Princípios de Química Medicinal

MedChem

24ª Semana da Química do Instituto de Química da UFRJ
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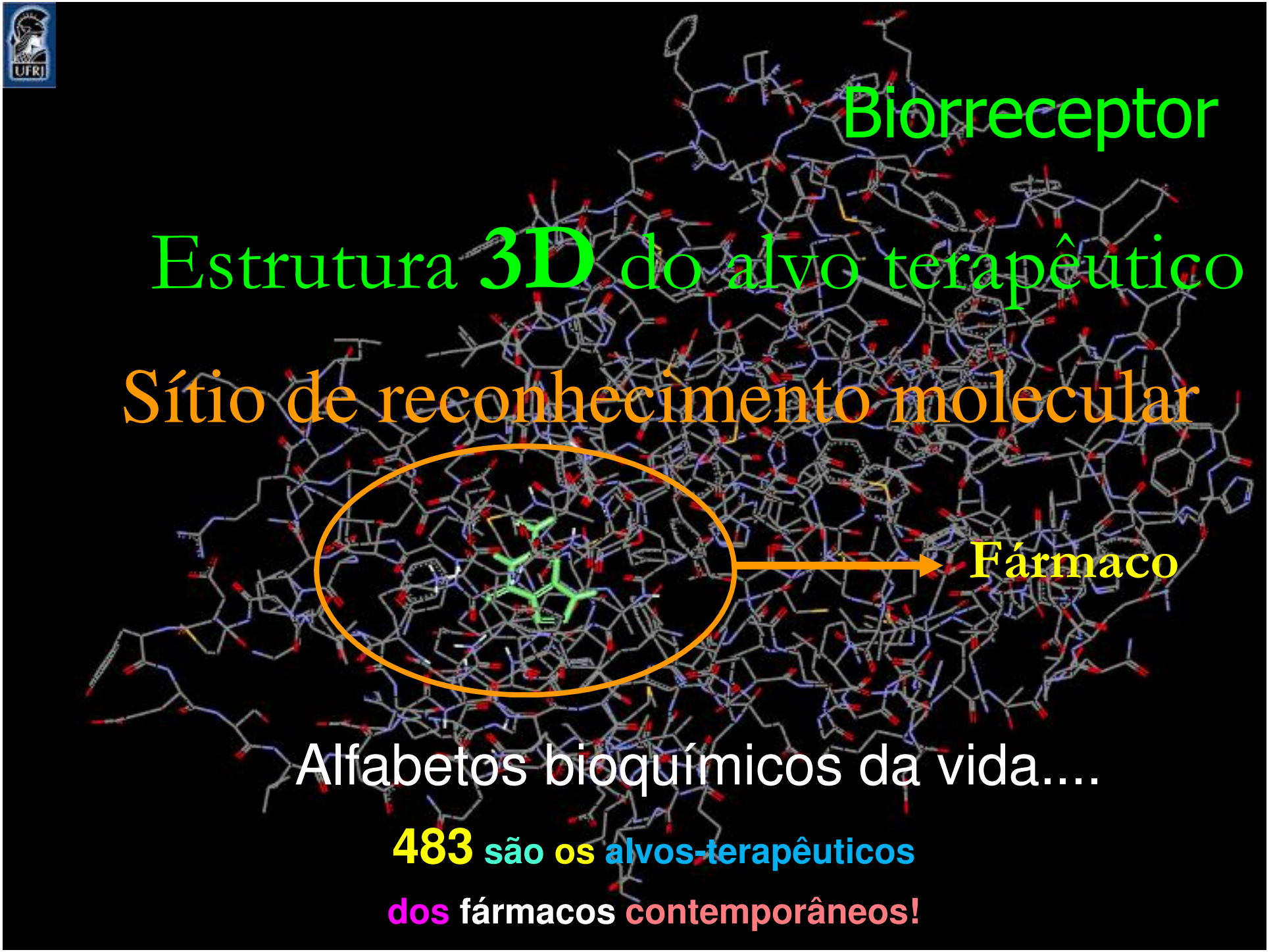
Professor Titular
Instituto de Ciências Biomédic
Universidade Federal do Rio de Janeiro

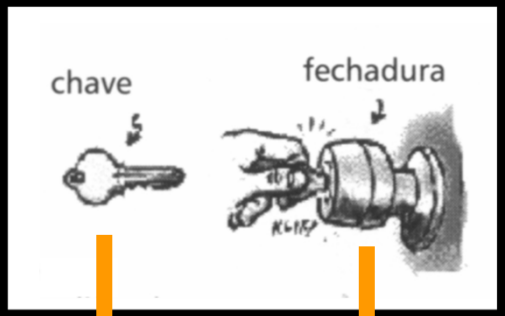
Parte 2

Sumário

Introdução; O processo de inovação de fármacos; O paradigma de Ehrlich & Fischer; Os alfabetos bioquímicos; As fases da ação dos fármacos; Aspectos moleculares da ação dos fármacos; Breve noção sobre o papel dos produtos naturais na descoberta de fármacos; Aspectos da química computacional: modelagem molecular; Estratégias para o desenho de novos candidatos a fármacos; Exemplos selecionados: LASSBio-UFRJ.

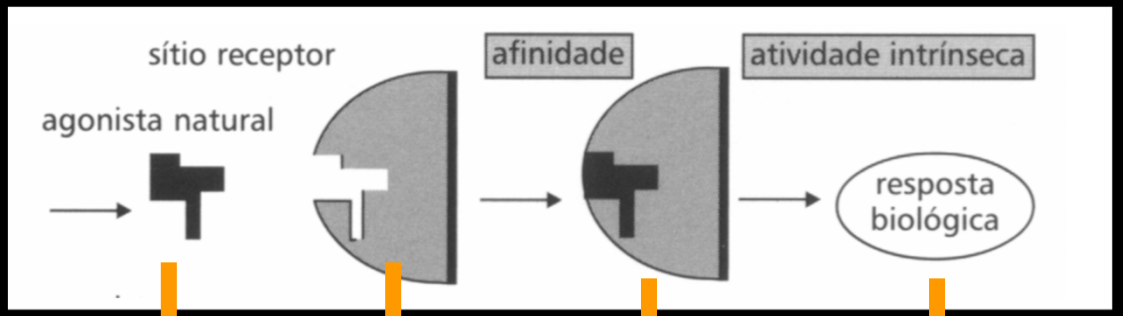

Biorreceptor
Estrutura 3D do alvo terapêutico
Sítio de reconhecimento molecular
Fármaco
Alfabetos bioquímicos da vida....
483 são os alvos-terapêuticos
dos fármacos contemporâneos!

O Centenário Modelo *"Chave-Fechadura"*



Fármaco Substrato natural

Enzima = Alvo terapêutico

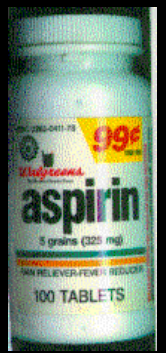


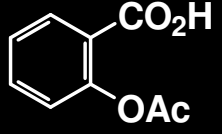
Ácido araquidônico

PGHS-1
PGHS-2

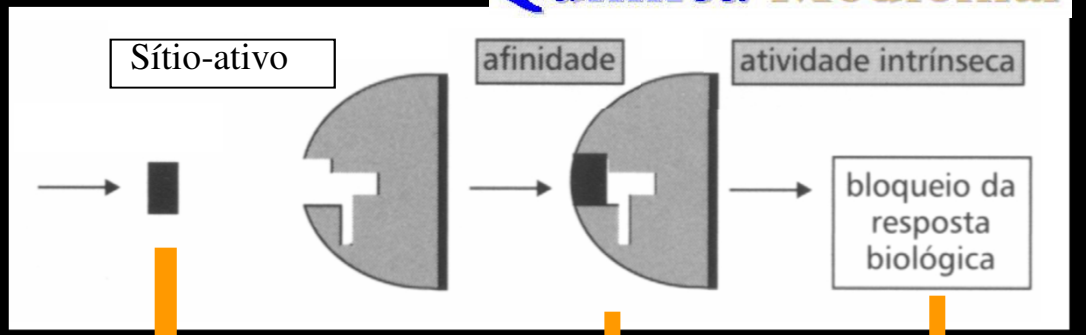
PGE_2 icosanóide

inflamação





Química Medicinal



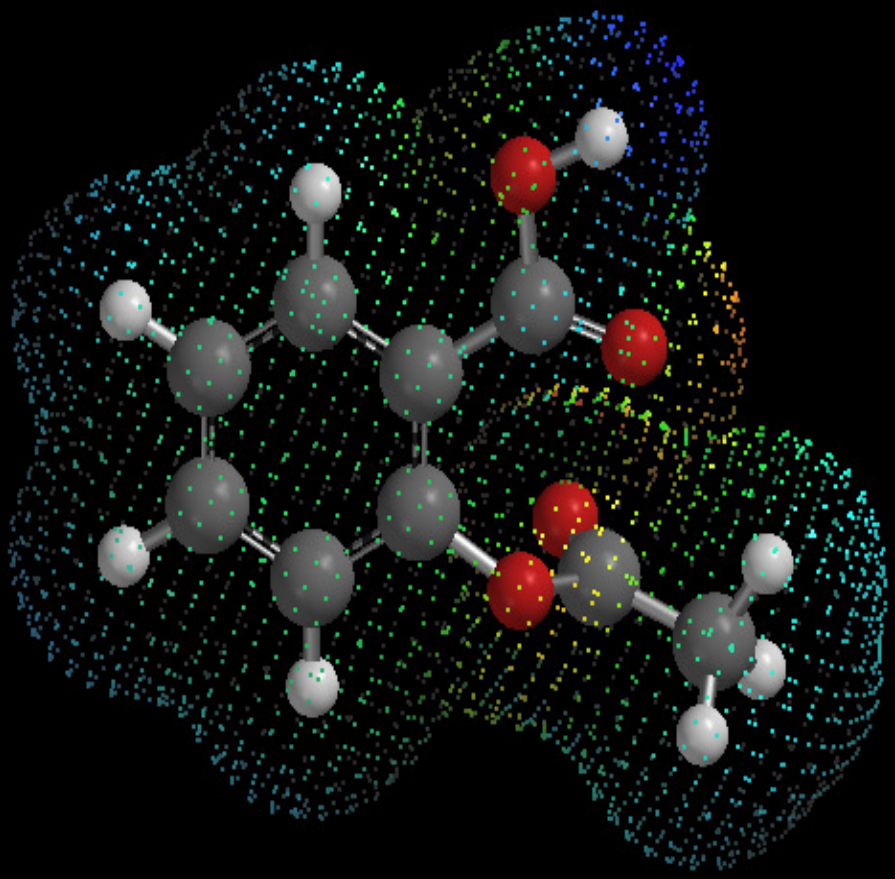
Inibidor: AAS

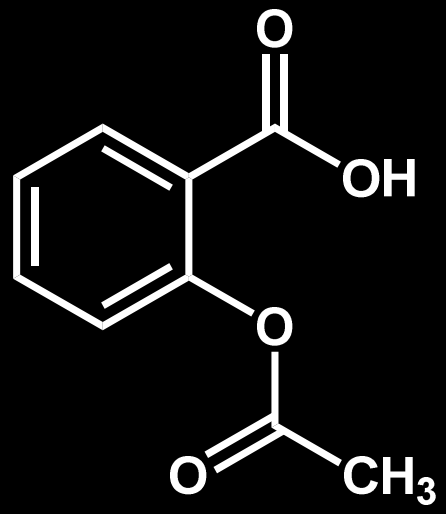
PGHS-2
PGHS-1

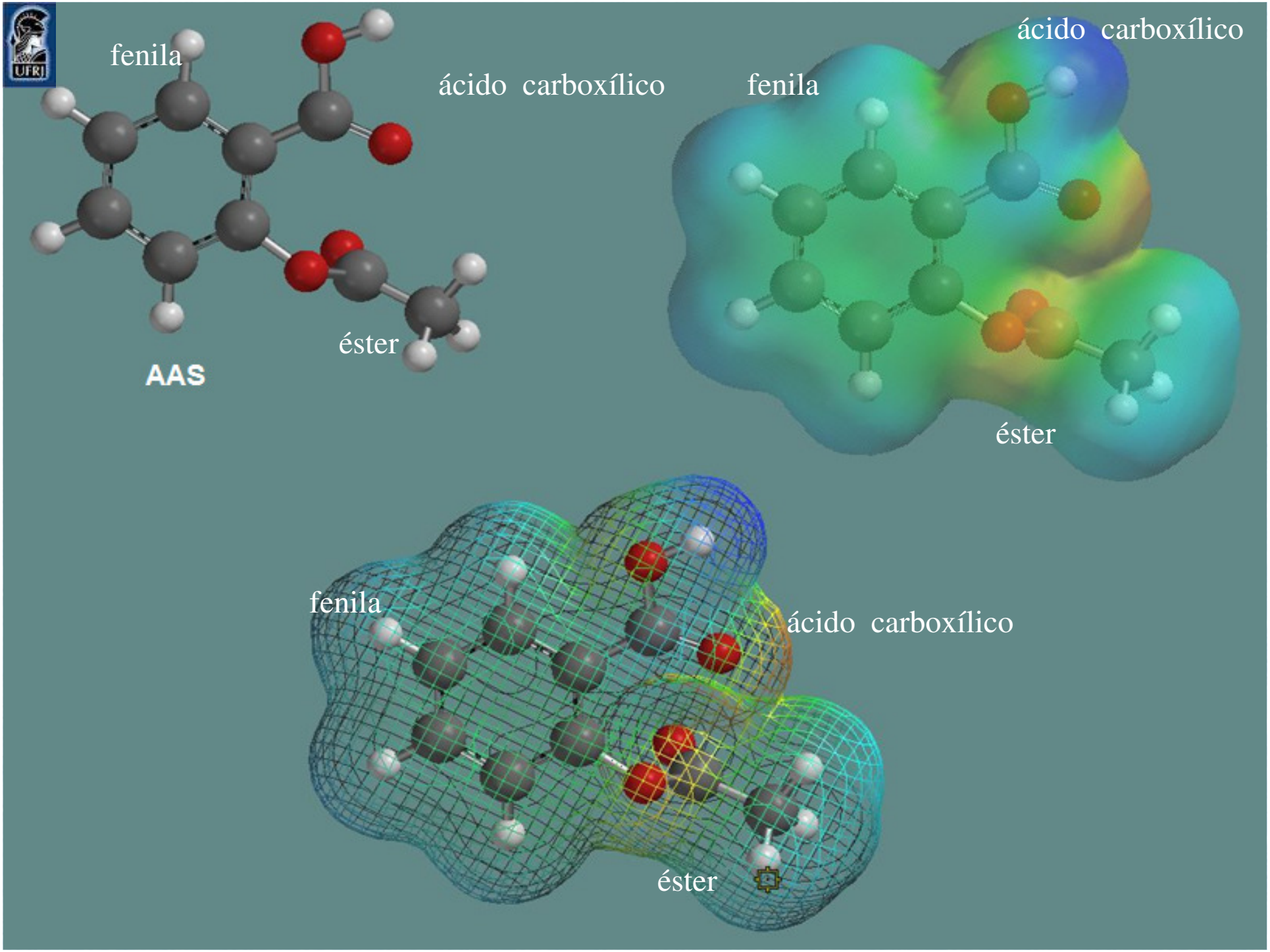
NSAI

NSAI = antiinflamatórios não-esteróides

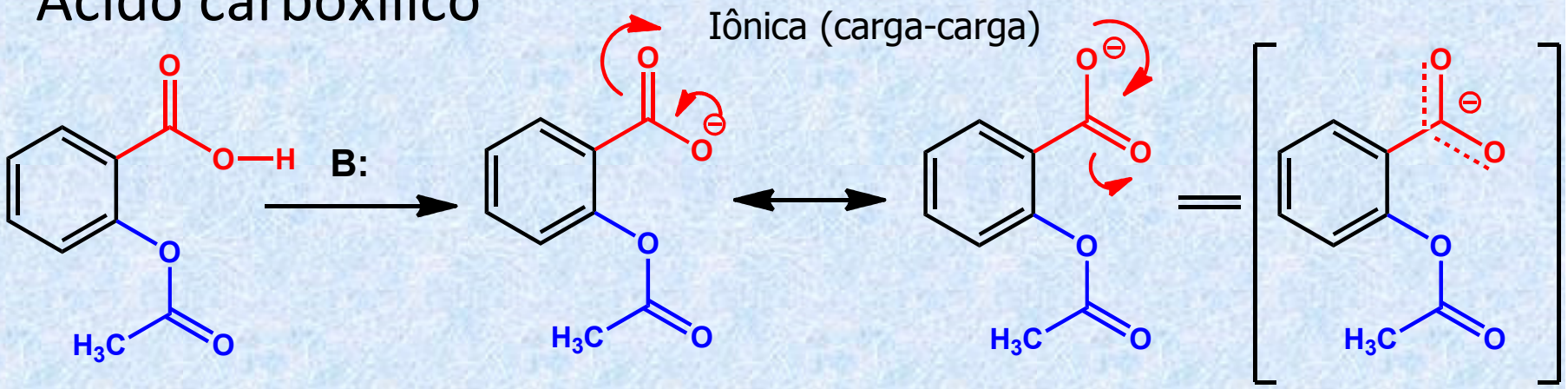
Ácido acetil salicílico



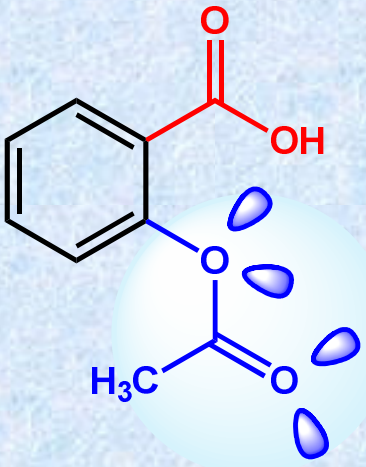



fenila
ácido carboxílico
éster
AAS
ácido carboxílico
fenila
éster
fenila
ácido carboxílico
éster

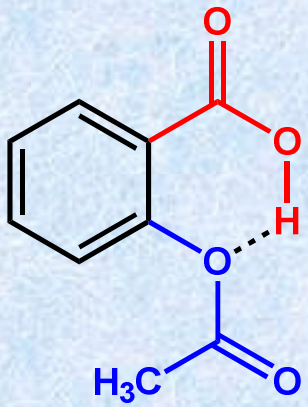
Ácido carboxílico



Éster

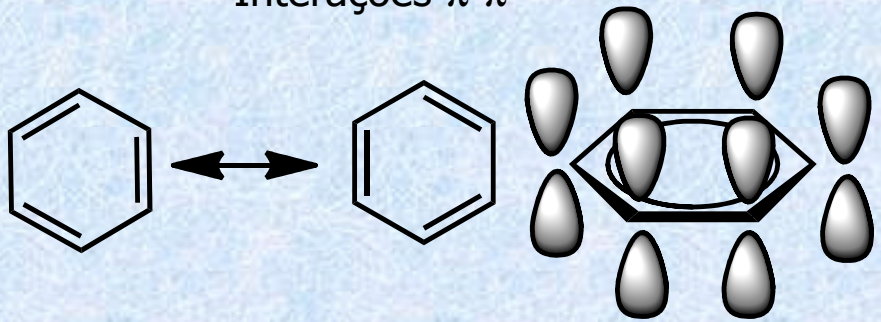


Ligação-H



Fenila

Interações π-π



Grupos funcionais

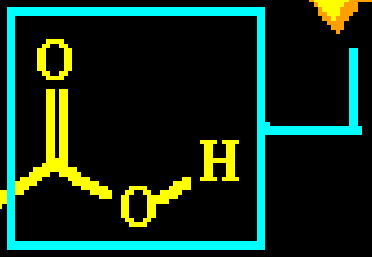
Molecularizando o Modelo *"Chave-Fechadura"*

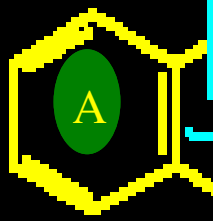
Complementaridade do modelo Chave-fechadura

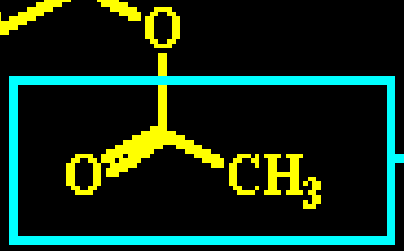
complementaridade molecular

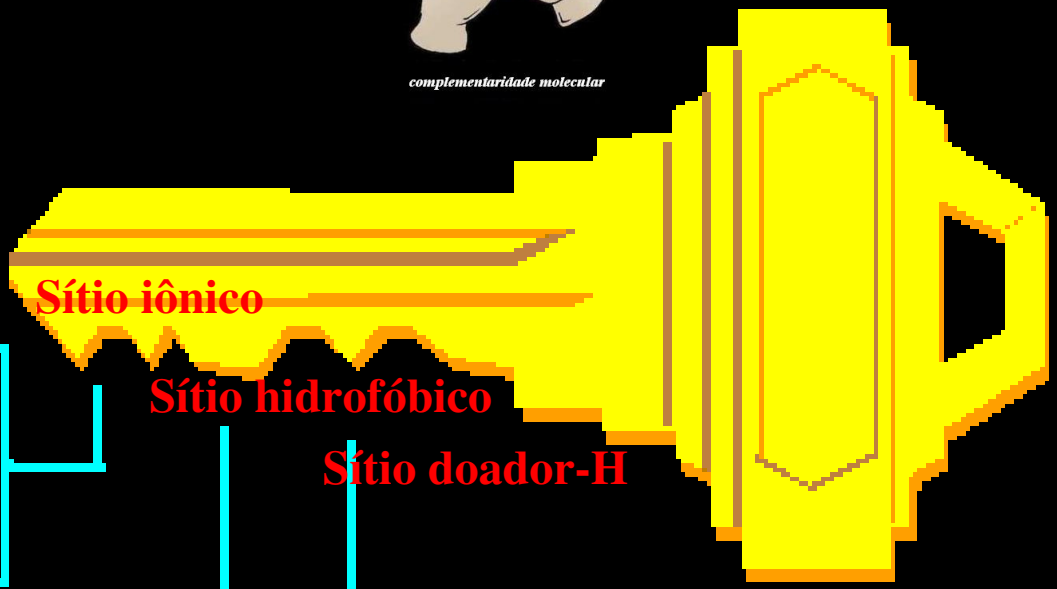
Sítio iônico

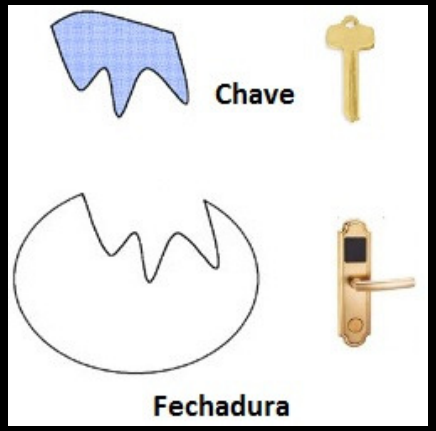
AAS

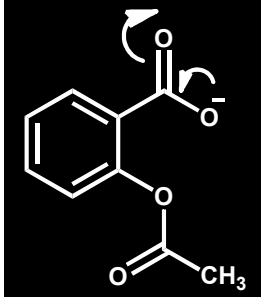






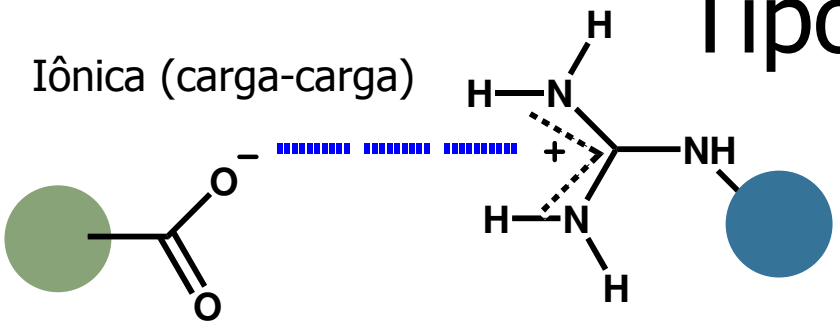






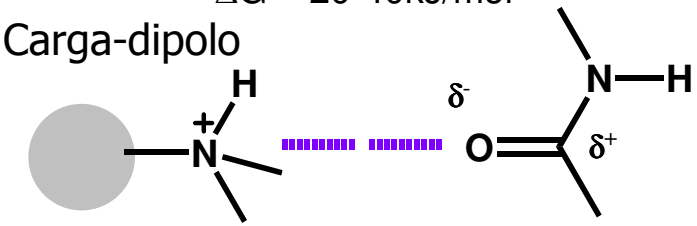
Tipos de interações F-R

Iônica (carga-carga)



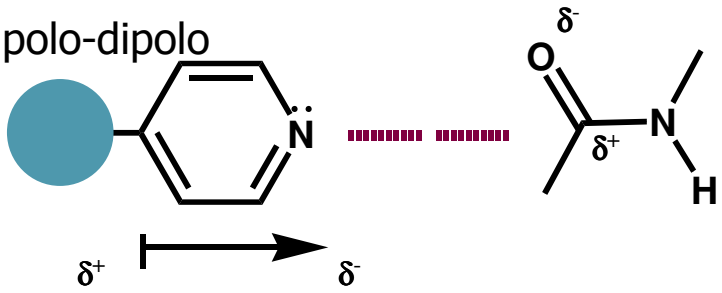
ΔG = 20-40kJ/mol

Carga-dipolo



ΔG = 12-20kJ/mol

Dipolo-dipolo

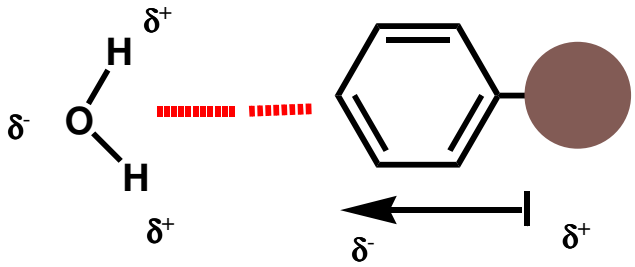


ΔG = 4-12 kJ/mol

Carga-dipolo induzido

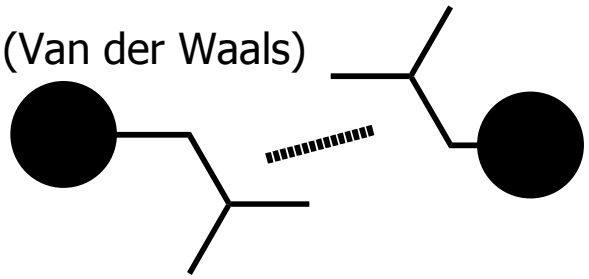
ΔG = 2-10 kJ/mol

Dipolo induzido-dipolo



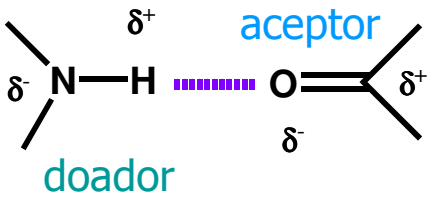
ΔG = 2 kJ/mol

Dispersão (Van der Waals)



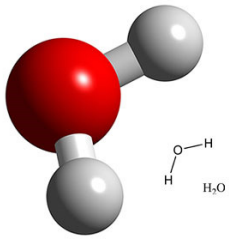
ΔG = 2-4 kJ/mol

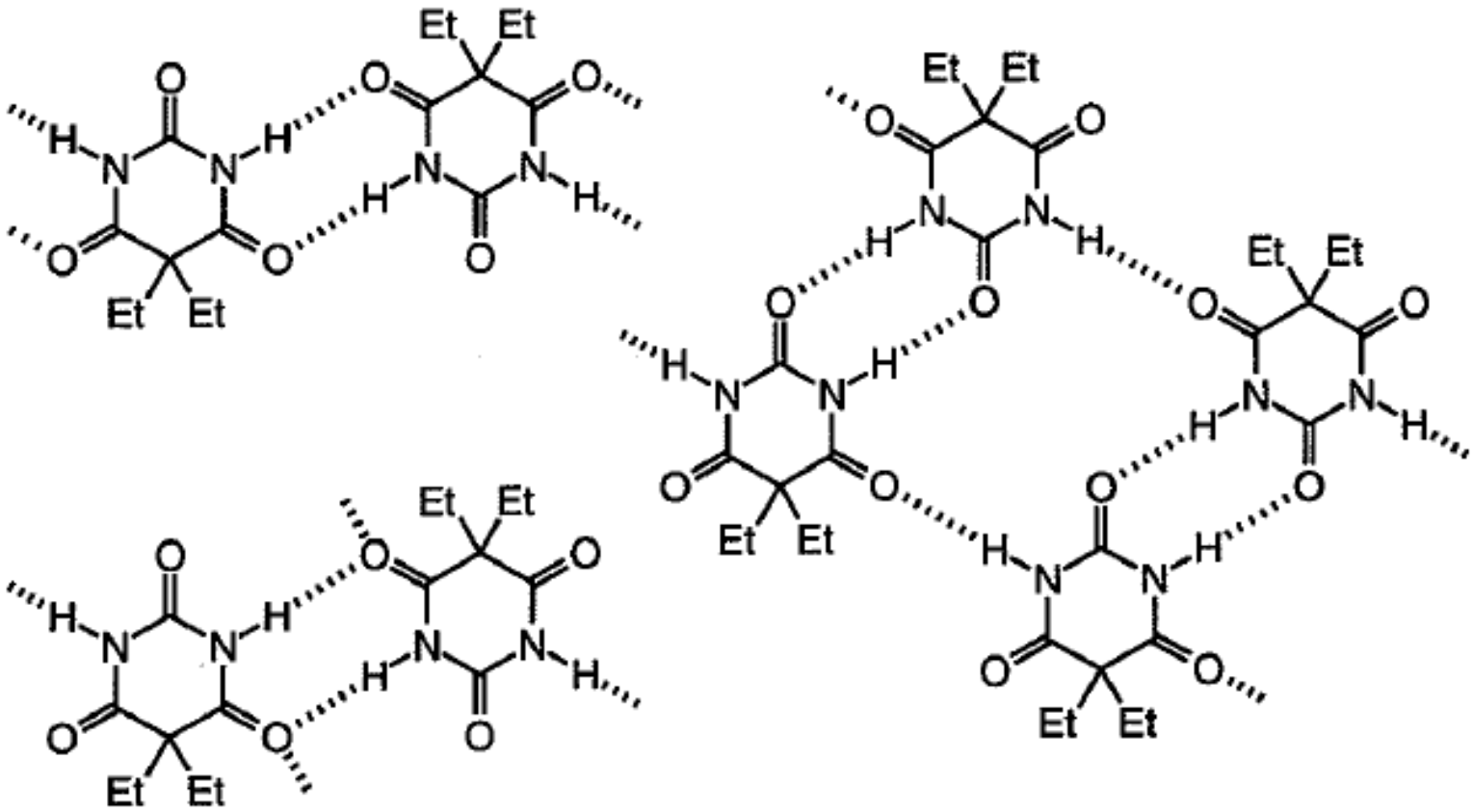
Ligação-H



ΔG = 4-30 kJ/mol

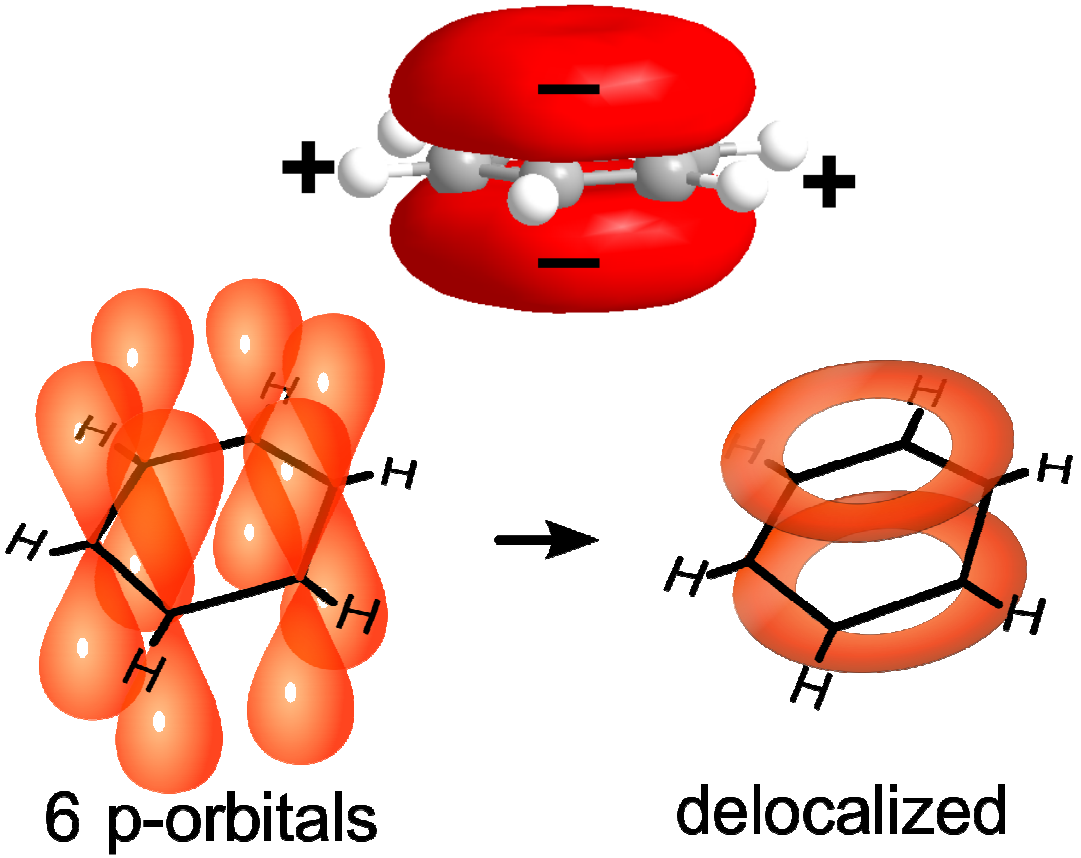
Consequências ligação-H

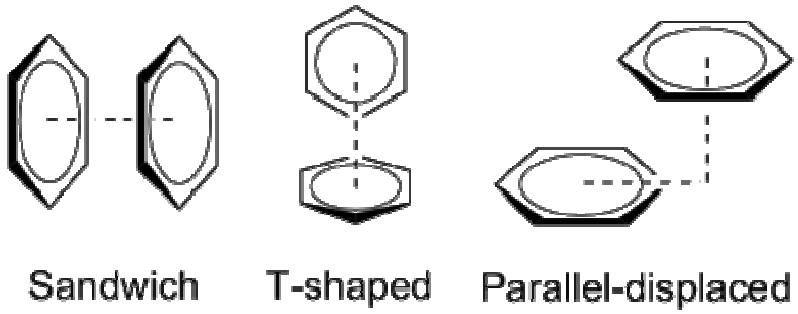


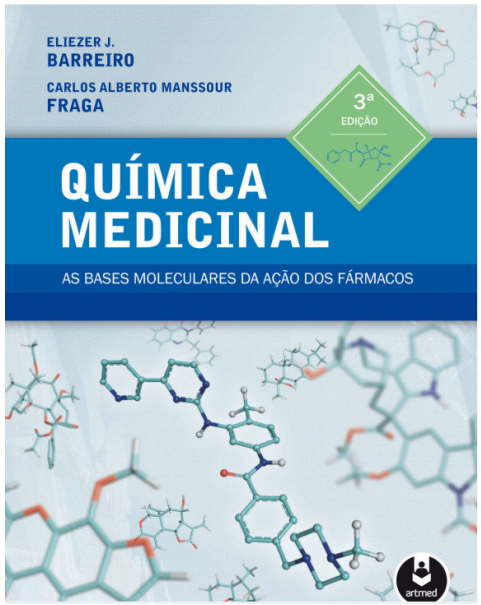


polymorphs of 5,5-diethylbarbituric acid.

Interações π



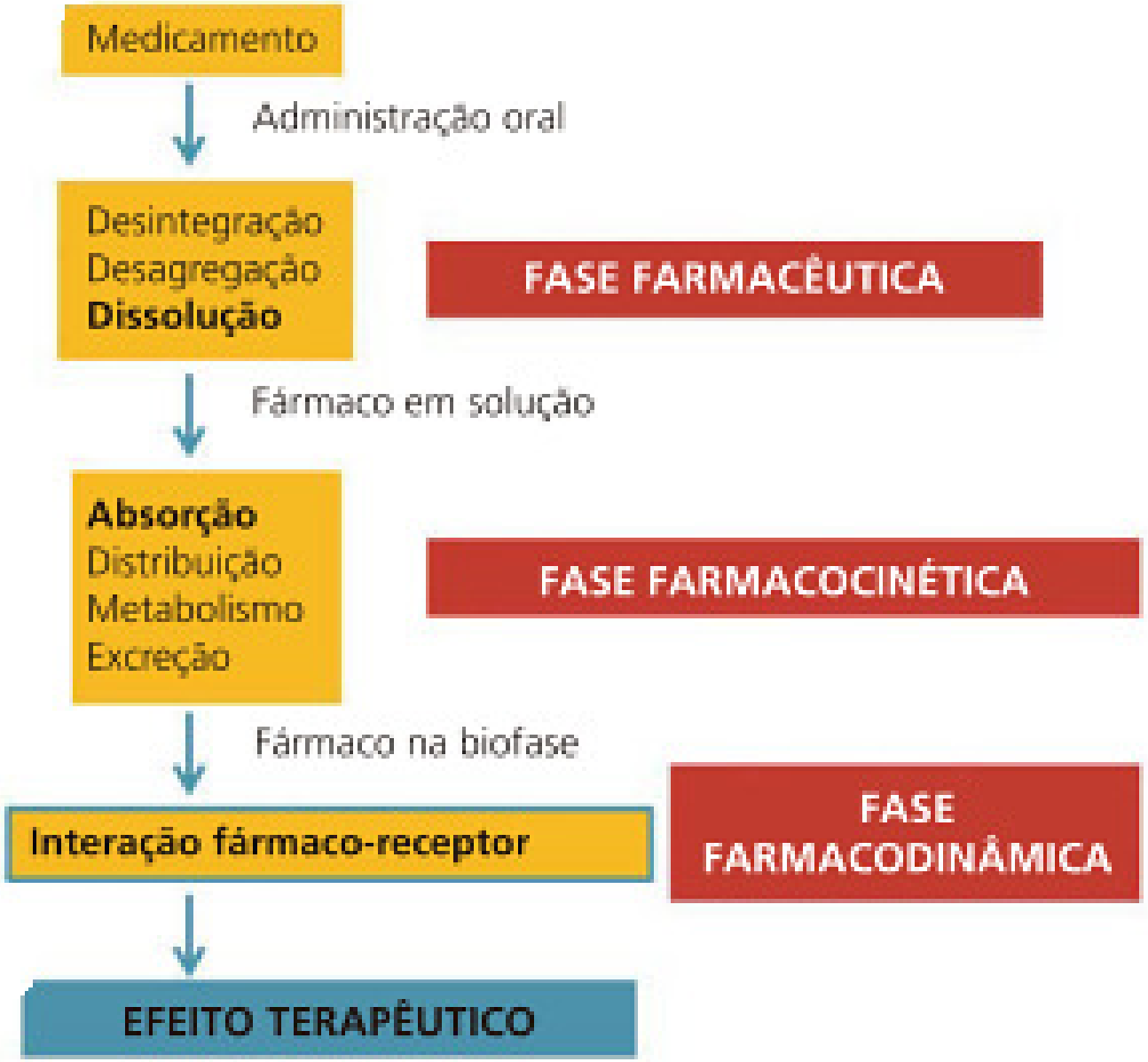


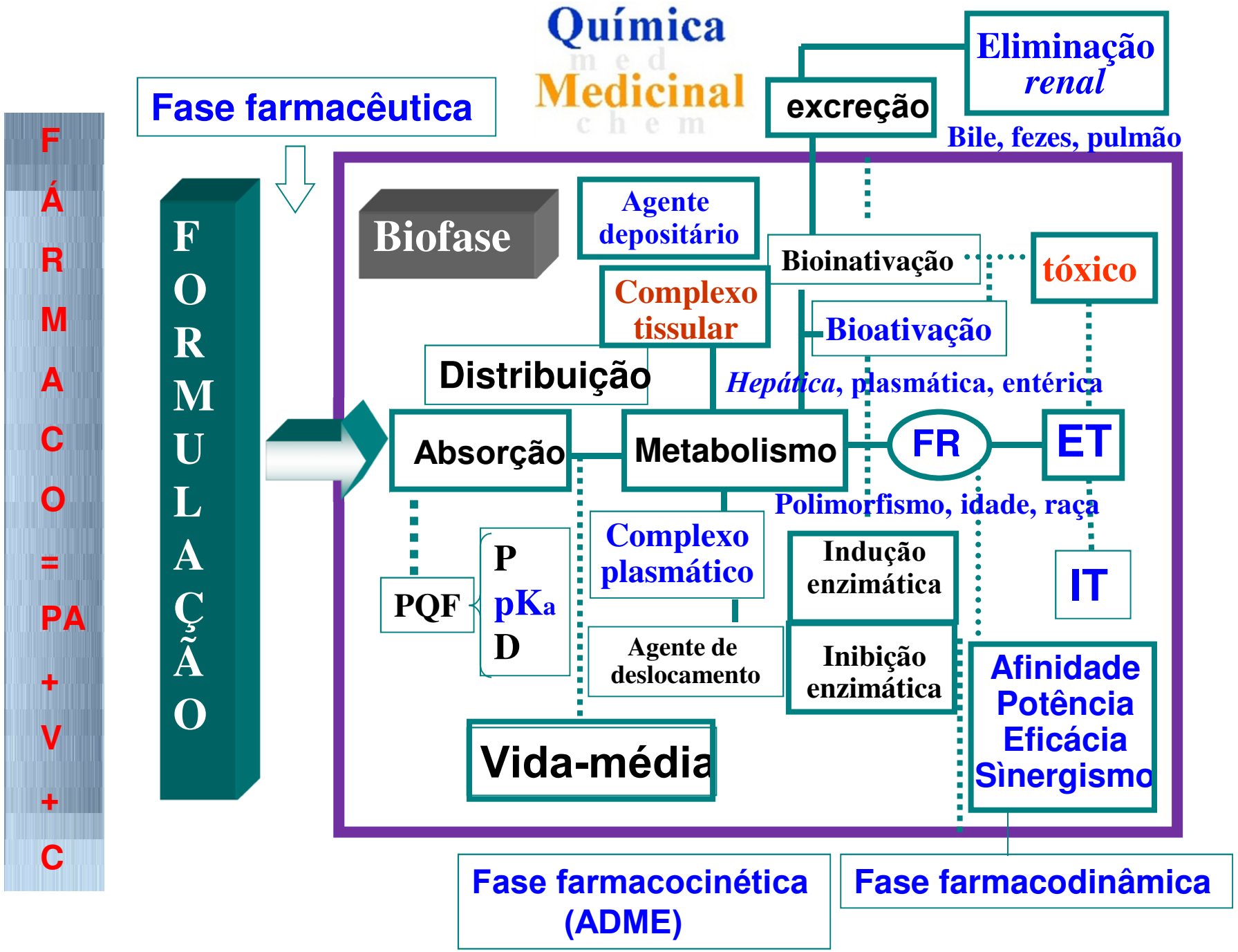


CAPÍTULO 1

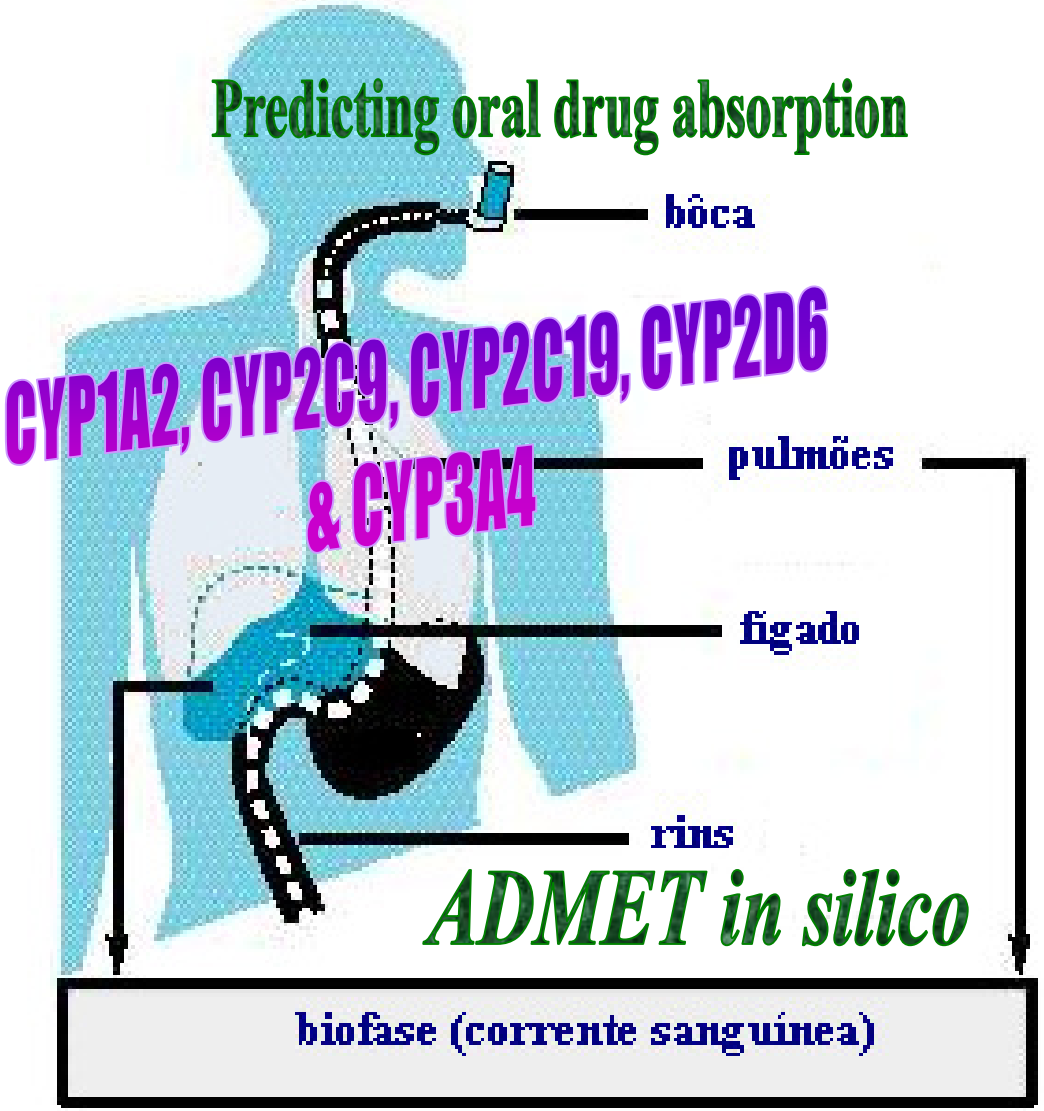
ASPECTOS GERAIS DA AÇÃO DOS FÁRMACOS 1

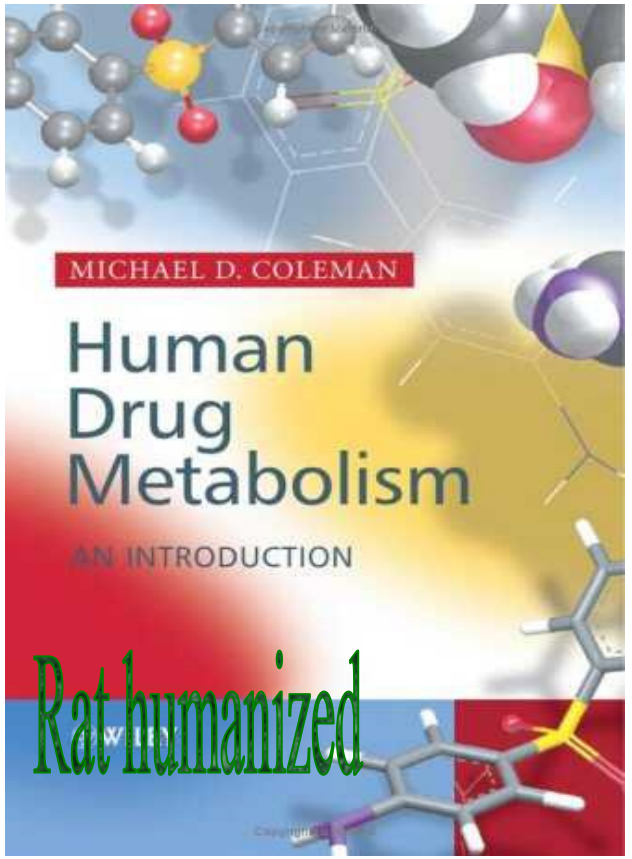
As fases da ação dos fármacos




Química
med
Medicinal
chem
FÁRMACO = PA + V + C
Fase farmacêutica
FORMULAÇÃO
Biofase
Agente depositário
Complexo tissular
Distribuição
Absorção
Metabolismo
FR
ET
IT
PQF
P
pKa
D
Complexo plasmático
Agente de deslocamento
Indução enzimática
Inibição enzimática
Vida-média
Afinidade
Potência
Eficácia
Sinergismo
excreção
Eliminação renal
Bile, fezes, pulmão
Bioinativação
tóxico
Bioativação
Hepática, plasmática, entérica
Polimorfismo, idade, raça
Fase farmacocinética (ADME)
Fase farmacodinâmica

Fase Farmacocinética



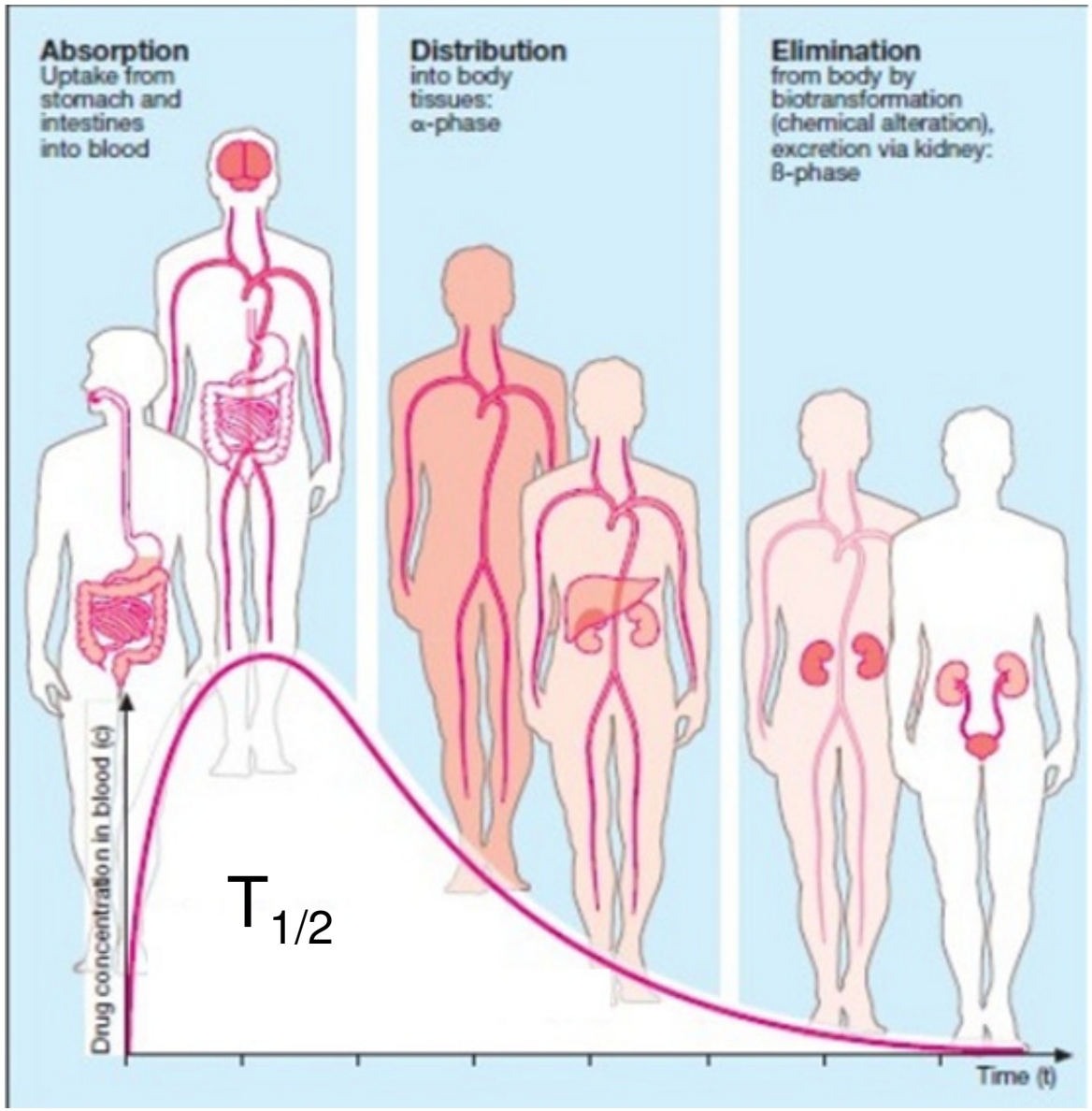


- absorção, distribuição, metabolismo & eliminação

PK

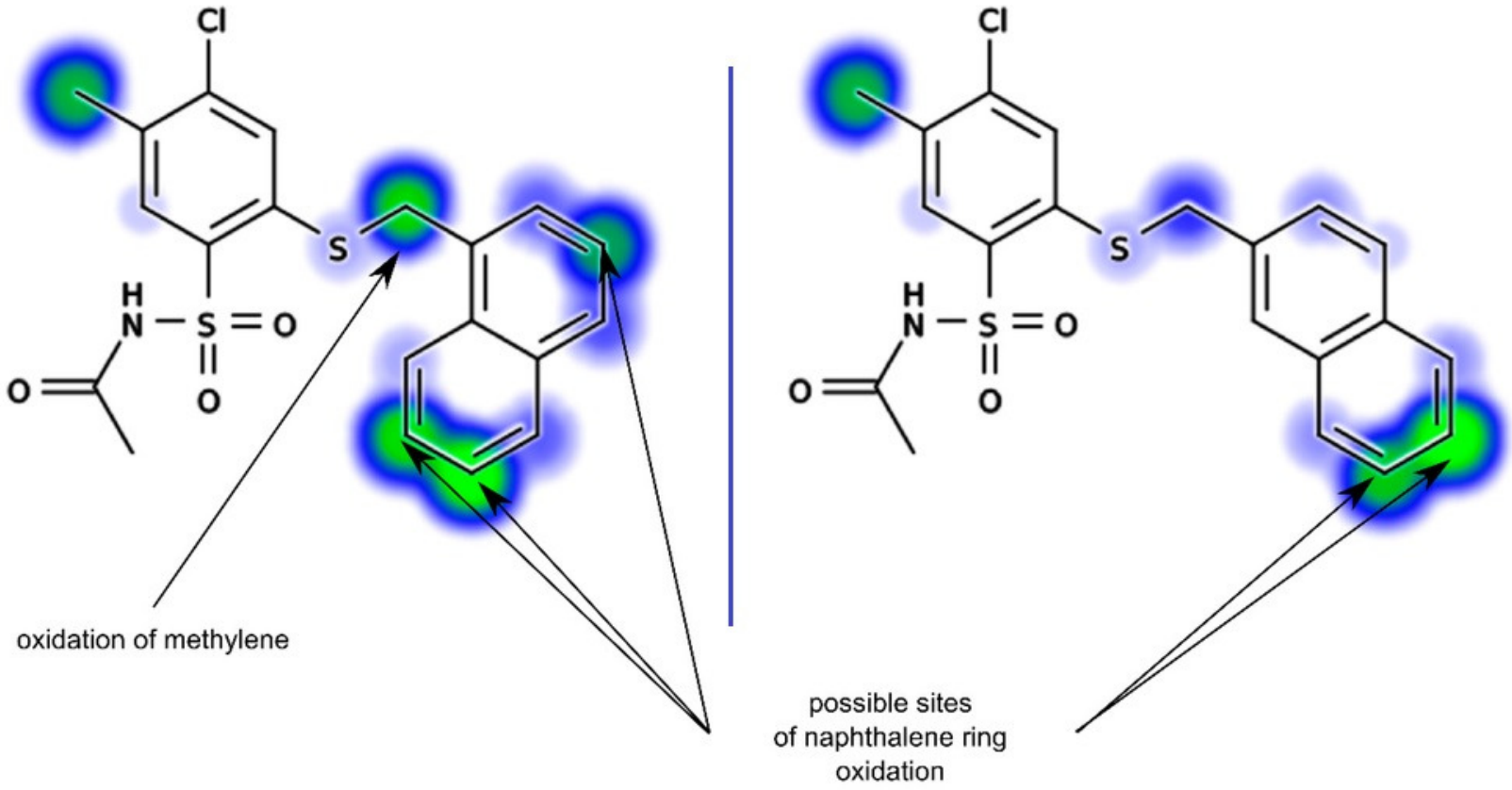
A D E

A D M E

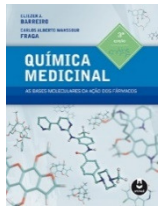


Posologia

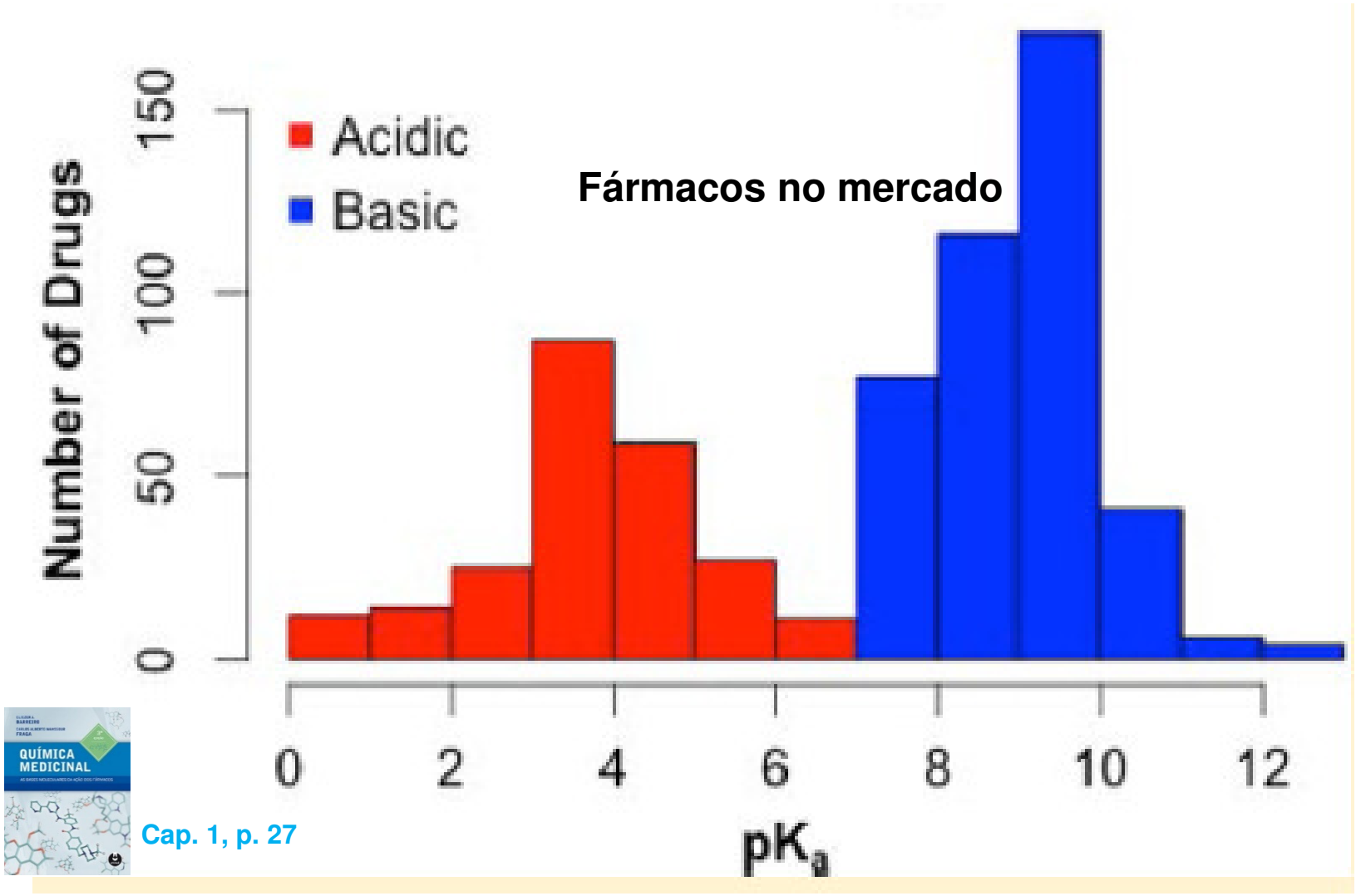
Metabolismo de fármacos



CAPÍTULO 2
FUNDAMENTOS DO METABOLISMO DE FÁRMACOS 43

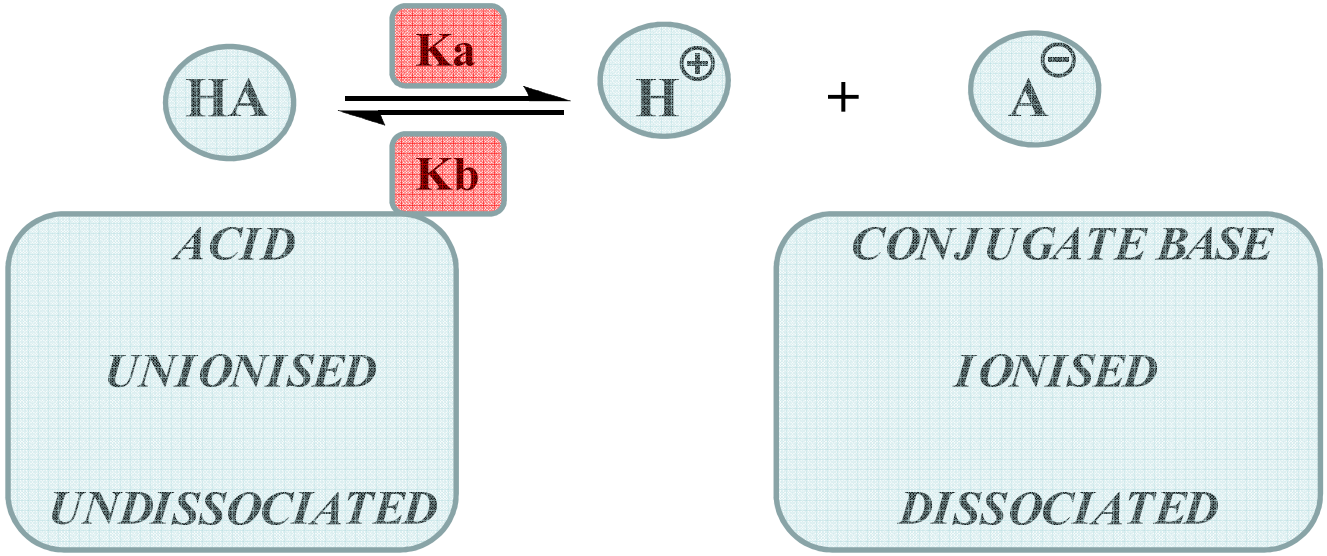


Propriedades físico-químicas

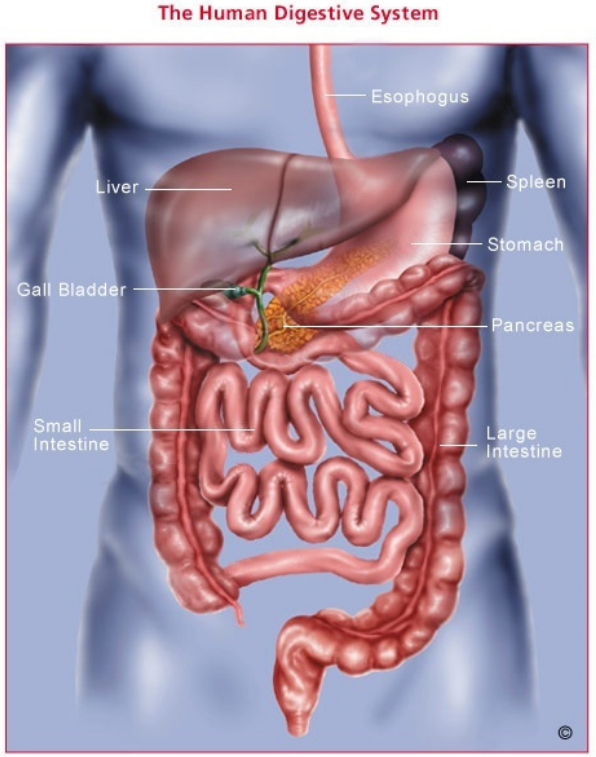


Cap. 1, p. 27

OS Charifson, WP Walters, Acidic and basic drugs in medicinal chemistry: a perspective, *J. Med. Chem.* **2014**, *57*, 9701

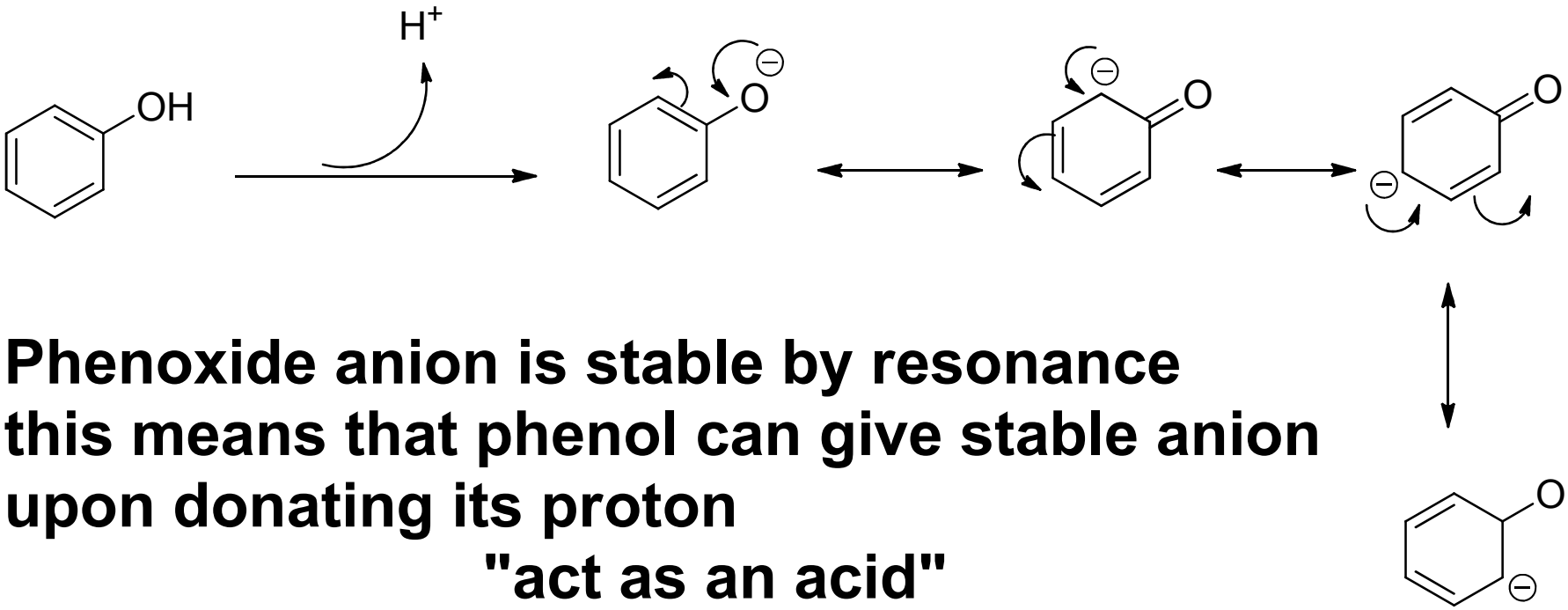


Plasma	7.35 – 7.45
Buccal cavity	6.2 – 7.2
Stomach	1.0 – 3.0
Duodenum	4.8 – 8.2
Jejunum & ileum	7.5 – 8.0
Colon	7.0 – 7.5



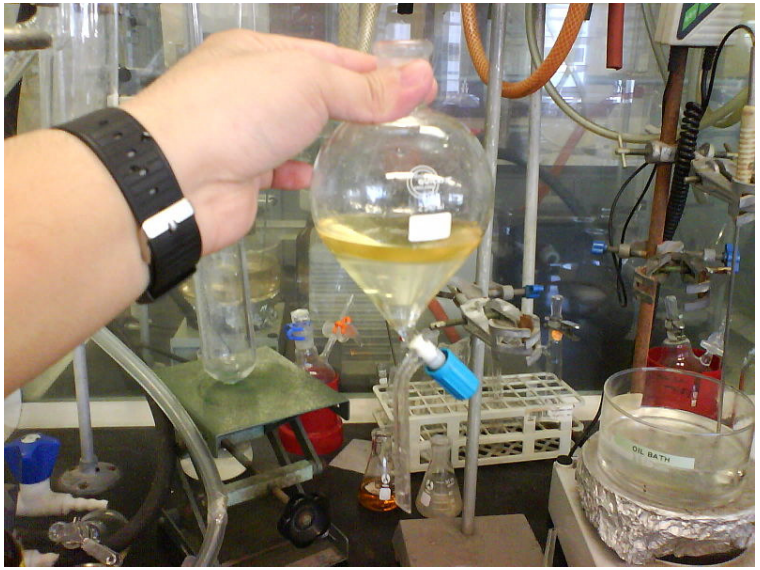
Propriedades Moleculares

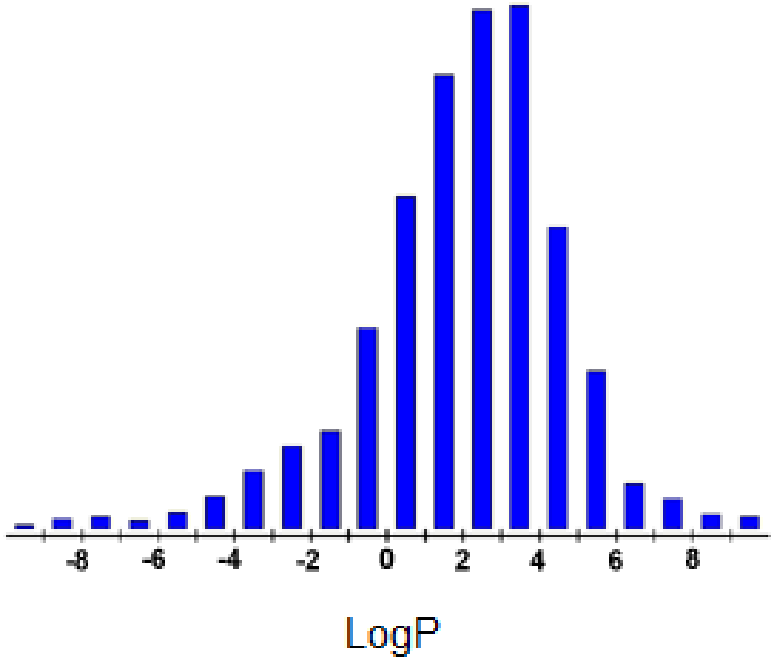
Acidez & basicidade



Phenoxide anion is stable by resonance
this means that phenol can give stable anion upon donating its proton
"act as an acid"

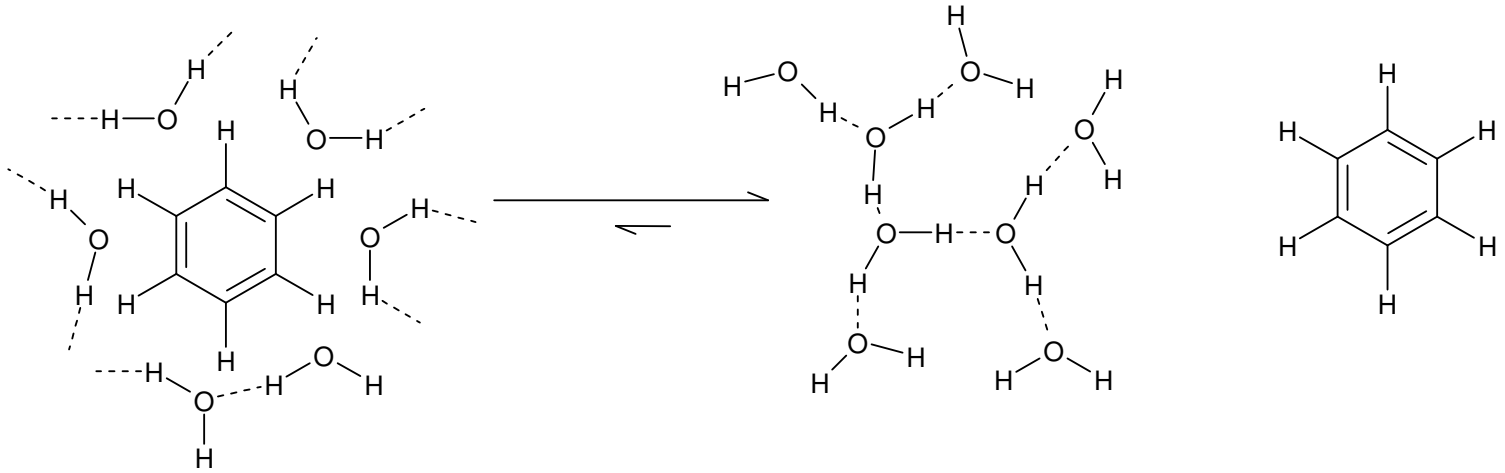
Coeficiente de Partição





$$\log\ P_{\mathrm{oct/wat}} = \log\left(\frac{[\mathrm{solute}]^{\mathrm{un-ionized}}_{\mathrm{octanol}}}{[\mathrm{solute}]^{\mathrm{un-ionized}}_{\mathrm{water}}}\right)$$

O efeito hidrofóbico

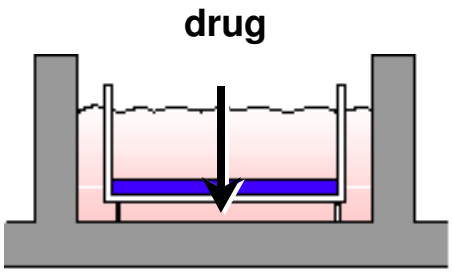


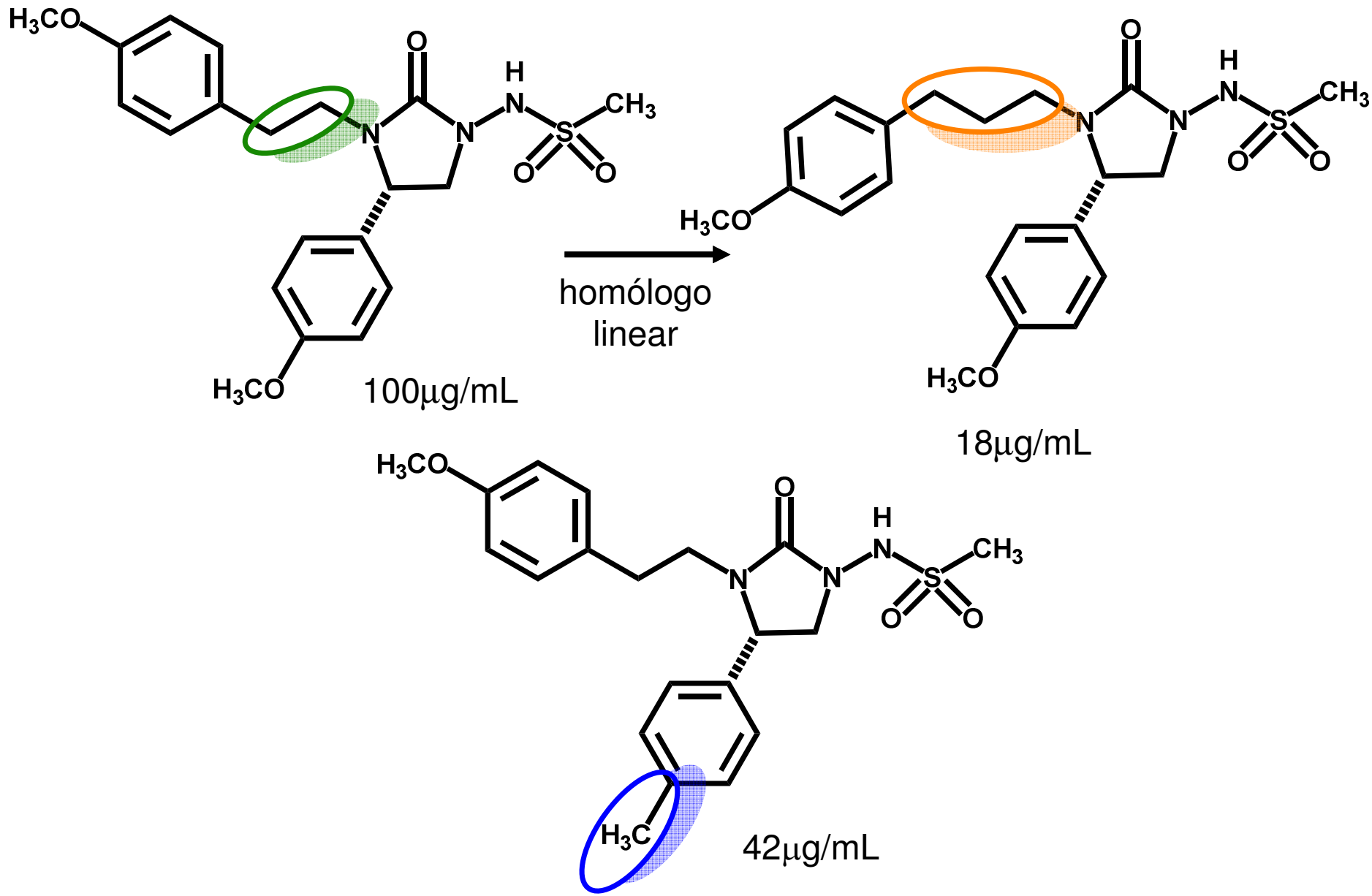
Pampa (Parallel Artificial Membrane Permeability Assay)

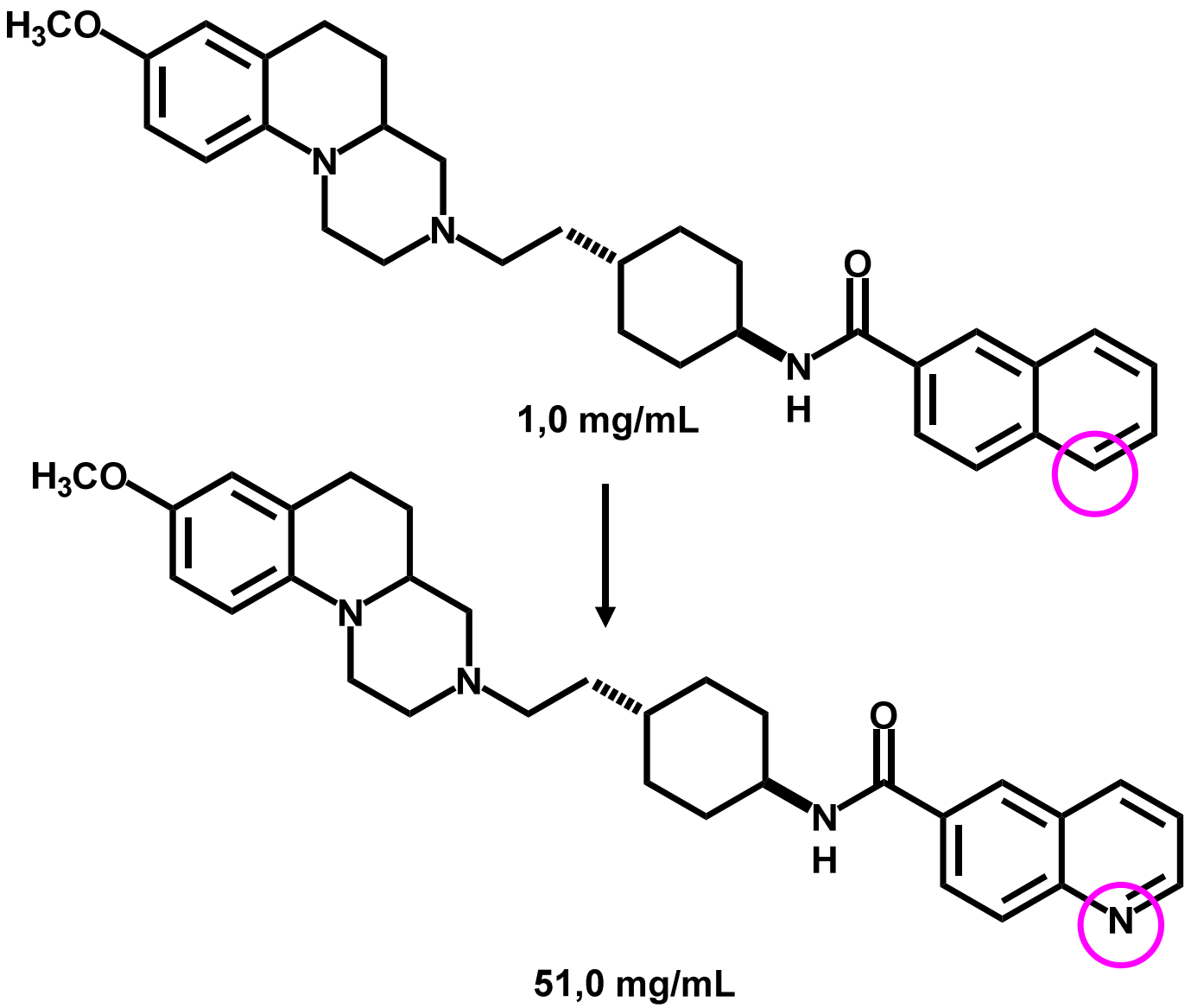
Artificial membrane separates 2 compartments

Models transcellular (passive) absorption only

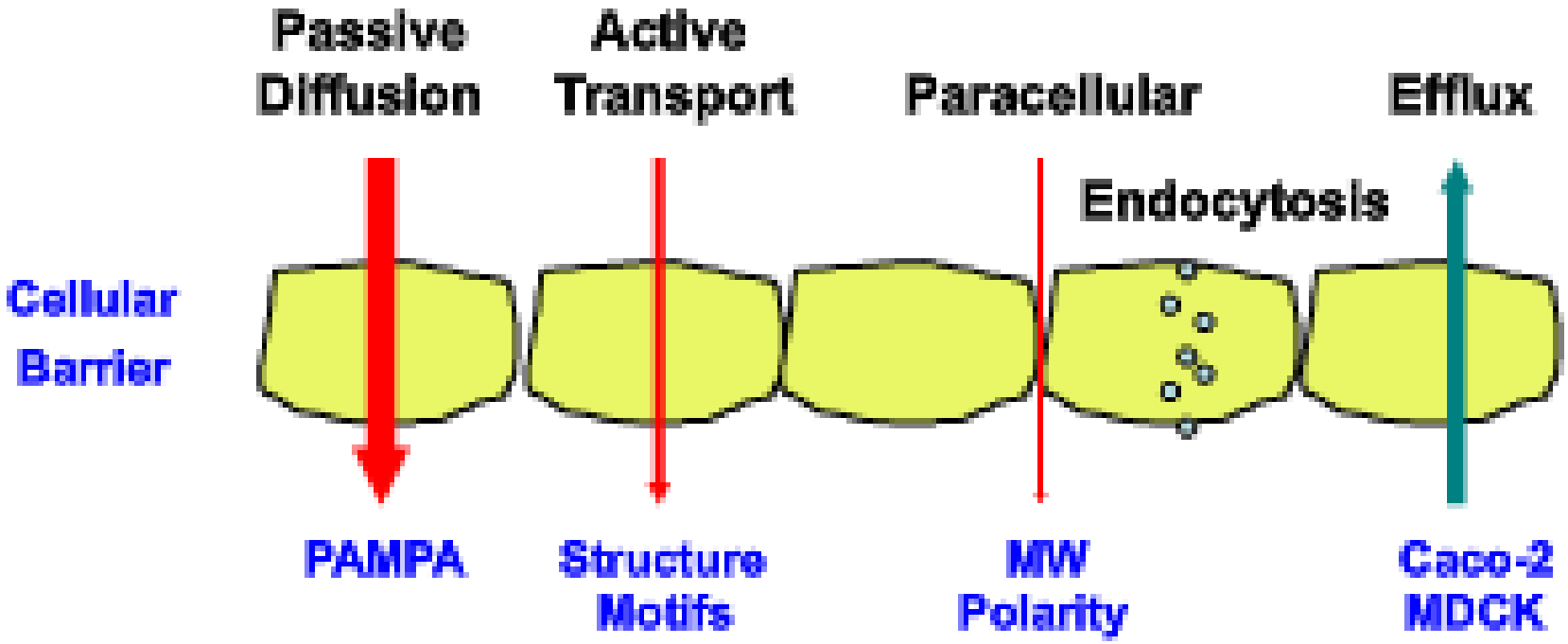
No tissue culture



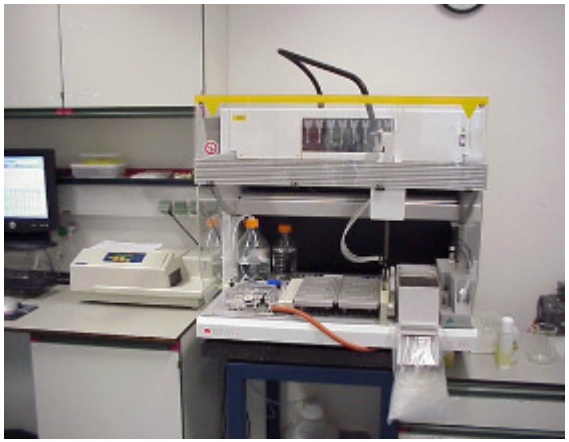

homólogo
linear
100µg/mL
18µg/mL
42µg/mL


H3CO
N
N
O
N
H
1,0 mg/mL
H3CO
N
N
O
N
H
N
51,0 mg/mL

Bioensaios de permeabilidade

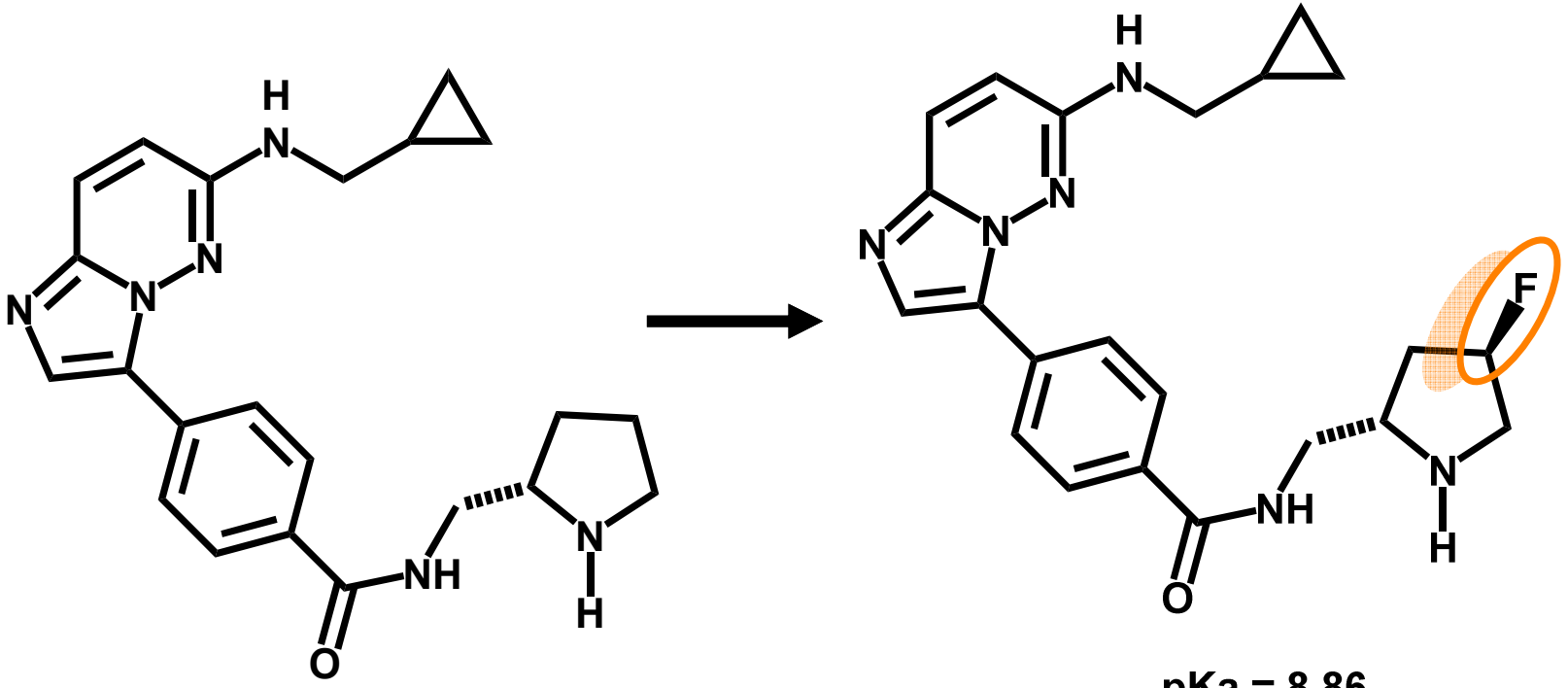


LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas



Substâncias muito básicas (pKa > 8,8) têm baixa permeabilidade

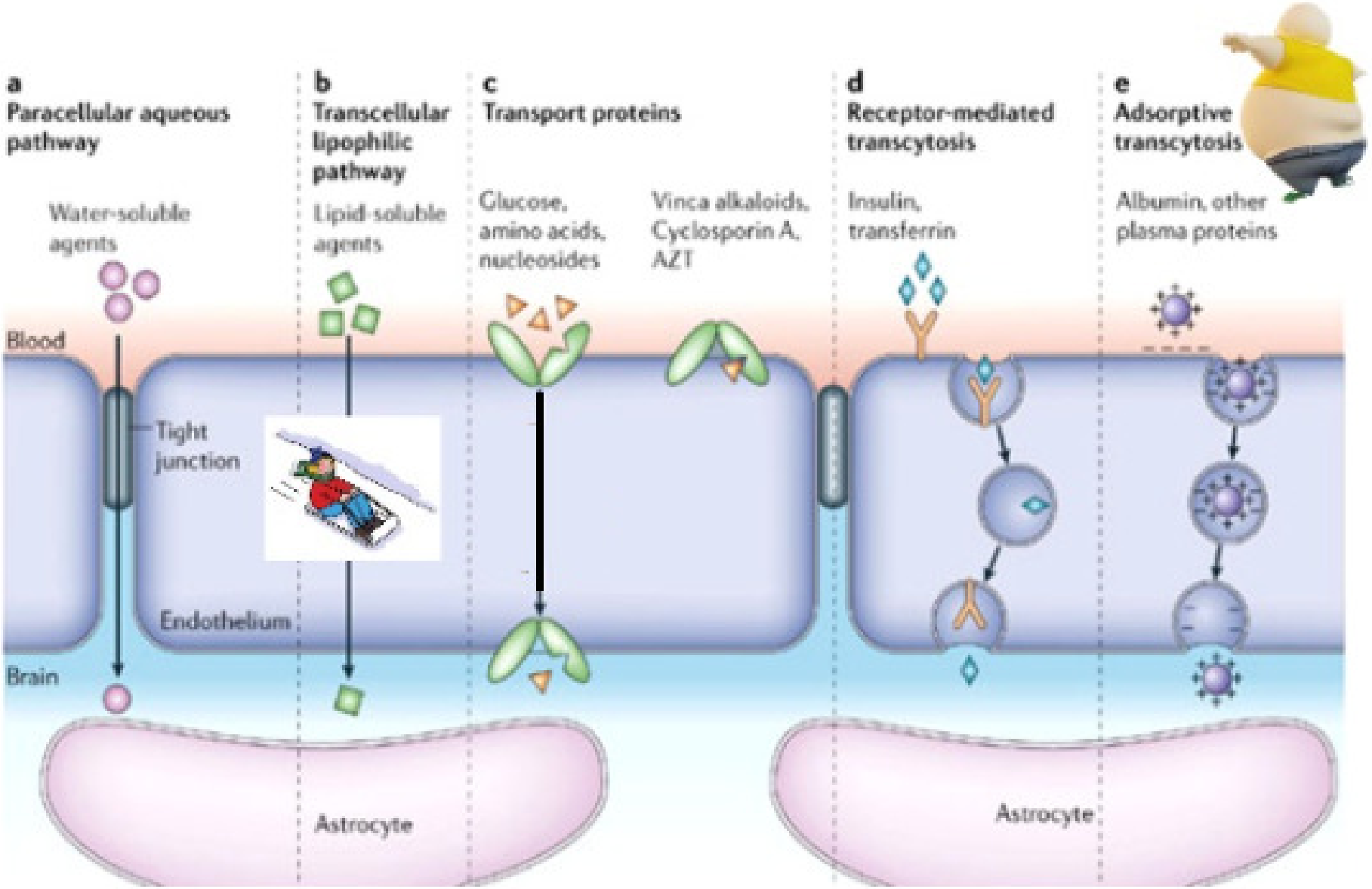
Modulando a permeabilidade



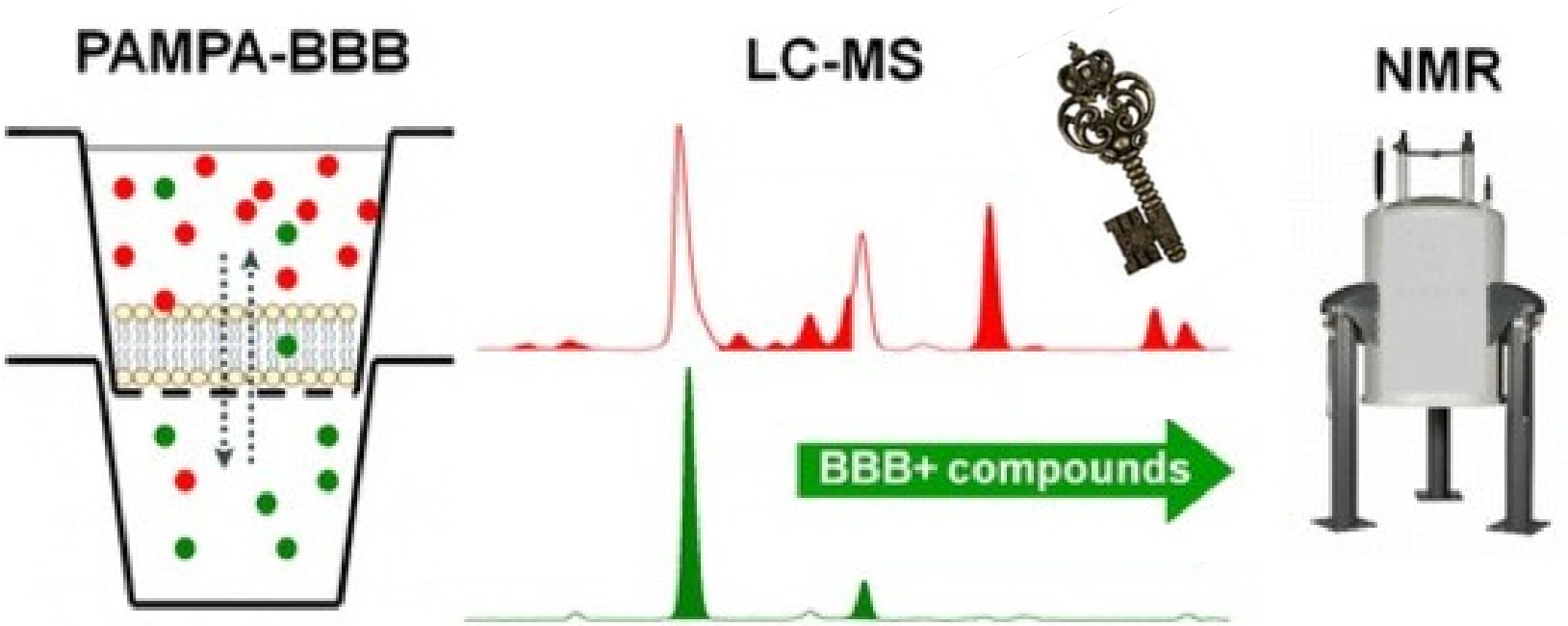
pKa = 10,56

pKa = 8,86

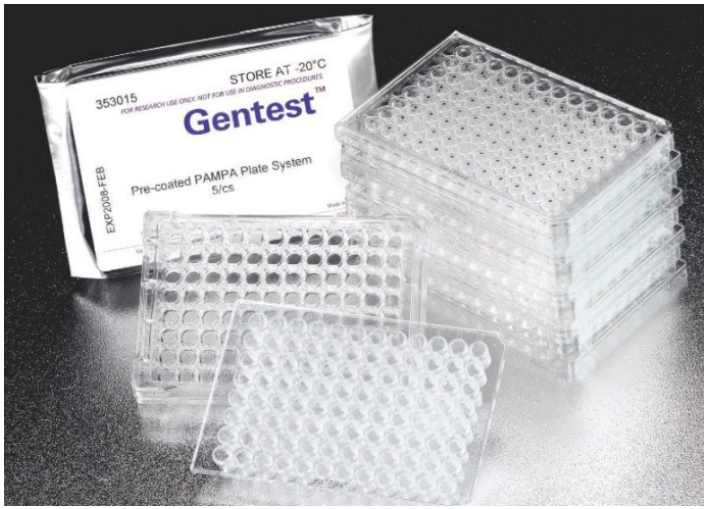
BBB


a
Paracellular aqueous pathway
b
Transcellular lipophilic pathway
c
Transport proteins
d
Receptor-mediated transcytosis
e
Adsorptive transcytosis
Water-soluble agents
Lipid-soluble agents
Glucose, amino acids, nucleosides
Vinca alkaloids, Cyclosporin A, AZT
Insulin, transferrin
Albumin, other plasma proteins
Blood
Tight junction
Endothelium
Brain
Astrocyte
Astrocyte

Barreira hemato-encefálica (BBB)



Parallel Artificial Membrane Permeability Assay

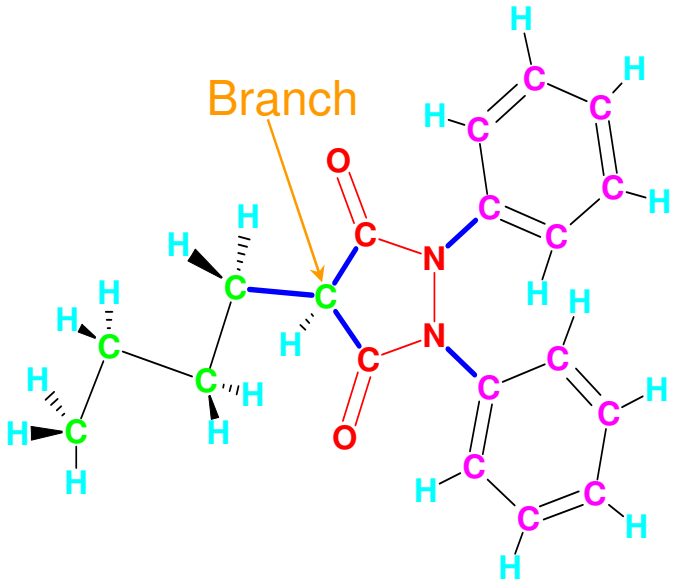


In silico

Cálculo do LogP

LogP for a molecule can be calculated from a sum of fragmental or atom-based terms plus various corrections.

$$\log P = \Sigma \text{ fragments} + \Sigma \text{ corrections}$$



Phenylbutazone

clogP

C: 3.16 M: 3.16 PHENYLBUTAZONE

Class	Type	Log(P) Contribution Description	Value
FRAGMENT	# 1	3,5-pyrazolidinedione	-3.240
ISOLATING |CARBON|	5	Aliphatic isolating carbon(s)	0.975
ISOLATING |CARBON|	12	Aromatic isolating carbon(s)	1.560
EXFRAGMENT|BRANCH|	1 chain and 0 cluster	branch(es)	-0.130
EXFRAGMENT|HYDROG|	20	H(s) on isolating carbons	4.540
EXFRAGMENT|BONDS	3 chain and 2 alicyclic	(net)	-0.540
RESULT	2.11 |All fragments measured	clogP =	3.165

Propriedades FQ *In silico*

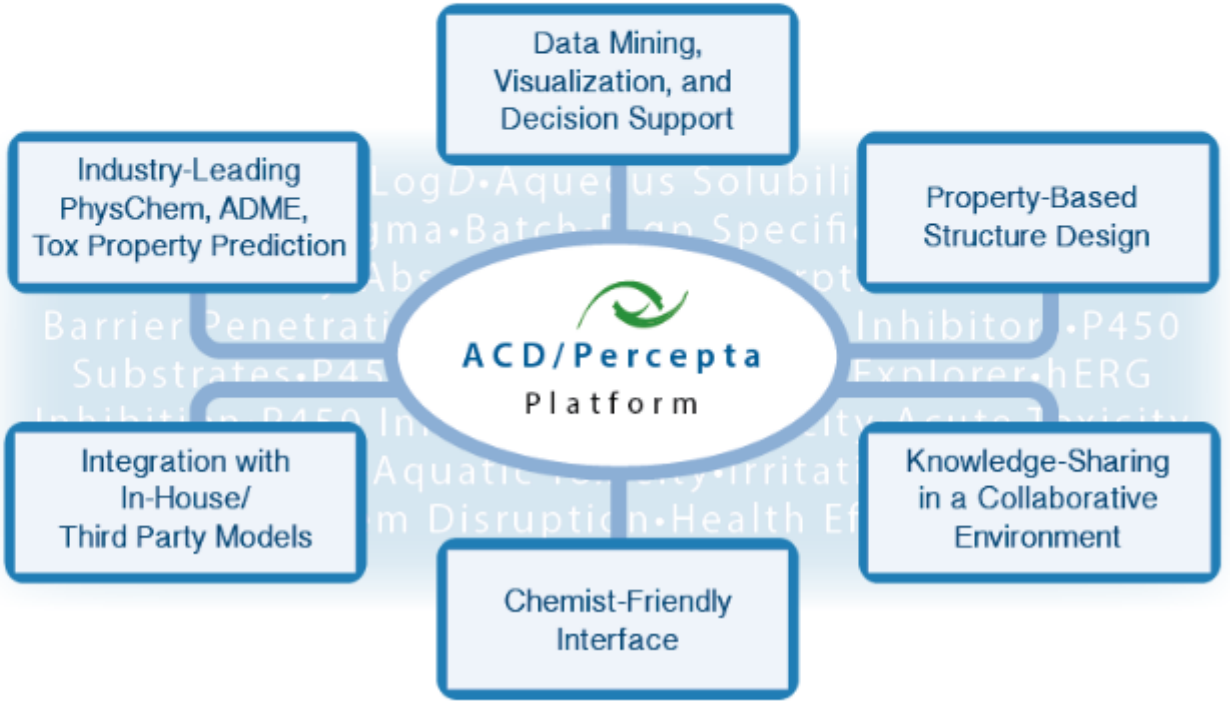
Platforms and Products > ACD/Percepta Platform

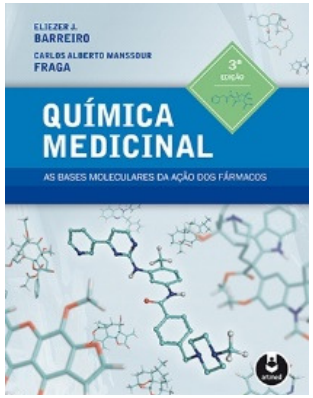
ACD/Labs Percepta Platform—Insight-driven Decision Support for Teams That Design and Synthesize New Chemical Entities

In Silico Prediction of Physicochemical, ADME, and Toxicity Properties

ACD/Percepta Platform

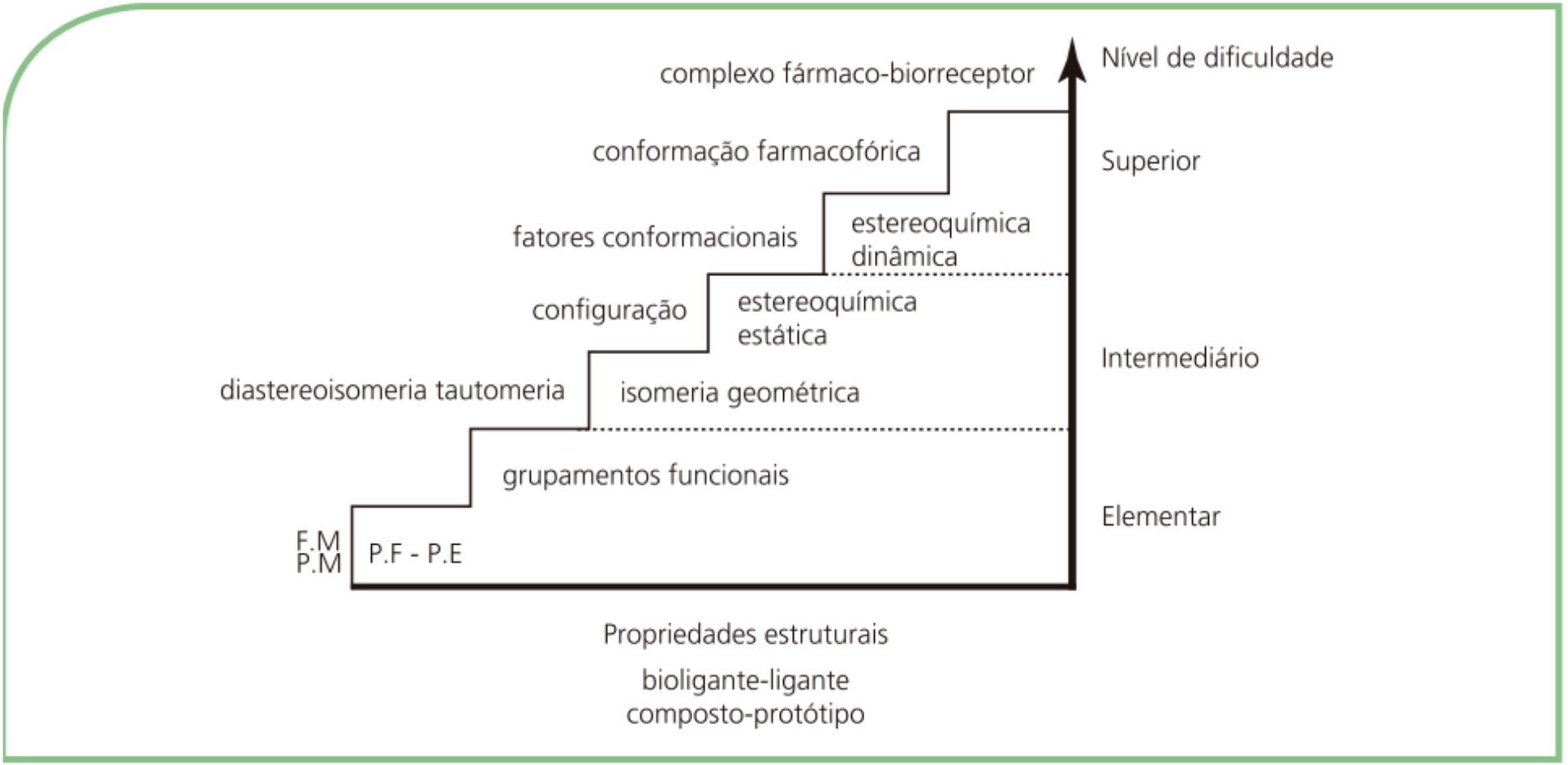
- ACD/Percepta Portal
- Desktop Modules for ACD/Percepta
- Batch Modules for ACD/Percepta



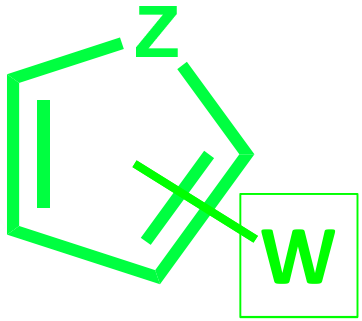


CAPÍTULO 7

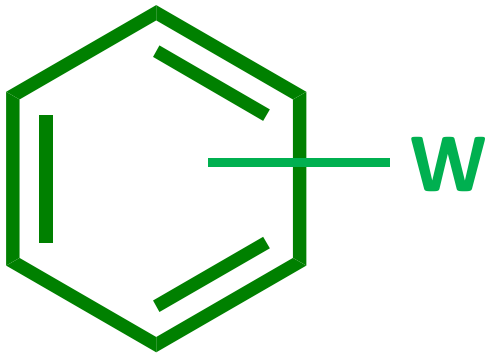
A IMPORTÂNCIA DOS FATORES ESTRUTURAIS NA ATIVIDADE DOS FÁRMACOS

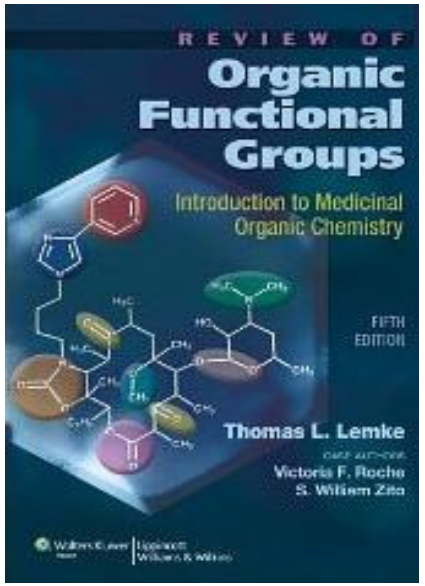


A estrutura química e a atividade

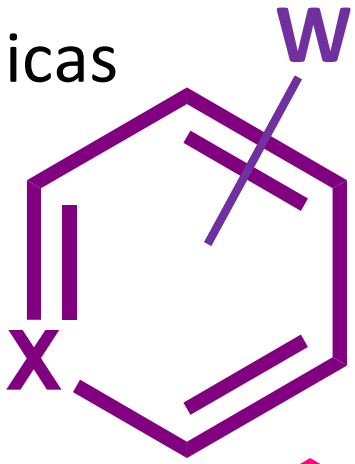


Z = NH, O, S





Propriedades eletrônicas

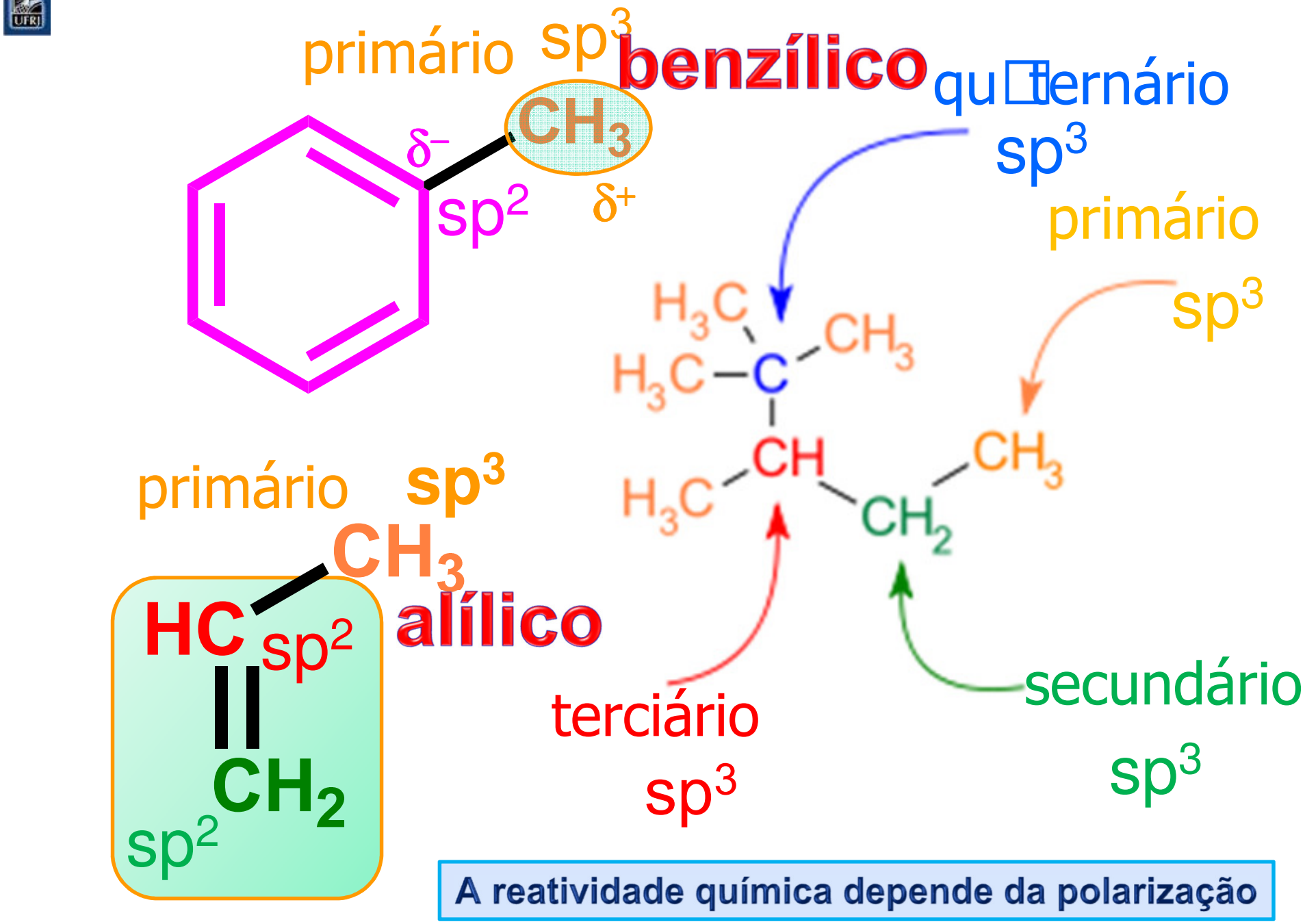


X = N

6, 10, 14, 18 π

<u>> 50% dos fármacos contêm pelo menos *um anel aromático*, capaz de sofrer substituições!</u>

Os grupos funcionais mais frequentes nos fármacos


primário
sp3
benzílico
quaternário
sp3
δ–
CH3
δ+
sp2
primário
sp3
H3C
CH3
H3C
C
CH
CH3
H3C
CH2
primário
sp3
CH3
alílico
HC
sp2
CH2
sp2
terciário
sp3
secundário
sp3
A reatividade química depende da polarização