



MINI-CURSO: Metabolismo de Fármacos: aplicações em toxicologia e interações medicamentosas



UFRJ

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PARTE 1





Metabolismo de Fármacos: Definição? Papel? Fármaco?

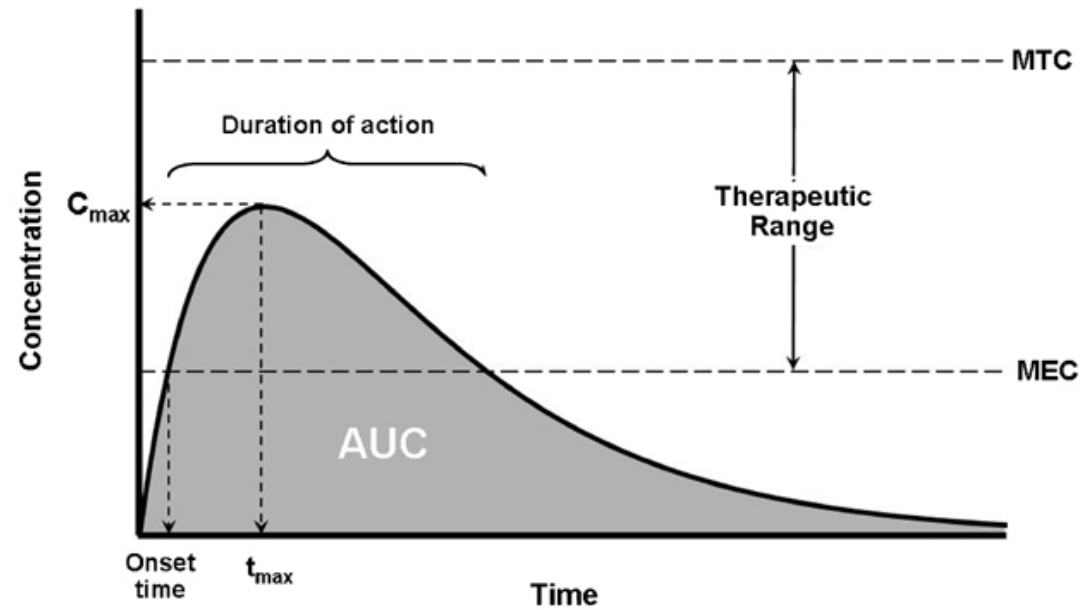


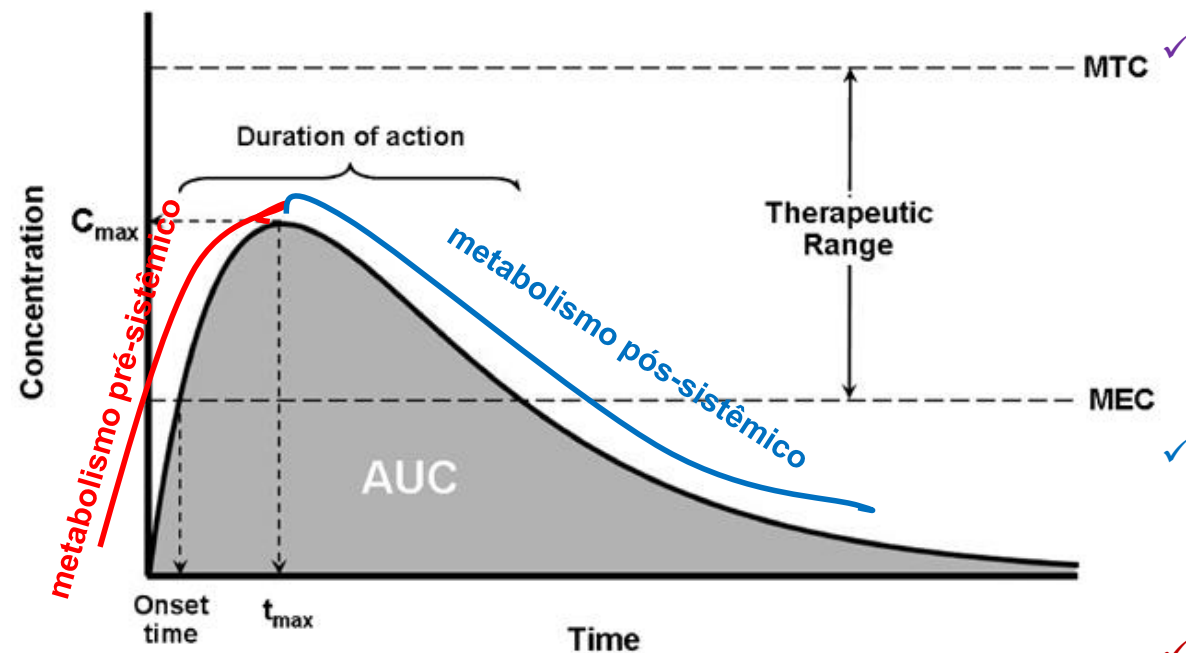


SAÚDE

DOENÇA

FÁRMACOS





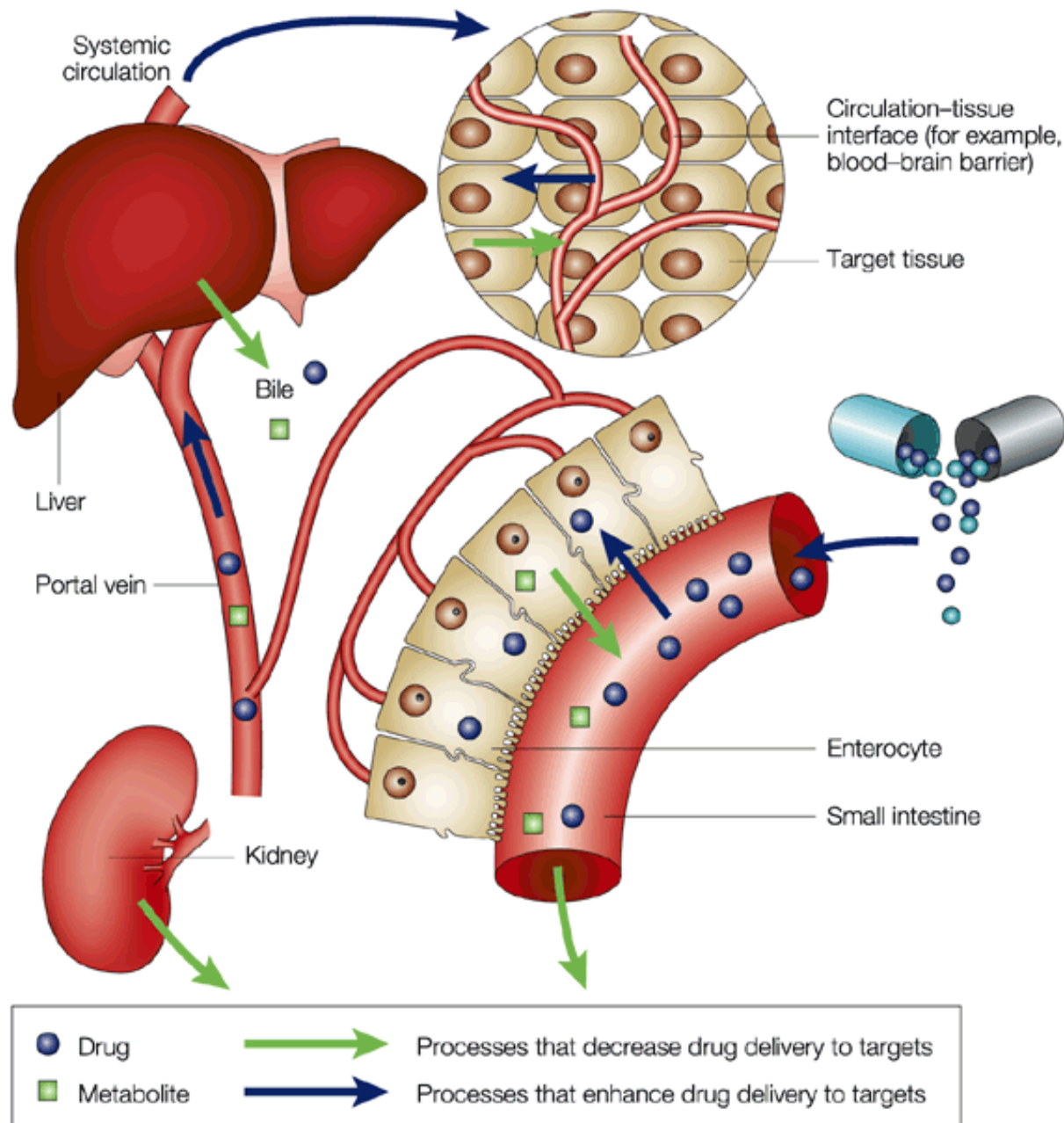
✓ O papel fisiológico do metabolismo de fármacos pode ser medido através dos parâmetros farmacocinéticos de biodisponibilidade (F) e clearance (Cl);

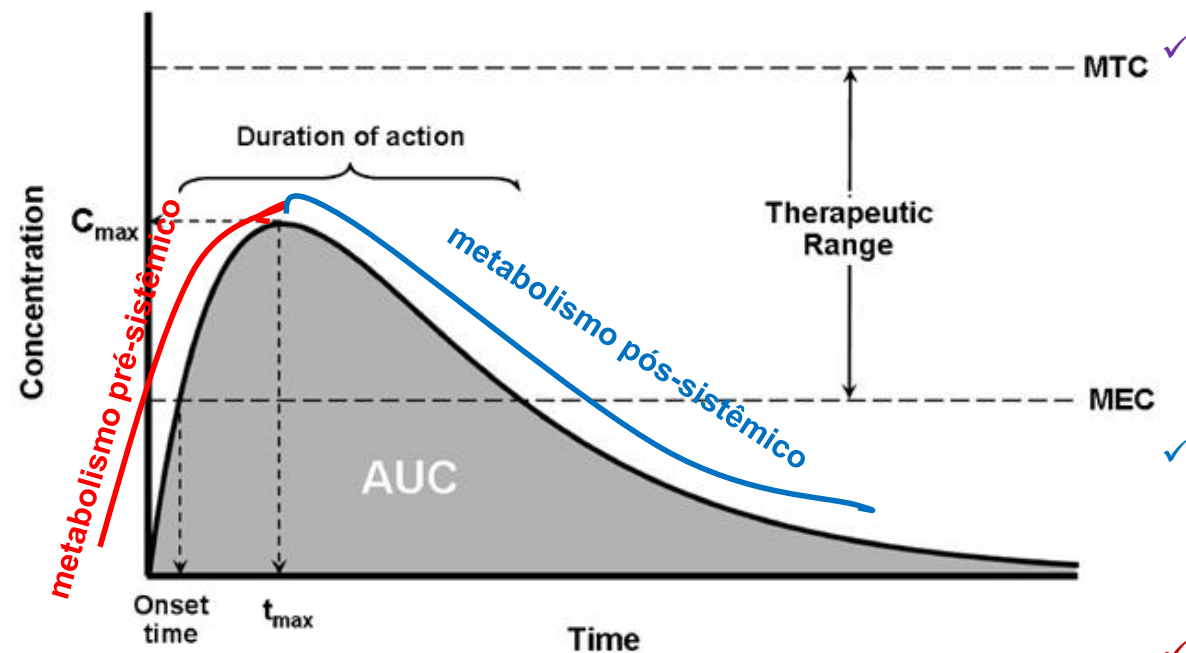
✓ Combinados a F e Cl afetam a quantidade total de fármaco no sangue (AUC) x tempo.

✓ A estabilidade metabólica de um determinado composto (e.g. fármacos) é inversamente proporcional a sua clearance.

“O metabolismo influencia a natureza, a intensidade e a duração dos efeitos terapêuticos e/ou tóxicos dos fármacos e seus eventuais metabólitos bioativos”

Fármaco ativo	Metabólito inativo (Bioinativação)
Fármaco ativo	Metabólito ativo (Bioativação ou Toxificação)
Fármaco inativo (pró-fármaco)	Metabólito ativo (Bioativação)





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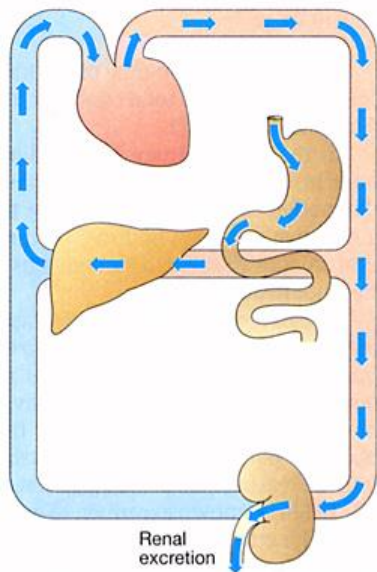
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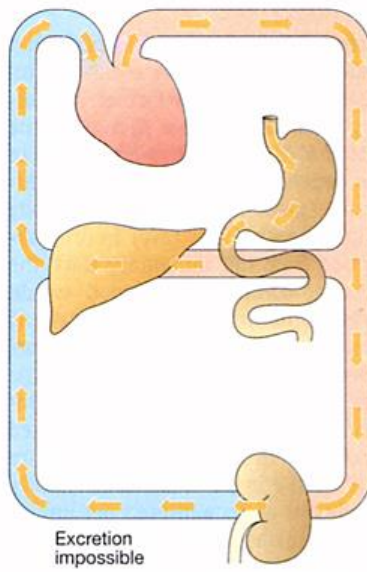
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Hydrophilic drug



Lipophilic drug
no metabolism



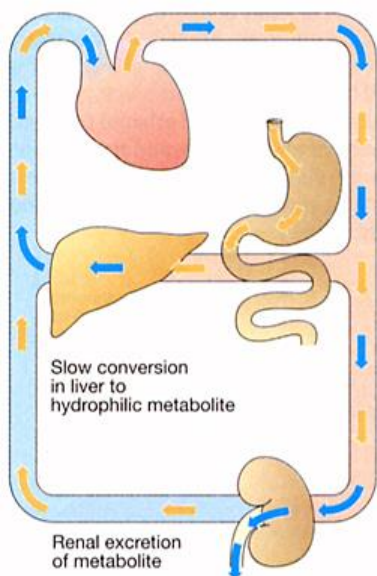
Fármacos lipofílicos são reabsorvidos após filtração glomerular, retornando a circulação sistêmica.



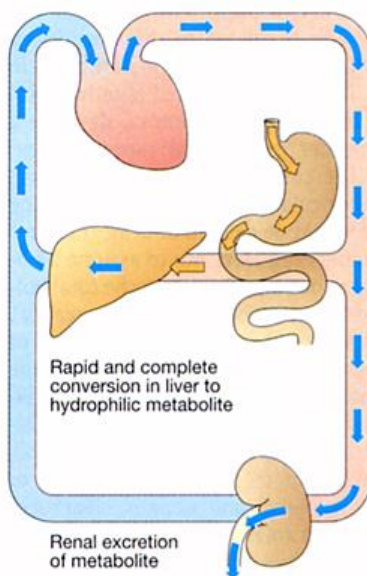
Metabolismo de Fármacos: fase 1 & fase 2



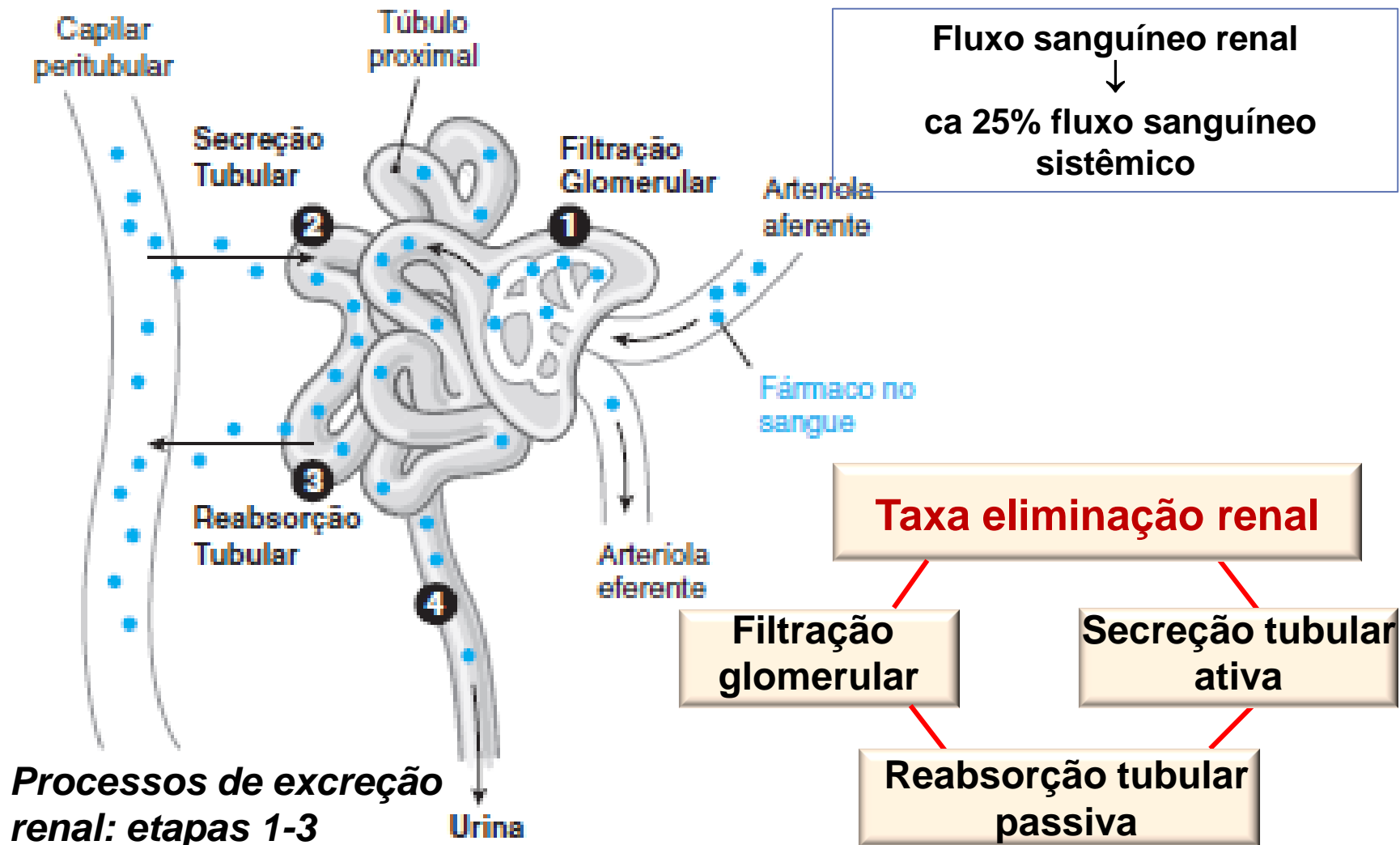
Lipophilic drug



Lipophilic drug

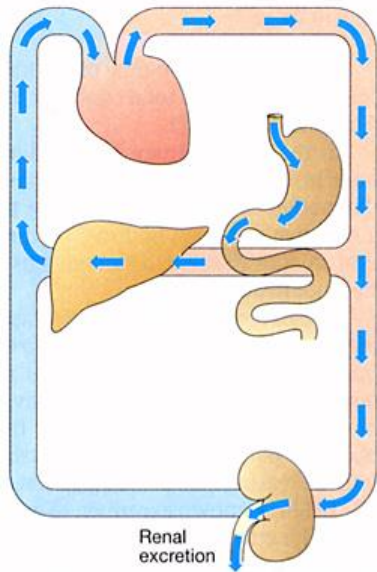


As reações metabólicas de fase 1 e fase 2 tem como principal objetivo transformar fármacos lipofílicos ($\uparrow \text{LogP}$; $\text{LogD}_{7,4} > 0$; $\downarrow \text{PSA}$) em: metabólitos hidrofílicos ($\downarrow \text{LogP}$; $\text{LogD}_{7,4} < 0$; $\uparrow \text{PSA}$), favorecendo a eliminação por via renal.

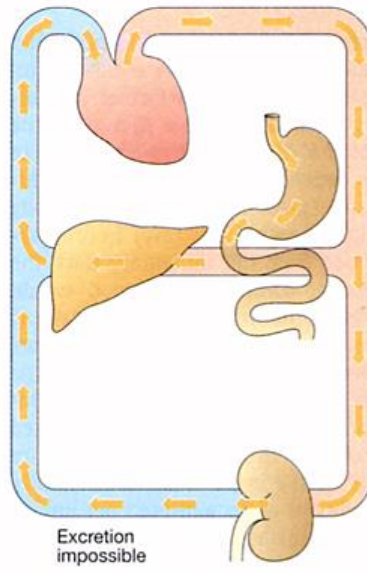


Fonte: LaMattina, JC & Golan, DE. Em: Princípios da Farmacologia. A Base Fisiopatológica da Farmacoterapia, 2ª Edição (Guanabara Koogan)

Hydrophilic drug



Lipophilic drug
no metabolism



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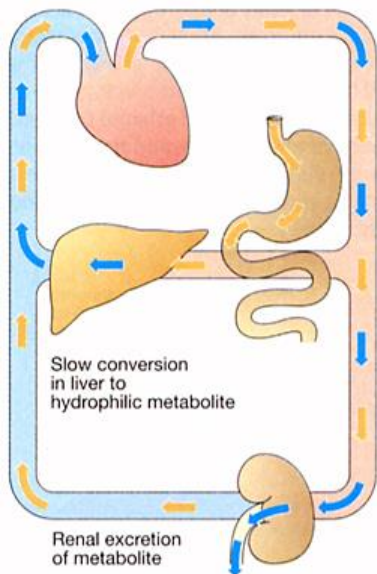


Metabolismo de Fármacos: fase 1 & fase 2

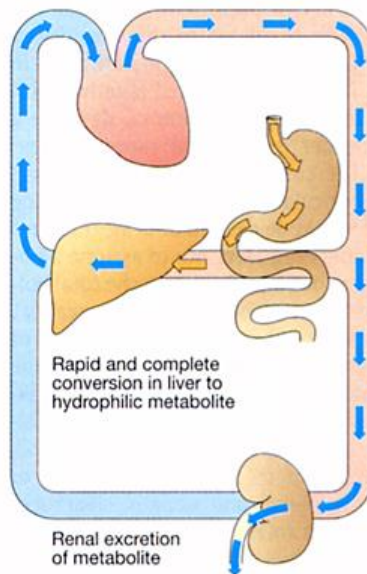


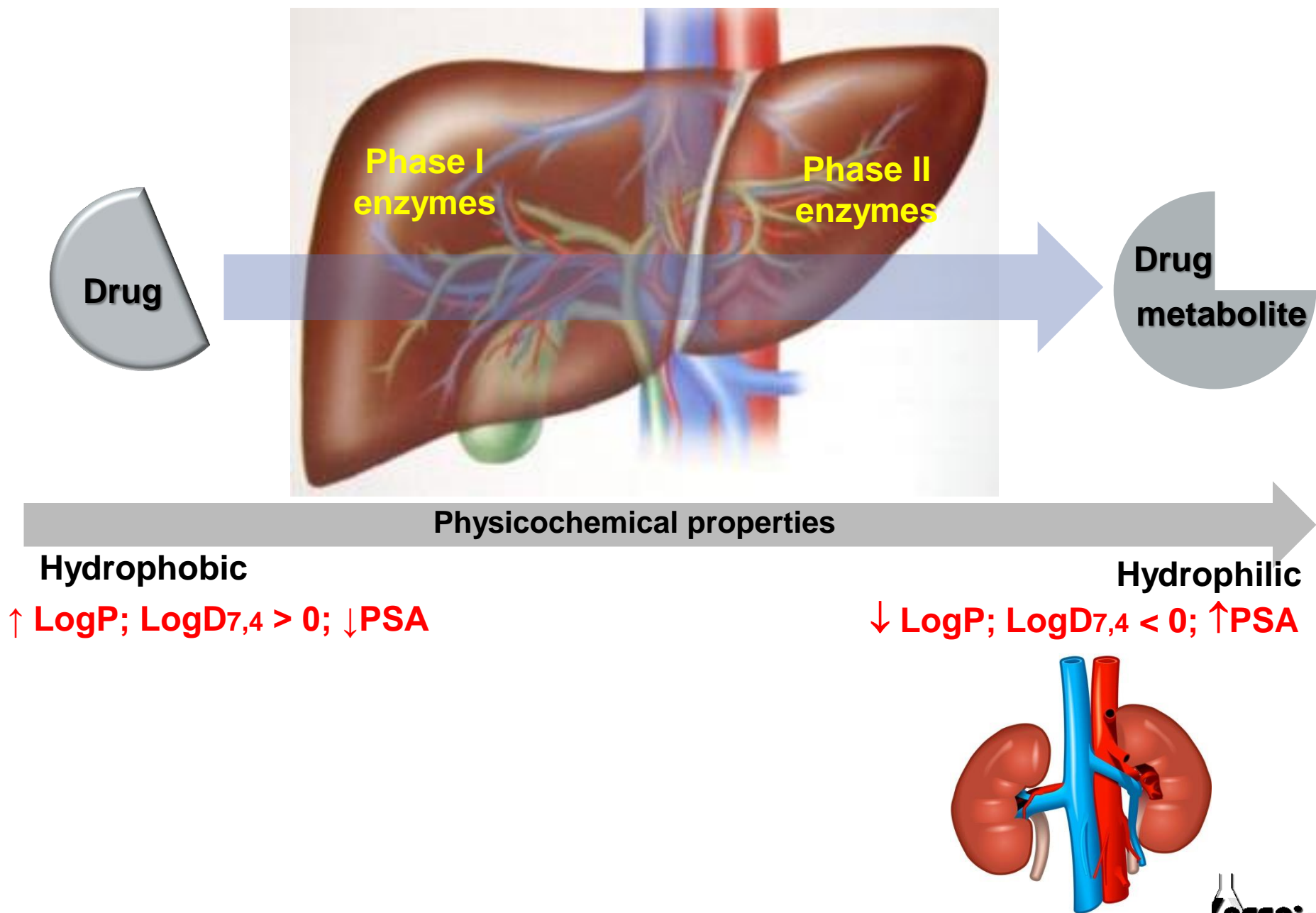
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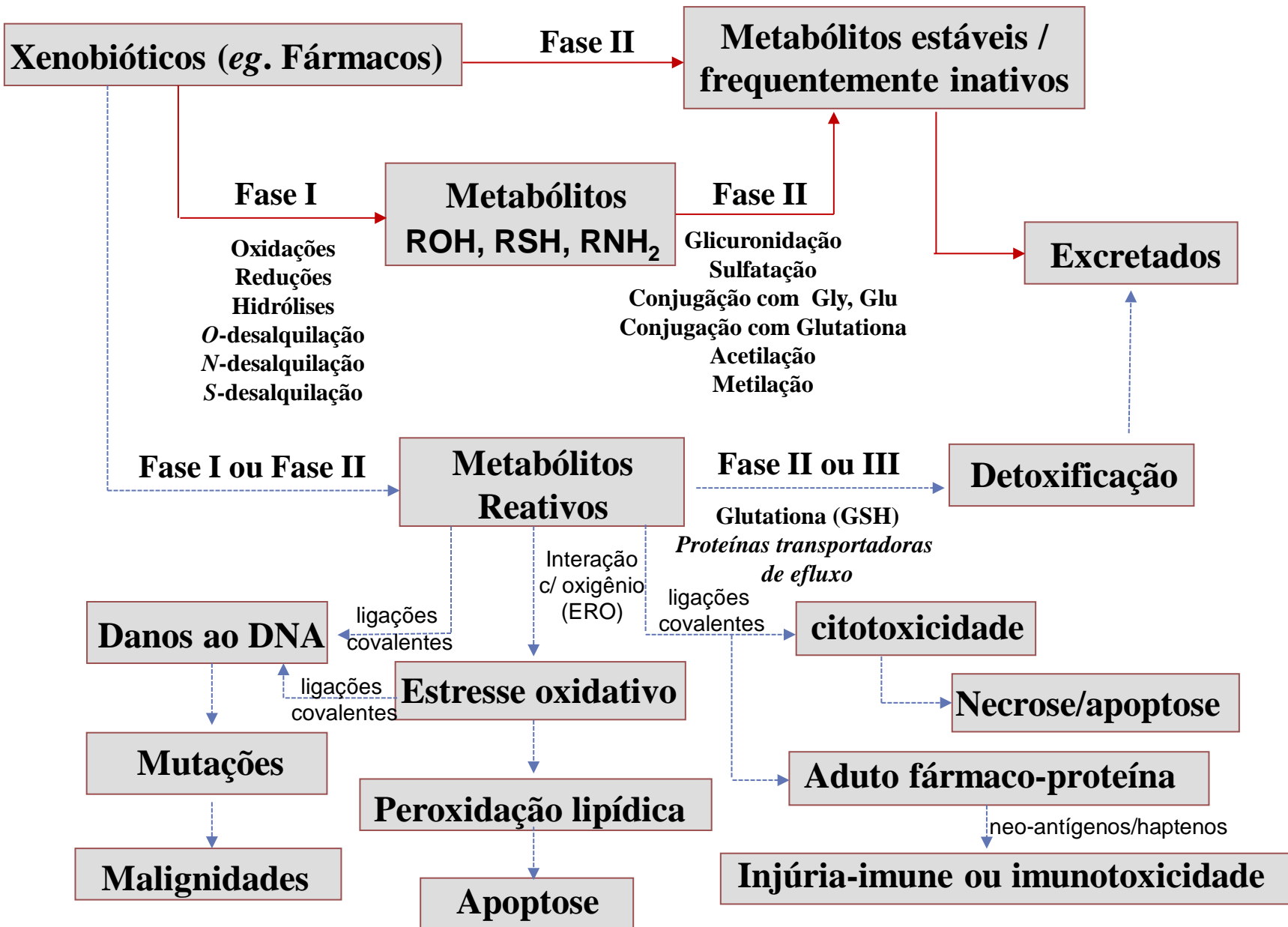
Lipophilic drug



Lipophilic drug







Metabolismo de Fase 1

Complexo Enzimático	Localização subcelular principal
Citocromo P450 monooxigenases	Microssoma e mitocôndria
Flavina monoamina oxidase	Microssoma
Aldeído desidrogenase	Citosol, microssomal e mitocôndria
Álcool desidrogenase	Citosol
Monoamina oxidase	Mitocôndria
Xantina oxidase	Citosol
Azo ou nitro-redutases	Citosol
Aldo/ceto-redutases	Citosol
Óxido-redutases	Citosol
Epóxido hidrolase	Microssoma e citosol
Hidrolases (esterases, amidases, lipases)	Citosol e microssoma

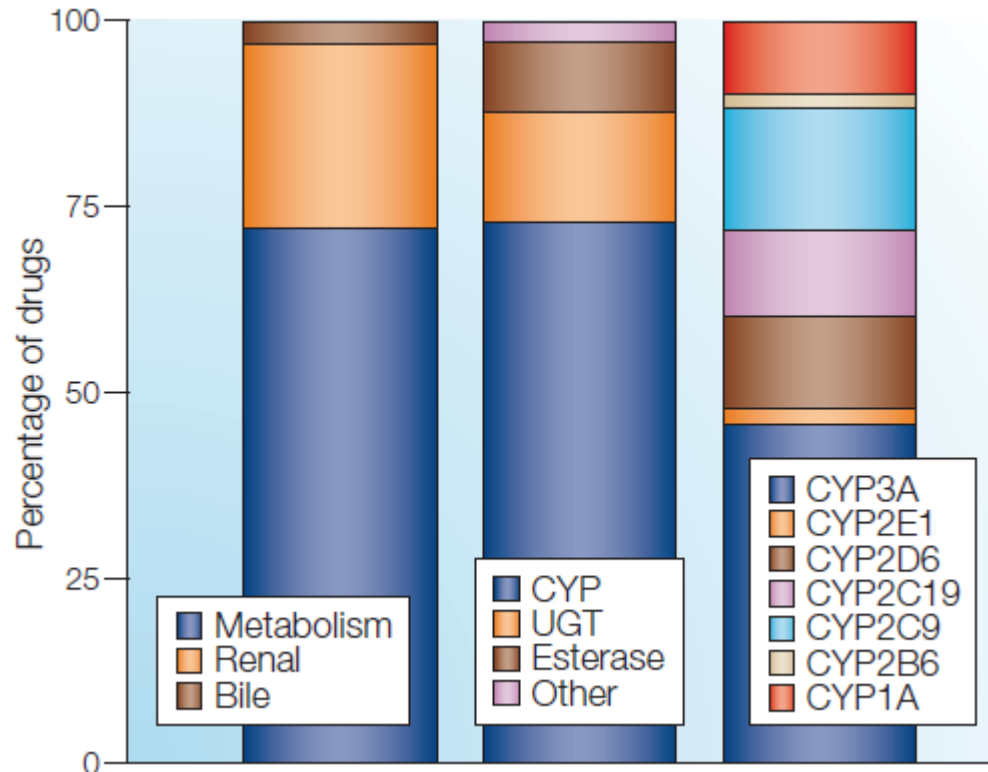
Barreiro, E.J. & Fraga, C.A.M., *Química Medicinal: As Bases Moleculares da Ação dos Fármacos*, ArtMed Editora Ltda, Porto Alegre, RS, 3ª Edição, 2014.

Reações metabólicas de Fase 1: Oxidação, Redução e Hidrólise

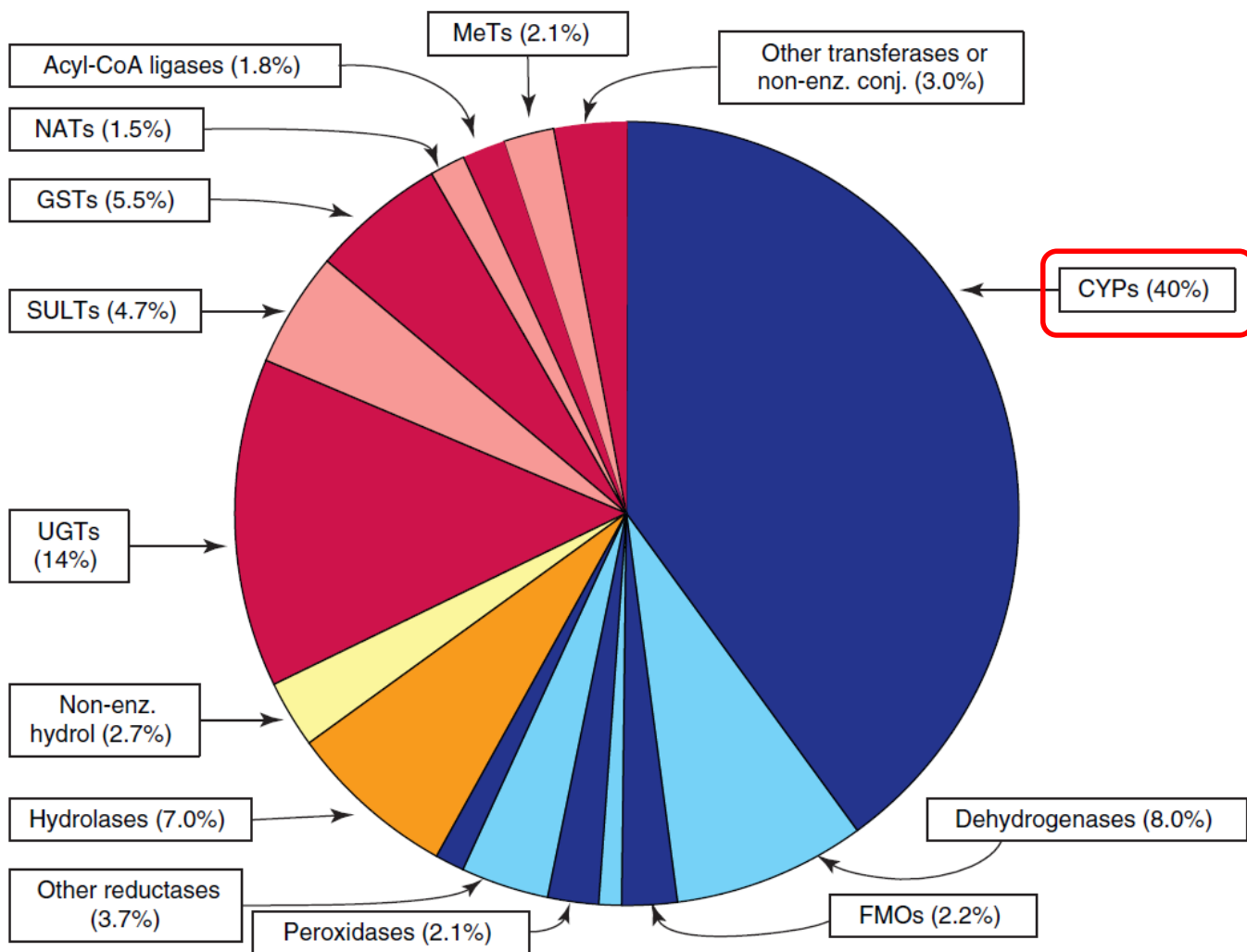
Metabolismo de Fase 2

Complexo Enzimático	Localização subcelular principal
Glicuroniltransferase	Microssoma
Glutationatransferase	Citosol
Sulfotransferase	Citosol
Metiltransferases não específicas	Citosol
Catecol o-metil transferase	Citosol
Acetiltransferase	Citosol

Reações metabólicas de Fase 2: Conjugação



Routes of elimination of the top 200 most prescribed drugs in 2002. Metabolism represents the listed clearance mechanism for ~73% of the top 200 drugs. Of the drugs cleared via metabolism, about three-quarters are metabolized by members of the cytochrome P450 (CYP) superfamily. For the CYP-mediated clearance mechanisms, the majority of drug oxidations (46%) were carried out by members of the CYP3A family; followed by 16% by CYP2C9; 12% for both CYP2C19 and CYP2D6; 9% for members of the CYP1A family; and 2% for both CYP2B6 and CYP2E1. UGT, uridine diphosphate glucuronyl transferase



Drug Discovery Today

Distribution of metabolites according to enzyme (super) families or categories. The percentages shown refer to 6967 enzyme occurrences = 100%; they were rounded to two significant digits. The colour code is as follows: **Redox reactions blue**; **hydrolyses yellow**; **conjugations red**. Alternating dark and light fields are used simply for graphical clarity.

CYP450: 57 genes, divididos em 18 famílias e 44 subfamílias

Famílias de CYP450 humana	Membros funcionais	Principais funções
CYP1	1A1, 1A2, 1B1	Metabolismo de xenobióticos
CYP2	2A6, 2A7, 2A13, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 2F1, 2J2, 2R1, 2S1, 2U1, 2W1	Metabolismo de xenobióticos & Metabolismo de esteroides
CYP3	3A4, 3A5, 3A7, 3A43	Metabolismo de xenobióticos
CYP4	4A11, 4A22, 4B1, 4F2, 4F3, 4F8, 4F11, 4F12, 4F22, 4V2, 4X1, 4Z1	Metabolismo de ácidos graxos e ácido araquidônico
CYP5	5A1	Síntese de tromboxana A2 (tromboxana sintase)
CYP7	7A1, 7B1	Esteróide 7 α -hidroxilase
CYP8	8A1, 8B1	Síntese de prostaciclina (prostaglandina sintase) e biossíntese de ácidos biliares
CYP11	11A1, 11B1, 11B2	Biossíntese de esteróides
CYP17	17A1	Biossíntese de testosterona e estrogênio (esteróide 17 α -hidroxilase)
CYP19	19A1	Biossíntese de estrogênio (aromatase)
CYP20	20A1	Desconhecidas
CYP21	21A2	Biossíntese de esteroides
CYP24	24A1	Metabolismo da vitamina D
CYP26	26A1, 26B1, 26C1	Metabolismo do ácido retinóico (hidroxilase da ácido retinóico)
CYP27	27A1, 27B1, 27C1	Biossíntese de ácidos biliares e ativação da vitamina D3
CYP39	39A1	Metabolismo do colesterol
CYP46	46A1	Metabolismo do colesterol (colesterol 24-hidroxilase)
CYP51	51A1	Metabolismo do colesterol (lanosterol 14 α -demetilase)

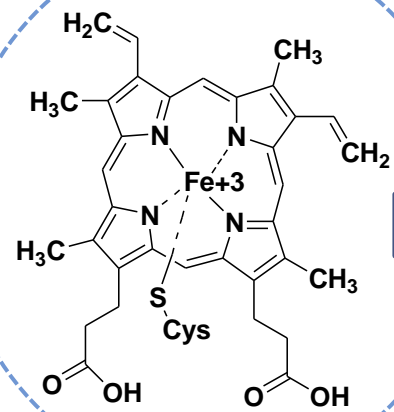
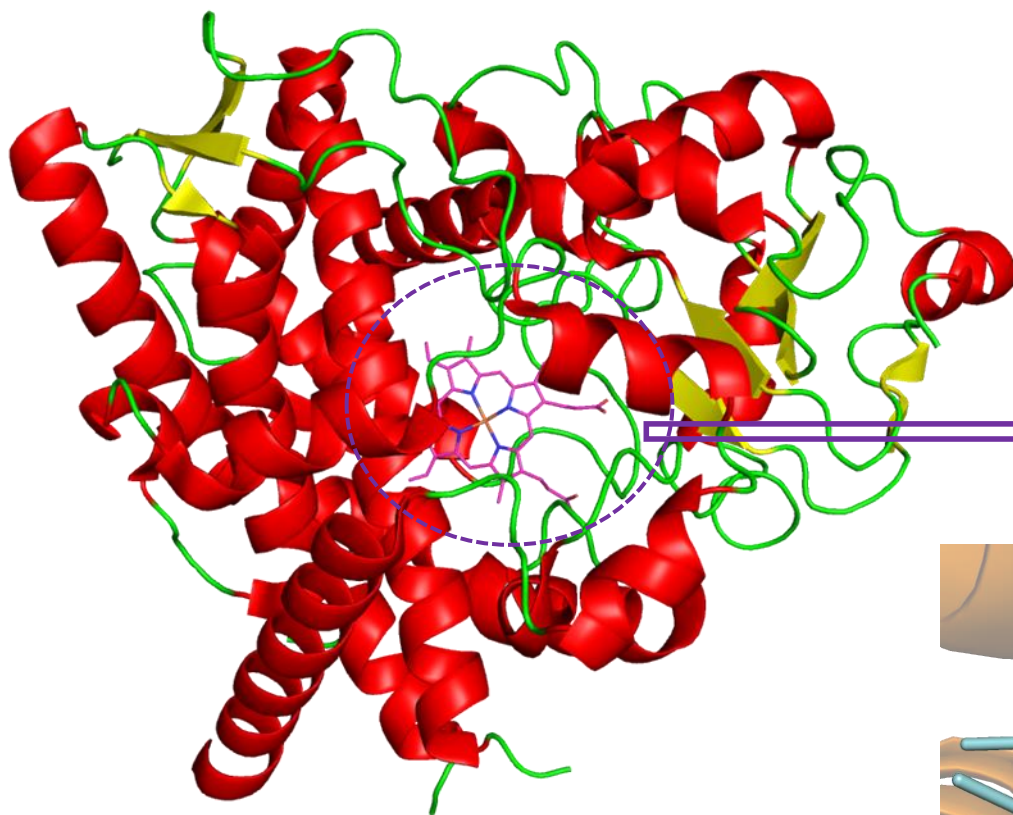
CYP450 & CARACTERÍSTICAS BIOQUÍMICAS

Number of human CYP450 estimated at 57 genes: divided in 18 families e 44 subfamilies

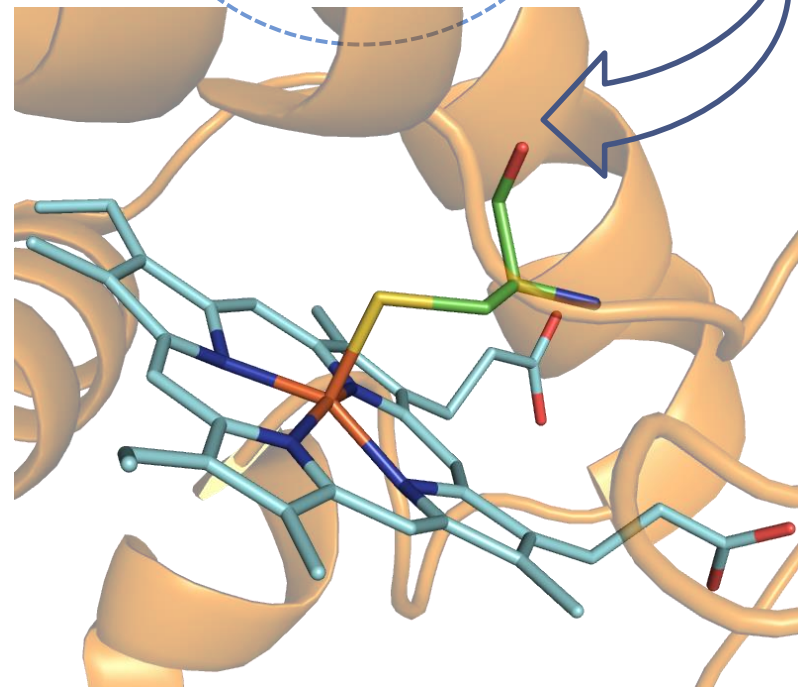
- 1- They are all monooxygenases
- 2- So that all Cytochrome P450's are heme proteins (can also be called mixed function oxidases)
- 3-They all catalyze a reaction: $\text{NAD(P)H}(\text{electron donor})^* + \text{O}_2 \text{RH} + \text{H}^+ \rightarrow \text{NAD(P)}^+ + \text{ROH} + \text{H}_2\text{O}$
- 4- The O_2 is split, so one molecule of the oxygen goes into the substrate, and the other is reduced to H_2O
- 5- the oxygen is carried on a Heme (Heme is the prosthetic group of the enzyme)
- 6- This is the same type of heme as in hemoglobin and myoglobin
- 7- The heme in the reaction cycles between Fe^{+3} to Fe^{+2} back to Fe^{+3} , whereas in hemoglobin or myoglobin, you want the heme to be Fe^{+2}
- 8- require a **Cytochrome P450 oxidoreductase (POR)** to transfer electrons from NADPH to their substrate.

*NADH is the reducing cofactor in bacterial and NADPH is the reducing cofactor in all mammalian

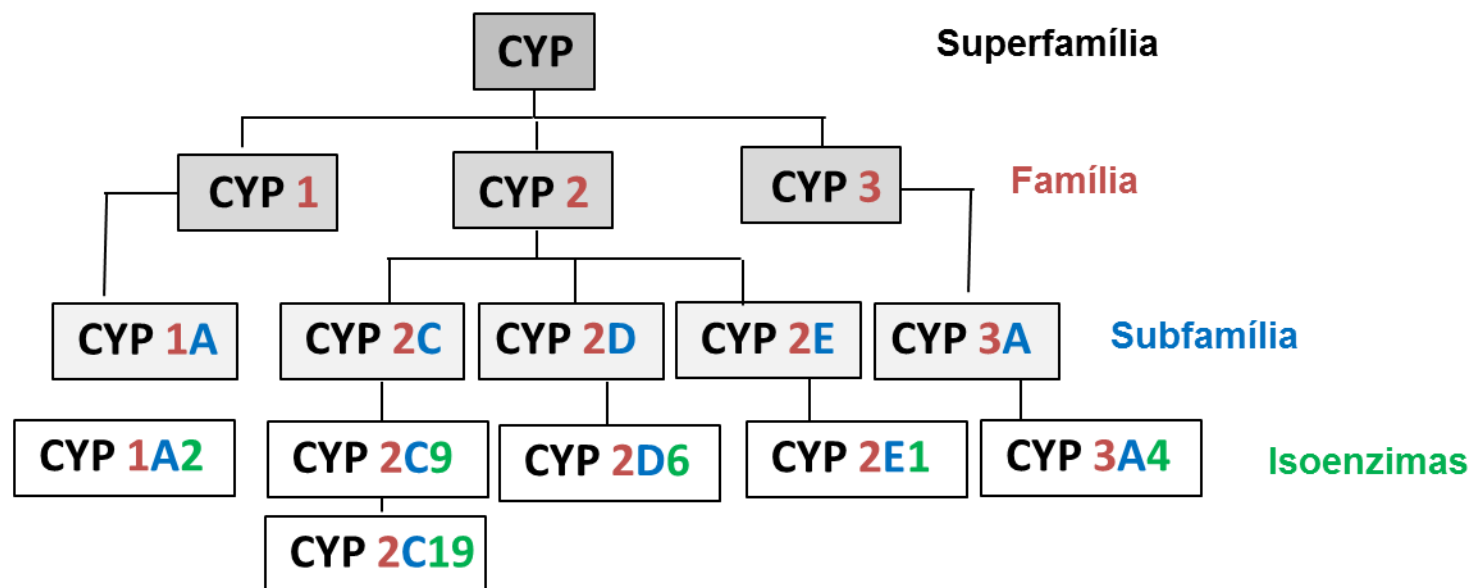
POR can directly metabolize a number of drugs by 1-electron reduction reactions. This is particularly the case for drugs with quinone moieties, including several anticancer prodrugs such as menadione, mitomycin C, tirapazamine



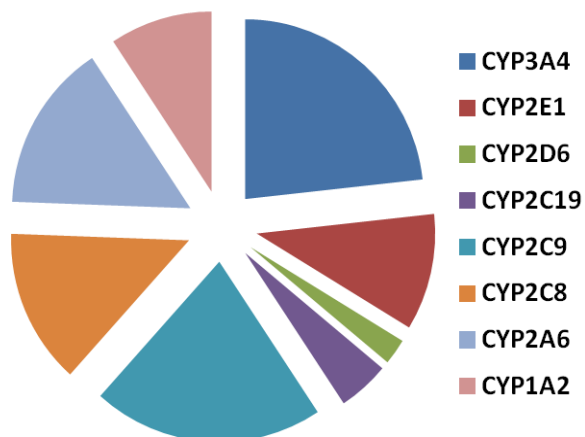
Estrutura cristalográfica do CYP3A4 (PDB 4K9W)



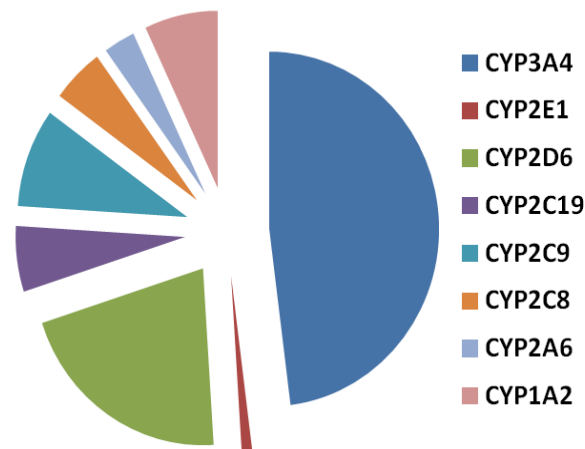
CYP450: NOMENCLATURA & RELEVÂNCIA



CYP contents in human liver microsomes

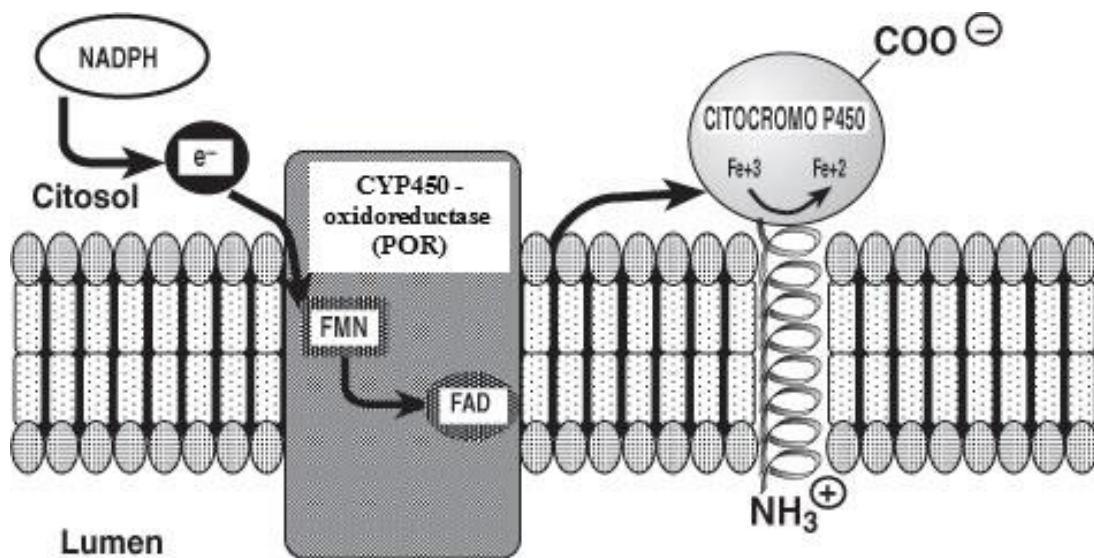


CYP contribution to drug metabolism



CYP450: DISTRIBUIÇÃO & LOCALIZAÇÃO

- São proteínas ligadas a membrana do retículo endoplasmático liso (*i.e.* microsomas) e mitocôndrias
- Presentes em alta concentração no retículo endoplasmático de órgãos como: **fígado**, rins, vias nasais, cérebro, pele e **intestino**



“NADPH-citocromo P450 redutase”

Substratos de baixo a elevado PM
[eg. MeOH (PM = 42 g/mol) e Ciclosporina (PM = 1203 g/mol)]

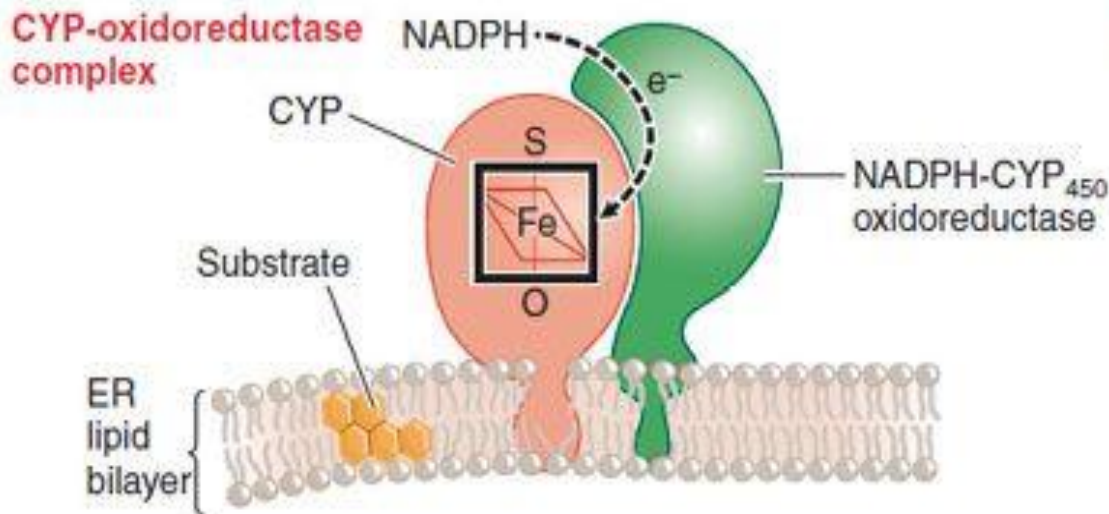
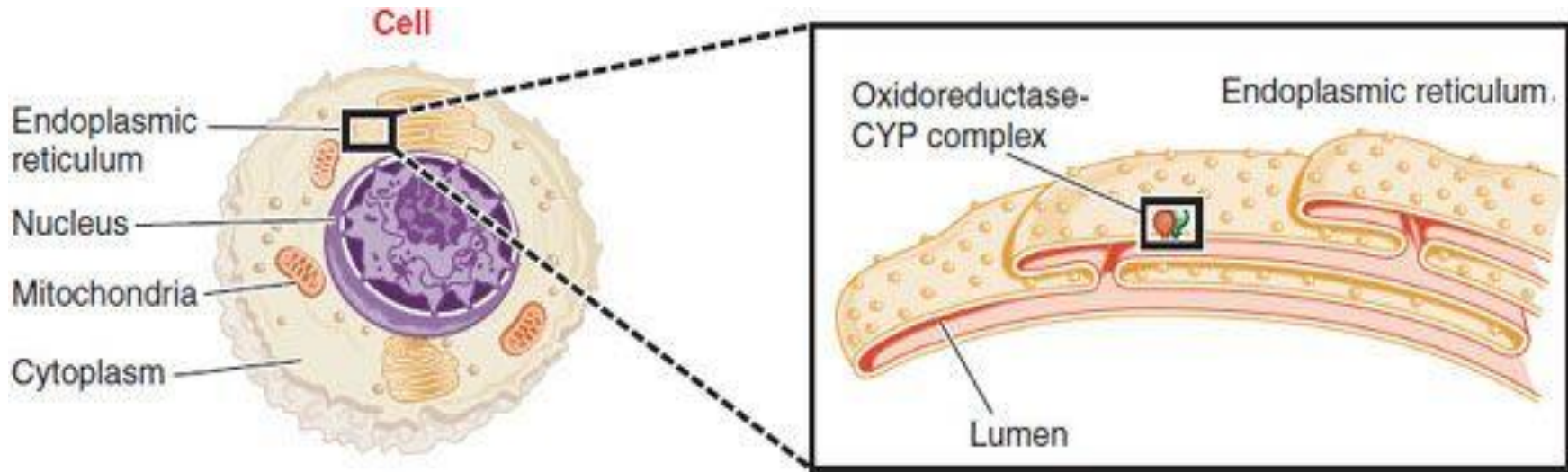
- ❖ *Substratos de elevada diversidade química*
- ❖ *Hidrofóbicos*

Sítio ativo

Volume variável entre as ≠ isoformas: 630 Å³ (CYP1A2) a 1500 Å³ (CYP3A4)
Distância entre heme e SoM ≤ 4,0Å.

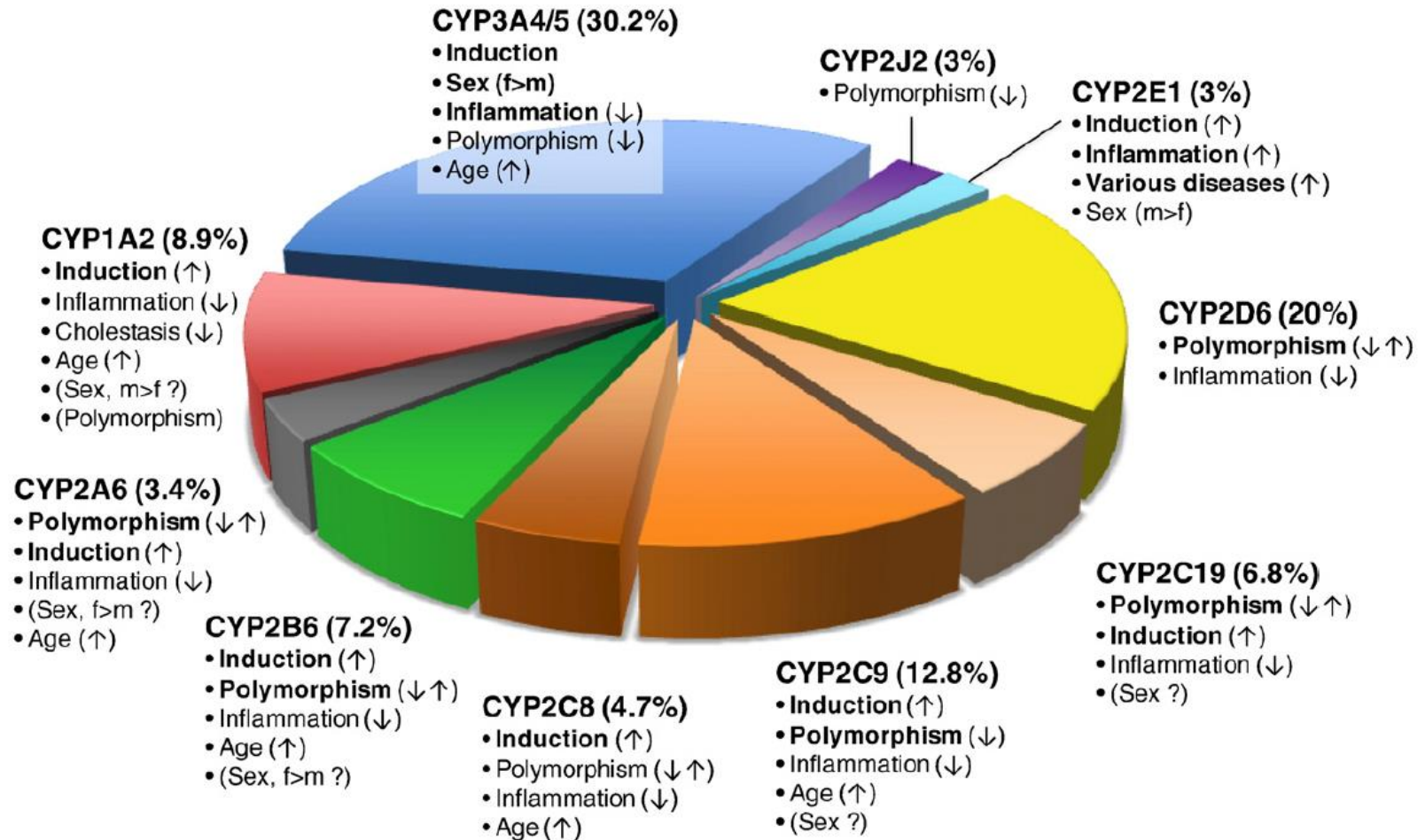
Rev Méd Chile 2004; 132: 85-94
Methods Princ. Med. Chem. 2006, 27, 273-290

CYP450: DISTRIBUIÇÃO & LOCALIZAÇÃO

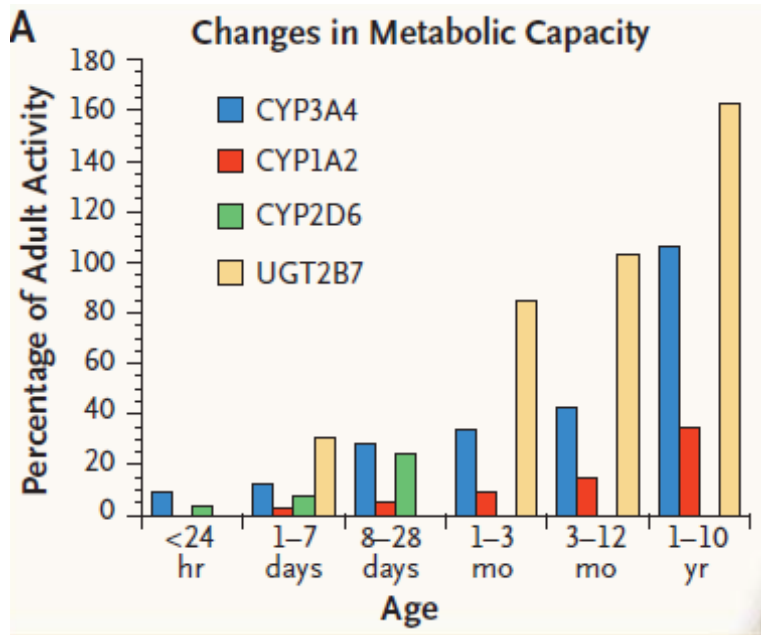


Location of CYPs in the cell. The figure shows increasingly microscopic levels of detail, sequentially expanding the areas within the *black boxes*. **CYPs are embedded in the phospholipid bilayer of the endoplasmic reticulum (ER).** Most of the enzyme is located on the cytosolic surface of the ER. A second enzyme, **NADPH-cytochrome P₄₅₀ oxidoreductase**, transfers electrons to the CYP where it can, in the presence of O₂, oxidize **xenobiotic substrates**, many of which are hydrophobic and dissolved in the ER. A single NADPH-CYP oxidoreductase species transfers electrons to all CYP isoforms in the ER.

FATORES QUE INFLUENCIAM FUNÇÃO E EXPRESSÃO DO CYP450



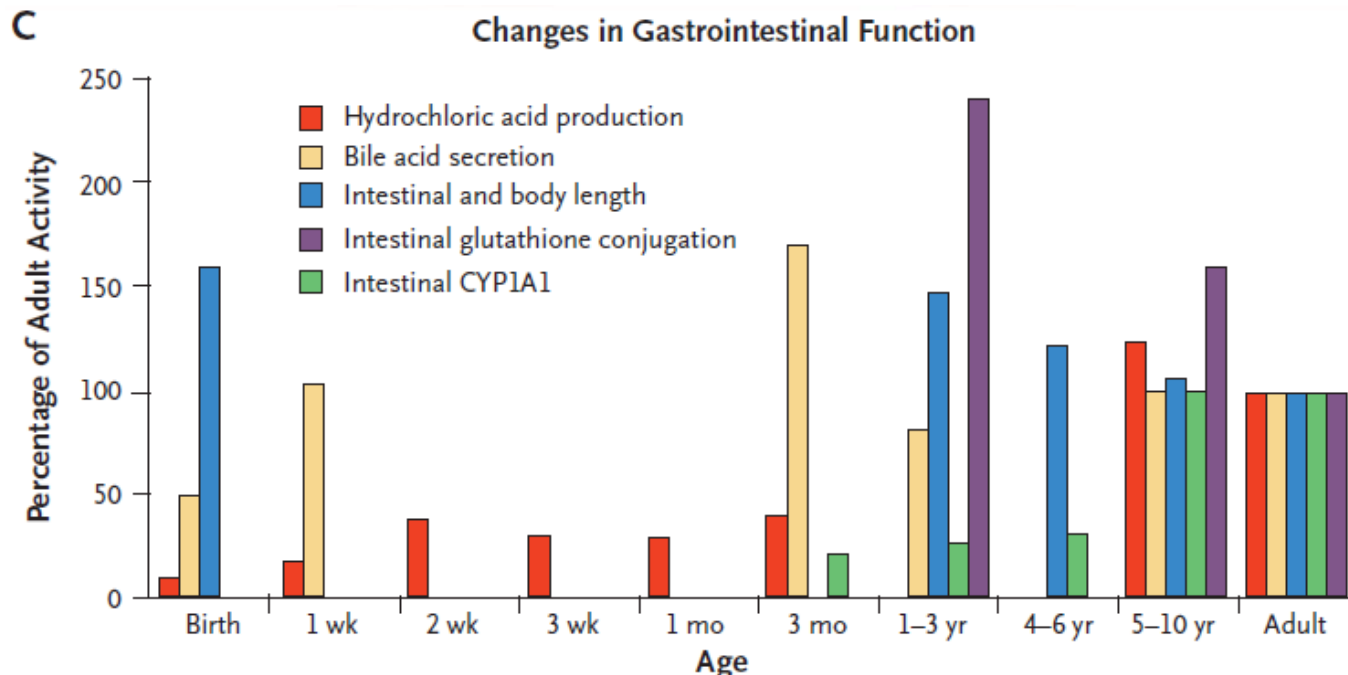
Fraction of clinically used drugs metabolized by P450 isoforms and factors influencing variability. A total of 248 drug metabolism pathways with known CYP involvement were analyzed. Each metabolic pathway was only counted once for the major contributing CYP isoform. **Important variability factors are indicated by bold type with possible directions of influence indicated (↑, increased activity; ↓, decreased activity; ↑↓, increased and decreased activity). Factors of controversial significance are shown in parentheses.**



Panel A, the activity of many cytochrome P-450 (CYP) isoforms and a single glucuronosyltransferase (UGT) isoform is markedly diminished during the first two months of life.

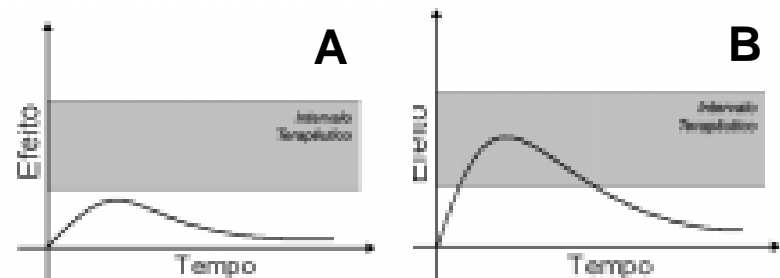
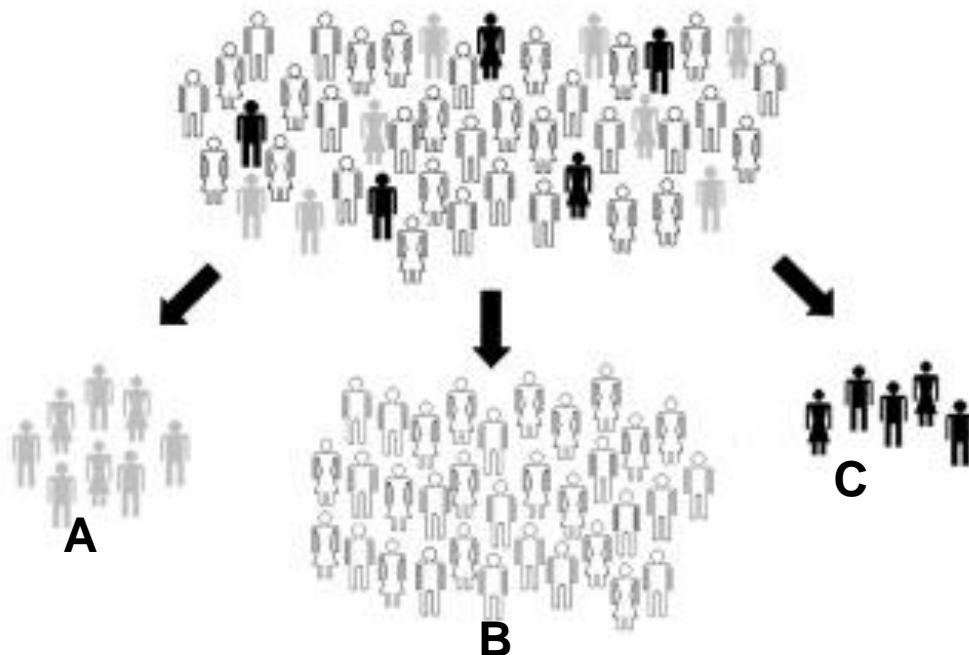
Panel C shows the age-dependent changes in both the structure and function of the gastrointestinal tract. As with hepatic drug-metabolizing enzymes (Panel A), the activity of cytochrome P-450 1A1 (CYP1A1) in the intestine is low during early life.

G. L. Kearns et al., *N Engl J Med*, 2003, 349:1157-67



CYP450 & POLIMORFISMO

Variações nas sequências de nucleotídeos do DNA, que ocorrem na população geral de forma estável, sendo encontradas com frequência de 1% ou superior, são denominadas polimorfismos genéticos

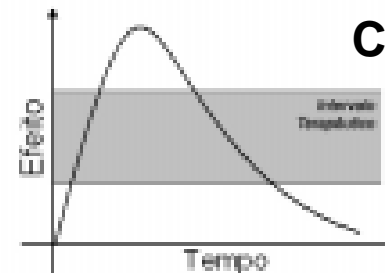


METABOLIZADORES RÁPIDOS

METABOLIZADORES INTERMEDIÁRIOS

Sem Efeito

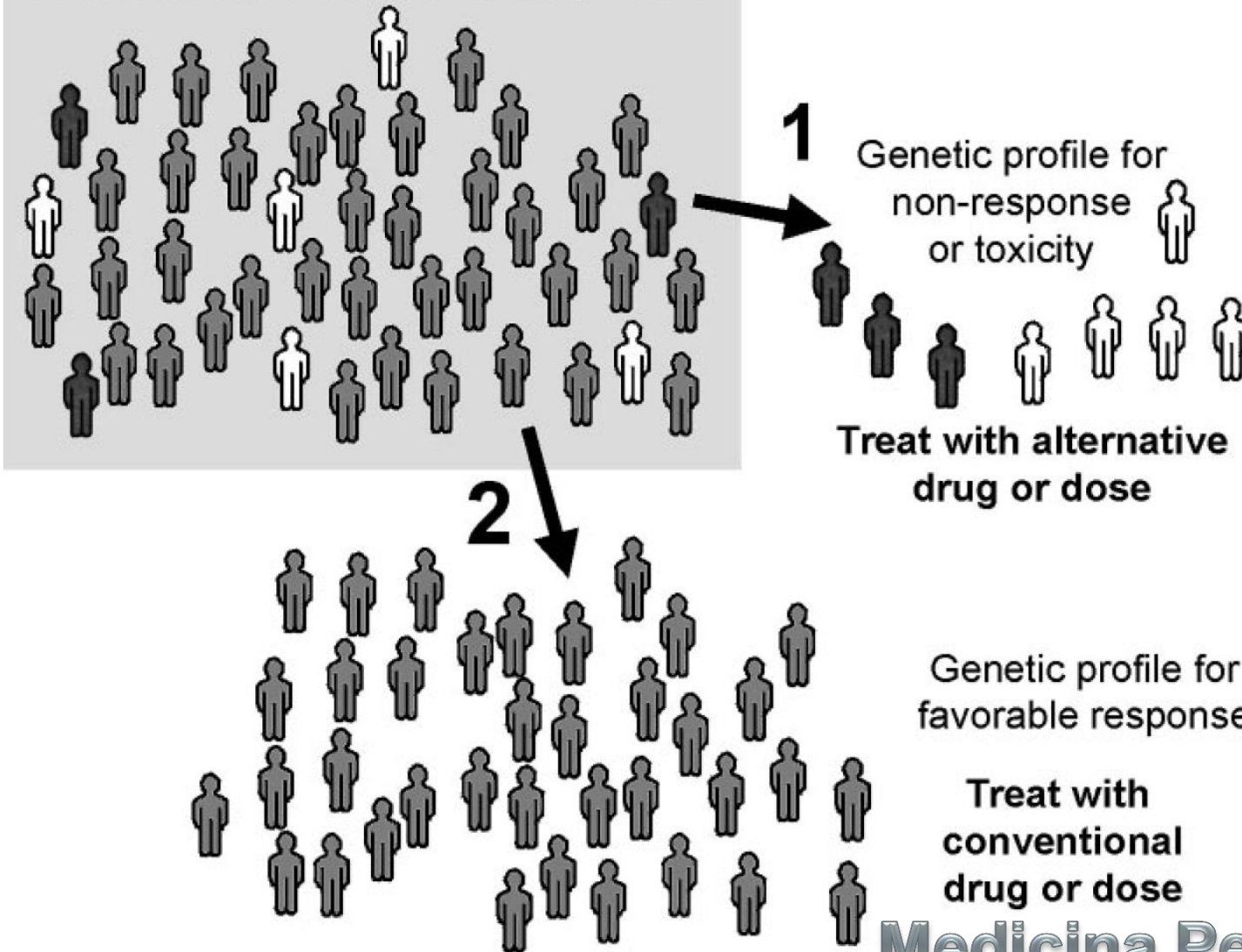
Efeito Esperado



METABOLIZADORES LENTOS

Reações Adversas / Toxicidade

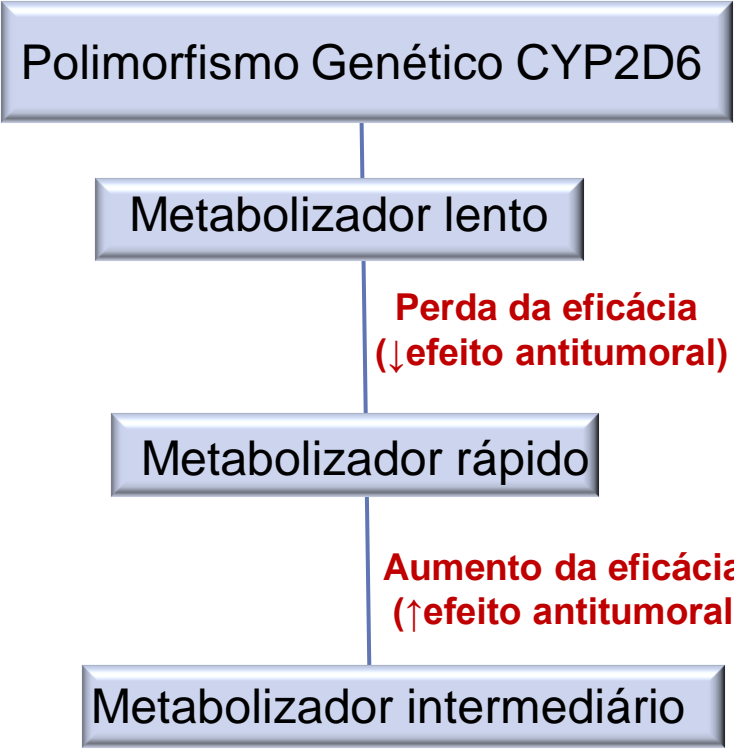
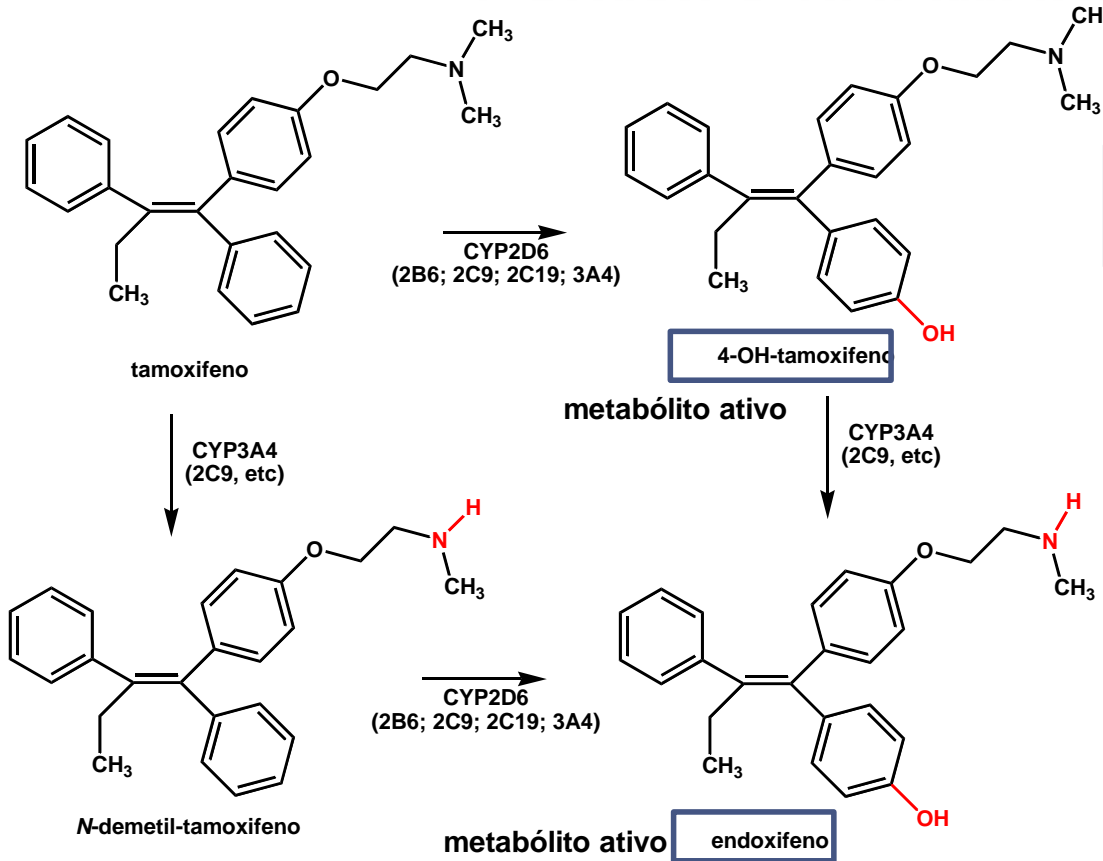
All patients with same diagnosis



The potential of pharmacogenomics is to identify patients within a population with the same diagnosis (e.g., hypertension, leukemia, asthma, etc.), who are genetically pre-disposed either not to respond to therapy or to develop unacceptable toxicity, and then to prospectively alter their therapy to avoid treatment that is not likely to be optimal. The remaining, now more homogeneous population, can then be treated with conventional therapy in which they are not genetically predisposed to fail.

Medicina Personalizada

CYP450 & POLIMORFISMO

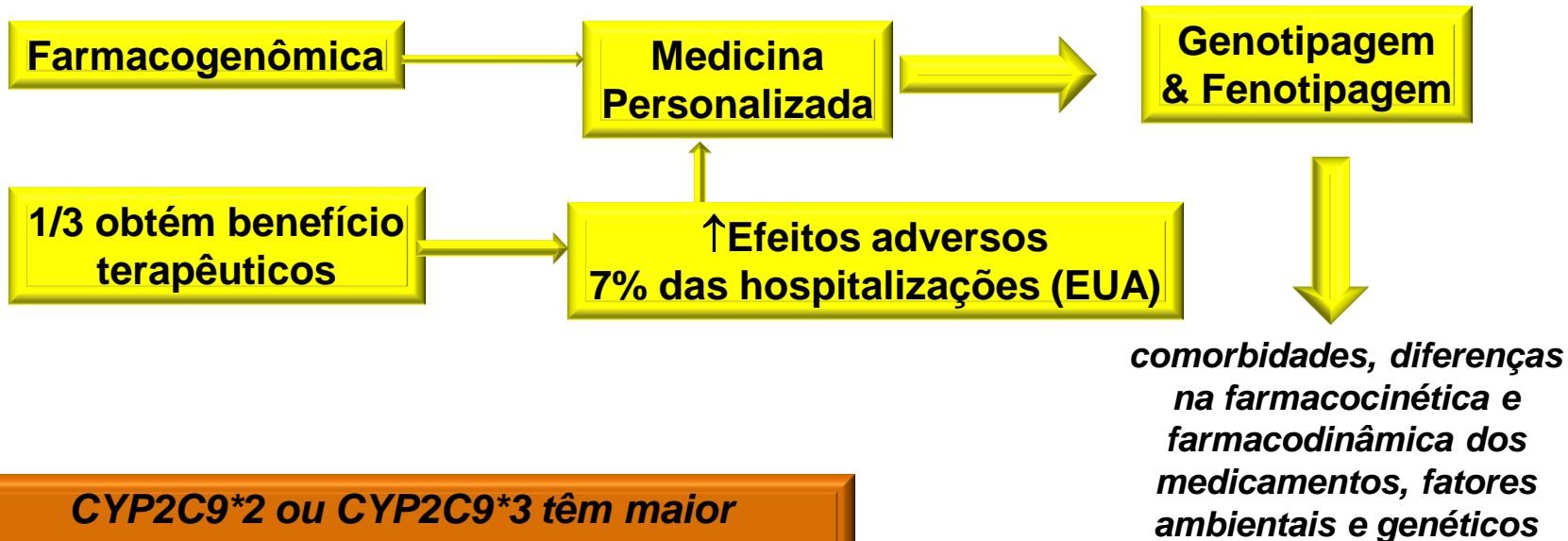


Endoxifen

Only potential drug for ER positive premenopausal women with CYP2D6 deficiency

http://jinapharma.com/?page_id=184

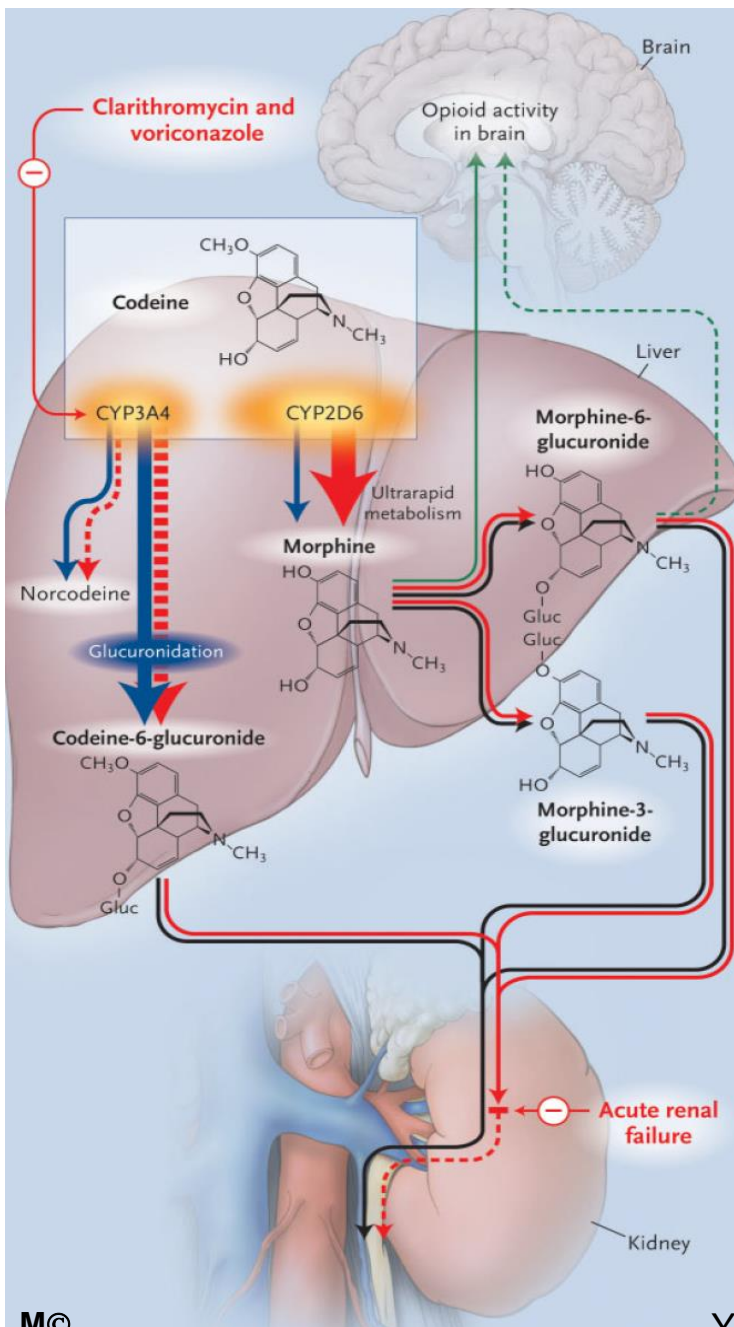
CYP450 & POLIMORFISMO



CYP2C9*2 ou CYP2C9*3 têm maior susceptibilidade a complicações hemorrágicas com o tratamento com warfarina



Monçores et al. Rev SOCERJ. 2008;21(3):184-193



The conversion of codeine into norcodeine by CYP3A4 and into codeine-6-glucuronide by glucuronidation usually represents 80 percent of codeine clearance, and conversion of codeine into morphine by CYP2D6 represents only 10 percent of codeine clearance (blue arrows).

Morphine is further metabolized into morphine-6-glucuronide and into morphine-3-glucuronide. Morphine and morphine-6-glucuronide have opioid activity (green arrows). Glucuronides are eliminated by the kidney and are thus susceptible to accumulation in cases of acute renal failure. The patient (red arrows) had ultrarapid CYP2D6 metabolism, inhibition of CYP3A4 as a result of treatment with clarithromycin and voriconazole, and glucuronide accumulation due to acute renal failure. Red arrows with dotted lines indicate low levels of drug conversion or elimination, green arrows with dotted lines indicate low levels of brain penetration, and thick arrows indicate high levels.

CYP2D6 ultrarapid-metabolism genotype and phenotype, in combination with drug-induced inhibition of CYP3A4 activity and a reduction in renal function → central nervous system depression

TABLE 1 Genetic polymorphisms of human drug metabolizing enzymes and transporters

Enzyme	Substrates	Consequences of polymorphism for drug effects
Phase I enzymes		
CYP1A1	Benzo(a)pyrene, phenacetin	Not yet elucidated
CYP1A2	Acetaminophen, amonafide, caffeine, paraxanthine, ethoxyresorufin, propranolol, fluvoxamine	Not yet elucidated
CYP1B1	Estrogen metabolites	Not yet elucidated
CYP2A6	Coumarin, nicotine, halothane	Cigarette addiction
CYP2B6	Cyclophosphamide, aflatoxin, mephenytoin	Not yet elucidated
CYP2C8	Retinoic acid, paclitaxel	Not yet elucidated
CYP2C9	Tolbutamide, warfarin, phenytoin, non-steroidal anti-inflammatories	Anticoagulant effect of warfarin
CYP2C19	Mephenytoin, omeprazole, hexobarbital, mephobarbital, propranolol, proguanil, phenytoin	Peptic ulcer response to omeprazole
CYP2D6	Beta blockers, antidepressants, antipsychotics, codeine, debrisoquin, dextromethorphan, encainide, flecainide, fluoxetine, guanoxan, methoxy-amphetamine, N-propylajmaline, perhexiline, phenacetin, phenformin, propafenone, sparteine	Tardive dyskinesia from antipsychotics narcotic side effects, efficacy, and dependence, imipramine dose requirement, beta blocker effect
CYP2E1	N-nitrosodimethylamine, acetaminophen, ethanol	Possible effect on alcohol consumption
CYP3A4/3A5/3A7	Macrolides, cyclosporin, tacrolimus, calcium channel blockers, midazolam, terfenadine, lidocaine, dapsone, quinidine, triazolam, etoposide, teniposide, lovastatin, alfentanil, tamoxifen, steroids, benzo(a)pyrene	Not yet elucidated, polymorphic 3A5 expression linked to 3A5 polymorphism
Aldehyde dehydrogenase (ALDH2)	Cyclophosphamide, vinyl chloride	SCE frequency in lymphocytes
Alcohol dehydrogenase (ADH3)	Ethanol	Increased alcohol consumption and dependence
Dihydropyrimidine dehydrogenase	Fluorouracil	5-fluorouracil neurotoxicity
NQO1 (DT-diaphorase)	Ubiquinones, menadione, mitomycin C	Menadione-associated urolithiasis

Phase II Enzymes

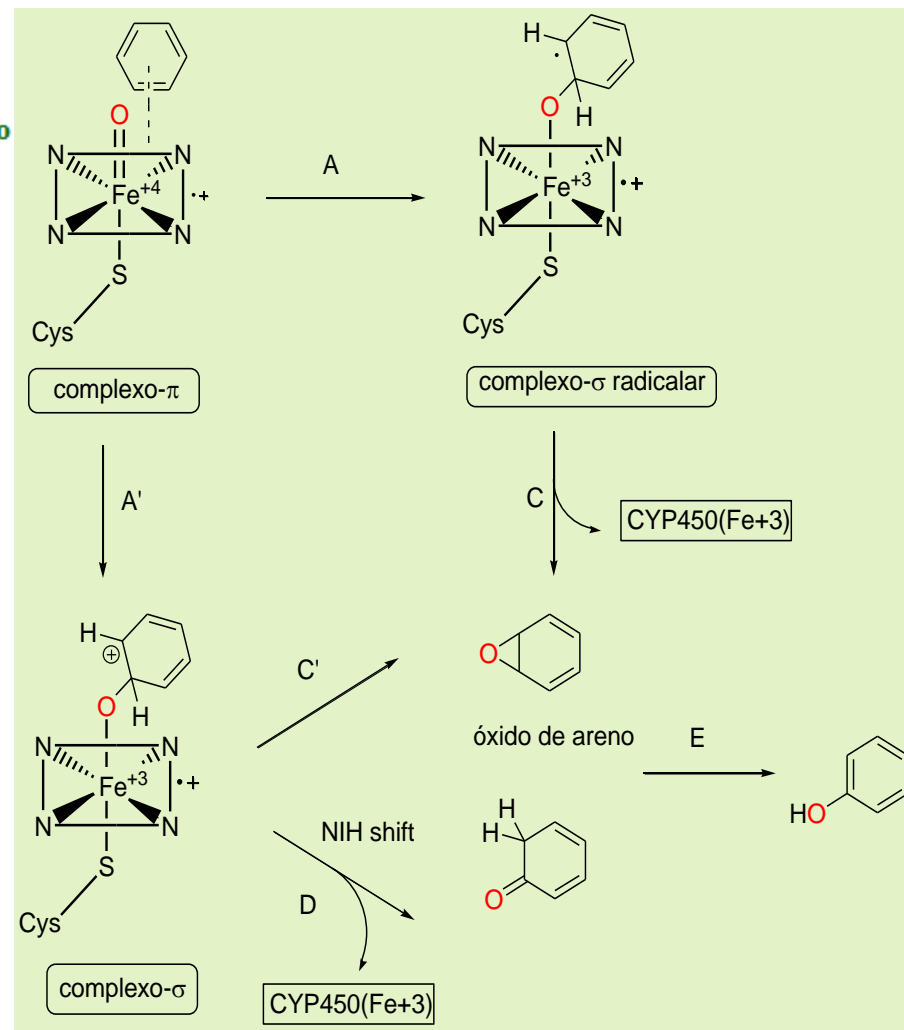
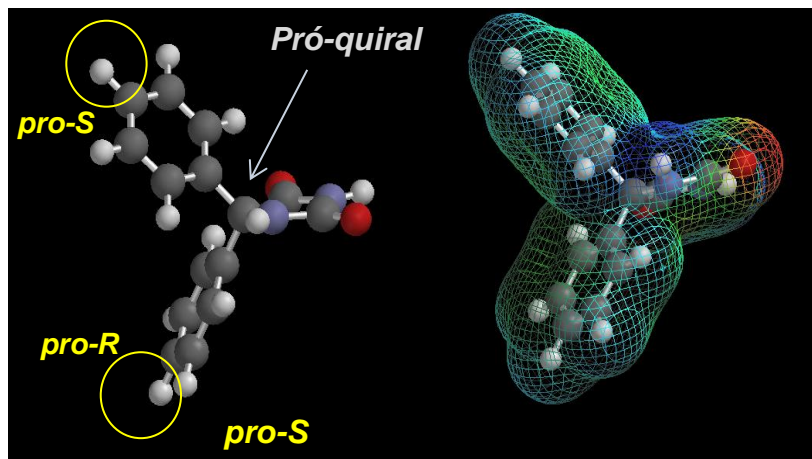
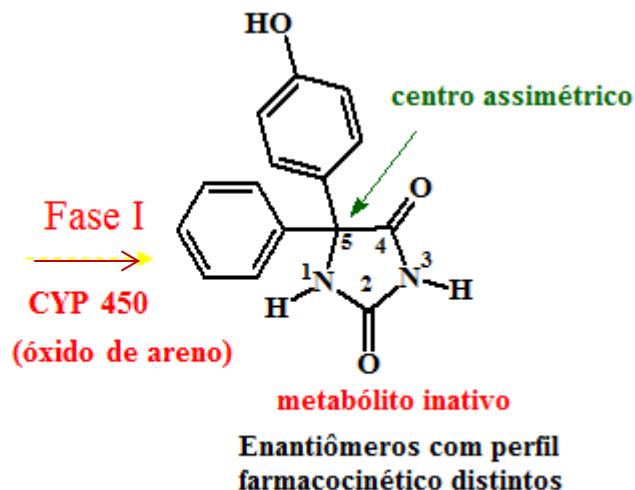
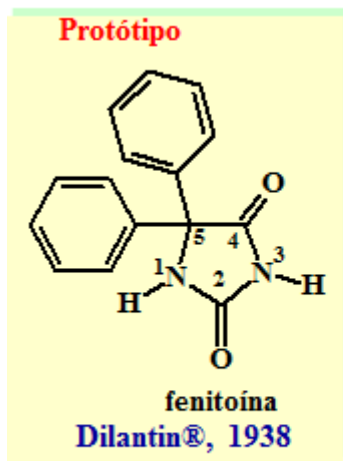
N-acetyltransferase (NAT1)	P-aminosalicylic acid, p-aminobenzoic acid, sulfamethoxazole	Not yet elucidated
N-acetyltransferase (NAT2)	Isoniazid, hydralazine, sulfonamides, amonafide, procainamide, dapsone, caffeine	Hypersensitivity to sulfonamides, amonafide toxicity, hydralazine-induced lupus, isoniazid neurotoxicity
Glutathione transferase GSTM1, M3, T1	Aminochrome, dopachrome, adrenochrome and noradrenochrome	Not yet elucidated
Glutathione transferase GSTP1	13-cis retinoic acid, ethacrynic acid, acrolein, epirubicin	Not yet elucidated
Sulfotransferases	Steroids, acetaminophen, estrogens, dopamine, epinephrine, naringenin	Not yet elucidated
Catechol-O-methyltransferase	Estrogens, levodopa, ascorbic acid	Substance abuse, levodopa response
Histamine methyltransferase	Histamine	Not yet elucidated
Thiopurine methyltransferase	Mercaptopurine, thioguanine, azathioprine	Thiopurine toxicity and efficacy, risk of second cancers
UDP-glucuronosyl-transferase UGT1A1	Irinotecan, bilirubin	Irinotecan glucuronidation
UDP-glucuronosyl-transferase UGT2Bs	Opioids, androgens, morphine, naproxen, ibuprofen	Not yet elucidated
Transporters		
BSEP	Conjugates	Not yet elucidated
MDR-1	Natural product anticancer drugs, CYP3A4 substrates, digoxin	Not yet elucidated
MRPs	Glutathione, glucuronide, and sulfate conjugates, nucleoside antivirals	Not yet elucidated

CYP450: REGIOSSELETIVIDADE DO PROCESSO OXIDATIVO

Ligação C-H	Tipo de Ligação	Energia de dissociação em KJ/mol
H-C₆H₅	fenila	464
H-CH ₃	metano	438
H-CH ₂ CH ₃	alquila primário	420
H-CH ₂ CH ₂ CH ₃	alquila primário	417
H-CH ₂ C(CH ₃) ₃	alquila primário	418
H-CH(CH ₃) ₂	alquila secundário	401
H-C(CH ₃) ₃	alquila terciário	390
H-CH₂Ph	benzílica primária	368
H-CH(CH ₃)Ph	benzílica secundário	357
H-CH(CH ₃) ₂ Ph	benzílica terciário	353
H-CH ₂ CH=CH ₂	alílica primária	361
H-CH(CH ₃)CH=CH ₂	alílica secundária	345

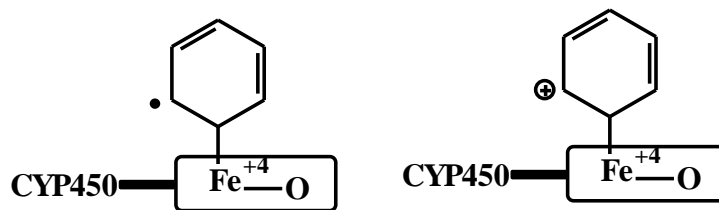
PONDERAÇÕES: FORÇA DA LIGAÇÃO C-H x ESTABILIDADE do RADICAL x EFEITO ESTÉRICO

1. Oxidação Aromática = Hidroxilação Aromática



An NIH shift is a chemical rearrangement where a hydrogen atom on an aromatic ring undergoes an intramolecular migration primarily during a hydroxylation reaction. This process is also known as a 1,2-hydride shift.

“balanço entre efeito eletrônico & estérico”

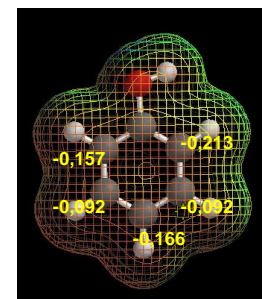
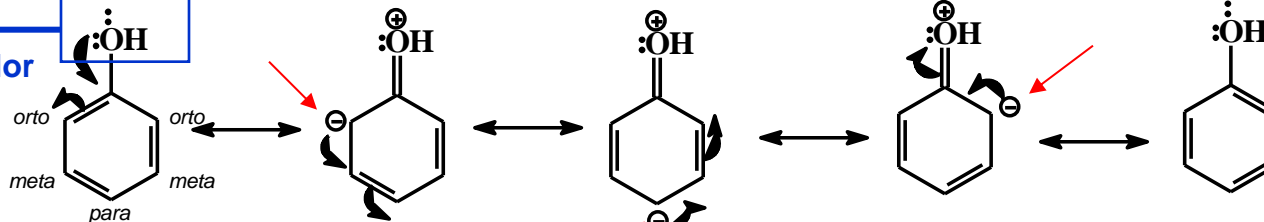


espécies deficientes em elétrons

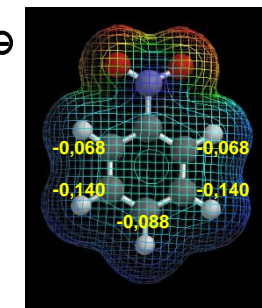
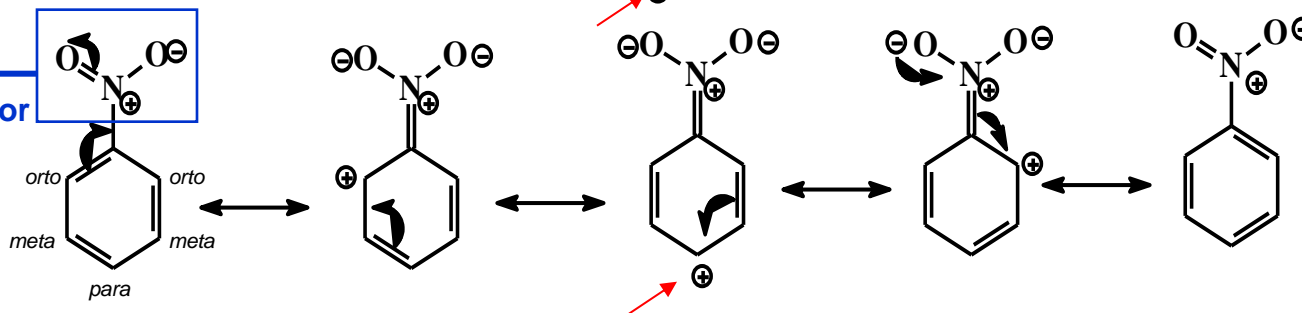
Papel dos Substituintes no Anel Aromático???



Grupo elétron doador



Grupo elétron retirador



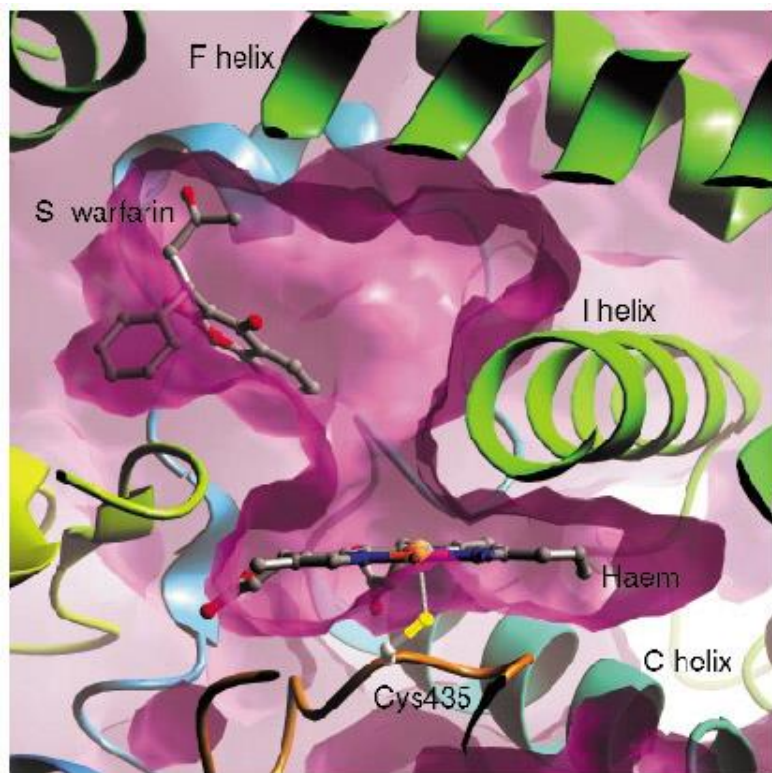
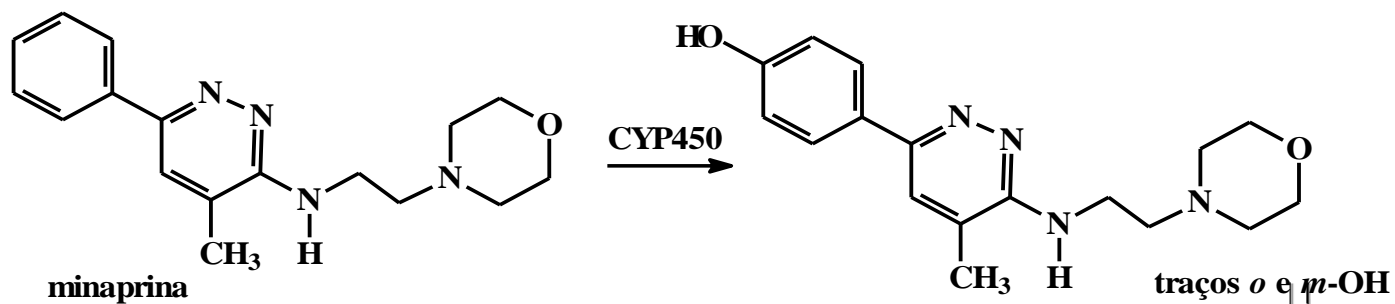
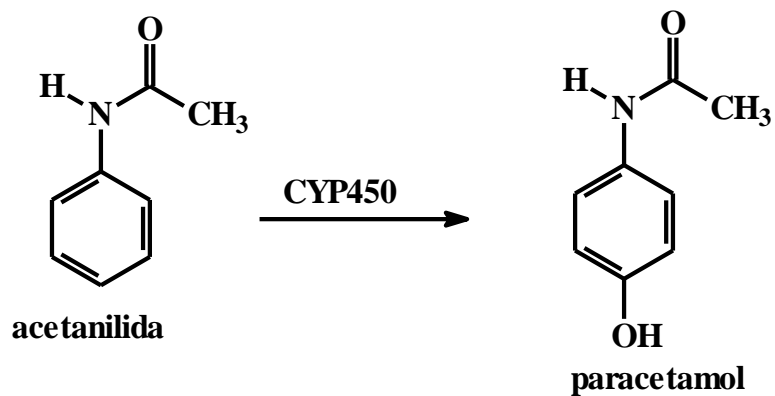
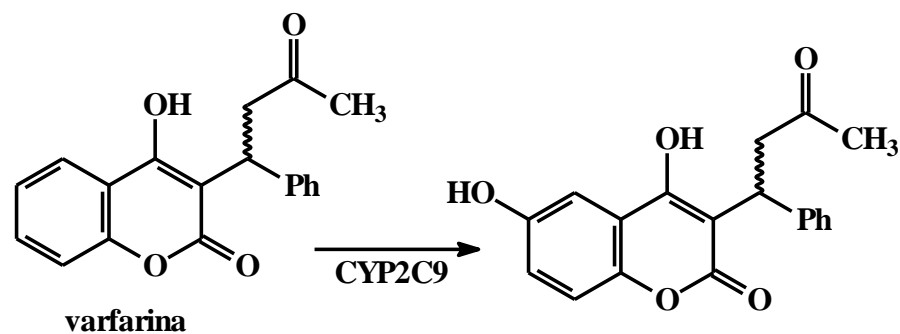
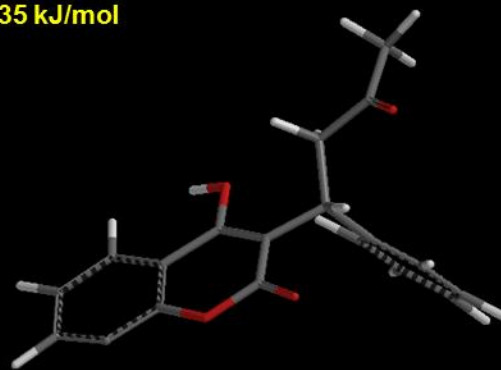
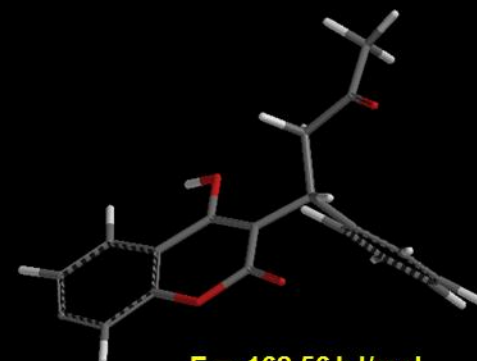
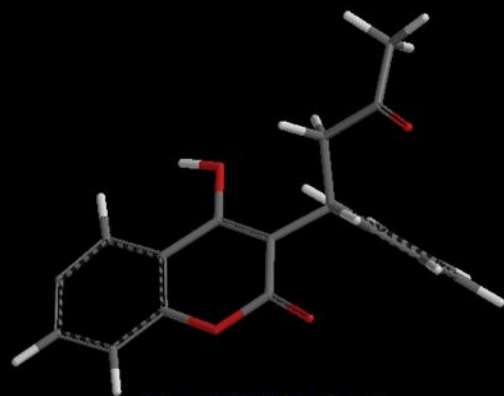
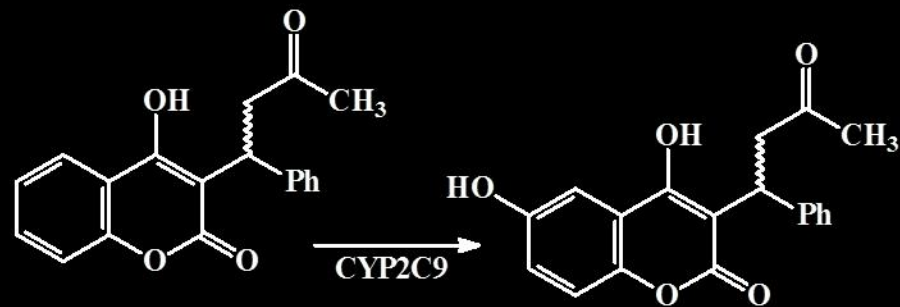
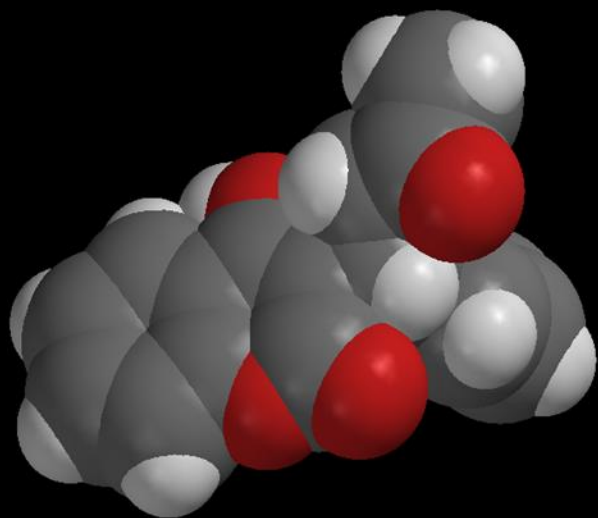
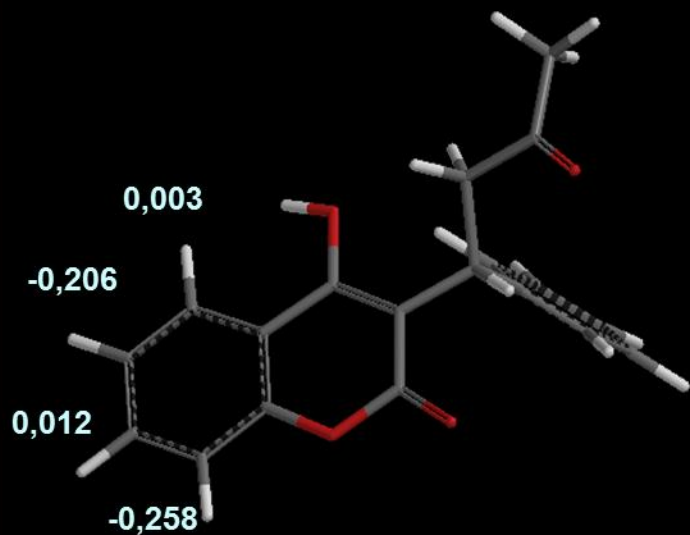


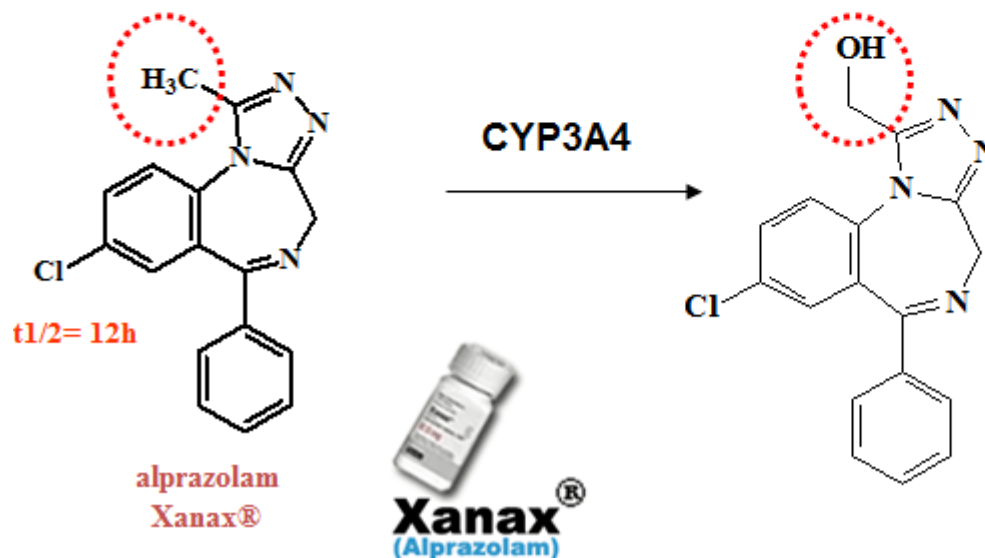
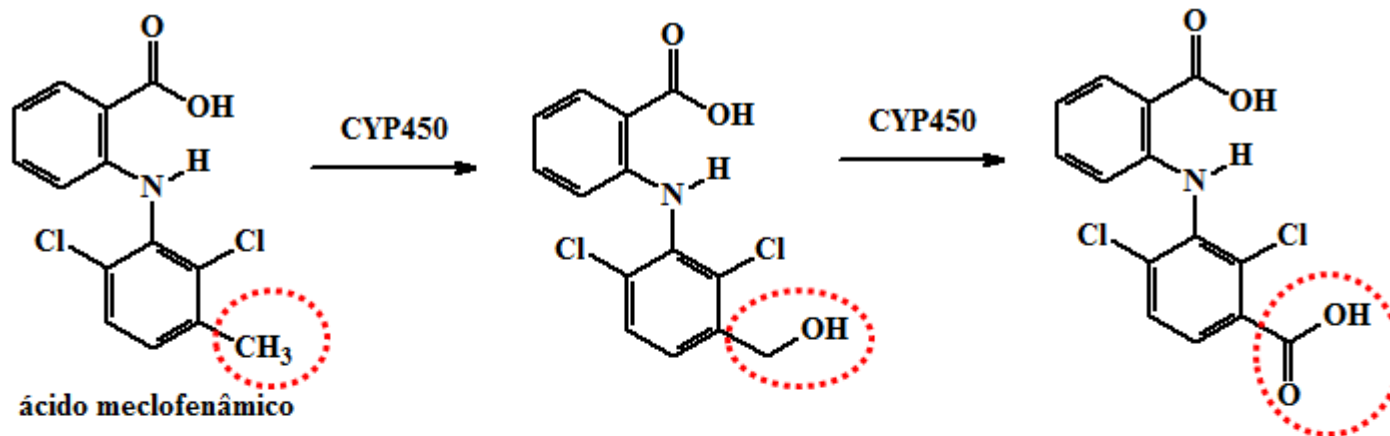
Fig. 1: The binding site of S-warfarin within the active site of CYP2C9 leaves the haem, shown edge on in the figure, accessible to other compounds [www.esrf.fr/.../Highlights/2003/MX/MX06].



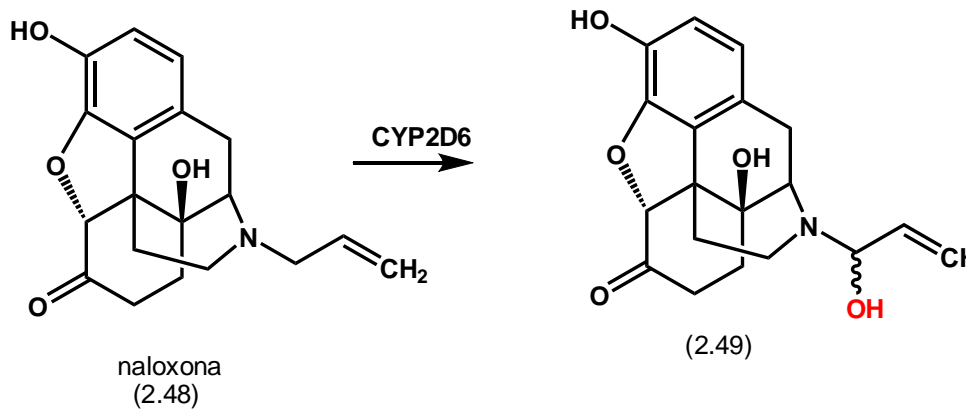
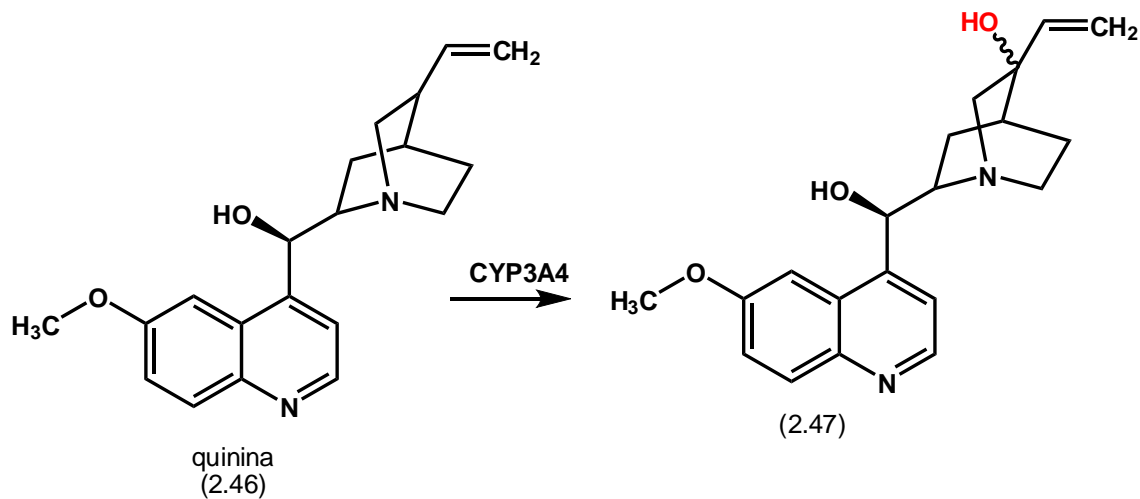
CARGA ELETROSTÁTICA



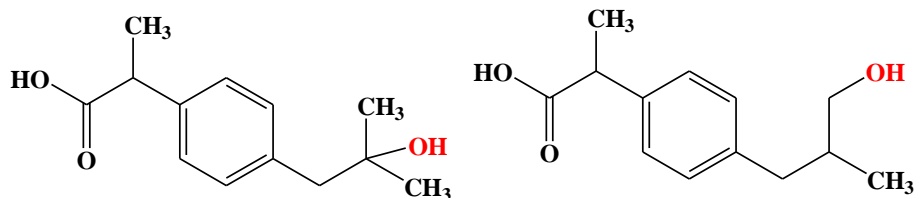
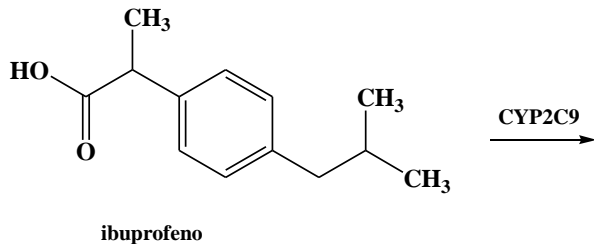
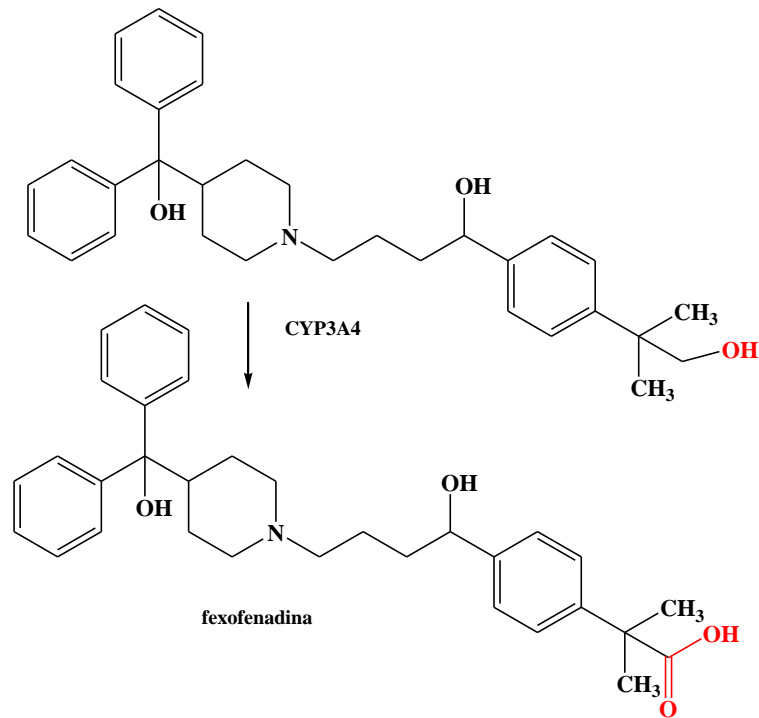
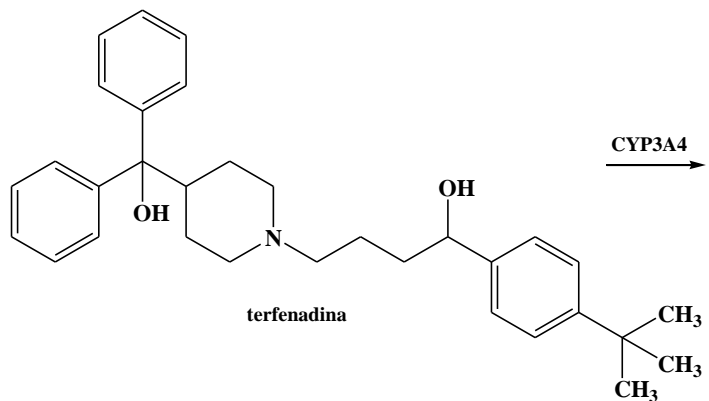
2. Hidroxilação benzílica



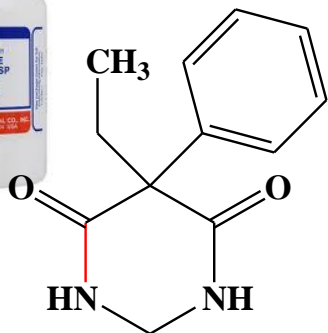
3. Hidroxilação alílica



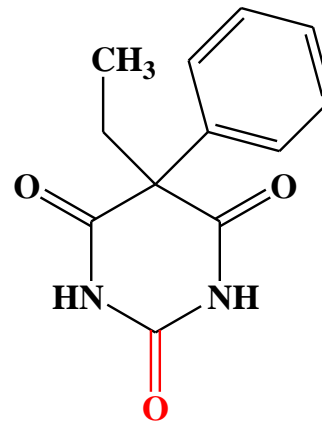
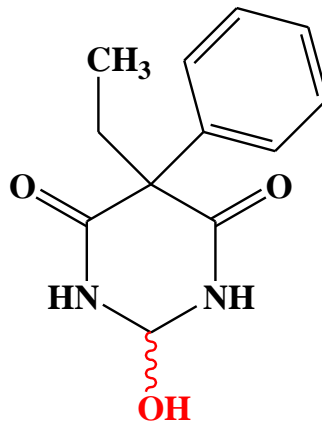
4. Hidroxilação alifática



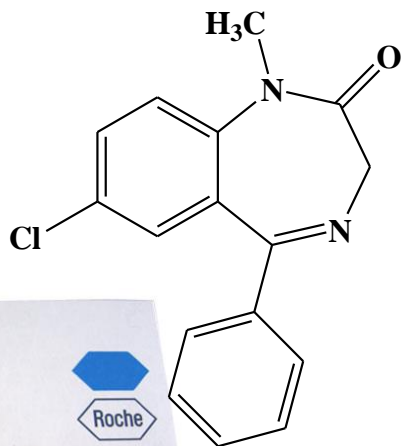
5. Hidroxilação α -heteroátomo



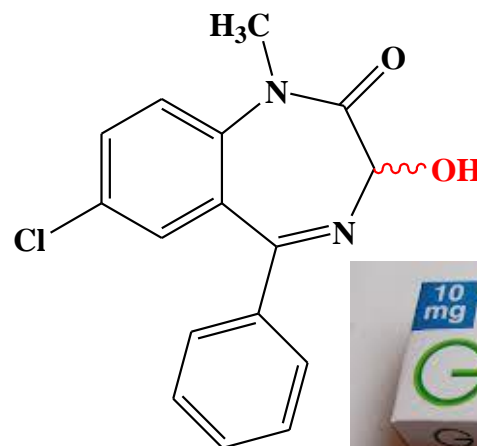
primidona



fenobarbital



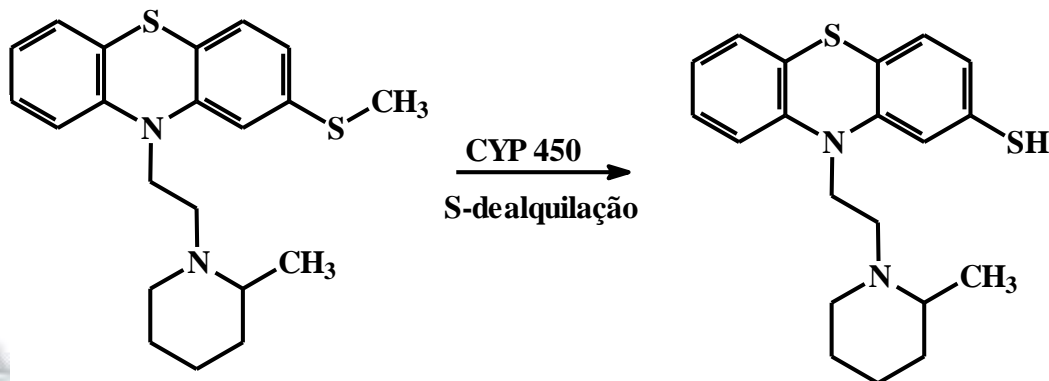
diazepam



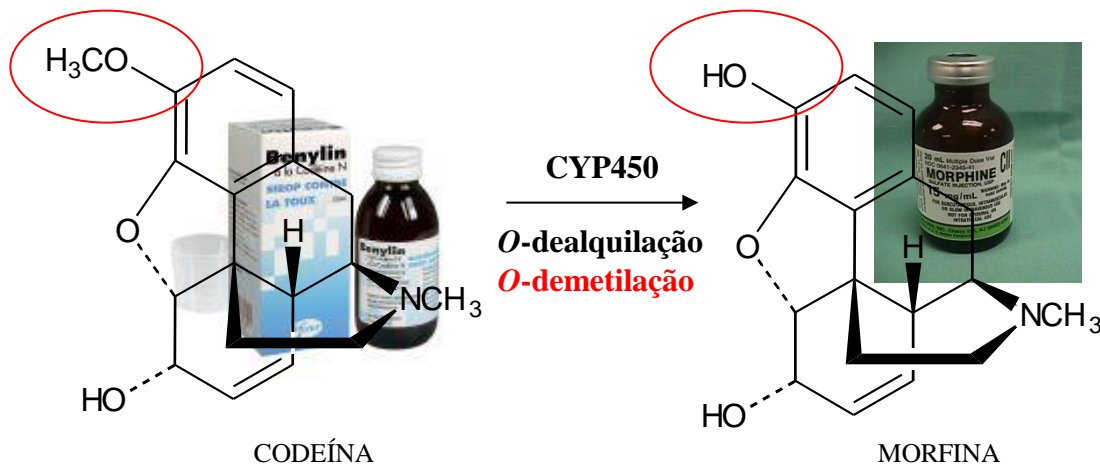
temazepam



6. X-Desalquilação (X = S, N, O)



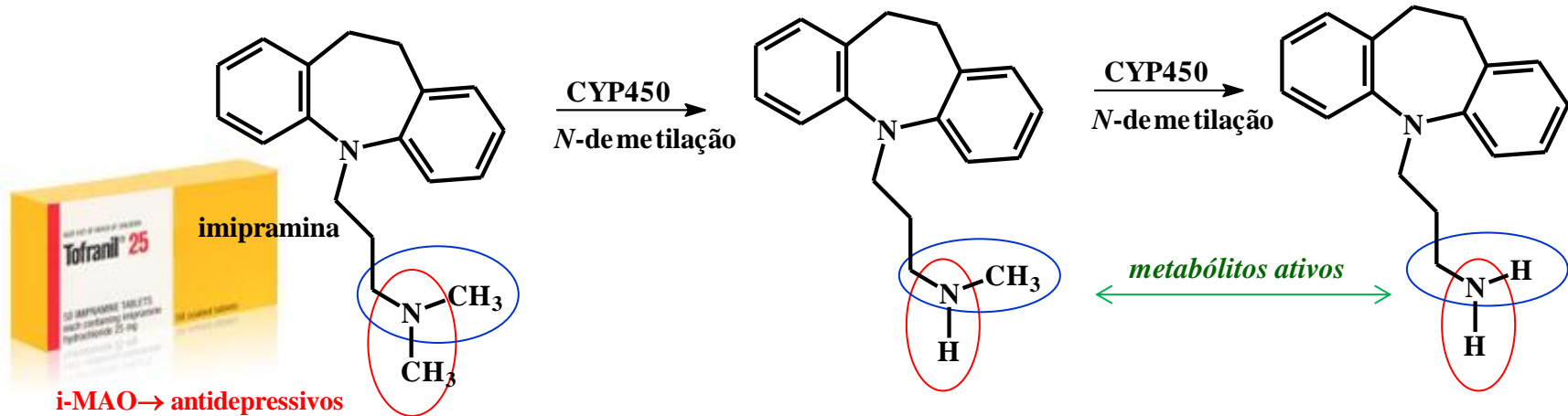
tioridazina (antipsicótico)



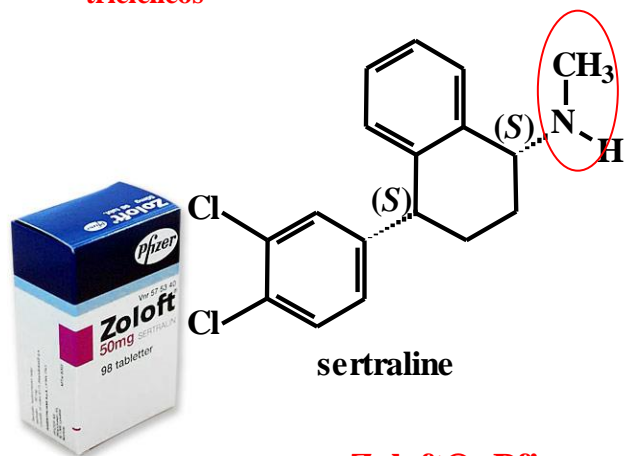
CODEÍNA

MORFINA

6. X-Desalquilação (X = S, N, O)



i-MAO → antidepressivos tricíclicos



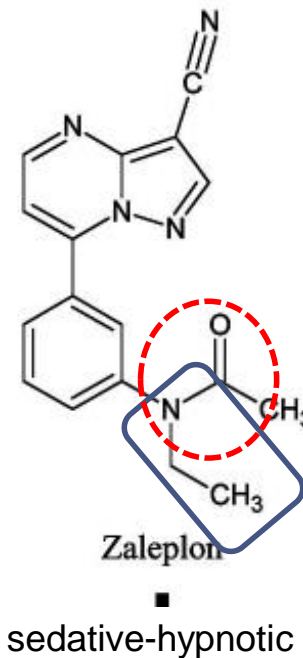
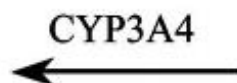
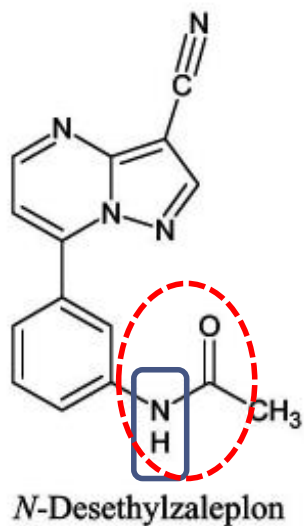
Zoloft®, Pfizer
SSRI → Antidepressivo

Metabólito ativo

$t_{1/2} = 60-100 \text{ h}$

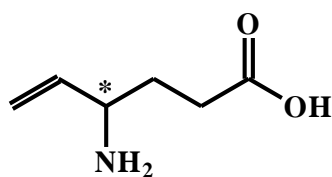
Inibidor Enzimático da CYP 2D6

6. X-Desalquilação (X = S, N, O)



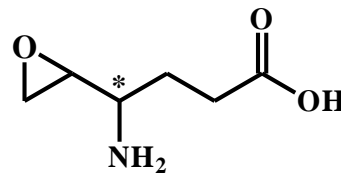
Mandrioli, R. et al, Current Drug Metabolism, 2010, 11, 815-829

7. Epoxidações

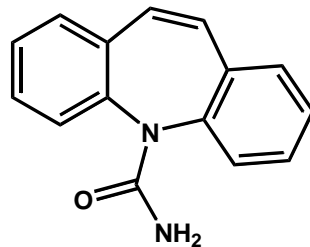


vigabatrin
(S)-eutômero

CYP 450

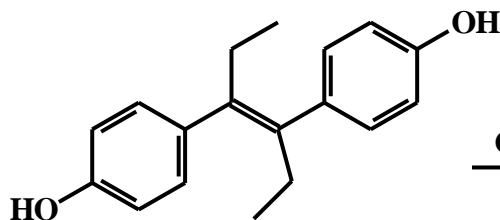
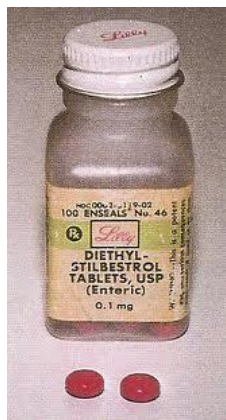
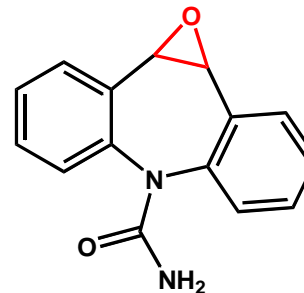


vigabatrin
(S)-eutômero



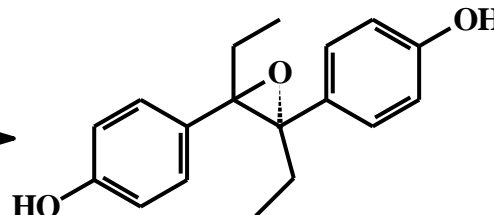
carbamazepina

CYP2C9



diestilbestrol

CYP450



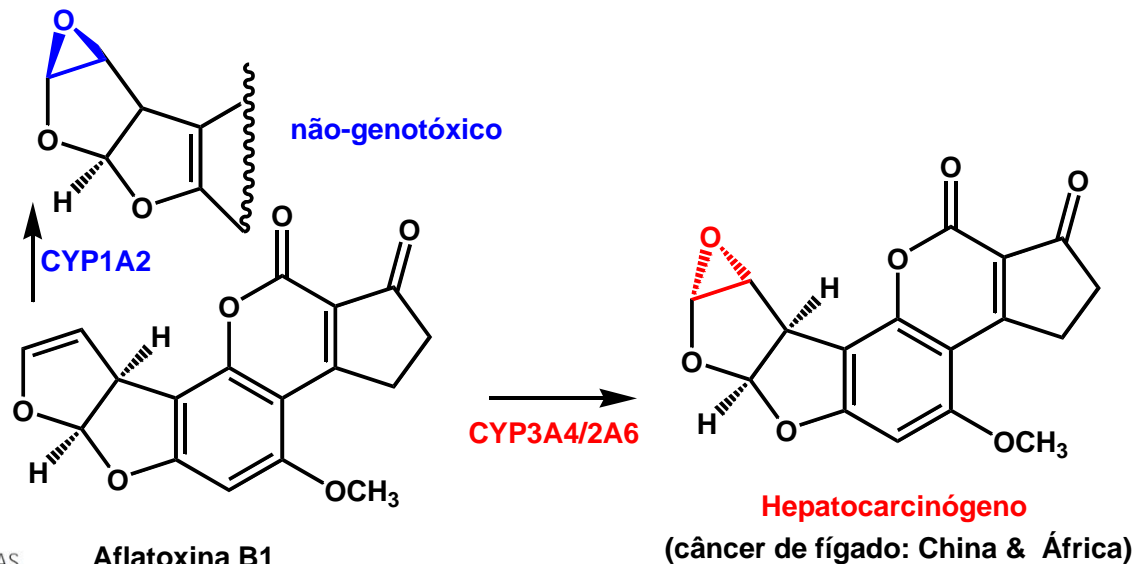
(DES, FDA 1941) Estrogênio não-esteróide sintético, prescrito para tratamento de sintomas da menopausa, vaginites (atrófica e gonorreica), câncer de mama e próstata, etc

Proscrito em 1975: vaginal clear cell adenocarcinoma in girls and young women who had been exposed to this drug *in utero*


7. Epoxidações



micotoxina encontrada em alimentos (e.g. amendoim, milho). Produzida por fungos Aspergillus



Ingestão de aflatoxina pode causar câncer

 A presença dessa micotoxina nos alimentos contribui sobremaneira para que mais de um terço dos casos de neoplasias tenha relação com a dieta

<http://www.cib.org.br/pdf/biotech09.pdf>

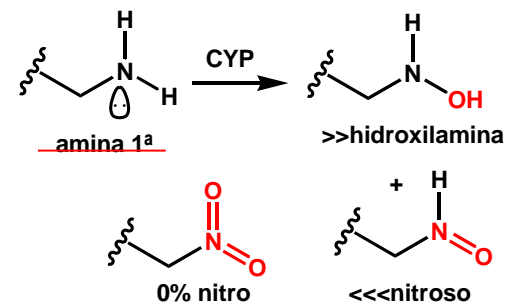
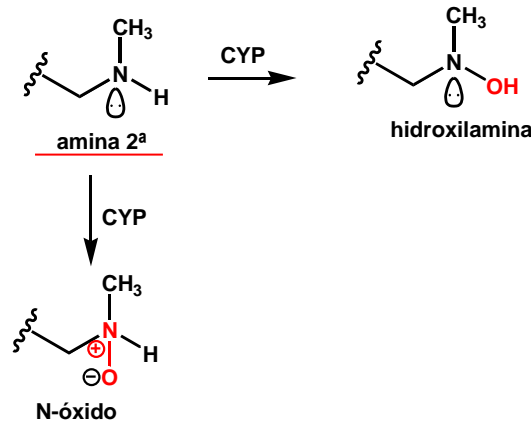
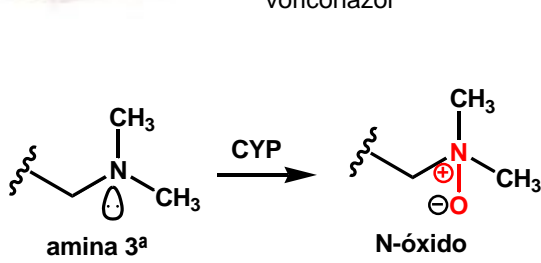
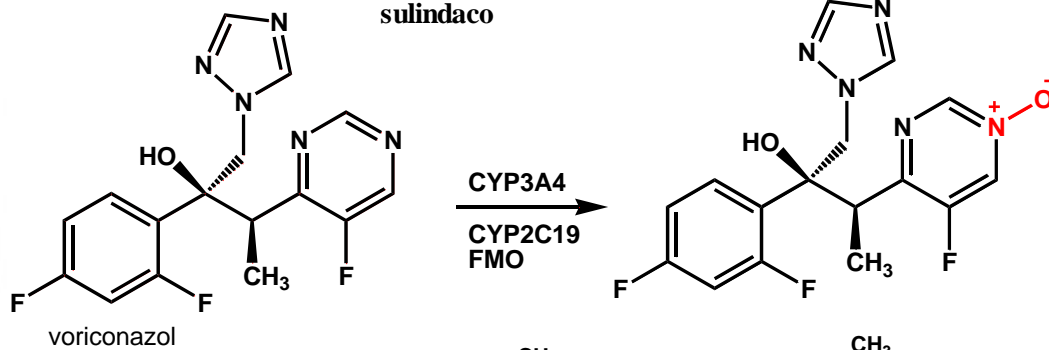
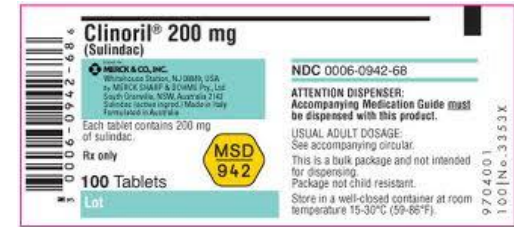
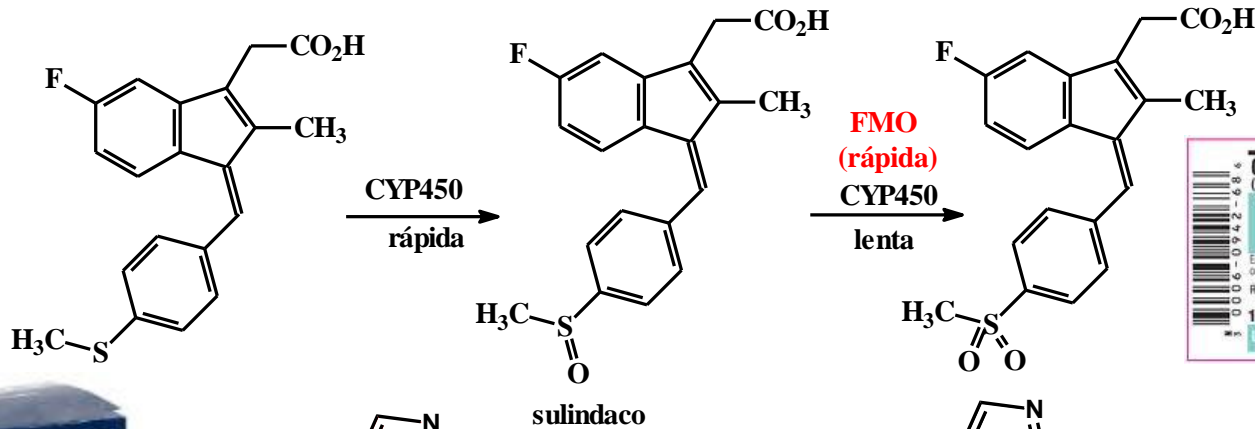
As aflatoxinas continuam sendo objeto de grande atenção quando se trata das micotoxicoses, manifestações clínicas ocasionadas pelo consumo de alimentos contaminados com micotoxinas. A aflatoxina B1 (AFB1) está epidemiologicamente associada à alta incidência de câncer hepático, sobretudo em países tropicais. Além disso, estima-se que cerca de 35% dos casos de neoplasias tenham relação direta com a dieta. Evidentemente, a presença dessas toxinas nos alimentos é considerada um fator importante em tais estatísticas.

A grande suscetibilidade do amendoim ao fungo *Aspergillus flavus*

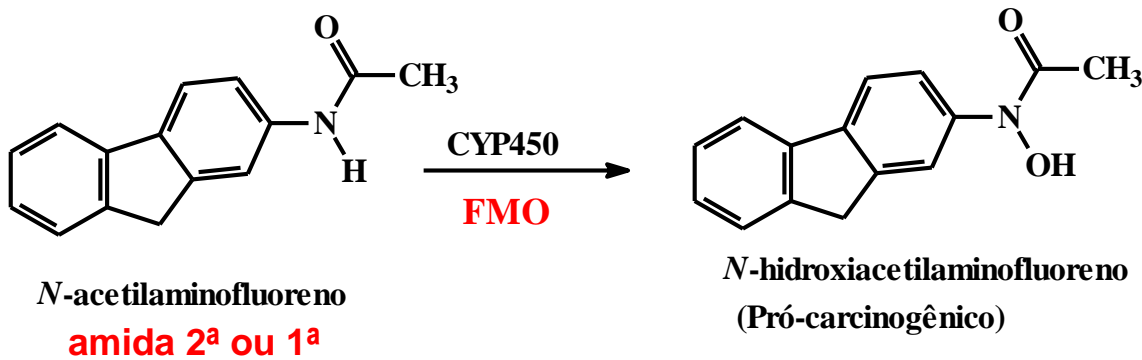
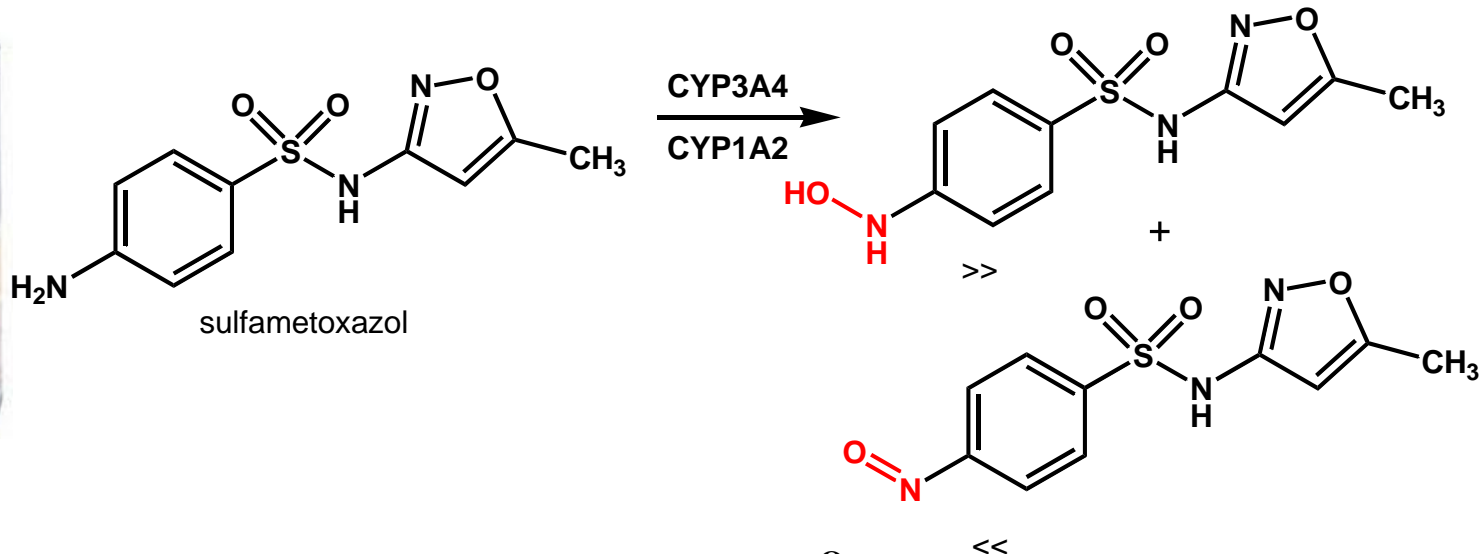


Fungo *Aspergillus* se desenvolve principalmente no milho

8. Oxidação de heteroátomos (S, N)



8. Oxidação de heteroátomos (S, N)



MINI-CURSO:

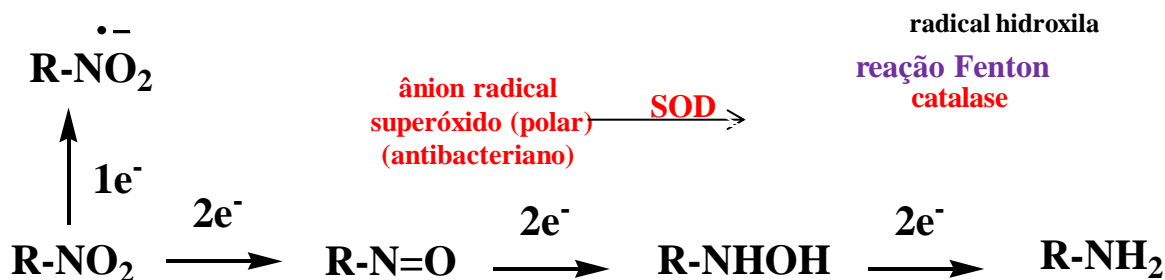
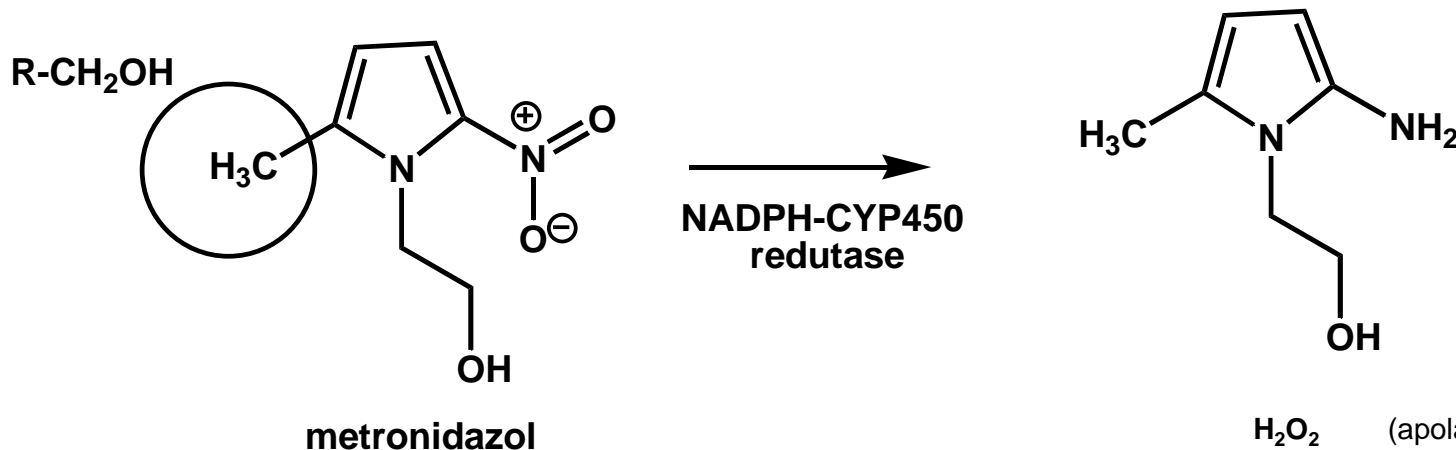
Metabolismo de Fármacos: aplicações em toxicologia e interações medicamentosas

PARTE 2



REAÇÕES METABÓLICAS DE FASE 1: REDUÇÃO

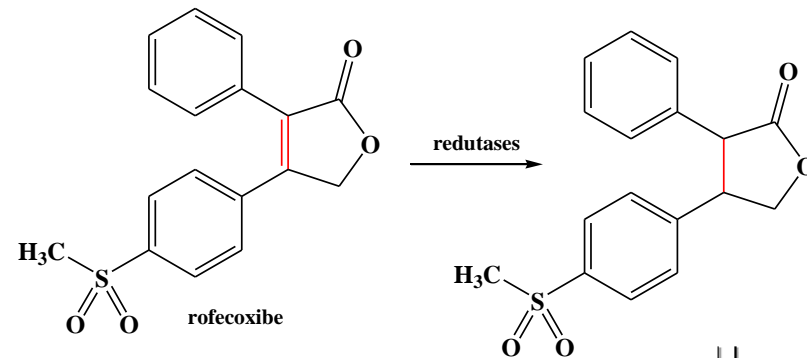
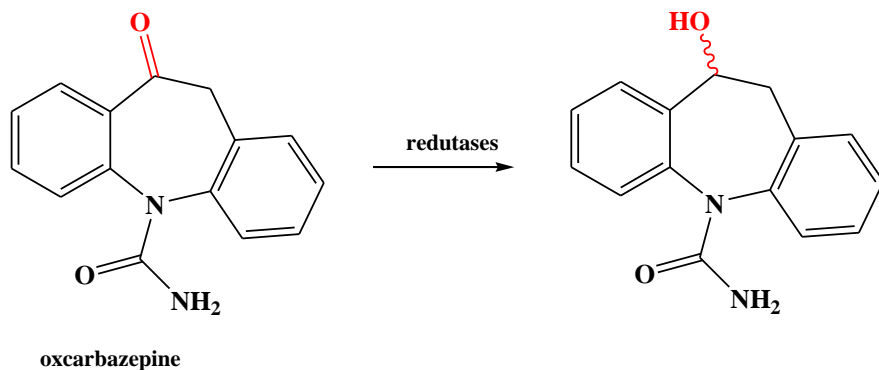
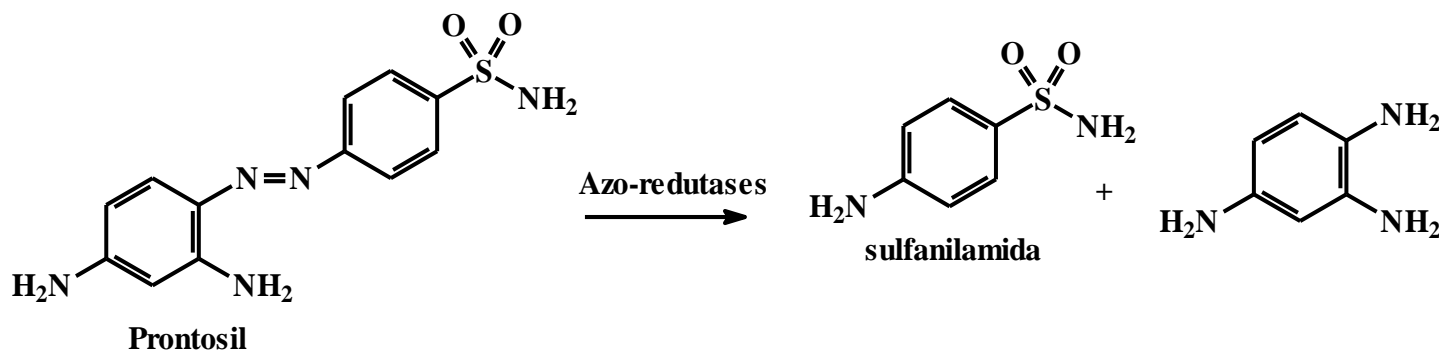
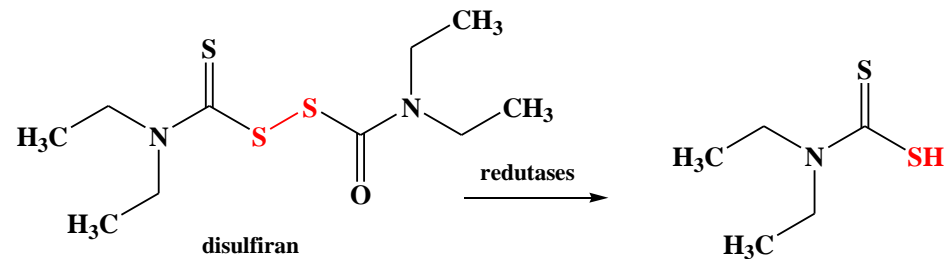
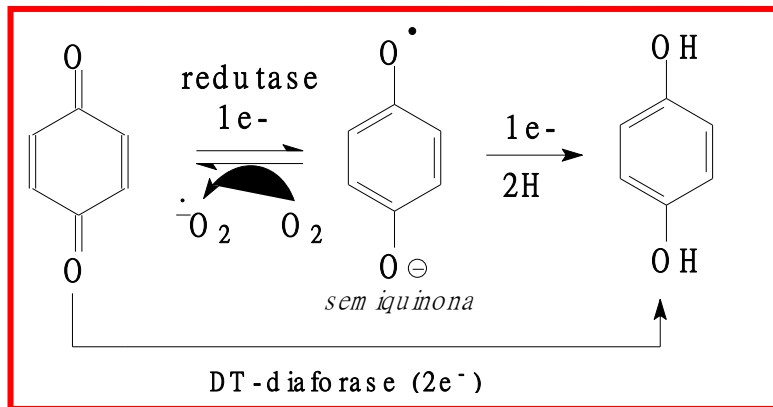
Substratos: azo-derivados (N=N), nitro-derivados (NO₂), cetonas (R(C=O)R), aldeídos (R(C=O)H), sulfonas (SO₂), sulfóxidos (SO), disulfetos (S-S), alcenos (C=C)



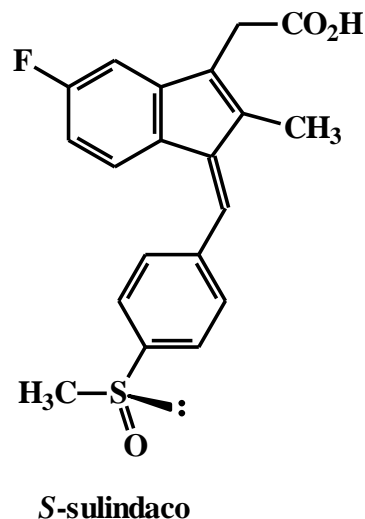
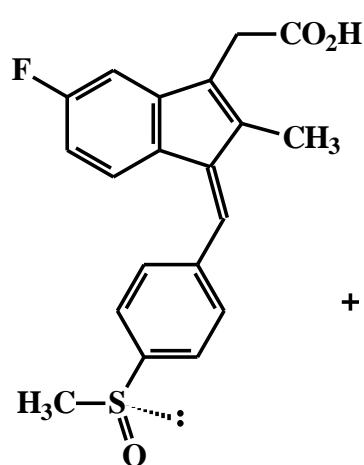
H₂O₂ (apolar) atravessa membranas por difusão simples, oxidando íons o ferro(II) e o cobre(I) (reação de Fenton), ocorrendo a formação do radical hidroxila (-OH (apolar); é o ROS mais reativo). Este mecanismo é responsabilizado por danos encontrados no DNA em situações de stress oxidativo e em ácidos graxos das membranas (peroxidação lipídica)

superóxido ($\cdot\text{O}_2^-$) reage com centros de ferro-enxofre existentes em proteínas destruindo-os e levando à liberação de ferro dentro da célula. Compostos contendo enxofre, como o aminoácido cisteína, são também alvos da ação destrutiva do superóxido, formando sulfóxidos.

REAÇÕES METABÓLICAS DE FASE 1: REDUÇÃO

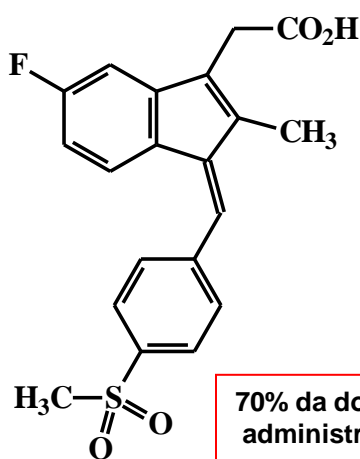


REAÇÕES METABÓLICAS DE FASE 1: REDUÇÃO



acumulado na urina e plasma

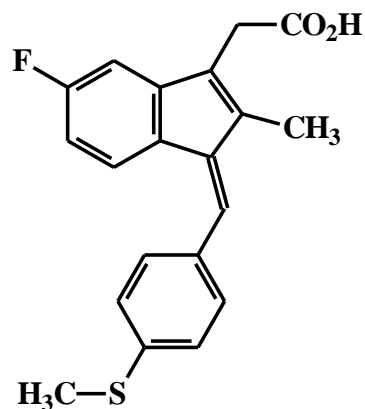
metabolismo Estereoespecífico enantiômero S



70% da dose administrada

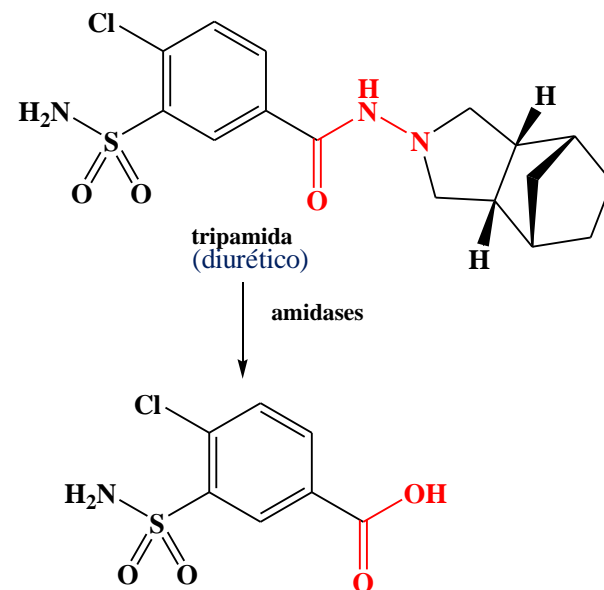
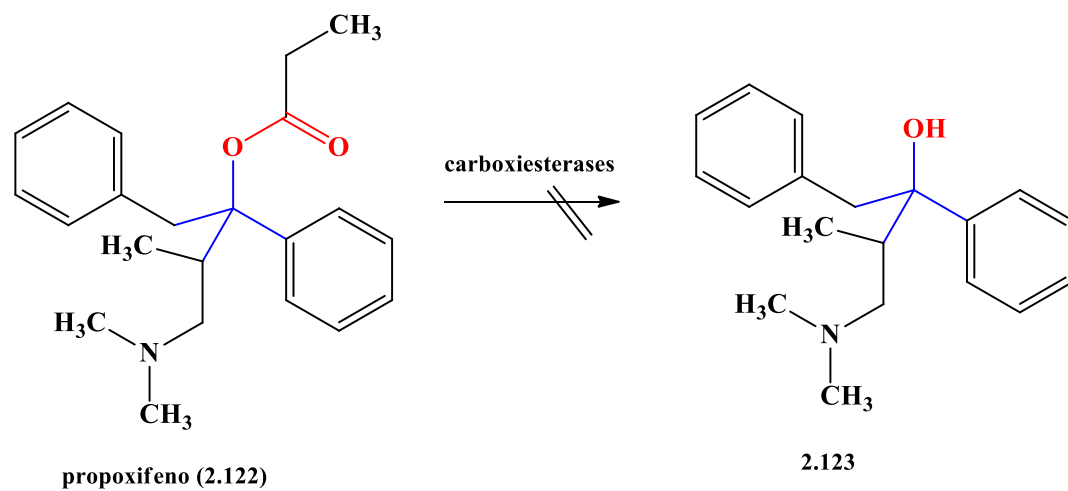
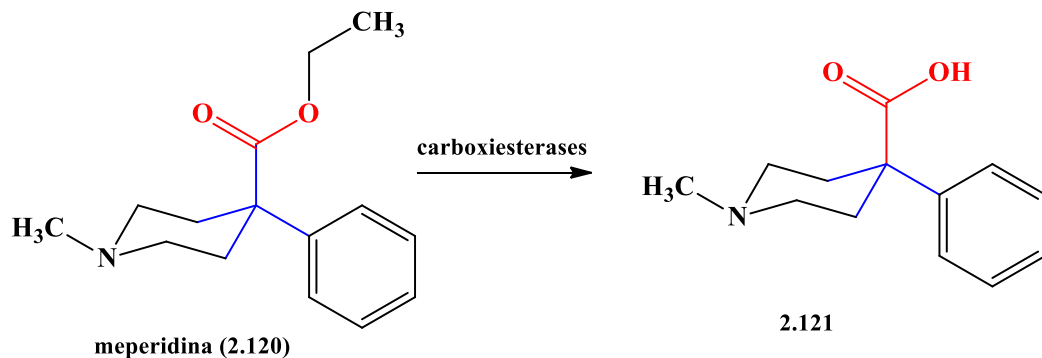
FMO [O]

CYP450 [H]

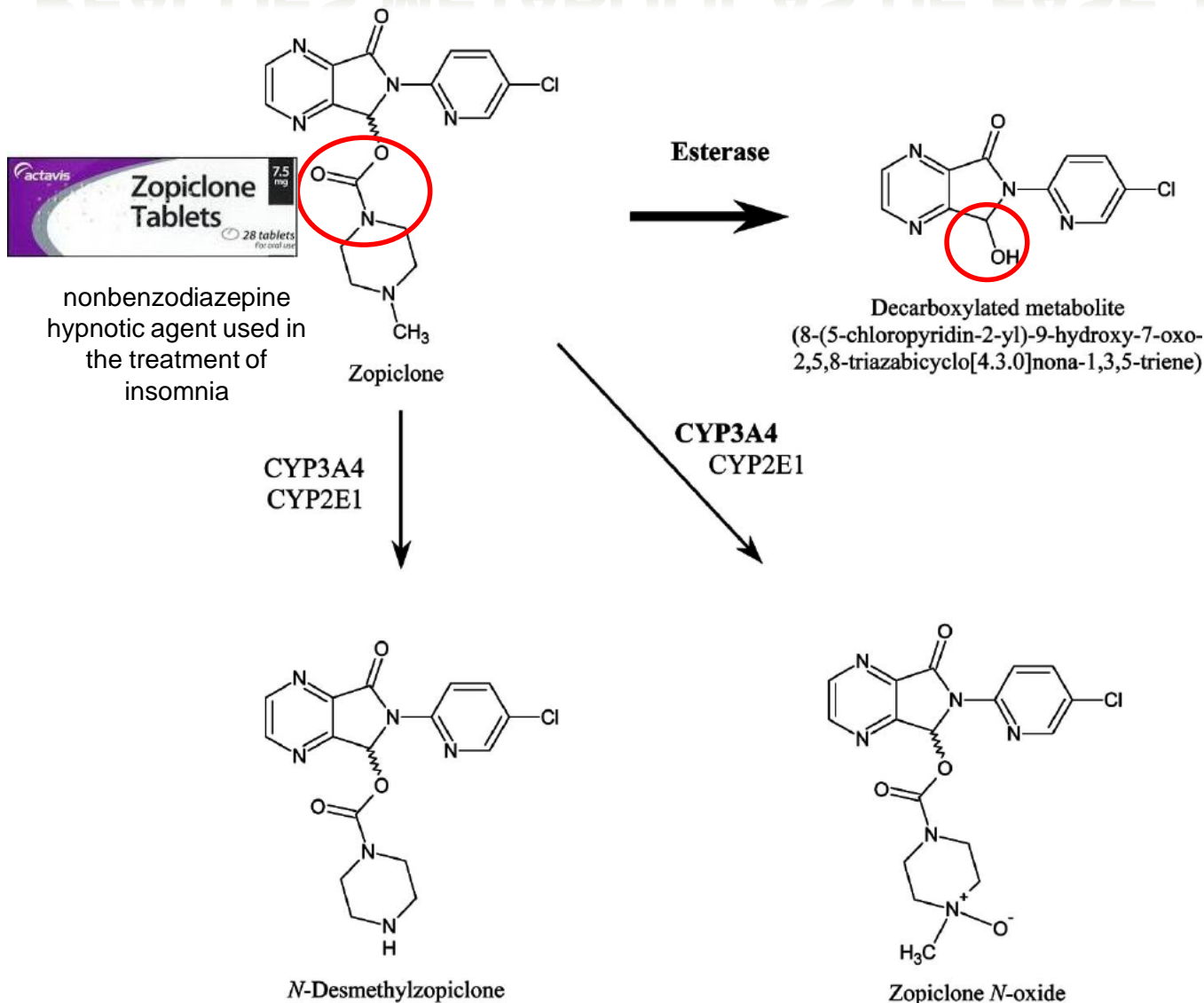


REAÇÕES METABÓLICAS DE FASE 1: HIDRÓLISE

Substratos: Derivados de ácidos carboxílicos: éster, amida, imida, ureia, tioamida, tioéster, tioureia, carbamato, ácido hidroxâmico, hidrazida, sulfonilureia, etc



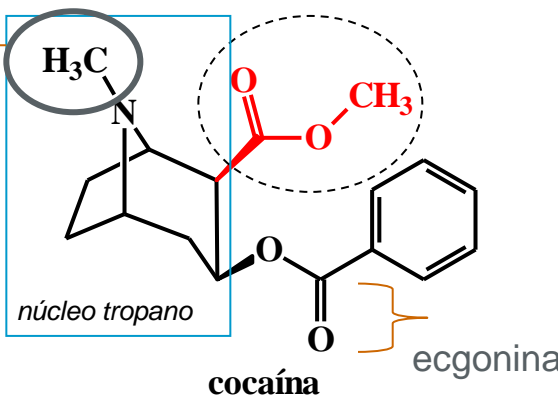
REAÇÕES METABÓLICAS DE FASE 1: HIDRÓLISE



Substratos:
 Derivados de ácidos carboxílicos: éster, amida, imida, ureia, tioamida, tioéster, tioureia, **carbamato**, ácido hidroxâmico, hidrazida, sulfonilureia, etc

REAÇÕES METABÓLICAS DE FASE 1: HIDRÓLISE

norcocaína

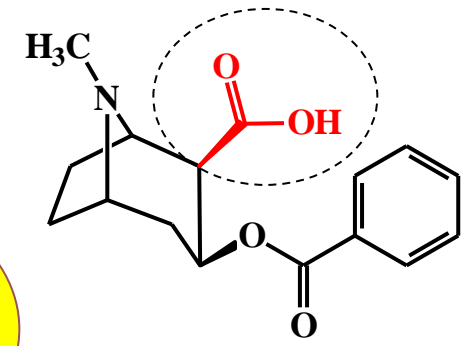


cocaína
(*Erythroxylon coca*; América do Sul)

Cocaetileno
(transesterificação com EtOH)

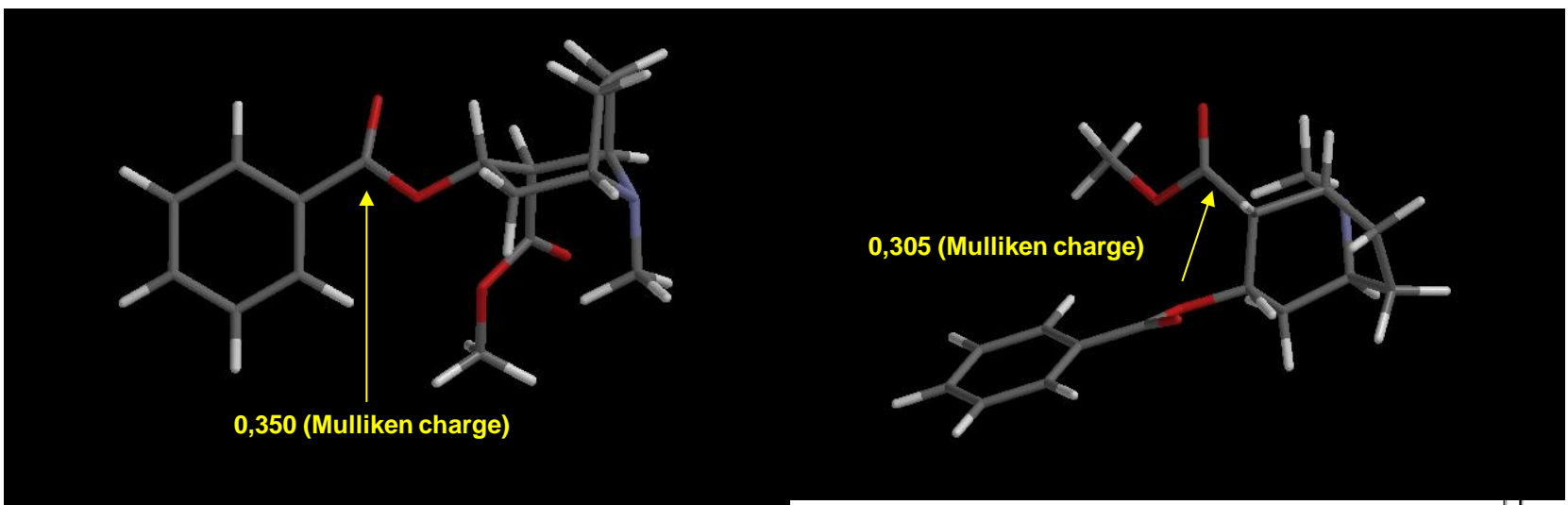
esterases plasmáticas

resiste às esterases plasmáticas, mas é hidrolisado por esterases hepáticas inespecíficas (carboxiesterases).
(-)



benzoilecgonina

“detectada até 48h após o uso da cocaína”



Most controlled drugs and drugs of abuse are integrated into the hair matrix in a number of ways: (i) an endogenous-exogenous pathway; transfer or absorption of drug molecules into hair duct in the form of sweat and sebum from transdermal secretion, or (ii) by an endogenous pathway; the drug molecules diffuse into growing hair from circulatory system using passive transport.

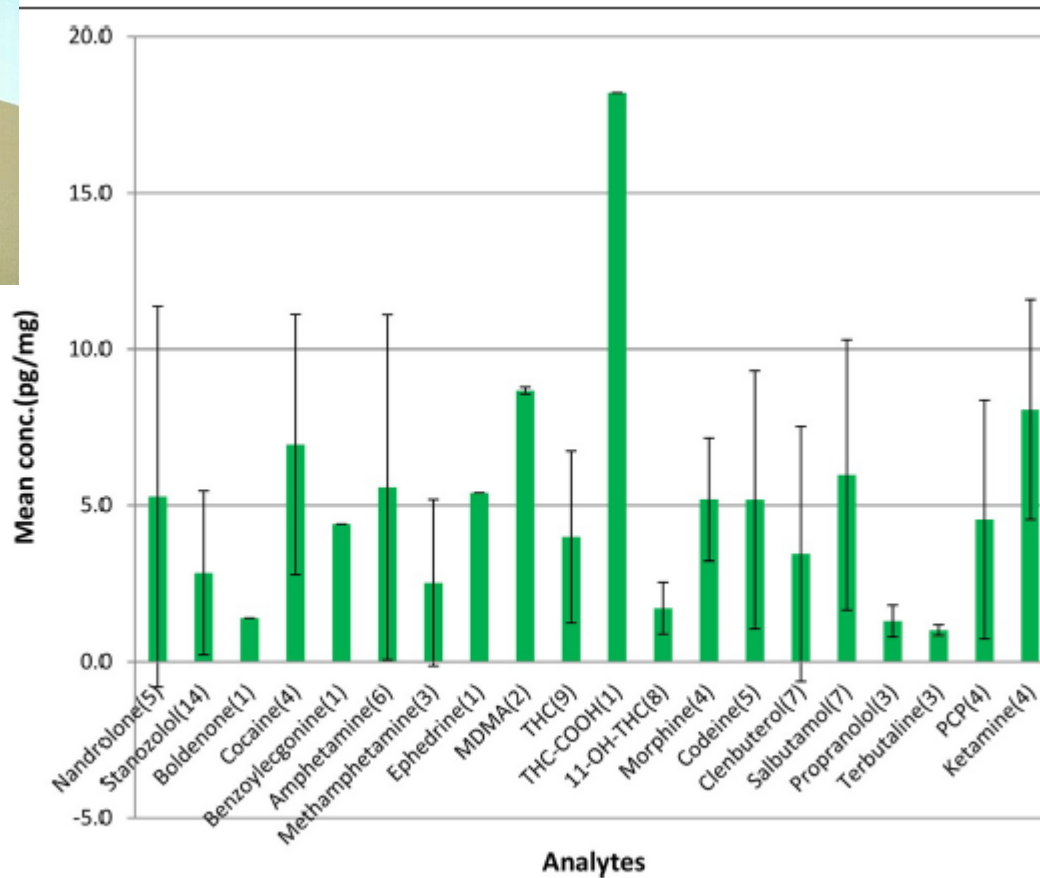
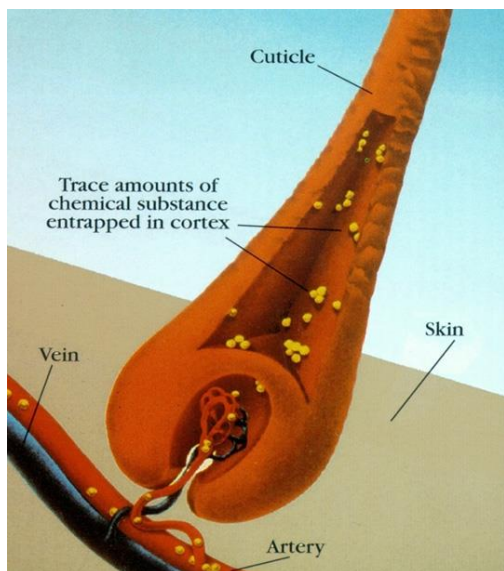
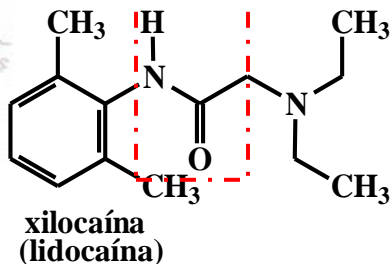
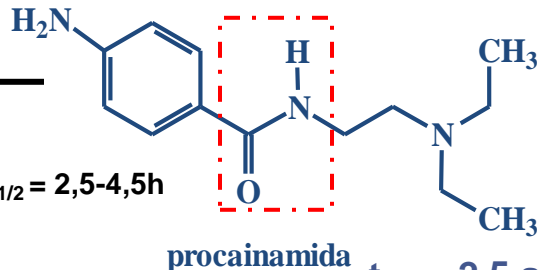
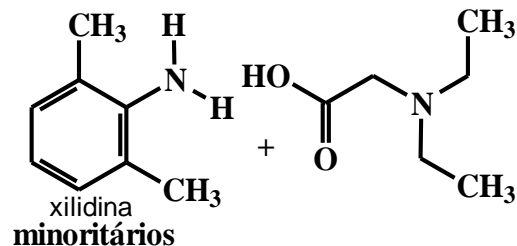


Figure 3 Mean concentrations of analytes along with the frequency of positive occurrences (shown in brackets). The error bars represents standard deviation.

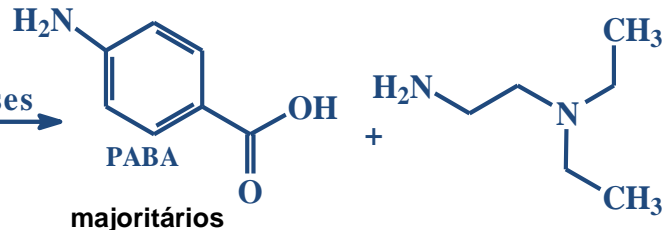
REAÇÕES METABÓLICAS DE FASE 1: HIDRÓLISE



amidases

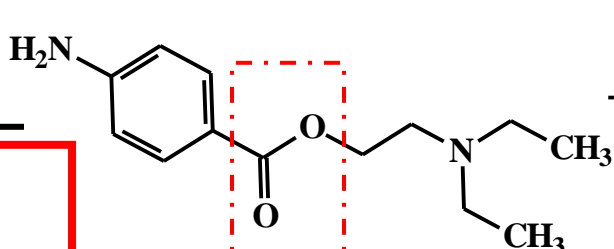


amidases

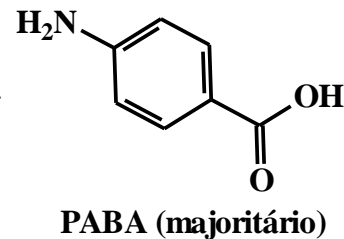


$t_{1/2} = 2,5 \text{ a } 4,5 \text{ h}$

alteração na velocidade de metabolização

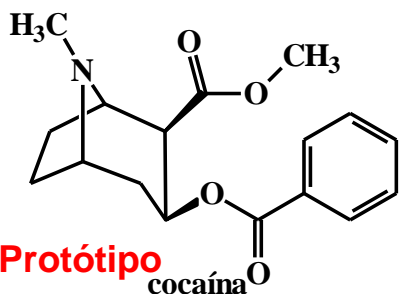


esterases

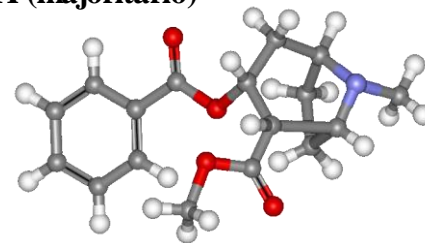


$t_{1/2} = 40 \text{ a } 84 \text{ seg}$

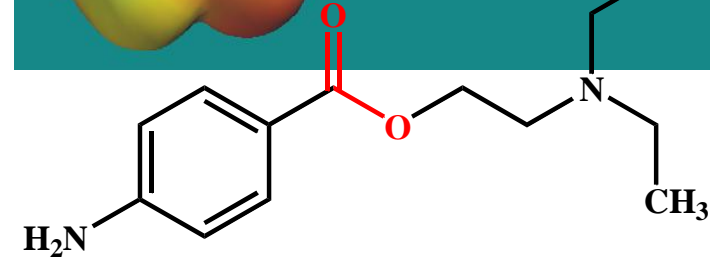
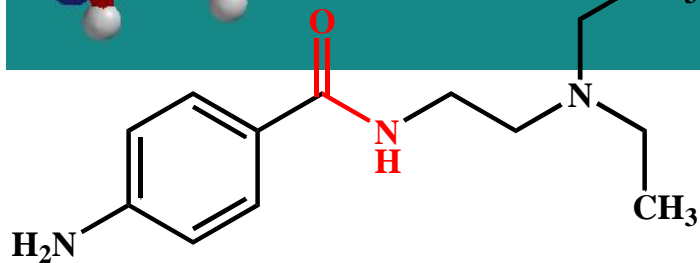
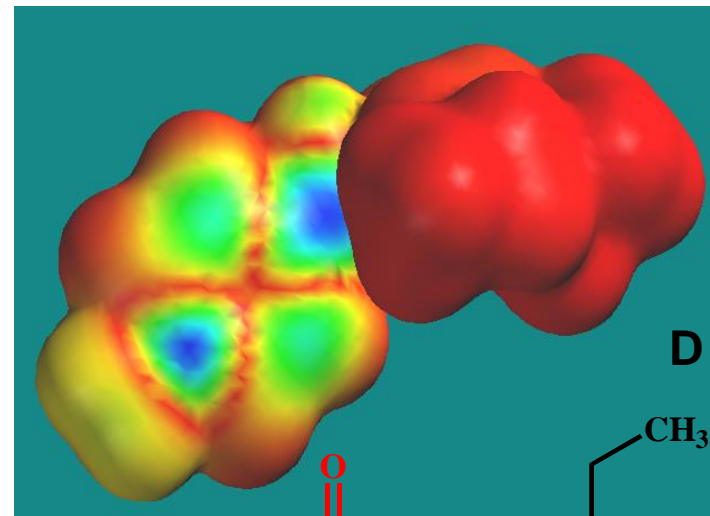
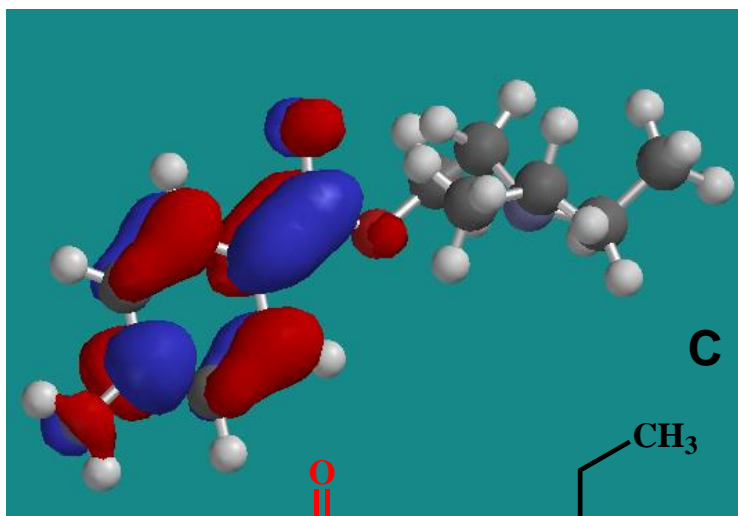
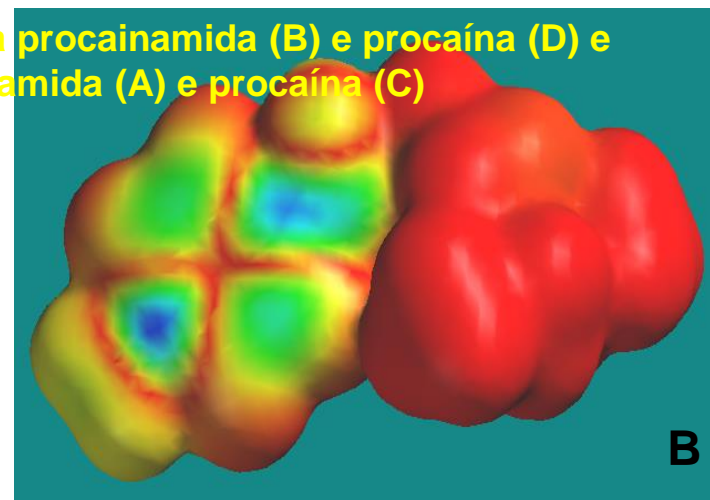
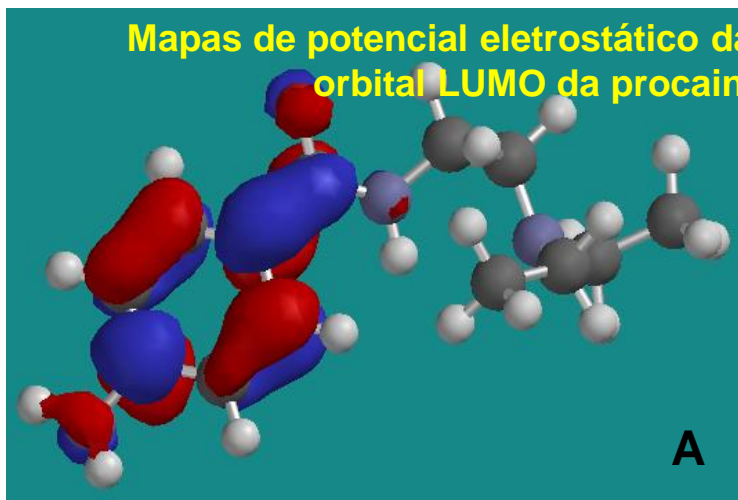
PABA (reações alérgicas)
Adm intramuscular e subcutânea



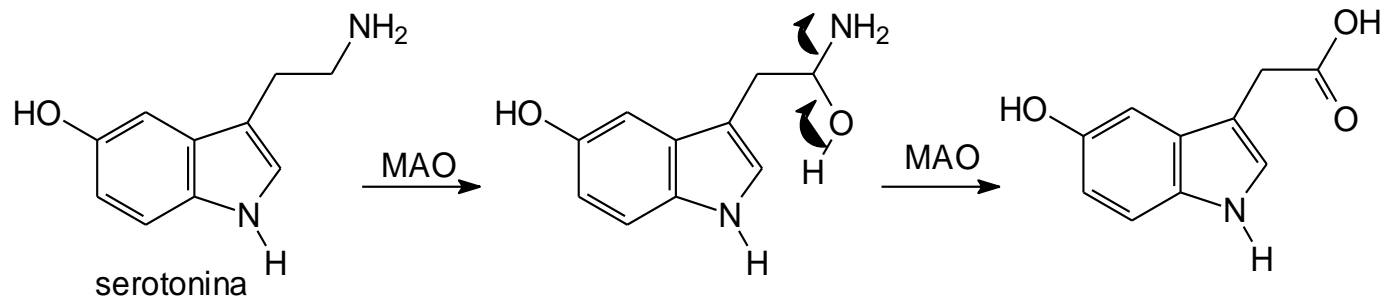
(*Erythroxylon coca*; América do Sul)



Mapas de potencial eletrostático da procainamida (B) e procaina (D) e orbital LUMO da procainamida (A) e procaina (C)

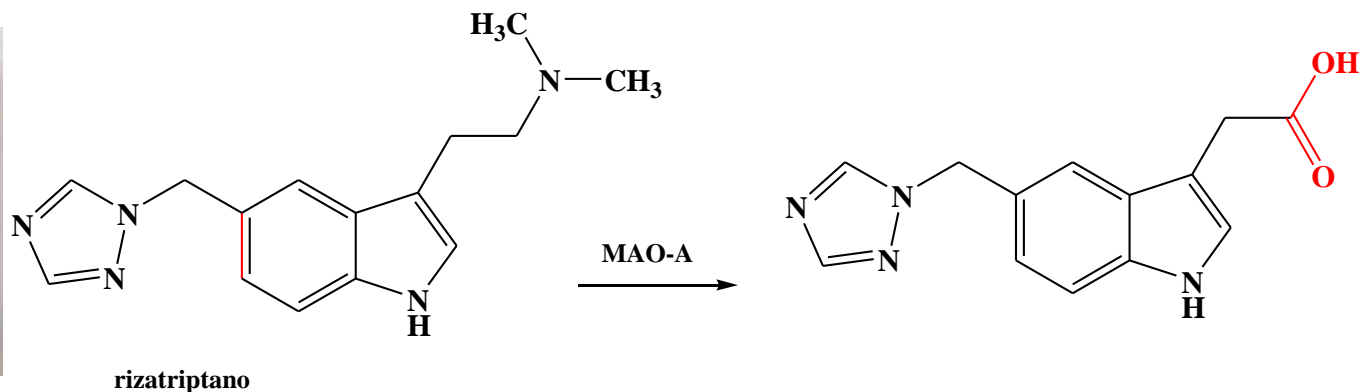
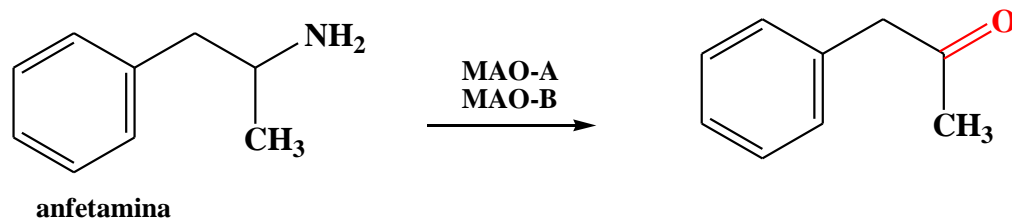


BIOTRANSFORMAÇÕES NÃO MICROSSOMAIS

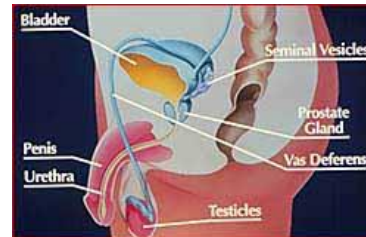
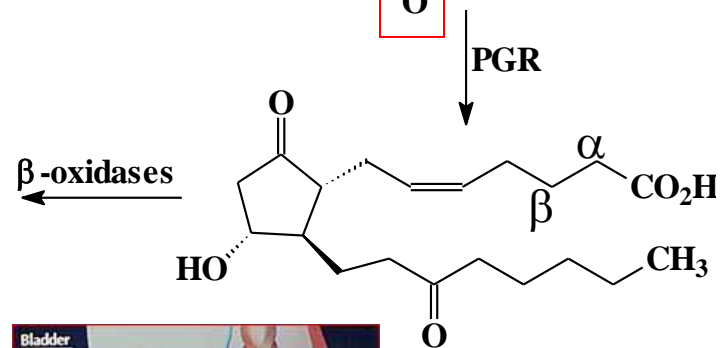
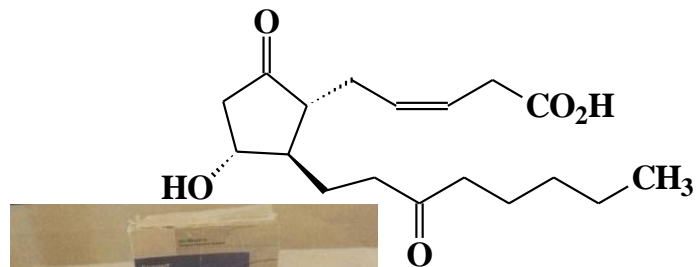
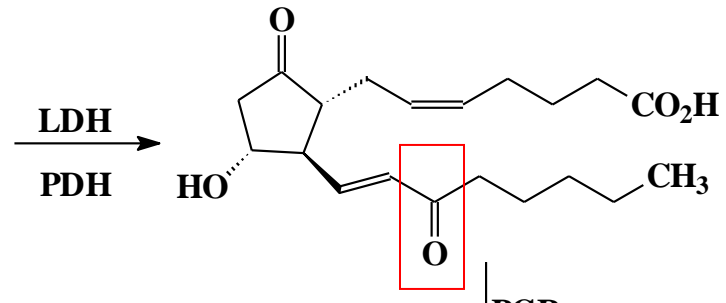
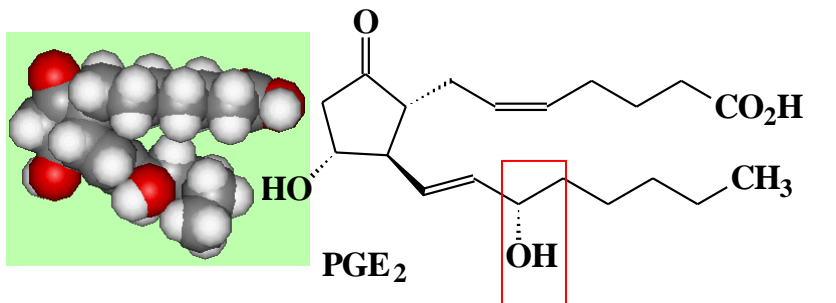
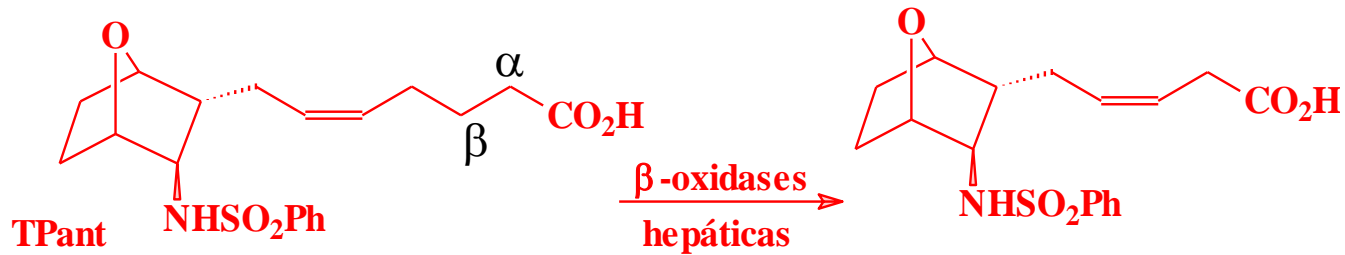


MAO-A ⇒ substrato preferencial serotonina (SNC, GI, fígado, placenta)

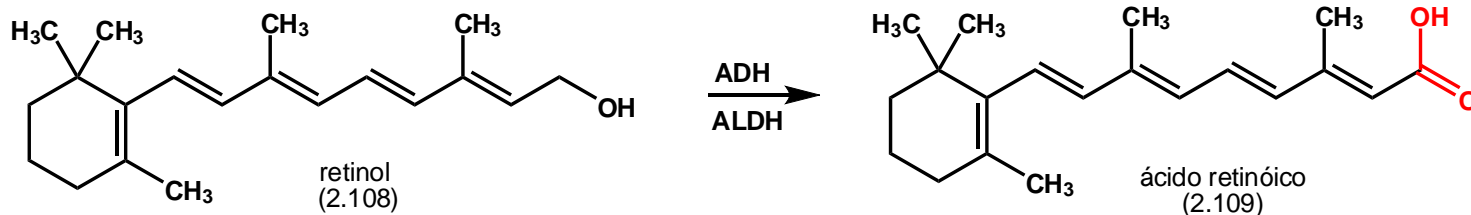
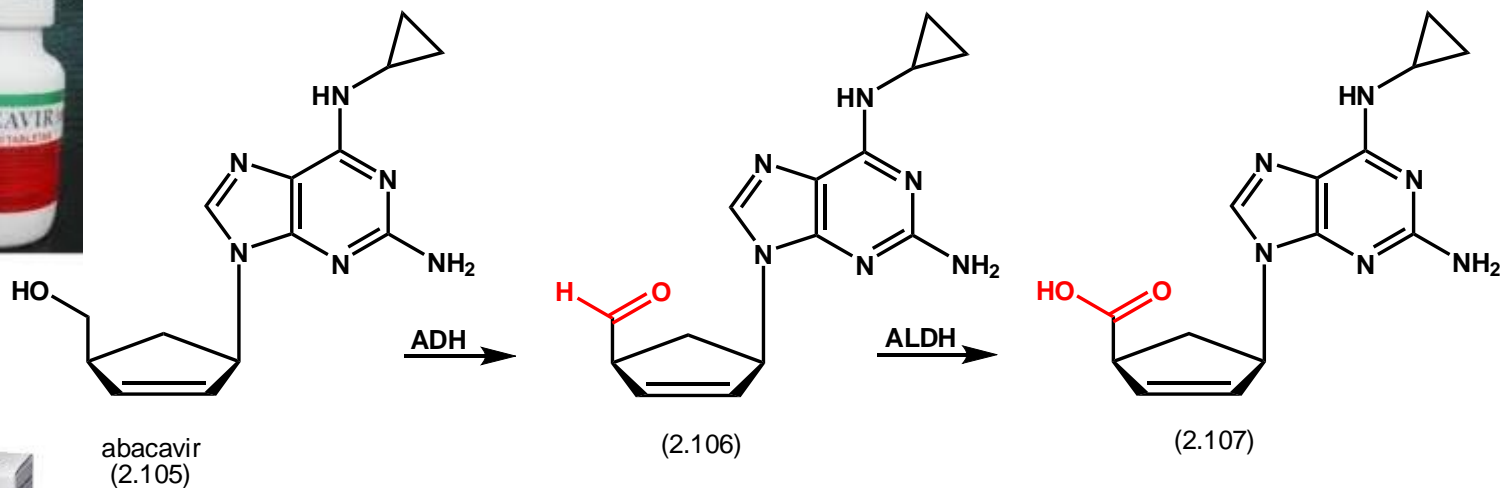
MAO-B ⇒ substrato preferencial feniletilamina (SNC e plaquetas)



BIOTRANSFORMAÇÕES NÃO MICROSSOMAIS



BIOTRANSFORMAÇÕES NÃO MICROSSOMAIS

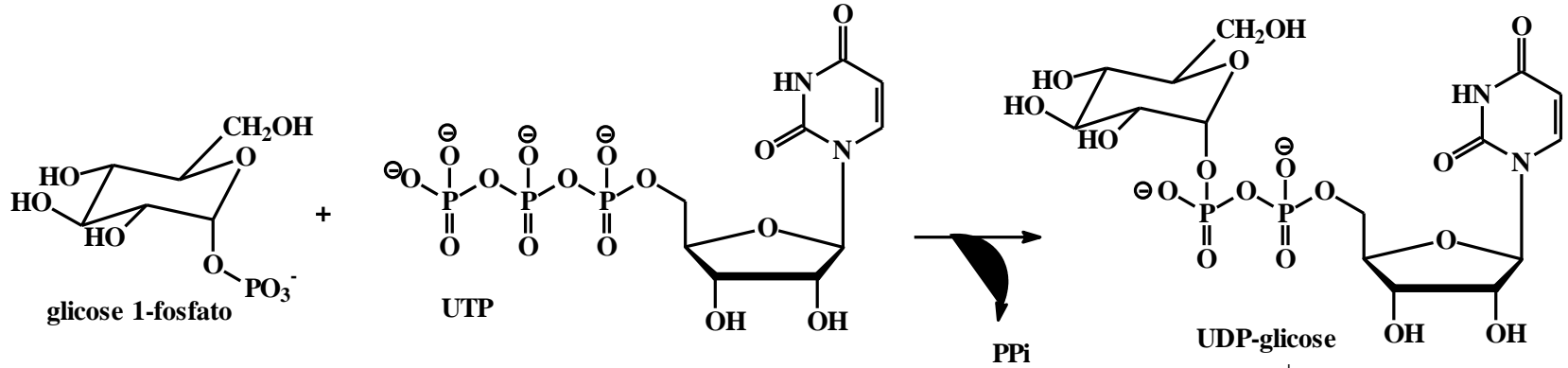


METABOLISMO DE FASE 2

CARACTERÍSTICAS: 1. São catalisadas por enzimas conhecidas pelo termo geral de transferases; 2. Participação de um co-fator que se liga à enzima nas proximidades do substrato e carrega uma molécula endógena ou uma unidade a ser transferida; 3. **Transfere uma molécula endógena altamente polar e de tamanho comparável ao substrato;** 4. **Exceções: reações de metilação e acetilação**

Reação	Enzima	Localização subcelular	Cofator ou Doador ativo
Glicuronidação	UDP-glicuronil Transferase (UGT)	Microsoma	UDP-ácido glicurônico (UDPGA)
Sulfatação	Sulfotransferase (SULT)	Citosol	3'-fosfoadenosina-5'-Fosfosulfato (PAPS)
Conjugação com glicina	—	Citosol	Acetil-coenzima A (acetilCoA)
Metilação	Metiltransferase (MT)	Citosol	S-adenosilmetionina (SAM)
Acetilação	Acetiltransferase (AC)	Citosol	S-acetilcoenzima A (S-acetilCoA)
Conjugação com glutatona	Glutathione-S-transferase (GTS)	Citosol	Glutathione (GSH)

1. GLICURONIDAÇÃO

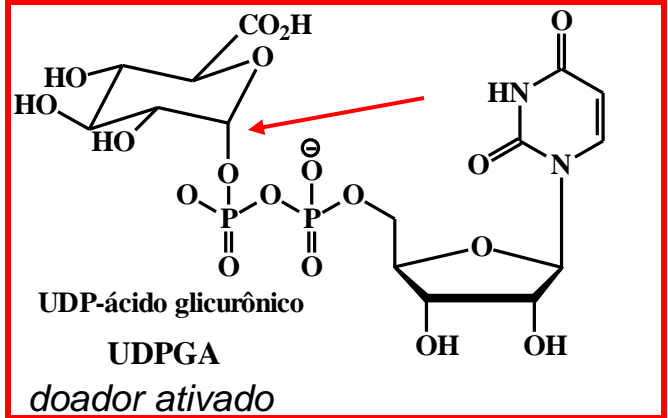


UTP = uridina trifosfato; UDP = Uridina difosfato

2 NAD⁺
2 NADH + H⁺

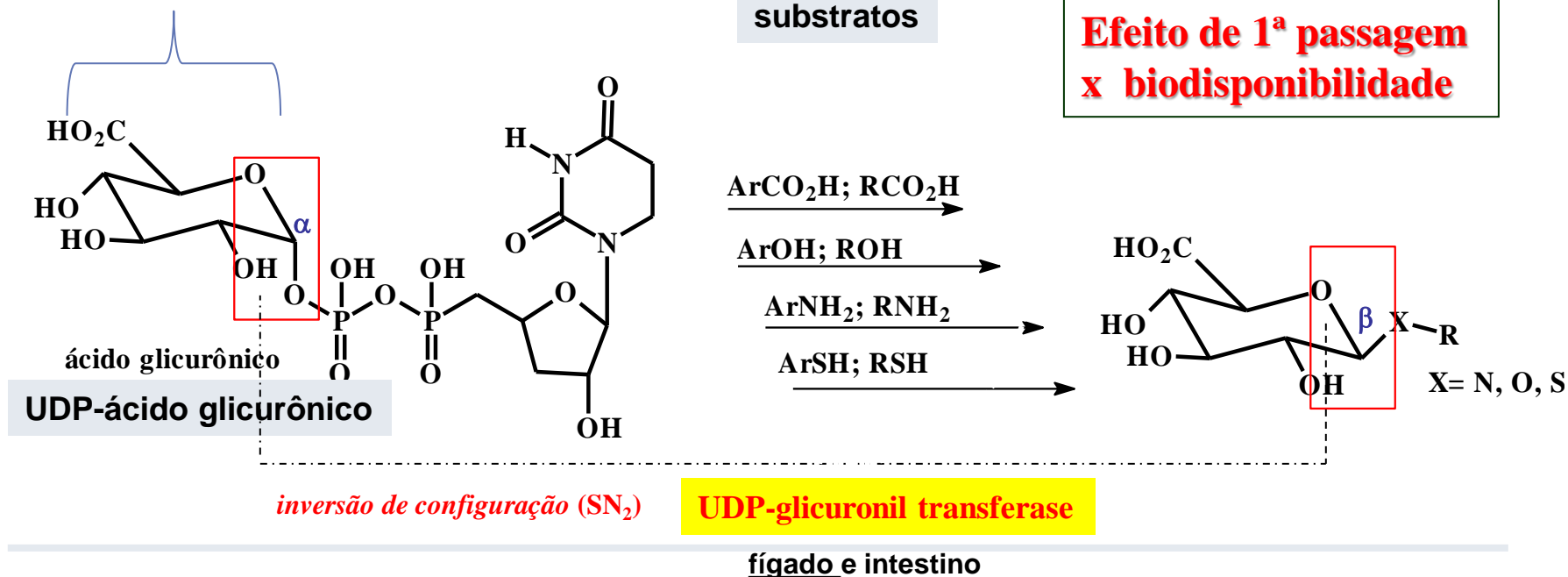
**METABÓLITOS
GLICURONADOS
=
X-Glicuronídeos**

UDP-glicuronil
transferase
←
Substratos
Nucleofílicos
(ROH, RNH, RSH)



- ✓ In human up to 22 UGT isoforms have been identified to date belonging to 1A, 2A, 2B, 3A and 8A subfamilies;
- ✓ Among these families, UGT1A, 2A and 2B are particularly active in xenobiotic biotransformation;
- ✓ UGT isoforms exhibit tissue specificity in terms of isoform present and level of expression
- ✓ **If liver contains the greatest amount and variety of UGT isoforms, other organs, such as kidney or the intestinal tract are known to express several isoforms in significant amount;**
- ✓ UGT has also been found in brain and associated tissues;
- ✓ **The nasal cavity which affords a direct route of entry for xenobiotics to the brain contains specific UGTs isoform that are highly expressed in the olfactory tissue.**

1. GLICURONIDAÇÃO

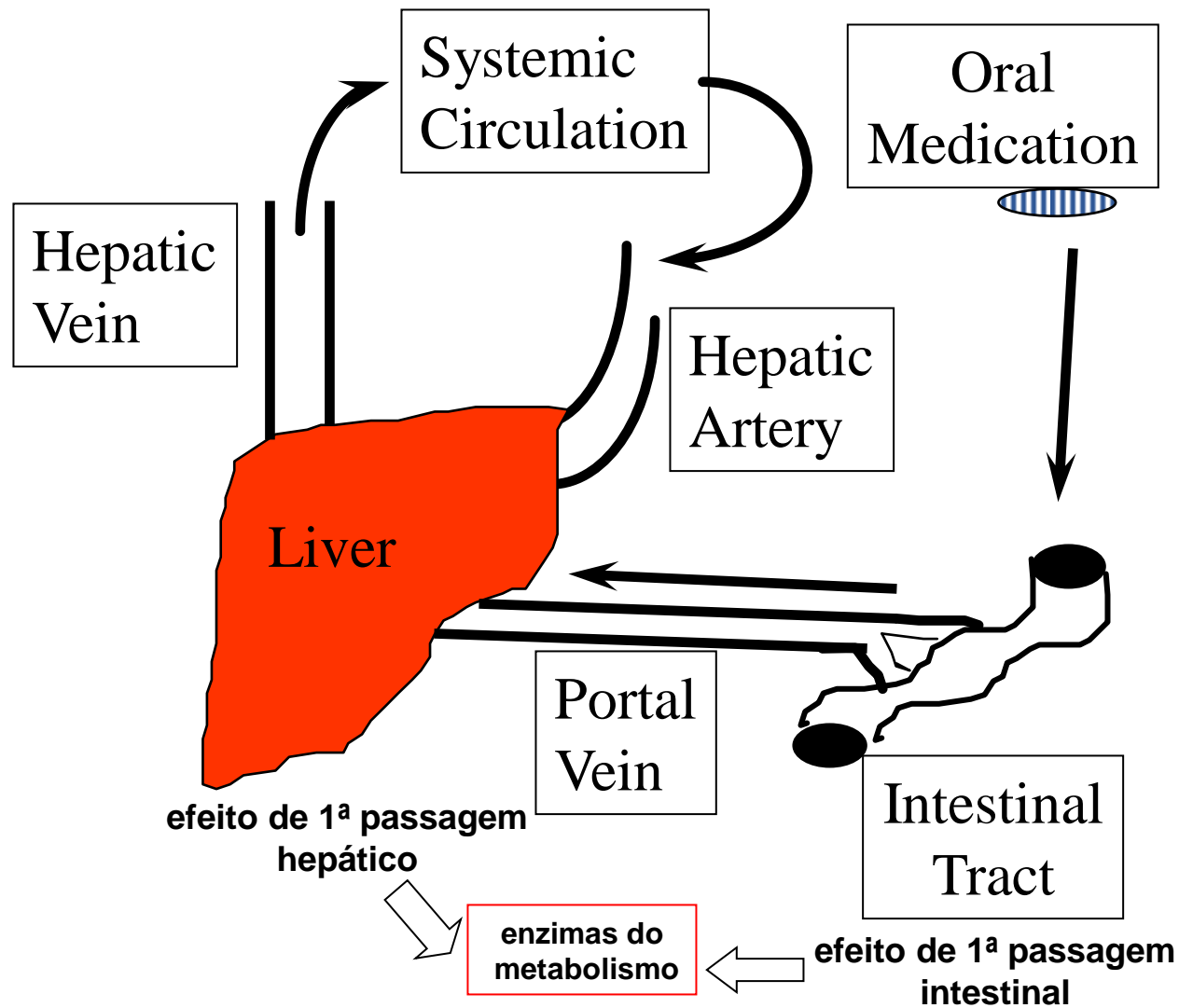


BIODISPONIBILIDADE

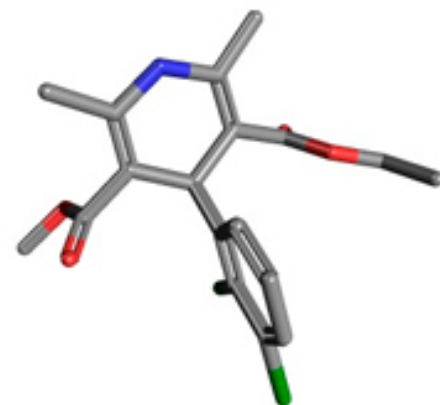
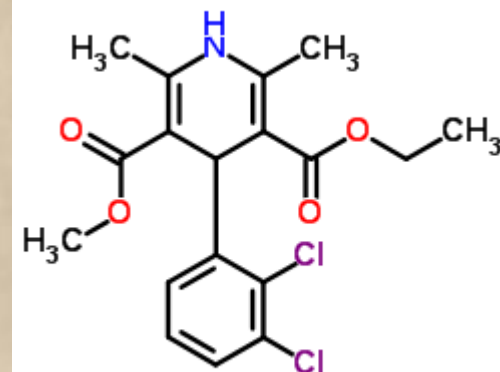
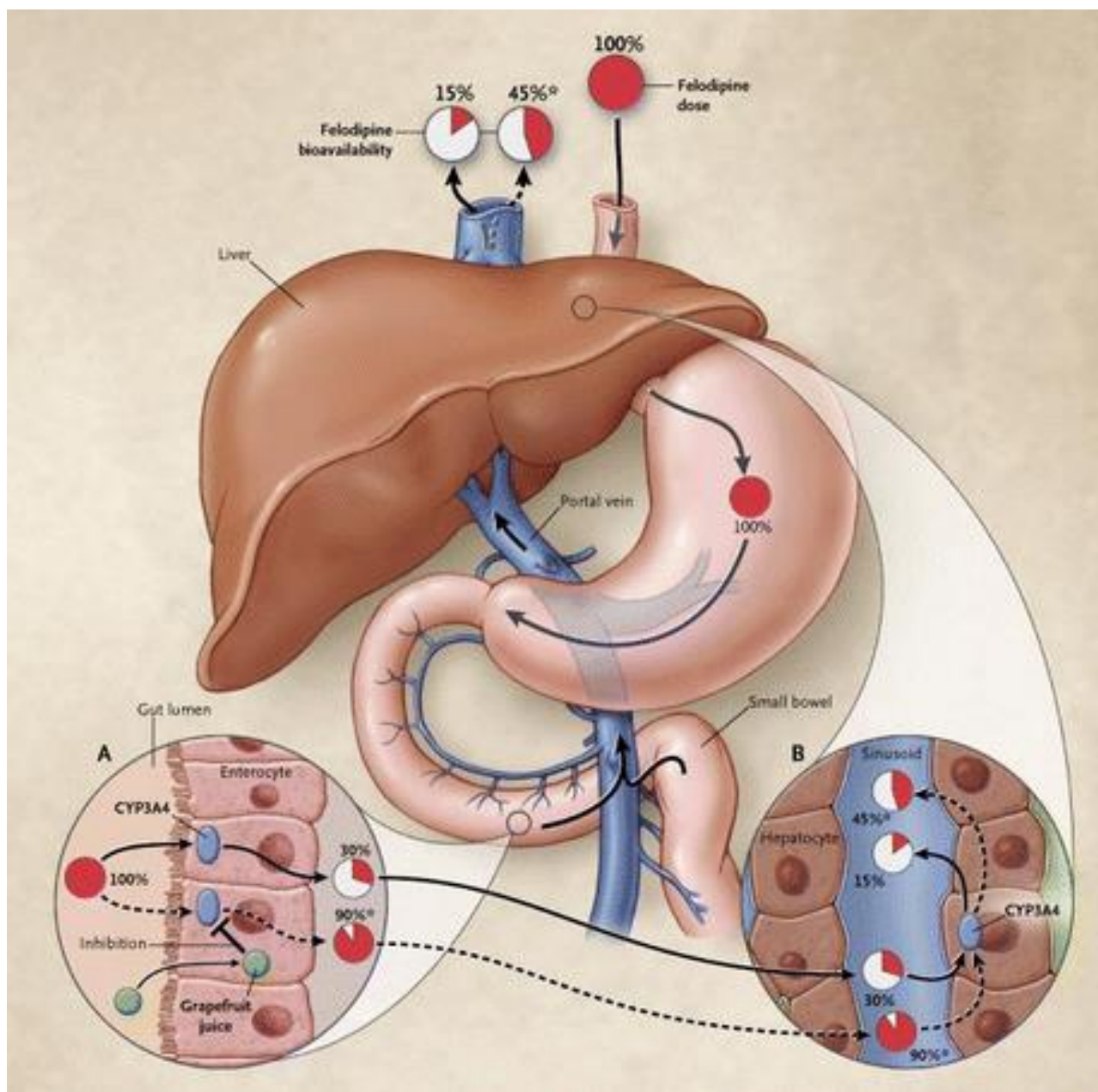
Fração ou percentagem do fármaco (xenobiótico) que atinge a circulação sistêmica a partir do local de sua administração

Relação entre quantidade absorvida e quantidade eliminada pelas diferentes etapas metabólicas de 1ª passagem

Absorção e Metabolismo

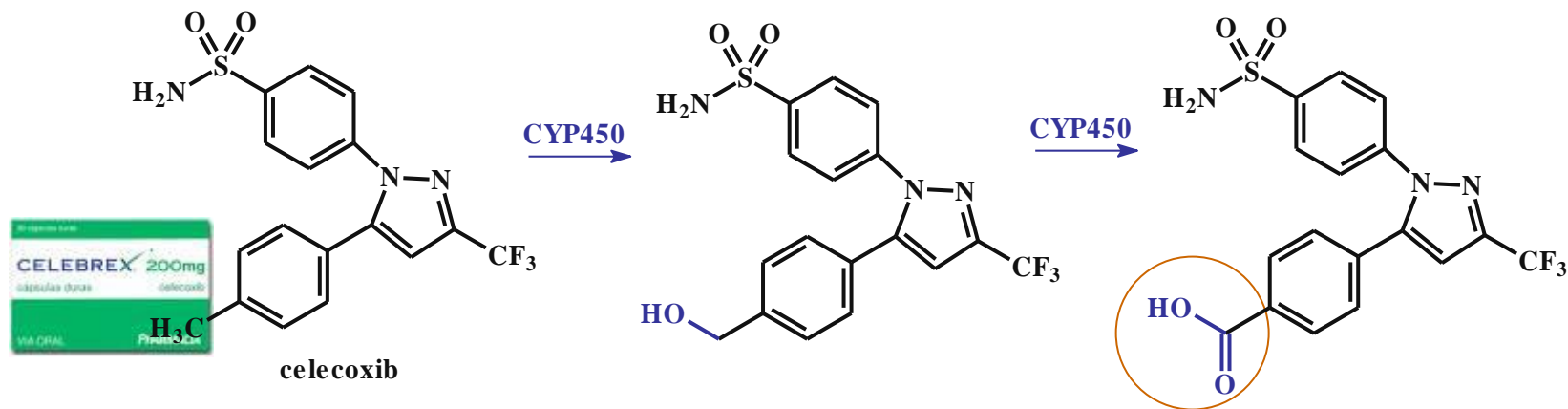


Metabolismo → Aumento da Depuração (Clearance) → Compromete Efeito Terapêutico



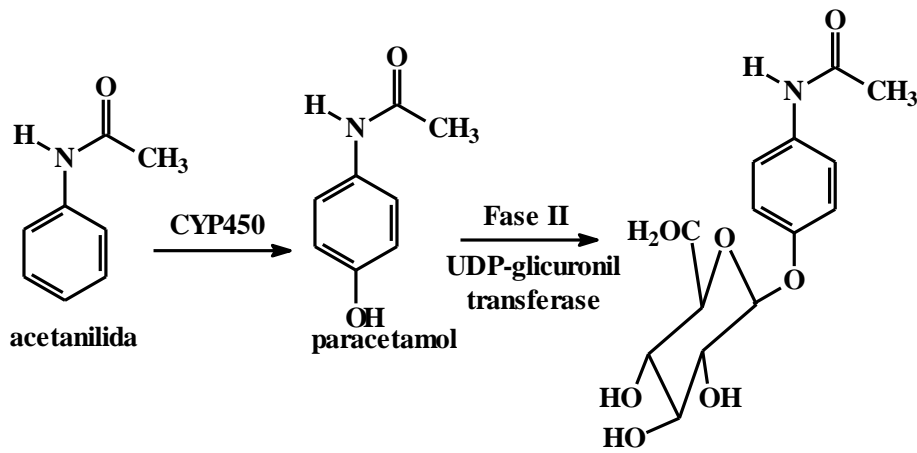
felodipine

1. GLICURONIDAÇÃO



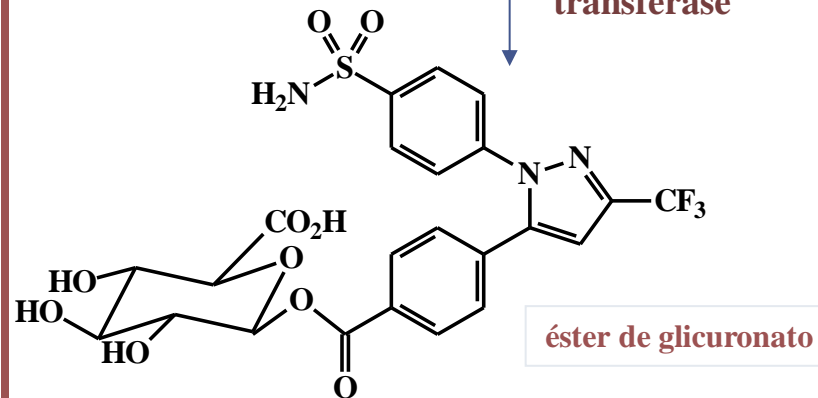
celecoxib

Fase II
UDP-glicuronil-
transferase



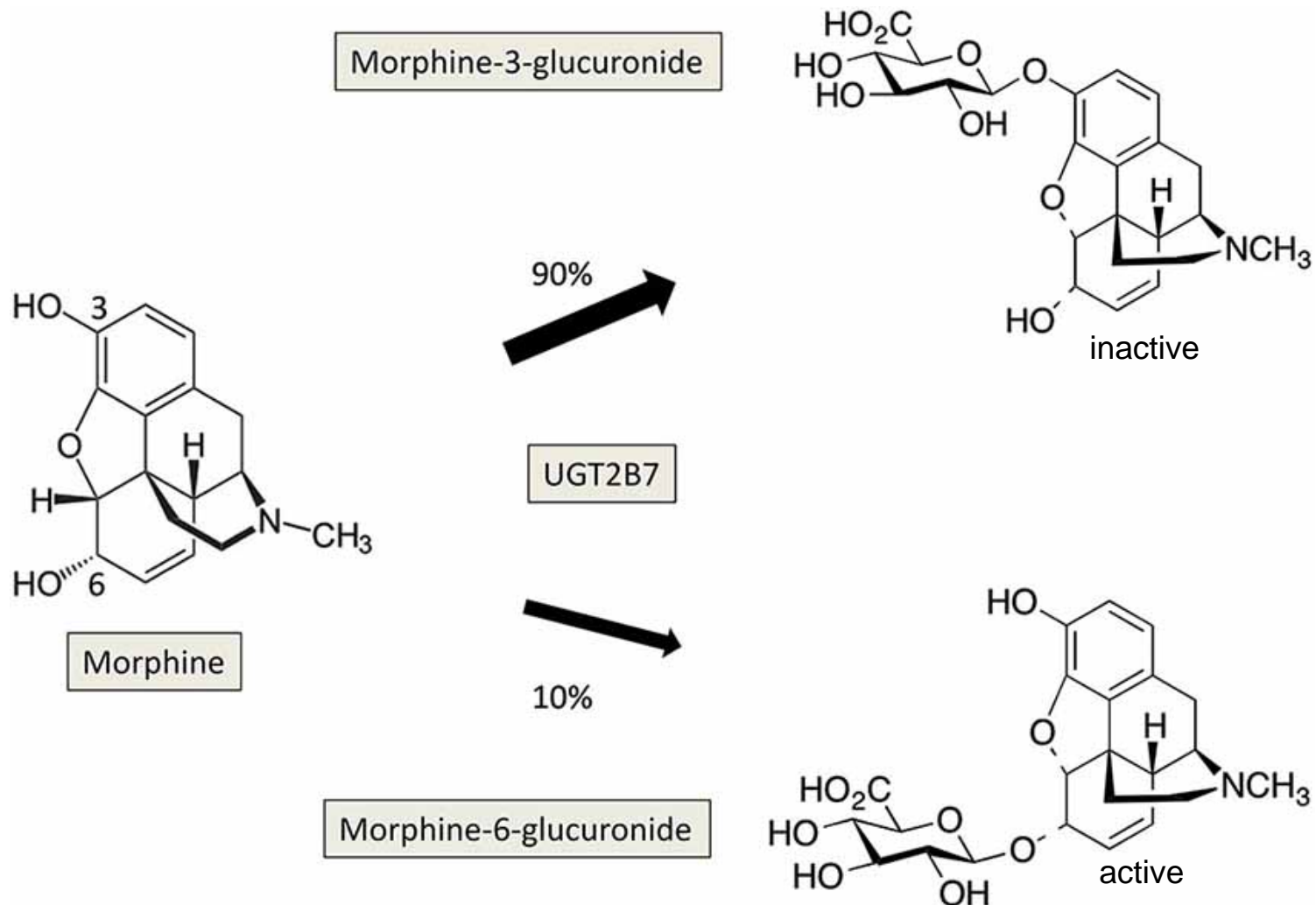
acetanilida

paracetamol



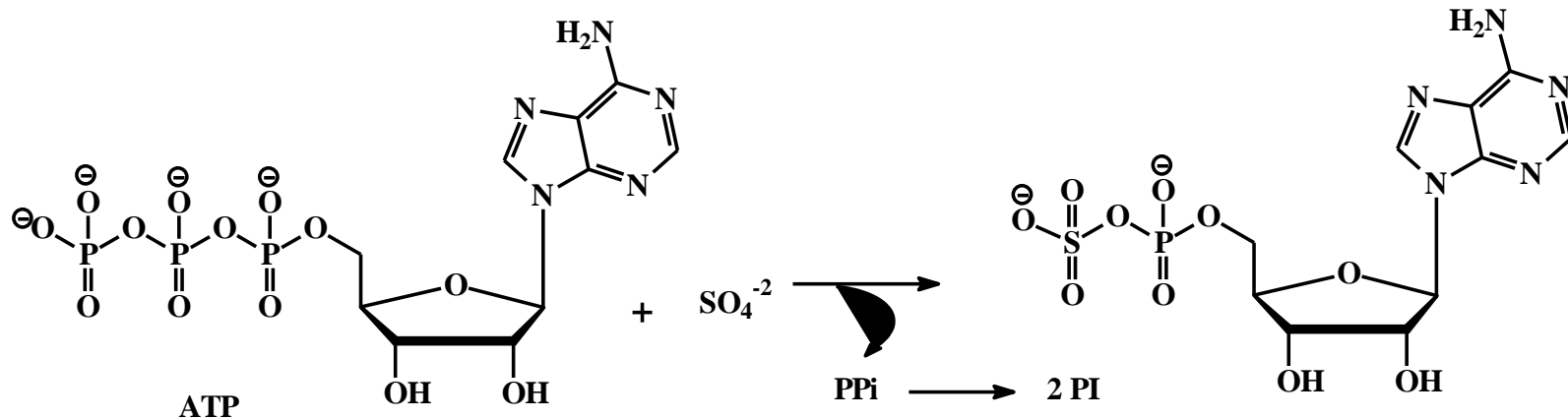
éster de glicuronato

1. GLICURONIDAÇÃO



It presents a higher analgesic potency than morphine. It has been shown that morphine-6-O-glucuronide exhibited a slow transport across the BBB compared to morphine, therefore the presence of UGT2B7 in brain may lead to local formation of morphine-6-O-glucuronide that can exert its analgesic actions.

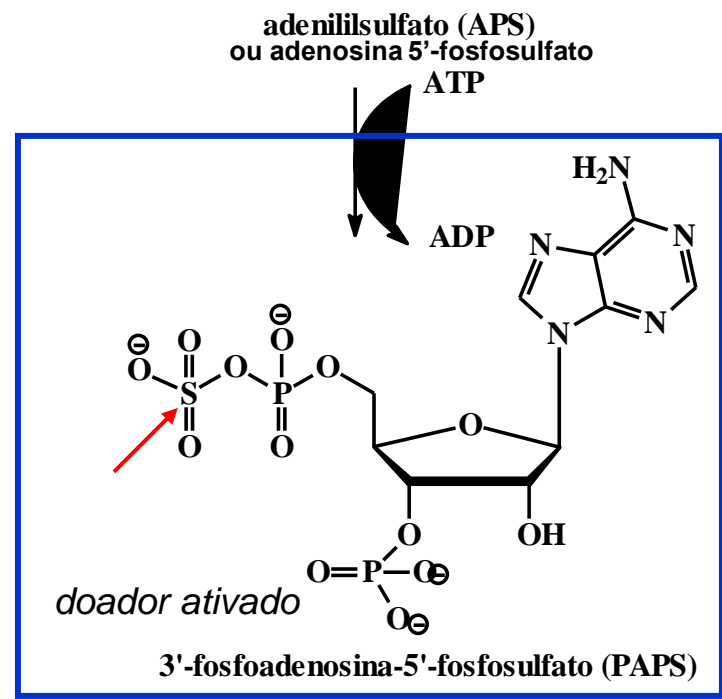
1. Sulfatação ou Sulfoconjugação

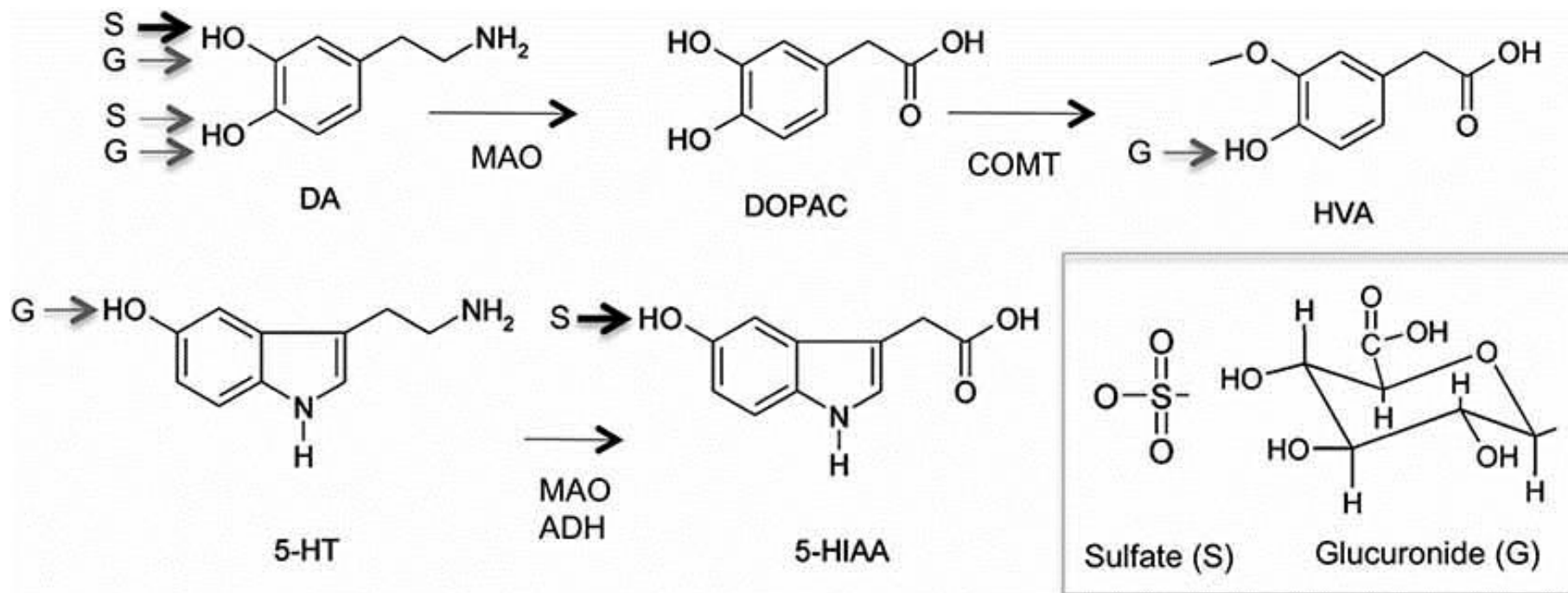


METABÓLITOS
Ésteres de sulfonatos

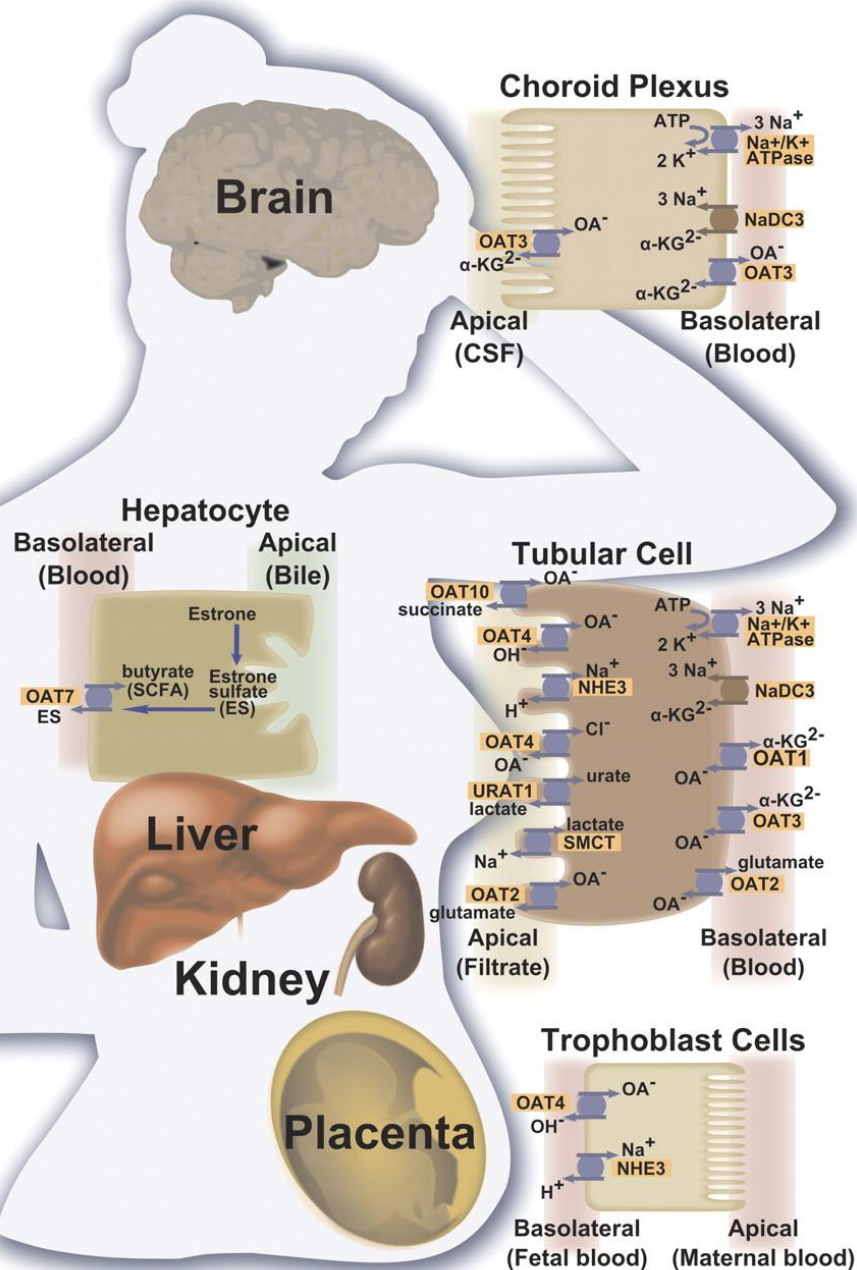
← sulfotransferase

Substratos Nucleofílicos (ROH, RNH₂)
fígado e intestino





Major metabolic pathway of serotonin (5-hydroxytryptamine) and dopamine (DA) to Phase I and Phase II metabolites (sulfate, S; glucuronide, G). Monoamine oxidase (MAO), aldehyde dehydrogenase (ADH) 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), catechol-O-methyltransferases (COMT), 5-hydroxyindoleacetic acid (5-HIAA). Main sulfo- and glucuronid conjugate found in human brain are indicated by arrows (data from Suominen et al., 2013).

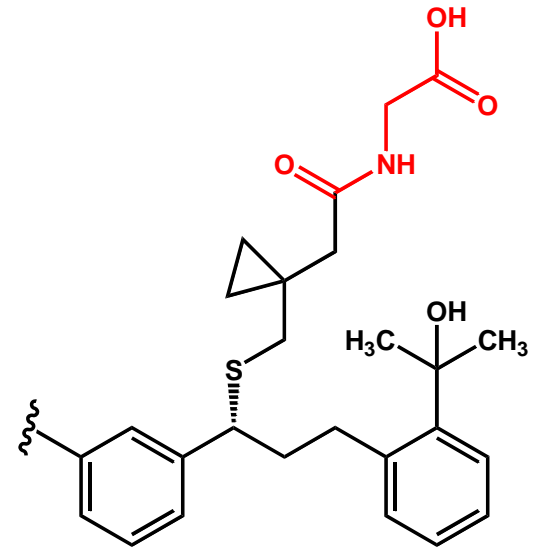
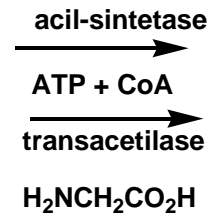
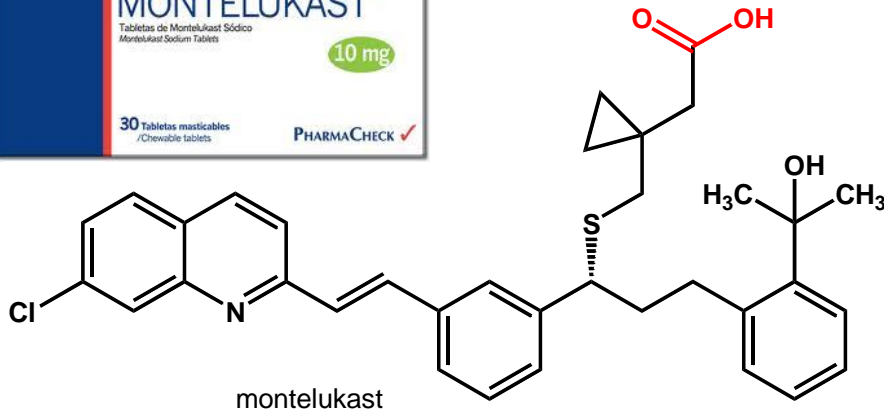
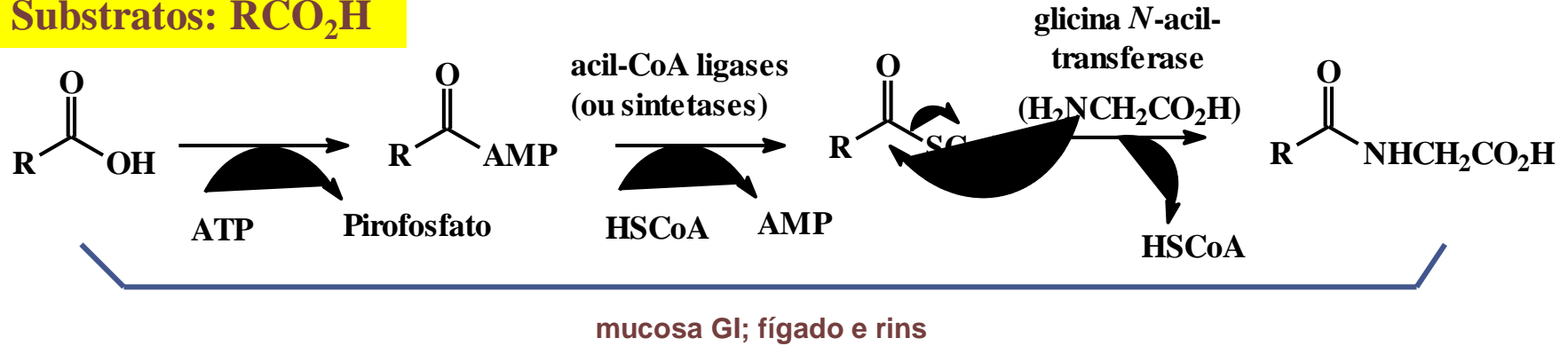


Tissue localization of **selected human organic anion transporter proteins** and their mechanism of action. Transporters located on the membrane domains of kidney proximal tubules, hepatocytes, choroid plexus epithelial cells, and placenta trophoblast cells are presented. OA^- , organic anion; $\alpha\text{-KG}$, α -ketoglutarate; SMCT, sodium-coupled monocarboxylate transporter I (SLC5A8); NHE3, sodium-hydrogen antiporter 3 (SLC9A3); NADC3, sodium-dependent dicarboxylate transporter 3 (SLC13A3); SCFA, short-chain fatty acid.

- ✓ OATs act in secretion of drugs and their metabolites between blood and intracellular fluid in a protein-mediated process that frequently involves direct or indirect expenditure of energy
- ✓ All OATs are expressed in the two major excretory organs of the body (i.e., kidney and/or liver)

3. Conjugação com aminoácido (Gly,

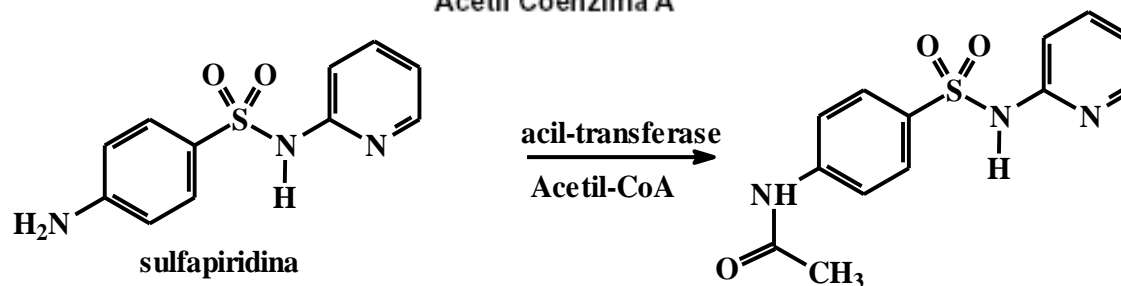
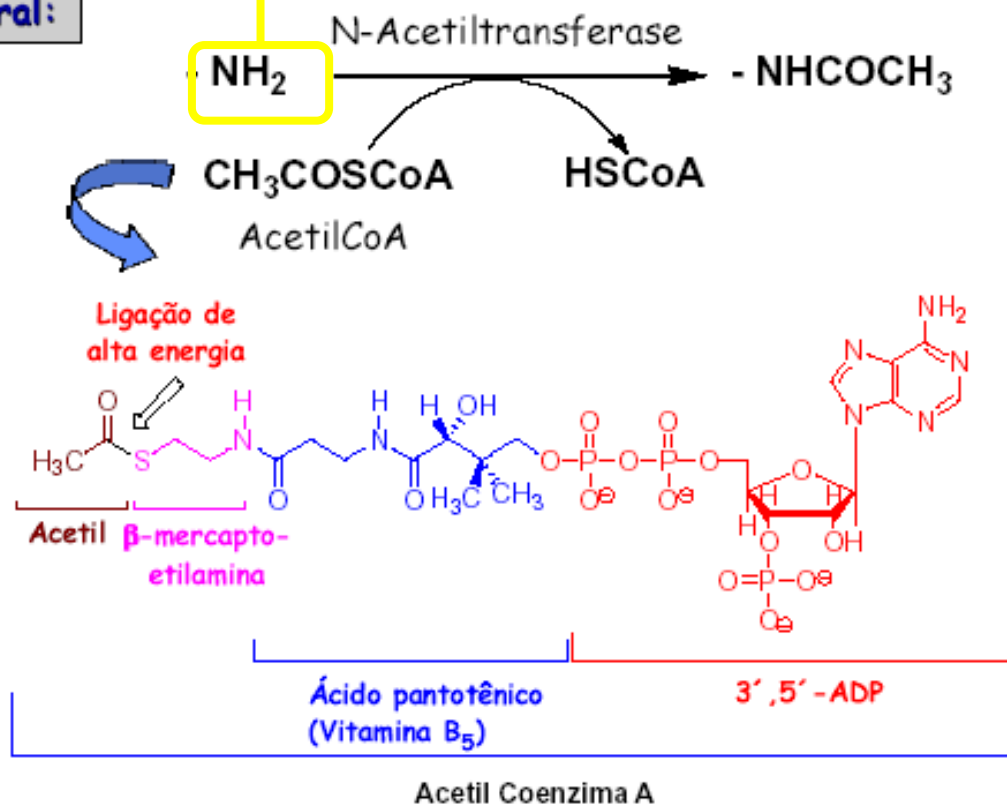
Substratos: RCO_2H



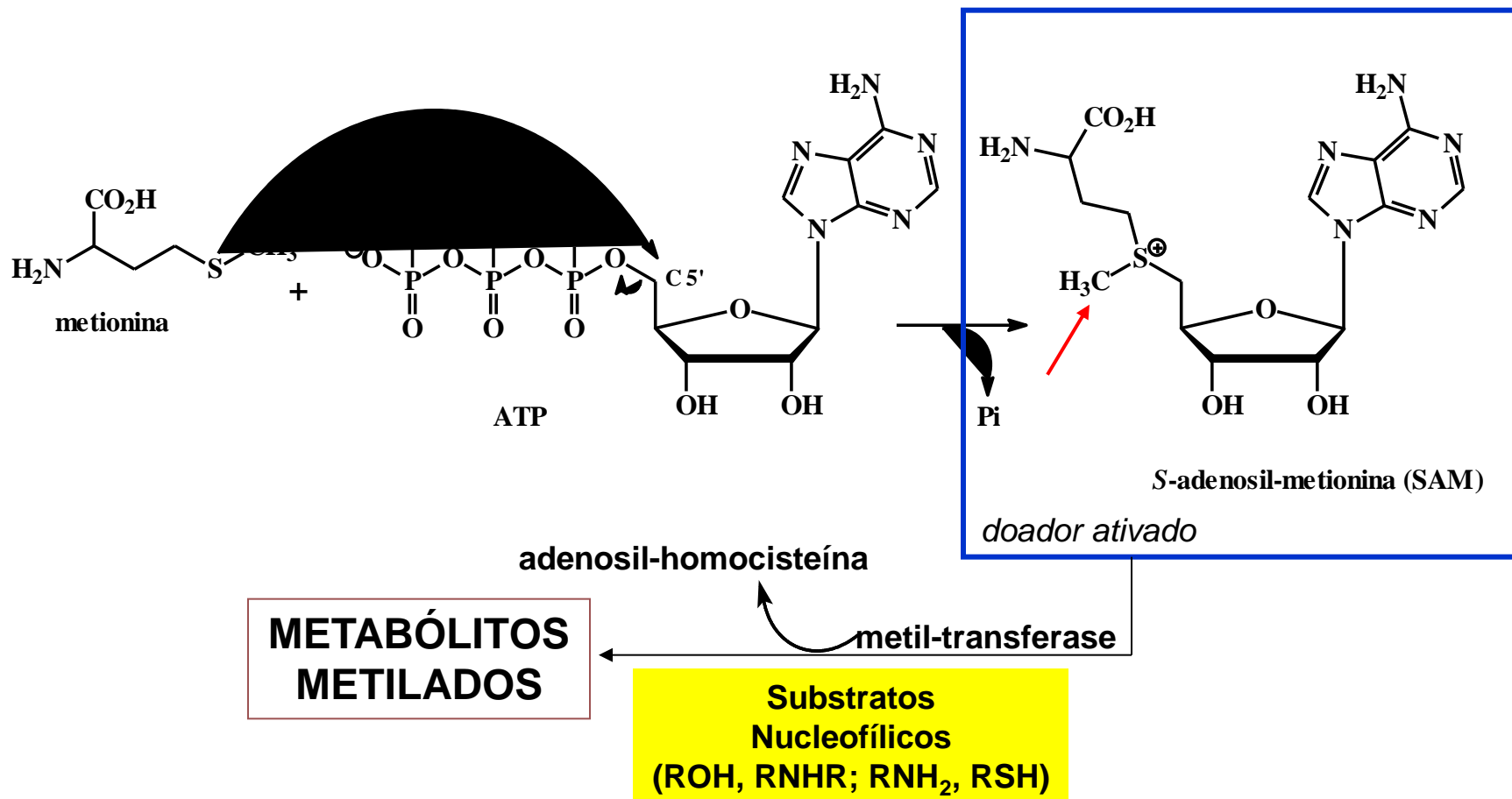
4. Acetilação

Reação geral:

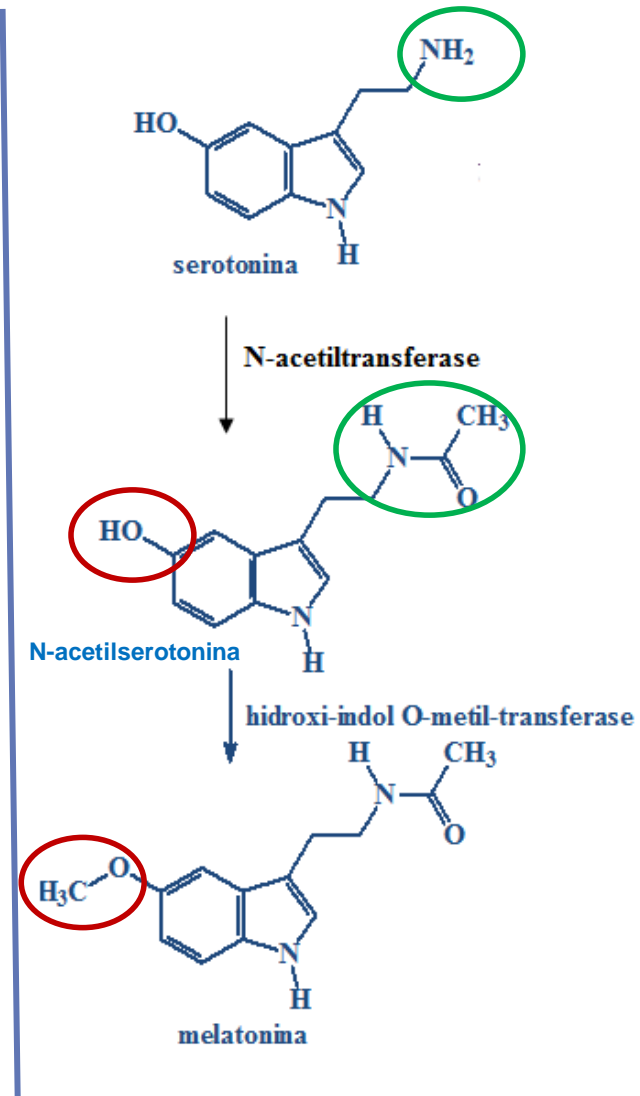
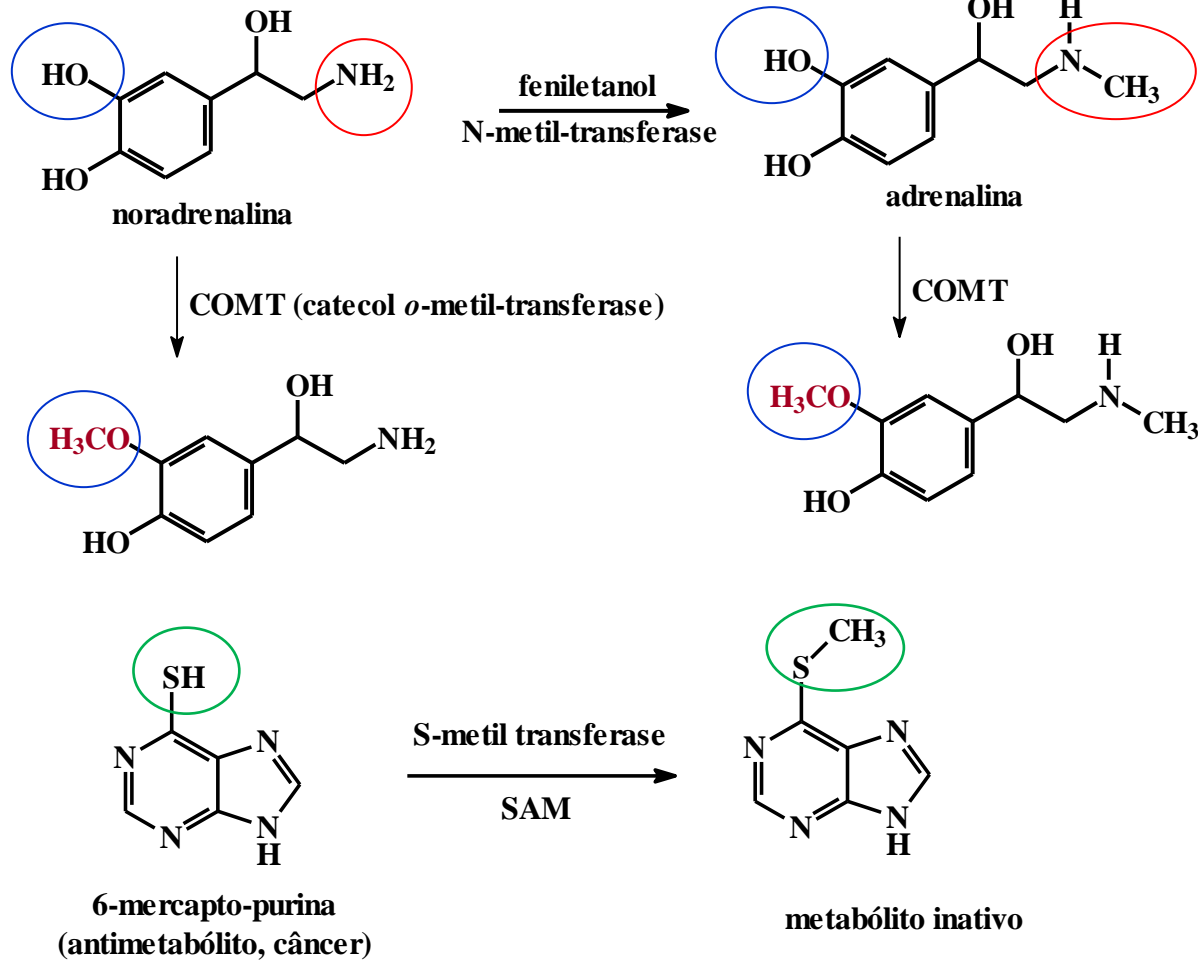
Substratos: OH, NH₂, NH, SH



5. Metilação



5. Metilação



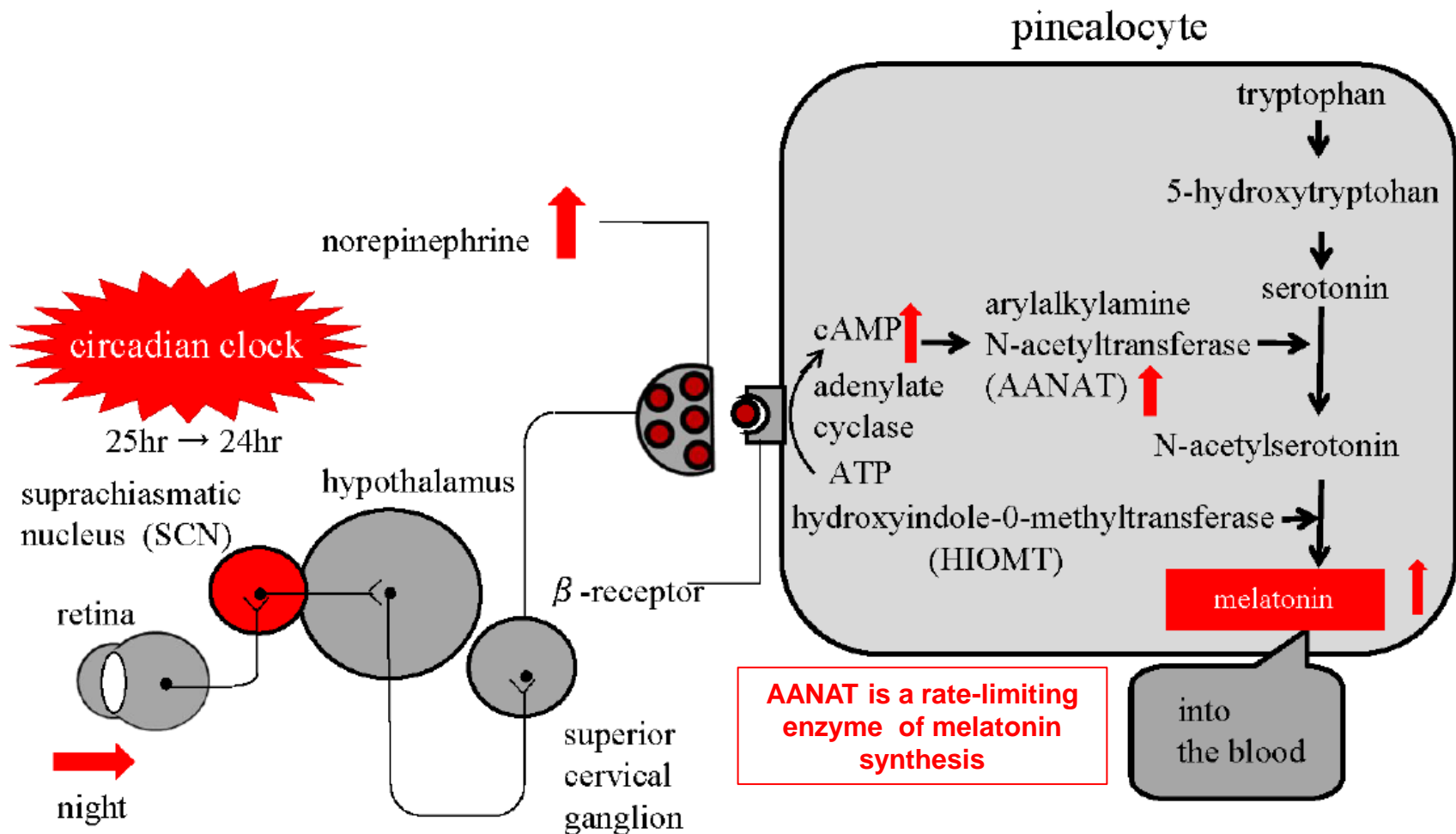
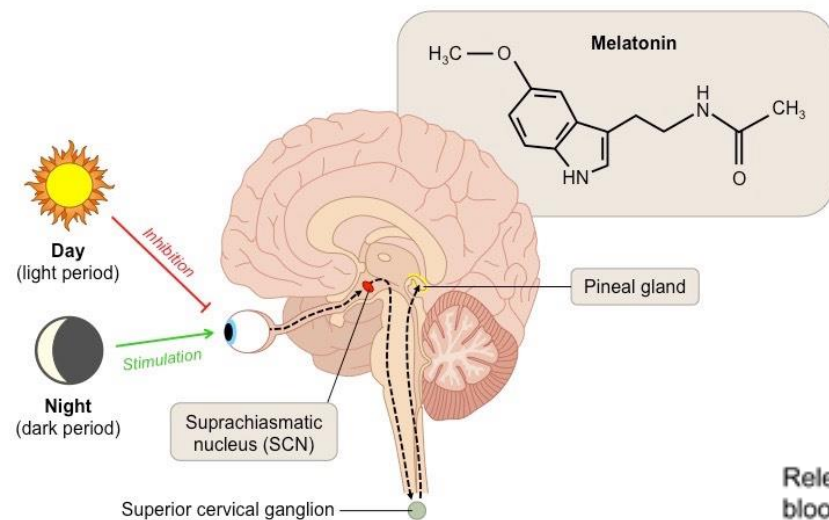


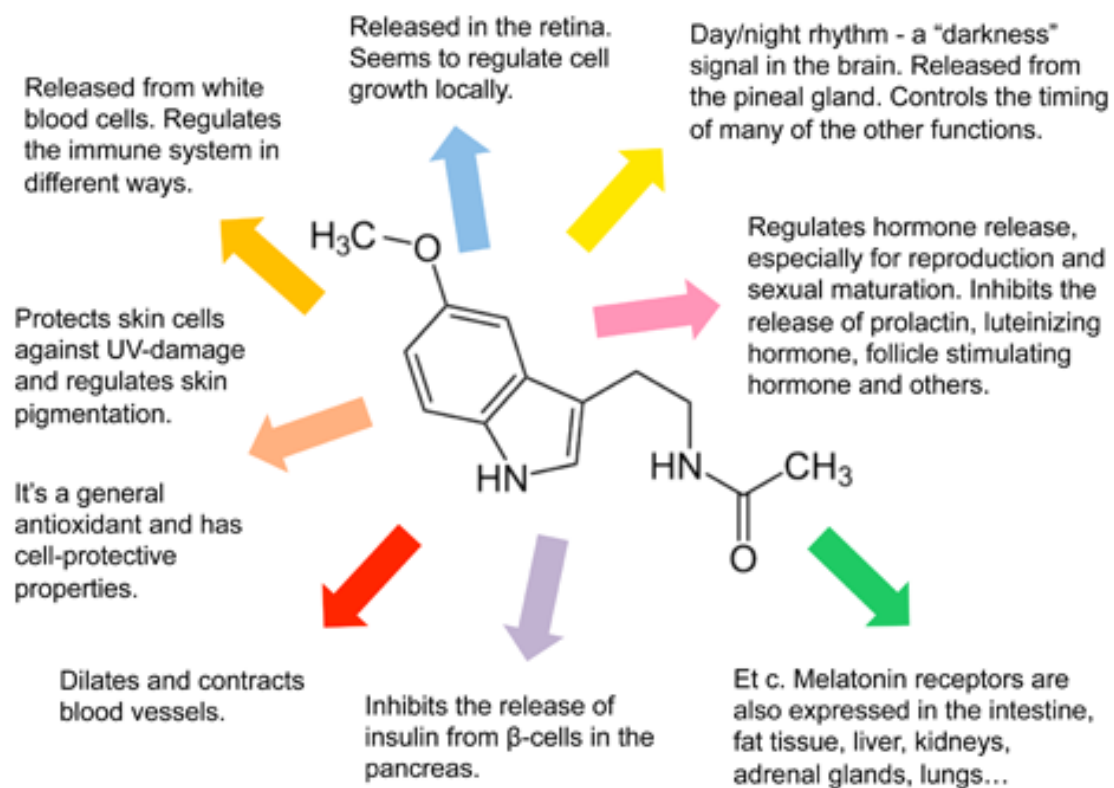
Fig. 1. Pathway of melatonin synthesis in the human pineal gland

Adapted from Reference No. 9 (Hattori A. The basic information for melatonin. Modern Physician 27: 1053-1056, 2007)

- ✓ The presence of melatonin receptors has so far been confirmed in the brain (including the SCN), spinal cord, pituitary gland, retina, spleen, thymus, adrenal gland, liver, kidney, heart, lungs, testes, ovaries, blood vessels, lymphocytes, and osteoblasts.

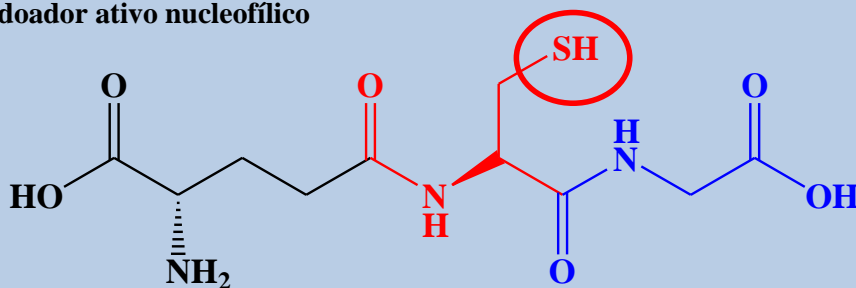


Melatonin: conductor of a large orchestra



6. Conjugação com Glutathiona

doador ativo nucleofílico



glutathiona (GSH)

ENZIMA: GLUTATHIONA
TRANSFERASE

Bionucleófilos

Endógenos

Glutathiona

Adenina

Guanina

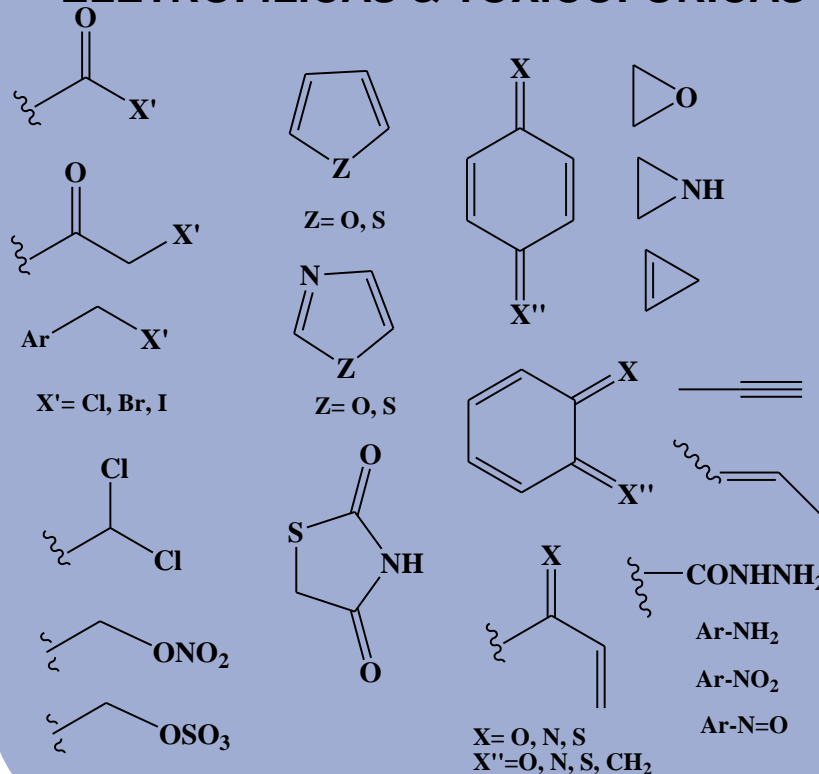
Serina

Lisina

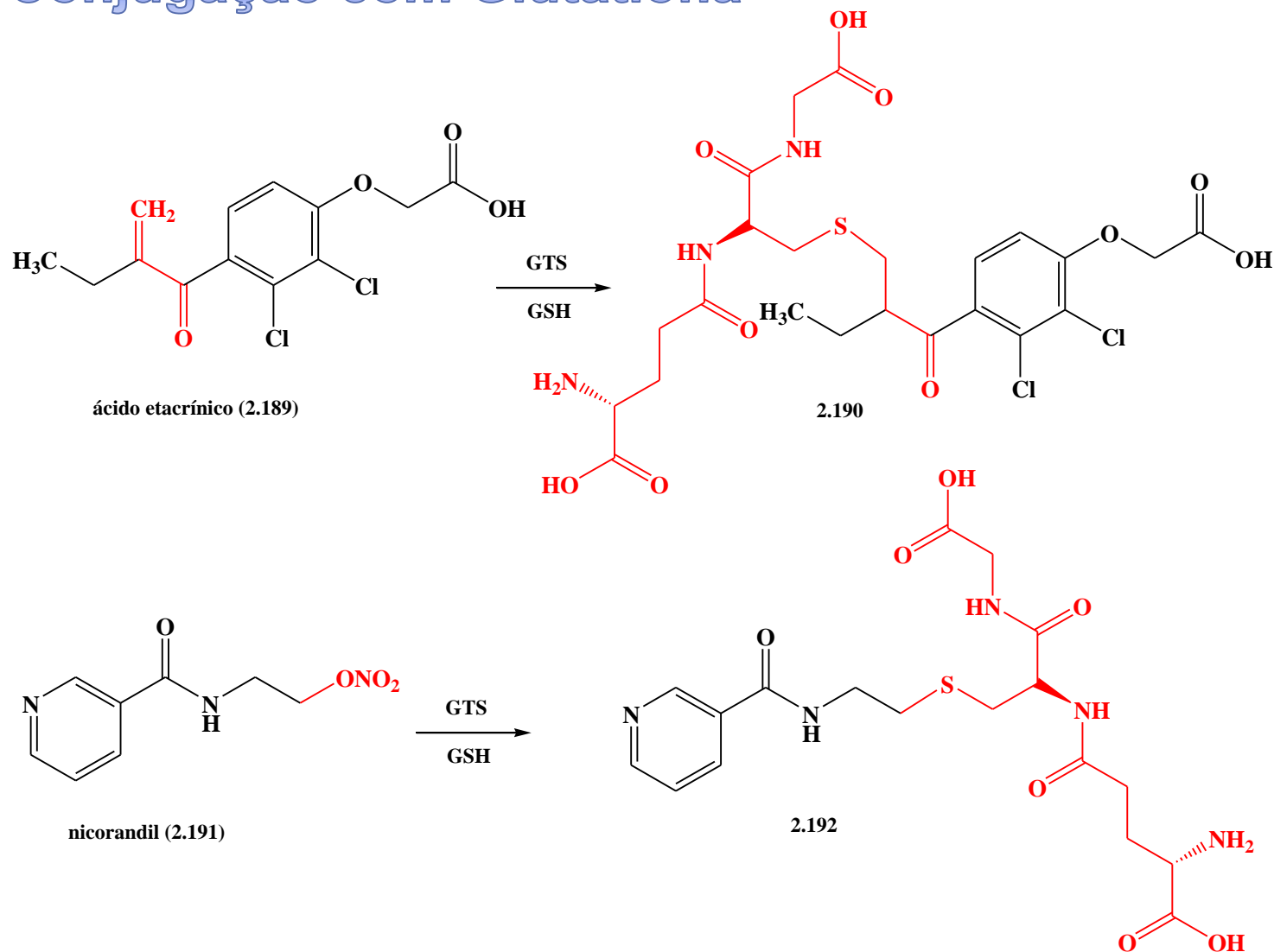
DNA

RNA

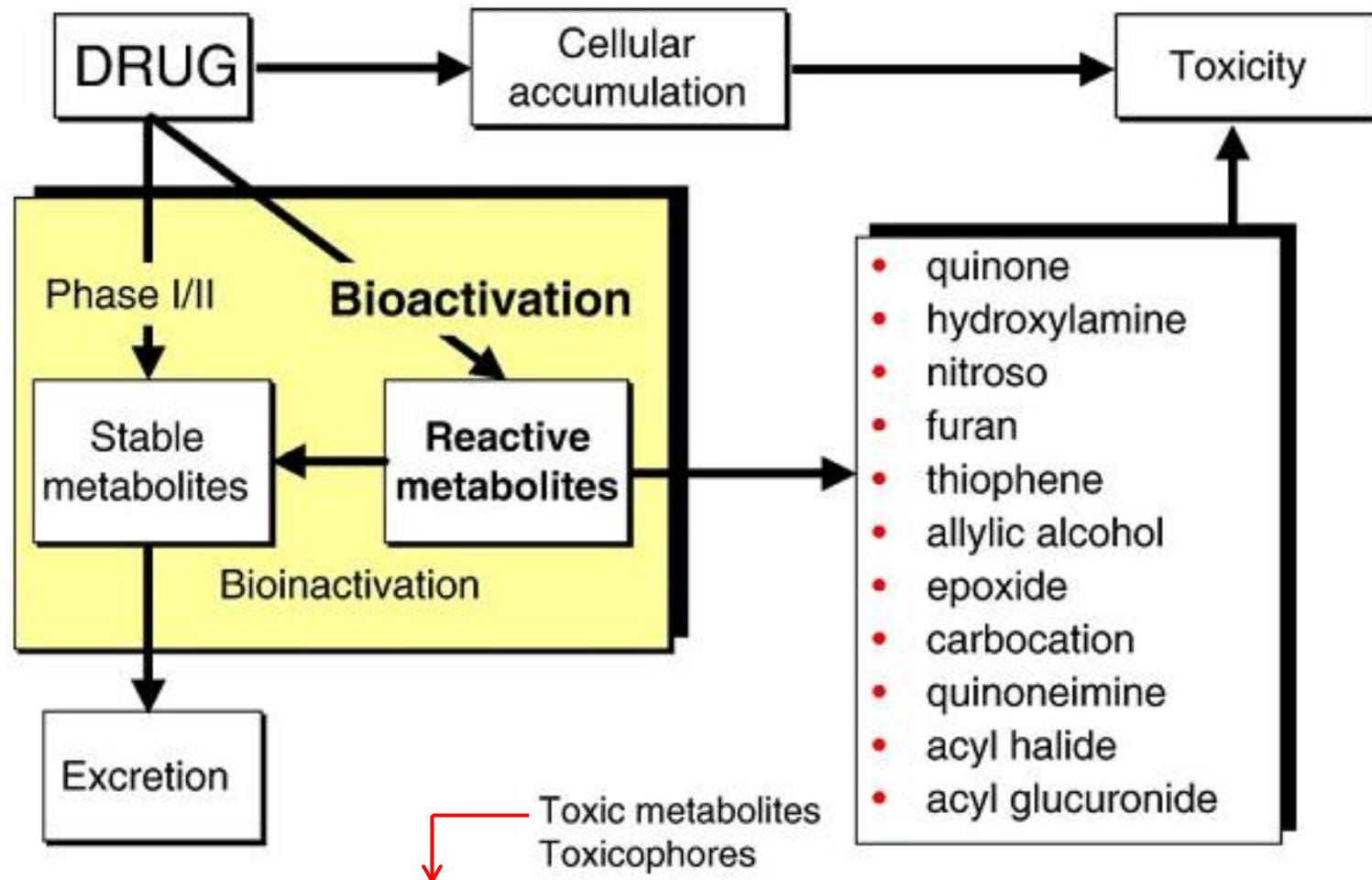
SUBSTRATOS: SUBUNIDADES
ELETROFÍLICAS & TOXICOFÓRICAS



6. Conjugação com Glutationa



PAPEL DO METABOLISMO NA TOXICIDADE DE FÁRMACOS



Meia vida menor de 1 min; Não detectáveis em plasma; Formação de eletrófilos

PAPEL DO METABOLISMO NA TOXICIDADE DE FÁRMACOS

Efeitos adversos/tóxicos induzidos por fármacos

Reversíveis/PREVISÍVEIS

Irreversíveis/IMPREDIZÍVEIS

Tipo A

~80%

- Previsíveis farmacologia primaria e/ou secundaria
- Efeito farmacológico exagerado
- Doses-dependente
- Variação Inter-indivíduos
- 80% de todos os casos
- Pode tratar-se com ajuste de doses

Tipo B

20%

- Não previsíveis (idiossincrático)
- No mostram relações dose-resposta
- Potencialmente mortais
- Os mecanismos de ação não são conhecidos ou entendidos completamente
- Susceptibilidade inter-indivíduos
 - Metabolismo
 - Resposta imune
 - Ambiente
 - Genética
 - Estrutura Química

Table 1. Idiosyncratic Drug Reactions and the Cells That Are Affected.

Type of Reaction	Effect on Cells	Examples of Drugs
Hepatocellular	Direct effect or production by enzyme–drug adduct leads to cell dysfunction, membrane dysfunction, cytotoxic T-cell response	Isoniazid, trazodone, diclofenac, nefazodone, venlafaxine, lovastatin
Cholestasis	Injury to canalicular membrane and transporters	Chlorpromazine, estrogen, erythromycin and its derivatives
Immunoallergic	Enzyme–drug adducts on cell surface induce IgE response	Halothane, phenytoin, sulfamethoxazole
Granulomatous	Macrophages, lymphocytes infiltrate hepatic lobule	Diltiazem, sulfa drugs, quinidine
Microvesicular fat	Altered mitochondrial respiration, β -oxidation leads to lactic acidosis and triglyceride accumulation	Didanosine, tetracycline, acetylsalicylic acid, valproic acid
Steatohepatitis	Multifactorial	Amiodarone, tamoxifen
Autoimmune	Cytotoxic lymphocyte response directed at hepatocyte membrane components	Nitrofurantoin, methyldopa, lovastatin, minocycline
Fibrosis	Activation of stellate cells	Methotrexate, excess vitamin A
Vascular collapse	Causes ischemic or hypoxic injury	Nicotinic acid, cocaine, methylenedioxymethamphetamine
Oncogenesis	Encourages tumor formation	Oral contraceptives, androgens
Mixed	Cytoplasmic and canalicular injury, direct damage to bile ducts	Amoxicillin–clavulanate, carbamazepine, herbs, cyclosporine, methimazole, troglitazone

Lee, W. M. N Engl J Med 2003;349:474-85.

PAPEL DO METABOLISMO NA TOXICIDADE DE FÁRMACOS

Efeitos adversos/tóxicos induzidos por fármacos

Reversíveis/PREVISÍVEIS

Irreversíveis/IMPREDIZÍVEIS

Tipo A

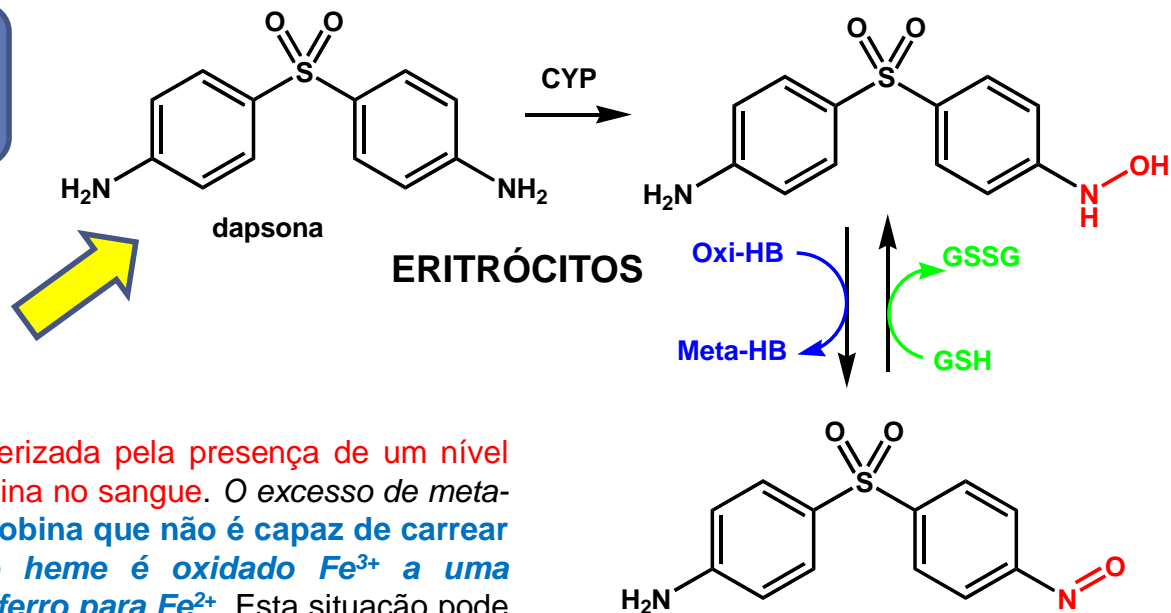
~80%

Tipo B

20%

Tipo A1: Dependente da concentração (↑janela terapêutica).
Exemplos: digoxina, varfarina

Tipo A2: Dependente da concentração de metabólitos ativos.
Exemplos: benzocaína; dapsona



Níveis de GSH aumentam
concentração da meta-HB via redução
nitroso a hidroxilamina

Meta-hemoglobinemia → desordem caracterizada pela presença de um nível mais alto do que o normal de meta-hemoglobina no sangue. O excesso de meta-hemoglobina (>1%), isto é forma de hemoglobina que não é capaz de carrear oxigênio, acontece quando o ferro do heme é oxidado Fe^{3+} a uma velocidade superior do que a redução do ferro para Fe^{2+} . Esta situação pode acontecer devido à presença de algumas substâncias tóxicas (e.g. fármacos) ou devido a deficiências enzimáticas congênitas (e.g. glicose 6-fosfato desidrogenase).

A metemoglobina redutase dependente de NADH (diaforese I) é responsável pela conversão de metemoglobina de volta à hemoglobina

consequências: Fadiga, náuseas, dor de cabeça, anemia

PAPEL DO METABOLISMO NA TOXICIDADE DE FÁRMACOS

Efeitos adversos/tóxicos induzidos por fármacos

Reversíveis/PREVISÍVEIS

Tipo A

Irreversíveis/IMPREDIZÍVEIS

sem relação direta com dose

Tipo B

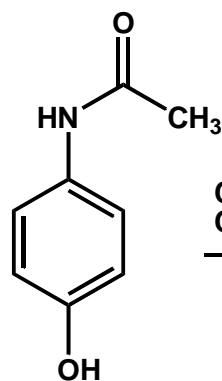
Tipo B1: Necrose
e.g. paracetamol

Tipo B2: imune
e.g. penicilina

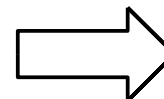
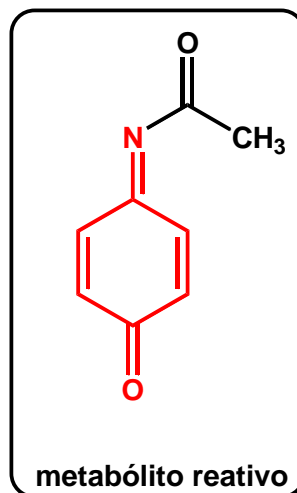
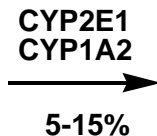
Tipo B3: câncer
e.g. antineoplásicos

reações adversas idiossincráticas

subunidades ou metabólitos ou reativos (eletrofílicos)



paracetamol



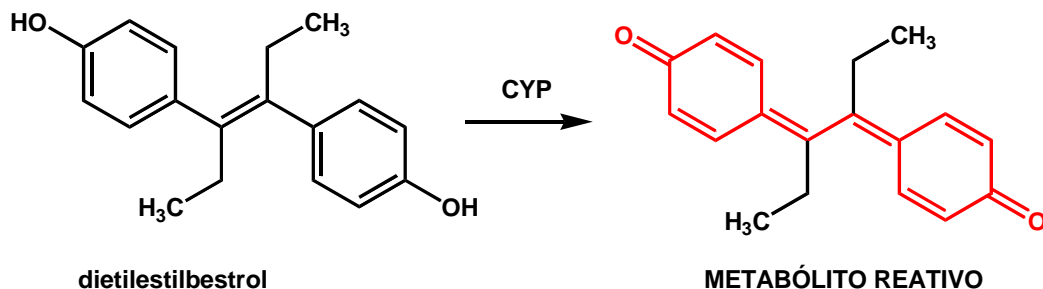
NECROSE HEPÁTICA

Ligação covalente com
proteínas dos hepatócitos

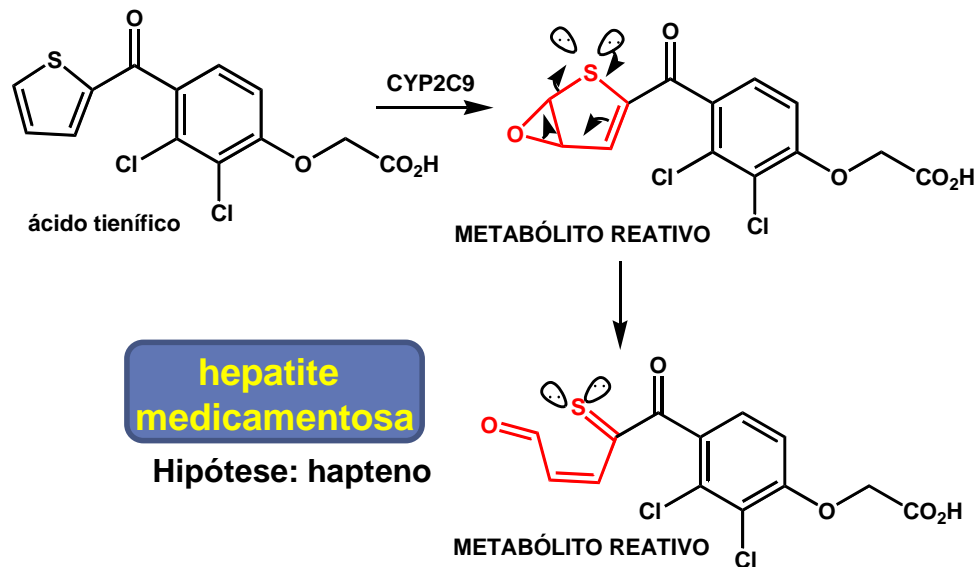
PAPEL DO METABOLISMO NA TOXICIDADE DE FÁRMACOS

Reações adversas: Tipo B

Discrasias sanguíneas; anafilaxia; hepatotoxicidade, alergias, carcinogenicidade; teratogenicidade



Proscrito em 1975: vaginal clear cell adenocarcinoma in girls and young women who had been exposed to this drug *in utero*

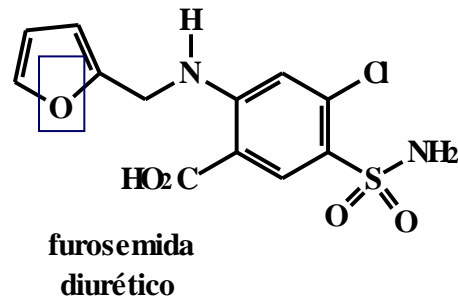


hepatite medicamentosa

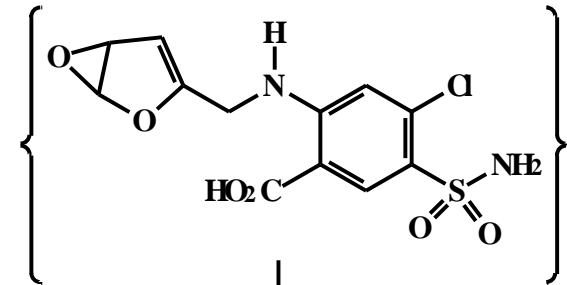
Hipótese: hapteno

PAPEL DO METABOLISMO NA TOXICIDADE DE FÁRMACOS

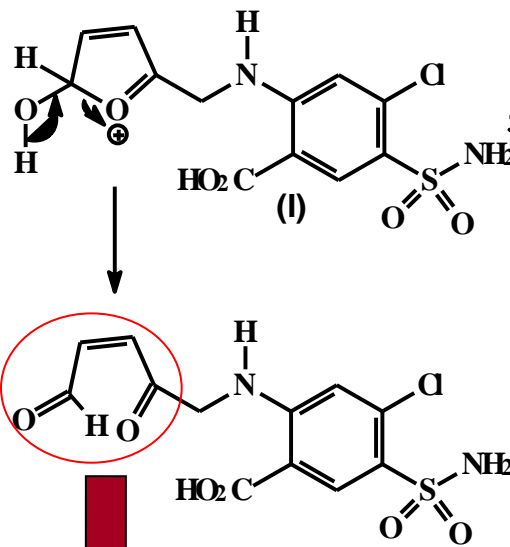
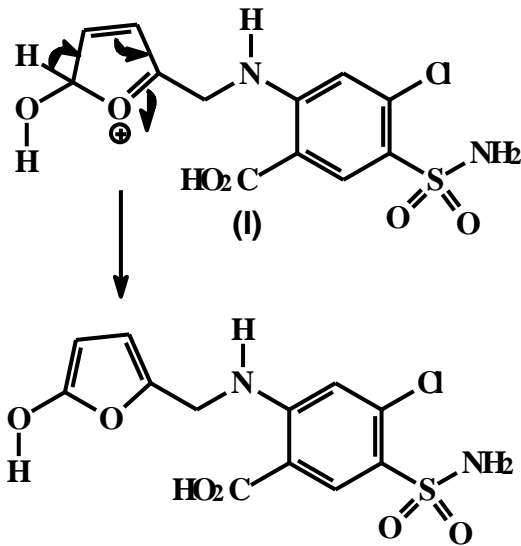
Reações adversas: Tipo B (Discrasias sanguíneas; anafilaxia; hepatotoxicidade, alergias, carcinogenicidade; teratogenicidade)



CYP450



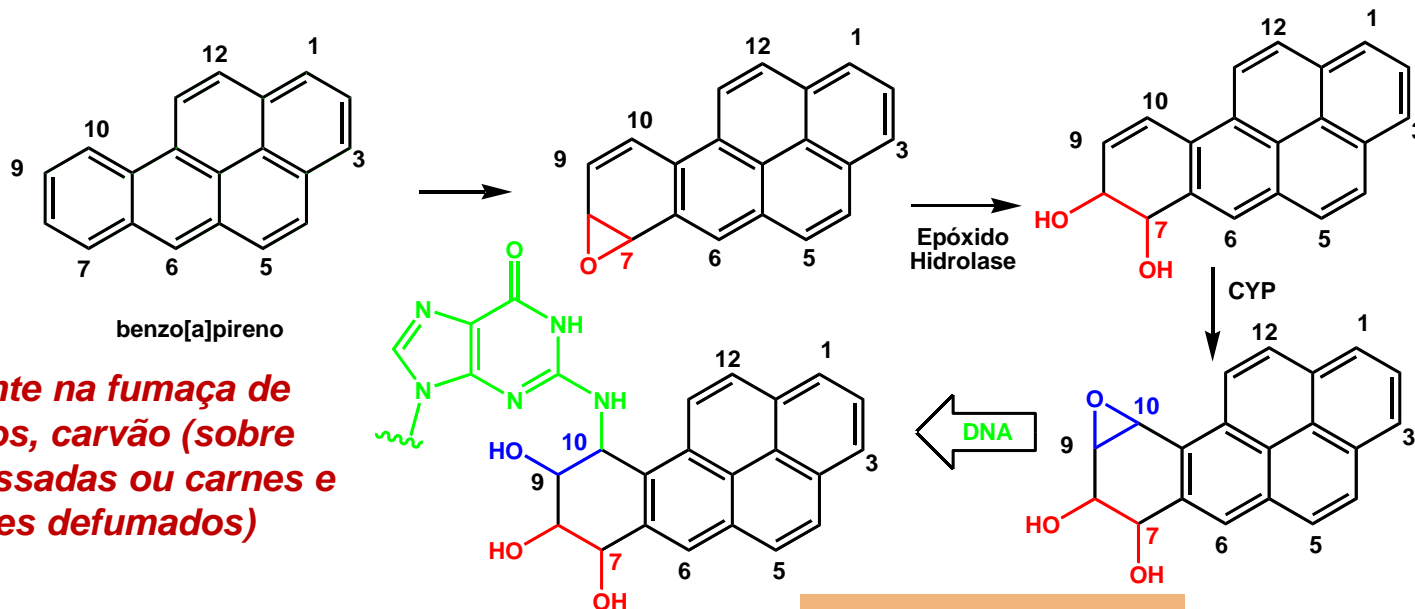
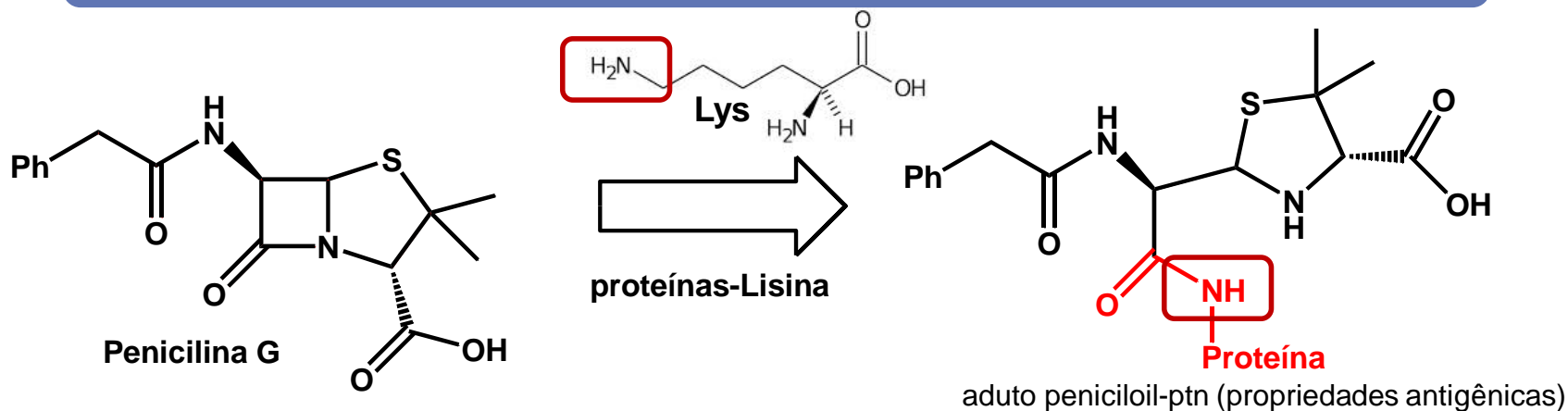
b



Necrose hepática e renal

PAPEL DO METABOLISMO NA TOXICIDADE DE FÁRMACOS

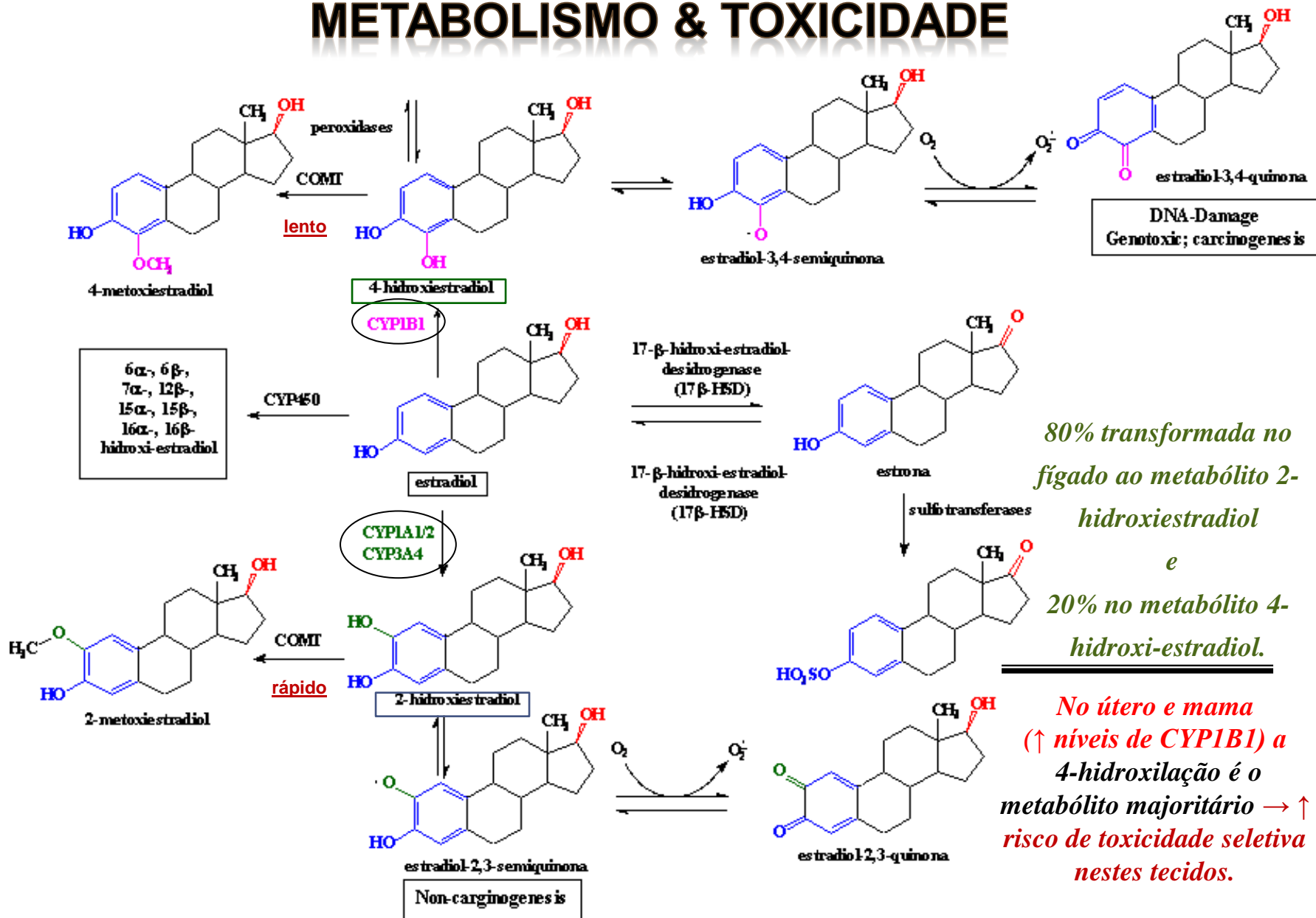
Reações adversas: Tipo B (Discrasias sanguíneas; anafilaxia; hepatotoxicidade, **alergias, carcinogenicidade**, teratogenicidade)



presente na fumaça de cigarros, carvão (sobre carnes assadas ou carnes e peixes defumados)

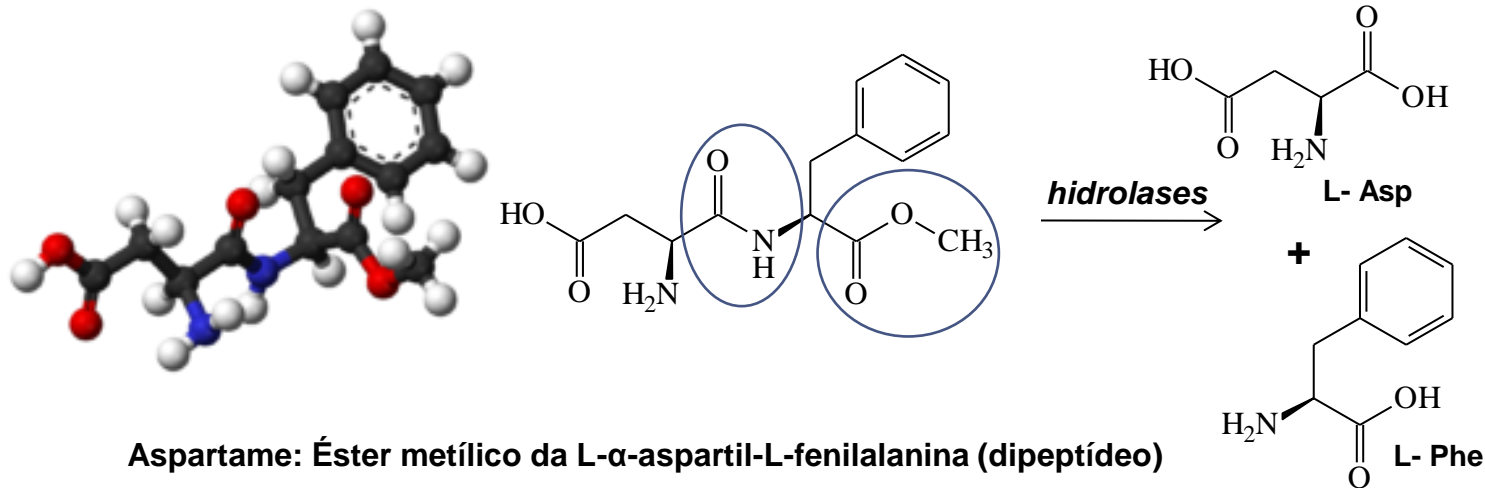
carcinogenicidade

METABOLISMO & TOXICIDADE



80% transformada no fígado ao metabólito 2-hidroxiestradiol e 20% no metabólito 4-hidroxi-estradiol.

No útero e mama (↑ níveis de CYP1B1) a 4-hidroxição é o metabólito majoritário → ↑ risco de toxicidade seletiva nestes tecidos.



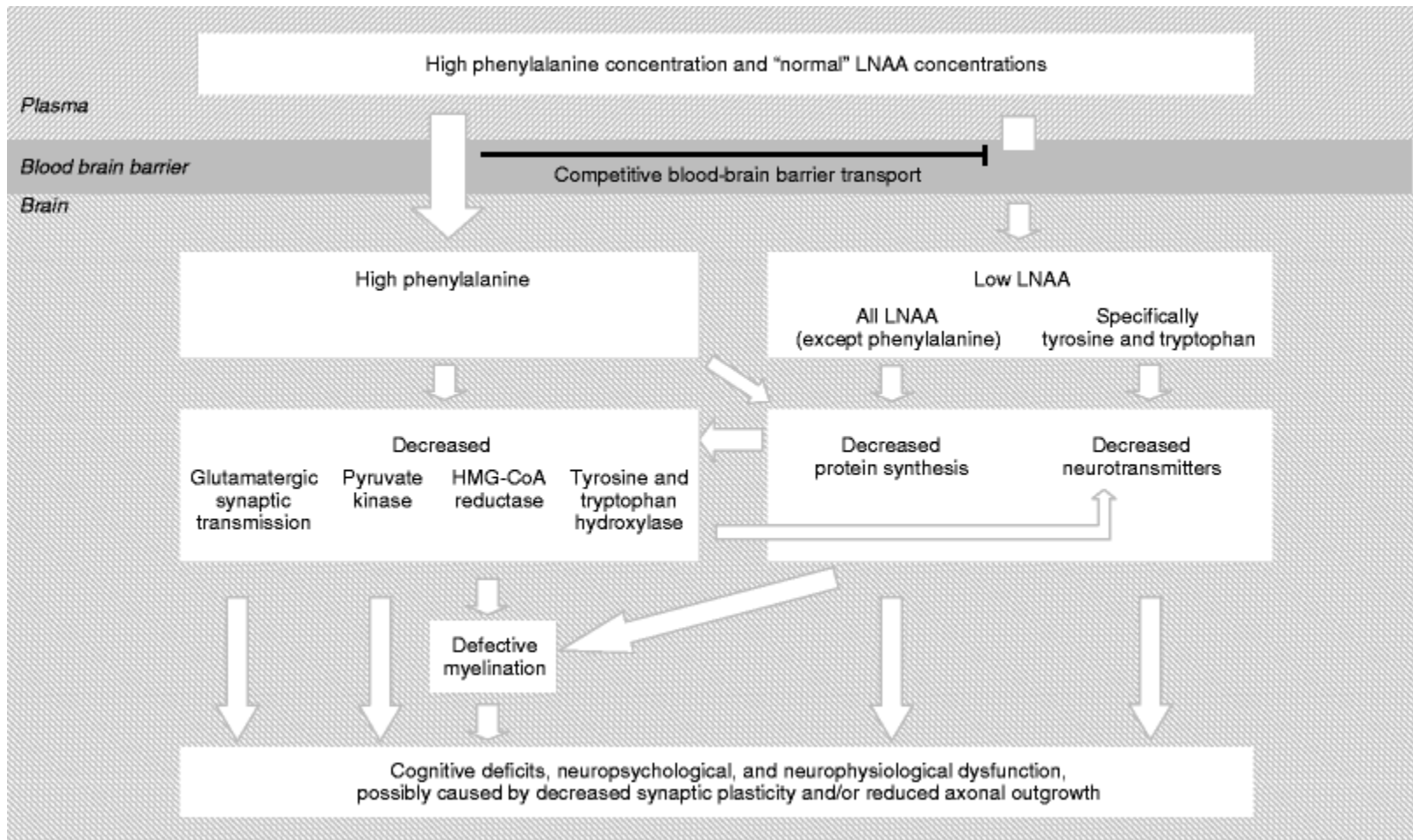
Fenilcetonúria → doença genética caracterizada pelo defeito ou ausência da enzima **fenilalanina hidroxilase** (**Phe** → **Tyr** ⇒ síntese de melanina). Sintomas: oligofrenia (QI ≤ 90 ; deficit de inteligência), atraso do desenvolvimento psicomotor (andar ou falar), convulsões, hiperatividade, tremor e microcefalia.

Efeitos adversos : neurotoxicidade e carcinogenicidade

□ Russel L. Blaylock (*J Neuropathology Experimental Neurology*. 1996;55:1115-23) ao estudar o ácido aspártico que é um aminoácido que constitui 40% do aspartame descreveu mais de 500 experiências científicas comprovando a deterioração das células neurais

□ Brain dysfunction in phenylketonuria: is phenylalanine toxicity the only possible cause? *J Inherit Metab Dis*. 2009 Feb;32(1):46-51.

The pathophysiology of brain dysfunction in phenylketonuria



F. J. van Spronsen et al., *Inherit Metab Dis.*, 2009, 32: 46-51

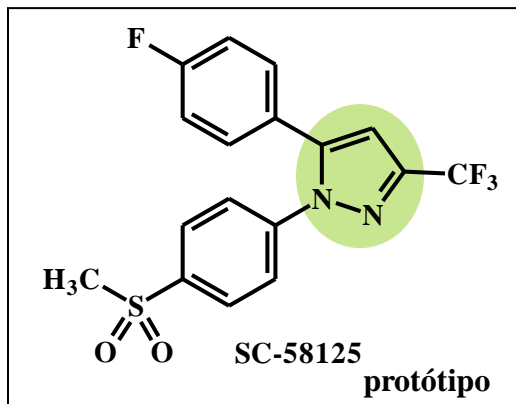
MINI-CURSO:

Metabolismo de Fármacos: aplicações em toxicologia e interações medicamentosas

PARTE 3

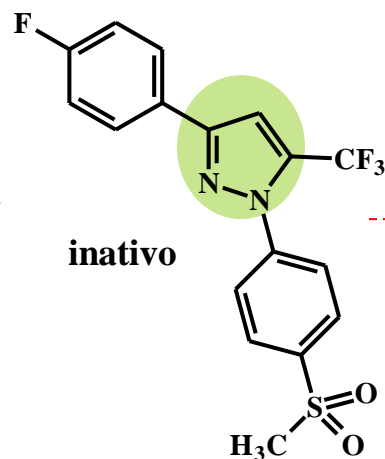


METABOLISMO & DESENHO DE FÁRMACOS

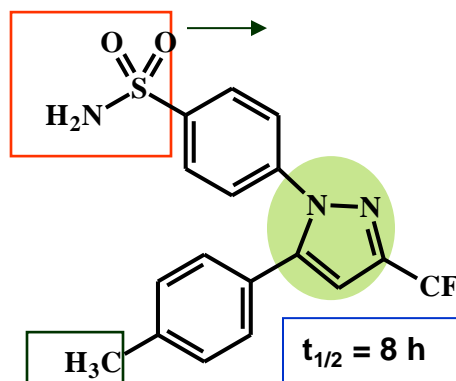
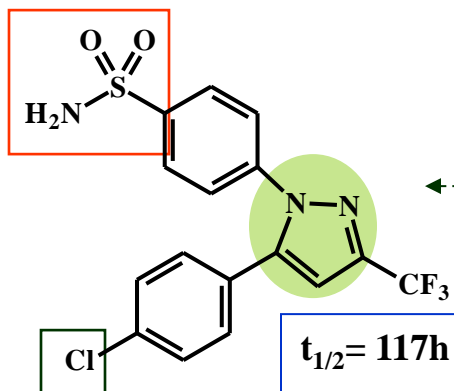
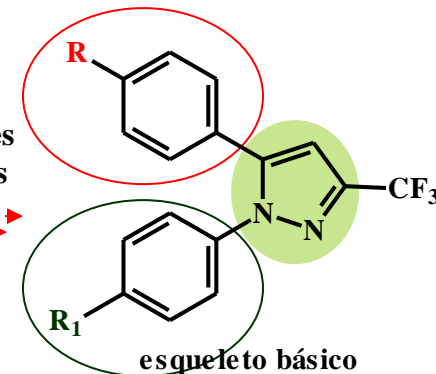


IC₅₀ > 100 μM (COX-1)
IC₅₀ = 0,1 μM (COX-2)

Modificações
Moleculares



Modificações
Moleculares



celecoxib
COX-2 seletivo

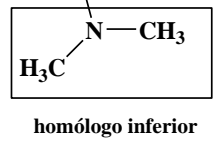
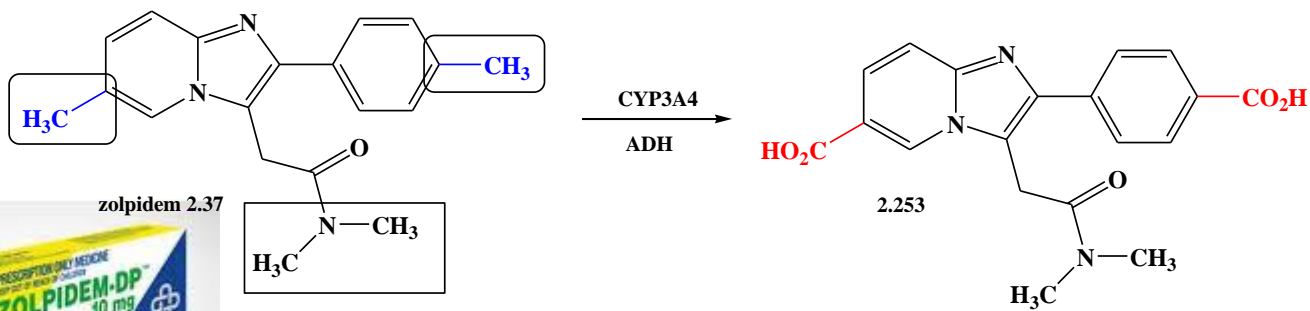
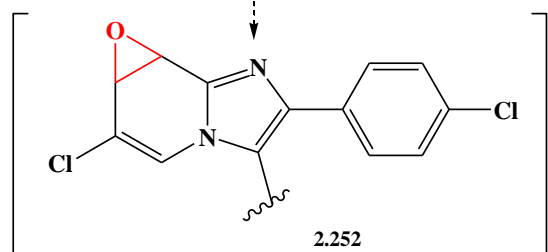
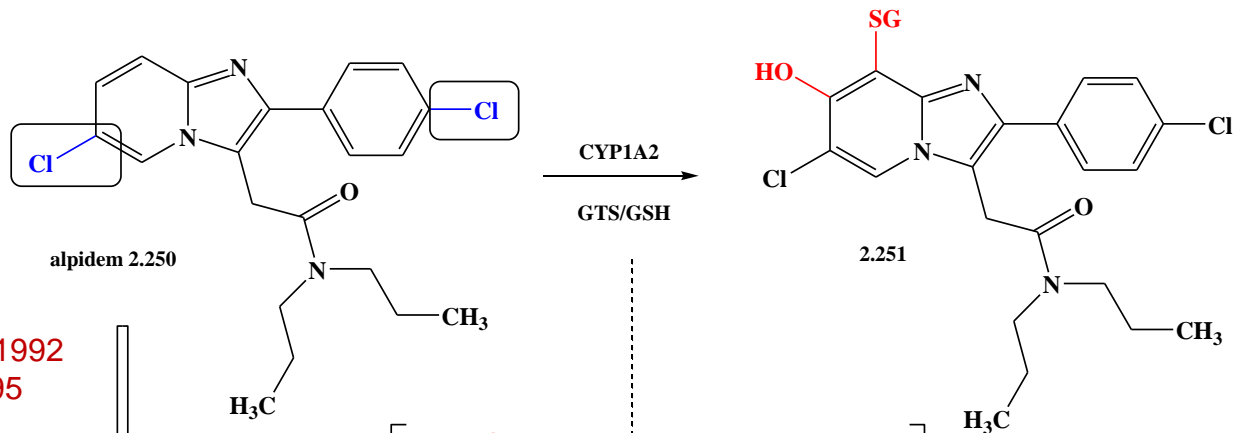
IS=460

R ₁	R	IC ₅₀ (COX-1)	IC ₅₀ (COX-2)
SO ₂ NH ₂	CF ₃	<100 μM	8,23 μM
SO ₂ NH ₂	Cl	17 μM	0,01 μM
SO ₂ NH ₂	F	25 μM	0,041 μM
SO ₂ NH ₂	CH ₃	15 μM	0,04 μM
SO ₂ NH ₂	OCH ₃	2,58 μM	0,008 μM
SO ₂ NH ₂	SCH ₃	1,19 μM	0,009 μM
SO ₂ NH ₂	NHCH ₂	13,8 μM	0,016 μM
SO ₂ NH ₂	CO ₂ H	>250 μM	11,2 μM
SO ₂ NH ₂	3-CH ₃	33,9 μM	0,069 μM
SO ₂ NH ₂	2-CH ₃	18,1 μM	0,11 μM

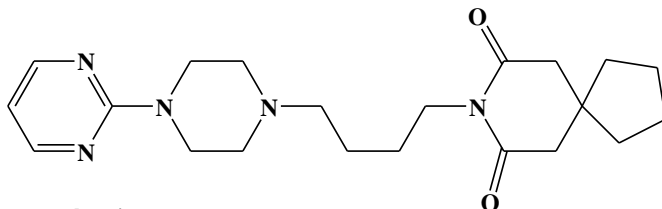


METABOLISMO & DESENHO DE FÁRMACOS

Alpidem:
Aprovado FDA em 1992
Proscrito em 1995
Hepatotóxico

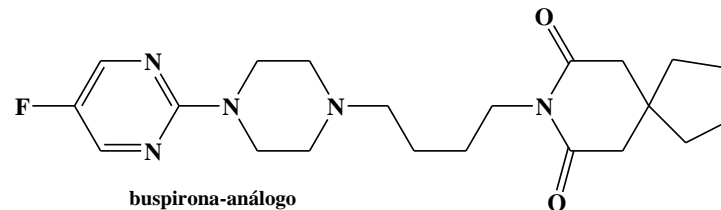


METABOLISMO & DESENHO DE FÁRMACOS

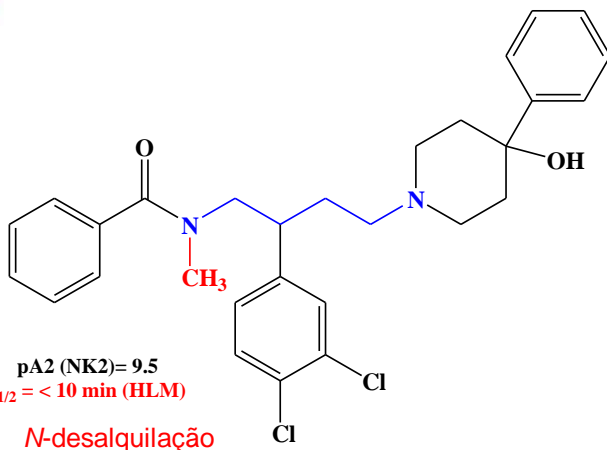


buspirona $IC_{50} (5HT_{1A}) = 0,025$
 $t_{1/2} = 4,6 \text{ h}$

ansiolítico (agonista de receptores de serotonina);
↑efeito 1ª passagem; ↓ biodisponibilidade oral

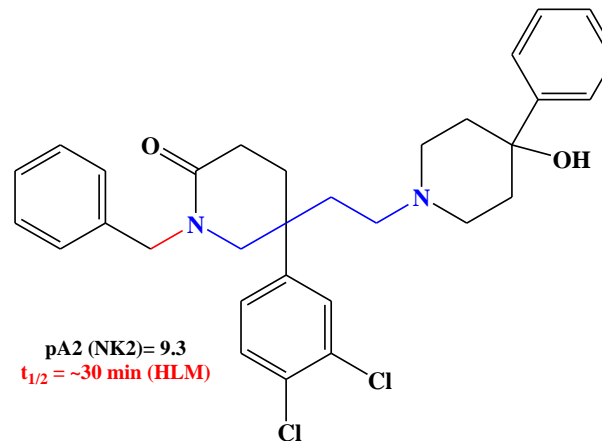


buspirona-análogo
 $IC_{50} (5HT_{1A}) = 0,063$
 $t_{1/2} = 52,3 \text{ h}$



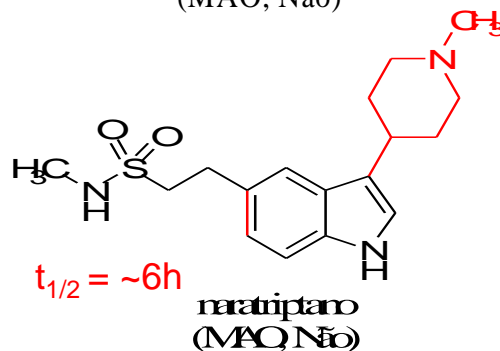
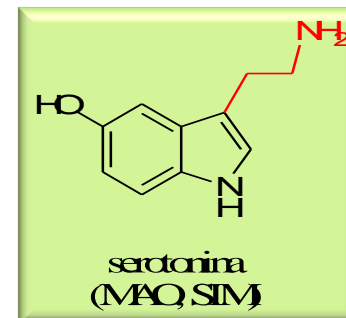
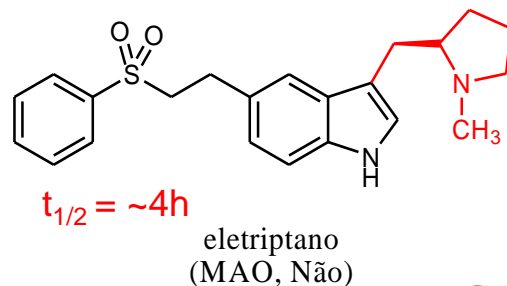
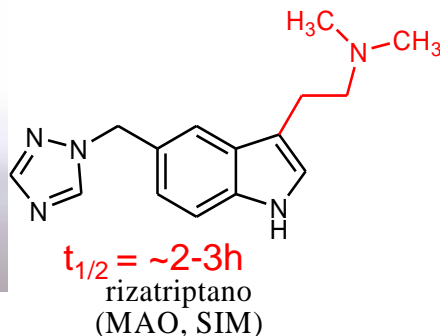
pA2 (NK2) = 9.5
 $t_{1/2} = < 10 \text{ min (HLM)}$

N-desalquilação



pA2 (NK2) = 9.3
 $t_{1/2} = \sim 30 \text{ min (HLM)}$

METABOLISMO & DESENHO DE FÁRMACOS



Agonistas 5-HT₁

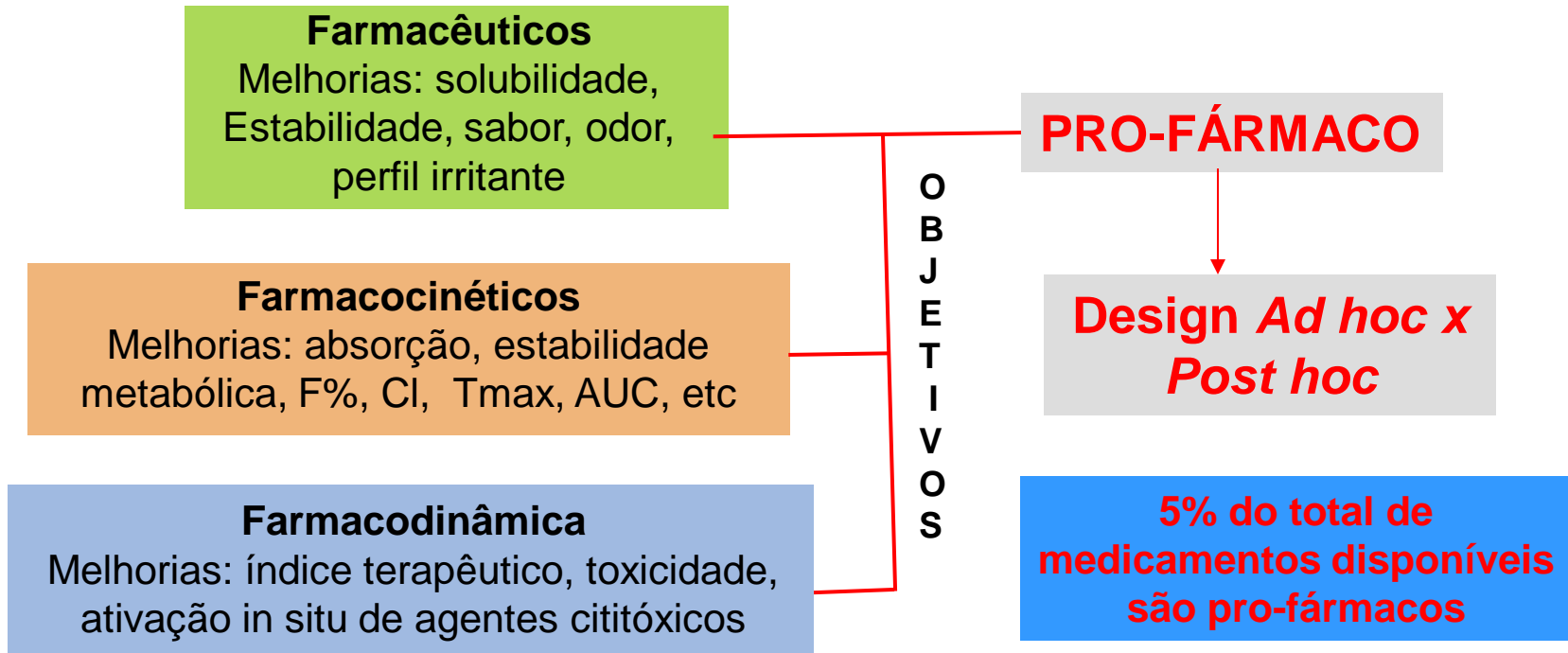
Stepan, A. F. et al., Med. Chem. Commun., 2013, 4, 631–652

Pró-Fármaco: Substância desprovida de atividade farmacológica intrínseca, termo cunhado por Albert em 1958.

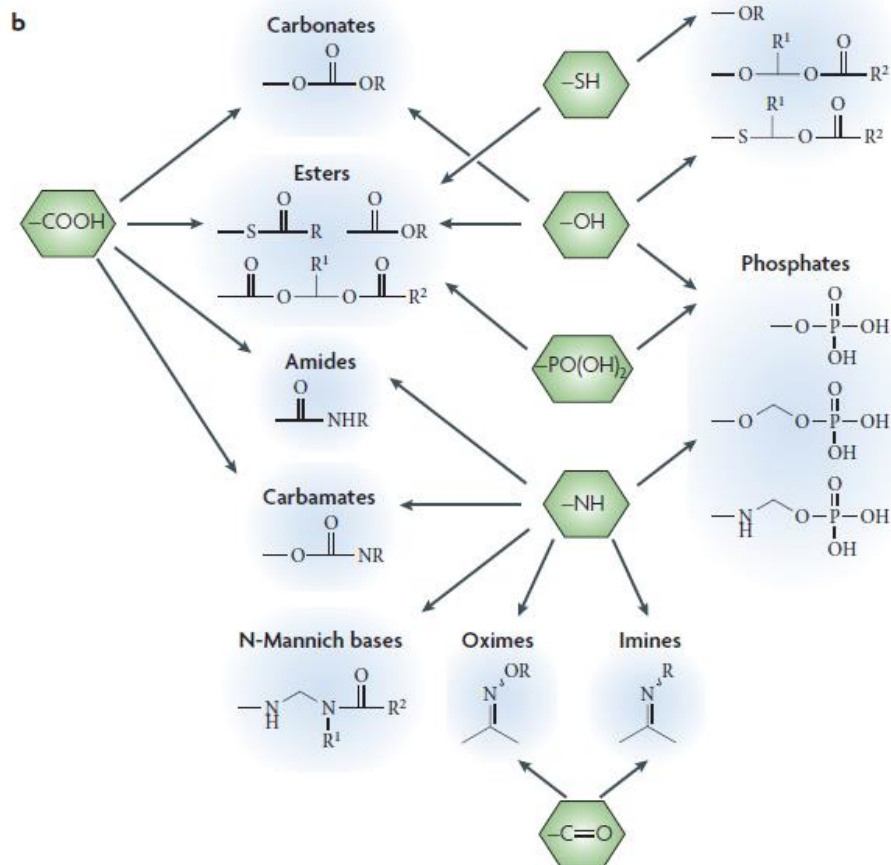
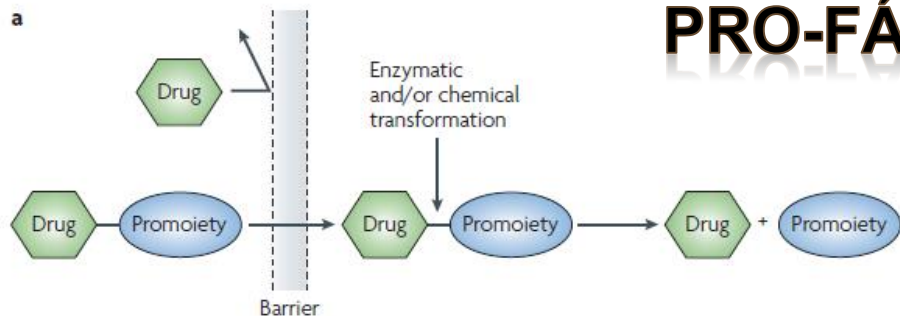
Posteriormente modificado para:

1) *substância com nenhuma ou pouca atividade farmacológica, sofrendo biotransformação a metabólitos ativos terapêuticamente.*

2) *Derivado de um fármaco conhecido, de propriedades físico-químicas melhoradas, aumentando a biodisponibilidade do fármaco original, e que mediante processo enzimático ou químico é transformado no fármaco que lhe deu origem, antes de atingir o seu local de ação ou ainda no próprio local de ação (Korolkovas & Burckhalter, 1988).*



PRO-FÁRMACOS



A simplified representative illustration of the prodrug concept.

a | The drug-promoiety is the prodrug that is typically pharmacologically inactive.

In broad terms, the barrier can be thought of as any liability or limitation of a parent drug

that prevents optimal (bio)pharmaceutical or pharmacokinetic performance, and which

has to be overcome for the development of a marketable drug. The drug and promoiety

are covalently linked via bioreversible groups that are chemically or enzymatically labile,

such as those shown here. The 'ideal' prodrug yields the parent drug with high recovery

ratios, with the promoiety being non-toxic. **b** | Common functional groups on parent

drugs that are amenable to prodrug design (shown in green). Most prodrug approaches

require a 'synthetic handle' on the drug, which are typically heteroatomic groups.

J. Rautio et al., *Nature Reviews Drug Discovery*, 2008, **7**, 255-270

P-W. Hsieh et al., *Current Pharmaceutical Design*, 2009, **15**, 2236-2250

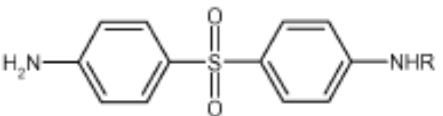
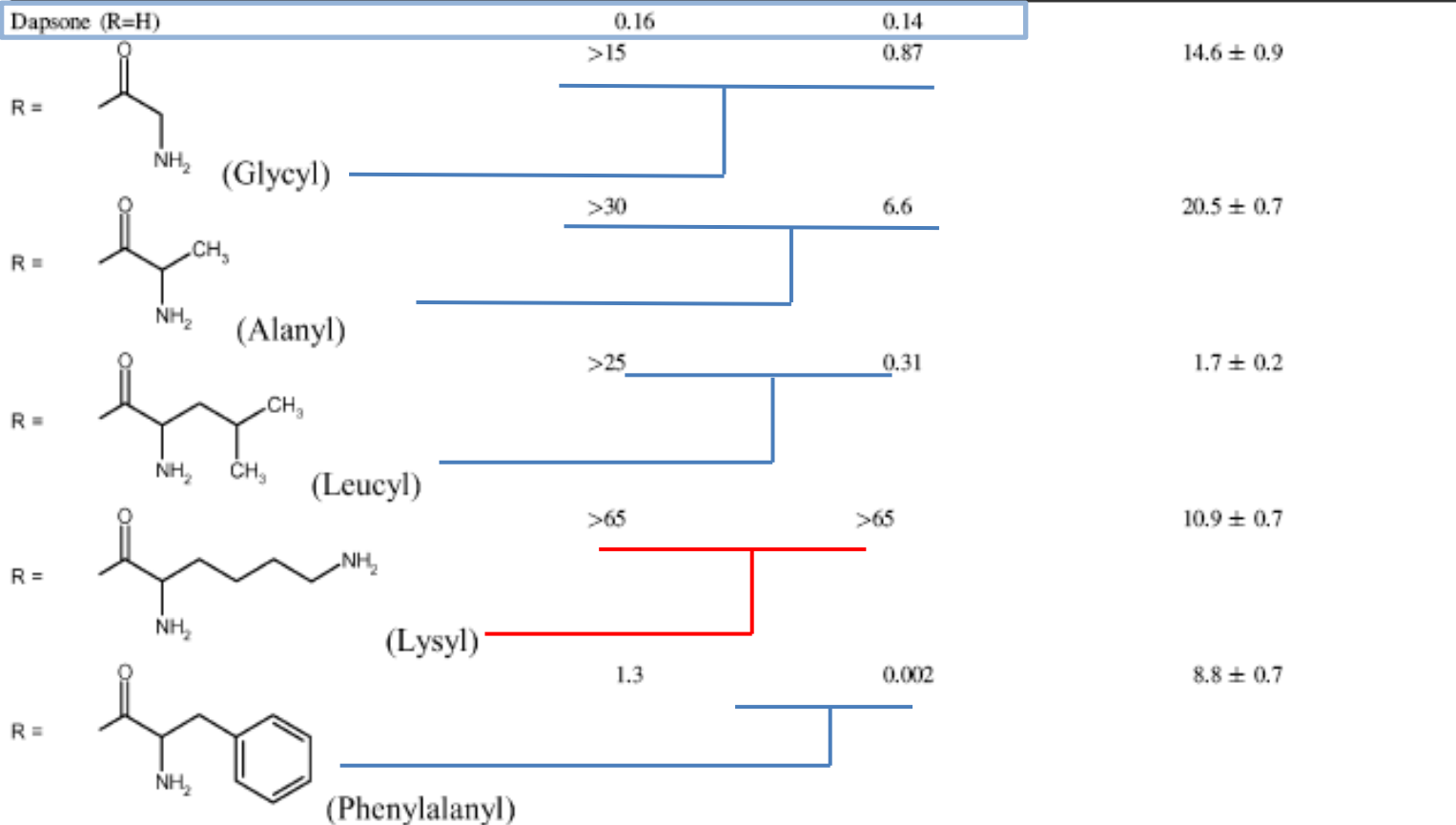
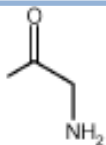
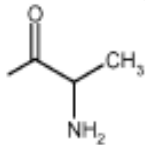
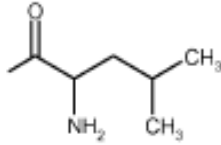
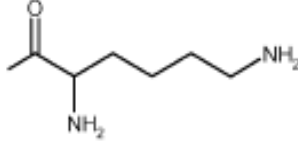
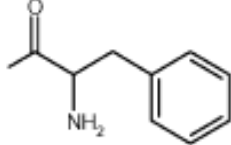
The rationale behind the use of the prodrug approach

Barrier to Overcome	Examples of Applicable Prodrugs	Preferable Site of Bioconversion	Common Functional Groups Amenable to the Prodrug Method
Formulation and administration <ul style="list-style-type: none"> • Low aqueous solubility • Low shelf-life • Pain or irritation after local administration • Unpleasant taste/odor 	Introducing ionizable or polar neutral group <ul style="list-style-type: none"> • Phosphates • Amino acid esters/amides • Sugar derivatives 	During or after absorption <ul style="list-style-type: none"> • at the brush border of enterocytes • in the systemic circulation or after local administration • in the systemic circulation by hydrolytic enzymes 	-OH -SH -NH (via spacer) -COOH
Absorption <ul style="list-style-type: none"> • Poor membrane permeation • Low stability in GI tract • Substrate of efflux transporters 	Masking polar ionized/non-ionized group(s) <ul style="list-style-type: none"> • Alkyl/aryl esters • Amino acid esters/amides 	After absorption <ul style="list-style-type: none"> • in the systemic circulation by hydrolytic enzymes 	-OH -SH -NH -COOH -OPO(OH) ₂
Distribution <ul style="list-style-type: none"> • Lack of site specificity • High degree of plasma protein binding 	Targeting cell- or tissue-specific transporters or enzymes <ul style="list-style-type: none"> • Amino acid esters/amides • Sugar derivatives 	In the target tissue <ul style="list-style-type: none"> • by cell-specific hydrolytic enzymes or • oxidoreductases 	-OH -SH -NH -COOH
Metabolism and excretion <ul style="list-style-type: none"> • Short duration of action 	Masking metabolically labile group(s) or polar ionized/nonionized group(s) <ul style="list-style-type: none"> • Alkyl/aryl esters • Amino acid esters/amides 	After absorption <ul style="list-style-type: none"> • in the systemic circulation • in the target tissue by hydrolytic enzymes 	-OH -SH -NH -COOH -OPO(OH) ₂
Toxicity <ul style="list-style-type: none"> • Lack of site specificity 	Targeting tissue-specific enzymes or divergent conditions of target tissue <ul style="list-style-type: none"> • Various different prodrug methods 	In the target tissue <ul style="list-style-type: none"> • by cell-specific enzymes • because of altered pH or hypoxia 	Depending on the selected prodrug method (these prodrugs are often bioprecursors)
Life-cycle management	Introducing any kind of promoiety <ul style="list-style-type: none"> • Various different prodrug methods 	Depending on the selected prodrug method	Depending on the selected prodrug method (these prodrugs are often carrier-linked prodrugs)

Pro-Fármacos: Aumento da solubilidade

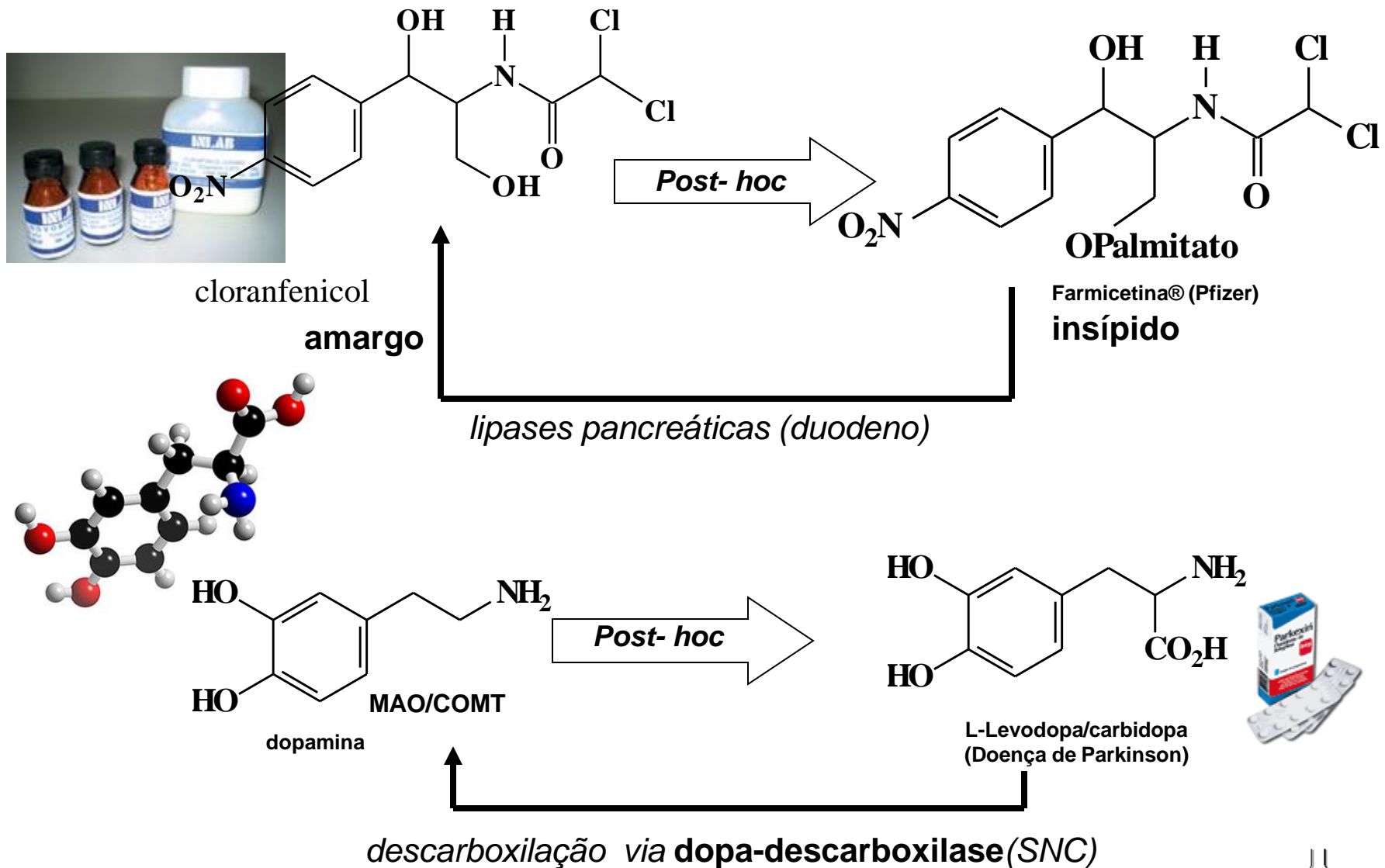
Table 1

Solubility and enzymatic lability of amino acid derivatives of dapsone as water-soluble prodrugs [26]

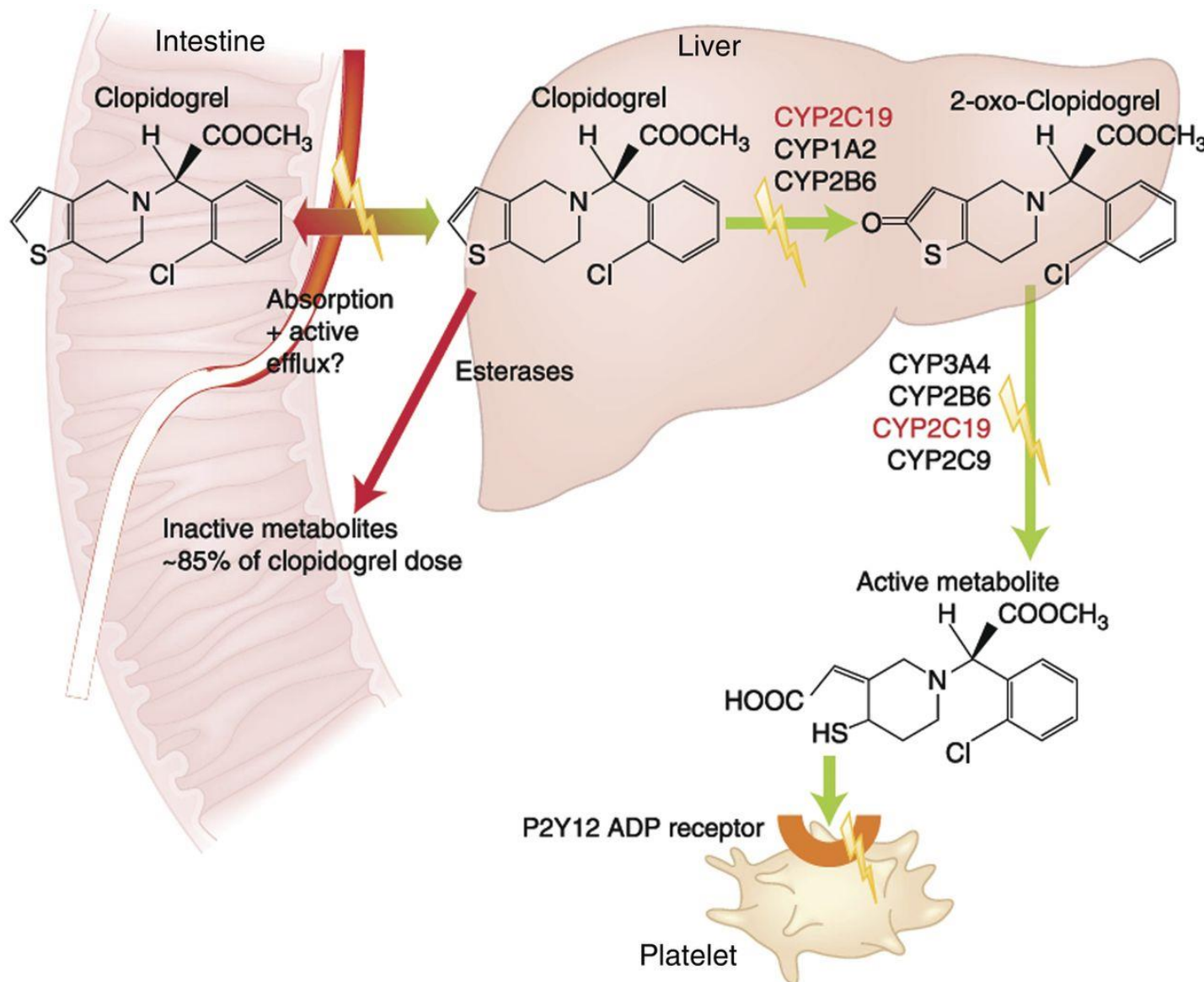
	Solubility at 25 °C (in mg dapsone equivalent/mL)		$t_{1/2}$ at 37 °C in human blood (in min \pm S.D.)
	In water as HCl salt	In pH 7.4 phosphate buffer	
Dapsone (R=H)	0.16	0.14	
R =  (Glycyl)	>15	0.87	
R =  (Alanyl)	>30	6.6	
R =  (Leucyl)	>25	0.31	
R =  (Lysyl)	>65	>65	
R =  (Phenylalanyl)	1.3	0.002	

B. Testa/Biochemical Pharmacology 68 (2004) 2097–2106

Pro-Fármacos: sabor e ↑ estabilidade metabólica

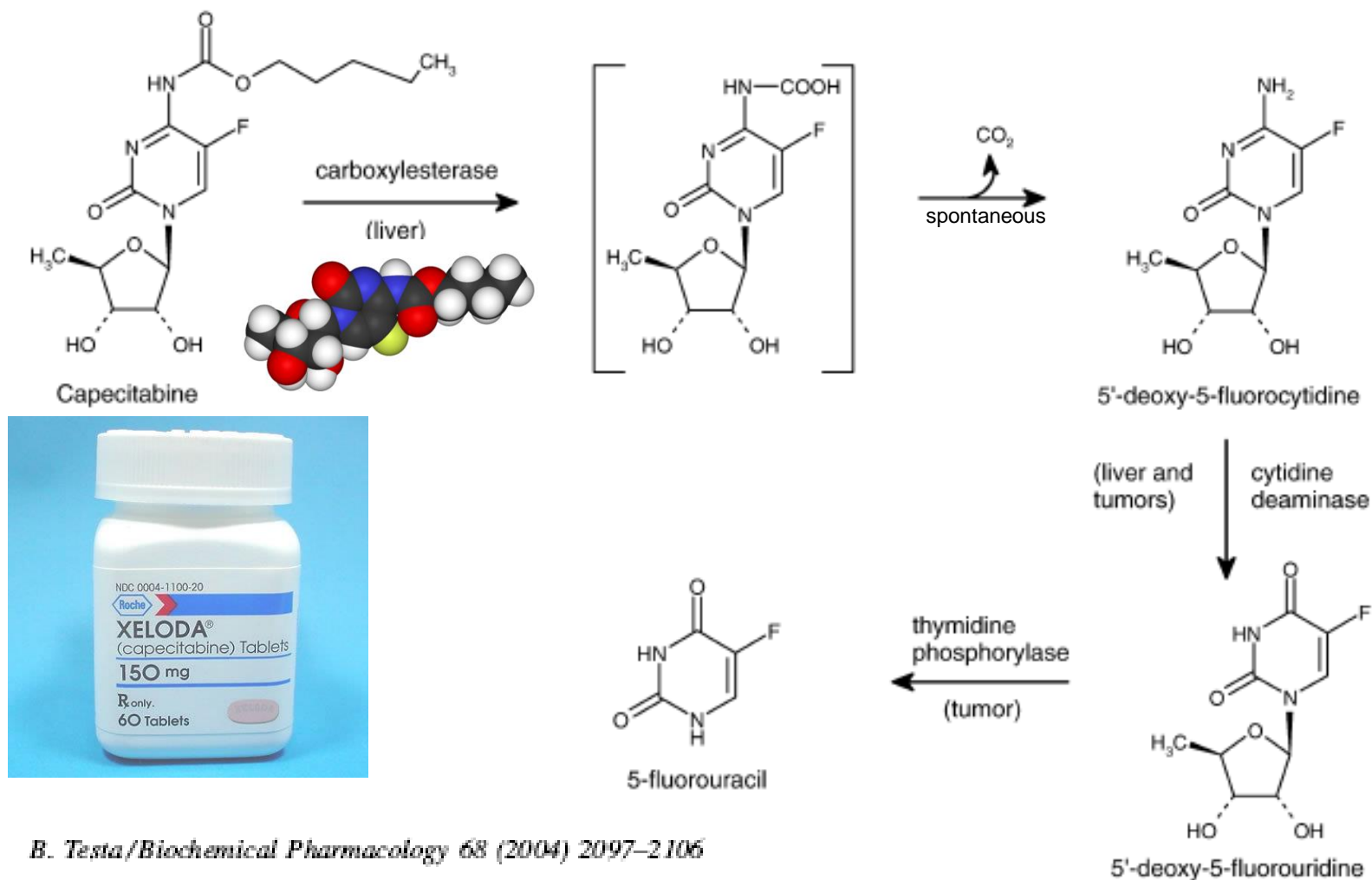


Pro-Fármacos: Aumento de seletividade



Two-step metabolic activation of clopidogrel. Bioavailability of the pro-drug is determined by intestinal absorption, which might be limited by the efflux pump MDR1 (encoded by *ABCB1*). Subsequently, 85% of the pro-drug is converted into inactive metabolites by ubiquitous esterases. The remaining 15% is converted into a thiol-containing active metabolite through two-step oxidations that involve several cytochrome P450 enzymes. The first oxidative step is catalysed by CYP2C19, CYP1A2 and CYP2B6 isoenzymes, producing the intermediate 2-oxo-clopidogrel. The second step is mediated by CYP3A4, CYP2B6, CYP2C19, and CYP2C9 and yield the bioactive metabolite, the cis-thiol isomer which irreversibly binds to platelet P2Y₁₂ receptors inhibits ADP-induced platelet activation.

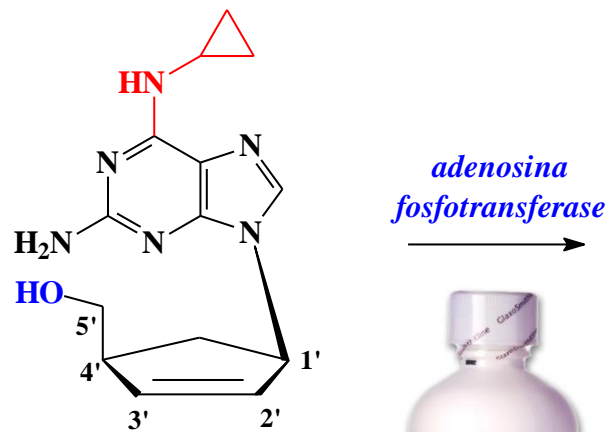
Pro-Fármacos: Diminuição da Toxicidade



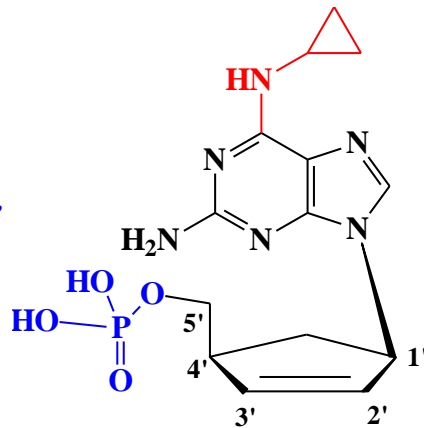
B. Testa/Biochemical Pharmacology 68 (2004) 2097-2106

Fig. 6. The stepwise activation of capecitabine to the antitumor drug 5-fluorouracil. Note the tissue-selectivity of the last step.

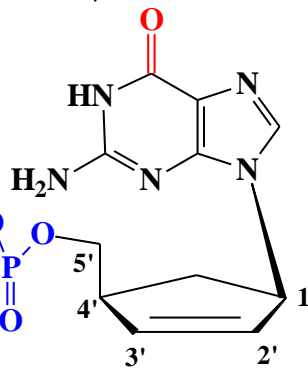
Pro-Fármacos: Aumento da Biodisponibilidade



*adenosina
fosfotransferase*

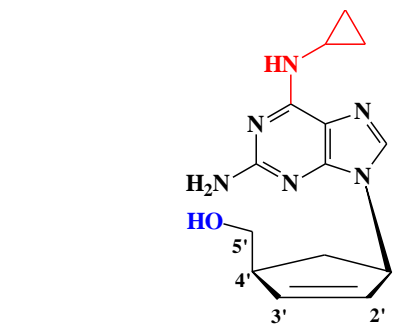
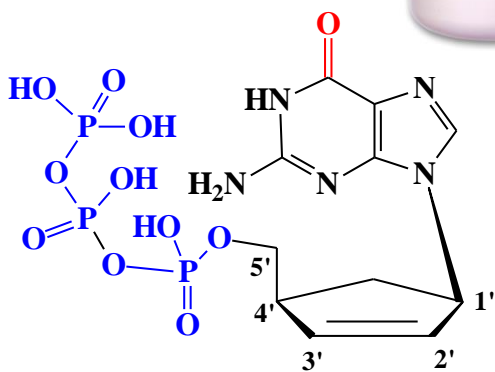


*desaminase
citossólica*

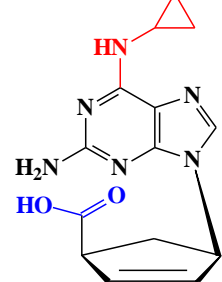


[metabólito ativo $t_{1/2} = 15\sim 20h$]

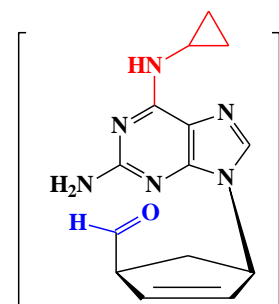
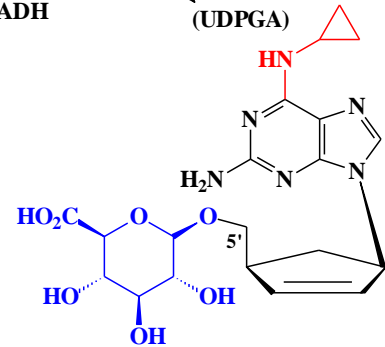
*quinases
celulares*



Fase 1
(Alc. desidrogenase = ADH
hepática)

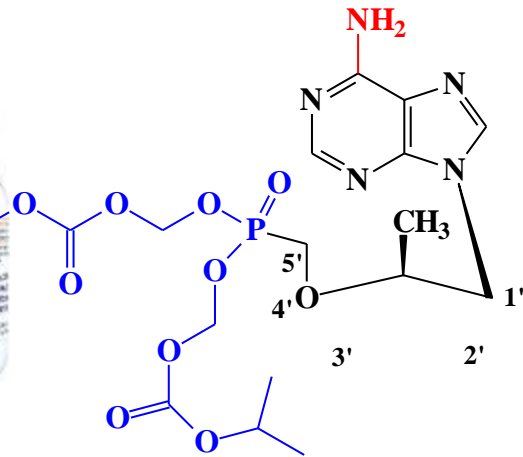


Fase 2
(UDPGA)



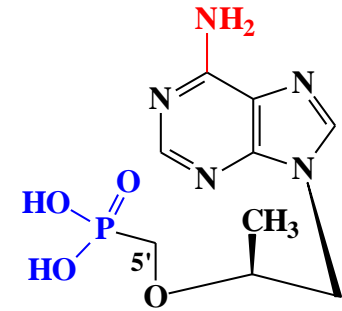
reações
alérgicas
e/ou tóxicas

Pro-Fármacos: Aumento da eficácia



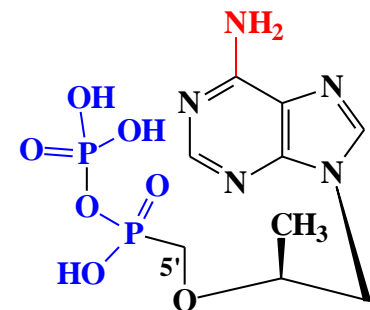
Tenofovir disoproxilfumarato

*Esterase
CYP(?)*

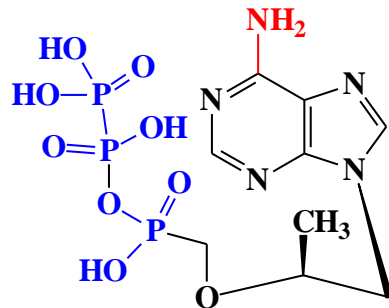


Tenofovir

*adenilato
quinase*



*nucleosideo
difosfoquinase*



Tenofovir difosfato

Estudo do Metabolismo

In vitro:

Hepatócitos isolados
(humanos ou de espécies animais)

Microsoma hepático
(humanos ou de espécies animais)

CYP450 recombinantes

In vivo:

Ratos, coelhos, primatas
e humanos (plasma e urina)

Animais transgênicos

In silico

QSAR, docking,

Programas de predição
metabólica

(e.g. Pallas, Metasite e Meteor)

Instrumental Analítico



LC-MC; LC-MS-MS; LC-NMR; NMR-MS
HPLC-MS; HPLC-NMR

Métodos extração



Animais

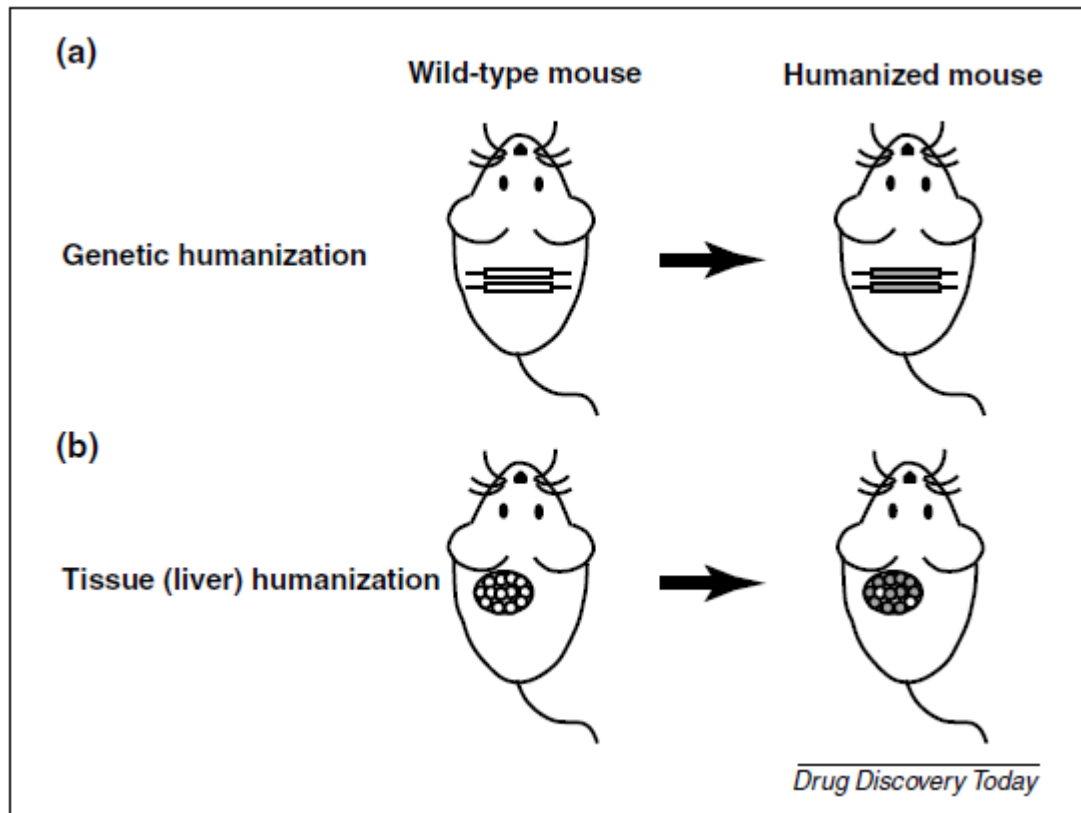


Nassar, A-E.F. et al (2004) *Drug Discov. Today* 9: 317

Scheer N; Wilson Y.D. (2016) *Drug Discov. Today* 21: 250

Estudo do Metabolismo *in vivo*

- (i) the introduction of human genes into the mouse genome to generate genetically **humanized mouse models**;
- (ii) the transplantation of human cells into competent recipients resulting in **tissue humanized mouse models** (Fig. 1).



Concept of generating genetically and tissue humanized mouse models. The principle of genetic humanization (a) is illustrated by a homozygous replacement of a murine gene (white bars) with the corresponding human gene (grey bars). For the sake of simplicity other approaches of genetic humanization, such as random transgenesis or introduction of a freely segregating human chromosome, are not shown. Tissue humanization (b) is exemplified by the replacement of mouse hepatocytes (white circles) with human hepatocytes (grey circles) in chimeric liver humanized mice. Some residual mouse hepatocytes are usually maintained after transplantation with human hepatocytes, as indicated by the remaining white circles in the chimeric liver humanized mice.

Estudo do Metabolismo *in vivo*

- (i) the introduction of human genes into the mouse genome to generate genetically **humanized mouse models**;
- (ii) the transplantation of human cells into competent recipients resulting in **tissue humanized mouse models**.

TABLE 3

Advantages and disadvantages of genetically and chimeric liver humanized mice

Genetically humanized mice

Advantages

- Permanent model without recreation
- Low cost of production
- High consistency between individual mice
- Human gene expressed in various organs
- Human gene expressed in all liver cells
- Availability of knockout controls
- Usually healthy

Disadvantages

- Expression of selected human genes only
- Different genes of interest require different mouse lines
- High effort to generate donor variability
- No infection with human specific pathogens
- Nontransplantable with human cells
- More challenging human extrapolation through *in vitro*–*in vivo* correlations
- Potential compensatory gene expression changes

Liver chimeric mice

Disadvantages

- Continuous recreation required
- High cost of production
- Varying degree of humanization
- Humanization restricted to the liver
- Residual mouse hepatocytes express murine gene
- Knockout controls usually not available
- Immune compromised

Advantages

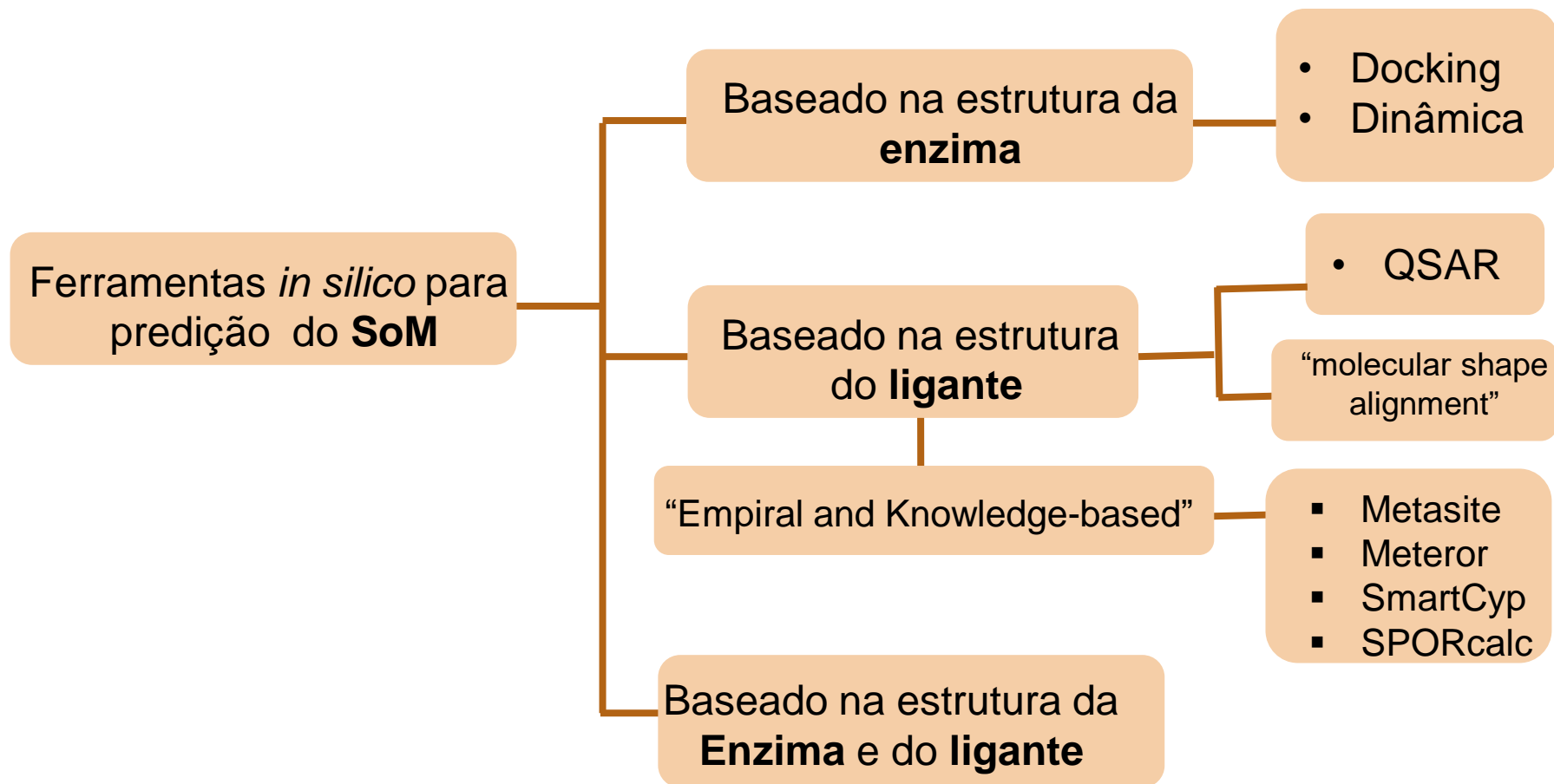
- Human hepatocytes express all human genes
- One mouse line fits different purposes
- Ease of generating donor variability
- Susceptible to human-specific pathogens
- Transplantable with various human cells
- Combined use with human hepatocytes supports extrapolation to humans
- No compensatory gene expression changes reported

Predição Metabólica in Silico

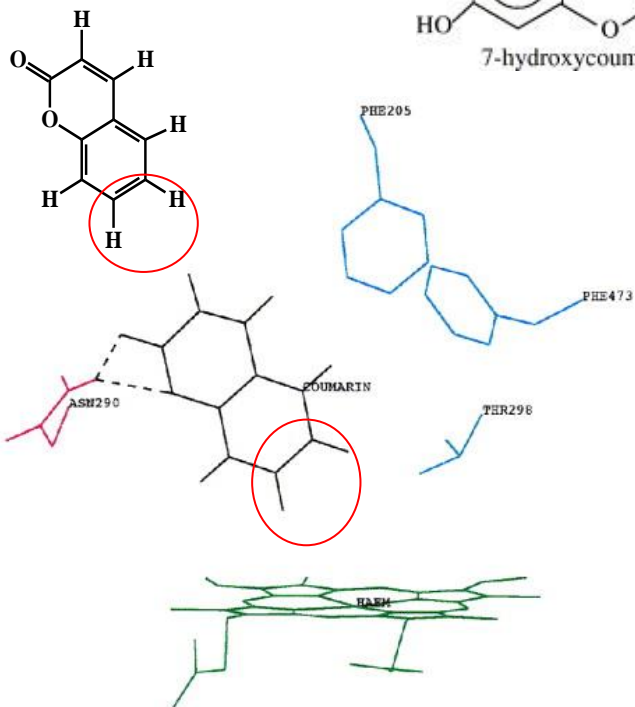
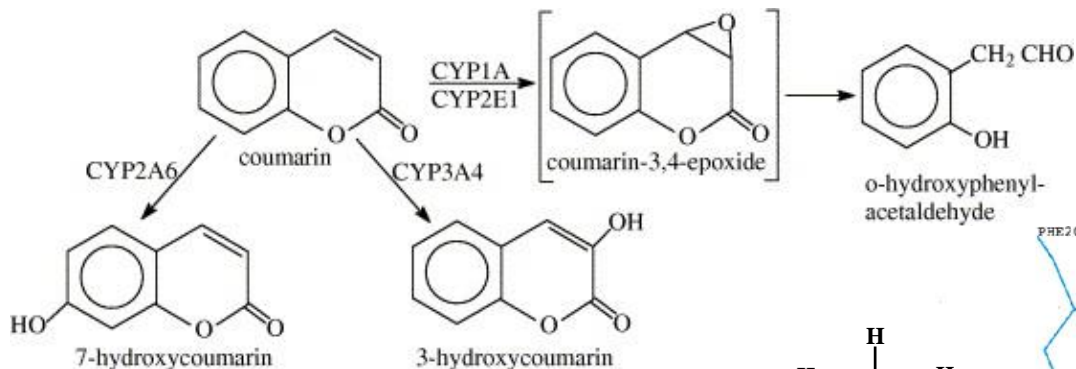
- QSAR
 - Docking
 - Reatividade Química
 - Banco de dados de transfor. metabólicas
-
- ✓ Qual(is) é (são) a posição mais provável (is) do metabolismo?
 - ✓ Qual a transformação metabólica mais provável?
 - ✓ Qual isoenzima participa do metabolismo?

Estudo do Metabolismo *in Silico*

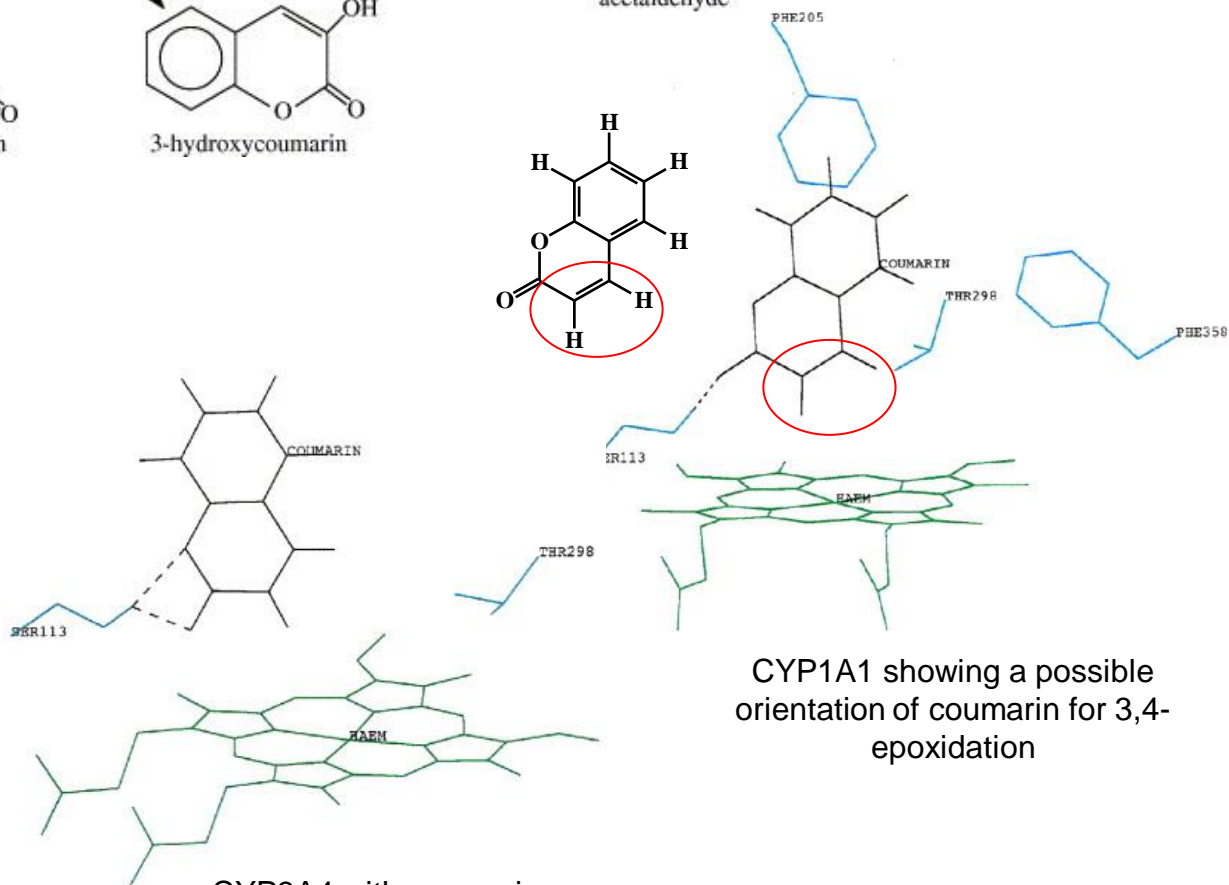
• Identificação do “SoM ou Soft Spots”



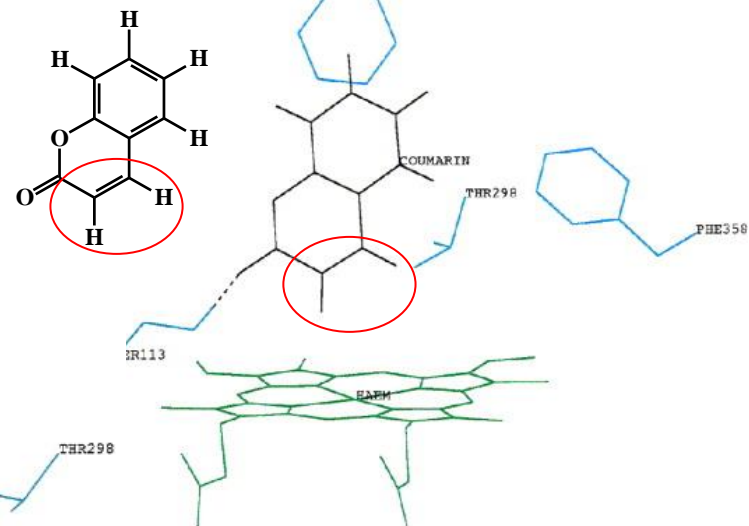
Estudo do Metabolismo *in Silico*



CYP2A6 showing an orientation of coumarin for 7-hydroxylation



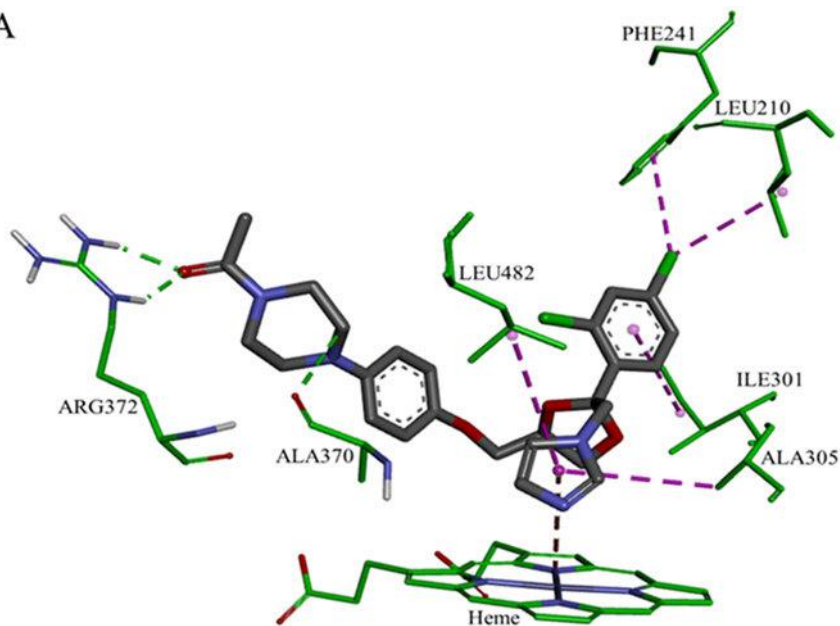
CYP3A4 with coumarin positioned for 3-hydroxylation.



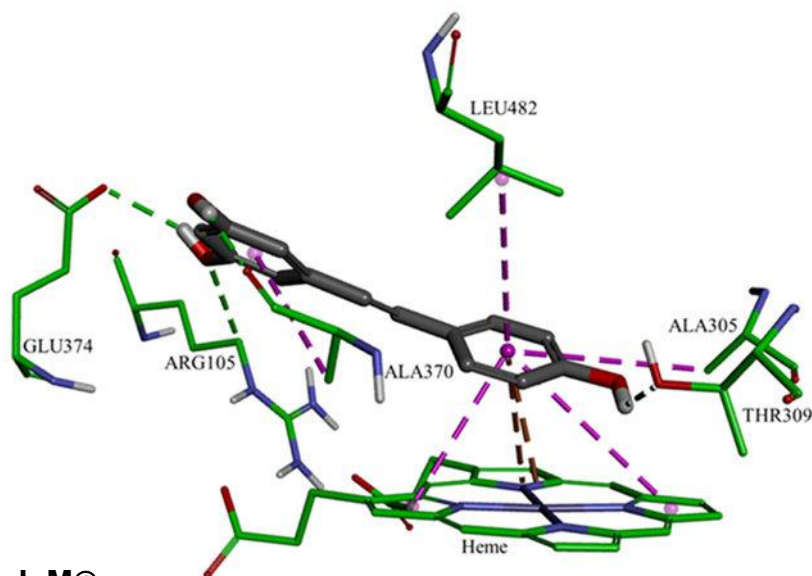
CYP1A1 showing a possible orientation of coumarin for 3,4-epoxidation

Estudo do Metabolismo *in Silico*

A



B

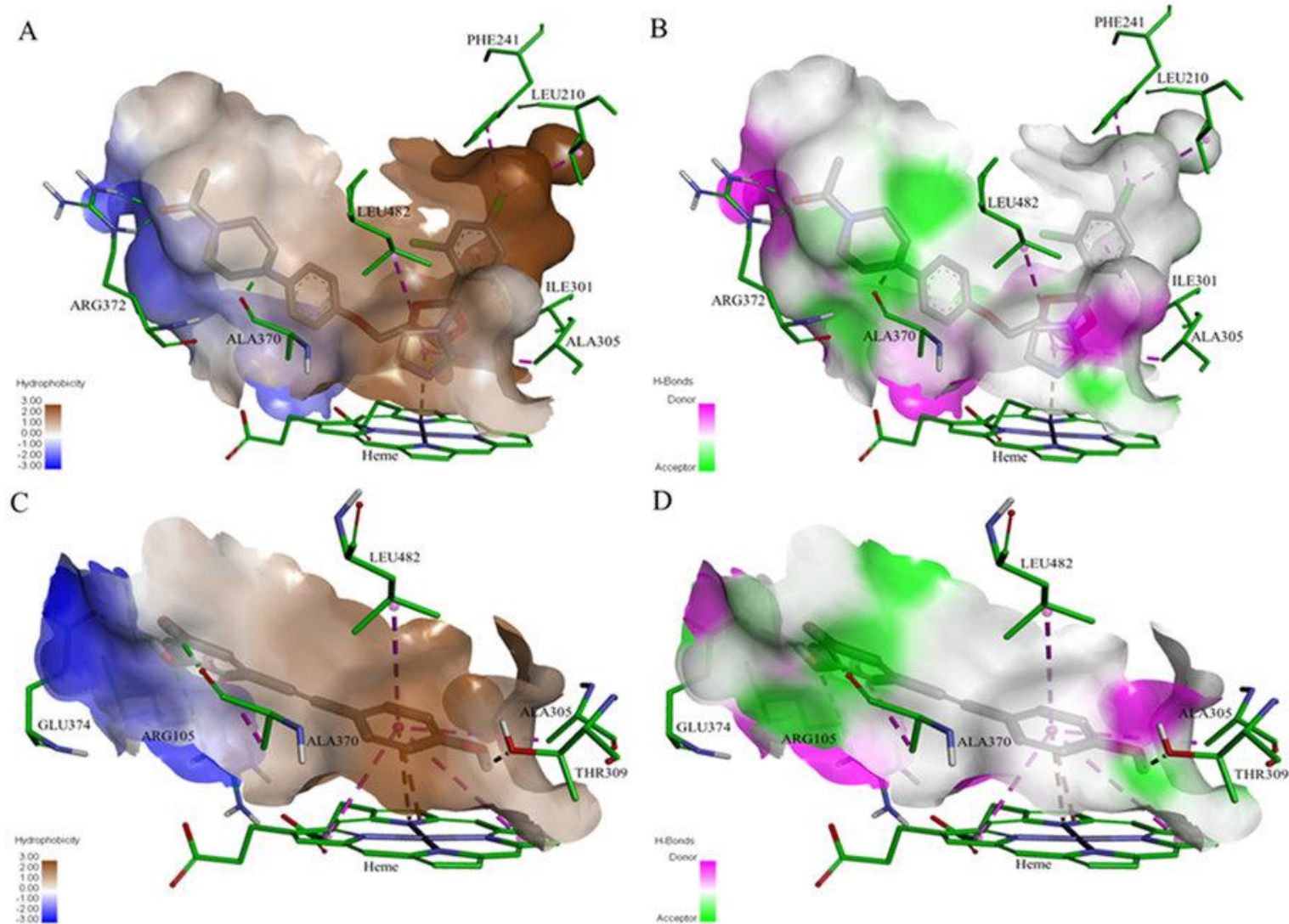


Docking results of the ligands at the binding site of CYP3A4 showing the interacting residues: ketoconazole (**A**, CDOCKER energy = -40.752 kcal/mole; CDOCKER interaction energy = -60.612 kcal/mole) and resveratrol (**B**, CDOCKER energy = -25.504 kcal/mole; CDOCKER interaction energy = -33.960 kcal/mole).

Ligands are shown as gray sticks and receptor residues are shown as green sticks. Bonds are shown as dashed lines color-coded as follows: hydrophobic interactions in magenta, electrostatic interaction in brown and hydrogen bonds in green. X-ray structure of human CYP3A4 (PDB code 2V0M)

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Estudo do Metabolismo *in Silico*



Maps of the hydrophobicity (A,C) and hydrogen bonds (B,D) at the binding site of CYP3A4 docked with the different ligands: ketoconazole (A,B); resveratrol (C,D). Ligands are shown as gray sticks and receptor residues are shown as green sticks.

Estudo do Metabolismo *in Silico*

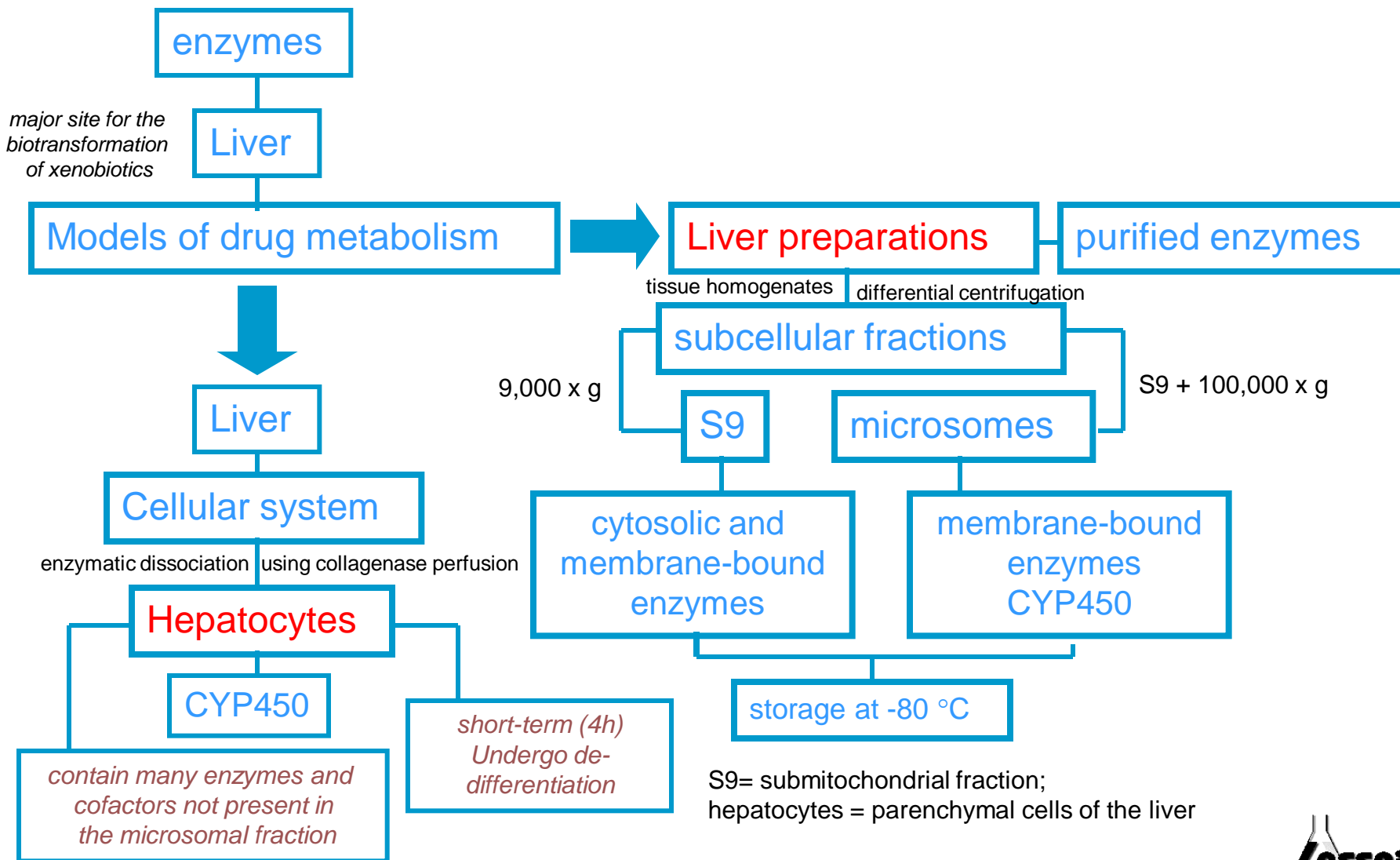
Table 1 | Experimental methods for characterizing metabolic stability and identifying sites of metabolism

Experimental approach	Scope
Incubations with individual drug-metabolizing enzymes (for example, CYPs, UGTs)	<ul style="list-style-type: none"> • Method for determining enzyme involvement and specificity, mechanism-based inhibition and drug–drug interactions
Microsomal incubations+NADPH	<ul style="list-style-type: none"> • More detailed determination of oxidative metabolism, metabolic stability
Microsomal incubations+UDPGA	<ul style="list-style-type: none"> • Determination of glucuronidation
Incubations with hepatocytes (from a range of species, including human)	<ul style="list-style-type: none"> • Determination of hepatic metabolite profiles, including conjugations and reactive metabolite trapping, and metabolic stability
Specific reactive metabolite trapping in microsomal incubations (trapping of soft nucleophiles using, for example, glutathione or cysteine, and trapping of hard nucleophiles with, for example, cyanide)	<ul style="list-style-type: none"> • Identification of hot spots leading to reactive intermediates, using high-resolution MS or, in complicated cases, NMR for precise structures • If reactive intermediates are detected, LC–MS-based proteomics can be used for further identification of sites of binding and the nature of the reactive intermediate • If radiolabelled compounds are available then quantitative studies of the covalent binding of reactive intermediates to proteins can be performed
Animal models: most commonly rodents (mice and rats), including complex models designed to look at, for example, biliary elimination. Newer models include genetically modified and ‘humanized’ strains (usually mice) as well as ‘chimeric’ animals containing, for example, human hepatocytes	<ul style="list-style-type: none"> • Used to solve problems in which, for example, <i>in vivo</i> pharmacokinetics are poorly predicted by <i>in vitro</i> studies, for example, owing to unchanged excretion, drug–drug interactions or when more information on compound distribution is needed

CYP, cytochrome P450; LC, liquid chromatography; MS, mass spectrometry, NMR, nuclear magnetic resonance; UDPGA, uridine diphosphate glucuronic acid; UGT, UDP-glucuronosyltransferase.

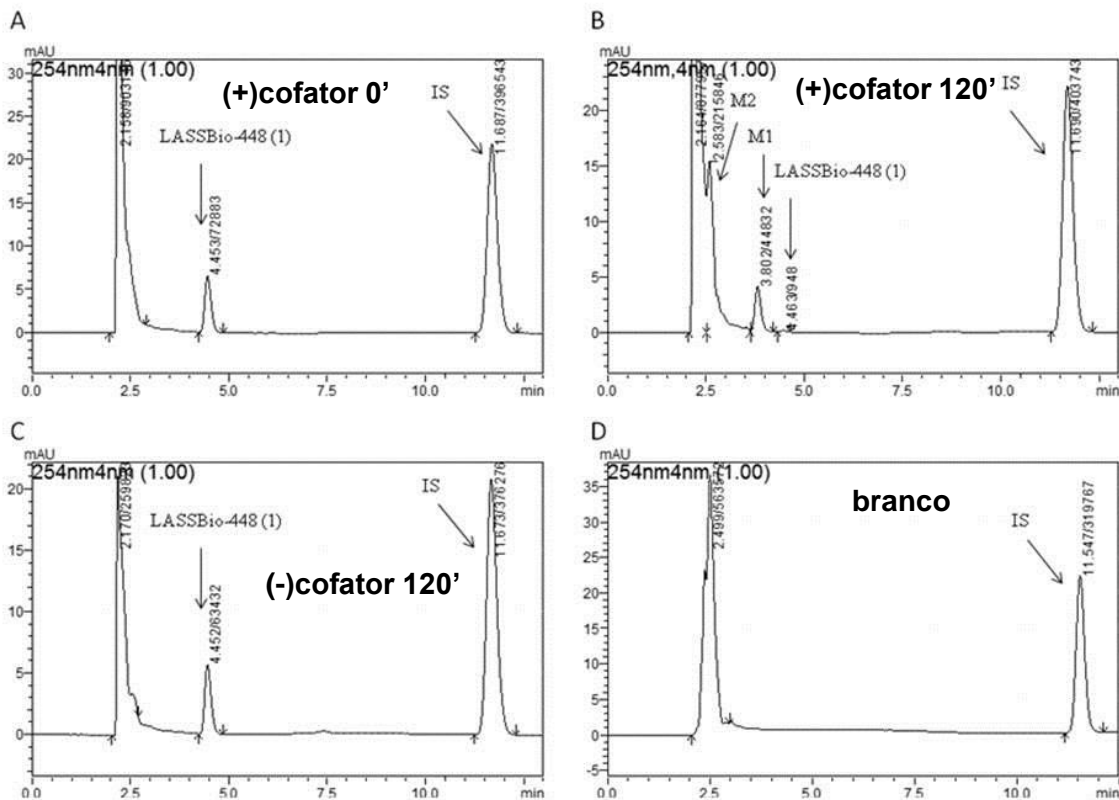
Estudo do Metabolismo *in Silico*

In vitro techniques for investigating drug metabolism



Estudo do Metabolismo

Reaction	Enzyme	Cellular location
Hydrolysis	esterases peptidases	cytosol, mitochondria, microsomes , blood cytosol, lysosomes, microsomes , blood
Reduction	MFO (CYP450)	microsomes
Oxidation	Alcohol desid.	cytosol
	MFO (CYP450)	microsomes
	MAO	mitochondria
	Alcohol desid. Aldehyde desid.	cytosol cytosol
Glutathione Glucuronide Sulphate	G. transferase Glu. transferase sulfotransferases	microsomes microsomes cytosol
Methylation	Methyl transferase	cytosol, microsomes
Acetylation	Acetyl transferase	cytosol
aa. Conjug	transferases	cytosol, mitochondria



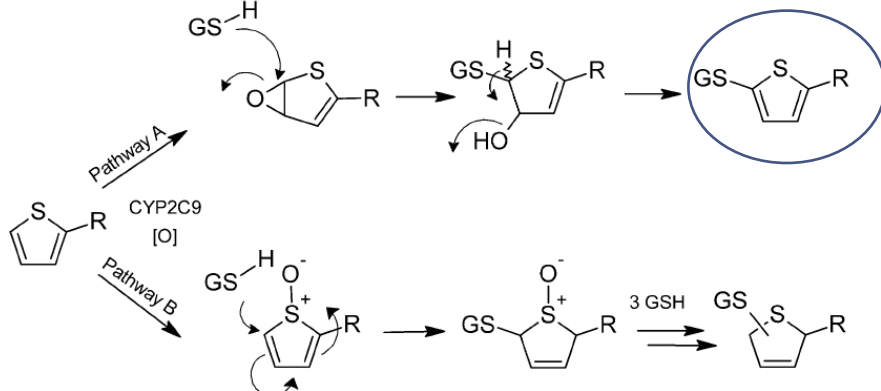
HPLC chromatograms of LASSBio-448 and its metabolites formed by incubation with rat liver microsomes (1mg/mL). **A)** Incubation in the presence of NADPH generating system at time = 0 min; **B)** Incubation in the presence of NADPH generating system and the formation of LASSBio-448-related metabolites at time =120 minutes; **C)** Incubation in the absence of NADPH generating system at time = 120 minutes; **D)** Blank test: 1mg/mL microsomes proteins from rat liver, in addition to NADPH generating system and in the absence of LASSBio-448.

IS = internal standard (e.g. biphenyl-4-carboxylate Methyl, C=20 µM). Apparatus: Shimadzu - LC20AD, column: Kromasil 100-5 C18 250 to 4.6 mm; Mobile phase: 70% ACN, 30% water, 0.1% TFA, flow: 1mL/min; Detector: SPD-M20A (Diode array); Wavelength: 254 nm.

Aplicações:

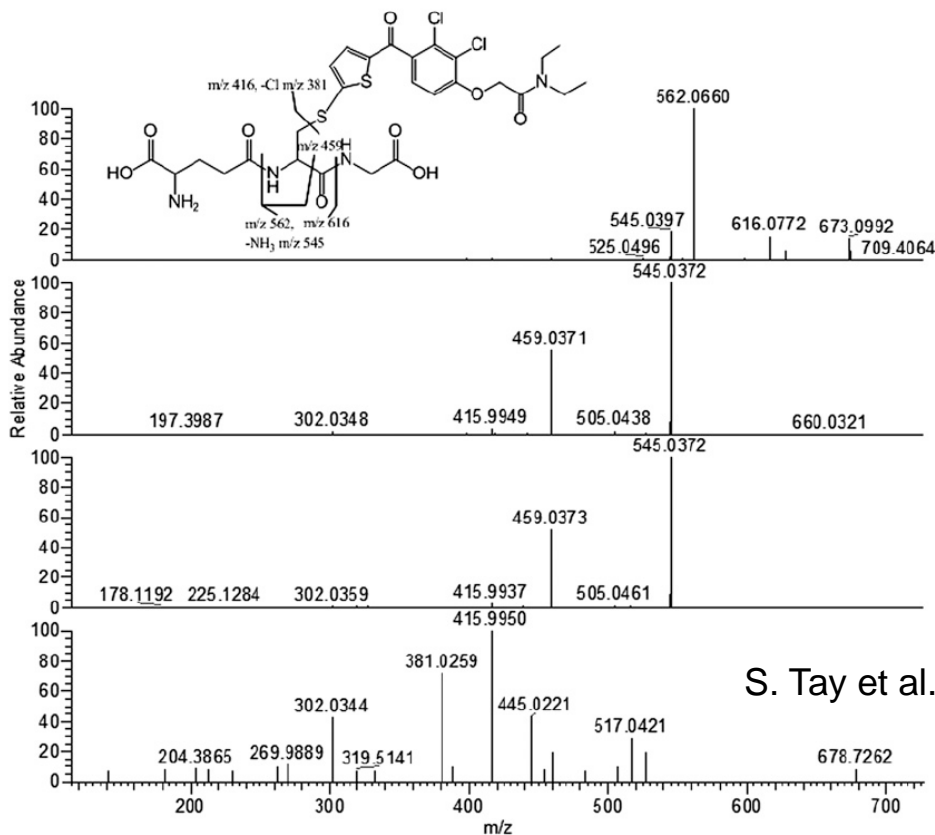
- ✓ Determinação da estabilidade metabólica
- ✓ Determinação do $t_{1/2}$ e Cl_{intr}
- ✓ Caracterização do(s) metabólito(s)
- ✓ Determinação dos “soft spots”
- ✓ Enzimas e isoenzimas
- ✓ Estudos de inibição enzimática
- ✓ Estudos de indução enzimática
- ✓ Metabolismo de Glicuronidação
- ✓ Metabolismo hidrolítico x oxidativo

Estudo do Metabolismo *in vitro* e *in silico*



CYP2C9 Supersomes (20 pMol)
 TA analogs (100 μM)
 Glutathione (GSH) (1 mM)
 potassium phosphate buffer
 NADPH (1 mM final concentration)

↓
 incubated at 37C for 1 hour.



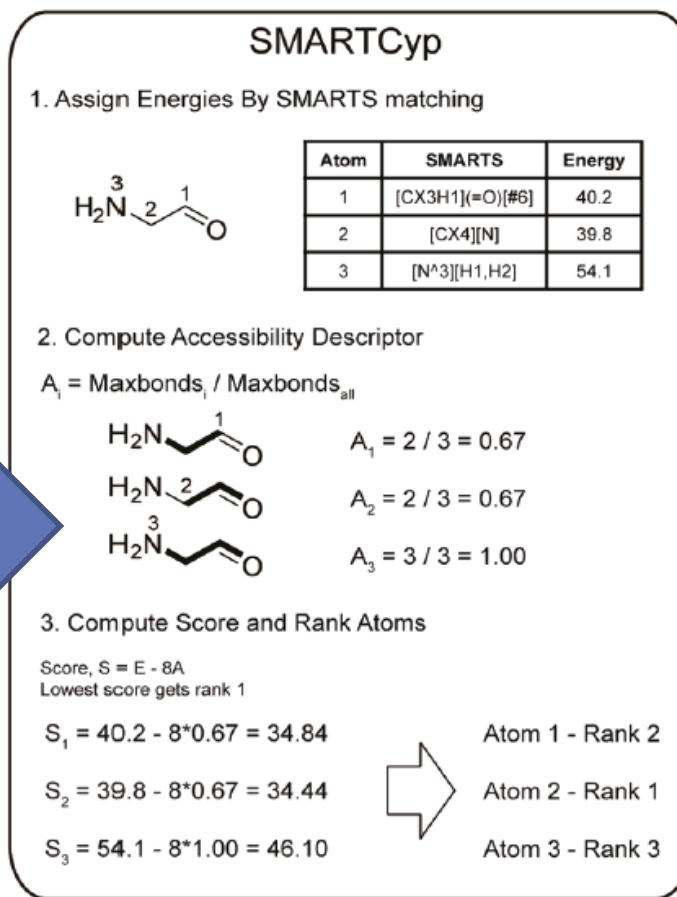
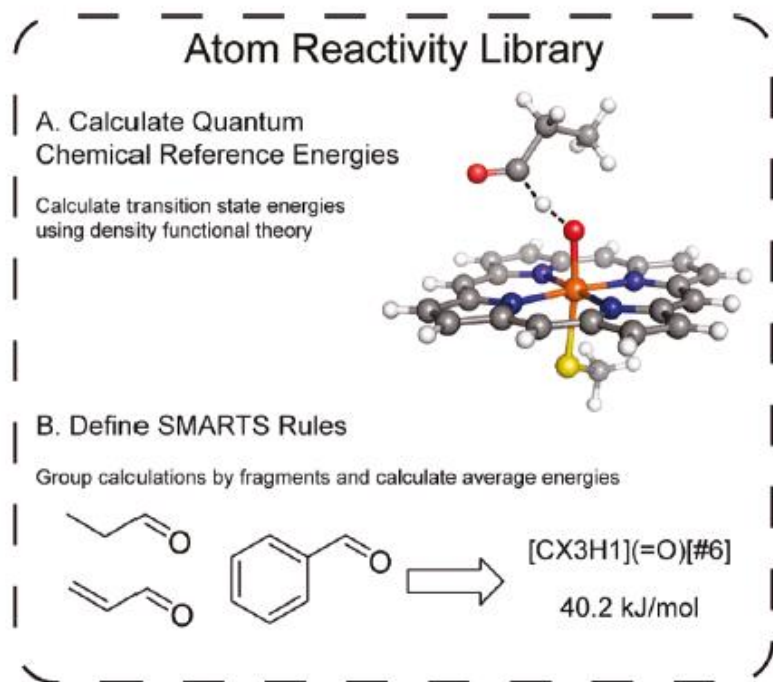
S. Tay et al., Drug Metab Dispos, 2014, 42:1955–1963

SmartCYP

The method is foremost a reactivity model, and as such, it shows a preference for **predicting sites that are metabolized by the cytochrome P450 3A4 isoform. SMARTCyp predicts the site of metabolism directly from the 2D structure of a molecule**, without requiring calculation of electronic properties or generation of 3D structures.

SMARTCyp uses a very simple algorithm (see Figure 1), which **involves a reactivity descriptor and an accessibility descriptor**.

The accessibility descriptor, A , is defined as the longest bond path distance from a given atom divided by the longest bond path distance in the whole molecule. This is a measure of how far from the 2D center of the molecule an atom is positioned and is always a number between 0.5 and 1.

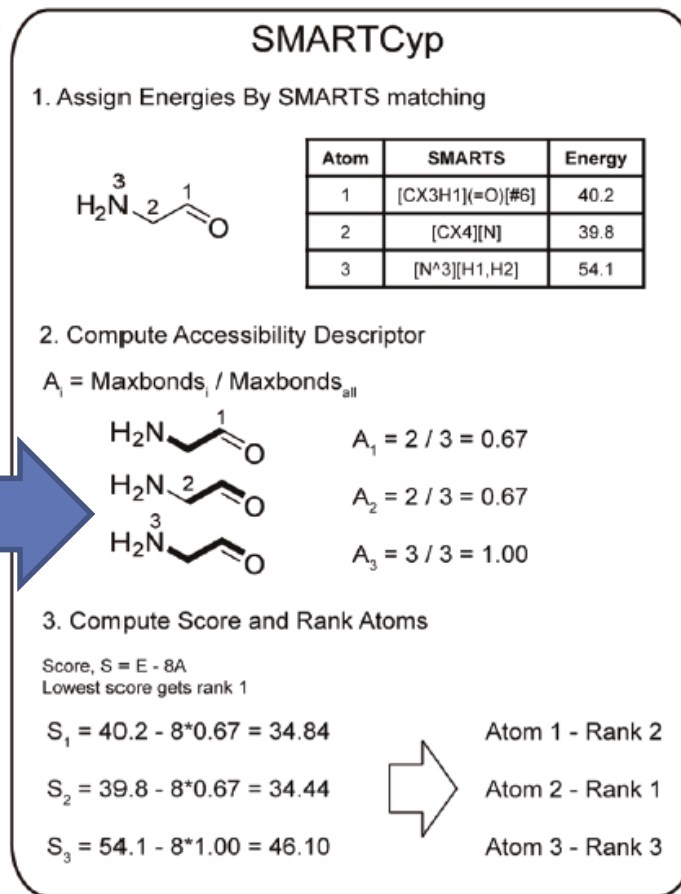
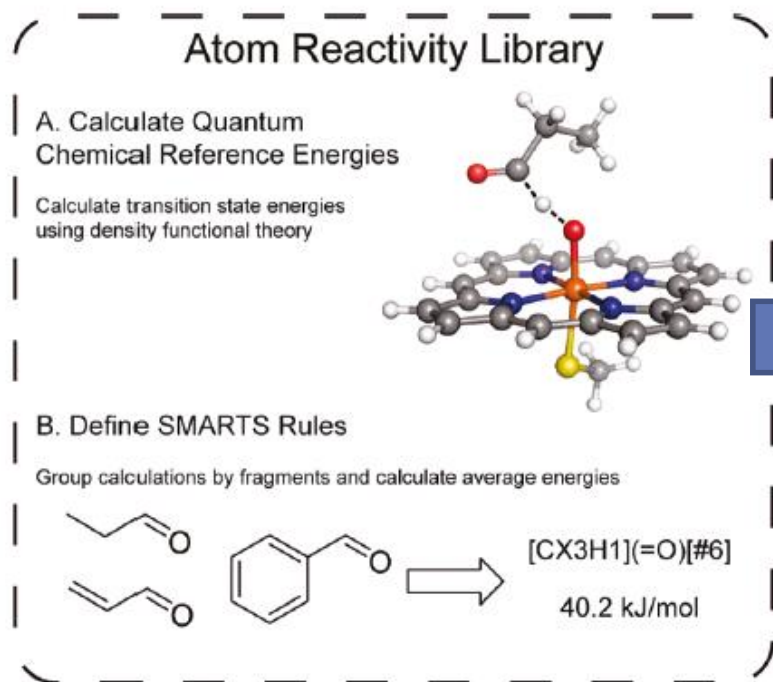


SmartCYP

The method is foremost a reactivity model, and as such, it shows a preference for **predicting sites that are metabolized by the cytochrome P450 3A4 isoform**. SMARTCyp predicts the site of metabolism directly from the 2D structure of a molecule. It uses a very simple algorithm (see Figure 1), which **involves a reactivity descriptor and an accessibility descriptor**.

The reactivity descriptor, E , which is an estimation of the energy required for a CYP to react at this position (kJ/mol).

The accessibility descriptor, A , is a measure of how far from the 2D center of the molecule an atom is positioned and is always a number between 0.5 and 1. Hence, it is not a measure of the accessible surface area, but **it describes how atoms at the end of a molecule are more likely to end up close to the reactive heme group in the CYP active site**



Finally, **the score, S** is computed for each atom as $S = E - 8A$.

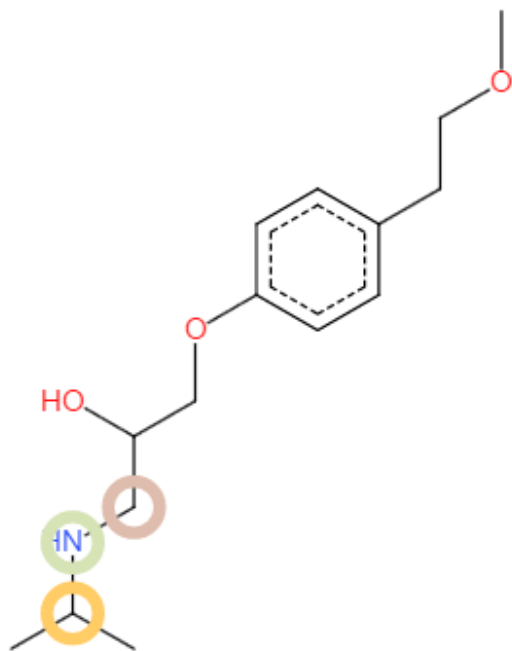
A lower score indicates a higher probability of being a SOM

SmartCYP

Results from SMARTCyp version 2.4.2

These results were produced: 2017-01-23_12-28-20. The infiles were: [smiles.smi].

To alternate between heteroatoms and atom numbers, move the mouse cursor over the figure.



Standard CYP2C CYP2D6

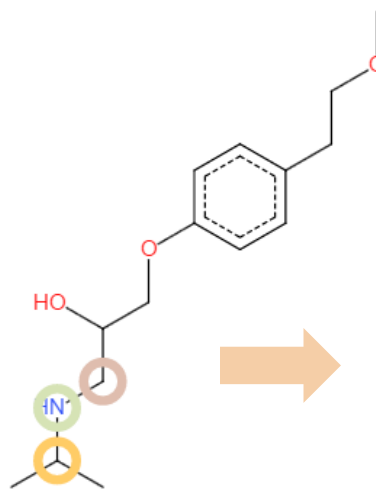
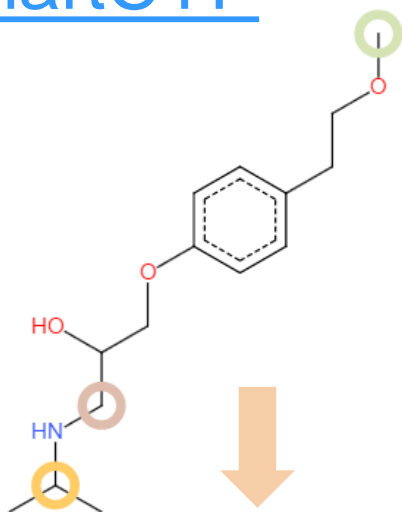
1: null

Rank	Atom	Score	Energy	Accessibility	2DSASA
1	C.15	33.26	41.1	0.93	10.19
2	C.13	33.86	41.1	0.79	23.82
3	N.14	46.72	54.1	0.86	13.03
4	C.1	51.4	62.2	1	70.08
5	C.3	54.14	62.2	0.86	30.05
6	C.10	56.08	62.2	0.64	24.33
7	C.11	56.13	62.2	0.71	8.86
8	C.4	59.01	66.4	0.79	27.66
9	C.7	71.48	77.2	0.57	28.6
10	C.16	79.04	89.6	1	63.9
11	C.6	80.06	86.3	0.64	27.46
12	C.5	993.11	999	0.71	4.31
13	C.8	994.78	999	0.5	5.55

Finally, the score, **S** is computed for each atom as
 $S = E - 8A$.

A lower score indicates a higher probability of being a SOM

SmartCYP



Standard CYP2C CYP2D6

1: null

Rank	Atom	Score	Energy	Accessibility	2DSASA
1	C.15	33.26	41.1	0.93	10.19
2	C.13	33.86	41.1	0.79	23.82
3	N.14	46.72	54.1	0.86	13.03
4	C.1	51.4	62.2	1	70.08
5	C.3	54.14	62.2	0.86	30.05
6	C.10	56.08	62.2	0.64	24.33
7	C.11	56.13	62.2	0.71	8.86
8	C.4	59.01	66.4	0.79	27.66
9	C.7	71.48	77.2	0.57	28.6
10	C.16	79.04	89.6	1	63.9
11	C.6	80.06	86.3	0.64	27.46
12	C.5	993.11	999	0.71	4.31
13	C.8	994.78	999	0.5	5.55

Standard CYP2C CYP2D6

1: null

Rank	Atom	Score	Energy	S2End	COODist	2DSASA
1	C.15	46.59	41.1	1	-	10.19
2	C.13	57.85	41.1	3	-	23.82
3	C.1	59.4	62.2	0	-	70.08
4	N.14	65.38	54.1	2	-	13.03
5	C.3	72.8	62.2	2	-	30.05
6	C.4	82.99	66.4	3	-	27.66
7	C.10	84.88	62.2	5	-	24.33
8	C.11	85.49	62.2	4	-	8.86
9	C.16	87.04	89.6	0	-	63.9
10	C.7	99.72	77.2	6	-	28.6
11	C.6	108.85	86.3	5	-	27.46
12	C.8	1,022.45	999	7	-	5.55
13	C.5	1,022.47	999	4	-	4.31

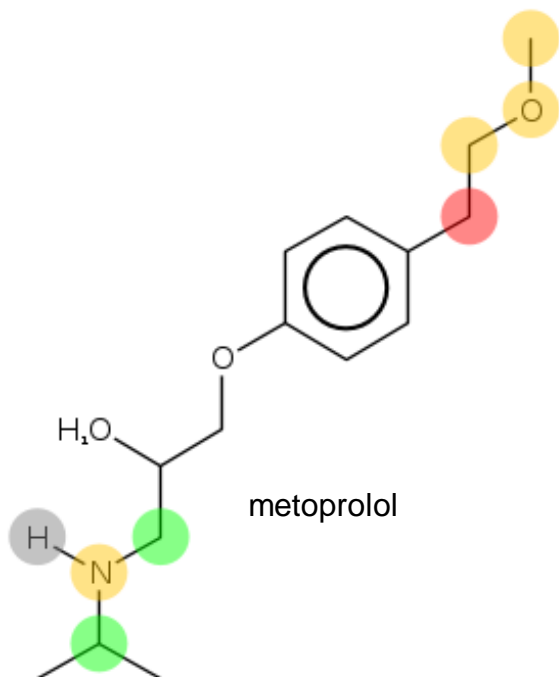
Standard CYP2C CYP2D6

1: null

Rank	Atom	Score	Energy	S2End	N+Dist	2DSASA
1	C.1	59.4	62.2	0	12	70.08
2	C.3	74.4	62.2	2	10	30.05
3	C.4	85.39	66.4	3	9	27.66
4	C.15	94.29	41.1	1	1	10.19
5	C.13	107.15	41.1	3	1	23.82
6	C.7	116.32	77.2	6	6	28.6
7	C.6	118.75	86.3	5	7	27.46
8	N.14	120.58	54.1	2	0	13.03
9	C.10	121.58	62.2	5	3	24.33
10	C.16	127.24	89.6	0	2	63.9
11	C.11	128.89	62.2	4	2	8.86
12	C.5	1,025.67	999	4	8	4.31
13	C.8	1,045.75	999	7	5	5.55

MetaPrint2D

is a tool that **predicts xenobiotic metabolism through data-mining and statistical analysis of known metabolic transformations reported in scientific literature**. It predicts **sites of phase I metabolism**.



Input

SMILES: COCCCC1=CC=C(OCC(O)CN([H])C(C)C)C=C1

Model: ALL (Metabolite 2010.2)

Settings: DEFAULT

Instructions

The colour highlighting an atom indicates its normalised occurrence ratio (NOR). A high NOR indicates a more frequently reported site of metabolism in the metabolite database.

Note: The normalised occurrence ratio does not indicate how likely a molecule is to be metabolised, but rather the relative likelihood of metabolism occurring at a particular site in the molecule, assuming it is metabolised.

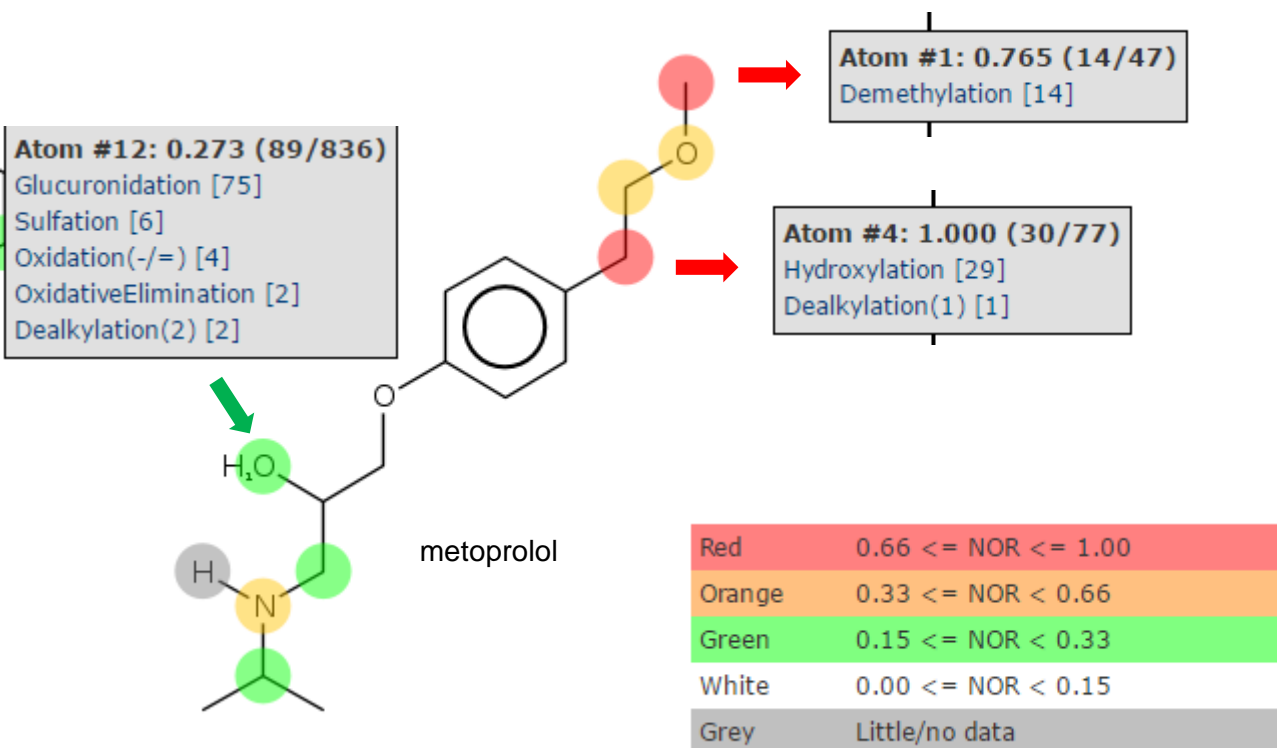
Results Colour Scheme

Red	$0.66 \leq \text{NOR} \leq 1.00$
Orange	$0.33 \leq \text{NOR} < 0.66$
Green	$0.15 \leq \text{NOR} < 0.33$
White	$0.00 \leq \text{NOR} < 0.15$
Grey	Little/no data

Boyer S. and Zamora I. *Journal of Computer-Aided Molecular Design*. 2002, 16: 403-413

MetaPrint2D-React

It can make predictions concerning a wider range of reactions, and **is able to predict the types of transformation** that can take place at ease site of metabolism, **and the likely metabolite formed.**



Boyer S. and Zamora I. *Journal of Computer-Aided Molecular Design*. 2002, 16: 403-413

RS-WebPredictor

RegioSelectivity-Predictor (RS-Predictor) is a new *in silico* method for generating predictive models of P450-mediated metabolism for drug-like compounds. Within this method, **potential sites of metabolism (SOMs) are represented as “metabolophores”**: A concept that describes the hierarchical **combination of topological and quantum chemical descriptors** needed to represent the reactivity of potential metabolic reaction sites.

A metabolophore is therefore a mathematical representation of an oxidizable region of a molecule that is defined by its local electronic environment and its potential oxidative reaction mechanism.


RS-WebPredictor

Predict cytochrome P450-mediated sites of metabolism on drug-like molecules

Please upload substrate file in SDF format:

Nenhum arquivo selecionado

Or draw a molecule below:



ChemDoodle™

Make predictions for checked isozymes:

1A2
 2A6
 2B6
 2C8
 2C9
 2C19
 2D6
 2E1
 3A4

Combined

Have results sent to email:

MINI-CURSO:

Metabolismo de Fármacos: aplicações em toxicologia e interações medicamentosas

PARTE 4



Polifarmácia (ou Politerapia ou Polimedicação): administração de vários medicamentos, concomitantemente, em tratamento prolongado (mais de 3 meses) a um paciente. **Considera-se que um paciente está polimedicado quando o número de medicamentos que toma diariamente é superior a cinco**, tendo os estudos sido efetuados sobretudo em pessoas de 3ª idade. *Outros autores incluem na polimedicação os casos em que a medicação, apesar de inferior a 5, inclui medicamentos desnecessárias para esse paciente.*



Polifarmácia (ou Politerapia) ???????

Bem... A pílula da Glaxo Protege o coração dos efeitos secundários da pílula Pfizer que impede a insuficiência hepática devido à pílula Merck que minimiza o risco de acidente vascular cerebral colocados pela pílula Novartis que reduz os coágulos de sangue causado pela pílula Glaxo.

O pior é que, eu não consigo lembrar qual doença, começou tudo isso...

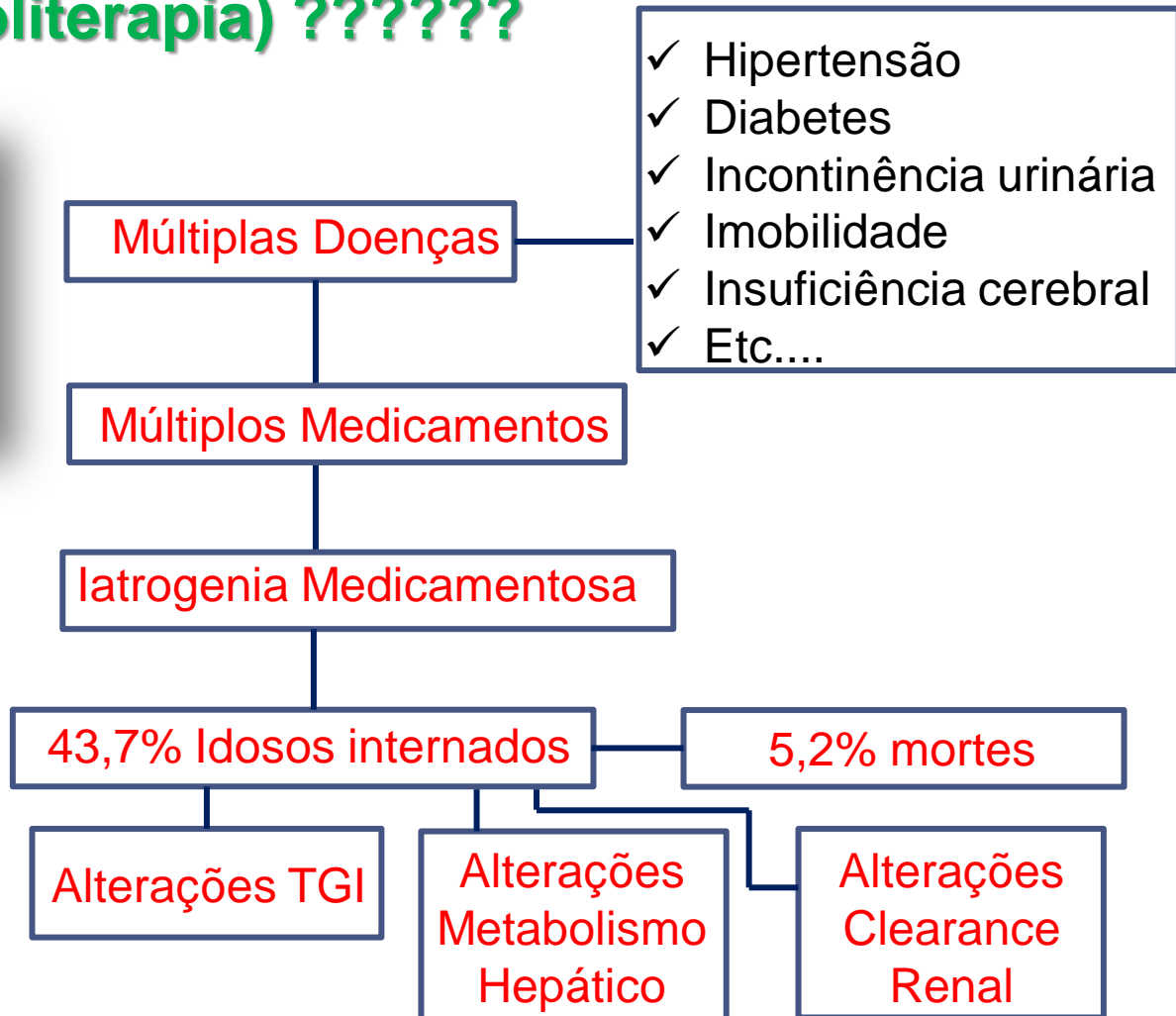


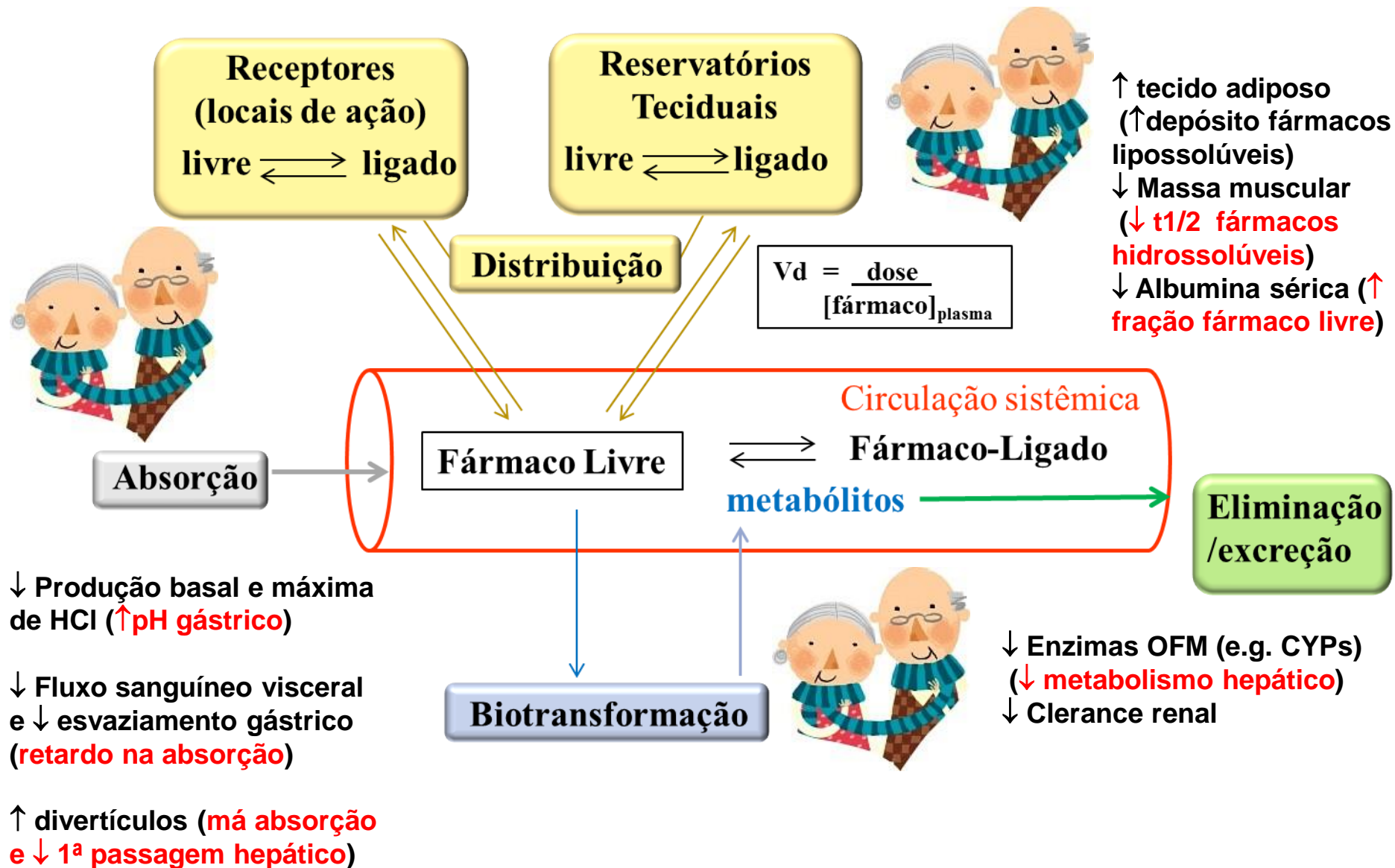
Polifarmácia (ou Politerapia) ???????



“frequência de reações medicamentosas iatrogênicas é três a sete vezes mais observada nos idosos em relação aos mais jovens” (Silva et al, 2012)

23% da população brasileira consomem 60% da produção nacional de medicamentos, principalmente as pessoas acima de 60 anos





Patients with DM (India)

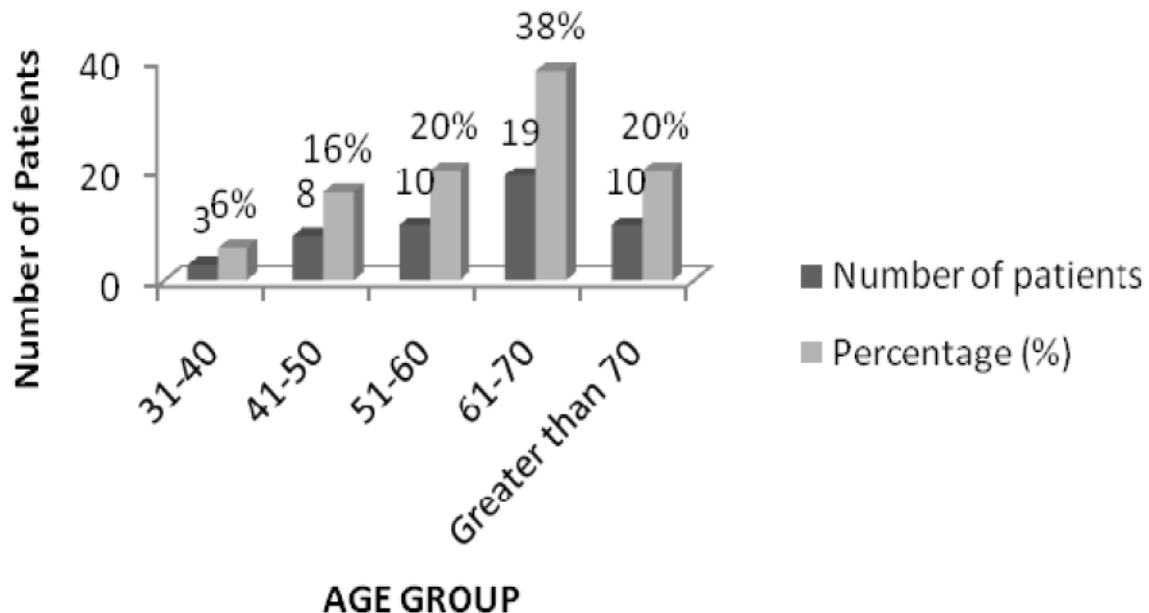
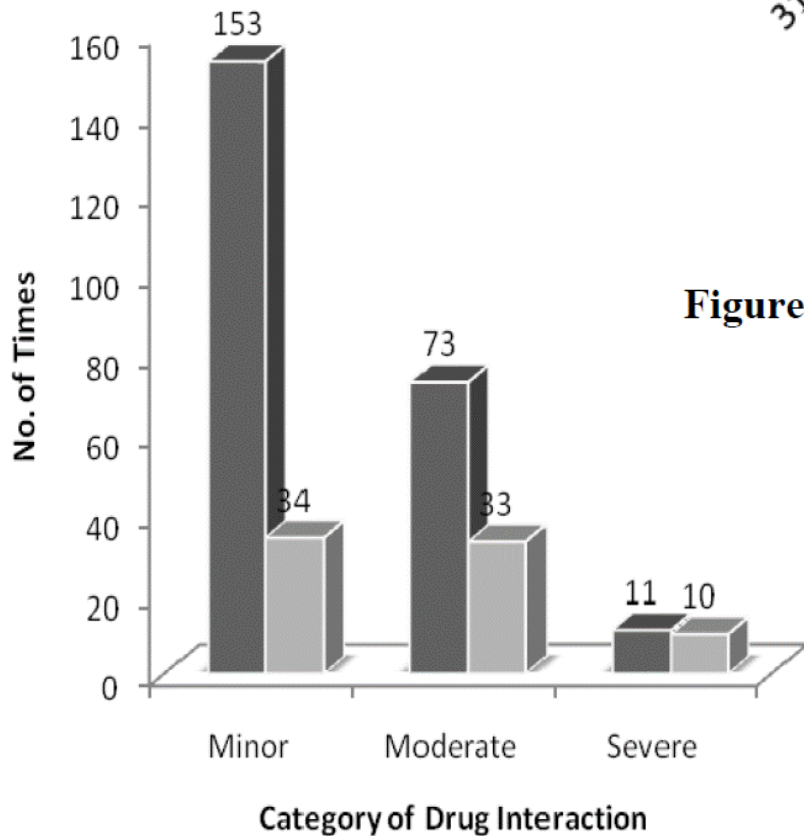
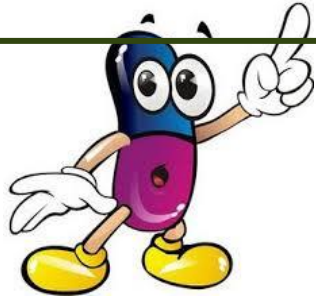


Figure 1. Age distribution of patients with drug interactions.

■ Number of times
 ■ Number of Prescriptions



Polifarmácia



Associação Medicamentosa

Objetivos

Interações Medicamentosas

- Potencializar os efeitos terapêuticos
- Diminuição de efeitos colaterais e doses
- Prevenção de Resistência

**Benéficas; Insignificantes;
Deletérias**

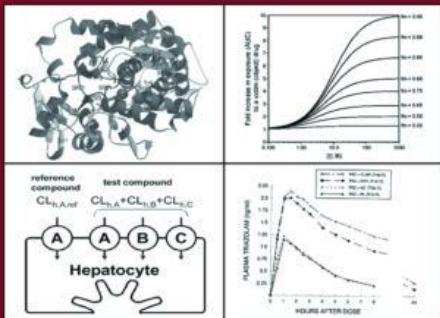
Categoria de Interação Medicamentosa	Relevância Clínica
Interação medicamentosa do tipo A (A-DDIs)	Sem importância clínica
Interação medicamentosa do tipo B (B-DDIs)	Não foi estabelecido
Interação medicamentosa do tipo C (C-DDIs)	Efeitos adversos (evitáveis com ajustes de dose)
Interação medicamentosa do tipo D (D-DDIs)	Efeitos adversos severos, ausência de efeito terapêutico (ajustes de dose são difíceis)

INTERAÇÕES MEDICAMENTOSAS

DRUGS AND THE PHARMACEUTICAL SCIENCES

VOLUME 179

Drug-Drug Interactions Second Edition



edited by

A. David Rodrigues

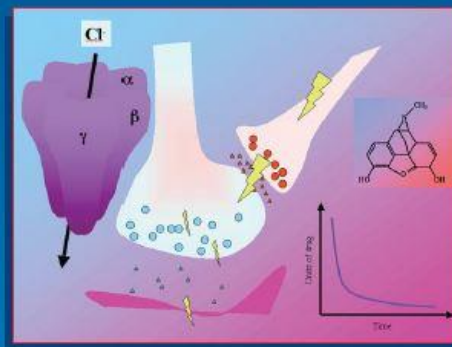
informa
healthcare

Handbook of Drug Interactions *A Clinical and Forensic Guide*

Edited by

Ashraf Mozayani, PharmD, PhD

Lionel P. Raymon, PharmD, PhD



HUMANA PRESS

PP
Pharmaceutical Press

Stockley's Drug Interactions

Tenth edition

Edited by Karen Baxter and Claire L Preston

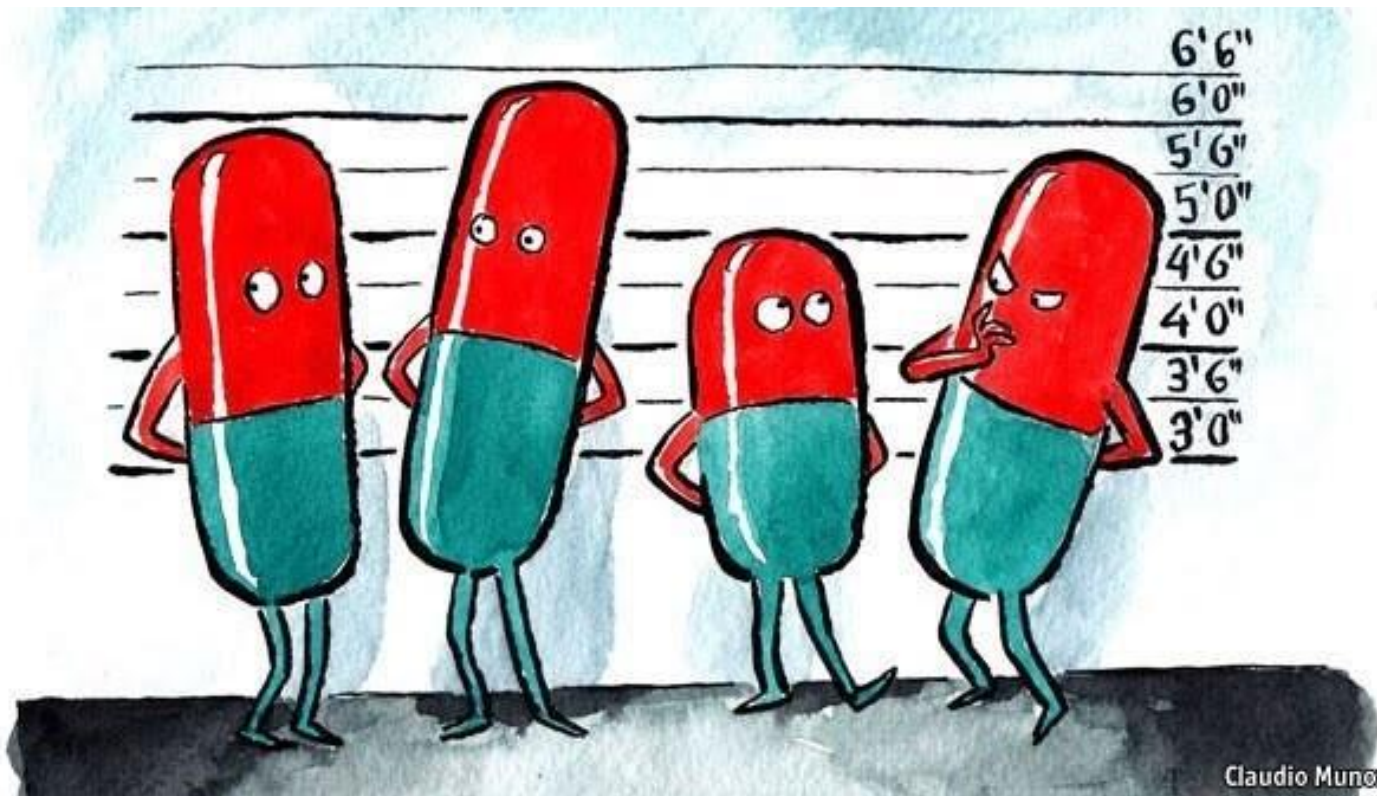
INTERAÇÕES MEDICAMENTOSAS

Table 1 | **Examples of drugs withdrawn because of CYP-related DDIs**

Drug name (generic)	Therapeutic use	Safety problem	Year withdrawn
Seldane (terfenadine)	Allergy	QTc prolongation	1998
Posicor (mibefradil)	Hypertension	QTc prolongation	1998
Duract (bromfenac)	Nonsteroidal anti-inflammatory drug	Toxicity	1998
Hismanal (astemizole)	Allergy	QTc prolongation	1999
Propulsid (cisapride)	Heartburn	QTc prolongation	2000
Lotronex (alosetron)	Irritable bowel syndrome	Toxicity	2000
Baycol (cerivastatin)	Hyperlipidaemia	Toxicity	2001
Serzone (nefazodone)	Antidepressant	QTc prolongation	2003

CYP, cytochrome P450; DDIs, drug–drug interactions.

Polifarmácia, Automedicação, Transgressão terapêutica, Uso incorreto, Função hepática Função Renal, Estado nutricional, Alterações PK e PD



Classificação das Interações Medicamentosas

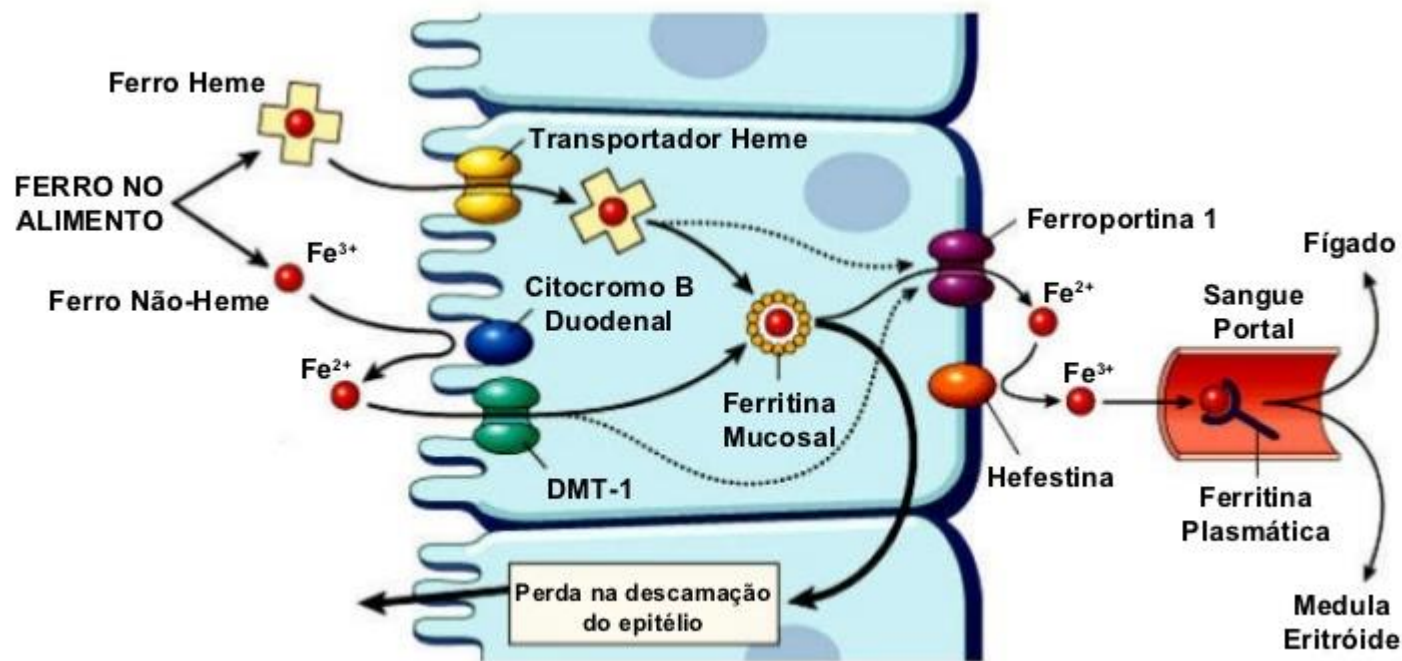
- ❑ Interações Físico-Químicas;
- ❑ Farmacodinâmica;
- ❑ Farmacocinética

INTERAÇÕES MEDICAMENTOSAS

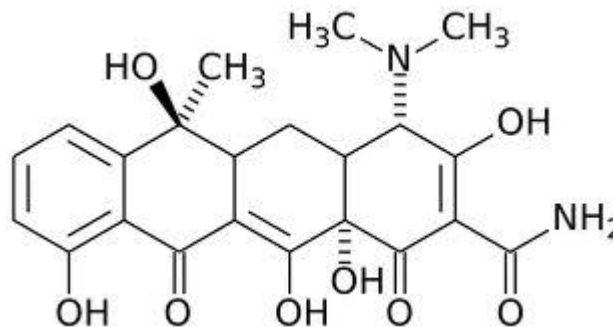
Interações Físico-Químicas ⇒ onde duas ou mais substâncias reagem entre si, por mecanismos puramente físicos ou químicos.

Exemplos:

- 1) Vitamina C na anemia Ferropriva → Manter o Ferro no estado ferroso (Fe^{2+}) ao nível intestinal;
- 2) Derivados Tetraciclínicos com Leite;
- 3) carvão ativo x alcalóides (adesão a superfície porosa). Carvão ativo usado na desintoxicação por adm oral. (proc. de adsorção)



INTERAÇÕES MEDICAMENTOSAS

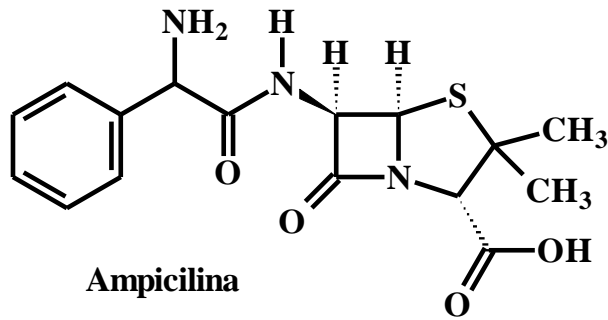
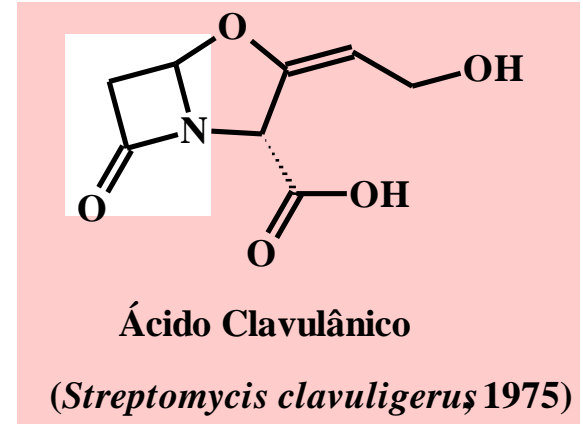
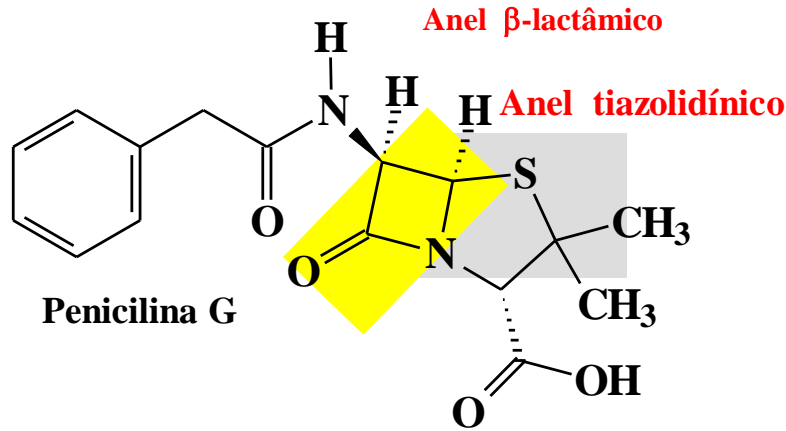


Interação Medicamentosa Farmacodinâmica ⇒ Os efeitos finais são resultantes das ações farmacodinâmicas próprias dos fármacos (ou compostos) associados. Podem resultar em sinergismo [adição (mesmo mecanismo de ação), somação (mec diferentes) e potencialização] ou antagonismo.

Exemplos:

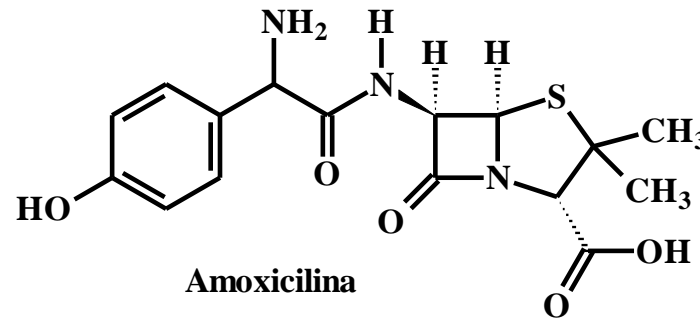
- 1) canamicina (antibiótico da família dos aminoglicosídeos) com ácido etacrínico (aumento de toxicidade) possibilidade de surdez irreversível);
- 2) Psicolépticos com Etanol (potencialização do efeito depressor do SNC)

INTERAÇÕES MEDICAMENTOSAS



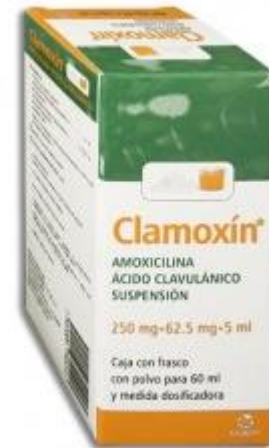
(estável em pH ácido)

(sensível à β -lactamases)

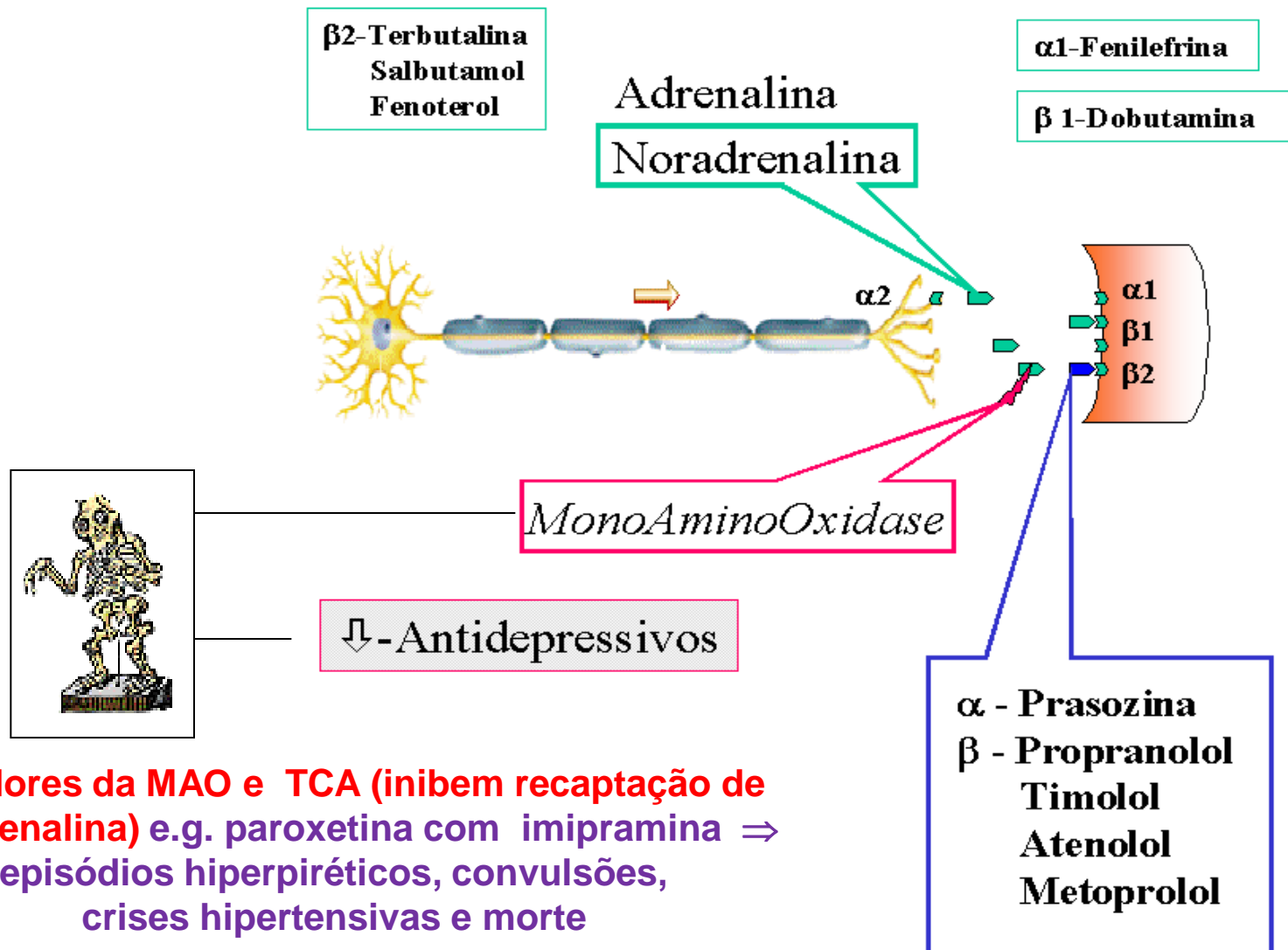


(estável em pH ácido)

(sensível à β -lactamases)

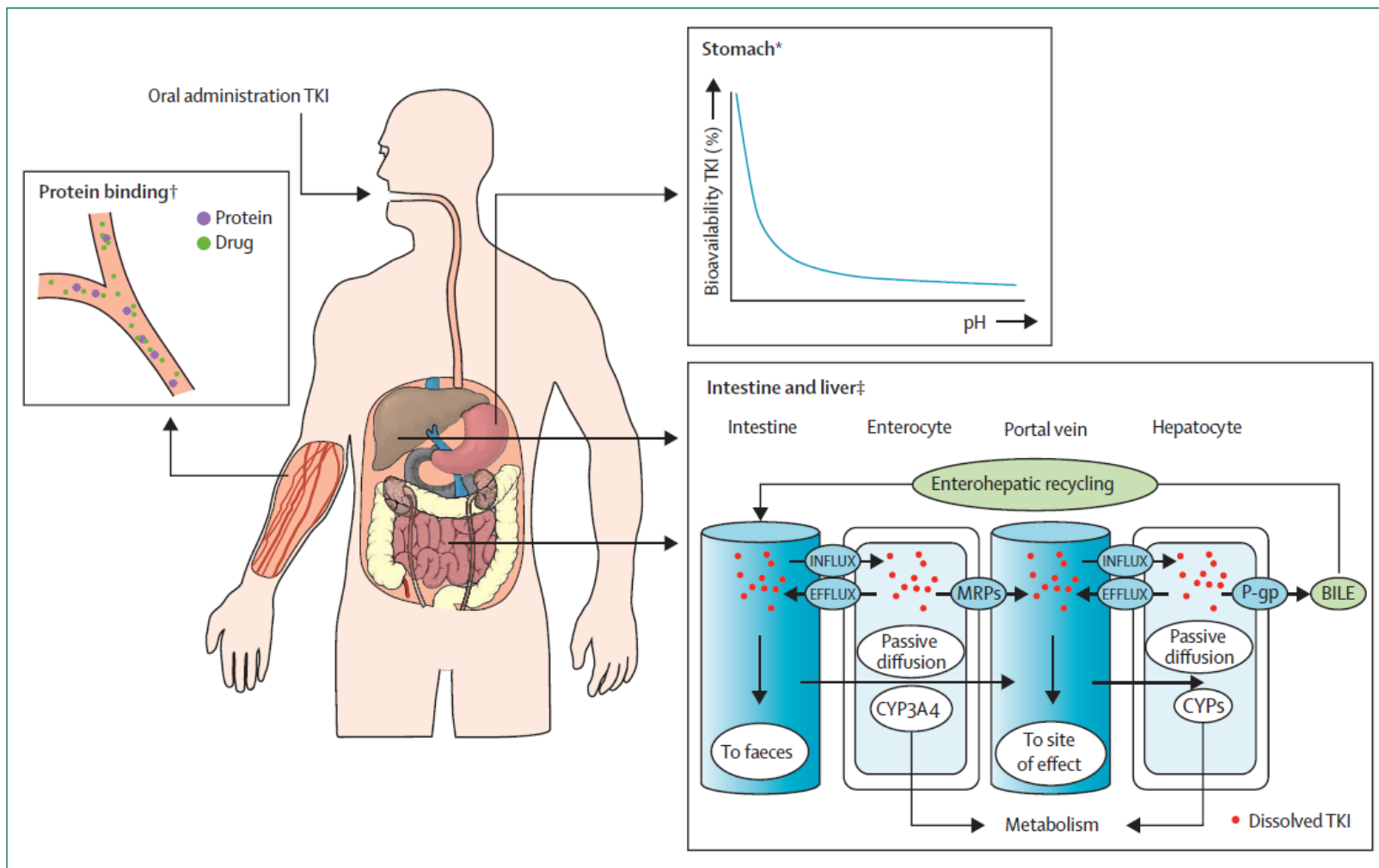


INTERAÇÕES MEDICAMENTOSAS



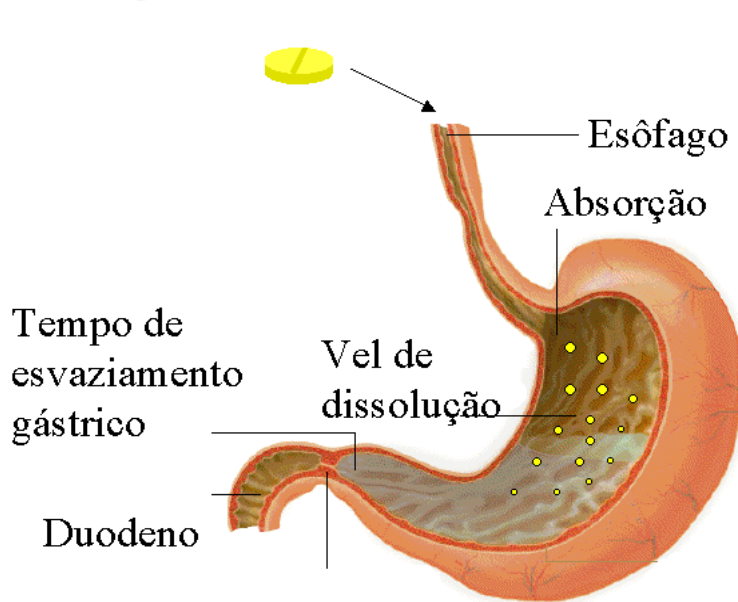
INTERAÇÕES MEDICAMENTOSAS

Interação Medicamentosa Farmacocinética: Um dos agentes (e.g. fármacos) é capaz de modificar a absorção, distribuição, biotransformação ou a excreção de outro agente administrado concomitantemente.



INTERAÇÕES MEDICAMENTOSAS

Interação Medicamentosa Farmacocinética



Absorção \Rightarrow 1. reduzida por fármacos que diminuem motilidade GI (e.g: atropina, opiáceos) ou acelerada por drogas procinéticas (exemplos: metoclopramida, aumenta vel. Esvaziamento gástrico);

2. Fármacos que são ácidos fracos são absorvidas em meio ácido, logo sua absorção será diminuída por antiácidos (exemplos: bloqueador H2 e barbitúricos), o contrário vale para os fármacos que são bases;

Consequências: alteram a velocidade de absorção ou a quantidade absorvida, interferindo com os parâmetros t_{max} e C_{max} , respectivamente.

Prop. físico-químicas importantes para a absorção: pH (GI) x pKa (fármaco)

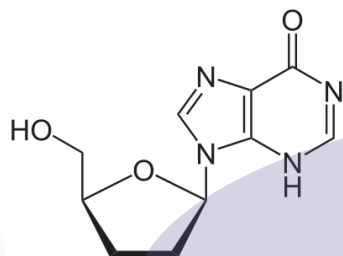
ácidos fracos: Qdo $pH = pKa \rightarrow 50\%$ ionização
 pH 1 unidade $> pKa \rightarrow 90\%$ ionizado
 pH 2 unidades $> pKa \rightarrow 99\%$ ionizado
 pH 1 unidade $< pKa \rightarrow 90\%$ não-ionizado
 pH 2 unidades $< pKa \rightarrow 99\%$ não-ionizado

bases fracas: Qdo $pH = pKa \rightarrow 50\%$ ionização
 pH 1 unidade $> pKa \rightarrow 90\%$ não-ionizado
 pH 2 unidades $> pKa \rightarrow 99\%$ não-ionizado
 pH 1 unidade $< pKa \rightarrow 90\%$ ionizado
 pH 2 unidades $< pKa \rightarrow 99\%$ ionizado

INTERAÇÕES MEDICAMENTOSAS

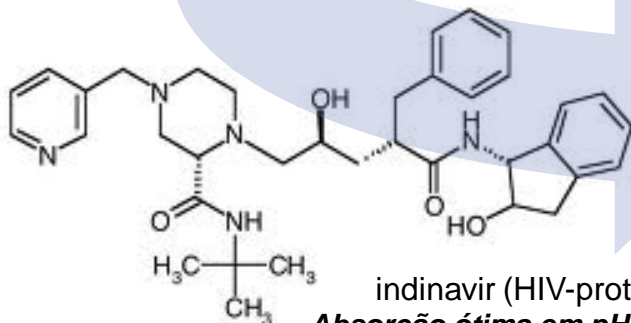
Interação Medicamentosa Farmacocinética: Absorção

Prop. físico-químicas importantes para a absorção: pH (GI) x pKa (fármaco)



Didanosina (NRTI)

degrada em meio ácido, formulada com agentes tamponantes que ↑pH

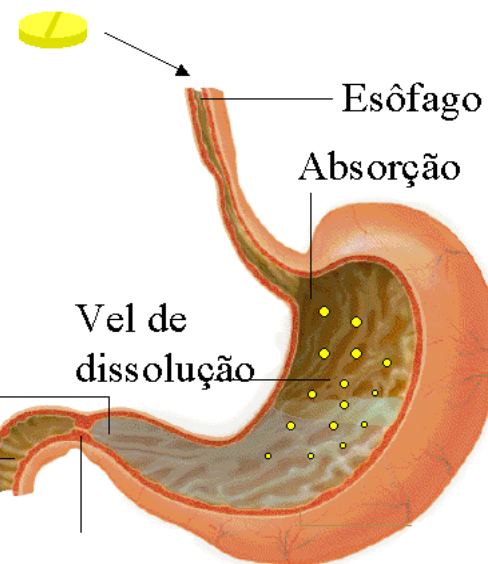


indinavir (HIV-protease-Inib)

Absorção ótima em pH ácido (normal)

Tempo de esvaziamento gástrico

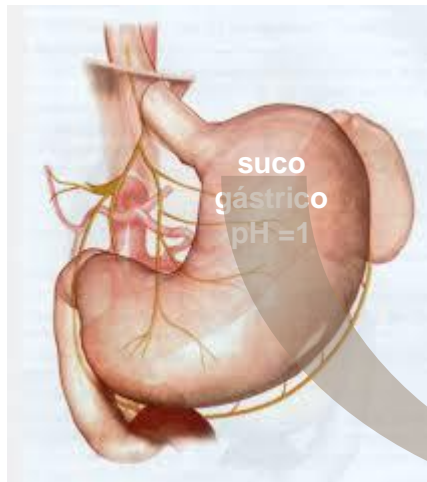
Duodeno



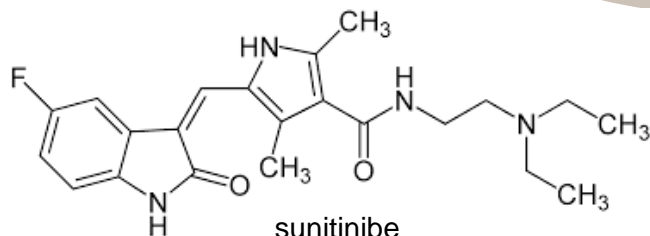
↓ velocidade de absorção do indinavir;
↓ C_{max} [indinavir]; ↑ T_{max}
→ comprometimento do efeito terapêutico

INTERAÇÕES MEDICAMENTOSAS

Interação Medicamentosa Farmacocinética



- ✓ Antiácidos
- ✓ Antagonistas H2
- ✓ Inibidores da bomba de prótons

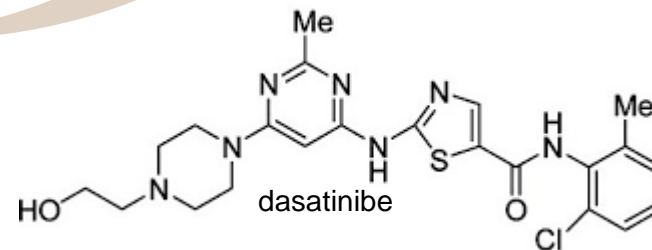


sunitinibe
pKa = 8.5

Tratamento carcinoma renal e tumor stromal GI



Não interfere na absorção



dasatinibe
pKa = 6, 8 e 3,1

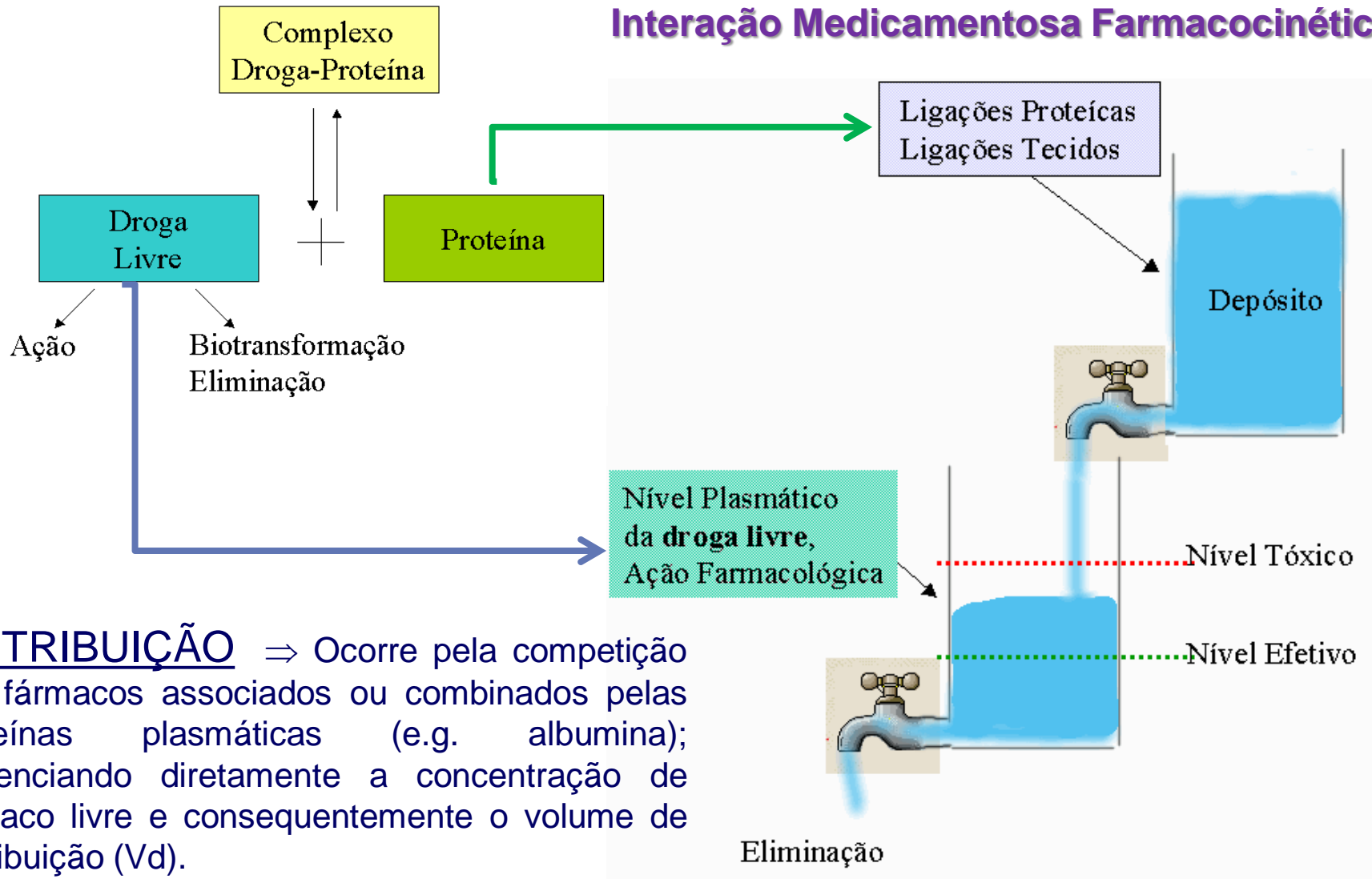
Tratamento da leucemia mieloide crônica e leucemia linfoblástica aguda



↑ [forma não ionizada]
↓ solubilidade em H₂O
↓ absorção

INTERAÇÕES MEDICAMENTOSAS

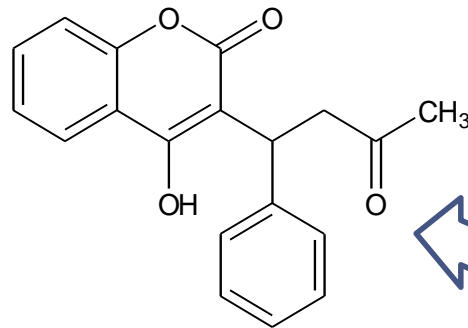
Interação Medicamentosa Farmacocinética



DISTRIBUIÇÃO ⇒ Ocorre pela competição dos fármacos associados ou combinados pelas proteínas plasmáticas (e.g. albumina); influenciando diretamente a concentração de fármaco livre e conseqüentemente o volume de distribuição (V_d).

↑ V_d → ↑ distribuição tecidual; ↓ ligação a ptn

INTERAÇÕES MEDICAMENTOSAS



99,5% ligação a ptn plasmática
2,85 mg complexada a albumina (reservatório)
0,15 mg livre (efeito terapêutico)

↑Vd → ↑distribuição tecidual da varfarina.

Consequências:
↑ risco acidente hemorrágico;
pocoagulabilidade

Ligações Proteicas
Ligações Tecidos

Depósito

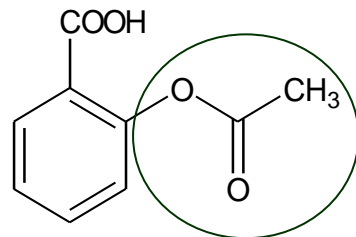
Nível Plasmático da droga livre, Ação Farmacológica

Nível Tóxico

Nível Efetivo

Eliminação

Agentes deslocadores:
AAS, fenilbutazona,
paracetamol, dicumarol



INTERAÇÕES MEDICAMENTOSAS

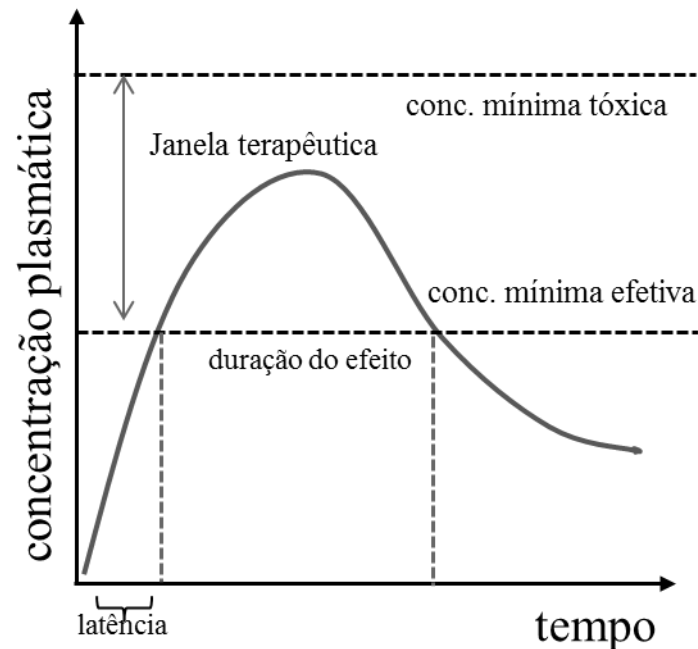
DISTRIBUIÇÃO ⇒ Ocorre pela competição dos fármacos associados ou combinados pelas proteínas plasmáticas (e.g. albumina); influenciando diretamente a concentração de fármaco livre e conseqüentemente o volume de distribuição (Vd).

Table 4 Drugs that are highly protein bound (>95%).

Drug	Protein Bound (%)
Amitriptyline	96
Chlorpromazine	96
Clofibrate	95
Diazepam	97
Dicloxacillin	96
Diphenhydramine	98
Furosemide	99
Glyburide	95
Ibuprofen	99
Imipramine	96
Indomethacin	97
Ketoconazole	99
Mebendazole	95
Naproxen	99
Nifedipine	98
Nortriptyline	95
Oxazepam	96
Phenytoin*	89-93
Thyroxine	99
Valproic acid*	90
Warfarin	99.5

* Narrow therapeutic window.

**Agentes deslocadores:
fenilbutazona, aspirina,
paracetamol, dicumarol**



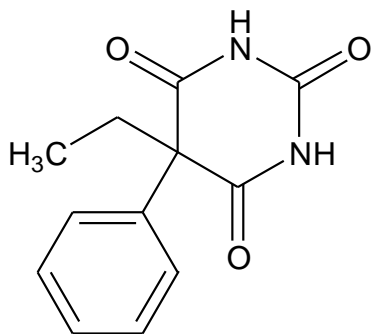
INTERAÇÕES MEDICAMENTOSAS

Interação Medicamentosa Farmacocinética:

METABOLISMO ⇒ Quando um fármaco interfere com o metabolismo do outro fármaco utilizado em associação ou concomitante. Este processo frequentemente decorre **de fenômenos de indução ou inibição das enzimas** envolvidas com o metabolismo de Fase 1 e Fase 2.

Indução Enzimática: aumento da quantidade e/ou atividade de enzimas que metabolizam xenobióticos (CYP450 principalmente). **Resulta na diminuição do $t_{1/2}$.** *Classicamente a definição de indução se refere a síntese de novo de novas moléculas de enzimas envolvidas no metabolismo de xenobióticos e resulta do aumento da transcrição de genes que codificam estas enzimas, após um estímulo químico apropriado.*

HISTÓRICO



Fenobarbital



1962 → uso crônico ↓ Efeitos anticonvulsivantes e sedativos
(autoindutor enzimático)

Indutor CYP1A2; 2C9 e 3A4/5

INTERAÇÕES MEDICAMENTOSAS

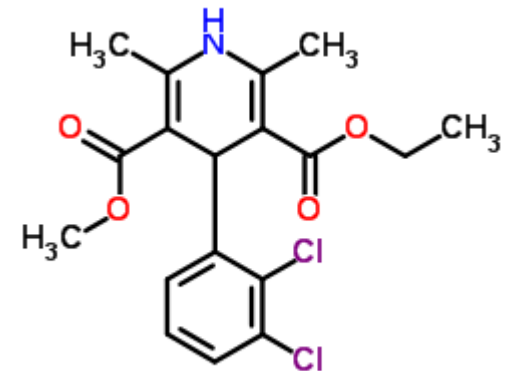
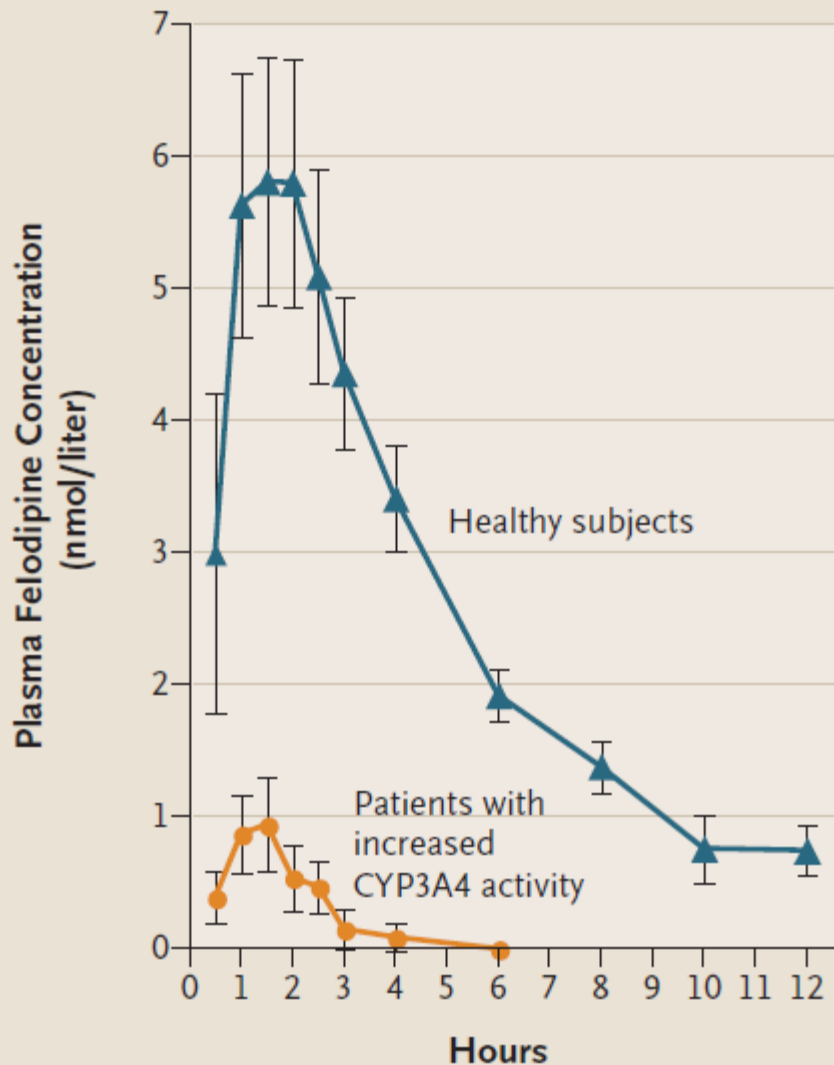
Table 5 continued

1A2	2C9	2C19	2D6	2E1	3A3/4
			Paroxetine Perphenazine Propoxyphene Quinidine Ranitidine Ritonavir Sertraline Terbinafine Thioridazine Ticlopidine		
Inducers					
<u>Broccoli</u>	Carbamazepine	Carbamazepine	Pregnancy	Chronic ethanol	Carbamazepine
Brussel sprouts	Ethanol	Norethindrone		Isoniazid	Dexamethasone
Carbamazepine	<u>Phenobarbital</u>	Prednisone		Ritonavir	Efavirenz
Charbroiled food	Phenytoin	Rifampin		<u>Tobacco</u>	Griseofulvin
<u>Cigarette smoke</u>	Primidone				Nevirapine
Modafinil	Rifabutin				<u>Phenobarbital</u>
Nafcillin	Rifampin				Phenytoin
Omeprazole	Secobarbital				Prednisone
<u>Phenobarbital</u>					Rifabutin
Phenytoin					Rifampin
Rifampin					Ritonavir
Ritonavir					<u>St John's wort</u>
Tobacco					Sulfinpyrazone
					Troglitazone

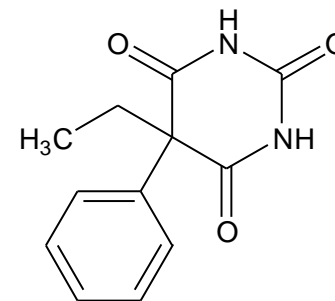
Data from <http://medicine.iupui.edu/flockhart/table.htm>; [19] Shannon M. *Pediatr Emerg Care* 1997;13(5):350-3; Taketomo CK, Hodding JH, Kraus DM. *Pediatric Handbook*. 10th ed. Cleveland: Lexicomp Inc, 2003-2004.

* S-Warfarin isomer has 2 to 5 times more anticoagulant activity than R-warfarin isomer. Therefore, 2C9 interactions most significantly affect warfarin acti

INTERAÇÕES MEDICAMENTOSAS

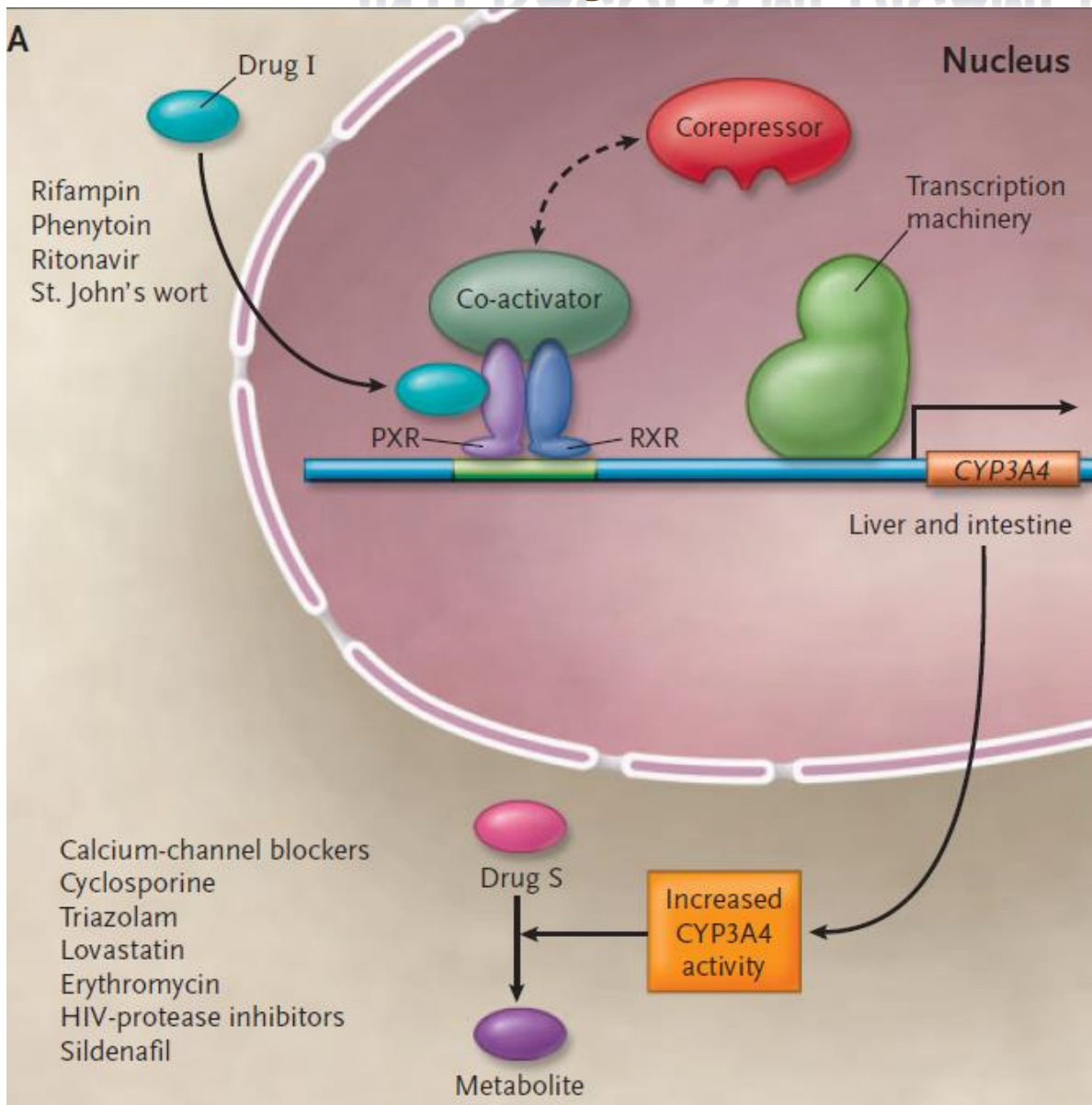


Felodipino
(anti-hipertensivo)
substrato da CYP3A4



Fenobarbital
(anti-convulsivante)
indutor da CYP3A4

INTERAÇÕES MEDICAMENTOSAS



Drug interacts with the nuclear receptor PXR (pregnane X receptor), which forms a heterodimer with the retinoid X receptor (RXR), which in turn binds to cognate recognition sites in the 5' regulatory region of the CYP3A4 gene. As a result, transcription of DNA is up-regulated, leading to increased synthesis of CYP3A4 enzyme and enhanced oxidative metabolism of its substrates (Drug S).

INTERAÇÕES MEDICAMENTOSAS

Inibição Enzimática: Diminuição da atividade catalítica de enzimas que metabolizam xenobióticos (CYP450 principalmente). **Resulta no aumento do $t_{1/2}$.**

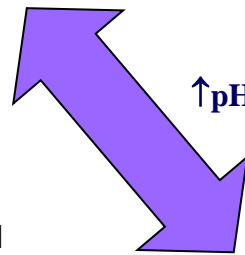
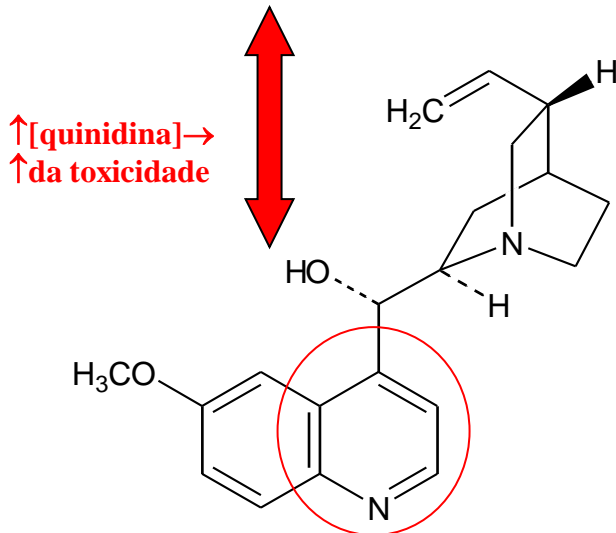
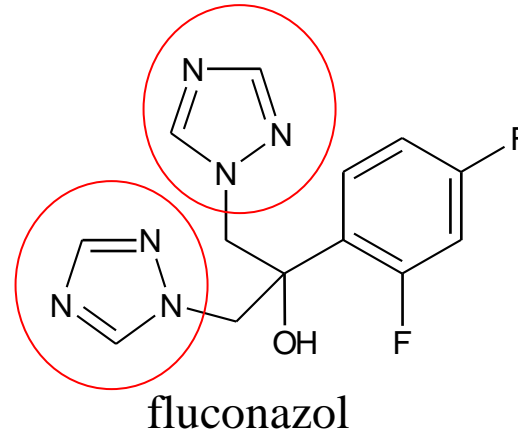
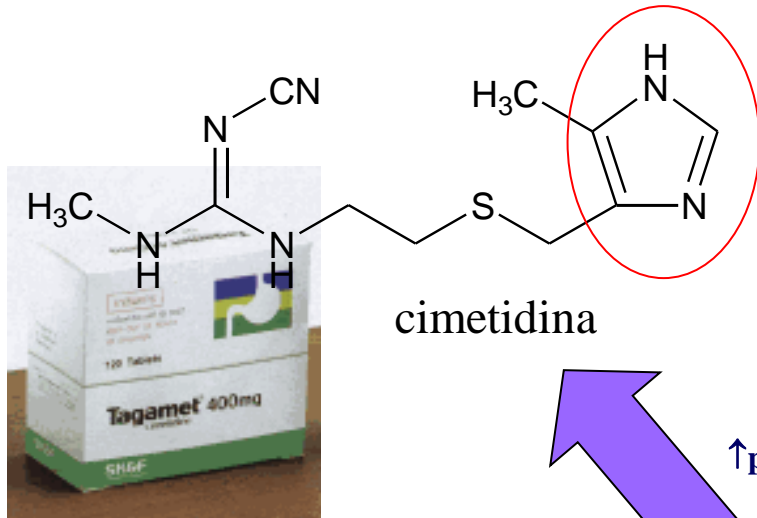
Mecanismos de inibição: 1. Reversível (competição e não competitiva); 2. Irreversíveis

Table 5 continued

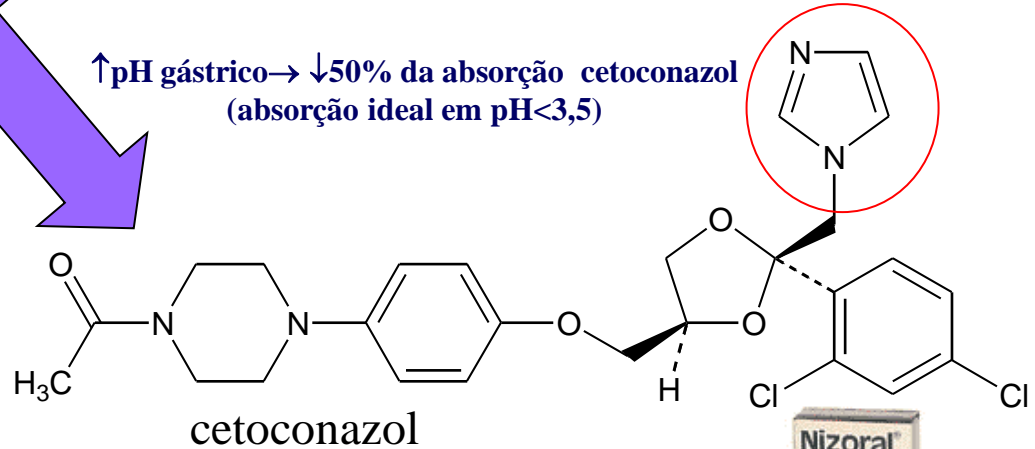
1A2	2C9	2C19	2D6	2E1	3A3/4
Inhibitors					
Amiodarone	Amiodarone	Cimetidine	Amiodarone	Disulfiram	Amiodarone
Cimetidine	Cimetidine	Felbamate	Bupropion	Methylpyrazole	Cimetidine
Ciprofloxacin	Clopidogrel	Fluoxetine	Celecoxib		Ciprofloxacin
Clarithromycin	Fluconazole	Fluvoxamine	Chloroquine		Clarithromycin
Erythromycin	Fluoxetine	Indomethacin	Chlorpheniramine		Diltiazem
Fluoxetine	Fluvastatin	Ketoconazole	Chlorpromazine		Erythromycin
Fluvoxamine	Fluvoxamine	Lansoprazole	Cimetidine		Fluconazole
Gatifloxacin	Isoniazid	Omeprazole	Citalopram		Fluoxetine
Grapefruit juice	Lovastatin	Paroxetine	Clemastine		Fluvoxamine
Interferon	Metronidazole	Ritonavir	Clomipramine		Grapefruit juice
Levofloxacin	Paroxetine	Ticlopidine	Cocaine		Itraconazole
Mexiletine	Phenylbutazone	Topiramate	Diphenhydramine		Ketoconazole
Ofloxacin	Probenecid		Doxorubicin		Nefazodone
Nefazodone	Ritonavir		Escitalopram		Nifedipine
Ticlopidine	Sertraline		Fluoxetine		Omeprazole
	Sulfamethoxazole-		Haloperidol		Propoxyphene
	trimoprim				
	Teniposide		Hydroxyzine		Protease inhibitors
	Zafirlukast		Indinavir		Verapamil
			Methadone		
			Metoclopramide		

INTERAÇÕES MEDICAMENTOSAS

✓ INIBIDORES REVERSÍVEIS DE CYP450

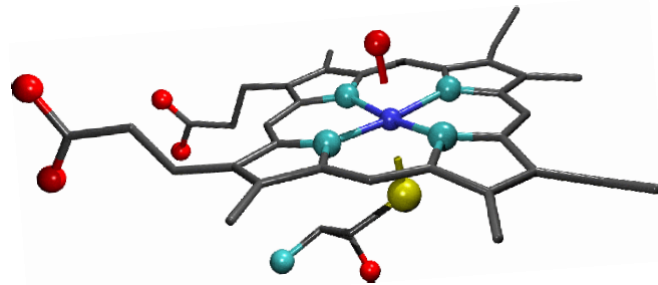
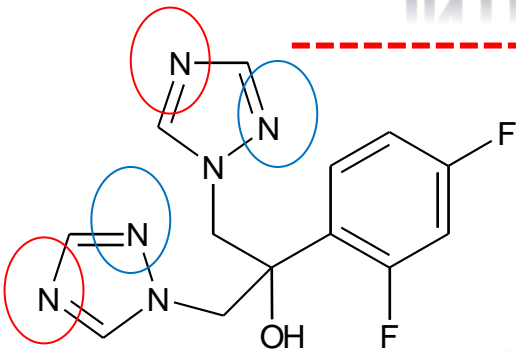


↑pH gástrico → ↓50% da absorção cetoconazol
(absorção ideal em pH < 3,5)

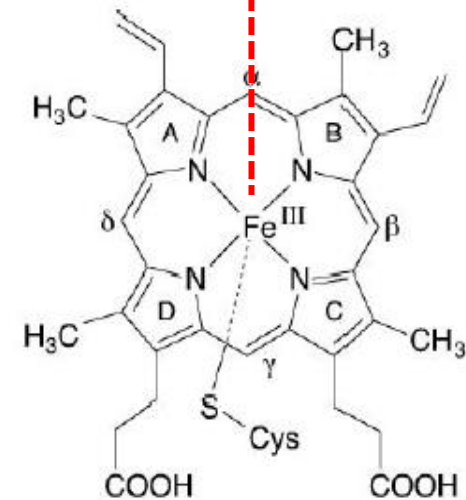


Inibidores enzimático

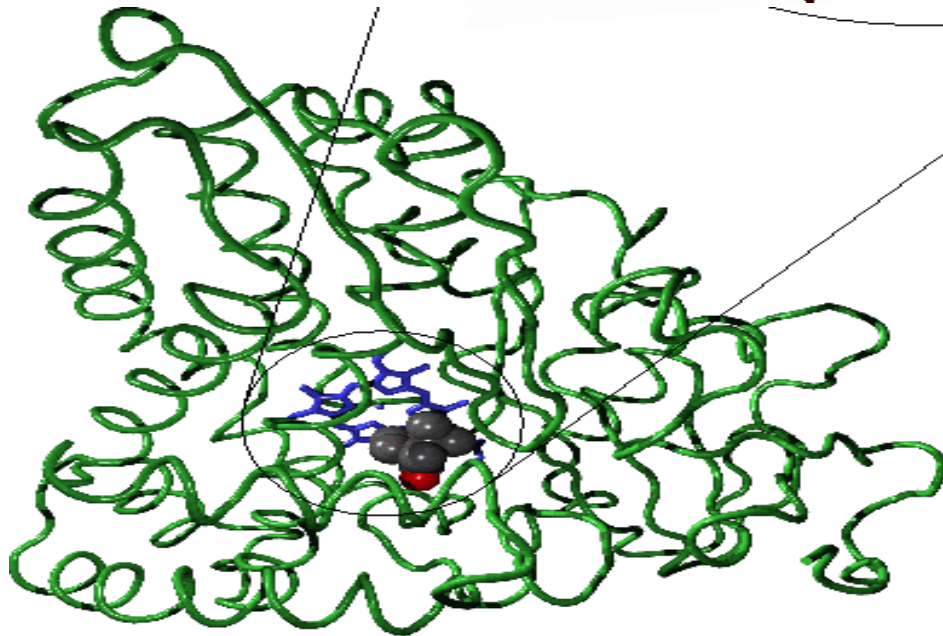
INTERAÇÕES MEDICAMENTOSAS



O núcleo HEME do citocromo P₄₅₀



Cisteinato-Fe(III) protoporfina IX

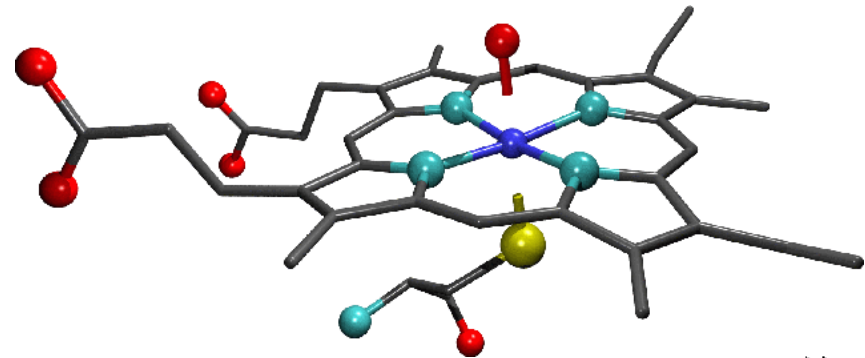
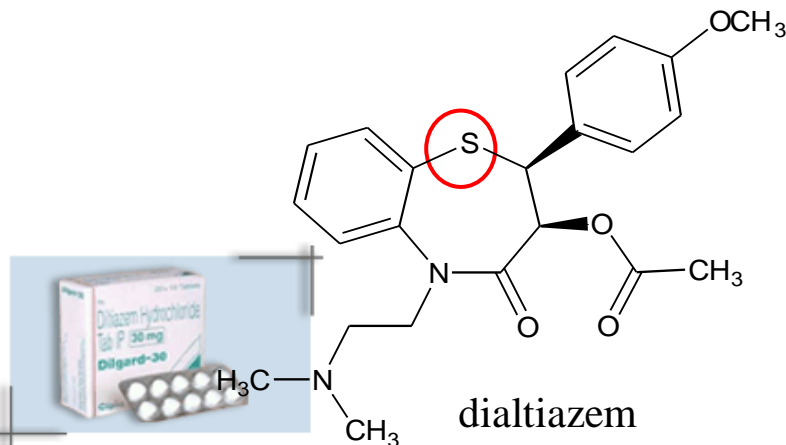
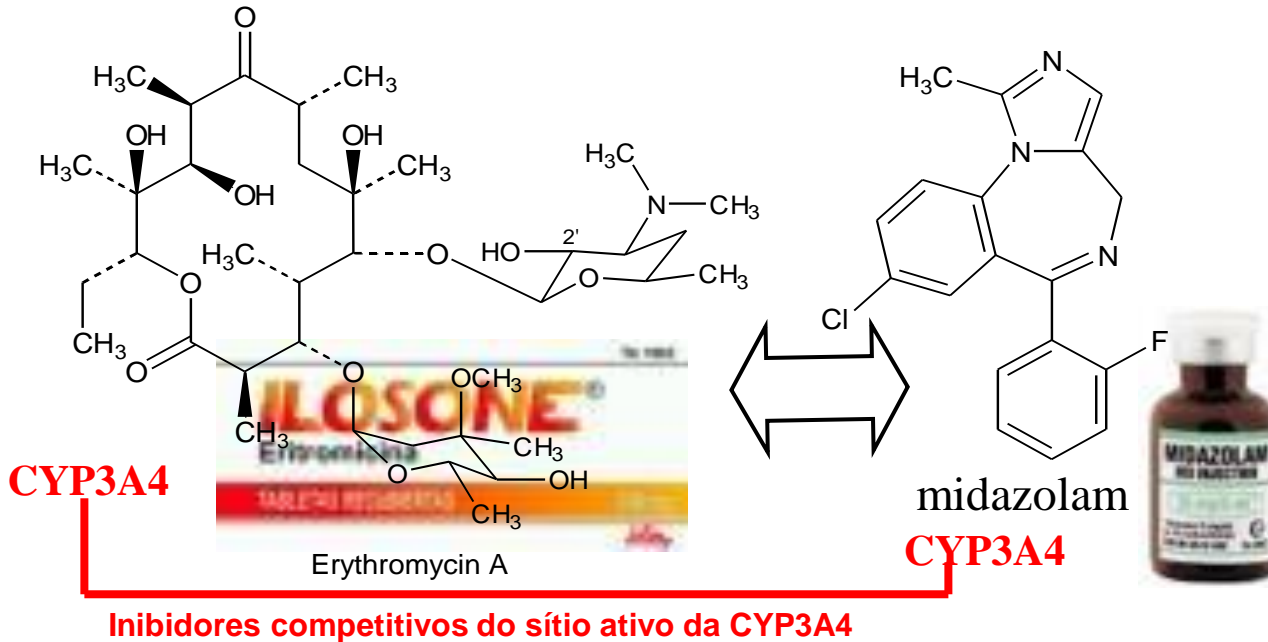


"A representation of with bound camphor. The enlarged active site region shows the camphor substrate, haem moiety and cysteine residue which forms the distal haem ligand. In the representation of the full enzyme the protein backbone is shown in green, the haem moiety in blue and the substrate is coloured according to atomic species. Oxygen atoms are shown in red, carbon in grey, nitrogen in light blue, sulphur in yellow and iron in dark blue."

www.pharmacology2000.com/

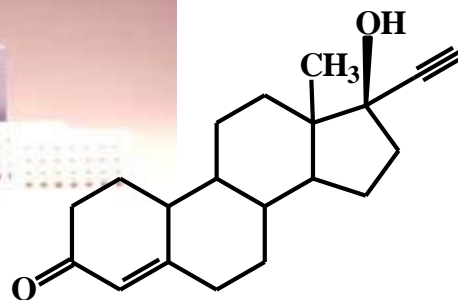
INTERAÇÕES MEDICAMENTOSAS

✓ INIBIDORES REVERSÍVEIS DE CYP450



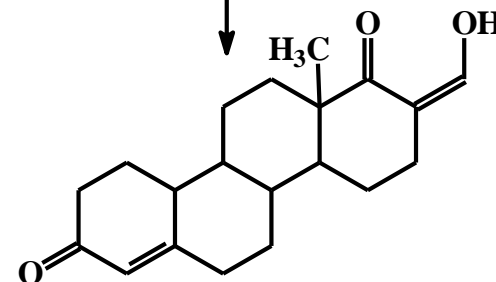
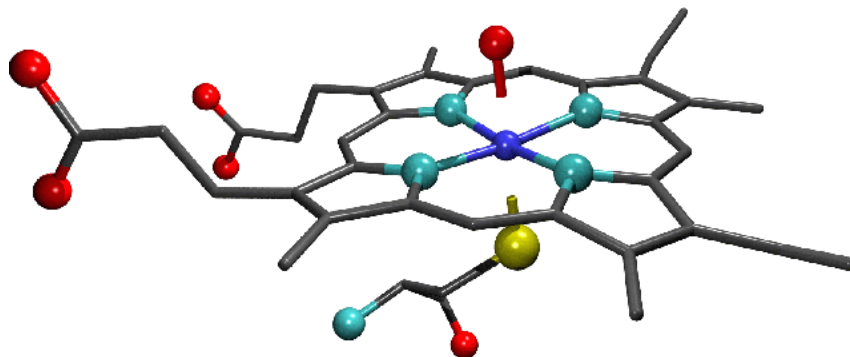
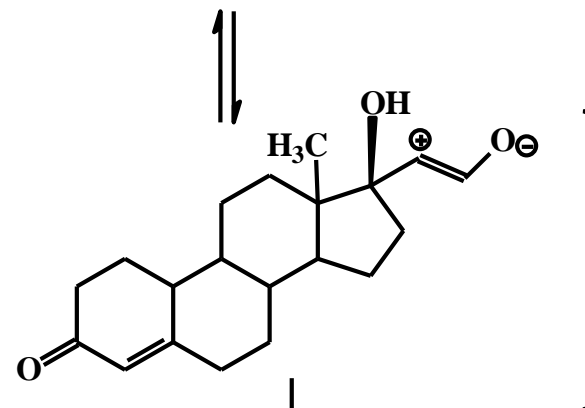
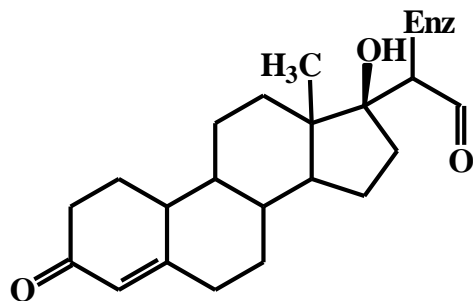
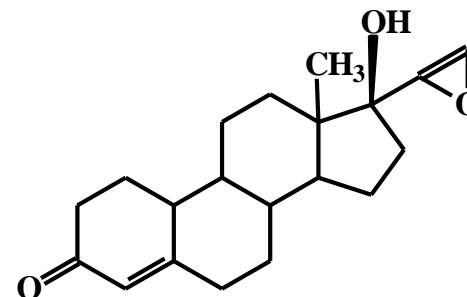
INTERAÇÕES MEDICAMENTOSAS

✓ INIBIDORES IRREVERSÍVEIS DE CYP450

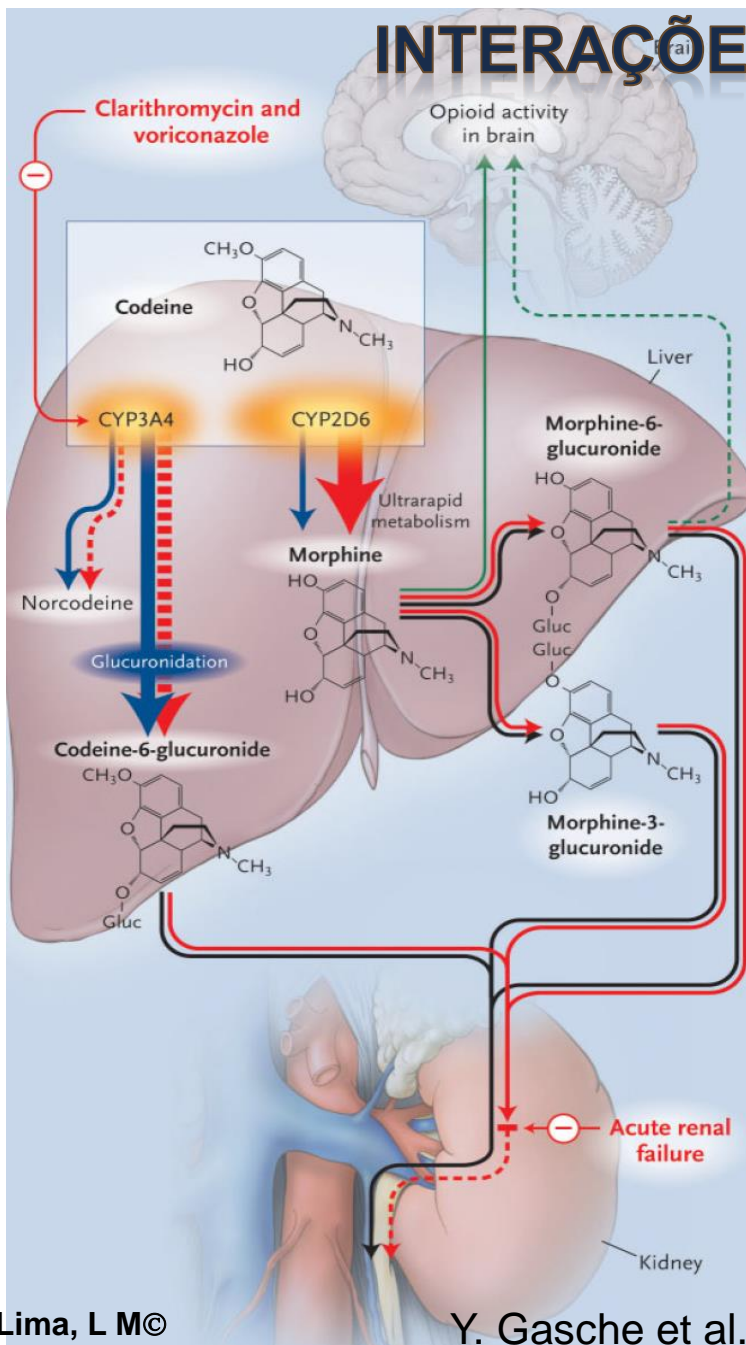


norethisterone

CYP450



INTERAÇÕES MEDICAMENTOSAS



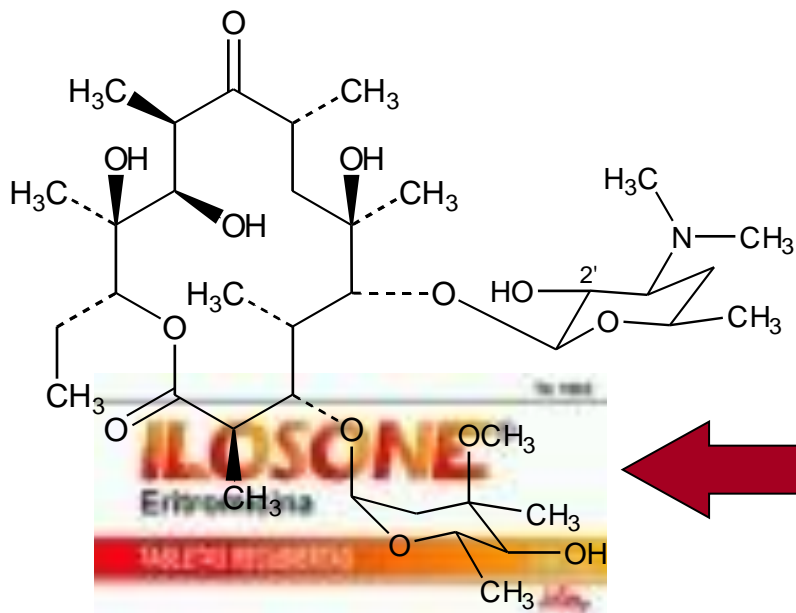
The conversion of codeine into norcodeine by CYP3A4 and into codeine-6-glucuronide by glucuronidation usually represents 80 percent of codeine clearance, and conversion of codeine into morphine by CYP2D6 represents only 10 percent of codeine clearance (blue arrows).

Morphine is further metabolized into morphine-6-glucuronide and into morphine-3-glucuronide. Morphine and morphine-6-glucuronide have opioid activity (green arrows). Glucuronides are eliminated by the kidney and are thus susceptible to accumulation in cases of acute renal failure. **The patient (red arrows) had ultrarapid CYP2D6 metabolism, inhibition of CYP3A4 as a result of treatment with clarithromycin and voriconazole, and glucuronide accumulation due to acute renal failure.**

Red arrows with dotted lines indicate low levels of drug conversion or elimination, green arrows with dotted lines indicate low levels of brain penetration, and thick arrows indicate high levels.

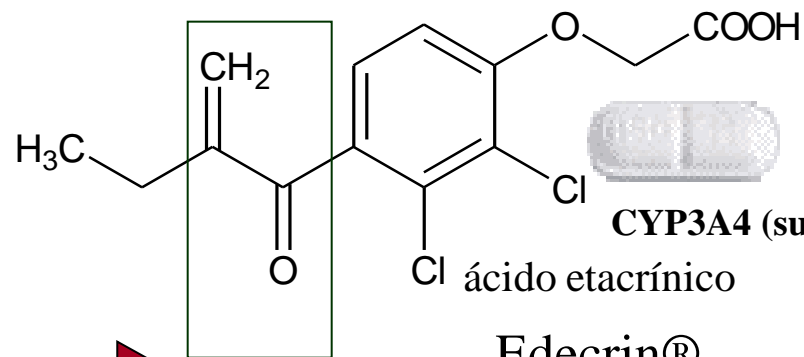
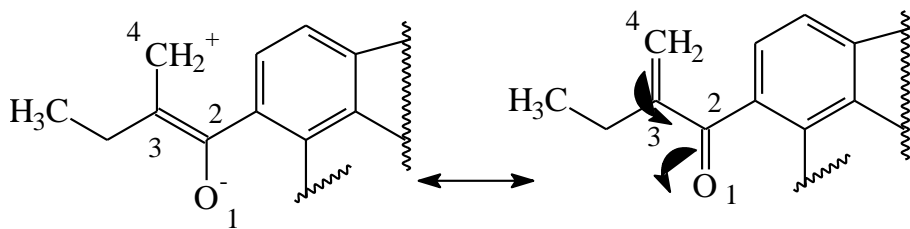
*CYP2D6 ultrarapid-metabolism genotype and phenotype, in combination with drug-induced inhibition of CYP3A4 activity and a reduction in renal function → **central nervous system depression***

INTERAÇÕES MEDICAMENTOSAS



Erythromycin A
CYP3A4 (inibidor)

↑ *risco de ototoxicidade*

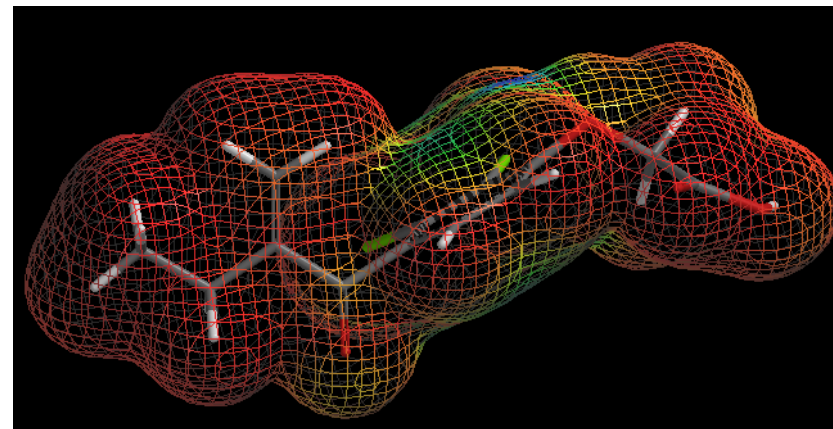


CYP3A4 (substrato)

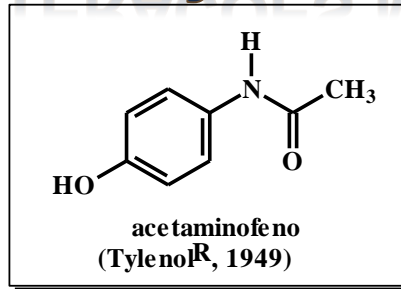
Edecrin®

LD₅₀ = 175 mg/kg

↑ *agranulocitose, neutropenia*



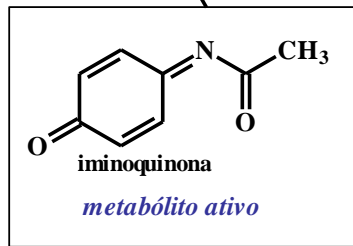
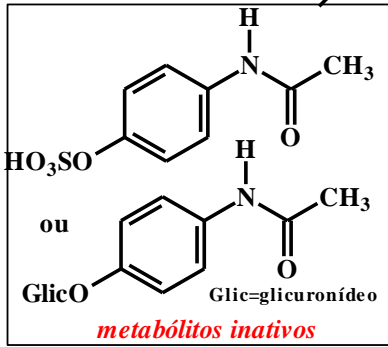
INTERAÇÕES MEDICAMENTOSAS



induzida por:
overdose; álcool;
isoniazida; fenobarbital

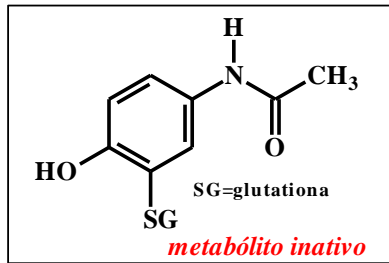
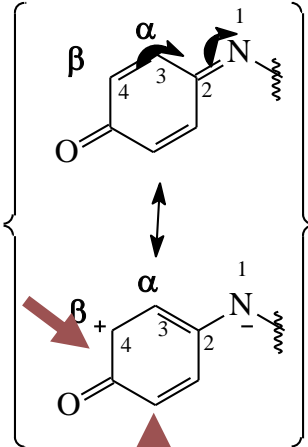
sulfatação
Glicuronidação

ca. 5-15%
CYP450 1A2
CYP450 2E1

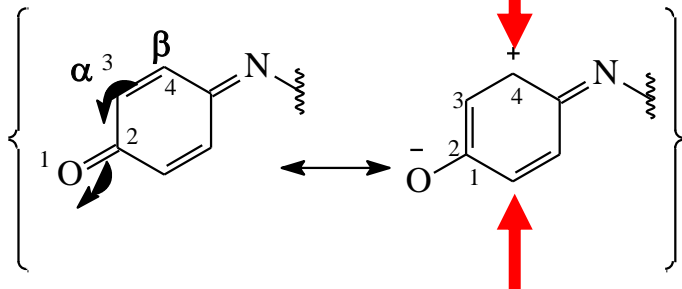
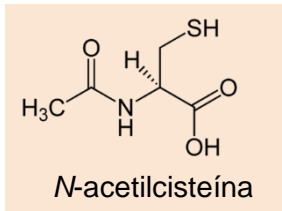


acelerada pelo álcool

ausência/ou deficiência
de Glutaciona

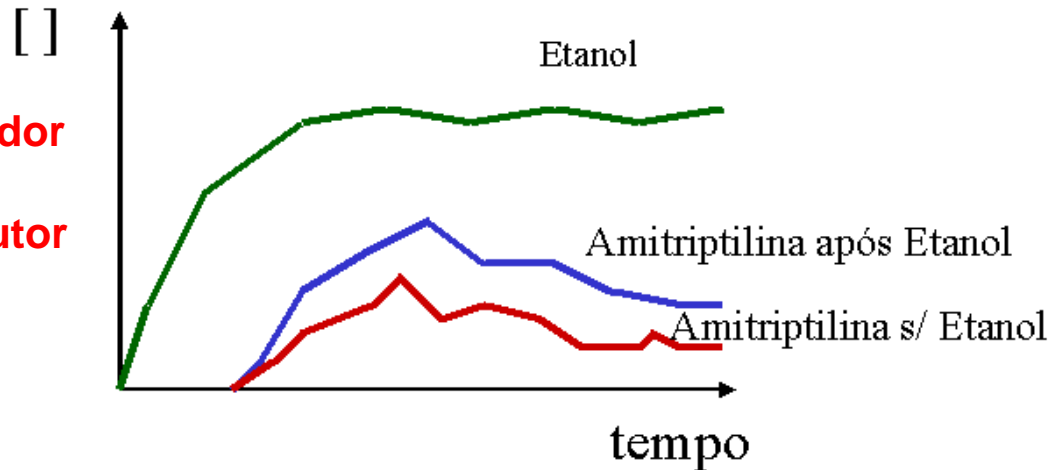


necrose celular
necrose hepática

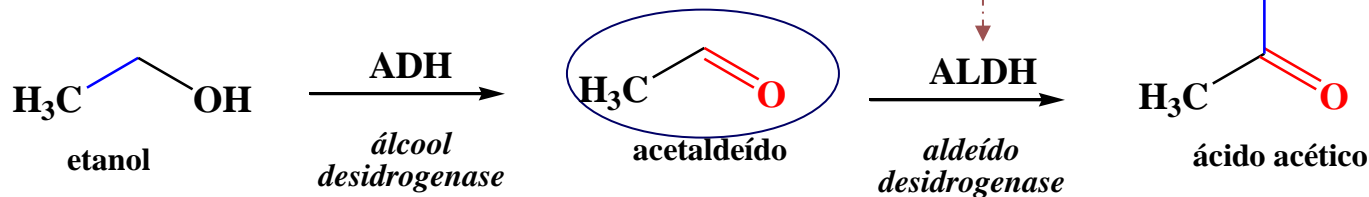
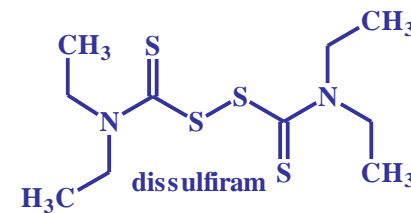
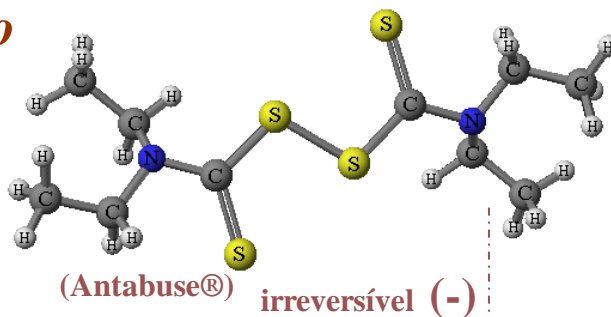


INTERAÇÕES MEDICAMENTOSAS

- ✓ Álcool “agudo” → inibidor enzimático
- ✓ Álcool “crônico” → indutor enzimático

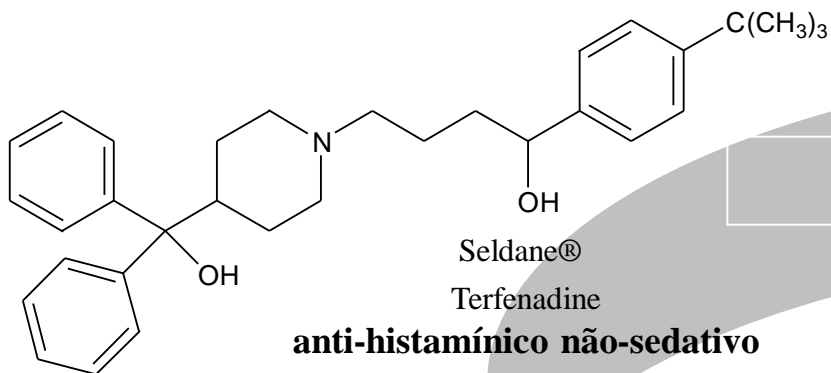


Tratamento do alcoolismo



“síndrome do acetaldeído” (náuseas, vômito, hipotensão, palpitação, dor de cabeça, etc)

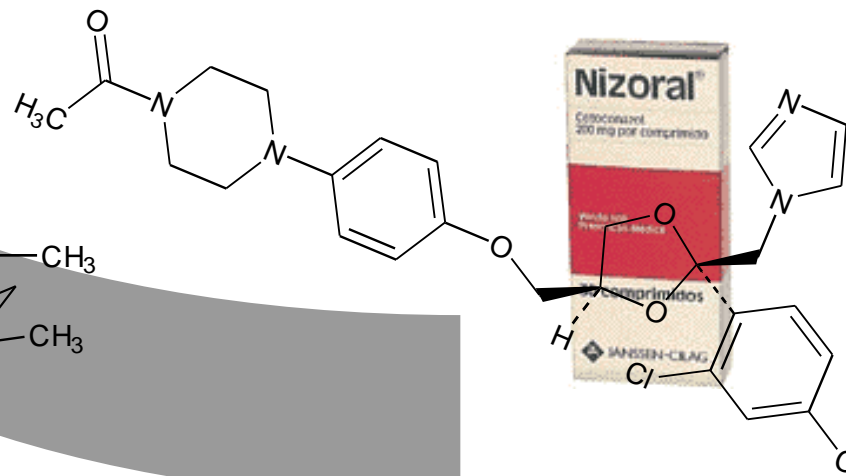
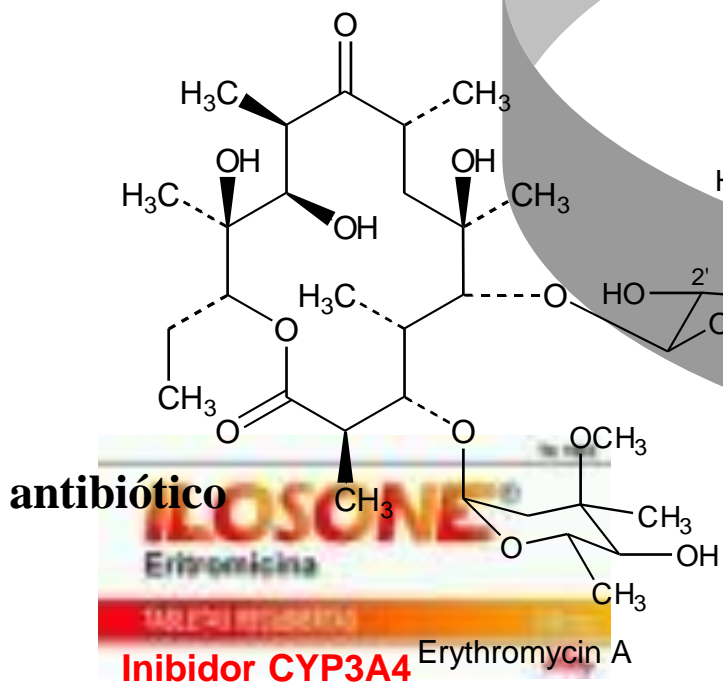
INTERAÇÕES MEDICAMENTOSAS



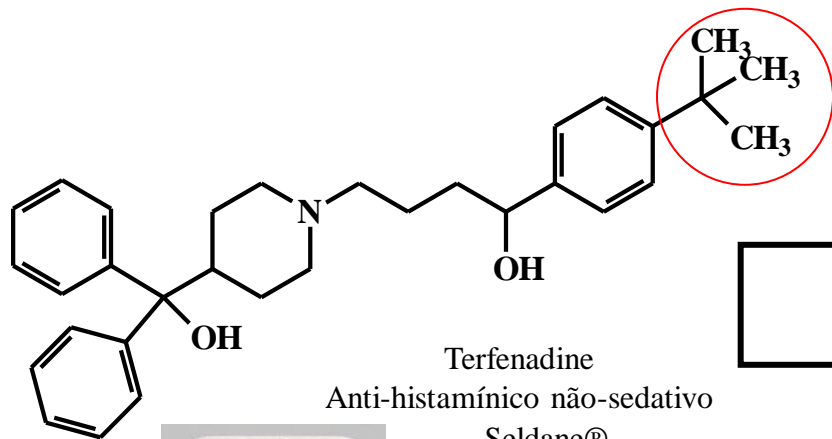
anti-histamínico não-sedativo
Substrato CYP3A4

FDA → Proscrito, USA?

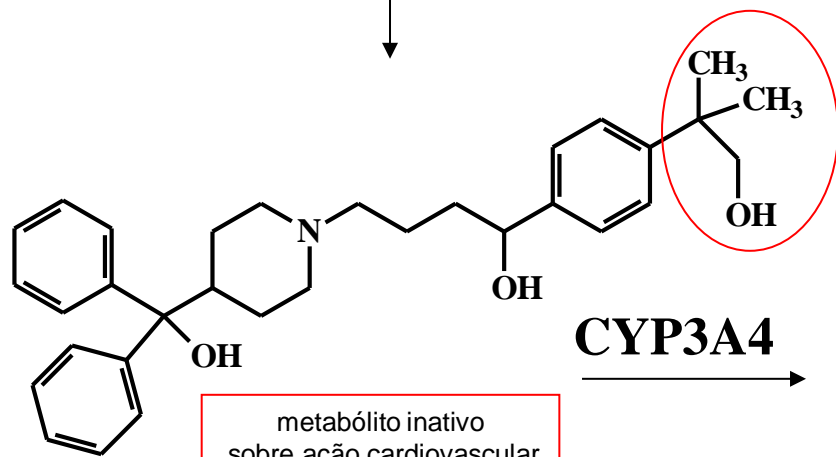
Rare, but serious
heart problems



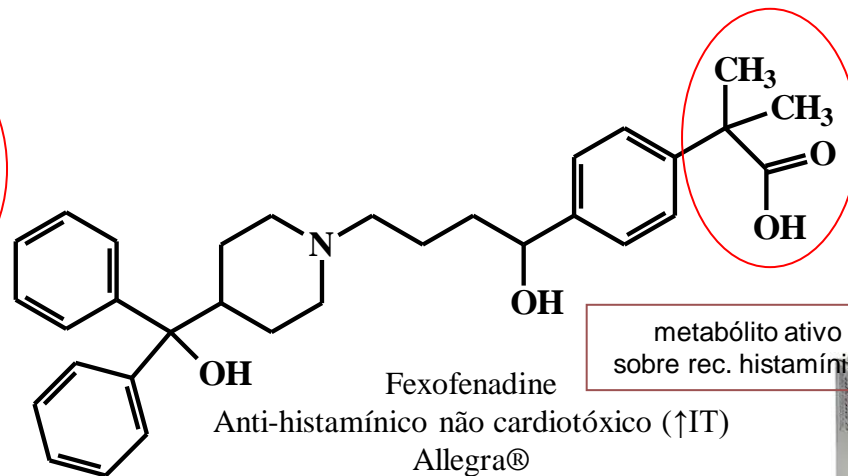
INTERAÇÕES MEDICAMENTOSAS



CYP3A4

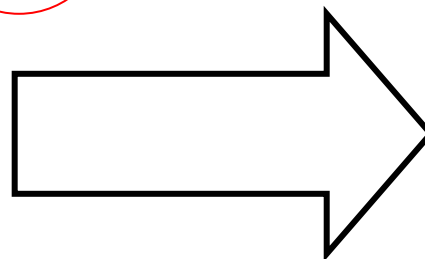


CYP3A4



metabólito inativo
sobre ação cardiovascular

FDA → Proscrito, USA & Europa



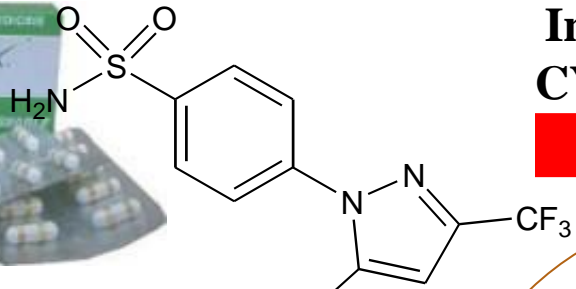
Arritmia cardíaca &
Fibrilação ventricular

Alvo Molecular: canais de potássio (hERG)

Badyal, D.K. & Dadhich (2001) *Indian J. Pharmacol.* 33: 248

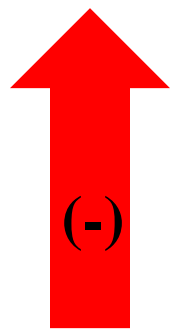


INTERAÇÕES MEDICAMENTOSAS

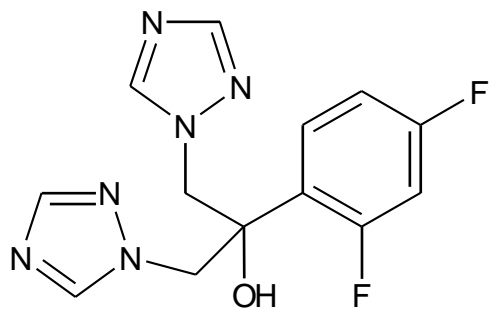


Inibidor da CYP450 2D6
(-)

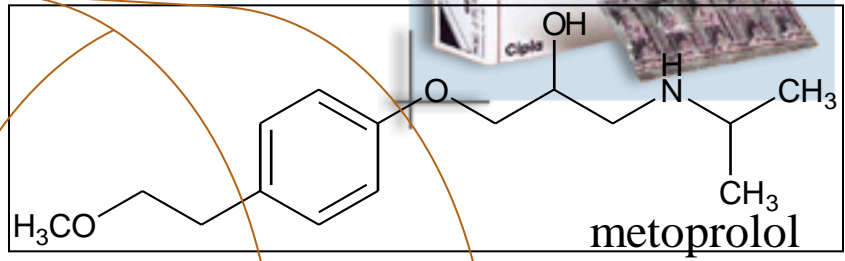
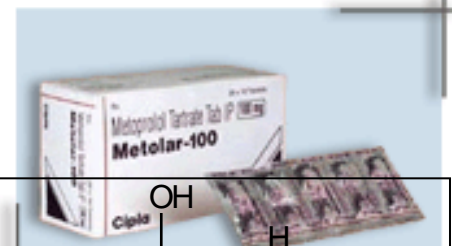
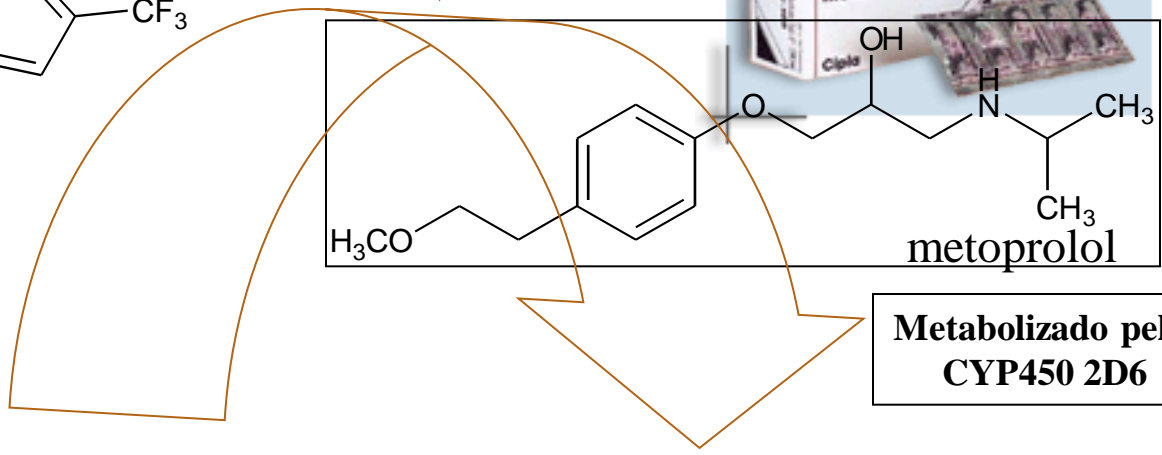
Metabolizado pela CYP450 2C9



Inibidor da CYP450 2C9
(-)



fluconazol

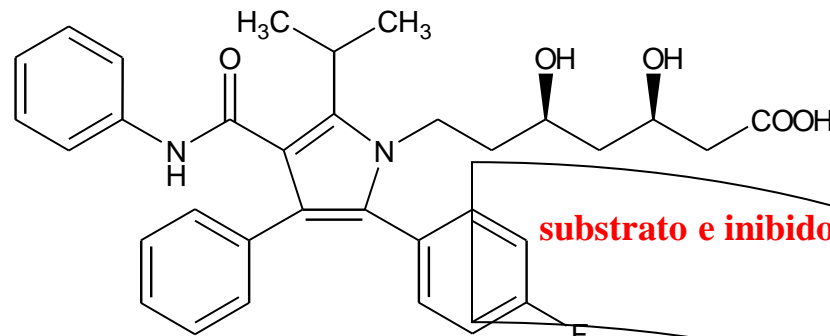


Metabolizado pela CYP450 2D6

↓[conc] metoprolol
Bradicardia sintomática

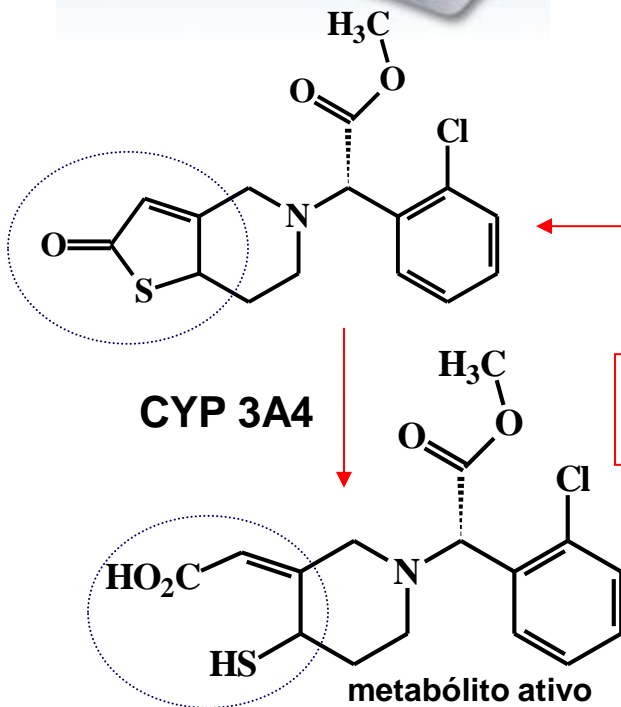
O acúmulo de metoprolol pode levar a profunda hipotensão como resultado do output cardíaco devido a efeitos cronotrópicos e inotrópicos resultantes do bloqueio dos receptores β-adrenérgicos.

INTERAÇÕES MEDICAMENTOSAS

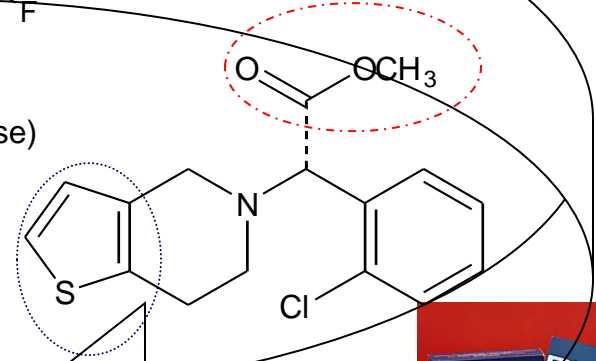


atorvastatina
antilipidêmico
(inibidor da HMGCoA-redutase)

substrato e inibidor da CYP 3A4



Perda da propriedades anti-plaquetárias



Clopidogrel (antiplaquetário)
tratamento da doença arterial coronariana



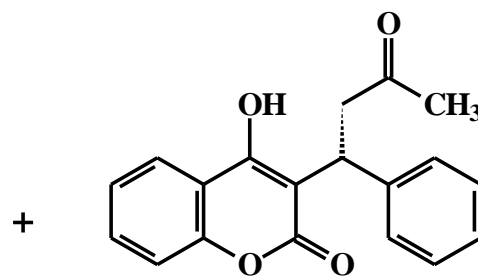
*Pravastatina, alternativa?
única estatina eliminada na forma não modificada*

Neubauer, H. et al. (2003) Eur. Heart Journal 24: 1744

INTERAÇÕES MEDICAMENTOSAS



R-varfarina
distômero (4 x menos ativo)



S-varfarina

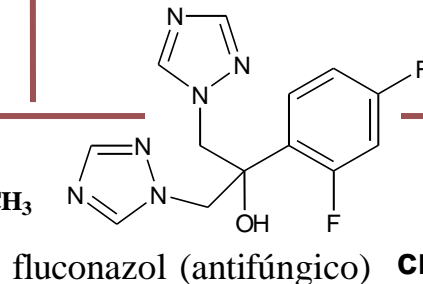
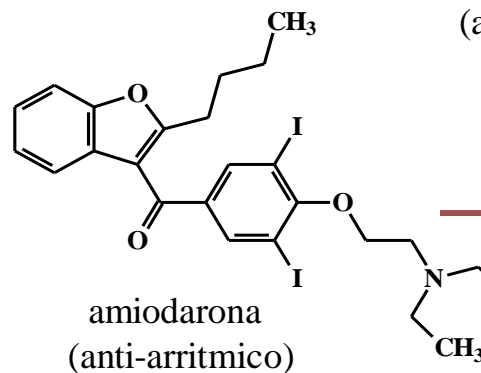
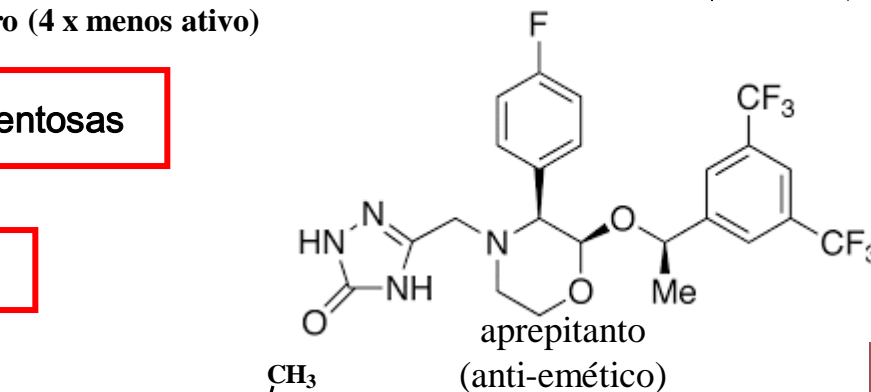
Taxa de complicações com Tratamento crônico: 7.6 a 16.5 pacientes por cada 100.

Falência renal crônica;
Disfunção hepática;
Alto risco de sangramentos.

Interações Medicamentosas

Inibidores CYP2C9

↑ risco de falência renal crônica; disfunção hepática e sangramentos.



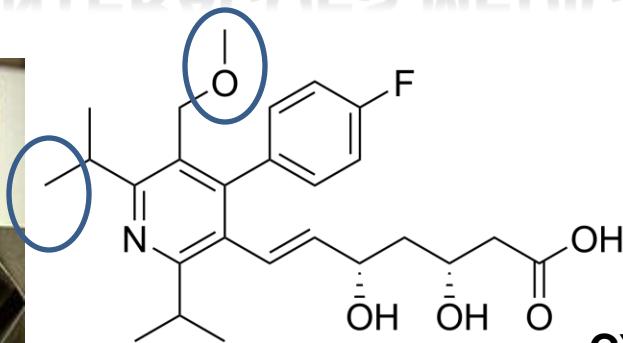
Interações Medicamentosas

Indutores CYP2C9

rifampicina,
carbamazepina,
barbituratos

↑ risco de embolia pulmonar & complicações cardiovasculares

INTERAÇÕES MEDICAMENTOSAS

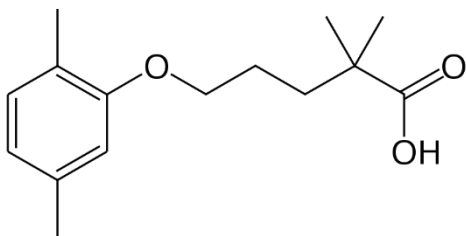


Cerivastatina
(inibidor da HMGCoA-redutase)
Tratamento da hipercolesterolemia e prevenção de doenças cardiovasculares

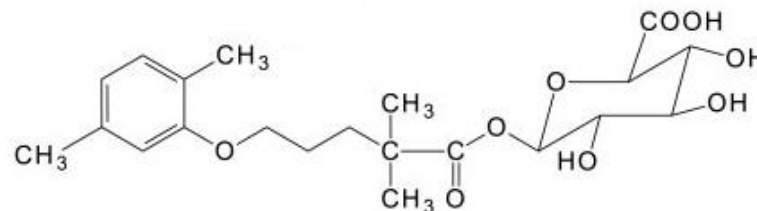
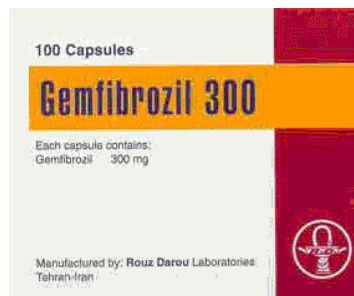
CYP3A4
CYP2C8 (> 80%)

Rabdomiólise
(quebra (lise) rápida de músculo esquelético (rabdomio) devido a lesão no tecido muscular)
Não há tratamento

“Medicamentos antiolesterol matam quatro pessoas em Espanha”



Gemfibrozil
(agonista PPAR α)
Tratamento da hiperlipidemia, hipertrigliceremia e prevenção de doenças cardiovasculares

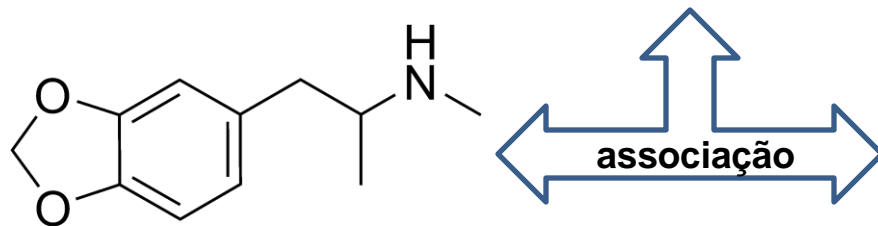
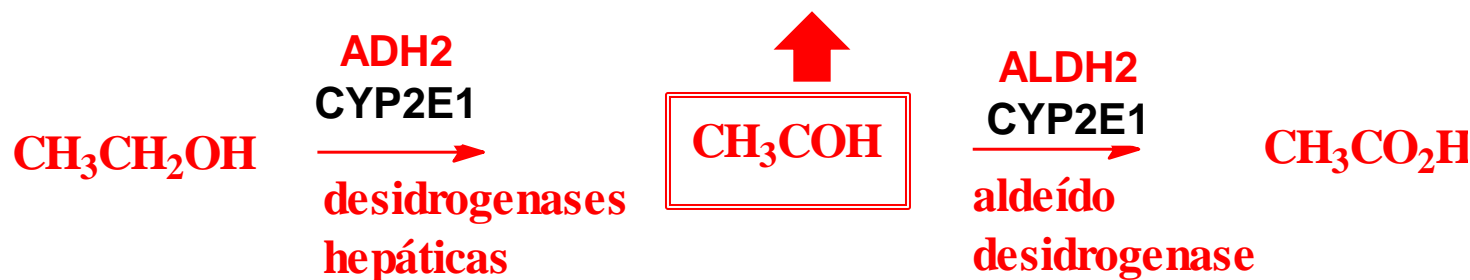


Gemfibrozil 1-O- β -glucuronide

Inibidor da CYP2C8 (metabólito glicuronado)

INTERAÇÕES ENTRE DROGAS

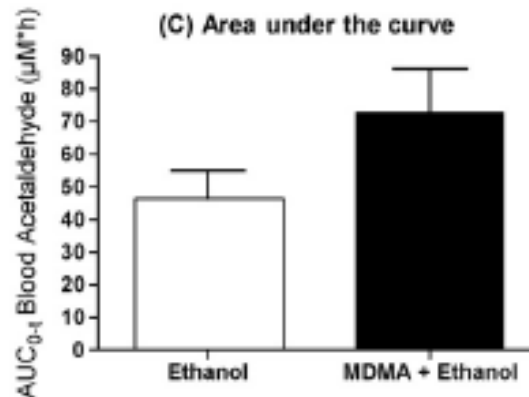
Taquicardia reflexa, hipotensão, palpitação, cefaleia, náuseas e vômitos



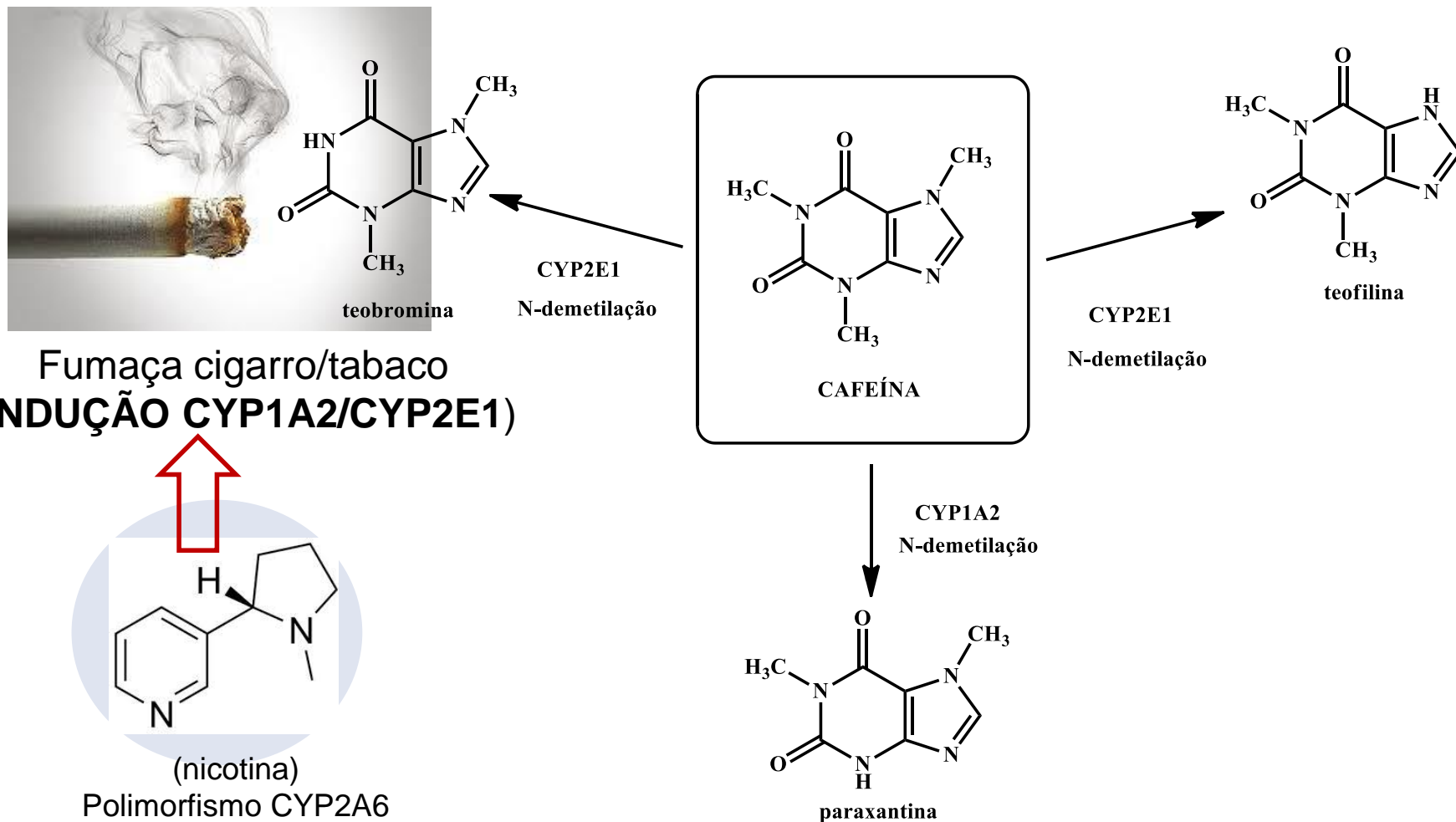
metilenedioximetanfetamina (MDMA, "ecstasy")

MDMA Inibe ALDH2 $\Rightarrow \uparrow [\text{CH}_3\text{COH}] \Rightarrow$
 Efeitos tóxicos \Rightarrow **ligação a bionucleófilos** \Rightarrow
carcinogenicidade, complicações hepáticas e neurológicas

diminuição da reabsorção da serotonina, dopamina e noradrenalina no cérebro \Rightarrow a família das anfetaminas \Rightarrow euforia \Rightarrow são neutóxicas



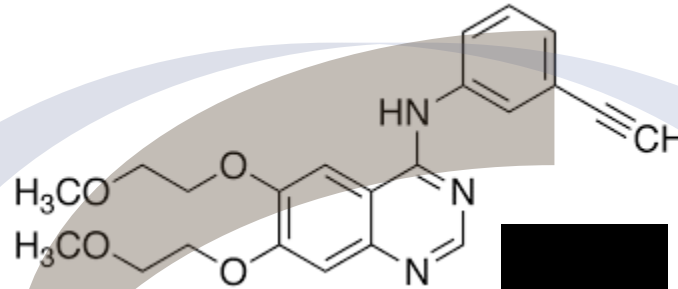
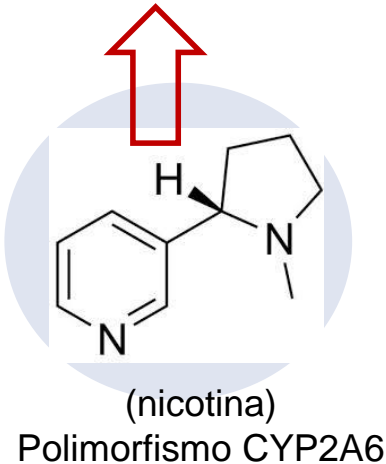
INTERAÇÕES ENTRE DROGAS & ALIMENTOS



INTERAÇÕES MEDICAMENTOSAS



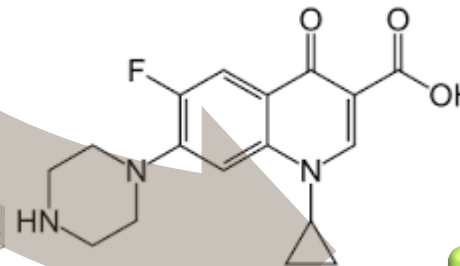
Fumaça cigarro
(INDUÇÃO CYP1A2)



erlotinibe
Tratamento do câncer de pulmão de células não pequenas & pâncreas metastásico



↓ C_{max} do erlotinibe



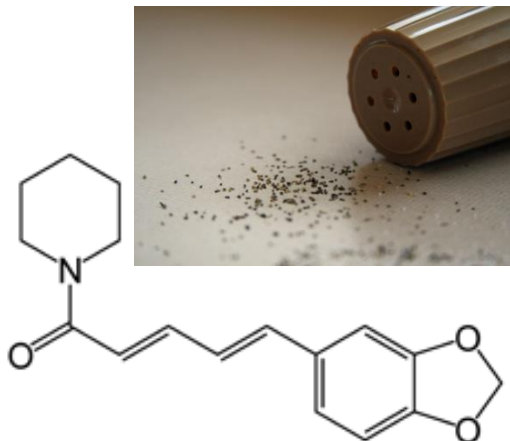
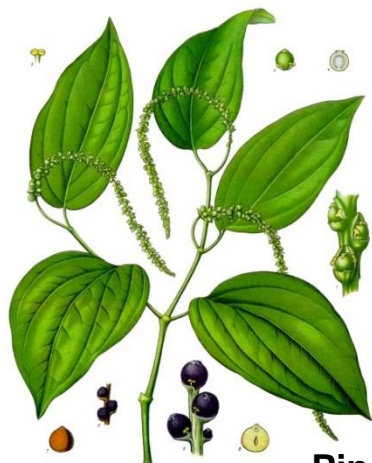
ciprofloxacino
Antimicrobiano (gram -)

↑ C_{max} do erlotinibe

(INIBIDOR CYP1A2)

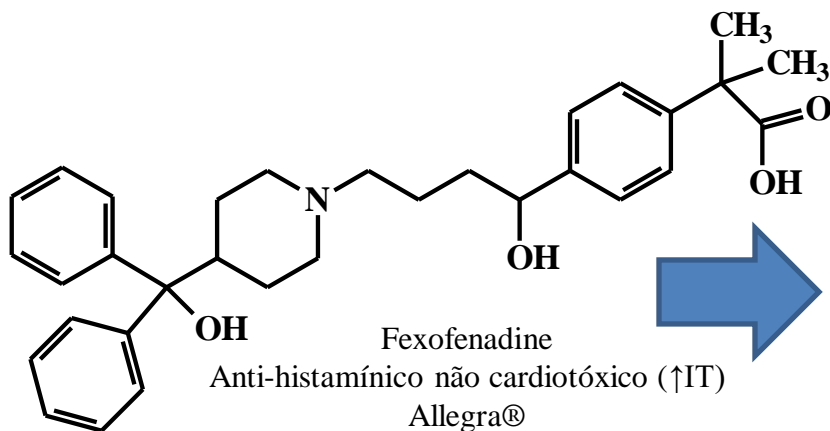
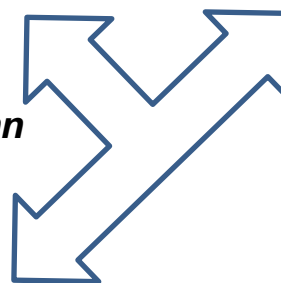
S. Peters *et al.* Cancer Treatment Reviews 40 (2014) 917–926

INTERAÇÕES MEDICAMENTOS & ALIMENTOS



Piperina (alcaloide) \Rightarrow *Piper nigrum* Linn

Aumenta concentração plasmática da fexofenadina \Rightarrow (Piperina) inibe P-gp (ptn transportadora e de excreção)



Biodisponibilidade oral = 33%
Baixa permeabilidade intestinal
Baixo metabolismo
Substrato da (P-glicoproteína) P-gp

INTERAÇÕES MEDICAMENTOS & ALIMENTOS



Erva de São João (*Hypericum perforatum*)
ou Hipericão

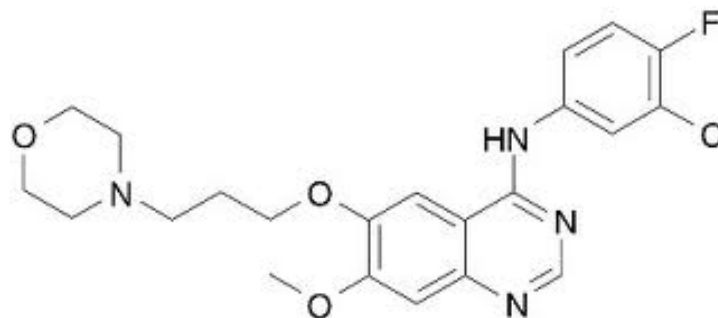


Indutor CYP3A4

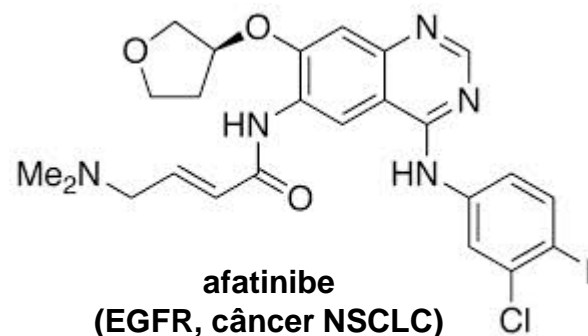
Indutor gp-P



↓ C_{max} **gefitinibe**
↓ C_{max} **afatinibe**



gefitinibe
(EGFR, câncer NSCLC)



afatinibe
(EGFR, câncer NSCLC)

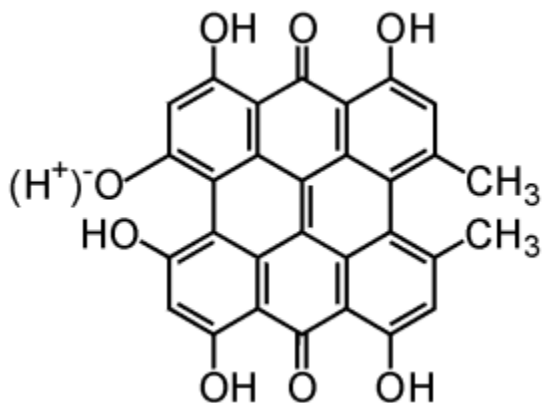
S. Peters *et al.* Cancer Treatment Reviews 40 (2014) 917–926

INTERAÇÕES MEDICAMENTOS & ALIMENTOS



Pode reduzir a eficácia de contraceptivos orais e produz reações adversas quando utilizado com inibidores da recaptação da serotonina (por exemplo paraxetina). ??????

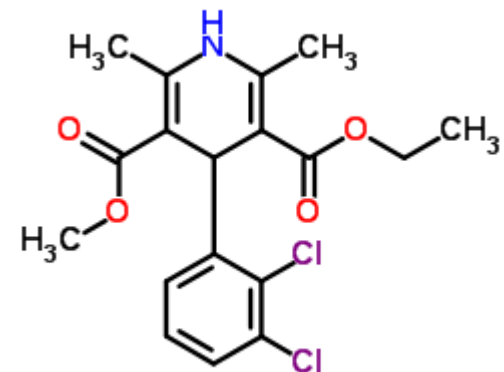
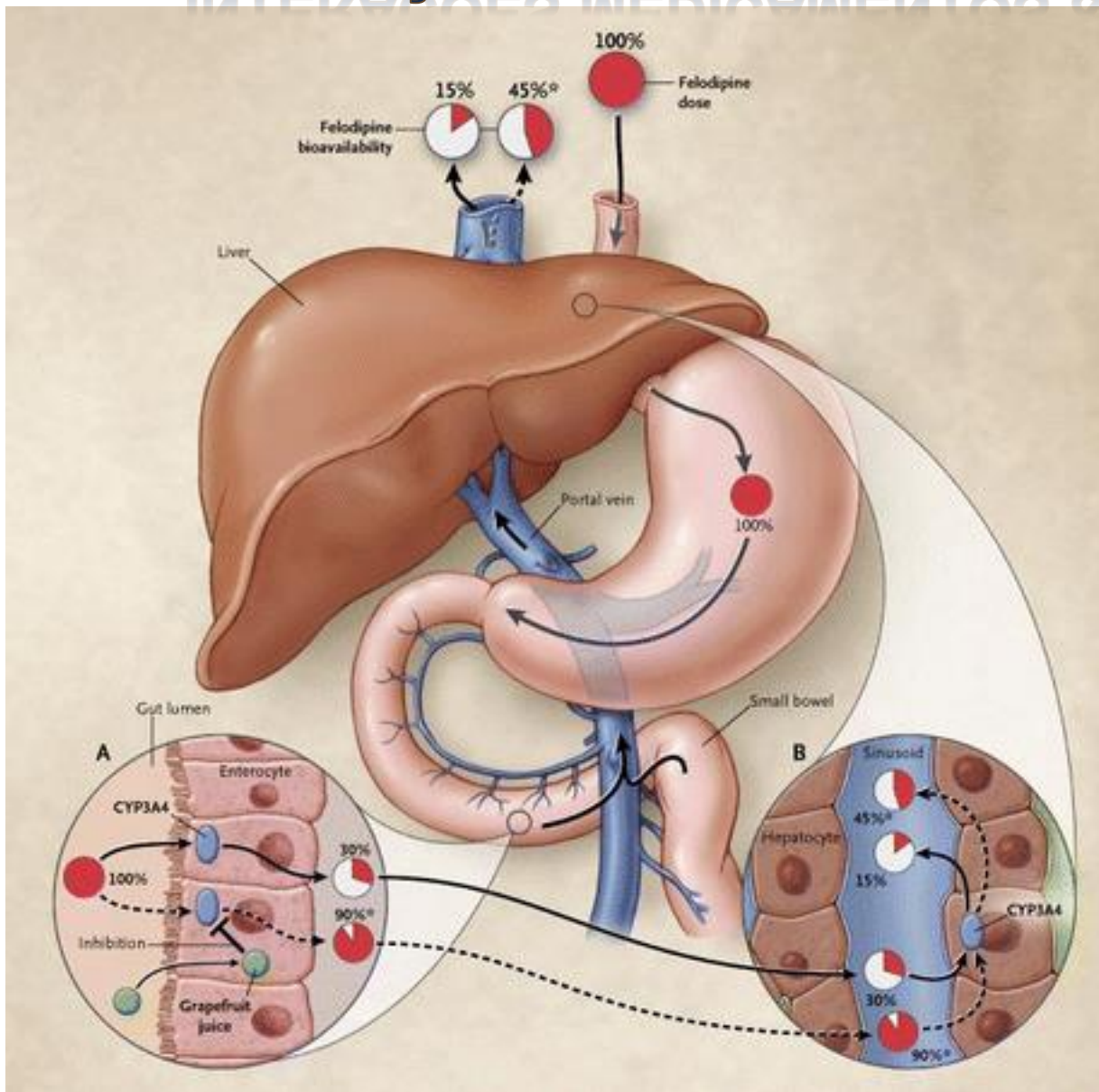
Erva de São João (*Hypericum perforatum*)
ou Hipericão



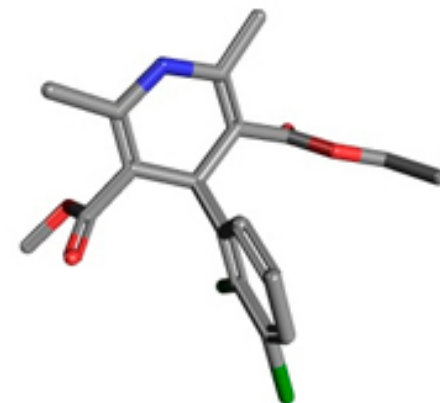
Princípio ativo: Hipericina

***Inibidor da MAO e COMT
Em ↑ dose: Fotosensibilização
Inibidor dopamina β-ibroxilase***

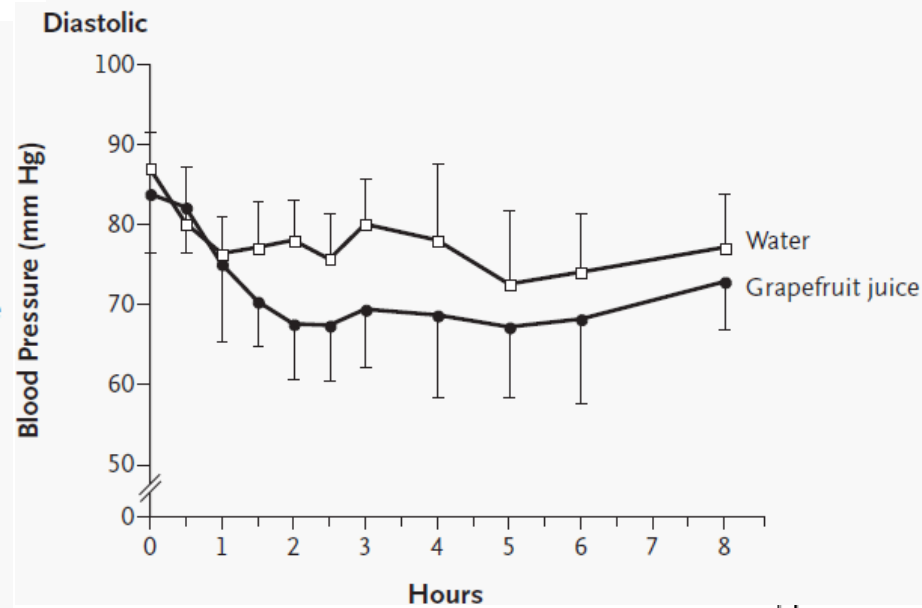
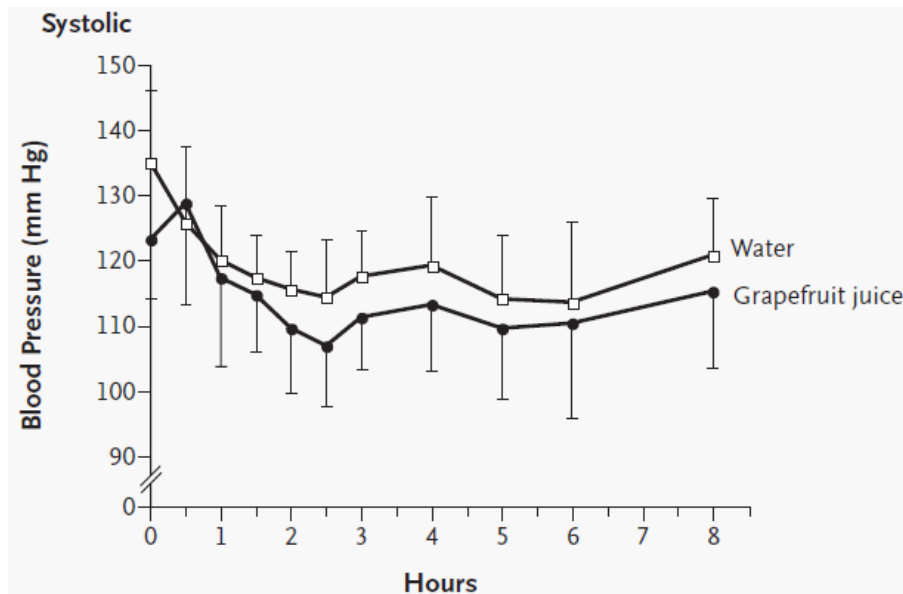
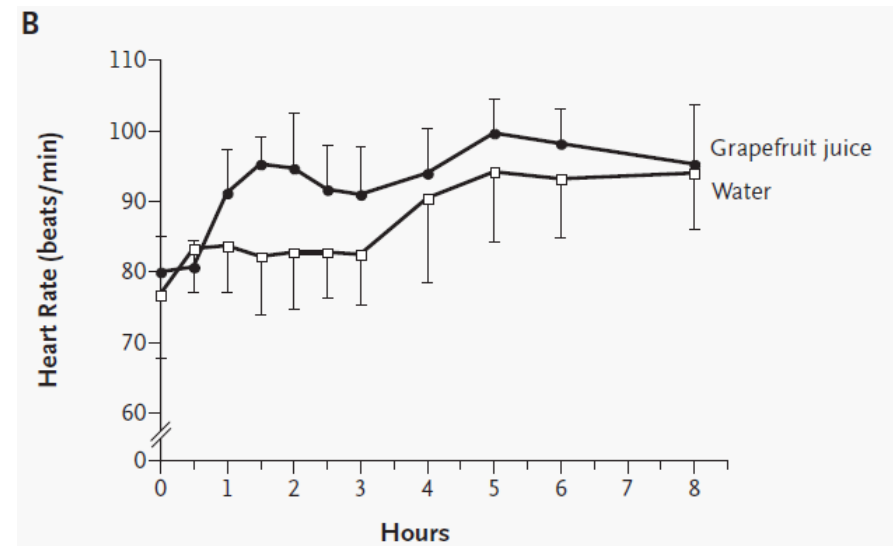
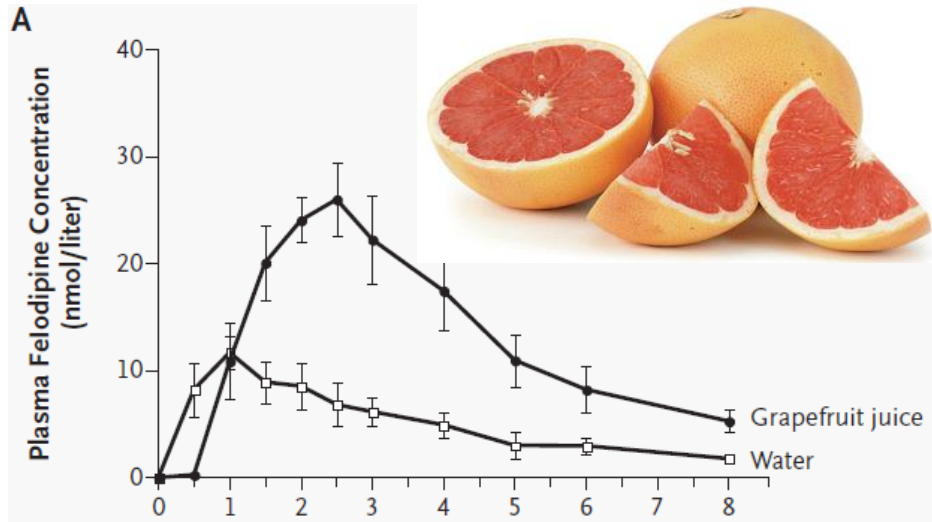
INTERAÇÕES MEDICAMENTOS & ALIMENTOS



felodipine

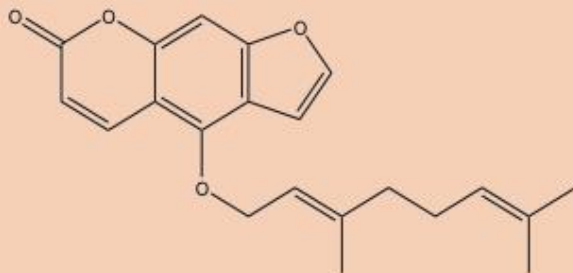


Consequences of the Inhibition of First-Pass Metabolism, as Exemplified by the Interaction between Felodipine and Grapefruit Juice.



THE CHEMISTRY OF A GRAPEFRUIT

INTERACTIONS WITH DRUGS



BERGAMOTTIN

Grapefruit, and grapefruit juice, is known to interact with a large number of drugs, usually resulting in adverse effects. These interactions are caused by a class of compounds called furanocoumarins, in particular the compounds bergamottin and dihydroxybergamottin.

These compounds inhibit some forms of an enzyme responsible for breaking down drugs in the body. As the prescribed dose of drugs takes into account how quickly the drug is broken down in the body, this can lead to higher concentrations of the drug in the bloodstream, which in turn can result in unpleasant side effects.



WHAT CAUSES A GRAPEFRUIT'S COLOUR?



LYCOPENE

The colour of pink and red grapefruits is caused by the compound lycopene. This is a compound composed entirely of carbon and hydrogen atoms. The compound absorbs all but the longest wavelengths of visible light, causing it to appear red.

Lycopene is also the compound responsible for the colouration of tomatoes. It is also used as a food colouring due to its strong colour and lack of toxicity.

Table 3. Fruit-drug interactions [Fragoso and Esparza 2013]

Fruit	Molecular target	Drug interactions
Grapefruit	inhibits CYP3A4, CYP1A2, MRP2, OATP-B and P-glycoprotein	calcium channel antagonist, central nervous system modulators, HMG-CoA reductase, immunosuppressants, antivirals, phosphodiesterases-5 inhibitor, antihistamines, antiarrhythmics and antibiotics
Sevilla orange	inhibits CYP3A4, P-glycoprotein, OATP-A, OATP-B	vinblastine, fexofenadine, glibenclémida, atenolol, ciprofloxacina, ciclosporina, celiprolol, levofloxacina and pravastatin
Tangerine	stimulates CYP3A4 activity and inhibits P-glycoprotein	nifedipine, digoxina
Grapes	inhibits CYP3A4 and CYP2E1	cyclosporine
Mango	inhibits CYP1A1, CYP1A2, CYP3A1, CYP2C6, CYP2E1, P-glycoprotein	midazolam, diclofenac, chlorzoxazone, verapamil
Apple	inhibits CYP1A1, OATP family	fexofenadine
Papaya	inhibits CYP3A4	not documented

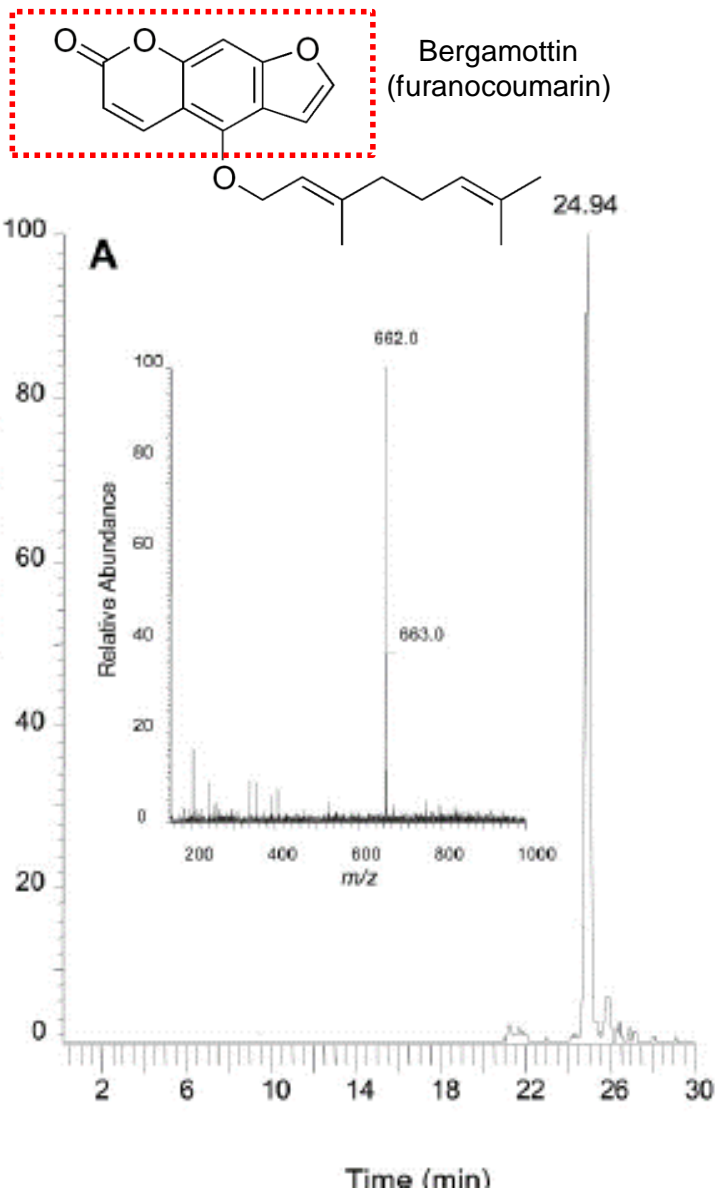
Table 4. Vegetable-drug interactions [Fragoso and Esparza 2013]

Fruit	Molecular target	Drug interactions
Broccoli	inhibits CYP1A1, CYP2B1/2, CYP3A4, CYP2E1, hGSTA1/2, MRP1, MRP2, BCRP, UDP-glucosyltransferases, dulfo-transferases, quinone reductases phenolsulfotransferases induces: UDPglucuronosyl-transferases, (UGTs), sulfotransferases (SULTs) and quinone reductase (QRs)	not documented
Spinach	possible inhibition of CYP1A2	heterocyclic aromatic amines
Tomato	inhibits CYP1A1, CYP1B1, UGP increases UGT and CYP2E1	diethylnitrosamine, N-methyl-N-nitrosourea and 1,2 dimethylhydrazine
Carrot	induces phenolsulfotransferases and ethoxycoumarin O-deethylase ECD inhibits CYP2E1	not documented
Red pepper	inhibits CYP1A2, CYP2A2, CYP3A1, CYP2C11, CYP2B1, CYP2B2, CYP2C6	in vitro and in vivo

INTERAÇÕES MEDICAMENTOSAS

LC-ESI-MS/MS analysis of BG-GS conjugates isolated from incubation mixtures with P450 3A5. Incubation conditions and extraction/analysis procedures were as described under Materials and Methods.

A) representative extracted ion chromatogram of the [MH]⁺ ion with an m/z of 662 eluting at 25 min. The inset shows the mass spectrum of the peak at 25 min. **B)** MS/MS pattern of the 662 ion eluting at 25 min showing the proposed structure of the conjugate in the inset.



Mensagem



Que degrau você já atingiu hoje?

Há três métodos para ganhar sabedoria: **primeiro, por reflexão, que é o mais nobre**; **segundo, por imitação, que é o mais fácil**; e **terceiro, por experiência, que é o mais amargo**.