تفريغ ميديسينال

محاضرة: HTN drugs part 1

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لجان الدُّفعات

Soul Academy

ANTI-HYPERTENSIVE AGENTS

Anti-hypertensive agents

1. Adrenergic inhibitors:
   - Catecholamine storage and release inhibitors…reserpine and guanethidine.
   - β-blockers such as propranolol.
   - □1-receptor antagonist such as pentazocin
2. Angiotensin converting enzyme inhibitors (ACE inhibitors).
3. Calcium channel blockers.
   - .
4. Direct acting vasodilator…such as hydralazine and sodium nitroprusside.

1- Adrenergic inhibitor

α ← هي المسؤولة عن الـ HTN

β

] → blocker

2- ACE I

Angiotensin I —ACE→ Angiotensin II

Angiotensin II → يعمل Fluid retention + Na^+ → وهيك رح يزيد الـ BP

عشان هيك لازم اعمله inhibition

3- CCB → HTN رح نقل الـ Blocked → يعني عم بالعم

ADRENERGIC RECEPTOR ANTAGONISTS (BLOCKERS)

α-Blockers

agonist يسمى ال

- Unlike the β-blockers, which bear clear structural similarities to the adrenergic agonists NE E, the **α** -blockers consist of several compounds of diverse chemical structure that bear little obvious resemblance to the **α** -agonists

α_1 agonist → V.C → BP ↑
α_1 antagonist → V.D → BP ↓
α_2 antagonist → tachy cardiac

NONSELECTIVE α -BLOCKERS

Tolazoline (Priscoline) and phentolamine (Regitine)

- are imidazoline competitive **α** -blockers, The structure of tolazoline are similar to the imidazoline **α** 1-agonists, but does not have the lipophilic substituents required for agonist activity.
- Phentolamine is the more effective **α** -blocker, but neither drug is useful in treating essential hypertension for following reasons. both **α** 1- and **α** 2-blocking activity and produce tachycardia. Presumably, the blocking actions of these agents at presynaptic 2-receptors contribute to their cardiac stimulatory effects by enhancing the release of NE.

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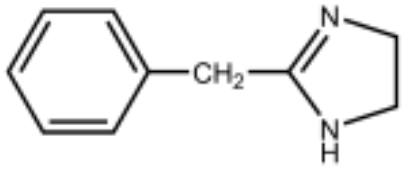
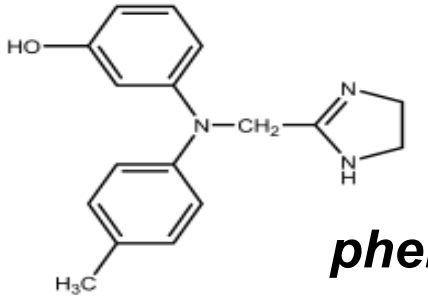
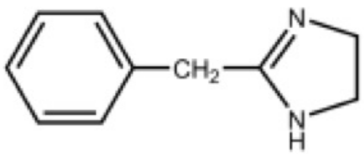


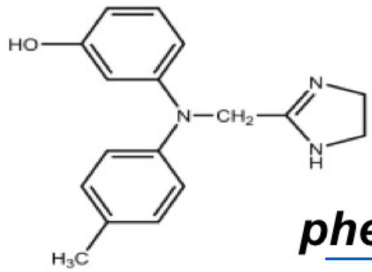
Tolazoline



phentolamine



Tolazoline



phentolamine non - selective α blocker

ال α antagonist بتشبهوا ال agonist كثير عندهم Benzyl ring ← [Imadozolin] بس ما في substitution ← كل ال Benzen ring

بسبب عدم وجود ال substitution رح يكون antagonist .

زي ما اخذنا بالشابتر السابق، ال agonist α2 رح تمنع ال release for NE وهيك رح يصير تمصان ال BP ولما اعمل الها blocking رح يصير العطس.

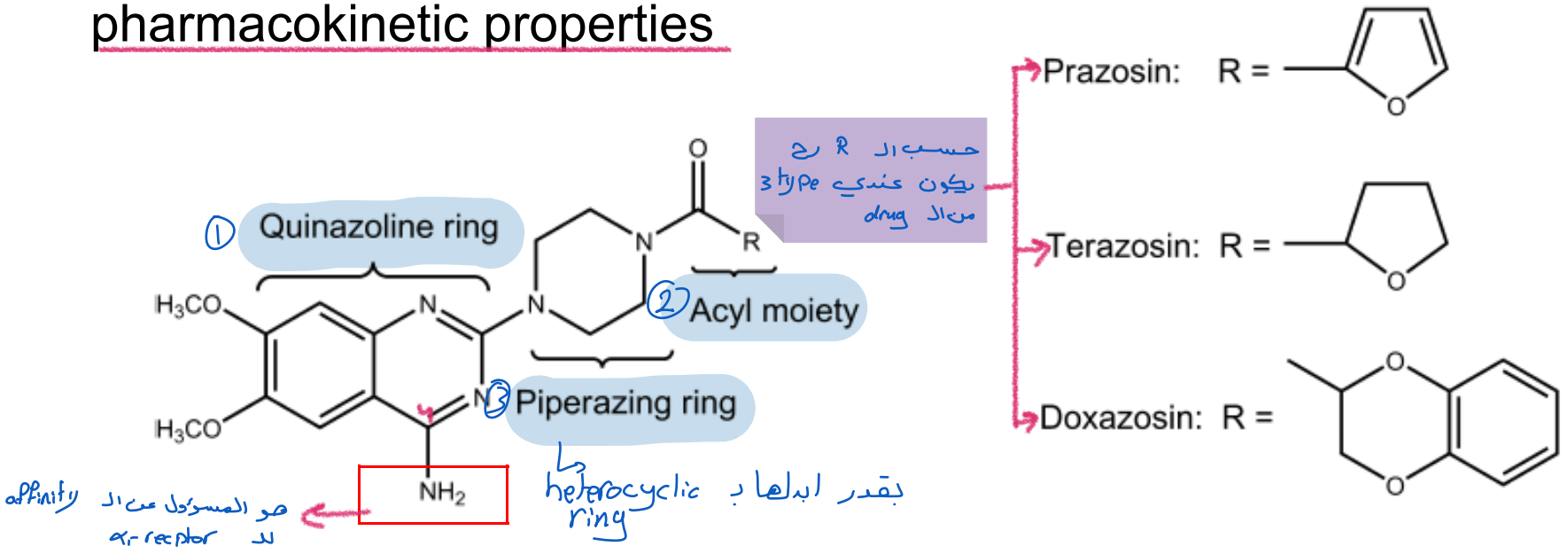
ال α1 موجودين على ال Post-synaptic فلما اعمل الهم blocking رح يعملوا V.D .

وال α2 موجودين على Pre-synaptic فلما اعمل الهم blocking وهيك رح يصير ال release لل NE وهيك

وهيك رح يزيد ال CO وهيك زاد ال BP . عشان هيك ما بقدر استخدم ال α non-selective blocker لعلاج ال HTN

SELECTIVE α 1-BLOCKERS

- ***Prazosin (Minipress), terazosin (Hytrin), and doxazosin (Cardura)*** are quinazoline **α** 1-blockers. As a result, in part, of its greater **α** 1-receptor selectivity, the **quinazoline class** of **α** -blockers exhibits greater clinical utility.
- Structurally, consist of three components: the **quinazoline** ring, the **piperazine** ring, and the **acyl moiety.**
- **The 4-amino group** on the quinazoline ring is very important for **α** 1-receptor affinity.
- a piperazine moiety can be replaced with other heterocyclic moieties (e.g., piperidine moiety) without loss of affinity
- The nature of the acyl group has a significant effect on the pharmacokinetic properties



- These drugs dilate both arterioles and veins and are thus used in the treatment of **hypertension**. They offer distinct advantages over the other **α** -blockers, because they **produce peripheral vasodilation** without an increase in heart rate or cardiac output. This advantage is attributed, at least in part, to the fact that prazosin blocks post-junctional **α** 1-receptors selectively without blocking presynaptic **α** 2-receptors.
- relaxes the smooth muscle of prostate gland, help improve urination flow rates.

صار يشتغلوا على وجهك
صار تعطي التأثير الي حطينا عنه فوق

- the adverse effects of these drugs are usually minimal,

- the most frequent one, known as the *first-dose phenomenon*, This is a dose-dependent effect characterized by marked excessive **postural hypotension** and **syncope,** and can be minimized by giving an initial low dose at bedtime.

الناس اكي بتاخذ هاي الادوية لأول مره رح يصير عندها Postural hypotension و Synocop
لانه blood-vessel ما بصير الها constriction بشكل immediately ← لا الـ V.D رح يكون اله effect كثير فلازم نبلش معهم بـ dose قليله بعدين نزيدها

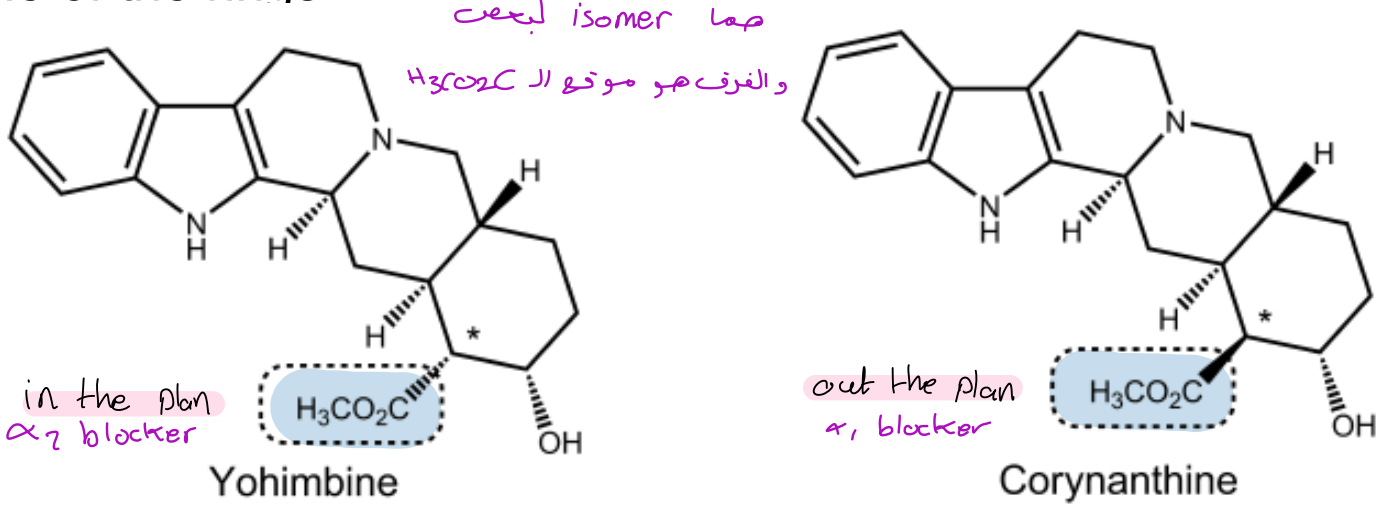
- The main difference between prazosin, terazosin, and doxazosin lies in their pharmacokinetic properties. → affinity صار يأثروا على الـ

- these differences are dictated by the nature of the acyl moiety attached to the piperazine ring.

SELECTIVE α 2-BLOCKERS

Yohimbine and Corynanthine. competitive and selective **α** 2-blocker. an **indolealkylamine alkaloid** and is found in the bark of the tree *Pausinystalia yohimbe* and in *Rauwolfia* root; its structure resembles that of reserpine.

- These isomeric indole alkaloids known as the yohimbanes exhibit different degrees of selectivity toward the **α** 1- and **α** 2-receptors, depending on their stereochemistry.
- yohimbine is a selective **α** 2-blocker, whereas corynanthine is a selective **α** 1-blocker.
- The only difference between these two compounds is the relative stereochemistry of the carbon containing the **carbomethoxy** substituent. In yohimbine, this group lies in the plane of the alkaloid ring system, whereas in corynanthine, it lies in an axial position and thus is out of the plane of the rings



β-Blockers

STRUCTURE–ACTIVITY RELATIONSHIPS

β -Blockers :antihypertensives and glaucoma. Most of **β** -blockers are in the chemical class of aryloxypropanolamine

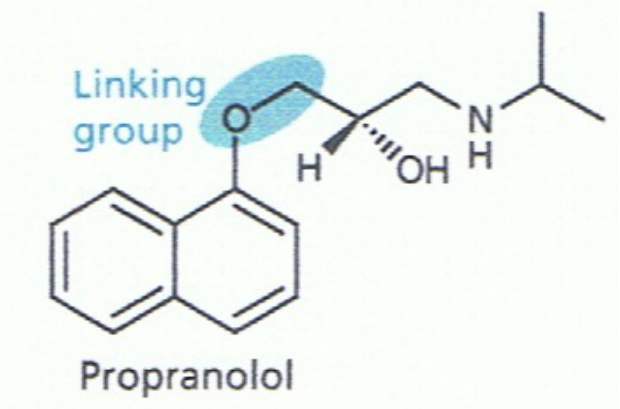
β-blocker non-selective ← glucoma لل بالعاده يستخدم

Aryloxypropanolamines

•This term reflects the incorporation of an **-OCH$_2$-** group between the aromatic ring and the ethylamino side chain.

•Although many β-blockers have this **-OCH$_2$-** group, it is **not responsible** for antagonistic properties.Some molecules with **-OCH$_2$-** are actually **potent β-agonists**.

•Propranolol was the first β blocker of pure antagonist activity.



Propranolol

•**Key determinant** of β-antagonistic activity:

→ The **nature of the aromatic ring** and its **substituents**.

•The **aryl group** also influences absorption, excretion, and metabolism of β-blockers.

•Structural note: the side chain has moved from **C2** to **C1** on the naphthyl ring.

•Like β-agonists, β-directing **tert-butyl** and **isopropyl** groups are commonly found on the amino function of aryloxypropanolamine β-blockers.

•For optimal activity, the amino group must be a **secondary amine**.

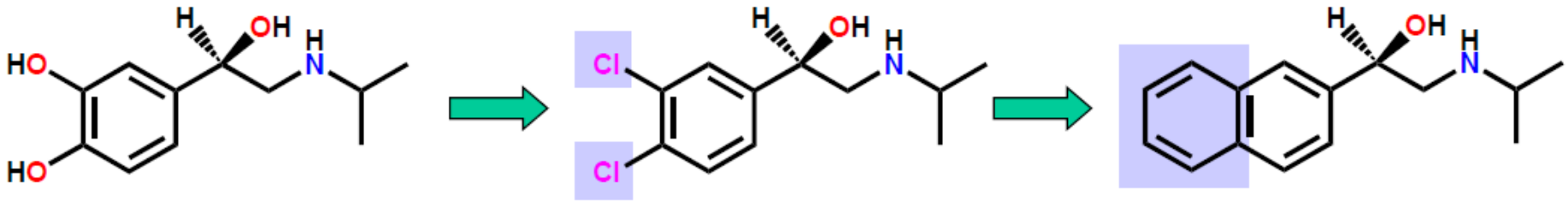
•**Stereochemistry**:

→ In arylethanolamine adrenergic agonists, the β–OH carbon must be in the **R configuration**.

→ In β-blockers, the β–OH carbon must be in the **S configuration** for maximal β-blocking activity.

•The insertion of an oxygen atom in the side chain alters stereochemical requirements.

4. Converting an agonist to a partial agonist



β1, β2 agonist

Isoprenaline (agonist)

حكينا عنه بشبه الـ NE بس عنده اوpropyl هذا عكس الـ N

Dichloroisoprenaline (partial agonist)

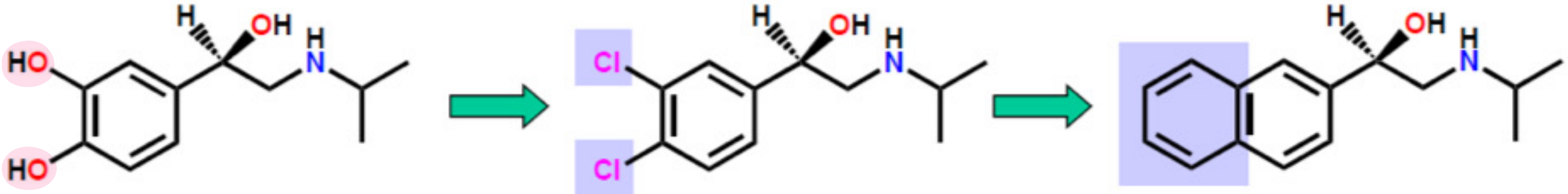
Pronethalol (partial agonist)

➢Isoprenaline (nonselective β-agonist) was selected as lead compound

- Phenol groups are not required for antagonist activity
- Add extra binding groups to convert an agonist to an antagonist
- Hydrophobic groups form extra van der Waals interactions
- Structure binds but produces a different induced fit
- Act as partial agonists
  - weakly activate receptors
  - block natural messenger

4. Converting an agonist to a partial agonist

اول اشي فكروا فيه انهم يبدلوا ال 2 hydroxyl فبدلوهم ب 2 Cl



B1, B2 agonist — **Isoprenaline (agonist)** → NE حكينا عنه بشبه ال
بس عنده isopropyl على ال N

Dichloroisoprenaline (partial agonist)

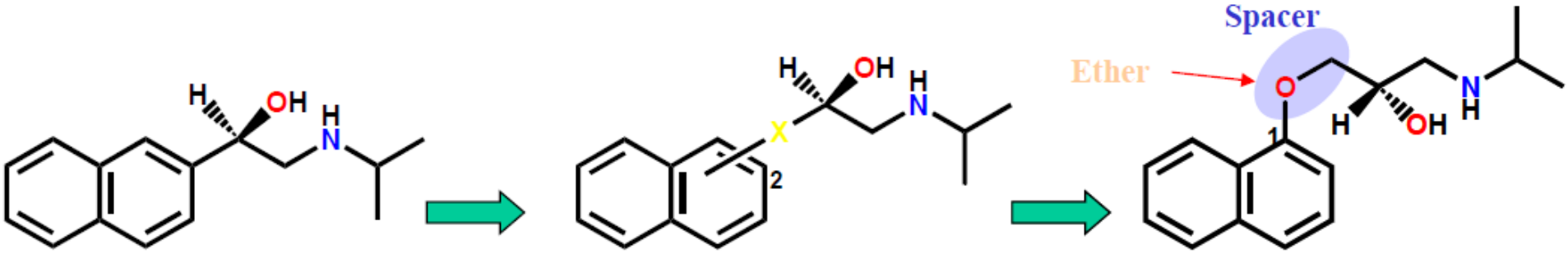
Pronethalol (partial agonist)

لما بدلوا ال 2hydroxyl ب 2Cl هذا الدوا agonist لل B1 وال B2
صار Partial agonist يعني لا هو فعشان اقدر اقلل من ال HTN
لازم اخليه ما يشتغل كل ال B1
قادر يسكر ال receptor بشكل
كامل و لا يعطي ال effect كامل
رجعوا طوروه وبدلوا ال 2Cl
ب aromatic ring

هون لما بدلوا ال Cl ب aromatic ring
صار فيه van-der rxn أكثر و
hydrophobic rxn أكثر بس مع
هيك ضل Partial agonist فشافوا
انه ال ring ما كانت كافيه عشان
يكون antagonist

عشان يخلوا الدوا
antagonist شو بعملوا؟!
بزيدوا aromatic ring
و van-der rxn وبجيبوا
Fit with the receptor بيكون groub
هذا الحكي بشكل عاااام

5. Converting a partial agonist to an antagonist



Pronethalol
(partial agonist)

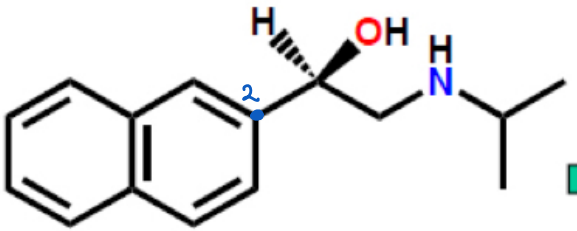
- **Introduce spacer**
  (chain extension)
- **Vary substituent position**

Propranolol
(antagonist)

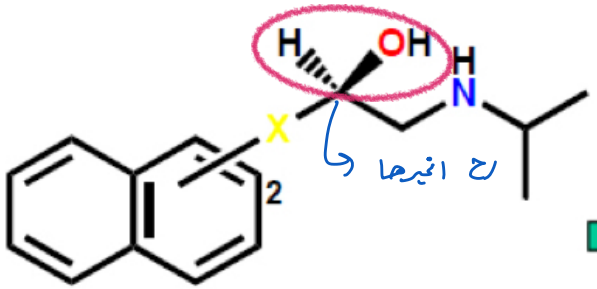
Notes on propranolol

- **Spacer introduced - chain extension strategy**
- **Substituent is positioned at a different part of the ring**
- **Ether group acts as a hydrogen bond acceptor (extension strategy)**
- **10-20 times greater antagonist activity**
- **Used clinically as a racemate**
- ***S*-Enantiomer is the active enantiomer**
- **Aryloxypropanolamine structure**
- **Activates β_1 and β_2 adrenoceptors** → يعني لح يكون antagonist الـ β_1 و β_2 وهيك

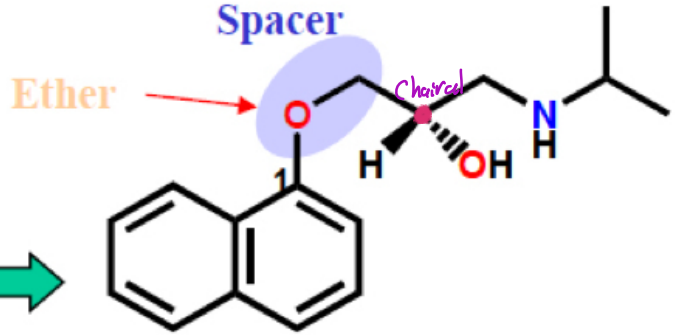
(bronchoconstriction) بدي لح يسبب مشاكل لمرضى الـ Ashma لانه لح يسكر الـ β_2 اللي الموجودة بال



Pronethalol
(partial agonist)



- **Introduce spacer** → chain طولت الـ زيدوا X اي ضفتها
  (chain extension)
- **Vary substituent position** reposition for substitution



Propranolol
(antagonist)

هون قرروا يخلوا الـ aromatic ring

و يحلوا تعديلات ثانيه ٥

راحوا للـ ٢ رقم 2 وحاولوا

يحلوا الـ reposition لـ substitution

باي عليها ٥ ومسكوا الـ ethylen bridge

و ضافوا عليه heteroatom (X)

هذا الناتج النهائي وآخيراً

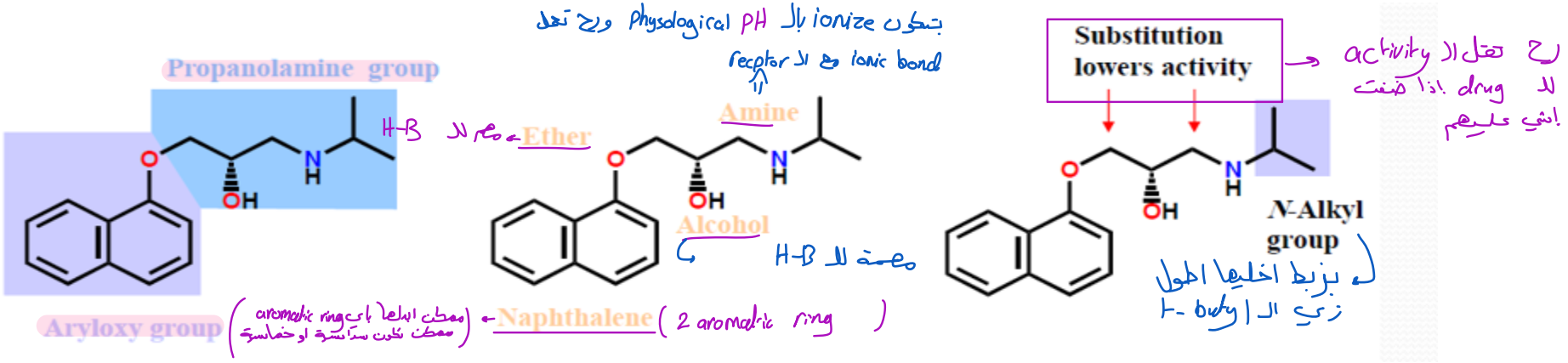
صار antagonist

الـ spacer عبارة عن O و methy (ether)

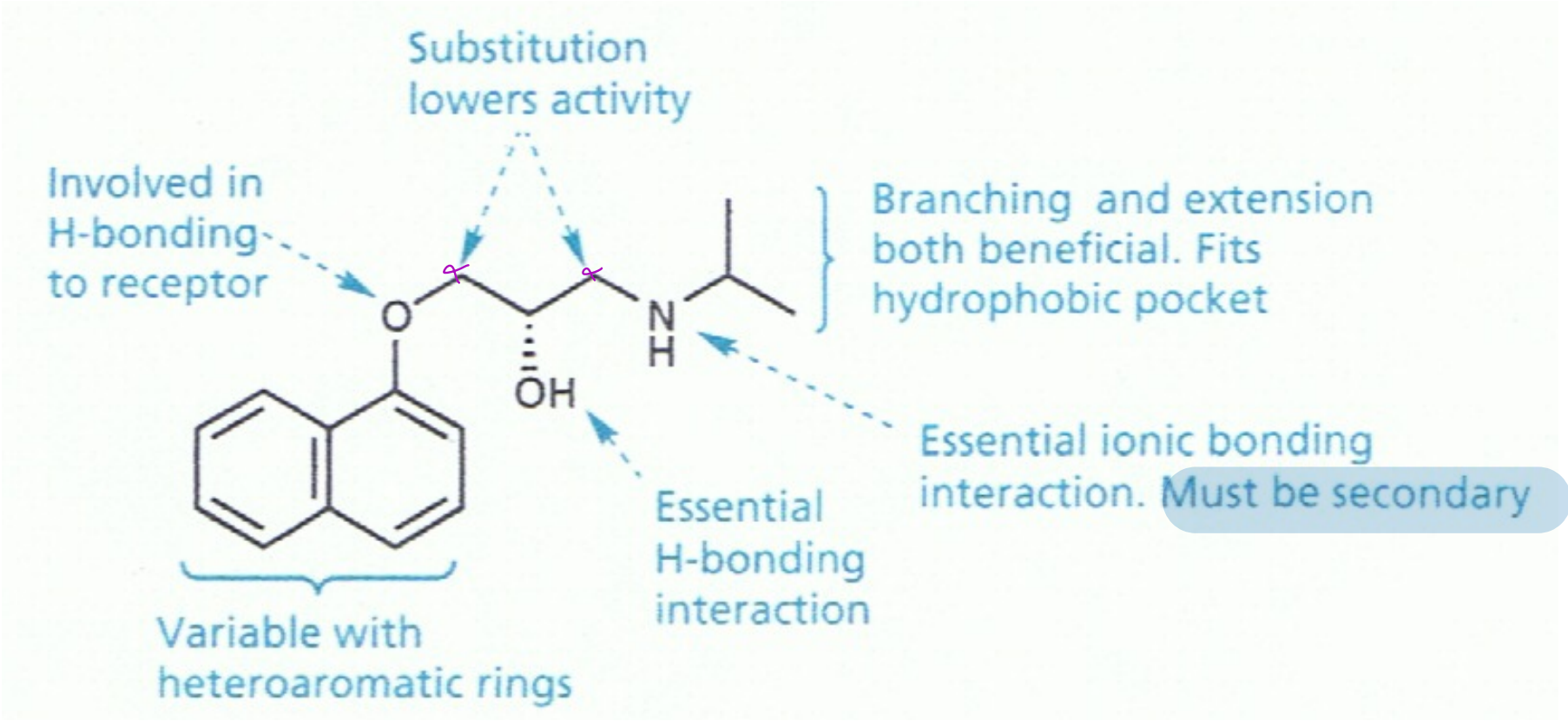
صار على position الـ 2 والـ substitution

رقم 1

SAR of antagonist

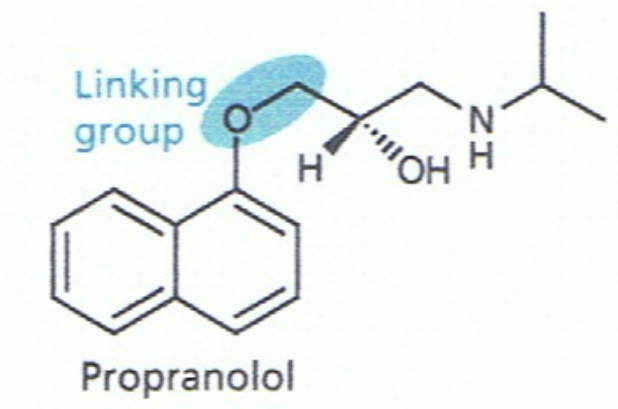


- OH on the side chain is essential for activity
- Alcohol is essential as a hydrogen bonding group.
- Ether acts as a hydrogen bond acceptor.
- Replacement of ether O by S, CH2, NMe is detrimental.
- Amine is ionized and forms an ionic bond with the binding site. Amine must be secondary.
- Naphthalene is replaceable with heteroaromatic rings.
- N-alkyl substituent longer than isopropyl or t-butyl are less effective
- Adding an N-arylethyl group such as CHMe, CH2Ph or CHMeCH2Ph is beneficial
- Alkyl group as isopropyl or t-butyl
- Heteroaromatic ring can replace the aromatic ring
- Substitution on the side chain by methylene group increases the stability and reduces activity


Substitution
lowers activity
Involved in
H-bonding
to receptor
Branching and extension
both beneficial. Fits
hydrophobic pocket
O
N
H
OH
Essential ionic bonding
interaction. Must be secondary
Essential
H-bonding
interaction
Variable with
heteroaromatic rings

hydrophobic يعني

- Propranolol (log P 3.10) is the most lipophilic drug among the available **β** -blockers, and thus it enters the CNS much better
- The use of lipophilic **β** -blockers such as propranolol has been associated with more CNS side effects, such as **dizziness, confusion, or depression**.
- These side effects can be avoided, however, with the use of hydrophilic drugs, such as atenolol or nadolol. → No CNS effect
- The more lipophilic drugs are primarily cleared by the liver,



Propranolol

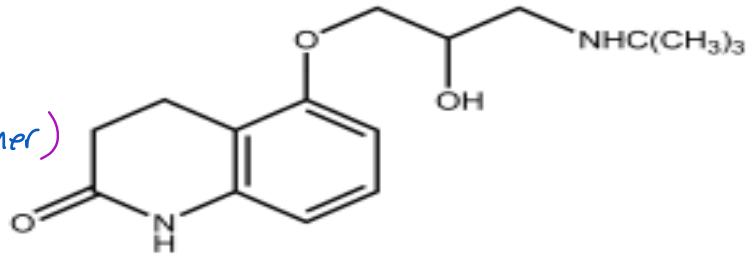
Other Nonselective* β *-Blockers. (most of these drugs have antihypertensive effect) but mainly used for:

الهم بال HTN بس effect
غالباً هيك استخداماتهم

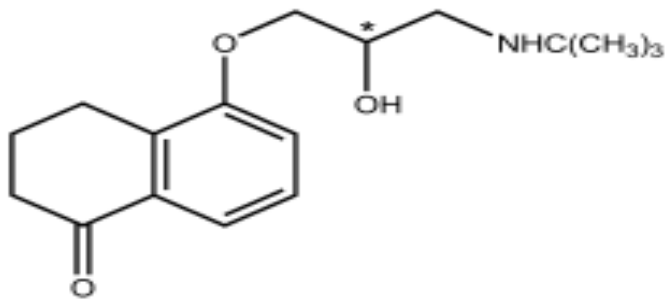
- Nadolol is also used in the longterm management of angina pectoris
- timolol :prophylaxis of migraine headaches and in the therapy following myocardial infarction.
- Sotalol : an antiarrhythmic.
- Carteolol, timolol, levobunolol, and metipranolol are used topically to treat open-angle glaucoma.

اشياء مشتركة بال non-selectiv β blocker

① aryl group
② spacer
③ β hydroxyl (in "S" isomer)
④ substitution in amin 1's isopropyl and t-butyl

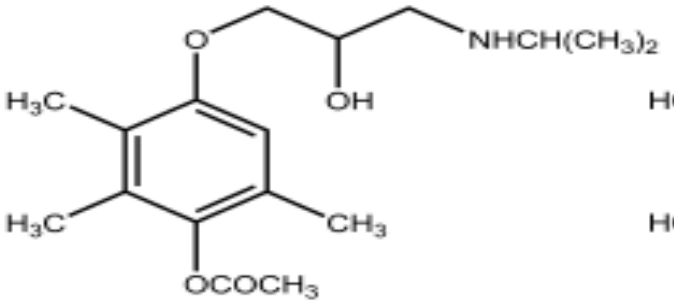


Carteolol: antihypertensive & antiglaucoma

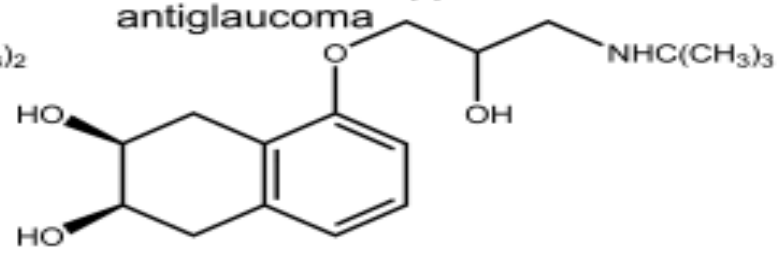


Bunolol
Levobunolol, S(-) isomer of bunolol
antiglaucoma

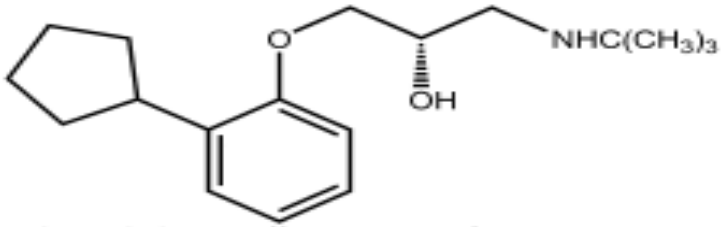
كل هاي الادويه non-selectiv عشان صيدلي ما يقدر استخدمهم مع التالي معهم Ashma



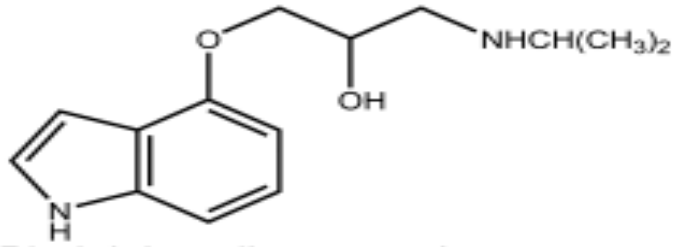
Metipranolol: antiglaucoma



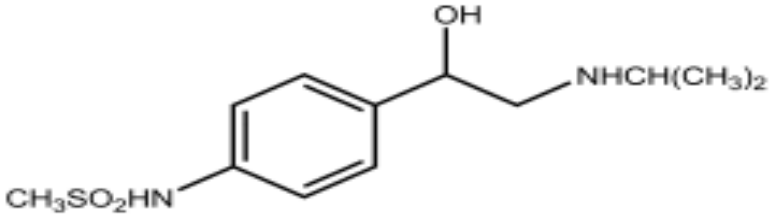
Nadolol: antihypertensive



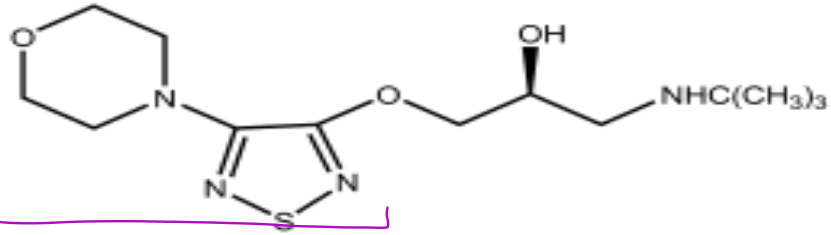
Penbutolol: antihypertensive



Pindolol: antihypertensive



Sotalol: antiarrhythmias & only phenylethylamine



Timolol: antihypertensive & antiglaucoma

تطرح العين

Figure 16.15 • Nonselective β-blockers.

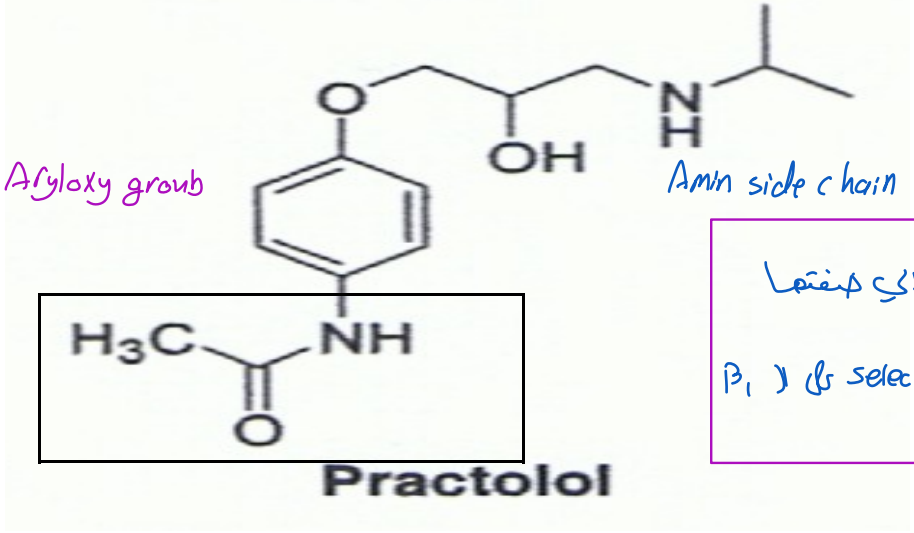
Second generation β1-blockers

- Propranolol acts against both β_1 and β_2-adrenoceptors and cannot be used with asthmatic patients because antagonism of β_2-adrenoceptors constricts airways

- Due to the many side effects of the first generation, Second generation β-blockers are designed to be β_1-selective. Practolol was synthesized.
- Practolol is not as potent as propranolol but selective β1-blocker and more polar which give less CNS effect properties
- Amido group has to be para for β1 selectivity
- Replacement of acetamido group with other groups capable of H-bonding produced cardioselective β1-blockers (Acebutolol, atenolol, metoprolol and betaxolol)

ortho + Meta Subsitution ← بخلوا موجودين وهون بالاختلاف الاول عن الـ Propanolol

Para → Amid ضعفت عليها وبح بيعمل H-B أكثر وهون بالاختلاف الثاني

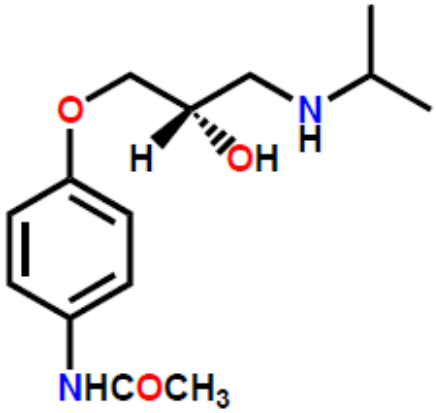


Practolol

الـ Amid بالي حكيتها ع تخليه selectiv على β_1

9. Second generation β-blockers

Practolol



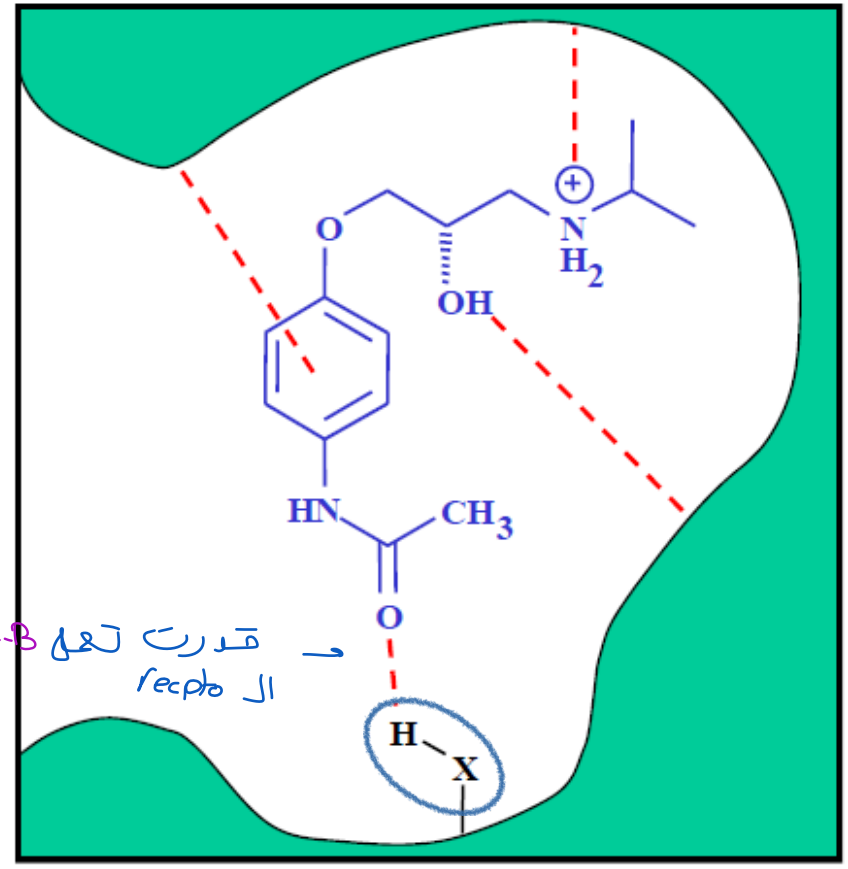
Notes

- Selective cardiac β_1-antagonist
- More polar → لانه ضفت ال Amid و حذفت ال hydrophobic group
- Less CNS side effects
- First cardioselective β_1-blocker used for the treatment of angina and hypertension
- Withdrawn due to serious side effects in some patients → ما بنستخدمه لانه إله side-effect

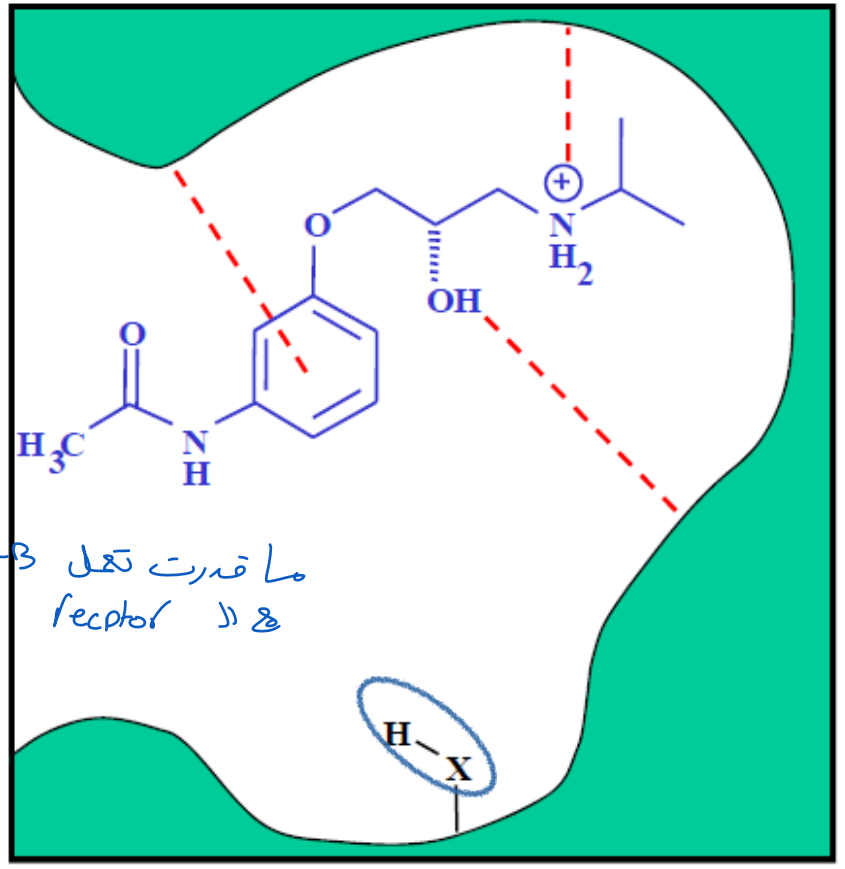
9. Second generation β-blockers

Practolol - binding interactions

- Amido group must be *para* for β_1-selectivity
- Extra hydrogen bonding interaction takes place
- Not possible with β_2-adrenoceptor



para substitution
Extra H-bonding interaction



meta substitution

β 1-SELECTIVE BLOCKERS (SECOND GENERATION)

- cardioselective agents should provide two important therapeutic advantages.

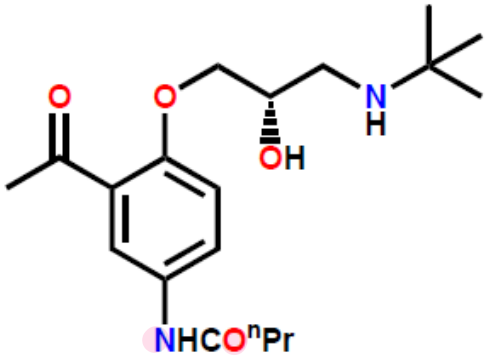
1. the lack of a blocking effect on the β 2-receptors in the bronchi. Theoretically, this would make β 1-blockers safe for use in patients who have bronchitis or bronchial asthma.

2- the absence of blockade of the vascular receptors, which mediate vasodilation. This would be expected to reduce or eliminate the increase in peripheral resistance that sometimes occurs after the administration of nonselective β -blockers.

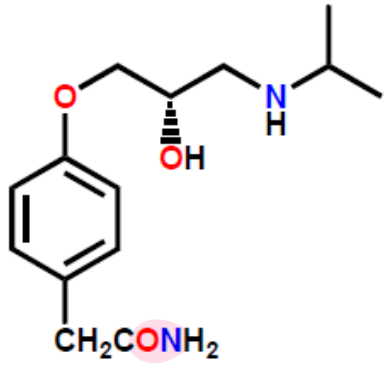
- Unfortunately, cardioselectivity is usually observed with β 1-blockers at only relatively low doses. At normal therapeutic doses, much of the selectivity is lost.

9. Second generation β-blockers

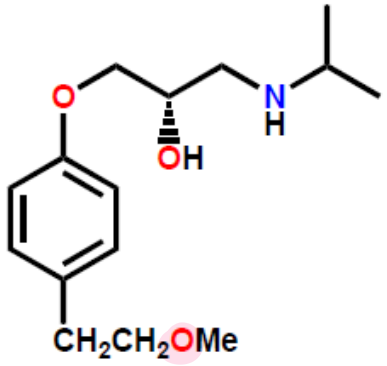
Other agents



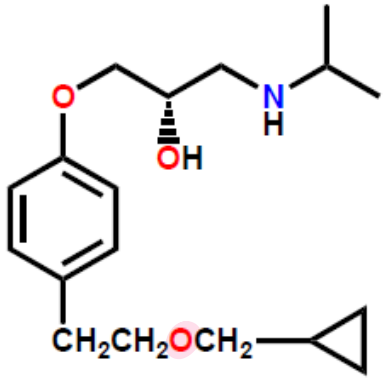
Acebutolol



Atenolol



Metoprolol



Betaxolol

β -BLOCKERS WITH α1-ANTAGONIST ACTIVITY (THIRD GENERATION)

بستخدمهم على الـ α و الـ β مع بعض
كتير فائده لانهم رح يستخدموا على الـ α اي رح تعمل تقليل للضغط والـ β اي رح تمنع الـ reflex-tachycardia

Several drugs have been developed that possess both β – and **α** -receptor–blocking activities within the same molecule.

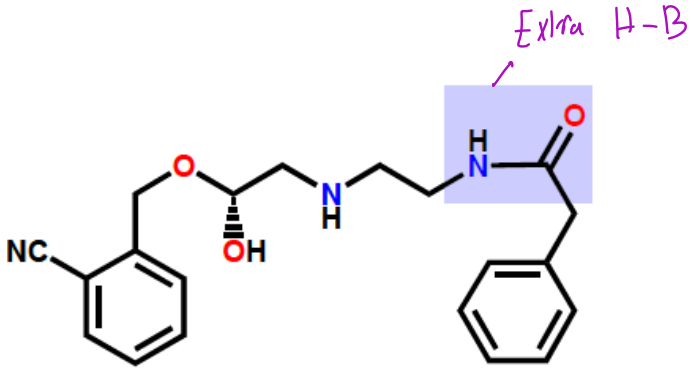
- Two examples of such molecules are labetalol (Normodyne) & carvedilol (Coreg). **The arylalkyl group** with nearby methyl group in these molecules is responsible for its **α** 1-blocking activity. The bulky *N*-substituents and another substituted aromatic ring are responsible for its β -blocking activity.

The rationale for its use in the management of hypertension is that its - **α** receptor–blocking effects produce vasodilation and its β -receptor–blocking effects prevent the reflex tachycardia usually associated with vasodilation

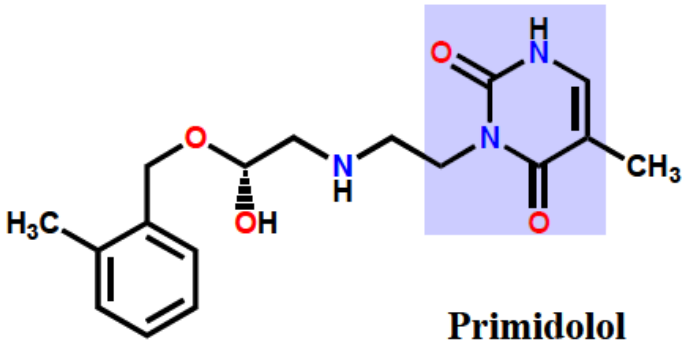
10. Third generation β-blockers

Notes

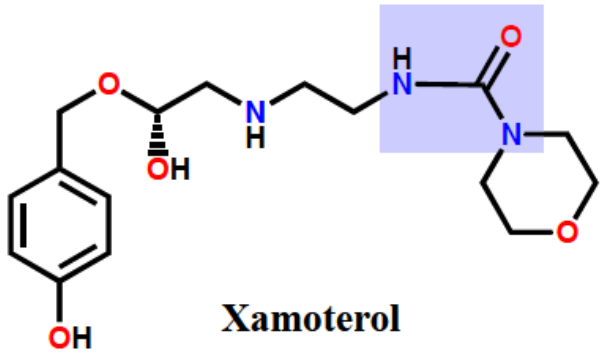
- Includes an *N*-arylalkyl group
- Additional hydrogen bonding interactions are possible
- Extension strategy



Epanolol



Primidolol

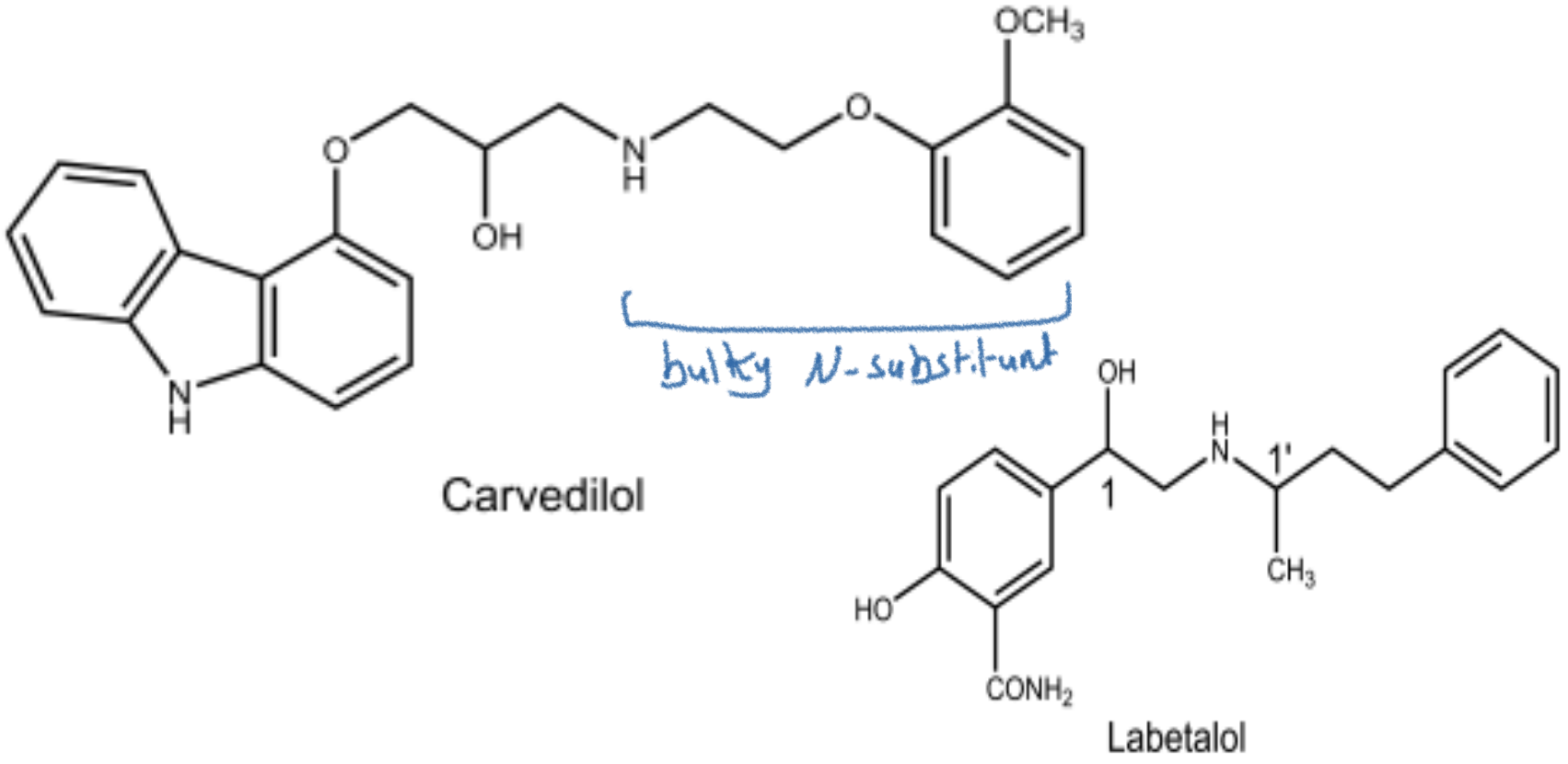


Xamoterol

Extra H-bonding interactions

Carvedilol..

This drug is also unique in that it possesses antioxidant activity and an antiproliferative effect on vascular smooth muscle cells. It thus has a neuroprotective effect and the ability to provide major cardiovascular organ protection. It is used in treating hypertension and congestive heart failure



لمعلميكم العافية

لا تنسوا زميلنا ايهم من دعائكم