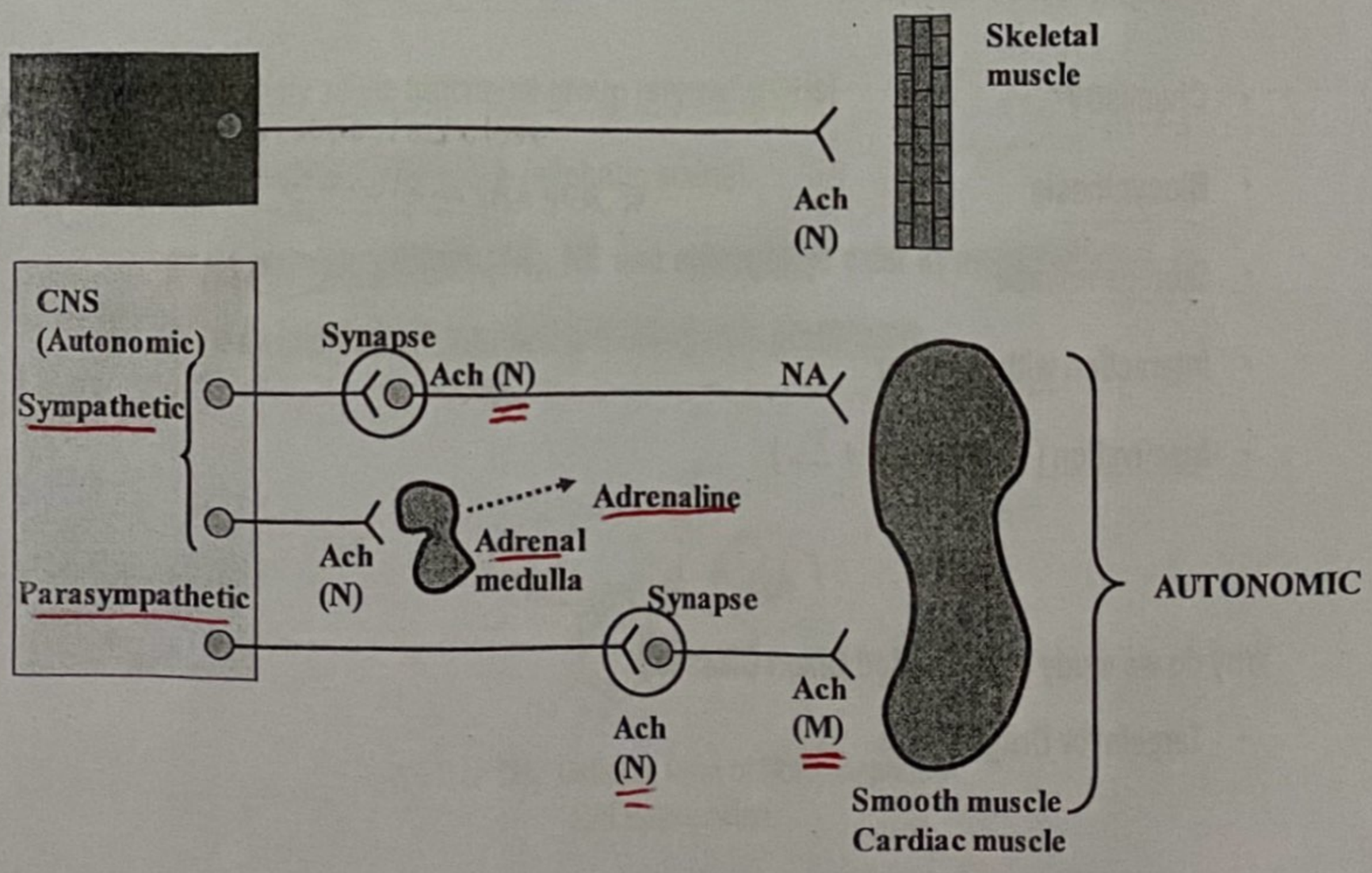
Drugs Acting on the Adrenergic (Sympathetic) Nervous System

1. Nerve Transmission

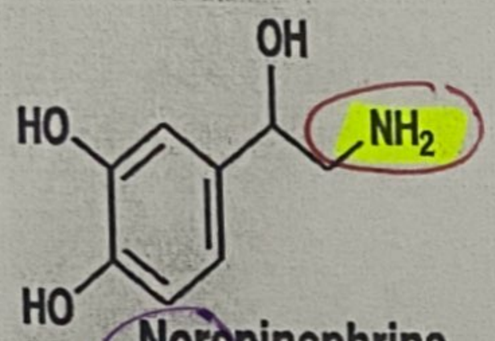
Peripheral nervous system



Adrenergic Neurotransmitters

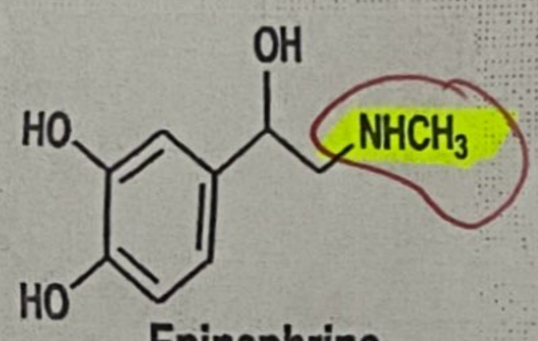
- Norepinephrine (NE) is the main adrenergic neurotransmitter.
- It is liberated from the post-ganglionic sympathetic neurons as a result of sympathetic nerve stimulation.
- Epinephrine (Adrenaline) is synthesized and stored in the adrenal medulla. Neurohormone.

الفرق بين adrenaline و الـ noradrenaline (one methyl grup)



Norepinephrine

methyl نفقد



Epinephrine (Adrenaline)

يختلفوا في اختلاف الهرمون بين أمريكية و البريطانية

Neurotransmitters

What is important about *Neurotransmitters* in our Med Chem Classes

- Chemistry
- Biosynthesis
- Storage/release
- Interaction with receptor
- Inactivation (Metabolism + ...)

* شو الانزيم اللي عمل metabolism لـ noradrenaline و adrenaline؟

COMT

Why do we study these in Med Chem Classes?

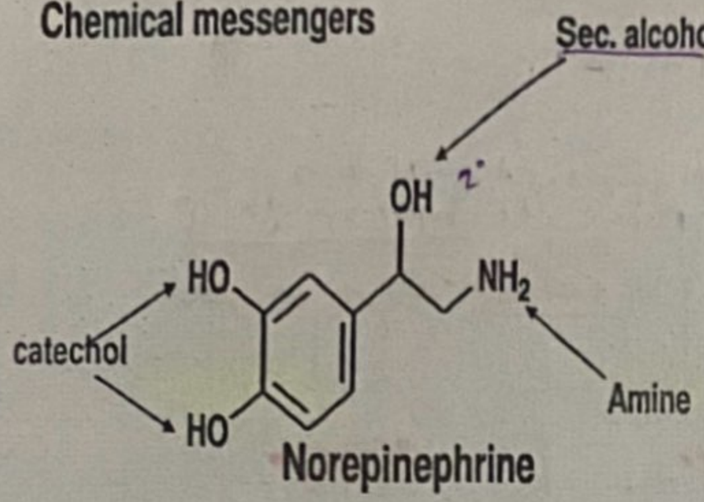
- Targets for Drug Design

Neurotransmitters

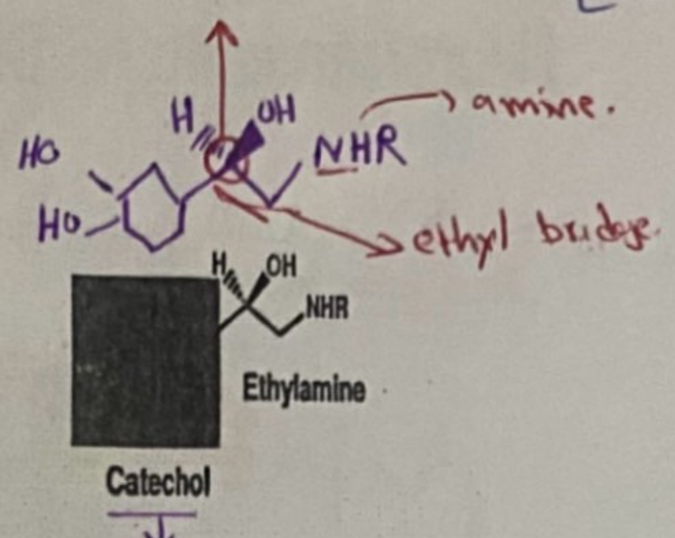
Chairul centar.

[بس تكون مرتبطه بذرة مجموعات ثانية]

Chemical messengers

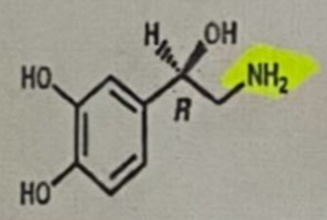


Norepinephrine



يشتمل عليها انزيم COMT

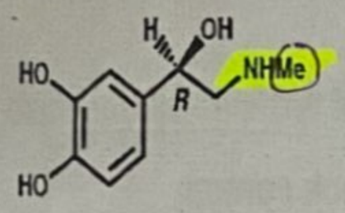
Noradrenaline – neurotransmitter



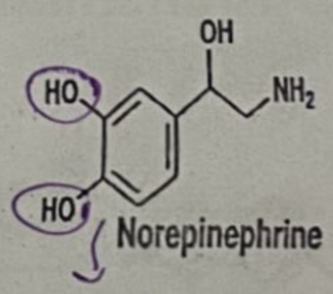
ال aldrenaline بتشوفوا:-

1. Catecholamine derivative
2. Phenylethylamine derivative

Adrenaline – hormone



Neurotransmitters. Chemistry

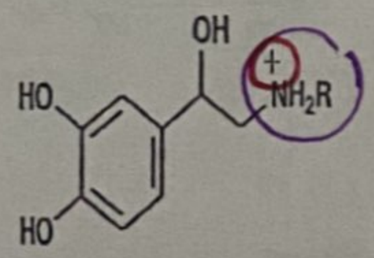


Norepinephrine

two phenols

ال Phenol الكحولات عطريّة

- Slightly acidic functional group (aromatic OHs)
- Basic functional group (aliphatic amine).
- At physiological pH (7.4), NE and epinephrine exist in more than 95% in the cationic form in which the nitrogen is protonated.



R = H or CH_3: Cationic form of Norepinephrine and Epinephrine

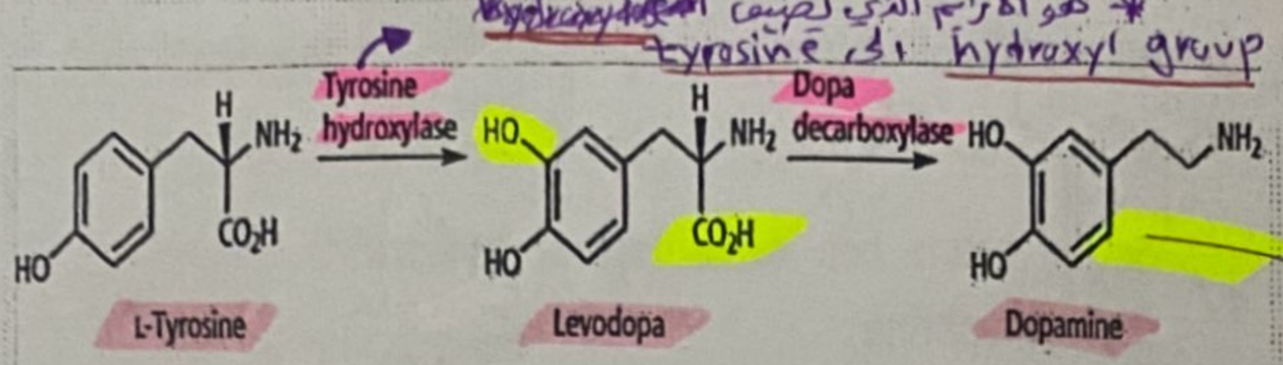
Neurotransmitters. Biosynthesis

* كيف يُصنع الـ adrenaline في جسم الإنسان؟؟؟

يبلش من حاد الـ amino

From amino acid tyrosine

* هو الانزيم الذي يضيف hydroxyl group الى tyrosine



* حال الـ Carboxyl group تكون الـ Dopamine

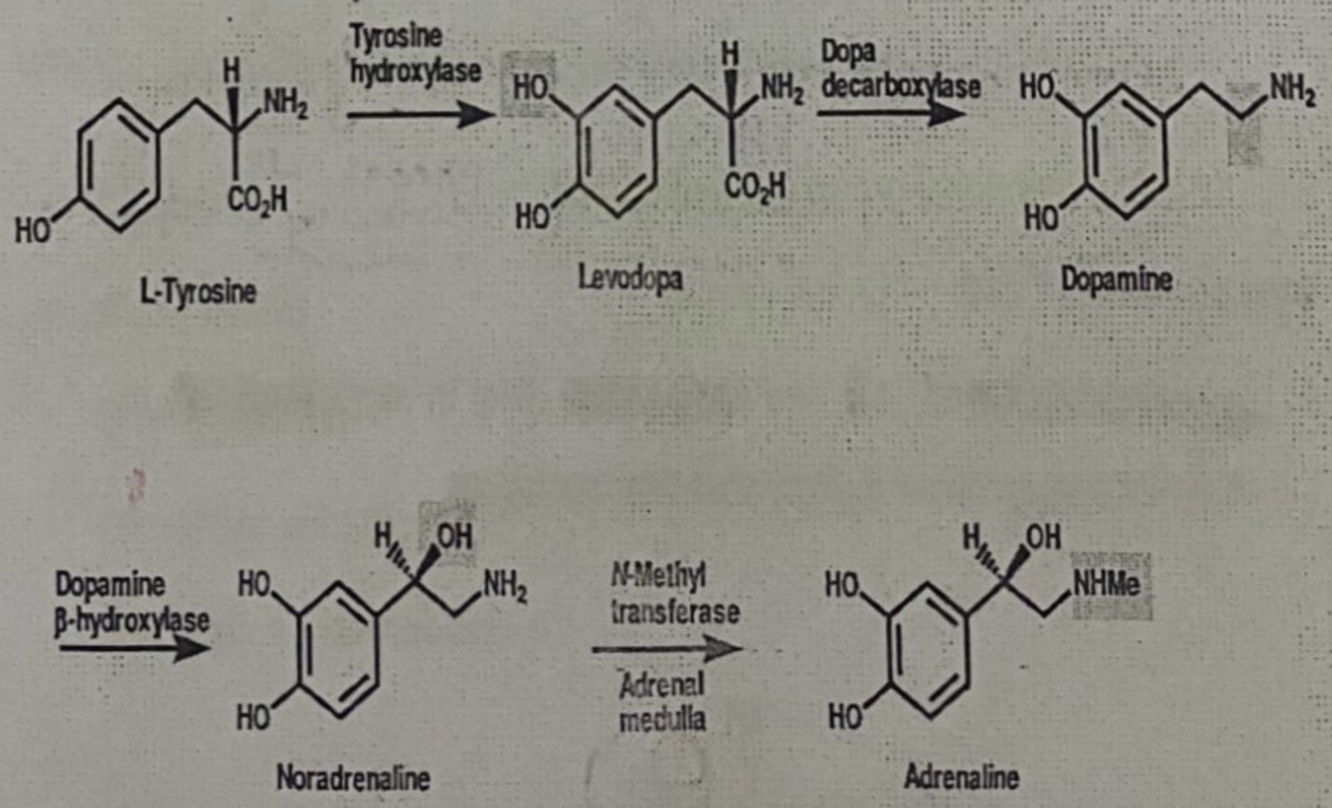
hydroxyl الإضافة

Methyl فاقد الـ

* أي اخيا كونك اخذت جرعة الـ Aldrenaline

- Pathway controlled by regulation of tyrosine hydroxylase
- Inhibited by noradrenaline - feedback control

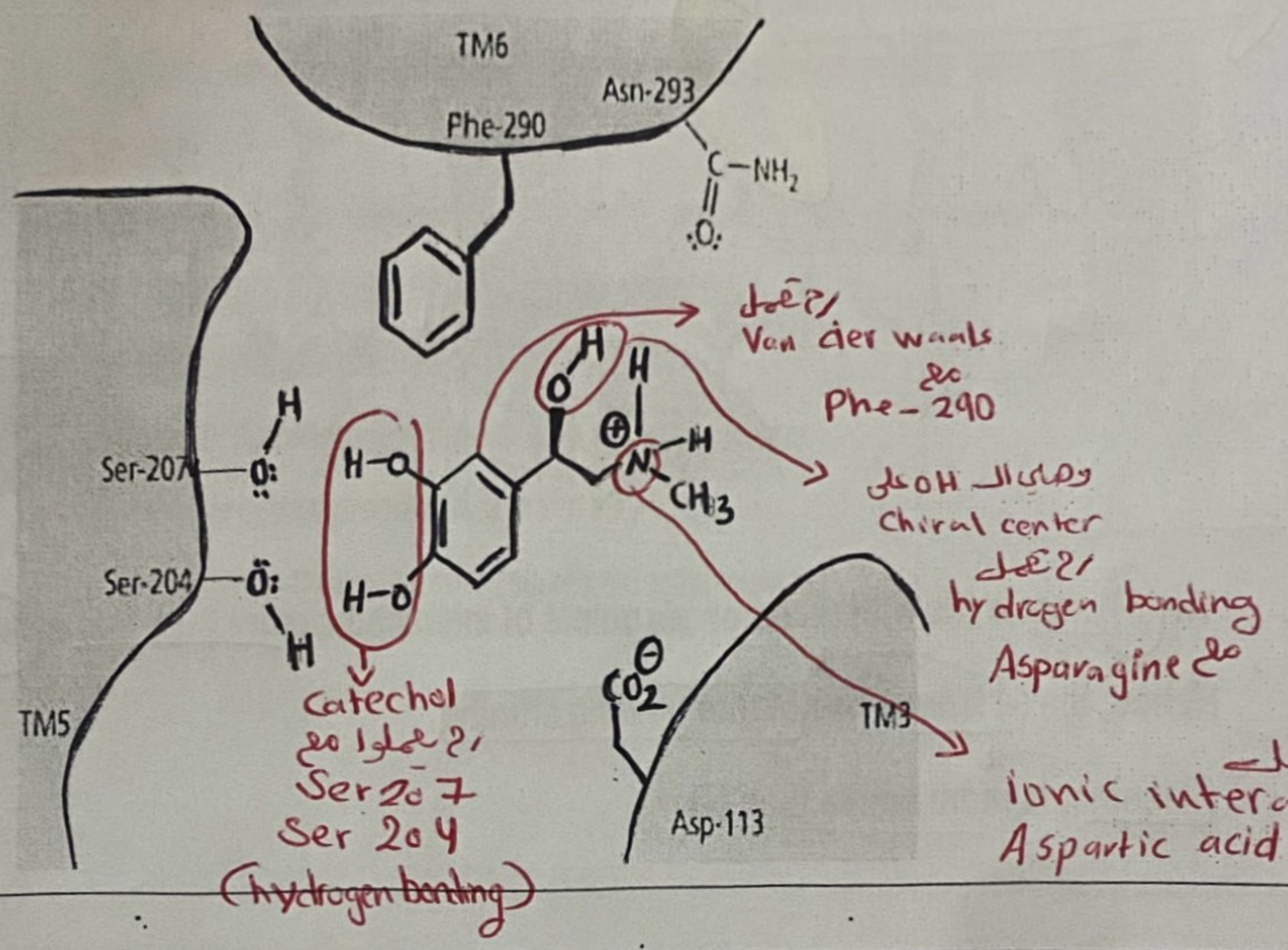
Neurotransmitters. Biosynthesis



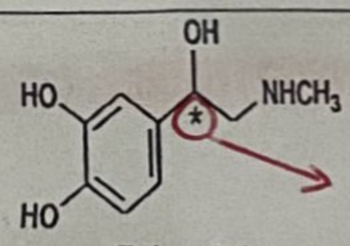
Adrenergic binding site

Drug Receptor Interaction.

D-R interaction



Stereochemistry of NE and Epi



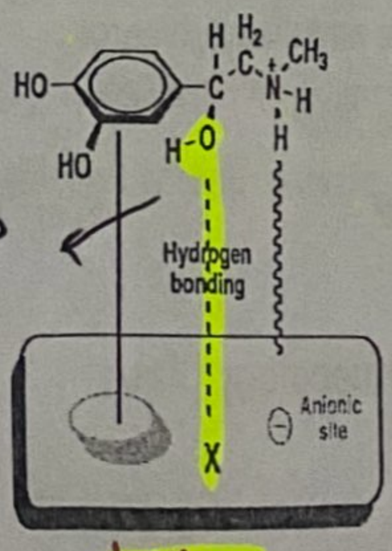
* للارتباط على Chiral center

- There is a chiral carbon.
- There are two optically active isomers: (-) and (+)
- (-) Epinephrine is more active than (+) Epinephrine. Why?
- Different binding
- (-) isomer fits with receptor *via* points of interaction, more than that of (+).
- Hence, the (-) isomer has higher affinity and activity.

levo
(-) Epinephrine

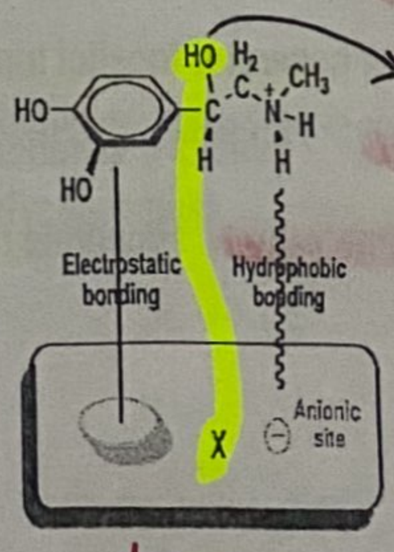
(+) Epinephrine
dextro

هاد للي فيني آنه د



هون مع Aspergine بكون hydrogen bonding

levo
(-)

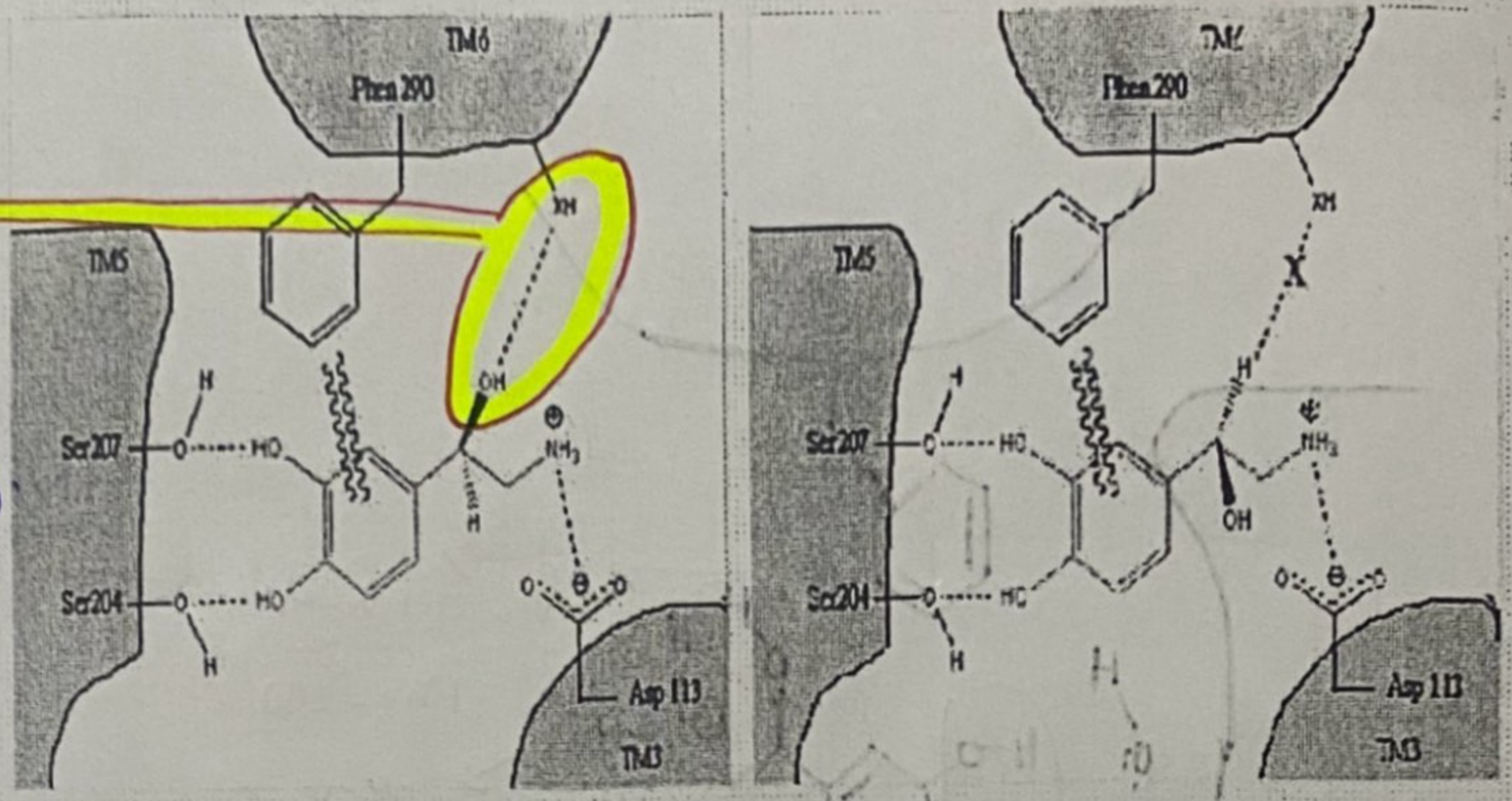


هاد بكون بعيد ع انه بعمل hydrogen bonding.

dextro
(+)

Binding of (-) and (+) isomers

levo هون الـ
قد يعمل على
Asparagine
↓
hydrogen bonding



The (-) isomer fits with receptor *via* points of interaction, more than that of (+).

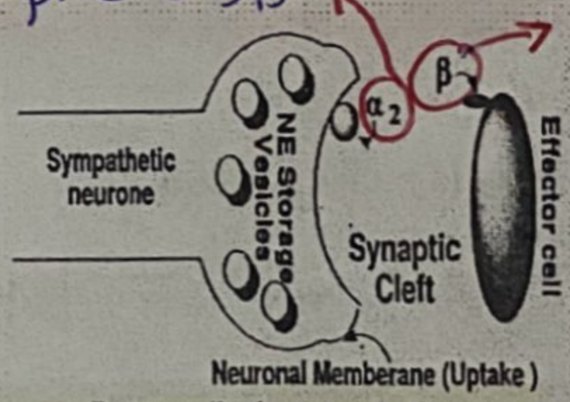
Hence, the (-) isomer has higher binding affinity.

(-) isomer is more active than (+)

سبب نفهم مكان وجود subtype و receptor خليانا نفهم اكثر كيف الأدوية تشتغل ع هاد الـ receptors.

Adrenergic Receptors

Presynaptic موجودة



Postganglionic sympathetic neuron, synaptic cleft and effector cell

موجودة ع effector cell (post synaptic)

- Two types of adrenoceptor (α and β)
- Subtypes (α_1 and α_2; β_1, β_2 and β_3)
- Subtypes of subtypes (α_{1A} α_{1B} α_{1D} α_{2A} α_{2B} α_{2C})

(α, β) → G-protein coupled receptors

Signal transduction

- α_1-adrenoceptor : generates inositol triphosphate and diacylglycerol
- α_2-adrenoceptor : inhibits generation of cyclic AMP
- β_1, β_2 and β_3-adrenoceptors : generate cyclic AMP

Adrenergic Receptors (adrenoceptors)

Distribution and effects Pharmacology Class

- Receptors are distributed differently in different organs and tissues
- Receptor selective drugs act selectively at different organs and tissues
- Activating α_1-adrenoreceptors generally (contracts) smooth muscle (except gut = relaxation of GIT smooth muscle)
- β_1- Adrenoceptors predominate in the heart
- Activating β_1-adrenoceptor contracts cardiac muscle
- β_2-Adrenoceptors predominate in the airways
- Activating β_2-adrenoreceptors relaxes smooth muscle

* الا بالـ ان تعمل relaxation بدنه احنا مش بحاجه لعضله
ال tract ال تشتغل بحالة لخوف.

Receptor activation

Pharmacology Class

The receptor activation may result in:

1. α_1- Adrenergic receptors: Vasoconstriction, relaxation of GIT smooth muscle, salivary secretion and hepatic glycogenolysis.
2. α_2- Adrenergic receptors (Auto-receptor): Inhibition of transmitter release including NE from autonomic nerves, platelet aggregation.
3. β_1- Adrenergic receptors: Increase cardiac rate and force, relaxation of GIT smooth muscle and lipolysis.
4. β_2- Adrenergic receptors: Bronchodilation, vasodilatation, relaxation of visceral smooth muscle, hepatic glycogenolysis and muscle tremors.

هناك 3 طرق

Inactivation of Catecholamines

* الله سبحانه وتعالى خلق عمل الـ adrenaline يتوقف عن طريق reuptake. حيث الـ adrenaline يتنقل شغله بعدين يرتبط بـ receptor α_2 ويرجع لـ Vesicle مرة ثانية.

1. **Reuptake into the adrenergic nerve ending, stored into storage granules until sympathetic nerve stimulation.**

(1) الطريقة

2. **Enzymatic metabolism: Two principle enzymes involved in Catecholamines metabolism:**

(2) الطريقة

a) **Monooxidase (MAO), acts via oxidative deamination of catecholamines**

هو انزيم بحول الـ (amine) ← (Carboxylic acid)

عليه فقدان الـ H

b) **Catechol-O-methyltransferase (COMT), methylates the meta hydroxyl group of catecholamines.**

موجود بالأعضاء لهيك ما نقدر أخذ الـ adrenaline عن طريق الفم، لإنه حيرجي COMT ويعمل عليه metabolism وبحوله الى inactive

عن طريق metabolism يعمل إضافة OH يضيف Methylgroup

عن طريق إزالة الـ amine وثم إضافة الـ OH في الله سبحانه وتعالى خلق هاد الانزيم لحتى يتوقف عمل الـ noradrenaline ويتوقف أثره لفترة بحالة بخوف مثلاً.

Metabolism by MAO and COMT

فقدان الـ H

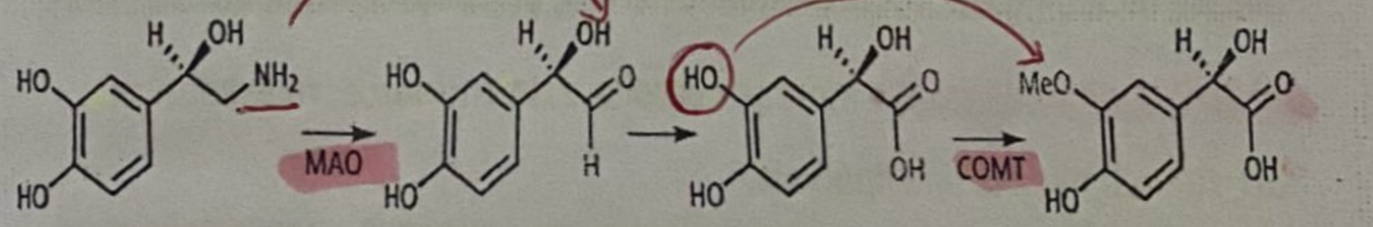
- **Effect of MAO: Oxidative deamination. i.e. Oxidation of the carbon carrying the nitrogen accompanied by loss of the nitrogen atom.**

فقدان الـ H

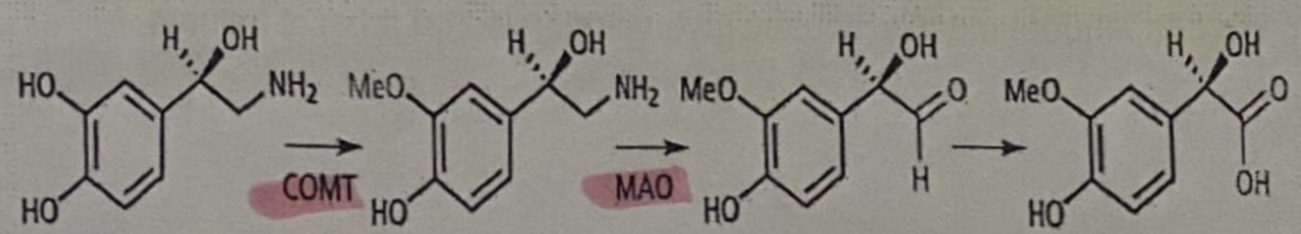
$$R\text{-}CH_2\text{-}NH_2 \longrightarrow (R - CH = NH) \longrightarrow R\text{-}CHO \longrightarrow \text{Acid or alcohol}$$

amine → Carboxylic acid

OH → MeO تحولت



Noradrenaline → Vanillylmandelic acid

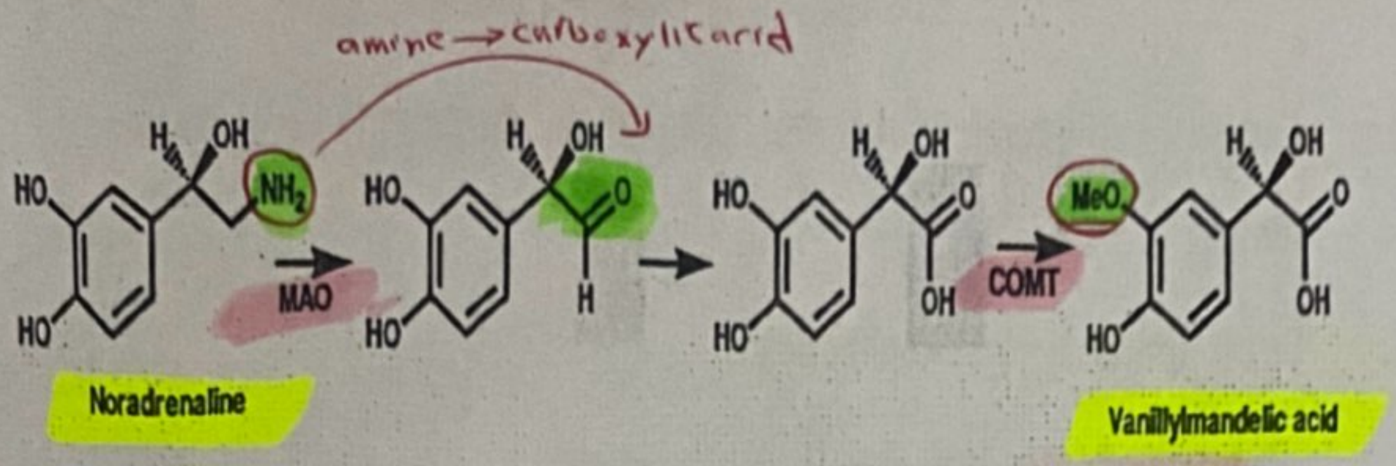


Noradrenaline → Vanillylmandelic acid

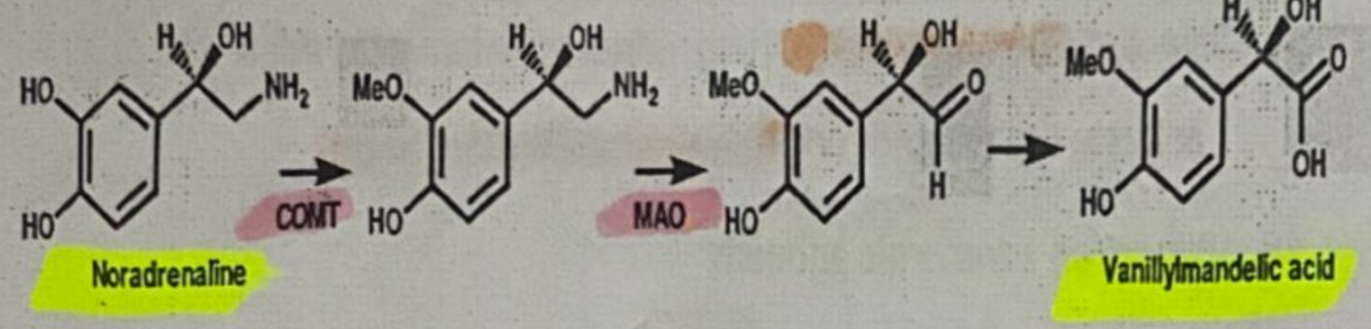
هو عبارة عن مركب بكون بالبول بعد metabolism of adrenaline

يا رب توفيقك ♥

Metabolism of Noradrenaline



اذا اشتغل ال MAO وتم يتبعه COMT



اذا اشتغل ال COMT وتم تتبعه MAO

Adrenergic Drugs

* هي ال drugs اللي احنا بندرسها

- The drugs that act on the peripheral sites of the sympathetic nervous system are collectively named adrenergic drugs.
- They act via either enhancing or inhibiting the sympathetic activity.

Stimulating.	Inhibiting.
Sympathomimetic.	Sympatholytic.
Adrenomimetics.	antiadrenergic.
or adrenergic stimulants.	or adrenergic-blocking agents.
Agonists.	Antagonists.

تعني يشابه ←

lytic → باللغة الانجليزية تعني تحلل / تزيل اثر الـ aldrenergic

Sympathomimetic Drugs

According to the mechanism of action, sympathetic drugs may be classified into :

1. **Direct acting Sympathomimetics.**

   (interact directly with adrenergic receptors)

2. **Indirect acting Sympathomimetics.**

   (initiate the release of NEpi from adrenergic nerve terminal which activate the receptor or inhibit its uptake mechanism)

3. **Mixed function adrenergic agonists**

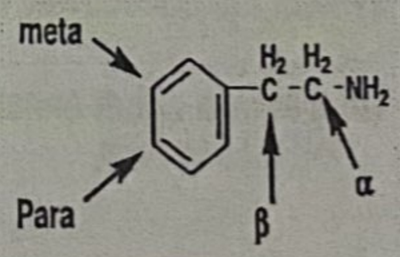
   (interact directly with the receptor and act indirectly by increasing the conc. of Nepi at the receptor site)

Direct-Acting Sympathomimetics

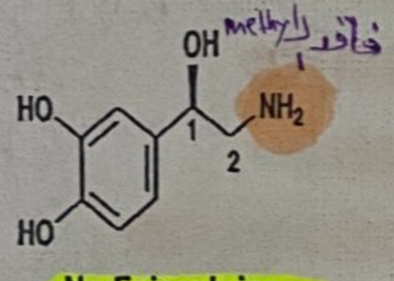
Prototype of direct-acting sympathomimetics: Norepinephrine, epinephrine and isoproterenol.

They are phenylethylamine derivatives that contain the appropriate substituents.

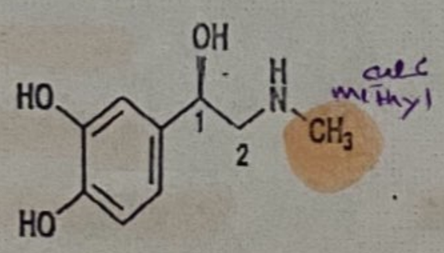
Also, they are Catecholamines.



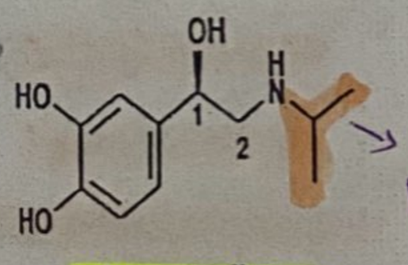
Phenylethylamine



NorEpinephrine



Epinephrine

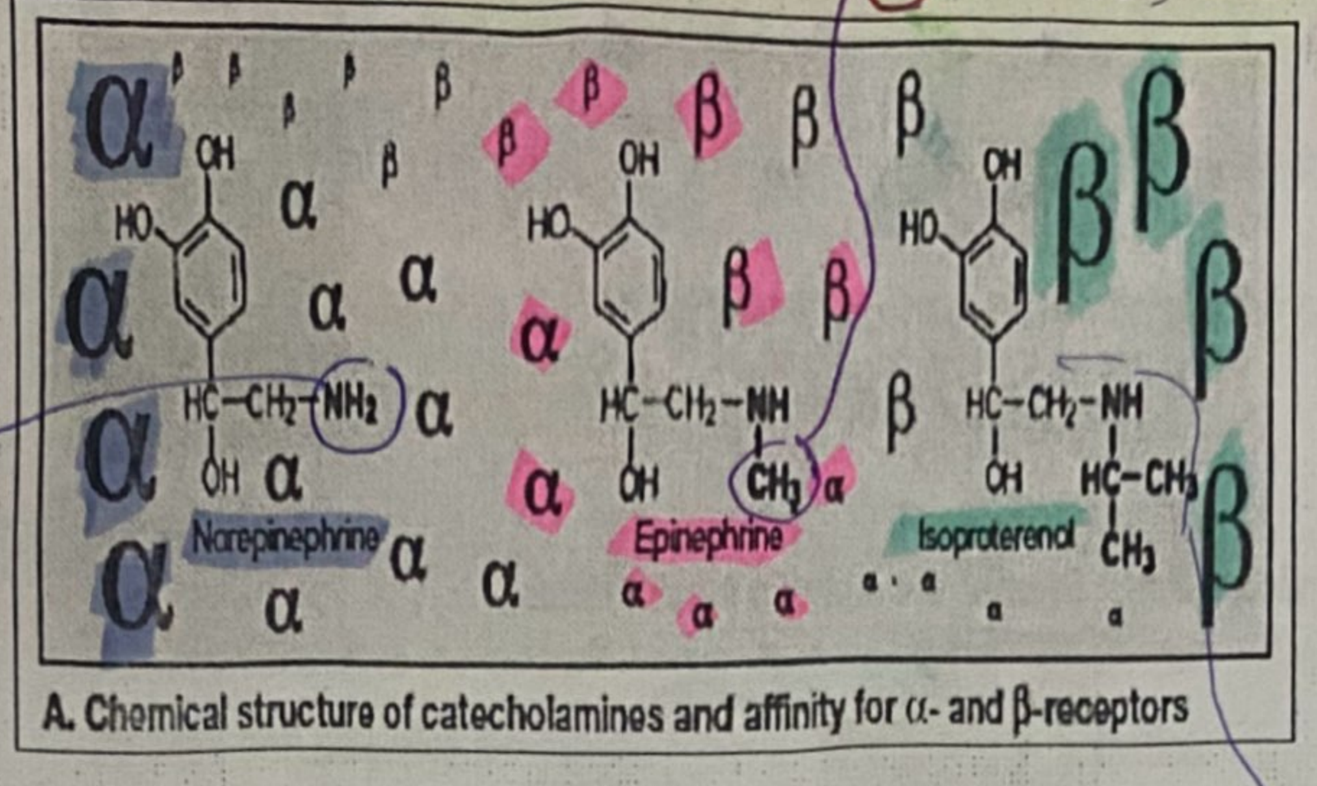


Isoprenaline

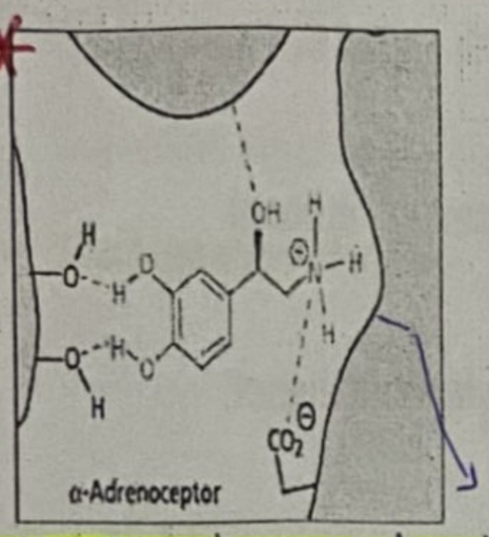
Norepinephrine and Epi are natural neurotransmitter and neurohormone.

Isoproterenol is a synthetic compound.

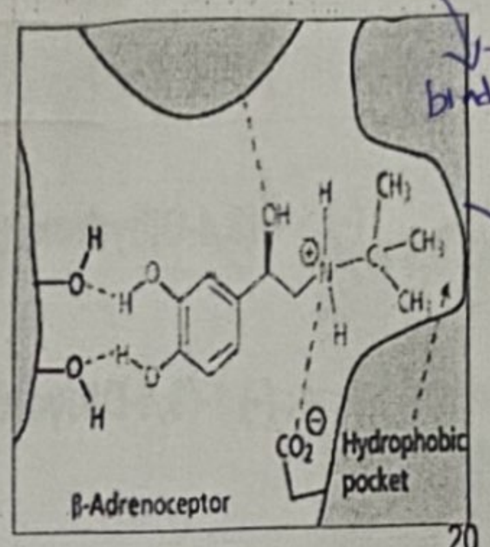
Catecholamines



A. Chemical structure of catecholamines and affinity for α- and β-receptors



Chemistry explains the differences. isopropyl is β-directing

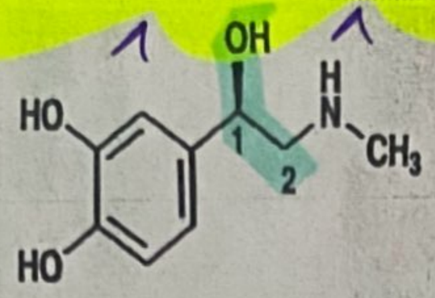


Members of Direct-Acting Drugs

What we discuss in Med Chem Class:

- ❑ Chemical structure / Chemical name
- ❑ Structural features / Effect of structure on activity
- ❑ Properties / Physico-chemical properties
- ❑ Mode of action
- ❑ Metabolism / Duration of Action
- ❑ Uses
- ❑ ...
- ❑ Synthesis
- ❑ Analysis

Epinephrine (Adrenaline) as a drug



Epinephrine (Adrenaline)

Chemical name: Choose the suitable parent name:

Name it as ethanol derivative

Name it as benzyl alcohol derivative

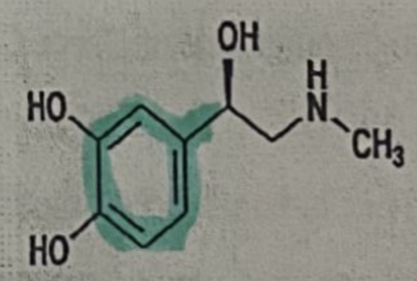
Name it as catechol derivative

(-)	1-(3,4-Dihydroxyphenyl)-	2-methylamino	ethanol

Chemical name: (-) 1-(3,4-Dihydroxyphenyl)-2-methylaminoethanol

Epinephrine (Adrenaline)

Chemical name as benzyl alcohol derivative.

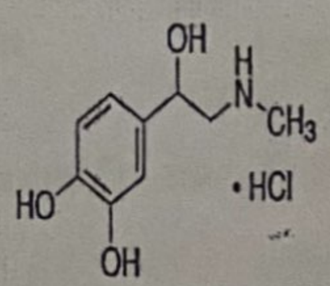


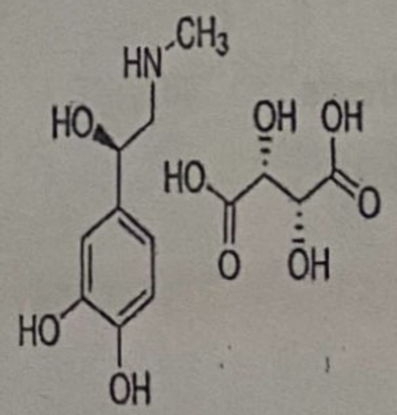
(-) 3,4-Dihydroxy- α-[(methylamino)methyl] benzyl alcohol

Chemical name: (-) 3,4-Dihydroxy-α-[(methylamino)methyl]benzyl alcohol

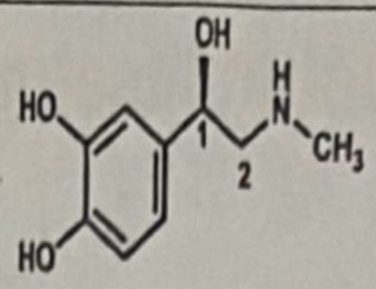
Salts:

Present as acidic salt: HCl or bitartarate





Structural features



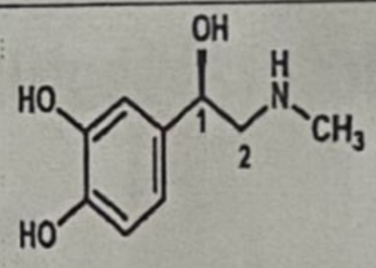
Epinephrine (Adrenaline)

- Prototype.
- Direct adrenergic agonist, due to the presence of the catechol OHs, the β-OH and a secondary amine group.

Primary amine بتكون norepinephrine الـ

- The (N) atom is a secondary amine with a methyl substituent, which provides non selective adrenergic activity: both α- and β- activities.
- Epinephrine has both α and β-effects. No selectivity (α and β)
- The amine function is affected by MAO.
- Short duration of action

Structural features



Epinephrine (Adrenaline)

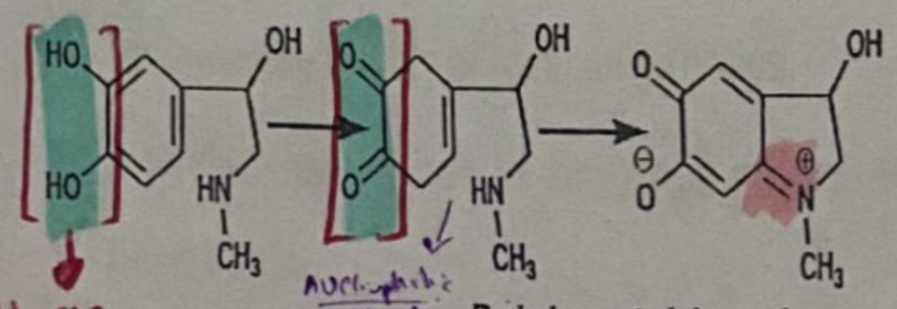
الـ Epinephrine بتأثر عليها COMT وبالتالي orally بنعطيها

- Because of the catechol nucleus, it is metabolically vulnerable; rapidly affected by COMT.
- Short duration of action and oral inactivity.

بسبب COMT

- Highly polar molecule: decreased penetration into the eye.

- Because of the catechol nucleus, it is oxidized easily and darkens slowly on exposure to air (chemical instability) due to formation of inactive quinone.



Red pigment, Adrenochrome

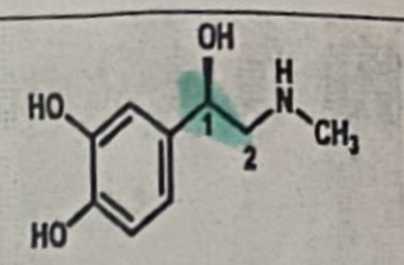
Thus, solutions are stabilized by adding reducing agents as ascorbic acid.

هاد الـ reaction بكون irreversible

Catechol هاي الـ عرضة بسهولة ليتصير عليها oxidation

هاي الألوان طالما بكون فيها Conjugated System

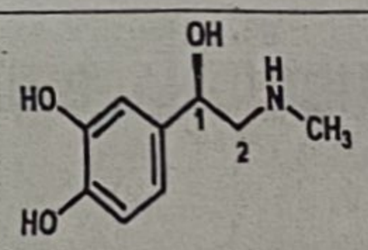
Structural features



Epinephrine (Adrenaline)

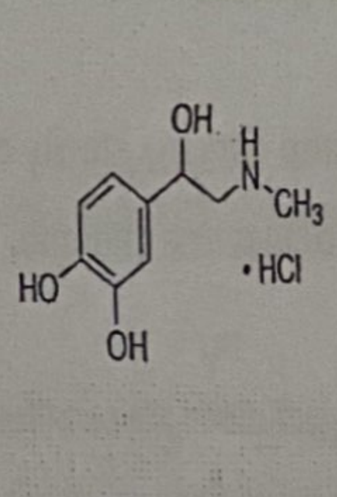
- There is a chiral carbon
- There are 2 isomers
- The *levorotatory* isomer of epinephrine is more active than other isomer.
- So, the drug should be prepared as R(-) isomer.

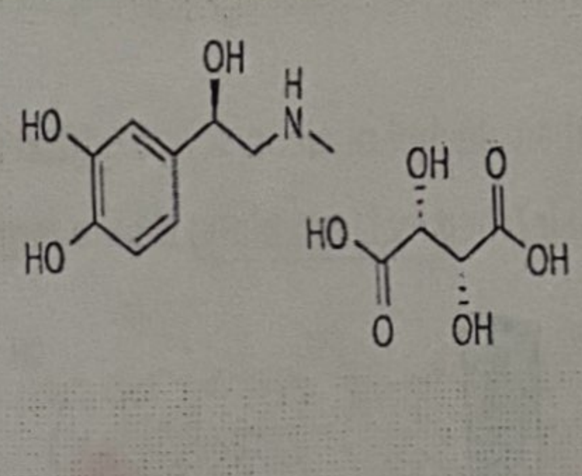
Structural features



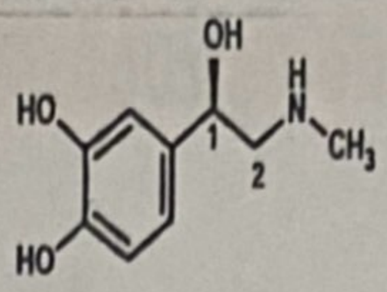
Epinephrine (Adrenaline)

- As a drug, epinephrine is available as HCl and bitartarate salts.
- Salts are of high degree of water solubility.
- Bitartarate salt shows increased *in vitro* stability against alkaline media.



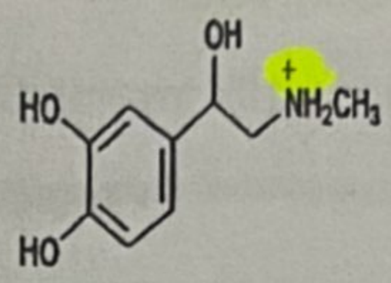


Structural features



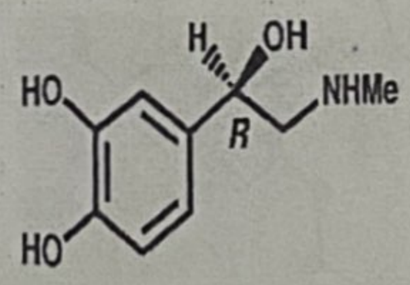
Epinephrine (Adrenaline)

- At physiological pH (7.4), NE and Epi are found to exist in more than 95% in the cationic form in which nitrogen is protonated.
- Henderson–Hasselbalch equation
- pKa of epinephrine = 8.55



See introductory part of Med Chem

Adrenaline. Uses



صدمة الحساسية

- Adrenaline used for severe anaphylactic shock
- Vasoconstrictor in patient with hemorrhage.
  - fast acting, but short acting
  - unsuitable for long term medication
  - cardiovascular side effects

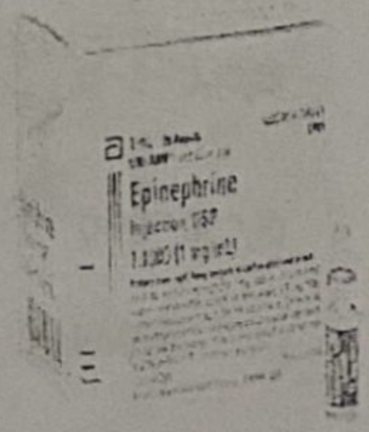
Disadvantages

Short duration.

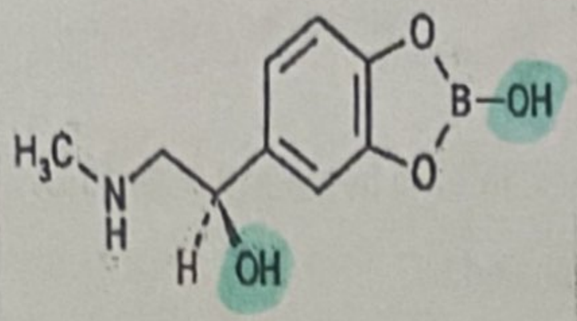
(rapid metabolism)

Not taken orally

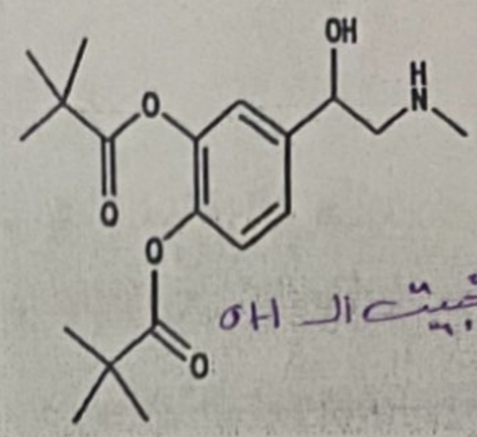
- Vasoconstrictor in nasal decongestion.
- Increase the activity of local anesthetics.
- a limited use in case of bronchial asthma and heart block



Modified structures of Epinephrine



- **Epinephryl borate**
- It is used in the treatment of primary open angle glaucoma.
- Less irritant than epinephrine.



- **Dipivefrin**
- Ophthalmic for Glaucoma
- Less irritant than epinephrine

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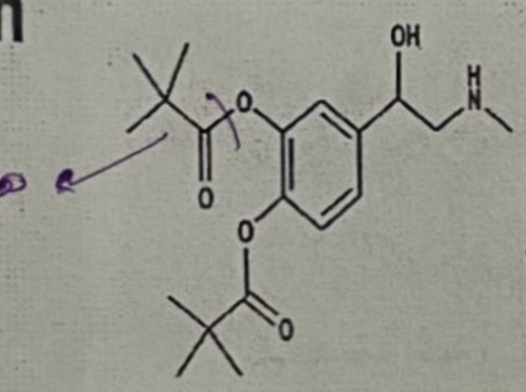
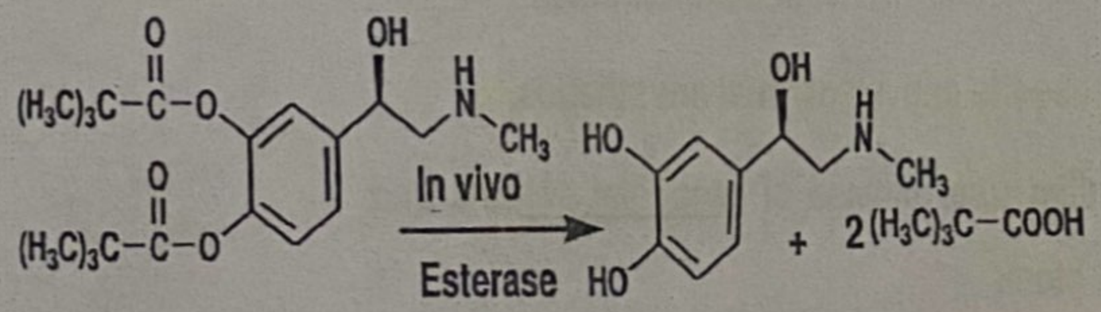
Dipivefrin



- It is the pivalic acid prodrug of epinephrine, with higher lipophillic character so with better ocular penetration when used in glaucoma
- Less irritant than epinephrine.
- A Prodrug. It is converted to epinephrine by esterases in in the cornea and anterior chamber.



Dipivefrin — Epinephrine — Pivalic acid

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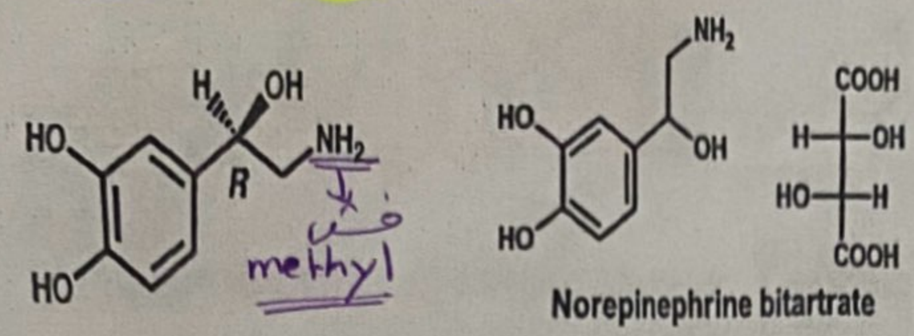
(∝)

Norepinephrine, bitartrate

(methyl) لدرجة تشرع B لانه فاقد ال



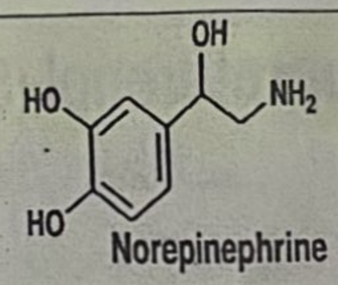
Norepinephrine bitartrate

(-) 2-Amino1-(3,4-Dihydroxyphenyl)ethanol, bitartrate

- The bitartarate salt forms stable injectable solution.
- Used to maintain blood pressure in acute hypotensive states.
- Not used as bronchodilator. Why??

methyl ← لانه فاقد ال =

Norepinephrine

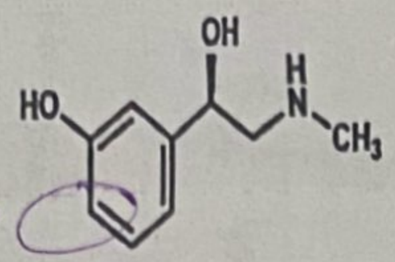


Norepinephrine

- ❑ Presence of the β-OH and the catechol OHs and the amine, so optimal direct action.
- ❑ It is a 1ry amine; so, α-adrenergic activity. Mainly α agonist activity.
- ❑ Metabolically vulnerable to MAO and COMT, so short duration of action and no oral activity.
- ❑ Short acting: Unsuitable for long term medication
- ❑ Chemically unstable where photo-oxidation is possible, so protect from light and OH^-.

Phenylephrine HCl

Epinephrine



OH خافد لا

Phenylephrine HCl

(-) 1-(3-hydroxyphenyl)-2-(methylamino) ethanol, hydrochloride

- α-agonist.
- Duration of action twice epinephrine.
- Used as nasal decongestant
- and to maintain blood pressure.
- Effective orally and by injection.

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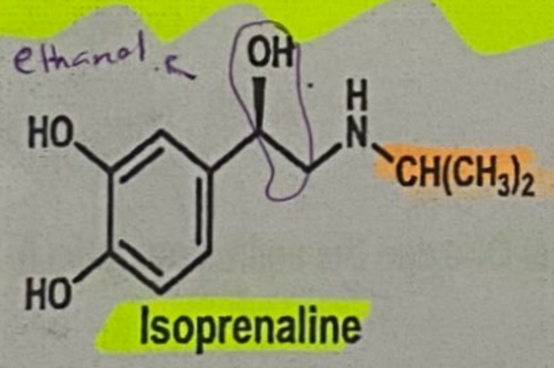
Isoproterenol (Sulfate) (Medihaler Iso)



Isoprenaline

(-) 1-(3,4-dihydroxyphenyl)-2-(isopropylamino)ethanol
(-) 3,4-Dihydroxy-α-[(isopropylamino)methyl]benzyl alcohol

β-adrenergic agonist

Medihaler Iso is used for treatment of bronchial asthma.

But

Non-selective (affects both β_1 and β_2 receptors)

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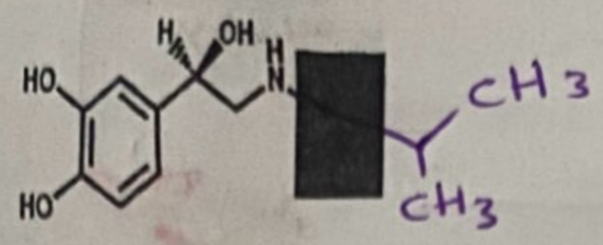
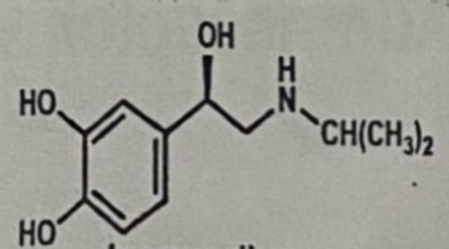
Isoproterenol = Isoprenaline



- Shows selectivity for β-adrenoceptors over α receptors
- Bulky isopropyl group introduces β-selectivity
- But, No selectivity between β-subtypes (β_1 and β_2)
- Cardiovascular side effects

- a non selective β-adrenergic agonist, it acts equally on :
  - β_1 receptors resulting in cardiac stimulation.
  - β_2 receptors resulting in bronchodiltation.
- This non selectivity reduce utility for treatment of bronchial asthma.

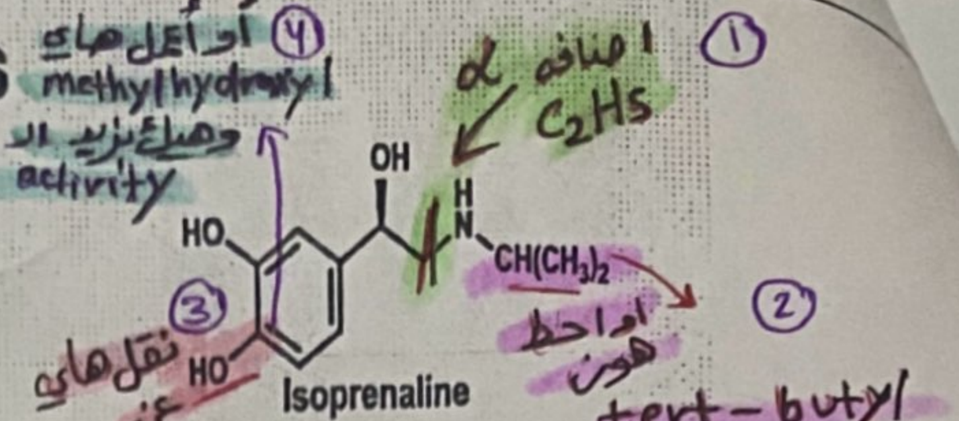
β-Adrenergic Agonists



Isoprenaline

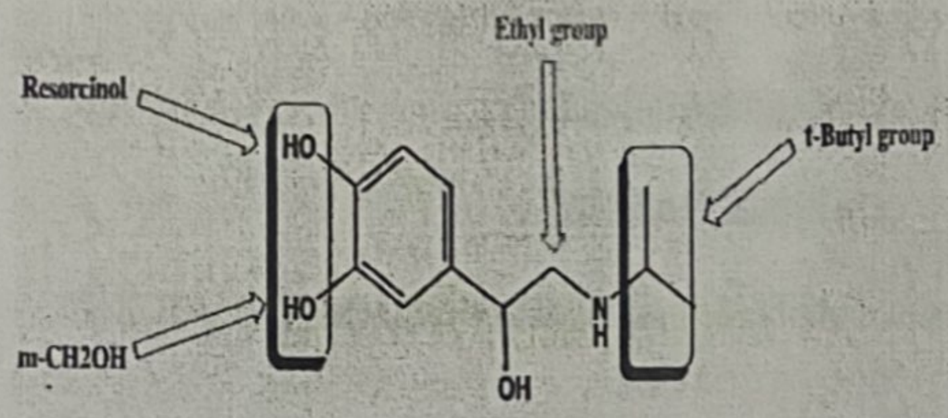
- The selective affinity towards β-receptors over α-receptor is achieved by replacement of the methylamine of the epinephrine by a bulk alkylamine group (e.g. isopropylamine).
- The bulkiness of the alkyl group appears to hinder the interaction of the drug with the α-receptor, but it has no inhibition on β-receptors.
- Isoproterenol is the prototype
- But, the non selectivity (β1 and β2) of isoproterenol reduces its utility for treatment of bronchial asthma.
- How would you get a selective β2-agonist ???

β_2-Adrenergic Agonists



Structural modification in isoprenaline to enhance the β_2-agonist selectivity

1) Insertion of C_2H_5- at α-carbon atom.
2) Replacement of the isopropyl moiety with *tert*-butyl.
3) Replacement of the catechol moiety by resorcinol.
4) Replacement of the *meta* -OH by CH_2OH.



Structural modifications in Isoprenaline

result in β_2-agonists used mainly as bronchodilator.

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B_2-Adrenoceptor

Pharmacology Class

- G-Protein-coupled receptor
- Activates the generation of cyclic AMP
- Predominant receptor in bronchial smooth muscle
- Activation results in smooth muscle relaxation
- Dilates or opens airways
- Agonists for the β_2-adrenoceptor are potential anti-asthmatic agents (bronchodilator effect)

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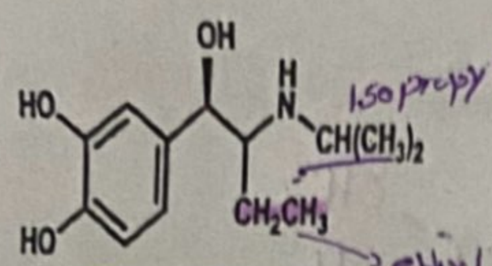
أمثله يوضح فيها الحالات الاربعه بالسلايد الى قبل:-

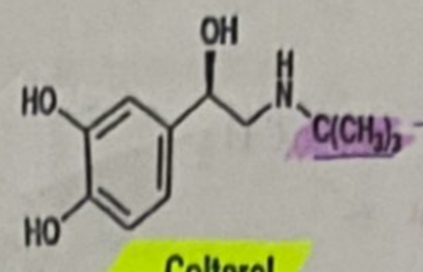
B_2-Adrenoceptor



Isoetharine

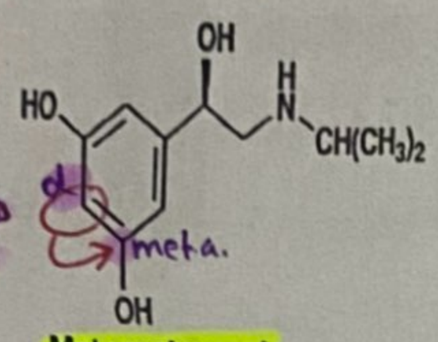
active في B_2 اكثر من B_1

ethyl group اضافة



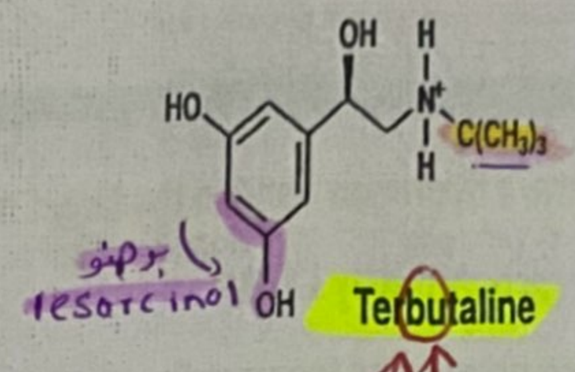
Colterol

بدلت الـ isopropyl group بالـ tert group



Metaproterenol

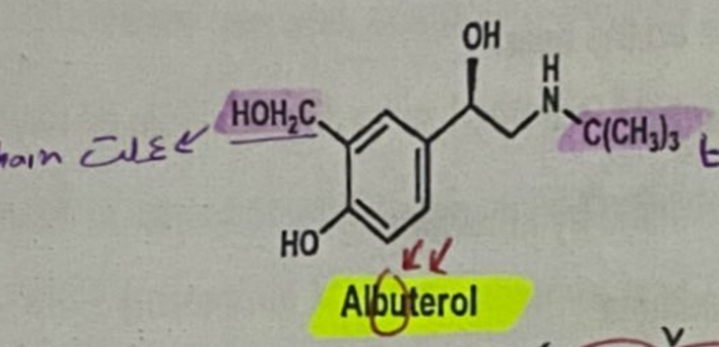
هون حركنا الـ OH من الـ meta الى وهيك صنعت هذا resorcinol



tert butyl.

resorcinol بدون

Terbutaline



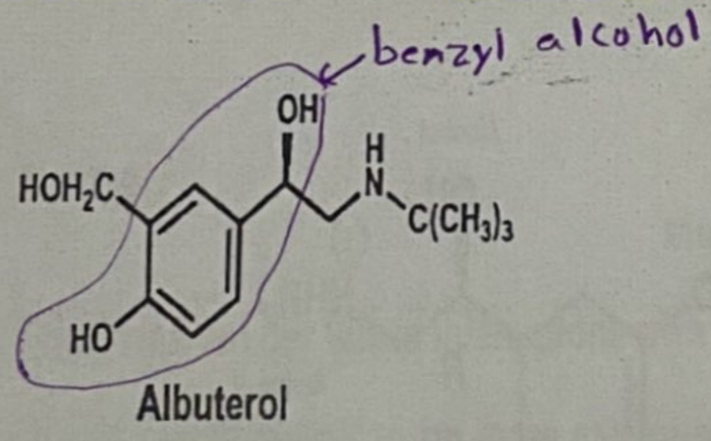
methyl sidechain عملت

tert butyl

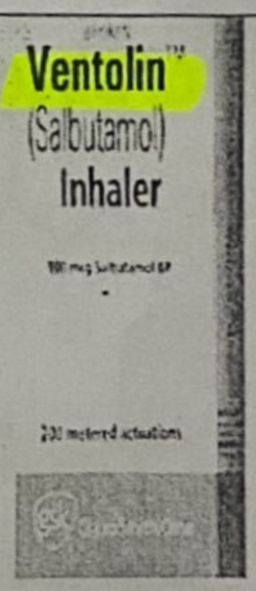
Albuterol

tert - butyl 40 تعني (bu) كلمة *

Salbutamol = Albuterol (Ventolin®)

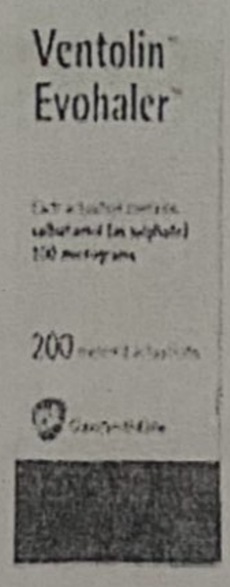


Albuterol

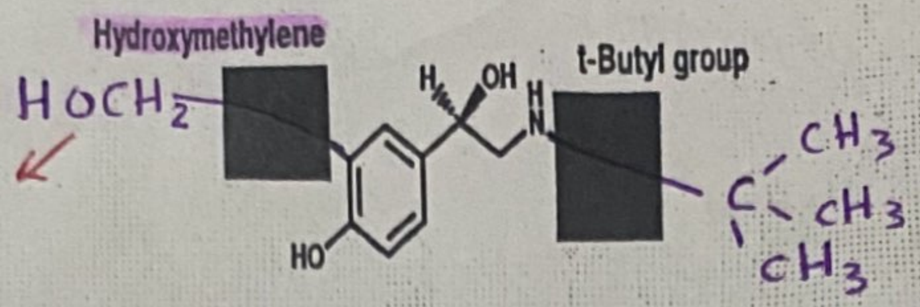


3-hydroxymethyl-4-hydroxy-a-[(t-butylamino)methyl]benzyl alcohol

- The hydroxymethyl group has an obstructive effect towards the action of COMT.
- longer duration of action compared to the catechol analogues.
- Albuterol is used in treatment of bronchospasm associated with asthma.



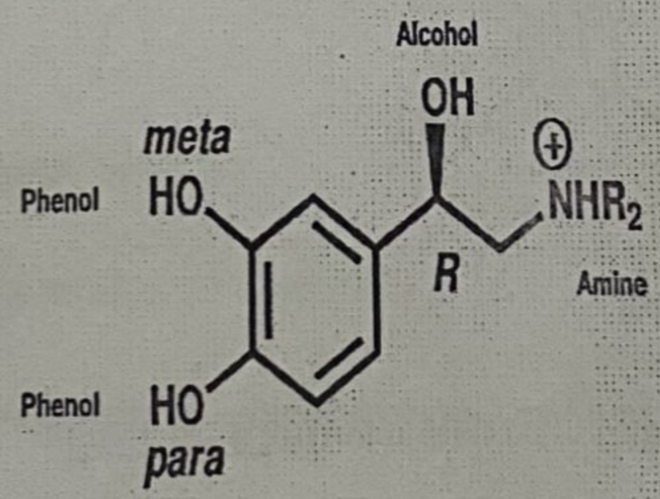
Salbutamol = Albuterol (Ventolin®)



ال OH بعدت عن ال aromatic ring بـ one methy lgroup

- Hydroxymethylene group retains β_2-agonist activity
- OH shifted from aromatic ring by one bond length
- Forms a hydrogen bond to the target receptor
- Not recognized by COMT
- Same potency as isoprenaline
- 2000 times less active on the heart
- 4 hours duration of action
- Administered as a racemate by inhalation
- For the treatment of asthma

SAR of Direct-acting Adrenomimetics



- ❑ Catechol and Aromatic ring
- ❑ Distance and alcoholic group
- ❑ Amine and N-alkyl substituent

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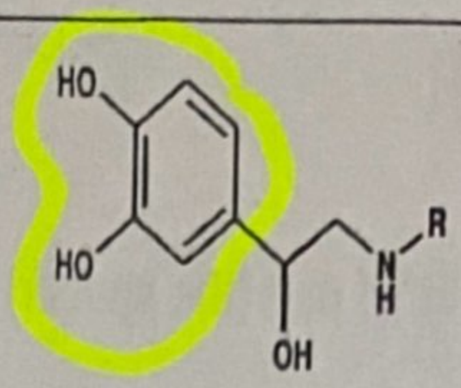
Summary

SAR of Direct-acting Adrenergics



A. Aromatic ring

- Catechol hydroxyl groups in the *meta*- and *para*- positions of the aromatic ring, relative to the phenethylamine moiety.
- The catechol OH groups are more important for β-activation (β-agonist activity) than for α-activity. (form H-bonds to binding site (especially β)
- So, removal of one of them results in loss of β-activity. (but keeping α-agonist activity)
- When OH groups are removed, compound retains α affinity.
- *meta*-OH can be replaced with other hydrogen bonding groups, CH2OH
- Replacement of catechol with resorcinol afford compound with longer duration, why? (resorcinol is not a substrate for COMT), and enhances β_2-selectivity

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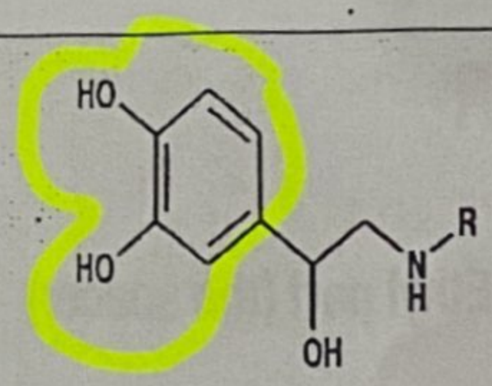
SAR of Direct-acting adrenergics

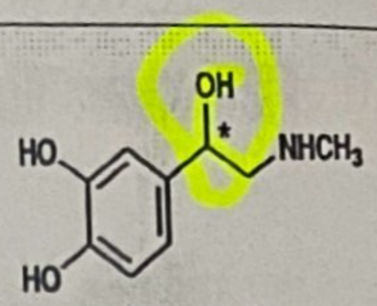


A. Aromatic ring

- Aromatic ring forms van der Waals interactions with the binding site
- The aromatic ring itself seems to be more essential for β-activity rather than α-activity,
- so replacement of the aromatic ring with aryl or alkyl or alicyclic ring resulting in compounds with α-adrenergic activity.
- Reduction of the aromatic ring or its replacement with an alkyl group does not affect the α–effects (the pressor activity).

45

SAR

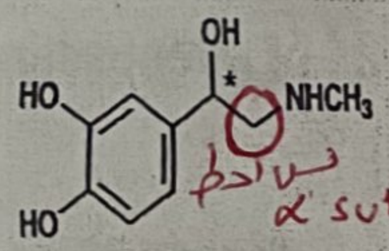


Epinephrine

B) Ethyl part (the spacer)

- Two C-atoms separating the amino from the aromatic ring provide optimal activity.
- β-Hydroxyl group on the ethylamine portion of the molecule enhances the activity since it is involved in binding of the compound with receptor (direct action).
- Alcohol forms a hydrogen bond to the binding site
- Stereochemistry of the –OH is important, since it is involved in the binding of the compound with the receptor.
- Proper stereochemistry of the β–OH group enhances the activity of NE and other catecholamines since it is involved in the binding of the compound with the receptors.
- R(-)NE fits with the receptor better than the other enantiomer.

SAR

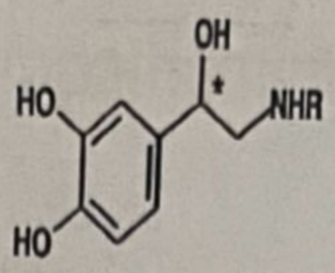


Epinephrine

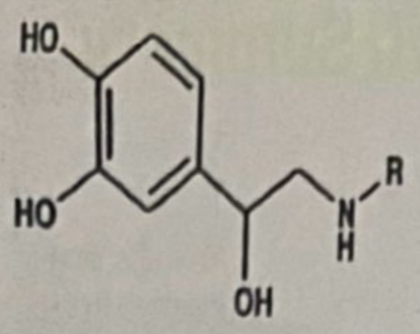
B) Ethyl part (the spacer)

- Alkyl substitution on the α-carbon atom increases the duration of action of the phenethylamine agonists by making the compound resistant to metabolic deamination by MAO.
- Methyl substitution on the α-carbon increase the duration of action by making the compound resistant to metabolic deamination by MAO.
- The presence of α-ethyl group enhance β_2-agonist activity with less cardiac stimulation.

SAR



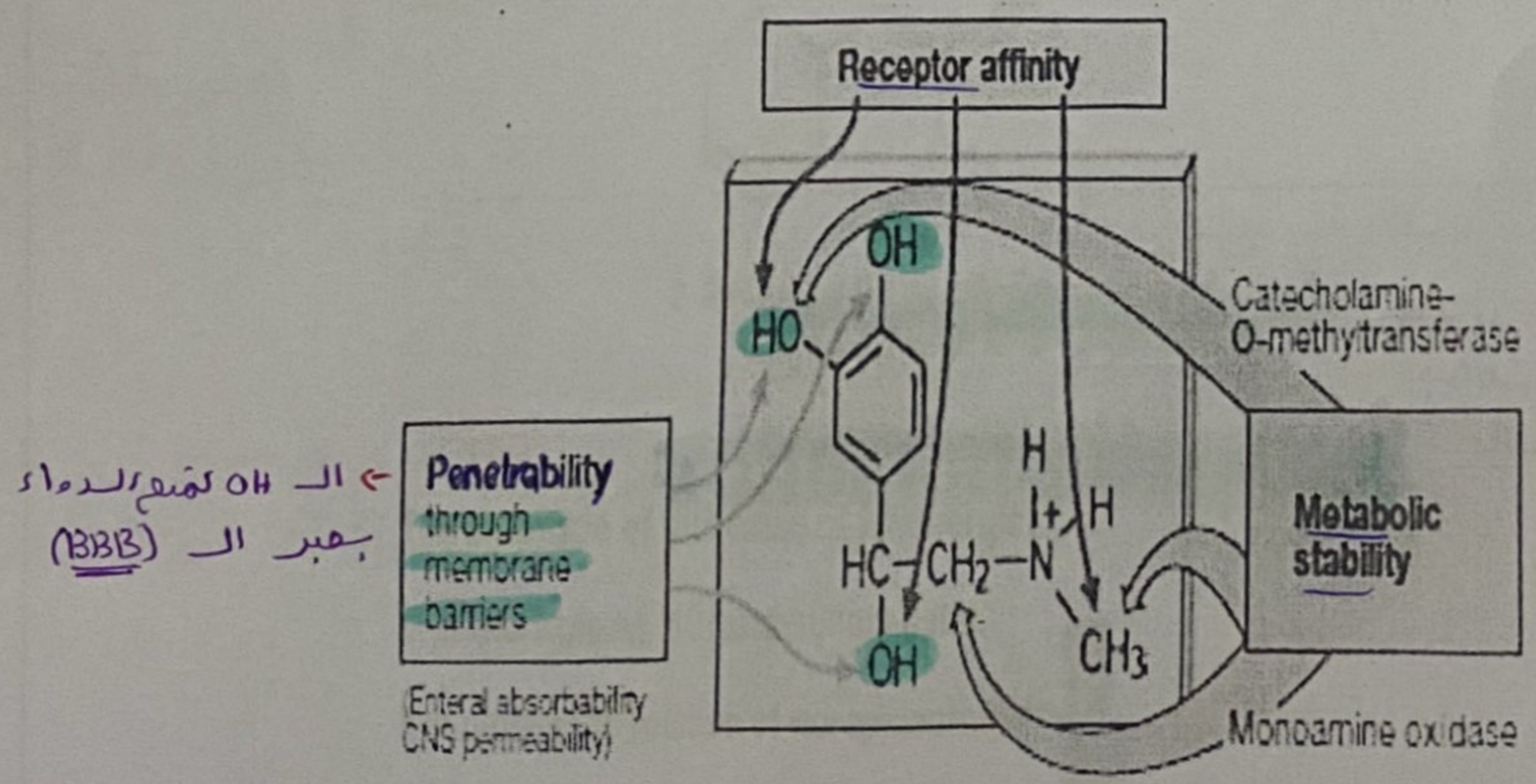
Epinephrine



C) The amine part

- Amino group is essential for binding. (protonated)
- ammonium ion (after protonation) forms an ionic bond to the binding site
- Amino group: is either primary or secondary. No tertiary.
- In case of 2ry amines, *N*-alkyl substitution affect selectivity (α and β)
- increasing the size of the alkyl grope, enhances the β-affinity.
- Larger *N*-alkyl groups lead to selectivity for β-adrenoceptors
- Large alkyl groups on the N atom diminish stimulation of the α-receptors.
- isopropyl or tert. Butyl are named β-directing groups
- tert. Butyl is a β2-directing groups

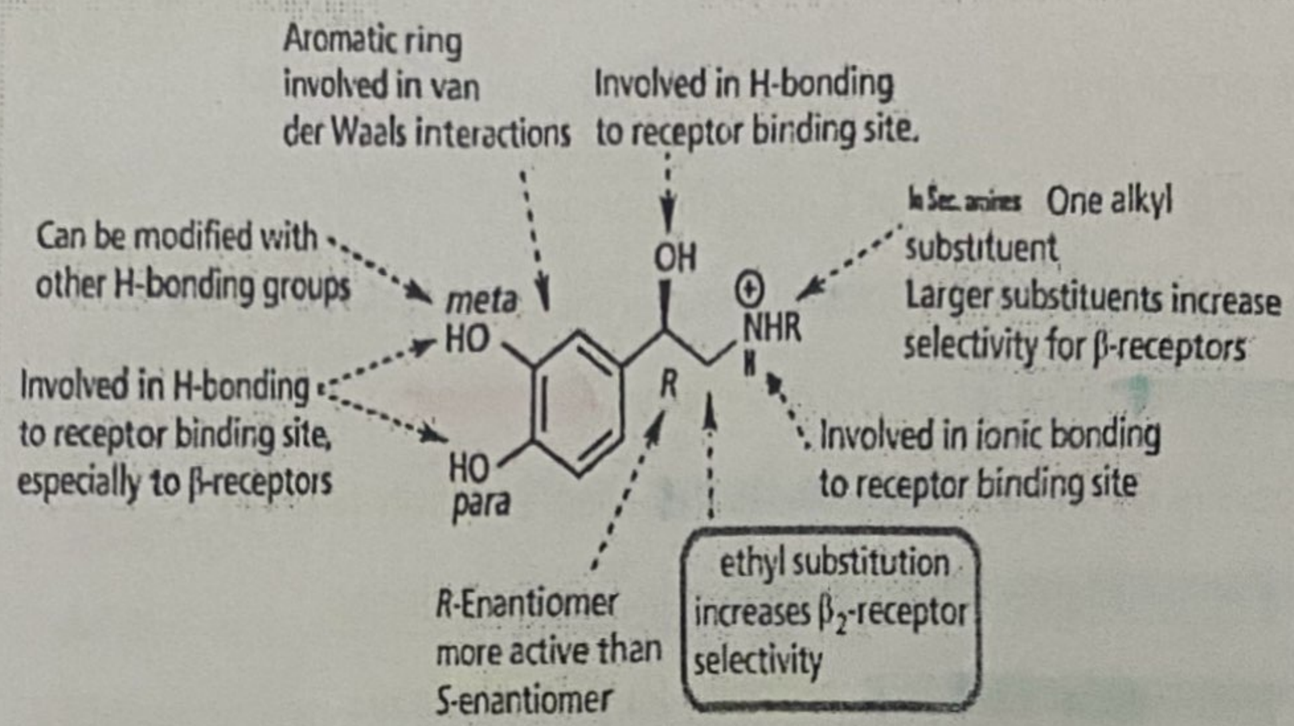
Structural Features and SAR



← الـ OH تمنع الدواء
يعبر الـ (BBB)

Question: Discuss the effect of the structural features in Epinephrine on its pharmacokinetic and pharmacodynamic properties.

SAR. Summary



Effect of:

- **Replacement of Catechol by Resorcinol**
- **N-isopropyl substitution**
- **N-tert. Butyl sbstitution**
- **Replacement of the m-OH by –CH2OH**

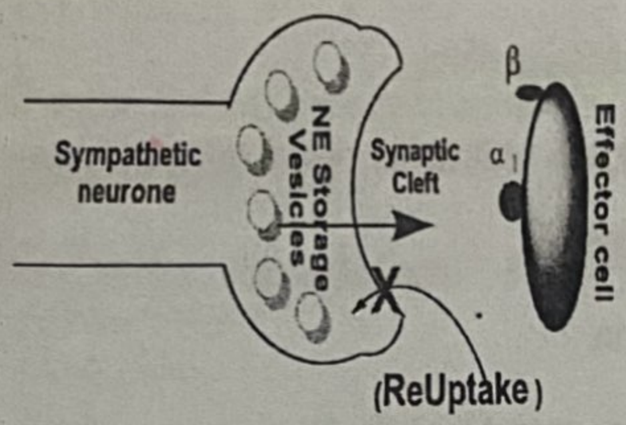
يزيد الـ adrenergic ←
يشتغل عن طريق الإرتباط بالـ receptors

Indirect Acting Sympathomimetics

Indirect–Acting Sympathomimetics

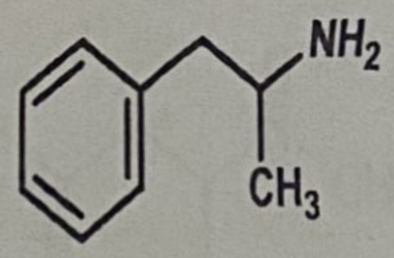
Indirect adrenergic drenergics are taken up by the pre-synaptic neurons, where they:

- stimulate release of NEpi from adrenergic nerve terminals, which activates the receptors
- inhibit reuptake mechanism of neurotransmitter



Amphetamine

يعني فش Catecole

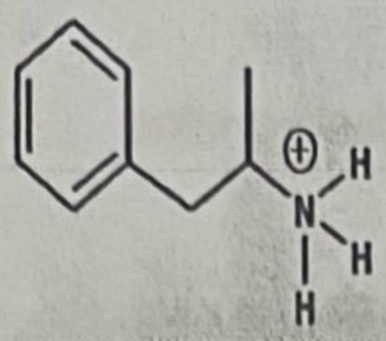


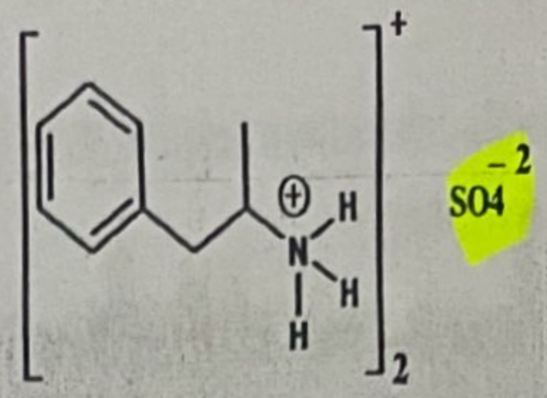
2-Amino-1-phenyl-propane

- The prototype of this class of adrenergics.
- It is available as HCl and sulfate salts.
- It stimulate the release of norepinephrine.
- No direct action
- No phenolic OHs, no alcoholic OH ... no direct action
- The absence of phenolic and alcoholic OH group increase the lipophilicity, so penetrate the BBB giving CNS activity.

Amphetamine

ما بقطن فترة طويلة لإنه بسبب إدمان





It is available as HCl and sulfate salts.

- The clinical utilities of Amphetamine are based on CNS stimulant and central appetite suppressant effects.
- Uses: Narcolepsy / Hyperkinetic syndrome of children / Attention-deficit disorders / obesity.
- There is a chiral carbon.
- The S(+) isomer is more potent than the R(-) isomer.

يكون الشخص قاعد عادي وبنام فجأة فهو أحد اضطرابات النوم بجعل الأشخاص يشعرون بالنعاس الشديد اثناء النهار ويحبوا صعوبة في إبقاء مستيقظين لفترة طويلة من اليوم، او يغلبهم النوم فجأة.

ما نقدر الشخص يدخل قاعد لينجز مهمة معينة مثلاً يكونش قادر يقعد فترة لنيدرس فنعطوا amphetamine لحتى يقدر يقعد ويدرس.

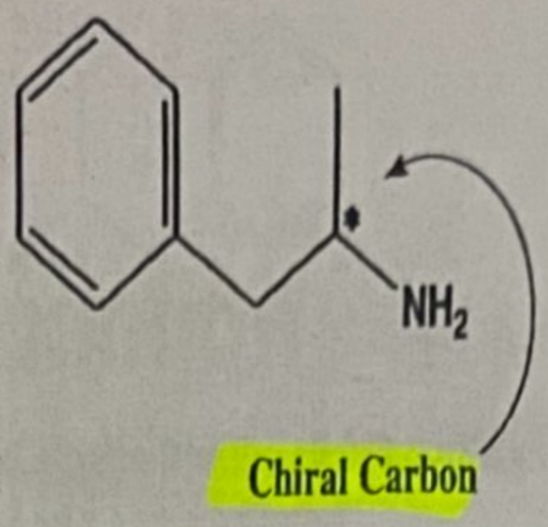
اضطراب فرط الحركة.

Hyperkinetic disorder is a psychiatric syndrome emerging in early childhood that features an enduring pattern of severe, developmentally inappropriate inattention, hyperactivity and impulsivity across different settings (e.g., home and school) that significantly impair academic, social and work performance

يظهر في مرحلة الطفولة

Dextroamphetamine

S(+) Amphetamine



Also available as sulphate or hydrochloride

- Has greater CNS action and less peripheral action
- Is generally preferred to amphetamine
- it is used in obesity, narcolepsy, and attention-deficit hyperactivity disorder

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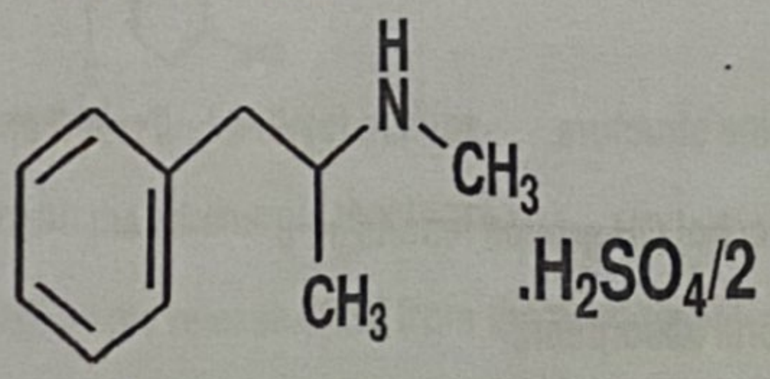
Methamphetamine Sulfate

(ممنوع دواء
النوع من انواع
المخدرات)



Chemical name: ..... think about it !!!!

the N-methyl derivative of amphetamine

Available as sulphate salt

Structure: No catechol OHs, no beta-OH, an alpha methyl, N-methyl.

Discuss the effect of each??

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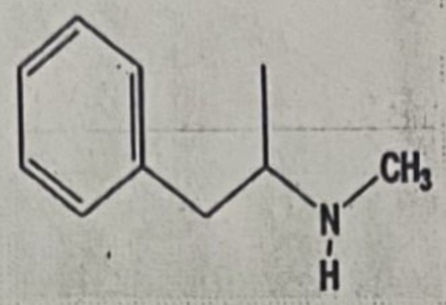
Methamphetamine

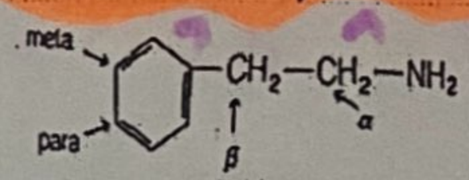


It is used principally for its central effects, which are more pronounced than those of amphetamine and are accompanied by less prominent peripheral actions.

Meth is an abused drug.

Chemistry of indirect acting Structural Features

Phenylethylamine



Phenylethylamine

- Phenylethylamine structure
- Absence of catechol OH groups results in:
  - Increase oral absorption.
  - COMT has no effect. Increase duration of action.
  - Increase lipophilicity so pass through blood-brain barrier.
- Phenyl group may be replaced by other systems as cyclo / alkyl group.
- Presence or absence of β-hydroxyl group.
  - If present, stereochemistry is not important.
  - Its absence provides more lipophilic agents with central stimulation
- α-CH_3 in the phenethylamine structure provides more resistance to MAO.
- The amino nitrogen: primary, or secondary (small alkyl gr).

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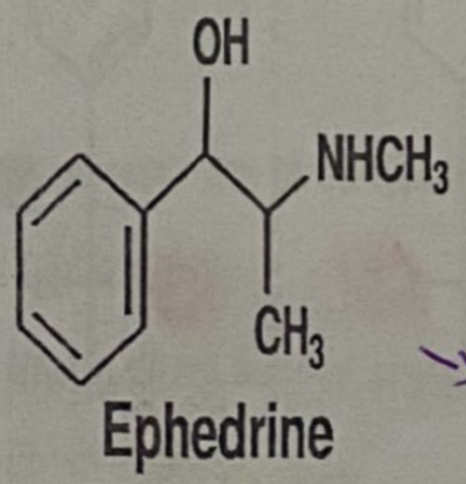
Dual Function Adrenomimetics

Direct
Indirect

Mixed-Action Adrenergic Agonists

- Mixed means Direct and Indirect actions.
- direct action on the adrenergic receptors.
- indirect effect on the release of NE from the storage site
- The prototype of this group is the natural alkaloid ephedrine.

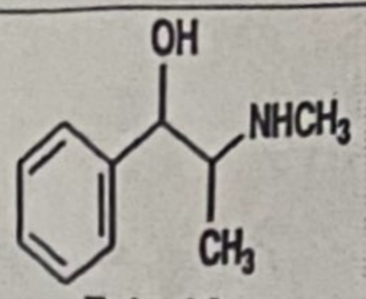


Ephedrine

من شجرة الماهوانج

What are the structural Features?

Ephedrine: Structural Features



Ephedrine

1. Absence of phenolic OH groups leads to increase oral absorbance, increase lipophilicity and a CNS effect. Also, it is not a substrate for COMT, similar to indirect adrenergic agonists.
2. The presence of β-hydroxyl group brings similarity to other catecholamines acting directly on adrenergic receptors
3. Presence α-methyl group provides resistant to MAO and hence longer duration.
4. ephedrine is less polar than the catechol derivatives, so it can cross blood-brain-barrier, so used as CNS stimulant.

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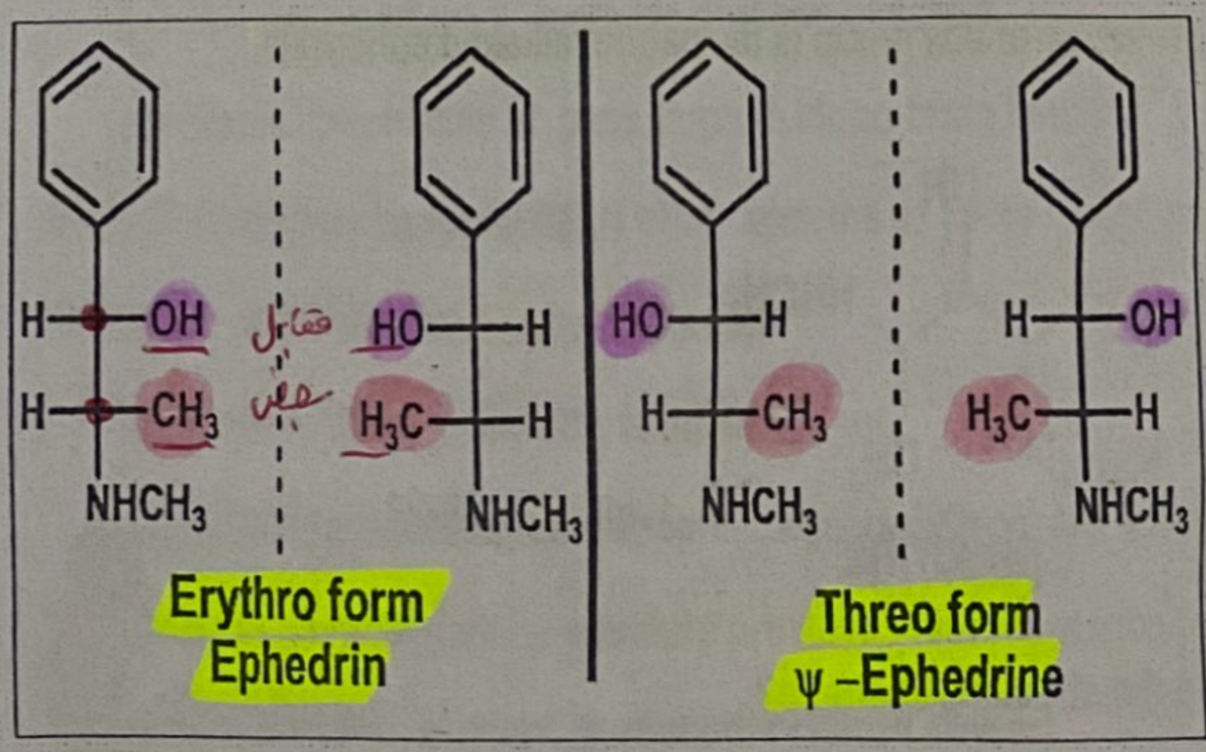
Ephedrine

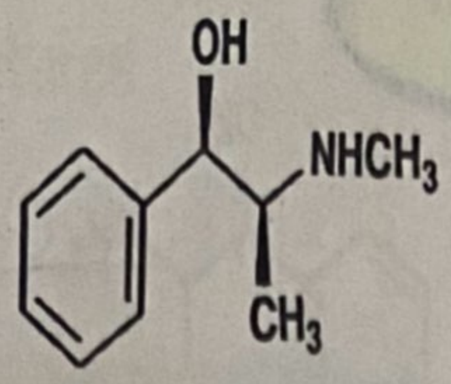
Ephedrine has two (asymmetric) chiral carbons: so four stereoisomers (4 optically active isomers that exist as two pairs of enantiomers.)

- The *erythro* pair is known as ephedrine.
- The *threo-* is known as pseudoephedrine (ψ-ephedrine).



See introductory part about stereochemistry of drug molecules 62

Ephedrine



(-)-*Erythro*-2-(methylamino)-1-phenyl-1-propanol
(-)-*Erythro*- α-[(1-methylamino)ethyl] benzyl alcohol.

- It is available as HCl or as Sulphate. Can U draw ???
- Used by injection and orally.
- Used as adrenergic, as vasopressor, cardiac stimulant, nasal decongestant and bronchodilator and CNS stimulant activity .
- in hypotensive conditions
- In allergic disorders, colds, nasal congestion
- In asthma
- in narcolepsy

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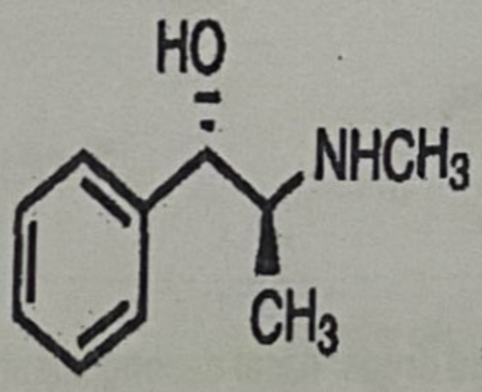
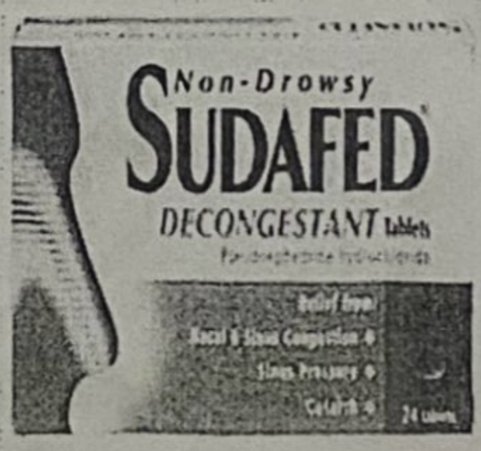
Pseudoephedrine





(+)-*Threo*-2-(methylamino)-1-phenyl-1-propanol

(+)-*Threo*-α-[(1-methylamino) ethyl] benzyl alcohol

- Pseudoephedrine is the *threo*-diastereoisomer of ephedrine
- HCl and Sulphate salts
- has virtually no direct activity
- Mainly indirect action.
- widely used as nasal decongestant.

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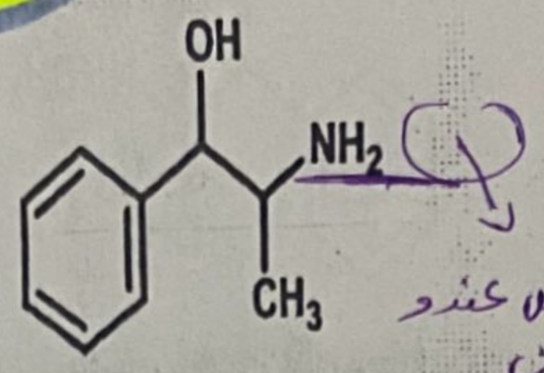
Phenylpropanolamine

(Norephedrine)

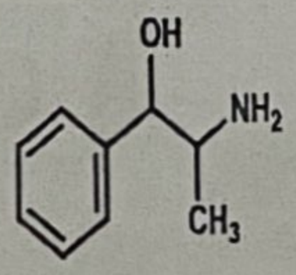


(±)-2-Amino-1-phenyl-1-propanol

فشه عنده هون methyl زي ephedrin لبه هم بشبهو بعض.

- Used as HCl salt
- (+) phenylpropanolamine
- Mainly indirect action
- N-desmethyl analog of ephedrine. Lacking N-methyl group ,
- So, no β_2 agonist activity, no bronchodilator as ephedrine
- Slightly less lipophilic, low CNS activity.

Phenylpropanolamine



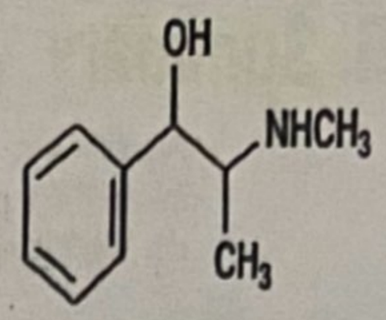
- It is an active ingredient in OTC cold drugs: nasal decongestant.
- It was active ingredient in OTC appetite suppressants (anorexiants)
- In 2000, cerebral hemorrhage in women
- Risk of haemorragic stroke

مسحوبين من السوق لانه بيحمل تزيف للدماغ

But still available in the Egyptian Market

SAR :—

Mixed Function Adrenomimetics: Structural Features



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3. Presence α-methyl group provides resistant to MAO and hence longer duration.
4. ephedrine is less polar than the catechol derivatives, so it can cross blood-brain-barrier, so used as CNS stimulant.

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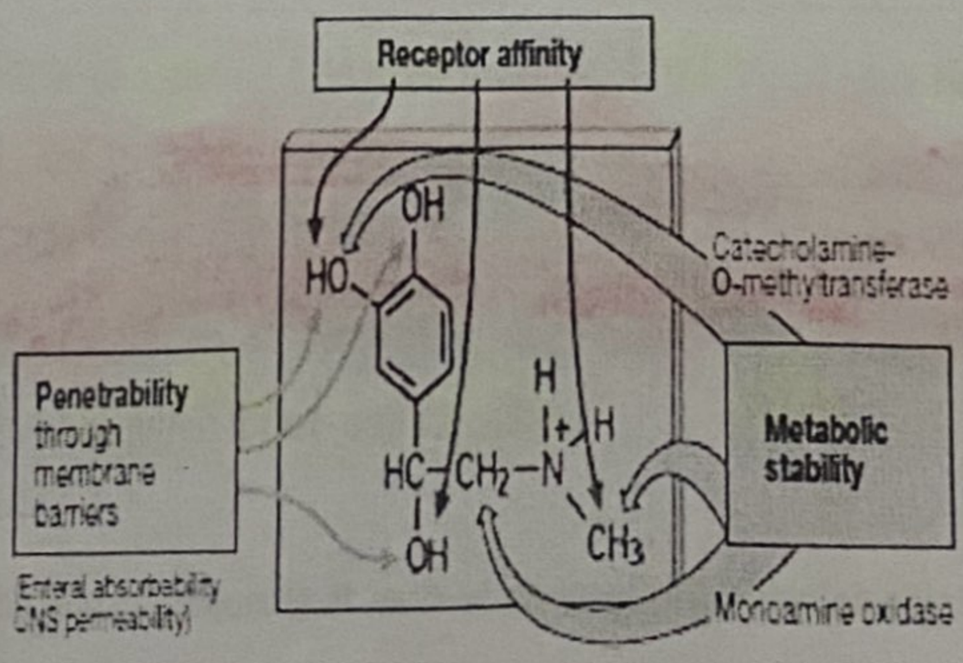
SAR of all phenethylamines

Think about it !!!!!!



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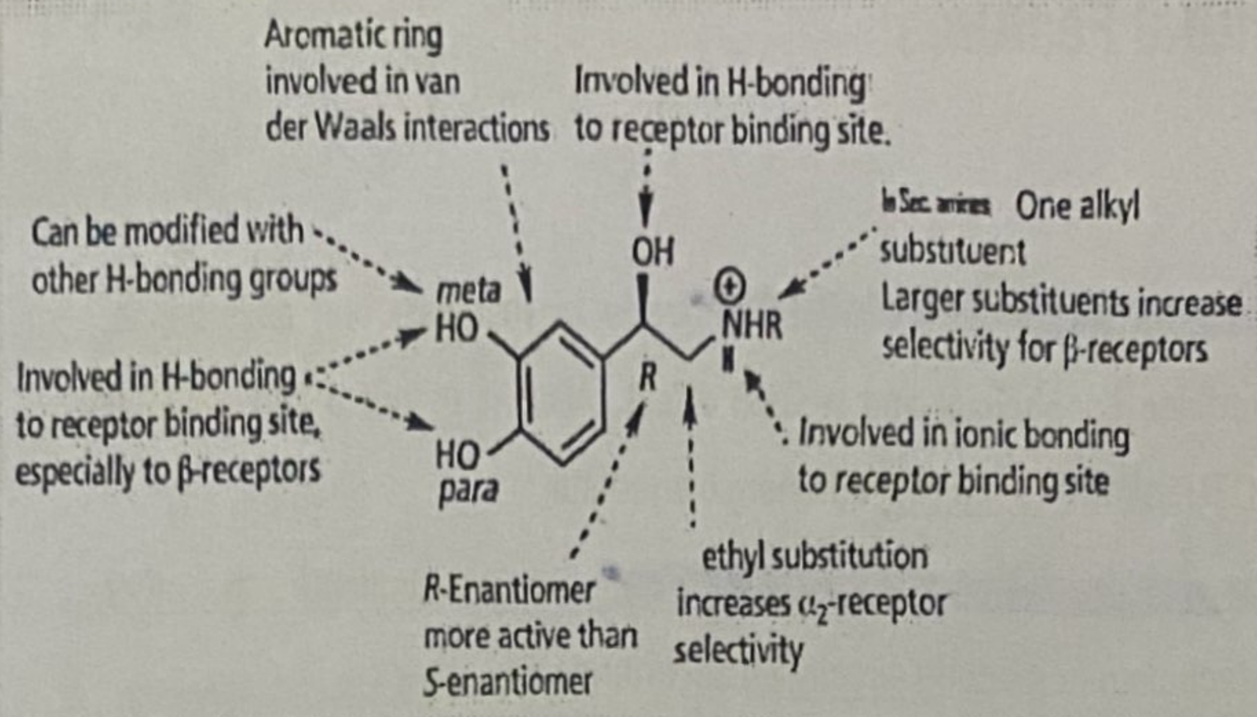
SAR. Summary



Also discuss the effect of:

- Replacement of Catechol by Resorcinol
- N substitution (methyl, isopropyl, t-butyl)
- Replacement of the m-OH by $-CH_2OH$
- Removal of catechol OHs
- Removal of β-OH
- α-alkyl substitution (methyl or ethyl)
- Presence of 2 chiral centers
- .....

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Imidazoline Adrenergic Agonists

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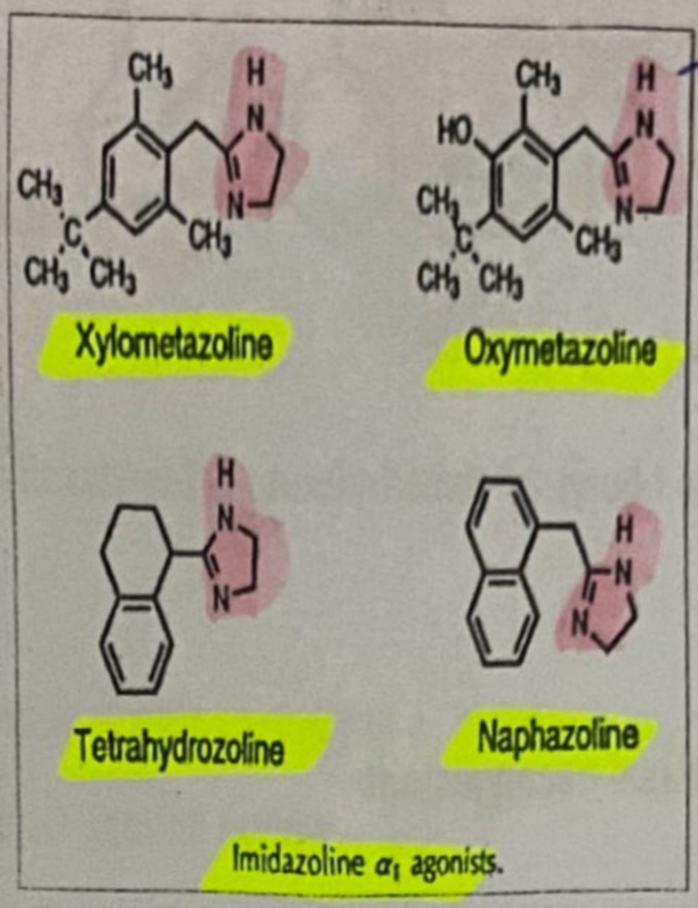
Imidazoline Adrenergic Agonists

imidazole group

They act on α1- and α2-receptors.

Those that act on α1- receptors have vasoconstrictor activity and are used as:

nasal decongestive agents and eye drops.



Imidazoline α_1 agonists.

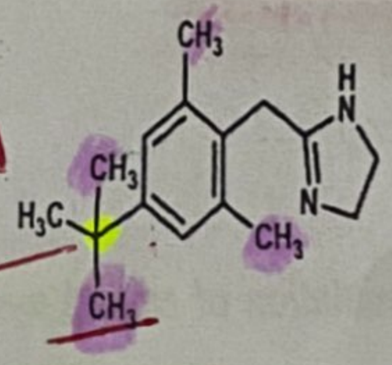
α_1

Used in the form of HCl salts.

Is there any similarity with the phenylethylamine structure ?

Imidazolines: SAR

هاي المركبات اصلاً تأثر على α_1/α_2
حطيت tert butyl لحتى ما تأثر ع α_2

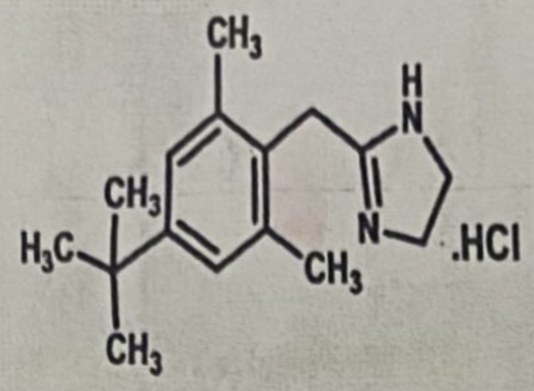


They contain one carbon bridge between C-2 of the imidazoline ring and a phenyl moiety. Therefore, the skeleton of the phenethylamine is present.

Lipophilic substitution on the phenyl group *ortho* to the methylene bridge appears to be required for α1- and α2- affinity.

Bulky lipophilic substituents at *meta* or *para* position diminish affinity for α2-receptors and thus provide selectivity for α1-receptors.

Xylometazoline Hydrochloride (Otrivin)



2-(4-t-butyl-2,6-dimethylbenzyl)-2-imidazoline HCl

Nasal decongestant

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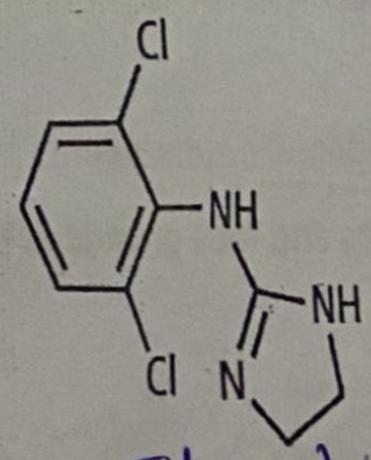
α_2-Agonists

- Stimulation of central α_2-receptors (agonist effect) plays a regulatory role in the release of NE.
- Thus, compounds possessing central α_2-receptors agonist activity could be used for management of hypertension.
- The imidazoline derivative, clonidine, is an important α_2-agonist.



Clonidine.

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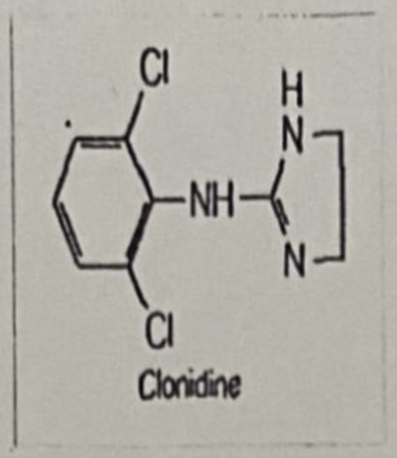
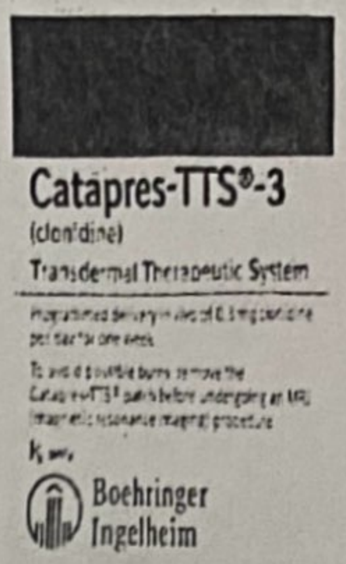
Clonidine Hydrochloride



Clonidine



2-(2,6-Dichloroanilino)-2-imidazoline.

- It is an imidazoline dr.
- The chlorine atoms : lipophilic; compound acts centrally at α_2-receptors.
- The compound has some peripheral α1-agonist activity.
- There is no methylene bridge but an -NH- which makes a guanidine moiety.
- The imidazoline nucleus is not essential for central α2-agonist activity
- Oral and transdermal therapeutic system

زميلتكم ريماس الشوابكه ☺

Best wishes