



تفريغ ميديسينال

محاضرة: Lec 3 Part 2

الصيدلانية: Rahaf Zyoud



لجان الرفعات



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. *صالح یا اثر علی ال enzyme*
 - **inducers**, increase the enzyme activity by increasing enzyme synthesis. Examples: rifampicin, phenytoin, carbamazepine and phenobarbital. *بزیه ال enzyme نشاط*
 - **inhibitors**: slow down the metabolism of substrates leading to an increased drug effect (reversible inhibitors and irreversible inhibitors). Examples: fluoxetine, ketoconazole, grapefruit. *ببط عمل ال enzyme*

إذا كنت تأخذ 2 drug وتأخذهم مع بعض وكانوا هذول ال 2 drug

بعضهم metabolism بنفس ال isoenzym شو رح يهر؟

زي ما تنصنا قبل انه هذول ال isoenzym لهم binding site واحد فقط يعني one attachment

فهذا ال isoenzym رح يرتبط بواحد فقط وهذا الـ blocking يعمل لهذا ال isoenzym

رح يهر الـ metabolism والوا الثاني ما رح يرتبط بال isoenzym ونتيجة ذلك ما رح يهر الـ metabolism

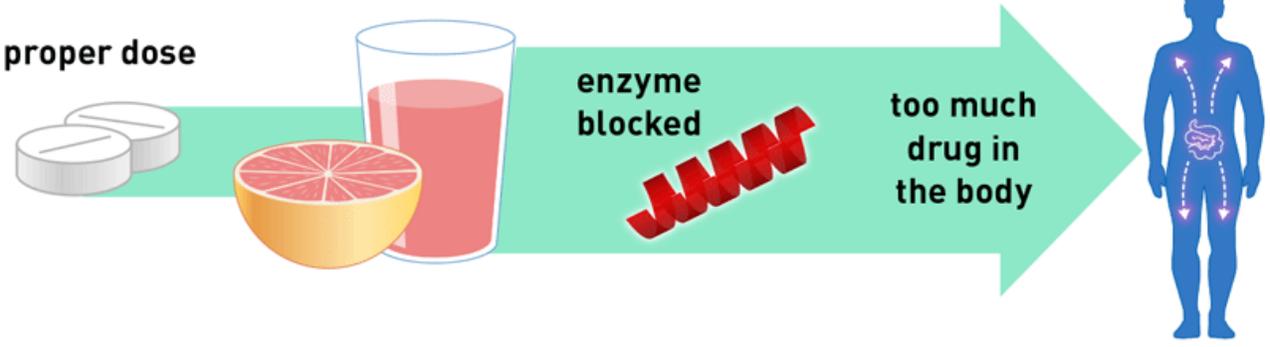
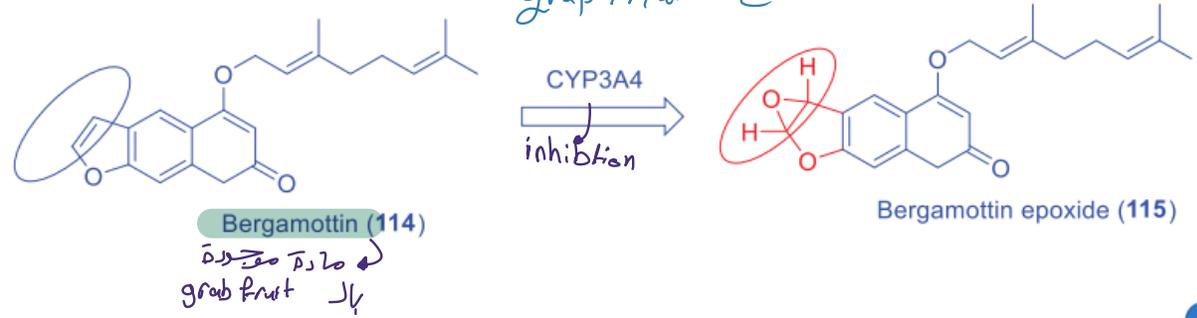
وهيك رح يهر منه side-effect

- 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.

الادوية التي يعبرها
 عن طريق هذا الenzym
 grape fruit مع
 metabolism

فالتسبب!
 bioavailability ↑
 side effect ↑



Oxidative React

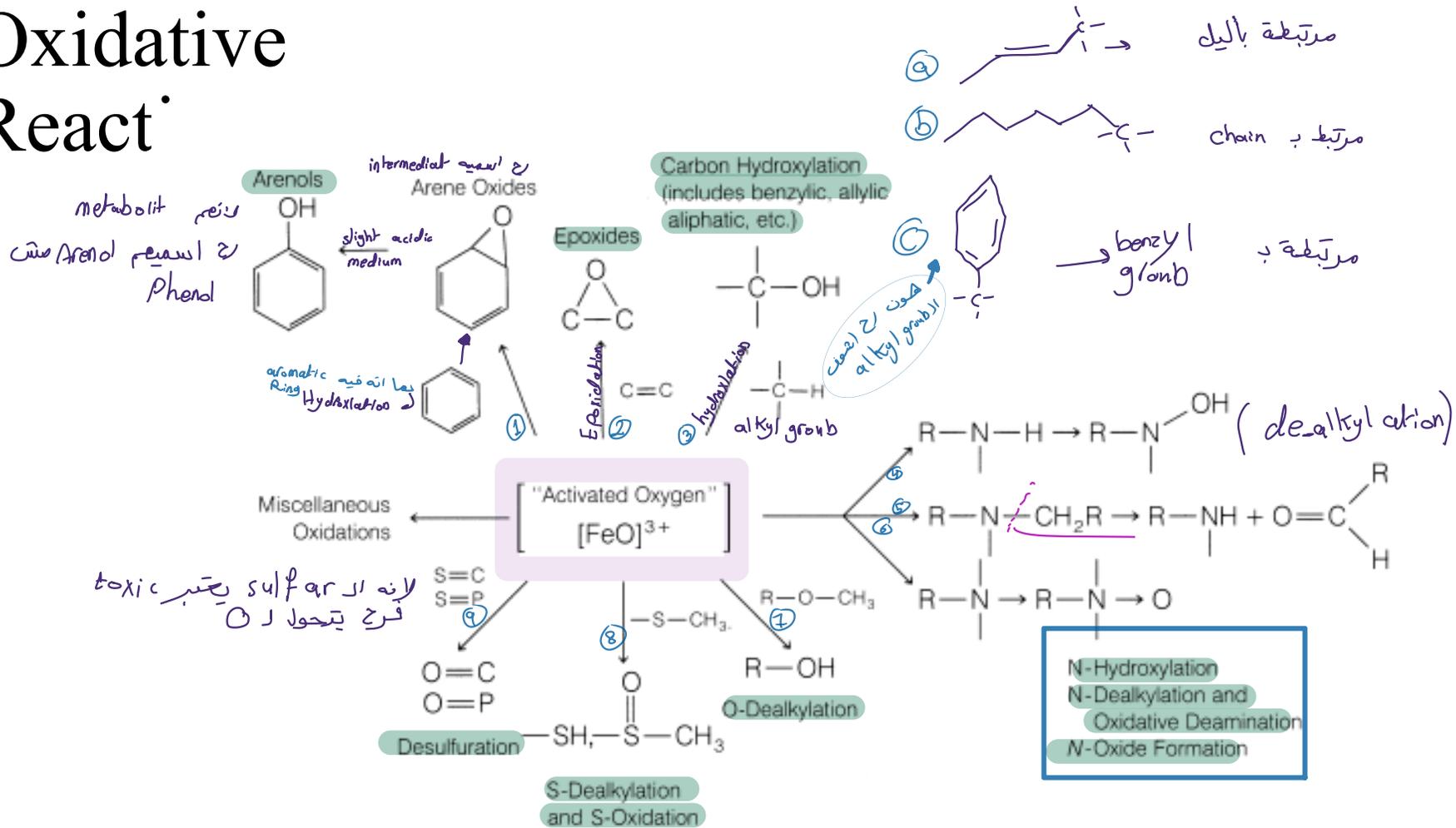
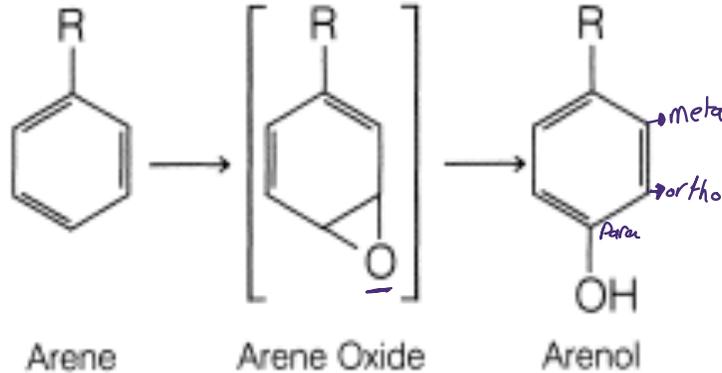


Figure 3.3 • Schematic summary of cytochrome P450-catalyzed oxidation reactions. (Adapted from Ullrich, V.: Top. Curr. Chem. 83:68, 1979.)

Aromatic oxidation → النتيجة Arenol

هذا التفاعل Spontaneous ويعتبر *intermediat reaction*



هذا ال *intermediat*
 not stable (epoxid)

نكه صاحبنا ال *substitution*
 رح يكون لك *Para* و اذا كانت ال
 Para عليها انب رح يروح للـ *meta*

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.

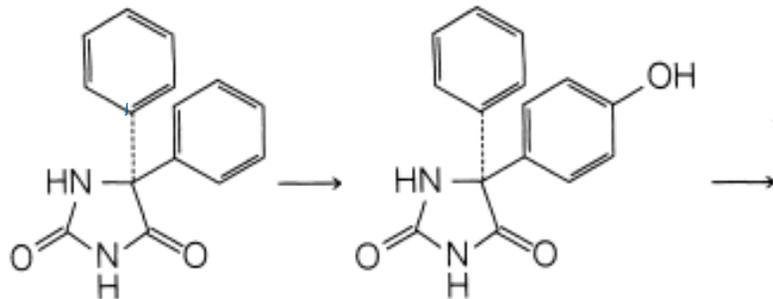
Important therapeutic agents such as **propranolol**, **phenobarbital**, **phenytoin-**, **atorvastatin**, **17 α - ethinylestradiol** and **S- warfarin** undergo extensive aromatic oxidation. In most of the drugs just mentioned, hydroxylation occurs at the para position.

زیر ما حکینا سابقاً اذ انصحه اکثر من Ring بح یصیر الـ metabolism

بح تصیر الـ Ring الی الـ "e-density" المبرس بالـ Phenyton الـ

"2" rings الـ نفس الـ "e-density" فالـ metabolism بتصیر کل الـ

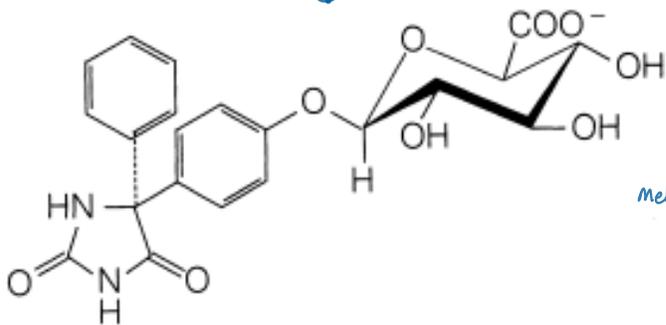
ring وزیر ما حکینا الـ Para و Met فقط .



Phenytoin

p-Hydroxyphenytoin

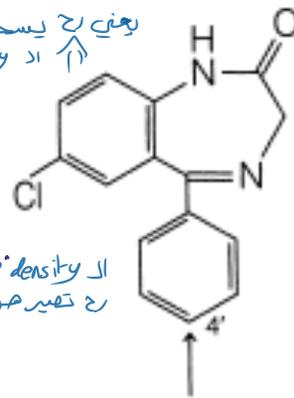
Conjugation Phase II



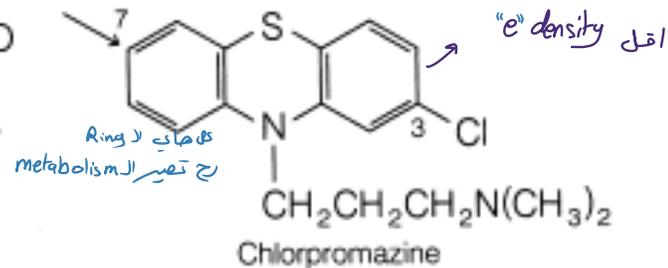
O-Glucuronide Conjugate

الـ "e density" اقل بسبب وجود الـ "e" الی یعتبر طوب "e" withdrawing group یعنی بح یسحب الـ e باتجاهه دهیلة قلت الـ "e density" ↑

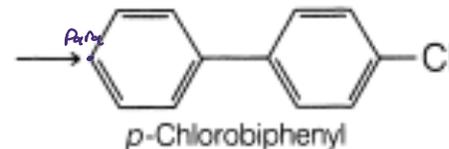
الـ "e density" اقل اذا الـ metabolism بح تصیر الـ Para و



Diazepam



Chlorpromazine



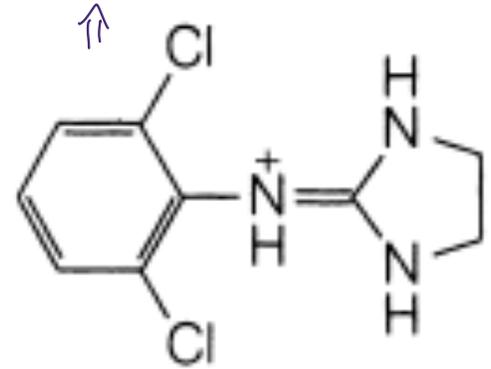
p-Chlorobiphenyl

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) and in the para-hydroxylation of p-chlorobiphenyl to p-chloro-p'-hydroxybiphenyl.

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, $-N^+R_3$, COOH, SO_2NHR) 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.

إذا ارتبطوا بال Ring لعلوا ال density "e"

ال ring السالبة عليها withdrawing group 2
إذا صارت يصير عليها metabolism وإذا صار
minor يكون Cl^-



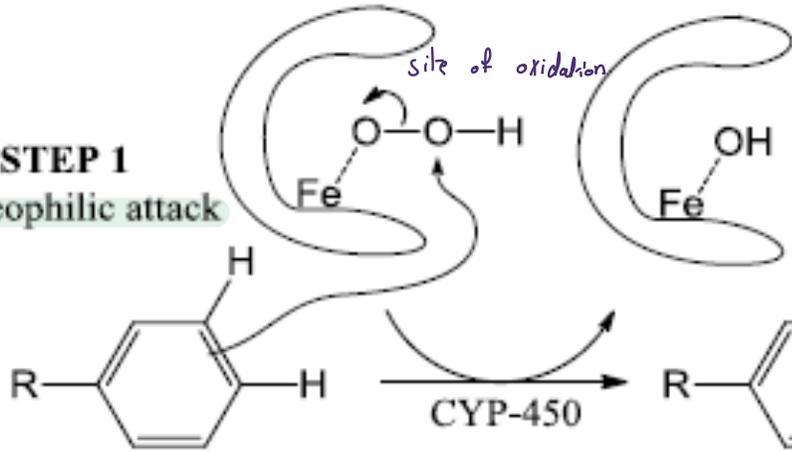
Clonidine Hydrochloride

وال ring الخماسية عليها "NH" ربح
يصير ال density "e" بضعه قليله وصارت يصير
oxidation

خلوفا نشوق خلال ال oxidation كيف رح ترتبه

المركبات بل isoenzym وكيف رح يصير Hydroxylation

STEP 1
Nucleophilic attack

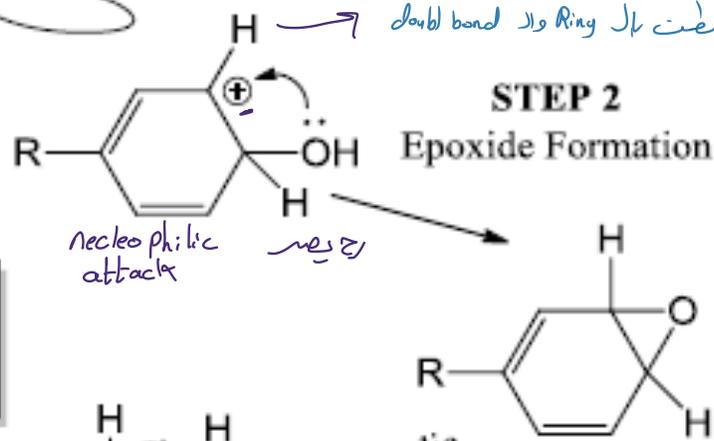


Unstable
+ve intermediate

هي ال H ارتبطت بل Ring وال double bond راحت

شأنفمت حاي ال aromatic ring
تعتبر "e rich" واحد من ال double bond
لي هي e rich نحتاجم ال weak bond

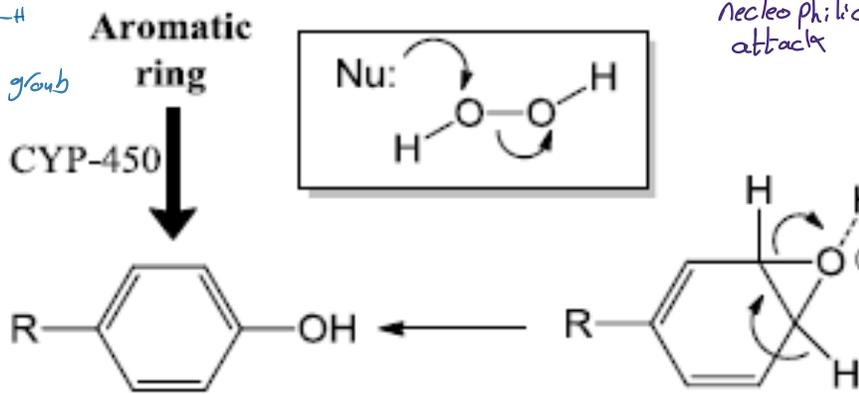
STEP 2
Epoxide Formation



nucleophilic attack
رح يصير

Acidic media
Protonation
رح يصير

STEP 3
Epoxide Protonation then,
Epoxide opening

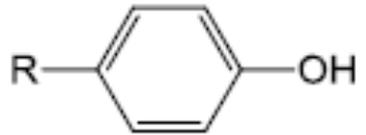


Phenol

metabolite (Arenol) لانه

hydroxyl (موجوده بل isoenzym) ال
bond ال ترتبه بل ring

CYP-450



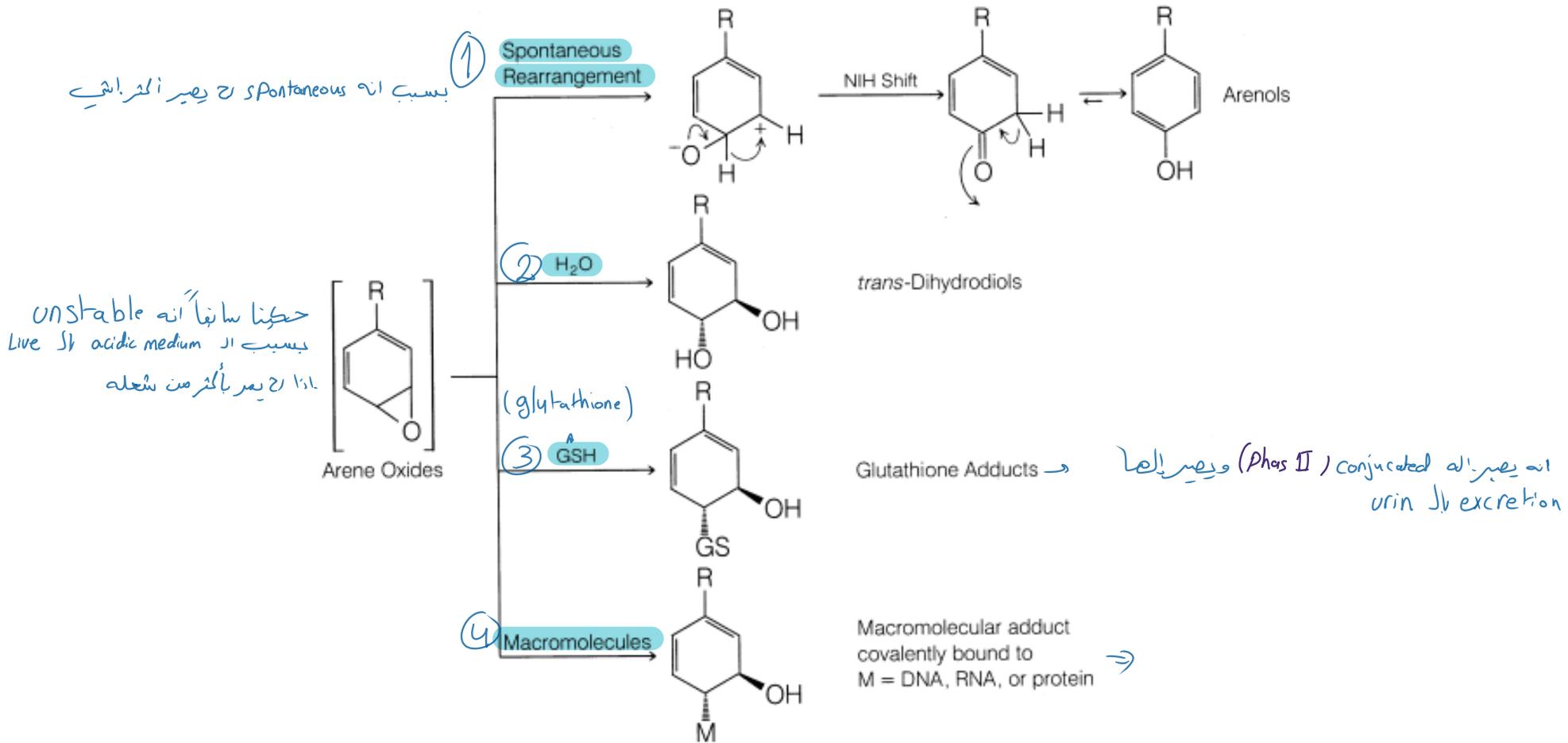
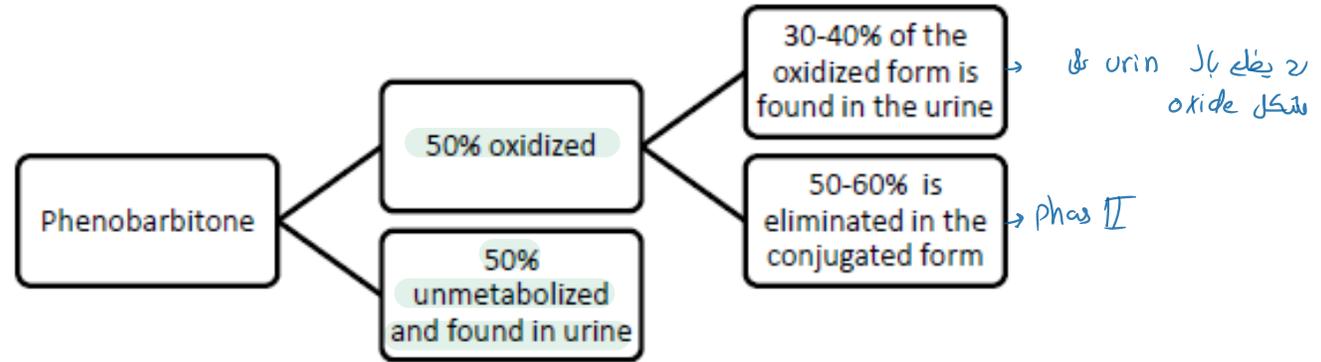
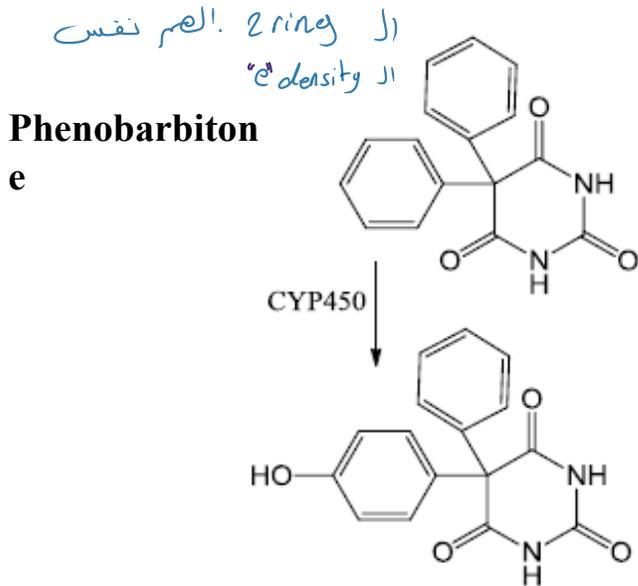


Figure 3.5 • Possible reaction pathways for arene oxides. (Data are from Daly, J. W., et al.: *Experientia* 28:1129, 1972; Jerina, D. M., and Daly, J. W.: *Science* 185:573, 1974; and Kaminsky, L. S.: In Anders, M. W. [ed.]. *Bioactivation of Foreign Compounds*. New York, Academic Press, 1985, p. 157.)

- 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.



يعني ح اشوف ال Phenobarbitone بال urin زي ما هو (unchang)

2. Benzylic oxidation

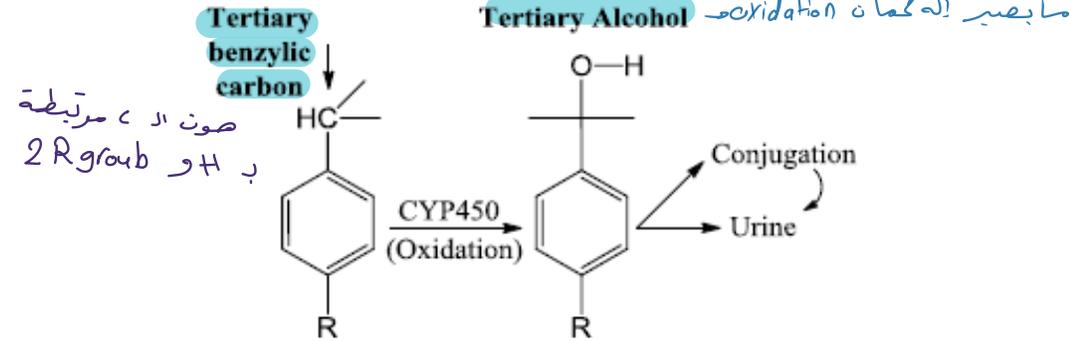
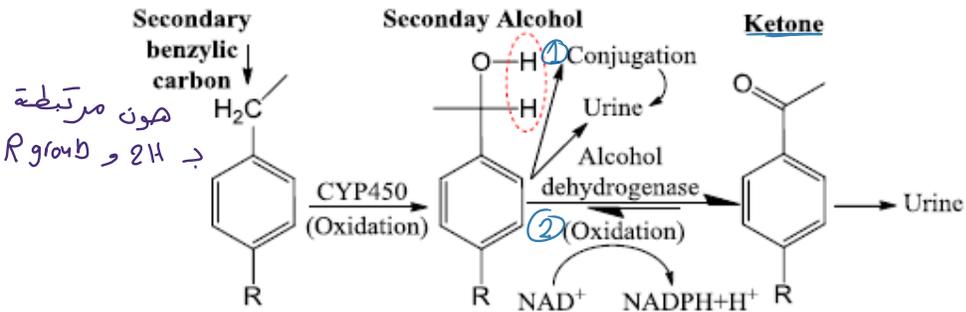
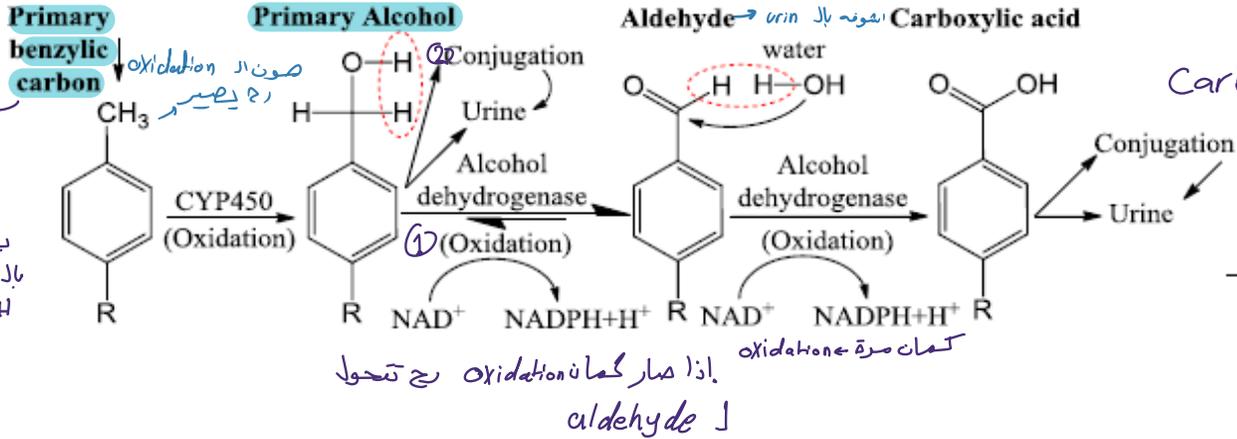
إذا المركب كان فيه benzylic carbon group و aromatic ring ثانية رح يصير ال metabolism هون

هذا التفاعل سريع جدا

benzylic carbon ال عبارة عن aromatic ring مرتبطة فيها carbon

يخلى CH_3 صحن مرتبطة عليها البقية

step 1 ب وحدة من ال H المرتبطة بال carbon رح يرتبط مكانها OH و رح يعطى Primary alcohol

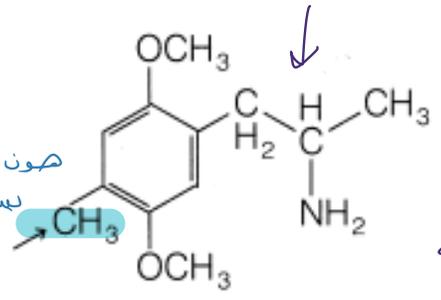


4° carbon, no oxidation because there is no H to replace (remember that H must exist to replace it with -OH).

N-dealkylation نزع إيثير برفقه

صون ال metabolism ح يصير
بسبب وجود ال benzylic carbon

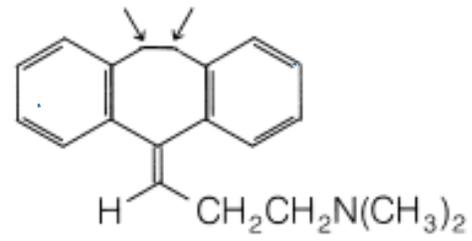
Primary benzylic
Carbon



"STP"

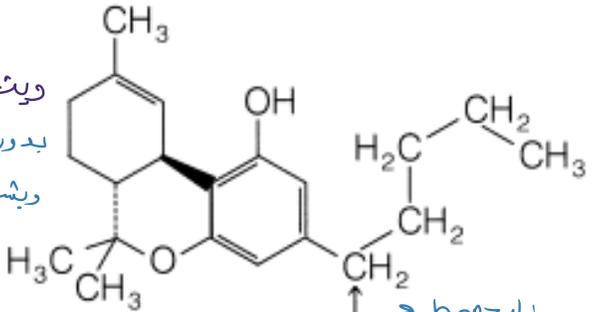
1-(2,5-Dimethoxy-4-methylphenyl)-
2-aminopropane (DOM)

لانه Primary
لا يسلك Pathway
زيه الي حكينا منه قوت



Amitriptyline

ويت ال benzylic carbon
يدور على حلقة ال benzen
ويشوف اذا مرتبط فيها
Carbon

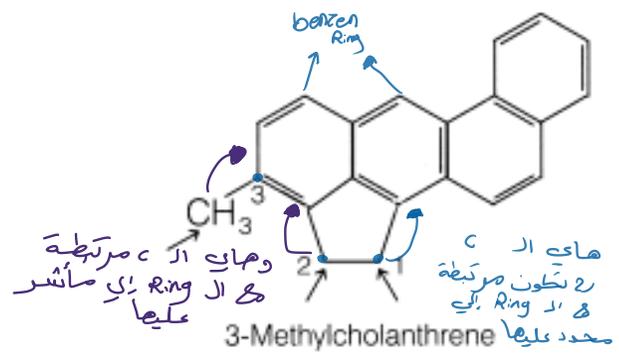


Δ¹-Tetrahydrocannabinol

benzylic
Carbon

هون ال

3 benzylic
Carbon



3-Methylcholanthrene

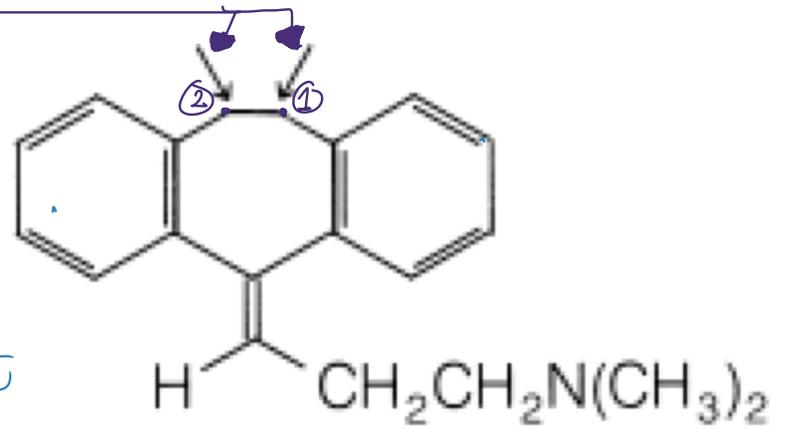
وهناك ال C مرتبطة
مع ال Ring الي ماشر
عليها

هناك ال C
تكون مرتبطة
مع ال Ring الي
محدد عليها

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

دیت ال benzylic carbon؟

ہمسایہ شایفیت انفرادی cycle پس



Amitriptyline

تعبیر aliphatic میں aromatic ring لوگات
فی double bond کے لیے "مثلاً" . ما ح

یہ oxidation پس ما انہ ما فی double bond
ہیون فیہ benzylic carbon

Example

Tolbutamide will be eliminated in urine in 3 forms:

1. Alcohol
2. Carboxylic acid
3. Conjugated

تسويح اشوف بال Urin
 ① + ② + ③

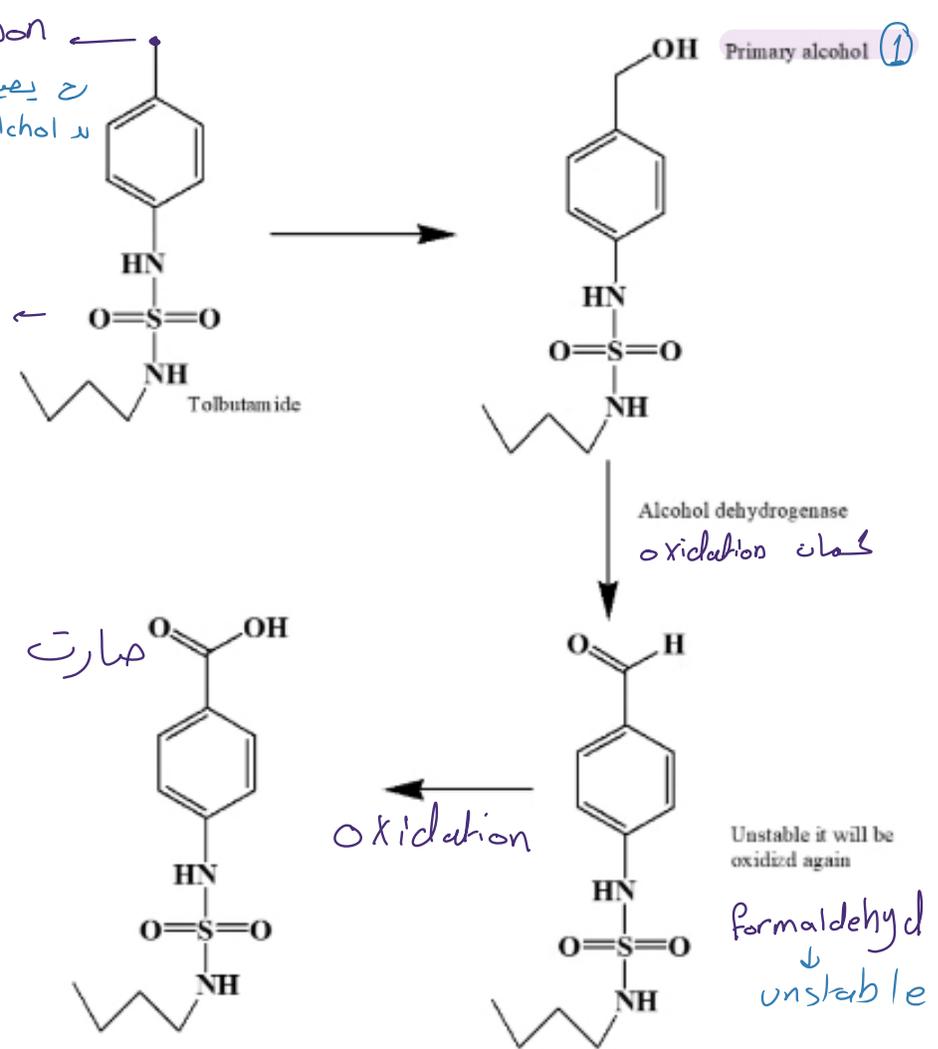
③ conjugated

(alcohol + carboxylic acid)

② Carboxylic acid

benzylic carbon
 يح يغير الـ oxidation راح تتحول
 Primary alcohol

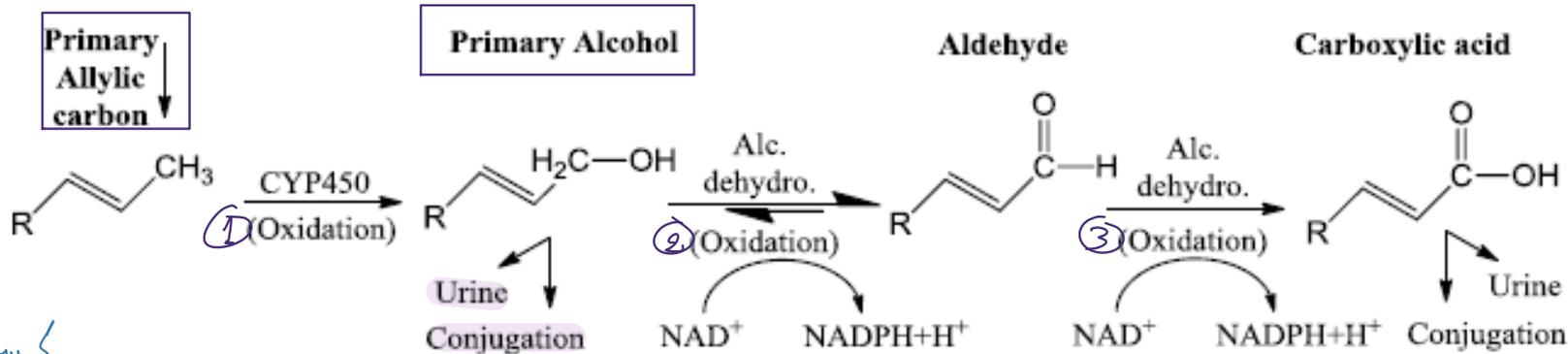
sulfonamide



عبارة عن "مرتبطه بكاربوتين: allylic carbon
بينهم double bond

3. Allylic oxidation

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.



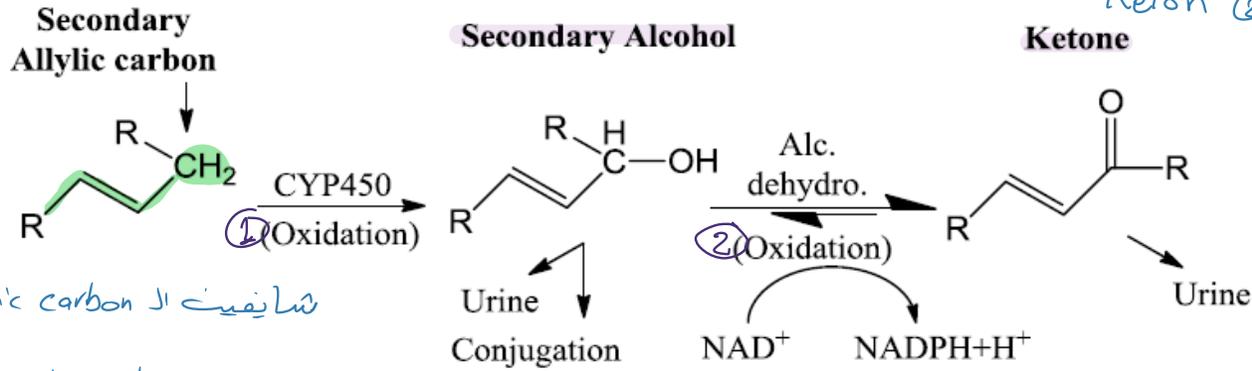
كسرية التفاعل
 ال benzylic carbon اسرع
 ال allylic carbon وبعدين ال

شوح اشوف بال Urin !!

Conjugated + Carboxylic acid ②
 Conjugated + alcohol ① form

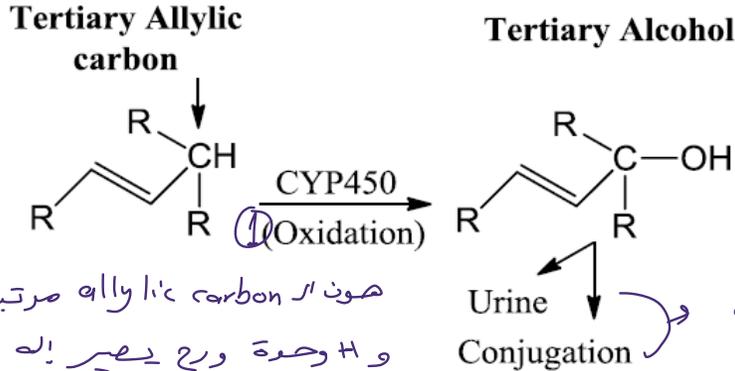
شورج اشوف بال URIN

Ketone @ conjugated + Secondary alcohol @



شايضت ال allylic carbon مرتبطة ب R

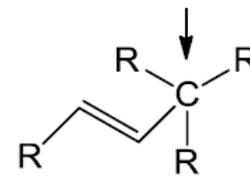
group ثانية د لي CH₂ ميس زي ار Primary
CH₃



هون ال allylic carbon مرتبطة ب 2 R group
و H وحدة ورج يصير ال hydroxlation

صنول الي
شورج اشوف
بال URIN

Quaternary Allylic carbon



Not oxidized
nor conjugated
nor excreted in urine

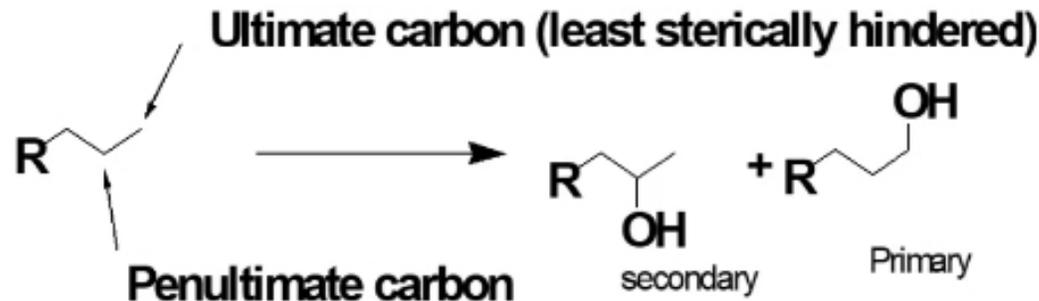
هون ال allylic carbon ما عليها
H فما ز يصير ال oxidation

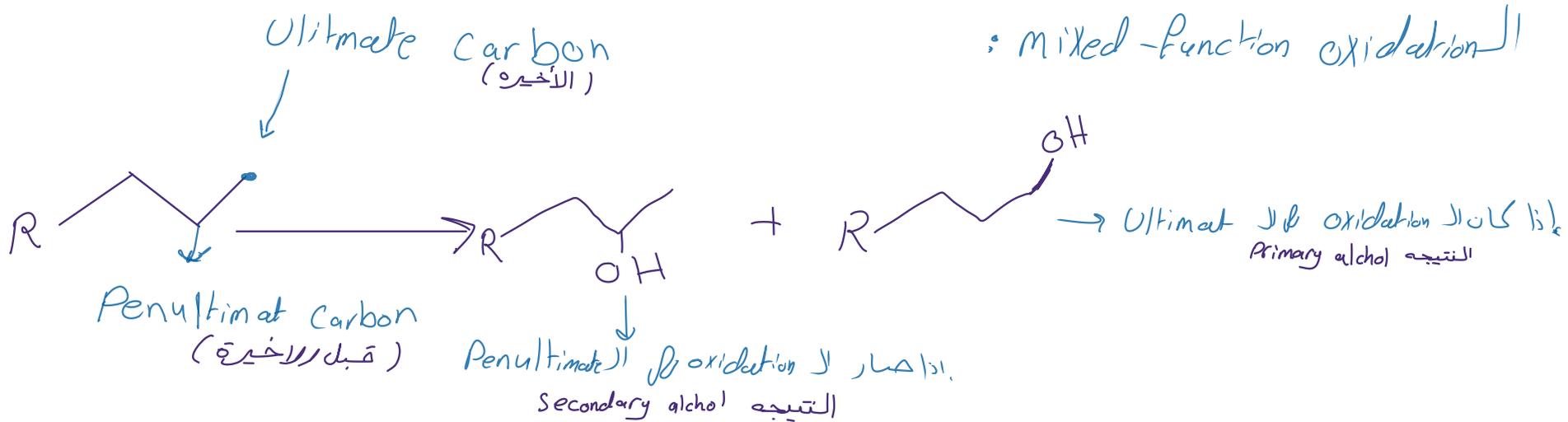
Oxidation at Aliphatic and Alicyclic Carbon Atoms

↳ alkyl chain

↳ aromatic cycle أو سب cycle أو سب alkyl chain

- 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.





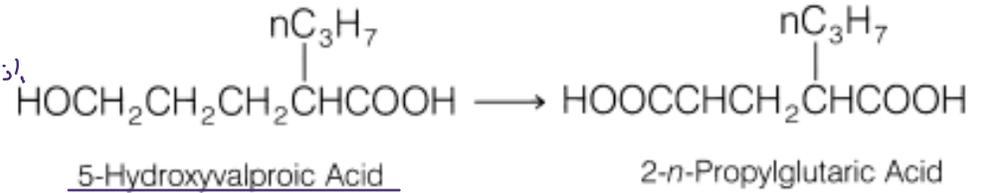
زبي ما شغنا ال oxidation بصير ال 2 site فيها الي بنسميه mixed-function oxidation

Ultimate carbon \rightarrow ω -oxidation

ال ω لفظها omega

Penultimate carbon \rightarrow $\omega-1$ oxidation

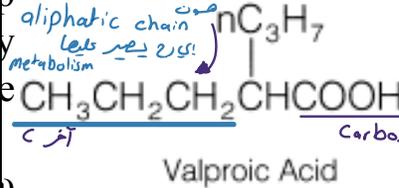
بما انه يحتوي على Carboxylic acid
 اذا جزئ كبر منه ح يطلع زي ما هو
 بال uric جزئ بسيط ح يصير الـ metabolism



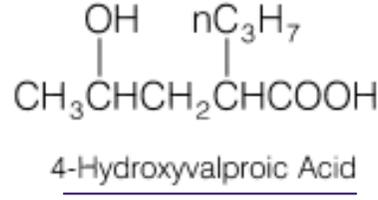
Valproic acid (Anti-seizure; Depakin®)

This drug has a carboxylic acid group so it's readily filtered and actively secreted to be eliminated in the urine unchanged.

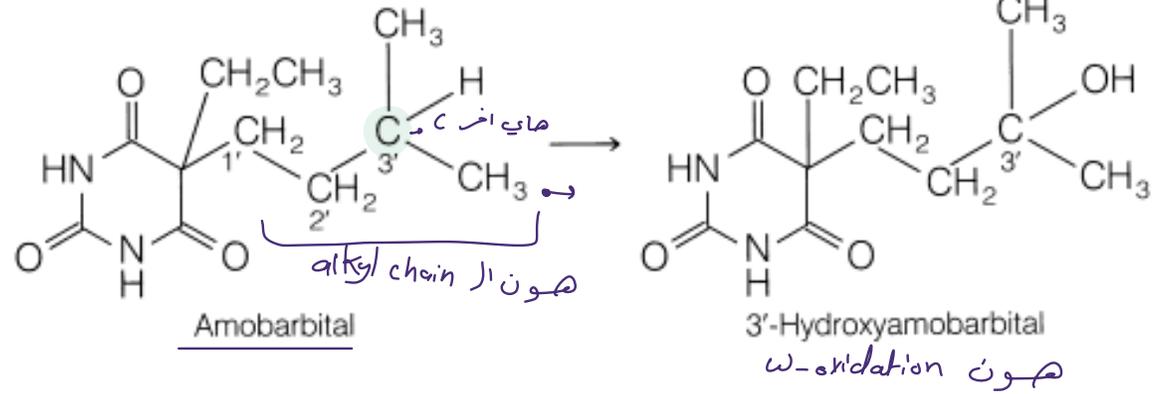
It also gets oxidized, around 5%, in a ω and $\omega-1$ oxidation. But mostly is eliminated unchanged.



ω Oxidation
 $\omega-1$ Oxidation

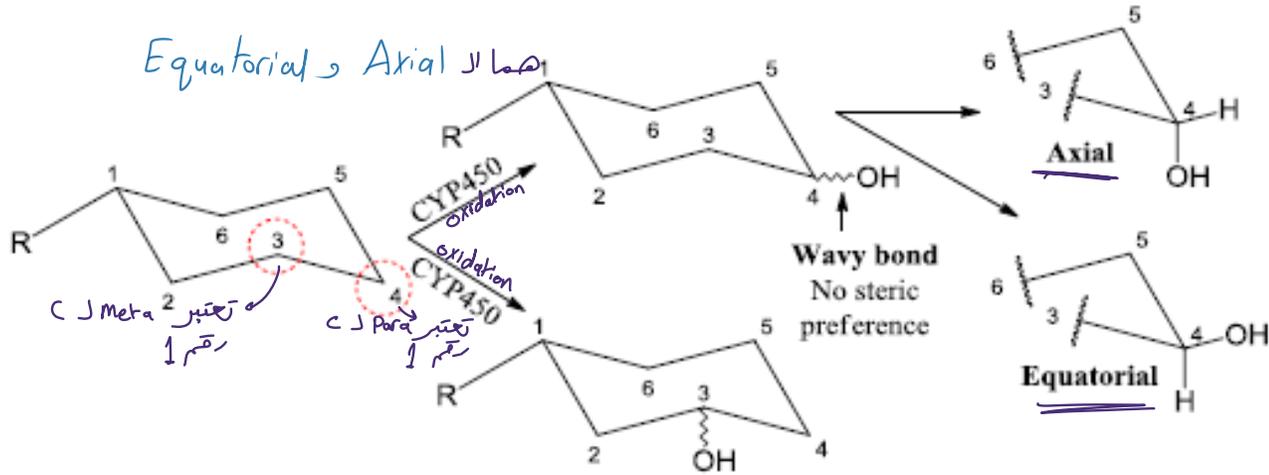


زي ما حكيئا سابقاً انه الـ Carboxylic acid ح يصير الـ
 absorption بنسبة 50% بال stomach وبال intestine ح يكون totally ionize



بالحلقة المشبعة يكون فيه 2 isomer metabolite

عوامل Axial و Equatorial



تعتبر C Meta رقم 2

تعتبر C Para رقم 4

صوت رخيص ال oxidation

