

Cardiovascular agents

Antianginal drugs and vasodilators

Introduction

الذبحة الصدرية .
Angina Pectoris: strangulation in chest.

إنه بالصدر
وتشير للكتف
التي
داخل الذراع
It is characterized by severe constricting pain in the chest, often radiating to left shoulder and down the arm.

أهم علامات
أمراض القلب
[Angina] is considered the principal symptom of ischemic heart disease.

شوالسبب؟

Etiology

نقص تدفق الدم في شريان التاجي

- **Insufficiency of the coronary blood flow**
(mainly due to atherosclerosis) بسبب تصلب الشرايين

+

- **Inadequate blood supply to the tissue**
عدم كفاية إمدادات الدم في الأنسجة

- **Cardiac discomfort (Angina)**

Goal of treatment

The main goal in the prevention & relief of angina is to **limit the O_2 requirement of the heart**, so that the **amount of blood supplied by the incapable arteries is adequate.**

Vasodilators are used to:

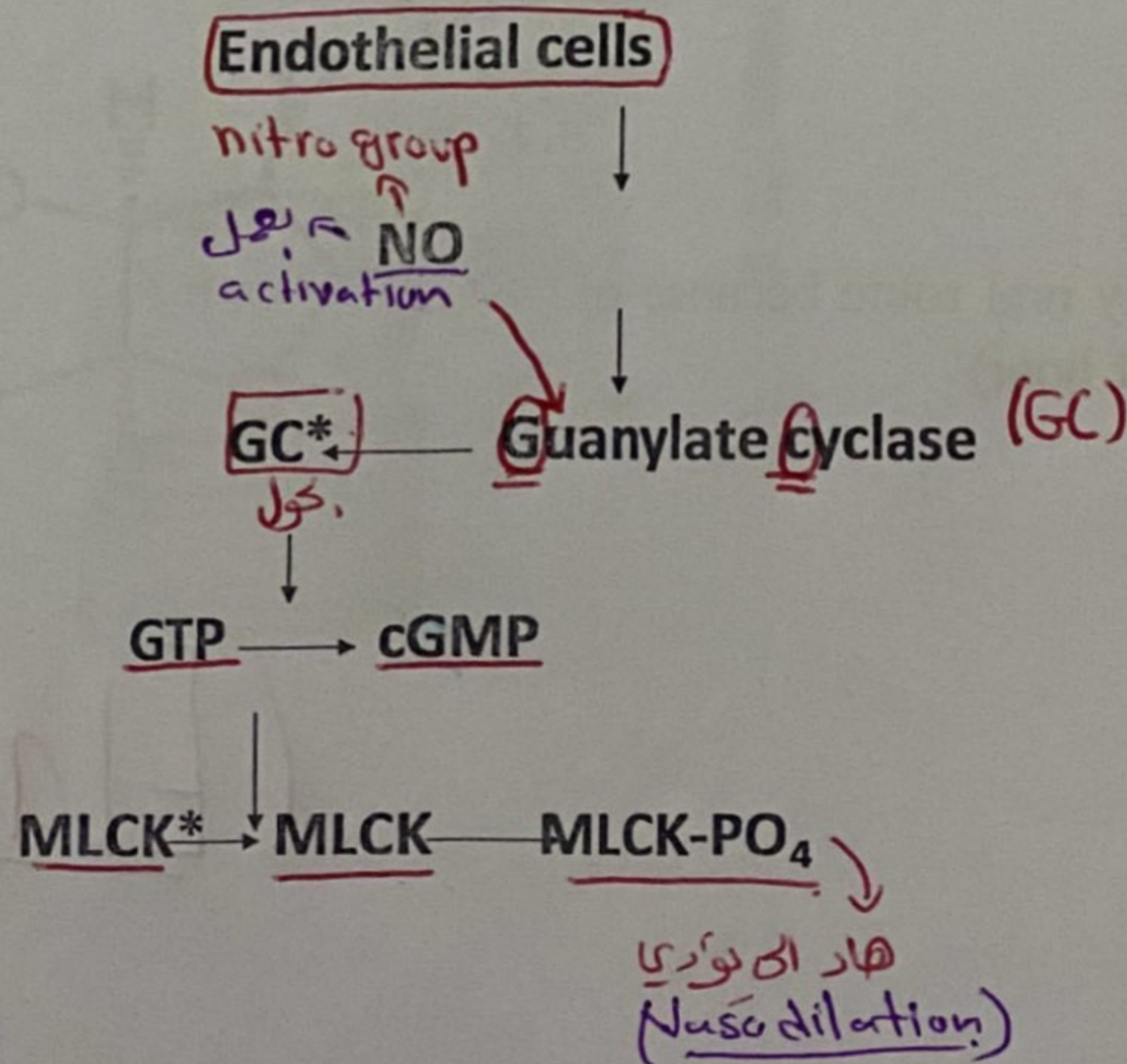
1. **Reduce cardiac consumption of O_2 .**
2. **Reduce peripheral vascular resistant.**
3. **Useful in patients with C.H.F.**

هدف ادوية
ال Vasodilators
منع لزيادة استهلاك
تقليل حاجة
القلب لل O_2

Antianginal agents:

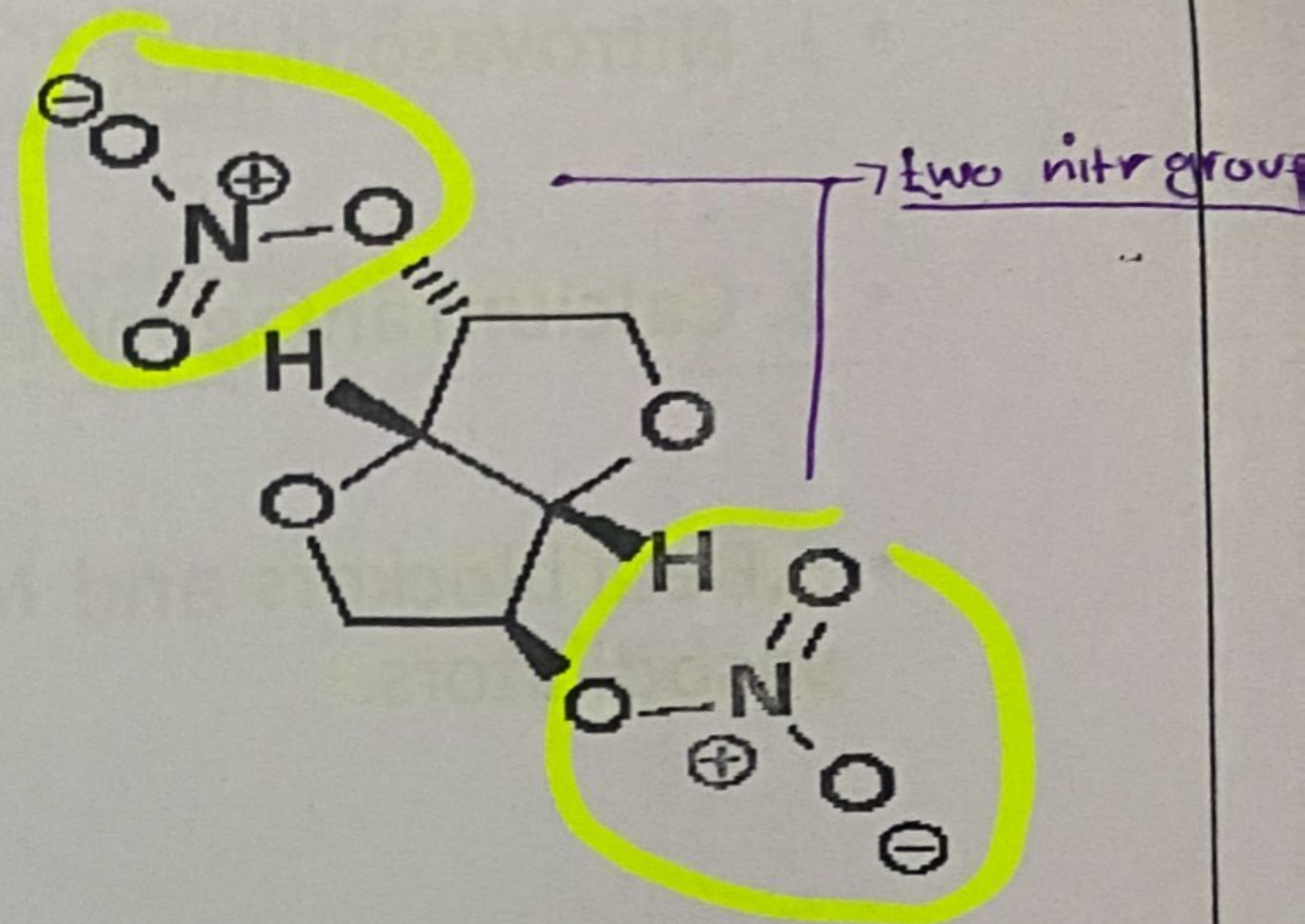
- 1. Nitrovasodilator.
- 2. Calcium antagonists.
- 3. Beta blockers and Miscellaneous vasodilators.

M.O.A of Nitrovasodilators:



Isosorbide dinitrate (Isoket)

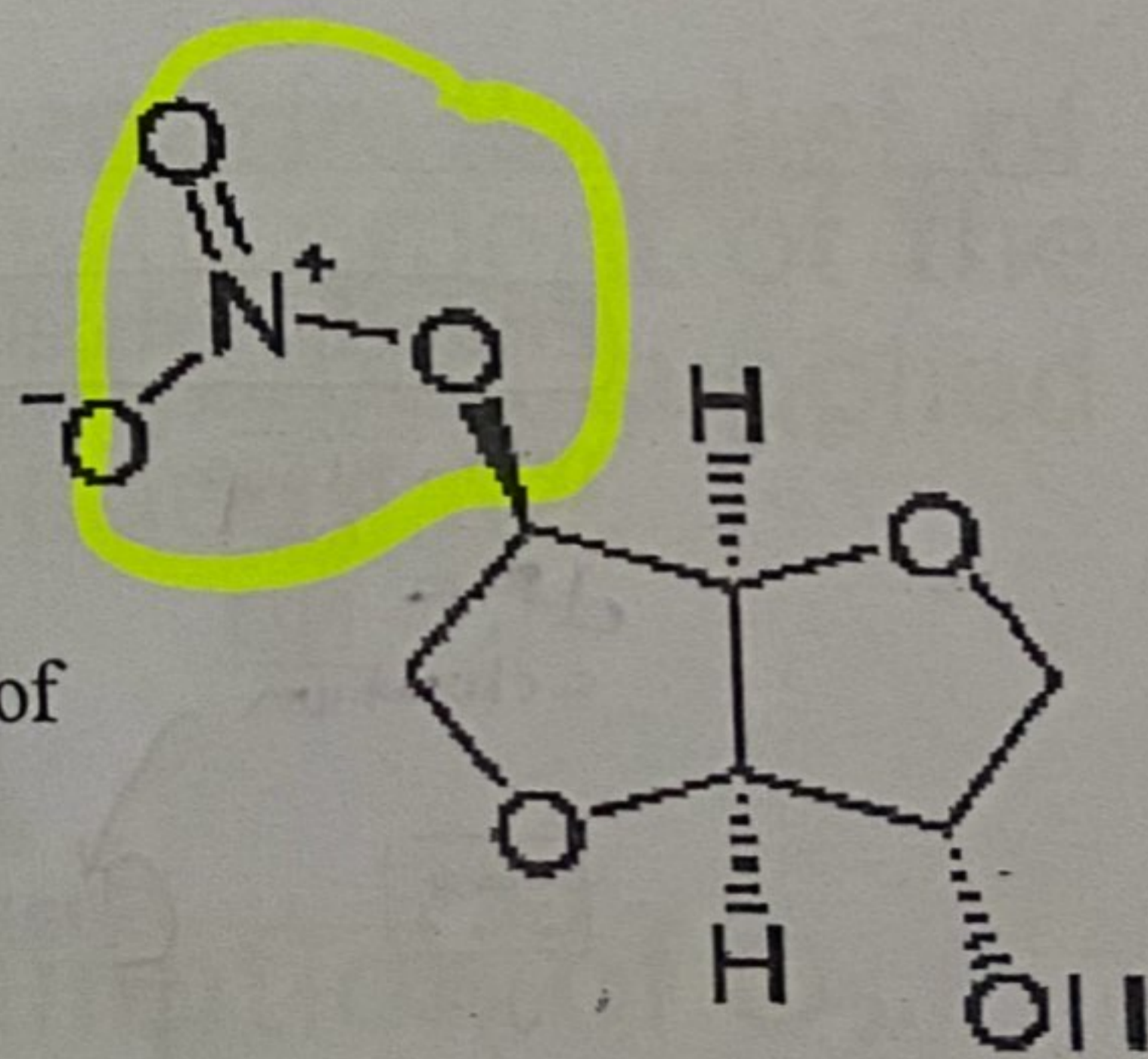
- Mechanism of action: generating nitric oxide.
- Therapeutic uses: decreasing the spasm of coronary arteries. Relax vein so it decreases preload. (Sublingual and oral).
- Gas, quick onset, 5 min duration
- Nitric oxide N_2O
- Nitrous Oxide 2ed msgner



(Isoket)

Isosorbide mononitrate (Elantan)

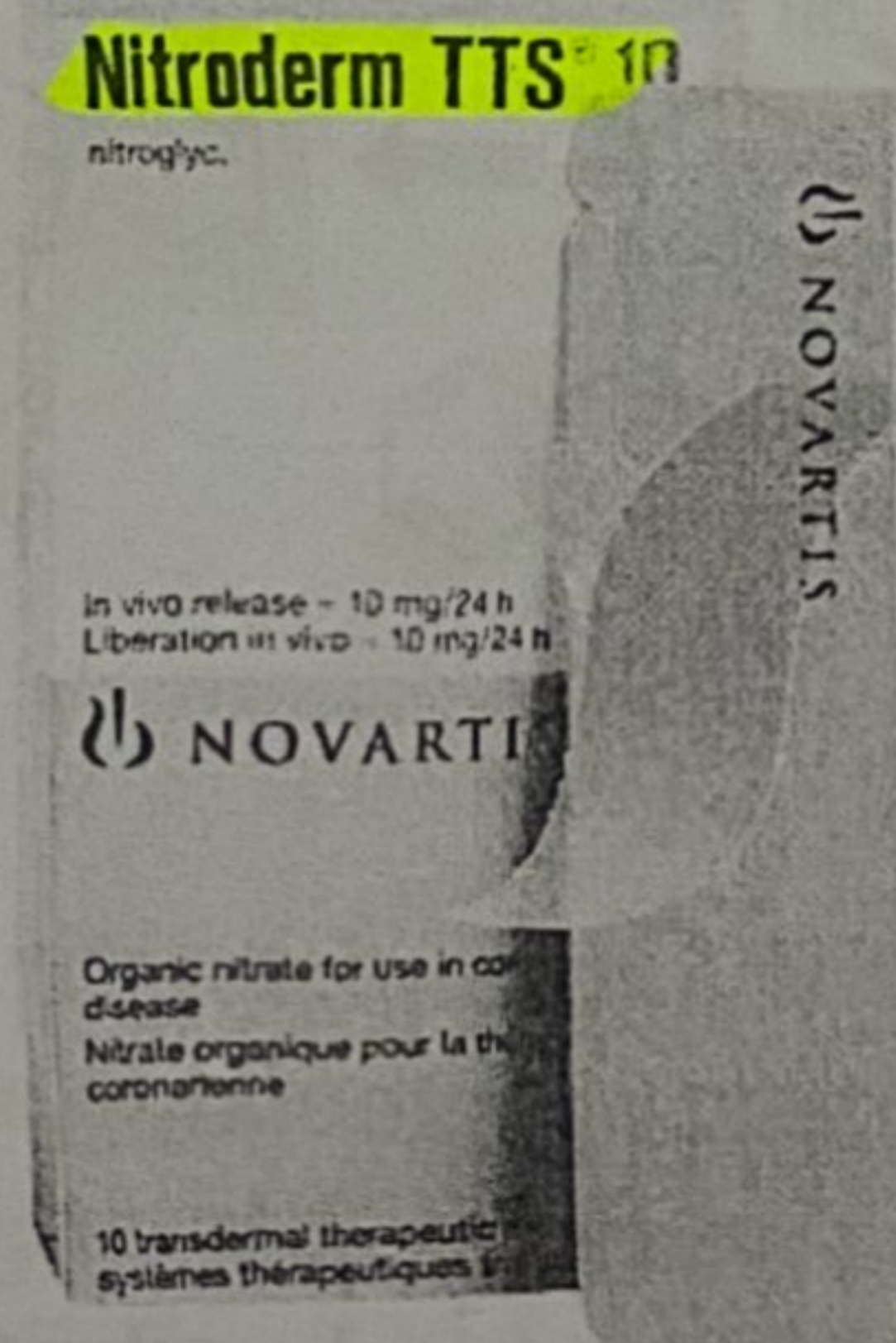
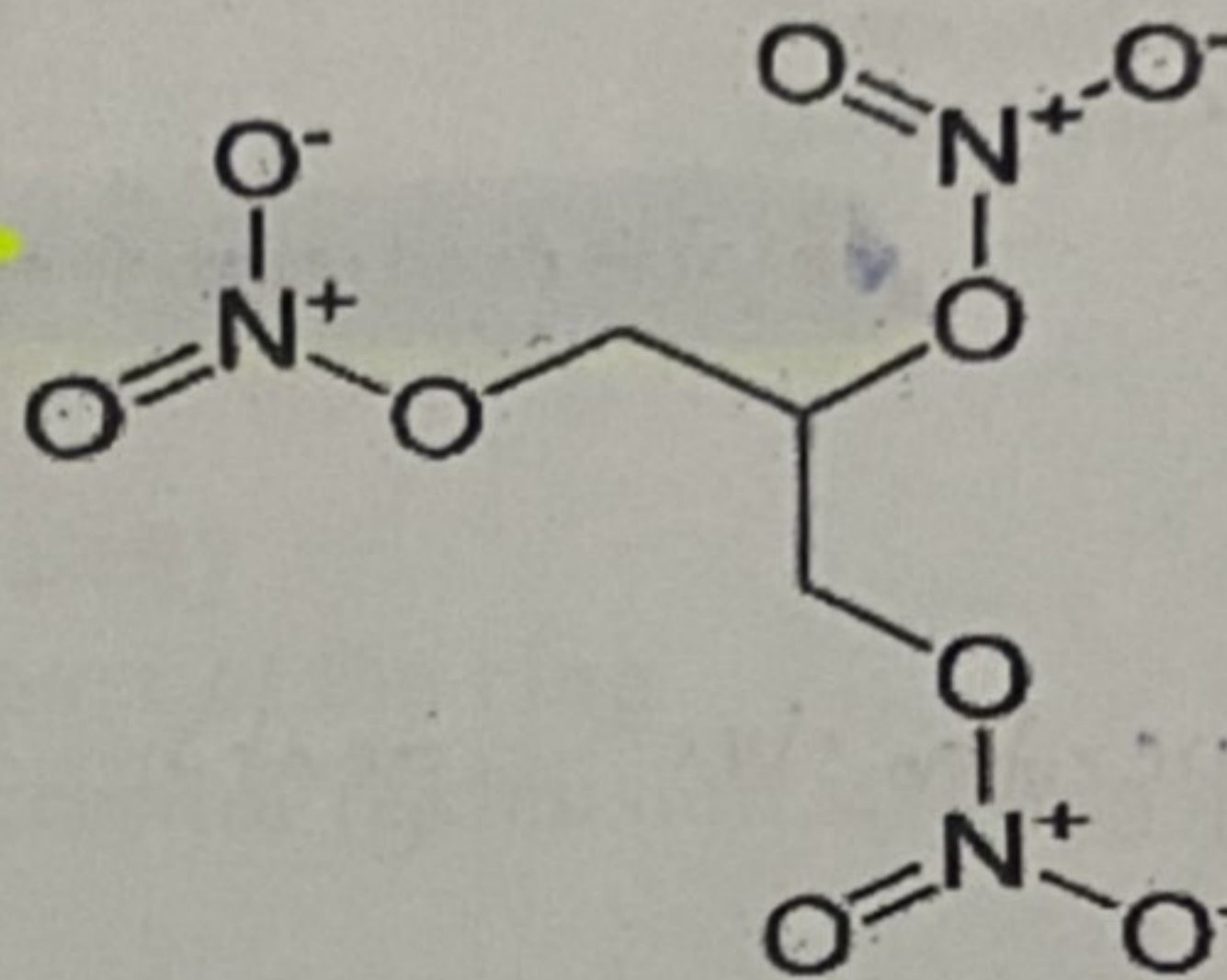
- Mechanism of action:
- Therapeutic uses: only oral route because of slow onset of action (1 hour)



(Elantan)

Nitroglycerin (Nitroderm TTS-10 Nitroderm TTS-5)

- Mechanism of action:
- Therapeutic uses: (Oral, sublingual (2 min) and transderma.
- Gas, rapid onset, short duration.

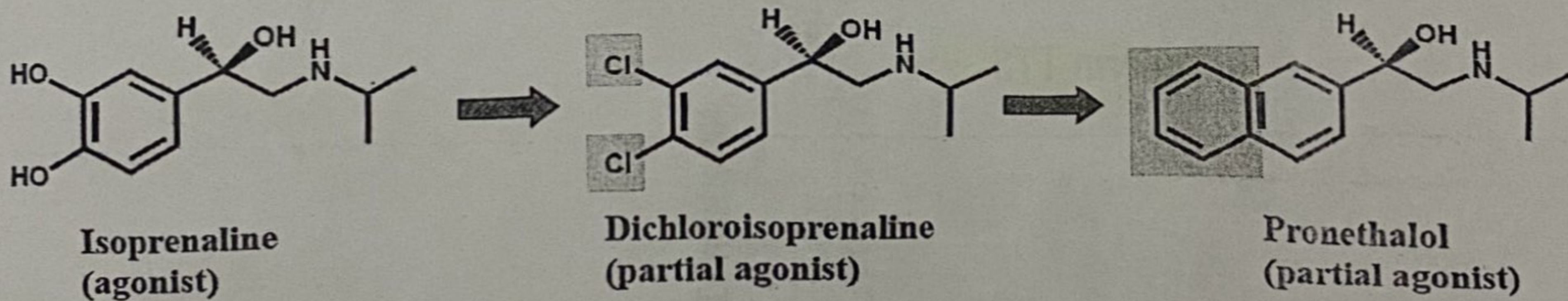


Nitroderm TTS 10
nitroglyc.

مراجعة
اسم الدواء
من حيث
Anti hypertensive agents.

Beta Blockers

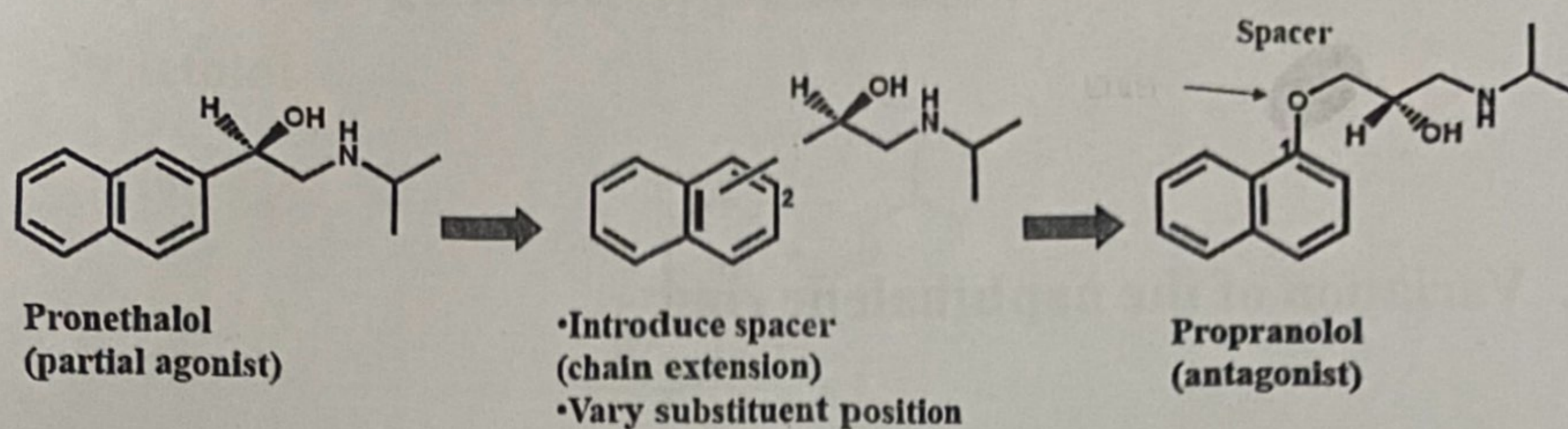
4. Converting an agonist to a partial agonist



Notes

- 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

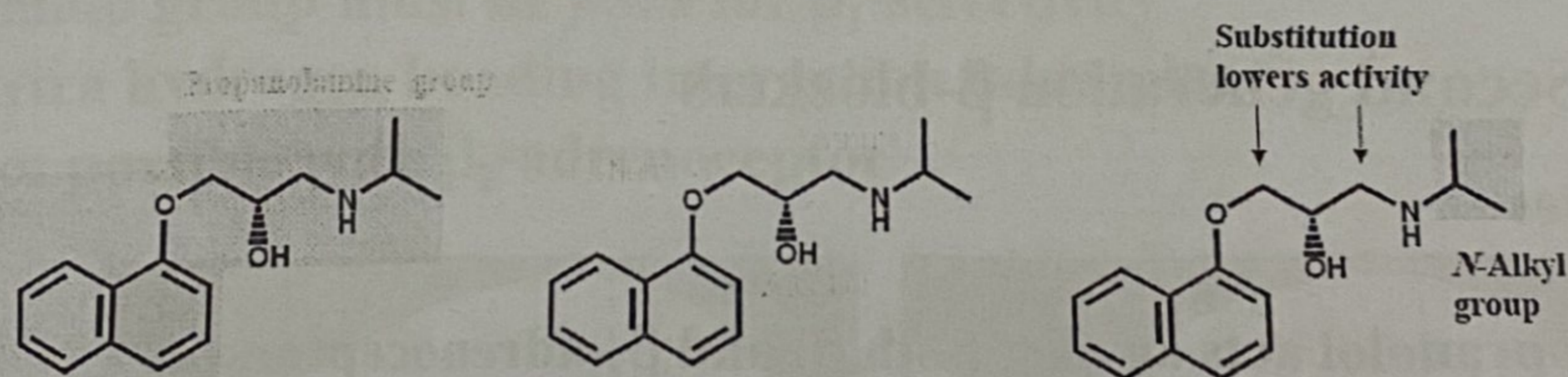
5. Converting a partial agonist to an antagonist



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

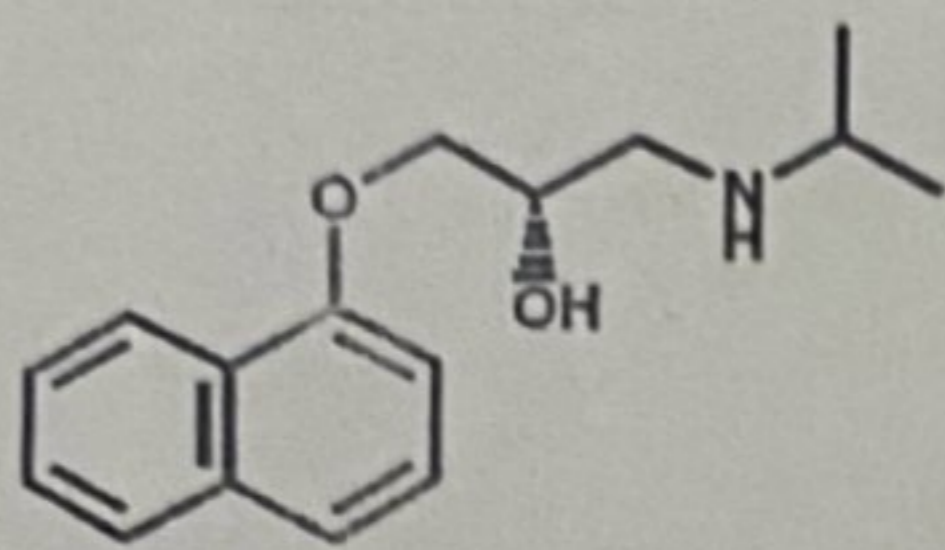
7. SAR on aryloxypropanolamines



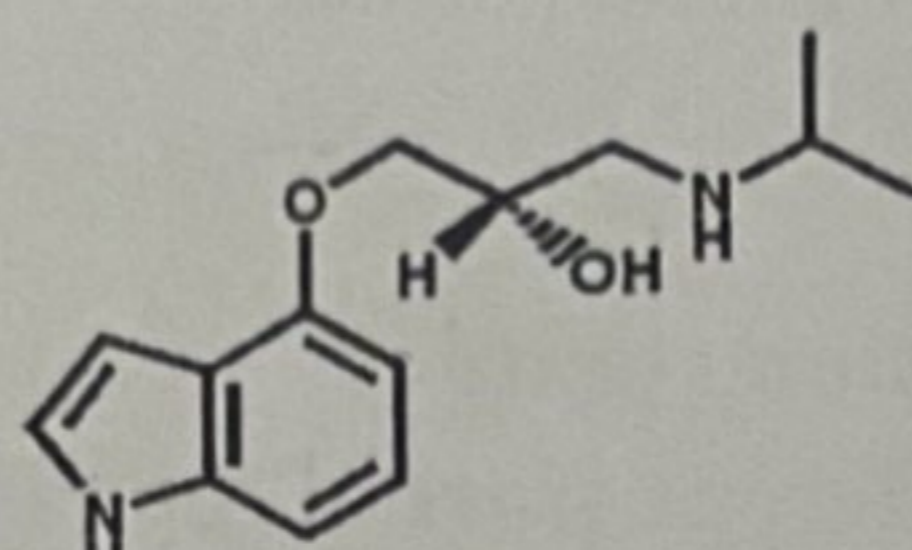
Notes

- Ether acts as a hydrogen bond acceptor
- Ether can be replaced with an alternative HBA (O or NH)
- Alcohol is essential as a hydrogen bonding group
- Amine is ionised and forms an ionic bond with the binding site
- Amine must be secondary
- Naphthalene is replaceable with heteroaromatic rings
- Branched *N*-alkyl group fits a hydrophobic pocket
- Extension of *N*-alkyl group with *N*-arylethyl group is beneficial

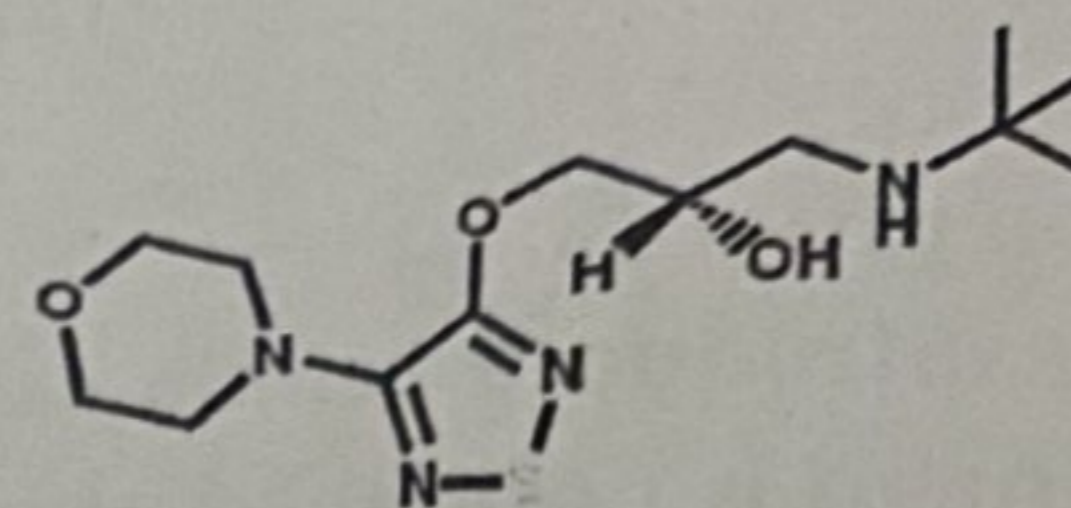
8. Variation of the naphthalene ring



Propranolol



Pindolol



Timolol

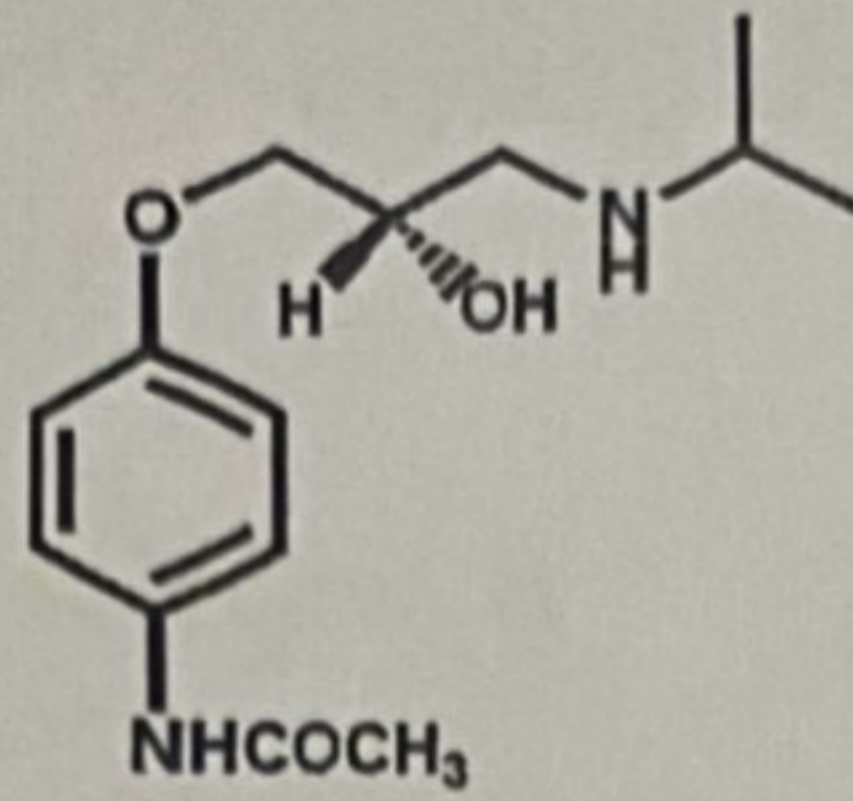
9. Second generation β -blockers

Notes

- Propranolol acts against both β_1 and β_2 -adrenoceptors
- Cannot be used with asthmatic patients
- Antagonism of β_2 -adrenoceptors constricts airways
- Second generation β -blockers are designed to be β_1 -selective

9. Second generation β -blockers

Practolol



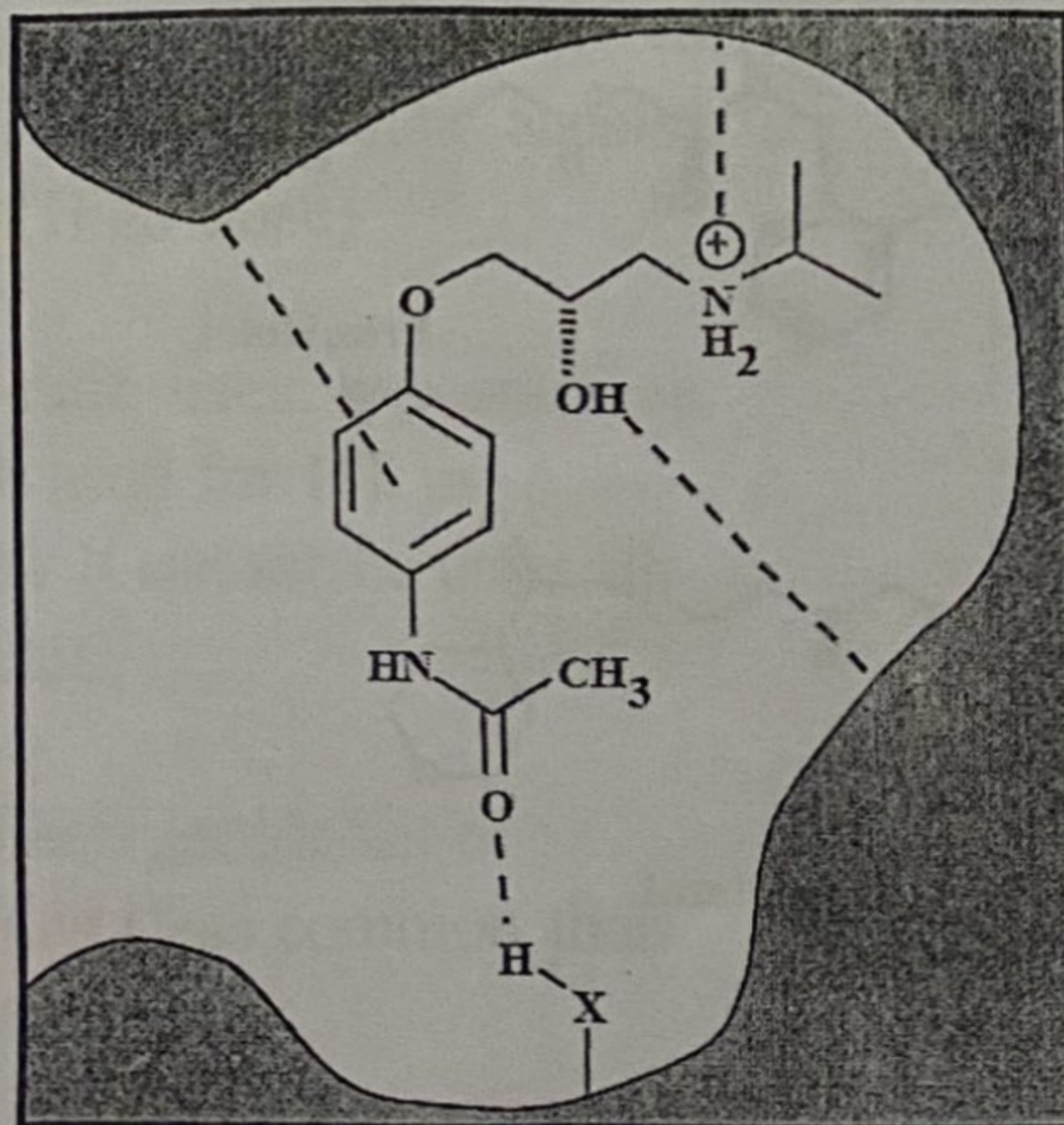
Notes

- Selective cardiac β_1 -antagonist
- More polar
- 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

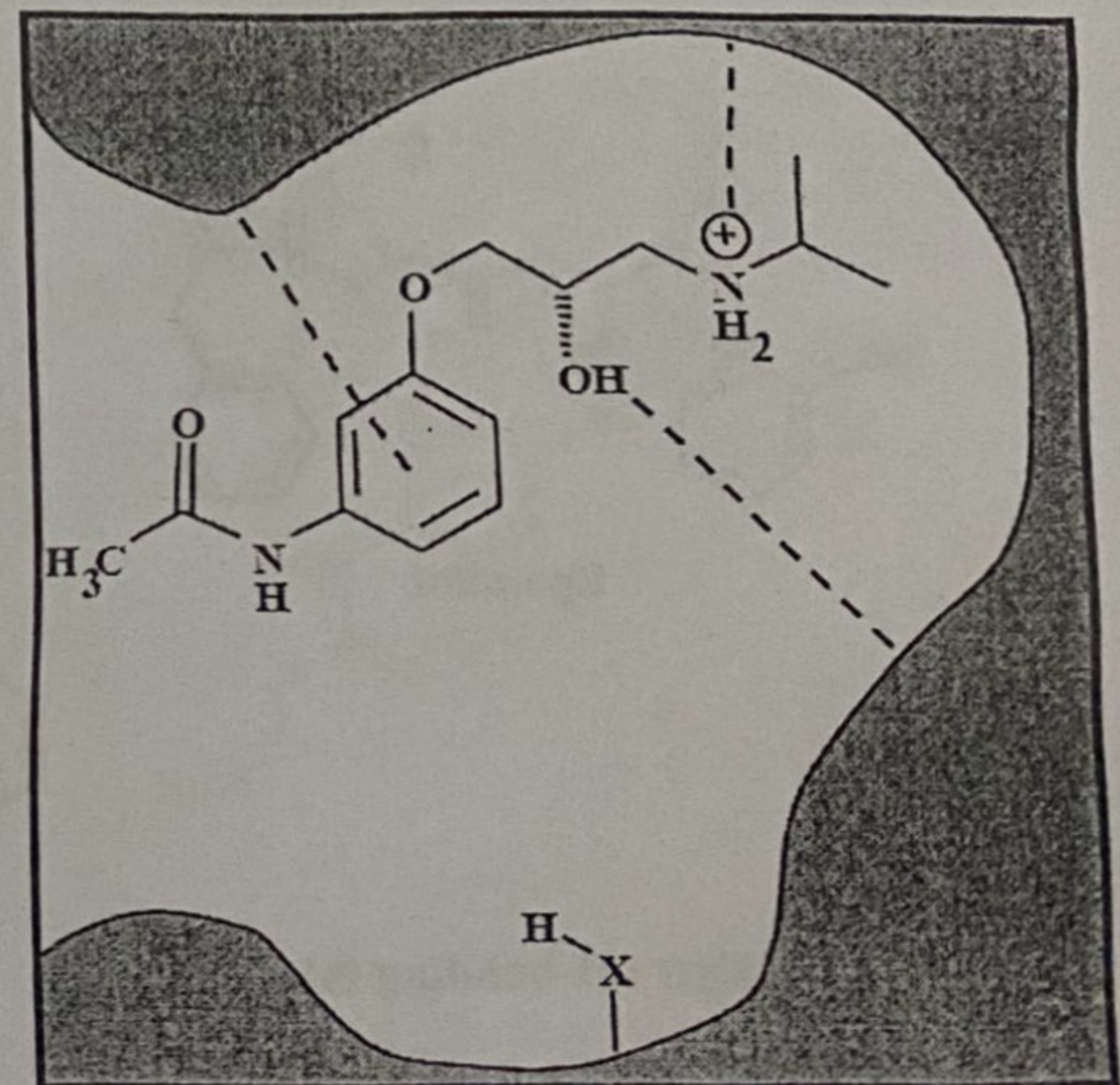
9. Second generation β -blockers

Practolol - binding interactions

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



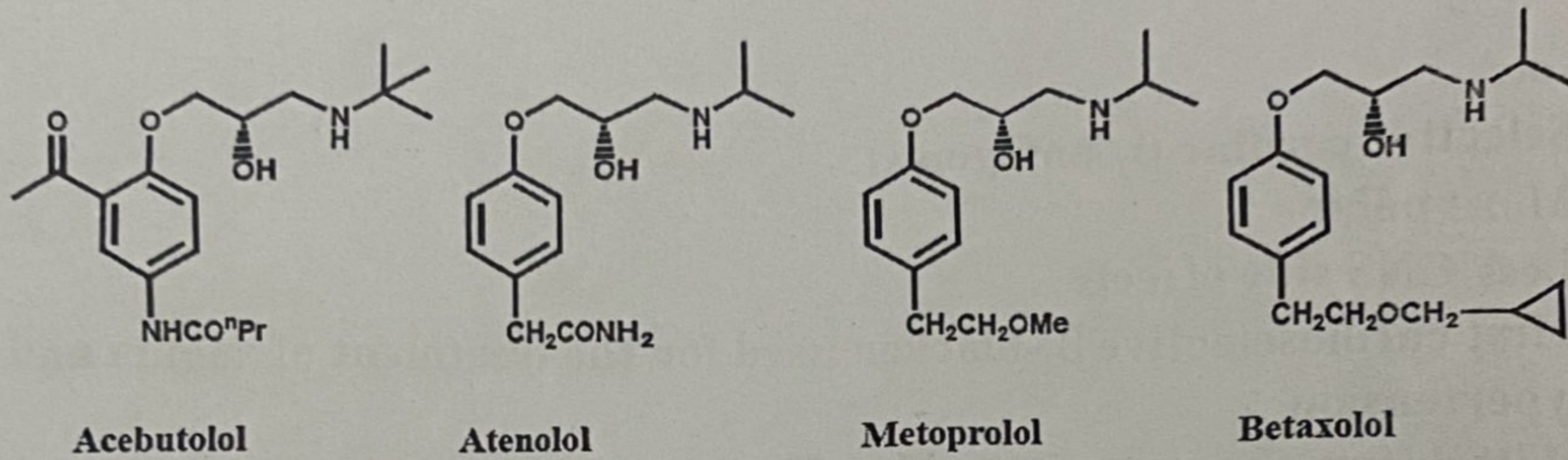
para substitution
Extra H-bonding interaction



meta substitution

9. Second generation β -blockers

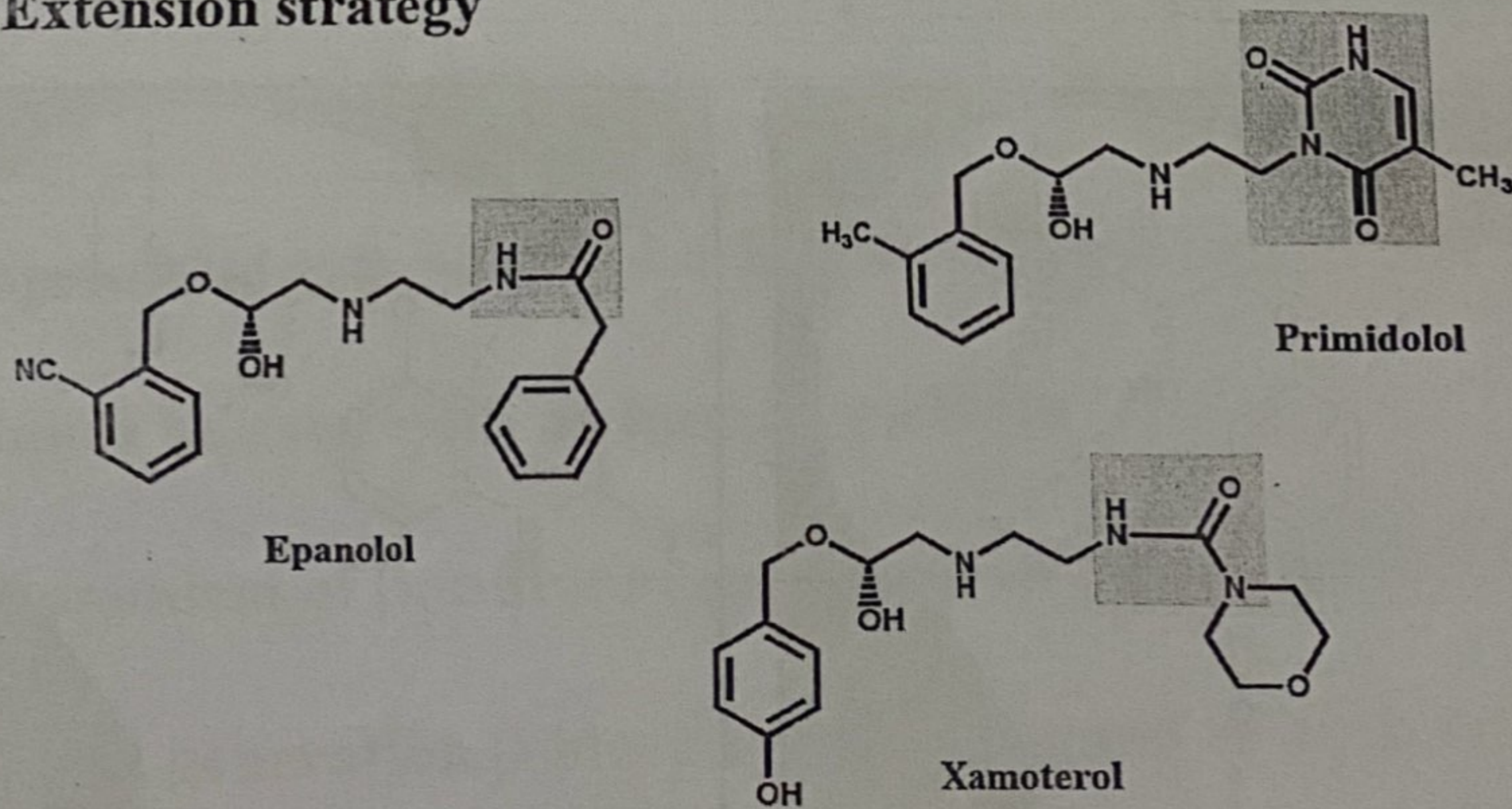
Other agents



10. Third generation β -blockers

Notes

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



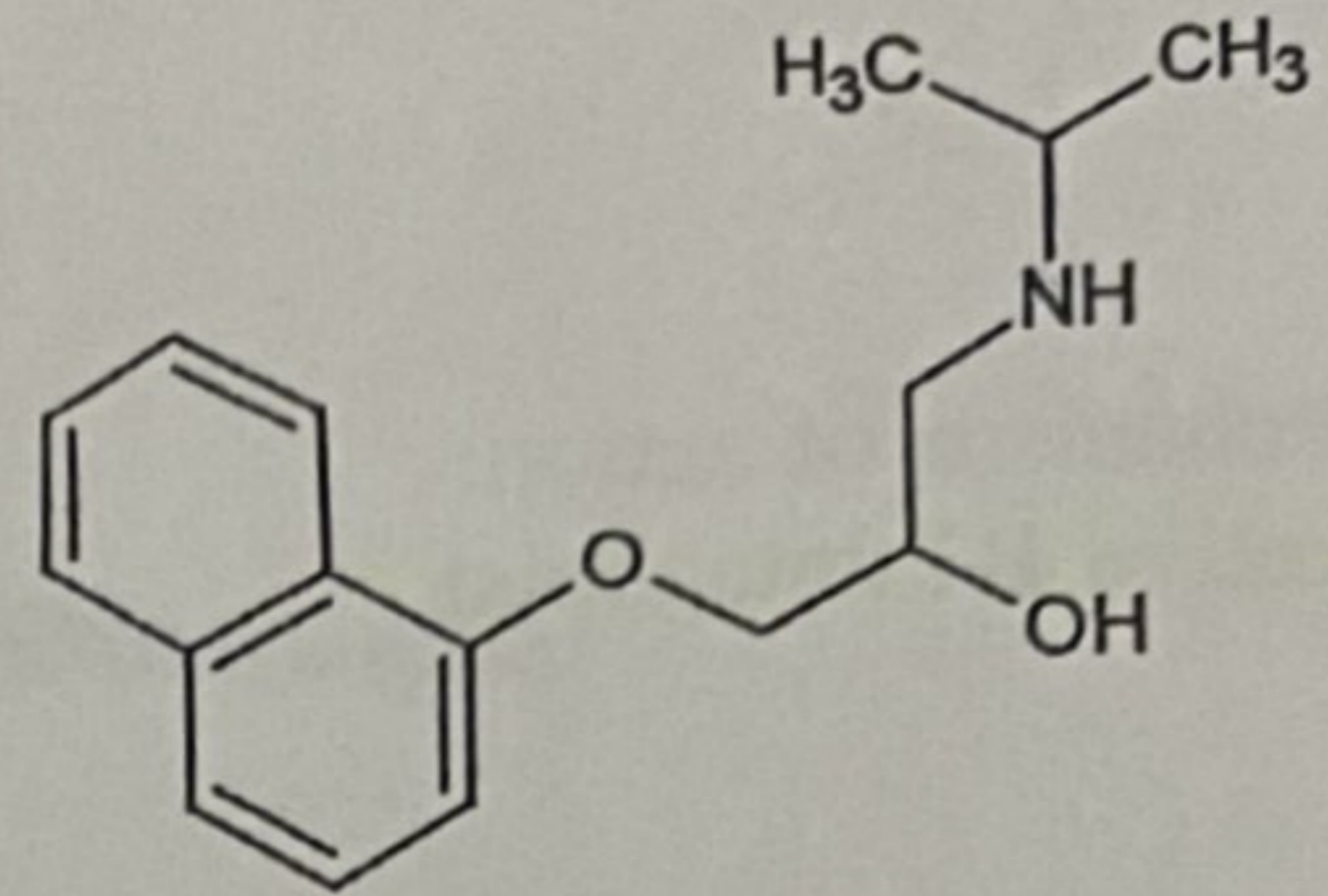
Extra H-bonding interactions

Propranolol (Inderal)

• Mechanism of action: non selective β Blocker

• Therapeutic uses: effect on heart, eye and lungs. Used for migraine, hyperthyroidism

• Side effects: bronchoconstriction, (1)
(2) sexual impairment, increases sodium (3)
retention, (4) masking hypoglycemia, and (5) reduces glycogenolysis

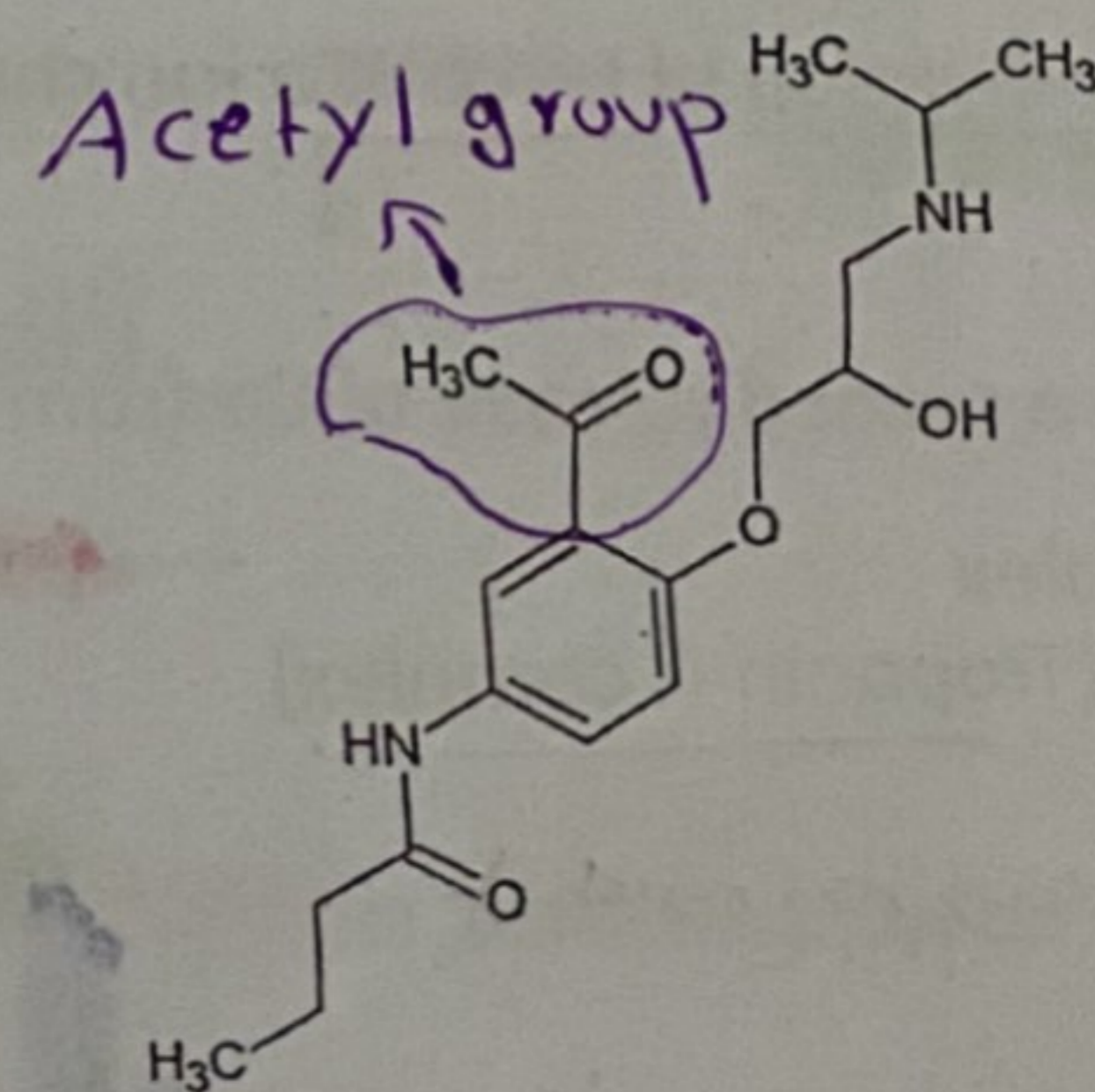


Acebutolol (Sectral)

• Mechanism of action: selective β_1 antagonist with intrinsic agonist activity (High dose)

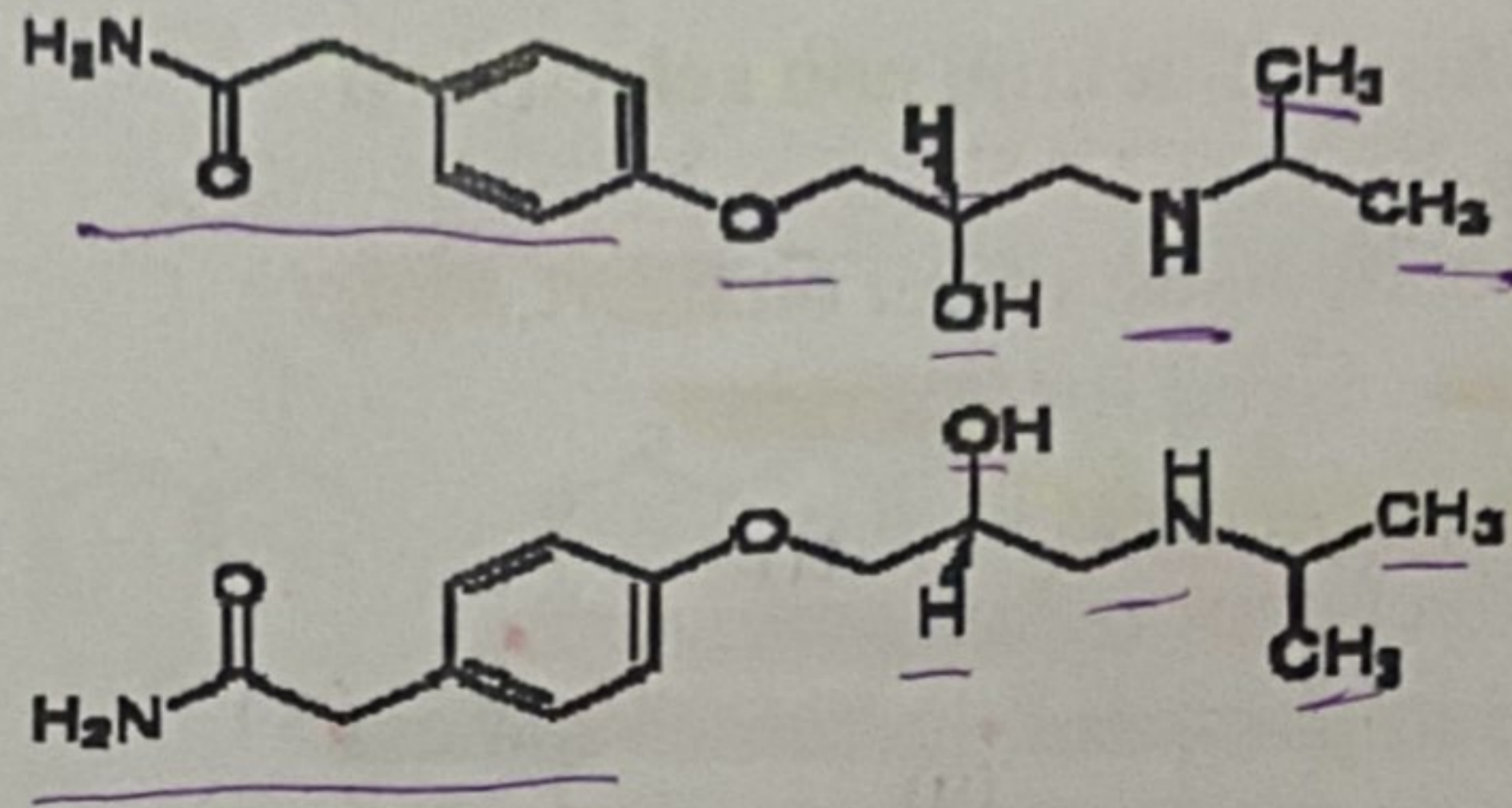
• Therapeutic uses: hypertension
It can be used for HT in diabetics. It cannot be used for Arrhythmia.

• Side effects: coldness of extremities (less common than non selective).



(Atenolol (BLOKIUM Tab.

• Mechanism of action:
selective B1 antagonist



Calcium channel blockers:

تحفيز خلايا إقلىب ببدأ
الانارة من خلاى
تدفق الونائات
غير عشاء جلية

موجود receptors
بعضة إقلىب

Stimulation of cardiac cells initiates excitation through ion fluxes through the cell membrane.

• Depolarization mediates 2 ionic current:

1. Entrance of Na through ion channels rapid process (Phase 0)
2. Slow activation of L-type Ca ion channels that allow the entrance of Ca (Phase 2))

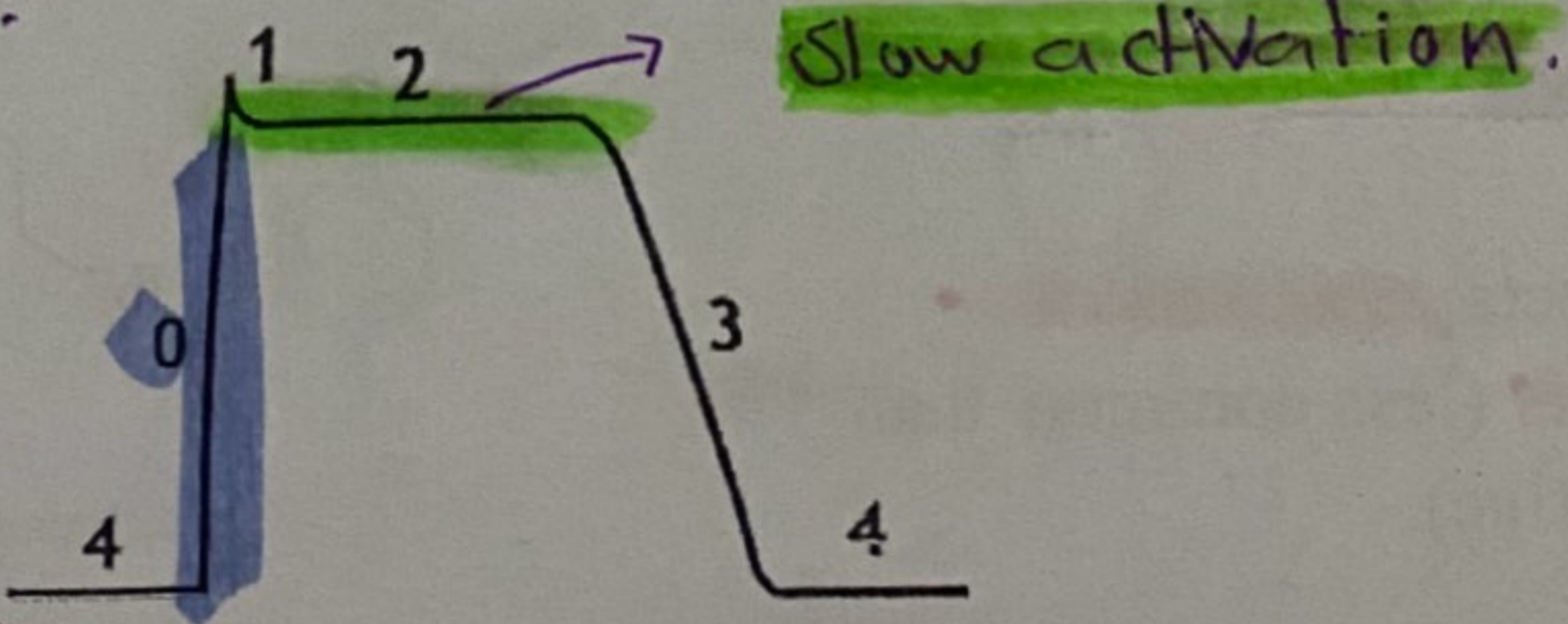
initiate a second release of Ca from the sarcoplasmic reticulum

A complex protein (Troponin-C complex) → contraction.

Depolarization of the heart muscle
ليس يصير عندى

بغيره تمشى الكوار بعضة إقلىب
بصير دخول لـ Na عبر القنوات
وهاد بعضة

Phase (0) → depolarization



Types of Ca channels:

- 1) L-type in skeletal, cardiac & smooth muscles.
- 2) T-type in pacemaker cells.
- 3) N-type in neurons.
- 4) P-type in Purkinje cells.

Note: L-type channel is composed of 5 subunits ($\alpha_1, \alpha_2, \beta, \gamma, \delta$)

Ca channel blockers (prototype drugs):

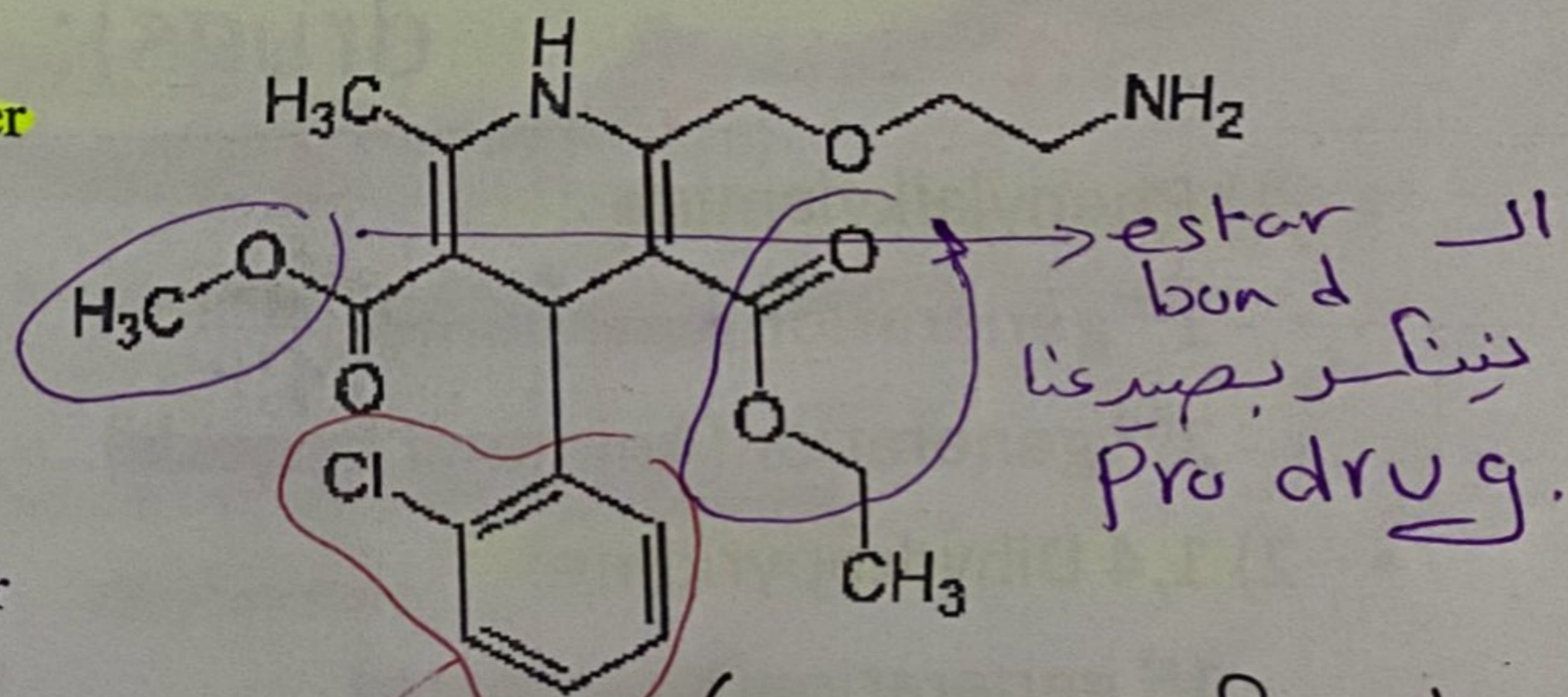
- 1) Phenylalkylamines:
 - 1st generation (Verapamil).
 - 2nd generation (Anipamil, bepridil).
- 2) 1,4 Dihydropyridine:
 - 1st generation (Nifedipine)
 - 2nd generation (Amlodipine, Felodipine, Nicardipine, Isradipine, Nimodipine).
- 3) Benzothiazepine:
 - 1st generation (Diltiazim).

Generally CCB are used:

- 1) As vasodilators.
- 2) To ↓ artery muscle tone.
- 3) To ↓ peripheral arteriole resistance.
- 4) Have cardiac actions
 depress the cardiac neuronal network decrease myocardial contractility.
- 5) Reduce peripheral vascular resistance.

Amlodipine (Amlodar Cap)

- Mechanism of action: greater affinity for Ca channels of vascular system than the heart's
- Therapeutic uses: used also for hypertension, intrinsic natriuretic effect (no need for diuretic)
- Side effects: constipation, oedema and fatigue.
- Prodrug? Yes
- Why long duration? ~~because~~

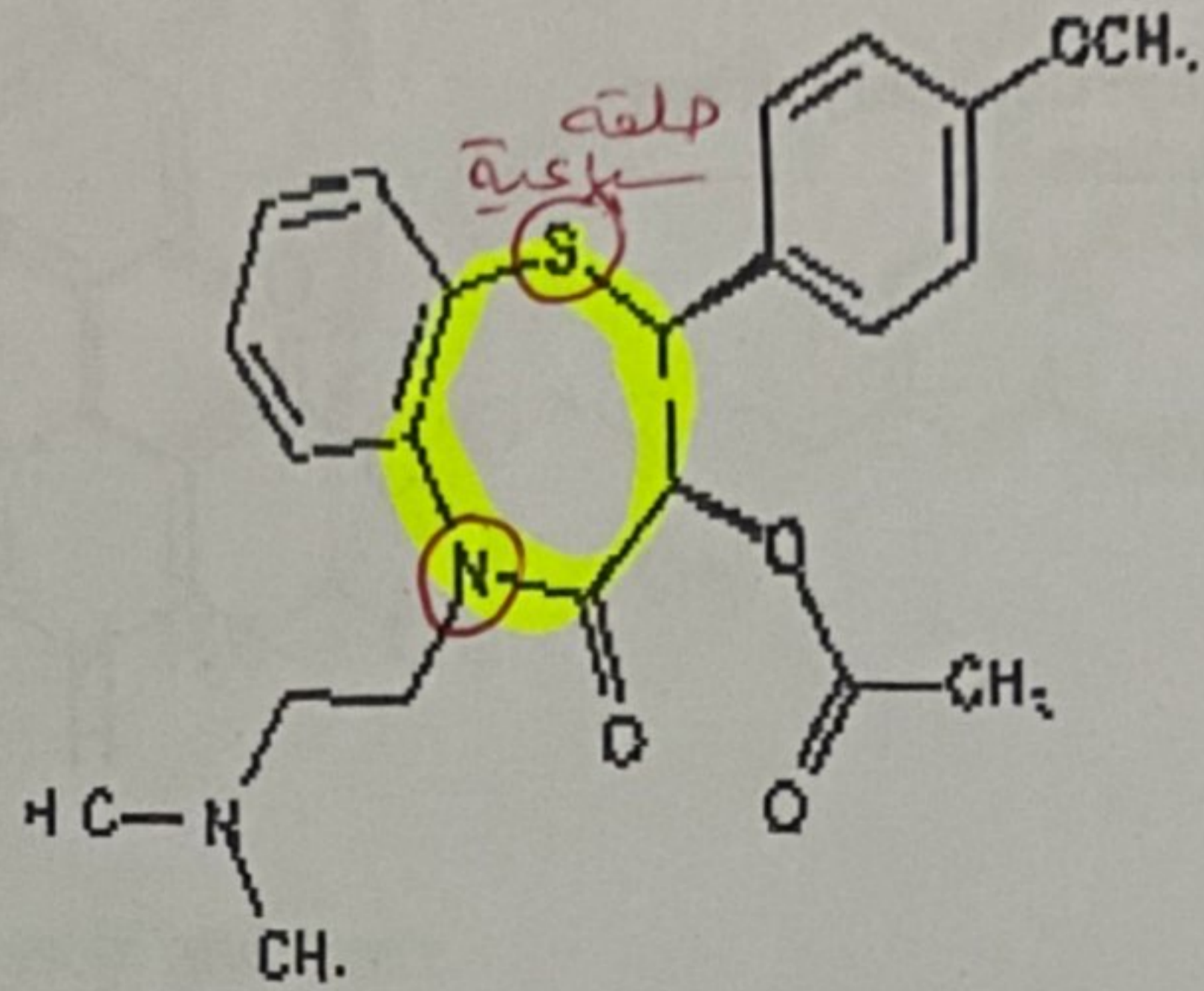


(no need for diuretic)

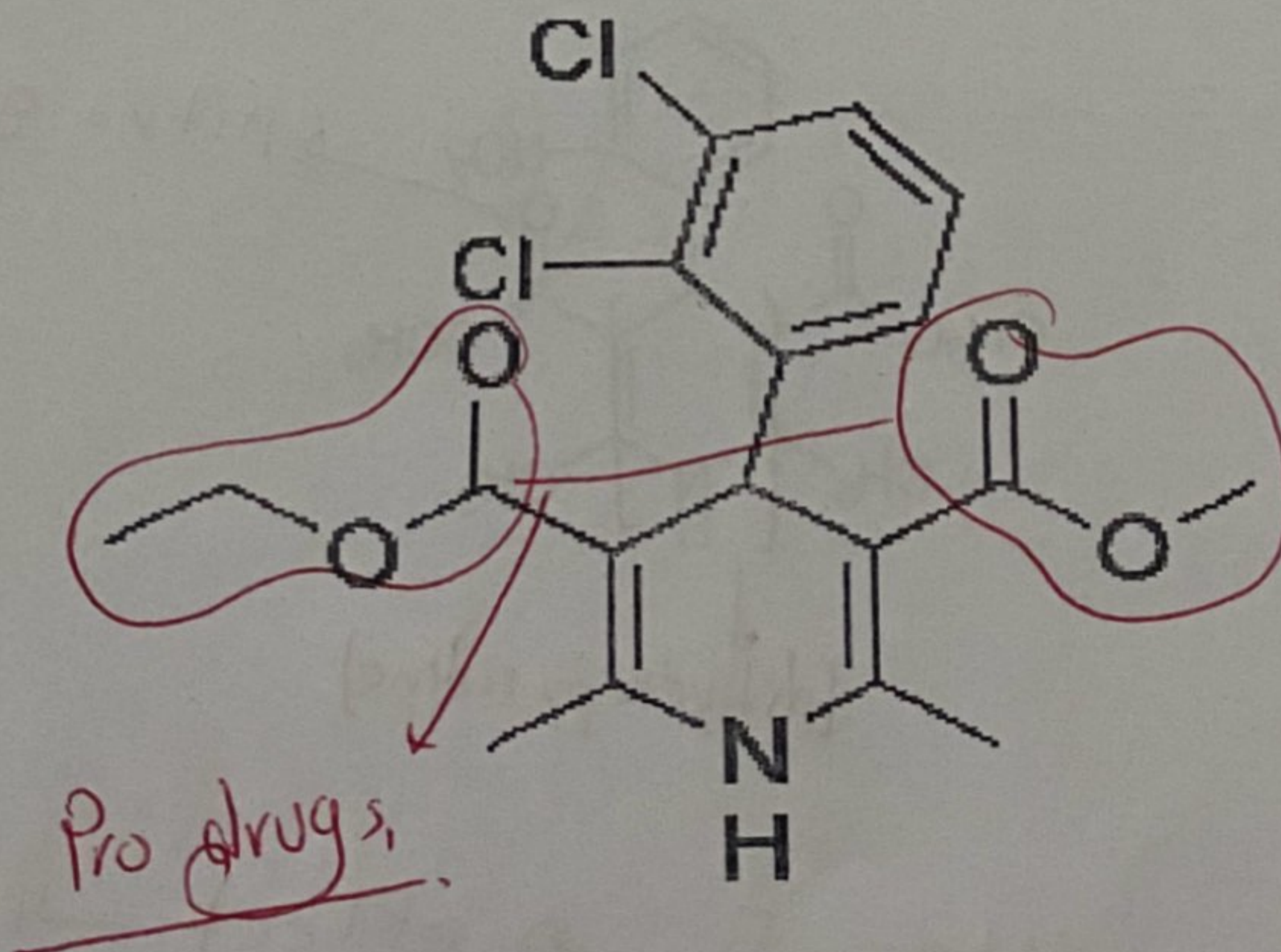
لأنه هو دواء طويل المفعول
 لأنه فترة طويلا في الجسم

Diltiazem (Cardizem)

- Mechanism of action: affect both vessels and heart.
- Non-dihydropyridine benzothiazepine

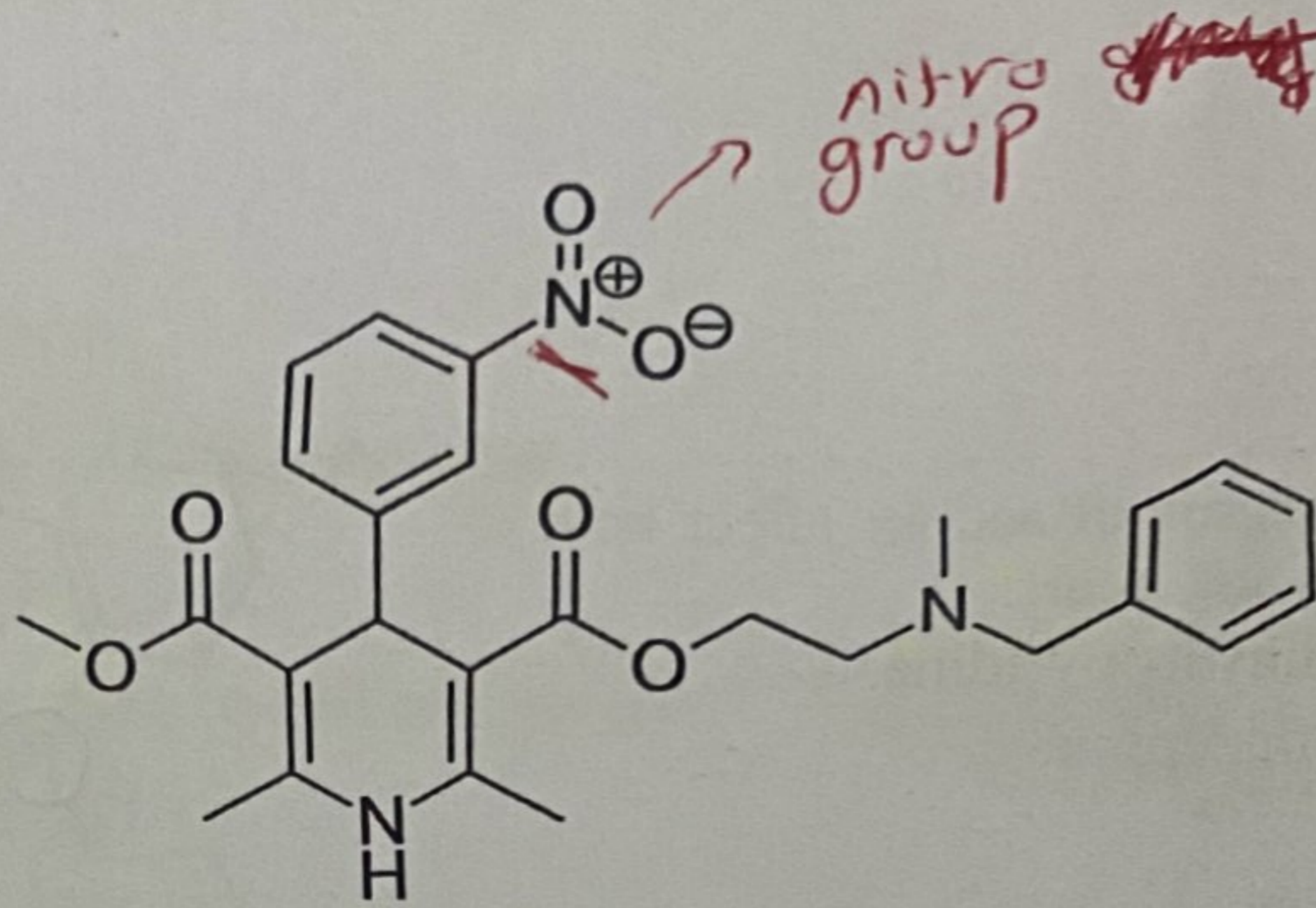


Felodipine (PLENDIL TAB)



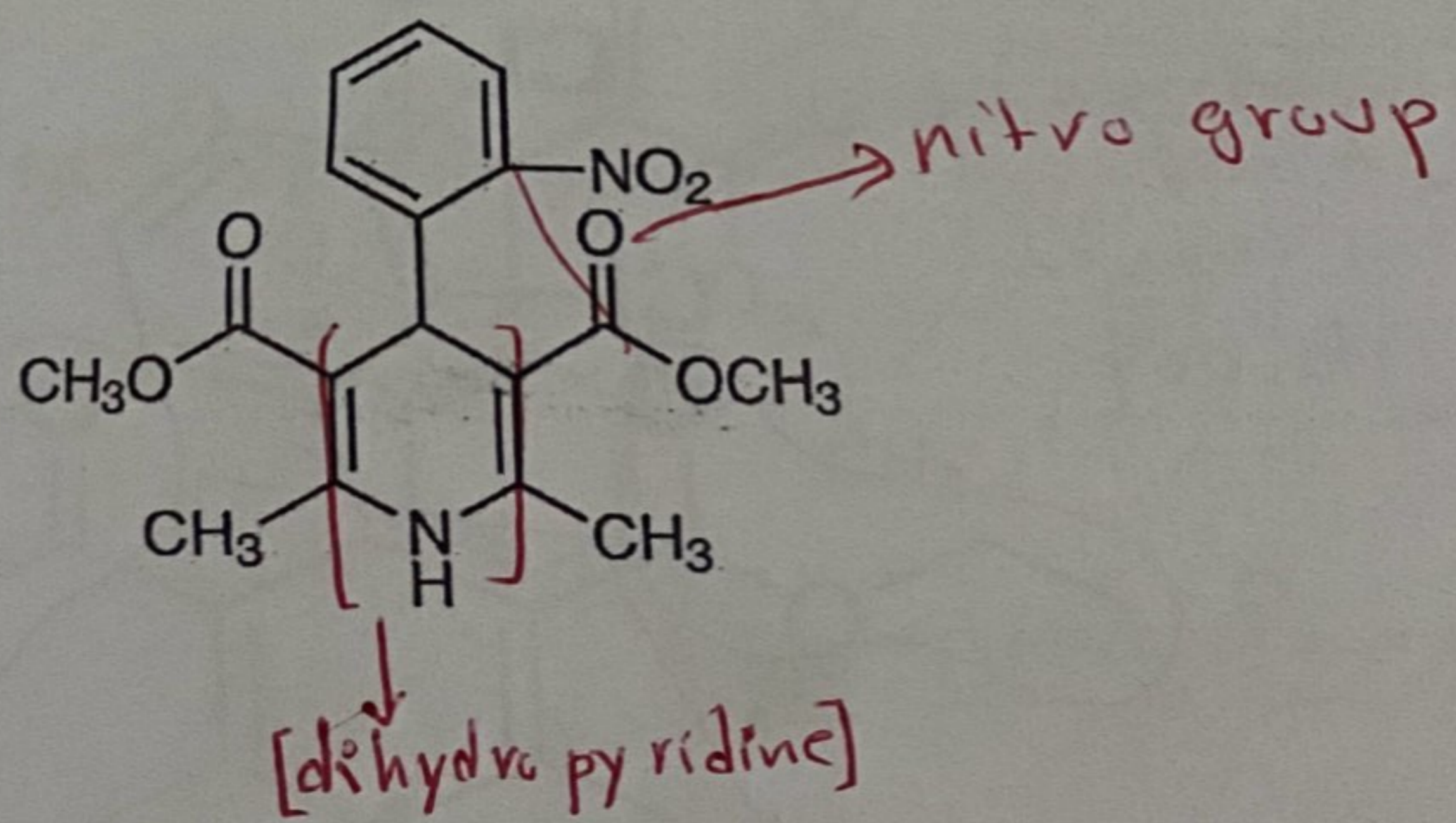
Nicardipine

Nitro group: Coronary artery vasodilatation



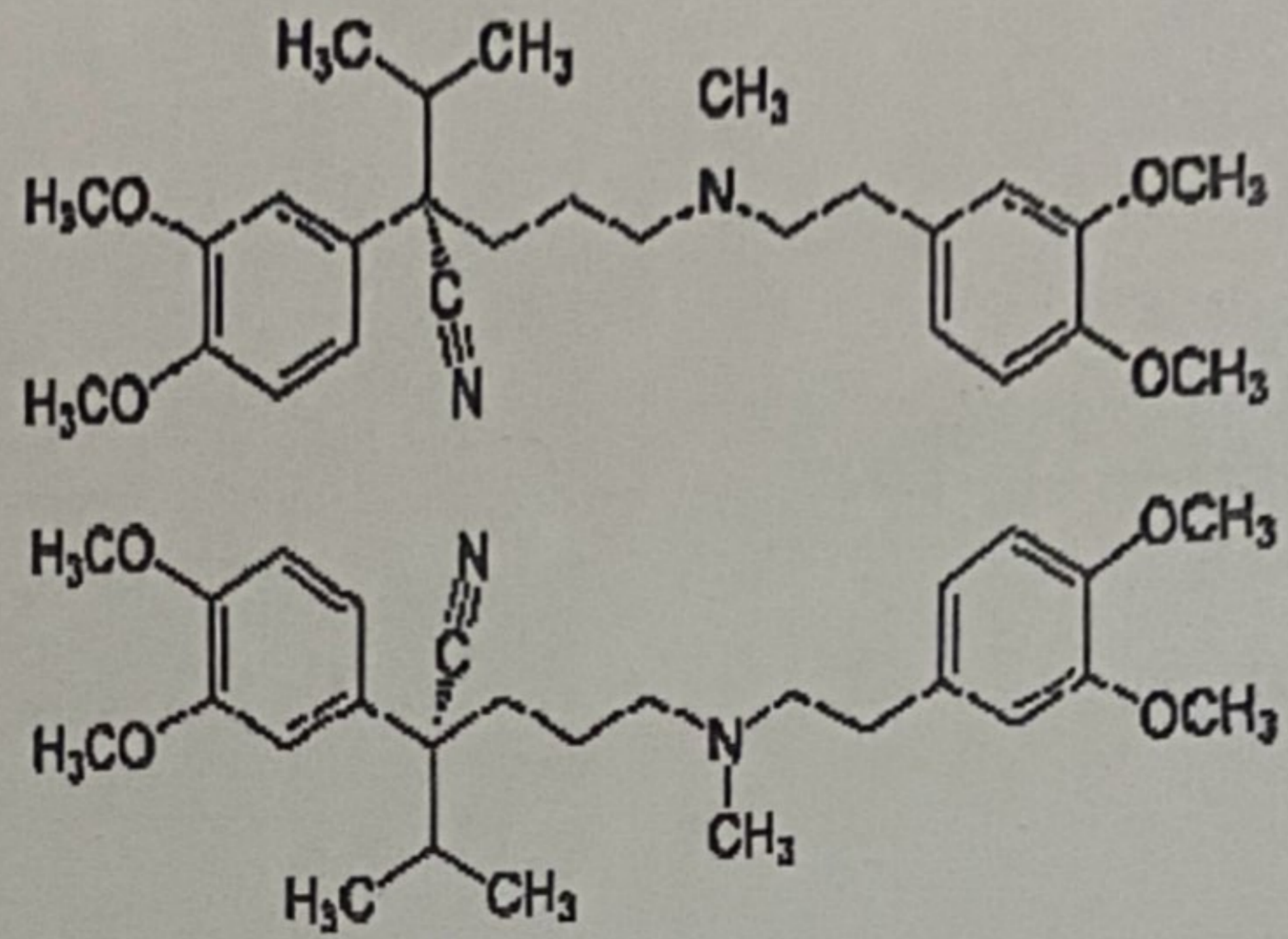
Nifedipine (Adalat)

Nitro group



ال effect هون تكون مضاعف .

Verapamil (ISOPTIN)



- phenylalkylamine
- Mechanism of action: affect both vessels and heart.

برياس الشويكة