تفريغ ميديسينال

محاضرة: Adrenegic Part 2

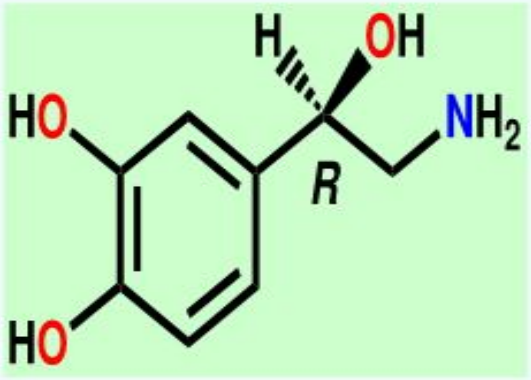
الصيدلاني\ة: Rahaf Zyoud

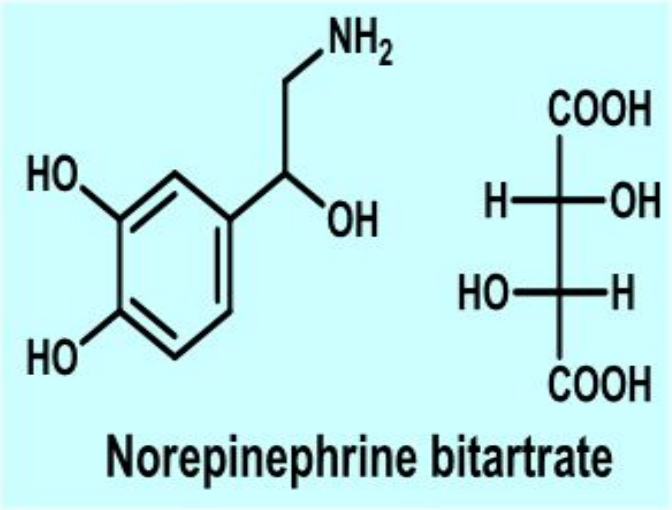
لجان الدُّفعات

Soul Academy

Norepinephrine, bitartrate

methy group عنده أكثر لانه ما α selective يكون NE الـ رح
مرتبطه على N ، إذا رح يكون fit داخل الـ α receptor





Norepinephrine bitartrate

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

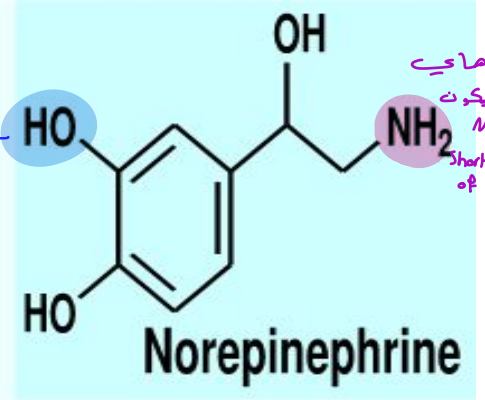
- The bitartarate salt forms stable injectable solution.
- Used to maintain blood pressure in acute hypotensive states.
- Not used as bronchodilator. Why?? →

لانه ما بشتغل على الـ β

Norepinephrine

COMT الـ substrate يكون ر OH الـ بسبب

oral inavaliable إذا



بسبب ماهي الـ Amin ر يكون MAO الـ substrate

Short duration إذا of action

- Presence of the β-OH and the catechol OHs and the amine, so optimal direct action.

حكينا عنهم سابقاً

- 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.

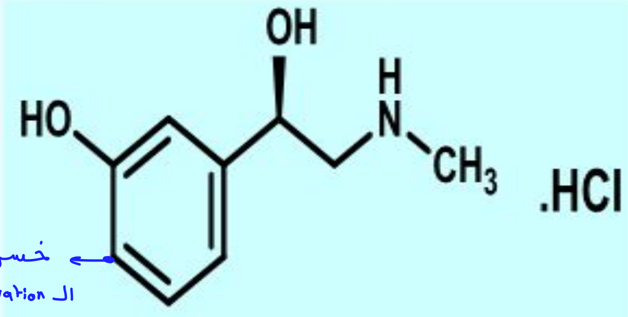
- Short acting: Unsuitable for long term medication

- Chemically unstable where photo-oxidation is possible, so protect from light and OH^-.

الـ catchol ring ر يصير إلها oxidation

Phenylephrine HCl

ال a2 موجودة بال presynaptic neru



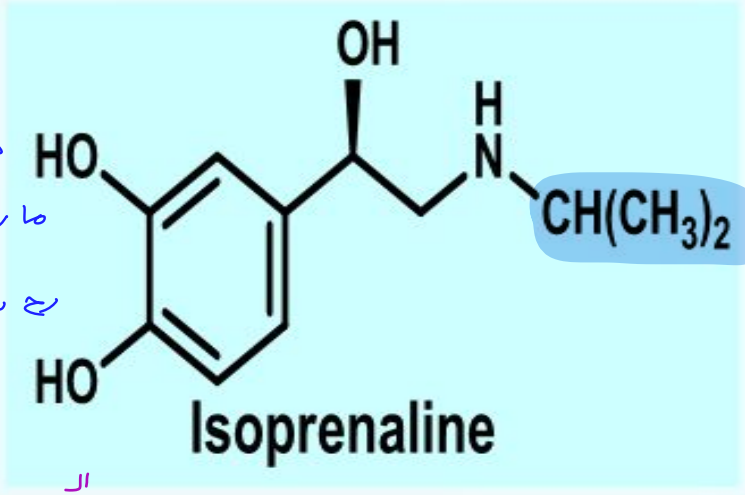
خسرت ال OH اذا رح تخسر
ال activation عل ال receptor بس بطلت
substrate ع COMT اذا بتكون oral avaliable

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.

Isoproterenol (Sulfate) (Medihaler Iso)



Isoprenaline

(-) 1-(3,4-dihydroxyphenyl)-2-(isopropylamino)ethanol

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

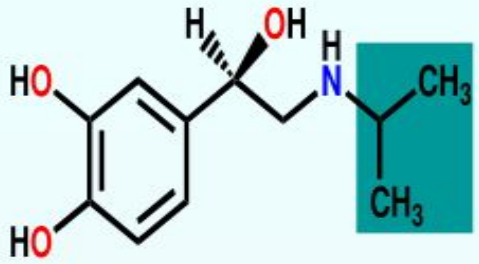
β-adrenergic agonist

Medihaler Iso is used for treatment of bronchial asthma.

But

Non-selective (affects both β_1 and β_2 receptors)

Isoproterenol = Isoprenaline

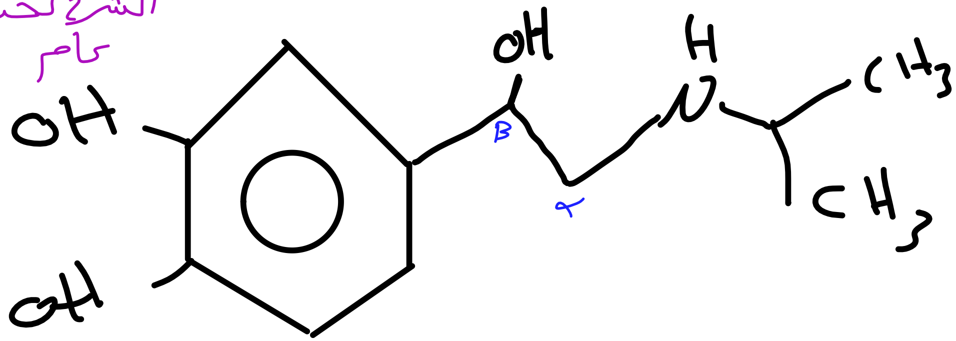


- Shows selectivity for β-adrenoceptors over α receptors
- Bulky isopropyl group introduces β-selectivity
- But, No selectivity between β-subtypes (β_1 and β_2)
- Cardiovascular side effects

يعني مارح يشتغل على β_1 الرئتين β_2
او العكس (نفس قوة الـ effect)

- 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.

هذا مثال نقط و الشرح تحت بشكل عام



كيف رح احسن ال selectivity و ما اخلي

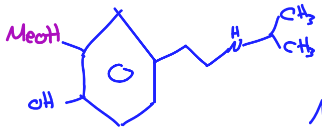
ال substrat لل COMT و MAO ؟؟

① اولا إشي بقدر اضيف methyl group عال ال α carbon (اول c قبل ال N) وهيك رح امنع انه يكون

ال substrat لل MAO

② اذا ضفت ethyl group عال ال α carbon هذا الإشي رح يخليه selective عال B_2

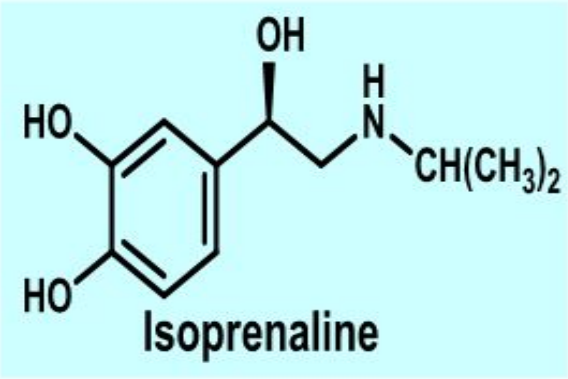
③ اذا بدلت وحدة من 2OH الموجودة عال ال catchol ب MeOH



وهيك بطل ال substrate عال ال COMT و رح يضل direct acting لانه رح يحل 2HB مع ال Ser

④ ابدل ال Me الموجودة عال ال amin ب bulky group وهيك صار selective عال B أكثر من α

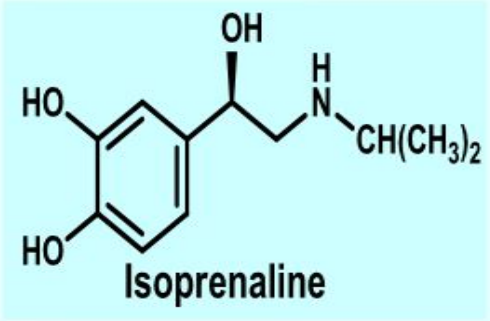
β-Adrenergic Agonists



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 ???

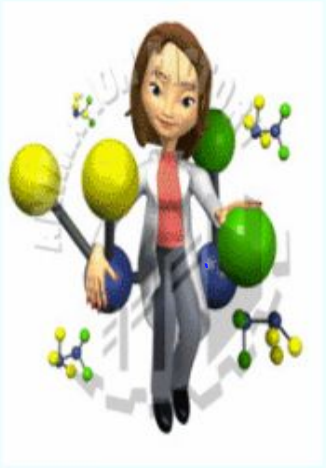
β_2-Adrenergic Agonists

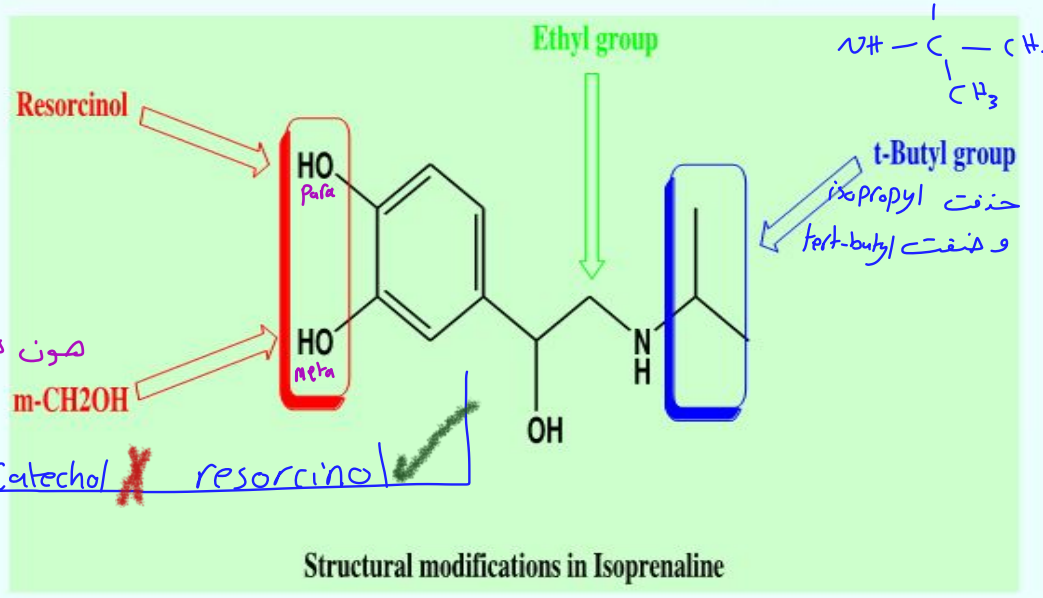


Isoprenaline

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.

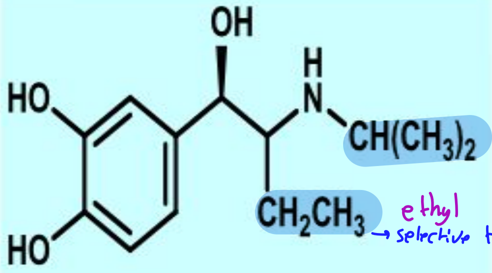
B_2-Adrenoceptor

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)

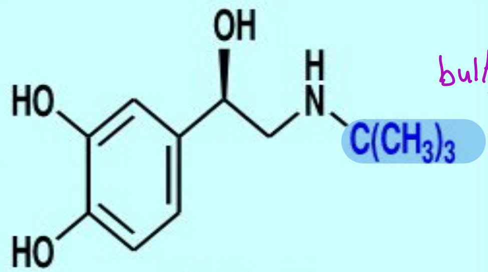
هاي الادويه β-selectiv



Isoetharine

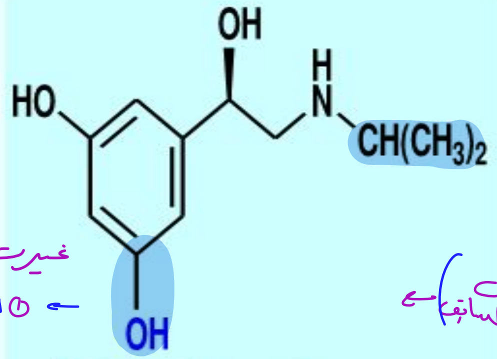
bulky groub → selective to β

ethyl → selective to β_2



Colterol

bulky groub (tert-butyl) → selective to β



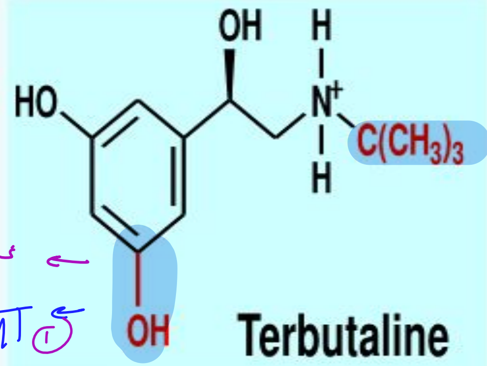
Metaproterenol

bulky groub selective to β

غيرت مكان الOH ل Para

← ① بطلت Catechol وصارت resorcinol ، لهيك لا تعتبر Substrat لل COMT

③ selective to β_2

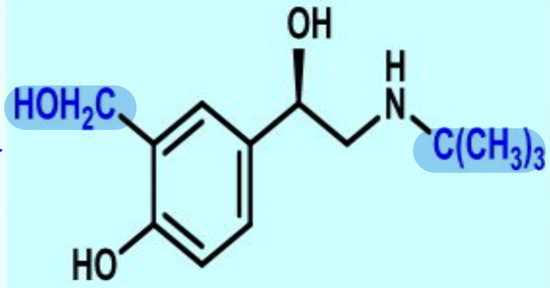


bulky groub → Selective to β

← غيرت مكان ال OH

① not substrate to COMT (شرحت ليش بالمثال السابق) ←

② selective to β_2



Albuterol

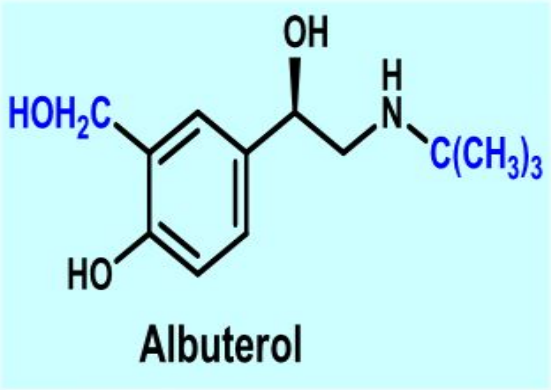
بدلت ال OH ب MeOH

← not substrat to COMT

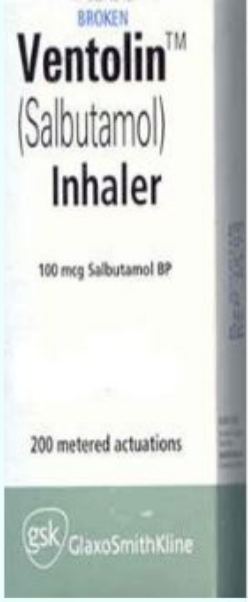
selective to β_2

Rapid onset of action

Salbutamol = Albuterol (Ventolin®)



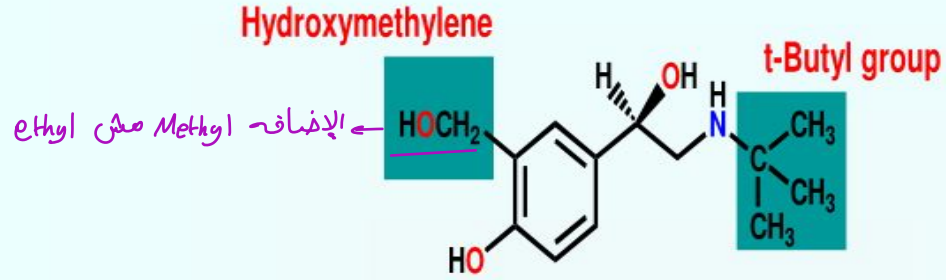
Albuterol



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

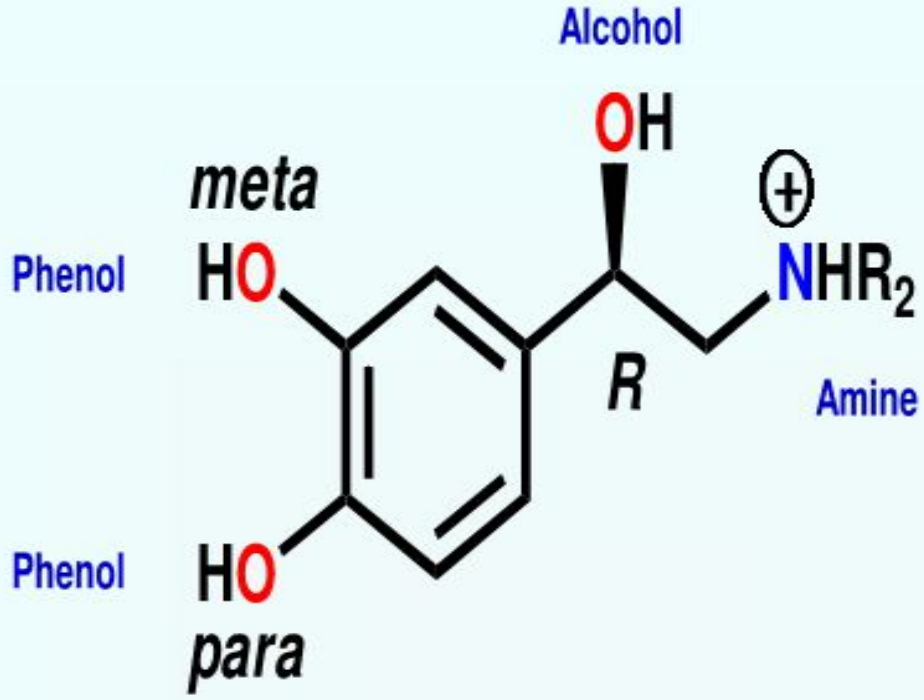
- The hydroxymethyl group has an obstructive effect towards the action of COMT.
- longer duration of action compared to the catechol analogues.
- Albuterol is used in treatment of bronchospasm associated with asthma.

Salbutamol = Albuterol (Ventolin®)



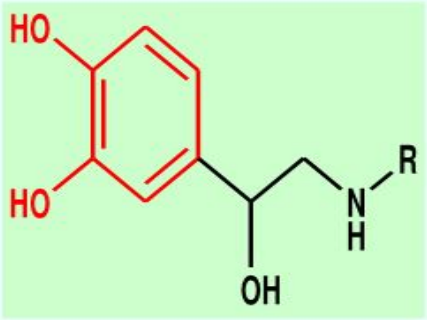
- Hydroxymethylene group retains β_2-agonist activity
- OH shifted from aromatic ring by one bond length
- Forms a hydrogen bond to the target receptor
- Not recognized by COMT
- Same potency as isoprenaline
- 2000 times less active on the heart
- 4 hours duration of action
- Administered as a racemate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

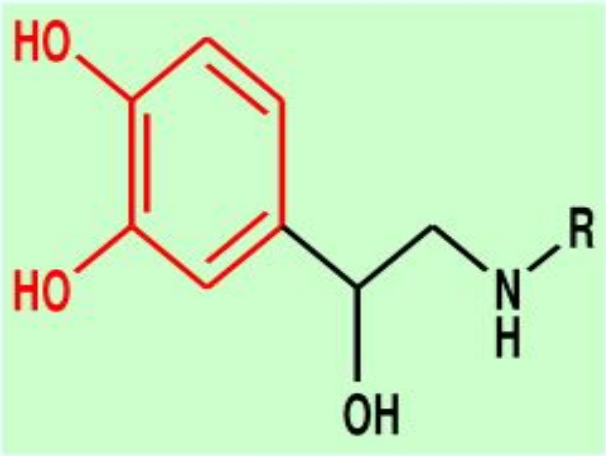
SAR of Direct-acting Adrenergics



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

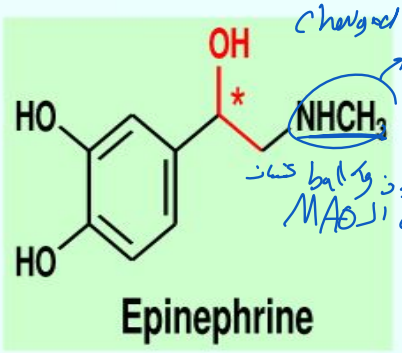
SAR of Direct-acting adrenergics



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).

SAR

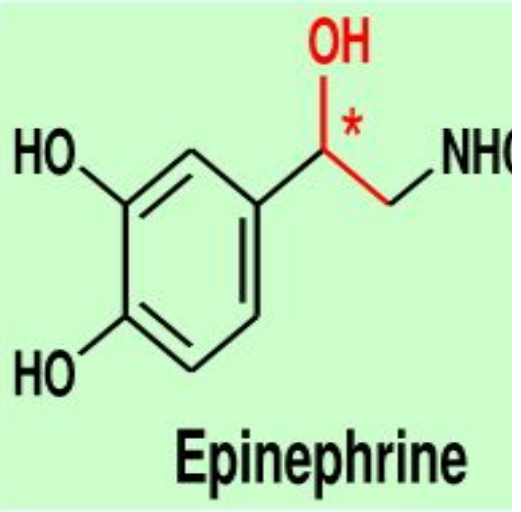


B) Ethyl part (the spacer)

- 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

لو الـ OH مكانتش
مش هيرتبط بالـ receptor
وبتبطل direct

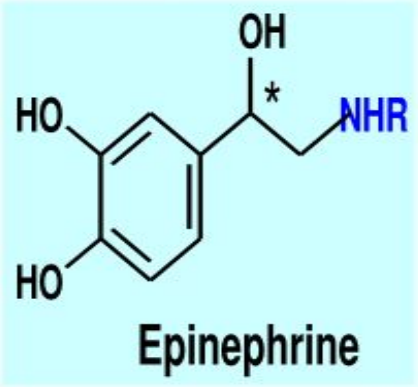


Epinephrine

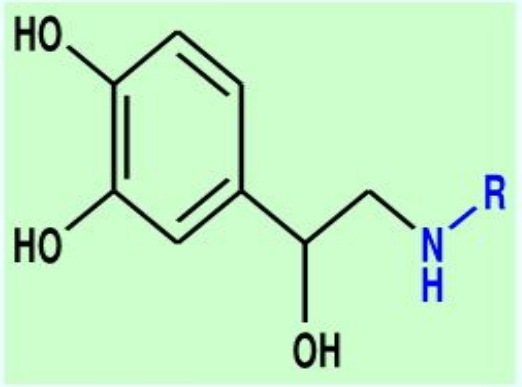
B) Ethyl part (the spacer)

- **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

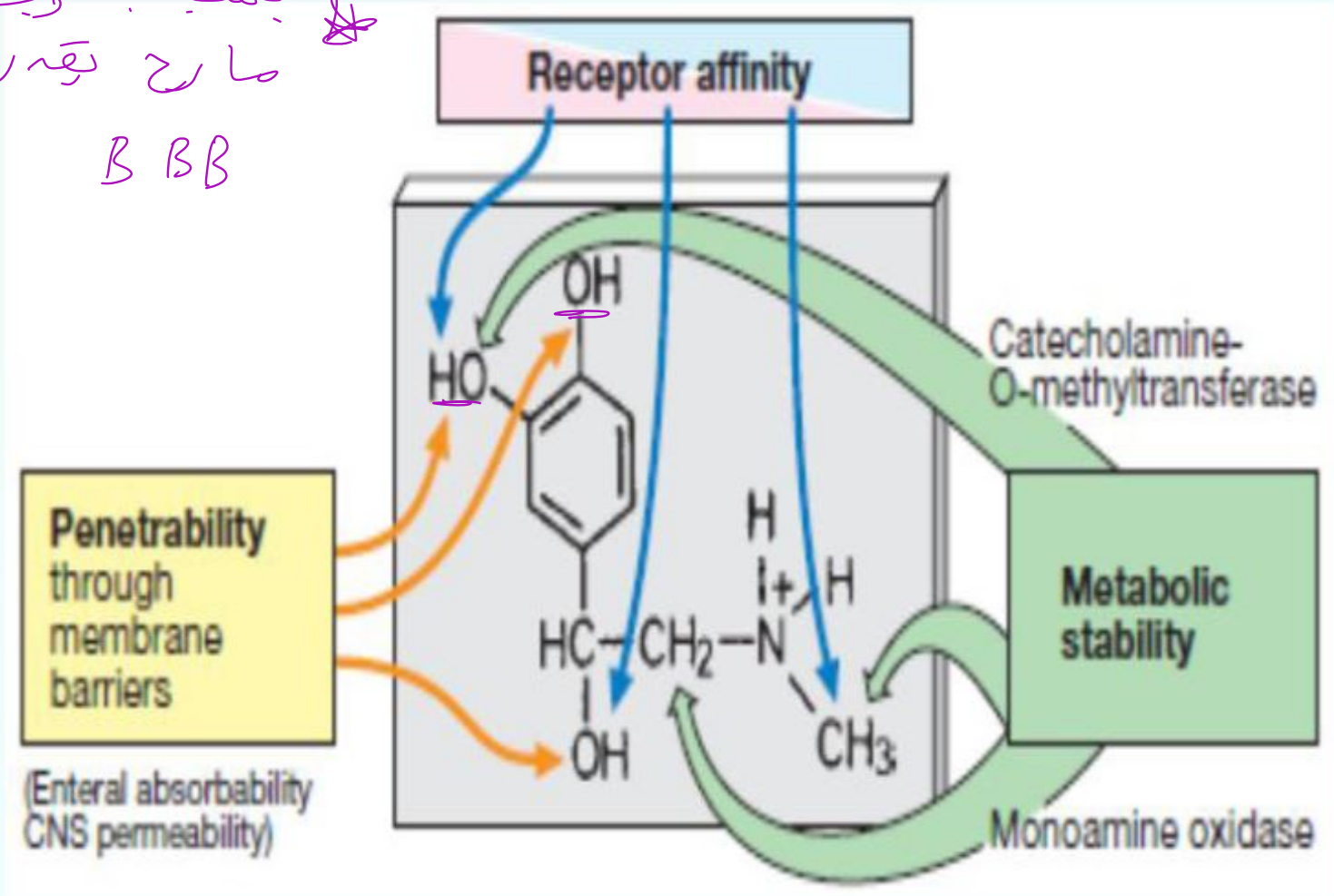


C) The amine part

- 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

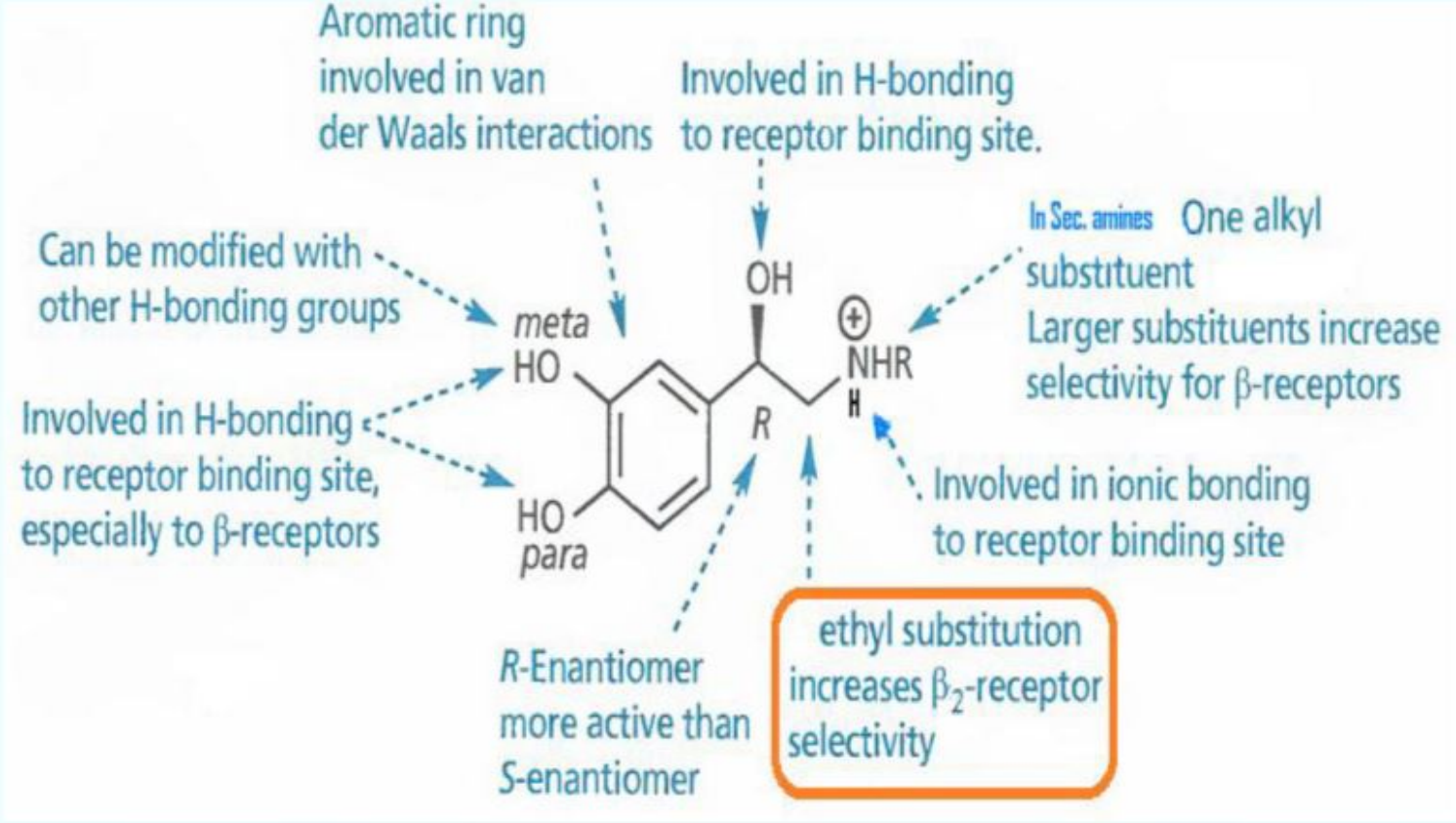
Structural Features and SAR

بسبب وجود الـ OH
صارح يقدر يدخل 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**

في الشغله عدلتها بال Part 1 باربت
تتنبهوا الها (موجوده ع التيلغرام)

لا تنسوا زميلنا ايهم من دعائكم