تفريغ ميديسينال

محاضرة: Lec 3 Part 3

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لجان الدُّفعات

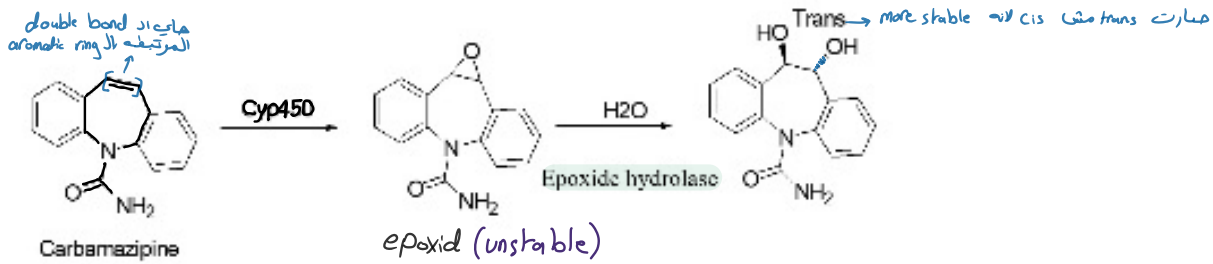
Soul Academy

Double bond oxidation

double bond حكينا لما نحكي
epoxid ؟؟ metabolism شو رح تصير بعد ال

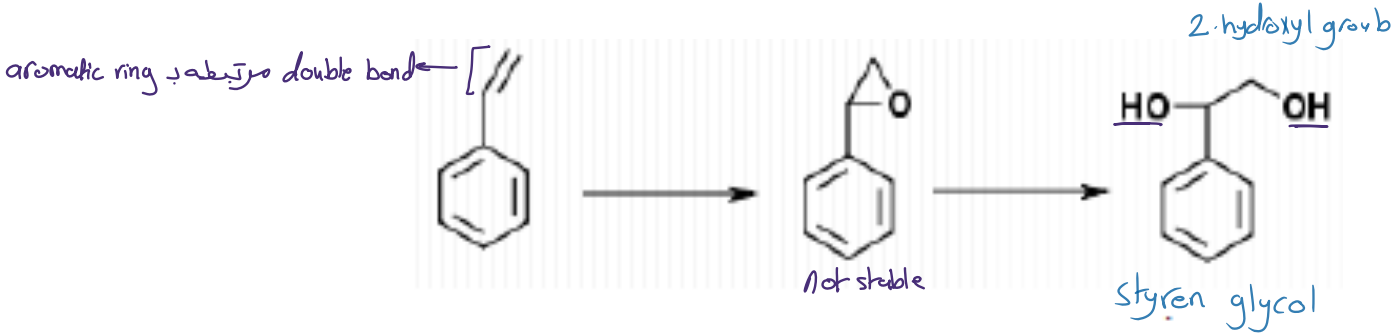
- Alkene epoxidation: very spontaneous هذا التفاعل
- In order for a double bond to be oxidized it has to be conjugated to at least one aromatic ring
- - Rate is similar to aromatic ring oxidation but slightly higher; still moderate rate aromatic oxidation اسرع من
- - Yield 50-60%.

double bond مرتبطة بـ
aromatic ring



Epoxide hydrolase

Styrene (polystyrene monomer)



سوف نشوف بال urin
Carboxlic acid alchol ①
+
Conjugated
Ketoalchol + conjugated ②
Keto carboxlic acid + conjugated ③
styren glyclol ④

What is the fate of this styrene glycol?

(1) Further oxidation by alcohol dehydrogenase on one of the OH or both. It could give:

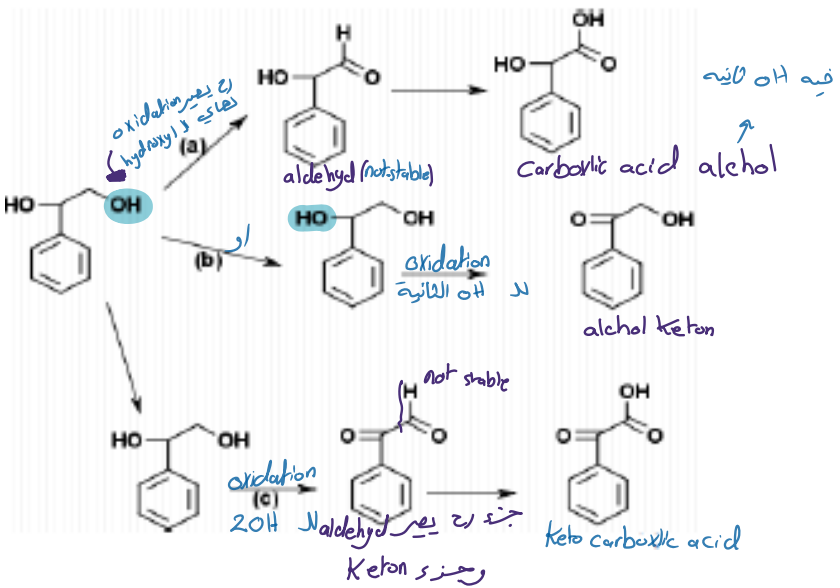
(a) An aldehyde which gets further oxidized into a carboxylic acid. An alcohol carboxylic acid is found in the urine.

(b) A ketone. An alcohol ketone is eliminated in the urine.

(c) A ketone and a carboxylic acid. (eliminated in the urine).

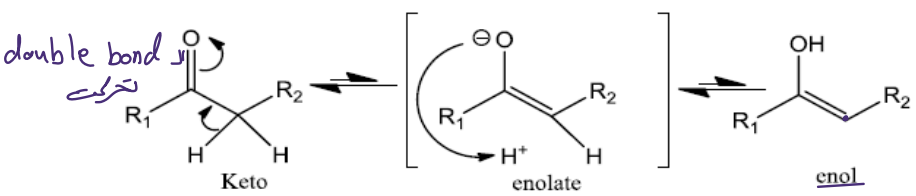
(2) Gets conjugated on one of the hydroxyls with glucuronic acid and eliminated.

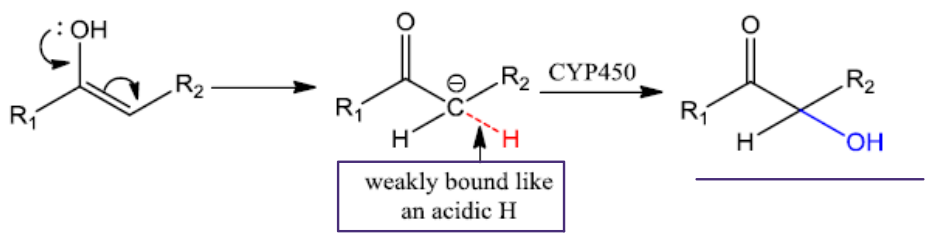
(3) Eliminated in the urine as the oxidized form (glycol).



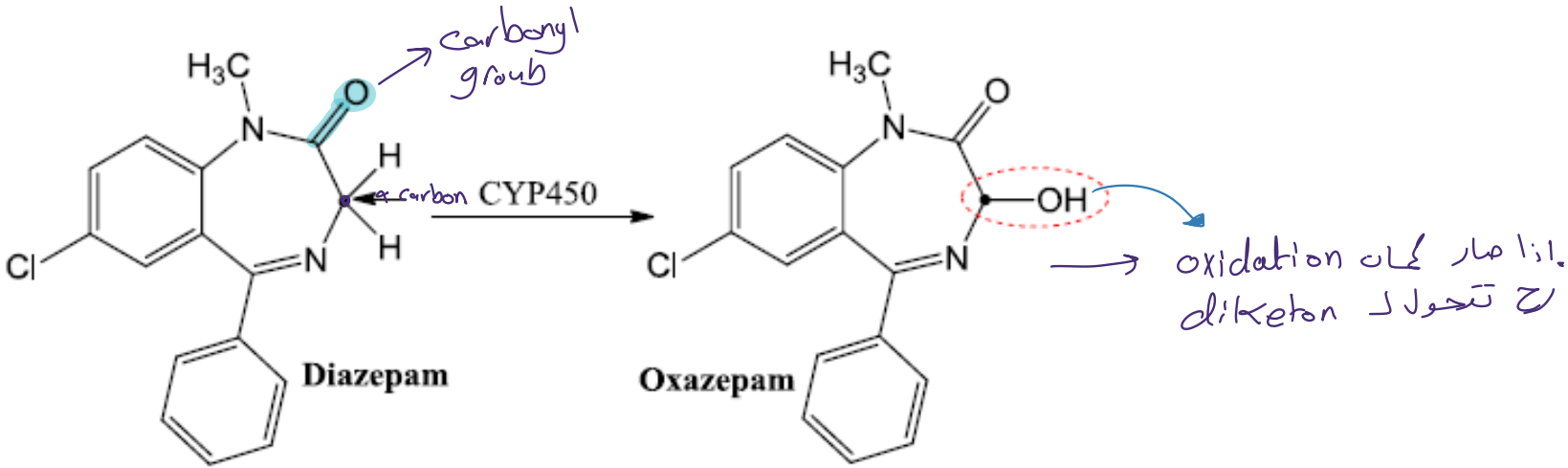
Oxidation to α carbon to carbonyl

- Aldehyde, Ketone, Ester, Enole, Carboxylic acid, Thioester
- Carbonyl is electron withdrawing group → α 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.





Example

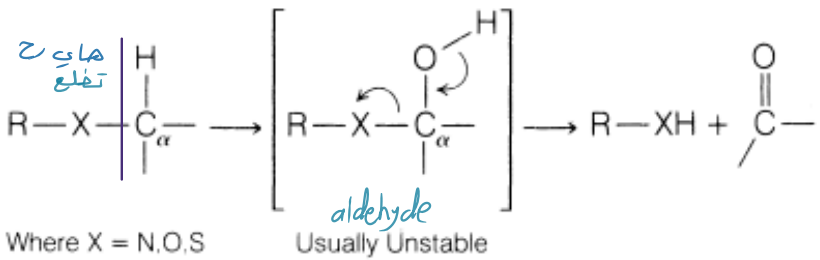


Aromatic ring oxidation is very minor because it's slower. The oxidation of the alpha carbon is much faster and more likely to happen.

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:

1. 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 α-carbon is likely to get oxidized and is easier to be oxidized than the nitrogen

Oxi ative deamination reactions fall under this mechanistic pathway.

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

- oxidation involve Hetero atom الـ

تبكون C جنب Heteroatom (O, S, N)

لما يكون فيه S, N رح يكون في 2Pathway الاول بكون oxidation

(oxidation الما بصير الها O ما عدا الـ Hetero atom نفسها (ما oxidation لا يصير الثاني انه يصير α carbon لا

اذا صار oxidation لـ α carbon رح يصير كمان dealKylation يعني الـ bond اللي بينه

الـ Hetero atom و الـ α carbon رح تنفصل . اذا طلعت C وحدة بشو الـ (metabolit

رح تطلع 2C واذا طلعوا formic acid لـ رح تتحول لـ formaldehyd

رح تطلع 3C واذا طلعوا acetic acid لـ بتحول لـ Acetyl aldehyd

Propandic acid

N- systems

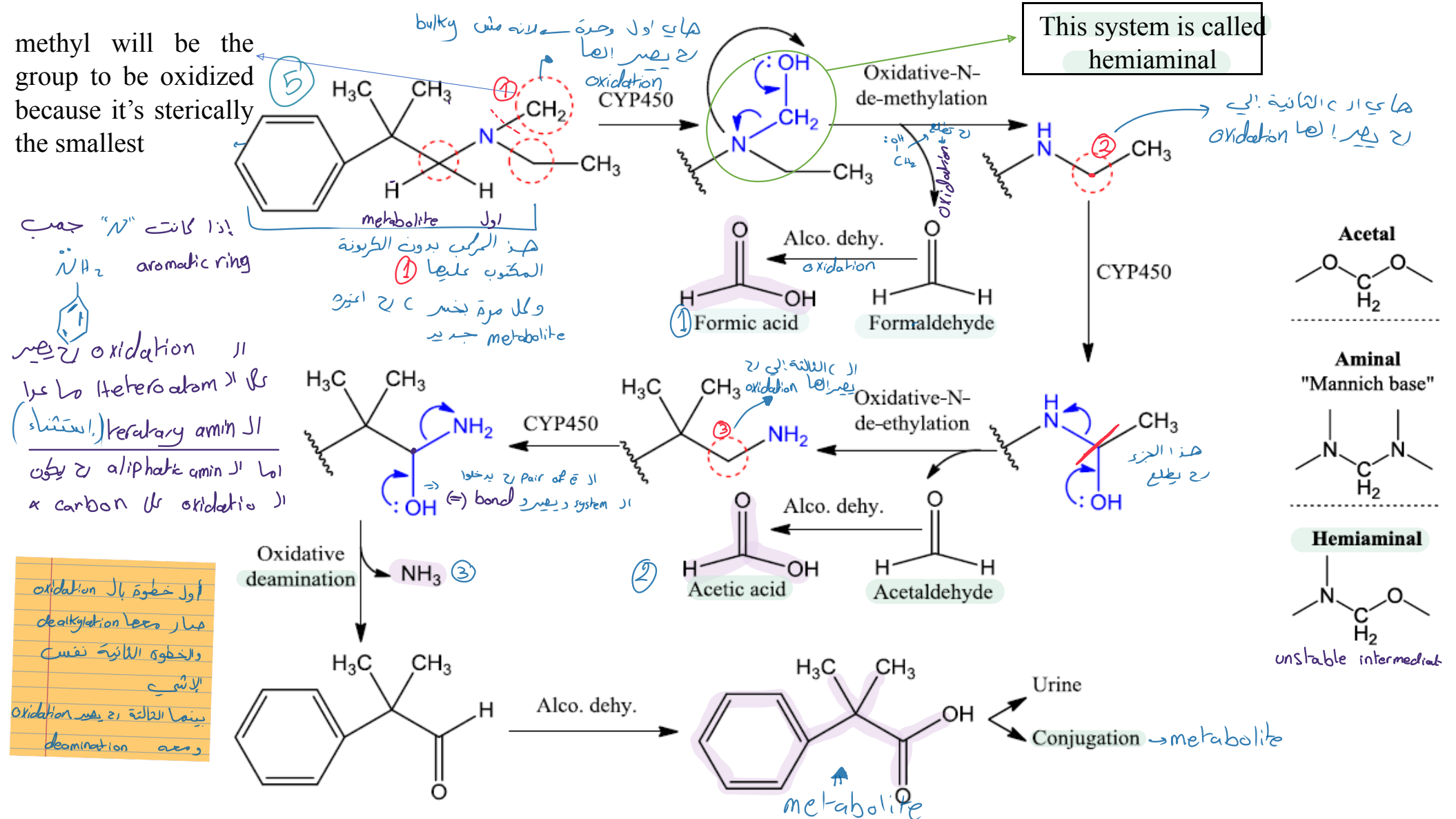
Amines are ***ionizable*** groups with a pKa= 9.5. The plasma's pHa= 7.5 so amines are ionized in physiological conditions. عشان لما pKa > pH بيصير ionization

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**.

methyl will be the group to be oxidized because it's sterically the smallest



amino group المركبات التي تحتوي ionize بالعادة تكون

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

معظم الدوا اي كيه له يكون ionize و 80% مارح يصير metabolism اما الي يصير له 20% رح يكون العم metabolite زي الي ذكرناه بالسلايد السابق

1) • Ionized drug unchanged (mostly)
2) • - Conjugated drug (to a lesser extent) كميه صغيرة
   • To a much lesser extent:
3) • Ionized secondary and primary amines and their conjugates
4) • Ammonia
5) • Carboxylic acids (formic acid, acetic acid and the final carboxylic acid product of the last reaction)

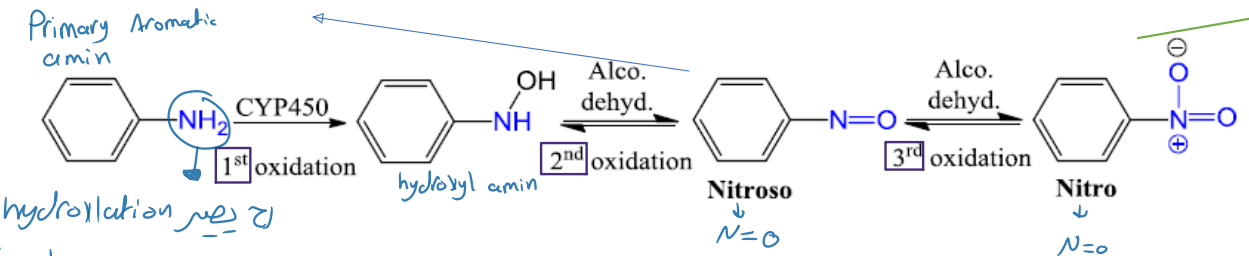
ضروري نخفظ شو رح يكون موجود بال urin ضروري جداً جداً

مارح الشوفهم بال urin
- **NO** aldehyde (unstable)
- **NO** hemi-aminal (unstable)

ال ionize form رح يظهع بال urin زي ما هو

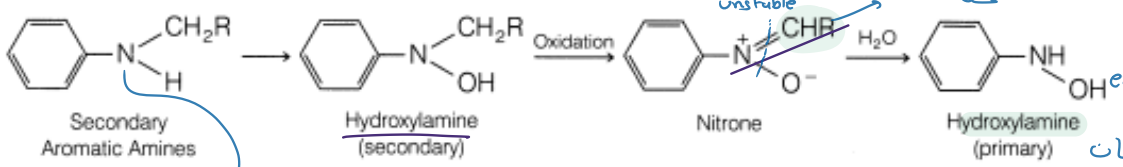
بدون metabolism

N-oxidation



hydroxylation يصير
لوجود H ويرتبط مكانها OH

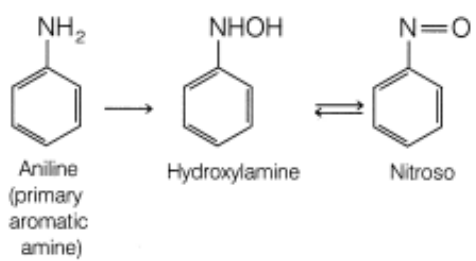
نفس الشي بال
secondary Aromatic Amin



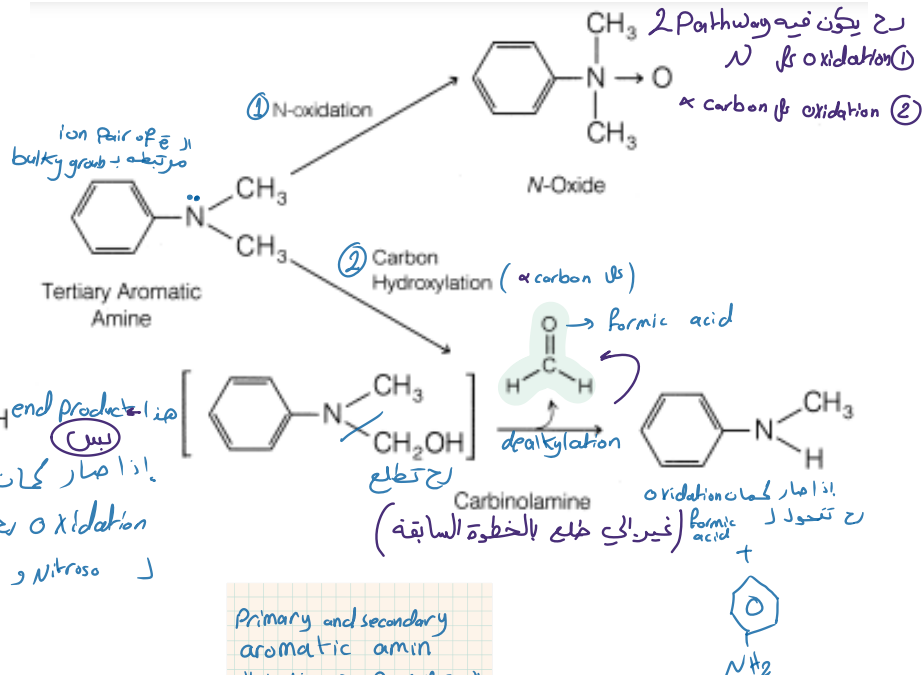
هاي الـ bond unstable
هاي ح تفك عنه

هذا end product
بس
اذا صار كمان oxidation ح يتحول لـ Nitro و Nitroso

هاي الـ ح يصير الها Hydroxylation



tertiary aromatic amin بال
ح يكون فيه 2 Pathway
N ال oxidation ①
α carbon ال oxidation ②

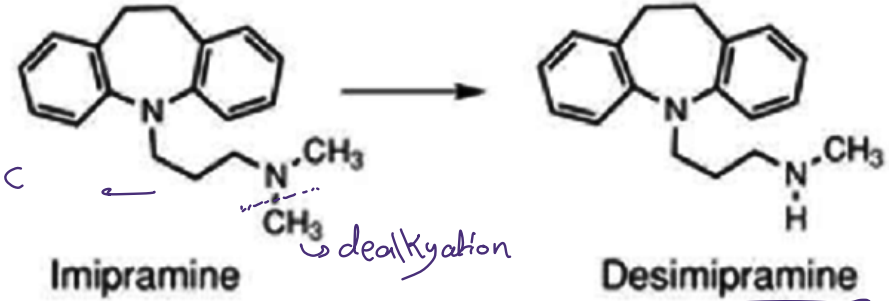


ح تطلع (غير اللي طلع بالخطوة السابقة)

ح تتحول لـ

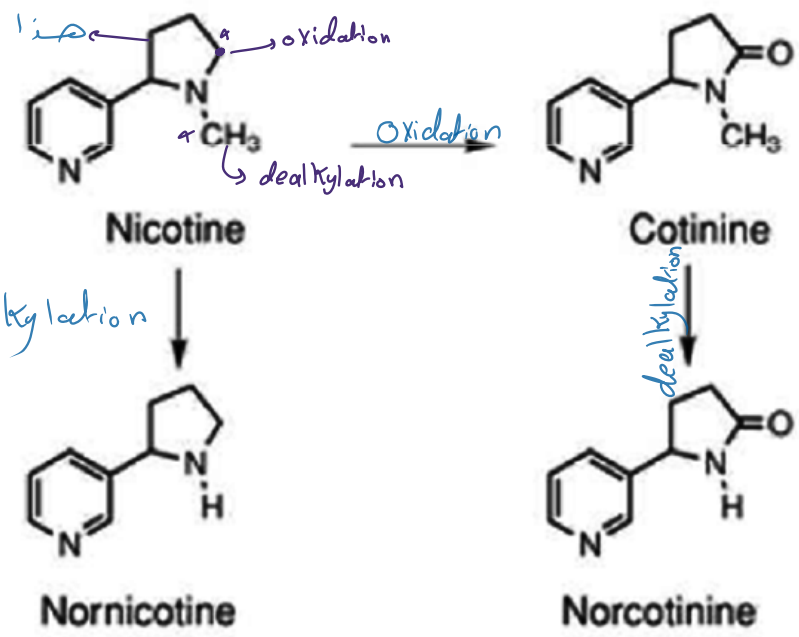
Primary and secondary aromatic amin
ال Pair of ē ح يدخلوا ال Conjugated
بس بال teritary لانه التركيب ح يصير bulky مارح يعدي يدخلوا ال conjugated

Example



aromatic ring ممكن cycle ايضا

aliphatic amin يعتبر

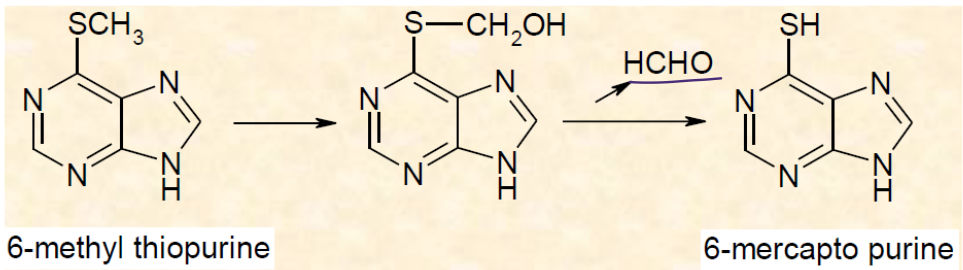


ممكن يكون في اكثر من site لـ metabolism بس اسرع metabolism هو الي يعتبر Major

S-Oxidation

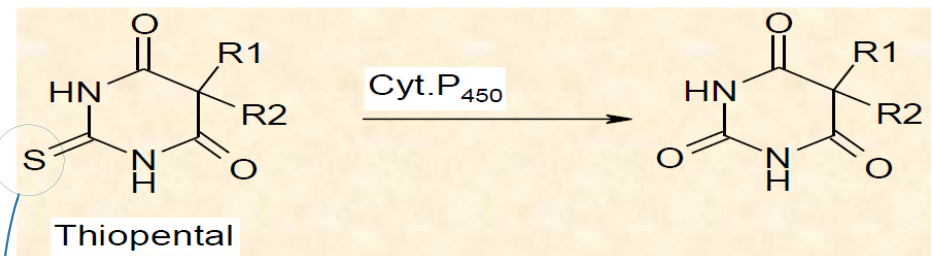
1) S-dealkylation:

S + alkyl → dealkylation



6-methyl thiopurine — 6-mercapto purine

2) Desulphuration:

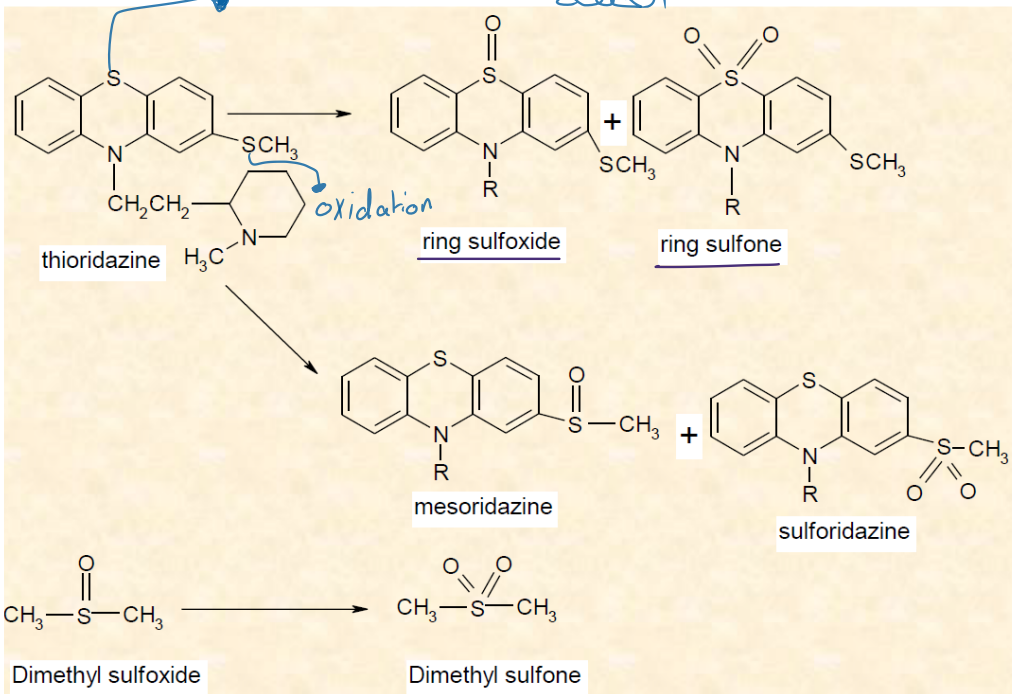


Thiopental

ح استبدل الاكسجين بـ

3) S-oxidation:

ح يصير الـ oxidation جوا الحلقه

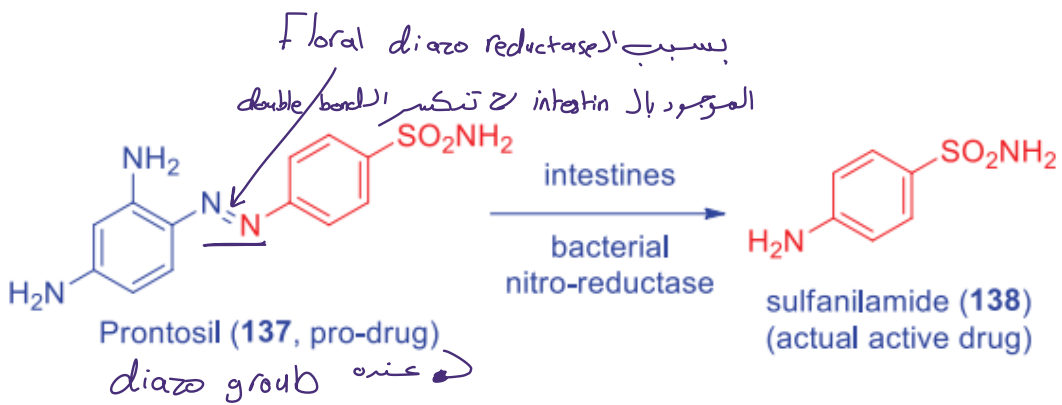


thioridazine — ring sulfoxide — ring sulfone

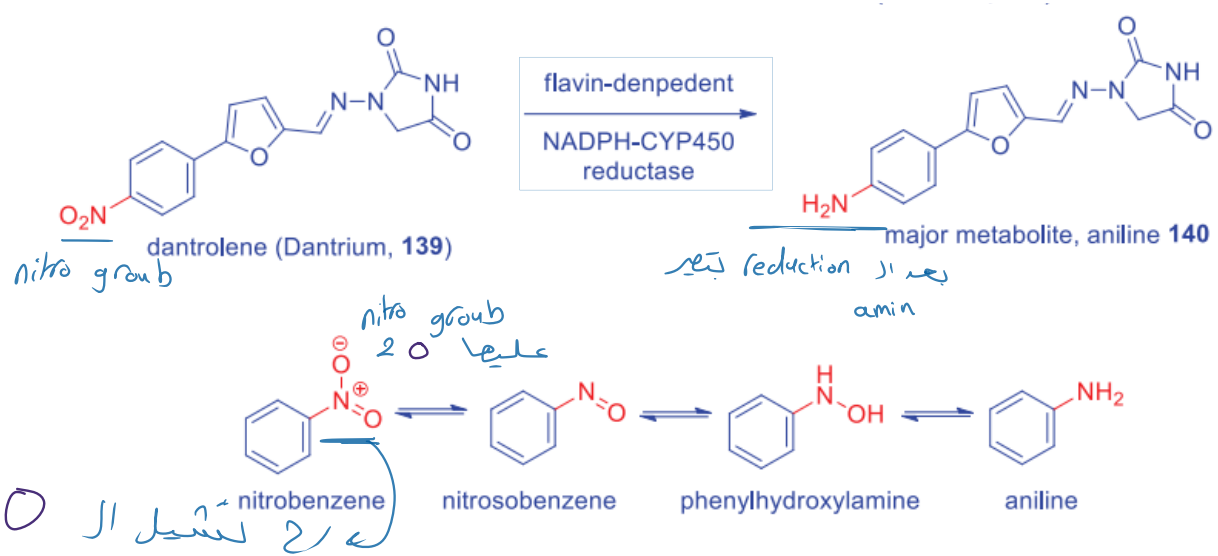
mesoridazine — sulforidazine

Dimethyl sulfoxide — Dimethyl sulfone

REDUCTION

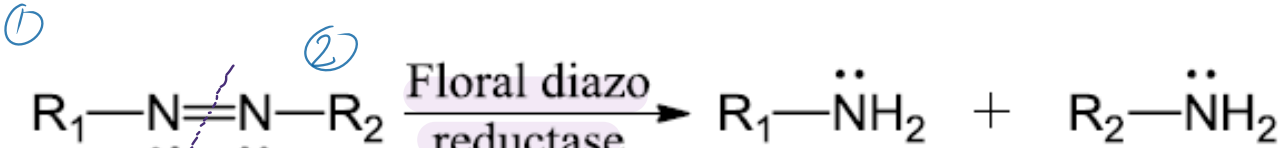


- Reduction is the reverse of oxidation and involves CYP450 enzymes working in the opposite direction.



Example on reduction reactions

- An enzyme called “ floral diazo reductase “, is involved in the metabolism of Diazo compounds , actually it’s the major one.
- floral diazo reductase enzymes are present in the large intestine

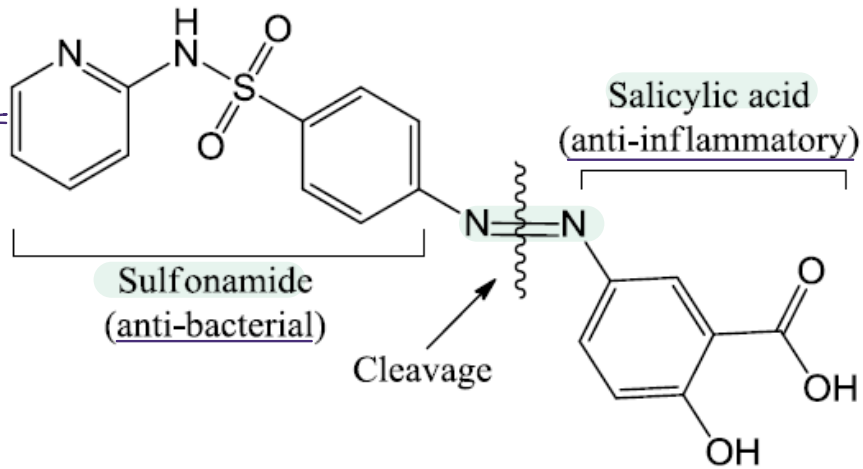


Sulfasalazine

- The presence of the floral Diazo reductase enable us to build prodrug to treat a disease called Crohn's disease (autoimmune disease leads to colon ulcers , these ulcers make the colon prone to infectious agents like bacteria) , our drug which is actually a prodrug is **Sulfasalazine**
- Normal flora will reduce sulfasalazine (prodrug) by "floral Diazo reductase ", the reduction will cleave our drug in the line position. (At the Diazo group, where the reductase enzyme acts)

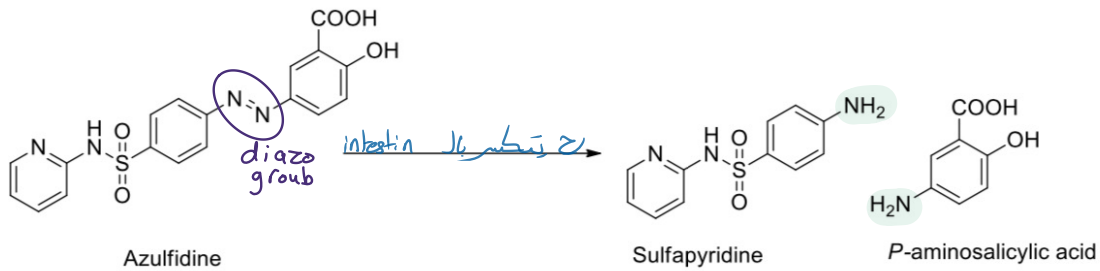
Sulfasalazine is not absorbable, so it acts locally
at the large intestine .and it is a prodrug that has to be activated in vivo,

GI inflamation ⇐ إلي ح يعالج اذ



Azo and Nitro Reduction

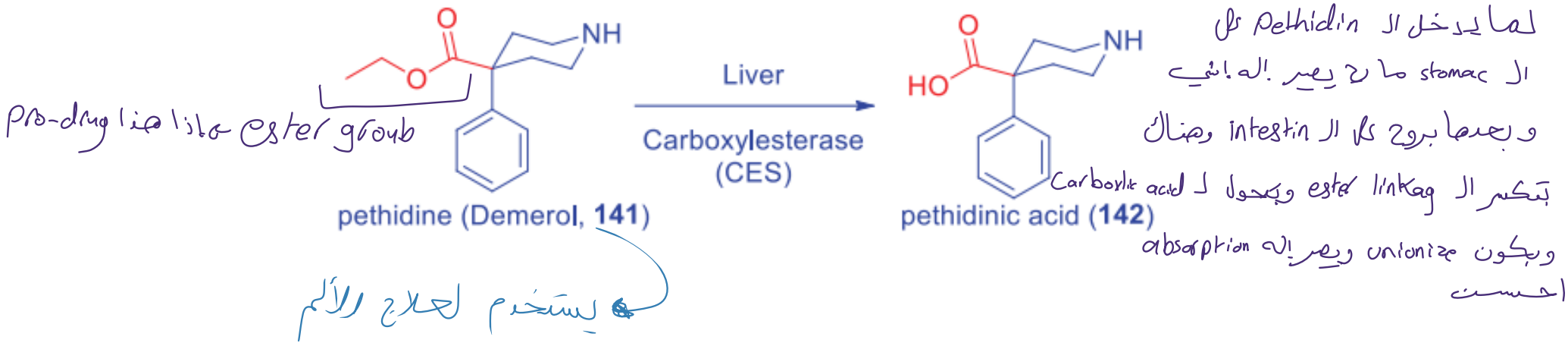
- A number of azo compounds, such as Prontosil and sulfasalazine, are converted to aromatic primary amines by azoreductase



ليش بعطي الدوا pro-drug عشان ما يتكسر

HYDROLYSIS

- 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.



pro-drug هذا لما يكون ester group

pethidine (Demerol, **141**)

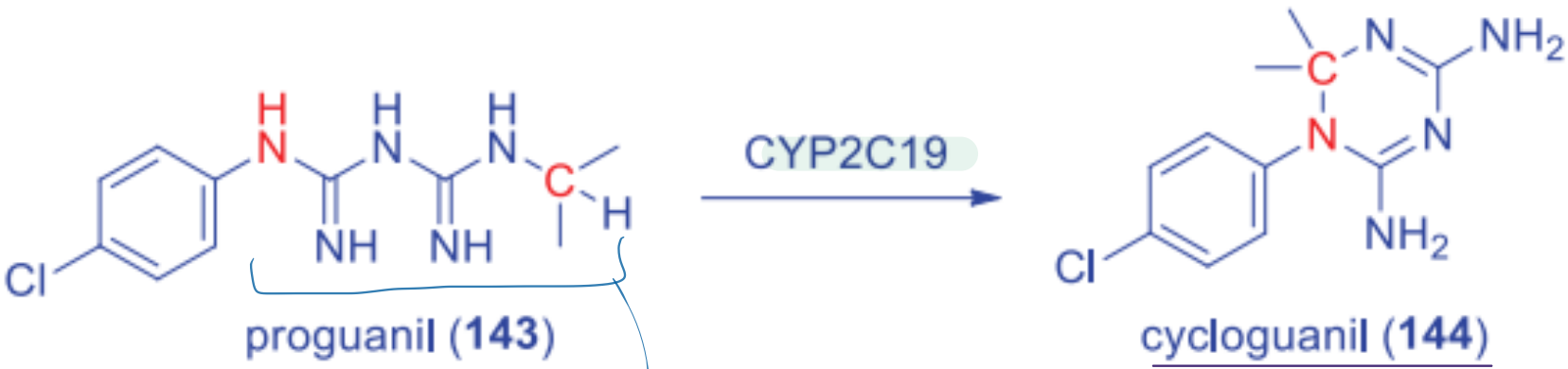
يستخدم لعلاج الألم

pethidinic acid (**142**)

لما يدخل ال Pethidin في ال stomac ما رح يصير له اشي وبعدها بروح على ال intestin وهناك بتكسر ال ester linkag ويتحول لـ Carboxlic acid ويكون unionize ويصير له absorption احسن

CYCLIZATION

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

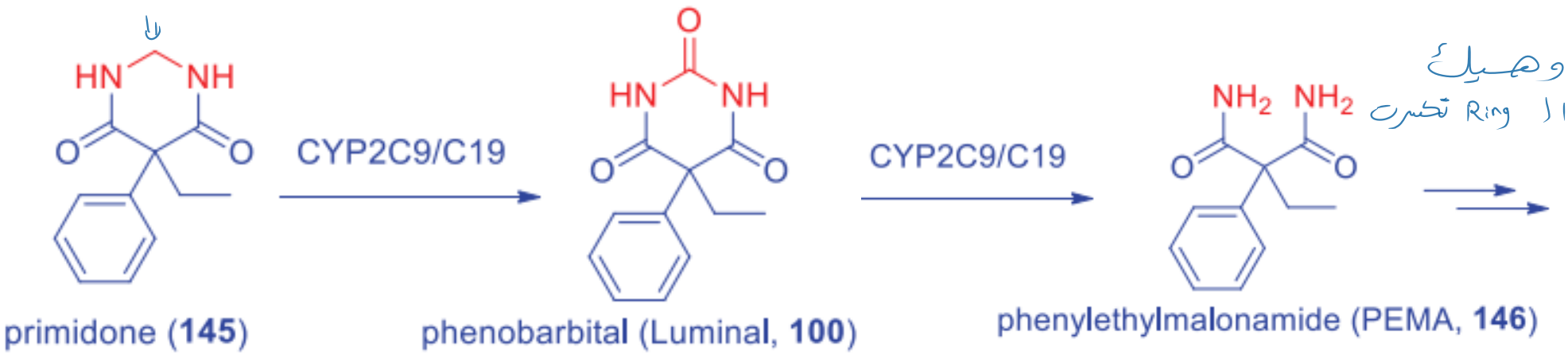


aliphatic part هذا
راح يتحول ل cycle

DECYCLIZATION → يعني cycle راح تتكسر

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

oxidation' يصير راح

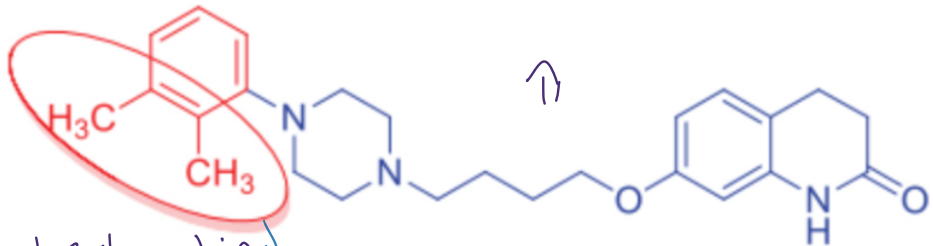


primidone (**145**) phenobarbital (Luminal, **100**) phenylethylmalonamide (PEMA, **146**)

- 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;
- (ii) Blocking a site of hydroxylation by replacing the hydrogen(s) with fluorine(s);
- (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.

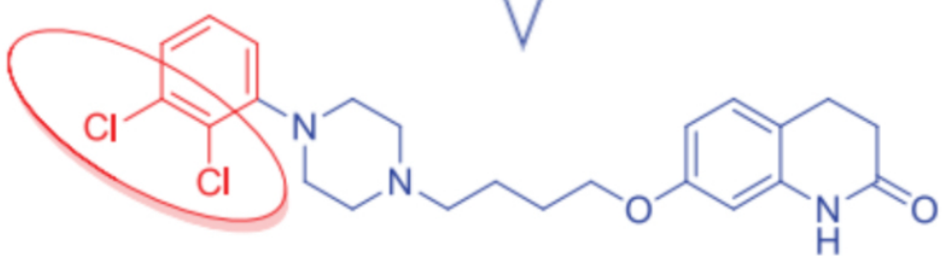
بصير إله metabolism لحتى



benzyl carbon هنول
ح يصير الهم hydroxlation
فحشان اتجنب الـ metabolism
بغيرهم لـ Cl وهيك ما رح يصير
تقل ح metabolism والـ hydroxlation

OPC-4392 (**151**), ED_{50} = 41 μmol/kg, p.o.

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



aripiprazole (Abilify, **152**), ED_{50} = 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_{50} of 0.6 mmol/kg, p.o.
It was approved by the FDA in 2002 as an effective and unique antipsychotic.

وهيك بتكون خلصنا Metabolism phase I بنزل Metabolism phase II نزلته دكتورة

اسماء صسجل لل التيمز . اعذروني إذا كان في اي اخطاء إملائية

اعتذر عن تفريغ Metabolism phase II لضيق الوقت .