

The USP logo is displayed in a large, black, stylized font. The background of the top banner features a hand holding a green leaf, overlaid with a blue molecular structure and a yellow molecular structure. The background is a gradient of blue and green with a water ripple effect.The logo of the Faculdade de Ciências Farmacêuticas is located in the top right corner. It features a shield with a red border, containing a red snake coiled around a staff with a leaf. The text "FACULDADE DE CIÊNCIAS FARMACÊUTICAS" is written in red above the shield, and "1828" and "1954" are written in red below it. The background of the top banner features a hand holding a green leaf, overlaid with a blue molecular structure and a yellow molecular structure. The background is a gradient of blue and green with a water ripple effect.

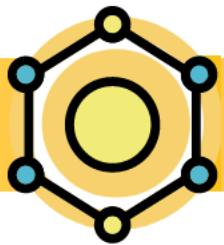
FBF0604 - Planejamento de Fármacos (2024)

Fase Farmacocinética –
Metabolismo no Planejamento de
Fármacos

Prof. Dr. Rodrigo Vieira Gonzaga

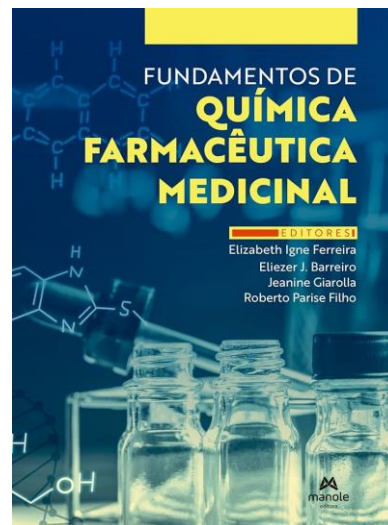
2024

**Faculdade de Ciências
Farmacêuticas
Universidade de São Paulo**

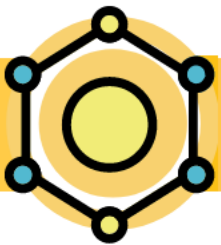


FASES DA AÇÃO DE UM FÁRMACO

1. Farmacêutica
2. Farmacocinética
3. Farmacodinâmica



- Fernandes, T.B.; Parise Filho, R. Ferreira, E.I; Barreiro, E.J; Giarolla, J.; Parise Filho, R. **Fundamentos de Química Farmacêutica Medicinal**. 2022.
- PATRICK, G. L. **An introduction to medicinal chemistry**, 6 ed. Oxford: Oxford University Press, 2017. 875p
- Lemke, T.L.; Williams, D.A. In: Fifer, K.E. **Foye's Principles of medicinal chemistry**. Filadelfia: Lippincott and Wilkins, 2013.



FASES DA AÇÃO DE UM FÁRMACO

FASE FARMACÊUTICA

HIDROSSOLUBILIDADE

DESINTEGRAÇÃO

DISSOLUÇÃO

FASE FARMACOCINÉTICA

ABSORÇÃO

LIPOSSOLUBILIDADE

DISTRIBUIÇÃO

RELAÇÃO pH/pKa

METABOLISMO

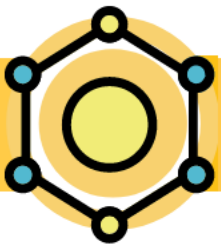
EXCREÇÃO

FASE FARMACODINÂMICA

EFEITOS ESTÉRICOS

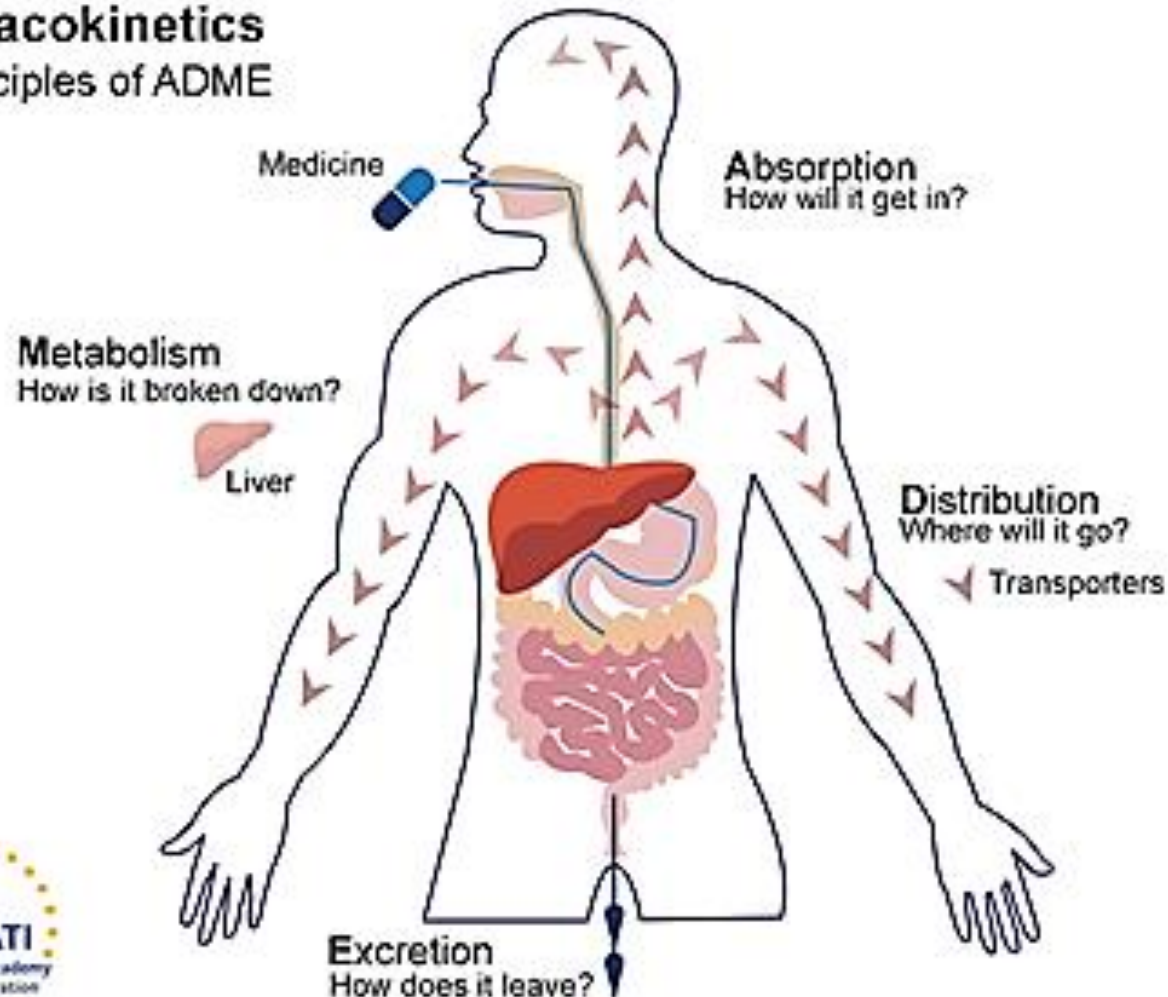
INTERAÇÃO FÁRMACO-RECEPTOR

EFEITO BIOLÓGICO

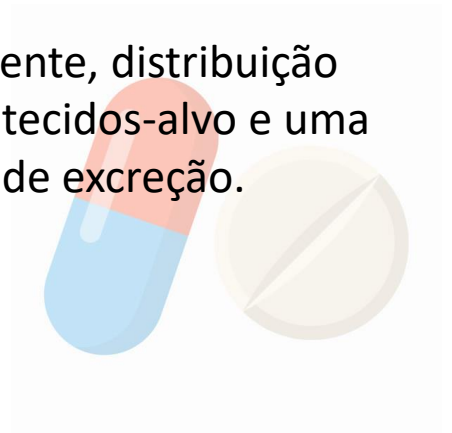


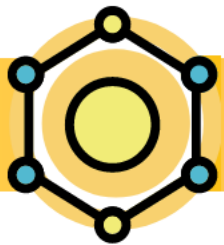
CAMINHO DO FÁRMACO - VIA ORAL

Pharmacokinetics The principles of ADME



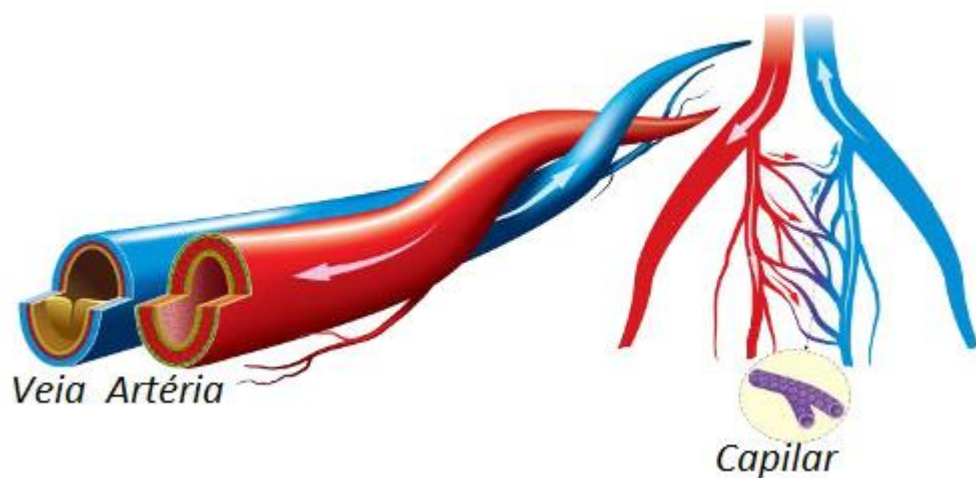
- ✓ Deve ser estável ao ataque químico e enzimático.
- ✓ Ele também deve ter as propriedades físico-químicas corretas para permitir que ele atinja seu alvo em concentrações terapêuticas.
 - ✓ Absorção eficiente, distribuição eficaz para os tecidos-alvo e uma taxa aceitável de excreção.



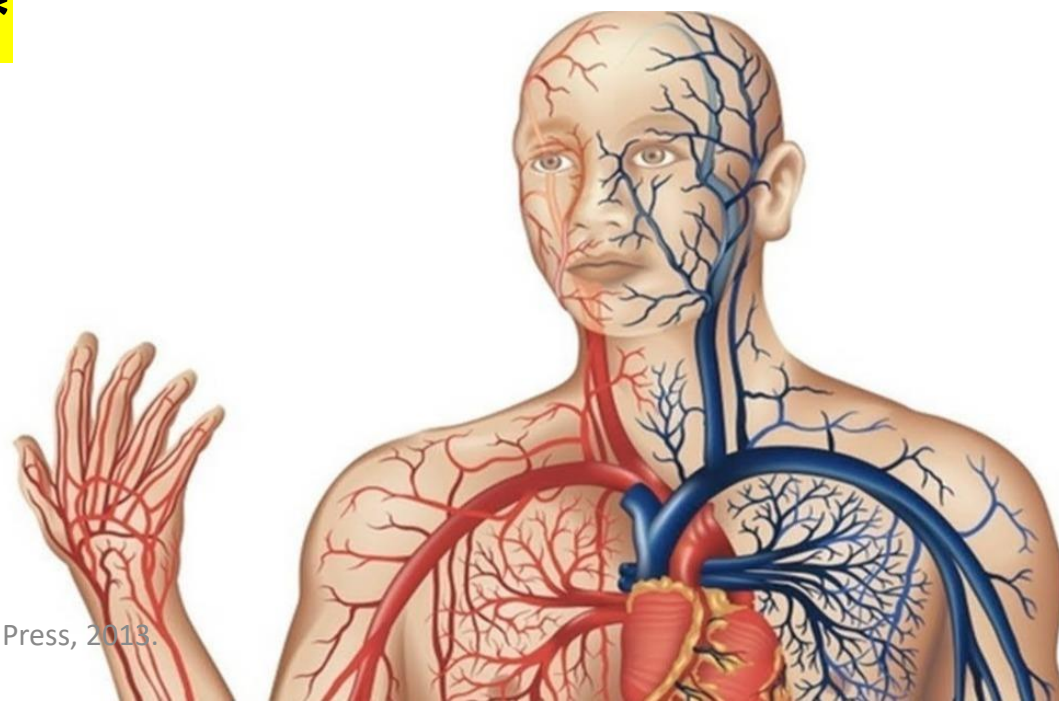


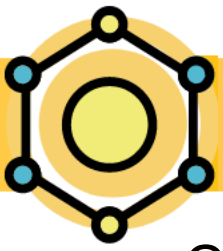
DISTRIBUIÇÃO

- Absorvido → corrente sanguínea
- 10 bilhões de capilares com 200 m²
- Poros 90-150 Å de diâmetro → passagem fármaco
 - Proteínas do plasma não passam*



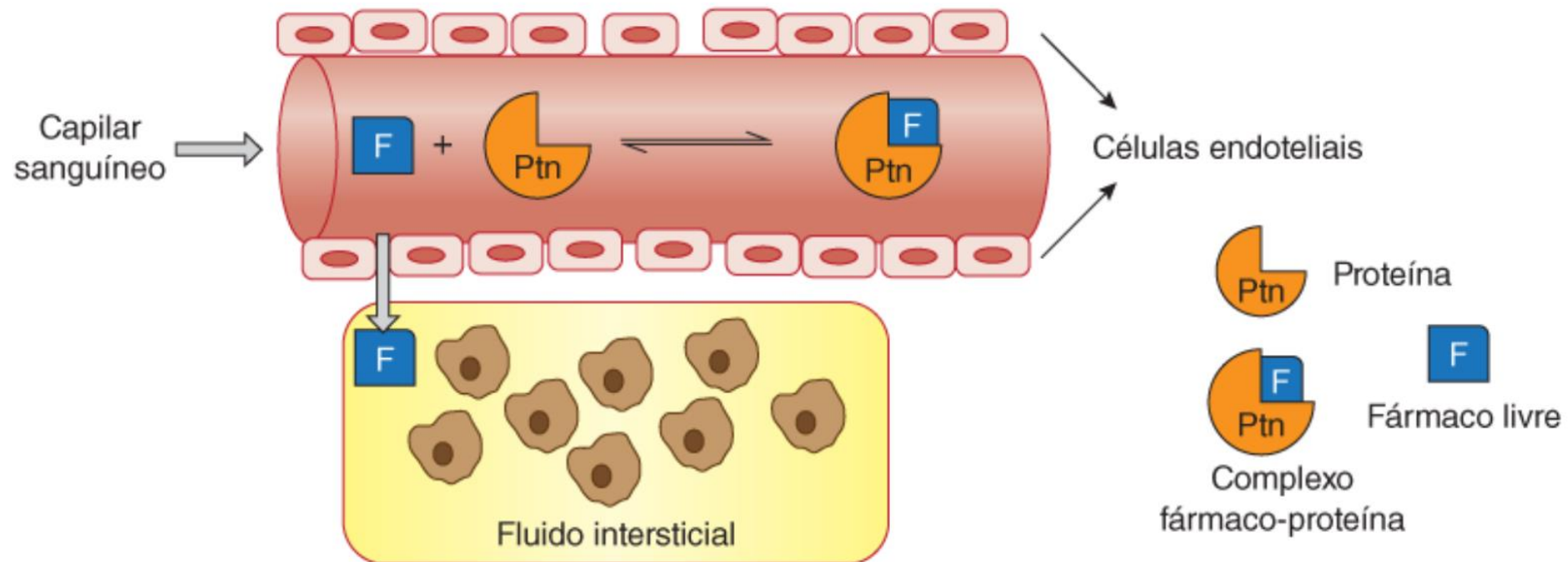
Oxford, University Press, 2013.

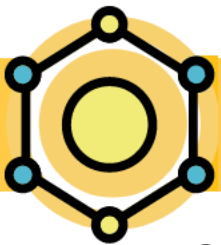




DISTRIBUIÇÃO

- O volume de distribuição aparente (V_d) indica a razão entre a quantidade de fármaco no plasma (QP) e a quantidade total no organismo (C) e é o parâmetro que pode ser utilizado para medir a distribuição. Volumes de distribuição muito baixos indicam que a maior parte da dose do fármaco se encontra no sangue e não nos tecidos.



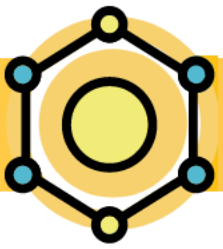


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TABELA 1 Relação entre o coeficiente de distribuição no pH 7,4, permeabilidade, solubilidade e seu impacto na absorção

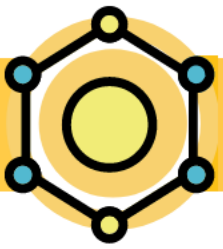
Faixa de Log $D_{7,4}$	Permeabilidade	Solubilidade	Absorção
< 1	Muito baixa	Alta	Baixa
$1 < \text{Log } D_{7,4} < 3$	Adequada	Adequada	Adequada
$3 < \text{Log } D_{7,4} < 5$	Média – Alta	Baixa	Média
$\text{Log } D_{7,4} > 5$	Alta	Baixa	Baixa



DISTRIBUIÇÃO

Distribuição aos tecidos/células

- Ser hidrofóbico suficiente para passar membrana
- Fármacos mais hidrofóbicos → tecido adiposo
 - Obesos precisam de maior dose anestésico → problema recuperação
- Fármacos se ligam a proteínas plasmáticas
- Uma pequena porção do fármaco fica disponível a ação



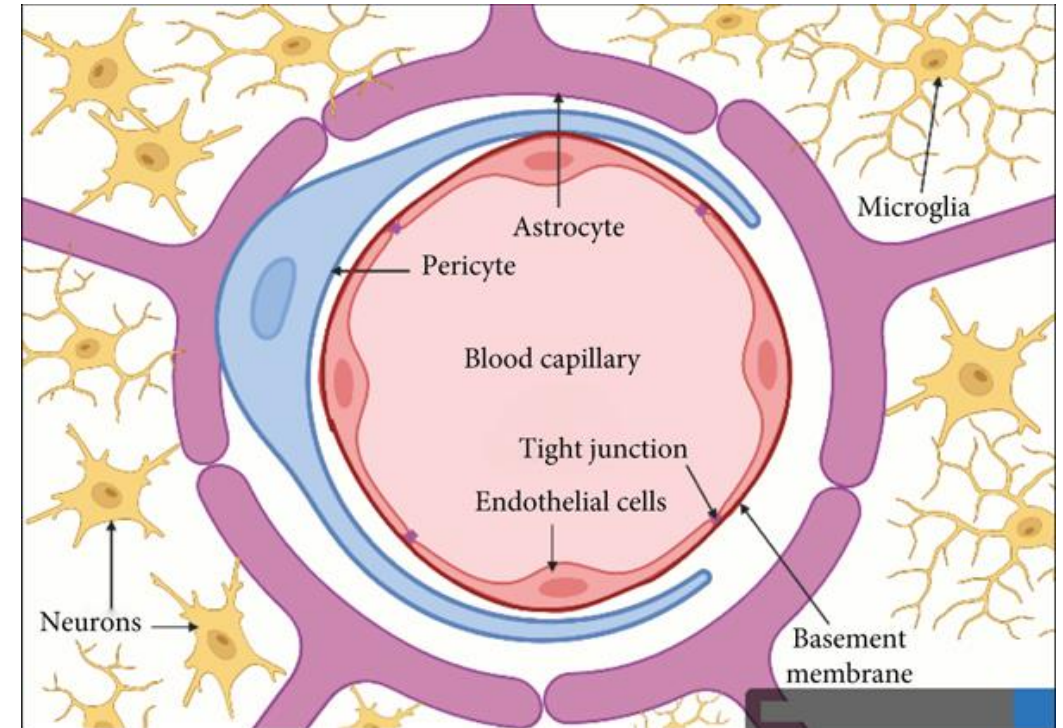
DISTRIBUIÇÃO

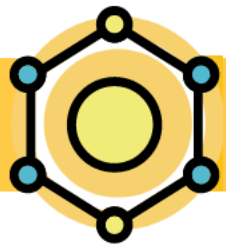
Barreira hematoencefálica (BHE)

- Capilares não tem poros
- Revestidos de uma camada lipídica
- Proteção do SNC
- Pinocitose ocorre

Interações fármaco-fármaco

- Fármacos competem com proteínas plasmáticas → liberação

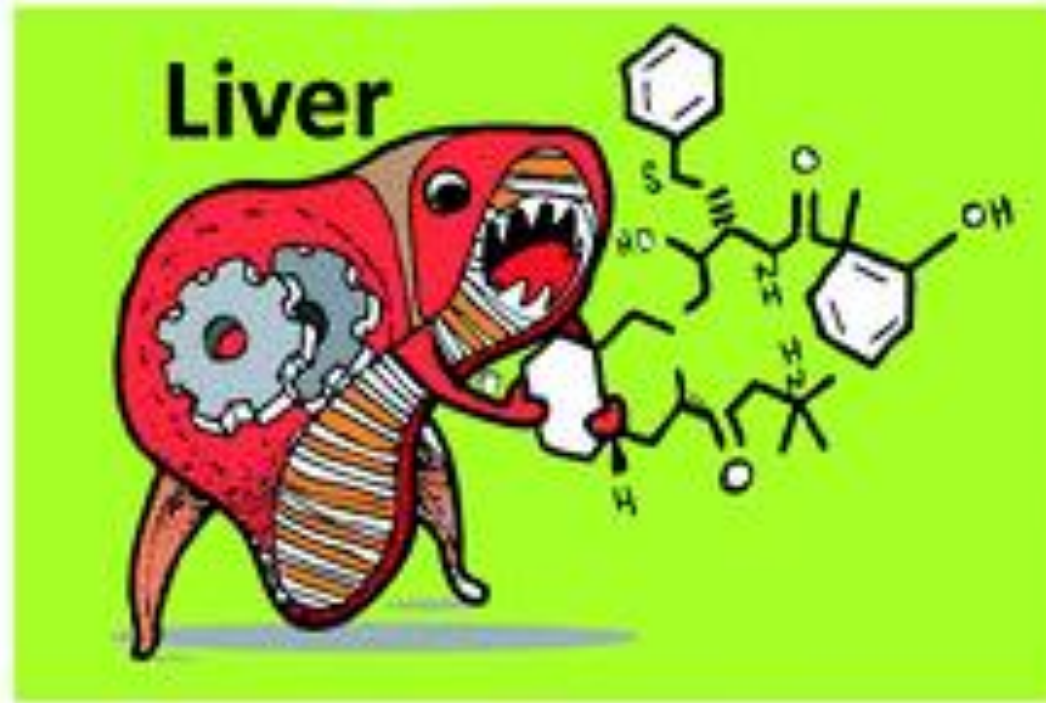




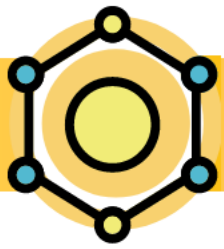
METABOLISMO (BIOTRANSFORMAÇÃO) DE FÁRMACOS

In vitro Metabolic Stability *In Vivo* Pharmacokinetics

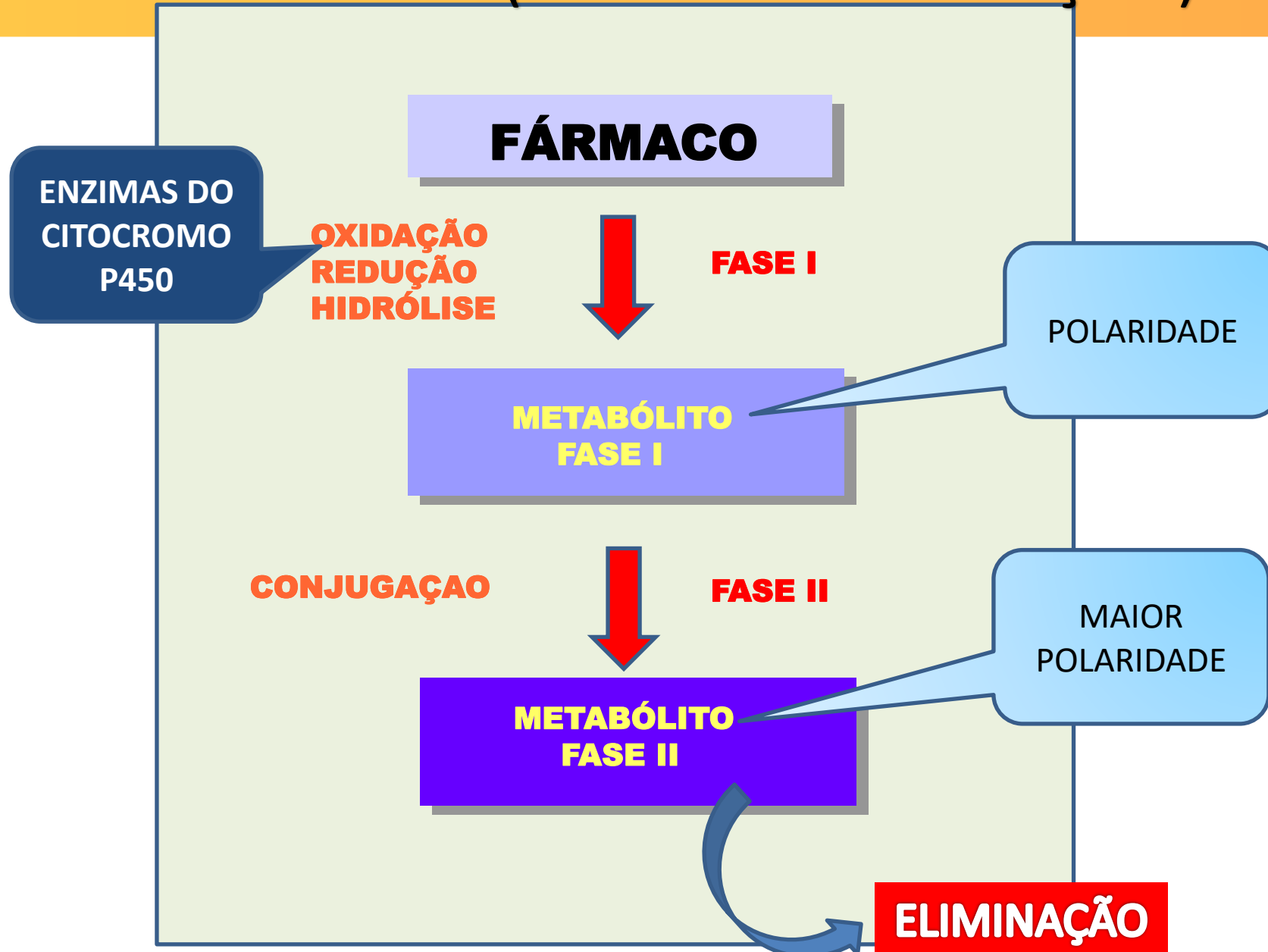
$\uparrow t_{1/2}$ $\downarrow CL_{int}$ \rightarrow $\downarrow CL_{plasma}$ $\uparrow t_{1/2}$ \uparrow oral F

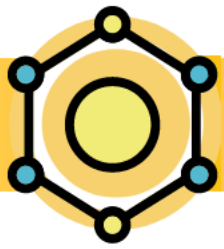


STEPAN et al. *MedChemComm*, v.4, p.631-652, 2013

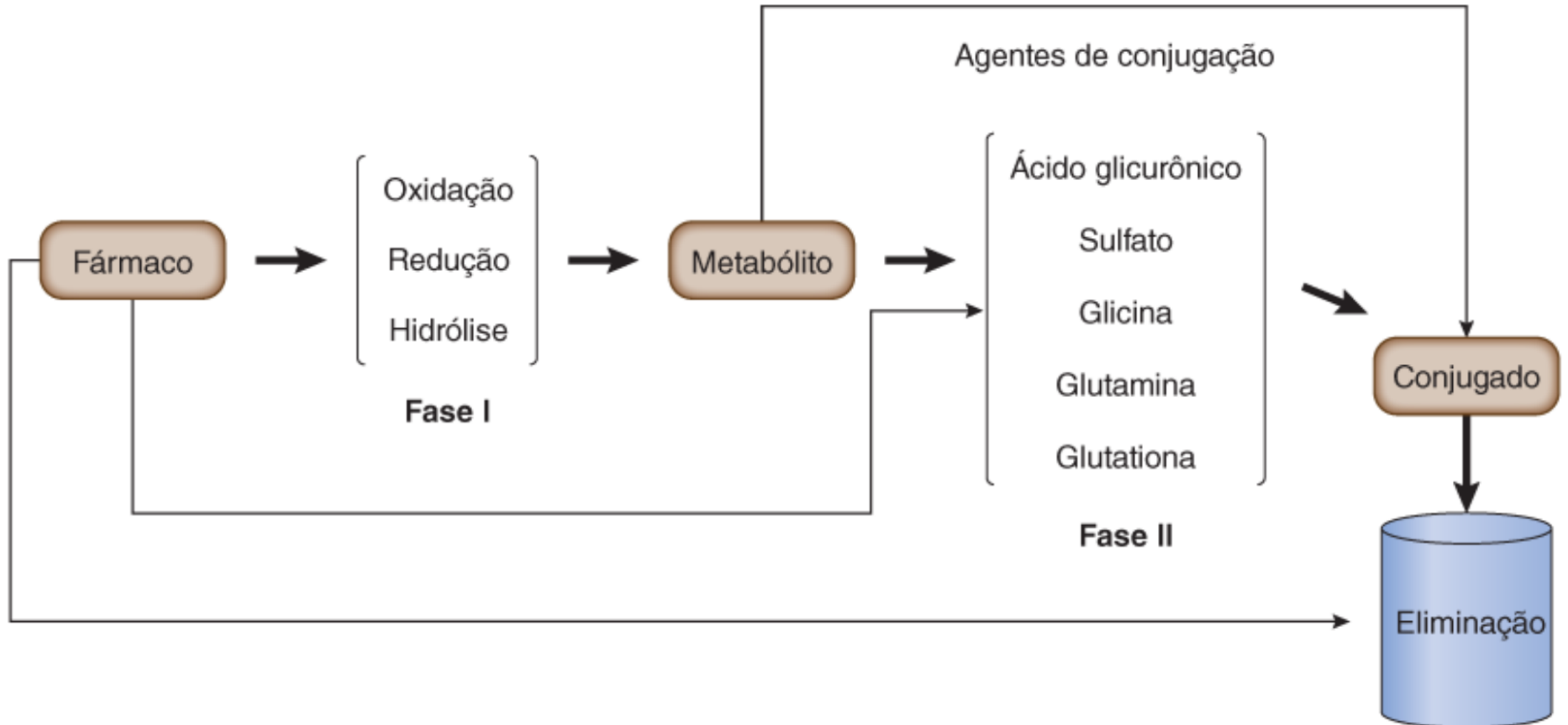


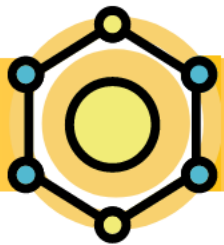
METABOLISMO (BIOTRANSFORMAÇÃO)





METABOLISMO (BIOTRANSFORMAÇÃO)





METABOLISMO (BIOTRANSFORMAÇÃO)

A isoforma **CYP3A4** metaboliza quase 40% dos xenobióticos → substratos grandes

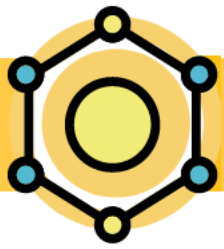
A isoforma **CYP2D6** → ligações de hidrogênio e iônicas, NH₂ nprotonados no pH 7,4

A isoforma **CYP1A2** → aminas e amidas planares

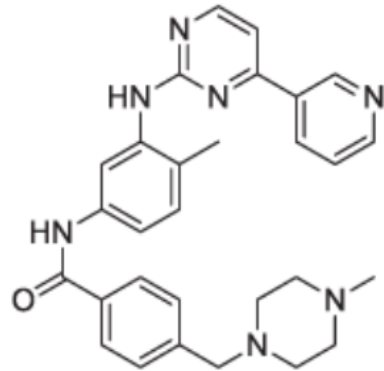
A isoforma **CYP2C9** → substratos não muito grandes com grupo carboxilato

TABELA 2 Principais isoformas P450 e especificidade para substratos⁶

Isoformas	Características	Log P	Exemplo
CYP3A4	Moléculas grandes	0,94 – 7,54	Imatinibe
CYP2D6	Básicas	0,75 – 5,04	Paroxetina
CYP1A2	Aminas planares e amidas	0,08 – 3,61	Tacrina, Paracetamol
CYP2C9	Ácidas	0,89 – 5,18	Ibuprofeno

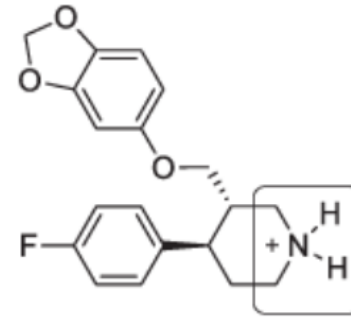


METABOLISMO (BIOTRANSFORMAÇÃO)



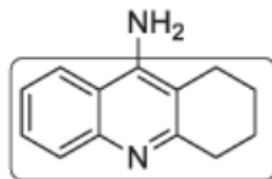
Imatinibe (CYP3A4)

PM = 493 g/mol Alto Peso Molecular



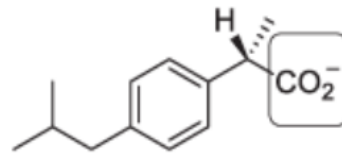
Paroxetina
(CYP2D6)

Grupo básico ionizado



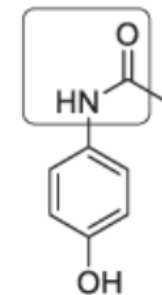
Tacrina (CYP1A2)

Amina planar



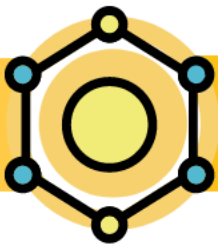
(S)-Ibuprofeno (CYP2C9)

Grupo ácido ionizado



Paracetamol (CYP1A2)

Amida planar



CYP3A4

METABOLISMO

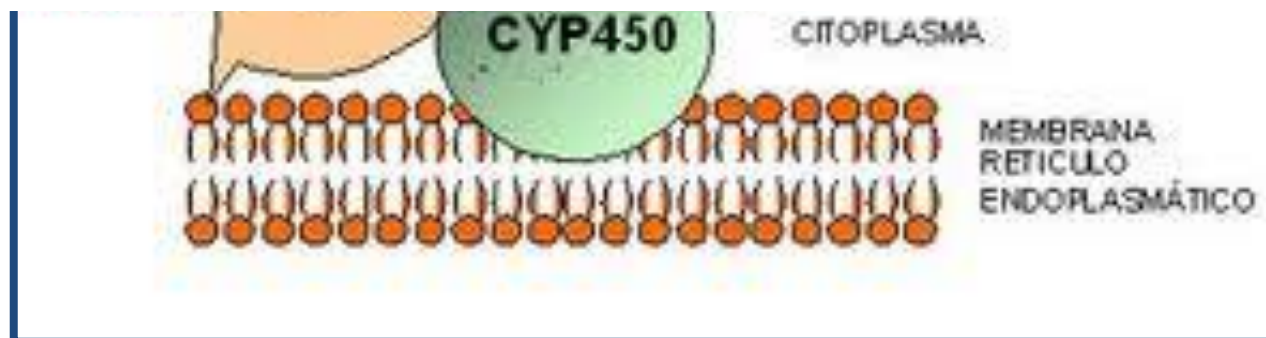
Principais isoformas de Cyp450 e especificidade para substratos

ENZIMAS DO CITOCROMO P450

- FÍGADO
- 4 FAMÍLIAS – HUMANOS
- CYP1-CYP4
- DIFERENÇAS INDIVIDUAIS
- SUSCETIBILIDADE DIFERENTE A FÁRMACOS
- INTERAÇÃO FÁRMACO-FÁRMACO PODE AFETAR



Li, D.; Kerns, E.H. Metabolic stability. In: Drug-like Properties: concepts, structure, design and methods. Oxford, UK: Elsevier Inc., 2008



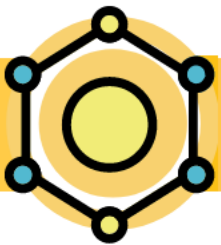
FARMACOGENÔMICA

MEDICINA PERSONALIZADA

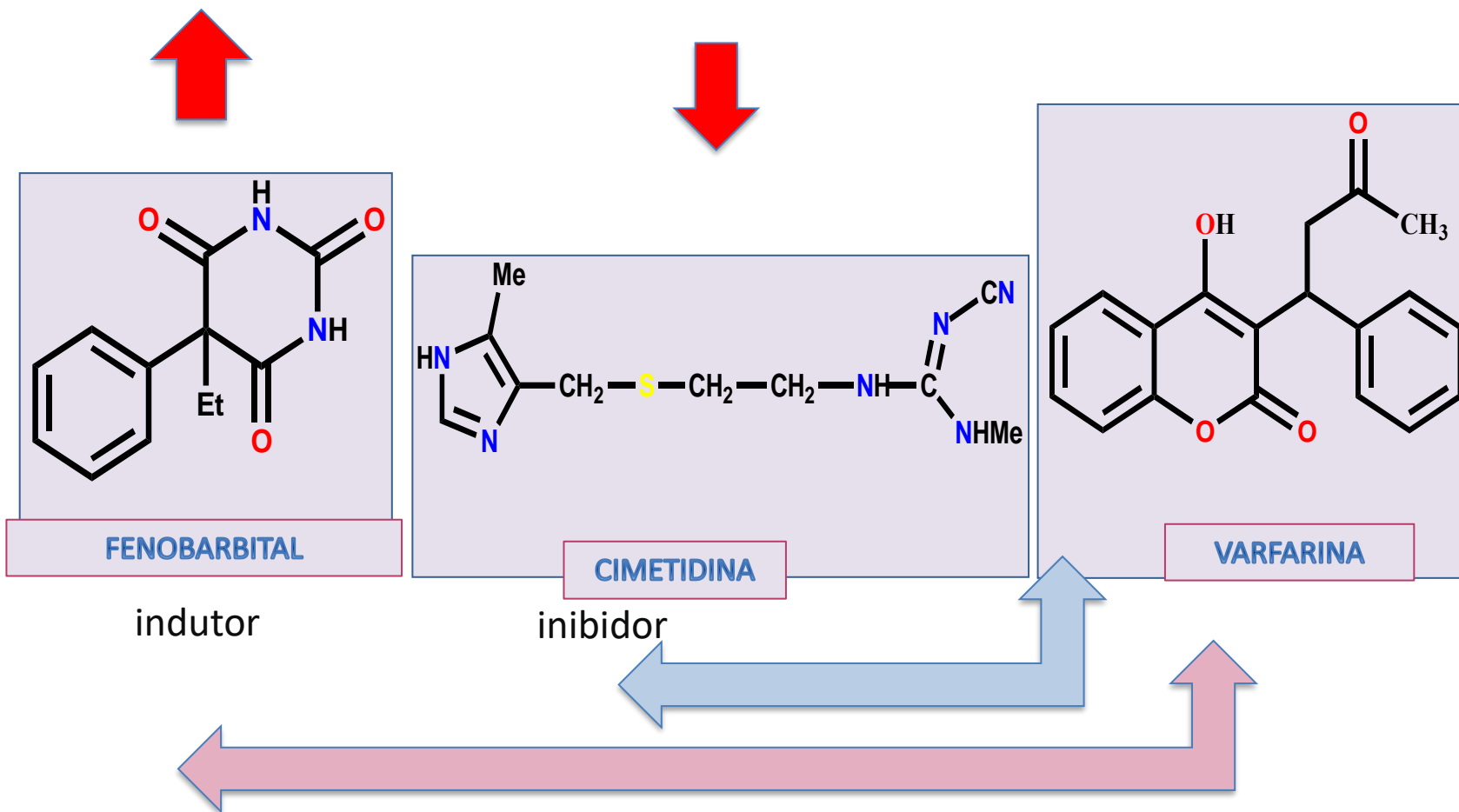
VARIAÇÃO GENÉTICA

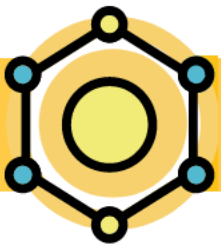
Lamba *et al.* *Adv. Drug Delivery Rev.*, v.64, p.256-269, 2012.

Bozina *et al.* *Arh. Hig. Rada Toksikol.* v.60, p.217-242, 2009.

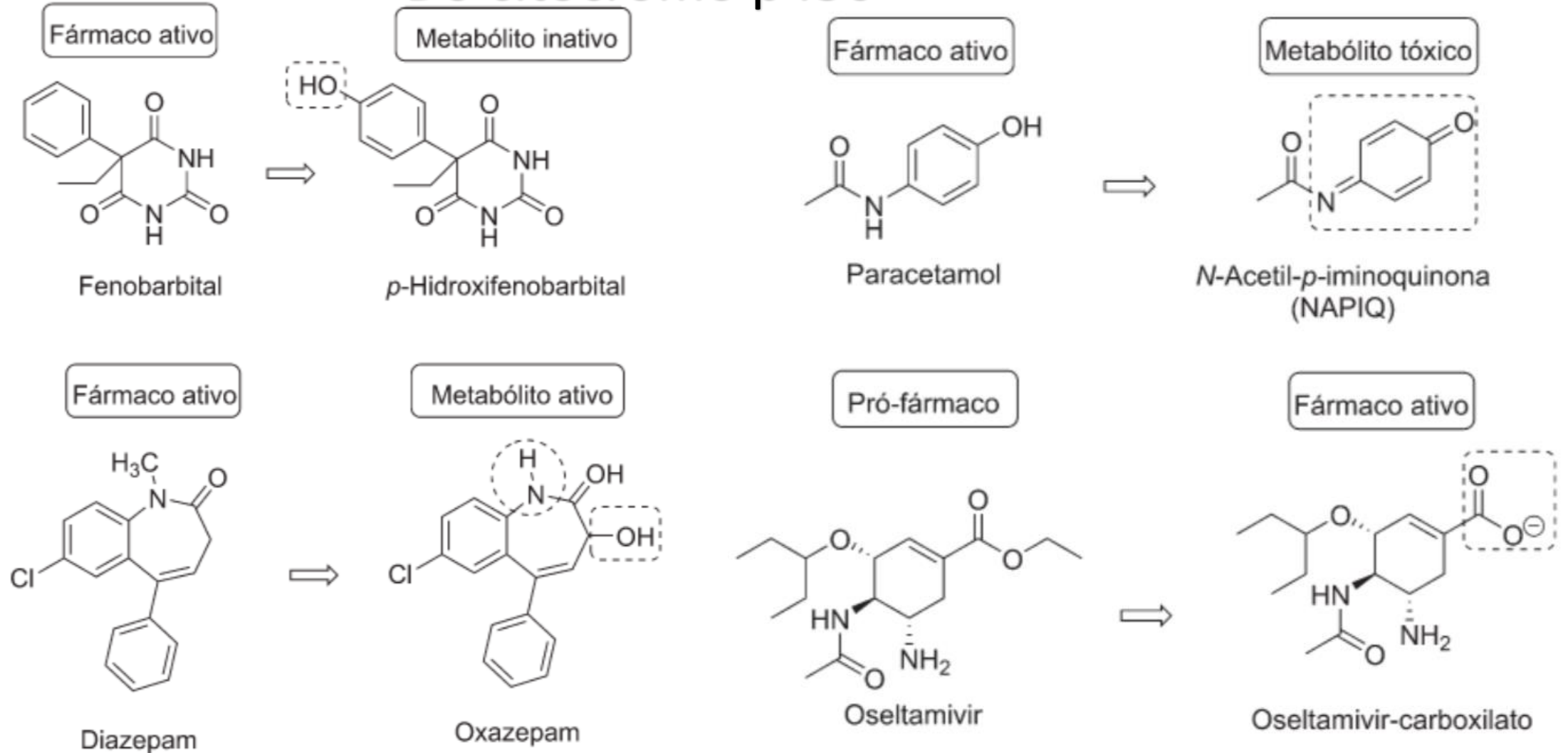


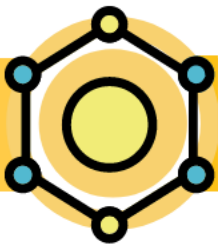
Fármacos que afetam a atividade Do citocromo p450



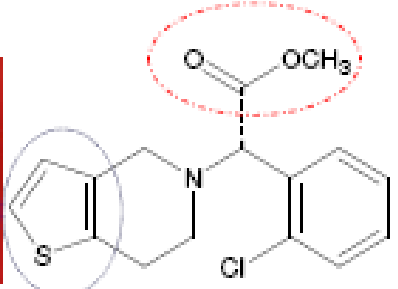


Fármacos que afetam a atividade Do citocromo p450





INTERAÇÃO FÁRMACO-FÁRMACO E METABOLISMO



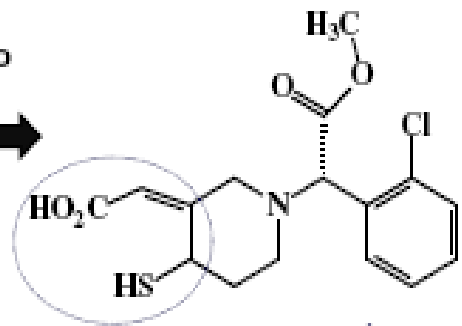
clopidogrel (antiplaquetário)
tratamento da doença
arterial coronariana

*Perda das propriedades
antiplaquetárias*

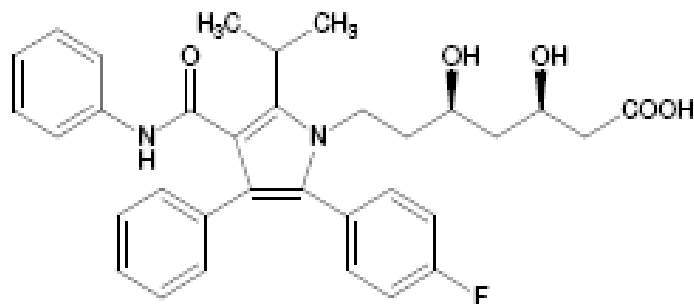
extenso metabolismo
hepático



CYP3A4
CYP2C19
CYP2C9
CYP2B6



metabólito ativo

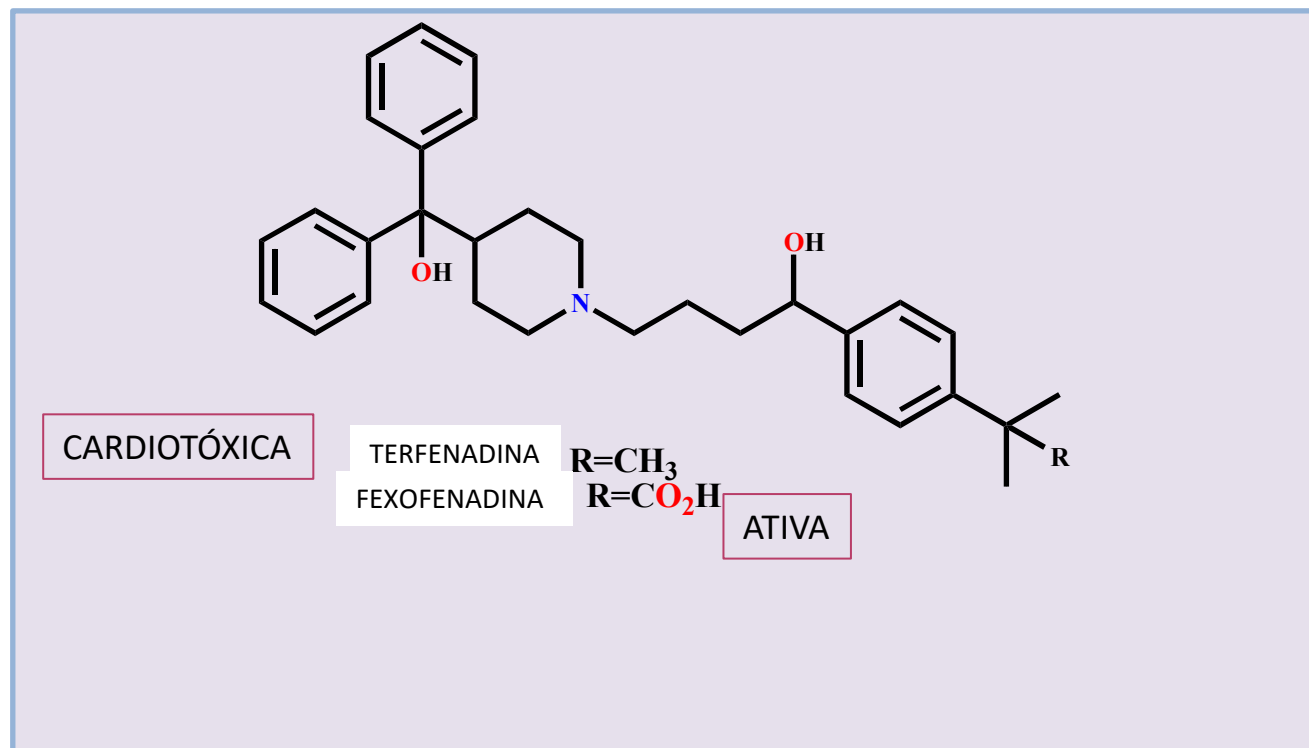


atorvastatina
antilipidêmico
(inibidor da HMGCoA-redutase)

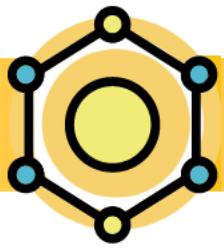
**substrato e
inibidor da CYP 3A4**



INTERAÇÃO FÁRMACO-ALIMENTO E METABOLISMO

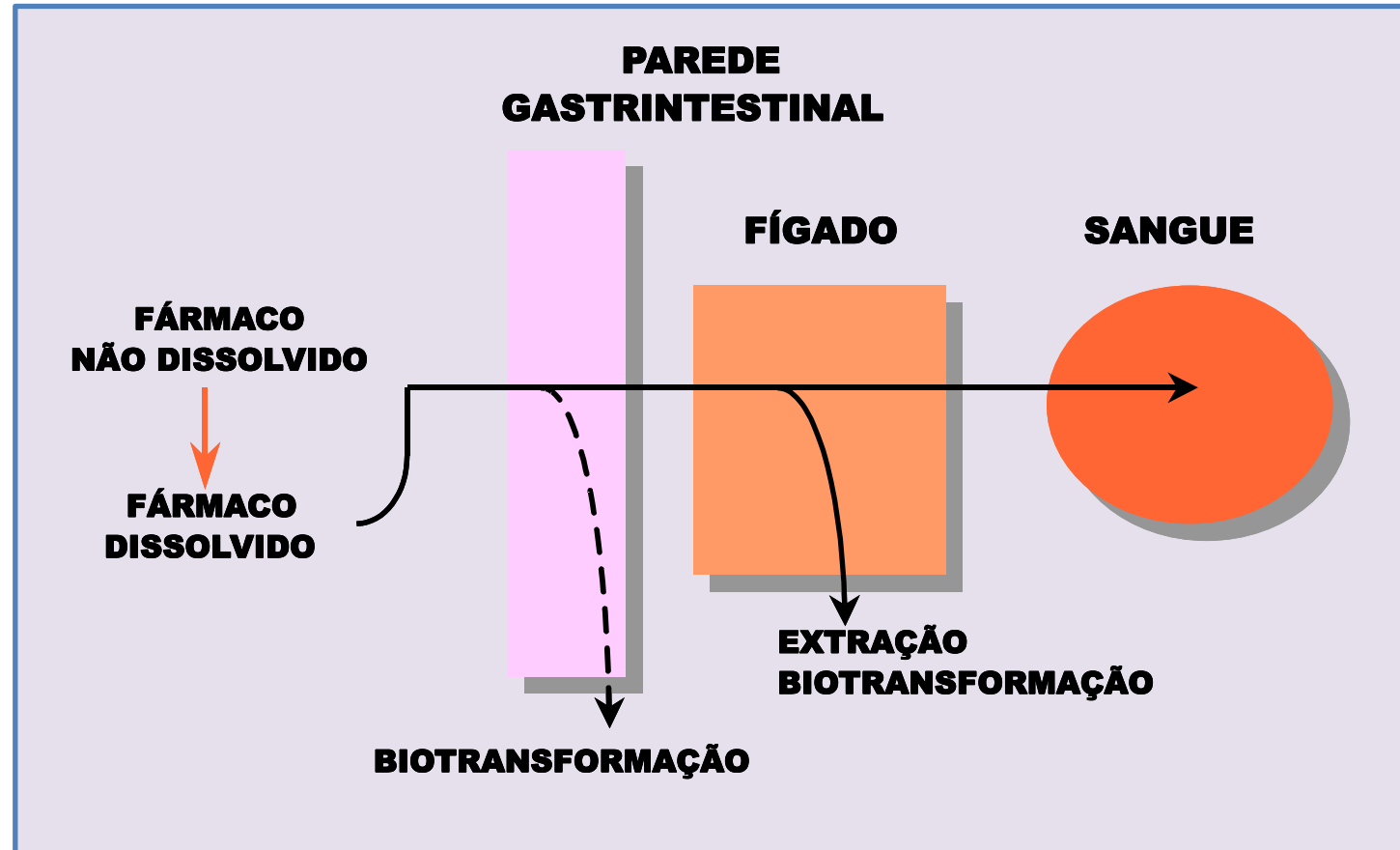


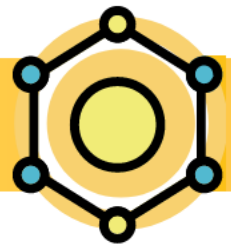
METABOLISMO DIMINUÍDO POR *GRAPE FRUIT*



METABOLISMO

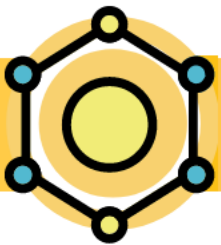
ELIMINAÇÃO PRÉ-SISTÊMICA





METABOLISMO

REAÇÕES DE FASE I

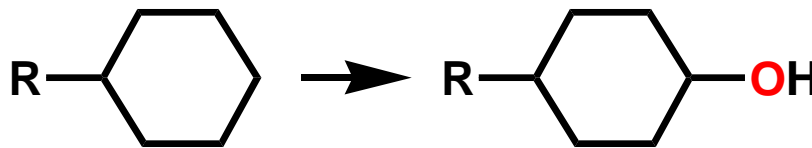


METABOLISMO

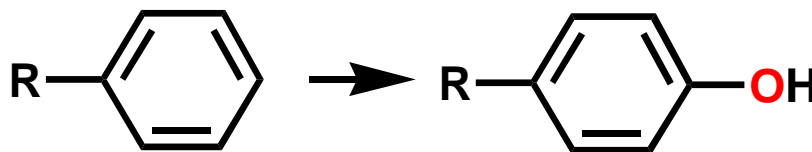
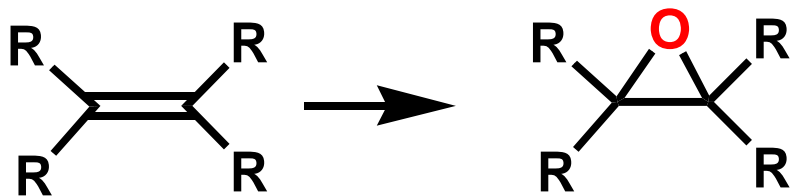
FASE I

OXIDAÇÃO

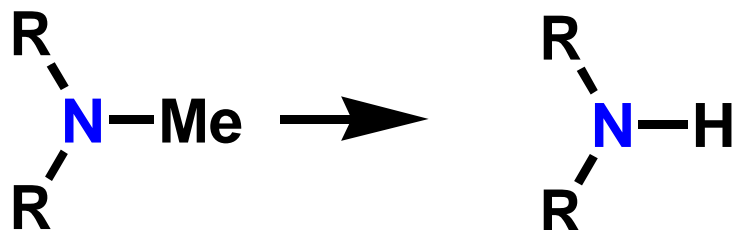
GRUPOS ALQUÍLICOS



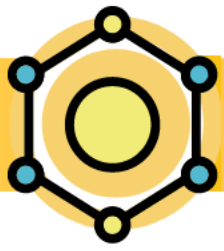
ALCENOS E AROMÁTICOS



GRUPOS N-ALQUÍLICOS

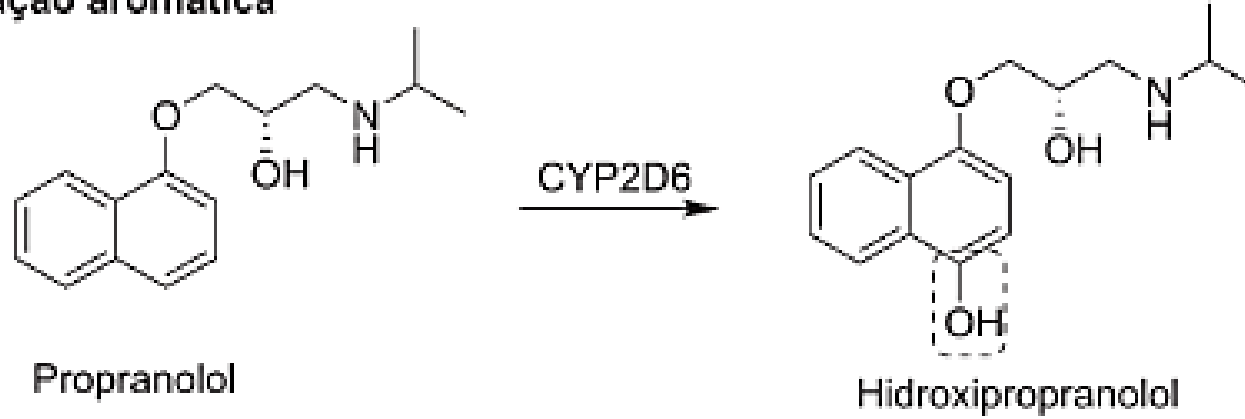


DESMETILAÇÃO

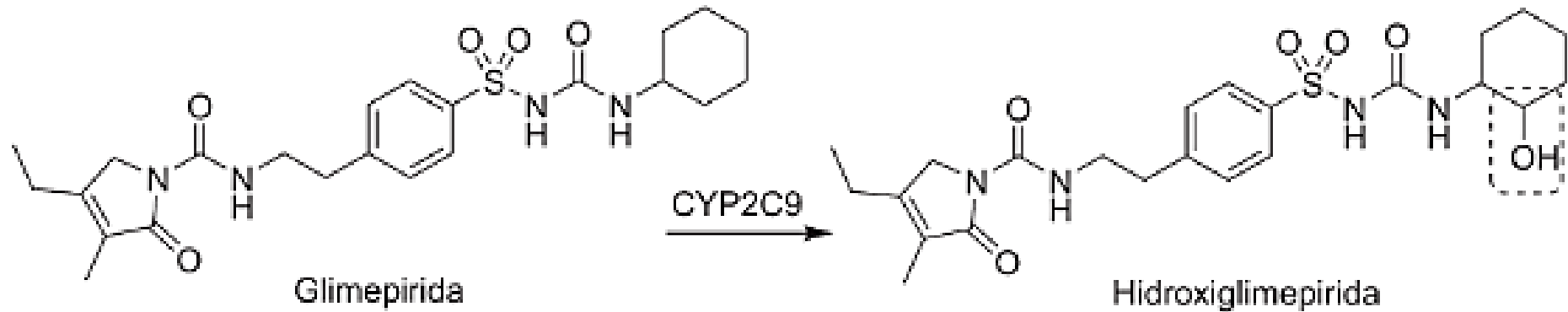


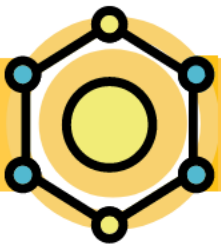
METABOLISMO

a) Hidroxilação aromática



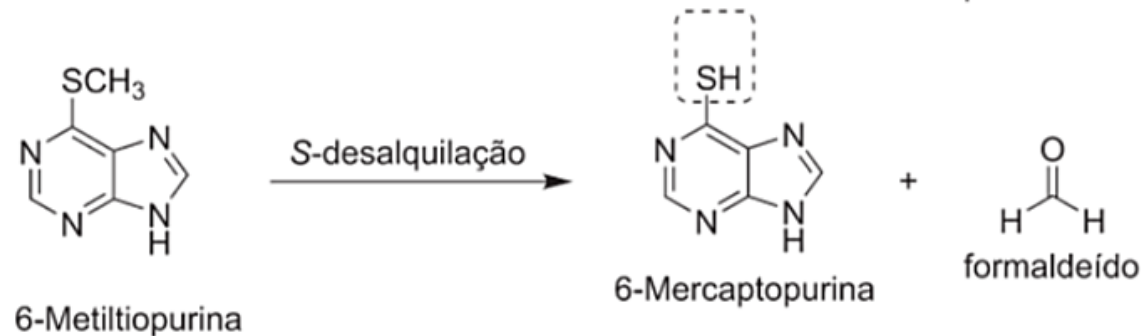
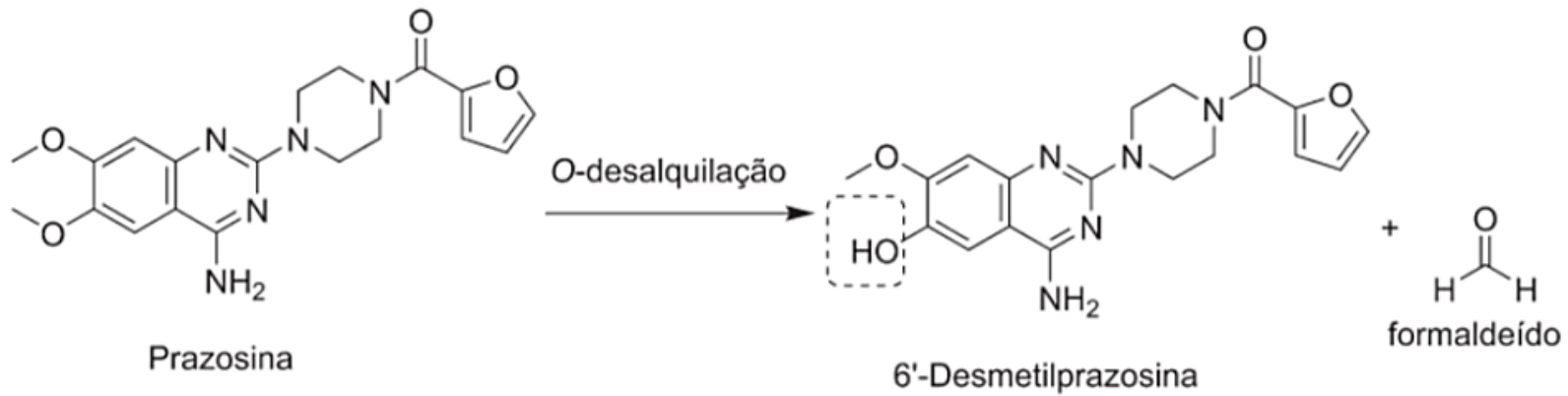
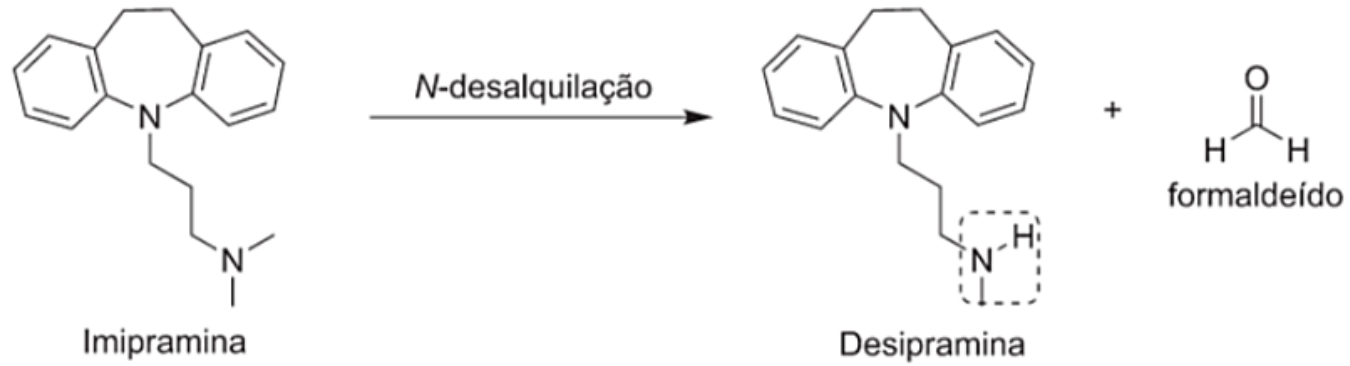
b) Hidroxilação alifática

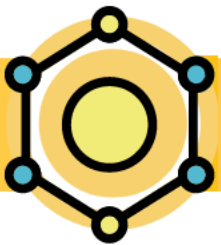




METABOLISMO

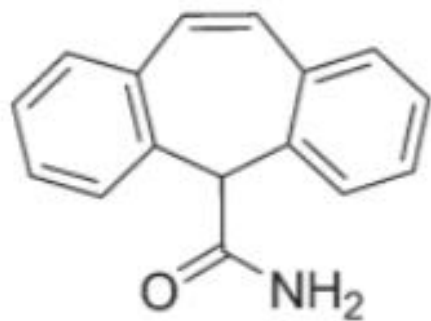
c) Reações de Desalquilação



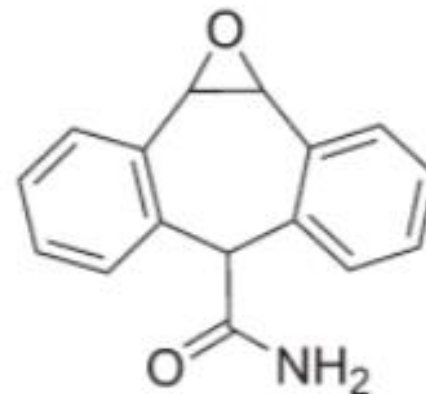


METABOLISMO

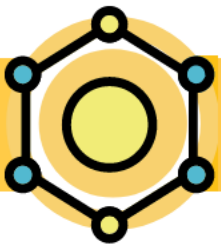
d) Epoxidação



Carbamazepina



10,11-Epoxi-carbamazepina

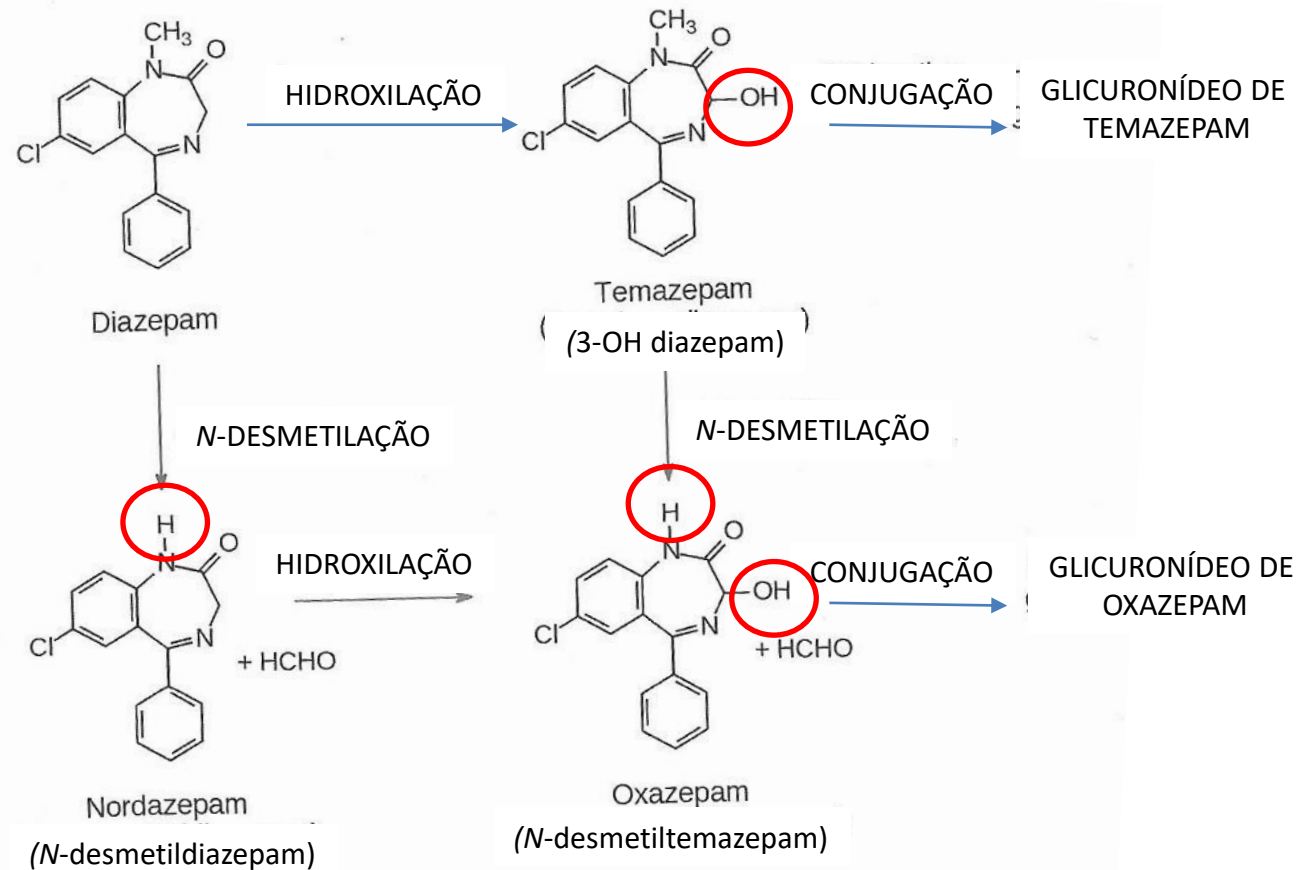


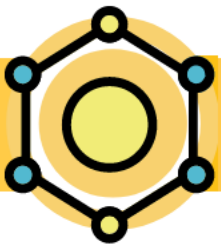
METABOLISMO

OXIDAÇÃO

FASE I

HIDROXILAÇÃO e N-DESMETILAÇÃO





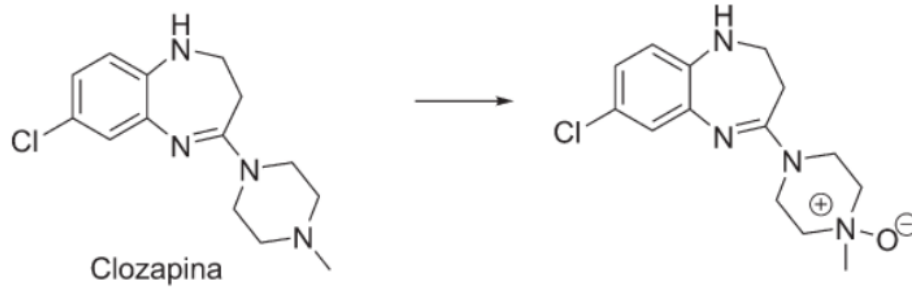
METABOLISMO

FASE I

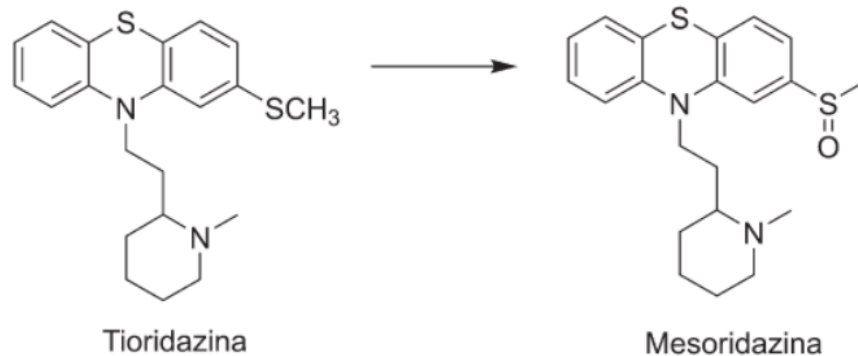
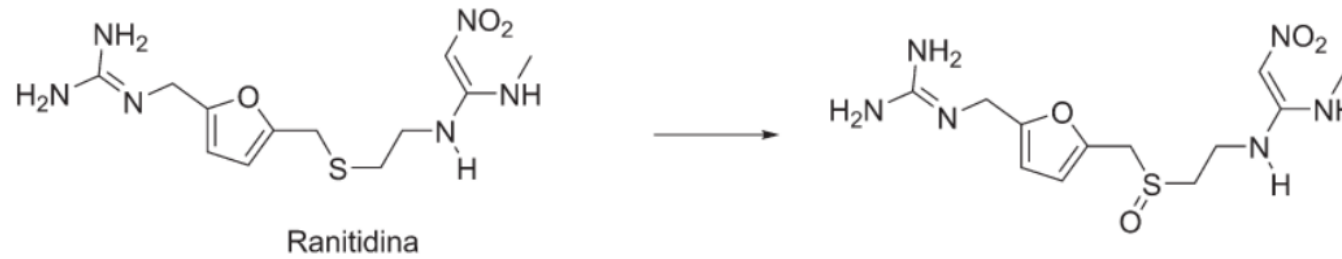
OXIDAÇÃO

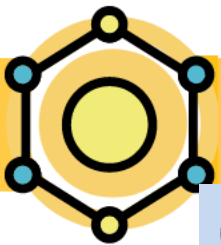
N e S OXIDAÇÃO

a) N-Oxidação



b) Sulfoxidação



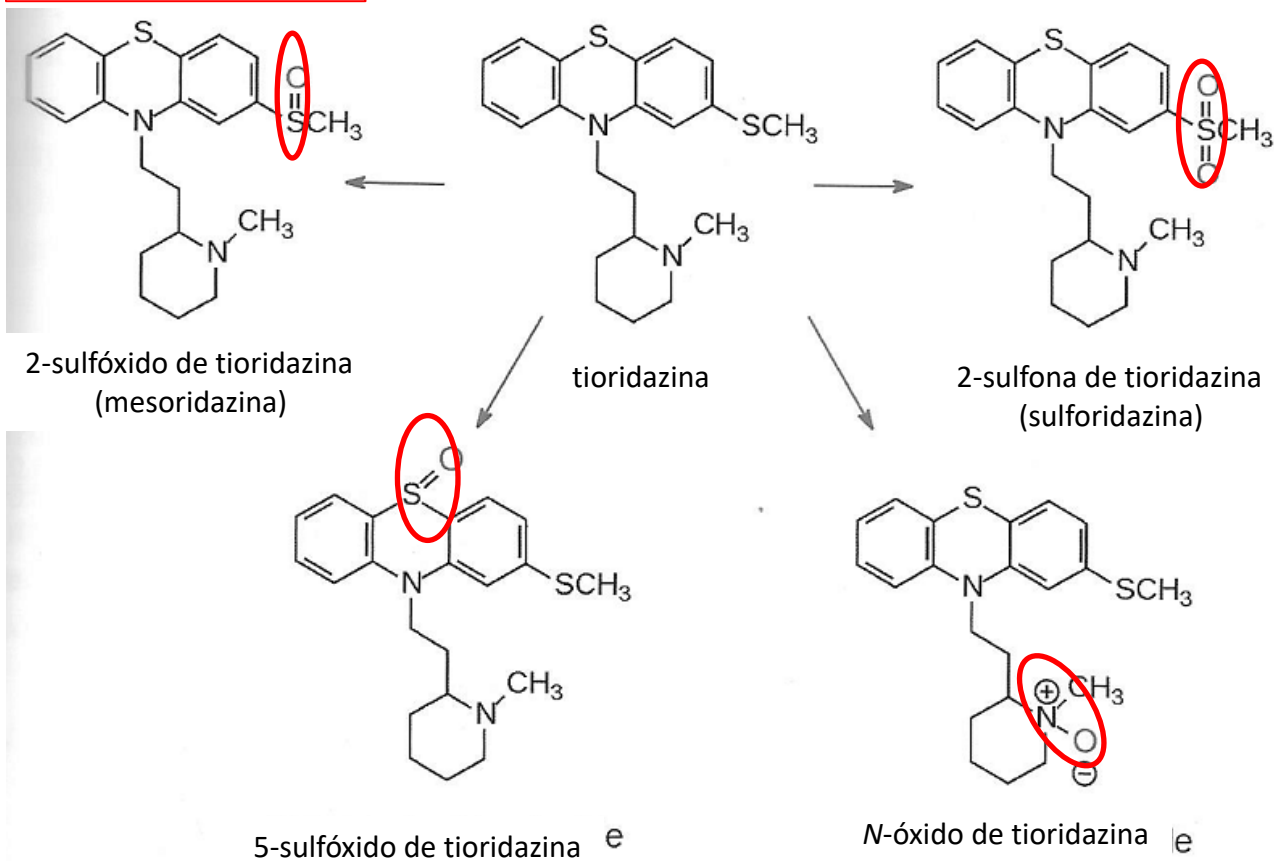


METABOLISMO

FASE I

OXIDAÇÃO

N e S OXIDAÇÃO



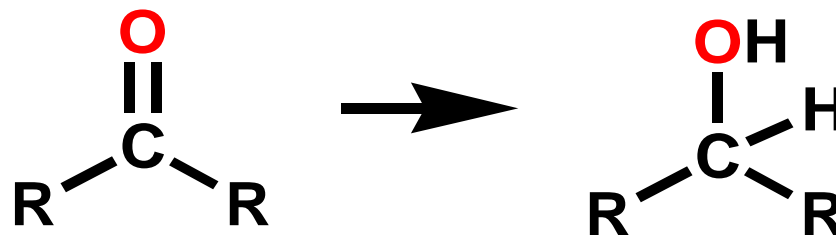


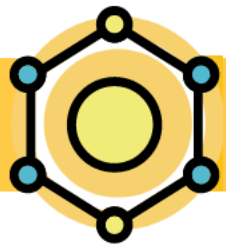
REDUÇÃO

METABOLISMO

FASE I

GRUPOS NITRO, AZO E CARBONILA

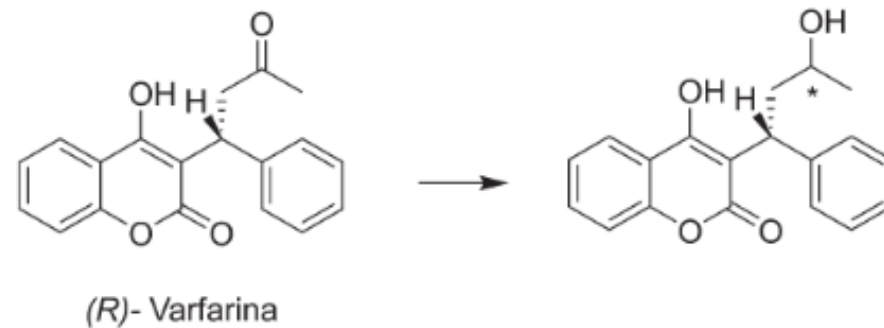
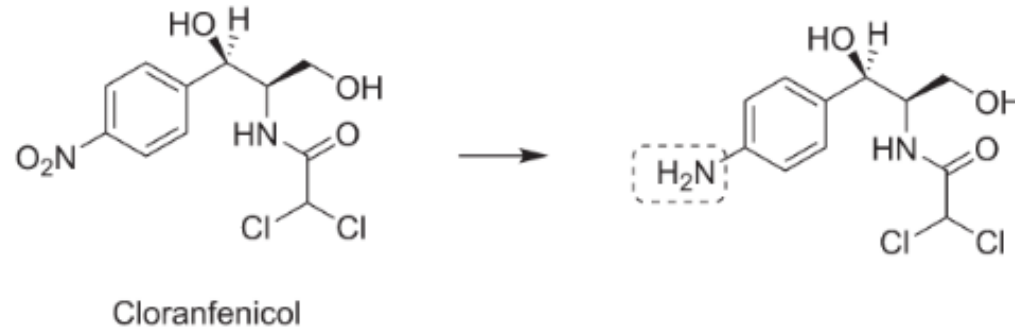
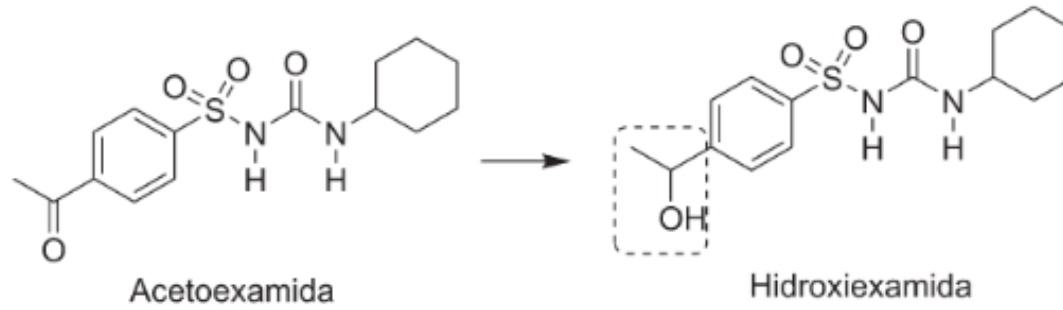


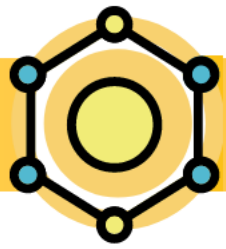


METABOLISMO

FASE I

REDUÇÃO

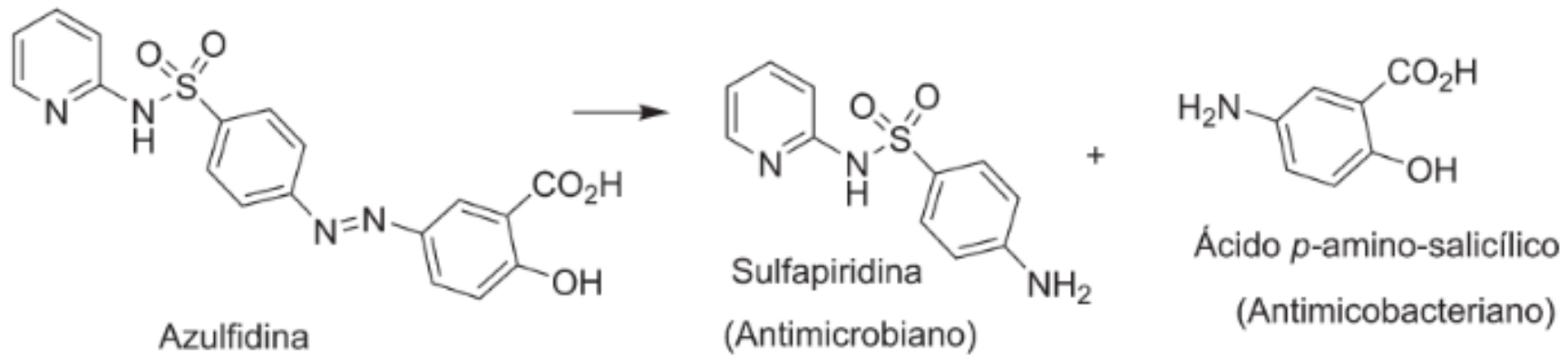
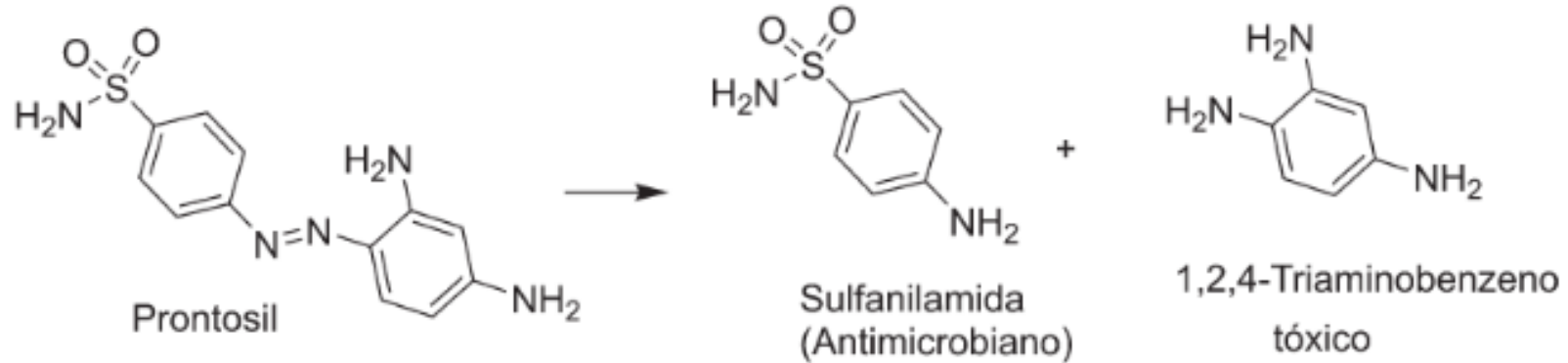




METABOLISMO

FASE I

REDUÇÃO

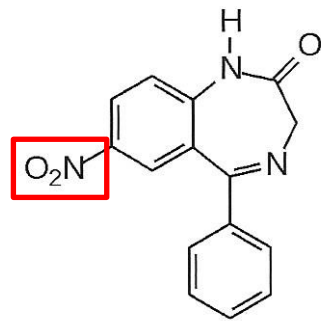




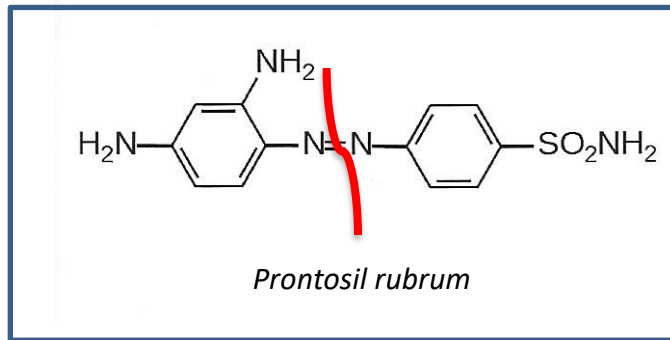
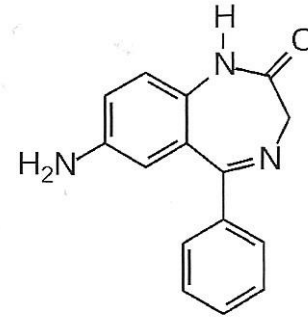
REDUÇÃO

METABOLISMO

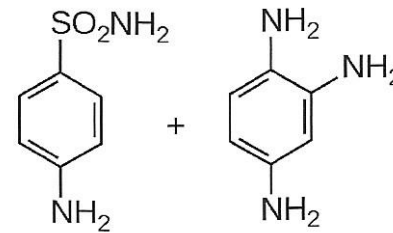
FASE I



Nitrazepam

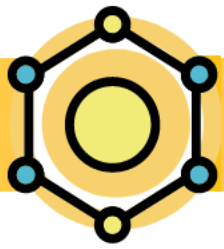


Prontosil rubrum



sulfanilamida

Pró-fármaco

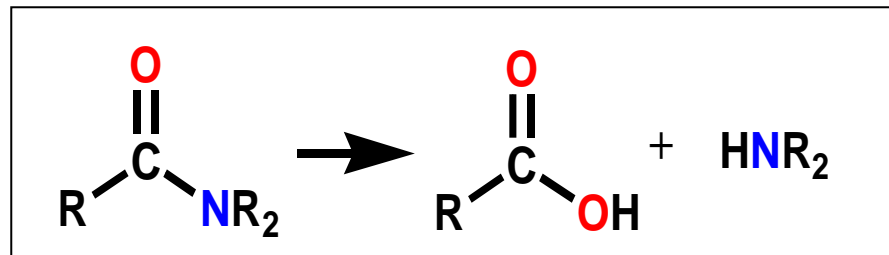
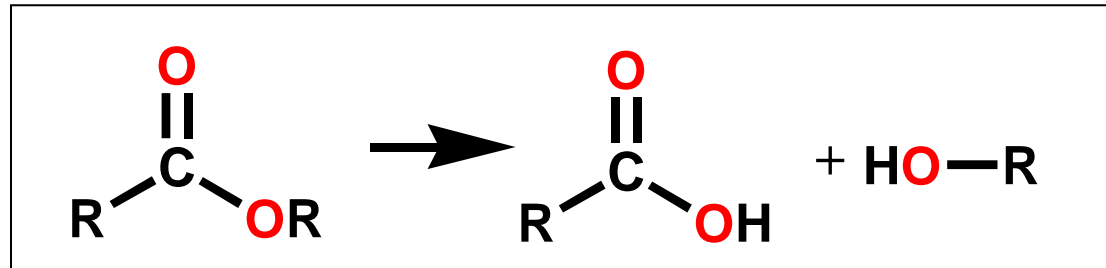


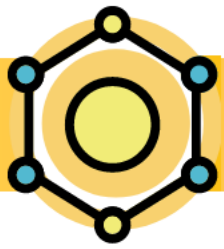
METABOLISMO

FASE I

HIDRÓLISE

GRUPOS ÉSTER E AMIDA

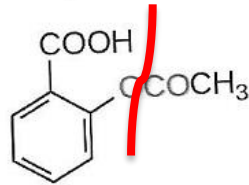




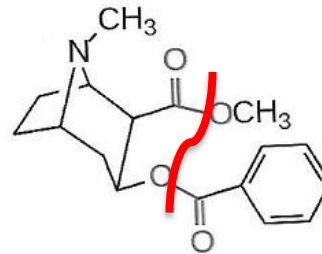
METABOLISMO

FASE I

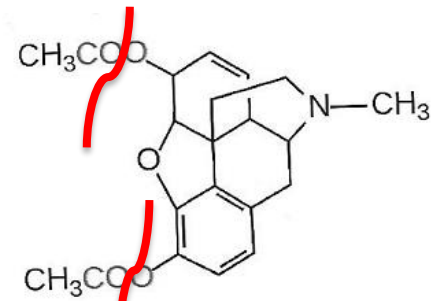
HIDRÓLISE



ácido acetilsalicílico

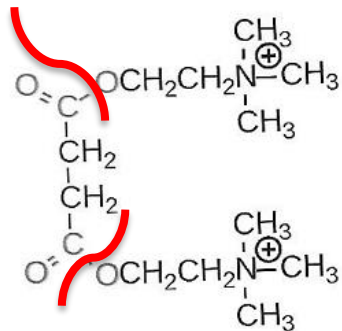


cocaina

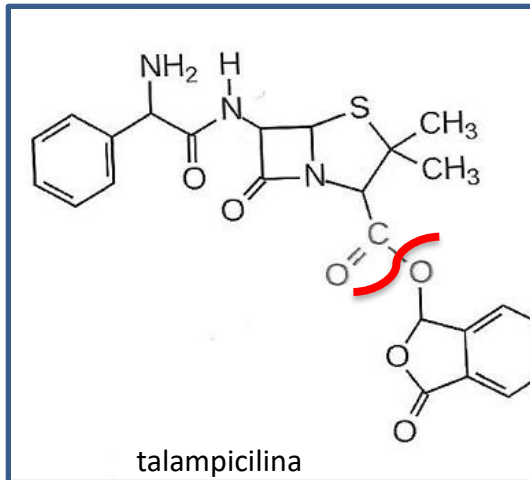


diacetilmorfina (heroína)

Pró-fármaco



suxametônio
(succinilcolina)

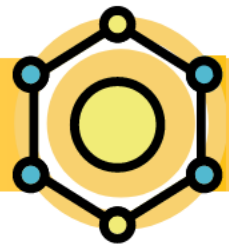


talampicilina

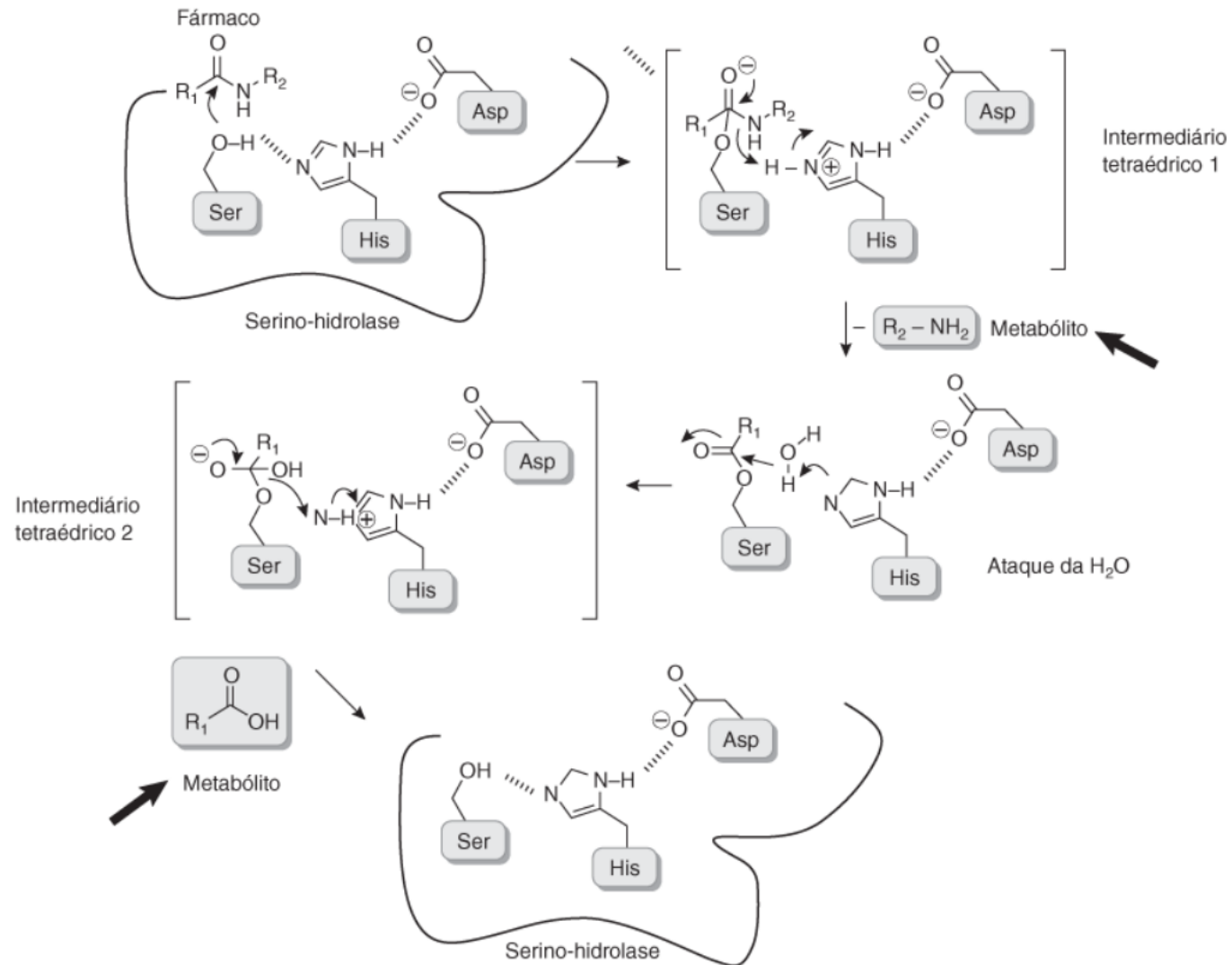
Pró-fármaco



fisostigmina

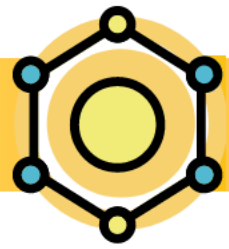


Mecanismo de hidrólise por uma serino-hidrolase



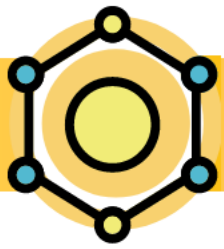


REAÇÕES DE FASE II

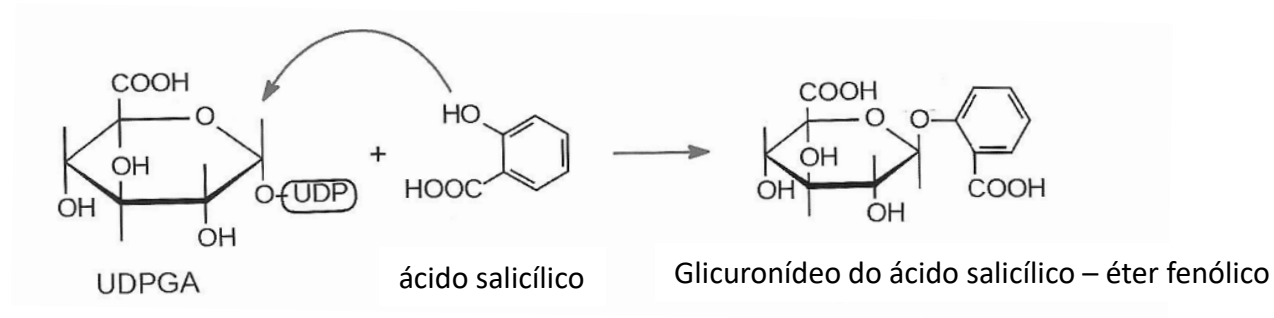
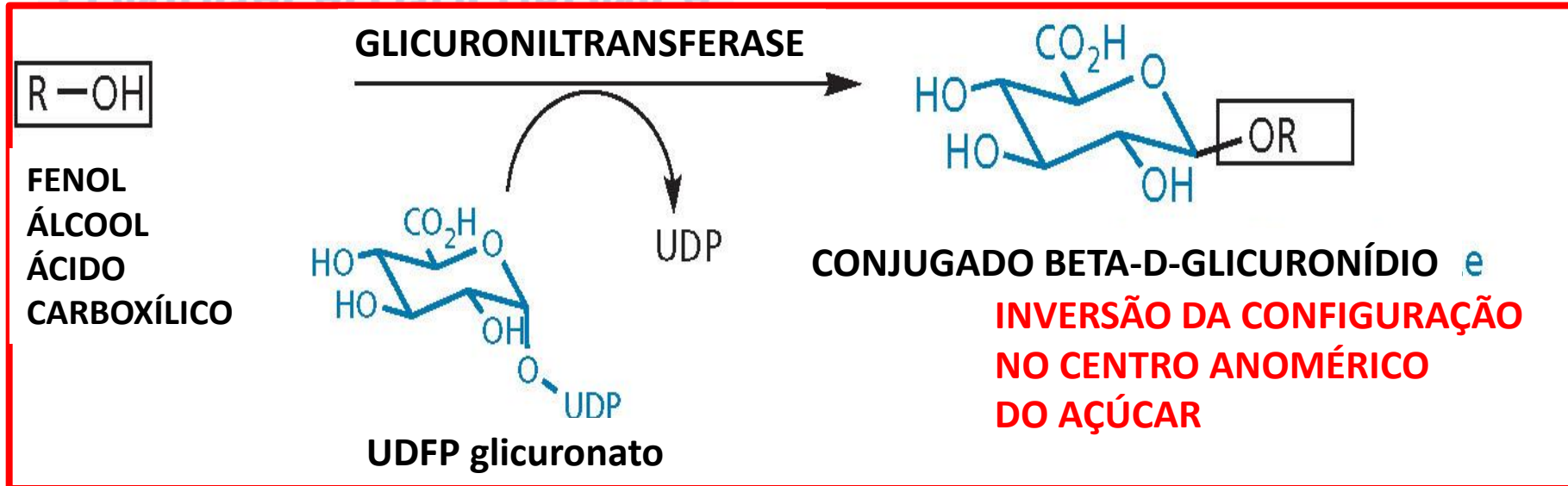


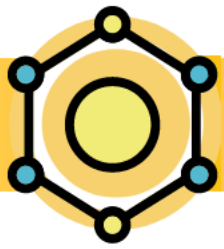
REAÇÕES DE FASE II

Quando analisamos as reações da Fase I, é possível observar que a biotransformação introduz grupos polares e nucleofílicos na estrutura do xenobiótico, possibilitando que o metabólito participe de reações de conjugação (Fase II)



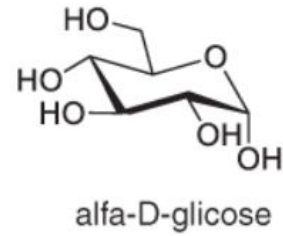
CONJUGAÇÃO GLICURÔNICA





METABOLISMO

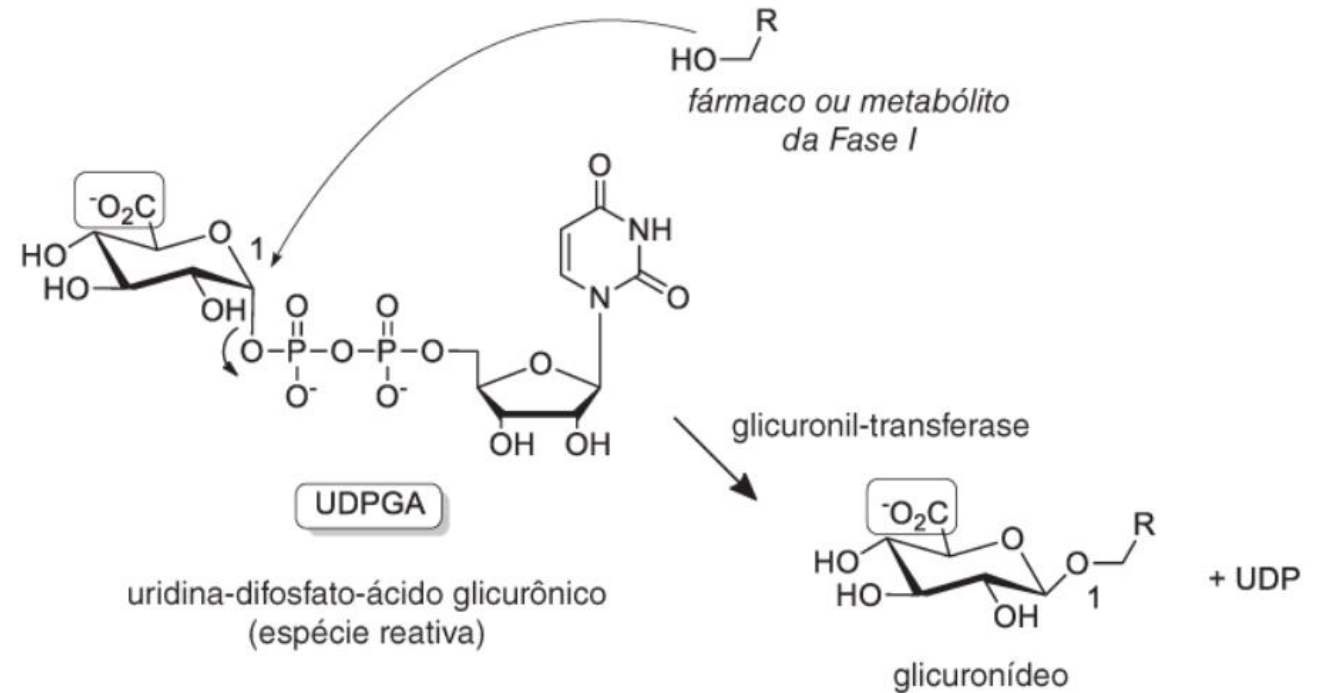
FASE II

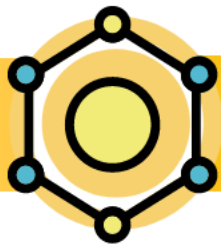


Grupos funcionais reativos frente à UDPGA

- R-OH
- Ar-OH
- R-CO₂H
- R-NHR', R-NH₂
- R-SH

CONJUGAÇÃO GLICURÔNICA

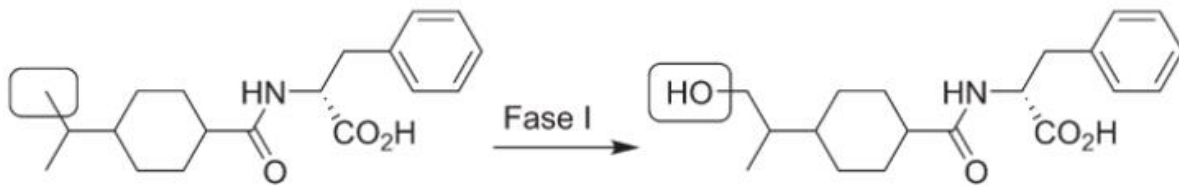




METABOLISMO

FASE II

CONJUGAÇÃO GLICURÔNICA



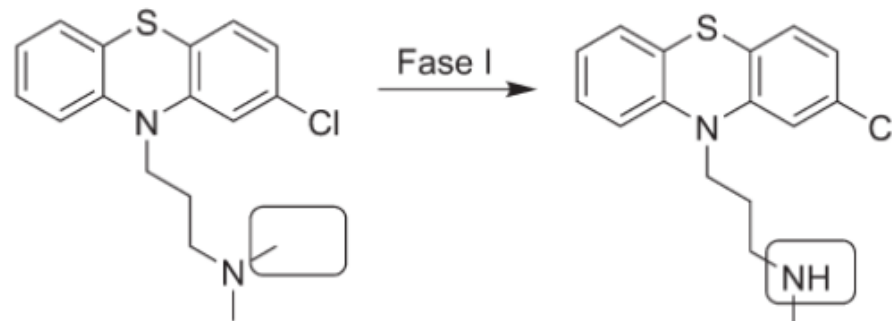
Nateglinida

Nateglinida M1

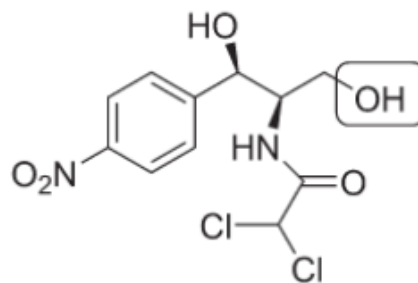


Dissulfiram

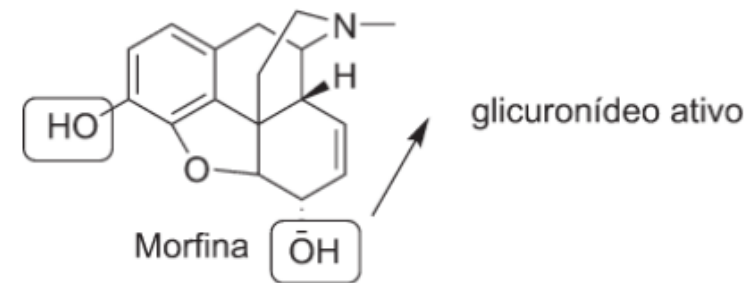
Dissulfiram M1
(Ácido ditiocarbamâmico)



Clorpromazina

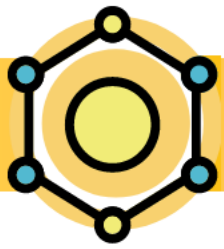


Cloranfenicol

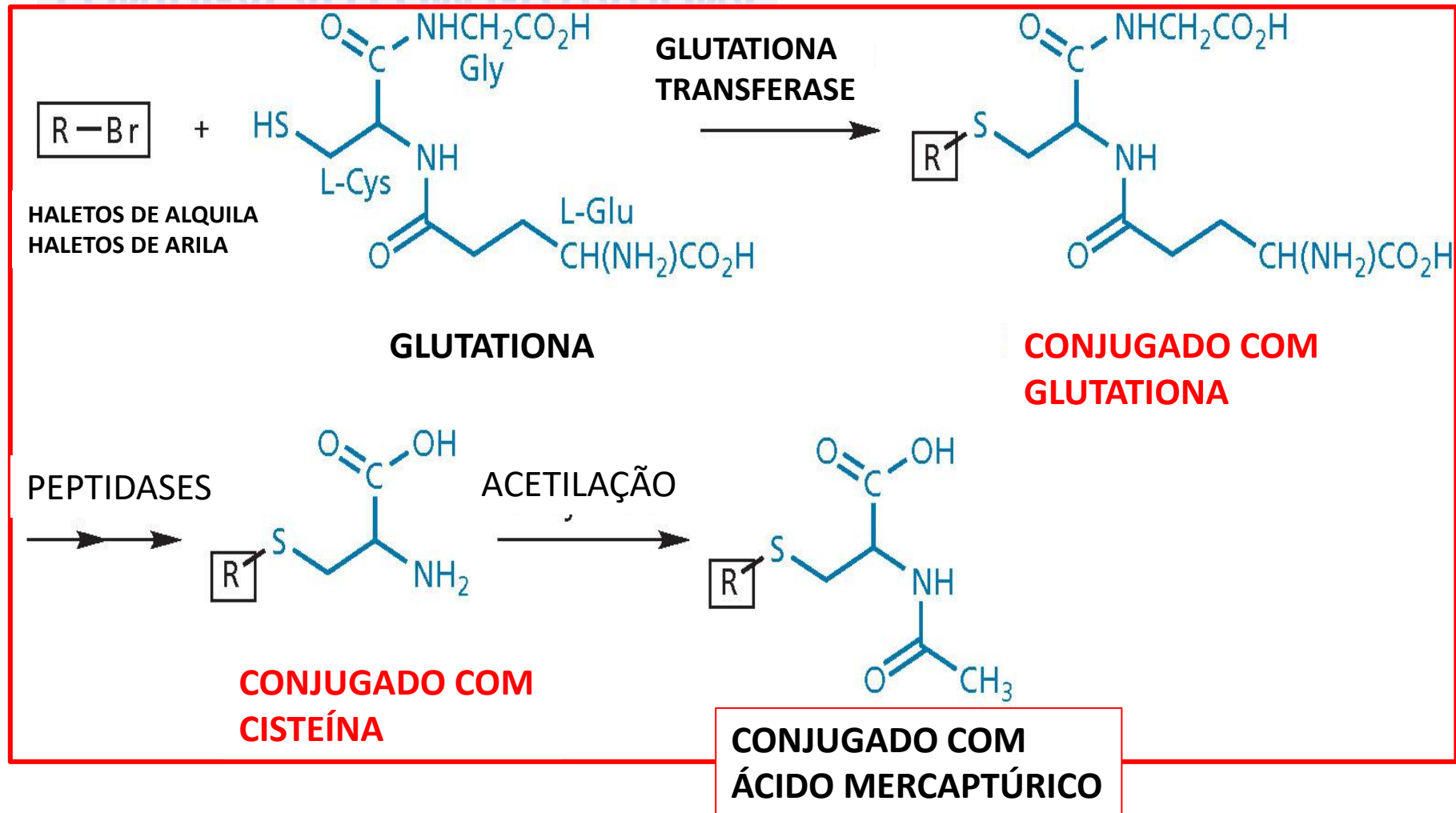


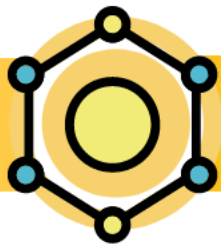
Morfina

glicuronídeo ativo



CONJUGAÇÃO COM GLUTATIONA

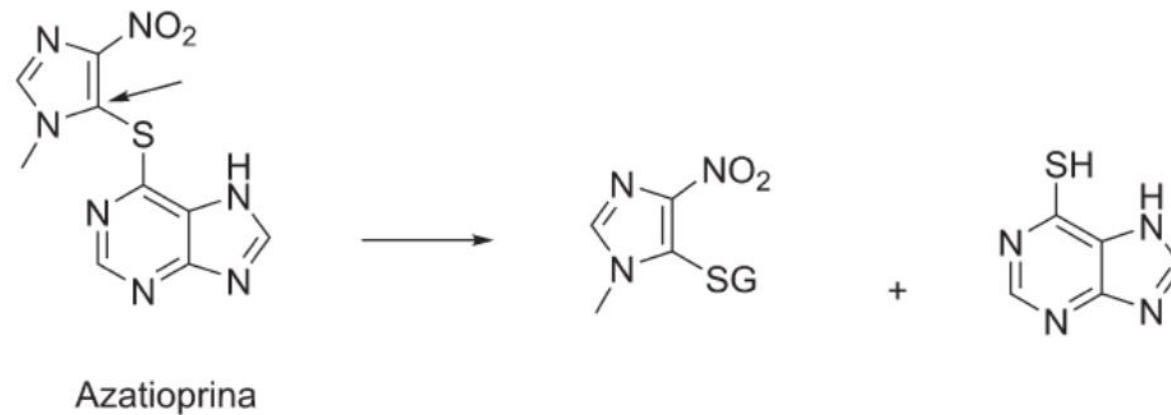
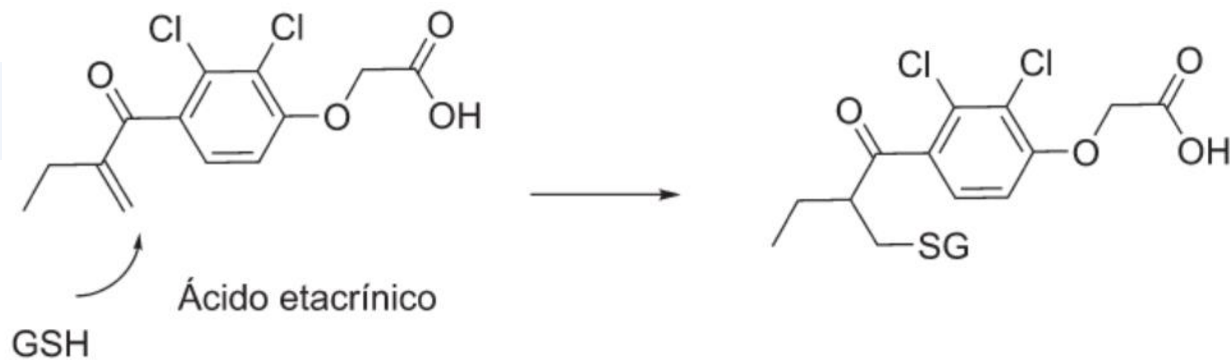




METABOLISMO

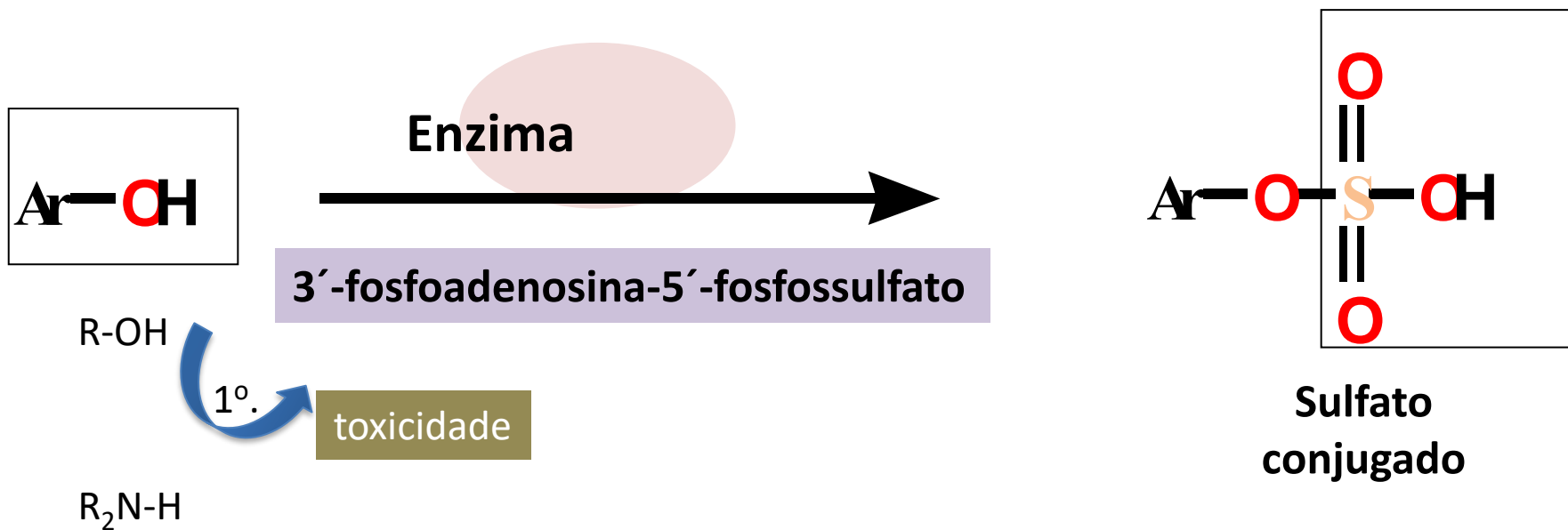
FASE II

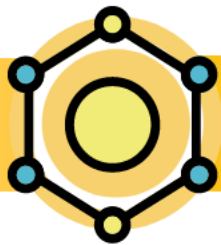
CONJUGAÇÃO COM GLUTATIONA





CONJUGAÇÃO COM SULFATOS

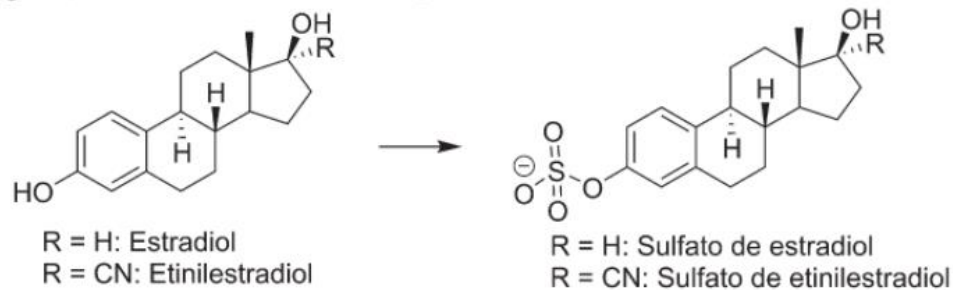
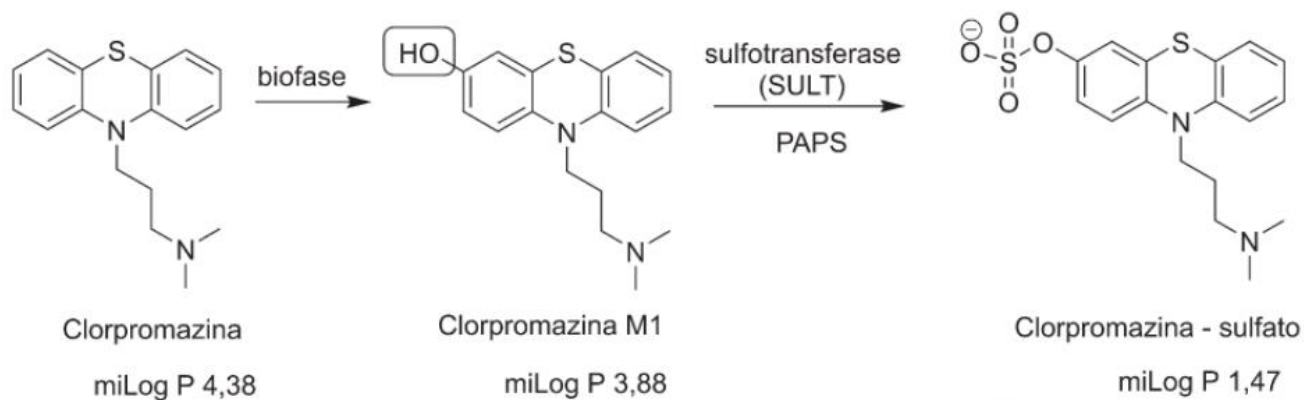
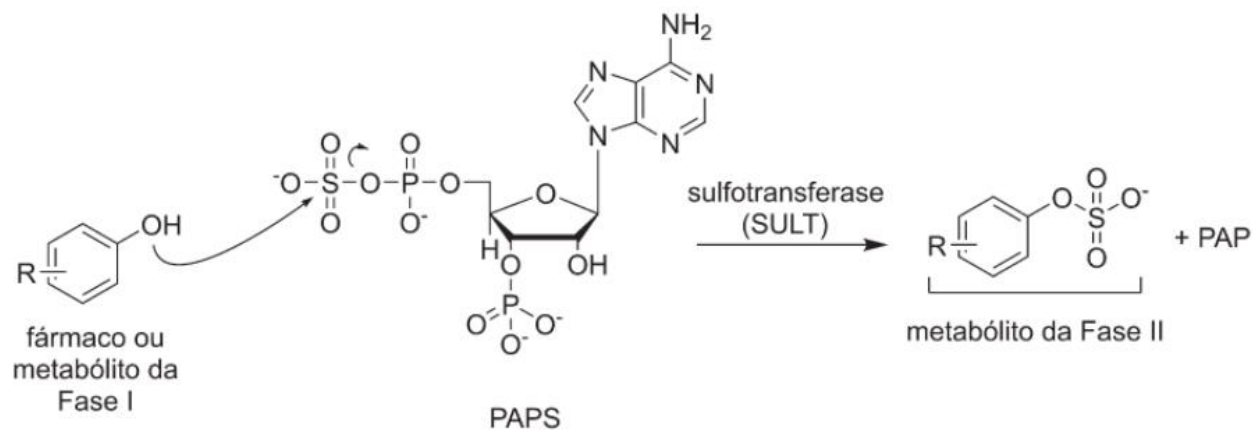


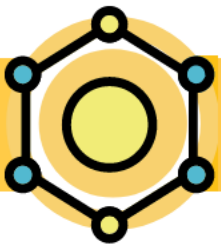


METABOLISMO

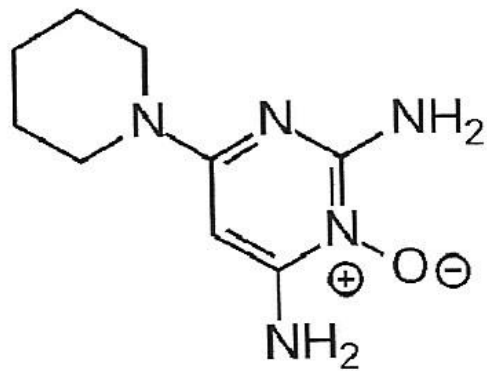
FASE II

CONJUGAÇÃO COM SULFATOS

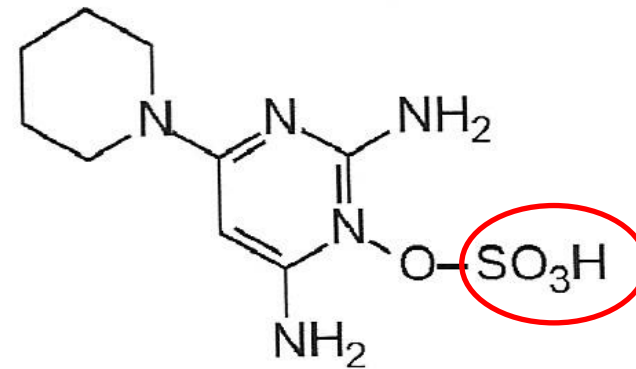




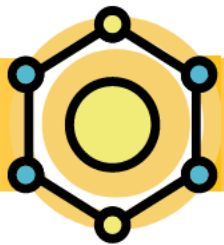
CONJUGAÇÃO COM SULFATOS



minoxidil



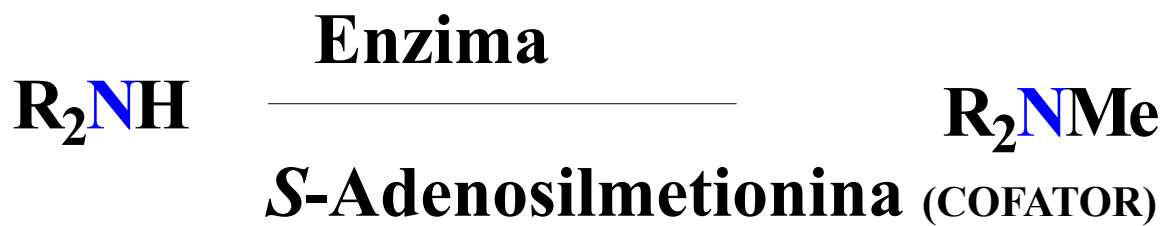
sulfato de minoxidil

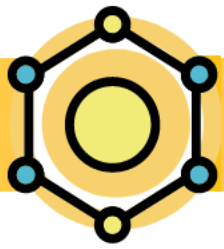


METABOLISMO

FASE II

METILAÇÃO E ACETILAÇÃO



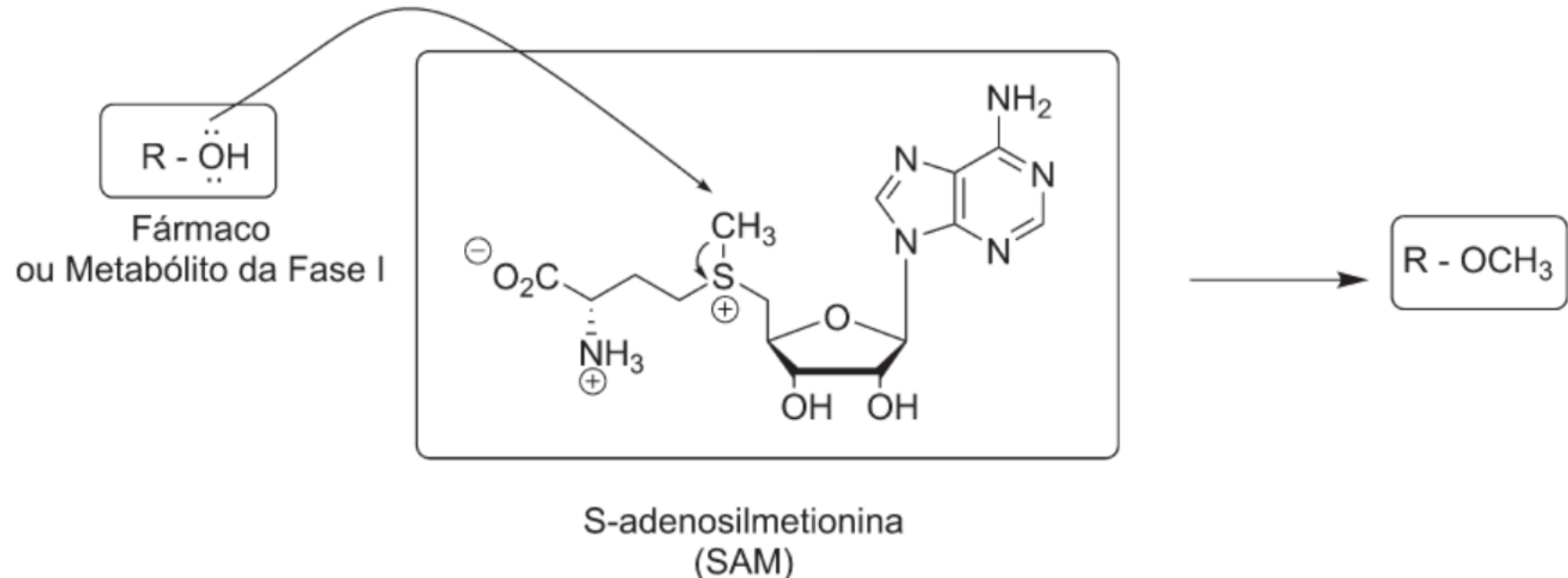
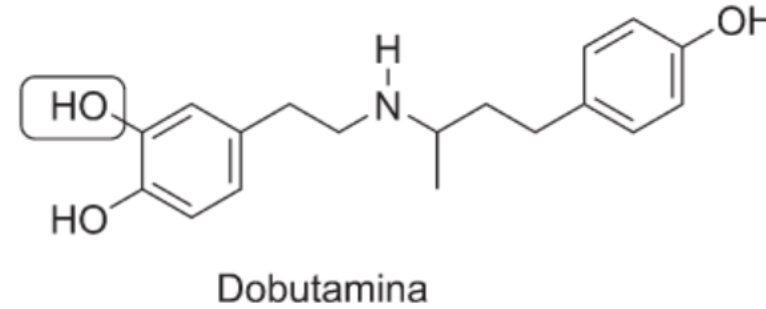
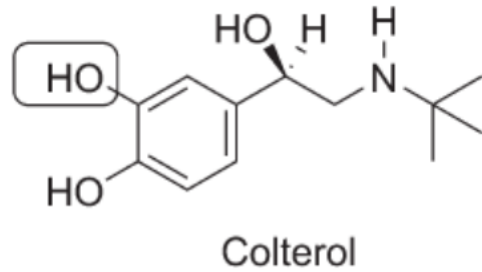


METABOLISMO

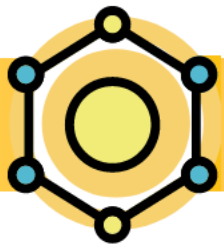
FASE II

METILAÇÃO E ACETILAÇÃO

O-Metilações mediadas pela COMT



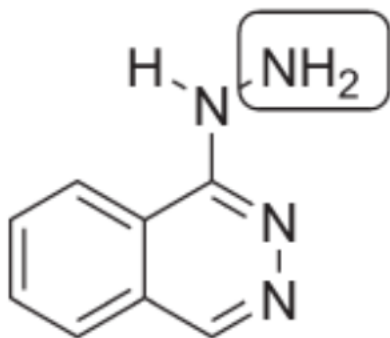
METILTRANSFERASES – CATECOL O-METILTRANSFERASE



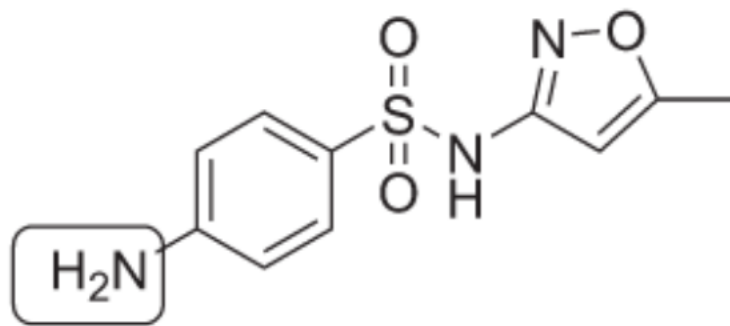
METABOLISMO

METILAÇÃO E ACETILAÇÃO

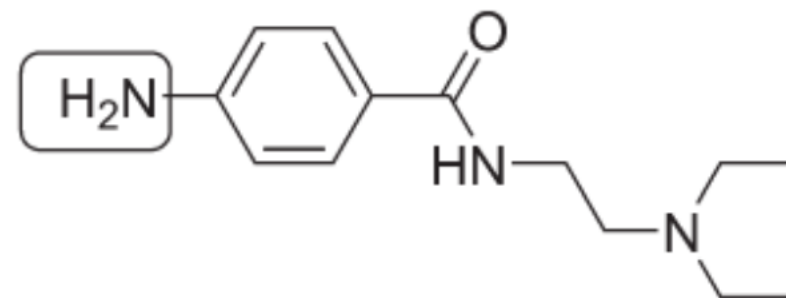
FASE II



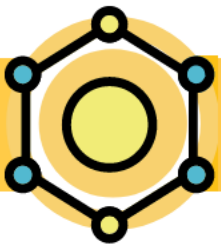
Hidralazina



Sulfametoxazol



Procainamida



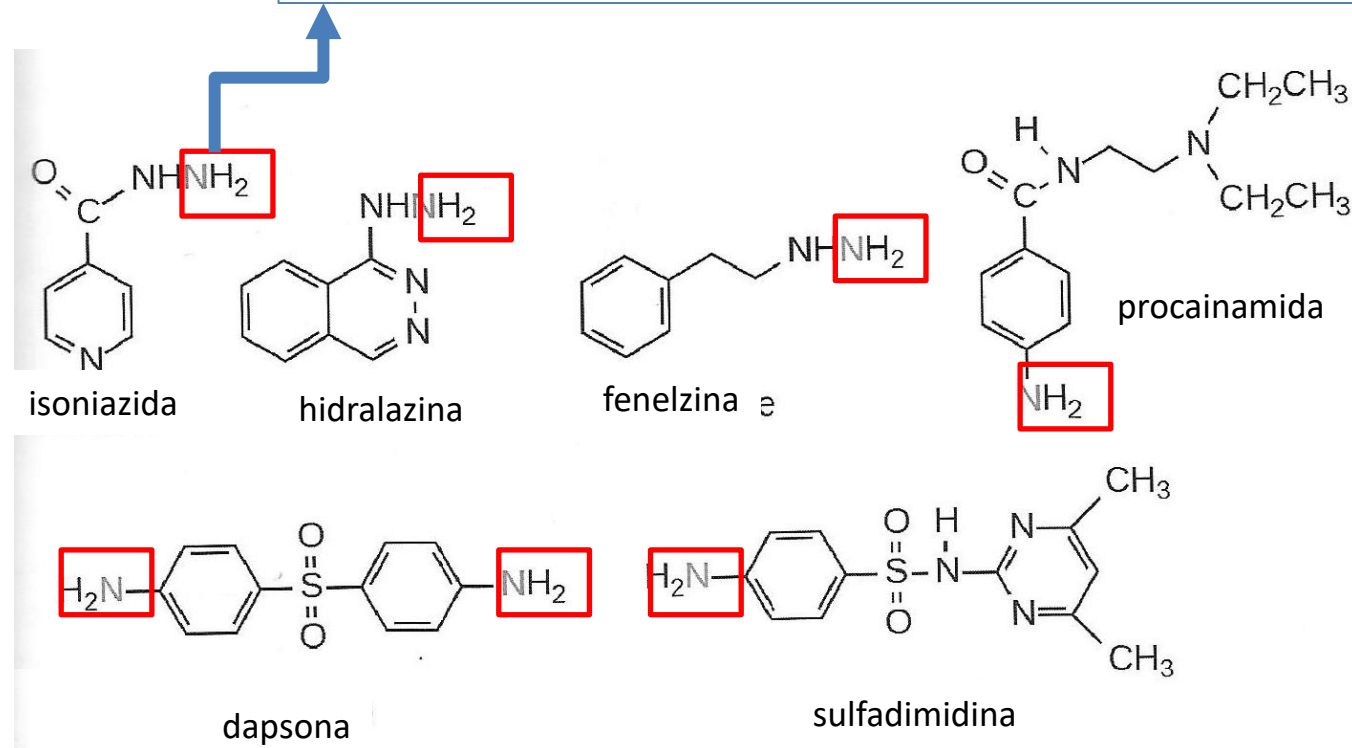
METABOLISMO

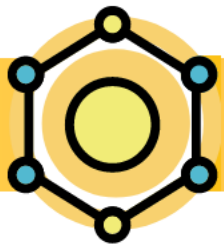
FASE II

N-ACETILAÇÃO

ASIÁTICOS – ACETILADORES RÁPIDOS

EUROPEUS E NORTEAMERICANOS - ACETILADORES LENTOS

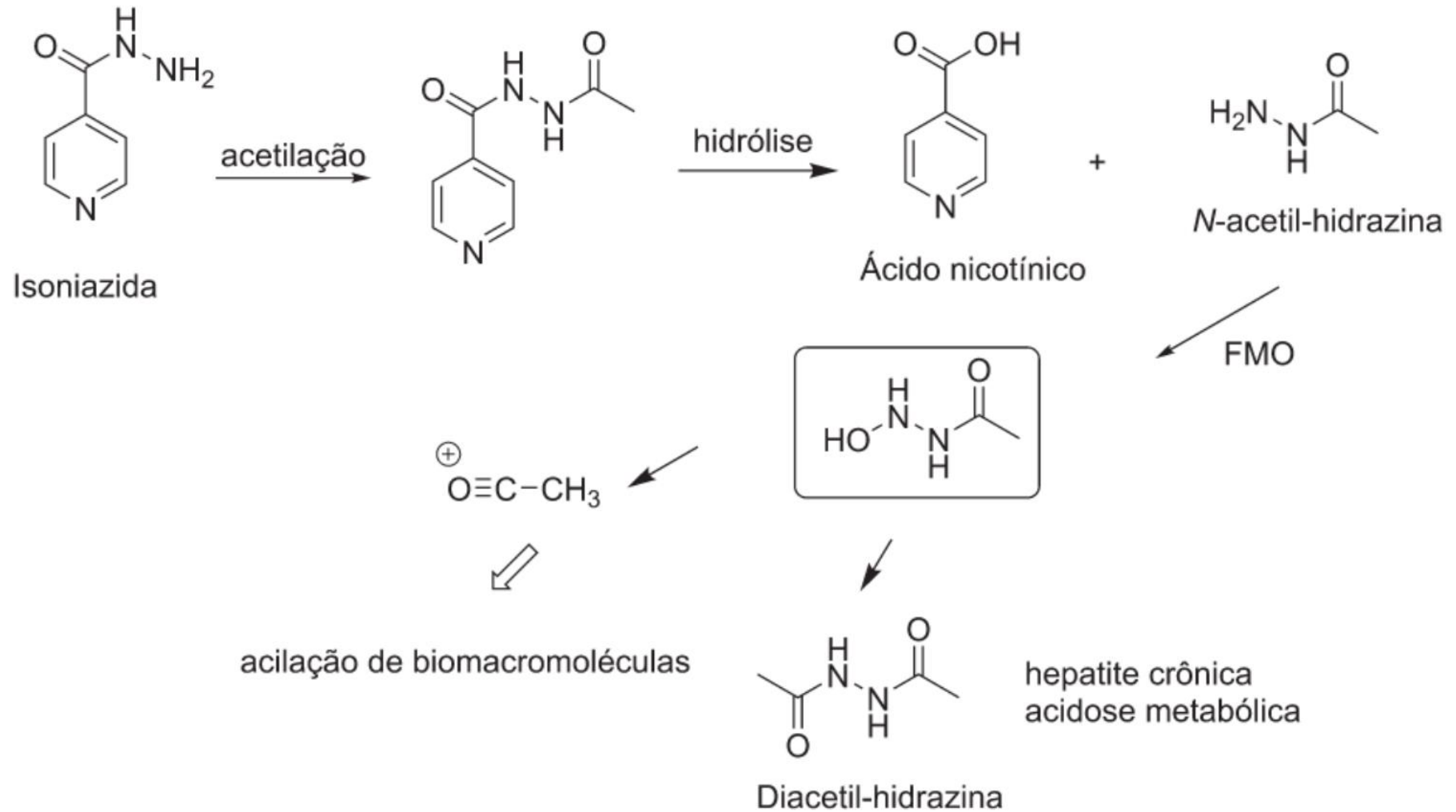




METABOLISMO

FASE II

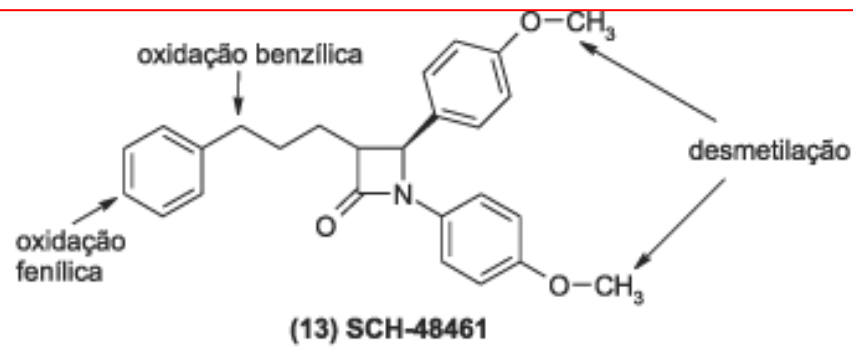
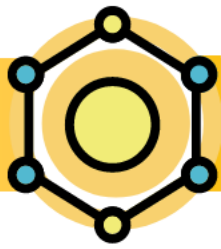
N-ACETILAÇÃO





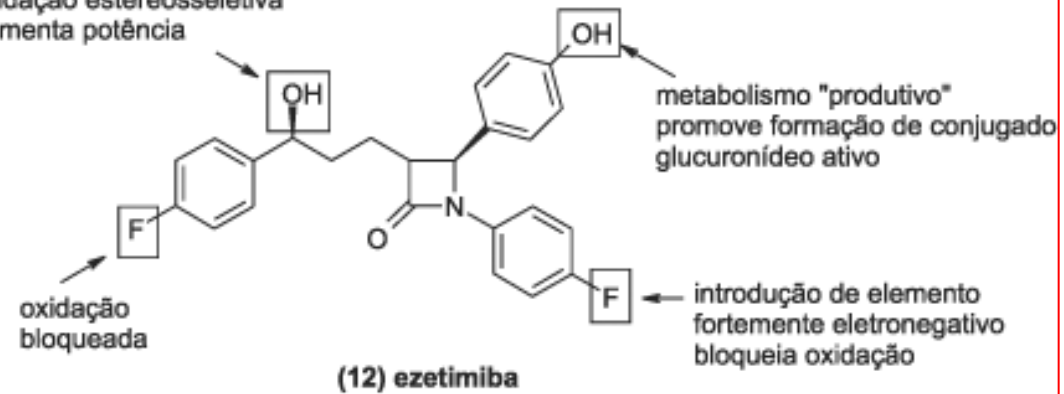
METABOLISMO E MODIFICAÇÃO MOLECULAR

STEPAN et al. *MedChemComm*, v.4, p.631-652, 2013.

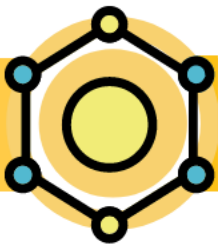


Otimização do
 metabolismo
 dirigida pela R.E.A.

metabolismo "produtivo"
 oxidação estereosseletiva
 aumenta potência

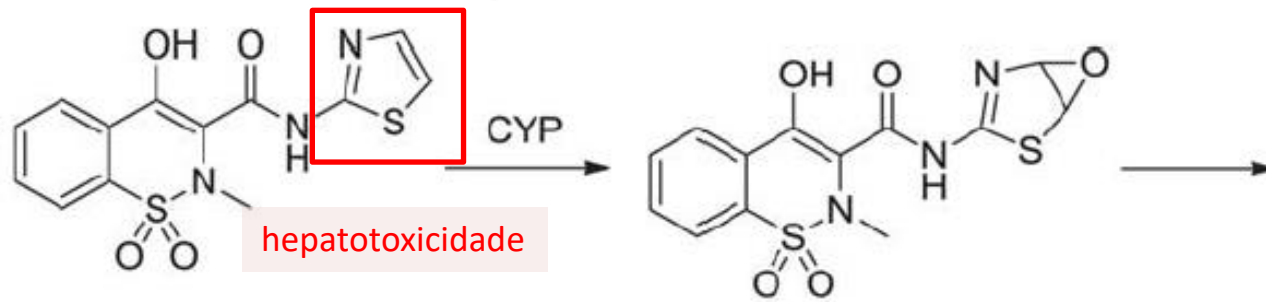


DE_{50} :	(12) SCH-48461	(13) ezetimiba
Hamster:	2,2 mg/kg	0,04 mg/kg
Rato:	2,0 mg/kg	0,03 mg/kg
Macaco:	0,2 mg/kg	0,0005 mg/kg
Cão:	0,1 mg/kg	0,007 mg/kg



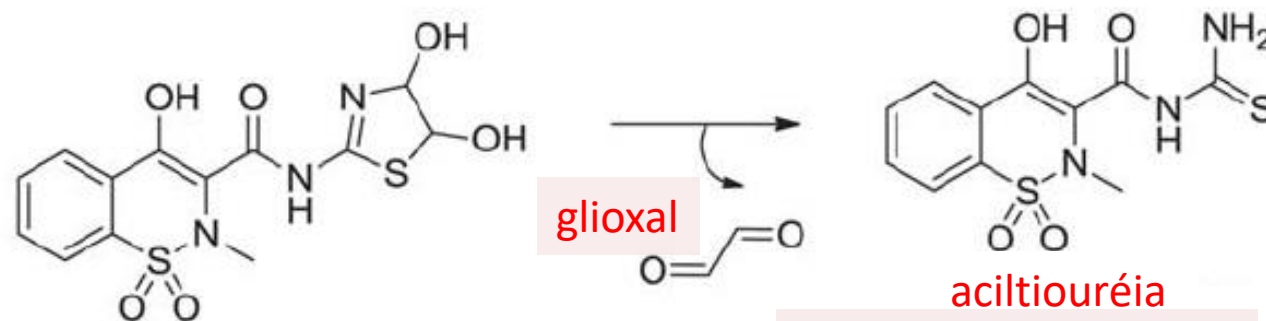
Anti-inflamatórios da classe dos oxicans

DIMINUIÇÃO DE TOXICIDADE

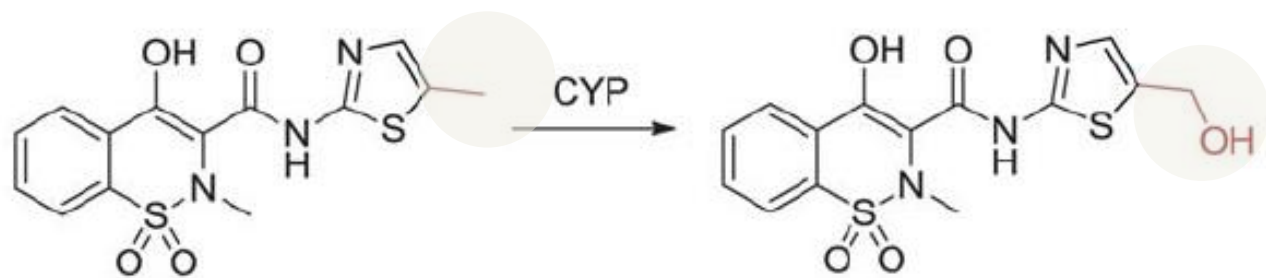


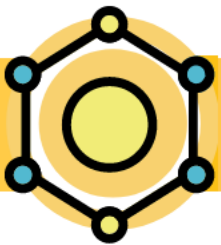
Sudoxicam

epóxido correspondente

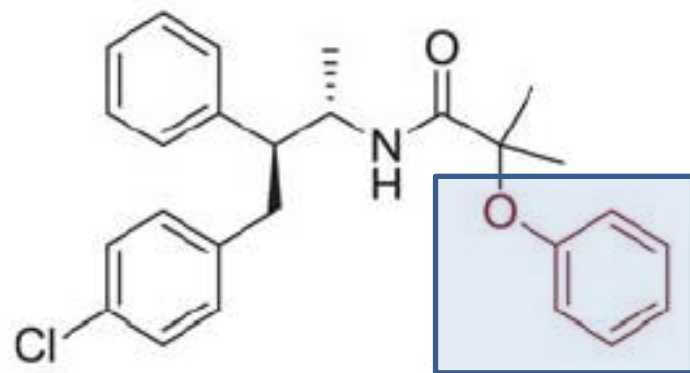


Oxidação de GSH e proteínas



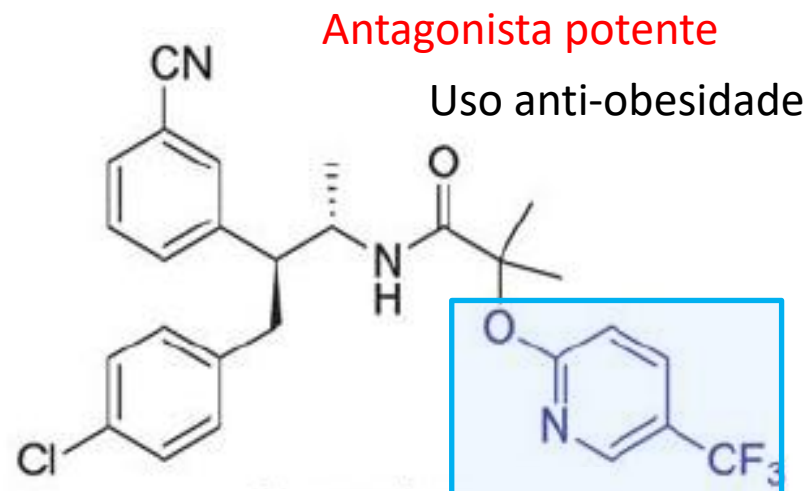


DIMINUIÇÃO DE TOXICIDADE



CB-1 IC_{50} : 2,0 nM

Metabólito reativo (óxido aromático)
Ligação covalente aos microsossomos

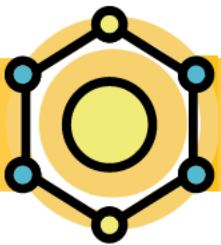


Taranabanto

CB-1 IC_{50} 0,3 nM

Metabólito não reativo ;
Sem ligação covalente

CB-1 – receptor canabinóide 1

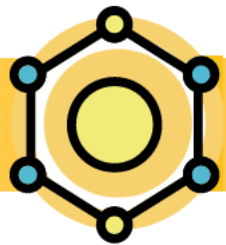


METABOLÔMICA

ÔMICA EMERGENTE E PROMISSORA PARA ENTENDER
OS MECANISMOS BIOLÓGICOS

APLICAÇÃO: ÁREAS CLÍNICAS, MEIO AMBIENTE, ALIMENTOS E
NUTRIÇÃO, TOXICOLOGIA FORENSE, MICROBIOLOGIA,
PARASITOLOGIA, PLANTAS E ESPORTES

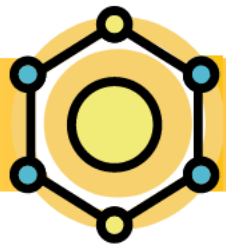
USO: TÉCNICAS ANALÍTICAS SOFISTICADAS E TRATAMENTO AVANÇADO DE
DADOS E DE ANÁLISES ESTATÍSTICAS



ELIMINAÇÃO

Fármacos podem ser eliminados por depuração biliar ou êntero-hepática, porém a eliminação por via urinária é mais importante.

- Idade
- Lipofilicidade
- Ionização
- pH da Urina



ELIMINAÇÃO

RINS - PRINCIPAL

PULMÕES

PELE

LEITE MATERNO

DUTO BILIAR

