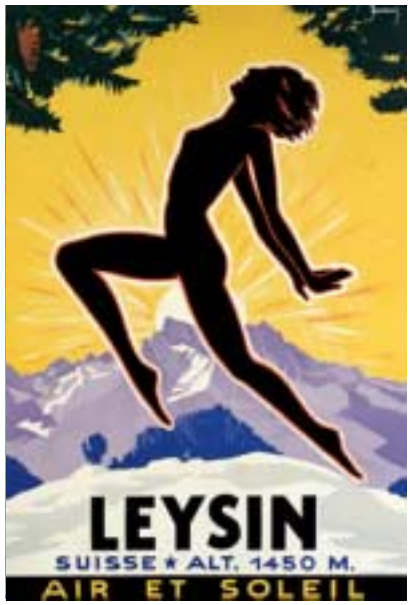

Drug Metabolism

Hugo Kubinyi

Germany

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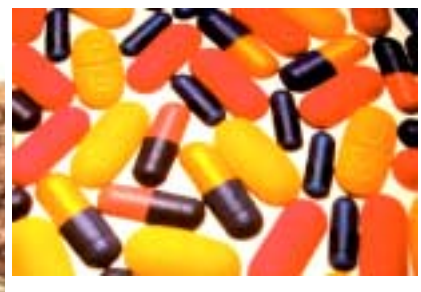
HomePage www.kubinyi.de

Hugo Kubinyi, www.kubinyi.de

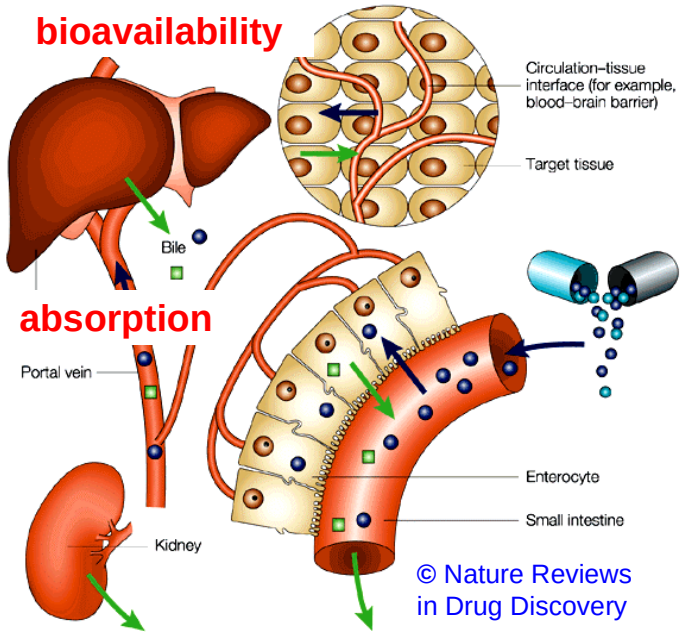
Pharmacodynamics

the action of the drug on the body



Metabolism

the action of the body on the drug

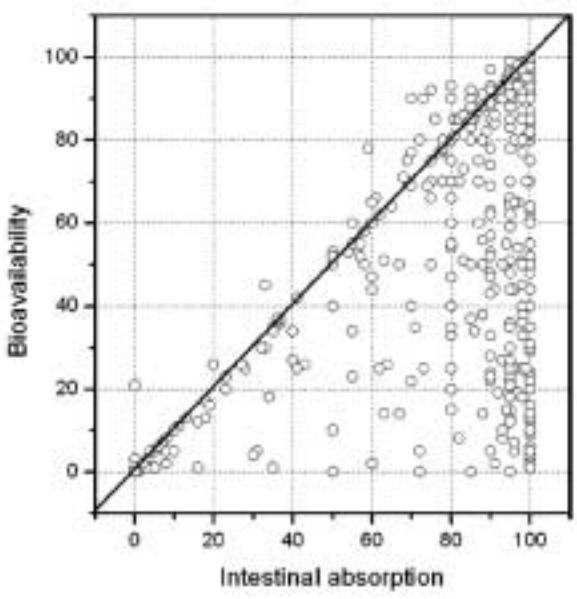


Sites of Drug Metabolism:

(intestinal wall), liver, (organs)

Sites of Drug Elimination:

kidneys (polar compounds), bile, feces (lipophilic analogs), lung



Bioavailability vs. Human Intestinal Absorption (n = 470)

T. Hou et al., J. Chem. Inf. Model. 47, 208-218 (2007)

Drug Metabolism

For the elimination of xenobiotics, mainly in the liver.

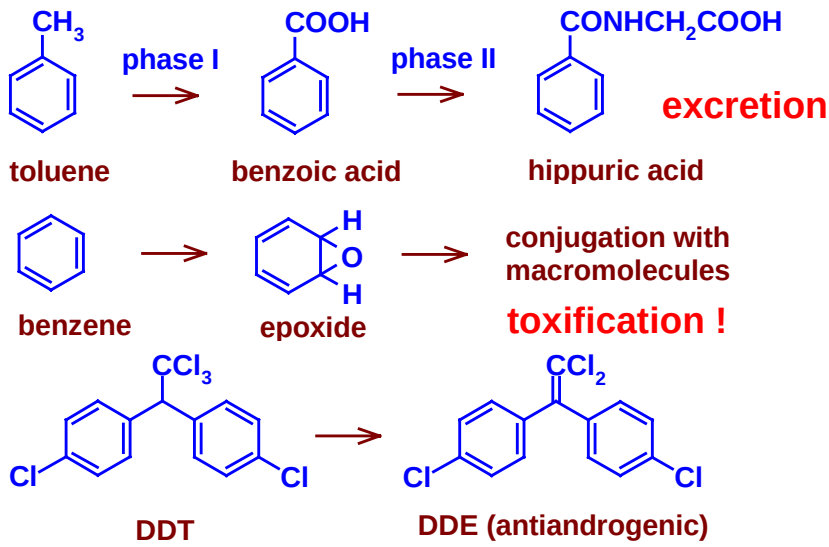
- **oxidations, reductions and hydrolyses (phase I reactions),** and
- **conjugations with small molecules (phase II reactions).**
- drug elimination by transporters is sometimes defined as **phase III reaction.**

The most important phase I enzymes are the group of **cytochrome P450 enzymes (or CYPs).**

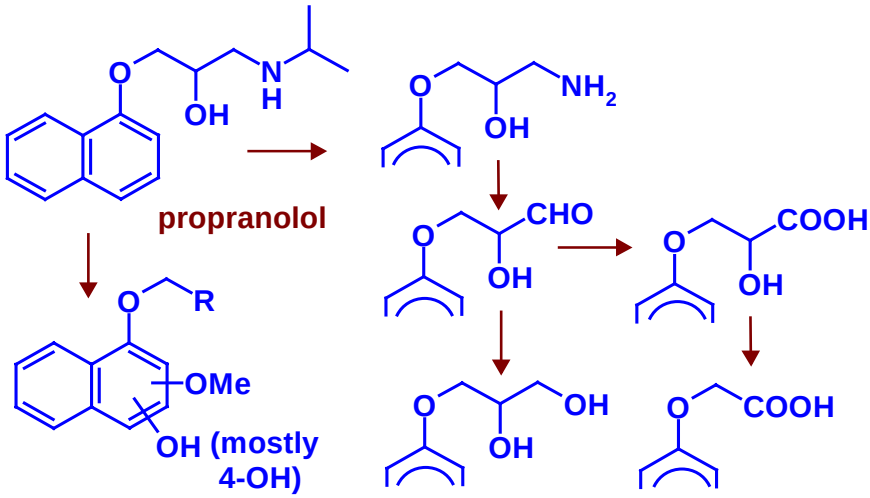
First pass effect: extensive metabolism and/or biliar elimination of drugs of (either) lipophilic character, MW >500-600, or specific affinity to transporters, in their **first liver passage.**

Hugo Kubinyi, www.kubinyi.de

Metabolic Pathways of Xenobiotics

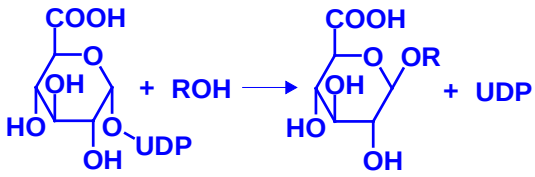


Metabolism of Propranolol



and their glucuronide and sulfate conjugates

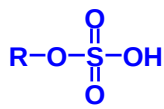
Phase II Metabolic Processes



glucuronidation

acetaminophen, morphine, diazepam, trichloroethanol

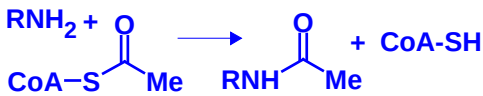
RXH + 3'-phospho adenosine-5'-phospho-sulfate (PAPS)



+ PAP

sulfatation (X = O, NH)

phenol, steroids, acetaminophen, methyldopa



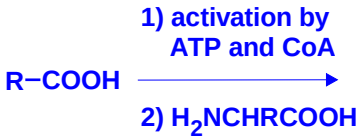
acetylation

sulfonamides, isoniazid, dapsone, clonazepam

epoxide → mercapturic acid

mercapturic acids
(via glutathione addition)

Phase II Metabolic Processes

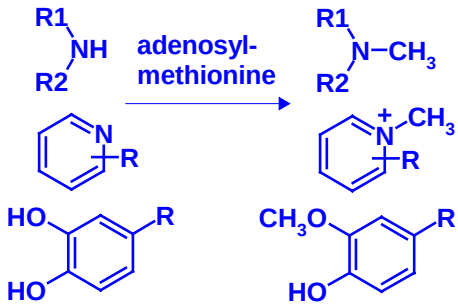


conjugation with glycine (R = H)

benzoic acid,
isonicotinic acid

conjugation with glutamine ($R = -(CH_2)_2-CONH_2$)

indolylacetic acid,
phenylacetic acid



O-, N- and S-methylation

methadone, nicotinamide,
norepinephrine

catecholamines
(catechol-O-methyl
transferase)

Phase I Metabolic Processes

Hydrolysis

- of esters and amides by esterases and amidases
- of epoxides by epoxide hydrolases
- of acetals by glycosidases
- of glucuronides by glucuronidases

Decarboxylation of e.g. amino acids

Reduction

- of carbonyl compounds by alcohol dehydrogenases or aldo-keto reductases
- of azo compounds (via hydrazo compounds to amines) by NADPH-cytochrome P450 reductase and others
- of nitro compounds

Reductive dehalogenation of aliphatic compounds

Phase I Metabolic Processes

Oxidation Reactions

of alcohols and aldehydes: $RCH_2OH \rightarrow RCHO \rightarrow RCOOH$

of aliphatic chains: $R\text{-}CH_2CH_3 \rightarrow R\text{-}CH(OH)CH_3$ (e.g. in barbiturates)

of aromatic amines: $R\text{-}NH_2 \rightarrow R\text{-}NHOH \rightarrow R\text{-}N{=}O$

of tertiary amines: R1-N(R2)-R3 → R1-N(→O)(R2)-R3

of sulfides: R1-S-R2 → R1-SO-R2 → $R1\text{-}SO_2\text{-}R2$

of alkenes to epoxides

of aromatic compounds to phenols (para-hydroxylation)

Oxidative O- and N-dealkylation: $R1\text{-}X\text{-}CH_2\text{-}R2 \rightarrow$ R1-X-H + R2-CH=O (X = O, NH)

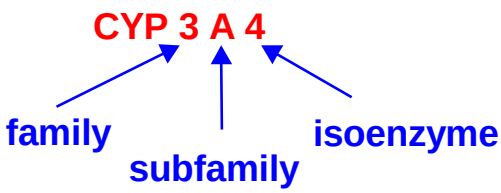
Oxidative deamination (MAO): $R\text{-}CH_2\text{-}NH_2 \rightarrow R\text{-}CH{=}O$

Oxidative desulfuration: R1-C(=S)-R2 → R1-C(=O)-R2

Phase I Metabolic Processes: Oxidases

Cytochrome P450 isoenzymes

are (microsomal) haem monooxygenases with MW = 35-45 kD; there are 51 CYP families (homology >40%), with up to 10 subfamilies (homology >55%).



Low specificity, different sites, different CYPs at same drug, at same site.

Flavin monooxygenase isoenzymes

Alcohol dehydrogenase

Aldehyde oxidase

Monoamine oxidase (MAO)

Cytochrome P450 Enzyme Families

> 1000 genes discovered so far; complete?

Human CYP families (about 50 isoforms in 17 families)

CYP 1-5, 7, 8, 11, 17, 19, 21, 24, 26, 27, 39, 46 and 51

hCYPs that mainly degrade xenobiotics (drugs):
CYP 1, 2A...E, 3

hCYPs in steroid metabolism:
CYP 2G1, 7, 8B1, 11, 17, 19 (aromatase), 21, 27A1, 46, 51

hCYPs in fatty acid metabolism:
CYP 2J2, 4, 5, 8A1

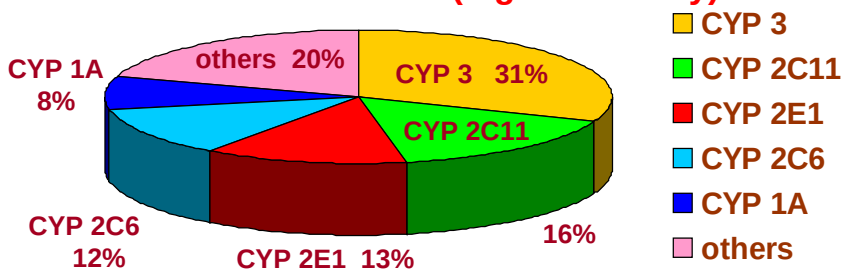
other hCYPs:
CYP 2R1 (?), 2S1 (?), 24 (vitamine D), 26 (retinoic acid), 27B1 (vitamine D), 39 (?)

The dual, ambivalent character of CYPs: oxidative degradation of natural products for better elimination; toxification of chemicals and drugs to chemically highly reactive compounds.

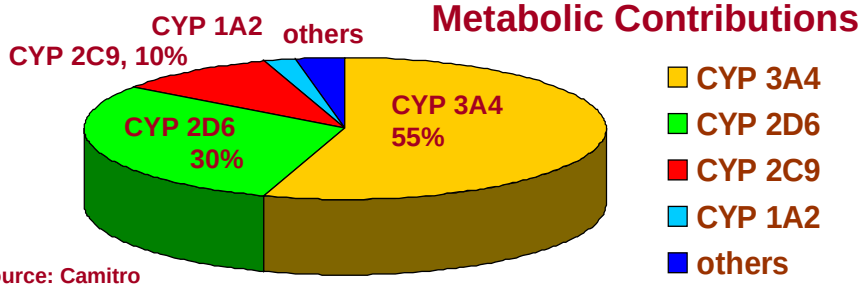
→ **there were only about 8 human generations since 1800**

Hugo Kubinyi, www.kubinyi.de

hCYP450 Concentrations (high variability)



Metabolic Contributions



Source: Camitro

Specificity of Cytochromes (incomplete list)

CYP 1A2: amitryptiline, caffeine, imipramine, paracetamol, theophylline, verapamil
CYP 2A6: nicotine
CYP 2B6: cyclophosphamid
CYP 2C9: diclofenac, naproxen, piroxicam, tolbutamide, warfarin
CYP 2C19: diazepam, omeprazole, S-mephenytoin, phenytoin, propranolol
CYP 2D6: amitryptiline, captopril, chlorpromazine, codeine, debrisoquine, dextromethorphan, flecainide, fluoxetine, imipramine, metoprolol, mianserin, paroxetine, perhexilene, propafenone, thioridazine, venlafaxine.
CYP 2E1: dapsone, ethanol, halothane, paracetamol
CYP 3A4: alprazolam, amiodarone, amitryptiline, carbamazepine, ciclosporin, cisapride, clarithromycin, dexamethasone, erythromycin, ethinyl estradiol, ketoconazole, midazolam, nifedipine, paclitaxel, paracetamol, terfenadine, verapamil, warfarin

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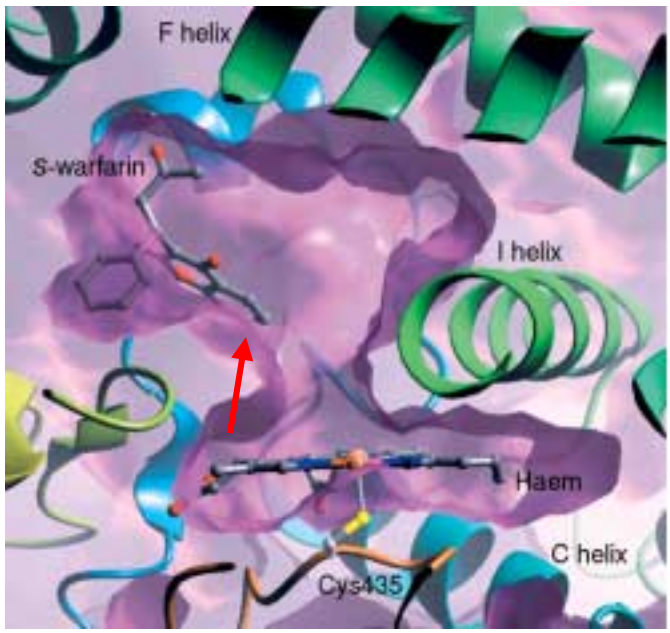
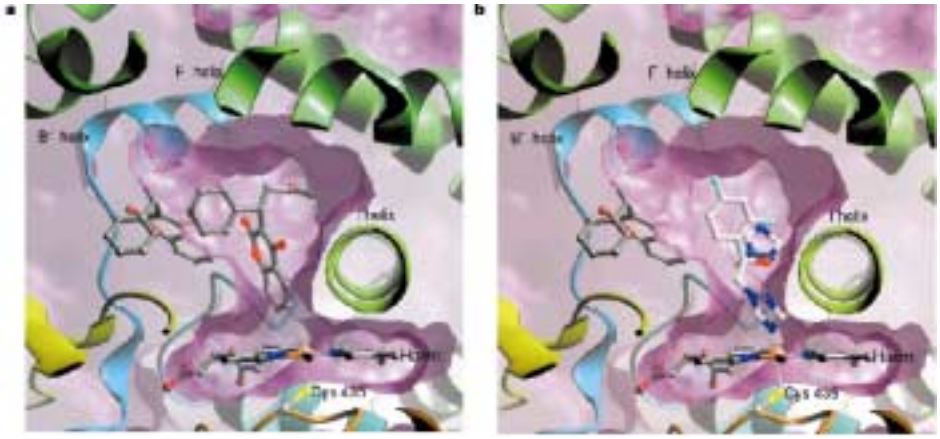


Binding Mode of (S)-Warfarin to hCYP 2C9

the red arrow indicates the site of oxidation (7- but also 6-position)

P. A. Williams et al., Nature 424, 464-468 (2003)

Binding of (S)-Warfarin to hCYP 2C9, Complexes with

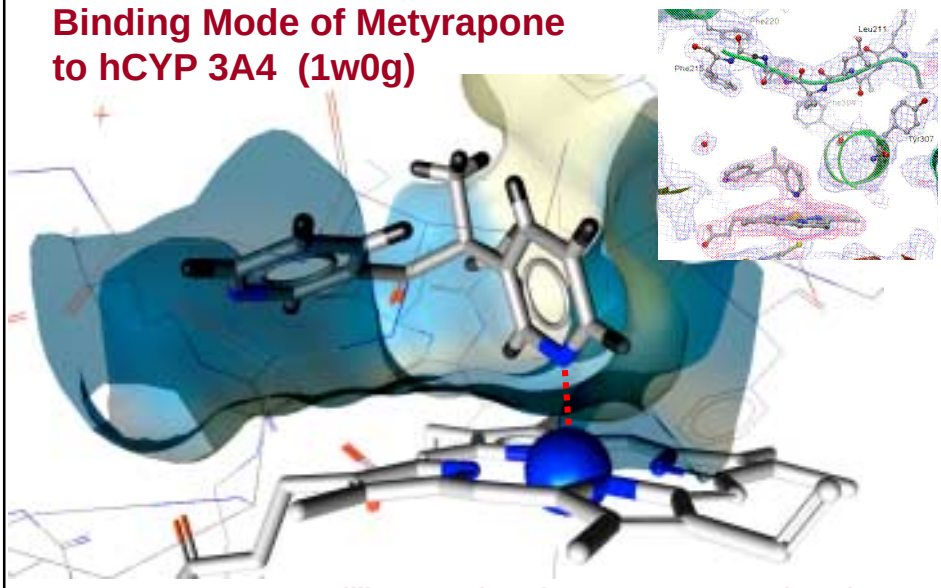


a) a second warfarin molecule

b) the CYP inhibitor fluconazole (modelled from CYP51 complex)

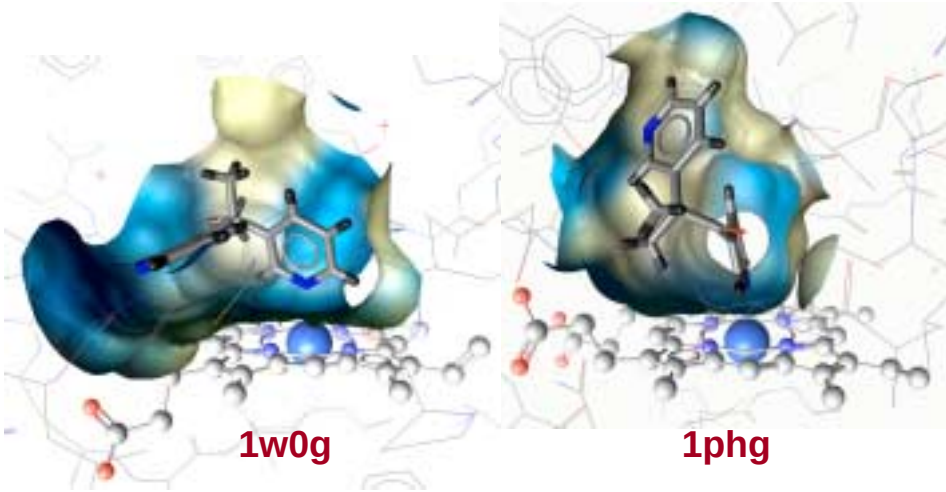
P. A. Williams et al., Nature 424, 464-468 (2003)

Binding Mode of Metyrapone to hCYP 3A4 (1w0g)



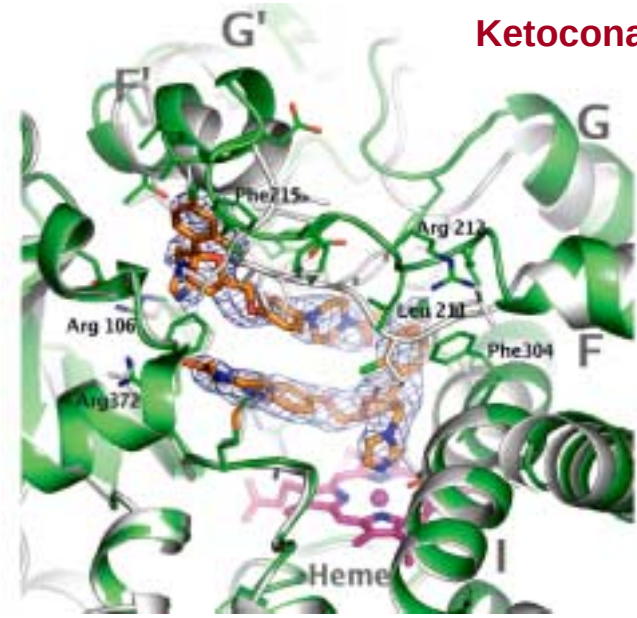
P. A. Williams et al., Science 305, 683-686 (2004)

Binding modes of Metyrapone to hCYP 3A4 (1w0g) and $CYP450_{cam}$ (1phg)



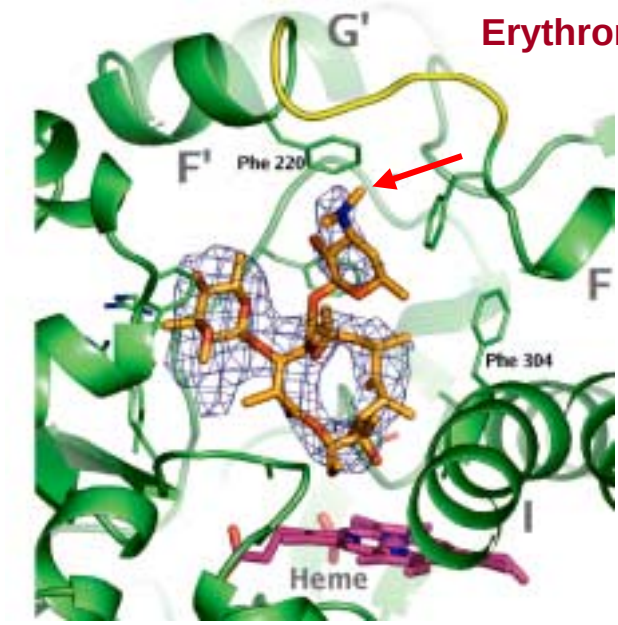
1w0g 1phg

Ketoconazole Binding to hCYP 3A4



M. Ekroos and T. Sjögren, Proc. Natl. Acad. Sci. USA 103, 13682-13687 (2006)

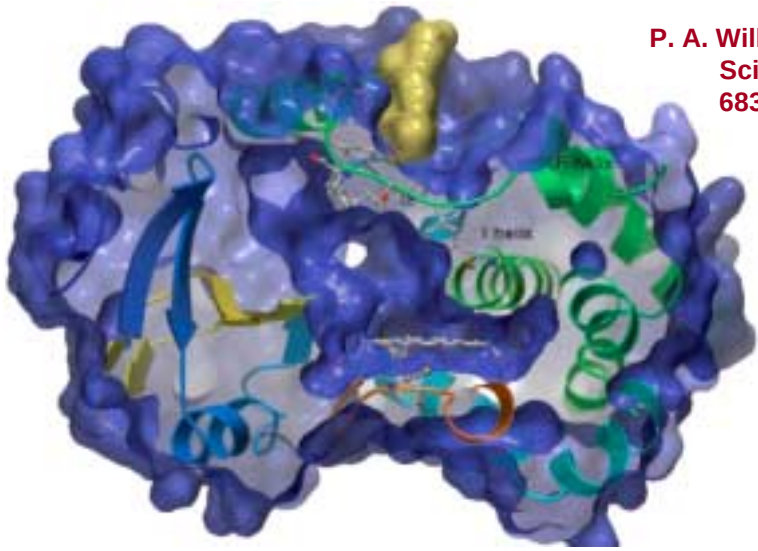
Erythromycin Binding to hCYP 3A4



red arrow:
site of oxidative N-demethylation

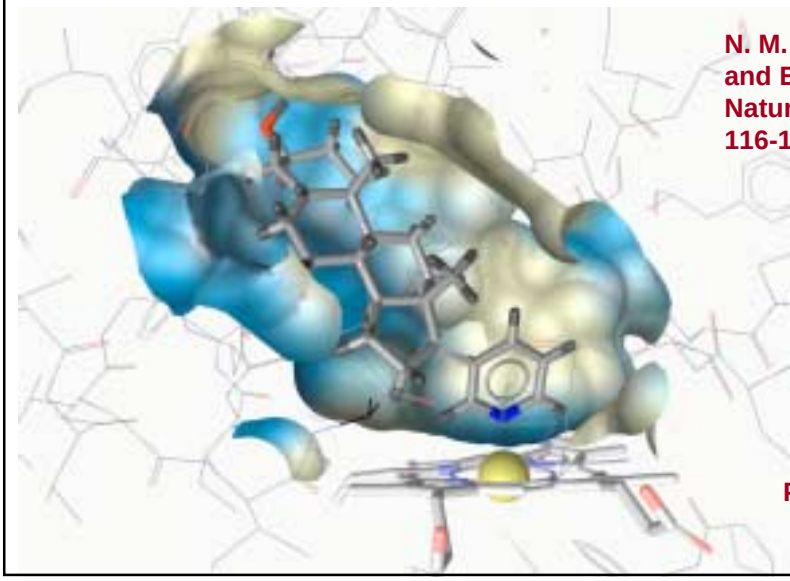
M. Ekroos and T. Sjögren, Proc. Natl. Acad. Sci. USA 103, 13682-13687 (2006)

Binding Mode of Progesterone to hCYP 3A4



P. A. Williams et al., Science 305, 683-686 (2004)

Binding Mode of Abiraterone to hCYP17A1

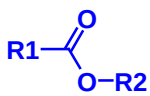


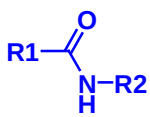
N. M. DeVore and E. E. Scott, Nature 482, 116-119 (2012)

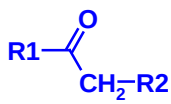
PDB 3rum

Modulation of Biological Halflife Time

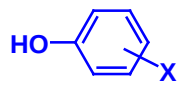
Metabolism by a) hydrolysis

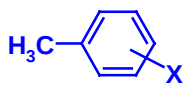


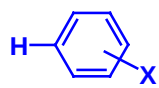


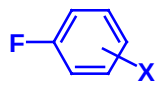


b) oxidation



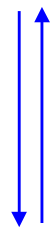






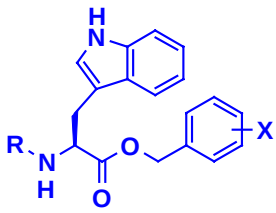
Metabolic degradation

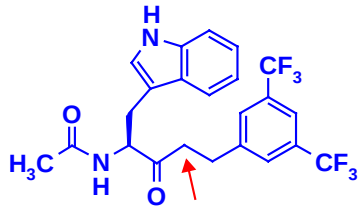
fast



slow

Optimization of an NK1 Receptor Antagonist





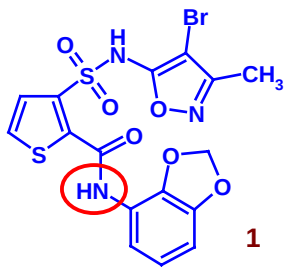
orally available analog

IC_{50} = 3 nM

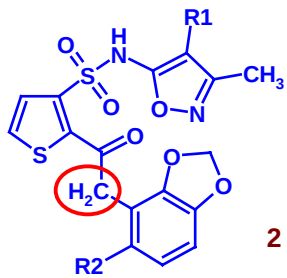
R = Et, X = H	IC_{50} = 3,800 nM
R = H, X = H	IC_{50} >10,000 nM
R = H, X = 3,5-di-CH_3	IC_{50} = 1,533 nM
R = Ac, X = 3,5-di-CH_3	IC_{50} = 67 nM
R = Ac, X = 3,5-di-CF_3	IC_{50} = 1.6 nM

A. M. MacLeod et al., J. Med. Chem. 37, 1269-1274 (1994);
A. M. MacLeod et al., J. Med. Chem. 38, 934-941 (1995)

Optimization of an ET_A Receptor Antagonist



1

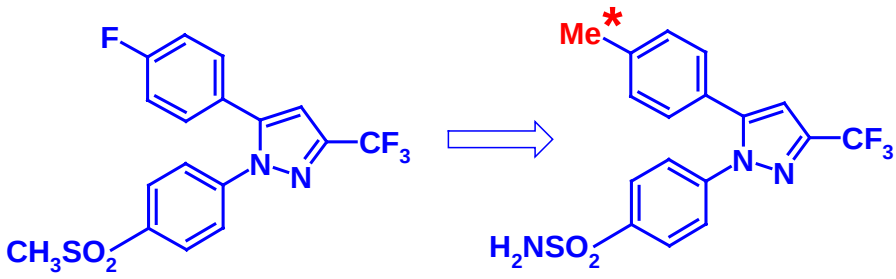


2

Compound	oral bioavailability, %	$t_{1/2}$, h
1	0	< 0.5
2a, R1 = Cl, R2 = H	30	1.5
2b, R1 = CH_3, R2 = CH_3	100	7

C. Wu et al., J. Med. Chem. 40, 1690-1697 (1997)

Oxidative Metabolism and Drug Design



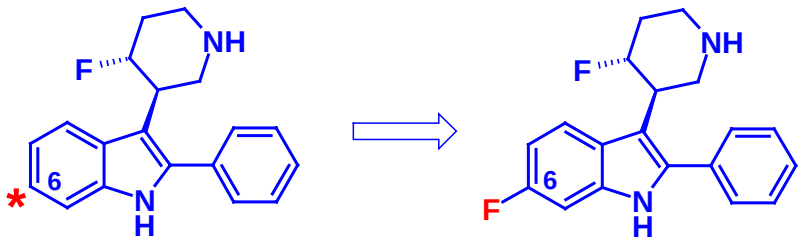
early COX2 inhibitor
$t_{1/2}$ (rat) up to 220 h

celecoxib
$t_{1/2}$ (rat) = 3.5 h

T. D. Penning et al., J. Med. Chem. 40, 1347-1365 (1997);
D. A. Smith, H. van de Waterbeemd and D. K. Walker, Pharmacokinetics and Metabolism in Drug Design, Wiley-VCH, 2001, p. 83

Hugo Kubinyi, www.kubinyi.de

Oxidative Metabolism and Drug Design



K_i h5-HT_{2A} = 0.43 nM

rat:
bioavailability = 18%
$t_{1/2}$ = 1.4 h

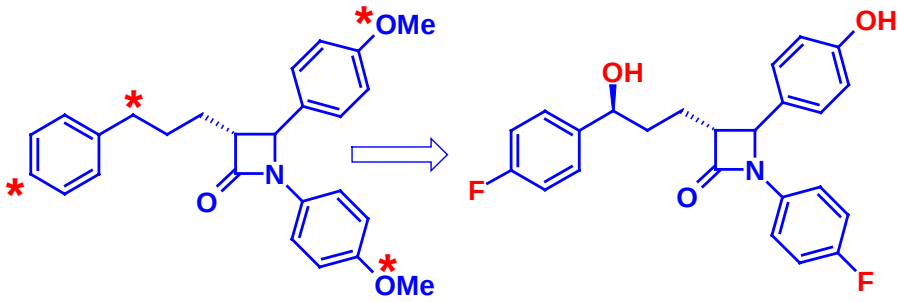
major metabolite: 6-OH

K_i h5-HT_{2A} = 0.06 nM

rat:
bioavailability = 80%
$t_{1/2}$ = 12 h

M. Rowley et al., J. Med. Chem. 44, 1603-1614 (2001)

Oxidative Metabolism and Drug Design

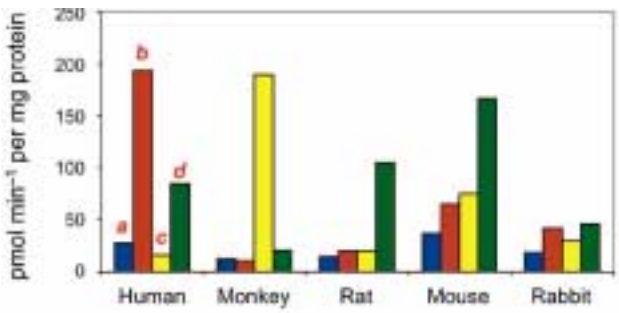


SCH 48461
ED_{50} (hamster) = 2.2 mg/kg

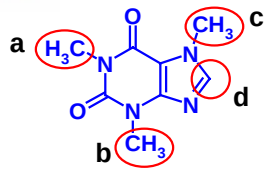
Ezetimib (SCH 58235, oral cholesterol absorption inhibitor)
ED_{50} (hamster) = 0.04 mg/kg

M. van Heek et al., J. Pharmacol. Exp. Ther. 283, 157-163 (1997);
D. A. Smith, H. van de Waterbeemd and D. K. Walker, Pharmacokinetics and Metabolism in Drug Design, Wiley-VCH, 2001, p. 85

Species Differences of Caffeine Oxidation

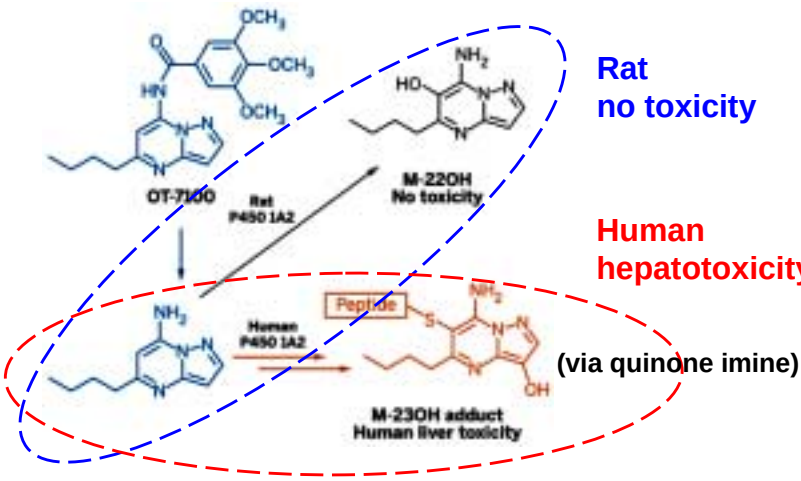


production of caffeine metabolites by liver microsomes of different species



F. Berthou et al., Xenobiotica 22, 671-680 (1992); figure from
S. D. Krämer and B. Testa, Chemistry & Biodiversity 5, 2465-2578 (2008)

Biological Activities of Metabolites



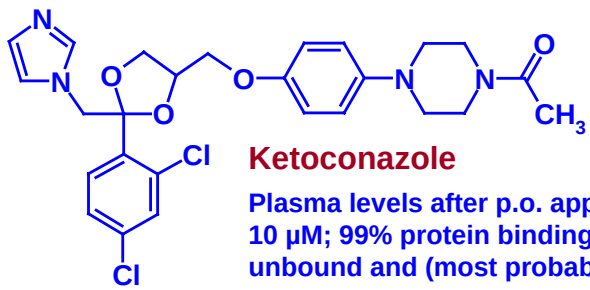
Rat
no toxicity

Human
hepatotoxicity

(via quinone imine)

S. Kuribayashi et al., Chem Res. Toxicol. 22, 323-331 (2009);
cf. Chem. &Eng. News, August 31, 2009, p. 27

Ketoconazole and Other Azoles Inhibit CYP 3A4



Ketoconazole

Plasma levels after p.o. application = about 10 µM; 99% protein binding → about 100 nM unbound and (most probably) intracellular concentration. K_i **CYP 3A4 = 15 nM**

Side effect of ketoconazole: enhanced nephrotoxicity of cyclosporin (a CYP 3A4 substrate)

Therapeutic application of ketoconazole (or diltiazem, another CYP 3A4 inhibitor): combination with cyclosporin reduces the dose of this (expensive) drug!

A Clinical Case Study

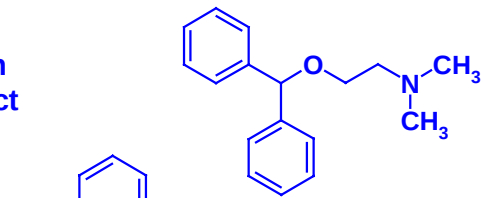
(M. D. Coleman, Human Drug Metabolism. An Introduction, Wiley, Chichester, 2005, pp. 75-76)

A previously healthy 29-year-old male used terfenadine for one year to treat allergic rhinitis. Occasionally he drank grapefruit juice. One day he consumed two glasses of grapefruit juice, took his terfenadine dose and then worked in the garden. Within one hour he became ill, collapsed and died. Although usually undetectable, post-mortem terfenadine levels were reported as 35 ng/mL.

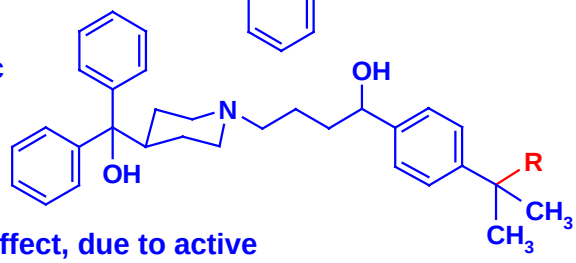
The grapefruit juice appears to have accumulated high levels of the parent drug in the patient's plasma. Some component of the juice prevented the clearance of the drug, leading to a fatal cardiac arrhythmia.

Oxidative Metabolism and Drug Design

diphenhydramine
H_1 antagonist with sedative side effect

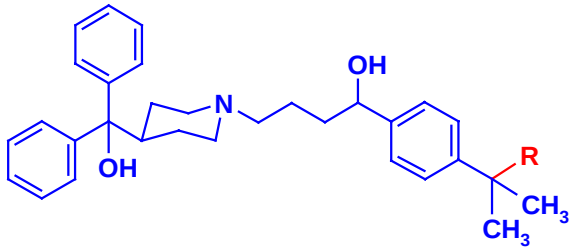


terfenadine (Seldane®), R = CH_3: lipophilic H_1 antagonist (originally designed as antipsychotic; no sedative side effect, due to active elimination by drug transporter, but cardiotoxic, especially in combination with CYP 3A4 inhibitors)



fexofenadine (Allegra®), R = COOH: active terfenadine metabolite (no sedative side effect, no cardiotoxicity)

SAR of hERG Channel Ligands
Terfenadine analogs



R = CH_3, Terfenadine	IC_{50} = 56 nM
R = OH	IC_{50} = 460 nM
R = COOH, Fexofenadine	IC_{50} = 23,000 nM

R. A. Pearlstein et al., Bioorg. Med. Chem. Lett. 13, 1829-1835 (2003)

Hugo Kubinyi, www.kubinyi.de

Cytochrome P450 Inhibitors (incomplete list)

CYP 1A2: cimetidine, fluvoxamine, grapefruit juice, quinolone antibiotics (ciprofloxacin, enoxacin, norfloxacin)

CYP 2C9: amiodarone, chloramphenicol, cimetidine, fluconazole, fluoxetine, isoniazid, omeprazole, sertraline, sulfaphenazole, sulfinpyrazone

CYP 2C19: fluoxetine, fluvastatin, fluvoxamine, isoniazid, omeprazole, sertraline, ticlopidine, tranylcypromine

CYP 2D6: amiodarone, cimetidine, fenfluramine, haloperidol, mibefradil, quinidine, propafenone, ritonavir, all SSRIs (fluoxetine and paroxetine being most potent), thioridazine, yohimbine

CYP 2E1: cimetidine, disulfiram (ethanol intoxication!)

CYP 3A4: amiodarone, cannabinoids, cimetidine, clotrimazole, diltiazem, erythromycin, norfluoxetin (metabolite of fluoxetin), fluvoxamine, grapefruit juice, ketoconazole, metronidazole, miconazole, paroxetine, HIV protease inhibitors (ritonavir being most potent), and many others.

A Clinical Case Study

(H. Schneemann, L.Y. Young and M. A. Koda-Kimple, Angewandte Arzneimitteltherapie, Springer-Verlag, Berlin 2001, p. 110)

B. D., a 32-year old man, suffers since 18 years from chronic pain. In addition, he developed stomach ulcers and a grand mal epilepsy. In the past he received opioid as well as non-narcotic analgesics. Recently he was treated with 10 mg methadone, every 6 hours, with good success. However, after some time withdrawal symptoms and insufficient pain control were observed. In the mean-time, a neurologist had prescribed phenytoin.

Phenytoin increases methadone metabolism by CYP 450 enzyme induction. The methadone dose has to be increased to 20 mg per 6 hours, under clinical control.

Hugo Kubinyi, www.kubinyi.de

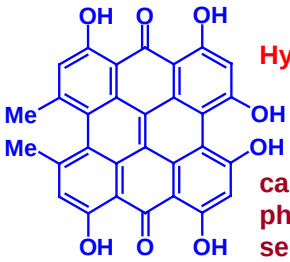
A Clinical Case Study

(M. D. Coleman, Human Drug Metabolism. An Introduction, Wiley, Chichester, 2005, p. 59)

A 64-year-old obese man was prescribed the cholesterol-lowering simvastatin, 10 mg daily. Over the next three months, lack of clinical response led to a fivefold increase in dosage. After some time he was admitted to hospital with rhabdomyolisis. On his own initiative, he had self-administered St. John‘s Wort, which he discontinued when his mood was sufficiently elevated, around 10 days prior to the toxicity manifesting itself.

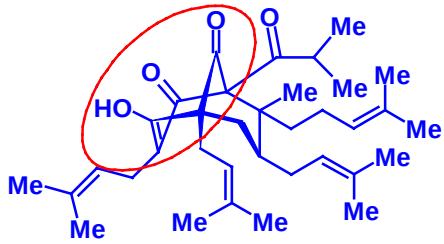
The statin was not effective unless considerably higher doses than normal were used. The patient stopped taking the herbal extract, so the statin accumulated.

St. John‘s Wort (Johanniskraut, *Hypericum performatum*), originally a herb for healing wounds (“doctrine of signatures“), is commonly used as „mild antidepressant“



Hypericin

causes photo-sensitivity



Hyperforin, a six-fold prenylated phloroglucin, is the highest affinity ligand of hPXR, K_d = 27 nM.

Cytochrome P450 Induction by Xenobiotics

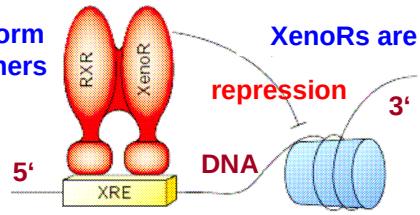
CYP 450 induction is a special case of drug-drug interaction. In addition, cigarette smoking and dietary-derived substances can induce CYP 450s and thus, increase metabolic degradation of certain drugs

(coffee drinkers, who decide to stop smoking, experience headache and agitation, due to an increase of plasma caffeine concentrations).

CYP 1A2: broccoli (?), cigarette smoking, insulin, omeprazole, phenobarbitone, aromatic hydrocarbons (e.g. char-broiled meat)
CYP 2C9: rifampicin, secobarbital
CYP 2C19: carbamazepine, norethindrone, prednisone, rifampicin
CYP 2D6: dexamethason, rifampicin (?)
CYP 2E1: ethanol, isoniazid
CYP 3A4: carbamazepine, efavirenz, ethosuximide, glucocorticoids, phenobarbitone, rifampicin, St. John‘s wort, sulfadimidine, nevirapine, sulfinpyrazone, troglitazone

CYP450 Induction is Nuclear Receptor-Mediated

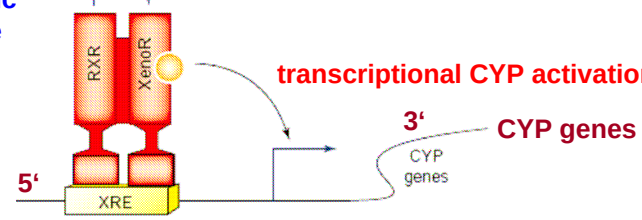
XenoRs form heterodimers with the retinoid receptor (RXR)



XenoRs are the pregnane X receptor (PXR), the constitutive androgen receptor (CAR) and the peroxisome proliferator-activated receptor (PPAR).

XRE = xenobiotic response element of DNA

xeno- or endobiotics, e.g. drugs



W. Xie and R. M. Evans, Drug Discov. today 7, 509-515 (2002)

Hugo Kubinyi, www.kubinyi.de

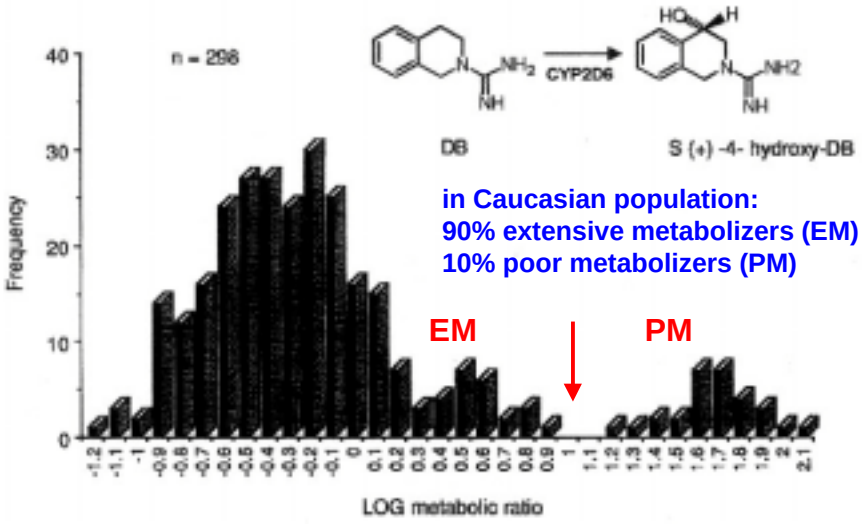
Humanized Mouse Model for the PXR Receptor

(W. Xie and R. M. Evans, Drug Discov. today 7, 509-515 (2002))

wild type
mPXR+
transgenic
mPXR+, hPXR+
transgenic k.o.
mPXR-, hPXR+

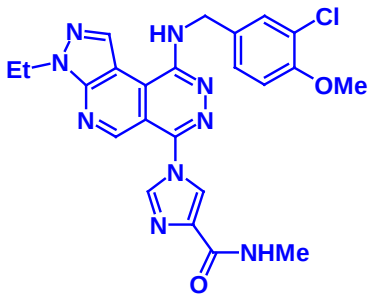
mPXR and hPXR show **species-specific ligand profiles. A humanized mouse model (mPXR-, hPXR+)** displays a human drug-response profile, with drug-induced over-expression of CYP 3A isozymes. This xeno-sensor allows the investigation of **drug-drug interactions in humans.**

Genetic Variability of Drug Metabolism
(CYP 2D6 = „debrisoquine-4-hydroxylase“)



in Caucasian population:
90% extensive metabolizers (EM)
10% poor metabolizers (PM)

Genetic Variability of Biological Half-life Time



BMS 341 400
K_i PDE5 = 0.3 nM
(10 times Sildenafil)
Selectivity > 100

Advantage, as compared to Sildenafil (Viagra®):
higher selectivity vs. PDE6, thus no nausea or blue vision;
well-tolerated in humans, only mild headache in a few cases;
half-life time in humans: 12 h

Problem:
about 7% healthy Caucasian volunteers experienced an un-explained 80 h half-life time

IDdb News focus, Curr. Drug Discov., July 2002, p. 12-13;
M. Hendrix and C. Kallus, in: H. Kubinyi and G. Müller, Chemogenomics in Drug Discovery,Wiley-VCH, 2004, pp. 243-288

Genetic Variability in CYP Expression (incomplete)

CYP 1A2: significant inter-individual variability; e.g. high, intermediate, and low caffeine metabolizers

CYP 2B6: lack of enzyme in 3-4% caucasians

CYP 2C9: deficiency (1-3% in Caucasians) leads to an inability to metabolize (S)-warfarin (doses have to be reduced from 5-10 mg to 0.5 mg/day); codeine, tramadol and losartan will not be activated.

CYP 2C19: individuals with defective enzyme (3-6% Caucasians, 15-20% Asians) experience greater healing rates of their peptic ulcers, after treatment with omeprazole.

CYP 2D6: most extensively studied example of genetic polymorphism („sparteine-debrisoquine polymorphism"); poor metabolizers in about 10% of Caucasian population, less then 1% in Japanese population. High expression in many Ethiopians and Saudi Arabians (multiple gene copies).

CYP 3A4: only certain mutations (associated with MDR1 gene polymorphism)

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G. Cruciani, J. Med. Chem. 48, 6970-6979 (2005).

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Aspet Division for Drug Metabolism / Cytochrome P450 (www.aspet.org/public/divisions/drugmetab/cytochrome_p450.htm)
CYP 450 Drug Interactions (http://medicine.iupui.edu/flockhart)
CYP 450 Gene Databases (http://drnelson.utmem.edu/Databases.html)
Brookhaven Protein Database (www.rscb.org/pdb or www.biochem.ucl.ac.uk/bsm/pdbsum)

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JOURNAL OF CHEMICAL INFORMATION AND MODELING — Perspective

J. Kirchmair et al., J. Chem. Inf. Model. 52, 617-648 (2012)

Computational Prediction of Metabolism: Sites, Products, SAR, P450 Enzyme Dynamics, and Mechanisms

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ABSTRACT: Metabolism of xenobiotics remains a central challenge for the discovery and development of drugs, cosmetics, nutritional supplements, and agrochemicals. Metabolic transformations are frequently related to the incidence of toxic effects that may result from the emergence of reactive species, the systemic accumulation of metabolites, or by induction of metabolic pathways. Experimental investigation of the metabolism of small organic molecules is particularly resource demanding; hence, computational methods are of considerable interest to complement experimental approaches. This review provides a broad overview of structure- and ligand-based computational methods for the prediction of xenobiotic metabolism. Current computational approaches to address