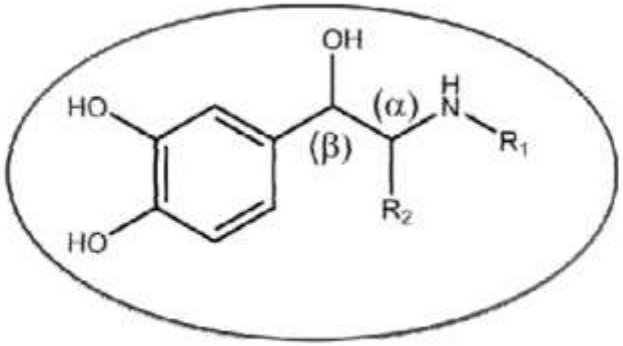
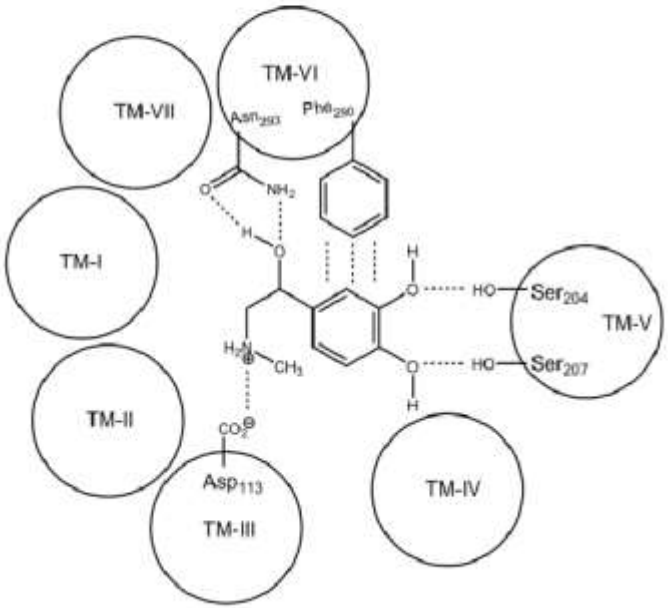


SympathoMimetics



Amit Z Chaudhari

INTRO

Defination:

- Compounds that produce effects similar to stimulation of sympathetic nervous activity are known as *sympathomimetic* .

Synonym: *Adrenergic stimulants*

Act by:

stimulating adrenergic receptors (adrenoceptors, ARs)

or

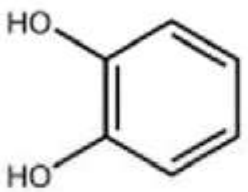
affect the life cycle of adrenergic neurotransmitters (NTs)

NEUROTRANSMITTERS

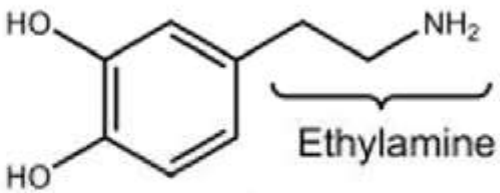
- Norepinephrine (NE, noradrenaline),
- Epinephrine (E, adrenaline) , dopamine (DA)

Structure :

- Chemically are catecholamines (CAs)



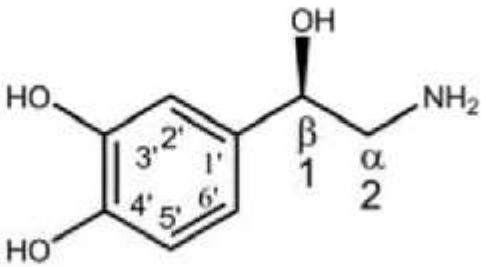
Catechol



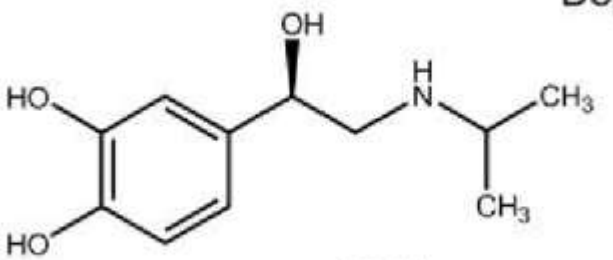
Catechol

Catecholamine

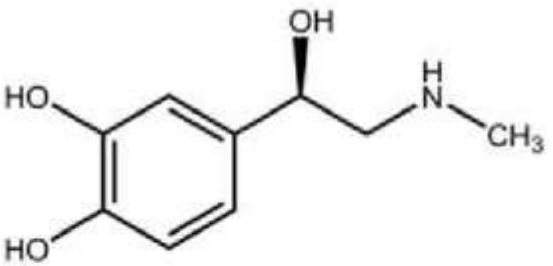
Dopamine (DA)



Norepinephrine (NE)

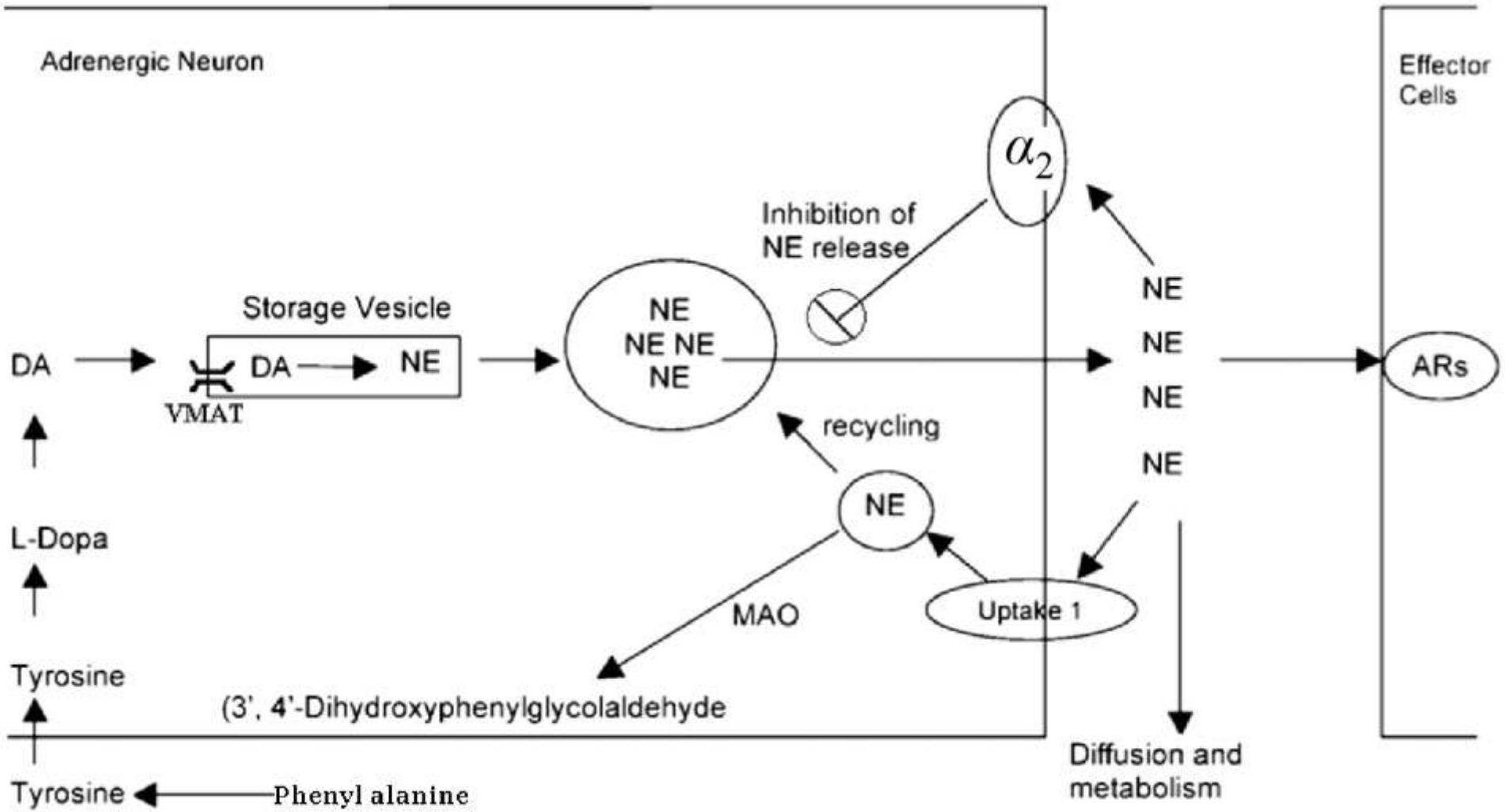


Isoproterenol (ISO)

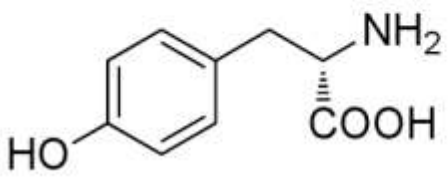


Epinephrine (E)

Model of life cycle of NE



Biosynthesis :

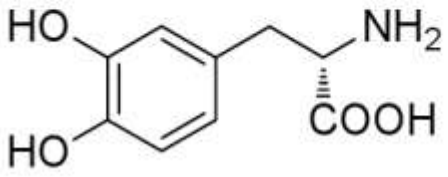


L -Tyrosine

Tyrosine Hydroxylase

rate-limiting step

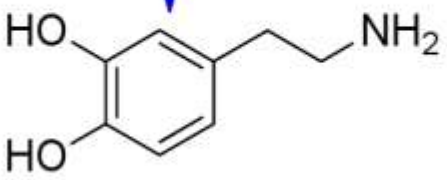
Step_1



L - DOPA

Step_2

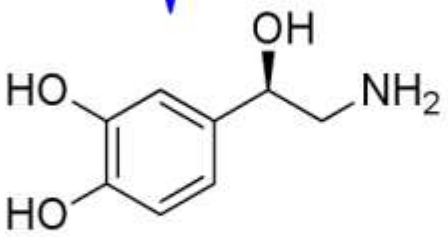
DOPA decarboxylase



Dopamine

Step_3

dopamine β-hydroxylase

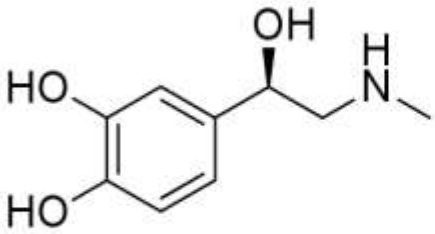


Norepinephrine

Phenylethanolamine-N-methyltransferase

(adrenal medulla)

Step_4

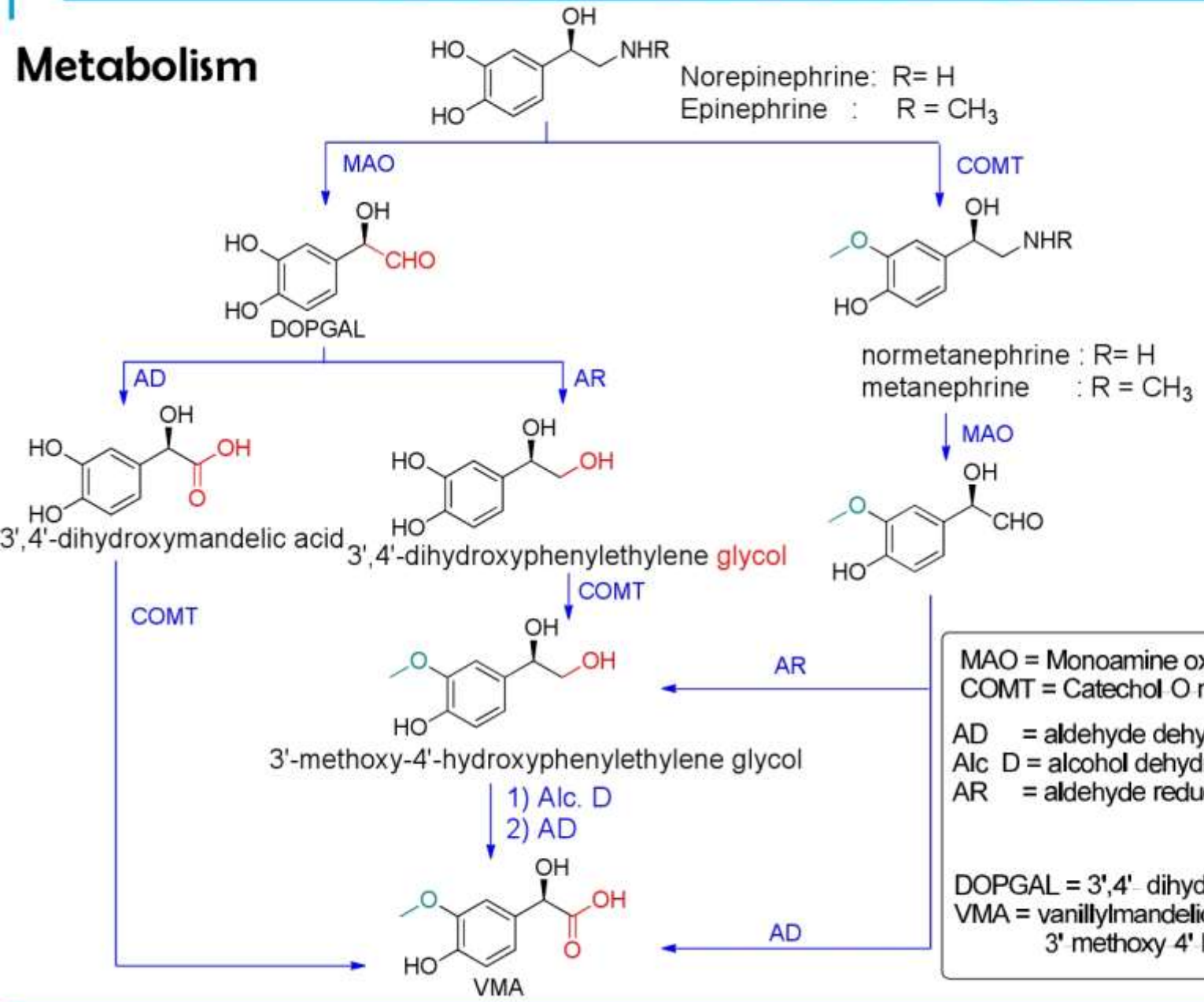


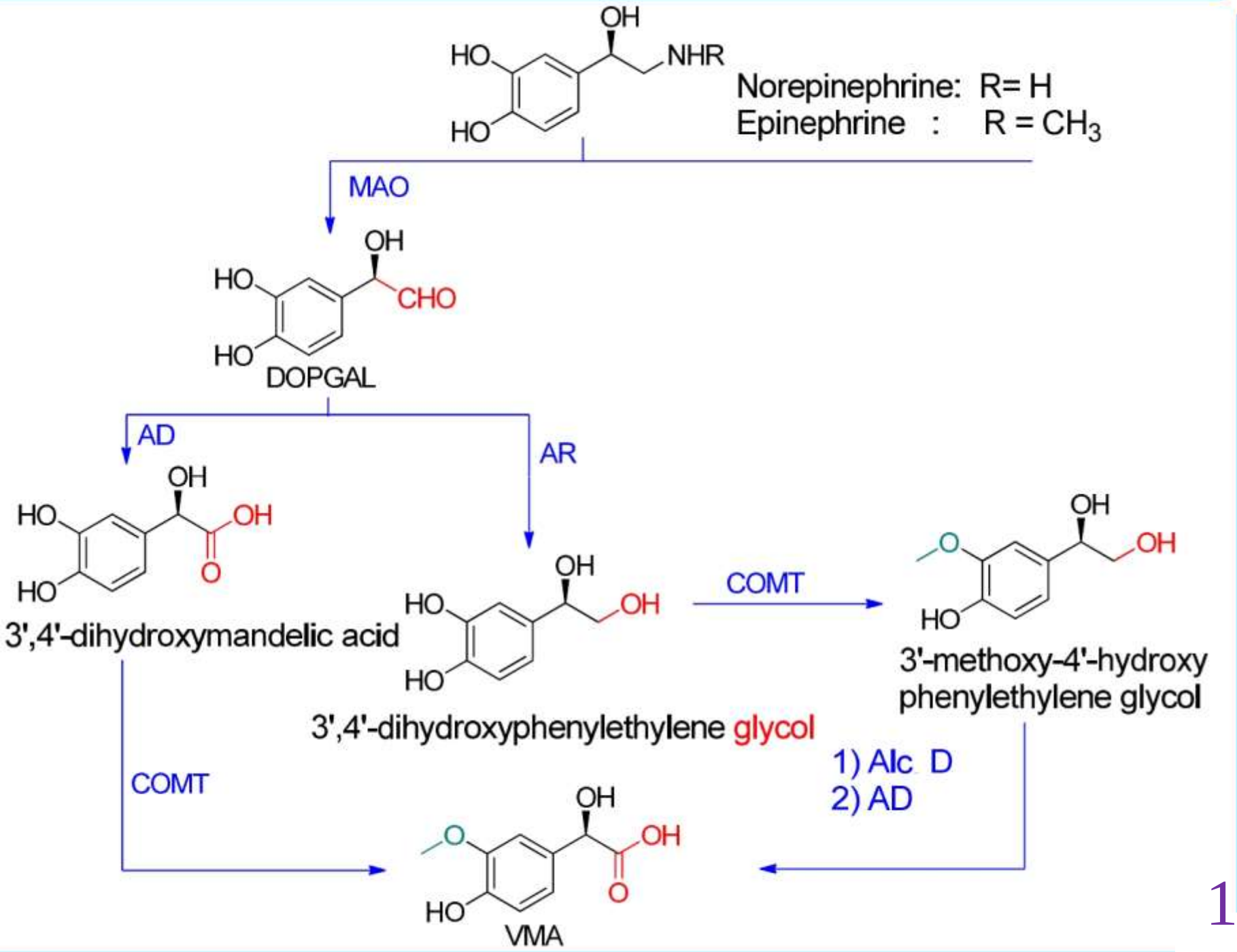
Epinephrine

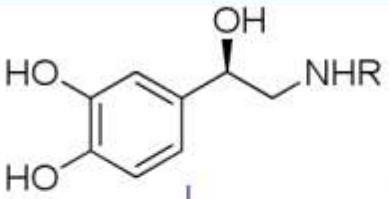
(*R*) Configuration of NE and E

NEUROCHEMISTRY

Metabolism

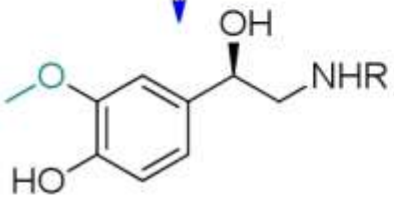



OH
HO
NHR
HO
Norepinephrine: R= H
Epinephrine : R = CH3
MAO
OH
HO
CHO
HO
DOPGAL
AD
AR
OH
HO
OH
O
HO
3',4'-dihydroxymandelic acid
OH
HO
OH
HO
3',4'-dihydroxyphenylethylene glycol
COMT
OH
O
OH
HO
3'-methoxy-4'-hydroxy
phenylethylene glycol
1) Alc D
2) AD
COMT
OH
O
OH
HO
O
VMA



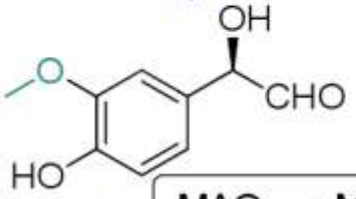
Norepinephrine: R= H
Epinephrine : R = CH_3

COMT

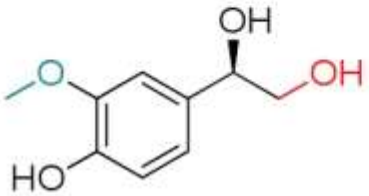


normetanephrine : R= H
metanephrine : R = CH_3

MAO

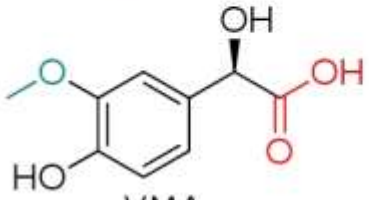


AR



3'-methoxy-4'-hydroxyphenylethylene glycol

1) Alc. D
2) AD



VMA

AD

MAO = Monoamine oxidase
COMT = Catechol-O-methyltransferase
AD = aldehyde dehydrogenase
Alc. D = alcohol dehydrogenase
AR = aldehyde reductase

DOPGAL = 3',4'- dihydroxyphenylglycolaldehyde
VMA = vanillylmandelic acid, *or*
3'-methoxy-4'-hydroxymandelic acid

Drugs affecting life cycle of NTs

Drugs Affecting CAs Biosynthesis

Metyrosine (α-Methyl-L-tyrosine)

Drugs Affecting Catecholamine Storage and Release

1. Reserpine
2. Guanethidine

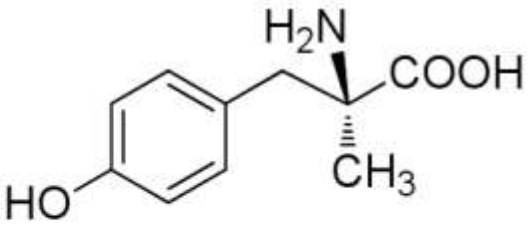
Drugs affecting life cycle of NTs

Drugs Affecting CAs Biosynthesis

Metyrosine

- inhibits any of the three enzymes involved in CA biosynthesis
- decrease CAs,

tyrosine hydroxylase
DOPA decarboxylase
dopamine β-hydroxylase



(-) Metyrosine

M/A

- Metyrosine differs structurally from tyrosine only in the presence of an α-methyl group . i.e. structurally similar substrate for enzyme. Thus metyosine competate with natural molecules for binding with the enzymes → ↓ CA syn.

Use

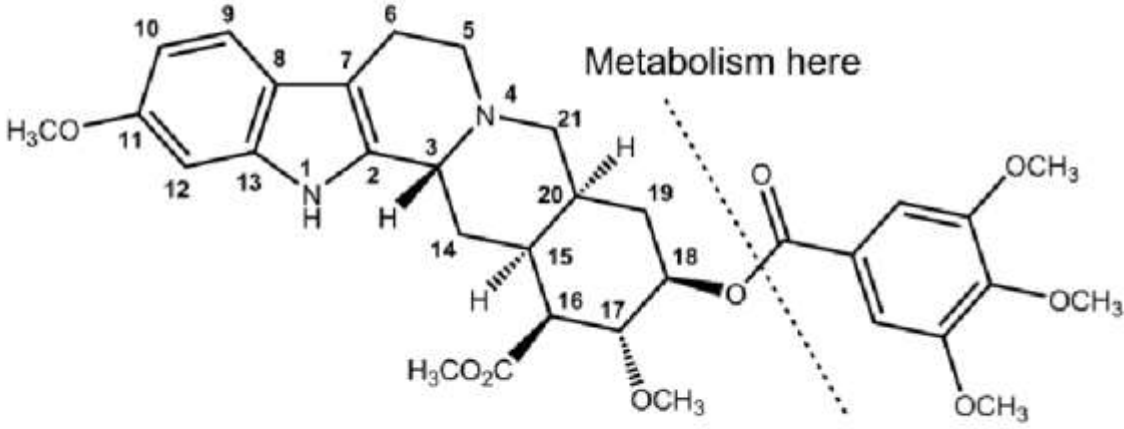
- Manegment of pheochromocytoma (tumor of pheochromocytes)

Drugs affecting life cycle of NTs

Drugs Affecting CAs Storage and Release

(1) Reserpine

- B.S. *Rauwolfia serpentina*
  - *sarpgandha - Ayurvedic*



Chemistry:

- indole alkaloid

M/A

- Reserpine binds extremely tightly with and blocks VMAT → ↓ transport of CAs from cytoplasm into the storage vesicles → retained NE will be metabolized by mitochondrial MAO within cytoplasm
- thus depletion of NE release in sympathetic cleft
- blood vessels will relax and dilate → lowers b. p.
- PNS, CNS, adrenal medulla and also depletes storage of serotonin and DA

ADRENERGIC RECEPTORS

Adrenergic Receptor Subtypes

- are membrane-associated G-protein–coupled receptors receptors
- G-protein = guanine nucleotide-binding proteins
- In *1948*, Ahlquist proposed and designated α- and β- adrenoceptors based on their apparent drug sensitivity.

Result of agonists affinity toward isolated heart muscles and isolated bronchial smooth muscle.

Isolated organs	Sensitivity	Designation
Blood vessel	E > NE > ISO	α
Heart	ISO > E > NE	β

ADRENERGIC RECEPTORS

Adrenergic Receptor Subtypes

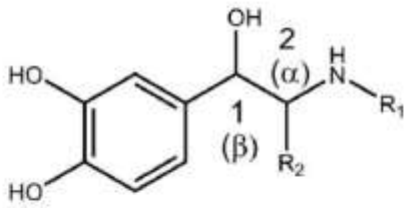
TABLE 16.3 Distribution and Effects of Adrenoceptors and Main Uses of the Adrenergic Drugs

Organ or Tissue	Predominant Adrenoceptors	Effect of Activation	Physiological Effect	Drugs	Therapeutic Uses
Blood vessels and skin	α_1	Vasoconstriction	↑ Blood pressure	α_1-Agonists	Shock, hypotension
Mucous membranes	α_1	Vasoconstriction		α_1-Agonists	Nasal congestion
				α_1-Antagonists	Hypertension
Prostatic gland muscle	α_{1A}	Contraction	Prostatic hyperplasia	α_{1A}-Antagonists	BPH
CNS	α_2	↓ NE release	↓ Blood pressure	α_2-Agonists	Hypertension
Heart muscle	β_1 (minor β_2, β_3)	Muscle contraction	↑ Heart rate & force	β_1-Antagonists	Hypertension Arrhythmias
Bronchial smooth muscle	α_1	Smooth muscle contraction	Closes airways		
	β_2 (Bronchodilation)	Smooth muscle relaxation	Dilates & opens airways	β_2-Agonists	Asthma and COPD
Uterus (pregnant)	α_1	Muscle contraction			
	β_2	Smooth muscle relaxation	(−) Uterine contractions	β_2-Antagonists	Premature labor
Kidney	β_1	Increases rennin secretion	↑ Blood pressure		

SAR (phenylethylamine)

Structure required for activity:

1. β-Phenylethylamine
2. Catechol ring
3 (1R)-OH



Aromatic substituents

3', 4'-diOH for both α & β agonist activity
metabolized by COMT→
poor oral activity and short DOA
hydrophilic → poor CNS activity

3', 5'-diOH (e.g., metaproterenol)
3'-CH_2OH, 4'-OH (e.g., albuterol)
↑ β_2 activity
↓ degradation by COMT →
↑ absorption, oral activity, & DOA

4'-OH is more important for β activity
3'-OH is more important for α activity
(e.g., phenylephrine: α-agonist)

No phenolic substitution:
↓both α and β activity
direct or indirect activity

R_1-Substitution on N

↑ the size of R_1→ ↑ β activity
↓ α activity
↓ degradation by MAO

t-butyl: ↑ β_2 activity
e.g. Colterol

large LPL : α_1-blocking activity
e.g. labetalol

R_2-Sustitution on C_2

small alkyl groups (Me, Et) tolerated

↓ degration by MAO

still substrates for COMT → little effect on DOA

Et group:

↓ α >> β (more β–selective, e.g., ethylnorepinephrine)

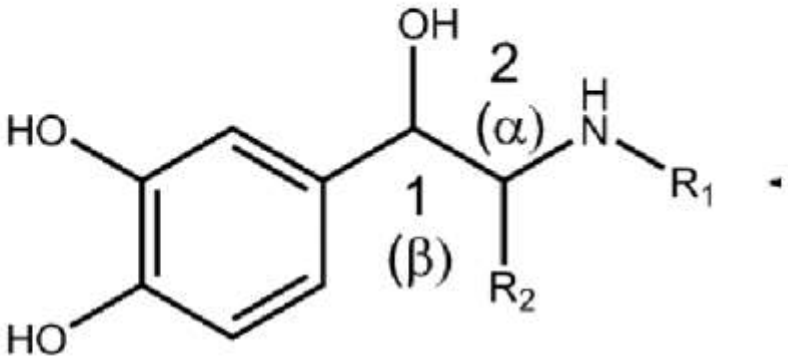
↑ CNS activity

↑ oral activity & DOA

(2S) methyl group: ↑ α_2 activity

Structure required for activity:

1. β-Phenylethylamine
2. Catechol ring
3 (1R)-OH

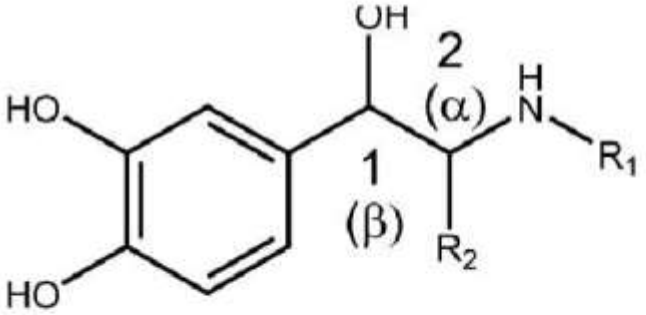


1. Optical Isomerism

- For CAs, the more potent enantiomer has the (1*R*) configuration. This enantiomer is typically several 100-fold more potent than the enantiomer with the (1*S*) configuration.

2. R_1, Substitution on the Amino Nitrogen

- Determines α or β - Receptor Selectivity.
- Primary and secondary amines have good adrenergic activity, whereas tertiary amines and quaternary ammonium salts do not.



R_1-Substitution on N

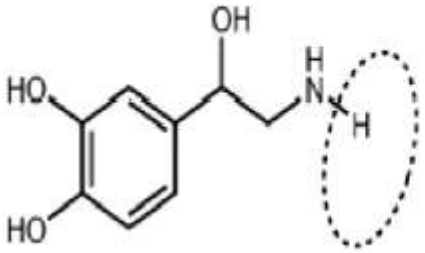
↑ the size of R_1→ ↑ β activity
↓ α activity
↓ degradation by MAO

t-butyl: ↑ β_2 activity
e.g. Colterol

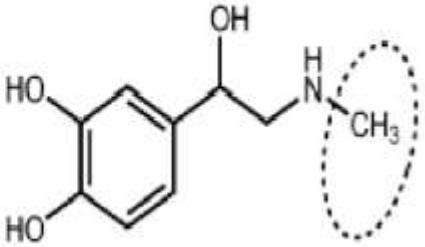
large LPL : α_1-blocking activity
e.g. labetalol

2. R_1, Substitution on the Amino Nitrogen

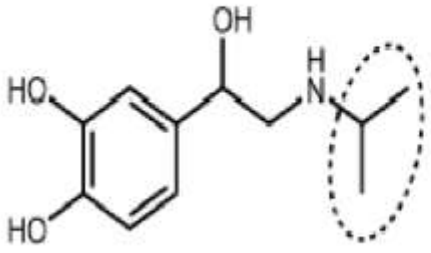
- As the size of the nitrogen substituent increases, α -receptor agonist activity generally decreases and β -receptor agonist activity increases
  + protect the amino group from undergoing metabolism by MAO



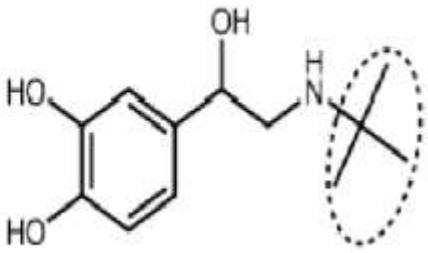
Norepinephrine (NE)
α > β agonist
α agonist



Epinephrine (E)
α, β_1 and β_2 agonist
nonselective α and β agonist



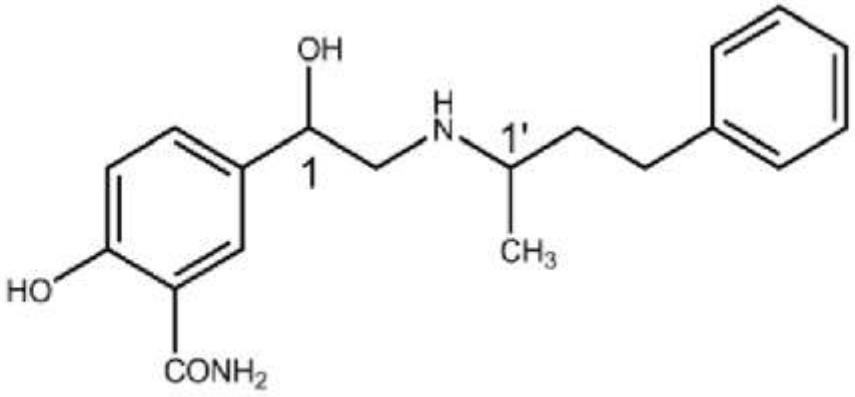
Isoproterenol (ISO)
β_1 and β_2 agonists
nonselective β agonist



N-*t*-Butylnorepinephrine (Colterol)
selective β_2 agonist

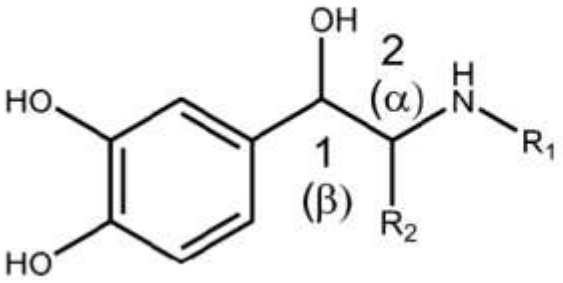
2. R_1, Substitution on the Amino Nitrogen

- large lipophilic (LPL) groups have can α_1-blocking activity e.g. labetalol



Labetalol

3. R_2, Substitution on the α –Carbon



R_2-Sustitution on C_2

small alkyl groups (Me, Et) tolerated

↓ degration by MAO

still substrates for COMT → little effect on DOA

Et group:

↓ α >> β (more β–selective, e.g., ethylnorepinephrine)

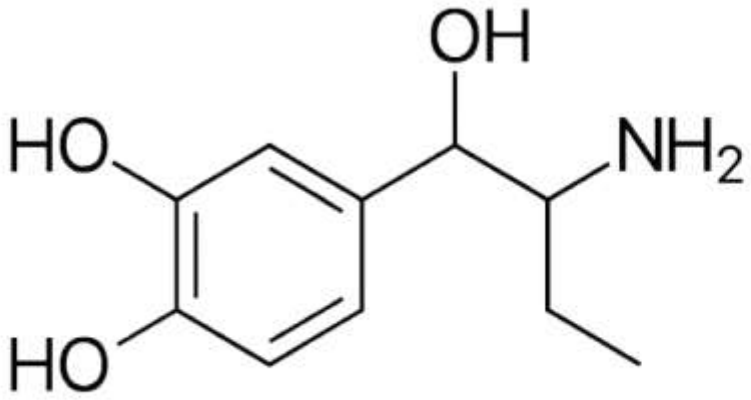
↑ CNS activity

↑ oral activity & DOA

(2S) methyl group: ↑ α_2 activity

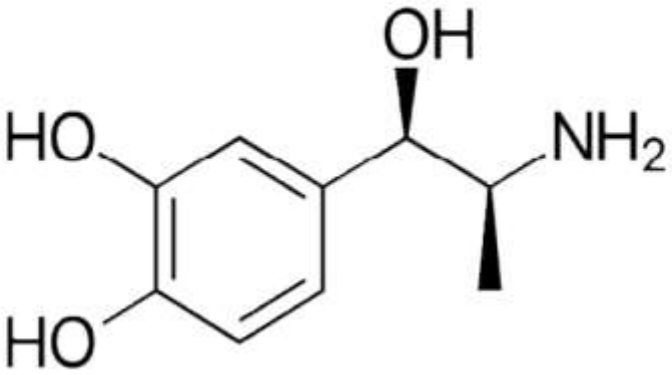
3. R_2, Substitution on the α –Carbon

- Substitution by small alkyl group slows metabolism by MAO with little effect on DOA
- Lipophilicity of R_2 substituted compounds often exhibit enhanced oral effectiveness and greater CNS activity.
- An ethyl group in this position diminishes α -activity far more than β -activity, affording compounds with β - selectivity (e.g., ethylnorepinephrine and isoetharine).

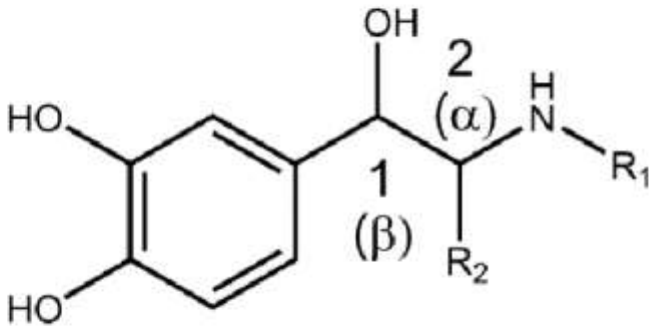


3. R_2, Substitution on the α –Carbon

- α - methylnorepinephrine, it is the erythro (1R,2S) isomer that possesses significant activity at α_2-receptors



4. *OH substitution on the β –carbon*



- Essential
- generally decreases CNS activity largely because it lowers lipid solubility
- Compounds lacking the -OH group (e.g. DA) have a greatly reduced adrenergic receptor activity.

5. *Substitution on the Aromatic Ring*

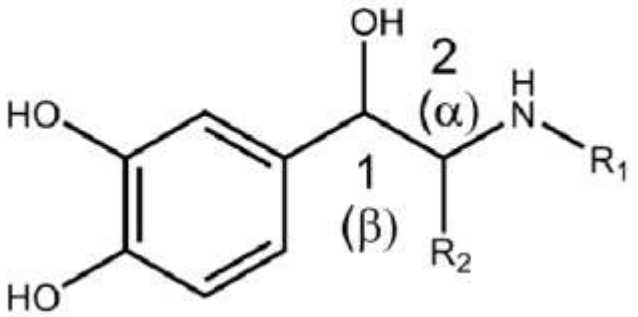
Aromatic substituents

3', 4'-diOH for both α & β agonist activity
metabolized by COMT→
poor oral activity and short DOA
hydrophilic → poor CNS activity

3', 5'-diOH (e.g., metaproterenol)
3'-CH_2OH, 4'-OH (e.g., albuterol)
↑ β_2 activity
↓ degradation by COMT →
↑ absorption, oral activity, & DOA

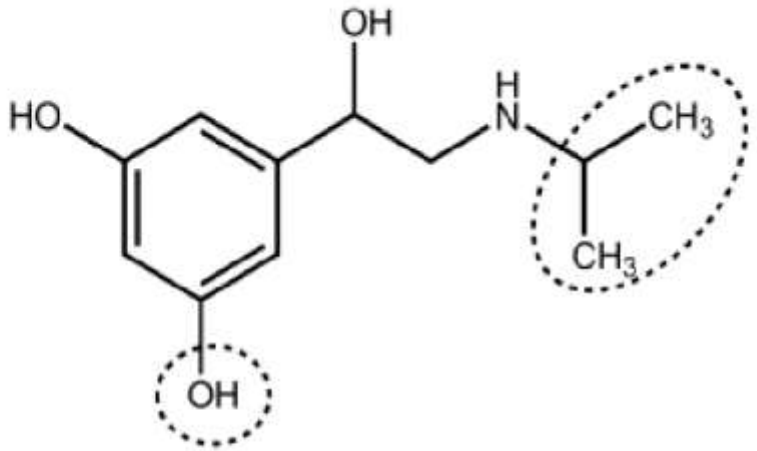
4'-OH is more important for β activity
3'-OH is more important for α activity
(e.g., phenylephrine: α-agonist)

No phenolic substitution:
↓both α and β activity
direct or indirect activity



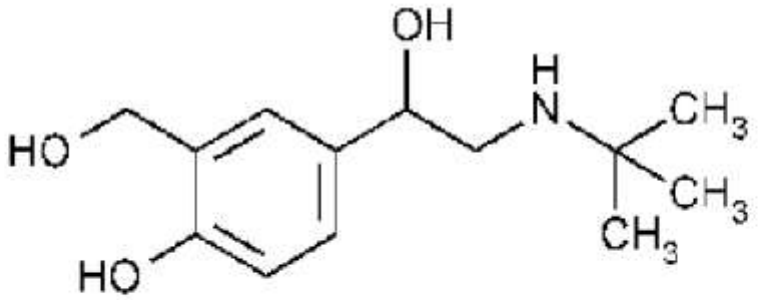
5. *Substitution on the Aromatic Ring*

- replacement of the catechol function of ISO with the resorcinol structure gives a selective β_2-agonist, e.g. metaproterenol
- It will longer the DOA as because the resorcinol ring is not a substrate for COMT

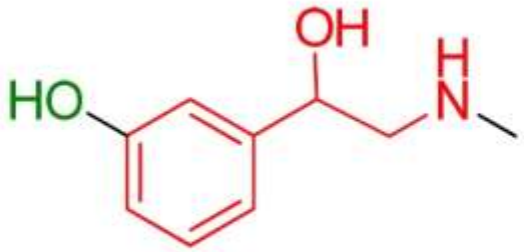


5. *Substitution on the Aromatic Ring*

- replacement of the meta-OH of the catechol structure with a hydroxymethyl group gives agents, such as albuterol selective β 2-agonist

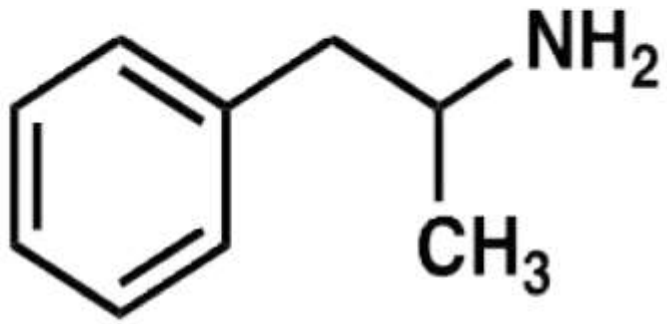


- removal of the *p*-OH group from E gives phenylephrine which lacks β action but has less α_1-agonist property



6. *CAs without OH Groups*

- loss of direct sympathomimetic activity becomes indirectly sympathomimetics
- not metabolized by COMT, and they are orally active and have longer DOA
- e.g. amphetamine



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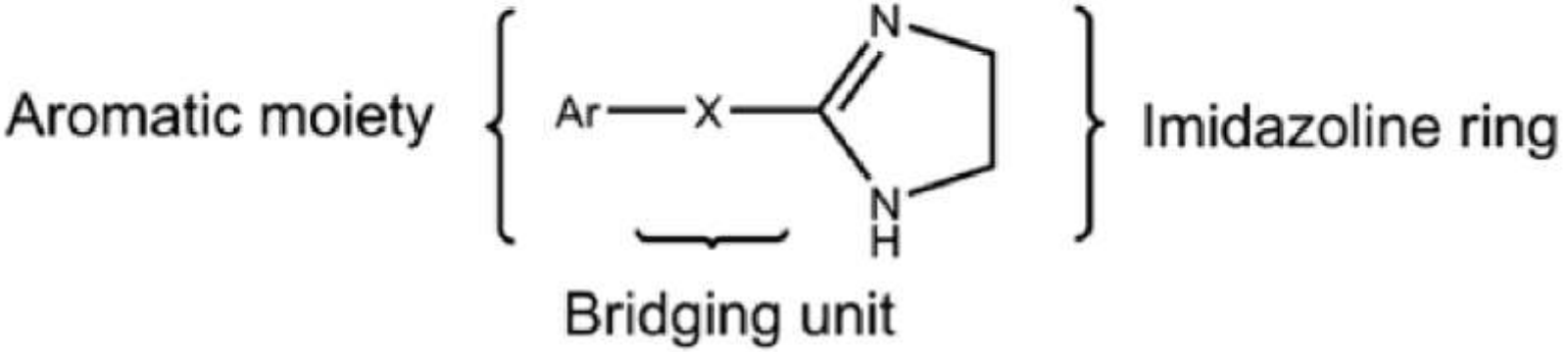
SAR (imidazoline)

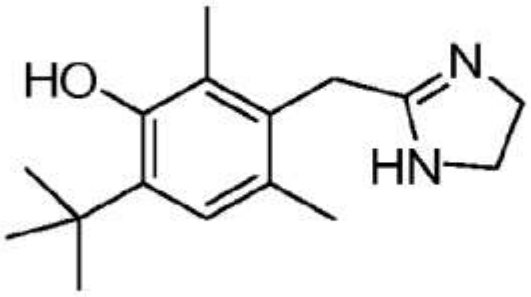


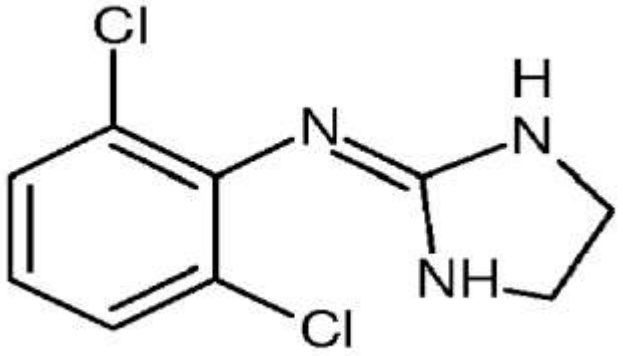
1. bridging unit (X)

X = usually CH_2 (α_1 agonists) or NH (α_2 agonists)

- usually a single methylene group [are 2-Arylimidazoline derivatives] & a amino group [2-Aminoimidazoline derivatives].

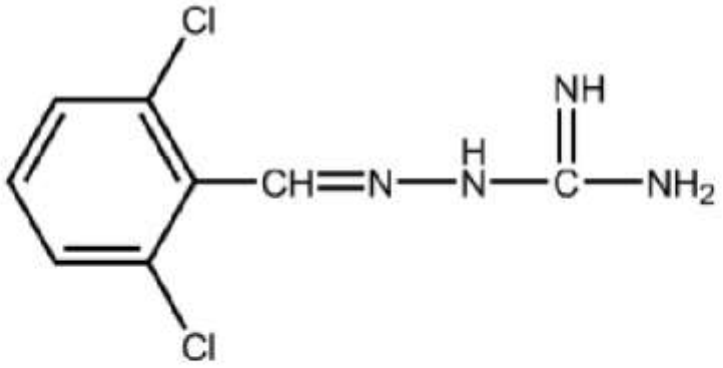
e.g. Oxymetazoline & Clonidine





2. Imidazoline ring

- open-ring imidazolines that are highly active α_2-agonists.



Guanabenz

3. aromatic ring

- agonist activity is enhanced when the aromatic ring is substituted with halogen substituents like chlorine (Cl) or small alkyl groups like methyl group, particularly when they are placed in the two *ortho* positions.