Metabolism

- **Chemical transformaion of *xenobiotics***
- **Occurs in mostly in liver (enzymatic prosesses)**
- **Convertion into more hydrophil. subst. - excretion urine**
- **May convert procarciogenics into cytotox., muthagenic compounds**
- **Different persons may have differences in methabolism (genetic diff., physiol. factors)**
- **Methabolism of one xenobiotic may influence metab. of amother**

Xenobiotics

- **Drugs**
- **Other foreign non-essential compounds**

Metabolism in non-hepatic tissue

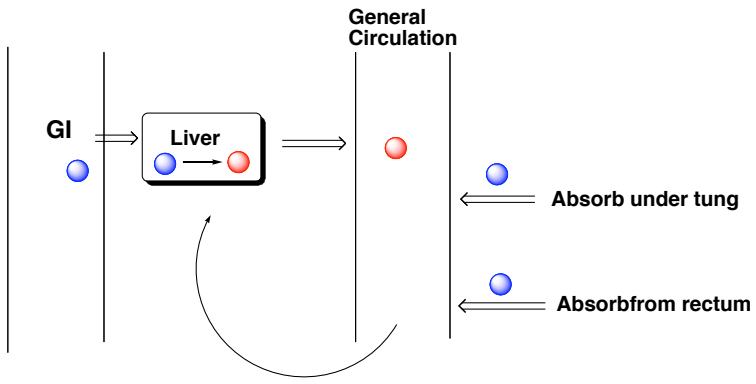
- **Intestine mucosa**
- **Kidney**
- **Lung**
- **Bacteria in GI-tract**

First-pass metabolism:
Xenobiotic metabolized before reaching general circulation

First-pass metabolism:
Xenobiotic metabolized before reaching general circulation

A) Metab. lungs (inhaled subst)
Intestine mucosa, GI bacteria

B)



Pathways of metabolism

Phase 1: Biotransformation

Attachment of new functional groups, transformation of exist. funct. groups oxidation, reduction, hydroxylation, hydrolysis etc.

Phase 2: Conjugation.

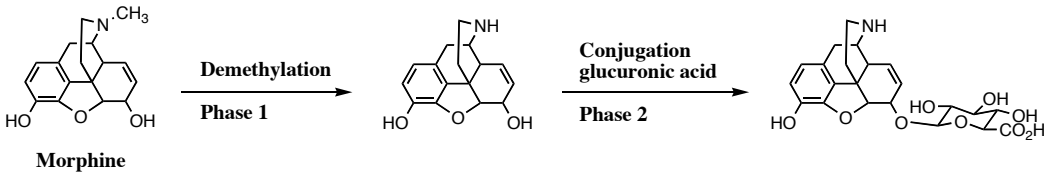
Masking of an exist. funct. group by for instance acetylation, glycosylation, attachment amino acid etc

⇓

More hydrophilic drug

⇓

Renal excretion

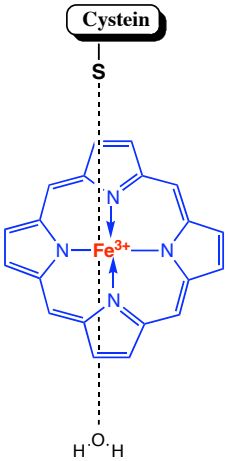


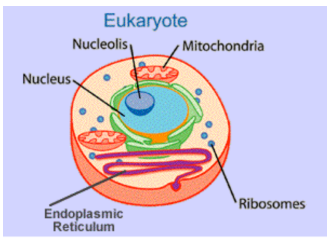
Morphine

Phase 1

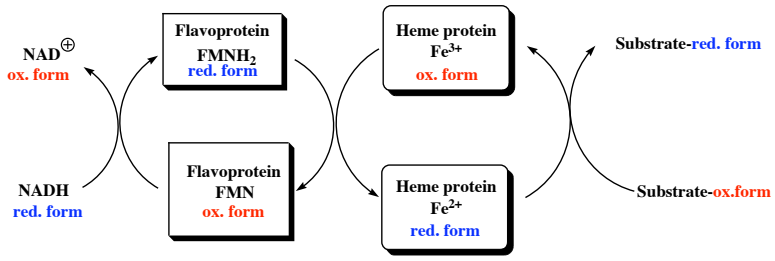
Metabolism by cytochrome P450 enzyme systhem (CYP450)

- **Located in endoplasmatic reticulum (liver and other cells)**
- **Electron transport systhem - oxidation, monooxygenase**
- **Heme protein + flavoprotein**
- **Capablee of oxidation - many differen xenobiotics**

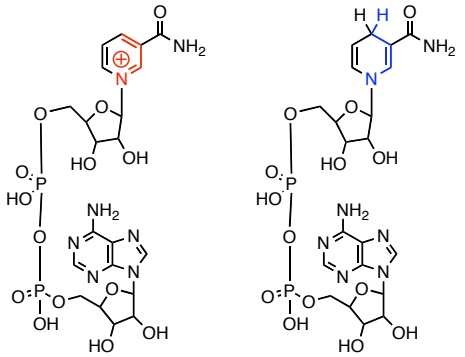




CHEMICAL REVIEWS
Volume 104, Issue 9 (September 8, 2004)
3947-3980 **Mechanism of Oxidation Reactions Catalyzed by Cytochrome P450 Enzymes**
Bernard Meunier, Samuël P. de Visser, and Sason Shaik
<http://dx.doi.org/10.1021/cr020443g>http://dx.doi.org/10.1021/cr020443g

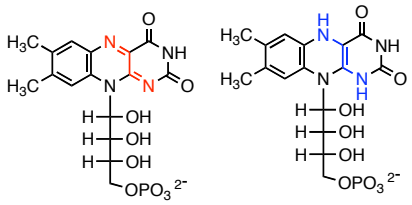


Nicotinamid adenine dinucleotide



NAD⊕ NADH

Flavin mononucleotide



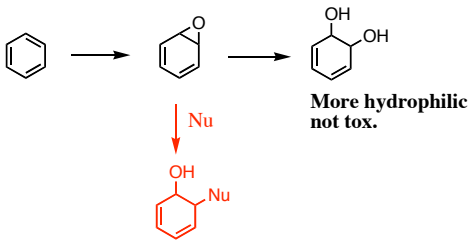
FMN $FMNH_2$

CYP450 families and sub-families

Family 1:

CYP1A1

Aromatic hydrocarbon hydroxylase, metabol. PAH etc.



More hydrophilic not tox.

CYP1A2

Ox of arylamines, nitrosamines, aromatic hydrocarbons

Family 2:

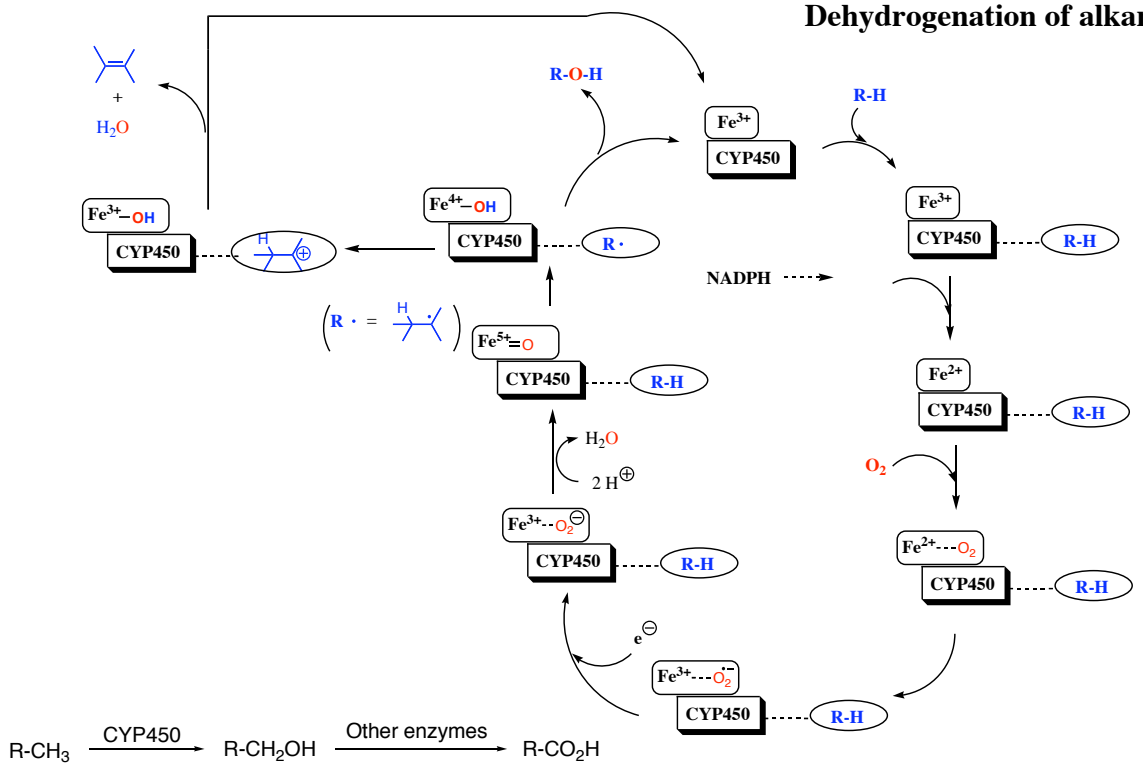
CYP2A6
CYP2B6
CYP2C
CYP2D6: Often enantioselective, lipophil. amines
CYP2E1: Halogenated hydrocarbons, other org solvents

Family 3:

CYP3A4

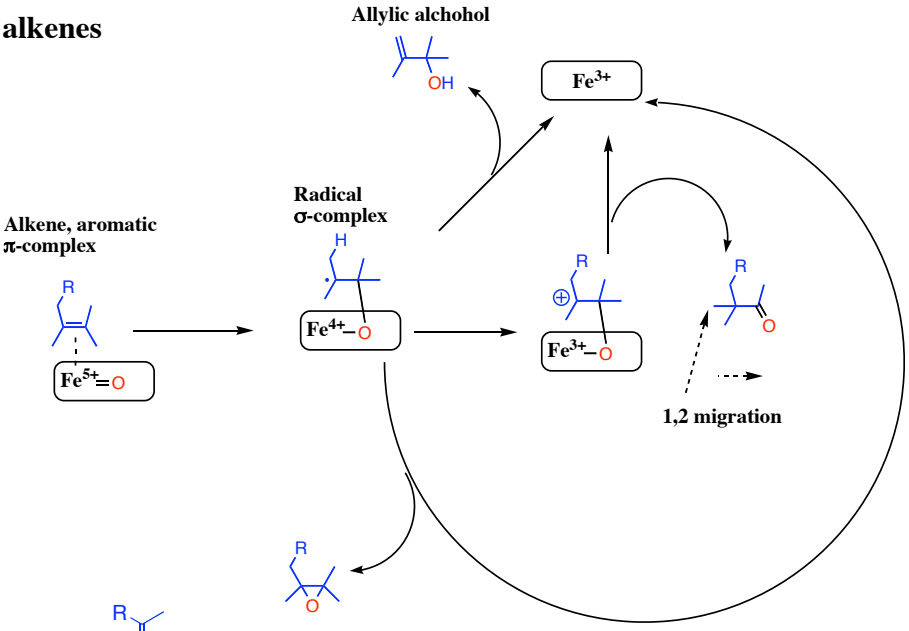
CYP450 / Mechanisms of metobolic transformations

Hydroxylation of alkane
Dehydrogenation of alkane

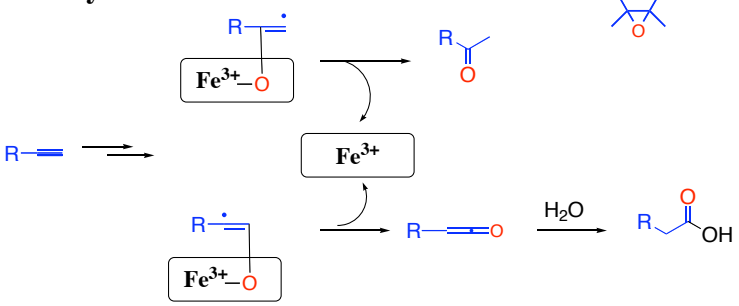


$R\text{-}CH_3 \xrightarrow{\text{CYP450}} R\text{-}CH_2OH \xrightarrow{\text{Other enzymes}} R\text{-}CO_2H$

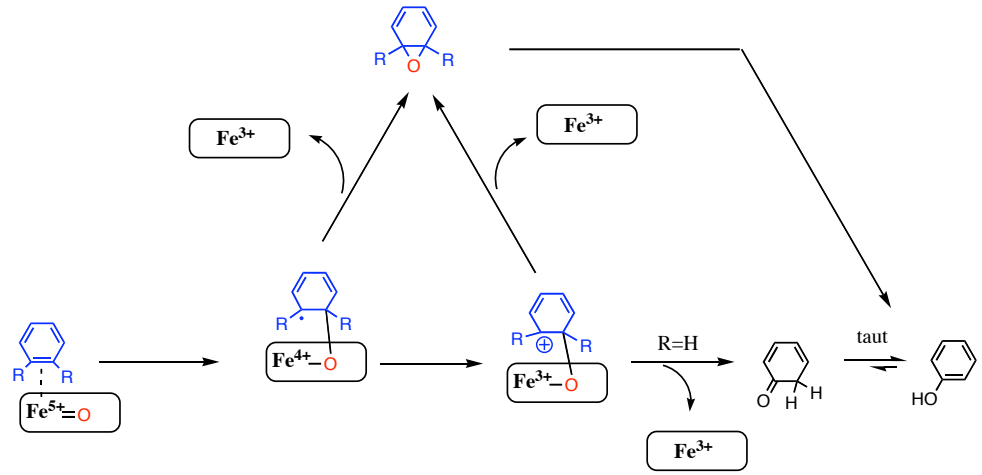
Proposed mech. ox of alkenes



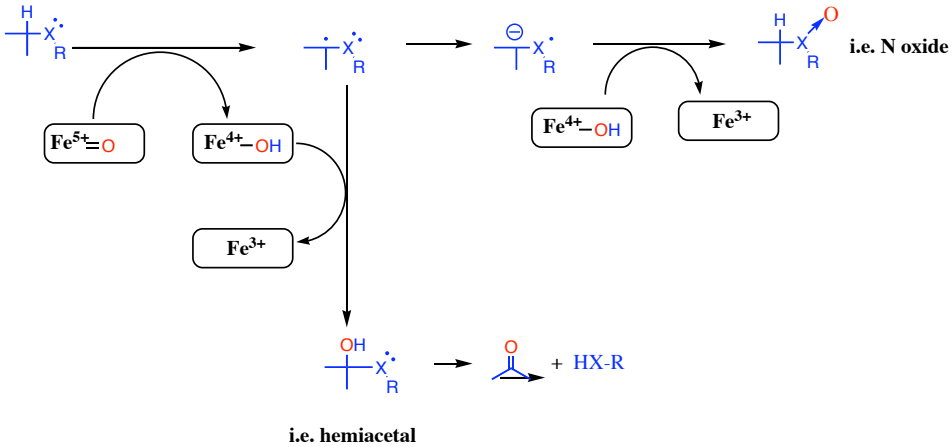
alkynes



Proposed mech. ox of aromatics



Proposed mech. react. on heteroatom cont. compounds

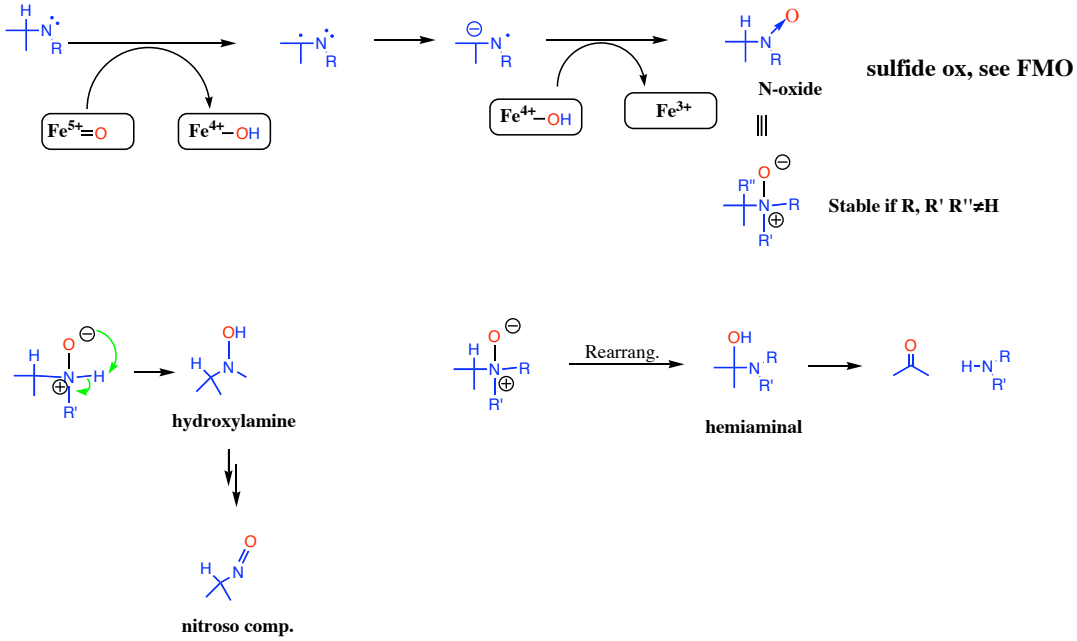


i.e. hemiacetal

N, O, S dealkylation
cleav. of small alkylgroups (Me)

Dehalogenation: HX + carbonyl comp.

Proposed mech. react. on heteroatom cont. compounds

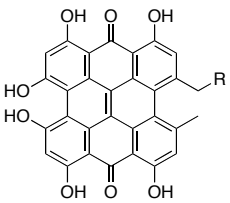


CYP450 Induction / inhibition by xenobiotics

Xenobiotics may enhance metabol. of them selvs as well as other comp. taken at the same time
Induce transcript CYP450 mRNA - Synth. CYP450 enzymes (enzyme induction)

- **Drugs**
- **Ethanol**
- **Organic solvents**
- **Components in cig. smoke**

St. Johns Worth
(Johannesurt, prikkperikum)

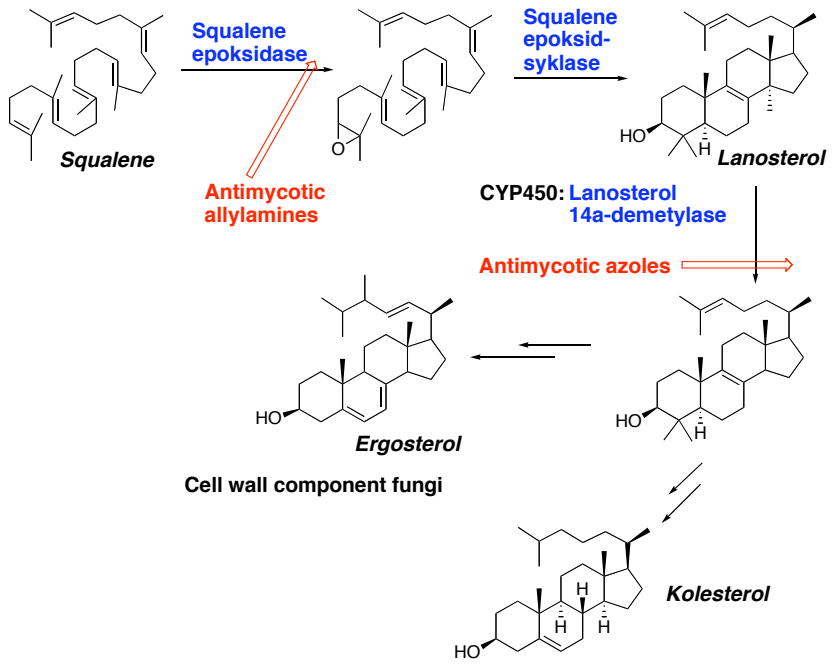


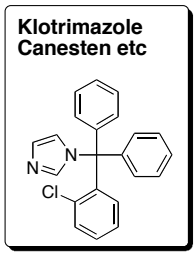
R=H:
Hypericin

R=OH
Pseudohypericin

CYP450 Inhibitors

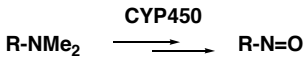
Reversible CYP enzyme inhibitors: Several drugs
ex. antimycotic azoles





CYP450 Inhibitors

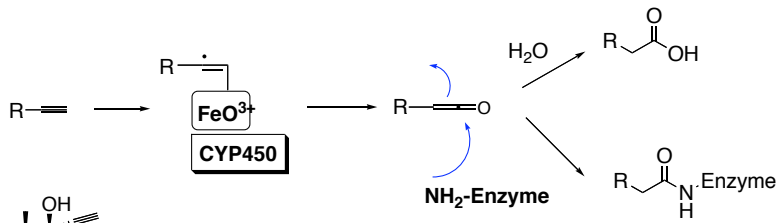
Complexation inhibitors
ex. metabolites from alkylamines

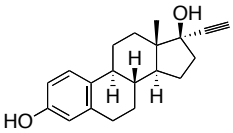


Alkylamine
No inhib. activity

Nitrosoalkane
Irreversible complexation with Fe(II) heme in CYP sub families

Mechanism based inhibitors (suicide inhib)
ex. alkynes



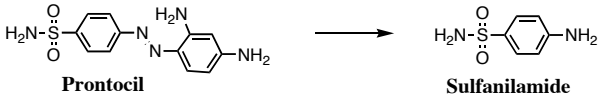


Ethynyl estradiol

Phase 1 react. not involving CYP450

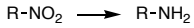
Other microsomal enzymes

Azoreductase



Prontocil **Sulfanilamide**

Nitroreductase



Flavinmonooxygenase-FMO (N and S-ox.)

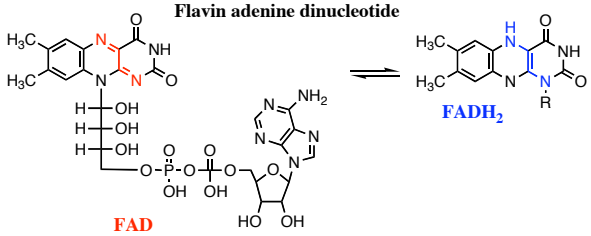
Peroxidases

microsome: Artefactual spherical particle, not present in the living cell,
derived from pieces of the endoplasmic reticulum present in homogenates of tissues or cells:
microsomes sediment from such homogenates when centrifuged at *100 000 g* and higher:
the microsomal fraction obtained in this way is often used as a source of mono-oxygenase enzymes.

Flavinmonooxygenase-FMO

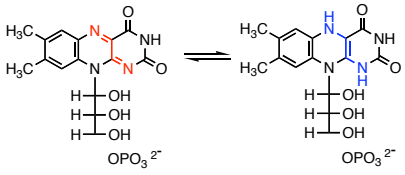
Cont. FAD

Flavin adenine dinucleotide



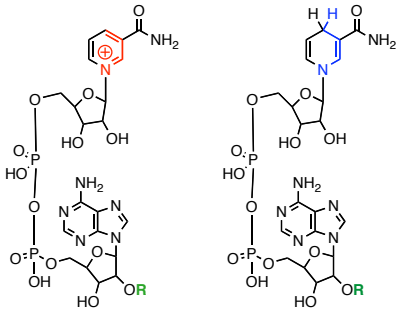
FAD **$FADH_2$**

Flavin mononucleotide



FMN **$FMNH_2$**

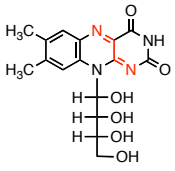
Nicotinamid adenine dinucleotide

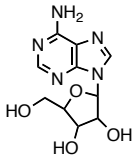


R=H **NAD⊕** **NADH**

R=Phosphate: $NADP^+$, NADPH

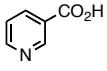
Riboflavin (Vit B2)





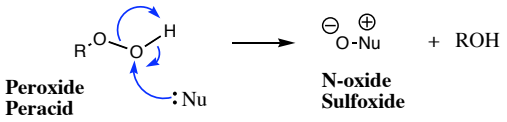
Adenine (Vit. B4)

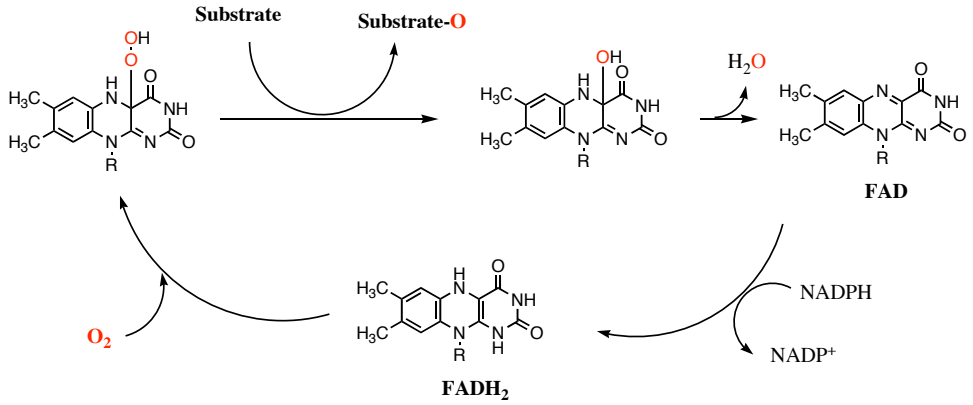
Nicotinic acid / Niacin (Vit. B3)



Flavinmonooxygenase-FMO

Ox of soft Nu

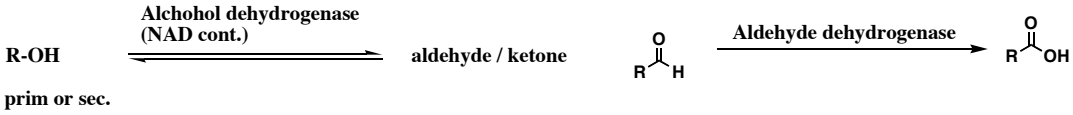


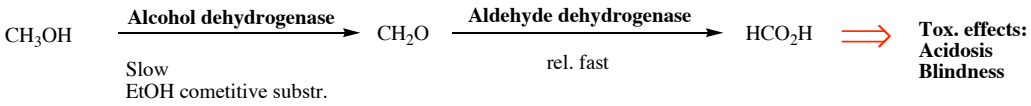


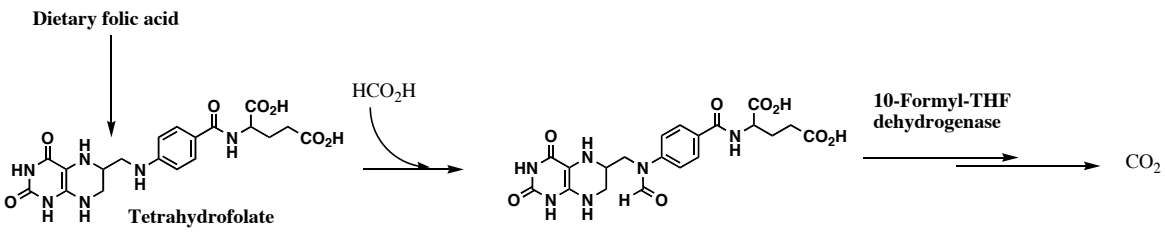
- **Amine: ox. to N-oxide / hydroxylamine**
- **Sulfide: ox to sulfoxide , furter to sulfone**
- **Thiol:** R-SH → R-S-S-R → R-S(=O)-S-R

Non-microsomal enzymes

- **Enzymes in mitokondria**
- **Enzymes in soubile tissue fractions**







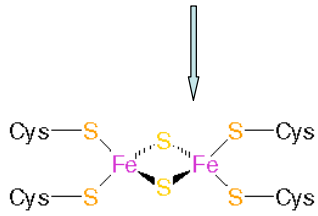
Non-microsomal enzymes (Phase 1)

Molybdenum Hydroxylases

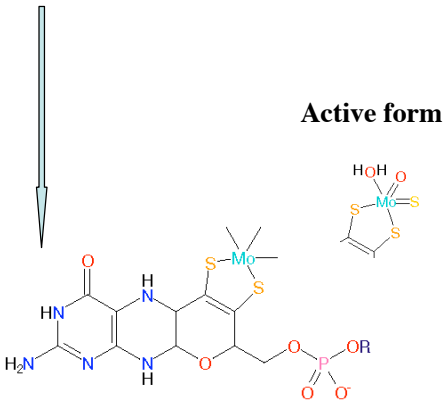
- **Aldehyde oxidase**
- **Xantine oxidase**
- **Xantine dehydrogenase**

Cont. Mo in cat. site
Cont FAD and 2 Fe/s clusters
Use H_2O not O_2

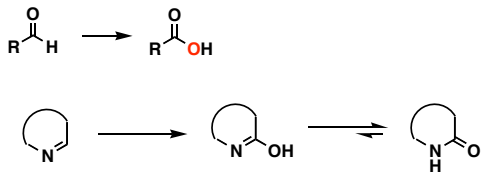
Xanthine oxidase
Electron transfer: FAD - Fe2S2ˇI - Fe2S2ˇII - Moco - Substrate



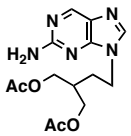
Active form



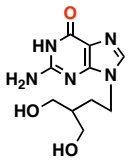
•Aldehyde oxidase



Aza heterocycle



Aldehyde oxidase
Esterase / hydrolysis



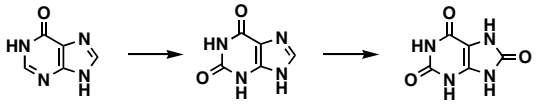
Famciclovir
Antiviral (Herpes etc)
Pro-drug

Penciclovir

- **Xantine oxidase**
- **Xantine dehydrogenase**

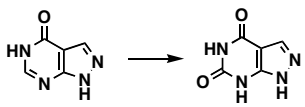
} **xanthine oxidoreductase**

(requires NAD^+)



Hypoxanthine **Xanthine** **Uric acid**

Treatment of gout (podagra)



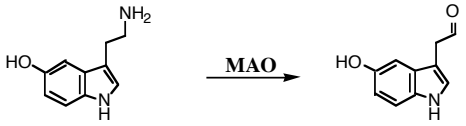
Allopurinol **Alloxanthine**
Inhib. enzyme

Non-microsomal enzymes (Phase 1)

Oxidative deamination of amines

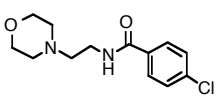
- **•Monoamine oxidase (MAO)**
- **•Diamine oxidase (DAO)**

$$R\text{-}CH_2\text{-}NH_2 + O_2 \longrightarrow [R\text{-}CH{=}NH] \longrightarrow R\text{-}CHO + NH_4^+$$



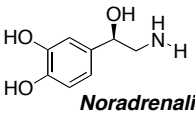
Serotonin
5-Hydroksotryptamin (5-HT)

Serotonine:
- **•Neurotransmittor; temp. control, mood**
- **•Depresion: Low serotonine activity**
- **•MAO Inhibitors - Older antidepresants (low selectivity)**

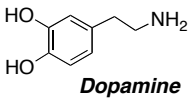


Moklobemid
Aurorix® Moklobemid®

Other MAO substrates:

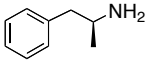


Noradrenaline



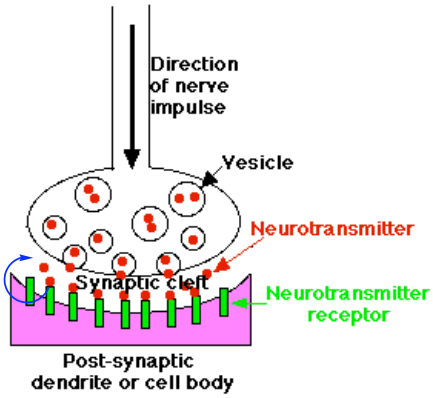
Dopamine

Not MAO substrates (subst at α-C):



(S)-amfetamin

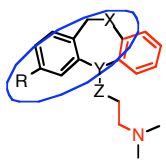
Low dopamine conc. ≈ Parkinston



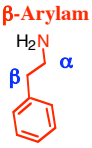
Active transport re-uptake transmittor (not Acetylcholine)

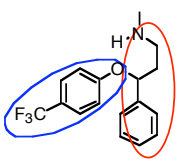
Non-selective monoamine re-uptake inhib.
Tricyclic antidepressants

SSRI (selective serotonine re-uptake inhib.)
"Lykkepiller" Prozac etc (Fontex)



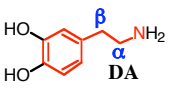
≈ β-Arylamin



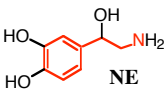


Stor gruppe / sterisk hinding
Hindrer reopptak

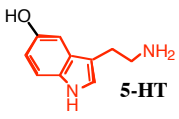
β-Arylaminer



DA



NE



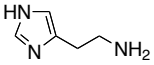
5-HT

Non-microsomal enzymes (Phase 1)

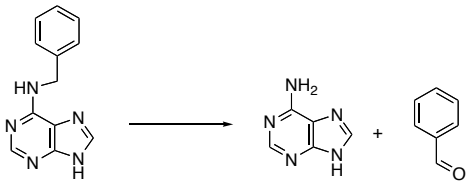
Oxidative deamination of amines

- **Monoamine oxidase (MAO)**
- **Diamine oxidase (DAO)**

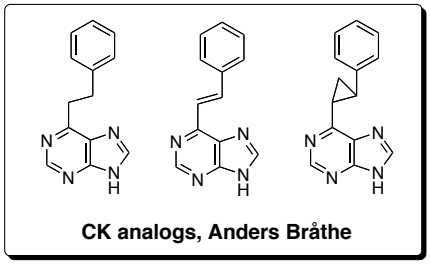
Oxidize diamines, histamine



MAO like enzymes in plants



BAP
CYtokinin (Plant growth hormone)

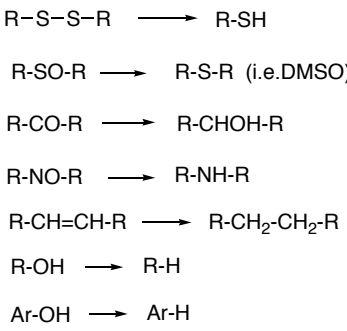


CK analogs, Anders Bråthe

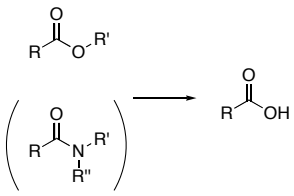
Non-microsomal enzymes (Phase 1)

Miscellaneous react.

Reductions

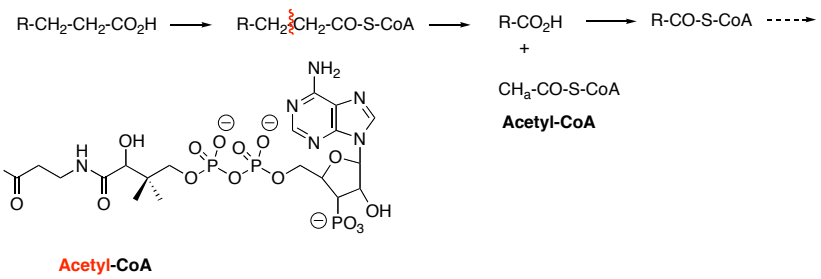


Hydrolysis - Esterases



Esters as pro-drugs

β-Oxidation



Acetyl-CoA

Pathways of metabolism

Phase 1: Biotransformation

Attachment of new functional groups, transformation of exist. funct. groups oxidation, reduction, hydroxylation, hydrolysis etc.

Phase 2: Conjugation.

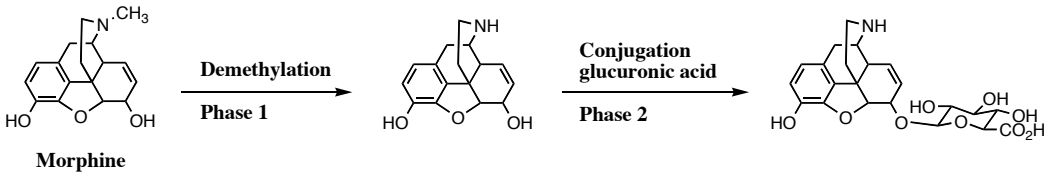
Masking of an exist. funct. group by for instance acetylation, glycosylation, attachment amino acid etc

⇓

More hydrophilic drug

⇓

Renal excretion



Morphine

Phase 2: Conjugation

Most comp. excreted as cojugates, ionic, hydrophilic groups added, most common glucuronation

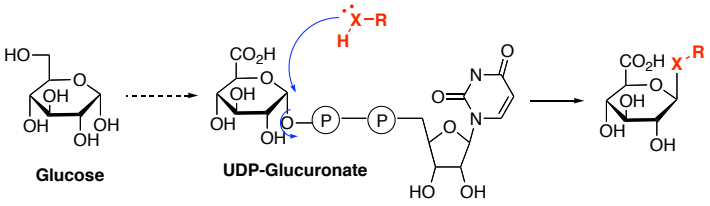
- **Glucuronic acid conjugation**
- **Sulfate conjugation**
- **Conjugation with amino acids**
- **Acetylation**
- **Glutathione conjugation**
- **Methylation**

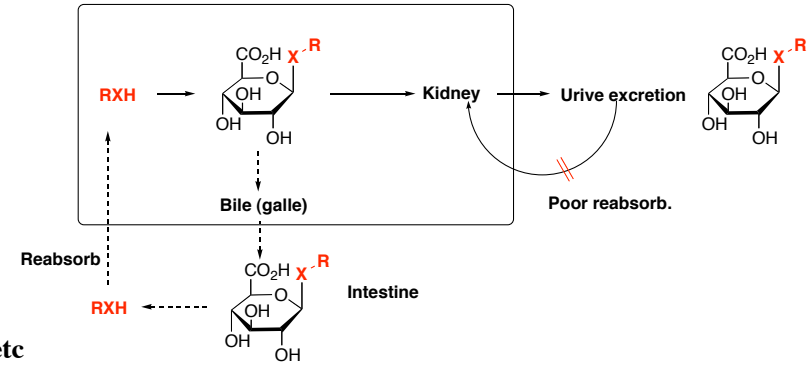
Phase 2: Conjugation

•Glucuronic acid conjugation

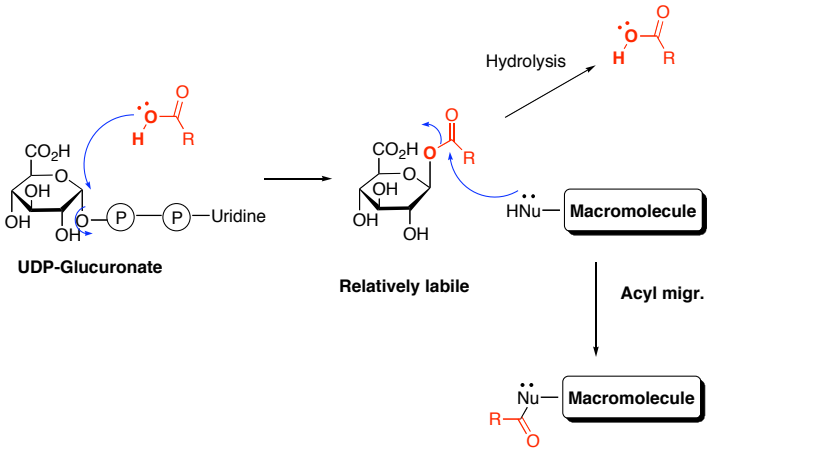
Substrates: **RXH: Xenobiotic / Phase 1 metabolite**

- **•Alchohols**
- **•Phenols**
- **•Amines**
- **•Sulfides**
- **•Carboxylic acids**
- **•1,3-Dicarbonyls**



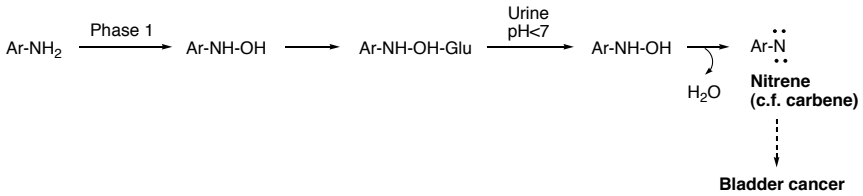


Entro-hepatic recycling
Important for many hormones etc



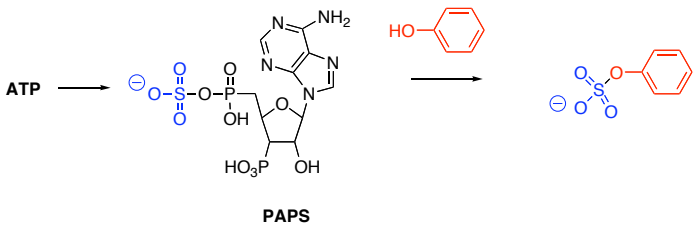
Altered protein (hapten)
Unwanted immune responce / allergic react.

ex. NSAIDs

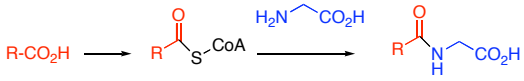


Phase 2: Conjugation

•Sulfate conjugation: Phenols, (alcohols, N-compounds)



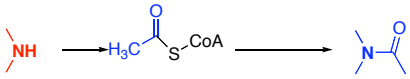
•Conjugation with amino acids (Most ofthen Gly): Carboxylic acids



No tox. conjugates known

Phase 2: Conjugation

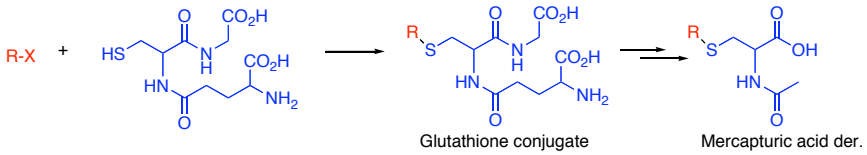
•Acetylation: N-compounds

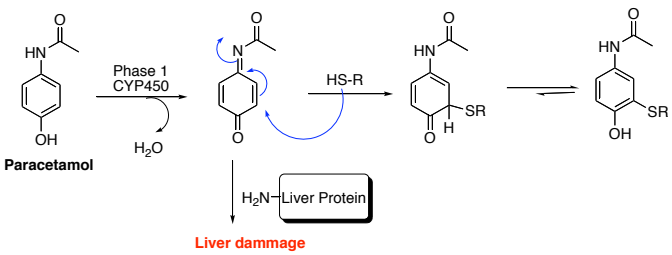


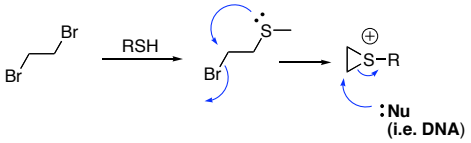
•Glutathione conjugation: Electrophilic species

- **•Alkylhalides**
- **•Epoxides**
- **•Michael acceptors etc**

} **may otherwise alkylate biomolecules**







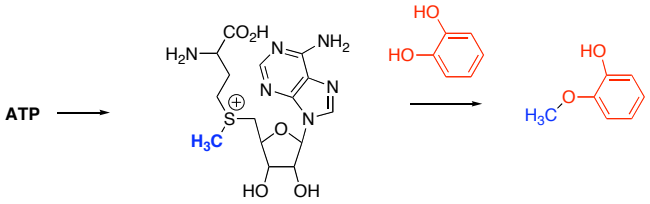
Phase 2: Conjugation

•Methylation (O and N- compd)

Prod. may be more lipophilic

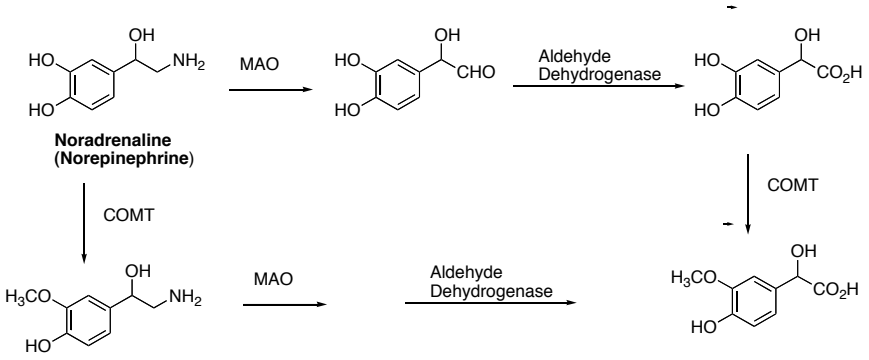
React. mainly aimed at converting endogenic compouds

O.Metylation by COMT (catecol O-methyl transferase)

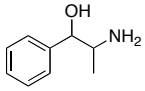


SAM (S-adenocyl methionine)

SAM may also methylate N-comp.



Noradrenaline
(Norepinephrine)



Ephedrine
Adrenerg agonist