Revised Third Edition

Medicinal Chemistry

Alaa malkawi

Phase II reactions

- Reactions which conjugate the drug or its phase-I metabolite with a hydrophilic, endogenous species (conjugation reactions).
- These endogenous compounds are:

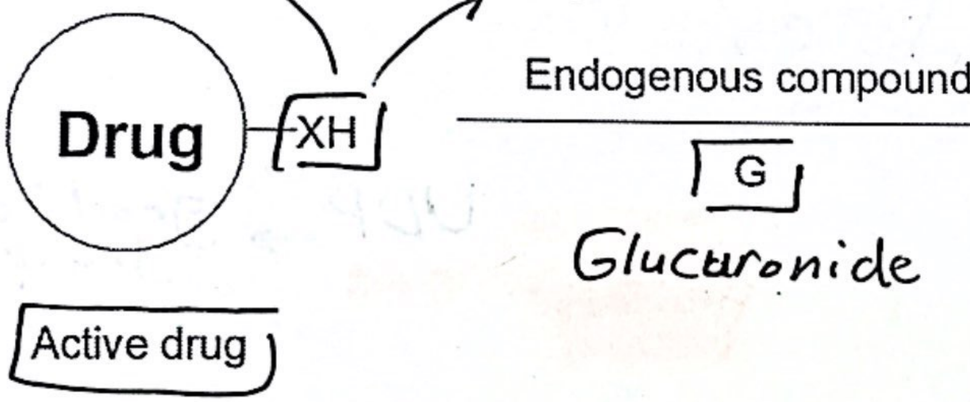
↳ المجموعات الي تحت هصه اصلاً موجودين بالجسم للتخلص من السموم

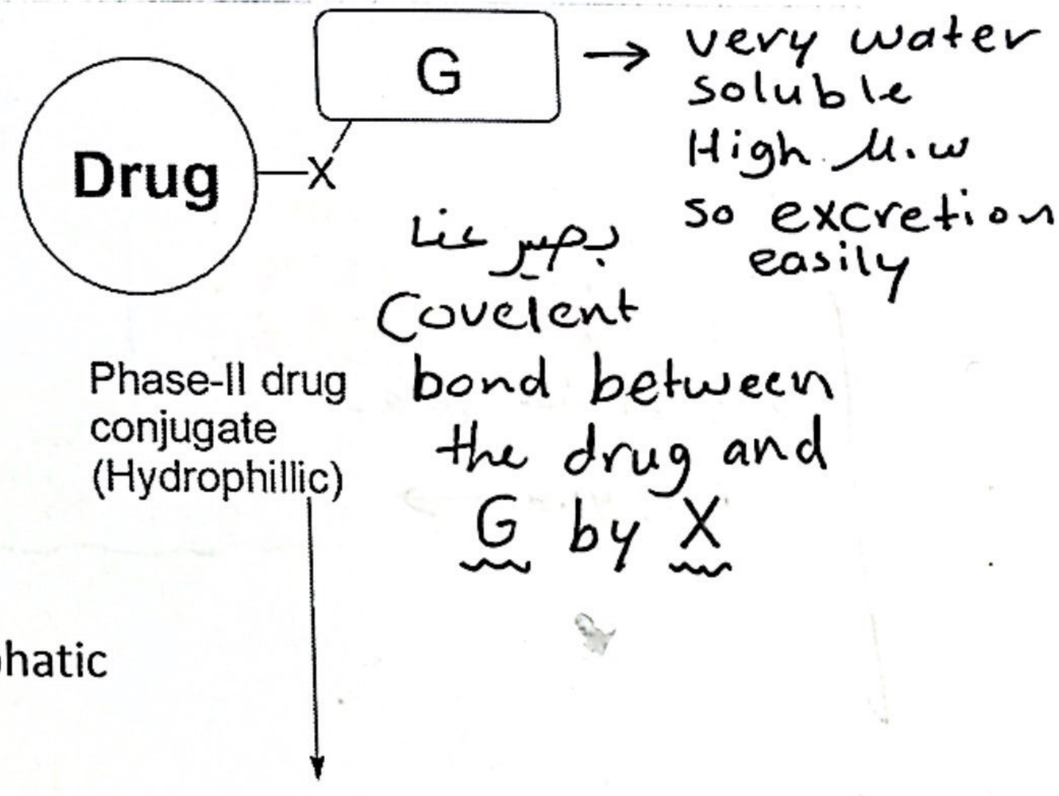
- Glucuronic acid → Glucuronide
- Sulfate group → sulfation
- Amino acid (Glycine) →
- Methyl group (as SAM) Methylation
- Acetyl group (as acetyl CoA) acetylation
- Glutathione (tripeptide)

Aim of Conjugation

functional group الي اتضافت من phase I ال

nucleophilic attack يتعمل على ال G





Hetero atoms like X = O, N, S have lone pair of electrons لـ حتى يقدر يعمل attack

Phenol, alcohol and carboxylic acid Amine (aliphatic and aromatic), Thiol

* بتضيف Highly water soluble drug ← to facilate excretion of the kidney

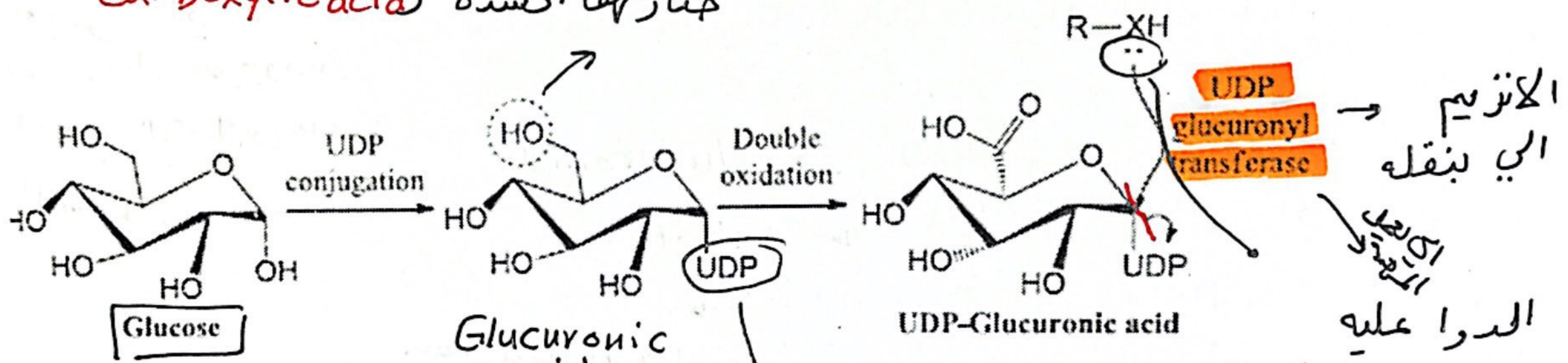
* لازم نعرف enzyme / active form

From Glucose to UDP glucronyl transferase

كيف بصنع الجسم The active glucoronic acid ؟

the active form of glucorinic acid → UDP glucronyl

carboxylic acid حبارلهما اكسده



الانزيم الي بنقله

الذرا عليه الكاربون الهيدروكسيل

2 pairs of unshared electrons

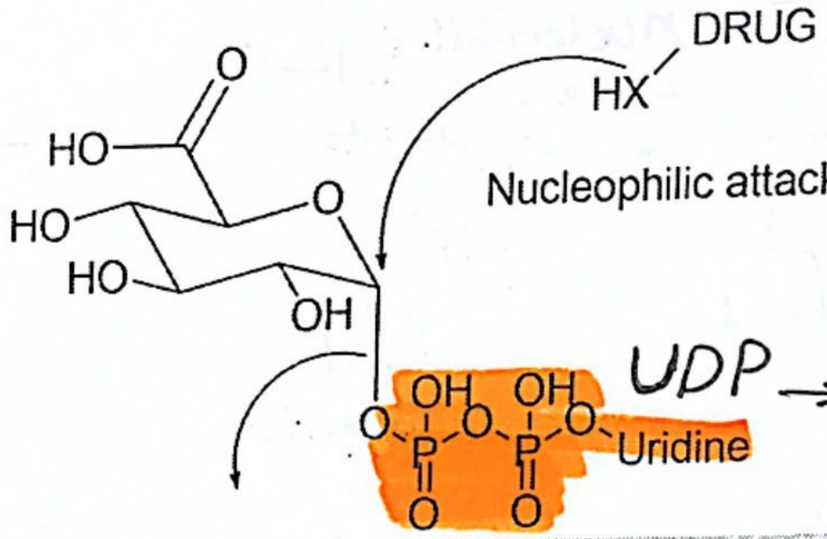
بيجي من Glucose ال

Glucurinic acid ال

الفرق بينه وبين ال Glucose وجود ال Uridine Diphosphate

لح يعمل nucleophilic attack من عند UDP وبتطلع صاي UDP as a good ← Leaving group

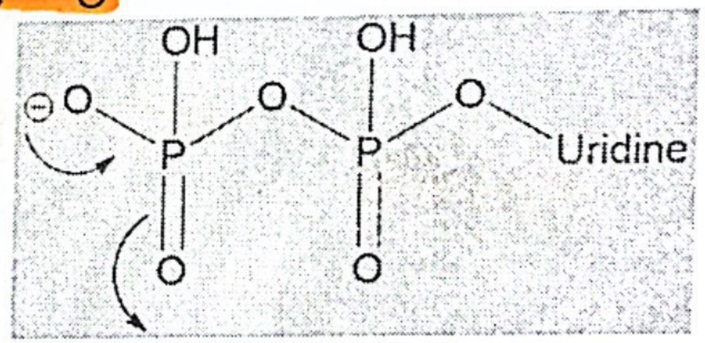
Mechanism of conjugation
Glucorodination reaction

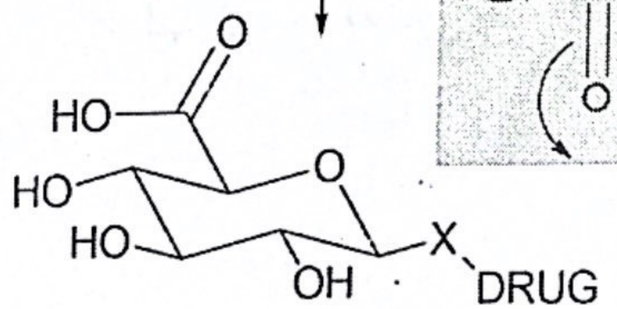


The deficiency of this enzyme in neonates causes Jaundice

العضار عند الصغار

enzyme → UDP-glucuronosyl transferase





Drug-Glucuronide conjugate

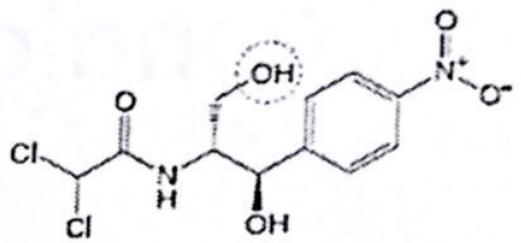
الطفل بينولد عنده نقص ببعض الانزيمات زي UDP-glucuronsyl transf هاد الانزيم موبس بخلينا نتخلص من السموم والادوية

السامة كمان من بعض العصاره الصفراء

اول ما ينولد بظهر العضار عليه لانه موقاعد يتخلص من العصاره الصفراء مع تعرض الطفل للفود ← enzyme الـ

UDP يتطلع وبهبس عنا Conjugation Between drug + C by X

Chloramphenicol



Chloramphenicol

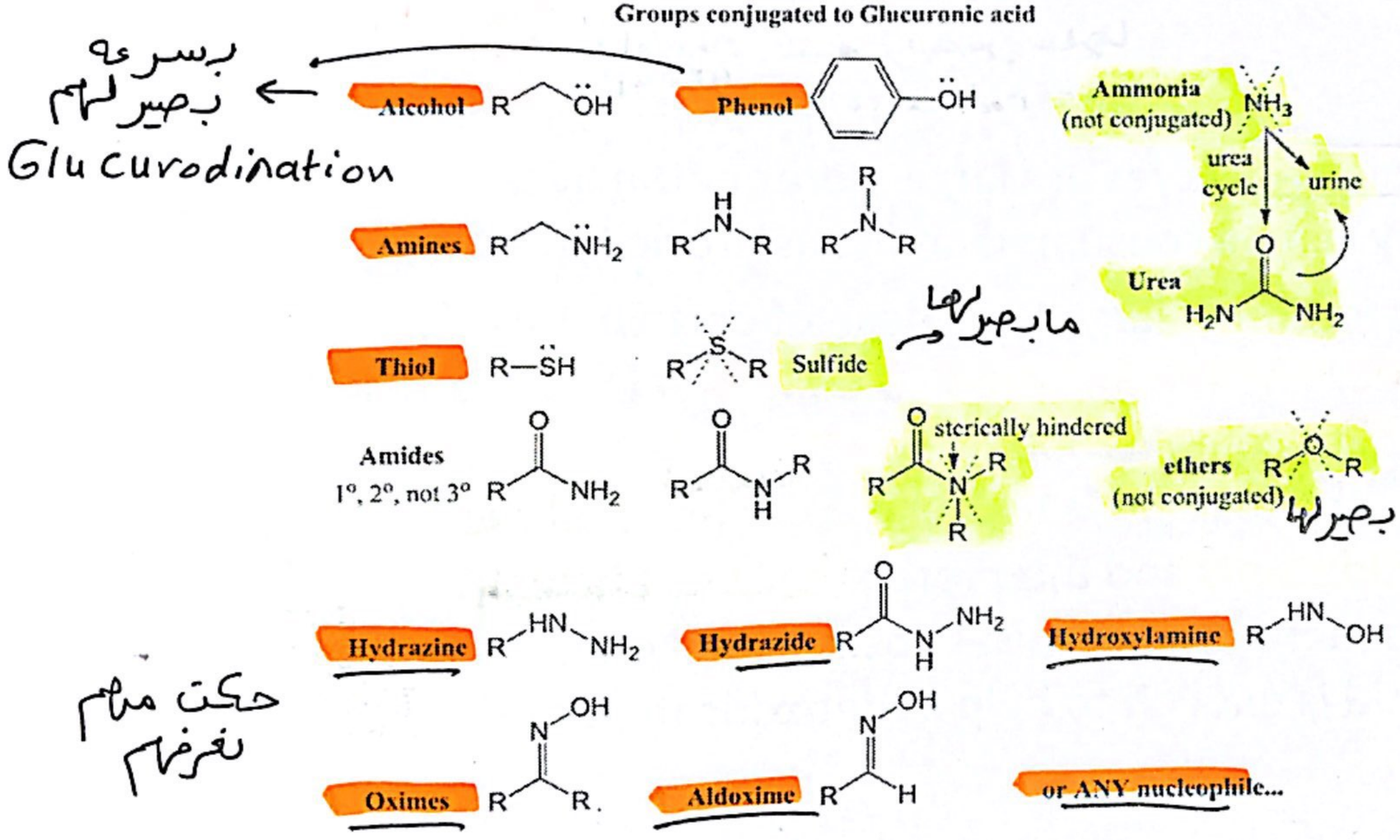
- Sometimes UDP-Glucoronyl Transferase enzyme is deficient in the newborns that their livers are immature after delivery which results in **"Neonate Jaundice"**, in those babies any drug that needs to be conjugated in order to be eliminated will accumulate in their bodies.

الي حكيناه قبل

- For example "Chloramphenicol", an antibacterial agent, has two alcohols that can be conjugated so if there is no enough gluocornide conjugation due to problems in the liver, "Grey-Baby syndrome" will be result (Babies that have immature livers with little amount of UDP-Glucoronyl Transferase enzyme so they tend to accumulate بسبب نقص هذا الانزيم
- Chloramphenicol in their bodies and terminating at Grey color).

→ side effect لهاد الدوا بتحول لون الطفل للرمادي بسبب تراكم الدوا عنده

Candidates for Glucurodination reaction



بسرعة بصير لهم Glucurodination

ما بصير لها

ما بصير لها

حكت مهم نعرفهم

All the nucleophiles can be conjugated to the Glucoronic acid

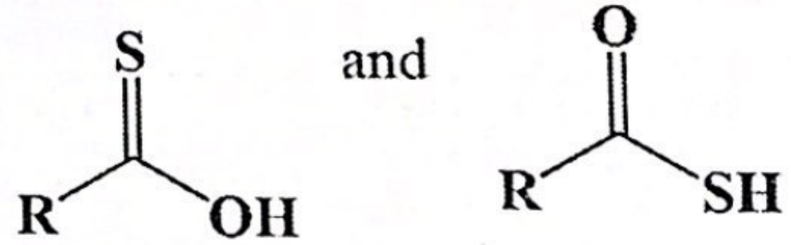
الي ما بصير لهم Glucurodination?

1. ethers
2. sulfides
3. 3° Amides
4. Amonia بسبب ال sterically hindered

enzyme ال نعرف ال active form Candidates of reaction (هو الي بصير له reaction) نعرف صدول كمان

Candidates for Glucurodination reaction

- 1. Aliphatic alcohols, Aromatic alcohols (Phenols)
- 2. Aliphatic amines, Aromatic Amines
- 3. Carboxylic acids بسهوله
- 4. Thiols (but not sulfides)
- 5. Amides (but not 3° amides)
- 6. Thioacids (it's abundant in liver)



Thioacids

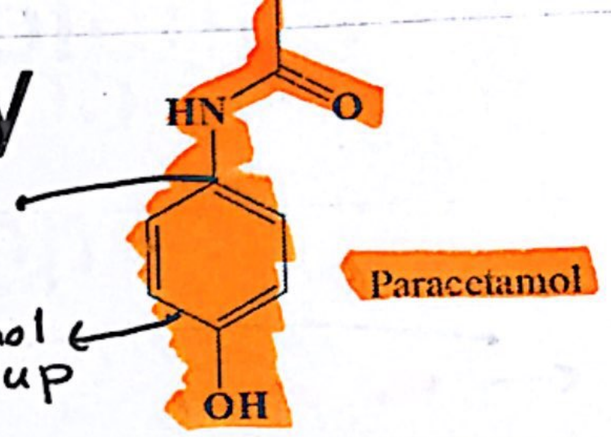
Paracetamol toxicity

acetamino group

Lic para position على ال

بصير عليها ← phenol group

Glucorodination

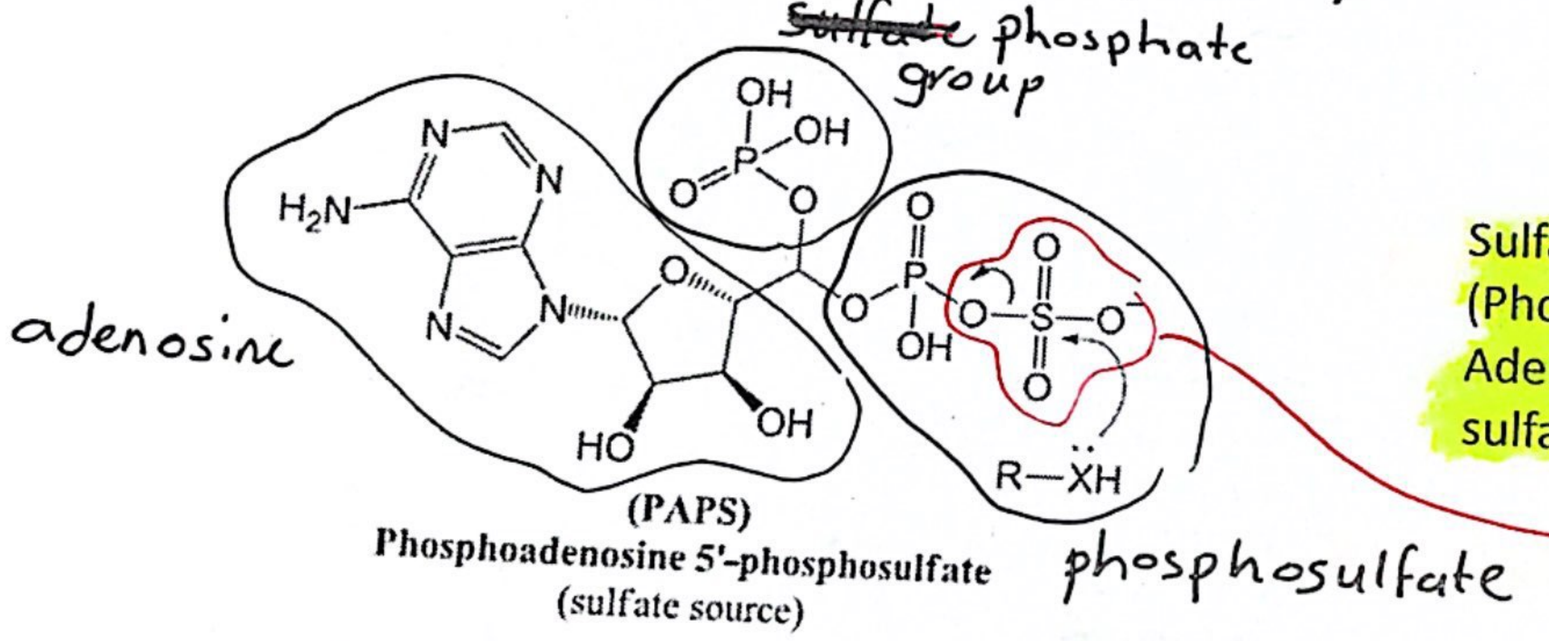


- The Glucoronic acid stores are large stores in the liver although they can be consumed and cause toxicity.
- After administration of large toxic dose of certain drug, for example if a patient administered 20 tablets of Paracetamol at once (each tablet contains 500mg so 20 tablets contain 10g), it can reaches the toxic dose because it depleted (نقصان) all the Glucoronic acid stores and therefore it will start having toxicity, But under normal clinical doses usually the amount of Glucoronic acid is enough to help in detoxification of the drugs.

Sulfate conjugation

sulfate
~~phosphate~~ donor → مين sulfate

- Phospho adenosyl phospho sulfate PAPS", and is the form added to nucleophiles in the conjugation reactions (the liver uses it to add sulfate to different nucleophiles).



Sulfate donor is **PAPS** (Phosphorylated Adenosine phospho sulfate)

Sulfate group هاي
الي ال drug تبعنا
رح يعمل nucleophilic attack
عليها فلما تطلع من
ال paps رح تلزق بالدواء
donor تبعنا

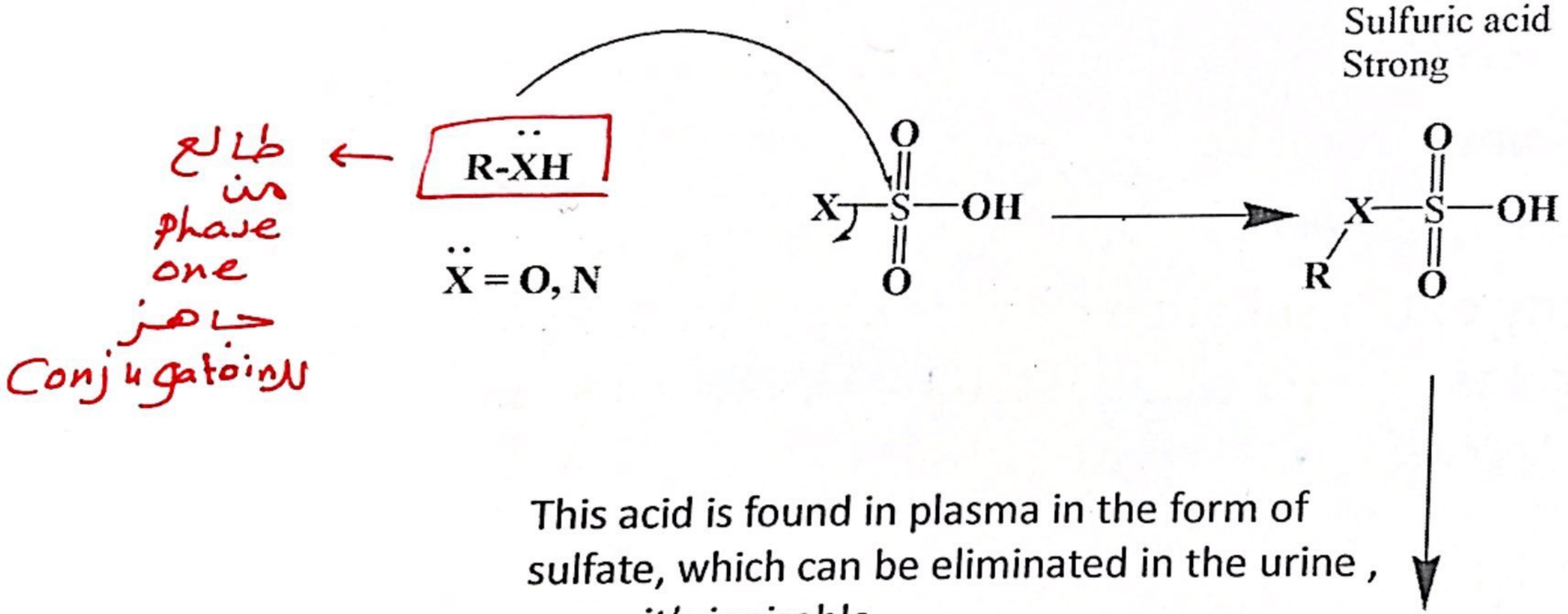
* مشكلة عليه ال Sulfation
ال sulfate مصادره قليله
جداً بالتالي بخلص بسرعة
فإذا اخدنا جرعة عالية من الدوا
ال sulfate ما رح تكفي لحالها حتى
detoxification تعمل group

← اضافة sulfate group

Sulfate conjugation

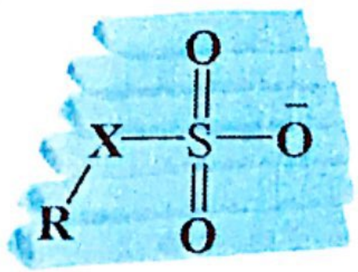
Sulfate conjugation

إضافة ← sulfate group



طالع ← in phase one جاهز Conjugation

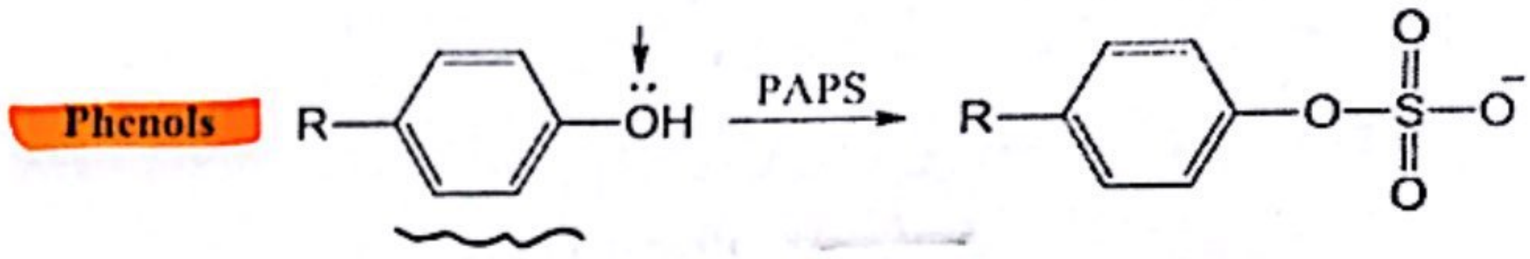
This acid is found in plasma in the form of sulfate, which can be eliminated in the urine , cause it's ionizable



Sulfate (plasma) → very Highly Soluble

Candidates for sulfation

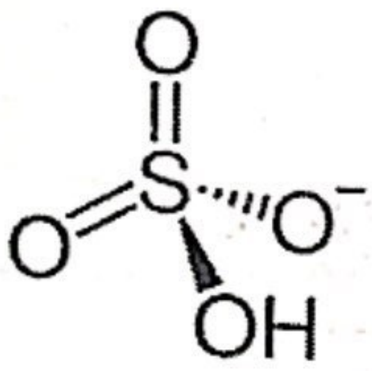
good Gandidates



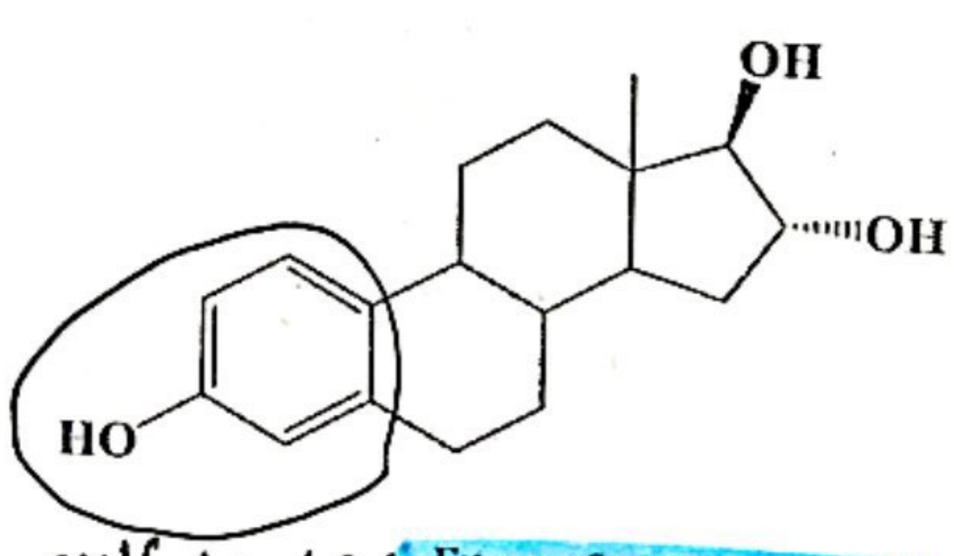
بصيرلهم
sulfation
and
Glucoridation

Candidates for sulfation

1. phenols (Aromatic alcohols) (not aliphatic)
2. Anilines (Aromatic amines) (not aliphatic)
3. Hydroxyl amines



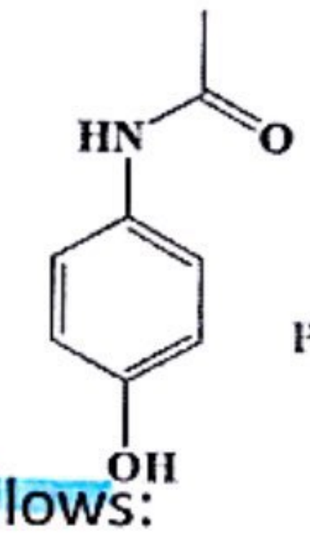
Majority of the sulfation process happens on the internal substrates like: (Bile salts, steroidal hormones such as testosterones, estrogens)



Estrogen female sex hormone ← sulfate عشه group

بسرعة بصيرله sulfation and Glucorodination

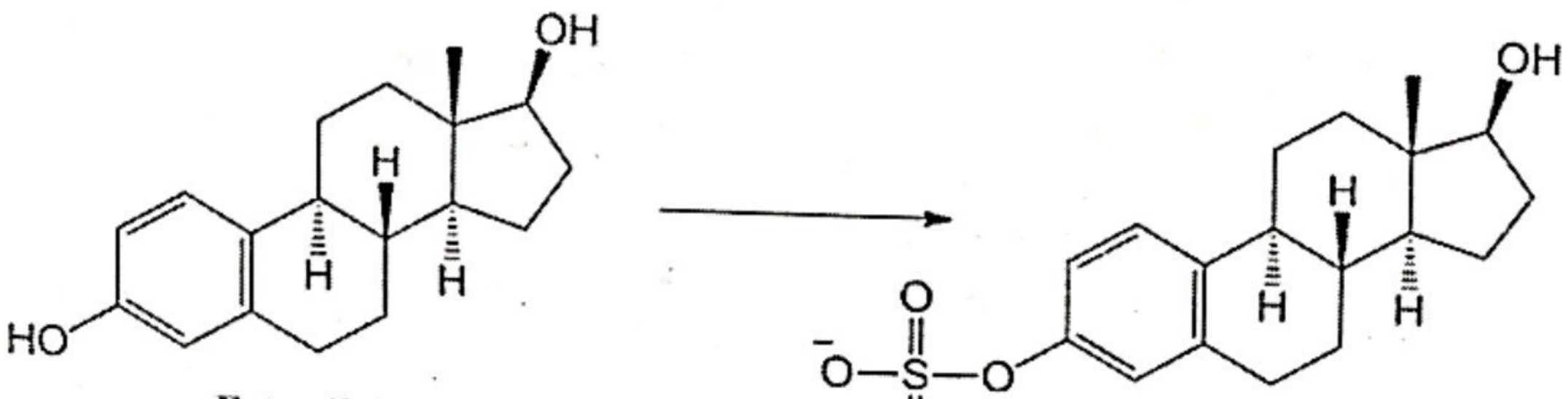
Paracetamol



Paracetamol

- If taken in a clinical low dose we will see it in the urine as follows:
- 1. 50% Sulfate conjugate
- 2. 50% Glucuronide conjugate
- If the dose is high the majority of the dose is excreted as Glucuronide conjugate
- The amounts of sulfates in the liver are much lower than the Glucoronic acid, for example the three previous groups that can be sulfated also can be conjugated to Glucoronic acid, so under low clinical doses there is a competition between sulfate conjugation and glucoronide conjugation (50:50), but if the clinical dose increases the sulfate will be reduced (depleted) and the glucoronide will be higher than it (higher clinical doses results in depletion of the sulfate and therefore the glucoronide will be higher than the sulfate).

This sulfation is very important for some hormones



Estradiol

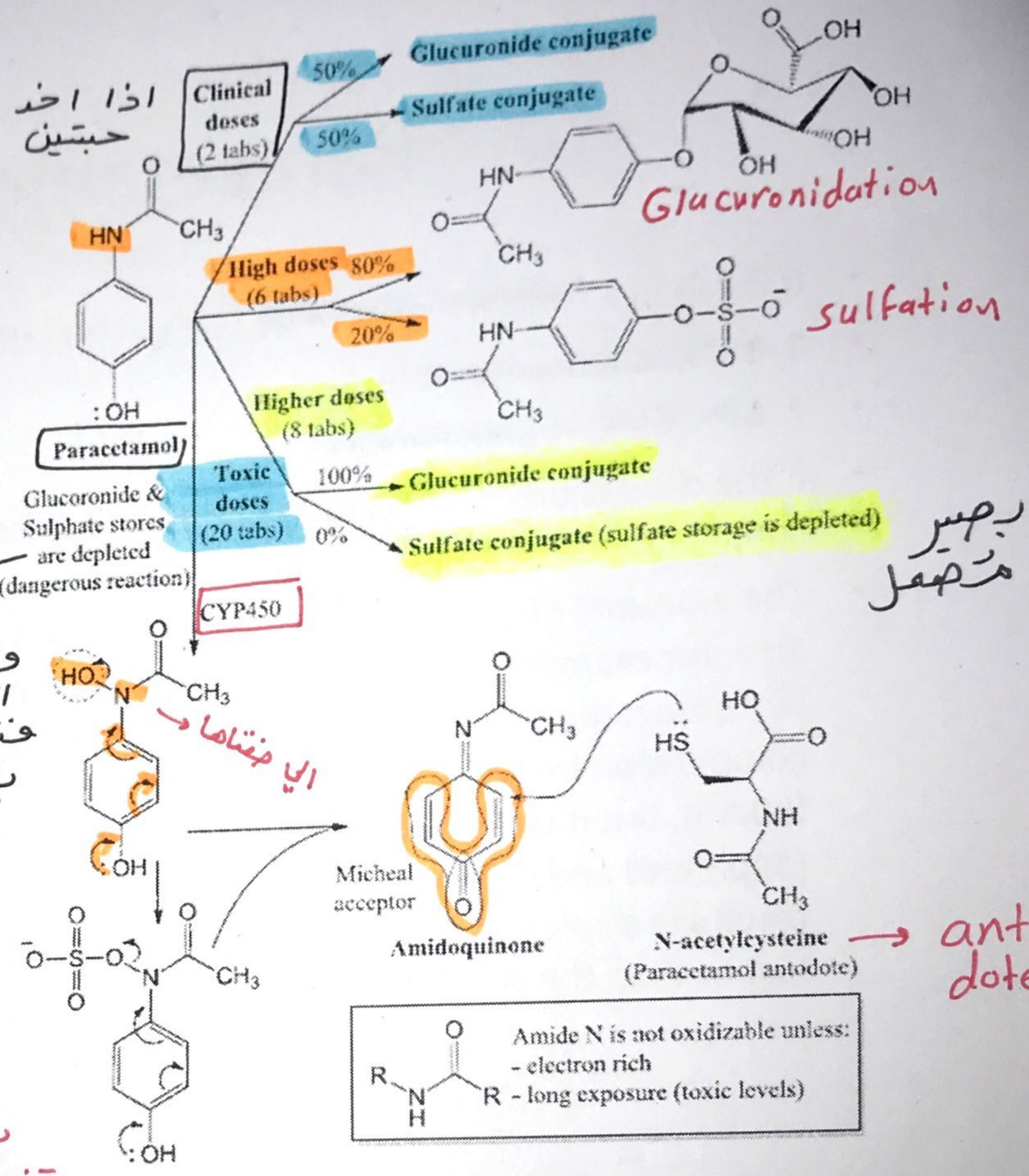
Estradiol-sulfate
can't enter cells

هرمونز بصيرلهم
sulfation

Paracetamol metabolism (Summery)

Reference:
Prof. Taha

* مهم حكت *



Micheal acceptor is a very reactive and very toxic that can react with any nucleophile

رح يجي CYP450 رح تعمل oxidation
وتضيف OH group على NH وهاي حاله
خطيره لانو المركب صار عنده
بال elect وحركة الالكترونات هاي رح
تزيد رح يصير انتقال لل OH تحت
ال Phenol رح يتكون عنا
Micheal acceptor
هاد رح يعمل Covelent bond مع ال
nucleophiles الموجودة على خلايا الكبد
تكملة ع الدفتر

Amino Acid conjugation

في ناس مثل بيأخدو Paracetamol
بفكرو عشيل معدة وبتنتهي المشكلة بس
هو هيك
اذا اخدت فوق ال 20 حبة لح يخلص ال
Glucuronide و ال sulfate بصير الكبد مستنزف
بأنزيمات فبصير عندها Liver toxcity (irreversable)

تكملة المكتوب ع السلايد

وهون الطبية بعد ال Covelent bond الي هيه
ال irreversable مع irreversable رح ترتبط بشكل
Micheal acceptor الي رح يكون على شكل amido-quinone
ورح يصير عندي موت نهائي للخلايا تاعت الكبد
والحل يكون زراعة كبد جديد

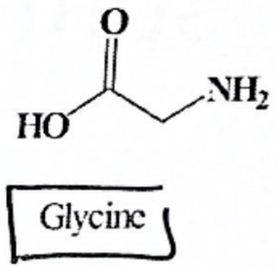
* اذا رحتو اطريحتن بيعطوه Very Strong nucleophile بس لازم
يسبق خلايا الكبد باية يهاجم ال amidoquinone وهاد
ال antidote اسمو N-acetyl cystiem بس الشرط
انو ينعطى بشكل مبكر)

الموجودة على خلاياي الجسم

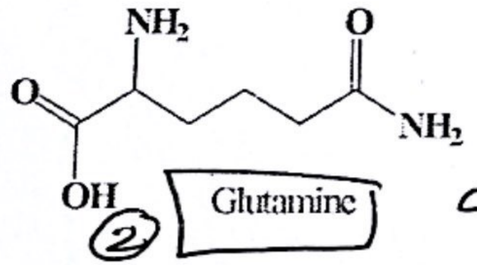
Amino Acid conjugation

Carboxylic acids are the only substrates for amino acid conjugation

- They are normally added to **carboxylic acids**



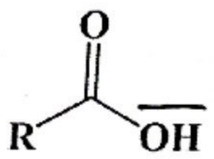
① Glycine



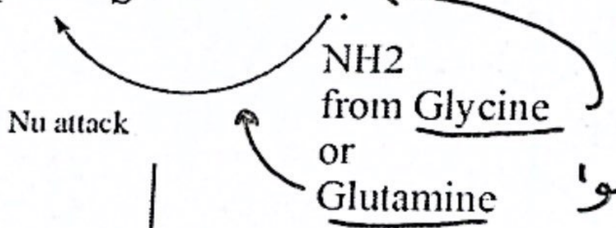
② Glutamine

a.a → بعملو Conjucated

هون الدواء هوه اللي رح ليتحول للـ active form



active



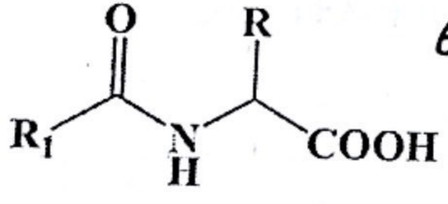
NH2 from Glycine or Glutamine

بيجو وبعلوا nucluphilic atack

Nu attack

This reaction is catalyzed by Glycine transferase or Glutamine transferase

على الـ COA فبيطلع as a good leaving group



~~Covetn~~ Covelnt بتكون bond between the drug and Glycine ok Glutamine

بال Glucurodination بكون activation

على ال Glucuronide عن طريق اضافة UDP

بصير attack من ال drug على ال carbon

اللي عليها UDP فبتطلع ال UDP ← as a leaving group

ليس بأهمية amino acid conjugation →

① Glucurodination لانو ما بصير عنيز على المركبات اللي عليها carboxylic acid

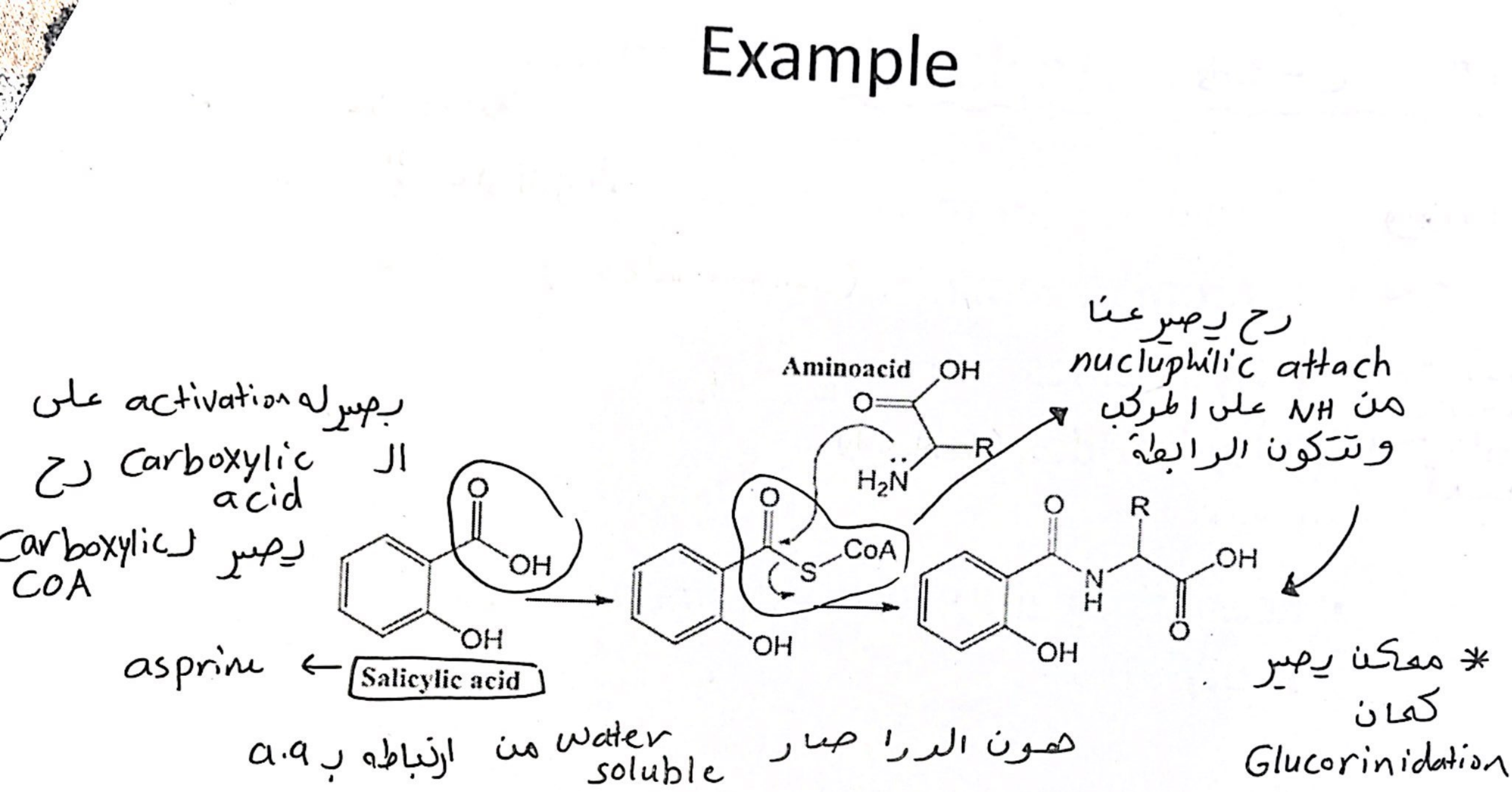
② carboxylic acid ← هو اللي بصيرله activation عن طريق إضافة ال COA وهاد التفاعل بده طاقة

بعدين بيجي ال Glycine / Glutamine ← عليهم NH group

وبيعملو رابطة ما بين drug / a.a / Glycine / Glutamine

رابطة أميدية

Example



بصير له activation على ال carboxylic acid

رح يصير لـ carboxylic COA

asprin ← Salicylic acid

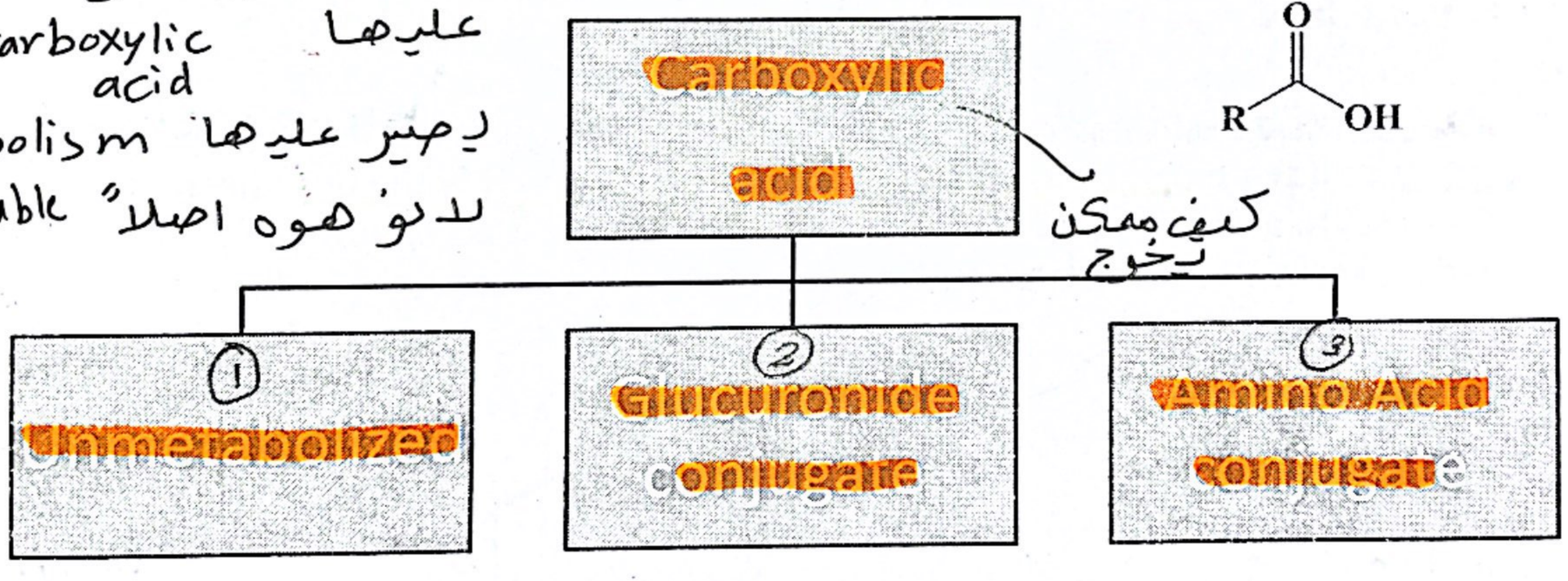
ارتباطه بـ a.a من water soluble صعب الدرا صار

رح يصير عنا nucluphilic attach من NH على الطرف وتتكون الرابطة

* ممكن يصير كمان Glucorinidation

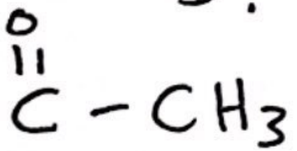
Fate of carboxylic acids in the body

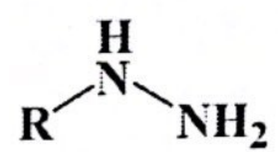
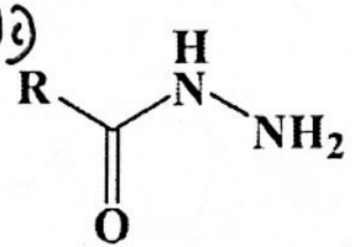
* حكينا قبل انو المركبات الى عليها carboxylic acid مرمم
metabolism يصير عليها
water soluble لانو هوه اصلاً



acetyl group ← 

Acylation reactions

* عباره عن اضافة  على الdrug

- Candidates for this reaction وين يصير
  - 1. Aromatic amines (sulfanamides)
  - 2.Hydrazines ادوية ليحتوي على أمينات 
  - 3.Hydrazides (izoniazid) 

- Secondary and tertiary amines are not acetylated.

Important facts about acetylation

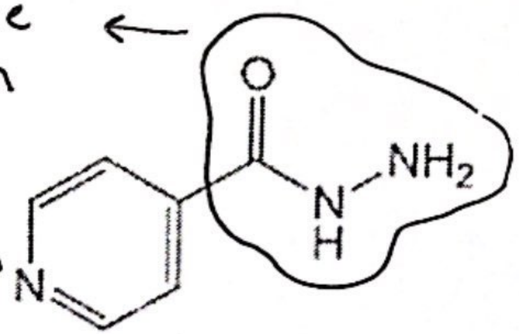
First Fact: People are divided into two groups according to the Acetylation:

- A- Slow acetylators 50% → العليه بطيئة → الدوا بقعد بجسمه فتره طويلة
- B- Fast acetylators 50%
- So before giving the Drug to a patient we should check if our patient is a slow or a fast acetylator especially if the drug is to be given for long period of time.
- For example "Isoniazide" drug that used for tuberculosis against Mycobacterium should be taken for long period of time (the treatment duration is 6 months to 2 years), so if the patient was fast acetylator we have to modify the dose (increase the dose) to accommodate the fact the individual is a fast acetylator while if the patient was a slow acetylator we have to decrease the dose.

hydrazide side chain

بصيرلها acetylation

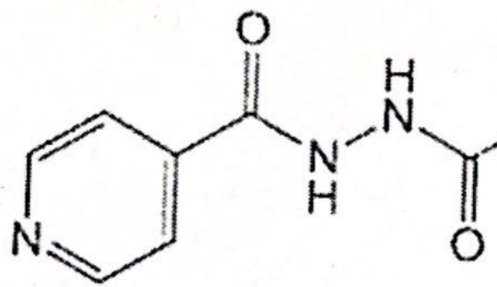
وهاد بصيرله انو بنتخلص من الدوا عن طريق feces ال



دوا لمرض السل

Isoniazid (active)

قبل ما نعطي الIsoniazed لمريض السل لازم نعرف هوه fast / slow acetylator حتى نعرف جرعة الدوا الي رح نعطيها

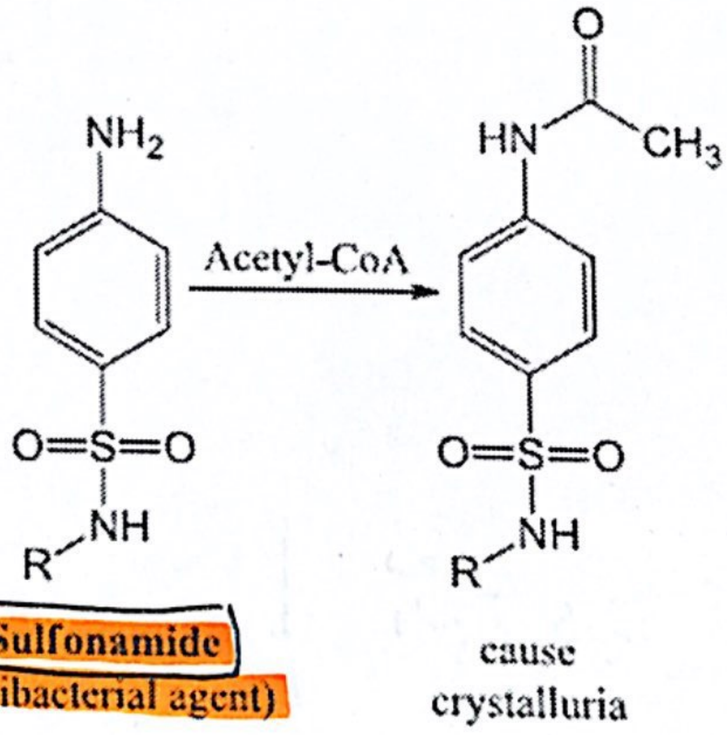


(inactive)

Second fact

- We said that the aim of Phase 2 reactions is increasing the water solubility of the compounds, but in Acetylation we are adding an acetyl group to the compound which increases its lipophilicity! ↓ solubilty
- So Acetylation makes the compounds less water soluble and leads to their precipitation in the kidney and causes "Crystalluria" or "Kidney stones"

Acety-CoA → هعوه الي بعطي acetyl



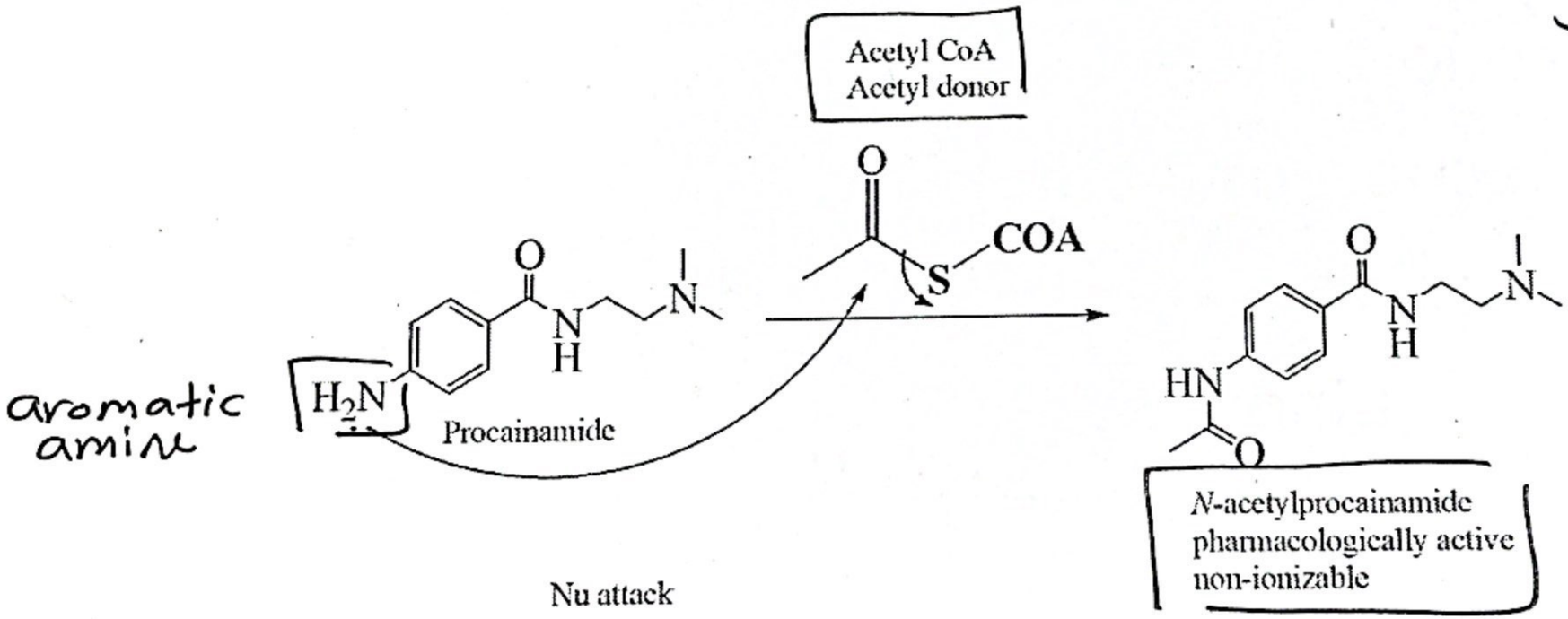
* عملية الacetylation بتقلل الذائبية ما بتزيدها

acetylization لما يصير لهم ← بصير الانسان معرض لـ Crystalluria → حصى الكلى عشان هيك لازم يشرب كتير مي

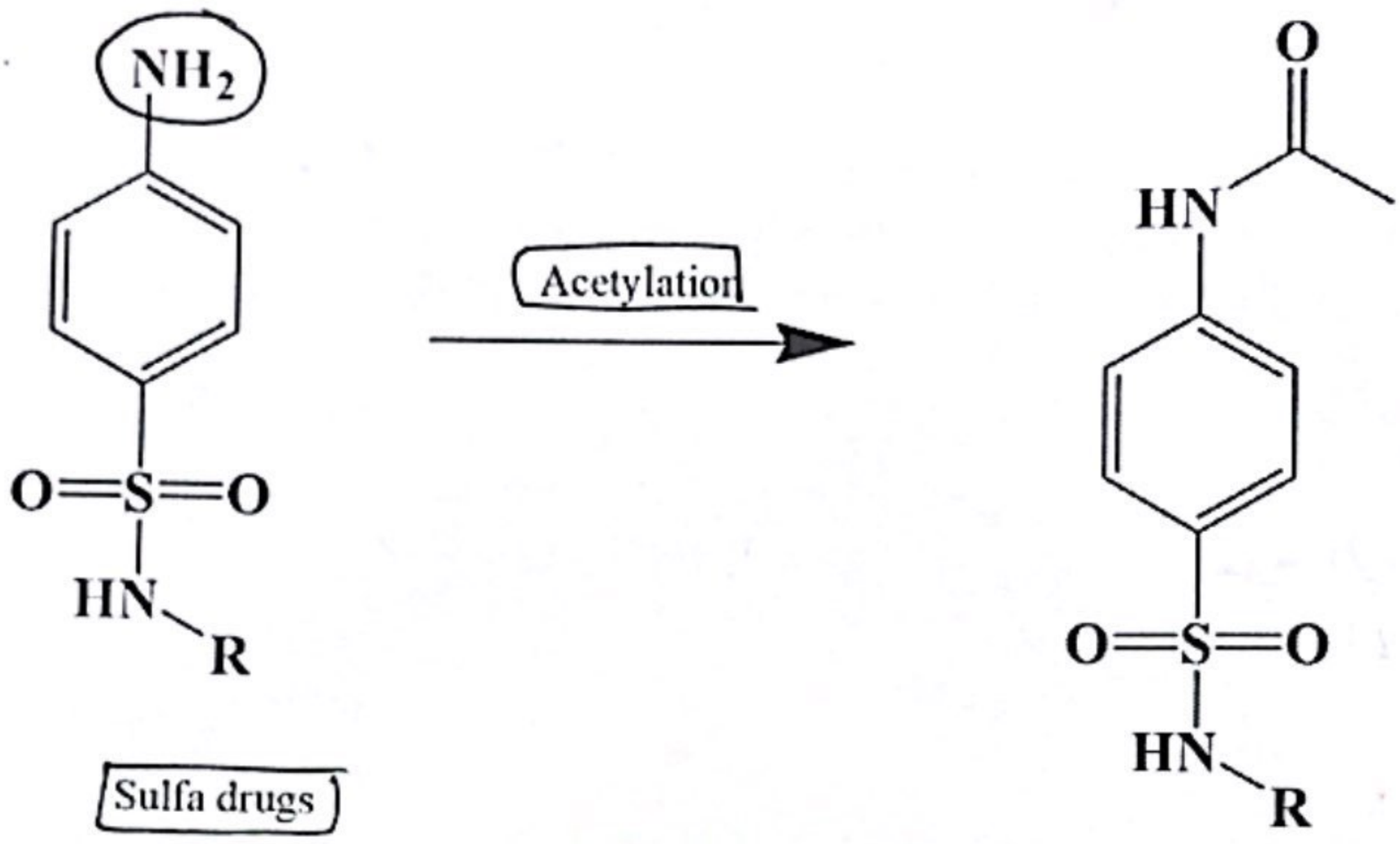
Example

- The product in this case is less soluble than the starting drug (special case)

مثال نحن



Metabolism of sulfonamides
Antibacterial drugs



Sulfa drugs

نفس الي حكينا

Not soluble , precipitates in kidnies
Cause of that we recomend to drink a lot of water during the intake of such drug

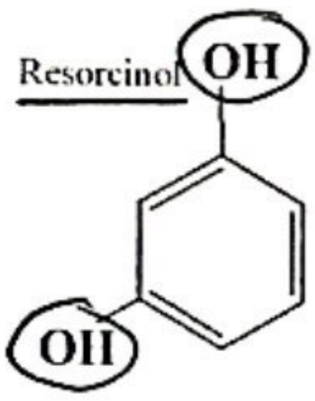
5 Methylation reaction

Methyl group إضافة ال

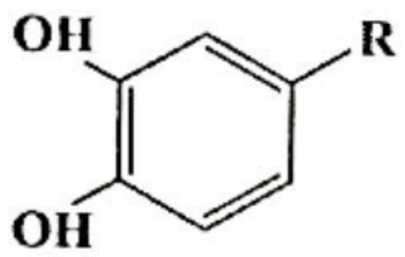
- Candidates for this reaction:
- 1. Amines
- 2. Alcohols
- 3. Catechols (majority)
- 5. Resorcinol
- 6. Hydroquinones

Hydroquinones

Para position



اذا كانو 2 Meta position



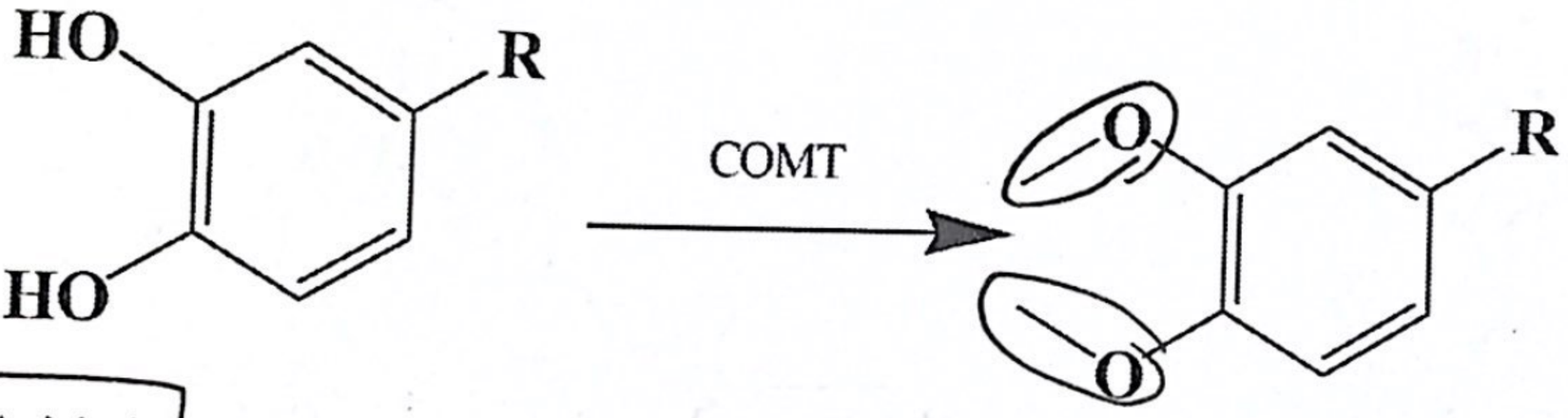
Catichols
as in epinphrin and norepinephrin

اصم ي
2 ortha (oH) group

Methylation reaction

بعطي Methyl group

COMT carries out O-methylation of such important neurotransmitters as epinephrine and dopamine and thus terminates their activity



Catichols as in Epinphrin

Catechols

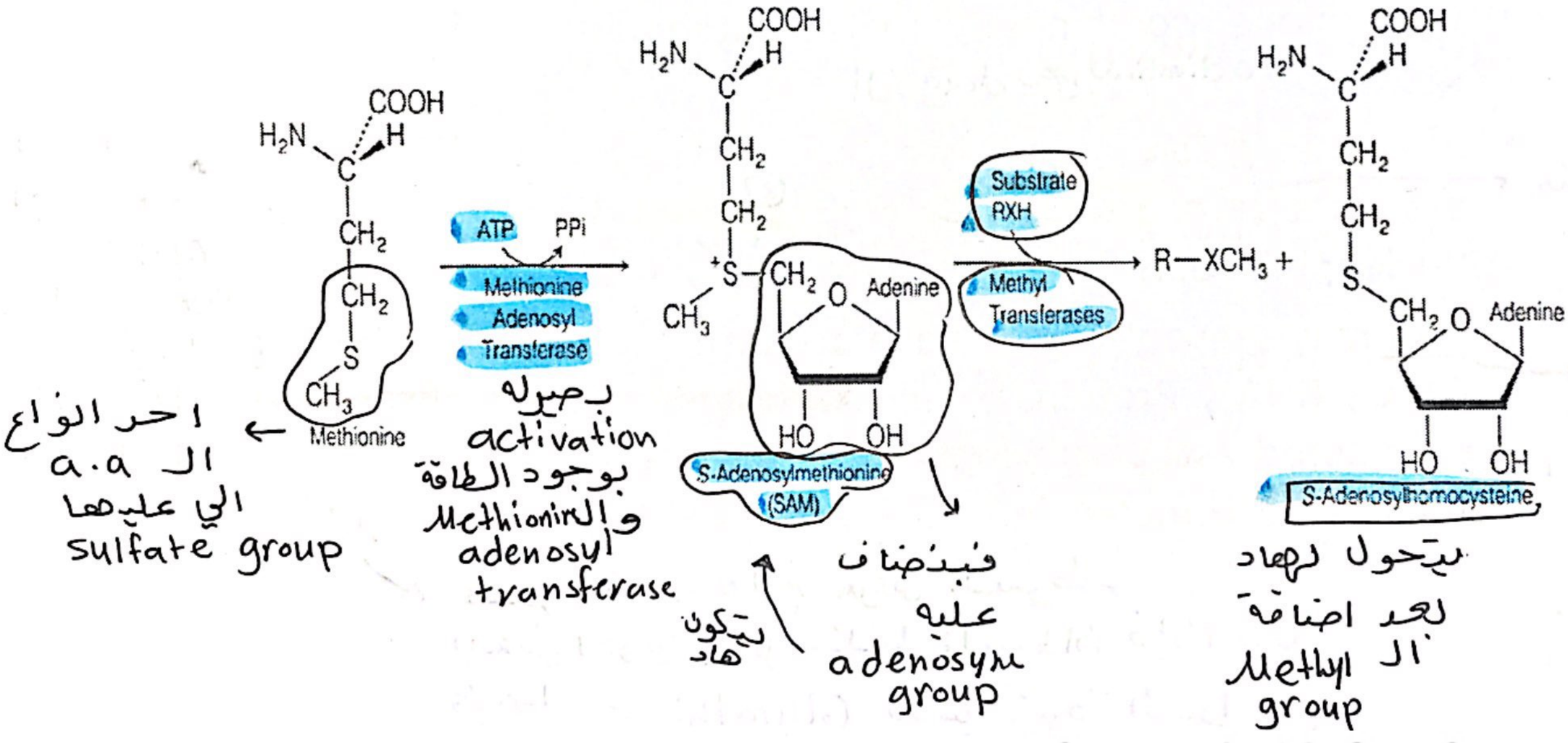
COMT: Catichols -O- methyl transferase enzyme helps in methylation reaction → بضيف Methyl group حتى يصير الدوا غير فعال بالتالي بتخف حالة الي بتصير عند الانسان fight or flight

S-Adenosylmethionine SAM

another methyl donor

methyl donors → CoMT
→ SAM

- SAM is a methyl donor



احد انواع ال a.a اللي عليها sulfate group

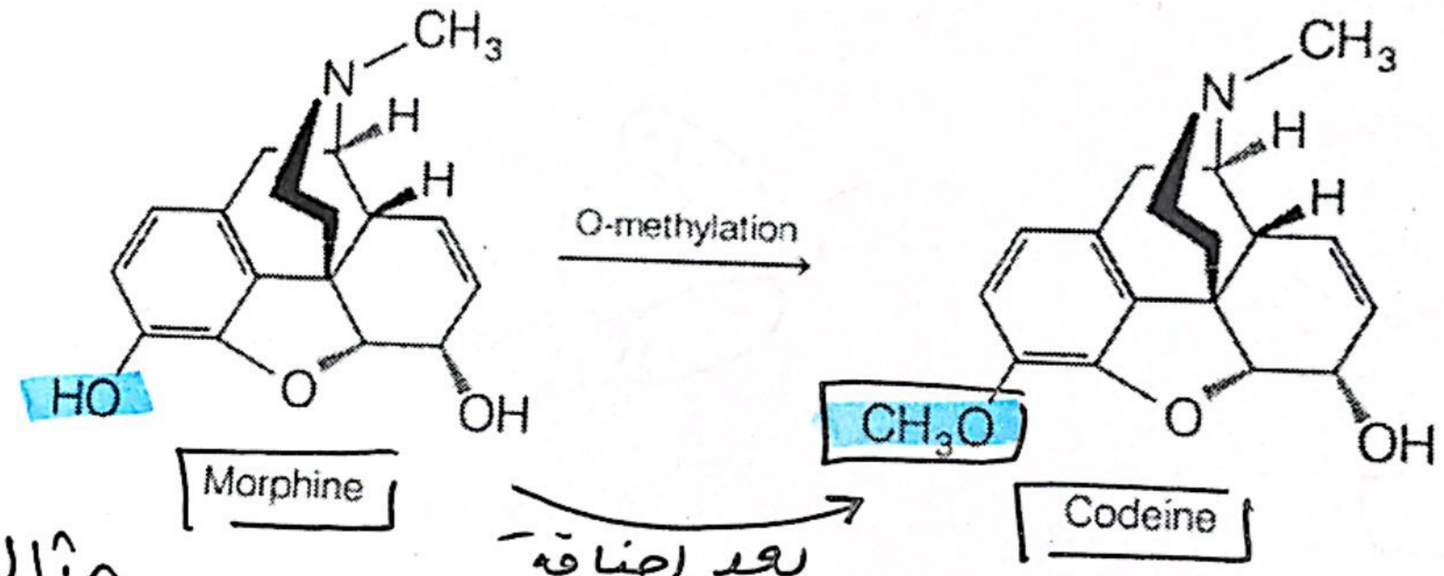
بصيرله activation بوجود الطاقة والـ Methionine و adenosyl transferase

بيتكون هاد

فبنضاف عليه adenosyl group

بيتحول لهاد بعد اضافة ال Methyl group

S-Adenosylmethionine SAM



Morphine

Codeine

بعد اضافة Methyl group لـ OH

مثال عليها كيف يتخلص الجسم من ال Morphine

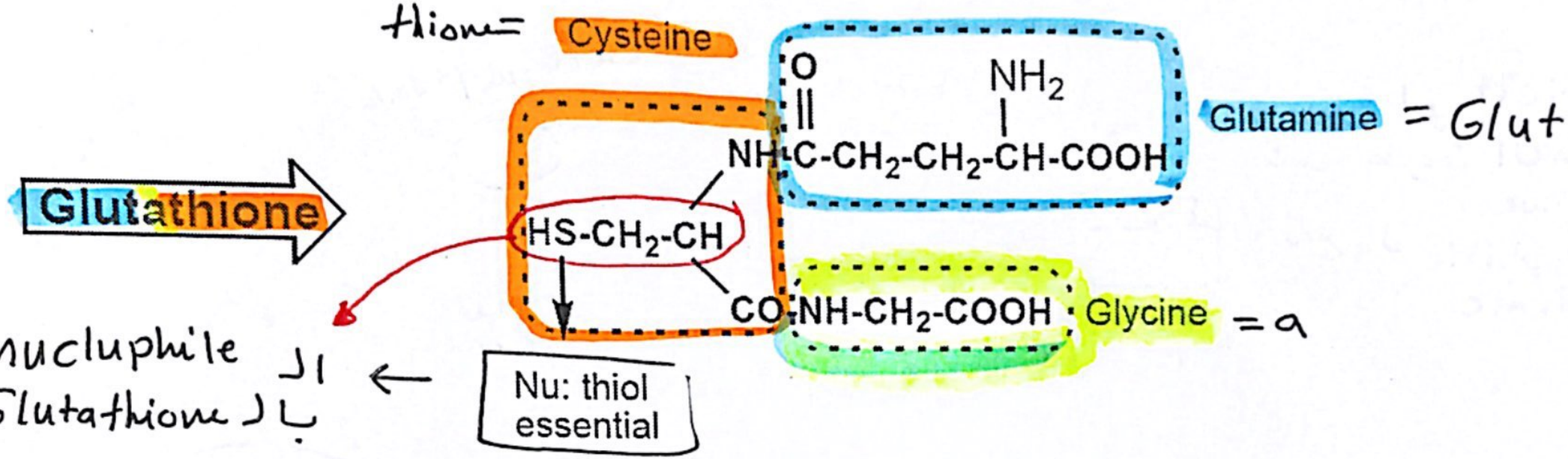
narcotic: مخدر يتسبب الادمان

[4] Glutathione or Mercaptouric Acid Conjugation

- GSH is **tripeptide**: [γ-glutamyl cysteinyl glycine] found in most tissues.
- Glutathione combines with activated drug (GSH is not activated).
- the driving force for this reaction is the electrophilicity of substrate (e.g. arene oxide and epoxide) & the reactivity of nucleophilic GSH towards elecrtophilic substrates.
- GSH may prevent any damage occurring to macromolecules (DNA , RNA , Proteins) by some activated drugs so it is considered as ***detoxifying pathway*** that function to protect cellular macromolecules against harmful electrophiles.

Donor : Glutathione tripeptide = Cysteine + glutamine + glycine
(activated inside the body)

thione = Cysteine

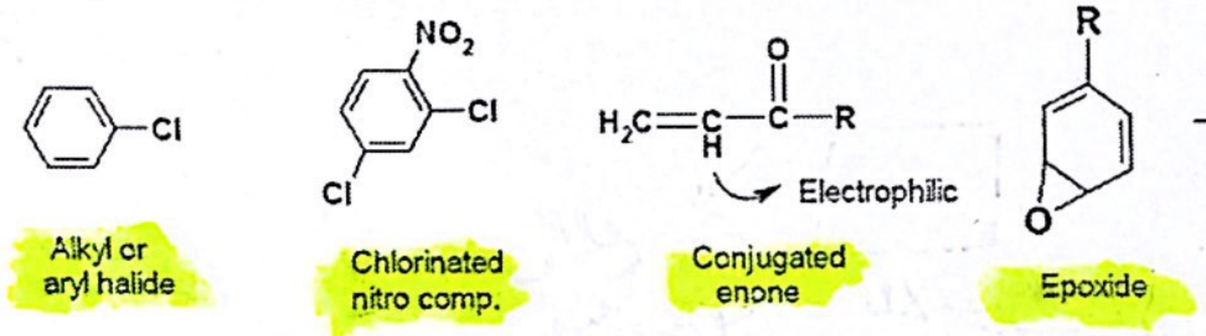


HS group ← nucluphile ← Glutathione

Acceptor : ***Electrophilic species*** (electron deffecient)

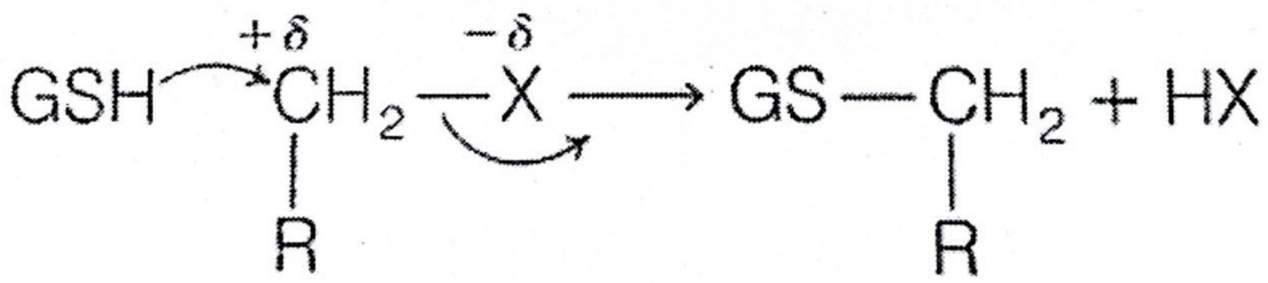
e.g . Alkyl or aryl- halide , Epoxide , Chlorinated nitro compound , Organic nitrate & Conjugated enone

acceptors



GSH or Mercapturic Acid Conjugates

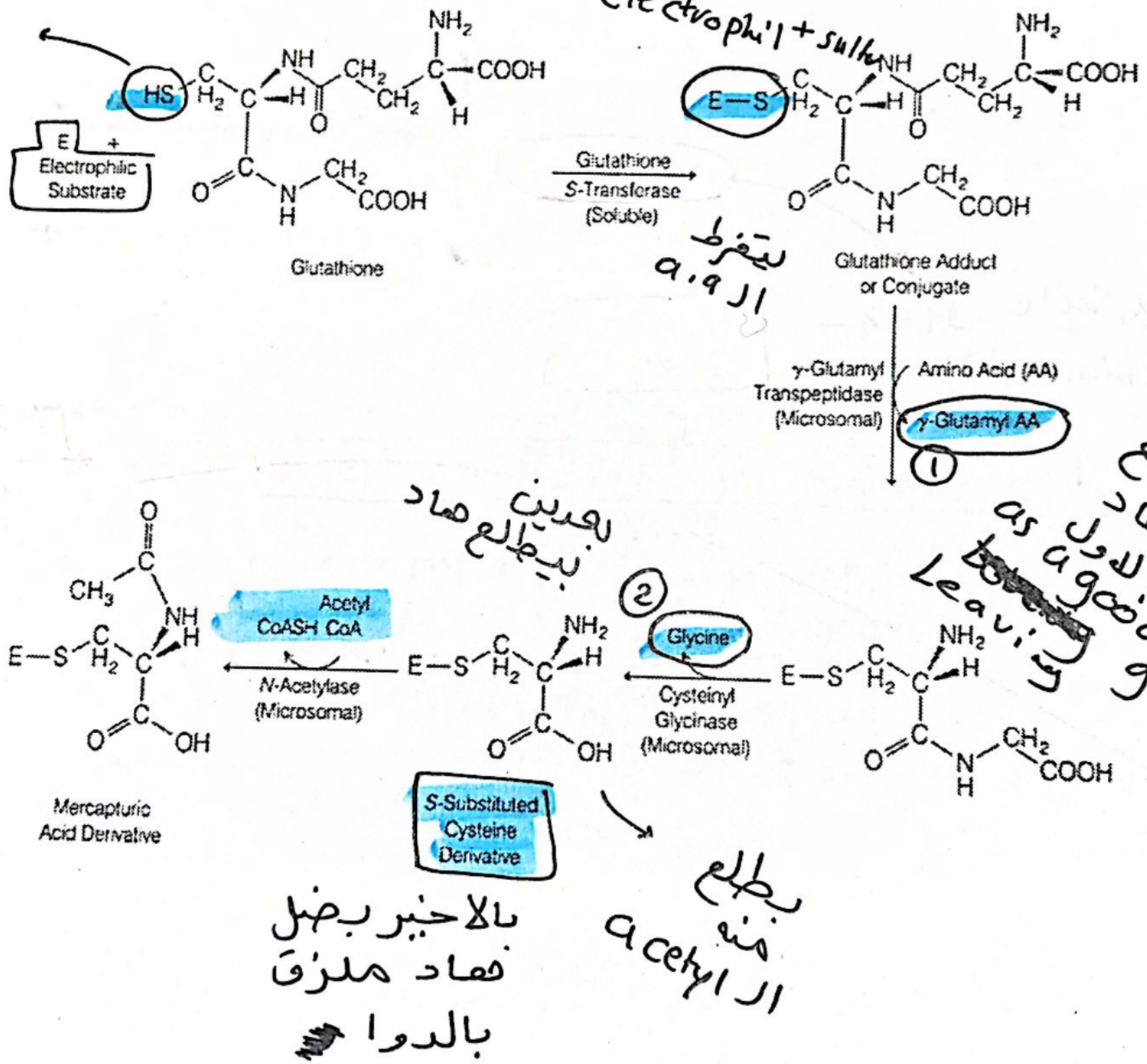
- Glutathione (GSH) protects vital cellular constituents against chemically reactive species by virtue of its nucleophilic SH group.
- The SH group reacts with electron-deficient compounds to form S-substituted GSH adducts



R = Alkyl, Aryl, Benzylic, Allylic
X = Br, Cl, I, OSO_3^-, OSO_2R, $OPO(OR)_2$

GSH or Mercapturic Acid Conjugates

addicit رح تعلم
Glutathione عن طريق الـ
Transferase
Electrophilic مع الـ
Substrate



electrophil + sulfur
يتفرط ال ٩,٩
بعدين بيطلع هاد
بطلع هاد بالاول as a good group Leaving
بالاخير بضل هاد ملزق بالدوا
بطلع منه ال acetyl