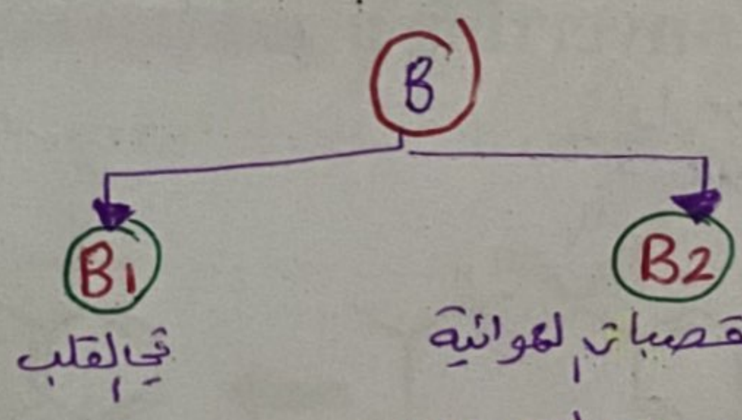
Anti-hypertensive agents

- Angiotensin converting enzyme inhibitors (ACE inhibitors).
- Calcium channel blockers.
- Adrenergic inhibitors:
  - Catecholamine storage and release inhibitors...reserpine and guanethidine.
  - β-blockers such as propranolol.
  - α_1-receptor antagonist such as pentazocin.
- Direct acting vasodilator…such as hydralazine and sodium nitroprusside.
- Angiotensin II receptor antagonists…such as losartan.

Beta Blockers



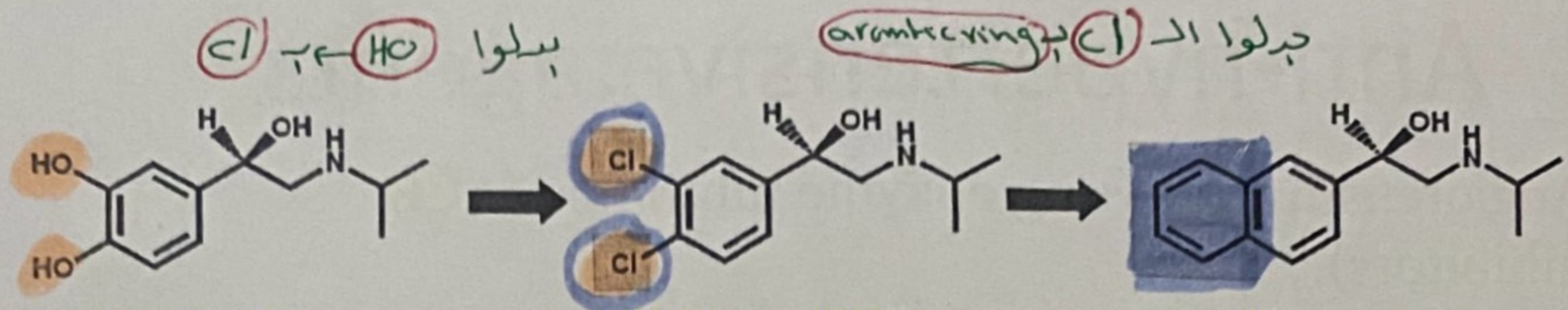
*agonist: تفتح القصبات الهوائيه وتزيد عدد دقات القلب

رح ناخد agonist حتا حدا يأثر ع B2 لعلاج الأزمة بدون ما يأثر ع عضلات القلب

*لحتى نعالج ضغط الدم لازم نعمل block→B1 لحتى ما يأثر ع التنفس

مثال هام:- في عليه تطوير antagonist يزيد الـ Van der Waals

4. Converting an agonist to a partial agonist



Isoprenaline (agonist) ← Agonist كان هاد وما كان في فرق بين B2 / B1

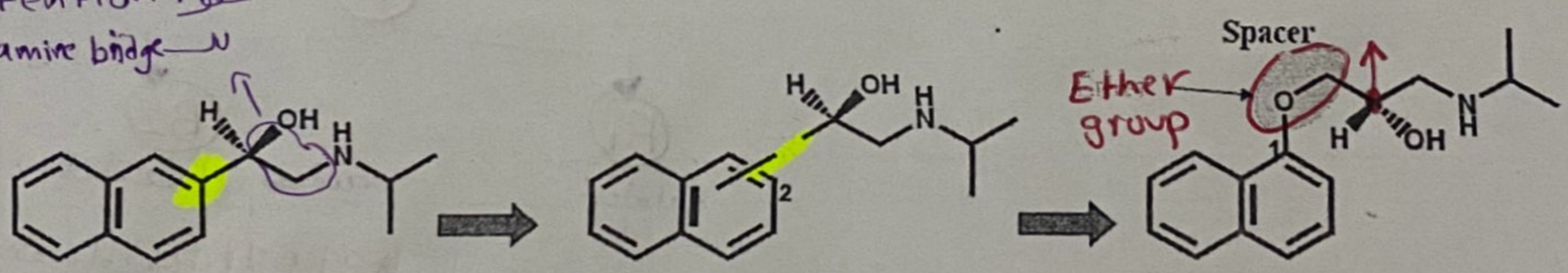
Dichloroisoprenaline (partial agonist)

Pronethalol (partial agonist) * صار عنده Hydrophobic أكتر و Van der Waals أكتر

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 :–
  1. - weakly activate receptors
  2. - block natural messenger

5. Converting a partial agonist to an antagonist



Pronethalol (partial agonist)

- Introduce spacer (chain extension)
- Vary substituent position

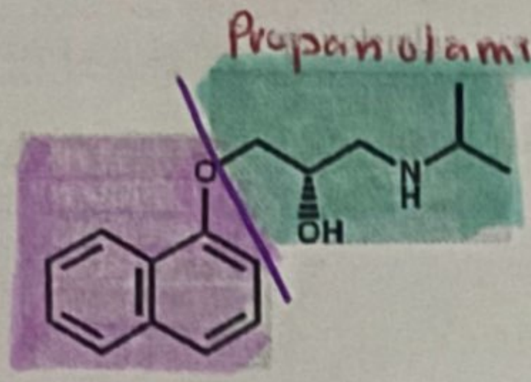
Propranolol (antagonist) → Inderal

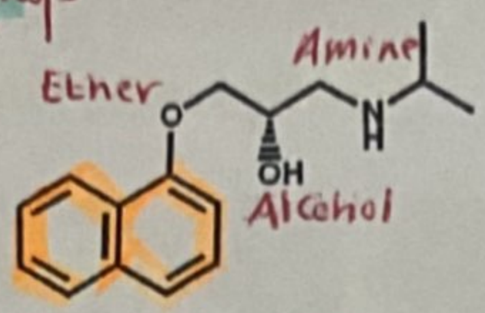
Notes on propranolol

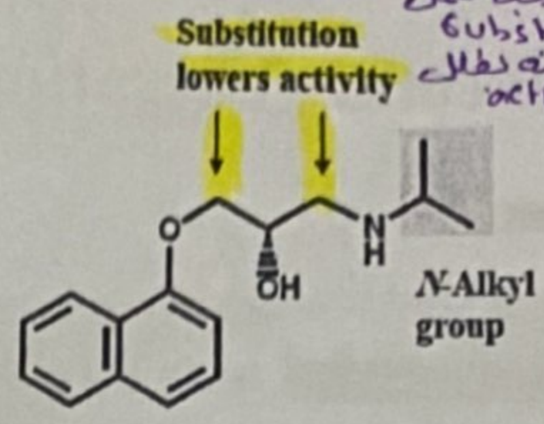
- Spacer introduced - chain extension strategy
- Substituent is positioned at a different part of the ring
- Ether group acts as a hydrogen bond acceptor (extension strategy)
- 10-20 times greater antagonist activity
- Used clinically as a racemate
- S-Enantiomer is the active enantiomer
- Aryloxypropanolamine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

(B_2/B_1 هاي هي مشكلة حاجزين)

7. SAR on aryloxypropanolamines



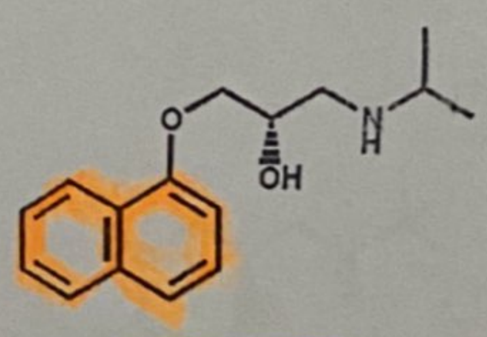


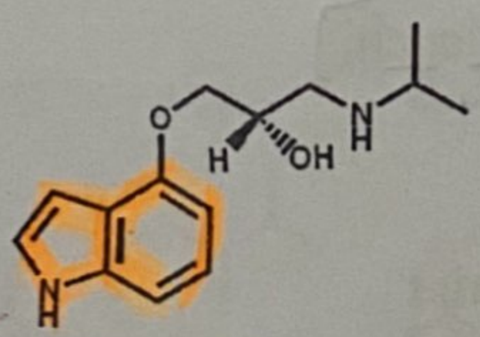


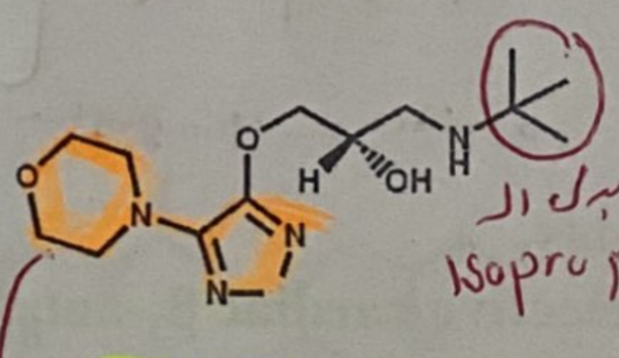
Notes

- **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 replacable 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







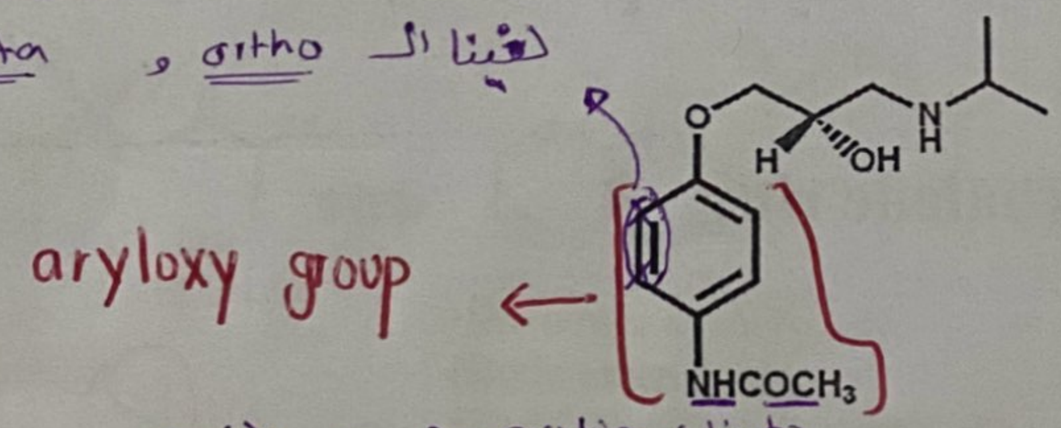
9. Second generation β-blockers

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



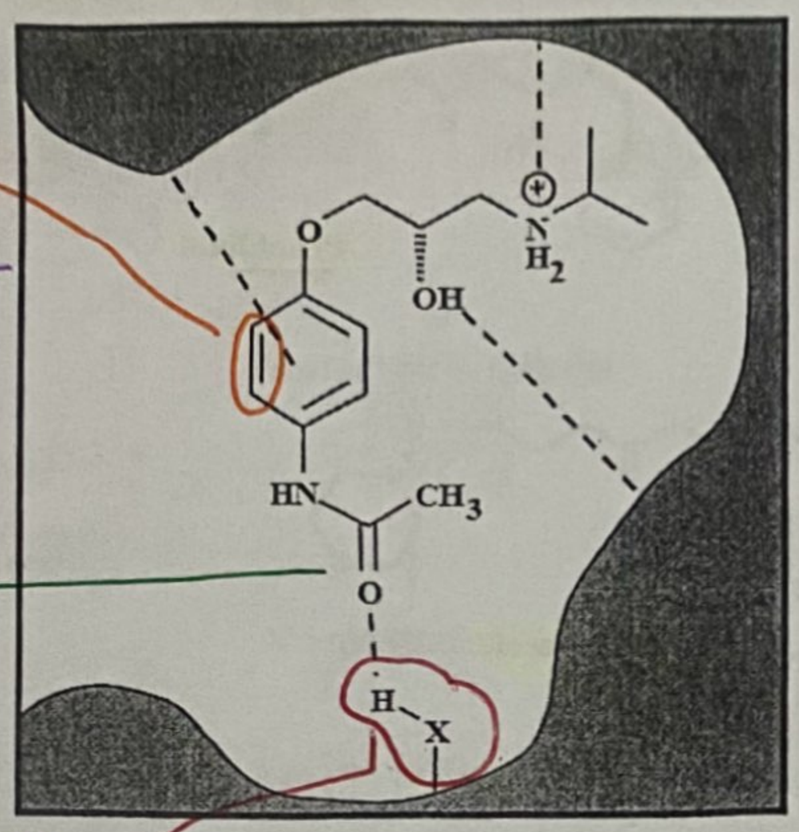
Notes

- **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**

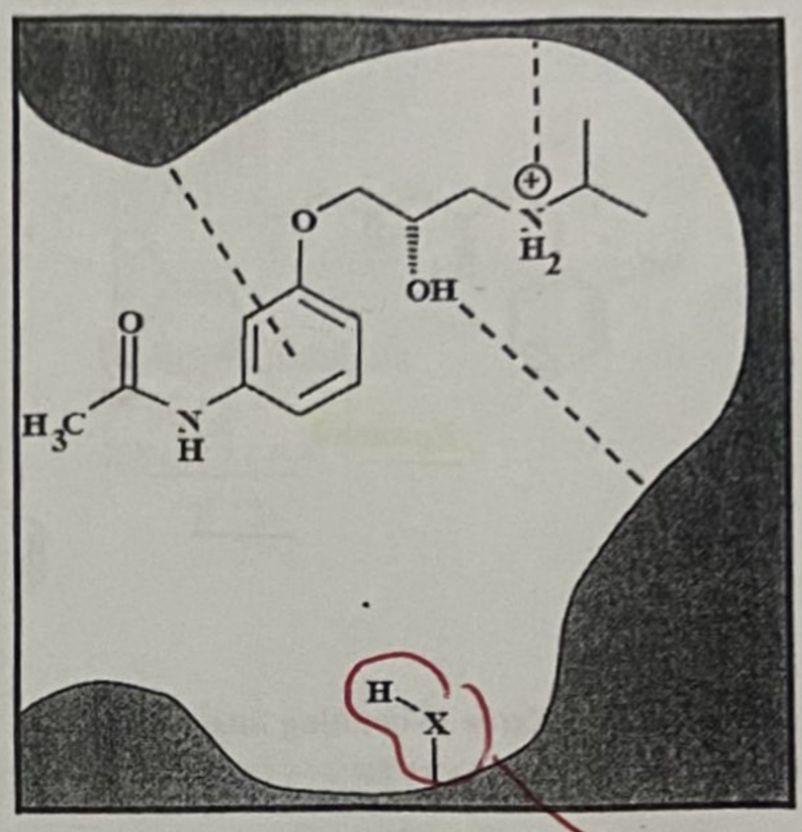
9. Second generation β-blockers

Practolol - binding interactions

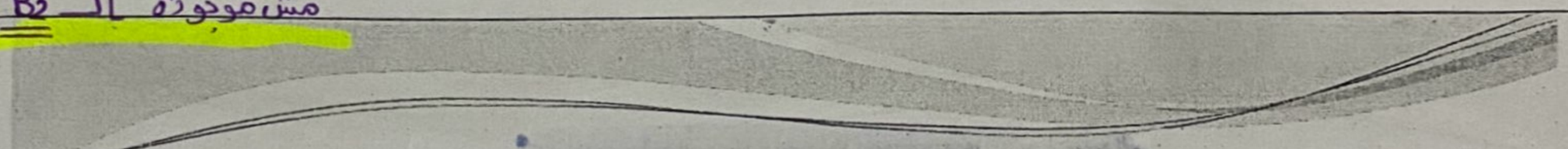
- **Amido group must be *para* for β_1-selectivity**
- **Extra hydrogen bonding interaction takes place**
- **Not possible with β_2-adrenoceptor**



para substitution
Extra H-bonding interaction

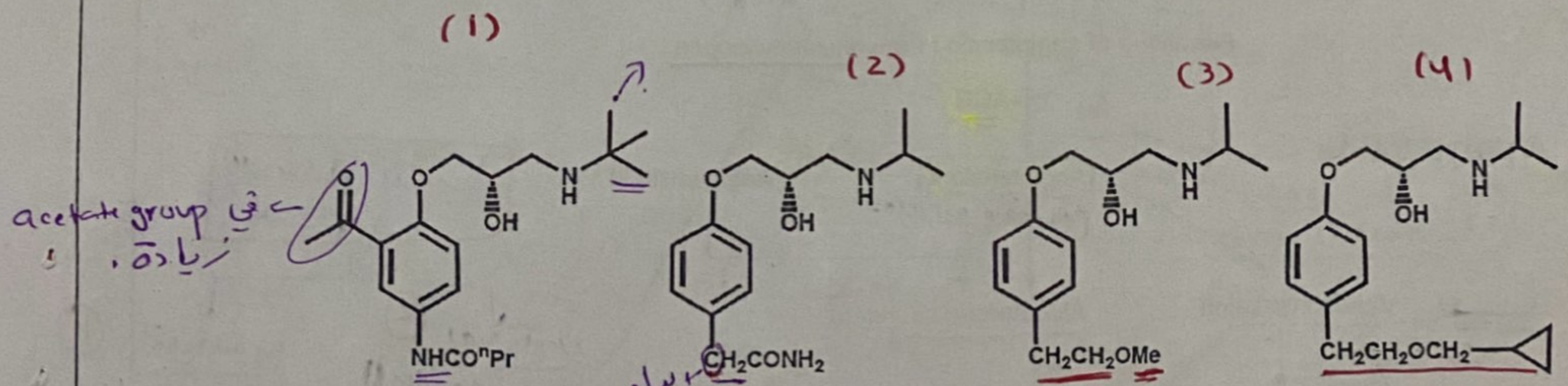


meta substitution



9. Second generation β-blockers

Other agents

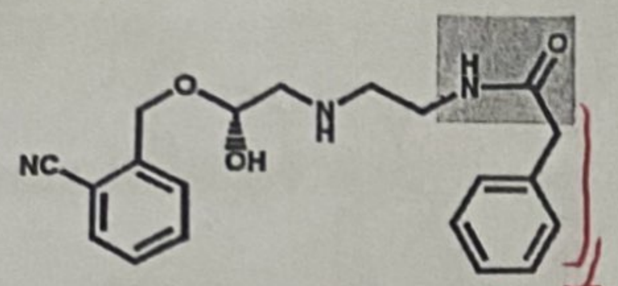


Acebutolol **Atenolol** **Metoprolol** **Betaxolol**

10. Third generation β-blockers

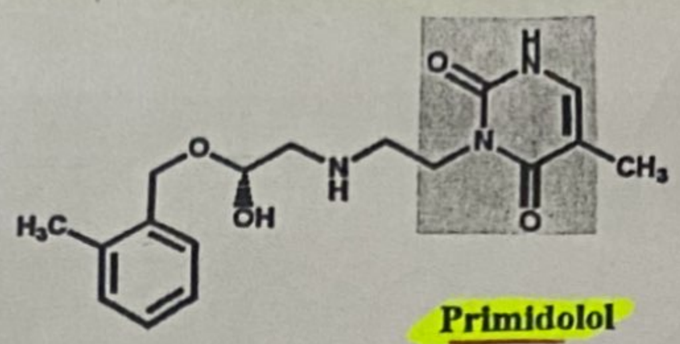
Notes

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

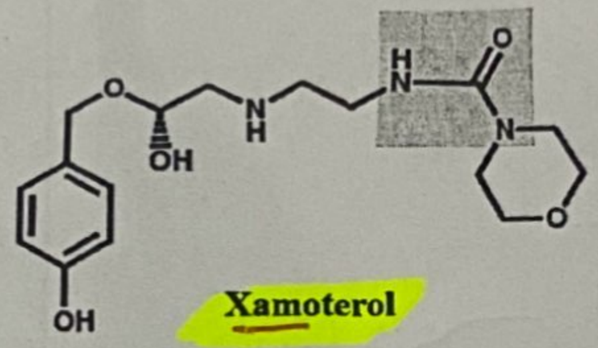


Epanolol

اضافه
Arylalkyl
group



Primidolol



Xamoterol

Extra H-bonding interactions

ACE inhibitors

Reduced blood pressure

lowered sodium excretion

Renin release from kidneys (Renin is an aspartate protease enzyme)

(angiotensinogen → angiotensin) تحول Renin الـ

(aspartic acid) من Protein بكسر الـ *

Formation of angiotensin I from angiotensinogen

ACE

A polypeptide

Angiotensin II — minimum → Angiotensin III

فعاله برفع ضغط الدم

Vasoconstriction

Aldosterone secretion

Increased peripheral resistance

Sodium and fluid retention

Increased blood pressure

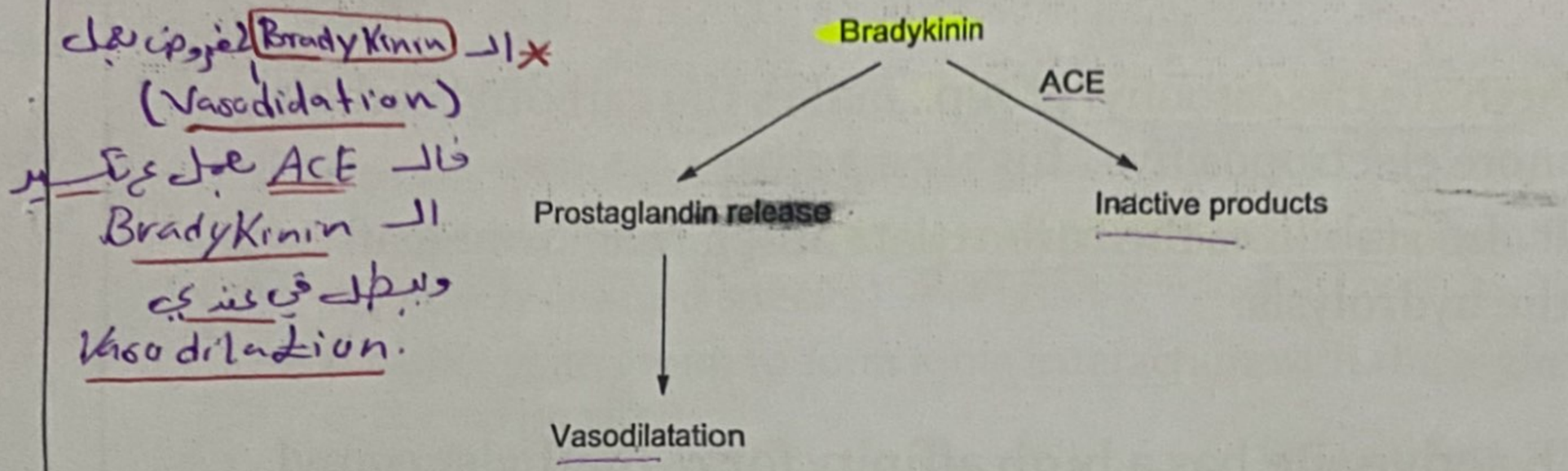
بس نعمل تثبيط لـ ACE

(2) لصنع تكوين angiotensin II

(1) تكسير BradyKinin الـ وهاد بعمل Vasodilation

ACE inhibitors

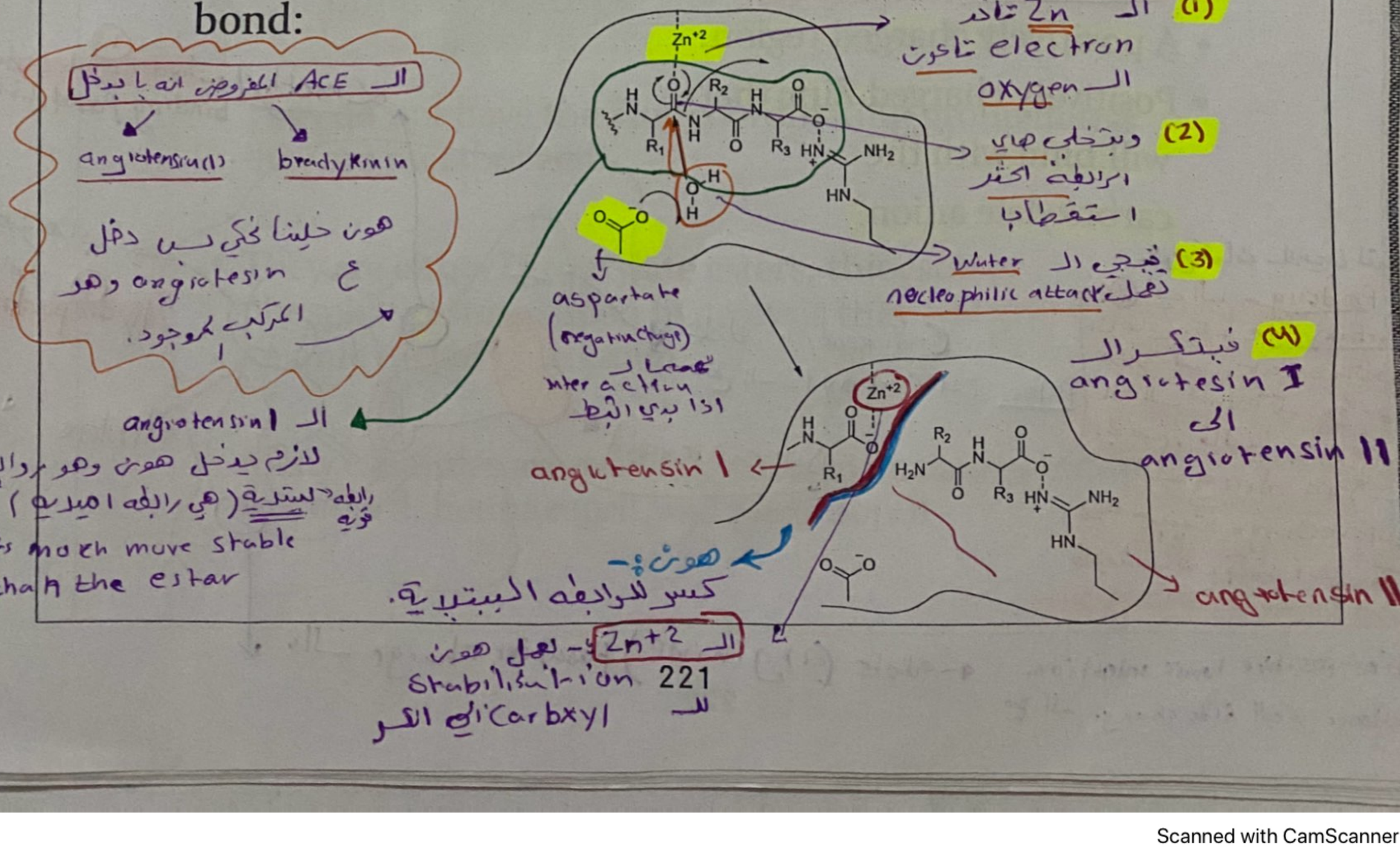
- An other action of ACE is through the metabolism of bradykinin into inactive products:



- Both mechanism will decrease blood pressure

ACE inhibitors

- ACE is a protease enzyme; it can break the peptide bond:



ACE inhibitors

- Zinc plays an important role in the hydrolysis mechanism:

(1) - Activate the carbonyl group...makes the carbonyl carbon more electropositive...highly reactive.

(2) - It also stabilizes the carboxylate anion that formed after the hydrolysis.

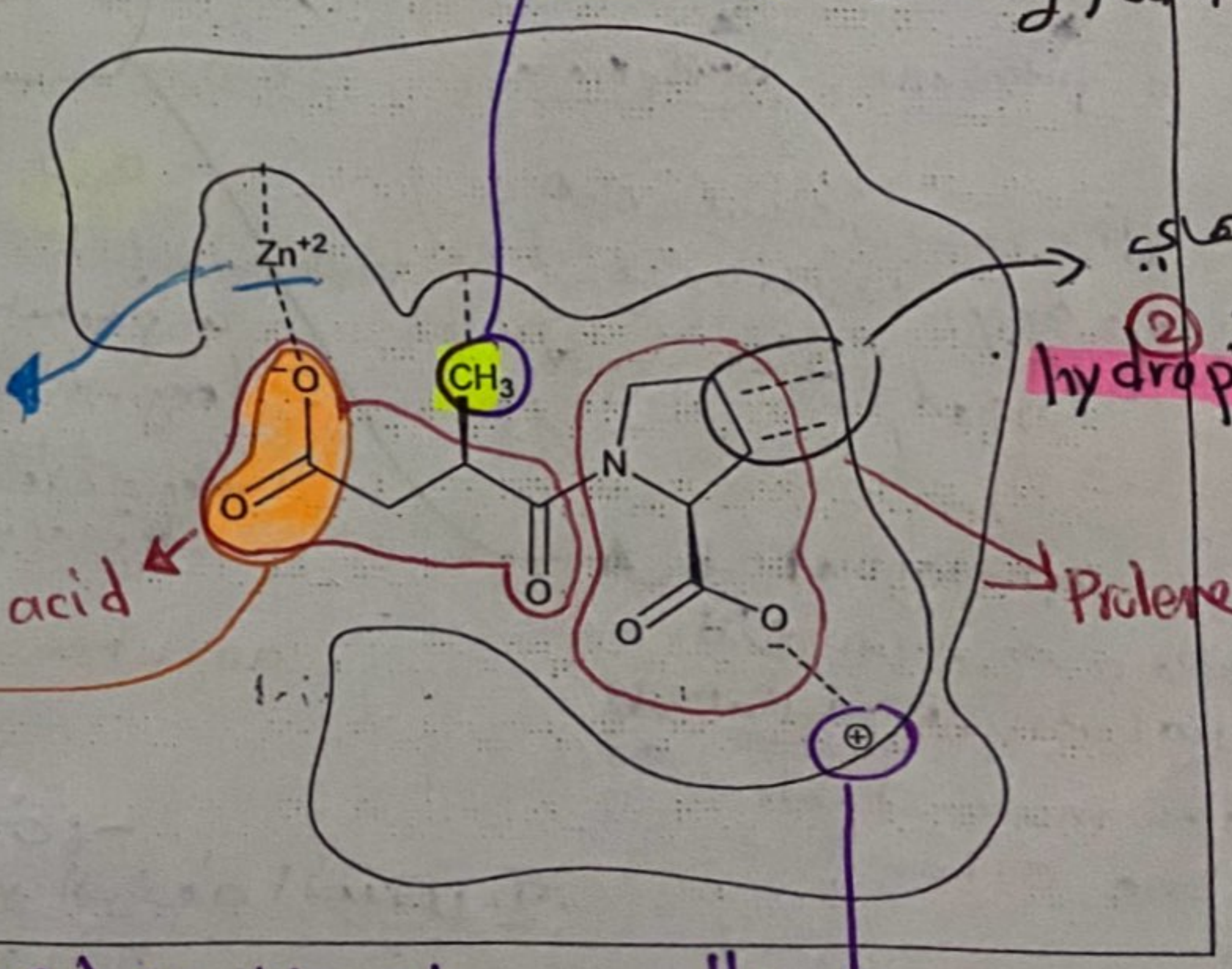
- ACE active site has a high affinity for α-methylsuccinyl proline

---

- ACE active site has a high affinity for α-methylsuccinyl proline:
  - Two hydrophobic pocket.
  - A positively charged region.
  - Positively charged Zinc that will bind with the carboxylate anion.

شرح كمان للإيدين لقدام.
(*) في الـ Prodrug
اذا هاي الـ carboxylate
حولتها لـ estar وانا بعرف
انه الـ estar تكسيره جوا داخل
الجسم، فالي بصير عندي
Pro drug
لانه خبيث negative charge
فالإمتصاص بكون أسهل وأسرع.

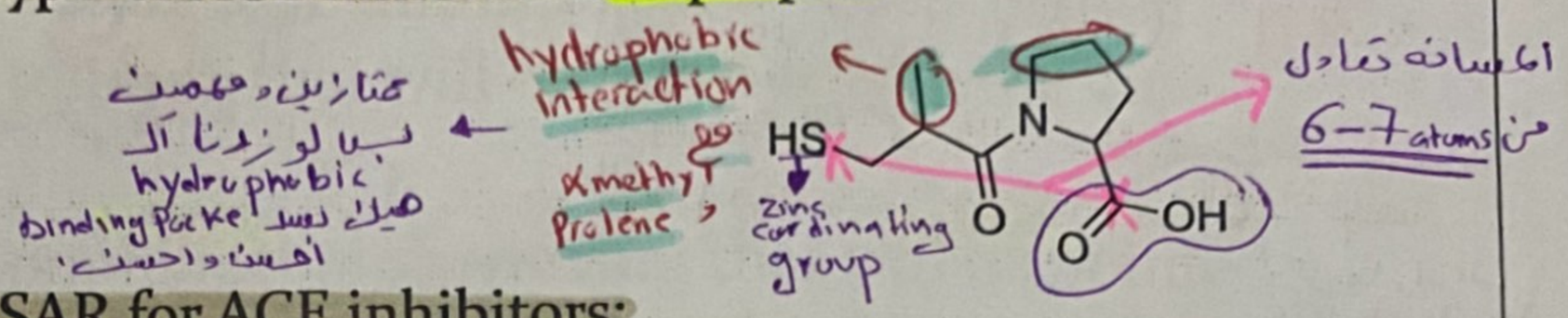
α methyl :- تعمل hydrophobic (1) داخل binding Pocket



والـ positive charge (arginine) عامله ← negative-positive ionic interation مع الـ side chang الجيع Prolene.

ACE inhibitors

- The prototype of ACE inhibitor is captopril:



- The main SAR for ACE inhibitors:
  - A zinc coordinating group (carboxylate anion or any other negatively charged species).
  - A carboxylate group to form ionic interaction with the arginin in the active site.
  - A 6-7 atom distance between the carboxylate and the zinc coordinating group.
  - Hydrophobic groups to interact with the two hydrophobic pockets.

ACE inhibitors

- ACE inhibitor prodrugs:
  - They do not have the Zinc coordinating group unless they are metabolized.
  - They are either carboxylate esters, thioester or phosphate esters...upon hydrolysis they will give the anionic carboxylate group.
  - Many examples are available such as enalapril, ramipril, fosenopril, bennazopril, and perindopril

zinc coordinating group تكون → CH / Carboxylate / phosphate
اي مروي غني بالالكترونات

(Zinc coordinating group) ✱ estar بتكون مغطيه تكل بدائي على تتميز بوجود الـ

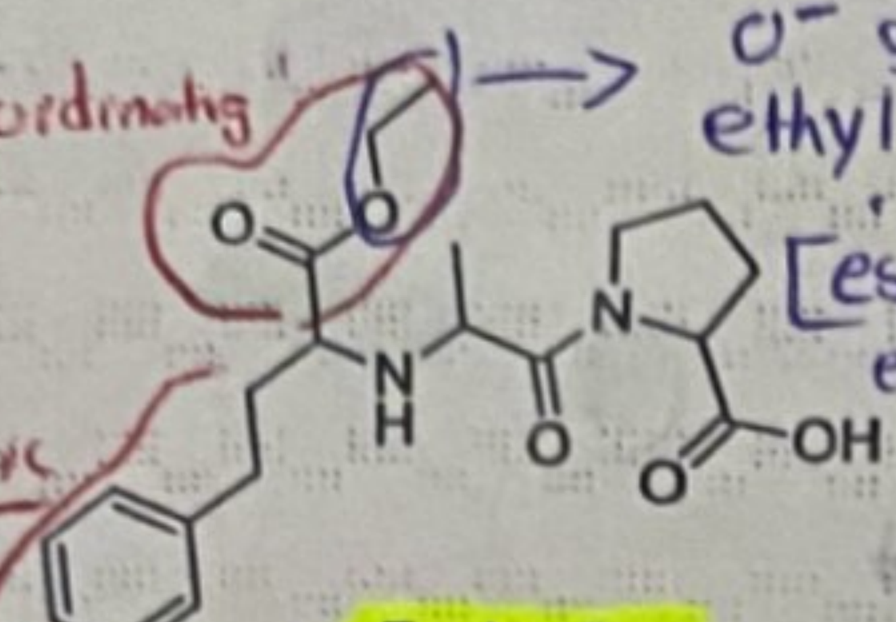
ACE inhibitor prodrugs

Zinc coordinating group

extra hydrophobic group

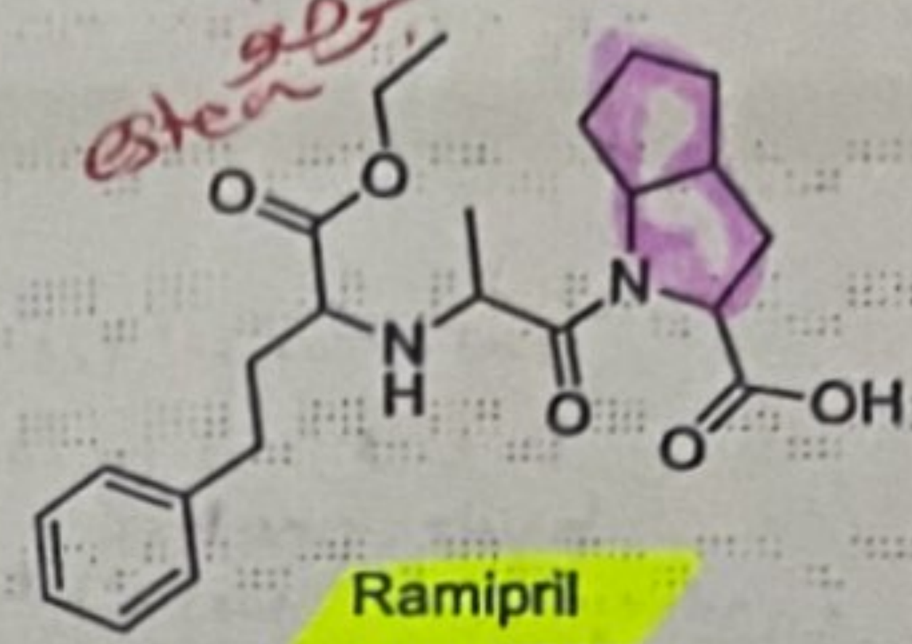
وكل ما زاد الـ hydrophobic كل ما كان أحسن ،

✱ هون ما عندي O⁻ هون عندي ethyl [يعني estar ، وهاد الـ estar بتكسر بهوله بالجسم ،

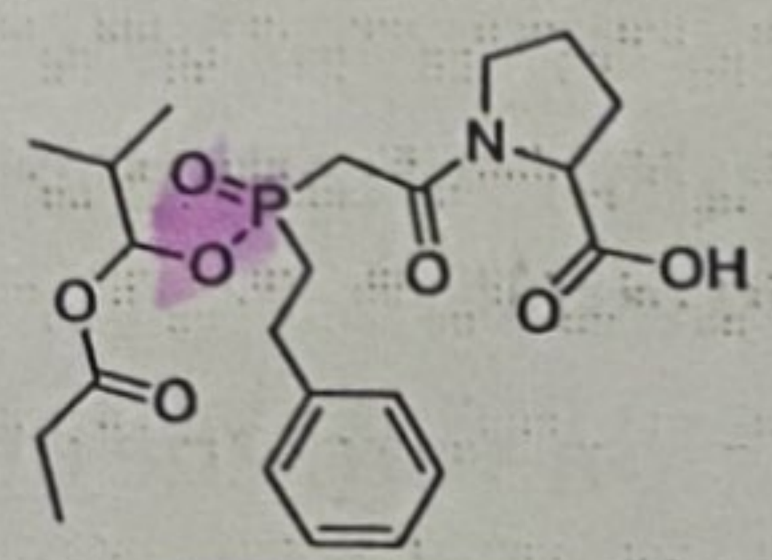


Enalapril

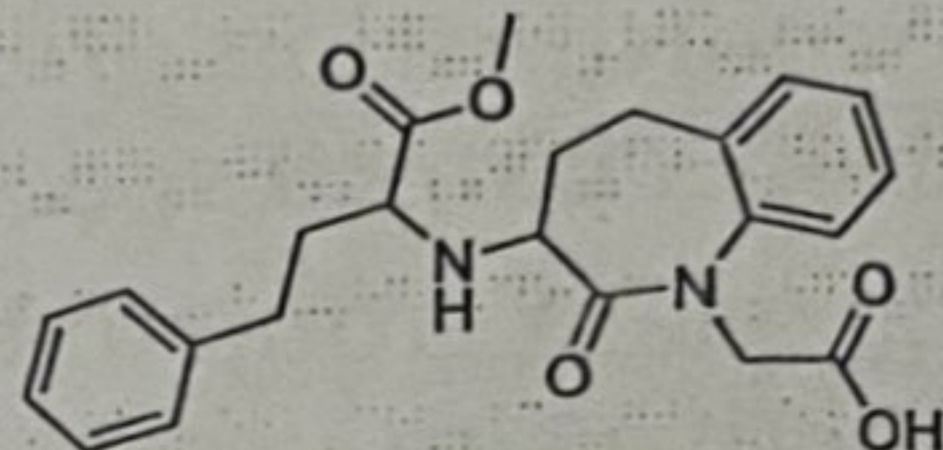
ester



Ramipril

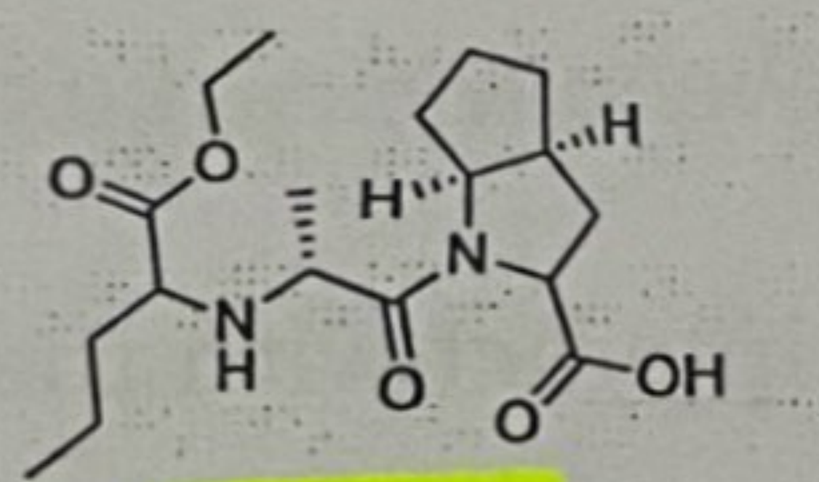


Fosenopril



Benazopril

لانه لما تسمع كلمة Foseno يعني في عندك Phosphate group.



Peridnopril

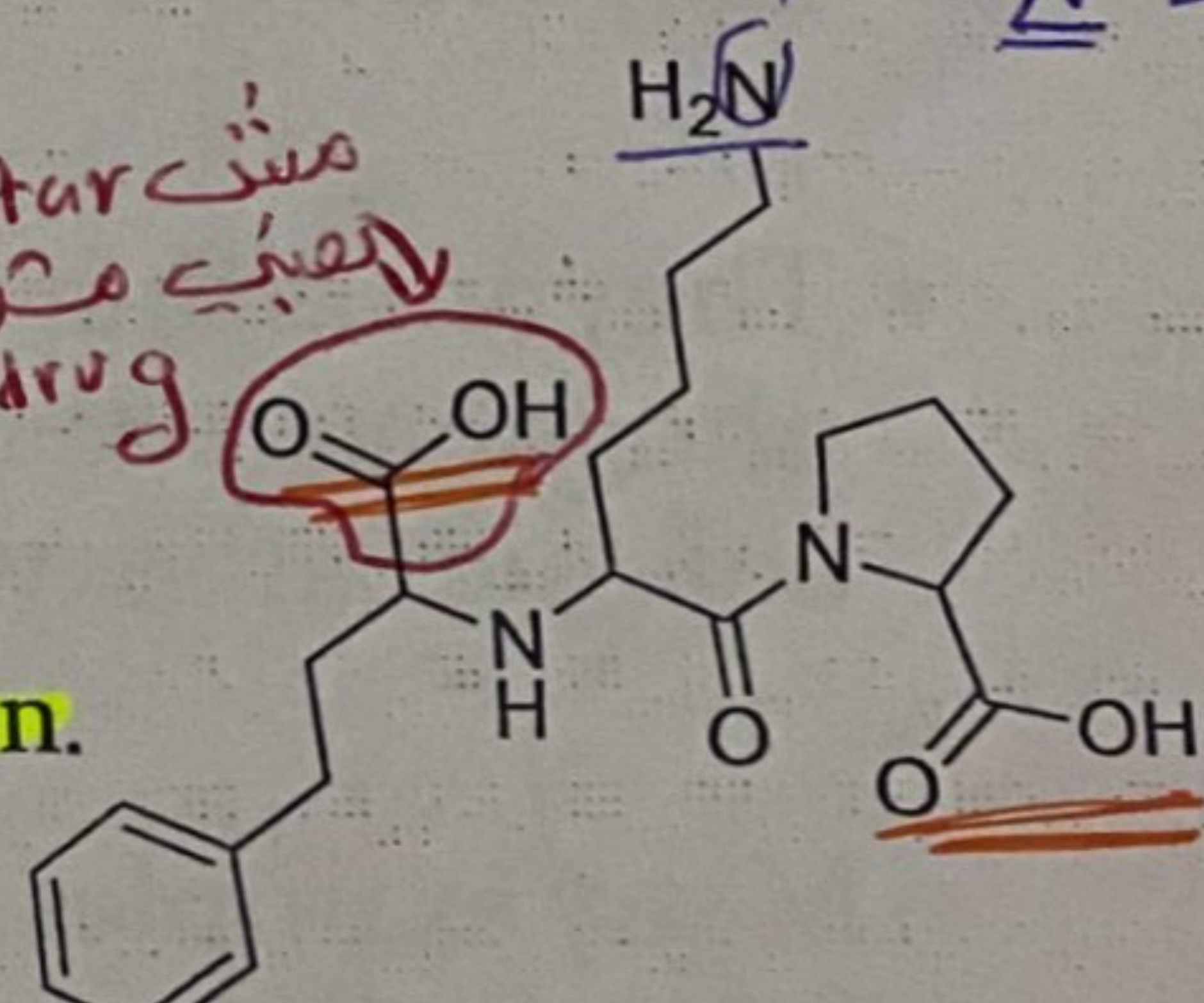
" هيك خلصنا موضوع Prodrug "

Lisinopril

- The third ACE inhibitor introduced in the market (1990).
- It differs from other ACE inhibitors in that:
  - It is more hydrophilic:
    - slow absorption.
    - High volume of distribution.
    - Long half life due to high tissue deposition.
  - It is mainly excreted unchanged in urine…is not metabolized.

slow absorption بسبب N

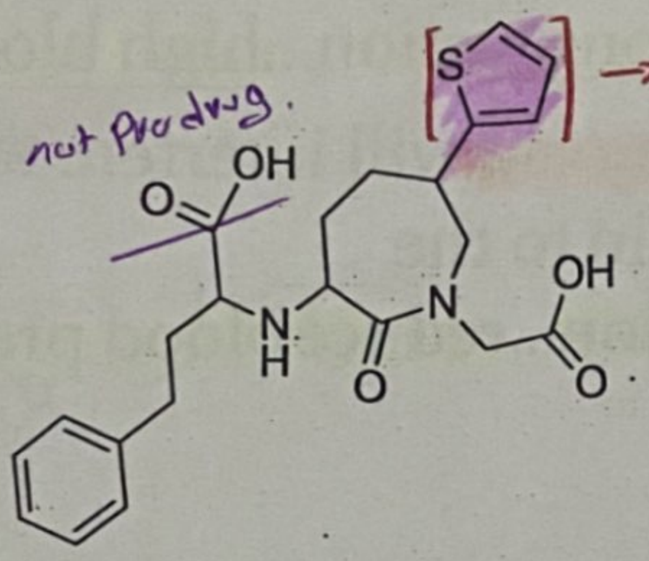
مش estar يعني مش Prodrug



لانه المركب فيه (Carboxylate) فش داعي للـ metabolism بصير الـ Secretion داخل الـ nephron مباشرة ؛

Temocapril

- Is a direct acting ACE inhibitor since it has the free carboxylate anion that will coordinate with the zinc cation.
- Has the lipophilic thiophene ring that will be pointed toward one of the hydrophobic pocket in the active site.



ACE inhibitors common S/E

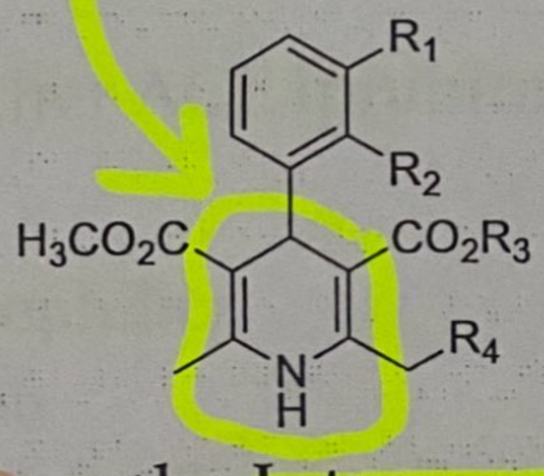
(1) Vasodilator edema
(2) Persistent dry cough
(3) Headache
(4) Dizziness
(5) Fatigue
(6) Nausea
(7) Renal impairment
(8) Might increase inflammation-related pain (Due to accumulation of pradykinin)

Calcium channel blockers (CCB)

- Calcium plays a major role in the regulation of many cellular processes, mainly in muscle contraction.
- The entry of extracellular Ca^{++} into the smooth muscle cytosol and their release from the intracellular storage sites is very important for the initiation of muscle contraction.....vasoconstriction...high blood pressure.
- Calcium channel blockers will interfere with the entrance of calcium in to the cytosol...vasodilatation...reduce blood pressure.

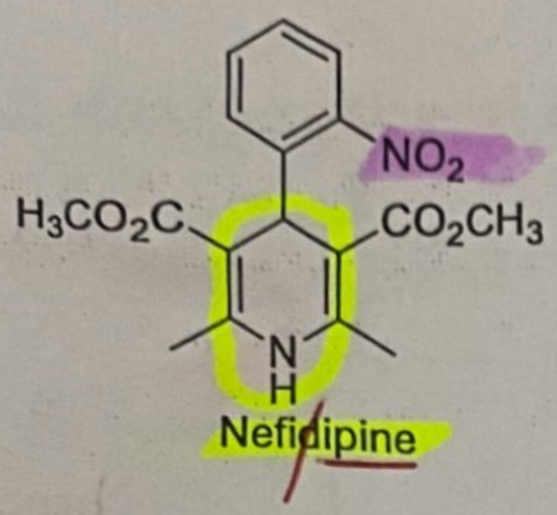
Calcium channel blockers

- The majority of calcium channel blockers are 1,4-dihydropyridine derivatives.

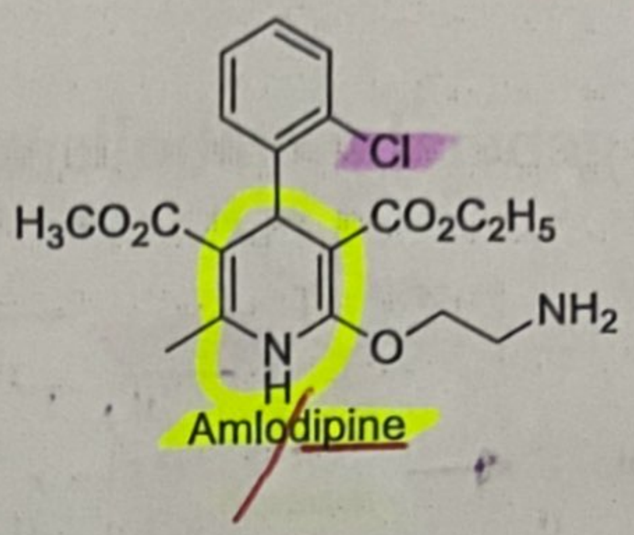


- They act mainly on the L-type calcium channel (L for long lasting effect)
- After binding they cause conformational changes that affect Ca^{++} movement .

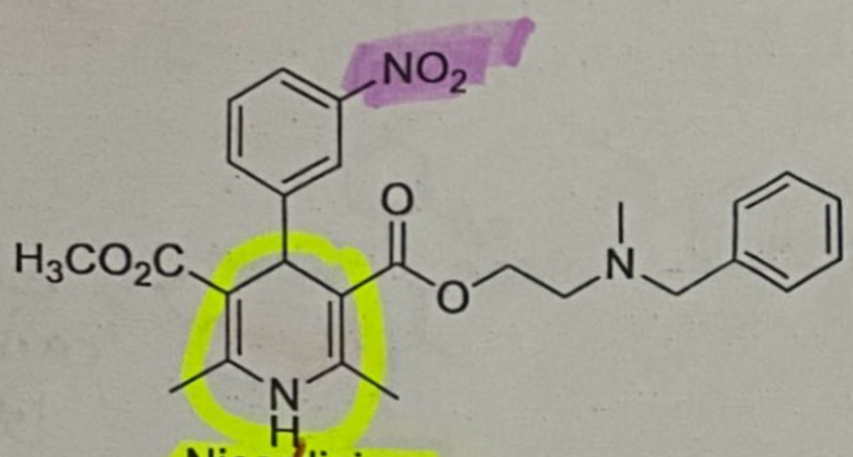
Calcium channel blockers



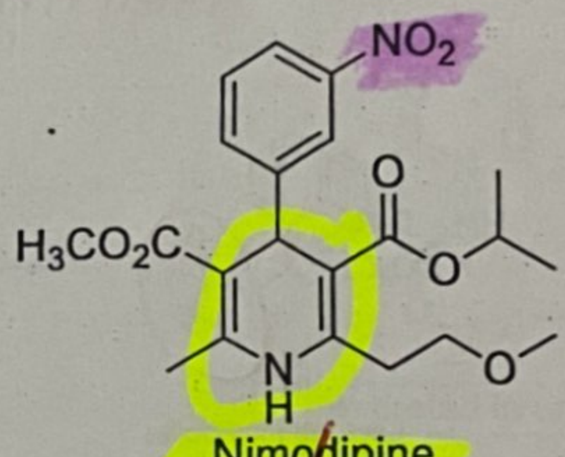
Nefidipine



Amlodipine



Nicardipine



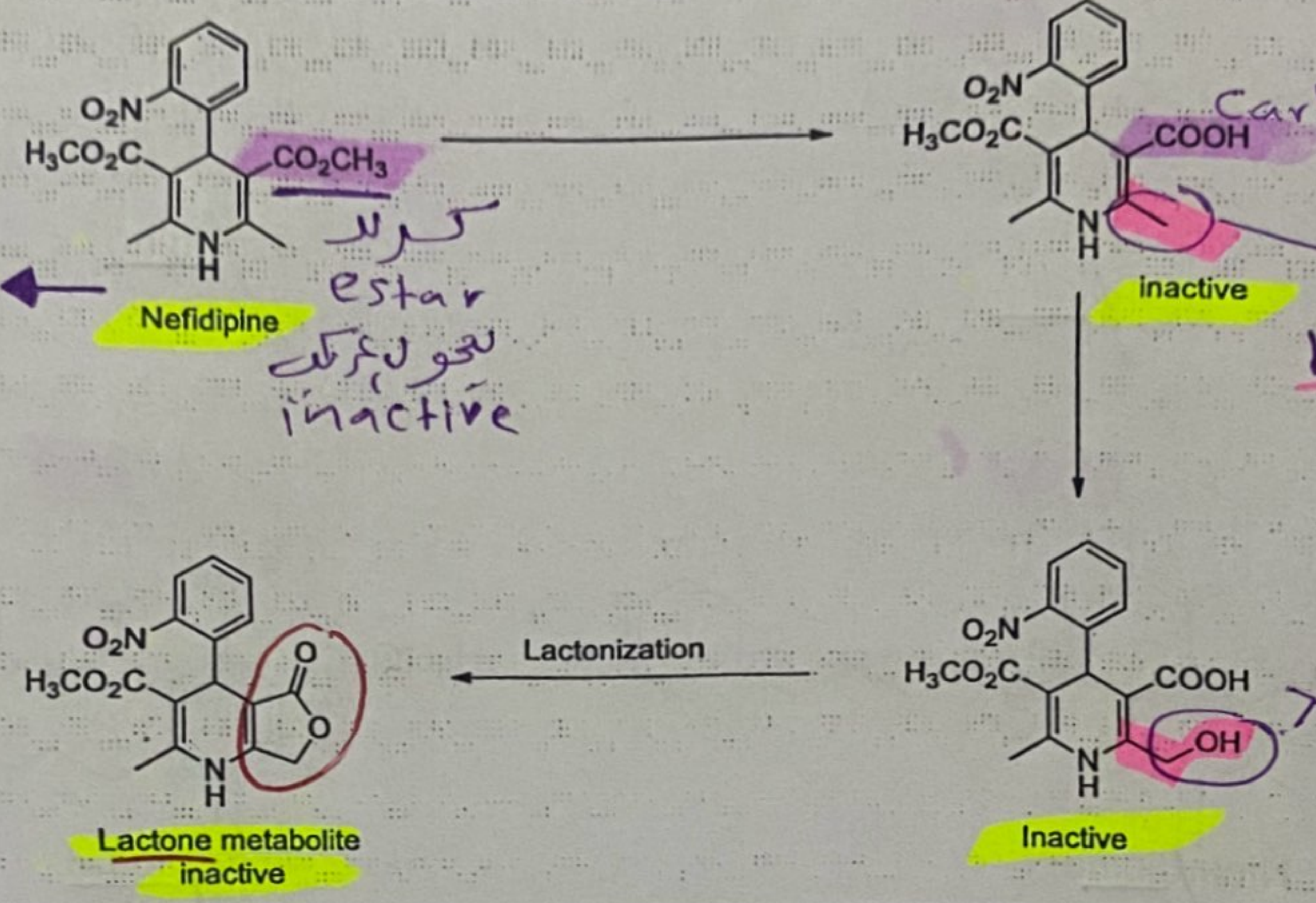
Nimodipine

Calcium channel blockers

- No clear SAR for these agents.
- The difference in their structure will mainly affect the pharmacokinetic profile not the activity or the binding to the calcium channel.

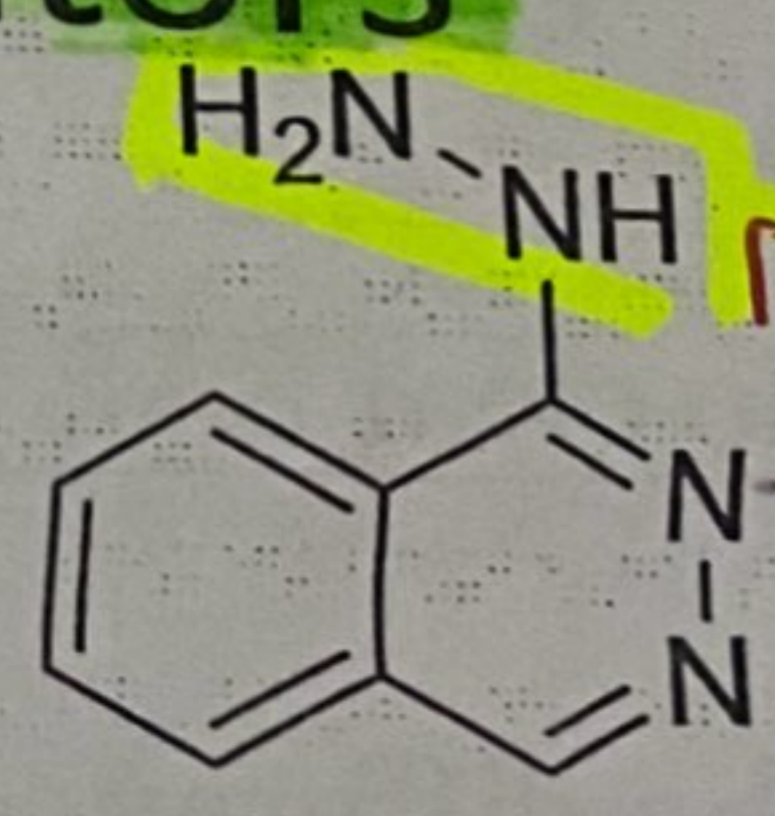
Calcium channel blockers

- The general metabolism for CCB:



Direct acting vasodilators

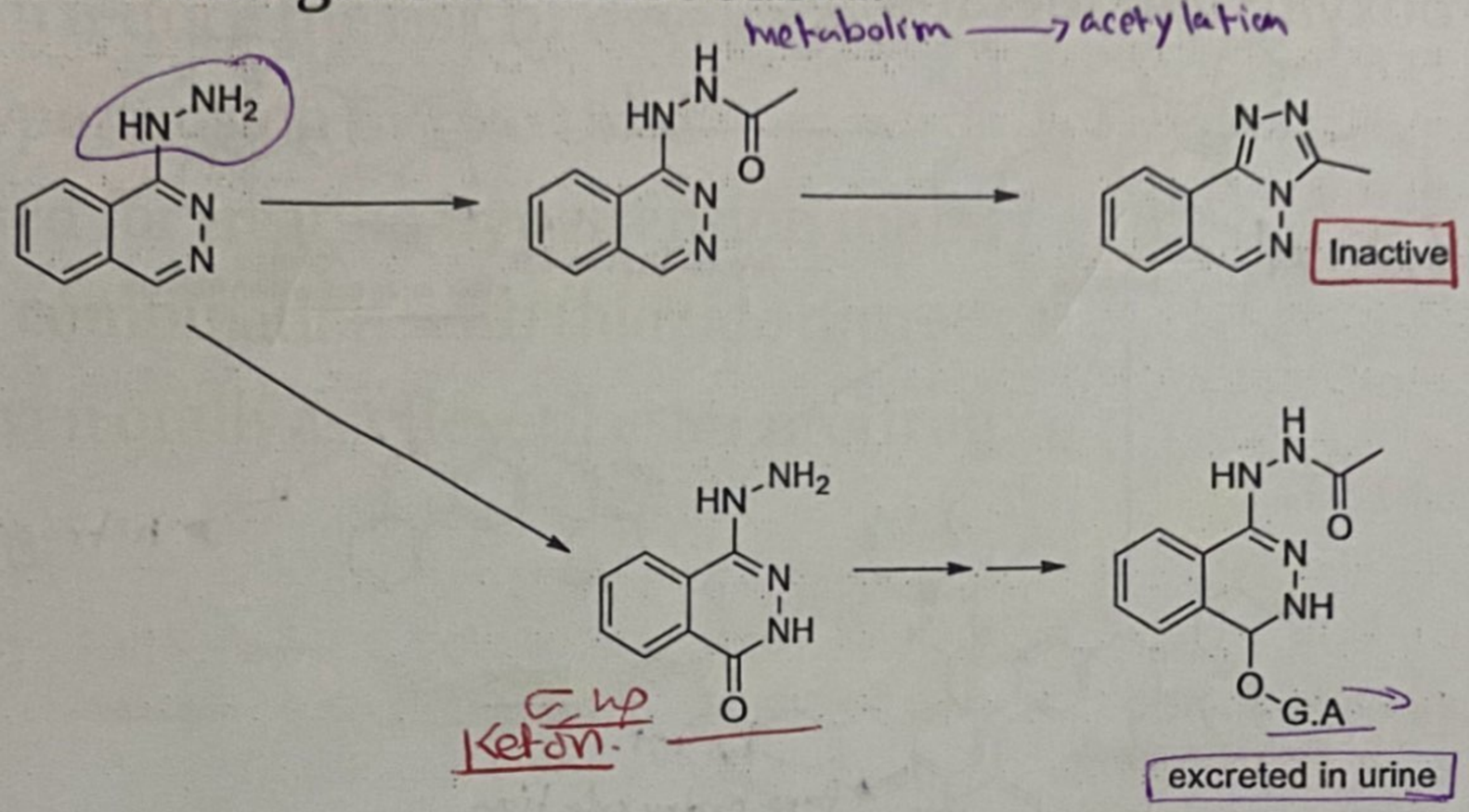
- Hydralazine:



  - Reduces arteriole peripheral resistance.
  - Interferes with calcium transport and activate guanylate cyclase…increases level of cGMP…vasodilatation.

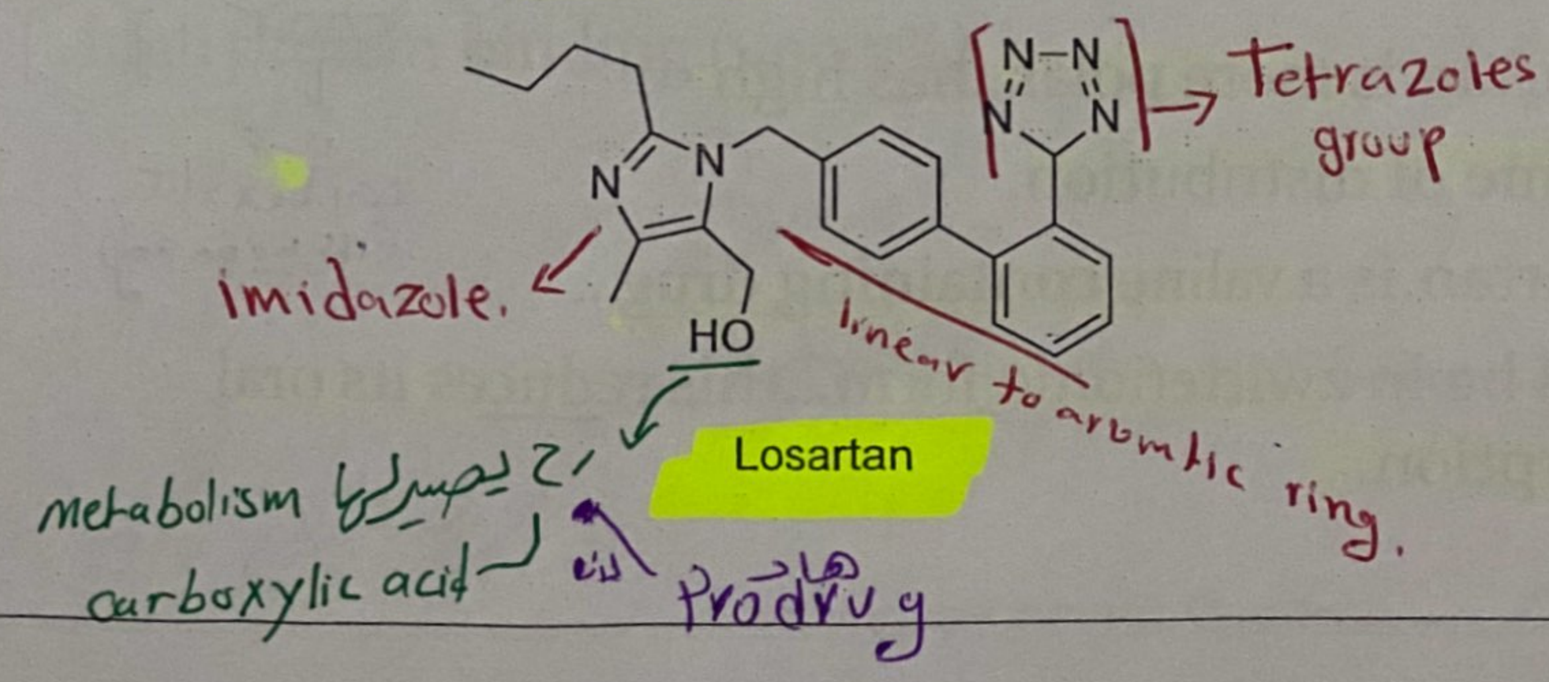
Direct acting vasodilators

- Hydralazine general metabolism:



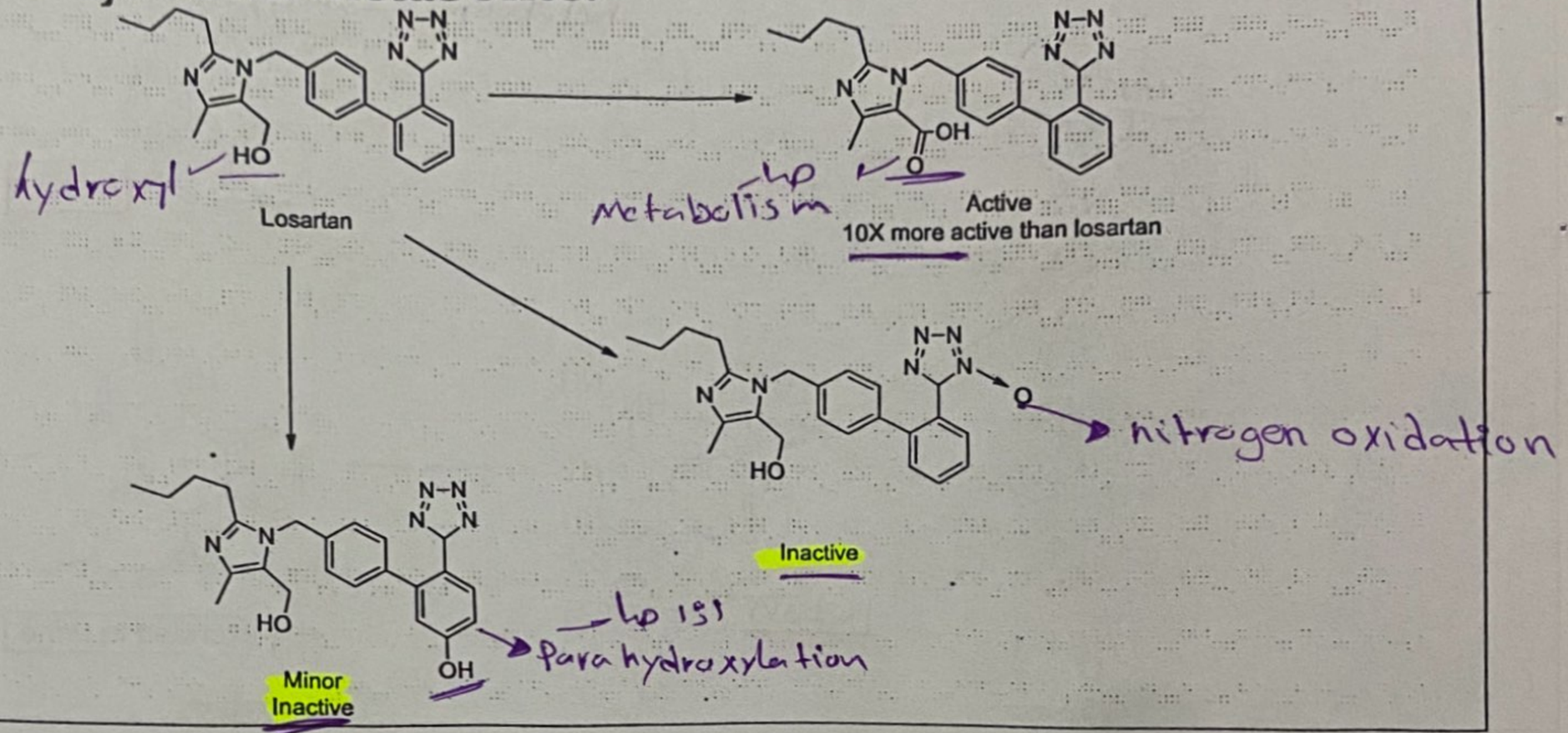
Novel anti-hypertensive agents

- Novel mechanism of action is targeting angiotensin II receptors...as blockers; they will prevent the binding of (angiotensin II) to its receptor...no vasoconstriction.
- They are competitive inhibitor for the enzyme.
- The prototype is losartan



Losartan metabolism

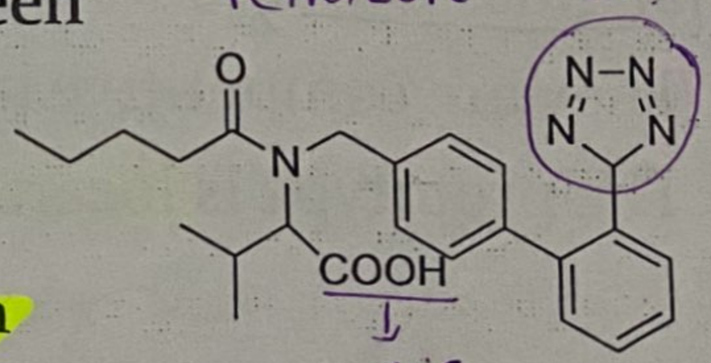
- It is metabolized into an active metabolite; the carboxylic acid metabolite:



Valsartan (Diovan)

- Valsartan is a new anti-hypertensive agent with the same mechanism as losartan.
- The difference in structure between losartan and valsartan is:

losartan تشبه ال
tetrazole باك

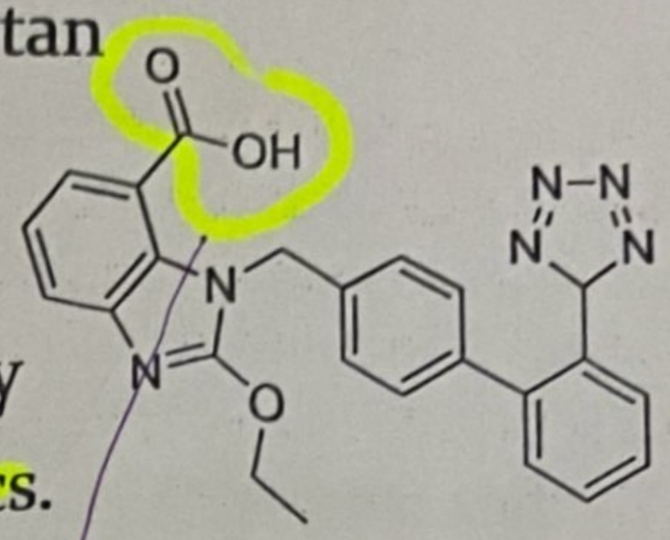


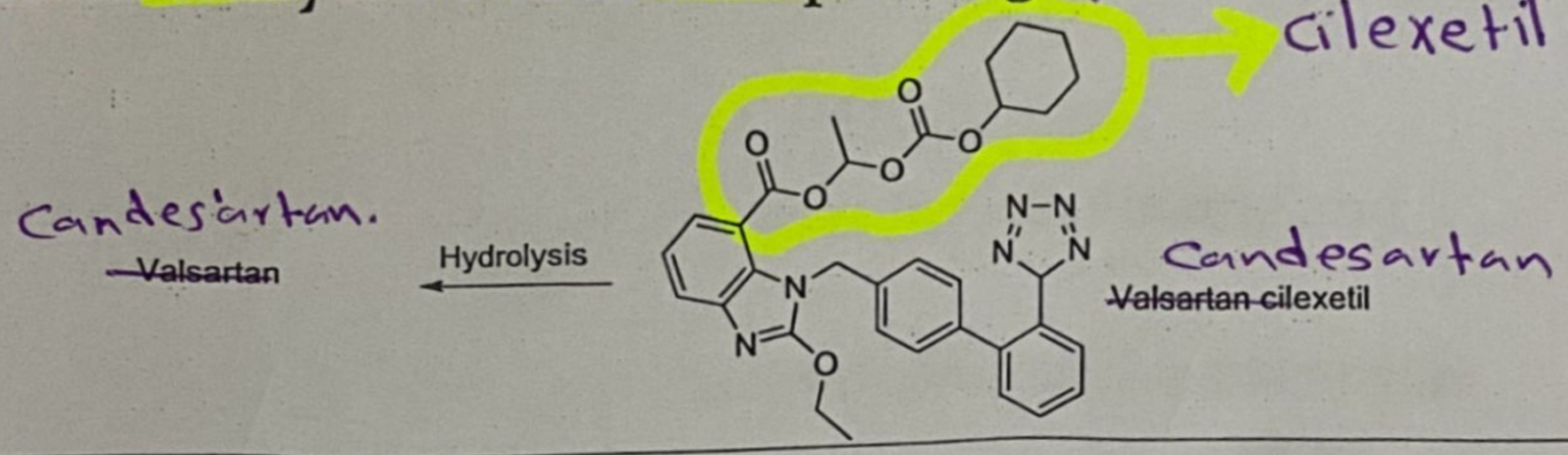
كنت
carboxylic
(its no pro drug)

  - Valsartan is more polar...has high volume of distribution.
  - Valsartan is a valine containing drug... it will be in zwitterionic form...this reduces its oral absorption.

Candesartan (Blopress® , Atacand®)

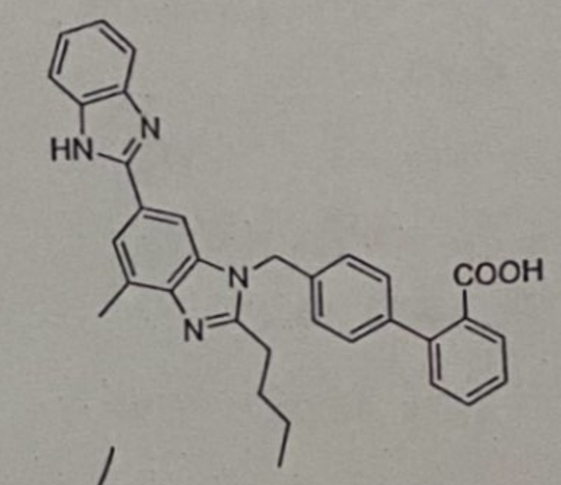
- Recent studies revealed that candesartan can reduce the risk of developing hypertension by two third.
- Used for treating hypertension mainly in combination with thiazide diuretics.
- Given orally as cilexetil ester prodrug:

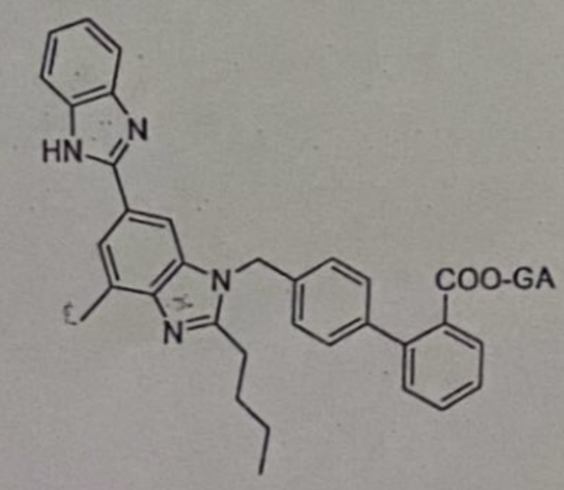




Telmisartan (Micardis®)

- Has the longest duration of action (t1/2= 24 hr) and the largest volume of distribution among all angiotensin II receptor blockers:
  - More lipophilic than other derivatives...more fat soluble and high protein binding (>99.5%).





only 3% of the drug

the only metabolite recovered for Telmisartan