

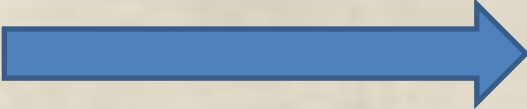
Farmasötik Toksikoloji 2014 – 2015

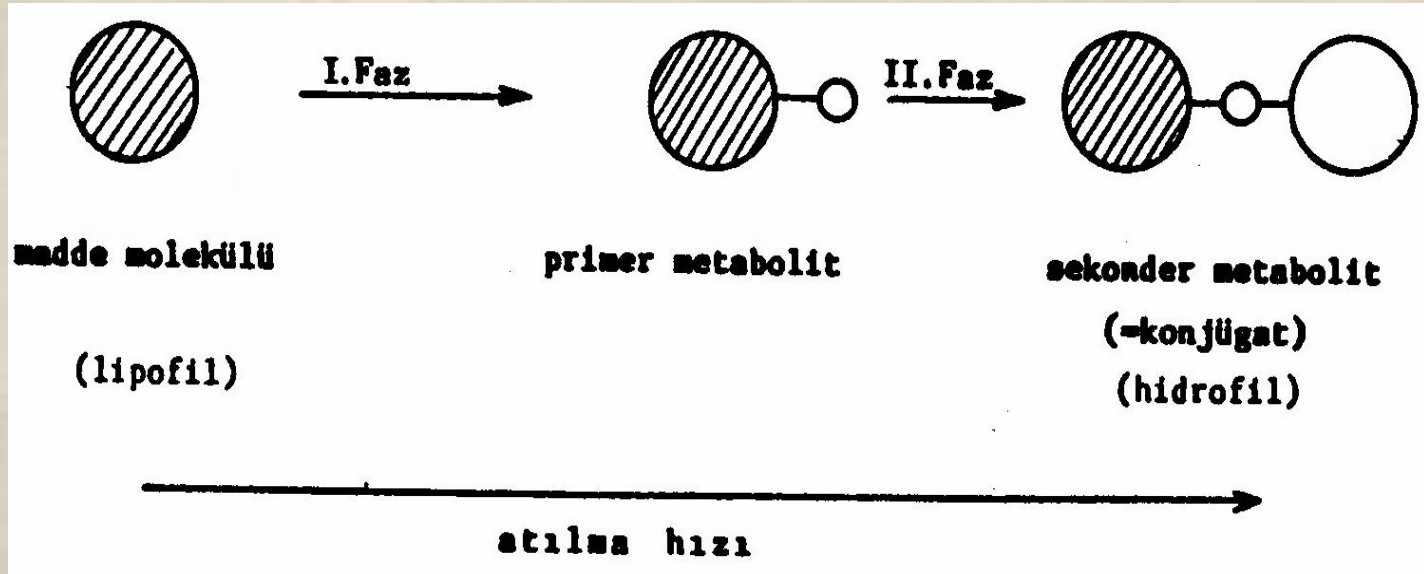
4.Not

Doç.Dr. Gül ÖZHAN

BİYOTRANSFORMASYON

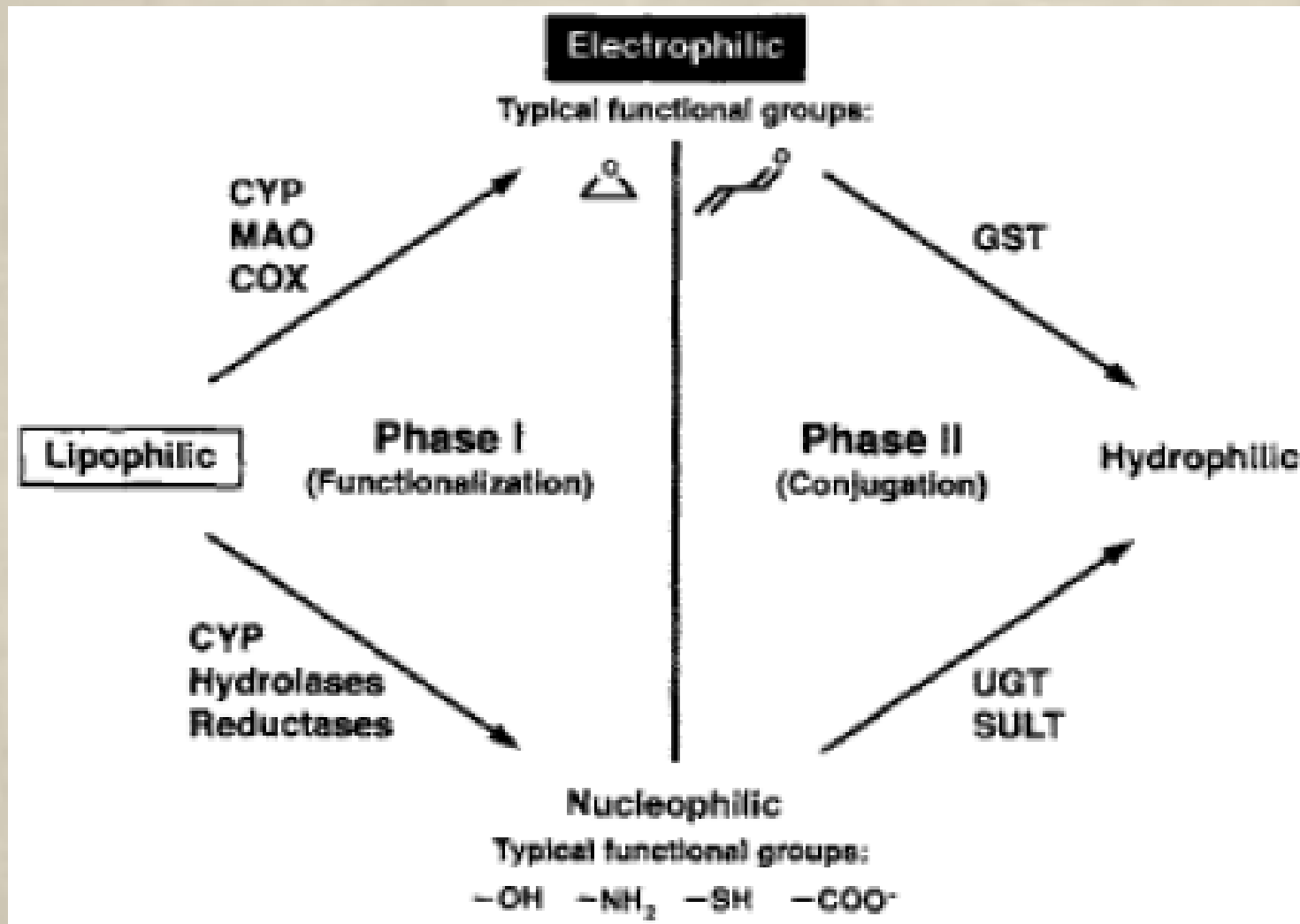
Endojen maddelerin ve ksenobiyotiklerin metabolizma reaksiyonları ile suda çözünen bileşiklere dönüştürülmesi.

Biyotransformasyon  Detoksikasyon



İstisna **Bioaktivasyon**

Ksenobiyotik biyotransformasyonda genel akış



Biyotransformasyon olaylarında;

- **Maddenin yapısı, fizikokimyasal özellikleri (stereo-kimyası, fonksiyonel grupları vs)**
- **Sorumlu enzimler önemlidir.**

Biyotransformasyon reaksiyonları

Faz I

Oksidasyon

Redüksiyon

Hidroliz

Faz II

Glukuronik asit ile konjugasyon

Sulfat ile konjugasyon

Asetilasyon

Metilasyon

Glutatyon ile konjugasyon

Amino asid ile konjugasyon

Biyotransformasyon enzimleri

Faz I

Oksidasyon

Sitokrom P450'ler (CYP)

Flavin monooksijenaz'lar (FMO)

Peroksidaz'lar (COX)

Monoamin oksidaz'lar (MAO)

Dehidrojenaz'lar

Redüksiyon

Sitokrom P450'ler (CYP)

Karbonil redüktaz

Hidroliz

Esterazlar

Peptidazlar

Hidrolazlar

Biyotransformasyon enzimleri

Faz II

Glukuroniltransferaz (UGT)

Sulfotransferaz (SULT)

N-Asetiltransferaz (NAT)

Metiltransferaz

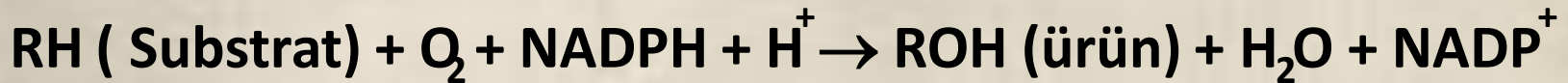
Glutasyon S-transferaz (GST)

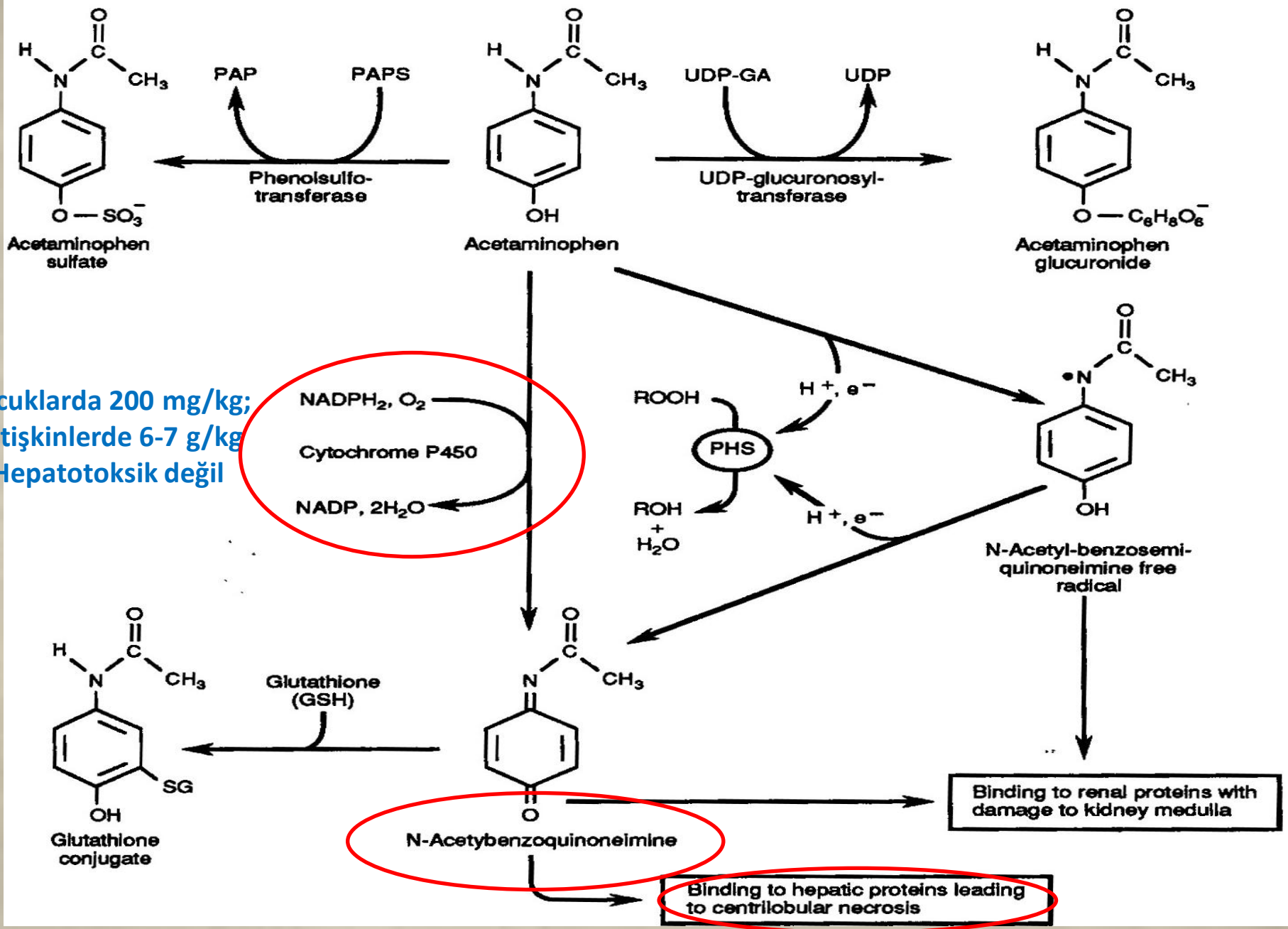
Amino asid transferaz

Glutasyon S-transferaz (GST)

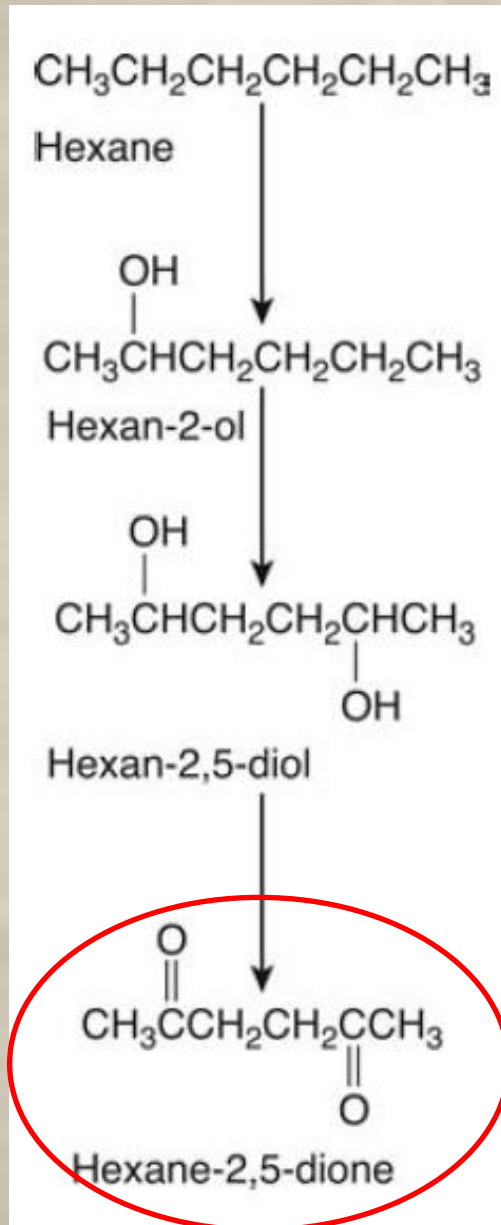
Mikrozomal oksidasyonlar

Enzim CYP'ler (Sitokrom P-450-monooksijenaz, CYP₄₅₀)





Alifatik zincir oksidasyonu

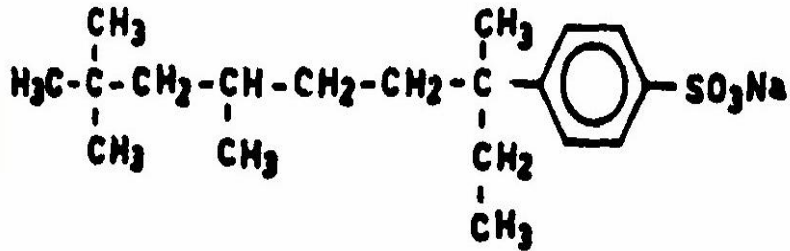
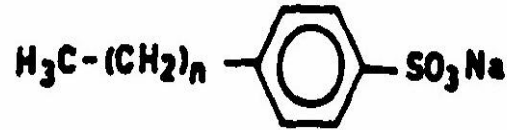
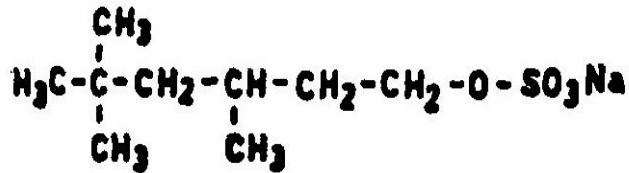
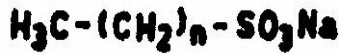
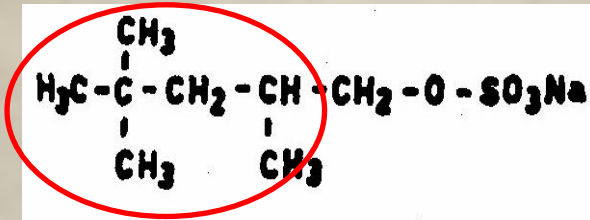


Hekzanın oksidasyonu

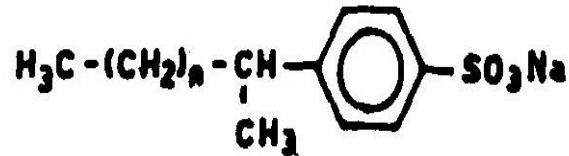
(biyoaktivasyon)

Nörotoksik etki

Alkil yan zincir oksidasyonu (β -oksidasyon)



(Dallanmış)



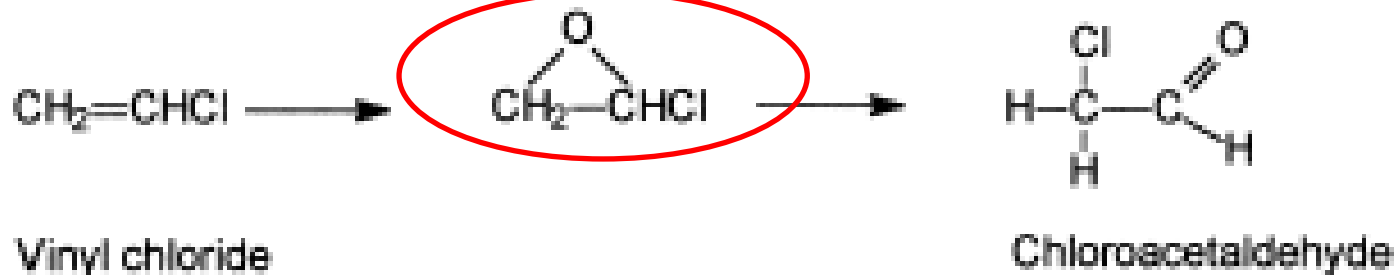
(Dallanmamış)

a) 3 hafta sonra
hiç parçalanma yok

b) 3-4 gün içinde
tamamen parçalanır

(Çevrede mikroorganizmalar tarafından)

Alifatik epoksidasyon

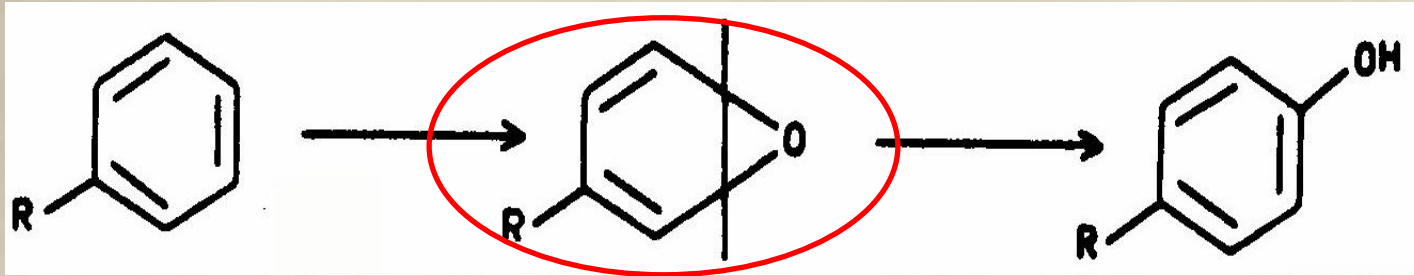


(biyoaktivasyon)

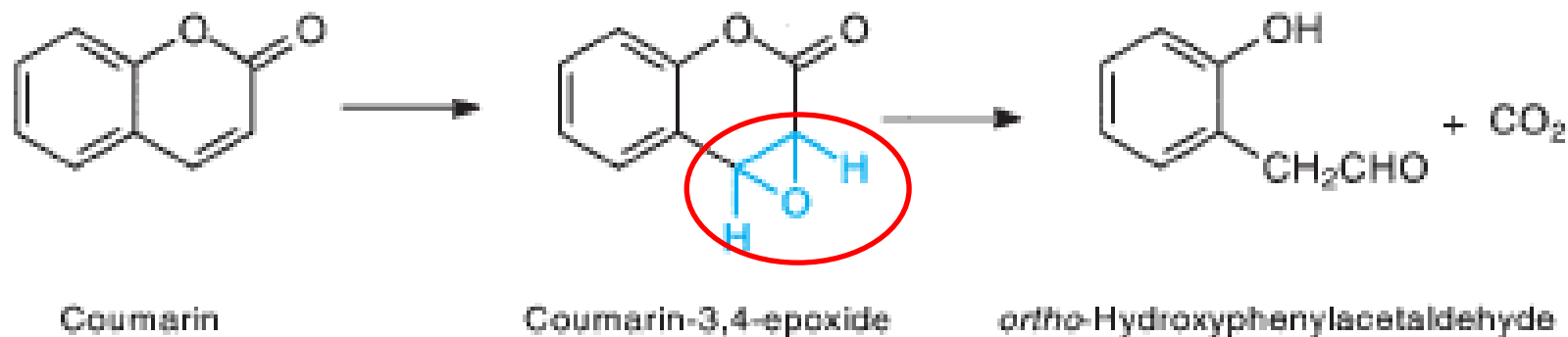
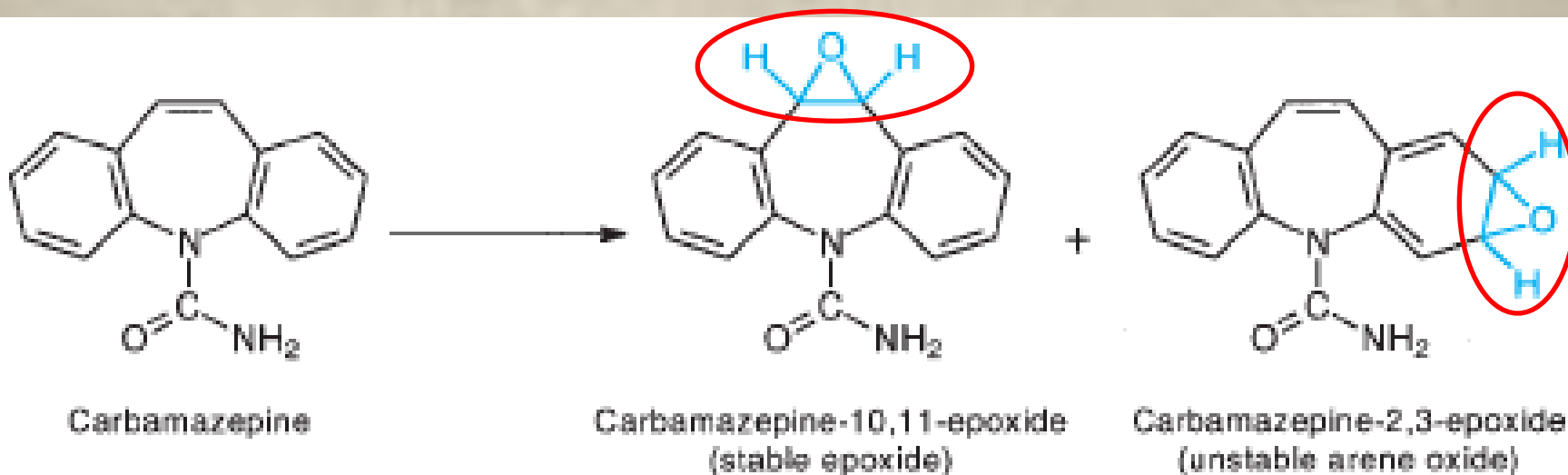
Tetrahidrokannibol (THC) 11-hidroksi tetrahidrokannibol (aktif)

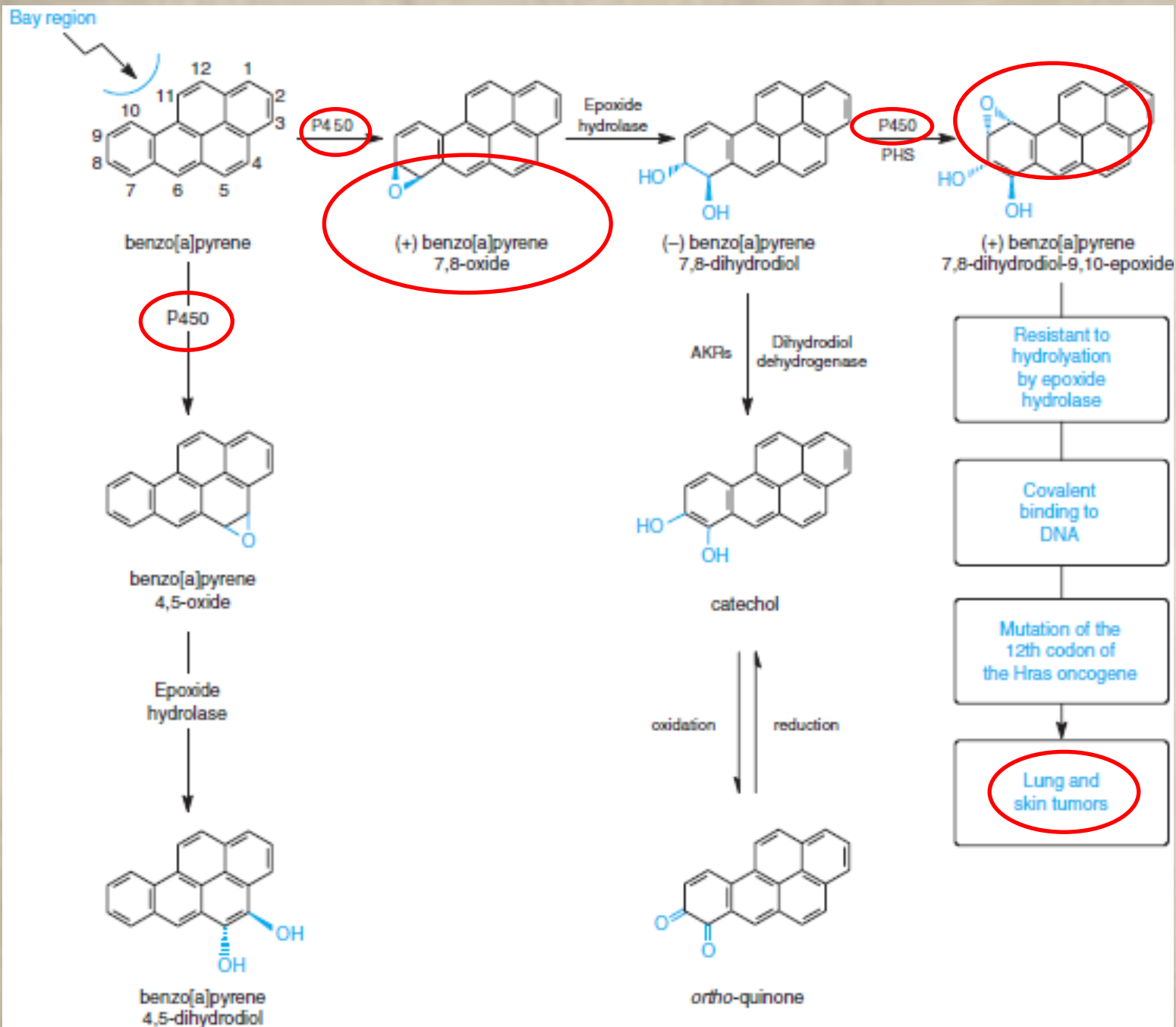
(biyoaktivasyon)

Aromatik epoksidasyon ve hidroksilasyon

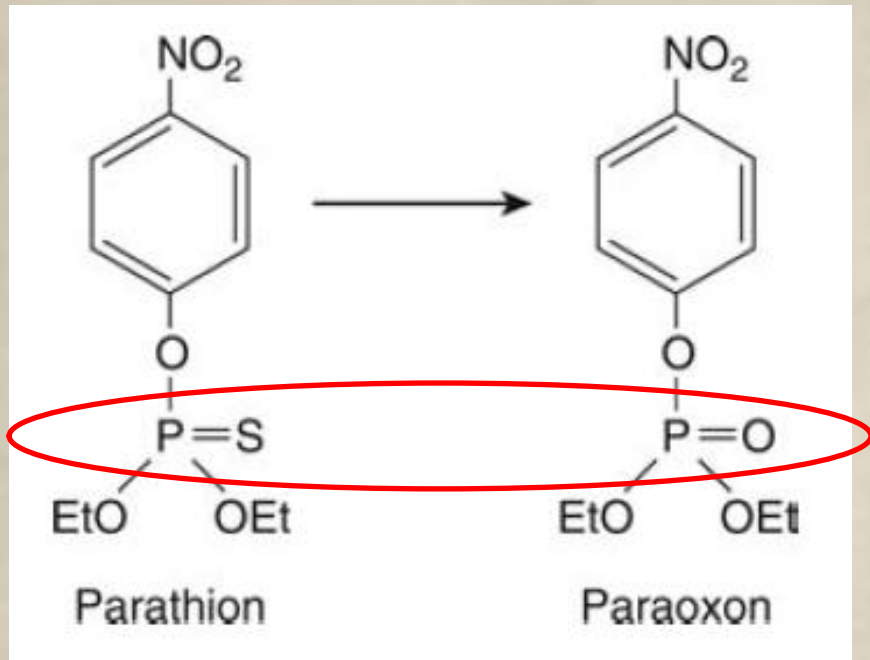


(biyoaktivasyon)





Oksidatif desülfürasyon



Parationun desülfürasyonu

(biyoaktivasyon)

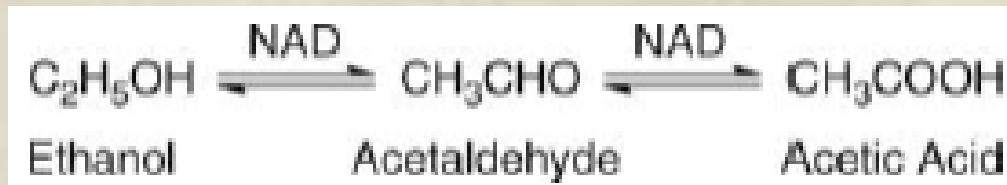
Mikrozomal olmayan oksidasyonlar

Alkol ve aldehitlerin oksidasyonu

Metanol → Formaldehit → Formik asit
(biyoaktivasyon)

Etanol → Asetaldehit → Asetik asit
(biyoaktivasyon)

Enzimler: Alkol dehidrojenaz ve Aldehit dehidrojenaz

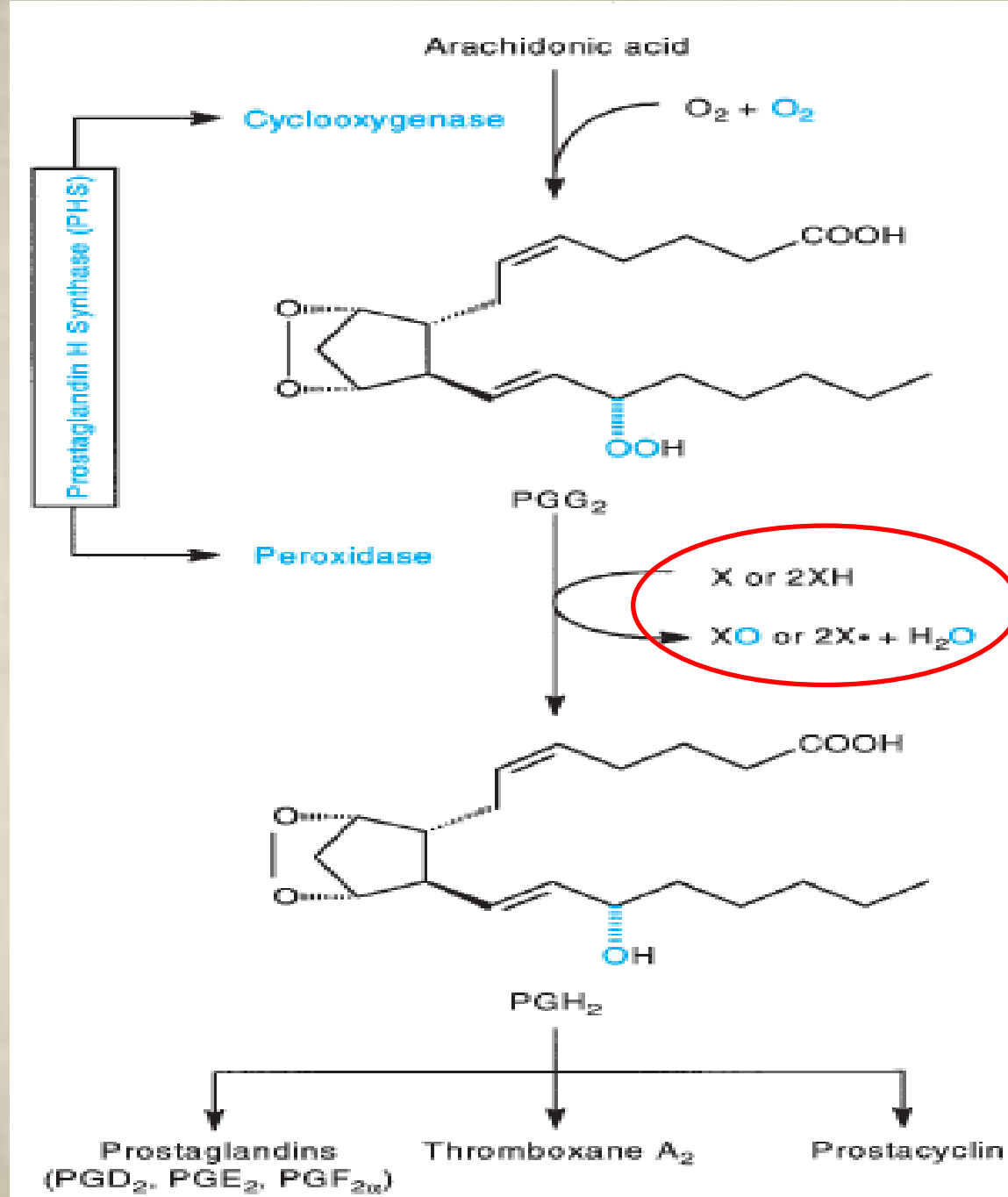


Peroksidazlar aracılığı ile gerçekleşen oksidasyonlar
Araşidonik asitten prostaglandin biyosentezi sırasında
ksenobiyotiklerin oksidasyonu (ko-oksidasyon)
(biyoaktivasyon)

**Enzimler: Prostaglandin sentaz (PHS; COX) (böbrek medullası, vasküler
endotel hücreleri, deri,
akciğer, mesane epiteli)**

Laktoperoksidaz (meme bezi epiteli)

Miyeloperoksidaz (lökositler)

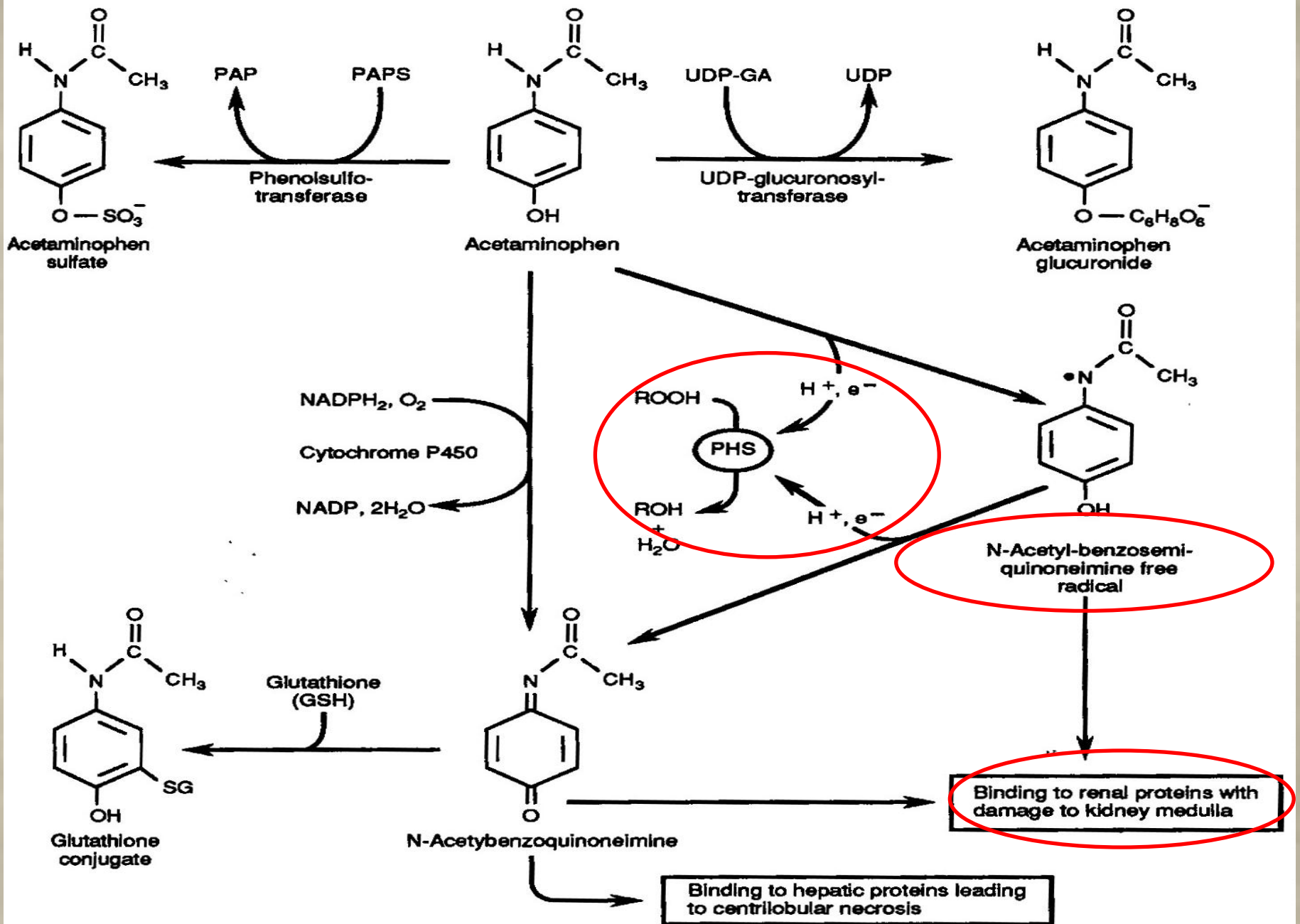


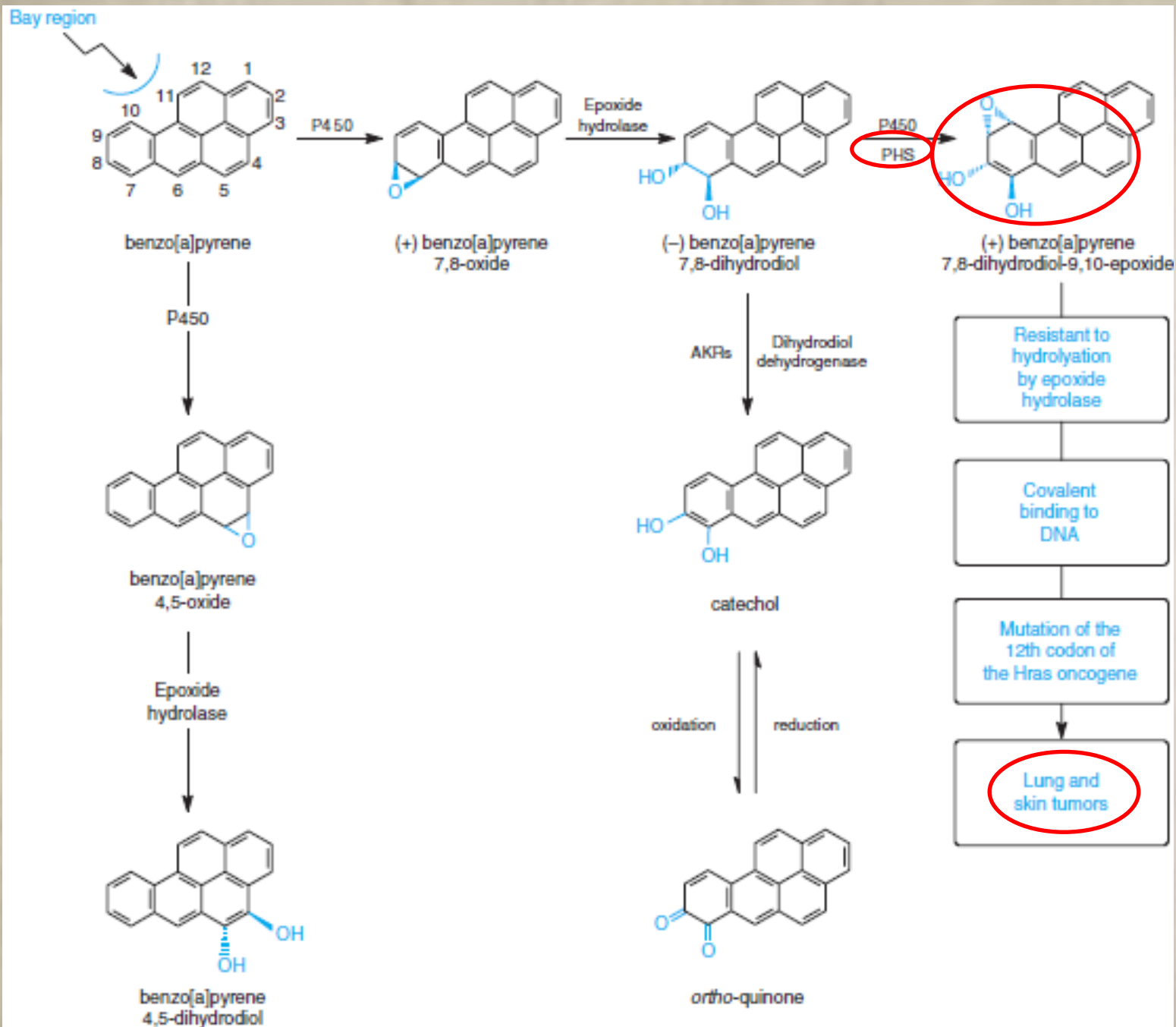
Kooksidasyona uğrayan maddelere örnek:

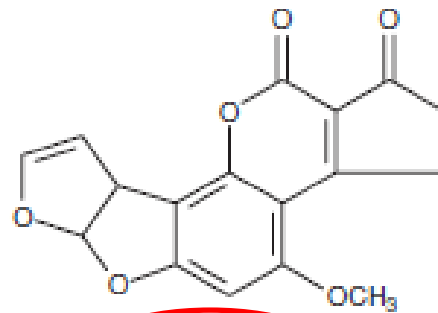
Benzopiren → Benzopiren-7,8-dihidrodiol-9,10-epoksit

Aflatoksin B1 → Aflatoksin B1 8,9-epoksit

Asetaminofen → N-asetil-benzosemikinonimin serbest radikali

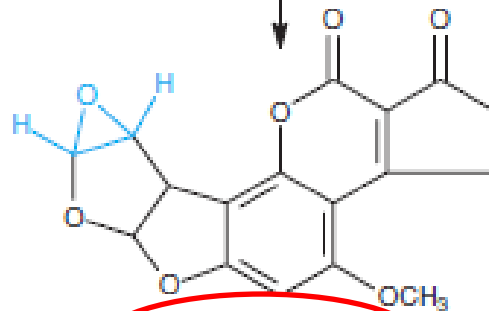






Aflatoxin B₁

Cytochrome P450 (Fe[O]³⁺)
Peroxidase or peroxy radical

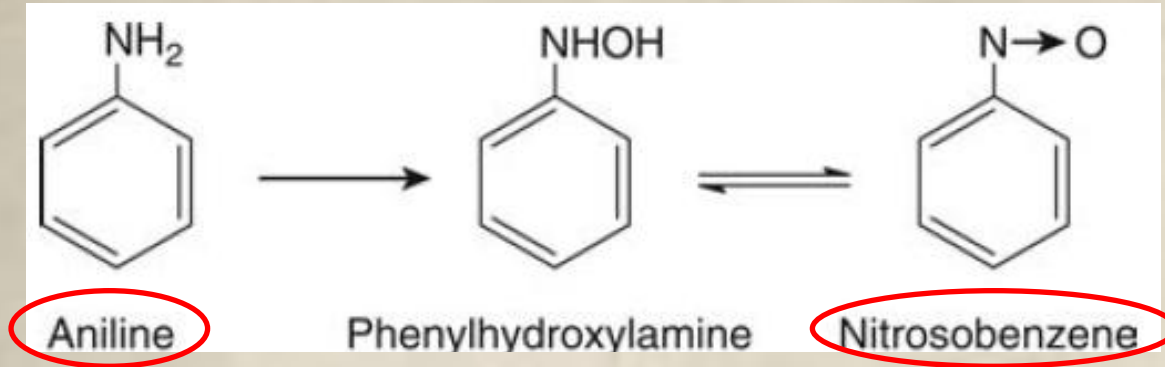


Aflatoxin B₁ 8,9-epoxide

Inactivation
by conjugation
with glutathione

DNA binding.
Liver tumors and
renal papilla neoplasia

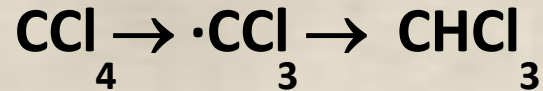
Primer ve sekonder aminlerin oksidasyonu



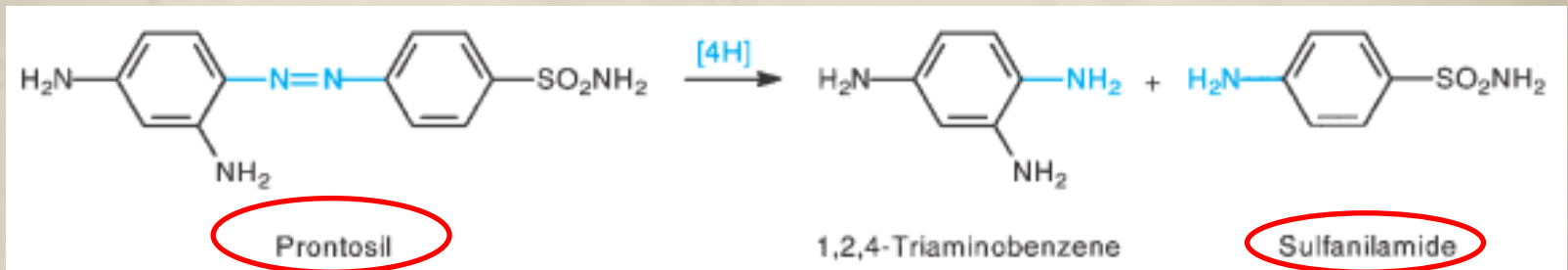
Enzim : MAO

Redüksiyon

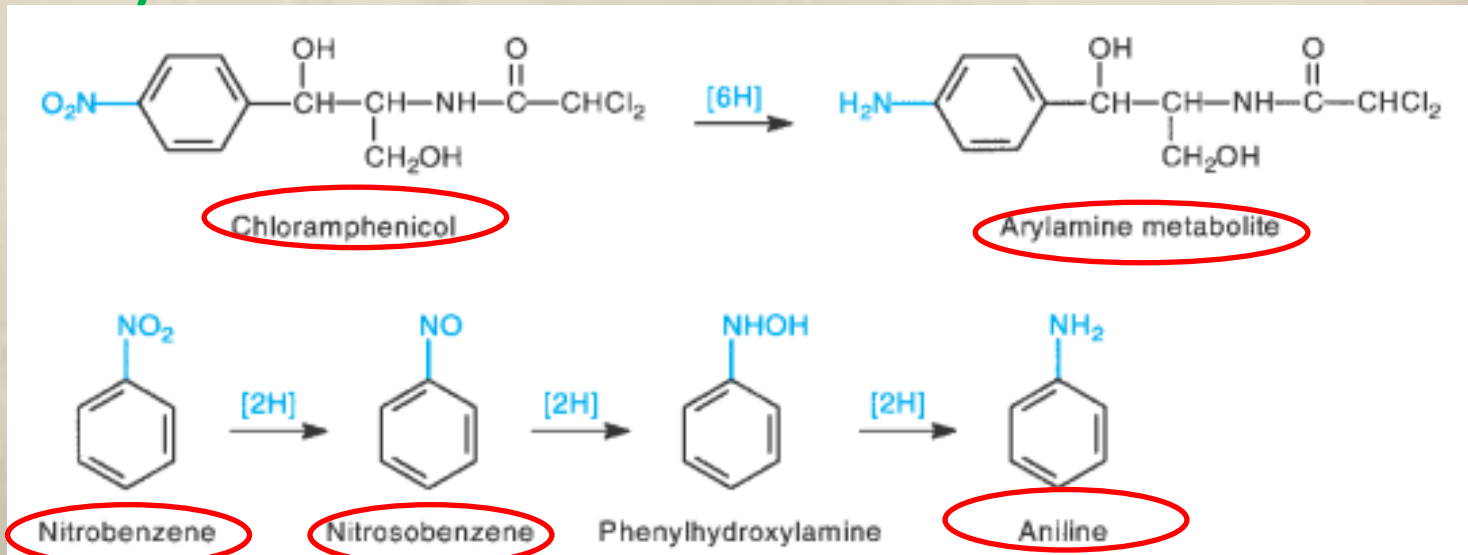
Redüktif dehalojenasyon

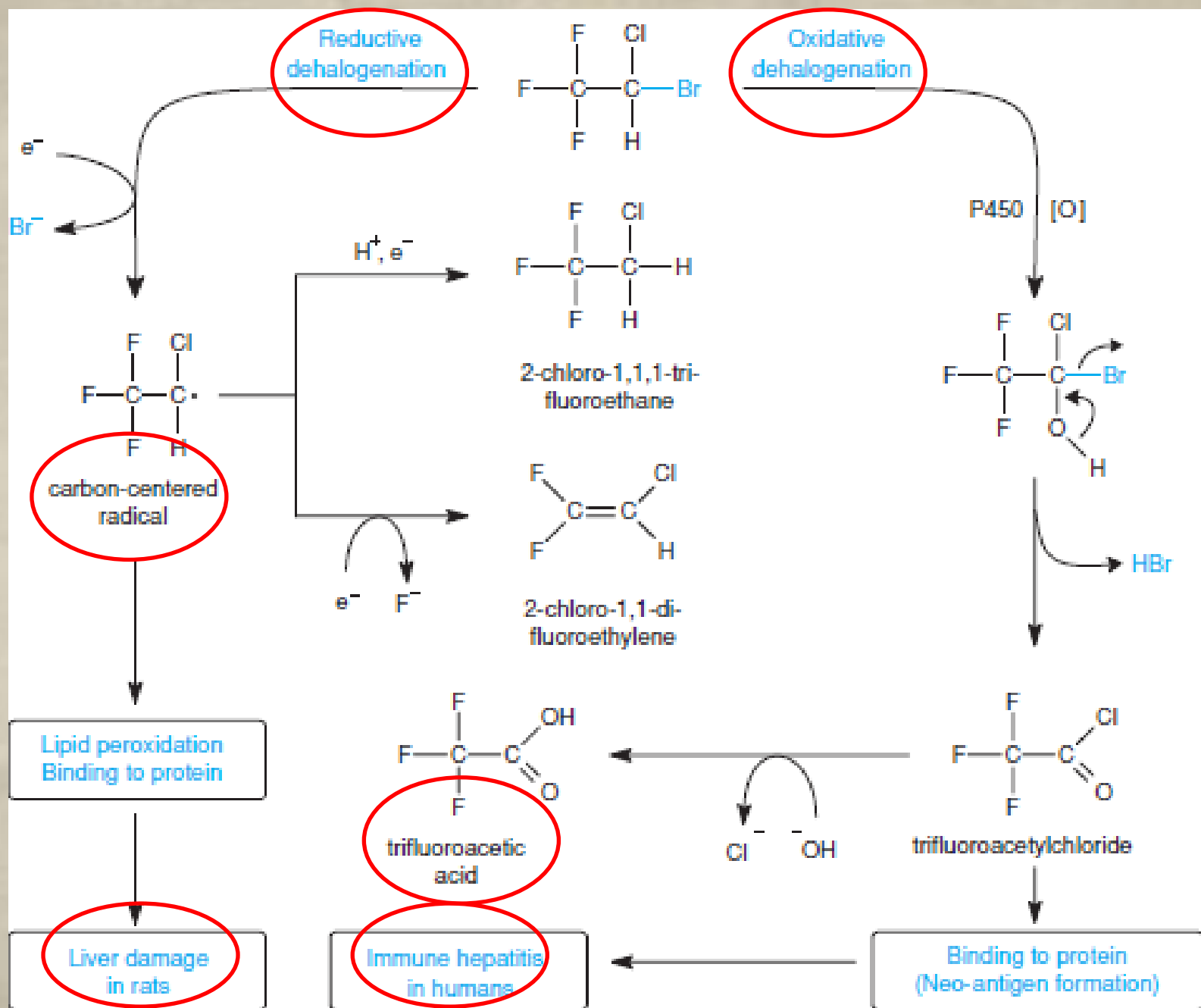


Azo redüksiyon



Nitro redüksiyon





Hidroliz

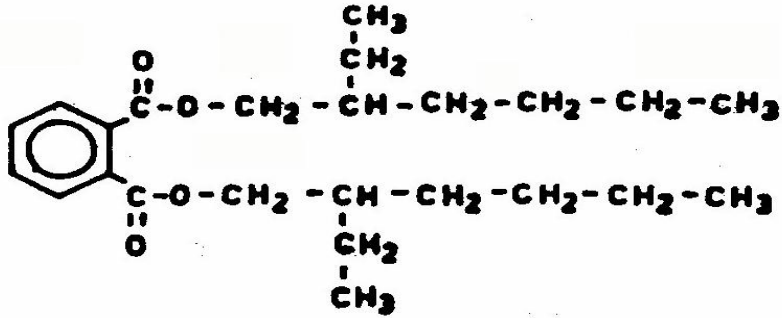
Ester hidrolizi (esterazlar)

Amid hidrolizi (amidazlar)

Glikozid hidrolizi (glikozidazlar)

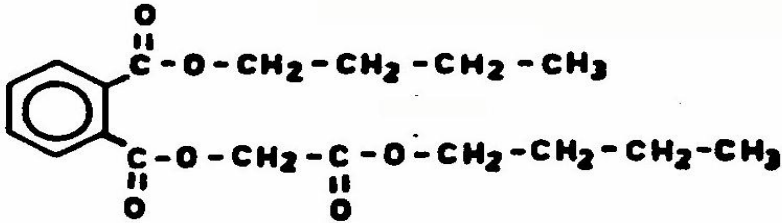
Arenoksit ve epoksit hidrolizi (epoksit hidrolazlar)

Ester hidrolizi



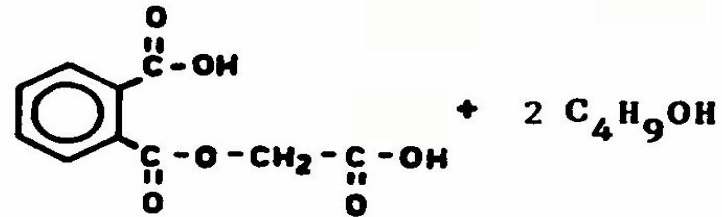
Diethylheksilftalat (DEHP)
yağda çözünür

Hidroliz olmaz,
yağ dokusunda birikir



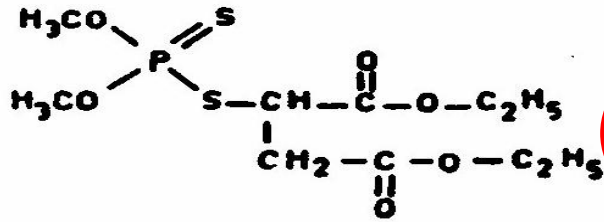
Butilftalilbutilglikolat (BGBP)
yağda çözünür

Hidroliz
(Karaciğer)



Suda çözünür, idrarla atılır

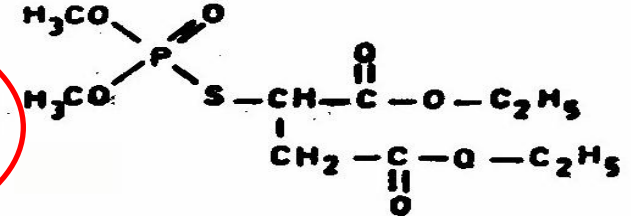
Plastik materyal yumuşatıcısı ftalat esterlerinin hidrolizi



Malatyon

Zayıf asetilkolinesteraz inhibitörü

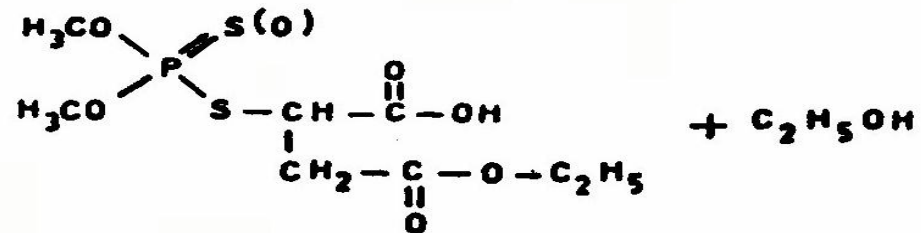
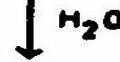
Oksidatif
biyoaktivasyon
(böcekler ve
memelilerde)



Malaokson

Kuvvetli asetilkolinesteraz inhibitörü

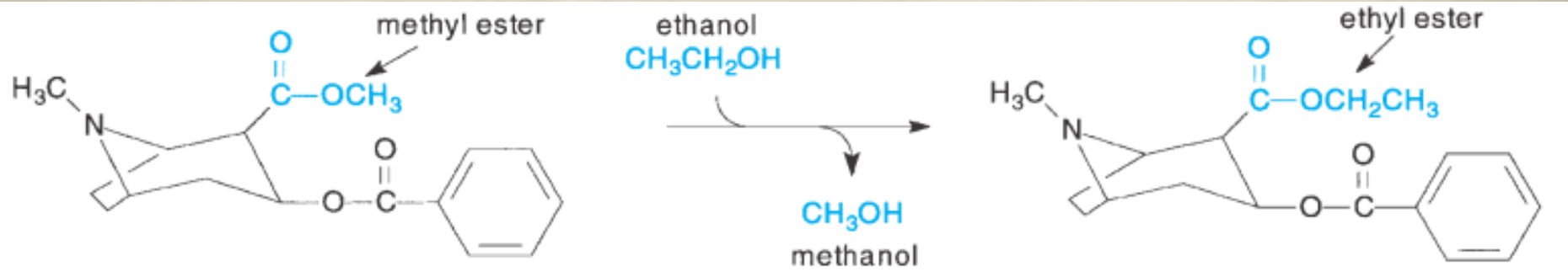
Hidrolitik biyo-
inaktivasyon
(memelilerde)



Malatyonik asid
inaktif

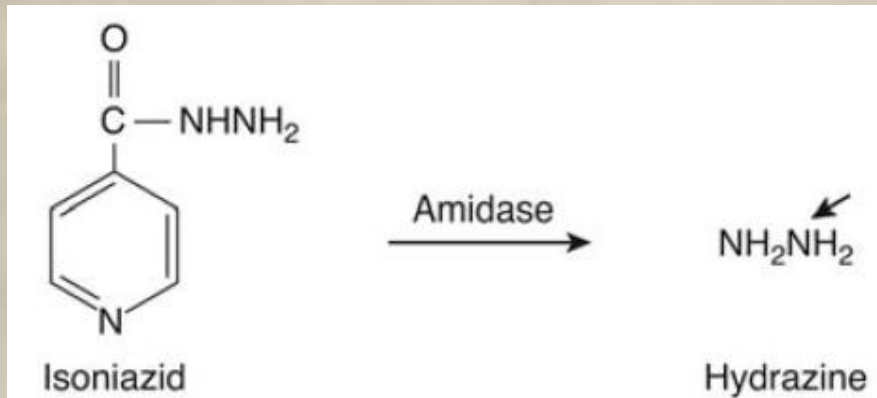
(Selektif toksisite)

Ester gruplarının değişimi (Karboksil esterazlar ile transesterifikasyon)

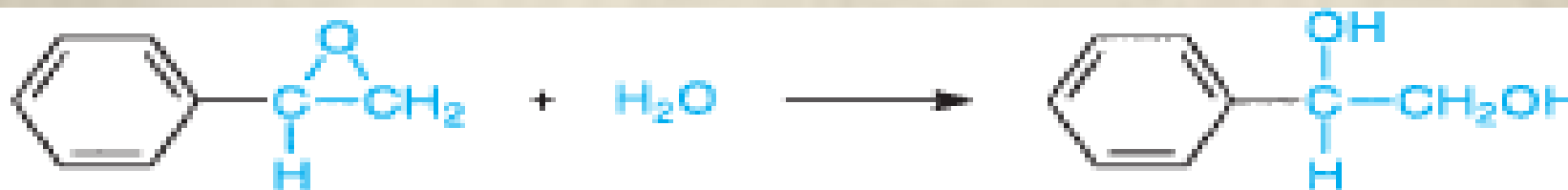
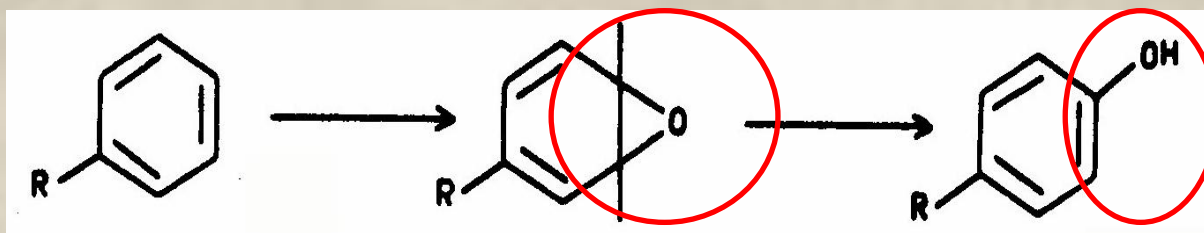


Kokain + alkol etilesteri (daha aktif ve lipofilik metabolit, hepatotoksik etki)

Amid hidrolizi



Epoksit hidrolizi



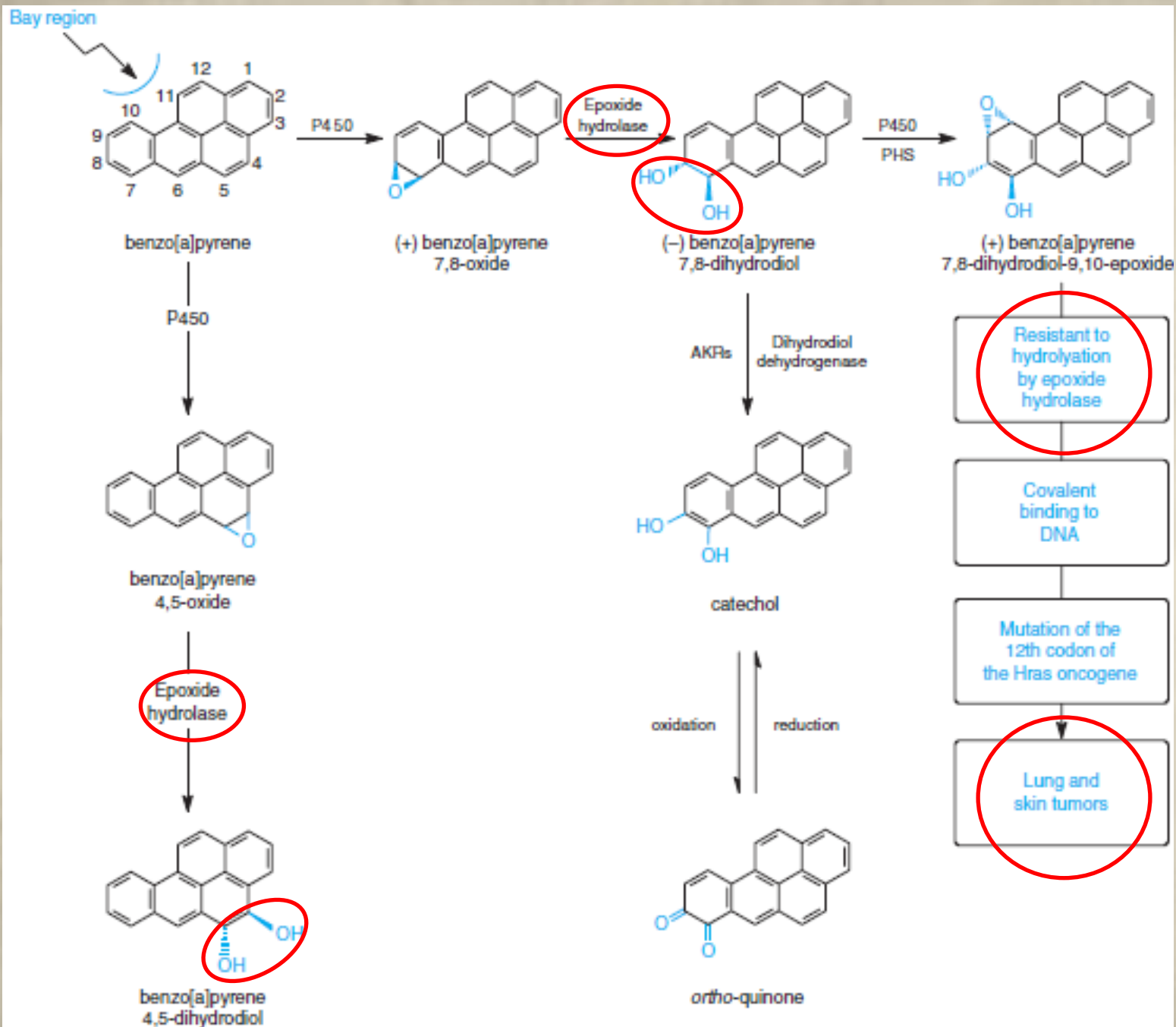
Styrene 7,8-epoxide

Styrene 7,8-glycol

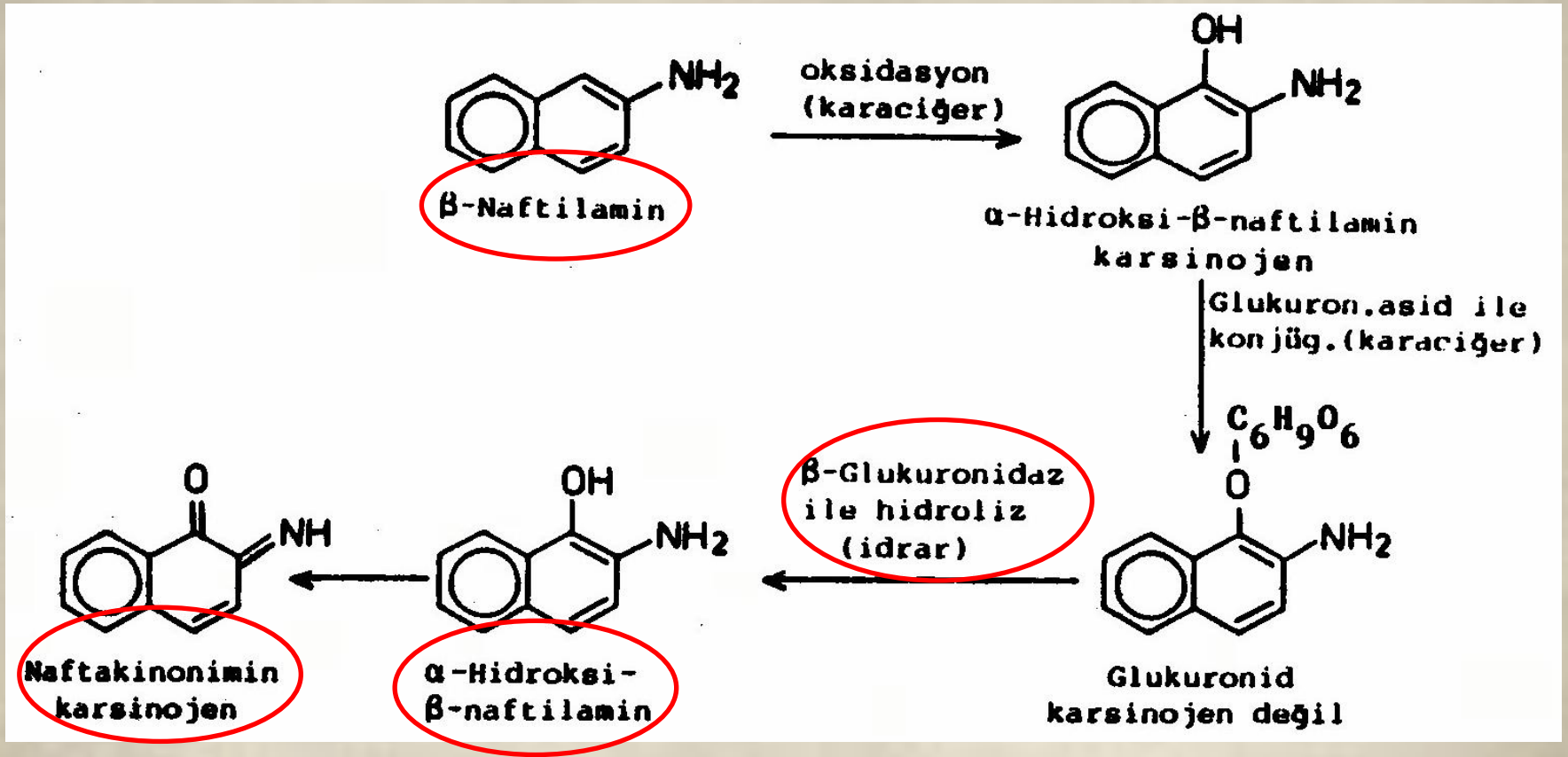


Naphthalene 1,2-oxide

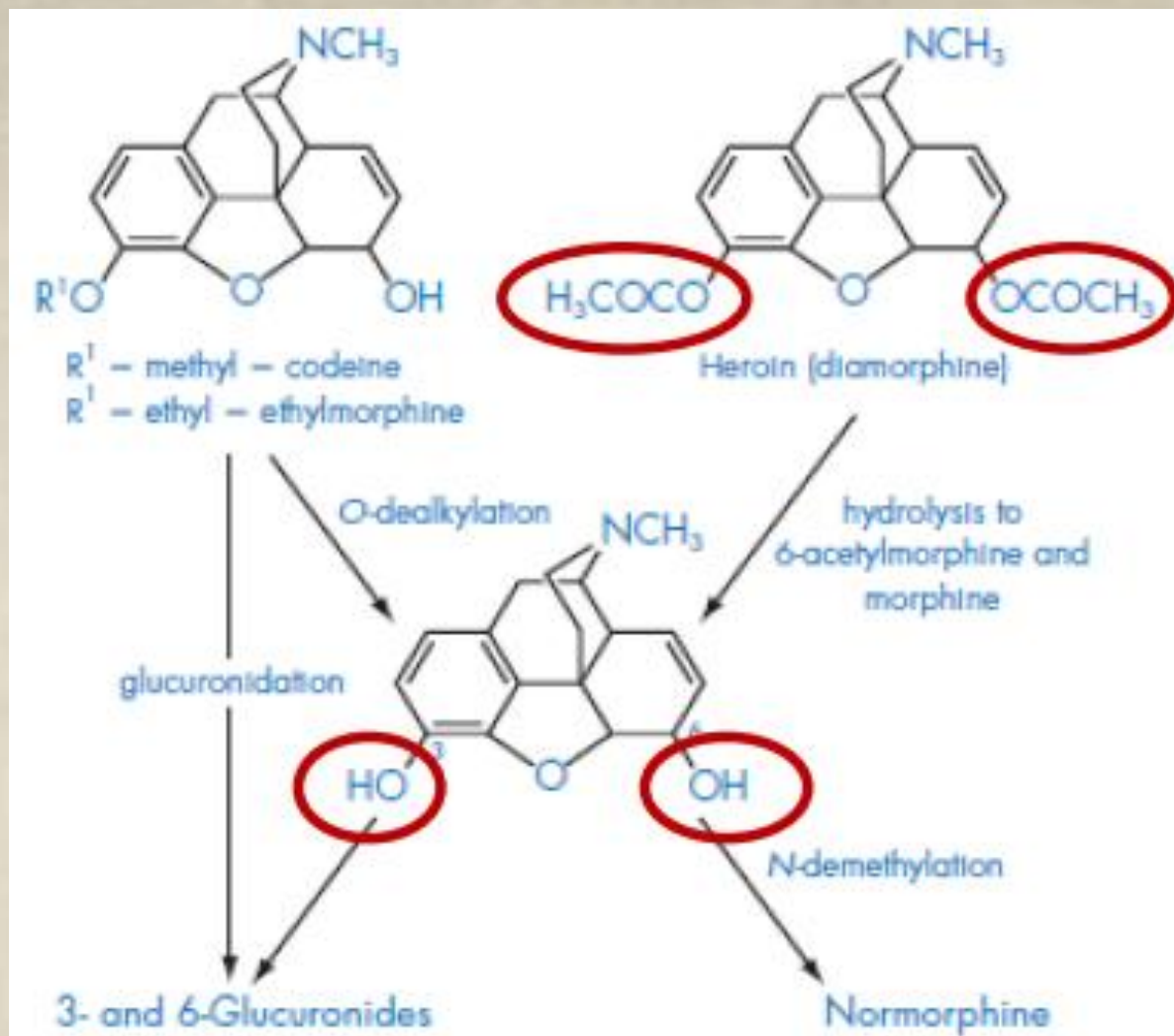
Naphthalene 1,2-dihydrodiol



Glikozid hidrolizi



β -naftilamin ve mesane kanseri oluşumu.



Morfin analoglarının metabolik yolağı

Biyotransformasyon reaksiyonları

Faz II

Glukuronik asit ile konjugasyon

Sulfat ile konjugasyon

Asetilasyon

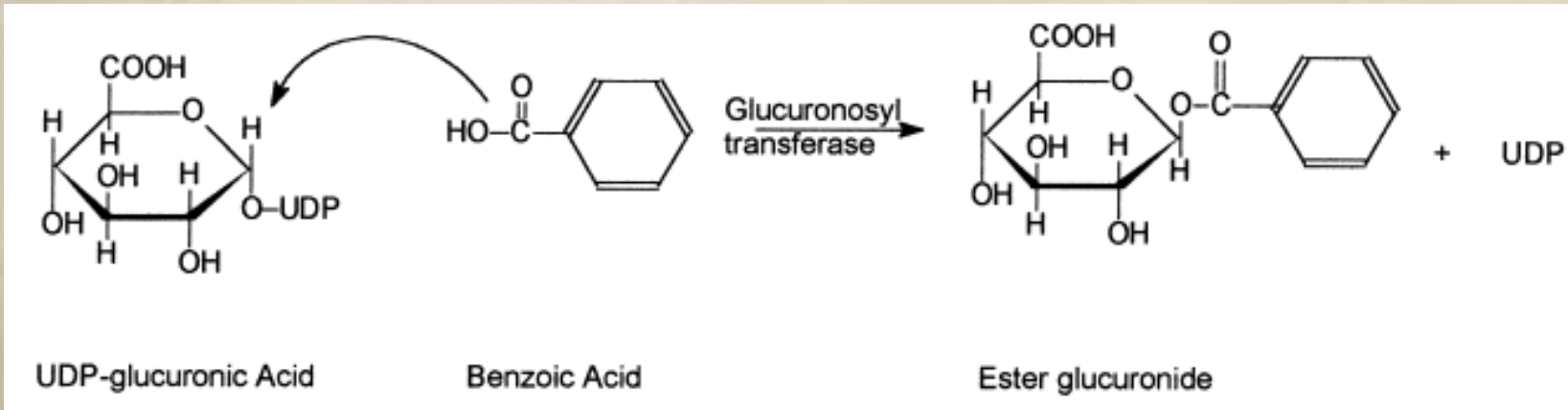
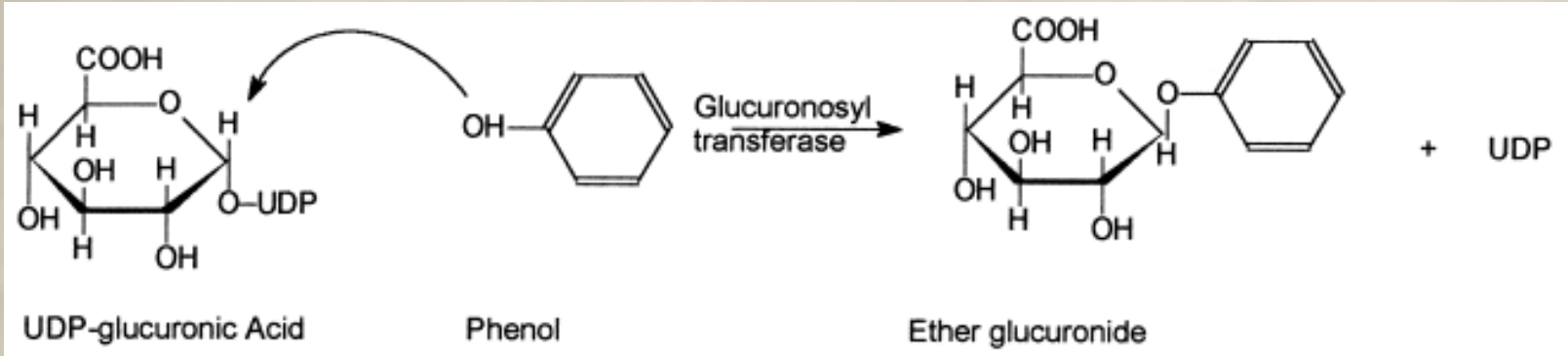
Metilasyon

Glutatyon ile konjugasyon (Merkaptürik asid sentezi)

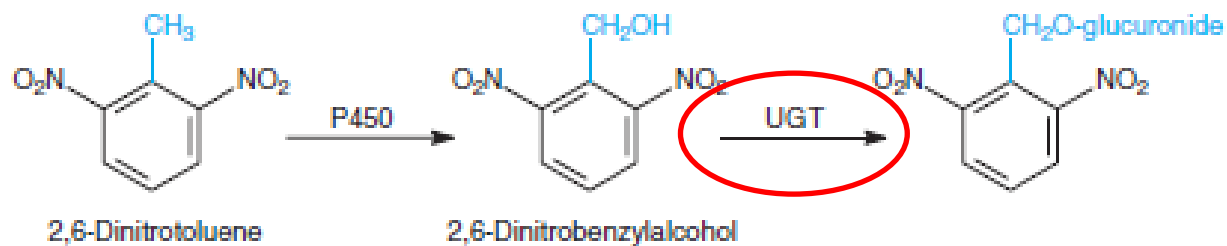
Amino asid ile konjugasyon (glisin, taurin, glutamik asid)

Glukuronik asit ve Sülfat konjugasyonu

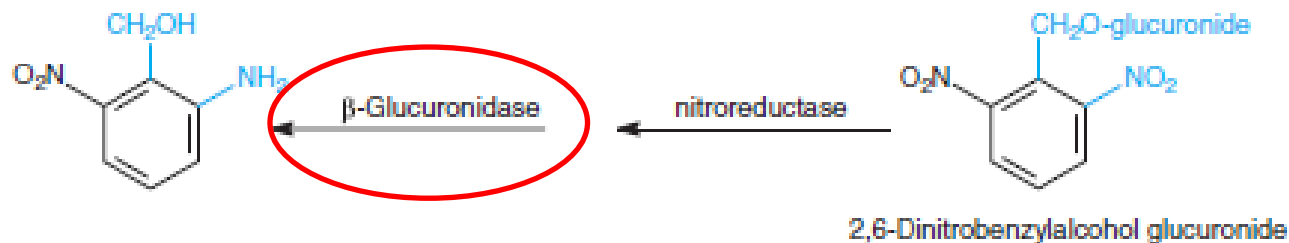
UDP-glukuronosiltransferazlar (UGT) ve Sulfotransferazlar (SULT)



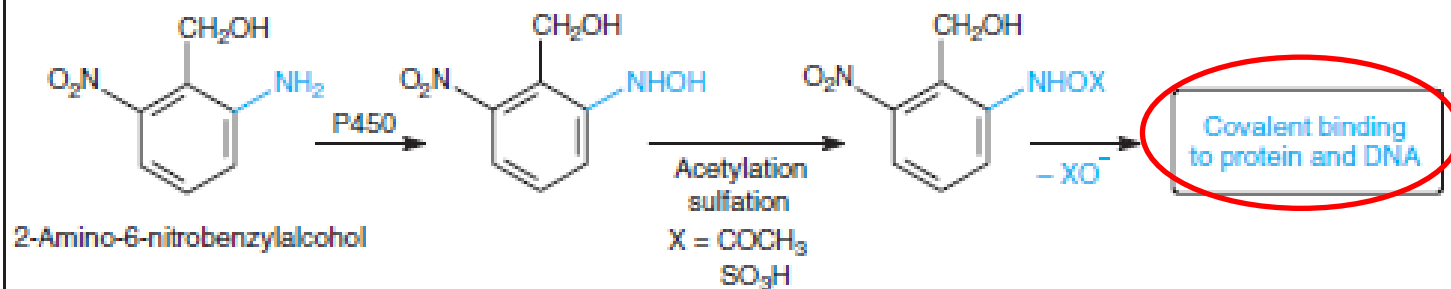
LIVER

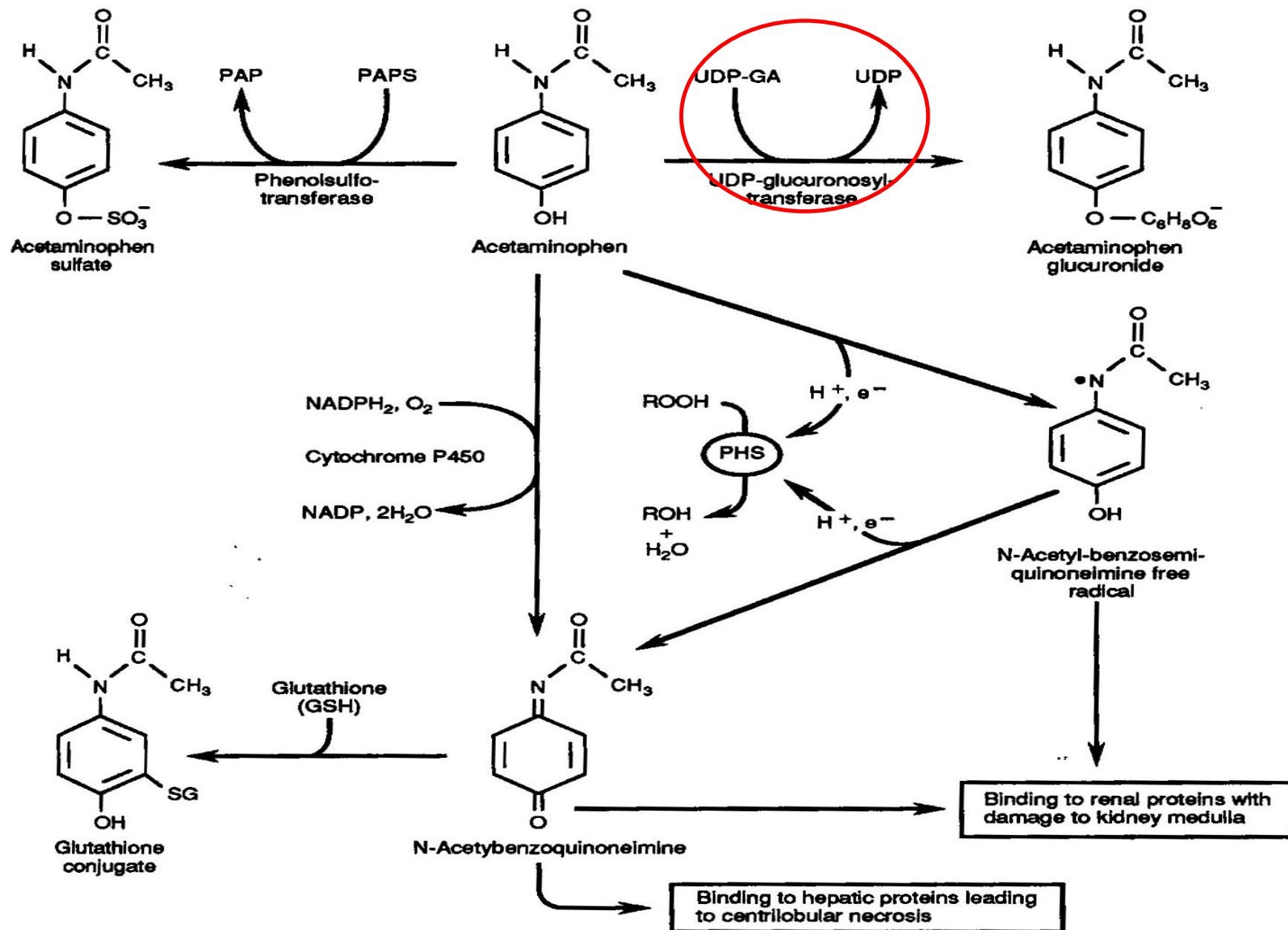


INTESTINE

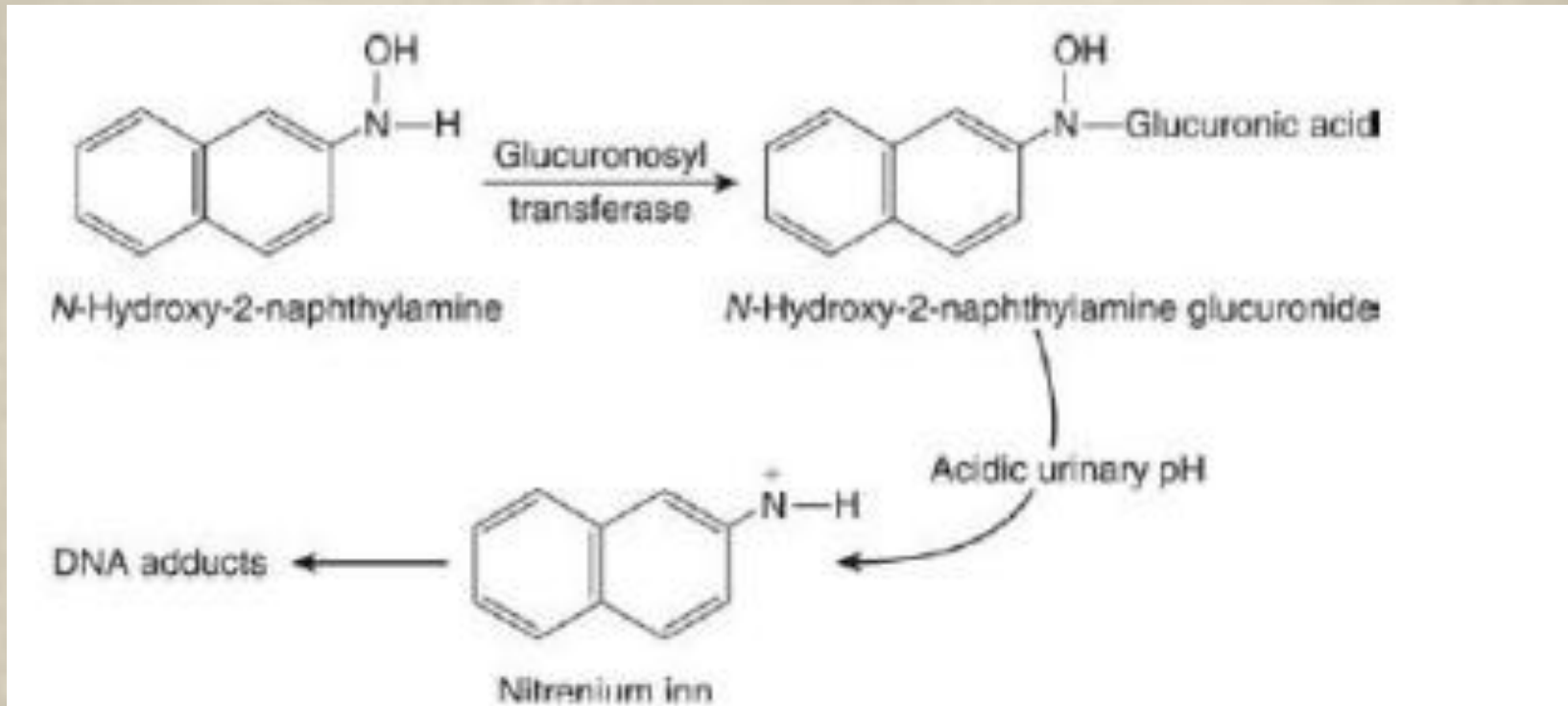


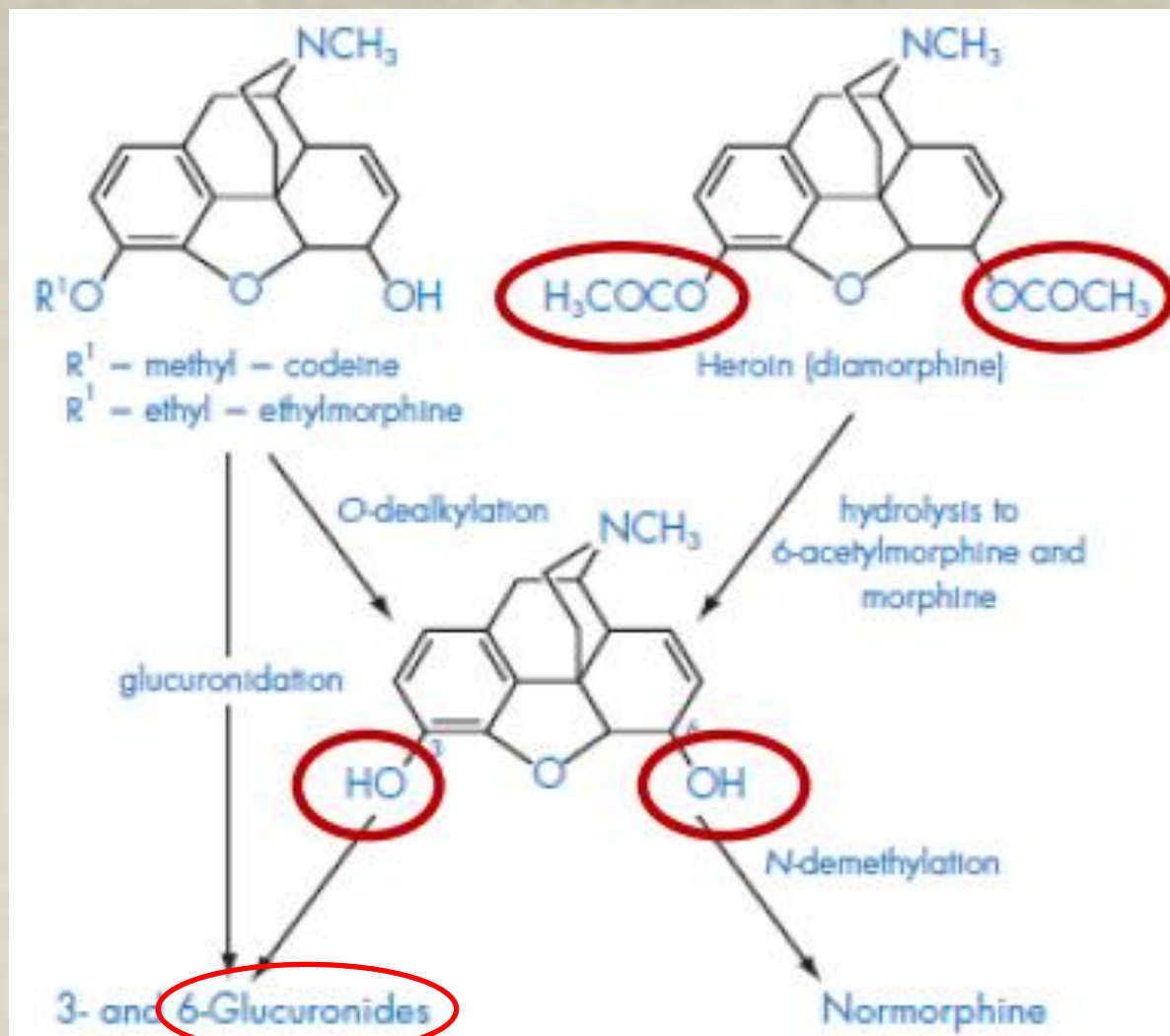
LIVER





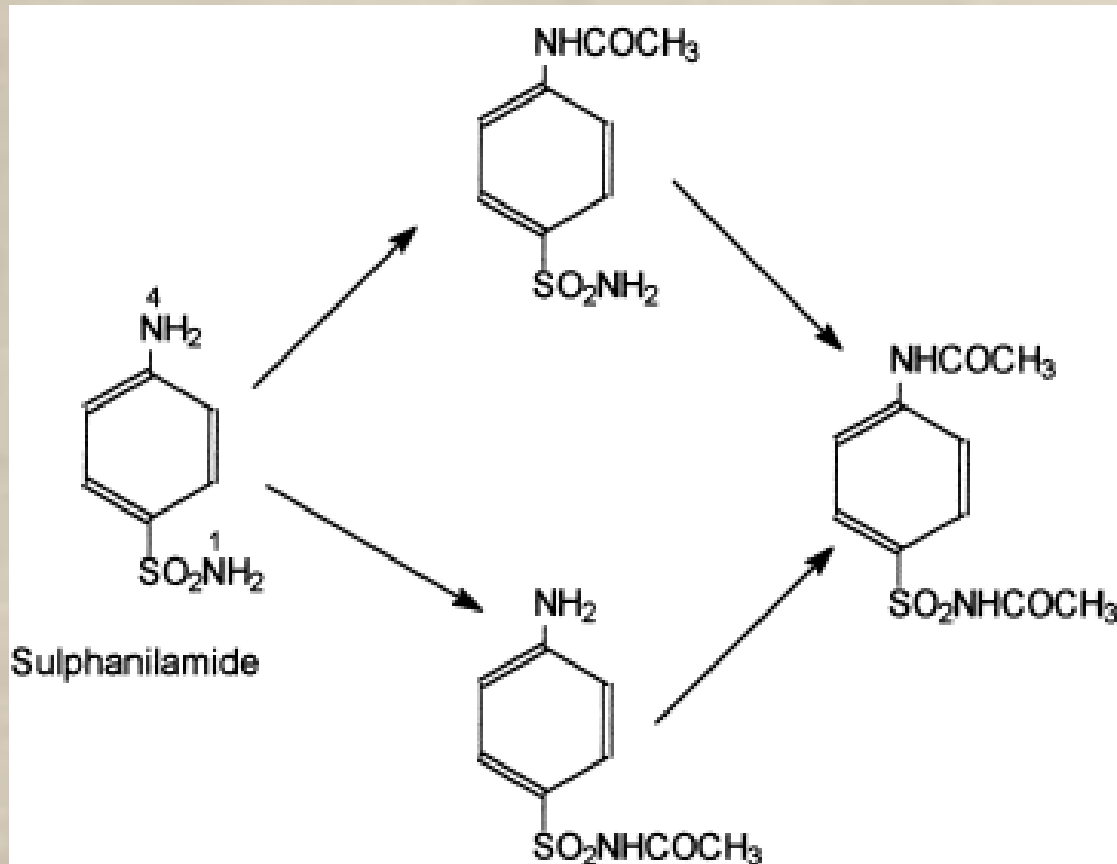
Mesane kanser oluşumunda glukuronik asit konjugasyonu oldukça önemli.





Morfin analoglarının metabolik yolağı

Asetilasyon



Sulfonamidlerin asetillenmesi (Biyoaktivasyon)
(Böbrek hasarı)

Metilasyon (!)



Elementlerin biyometilasyonu !!

Glutasyon (GSH) ile konjugasyon

Enzim : Glutasyon-S-transferaz (GST)

Reaktif elektrofillerin detoksikasyon reaksiyonu!

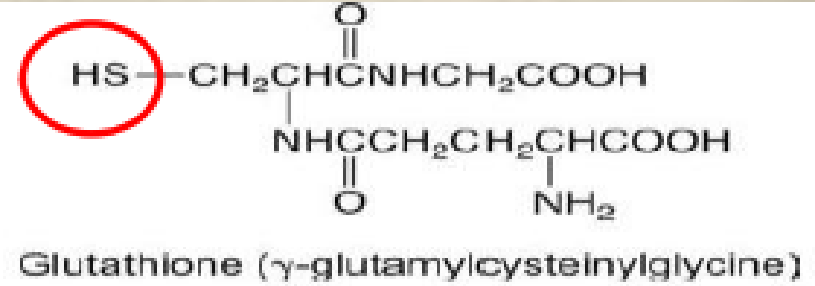
(Aromatik, alifatik, heterosiklik epoksitler, aril ve alkil halojenürler, aromatik nitro bileşikleri, doymamış alifatikler..)

GSH = glutamik asit + sistein + glisin

GSH, hücresel savunmada rol oynayan en önemli moleküllerden biri.

Karaciğerde konsantrasyonu yüksektir.

Aktif SH (nükleofilik!) grubu taşır.



Glutasyon ile konjügasyona girecek substrat:

- Hidrofobik olmalı.
- Elektrofilik bir atom içermeli.
- GSH ile non-enzimatik koşullarda reaksiyona girebilmeli.
- Glutasyon S-Transferazlar (GST) bu reaksiyonu hızlandırırlar.
- GSH miktarının azalması ! Proteince zayıf diyetler !

