Universidade Federal do Rio de Janeiro

Fundamentals of Medicinal Chemistry

Eliezer J. Barreiro

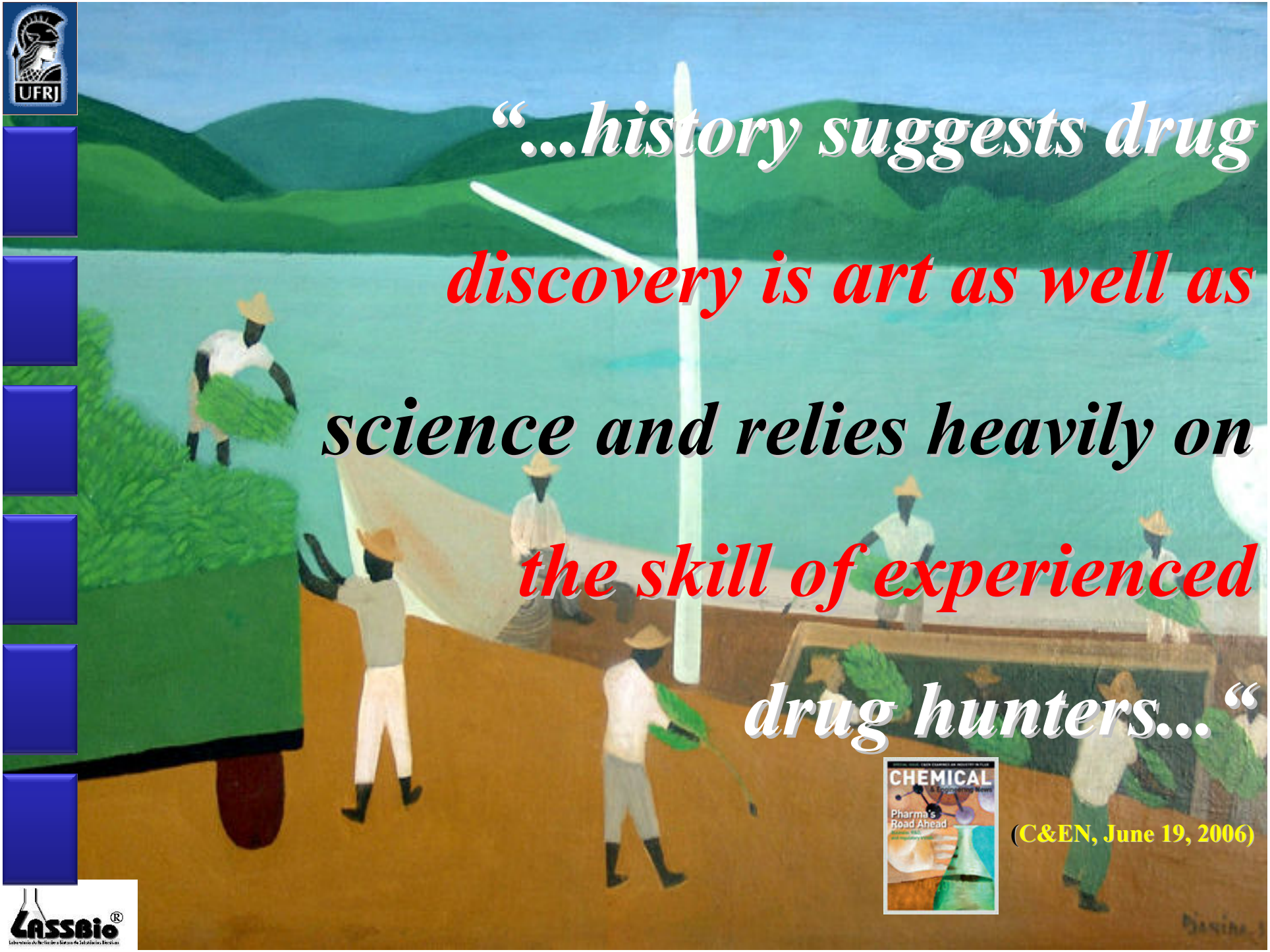
Professor Titular

Universidade Federal do Rio de Janeiro

Laboratório de Avaliação e Síntese de Substâncias Bioativas

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

Programa de Desenvolvimento de Fármacos - ICB


"...history suggests drug
discovery is art as well as
science and relies heavily on
the skill of experienced
drug hunters..."
CHEMICAL
Pharma's Road Ahead
(C&EN, June 19, 2006)

O fármaco…

É o fármaco formulado galenicamente…

O que é um fármaco ?

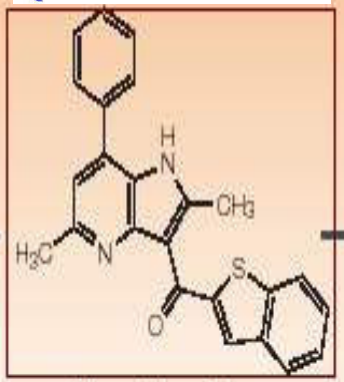
- **Fármaco…**
  - É uma substância orgânica (> 99%) com propriedades farmacoterapêuticas para uso médico, capaz de recuperar, promover, manter ou preservar o estado de Saúde;
  - Tem elevada eficácia para o alvo terapêutico (PD);
  - Não tóxico;
  - Potente *in vivo* com boa biodisponibilidade: ativo 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

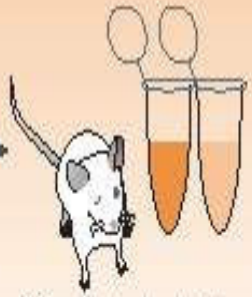
Química Medicinal

Preclinical studies

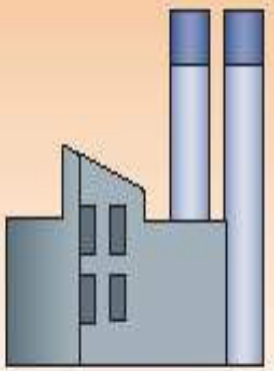
Research team formed and objectives set



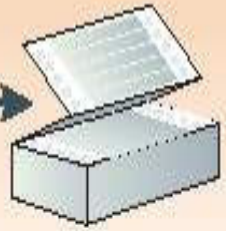
Novel chemicals synthesized



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

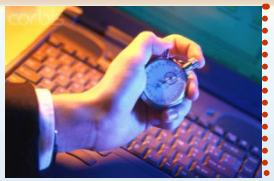


Formulation, stability scale-up synthesis, chronic safety in animals

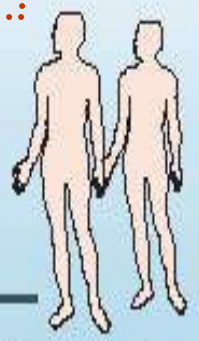


Company files Investigational New Drug (IND) application with FDA

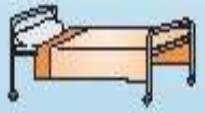
Clinical studies



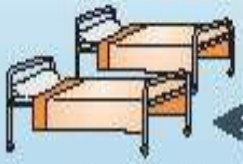
O processo do desenvolvimento de novos fármacos é complexo…



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

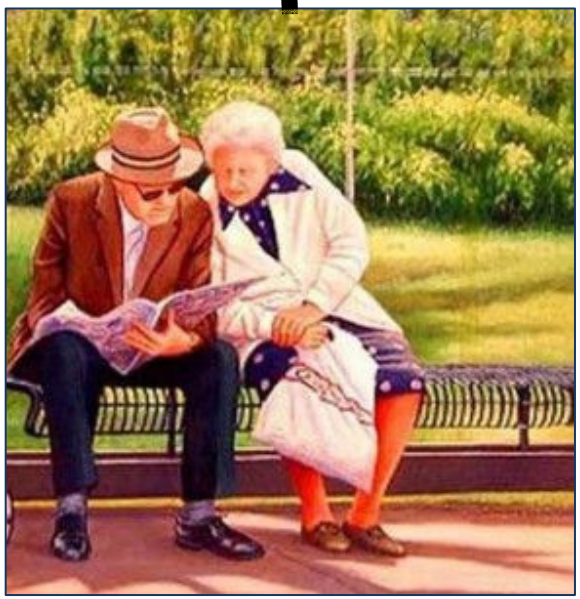
FDA

FDA reviews NDA

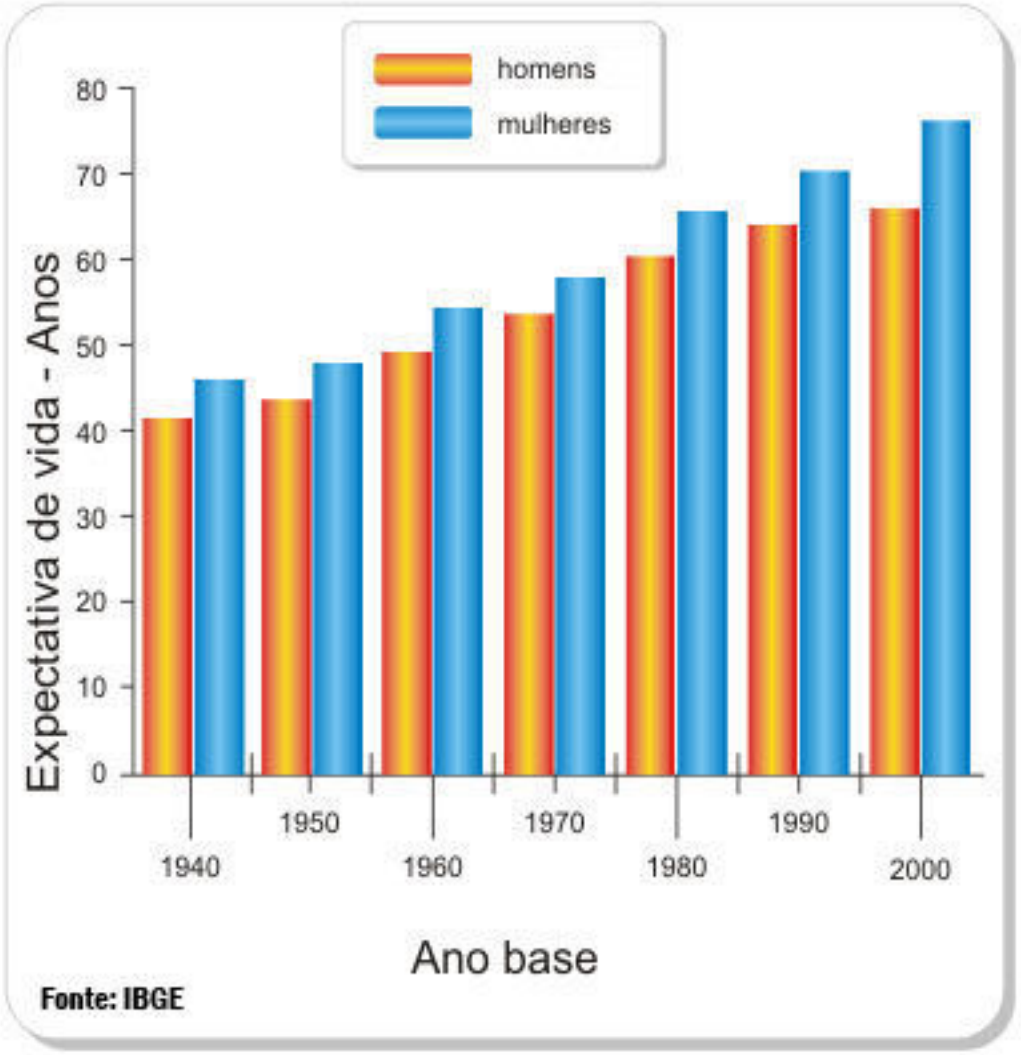
Drug is approved for marketing

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

Aumento na expectativa de vida...



http://clubeficaz.com.br/clubes/vivasaud
/files/2008/12/idosos-291x300.jpg



...os fármacos tem muito a ver com isso!

1. **Histórico do planejamento racional de fármacos: a Química Medicinal e a Química Farmacêutica**
2. **A cronologia da descoberta de fármacos e o prêmio Nobel**
3. **A contribuição dos produtos naturais para a descoberta de fármacos**
4. **Noções das interações fármaco-biorreceptores e o paradigma de Ehrlich-Fischer**
5. **Abordagem fisiológica no planejamento racional**
6. **Estratégias de desenho molecular de análogos-ativos:**
   - 6.1. Aplicação do bioisosterismo;
   - 6.2. Aplicação da simplificação molecular;
   - 6.3. Aplicação da anelação molecular
   - 6.4. Aplicação da hibridação molecular
   - 6.5. Aplicação de técnicas conjugadas
7. **Estudo de casos**

Bibliografia: *Química Medicinal: As razões moleculares da ação dos fármacos*, E. J. Barreiro & C. A. M. Fraga, Artmed, Porto Alegre, RS, 2008.

Definição:

Química Medicinal

é a disciplina que estuda os aspectos relacionados à descoberta, invenção e preparação de substâncias bioativas,de interesse terapêutico, i.e. fármacos.

Estuda os <u>fatores moleculares</u> do modo de ação dos fármacos, incluindo a compreensão da relação entre a estrutura química e a atividade terapêutica, absorção, distribuição, metabolismo, eliminação e toxicidade.

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

Chemistry and Human Health Division (VII)

Subcommittee on Medicinal Chemistry and Drug Development.

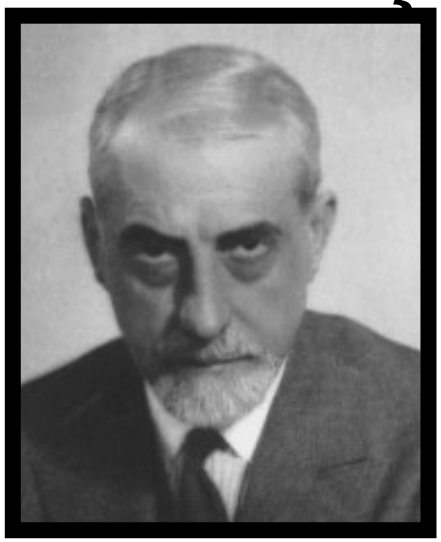
A Química Medicinal é uma disciplina chave, de vital importância para a indústria farmacêutica. Os Químicos Medicinais participam do processo da descoberta de novos fármacos e solucionam problemas relacionados à otimização das propriedades farmacológicas das moléculas.

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

LASSBio®

http://www.iupac.org

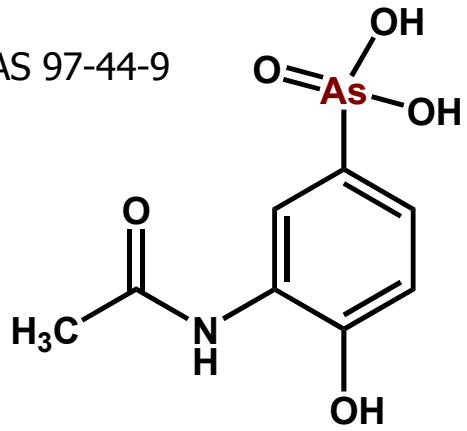
O berço da Química Medicinal



Ernest Fourneau
1872-1949

Stovarsol

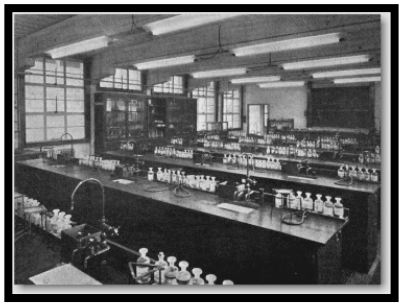
CAS 97-44-9



Institut Pasteur (1887)

1911- Laboratoire de Chimie Thérapeutique

Institut Pasteur (Emile Roux)



1911-1944 – J. Tréfouël, Th. Tréfouël, G. Benoit, D. Bovet, F. Nitti

Prontosil rubrum (sulfonamidas)

Curare: SAR

Daniel Bovet
1907-1992

Prêmio Nobel de Fisiologia/Medicina 1957

J-P Fourneau, « Ernest Fourneau foundateur de la Chimie Pharmaceutique française », *Revue de l´Histoire de la Pharmacie*, t.XXXIV, nº 275, 335-355

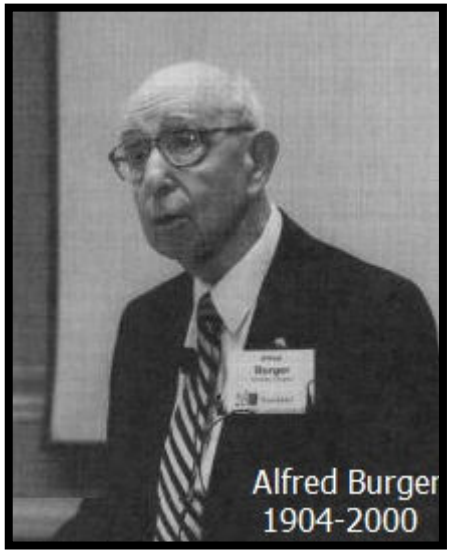
Química Medicinal

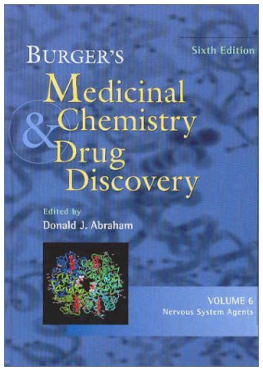
Prof. Alfred Burger

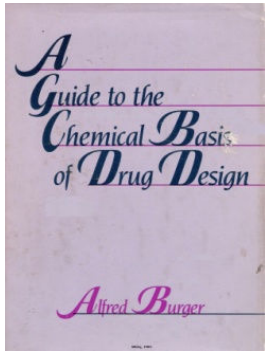
(1904-2000)

University of Virginia

EUA





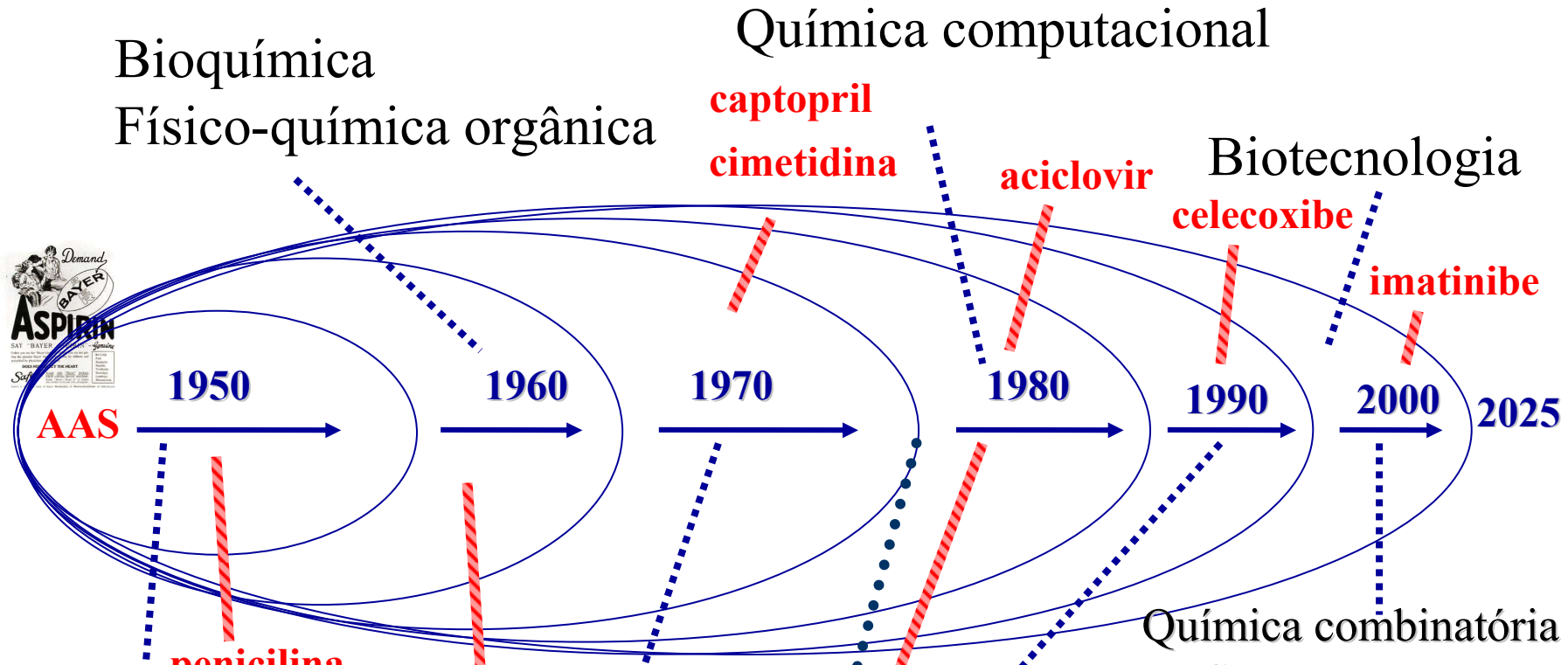


1958 – cria o Journal of the Medicinal and Pharmaceutical Chemistry → depois Journal of Medicinal Chemistry

"An Editor's Commentary on the Birth of a Journal"
J. Med. Chem. **1991**,*34*, 2-6

1978 - GlaxoSmithKline cria com ACS o "Alfred Burger Award" em Química Medicinal
T. Y. Shen - inventor da indometacina

A evolução da Química Medicinal



Adaptado de F. King

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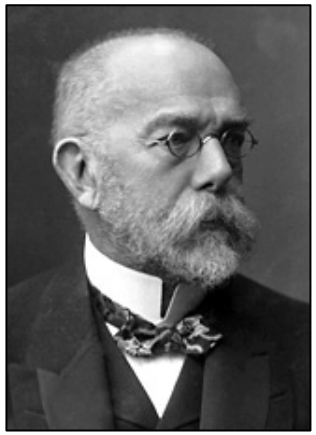
Universidade Federal do Rio de Janeiro

Química Medicinal

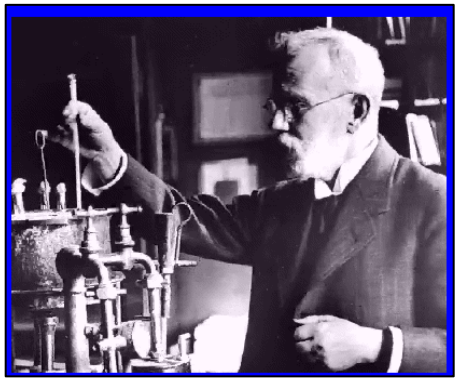
Os fármacos e o Prêmio Nobel

Os fármacos e o Nobel !

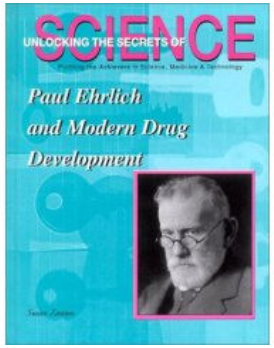
Emil Fischer
1852-1919
1902



Robert Koch
1843-1910
1905



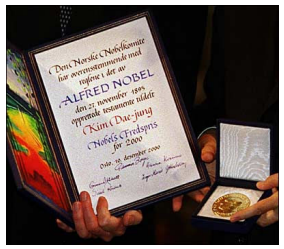
Paul Ehrlich
1854-1915
1908



P. Ehrlich, *Chemotherapeutics: scientific principles, methods and results*. *Lancet* 1913, **2**, 445

Os fármacos e o Nobel !

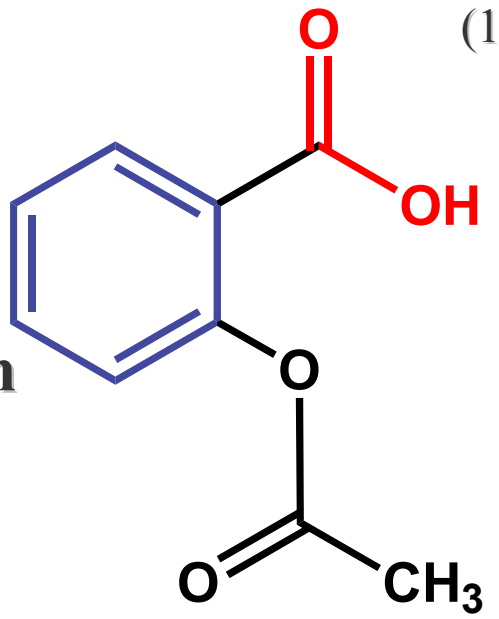
1982



John R. Vane
(1927-2004)

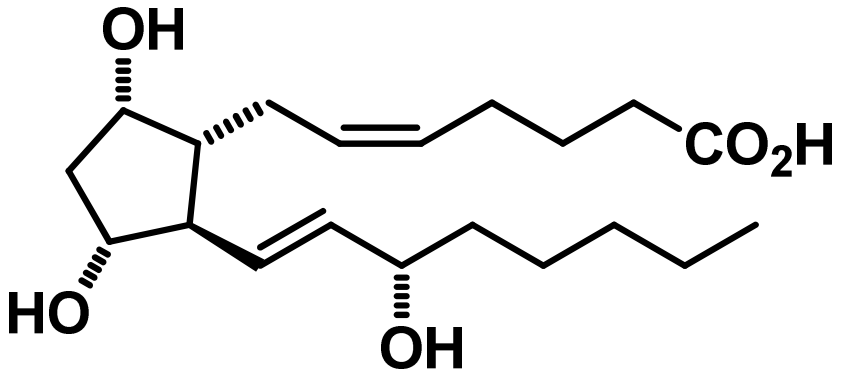
Sune K. Bergström
(1916-2004)

Bengt I. Samuelsson
(1934-



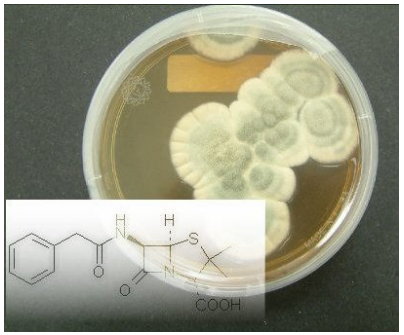
$C_9H_8O_4$

1982 – AAS



Prostaglandina $F_{2\alpha}$

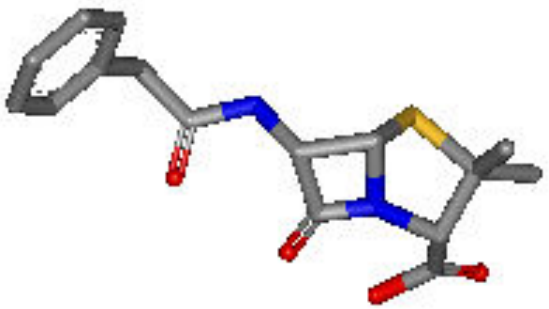
Os fármacos e o Nobel !



- 196 pesquisadores ganharam o Prêmio Nobel de Medicina (1901-2010)

Alexander Fleming

1881-1955



Penicilina

Howard W. Florey

1898-1968

http://nobelprize.org

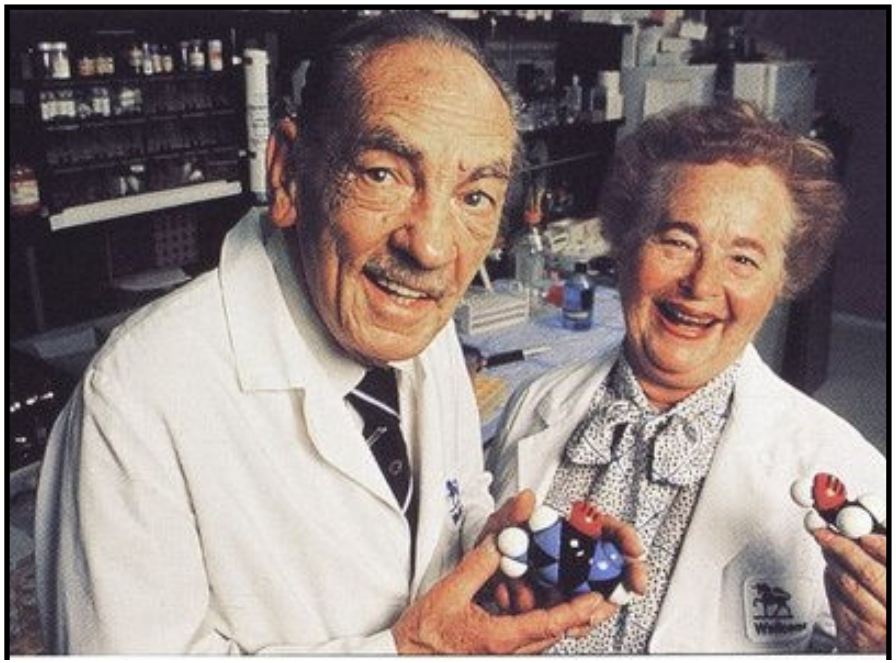
1945

Ernest B. Chain

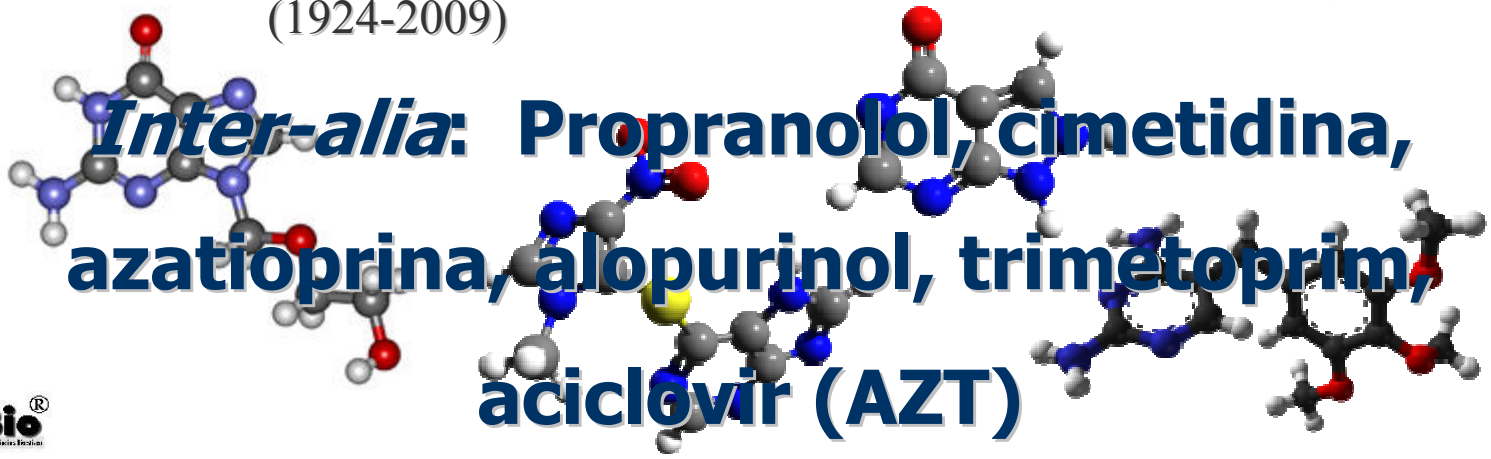
1906-1979

“for their discoveries of important principles for drug treatment"

James W. Black
(1924-2009)



George Hitchings (1905-1998) Gertrude B. Elion (1918-1999)



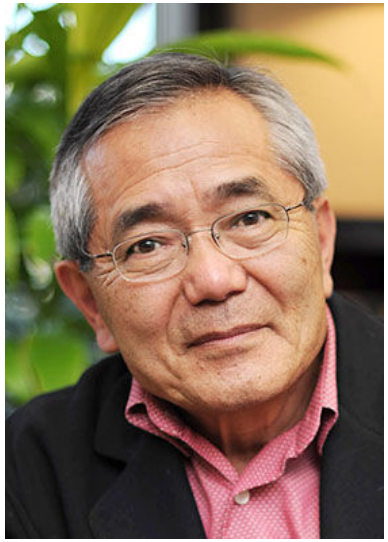
***Inter-alia*: Propranolol, cimetidina, azatioprina, alopurinol, trimetoprim, aciclovir (AZT)**

1988

Os fármacos e o Nobel !

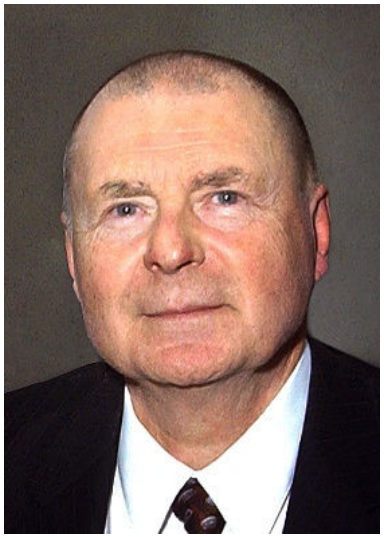
"for palladium-catalyzed cross couplings in organic synthesis".

2010



Ei-ichi Negishi

(1935-)



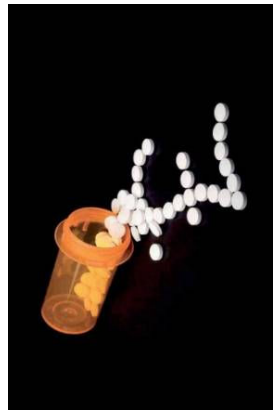
Richard F. Heck

(1931-)

Akira Suzuki

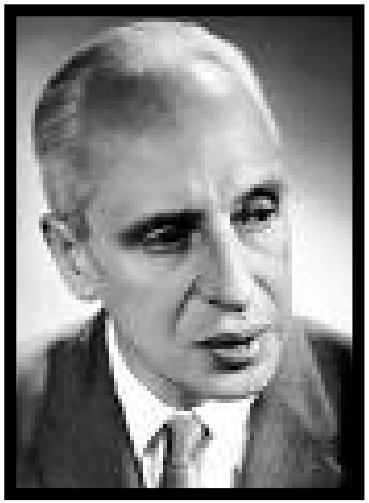
(1930-)

the essence of synthetic organic chemistry and the gateway to myriad compounds of value to medicine, agriculture and electronics

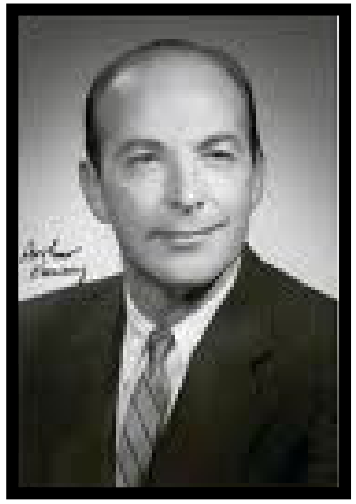


http://nobelprize.org/nobel_prizes/chemistry/laureates/20

Os fármacos e o Nobel !



Severo Ochoa
(1905-1993)



Arthur Kornberg
(1918-2007)

Prêmio Nobel de Fisiologia/Medicina 1959

"for their discovery of the mechanisms in the biological synthesis of RNA and DNA"

ARTHUR KORNBERG

The biologic synthesis of deoxyribonucleic acid

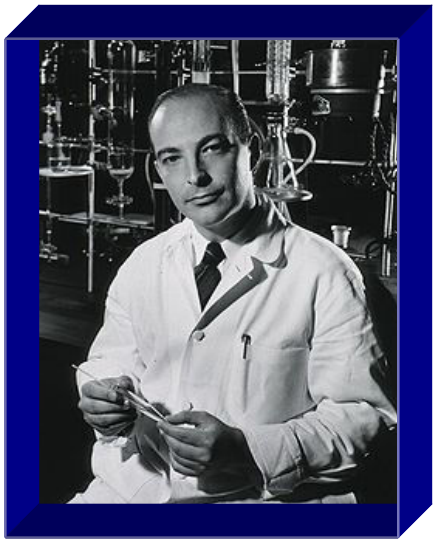
Nobel Lecture, December 11, 1959

A. Kornberg, Science & medicine at the millenium, *Braz J Med Biol Res* **1997**, *30*, 1379

Interdisciplinaridade

EJB5

UFRJ



Arthur Kornberg
1918-2007

Prêmio Nobel, 1959

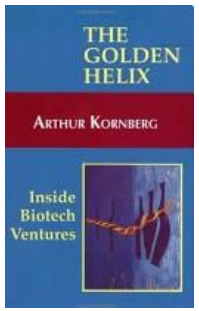
1987

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®

Química Medicinal

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

Slide 20

EJB5

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; 4/3/2010

med Química Farmacêutica Medicinal chem

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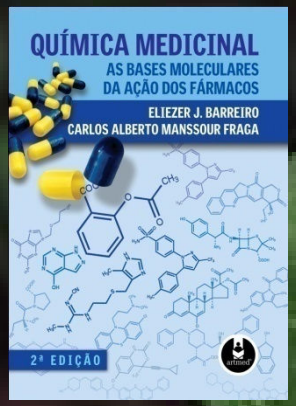
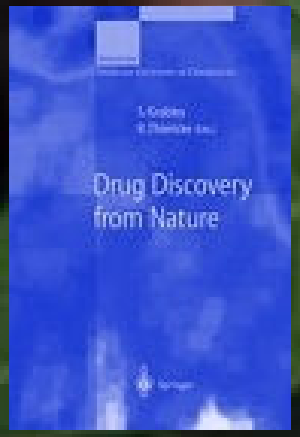
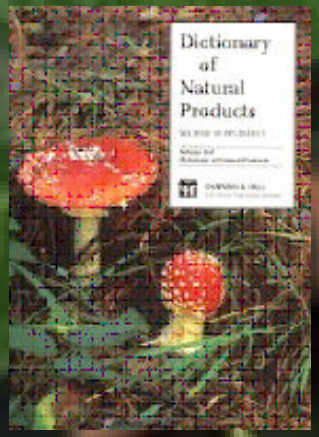
A origem dos fármacos:
O Papel dos Produtos Naturais

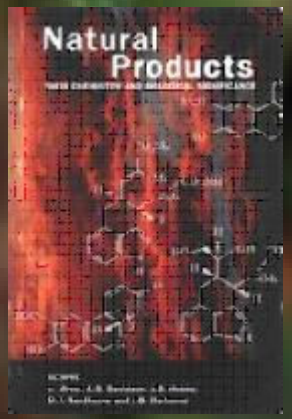


variedade de quimiotipos
terpenos, alcalóides,
esteróides, flavonóides

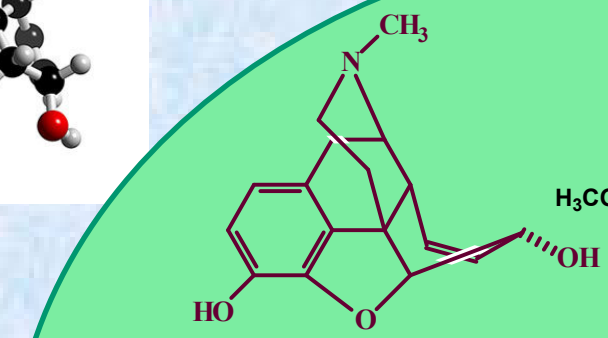




Quimiodiversidade



Quimiodiversidade

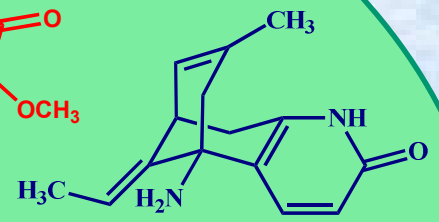


morfina
1806

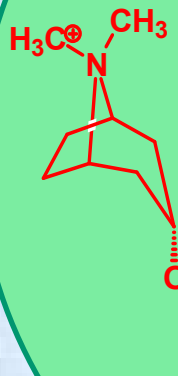
Colcichina

1820

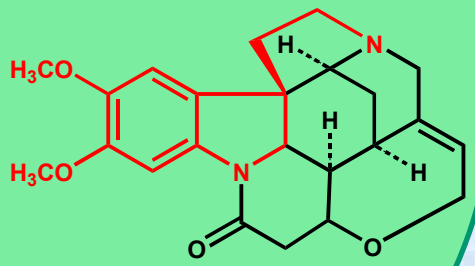
terpenos, alcalóides, esteróides, flavonóides, lignanas, ligninas, iridóides, policetídeos, quinonas, cumarinas



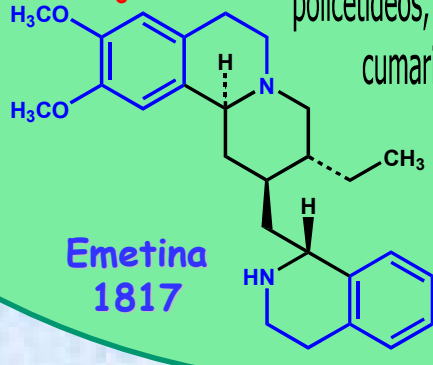
huperzina-A



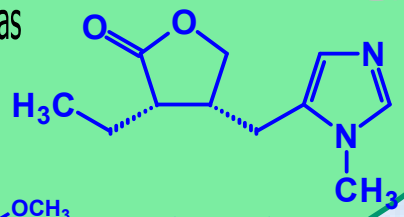
atropina



Estriquinina
1817



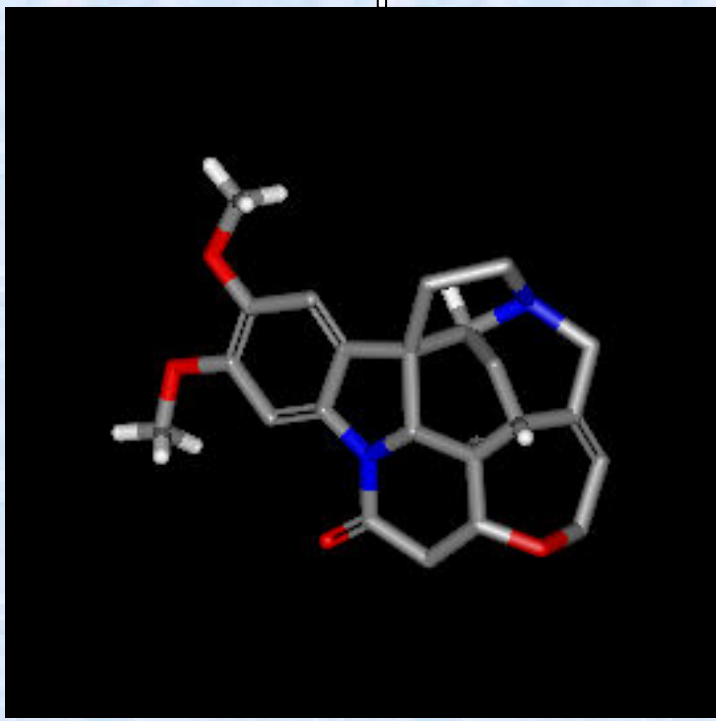
Emetina
1817

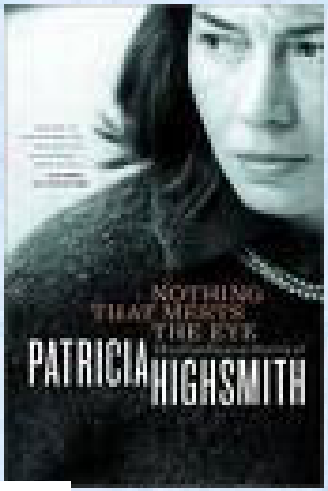


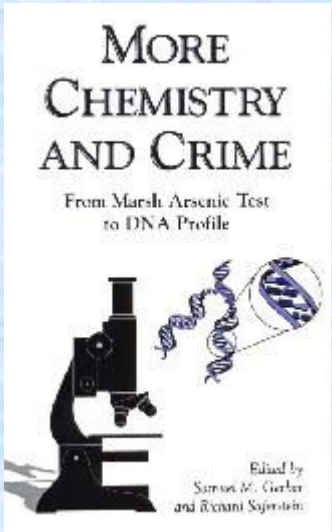
Pilocarpina

Moléculas mortais

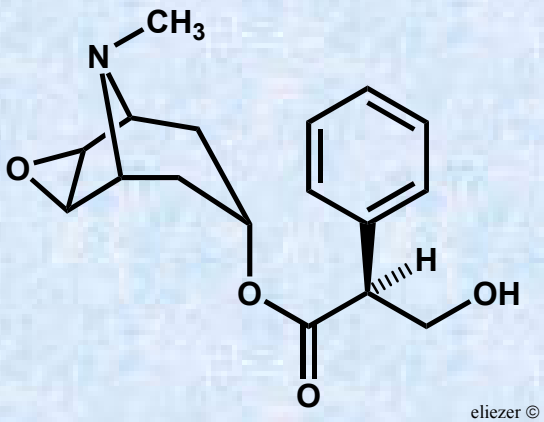
Estriquinina



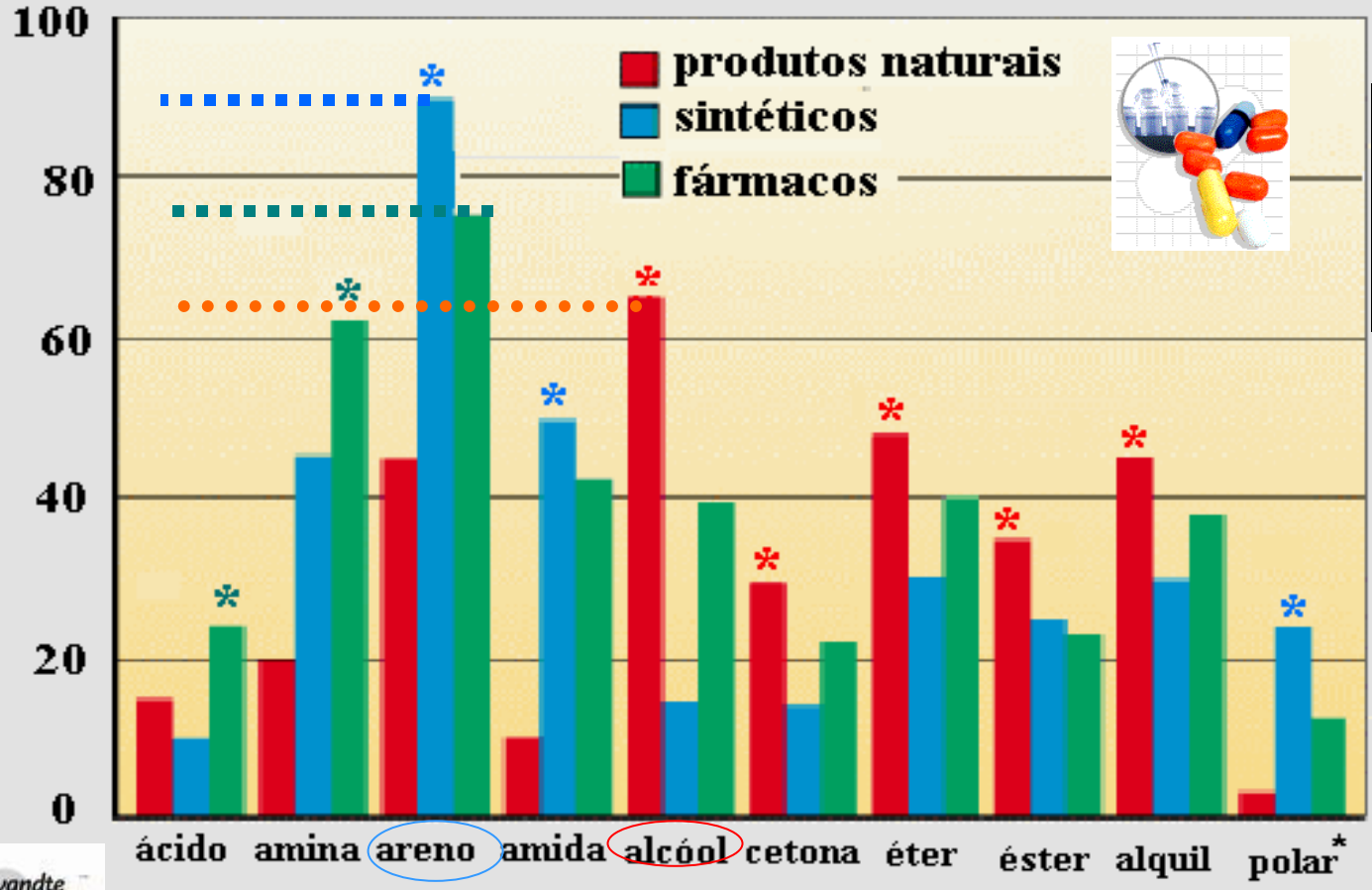


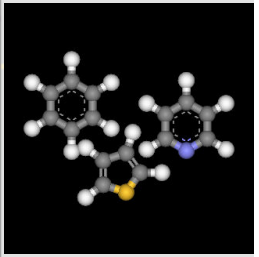


Escopolamina



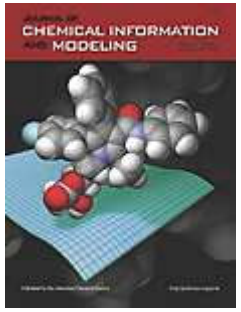
Freqüência dos Grupos Funcionais Clássicos em Diferentes Compostos



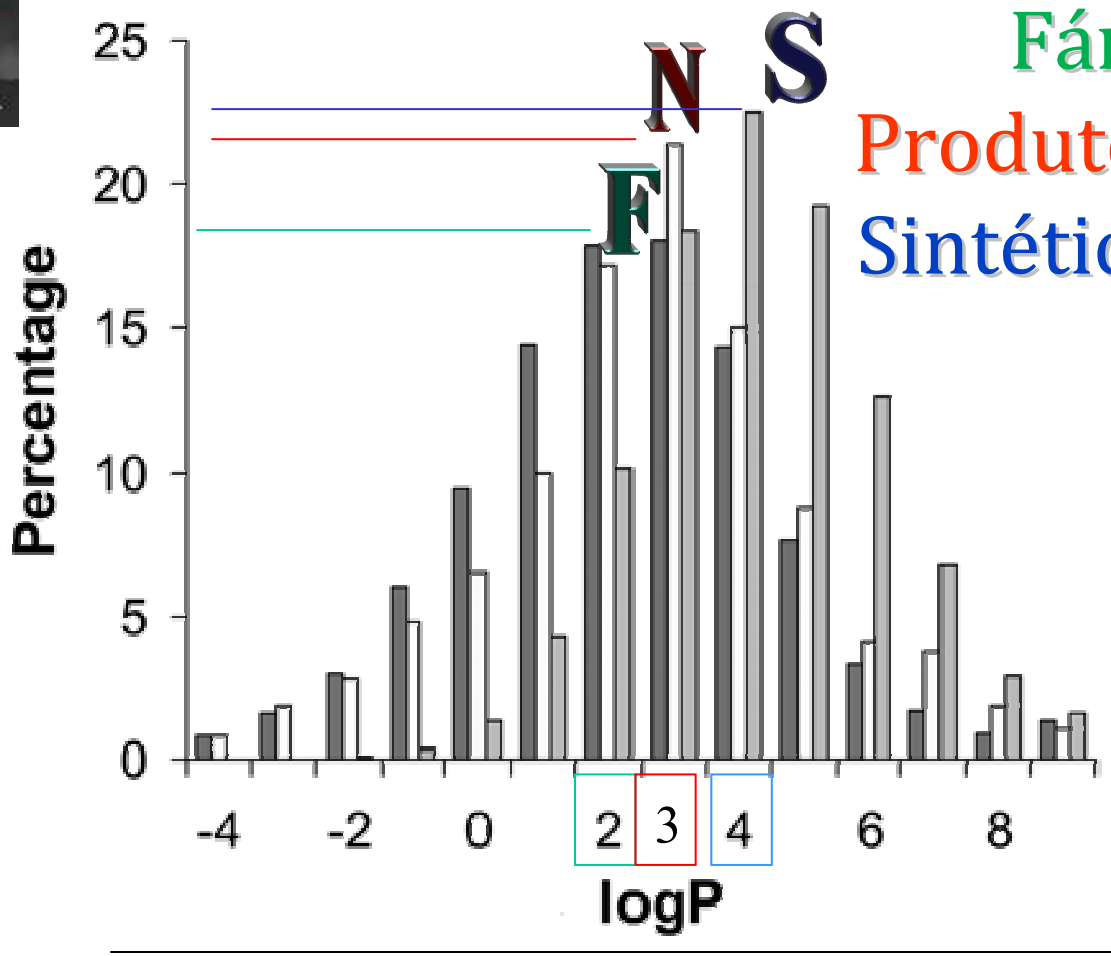


* grupos polares: F, CN, NO_2

Fonte: *Angewandte Chemie*



Propriedades estruturais e a atividade



Fármacos

Produtos Naturais

Sintéticos (comb.)

(M. Feher & JM Schmidt, J. Chem. Inf. Comput. Sci., 43 (1), 218 -227, 2003).

Universidade Federal do Rio de Janeiro

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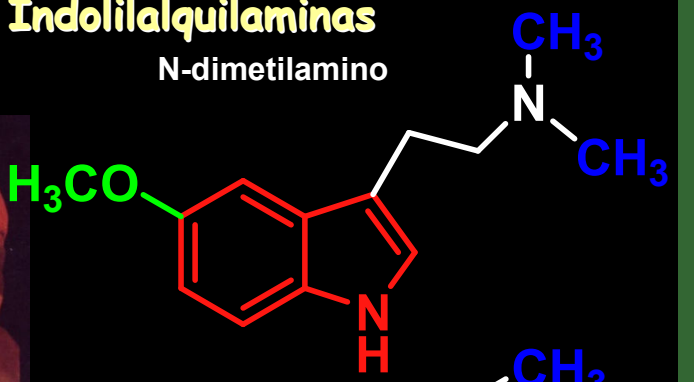
Índios & indóis

Virolas amazônicas

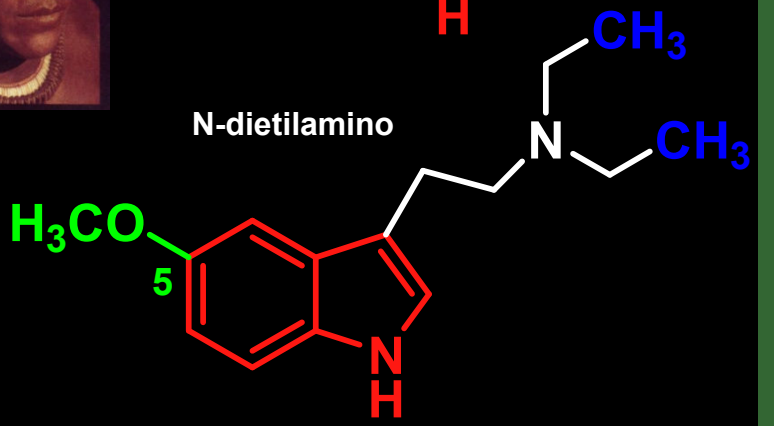
Alcalóides Indólicos

Indolilalquilaminas

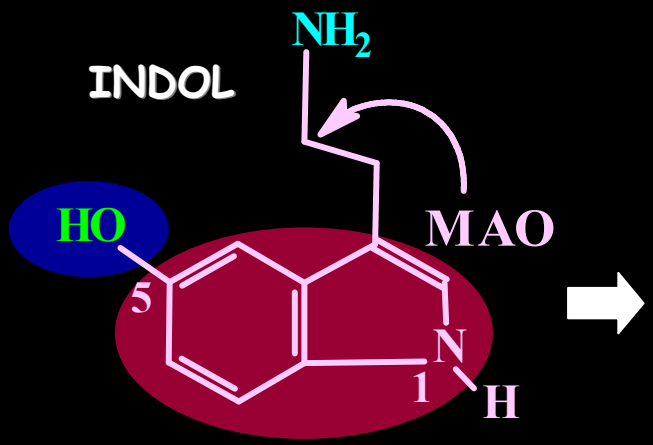
N-dimetilamino



N-dietilamino

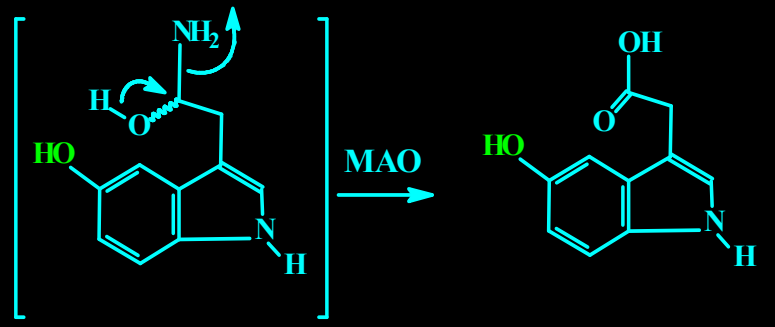


Compostos Alucinogênicos



Serotonina

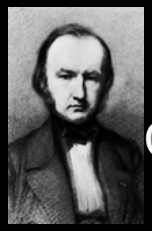
5-hidróxitriptamina



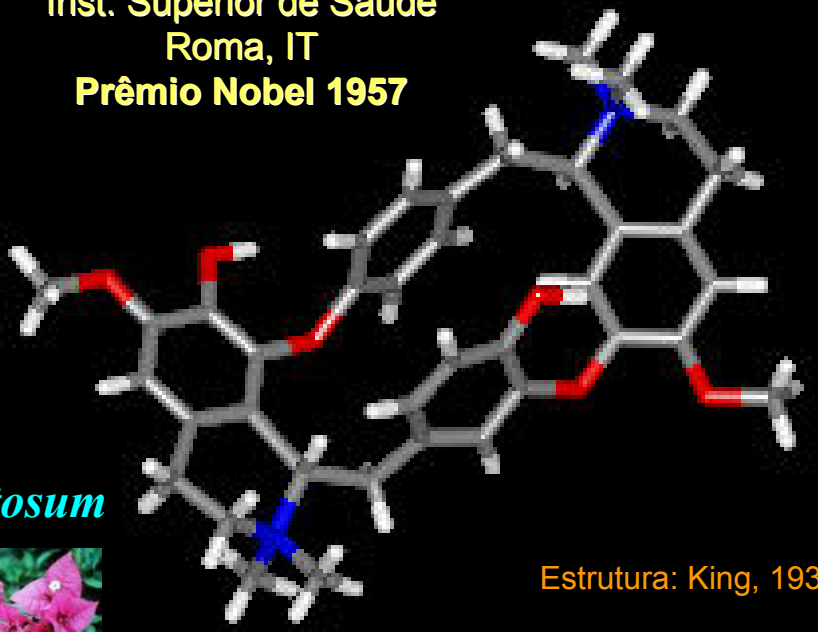
Curare

Fármaco dos Índios

Bloqueadores ganglionares



1947 - Daniel Bovet
Inst. Superior de Saúde
Roma, IT
Prêmio Nobel 1957

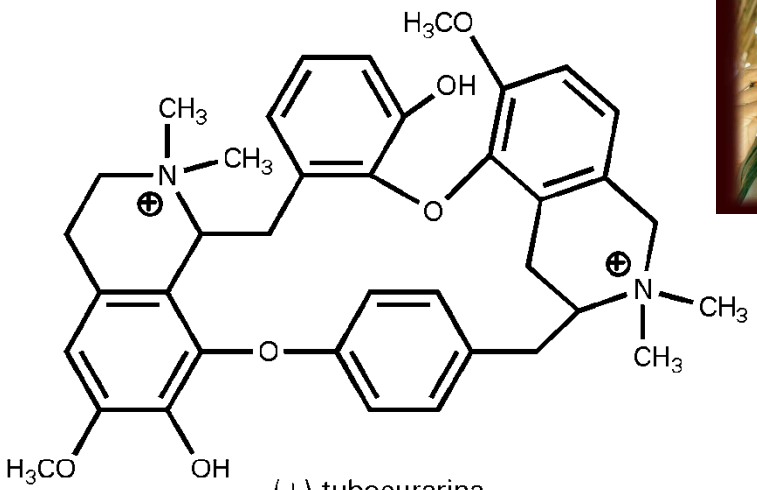


Estrutura: King, 1935

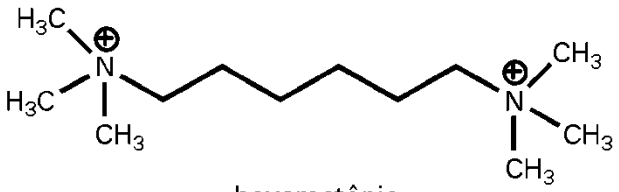
Chondrodendron_tomentosum
Loganiaceae
(urari)

d-tubocurarina

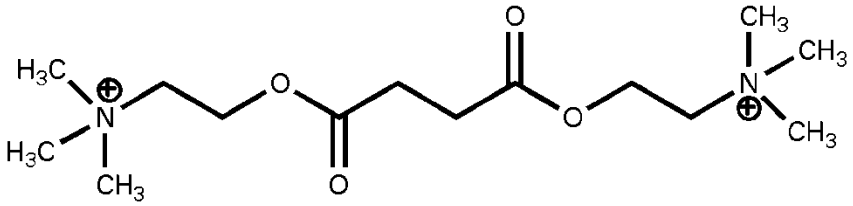
Bloqueadores ganglionares



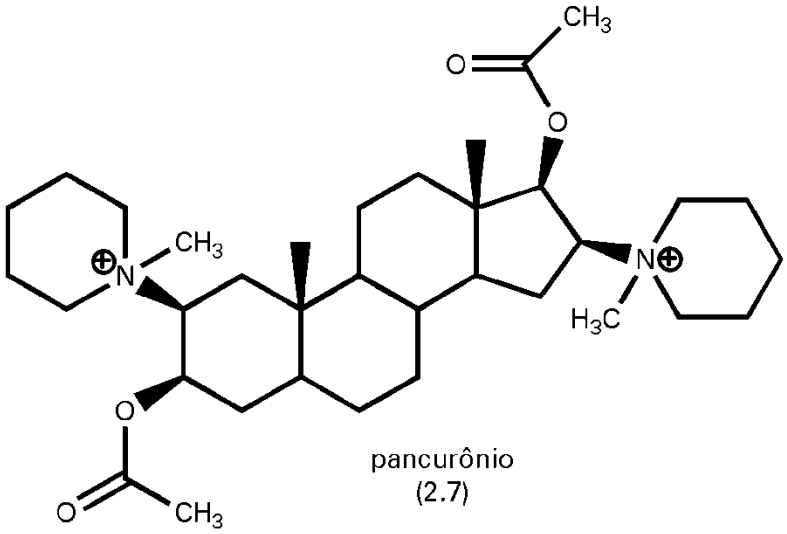
(+)-tubocurarina
(2.4)



hexametônio
(2.5)



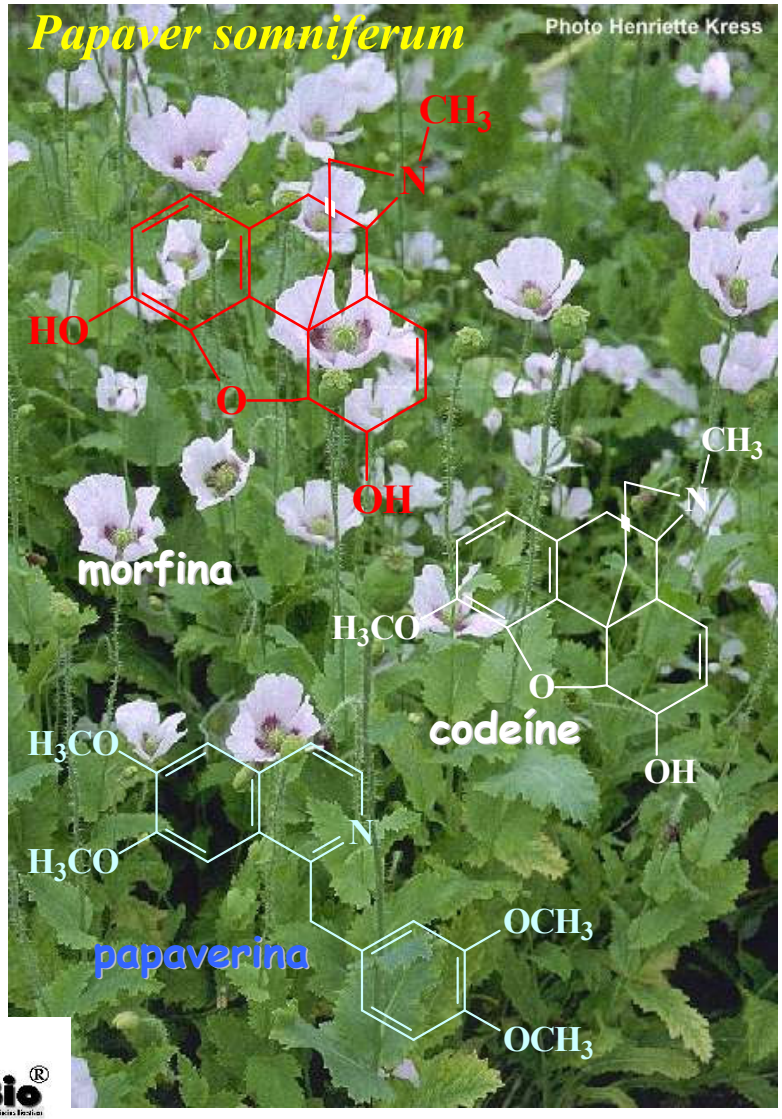
succinilcolina
(2.6)



pancurônio
(2.7)

Produtos Naturais: Morfina

Alcalóides fenantrênicos e benzilisoquinolínicos (papaverina 0,2%)



1493-1541 Marco Polo (Veneza) ⇒ Ópio

1806 ⇒ Friedrich Sertürner isola a morfina ("Morpheus") ⇒ hipno-analgesia

1954 - Beckett & Casey, Un. London

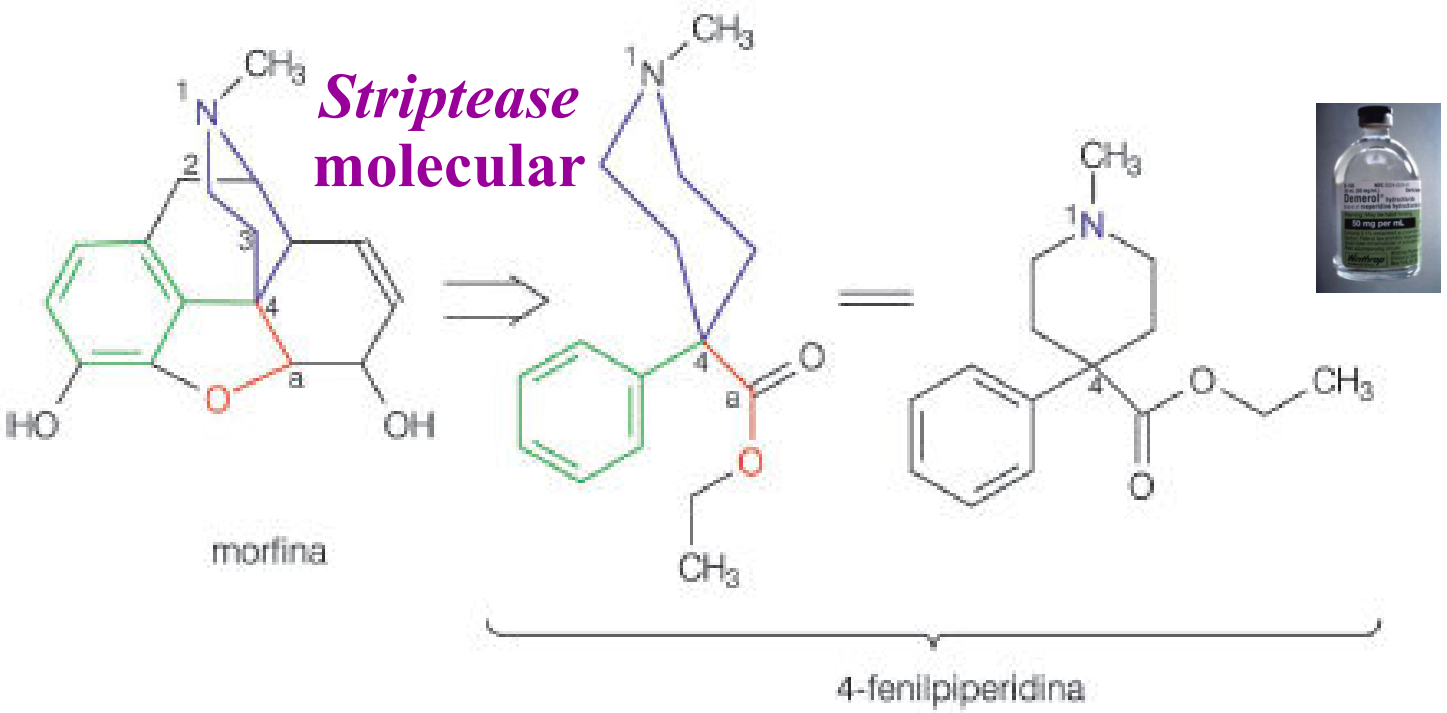
opiate effects were receptor mediated

Sub-tipos de receptores centrais: δ, κ, μ

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

analgesia central; tolerância; dependência química; síndrome de abstinência

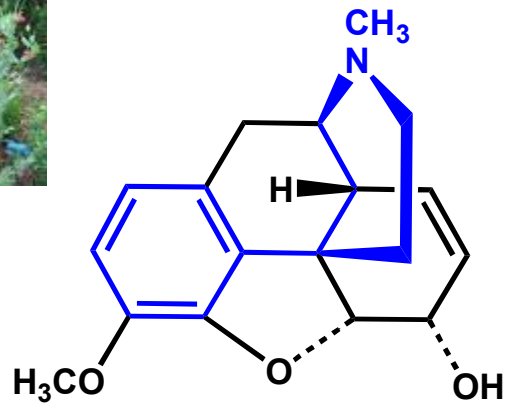
Domesticando produtos naturais

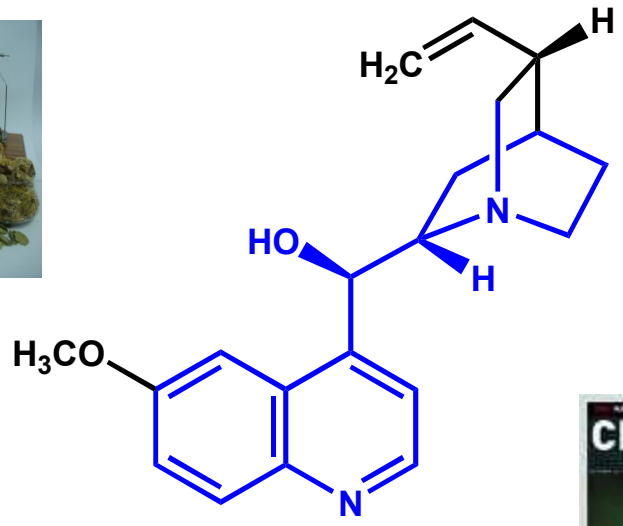


A origem dos analgésicos 4-fenilpiperidínicos a partir da estrutura da morfina: o anel piperidínico, em azul, substituído em C-4 no alcalóide por uma unidade fenila (verde) e um átomo de carbono quaternário oxigenado (a, em vermelho).

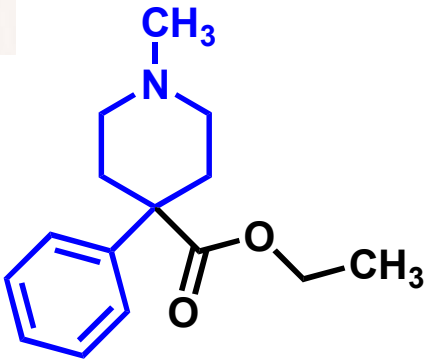
Produto natural como protótipo

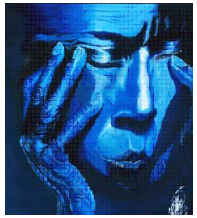
Domesticando produtos naturais

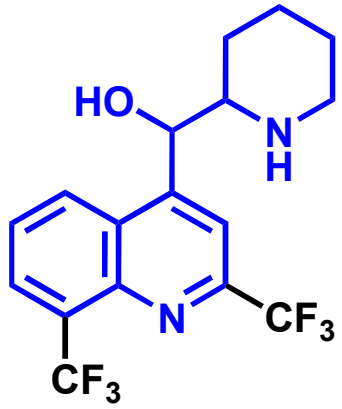




Streptease molecular



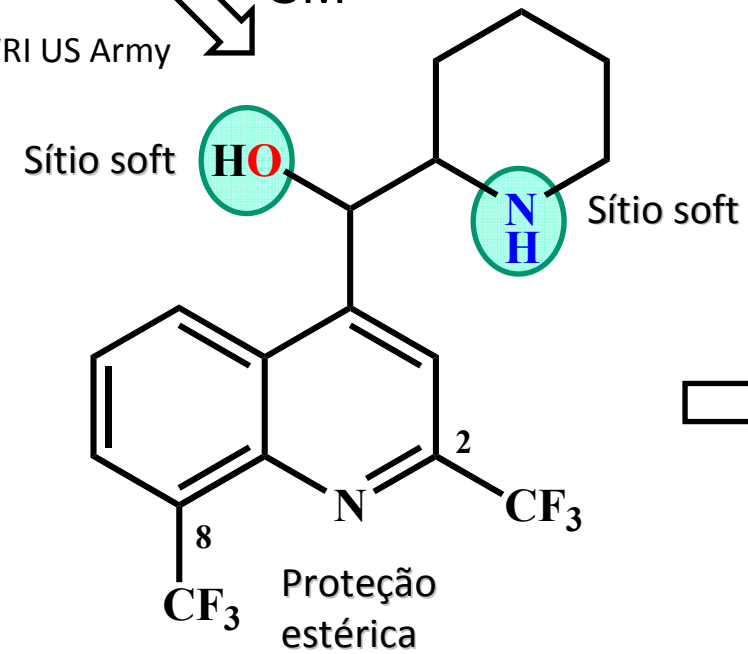


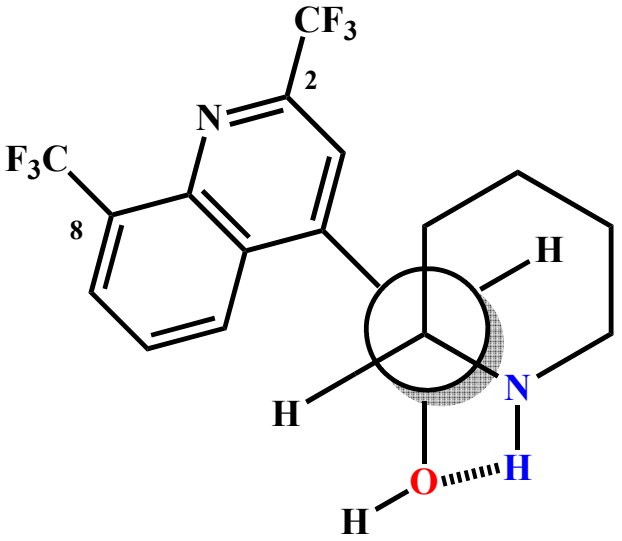


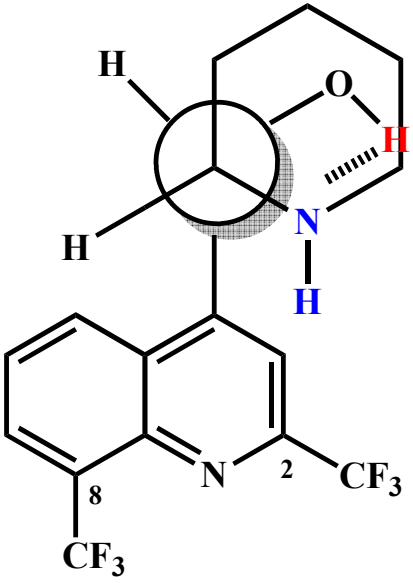
quinina

SM

1970 – WRI US Army





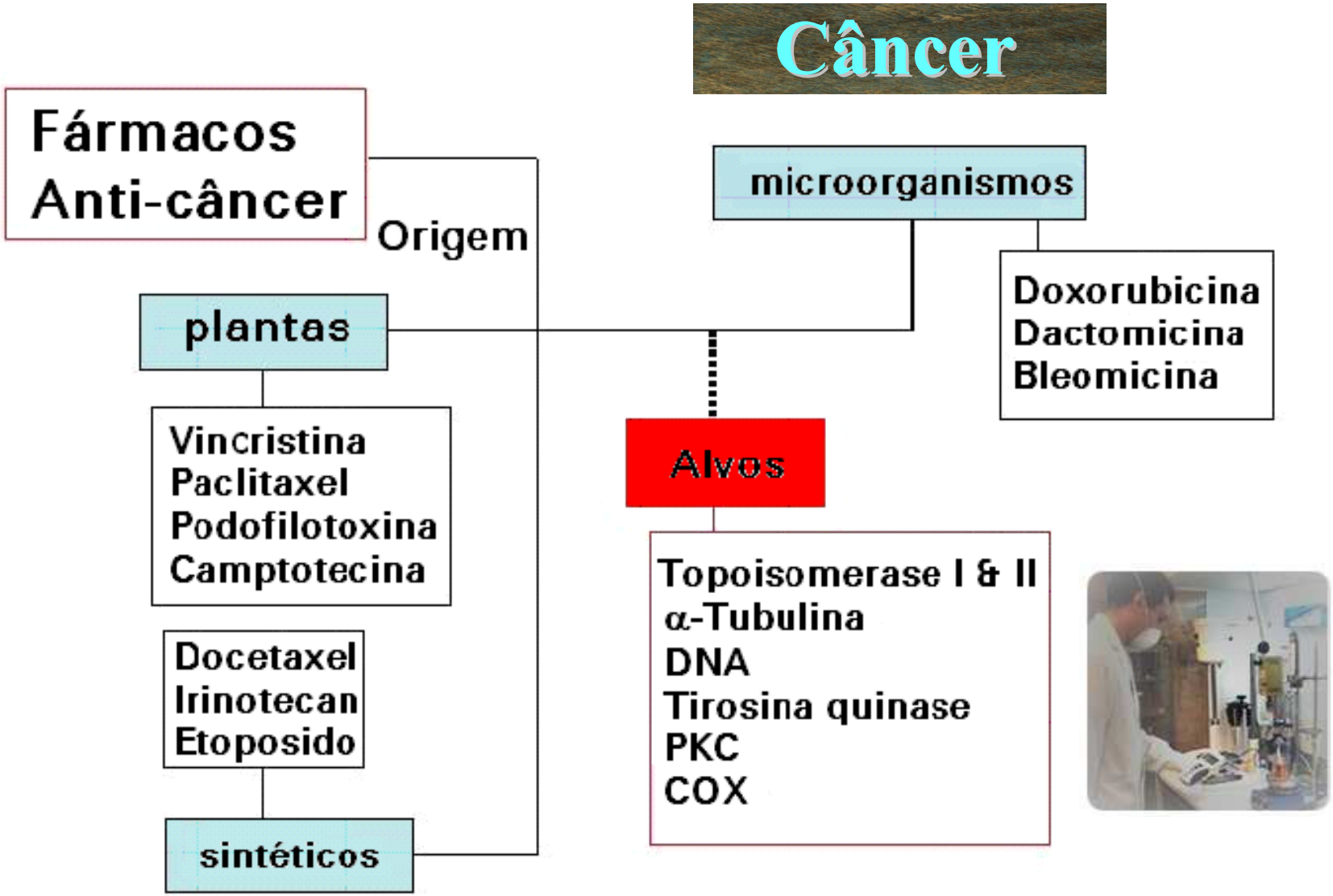


mefloquina

Single dose

Sítio soft = efeito de 1ª passagem

Produtos naturais com propriedades anti-câncer

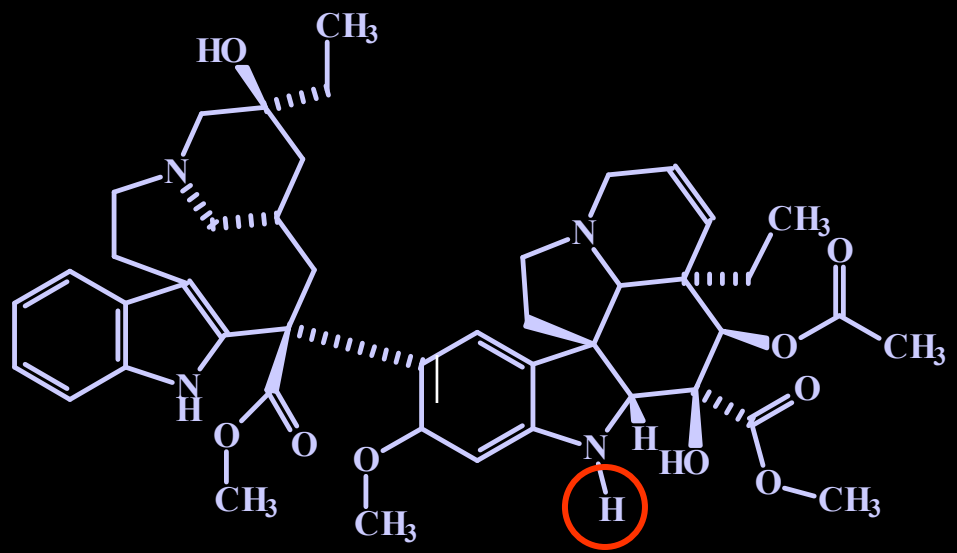


Agentes Anti-câncer de Origem Natural

Câncer

Vinca sp.

Catharanthus roseus



Alcalóides

E. Wenkert, 1955

Inibidor mitótico (metafase)

Alcalóides bis-indólicos

vinc ristina R= H
vim bla stina R= CHO

Câncer

Paclitaxel

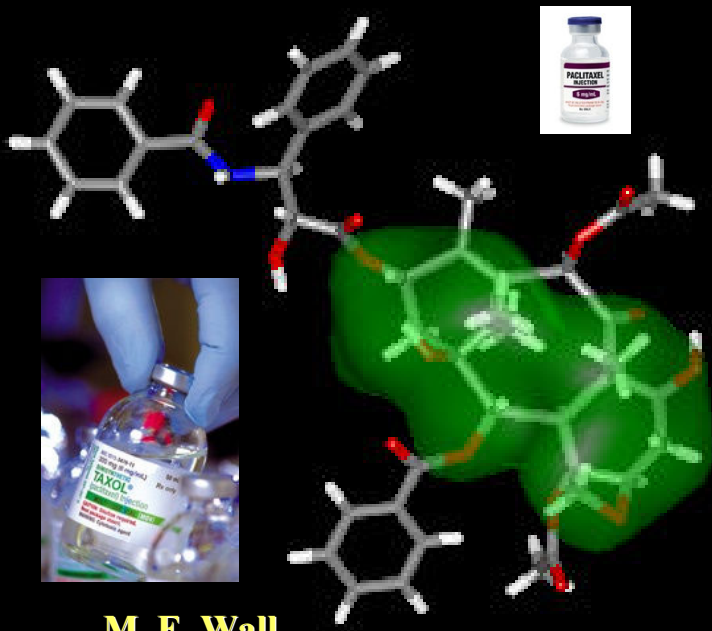
Taxol®

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

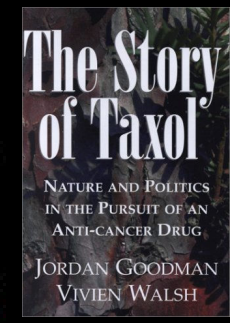
Res. Triangle Park, 1967

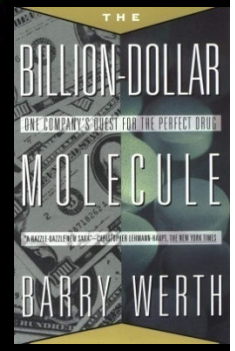
M. E. Wall & M. C. Wani

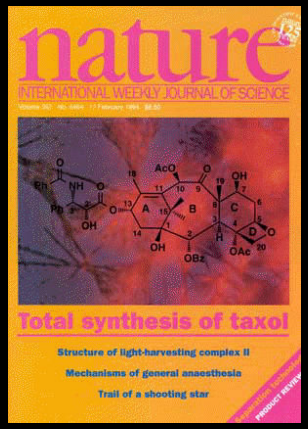
1996 - National Cancer Institute Award of Recognition

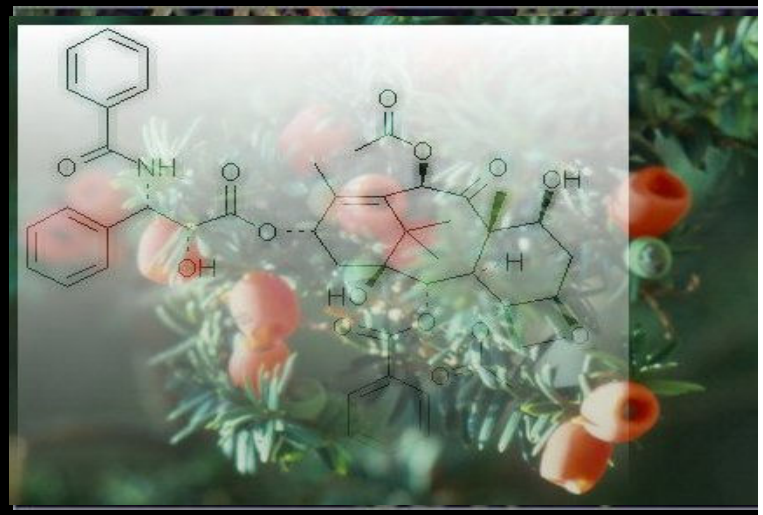


M. E. Wall,,
"Chronicles of Drug Discovery",
D. Lednicer, vol.3, ACS, 1993,
pp. 327-348



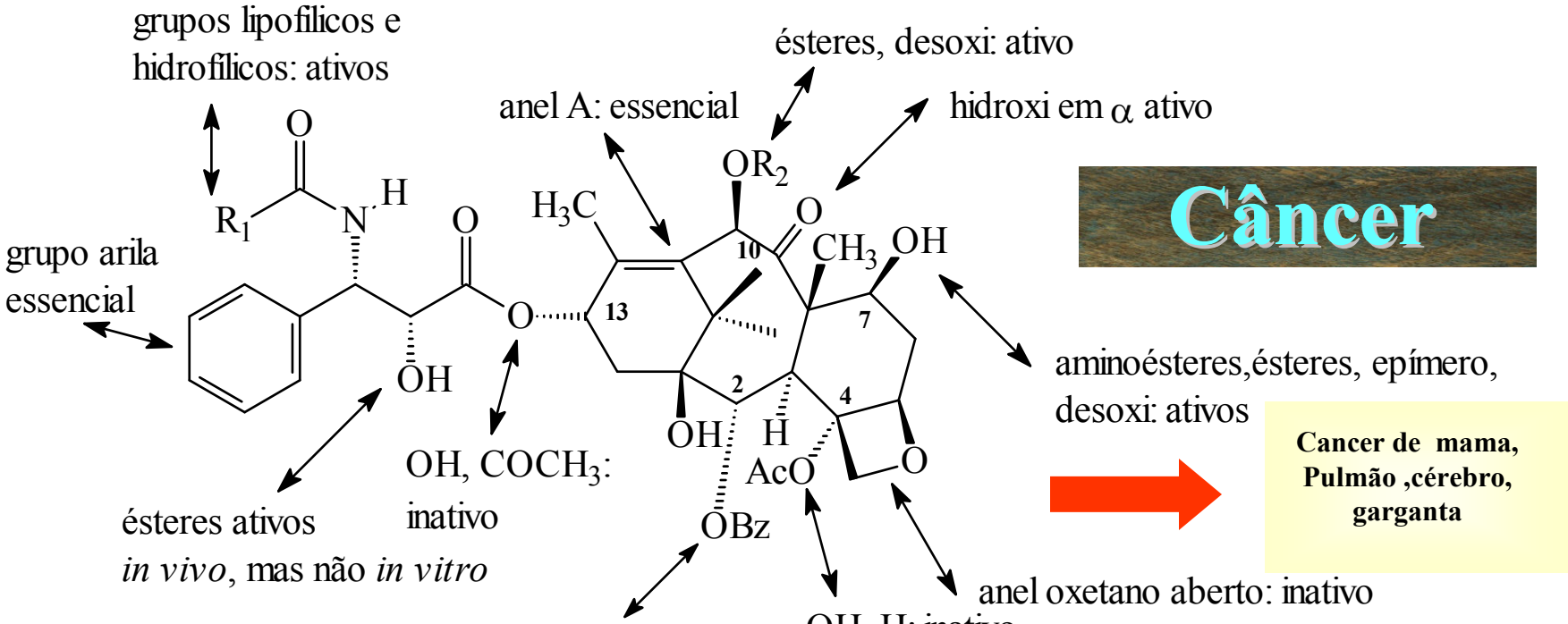






Taxus bacatta

SAR dos taxóides



Câncer

Cancer de mama, Pulmão ,cérebro, garganta

Taxotere (R_2= H, R_1= OBu)
Análogo sintético do taxol
(R_1= Ph, R_2= Ac)

Taxol (*taxus brevifolia*)

(Paclitaxel; Bristol-Myers Squibb, 1992)

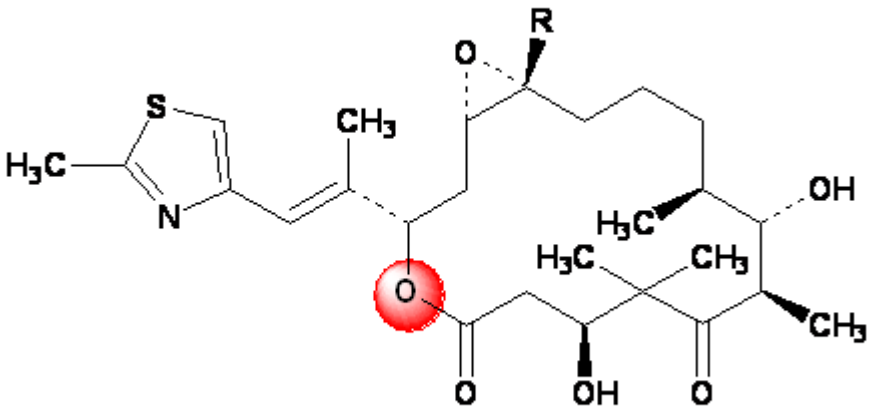
(uso: parenteral)

Toxicidade: Medula óssea
Neutropenia

Baixa biodisponibilidade

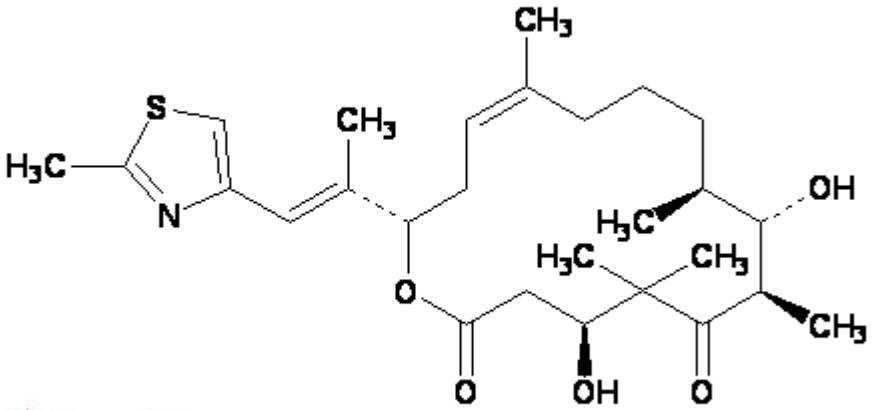
"Natural Compounds in Cancer Therapy: Promising Nontoxic Antitumor Agents from Plants and Other Natural Sources", J. Boik, Medical Press, Princeton, 2001.

Isolada de Sorangium cellulosum em 1993



Epotilona A R = H

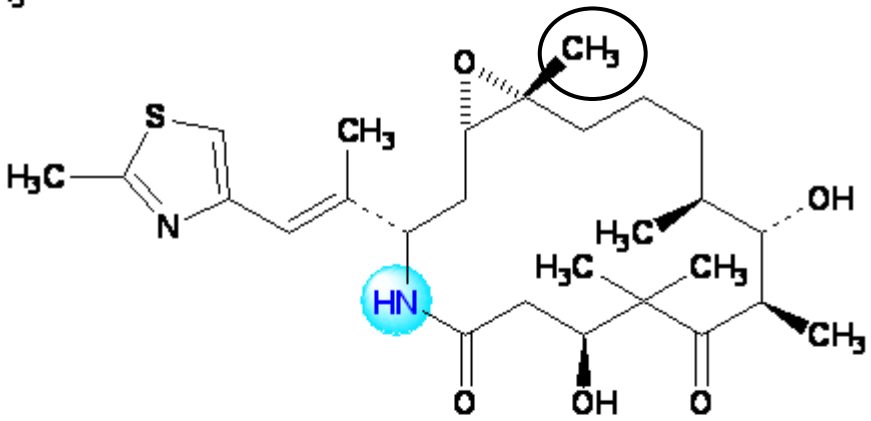
Epotilona B R = CH_3



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, 0ut. 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

Universidade Federal do Rio de Janeiro

Drug development from marine natural products

Tadeusz F. Molinski, Doralyn S. Dalisay*, Sarah L. Lievens*‡ and Jonel P. Saludes*‡*

Abstract | Drug discovery from marine natural products has enjoyed a renaissance in the past few years. Ziconotide (Prialt; Elan Pharmaceuticals), a peptide originally discovered in a tropical cone snail, was the first marine-derived compound to be approved in the United States in December 2004 for the treatment of pain. Then, in October 2007, trabectedin (Yondelis; PharmaMar) became the first marine anticancer drug to be approved in the European Union. Here, we review the history of drug discovery from marine natural products, and by describing selected examples, we examine the factors that contribute to new discoveries and the difficulties associated with translating marine-derived compounds into clinical trials. Providing an outlook into the future, we also examine the advances that may further expand the promise of drugs from the sea.

Nat. Rev. Drug Discov. **2009**, *8*, 69

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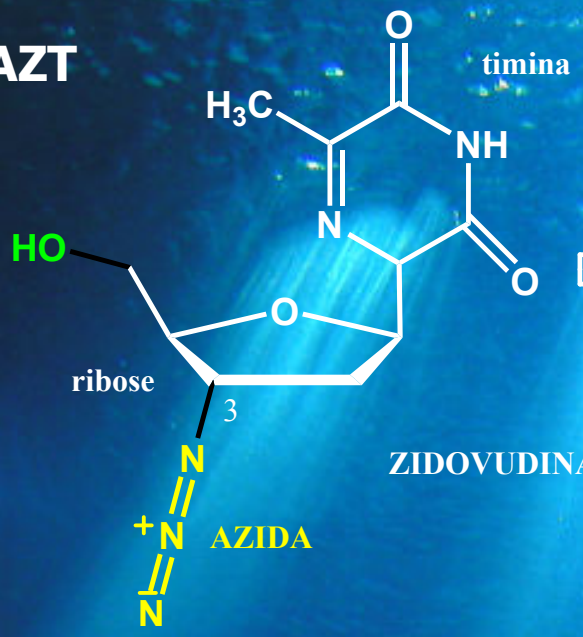
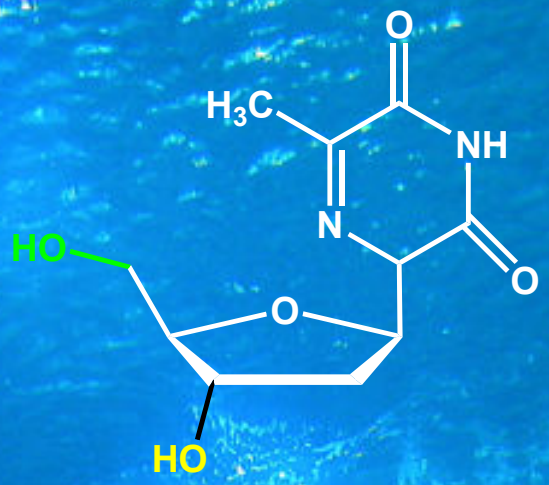
AZT

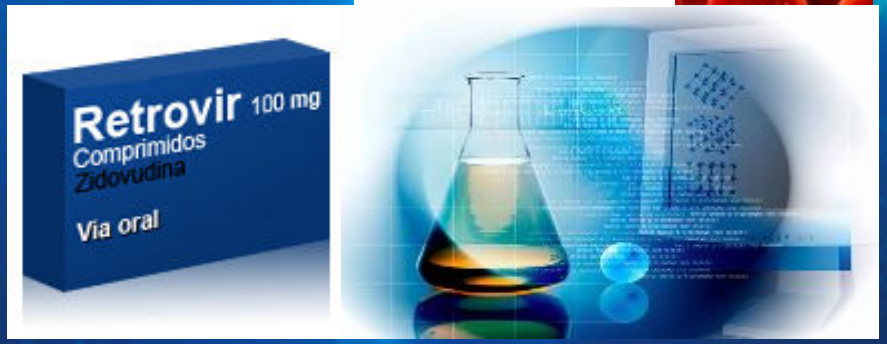


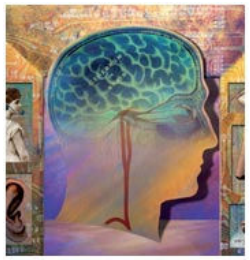
ZIDOVUDINA

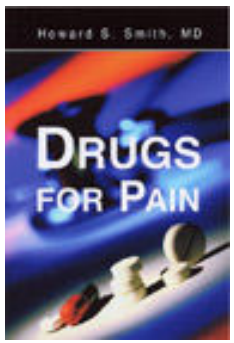


TIMIDINA

Primeiro anti-HIV inibidor da transcriptase-reversa







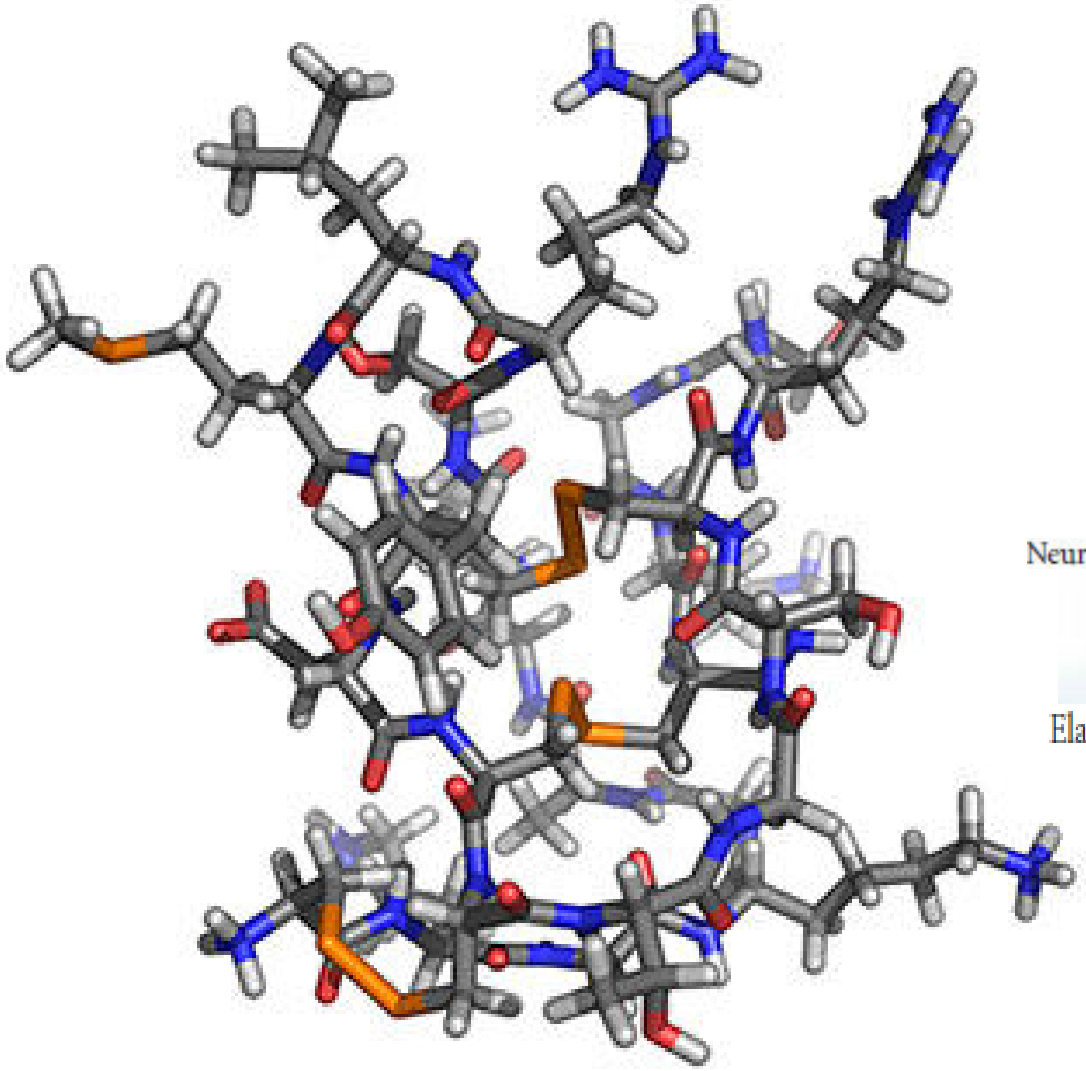
1980 - Michael McIntosh & Baldomero Olivera

Ziconotido

$C_{102}\ H_{172}\ N_{36}\ O_{32}\ S_7$

FDA em 28/12/2004; Eur Comm. em 22/02/2005

Uso intratecal



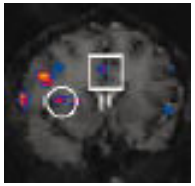
Conus magus

SNX-111

Neurex (Menlo Park, CA)

Elan Pharmaceuticals

(Dublin, Ireland



Antagonista de canais Ca^{++} voltagem dependentes tipo-N

Processo de descoberta de novos hits-naturais

amostra

Bioativa

concentrado

Extrato Bioativo ⋯⋯▶ Fracionamento biomonitorado

composto puro

Bioativo

novo composto

Determinação estrutural

banco de dados espectroscópia

protótipo potencial

Novo protótipo

Potência, seletividade, toxicidade

Bioensaios in vivo

scale-up da purificação

Técnicas de Química Medicinal

extração, concentração, fracionamento, purificação

identificação das substâncias

compostos conhecidos

amostra pura

HPLC
HPLC-MS
(LC-MS)

Quantidade de substância requerida

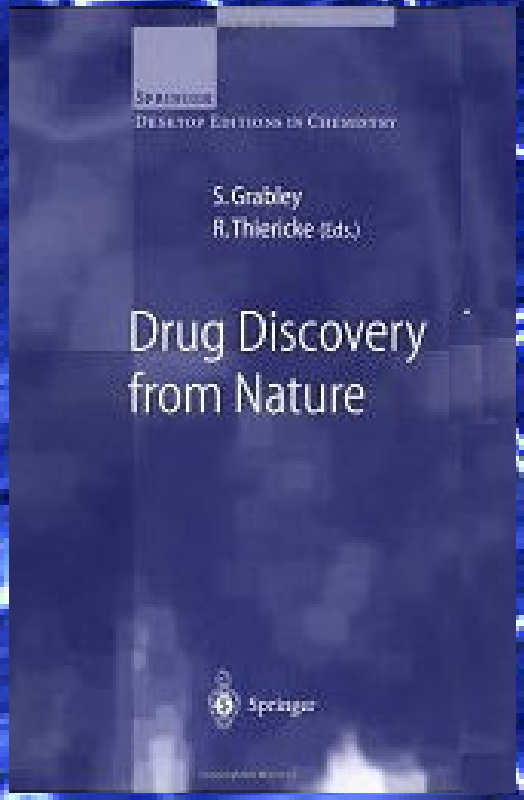
1-10 µg | 1-10 mg | 1-10 g | 100 g

modificações estruturais
preliminar "sar"
modulação das propriedades biológicas
otimização do perfil PK

Adaptado de

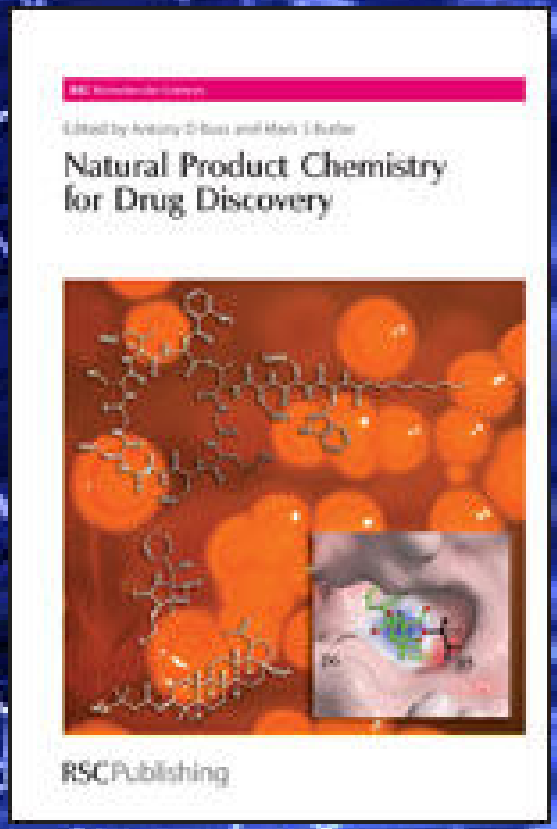
F. E. Koehn & G. T. Carter, The evolving role of natural products in drug discovery, Nature Review Drug Discovery, 2005, 4, 206-220

A corrida por novas moléculas...



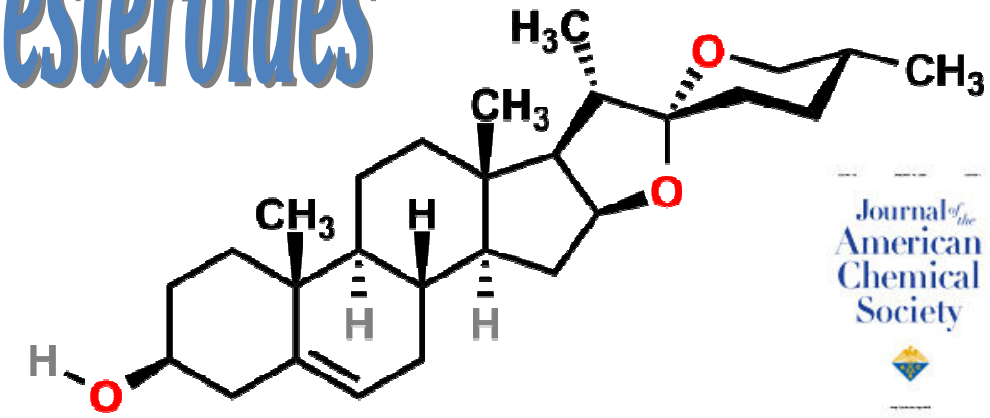
Ewan J T Chrystal (Editor),
Stephen K Wrigley (Editor),
Robert Thomas (Editor),
Neville Nicholson (Editor),
Martin Hayes (Editor)

RSC



Antony D Buss (Editor)

esteróides

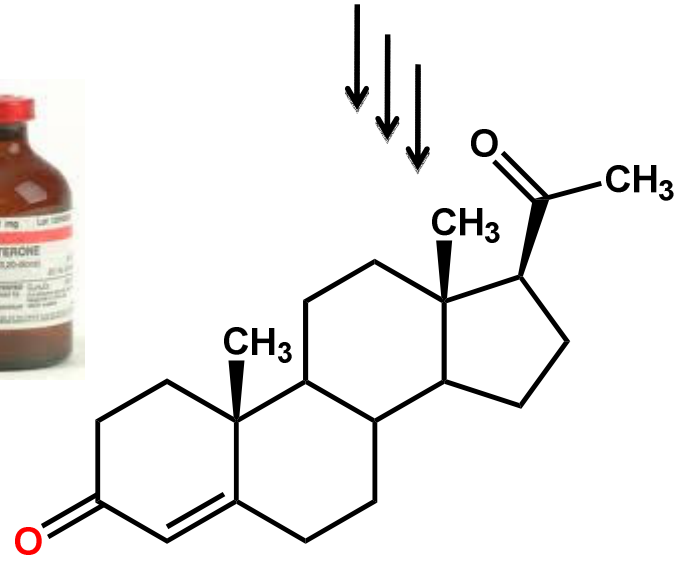


diosgenina

Laboratorios Syntex SA

Dioscorea mexicana Scheidw

RE Marker, Sterols. CXIII. Sapogenins. XLII. The conversion of the sapogenins to pregnenolones". *J. Am. Chem. Soc.*, **62** 3350–3352 (1940); P Lehmann, A Bolivar, R Quintero, Russell E. Marker - Pioneer of the Mexican steroid industry, *J. Chem. Ed.*, **50**, 195–9 (1973).

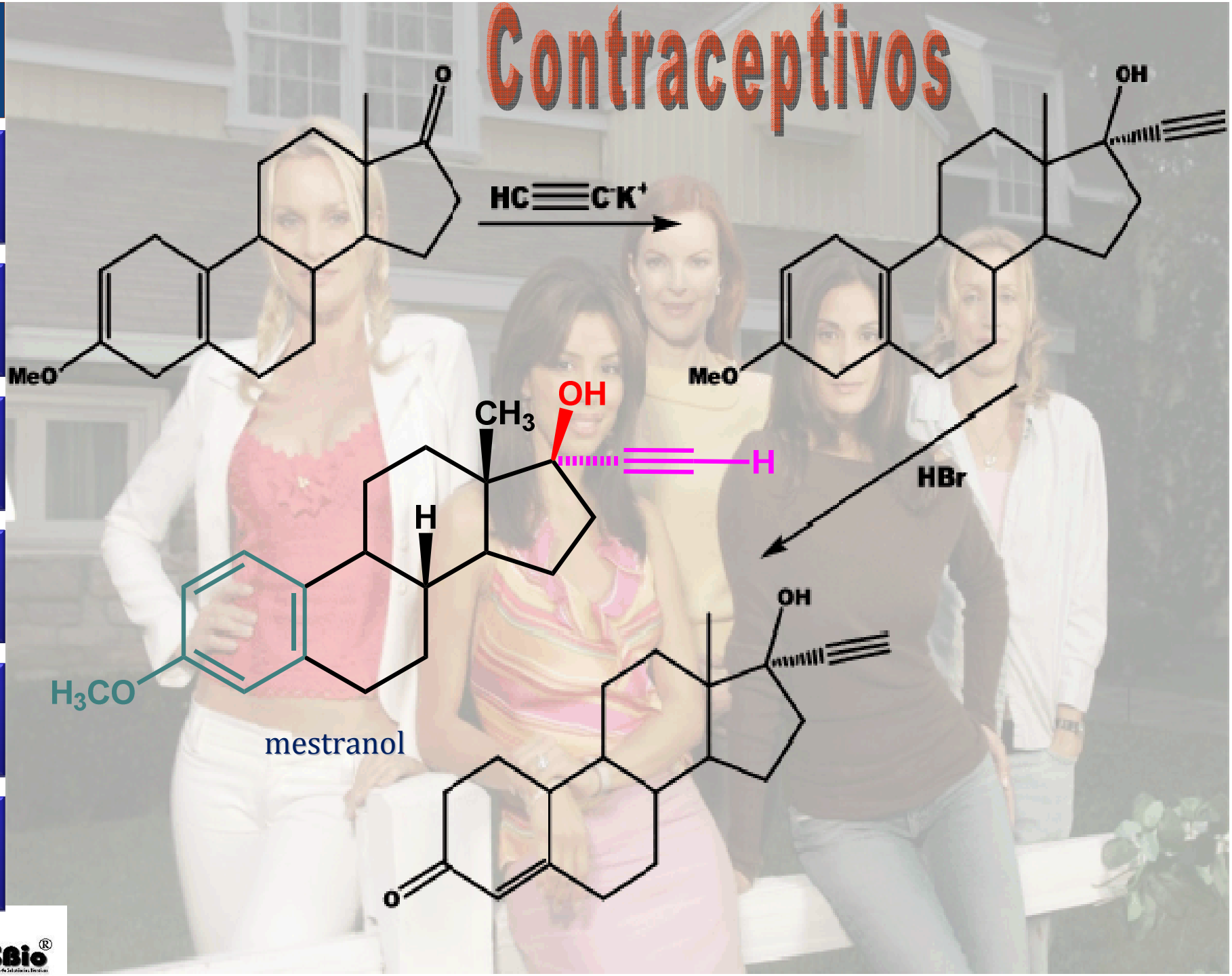


progesterona

A Pílula Contraceptiva

Carl Djerassi

Contraceptivos

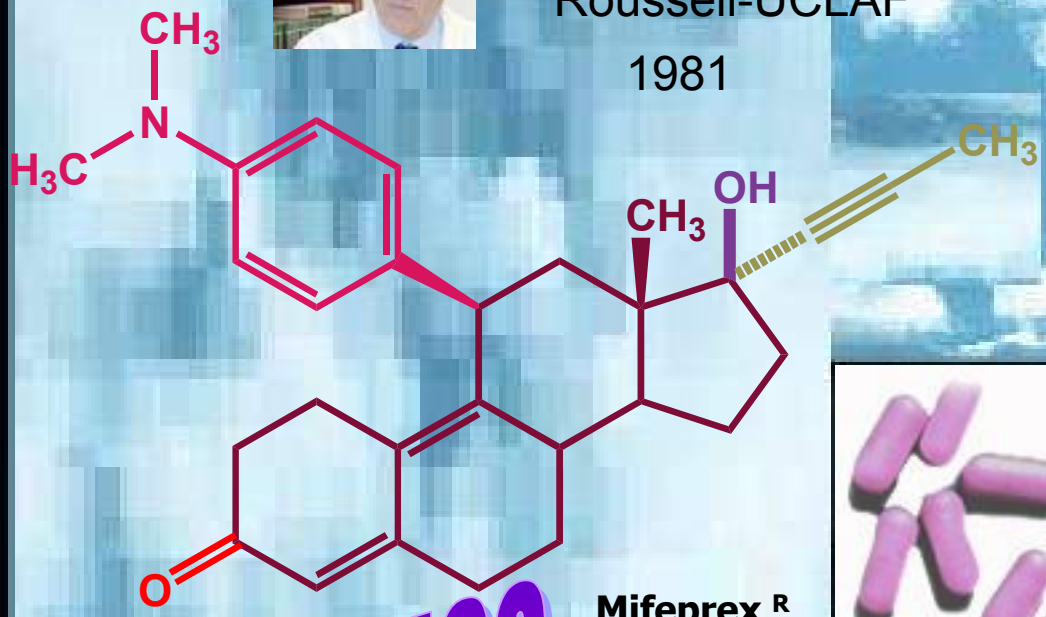


mestranol

mifepristona

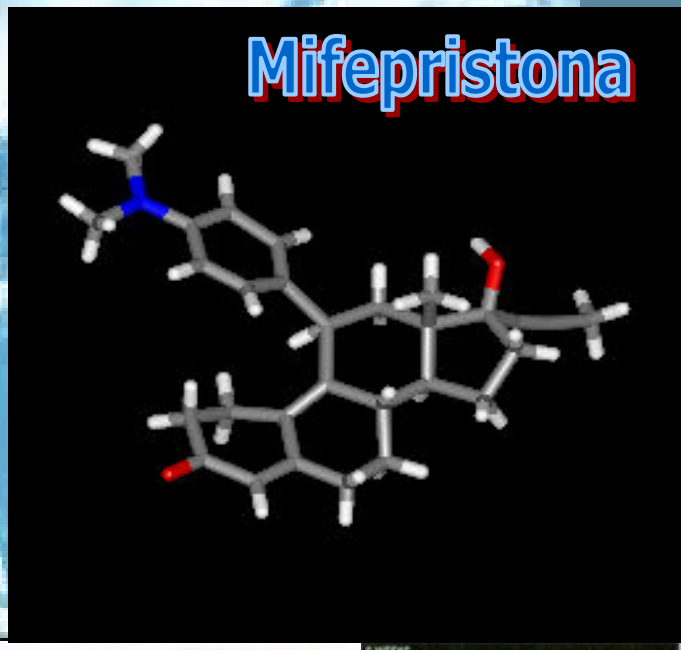
Etienne-Emile Beaulieu
Roussell-UCLAF

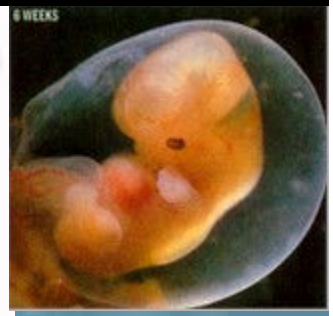
1981

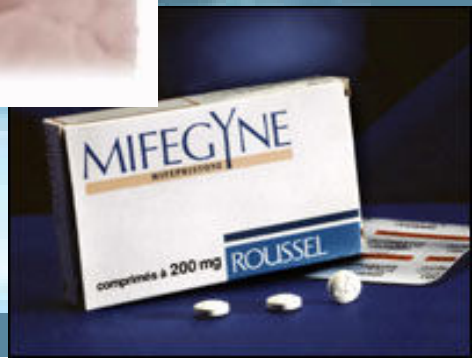


RU 486

Mifeprex R







Pílula do dia seguinte

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.

1. **Histórico do planejamento racional de fármacos: a Química Medicinal e a Química Farmacêutica**
2. **A cronologia da descoberta de fármacos e o prêmio Nobel**
3. **A contribuição dos produtos naturais para a descoberta de fármacos**
4. **Noções das interações fármaco-biorreceptores e o paradigma de Ehrlich-Fischer**
5. **Abordagem fisiológica no planejamento racional**
6. **Estratégias de desenho molecular de análogos-ativos:**
   - 6.1. Aplicação do bioisosterismo;
   - 6.2. Aplicação da simplificação molecular;
   - 6.3. Aplicação da anelação molecular
   - 6.4. Aplicação da hibridação molecular
   - 6.5. Aplicação de técnicas conjugadas
7. **Estudo de casos**

Bibliografia: *Química Medicinal: As razões moleculares da ação dos fármacos*, E. J. Barreiro & C. A. M. Fraga, Artmed, Porto Alegre, RS, 2008.

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.

LASSBio®

A maioria dos biorreceptores dos fármacos contemporâneos são enzimas …

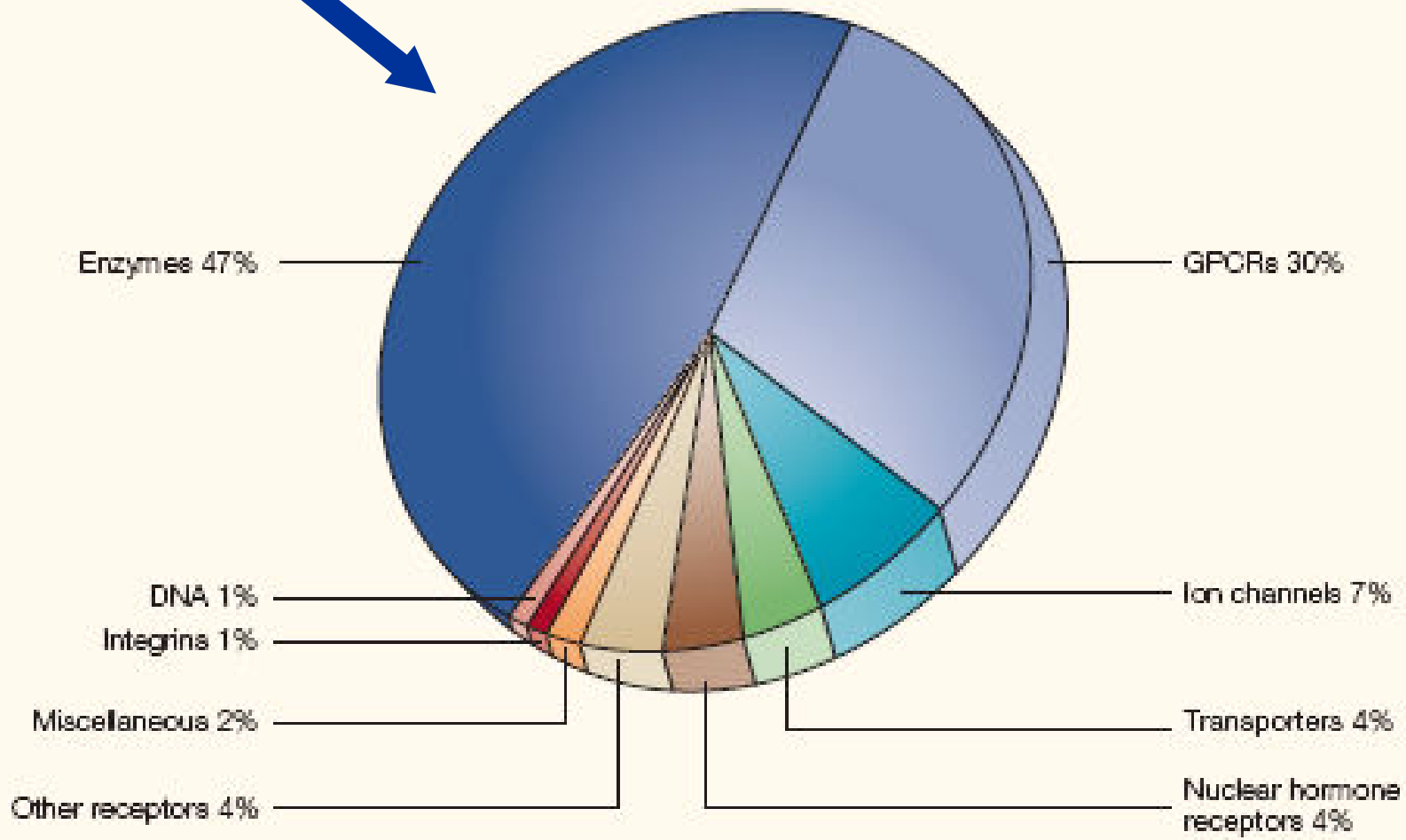
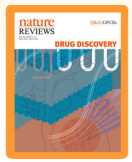
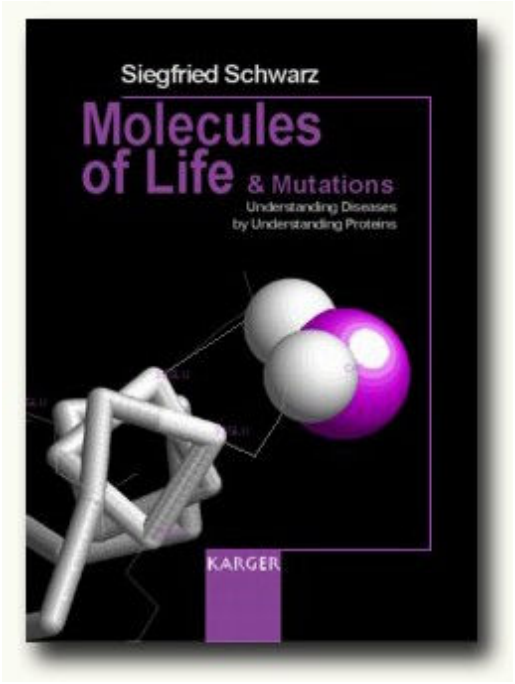


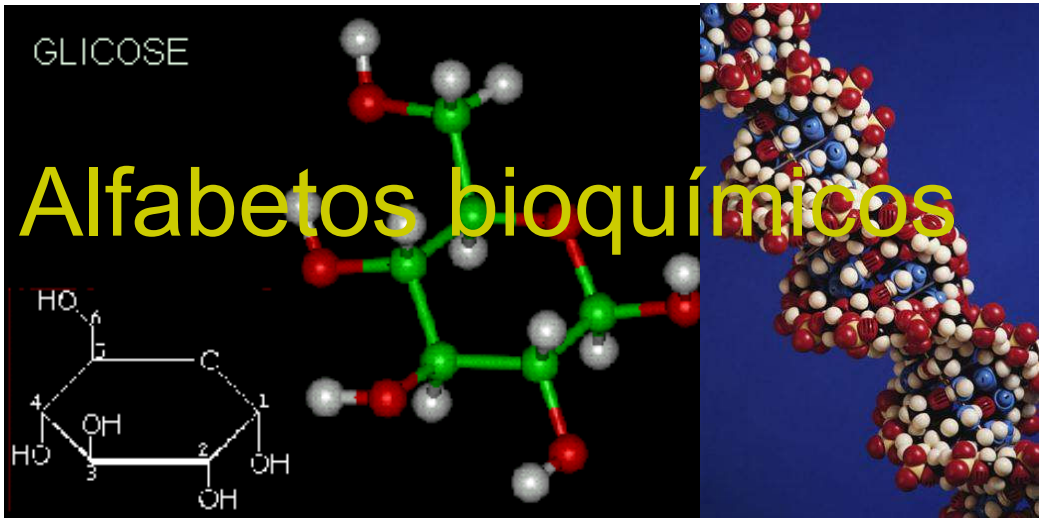
Figure 4 | **Marketed small-molecule drug targets by biochemical class.** GPCR, G-protein-coupled receptor.



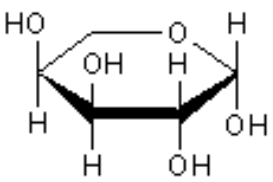
www.nature.com/reviews/drugdisc

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

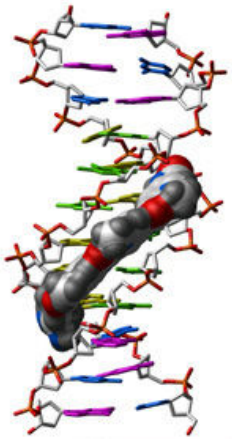




Alfabetos bioquímicos



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**)

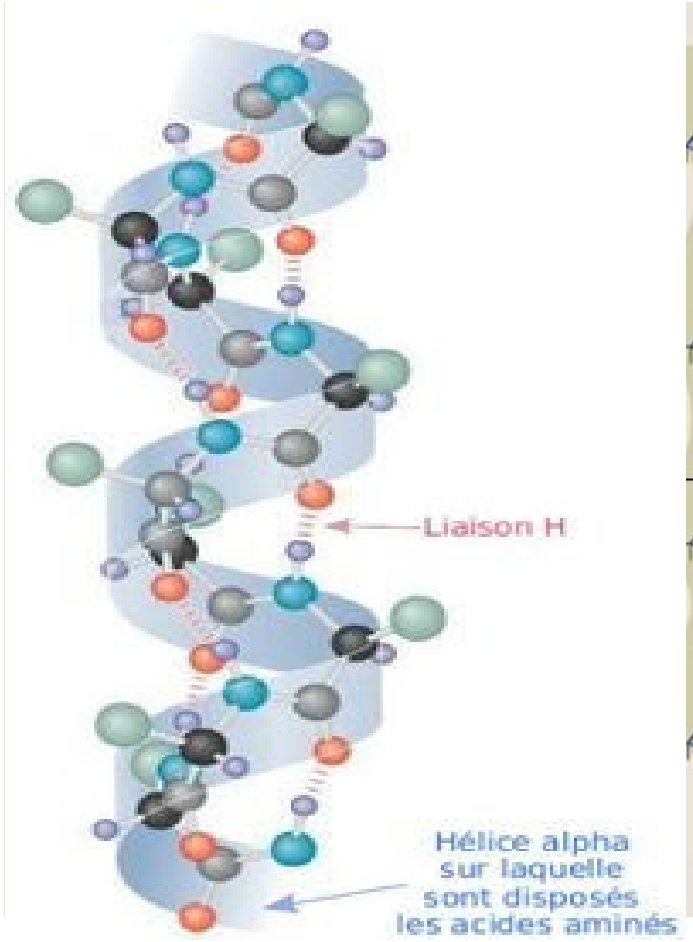
triptofano (**Trp**)

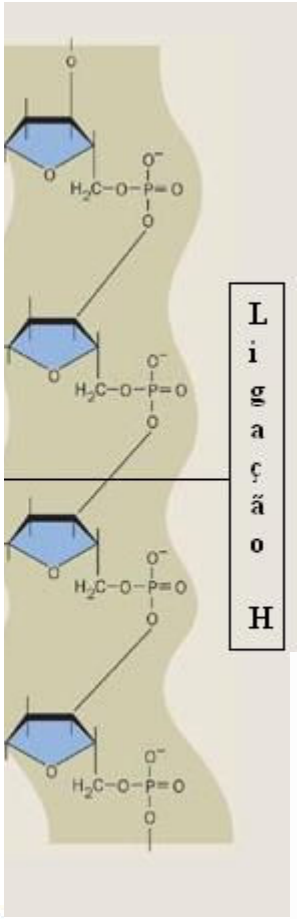
fenilalanina (**Phe**)

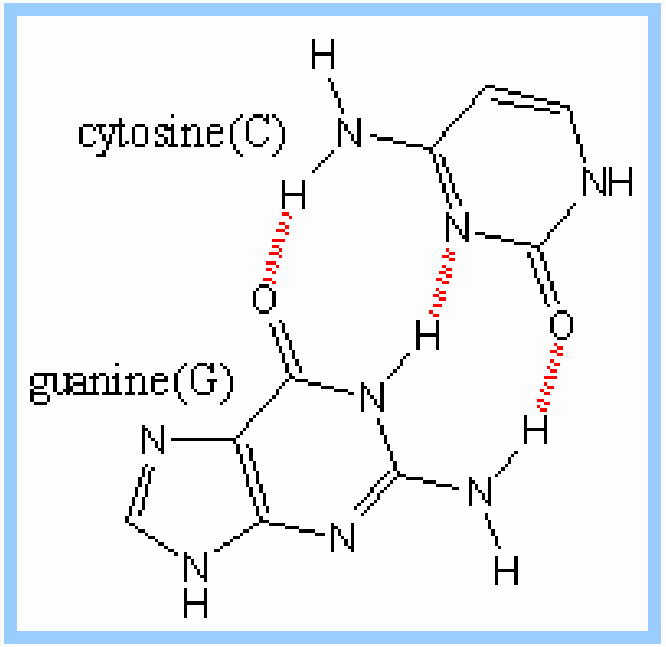
tirosina (**Tyr**)

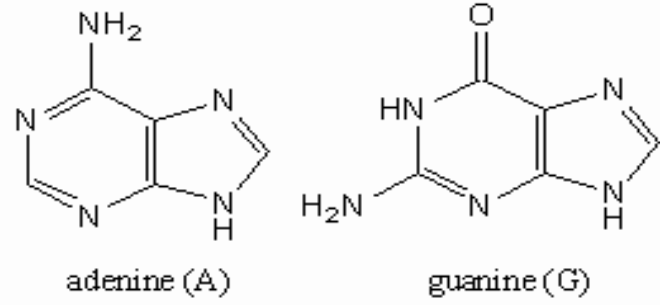
histidina

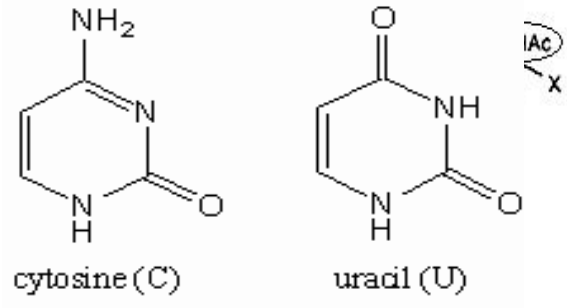
Proteínas, carboidratos, DNA, lipídeos, canais iônicos





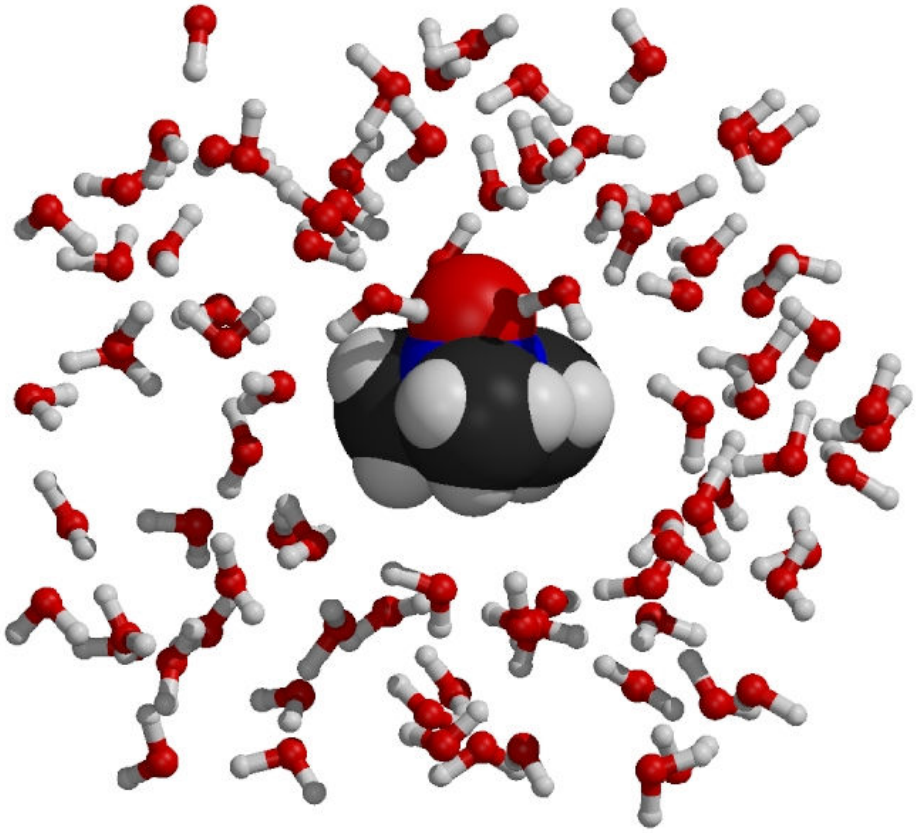


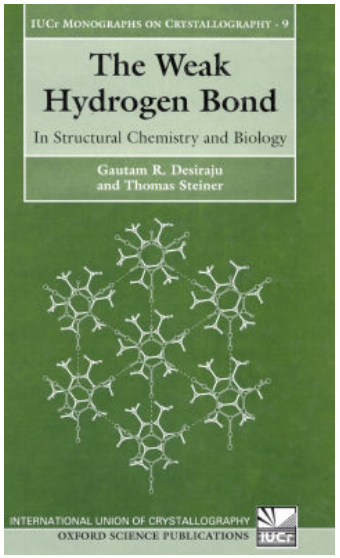




Ligação de hidrogênio = H_2O

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





"*ligações*" de hidrogênio ...

D—H.....A

Linus Pauling, 1939

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

↓

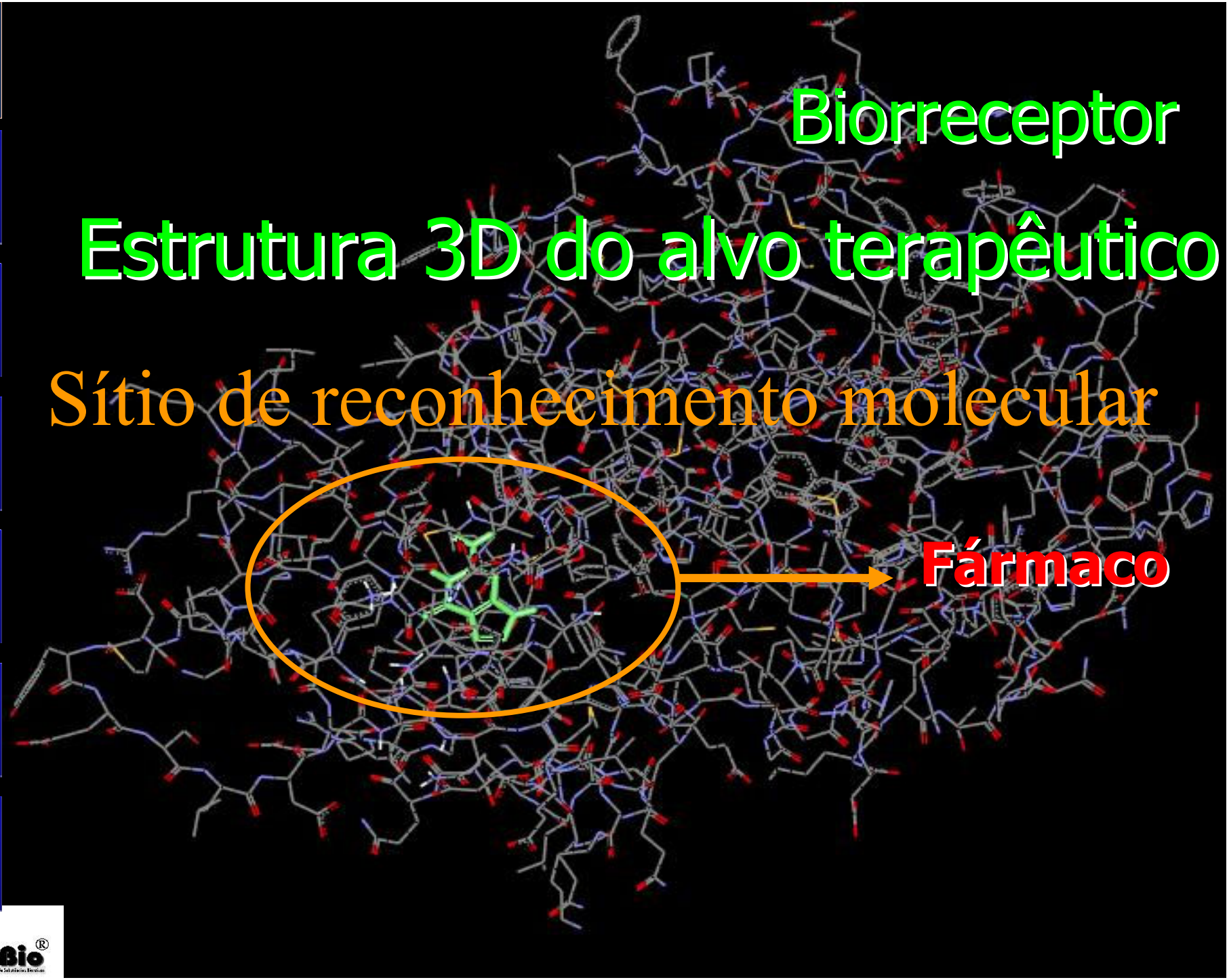
São conhecidos *ca.* 19 milhões de compostos orgânicos (300-500 Da)

100 amino-ácidos modificados

↓

ca. 1.000.000.000.000 hexapeptídeos...

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


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

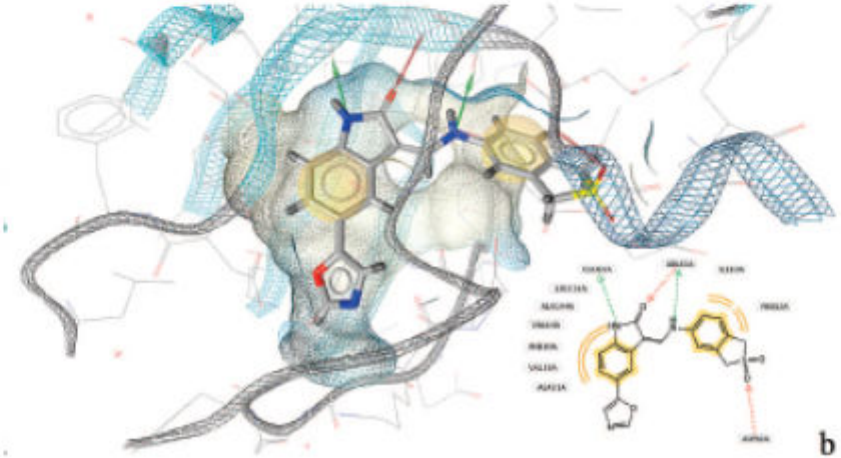
Journal of
Medicinal Chemistry

Perspective

The Protein Data Bank (PDB), Its Related Services and Software Tools as Key Components for In Silico Guided Drug Discovery

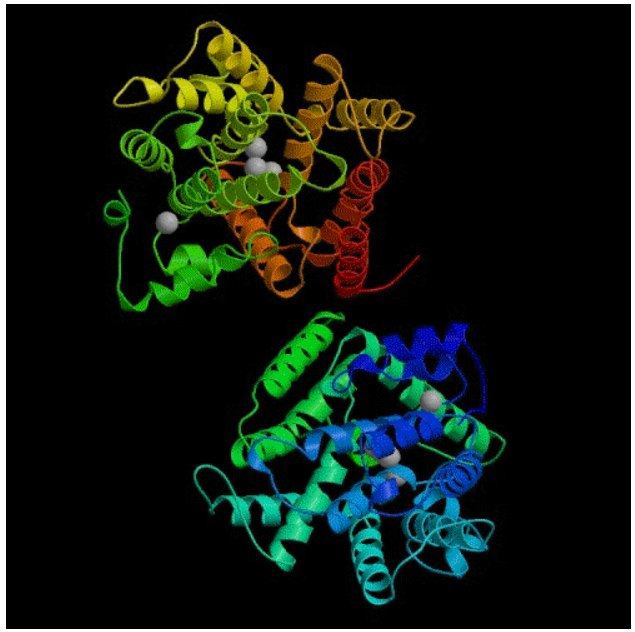
Johannes Kirchmair, Patrick Markt, Simona Distinto, Daniela Schuster, Gudrun M. Spitzer, Klaus R. Liedl, Thierry Langer, and Gerhard Wolber

J. Med. Chem., **2008**, 51 (22), 7021-7040 • Publication Date (Web): 01 November 2008



b

Estruturas cristalográficas disponíveis no PDB

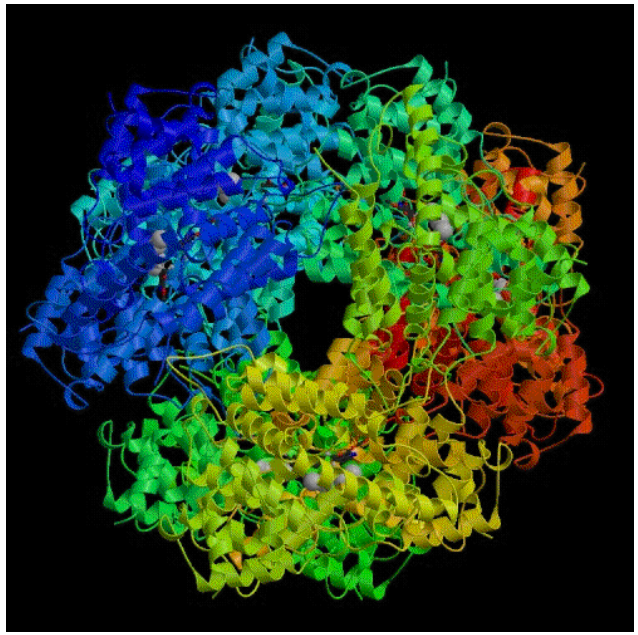


PDE4B - 1F0J

351 resíduos

Metodo: Difração de Raio-X

Resolução: **1.77 Å**



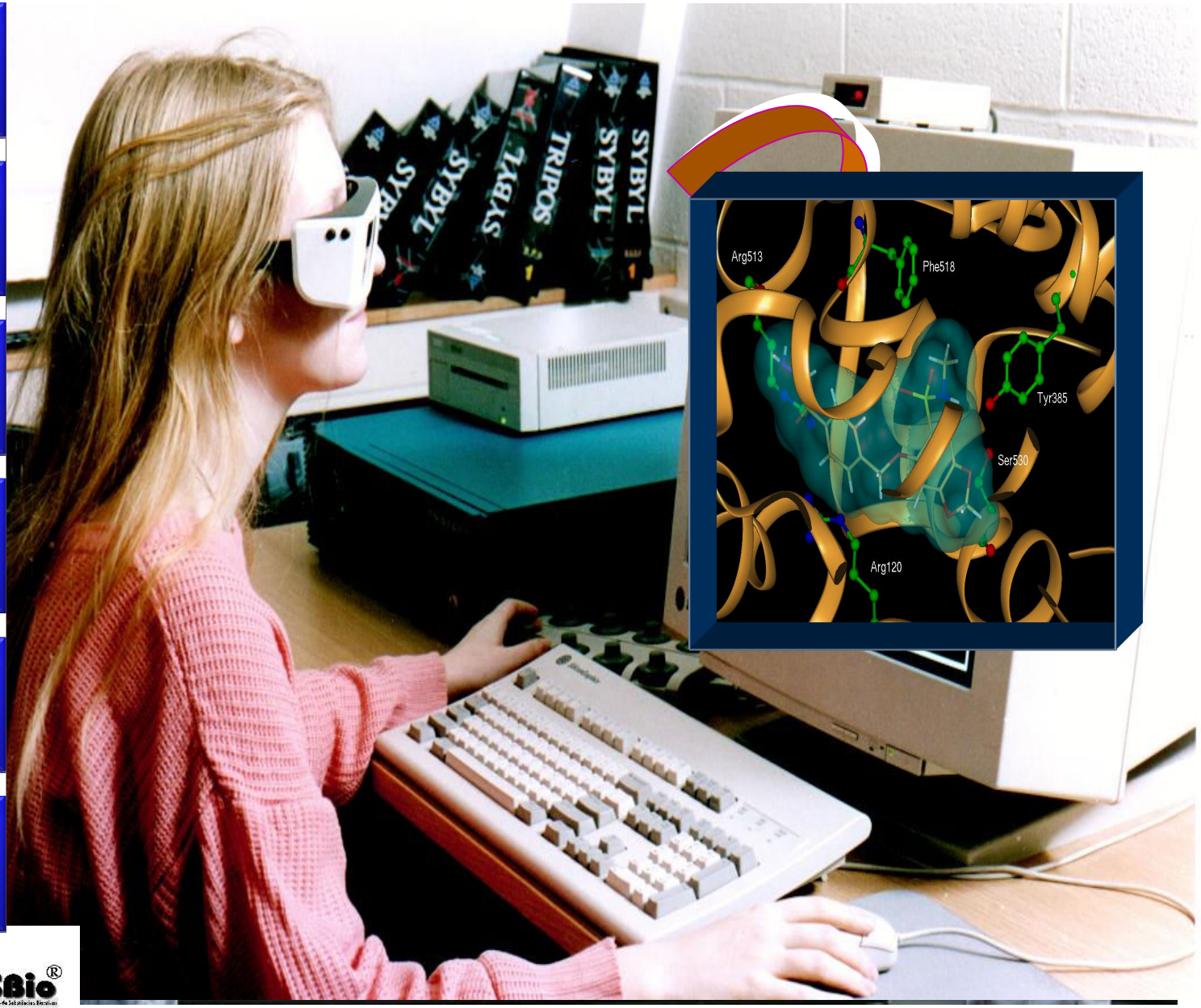
PDE4D - 1MKD

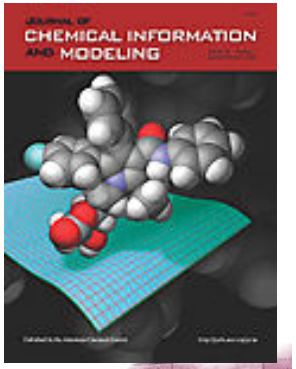
328 resíduos

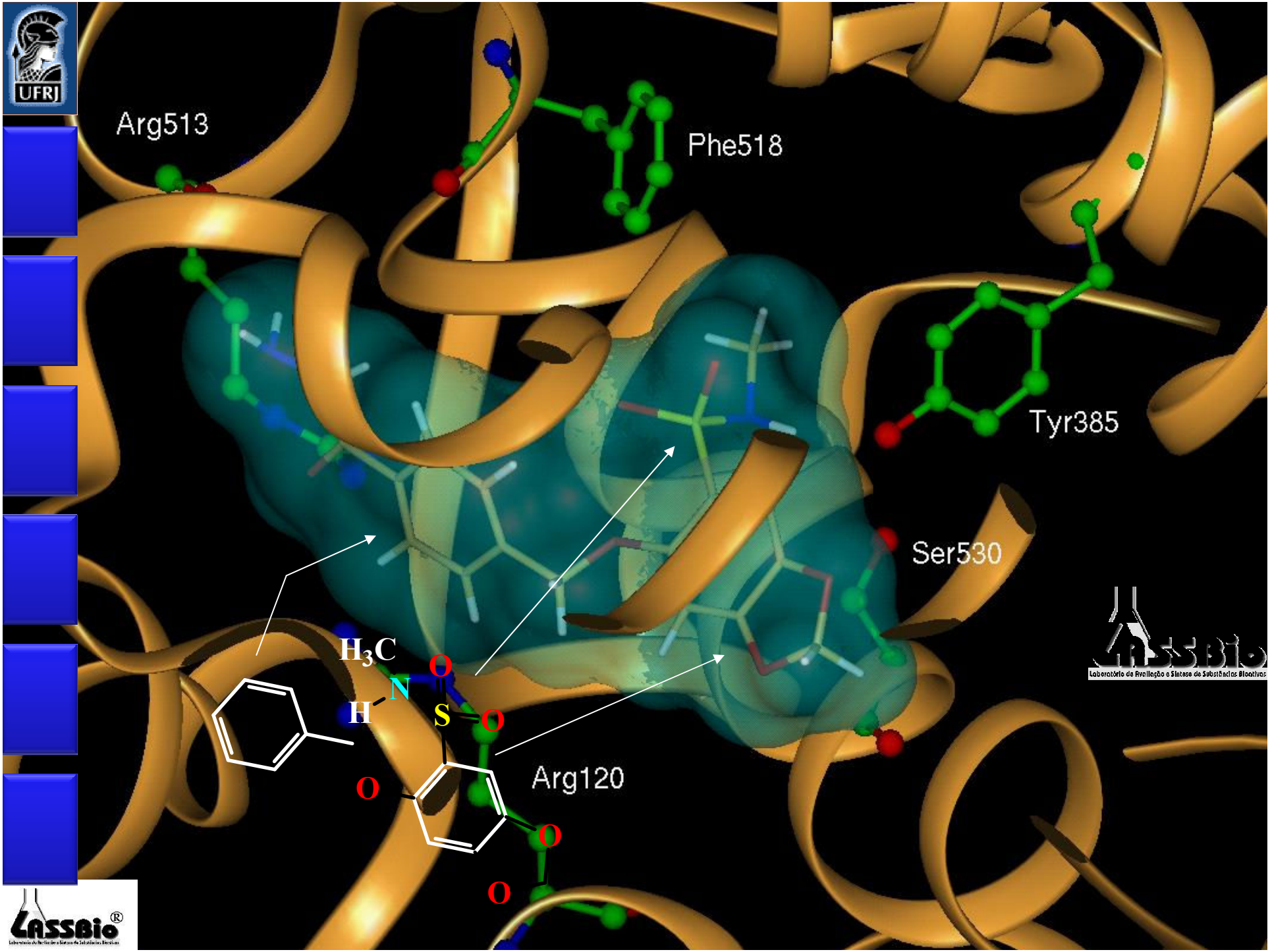
Metodo: **Difraçao de Raio-X**

Resolução: **2.90 Å**

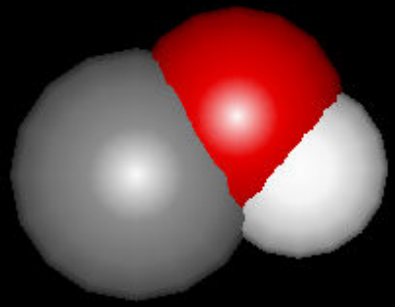
Bioformática

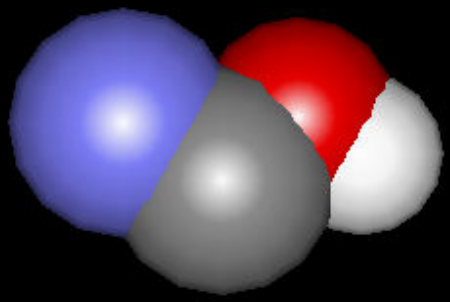





Arg513
Phe518
Tyr385
Ser530
Arg120
H3C
O
N
H
S
O
O
O
O
O

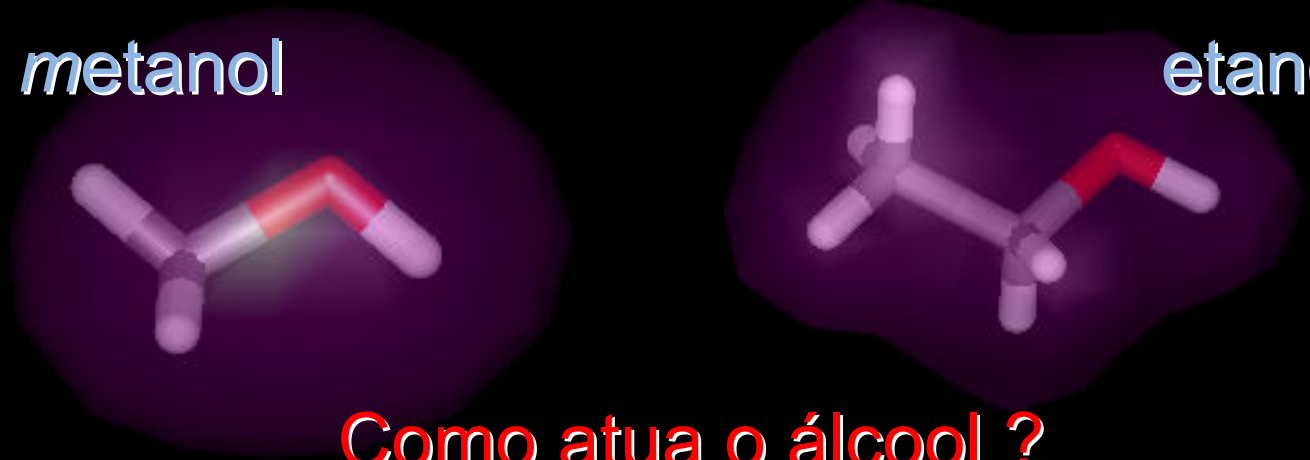
Efeitos estruturais





H-O-H H_3C-O-H H_3C-CH_2-O-H

*m*etanol etanol



Como atua o álcool ?

Dose ! canais iônicos = $GABA_A$;

O processo ...

(O Paradigma de Ehrlich & Fischer)

Química Medicinal

O paradigma de Ehrlich & Fischer

Emil Fischer

1852-1919

1902

E. Fischer, Ber. Dtsch. Chem. Ges. 1890, 23, 799

Paul Ehrlich

1854-1915

1908

LOCK & KEY CONCEPT

Planejamento racional

Biorreceptor

macrobiomolécula

baseado no sítio de reconhecimento

BSRM

BL-AA

Fármaco

micromolécula

baseado no ligante / análogo-ativo

The Magic Bullet Theory

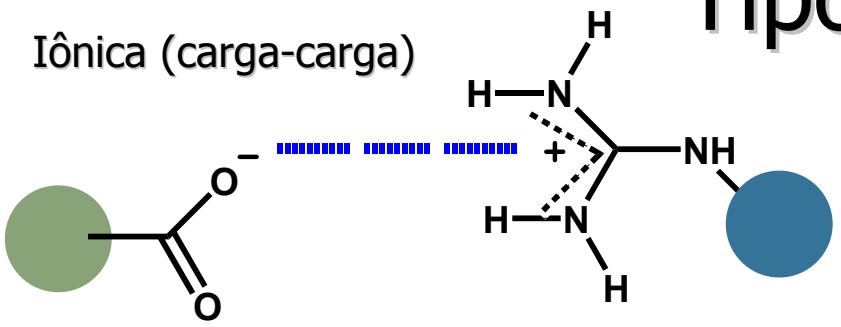
Physiologic approach

A abordagem fisiológica

P. Ehrlich, *Chemotherapeutics: scientific principles, methods and results*. *Lancet* 1913, **2**, 445

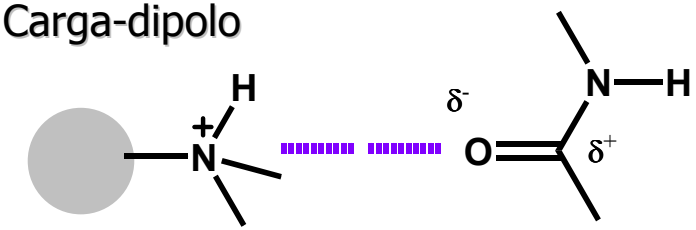
Tipos de interações F-Br

Iônica (carga-carga)



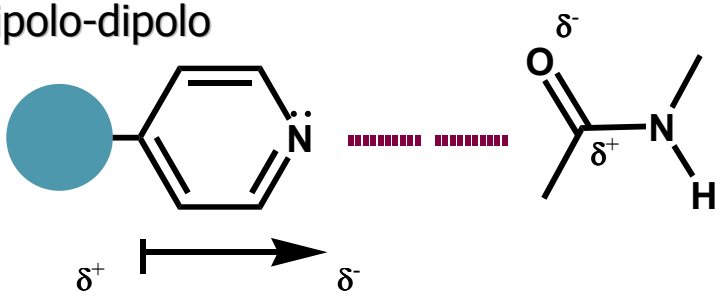
ΔG = 20-40kJ/mol

Carga-dipolo



ΔG = 12-20kJ/mol

Dipolo-dipolo

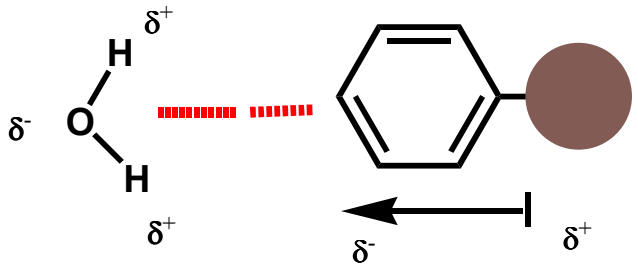


ΔG = 4-12 kJ/mol

Carga-dipolo induzido

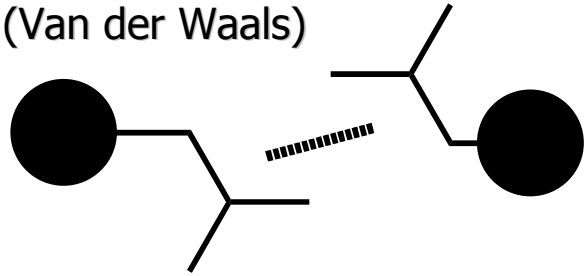
ΔG = 2-10 kJ/mol

Dipolo induzido-dipolo



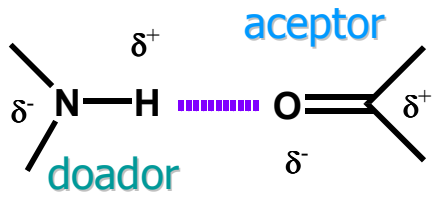
ΔG = 2 kJ/mol

Dispersão (Van der Waals)



ΔG = 2-4 kJ/mol

Ligação-H



ΔG = 4-30 kJ/mol

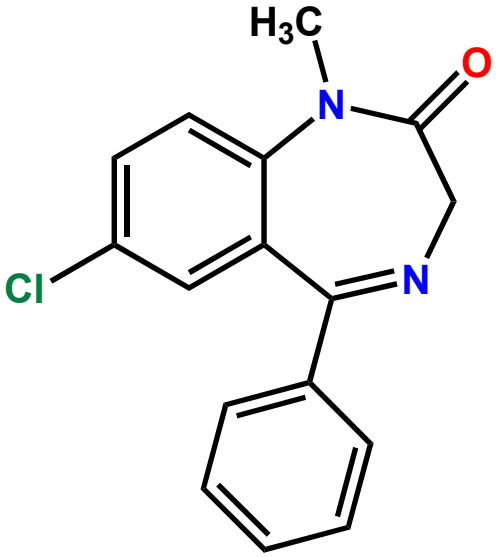
Nível hierárquico da descrição da complementaridade F-R

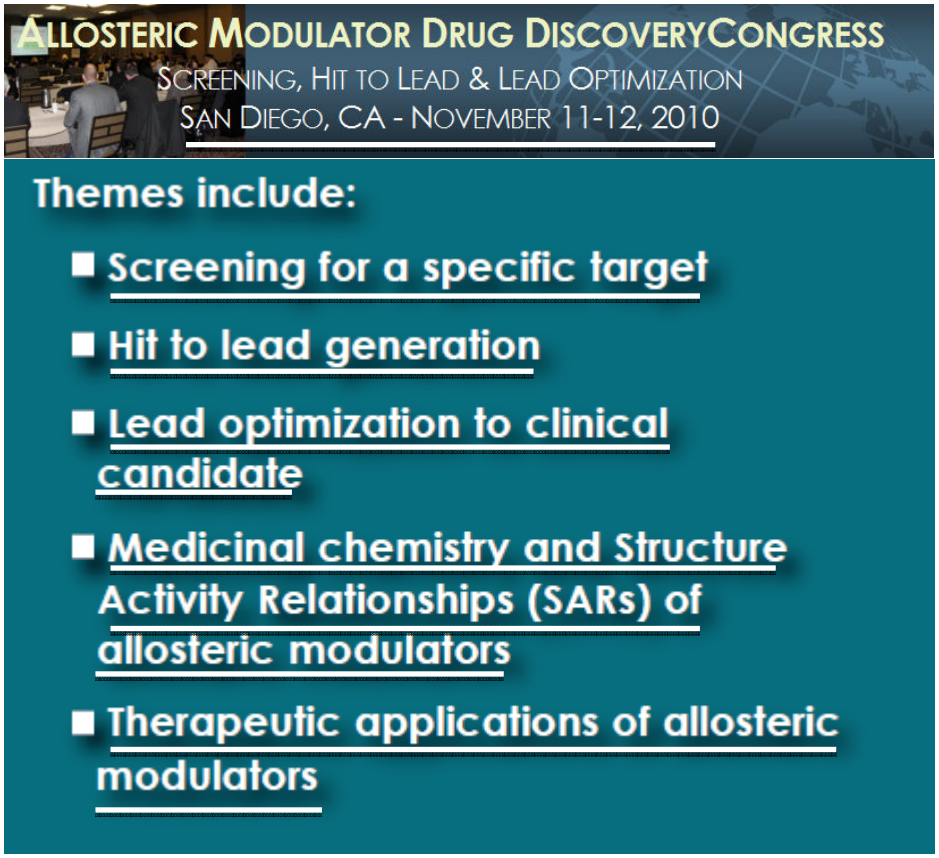
Complicadores:

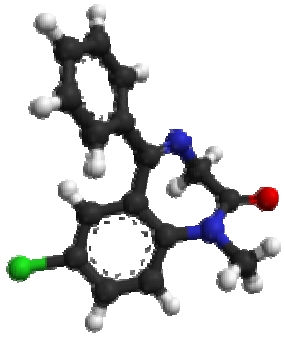
- Encaixe-induzido
- Conformação bioativa
- Inibição alostérica/ortostérica

Allosteric Modulator Drug Discovery Congress

Screening, Hit to Lead & Lead Optimization







Inibição alostérica X ortostérica

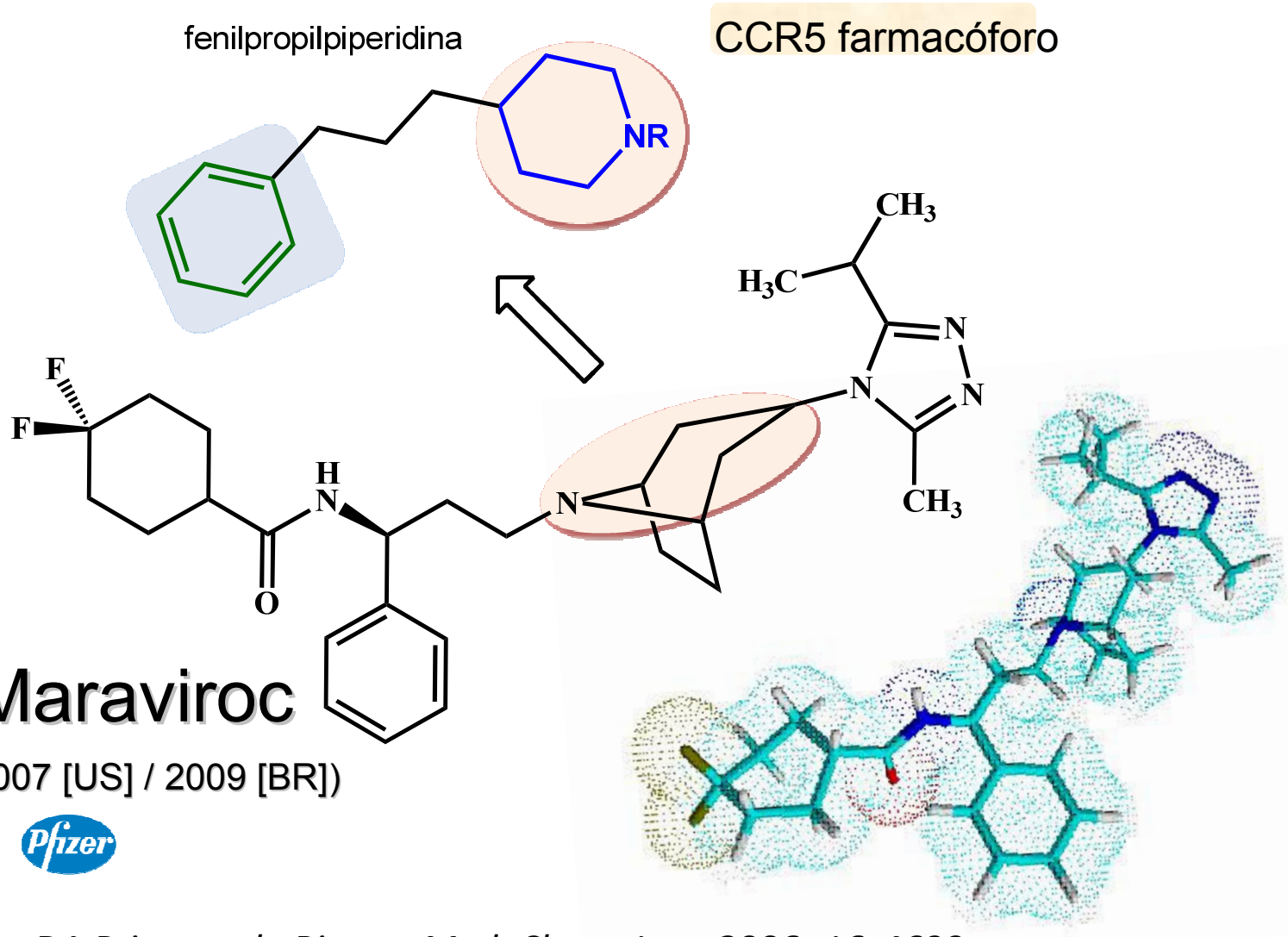
GPCR

G-protein-coupled receptors

Inter-alia: $GABA_{A,B,C}$ R, GlyR, nAChR, NMDAR, P2XR, AR, $\alpha 1,2_A,2_B$, βR, $D_{1,2}$R, ET_{A1}, mGLUR, CXCR3, CXCR4, 5-HT, NK1, M_1-M_5

A. Christopoulos, Nature Rev Drug Discov **2002**, *1*, 198

Inibição alostérica (>1990)



DA Price *et al., Bioorg. Med. Chem. Lett.* **2006**, *16*, 4633

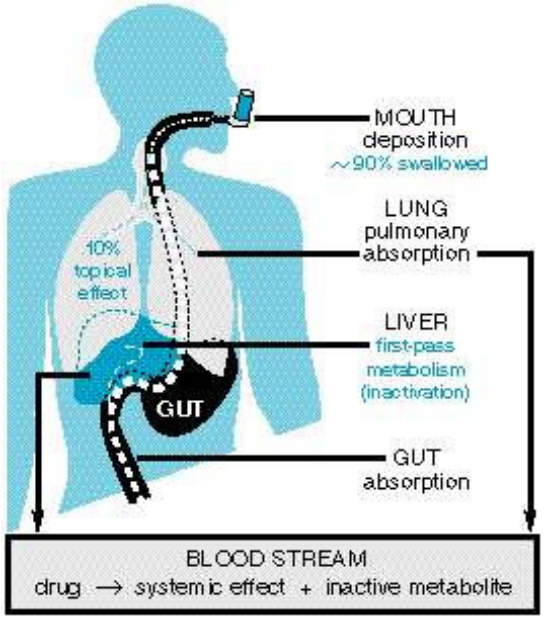
Química Medicinal

As *fases* da ação dos fármacos....

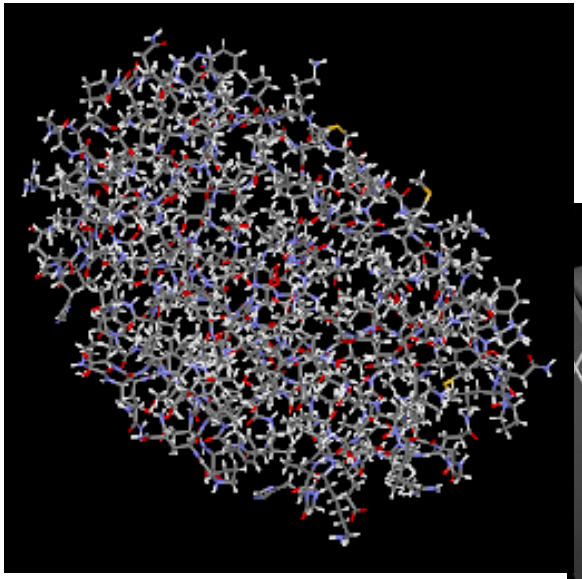
Fase farmacocinética

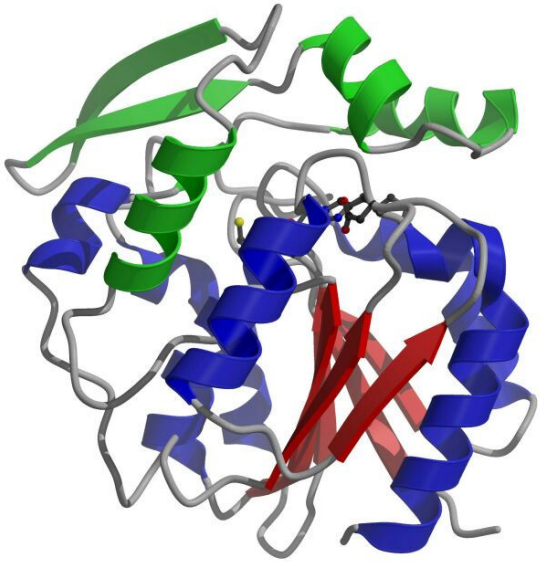
(PK)

Posologia

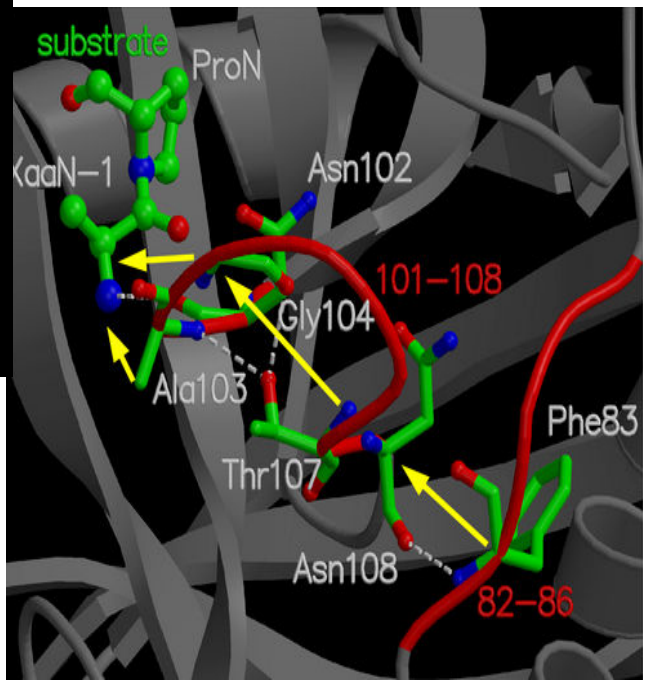


Biofase





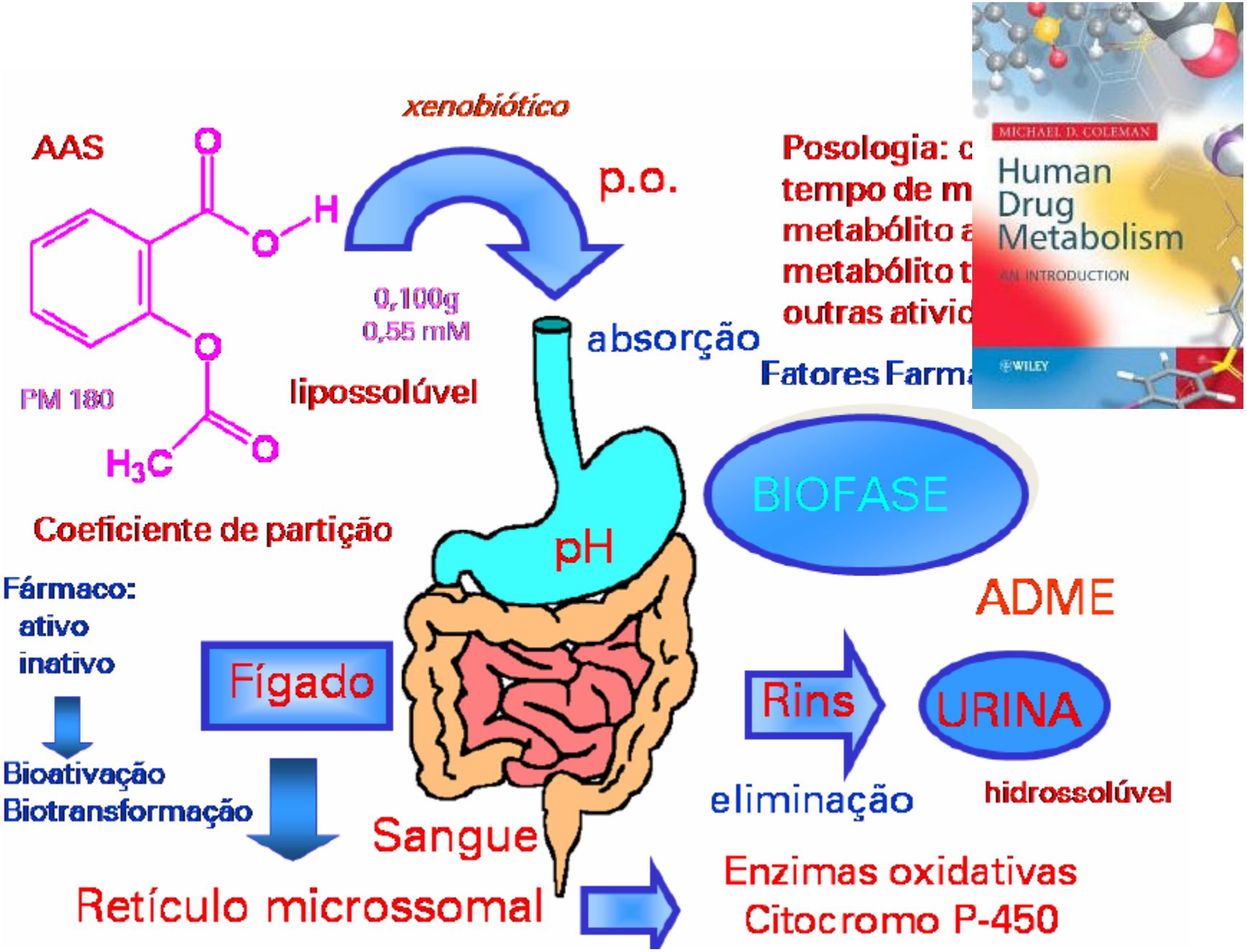
Biorreceptor



Efeito terapêutico

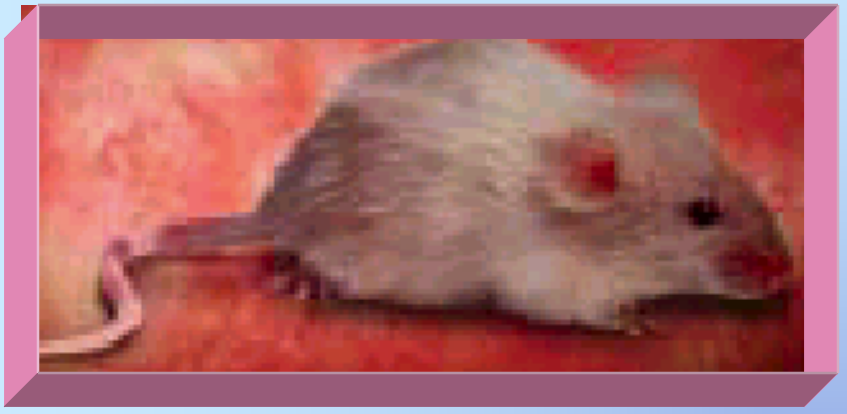
Fase farmacodinâmica

(PD)


xenobiótico
AAS
p.o.
0,100g
0,55 mM
PM 180
lipossolúvel
absorção
Posologia: c
tempo de m
metabólito a
metabólito t
outras ativid
Fatores Farma
MICHAEL D. COLEMAN
Human
Drug
Metabolism
AN INTRODUCTION
WILEY
BIOFASE
Coeficiente de partição
pH
Fármaco:
ativo
inativo
ADME
Fígado
Rins
URINA
Bioativação
Biotransformação
eliminação
hidrossolúvel
Sangue
Retículo microssomal
Enzimas oxidativas
Citocromo P-450

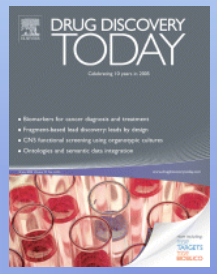
Rato Transgênico Humanizado

Humanized mouse model



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

Homology modeling of rat and human CYP 2D isoforms and computacional rationalization of experimental ligand-binding specifities, NPE Vermeulen *et al.*, *J. Med. Chem.* 2003, *46*, 74

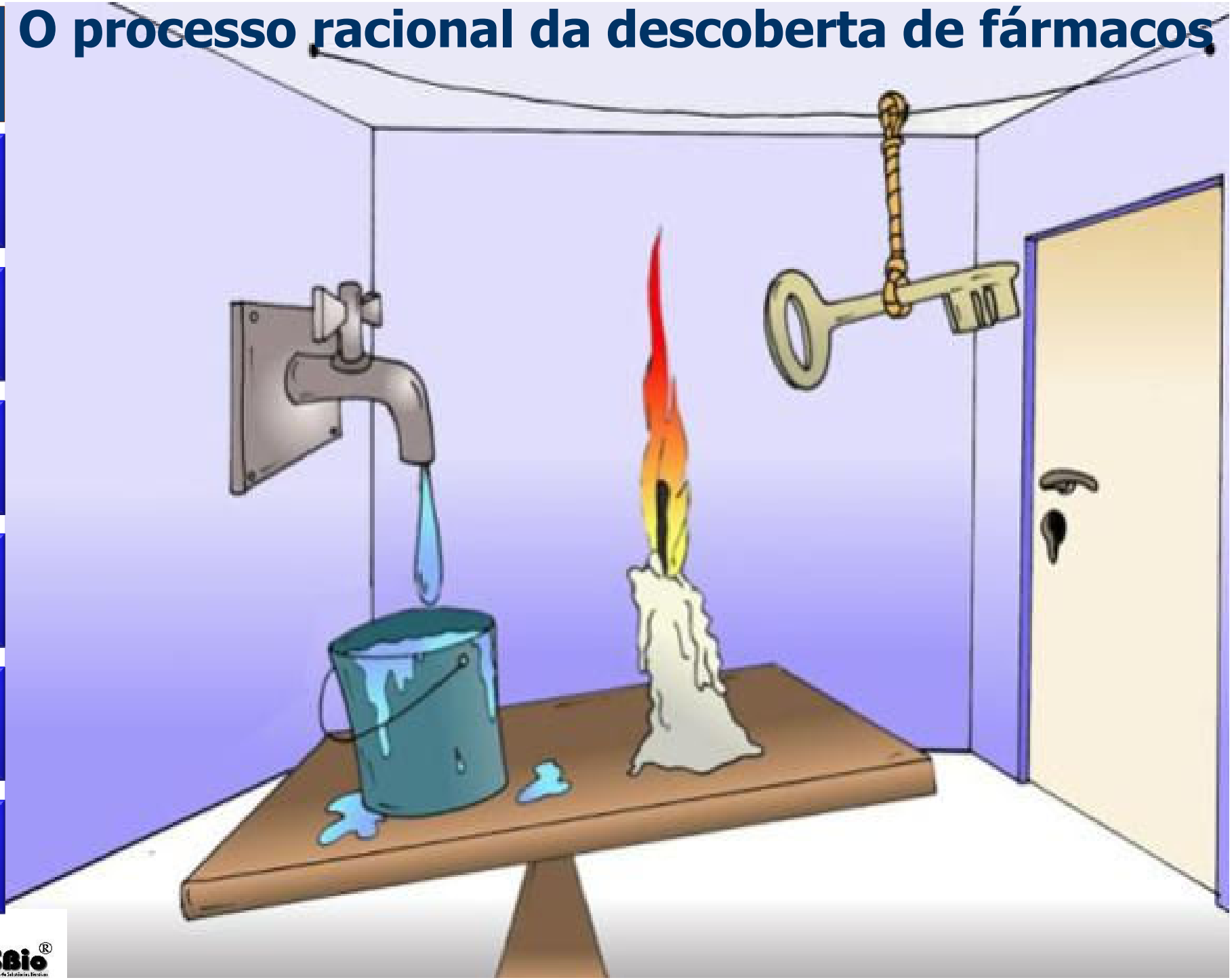


(Adaptado de Hugo Kubinyi 2002)

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.

P. Erhardt, Medicinal Chemistry in the new Millennium. A Glance into the Future, *Pure Appl. Chem.* 2002, *74*, 703.

O processo racional da descoberta de fármacos



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2. **A cronologia da descoberta de fármacos e o prêmio Nobel**
3. **A contribuição dos produtos naturais para a descoberta de fármacos**
4. **Noções das interações fármaco-biorreceptores e o paradigma de Ehrlich-Fischer**
5. **Abordagem fisiológica no planejamento racional**
6. **Estratégias de desenho molecular de análogos-ativos:**
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   - 6.2. Aplicação da simplificação molecular;
   - 6.3. Aplicação da anelação molecular
   - 6.4. Aplicação da hibridação molecular
   - 6.5. Aplicação de técnicas conjugadas
7. **Estudo de casos**

Bibliografia: *Química Medicinal: As razões moleculares da ação dos fármacos*, E. J. Barreiro & C. A. M. Fraga, Artmed, Porto Alegre, RS, 2008.

A invenção do propranolol

Raymond Ahlquist (1914

Am J Physiol 1948, 153, 586

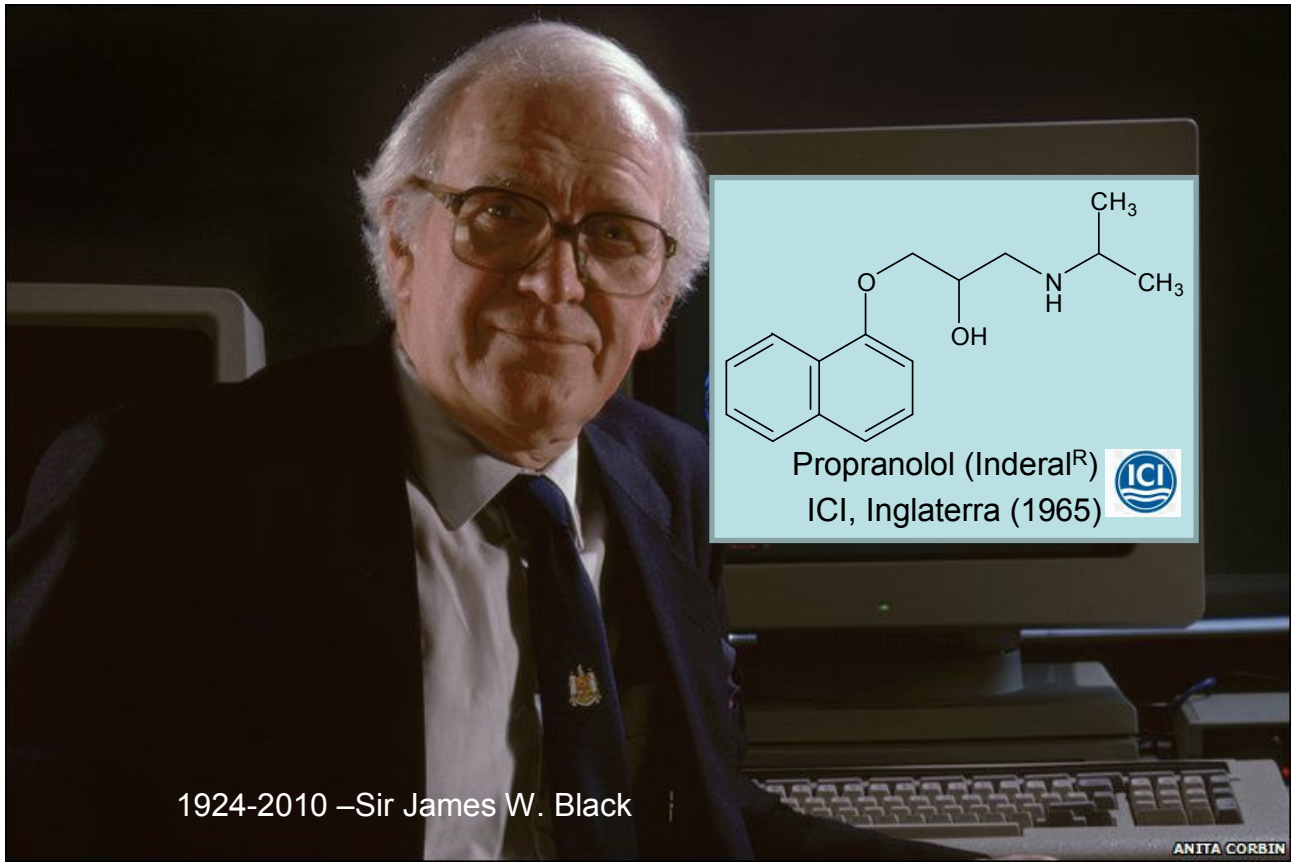
A STUDY OF THE ADRENOTROPIC RECEPTORS

RAYMOND P. AHLQUIST

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

AUGUSTA, GEORGIA

Premio Nobel
1988



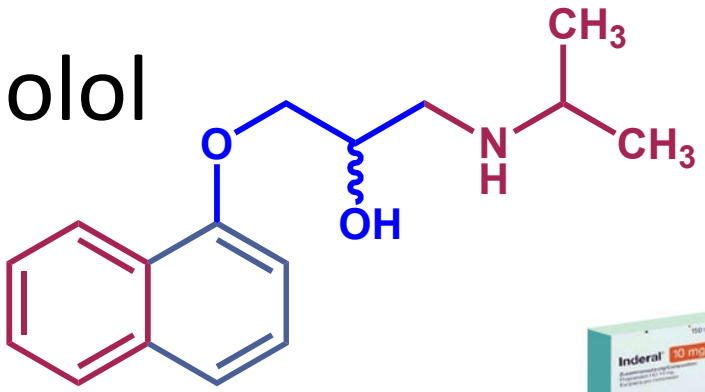
Química Medicinal

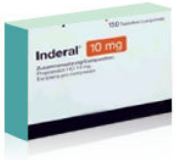
Pharmacology
Farmacologia

LASSBio®

A invenção do propranolol

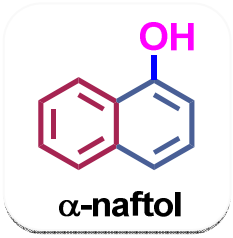
med Química Farmacêutica chem Medicinal



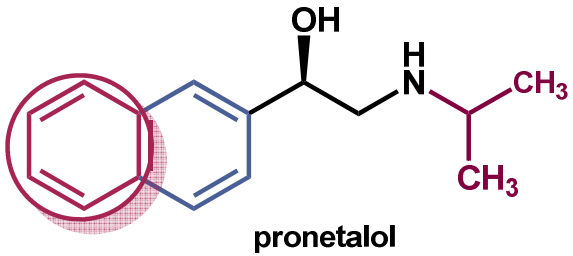


propranolol
1964

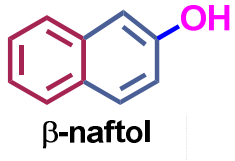
J. Black *et al*., *Br. J. Pharmacol. Chmother*. **1965**, *25*, 577



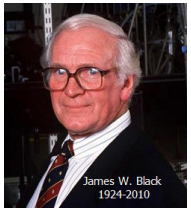
α-naftol



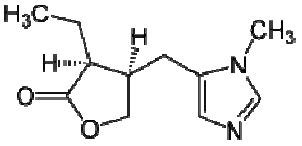
pronetalol
1959



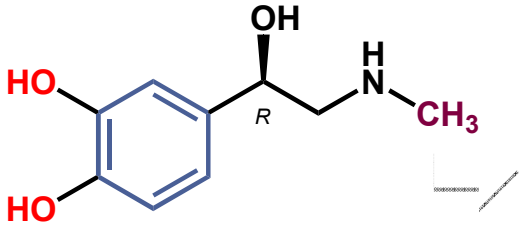
β-naftol



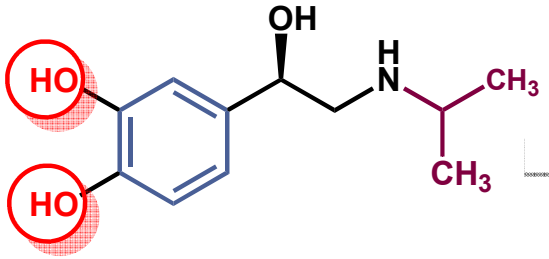
James W. Black, 1988 - "Pronethalol always seemed to us to be a prototype drug, good enough to answer questions of principle, but not good enough to be marketable"



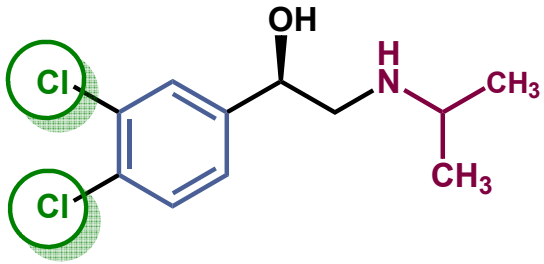
pilocarpina



adrenalina

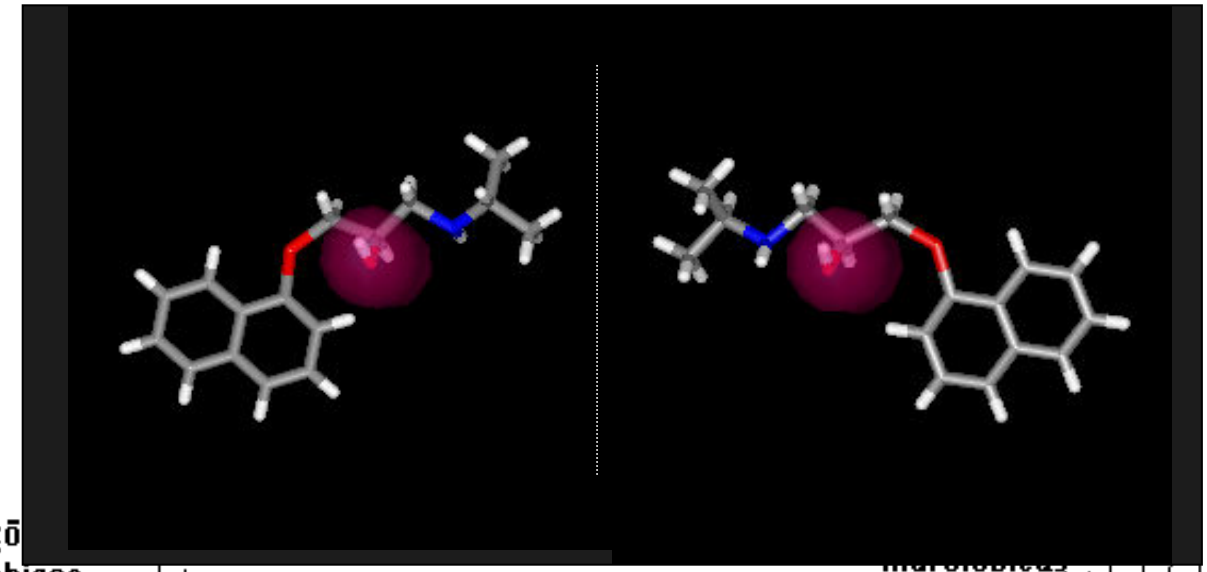


isoprenalina / isoproterenol



1958 - DCI
β-bloquedor

LASSBio®

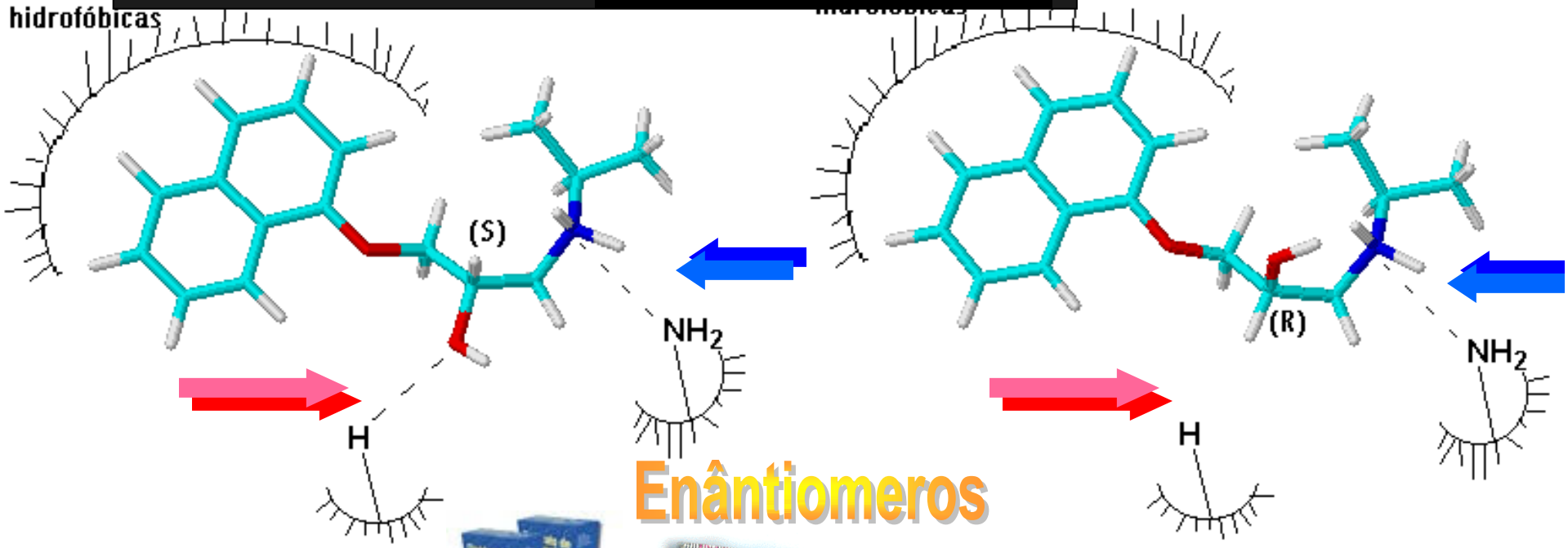


Eutômero

Distômero

Índice eudísmico

Interaçõ
hidrofóbicas



Enântiomeros

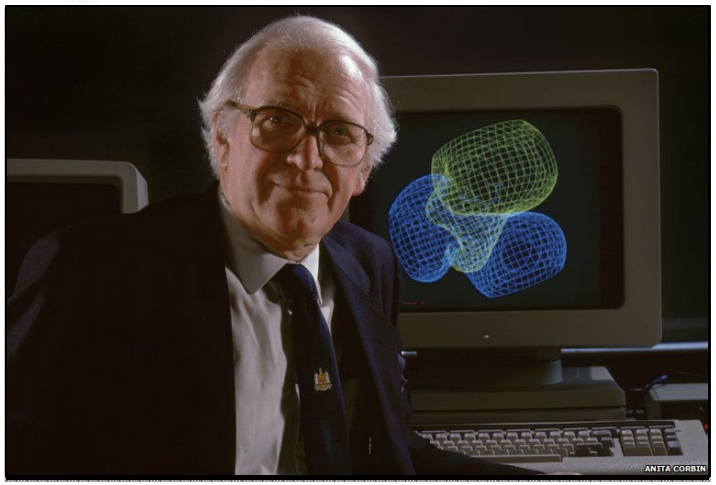
Sir James W. Black: *drug hunter*

Química Medicinal

Química & Biologia

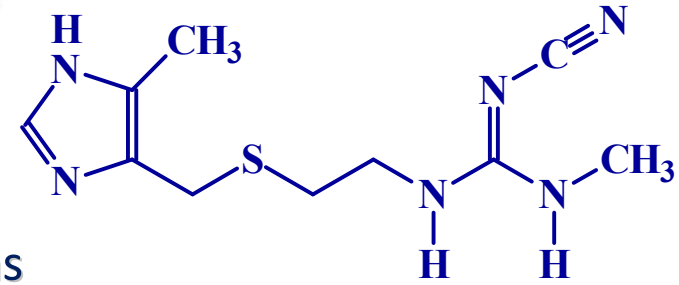
"During the last forty years I have seen the tremendous success that the pharmaceutical industry has achieved by basing its drug strategy around the naturally occurring molecules, hormone and substrates, etc. These native molecules were the leads. Close analogues and derivatives were then designed around these leads. Classical bioassays and biochemistry were able to select-in those compounds that competed with the native molecule for the same active site. Compounds with a high degree of selectivity were regularly produced. The new strategy (ie, combinatorial chemistry and HTS) may not be so lucky. Proteins are inherently 'sticky' molecules. There may well be a danger that the binding reactions used in the high-throughput screening that is used in conjunction with combinatorial chemistry will select-in nonspecific molecules. Non-selectivity may not become visible until the development stage involving intact animals is reached. Too much combinatorial chemistry might well come to be seen as a risk factor to the corporate health"[12].

J. Black, Future perspectives in pharmaceutical research. *Pharm. Policy Law*. *1*, 85–92 (1999).



James Whyte Black
1924-2010
[R Ganellin & W Duncan, *Nature* **2010**, *464*, 1292]

Prêmio Nobel de Medicina
1988



Cimetidina

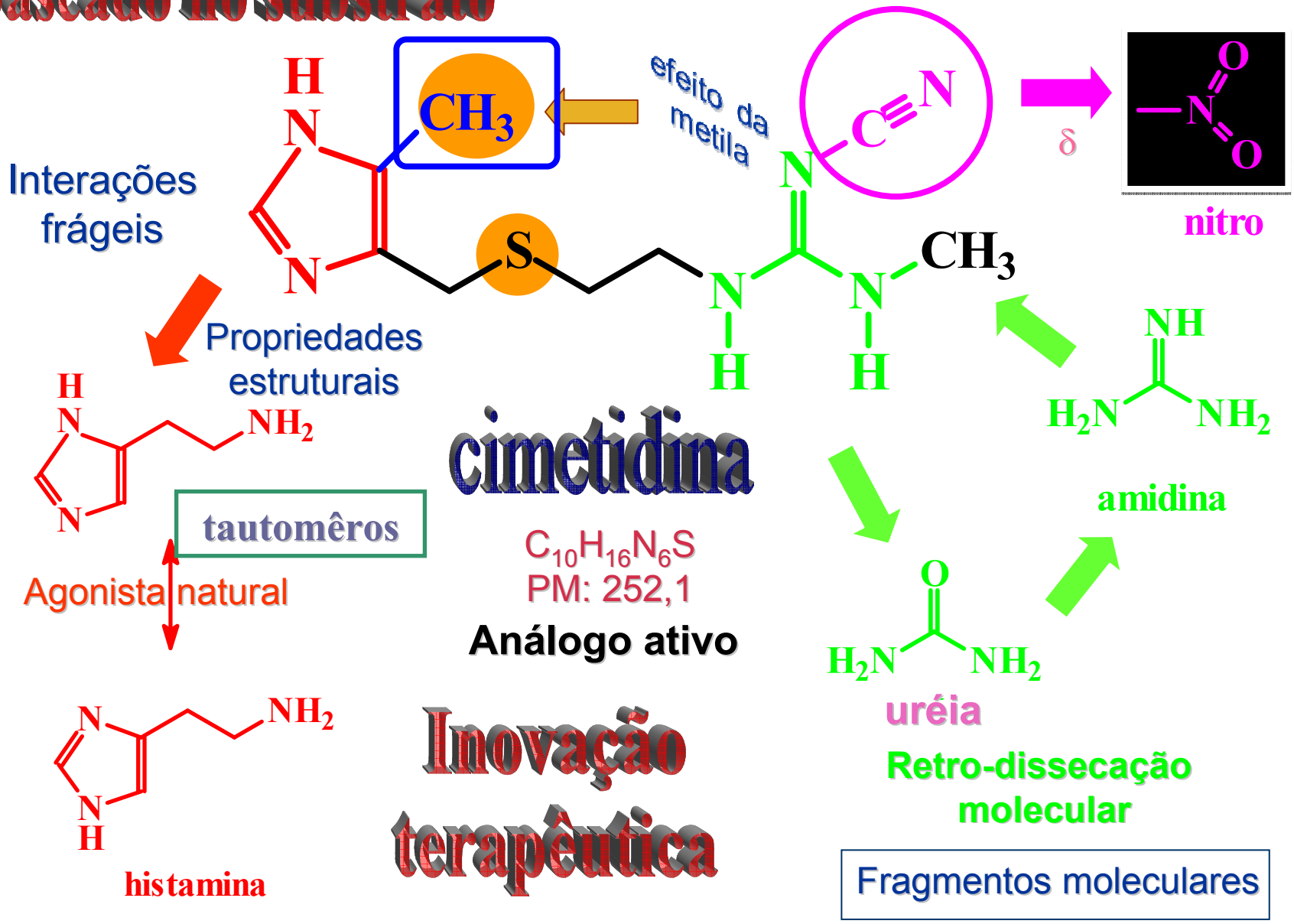
Inventor de moléculas mágicas & inovadoras

(Inovações terapêuticas)

LASSBio

Desenho estrutural baseado no substrato

Abordagem Fisiológica

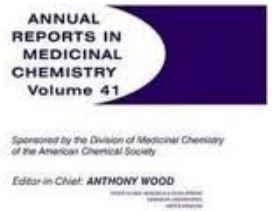


Considering the vast size of chemical space to be explored,* it is not surprising that <u>experience</u> and <u>intuition</u> are the characteristics that distinguish the most successful medicinal chemists.

A. L. Hopkins & A. Polinsky

Knowledge and Intelligence in Drug Design,

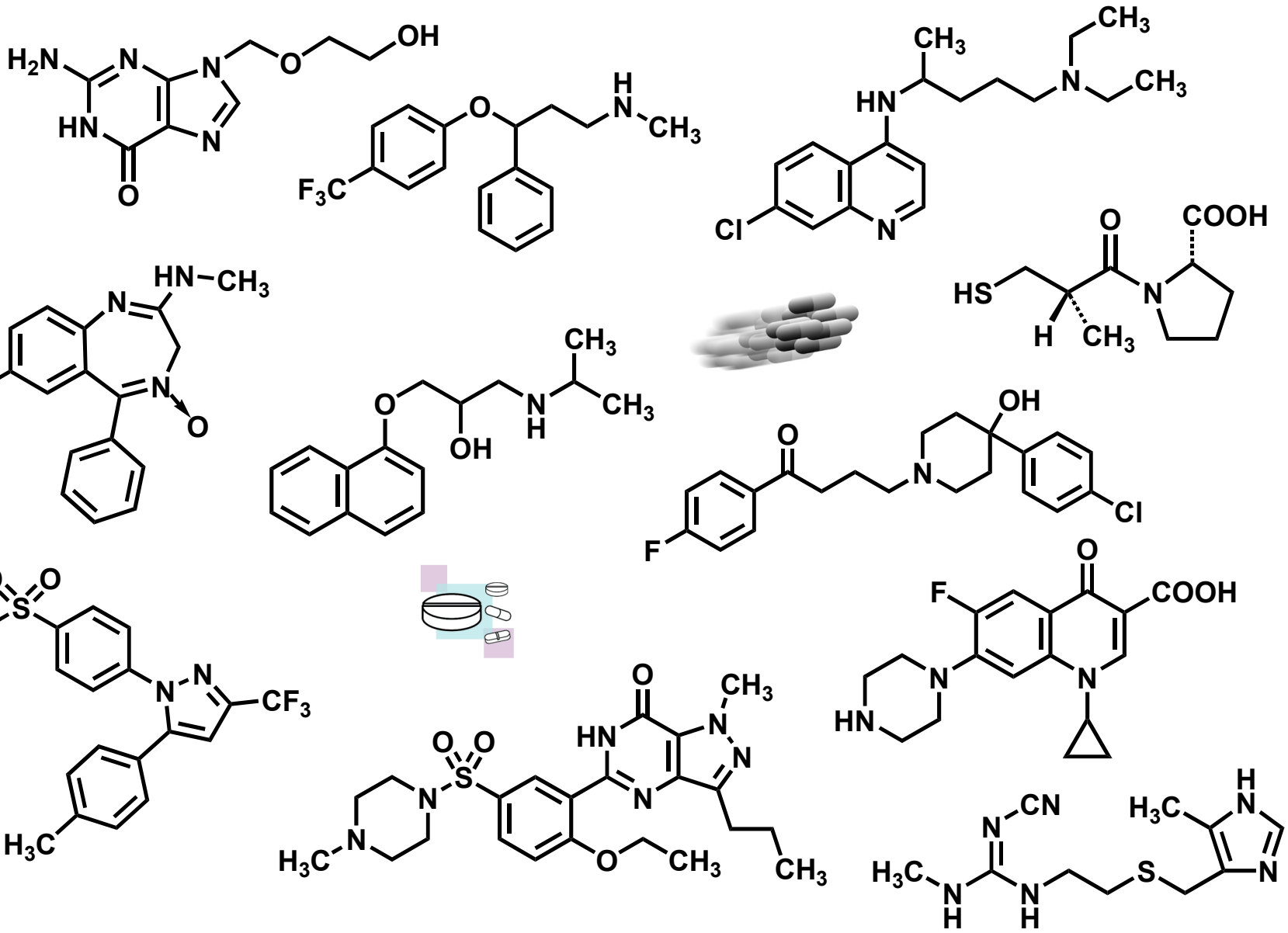
Annu. Rept. Med.Chem. 2006, *41*, 425.



* Número de possíveis moléculas com propriedades farmacêuticas *ca.* 10^{60}

J-L Reymond, R van Deursen, L C Blum, L Ruddigkeit, *Med Chem Commun* **2010**, *1*, 30

A quimiodiversidade dos compostos inaturais



Características estruturais comuns nos onze fármacos :

- Representam inovações terapêuticas importantes: aciclovir, fluoxetina, cloroquina, clordiazepóxido, propranolol, captopril, haloperidol, celecoxibe, sildenafila, ciprofloxacina, cimetidina;
- pertencem a 08 classes terapêuticas distintas: > SNC;
- São substâncias com singela diversidade química;
- Possuem apenas 7 elementos químicos: C,H,O,N,S,F,Cl;
- 10/11 possuem heteroátomos, 10/11 têm heterocíclos;
- 11/11 são multicíclicos (< cinco anéis);
- 10/11 possuem sub-unidades aromáticas;
- Têm 15 funções químicas: alcano, areno, álcool, tiol, haleto, éter, tio-éter, amina, cetona, amida, ácido carboxílico, *N*-óxido, amidina, sulfonamida, nitrila;
- *11/11 são de origem sintética, como > 88% dos fármacos;*

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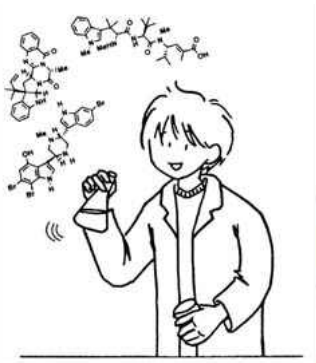
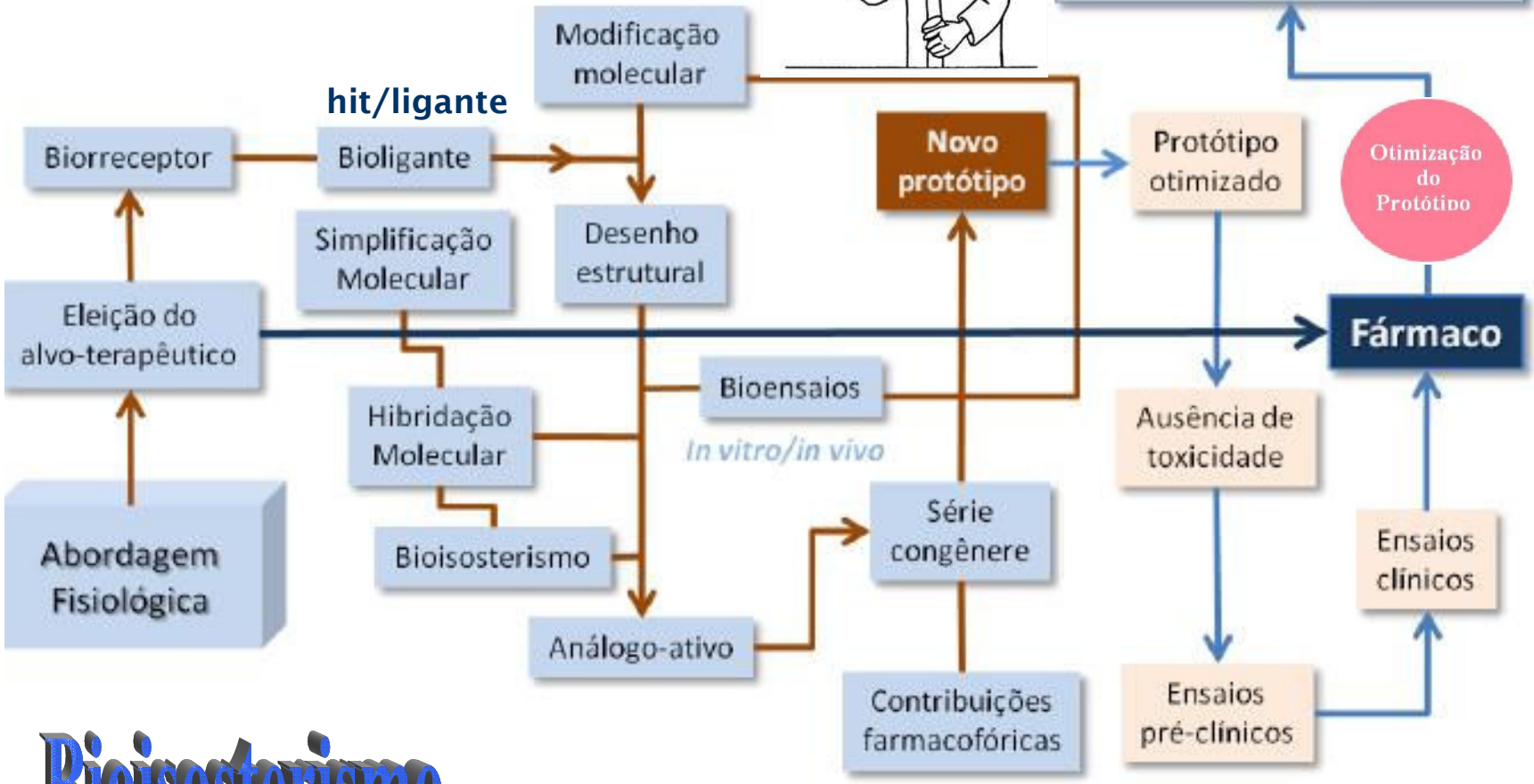
Physiologic approach
A abordagem fisiológica

Química Medicinal





Bioisosterismo...

validação precoce do alvo-terapêutico

Bioisóstero (Bio + isóstero)

Current Medicinal Chemistry, 2005, 12, 23-49;
http://www.bentham.org/cmc/samples/cmc12-1/0002C.pdf

Um *bioisóstero* é um composto resultante da troca *isostérica* de simples átomos ou subunidades estruturais, por outros átomos ou subunidades estruturais, similares em distribuições eletrônicas, volumes moleculares ou propriedades fisico-químicas, capazes de apresentarem propriedades *similares ao composto original.**

Adaptado do "Glossary of Terms Used in Medicinal Chemistry"

➧ ***As propriedades biológicas similares referem-se ao reconhecimento pelo mesmo biorreceptor, podendo ser agonista ou antagonista.***

Os elementos da Tabela Periódica

bioisosterismo

Isósteros

Chem. Soc. Rev. 1979, *8*, 563-580

Isosterism and Molecular Modification in Drug Design

By C. W. Thornber

IMPERIAL CHEMICAL INDUSTRIES LIMITED, PHARMACEUTICALS DIVISION, MERESIDE, ALDERLEY PARK, MACCLESFIELD, CHESHIRE, SK10 4TG

Chem. Rev. 1996, *96*, 3147–3176

Bioisosterism: A Rational Approach in Drug Design

George A. Patani and Edmond J. LaVoie*

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Current Medicinal Chemistry, 2005, *12*, 23-49

Bioisosterism: A Useful Strategy for Molecular Modification and Drug Design

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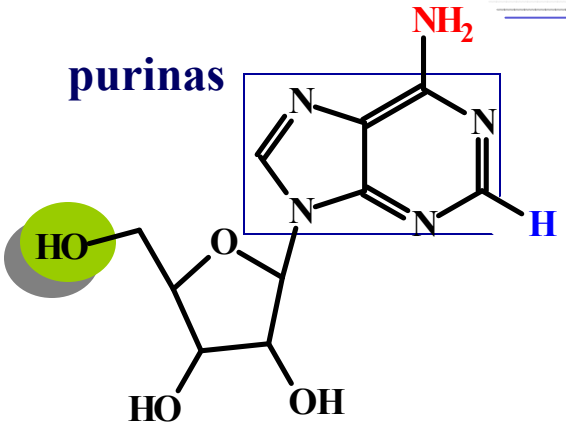
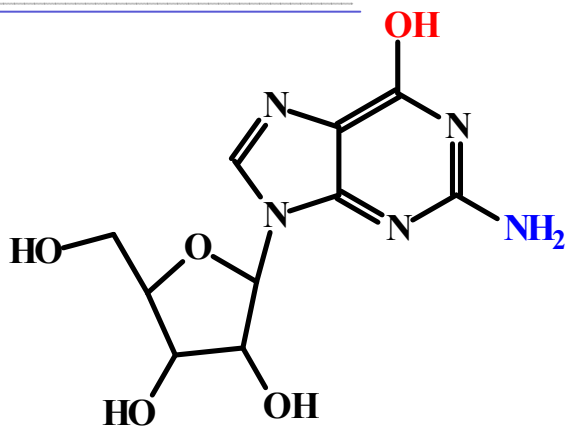
Abstract: This review aim to demonstrate the role of bioisosterism in rational drug design as well as in the molecular modification and optimization process aiming to improve pharmacodynamic and pharmacokinetic properties of lead compounds.

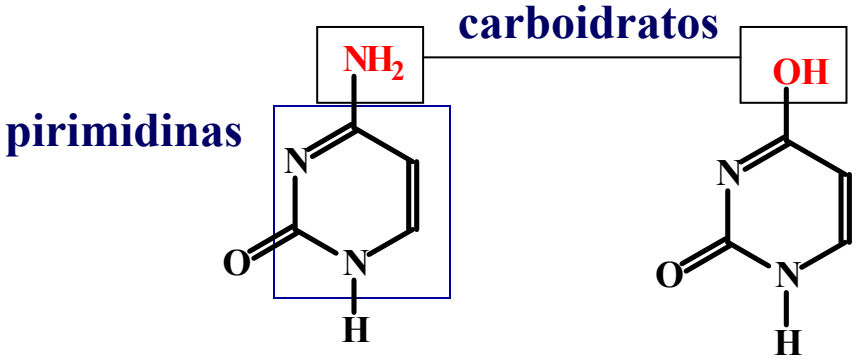
Bioisosterismo na Natureza





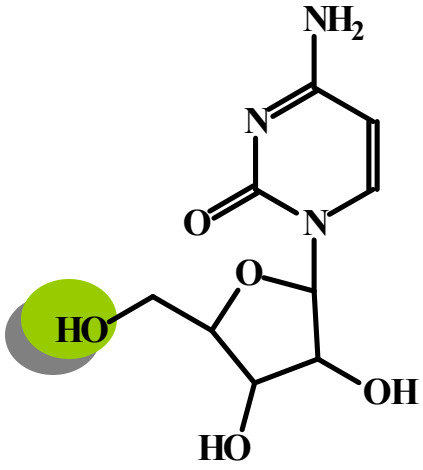
adenosina ← adenina

guanina → guanosina

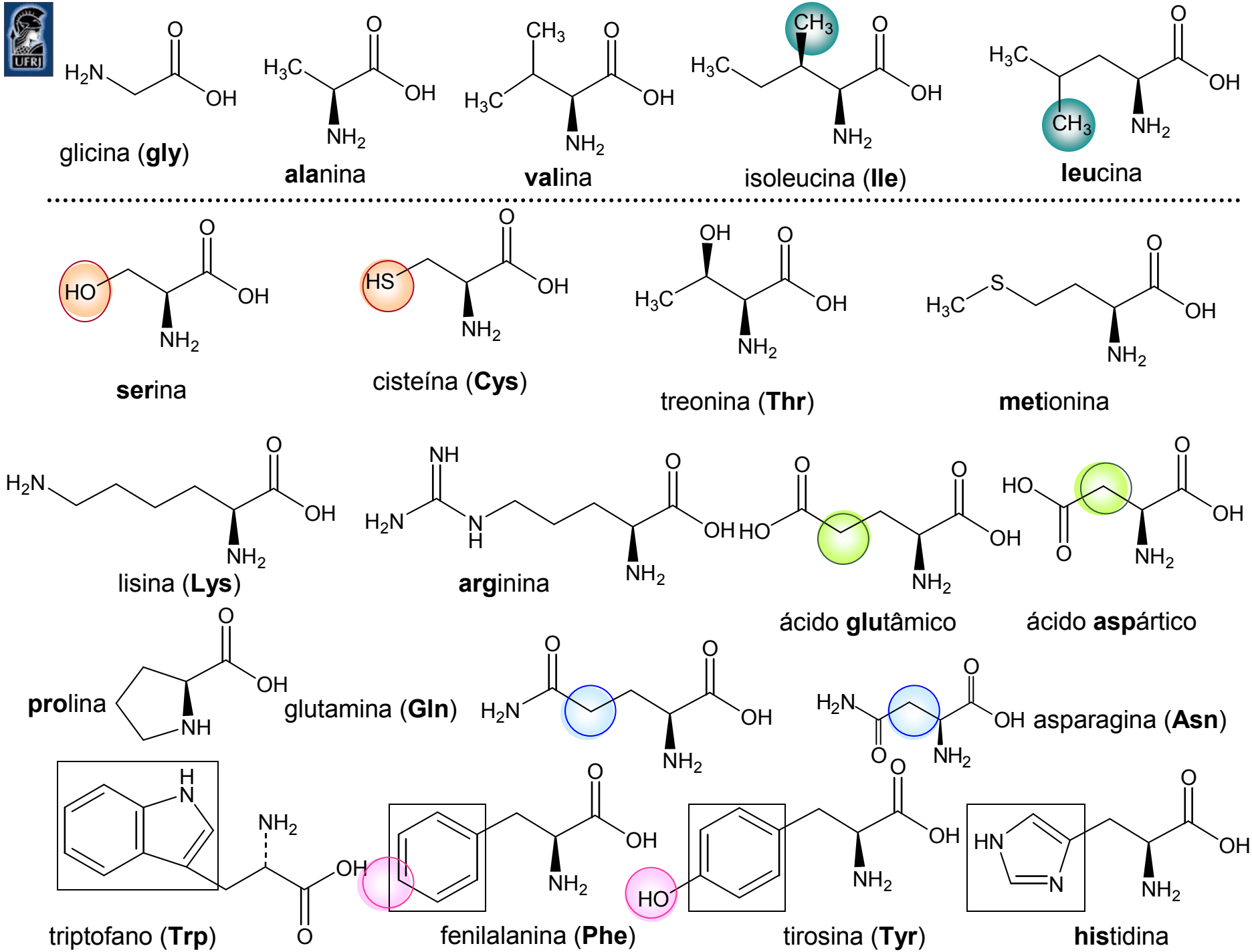


citosina

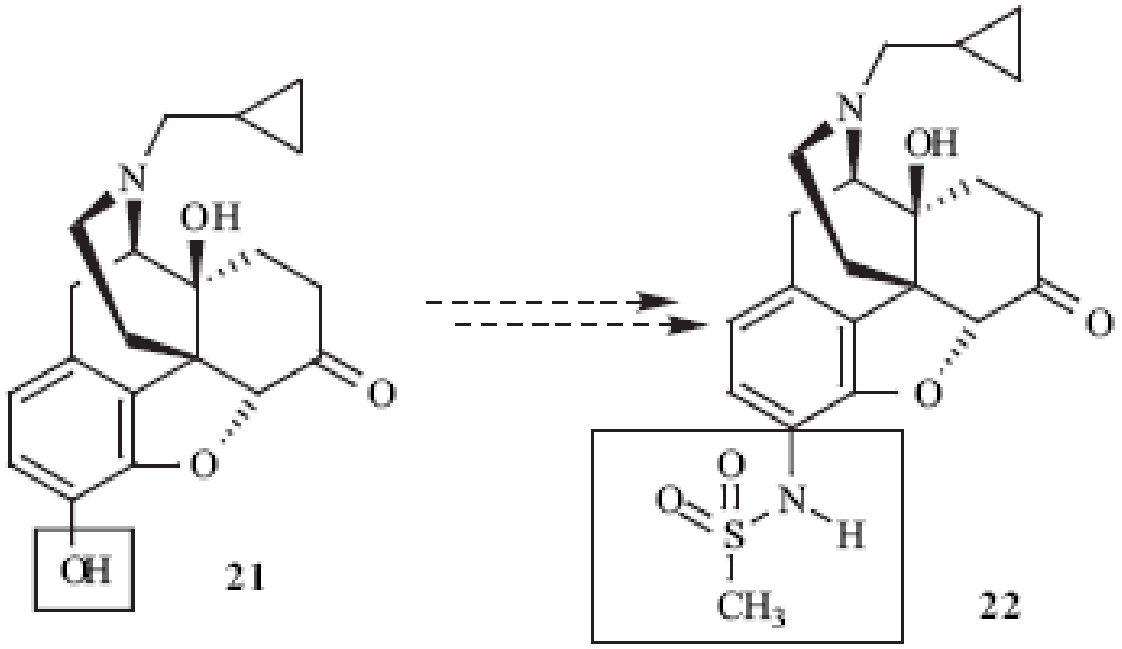
"uracilo"



nucleosídeo


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

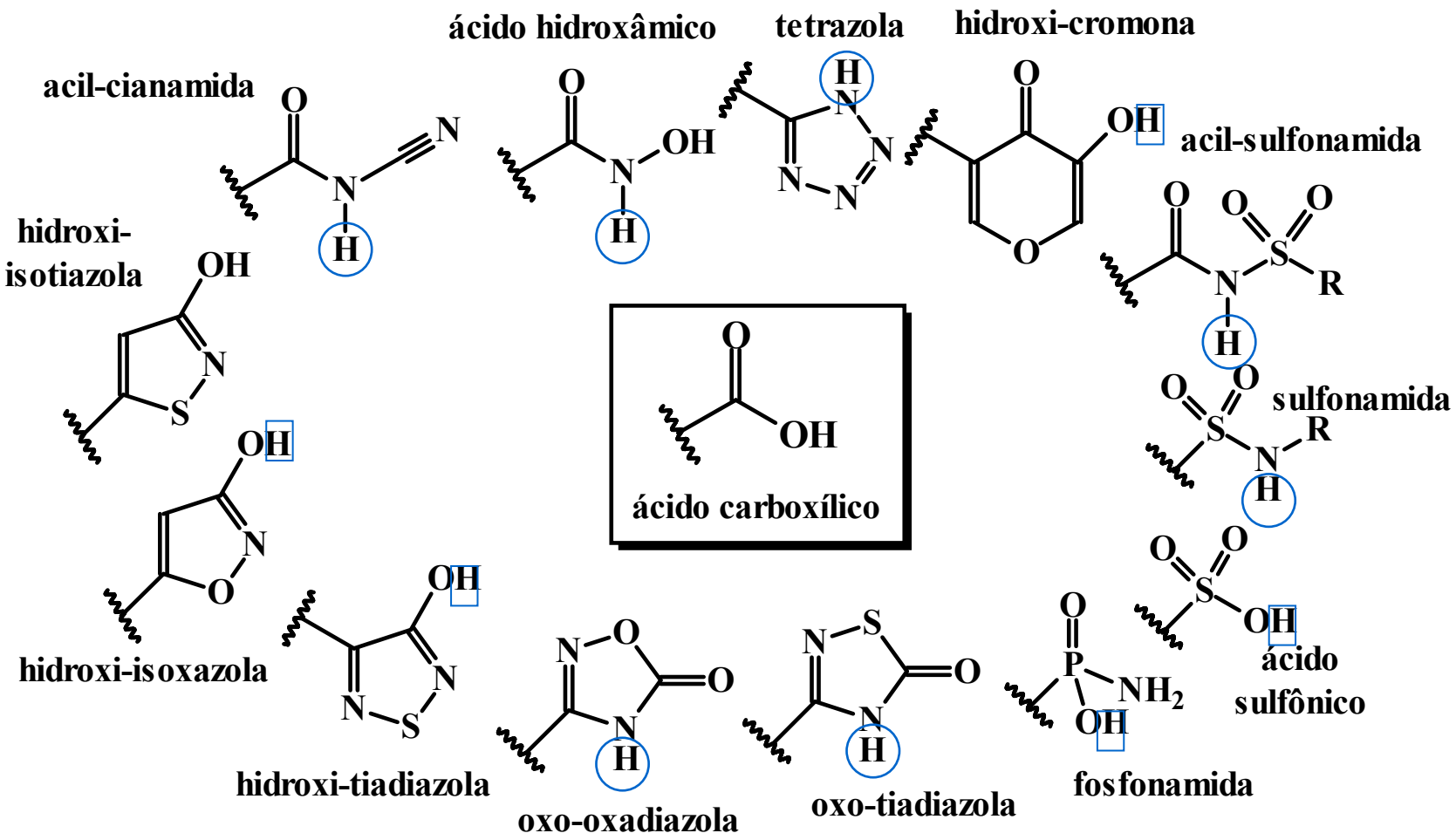
Bioisosterismo



McCurdy, C. R.; Jones, R. M.; Portoghese, P. S. *Org. Lett.* **2000**, *2*, 819-821.

As trocas isostéricas em um determinado padrão molecular que resultem em sucesso para um determinado alvo-terapêutico, *i.e.* biorreceptor, não necessariamente terão sucesso em outra série de compostos atuando ao nível de distintos biorreceptores.

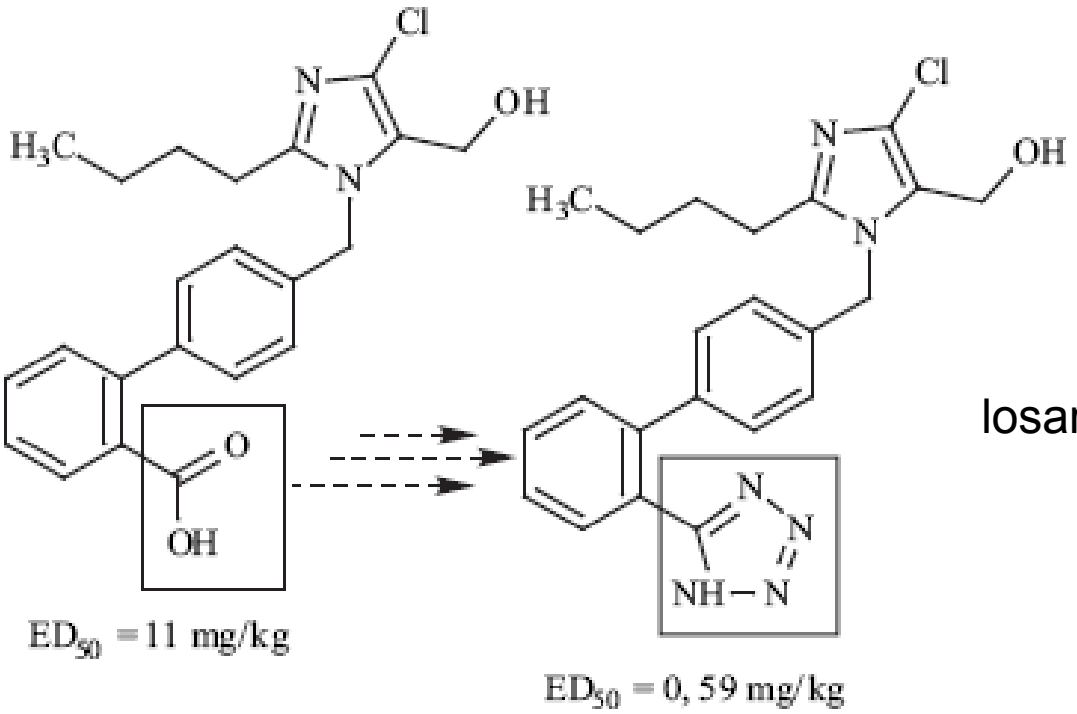
Bioisosterismo funcional



Isósteros do ácido carboxílico

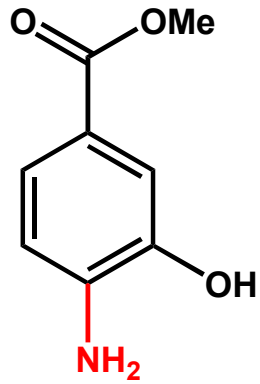
Todas as funções orgânicas têm a mesma diversidade de bioisósteros ?

Bioisosterismo funcional

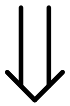


losartana

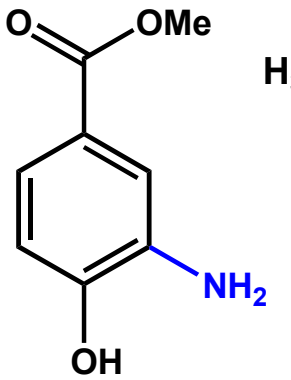
regioisomêros



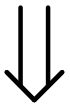
neo-ortocaína



***para*-amino = tóxico**

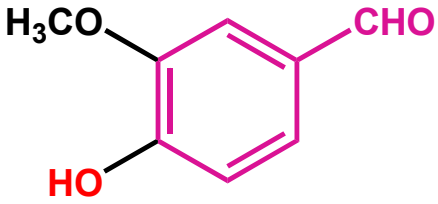


ortocaína



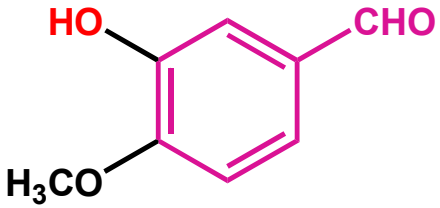
***meta*-amino não-tóxico**

regioisomêros



vanilina

odor característico

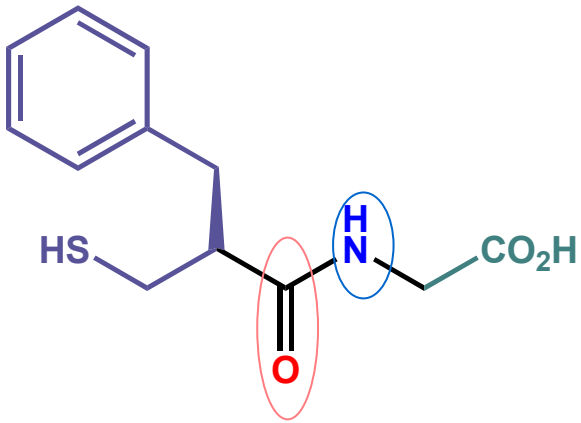


iso-vanilina

inodoro

Bioisosterismo funcional

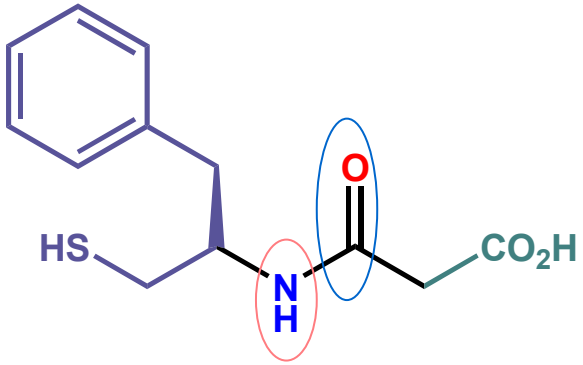
retroisosterismo



Tiorfana

ACE K_i = 0,14 μM

NEP K_i = 0,0019 μM



***retro*-Tiorfana**

ACE K_i = > 10,0 μM

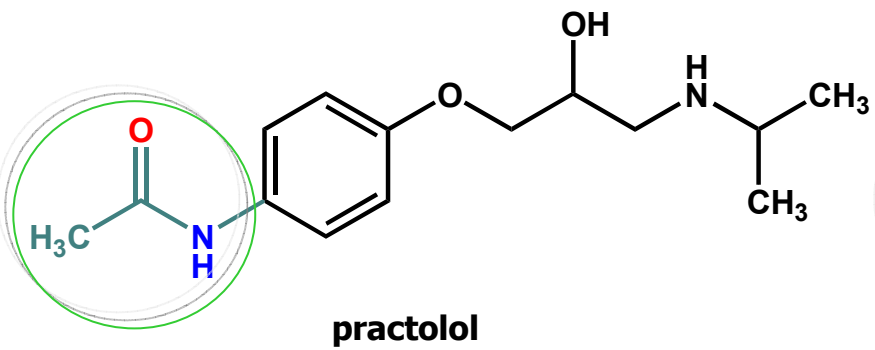
NEP K_i = 0,0023 μM

ACE = enzima conversora de angiotensina

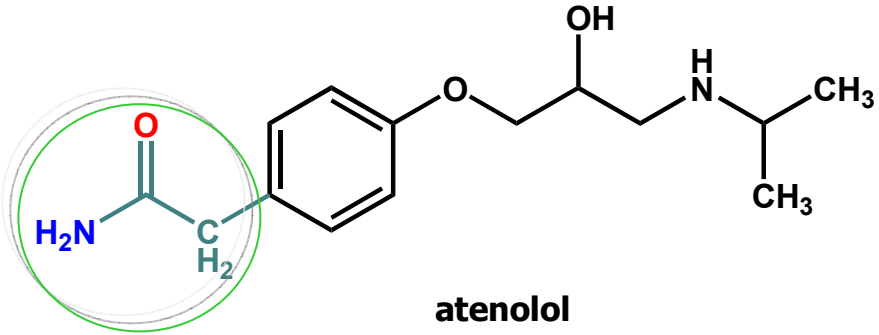
NEP = endopeptidase neutra

Bioisosterismo funcional

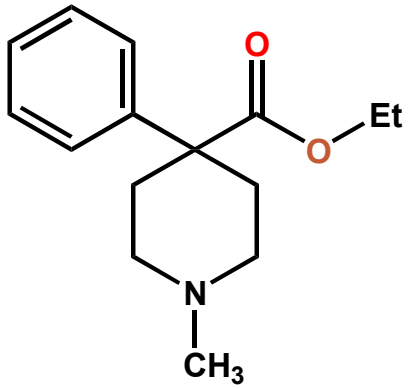
retroisosterismo



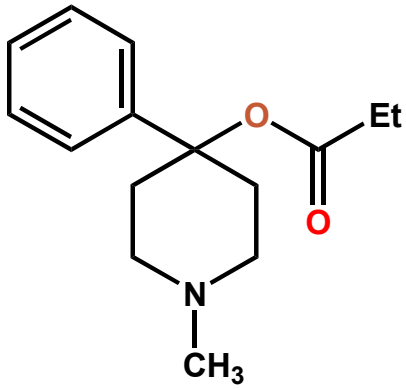
practolol



atenolol



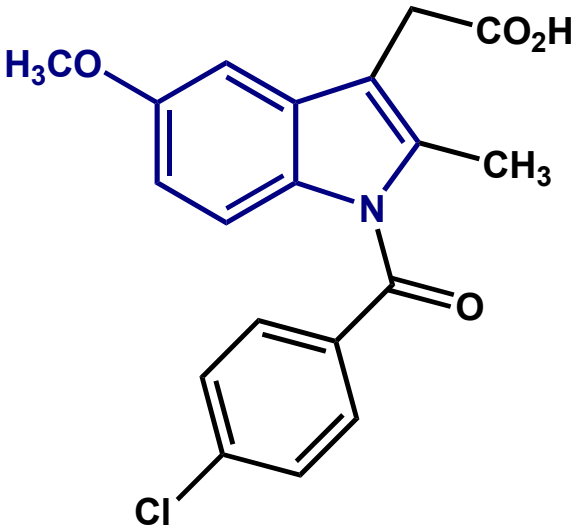
meperidina



retro-éster

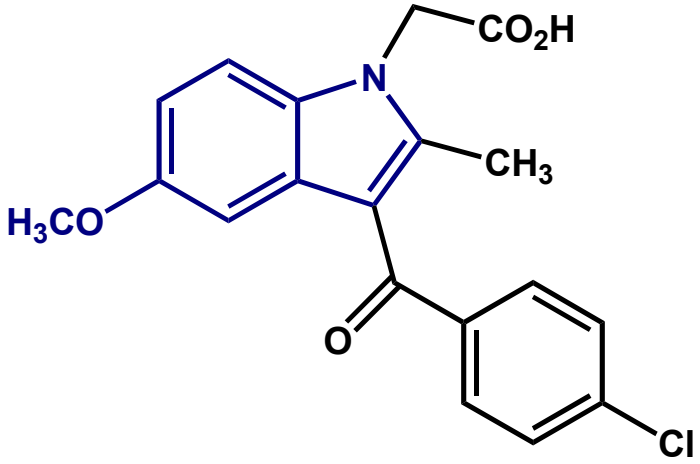
Bioisosterismo funcional

regioisomêros



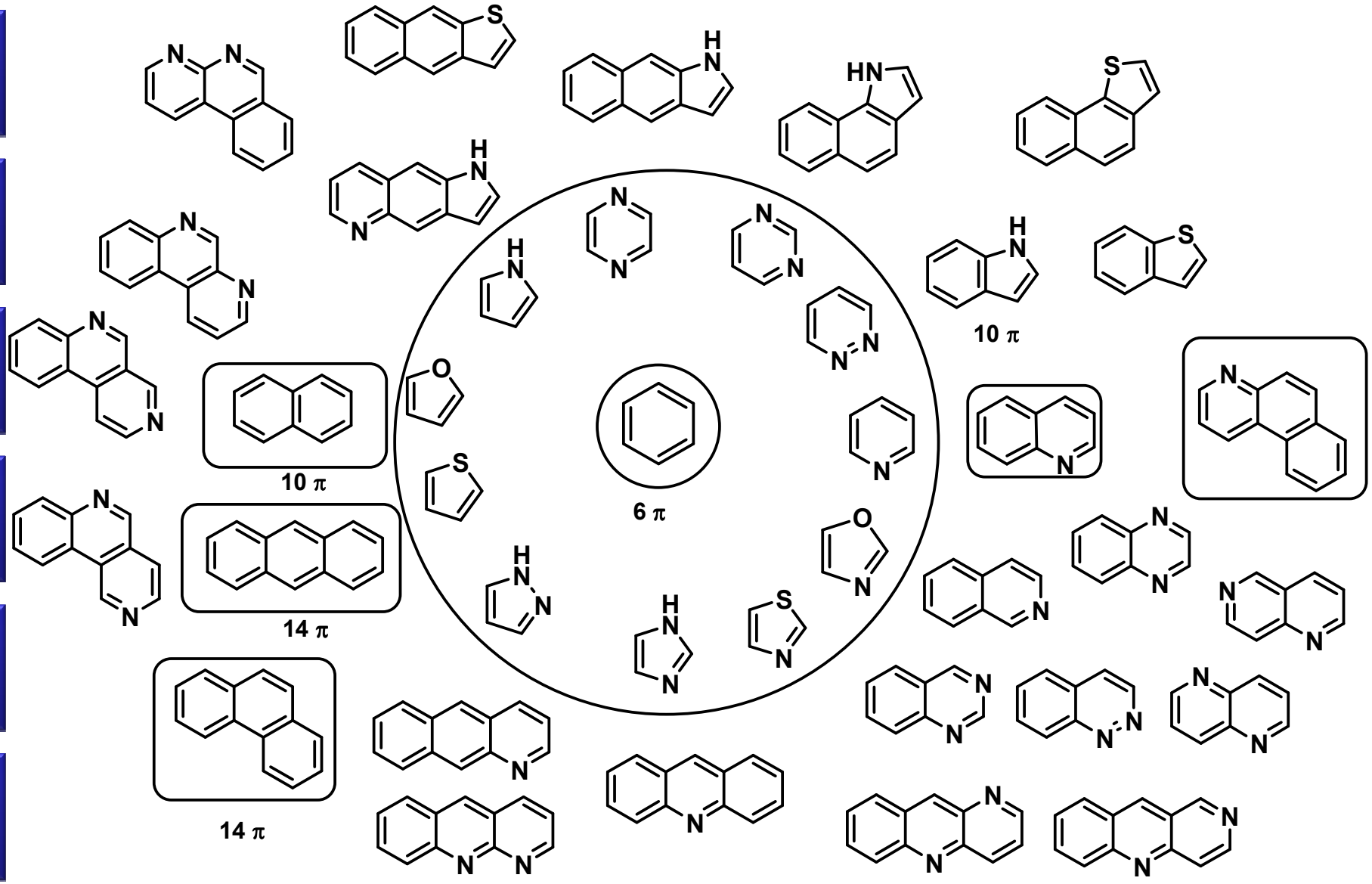
indometacina

retroisosterismo



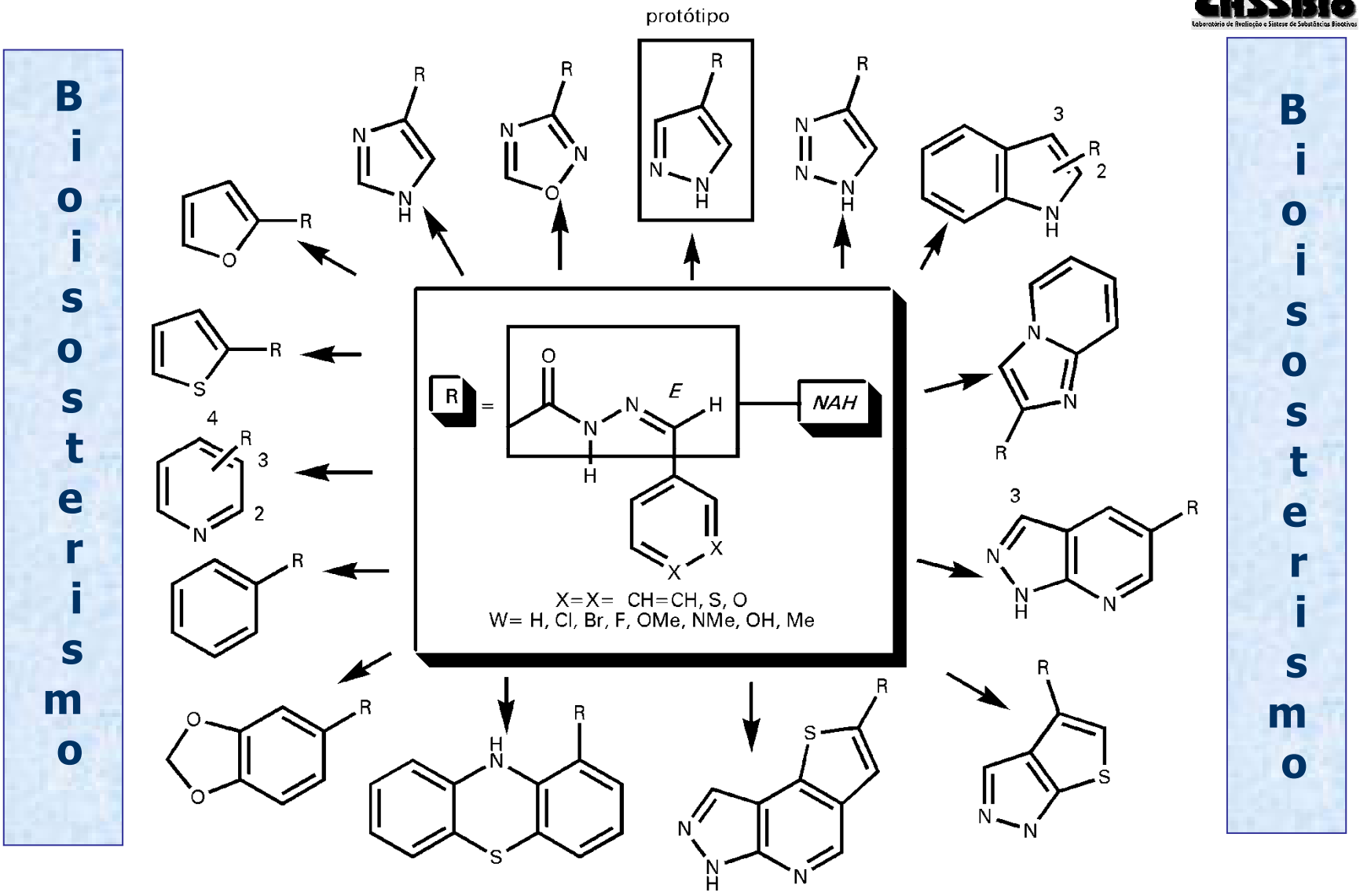
clometacina

Bioisosterismo clássico de anéis



Bioisosterismo na construção de série congênere

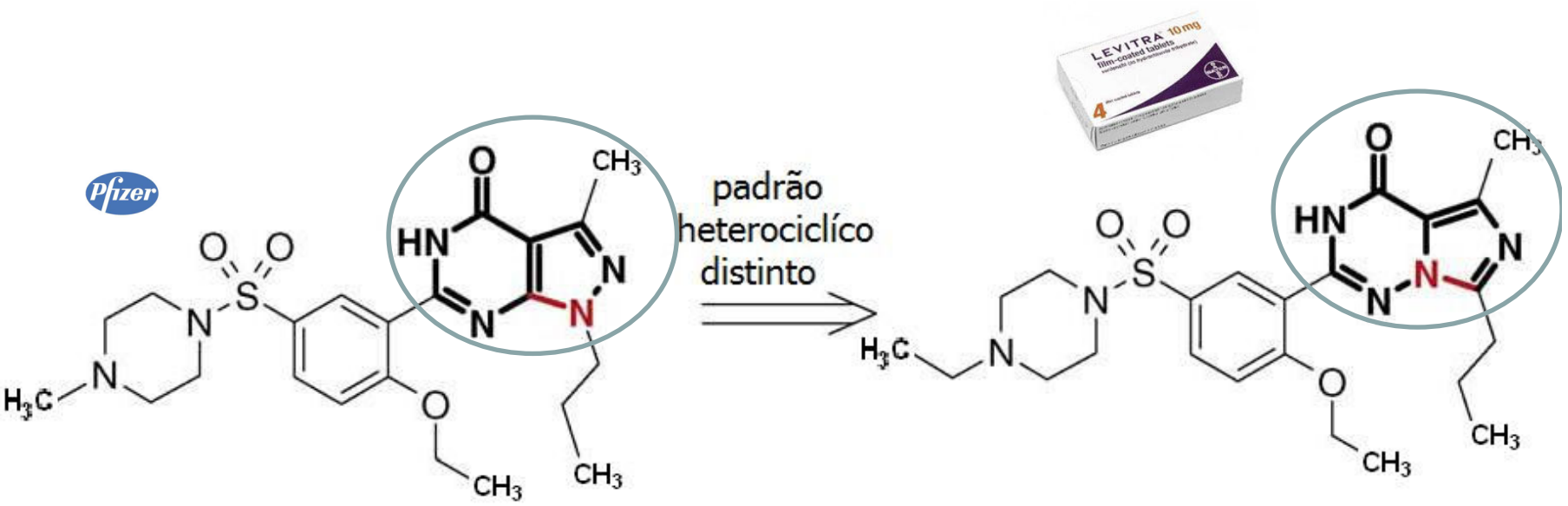
Bioisosterismo



Bioisosterismo

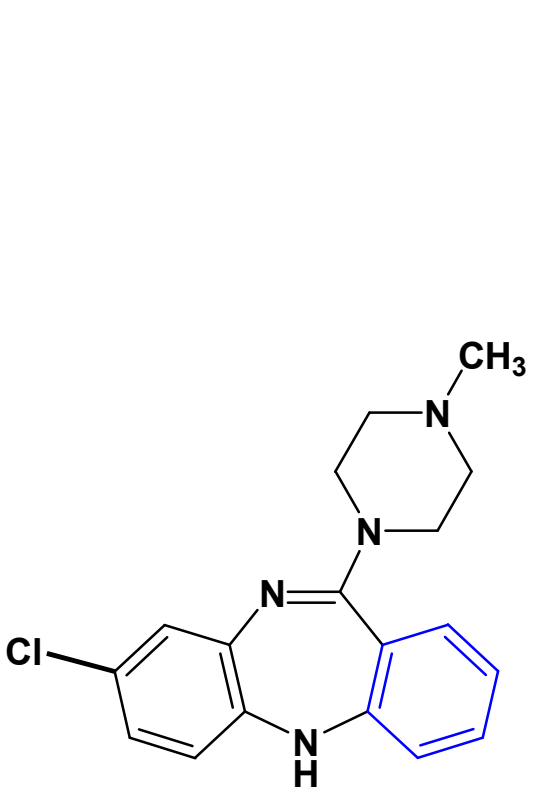
Derivados *N*-acilidrazônicos (NAH)

Fármacos análogos para DE

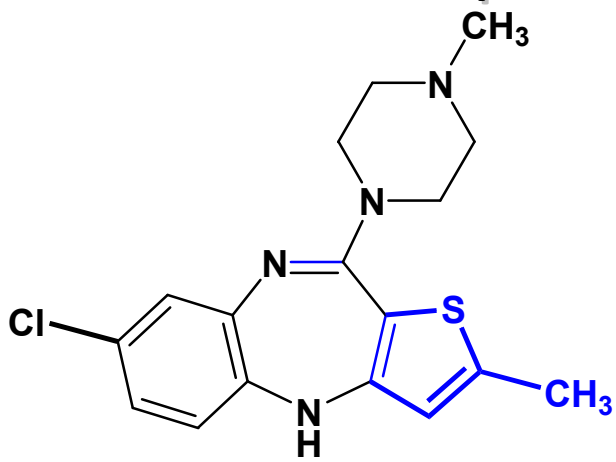


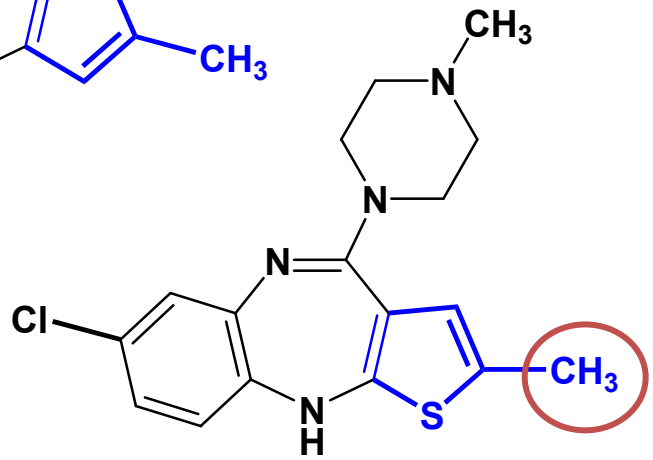
LM Lima & EJ Barreiro, Bioisosterism: A Useful Strategy for Molecular Modification and Drug Design, *Current Medicinal Chemistry*, 2005, **12**, 23-49

Quantos isósteros tiofênicos podemos ter?

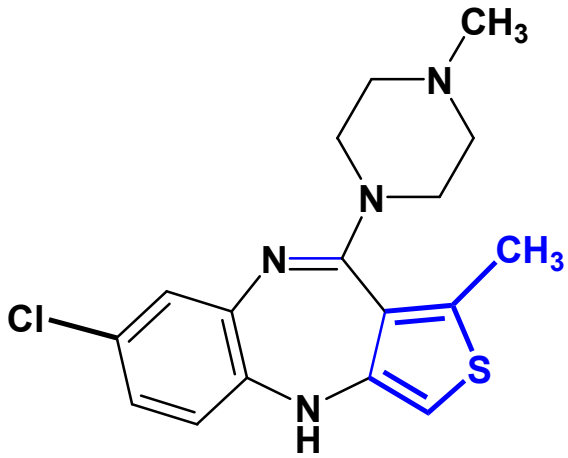


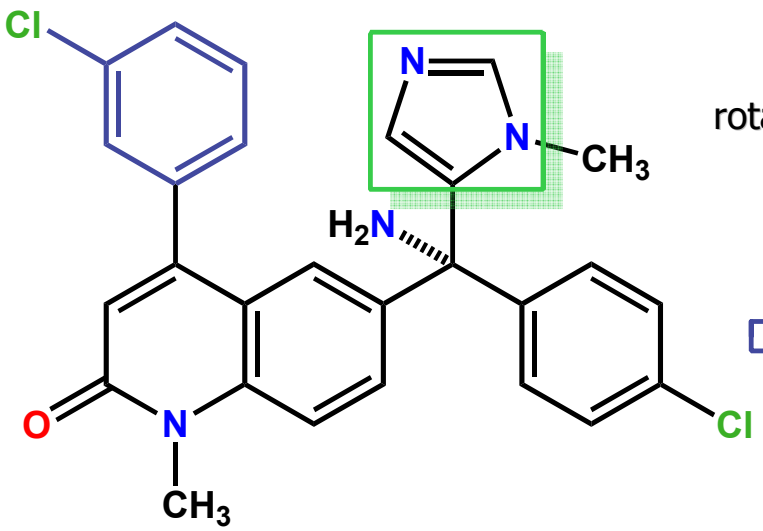
Clozapina





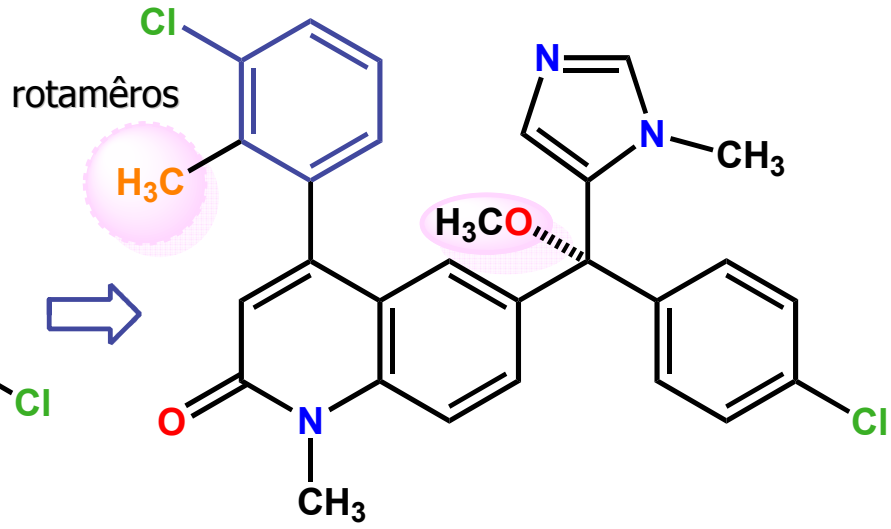
Olanzepina





Tipifarnib

Fase III como anti-câncer



Análogo (4 isomêros)

T cruzy [a)]	EC_{50} = 4 nM	→	6,0 pM
*h*PFT [b)]	IC_{50} = 0,7 nM	→	> 50 μM (<< toxicidez)
T cruzy PFT	inativo		
*h*CYP450 (CYP3A4)			

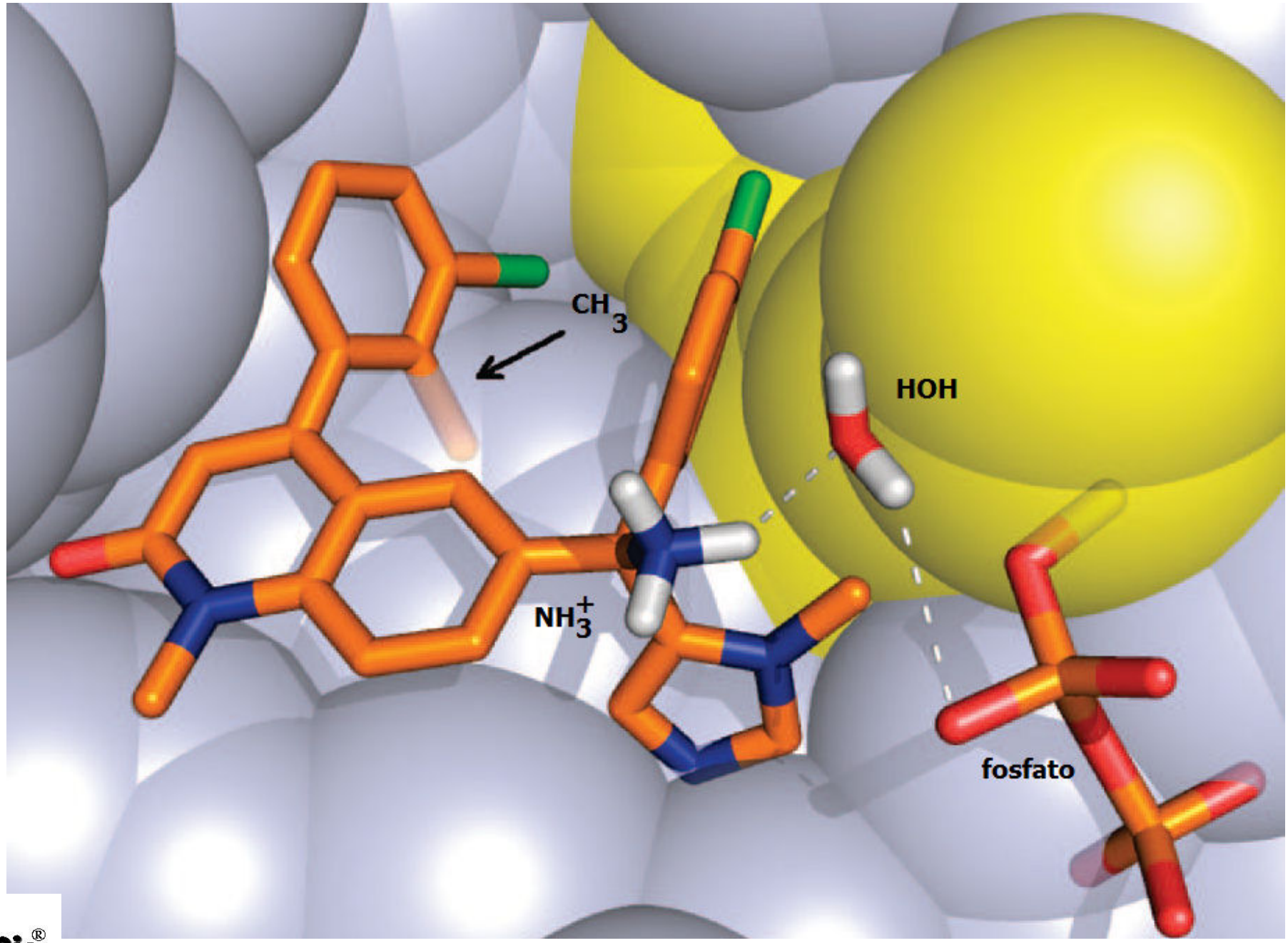
a) inibição da esterol 14α-demetilase (14DM)

b) proteína farnesiltransferase humana

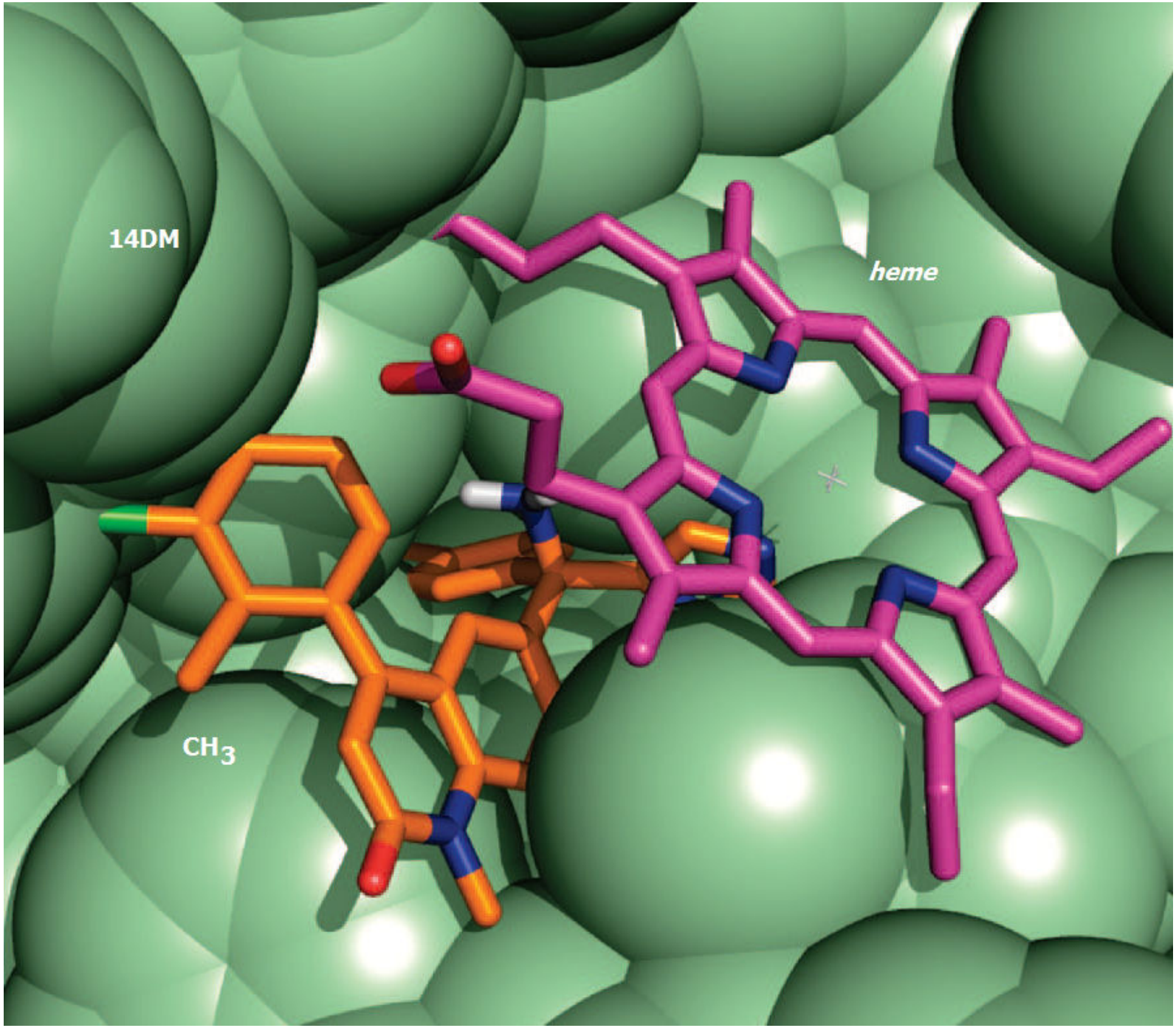
J. M. Kraus *et al*., *J. Med. Chem.* **2009**, *52*, 1639

J. M. Kraus *et al*., *J. Med. Chem*. 2010, *53*, 3887

Bioisosterismo

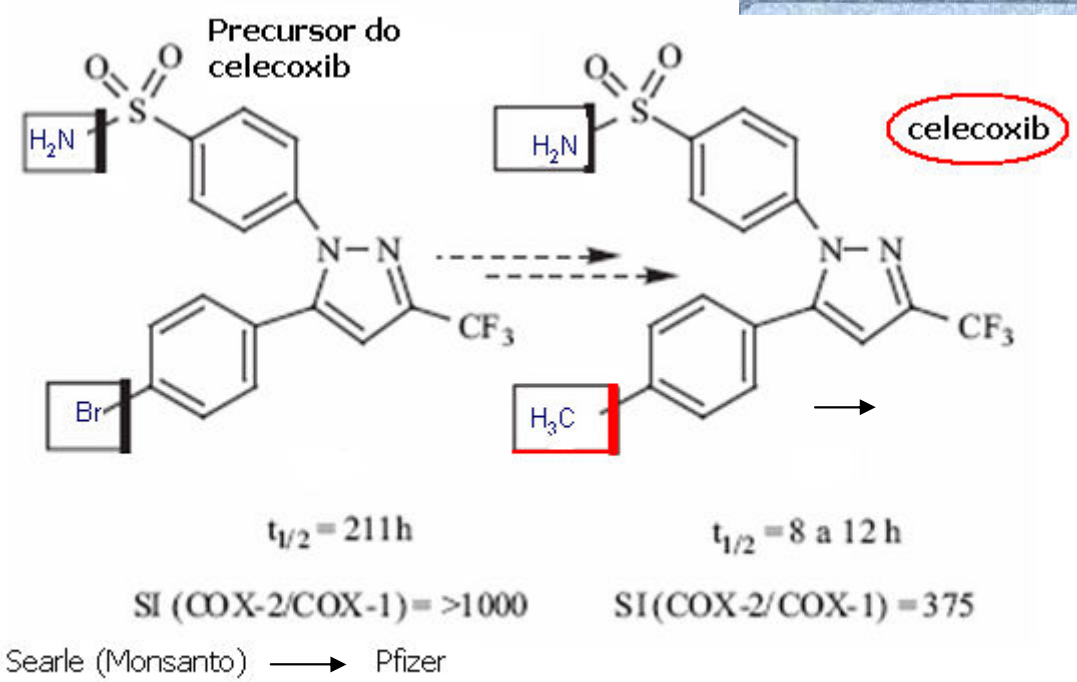


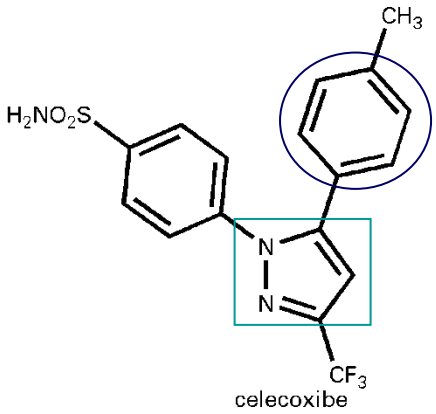
J. M. Kraus *et al., J. Med. Chem.* **2009**, *52*, 1639

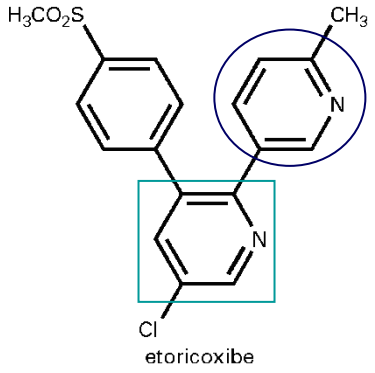


J. M. Kraus *et al., J. Med. Chem.* **2009**, *52*, 1639

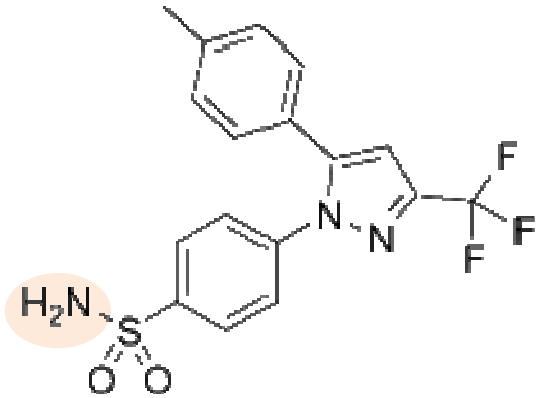
bioisosterismo



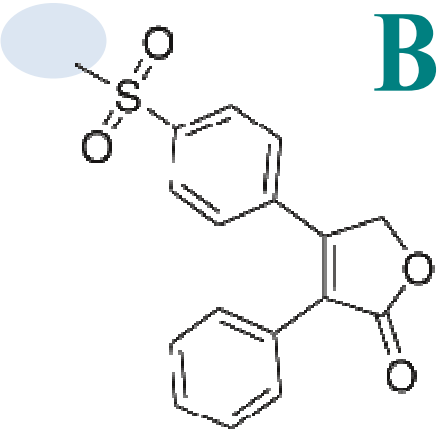




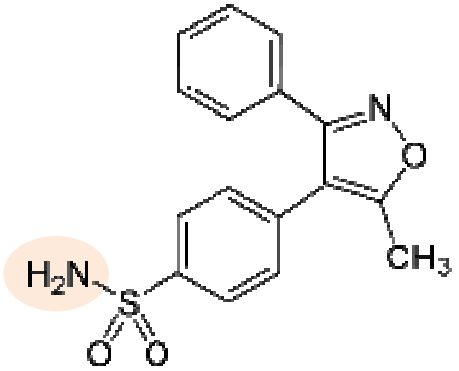
Bioisosterismo



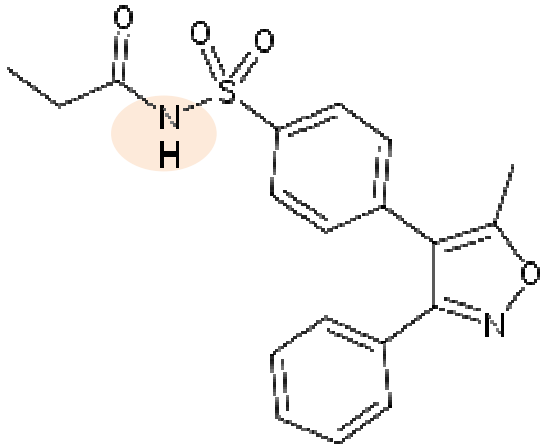
Celecoxibe (**Celebra**^{R})
1999 (Pfizer US$ 30 bi)



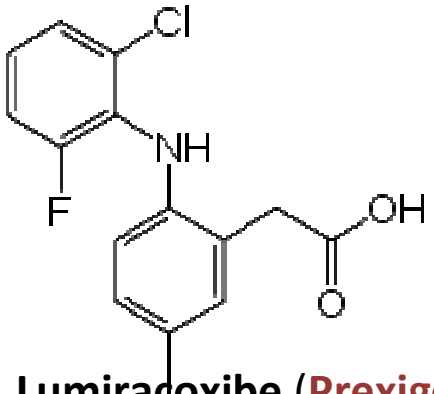
Rofecoxibe (**Vioxx**^{R})
1999 - 2006



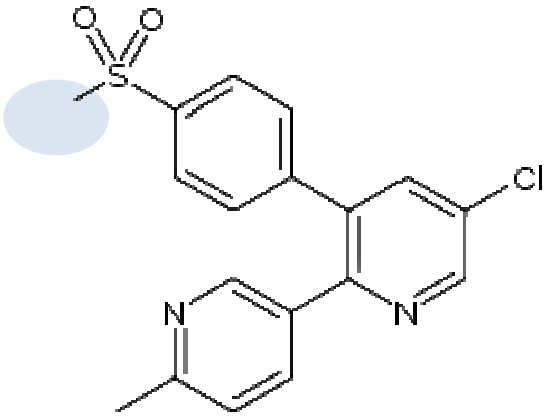
Valdecoxibe (**Bextra**^{R})
2004- 2006



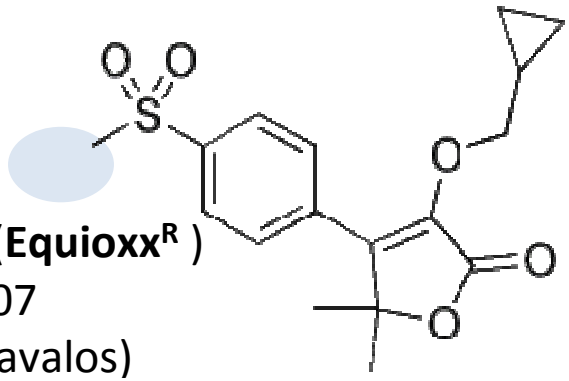
Parecoxibe (**Dynastat**^{R})
2005- 2006



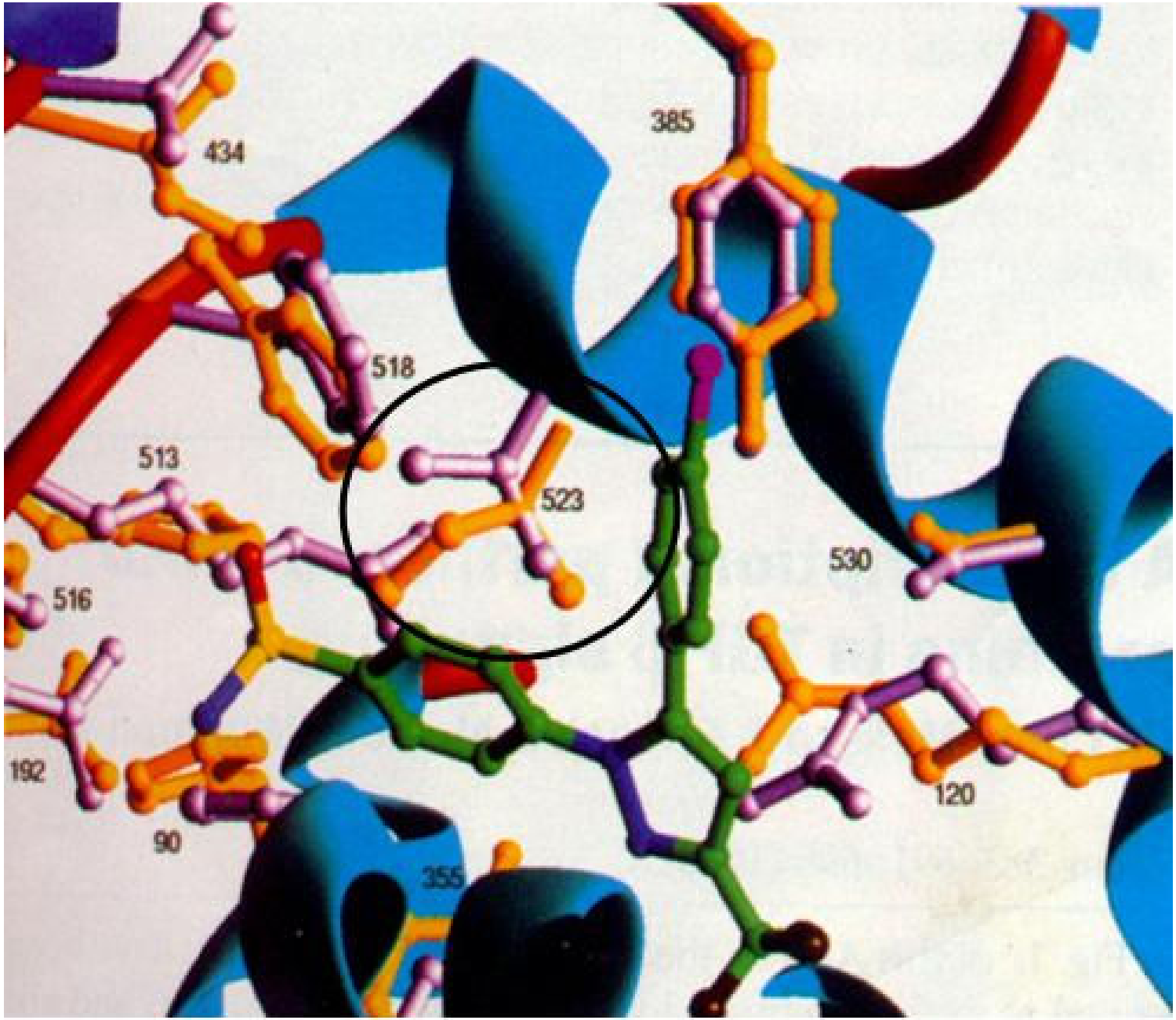
Lumiracoxibe (**Prexige**^{R})
2006- 2007



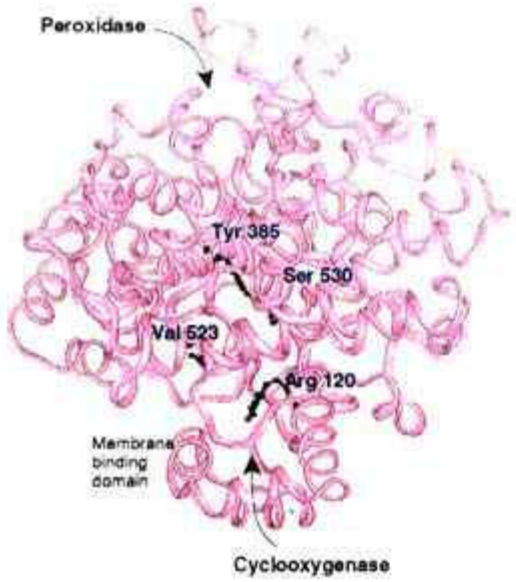
Etoricoxibe (**Arcoxia**^{R})
2007- 2008



Firocoxibe (**Equioxx**^{R})
2007
(FDA - cavalos)

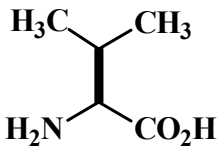


Kurumbail, R. G. *et. al.*, *Nature* (1996) 384: 644-648

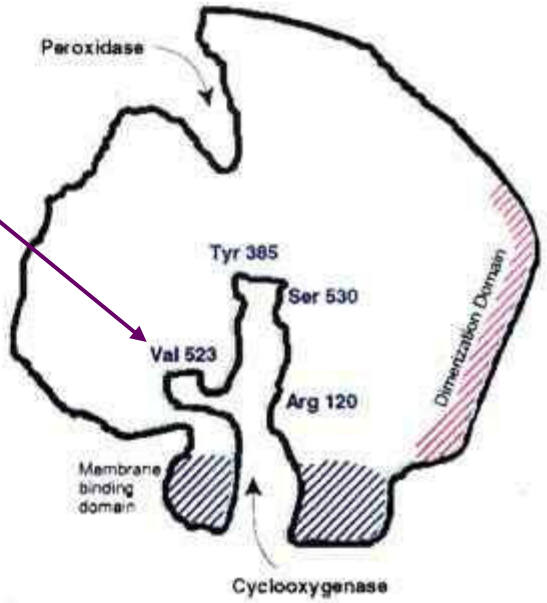


COX-2

Secundary pocket site

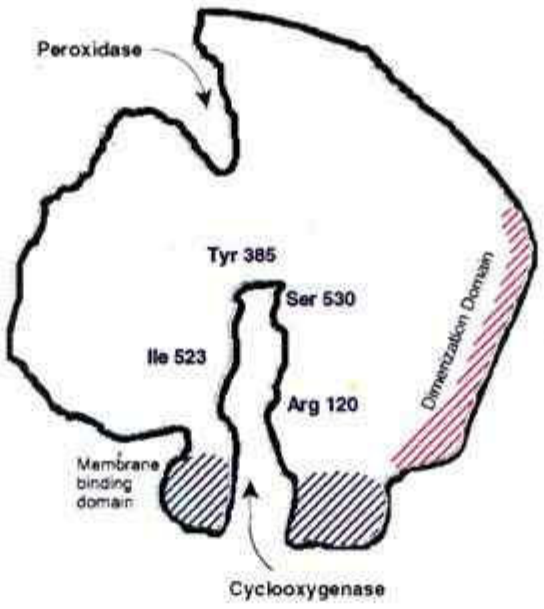


$C_5H_{11}NO_2$
Valina



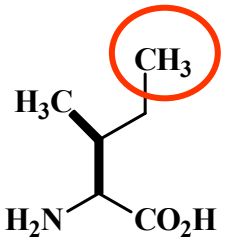
Inflamação,
Câncer
Endotélio vascular
Rins
Cérebro

COX - 2 Inhibitors

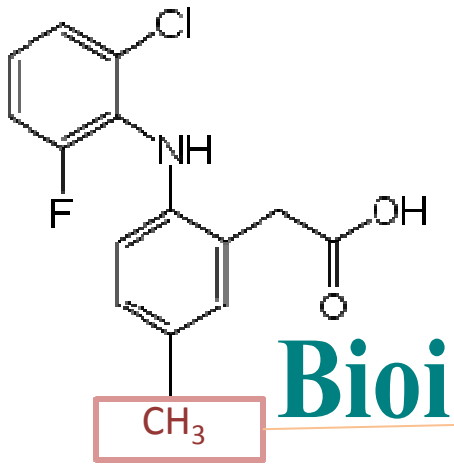


Plaquetas,
Estômago,
Rins

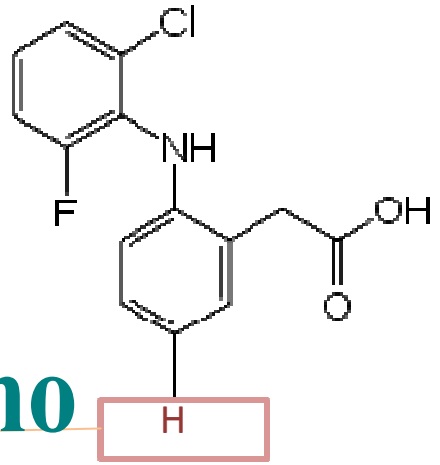
COX-1



$C_6H_{13}NO_2$
Isoleucina



Bioisosterismo



Lumiracoxibe

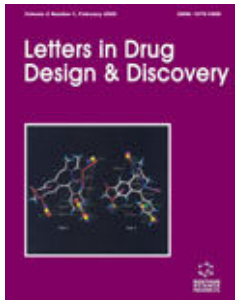
Diclofenaco

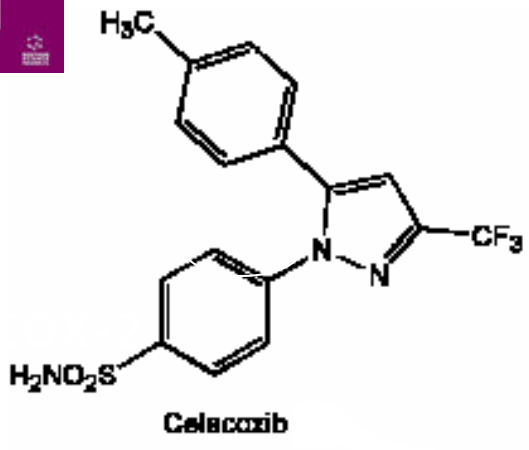
COX-2 > COX-1

COX-1 >>>>>> COX-2

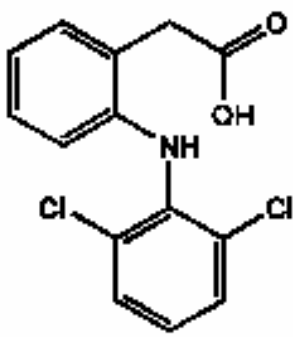
The Molecular Basis of COX-2 *versus* COX-1 Selectivity of Lumiracoxib by Molecular Docking

Célia Maria Corrêa, André Figueira de Paula, Gilberto M. Sperandio da Silva, Carlos M. R. Sant'Anna, Carlos A. M. Fraga, Eliezer J. Barreiro

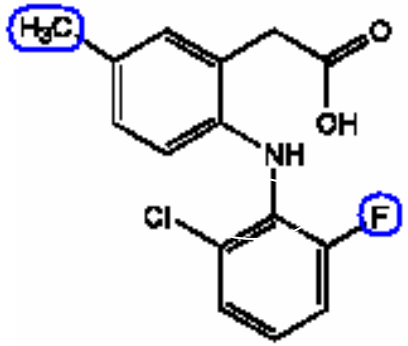




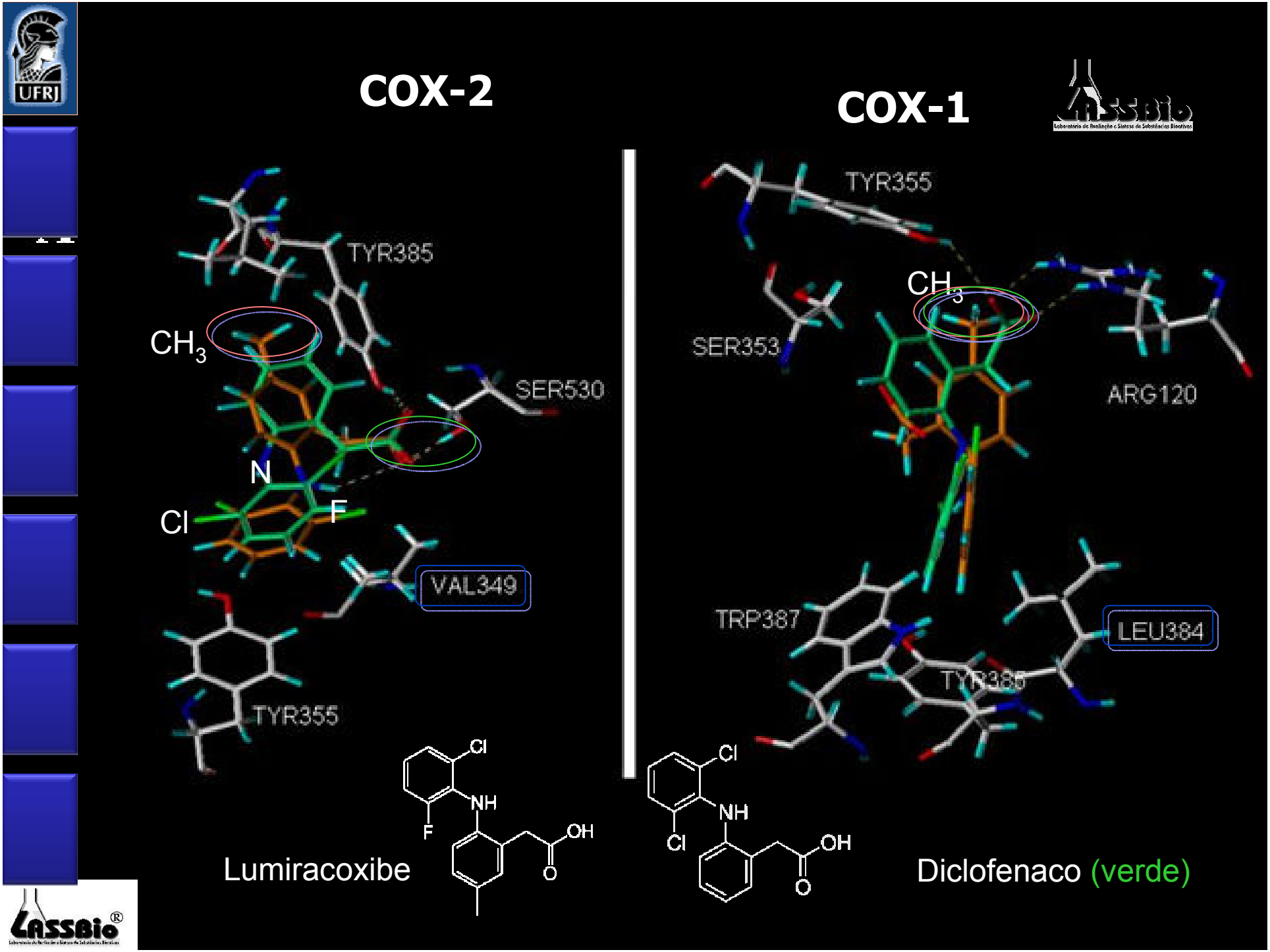
Celecoxib



Diclofenac

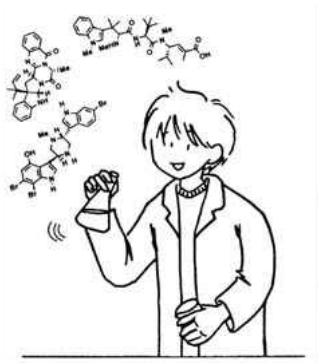


Lumiracoxib


COX-2
COX-1
TYR385
CH3
SER530
N
Cl
F
VAL349
TYR355
TYR355
CH3
SER353
ARG120
TRP387
LEU384
Cl
NH
F
OH
O
Cl
NH
Cl
OH
O
Lumiracoxibe
Diclofenaco (verde)

Physiologic approach
A abordagem fisiológica

Química Medicinal



Inovação farmacológica

Modificação molecular

hit/ligante

Biorreceptor

Bioligante

Novo protótipo

Protótipo otimizado

Otimização do Protótipo

Simplificação Molecular

Desenho estrutural

Eleição do alvo-terapêutico

Fármaco

Bioensaios

In vitro/in vivo

Hibridação Molecular

Ausência de toxicidade

Abordagem Fisiológica

Bioisosterismo

Série congênere

Ensaios clínicos

Análogo-ativo

Contribuições farmacofóricas

Ensaios pré-clínicos

A simplificação molecular...

validação precoce do alvo-terapêutico

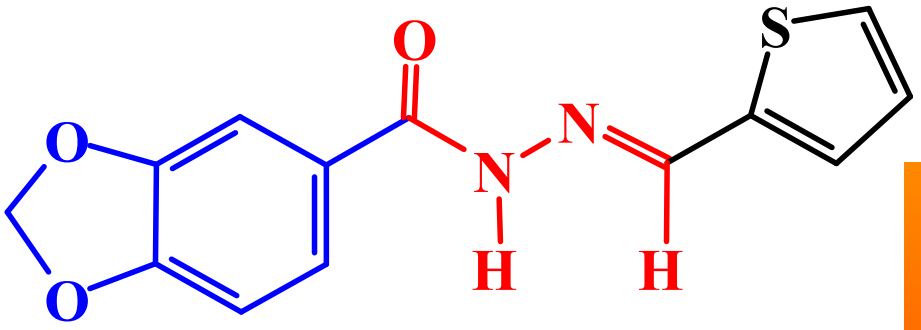
Química Medicinal

A estratégia da simplificação molecular

Compreende a utilização de técnicas de modificações estruturais, em um dado composto bioativo, de forma a reduzir sua complexidade estrutural originando uma nova substância com a mesma atividade farmacológica do padrão original

Novo Protótipo de Fármaco Cardioativo

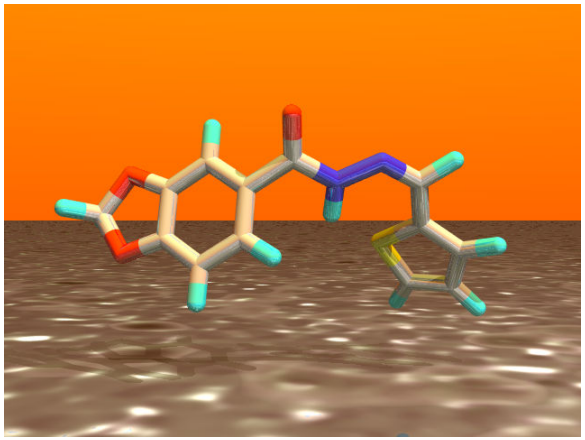
Simplificação molecular



$C_{13}H_{10}N_2O_3S$

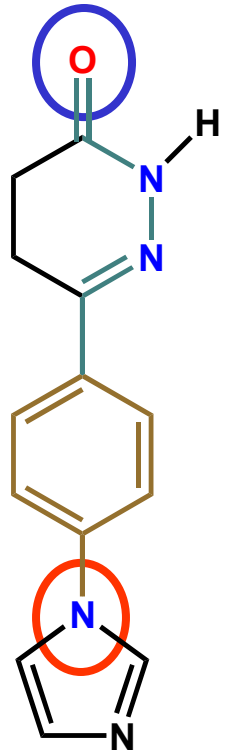
MW 274

LASSBio-294

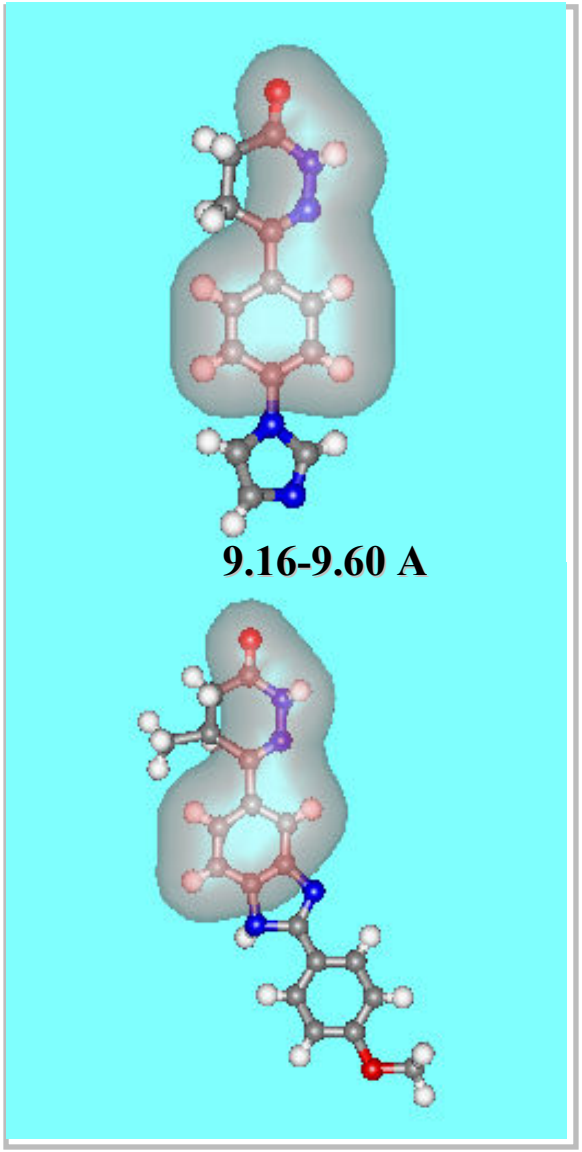


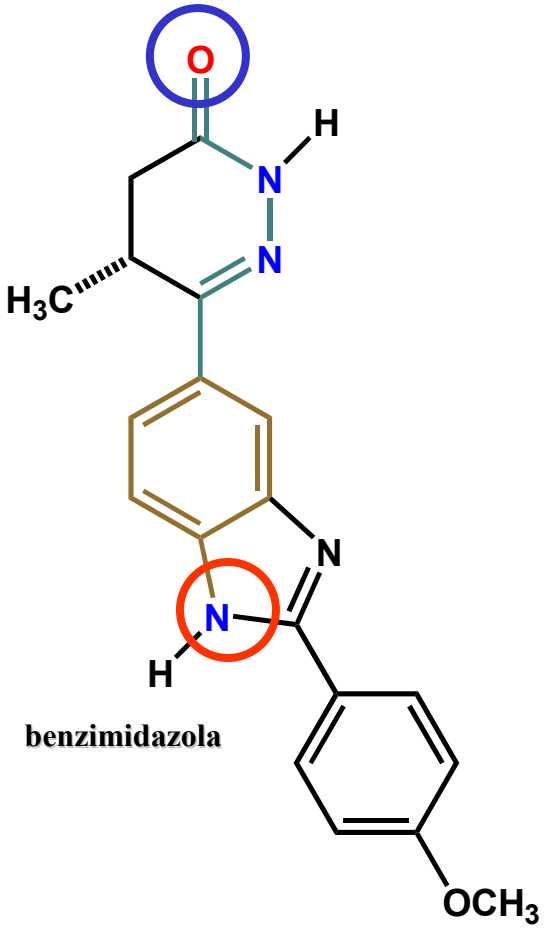
Inibidores de PDE-3

Efeito inotrópico positivo



imazodana



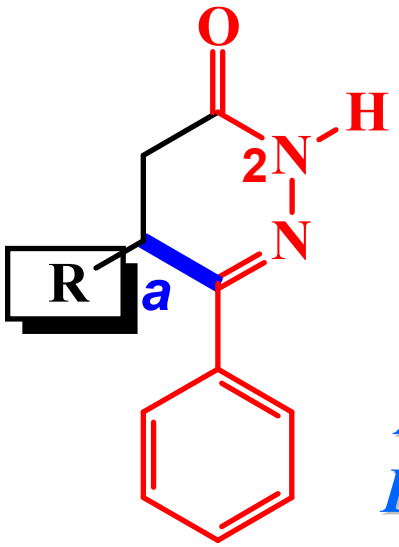


benzimidazola

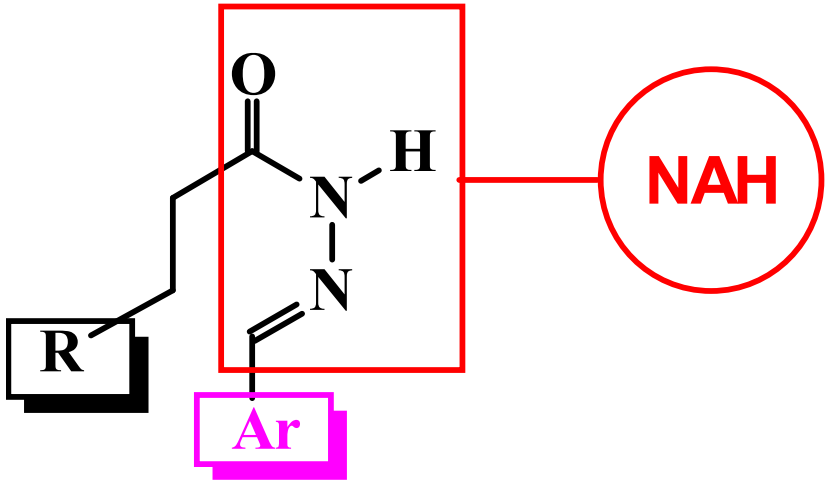
pimobendana

5-metil-3(*2H*)-piridazinona

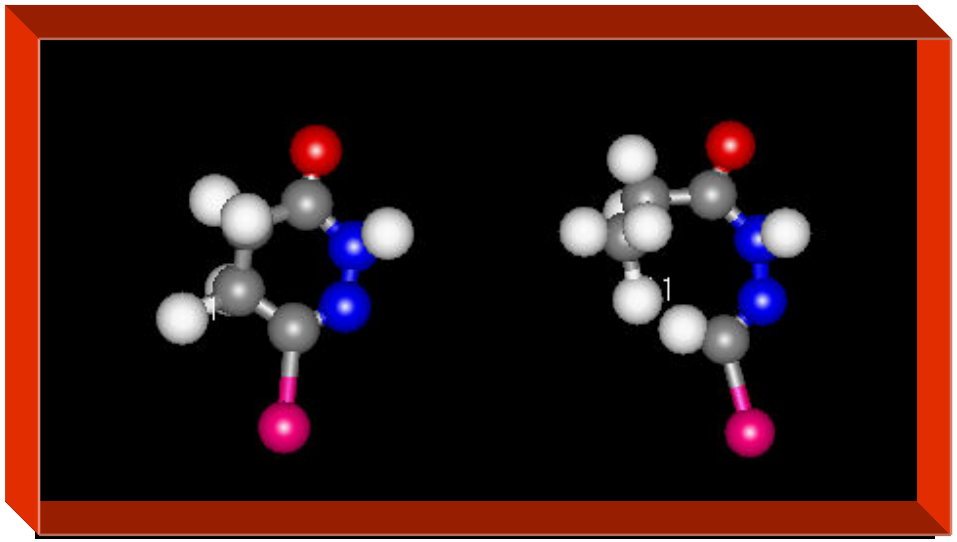
2*H*-piridazinonas & NAH



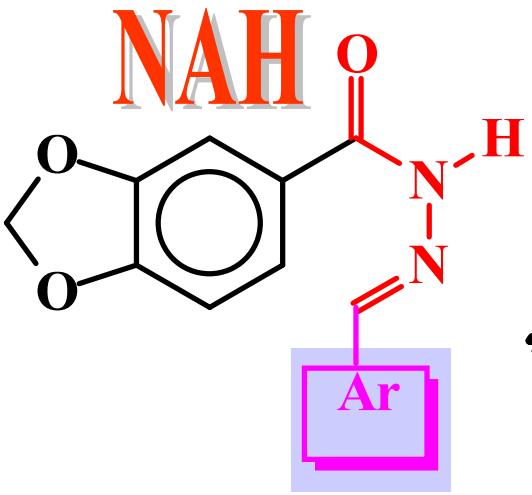
Abertura
Ligação a



Reconhecimento da similaridade molecular



Simplificação molecular



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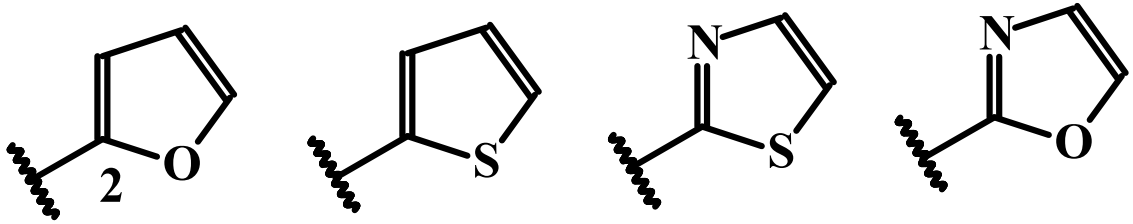
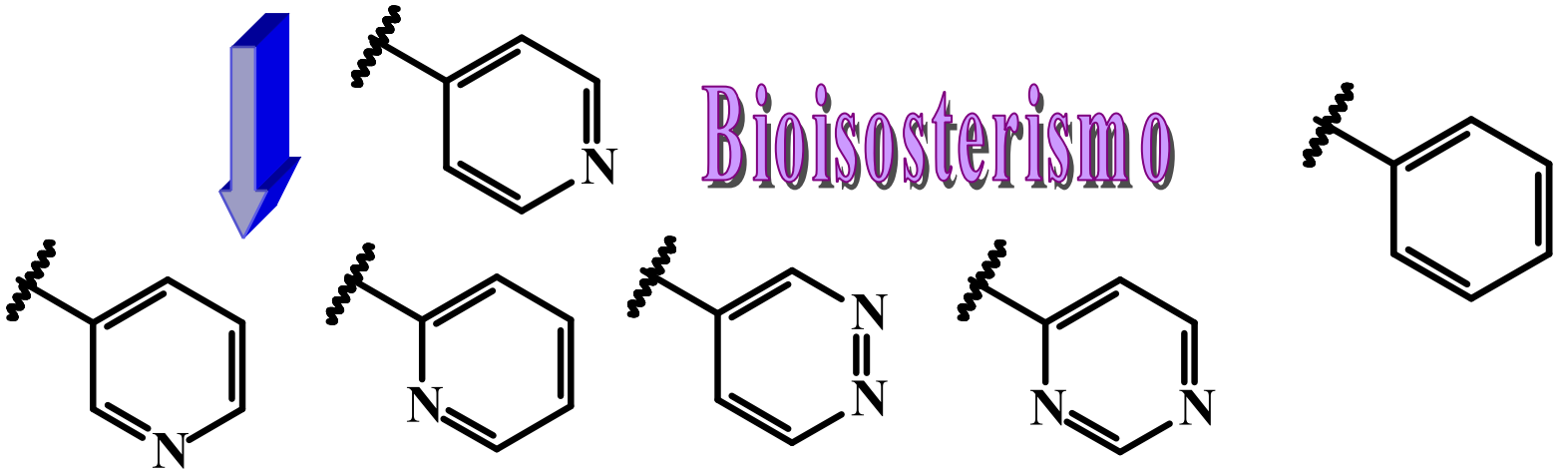


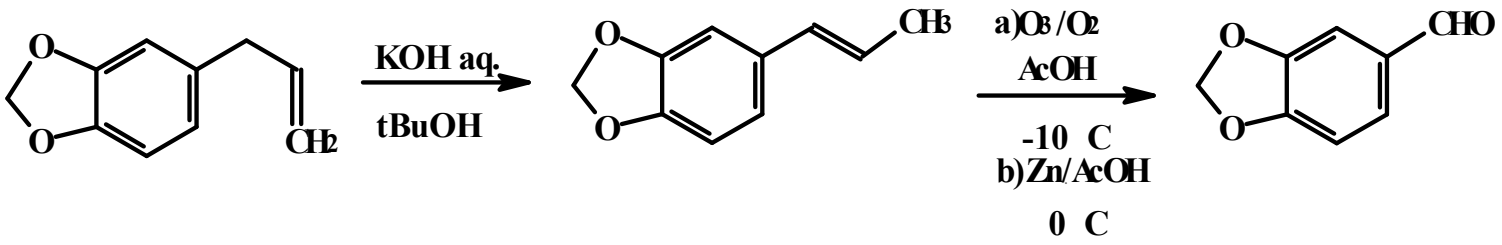
lead compound

Bioisosterismo

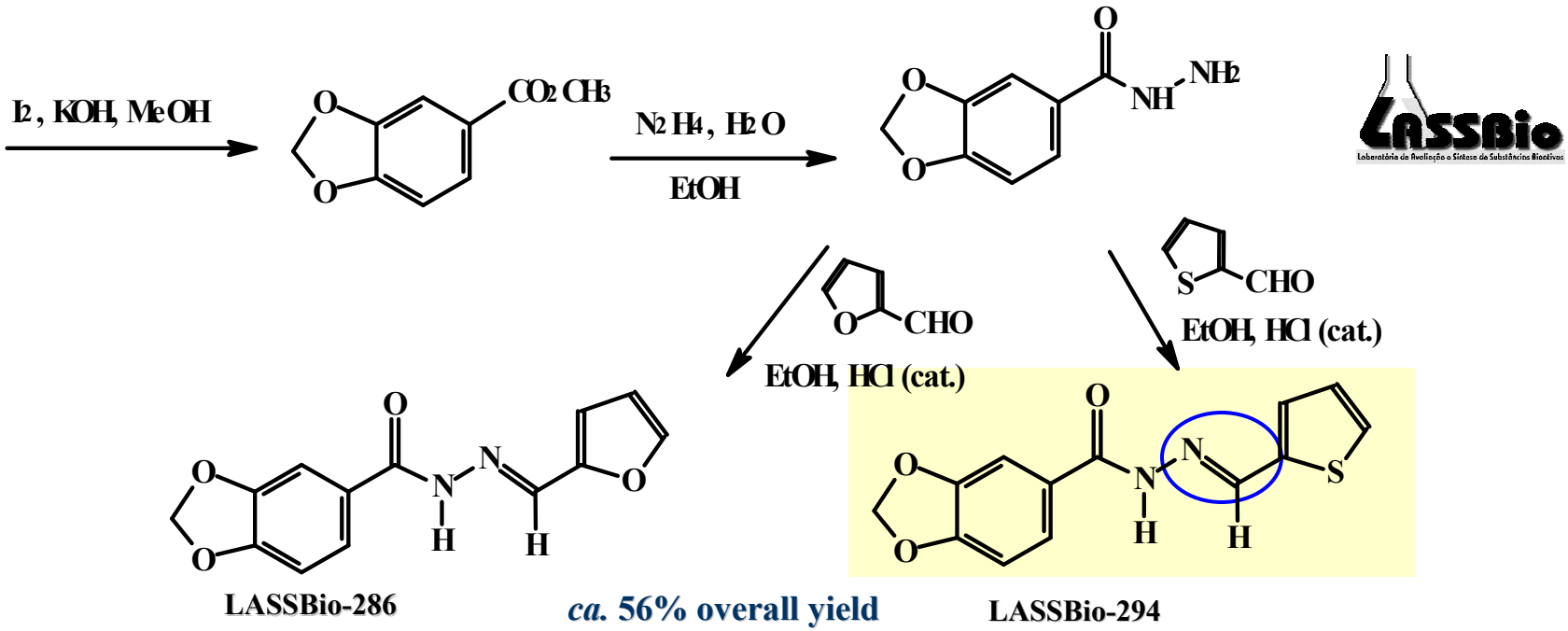


Lima, L. M. Lima, K. C. M. da Silva, P. H. O. Léda, A. L. P. Miranda, C. A. M. Fraga & E. J. Barreiro, "Synthesis and Non-ive Analgesic Activity of Novel *N*-acylarylhydrazones and Isosters, Derived from Natural Safrole", ***Eur. J. Med. Chem.*, *35***, 187 l.

Síntese do LASSBio-294



M.E.F. Lima & E. J. Barreiro, *J. Pharm. Sci.* 1992, *81*, 1219



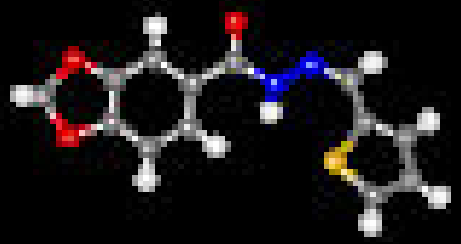
P. C. Lima, L. M. Lima, K. C. M. da Silva, P. H. O. Léda, A. L. P. Miranda, C. A. M. Fraga & E. J. Barreiro, "Synthesis and Non-addictive Analgesic Activity of Novel *N*-acylarylhydrazones and Isosters, Derived from Natural Safrole", ***Eur. J. Med. Chem.*, *35***, 187 (2000).

Propriedades estruturais

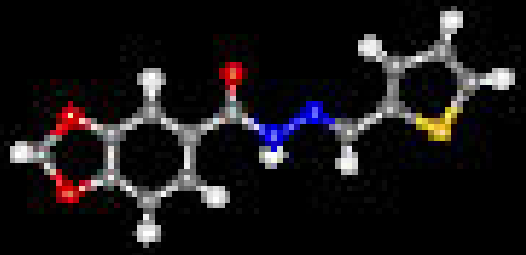
NMR ^{1}H/ ^{13}C

MS

raios-X



NAH



Z-isomêro

E-isomêro

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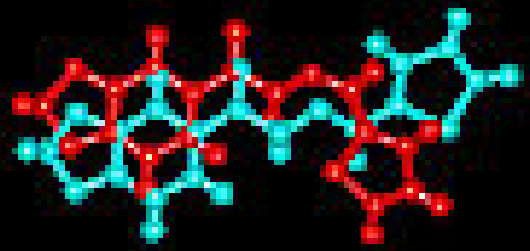


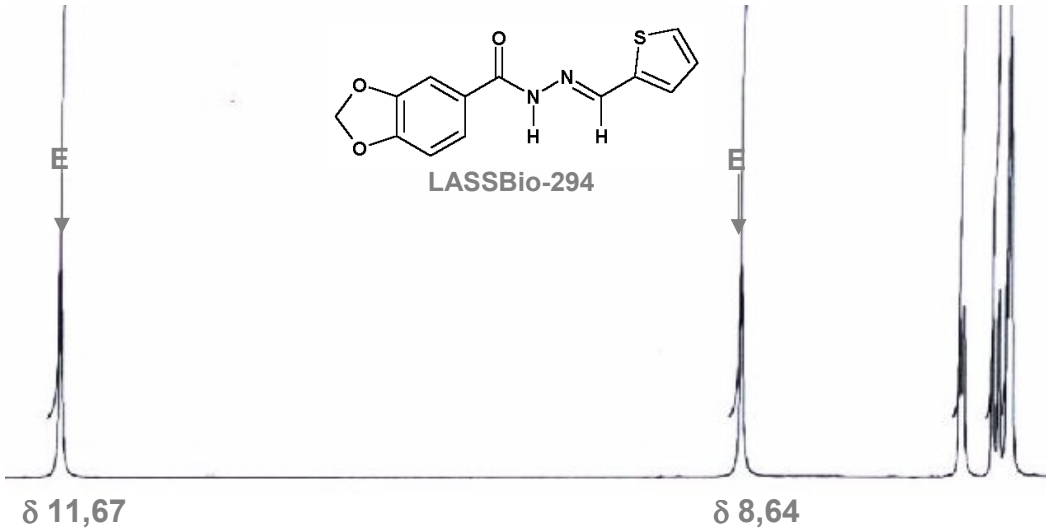
LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

M. R. L. Santos, M. G. de Carvalho, R. Bráz-Filho, E. J. Barreiro, "^{1}H and ^{13}C of New Bioactive Isochromanylactylarylhydrazone Derivatives", ***Magn. Reson. Chem.*** 1998, 36, 533.

L. F. C. C. Leite, E. J. Barreiro, M. N. Ramos, J. B. P. da Silva, S. L. Galdino & I. R. Pitta, "Electron Impact Mass Spectrometry of Some 3-[3-(4-aryl)-1,2,4-oxadiazole-5-yl] acyl arylaldehyde Hydrazone derivatives", ***Spectroscopy*** 2000, 14, 115.

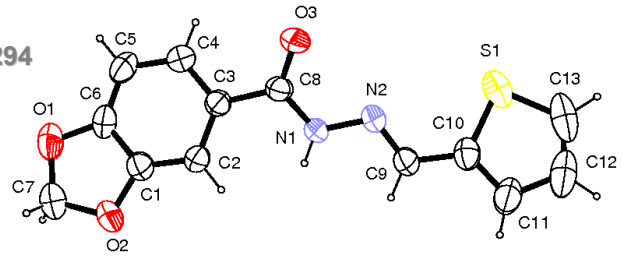
LASSBio®

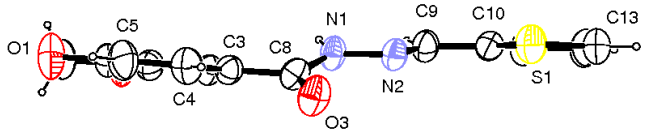
Composto	X	R	δ ¹H
LASSBio-129	O	H	8,32
LASSBio-294	S	H	8,64
LASSBio-787	S	CH_3	8,58
LASSBio 789	S	Br	8,55
LASSBio-790	S	NO_2	8,81 / 8,09
LASSBio-1028	NH	H	8,28



Karabatsos, G.J., *et al.* (1964) *J. Am. Chem. Soc.*, 86, 3351; Karabatsos, G.J., *et al.* (1967) *Tetrahedron*, 24, 3907; ibid (1967) *Tetrahedron*, 24, 3361.

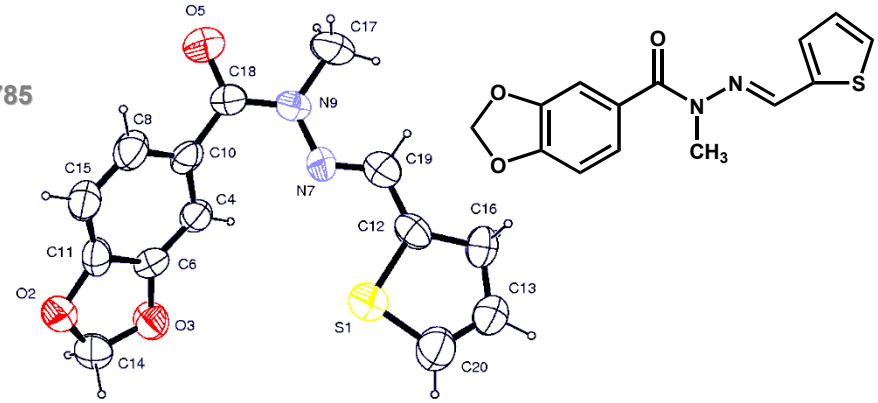
LASSBio-294

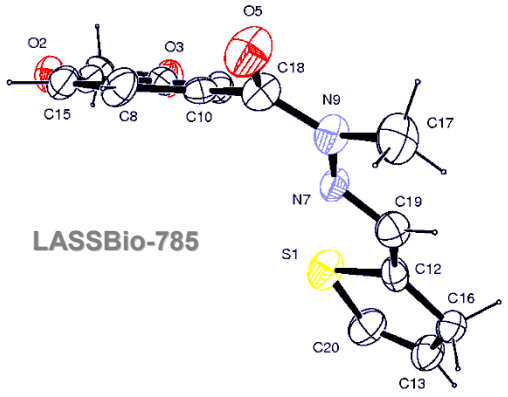




LASSBio-294

LASSBio-785





LASSBio-785

Office of Research & Development

515 West Lombard Street, Suite 500
Baltimore, Maryland 21201
Tel. (410) 706-1874; Fax. (410) 706-5035

LASSBio 294: a novel compound having digitalis-like cardiotonic properties and the potential to reduce muscle fatigue

Tech ID # 1558EA

Prous Sc. Ed., ES

Generic Name: n/a; **Code Name:** LASSBio-294

The functional groups incorporated in the synthetic compound were selected to avoid hepatotoxicity and discourage gastric ionization, thus assuring a reliable oral absorption. The synthesis method developed for compound LASSBio-294 has been optimized.

http://www.inventabrasil.hpg.ig.com.br/ytabela.htm
http://www.comciencia.br/reportagens/farmacos/farma08.htm

Patent (USPTO) 7.091.238 (15/08/2006) ➡ *Cardiotônicos vasoativos*

Patente obtida

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/870,328	Aug. 15, 2006	7,091,238	32360-178943	9691

25694 7590

VENABLE LLP
P.O. BOX 34385
WASHINGTON, DC 20043-9998

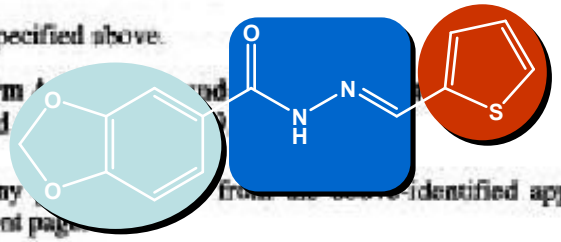
Thienylhydrazone with Digitalis-like properties (positive inotropic effects)

LASSBio-294

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term A... ...od
(application filed



The Patent Term Adjustment is 109 day(s). Any ... ...from the above-identified application include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571) 272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at (703) 305-8283.

Roberto Takashi Sudo, Rio de Janeiro, BRAZIL;
Edson X. Albuquerque, Baltimore, MD;
Eliezer J. Barreiro, Rio de Janeiro, MD;
Carlos Alberto Manssour Fraga, Rio de Janeiro, BRAZIL;
Ana Luisa Palhares De Miranda, Petropolis, BRAZIL;

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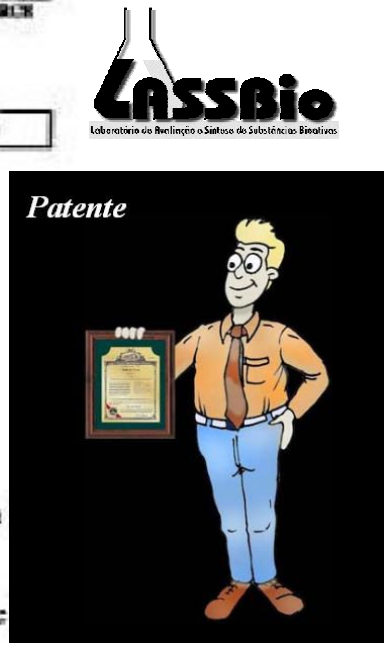
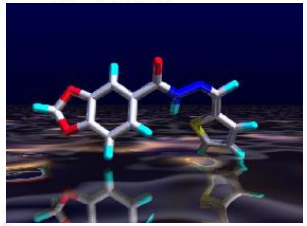
JUL 31 2006
VENABLE IP DOCKETING DEPARTMENT

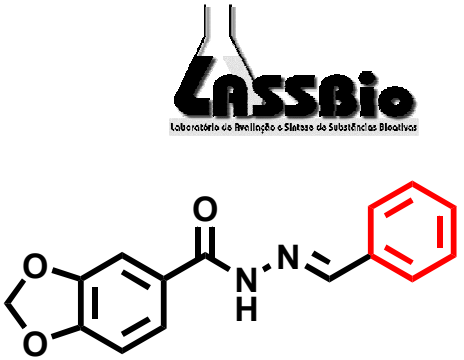
B.109 (Rev. 12/04)



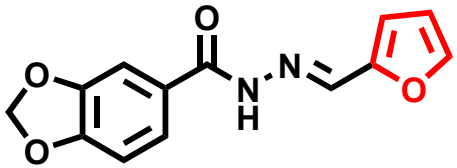
Thienylhydrazone with Digitalis-like properties (positive inotropic effects)



Otimização do protótipo



LASSBio-123



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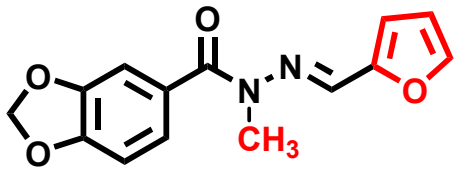

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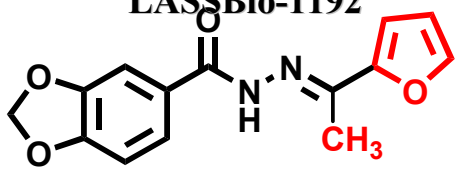

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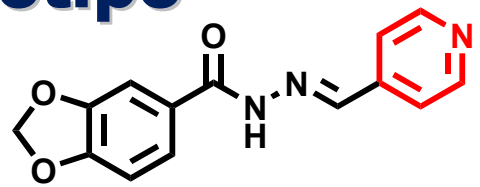
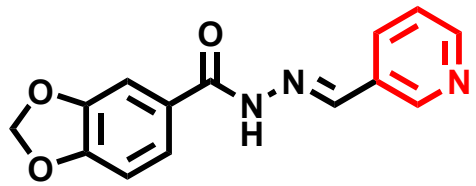
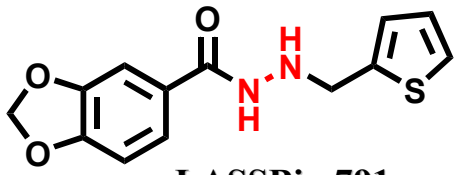
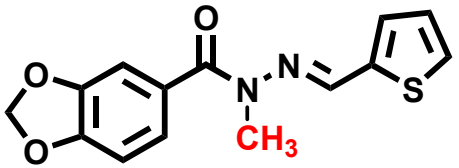




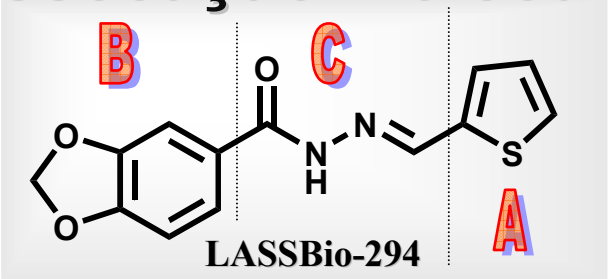


LASSBio-791

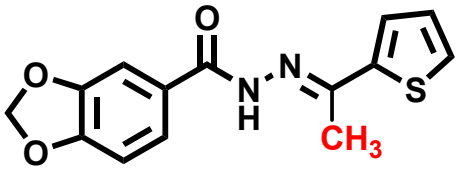


LASSBio-785
IC_{50} = 10,2 µM

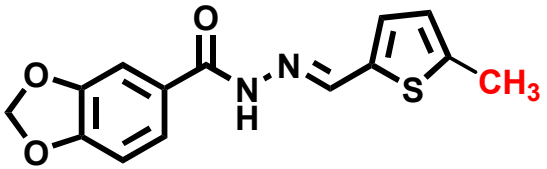
Dissecação Molecular



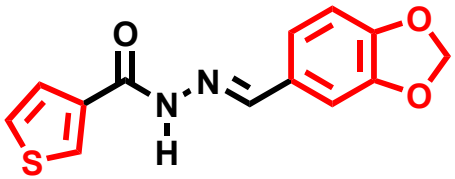
LASSBio-294
(VD) IC_{50} = 74,0 µM



LASSBio-1029



LASSBio-787



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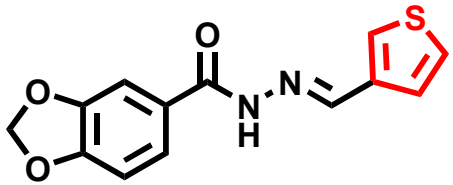

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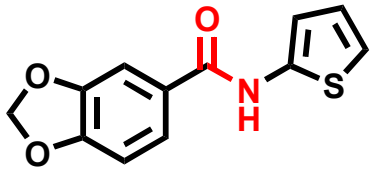
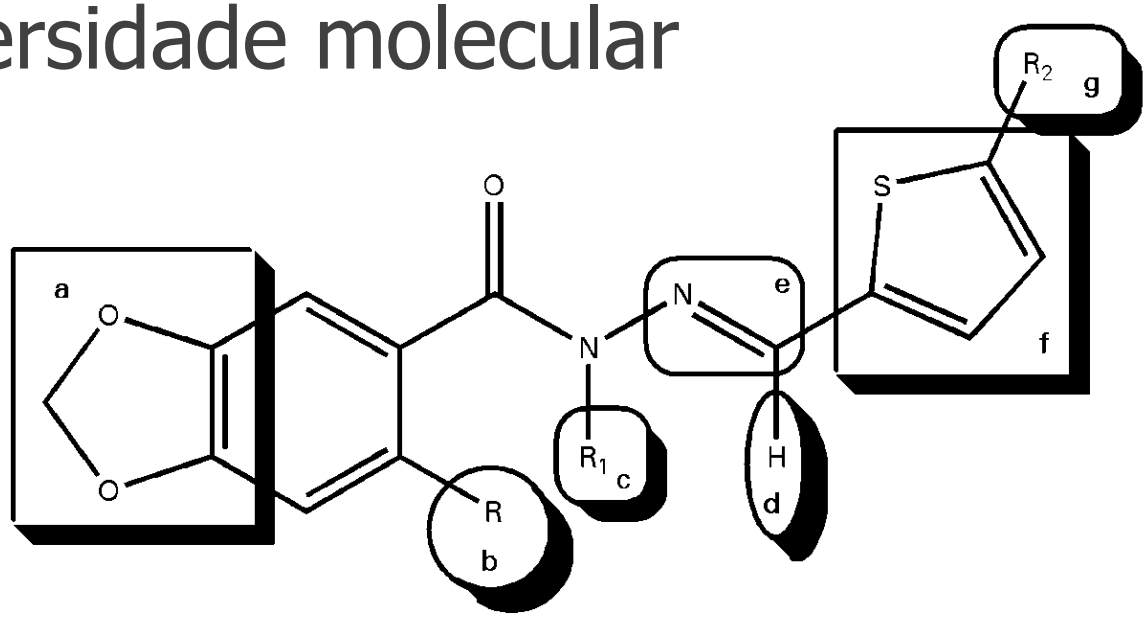


- *Bioorganic Medicinal Chemistry* 2005, **13**, 3431

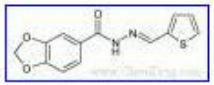
Patente BR PI0403363 9

Diversidade molecular



a= Introdução de grupos com diferente perfil de contribuição estereoeletrônica;
b= Substituinte R na posição 6 do anel benzodioxola- efeitos estereoeletrônicos;
c= Alquilação do grupamento farmacofórico- Modificação da habilidade como doador de ligação de H, Alterações conformacionais;
d= Introdução de substtuintes alquila- Efeitos estéricos e/ou conformacionais;
e= Redução da dupla ligação imínica- Modificações da extensão de conjugação do grupamento farmacofórico; aumento da liberdade conformacional;
f= Troca do anel tiofeno por núcleos isostéricos om diferentes contribuições eletrônicas;
g= Introdução de grupos com diferente perfil de contribuição estereoeletrônica.

Google lassbio-294 Pesquisar imagens Voltar aos resultados de imagens



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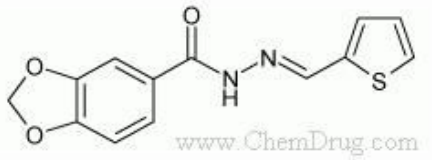
您现在的位置： >> 专业资料首页 >> 药物合成数据库 >> L-294, LASSBio-294,314021-07-3,C13-H10-N2-O3-S,(E)-N'-(Thien--药物合成数据库

【药物名称】 L-294, LASSBio-294

【化学名】 (E)-N'-(Thien-2-ylmethylene)-1,3-benzodioxole-5-carbohydrazide

【CAS登记号】 314021-07-3

【结构式】



【分子式】 C13-H10-N2-O3-S

【分子量】 274.299

【原研厂家】 LASSBio (Originator), University of Maryland (Originator)

【作用类别】 CARDIOVASCULAR DRUGS, Cerebrovascular Diseases, Treatment of, Heart Failure Therapy, NEUROLOGIC DRUGS, Positive Inotropic Agents, Phosphodiesterase III Inhibitors

AD-8717,181821-99-8,N-(2,6 DMP-802,,3-[2-[3-(4-Amidino

Zonampanel, YM-872,21024 SB-221284,196965-14-7,5-(

推荐专业资料

ZINC00145813,ST5197865,	Oprea1_826548,MLS000122
ZINC00151021	IUPAC Name: 3-(2-chlorophe
ZINC00257502	MLS000716050,BAS 078671
STK138182,ZINC00302421,	IUPAC Name: (3E)-3-[(4-etho
Oprea1_091018,ST031273,	ZINC00104509
ZINC00084075	IUPAC Name: (2R)-1-(4-meth
IUPAC Name: (1R,,6R)-6-[(2-	Oprea1_406105
IUPAC Name: 6-hydroxy-1-(2-	ZINC00081150
STOCK2S-20570,ZINC0026	ZINC00214910
ZINC00230690	Oprea1_042214,CBDivE_01

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Quim. Nova, Vol. 25, No. 6B, 1172-1180, 2002

Divulgação

ESTRATÉGIA DE SIMPLIFICAÇÃO MOLECULAR NO PLANEJAMENTO RACIONAL DE FÁRMACOS: A DESCOBERTA DE NOVO AGENTE CARDIOATIVO

Eliezer J. Barreiro*
Departamento de Fármacos, Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, Cidade Universitária, Ilha do Fundão, CP 68006, 21944-190 Rio de Janeiro - RJ

Recebido em 24/1/02; aceito em 17/4/02

STRATEGY OF MOLECULAR SIMPLIFICATION IN RATIONAL DRUG DESIGN: THE DISCOVERY OF A NEW CARDIOACTIVE AGENT. In this article are described examples of the successful use of molecular simplification strategy in the discovery of new drugs from bioactive natural products and synthetic compounds. The discovery of a new cardiotonic derivative (37, 2-thienylidene-3,4-methylenedioxybenzoylhydrazine; LASSBio-294), efficiently synthesized from Brazilian natural product and structurally designed by molecular simplification of active pyridazinone compounds reported in the literature, is described. A brief description of the pharmacological profile of this new cardiotonic lead-compound, belonging to the *N*-acylhydrazone (NAH) class, is also reported herein.

Keywords: new cardiotonic derivative; bioactive *N*-acylhydrazone compound; LASSBio-294.

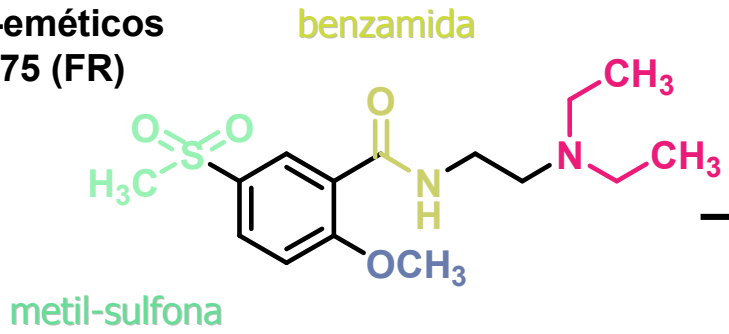
Química Medicinal

A estratégia de anelação molecular

Compreende a introdução planejada de modificações estruturais na molécula de um composto-protótipo ou de um fármaco conhecido, que reduzam sua liberdade conformacional, visando otimizar seu perfil de atividade.

Anelação Molecular

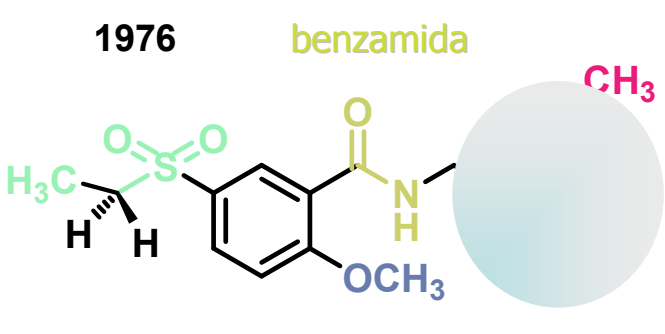
Anti-eméticos
1975 (FR)



tiaprida

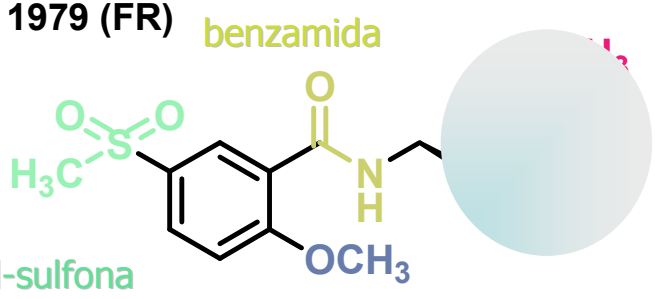
anelação molecular

1976



sultoprida

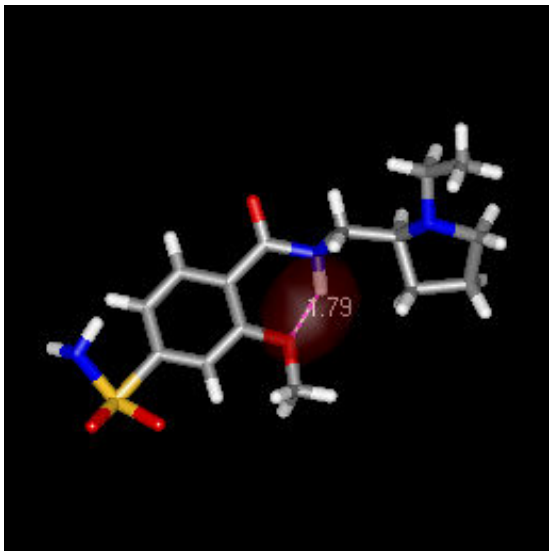
1979 (FR)



sulpirida

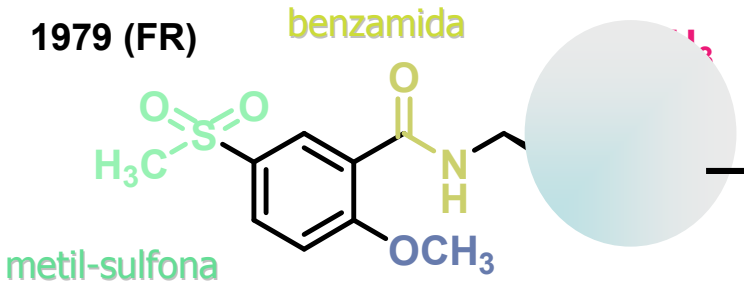
Dolmatil^{R}

Antagonista de receptor D2

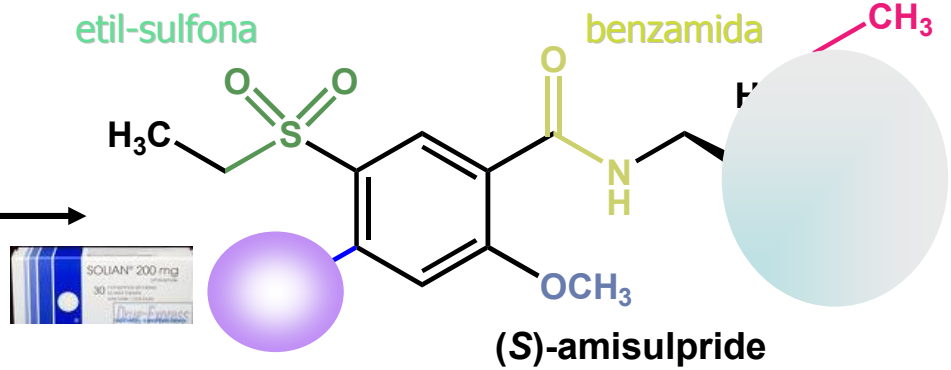


O eutômero S-(-) isômero
D2 >> D3-receptor antagonista
K_i (nM) D-2 = 10
D-1 = 100000

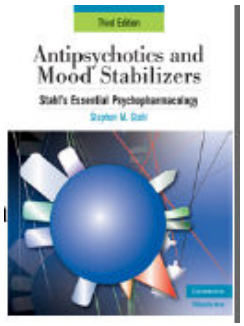
1979 (FR)

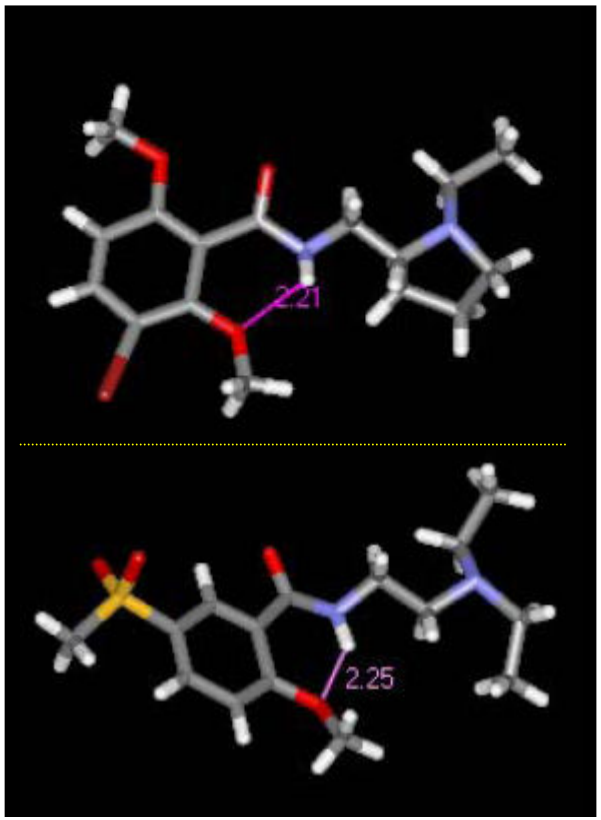


sulpirida

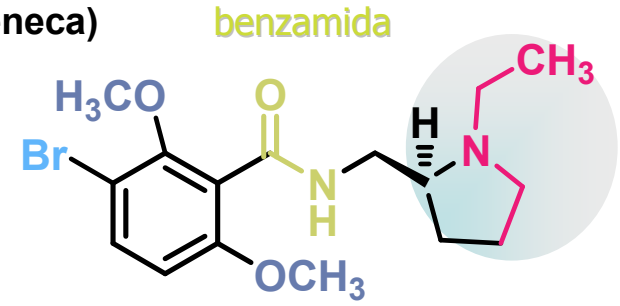


(*S*)-amisulpride

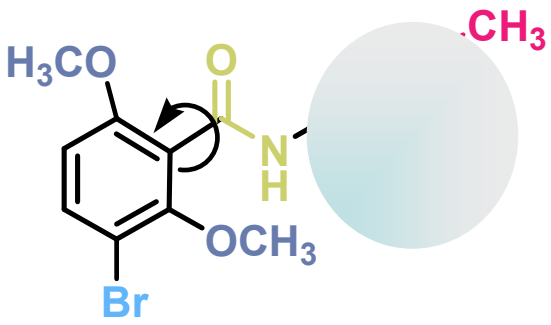




1982 (Astra-Zeneca)

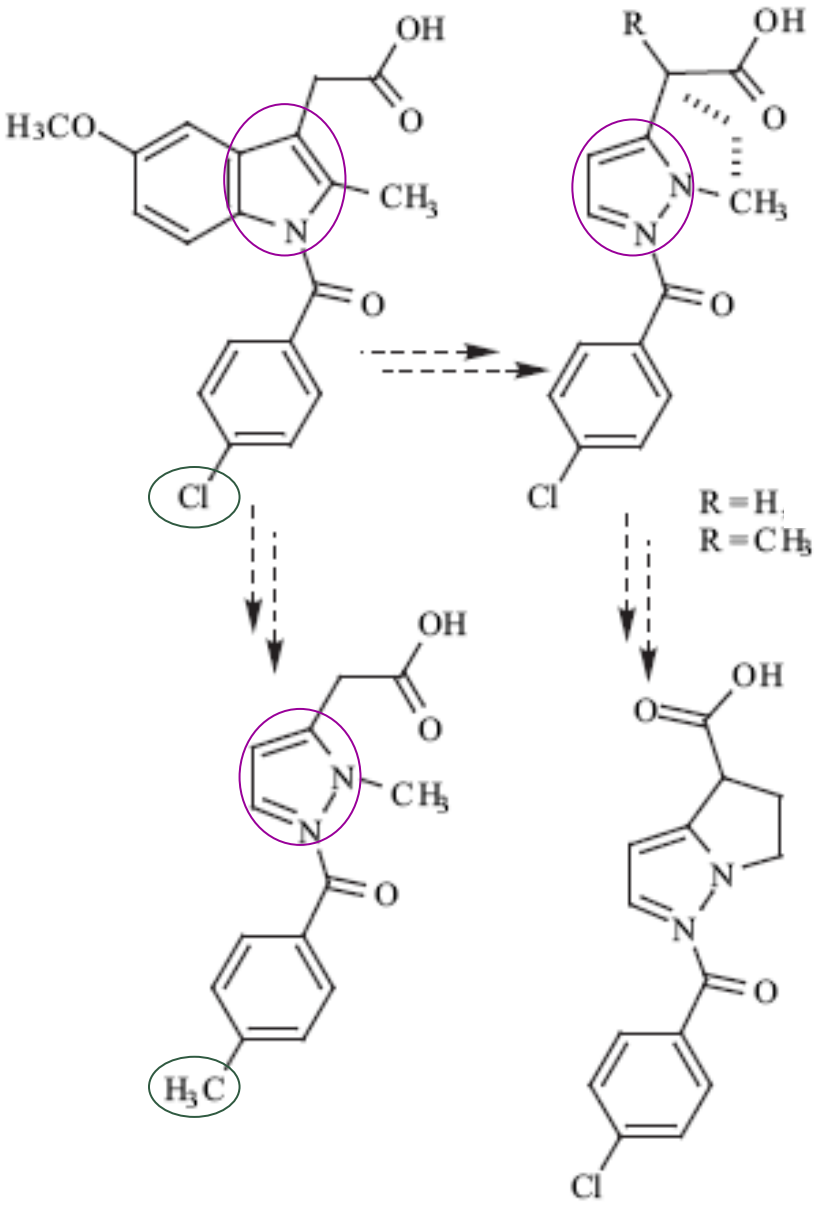


remoxiprida



Antagonista D_2 seletivo
anti-psicótico

bioisosterismo



Anelação molecular

Química Medicinal

A estratégia da Hibridação molecular

Compreende a reunião de características estruturais, parciais, de dois compostos bioativos distintos, numa única nova estrutura, originando uma nova substância que poderá ter a atividade de um dos padrões originais ou conjugar ambas atividades em uma única molécula.

Current Medicinal Chemistry, 2007, *14*, 103-112

Molecular Hybridization: A Useful Tool in the Design of New Drug Prototypes

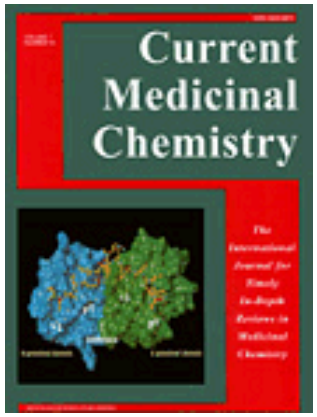
Cláudio Viegas-Junior[1], Amanda Danuello[1], Vanderlan da Silva Bolzani[1], Eliezer J. Barreiro[2] and Carlos Alberto Manssour Fraga[*,2]

[1]*Instituto de Química, Universidade Estadual Paulista "Júlio de Mesquita Filho", P.O. Box 355, 14801-970 Araraquara, São Paulo, SP, Brazil*

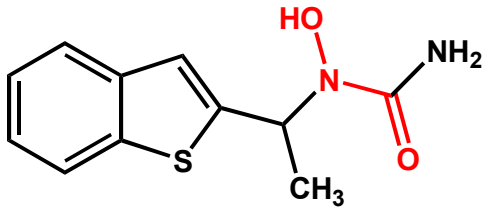
[2]*Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, P.O. Box 68023, 21944-971, Rio de Janeiro, RJ, Brazil*

Abstract: Molecular hybridization is a new concept in drug design and development based on the combination of pharmacophoric moieties of different bioactive substances to produce a new hybrid compound with improved affinity and efficacy, when compared to the parent drugs. Additionally, this strategy can result in compounds presenting modified selectivity profile, different and/or dual modes of action and reduced undesired side effects. So, in this paper, we described several examples of different strategies for drug design, discovery and pharmacomodulation focused on new innovative hybrid compounds presenting analgesic, anti-inflammatory, platelet anti-aggregating, anti-infectious, anticancer, cardio- and neuroactive properties.

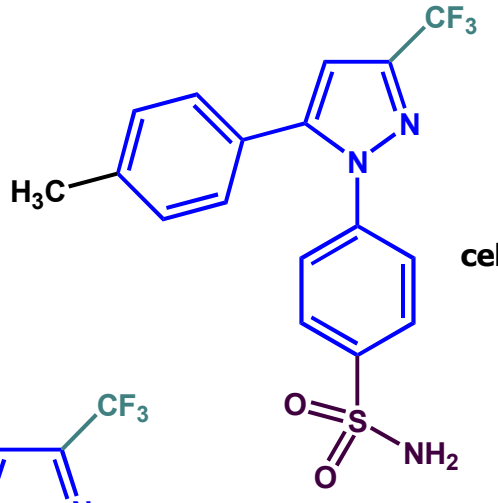
Keywords: Molecular hybridization, Drug design, Hybrid compounds, Pharmacophoric group combination.



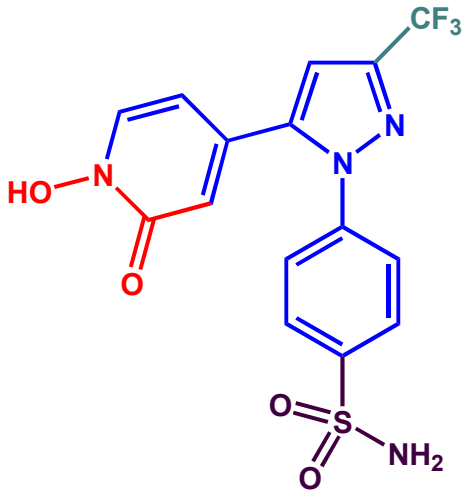
A hibridação molecular



zileuton

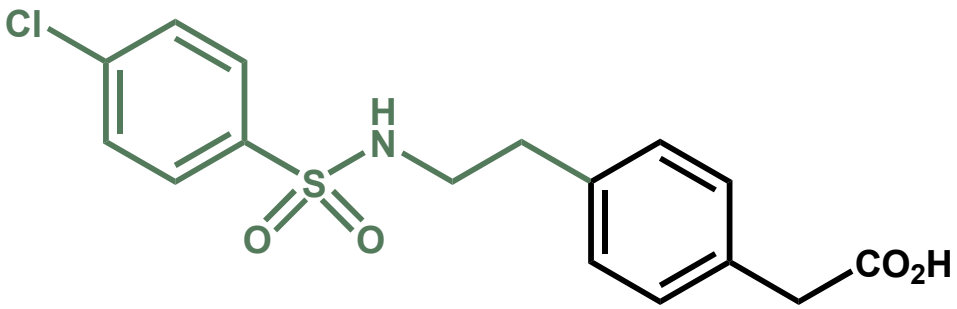


celecoxibe



COX-2/5-LOX

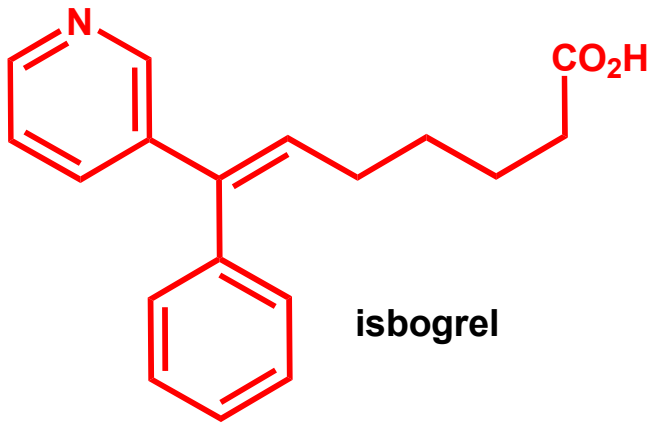
A hibridação molecular



daltrobano

TP IC_{50} = 150 nM

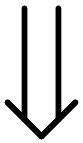
TxS IC_{50} = > 100 μM

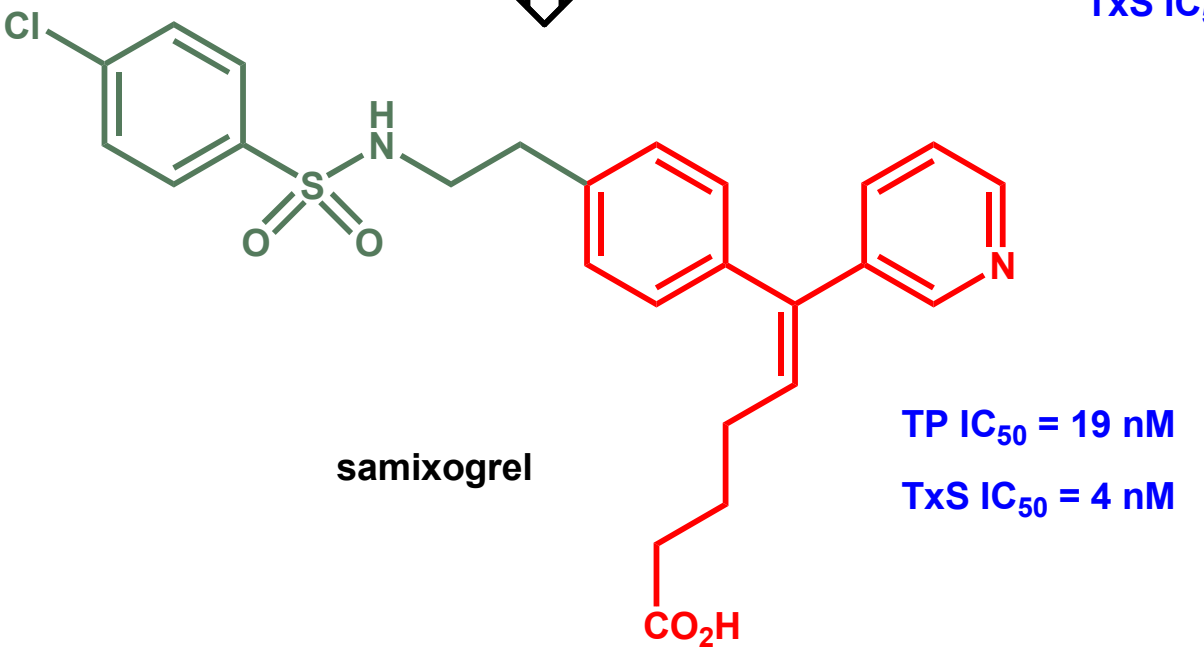


isbogrel

TP IC_{50} = 2,7 μM

TxS IC_{50} = 3 nM



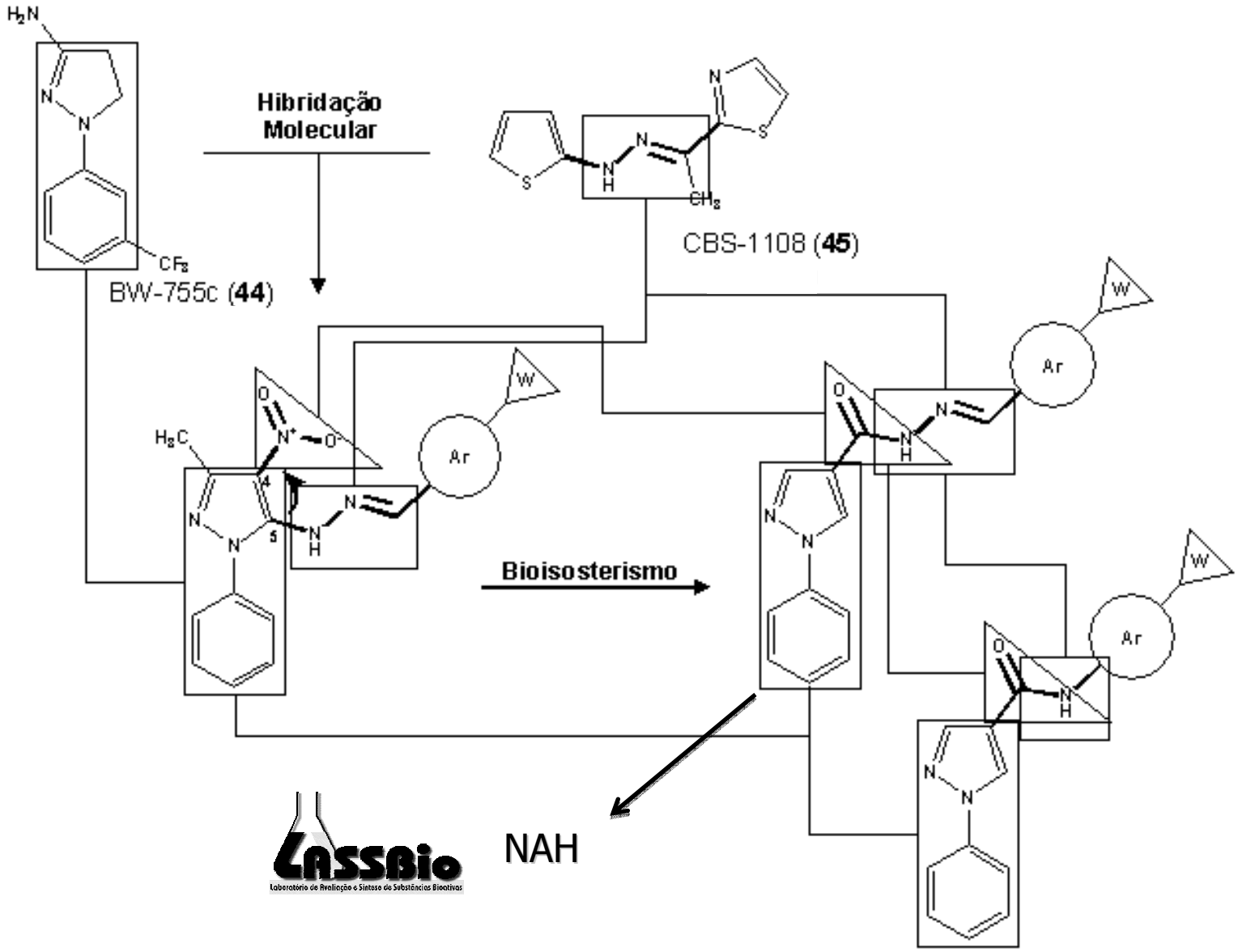


samixogrel

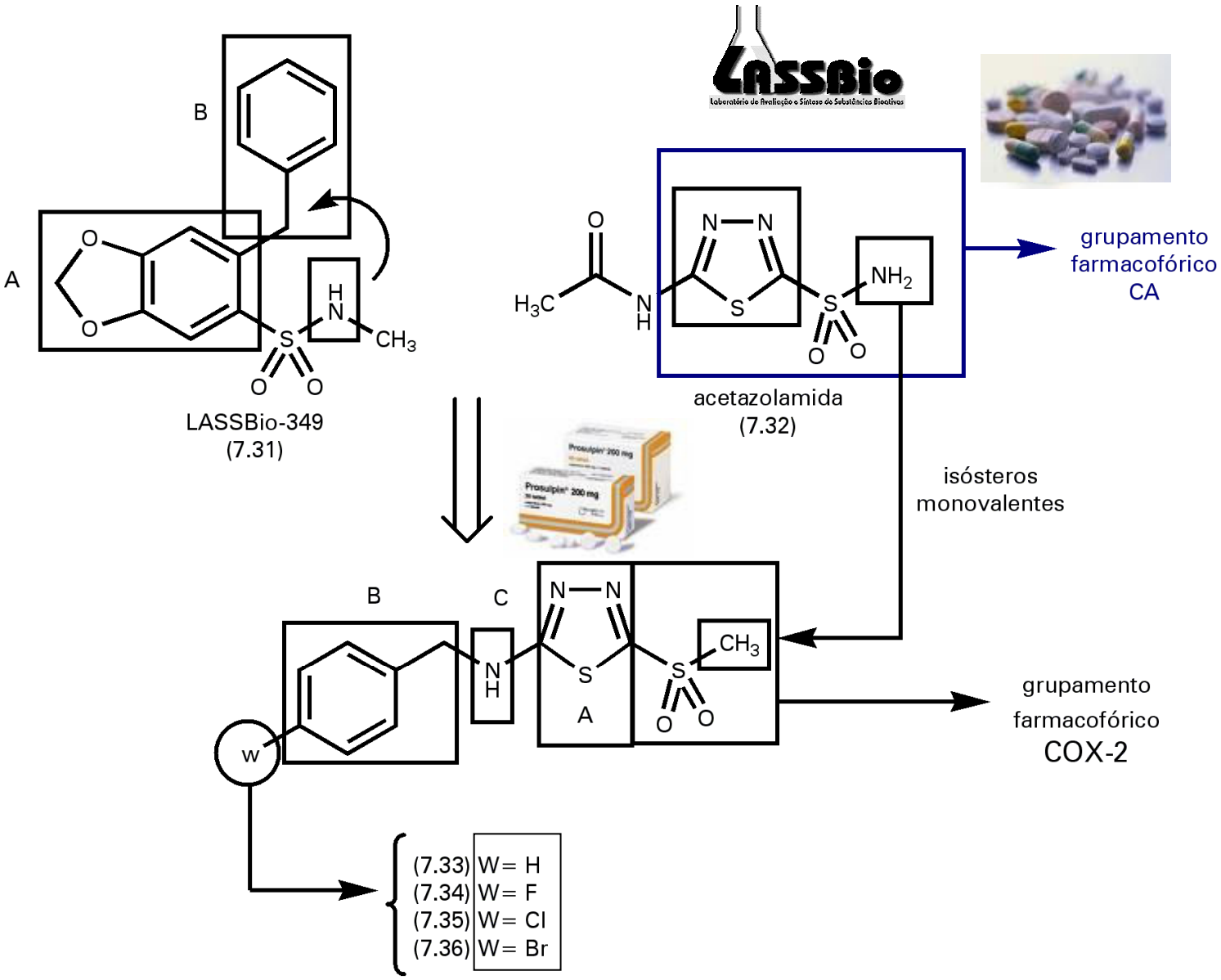
TP IC_{50} = 19 nM

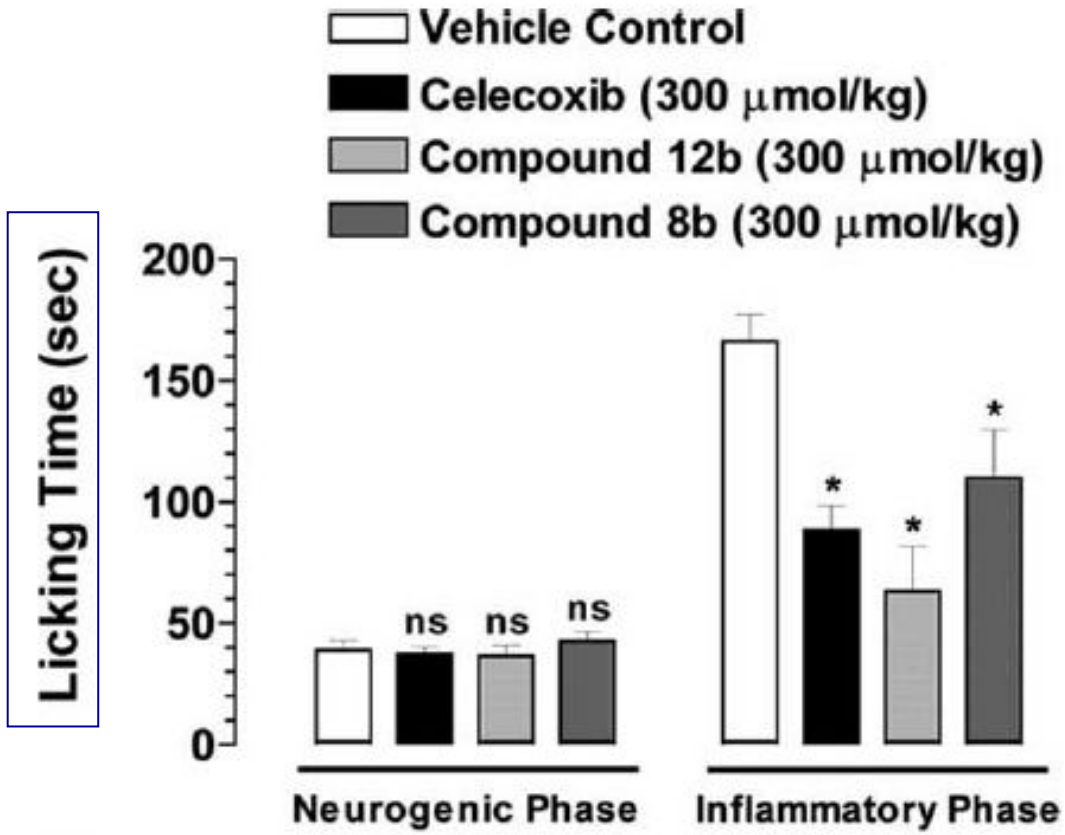
TxS IC_{50} = 4 nM

A hibridação molecular

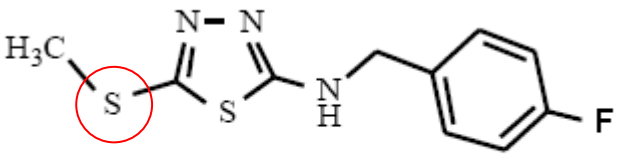


A hibridação molecular

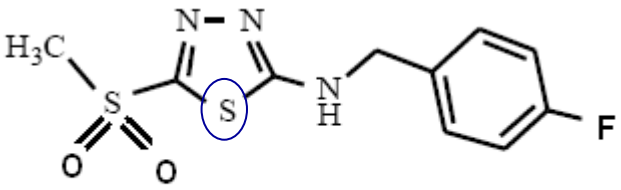




[a]all compounds were administered p.o. 60 min before formalin injection (2.5%; 2 μl/paw). * $p < 0.05$ (Student's t-test). n.s. – non significant. Results are expressed as mean ± SEM and compared with vehicle control group.

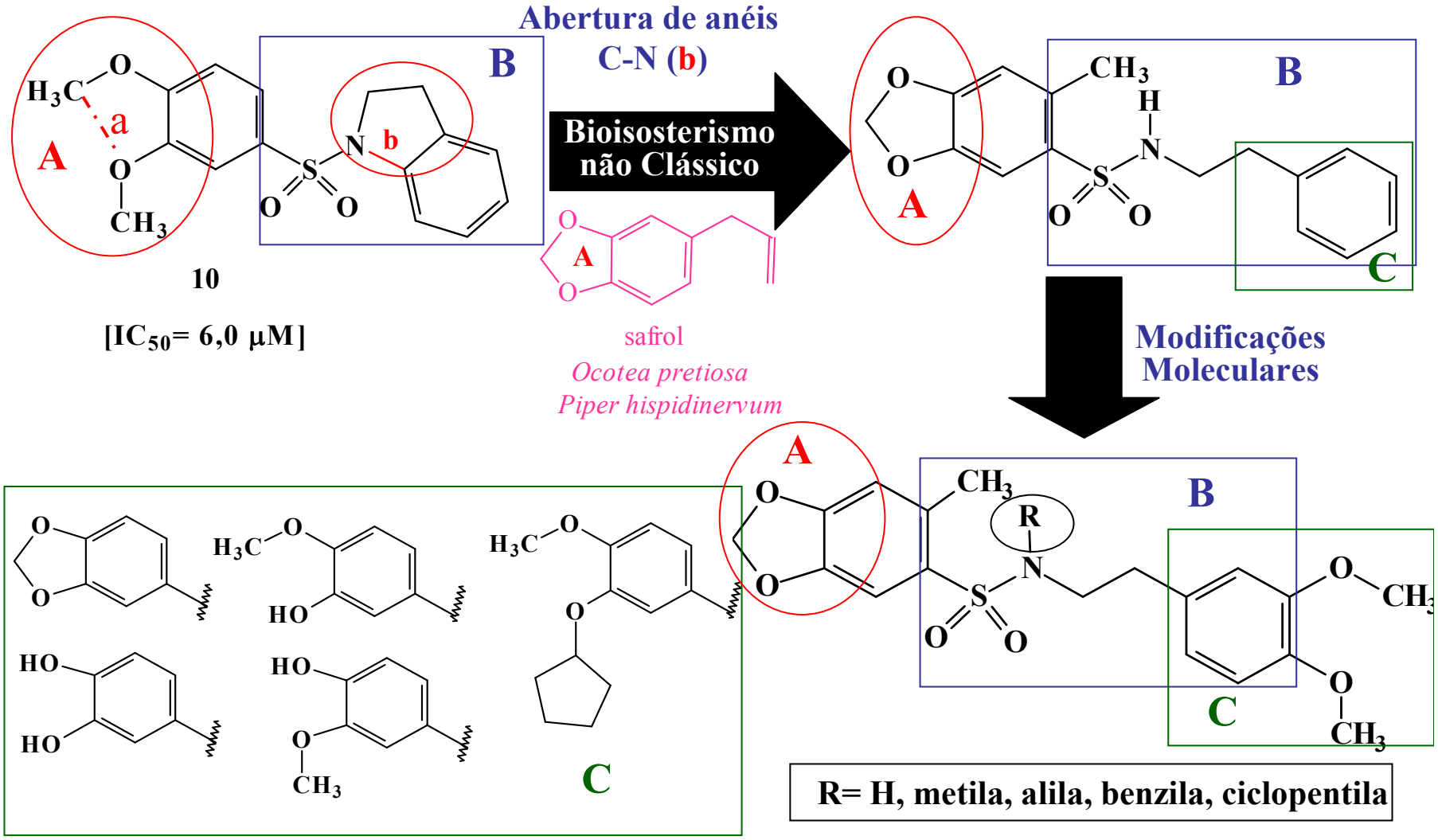


12b



8b

A hibridação molecular

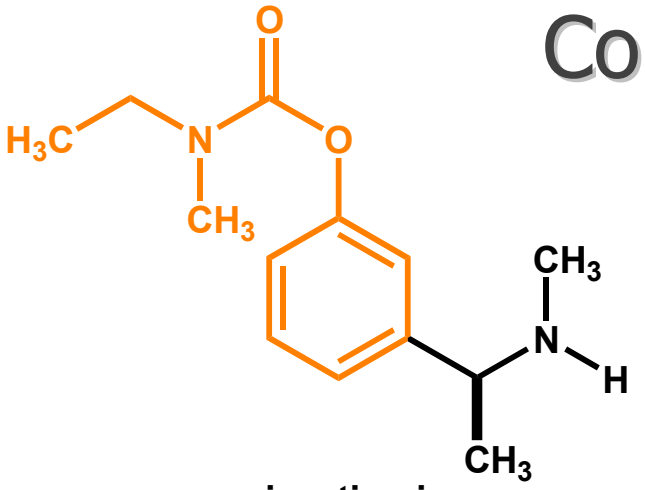


Gênese dos novos candidatos a fármacos antiinflamatórios, planejados como inibidores da PDE-4.

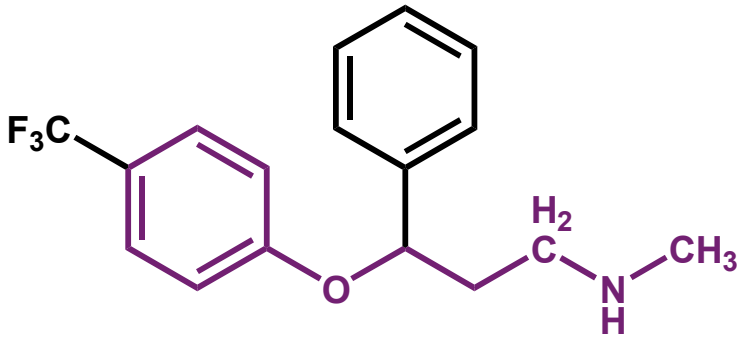
1. **Histórico do planejamento racional de fármacos: a Química Medicinal e a Química Farmacêutica**
2. **A cronologia da descoberta de fármacos e o prêmio Nobel**
3. **A contribuição dos produtos naturais para a descoberta de fármacos**
4. **Noções das interações fármaco-biorreceptores e o paradigma de Ehrlich-Fischer**
5. **Abordagem fisiológica no planejamento racional**
6. **Estratégias de desenho molecular de análogos-ativos:**
   - 6.1. Aplicação do bioisosterismo;
   - 6.2. Aplicação da simplificação molecular;
   - 6.3. Aplicação da anelação molecular
   - 6.4. Aplicação da hibridação molecular
   - 6.5. Aplicação de técnicas conjugadas
7. **Estudo de casos**

Bibliografia: *Química Medicinal: As razões moleculares da ação dos fármacos*, E. J. Barreiro & C. A. M. Fraga, Artmed, Porto Alegre, RS, 2008.

Combinação de técnicas

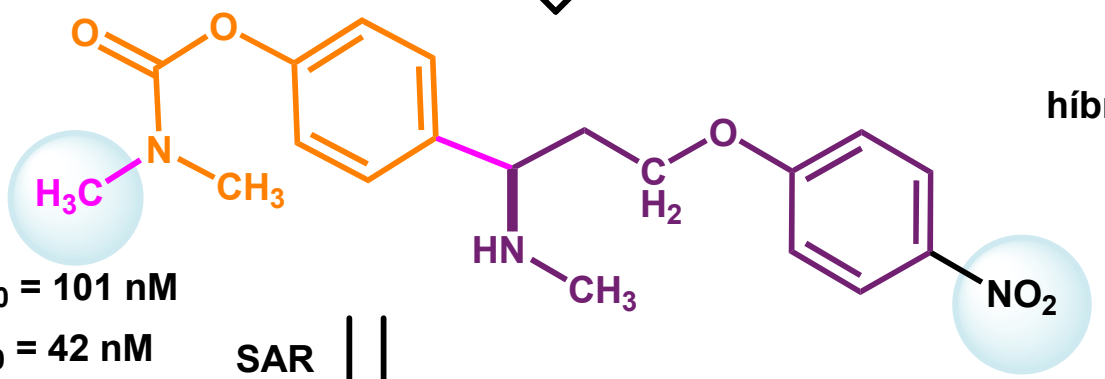


rivastigmina



fluoxetina

hibridação molecular

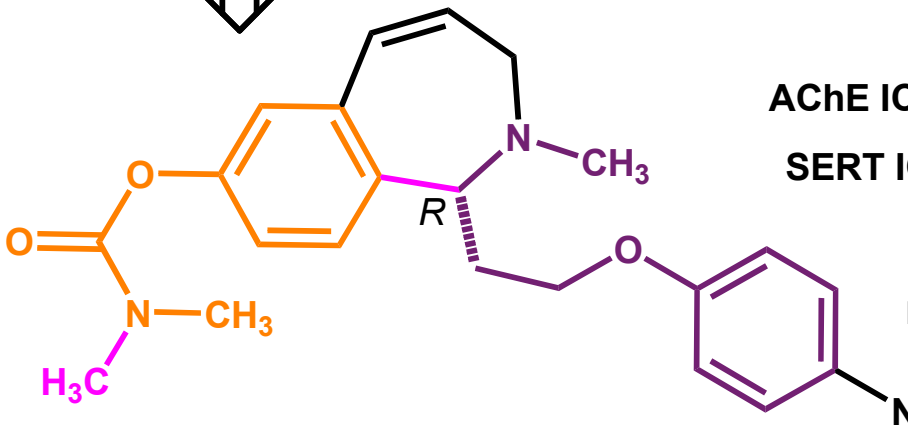


híbrido otimizado

AChE IC_{50} = 101 nM

SERT IC_{50} = 42 nM

SAR



AChE IC_{50} = 14 nM

SERT IC_{50} = 6 nM

N. Toda *et al*, 2003

APLICAÇÕES

- As técnicas de modificação molecular

da Química Medicinal podem ser empregadas separadamente ou combinadas, ampliando significativamente suas aplicações no desenho estrutural de novas entidades químicas de diversos quimiotipos.

Universidade Federal do Rio de Janeiro

Química Medicinal

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