Universidade Federal do Rio de Janeiro

2011 – Ano internacional da Química: A Química em nossas vidas

IQ, UFU, Uberlândia,MG, 29 de novembro-02 de dezembro de 2011

Minicurso 01

Aspectos do Planejamento de Fármacos

Eliezer J. Barreiro

Professor Titular

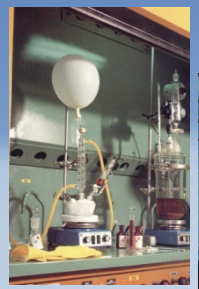
Universidade Federal do Rio de Janeiro

Laboratório de Avaliação e Síntese de Substâncias Bioativas

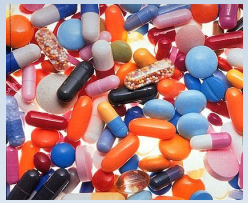
http://www.farmacia.ufrj.br/lassbio

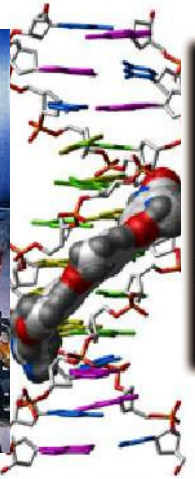
Instituto Nacional de Ciência e Tecnologia em Fármacos e Medicamentos – INCT-INOFAR

Programa de Desenvolvimento de Fármacos – ICB-UFRJ



Como se descobrem os fármacos ?

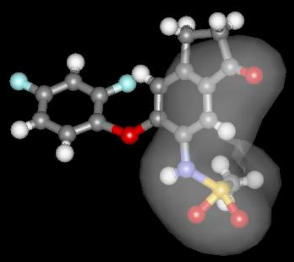




Química Medicinal

O curso

Atualmente, os **novos fármacos**, capazes de atuarem em **qualquer alvo-terapêutico**, são ***descobertos/inventados*** por **planejamento** (racional).



m e d f h e m Química Medicinal

EJ Barreiro, CAM Fraga, ALP Miranda, Estratégias em Química Medicinal para o Planejamento de Fármacos, *Braz. J. Pharm. Sc., 37*, 269-292 (2001).

Fármacos:

o que são?

- **Fármaco…**
  - É uma substância orgânica (> 99%) com propriedades farmacoterapêuticas para uso médico, capaz de recuperar, promover, manter ou preservar o estado de Saúde;
  - Tem elevada eficácia para o alvo terapêutico (PD);
  - Não tóxico;
  - Potente *in vivo* com boa biodisponibilidade: ativo em doses baixas, usado por oral em dose-única ao dia;
  - Bem absorvido e estável metabolicamente (PK):
    - Propriedades fisíco-químicas críticas para a atividade do fármaco por via oral: solubilidade, boa partição passiva membrana/água, pêso molecular, ligações-H;
  - Proteção intelectual (*i.e.* patenteável = conteúdo inventivo);
  - Acessível sinteticamente em custos aceitáveis (*scale-up*);
  - Tem aplicação médica segura & inovadora (?);

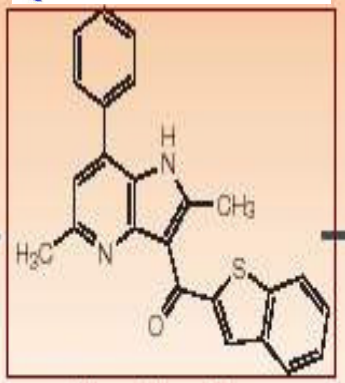
- **… as propriedades moleculares dos fármacos são objeto do estudo da**

Química Medicinal

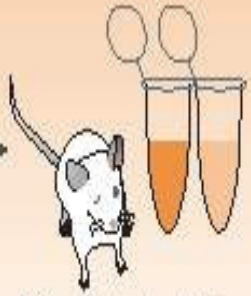
Preclinical studies

Química Medicinal

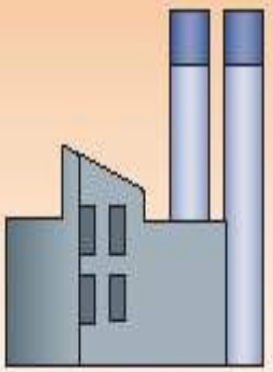
Research team formed and objectives set



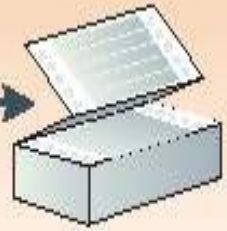
Novel chemicals synthesized



Chemicals tested for efficacy and safety in test tubes and animals. Results used to choose drug candidate.

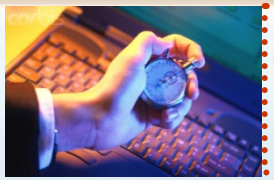


Formulation, stability scale-up synthesis, chronic safety in animals

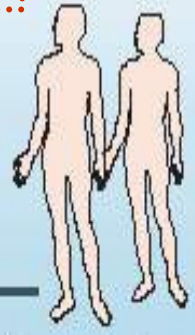


Company files Investigational New Drug (IND) application with FDA

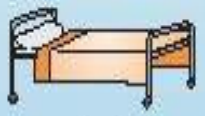
Clinical studies



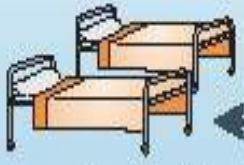
O processo do desenvolvimento de novos fármacos é complexo…



Phase I: studies in healthy humans (toleration)



Phase II: studies in patients (efficacy)



Phase III: large clinical trials in many patients

Company files New Drug Application (NDA)

ANVISA

FDA

FDA reviews NDA

Drug is approved for marketing

JA Lombardino & JA Lowe III, Nature Rev. Drug Disc. 2004, 3, 853

Universidade Federal do Rio de Janeiro

Química Medicinal

Definição

*estuda os **fatores moleculares** relacionados ao modo de ação dos fármacos, incluindo a compreensão da relação entre a **estrutura química** e a atividade (SAR), além das **propriedades** que governam sua absorção, distribuição, metabolismo, eliminação (ADME) e toxicidade.*

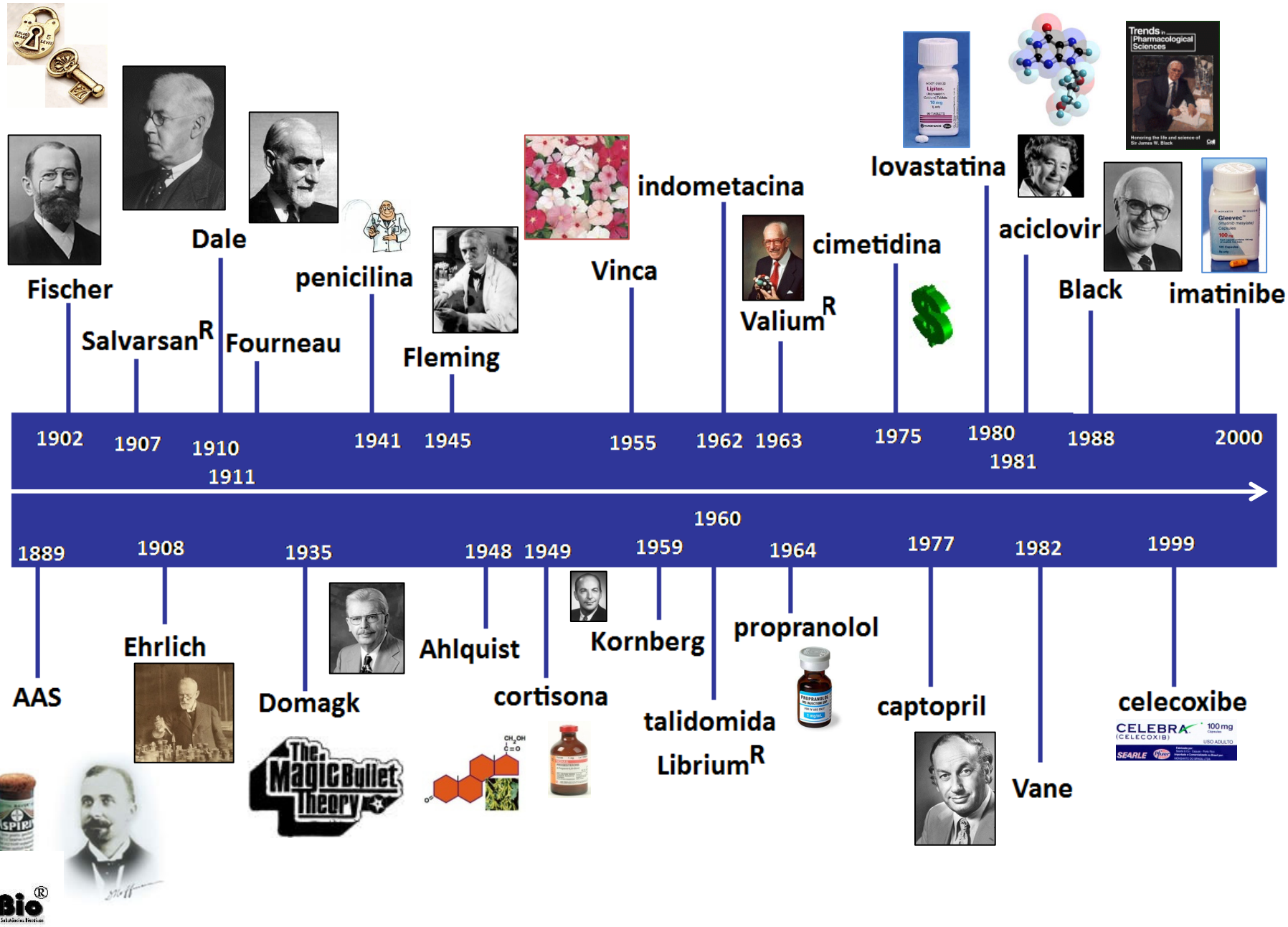
IUPAC
http://www.iupac.org
Chemistry and Human Health Division (VII)
Subcommittee on Medicinal Chemistry and Drug Development.

Eur. J. Med. Chem., 31, 747 (1996)

C. R. Ganellin et al., Eur. J. Med. Chem. 2000, 35, 163; A. Monge et al., Eur. J. Med. Chem. 2000, 35, 1121

LASSBio®

Cronologia histórica da Química Medicinal



Universidade Federal do Rio de Janeiro

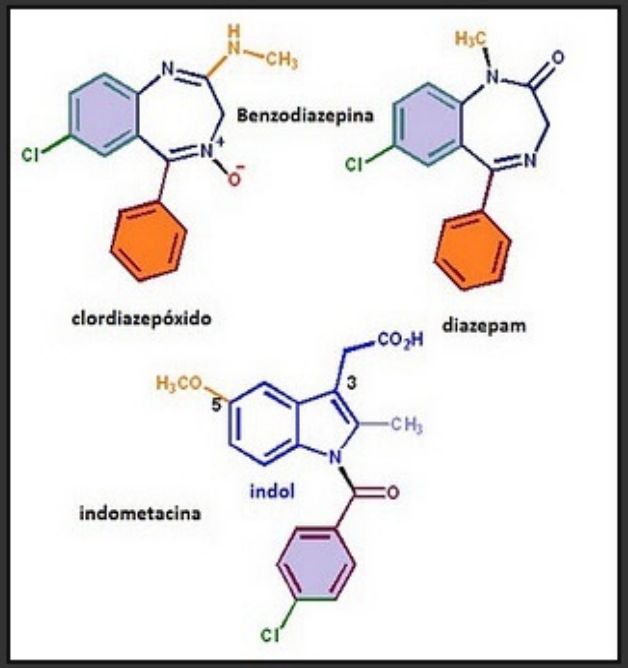
http://ejb-eliezer.blogspot.com

De fármacos e suas descobertas

Pretende-se tratar de temas, opiniões, comentários sobre a Ciência dos Fármacos, seu uso seguro e benefícios. Aspectos da formação qualificada de universitários e pós-graduandos nas Ciências dos Fármacos também são de interesse.

SÁBADO, 26 DE NOVEMBRO DE 2011

A Linha do Tempo da Química Medicinal: assim nascem os fármacos (IV)



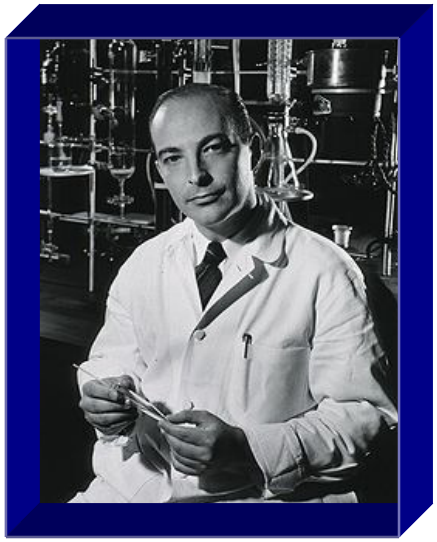
Nesta etapa da **Linha do Tempo da Química Medicinal: assim nascem os fármacos** atingimos a década de 50, a partir de quando surgiram inúmeras inovações terapêuticas significativas, resultado dos avanços importantes observados em várias disciplinas relacionadas à Química ou à Biologia.

http://ejb-eliezer.blogspot.com

LASSBio®

EJB2

UFRJ



Arthur Kornberg
1918-2007

Prêmio Nobel, 1959

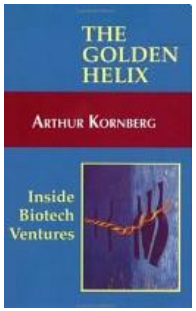
1987

The Two Cultures: Chemistry and Biology[1]

Arthur Kornberg

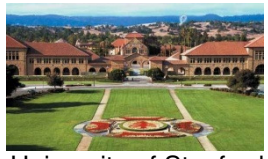
Department of Biochemistry, Stanford University, Stanford, California 94305

Received July 14, 1987



"Much of life can be understood in rational terms if expressed in the language of chemistry... the historical roots of ***chemistry*** *and* ***biology*** *are intertwined in many places…*

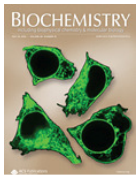
Pharmaceutical chemistry *was until recently the bastion of organic chemistry… in the search for alternative or superior drugs for the treatment of various diseases..."*



University of Stanford

LASSBio®

medicinal chemistry
Química Medicinal



Biochemistry **1987,** *26,* 6888-6891

Slide 10

EJB2

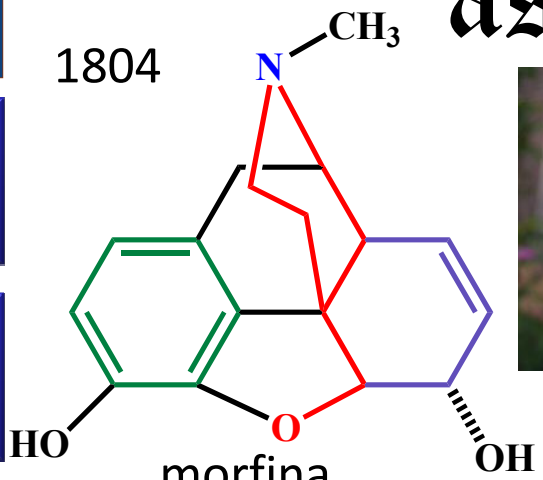
Kornberg definiu as bases da interdisciplinaridade das ciências dos fármacos quando antecipou a necessidade de aproximar-se a Química e a Biologia.

Eliezer J. Barreiro; 04/03/2010

Interdisciplinaridade...

as moléculas pioneiras ...

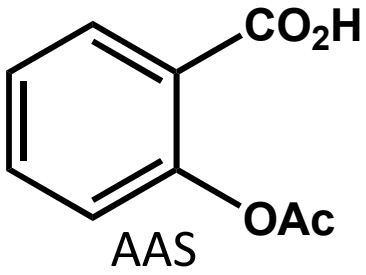
1804



morfina

$C_{17}H_{19}NO_3$

1897



AAS

$C_9H_8O_4$

Bayer

Se é Bayer, é bom.

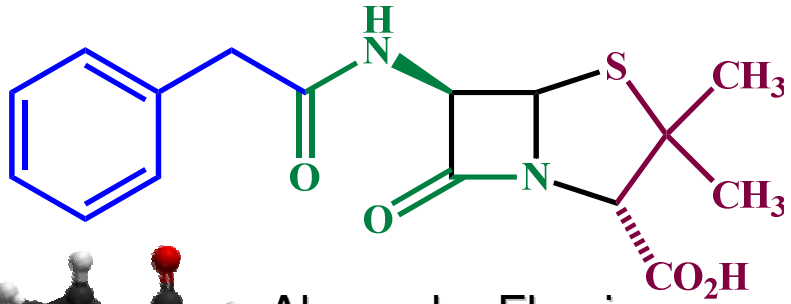
1929

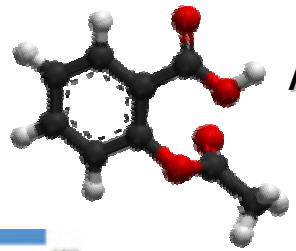
penicilina

$C_{16}H_{18}N_2O_4S$

Felix Hoffman

1868- 1946





Alexander Fleming

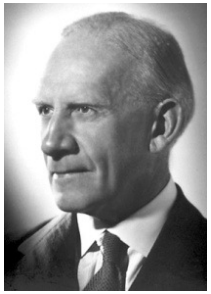
1881-1955

Nobel 1945

Library of Congress

Friedrich W. A. Sertürner

1783- 1841



Sir Robert Robinson

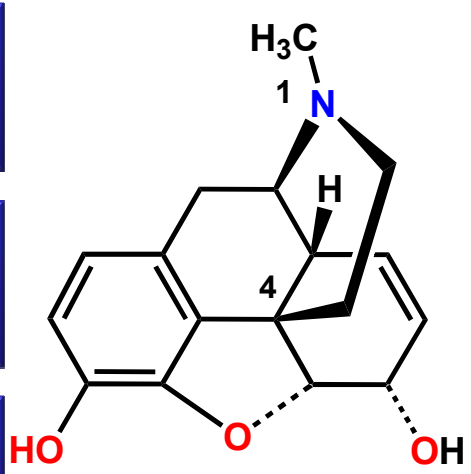
1886-1975

Nobel 1947

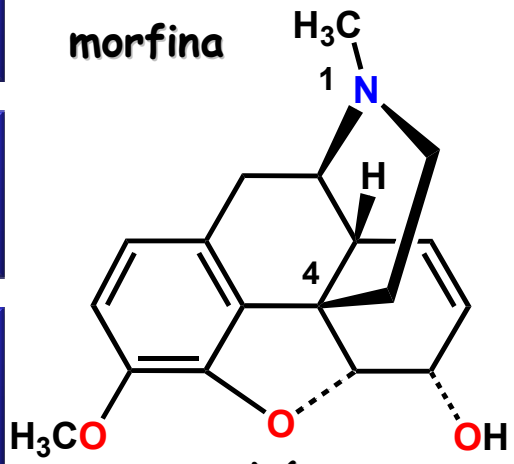
Produtos Naturais & Fármacos: Alcalóides

Alcalóides fenantrênicos e benzilisoquinolínicos (papaverina 0,2%)

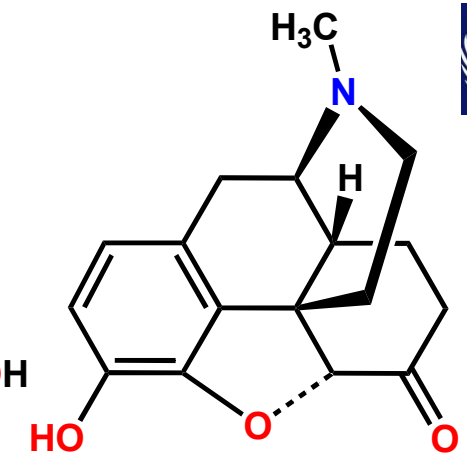
Papaver somniferum



morfina



codeína



diidromorfinona

1493-1541 Marco Polo (Veneza) ⇒ Ópio

1803 ⇒ Friedrich WA Sertürner isola a morfina ("Morpheus") ⇒ hipno-analgesia

1817 - Setürner Co

1827 - Darmstadt , Alemanha (Merck)

1924 – Diidromorfinona (Dilaudid) Knoll

1925 – *Sir* Robert Robinson (estrutura)

1952 – M. Gates primeira síntese total

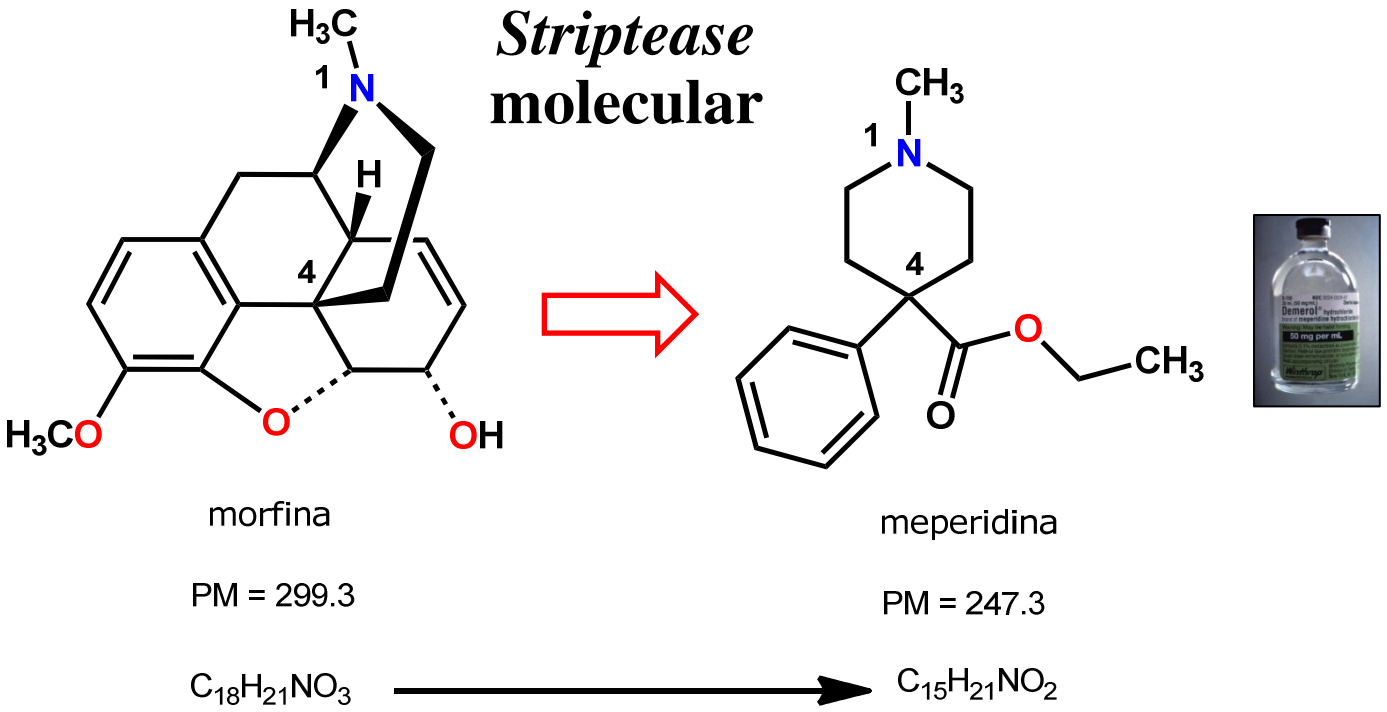
1954 - Beckett & Casey, Un. London

Descoberta dos receptores opióides: δ, κ, μ

P. W. Schiller, *Progr. Med. Chem.* *1991*, 28, 301

analgesia central; tolerância; dependência química; síndrome de abstinência

Domesticando produtos naturais



morfina

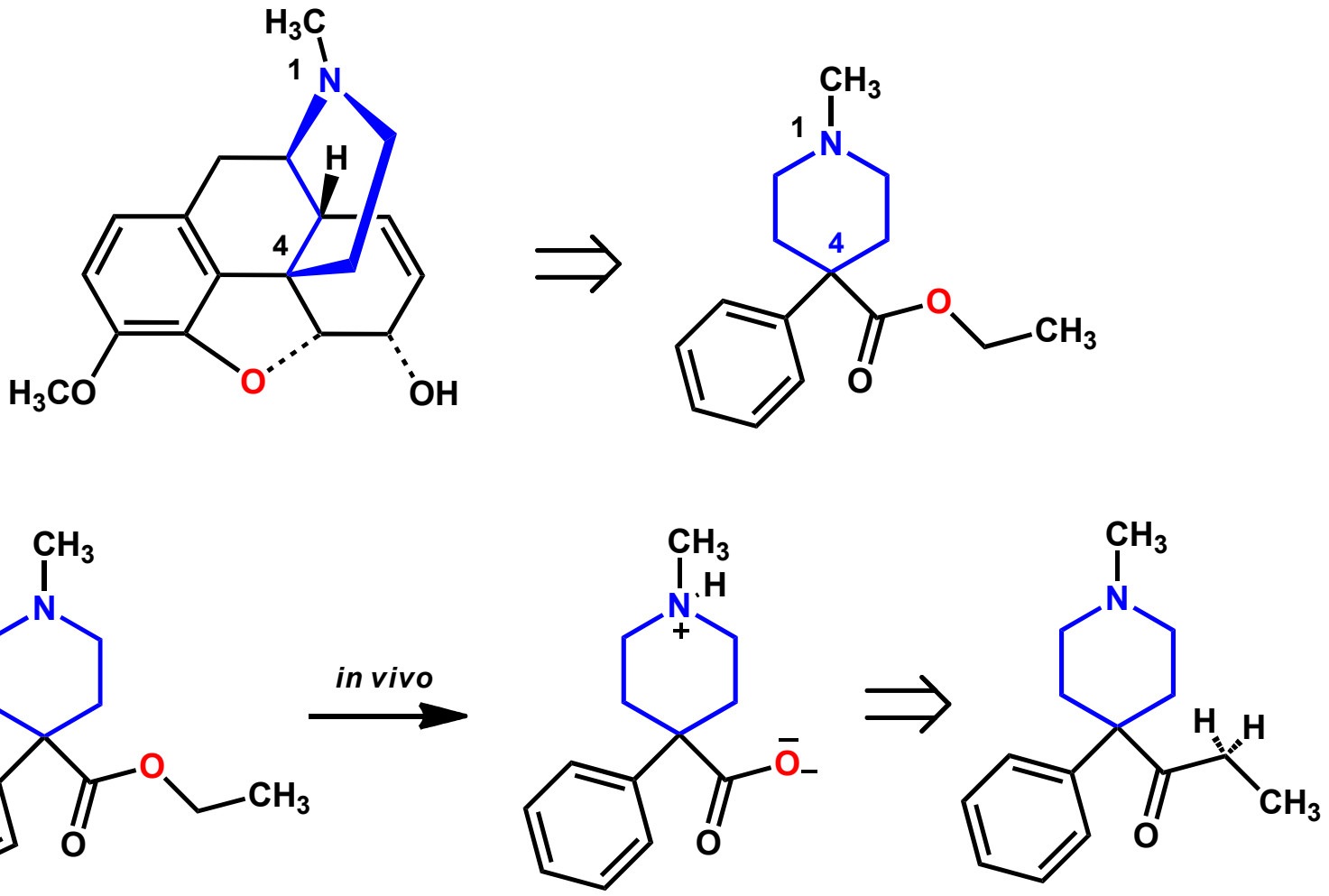
PM = 299.3

$C_{18}H_{21}NO_3$

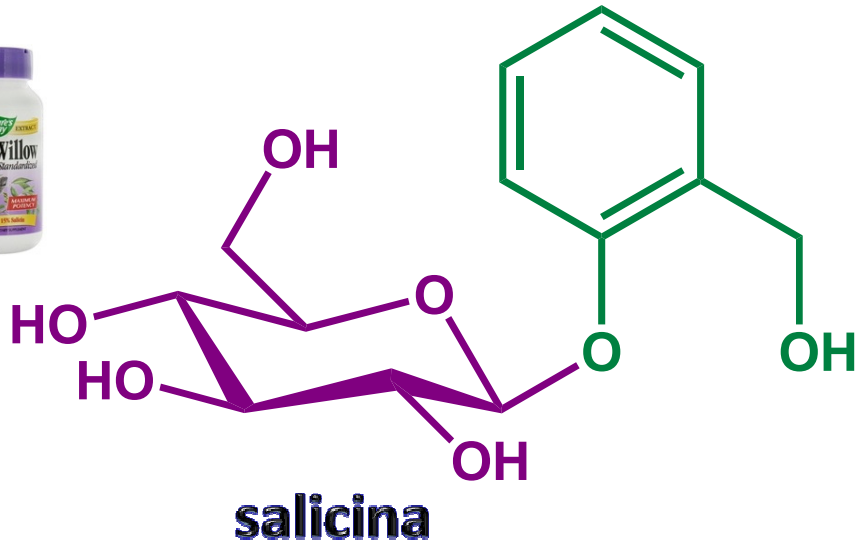
meperidina

PM = 247.3

$C_{15}H_{21}NO_2$



<< ClogP = 2,03 (calc.)



salicina

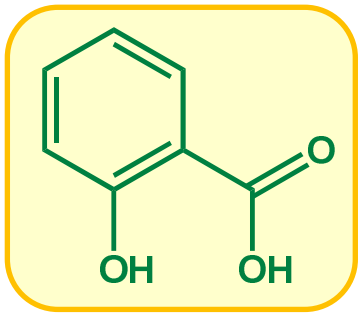
AAS

Salicina es un β-glucósido, com propiedad anti-inflamatoria obtenida de corteza de sauce (willow bark)

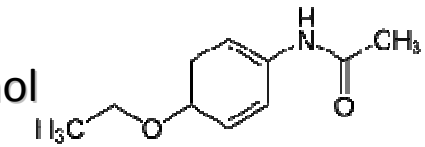
La teoría de las firmas

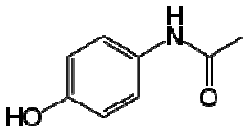
theory of signatures

1853 -Charles F.Gerhardt (impura)
1899 – Felix Hoffmann AAS
1886 – acetanilida (analgésico)
1887 -fenacetina
1953 - paracetamol



AS



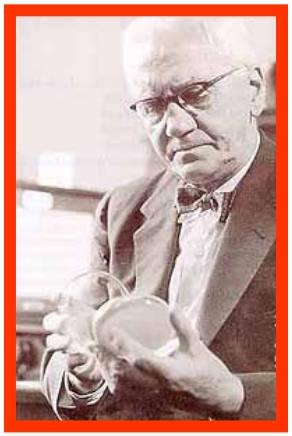


Antibioticoterapia

Moléculas Salva-vidas

E. B. Chain
1906-1979

1945 Nobel

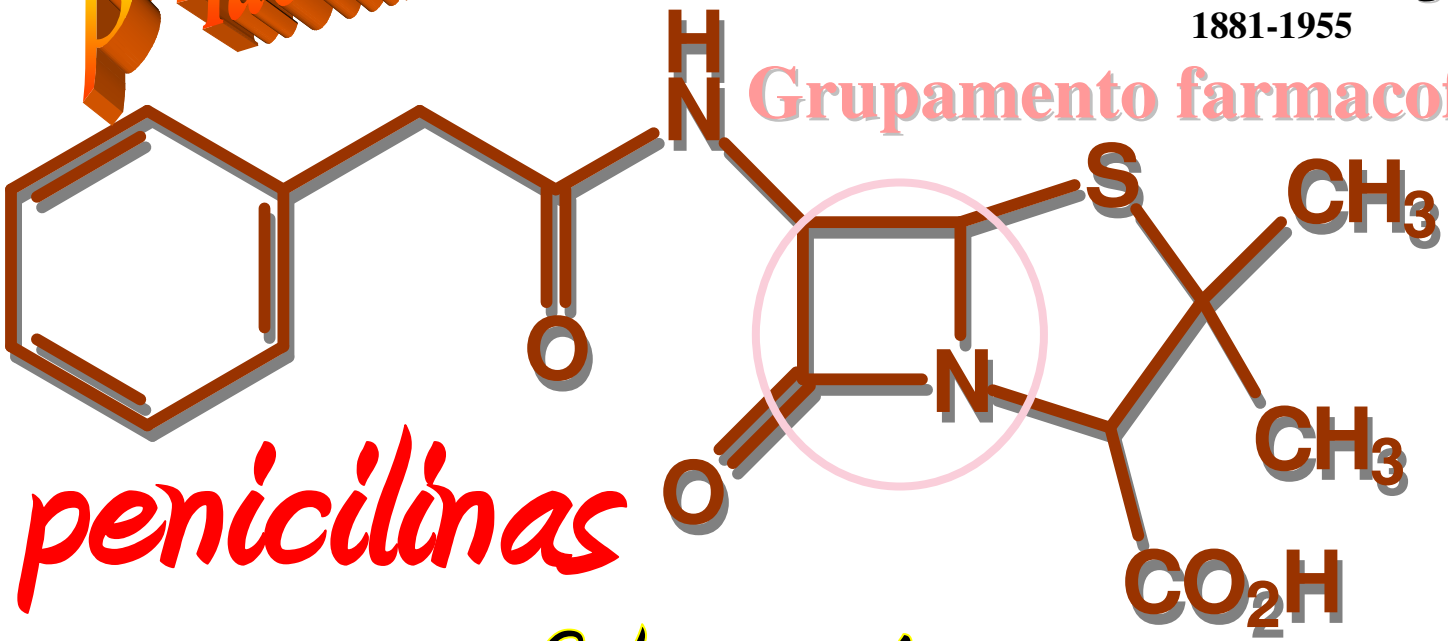


Sir A. Fleming
1881-1955

Sir H. W. Florey
1898-1968

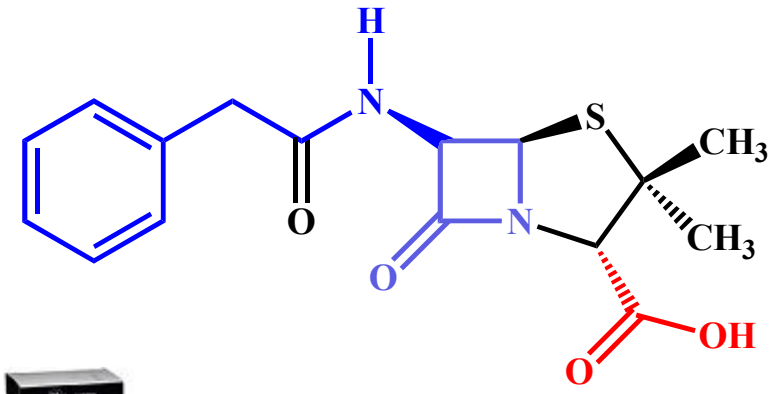
β-lactâmicos

Grupamento farmacofórico

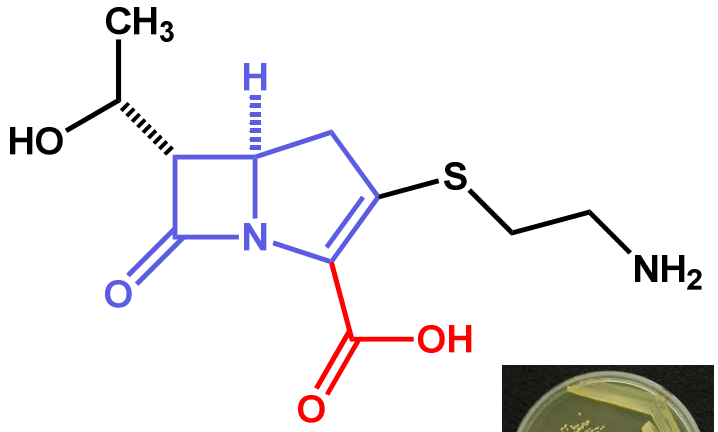


penicilinas

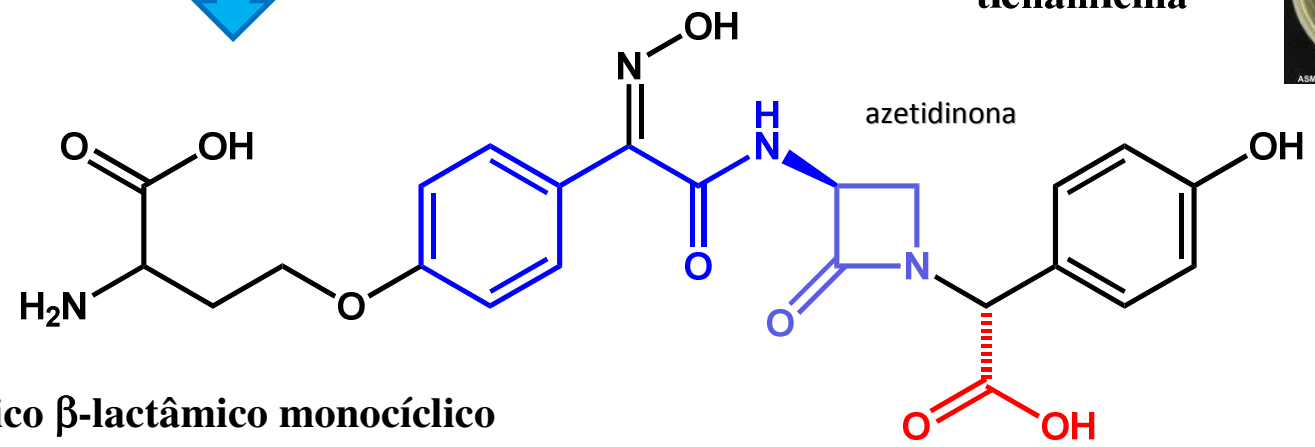
cefalosporinas



penicillin G



tienamicina



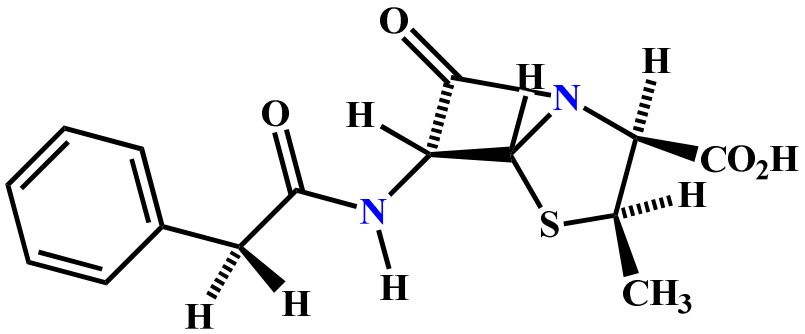
nocardicina

Antibiótico β-lactâmico monocíclico

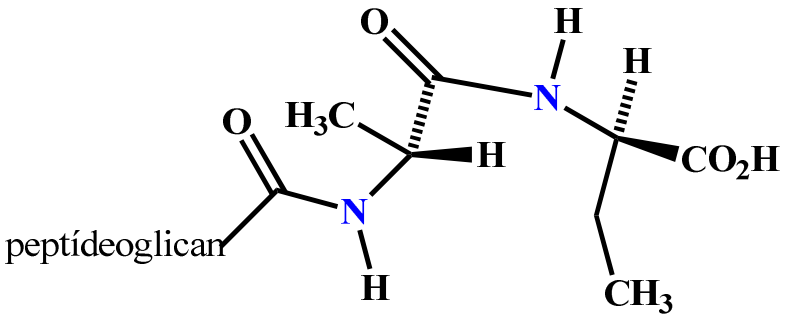
Nocardia uniformis

Ativo *via* oral

LASSBio®



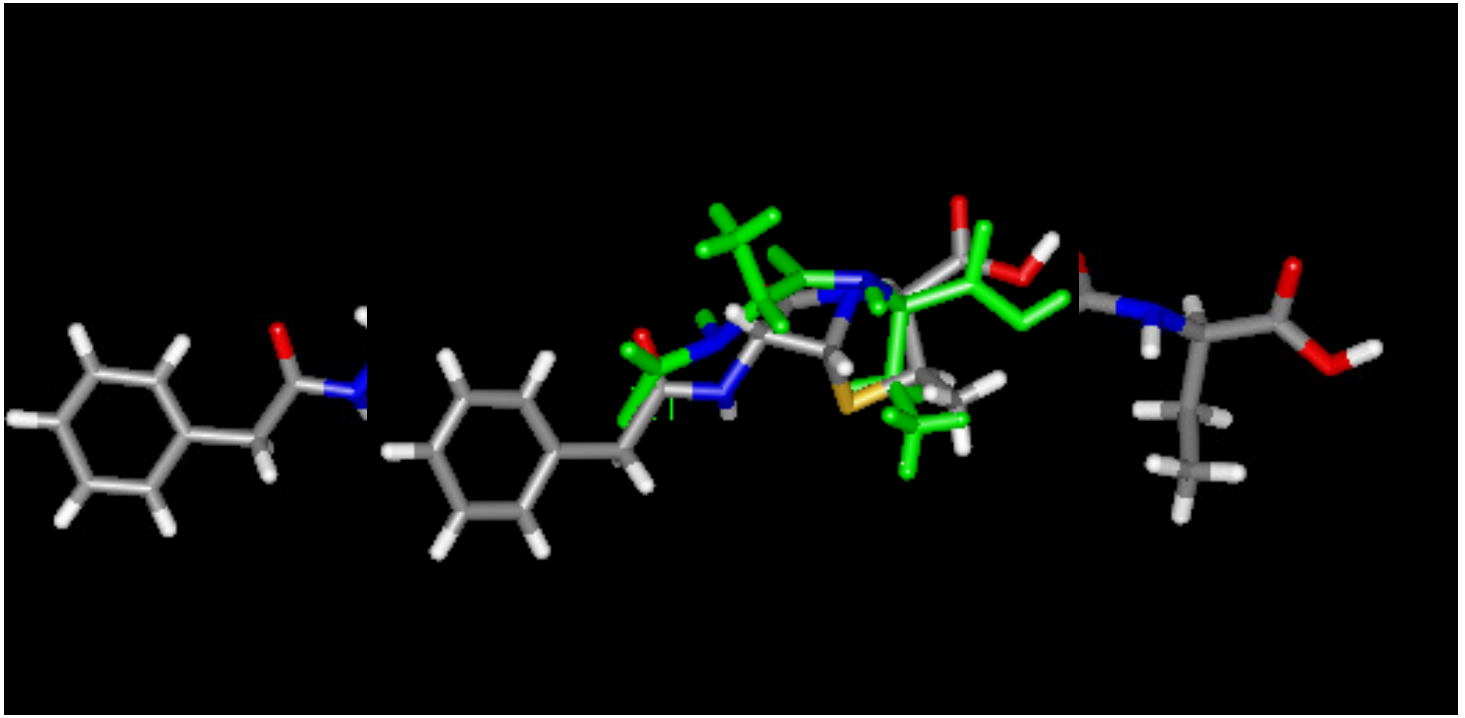
penicilina



peptídeoglicam

D-alanil-D-alanil

Mecanismo molecular de ação



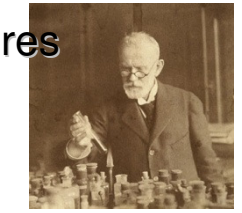
Universidade Federal do Rio de Janeiro

Química Medicinal

Conceito de grupamento farmacofórico

LASSBio®

Conceito de Grupo Farmacofórico

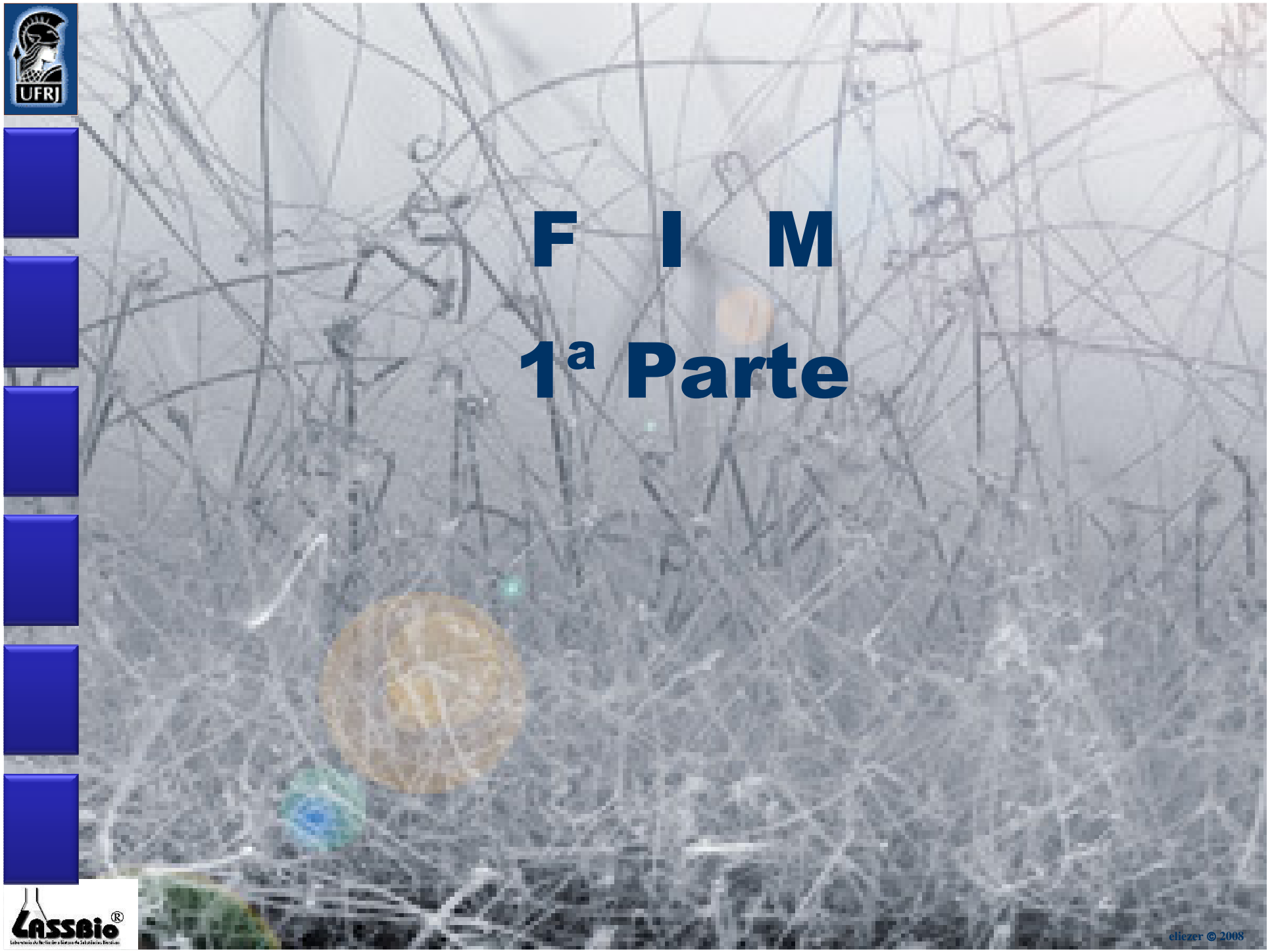


Paul Ehrlich (1909) – Um **farmacóforo** "carries (*phoros*) the essential features responsible for a drug's (= pharmacon's) biological activity"
(Ehrlich. *Dtsch. Chem. Ges.* 1909, 42: p.17).

Em 1977, **Peter Gund** atualizou a definição: "a set of structural features in a molecule that is recognized at a receptor site and is responsible for that molecule's biological activity"
(Gund. *Prog. Mol. Subcell. Biol.* 1977, 5: pp 117–143).

IUPAC: "an ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target and to trigger (or block) its biological response".

Barreiro & **Fraga**: **É o conjunto de características eletrônicas e estéricas que caracterizam um ou mais grupos funcionais ou subunidades estruturais, necessários ao melhor reconhecimento molecular pelo receptor e, portanto, para o efeito farmacológico desejado**. Farmacóforo não é uma molécula real, nem associações de grupos funcionais; ao contrário, é um conceito abstrato que representa as diferentes capacidades de interações moleculares de um grupo de compostos com o sítio receptor. O farmacóforo pode ser considerado como a "*parte*" molecular do fármaco essencial à atividade desejada.


F I M
1ª Parte
eliezer ©2008

Universidade Federal do Rio de Janeiro

2011 – Ano internacional da Química: A Química em nossas vidas

IQ, UFU, Uberlândia,MG, 29 de novembro-02 de dezembro de 2011

Universidade Federal de Uberlândia

Minicurso 01

Aspectos do Planejamento de Fármacos

Parte 2

Eliezer J. Barreiro

Professor Titular

Universidade Federal do Rio de Janeiro

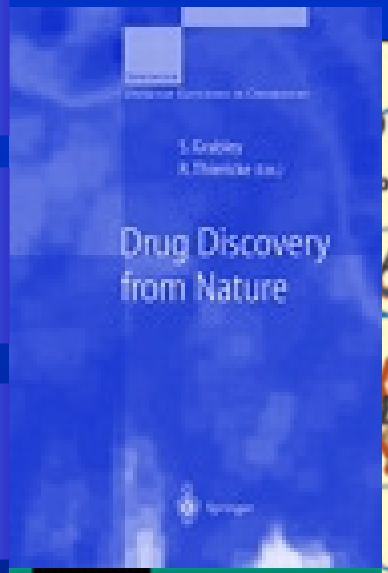
Laboratório de Avaliação e Síntese de Substâncias Bioativas

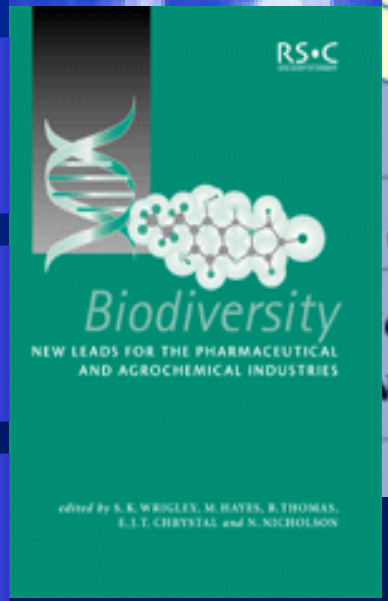
http://www.farmacia.ufrj.br/lassbio

Instituto Nacional de Ciência e Tecnologia em Fármacos e Medicamentos – INCT-INOFAR

Programa de Desenvolvimento de Fármacos – ICB-UFRJ

Patrimônio genético brasileiro





8.547.404 Km²

190.732.690 hab.

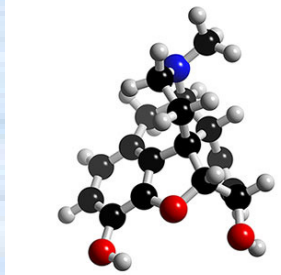
(6.952.867.116 hab.;mundo)

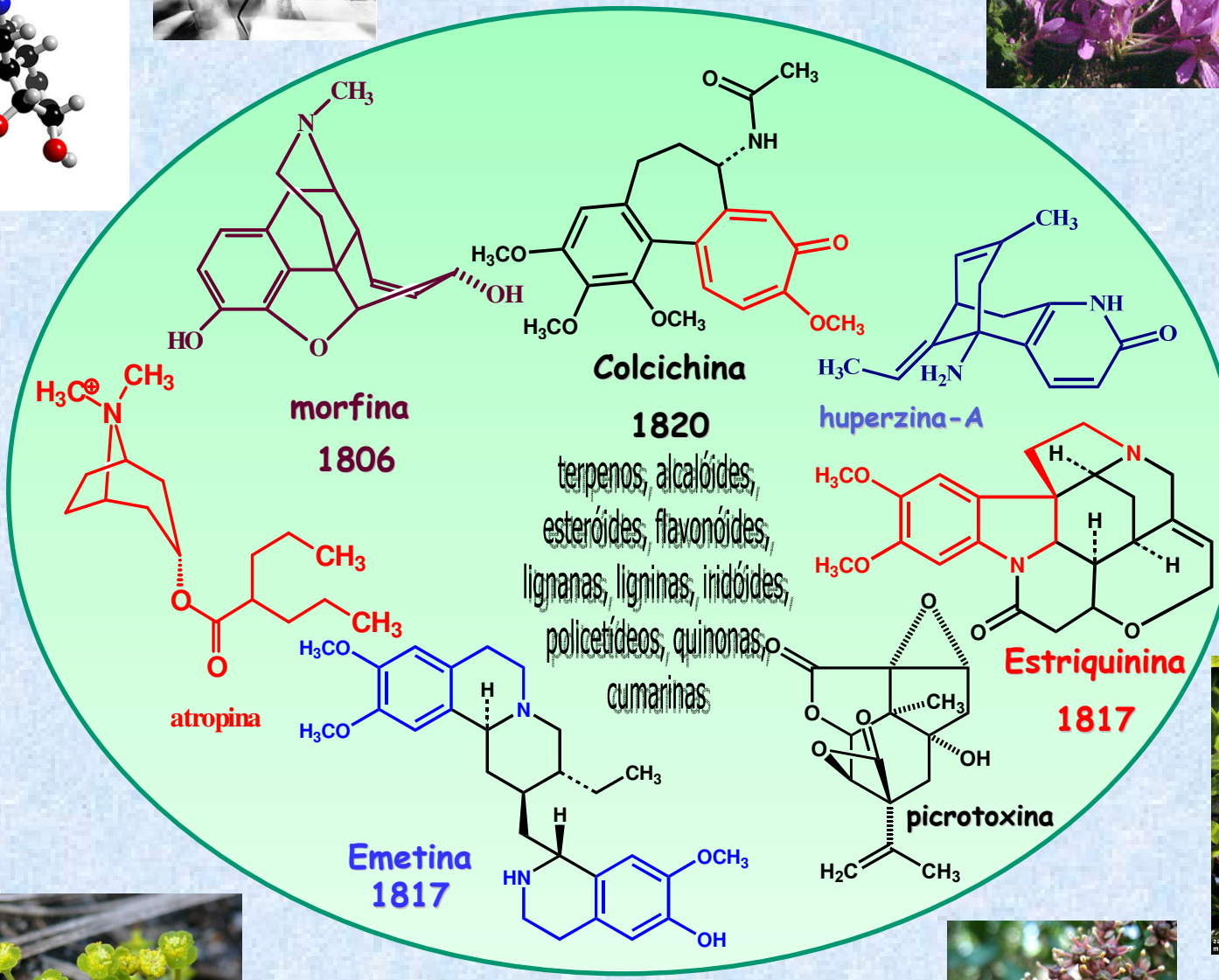
www.ibge.gov.br

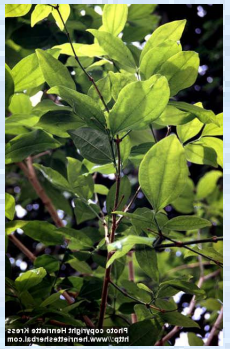
9.198 km²

costa Atlântica

Quimiodiversidade





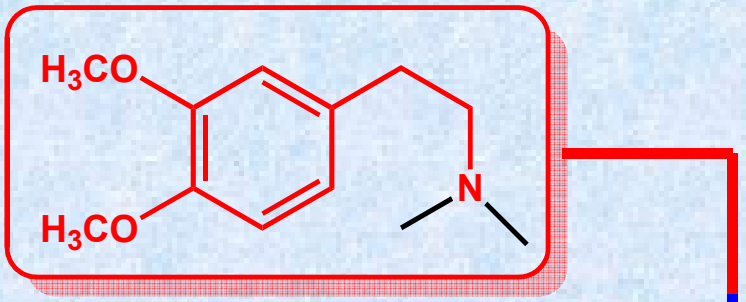


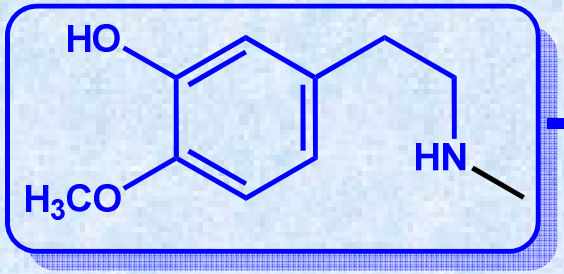
No tempo dos alcalóides...

emetina

Dissecação molecular

Fragmento molecular A



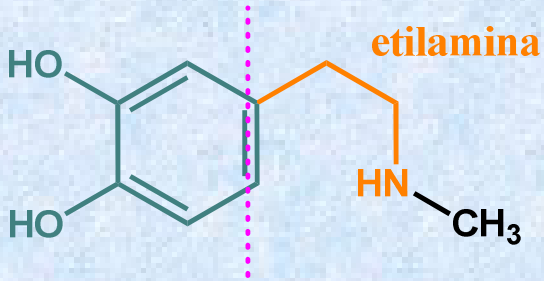


Fragmento molecular B

Similaridade molecular

sub-unidade

etilamina

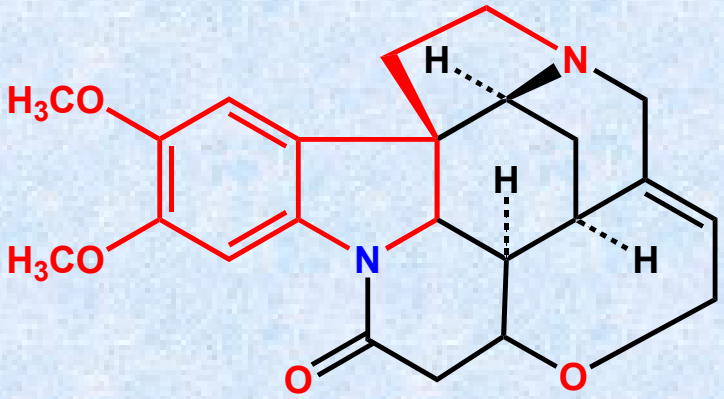


catecol

sub-unidade

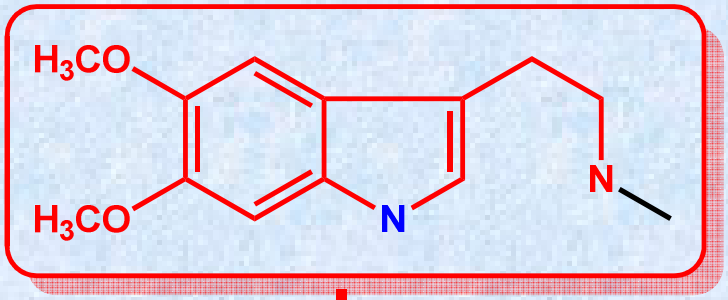
Padrão de similaridade molecular

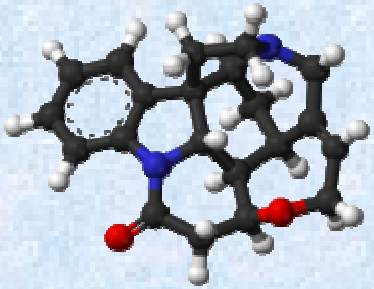
Biorreceptores adrenérgicos



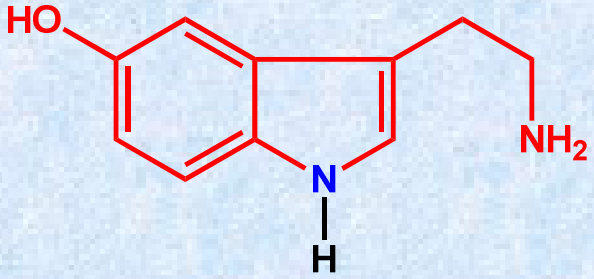
estriquinina

Dissecação molecular





Similaridade molecular



Serotonina

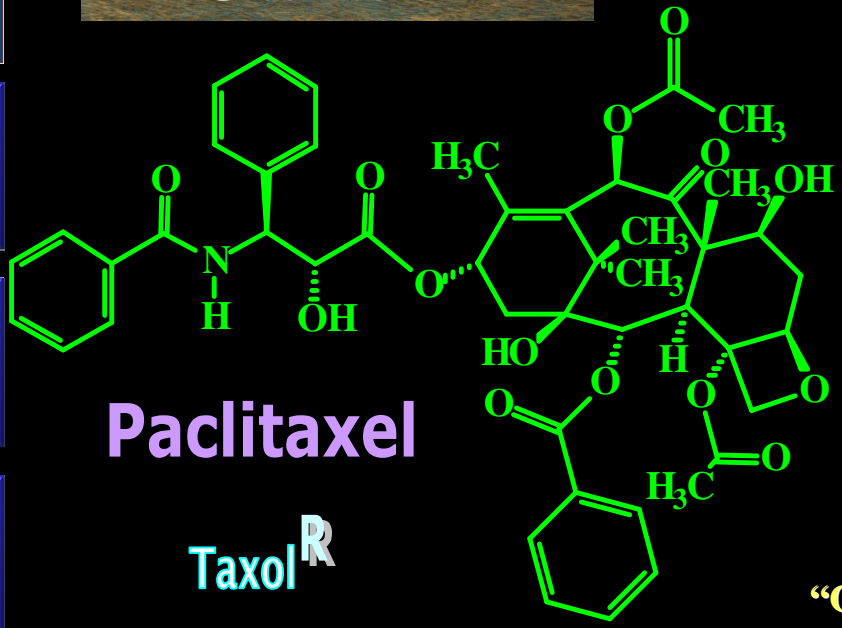
Padrão de similaridade molecular

Biorreceptores serotoninérgicos

Biorreceptores acetilcolina

Inter-alia: *Virola sp*, epibatidina

Câncer

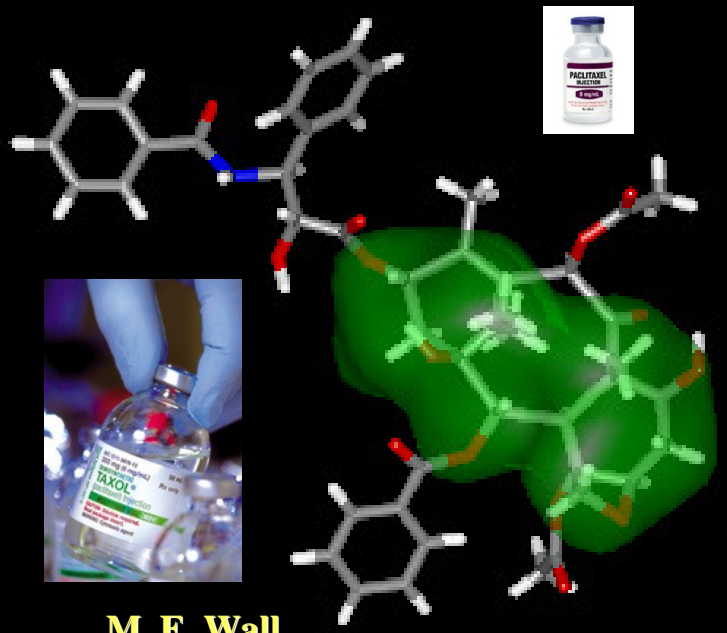


Paclitaxel

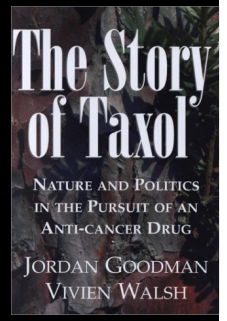
Taxol®

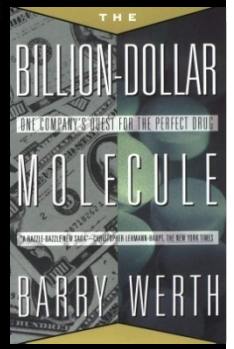
M. C. Wani *et al.*, J. Am. Chem. Soc. 1971, 93, 2325

Res. Triangle Park, 1967



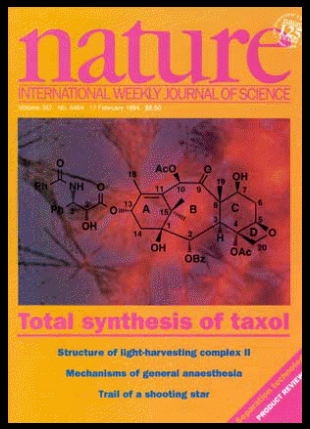
M. E. Wall,,
"Chronicles of Drug Discovery",
D. Lednicer, vol.3, ACS, 1993,
pp. 327-348

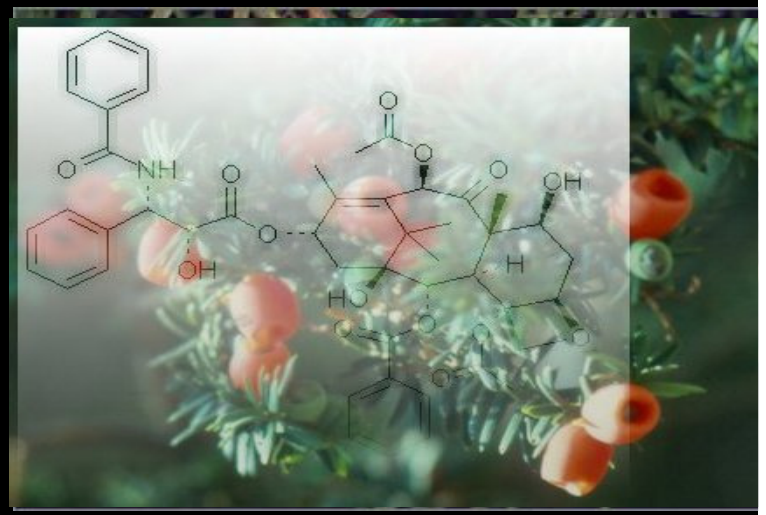




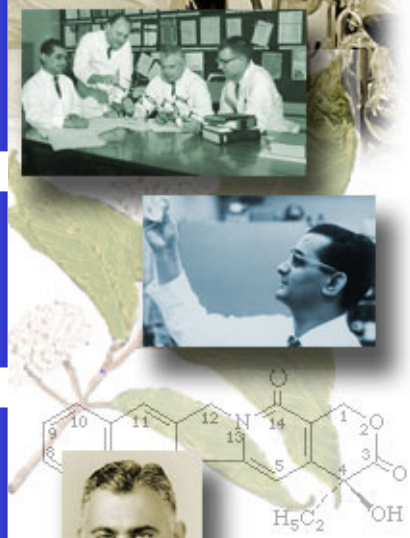
M. E. Wall & M. C. Wani

1996 - National Cancer Institute
Award of Recognition



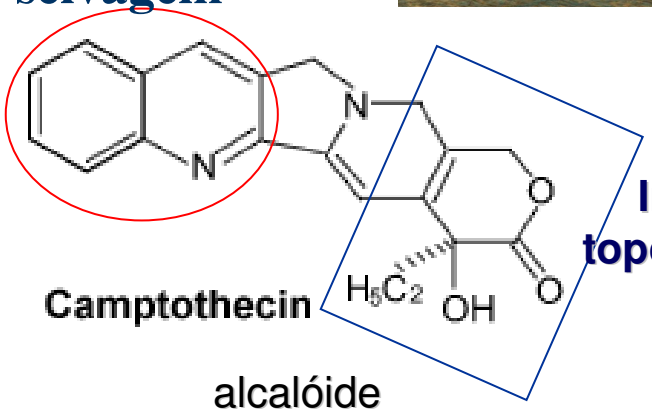


Taxus bacatta



Molécula "selvagem"

Câncer

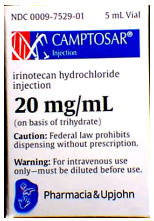


Camptothecin

alcalóide
quinolínico de biossíntese mista

Inibidor de topoisomerase-1

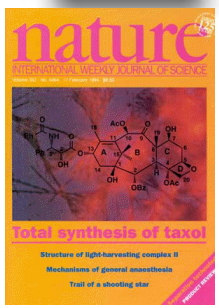
Molécula "domesticada"

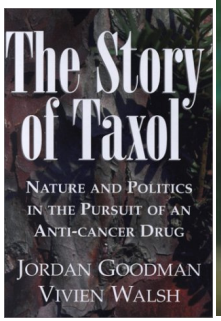


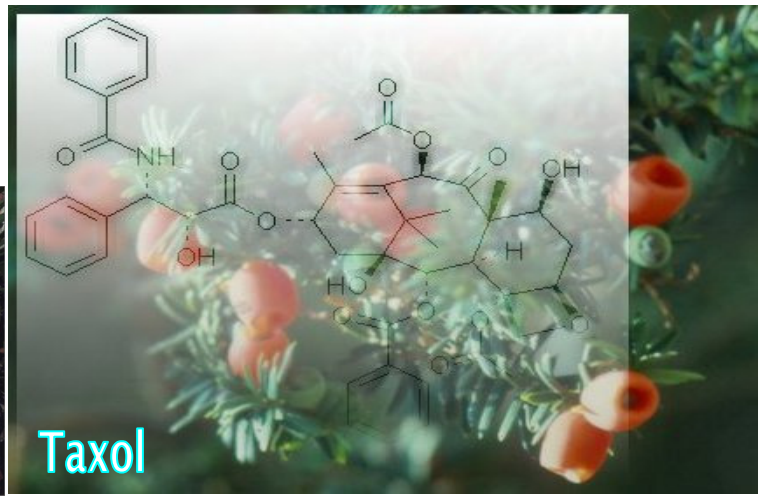
topotecan

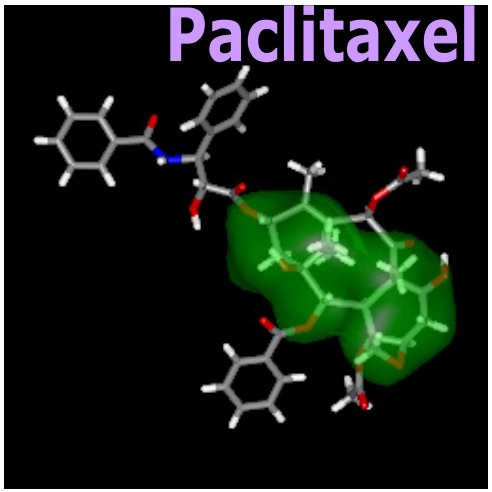
Wall, ME & Wani, MC "**Camptothecin: Discovery to Clinic**"
Annals of the New York Academy of Sciences 1996, 803, 1

Wall, ME, MC Wani, CE Cook, KH Palmer, AT McPhail, GA Sim, "Plant antitumor agents. 1. The isolation and structure of camptothecin, a novel alkaloidal leukemia and tumor inhibitor from *Camptotheca acuminata*" *J. Am. Chem. Soc.*1966, 88, 3888.

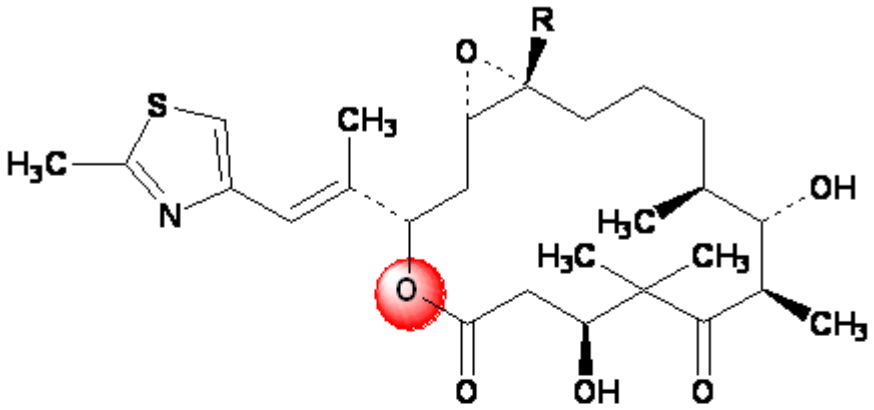






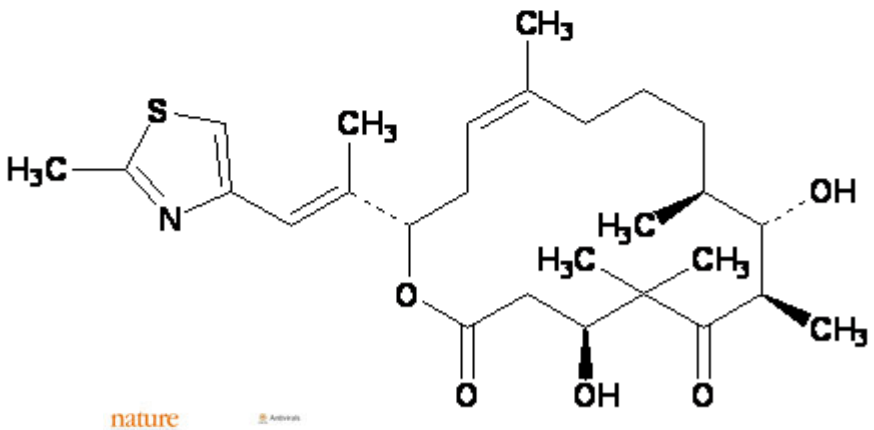


Isolada de Sorangium cellulosum em 1993



Epotilona A R = H

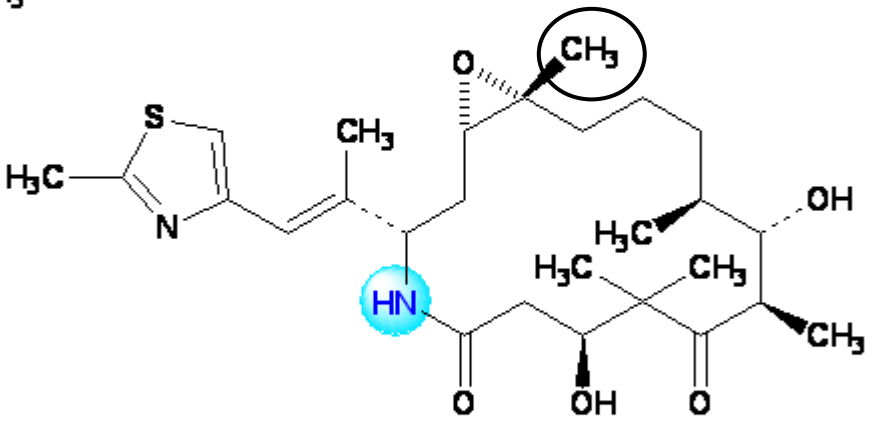
Epotilona B R = CH_3



Epotilona D

2007 - Primeiro membro da classe dos macrociclos de 16 membros (epotilonas) a ser aprovado pelo FDA para tratamento do câncer metastático de mama, atuando como inibidor de microtúbulos

Análogo semi-sintético



Ixabepilona

Ixempra^{R}

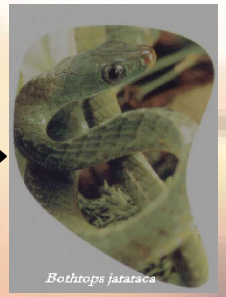
BMS, Out. 2007

Via fermentativa bacteriana, ativo em células taxano-R

A Conlin, M Fornier, C Hudiis, S Kar, P. Kirkpatrick, *Nat. Rev. Drug Discov.* **2007**, *6*, 953

Inovação terapêutica

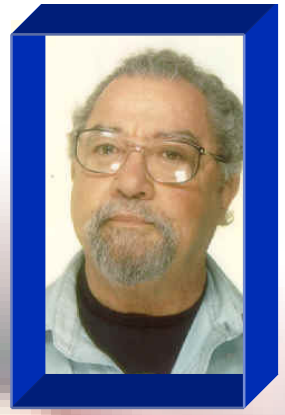
M. O. Rocha e Silva
1910-1983



jararacá

Fármacos Inteligentes

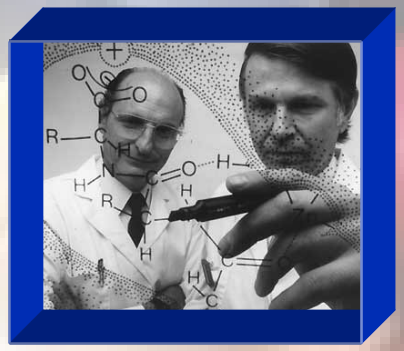
Bradicinina
(W. Beraldo, 1949)



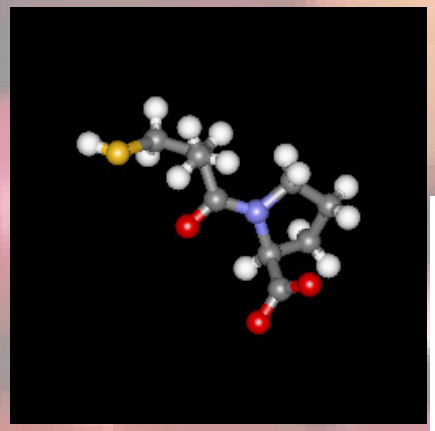
S. H. Ferreira
1934-

S.H. Ferreira, A Bradykinin-potentiating factor (BFP) present in the venon of *Bothrops jararaca, Brit. J. Pharmacol.* 1965, *24*, 163.

Inibidores da Enzima Conversora de Angiotensina



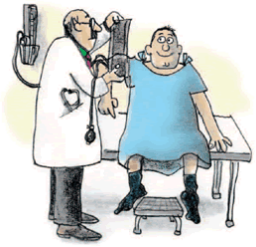
D. W. Cushman & M. A. Ondetti



Captopril

M. A. Ondetti, D. W. Cushman & B. Rubin, *Chronicles of Drug Discovery*, vol. 2, J.S. Bindra & D. Lednicer, Eds., Wiley, Nova Iorque, 1983, p. 1-32

Sistema Renina-Angiotensina



Angiotensinogênio

fígado

inibidores

renina

Asp-protease

rins

REDUÇÃO DA PRESSÃO ARTERIAL

Angiotensina I

Asp-Arg-Val-Tyr-Ile-His-Pro-Phe—His-Leu-OH

Bradicinina

inibidores

E C A

Zn-metalopeptidase

E C A

inibidores

Feedback Negativo

Angiotensina II

peptídeo inativo

Asp-Arg-Val-Tyr-Ile-His-Pro-Phe- OH

antagonistas

1934 – Harry Goldblat (EUA)
1940 – Bruno Menendez (ARG)
1949 – Maurício Rocha e Silva (BR)
1965 – Sérgio H. Ferreira (BR)

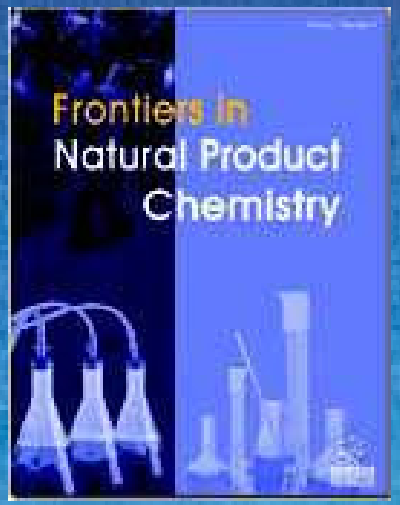
Receptores de Angiotensina II

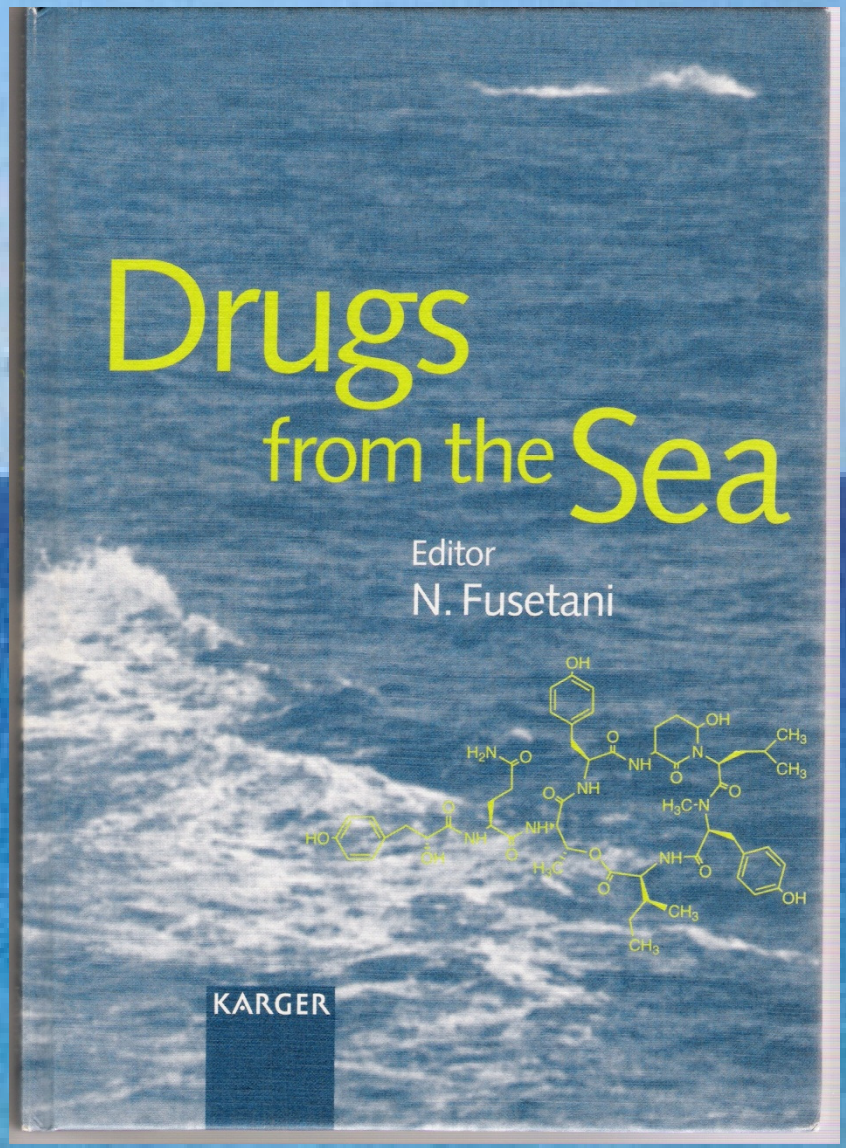
Vasoconstrição

AUMENTO DA PRESSÃO ARTERIAL

Produtos Naturais do Mar

N. Fusetani





ET-743: Promissor Agente para o Tratamento de Sarcomas

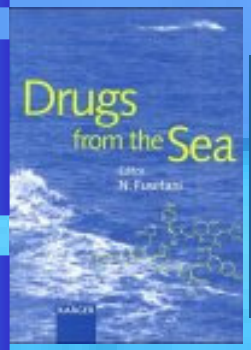
Nobel 1990

100 vezes mais ativo que Taxol^{R}

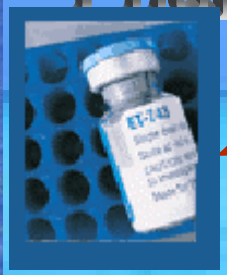
Pharma-Mar

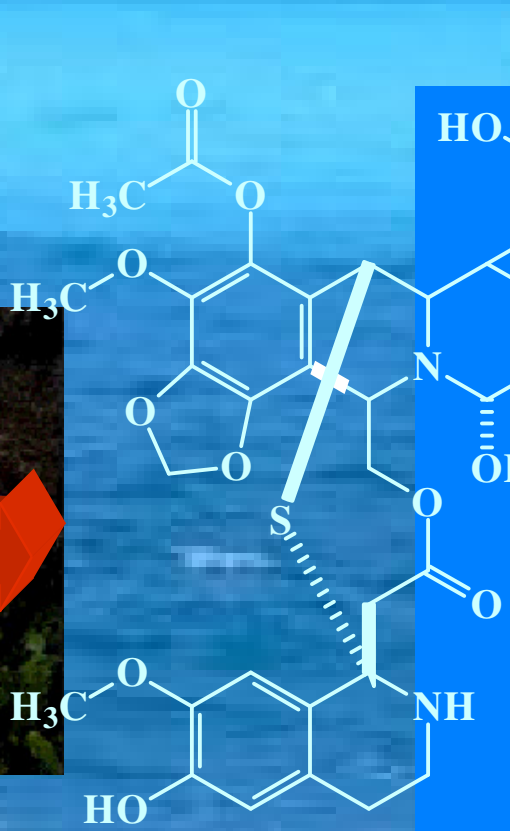
Sínteses: E. J. Corey & E. Martinez
Org. Lett. 2002, *2*, 943;
I. Manzanares *et al.*, *Org. Lett.* 2002, *2*, 2545.

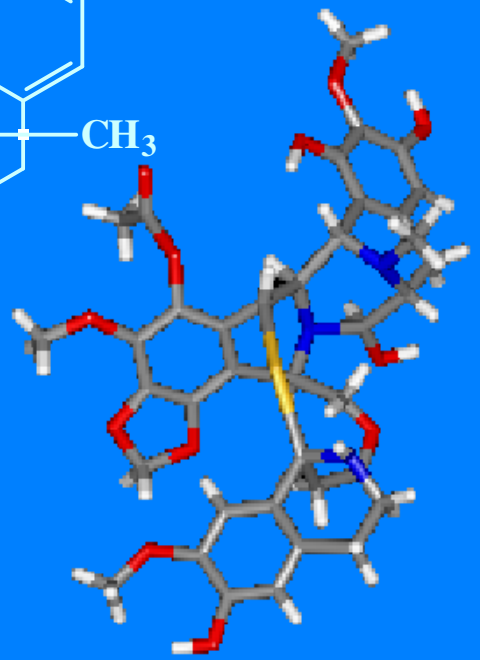
1928 -



Fusetani "Drug from the Sea", 2001







Ecteinascidina

Quim. Nova, Vol. 32, No. 3, 679-688, 2009

BIODIVERSIDADE: FONTE POTENCIAL PARA A DESCOBERTA DE FÁRMACOS

Eliezer J. Barreiro*

Departamento de Fármacos, Faculdade de Farmácia, Centro de Ciências da Saúde, Universidade Federal do Rio de Janeiro, CP 68006, 21944-910 Rio de Janeiro - RJ, Brasil

Vanderlan da Silva Bolzani***

Instituto de Química, Universidade Estadual Paulista, Rua Francisco Degni, s/n, 14800-900, Araraquara - SP, Brasil

Recebido em 16/1/09; aceito em 6/4/09; publicado na web em 9/4/09

BIODIVERSITY: POTENTIAL SOURCE FOR DRUG DISCOVERY. In economic terms, biodiversity transcends the boundaries usually given to conventional industries because it is a valuable source of biological and chemical data of great use to drug discovery. Certainly, the use of natural products has been the single most successful strategy in the discovery of novel medicines, and most of the medical breakthroughs are based on natural products. Half of the top 20 best-selling drugs are natural products, and their total sales amounted to US$ 16 billions shows the importance of natural products, which is evidenced by the new chemical entities (NCE) approved by regulatory authorities around the world in the past decade. Recently, the approval of the alkaloid galanthamine as a medicine to treat Alzheimer's disease shows that natural compounds from plants will continue to reach the market. The huge biological diversity of the Brazilian biomes, by its ability to generate new knowledge and technological innovation can be a fantastic alternative as raw material for drug discovery.

www.scielo.br

Metabólito de Fungo

1979 - A. Endo isola a lovastatina de Monascus ruber

1970 - Akira Endo isola, no Japão, a compactina de fungos

A.Endo, *J. Med. Chem*. 1985,*28*,401

1980 - A. Patchett (Merck) descobre a lovastatina em Aspergillus sp.

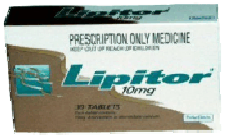
J. Med. Chem. 1986, *29*, 849

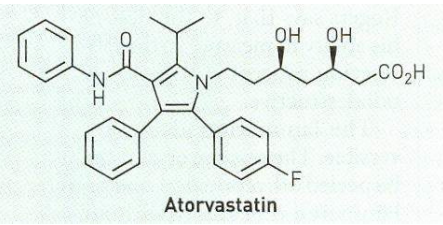
1986 - simvastatina, fluvastatina

E S T A T I N A S

a t o r v a s t a t i n a

1999 - rosuvastatina





ácido hidroxi-heptanóico

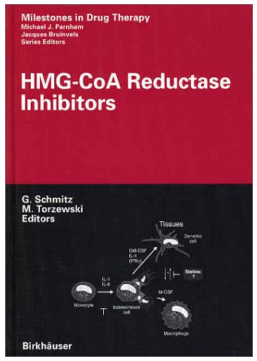
1950 - colesterol plasmático é relacionado ao risco de doenças coronarianas

a estrutura da compactina permite a eleição do alvo: HMG-CoA redutase

1987 - FDA (EUA) aprova a lovastatina

1988 - pravastatina (estudos do metabolismo da compactina)

1993



1 C

US$ 230 milhões

Fases da ação dos fármacos

Fase farmacodinâmica

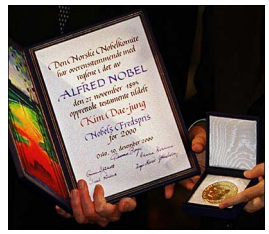
E. J. Barreiro *et al.*, Estratégias em Química Medicinal para o Planejamento de Fármacos, *Braz. J. Pharm. Sc*. **2001**, *37*, 269-292.

LOCK & KEY CONCEPT

(Emil Fischer, 1894)

"Um ein Bild zu gebrauchen, will ich sagen, dass Enzym und Glucosid wie Schloss und Schlüssel zueinander passen müssen, um eine chemische Wirkung aufeinander ausübe zu können".

Hermann Emil Fischer
1852-1919

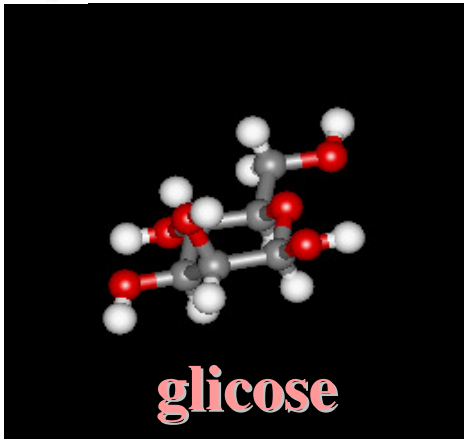


1902

fenilidrazina

medicinal chemistry

"Em termos figurados, eu gostaria de dizer que enzima e glicosído tem que encaixar como uma chave-fechadura, de maneira a interagir quimicamente uma com a outra".



glicose

O Modelo Chave-Fechadura

Os fármacos atuam em alvos terapêuticos...

Química Medicinal

... os biorreceptores.

Estima-se que hoje sejam 483* os alvos-terapêuticos envolvidos na resposta de todos os fármacos que totalizam 1204 moléculas.&

* J. Drews, "Editorial: What's in a number?", *Nature Rev. Drug Discov.* **2006**, *5*, 975;
J. Drews & S. Ryser, Classic drug targets, *Nature Biotechnol.* **1997**, *15*, 1318;
& J.P. Overington, A-L Bissan & A.L. Hopkins, *Nature Rev. Drug Discov.* **2006**, *5*, 993;
Estes autores estimam em 324 os biorreceptores de todos os fármacos contemporâneos.

A maioria dos biorreceptores dos fármacos contemporâneos são enzimas ...

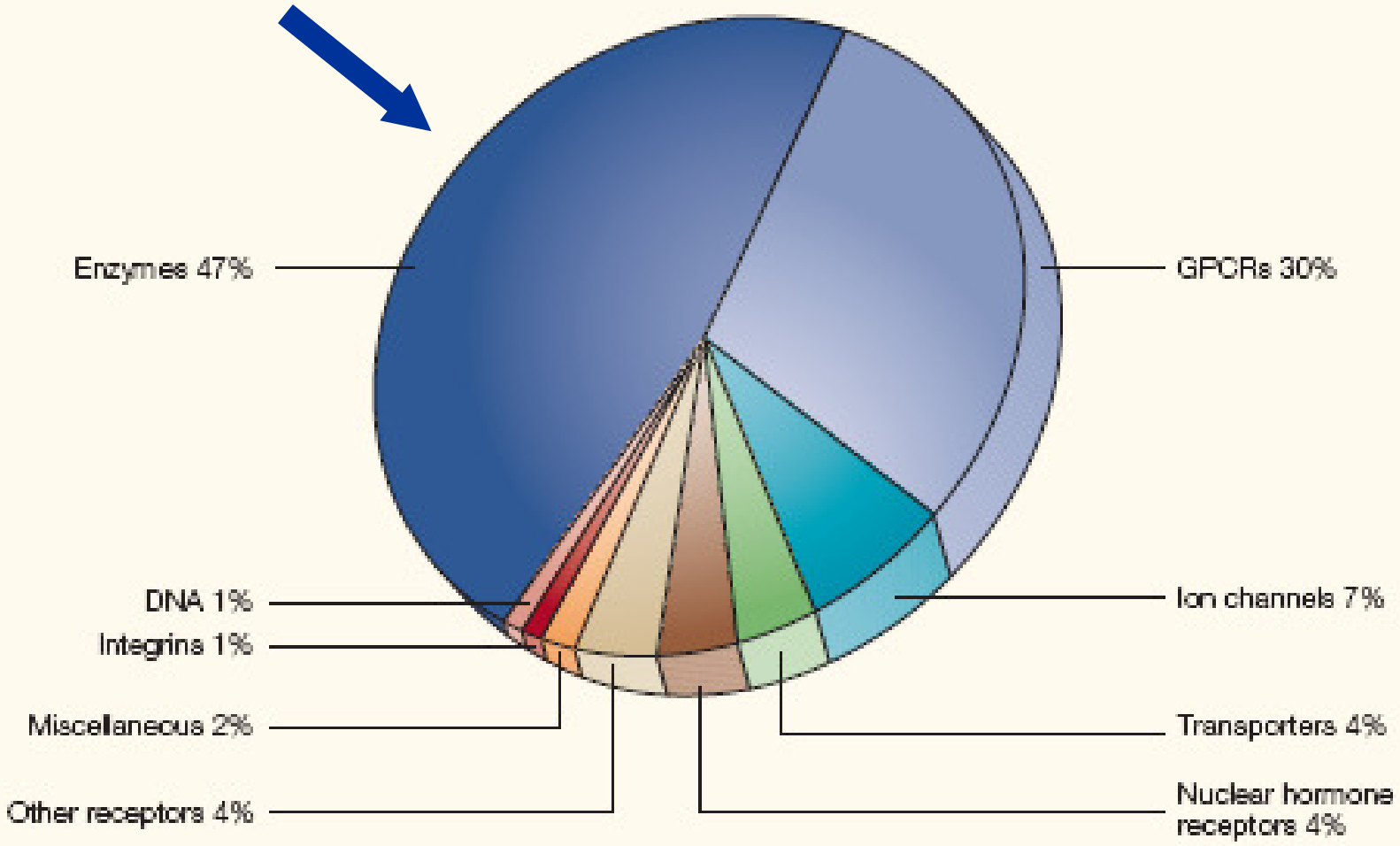
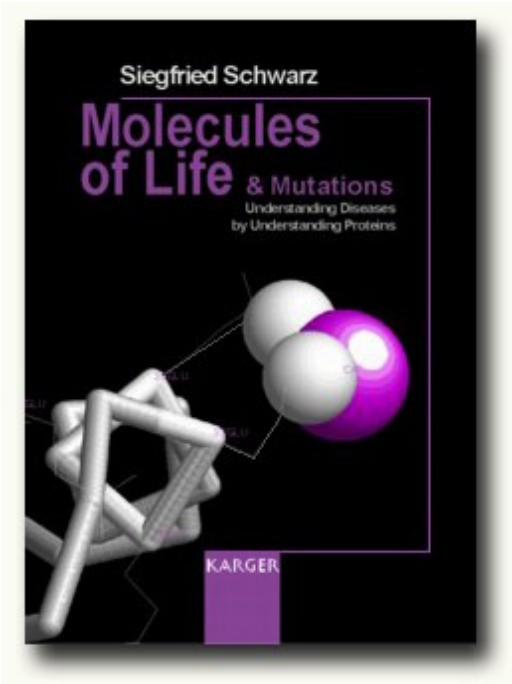
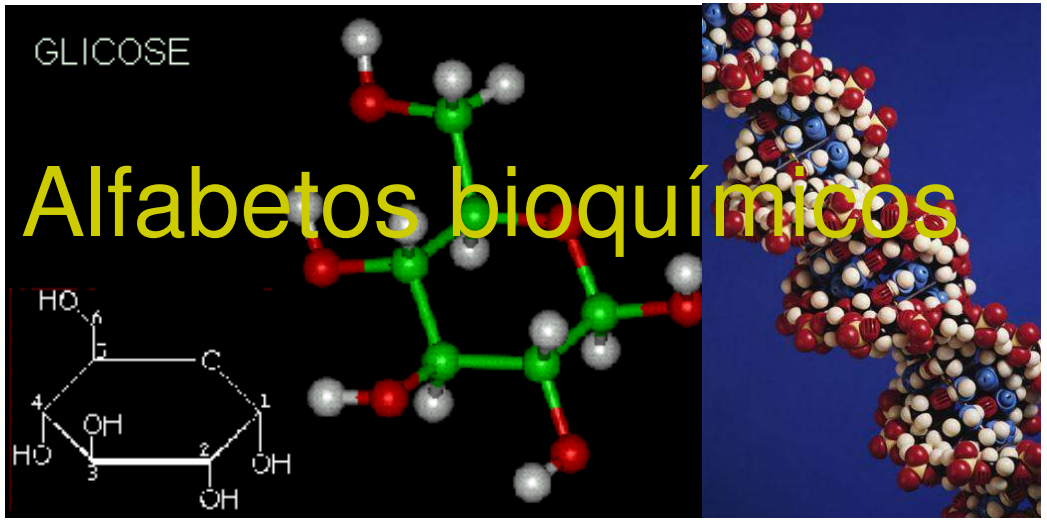


Figure 4 | **Marketed small-molecule drug targets by biochemical class.** GPCR, G-protein-coupled receptor.

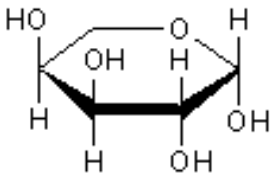
www.nature.com/reviews/drugdisc

Hopkins, A. L. & Groom, C. R. The druggable genome. *Nature Rev. Drug Discov.* 1, 727–30 (2002).

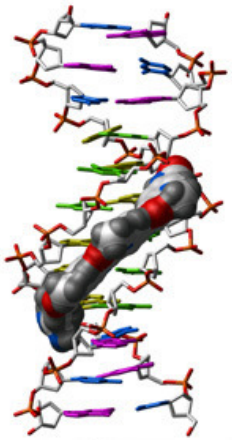




Alfabetos bioquímicos



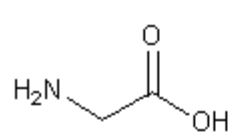
β-L-Arabinose



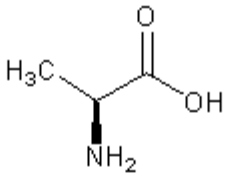
Model Compound Bound to the Minor Groove of a DNA Molecule

Carboidratos
Lipídeos
ácidos nuclêicos
proteínas

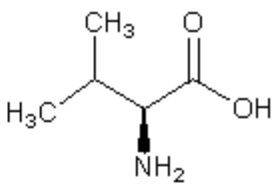
O "alfabeto" protêico ...



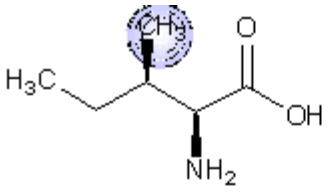
glicina (**gly**)



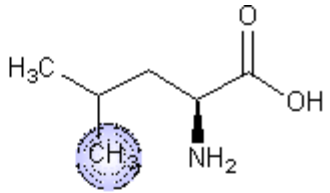
alanina



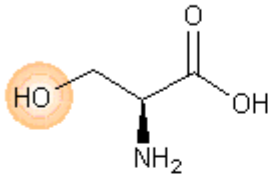
valina



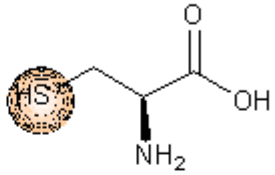
isoleucina (**Ile**)



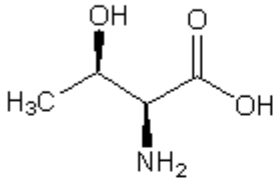
leucina



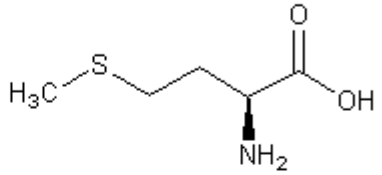
serina



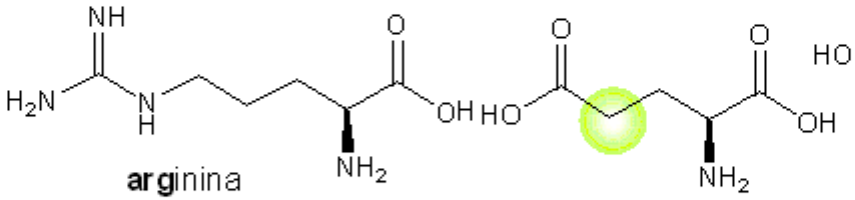
cisteína (**Cys**)



treonina (**Thr**)



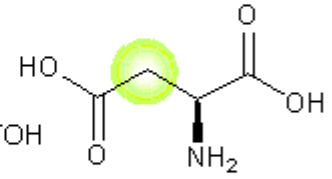
metionina



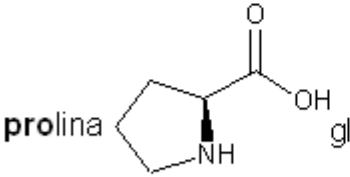
lisina (**Lys**)

arginina

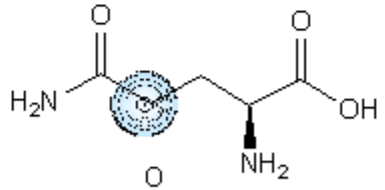
ácido **glu**tâmico



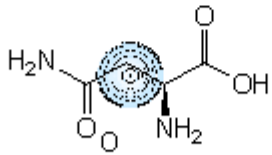
ácido **asp**ártico



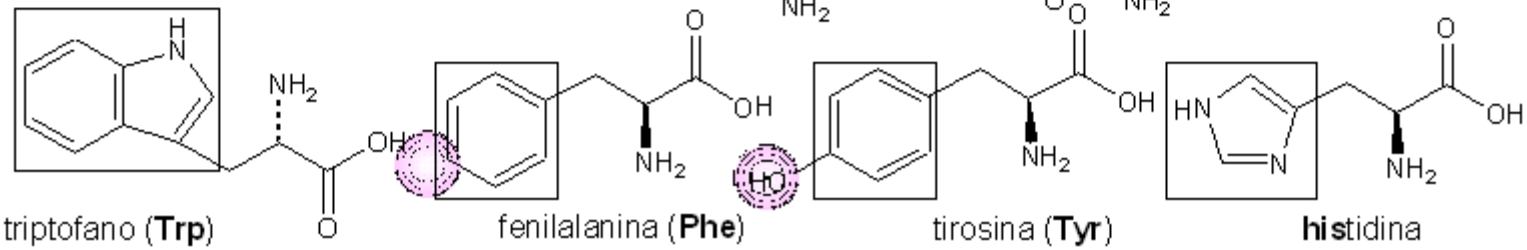
prolina



glutamina (**Gln**)



asparagina (**Asn**)



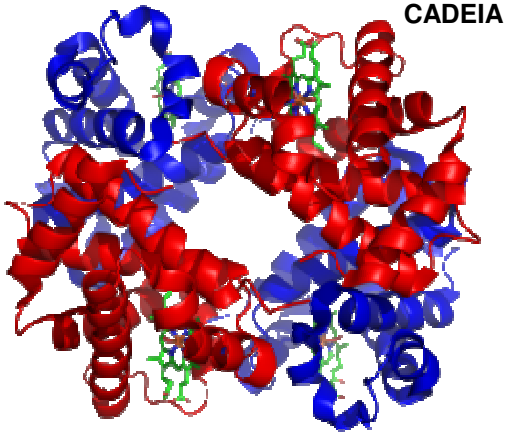
triptofano (**Trp**)

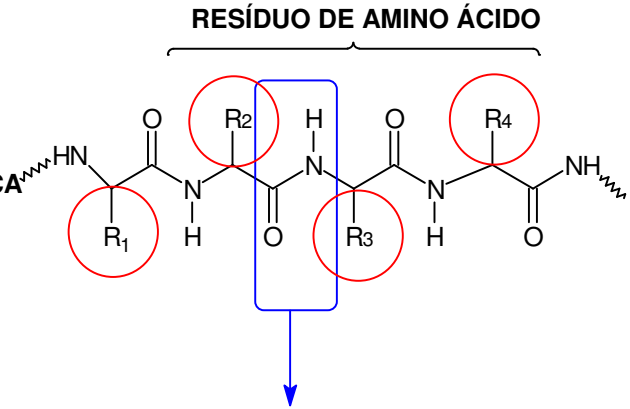
fenilalanina (**Phe**)

tirosina (**Tyr**)

histidina

Estrutura Primária das Proteínas



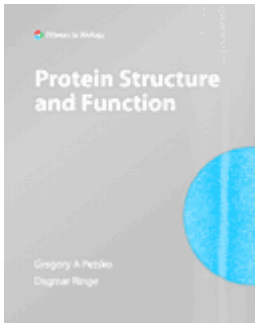


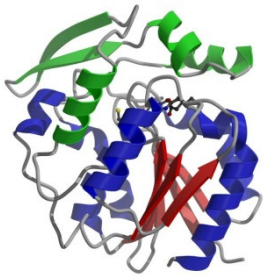
"Fechadura"

AMINO ÁCIDOS:

Essenciais: His, Ile, Leu, Lys, Met, Phe, Thr, Trp, Val

Não-essenciais: Ala, Arg, Asn, Asp, Cys, Glu, Gln, Gly, Pro, Ser, Tyr





A quimiodiversidade na natureza...

20 amino-ácidos essenciais

400 dipeptídeos

8.000 tripeptídeos...

64.000.000 hexa peptídeos

10^{400} proteínas com PM ~ 30 kD

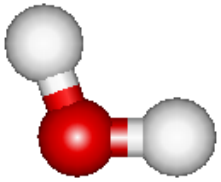
São conhecidos *ca*. 19 milhões de compostos orgânicos (300-500 Da)

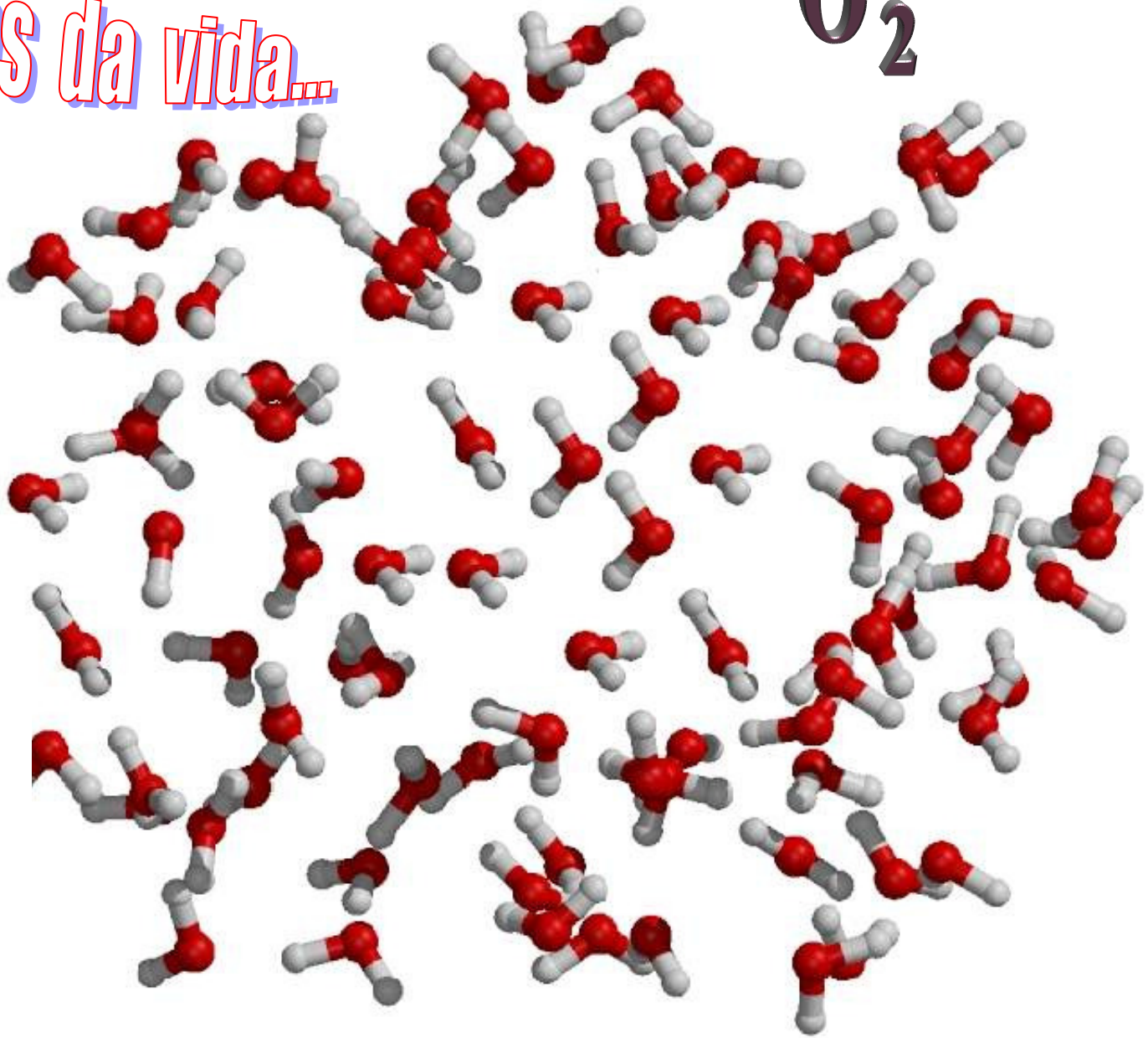
100 amino-ácidos modificados

ca. 1.000.000.000.000 hexapeptídeos...

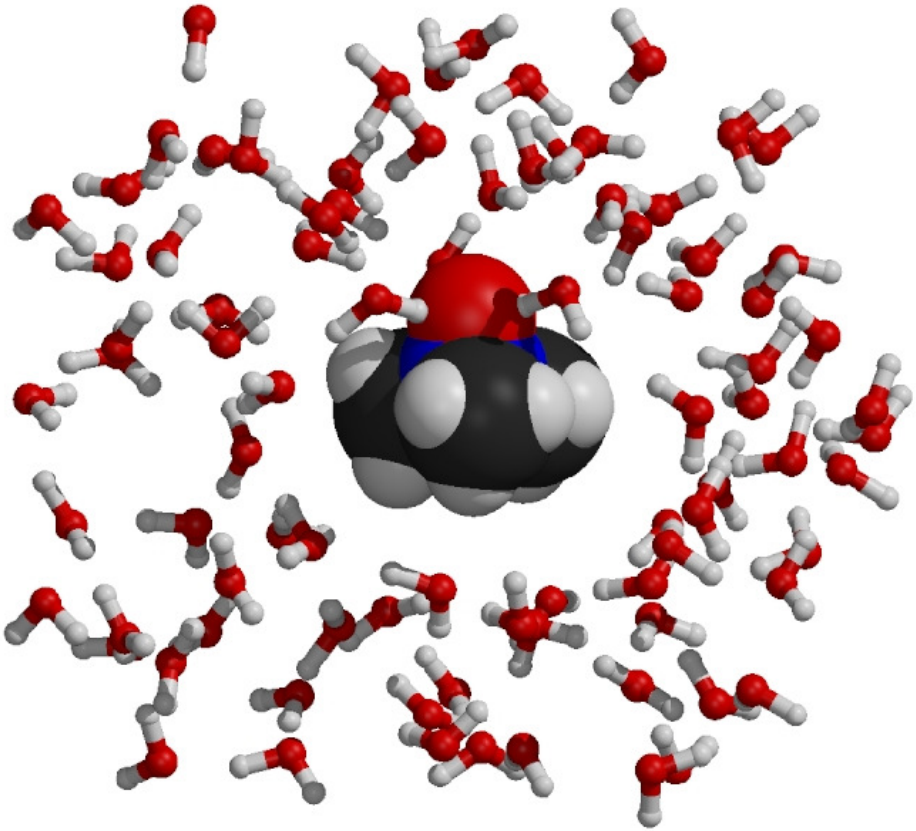
... e apenas 4 bases nucléicas codificam todos os organismos !

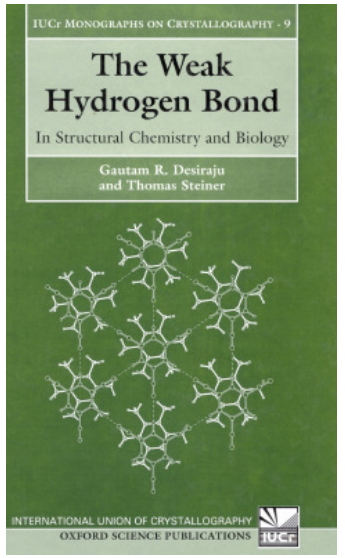
Moléculas da vida...





A importância das "*ligações*" frágeis...



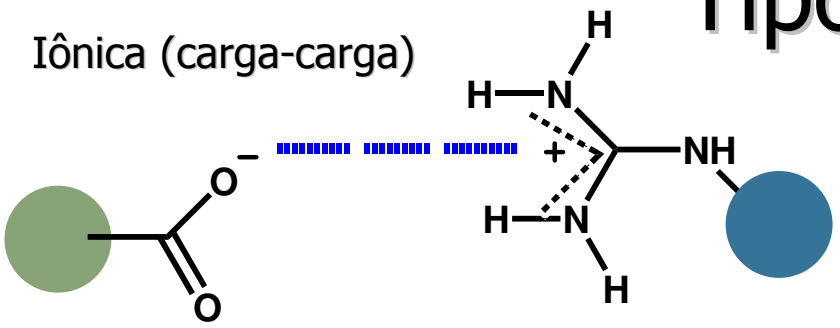


"*ligações*" de hidrogênio ...

D—H.....A **Linus Pauling, 1939**

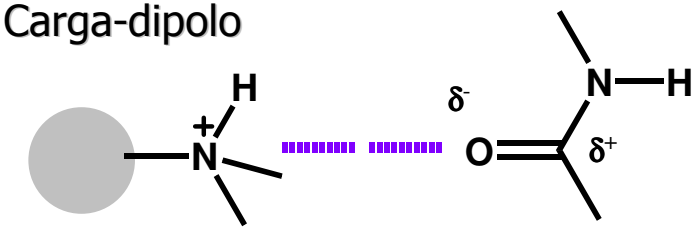
Tipos de interações F-R

Iônica (carga-carga)



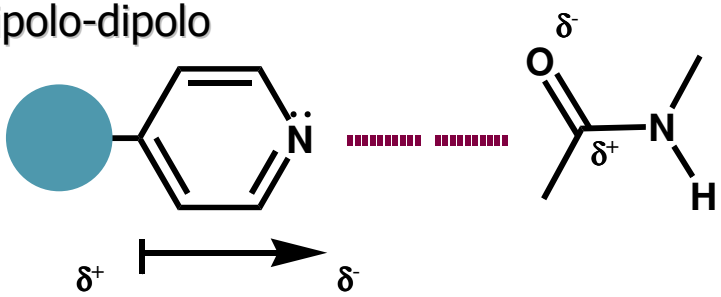
ΔG = 20-40kJ/mol

Carga-dipolo



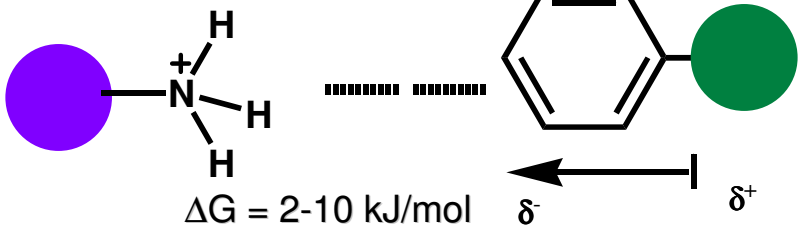
ΔG = 12-20kJ/mol

Dipolo-dipolo



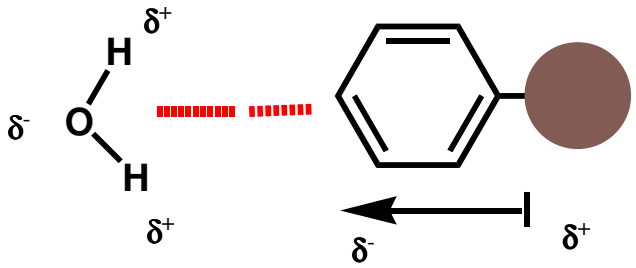
ΔG = 4-12 kJ/mol

Carga-dipolo induzido



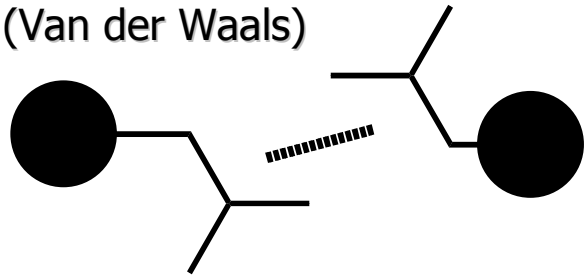
ΔG = 2-10 kJ/mol

Dipolo induzido-dipolo



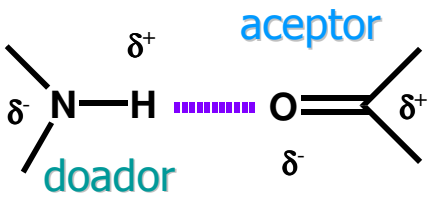
ΔG = 2 kJ/mol

Dispersão (Van der Waals)

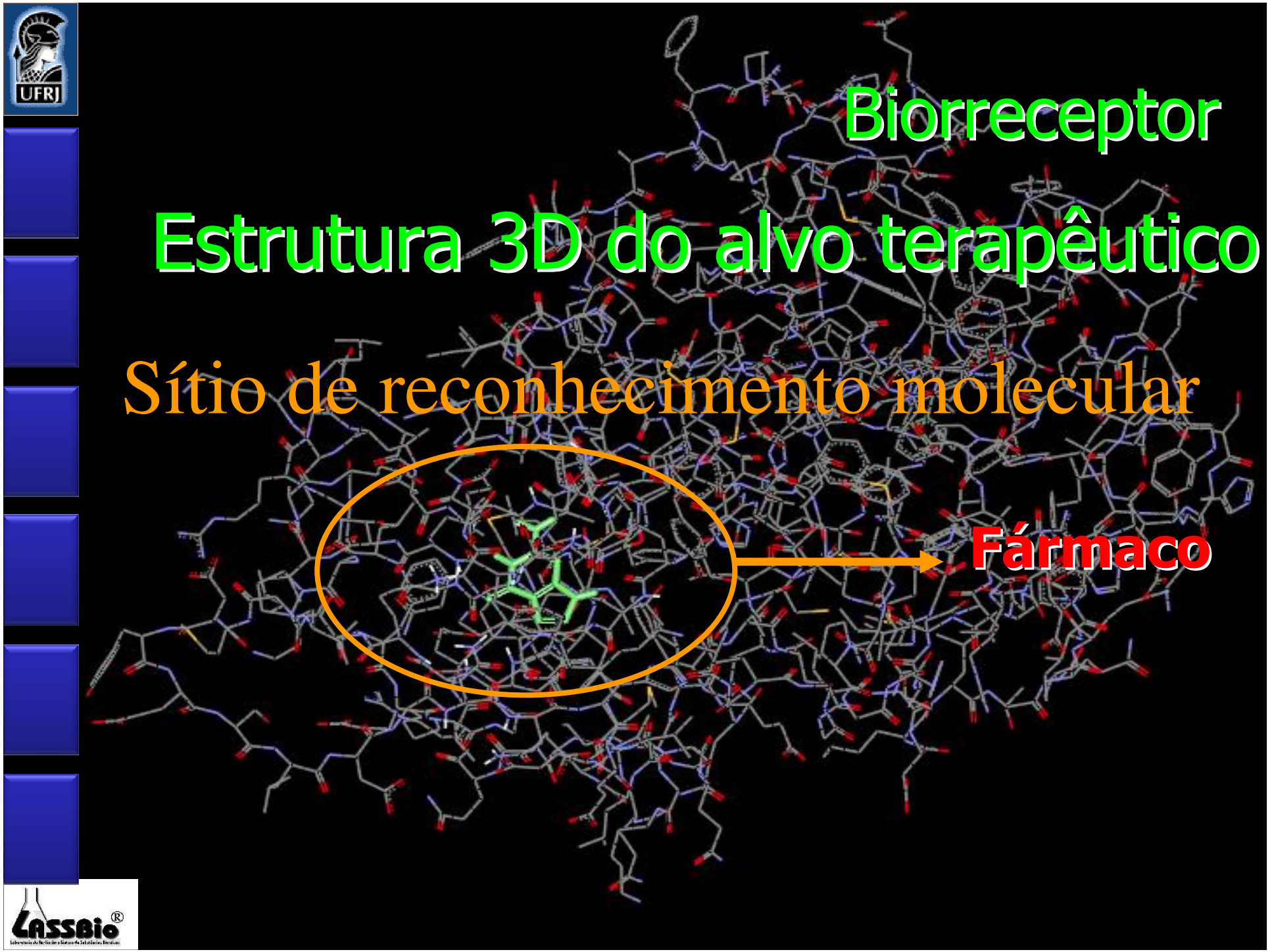


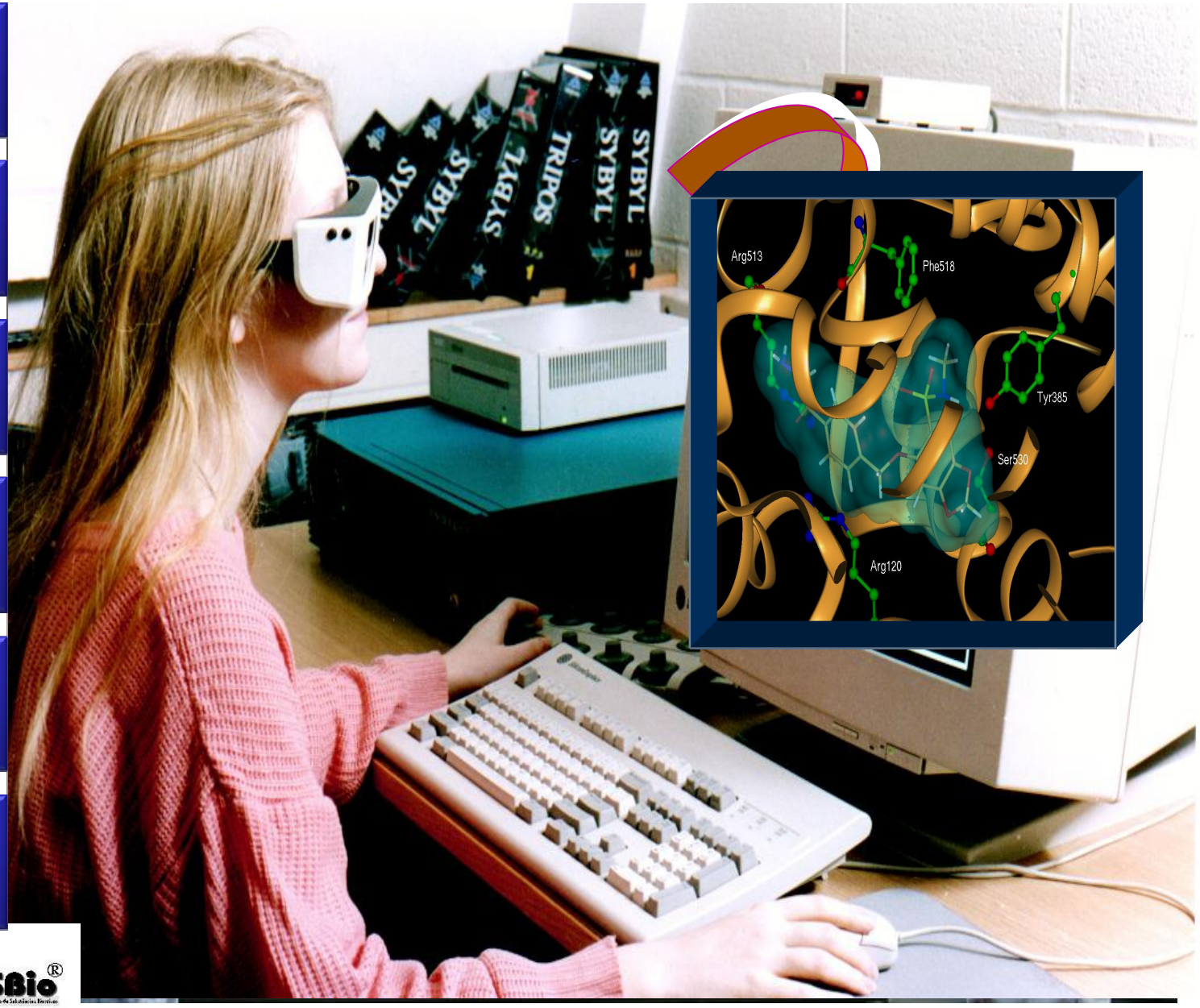
ΔG = 2-4 kJ/mol

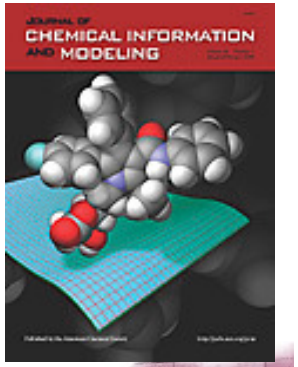
Ligação-H

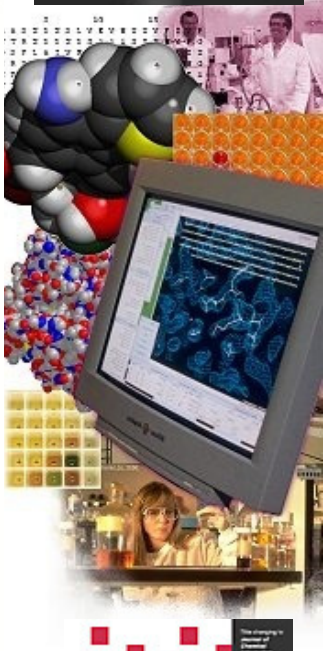


ΔG = 4-30 kJ/mol

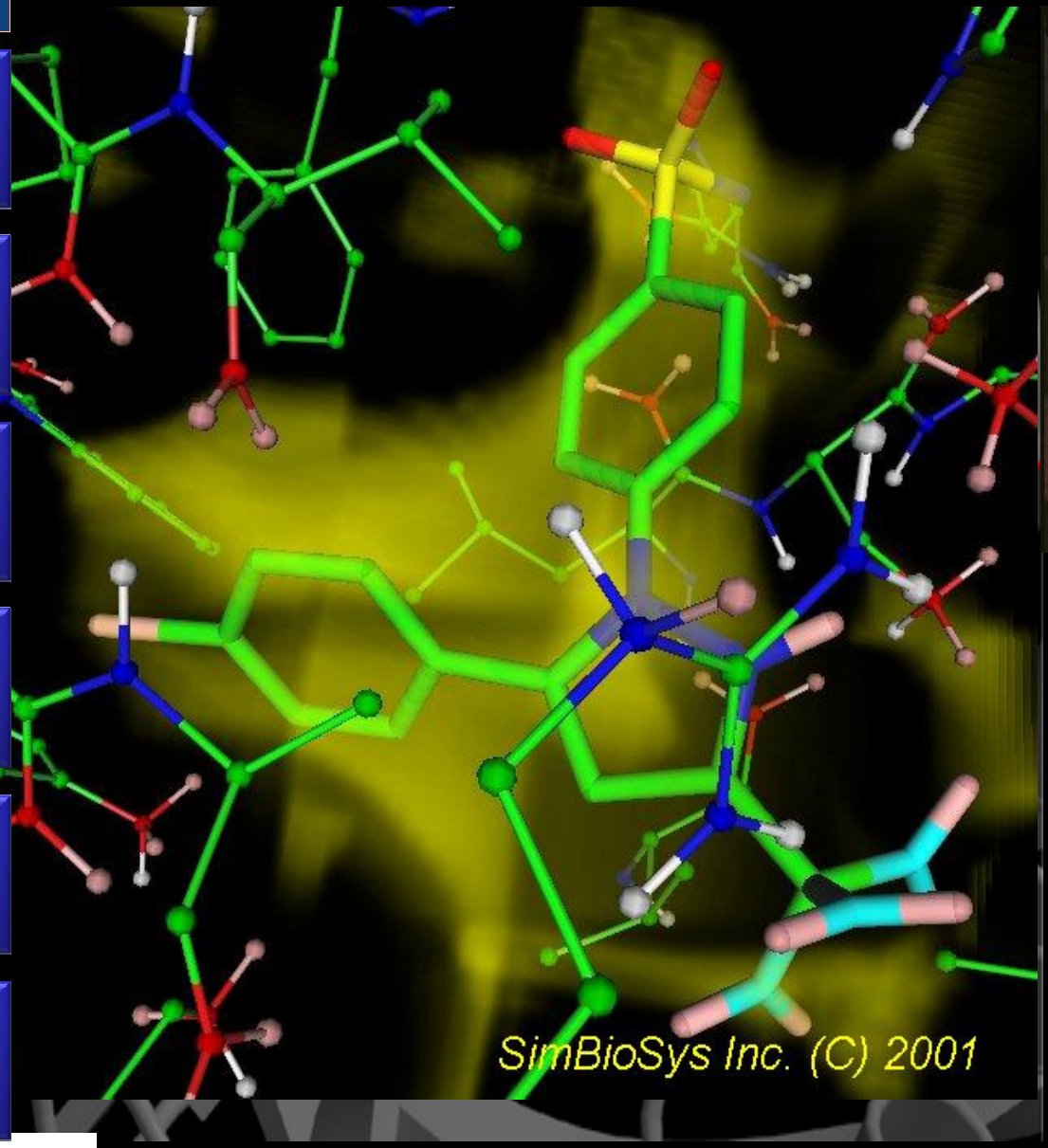

Biorreceptor
Estrutura 3D do alvo terapêutico
Sítio de reconhecimento molecular
Fármaco


SYBYL
TRIPOS
SYBYL
SYBYL
SYBYL
Arg513
Phe518
Tyr385
Ser530
Arg120

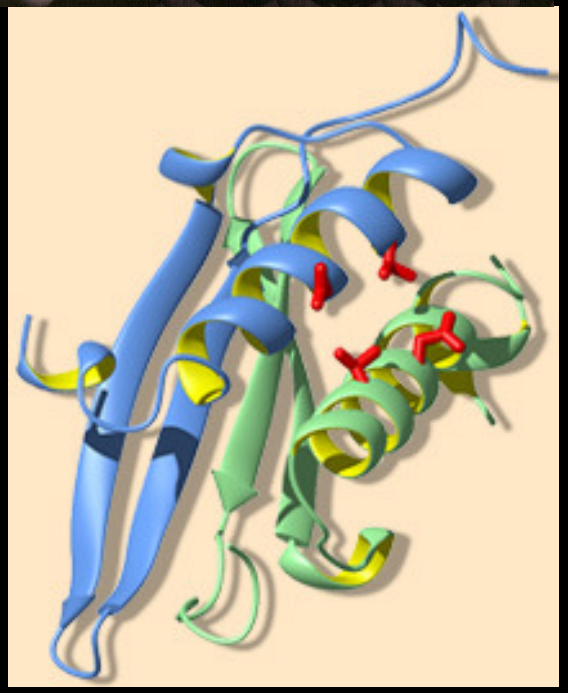

JOURNAL OF
CHEMICAL INFORMATION
AND MODELING

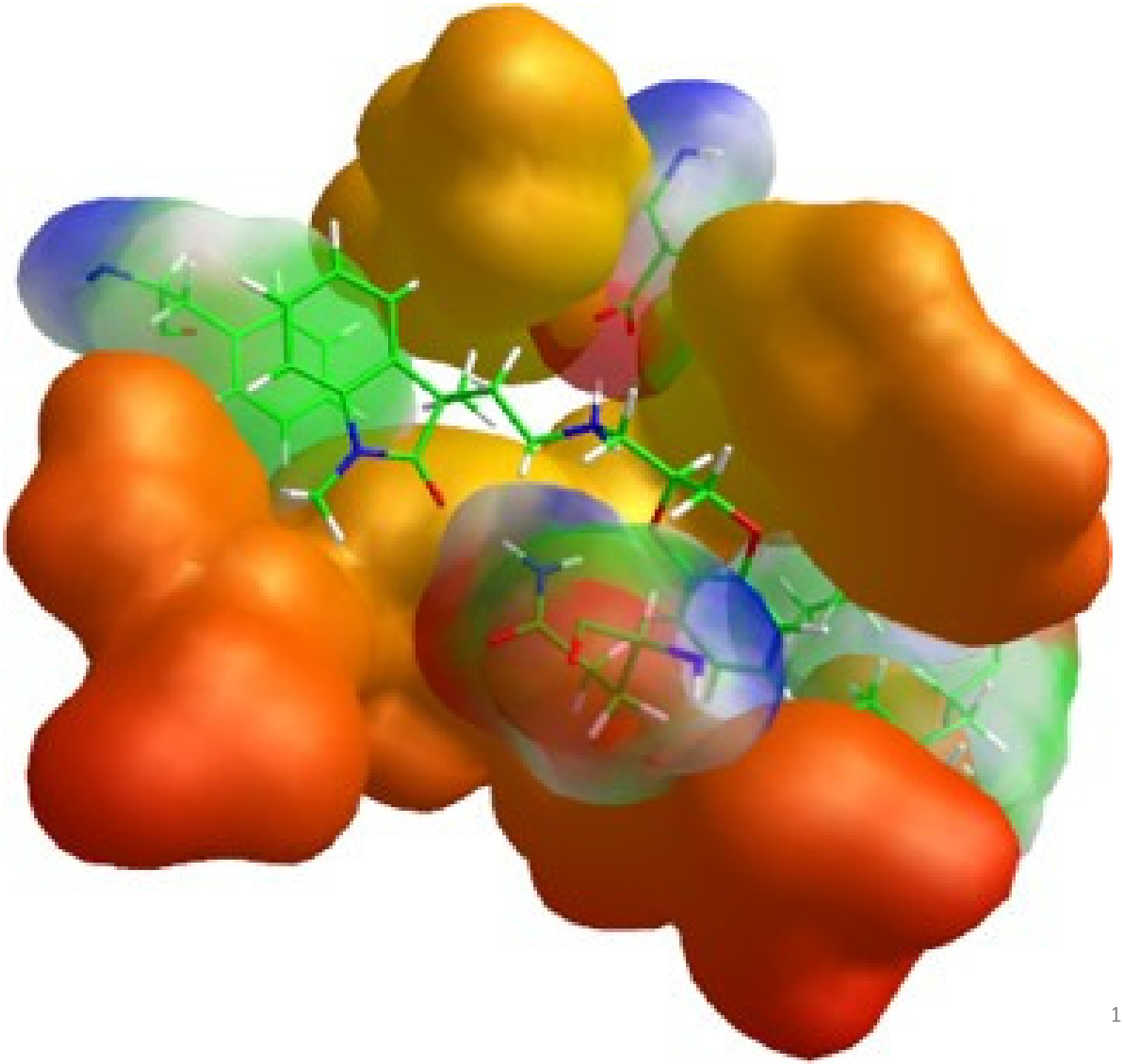


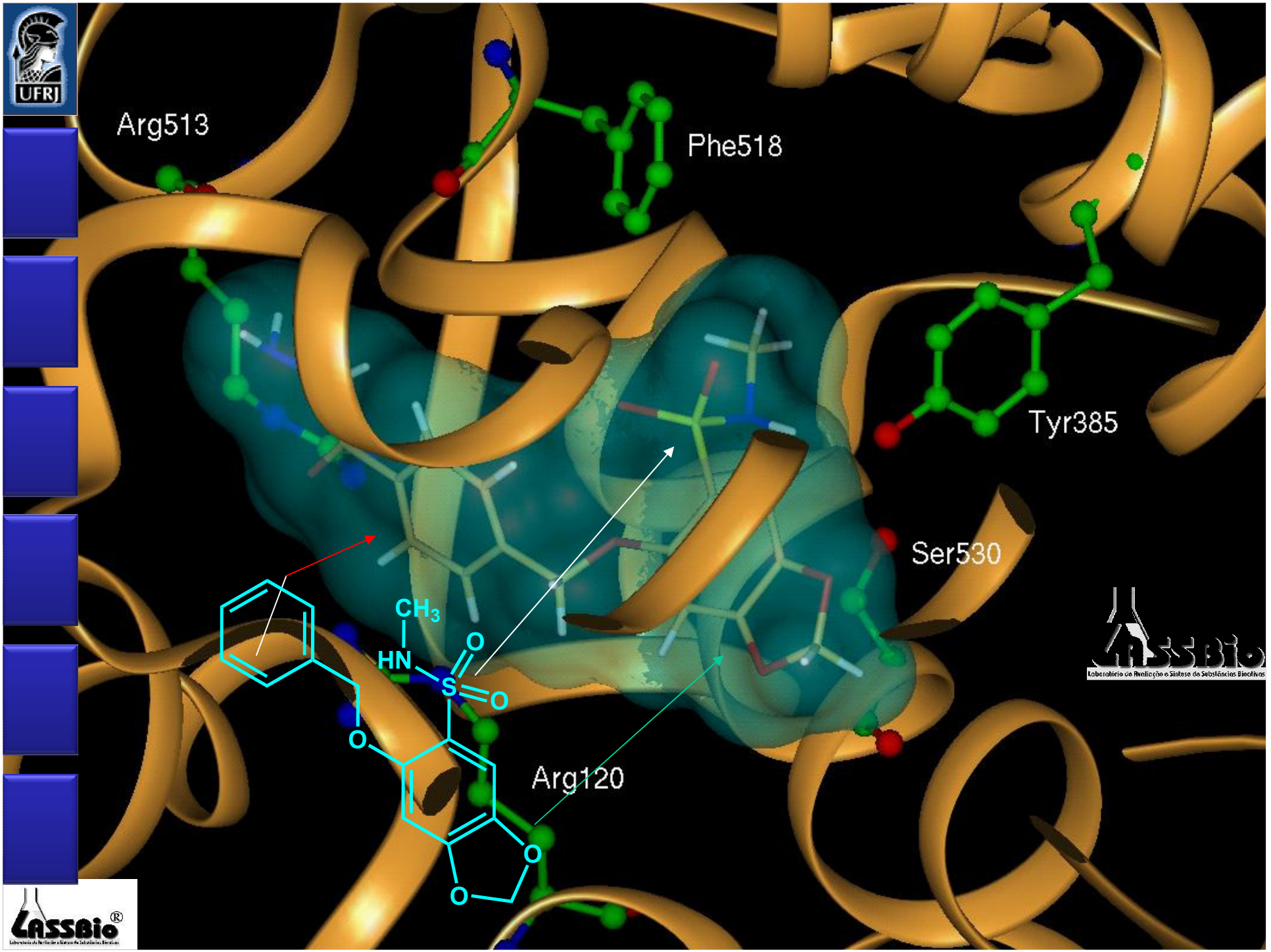

Journal of
Chemical
Information and
Computer Sciences


SimBioSys Inc. (C) 2001

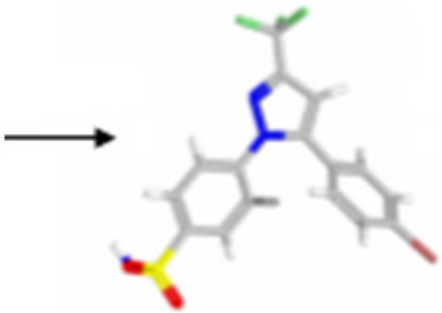

Química
Computacional



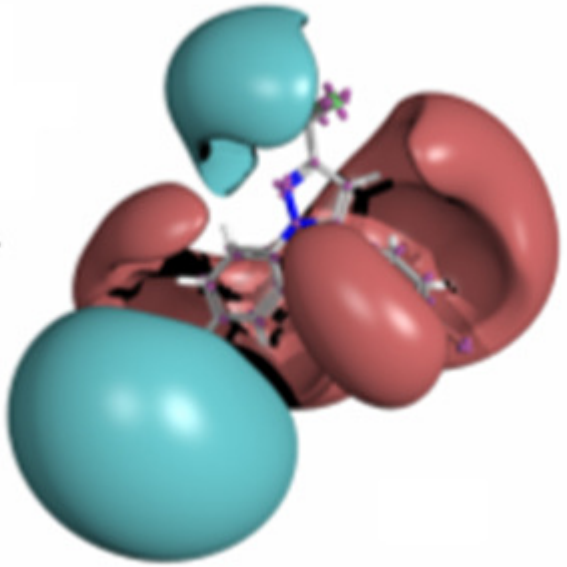



Arg513
Phe518
Tyr385
Ser530
Arg120
CH3
HN
S
O
O
O
O
O
O
LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

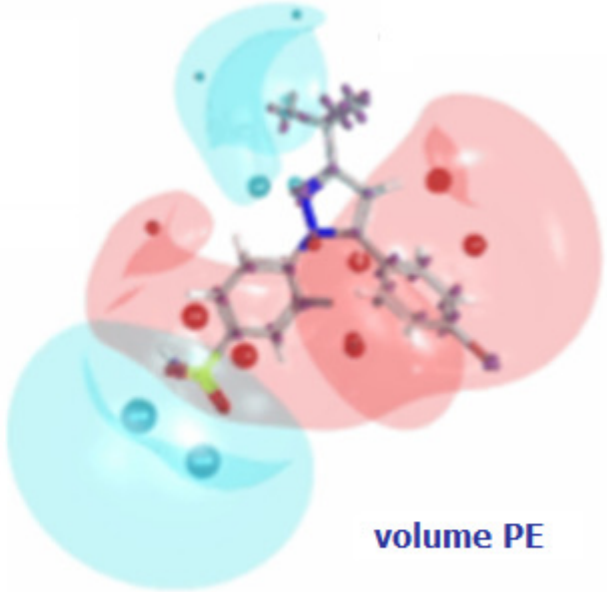
2D



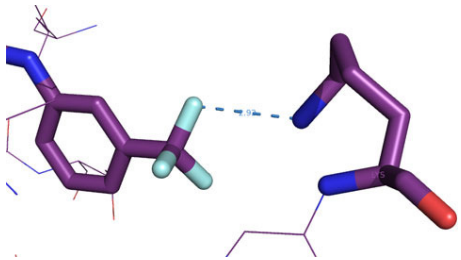
3D

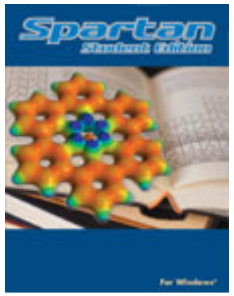


MPE



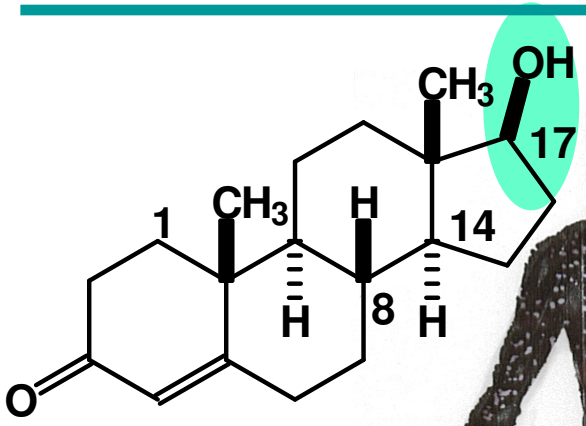
volume PE





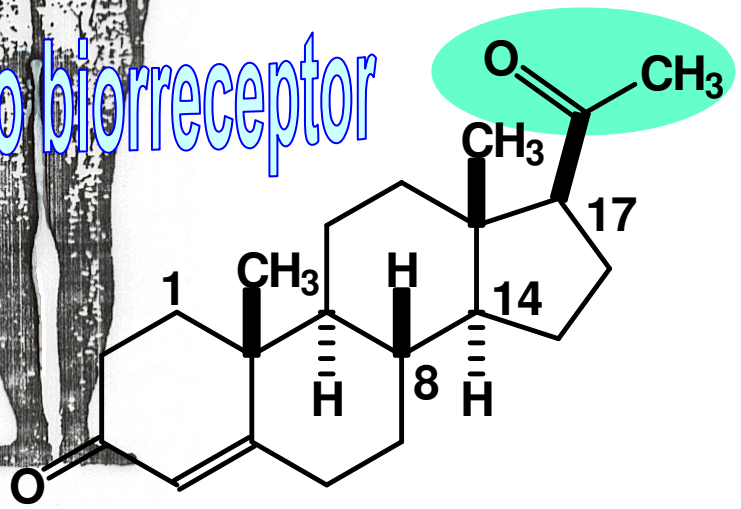
http://www.wavefun.com/products/spartan.html

Similaridade & Dissimilaridade Molecular



testosterona

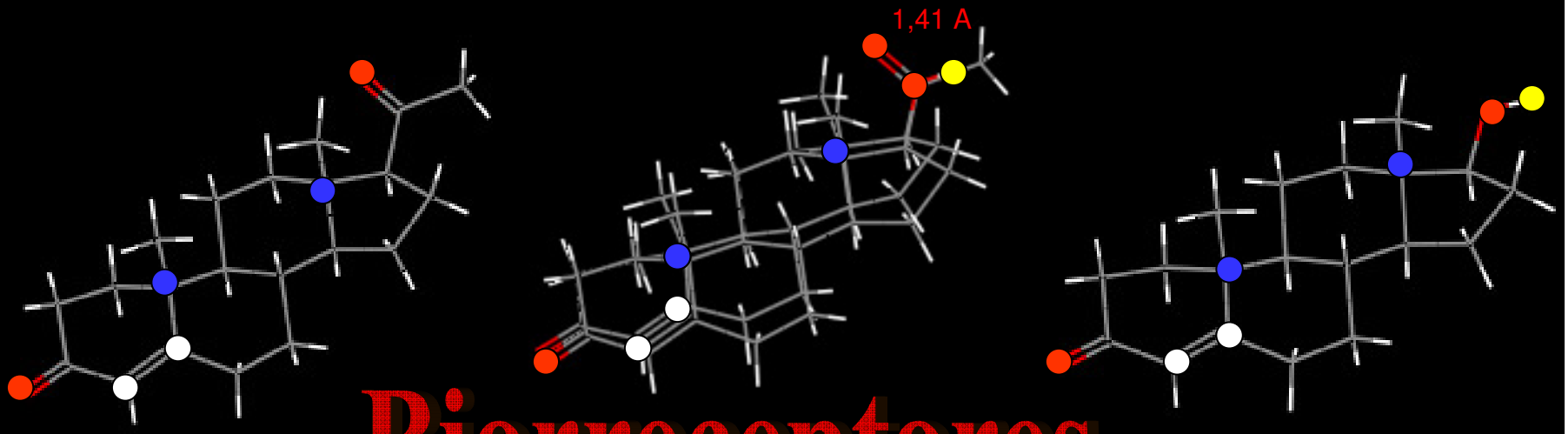
no reconhecimento molecular pelo biorreceptor



progesterona

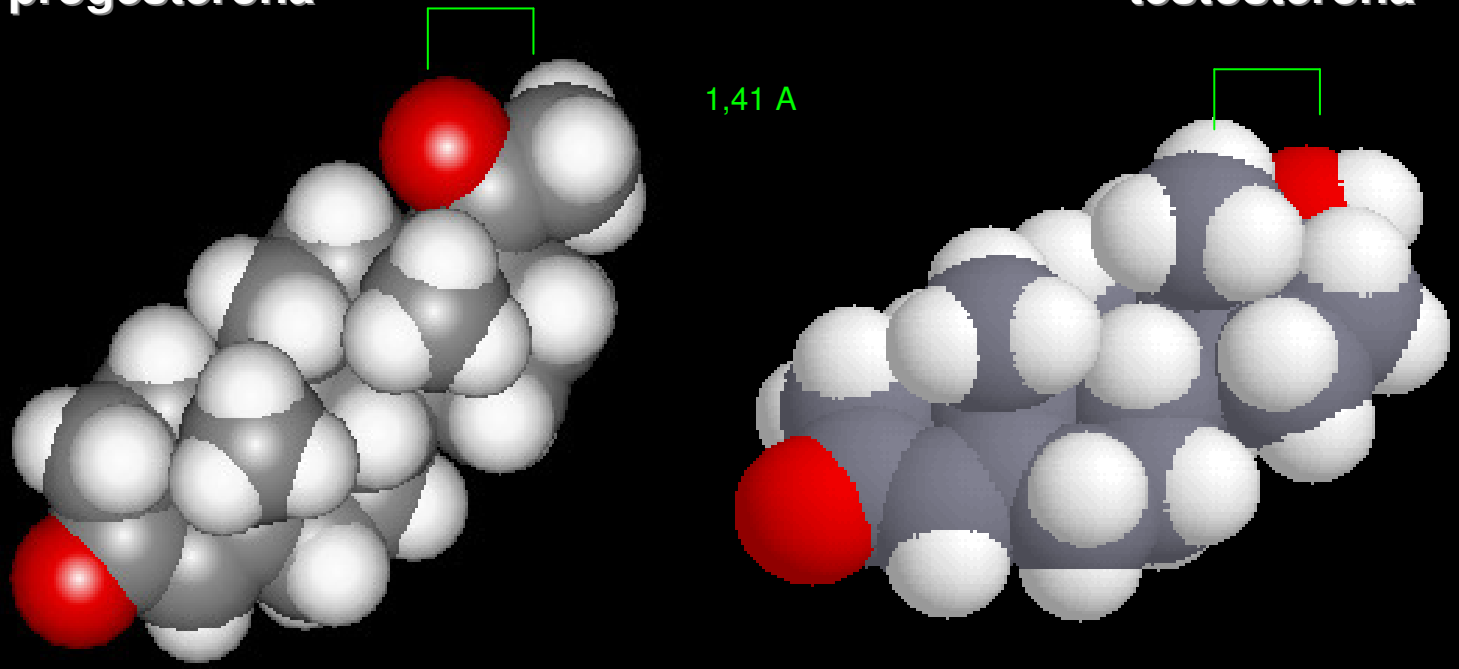
Biorreceptores

Biorreceptores

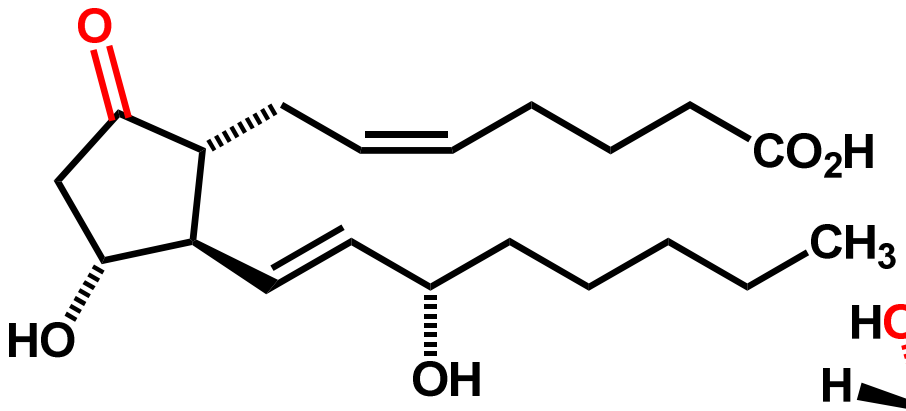


progesterona

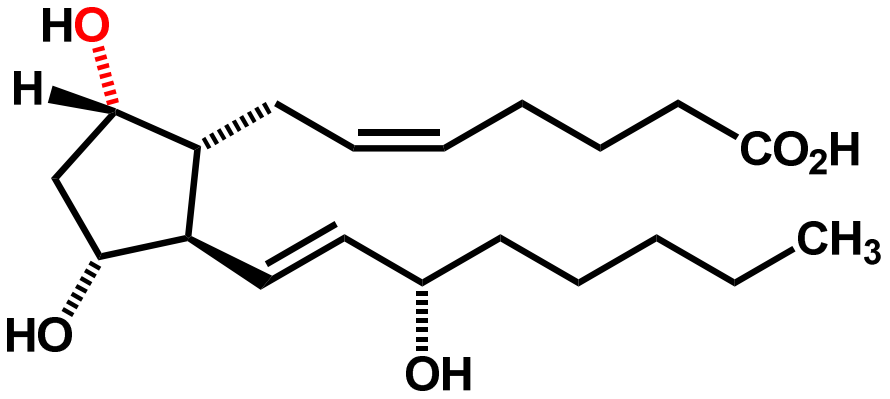
testosterona



Similaridad & Dissimilaridad Molecular



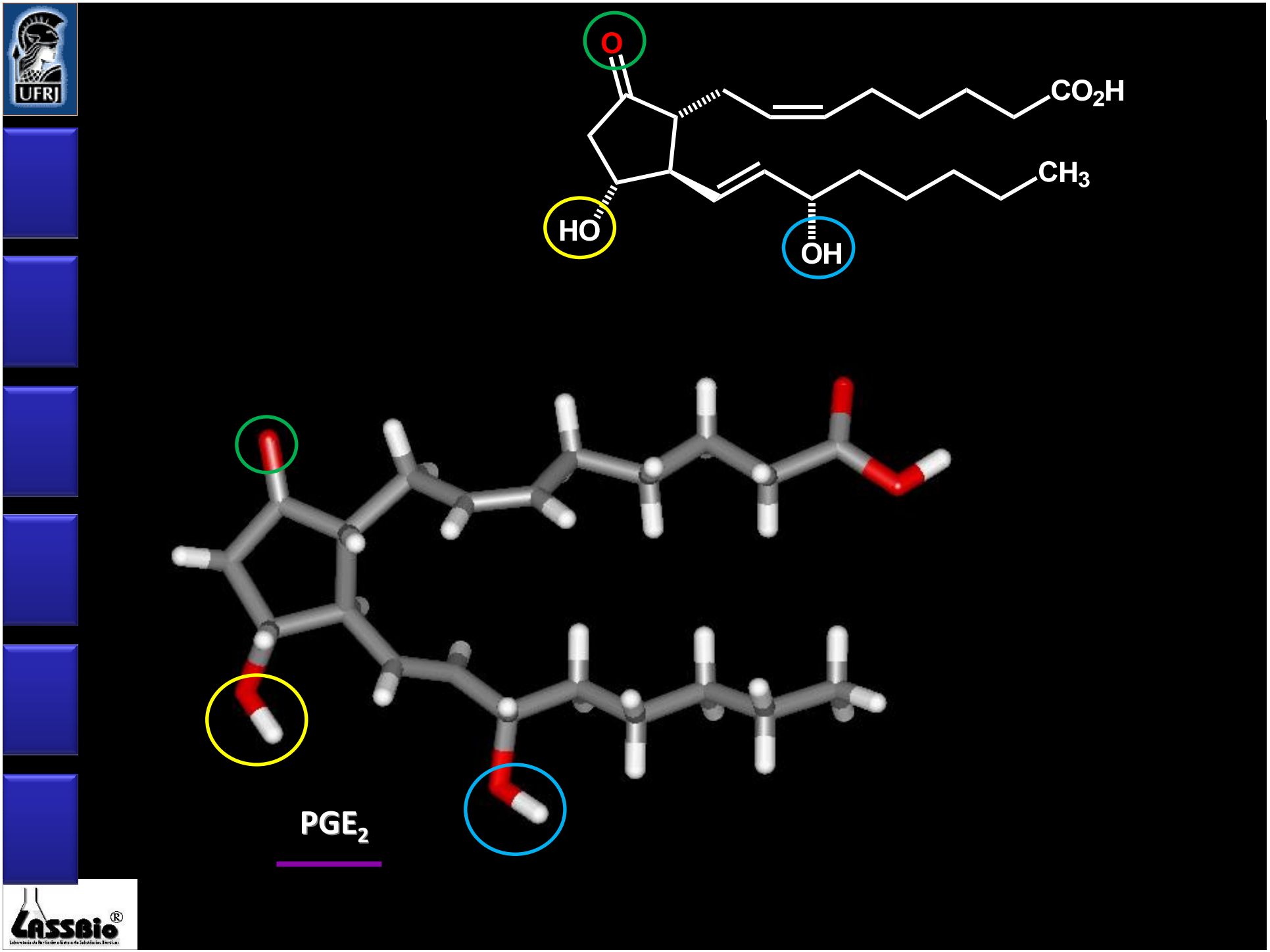
PGE_2

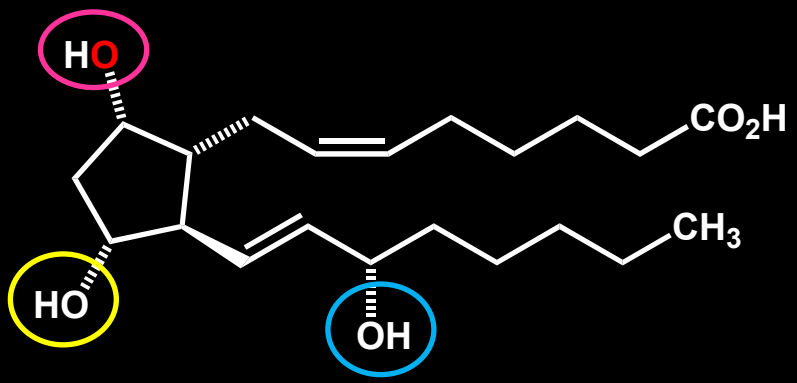


$PGF_{2\alpha}$

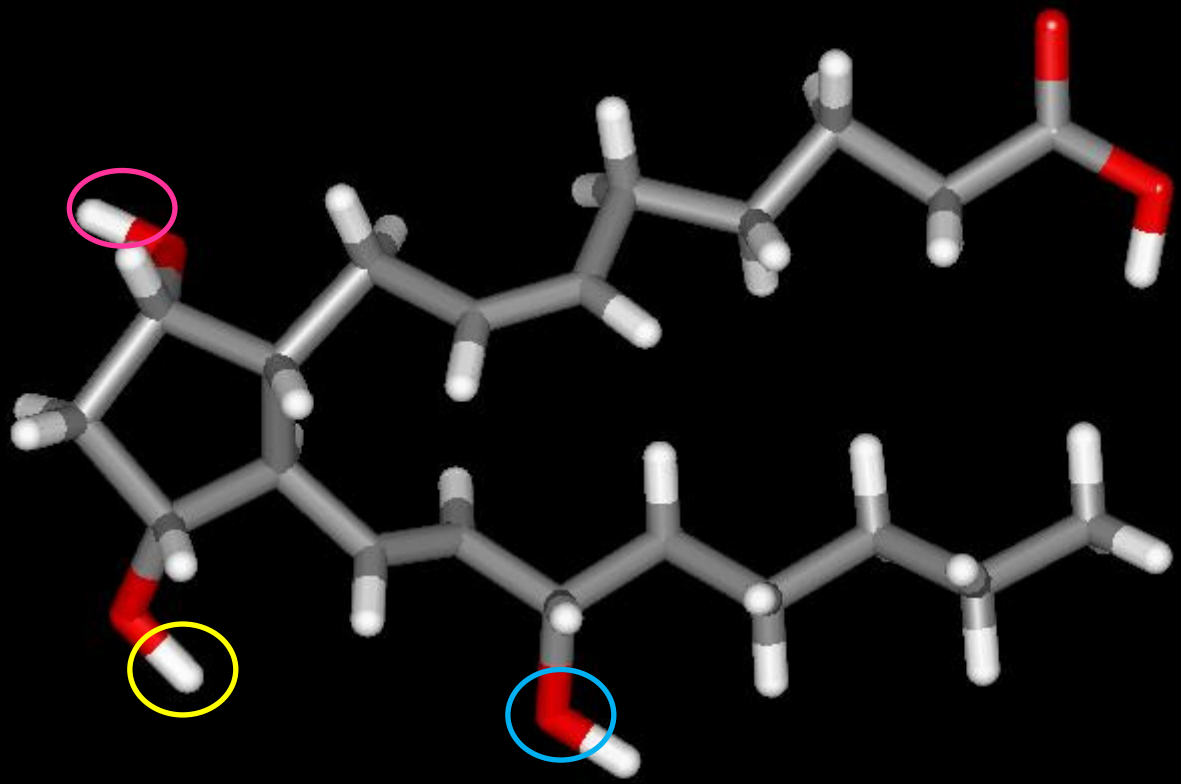
$PGF_{2\alpha}$ em cães provoca forte broncodilatação

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

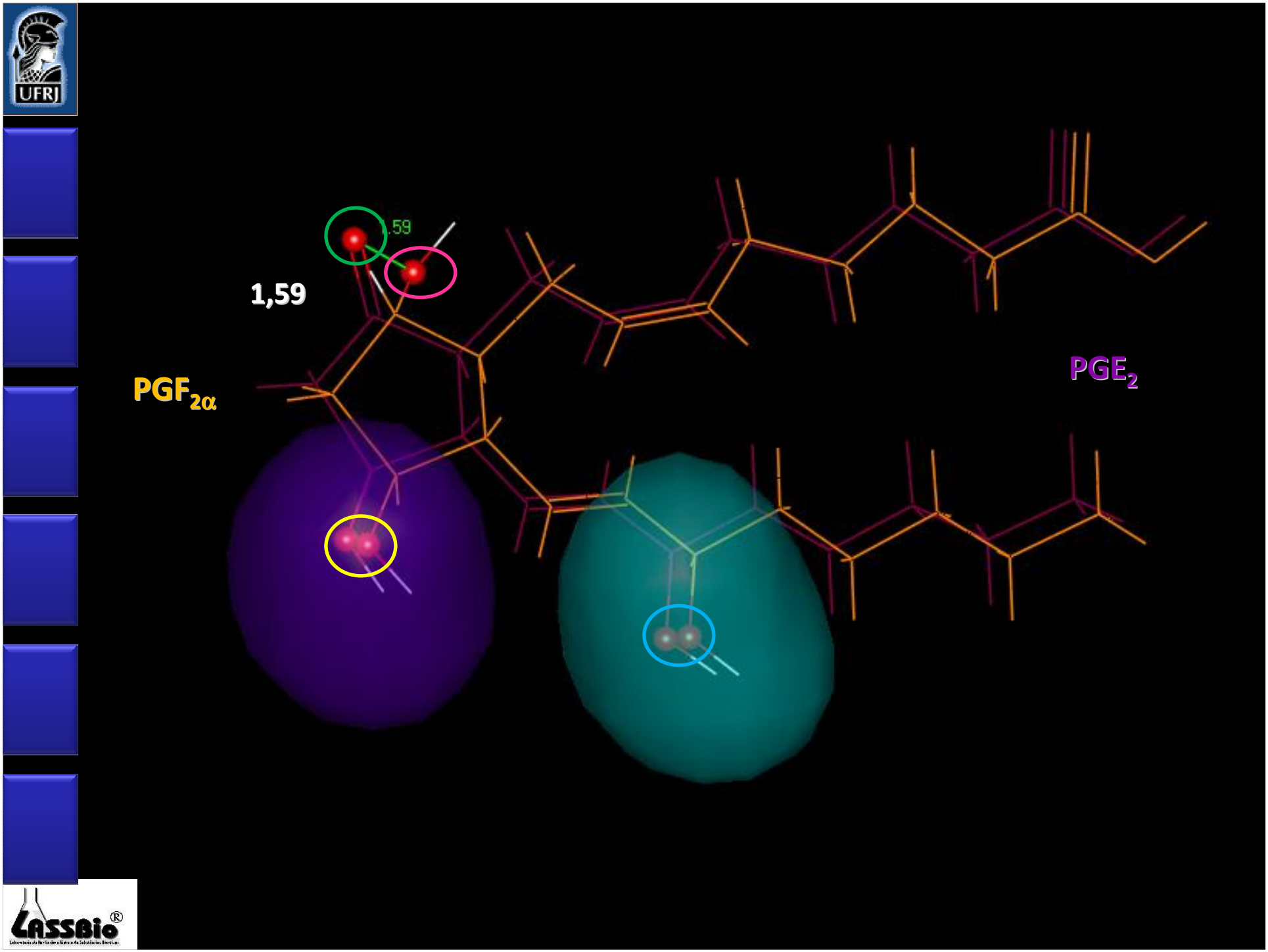

O
CO2H
CH3
HO
OH
PGE2



$PGF_{2\alpha}$



$PGF_{2\alpha}$


1,59
PGF2α
PGE2

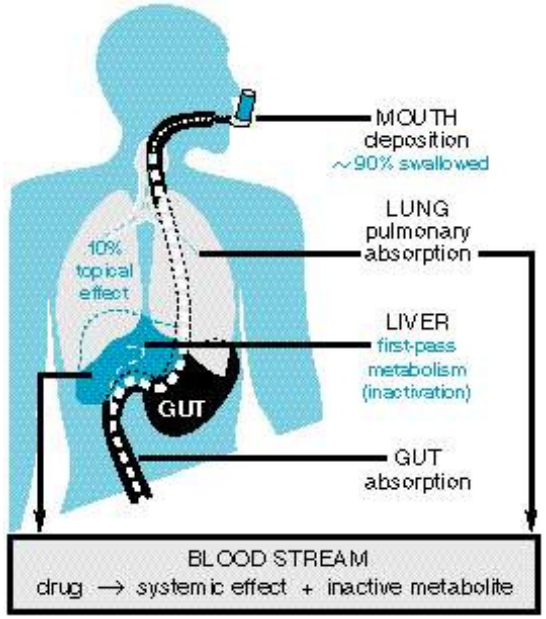
Fases da ação dos fármacos

Fase farmacocinética

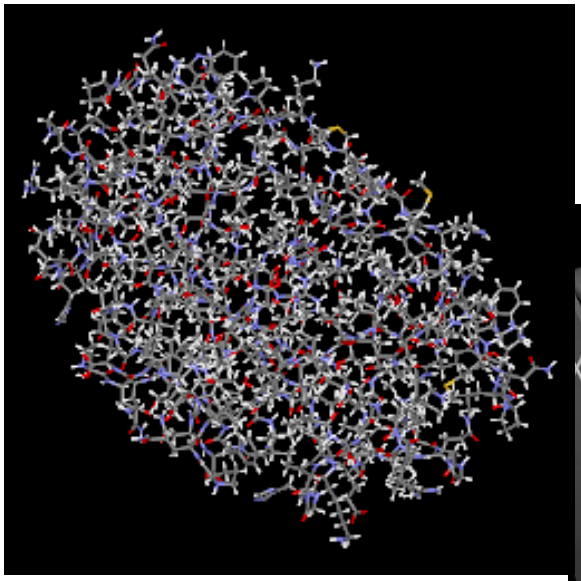
As *fases* da ação dos fármacos....

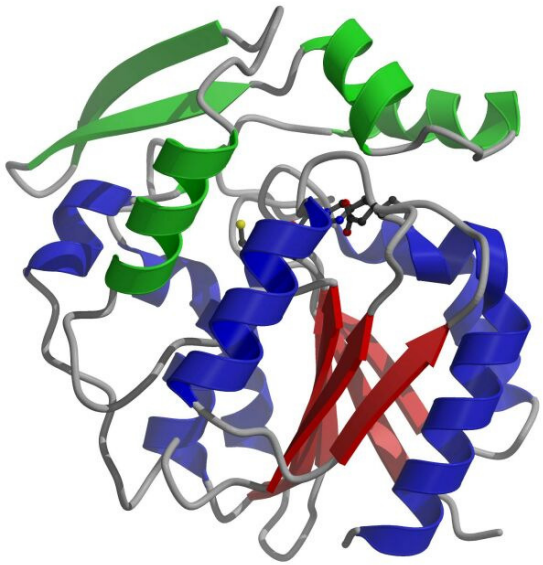
Fase farmacocinética (PK)

Posologia

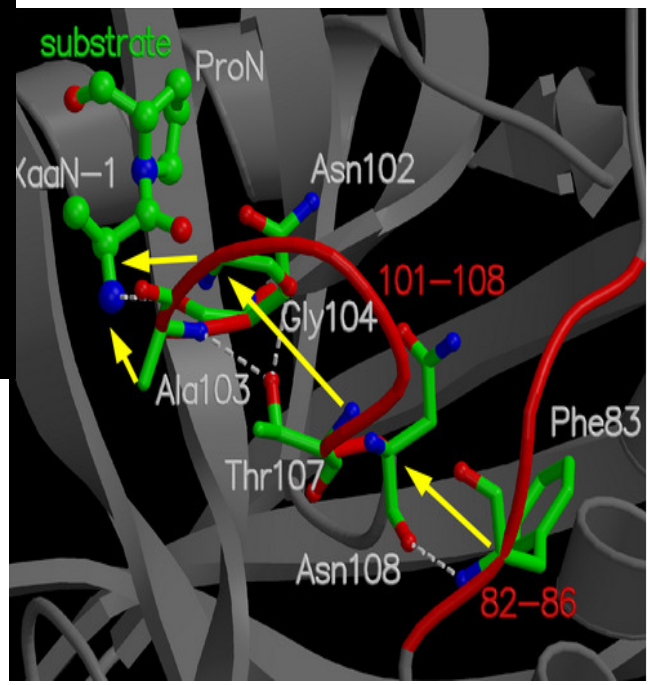


Biofase





Biorreceptor



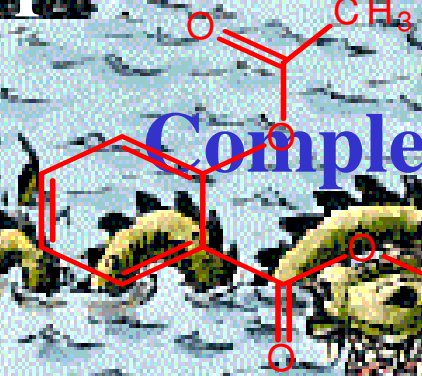
Efeito terapêutico

Fase farmacodinâmica (PD)

Biofase

Absorção

pH



Concentração

Meia-vida

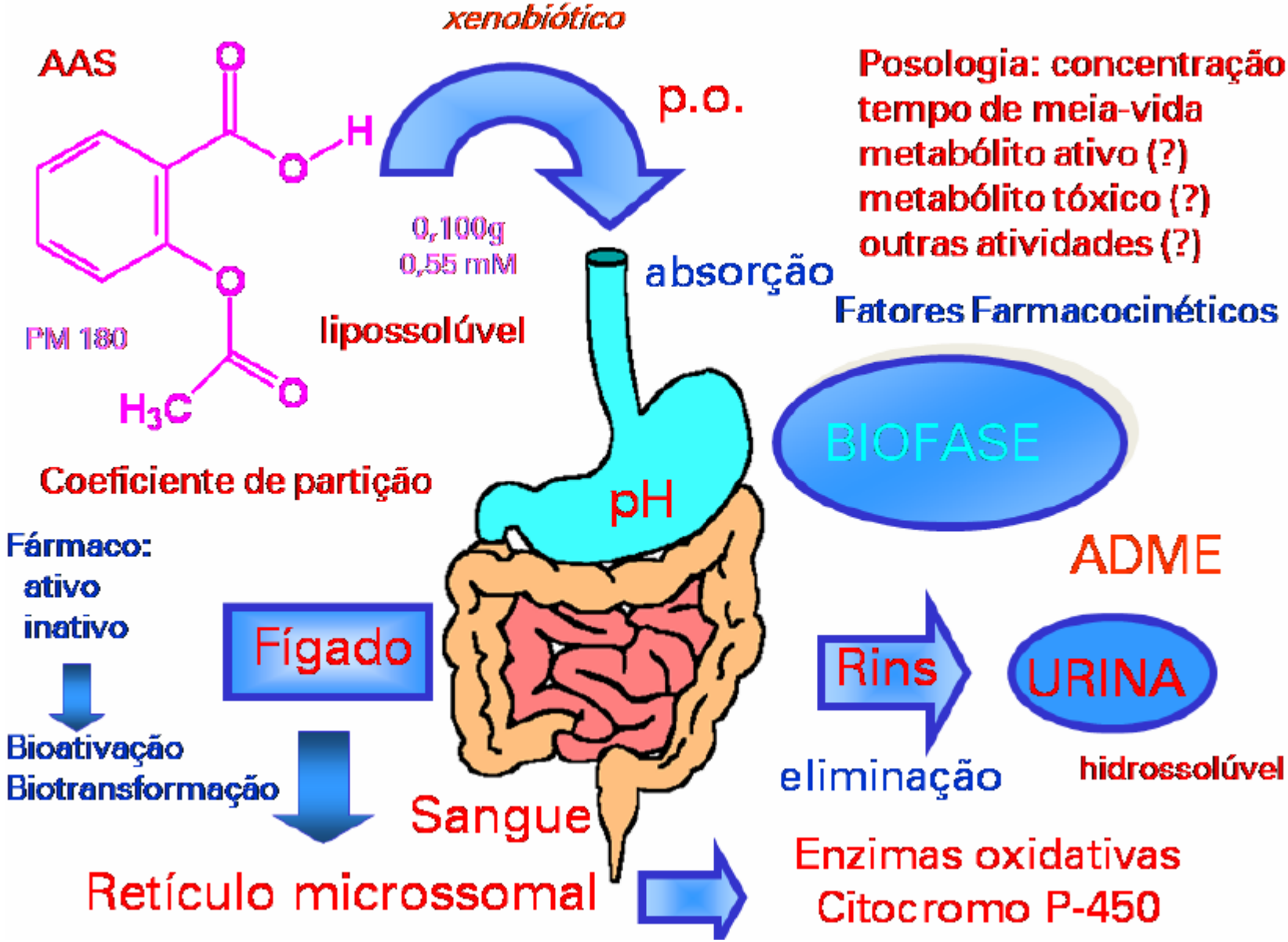
Posologia

Complexação plasmática

Deposito tissular

Metabolismo

Eliminação


xenobiótico
AAS
H
O
O
O
O
H_3C
PM 180
p.o.
0,100g
0,55 mM
lipossolúvel
absorção
Posologia: concentração
tempo de meia-vida
metabólito ativo (?)
metabólito tóxico (?)
outras atividades (?)
Fatores Farmacocinéticos
BIOFASE
pH
ADME
Coeficiente de partição
Fármaco:
ativo
inativo
Fígado
Rins
URINA
eliminação
hidrossolúvel
Bioativação
Biotransformação
Sangue
Retículo microssomal
Enzimas oxidativas
Citocromo P-450

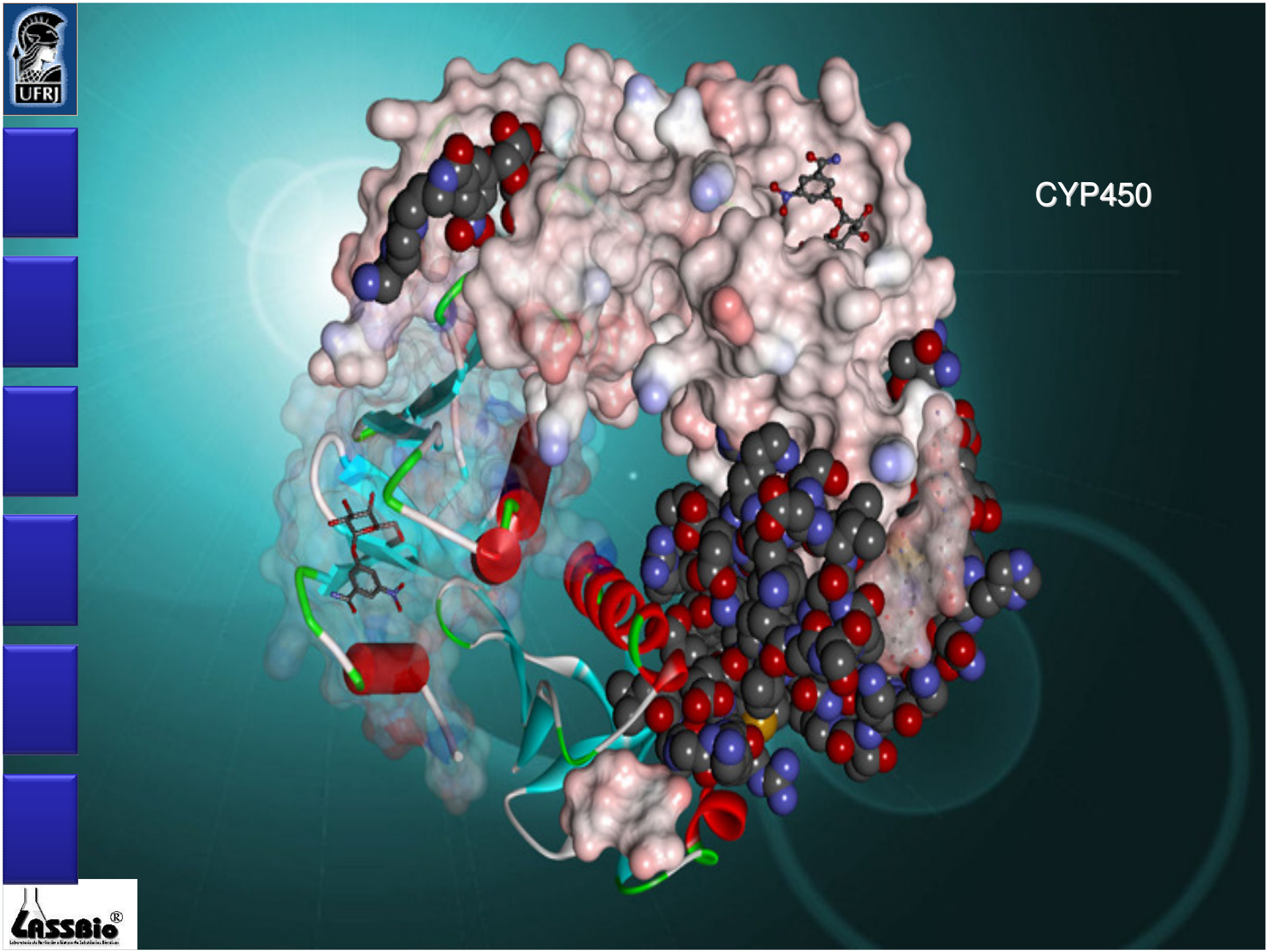
Rato Transgênico Humanizado

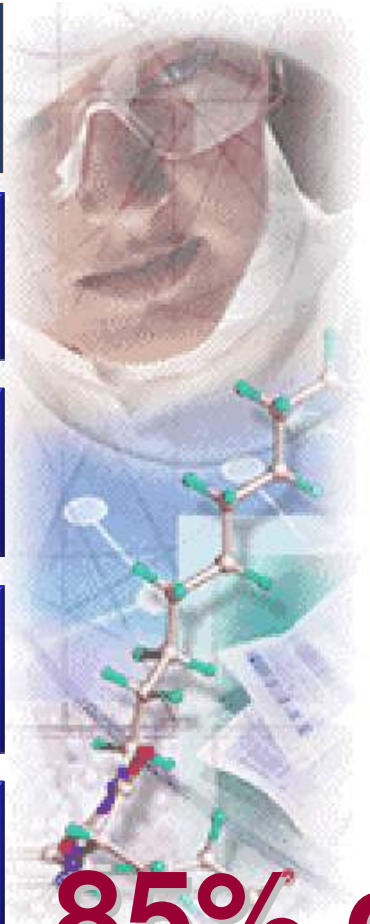
W. Xie & R. M. Evans, *Drug Discovery Today* 2002, *7*, 509-515

This mouse is a xeno-sensor allows the investigation of drug-drug interactions

Animal transgênico com mesmo perfil de resposta à ação de fármacos que humanos. Possui CYP3A isoenzimas (*xeno-sensor*) que permite o estudo de interações de fármacos, simulando o estudo em humanos.

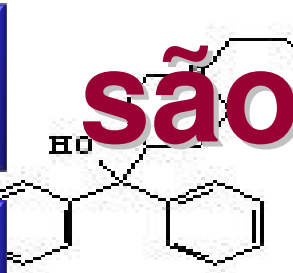
Humanized mouse model


CYP450

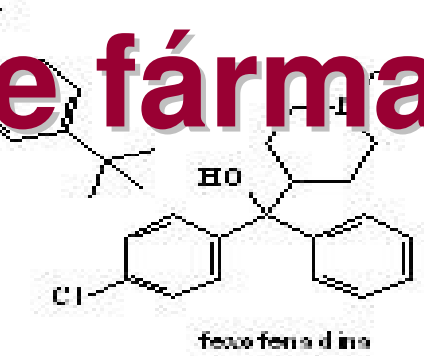


Os fármacos: sintéticos ...

85% do arsenal terapêutico são de fármacos sintéticos

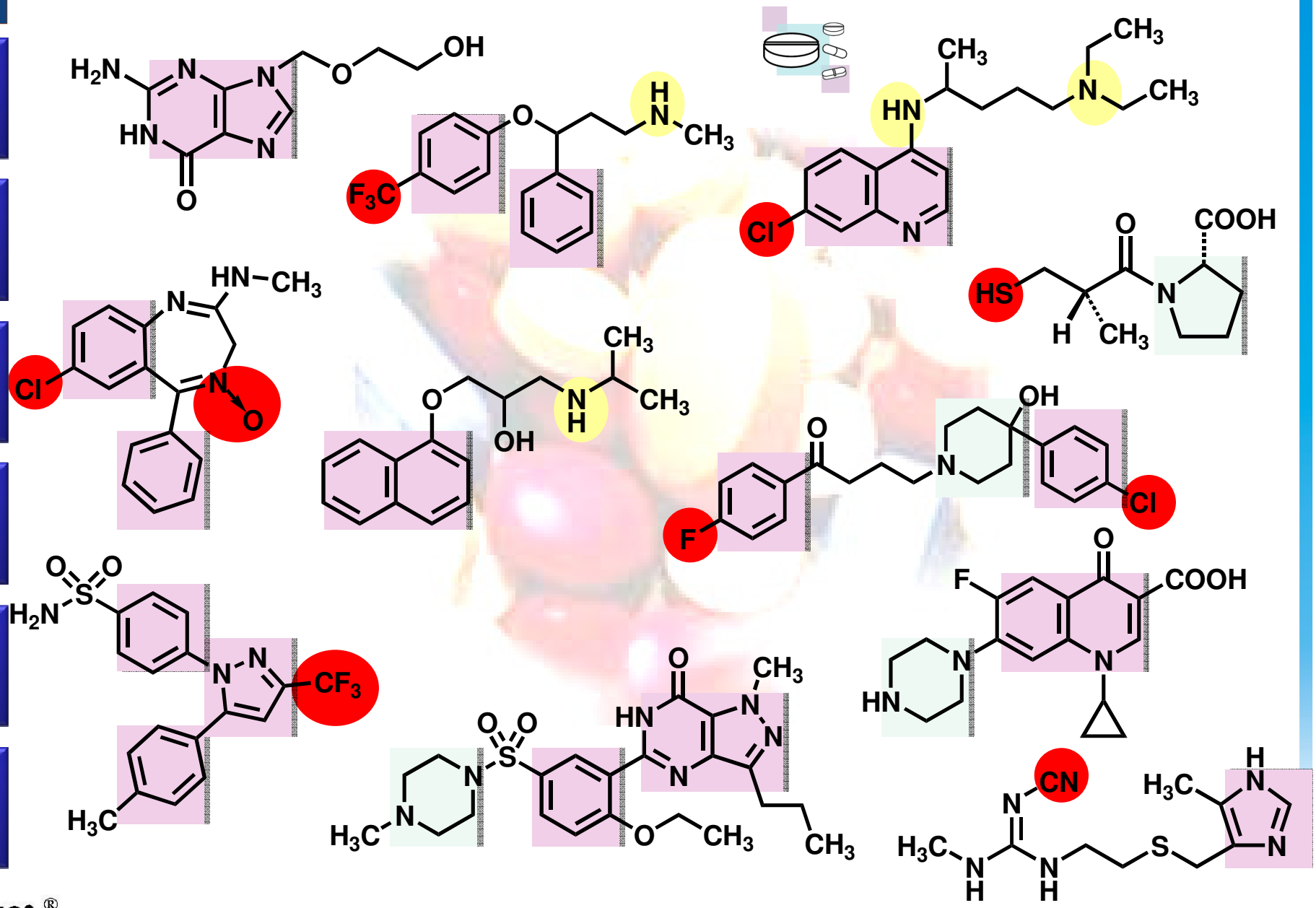


terfenadina



fexofenadina

A quimiodiversidade dos fármacos...é singela!



Physiologic approach

A abordagem fisiológica

Mechanism-based drug discovery

Abordagem racional

Descoberta do composto-protótipo

Estratégia do Análogo-ativo

Caracterização dos pontos & grupos farmacofóricos (bióforos)

cimetidina

antagonistas H2

inibidores da ACE

DHFR Inibidores

Estrutura do Biorreceptor Conhecida

Alternativa híbrida

Inovações Terapêuticas

Inibidores de HIV Asp-proteases

indinavir

Abordagem irracional

Identificação de novo hit ou ligante

Estratégias hifenadas

Abordagem irracional-racional

Imatinib

Bioinformática

Estrutura do Biorreceptor Desconhecida

A invenção do propranolol

Raymond Ahlquist (1914

Am J Physiol 1948, 153, 586

A STUDY OF THE ADRENOTROPIC RECEPTORS

RAYMOND P. AHLQUIST

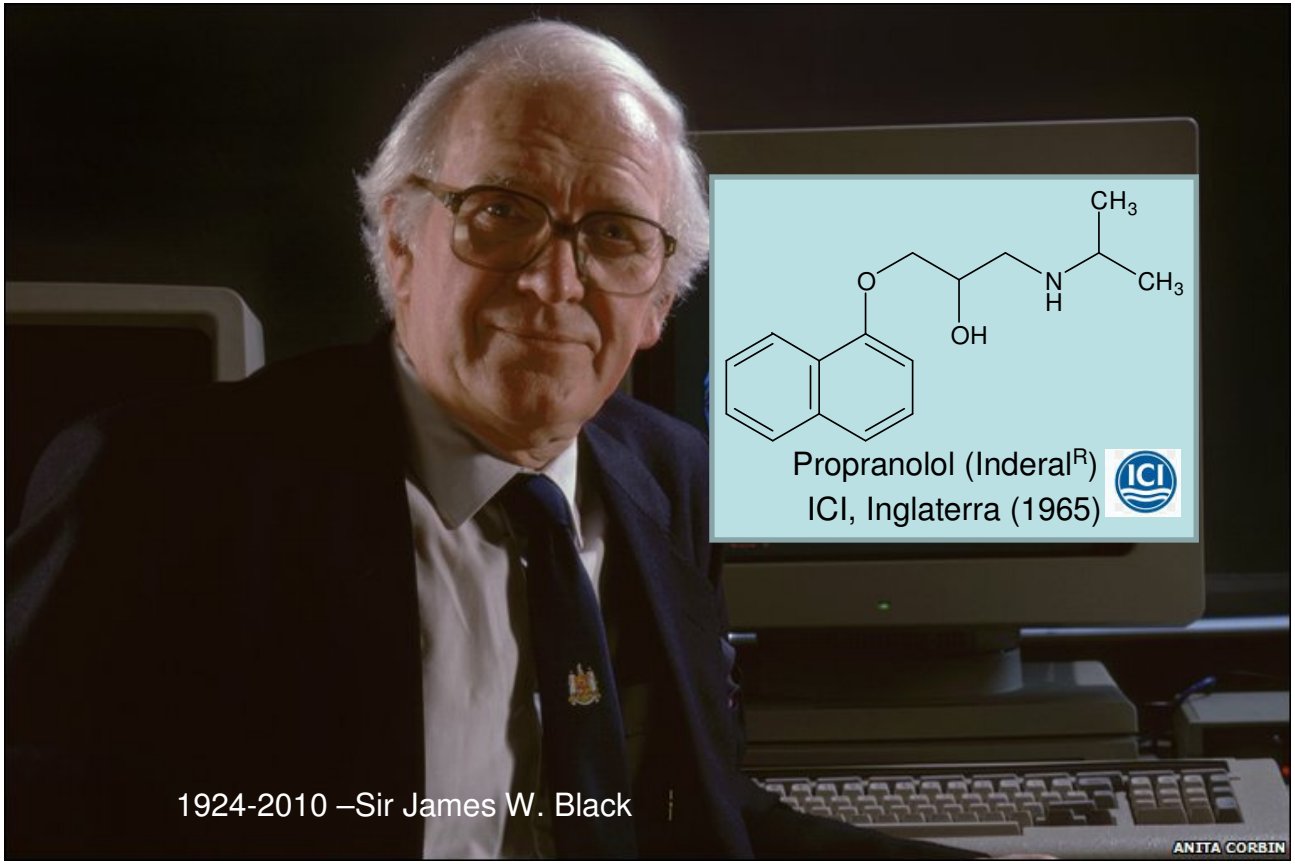
From the Department of Pharmacology, University of Georgia School of Medicine

AUGUSTA, GEORGIA

Premio Nobel
1988

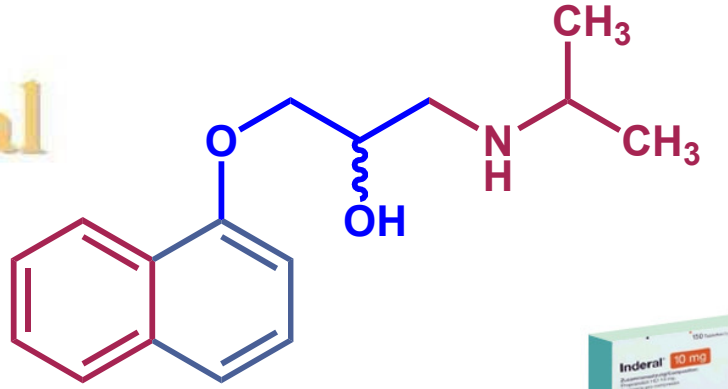
Química Medicinal

Pharmacology
Farmacologia

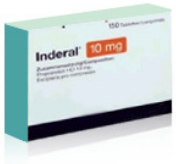


Química Medicinal

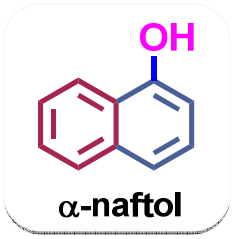
A invenção do propranolol



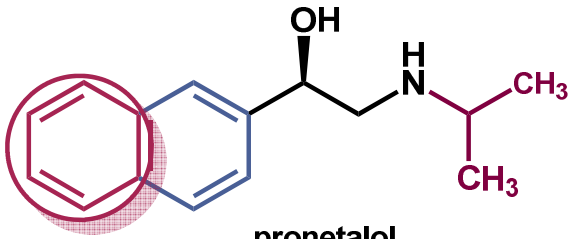
propranolol
1964



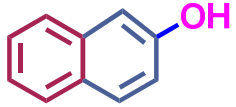
J. Black *et al.*, *Br. J. Pharmacol. Chmother.* **1965**, *25*, 577



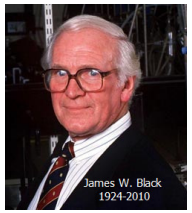
α-naftol



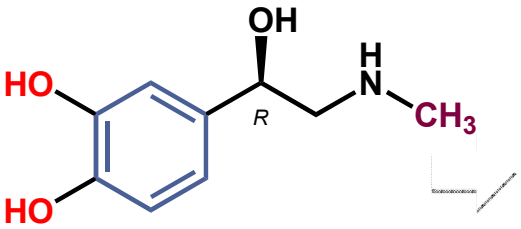
pronetalol
1959



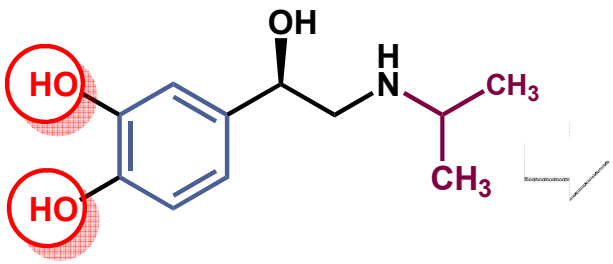
β-naftol



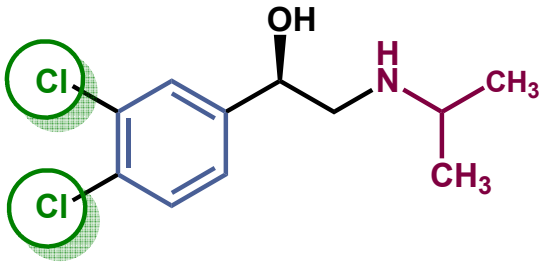
James W. Black, 1988 - "Pronethalol always seemed to us to be a prototype drug, good enough to answer questions of principle, but not good enough to be marketable"



adrenalina

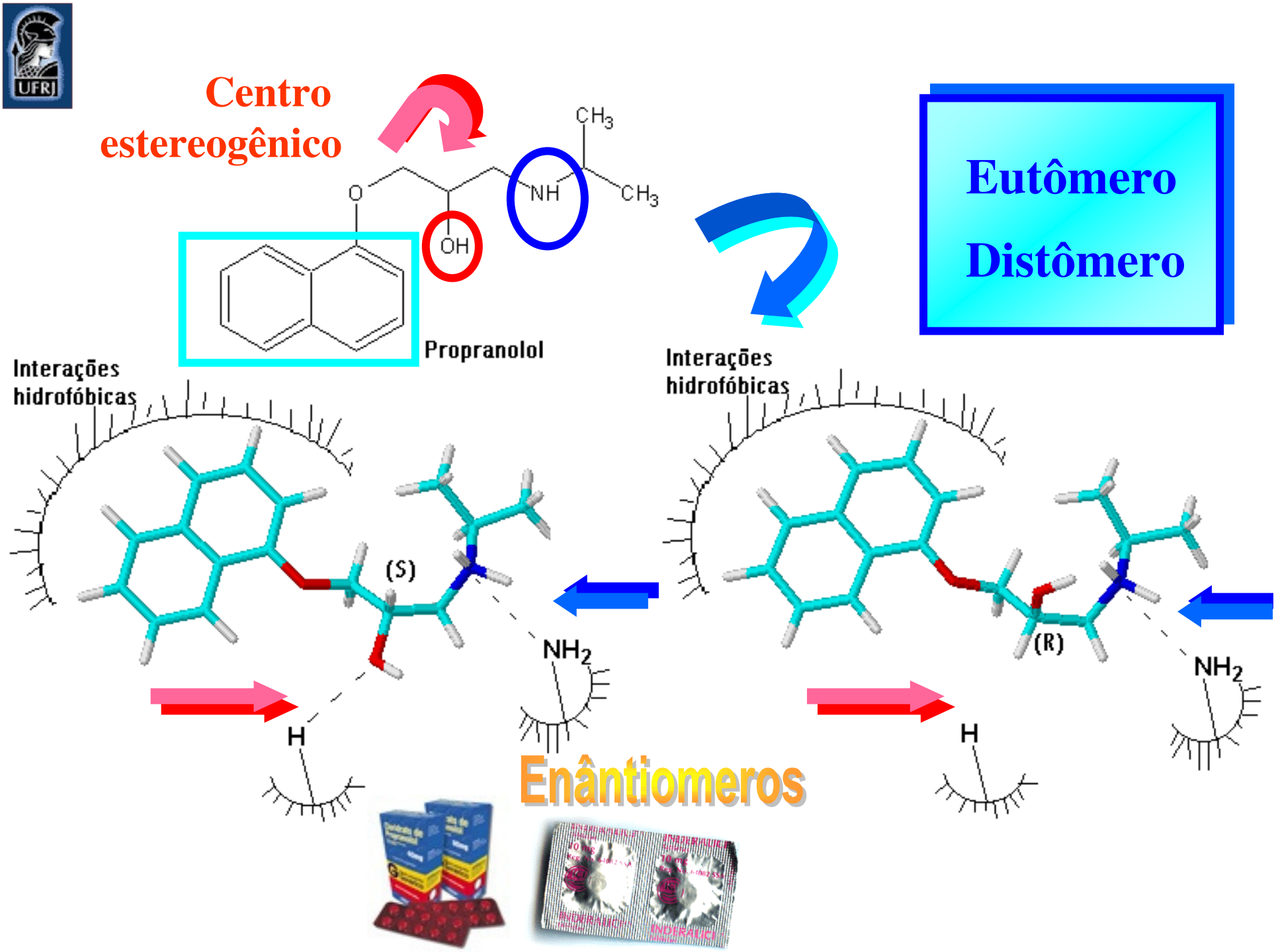


isoprenalina / isoproterenol



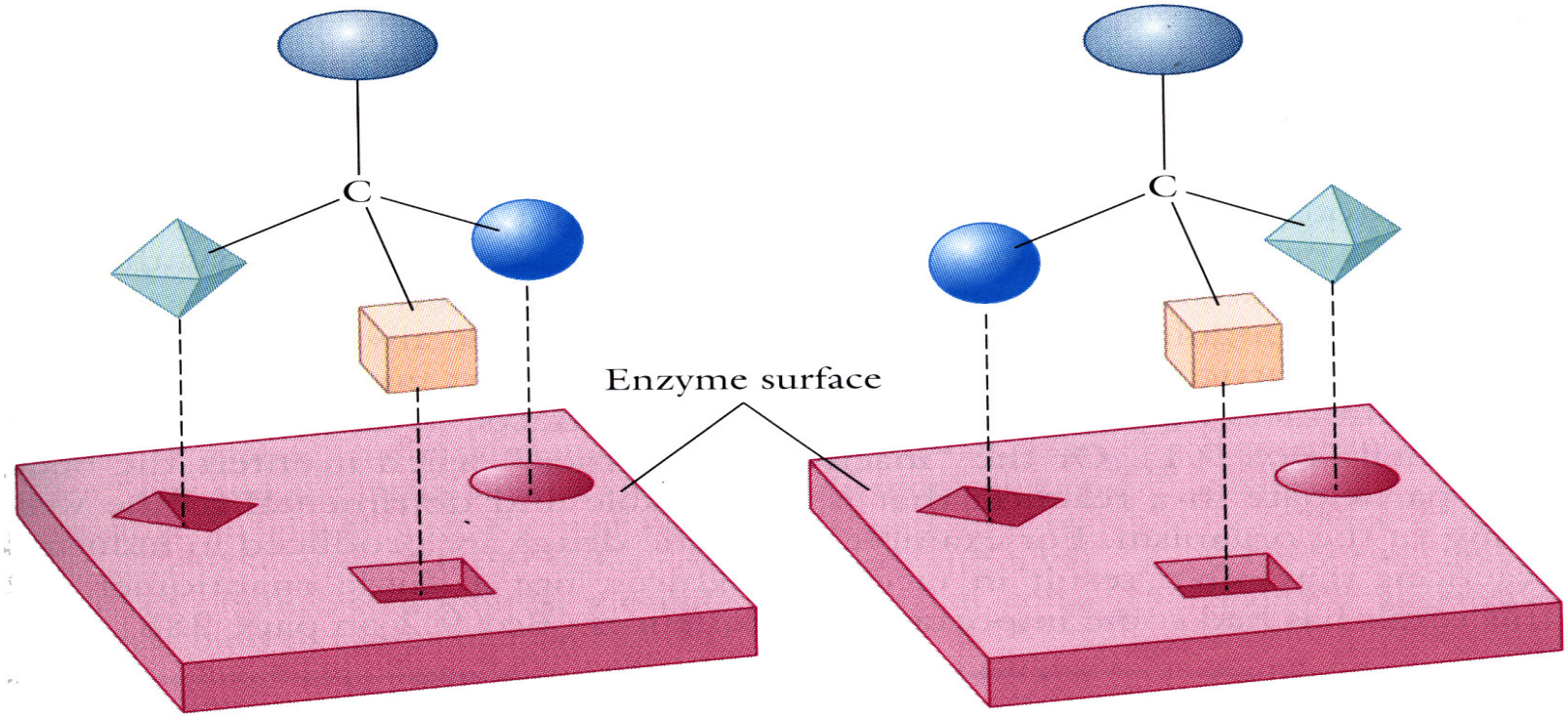
1958 - DCI
β-bloqueador

LASSBio®

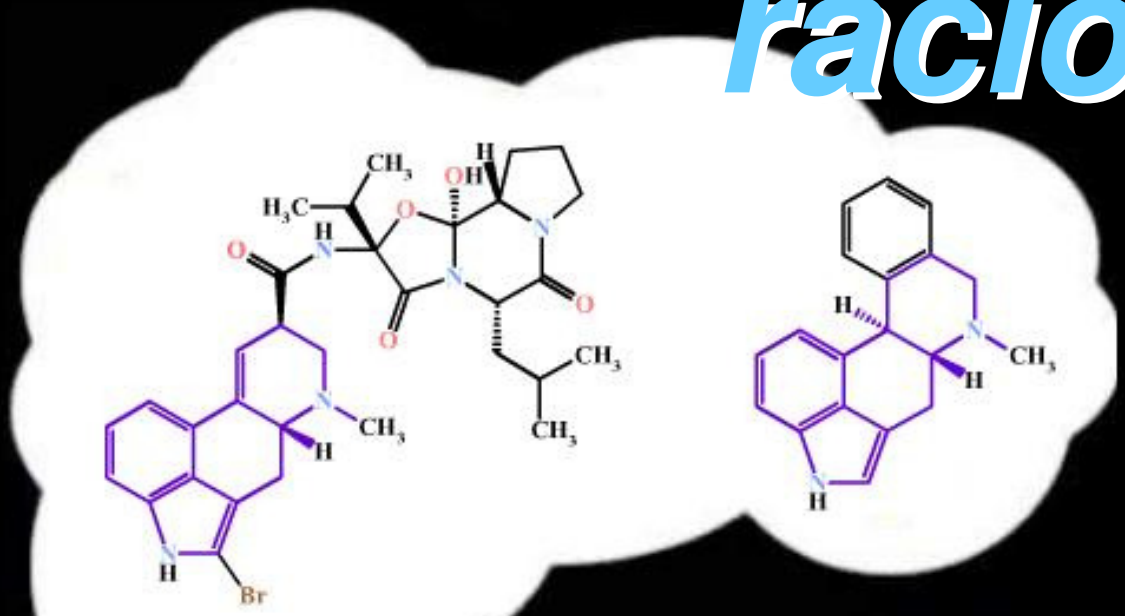

Centro
estereogênico
CH3
O
NH
CH3
OH
Propranolol
Eutômero
Distômero
Interações
hidrofóbicas
Interações
hidrofóbicas
(S)
(R)
NH2
NH2
H
H
Enântiomeros

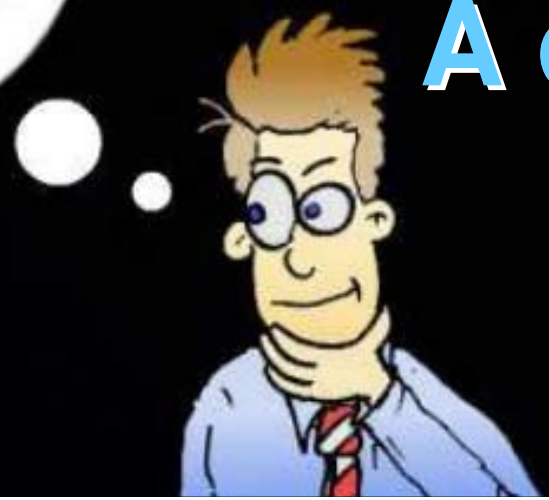
Modelo dos três pontos

Modelo de Easson-Stedman



Planejamento racional





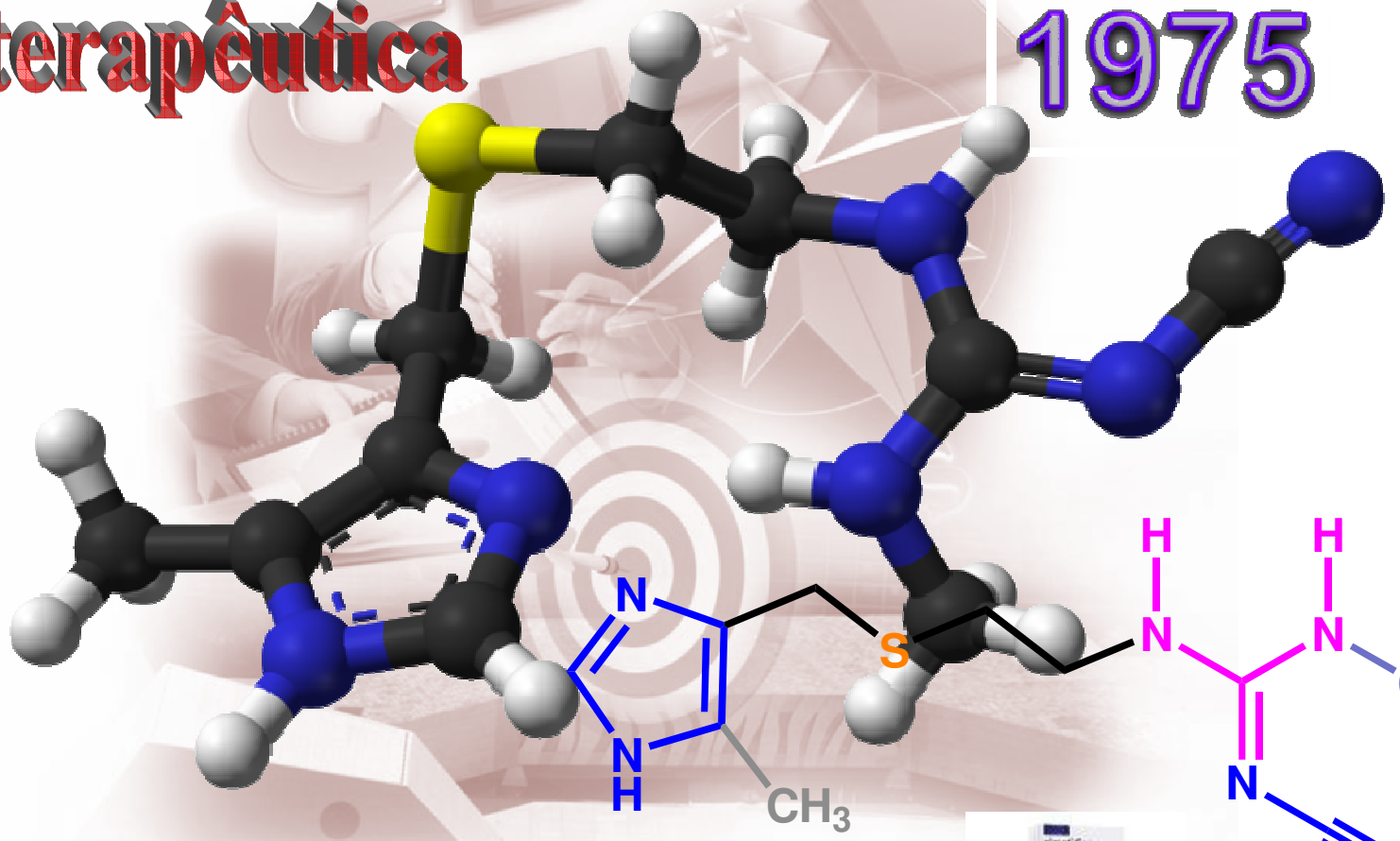
A descoberta da cimetidina

O planejamento racional

Inovação terapêutica

Cimetidina

1975



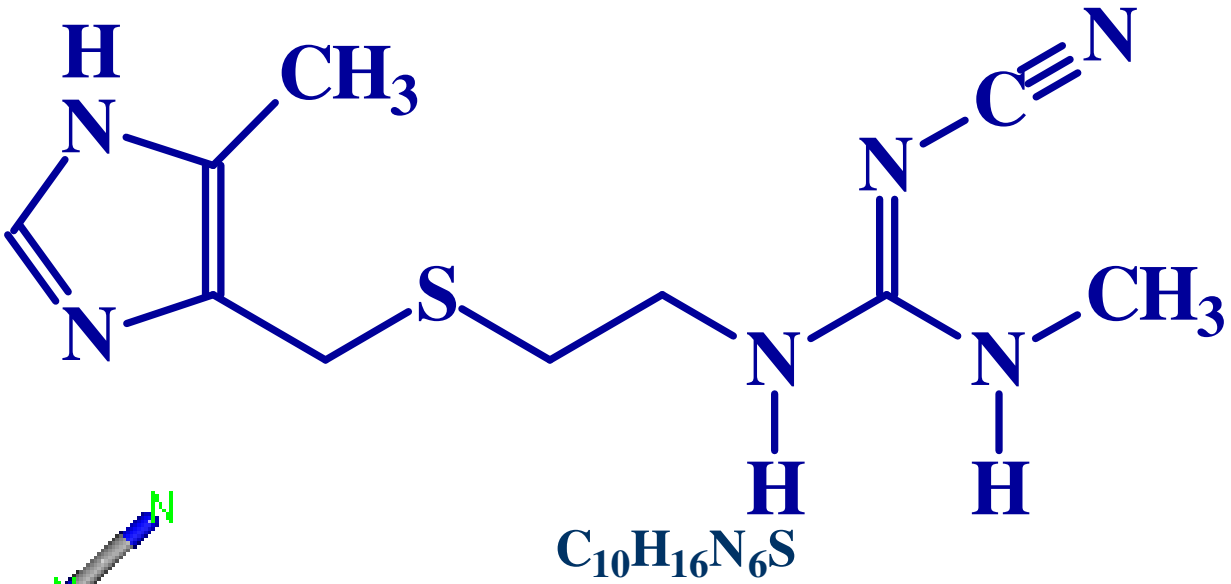
US 3950333 1974, 1976 - SK&F

Brit. J. Pharmacol. **53,** 435 (1975).

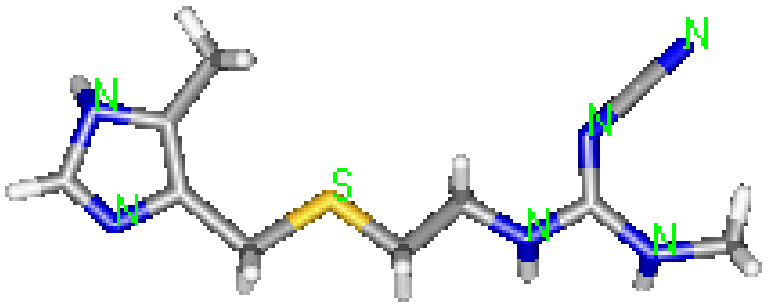
James Black, Robin Ganellin, Emmett, Durant

$C_{10}H_{16}N_6S$

Cimetidina



$C_{10}H_{16}N_6S$



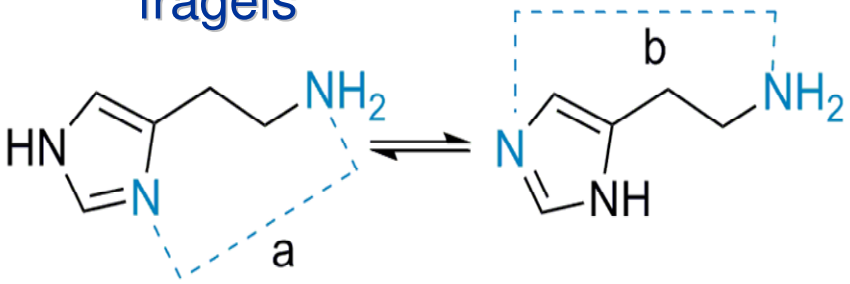
Inovação terapêutica

Os descobridores da cimetidina: Ganellim, Emmet, Durant & Black, da esquerda para a direita

Abordagem Fisiológica

Química Medicinal

Interações frágeis



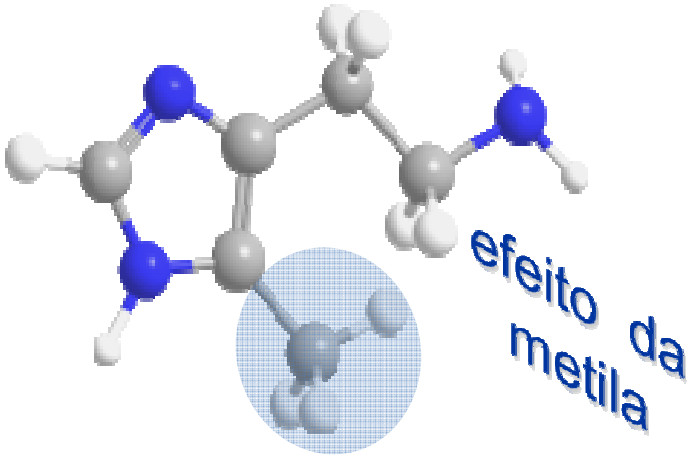
Forma A

a = 4,83 Å
b = 5,52 Å

Forma B

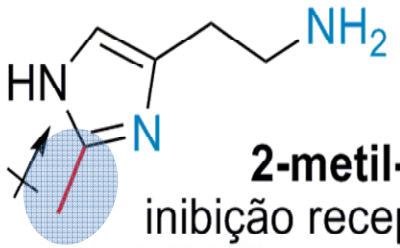
tautomêros

Propriedades estruturais



4-metil-histamina

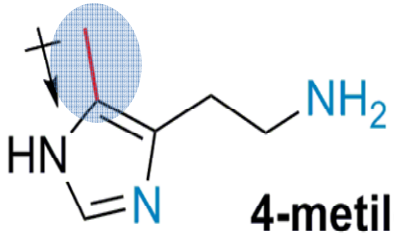
Análogo ativo



2-metil-histamina

inibição receptores H_1 = 17%

inibição receptores H_2 = < 2%



4-metil-histamina

inibição receptores H_1 = 0,2%

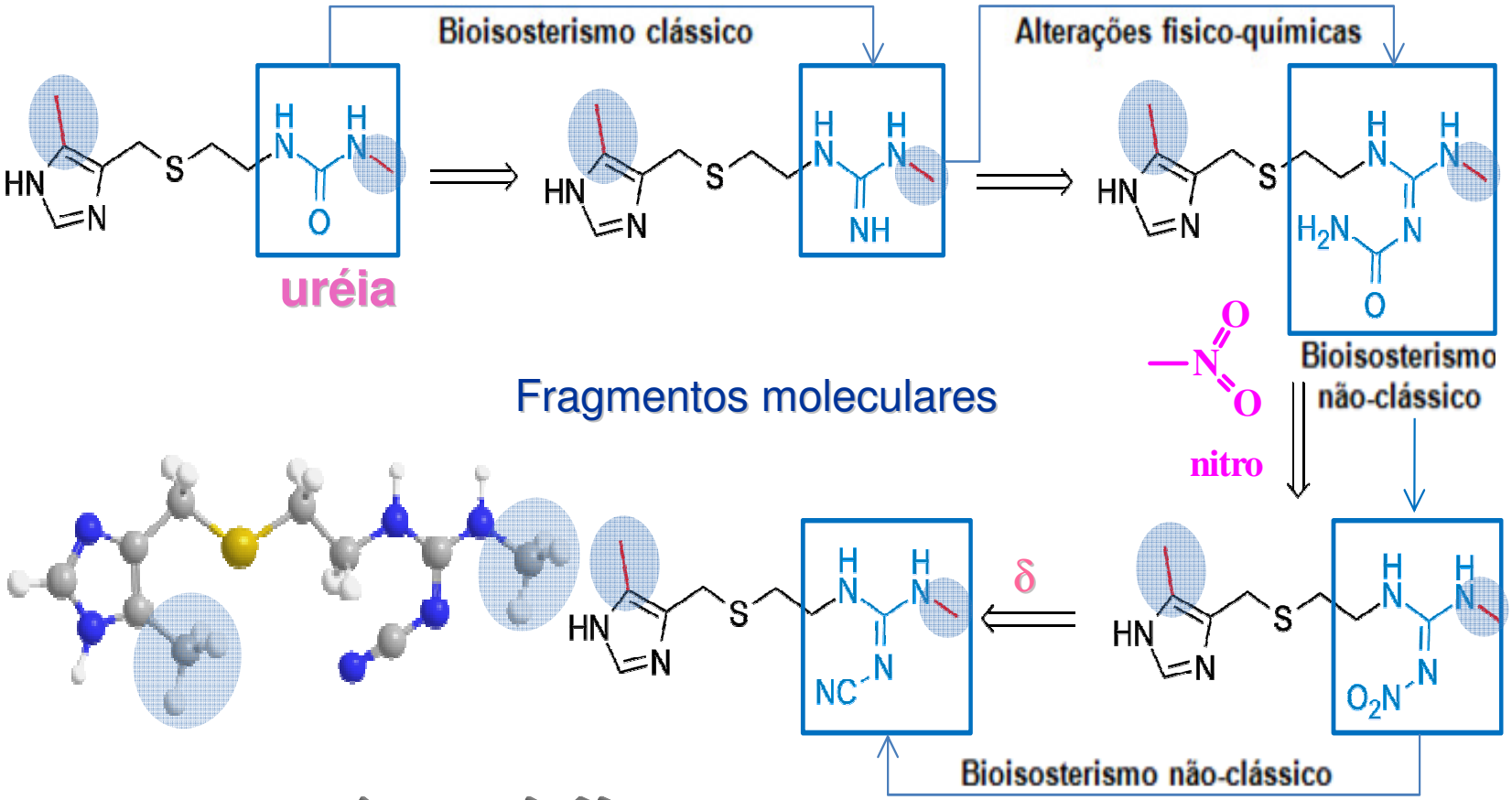
inibição receptores H_2 = 50%

Dois sub-tipos de H_R

Desenho estrutural baseado no substrato

Gênese da cimetidina

Química Medicinal



cimetidina

$C_{10}H_{16}N_6S$
PM: 252,1

Inovação terapêutica

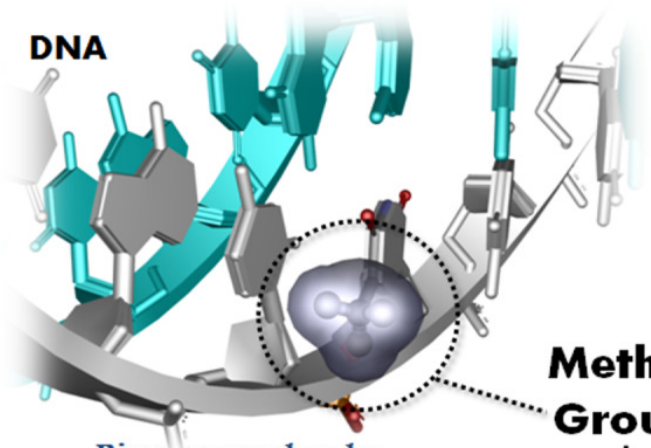
CHEMICAL REVIEWS
Chem. Rev. 2011, 111, 5215-5246
REVIEW
dx.doi.org/10.1021/cr200060g

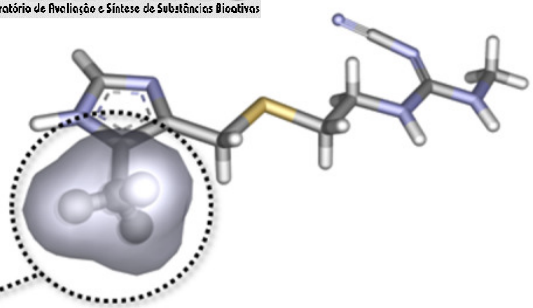
The Methylation Effect in Medicinal Chemistry

E. J. Barreiro, A. E. Kümmerle and C. A. M. Fraga

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

Química Medicinal





Methyl Group

Biomacromolecules

CH/π interactions from the methyl group of timine. Conformational changes, wich could be involved on maintenance of life.

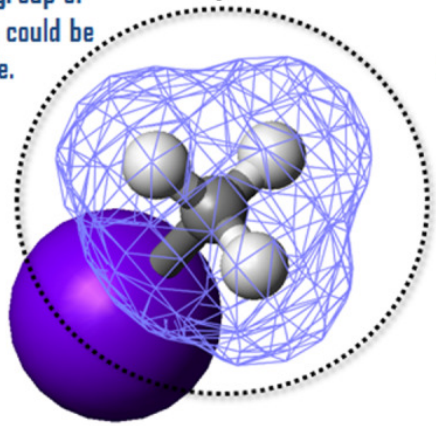
Micromolecules

The inductive eletronic effect of the methyl group is the responsible for the subtype receptors selectivity (H_2x H_1) on cimetidine

CH_3

15 Da

The stereoelectronic effects of the methyl group have great importance on biological events and are widely used by the Medicinal Chemistries in the development of new drugs.



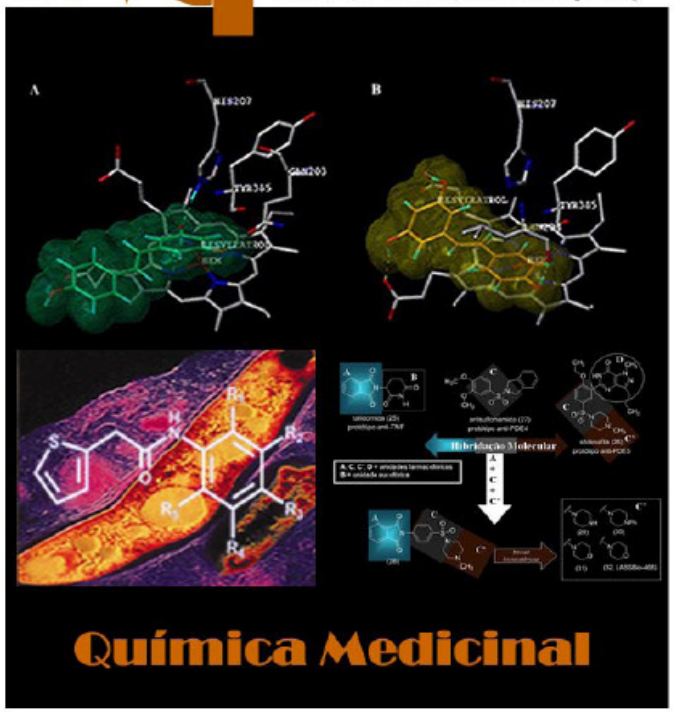
Stereoelectronic Properties

MW = 15,03
MR = 5,65 cm³/mol
π hansch = 0,56
σ hammett = -0,17

Revista Virtual de Química
www.uff.br/rvq
Volume 1, Número 1, Janeiro-Março 2009

www.uff.br/rvq

DICA



O medicamento é instrumento essencial à preservação, manutenção e promoção da Saúde. O acesso ao medicamento representa um importante fator de inclusão social que depende da disponibilidade do fármaco – princípio ativo contido no medicamento e que em 85% dos casos é de origem sintética. Neste cenário, a importância do saber-fazer fármacos e medicamentos passa a representar um componente estratégico para o pleno exercício da soberania de nosso País. A universalização do acesso ao medicamento, para o cumprimento do preceito de nossa Carta Magna de 1988, quanto ao direito de todos os brasileiros e brasileiras à Saúde, depende, mais do que possa parecer, deste componente.

1. A inovação em fármacos: O processo de planejamento racional
2. O principal paradigma da química medicinal moderna: A descoberta do composto-protótipo
3. Novos compostos-protótipos descobertos no *Laboratório de Avaliação e Síntese de Substâncias Bioativas* (LASSBio®)

Artigo de Divulgação

A Química Medicinal e o paradigma do composto-protótipo

Barreiro, E. J.*

Rev. Virtual Quim., **2009**, 1 (1), 18-26. Data de publicação na Web: 30 de Janeiro de 2009

http://www.uff.br/rvq

Portal dos Fármacos

www.portaldosfarmacos.ccs.ufrj.br

contato

Editorial | Missão | Perfis Históricos | 'Operários' das Ciências Farmacêuticas | Resenhas | Você Sabia?

Tribuna do Especialista | Atualidades | Entrevistas | Equipe | Página Inicial

Fármacos e Medicamentos (INCT-INOFAR).

Sexta-feira, 20 de Novembro de 2009

Parceiros:

LASSBio®

INCT Instituto Nacional de Ciência e Tecnologia de Fármacos e Medicamentos inofar www.inct-inofar.ccs.ufrj.br

A construção deste Portal foi possível graças ao apoio da FAPERJ através de seu programa de - *Edital FAPERJ 04/2007.*

Conheça os projetos contemplados

AGENDA

Em Destaque

CRACK

A destruição progressiva da sociedade.

A academia pode ajudar ?

07 de dezembro de 2009

Horário: 09:30h

Auditório da Farmacologia

ENTREVISTAS

Prof. Vitor Ferreira recebe II Prêmio UFF de Excelência Científica

"A doce arte de fazer moléculas com aplicabilidade social"

ATUALIDADES

strumento de divulgação e popularização das ciências relacionadas aos fármacos e medicamentos

Fale conosco

Desenvolvido por: **Cúpula Informática**


www. farmacia.ufrj.br/lassbio
LASSBio®
Laboratório de Avaliação e Síntese de Substâncias Bioativas
Faculdade de Farmácia
UFRJ
Área de Atuação
Links
Equipe
Contato
Home
LASSBio, interesses de pesquisa
Publicações Selecionadas
Teses e Dissertações
Escolas de Verão
Projetos de Pesquisa em Andamento
Aulas de Pós-Graduação
Tópicos de Interesse em Química Farmacêutica Medicinal
Cursos
Conferências
LASSBio 15 anos
Informativo Semanal do LASSBio
Links
Webmail
Visite também:
www. portaldosfarmacos.ccs.ufrj.com.br
ejb-eliezer.blogspot.com.br
2011
Aspectos do planejamento de fármacos
AIQ
ANO INTERNACIONAL DA QUÍMICA
International Year of CHEMISTRY 2011
QUÍMICA PARA UM MUNDO MELHOR
2016


Obrigado
Corcovado, uma das sete maravilhas do mundo moderno