*Lecture 15 (30th July. 2024)

- In this lecture we will discuss the reactions done by mixed function oxidases

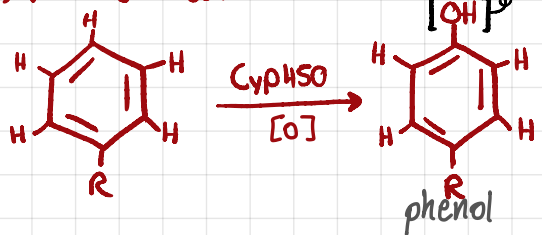
C N O F
Si P S Cl
Br
I
↑ Electronegativity increases (electrophilicity)

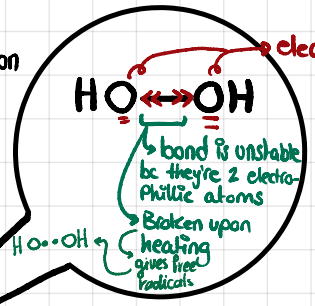
*Cyp450 can oxidize all atoms found in drug molecules (which are mosly organic; C,O,N,F,Br,I... -but not Si-) and the atoms attached to these atoms. نفسها اللي بنشوفها بالـmedicinal chemistry

*Oxidation of Carbon Atoms:

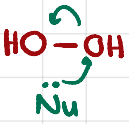
*Carbon can be oxidized while its in 7 different forms:

(1) Aromatic Carbon:



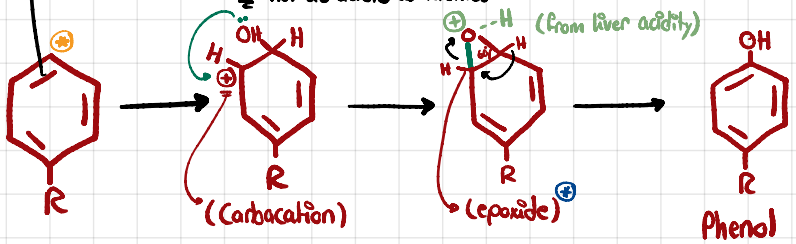


*to get it more stable it must find another source of e⁻s e.g: a nu⁻ with excess e⁻s:



•mechanisim:

*Cyp450's O_2 is turned to peroxide in slightly acidic conditions (in liver)
its a bit more acidic than other organs but not as acidic as kidnies



*This why the peroxide works as an Oxidizing agent, it takes e⁻s from other molecules & that what happens in Cyp450

*Aromatic rings are electron rich system bc. they have pi-orbitals
*CyP450 tries to attack the ortho position but there is steric hindrance, it tries meta position but still sterically hindered, so it attack the para position which is exposed and not sterically hindered

*It attacks para position because its e⁻ rich away from steric hinderance

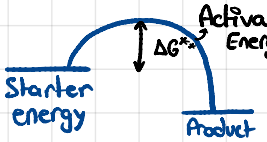
*how do I know that epoxide has formed?

- Some epoxide is eliminated in the urine, if a patient takes a drug with ⬡ like phenytoin, you'll find that 1% of the administered drug is in urine in the form of epoxide

*Epoxide is super unstable why?

- its a strained ring, it has 60° angles (and we know that Sp3 atoms normaly have 109.5°)

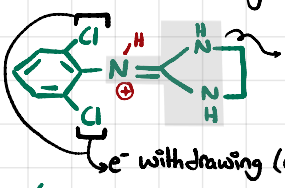
*This strained intermediate slows the reaction as it has a high energy transition state, for a rxn to be spontaneous the product must be more stable than the starter (ΔG is -ve -Downhill rxn-)



*the higher it is the slower the rxn
*So if the transition state is unstable it will be a slow reaction (thats why yeild ≈ 50%)

* معلومات إضافية عن التفاعل *

- OH is added on para
- The reaction doesn't happen without replacing H with an OH so having H on para is mandatory
- if Para is blocked or has no H, it can happen on meta to a lesser extent, but not on Ortho
- its a moderate yeild reaction, yeild = 50% ⟹ لو أعطيت مريض دوا فيه ⬡ بتركيز 100 mg تلاقي باليورين 2 بس
- the aromatic ring must be e⁻ rich, e.g: 0 = ortho ال, 20mg ≈ meta ال على, para position ال على Oxidized يعني 50mg ≈

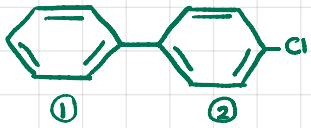


⟹ Ionized in plasma into guanidinium -Cationic Center- (e⁻ withdrawing)

(Clonidine - Anti-HTN-)

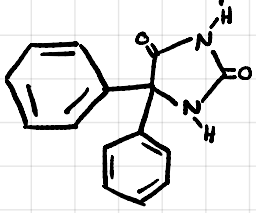
*Since it has many e⁻ withdrawing centers it wont be oxidized by Cyp450 as it wont detect a point with high e⁻ density

- Which of these rings will be oxidized?



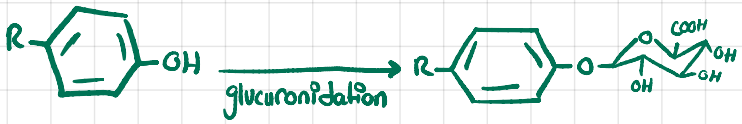
① will be oxidized bc ②'s para position is blocked & its meta position won't be oxidized as Cl is e⁻ withdrawing group

- This oxidation system only happens once to the compound (Single Oxidation)
  - even though phenytoin has two rings, only one will be oxidized by Cyp450 ∴ will be ready for glucuronidation step



Phenytoin

- the phenol product can pass into urine as it is (30% is eliminated in urine) or it can be conjugated by glucuronidation or by Sulfate conjugation



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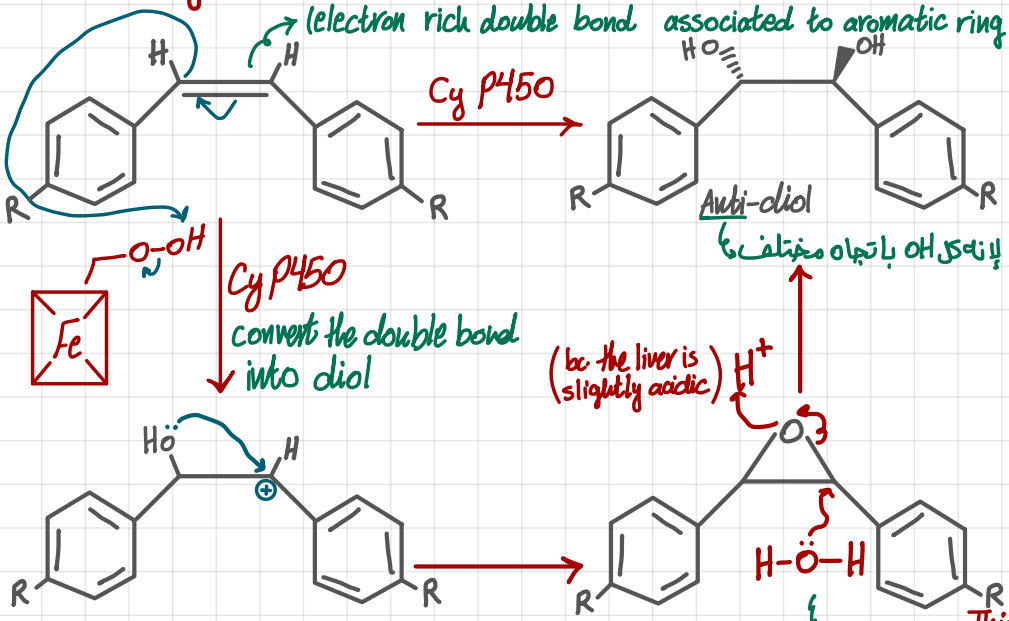
* Double bond oxidation

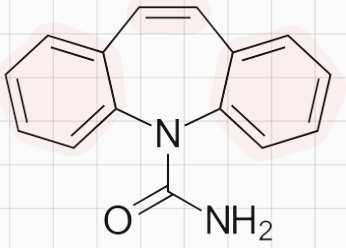
We are still talking about mixed function oxidase and how it deals with carbon systems

could be 1 or 2 but it must have at least 1

(electron rich double bond associated to aromatic ring system)



Example of this systems: double bond + 2 aromatic rings



Carbamazepine

- Anticonvulsant
- For neurological pain

خلال 24 hr من الجرعة بنلاقي 50% من الجرعة diol كـ urine بال

This intermediate is unstable but still can be found certain trace amount in urine

وهيك عرفنا إنه هاد الepoxide موجود بالتفاعل كـ intermediate (موجود بال urine وقدرنا نعزله منه)

About this interaction:

1- yield = 50% (مش سريع ولا بطيء)

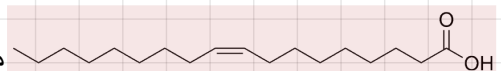
2- if there is no R-group on para position >> para hydroxylation

double bond oxidation عمل %50 بيكون عنا

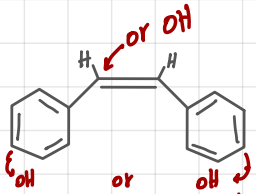
aromatic oxidation عمل %50 و

3- surrounded by aromatic ring (at least one) (electron rich double bond)

fatty acids زي ال isolated ما تكون (oleic acid زي ال)



double bond oxidation ما بتأكسد بطريقة ال



* إذا ما رح على وحدة من ال para ما بصير على التانية

* إذا ما رح على ال double bond ما بصير عال para

الدوا 50% منه مر، "اصلي diol" من هاي ال 50%

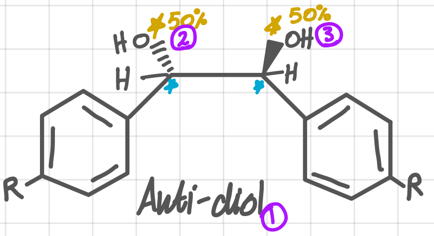
1← (30-40%) منهم ع ينزلوا بال urine (bc. it has some hydrophilic properties)

2← عنا 2 OH ← 50% ممكن يصير عليهم glucouronyl conjugation (مرة وحدة على وحدة منهم)*

→ 50% right 50% left (مش مع بعض - ليش)

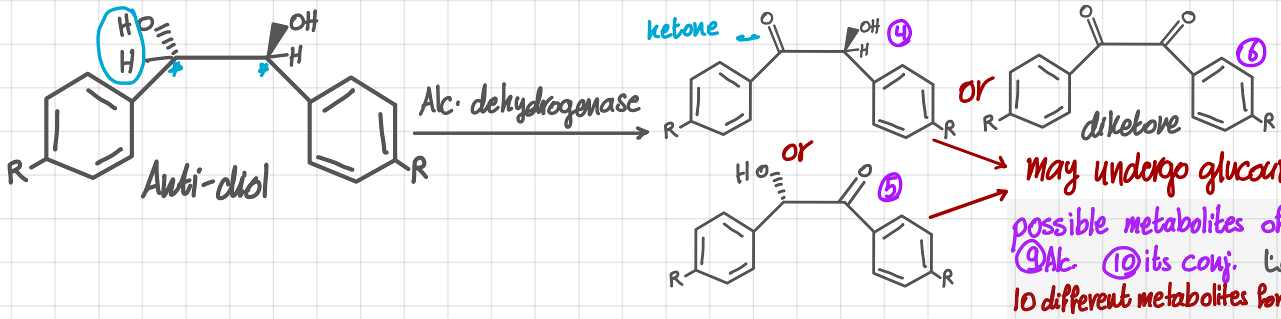
once you get glucouronyl conjugate → the molecule gets eliminated by the UT very quickly

(ما يلحق يصيرله كاتا: glucouronyl conj.)



3← لو عندي Alc. ع الكاربون الي عليه CH (عند *) بيجي إنزيم إسمه "alcohol dehydrogenase" & ~20%

وال co-factor تبعه هو NAD^+ (it's not a special liver enzyme, it can be seen in other organs)



may undergo glucuronyl conj. ⑦⑧

possible metabolites of this drug → 8 /
⑨Alc. ⑩its conj. وإذا كان في R ع الـ ring بيصير
10 different metabolites for single cpd.

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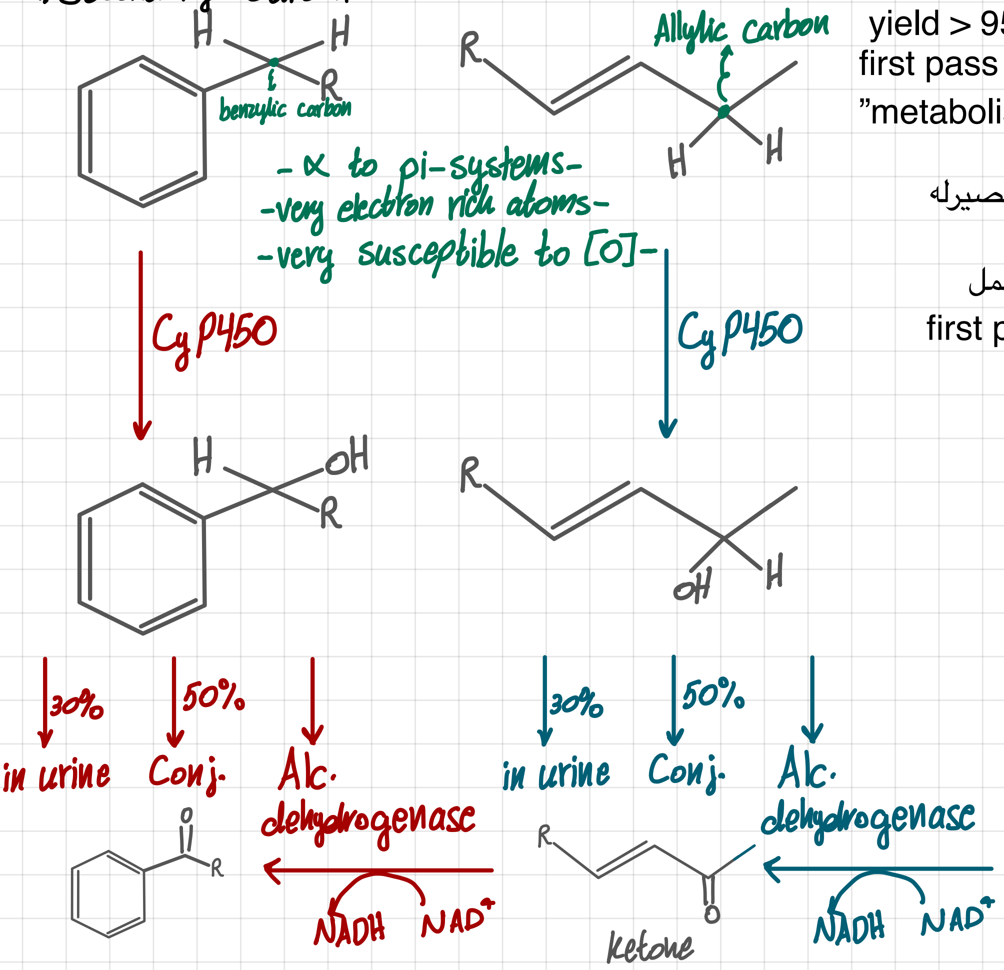
*Benzylic and Allylic oxidation ⇝ أسرع واحد

*Secondary Carbon

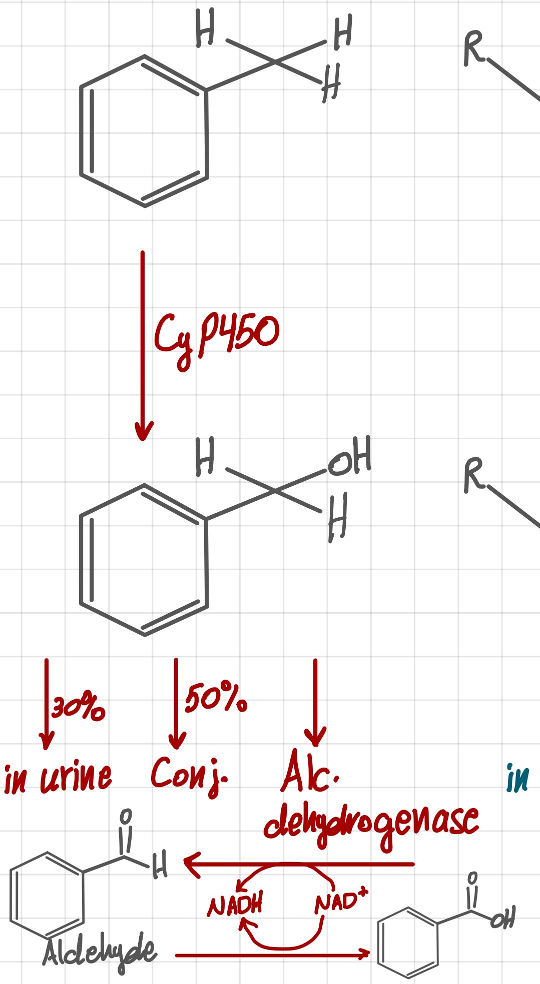
yield > 95% of the administered dose
first pass "very quick وبالأغلب بصير
metabolism"

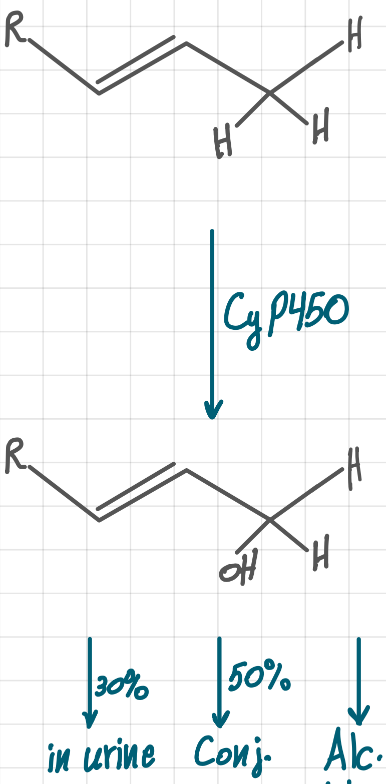
أول ما يعبر ال portal vein ويدخل عالكبد بصيرله first pass metabolism.
لنتفادى هاي المشكلة بنضطر نزيد الجرعة ونعمل saturation للenzymes اللي بتعمل first pass
(بنعطي جرعة عالية منه أكثر من مرة باليوم)

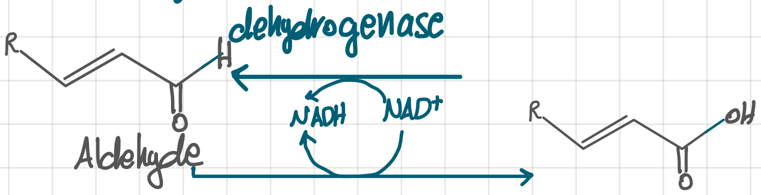


• النسب مش ثابتة بتختلف من شخص لشخص ومن دوا لدوا •

* Primary Carbon







Note:-

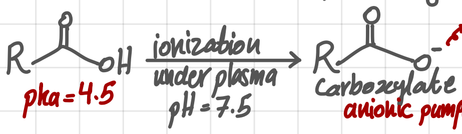
you wouldn't see Ald. in the urine

Ald. –
- 99% [O] by Alc. dehydrogenase (in the presence of water) → Carboxylic Acid
  - ↳ Ald. dehydrogenase مرات بنكيلها
- 1% by reductases (in the liver) → Come back to Alc.

ب phase I أهم تفاعل بالإثنان هو oxidation

بعدين ال Hydrolysis وأقلها أهمية هو ال reduction

* إذا تكون ال Carboxylic acid فهو أسهل إشي بنزل بال urine لإنه very hydrophilic ويصير له Ionization

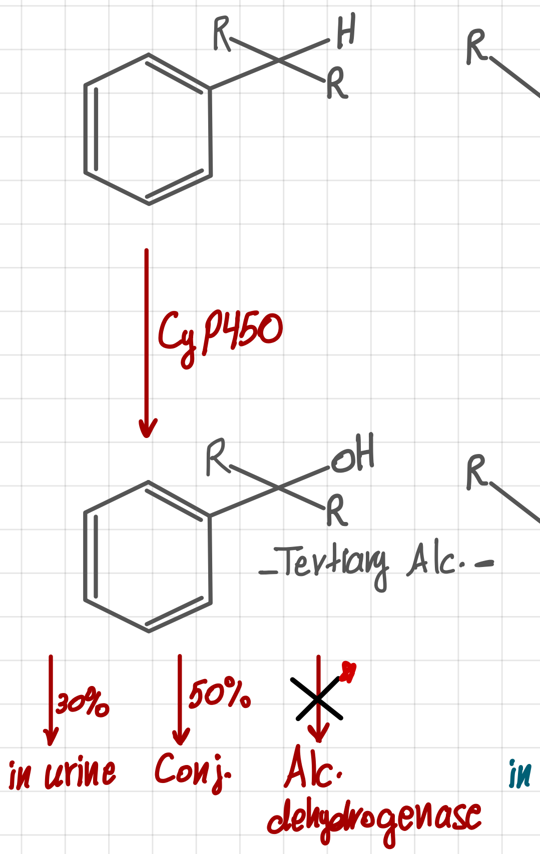


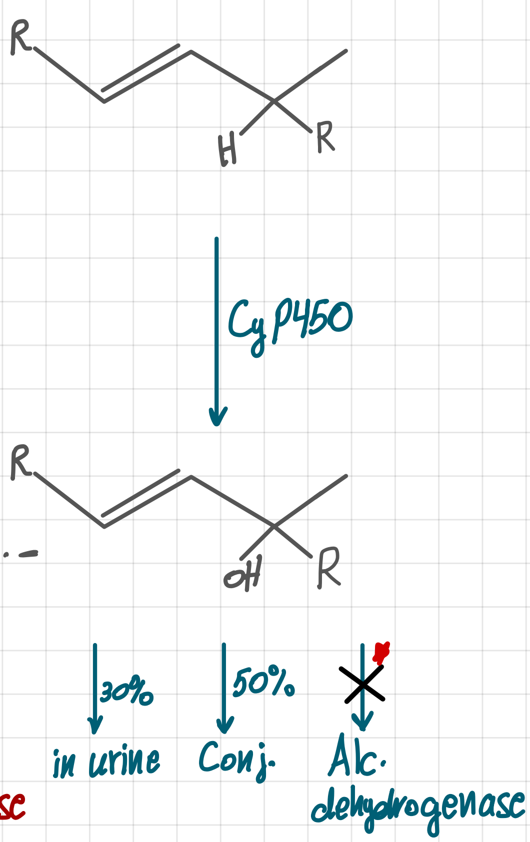
- لما يتفلتر بال renal sys. ما بصيرله abs.
- وبنفاية ال renal sys. في anionic pump الي بتخلص منه (renal secretion).
- وممكن ال Carboxylic acids يصير لهم Conj. وفي conjugants خاصة فيهم (glycine + glutamine)

(في أكثر من طريقة للتخلص منه)

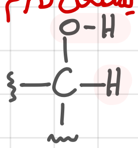
Quickly renally eliminated

* Tertiary Carbon

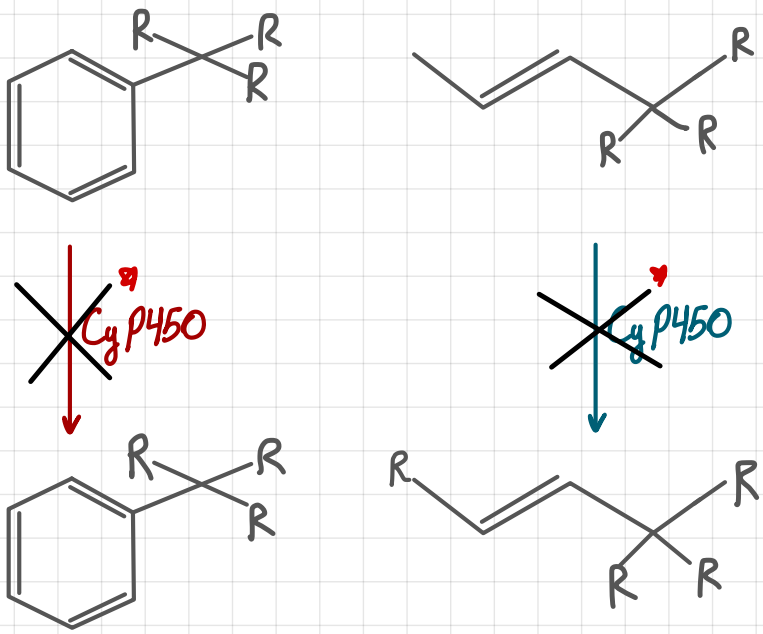




عشان ال alc. dehyd. يشتغل لازم يكون عندي OH جنبها CH



* Quaternary Carbon

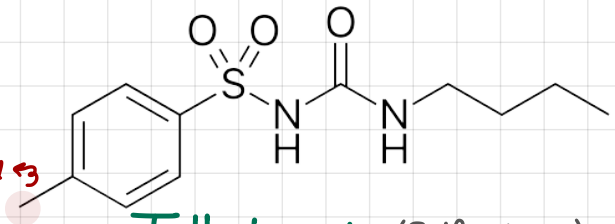


ماعنده H يشتغل عليها الCyp450 (يشيلها ويحط بدالها OH)

Example

first pass يتعطى بجرعات كبيرة بكل مرة حتى يشبع الـ ... hypoglycemic effect ويدخل جزء صغير منهم يعمل quickly they get metabolized وحتى هدول اللي بدخلوا and you end up having short half life

benzylic carbon ←3

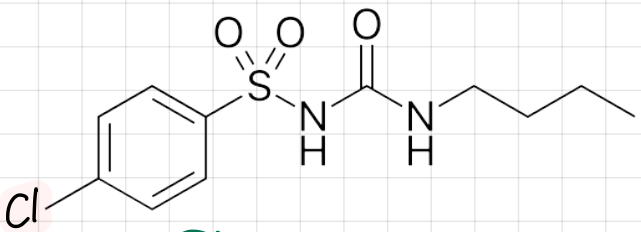


Tulbutamide (Sulfonylurea)
(Hypoglycemic effect)

sustained بيتعطى كل ساعتين مرة أو على شكل delivery

لو كان عندي benzylic carbon ما بتطلع الى double bond oxidation وولا aromatic oxidation، لإنها أسرع إشي وال oxidizing system بعمل oxidation مرة وحدة (إذا اشتغل عمكان سريع بترك أي مكان تاني)

حطينا Cl بدل ال benzyl carbon، ولإنه ال Cl very electrophilic/electronigative atom ما بتعطي الكتروناتها لل cytochrome P450
هاد المركب resistant لل oxidation لإنه ما عندي benzylic carbon وبطوّل بالجسم وبينعطى BID مرتين باليوم مرة الصبح ومرة المساء، ممكن يصيرله metabolism بأماكن تانية بس مش first pass



Chlorpropamide

C N O F Cl Br I ← كل الـ Halogens ما بتأكسدوا بالـ Cyp450