



تفريغ ميديسينال

محاضرة: Lec 3 Part 1

الصيدلانية: Raha f Zyoud



لجان الرفعات



ADME
Drug Metabolism

لنوع يصير بالدوا بال metabolism؟

1- الدوا رح يتحول لـ More Polar (more hydrophilic) ليطلع من الجسم

لانه معروف انه الأدوية الـ lipophilic بتفضل فترة طويلة بالجسم، بتفضل بتف بال blood

لـ other organ، يعني الـ toxicity إليها عالية

الدوا الي يكون oral bioavailable يصير الـ First Pass metabolism يعني انه الدوا بتحول لـ

metabolite ممكن تكون active وممكن تكون inactive حسب تأثير الـ metabolism عليها

* الـ IV والـ IM ما يصير الهم الـ First Pass metabolism

Main organ in Metabolism: Liver

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). → excreted in urin
- 2- Retain a certain level of activity.
- 3- Be more active than the parent drug (BIOACTIVATION: PRODRUGS)
From inactive to active →

كيف رح تكون ال metabolism

degradation ①

add different functional group ②

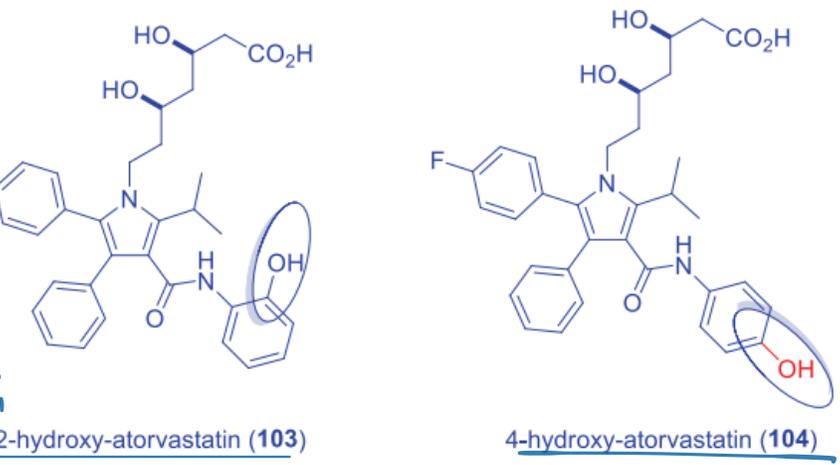
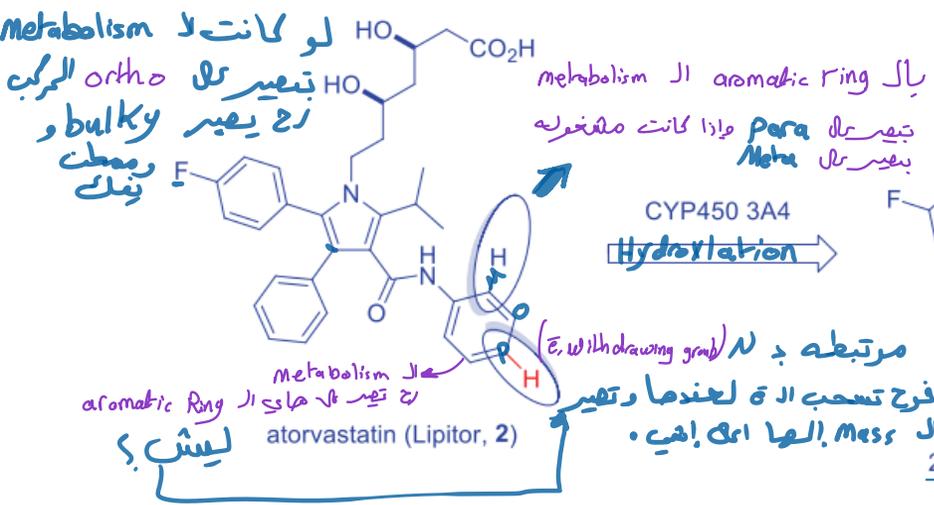
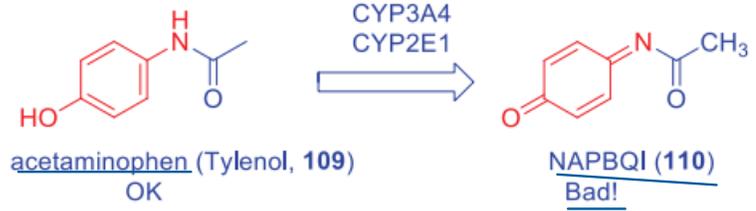
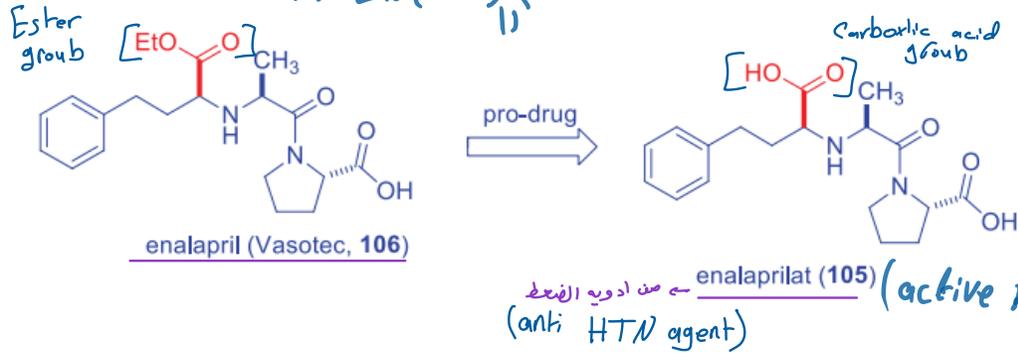
- Aside from water and most hydrophilic drugs, all other molecules/drugs are metabolized. This is actually essential because lipophilic drugs would circulate in the body for a long time, causing untoward side effects if not eliminated in due course. In most cases, metabolism converts lipophilic compounds 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.

له زجه الدوية السكرية

Examples

Polar group ← lipophilic drug
 Metabolism ← احييت له ال
 Excretion ← ليس!

activation
 in Live
 بصير له



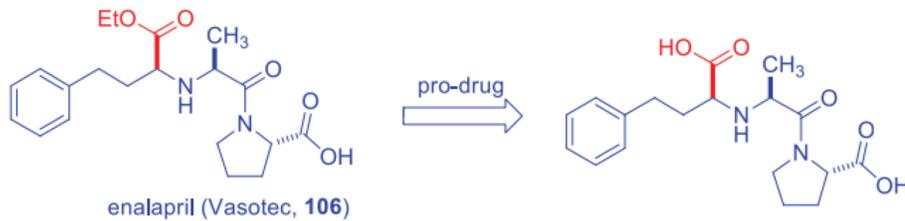
ليش في ادوية pro-drug؟؟

① ممكن تتكسر الدواء لما يدخل الجسم

② او ال absorption لها بالمعدة قليلة عشان هيكلها يعطوها بار Ester form فلما توصل

ال Liver ح تتكسر وتصبح Carboxylic acid وزيت ما يتعرف انه ال Carboxylic acid

ال absorption له بالمعدة 50% وهيك حست ان absorption



المركبات ال hydrophilic و ال water ما يصير لهم metabolism بال Liver بعد ال lipophilic عا يري ح يصير لهم metabolism (شرحنا فوق ايشو السبب)

ليس بتكفي انه في اما كن مختلفه بهير فيها ال metabolism ؟

لانه المسؤول عن ال Metabolism مجموعة من ال isoenzym ال يكونوا موجودين بالكثر

من مكان مش بس بال Liver . فمكن بهير Metabolism بالكثر من مكان زي

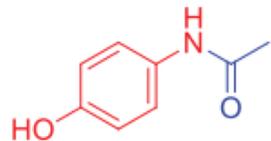
ال kidney وال intestine وال Lung ... etc .

Excretion *
من ال Liver

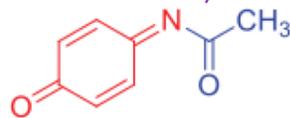
استو oxidation ال Hydroxyl group

↑

CYP3A4
CYP2E1



acetaminophen (Tylenol, 109)
OK



NAPBQI (110)
Bad!

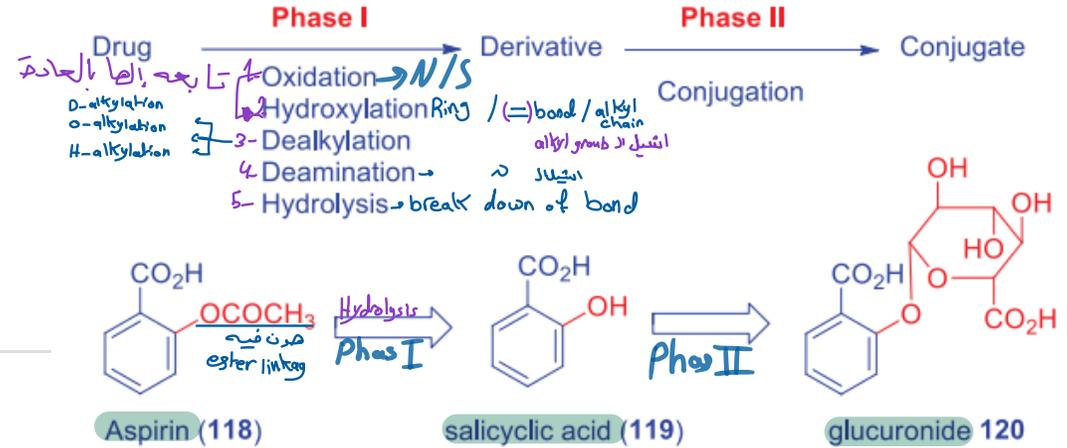
Hepatotoxic (عشان هيلع الجورة لازم تكون عليه)

النتيجه عندها مشاكل بال kidney اولي

بناخذ ادوية ال HTN أو ادوية السرطانيه (Metabolism in kidney) بتعطير ليحافظ ال kidney function

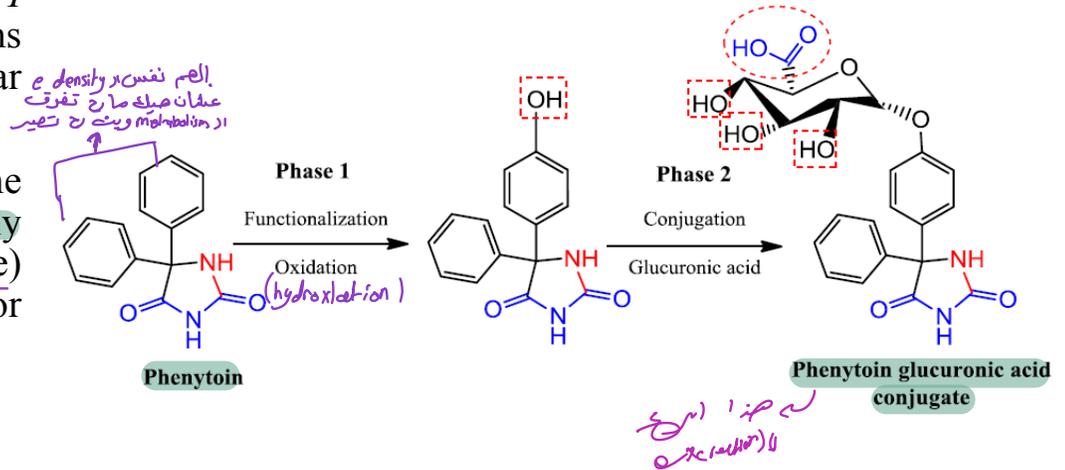
Phase II :- ربط المركب بـ sugar sulfate

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.

ليسه في الدم ليخرج من الكلى excretion



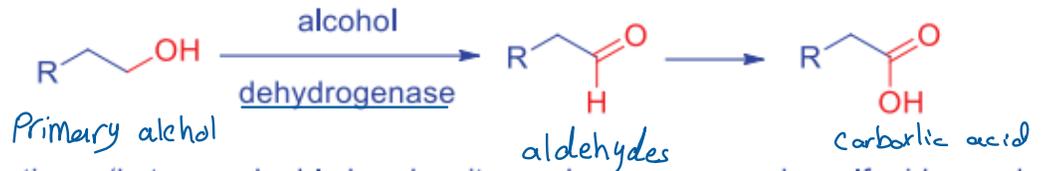
Phase I metabolism

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

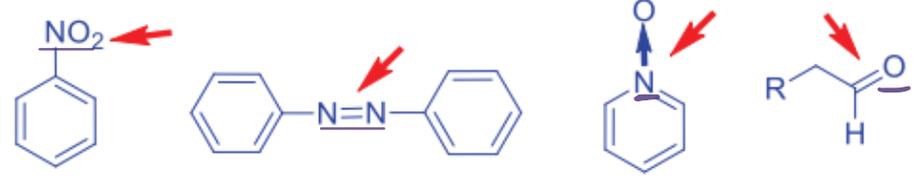
- ① aromatic Ring
- ② double bond / triple bond
- ③ Nitrogen / sulfur
- ④ Alkyl group

Keton
 ١:١ كات secondary alcohol
 و بعد بيك Carboxylic acid

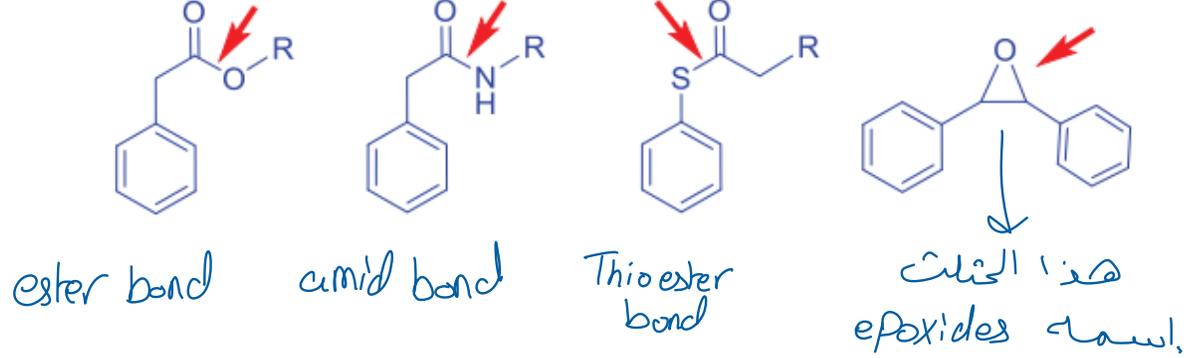
Oxidation (alcohols and aldehydes)



Reductions: (ketones, double bonds, nitro and azo compounds, sulfoxides and N-oxides, disulfides, quinone, dehalogenation)



Hydrolytic reactions (esters, amides, thioesters, epoxides, and peptides)



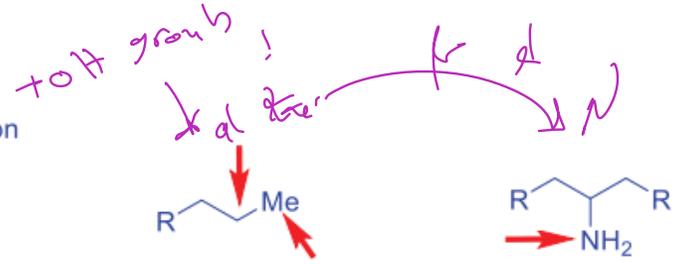
OXIDATION

أكثر واحد مهم وأكثر واحد يسهل

- 1- aromatic Ring → Hydroxyl group يرتبط
- 2- alkyl chain →
- 3- amid group →

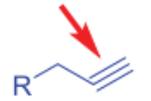
- Oxidation is the most important drug-metabolizing reaction.
- Phase I metabolism is largely an oxidative process.
- Various oxidative metabolisms are hydroxylation, oxygenation at carbon, nitrogen, or sulfur atoms; N-dealkylation or O-dealkylation, oxidative deamination, etc.
- Hydroxylation is a prevalent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

Hydroxylation

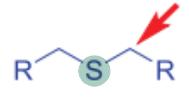
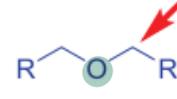
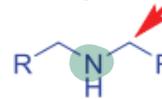


oxidation → Epoxidation (unstable)

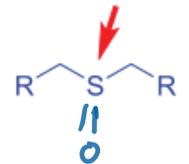
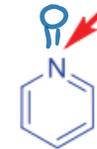
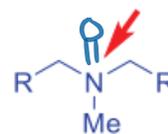
- double bond
- triple bond



Dealkylation

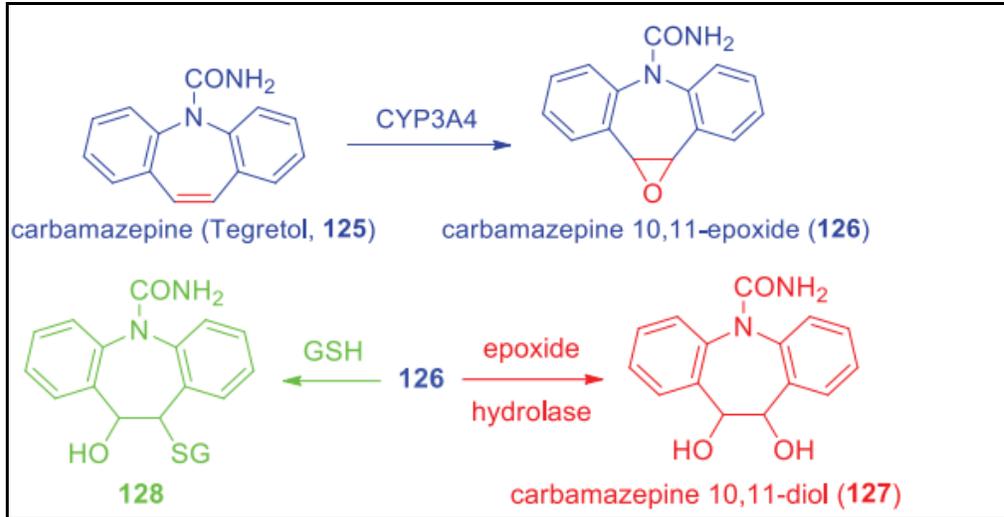
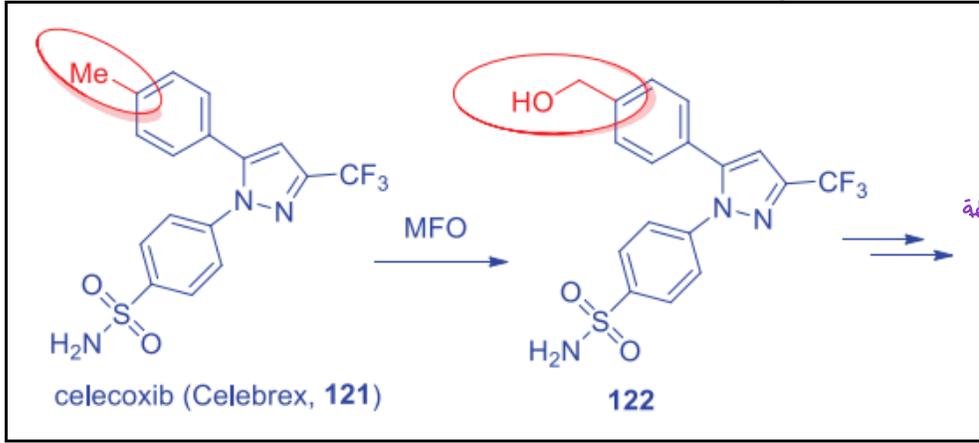


N- or S-oxidation

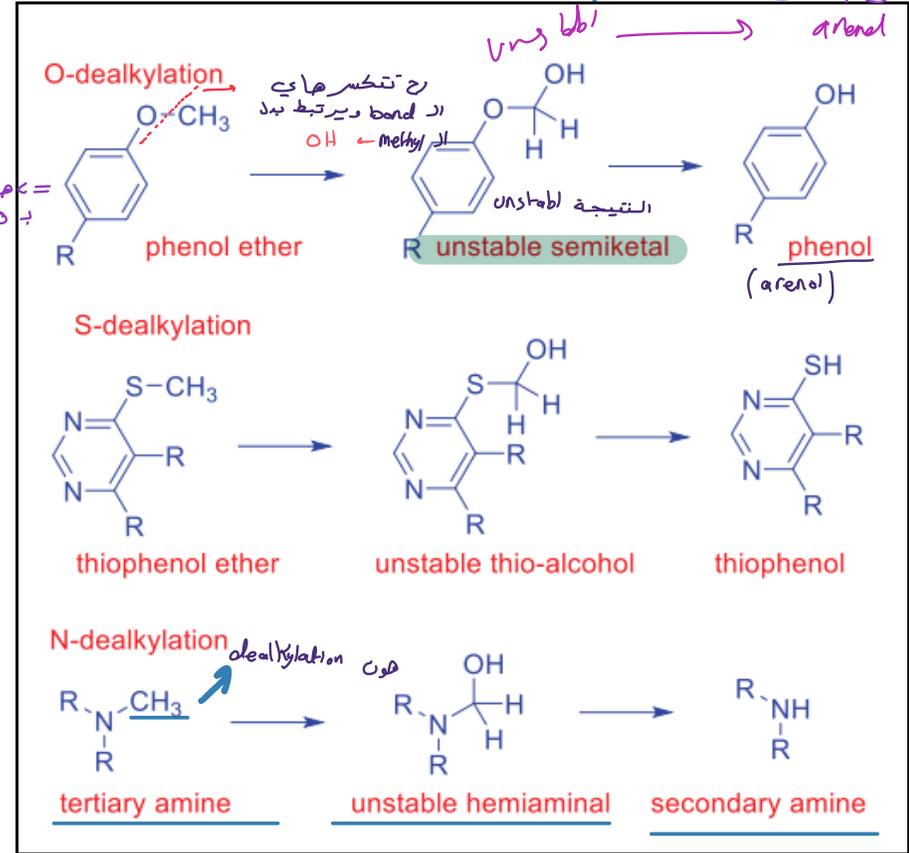


(unstable - تفسر بسرعة)
2 hydroxyl groups

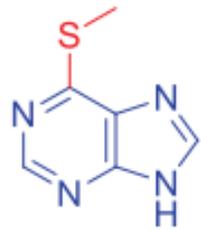
EXAMPLES



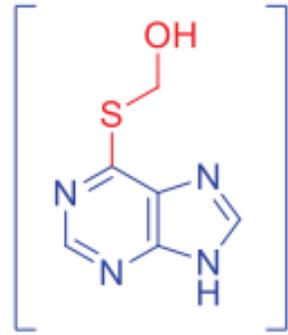
لما بدنا نحل dealkylation لما يكون ال alkyl group مرتبط مع S/N/O



سلفر وعلیه methyl اتنا ح
یہ "metabolism علیہ"



CYP450
dealkylation

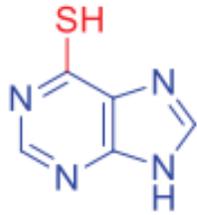


⇒ هذا المركب برفه
unstable

6-methylthiopurine (134)

135

spontaneous

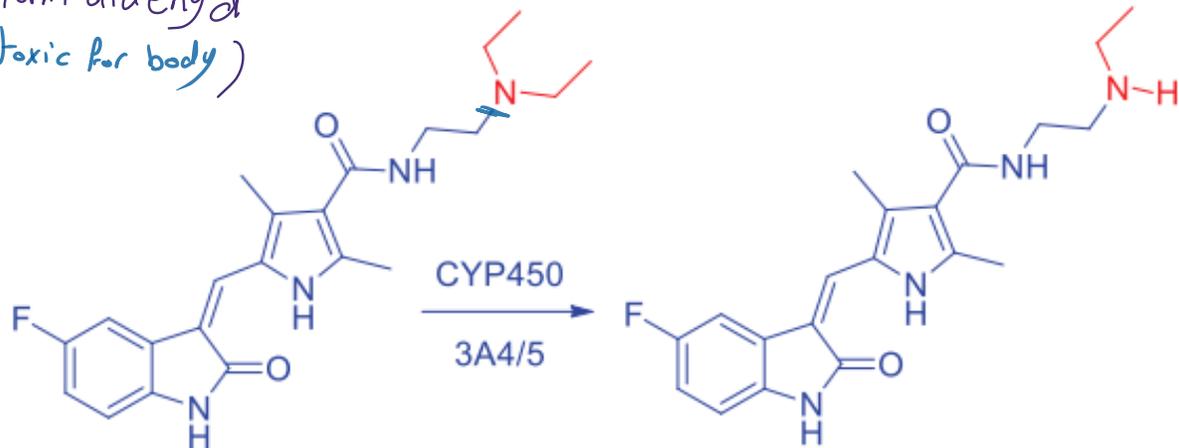


+ HCHO

form aldehyd
(toxic for body)

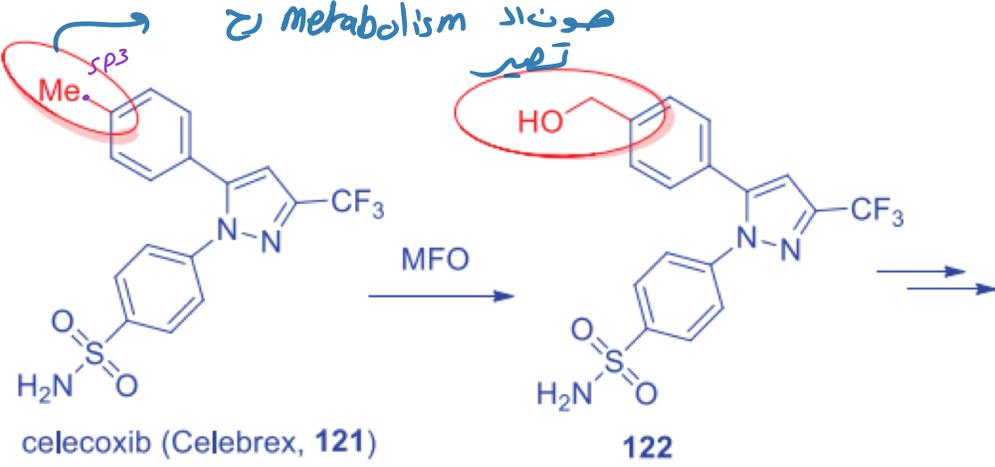
6-mercaptopyrimidine (136)

صون الا له علیہ 2 alkyl groups
وحده منهم ح یسر الہا dealkylation یسر
بدالها H



sunitinib (Sutent, 132)

SU-12662 (133)



في اشي اسمه benzylic reaction

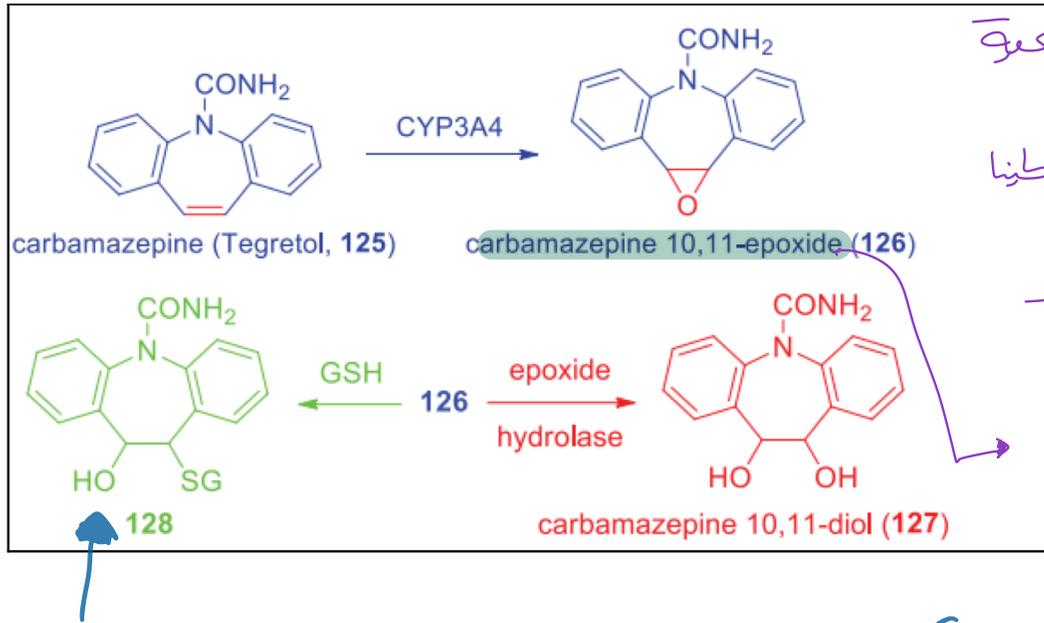
بعض يكون في حلقة بنزين عليها كربون (Me)

ويتاح تهر ال Metabolism اكيه بل هاتي

اد ح ح يهر لها hydroxlation بحيث حده من اد H الموجوده عليها

ح يهر لها oxidation وح تهر OH وهاتي OH ح يهر لها oxidation

كان صوره وح تحول ل aldehyd ويحديت Carboxylic acid



ال Metabolism رح تكون لكي الحلقة السباعية

إذا ما ريفيت فيها **double bond** إذا بتندكر حطينا

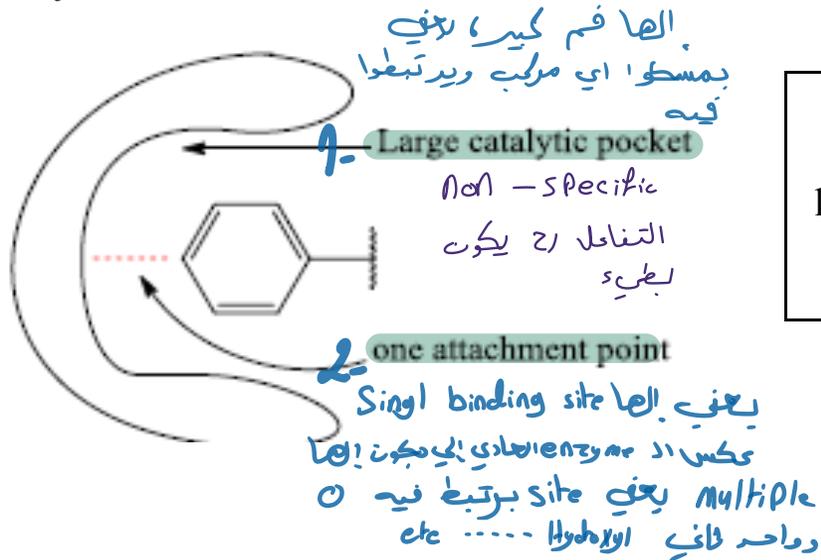
لوقت عن أكثر تفاعل يحدث لـ **double bond** الي هو اـ

epoxidation ونوعه ما حطينا ال **epoxid** يكون **unstable**

مع **acidic condition** بال liver رح تتكسر ال **Ring** وح

① تتحول لـ **alcohol** وجود انزيم ال **epoxide hydrolase** ② يرتبط فيها **hydroxyl** مع وحدة من ال **glucathal**

- 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

- Other metabolic enzymes involved in Oxidative reactions :
- **flavin-containing Monooxygenases**
- **Monoamine Oxidases**
- Alcohol Dehydrogenases
- Aldehyde Dehydrogenases
- Xanthine Oxidase

رنگی موجودیت ہاں
Cell membran

الہ Pigment

Cytochrome P450 (CYP450) Enzymes

- 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**.
- 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.
- 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**.
- CYP 3A4 carries out biotransformations of the largest number (~50%) of drugs.
- 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.
- **Inhibitors of CYP450 3A4:** erythromycin, clarithromycin, verapamil, ketoconazole, itraconazole, diltiazem, and a constituent of grapefruit juice: responsible for unwanted interactions with many drugs.

50% من الأدوية بهيـر الهم
Metabolism عن طريقه

شئو یعنی Inhibitor of CYP 3A4

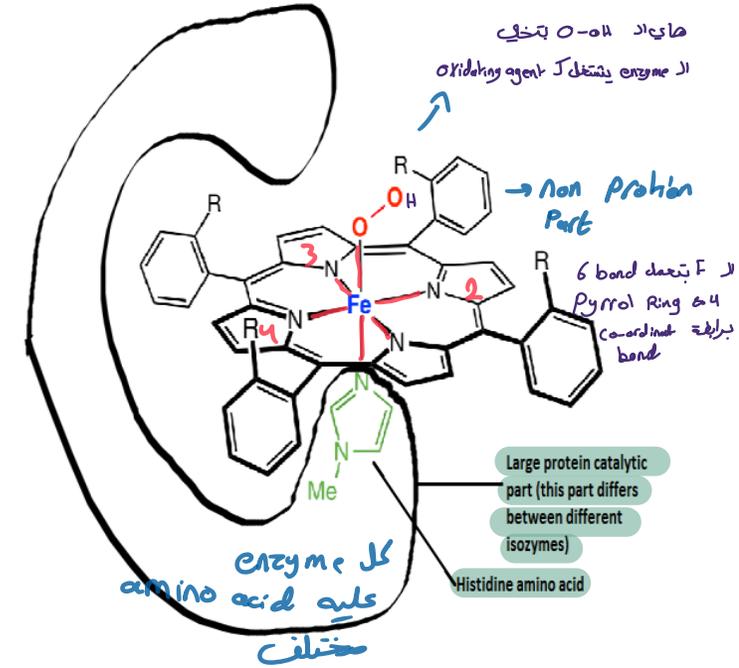
إذا باخنة دوا بعد inhibition لهزول ال enzyme ، برفقو باخنة دوا بهر الة
Metabolism عن طريق هزول ال enzyme ، بما انه مهمول الة inhibition ما رح بهر للدوا metabolism. اذا رح بهر

side-effect عشات هيك بتعتم بموضوع الة drug-drug Interaction لانه اذا هاي الة توتر كل هاي ال enzyme

الادوية الة تانيه اي باخنما ال activity الة رح تزيد و ال side-effect رح تزيد

پروتین ساختار ب بتكون مرتبطة ب
non-Protein structure

- 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**;
 - **The Iron is in the ferric state (Fe+3).**
- A similar molecule that contains a heme group is hemoglobin but the Iron in hemoglobin is a ferrous iron (Fe²⁺).



ان Fe ترتبط مع ال Pyrrd بئسگی Planner
وہج ال O-H و ال O-H بئسگی کا صوبے

- 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 (O₂)**. This oxygen is very

