

Revised Third Edition

# Medicinal Chemistry

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epoxide hydrolase

CYP450

enzyme

10/09/1444

في جسم الانسان

هم الي سيبا عدونا في زيادته

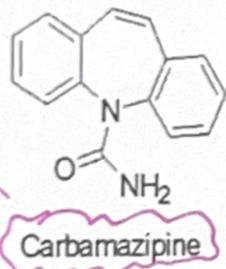
## Double bond oxidation

### Alkene epoxidation:

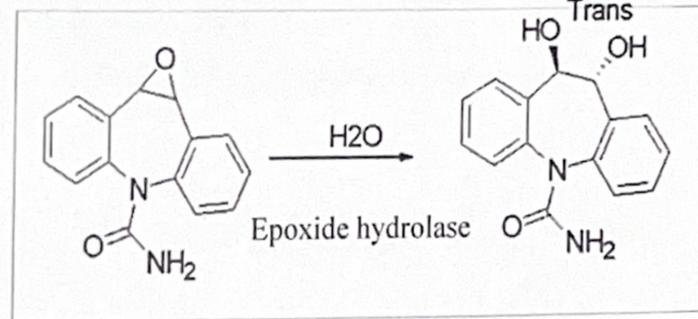
- In order for a double bond to be oxidized it has to be conjugated to at least one aromatic ring
- Rate is similar to aromatic ring oxidation but slightly higher; still moderate rate
- Yield 50-60%.

Urine unmetabolites  
metabolites 50%

سرعة زي (3) aromatic ring oxidation  
يعني من سريع ليس مشابه صيد بنا في نسبة 50%



Cyp450



ring oxidation

oxidation double bond ال double bond ال  
epoxide يتحول ال epoxide بعد ذلك

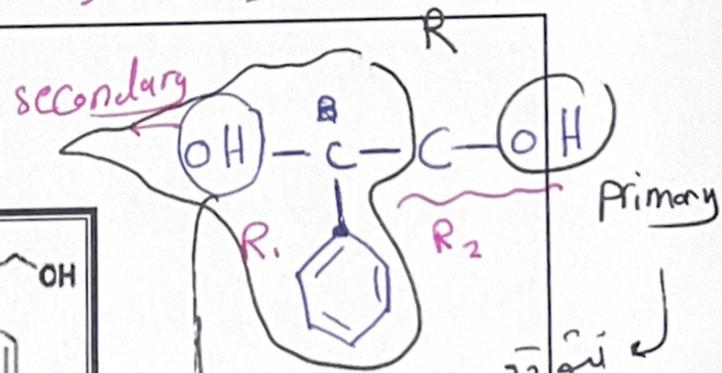
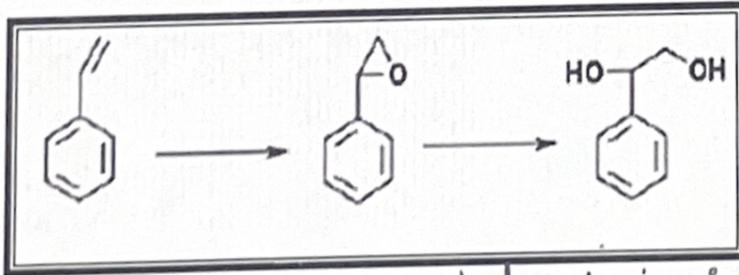
transdiol with water hydrolase يعطينا  
هاد الحكي ليعيانيا

ex2

## Styrene (polystyrene monomer)

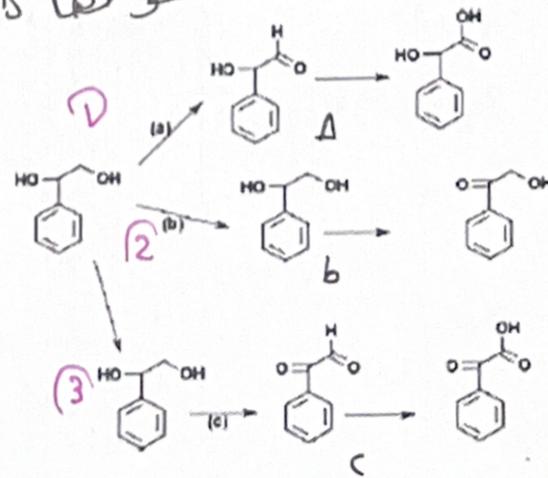
aromatic ring

single bond



### What is the fate of this styrene glycol?

- Further oxidation by alcohol dehydrogenase on one of the OH or both. It could give:
  - An aldehyde which gets further oxidized into a carboxylic acid. An alcohol carboxylic acid is found in the urine.
  - A ketone. An alcohol ketone is eliminated in the urine.
  - A ketone and a carboxylic acid. (eliminated in the urine).
- Gets conjugated on one of the hydroxyls with glucuronic acid and eliminated.
- Eliminated in the urine as the oxidized form (glycol).



Carboxylic acid  
arabiy  
conjugated  
بالا

از كل واحد كمال \*

Carboxylic acid ← A

← b  
Ketone ← B

as diol

Keto aldehyde

Keto carboxylic acid

① الخلاصة لا Carbonyl موهبة انه يصير لها

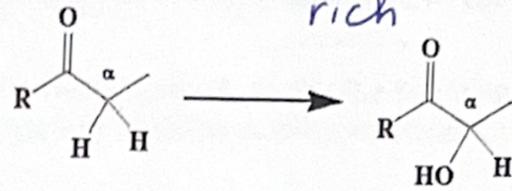
Oxidation

### Oxidation to $\alpha$ carbon to carbonyl

- Aldehyde, Ketone, Ester, Enole, Carboxylic acid, Thioester
- Carbonyl is electron withdrawing group  $\rightarrow$   $\alpha$  carbon is electron rich
- Very fast reaction: 90-100% yield
- Fate of the oxidized drug:
  - Eliminated in its oxidized form in the urine
  - Good candidate for conjugation to glucuronic acid
  - Further oxidation by alcohol dehydrogenase: If a primary alcohol it's oxygenated to a carboxylic acid and gives a carboxylic acid ketone group in the urine.
  - If it's a secondary alcohol it's oxidized to a ketone, giving a diketone in the urine.

السؤال صون؟ كيت

EWG  $\leftarrow$  Carbonyl  
 و ال  $\alpha$  electron rich



الجواب

ليس سريع

و نسبة

90-100%

②

③

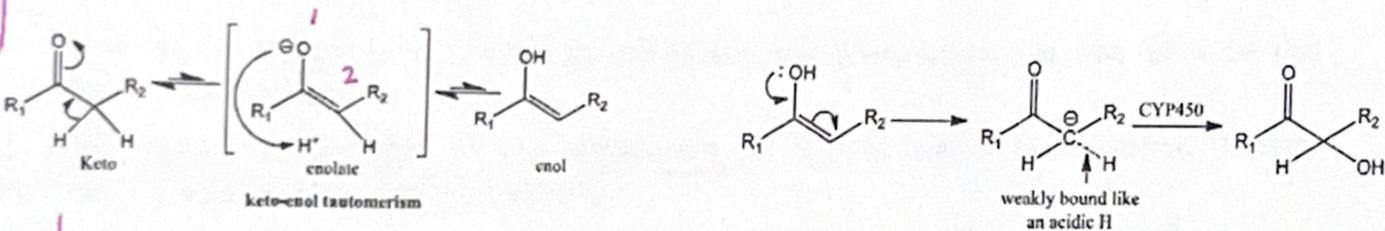
بصير له

elimination

بفرض شكله

بصير له conjugation

glucuronic acid



Keto-enol

tautomerism

ال Carbonyl ما يتكون موجوده جال system مثل هيد  $\leftarrow$  بصير ايت الله

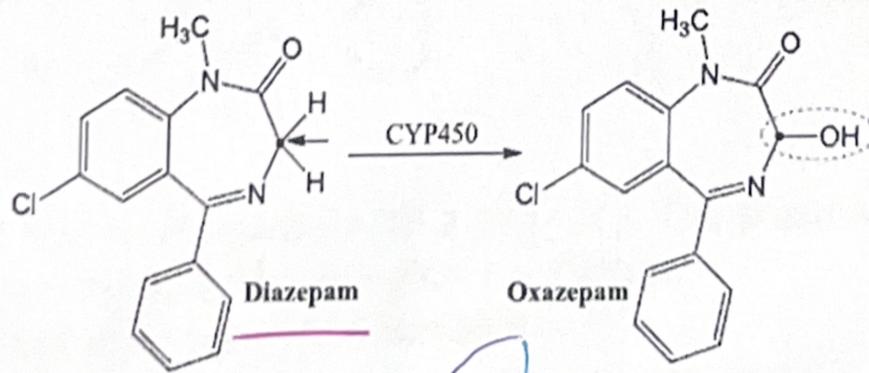
عقود Ketone. ياخذ من ال O الكتر داتها و بصير عند ي double bond فيغير

H ال

ما ي الكربونه ② عنبة بالالكترونات ، و بصير عند ي negative charge

Example طلعت بتاخذ الحان بعد ال B و بصير عند ي OH

فد بصير عند ي enol



⑥ بنتونه جال Urine

حسبه نوع ال Alcohol

از primary

بجور ال Carboxylic acid ketone group

ال الأتسم بتصير على ال alpha-carbon

Aromatic ring

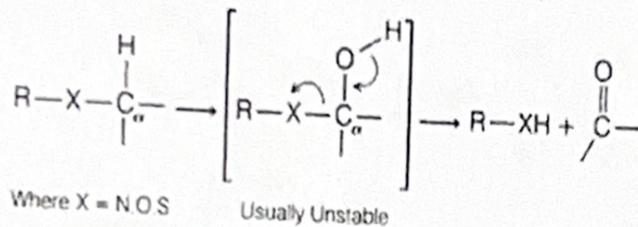
لانه أسرع من ال

Aromatic ring oxidation is very minor because it's slower. The oxidation of the alpha carbon is much faster and more likely to happen.

و اذا secondary  $\leftarrow$  diketone

# Oxidation Involving Carbon-Heteroatom Systems

- Nitrogen and oxygen functionalities are commonly found in most drugs and foreign compounds; sulfur functionalities occur only occasionally.
- Metabolic oxidation of carbon-nitrogen, carbon-oxygen, and carbon-sulfur systems involve two basic types of biotransformation processes:
  - Hydroxylation of the carbon atom directly attached to the heteroatom (N, O, S). The resulting intermediate is often unstable and decomposes with the cleavage of the heteroatom-carbon bond:



nitrogen is more electrophilic than carbon, the  $\alpha$ -carbon is likely to get oxidized and is easier to be oxidized than the nitrogen

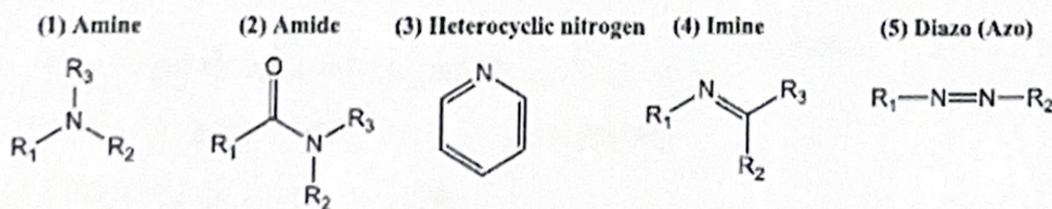
Oxidative N-, O-, and S-dealkylation as well as oxidative deamination reactions fall under this mechanistic pathway.

- Hydroxylation or oxidation of the heteroatom (N, S only, e.g., N-hydroxylation, N-oxide formation, sulfoxide, and sulfone formation).

\* علية ال oxidation ← على نوعين ←

1 - hydroxylation ← ال Carbon المرتبطة بشكل مباشر بال heteroatom  
 2 - hydroxylation ← ال heteroatom ← مع انه أسهل يكون على ال Carbon الـ

## N- systems



Amines are **ionizable** groups with a  $pK_a = 9.5$ . The plasma's  $pH = 7.5$  so amines are ionized in physiological conditions.

**How does that affect its renal elimination?**

Since it's ionizable that means it's water soluble and it's more likely to get eliminated in the urine **mainly** unchanged than reabsorbed. around **80%** of the amines get eliminated unchanged in the urine

- and around **10%** get conjugated. This means that amines aren't good candidates for metabolism by **CYP450**.

\* ما يدبير له metabolism عن طريق Cyp450

\* ما يدبير له oxidative dealkylation ← ال تصير

الا تسم على ال Carbon الـ على ال amine الـ  
 لـ يتكون مركب stable الـ

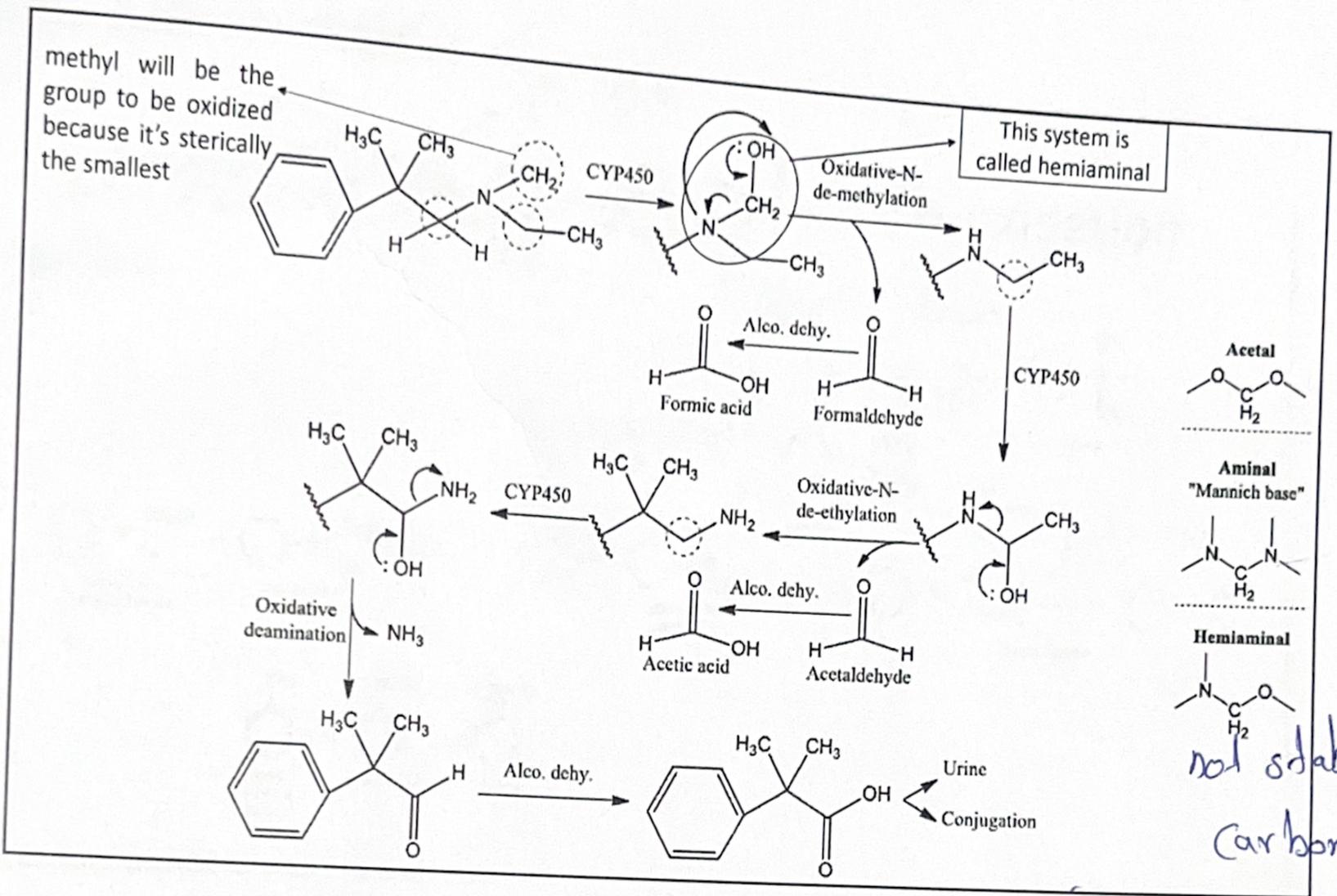
(O, N)

من لتير  
 متواجدا  
 بال drug

ازا كانت  
 usually ← O  
 ما يدبير عليه

\* ما يدبير له  
 metabolism  
 يدبير له  
 excretion  
 زي ما هم  
 80% ←

و 10% منهم  
 يدبير له conjugated



مع تا حد هيدروجيناته

وتحتاج ال N على شكل

Aldehyde (Formaldehyde) و يترجم ال انزيم Alco.dehy بـ Formic acid

### N-systems: What do we find in the urine?

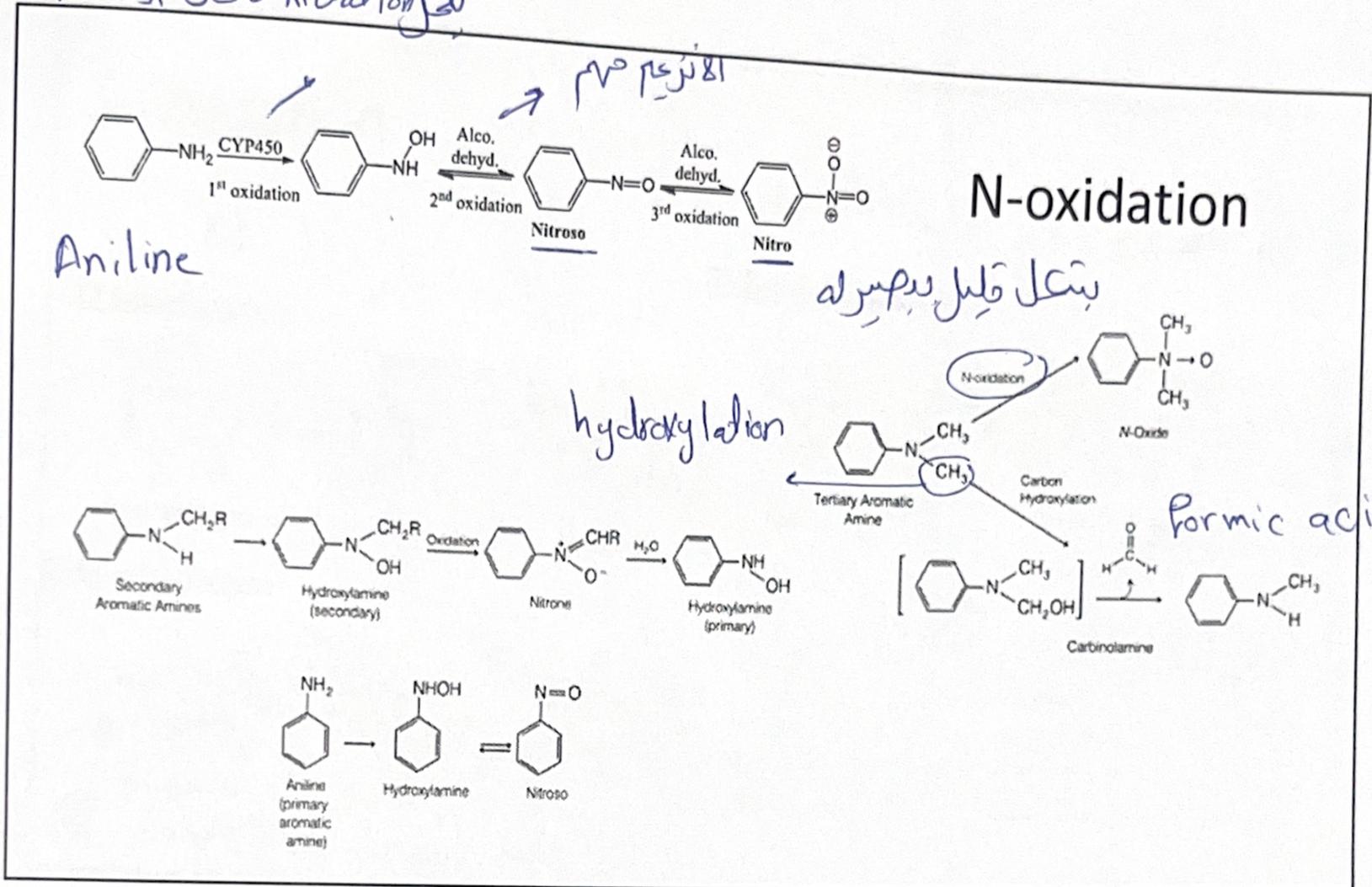
- Ionized drug unchanged (mostly) → water soluble → 90%
- - Conjugated drug (to a lesser extent)
- To a much lesser extent:
  - Ionized secondary and primary amines and their conjugates
  - Ammonia
  - Carboxylic acids (formic acid, acetic acid and the final carboxylic acid product of the last reaction)
  - **NO** aldehyde (unstable)
  - **NO** hemi-aminal (unstable)

موجودين بشكل قليل

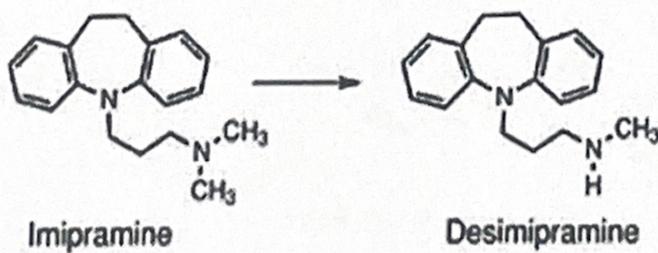
Conjugation 10%

ولا نه على طول  
من سنتر  
ما ضلله

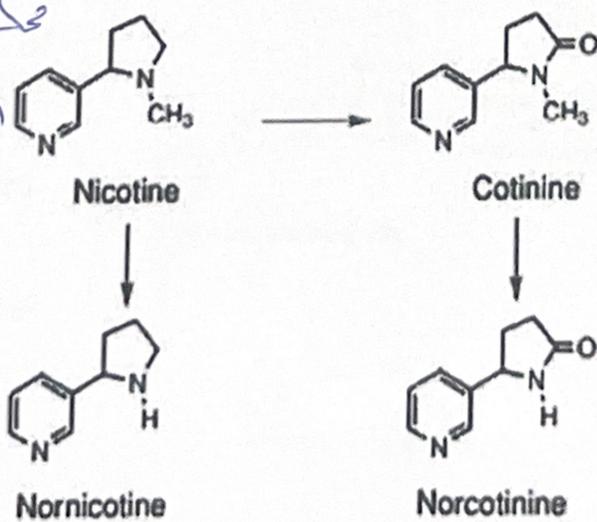
عملية Oxidation على الـ N



Example



عملية نزع ميثيل على الكربون الثانوي



ماتية، كحلج ← تحول لـ Keton

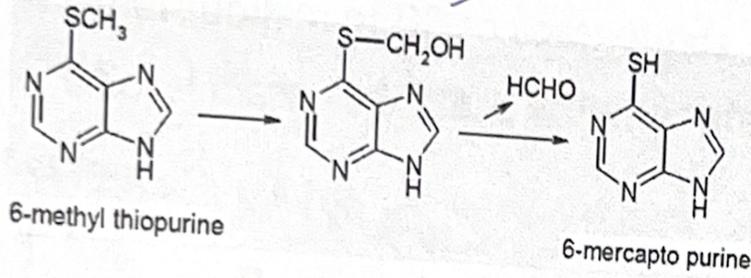
Demethylation

# S-Oxidation

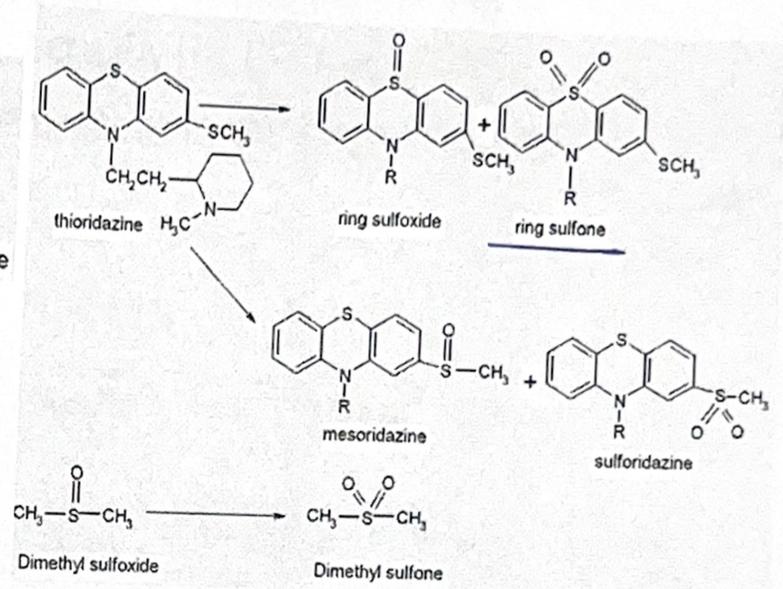
او (8) نفس رصير على oxidation

نفس الي صارت ن

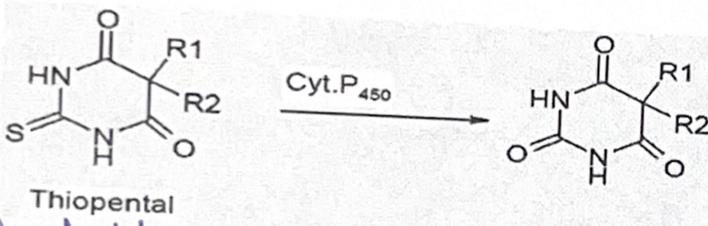
## 1) S-dealkylation:



## 3) S-oxidation:

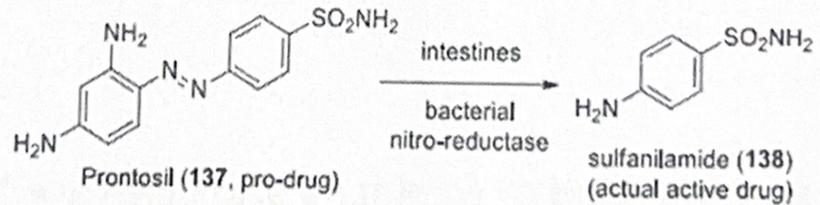


## 2) Desulphuration:

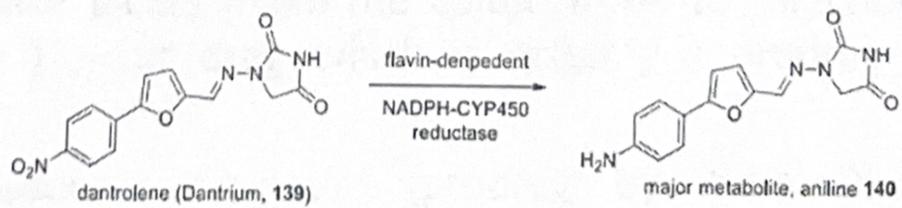


تحويل  
 ⑤ اذا كان عندك double bond الى double bond  
 ①

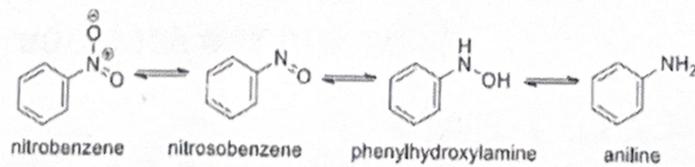
# REDUCTION



• Reduction is the reverse of oxidation and involves CYP450 enzymes working in the opposite direction.



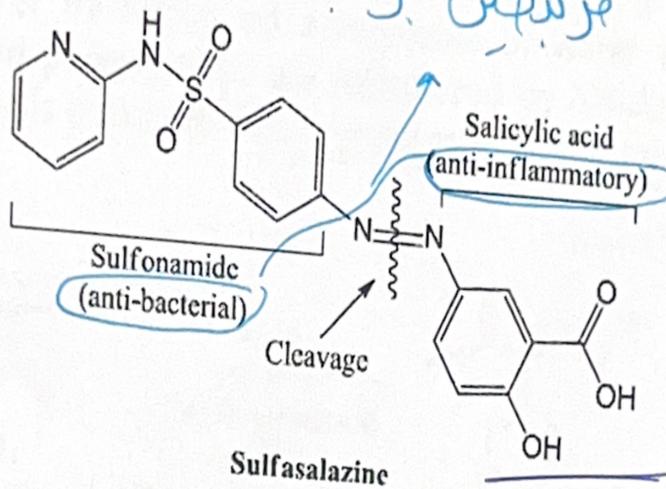
oxidation الى





Sulfasalazine is not absorbable, so it acts locally at the large intestine. and it is a prodrug that has to be activated in vivo,

يرتبطين برابطة الازو



عاد الازو لو تتركه طاله حيصيره امتحان بالعدة و طاحصيل  
للإعطاء الابنية قليلة جدا لصيد ريفية

عنا ما يصير له امتحان و يستغل بال Large intestine

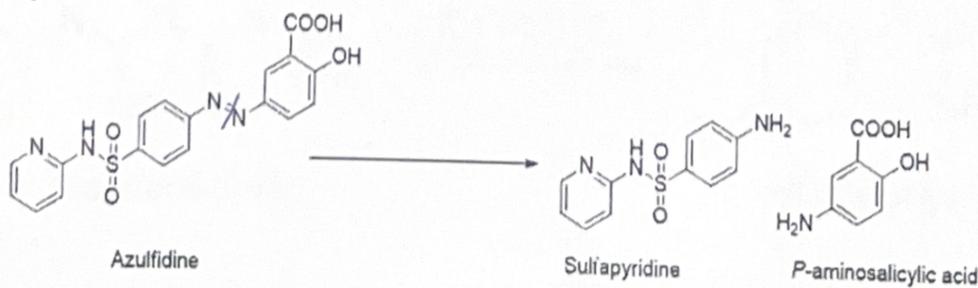
## Azo and Nitro Reduction

- A number of azo compounds, such as Prontosil and sulfasalazine, are converted to aromatic primary amines by azoreductase

breaking \* ليصير على

ازو group

amine ليصير



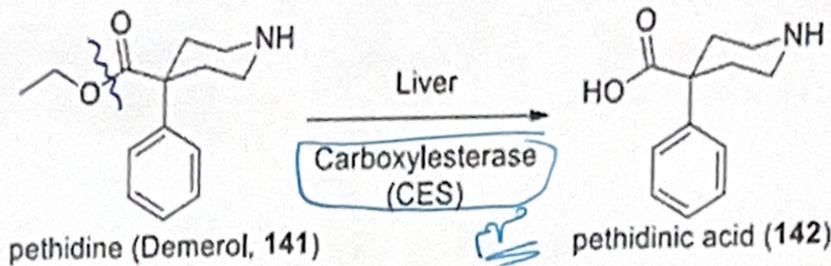
# HYDROLYSIS

ester containing drug ← water مضافا إلى الدواء

- Hydrolysis means adding water. For an ester-containing drug, hydrolysis is cleavage of the ester by taking up a molecule of water employing esterase. Similarly, amides and polypeptides are hydrolyzed by amidases and peptidases, respectively. Hydrolysis occurs in the liver, intestines, plasma, and other tissues.

ماء ←  
 & Carbon 11  
 Oxygen  
 O & C=O 11  
 مضافا إلى  
 esterase

و كبد  
 [ مضافا إلى جدار الكلى ]

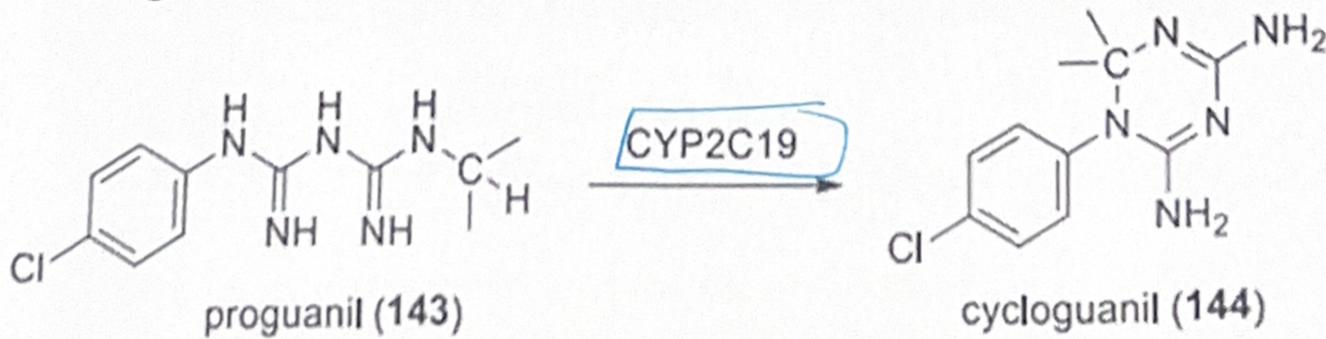


polypeptides 11 و amides 11  
 peptidase ← hydrolyzed by  
 amidases

# CYCLIZATION

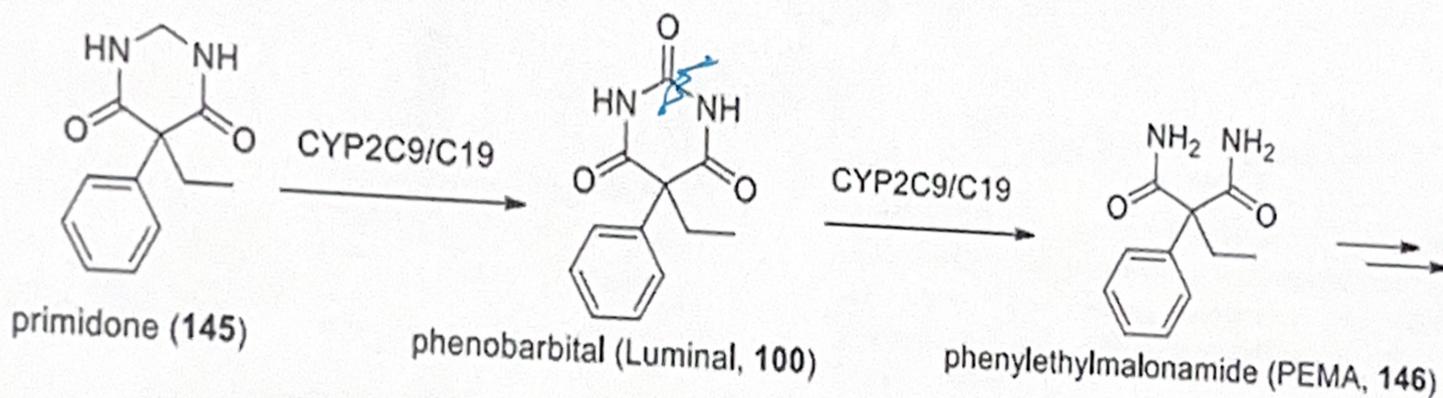
ring structure تكوين  
 Common

- Metabolic cyclization is formation of a ring structure from a straight-chain compound



# DECYCLIZATION

• Metabolic decyclization is ring-opening of a cyclic molecule such as phenytoin and barbiturates.



\* يكون عن ring بعد ان يتفك \*

كيف انعالج  
المشاكل  
وال  
issues  
بسبب  
الmetabolism

• Phase I metabolism is often problematic if the compound undergoes extensive metabolism to afford inactive metabolites, or worth still, reactive metabolites. There are many approaches to address Phase I metabolism issues:

- (i) Reducing the lipophilicity of the drug; → تقليل الlipophilicity
- (ii) Blocking a site of hydroxylation by replacing the hydrogen(s) with fluorine(s); وفيه يقل ال elimination
- (iii) Blocking a site of metabolism through cyclization;
- (iv) Eliminating or replacing a functional group with an isostere less susceptible to metabolism; or
- (v) Changing the chirality near or at the site of metabolism. This makes sense because the CYP enzymes are chiral, therefore metabolize different chirality differently. If the (R)-stereochemical center is metabolized, chances are the corresponding (S)-stereochemical center may be resistant to the metabolism.

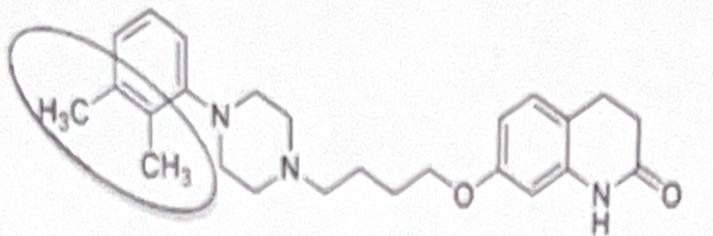
② ال sites الي بدبر عليهم hydroxylation بي له يايف تا نيه صح حذونه

③ الحانه الي بدبر فيه metabolism اعلاه blocking ← us حذونه cyclization

④ اسيل ال functional 26 الي بدبر عليه metabolism

⑤ بتغير جاز chirality ← فزيد على تزيده الحانه لا metabolism group

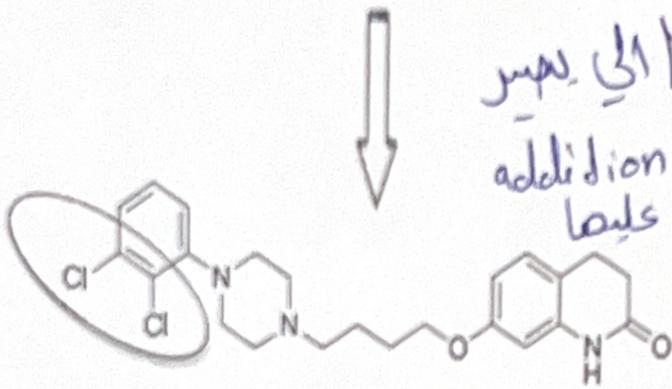
أقلية على الحلول



OPC-4392 (151), ED<sub>50</sub> = 41 μmol/kg, p.o.

The two methyl groups readily underwent hydroxylation and the diols were further oxidized to the corresponding inactive carboxylic acids.

هناك لو ال methyl group  
chlor د. methyl group  
بالتي عملو block ال hydroxyl group  
addition على



aripiprazole (Abilify, 152), ED<sub>50</sub> = 0.6 μmol/kg, p.o.  
Otsuka/BMS, 2002

Switching the two methyl groups to two chlorine atoms led to a molecule that is more resistant to the metabolism. The resulting compound OPC-14597 (aripiprazole, Abilify, 152) is more efficacious with an ED<sub>50</sub> of 0.6 mmol/kg, p.o.

It was approved by the FDA in 2002 as an effective and unique antipsychotic.

كان صحبه نصير على para أو ال meta ← لوجود FW  
\* more efficacious

👏👏 نهاية التشابتر ، موفقين