ROLE OF METABOLISM

- The role of metabolism step is to degrade or modify the foreign structure, such that it can be more easily excreted. As a result, most drugs undergo some form of metabolic reaction, resulting in structures known as metabolites.

Metabolites may:

1- Lose the activity of the original drug (DETOXIFICATION).

2- Retain a certain level of activity.

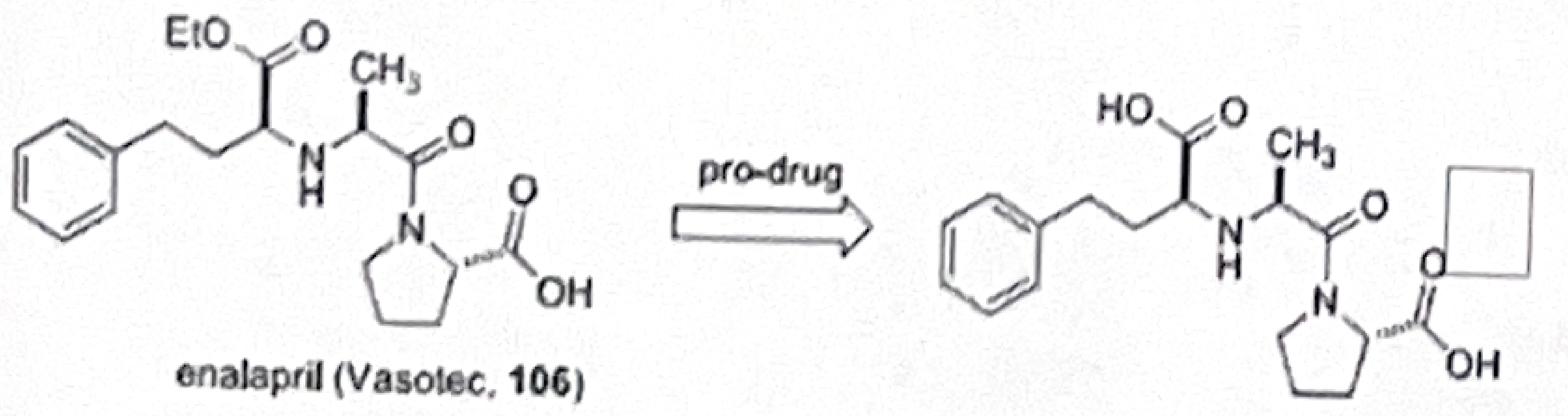
3- Be more active than the parent drug (BIOACTIVATION: PRODRUGS)

① ليه بيصير الـ metabolism للـ Lipophilic ؟
لأنه بيضل بالجسم بشكل أطول وما بيطلع
إلا إذا تحوّل لشكل hydrophilic أكثر
عشان ما نعاني من side effect

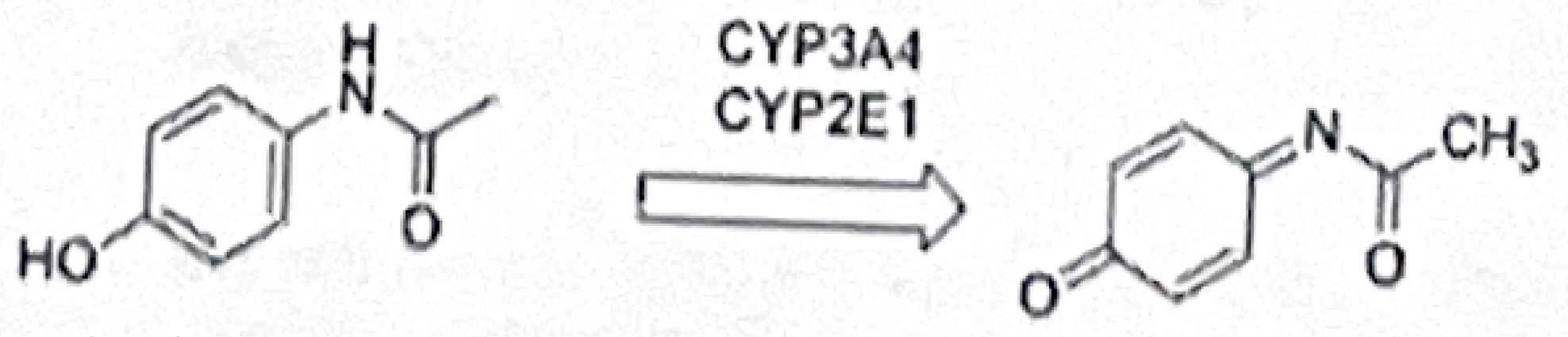
- Aside from water and most hydrophilic dugs, all other molecules/drugs are metabolized. This is actually essential because lipophilic drugs would circulate in the body for a long time, causing untoward side effects if not eliminated in due course. In most cases, metabolism converts lipophilic compounds to hydrophilic metabolites, which are then eliminated/excreted from the body.
- Metabolism is chemical alteration of the drugs in the body. The primary site for drug metabolism is the liver, which is of the uttermost importance with regard to a drug's biotransformations. Other sites of metabolism are the kidney, intestine, lungs, and plasma.

② 1- تعديل بال drug عشان يسهل عملية الـ excretion ولا
2- الـ metabolites عكس يحوّل الـ drug الى ← عادة يخسر الـ drug الـ activity
بتسمّى detoxification
او يحافظ على نشاطه
او يحوّله لشكل active أكثر prodrug.

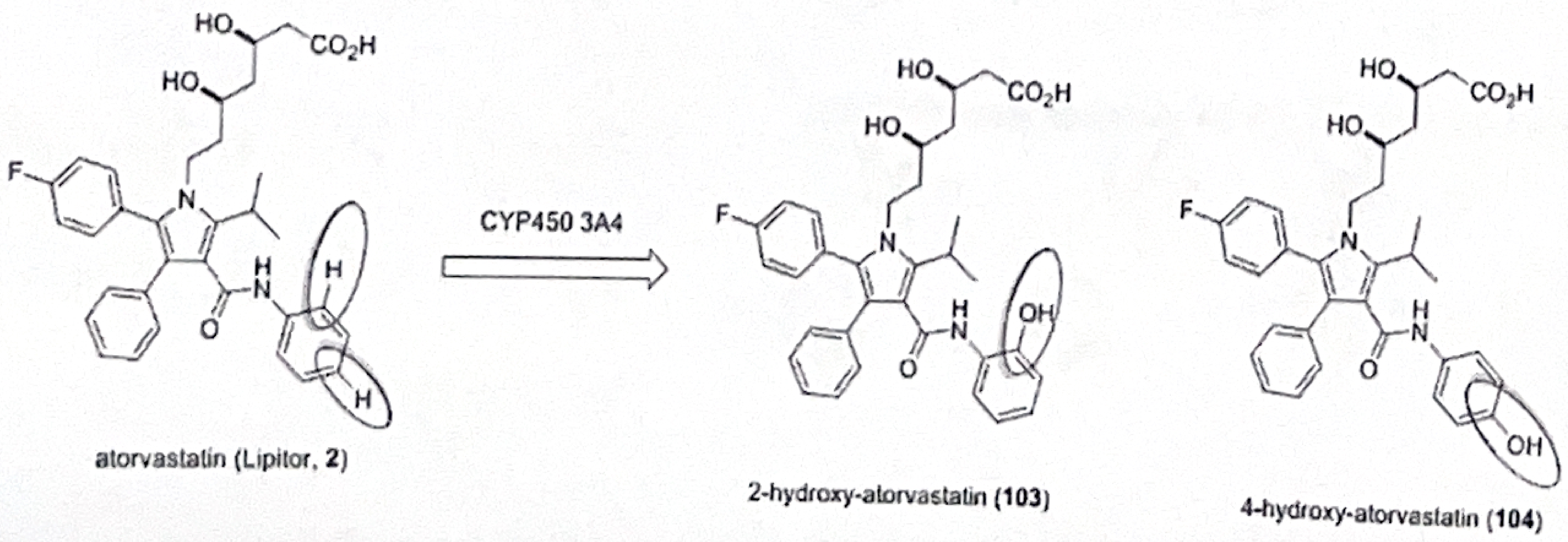
Examples



enalapril (Vasotec, 106) → enalaprilat (105)



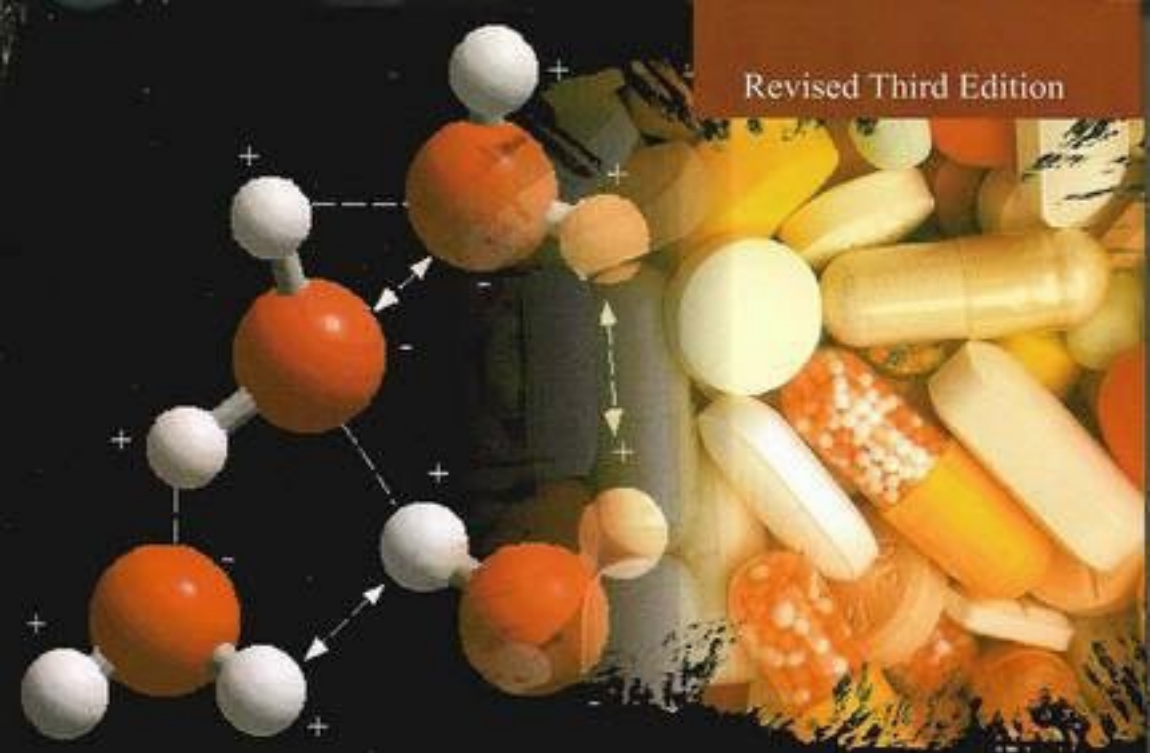
acetaminophen (Tylenol, 109) OK → NAPBQI (110) Bad!



atorvastatin (Lipitor, 2) → 2-hydroxy-atorvastatin (103), 4-hydroxy-atorvastatin (104)

③ المكان الأساسي لحصول الـ metabolism هو الـ Liver بس يحصل كمان بالـ Kidney والـ intestine والـ lungs والـ plasma

Revised Third Edition



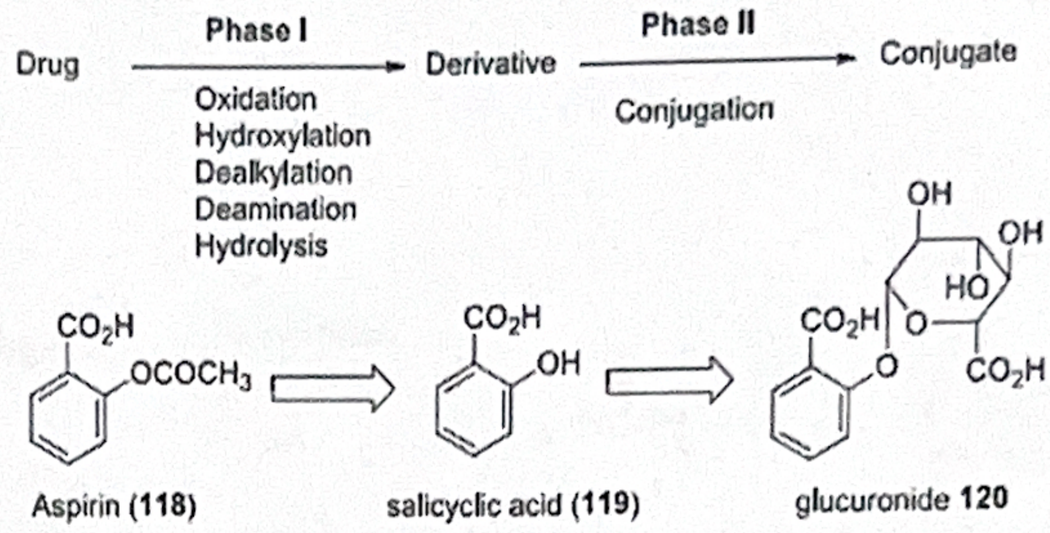
Medicinal Chemistry

Niveen Abualrub

Ashutosh Kar

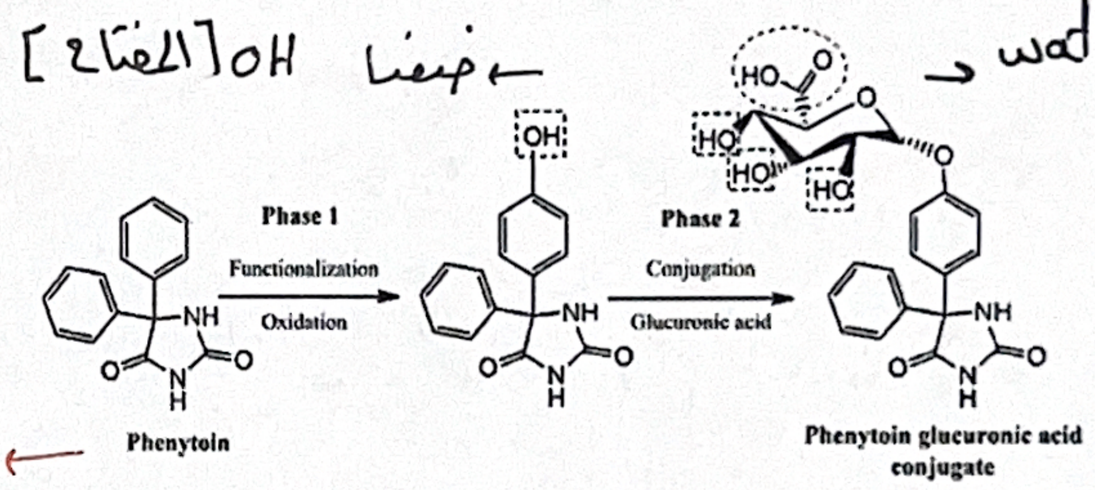
10/09/1444

Phases of Metabolism



- Drug metabolism may be divided to two phases: Phase I metabolism and Phase II metabolism. *Phase I metabolism* refers to functional group transformations of the original drug, converting it to a more polar molecule(s).
- *Phase II metabolism*, also known as conjugation, is the process of appending a very polar and highly hydrophilic molecule (glucose or sulfate, for example) to appropriately functionalized parent compound or Phase I metabolite.

[العقار] OH فيها ← water soluble →



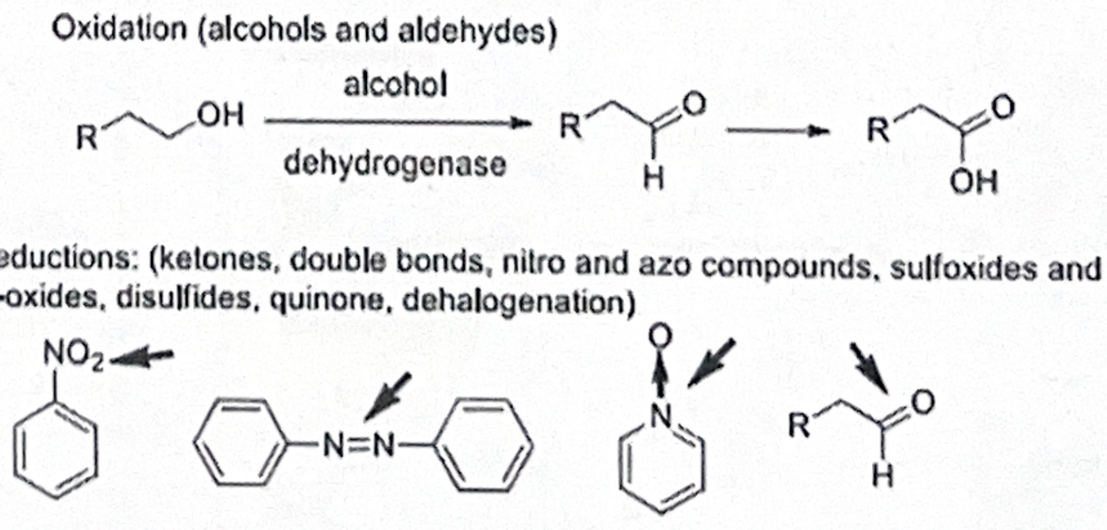
← اخذنا عنه بأول المادة

antiepileptic. ←

يتم اخراجه عن طريق Kidney. الـ

Phase I metabolism

- The types of reactions for Phase I metabolism are oxidation, reduction, hydrolysis, cyclization, and de- cyclization.



بنرجع OH عكسه تكون نتيجة oxidation أو reduction أو hydrolysis.

/ /

Drug Metabolism →

عن طريقه ال enzymatic transformation
ال metabolites عادة "Lose the activity of the original drug"
[Bioactivation] او بيصيروا more active than the original drug. ← pro-drug.
مرتبط بال pro-drug
زي ال L-dopa

* هنا 2 phases ←
phase I ← Functionalization ← بنضيف functional group ليصير more polar.
phase II ← Conjugation ← بنربط على ال functional group مركب بكون water soluble عشان يصير له excretion عن طريقه ال kidneys. زي ال glucuronic acid الي عنده 3 hydroxyl gro. & -charged
* معظم ال metabolism بيصير بال Liver

* هنا other sites لل metabolism الي هم ←
Kidney ←
intestine ←
lungs ←
plasma. ←

* once انه ال conjugation صار ← المركب بيصير مش قادر يدخل BBR او other tissues

* شو هي ال Mixed-function oxidases ← انزيمات موجودة بال Liver
اذا كانوا موجودين بال liver بنذكرهم بسميهم ← Microsomal oxidases.

* الـ hydroxylation ← اضافة الـ OH-group

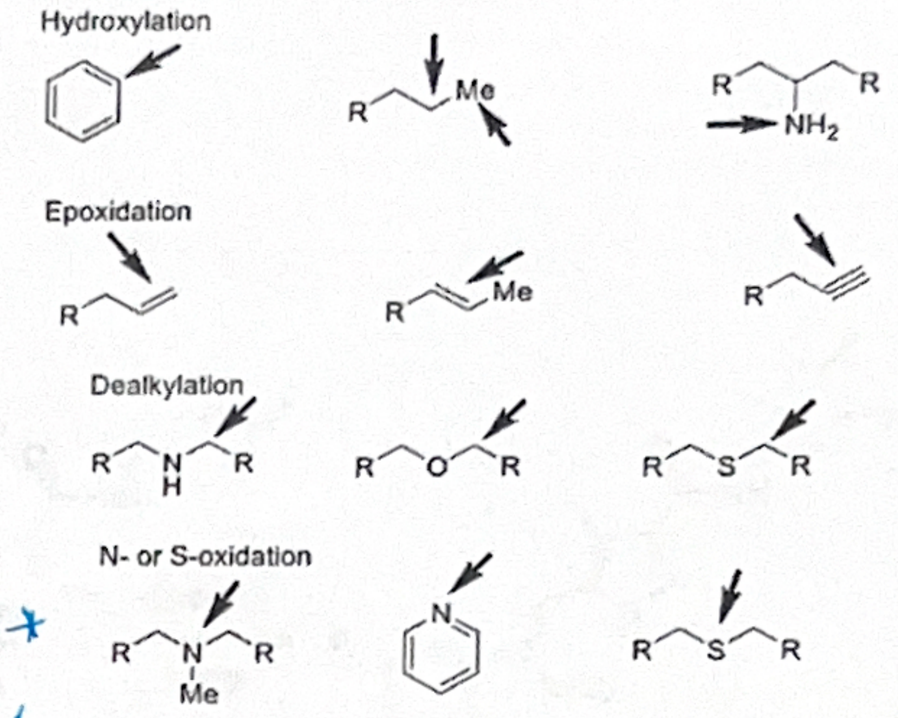
OXIDATION

- Oxidation is the most important drug-metabolizing reaction.
- Phase I metabolism is largely an oxidative process.
- Various oxidative metabolisms are hydroxylation; oxygenation at carbon, nitrogen, or sulfur atoms; N-dealkylation or O-dealkylation, oxidative deamination, etc.
- Hydroxylation is a prevalent oxidation process for Phase I metabolism.

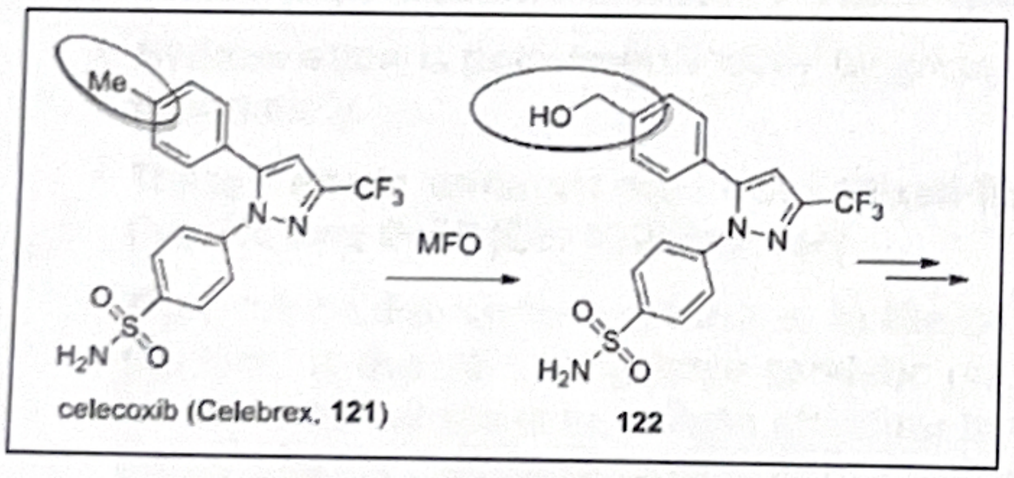
drug-metabolizing reaction هو من أهم الـ oxidation

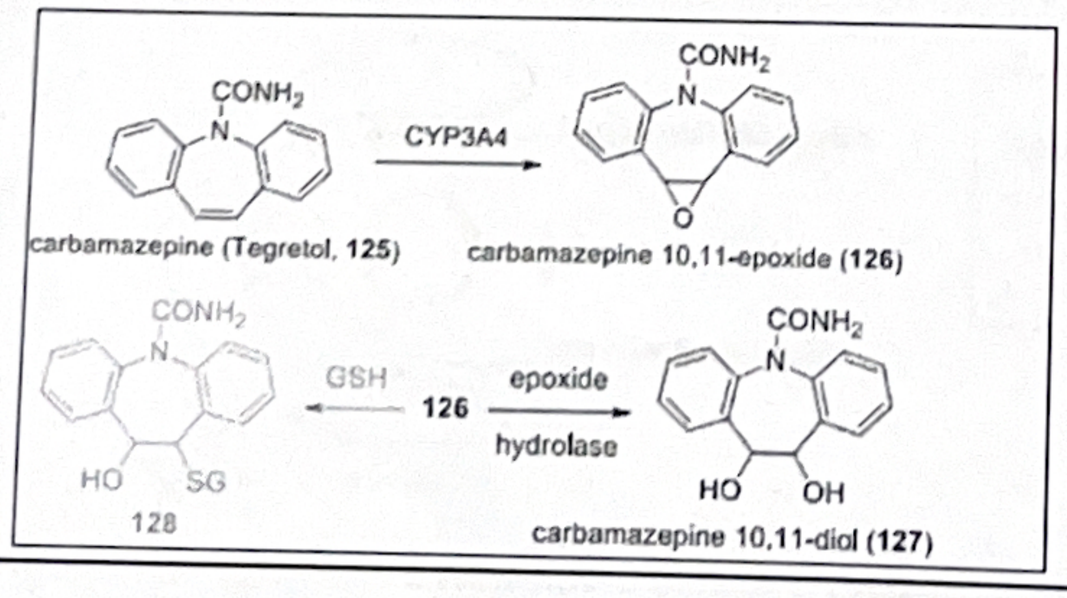
* الـ oxidative process في الـ phase I

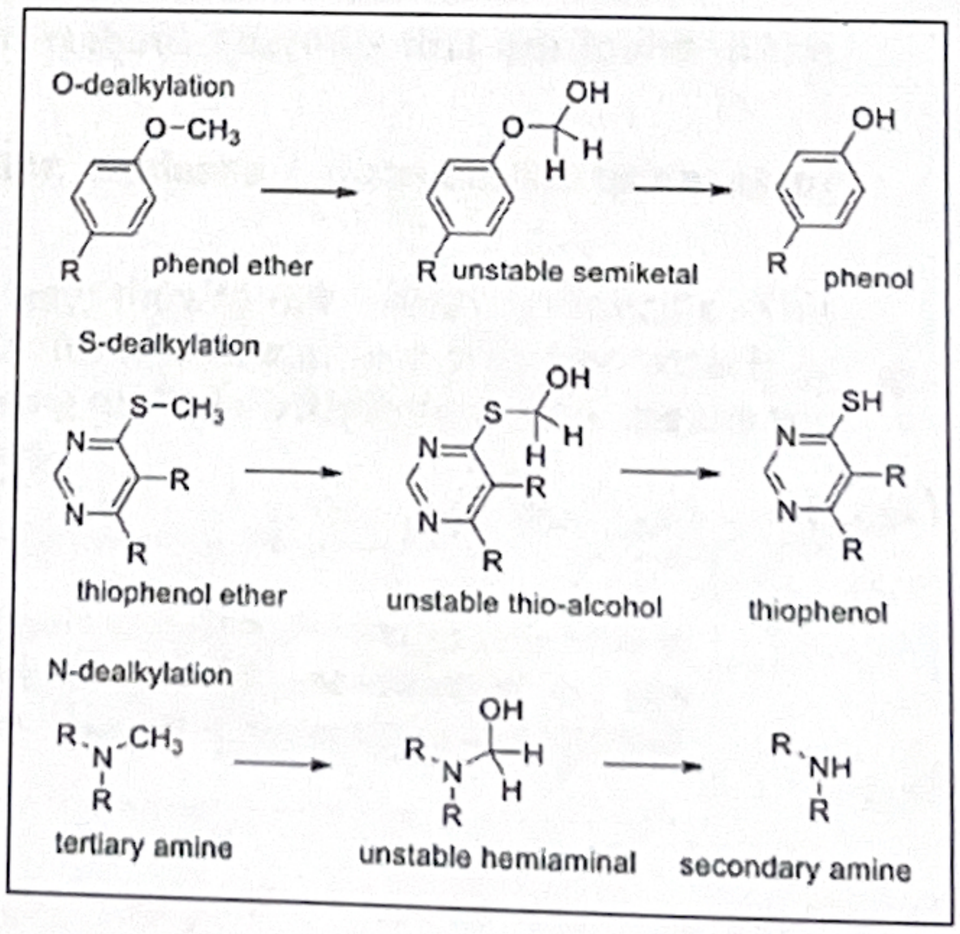
*



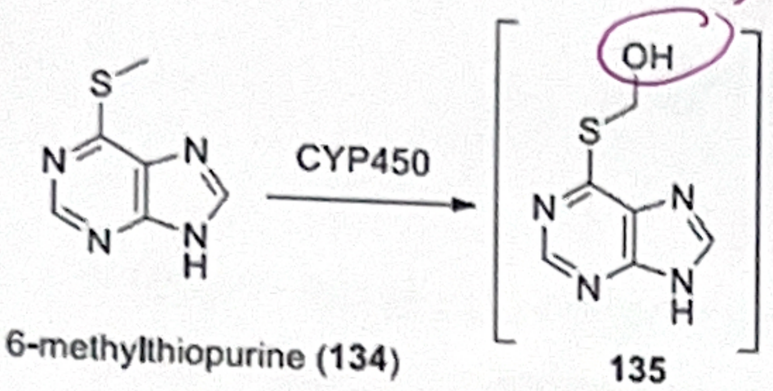
EXAMPLES



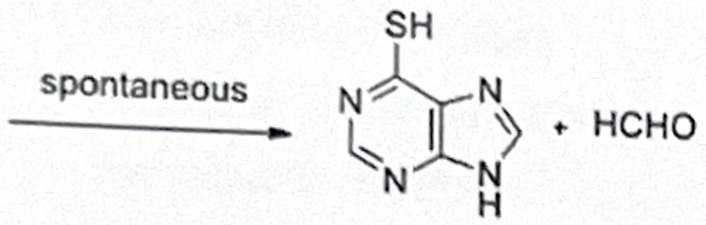




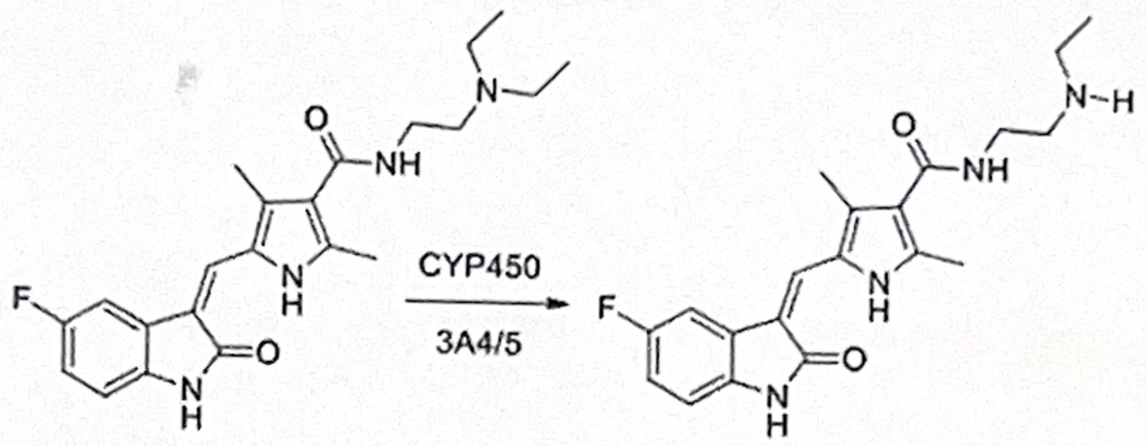
OH هيك



6-methylthiopurine (**134**) — **135**



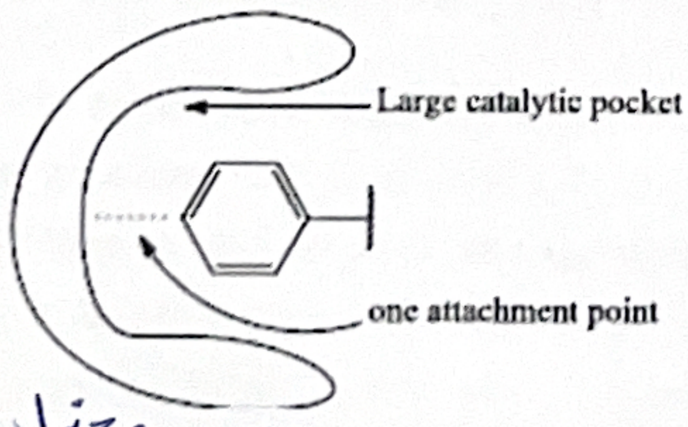
6-mercaptoopurine (**136**)



sunitinib (Sutent, **132**) — SU-12662 (**133**)

oxidation يعني اي مادة غريبة تدخل لجسم الانسان بأغلب الأحوال بدصير لها

- Oxidation probably is the most common reaction in xenobiotic metabolism
- Hydroxylation is performed mainly by group of metabolic enzymes that are found in the liver mainly.
- These hepatic enzymes are called **Mixed-function oxidases / Microsomal oxidases or Cytochrome P450 (CYP450) Enzymes.**
- They can oxidize various substrates in the same way; they're not 'substrate-specific'. This property is due to having large catalytic pockets (no hindrance) and they can attach or handle their substrate in a single attachment (having multiple attachment sites means the enzyme can act on some substrates but not others).



This low number of attractive interactions leads to low affinity, low specificity, no selectivity, and slow turnover. Therefore, they're slow rate enzymes

c'lari ,erythromycin, ← mycin الـ 2 ← 7 هم ← inhibidors الـ +

kito,itra conazole ← conazol 2

verapamil 1

grapefruit juice 1

diltiazem 1

- Other metabolic enzymes involved in Oxidative reactions :

1. • **flavin-containing Monooxygenases**
2. • **Monoamine Oxidases**
3. • Alcohol Dehydrogenases
4. • Aldehyde Dehydrogenases
5. • Xanthine Oxidase

امثلة على انزيمات ثانية بيشاركوا ← oxidative reactions بال

Cytochrome P450 → means
cyto → cell
chrome → red color
P450 → spectrophotometric peaks at 450nm

محلوة الك بس مش للحفظ ←

1 * هم عائلة من الانزيمات الهم different chemical structures اسمهم monooxygenase.

2 * ليه سموهم صبك ؟! لانها مرتبطة بـ membrane داخل الخلية " الهيمارة الحمرة = cyto "

وتحتوي على جزيئة ال heme الي هي عبارة عن " كوبالت وفسفور " ← بتخلي ال lights

Cytochrome P450 (CYP450) Enzymes → 450nm = ضوئي لطول موجي عند نزع جزيئها ال CO_2

1. • Drugs are metabolized mostly by a class of enzymes called cytochrome P450 (CYP450) enzymes. they belong to a general class of enzymes called the **monooxygenases**.
2. • They are so named because they are bound to membranes within a cell (cyto) and contain a heme pigment (chrome and P) that absorbs light at a wavelength of 450 nm when exposed to carbon monoxide.
3. • CYP450 enzymes are a superfamily of 18 heme-containing enzyme families, which may be further divided into 43 subfamilies and more than 200 CYP450 isoforms. Chief among them are **CYP450 3A4 and 2D6**.
4. • CYP 3A4 carries out biotransformations of the largest number (~50%) of drugs. → مسؤول عن التحولات لأكثر من 50% من الـ drugs
5. • Other important CYPs are 1A2, 2C9, 2C19, and 3A5.
   • In all, these six CYP enzymes are responsible for metabolizing 90% of drugs.
   • In addition to the liver, these isoforms are expressed in the intestine and the kidney too. → موجود بال Liver والـ Kidney والـ Intestine
   • Inhibitors of CYP450 3A4: erythromycin, clarithromycin, verapamil, ketoconazole, itraconazole, diltiazem, and a constituent of grapefruit juice: responsible for unwanted interactions with many drugs.

امثلة على مثبطات الـ CYP450 ← له مسؤول عن تفاعلات غير المرغوب فيها مع كثير من الـ drugs.

3. هاي الانزيمات زي ماقلنا هي عيلة كبيرة تتكون من 18 heme containing enzyme families تنقسم الى 43 subfamilies و 200 CYP450 isoforms اهمها 2D6 ، CYP450 3A4

4. مسؤول عن الـ biotransformation لأكثر من 50% من الـ drugs

5- الـ CYPs 1A2، 2C9، 2C19، 3A5 ← مسؤولين عنه. الـ metabolism لـ 90% من الـ drugs

Perric ← Fe^{3+} ← بالنالي الحديد

*معلومة اضافية ← من باب الربط الـ Cyp 450 عنده ارقام 3 ←

و الـ hemoglobin ← Fe^{2+} ← (Ferrous) كلمة اطول بس رقم اصغر ***

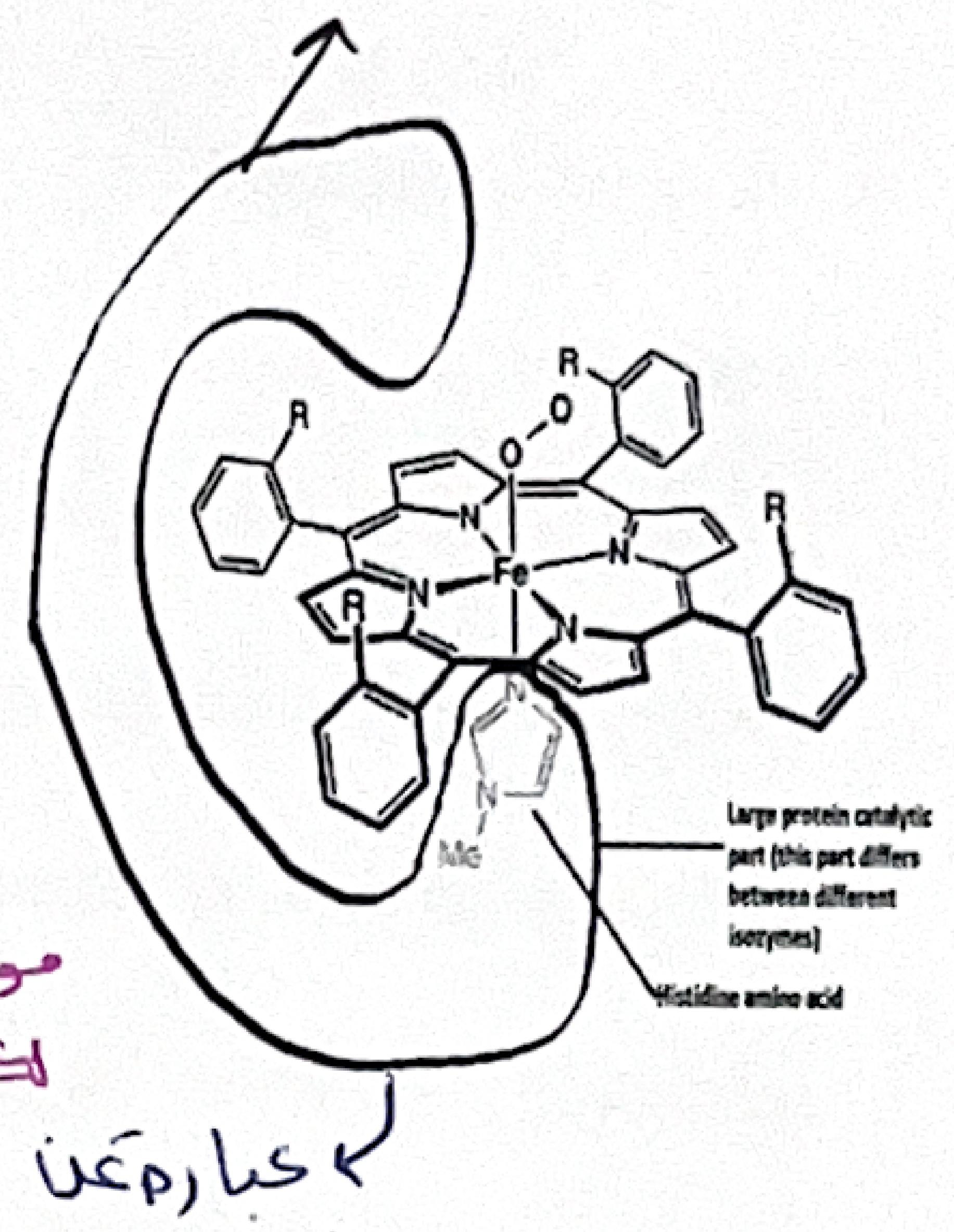
1 * اختلافهم بالـ Large catalytic part ← لكن كلهم بشتركوا بأنهم عندهم

الـ porphyrin ring "non-protein part" "heme cofactor" ↵

- Note in the figure the large protein catalytic part; this is the part that differs in different oxidases (different amino acid sequence).
- However, they all **share the non-protein part (heme cofactor)**
- As you can also see the **porphyrin ring** in the catalytic ring; made up of 4 pyrrole rings in a highly conjugated system.
- There's an Iron in the middle of the ring that forms coordinate bonds with Nitrogen atoms [Coordinate bond: a bond between an electron donor (Nitrogen in this case) that gives the electrons to the empty d-orbitals of a metal (Iron in this case)].
- The Iron in the porphyrin ring forms the **heme;** موجودة بالـ hemoglobin
- **The Iron is in the ferric state (Fe^{+3}).** → Ferric بالشكل لكن الحديد على

A similar molecule that contains a heme group is hemoglobin but the Iron in hemoglobin is a ferrous iron (Fe^{2+}).

* يعني الـ porphyrin موجود Fe^{3+} بالـ Cp450 hemoglobin ولكنه شكل الحديد يختلف Fe^{2+}



← عبارة عن protein من الخارج

2 * فيه شي اسمه catalytic domain الـ molecule وح يحصل عنده oxygen و يصير له oxidation

بيدخل داخله

3 * ذرة الحديد هي الي ماسكة كل الشي ← 4 pyrrole rings ← مع الـ N

وتكمم مع الحديد اسمها الـ porphyrin ring ← الرابطة الخامسة مع الـ imidazole ← "histidine" مع الـ N برضو

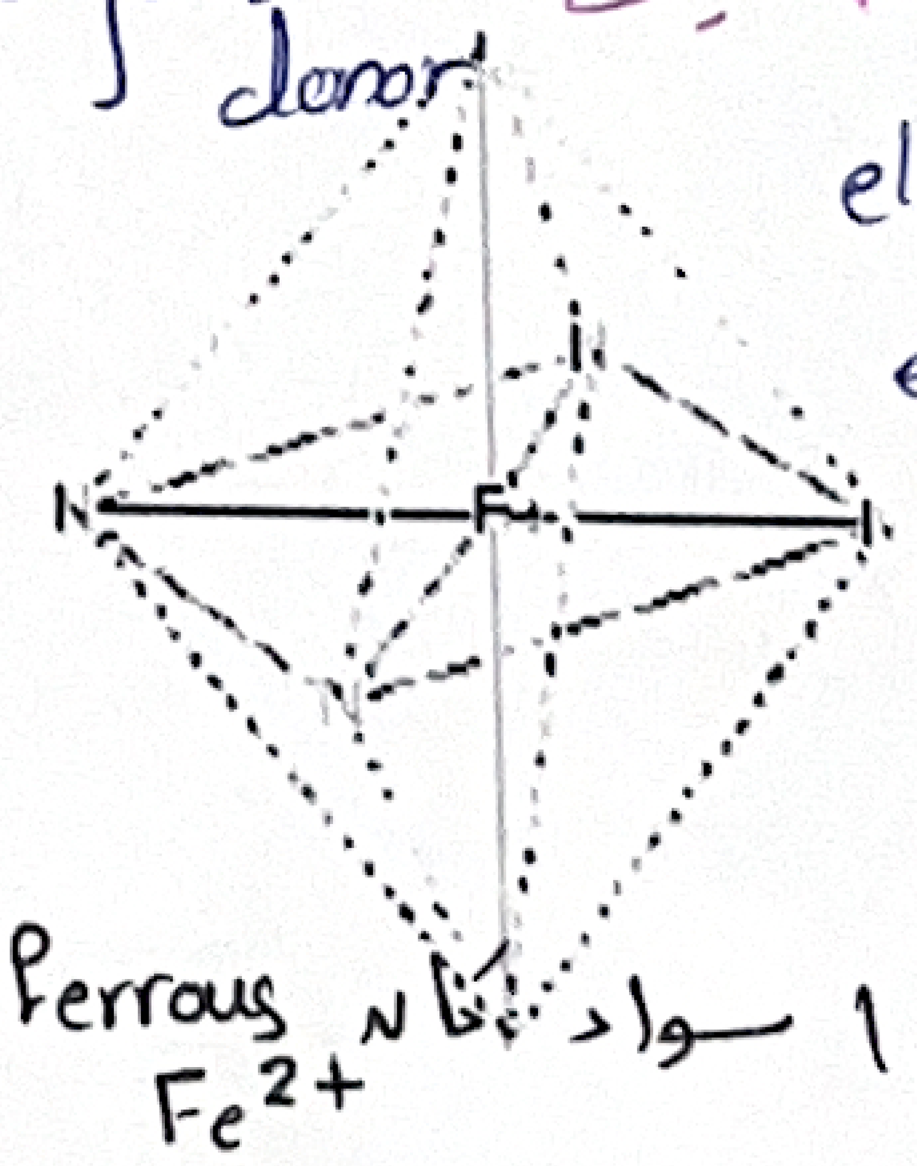
← الرابطة السادسة مع الـ oxygen molecule أو الـ peroxide

- The Iron (whether a ferrous or a ferric ion) can form up to **6 coordinate bonds** in a bipyramidal system as you can see in the figure.
- In the porphyrin ring, the Iron forms 4 bonds with the Nitrogen atoms in the pyrrole ring so that means there are two bonds left for the Iron to form:
- - One of the two bonds (**the 5th bond**) is formed with a Nitrogen atom in the imidazole group found in the amino acid histidine; this bond is responsible for holding this porphyrin ring structure in the catalytic pocket of the oxidase enzyme.
- The **6th bond** is formed between the Iron and **Oxygen molecule (O_2)**. This oxygen is very important since it's the oxygen atom that is donated in the oxidation reaction (act as oxidizing agent). Under the slightly acidic condition of the liver, the oxygen molecule is in the form of (—O—OH) and this –OH is donated in the oxidation reaction to the metabolized compounds to form (R—OH).
- **So, the source of the –OH** is the oxygen bound to the Iron in cytochrome P450 (CYP-450).

لـ هو الي ح يركب على الـ molecule الي حيصير له oxidation * يعني هي الـ oxidizing agent

4 * الـ Iron مع الـ N بيعملوا coordinate bonds

يعني رابطة بين [N] electron donor بيعطي electrons لـ empty d-orbitals of metals [Iron]



7. الـ Iron سواء كان Ferrous Fe^{2+} او Ferric Fe^{3+} ← بيعمل 6 روابط

$$Drug-H + O_2 + NADPH + H^+ \xrightarrow{\text{Cytochrome P450 enzymes}} Drug-OH + NADP + H_2O$$

معناهم هو بنقطة (3)

8. بيصير donation للـ oxygen atom ← under slightly acidic condions of the liver

بيصير oxidation للـ drug وبينتج R-OH

يعني الـ source للـ OH هو الـ oxygen bound

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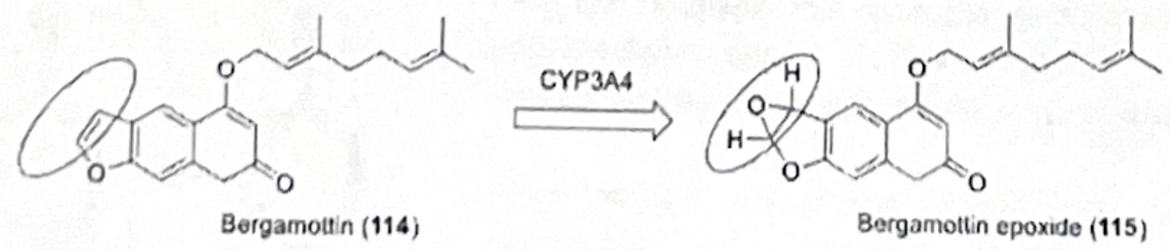
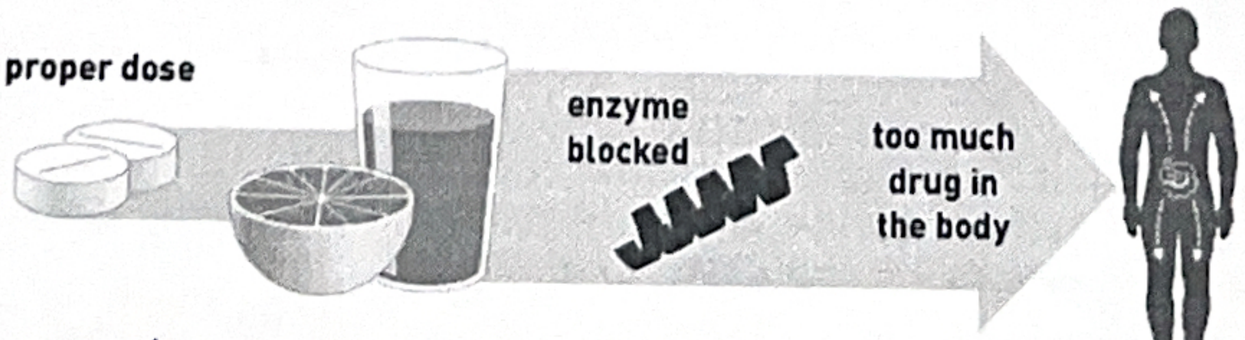
Drug–Drug Interactions

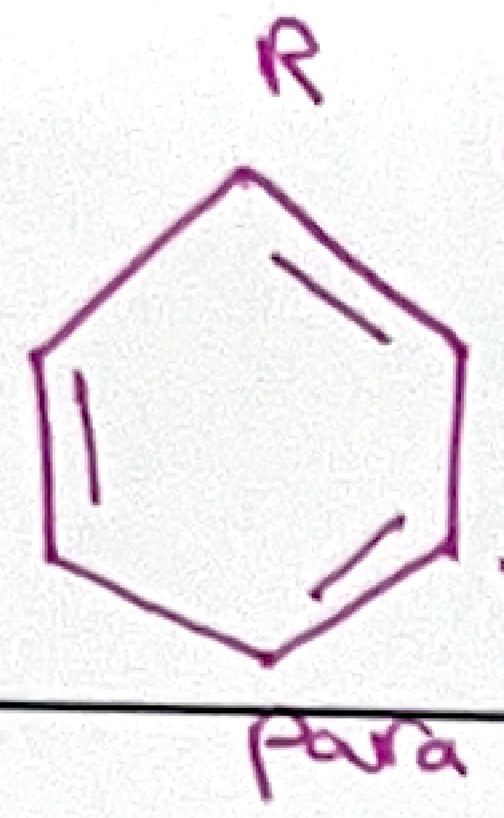
- DDI refers to the fact that toxicity often ensues when two co-administered drugs are metabolized by the same isoform of CYP450 enzymes.
- For example, if drugs A and B are both metabolized by CYP450 3A4, as it so often happens, the enzyme is preoccupied by metabolizing drug A, it no longer possesses the capacity to metabolize drug B. Without the benefit being biotransformed, untoward toxicities often manifest
- With regard to drugs as ligands for CYP450 enzymes, they may be divided into three categories:
  - Substrates: ligands that are metabolized by the enzymes. Examples: macrolide antibiotics, antifungal ketoconazole and grapefruit juice.
  - inducers, increase the enzyme activity by increasing enzyme synthesis. Examples: rifampicin, phenytoin, carbamazepine and phenobarbital
  - inhibitors: slow down the metabolism of substrates leading to an increased drug effect (reversible inhibitors and irreversible inhibitors). Examples: fluoxetine, ketoconazole, grapefruit

- Drinking a glass of juice in the morning is good for you. But if you take your medicine with it, you should be aware of *the grapefruit juice effect*.
- Grapefruits contain furanocoumarin derivatives that are rapid, potent, mechanism-based inhibitors (MBIs) of intestinal CYP3A4. Its major ingredient bergamottin is oxidized by CYP3A4 to bergamottin epoxide. Bergamottin inhibits CYP3A4 via protein modification. It also inhibits CYP1A2, 2A6, 2C9, 2C19, 2D6, and 2E1. Therefore, when a drug is taken with grapefruit juice, its bioavailability is frequently boosted.



Bergamottin (**114**) Bergamottin epoxide (**115**)





Oxidative Reactions

هاي كل ال oxidative reaction بنفصل فيهم
بعدين

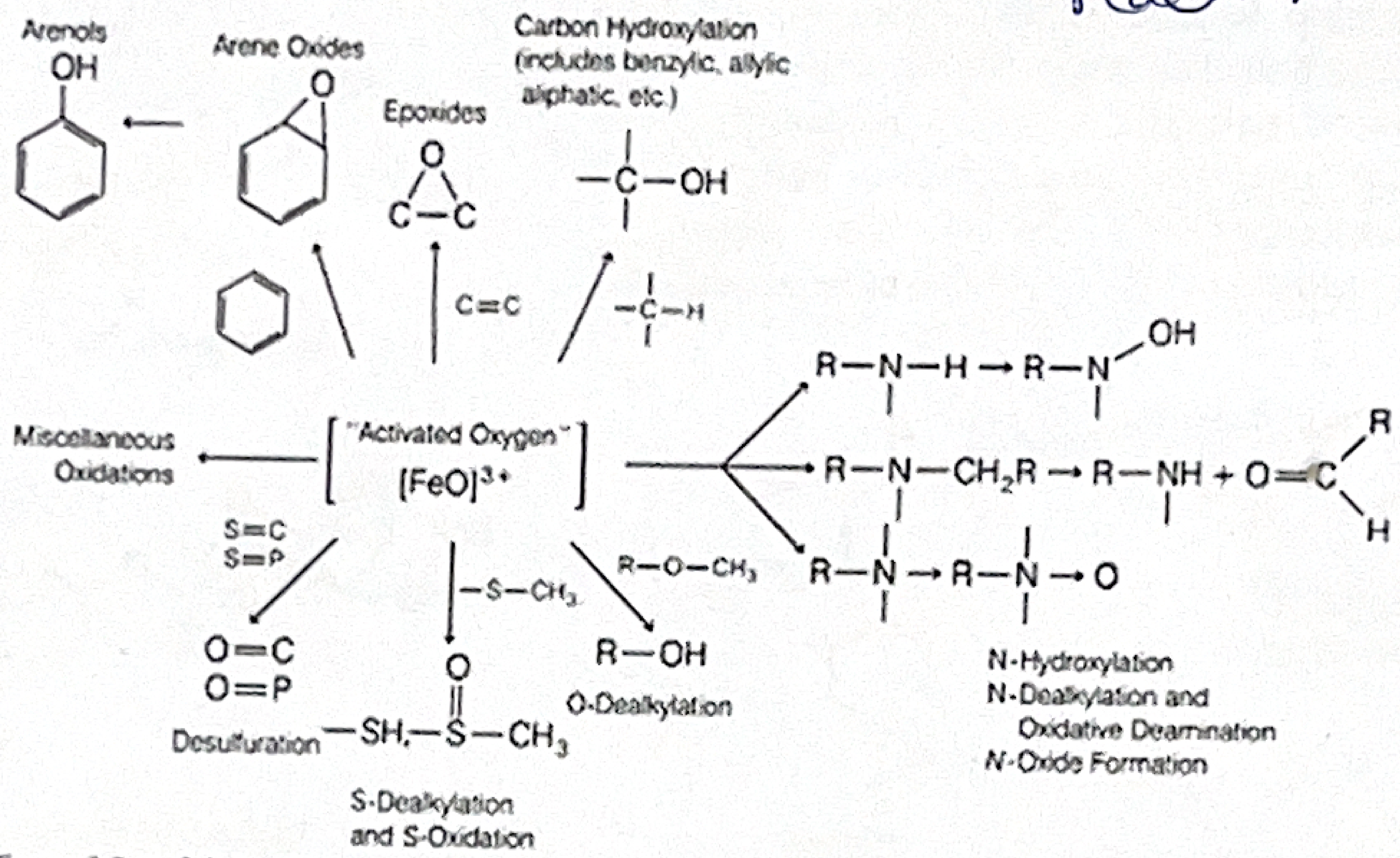
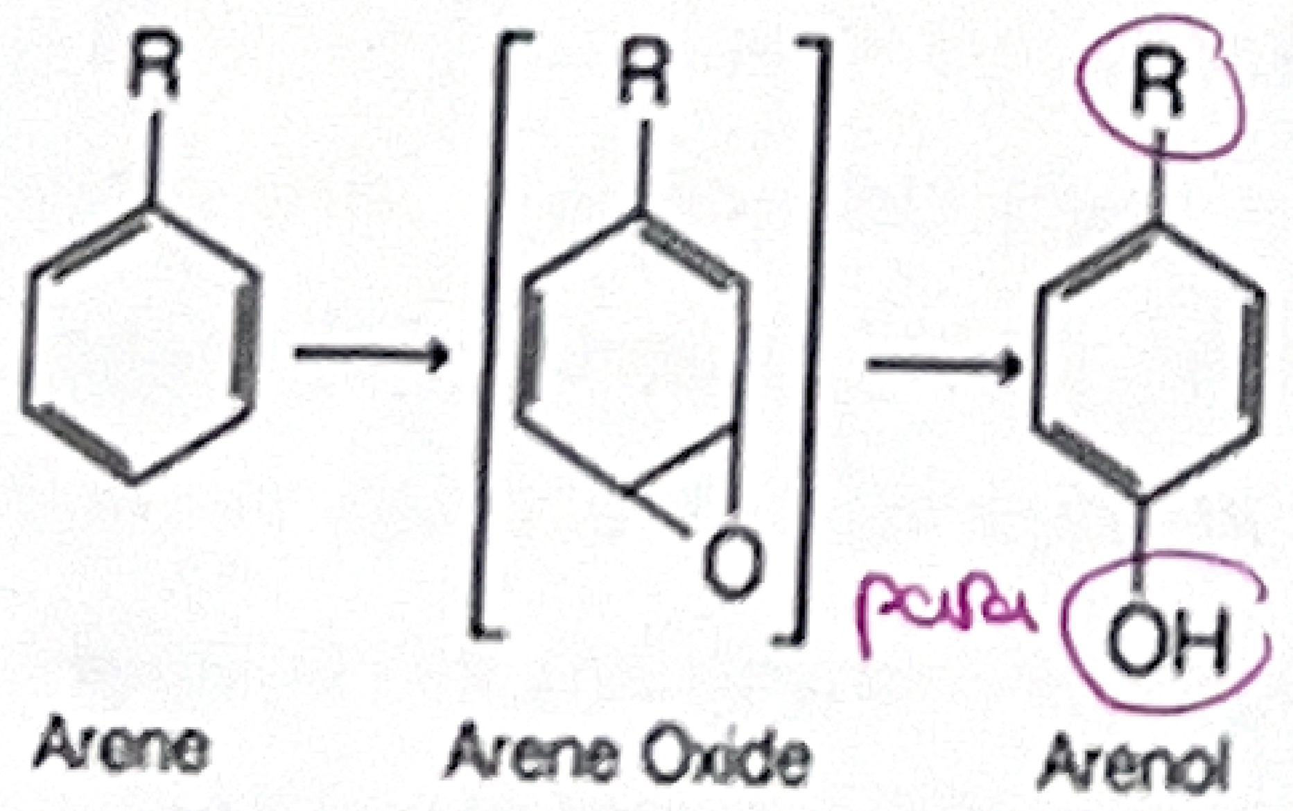


Figure 3.3 • Schematic summary of cytochrome P450-catalyzed oxidation reactions. (Adapted from Ullrich, V.: Top. Curr. Chem. 83:68, 1979.)

1- ال aromatic hydroxylation ← هي mixed functional oxidation of aromatic compounds [arenes] + their corresponding phenolic metabolites + [arenols]

2- تحصل عن طريق epoxide intermediate ← اسمه arene oxide.

Aromatic oxidation



The term aromatic hydroxylation refers to the mixed functional oxidation of aromatic compounds (arenes) to their corresponding phenolic metabolites (arenols). It is believed that almost all aromatic hydroxyl reactions proceed initially through an epoxide intermediate called "arene oxide". which quickly and spontaneously rearranges to the arenol product in most cases.

Most foreign compounds containing aromatic moieties are susceptible to aromatic oxidation. In humans, aromatic hydroxylation is a major route of metabolism for many drugs containing phenyl groups.

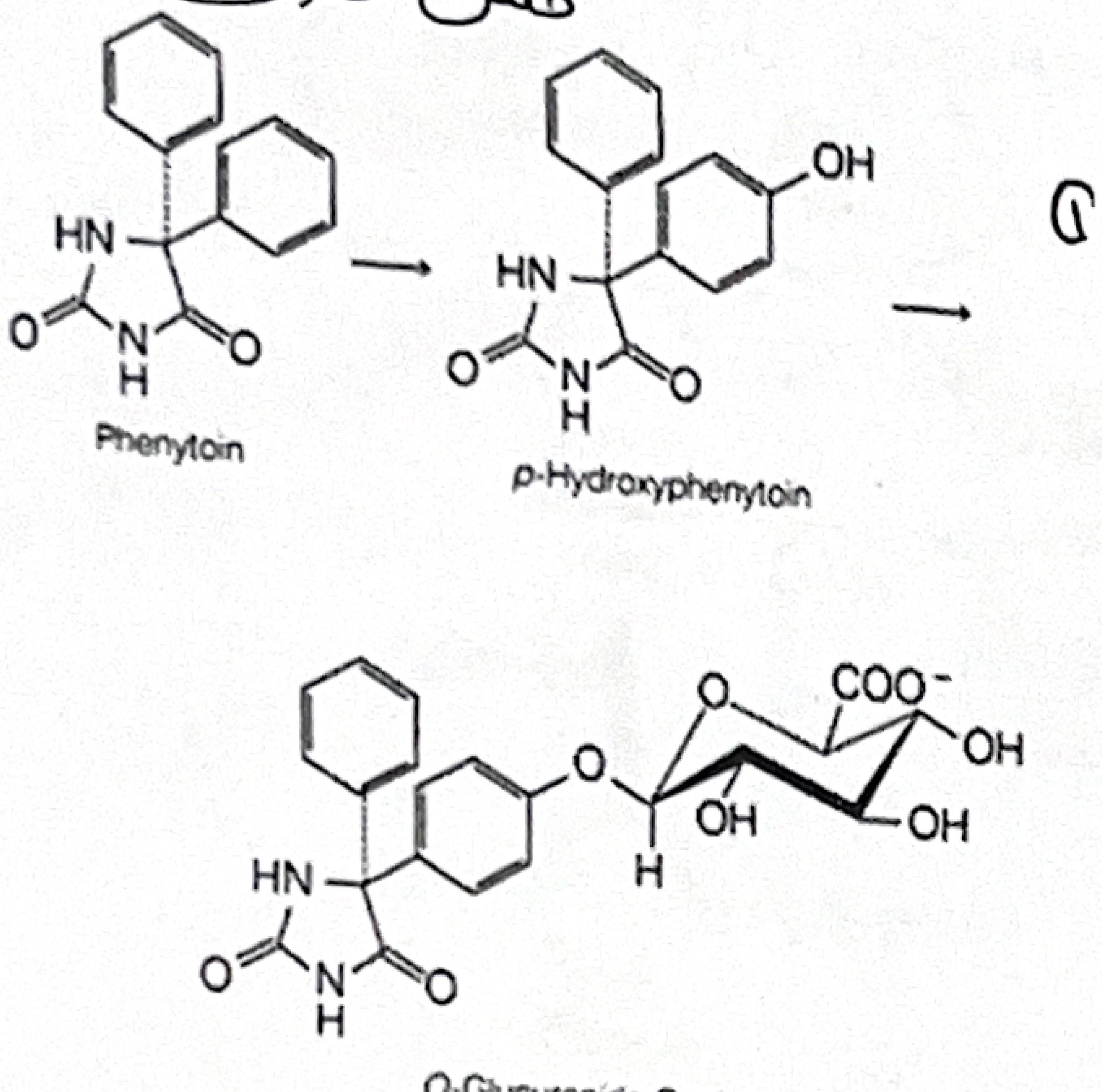
Important therapeutic agents such as propranolol, phenobarbital, phenytoin- , atorvastatin, 17α- ethinylestradiol and S- warfarin undergo extensive aromatic oxidation. In most of the drugs just mentioned, hydroxylation occurs at the para position. أمثلة

← aromatic hydroxylation

اغلب الادوية الي تحتوي على phenyl groups بيصير لها metabolism عن طريق ال aromatic hydroxylation

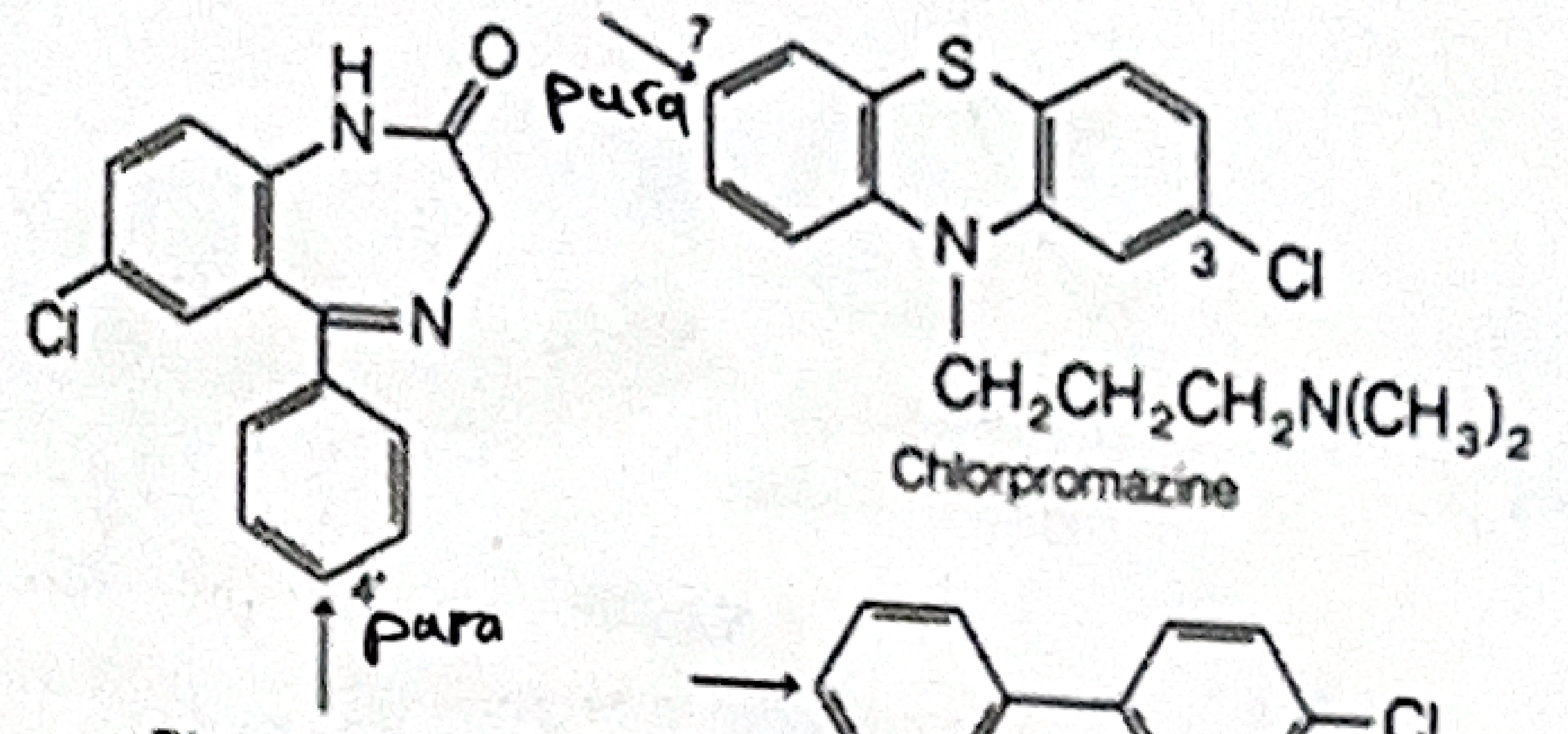
وبيحصل تحديداً على ال para position لأنه The least steric hindered لأنه سهل يشتغل الانزيم عليه لأنه أبعد نقطة عنه

حصلنا على وحدة من ال rings
مش تنتين



Phenytoin → p-Hydroxyphenytoin → O-Glucuronide Conjugate

① In compounds with **two aromatic rings**, hydroxylation occurs preferentially in the more electron-rich ring. For example, aromatic hydroxylation of diazepam (Valium) occurs primarily in the more activated ring to yield 4'-hydroxydiazepam. A similar situation is seen in the 7-hydroxylation of the antipsychotic agent chlorpromazine (Thorazine) ② and in the para-hydroxylation of p-chlorobiphenyl to p-chloro-p'-hydroxybiphenyl.



Diazepam

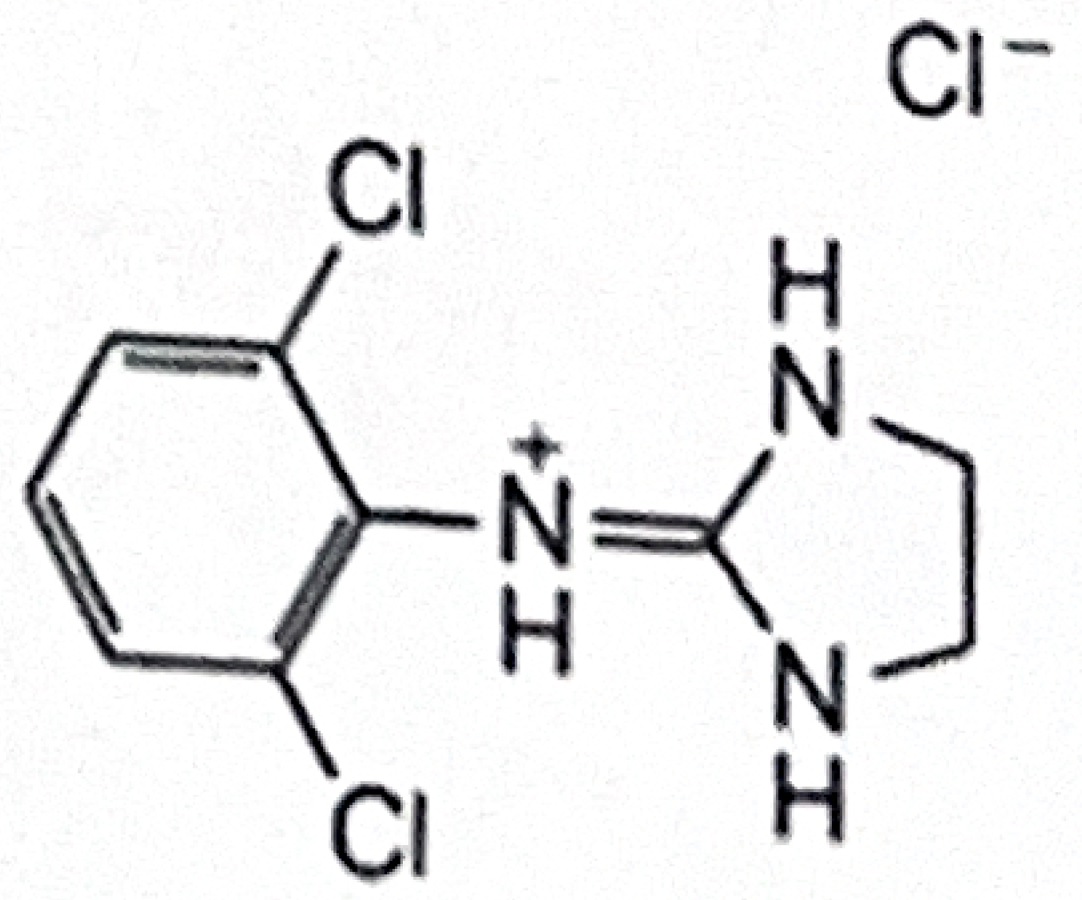
Chlorpromazine

p-Chlorobiphenyl

* في حالة عنا two aromatic rings ← بيحصل ال hydroxylation على ال more electron-rich ring يعني ال ring الي عليها substitution كتير.

ومكتوب امثلة

Often, the substituents attached to the aromatic ring may influence the ease of hydroxylation. As a general rule, microsomal aromatic hydroxylation reactions appear to proceed most readily in **activated (electron-rich) rings**, whereas deactivated aromatic rings (e.g., those containing electron-withdrawing groups Cl, -N+R3, COOH, SO2NHR) are generally slow or resistant to hydroxylation. The deactivating groups present in the antihypertensive clonidine may explain why this drug undergoes little aromatic hydroxylation in humans.



Clonidine Hydrochloride

* ال substituents بأثر على سهولة ال hydroxylation

* ال hydroxylation بيكون activated أكتر في حالة ال ring ال[electron-ring] أكتر من ال aromatic ring

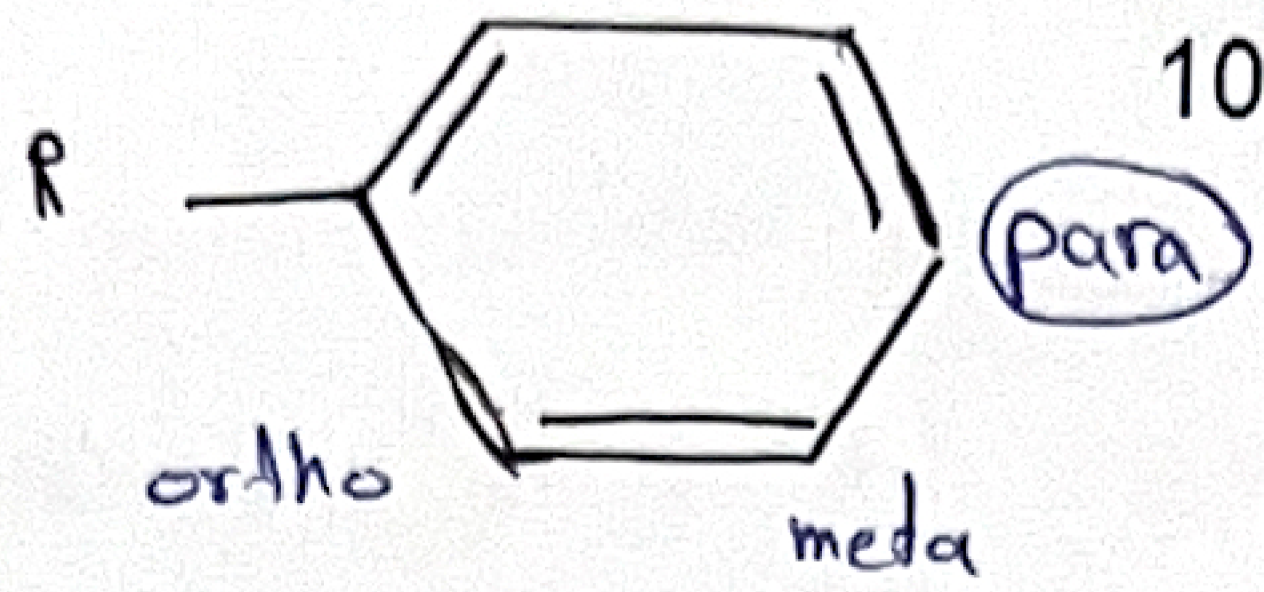
الي تحتوي على withdrawing group مجموعات سحب ال electrons زي ← Cl (1، N^+R_3 (2، COOH (3

SO_2NH_4 (4

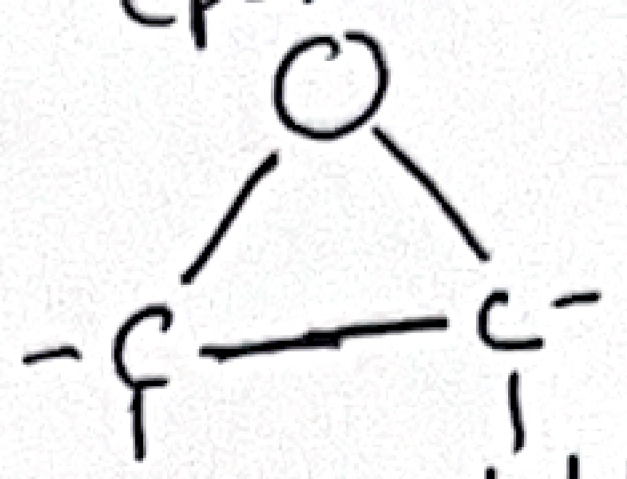
لهاي بتقلل أو بتكون بطيئة أو مقاومة لل hydroxylation.

* مثال: Clonidine ما بصير له hydroxylation كتير لأنه كل ال rings عليهم substituents

10/09/1444

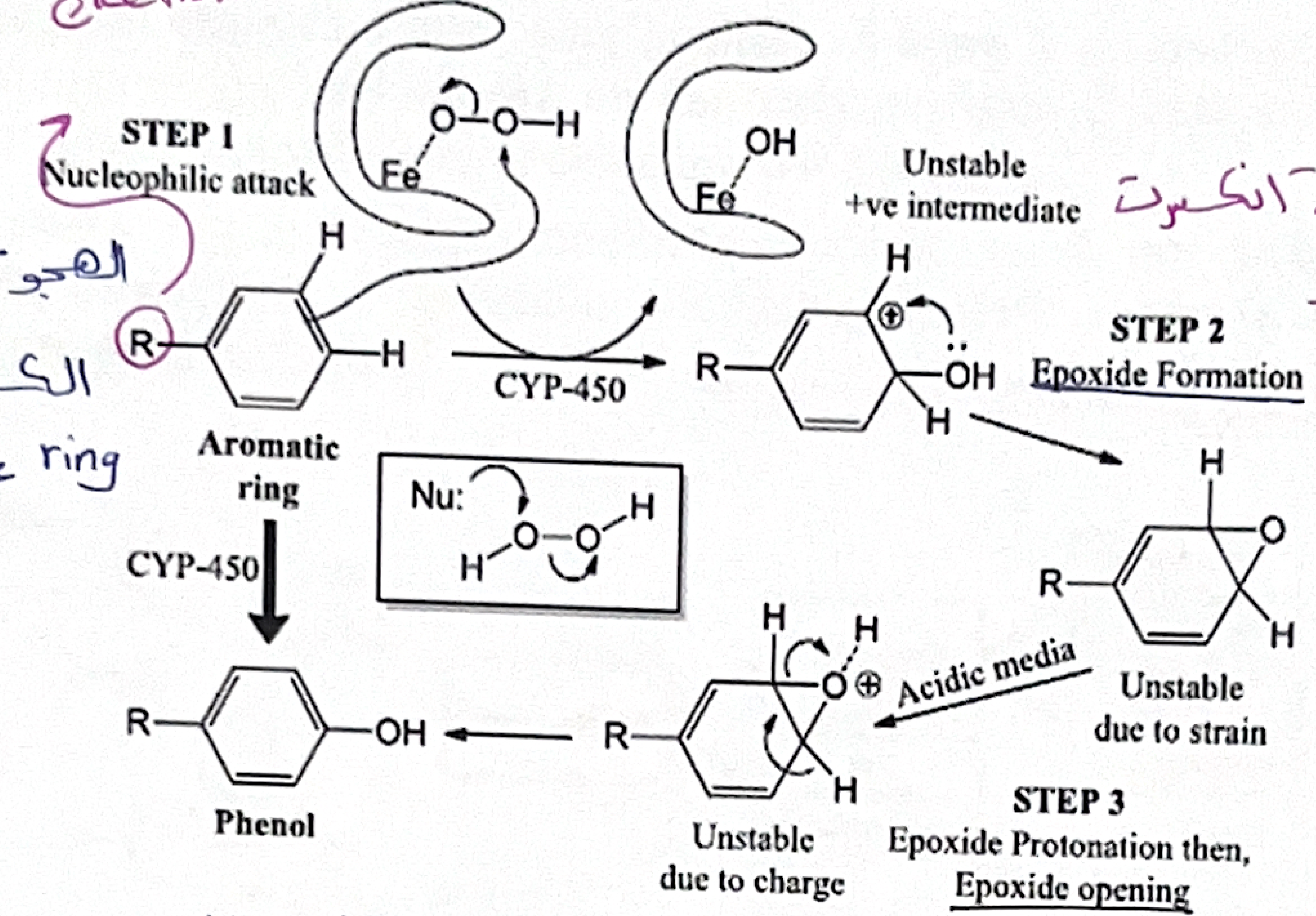


epoxide *



unstable
due to strain

electron donating



الهجوم بيصير من الكترونات ال aromatic ring على ال oxygen

الاروماتيكية انكسرت في المركب بحاول يسترجع حاله

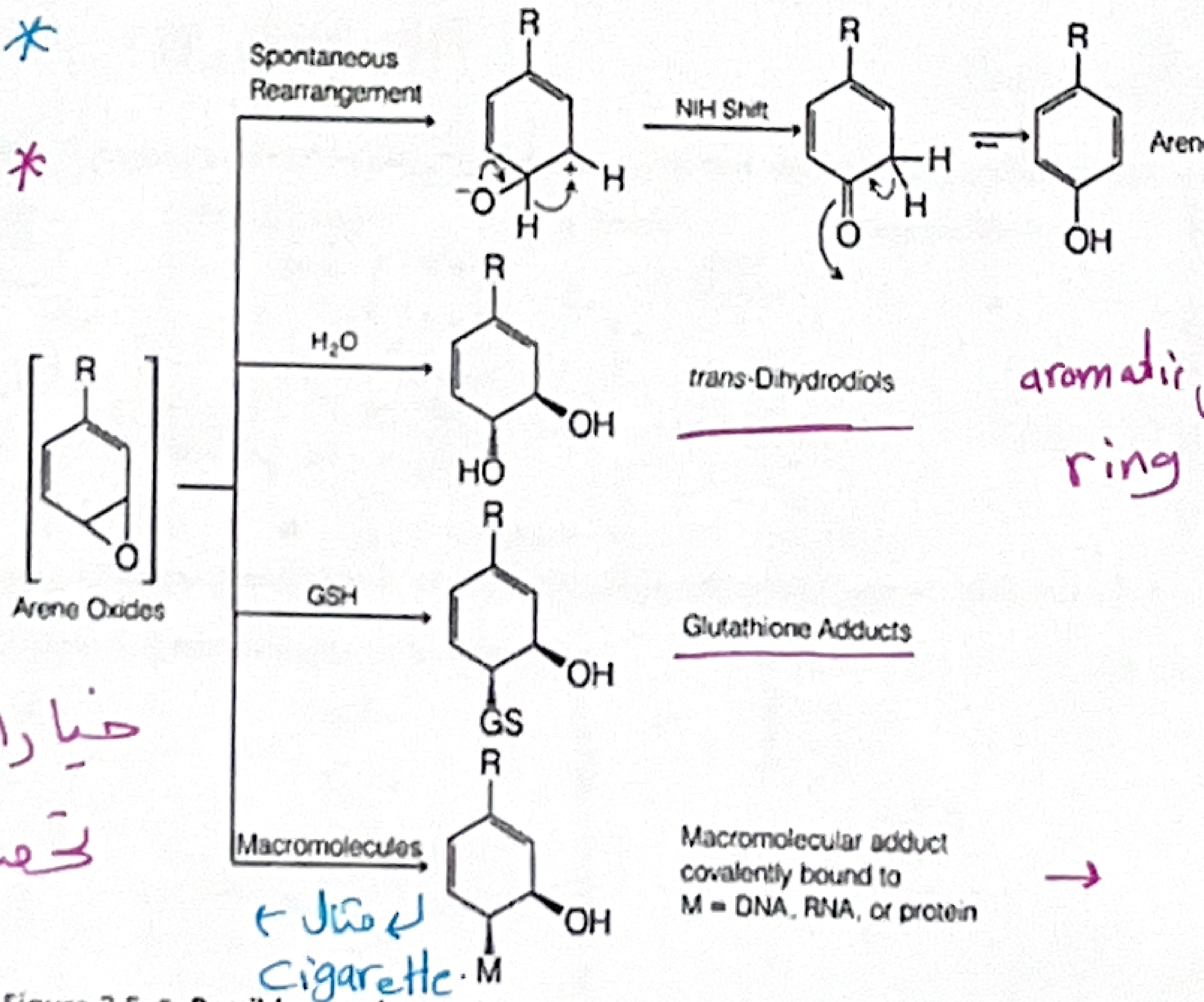
متجادل تفك

وصول ال O رح تفك ك OH group

رح يخسر المركب ال H و يا خذ الالكترونات يحل فيها دبل بوند ويحل الاروماتيكية

*NOTE *

* القصة الي تحت مشروح بالسلايدات القديمة لكن اسماء ذكرتها بالشرح فلا تنسها *



بيحل aromatic ring

خيارات غير محس تحصل على ال Arene oxides الي هي من

له مثال ← cigarette.

→ يصير لها intercalation مع ال DNA or RNA or protein.

Figure 3.5 • Possible reaction pathways for arene oxides. (Data are from Daly, J. W., et al.: Experientia 28:1129, 1972; Jerina, D. M., and Daly, J. W.: Science 185:573, 1974; and Kaminsky, L. S.: In Anders, M. W. [ed.]. Bioactivation of Foreign Compounds. New York, Academic Press, 1985, p. 157.)

step 2

[الي بيصير انه احيانا ال epoxide بيصير stable بالجسم ← ما يصير له metabolism

* بيعطيني stable epoxide وال compound بيكون planar ومعه electrophile center وهاد بيخلي ال epoxide قادر انه intercalate مع ال DNA strands

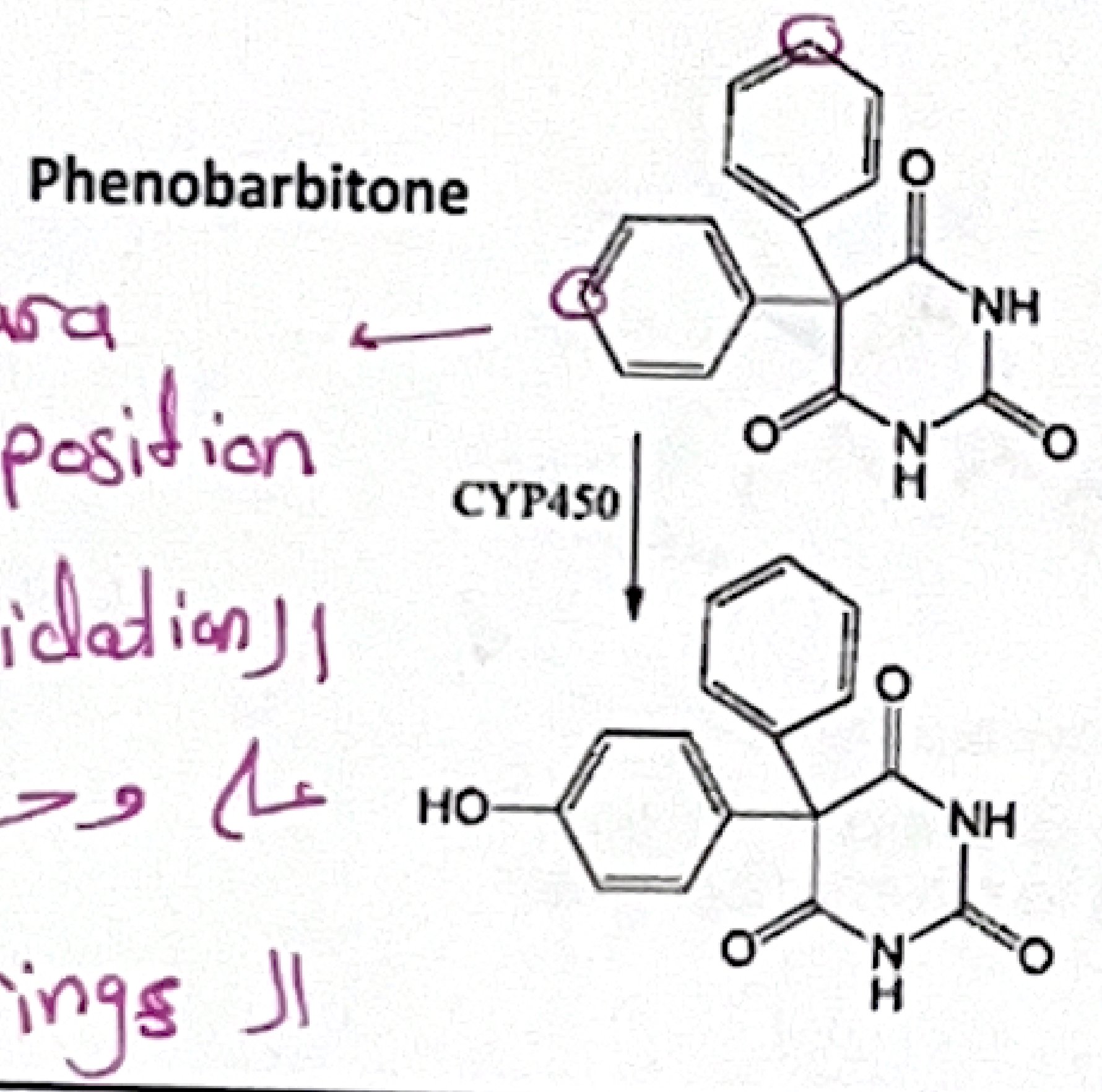
ال DNA ← intercalating agent

+ حكينا يحصل ال oxidation على ال para position ← اذا كان عنا substitution. بيحصل على ال meta اذا التنين عليهم substitution ما بيصير oxidation ابدًا

- Oxidation always occur at para position, if there is a substitution on the para then it will happen on the meta position , if both positions are being occupied then no oxidation will occur.
- Aromatic ring oxidation is moderate in speed usually not more than 50%, other kind of oxidations are faster, so their products will be extremely metabolized.

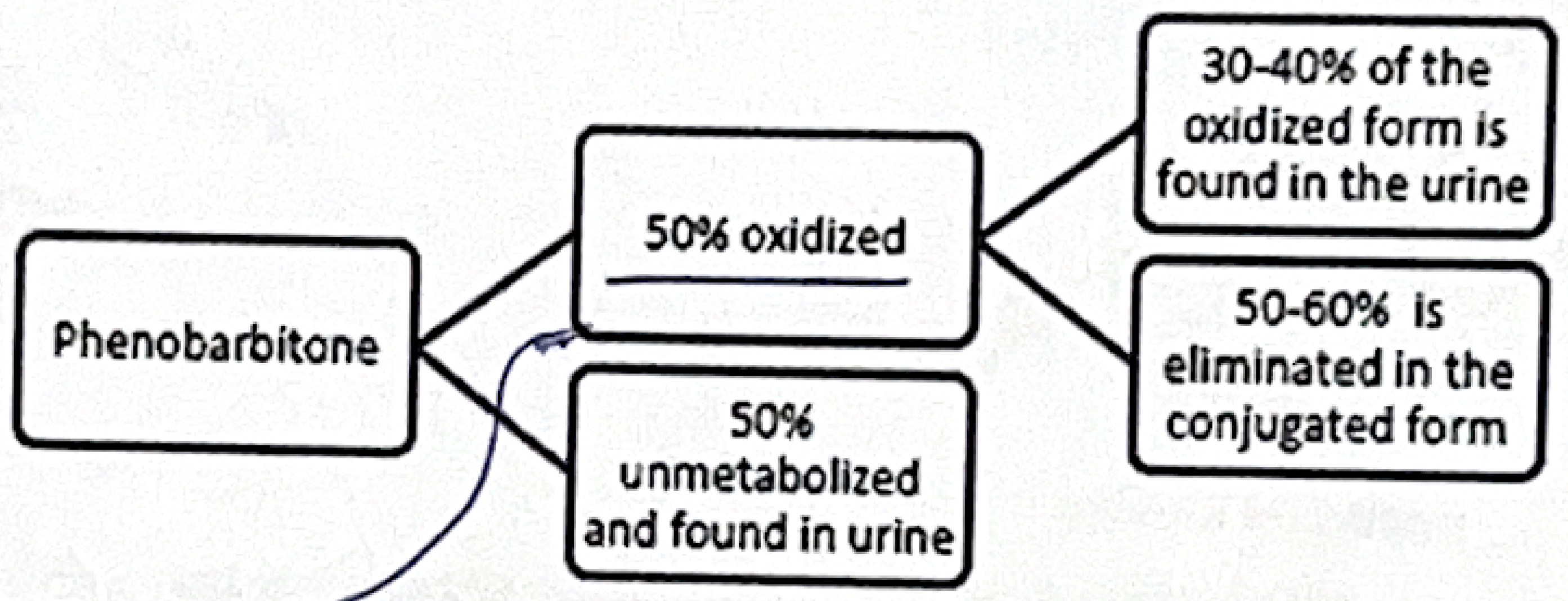
* Aromatic ring بيصير oxidation مش بسرعة

باقي ال oxidation أسرع



para position ←

ال oxidation. بيصير على وحدة من ال rings مش التنين سوا.



على هاد الشكل

[pheobarbitone]

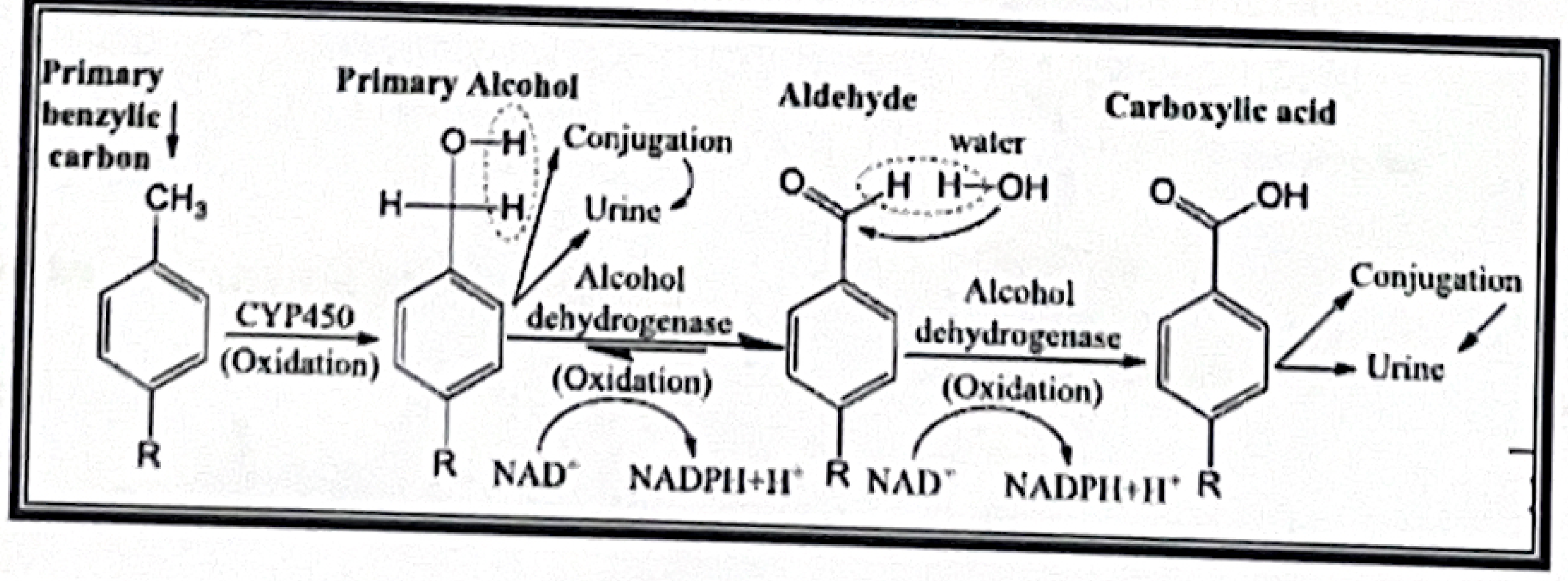
لو عملنا تحليل لعينة ال urine حيطلع عنا 50% oxidized و 50% unmetabolized.

وهاد بنقسم الى 30-40% ← بس oxidized ما صارله conjugation
50-60% ← conjugated form

⑤ ليه ال Aldehyde ما في منه conjugation؟ لأنه ما بيضل فترة طويلة ① سريع جدًا

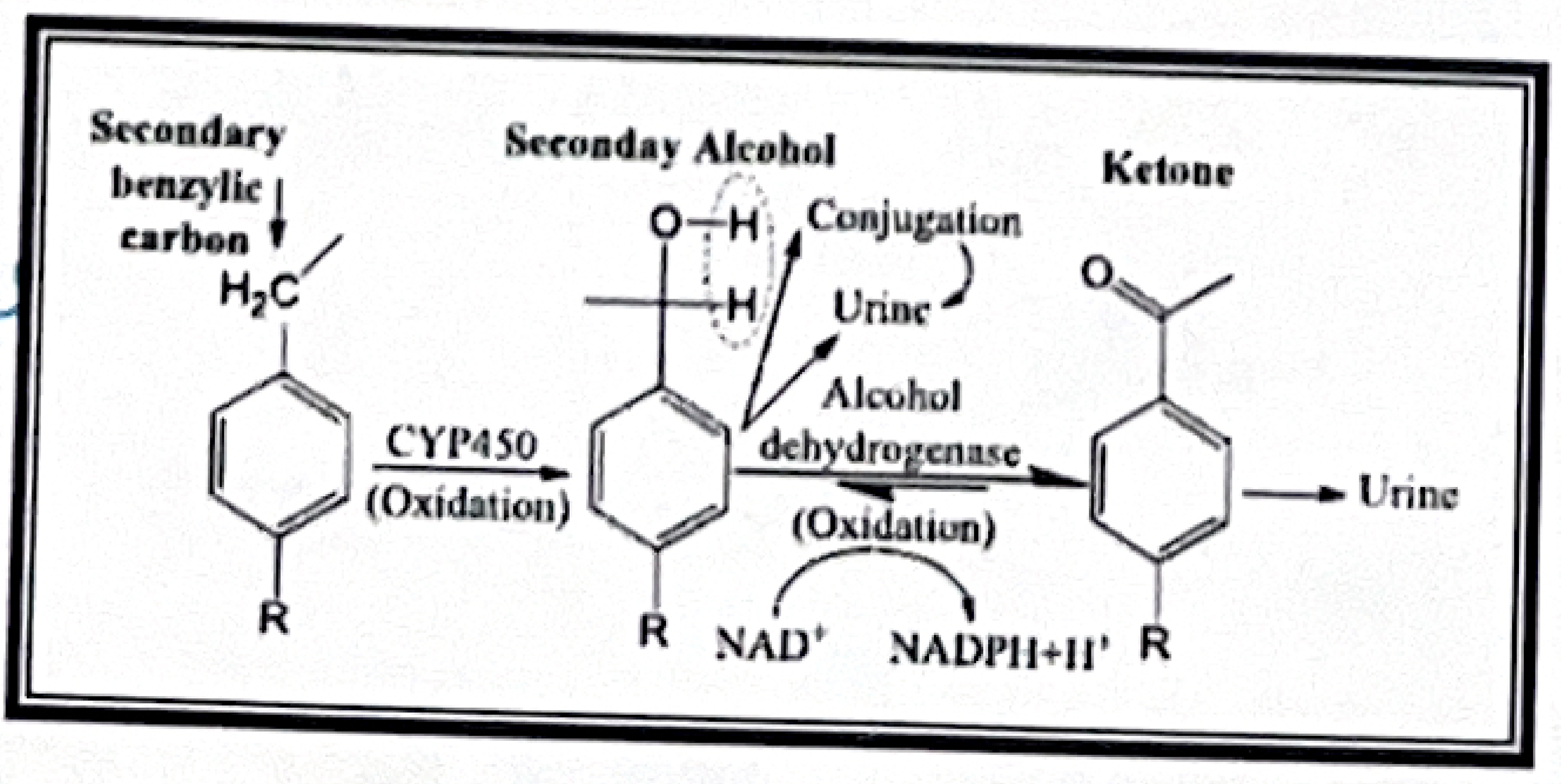
2. Benzylic oxidation

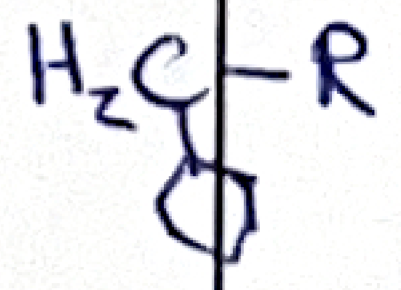
Benzylic carbon هي ال carbon الي على ال aromatic ring مش ال carbon الي جزء منها.

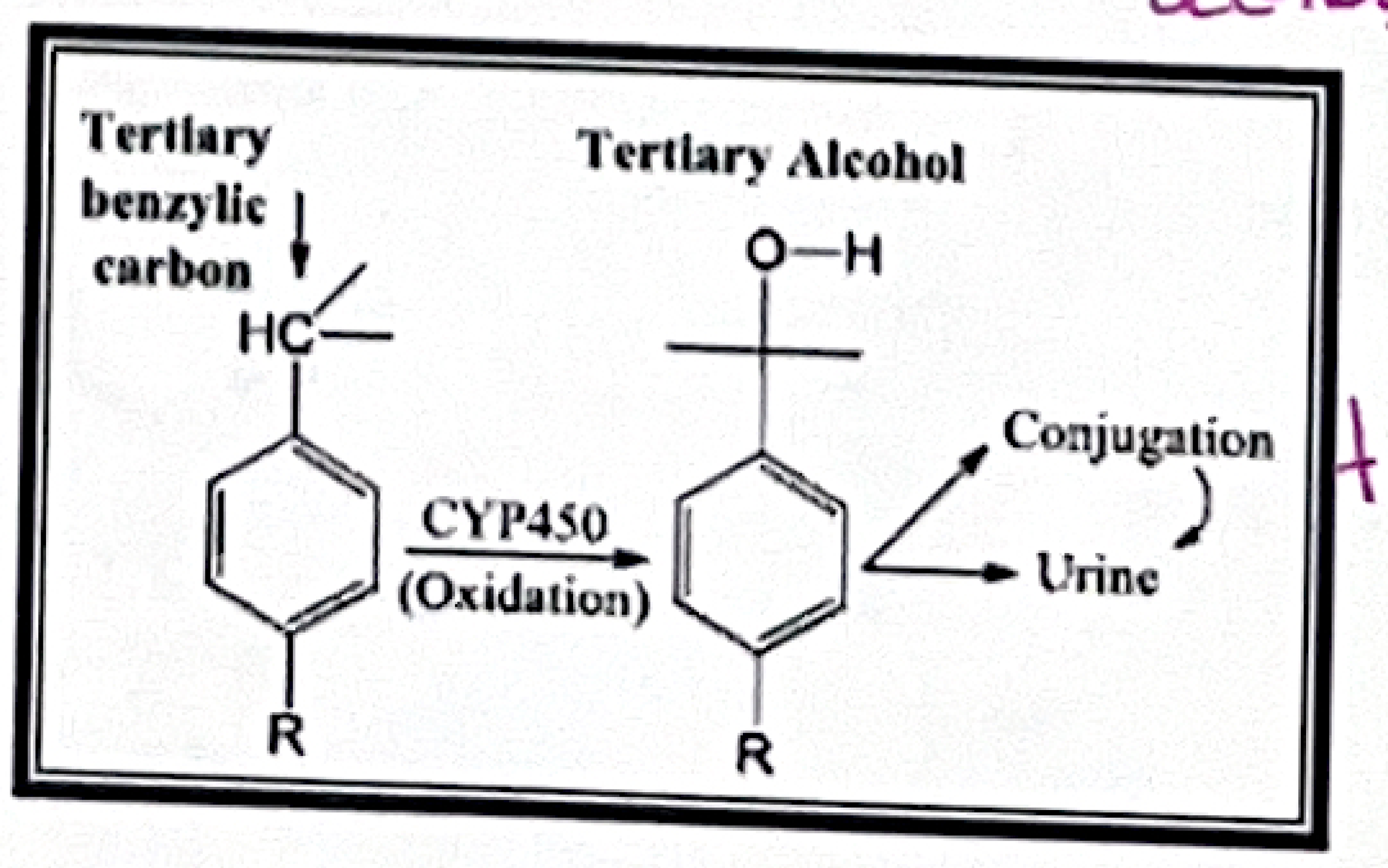


② + عشان تكون primary لازم عليها methyl group

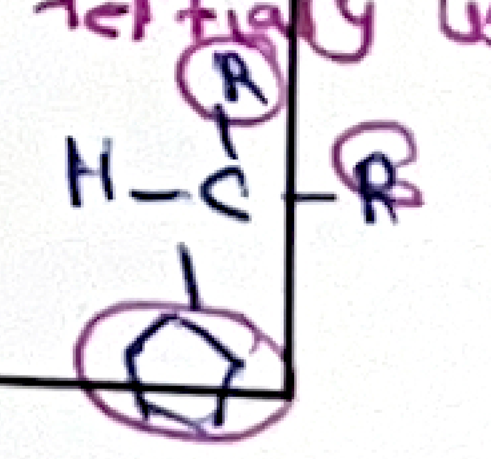
+ عشان تكون secondary







+ عشان تكون tertiary



4° carbon, no oxidation because there is no H to replace (remember that H must exist to replace it with –OH).

* extensively metabolized ④

③ * بال urine شو ممكن نلاقي ←
1- carboxylic acid كاله او 12 conjugated [primary]
2- ~~secondary~~ Ketone كاله هاد بشرح ليه
3- Tertiary alcohol ← conjugated او كاله
4- primary Alcohol كاله باحزل conjugated
5- secondary Alcohol كاله او conjugated

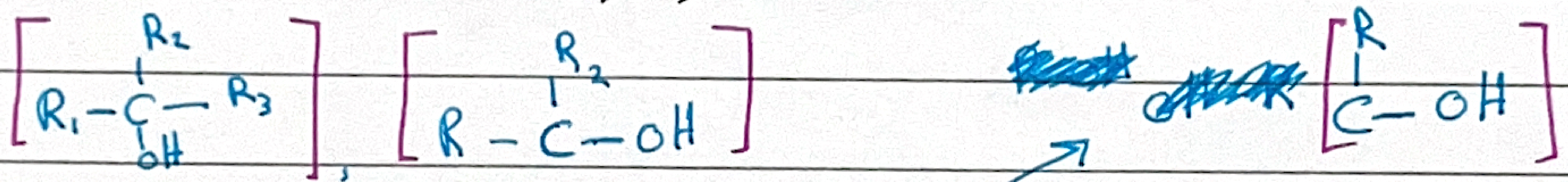
شرح اضافي للمهم فقط "مش ما تحكية الدكتورة" بس

شرحته رند

نعمل flashback للـ organic ←

* هلأ المركبات دام في امكانية يصير لها oxidation حيصير

أول مثال عنا CH3 ← بيصير لها oxidation بتحول لـ primary Alcohol



تذكير ← لتحديد primary أو secondary أو Tertiary حسب الي مرتبطين مع الـ carbons يعني عدد الـ Rgroups المختلفين

نرجع ← هلأ بنعرف انه الـ primary alcohol بيصيرله oxidation وبتحول الى الـ Aldehyde والـ Aldehyde بيصير له oxidation وبتحول للـ carboxylic acid

والـ secondary بتحول لـ Ketone والـ Ketone ما بصير له Oxidation خلاص بوقف

الـ tertiary Alcohol مستحيل يصير لهم Oxidation.

نرجع لأمثلة السلايدات ← عنا primary حيصير عليها الـ oxidation benzylic carbon.

عن طريق CYP450

تتحول الى primary Alcohol يا اما بيطلع بـ urine بحالة او Conjugated أو بيصيرله

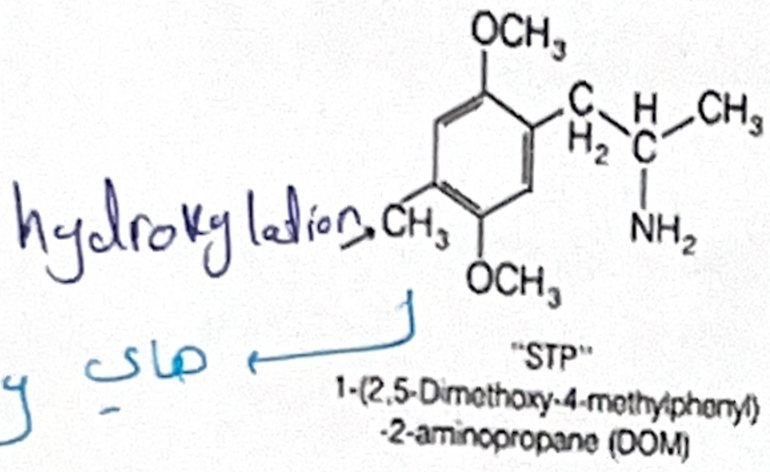
oxidation مرة ثانية عن طريق dehydrogenase الـ Alcohol الي بيحوله الى Aldehyde

والي بيصيرله oxidation عن طريق dehydrogenase الـ Alcohol ميحا وبتحول لـ Carboxylic acid

با بيطلع لحاله يا اما Conjugated, اتباع نفس القصة.

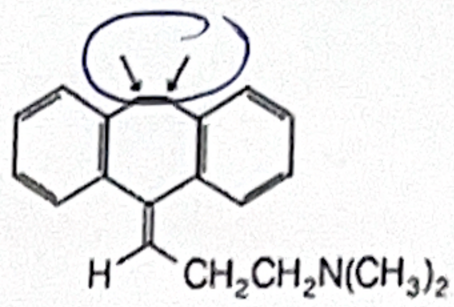
* examples →

hydroxylation

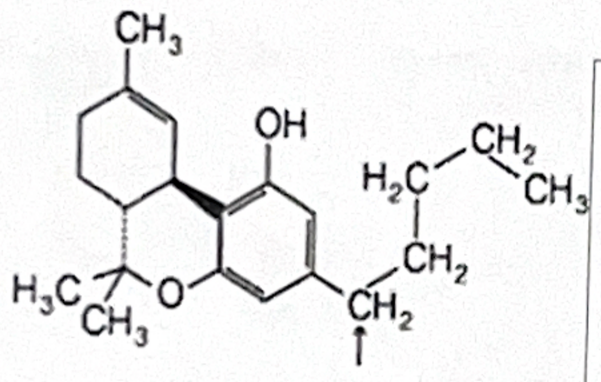


"STP"
1-(2,5-Dimethoxy-4-methylphenyl)
-2-aminopropane (DOM)

hydroxylation ← primary هاي

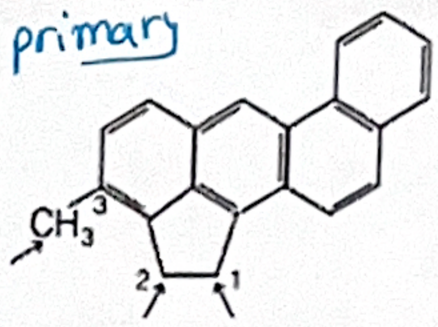


Amitriptyline



Δ¹-Tetrahydrocannabinol

primary



3-Methylcholanthrene

Figure 3.8 • **Examples of drugs and xenobiotics undergoing benzylic hydroxylation. *Arrow* indicates site of hydroxylation.**

* الـ Quaternary ← can't be oxidized. ليش؟ الشرط يكون عند H عشان يتحول لـ OH اصلًا

Example

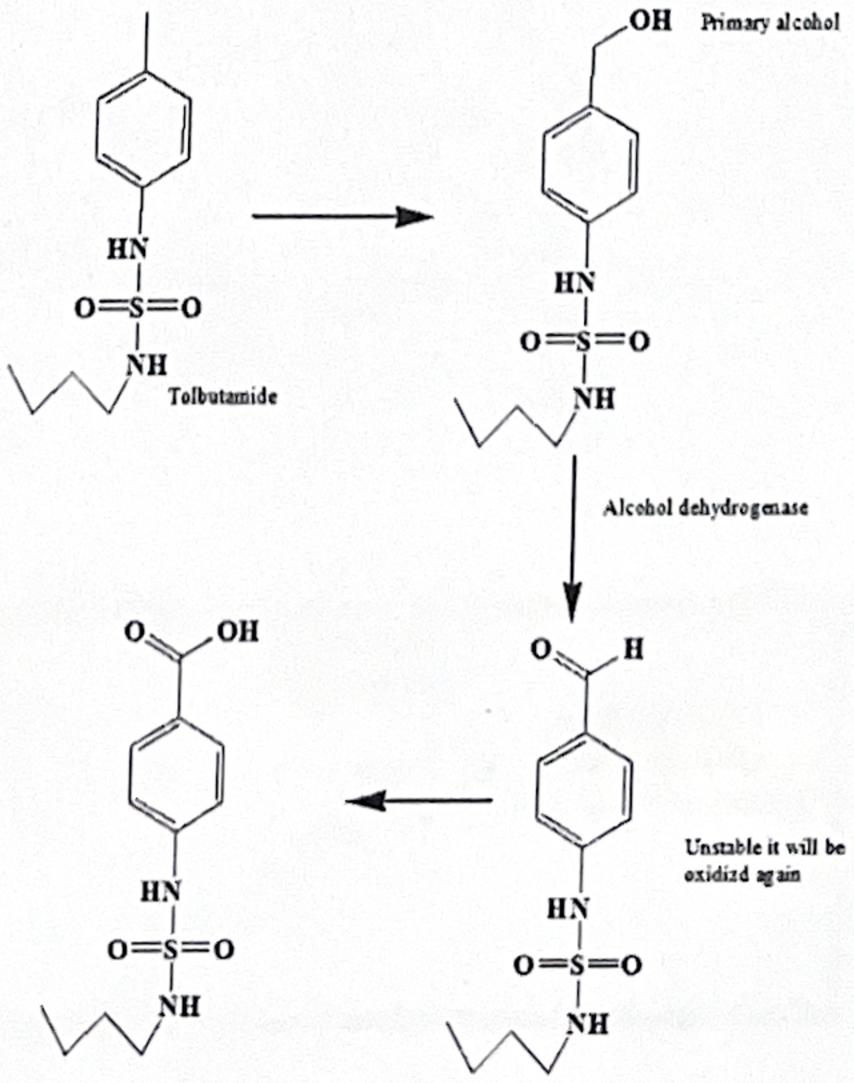
Tolbutamide will be eliminated in urine in 3 forms:
1. Alcohol
2. Carboxylic acid
3. Conjugated

elimination يصير له أربعة في جال Urine ثلاث أشكال

2 Carboxylic acid & Alcohol

primary يعني هي conjugated

benzylic carbon.



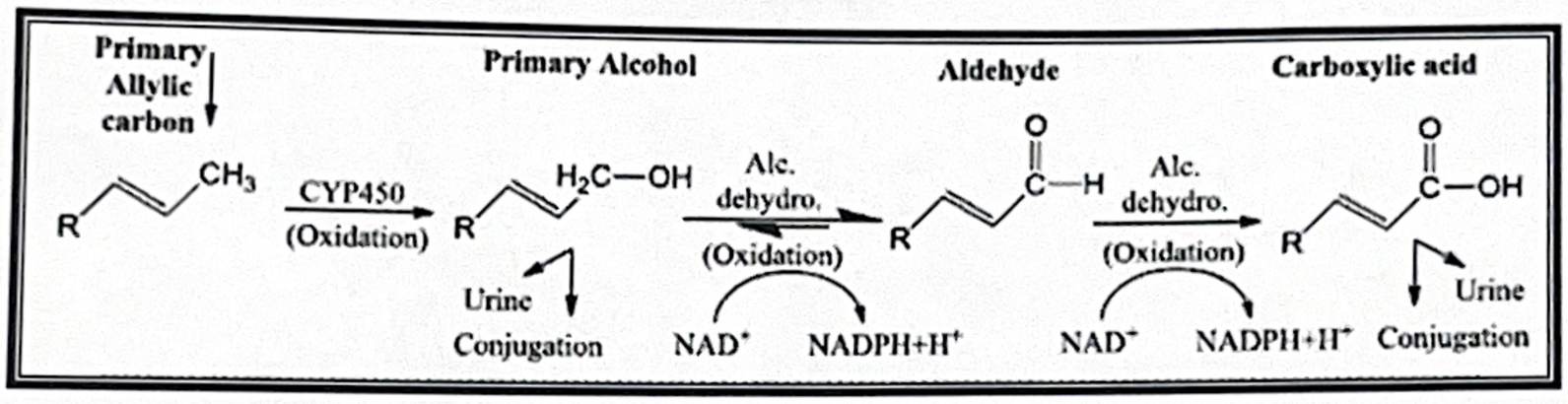
3. Allylic oxidation

* بر مز تفاعل سريع

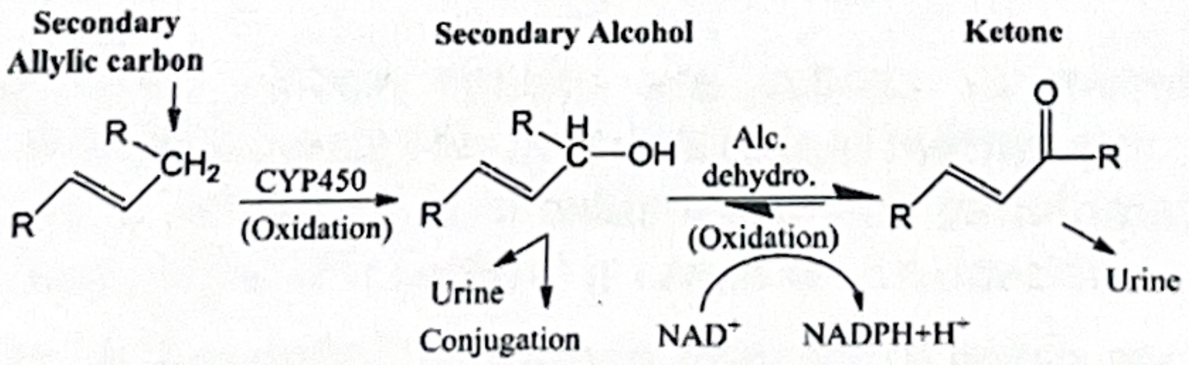
Allylic carbon is a carbon atom bonded to another carbon atom, which in turn is bonded doubly to another carbon atom

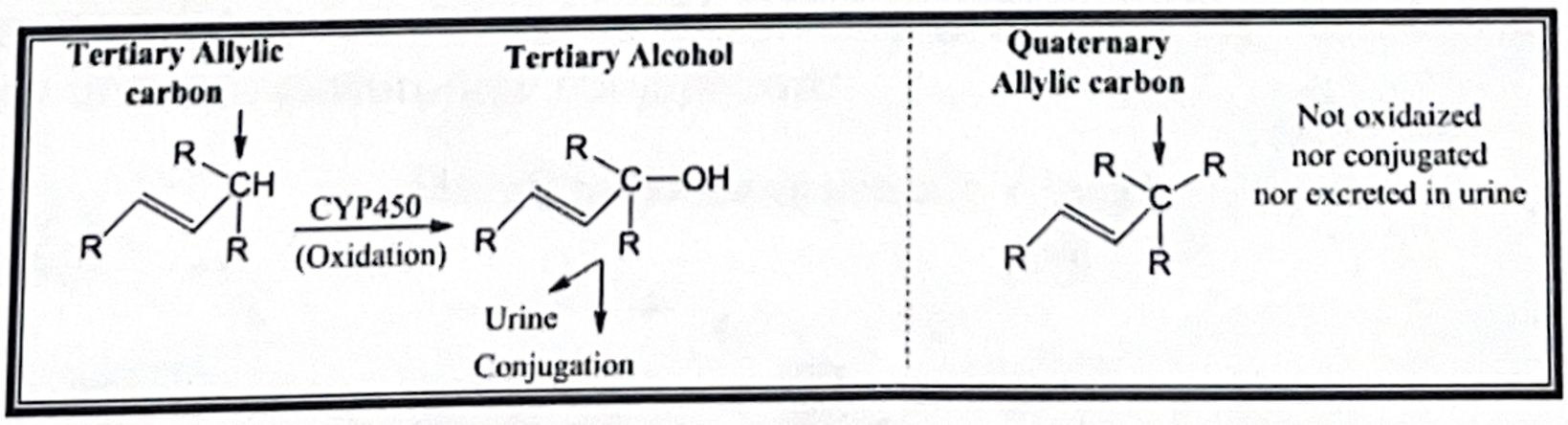
Considered as fast oxidation reaction.

* عبارة عن كربون متصلة بكربون ثانية الي متصلة بكربون ثالثة عن طريق double bond



نضس الي صار بال benzylic ونفس التحولات





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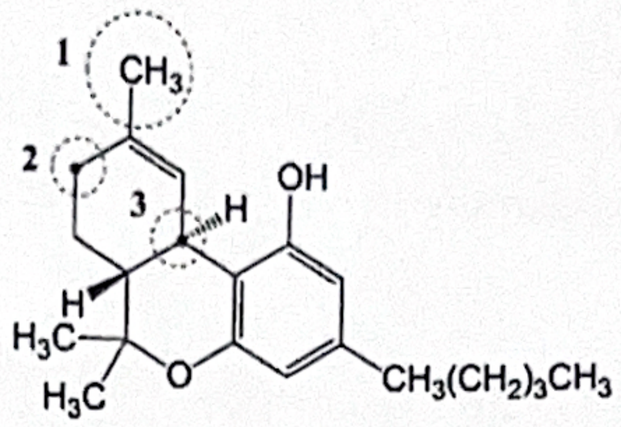
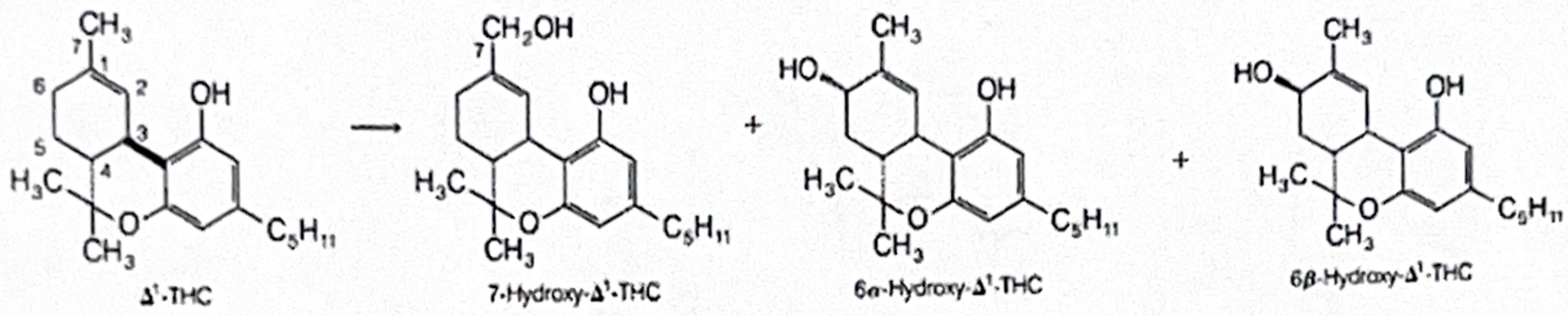
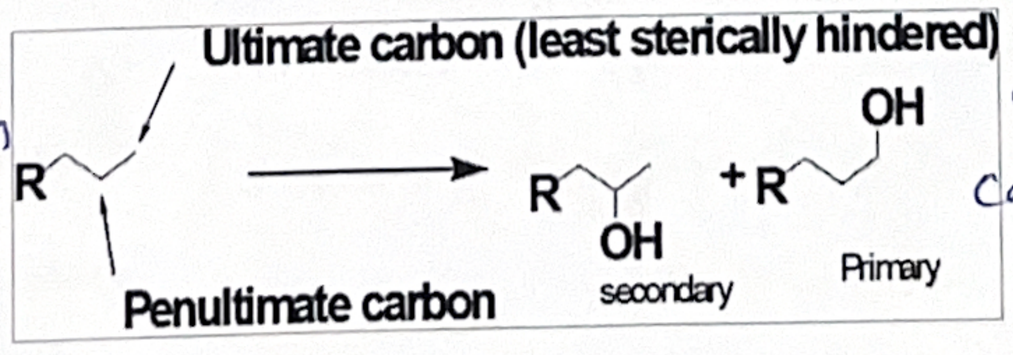


Tetrahydrocannabinol

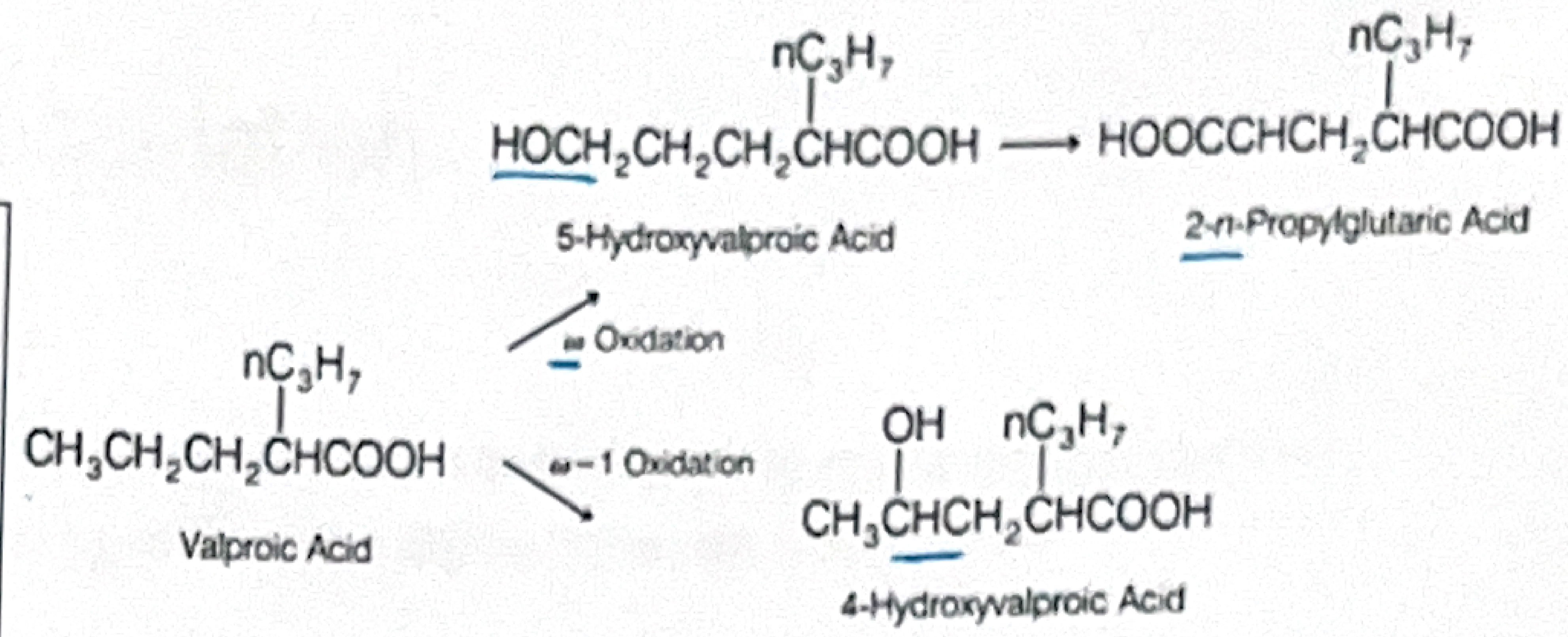


4- Oxidation at Aliphatic and Alicyclic Carbon Atoms

- Alkyl or aliphatic carbon centres are subject to mixed-function oxidation. Metabolic oxidation at the terminal methyl group often is referred to as ω -oxidation, and oxidation of the penultimate carbon atom (i.e., next-to-the-last carbon) is called ω -1 oxidation.
- The initial alcohol metabolites formed from these enzymatic ω and ω -1 oxidations are susceptible to further oxidation to yield aldehyde, ketones, or carboxylic acids. Alternatively, the alcohol metabolites may undergo glucuronide conjugation.

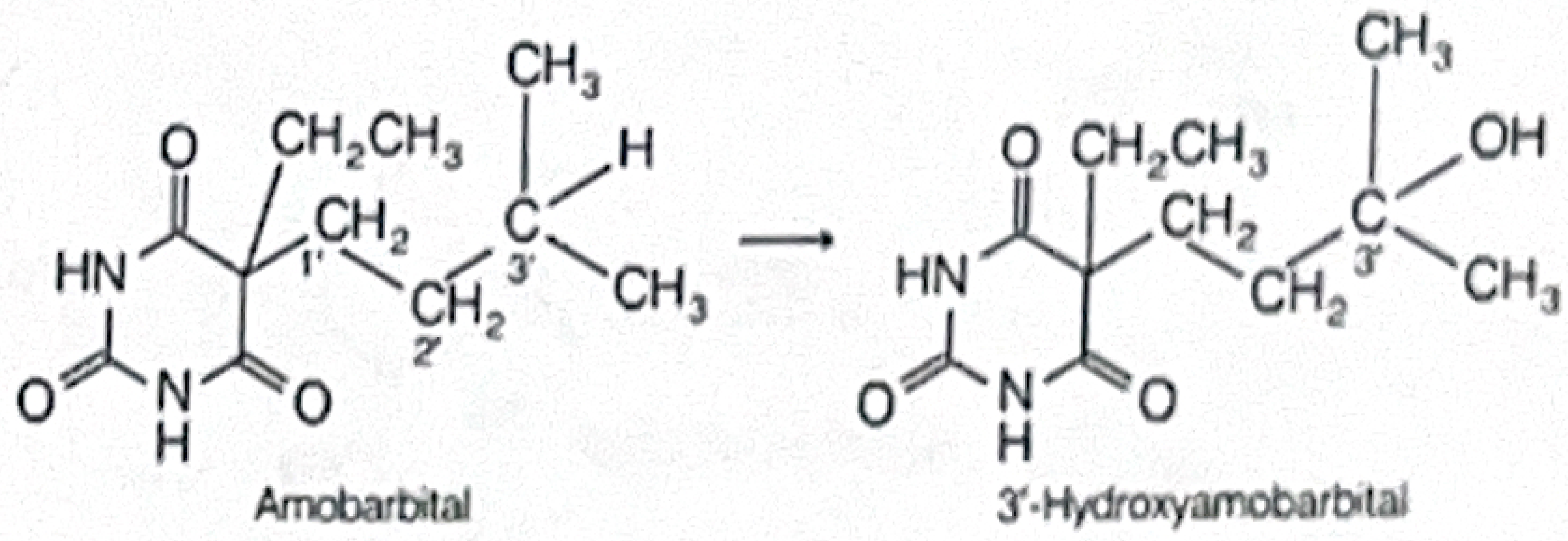


Valproic acid (Anti-seizure; Depakin®)
This drug has a carboxylic acid group so it's readily filtered and actively secreted to be eliminated in the urine unchanged.
It also gets oxidized, around 5%, in a ω and ω-1 oxidation. But mostly is eliminated unchanged.



هلا القصة انه كحـ
يصير للـ valproic acid ←
elimination بدون مايصير عليه
تغيير & انه Already عليه charge
من الـ carboxylic acid

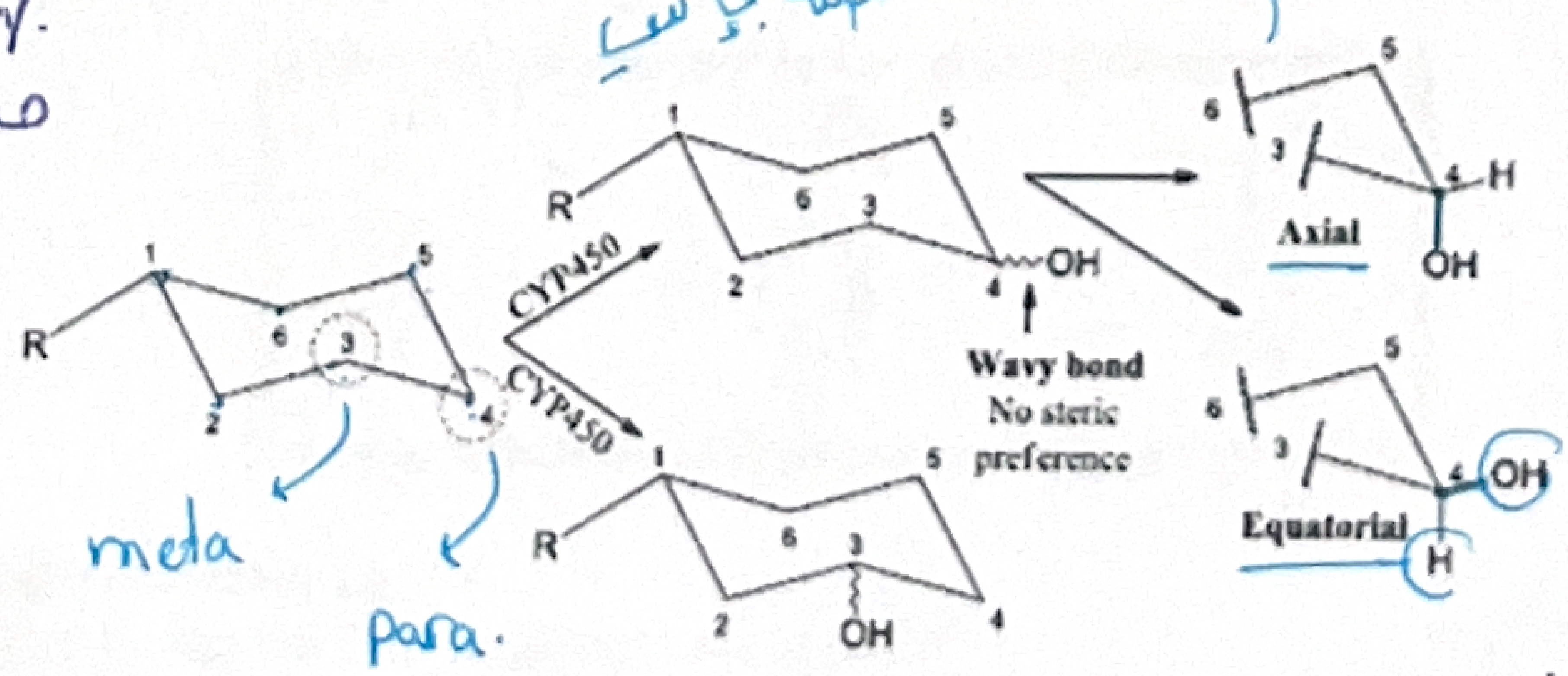
+ بس بيصيرله oxidized → 5٪ منه فقط.



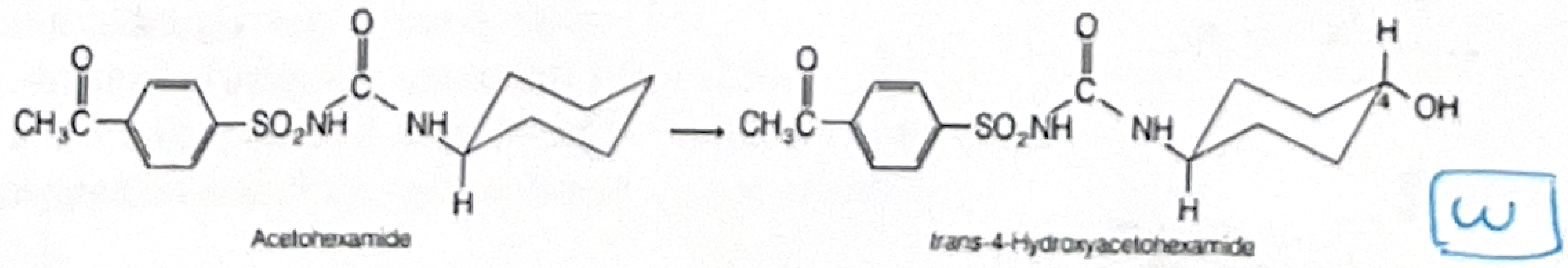
[و مثال phenobarbidal]

بيقصوا لأقرب الـ carbon موجودة باشي

* هون بيرضوا امثلة *



Alicyclic
يا للـ para
أو الـ meta.
اما الـ ortho
X



معلومة ← ا لعرف بين الـ Axial & Equatorial ←
متعامد على مستوى الحلقة
حول مستوى الحلقة
للعلم