

Metabolismo de Fármacos & Interação Medicamentosa

**XIII Escola de Verão em Química
Farmacêutica/Medicinal (XIII EVQF)**

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Metabolismo de Fármacos

- **Definição:** processos enzimaticamente catalisados capazes de produzir modificações estruturais na molécula do fármaco.
- **Importância:** Inativação dos fármacos; toxicidade; interações medicamentosas; ajuste das propriedades farmacocinéticas.
- **Classificação:** Reações de Fase 1 ou Biotransformação e Reações de Fase 2
- **Sistemas enzimáticos:** Enzimas microssomais hepáticas: Oxidases de função mista (MFO) ⇒ CYP 450 (hemoproteína oxidativa) e NADPH-citocromo c-redutase (flavoproteína); e enzimas não microssomais (eg. MAO, COMT, etc)
- **Sítios de Metabolização:** Fígado, pulmões, rins, trato gastrointestinal
- **Estudos do Metabolismo:** Estabelecer a cinética de formação e a estrutura dos metabólitos; Determinar a principal via de eliminação; Determinar os sítios moleculares metabolicamente vulneráveis e correlacioná-los com aqueles de natureza farmacofórica; Determinar a toxicidade dos metabólitos e correlacioná-la com a estrutura química; compreender possíveis interações medicamentosas; possibilitar o desenho de novos fármacos, etc.

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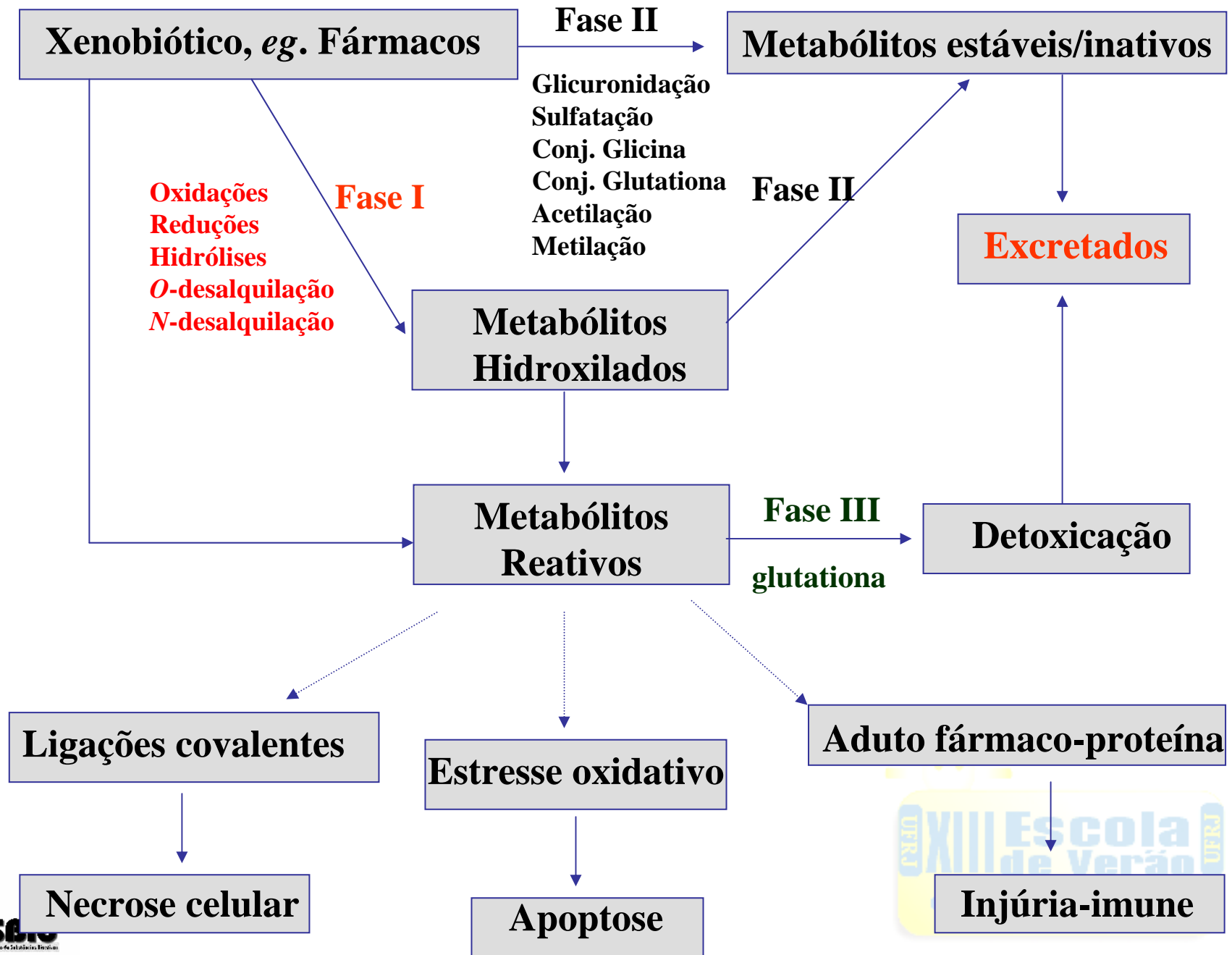
6-METABOLISMO & PLANEJAMENTO OU OTIMIZAÇÃO DE FÁRMACOS

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Metabolismo de Fármacos



CITOCROMO P450

There are at least 150 types of Cytochrome P450

(Number of human P450s estimated at 57, divided in 16 families)

- a.) They all catalyze a reaction: $RH + NADPH(\text{electron donor}) + O_2 \rightarrow ROH + NADP + H_2O$
- b.) They are all **monooxygenases**
- c) The O_2 is split, so one molecule of the oxygen goes into the substrate, and the other into H_2O
- d) the oxygen is carried on a “**Heme**”
- e) So that all Cytochrome P450's are heme proteins
- f) This is the same type of heme as in hemoglobin and myoglobin
- g) The only difference between the two heme's is that the heme in hemoglobin and myoglobin only carries oxygen. However, the heme in Cytochrome P450 can carry as well as split oxygen
- h) 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}
- i) Heme is the **prosthetic group** of the enzyme
- j) can also be called **mixed function oxidases** (MFO)

CITOCROMO P450

There are at least 150 types of Cytochrome P450

(Number of human P450s estimated at 57, divided in 16 families)

• **57 genes de CYP450 humano → 7 são responsáveis pelo metabolismo >90% do metabolismo de todos os fármacos [CYP1A2, 2C9, 2C8, 2C19, 2D6, 2E1, 3A4.]**

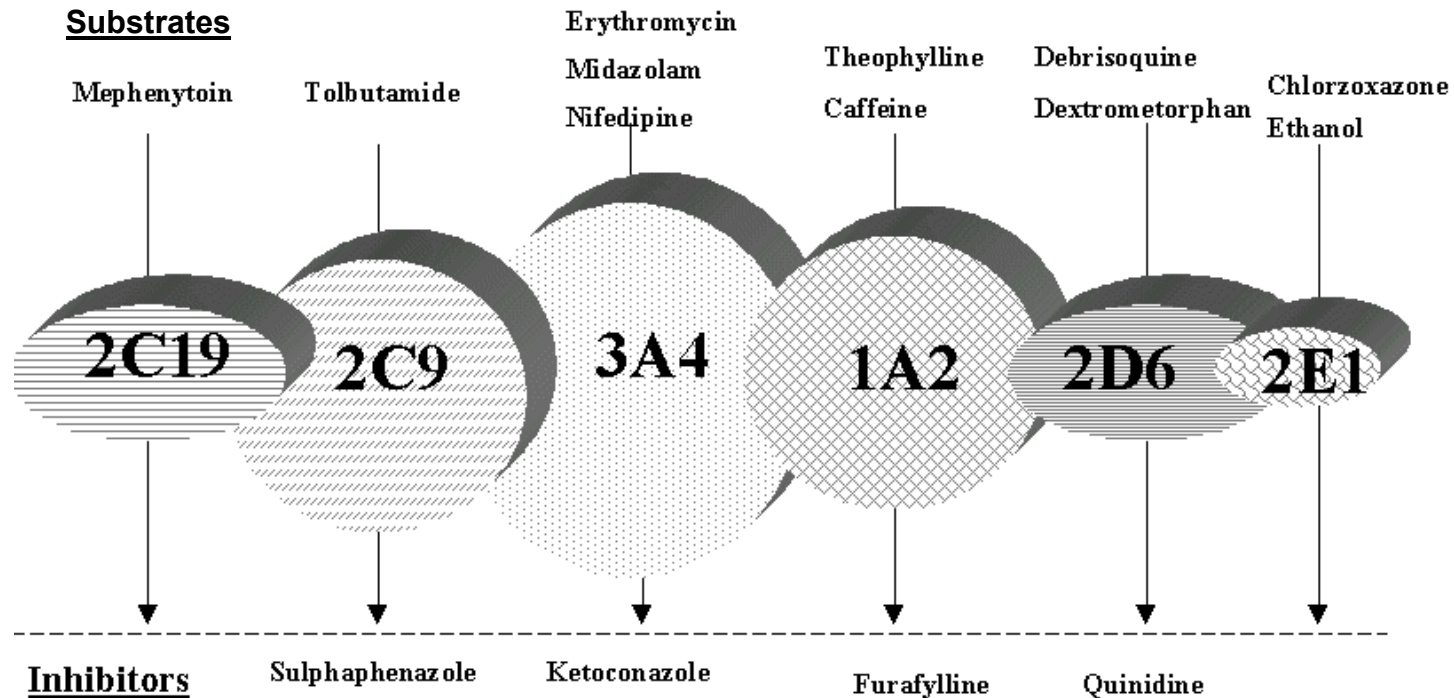
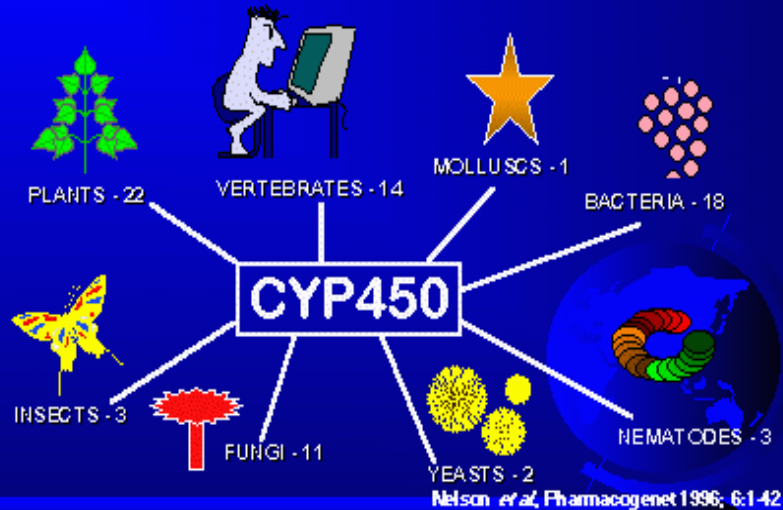


Figure 1. Schematic presentation of human CYP450 enzymes with model substrates and selective inhibitors (Breimer 1994)

[\[www.eurosis.org/.../Abstractoral/breimer.html\]](http://www.eurosis.org/.../Abstractoral/breimer.html)

CITOCROMO P450

Number of CYP450 Families



CYP450 Nomenclature

CYP450 SUPERFAMILY

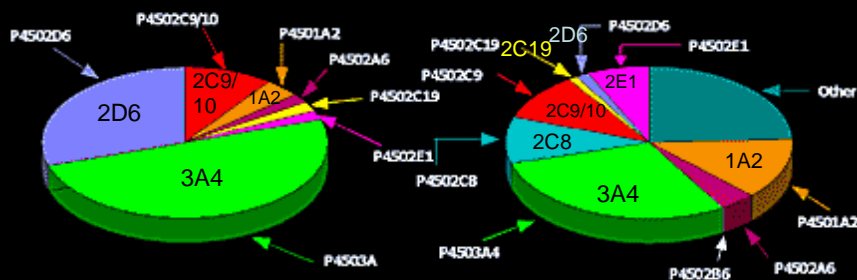
- * **FAMILIES** - CYP plus arabic numeral (>40% homology of amino acid sequence; eg CYP1)
- * **SUBFAMILY** - additional arabic letter & numeral (>55% homology of amino acid sequence; eg CYP1A2)
- * **Italics** for gene (*CYP2D6*) and normal (*CYP2D6*) for enzyme

Drug Oxidation — Major Route of Drug Metabolism

Family of Enzymes (CYPs) in Liver

Proportion of Pharmaceuticals Metabolized by Individual Cytochrome P450's

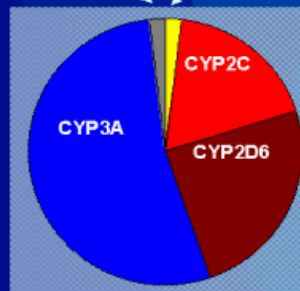
Major P450 Content of Human Liver



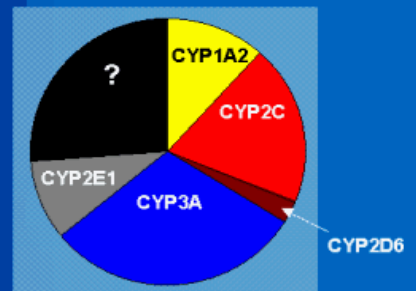
CYP450

www.fda.gov/cder/drug/drugReaction

Relative Importance of P450s in Drug Metabolism

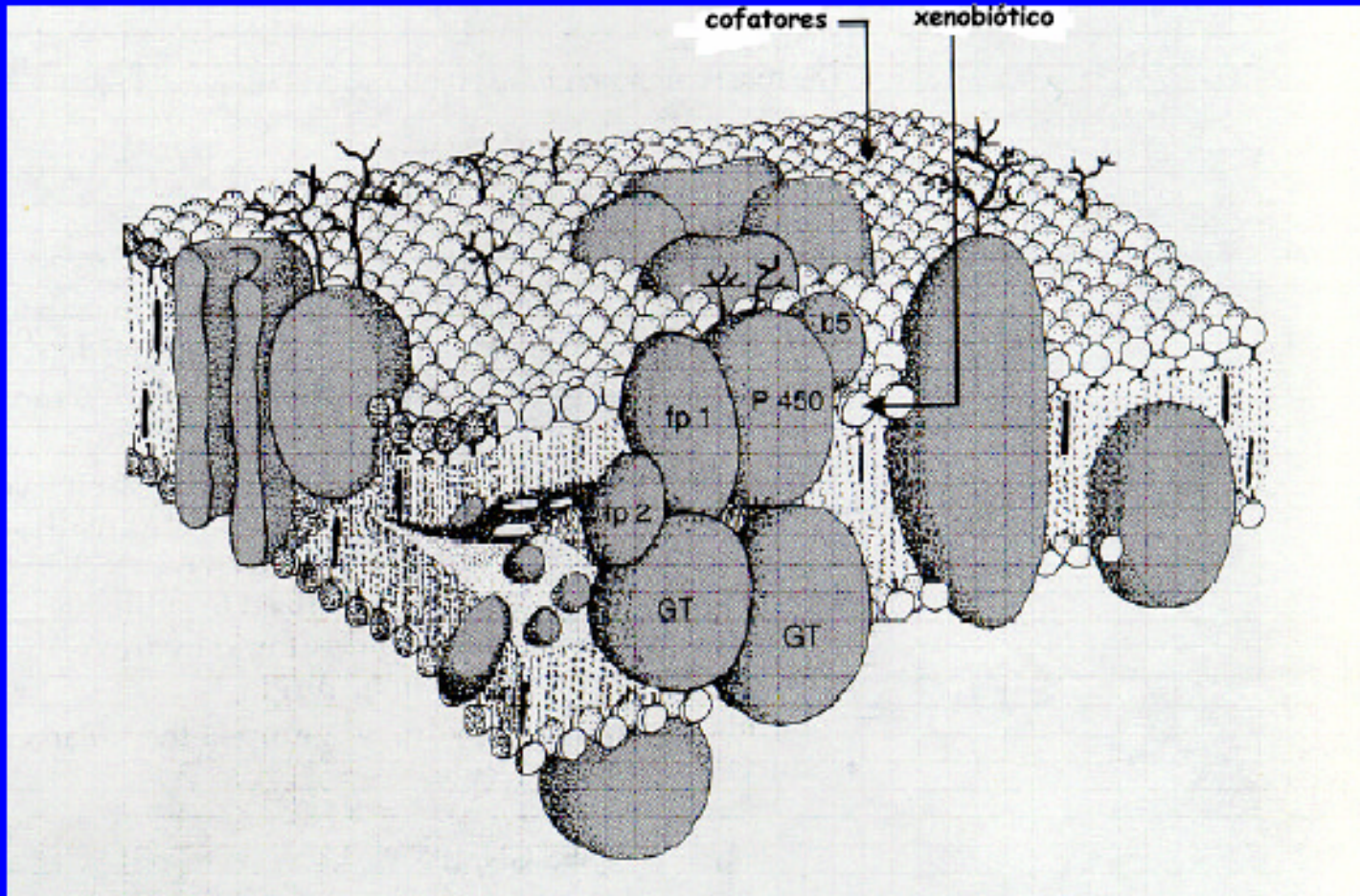


Relative Quantities of P450s in Liver



CITOCROMO P450

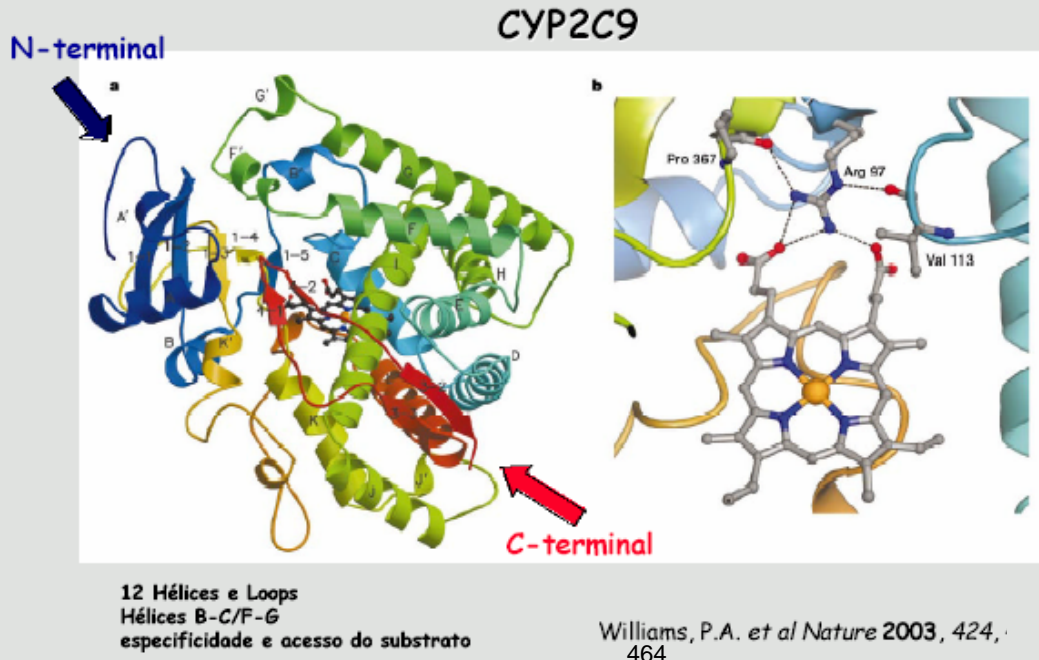
O complexo Citocromo P₄₅₀



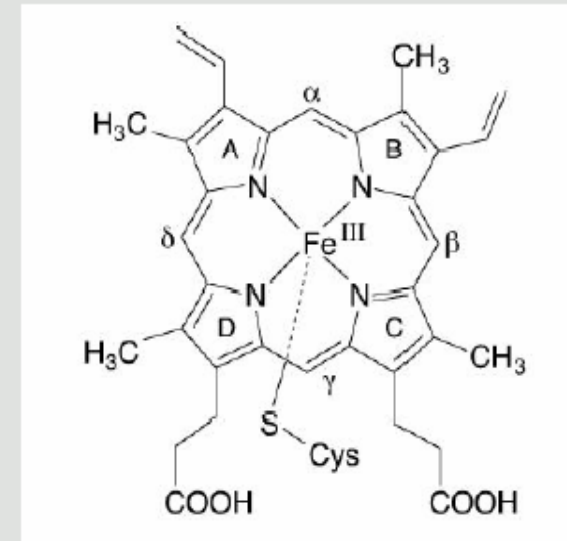
Localização do sistema de uma oxidase de função mista na membrana do retículo endoplasmático liso da célula

CITOCROMO P450

A estrutura tridimensional do citocromo P₄₅₀



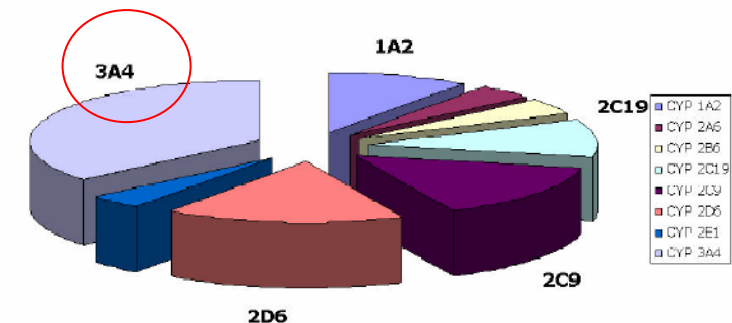
O núcleo HEME do citocromo P₄₅₀



Cisteinato-Fe(III) protoporfina IX

As isoformas da CYP450

Distribuição das isoformas de CYP em seres humanos



Nomenclatura do Citocromo P450

Exemplo CYP 2C9

CYP=citocromo P450

2= família genética (<40% de similaridade Na sequência de aa).

C= Subfamília genética (<60% de similaridade Na sequência de aa).

9= gem específico (localização)

CYP 3A4

Isoforma mais abundante no Fígado

Presente na Parede Intestinal

Diversidade de Substratos: ciclosporina, celecoxib, diltiazem, nifedipina, verapamil, teofilina, lovastatina, indinavir, etc.

Reações de Hidroxilação e N, O, S-dealquilação

Inibidores: cetoconazol, diltiazem, cimetidina, eritromicina, celecoxib, **narangenina**

Indutores: carbamazepina, rifampicina,

Ritonavir

Atividade Aumentada durante Gravidez

Mínimo efeito estérico.

Enzima promíscua: Vários substratos diferentes classes e natureza química



CITOCROMO P450

Cytochrome P450 2D6

- Absent in 7% of Caucasians, 1–2% non-Caucasians
- Hyperactive in up to 30% of East Africans
- Catalyzes primary metabolism of:
 - Codeine
 - Many β -blockers
 - Many tricyclic antidepressants
- Inhibited by:
 - Fluoxetine
 - Haloperidol
 - Paroxetine
 - Quinidine

Akiliu E et al. *J Pharmacol Exp Ther* 1996;278(1):441–446

Cytochrome P450 2C19

- Absent in 20–30% of Asians, 3–5% Caucasians
- Primary metabolism of:
 - Diazepam
 - Phenytoin
 - Omeprazole
- Inhibited by:
 - Omeprazole
 - Isoniazid
 - Ketoconazole

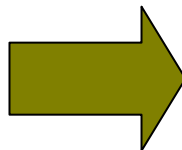
Cytochrome P450 2C9

- Absent in 1% Caucasians and African-Americans
- Primary metabolism of:
 - Most NSAIDs (including COX-2)
 - S-warfarin (the active form)
 - Phenytoin
- Inhibited by:
 - Fluconazole

Cytochrome P450 1A2

- Induced by smoking tobacco
- Catalyzes primary metabolism of:
 - Theophylline
 - Imipramine
 - Propranolol
 - Clozapine
- Inhibited by:
 - Many fluoroquinolone antibiotics
 - Fluvoxamine
 - Cimetidine

CYP 2E1



XENOBIOTIC-INDUCED DISEASES

etanol, 1,3-butadieno, acetaldeído, acetaminofeno, acrilamida, anilina, benzeno, tetracloreto de carbono, etil carbamato, cloreto de etileno, etileno glicol, cloreto de vinila, nitrosaminas

CITOCROMO P450 EXTRA-HEPÁTICO

Table 2
Human P450 orphans

| P450 | Reported expression site | Possible substrate | Heterologous expression |
|------|---|--------------------|--|
| 2A7 | (Liver) | | |
| 2S1 | Trachea, lung, stomach small intestine, spleen, skin, colon | Retinoic acid | <i>Escherichia coli</i> , CHO cells, baculovirus |
| 2U1 | Thymus, heart, brain (cerebellum), spleen, prostate | Arachidonic acid | Baculovirus |
| 2W1 | Prostate, pancreas, placenta, lung, colon, small intestine | | — |
| 3A43 | Liver, testis | | <i>E. coli</i> |
| 4A22 | (Kidney? Liver?) | | — |
| 4F11 | Liver, kidney, heart, skeletal muscle, brain | Erythromycin | <i>Saccharomyces cerevisiae</i> |
| 4F22 | | | — |
| 4V2 | Retina, cornea, lymphocytes | | — |
| 4X1 | Brain, trachea, aorta, pancreas, lung, kidney, prostate | | — |
| 4Z1 | Breast, breast carcinoma | | — |
| 20A1 | | | — |
| 27C1 | | | — |

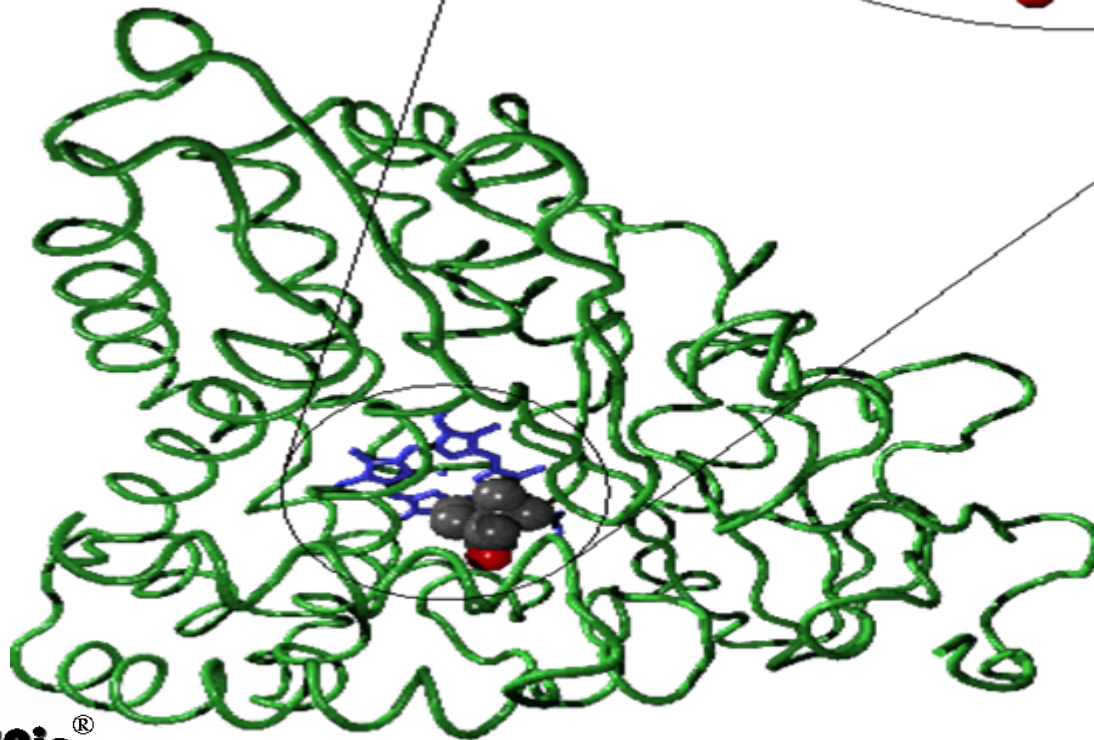
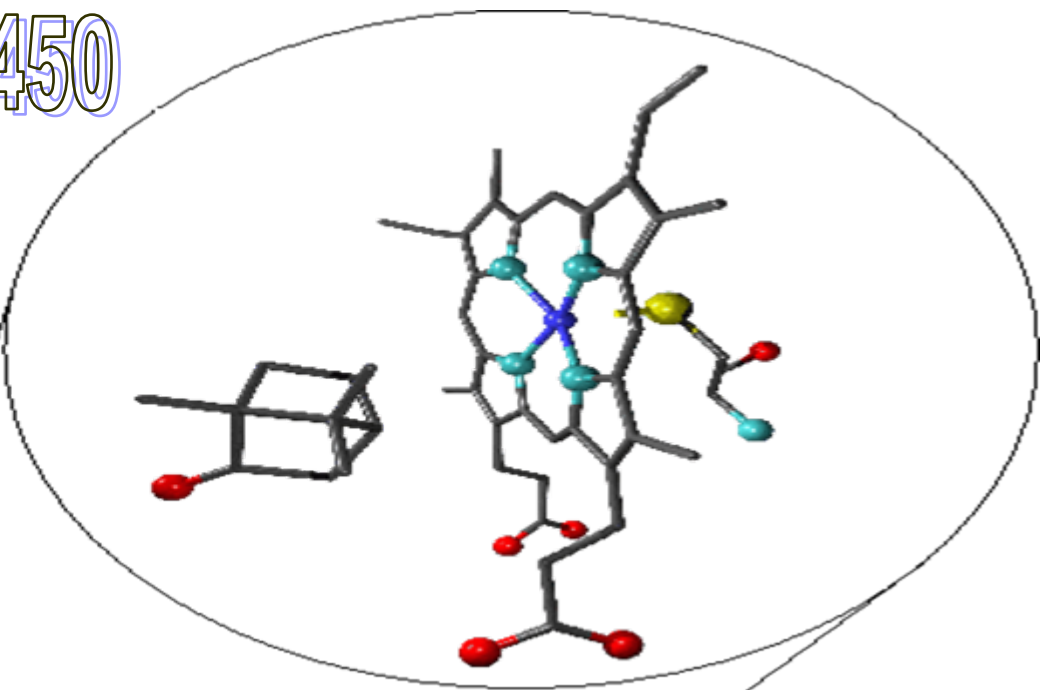
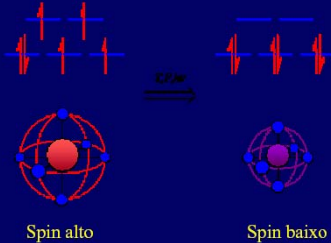
Guengerich, F P et al. *Biochem. Biophysical Res. Commun.* (2005) 338: 465-469

CITOCROMO P450

O sistema citocromo P₄₅₀ - maiores detalhes

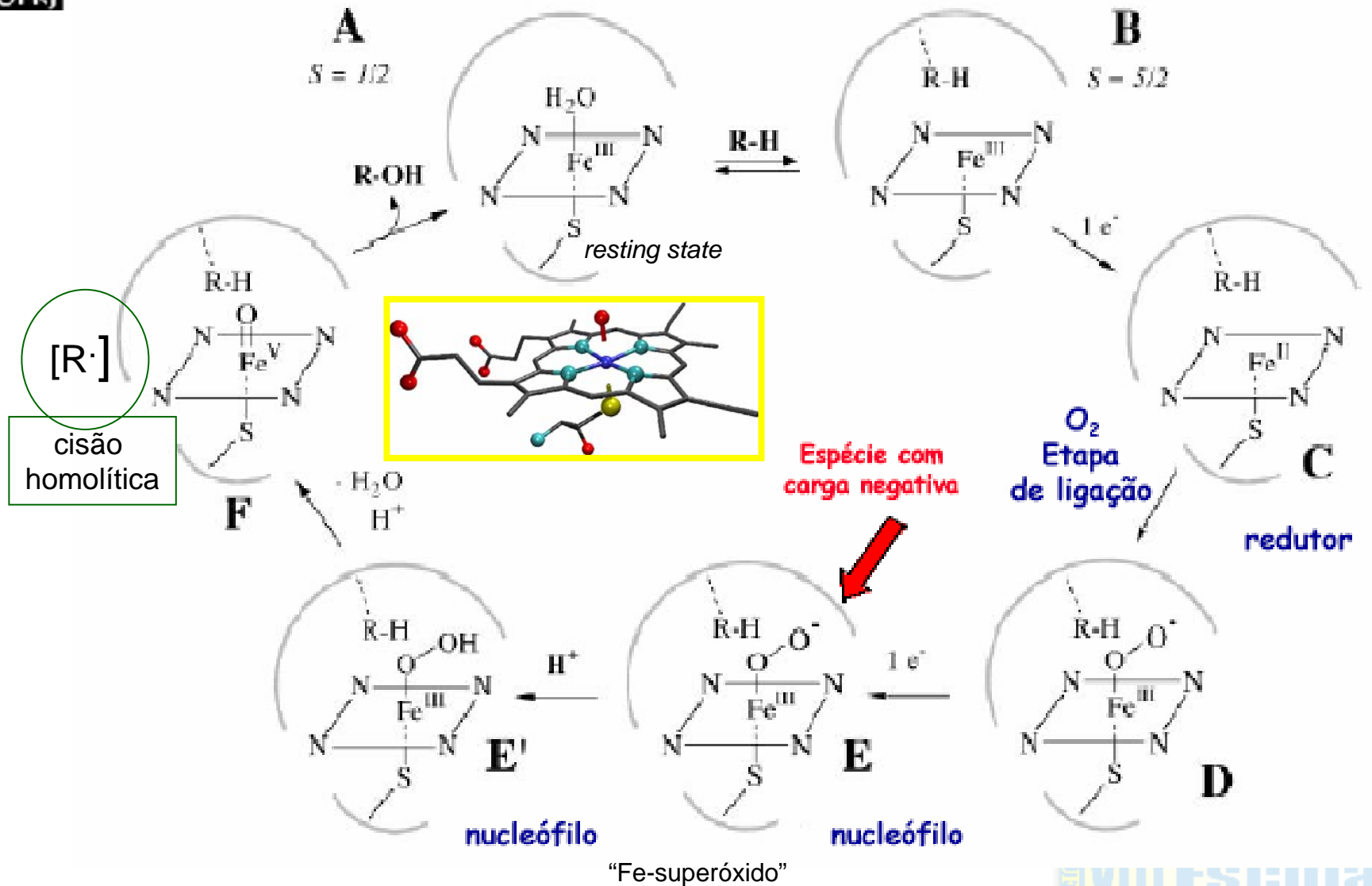
Microsomas do fígado

Os estados de spin do Ferro II - configuração [Ar]d⁶



"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.**" -

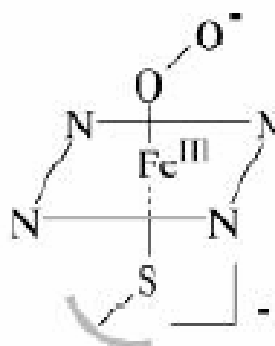
O processo de oxidação catalisado pelo sistema CYP



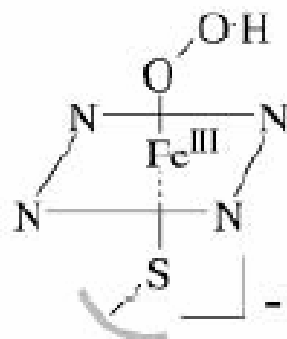
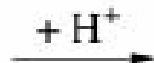
Ciclo catalítico

A espécie reativa

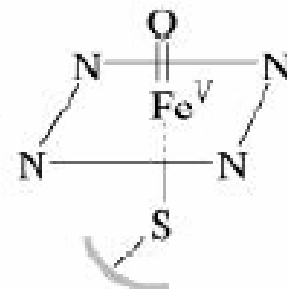
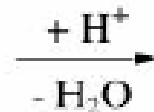
Espécie reativa



Ferro(III)-peroxo
Super-nucleófilo



Ferro(III)-hydroperoxo
nucleófilo

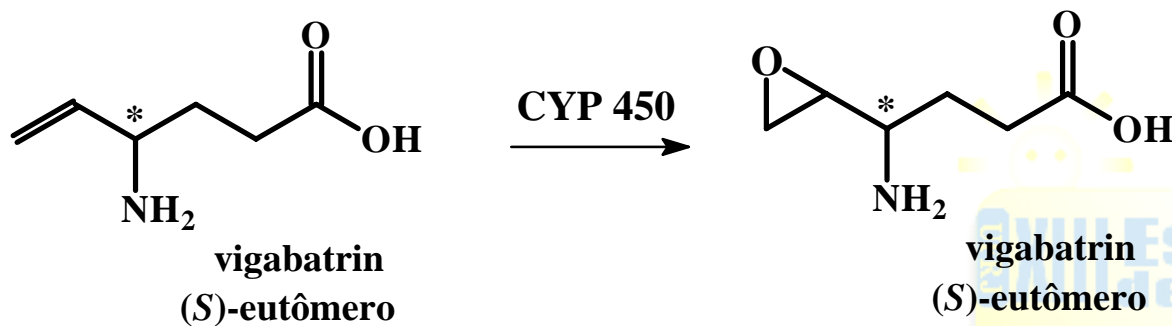
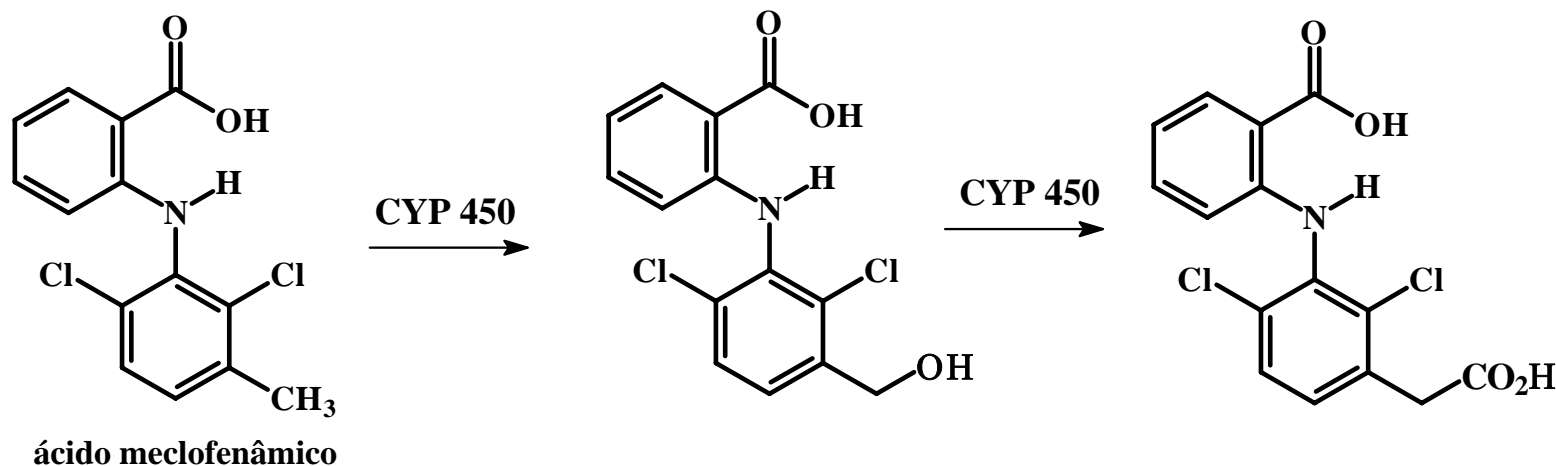


Ferro(V)-roxo
eletrófilo

Metabolismo de Fármacos: FASE I

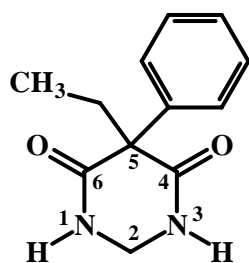
OXIDAÇÕES CATALISADAS PELO CYP450:

HIDROXILAÇÕES (AROMÁTICAS, ALIFÁTICAS, **BENZÍLICAS**, ALÍLICAS, C- α -HETEÓÁTOMO); DESALQUILAÇÃO (N,O,S); HETEROÁTOMO (N, S, P); **EPOXIDAÇÕES**.



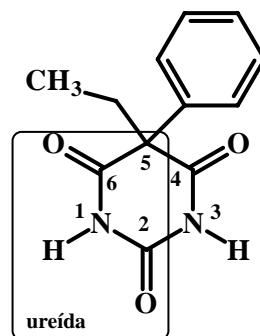
Metabolismo de Fármacos: FASE I

OXIDAÇÕES CATALISADAS PELO CYP450:
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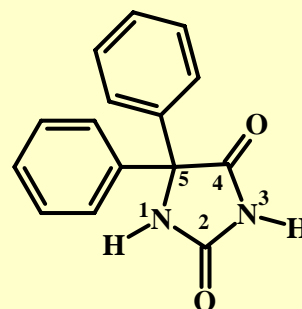
primidona
 <<<<Tóxico
 <<<Potente

CYP450
 Fase 1



fenobarbital

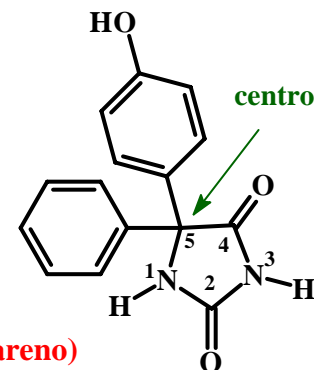
Protótipo



fenitoína
 Dilantin®, 1938

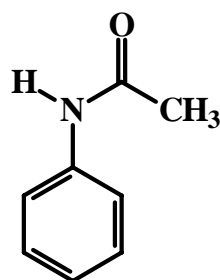
Fase I

CYP 450
 (óxido de areno)



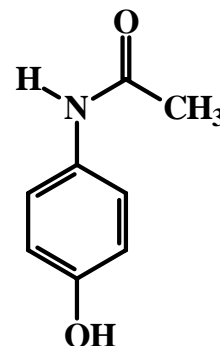
metabólito inativo

Enantiômeros com perfil farmacocinético distintos



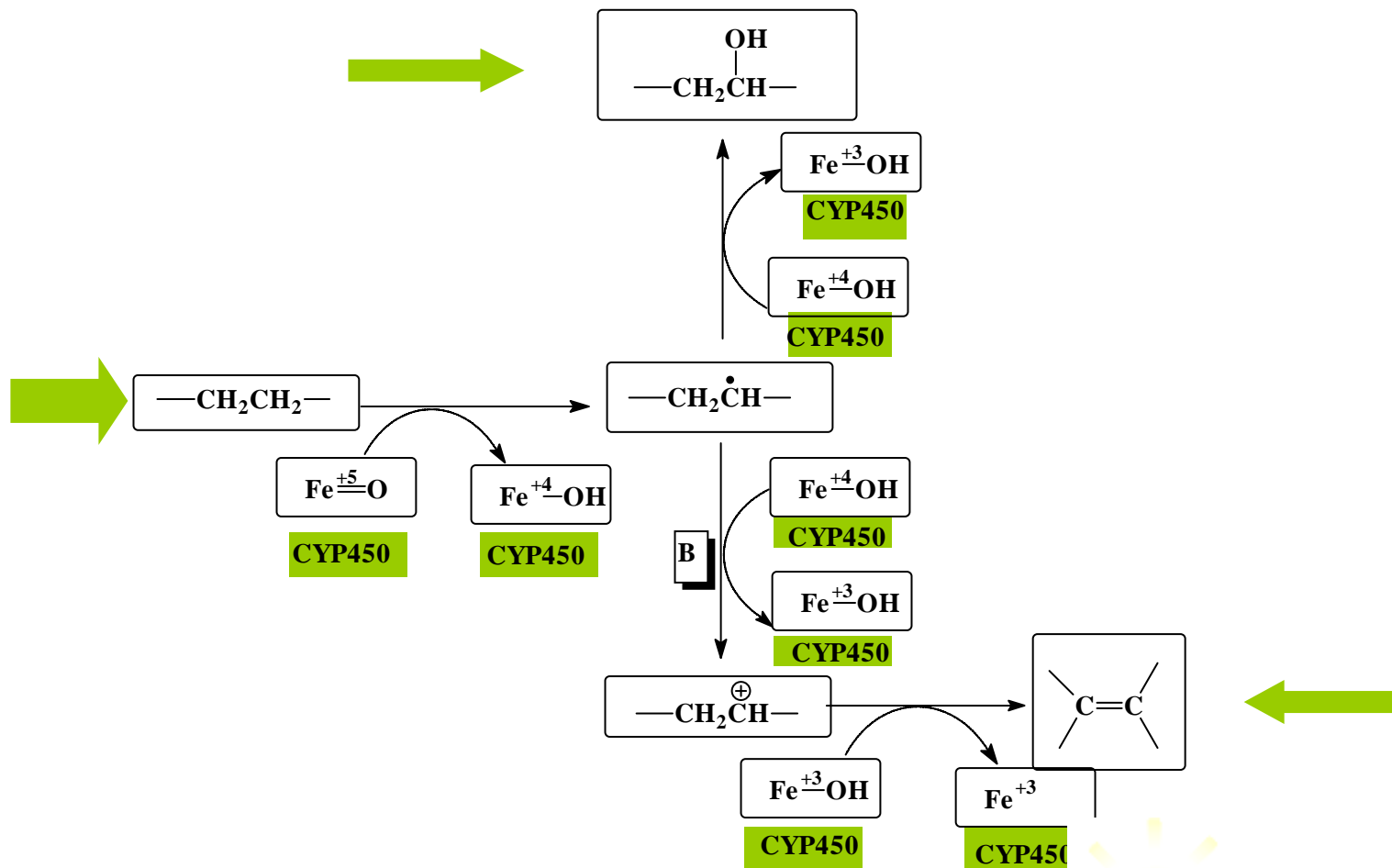
acetanilida

CYP450



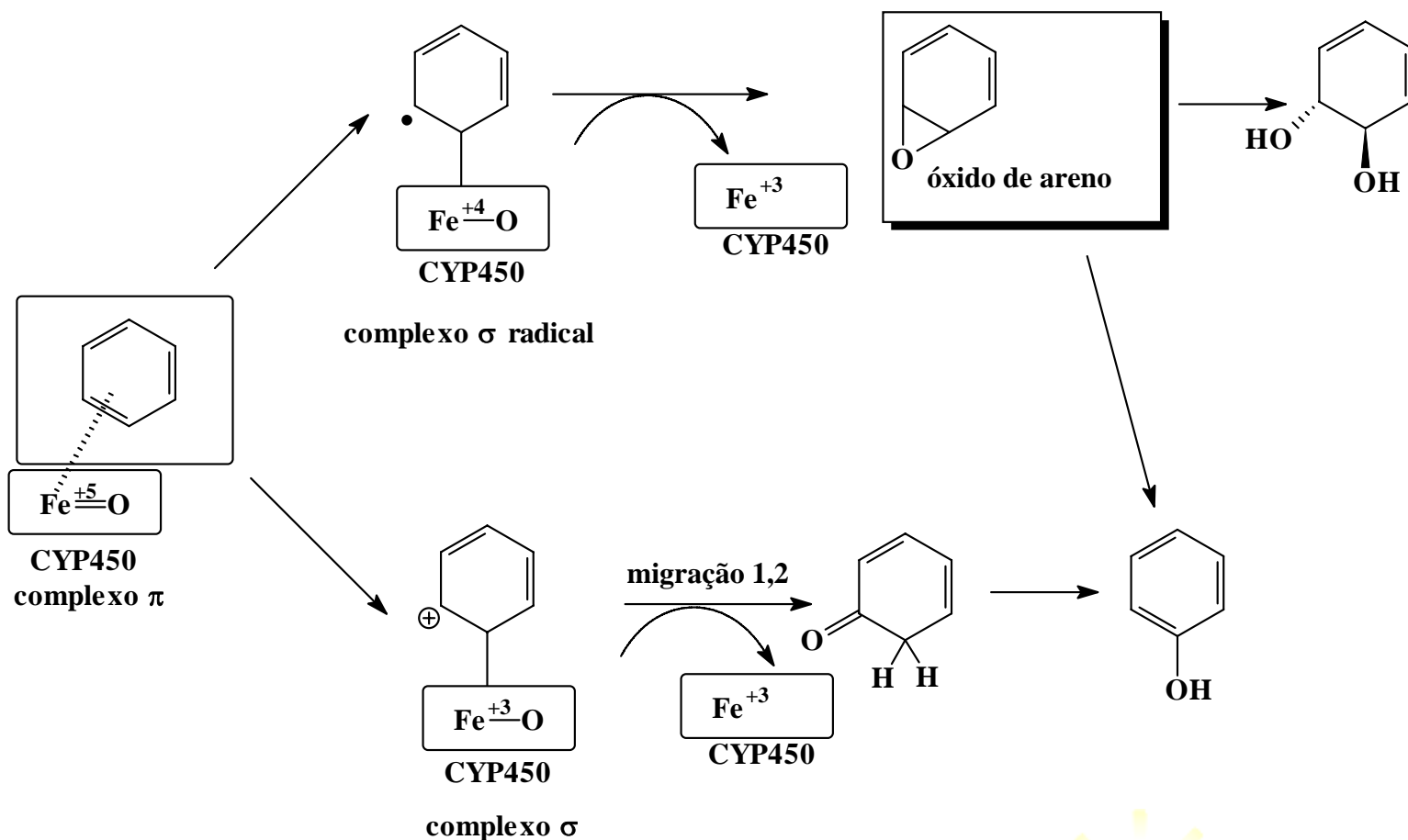
paracetamol

Mecanismo de Oxidação: CYP450



Mecanismo de hidroxilação e desidrogenação de alcanos catalisada pelo CYP 450

Mecanismo de Oxidação: CYP450



Mecanismo de oxidação aromática catalisada pelo CYP

Metabolismo de Fármacos: FASE I

OXIDAÇÕES CATALISADAS PELO CYP450:

HIDROXILAÇÕES (**AROMÁTICAS**, ALIFÁTICAS, BENZÍLICAS, ALÍLICAS, **C- α -HETEÓÁTOMO**); DESALQUILAÇÃO (N,O,S); HETEROÓTOMO (N, S, P); EPOXIDAÇÕES.

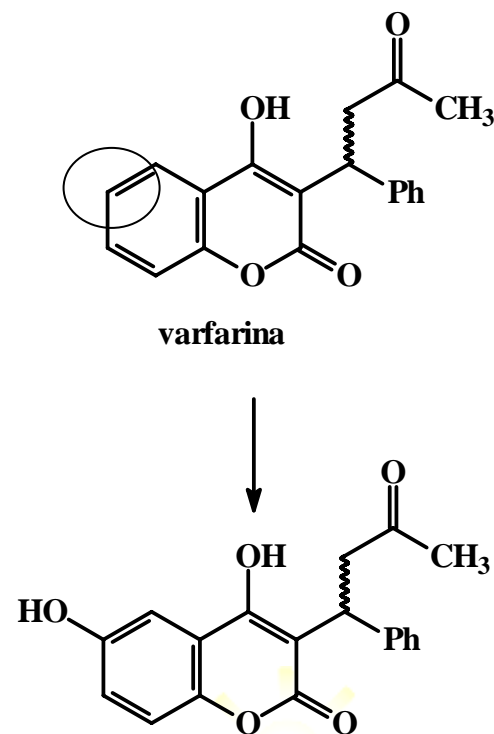
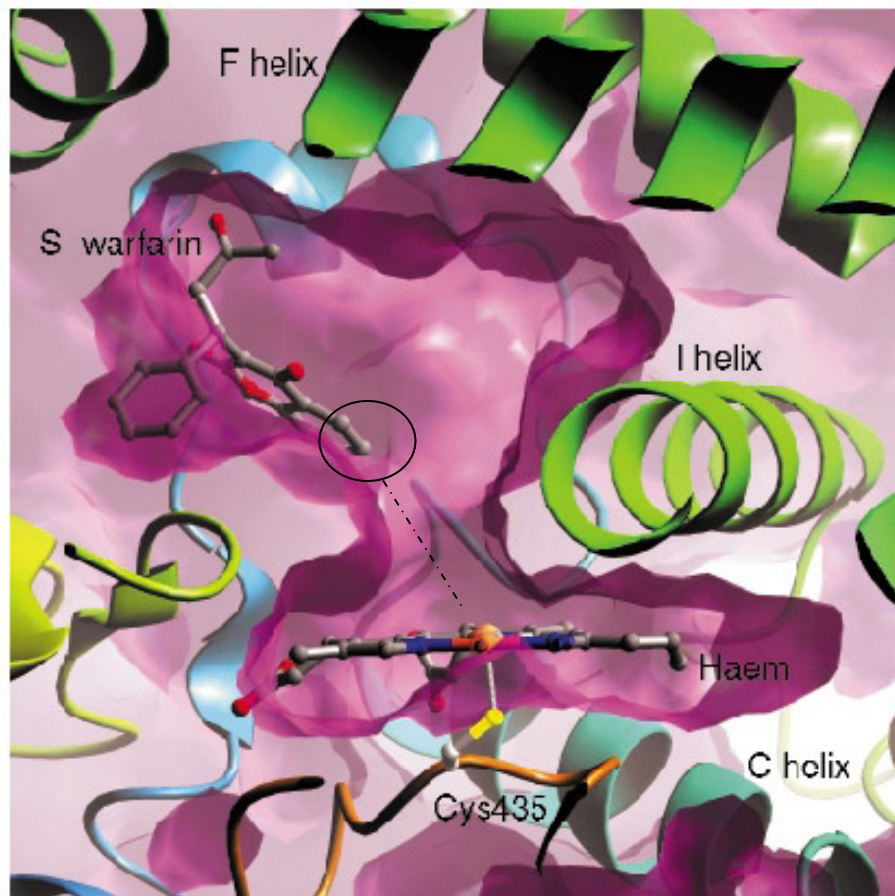
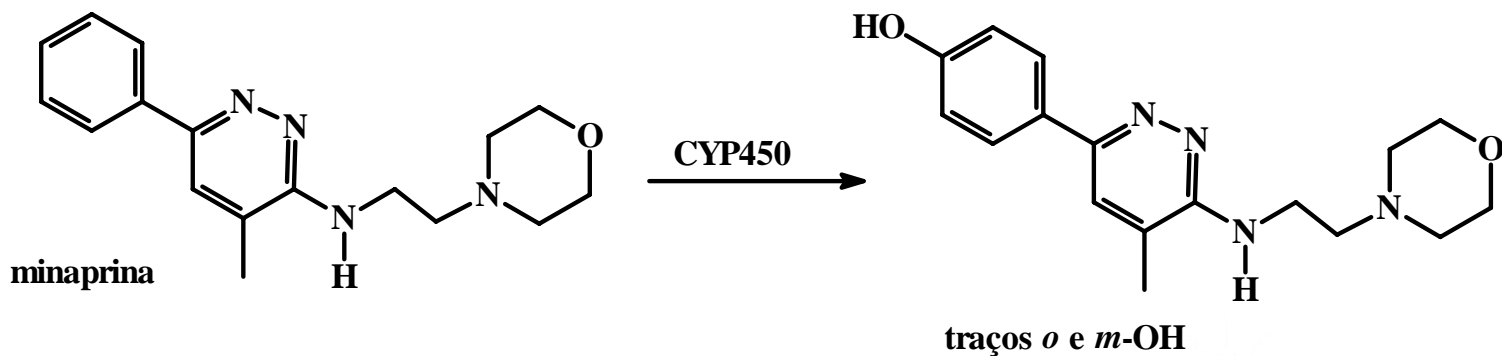
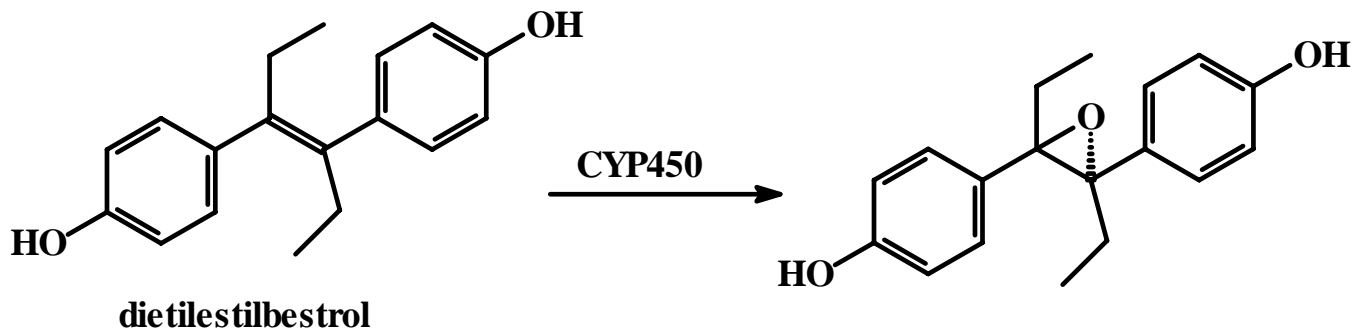


Fig. 27: The binding site of S-warfarin within the active site of 2C9 leaves the haem, shown edge on in the figure, accessible to other CYP450 compounds [www.esrf.fr/.../Highlights/2003/MX/MX06].

Metabolismo de Fármacos: FASE I

OXIDAÇÕES CATALISADAS PELO CYP450:

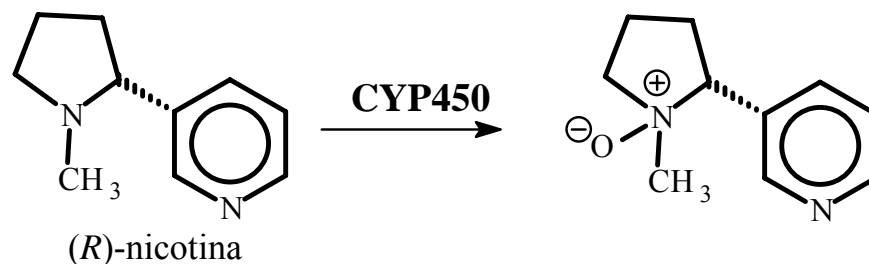
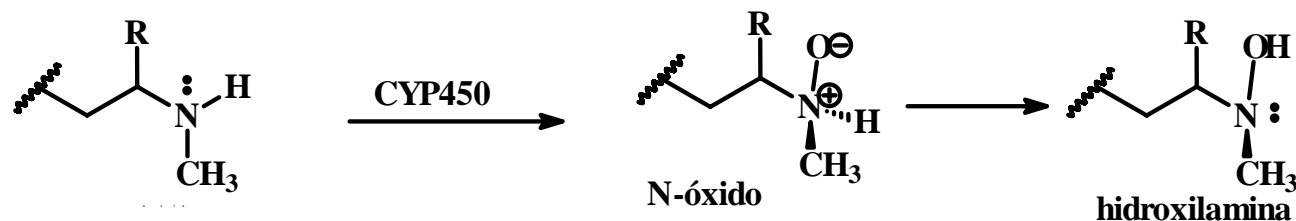
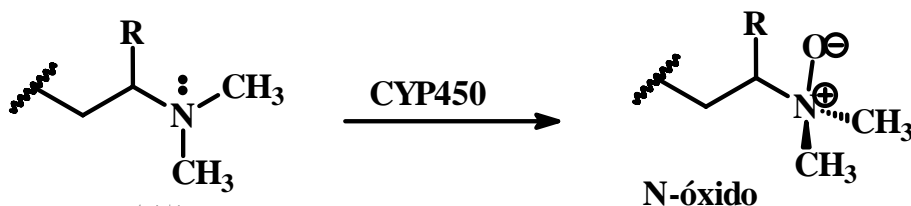
HIDROXILAÇÕES (**AROMÁTICAS**, ALIFÁTICAS, BENZÍLICAS, ALÍLICAS, **C- α -HETEÓÁTOMO**); DESALQUILAÇÃO (N,O,S); HETEROÁTOMO (N, S, P); EPOXIDAÇÕES.



Metabolismo de Fármacos: FASE I

OXIDAÇÕES CATALISADAS PELO CYP450:

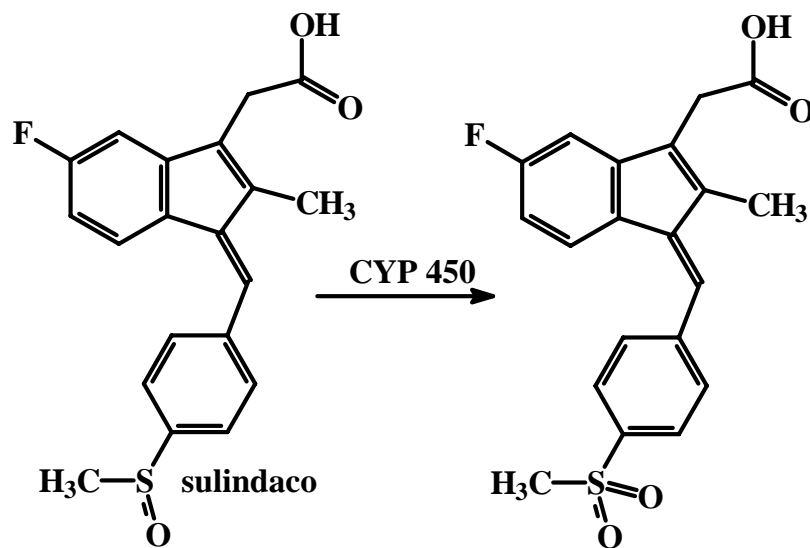
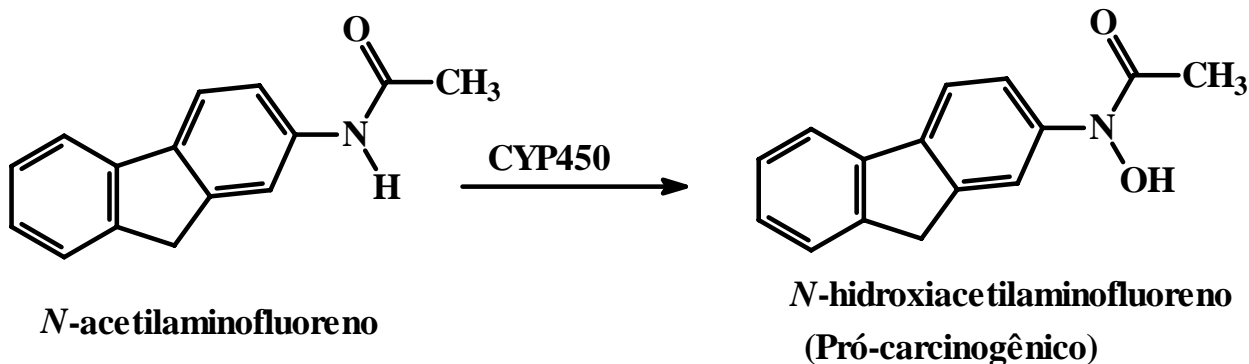
HIDROXILAÇÕES (AROMÁTICAS, ALIFÁTICAS, BENZÍLICAS, ALÍLICAS, C- α -HETEÓÁTOMO); DESALQUILAÇÃO (N,O,S); **HETEROÁTOMO** (N, S, P); EPOXIDAÇÕES.



Metabolismo de Fármacos: FASE I

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Metabolismo de Fármacos: FASE I

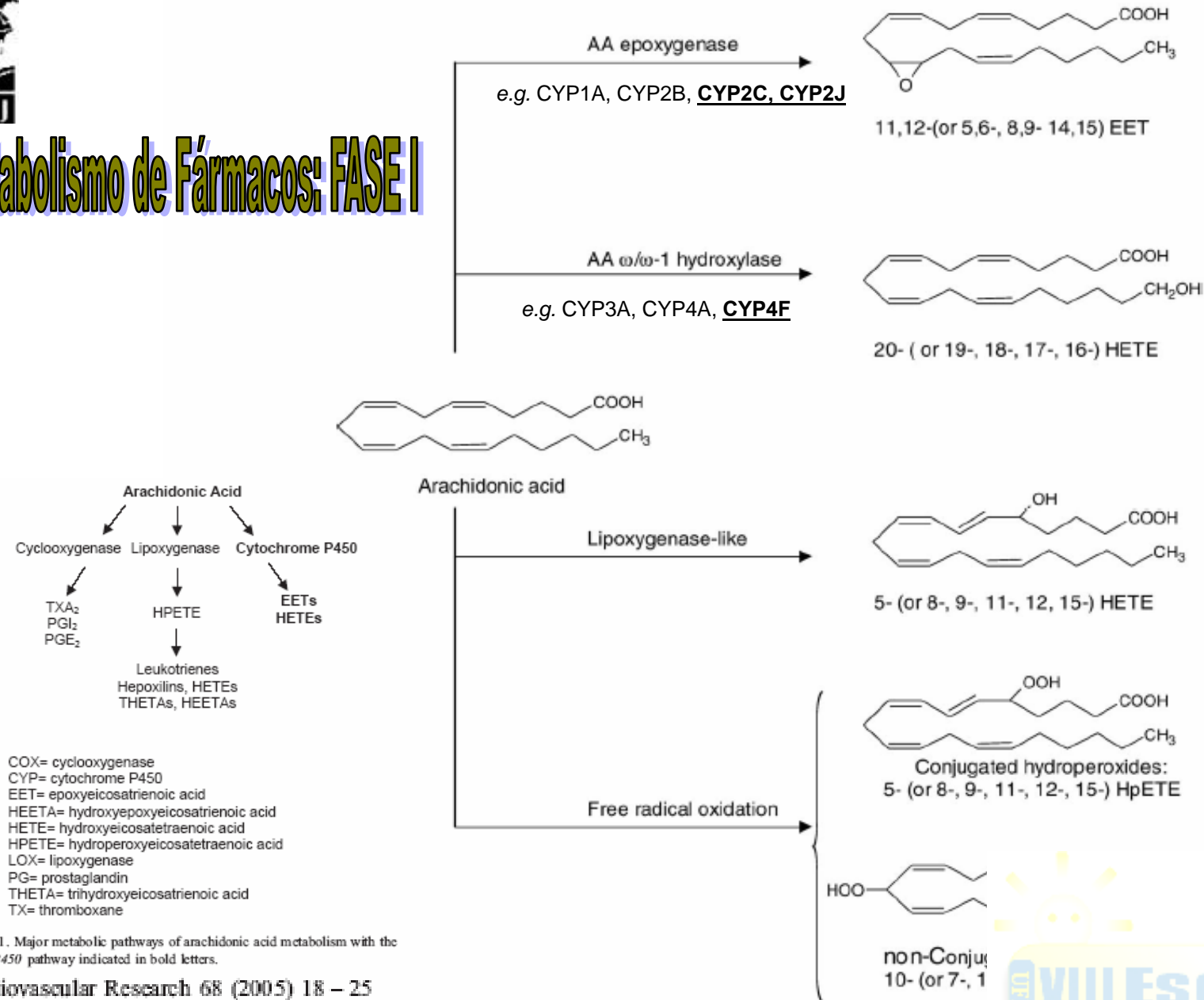


Fig. 1. Major metabolic pathways of arachidonic acid metabolism with the CYP450 pathway indicated in bold letters.

Cardiovascular Research 68 (2005) 18 – 25

Fig. 1. Pathways of arachidonic acid metabolism involving cytochrome P450 metabolism or cytochrome P4: epoxygenase products, AA $\omega/\omega-1$ hydroxylase products, lipoxygenase-like products, and primary free radical oxide (eicosatetraenoic acid), and thus HETE stands for hydroxyeicosatetraenoic acid, HpETE stands for hydroperoxyeicosatetraenoic acid.

Caro, A. A.; Cederbaum, A. I. Free Radical Biology & Medicine

Cinética oxidação de Fase I (CYP450)

Tabela 1: Energia de Dissociação de Ligações C-H selecionadas

| Ligação C-H | Tipo de Ligação | Energia de Dissociação Da Ligação em KJ/mol |
|--|----------------------|---|
| H-C ₆ H ₅ | Phenila | 464 |
| H-CH ₃ | Metano | 438 |
| H-CH ₂ CH ₃ | Primário | 420 |
| H-CH ₂ CH ₂ CH ₃ | Primário | 417 |
| H-CH ₂ C(CH ₃) ₃ | Primário | 418 |
| H-CH(CH ₃) ₂ | Secondário | 401 |
| H-C ₆ H ₁₁ | Secondário | 400 |
| H-C(CH ₃) ₃ | Terciário | 390 |
| H-CH ₂ Ph | Benzílico primário | 368 |
| H-CH(CH ₃)Ph | Benzílico secundário | 357 |
| H-C(CH ₃) ₂ Ph | Benzílico terciário | 353 |
| H-CH ₂ CH=CH ₂ | Alílico primário | 361 |
| H-CH(CH ₃)CH=CH ₂ | Alílico secundário | 345 |

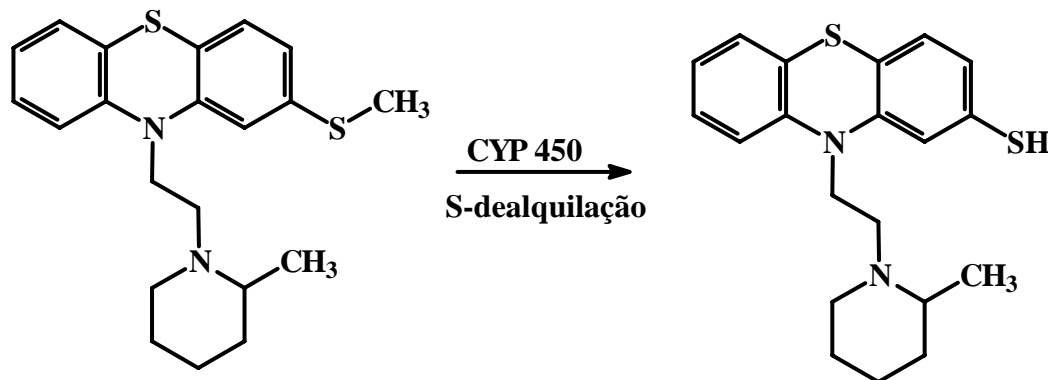
FORÇA DA LIGAÇÃO C-H x ESTABILIDADE do RADICAL

Metabolismo de Fármacos: FASE I

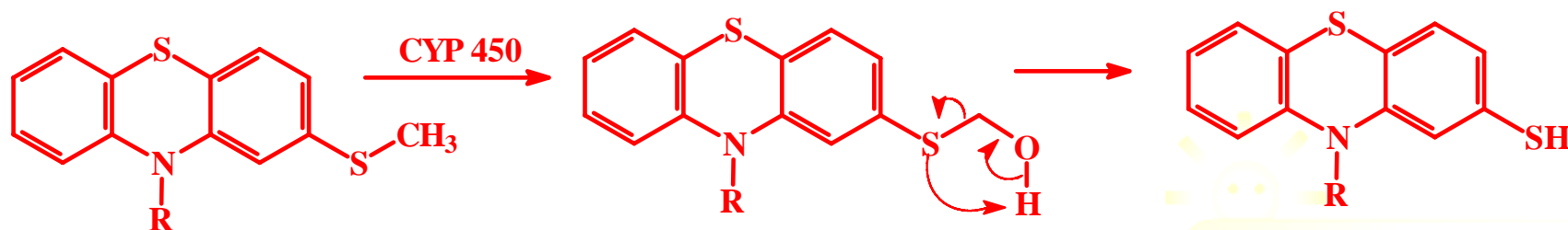
OXIDAÇÕES CATALISADAS PELO CYP450:

HIDROXILAÇÕES (AROMÁTICAS, ALIFÁTICAS, BENZÍLICAS, ALÍLICAS, C- α -HETEÓÁTOMO); **DESALQUILAÇÃO** (N,O,S); HETEROÁTOMO (N, S, P); EPOXIDAÇÕES.

S-dealquilação



thioridazina (antipsicótico)

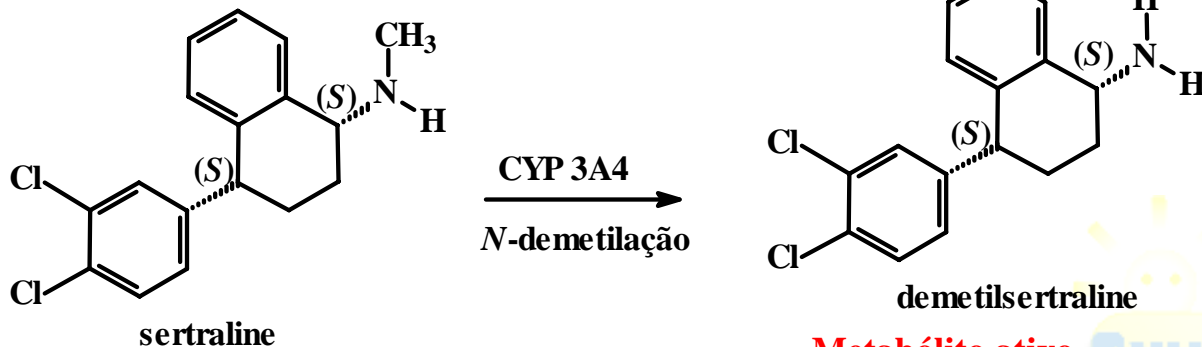
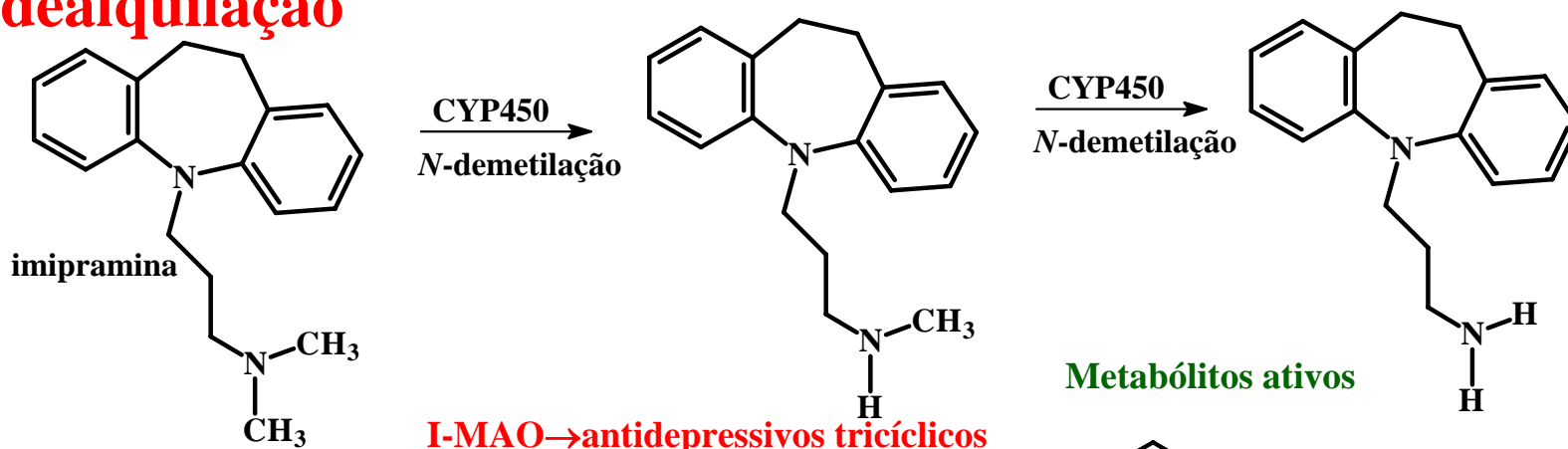


Metabolismo de Fármacos: FASE I

OXIDAÇÕES CATALISADAS PELO CYP450:

HIDROXILAÇÕES (AROMÁTICAS, ALIFÁTICAS, BENZÍLICAS, ALÍLICAS, C- α -HETEÓÁTOMO); **DESALQUILAÇÃO** (N,O,S); HETEROÁTOMO (N, S, P); EPOXIDAÇÕES.

N-dealquilação



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

Inibidor Enzimático da CYP 2D6

Metabolismo de Fármacos: FASE I

N-dealquilação

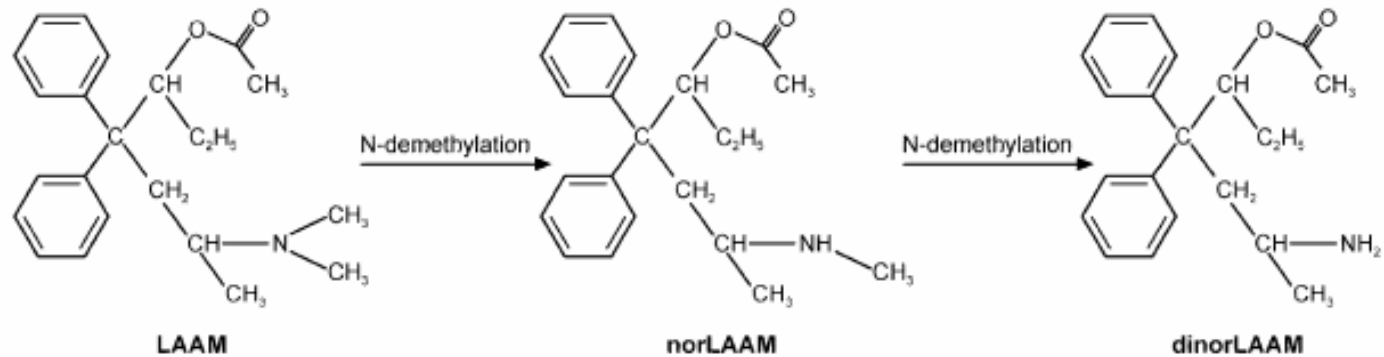


Fig. 1. Structure of LAAM and its major metabolites norLAAM and dinorLAAM.

Deshmukh, S. V. *Biochem. Pharmacol.* (2004) 67: 885-892

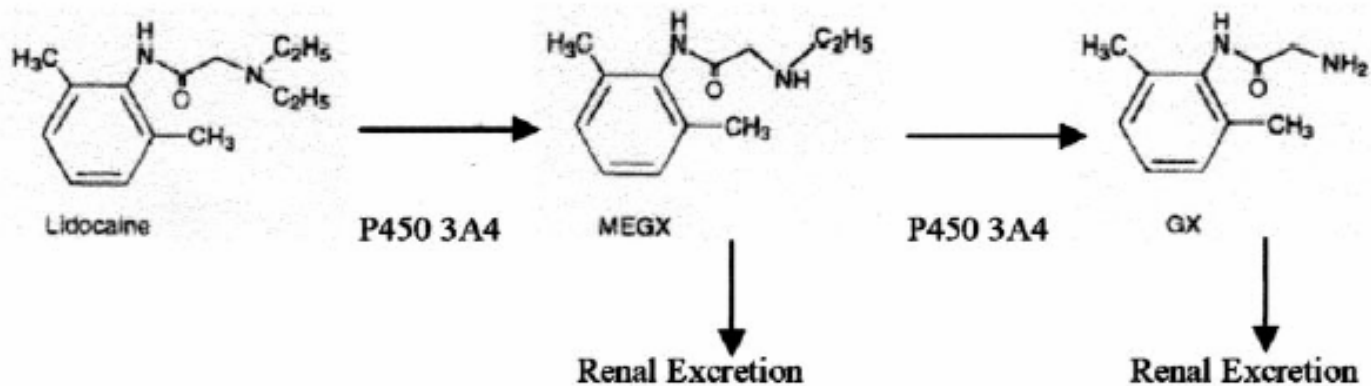
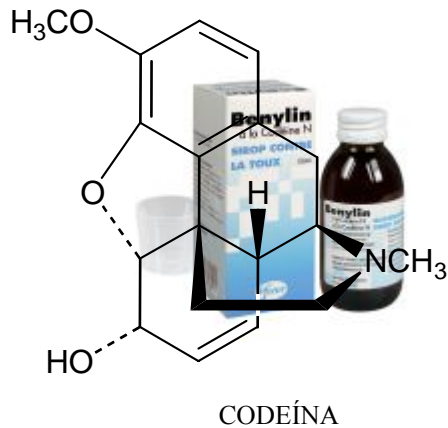


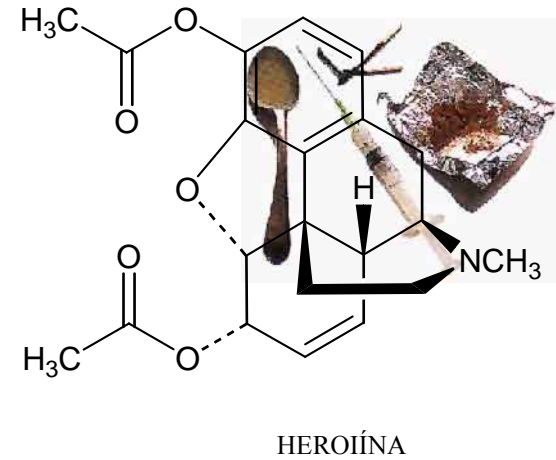
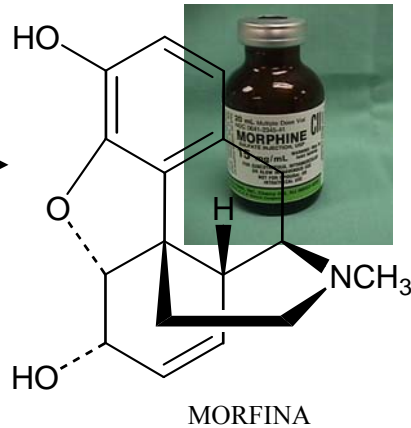
Figure. Lidocaine metabolism and excretion.

Metabolismo de Fármacos: FASE I

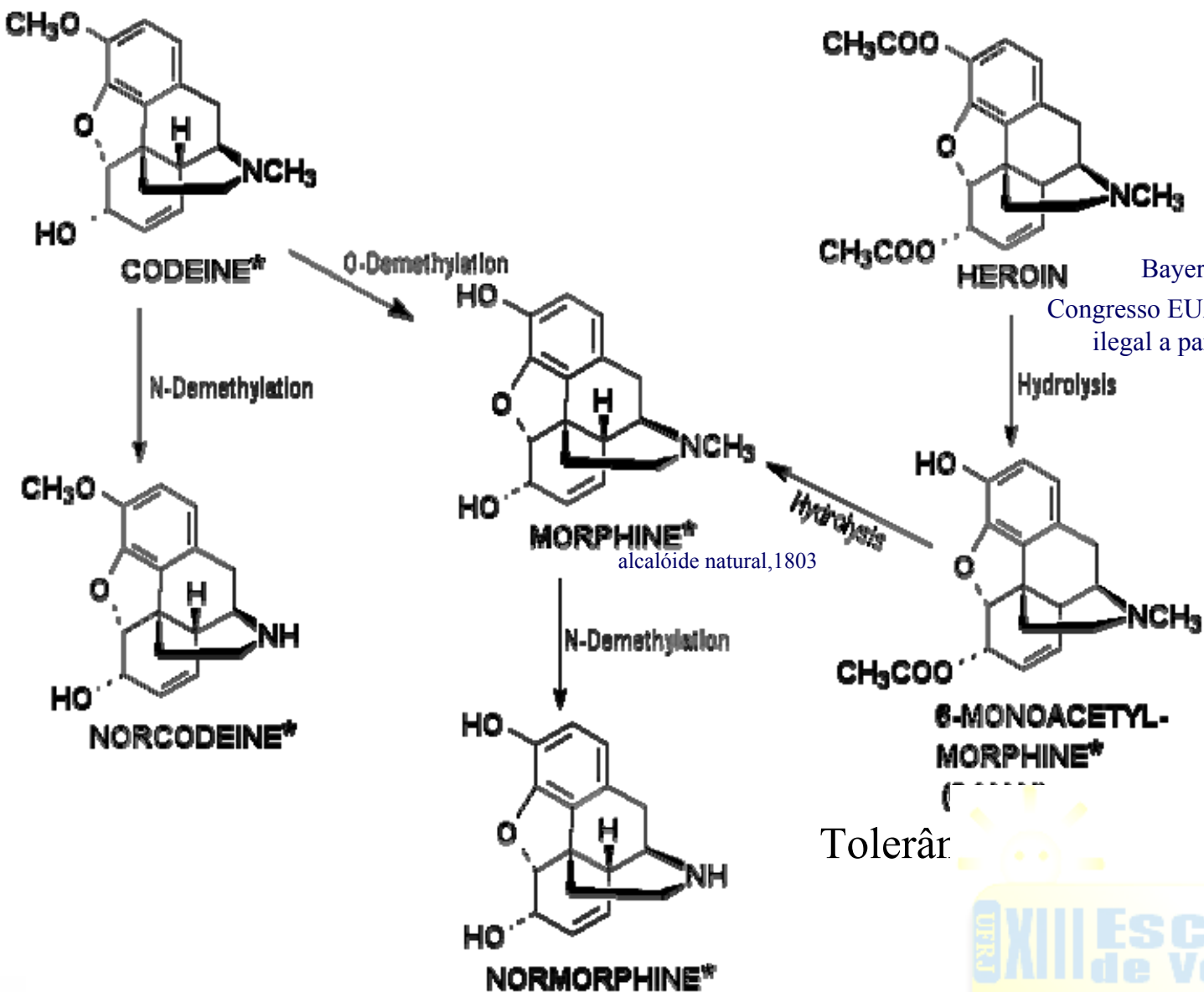
O-Dealquilção



CYP450



Metabolismo de Fármacos: FASE I



Bayer, 1898

Congresso EUA → Heroína ilegal a partir 1914

Heroin binds to opiate receptors on neurons (brain cells) in several parts of the brain. This creates a signal for the increased release of dopamine, a brain chemical linked to feelings of pleasure. The action of the drug triggers different responses in different parts of the brain.

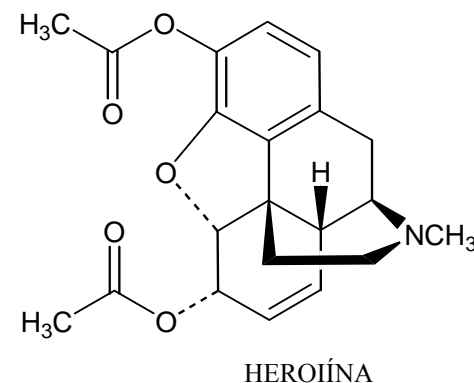


THE LIMBIC SYSTEM controls emotions and feelings of pleasure. Heroin acts here to produce an intense rush, which people addicted to the drug seek compulsively.



THE BRAIN STEM controls basic bodily functions, like heartbeat and breathing. Here, heroin can depress respiratory activity to the point that the user stops breathing and dies.

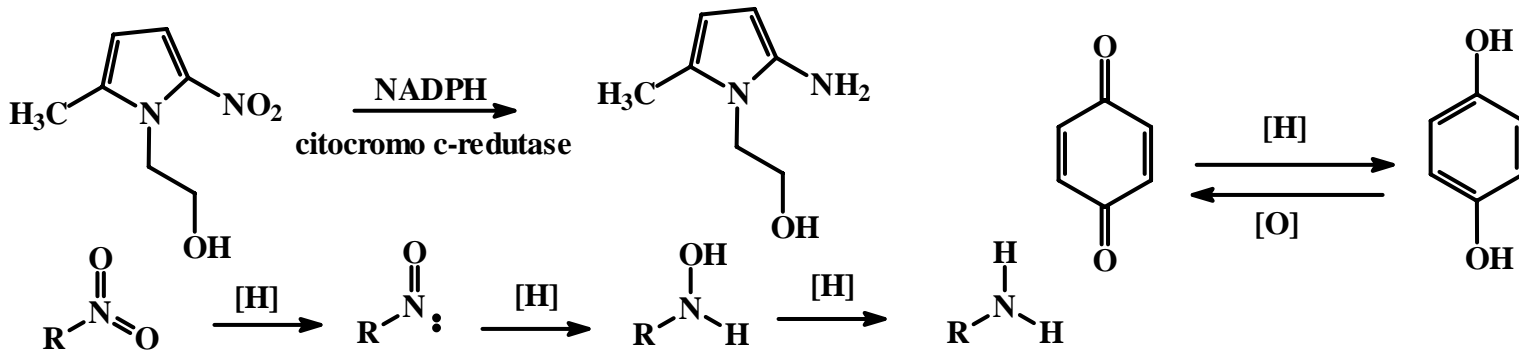
IN THE SPINAL CORD, heroin has an analgesic (pain-relieving) effect. It blocks the transmission of pain messages between neurons, preventing them from reaching the brain.



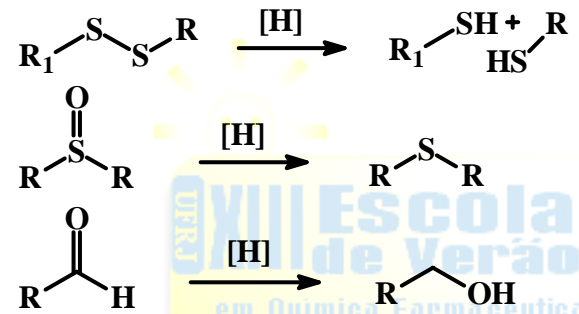
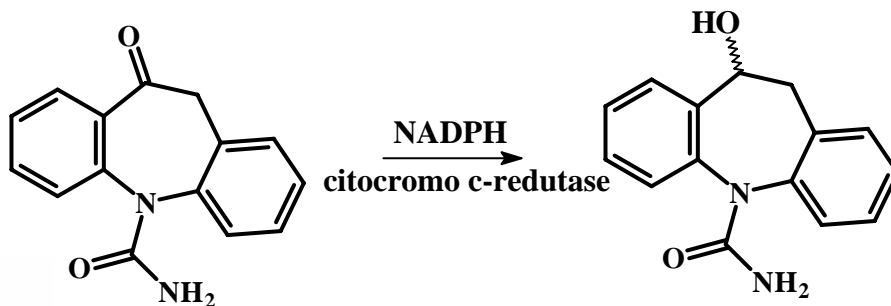
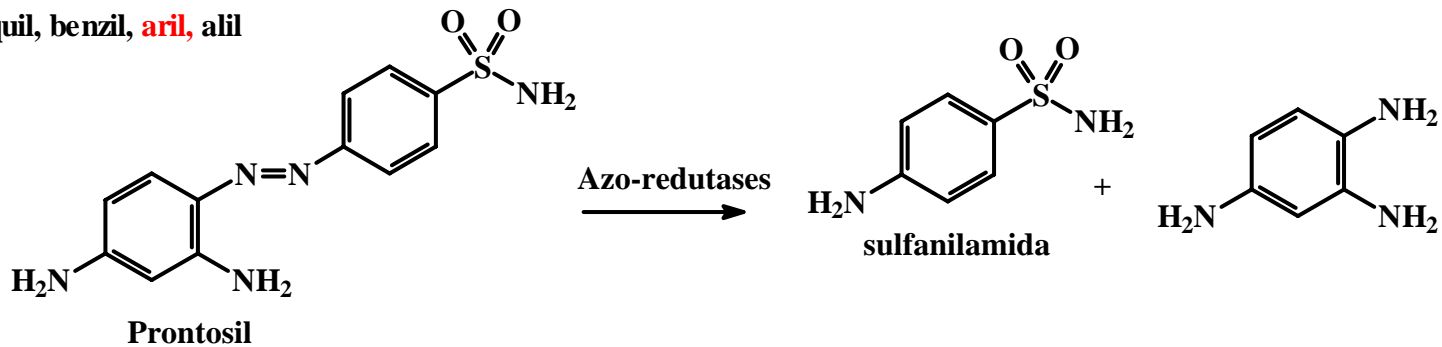
Metabolismo de Fármacos: FASE I

REDUÇÃO

Azo-derivados, nitro-derivados, cetonas, aldeídos, disulfetos (processos microsossomais)



R=alquil, benzil, **aril**, alil

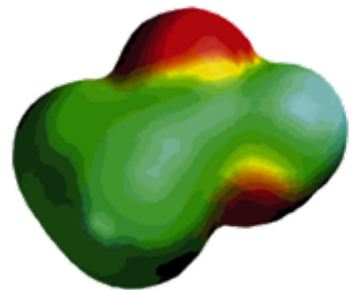


R=alquil, aril, benzil

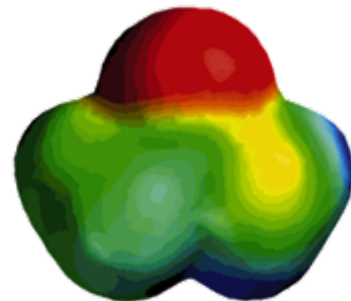
Metabolismo de Fármacos: FASE I

Reações de Hidrólise

Derivados de Ácido- Carboxílicos [Ésteres, amidas, carbamatos, uréidas, imidas, tioamidas, ácido hidroxâmico]

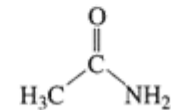
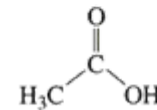
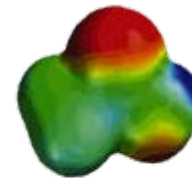
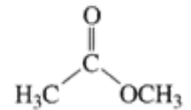
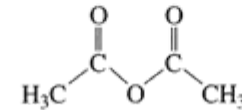
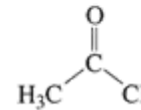
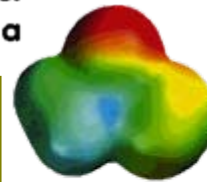
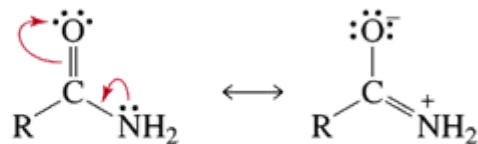
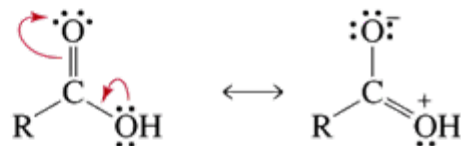
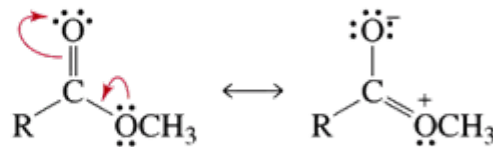


acetic acid



acetamide

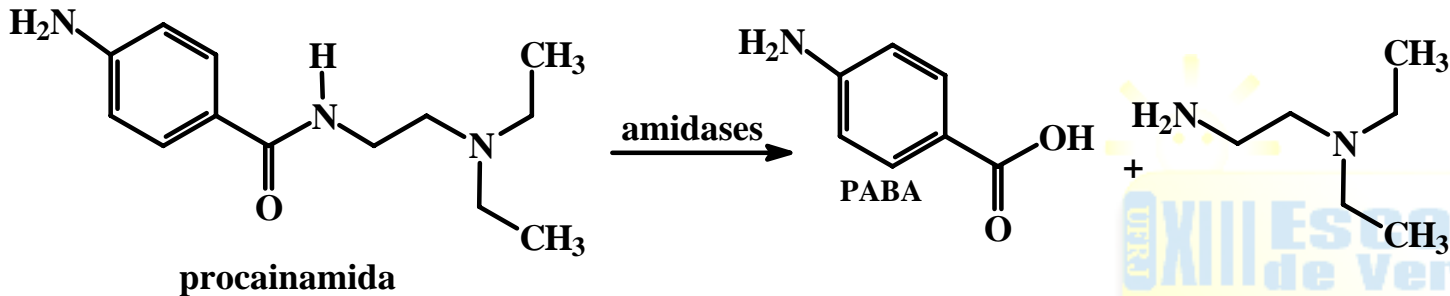
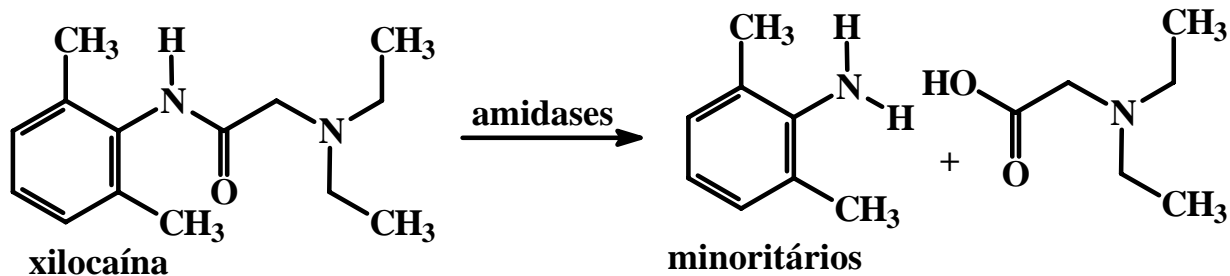
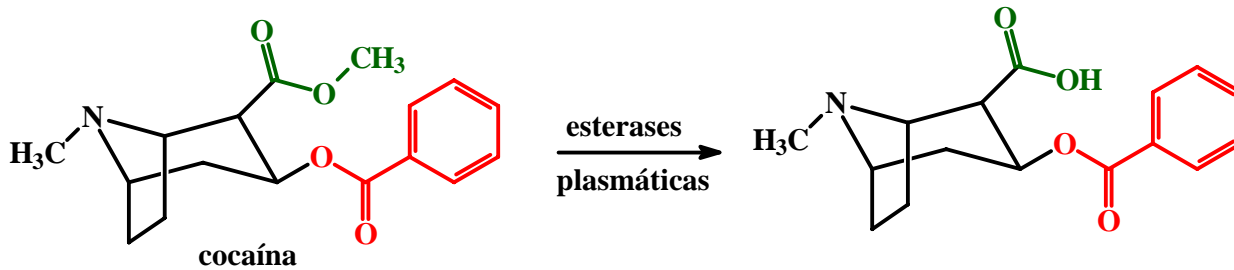
Compostos Carboxílicos:
Ressonância do grupo carboxila



Metabolismo de Fármacos: FASE I

Reações de Hidrólise

Ésteres, amidas, carbamatos, uréidas, imidas, tioamidas, ácido hidroxâmico

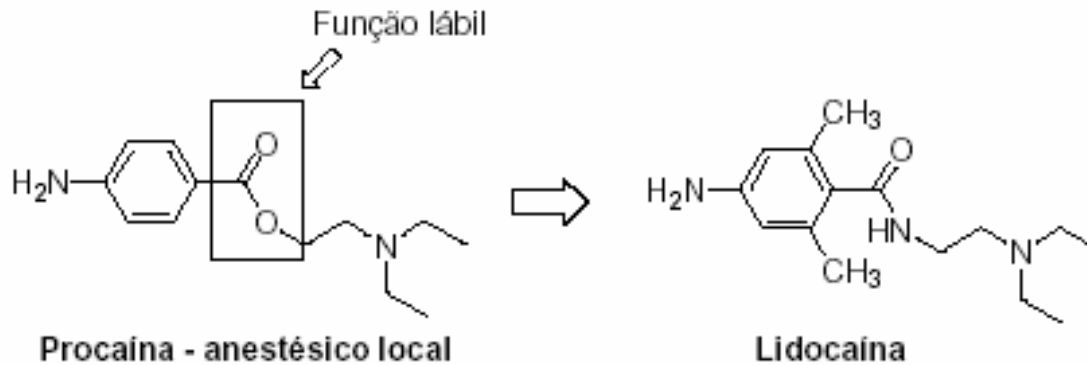


Metabolismo de Fármacos: FASE I

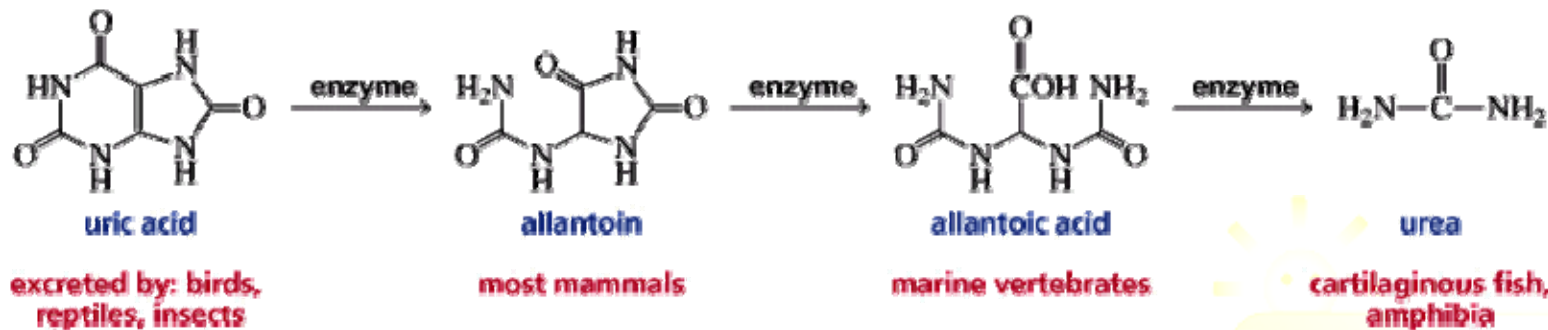
Reações de Hidrólise

Ésteres, amidas, carbamatos, uréidas, imidas, tioamidas, ácido hidroxâmico

Alteração na velocidade de metabolização



Quebra enzimática de amidas: metabólitos de excreção em seres vivos



enzyme

NH_4^+

ammonium salt

marine invertebrates

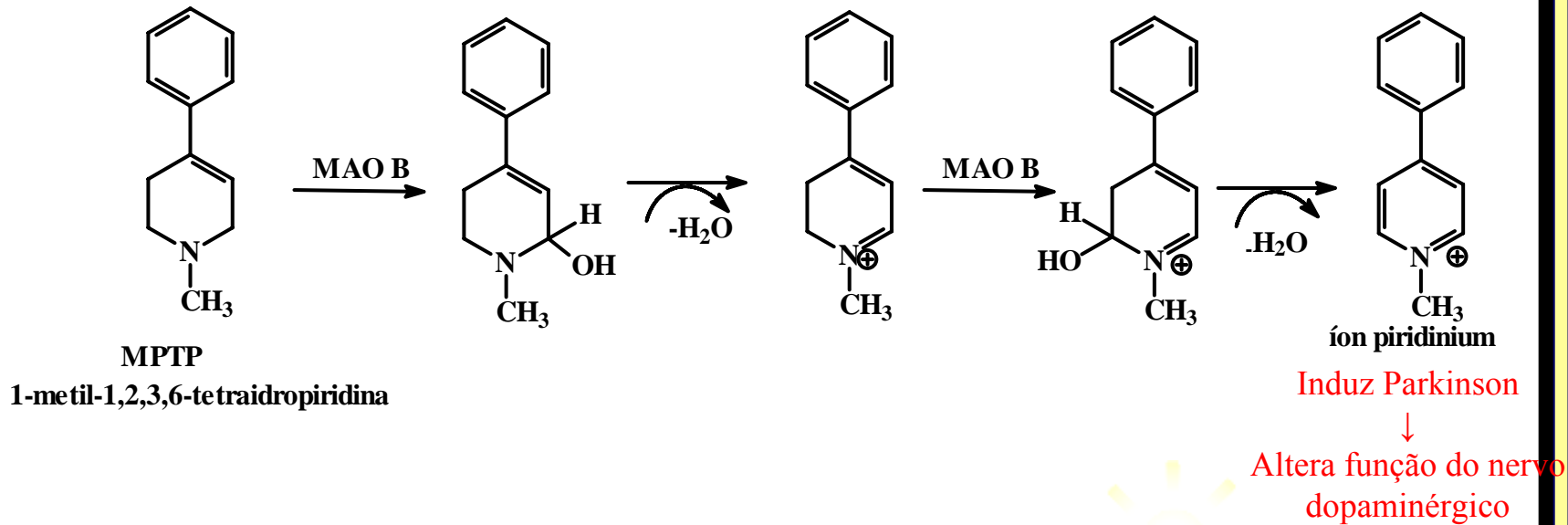
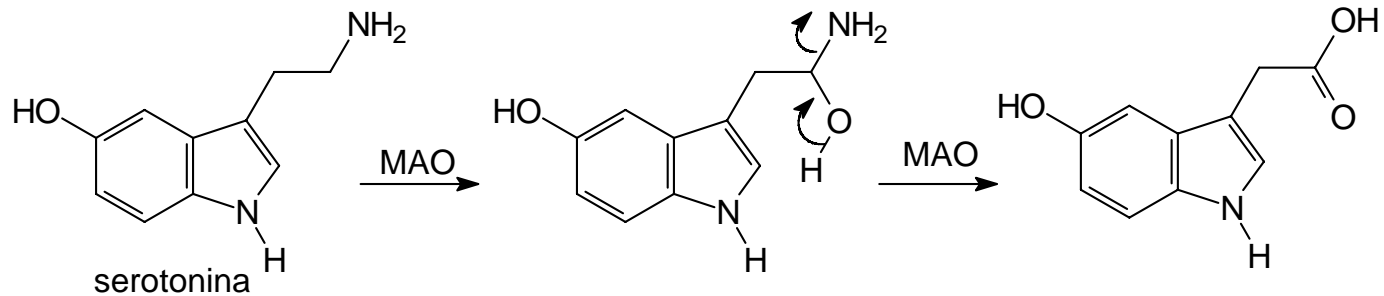
XIII Escola de Verão

em Química Farmacêutica

UFRJ

Metabolismo de Fármacos: FASE I

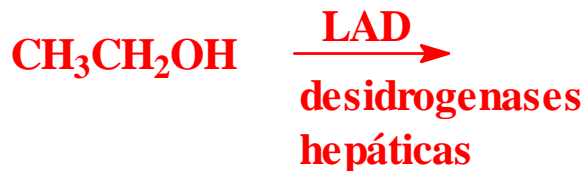
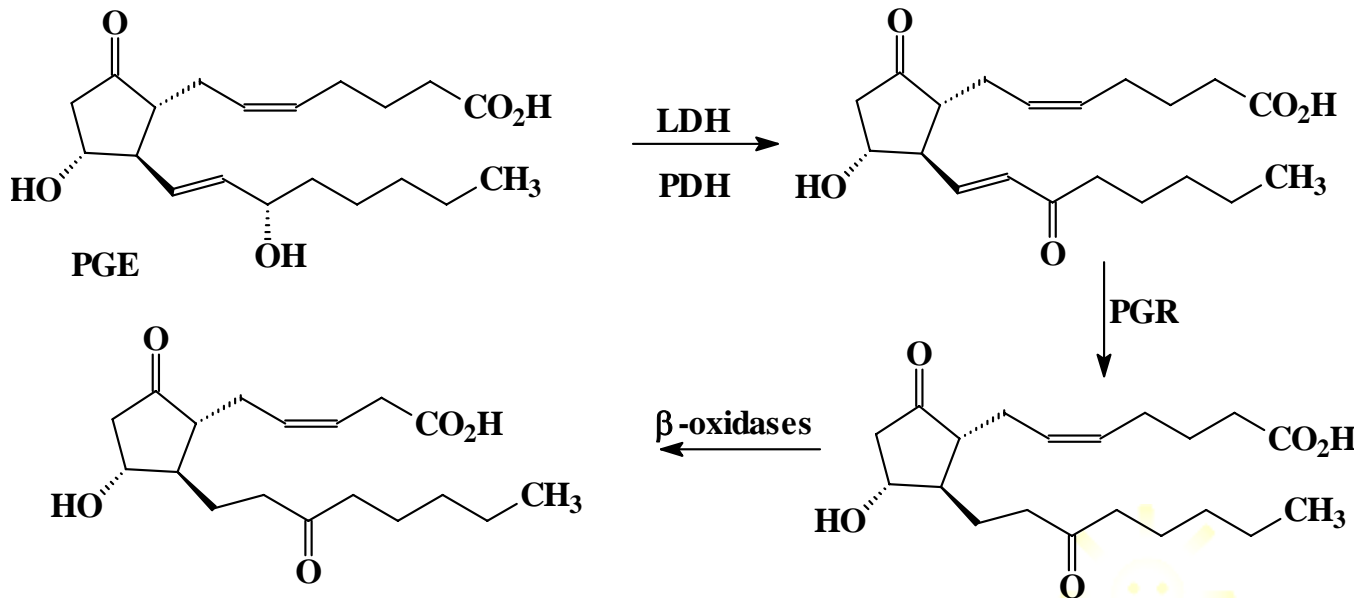
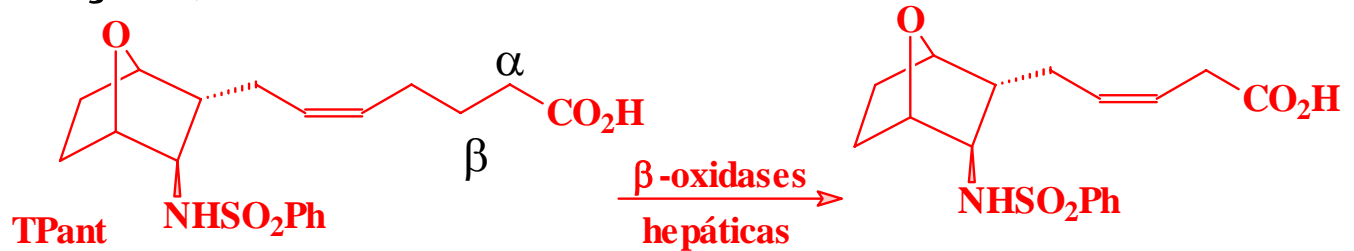
Biotransformações Não Microsossomais (e.g. Oxidações)



MAO ⇒ their physiological function is to deaminate endogenous amines, in particular catecholamines, but can be involved in oxidation of xenobiotics

Metabolismo de Fármacos: FASE I

Biotransformações Não Microsossomais (e.g., **Oxidações e Reduções**)

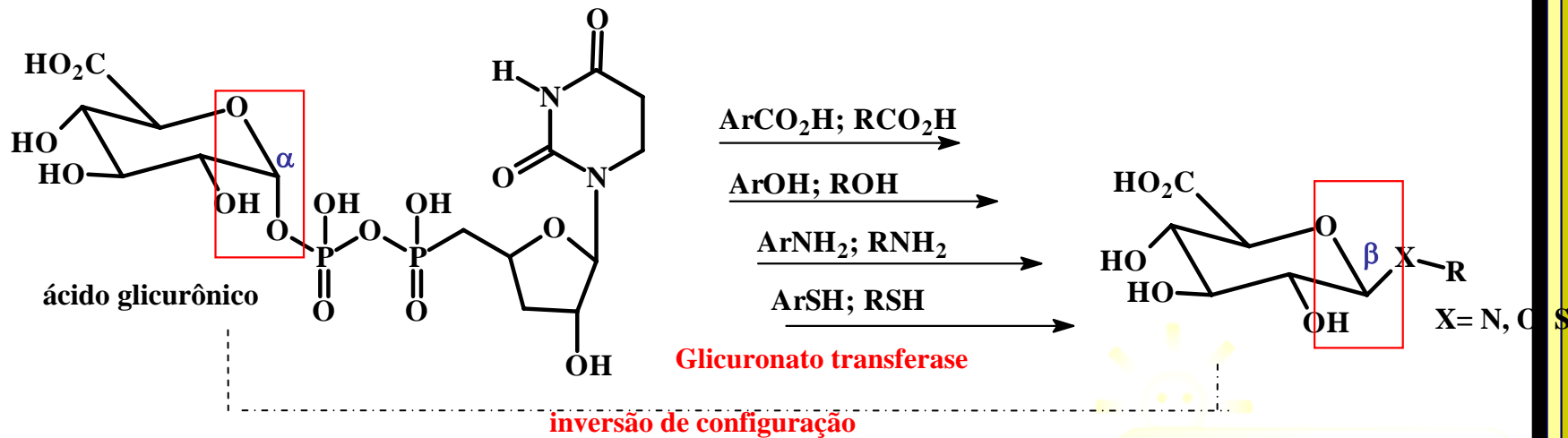


Metabolismo de Fármacos: FASE II

Características das Reações de Fase II:

São catalisadas por enzimas conhecidas pelo termo geral de transferases;
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;
Transfere uma molécula endógena altamente polar e de tamanho comparável ao substrato (exceção: reações de metilação e acetilação)

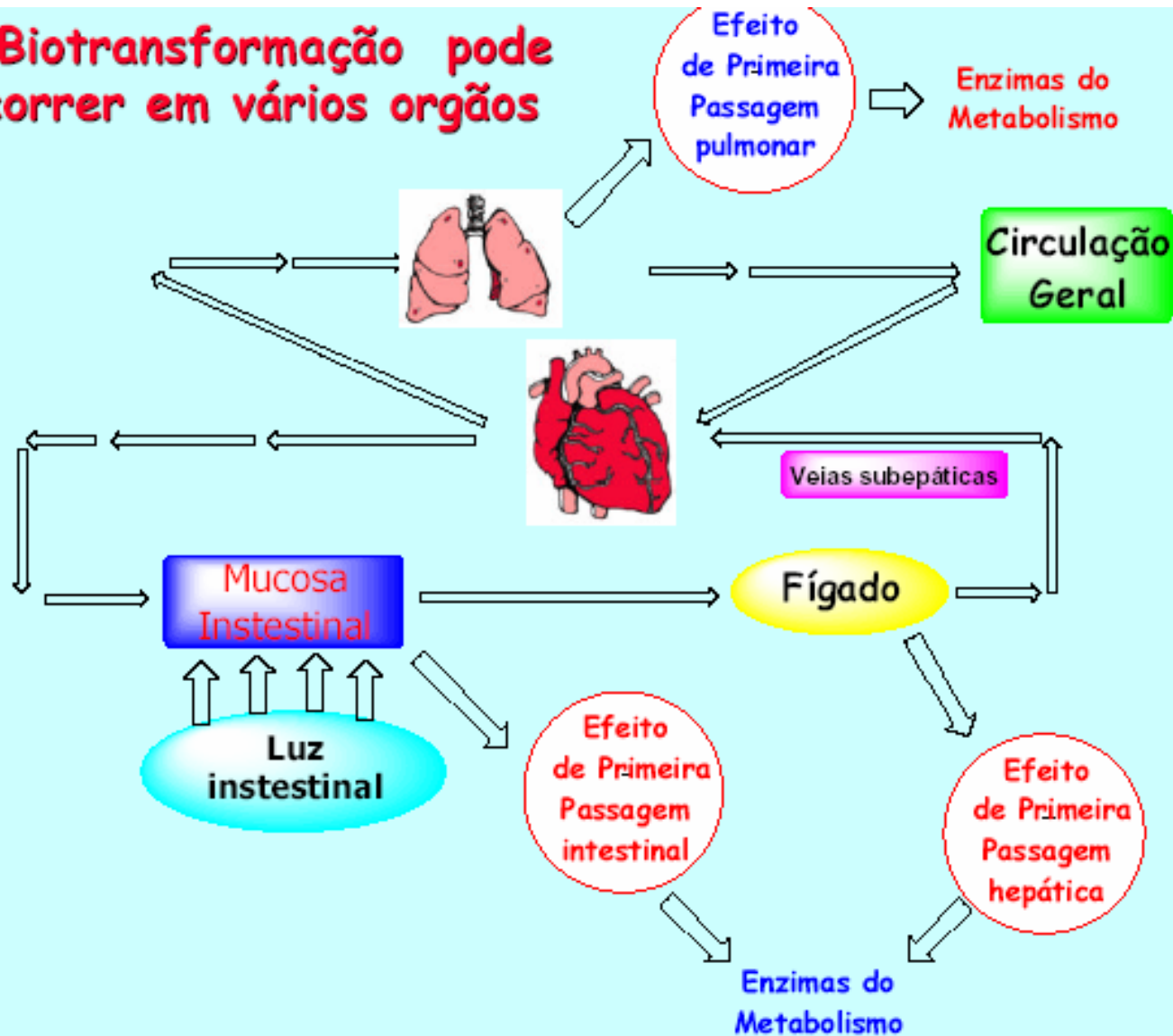
Reações de Conjugação: 1-Glicuronidação



Efeito de 1ª passagem x biodisponibilidade

Metabolismo de Fármacos

A Biotransformação pode ocorrer em vários órgãos



Metabolismo de Fármacos

Efeito de primeira passagem

O que é isso?

Consiste em uma perda do medicamento por bio-transformação (ou metabolismo) pela ação das enzimas de um órgão, desde o primeiro contato da substância medicamentosa com este órgão.

A substância se transforma em metabólitos.

Efeito de Primeira Passagem Pulmonar;
Efeito de Primeira Passagem Hepática;
Efeito de Primeira Passagem Intestinal.

Metabolismo e Biodisponibilidade

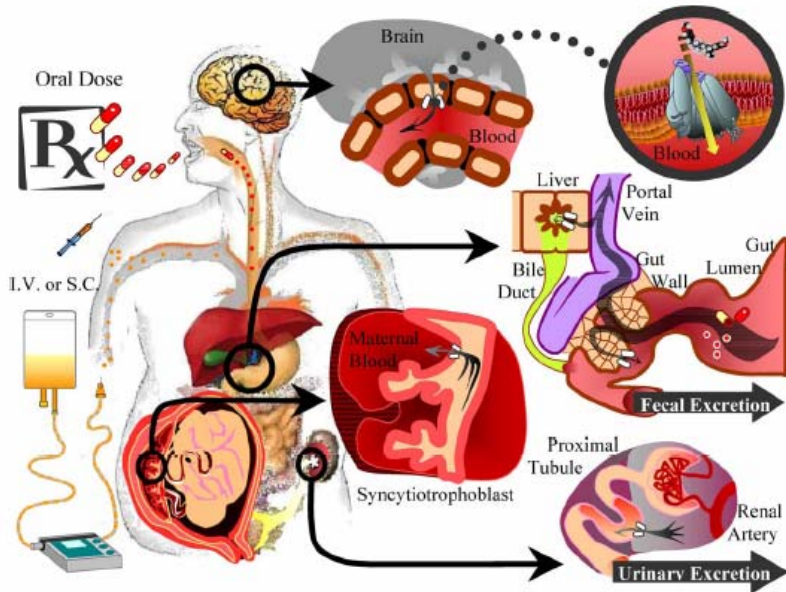


Fig. 1 - In humans, P-gp is present in several tissues important for drug absorption, distribution and elimination, such as the apical membrane of intestinal epithelial cells, the canalicular membrane of the hepatocytes, the capillary endothelial cells of the brain, the apical membrane of the placental syncytiotrophoblasts and the apical membrane of the renal proximal tubular cells. In these tissues, P-gp functions as an efflux pump, preventing the entry of xenobiotics into these tissues.

BIODISPONIBILIDADE
 Fração ou percentagem do
 Fármaco (xenobiótico)
 que atinge a circulação
 Sistêmica a partir do local
 de sua administração



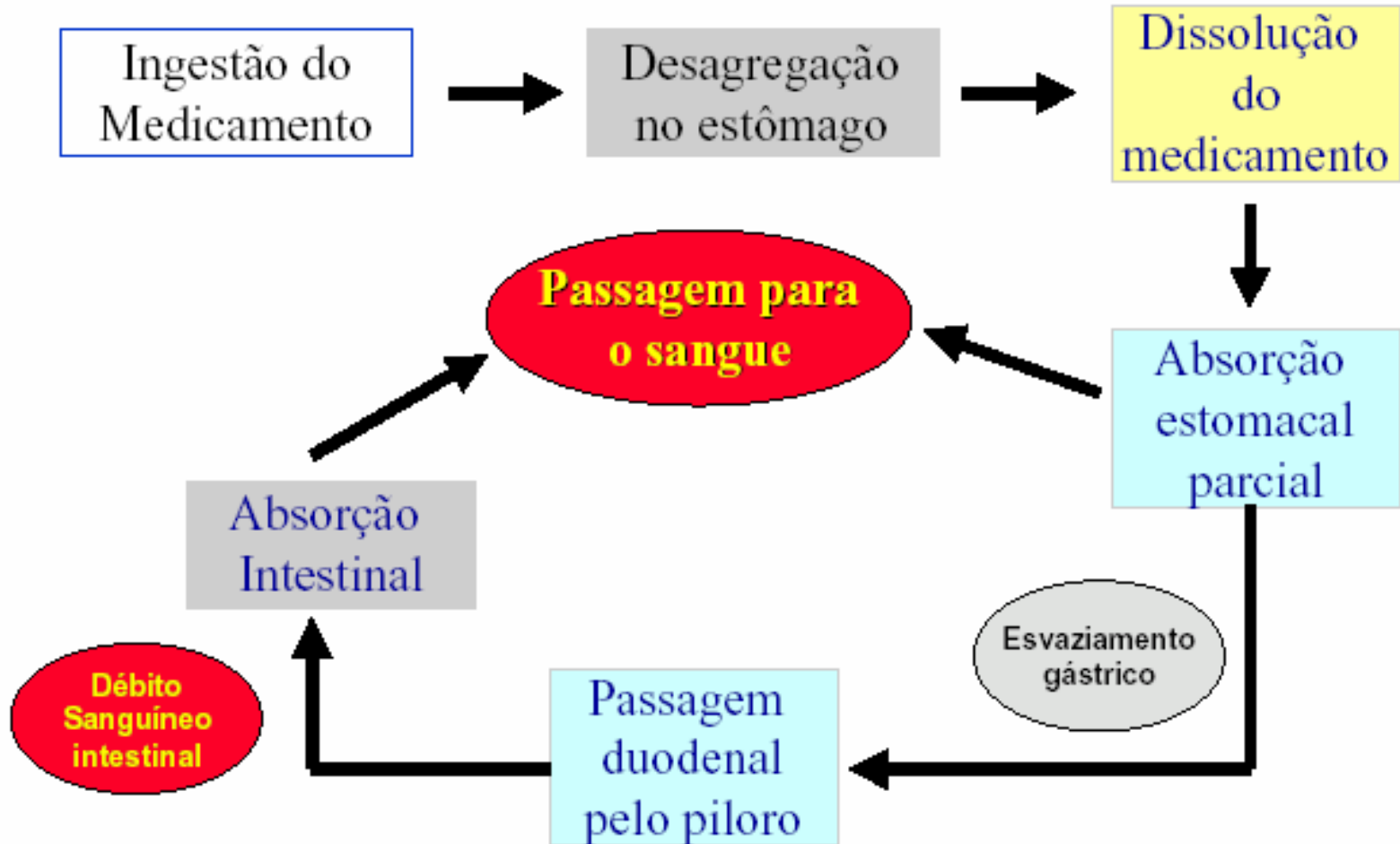
Quantidade absorvida
 Quantidade eliminada pelas
 Diferentes etapas de 1ª passagem



Absorção e Metabolismo

Metabolismo e Biodisponibilidade

As diferentes etapas da absorção



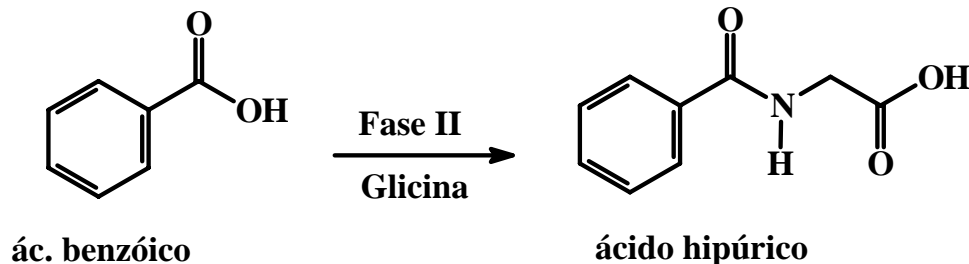
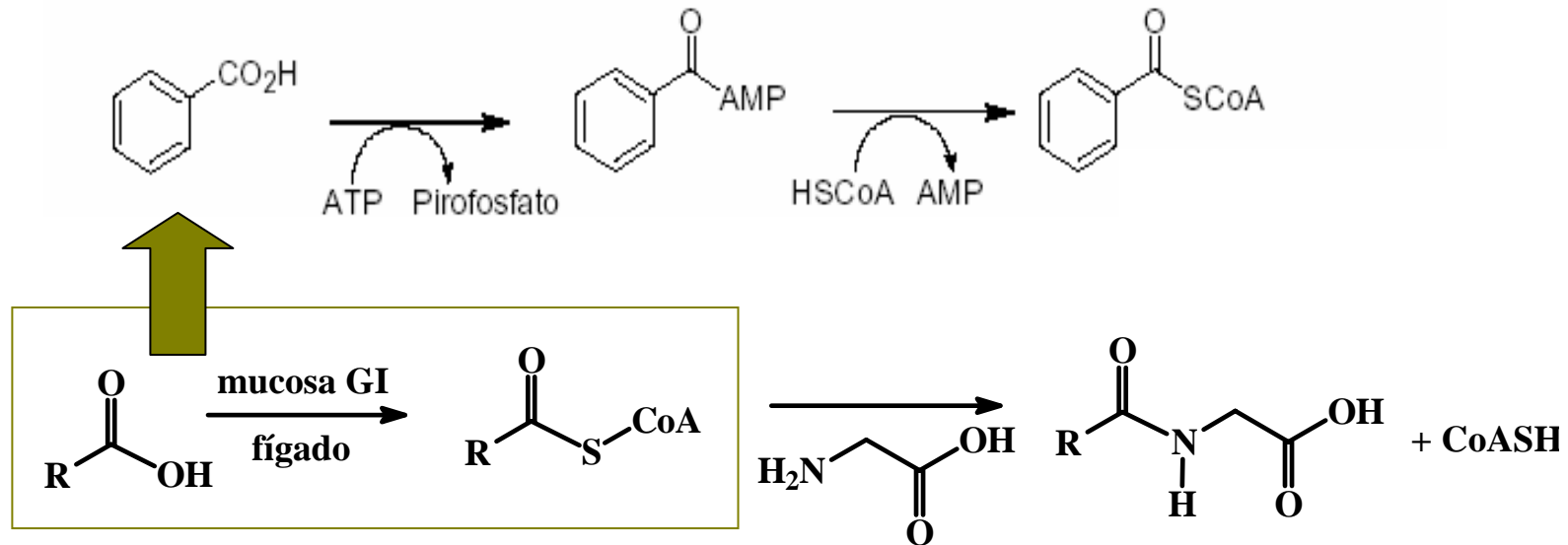
Metabolismo e Biodisponibilidade

- **Metabolismo hepático de 1ª passagem pré-sistêmico:** Abilidade do fígado e intestino metabolizar xenobióticos antes de chegar a circulação sistêmica, envolvendo reações de sulfatação e glicuronidação.
- **Metabolismo hepático de 1ª passagem:** Sofrem ação do metabolismo de 1ª passagem durante seu transporte para a circulação sistêmica a partir do trato GI (logo adm. Oral). Logo o fígado pode remover xenobióticos a partir do sangue após sua absorção GI, prevenindo sua distribuição aos diferentes compartimentos do corpo, reduzindo de forma significativa a quantidade de droga que alcança a circulação

Metabolismo de Fármacos: FASE II

Reações de Conjugação: 2-Conjugação com glicina

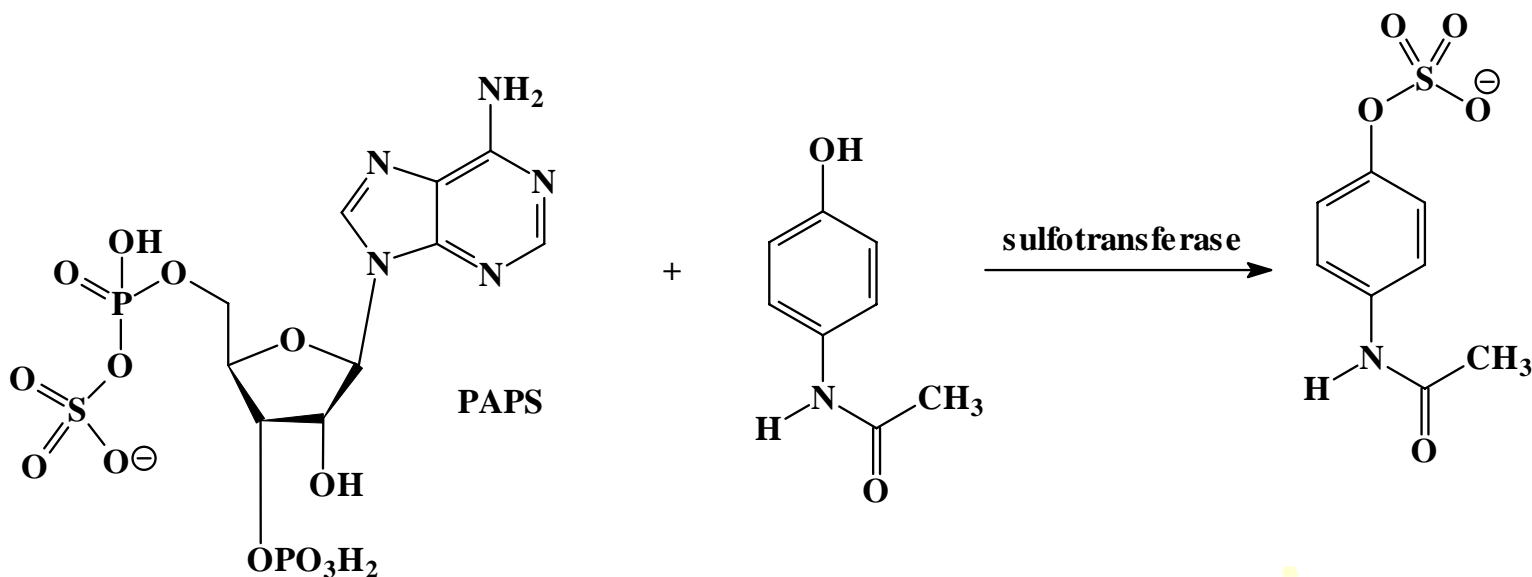
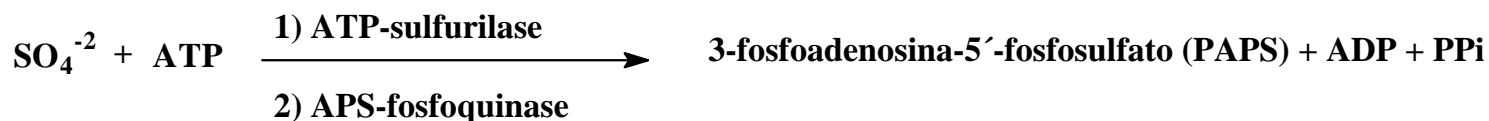
Substratos: Ácidos arilcarboxílicos e fenóis



**Primeiro estudo
de metabolismo**

Metabolismo de Fármacos: FASE II

Reações de Conjugação: 3-Sulfatação

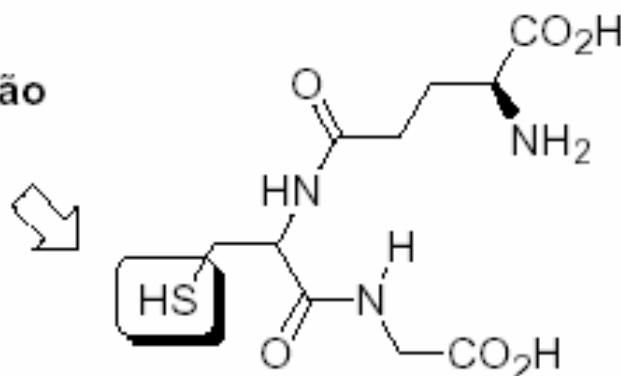


Metabolismo de Fármacos: FASE II

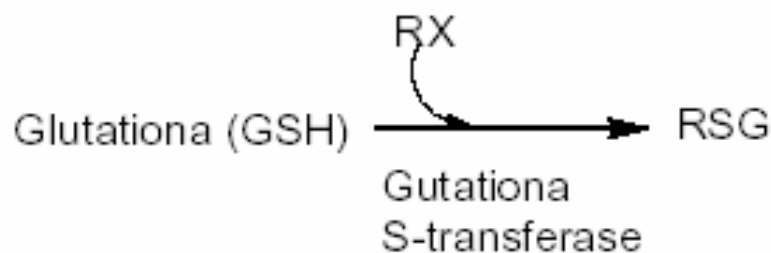
Reações de Conjugação: 4-Conjugação c/ Glutathiona

Reação geral:

Reações de Substituição
Doador de Michael

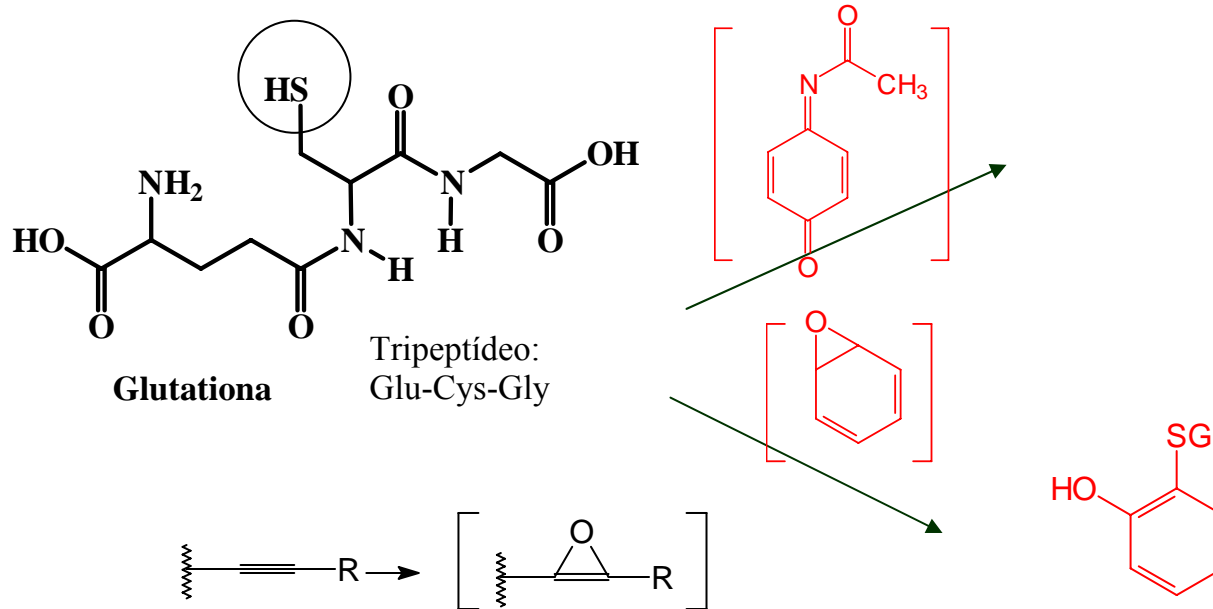


Glutathiona (GSH)



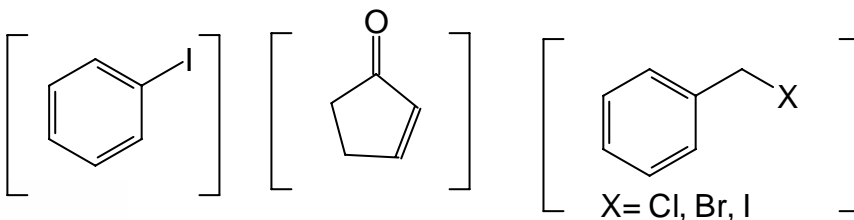
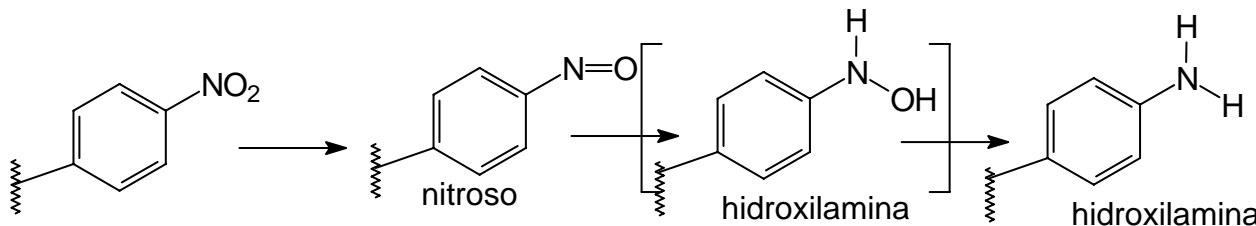
Metabolismo de Fármacos: FASE II

Reações de Conjugação: 4-Conjugação c/ Glutathiona



Bionucleófilos
Endógenos

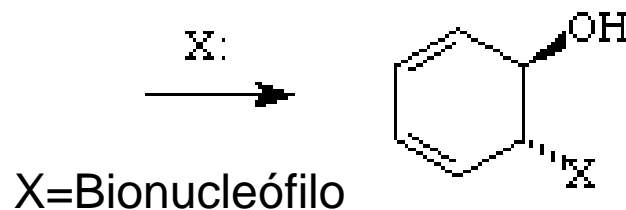
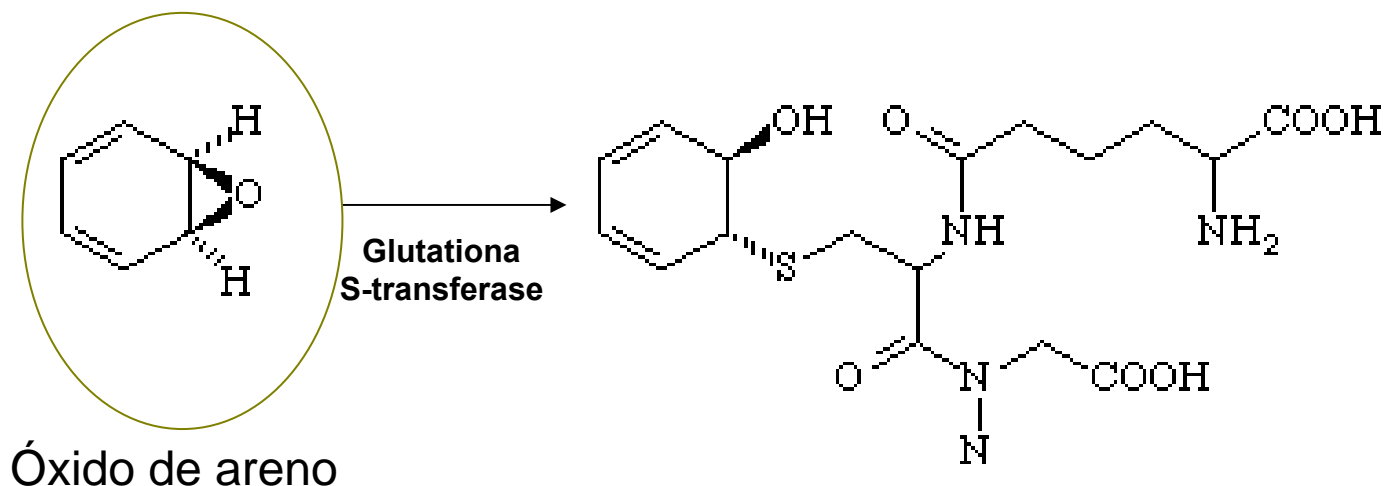
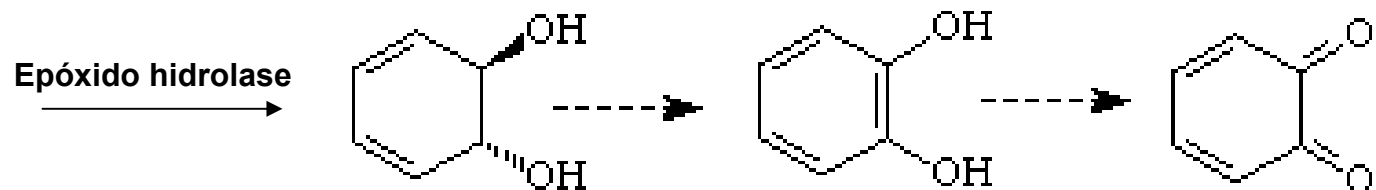
Glutathiona
 Adenina
 Guanina
 Serina
 Lisina
 DNA
 RNA



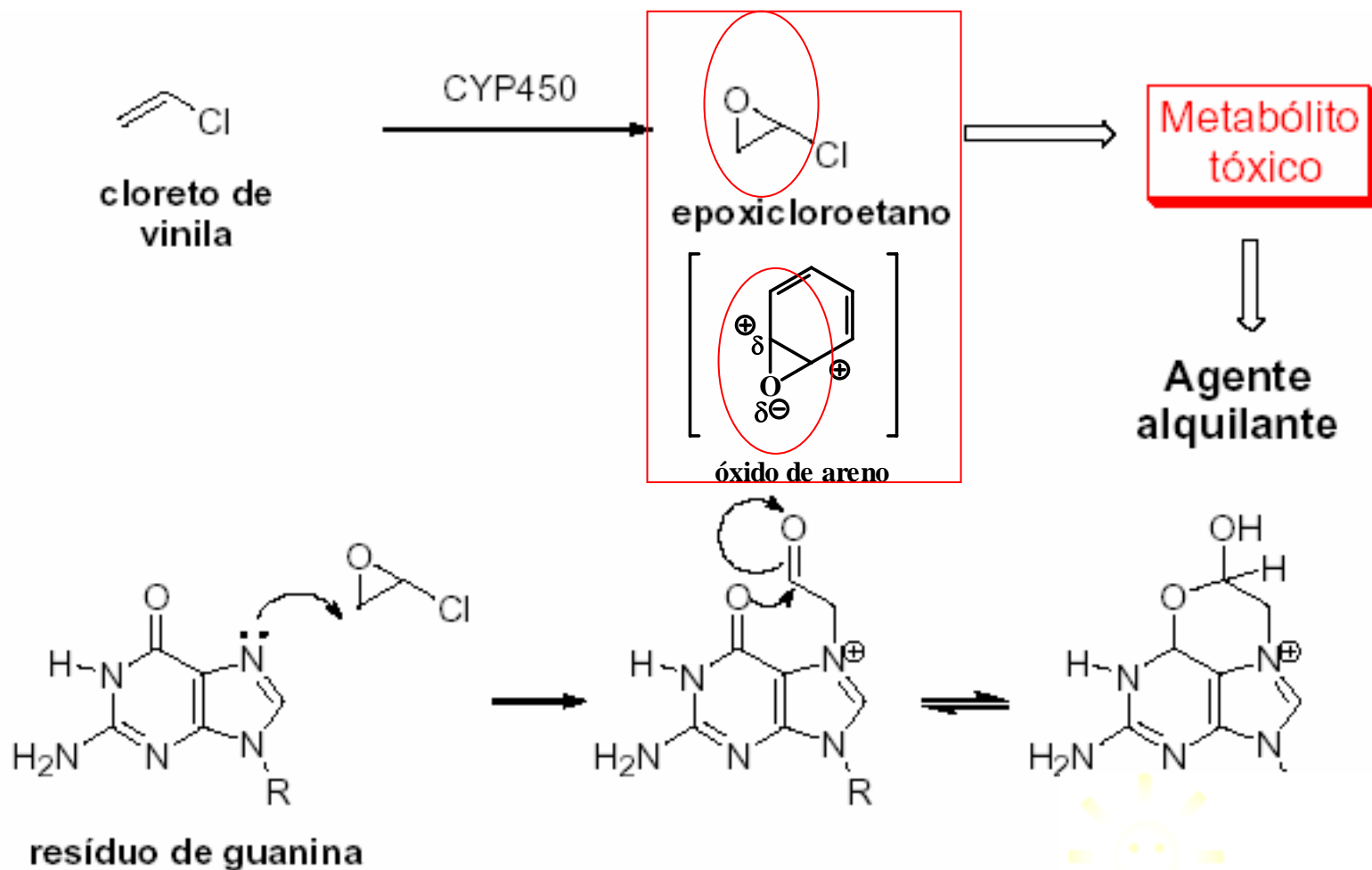
Grupos potencialmente
Toxicofóricos

Metabolismo de Fármacos: FASE II

4-Conjugação c/ Glutathiona (Reação de Detoxificação)



Metabolismo de Xenobióticos

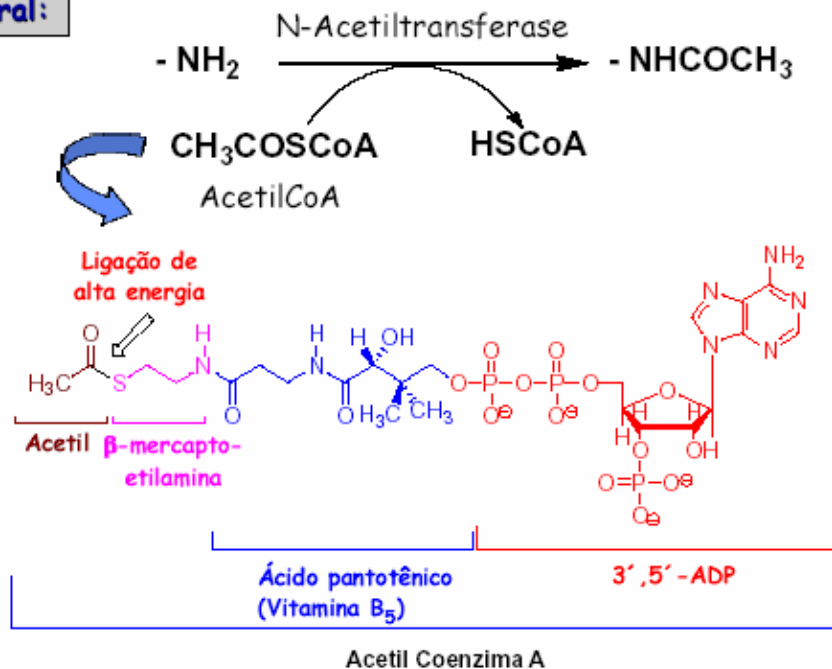


Metabolismo de Fármacos: FASE II

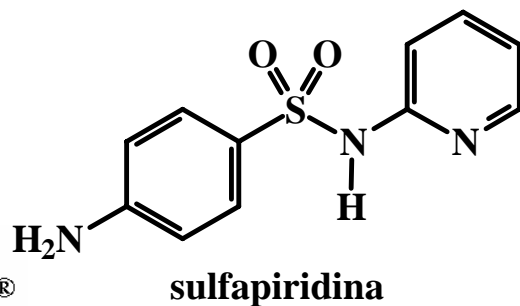
Acetilação

Acetilação

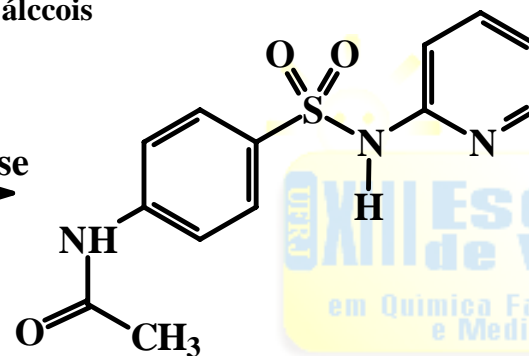
Reação geral:



SUBSTRATOS: Aminas aromáticas << Fenóis <<< Aminas alifáticas <<< álcoois

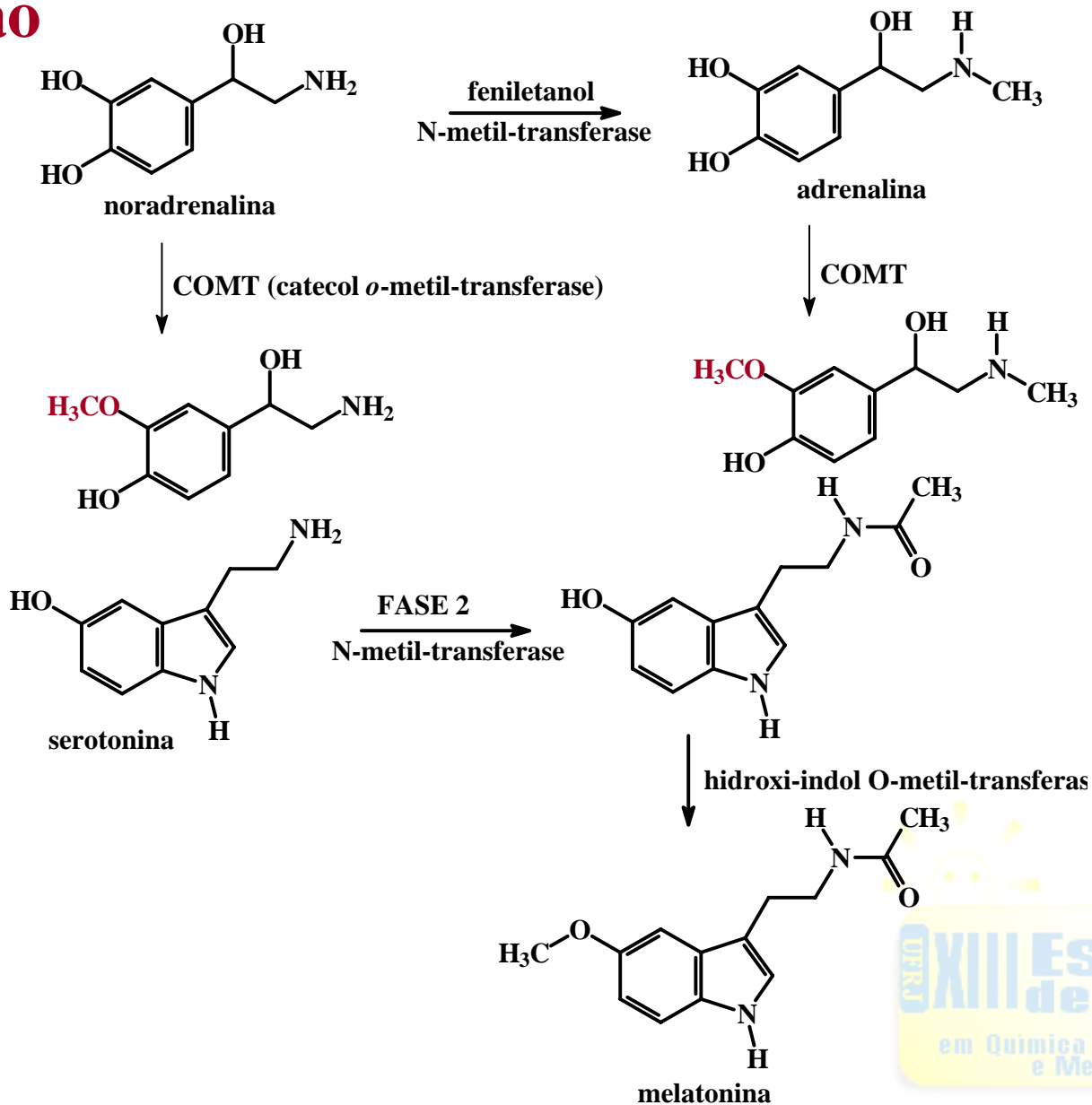


acil-transferase
 Acetil-CoA

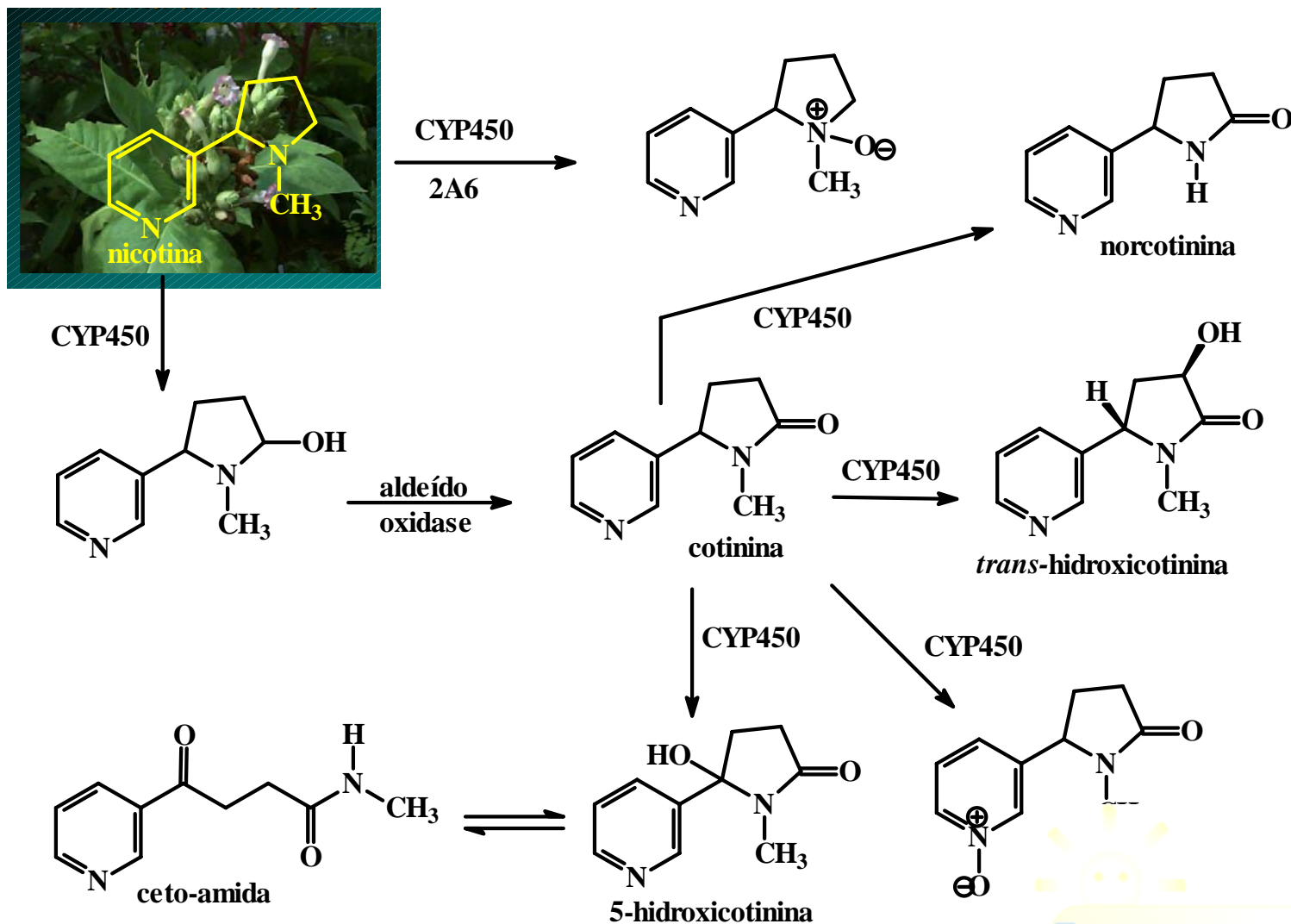


Metabolismo de Fármacos: FASE II

Metilação

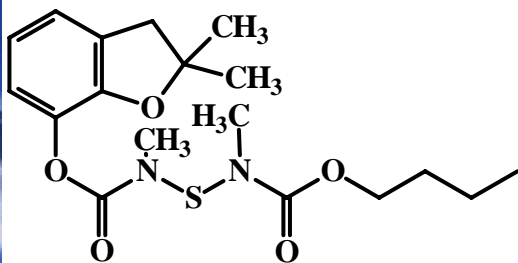


PREVISÃO DE METABÓLITOS COM BASE NA ESTRUTURA



Murphy S. E. et al., *Chem. Res. Toxicol.* (1999) 12: 639-645

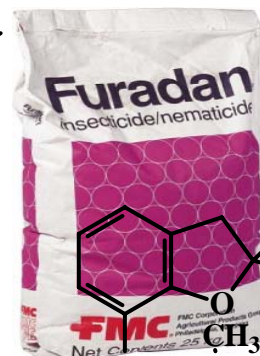
PREVISÃO DE METABÓLITOS COM BASE NA ESTRUTURA



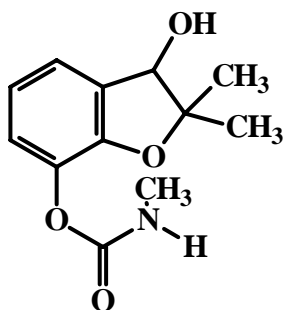
furathiocarb



carbosulfan



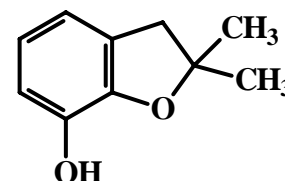
carbofuran



3-hidroxicarbofurano

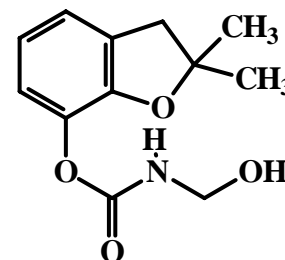
CYP450

hidrolases



7-fenol

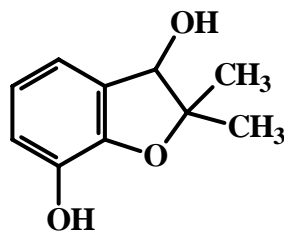
CYP450



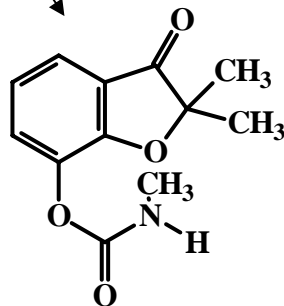
N-hidroximetilcarbofurano

hidrolases

CYP450

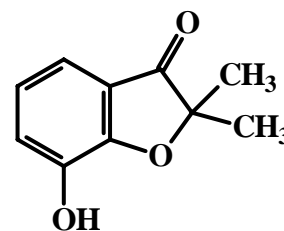


3-hidroxi 7-fenol



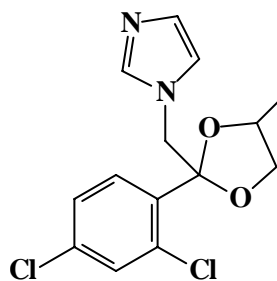
3-cetocarbofurano

hidrolases



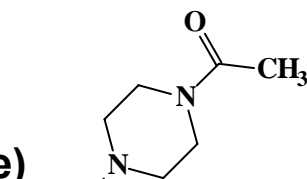
3-ceto7-fenol

Inibidores da Biossíntese do Ergosterol (C-14 desmetilase)



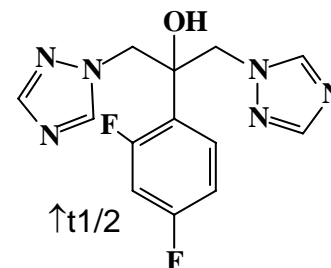
cetoconazol (5)

↓t_{1/2}



↑t_{1/2}

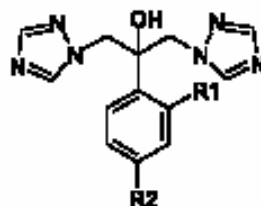
(4)



↑t_{1/2}

fluconazol (5)

Tabela 1. Dados de farmacocinética e de solubilidade de dois potentes derivados *bis*-triazólicos em cães

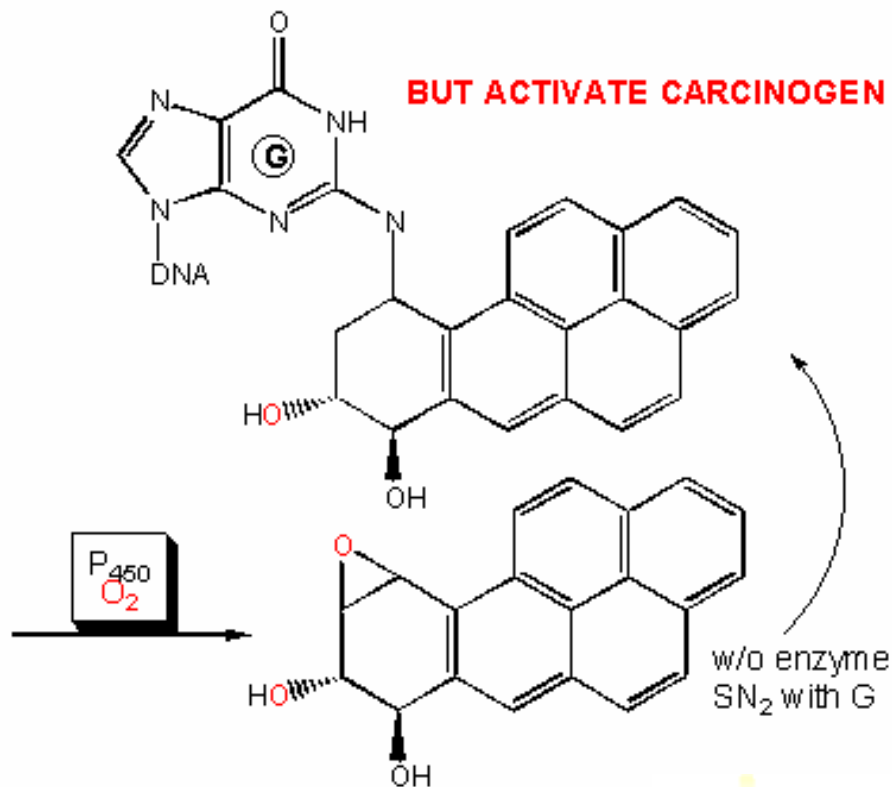
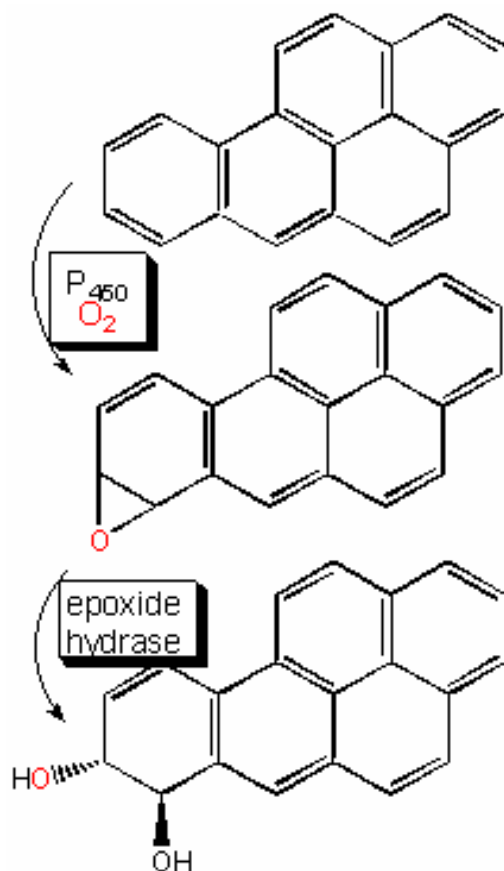


| Parâmetro | (4) | Fluconazol (5) |
|--|------|----------------|
| R ₁ | Cl | F |
| R ₂ | Cl | F |
| Log P | 1,5 | 0,5 |
| Ligação à proteína plasmática (%) | 43 | 11 |
| Depuração renal (não-metabolizado) (mL/min por kg) | 0,05 | 0,46 |
| Depuração não-renal (mL/min por kg) | 0,45 | 0,19* |
| Solubilidade em água (mg/mL) | <1 | 8 |

* Principalmente excreção na forma inalterada nas fezes.

Quanto mais lipofílico= maior reabsorção túbulo renal

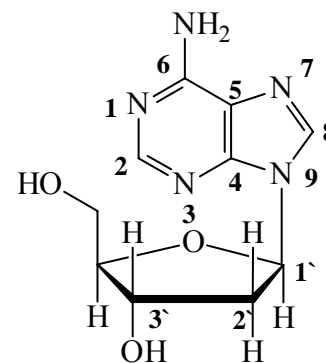
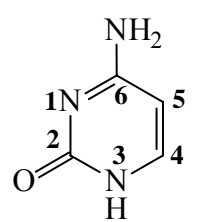
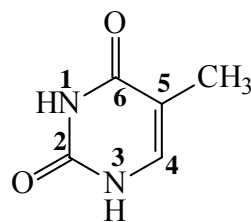
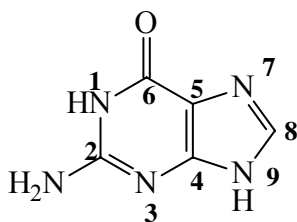
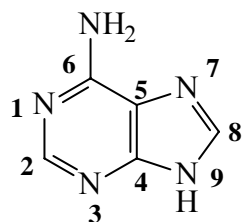
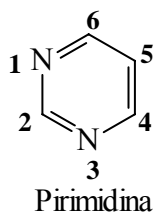
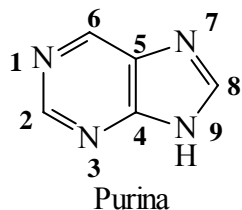
Metabolismo de Fármacos e Toxicidade



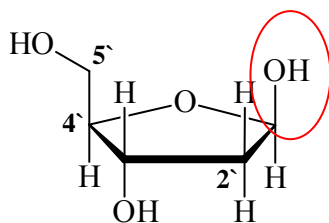
Metabolismo de Fármacos e Toxicidade

Definição: DNA é um polímero de unidades desoxirribonucleotídio

Nucleotídio: Uma base nitrogenada (purina ou pirimidina), um açúcar (desoxirribose) e um ou mais radicais fosfato



Nucleosídeo

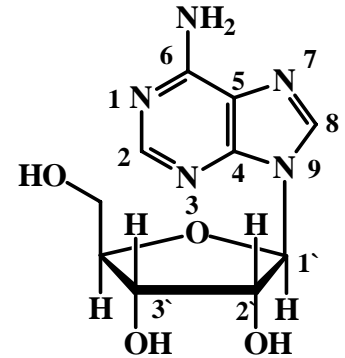
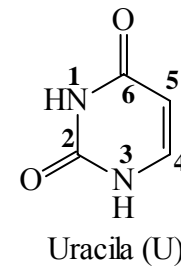
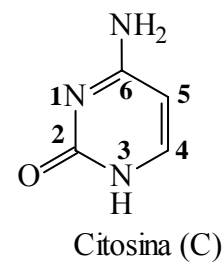
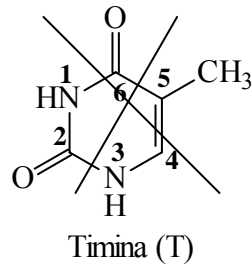
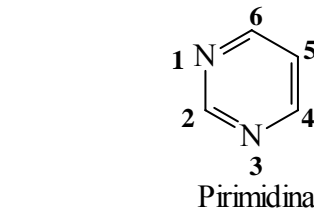
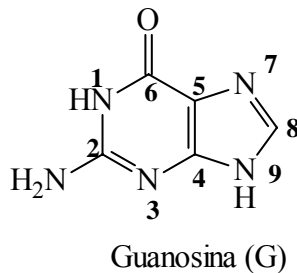
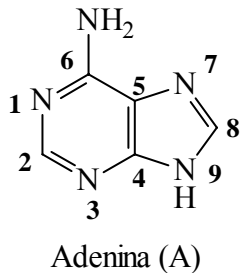
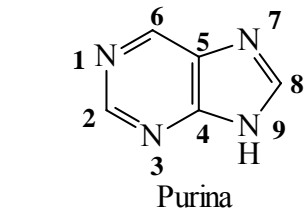


**Ligação C1- com N1
de uma pirimidina
ou N9 de uma purina**

Ligação N-glicosídica configuração β

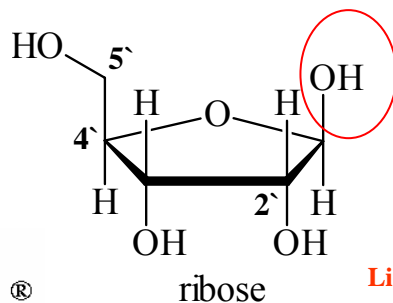
Metabolismo de Fármacos e Toxicidade

Definição: RNA é um polímero longo e não ramificado constituído de ligações Fosfodiéster 3'---5'



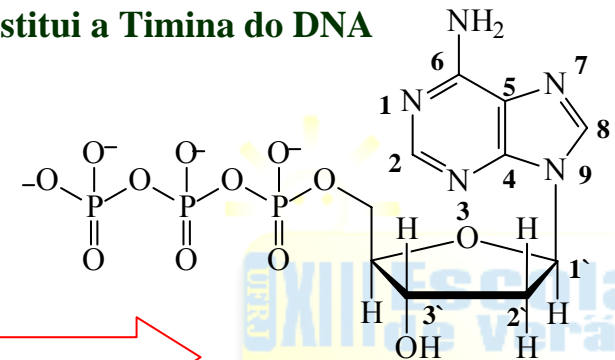
Nucleosídeo

Açúcar é a ribose e presença da base nitrogenada Uracila que substitui a Timina do DNA



**Ligação C1- com N1
de uma pirimidina
ou N9 de uma purina**

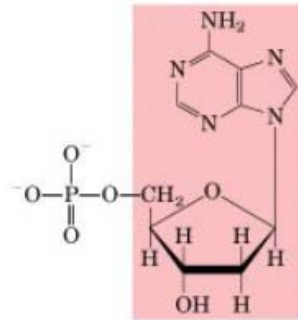
Ligação N-glicosídica configuração β



Nucleotídeo

Desoxiadenosina 5'-trifosfato (dATP)

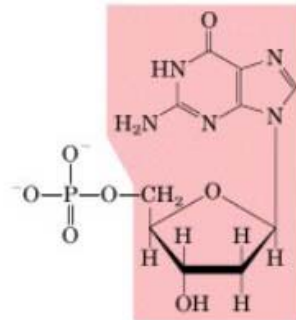
Metabolismo de Fármacos e Toxicidade



Nucleotide: Deoxyadenylate
(deoxyadenosine 5'-monophosphate)

Symbols: A, dA, dAMP

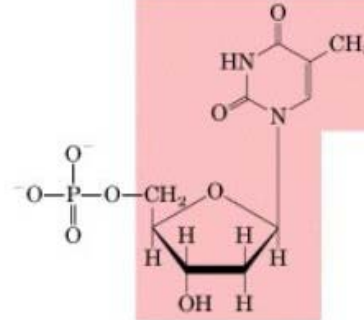
Nucleoside: Deoxyadenosine



Nucleotide: Deoxyguanylate
(deoxyguanosine 5'-monophosphate)

Symbols: G, dG, dGMP

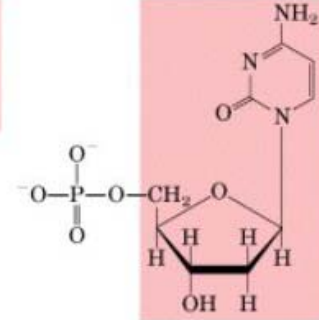
Nucleoside: Deoxyguanosine



Nucleotide: Deoxythymidylate
(deoxythymidine 5'-monophosphate)

Symbols: T, dT, dTMP

Nucleoside: Deoxythymidine

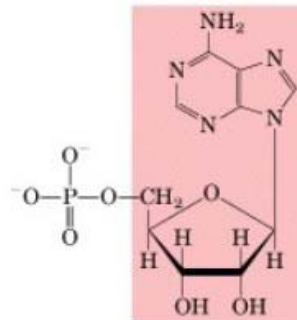


Nucleotide: Deoxycytidylate
(deoxycytidine 5'-monophosphate)

Symbols: C, dC, dCMP

Nucleoside: Deoxycytidine

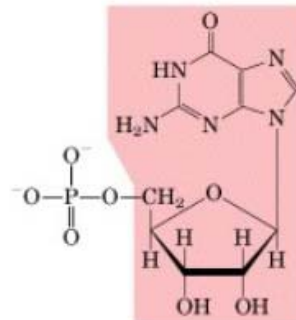
(a) Deoxyribonucleotides



Nucleotide: Adenylate (adenosine 5'-monophosphate)

Symbols: A, AMP

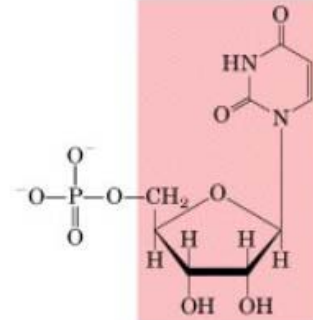
Nucleoside: Adenosine



Nucleotide: Guanylate (guanosine 5'-monophosphate)

Symbols: G, GMP

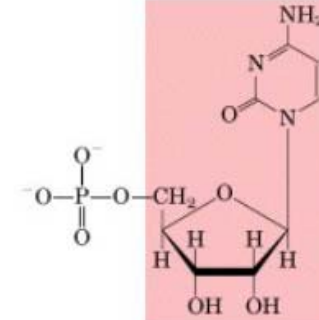
Nucleoside: Guanosine



Nucleotide: Uridylate (uridine 5'-monophosphate)

Symbols: U, UMP

Nucleoside: Uridine

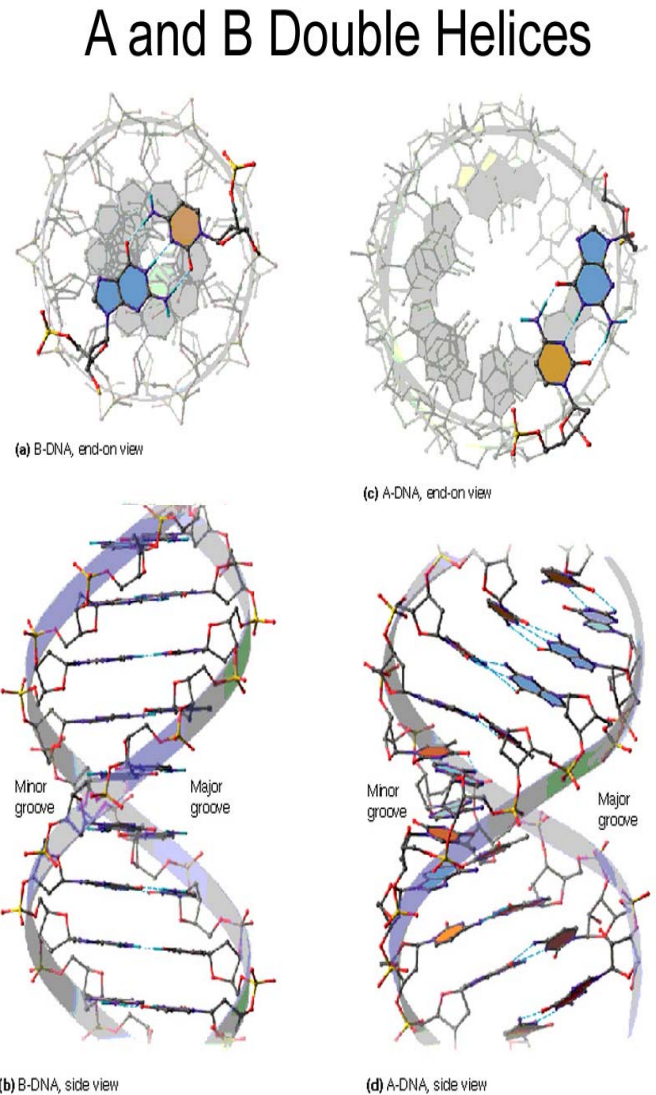


Nucleotide: Cytidylate (cytidine 5'-monophosphate)

Symbols: C, CMP

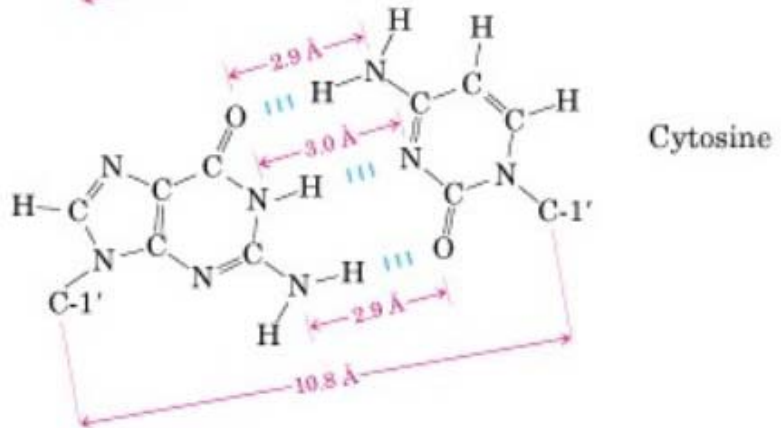
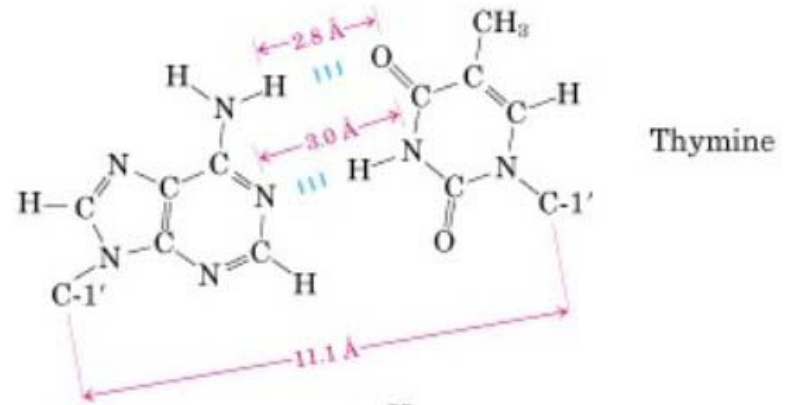
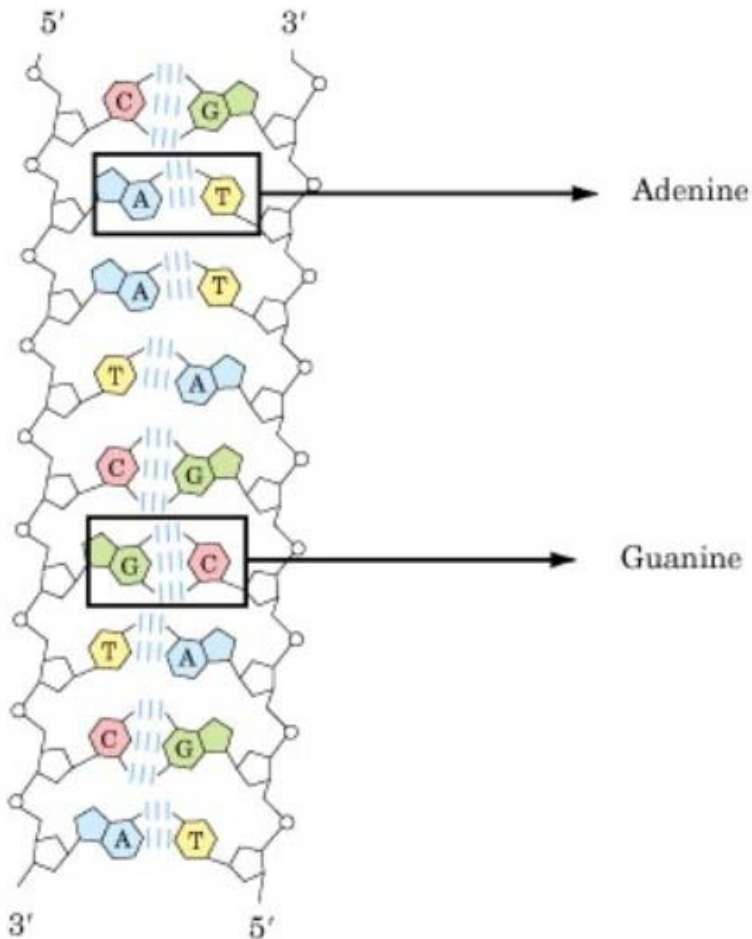
Nucleoside: Cytidine

(b) Ribonucleotides

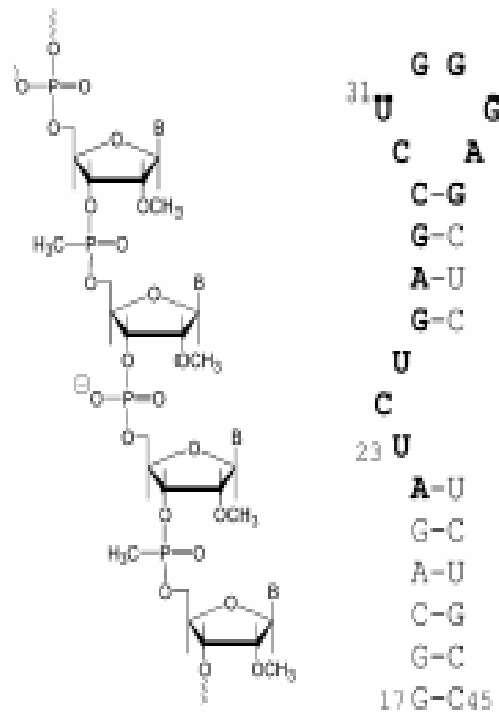
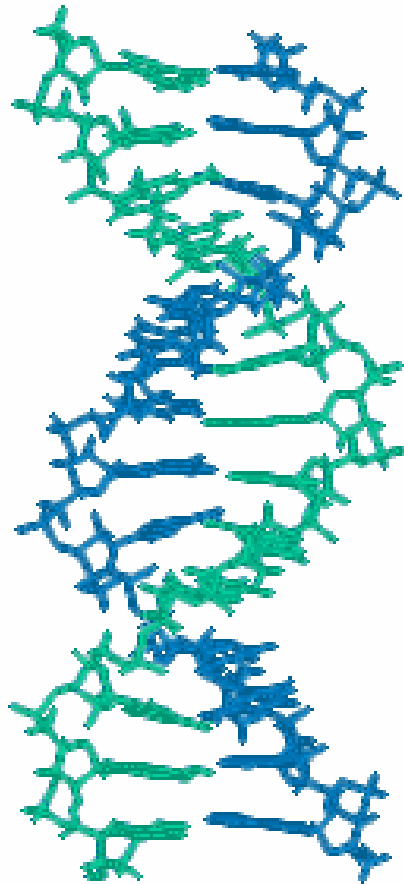


Metabolismo de Fármacos e Toxicidade

Base Pairing

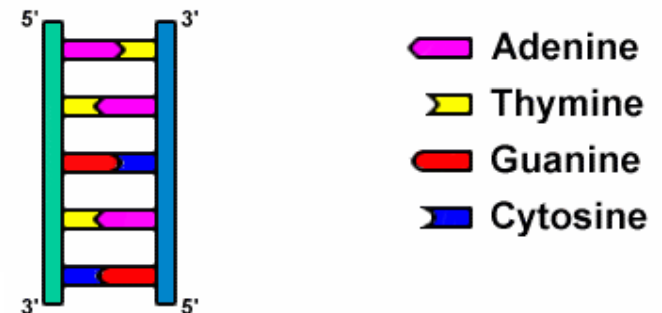
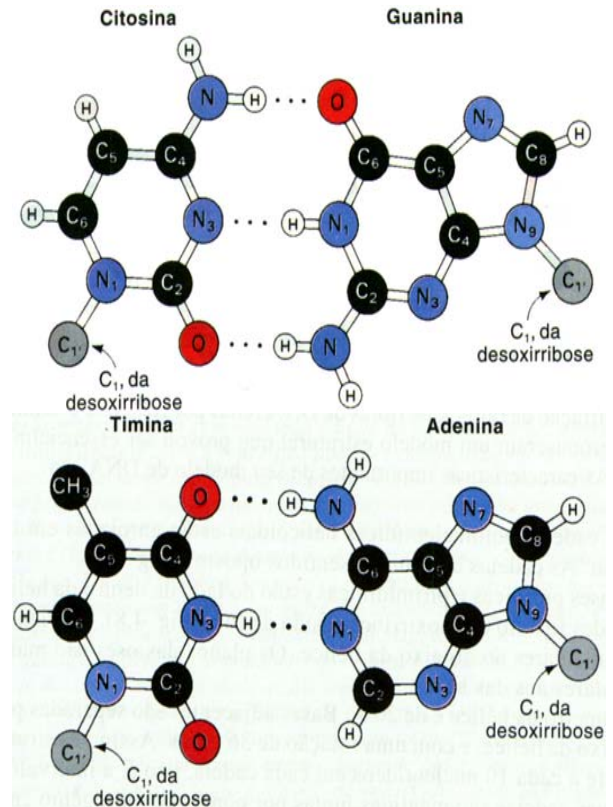


Metabolismo de Fármacos e Toxicidade

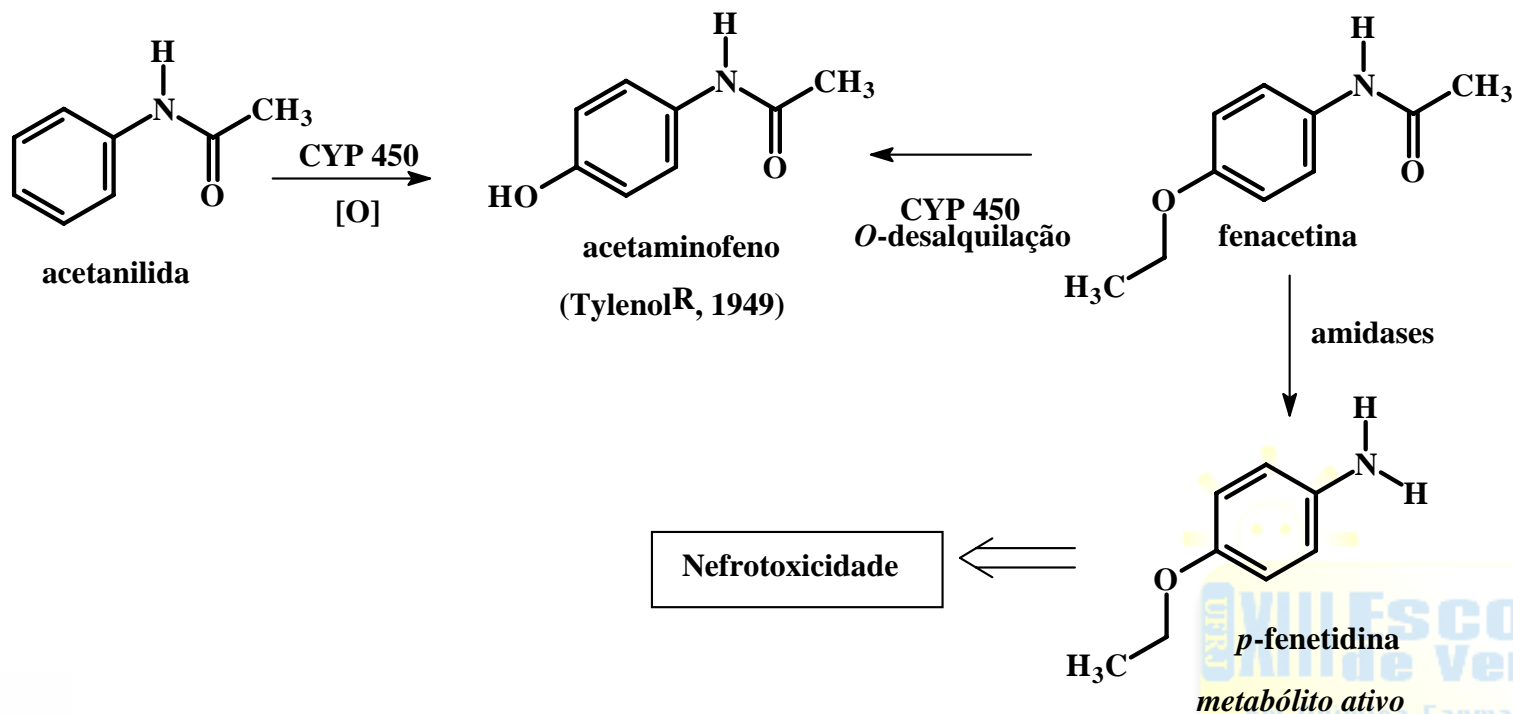
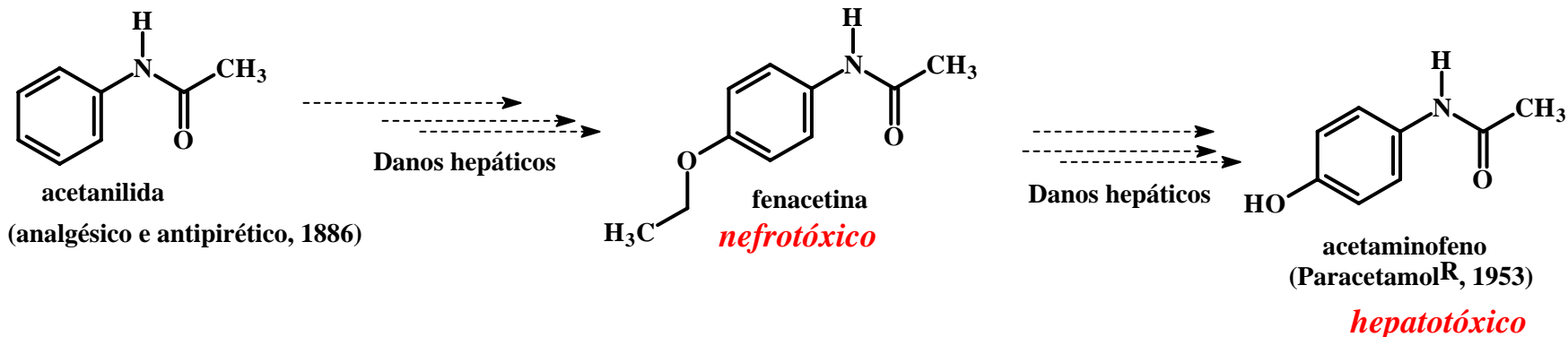


1676 mr-pCpUpCpCpCpApGpGpCpUpCpApGpApU
 1677 mr-pCpUpCpCpCpGpGpApGpCpUpCpApGpApU
 1707 mr-pCpUpCpCpCpApGpGpCpUpCpApGpApU
 1757 mr-pCpUpCpCpCpGpGpApGpCpUpCpApGpApU

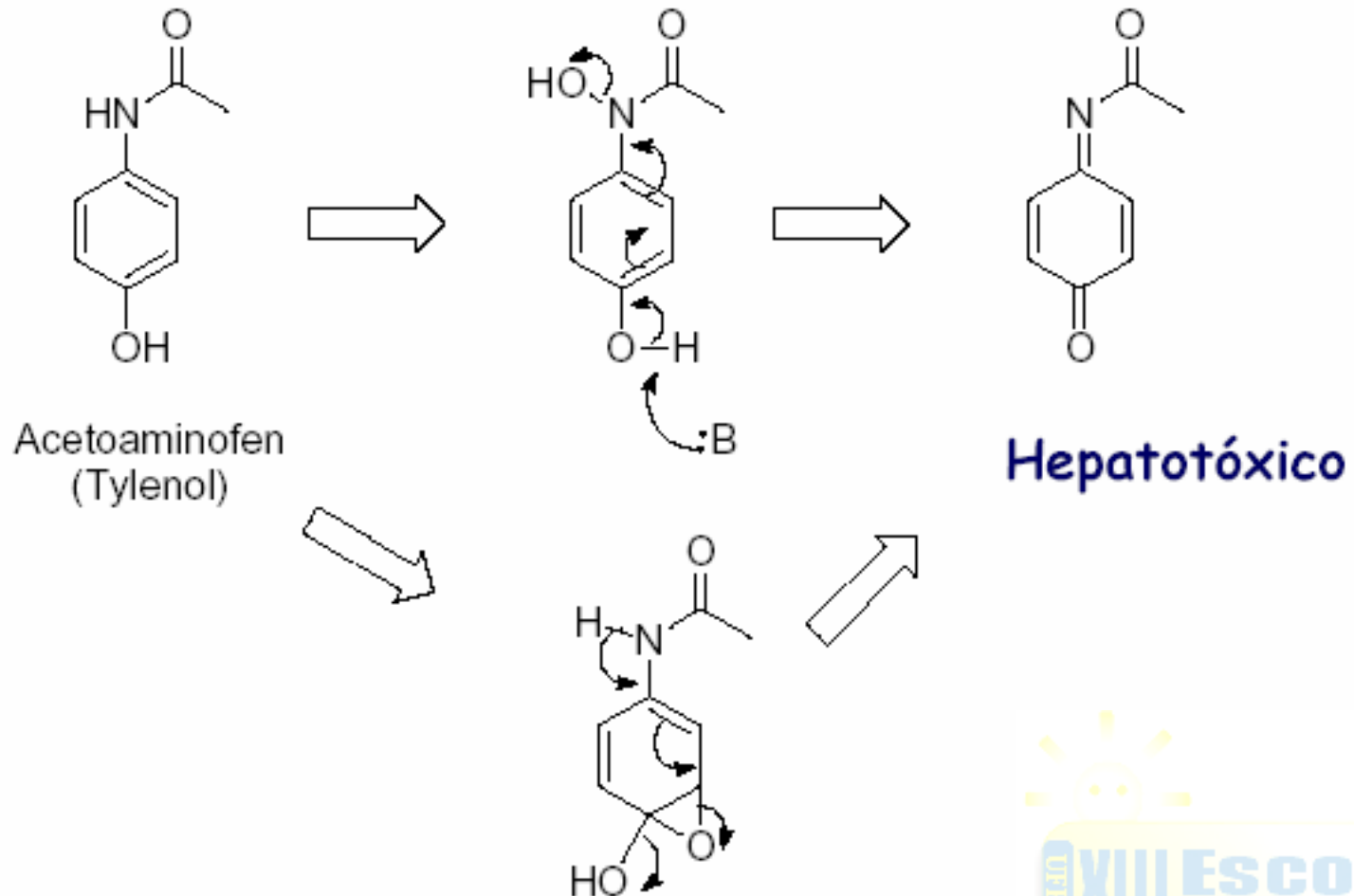
Figure 1. Structure of the alternating oligo-2'-O-methylthio nucleoside methylphosphonate backbone; the sequence of the TAR RNA target; and the sequences of the anti-TAR oligonucleotides. The symbol p is a phosphodiester linkage, *p* is a methylphosphonate linkage and mismatched bases are shown in *italics*. The oligomer binding site on TAR is shown in **bold**.



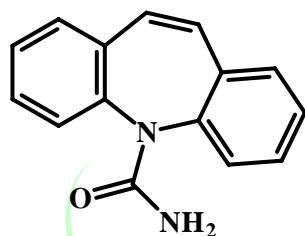
Metabolismo de Fármacos e Toxicidade



Metabolismo de Fármacos e Toxicidade



Metabolismo de Fármacos e Toxicidade



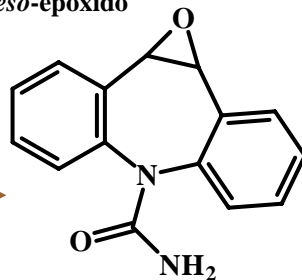
carbamazepina

Tegretol®, 1974

Indutor enzimático

Fase I
CYP450

meso-epóxido

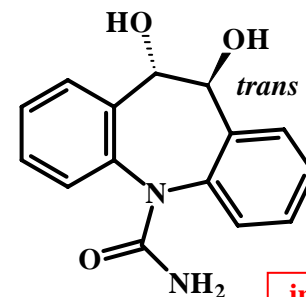


metabólito ativo

epóxido hidrolase
microssomal

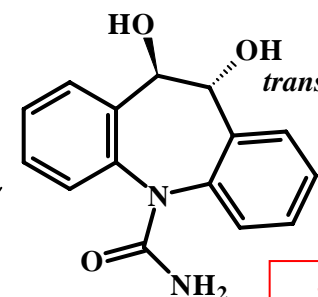
epóxido hidrolase
microssomal

toxicidade

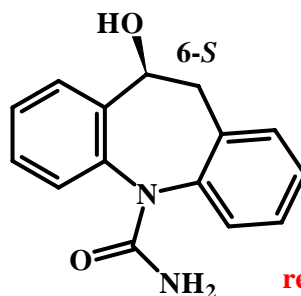


relação 9:1

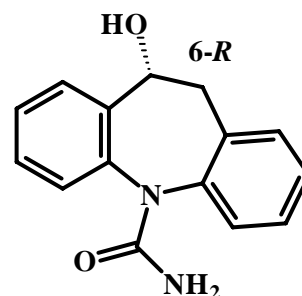
inativo



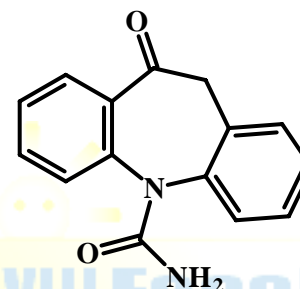
ativo



relação 4:1



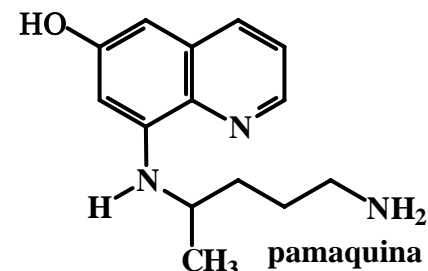
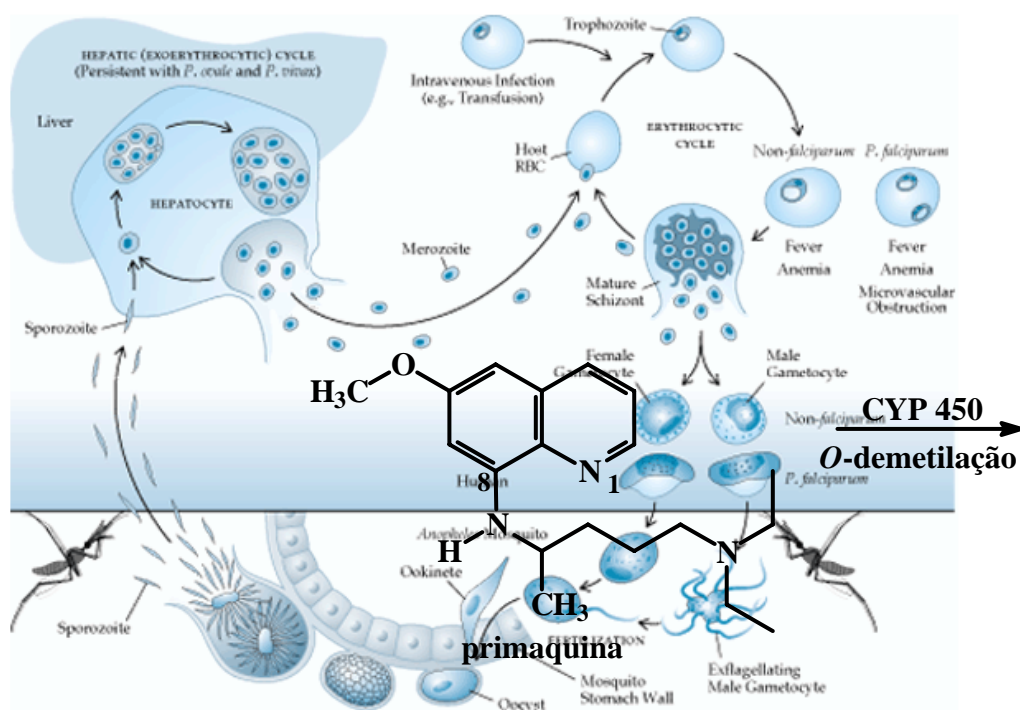
Fase I



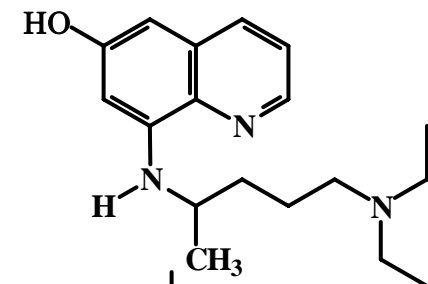
oxcarbazepina

<<<índice de toxicidade

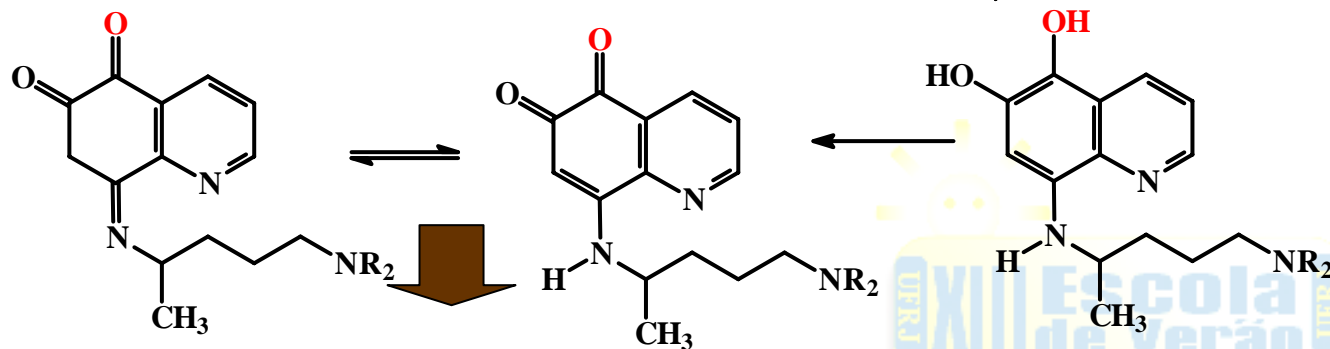
Metabolismo de Fármacos e Toxicidade



CYP 450
N-demetilação

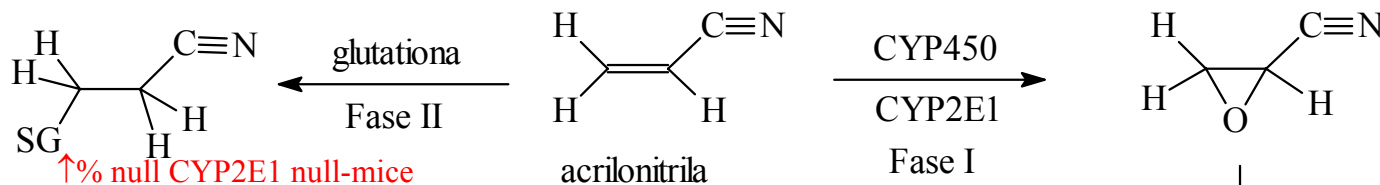


CYP 450



Inibe G6FDH (raça negra)
Mediador de reações de oxi-reduções

Metabolismo de Fármacos e Toxicidade



Polímeros/Resinas

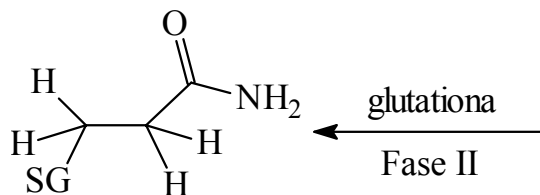
ESTE PRODUTO QUANDO QUEIMADO OU AQUECIDO PODE LIBERAR GASES TÓXICOS DE CIANETO DE HIDROGÊNIO E ÓXIDO DE NITROGÊNIO.

Toxicidade: Espécie: RATO

Via Respiração (CL50): LCLo (4 h) = 500 ppm

Via Oral (DL 50): 78 mg/kg "AGUDO"

Via Cutânea (DL 50): 96 mg/kg (SUBCUT.)

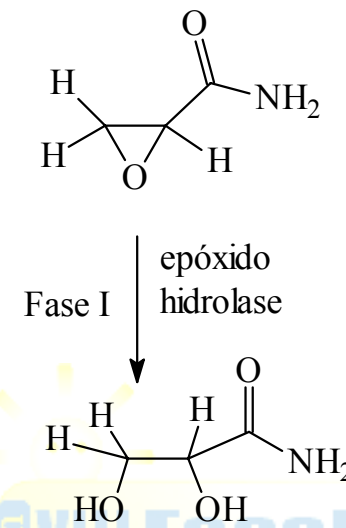
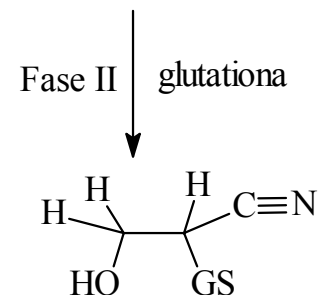


$\uparrow\%$ null CYP2E1 null-mice

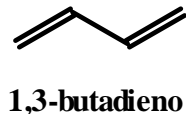
acrilamida

Formada espontaneamente em alimentos ricos em carboidratos quando preparados em temperaturas superiores a 120°C, a presença da acrilamida foi detectada depois de um acidente durante a construção de um túnel na Suécia, em 1997. Na ocasião, trabalhadores foram intoxicados por um produto usado para vedar vazamentos de água composto por acrilamida, que já era utilizada na indústria e conhecida por sua ação neurotóxica. Além de danos neurológicos, como dormência em membros inferiores e superiores, pesquisadores detectaram no sangue dos trabalhadores contaminados níveis elevados de adutos acrilamida-hemoglobina, um composto formado pela união substâncias tóxicas à hemoglobina

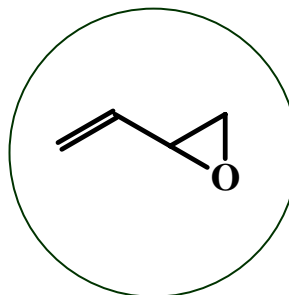
Role of CYP 450 2E1 in the metabolism of acrylamide and acrylon
 Sumner, S. C. J. *et al.*, Chem. Res. Toxicol. (1999)12: 1110-1116



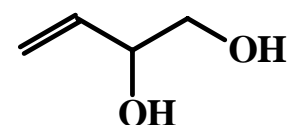
Metabolismo de xenobióticos e Toxicidade



CYP450

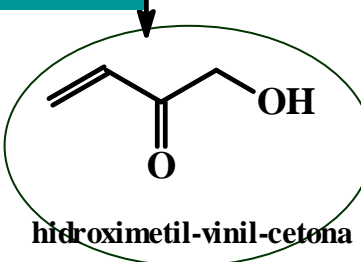
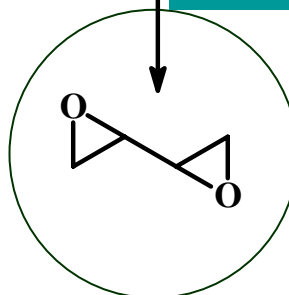


EH



CYP450

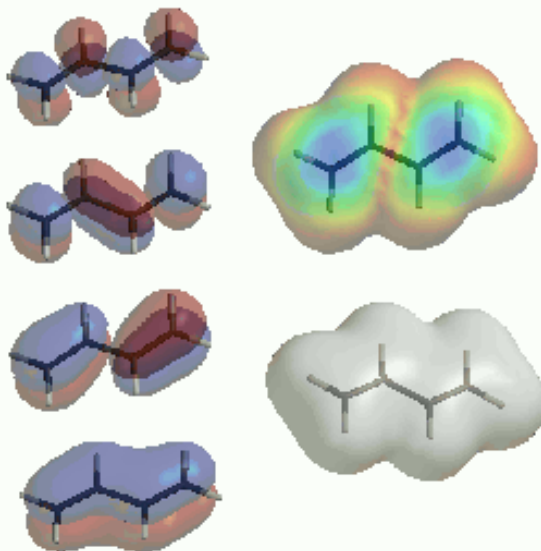
GSH + glutathione S-transferase



Aductos com DNA ou hemoglobina

Borrachas e Plásticos detectado em gasolina, fumaça de cigarro, ar urbano ⇒ "human carcinogen"

☛ cancer hematopoiético



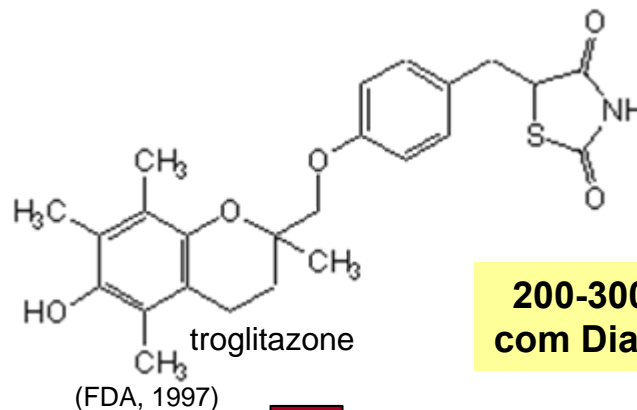
Espécies Eletrofílicas

X

?

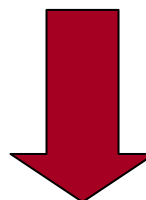
Bionucleófilos

Metabolismo de xenobióticos e Toxicidade



200-300 milhões de pessoas
com Diabetes Mellitus em 2010

Class: THIAZOLIDINEDIONES

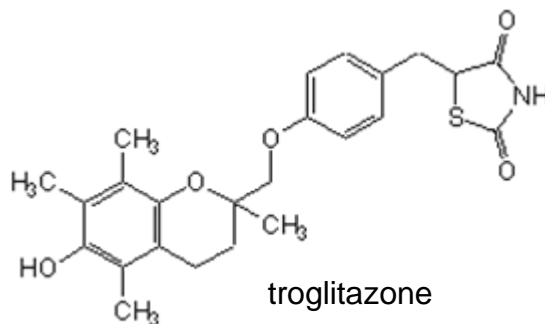


Proscrito em 2000 (Reações idiossincráticas com severa hepatotoxicidade)

Metabolismo de xenobióticos e Toxicidade



(FDA, 1997)



Proscrito em 2000 (Reações idiossincráticas com severa hepatotoxicidade)

Class: **THIAZOLIDINEDIONES**

K. He et al. / Biochemical Pharmacology 62 (2001) 191–198

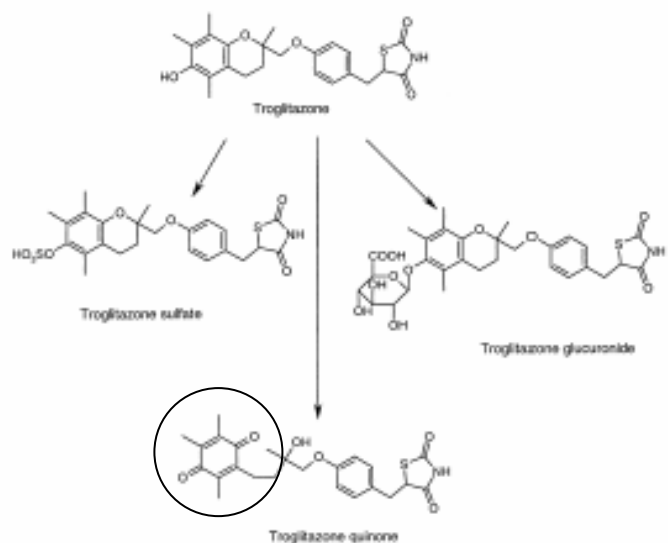


Fig. 1. Scheme of primary metabolic pathways involved in TGZ metabolism.

CYP3A4 was demonstrated to be the predominant CYP enzyme responsible for TGZ quinone formation in human liver microsomes and hepatocytes.

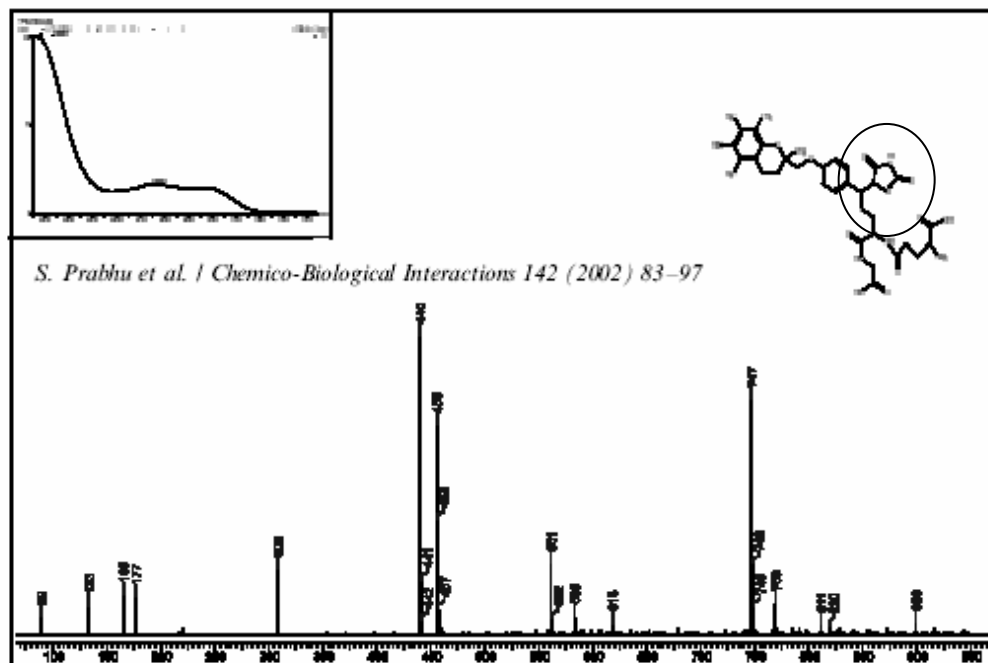
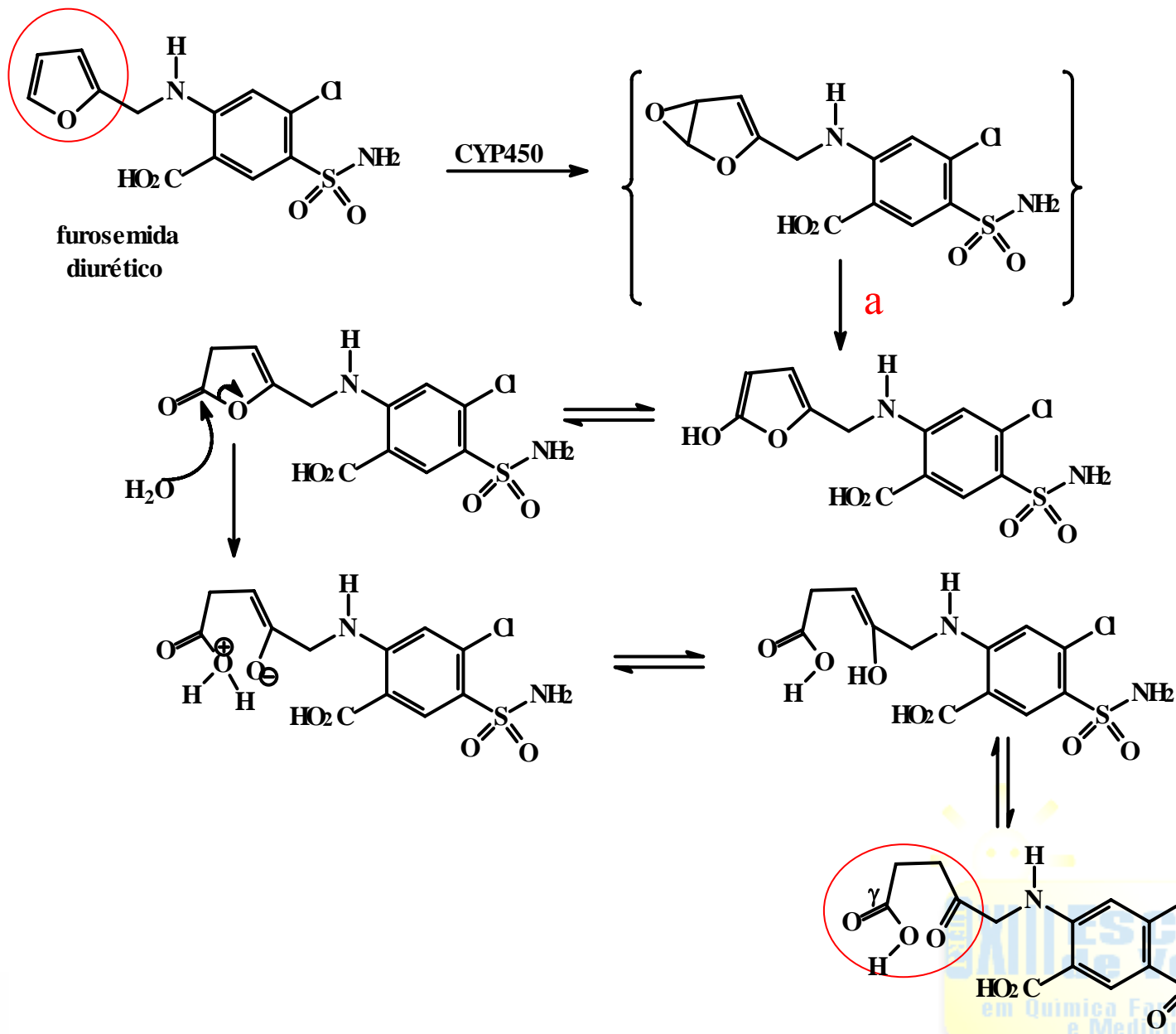
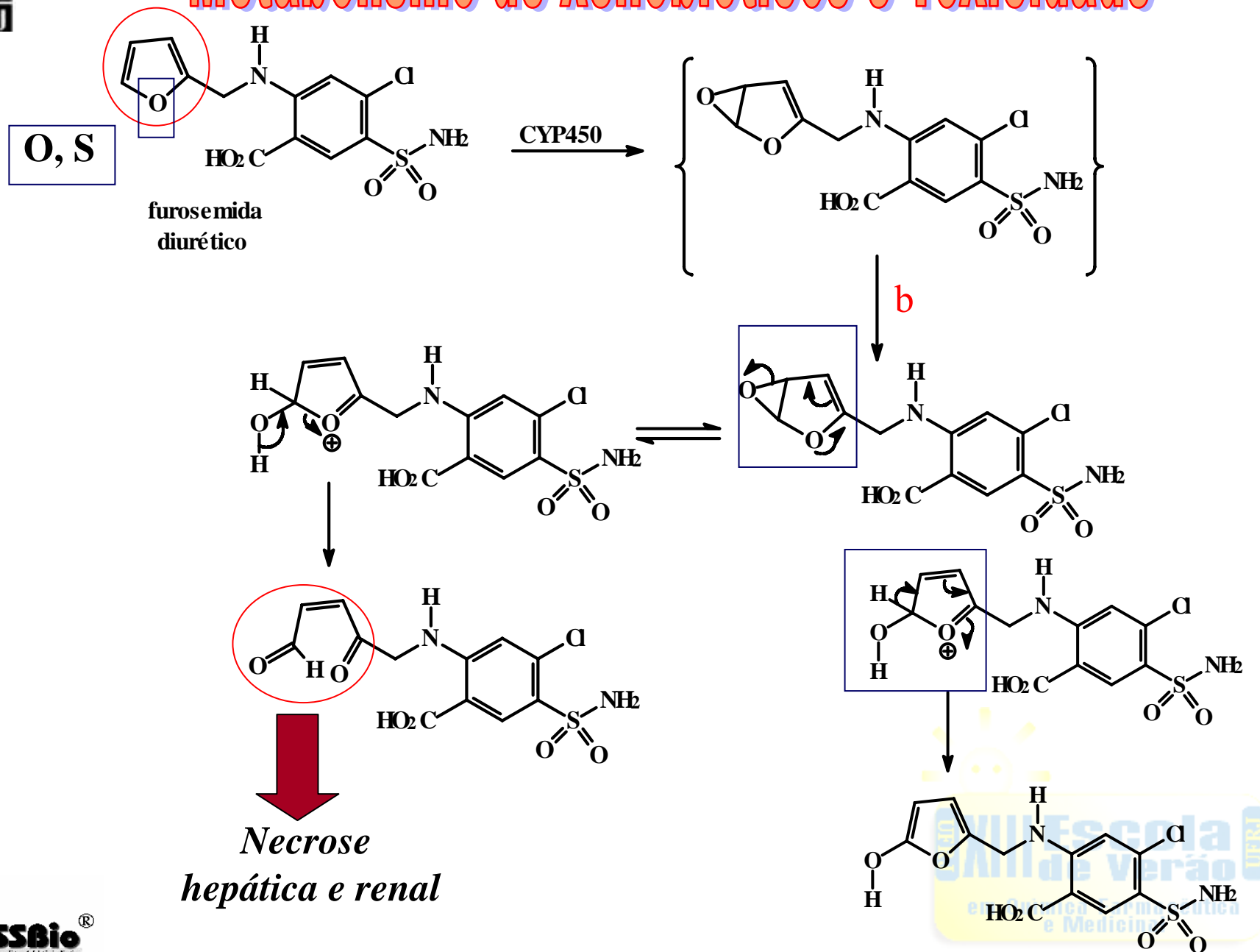


Fig. 2. Full scan MS spectra of MET-1 (MS range 50–1050 Da). The characteristic fragments included 747, 618, 440, and 308. The full scan MS as well as UV spectra of MET-2 were similar to MET-1. Inset shows the UV spectra of MET-1 ($\lambda_{max} = 275$ nm).

Metabolismo de xenobióticos e Toxicidade



Metabolismo de xenobióticos e Toxicidade



Estudo do Metabolismo de Xenobióticos

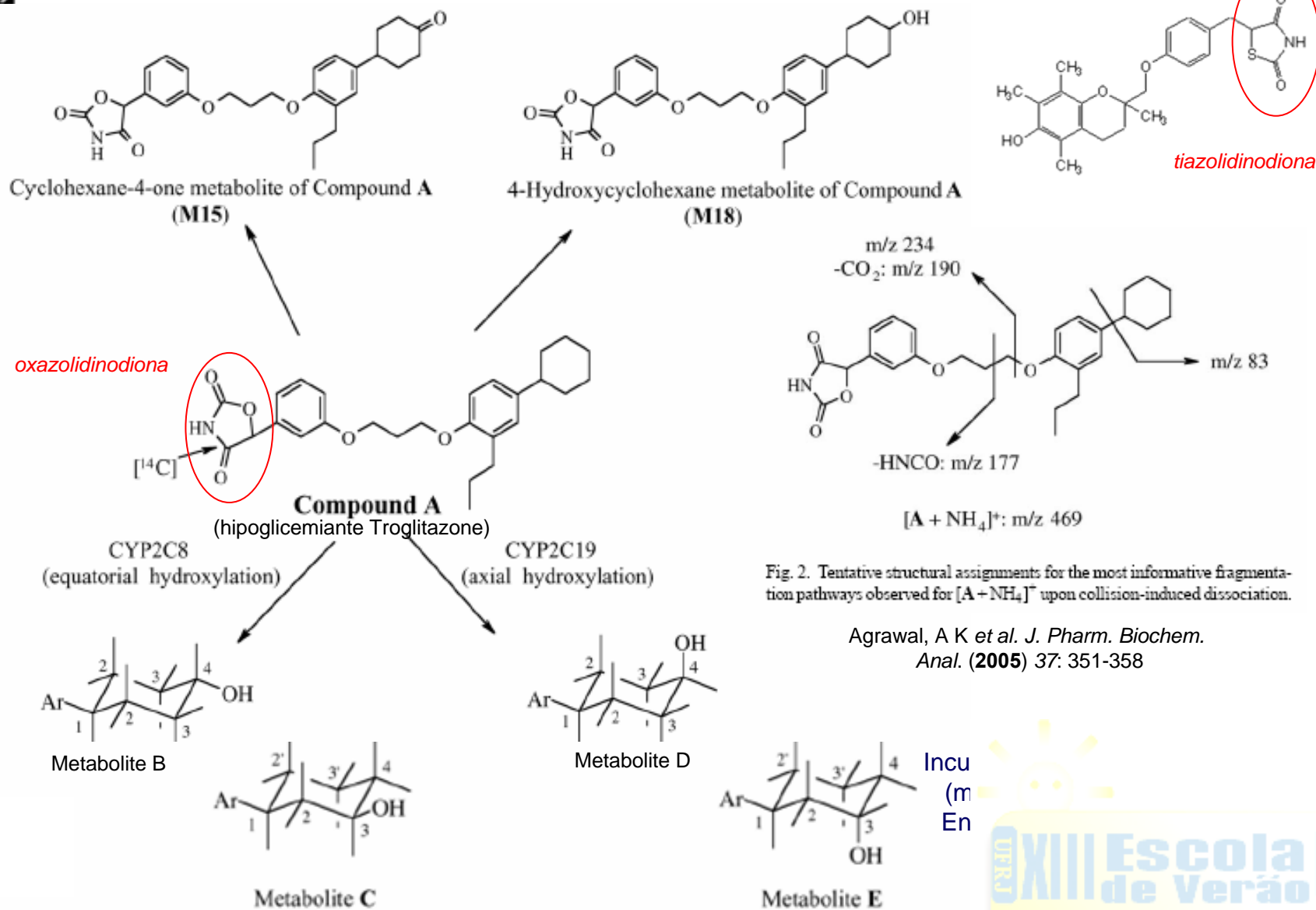


Fig. 2. Tentative structural assignments for the most informative fragmentation pathways observed for $[\text{A} + \text{NH}_4]^+$ upon collision-induced dissociation.

Agrawal, A K et al. *J. Pharm. Biochem. Anal.* (2005) 37: 351-358

Aspectos Estereoquímicos do Metabolismo de Fármacos

Estereoquímica: Parte da Química que estuda as estruturas tridimensionais das moléculas

Isomerismo: isômeros são compostos diferentes que possuem a mesma fórmula molecular

Tipos: isômeros de cadeia (*e.g.* butano x isobutano)

isômero de posição (*e.g.* 2-cloropropano x 1-cloropropano)

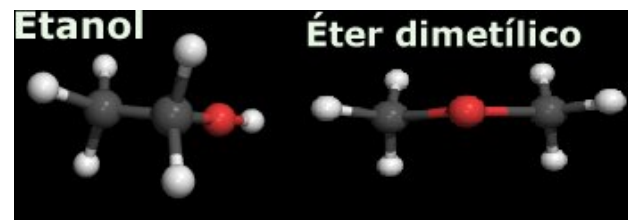
Estruturais ← isômero de grupo funcional (*e.g.* etanol x éter dimetílico)

isômero conformacionais (*e.g.* anti, sinperiplanar)

Estereo-isômeros ← isômero geométrico (*e.g.* (Z)-2-buteno x (E)-2-buteno)

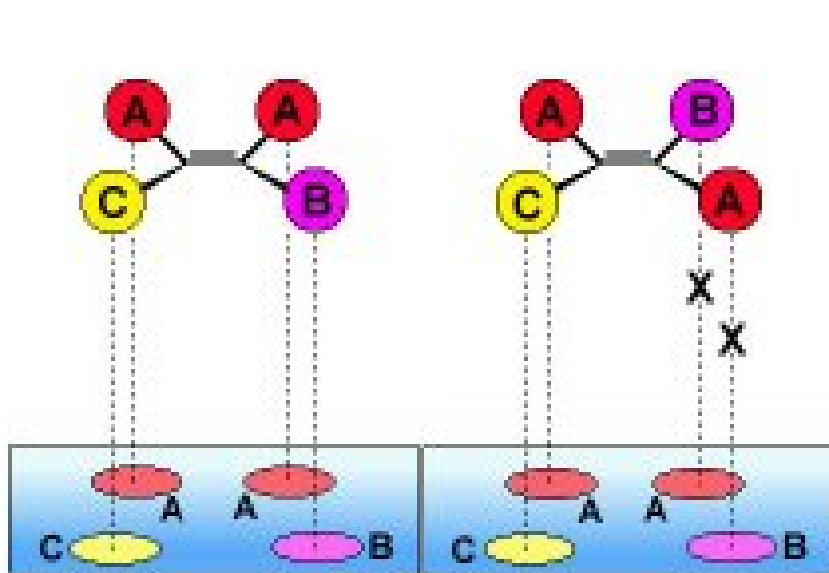
isômero ópticos (enantiômeros x diastereoisômero)

QUIRALIDADE ?

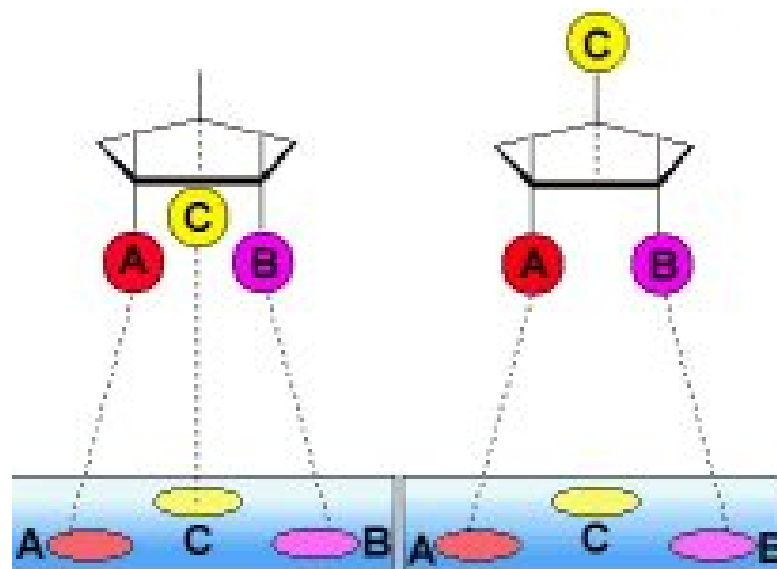


Aspectos Estereoquímicos do Metabolismo de Fármacos

ISOMERIA GEOMÉTRICA



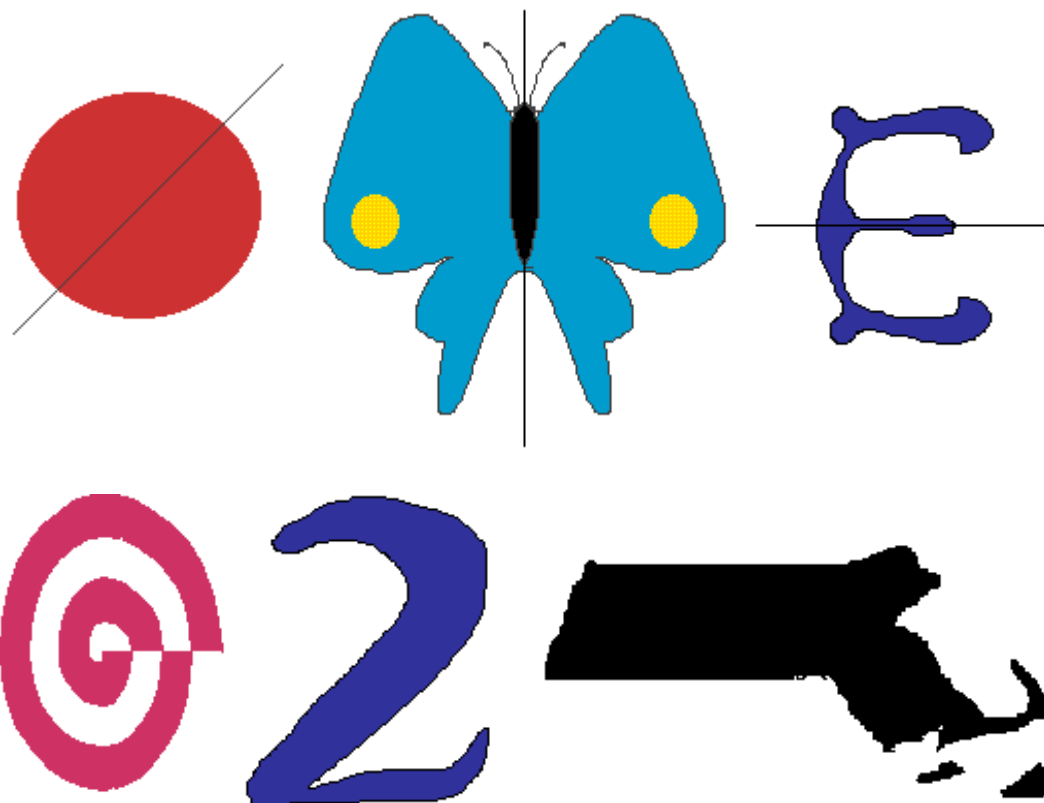
Neste caso, somente o primeiro enantiômero possui a configuração correta para o receptor: quando os grupos A estão em trans a molécula não "encaixa" com o sítio receptor.



Neste caso, o grupo C do segundo enantiômero está em uma posição desfavorável à interação com o receptor.

Aspectos Estereoquímicos do Metabolismo de Fármacos

QUIRALIDADE: Propriedade molecular relacionada à ausência na molécula de eixo de simetria ou presença de centro assimétrico ou quiral

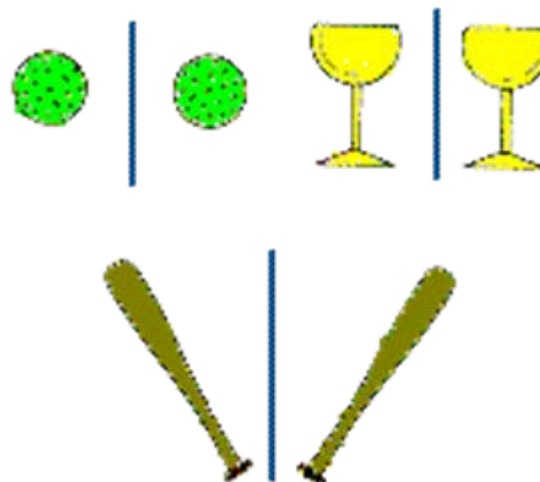
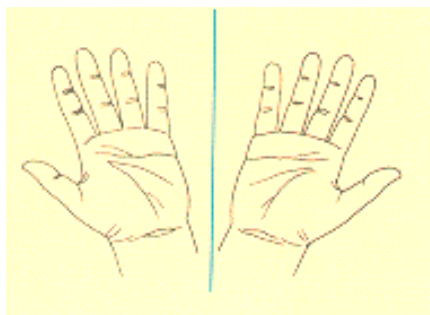


Jean-Baptisti Biot (1815): Propôs que a atividade ótica é a habilidade da substância rodar o plano da luz polarizada

Louis Pasteur (1848): Propôs os fundamentos da estereoquímica: atividade ótica de soluções orgânicas é determinada por assimetria molecular que produz estruturas de imagens especulares não sobreponíveis

Aspectos Estereoquímicos do Metabolismo de Fármacos

Louis Pasteur (1848): Propôs os fundamentos da estereoquímica: atividade ótica de soluções orgânicas é determinada por assimetria molecular que produz estruturas de imagens especulares não sobreponíveis

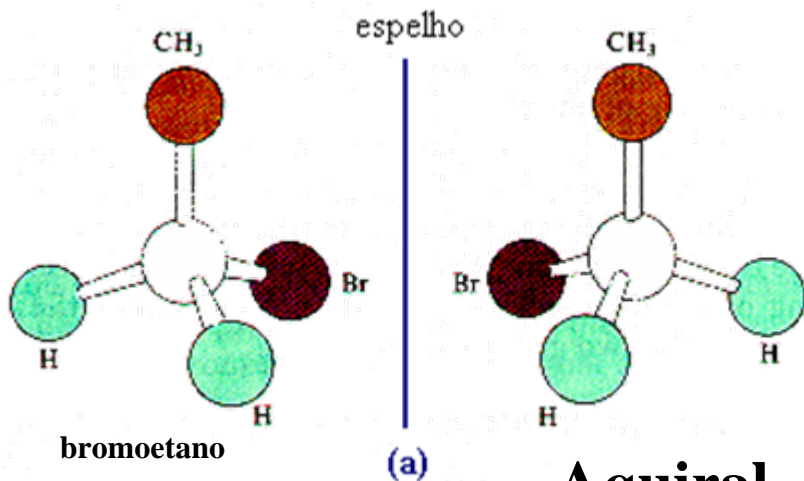


Jacobus Henricus Van't Hoff & Joseph Achille Le Bel (1874): Avanço sobre a teoria de estruturas orgânicas em 3 dimensões: propuseram que as quatro valências de um determinado átomo encontrava-se num arranjo espacial tetraédrico, e quando substituído por quatro grupos diferentes o tornaria assimétrico (centro estereogênico ou quiral), sendo capaz de existir em duas formas distintas (enantiômeros) não sobreponíveis.

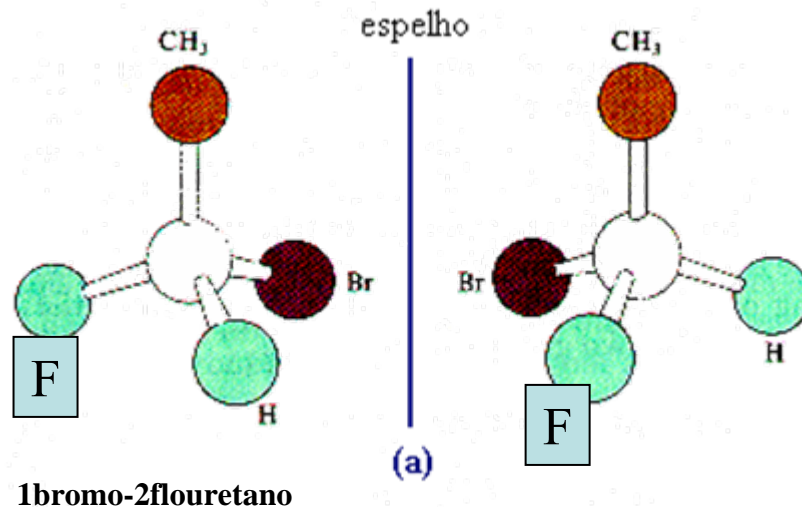
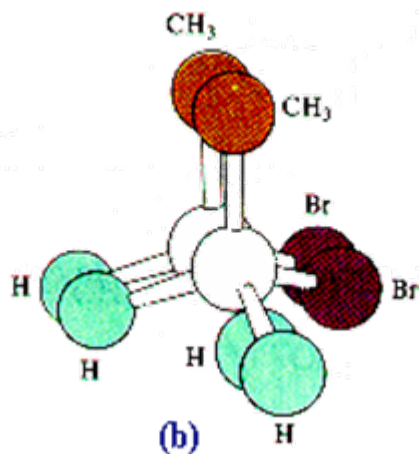
Estereoisômero (isômero óptico)
 ↗ Enantiômero
 ↘ Diastereoisômero

Substância opticamente ativa é aquela cuja estrutura tridimensional não é sobreponível a sua imagem especular

Aspectos Estereoquímicos do Metabolismo de Fármacos



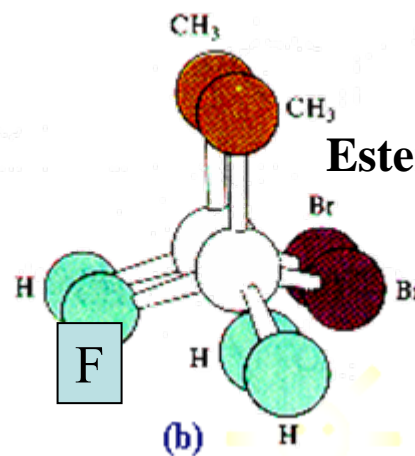
Aquiral



Quiral

Estereoisômeros

Quantos ?



Fórmula = 2^n , n = números de C quirais

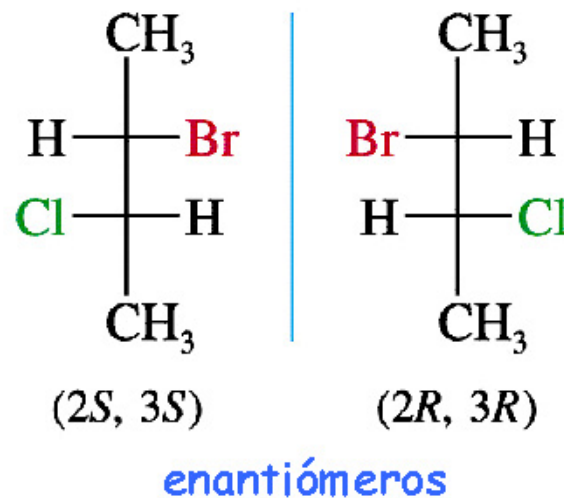
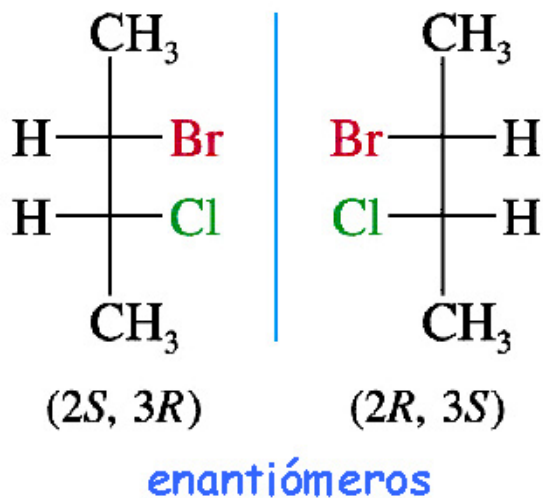
Aspectos Estereoquímicos do Metabolismo de Fármacos

Figura 6.5.

2-Bromo-3-clorobutano

Fórmula = 2^n , n = números de C quirais

4 estereoisómeros



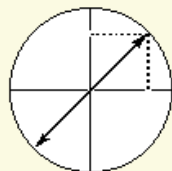
diastereoisómeros

Mistura racêmica ou racemato: mistura opticamente inativa, contendo mistura (1:1) de enantiômeros

Aspectos Estereoquímicos do Metabolismo de Fármacos

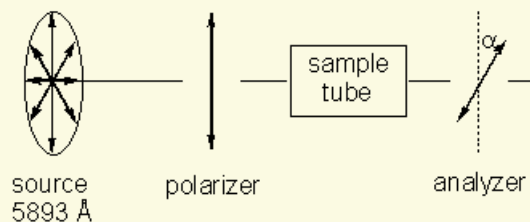
Plane-polarized light

Ordinary light is a moving wave whose vibrations take place in all directions perpendicular to the direction in which the light is travelling. One can envisage each vibration as the vector of two vibrations which are mutually at right angles.



One of these vectors can be eliminated by passing ordinary light through a polarizer - Polaroid filter. The resulting light is said to be polarized - all its vibrations are parallel to a single plane.

Polarimeter



Biot

Discovered
Optical Activity



Pasteur

Separated
Enantiomers



van't Hoff

Tetrahedral
Carbon Atom



Fisher

Identified the
16 Aldohexoses

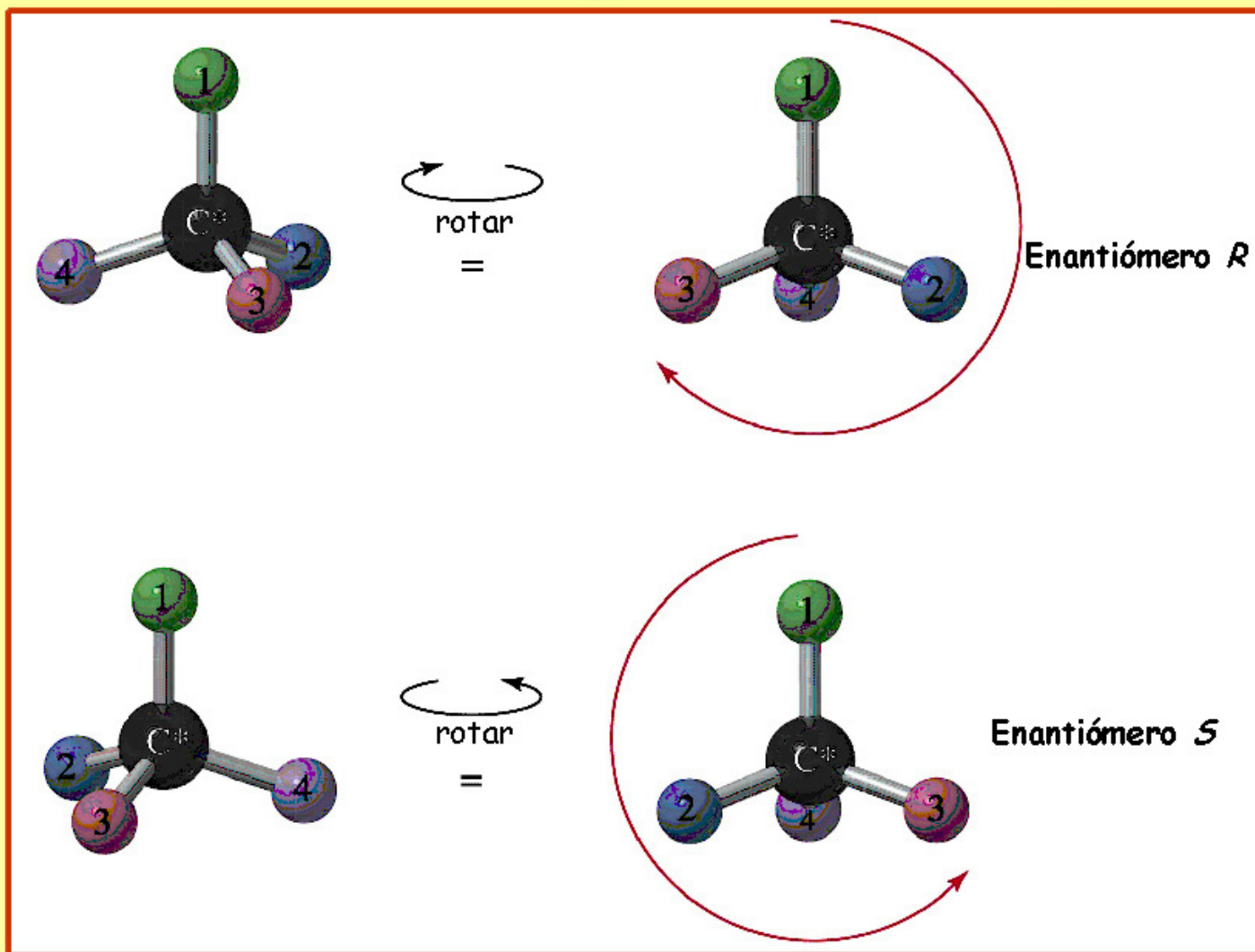


Prelog

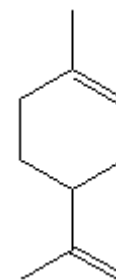
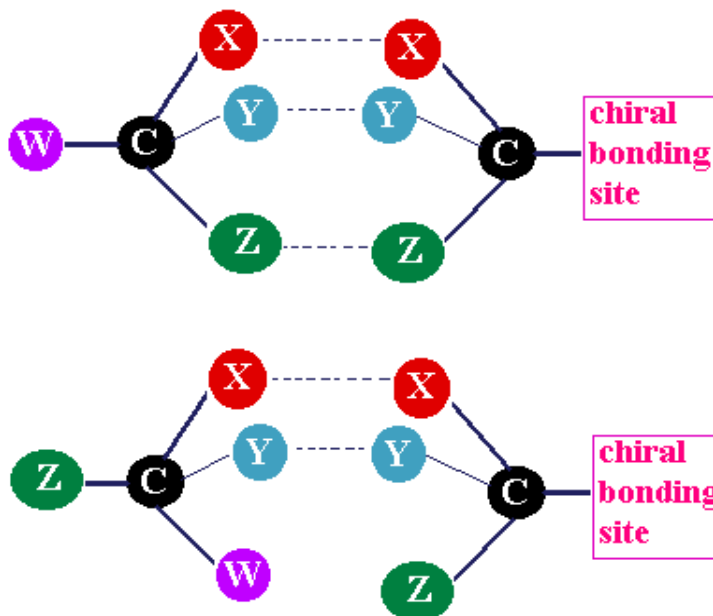
Devised
R/S & Z/E

Aspectos Estereoquímicos do Metabolismo de Fármacos

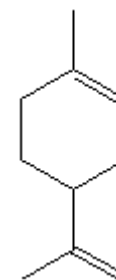
Notaciones Configuracionales *R* y *S* Figura 6.1



Aspectos Estereoquímicos do Metabolismo de Fármacos

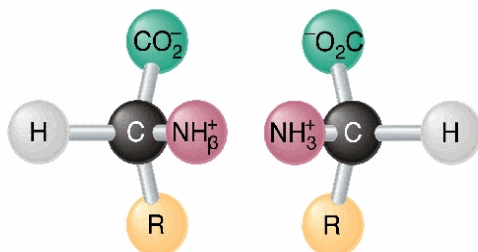


R-(+)-limoneno
laranja

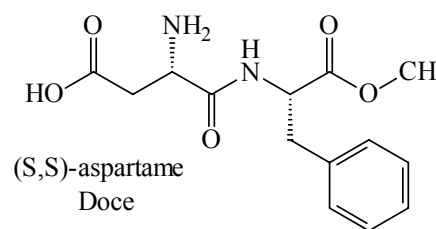
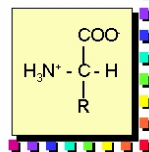


S-(-)-limoneno
limão

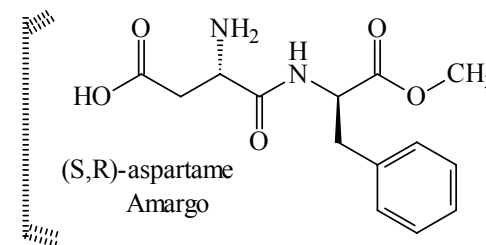
Stereochemistry of α -Amino Acids



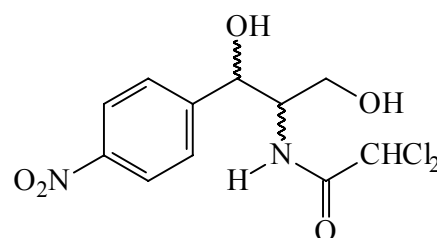
- It is the L-form (shown at right above) which exists in naturally-occurring amino acids, and thus in the proteins they form.
- See Fischer projection at right.



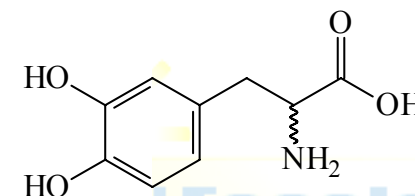
(S,S)-aspartame
Doce



(S,R)-aspartame
Amargo



(S,S)-clorfenicol (tuberculostático)
(R,R)-clorfenicol (cegueira)



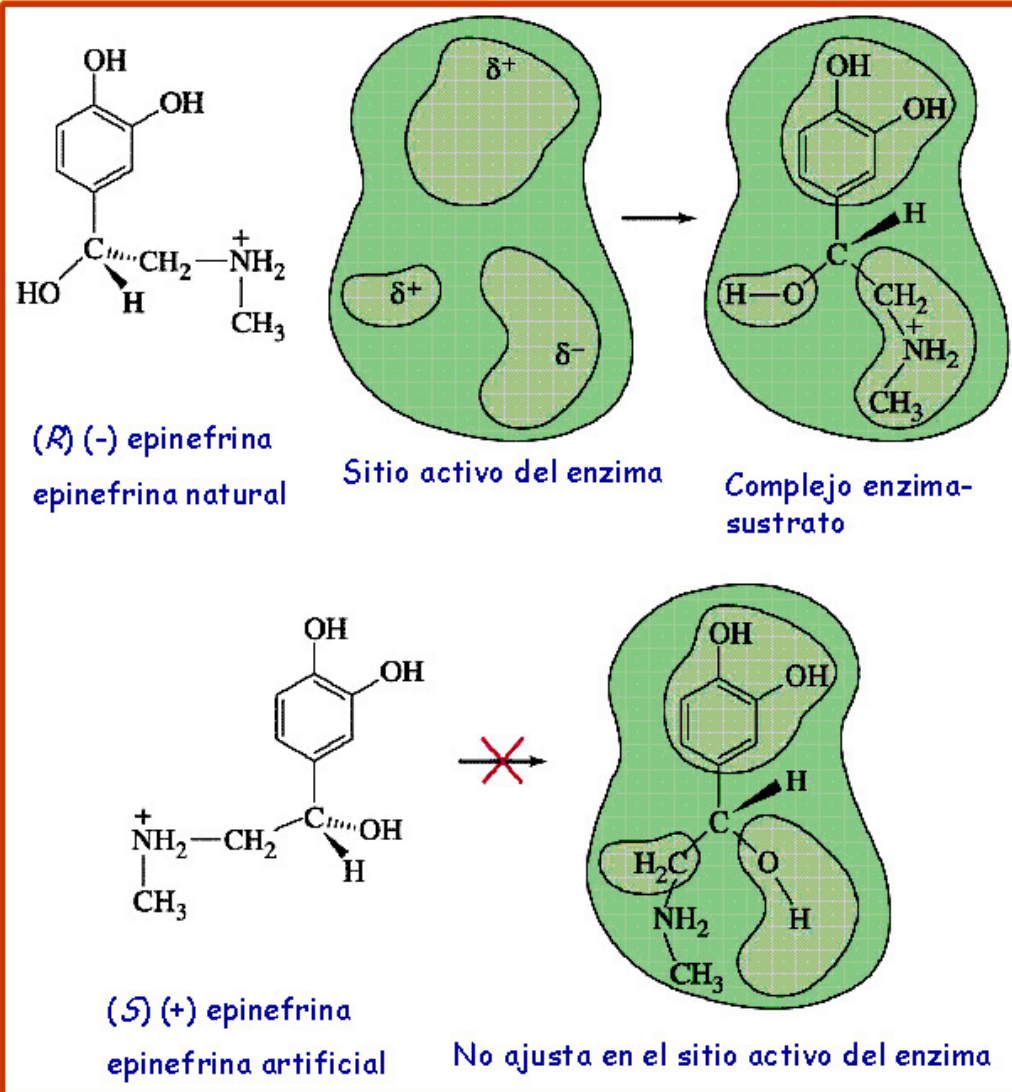
L-DOPA (antiparkinsoniano)
D-DOPA (granulocitopenia)

Aspectos Estereoquímicos do Metabolismo de Fármacos

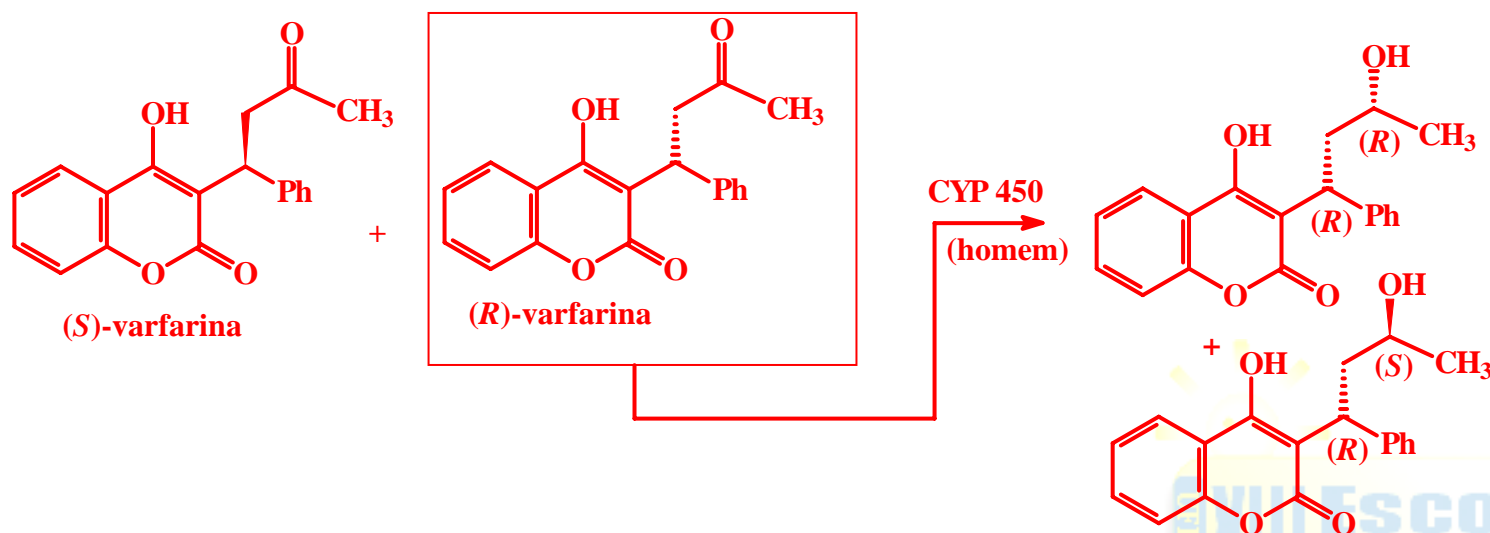
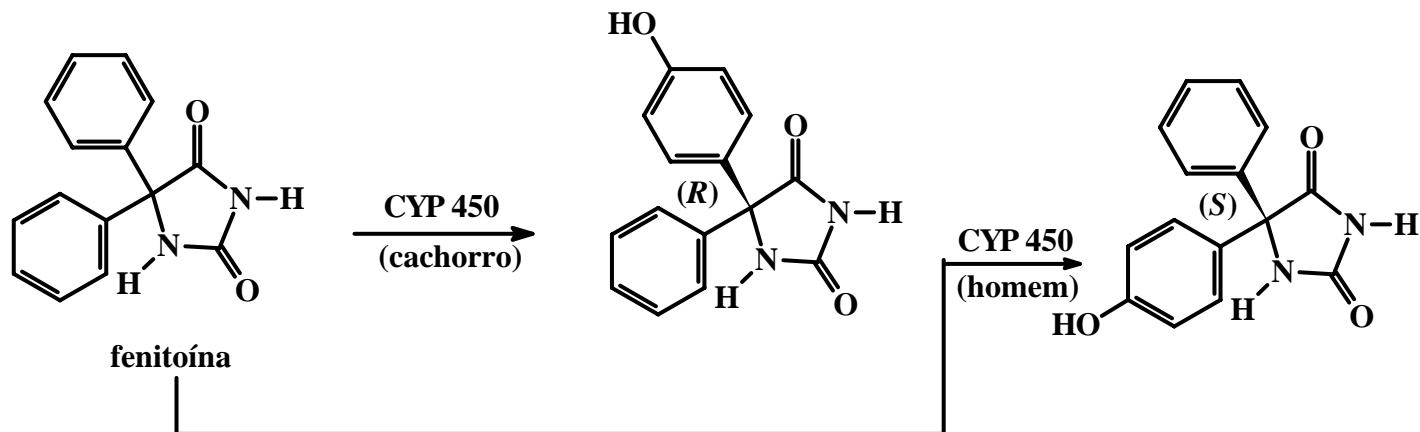
Reconocimiento quiral de la epinefrina por un enzima

Sólo el enantiómero levógiro ajusta en el sitio activo del enzima

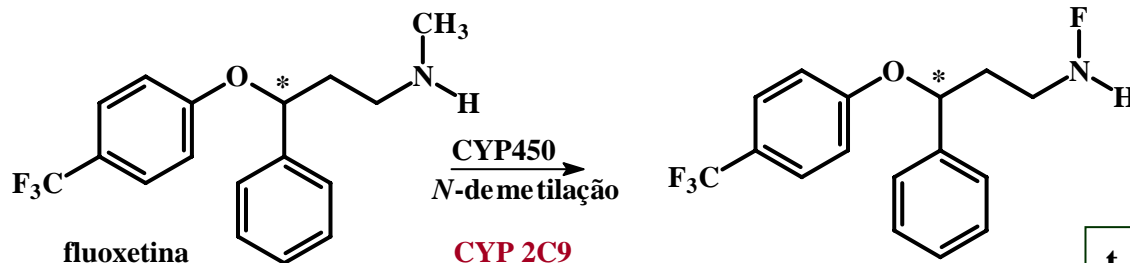
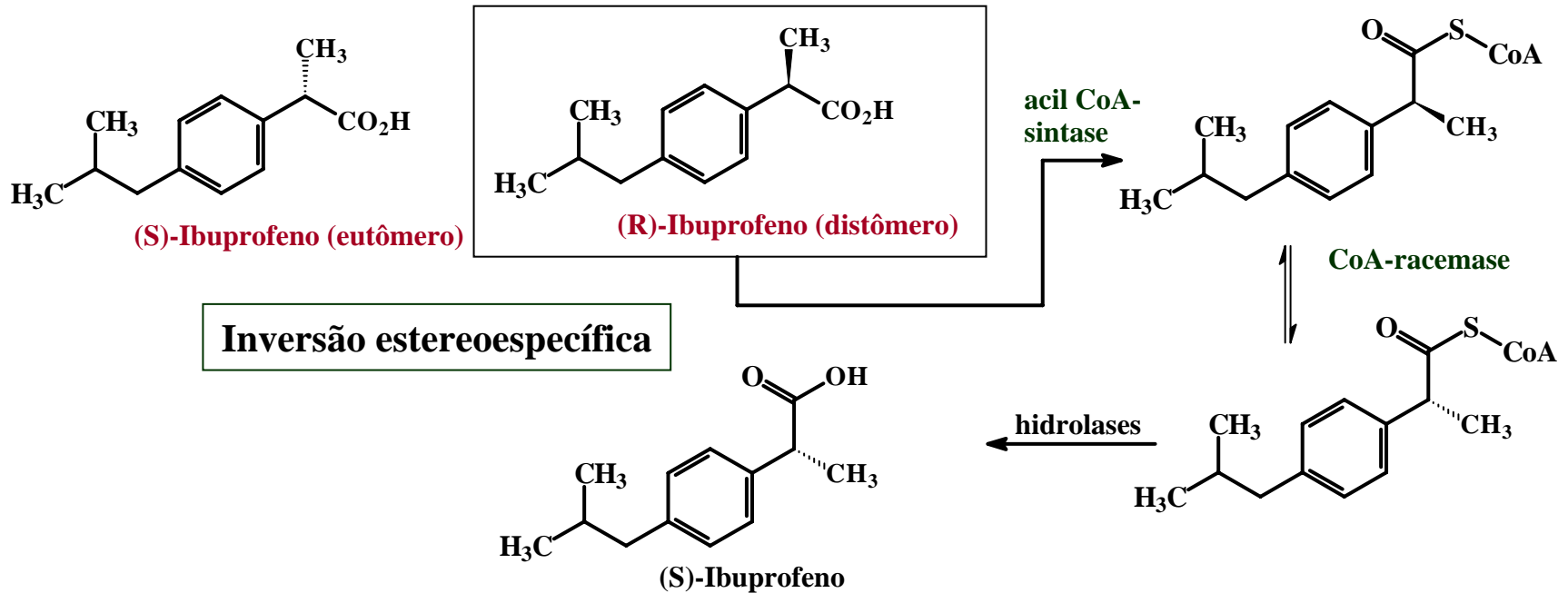
Figura 6.4.



Aspectos Estereoquímicos do Metabolismo de Fármacos



Aspectos Estereoquímicos do Metabolismo de Fármacos



Prozac®, Eli Lilly
(S)-1,5 x mais ativo
SSRI → Antidepressivo

CYP 2C9
CYP 2D6
CYP 2C19
CYP 3A4

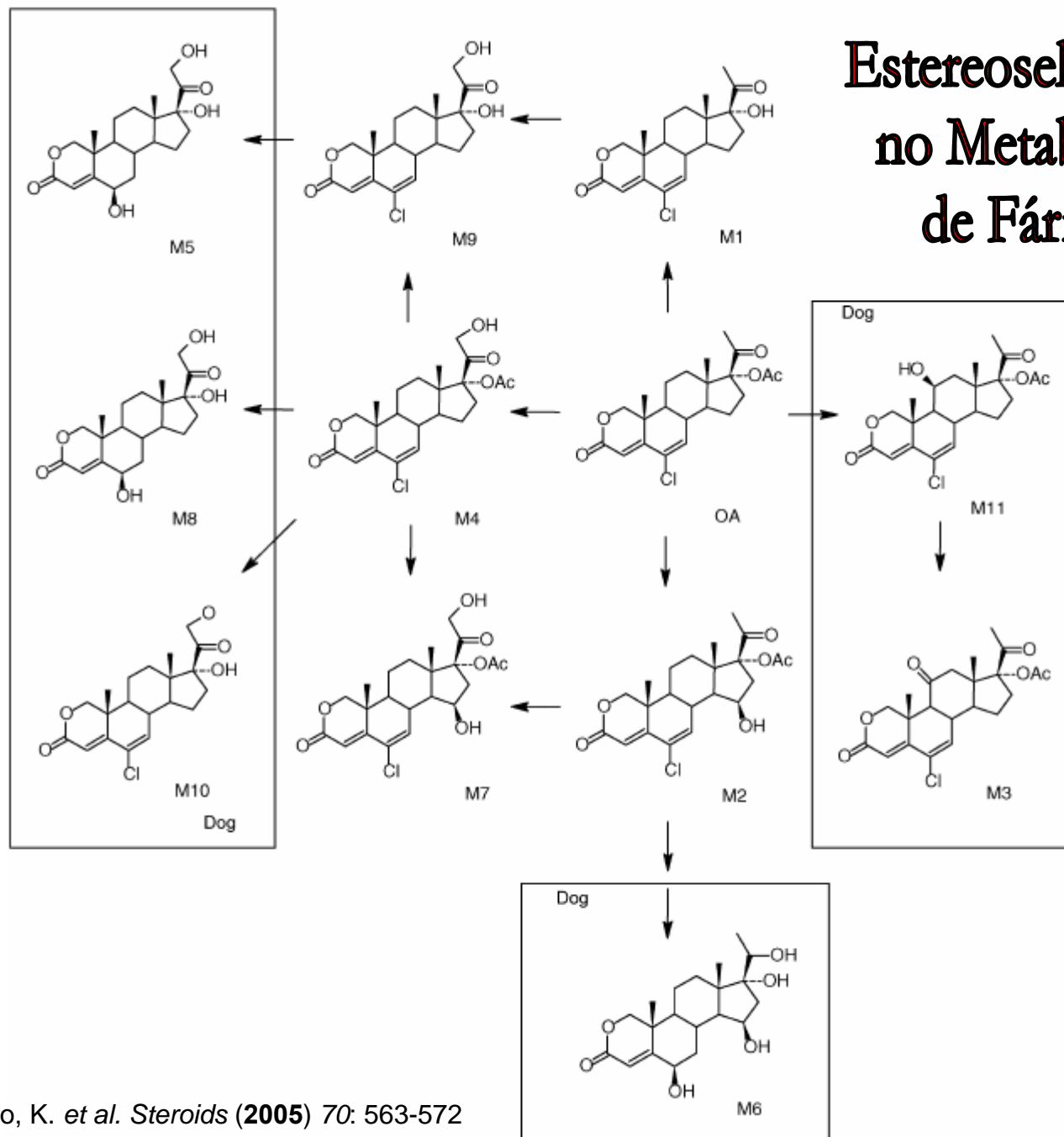
Metabólito ativo
(S)-20x mais ativo

Inibidor Enzimático da CYP 2D6
(S)-mais potente inibidor

$t_{1/2} = 7-15$ dias

(R)-norfluoxetina
<<< excreção lenta

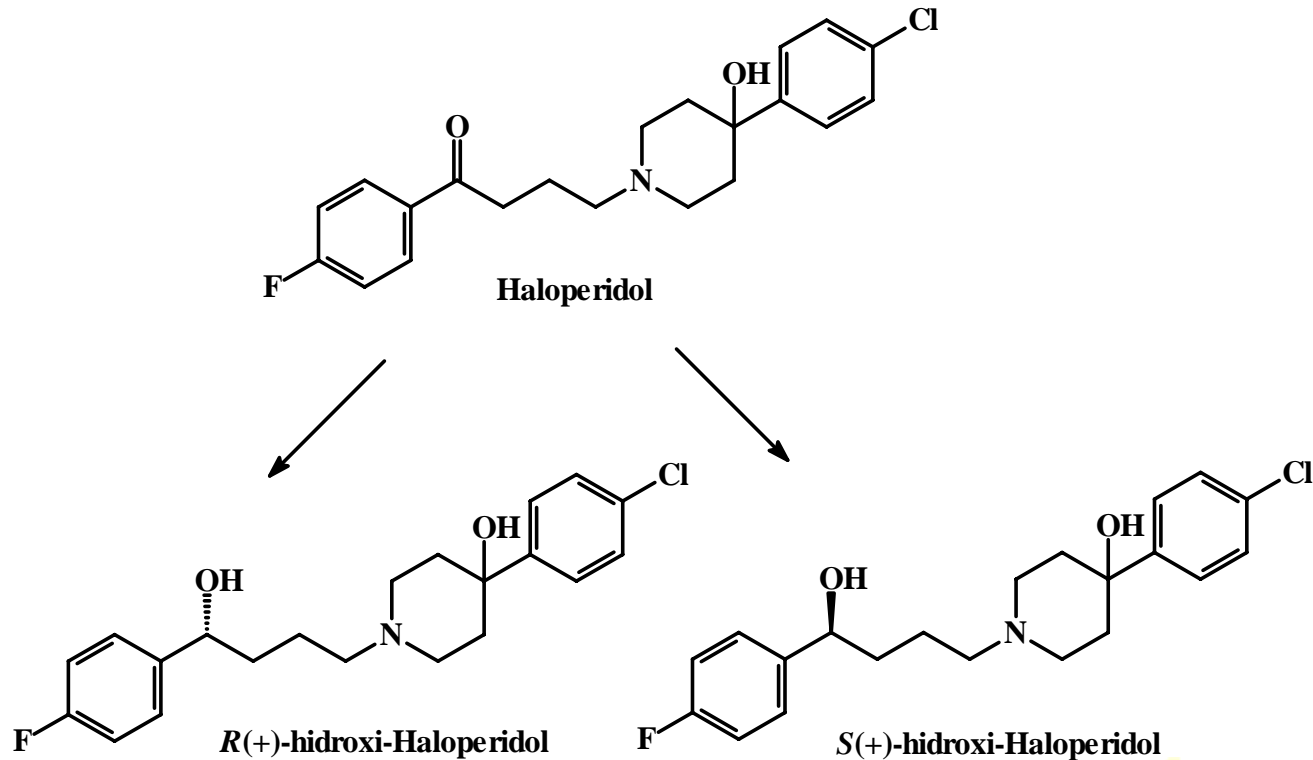
Estereoseletividade no Metabolismo de Fármacos



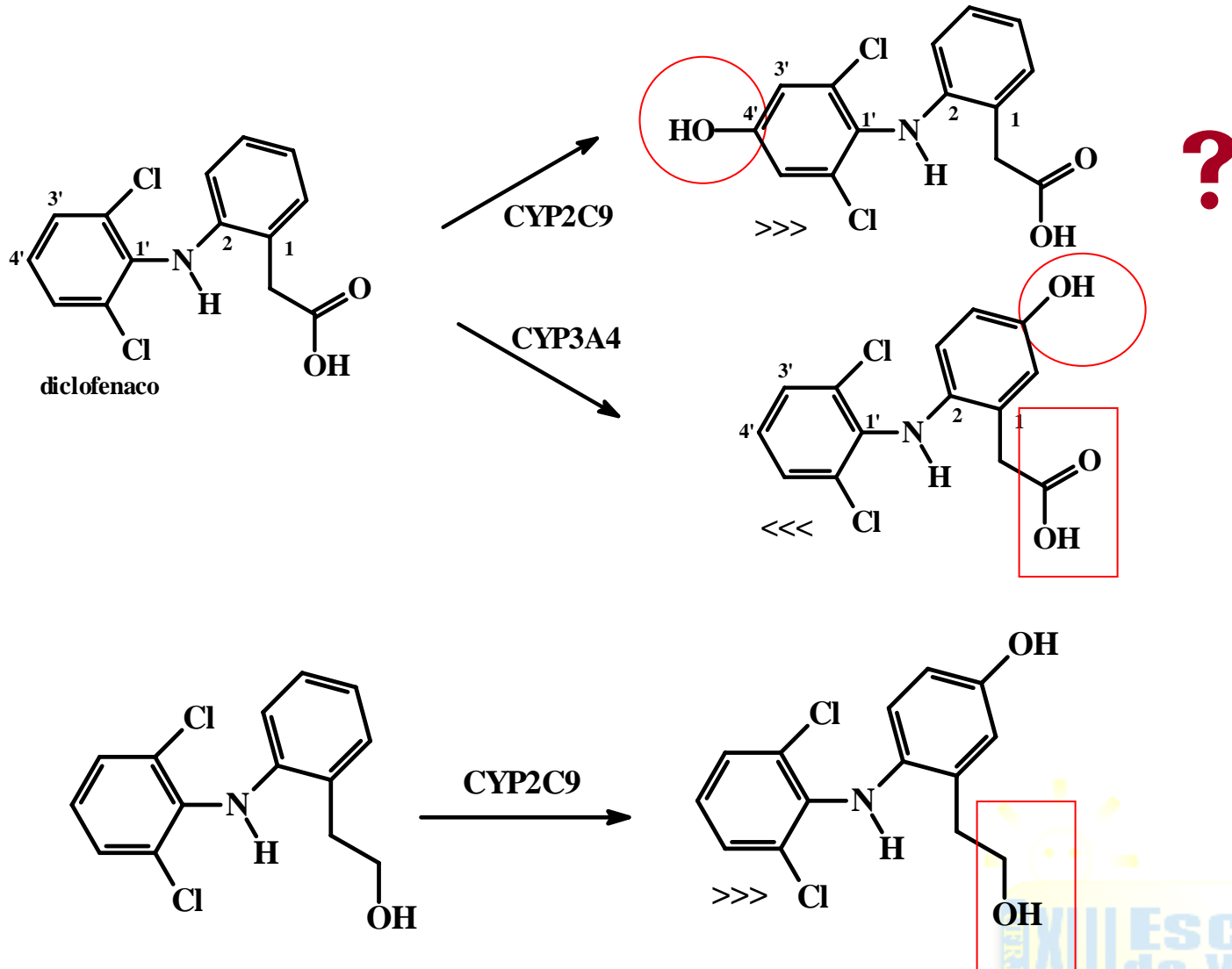
Minato, K. *et al. Steroids* (2005) 70: 563-572

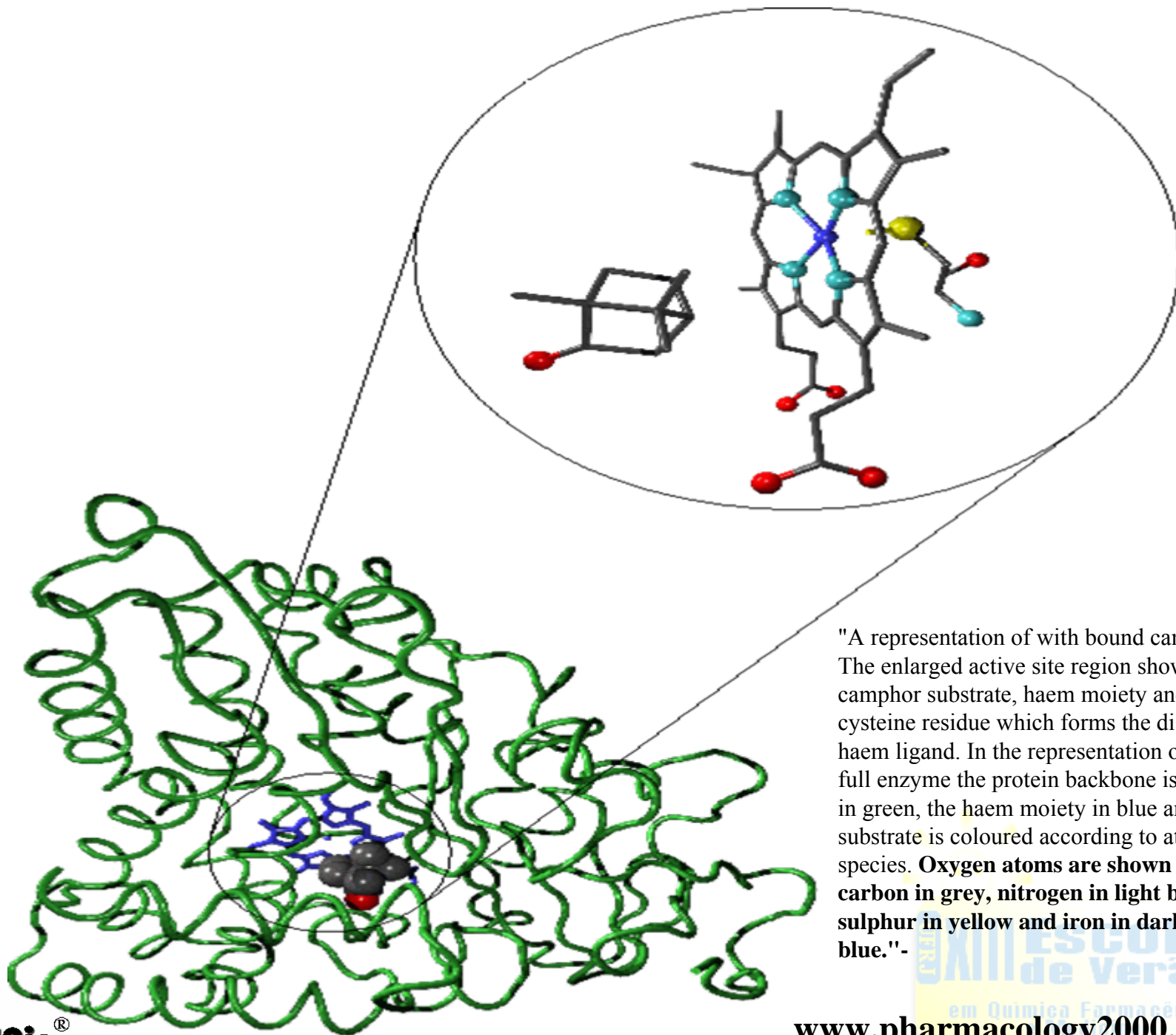
Fig. 1. Proposed biotransformation pathway for human and dog metabolites of OA in plasma, urine, and feces.

Estereoseletividade no Metabolismo de Fármacos



Regiosseletividade no Metabolismo de Fármacos





Regiosseletividade no Metabolismo de Fármacos

Tabela 1: Energia de Dissociação de Ligações C-H selecionadas

| Ligação C-H | Tipo de Ligação | Energia de Dissociação Da Ligação em KJ/mol |
|--|----------------------|---|
| H-C ₆ H ₅ | Phenila | 464 |
| H-CH ₃ | Metano | 438 |
| H-CH ₂ CH ₃ | Primário | 420 |
| H-CH ₂ CH ₂ CH ₃ | Primário | 417 |
| H-CH ₂ C(CH ₃) ₃ | Primário | 418 |
| H-CH(CH ₃) ₂ | Secondário | 401 |
| H-C ₆ H ₁₁ | Secondário | 400 |
| H-C(CH ₃) ₃ | Terciário | 390 |
| H-CH ₂ Ph | Benzílico primário | 368 |
| H-CH(CH ₃)Ph | Benzílico secundário | 357 |
| H-C(CH ₃) ₂ Ph | Benzílico terciário | 353 |
| H-CH ₂ CH=CH ₂ | Alílico primário | 361 |
| H-CH(CH ₃)CH=CH ₂ | Alílico secundário | 345 |

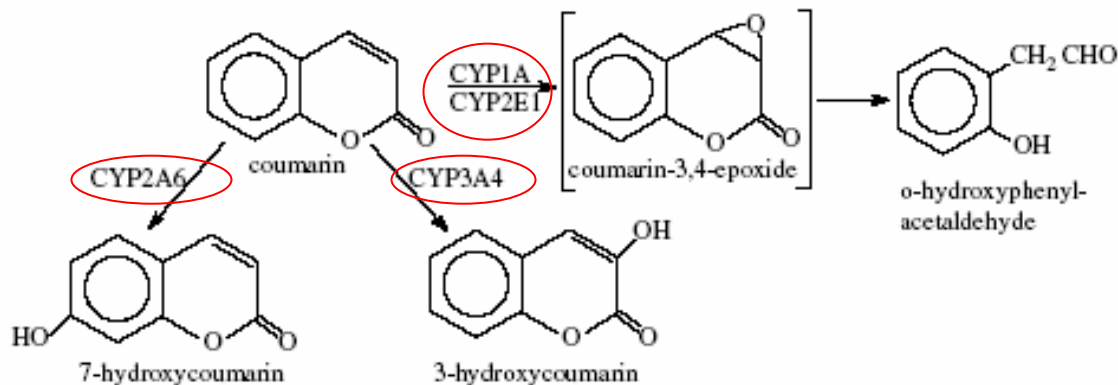
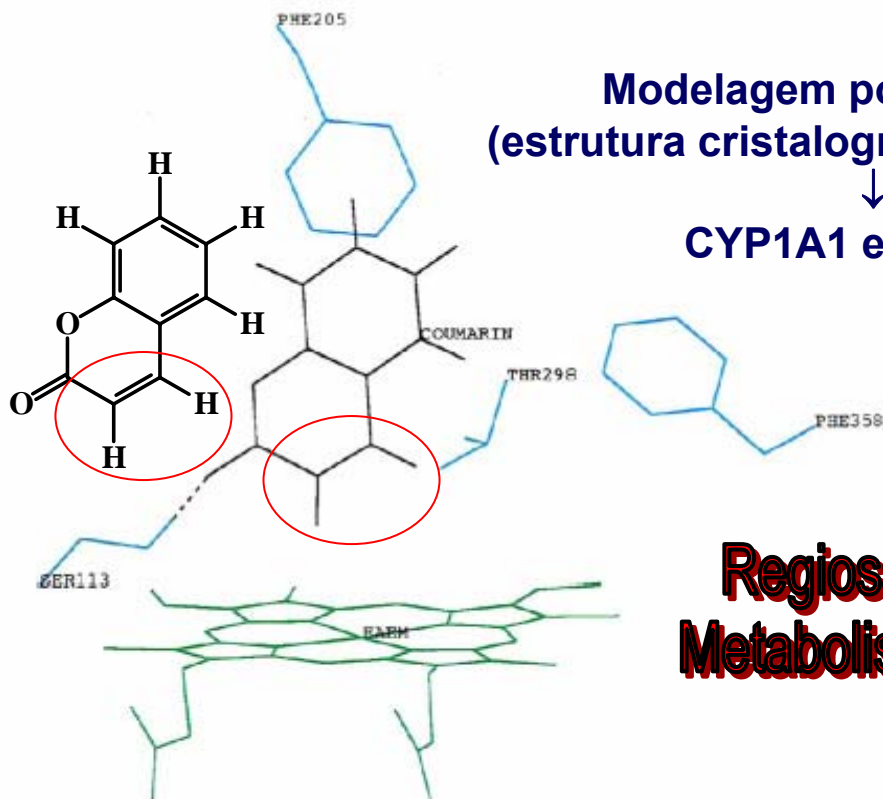


Fig. 1. Metabolism of coumarin in man by P450 enzymes (Note: There is some disagreement between the findings of Zhuo et al. (1999) and those of Born et al. (2002) on the formation of 3-hydroxycoumarin via CYP3A4, where the latter report this pathway and the former report generation of o-hy).



Regiosseletividade no Metabolismo de Fármacos

Fig. 2. The putative active site of human CYP1A1 showing a possible orientation of coumarin for 3,4-epoxidation. Key amino acid residues are labelled according to their alignment position (see Table 1) with the CYP2C5 crystallographic template, and hydrogen bonds are shown in dashed lines between coumarin and the protein.

D.F.V. Lewis et al. / Toxicology in Vitro 20 (2006) 256–264

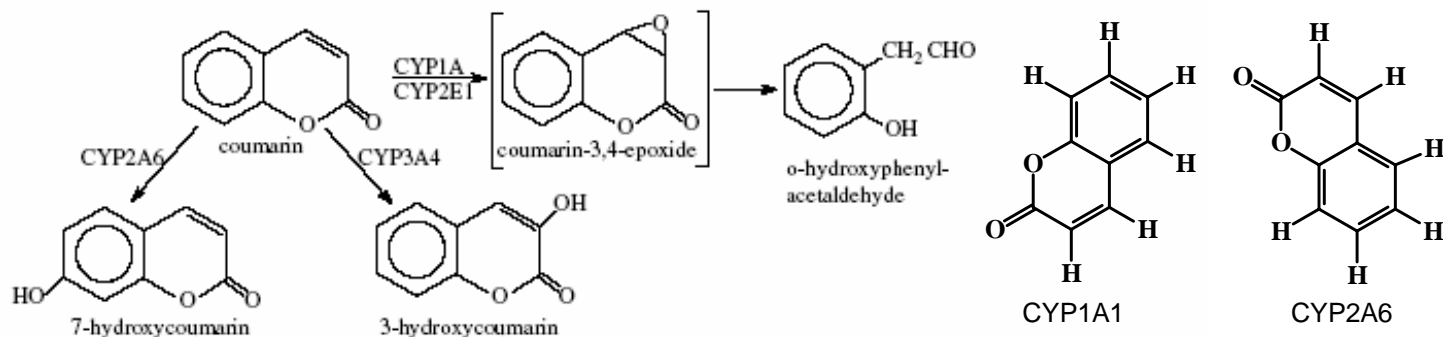
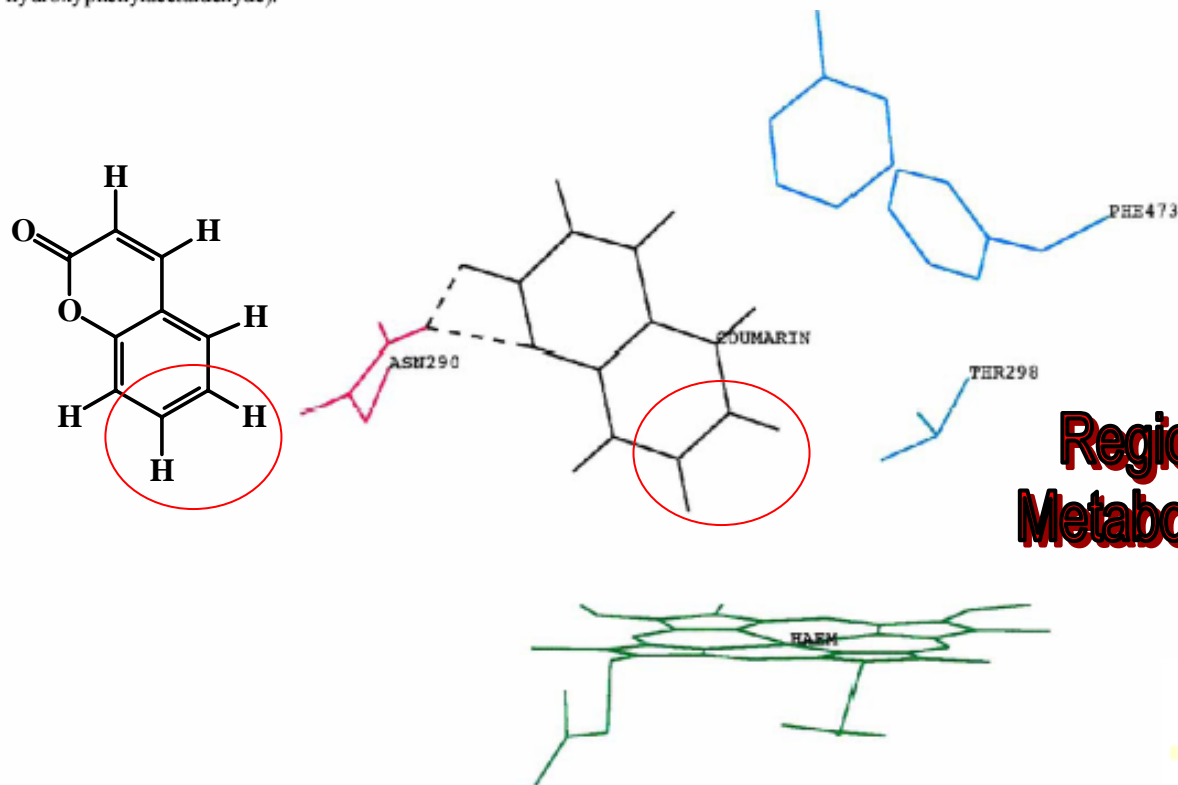


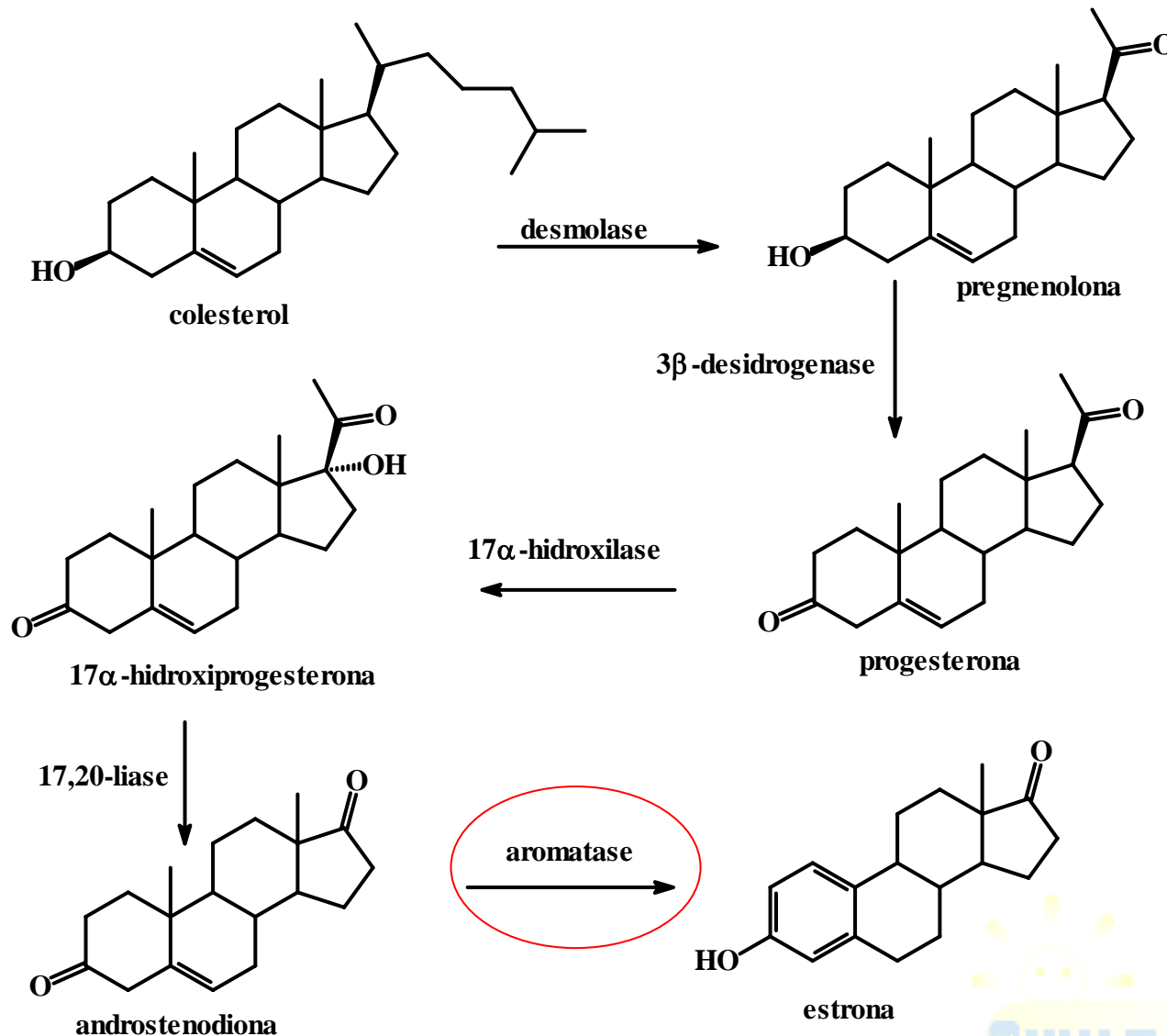
Fig. 1. Metabolism of coumarin in man by P450 enzymes (Note: There is some disagreement between the findings of Zhuo et al. (1999) and those of Born et al. (2002) on the formation of 3-hydroxycoumarin via CYP3A4, where the latter report this pathway and the former report generation of o-hydroxyphenylacetaldehyde).



Regiosseletividade no Metabolismo de Fármacos

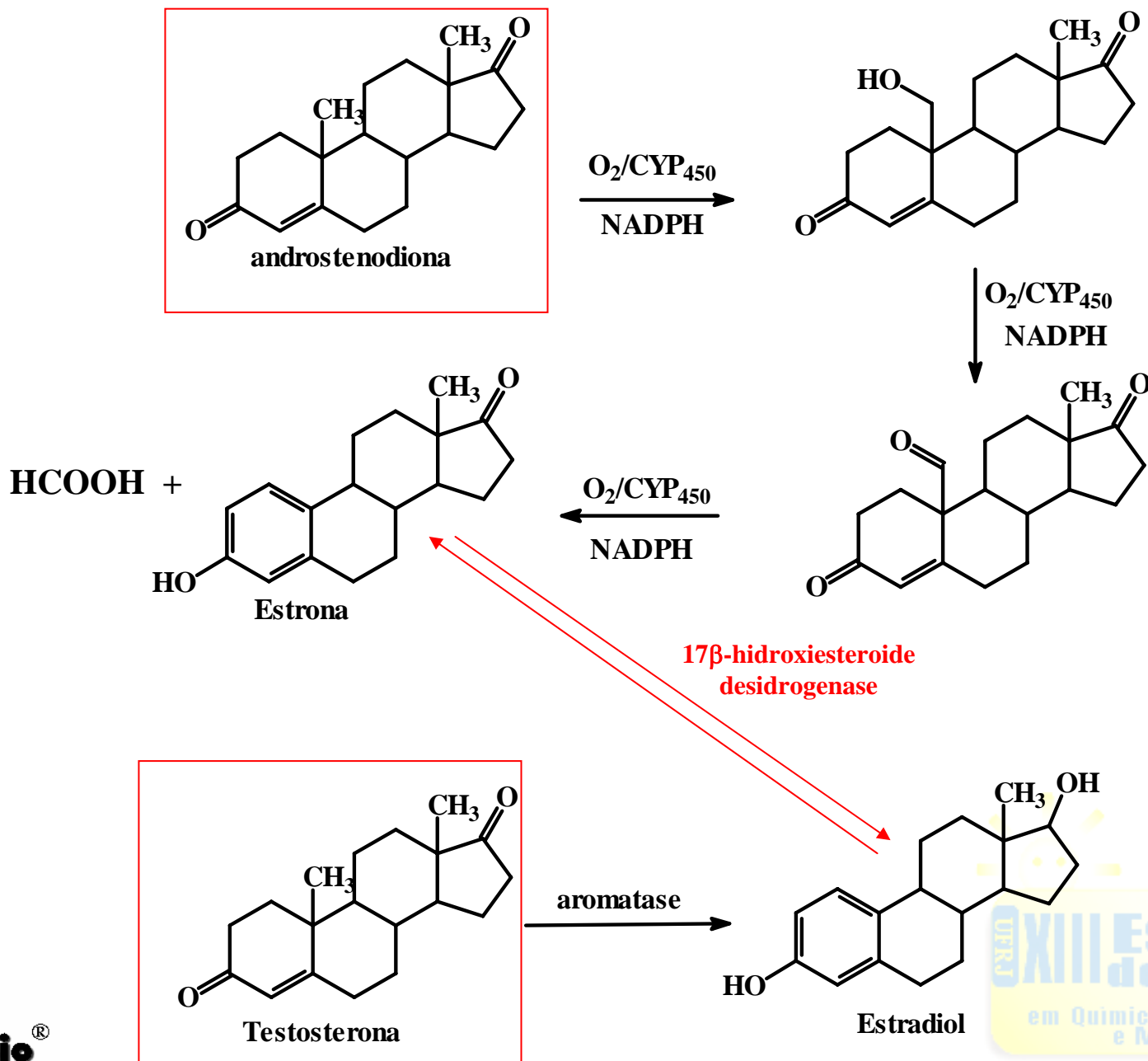
Fig. 3. The putative active site of CYP2A6 showing an orientation of coumarin for 7-hydroxylation. Key amino acids are shown in alignment position (see Table I) with respect to the CYP2C5 crystallographic template. Hydrogen bonds are shown between coumarin and the protein.

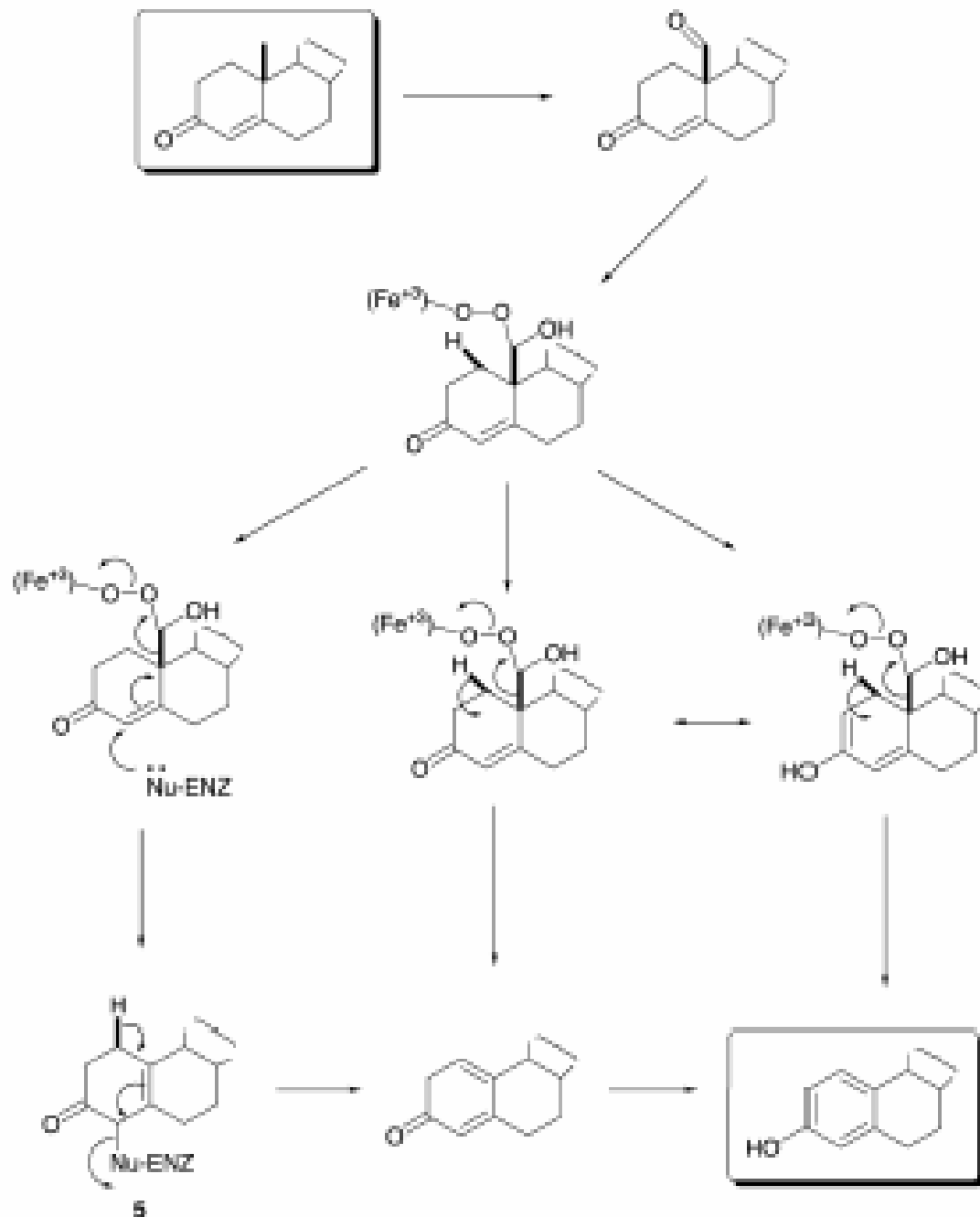
Metabolismo no Desenho de Fármacos

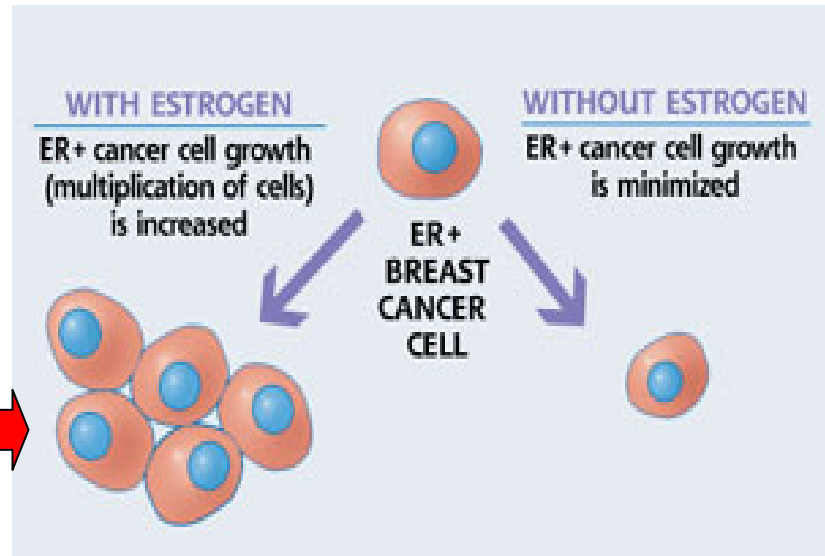
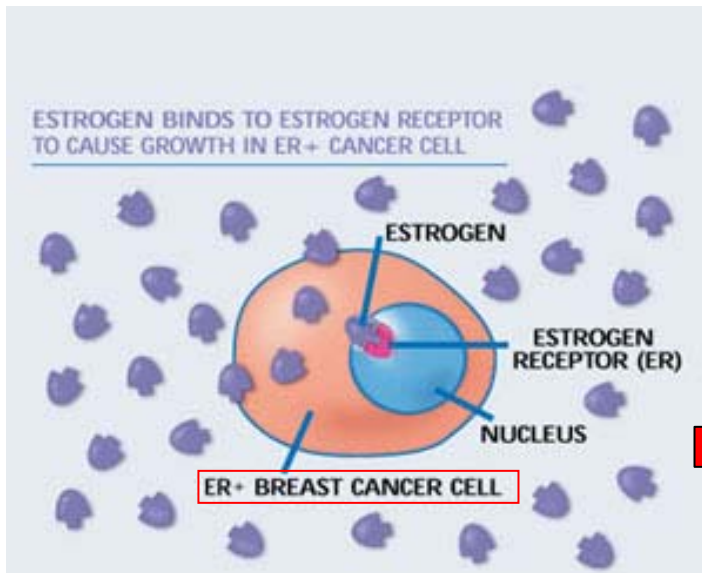


Estrógenos \Rightarrow Andrógenos (androstenodiona) via adrenal e (androstenodiona e testosterona) via tecidos periféricos \Rightarrow Pós-menopausa

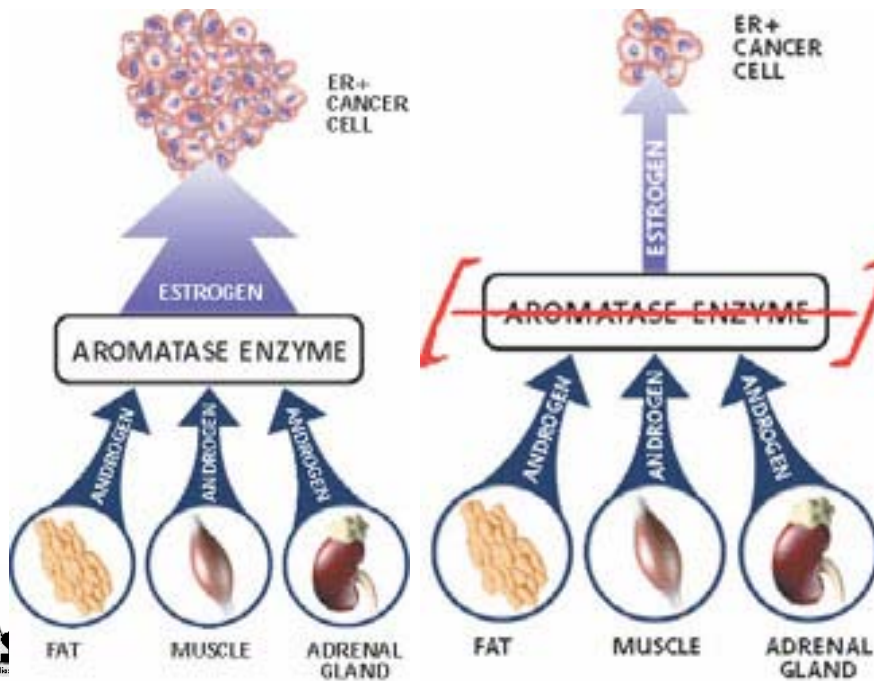
Metabolismo no Desenho de Fármacos





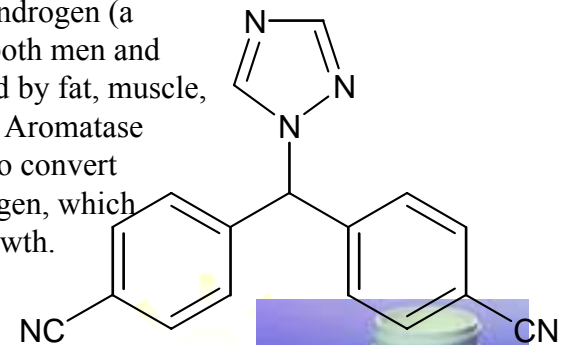


By interfering with the production of estrogen triggered by aromatase, aromatase inhibitors actually reduce the total amount of estrogen in the body. As a result, less estrogen can reach breast cancer cells.¹ Thus, these drugs help to starve breast cancer cells in postmenopausal women by depriving them of estrogen. The next illustration shows the effect of estrogen deprivation on the multiplication of breast cancer cells

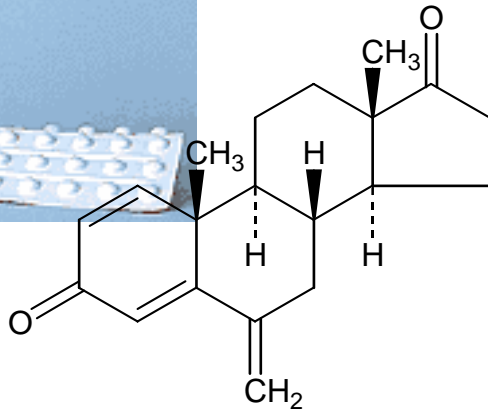


Before therapy: Androgen (a hormone found in both men and women) is produced by fat, muscle, and adrenal glands. Aromatase enzyme is needed to convert androgen into estrogen, which results in tumor growth.

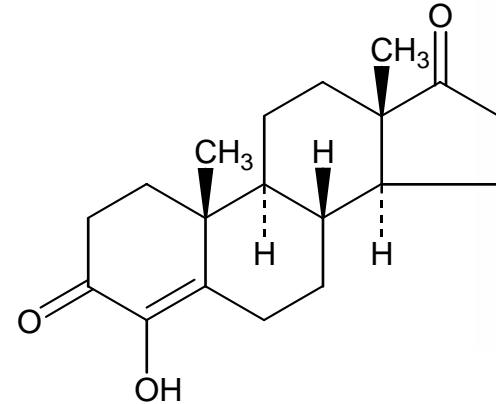
With therapy: FEMARA (Novartis) binds to the aromatase enzyme and blocks it from converting androgen to estrogen, thereby reducing growth of the tumor.



Metabolismo no Desenho de Fármacos

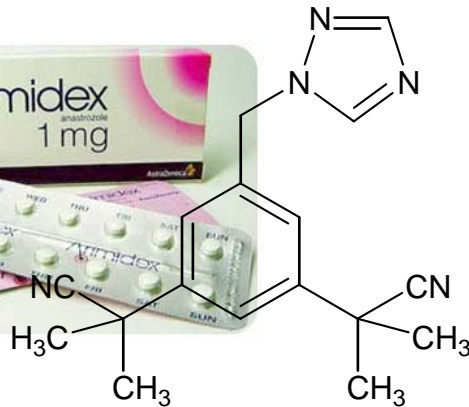


Exemestane (Aromasin®)

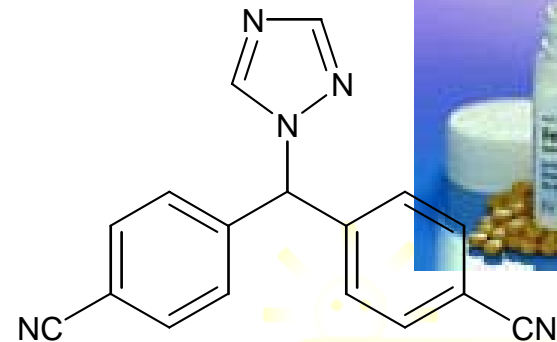


Formestane (Formastat®)

Inibidores do CYP450 19

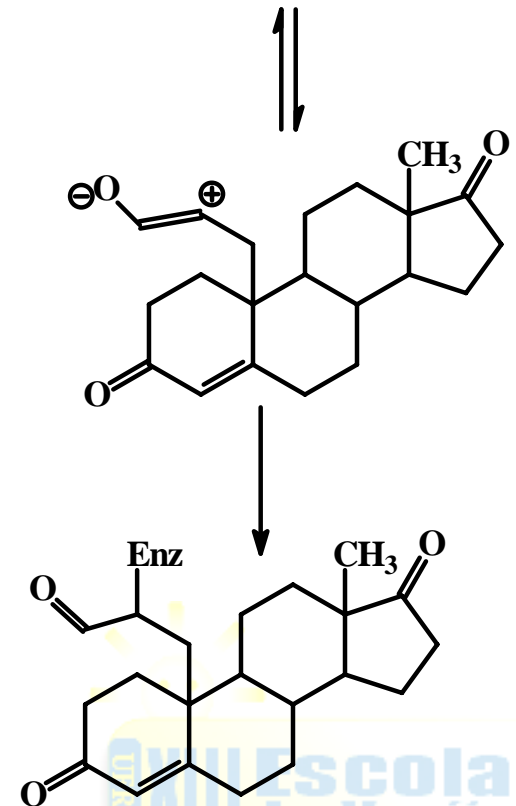
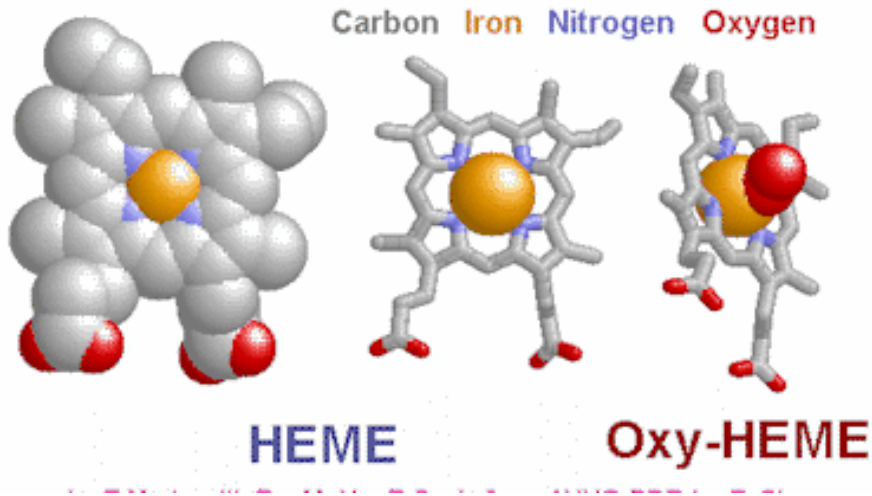
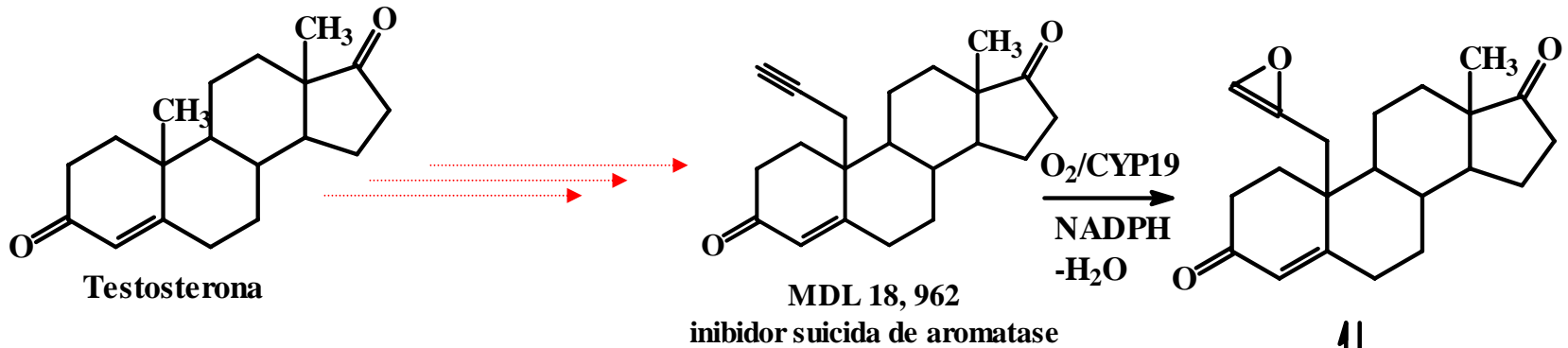


Anastrozole (Arimidex®)

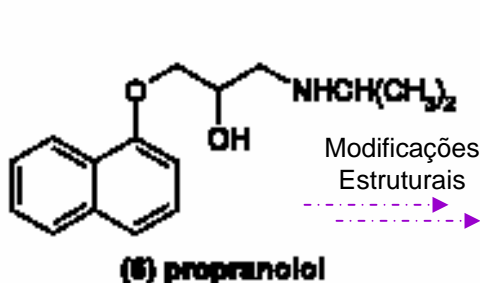


Letrozole (Femara®)

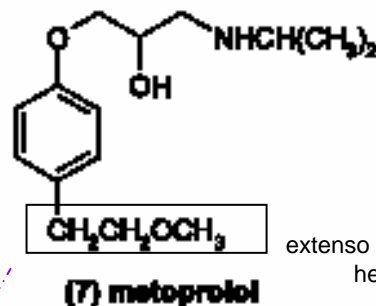
Metabolismo no Desenho de Fármacos



Metabolismo no Desenho de Fármacos



Extenso metabolismo de 1ª passagem → 25% biodisp. oral



> afinidade receptores β_1 .

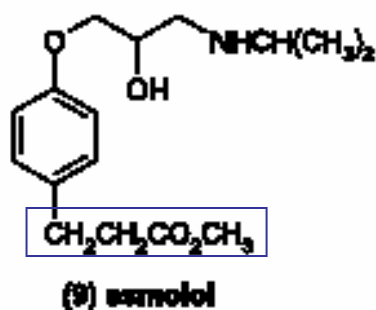
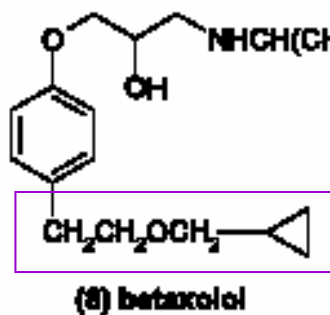
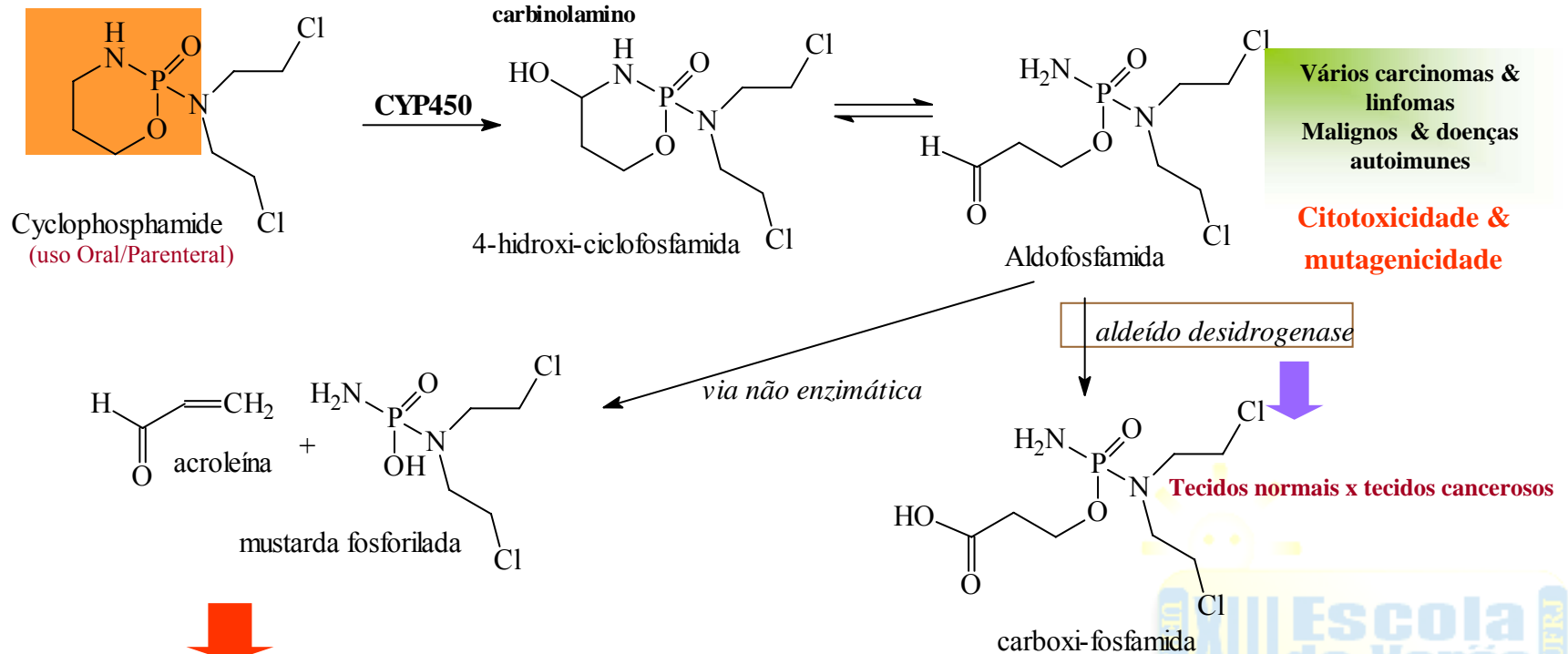
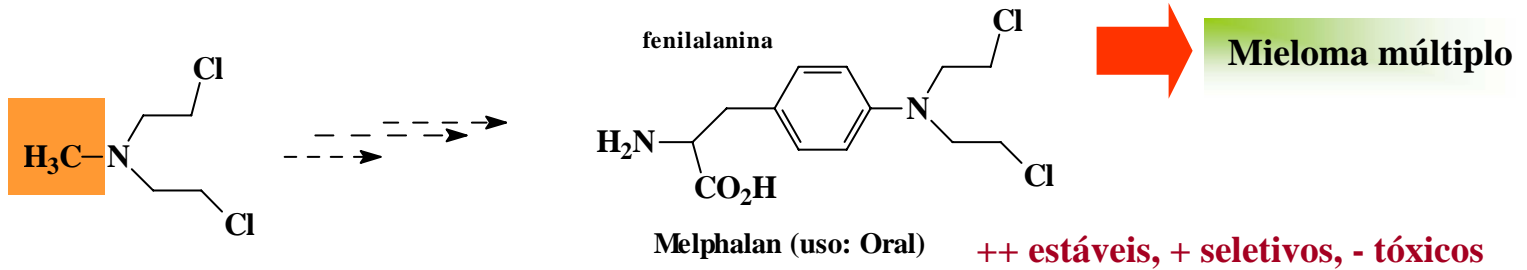


Tabela 2. Dados de farmacocinética de alguns β -bloqueadores em humanos

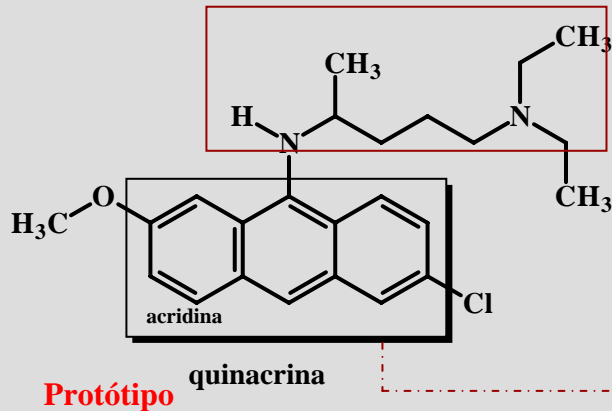
| Fármaco | Log P (octanol/água) ²⁴ | biodisponibilidade oral (em %) | tempo de meia-vida (em h) |
|---------------|------------------------------------|--------------------------------|---------------------------|
| → Propranolol | 3,65 | Cerca de 25 | 3-5 |
| → Metoprolol | 2,15 | Cerca de 40 | 3-4 |
| → Betaxolol | 2,81 | Cerca de 80 ¹⁹ | 14-22 ¹⁹ |
| → Esmolol | - | - | 0,13 |

Metabolismo no Desenho de Fármacos

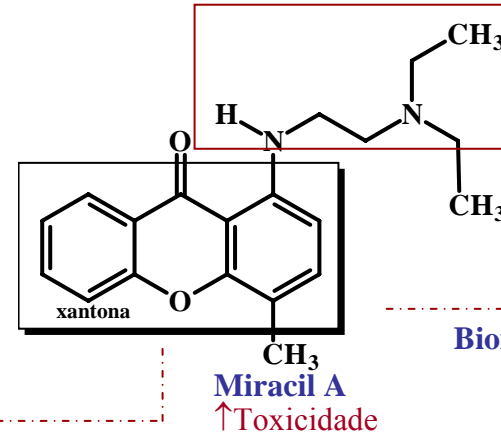


Metabolismo no Desenho de Fármacos

Anti-malário

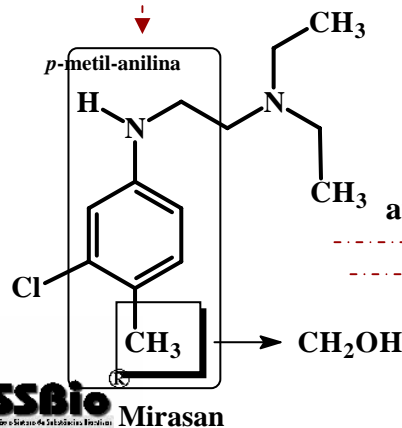


Alemanha



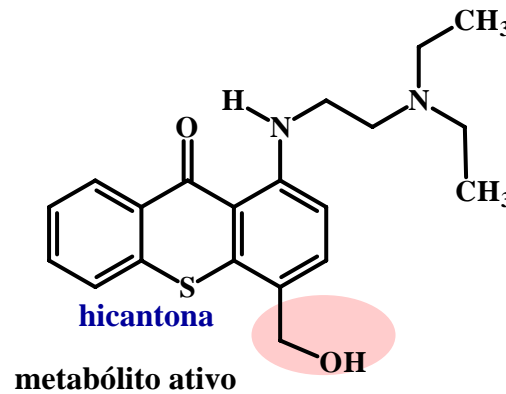
Bioisosterismo clássico

simplificação molecular



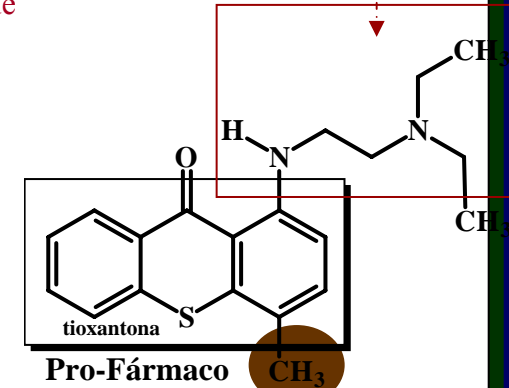
anelação

Pfizer



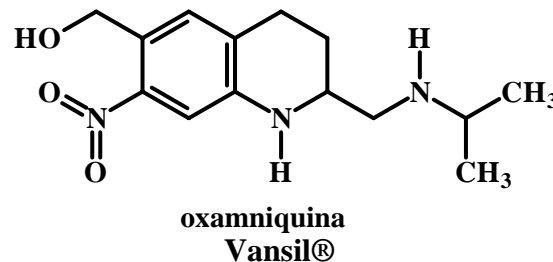
CYP 450

Aspergillus scleroticum

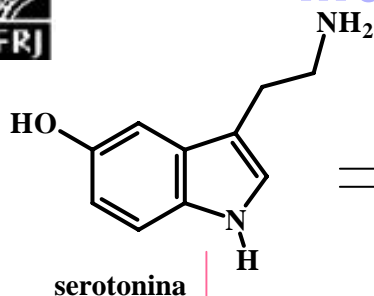


↑Índice de efeitos adversos
Tropas Alemãs na campanha do Norte da África, 2ª Guerra Mundial

Miracil D



Metabolismo na Otimização de Fármacos

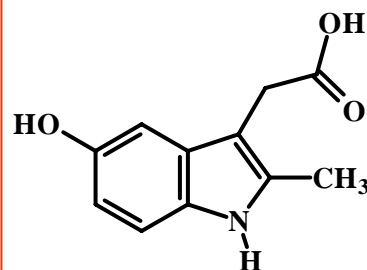
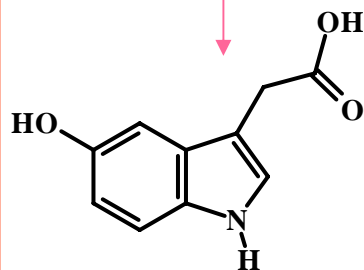


Mediador Inflamatório
Aumento da Permeabilidade
Vascular

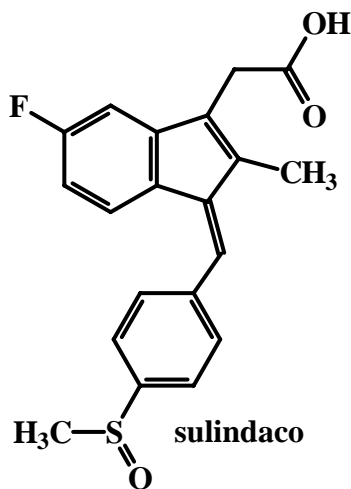
Merck
1963

Screening *ca.* 350 compostos
indólicos

MAO

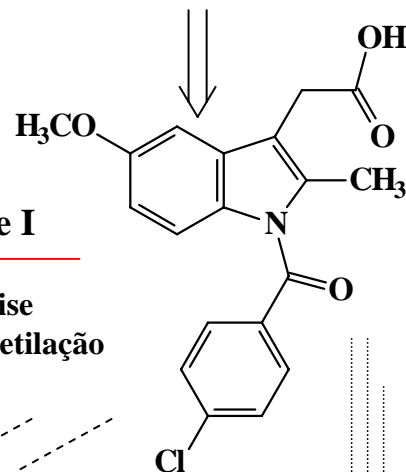


Similaridade estrutural



Fase I

Hidrólise
O-demetilação



Indometacina (Indocid®, 1963)
Psicose, cefaléia
frontal, depressão,
Vertigem,
alucinações, etc.

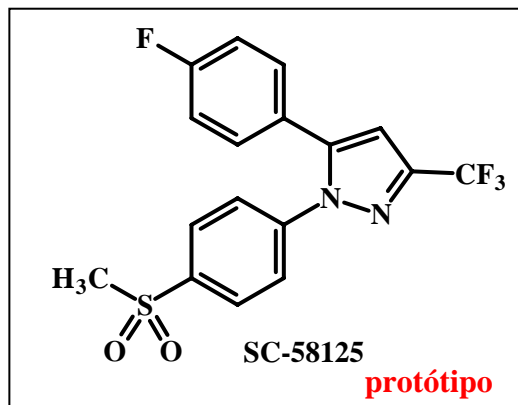
“efeito orto”

Proscrito 1983⇒
Reações
anafiláticas

Proteção
metabólica

Zomepirac (1980) Tolmetin (Tolectin®, 1976)

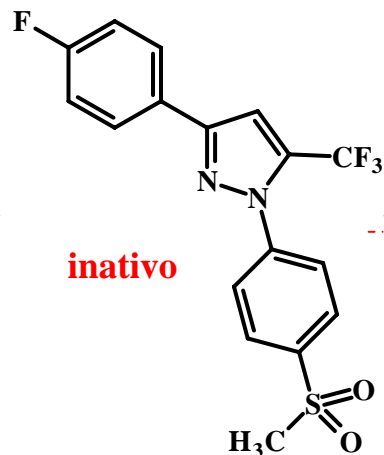
Metabolismo na Otimização de Fármacos



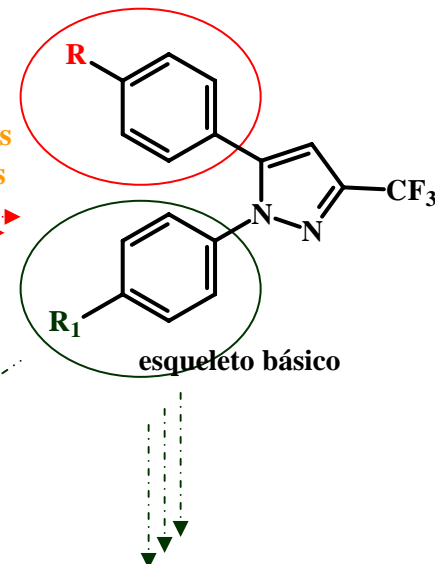
$IC_{50} > 100 \mu M$ (COX-1)

$IC_{50} = 0,1 \mu M$ (COX-2)

Modificações
Moleculares



Modificações
Moleculares



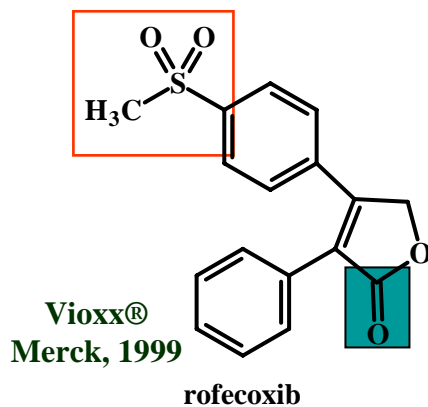
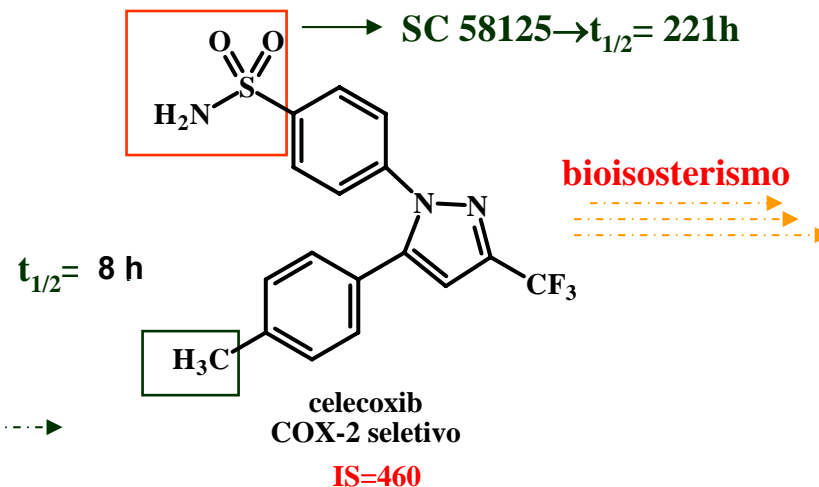
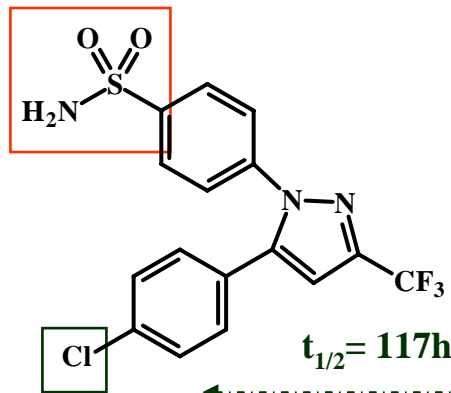
| R_1 | R | IC_{50} (COX-1) | IC_{50} (COX-2) |
|---------------------------------|-------------------------|-------------------|----------------------|
| SO ₂ NH ₂ | CF ₃ | <100 μM | 8,23 μM |
| SO ₂ NH ₂ | Cl | 17 μM | 0,01 μM |
| SO ₂ NH ₂ | F | 25 μM | 0,041 μM |
| SO ₂ NH ₂ | CH₃ | 15 μM | 0,04 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-CH₃ | 33,9 μM | 0,069 μM |
| SO ₂ NH ₂ | 2-CH₃ | 18,1 μM | 0,11 μM |

| R_1 | IC_{50} (COX-1) | IC_{50} (COX-2) |
|-----------------------------------|---------------------|-------------------|
| H | 0,97 μM | >100 μM |
| SO ₂ CH ₃ | >100 μM | 0,1 μM |
| SO ₂ NH ₂ | 25,5 μM | 0,041 μM |
| SO ₂ NHCH ₃ | >100 μM | >100 μM |
| NHSO ₂ CH ₃ | >100 μM | >100 μM |
| NO₂ | 1,75 μM | >100 μM |
| COCF ₃ | >100 μM | >100 μM |

Penning, TD *et al.* (1997) *J. Med. Chem.* 40: 1347-1365

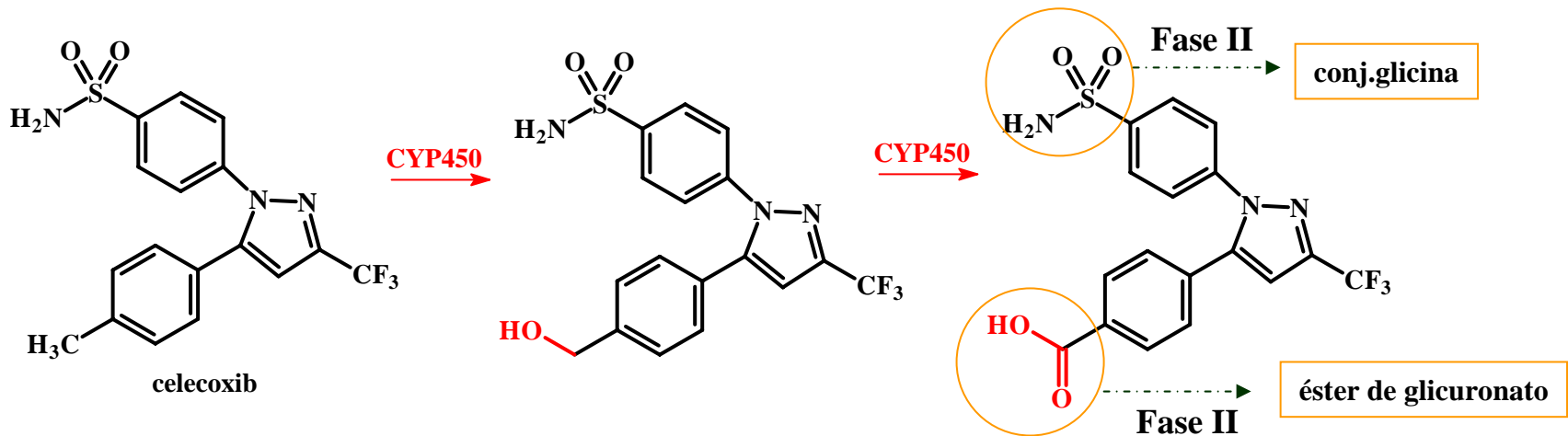
Metabolismo na Otimização de Fármacos

Diaryl-heterocíclicos



Metabolismo na Otimização de Fármacos

Diferenças Farmacológicas entre Celecoxib e Rofecoxib

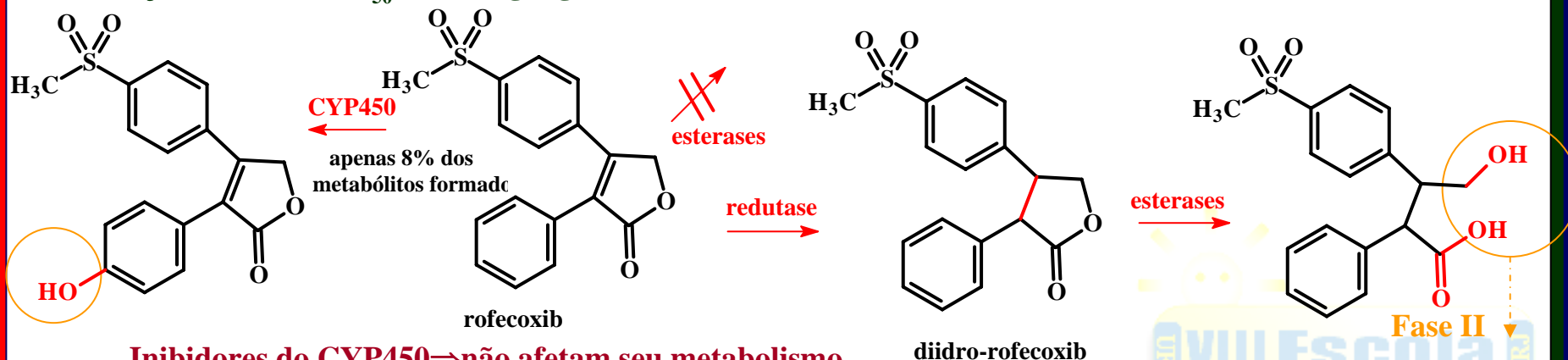


Inibidores do CYP450 ⇒ afetam seu metabolismo (através isoforma CYP450 2C9)

↑log P ⇒ atravessam barreira placentária; biodisponibilidade não calculada ⇒ ↓solubilidade em H₂O

Inflamação aguda ⇒ ED₅₀ = 7,1 mg/Kg

Inflamação crônica ⇒ ED₅₀ = 0,37 mg/Kg



Inibidores do CYP450 ⇒ não afetam seu metabolismo

↑log P ⇒ atravessam barreira placentária; biodisponibilidade ~93%

Inflamação aguda ⇒ ED₅₀ = 1,5 mg/Kg

Inflamação crônica ⇒ ED₅₀ = 0,7 mg/Kg

Metabolismo no Desenho de Fármacos

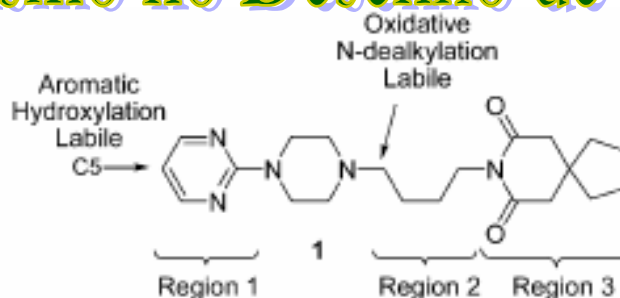
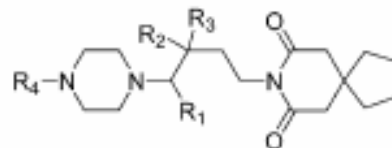


Figure 1. Metabolic landscape of buspirane 1 as predicted by CYP3A4 model (most labile sites shown).

Table 1. Region 1 and 2 SAR of the 3,3-tetramethyleneglutarimide containing analogues



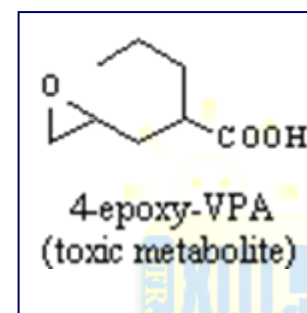
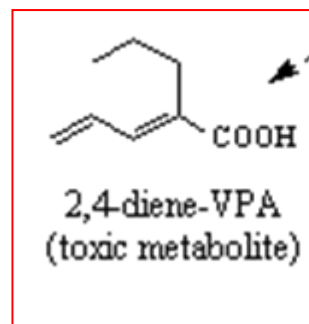
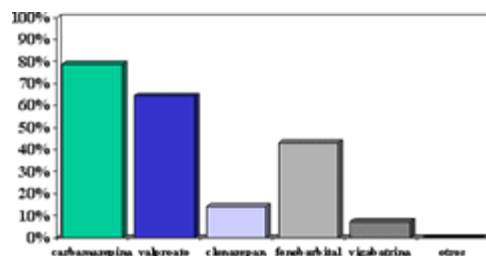
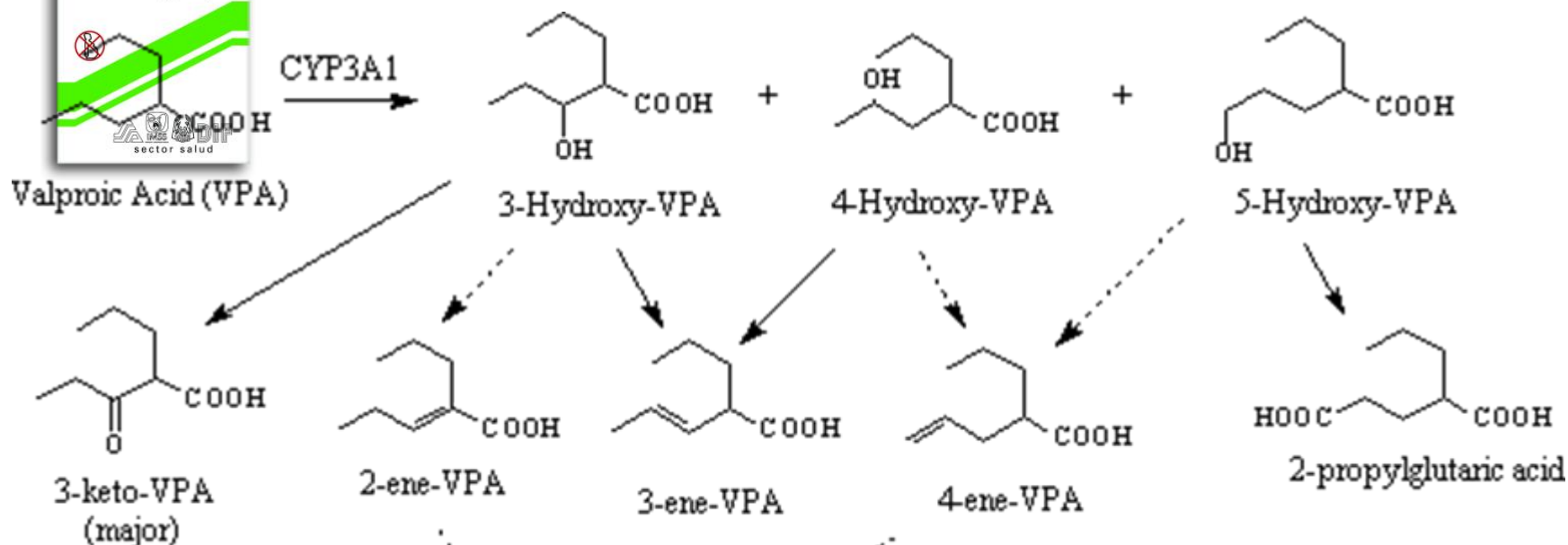
| Compd | R ₁ | R ₂ | R ₃ | R ₄ | 5-HT _{1A} IC ₅₀ (μM) ^a | CYP 3A4 t _{1/2} (min) ^b |
|-------|----------------|----------------|----------------|----------------------|--|--|
| 1 | H | H | H | Pyrimidine | 0.025 | 4.6 |
| 5 | H | H | H | 5-F Pyrimidine | 0.063 | 52.3 |
| 6 | H | H | H | <i>p</i> -F phenyl | 0.064 | 3.2 |
| 7 | H | H | H | 2-Pyrazine | 0.46 | 5.5 |
| 8 | H | H | H | <i>p</i> -OMe Phenyl | 0.93 | 21.1 |
| 9 | Me | H | H | Pyrimidine | 0.004 | 3.8 |
| 10 | Me | H | H | 5-F Pyrimidine | 0.046 | 14.8 |
| 11 | H | Me | Me | Pyrimidine | 0.71 | 2.9 |
| 12 | H | H | H | <i>o</i> -OMe Phenyl | 0.002 | 5.1 |
| 13 | H | OH | H | Pyrimidine | | |
| 14 | H | OH | Me | Pyrimidine | | |
| 15 | H | OH | H | 2-Pyrazine | | |
| 16 | H | OH | H | <i>o</i> -OMe Phenyl | | |
| 17 | H | OH | H | <i>p</i> -F phenyl | | |
| 18 | Me | H | H | <i>p</i> -F phenyl | | |
| 19 | H | H | H | Phenyl | | |

ity at 5-HT_{1A} receptors labeled with [³H]-8-OH-DPAT.

analysis of parent ion fragmentation at each time point, peak area reported normalized to inte

Tandon, M. et al. *Bioorg. Med. Chem. Lett.* (2

Metabolismo na Otimização de Fármacos



Metabolismo na Otimização de Fármacos

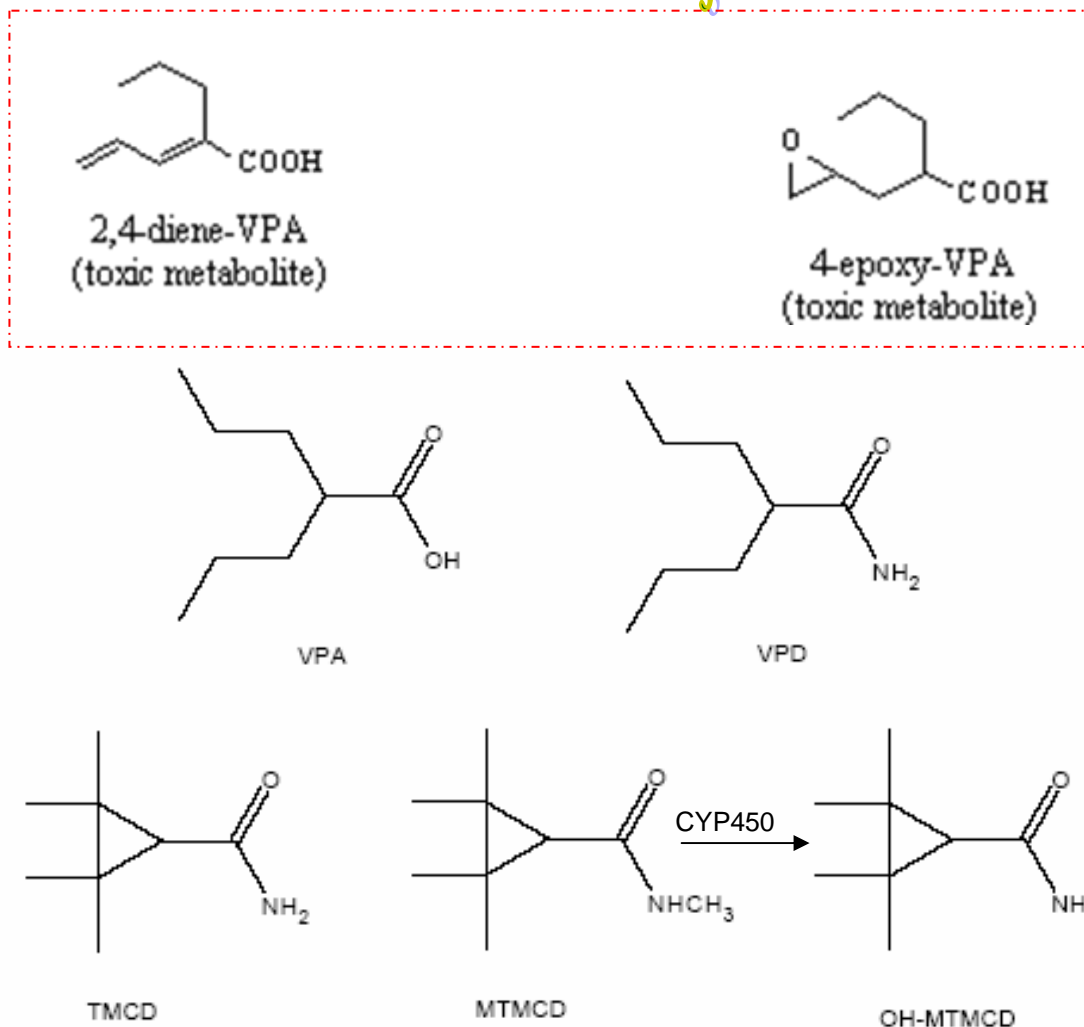


Fig. 1. Chemical structures of valproic acid (VPA), valpromide (VPD), tetramethylcyclopropanecarboxamide (TMCD), *N*-methyl-tetramethylcyclopropanecarboxamide (MTMCD), and *N*-hydroxymethyl-tetramethylcyclopropanecarboxamide (OH-MTMCD).

Isoherranen, N. *et al. Epilepsy Research* (2004) 58: 1-12

Metabolismo: Pro-Fármaco

Pró-Fármaco: Desprovido de atividade farmacológica intrínseca. Termo cunhado por Albert em 1958 para definir substância com nenhuma ou pouca atividade farmacológica, sofrendo biotransformação a metabólitos ativos terapêuticamente. 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). O processo de obtenção do pró-fármaco dá-se o nome de latenciação de fármacos. Consiste essencialmente em converter, mediante modificação química, um composto biologicamente ativo em forma de transporte inativa que, após ataque enzimático ou químico, liberará o fármaco ativo.

Overlaps

Pharmaceutical objectives

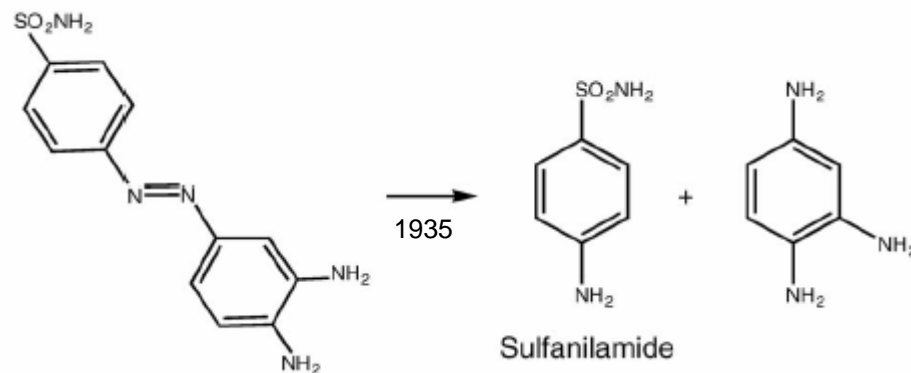
- improved solubility
- improved chemical stability
- improved taste, odor
- decreased irritation and pain

Pharmacokinetic objectives

- improved oral absorption
- decreased presystemic metabolism⁹
- improved absorption by non-oral routes
- improved time profile
- organ/tissue-selective delivery of active agent

Pharmacodynamic objectives

- masking of a reactive agent to improve its therapeutic index
- *in situ* activation of a cytotoxic agent



Prontosil, a fortuitous prodrug of sulfanilamide.

Design Ad hoc x Post hoc

Chemical Classification

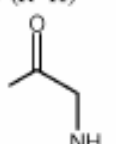
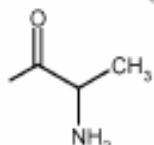
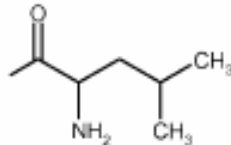
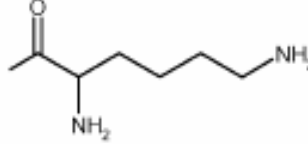
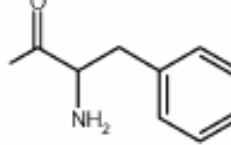
- *Carrier-linked prodrugs*: where the active agent (the drug) is linked to a carrier (also known as a promoiety), and whose activation occurs by hydrolysis (esters, amides, imines. . .), oxidation or reduction (e.g. Prontosil in Fig. 1);
- *Bioprecursors*: which do not contain a promoiety yet are activated by oxidation, reduction or hydrolysis [12];
- *Macromolecular prodrugs*: where the carrier is a macromolecule such as a PEG (polyethyleneglycol) [19];
- *Drug-antibody conjugates*: where the carrier is an antibody raised against tumor cells [1,20].

Fig. 9. List of objectives in prodrug research and their overlaps.

Metabolismo: Pro-Fármaco

Table 1

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

| $\text{H}_2\text{N}-\text{C}_6\text{H}_4-\text{SO}_2-\text{C}_6\text{H}_4-\text{NHR}$ | 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 | 14.6 \pm 0.9 |
| R =  (Alanyl) | >30 | 6.6 | 20.5 \pm 0.7 |
| R =  (Leucyl) | >25 | 0.31 | 1.7 \pm 0.2 |
| R =  (Lysyl) | >65 | >65 | 10.9 \pm 0.7 |
| R =  (Phenylalanyl) | 1.3 | 0.002 | 8.8 \pm 0.7 |

Metabolismo: Pro-Fármaco

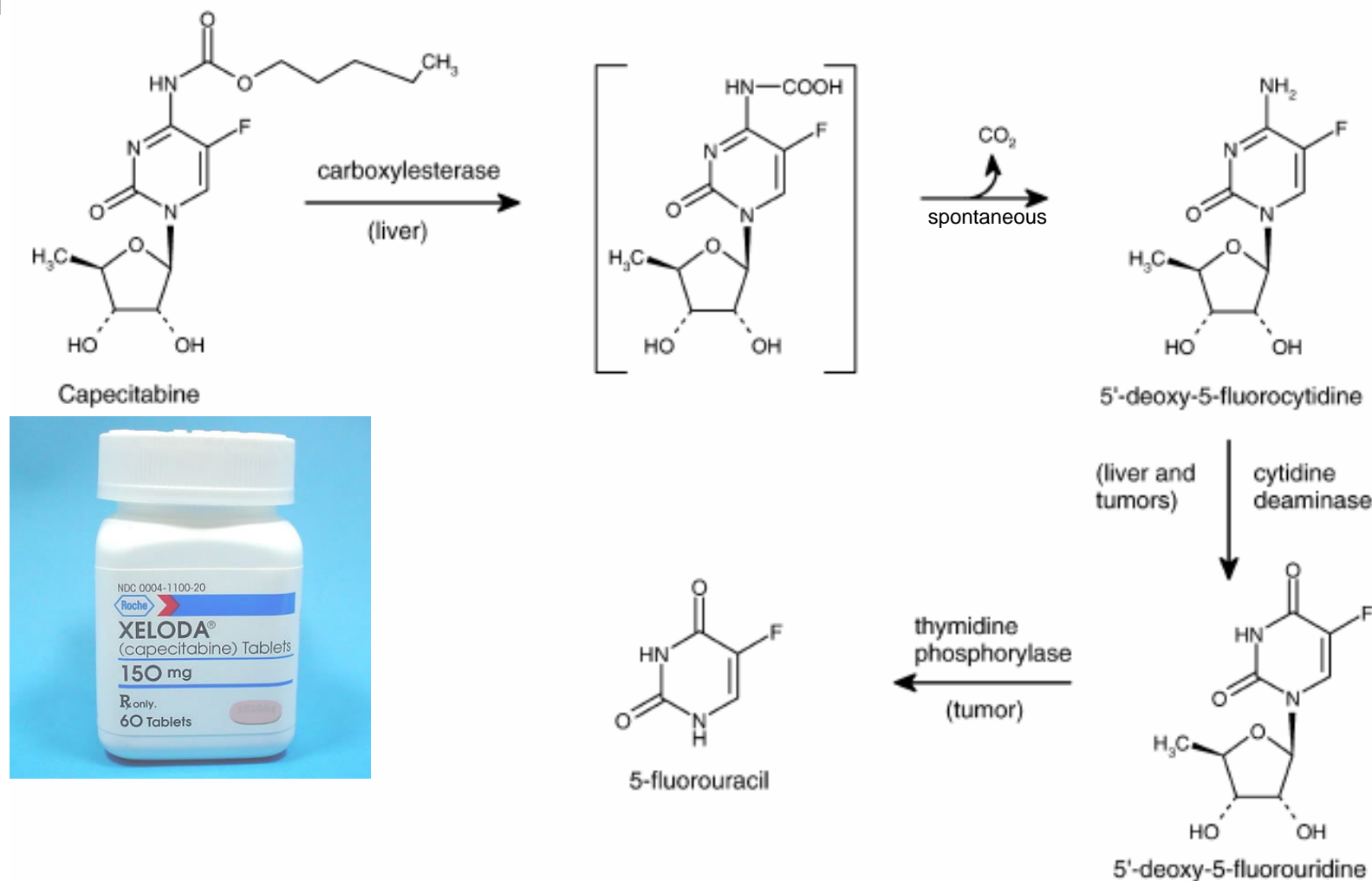


Fig. 6. The stepwise activation of capecitabine to the antitumor drug 5-fluorouracil. Note the tissue-selectivity of the last step.

Metabolismo: Pro-Fármaco

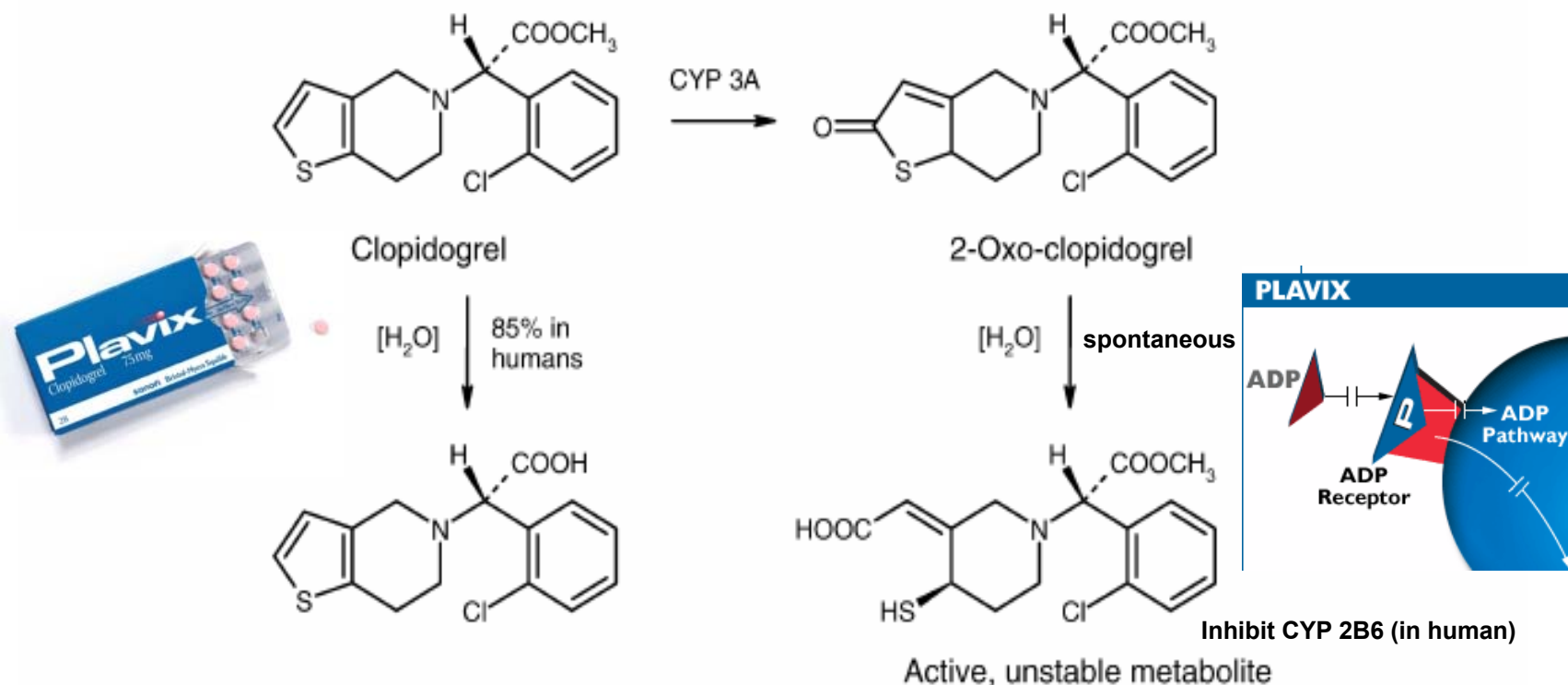
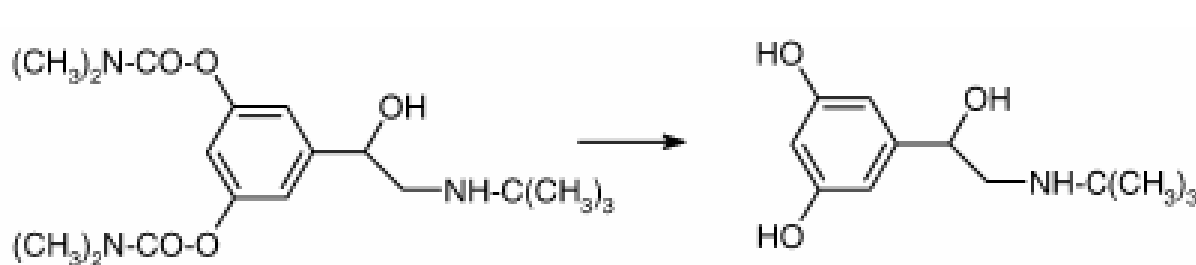
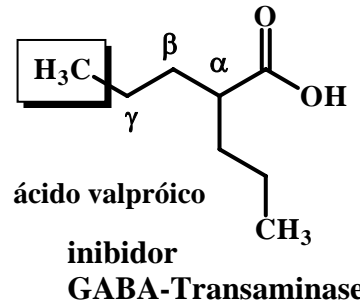
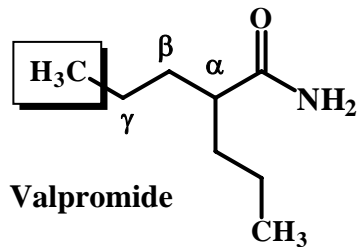
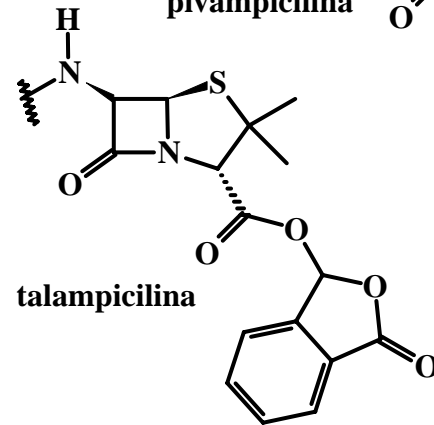
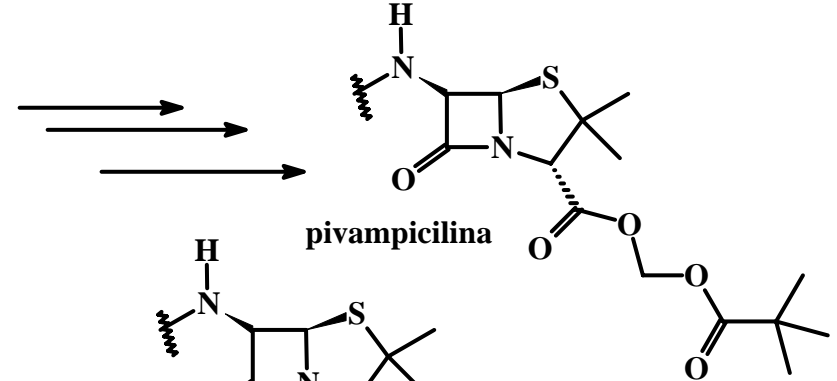
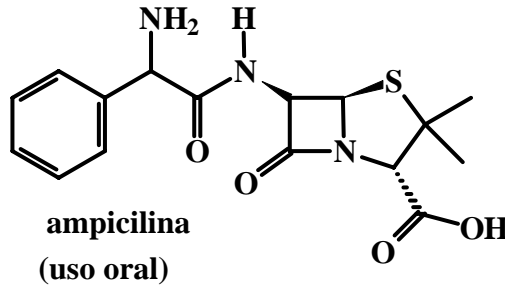


Fig. 7. Major metabolic reactions of clopidogrel in humans. Most of a dose is inactivated by hydrolysis, whereas a smaller part is activated by CYP3A to 2-oxo-clopidogrel, followed by spontaneous hydrolytic ring opening to the active agent, a highly reactive thiol metabolite which irreversibly antagonizes platelet ADP receptors via a covalent S-S bridge [37-38].

Metabolismo: Pro-Fármaco



Otimização de
Propriedades
farmacocinéticas

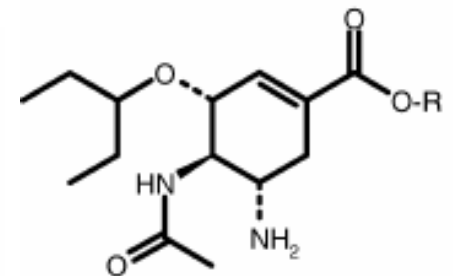


Bambuterol

Terbutaline

Hidrólise via colinesterases

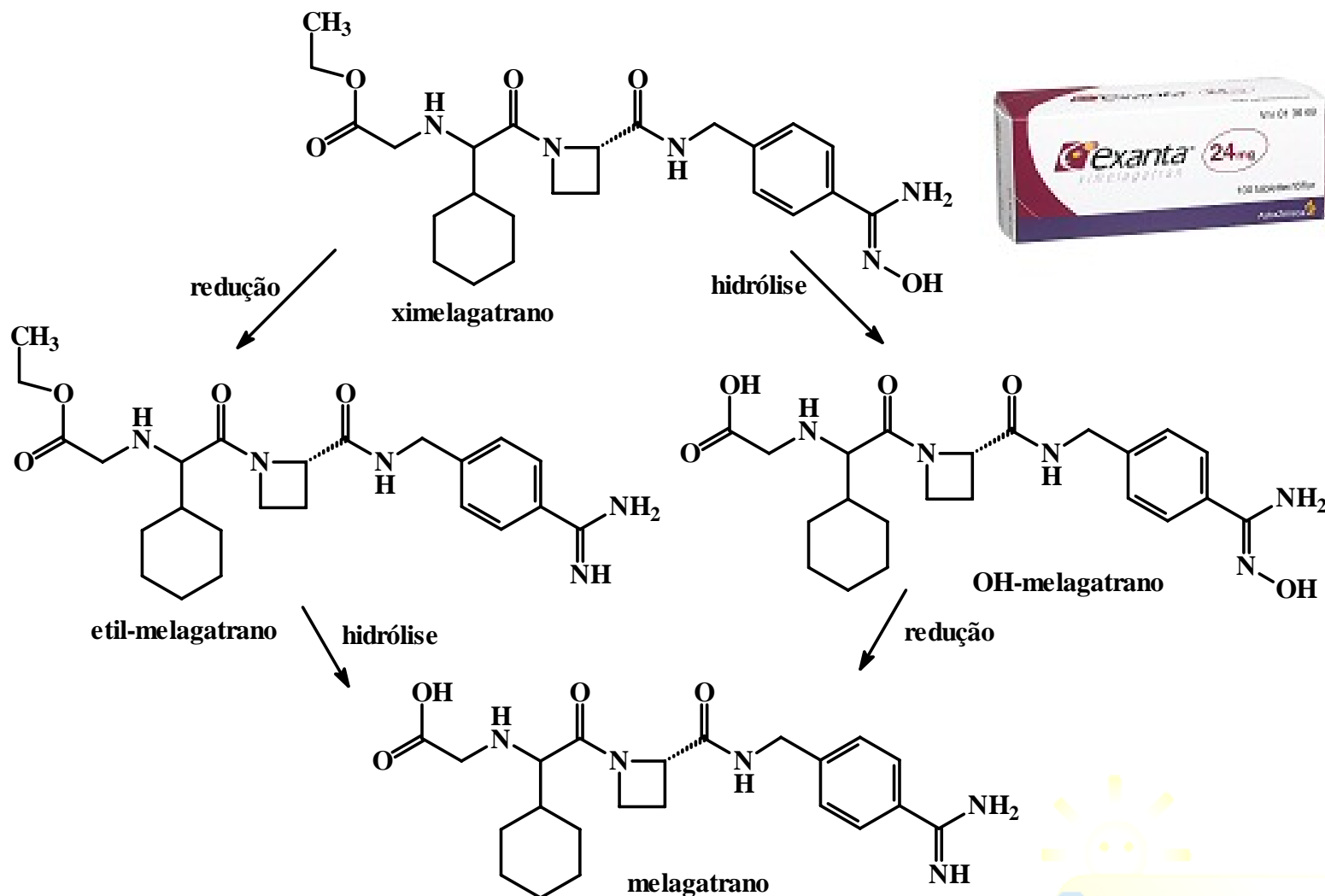
2000 vezes menos potente em inibir a acetilcolinesterase



R = H: Ro-64-0802

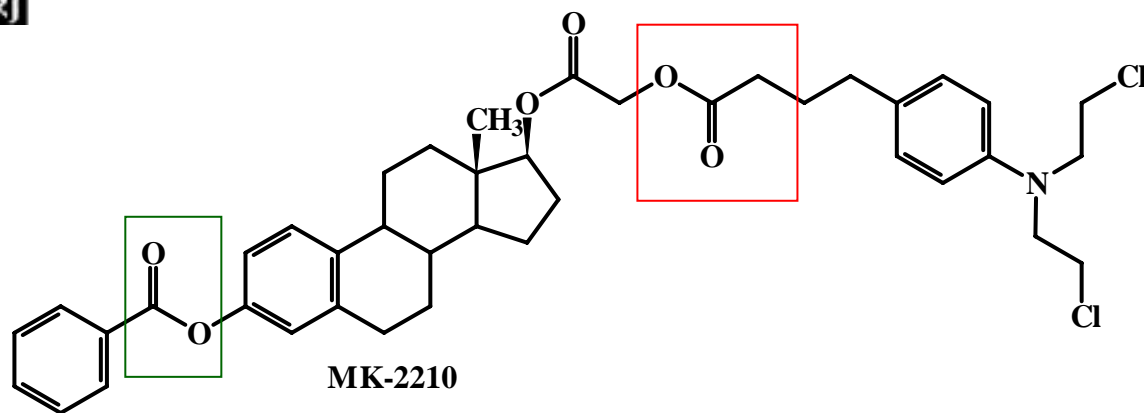
R = ethyl: Oseltamivir

Metabolismo: Pro-Fármaco



Halperin, J. L. *J. Am. Coll. Cardiol.* (2005) 45: 1-9

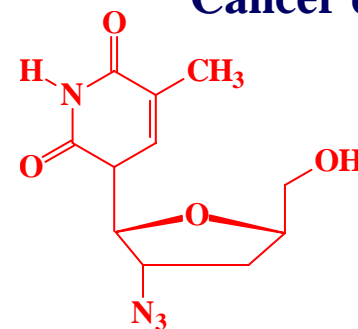
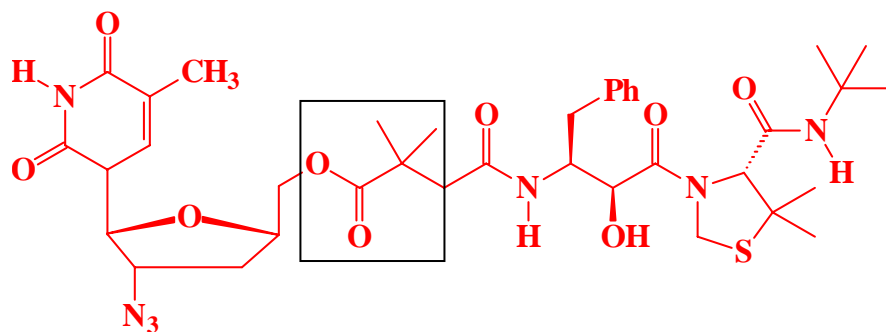
Metabolismo: Pro-Fármaco



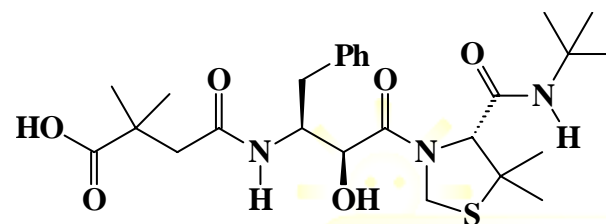
MK-2210

Estradiol
+
clorambucil

Câncer de mama



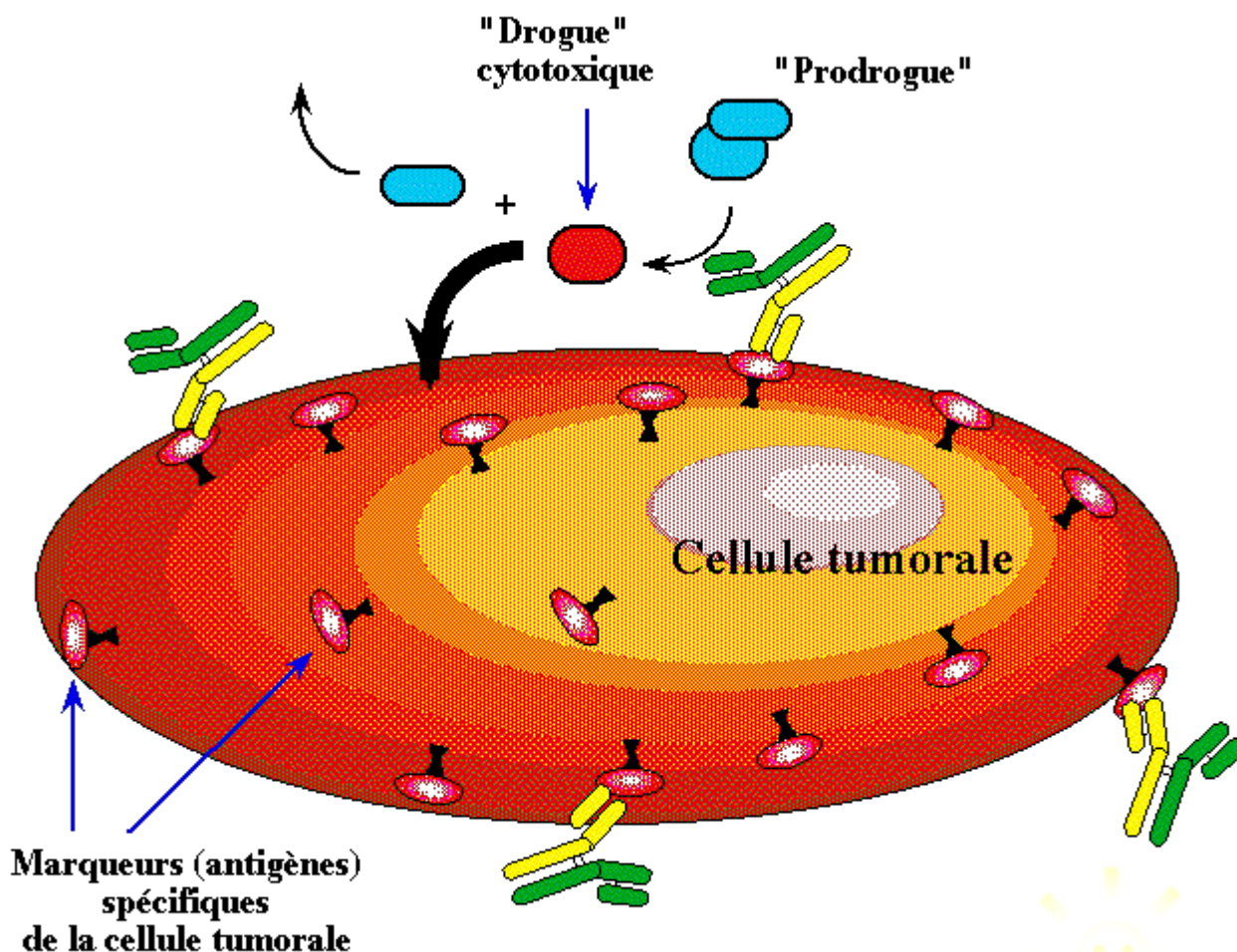
AZT (inibidor da TR)



KNI-413 (inibidor HIV-protease)

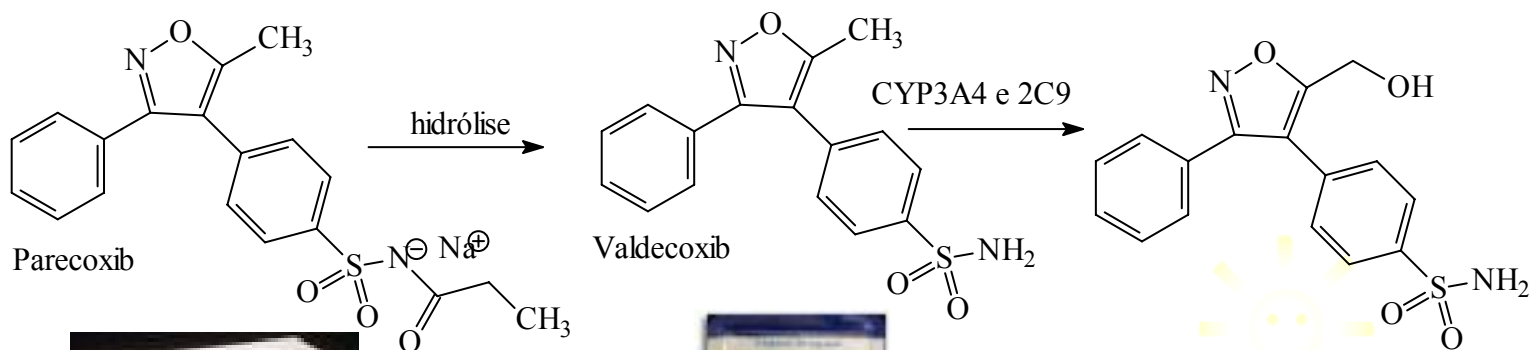
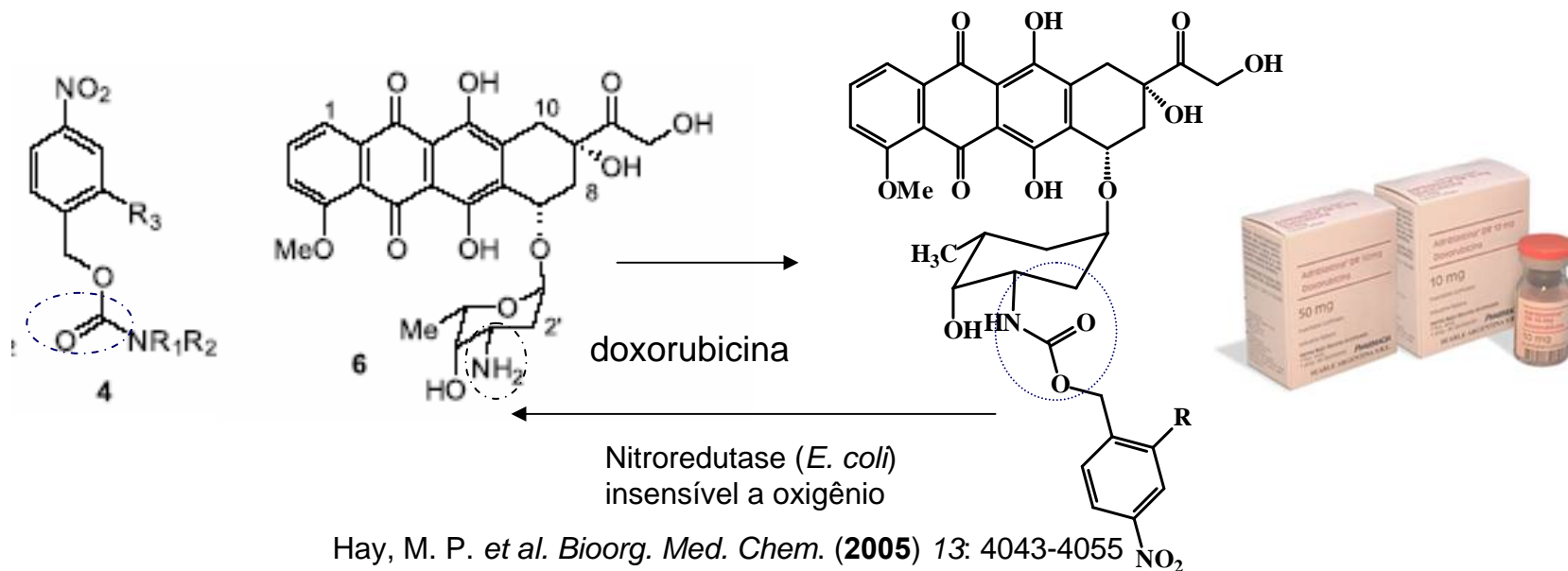
SIDA

Metabolismo: Pro-Fármaco

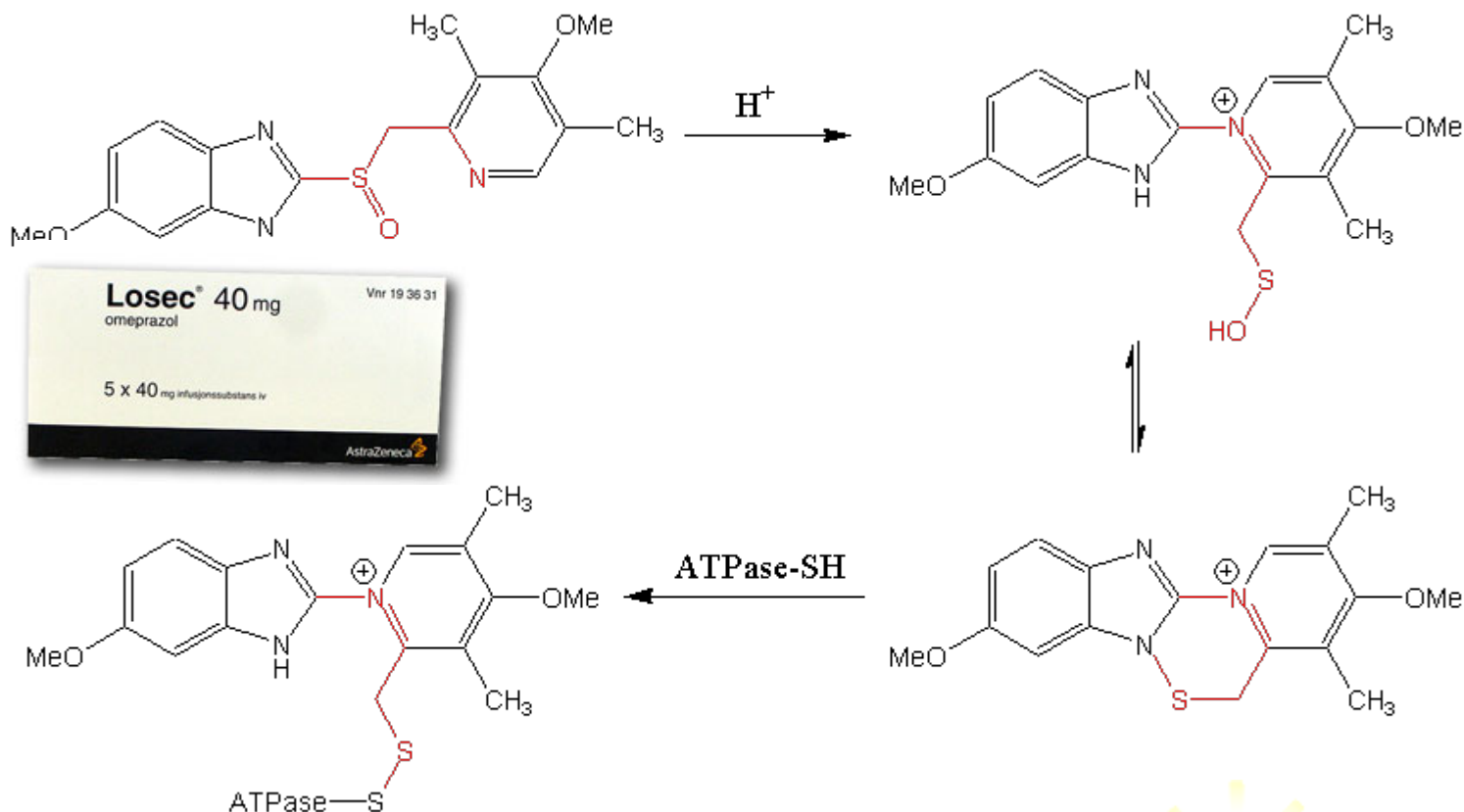


This anti-cancer therapy is designed as [Antibody-Directed Abzyme Prodrug Therapy \(ADAPT\)](#)

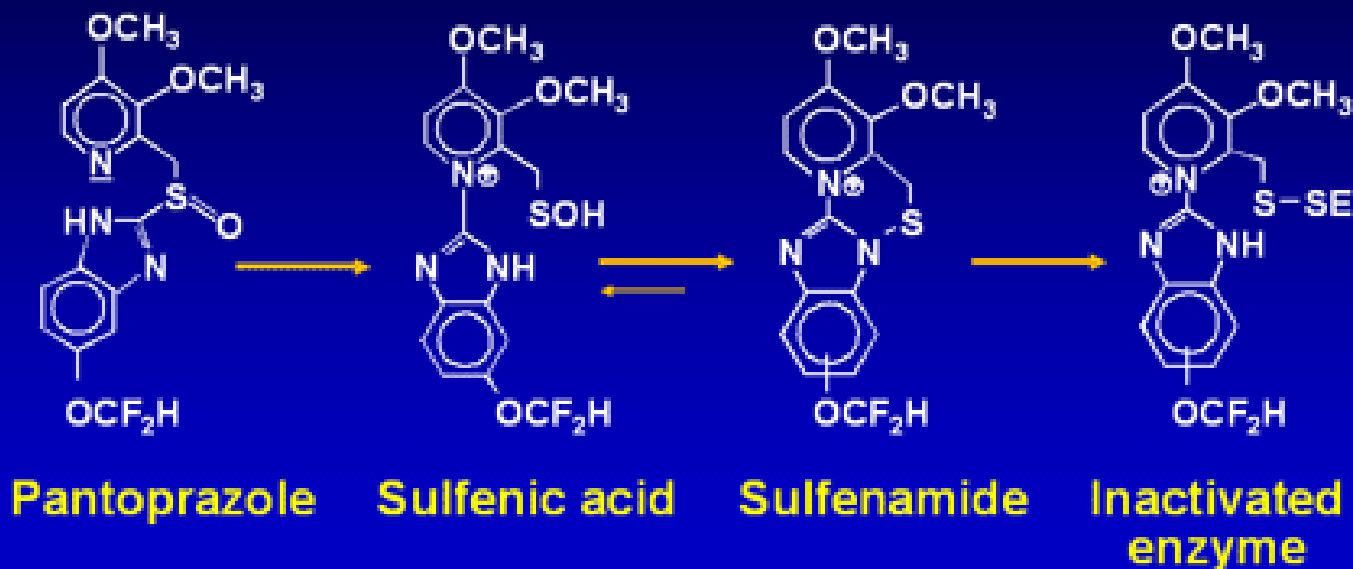
Metabolismo: Pro-Fármaco



Metabolismo: Pro-Fármaco

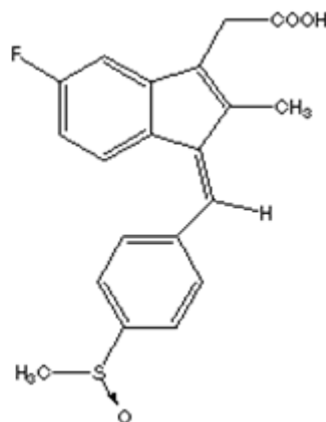


Activation of Substituted Benzimidazoles



Adapted with permission from Kromer W. *Digestion*. 1995;56:443-454.

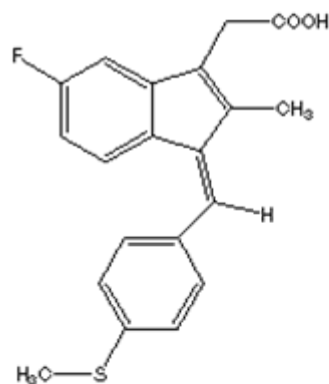
Metabolismo: Pro-Fármaco



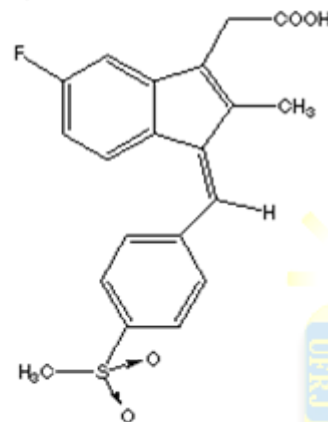
sulindac
(Clinoril®)
 $T_{1/2} = 7-8$ hrs

reversible

irreversible



sulfide
active metabolite
 $T_{1/2} = 16.4$ hrs



sulfone
inactive metabolite



UFRJ

XIII Escola de Verão

UFRJ

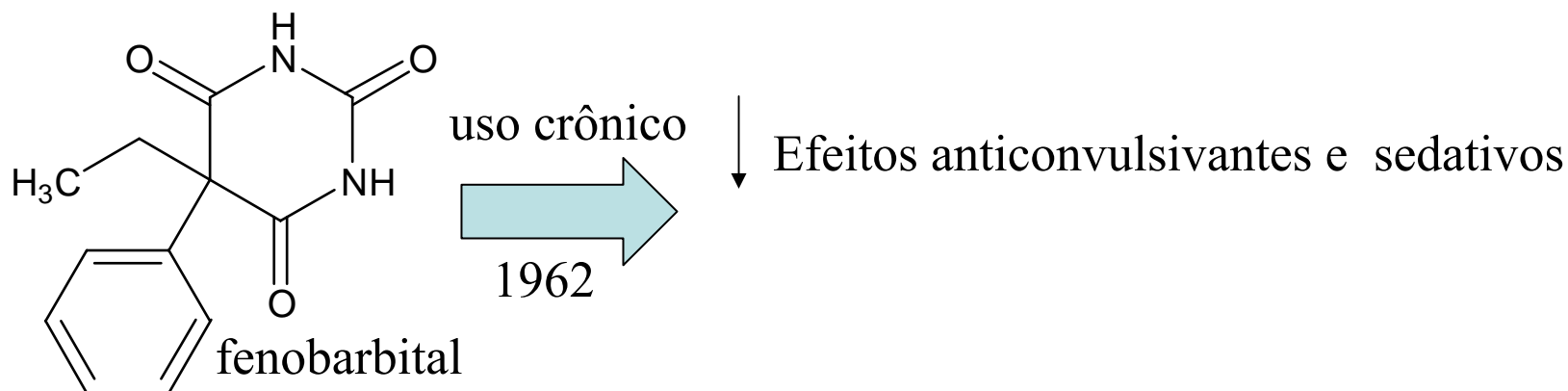
em Química Farmacêutica e Medicinal

Metabolismo: Indução e Inibição Enzimática

Indução Enzimática \Rightarrow Aumento da quantidade e atividade de enzimas que metabolizam xenobióticos, principalmente as \neq famílias de CYP450. **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



Inibição Enzimática \Rightarrow Diminuição da atividade catalítica de enzimas que metabolizam xenobióticos, principalmente as \neq famílias de CYP450. **Resulta no aumento da $t_{1/2}$ e é considerada como mecanismo de regulação pós-translacional de regulação.**

MECANISMOS DE INIBIÇÃO: Competição de \neq substratos
suicidas ; Inibidores alostéricos



INTERAÇÃO MEDICAMENTOSA

- ➡ Interações Benéficas (atenuar efeitos colaterais)
- ➡ Interações Insignificantes
- ➡ Interações Deletérias

★ *Polifarmácia & Medicamentos de múltiplo princípio ativo*

EUA → Paciente hospitalizado recebe em média 14 medicamentos

*ANVISA → ca. 50.000 especialidades farmacêuticas →
medicamentos de princípios ativos múltiplos, i.e. mais de um fármaco em
sua composição*

➡ Objetivos da Associação Medicamentosa

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

➡ Interações Físico-Químicas X Farmacodinâmica X Farmacocinética

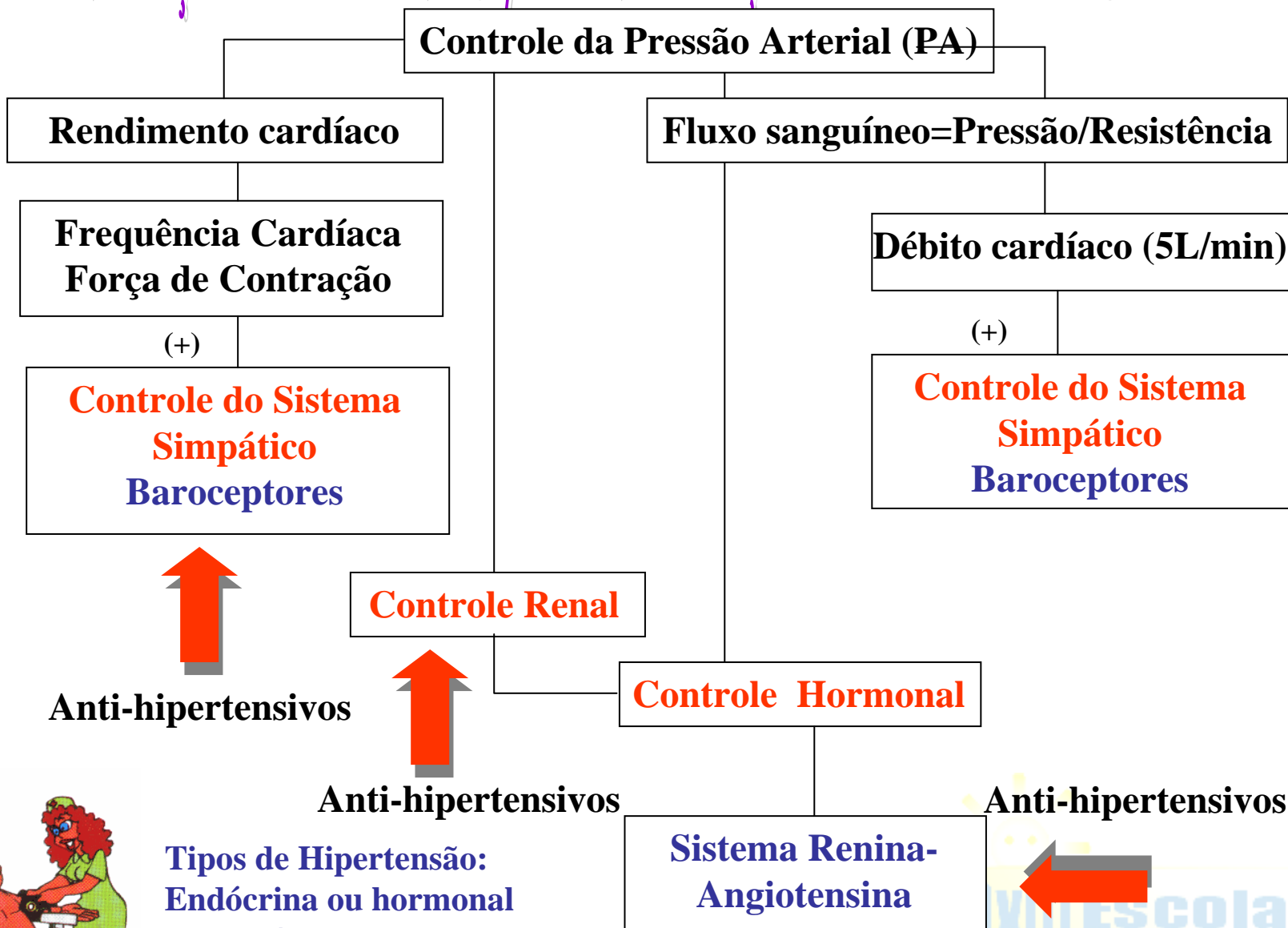
INTERAÇÃO MEDICAMENTOSA

Interações Físico-Químicas⇒ onde duas ou mais substâncias reagem Entre si, por mecanismos puramente físicos ou químicos. 1. Vitamina C na anemia ferropriva→ Manter o Ferro no estado ferroso 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)

Farmacodinâmica⇒ Os efeitos finais são resultantes das ações farmacodinâmicas próprias dos agentes concorrentes. Podem resultar em: adição, somação ou potencialização e antagonismo. 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)

Farmacocinética⇒ Um dos agentes é capaz de modificar a absorção, distribuição, biotransformação ou a excreção de outro agente administrado concomitantemente

INTERAÇÃO MEDICAMENTOSA/POTENCIALIZAÇÃO DO EFEITO TERAPÊUTICO



Tipos de Hipertensão:
 Endócrina ou hormonal
 Neurogênica
 Renal
Hipertensão essencial (>90%)



Anti-hipertensivos



INTERAÇÃO MEDICAMENTOSA/POTENCIALIZAÇÃO DO EFEITO TERAPÊUTICO

Características Ideais para Anti-Hipertensivos

Ativo adm. oral

$t_{1/2}$ adequado

Ser eficaz em todos os tipos de hipertensão

Baixo índice de efeitos adversos

Ausência de efeitos toxicológicos a longo prazo

Custo acessível



Classes de Agentes Anti-Hipertensivos

Antagonistas α_1 -adrenérgicos (prazosin)

Antagonistas β_1 -adrenérgicos (propranolol)

Agonistas α_2 -adrenérgicos (clonidina)

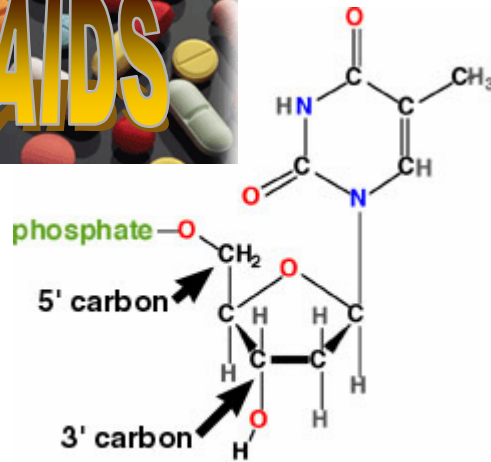
Bloqueadores de canais de cálcio (verapamil)

Inibidores da ECA (captopril)

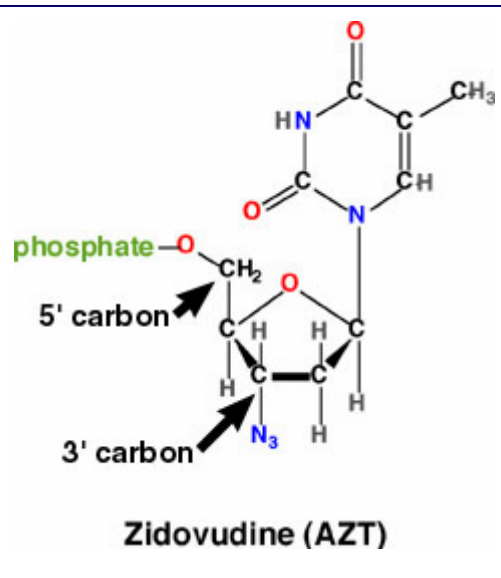
Antagonistas de receptores da angiotensina II
(losartan)

Diuréticos (hidroclorotiazida)

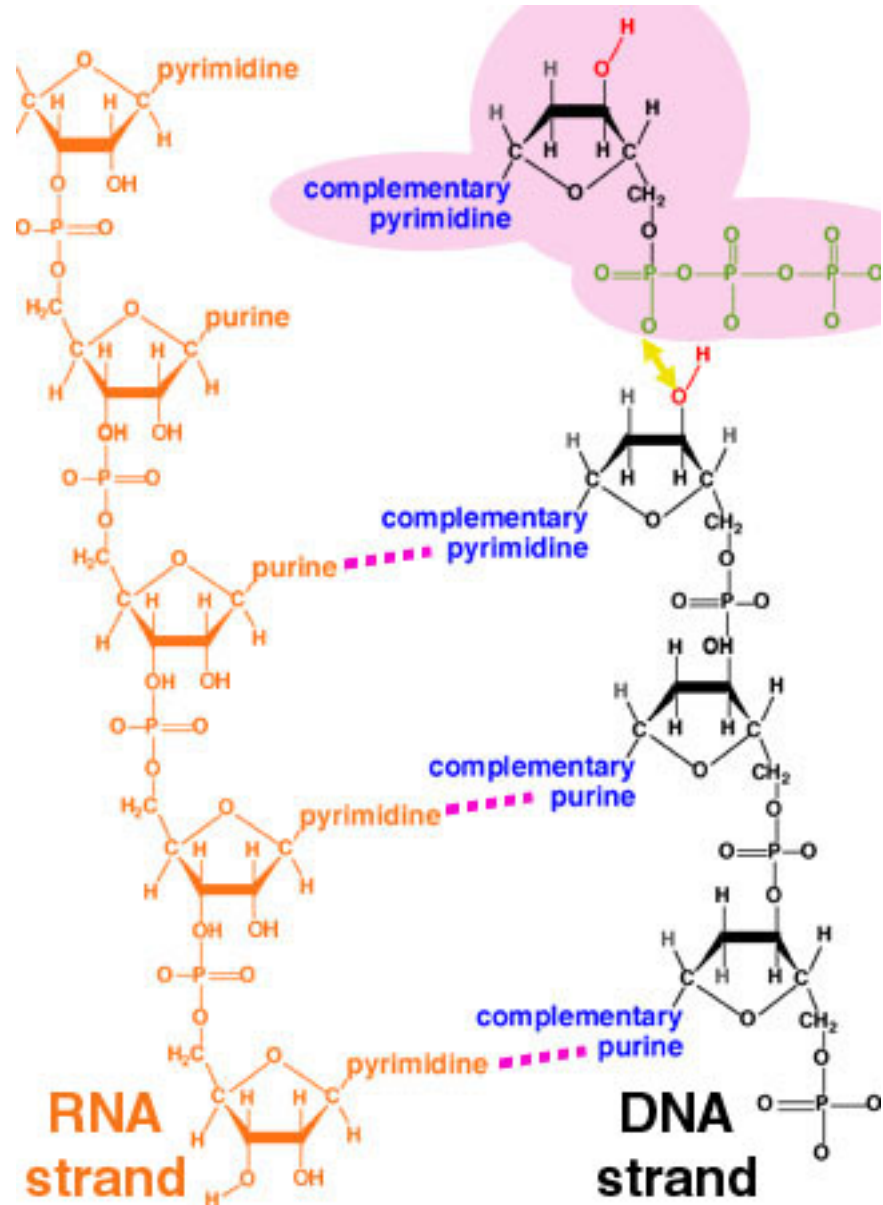
INTERAÇÃO MEDICAMENTOSA/DIMINUIÇÃO DE EFEITOS COLATERAIS



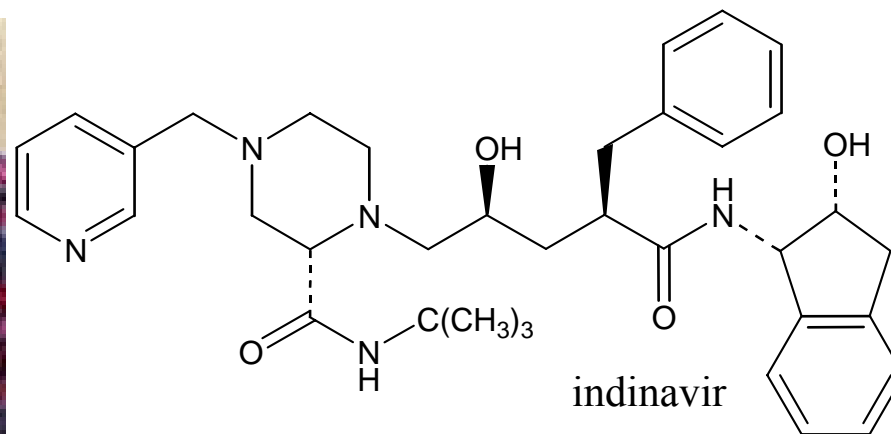
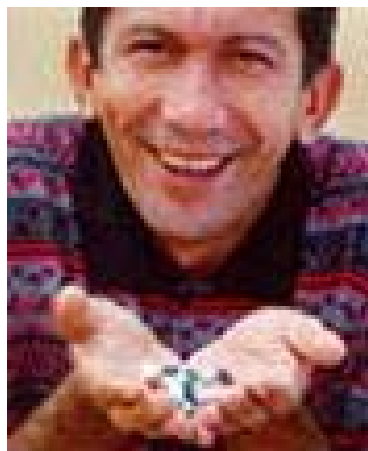
Thymidine



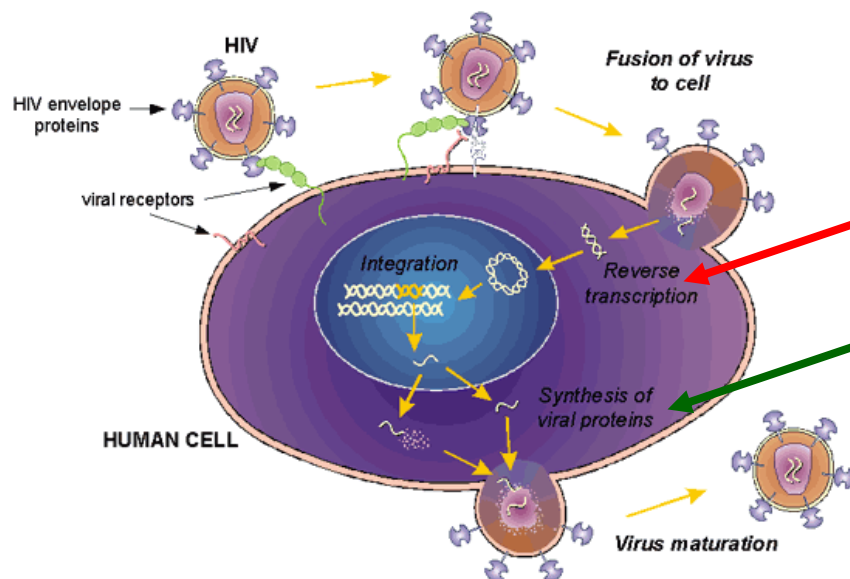
Zidovudine (AZT)



INTERAÇÃO MEDICAMENTOSA/DIMINUIÇÃO DE EFEITOS COLATERAIS

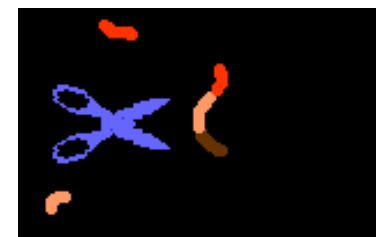


THE HIV LIFE CYCLE



(-) **AZT**

(-) **indinavir**



INTERAÇÃO MEDICAMENTOSA/DIMINUIÇÃO DE EFEITOS COLATERAIS

**TERAPIA
ANTI-RETROVIRAL**

Efeitos Adversos



reações de hipersensibilidade



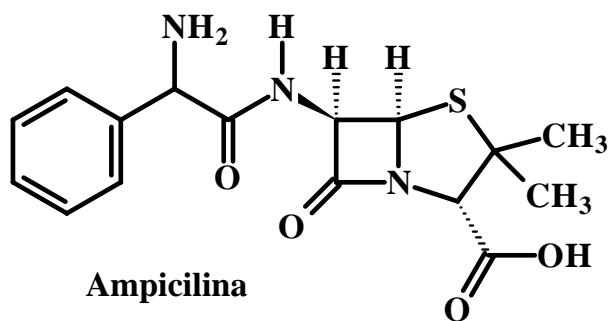
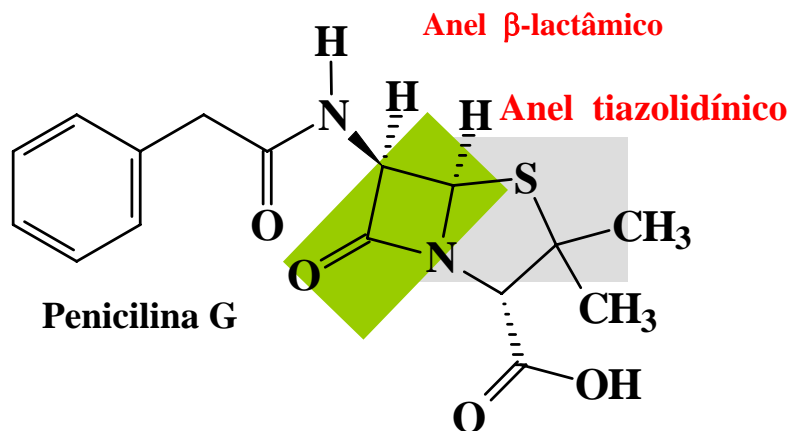
lipodistrofia

| Fármacos | Efeitos Adversos |
|-------------|---|
| Zidovudine | náuseas, dor de cabeça, pigmentação das unhas |
| Didanosine | náuseas, diarreia |
| Zalcitabine | úlceras bucais |
| Efavirenz | estimulação do SNC |
| Saquinavir | náuseas e diarreia |
| Ritonavir | náuseas, diarreia, “paraesthesiae perioral and flushing” |
| Indinavir | cálculo renal, hiperbilirrubinemia, anemia hemolítica, etc. |
| Nelfinavir | náuseas e diarreia |
| Amprenavir | hipersensibilidade, “paraesthesiae perioral”, CYP450 DI |

Some Antiretrovirals May Induce and Inhibit CYP450

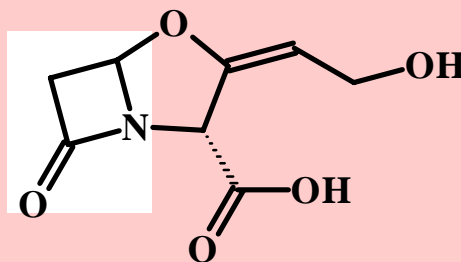
| | <u>Induction</u> | <u>Inhibition</u> |
|------------|--------------------------------------|----------------------------------|
| Nelfinavir | glucuronyl transferase | CYP3A, 2B6 |
| Ritonavir | CYP1A2, glucuronyl transferase | CYP3A, 2D6, 2C9, 2C19, 2B6 |
| Efavirenz | CYP3A4 | CYP3A, 2B6 |

INTERAÇÃO MEDICAMENTOSA/ PREVENÇÃO DE RESISTÊNCIA



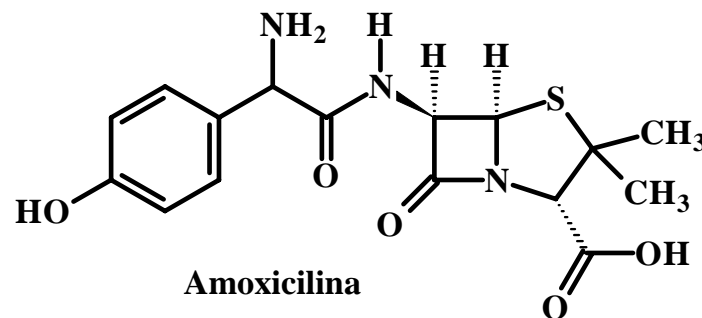
(estável em pH ácido)

(sensível à β -lactamases)



Ácido Clavulânico

(*Streptomyces clavuligerus*, 1975)



(estável em pH ácido)

(sensível à β -lactamases)

$t_{1/2}$ = 80 min; boa biodisponibilidade oral; uso oral, parenteral



Interação nos receptores colinérgicos

↓PA, vasodilatação,
↑secreção de saliva,
Secreção intestinais,
Motilidade GI, miose

INTOXICAÇÃO:

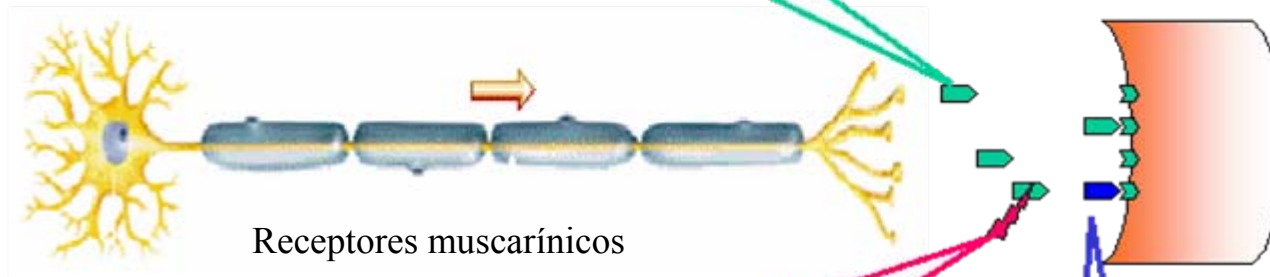
Diarréia, sudorese, miose,
Nauseas, incon. Urinária

Pilocarpina (+)

Acetilcolina

DESINTOXICAÇÃO:

Fármacos anticolinesterases e
Antagonistas de receptores da AChE



Acetil Colinesterase

irreversível

↓ Inseticidas

reversível

Neostigmina

↑ Pralidoxima

(-)

(+)

Atropina

Escopolamina

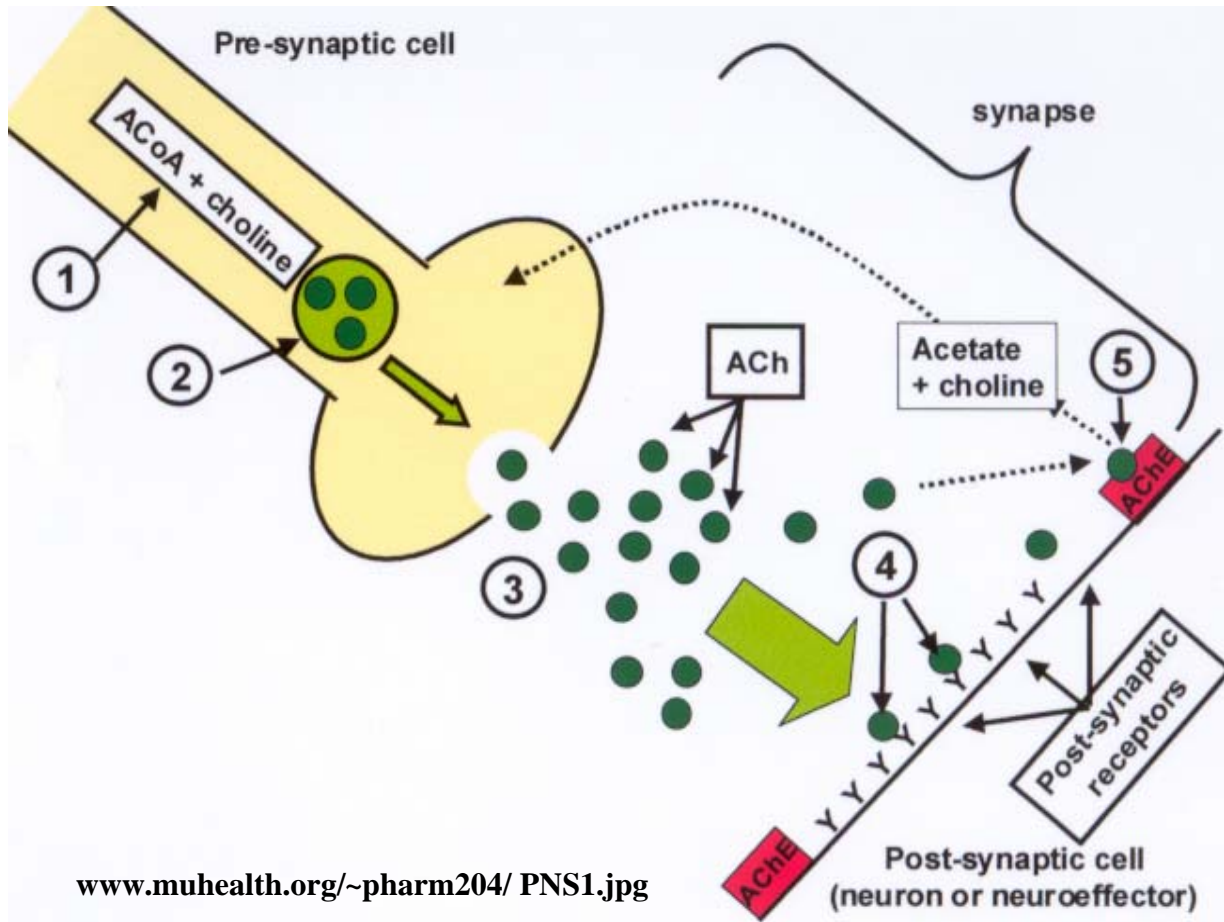
Hiosciamina

Homatropina

(-)

Antago-
nistas

Agonistas & Antagonistas Colinérgicos



www.muhealth.org/~pharm204/PNS1.jpg

- **synthesis** of acetylcholine (ACh) from acetyl CoA and choline

- **storage** of ACh in synaptic vesicles

- **release** of ACh (fusion of synaptic vesicle with presynaptic membrane and release of ACh into the synapse)

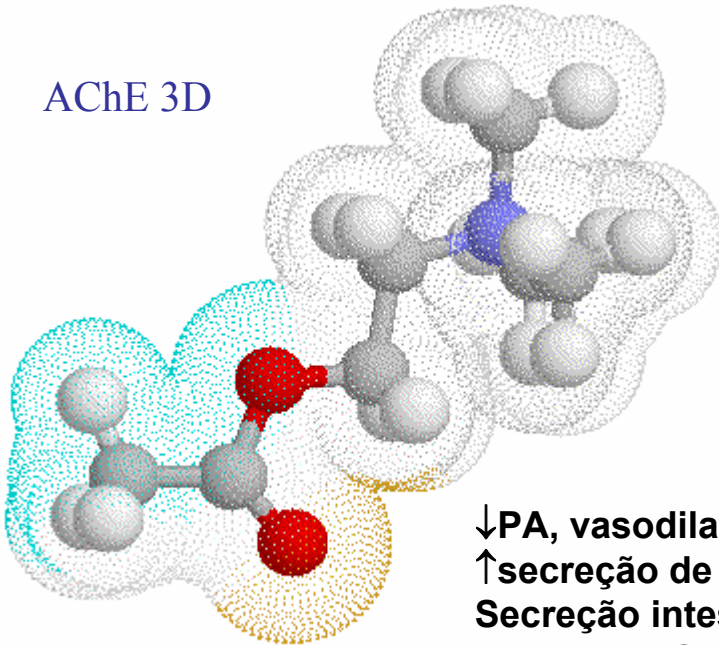
- **action** of ACh by binding to and activating receptors (nicotinic in autonomic ganglia and NMJ and muscarinic in many sites)

- **inactivation** by enzymatic breakdown of ACh by acetylcholinesterase (AChE) located in the synapse



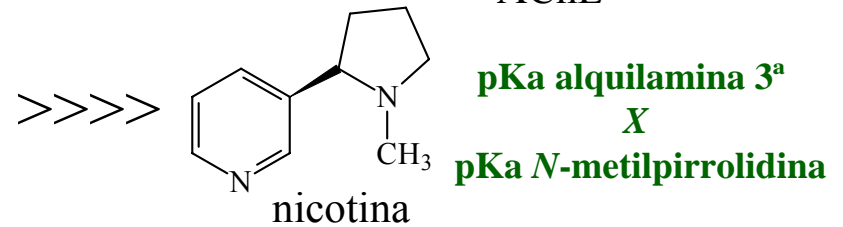
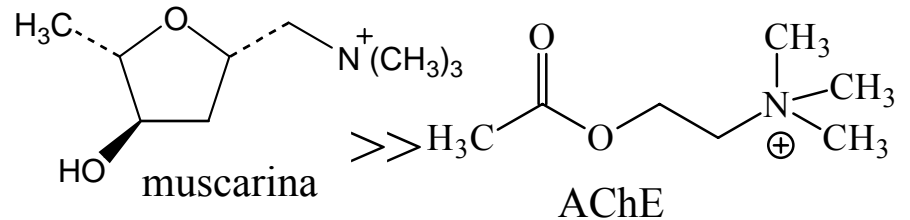
Agonistas Colinérgicos

AChE 3D



↓PA, vasodilatação,
↑secreção de saliva,
Secreção intestinais,
Motilidade GI, miose

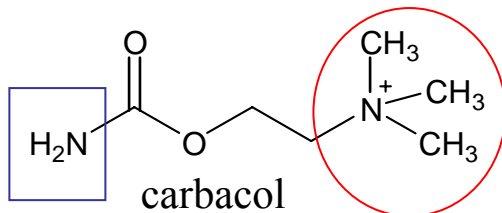
Receptores Muscarínicos (M1-M5)



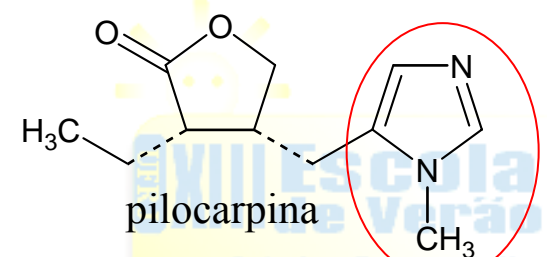
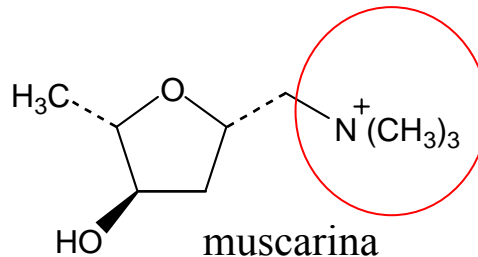
Receptores Nicotínicos

nicotina \gg AChE $\gg \gg \gg$ muscarina

pKa alquilamina 3ª X pKa N-metilimidazol



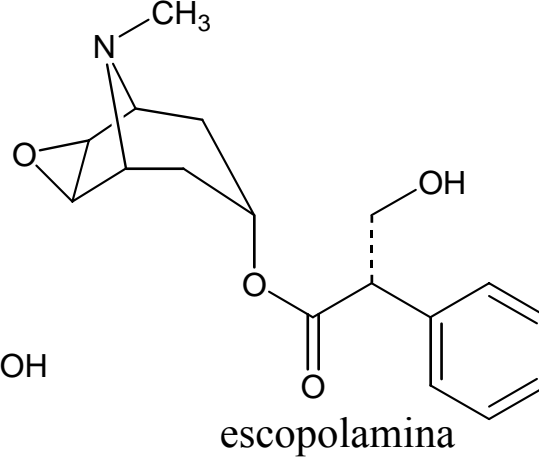
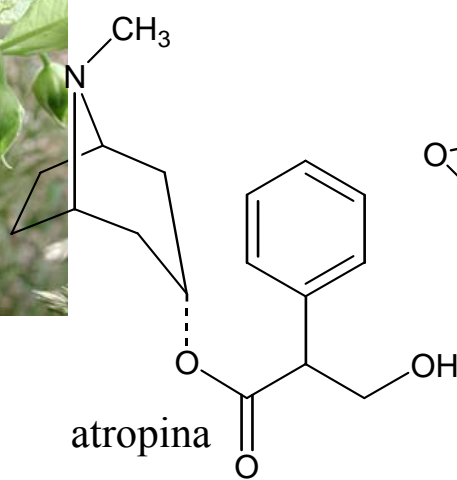
Cl⁻



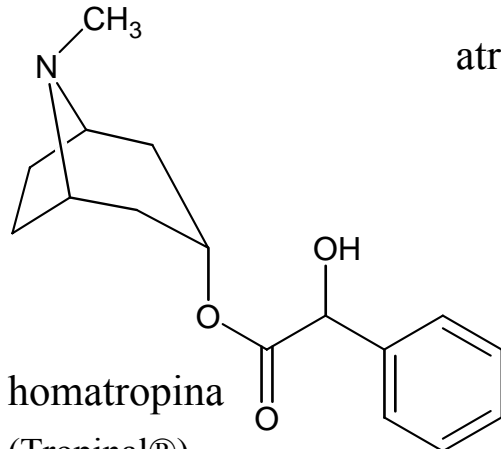
Antagonistas Colinérgicos



Atropa belladonna



Datura stramonium

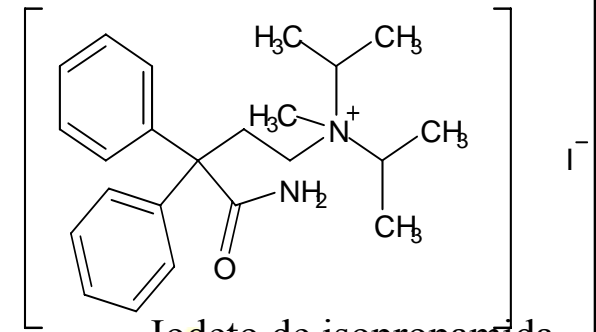
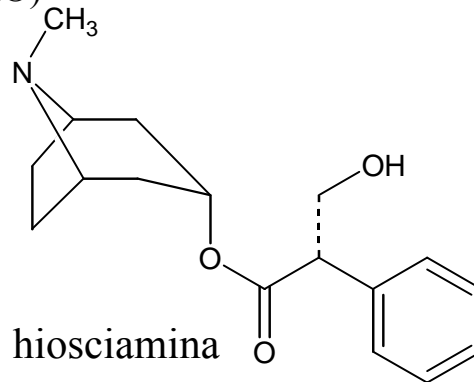


(Tropinal®)

Atropa belladonna

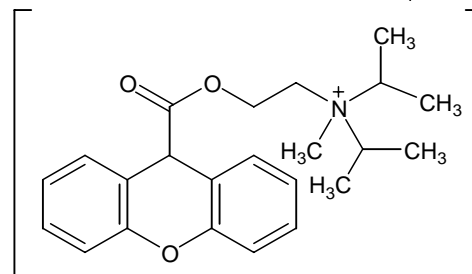
Datura stramonium

(Lomotil®)



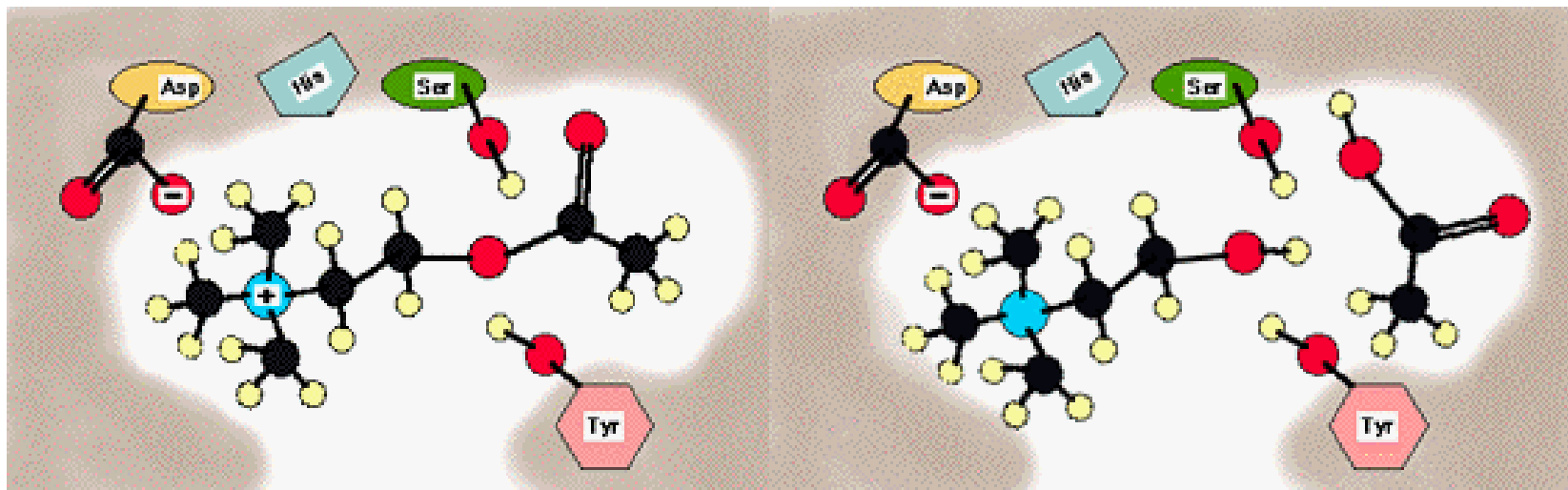
(Descon API®)

**Ações antiespasmódicas,
midríase (dilatação das pupilas),
Taquicardia (em altas doses), etc**



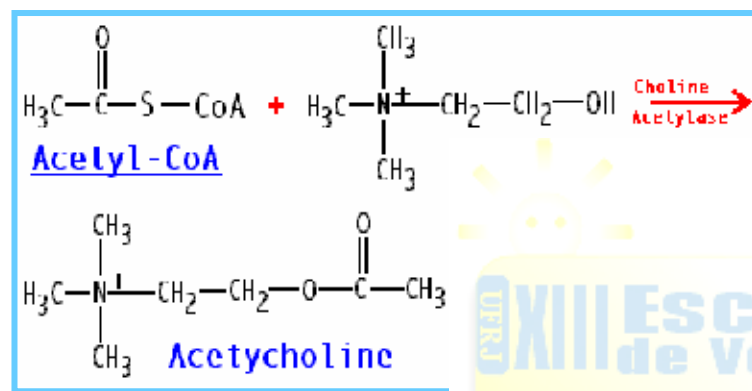
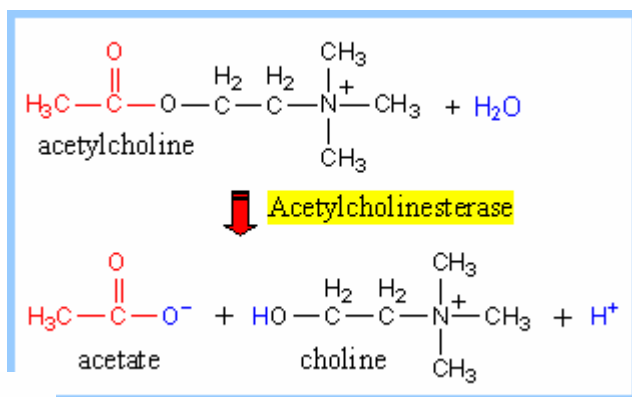
(Ansilive®)

Inibidores da Acetilcolinesterase

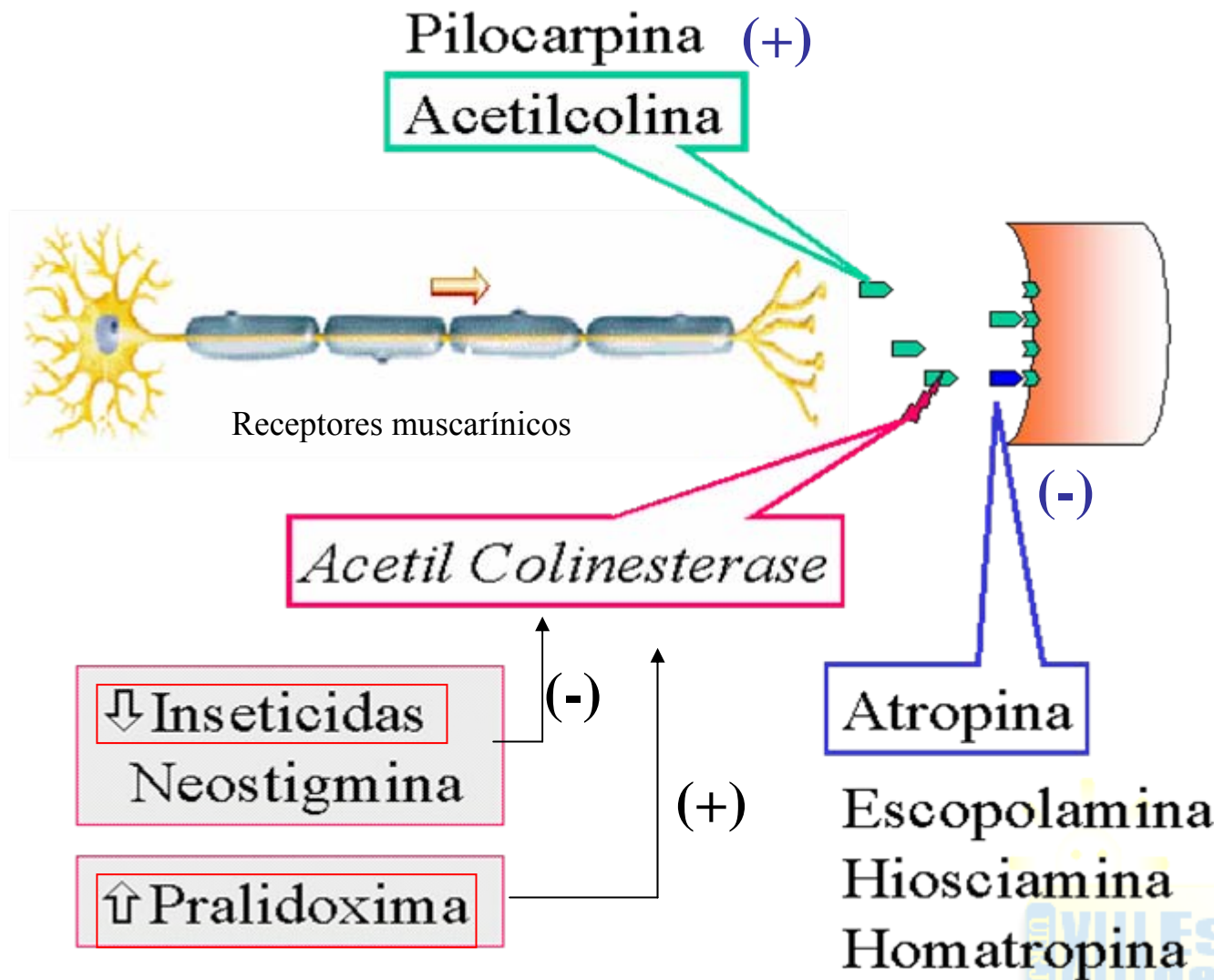


Acetylcholine bound to the active site of acetylcholinesterase. This is the enzyme-substrate (ES) complex

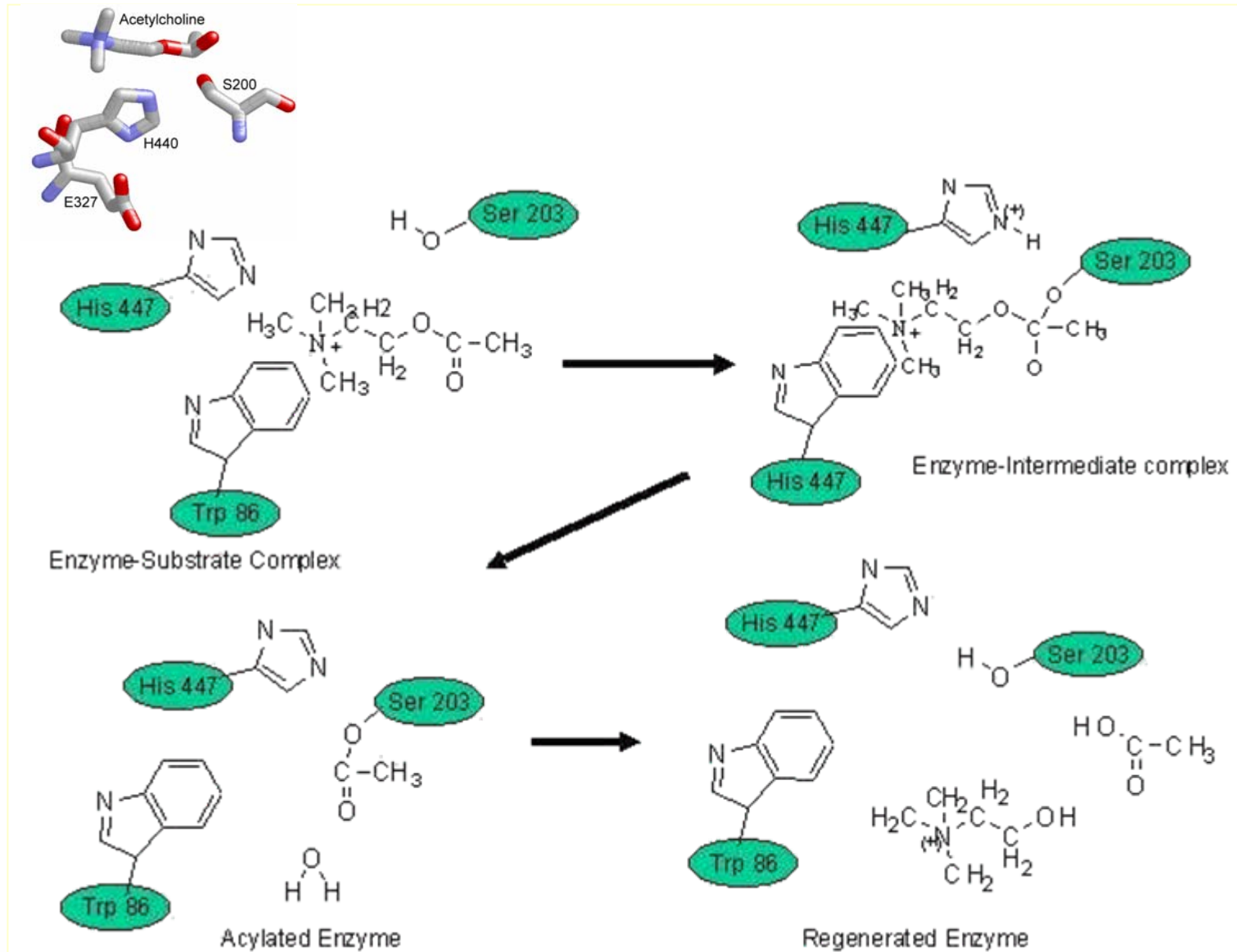
The the bond between the choline (left side) and acetate part (right side) of the molecule has been split. Choline and acetate will leave the enzyme and it will be ready to accept another acetylcholine molecule



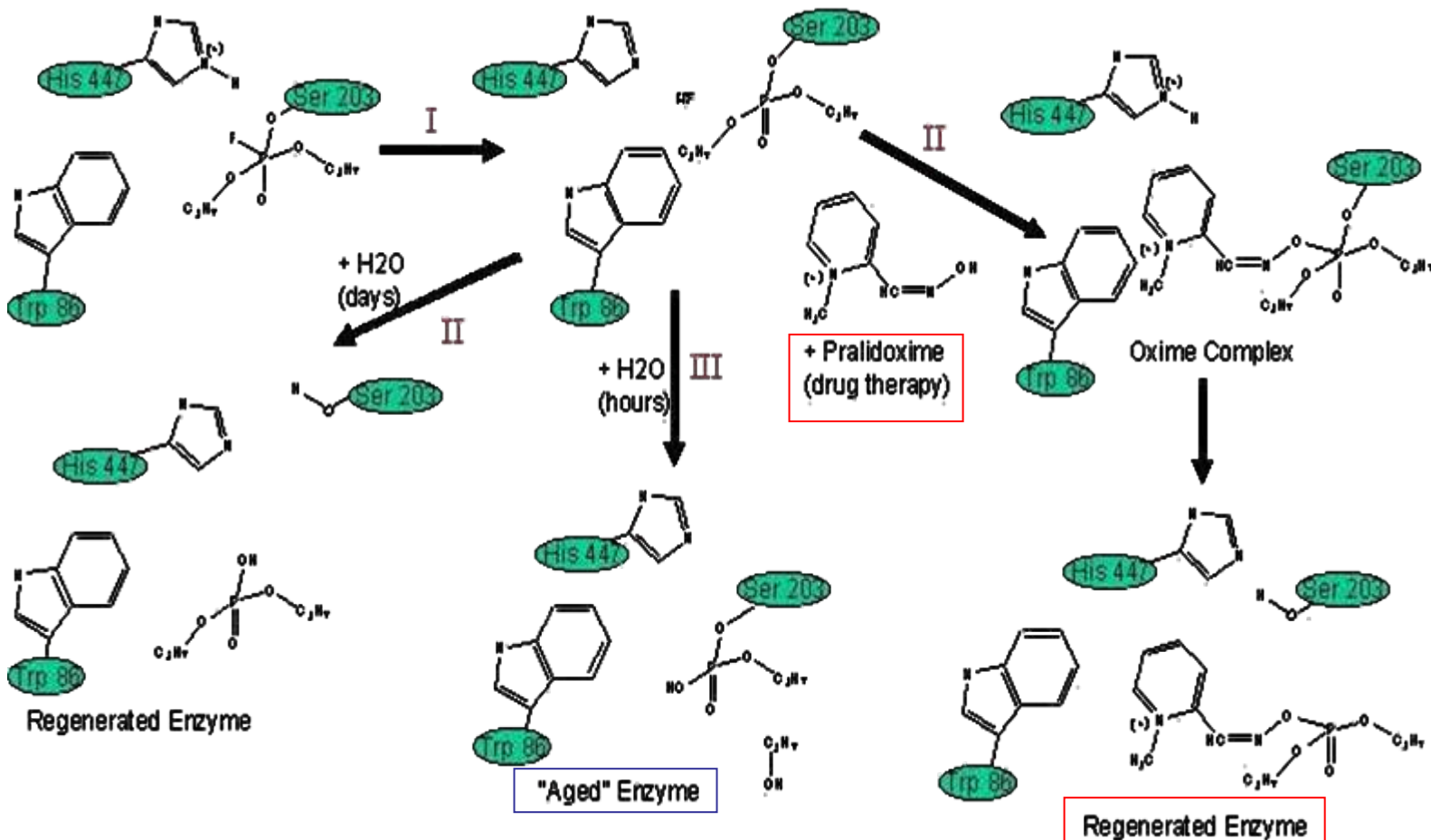
Interação nos receptores colinérgicos



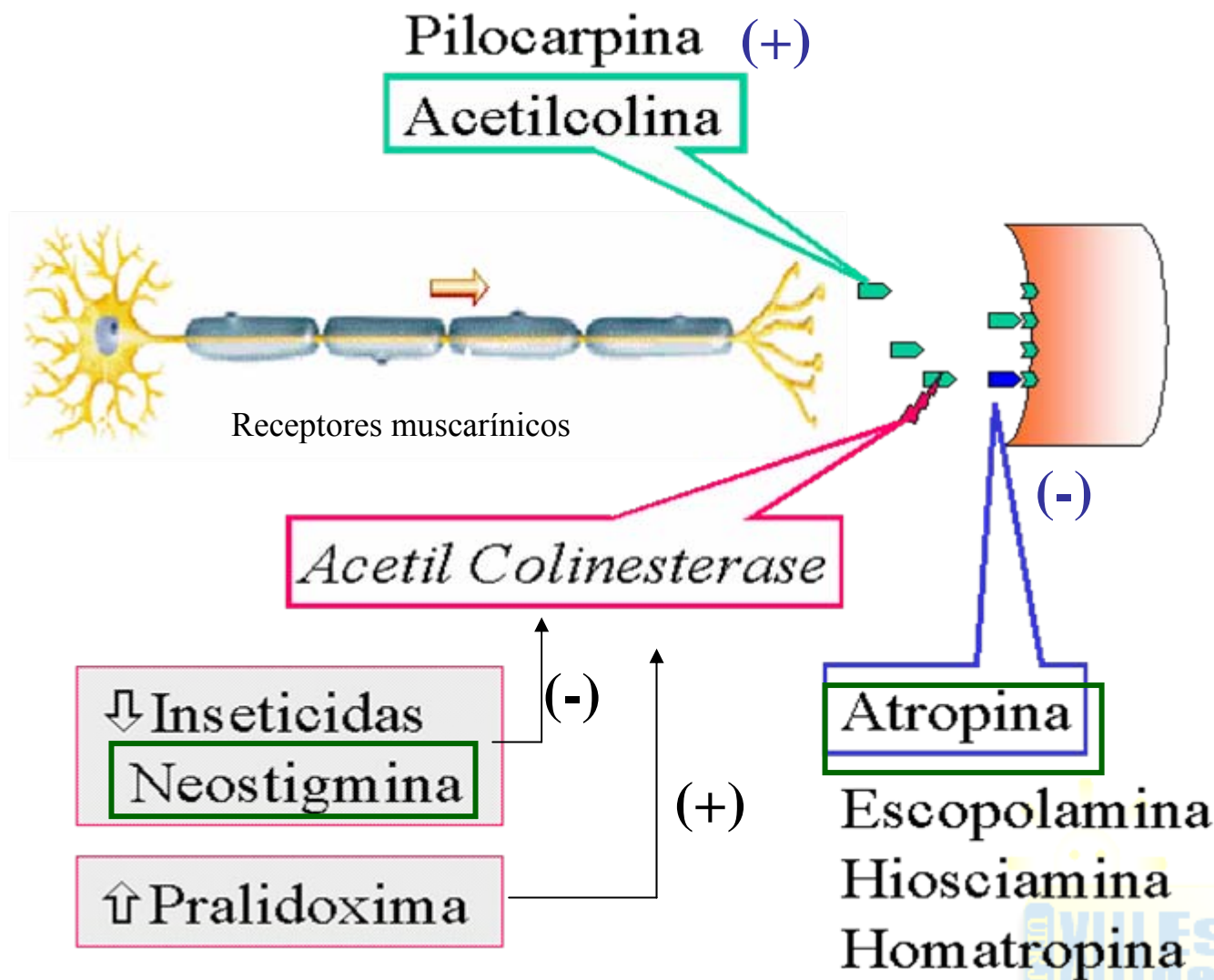
Hidrólise da Acetilcolina (AChE)



Hidrólise da Acetilcolina (AChE)



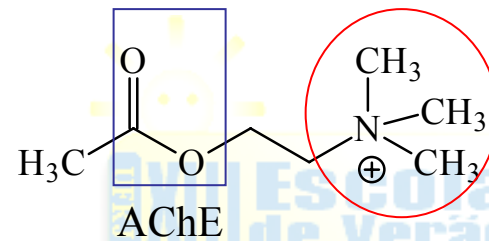
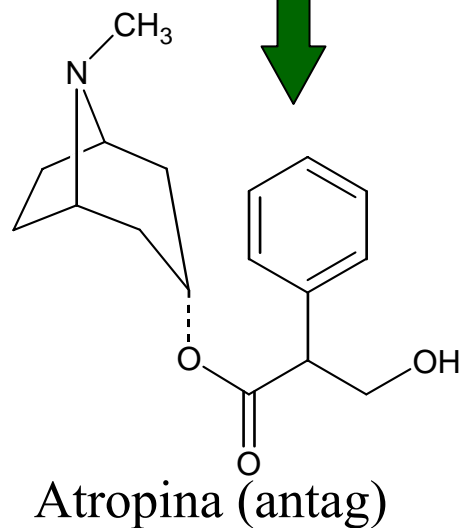
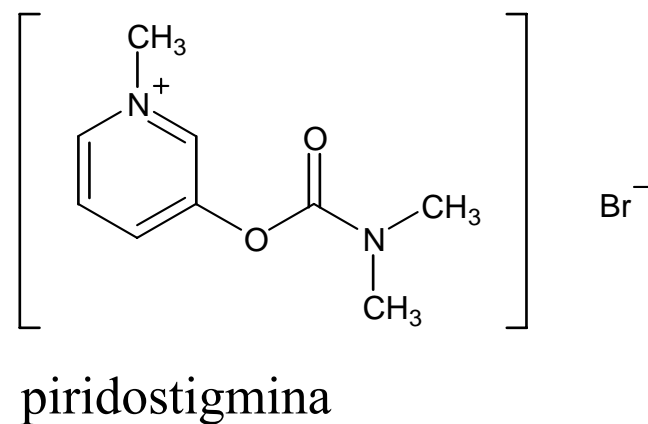
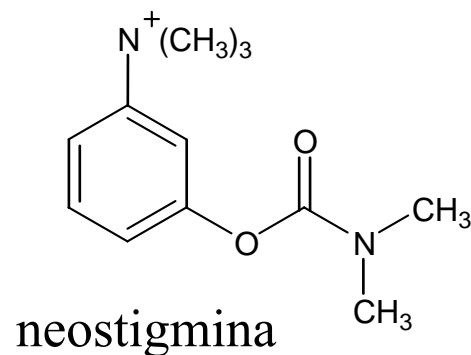
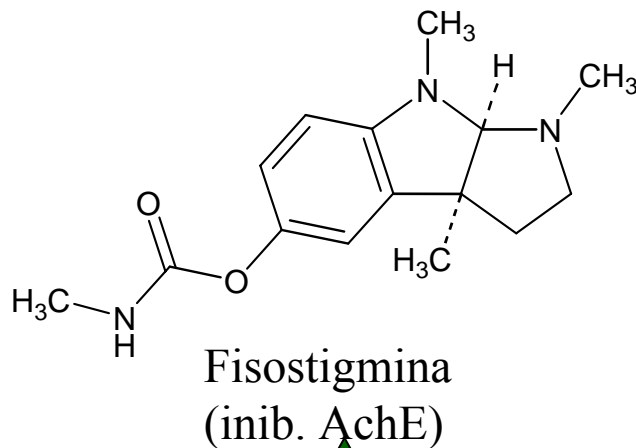
Interação nos receptores colinérgicos



Manifestações clínicas de Intoxicação Aguda por Anticolinérgicos

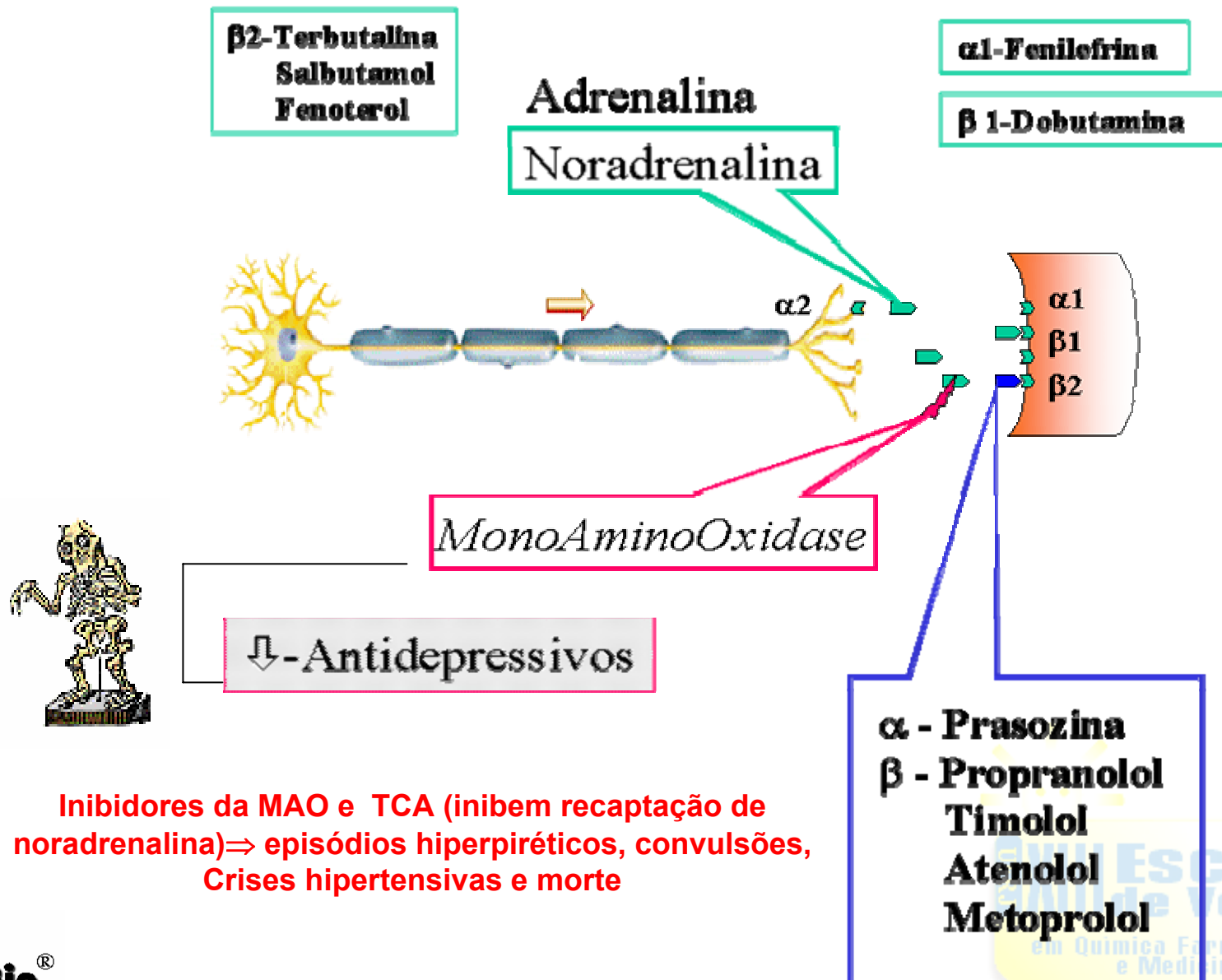
- **Distúrbios cutâneo-mucosos:** pele quente, seca e ruborizada, com erupções eritematosas ou escarlatiniformes. Secura das mucosas.
- **Distúrbios oculares:** pupilas dilatadas não reagentes, visão embaçada, fotofobia, paralisia da acomodação, aumento da pressão intra-ocular
- **Distúrbios cardiocirculatórios:** taquicardia, anormalidades no eletrocardiograma, hipertensão arterial
- **Distúrbios digestivos:** dificuldade de deglutição, ruídos abdominais diminuídos, constipação. Boca, lábios e língua secas. Sede intensa
- **Distúrbios periféricos / Sistema nervoso central:** agitação, inquietude, hiperreflexia, incoordenação muscular, ataxia, distúrbios de fala, desorientação, confusão mental e alucinações geralmente visuais, vivas e coloridas.
- **Outras manifestações:** hipertermia, retenção urinária (desejo, mas incapacidade de urinar), diminuição das secreções salivar, gástrica e sudorípara.
- **Em pacientes pediátricos:** fácies característico, com rubor da face e midríase bilateral e expressão desorientada. Hipertermia, grande agitação psicomotora e comportamento bizarro. Choro e risos alternados, linguagem incompreensível, desconexa, além de agressividade.

Inibidores Reversíveis da Acetilcolinesterase

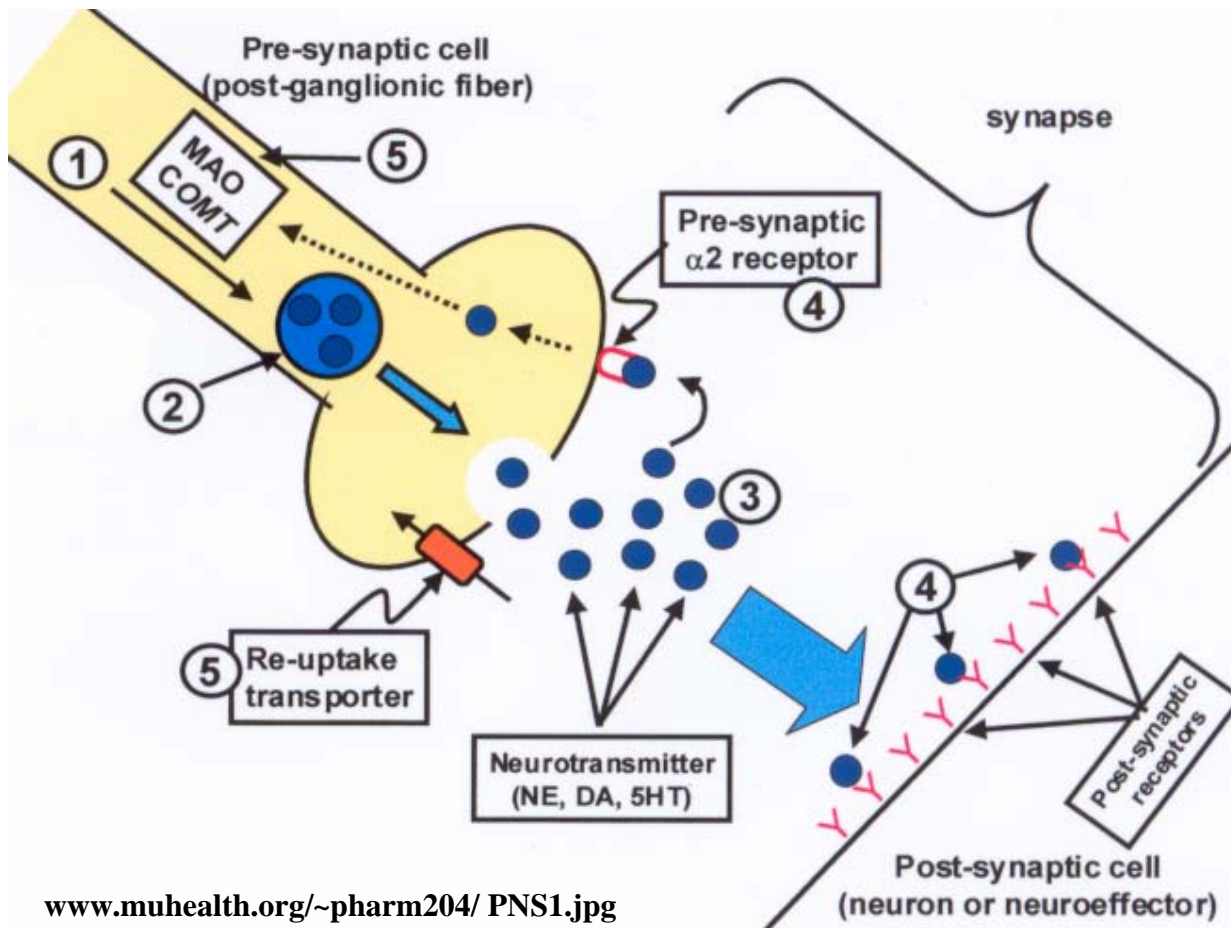


(anticolinérgico; Lomotil®; Atrosedina®)

Interação nos receptores adrenérgicos



Agonistas & Antagonistas Adrenérgicos



www.muhealth.org/~pharm204/PNS1.jpg

- **synthesis** of norepinephrine (NE - not pictured)

- **storage** of NE in vesicles

- **release** of NE: fusion of synaptic vesicles with presynaptic membrane and release of NE into the synapse

- **action** of NE through binding to and activating receptors (α_2 presynaptic and α and β post synaptic)

- **inactivation** by presynaptic re-uptake transporters (also presynaptic receptors shut off further NE release)

Interações Medicamentosas

Graves

Propranolol+haloperidol=hipotensão

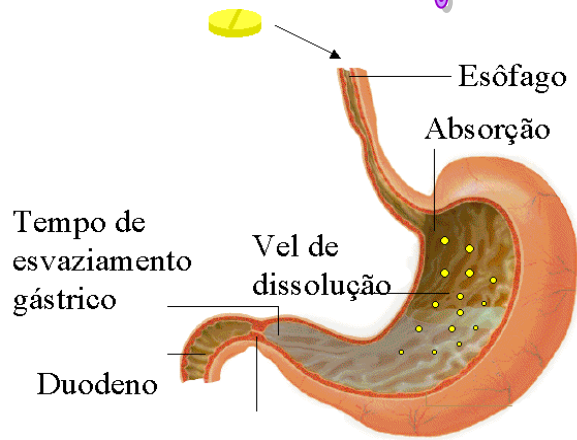
Penicilina+Cloranfenicol=antagonismo

Varfarina+AAS=hipocoagulabilidade

**Estreptomicina+ácidoetacrínico
=ototoxicidade**



Interação Medicamentosa: Farmacocinética



Absorção \Rightarrow reduzida por drogas que diminuem motilidade GI (e.g: atropina, opiáceos); Fármacos Básicos e Ácidos com Anti-ácidos.

Ligações Proteicas
Ligações Tecidos

Depósito

Nível Plasmático da droga livre, Ação Farmacológica

Nível Tóxico

Nível Efetivo

Eliminação

$\uparrow V_d \rightarrow \uparrow$ distribuição tecidual

Complexo Droga-Proteína

Droga Livre

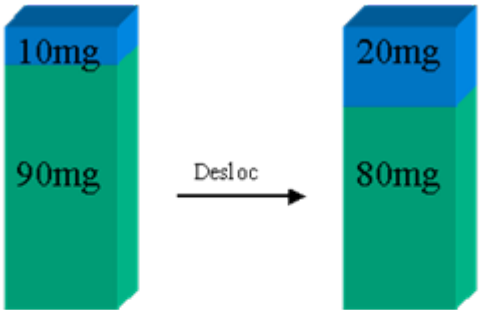
Proteína

Ação

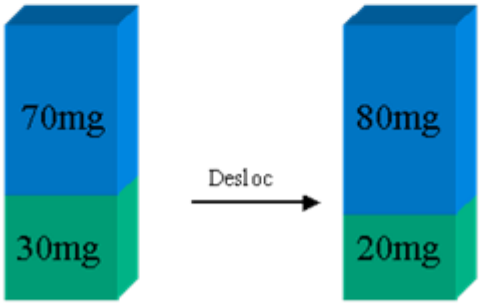
Biotransformação
Eliminação

Droga altamente ligada ($\downarrow V$)

Livre
Ligada



$\uparrow 100\%$



$\uparrow 14\%$

Droga fracamente ligada ($\uparrow V$)

Interação Medicamentosa: Farmacocinética

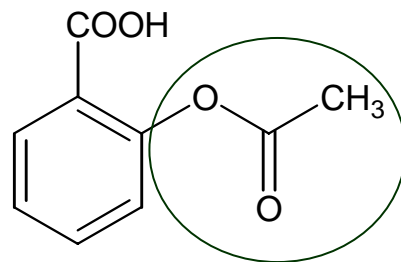
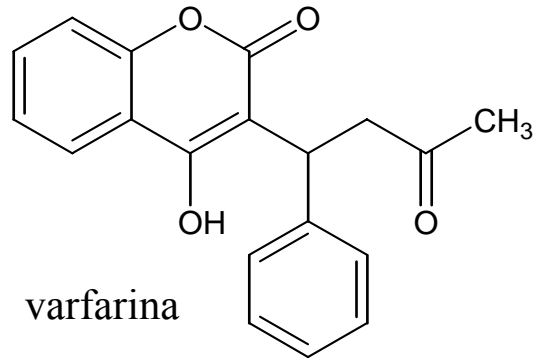
Table 4 Drugs that are highly protein bound (>95%).

| 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 |

Agentes deslocadores:
fenilbutazona, aspirina,
paracetamol, dicumarol

* Narrow therapeutic window.

Interação Medicamentosa: Farmacocinética



Ligações Proteicas
Ligações Tecidos

Depósito

Nível Plasmático da droga livre, Ação Farmacológica

Nível Tóxico

Nível Efetivo



Eliminação

↑Vd → ↑distribuição tecidual

Complexo Droga-Proteína

Droga Livre

Proteína

Ação

Biotransformação
Eliminação

Interação Medicamentosa: Farmacocinética

Indutores Enzimáticos

| Clase terapêutica | Fármacos |
|---------------------------|--|
| Hipnóticos | Etanol, Glutetimida |
| Anticonvulsivantes | Fenobarbital, Fenitoína |
| Ansiolíticos | Clordiazepóxido, Meprobamato |
| Antipsicóticos | Clorpromazina |
| Antiinflamatórios | Fenilbutazona, Corticosteróides |
| Antiasmáticos | Teofilina |

Inibidores Enzimáticos

| Clase terapêutica | Fármacos |
|--------------------------|-------------------------------------|
| Antibióticos | Cloranfenicol, Tetraciclinas |
| Antiparasitários | Metronidazol, Fluconazol |
| Antidepressivos | Fluoxetina, sertraline, etc |
| Ansiolíticos | Diltiazem |
| Anti-úlceras | Omeprazola, Cimetidina |
| Antiasmáticos | Zafirlucast |
| Antimalárico | Quinidina |

Interação Medicamentosa: Farmacocinética

Table 5 Cytochrome P450 substrates, inducers, and inhibitors.

| 1A2 | 2C9 | 2C19 | 2D6 | 2E1 | 3A3/4 | |
|-----------------|------------------|------------------|------------------|------------------|--------------------------|---------------------|
| Substrates | | | | | | |
| Acetaminophen | Amitriptyline | Amitriptyline | Amitriptyline | Acetaminophen | Alfentanil | Lidocaine |
| Amitriptyline | Celecoxib | Carisoprodol | Amphetamine | Benzene | Alprazolam | Loratadine |
| Caffeine | Diclofenac | Citalopram | Atomoxetine | Caffeine | Amiodarone | Lovastatin |
| Clomipramine | Fluoxetine | Clomipramine | Carvedilol | Chlorzoxazone | Amitriptyline | (Not pravastatin) |
| Clozapine | Flurbiprofen | Cyclophosphamide | Chlorpheniramine | Dapsone | Amlodipine | Methadone |
| Cyclobenzaprine | Fluvastatin | Diazepam | Chlorpromazine | Dextromethorphan | Atorvastatin | Midazolam |
| Estradiol | Glipizide | Fluoxetine | Clomipramine | Ethanol | Bromocriptine | Nefazodone |
| Fluvoxamine | Glyburide | Imipramine | Clozapine | Enflurane | Budesonide | Nicardipine |
| Haloperidol | Ibuprofen | Indomethacin | Codeine | Halothane | Bupropion | Nifedipine |
| Imipramine | Irbesartan | Lansoprazole | Desipramine | Isoflurane | Buspirone | Nimodipine |
| Mexiletine | Losartan | Nelfinavir | Dextromethorphan | Isoniazid | Caffeine | Omeprazole |
| Naproxen | Naproxen | Omeprazole | Encainide | Sevoflurane | Calcium channel blockers | Ondansetron |
| Olanzapine | Phenytoin | Pantoprazole | Flecainide | Theophylline | Carbamazepine | Paclitaxel |
| Ondansetron | Piroxicam | Phenytoin | Fluoxetine | Venlafaxine | Cisapride | Paroxetine |
| Pentazocine | Rosiglitazone | Primidone | Fluvoxamine | | Clomipramine | Pimozide |
| Propranolol | Sulfamethoxazole | Progesterone | Haloperidol | | Clonazepam | Progesterone |
| Ropivacaine | Tamoxifen | Proguanil | Imipramine | | Cocaine | Protease inhibitors |
| Tacrine | Torsemide | Propranolol | Lidocaine | | Codeine | Quetiapine |
| Theophylline | Tolbutamide | Teniposide | Methadone | | Cyclosporine | Quinidine |
| TCAs | S-Warfarin* | TCAs | Metoclopramide | | Dapsone | Quinine |
| Verapamil | | R-Warfarin* | Metoprolol | | Dexamethasone | Rifabutin |
| R-Warfarin* | | | Mexiletine | | Dextromethorphan | Rifampin |
| Zileuton | | | Nortriptyline | | Diazepam | Ritonavir |
| Zolmitriptan | | | Olanzapine | | Diltiazem | Salmeterol |
| | | | Ondansetron | | Disopyramide | Saquinavir |
| | | | Oxycodone | | Doxycycline | Sertraline |
| | | | Paroxetine | | Ergotamine | Sildenafil |
| | | | Perphenazine | | Erythromycin | Simvastatin |
| | | | Propafenone | | Ethinyl estradiol | Tacrolimus |
| | | | Propranolol | | Ethosuximide | Tamoxifen |
| | | | Risperidone | | Etoposide | Theophylline |

Interação Medicamentosa: Farmacocinética

Table 5 continued

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

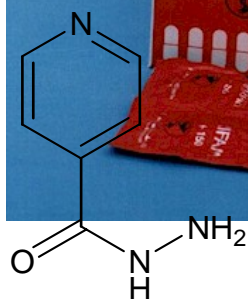
Table 5 continued

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

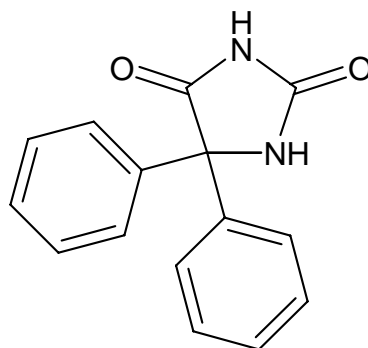
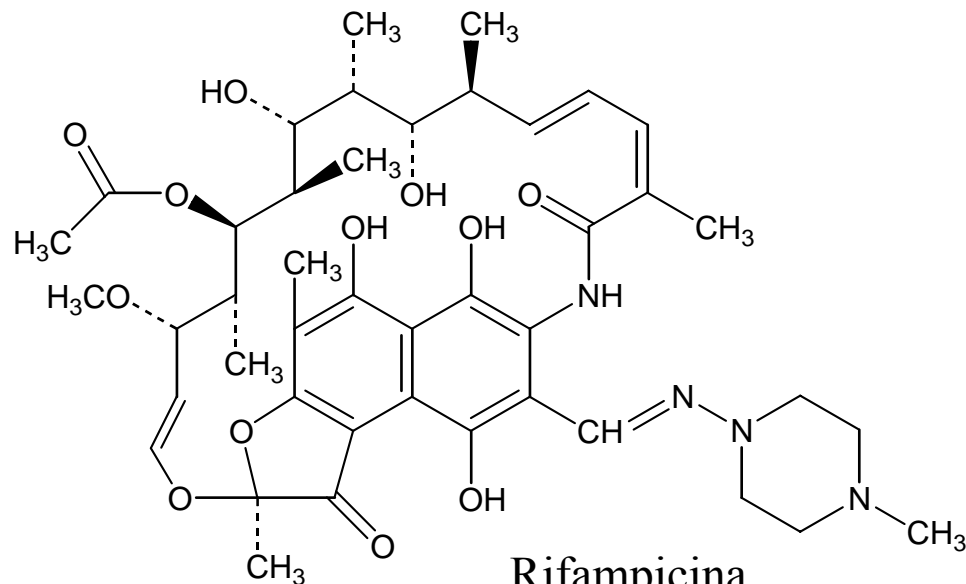
Data from <http://medicine.iupui.edu/flockhart/table.htm>; [19] Shannon M. *Pediatr Emerg Care* 1997;13(5):350-3; Taketomo CK, Hodding JH, Kraus DM. *Pediatric Dosage Handbook*. 10th ed. Cleveland: Lexicomp Inc, 2003-2004.

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

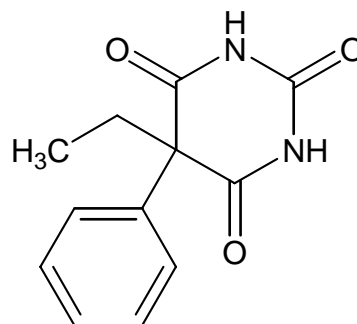
Manzi, S. F. *et al. Clin. Ped. Emerg. Med.* (2005) 6: 93-102



isoniazida

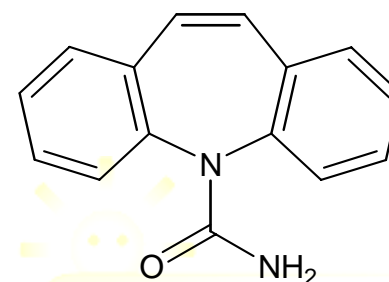


fenitoína



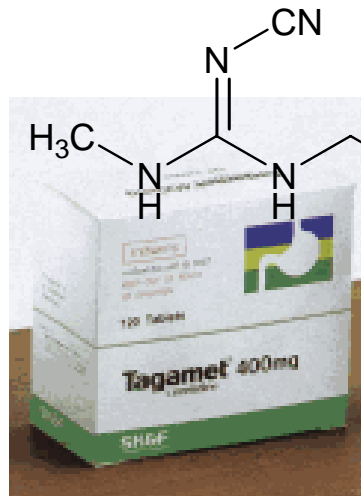
fenobarbital

auto-indutores

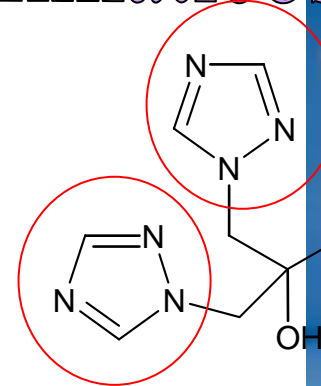
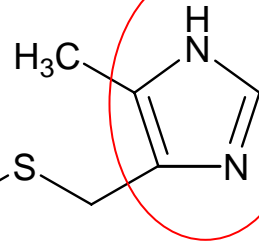


carbamazepina

Inibidores Enzimáticos



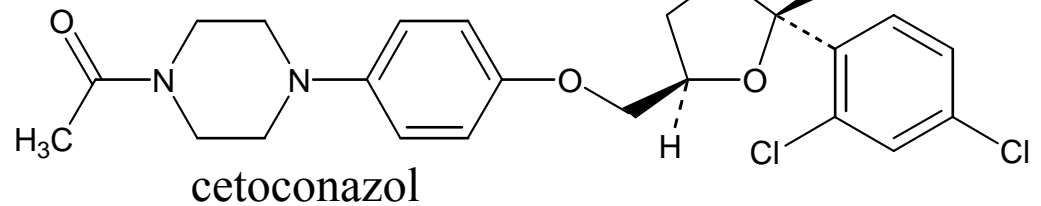
cimetidina



fluconazol

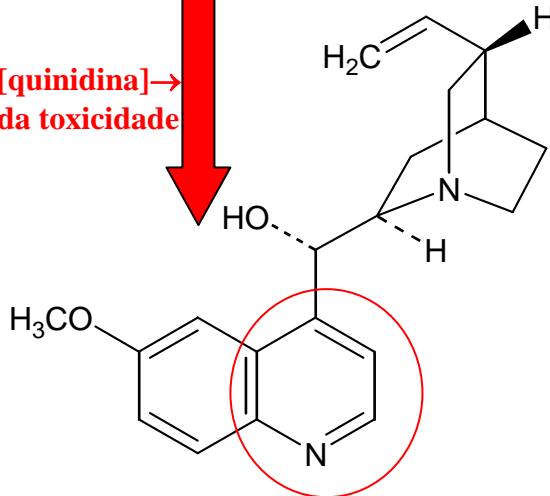


↑pH gástrico → ↓50% da absorção cetoconazol
(absorção ideal em pH < 3,5)



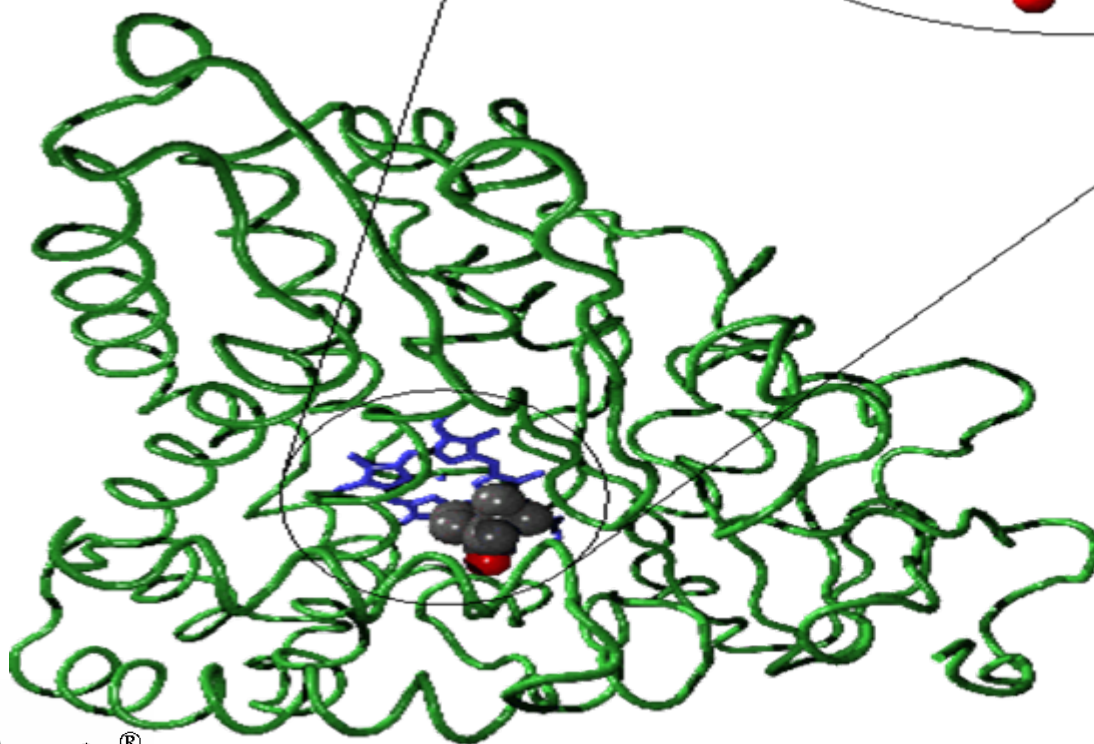
cetoconazol

↑[quinidina] →
↑da toxicidade



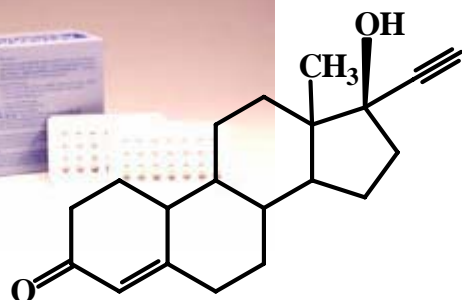
Quinidina (↓IT, SCV)



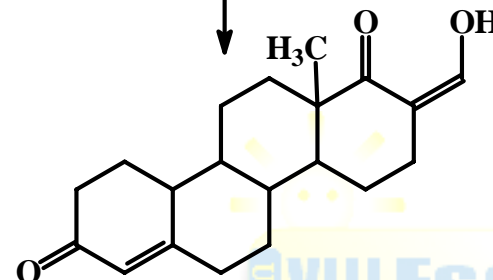
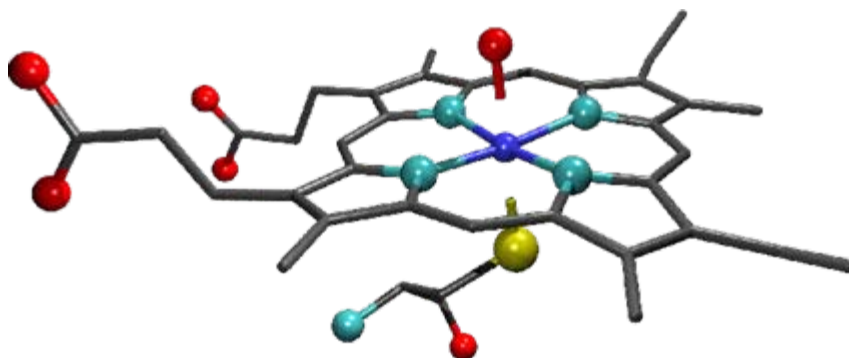
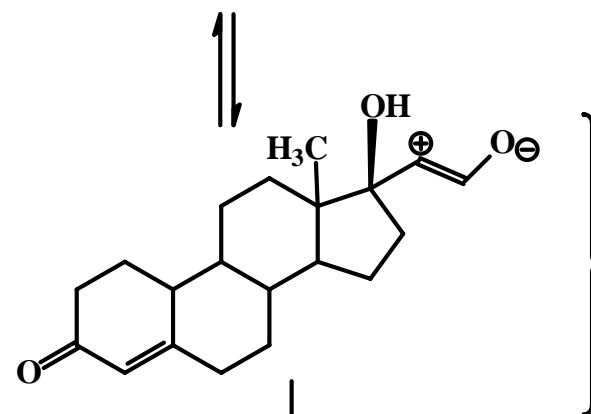
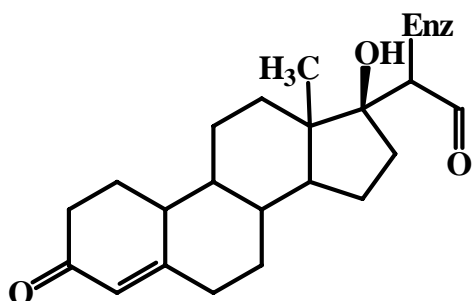
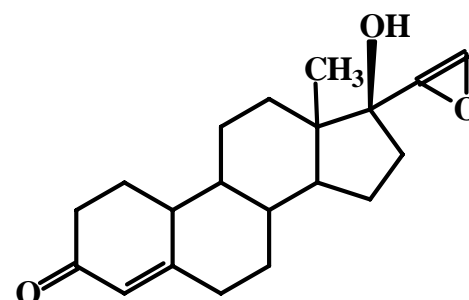


"A representation of with bound camphor. The enlarged active site region shows the camphor substrate, haem moiety and cysteine residue which forms the distal haem ligand. In the representation of the full enzyme the protein backbone is shown in green, the haem moiety in blue and the substrate is coloured 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.**"-

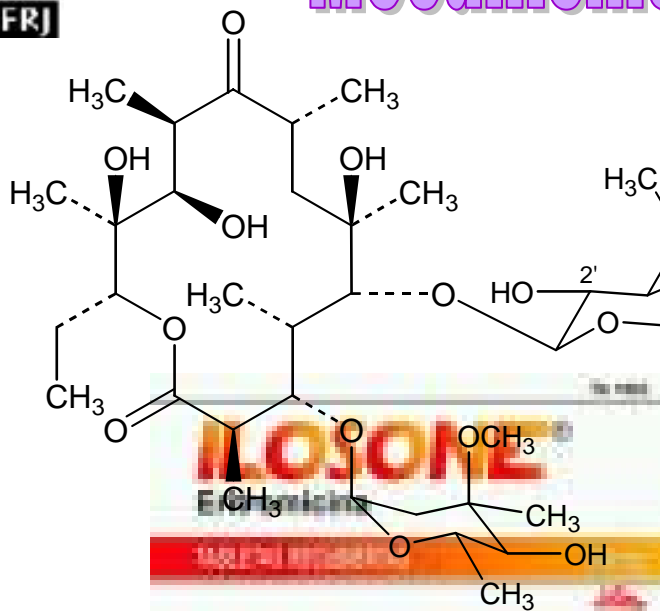
Mecanismos de Inibição Enzimática



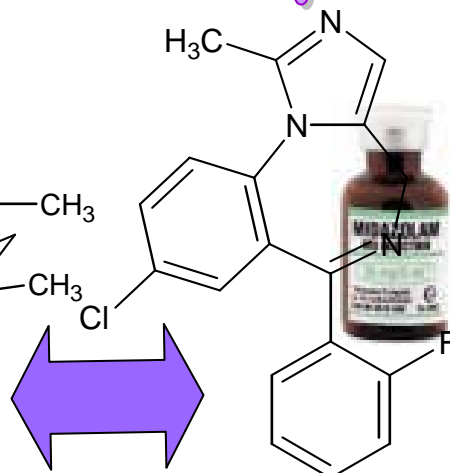
norethisterone



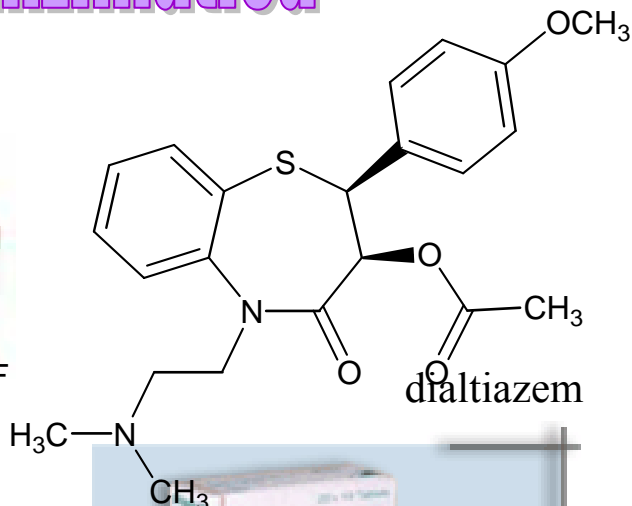
Mecanismos de Inibição Enzimática



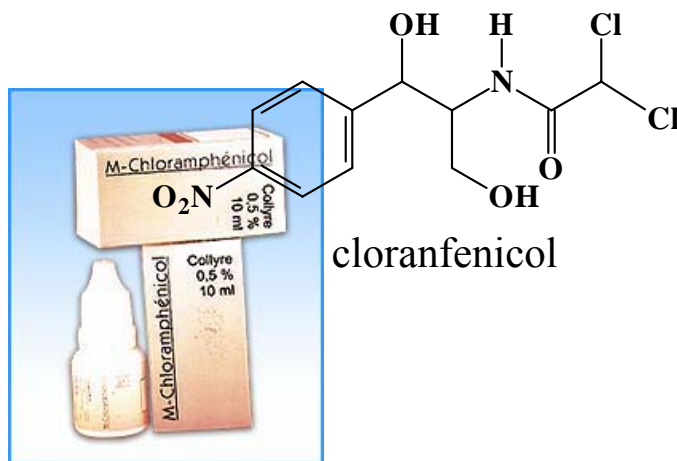
CYP3A4 Erythromycin A



CYP3A4 midazolam

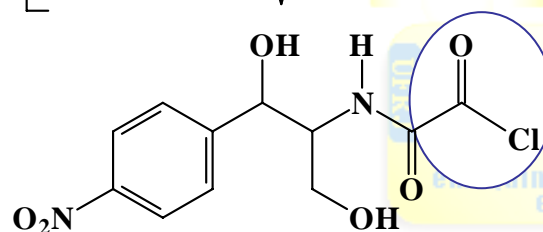
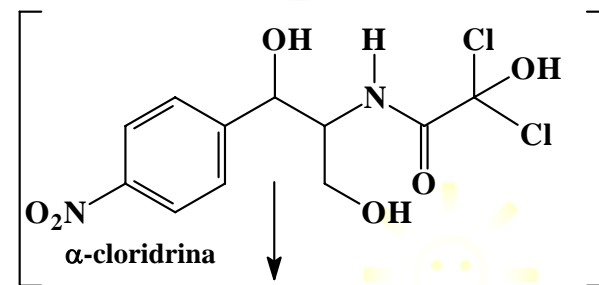


diazepam

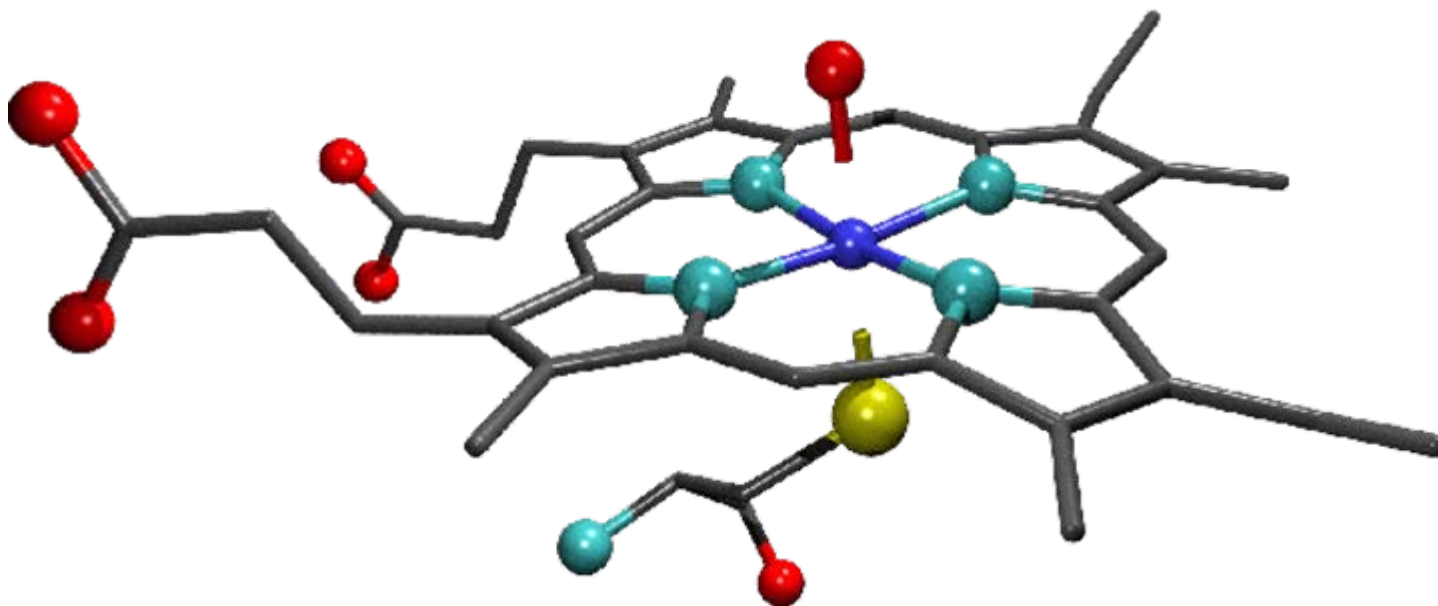


clorfenicol

$\xrightarrow{\text{CYP}_{450}}$

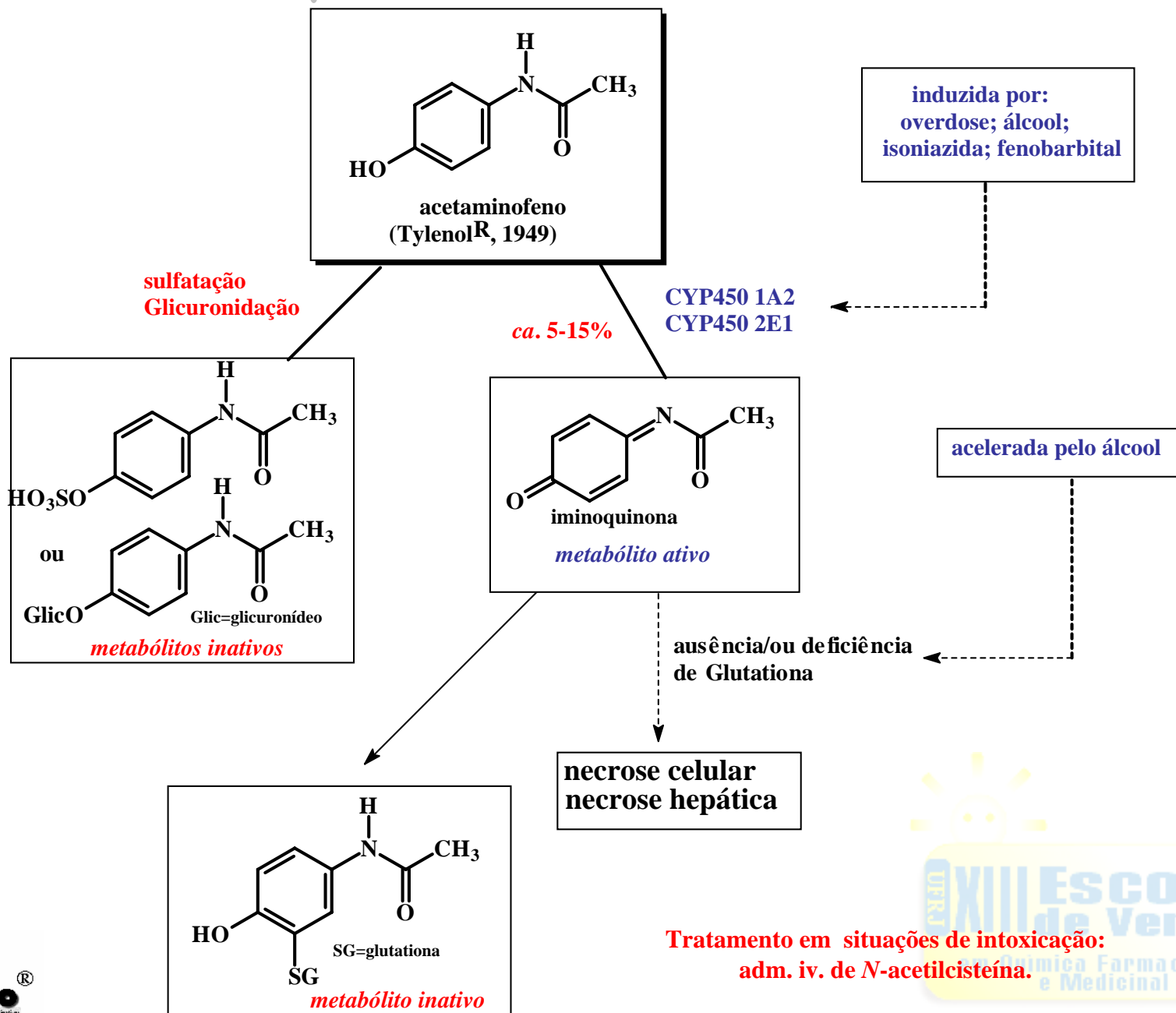


Interação Medicamentosa: Inibidores Enzimáticos

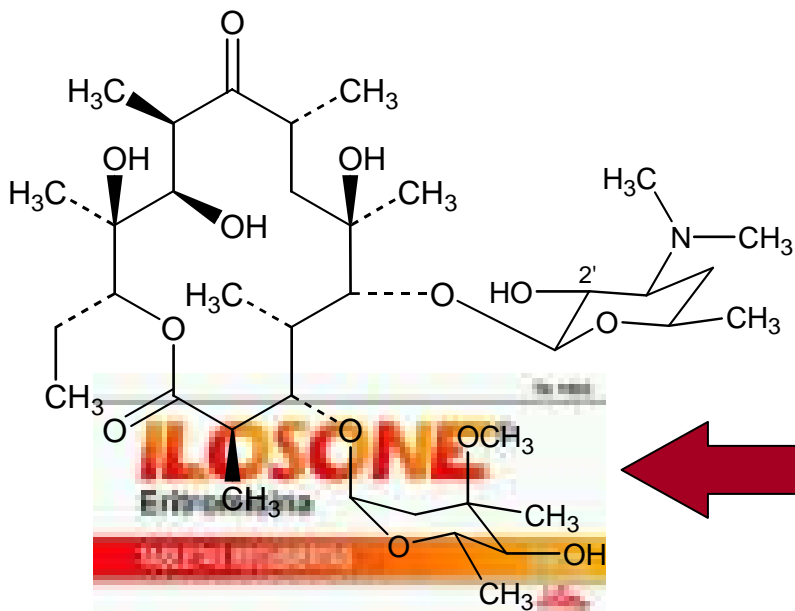


"The active site of substrate-free cytochrome p450: Note the water molecule (which can be seen as a single oxygen atom) that forms the sixth axial ligand of the haem iron. Oxygen atoms are shown in red, nitrogen in light blue, sulphur in yellow and **iron in dark blue**. Carbon atoms are shown in grey as bonds only and hydrogens have been omitted from this figure for clarity."

Interação Medicamentosa: Inibidores Enzimáticos



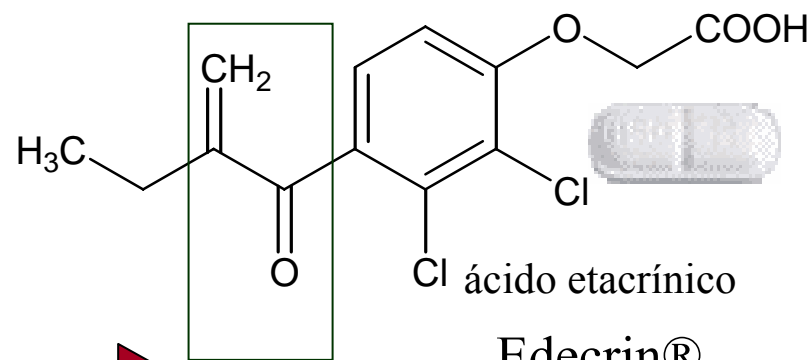
Interação Medicamentosa: Inibidores Enzimáticos



CYP3A4

Erythromycin A

↑risco de ototoxicidade

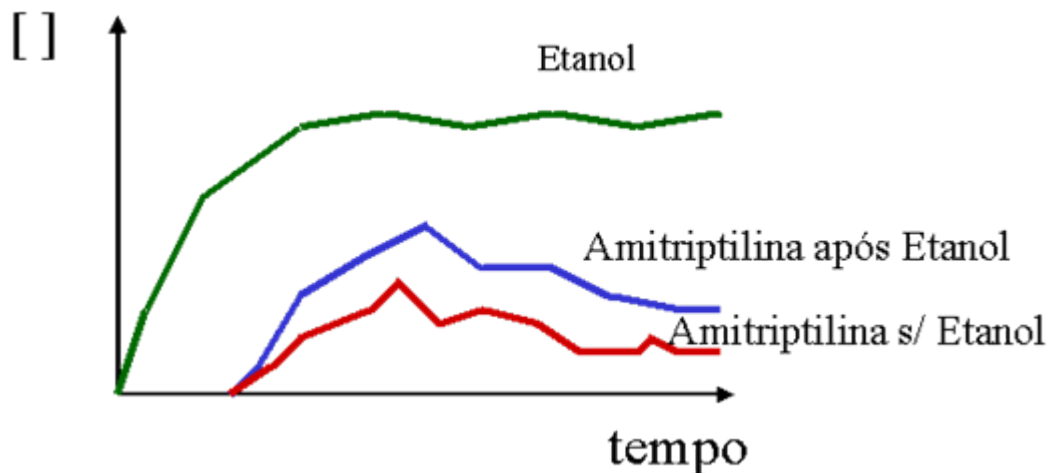


Edecrin®

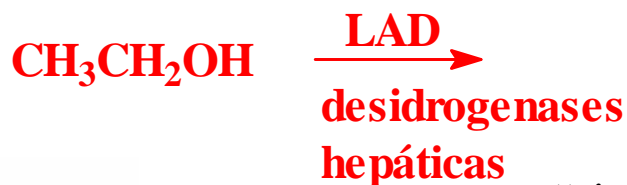
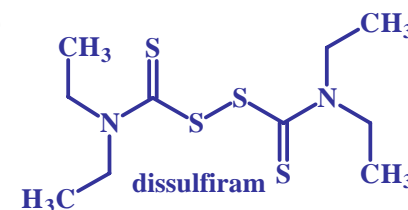
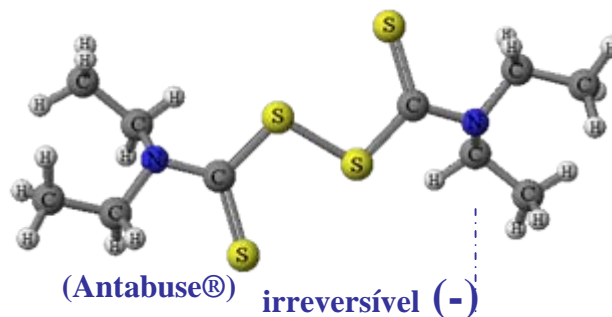
LD₅₀ = 175 mg/kg

↑agranulocitose, neutropenia

Interação Medicamentosa: Inibidores Enzimáticos



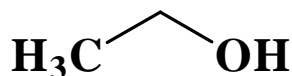
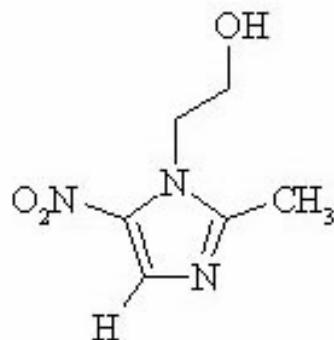
Tratamento do alcoolismo



“síndrome do acetaldeído”



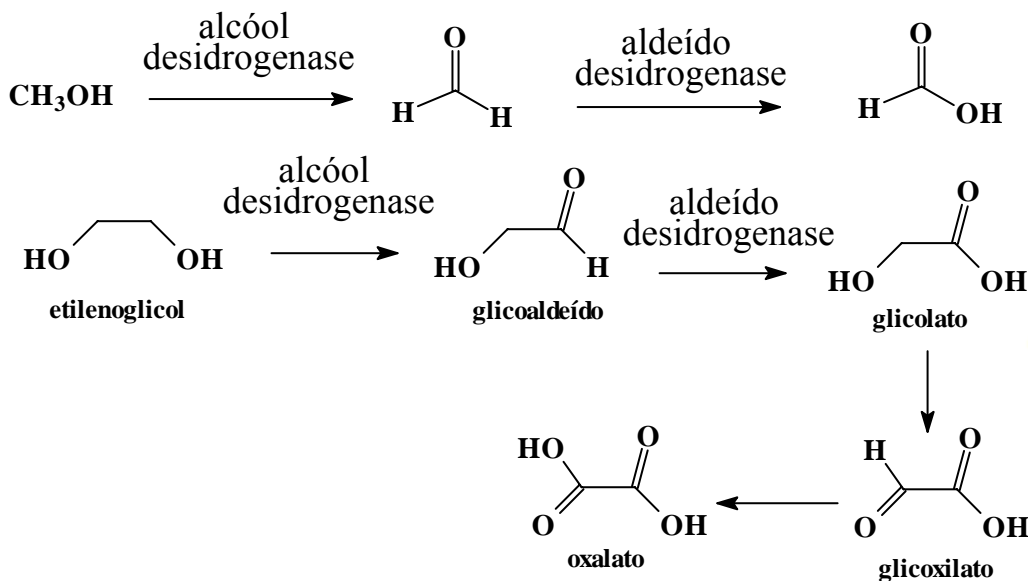
Interação Medicamentosa: Inibidores Enzimáticos

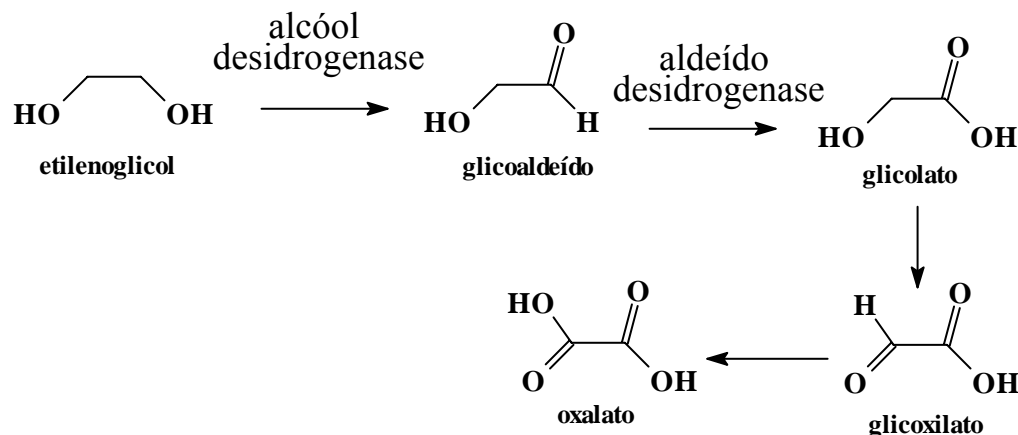


Inibidores da aldeído desidrogenase: **dissulfiram**, Dimetilformamida (seu metabólito a N-metilnormamida é inibidor desta enzima) ; **Isotretinoína** (anti-acne) e antibacterianos como: cefamandol, **isoniazida**, sulfametazol, (inibem face a sua cadeia lateral N-metil-tretrazoiltiol) etc; antifúngicos: **cetoconazol** e griseofulvina. Antiparasitário: **metronidazol** ⇒ **logo todos podem causar intolerância ao etanol em decorrência de acúmulo de acetaldeído no organismo, provocando reação do tipo dissulfiram como: rubor facial, taquicardia, náuseas, sudorese, cefaléia, dificuldade respiratória, hipotensão**

Inibidores da álcool desidrogenase eg. Fomepizol (4-metilpirazol): Útil??

•SIM. Usado na intoxicação por metanol e etilenoglicol



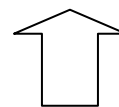


O **glicolato** e o **glicoxilato** produzem uma perigosa acidose metabólica e o oxalato remove cálcio da corrente sanguínea, resultando na deposição de oxalato de cálcio insolúvel no rim, fígado, vasos sanguíneos, cérebro e pericárdio, lesionando estes tecidos

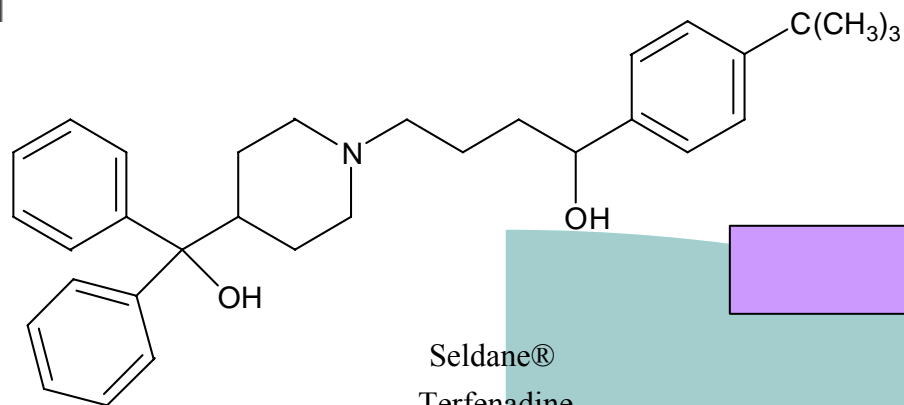
| Características | Metanol | Isopropil | Etilenoglicol |
|---------------------|---------------------|-----------------|---------------|
| Odor característico | Sim | Sim | Não |
| Acidose | Sim | Não | Sim |
| Formação de cetonas | Cetobutírico | Acetona | Nenhuma |
| "Anion gap" | +++ | + | +++ |
| "Osmolal gap" | Sim | Sim | Sim |
| Outras alterações | Alterações oculares | Gastrite severa | Cristalúria |

Inibidores Enzimáticos

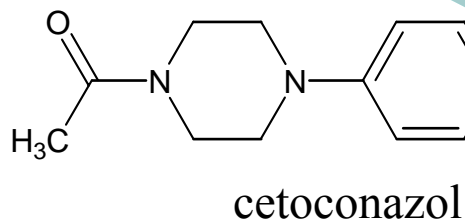
FDA → Proscrito, USA?



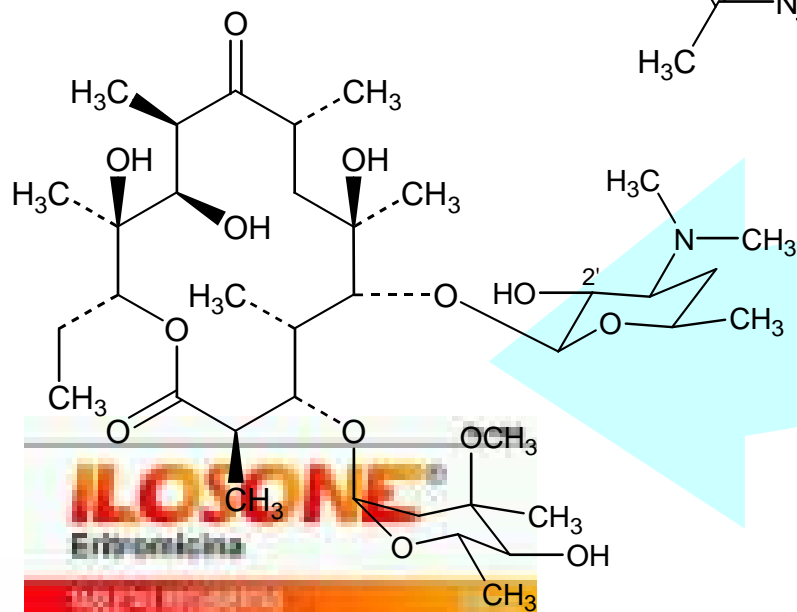
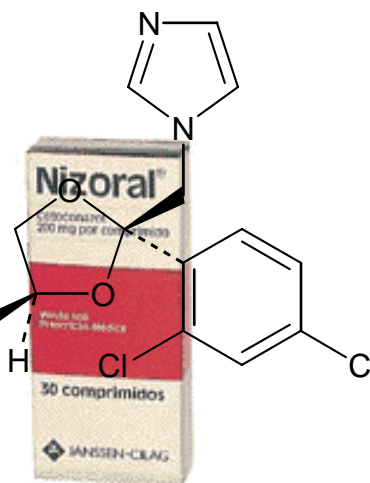
Rare, but serious
heart problems



Seldane®
Terfenadine
Anti-histamínico não-sedativo



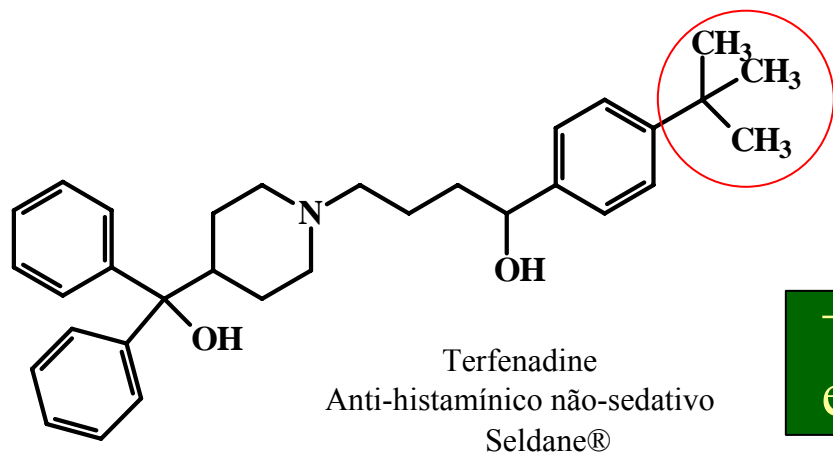
cetoconazol



ILOSONE®
Eritromicina

Erythromycin A

Inibidores Enzimáticos



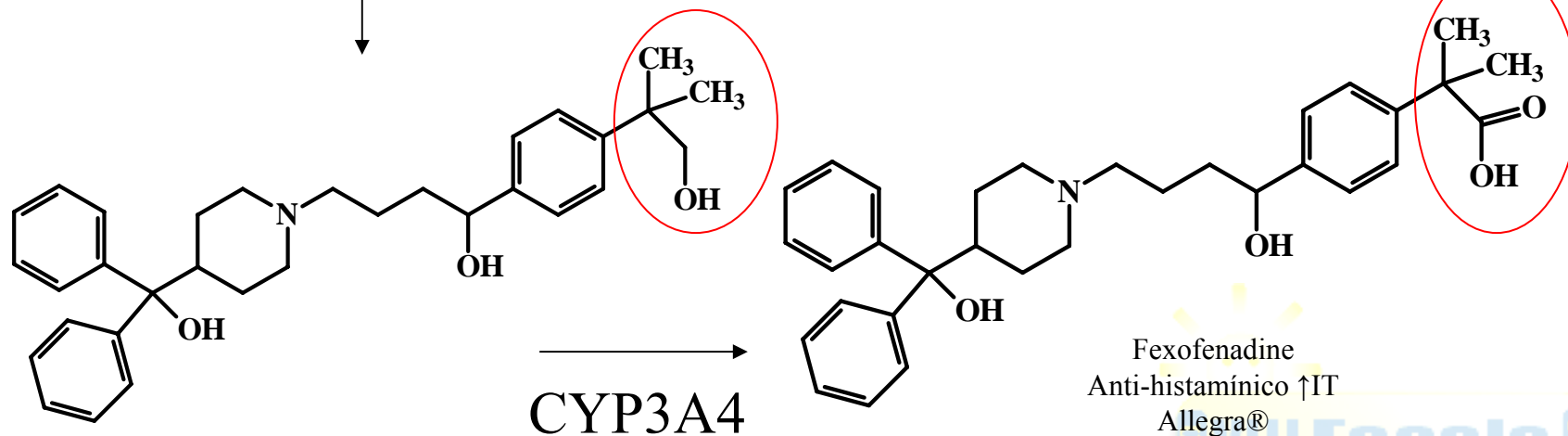
FDA → Proscrito, USA?

+ inibidores
enzimáticos

Rare, but serious
heart problems

Repolarization potassium
current blocker

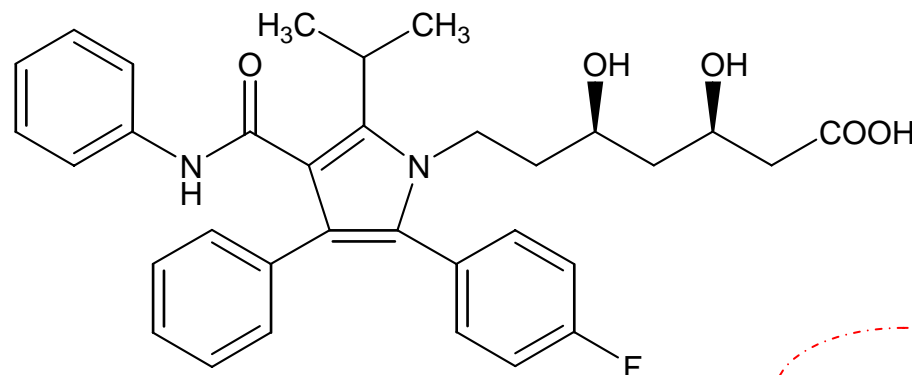
CYP3A4



CYP3A4

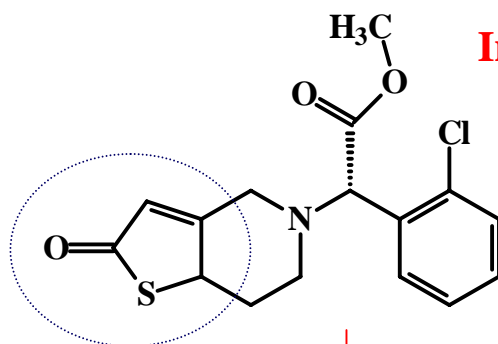
Interação Medicamentosa: Farmacocinética

Pravastatina, alternativa?



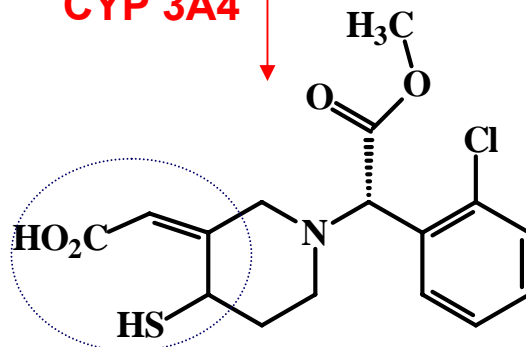
atorvastatina

Inibidor da CYP 3A4

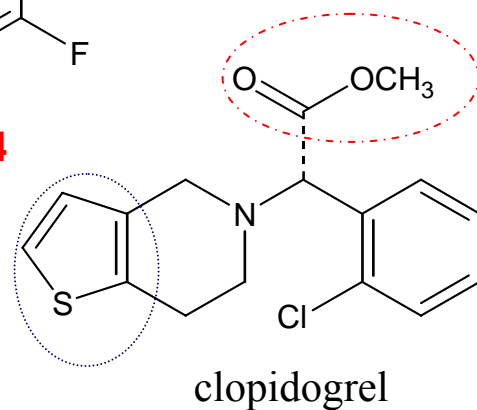


**Pró-Fármaco
via CYP 3A4**

CYP 3A4



Metabólito ativo



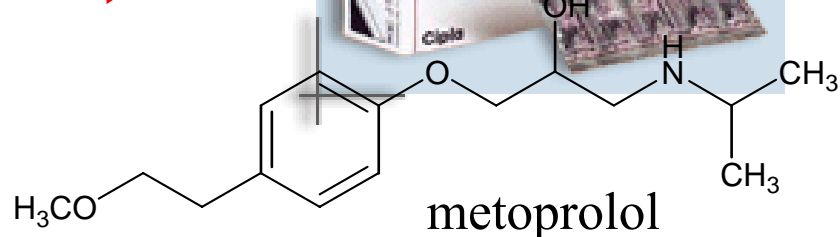
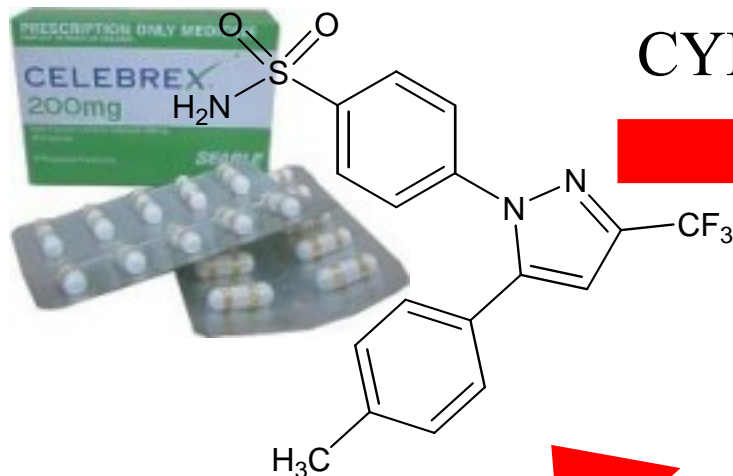
clopidogrel



Interação Medicamentosa: Farmacocinética

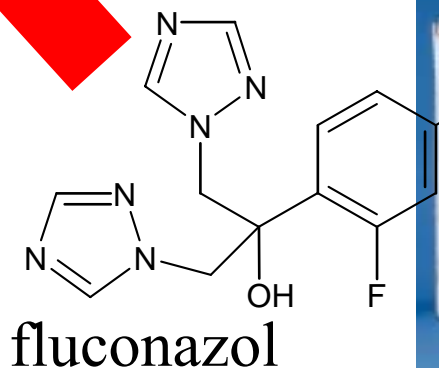
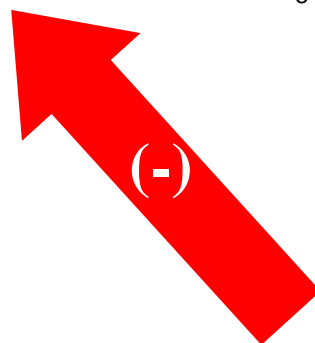
Vioxx®, alternativa?

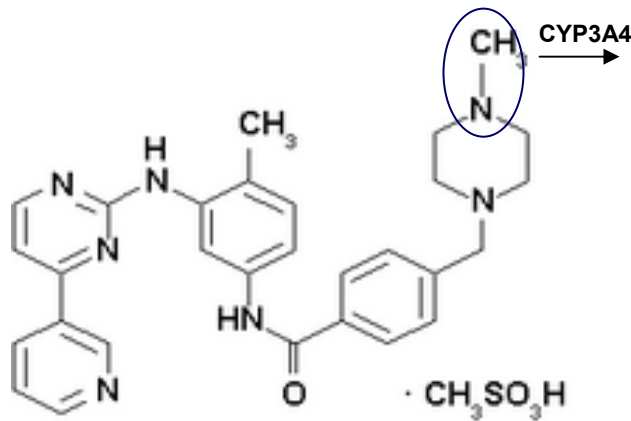
Inibidor da
CYP450 2D6



↑conc. Bradicardia sintomática

Metabolizado pela
CYP450 2C9

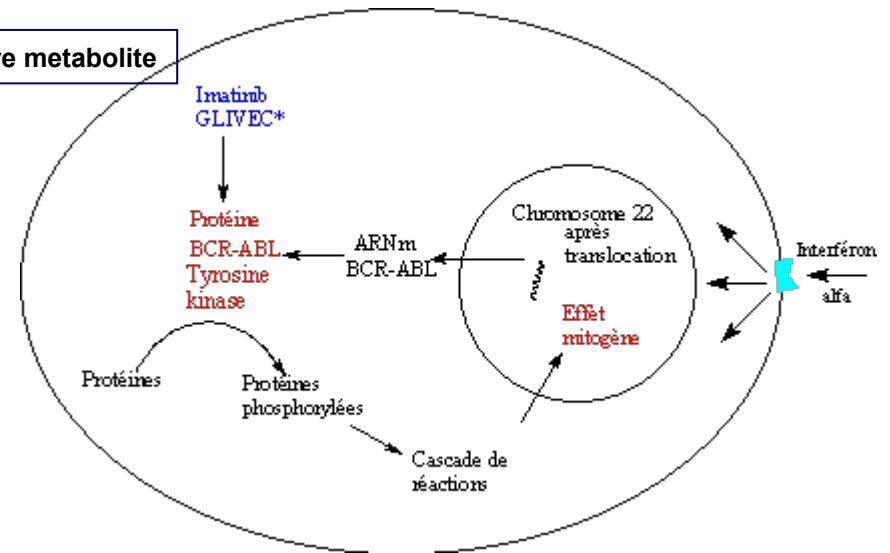




mesilato de Imatinib

inhibitor of a number of [tyrosine kinase enzymes](#).

[chronic myelogenous leukemia](#) (CML),
[gastrointestinal stromal tumors](#) (GISTs) and a
number of other [malignancies](#)



it is generally very well tolerated (eg. liver toxicity was much less than predicted). Broadly, side effects such as [edema](#), [nausea](#), [rash](#) and musculoskeletal pain are common but mild.

Table 4

Drugs with the potential to influence the plasma concentrations of imatinib
[34]

CYP3A inhibitors; likely
to increase imatinib levels

Erythronycin
Clarithromycin
Itraconazole
Ketoconazole

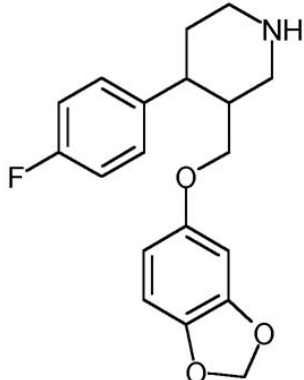
CYP3A inducers; likely
to decrease imatinib levels

Carbamazepine
Phenytoin
Phenobarbitol
Dexamethasone
Rifampine
St. John's Wort

The [half-lives](#) of imatinib and its main metabolite are 18 and 40 hours, respectively.

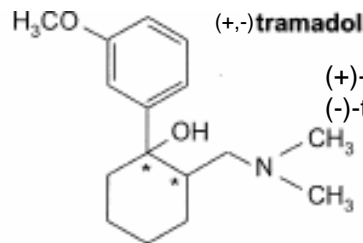


Inibidor CYP2D6

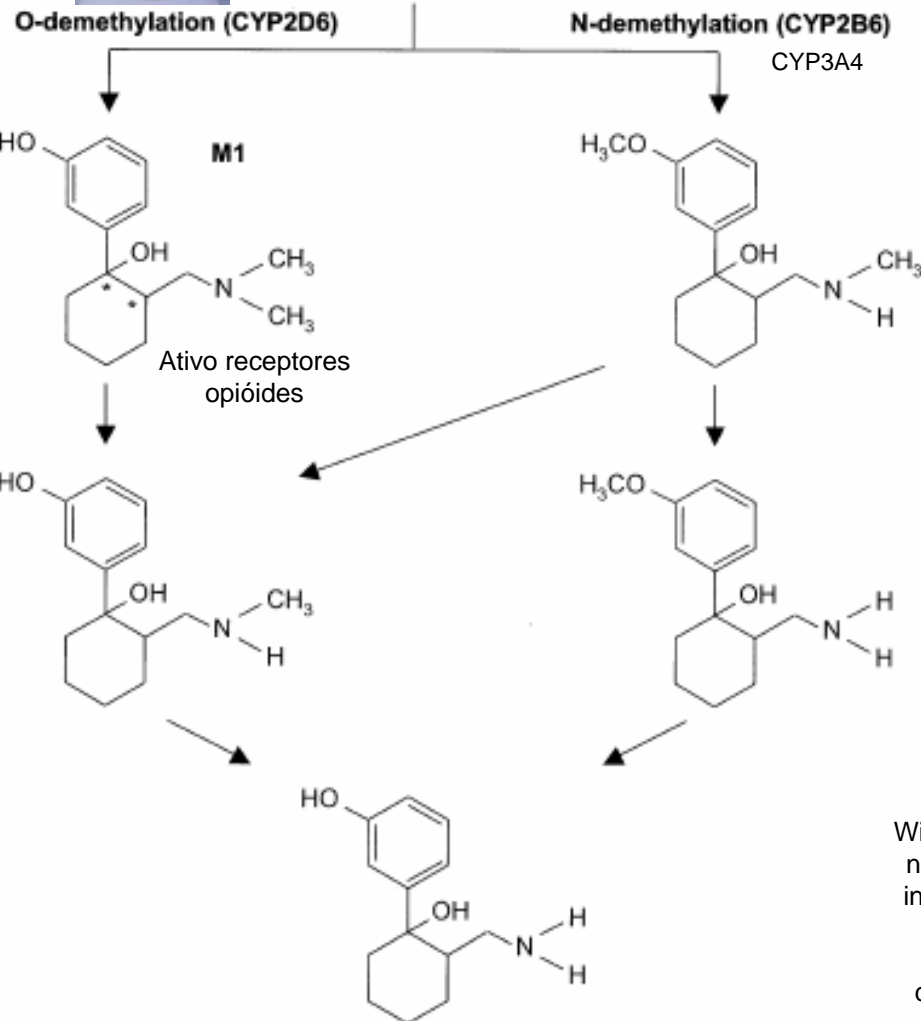


(inibidor reuptake de serotonina)
Depressão, ansiedade, síndrome
Pânico, etc.

Metabolizado pelo CYP2D6



(+)-tramadol: seletivo reuptake serotonina
(-)-tramadol: seletivo reuptake noradrenalina
Inativo receptores
opioides

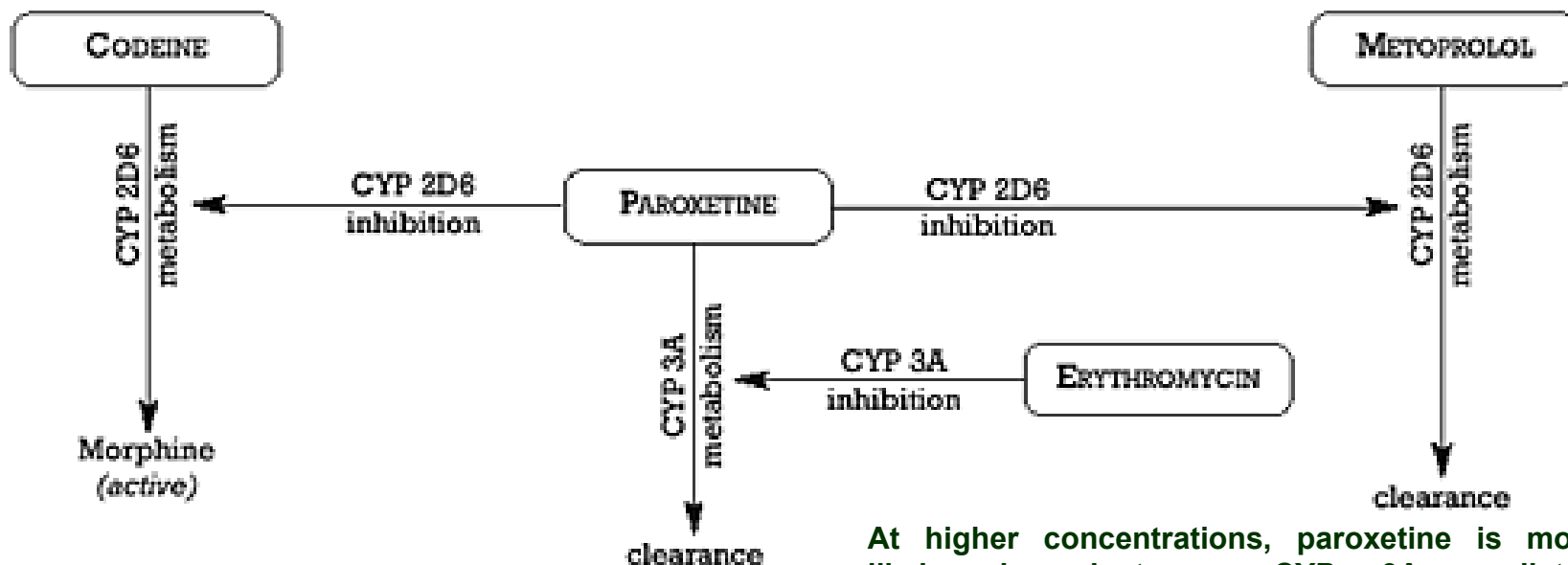


Withdrawal symptoms, including
nightmares, tremor, dizziness,
insomnia, myalgias, and a "flu-
like" syndrome have been
reported with abrupt
discontinuation of paroxetine

Fig 1. Pattern of biotransformation of tramadol. Tramadol and *O*-desmethylnortramadol (M1) are actively analgesic.^{13,14}

Interação Medicamentosa: Farmacocinética

A sufficient accumulation of metoprolol can lead to profound hypotension as a result of reduced cardiac output due to the chronotropic (i.e., decreased heart) and ionotropic (i.e., decreased stroke volume) effects of blockade of beta adrenergic receptors



Due to inhibition of the conversion of codeine to morphine, the patient should have less than optimal pain control. This could be construed correctly as lack of efficacy on the part of codeine

At higher concentrations, paroxetine is most likely dependent on CYP 3A mediated biotransformation for its elimination. [15,16](#) CYP 3A is substantially inhibited by erythromycin under usual dosing conditions. [17-19](#) The inhibition of CYP 3A by erythromycin should produce an increased accumulation of paroxetine, which in turn would produce more inhibition of CYP 2D6, which in turn would lead to less conversion of codeine to morphine and more accumulation of metoprolol

Interação Medicamentosa: Farmacocinética

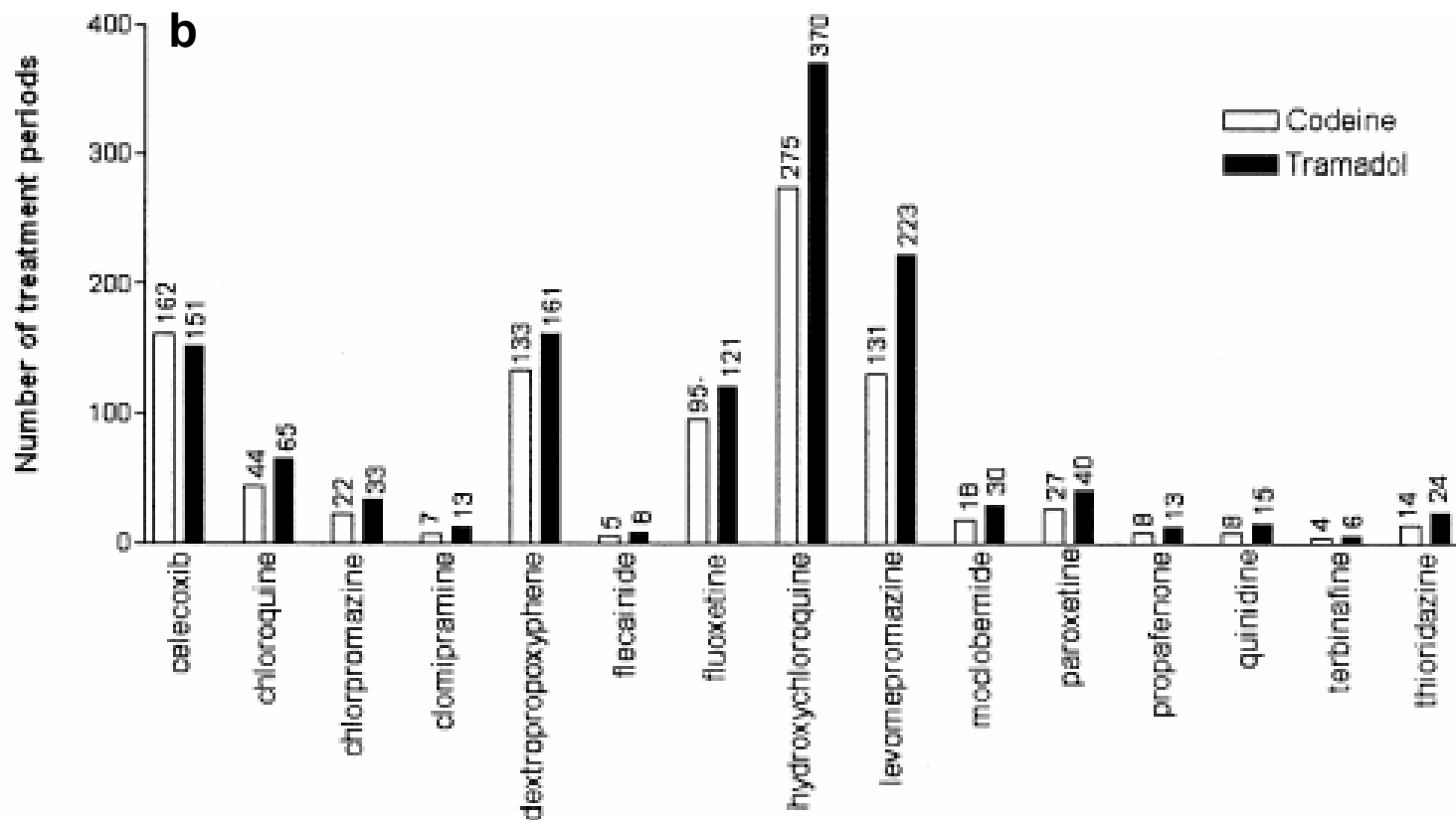


Fig 1. Incidence of concomitant use of CYP2C9 inhibitors with losartan (a) and CYP2D6 inhibitors with codeine (*open bars*) and tramadol (*solid bars*) (b).

Tirkkonen, T. *et al. Clin. Pharmacol. Ther.* (2004) 76: 639-647

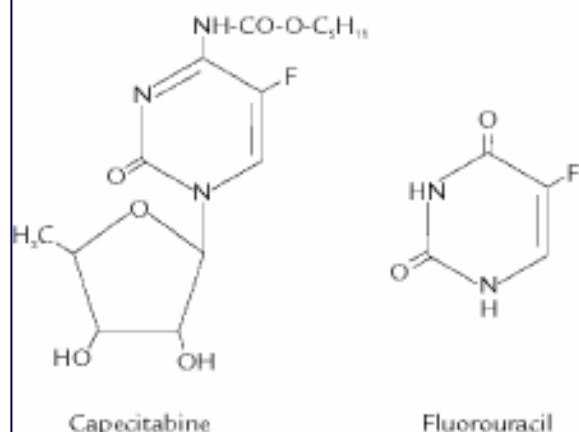
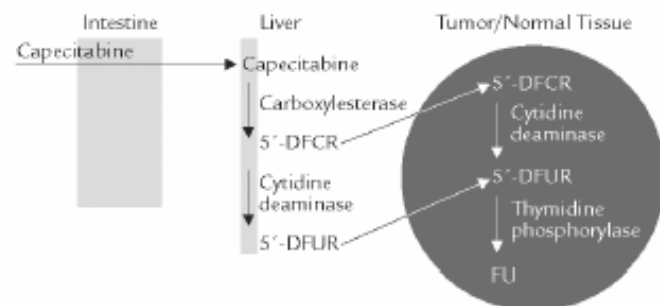


Figure 1. Chemical structures of the prodrug capecitabine and active drug fluorouracil.



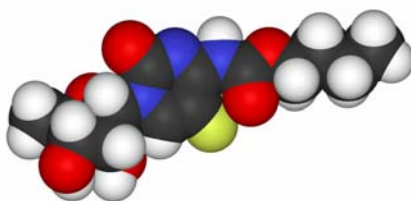
Three-step metabolic conversion of capecitabine to fluorouracil (FU). Capecitabine is absorbed through the intestine and converted to 5'-deoxy-5-fluorocytidine (5'-DFCR) by carboxylesterase and then to 5'-deoxy-5-fluorouridine (5'-DFUR) by cytidine deaminase, both steps taking place in the liver. Finally, thymidine phosphorylase converts 5'-DFUR to the active drug, FU. This occurs in both tumor and normal tissues; however, the enzyme is found at higher concentrations in most tumor tissue compared with normal healthy tissue.

Table 3

Interactions of 5-FU and its prodrugs (capecitabine, doxifluridine, uracil/tegafur)

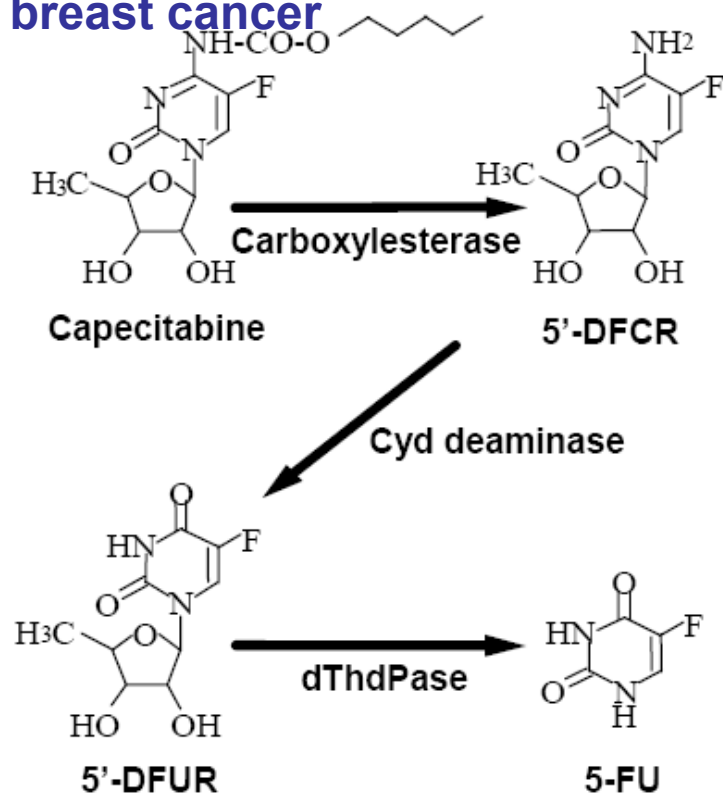
| Interaction with | Clinical effect | Comments | Reference |
|----------------------------|--|---|---|
| Antacids | Aluminium- and magnesium-containing antacids may increase capecitabine bioavailability | | Xeloda Product Information [192] |
| Anticoagulants | Altered coagulation parameters and/or bleeding have been reported in patients taking capecitabine concurrently with coumarin-type anticoagulants such as warfarin or phenprocoumon | Patients taking these drugs concurrently should have frequent monitoring of prothrombin time (PT) or international normalized ratio (INR) | Xeloda Product Information [192] |
| Anticonvulsants | Phenytoin toxicity has been reported during treatment with capecitabine; a similar effect may occur with tegafur or 5-FU | | Xeloda Product Information [192]; Zuccherro et al. [38] |
| Cimetidine | Pre-treatment with cimetidine for 4 weeks (but not 1 week) decreased 5-FU elimination | No 5-FU toxicity reported, but caution is advised | Zuccherro et al. [38] |
| Metronidazole ^a | Decreased 5-FU clearance, resulting in increased toxicity (esp. GI and hematological) without enhanced therapeutic effect | Avoid concomitant use if possible. If used together, monitor for increased toxicity | Hansten and Horn [40]; Zuccherro et al. [38] |
| Thiazides | Increased myelosuppression reported | Patients were also receiving cyclophosphamide and methotrexate; it is unclear which agent(s) caused the interaction | Hansten and Horn [40]; Zuccherro et al. [38] |

^a Metronidazole may inhibit initial step of 5-FU metabolism; decreased renal clearance also may be involved.



The enzyme dihydropyrimidine dehydrogenase hydrogenates 5-FU, the product of capecitabine metabolism, to the much less toxic 5-fluoro-5, 6-dihydro-fluorouracil (FUH2). Dihydropyrimidinase cleaves the pyrimidine ring to yield 5-fluoro-ureido-propionic acid (FUPA). Finally, b-ureido-propionase cleaves FUPA to a-fluoro-b-alanine (FBAL) which is cleared in the urine.

colorectal cancer
breast cancer



PATIENT INFORMATION
XELODA®
(capecitabine) TABLETS
CAUTION ABOUT POSSIBLE EFFECTS

STOP
TAKING XELODA
IMMEDIATELY
AND CONTACT
YOUR DOCTOR
IF ANY OF THESE
SYMPTOMS OCCUR.

If caught early, most of these side effects usually improve after you stop taking XELODA. If they do not improve within 2 to 3 days, call your doctor again. After side effects have improved, your doctor will tell you whether to start taking XELODA again or what dose to use.



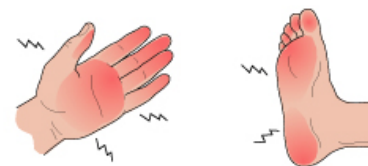
Moderate diarrhea.
(increase of 4-6 stools a day)



Diarrhea at night.



Moderate pain and redness of the mouth, swelling of the mouth or mouth sores.



Moderate pain, swelling and redness of hands and/or feet.

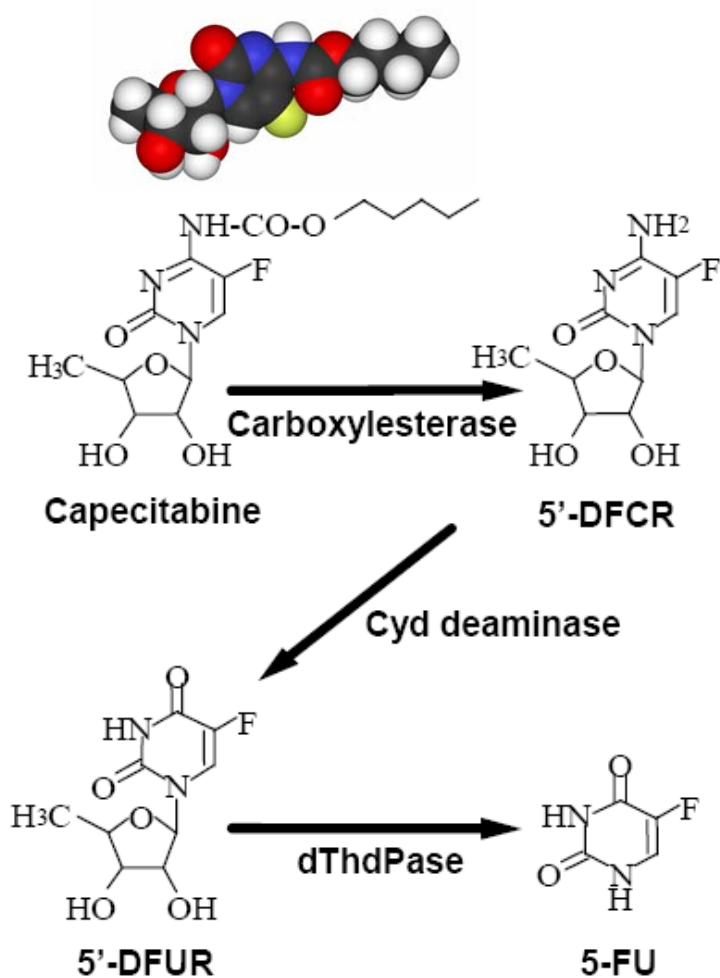


Nausea and vomiting.

If you have a temperature of 100.5°F or greater, or other signs of infection.

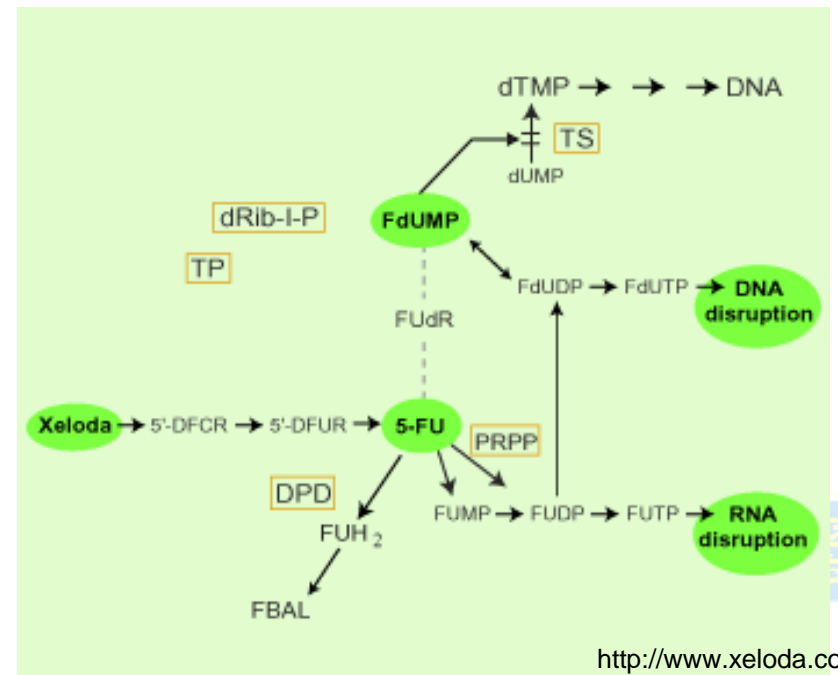
Not use Xeloda if you have severe kidney problems or the enzyme deficiency dihydropyrimidine dehydrogenase (DPD) deficiency

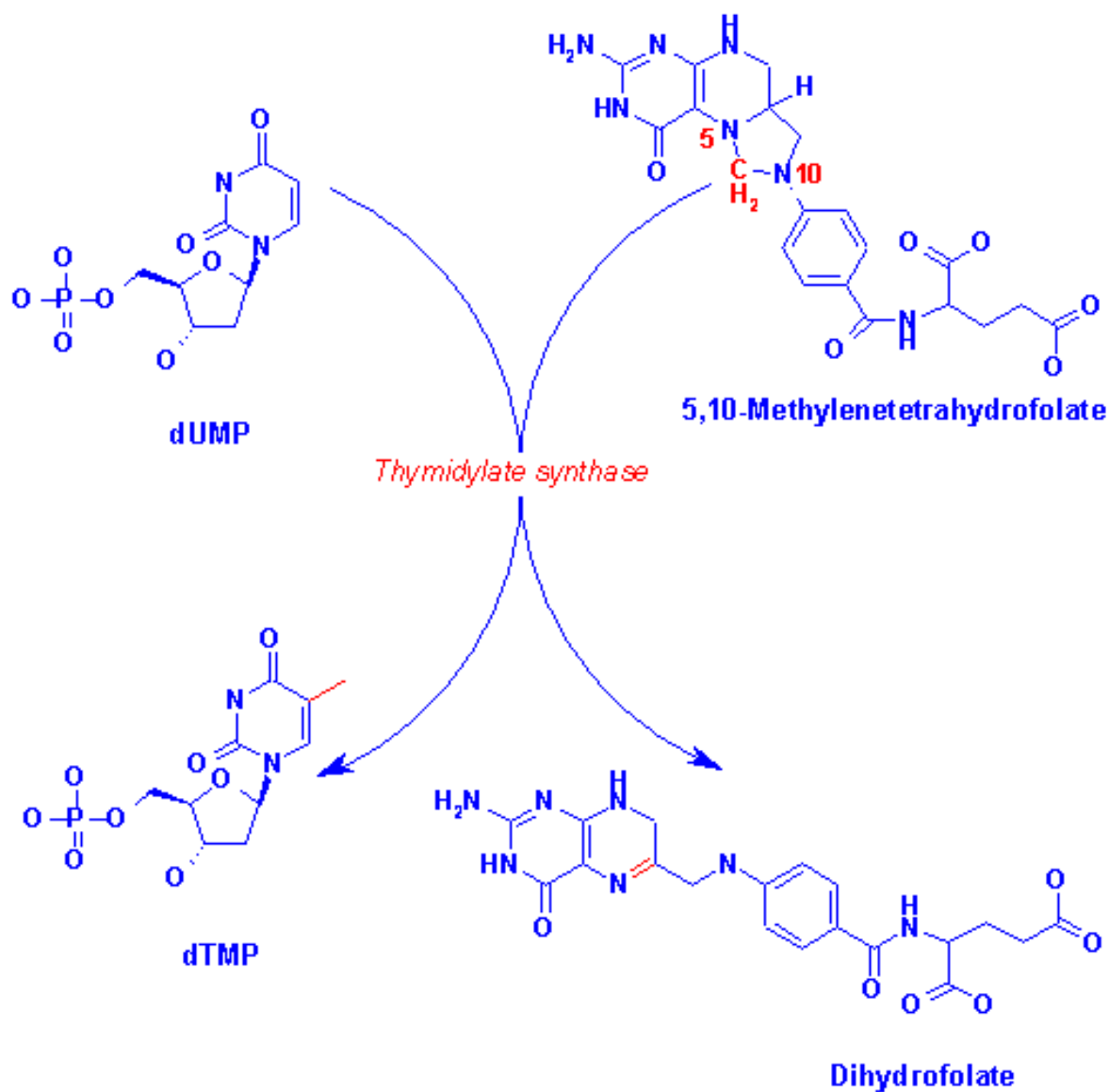




Bioactivation: XELODA is readily absorbed from the gastrointestinal tract. In the liver, a carboxylesterase hydrolyzes much of the compound to 5'-deoxy-5-fluorocytidine (5'-DFCR). Cytidine deaminase, an enzyme found in most tissues, including tumors, subsequently converts 5'-DFCR to 5'-deoxy-5-fluorouridine (5'-DFUR). Finally, the enzyme thymidine phosphorylase (dThdPase or TP), hydrolyzes 5'-DFUR to the active drug 5-FU.

Mechanism of Action of 5-FU: Both normal and tumor cells metabolize 5-FU to 5-fluoro-2'-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). These metabolites cause cell injury by two different mechanisms. First, FdUMP and the folate cofactor N5-10-methylene-tetrahydrofolate bind to thymidylate synthase (TS) to form a covalently bound ternary complex. This binding inhibits the formation of thymidylate from 2'-deoxyuridylate. Thymidylate is the necessary precursor of thymidine triphosphate, which is essential for the synthesis of DNA, so that a deficiency of this compound can inhibit cell division. Second, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine triphosphate (UTP) during the synthesis of RNA. This metabolic error can interfere with RNA processing and protein synthesis.





Metabolismo de Fármacos & Interação Medicamentosa

**XIII Escola de Verão em Química
Farmacêutica/Medicinal (XIII EVQF)**

5 a 9 de fevereiro de 2007

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OBRIGADA

