



تفريغ ميديسينال

HTN drugs محاضرة:

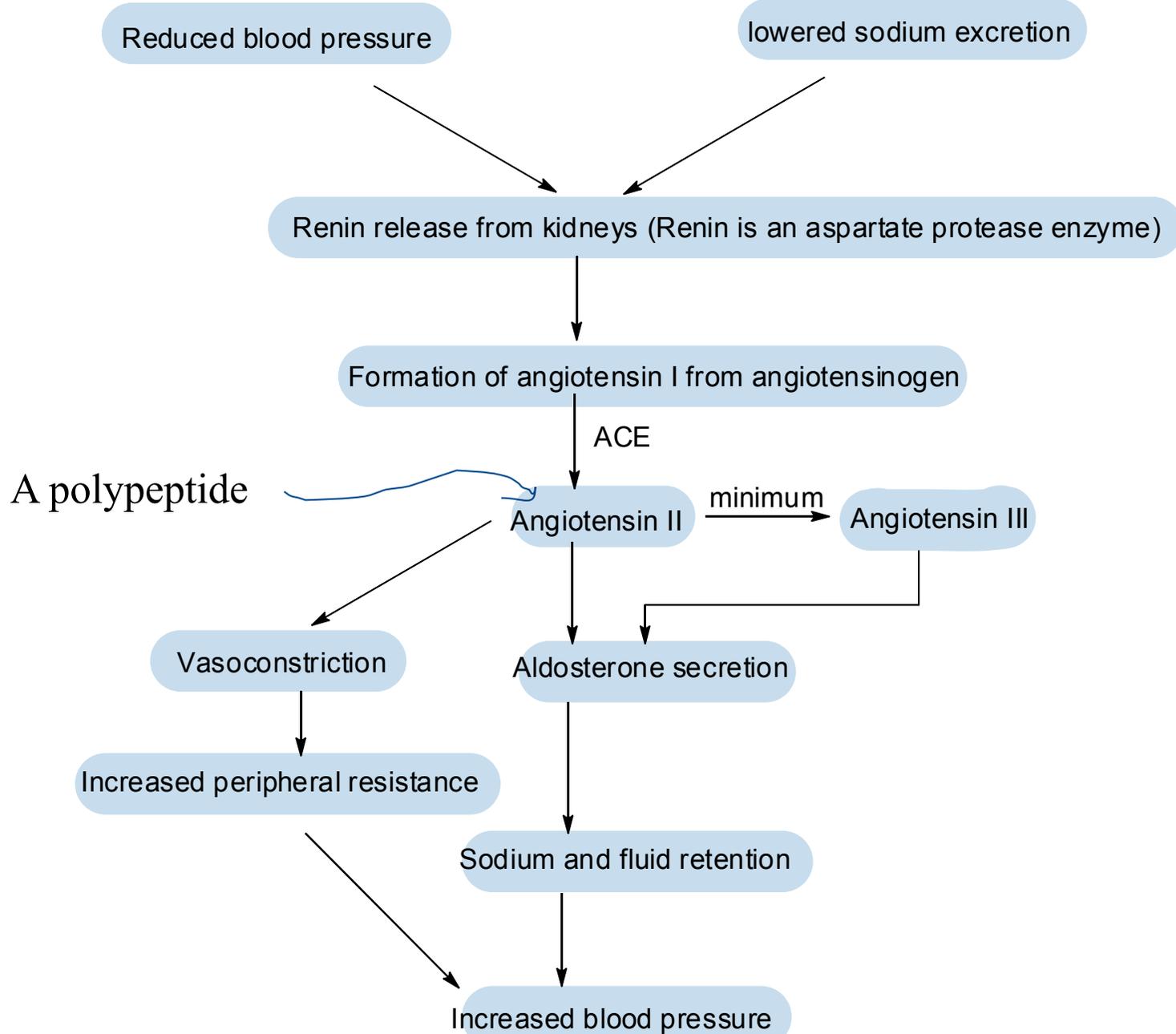
Rahaf Zayoud الصيدلانية:



لجان الرفعات



# ACE inhibitors

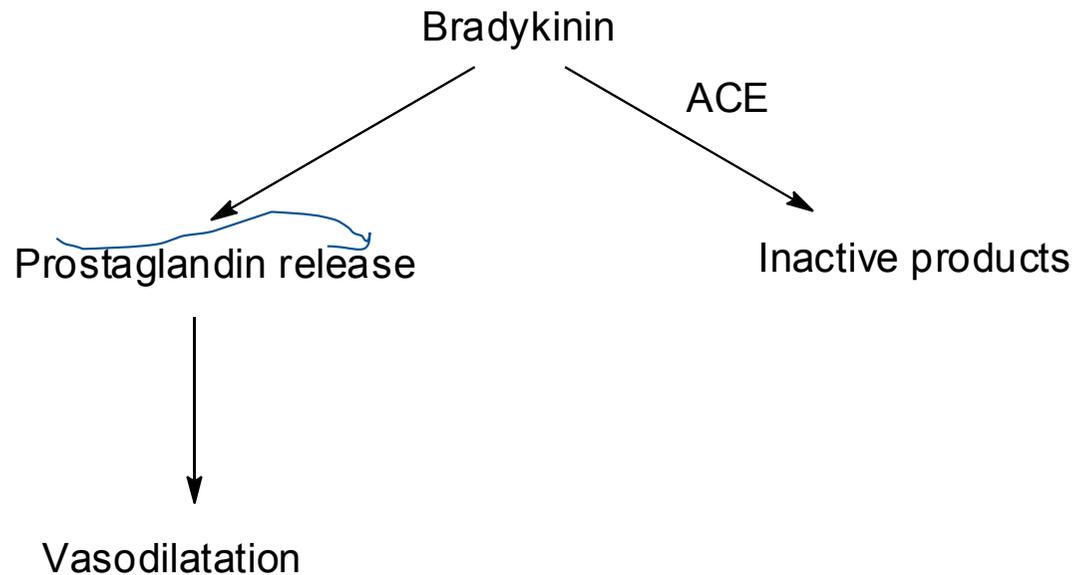


ACE → enzyme  
إذا وقفت هذا الـ enzyme  
رح نحلل الـ BP

الـ ACEI رح يصحوا تحول الـ  
Angiotensin I لـ Angiotensin II  
ويفرضه تفع تحول الـ bradykinin لـ  
inactive product

# ACE inhibitors

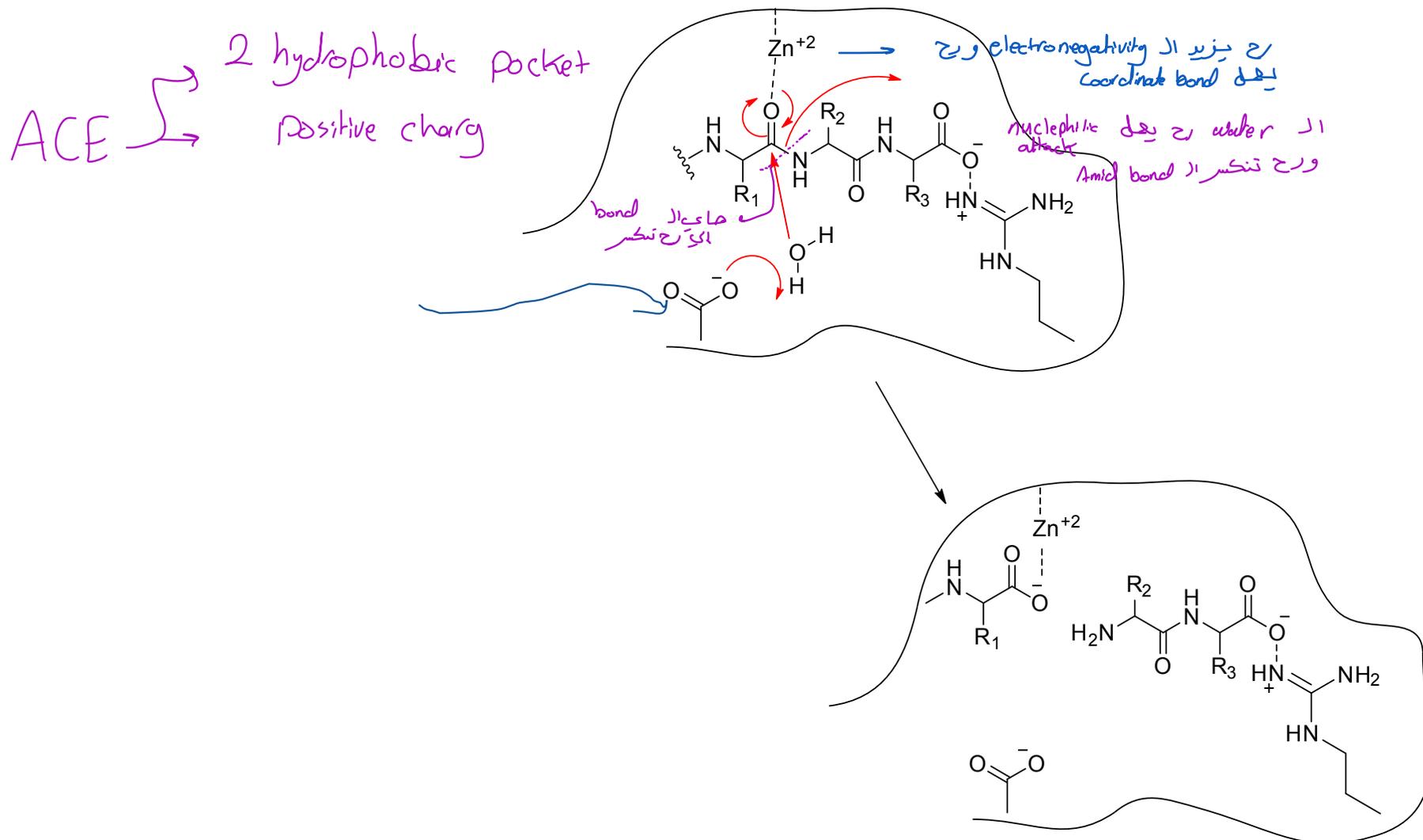
- An other action of ACE is through the metabolism of bradykinin into inactive products:



- Both mechanism will decrease blood pressure

# ACE inhibitors

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



# ACE inhibitors

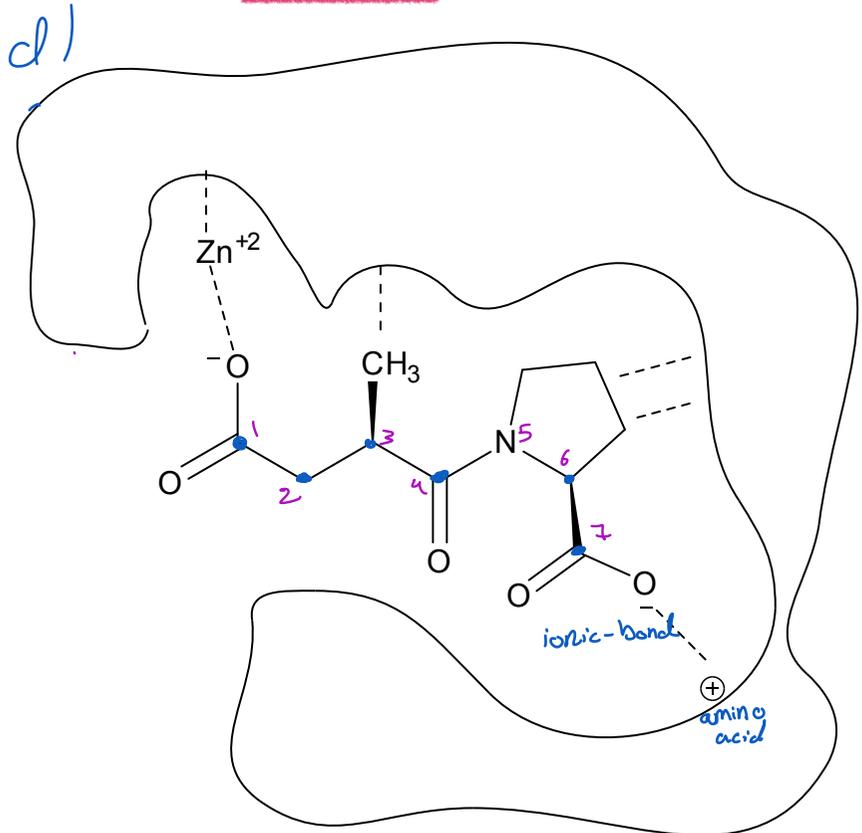
- Zinc plays an important role in the hydrolysis mechanism:
  - Activate the carbonyl group...makes the carbonyl carbon more electropositive...highly reactive.
  - It also stabilizes the carboxylate anion that formed after the hydrolysis.
- ACE active site has a high affinity for  $\alpha$ -methylsuccinyl proline

- ACE active site has a high affinity for  $\alpha$ -methylsuccinyl proline:

- Two hydrophobic pocket.
- A positively charged region.
- Positively charged Zinc that carboxylate anion. (coordinate bond)

①  $\alpha$ -methyl  
 ② Proline ring  
 Hydrophobic pocket  
 van-der waals  
 enzyme  $\rightarrow$  charge stabilizing  $Zn^{+2}$

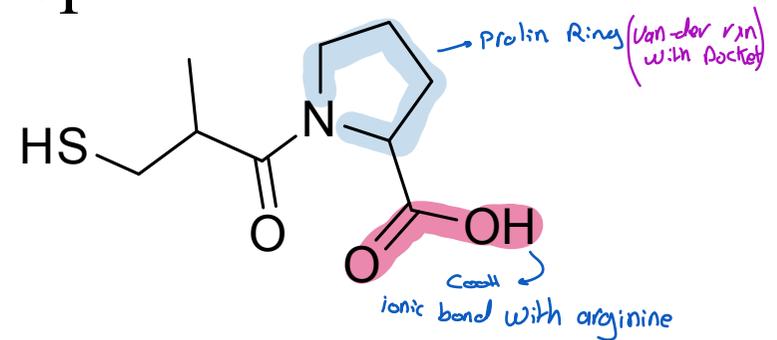
will bind with the carboxylate anion



الدوية التي راجد رسا راج تكون تشبه  
 $\alpha$ -methylsuccinyl proline  
 !دنا لازم يكون فيها  
 ① يكون فيها 2 group! لم charge (-) وجه  
 منهم راج تعمل coordinate-bond مع  $Zn^{+2}$   
 ② لازم يكون عنده 2 hydrophobic group  
 يعمل van-der waals  
 ③ المسافة بين  $Zn^{+2}$  و  $(COO^-)$  الالانويه  
 atom (6-7)

# ACE inhibitors

- The prototype of ACE inhibitor is captopril:



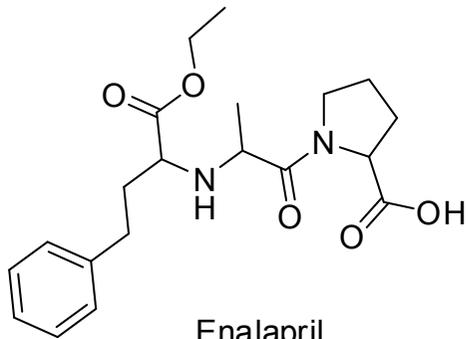
- The main SAR for ACE inhibitors:
  - A zinc coordinating group (carboxylate anion or any other negatively charged species).
  - A carboxylate group to form ionic interaction with the arginine in the active site.
  - A 6-7 atom distance between the carboxylate and the zinc coordinating group.

# ACE inhibitors

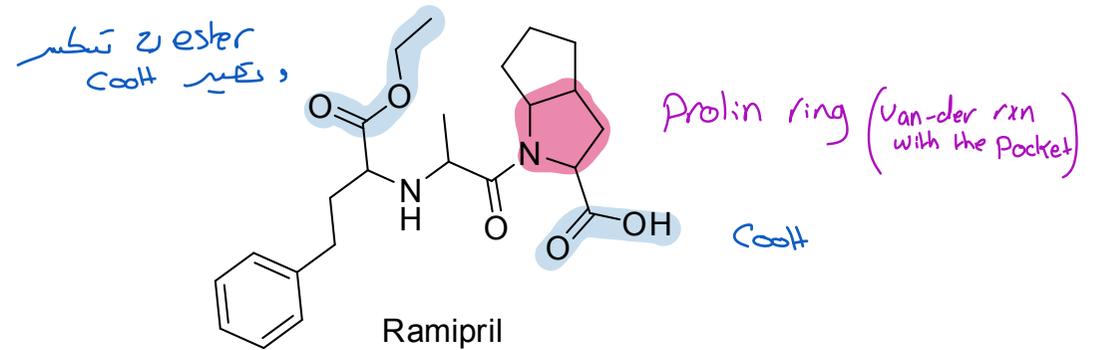
- ACE inhibitor prodrugs:
  - They do not have the Zinc coordinating group unless they are metabolized.
  - They are either carboxylate esters, thioester or phosphate esters...upon hydrolysis they will give the anionic carboxylate group.
  - Many examples are available such as enalapril, ramipril, fosinopril,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

ریح ایشون ال ACEI بئسائل ester  
 او Thio ester او phosphoester  
 لسا هه Pro-drug ریح یسه  
 الهم metabolism ویتحولوا ال Coalt

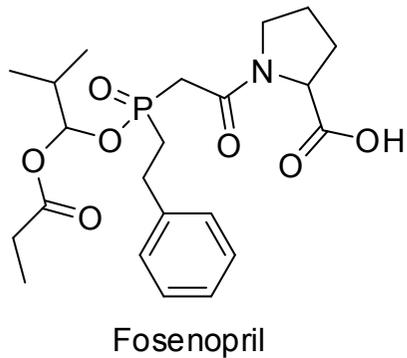
# ACE inhibitor prodrugs



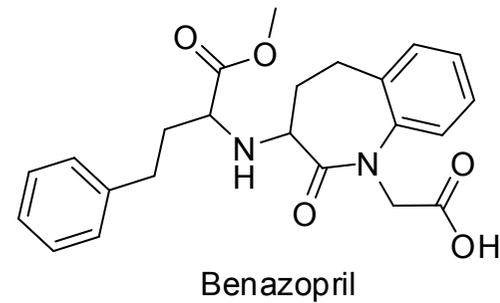
Enalapril



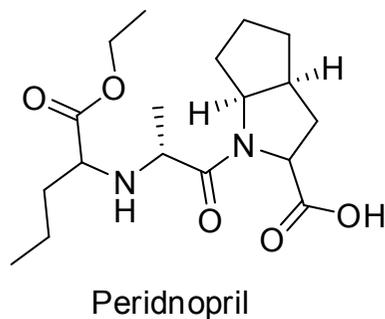
Ramipril



Fosinopril



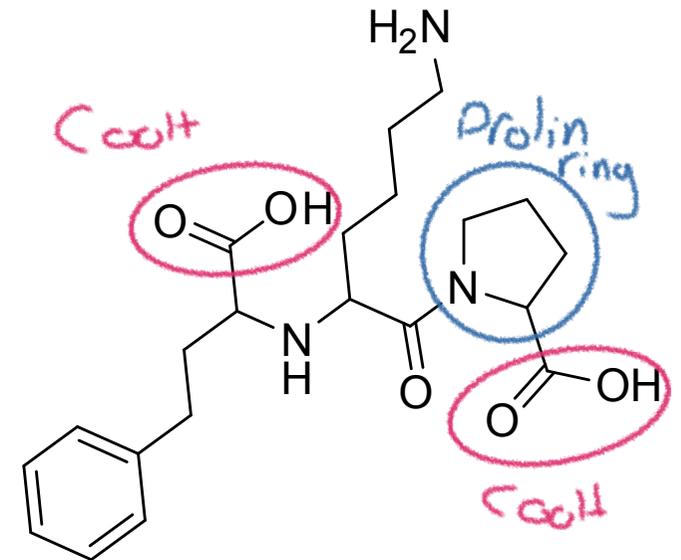
Benazopril



Perindopril

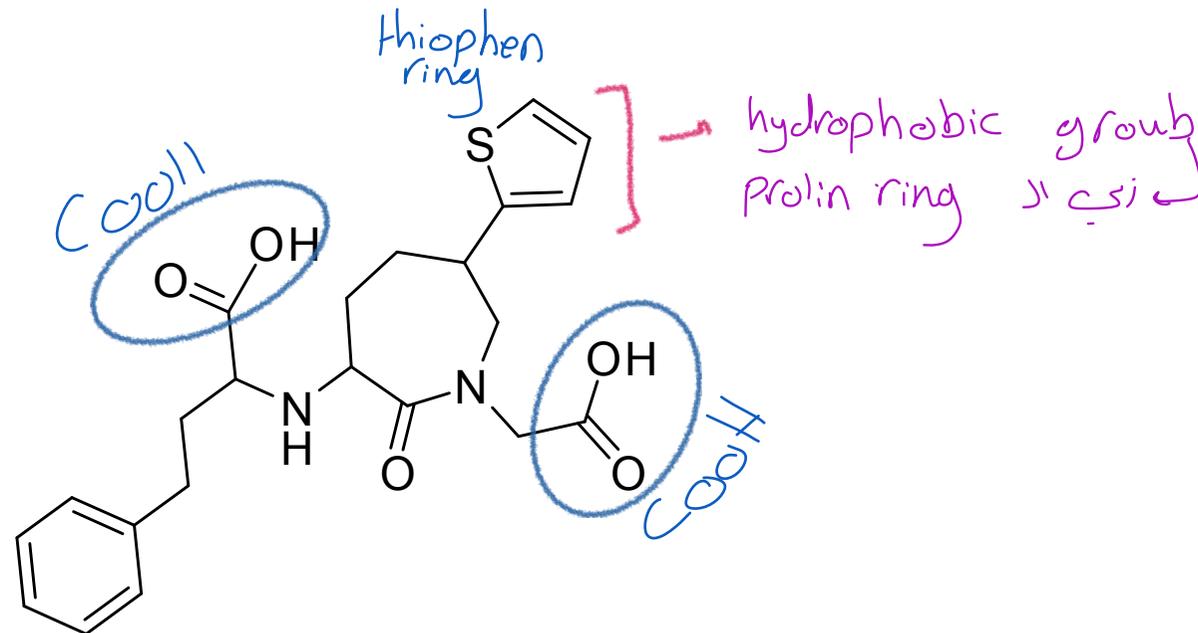
# Lisinopril

- 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.



# 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 → *تصير بأول اسبوعين من استخدام الدواء*
3. Headache
4. Dizziness → *تصير بأول اسبوعين من استخدام الدواء*
5. Fatigue
6. Nausea
7. Renal impairment
8. Might increase inflammation-related pain (Due to accumulation of pradykinin) *bradykinin يح امنع تحول ال inactive product ال*

# Calcium channel blockers (CCB)

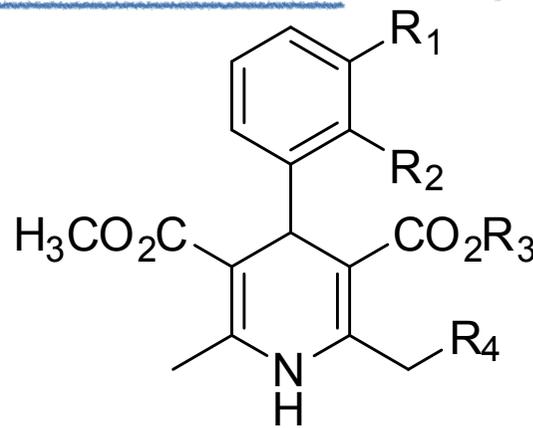
- Calcium plays a major role in the regulation of many cellular processes, mainly in muscle contraction.
- The entry of extracellular  $\text{Ca}^{++}$  into the smooth muscle cytosol and their release from the intracellular storage sites is very important for the initiation of muscle contraction.....vasoconstriction...high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

ال  $\text{Ca}^{++}$  لها يروح لال smooth muscle في يغير! لها contraction فلما امين دخول

ال  $\text{Ca}^{++}$  لال Cytosol وصلته يح يعل ل contraction روح قولا BP

# Calcium channel blockers

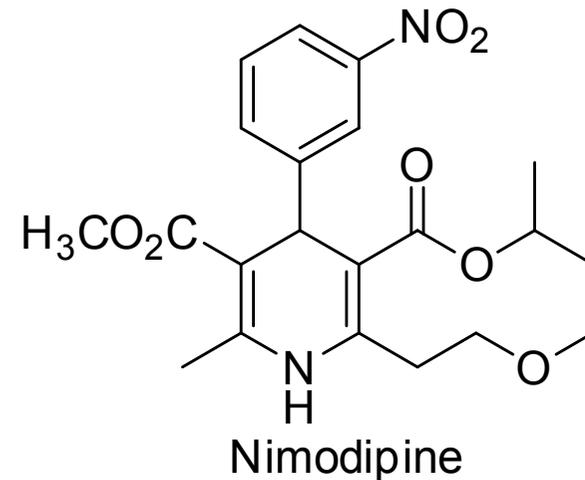
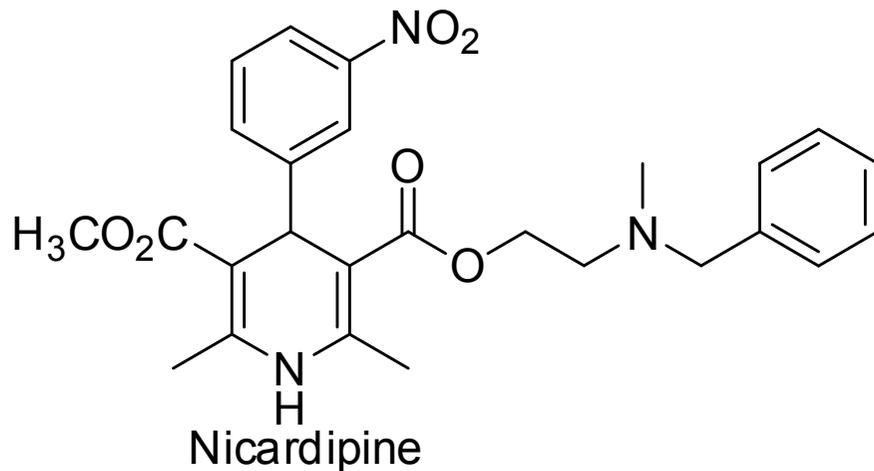
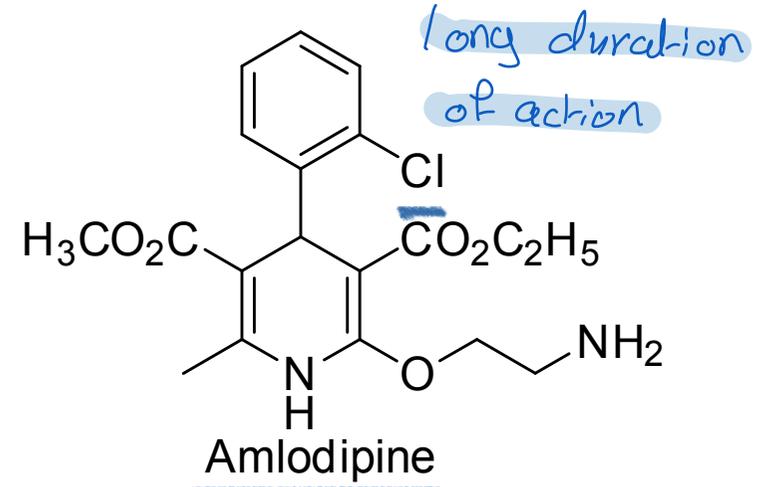
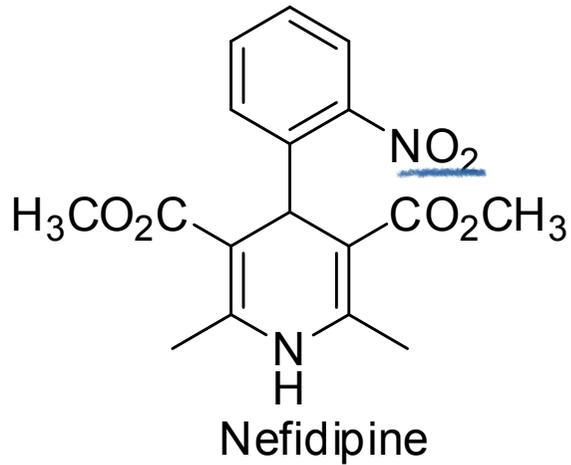
- The majority of calcium channel blockers are 1,4-dihydropyridine derivatives.



ليس الشون هذا  
الشكل يعرف انه CCB  
وبالاختلاف مع يكون  
بال substitution

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

# Calcium channel blockers

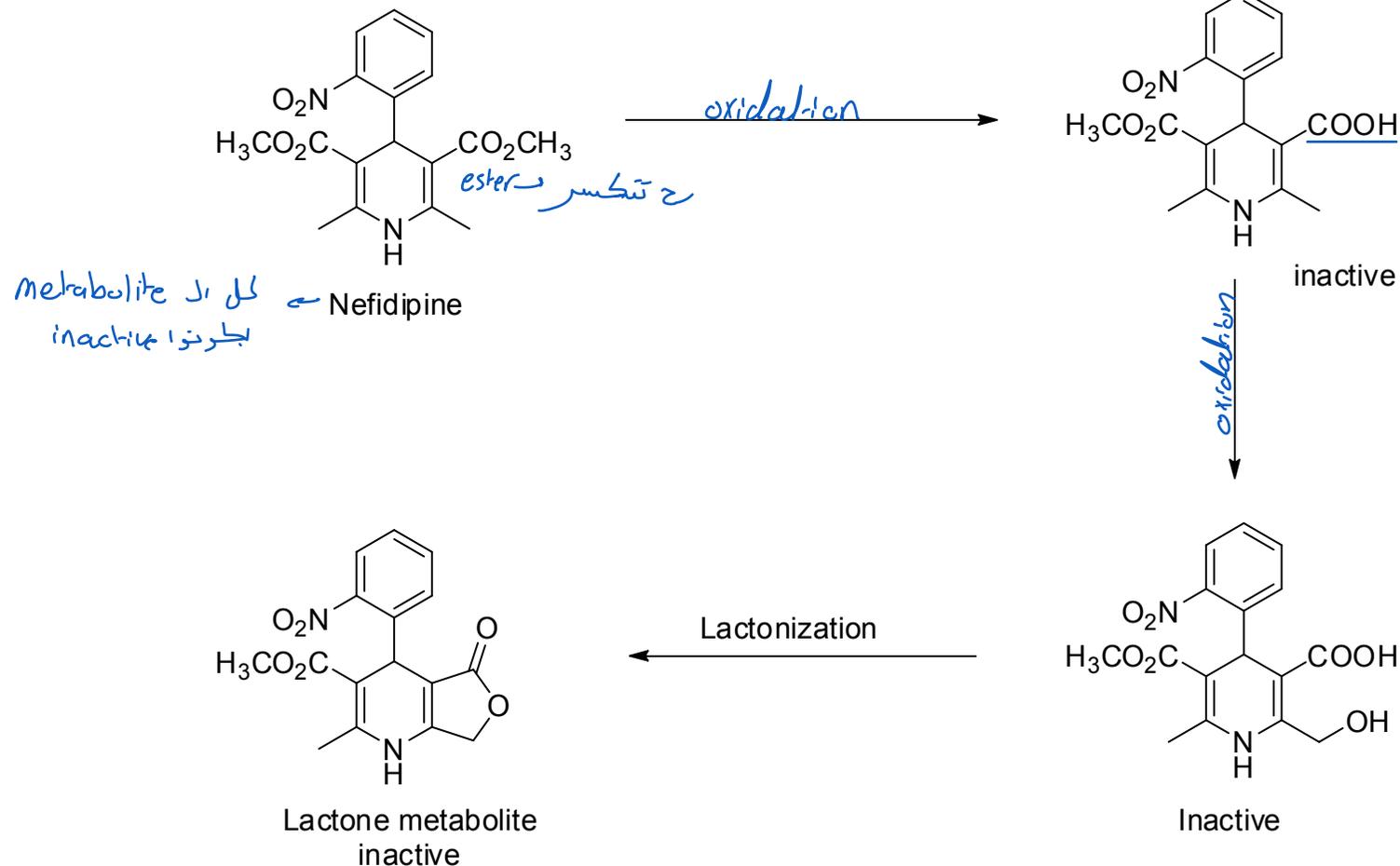


# Calcium channel blockers

- 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:

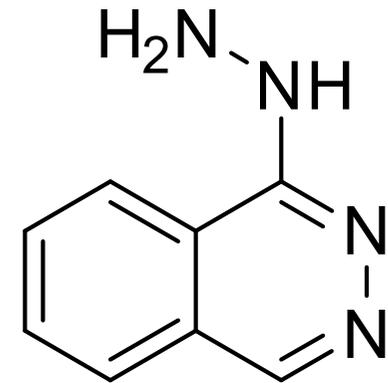


# Direct acting vasodilators

برفحة السكر صمغ

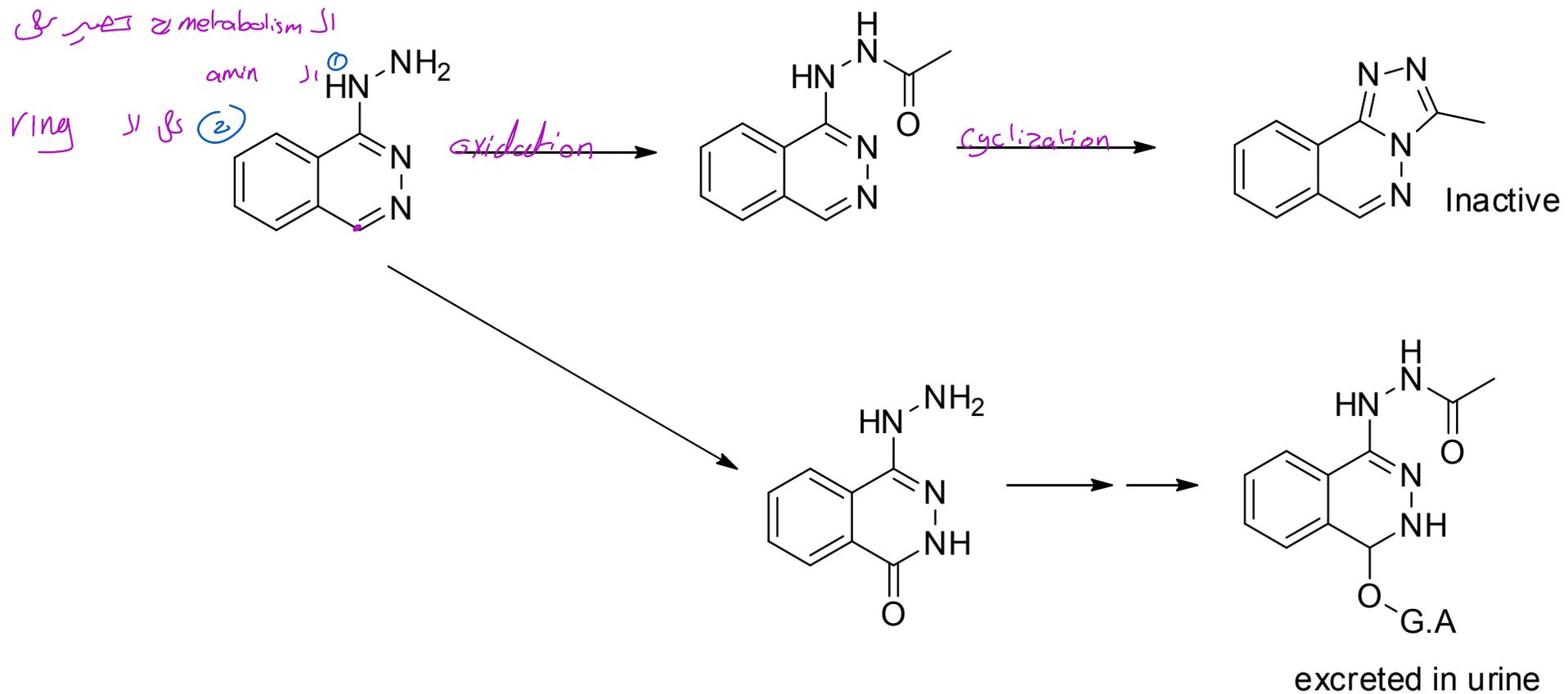
④ Hydralazine: →

- ① Reduces arteriole peripheral resistance.
- ② Interferes with calcium transport and activate guanylate cyclase... increases level of cGMP...vasodilatation.



# Direct acting vasodilators

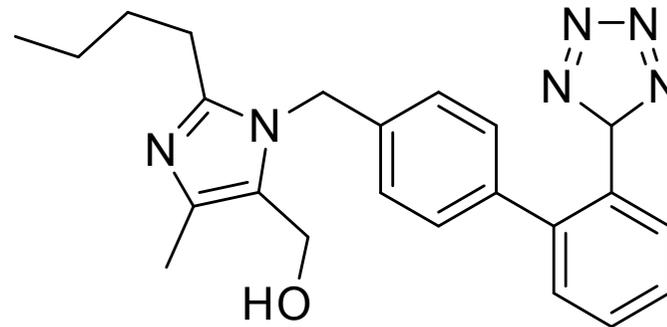
- Hydralazine general metabolism:



# 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

همه ال  
ARE

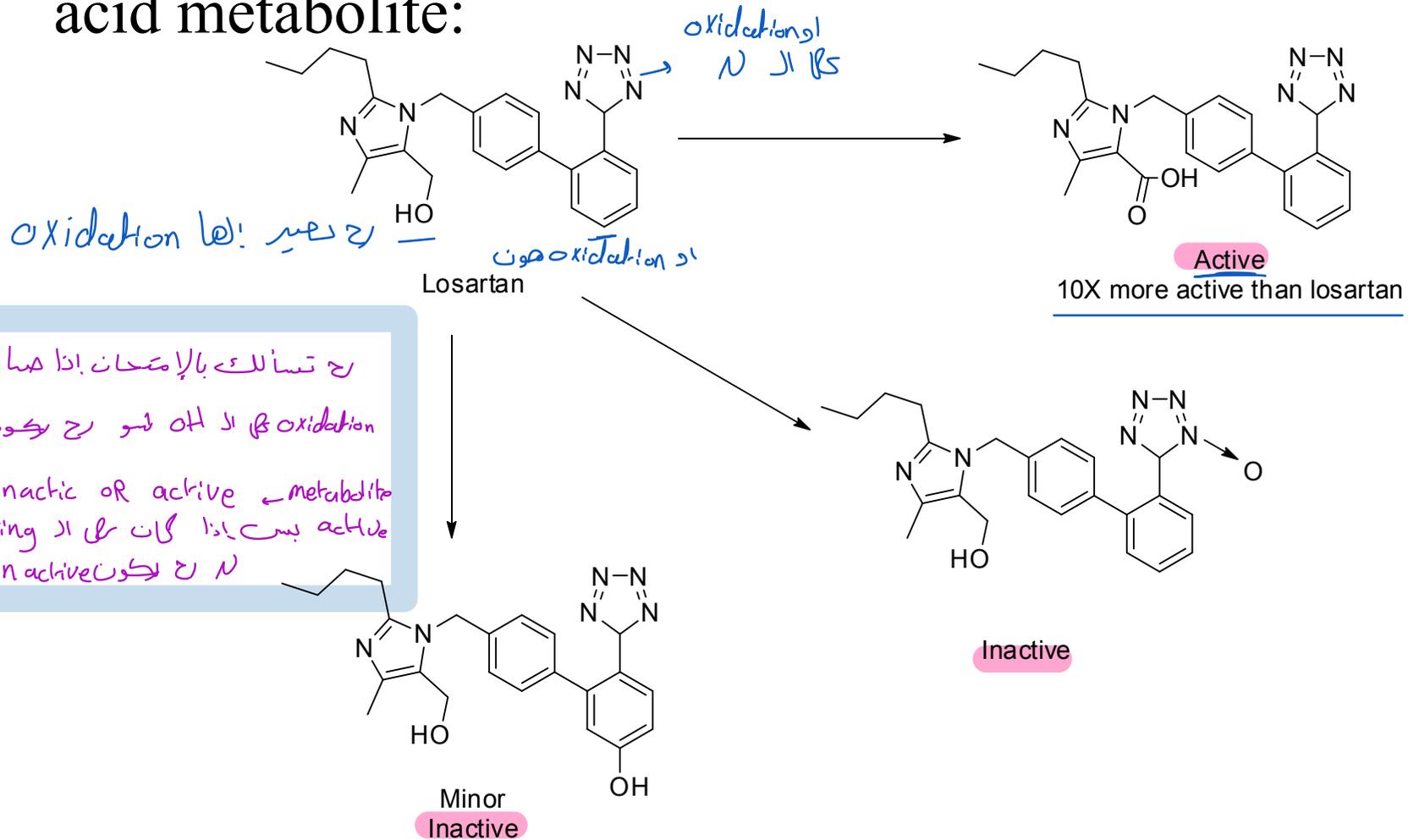


Losartan

شکلهم همینه برسه  
الم tetrazol و  
2aromatic ring مرتبطه  
و بعض

# Losartan metabolism

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



رح تسالک بالامتحان اذا هبار  
 oxidation في ال OH شو رح يكون ال  
 metabolite ← inactive or active والحواب  
 active بس اذا كان على ال ring او لا  
 N رح يكون inactive

# Valsartan (Diovan)

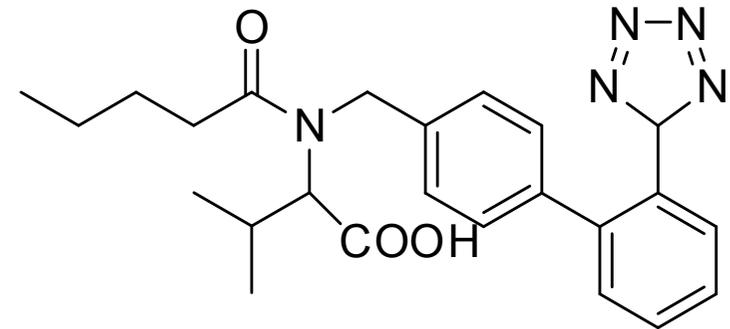
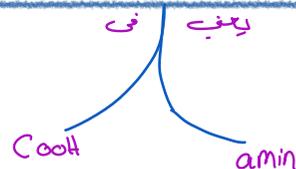
2. Valsartan is a new anti-hypertensive agent with the same mechanism as losartan.

ارجعوا لـ Structure لا losartan وقارنوا  
مع تشرّفوا انه  مش موجود بالـ Valsartan

• The difference in structure between losartan and valsartan is:

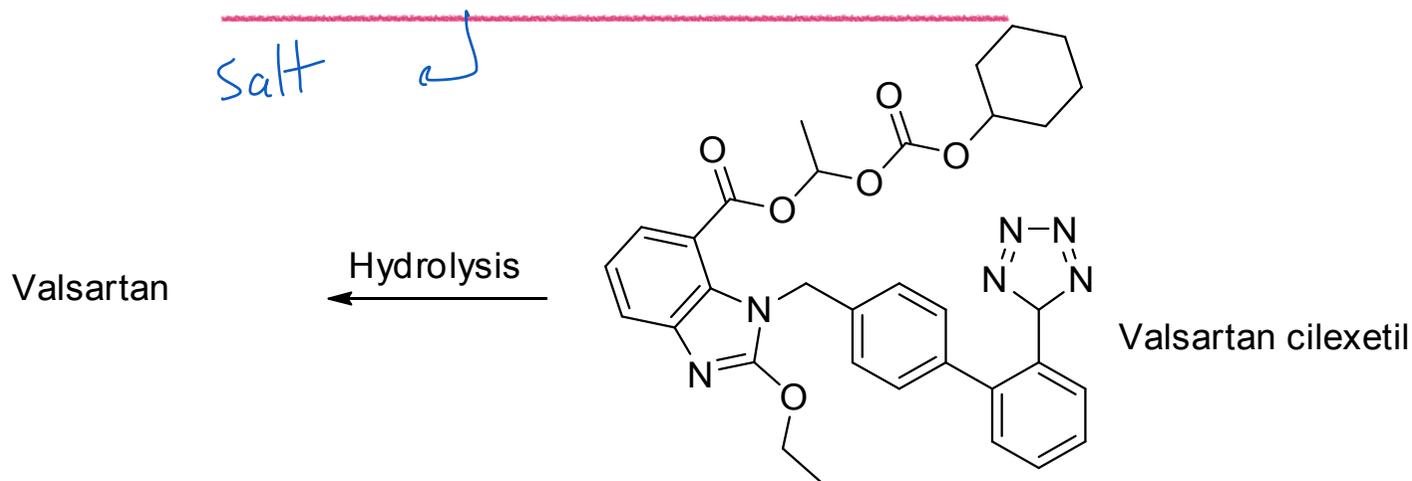
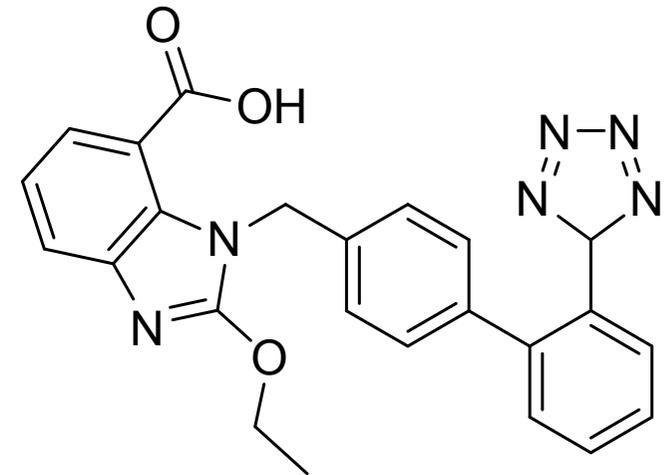
- Valsartan is more polar...has high volume of distribution.
- Valsartan is a valine containing drug...

it will be in zwitterionic form...this reduces its oral absorption.



# Candesartan (Blopress® , Atacand®)

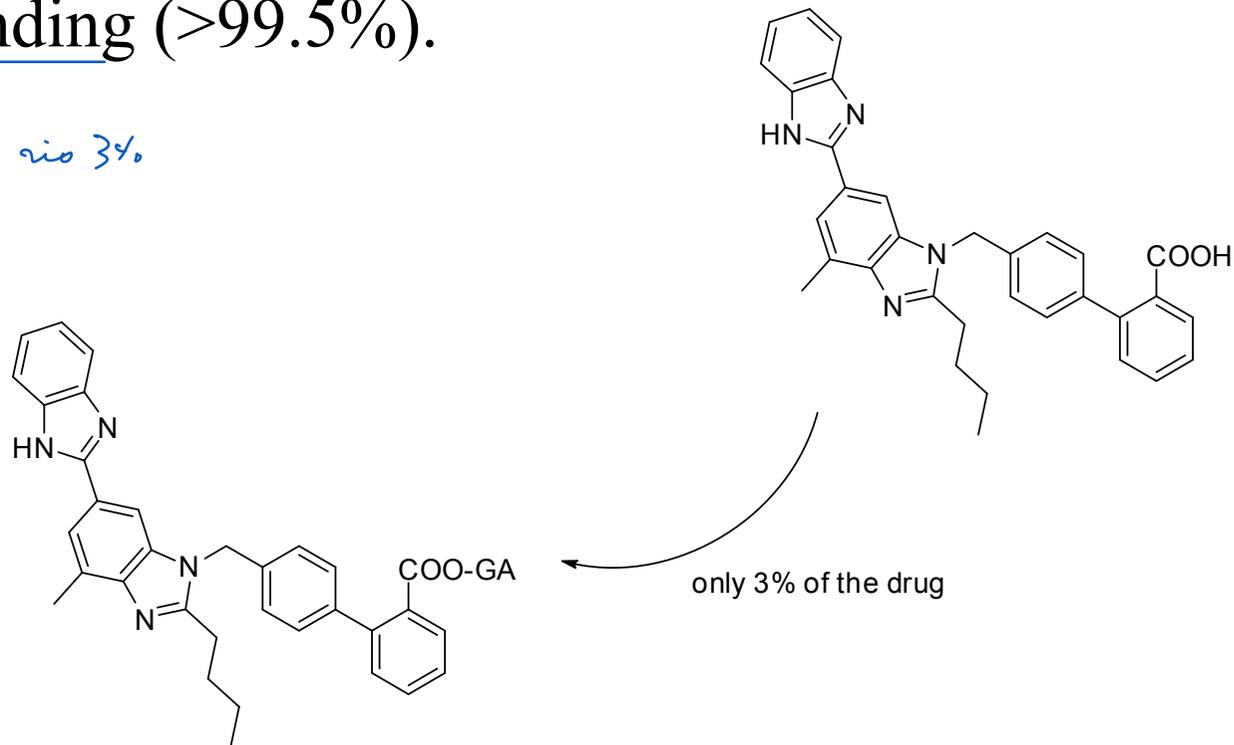
- Recent studies revealed that candesartan can reduce the risk of developing hypertension by two third.
- Used for treating hypertension mainly in combination with thiazide diuretics.
- Given orally as cilexetil ester prodrug:



# Telmisartan (Micardis®)

- Has the longest duration of action ( $t_{1/2} = 24$  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%).

3% منه رح يكون مرتبط بال  
glucuronic acid



the only metabolite recovered for Telmisartan

لا تنسوا زميلنا ايهم

من دعائكم

