FUNDAMENTOS DE QUÍMICA MEDICINAL -

Parte 3

COMO NASCEM OS FÁRMACOS

26ª Semana da Química do Instituto de Química da UFRJ

09-13 de abril de 2018

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Professor Titular

Universidade Federal do Rio de Janeiro

Resumo

Neste curso-curto apresentaremos os fundamentos da **Química Medicinal**, para o desenho molecular de novos candidatos a fármacos. A introdução abordará o histórico e a cronologia da disciplina, com ênfase ao seu caráter interdisciplinar. O processo de descoberta de fármacos ilustrará como "nascem" os fármacos. Apresentaremos alguns aspectos da inovação farmacêutica radical, em especial para os fármacos sintéticos. Em conclusão, alguns exemplos selecionados do trabalho realizado no Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio) do ICB da UFRJ, criado e coordenado pelo apresentador, serão apresentados.

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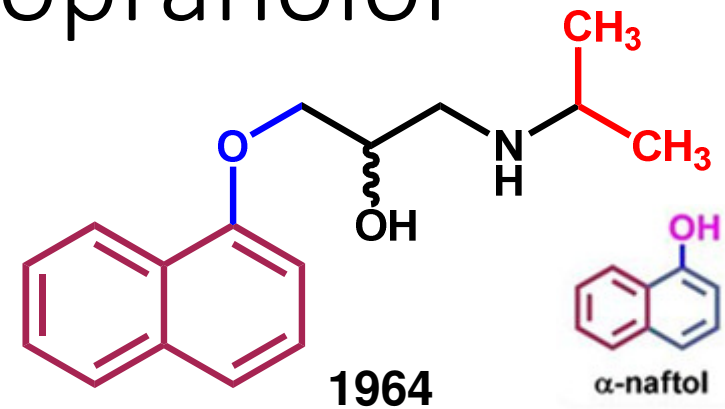
A invenção do propranolol

1988

James W. Black
(1924-2000)

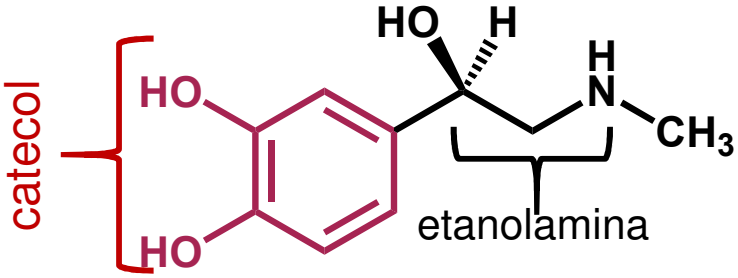


1964

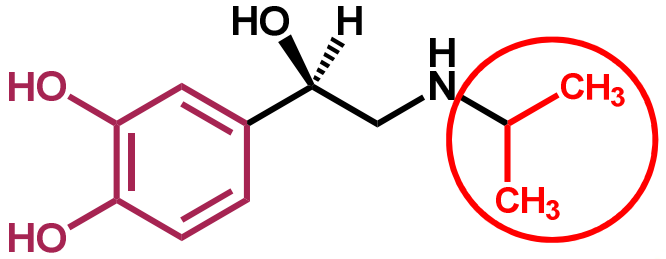
1º β-bloqueador seletivo

J. Black *et al.*, *Br. J. Pharmacol. Chmother.* **1965**, *25*, 577

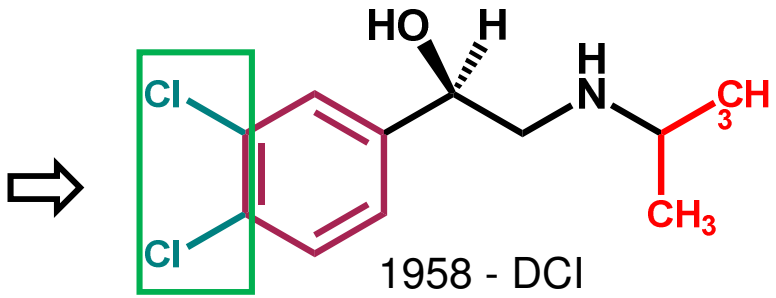
James W. Black, 1988 - "Pronethalol always seemed to us to be a prototype drug, good enough to answer questions of principle, but not good enough to be marketable"



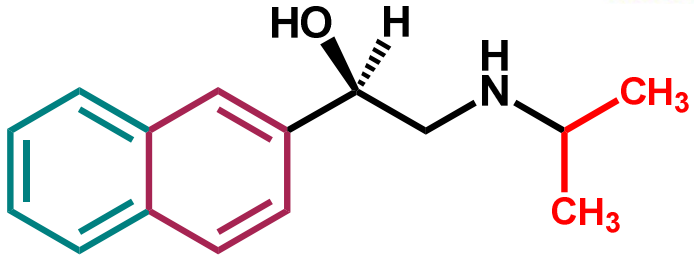
ADRENALINA



isoproterenol

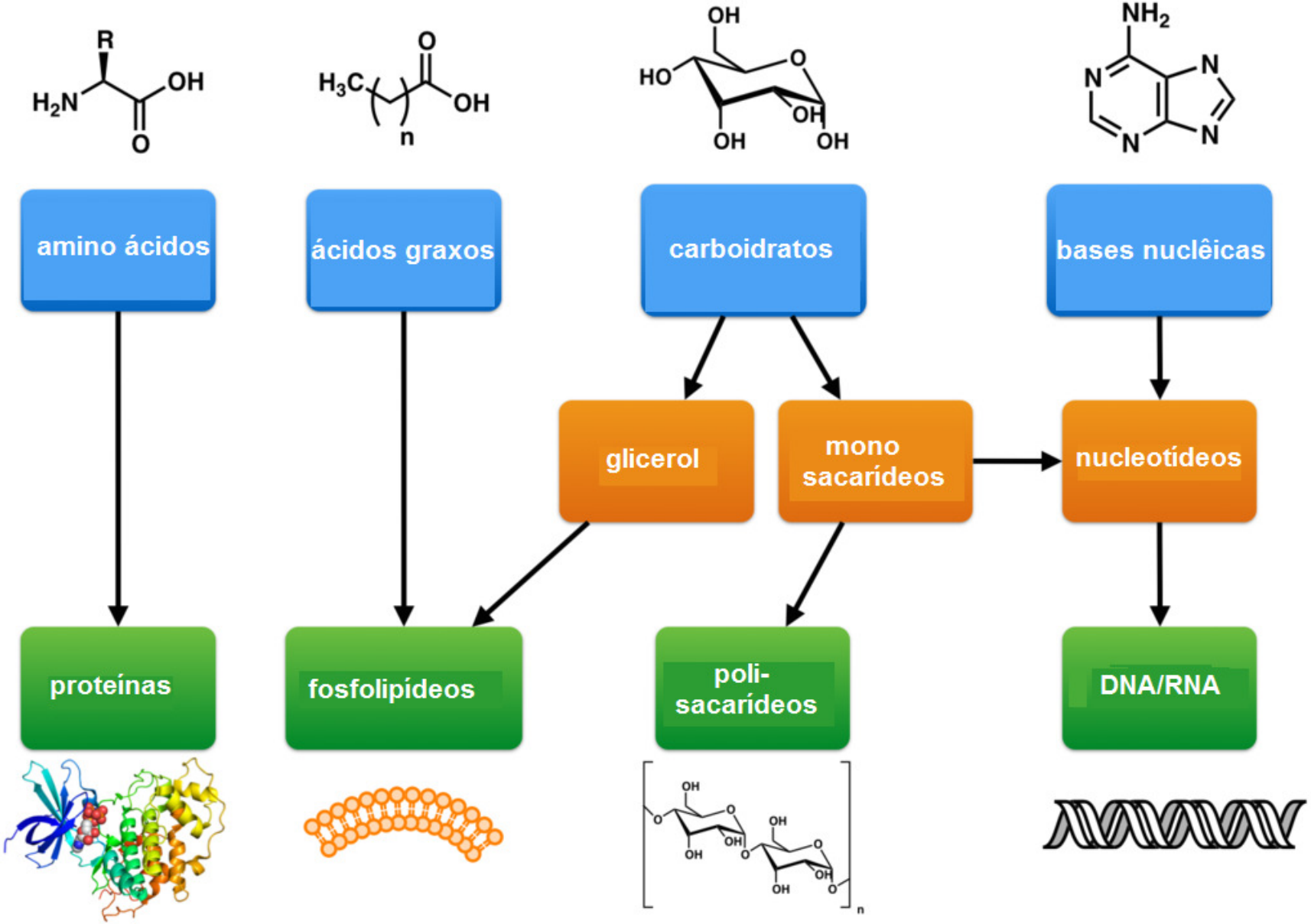


1958 - DCI

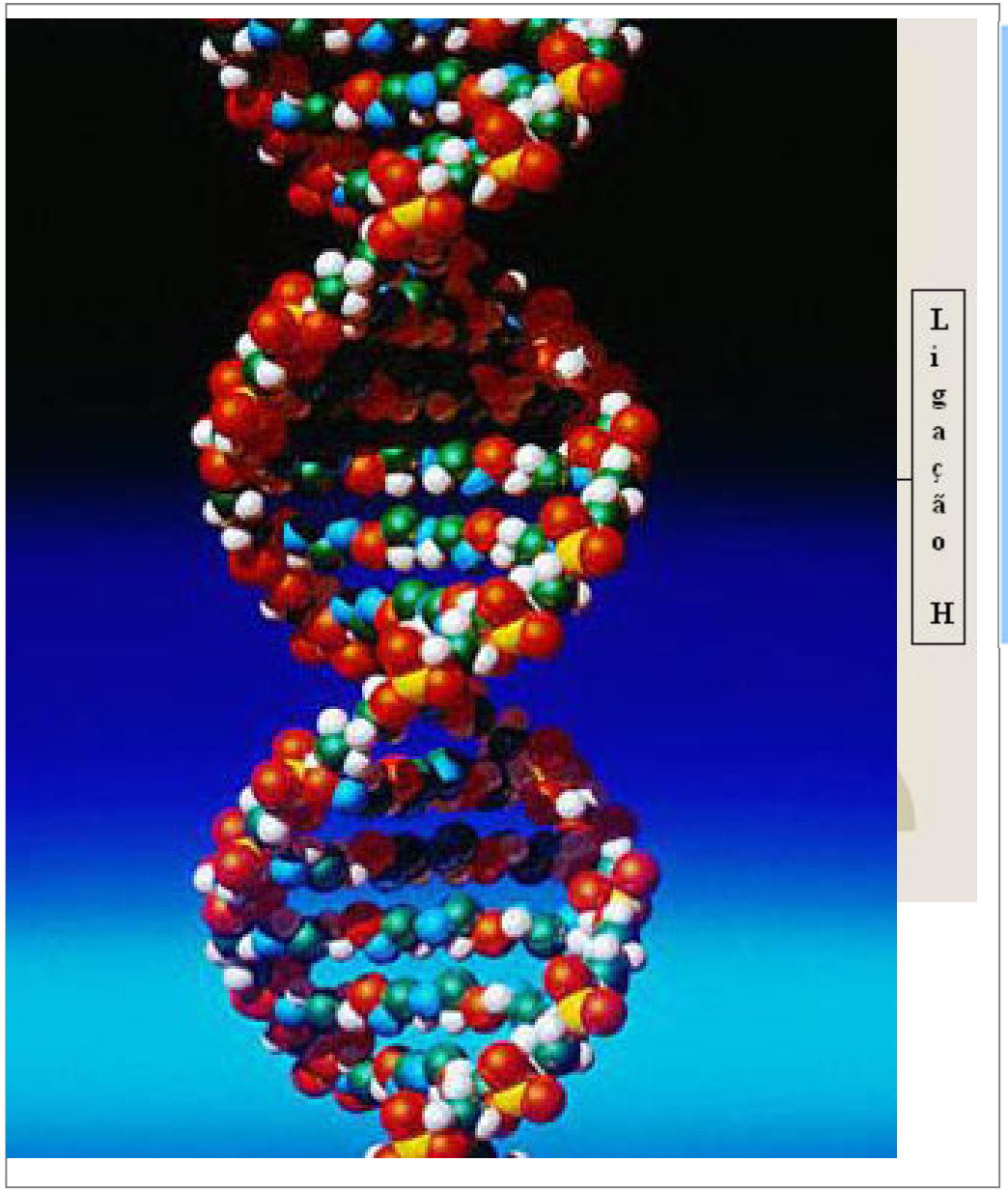


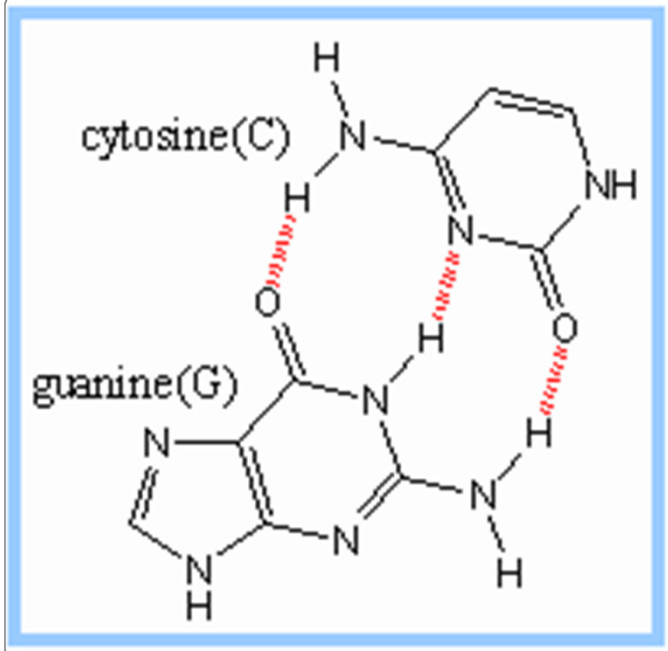
1959 -pronetalol

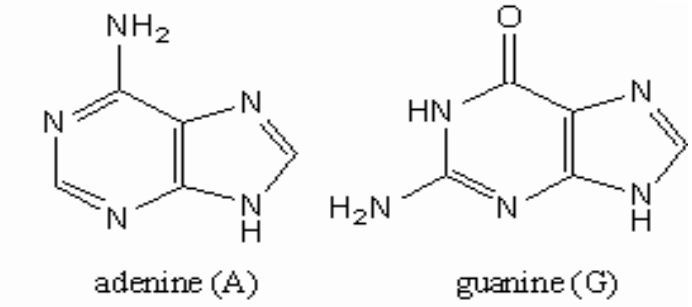
Os alfabetos bioquímicos

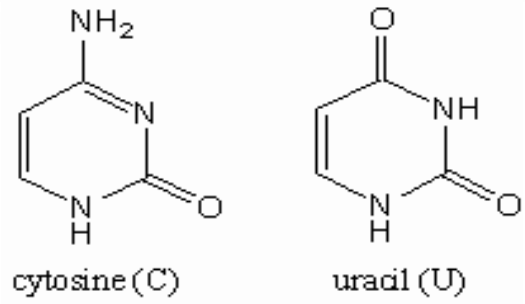


Proteínas, carboidratos, DNA, lipídeos, canais iônicos

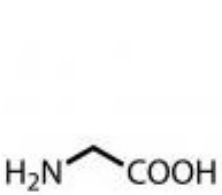




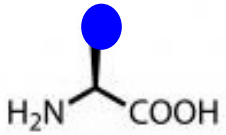




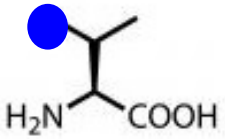
Os 20 amino-ácidos essenciais



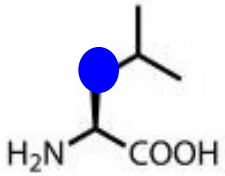
glycine (Gly, G)



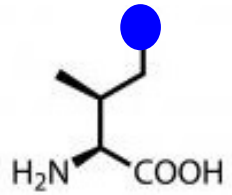
L-alanine (Ala, A)



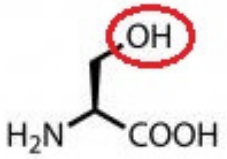
L-valine (Val, V)



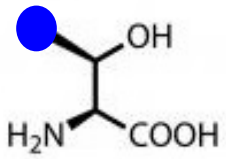
L-leucine (Leu, L)



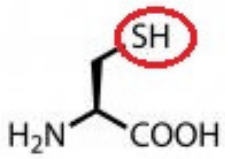
L-isoleucine (Ile, I)



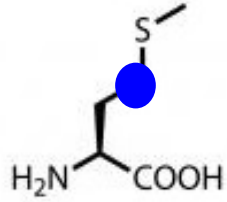
L-serine (Ser, S)



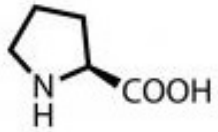
L-threonine (Thr, T)



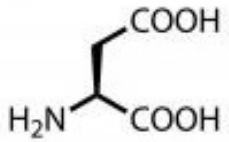
L-cysteine (Cys, C)



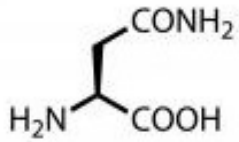
L-methionine (Met, M)



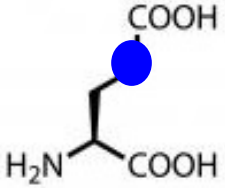
L-proline (Pro, P)



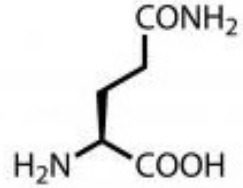
L-aspartic acid (Asp, D)



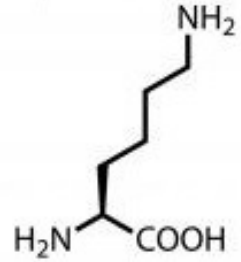
L-asparagine (Asn, N)



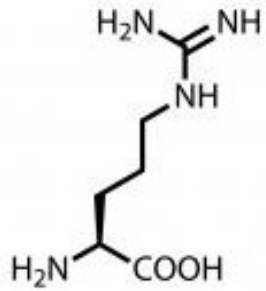
L-glutamic acid (Glu, E)



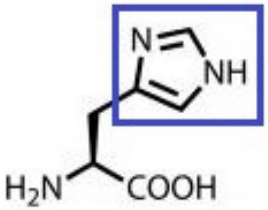
L-glutamine (Gln, Q)



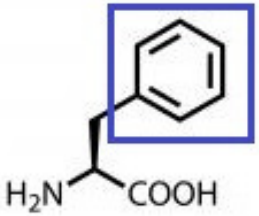
L-lysine (Lys, K)



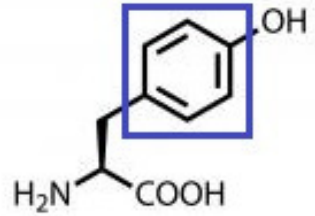
L-arginine (Arg, R)



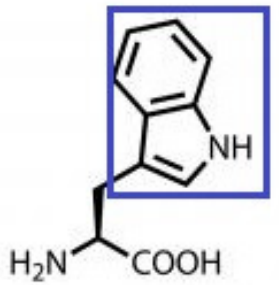
L-histidine (His, H)



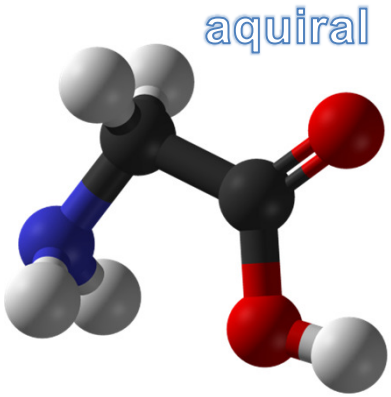
L-phenylalanine (Phe, F)



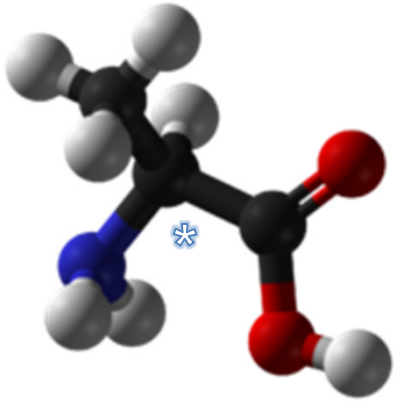
L-tyrosine (Tyr, Y)



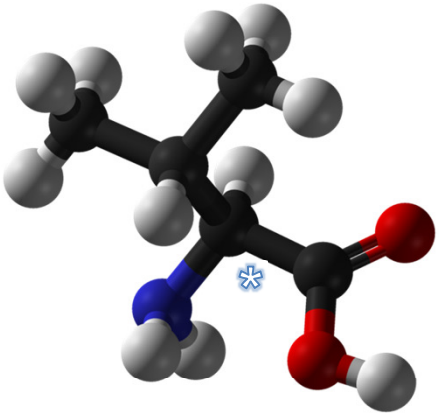
L-tryptophan (Trp, W)



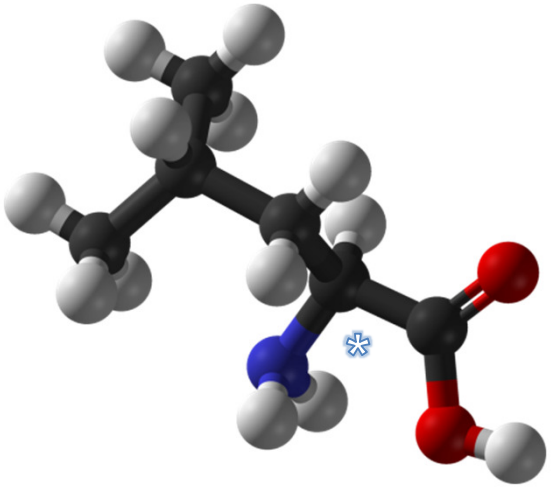
Glicina



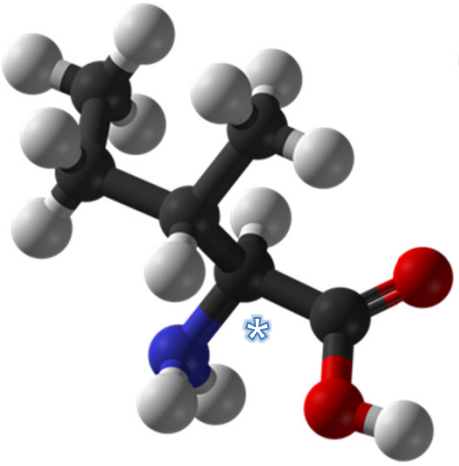
Alanina



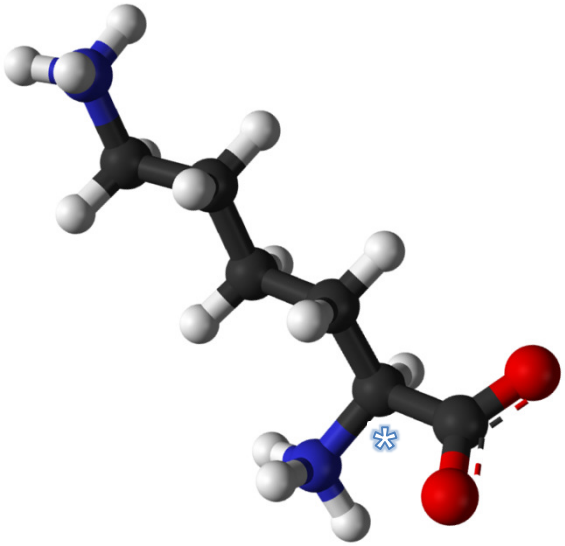
Valina



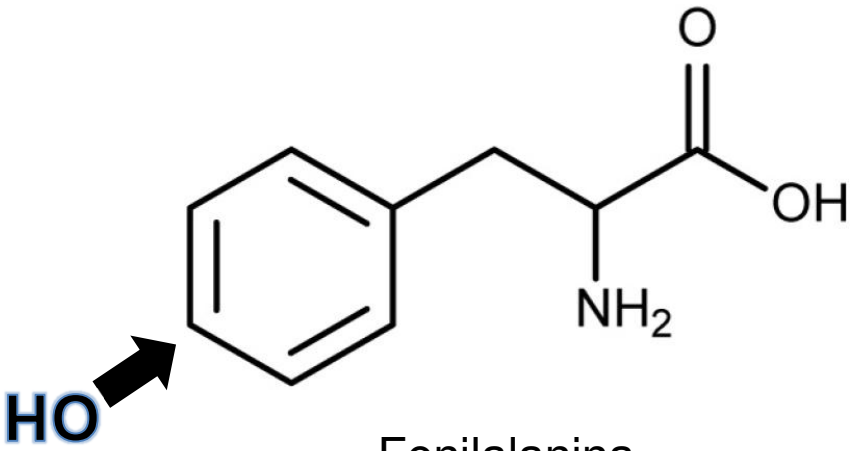
Leucina



Isoleucina

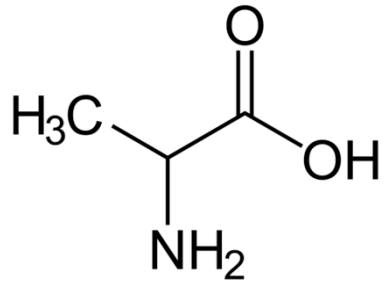


Lisina

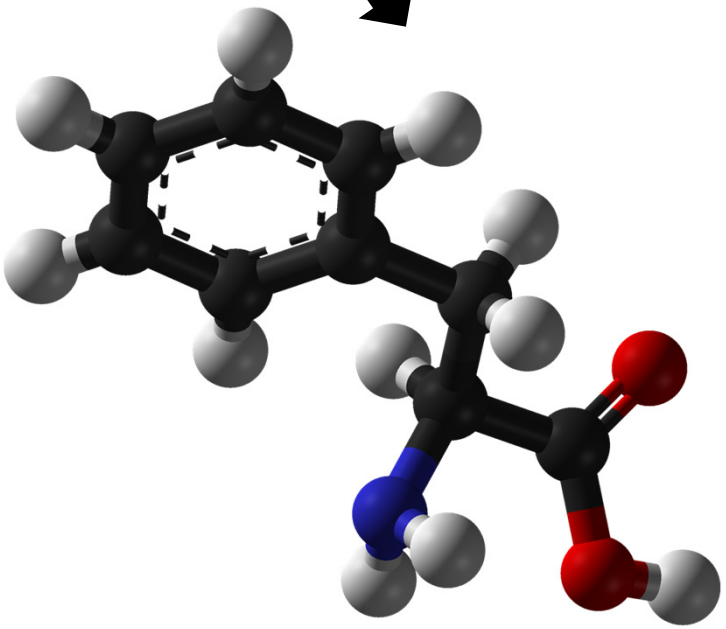


Tirosina

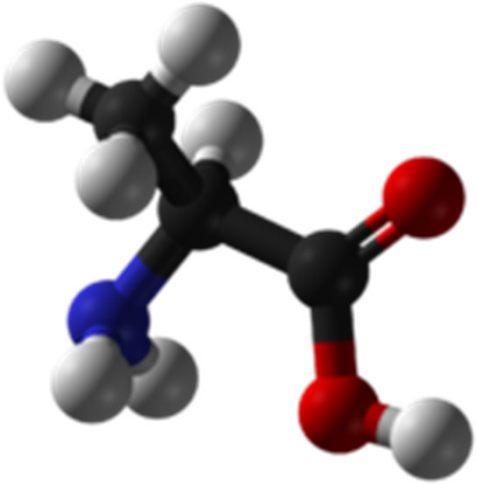
Fenilalanina



Alanina

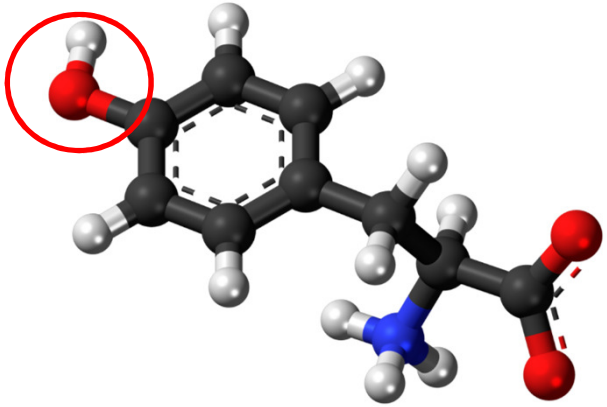


Fenilalanina



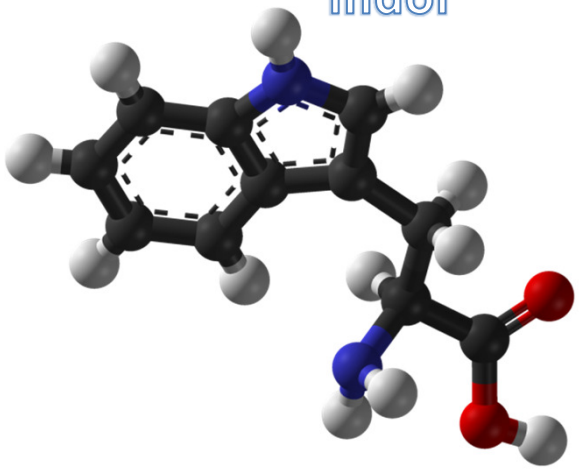
Alanina

fenol



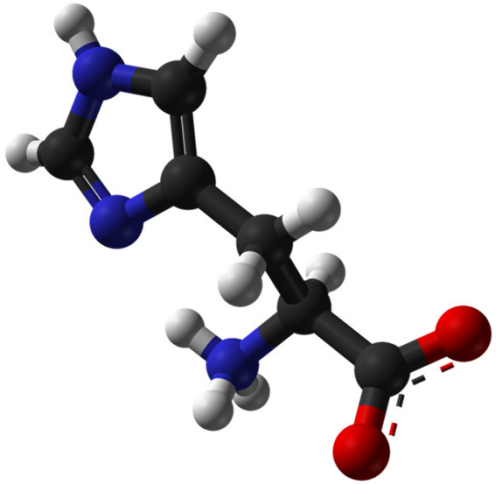
Tirosina

indol

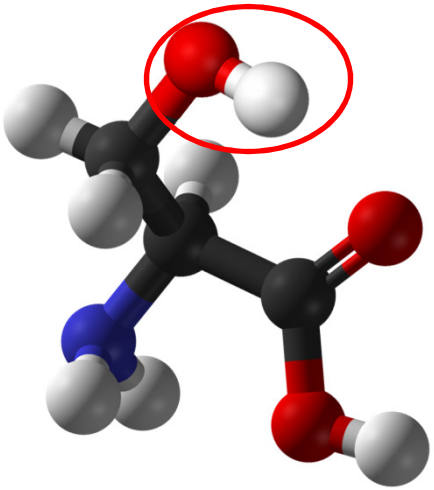


Triptofano

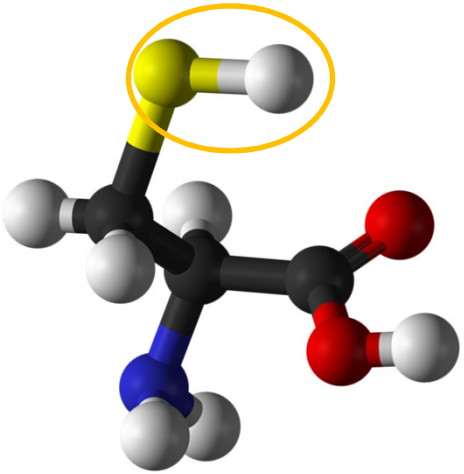
imidazol



Histidina

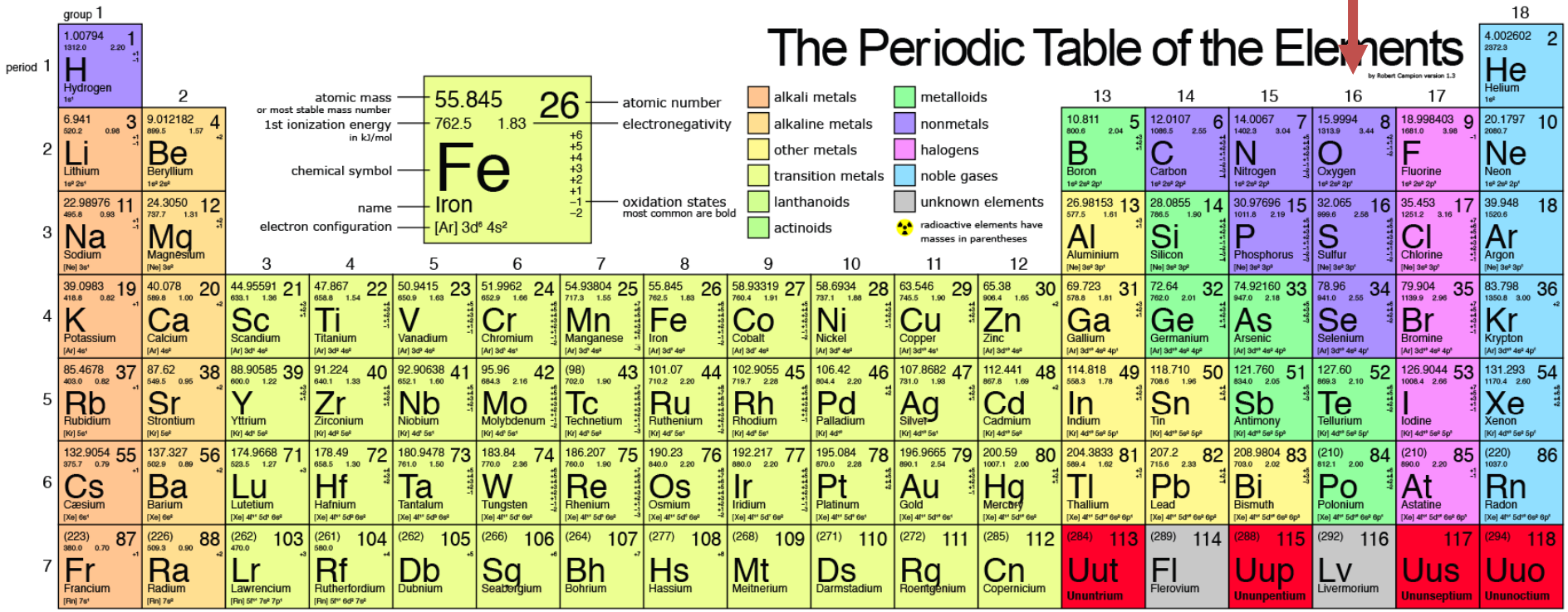


Serina



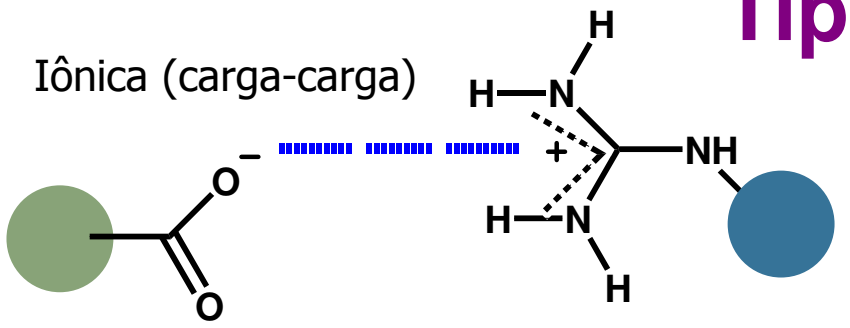
Cisteína

Tabela Periódica



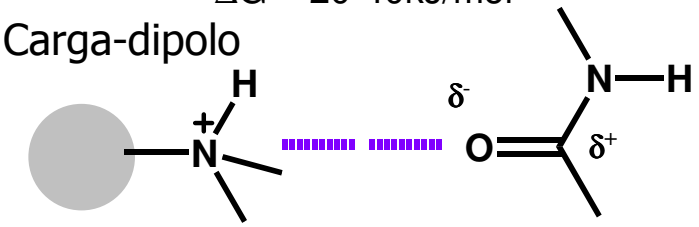
Tipos de interações F-R

Iônica (carga-carga)



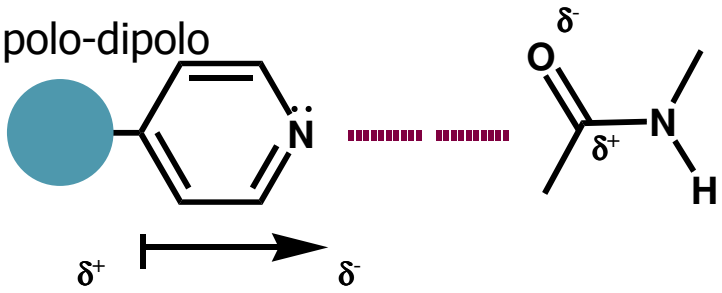
ΔG = 20-40kJ/mol

Carga-dipolo



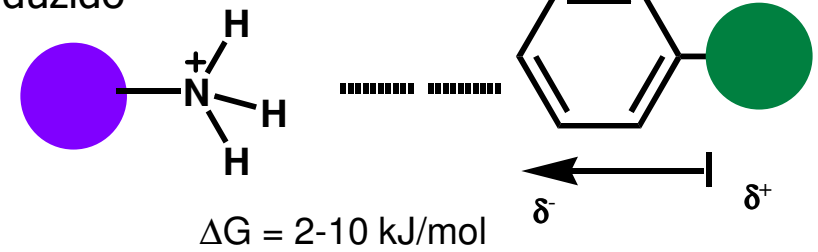
ΔG = 12-20kJ/mol

Dipolo-dipolo



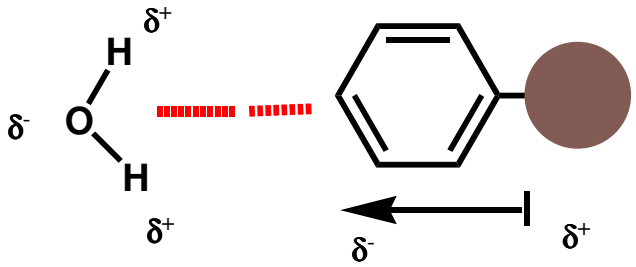
ΔG = 4-12 kJ/mol

Carga-dipolo induzido



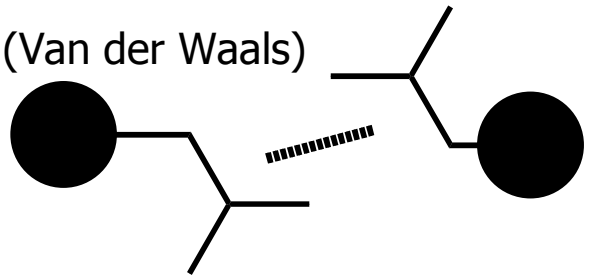
ΔG = 2-10 kJ/mol

Dipolo induzido-dipolo



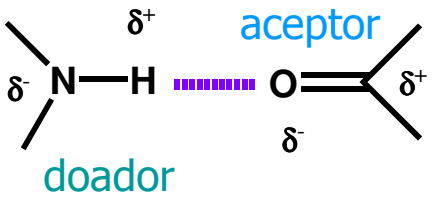
ΔG = 2 kJ/mol

Dispersão (Van der Waals)



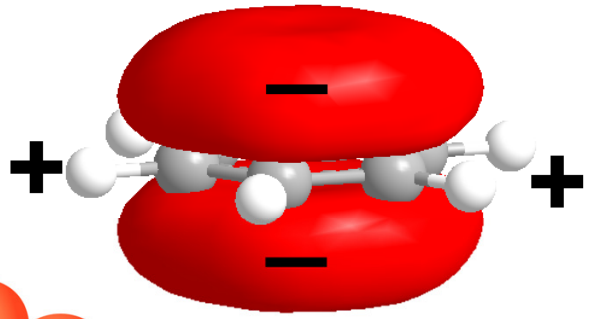
ΔG = 2-4 kJ/mol

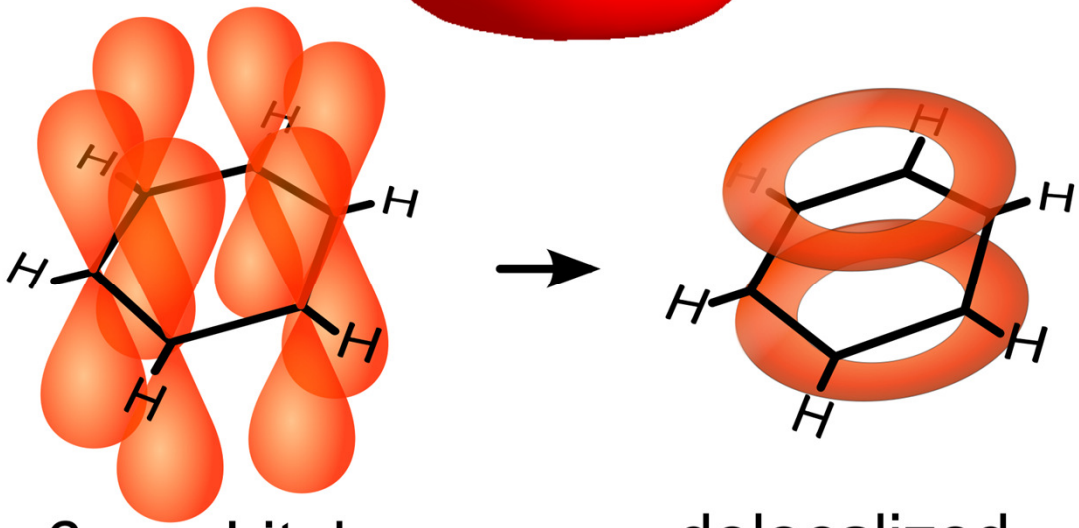
Ligação-H



ΔG = 4-30 kJ/mol

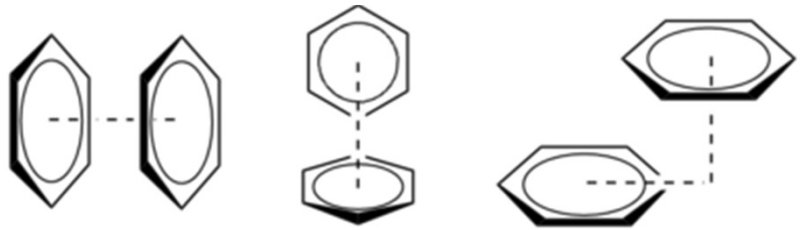
Interações π



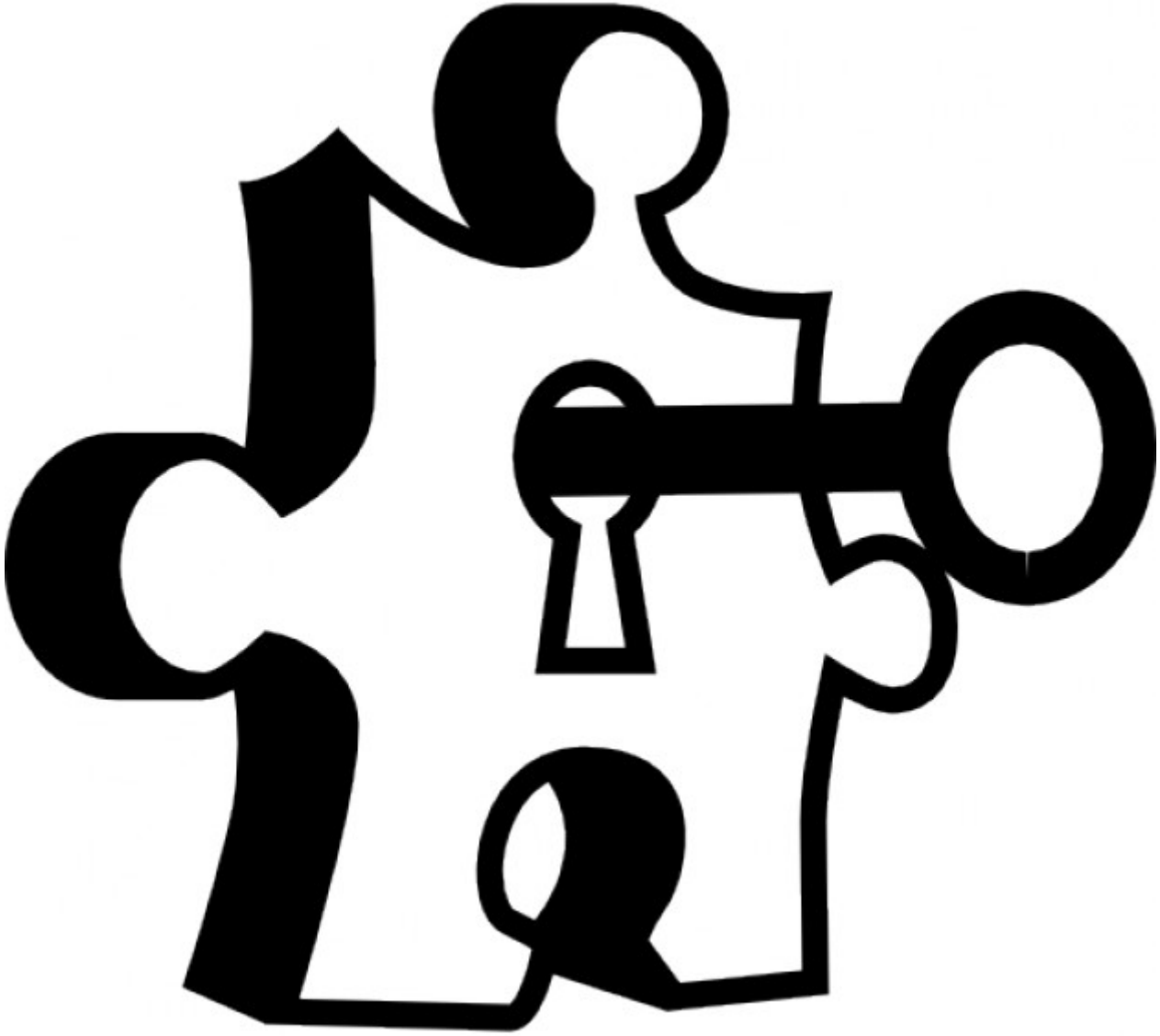


6 p-orbitals

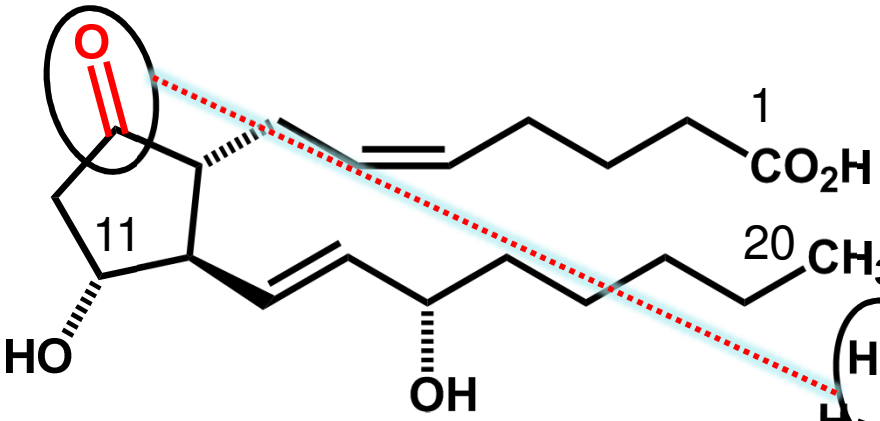
delocalized



Sandwich T-shaped Parallel-displaced



A *seletividade* dos biorreceptores

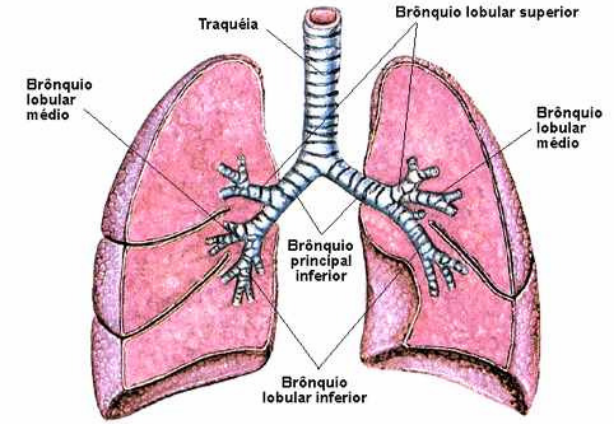


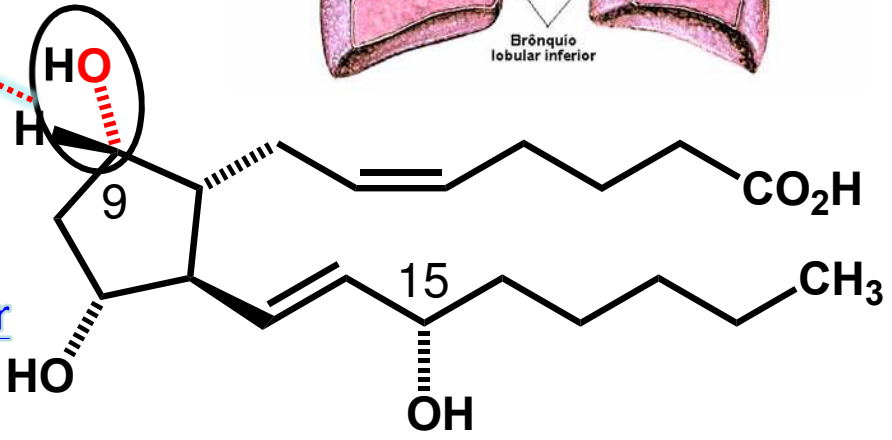
$C_{20}H_{32}O_5$

PGE_2

Similaridade molecular

$PGF_{2\alpha}$ em cães provoca intensa broncodilatação





$C_{20}H_{34}O_5$

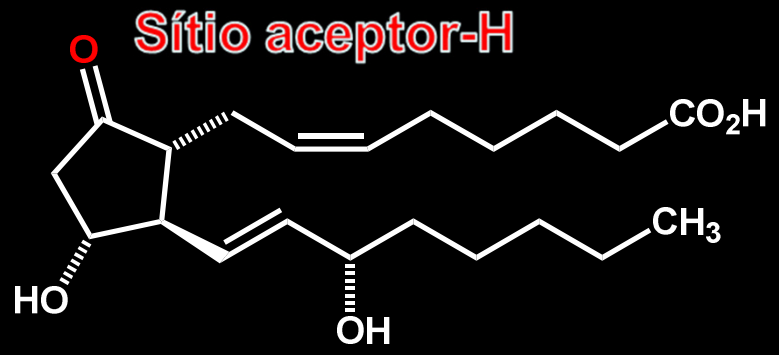
$PGF_{2\alpha}$

$PGF_{2\alpha}$ em cães provoca severa broncoconstrição

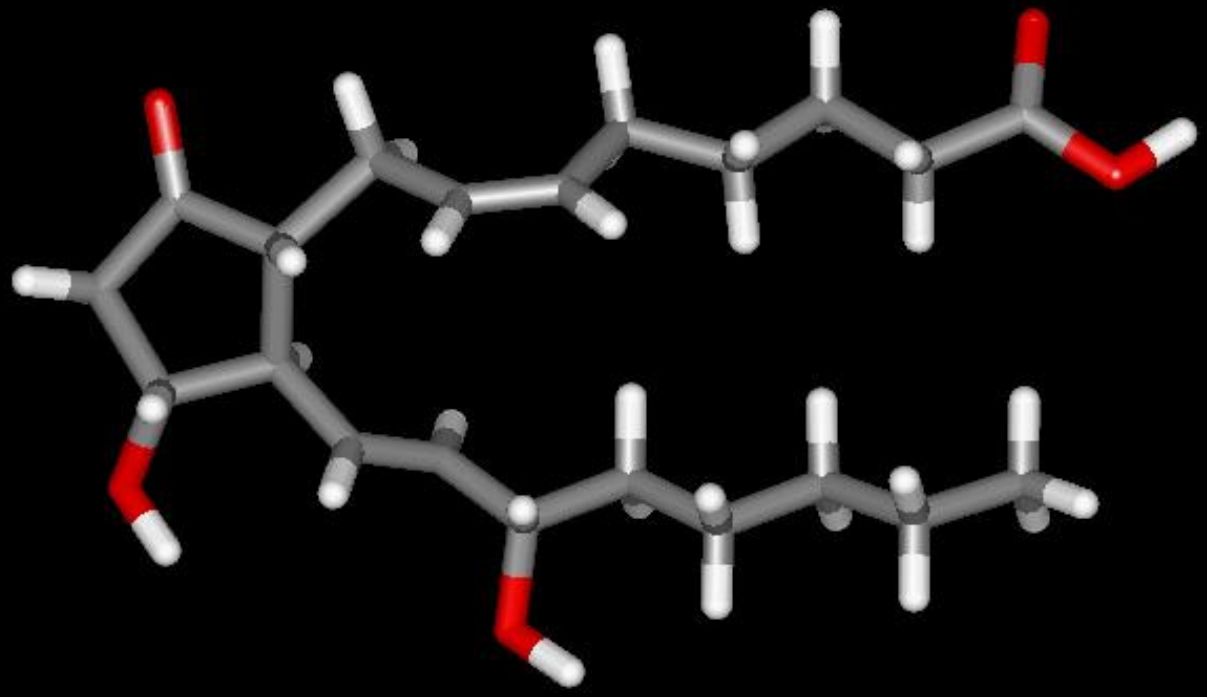
EPr

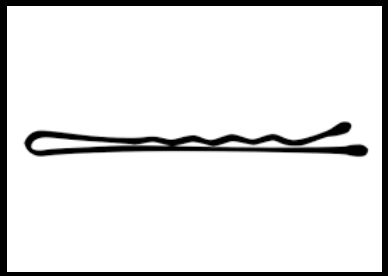
FPr

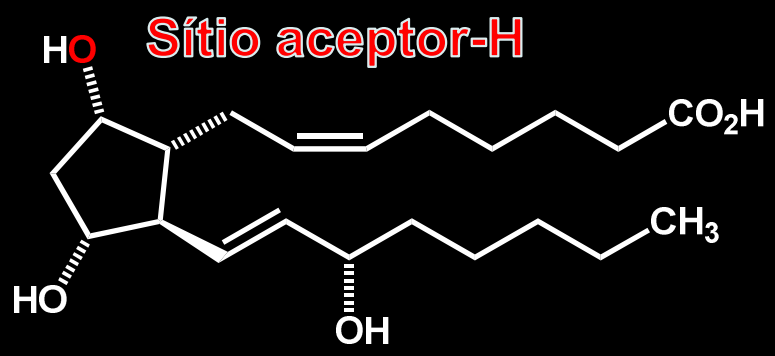
Reconhecimento Molecular



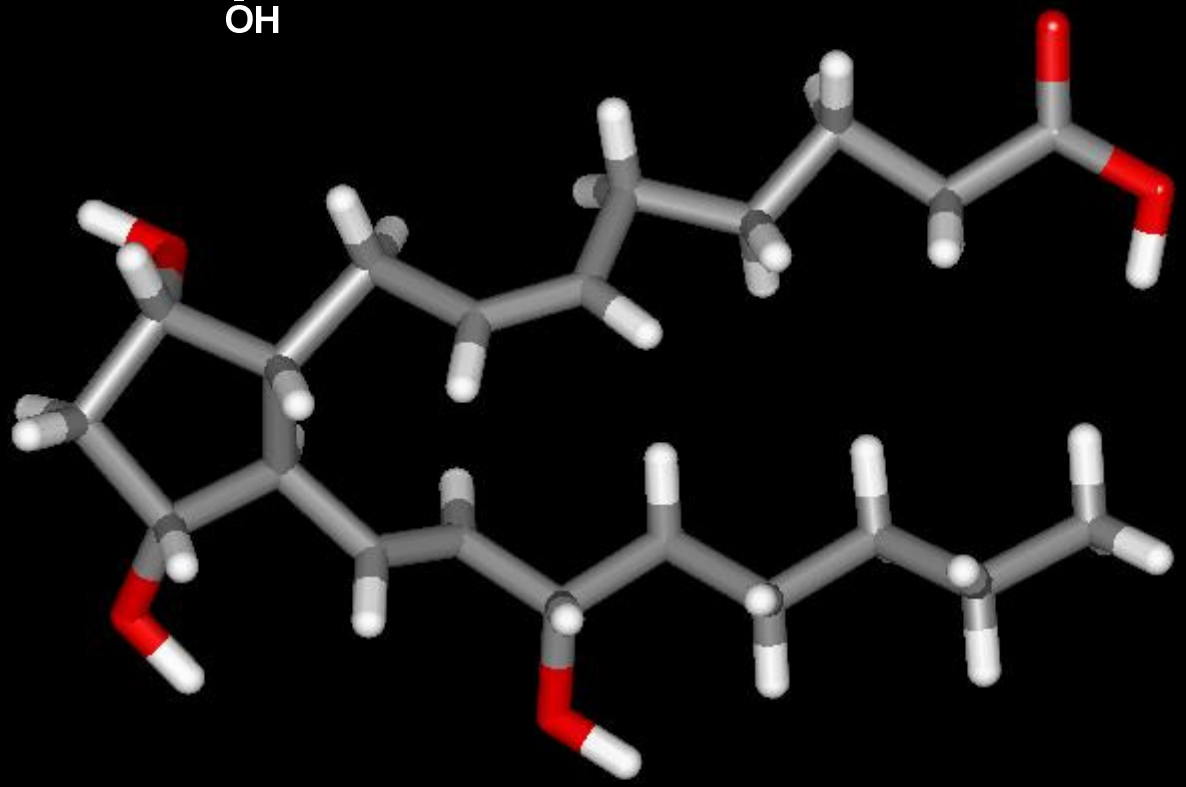
PGE_2

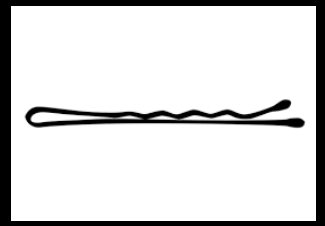






$PGF_{2\alpha}$

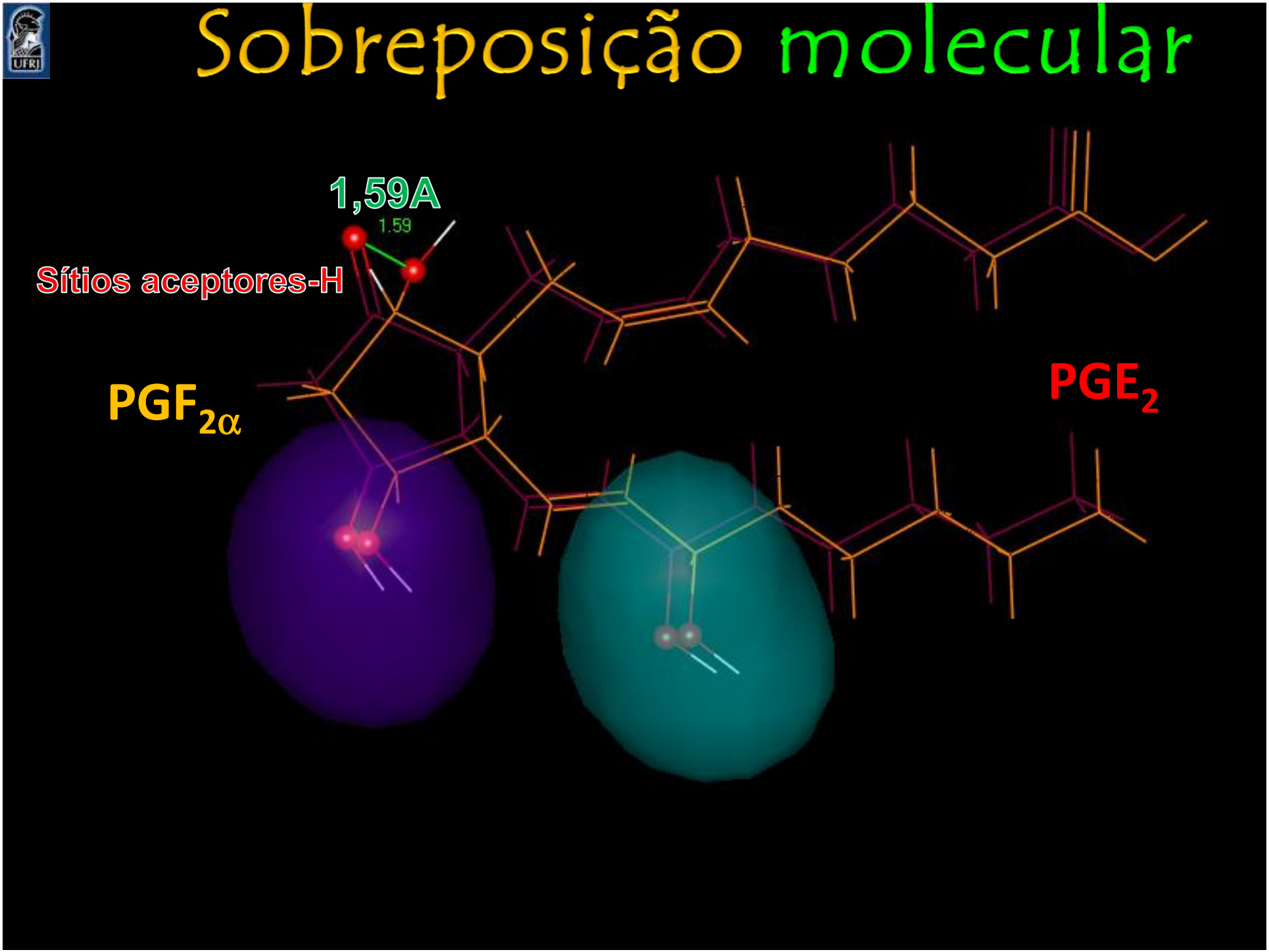


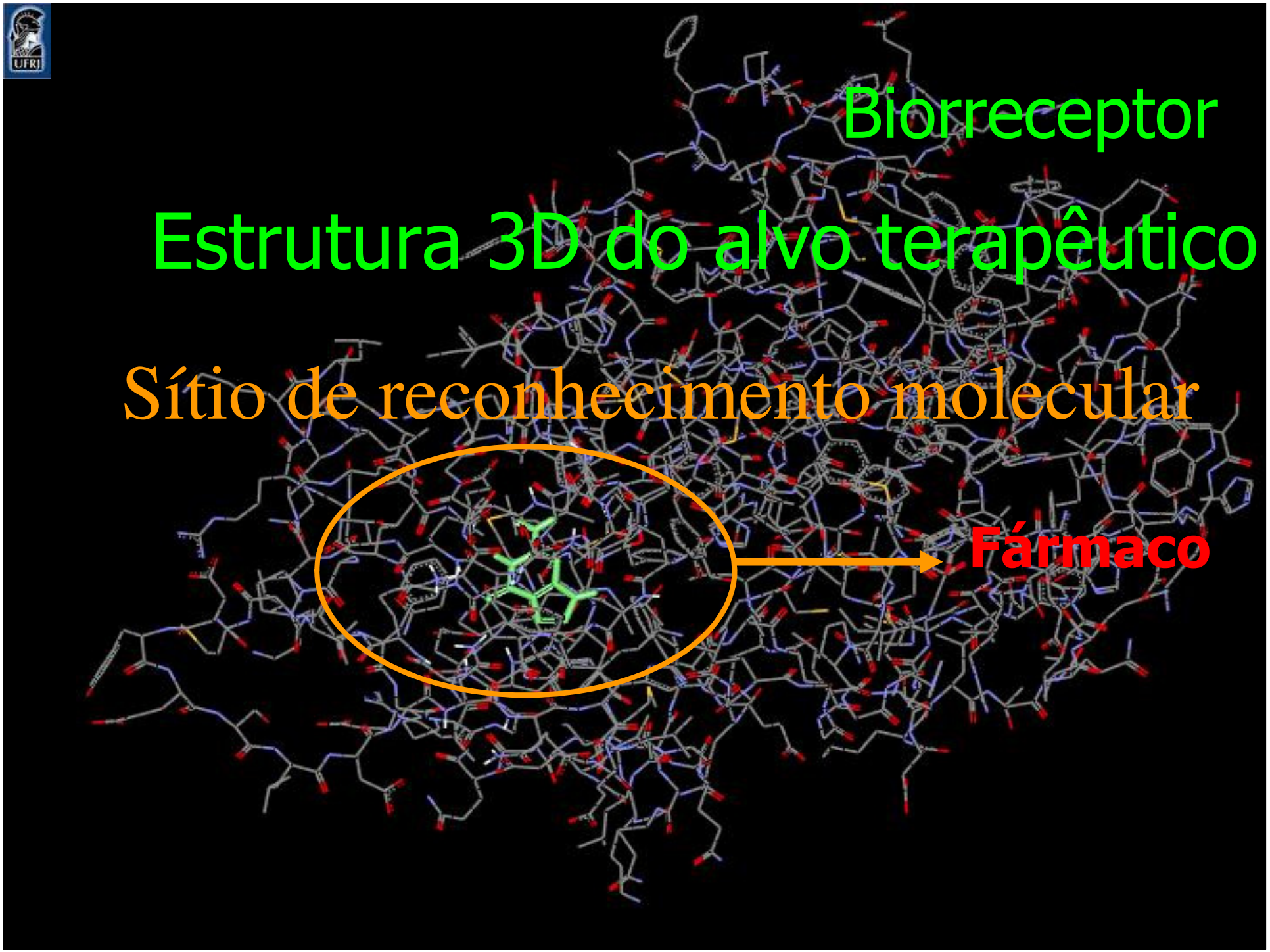


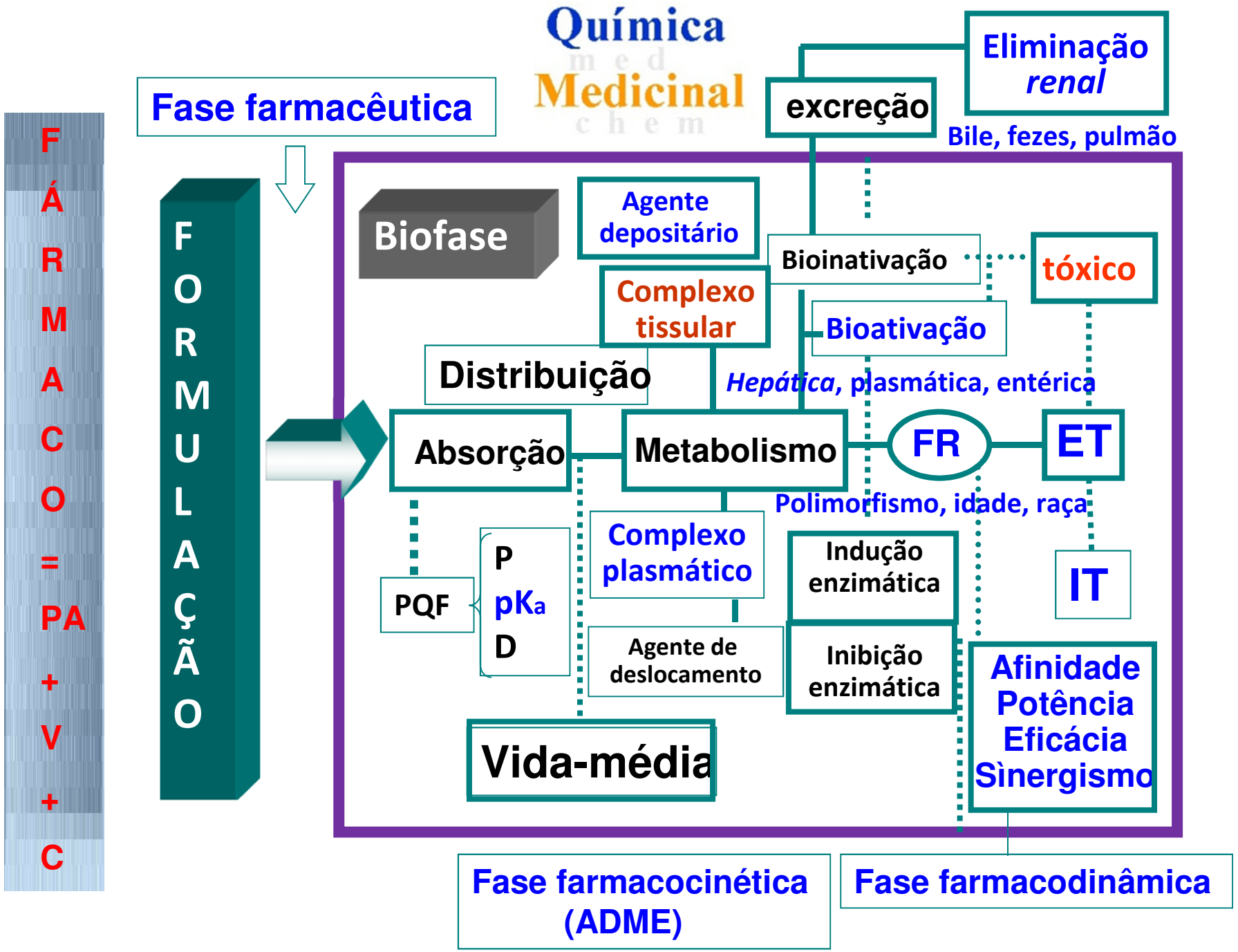
Grampo-de-cabelo

Conformação estável

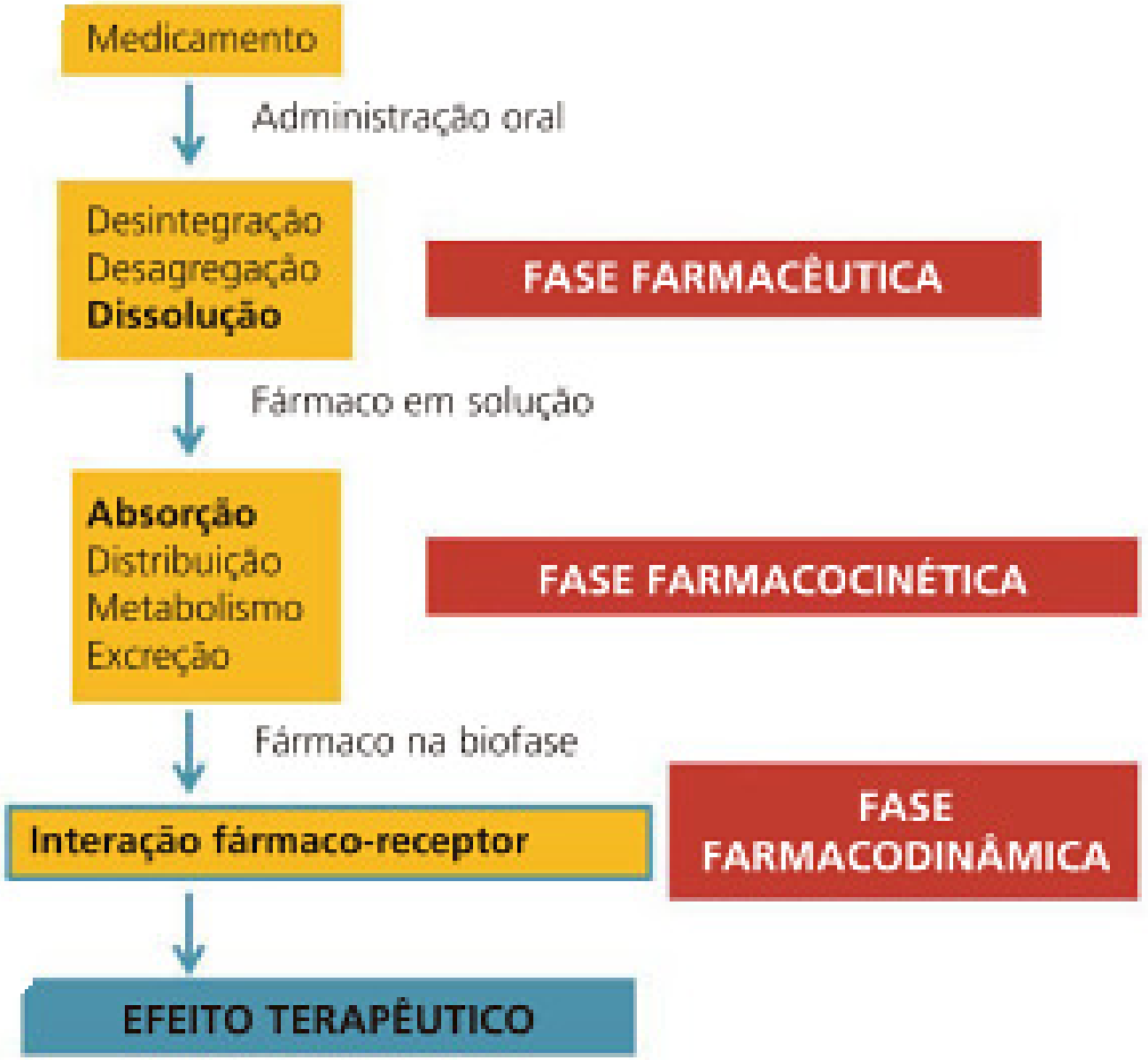
Sobreposição molecular



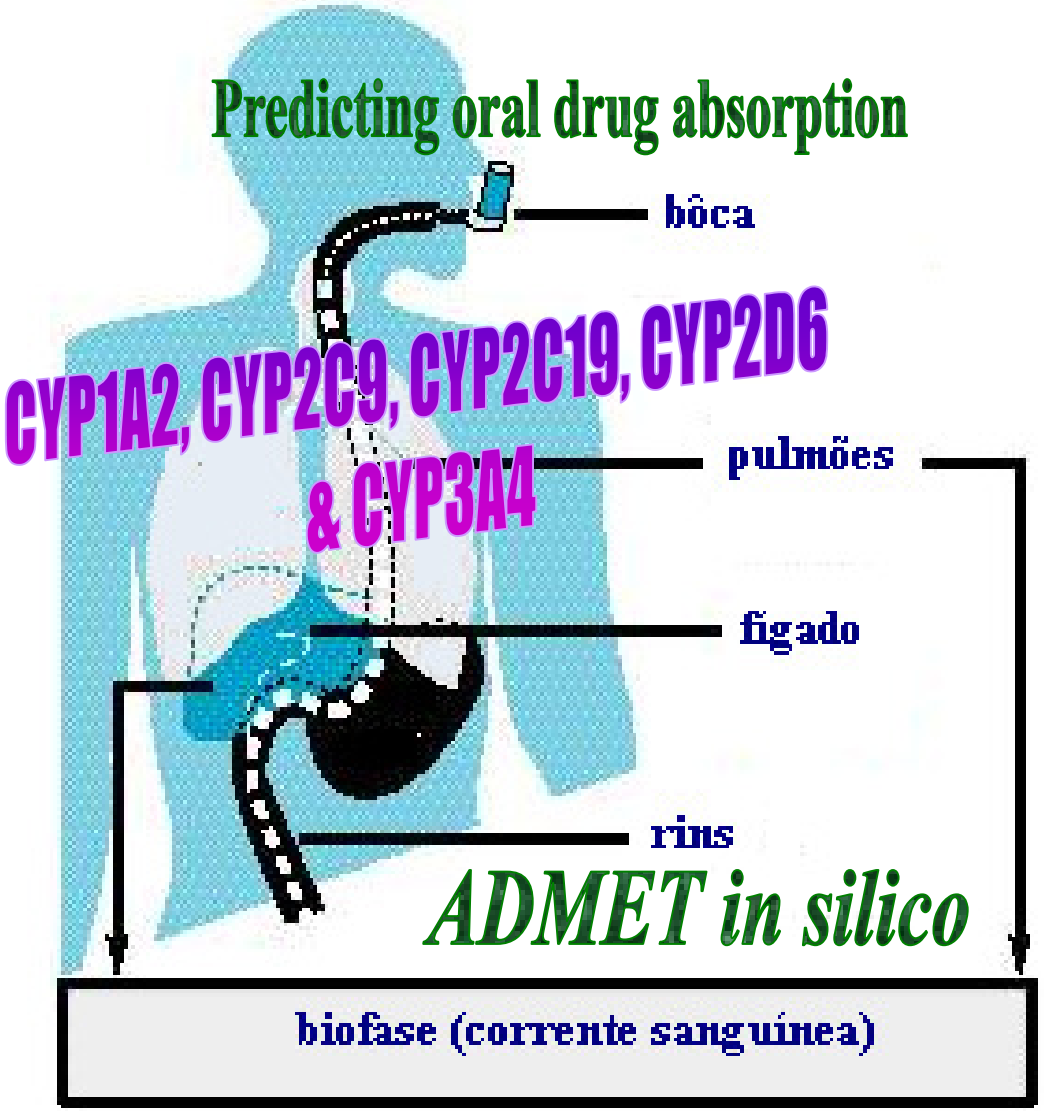

Biorreceptor
Estrutura 3D do alvo terapêutico
Sítio de reconhecimento molecular
Fármaco

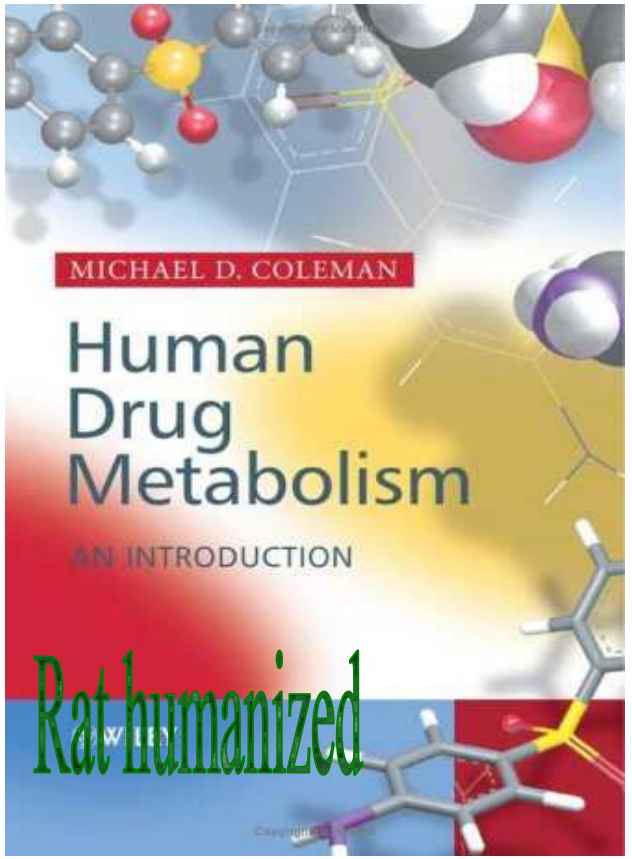

Química
med
Medicinal
chem
FÁRMACO = PA + V + C
Fase farmacêutica
FORMULAÇÃO
Biofase
Agente depositário
Complexo tissular
Distribuição
Absorção
Metabolismo
PQF
P
pKa
D
Complexo plasmático
Agente de deslocamento
Vida-média
Bioinativação
excreção
Eliminação renal
Bile, fezes, pulmão
tóxico
Bioativação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

As fases da ação dos fármacos



Fase Farmacocinética

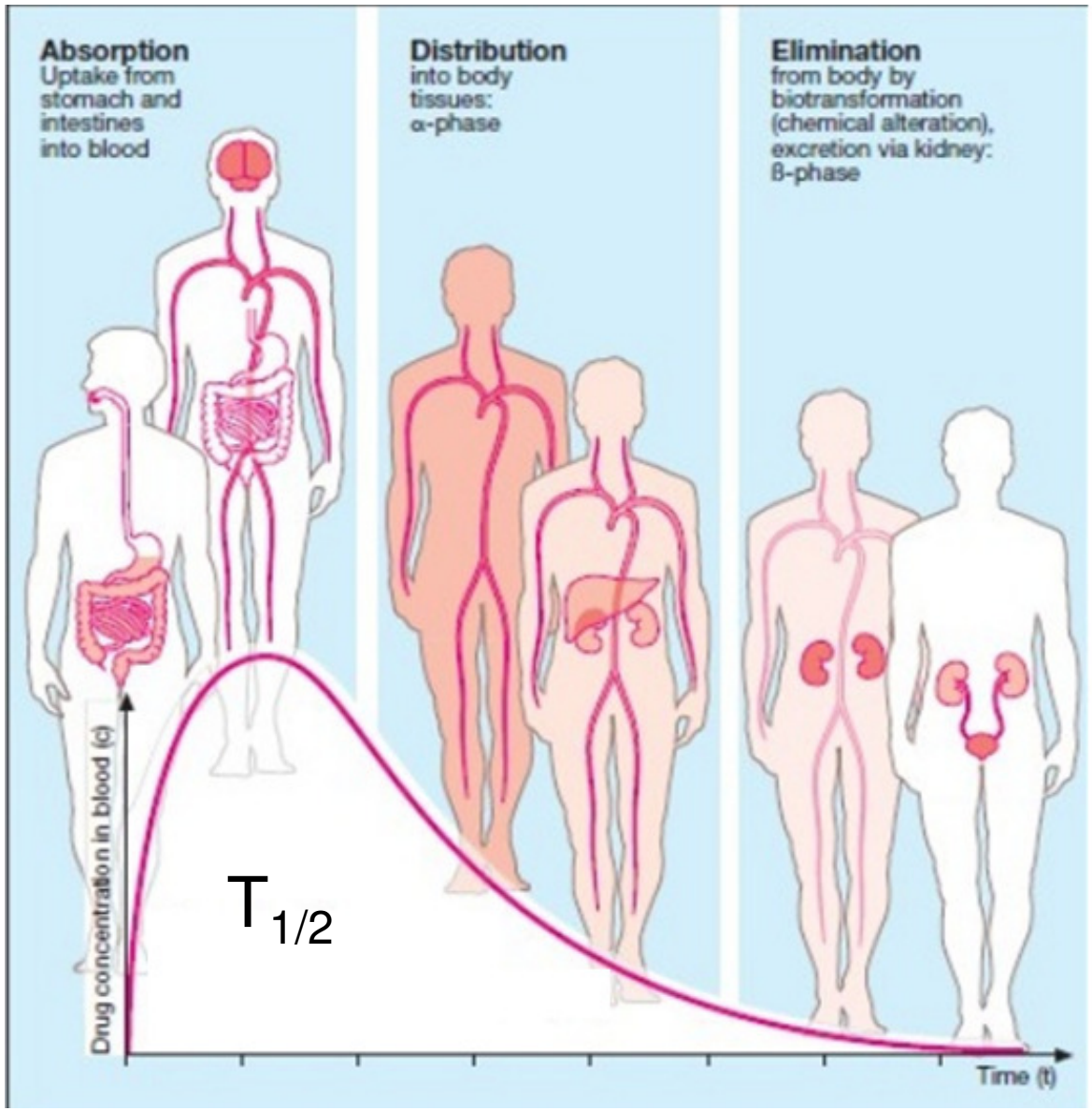




- absorção, distribuição, metabolismo & eliminação

PK

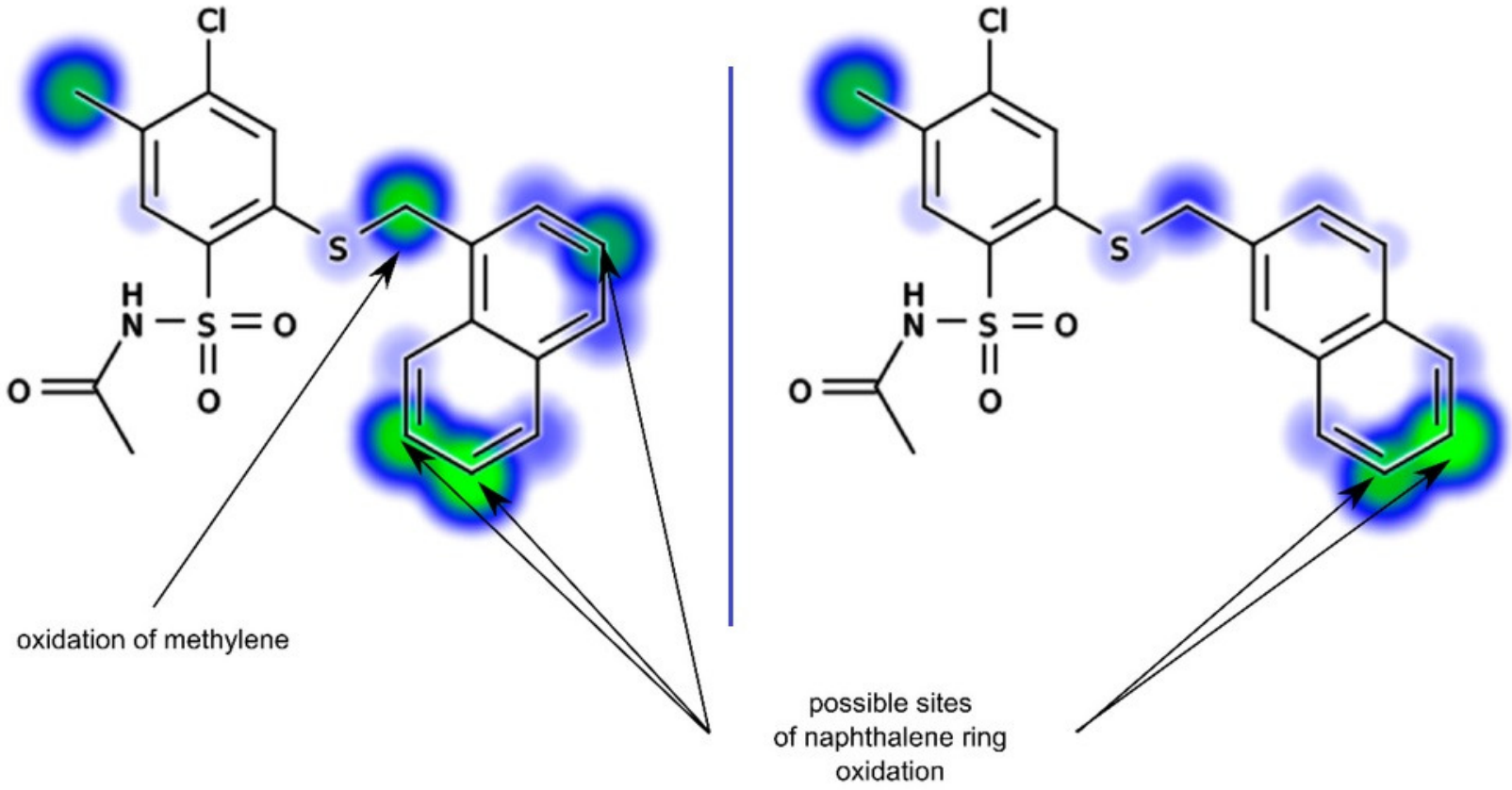
A
D
E



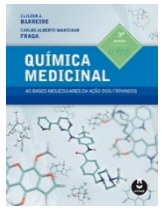
A
D
M
E

Posologia

Metabolismo de fármacos



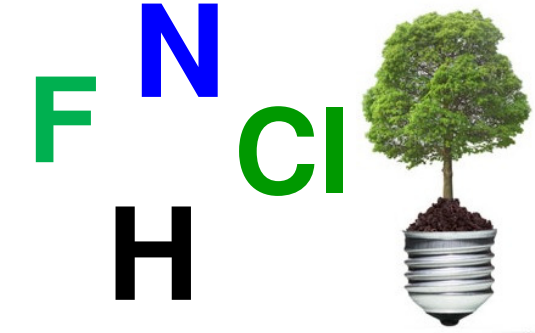
CAPÍTULO 2
FUNDAMENTOS DO METABOLISMO DE FÁRMACOS 43



Como inventar *um* fármaco?

Química
Medicinal

C O S
F N Cl
H



Como prever a atividade de uma molécula?

A abordagem fisiológica

Physiologic approach

A eleição do alvo-terapêutico

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

Conhecimento da fisiopatologia

Doenças multifatoriais

Quimioterapia
SNC
Doença crônica

Physiologic approach

A abordagem fisiológica

LOCK & KEY CONCEPT

identificação do ligante

identificação do farmacóforo

Estratégia do Análogo-ativo

Estrutura do Bioreceptor Conhecida

DHFR Inibidores

Abordagem híbrida

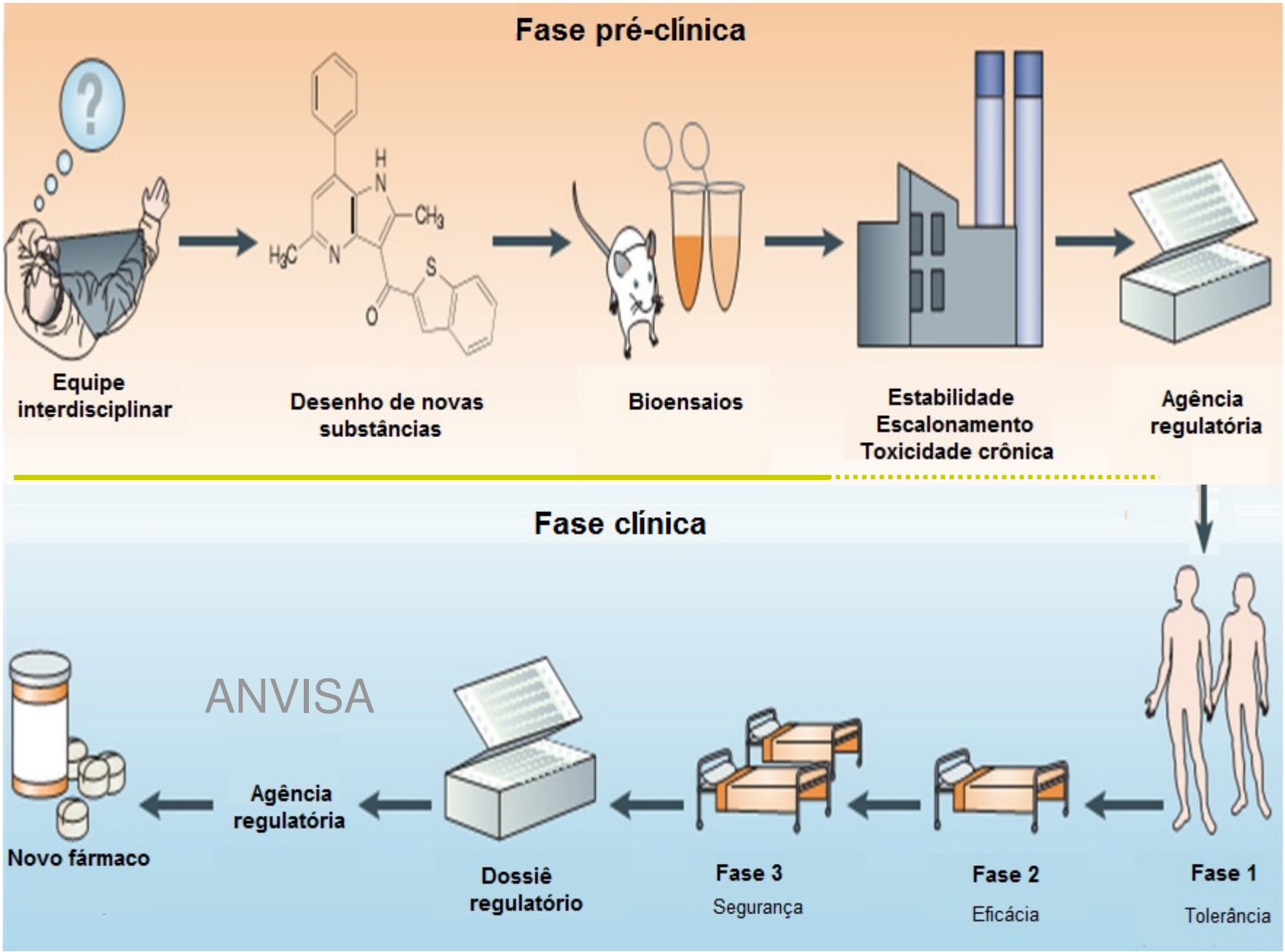
Estrutura do Bioreceptor Desconhecida

Inibidores de HIV proteases

Identificação do protótipo

med chem Química Medicinal

O processo da descoberta de fármacos



Adaptado de J.G. Lombardino & J. A. Lowe III, 2004.