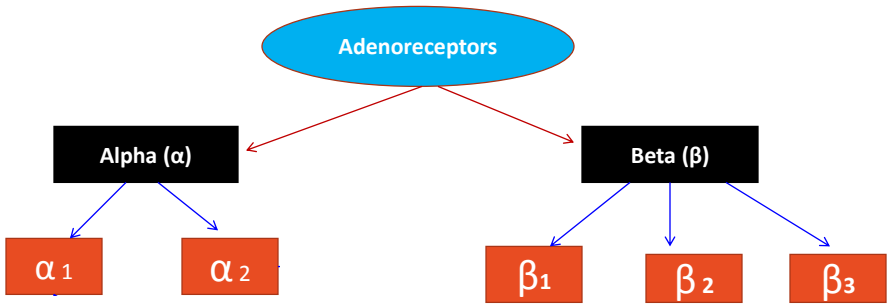



Epinephrine

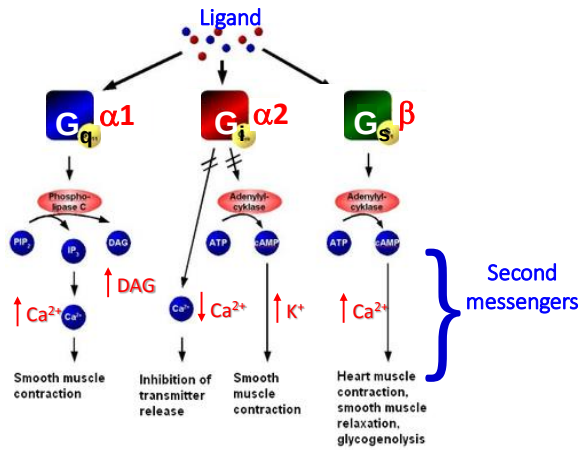



Isoproterenol

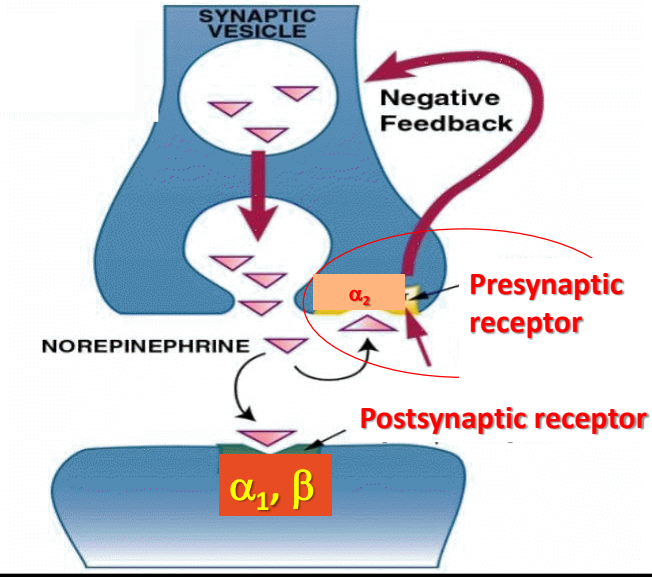
# Adrenergic receptors




**Adrenergic receptors are all GPCRs**

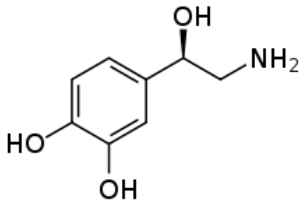



- $G_q$ increases phospholipase C activity and increases $Ca^{2+}$ currents – α 1
- $G_i$ decreases adenylyl cyclase activity and increases $K^+$ currents - α 2
- $G_s$ increases adenylyl cyclase activity and increases $Ca^{2+}$ currents - β1 , β2, β3

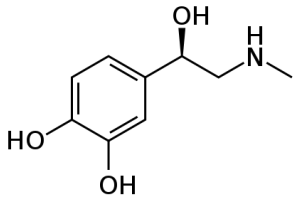



Presynaptic (inhibitory) – α 2
Postsynaptic (inhibitory) – α 1, β1 , β2, β3

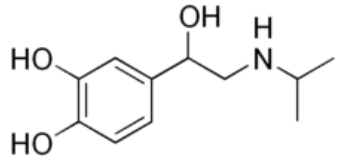
## Neurotransmitters




Norepinephrine




Epinephrine




Isoproterenol

**α receptors** Epinephrine > Norepinephrine > Isoproterenol

**β receptors** Norepinephrine < Epinephrine < Isoproterenol

Receptor localisation

| Organ or Tissue | Type Receptor Major | Response |
|---|---|---|
| Arterioles, vascular bed to skeletal muscle | $\alpha_1$, $\alpha_2$<br>$\beta_2$ | Constriction<br>Dilation |
| Eye (radial muscle) | $\alpha_1$ | Contraction (papillary dilation) |
| Heart | $\beta_1$ | Increased rate and force |
| Lungs | $\beta_2$ | Relaxation (bronchodilation) |

| Adrenoceptor | Drug Action | Therapeutic Uses |
|---|---|---|
| $\alpha_1$ | Agonists | Shock, hypotension (to raise blood pressure)<br>Nasal decongestants |
| | Antagonists | Antihypertensives<br>Benign prostatic hyperplasia (BPH) |
| $\alpha_2$ | Agonists | Antihypertensives<br>Glaucoma<br>Analgesia<br>Sedatives |
| $\beta_1$ | Antagonists | Antihypertensives<br>Antiarrythmics |
| $\beta_2$ | Agonists | Bronchodilators (asthma and COPD) |

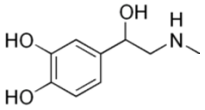
**Both β1 and β2 increase cAMP levels**

- β1 agonists stimulate the heart - enhances cardiac myocyte contraction
- β2 agonists cause bronchodilation by relaxing smooth muscles
  - The reason for this is that cAMP inhibits myosin light chain kinase that is responsible for phosphorylating smooth muscle myosin. Therefore, increases in intracellular cAMP caused by β2-agonists inhibits myosin light chain kinase thereby producing less contractile force (i.e., promoting relaxation)

# Study

- α receptors agonists
- α receptor antagonists
- β receptor agonists
- β receptor antagonists

# Adrenergic agonists




Epinephrine

- Adrenergic agonists are drugs that mimic the action of the sympathetic nervous system
- They exert their effects by direct or indirect stimulation of the adrenergic receptors
- These drugs are generally divided into two groups –
  - Catecholamines
  - Noncatecholamines
- Adrenergic agonists are also classified according to their selectivity
  - Nonselective adrenergic agonists stimulate both alpha and beta receptors
  - Selective alpha / beta adrenergic agonists
- Thus both catecholamines and noncatecholamines could be nonselective or alpha / beta selective agents.

**The prototype compound for nonselective catecholamine adrenergic agonist - Epinephrine**

# α adrenergic agonists

**<u>Chemical classification</u>**

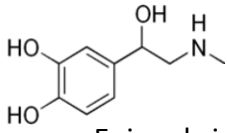
The catecholamines / noncatecholamines belong to 3 chemical classes

Phenylethanol amines

2-Aryl imidazolines

2-Amino imidazolines

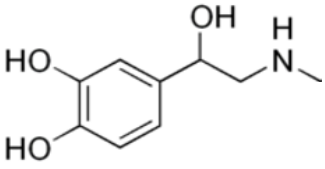
**The prototype compound for nonselective catecholamine adrenergic agonist - Epinephrine**



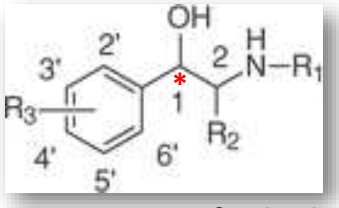

Epinephrine

# Phenylethanolamines

## SAR for α adrenergic agonist activity

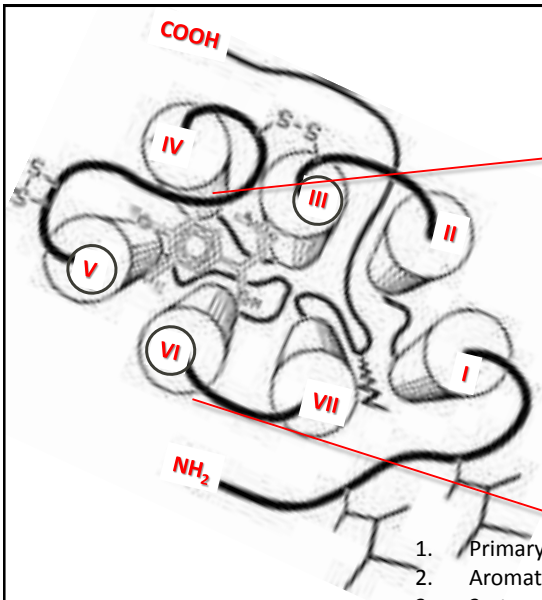



Epinephrine

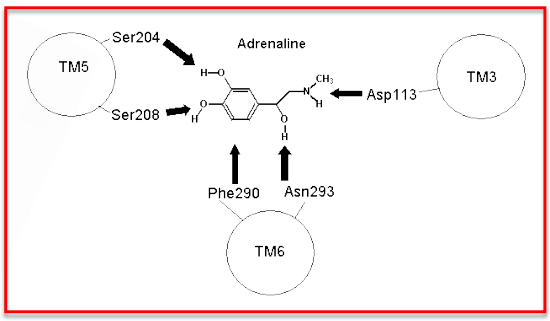



**Minimal requirement for high agonist activity**

1. Primary / secondary amine
2. Aromatic ring separated from amine by
3. 2-atom linker (eg. CH2CH2)
4. OH group on the carbon which is β to the amine
5. R configuration on chiral C (*)




## Binding interactions of Epinephrine

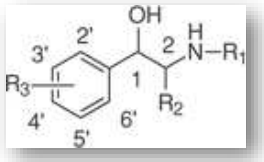



**Minimal requirement for high agonist activity**

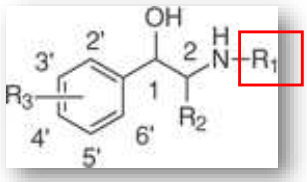
1. Primary / secondary amine – **Polar interaction with Asp113**
2. Aromatic ring – **hydrophobic interaction with Phe290**
3. 2-atom linker (eg. CH2CH2) – **correctly positions the pharmacophoric elements**
4. OH group on the carbon which is β to the amine – **H-bond with Asn 293**
5. R configuration on chiral C (*) - **correctly positions the pharmacophoric elements**

**Catechol OH groups make H-bonds with Ser204 and Ser208 – tolerant to change**

# α adrenergic agonists
## phenylethanol amines - SAR

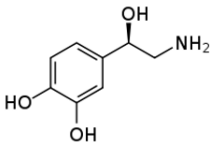



1. Minimal requirement for high agonist activity
   - Primary / Secondary aliphatic amine separated by 2 carbon atoms from a substituted benzene ring
2. All agents are positively charged at physiological pH
   - The amino group is highly basic (pka – 8.5 to 10)
3. By definition, all agents must have a OH group on the carbon which is β to the amine.
4. This chiral C must be in R configuration for maximal effect. Nevertheless, racemates of drugs are sold.
5. **The nature of the other substituents determines**
   1. **Receptor selectivity**
   2. **Duration of action**

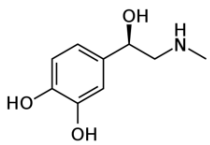



**R1 substitution on the amino nitrogen**

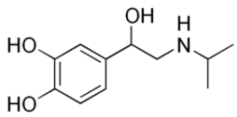
1. Increasing R1 size – Decrease α activity, Increase β activity




Norepinephrine



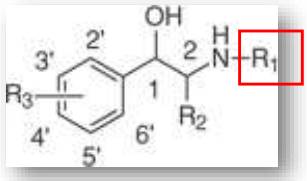

Epinephrine




Isoproterenol

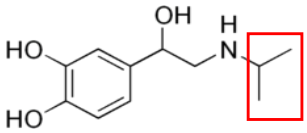
**α receptors** Epinephrine > Norepinephrine > Isoproterenol

**β receptors** Norepinephrine < Epinephrine < Isoproterenol

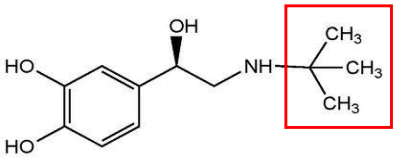



**R1 substitution on the amino nitrogen**

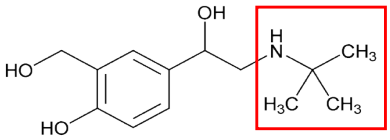
2. In addition, the N-substituent also can provide selectivity for different β-receptors, with a *t* -butyl group affording selectivity for β2- receptors.
   - For example, with all other features of the molecules being constant , colterol is a selective β2-agonist, whereas isoproterenol is a nonselective β-agonist .



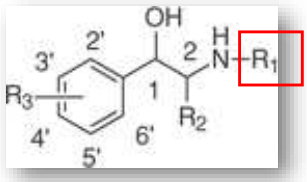

Isoproterenol
nonselective β-agonist
(shows undesirable
cardiac stimulatory activity (β1)
when used as a bronchodilator (β2)




Colterol
selective β2-agonist

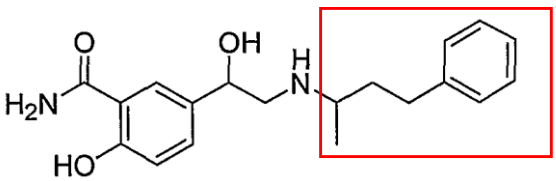



Albuterol
selective β2-agonist

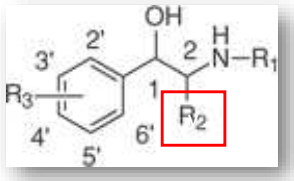



**R1 substitution on the amino nitrogen**

3. As R1 > t-butyl (aryl, a-methyl alkyl), affinity for α1, but not intrinsic activity returns
   - α1 blockers with large lipophilic N substituent eg. Labetalol (mixed α,β- antagonist)




Labetalol (mixed α, β - antagonist)




**R2, Substitution α to the Basic Nitrogen, Carbon-2**

- Presence of small alkyl groups, methyl or ethyl on the carbon adjacent to the amino nitrogen, carbon-2 affects the metabolism and hence the duration of action of these compounds.

# Catecholamines

## Metabolism and pharmacokinetics

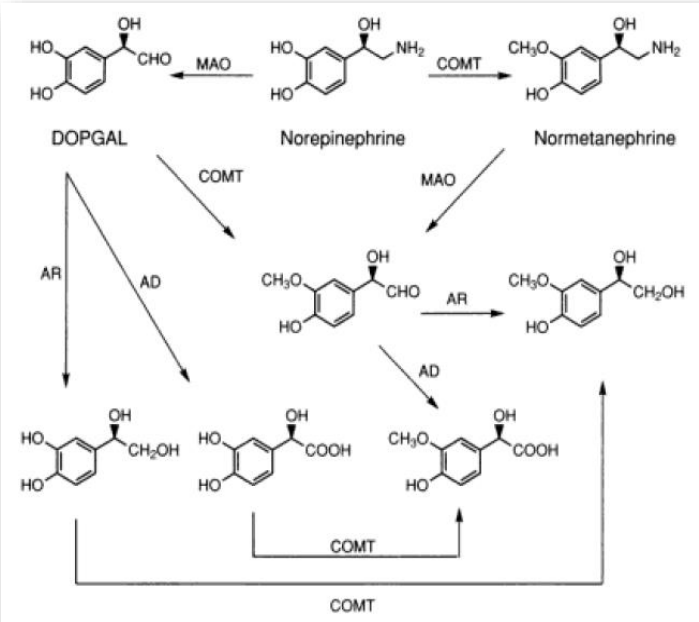
**Catecholamines**

- cannot be given orally
- short half-life, short duration

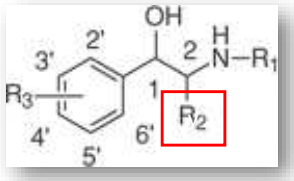
Reason – Rapid destruction by Monoamine oxidase (MAO) and Catechol-O-methyl transferase (COMT) located in gut wall, liver etc.

- Do not cross blood-brain barrier (BBB) – highly polar molecules

| Drug | Oral activity | Duration |
|---|---|---|
| **Catecholamines** | | |
| **Epinephrine** | **No** | **minutes** |
| **Norepinephrine** | **No** | **minutes** |
| **Isoproterenol** | **Poor** | **minutes** |

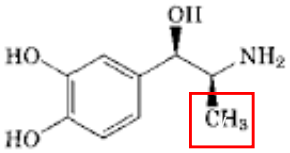



Metabolism of norepinephrine. MAO, monoamine oxidase; COMT, catechol-O-methyltransferase; AR, aldehyde reductase; AD, aldehyde dehydrogenase.

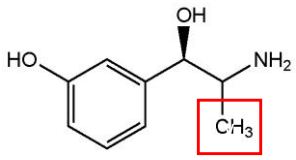



**R2, Substitution α to the Basic Nitrogen, Carbon-2**

- Small alkyl groups, methyl or ethyl, may be present on the carbon adjacent to the amino nitrogen, carbon-2 .

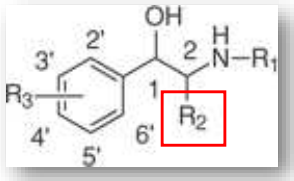


α–Methyl norepinephrine
MAO resistant
COMT sensitive



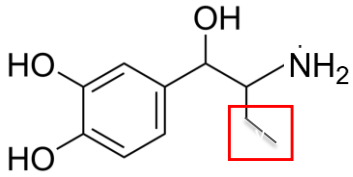
Metariminol
MAO resistant
COMT resistant

- Such substitution slows metabolism by MAO but has little overall effect on duration of action in catecholamines, because they remain substrates for COMT. Resistance to MAO activity is more important in noncatechol, indirect -acting phenylethylamines eg. metariminol.

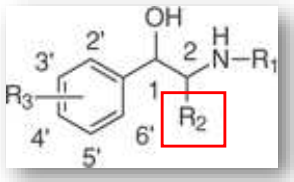



**R2, Substitution α to the Basic Nitrogen, Carbon-2**

- An ethyl group in this position diminishes α-activity far more than β-activity, affording compounds with β-selectivity, such as ethylnorepinephrine.




α–Ethyl norepinephrine
MAO resistant
COMT sensitive
**β-selective**




**R2, Substitution α to the Basic Nitrogen, Carbon-2**

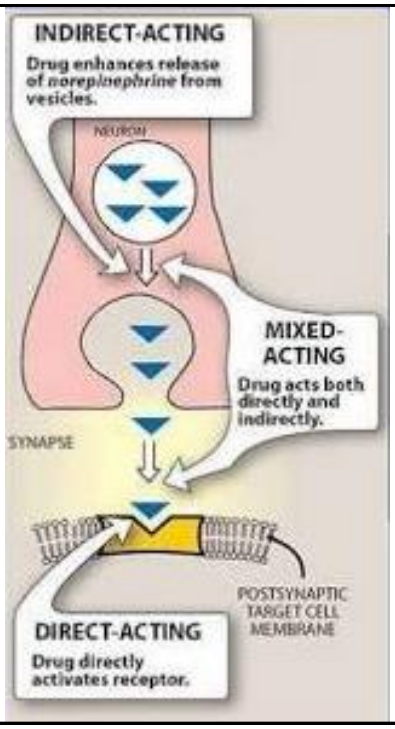
Chirality - Substitution on this carbon also introduces another asymmetric center into these molecules producing pairs of diastereomers, which can have significantly different biological and chemical properties.

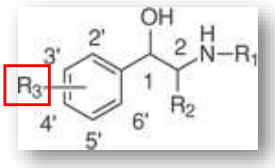
- The configuration of C2 of α-methylnorepinephrine has a great influence on receptor binding,
  - 1R,2S (erythro / syn) stereoisomer
    - Maximal direct activity
    - more selective for α2-adrenoceptors than for α1-adrenoceptors. (This has important consequences in the antihypertensive activity of α-methyldopa)
  - 1R,2R (threo / anti) diastereomer
    - Minimal direct activity
    - Has primarily indirect activity, even though the absolute configuration of the hydroxyl-bearing C1 is the same as in norepinephrine.


α–Methylnorepinephrine
direct acting stereoisomer

# Direct / Indirect activity

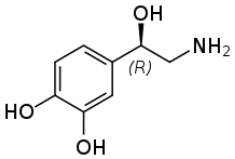
- Direct activity (i.e., agonist ) is the stimulation of an adrenoceptor by the drug itself;
- Indirect activity is the result of displacement of norepinephrine from its storage granules or reuptake inhibition, resulting in nonselective stimulation of the adrenoceptors by the displaced norepinephrine.
  - Because norepinephrine stimulates both α- and β-adrenoceptors, indirect activity cannot be selective.
  - Stereochemistry of the various substituents also may play a role in determining the extent of direct / indirect activity.



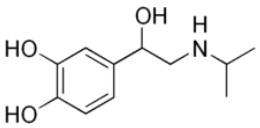




**R3, Substitution on the aromatic ring**

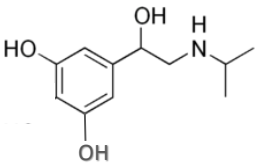
- The natural 3′,4′-dihydroxy–substituted benzene ring in norepinephrine provides
  - excellent receptor activity for both α- and β-sites.
  - Such catechol-containing compounds have poor oral activity, however, because they are rapidly metabolized by COMT.
- In particular, 3′,5′-dihydroxy compounds are not good substrates for COMT and, in addition, provide selectivity for β2-receptors.
  - selectivity for β2-receptors
  - not good substrates for COMT
- Thus, because of its ring substitution pattern, metaproterenol is an orally active bronchodilator with little of the β1 cardiac stimulatory properties possessed by isoproterenol.



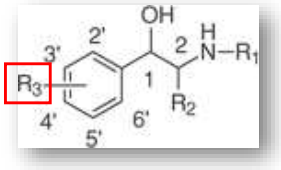

Norepinephrine




Isoproterenol

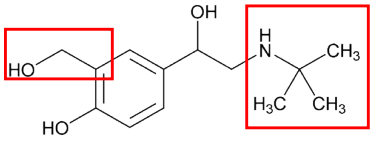



metaproterenol

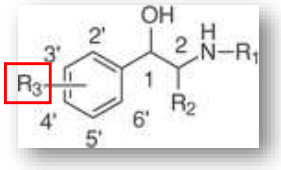



**R3, Substitution on the aromatic ring**

- Other substitutions are possible that enhance oral activity and provide selective β2-activity, such as the 3'-hydroxymethyl and 4'-hydroxy substitution pattern of albuterol

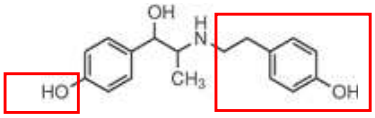



Albuterol
selective β2-agonist

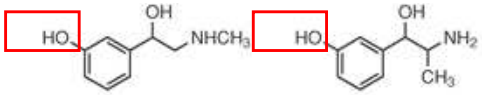



**R3, Substitution on the aromatic ring**

- At least one of the groups must be capable of forming hydrogen bonds, and if there is only one,
  - it should be at the 4' position to retain β-activity.
  - it should be at the 3' position to retain more α than β-activity.




Ritodrine



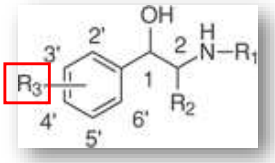

Phenylephrine Metaraminol

R3 **is only a 4'-OH - Selective β-agonists**

- ritodrine has only a 4'-OH for R3 yet retains good β-activity, with the large substituent on the nitrogen making it β2 selective.

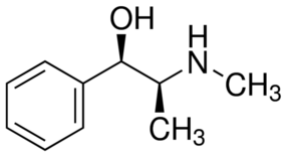
**R3 is only a 3'-OH - Selective α-agonists**

- reduced activity at α sites
- but activity almost eliminated at β sites

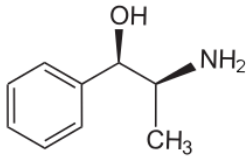



**R3, Substitution on the aromatic ring**

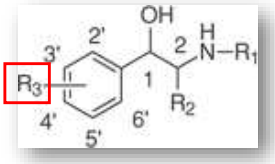
- When the phenyl ring has no phenolic substituents (i.e. , R3 = H), these phenylethanolamines may have both direct and indirect activity.
- Stereochemistry of the other substituents also may play a role in determining the extent of direct / indirect activity




Ephedrine
α + β

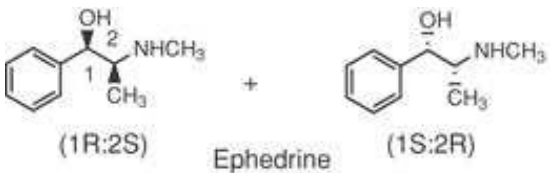



Phenylpropanolamine
α + β




**R3, Substitution on the aromatic ring**

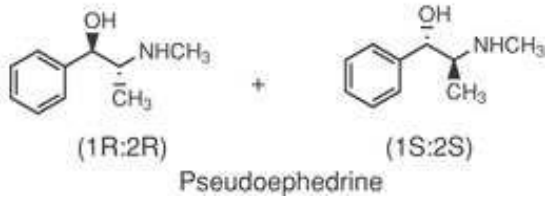
- Stereochemistry of the various substituents also may play a role in determining the extent of direct / indirect activity.
  - For example, ephedrine and pseudoephedrine have the same substitution pattern, but substitution of both carbons 1 and 2 means four stereoisomers are possible.




Naturally occuring stereoisomer
Primarily direct activity
mixed (α- and β)

primarily indirect activity

**Racemic (—)-ephedrine**




**Racemic (—)-pseudoephedrine**

primarily indirect activity