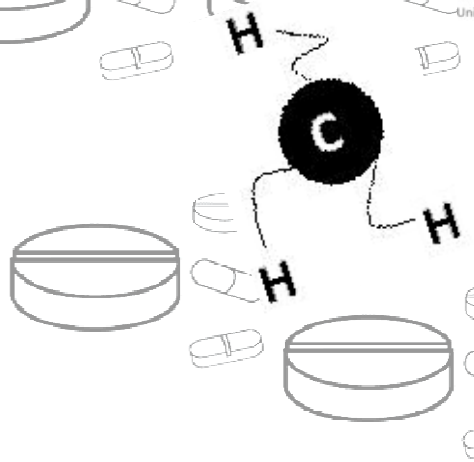
Universidade Federal do Rio de Janeiro

PRINCÍPIOS & FUNDAMENTOS da Química Medicinal

PARTE 2

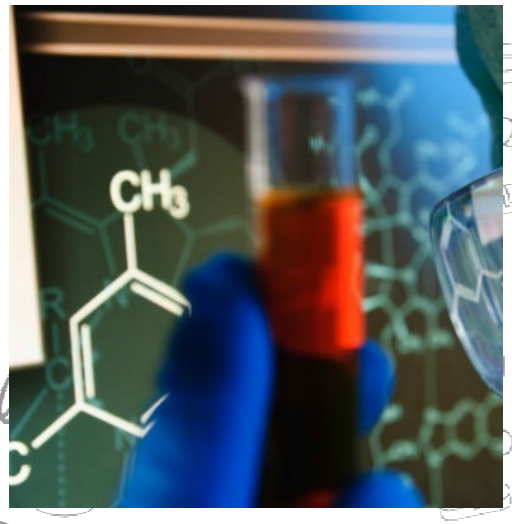


Eliezer J. Barreiro

Professor Titular

Universidade Federal do Rio de Janeiro

LASSBio® Laboratório de Avaliação e Síntese de Substâncias Bioativas 20 anos



Universidade Federal do Rio de Janeiro

Perguntas?

Dúvidas

UFRJ

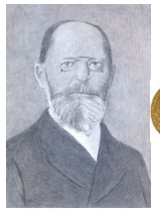
Universidade Federal do Rio de Janeiro

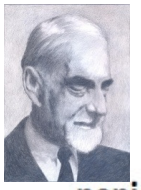
Um de cada vez....

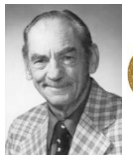
Universidade Federal do Rio de Janeiro

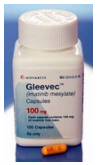
Linha do tempo...

Química Medicinal









Galeno

Fischer

Salvarsan^{R}

Fourneau

penicilina

Fleming

Bovet

indometacina

cimetidina

lovastatina

aciclovir

Elion

Hitchings

Black

imatinibe

estatina

indinavir

O melo...

150 | 1902 | 1907 | 1911 | 1941 | 1945 | 1957 | 1962 | 1975 | 1980 | 1981 | 1987 | 1988 | 1996 | 2001

500aC | 1889 | 1908 | 1935 | 1943 | 1948 | 1959 | 1964 | 1982 | 1985 | 1991 | 2013

Hipocrates

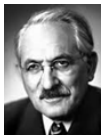
Paracelso

AAS

Ehrlich

Domagk

estreptomicina



Ahlquist

Kornberg

propranolol

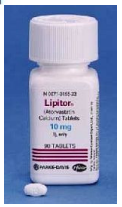
Hodgkin

Vane

Goldstein

Brown

atorvastatina

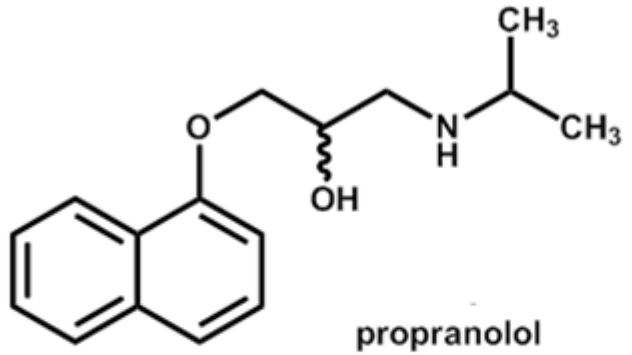


ponatinibe

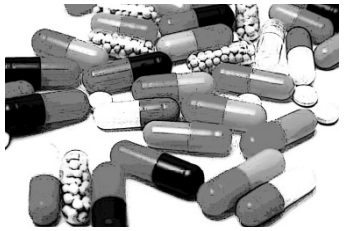
The Magic Bullet Theory

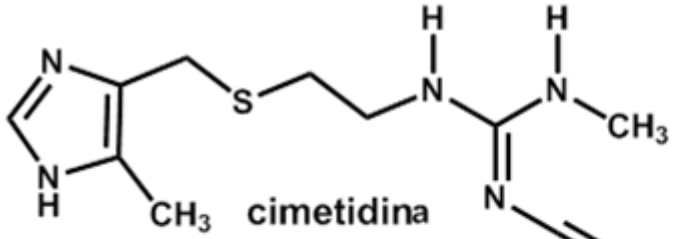
Os medicamentos foram uma das principais invenções do século 20

Universidade Federal do Rio de Janeiro

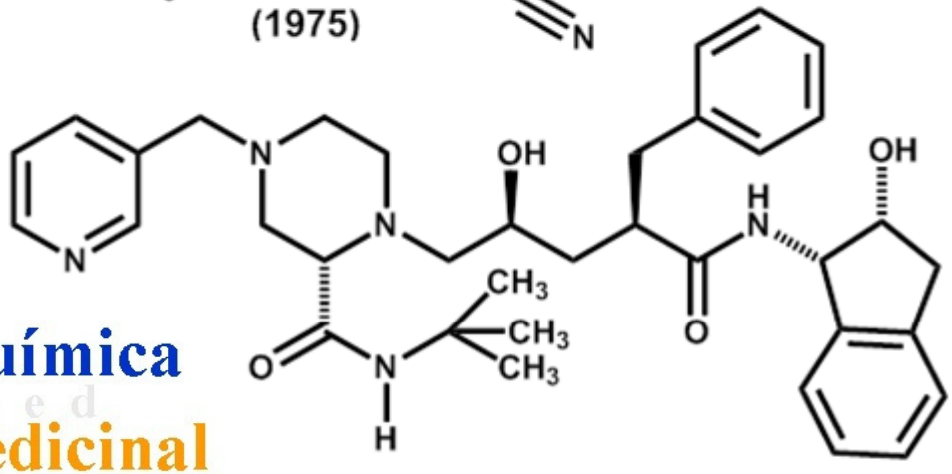


propranolol
(1964)





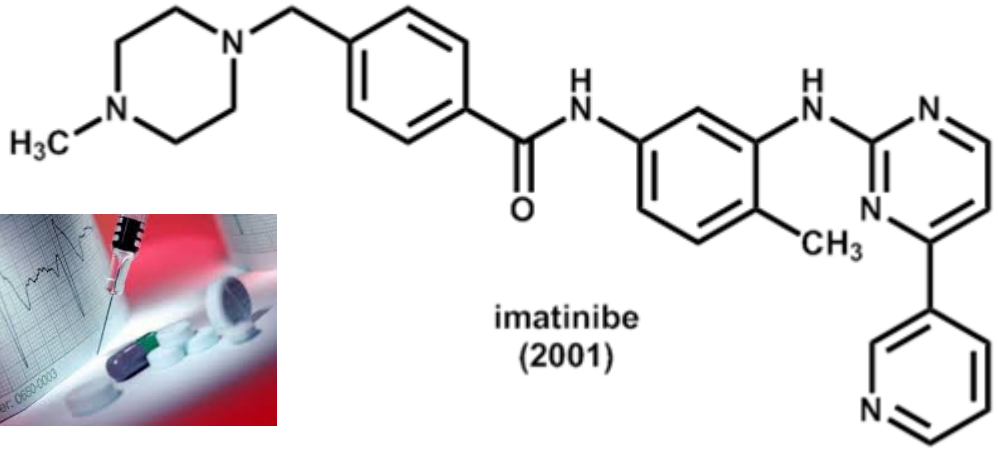
cimetidina
(1975)



indinavir
(1995)

sinvastatin
(1988)

Química
Medicinal



imatinibe
(2001)

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A invenção do propranolol

Raymond Ahlquist (1914

Am J Physiol 1948, 153, 586

A STUDY OF THE ADRENOTROPIC RECEPTORS

RAYMOND P. AHLQUIST

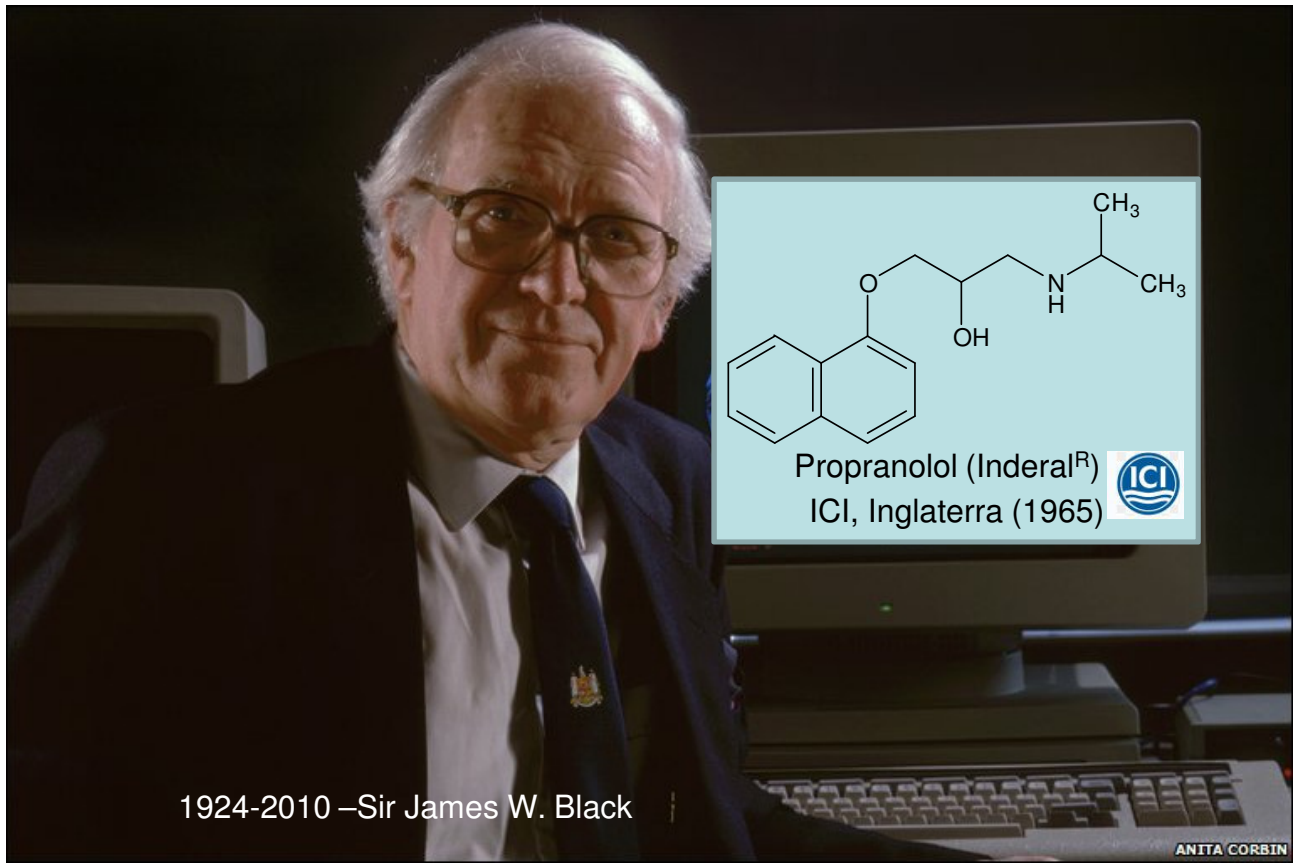
From the Department of Pharmacology, University of Georgia School of Medicine

AUGUSTA, GEORGIA

Premio Nobel
1988

Química Medicinal

Pharmacology
Farmacologia

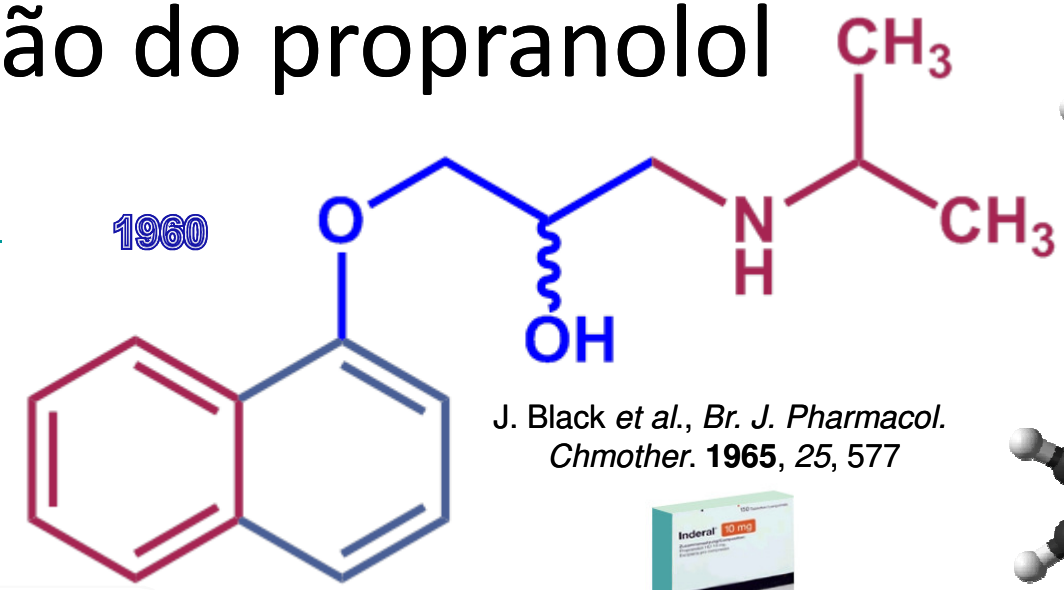


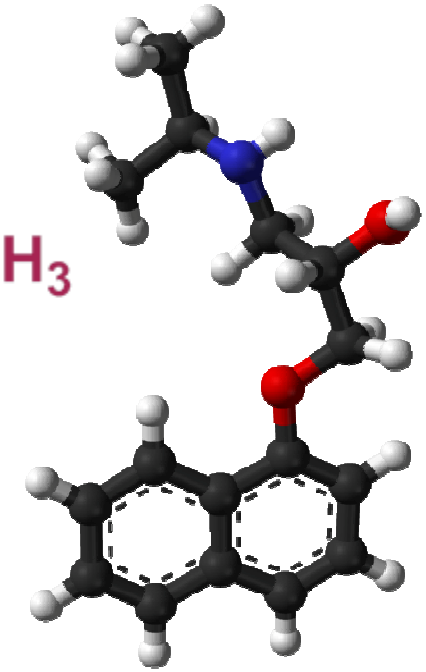
A invenção do propranolol

História do propranolol

Química Medicinal

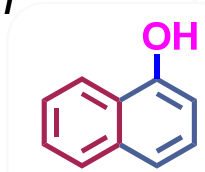
1960



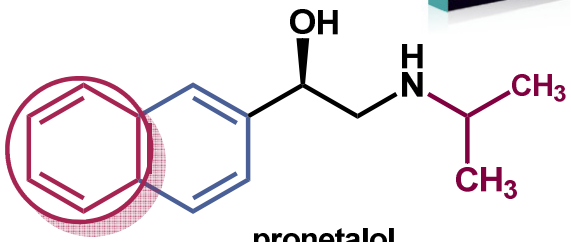


J. Black *et al.*, *Br. J. Pharmacol. Chmother.* **1965**, *25*, 577

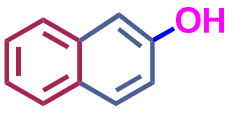
Rational drug design



α-naftol

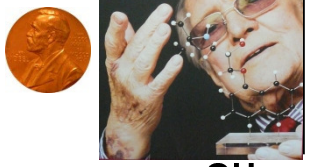


pronetalol
1959

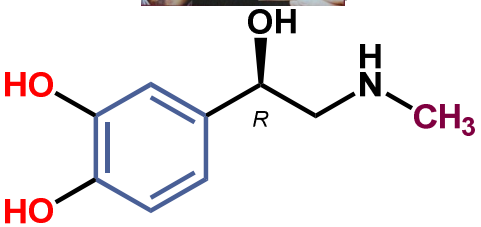


β-naftol

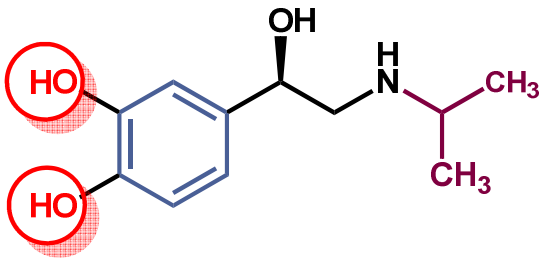
Analogue-based drug design



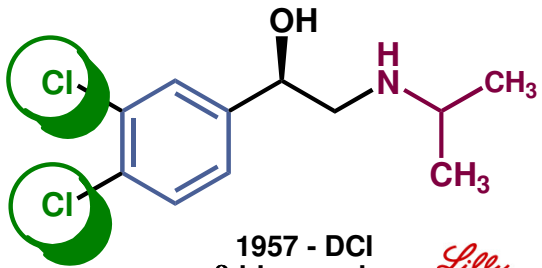
James W. Black, 1988 - "Pronethalol always seemed to us to be a prototype drug…" "The most fruitful basis to discovery of a new drug is to start from an old drug"



adrenalina



isoprenalina / isoproterenol



1957 - DCI
β-bloqueador

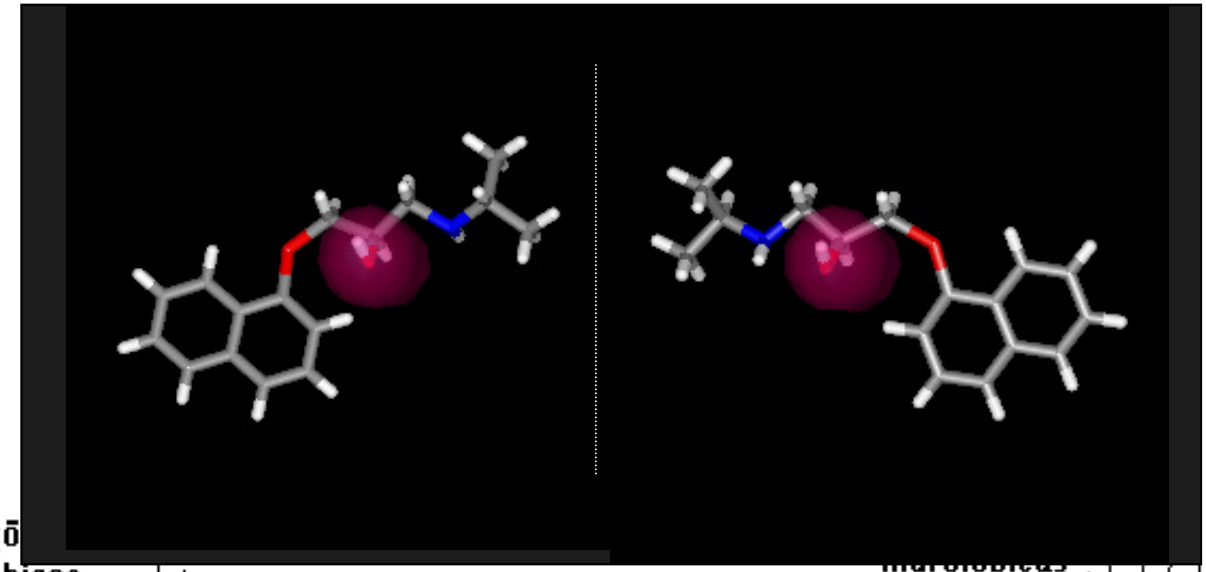
Lilly

Irwin H Slater & C. E. Powell
Eli Lilly

UFRJ

Universidade Federal do Rio de Janeiro

Como determinar o impacto de uma inovação terapêutica ?

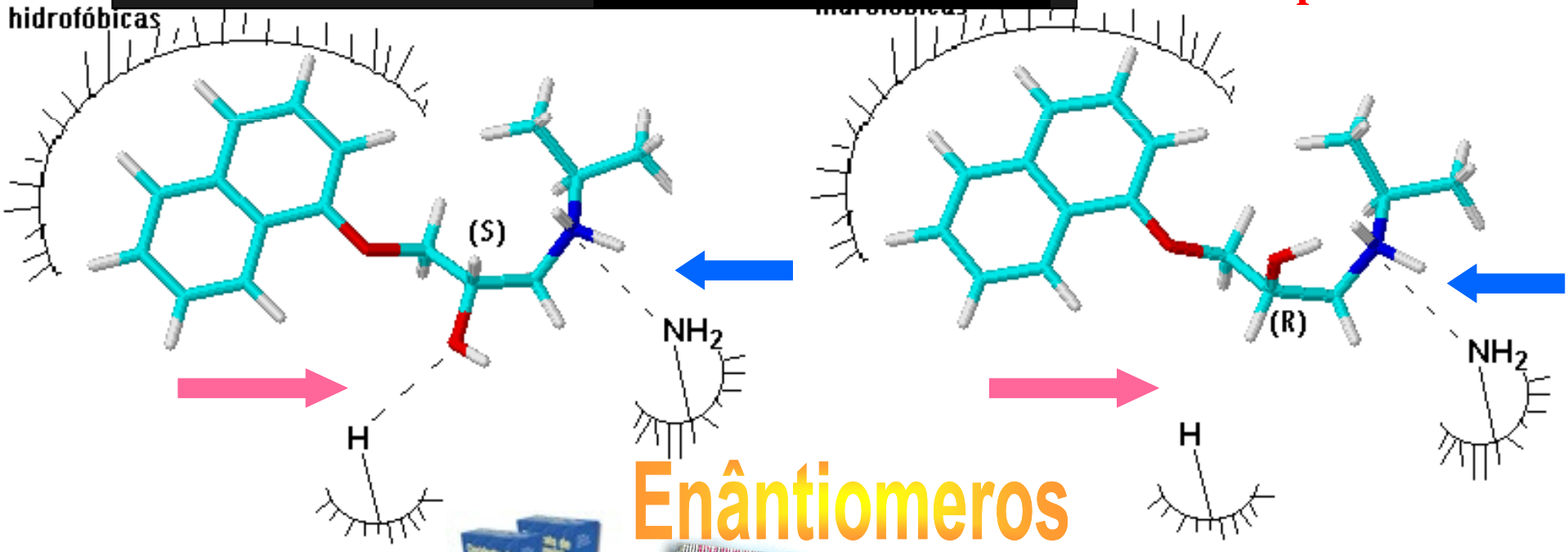


Eutômero

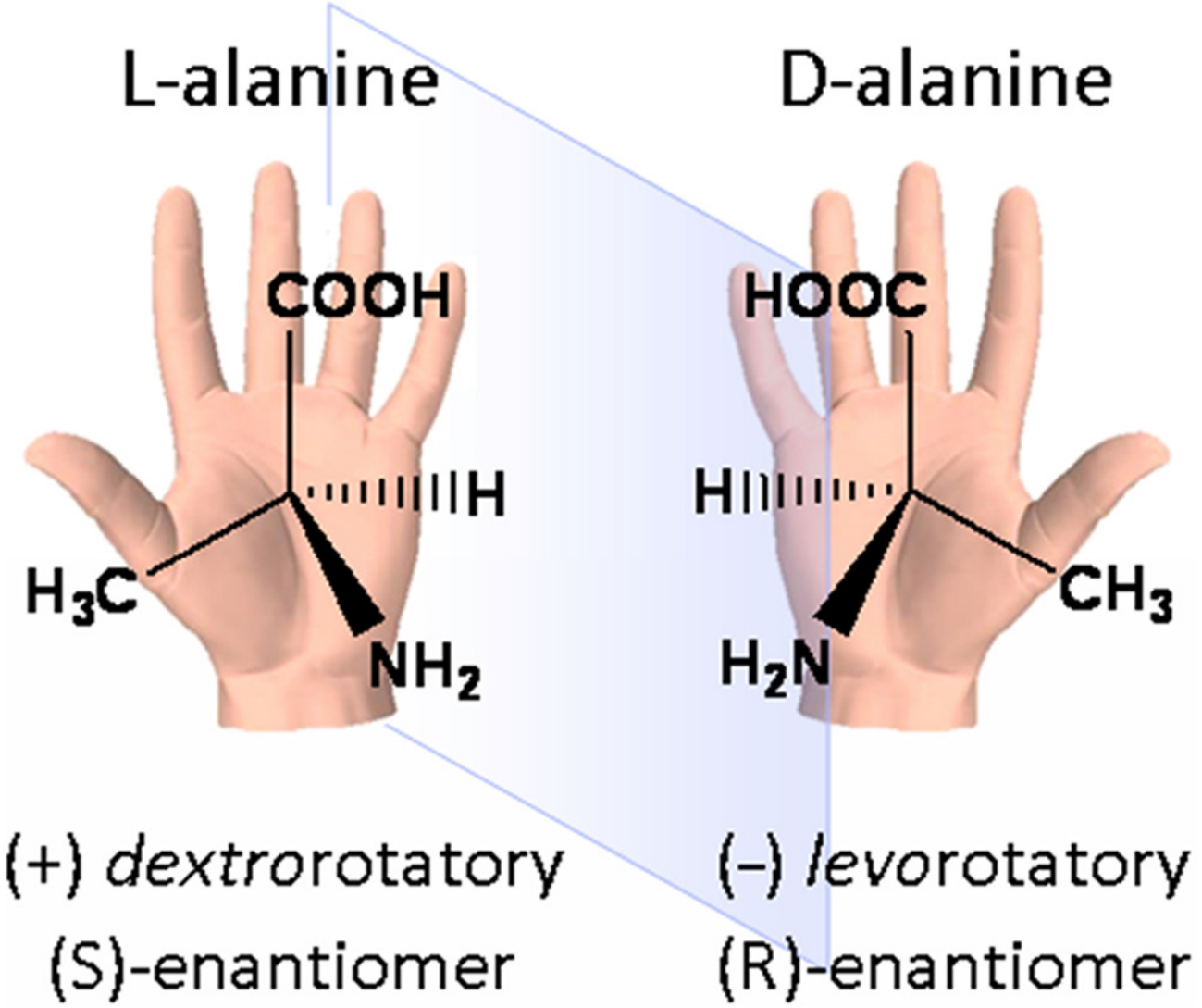
Distômero

estereoespecificidade

Interaçõ
hidrofóbicas

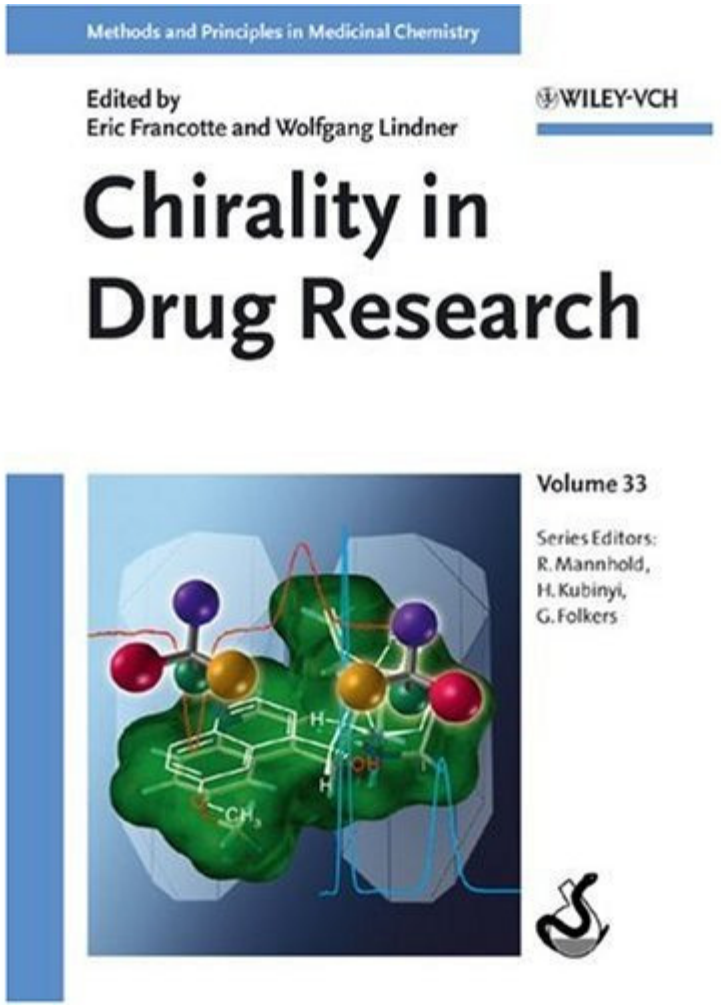


Enântiomeros

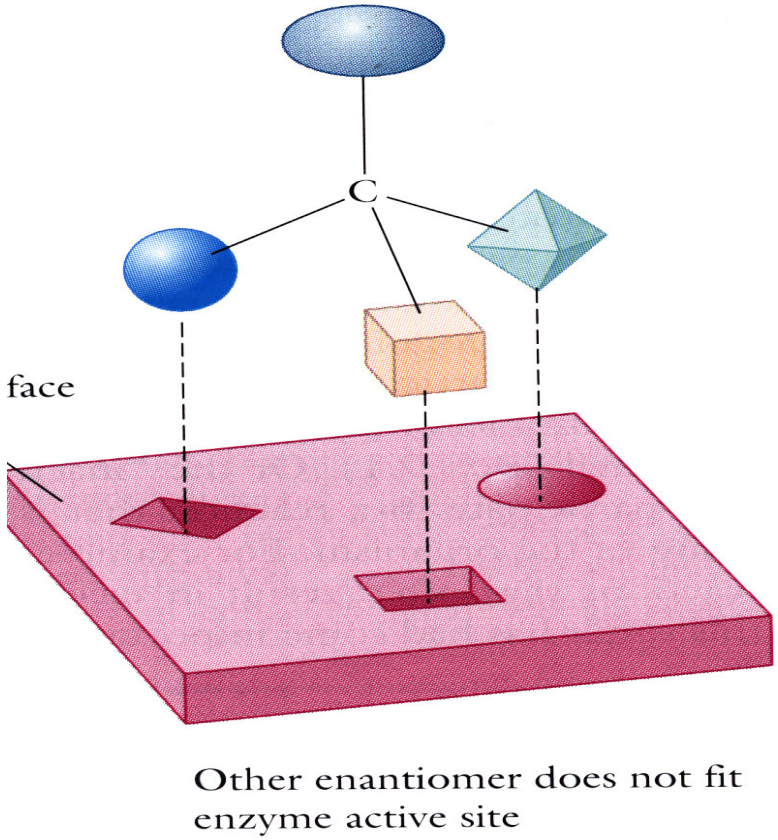


Quiralidade

A quiralidade e os fármacos



Reconhecimento molecular

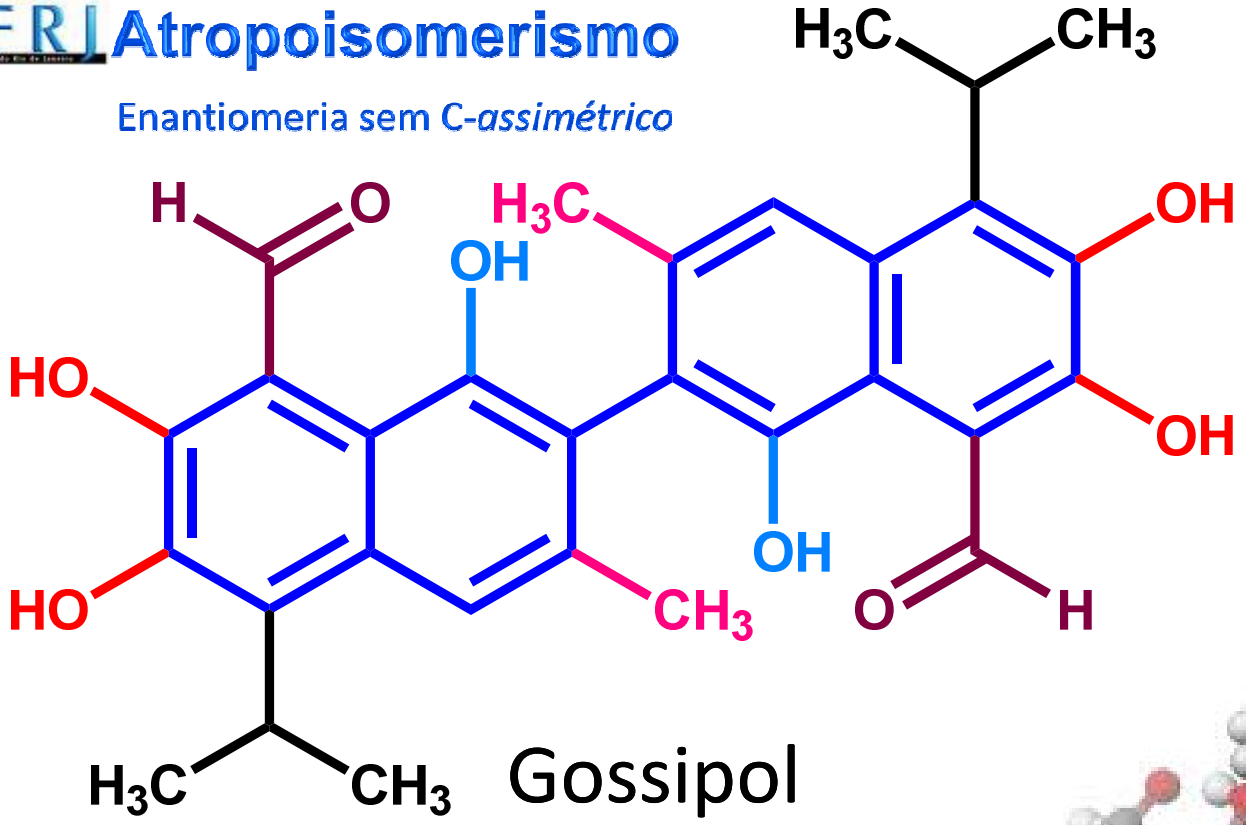


Modelo dos três pontos

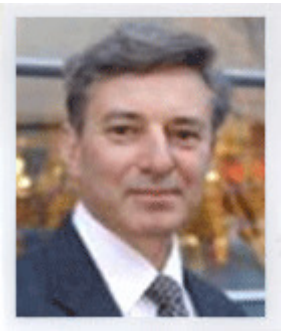
Modelo de Easson-Stedman

Atropoisomerismo

Enantiomeria sem C-*assimétrico*

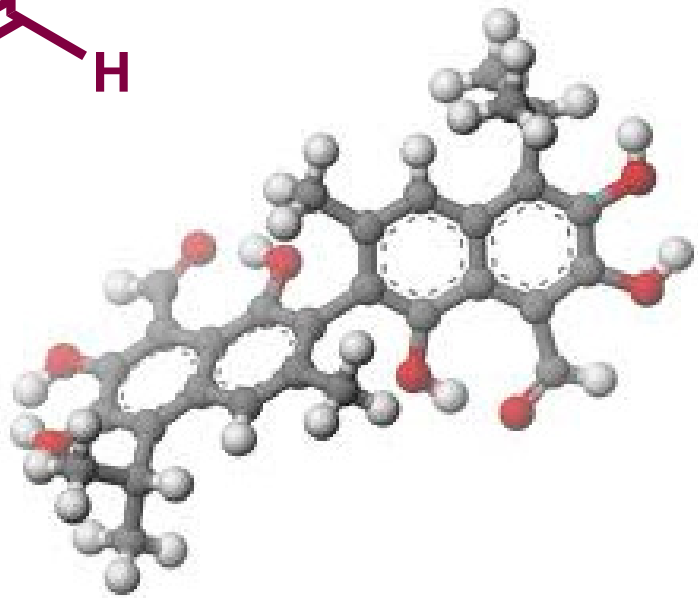


Gossipol



Prof. Stephen Matlin

Executive Director
Global Forum for Health Research
World Health Organization



Gossypium hyrsutum
G. autumnale

Contraceptivo masculino oral

1929 – região de Jiangxi (China)

1972 - Missão diplomática EUA

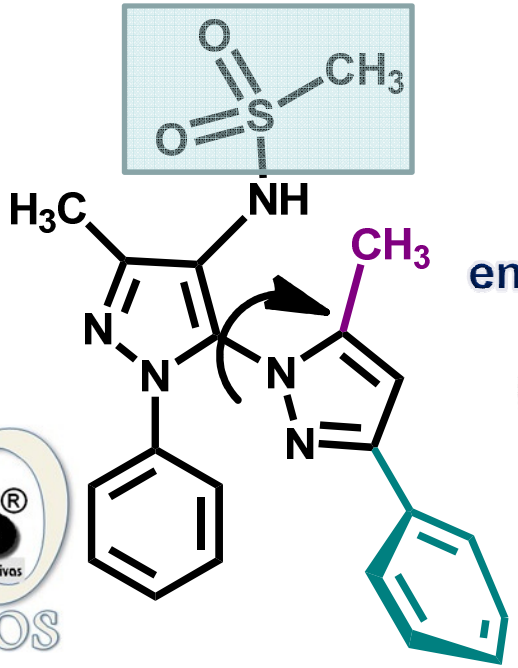
Universidade Federal do Rio de Janeiro

Synthesis and Characterization of the Atropisomeric Relationships of a Substituted *N*-Phenyl-Bipyrazole Derivative with Anti-inflammatory Properties

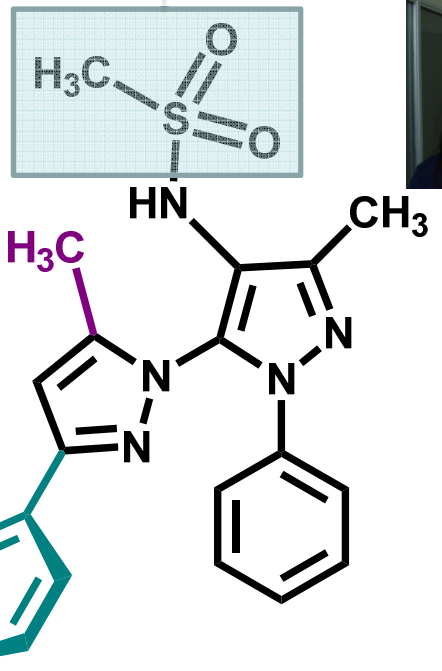
MARCIA P. VELOSO,
CHIRALITY 24:463–470 (2012)

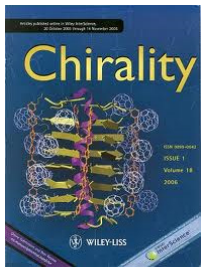
barreira de rotação

σ



enantiômeros



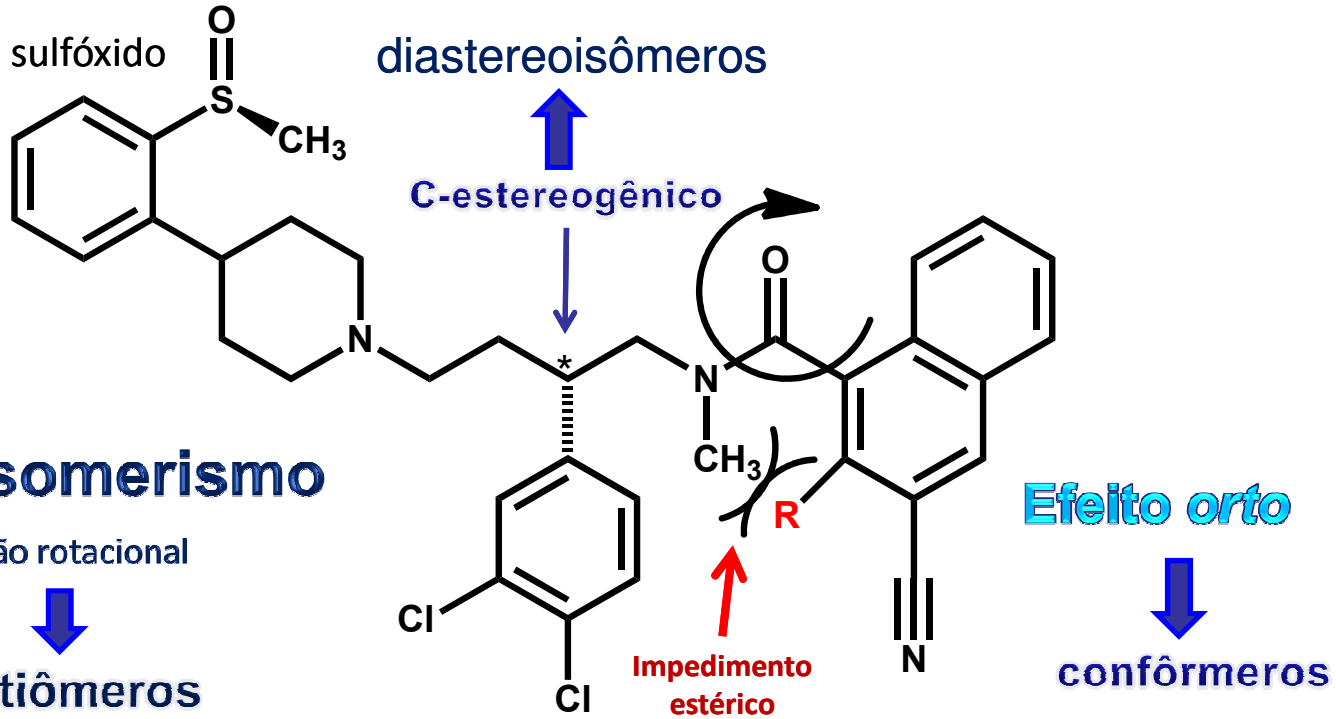


aS *aR*

LASSBio-456

Enantiomeria sem C-*assimétrico*

A quiralidade e os fármacos



Química Medicinal

ZD-6021 R = H

ZD-4974 R = OCH_3

J. S. Albert et al., Structural analysis & optimization of NK1 receptor antagonists through modulation of atropisomer interconversion properties, *J. Med. Chem.* **2004**, *47*, 519

Quim. Nova, Vol. 30, No. 1, 125-135, 2007

ATROPOISOMERISMO: O EFEITO DA QUIRALIDADE AXIAL EM SUBSTÂNCIAS BIOATIVAS

Anderson Rouge dos Santos, Alessandra Campbell Pinheiro, Ana Carolina Rennó Sodero, Andréa Sousa da Cunha, Monica Costa Padilha, Priscila Mesquita de Sousa e Silvia Paredes Fontes
Departamento de Química Orgânica, Instituto de Química, Universidade Federal do Rio de Janeiro, 21941-972 Rio de Janeiro – RJ, Brasil
Márcia Paranho Veloso
Universidade Federal de Alfenas, 37130-000 Alfenas – MG, Brasil
Carlos Alberto Manssour Fraga*
Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, CP 68023, 21944-270 Rio de Janeiro – RJ,

Recebido em 26/9/05; aceito em 30/3/06; publicado na web em 26/9/06

Revisão

www. scielo.org.br

ATROPISOMERISM: THE EFFECT OF THE AXIAL CHIRALITY IN BIOACTIVE COMPOUNDS. Atropisomerism is a special kind of stereoisomeric relationship that arises from the freezing of a certain conformation of an organic molecule, associated with a high rotational barrier about a single covalent bond. Atropisomerism has been originally described in *orto*-functionalyzed biphenyl derivatives, but a lot of other organic functionalities can present this structural phenomenon, characterized by the presence of chiral properties in compounds that don't present classical stereogenic centers. Atropisomeric compounds, intermediates and catalysts have well-know importance in organic synthesis, but the influence of the axial chirality in substances able to modulate biological systems is still not very exploited in drug design and development. In this context, the present account describes the importance of this structural property in the medicinal chemistry of different classes of bioactive compounds or therapeutic agents, emphasizing how atropisomerism could affect the molecular recognition of a ligand or a prototype by the target bioreceptor.

J Clayden, WJ Moran, PJ Edwards, SR LaPlante, The Challenge of Atropisomerism in Drug Discovery, *Angew Chem Int Ed* **2009**, *48*, 6398

SR LaPlante, PJ Edwards, LD Fader, A Jakalian, O Hucke, Revealing Atropisomer Axial Chirality in Drug Discovery, *ChemMedChem* **2011**, *6*, 505

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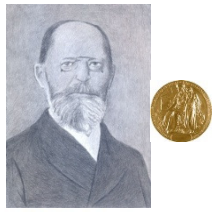
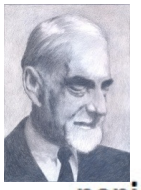
Linha do tempo...

Química Medicinal



Galeno

Fischer



Salvarsan^{R}

Fourneau

penicilina

Fleming

Bovet

indometacina

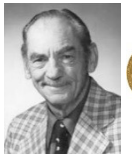
Inovação

cimetidina

lovastatina

aciclovir

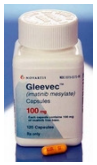
Elion



Hitchings

Black

imatinibe



estatina

indinavir

150 1902 1907 1911 1941 1945 1957 1962 1975 1980 1981 1987 1988 1996 2001

500aC 1889 1908 1935 1943 1948 1959 1964 1982 1985 1991 2013

Hipocrates

Paracelso

AAS

Ehrlich

Domagk

estreptomicina

Ahlquist

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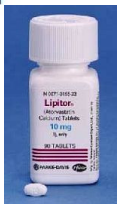
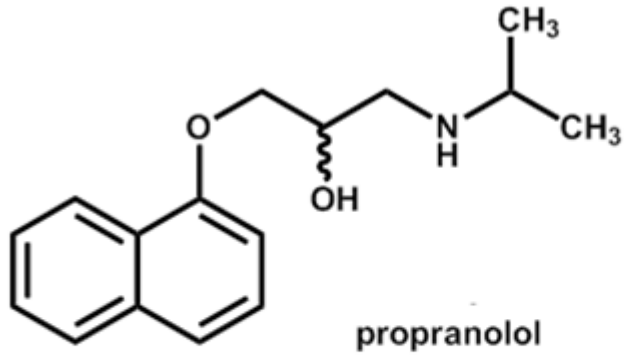


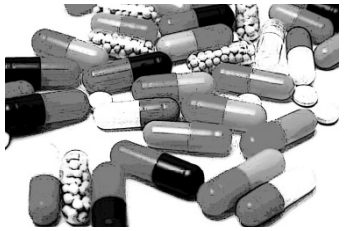
ponatinibe

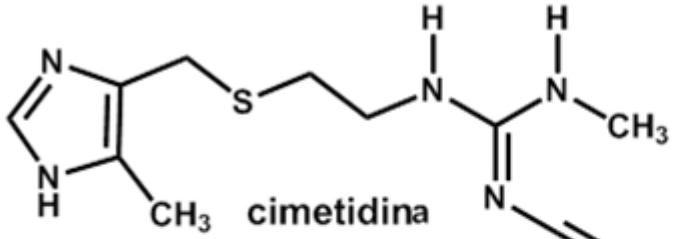
Os medicamentos foram uma das principais invenções do século 20

Universidade Federal do Rio de Janeiro

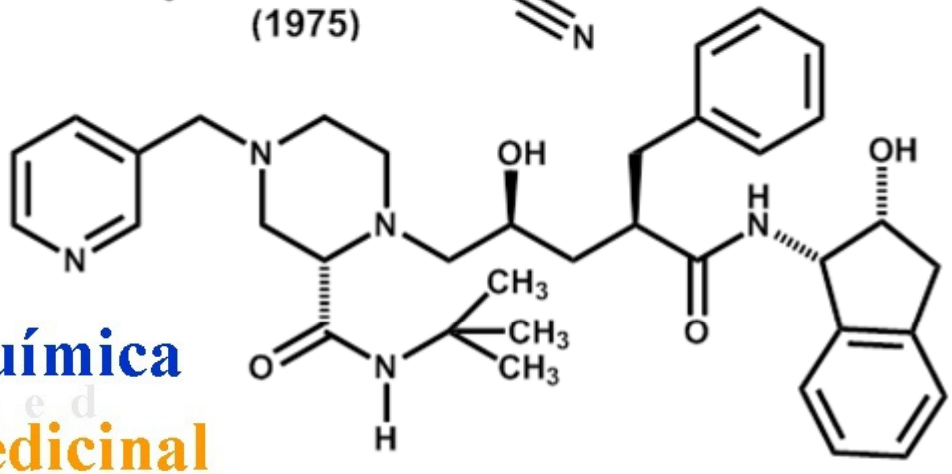


propranolol
(1964)





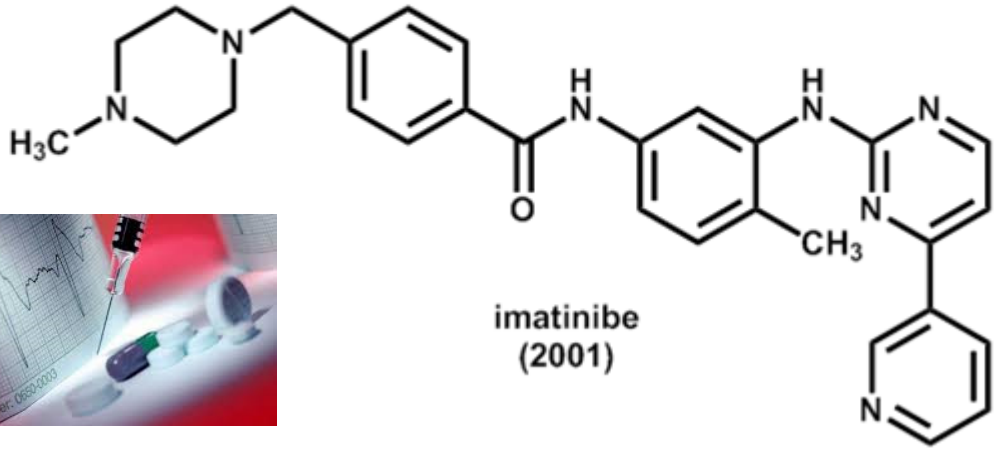
cimetidina
(1975)



indinavir
(1995)

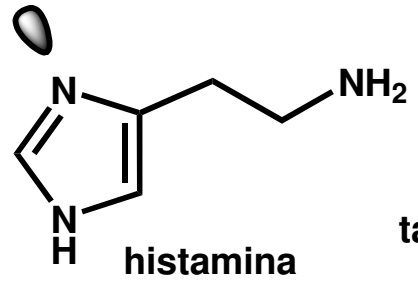
sinvastatin
(1988)

Química
Medicinal



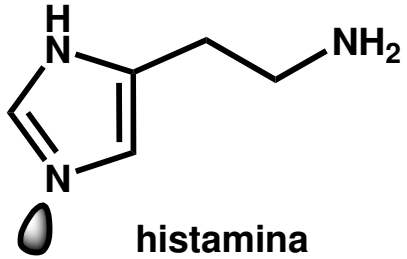
imatinibe
(2001)

A gênese da cimetidina



histamina

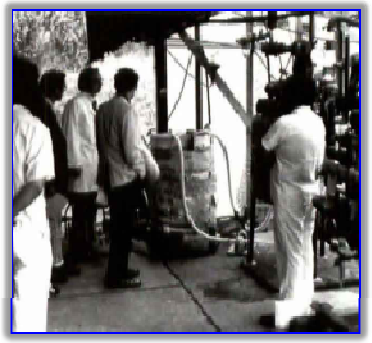
tautômeros

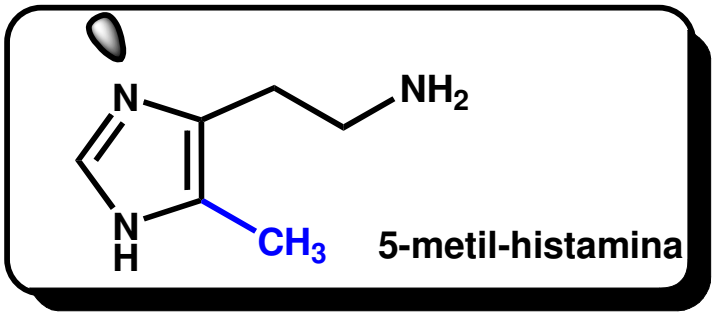


histamina

C Robin Ganellin

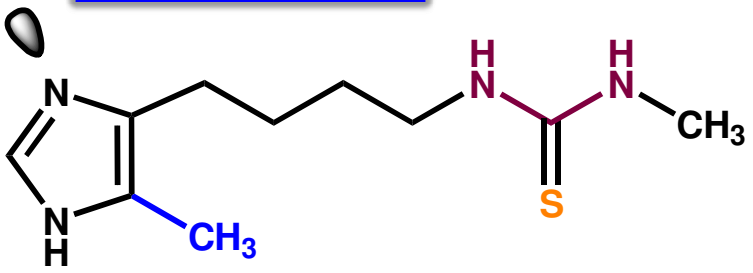
SK&F



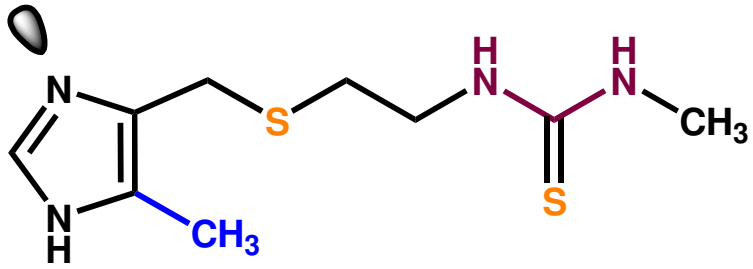


5-metil-histamina

Química Medicinal

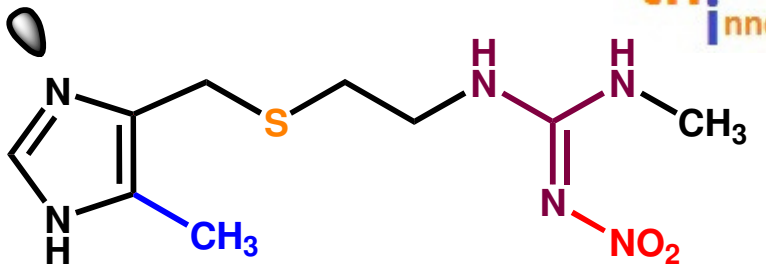


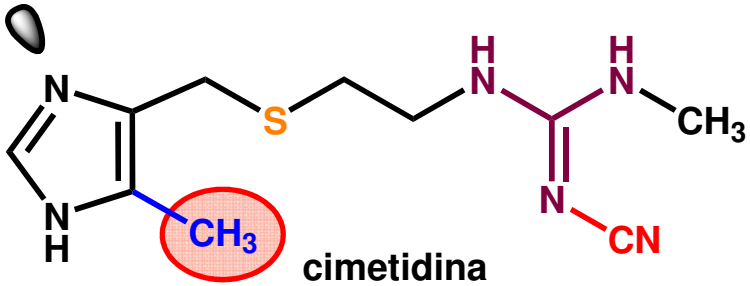
burinamida



metiamida

therapeutic innovation





cimetidina

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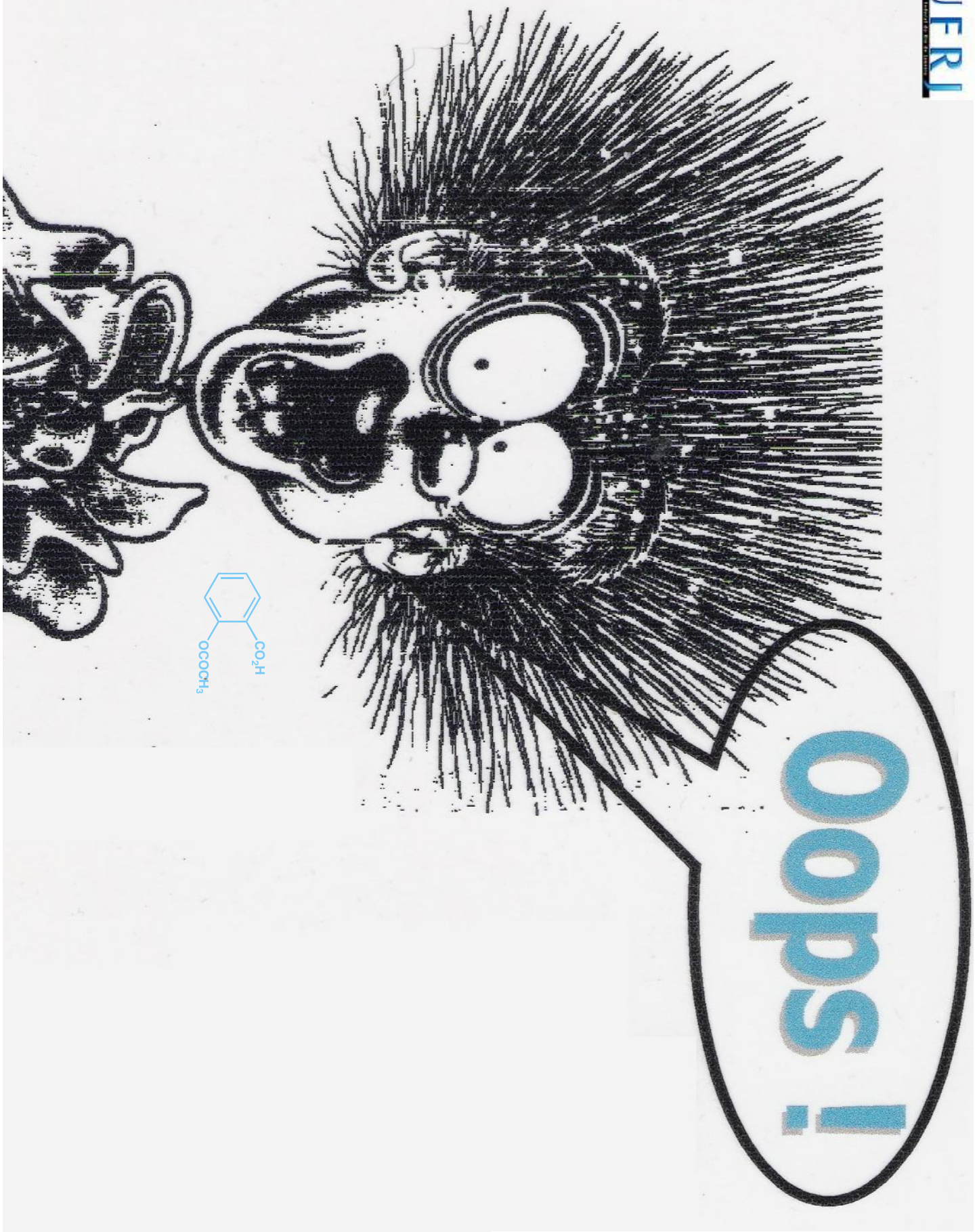
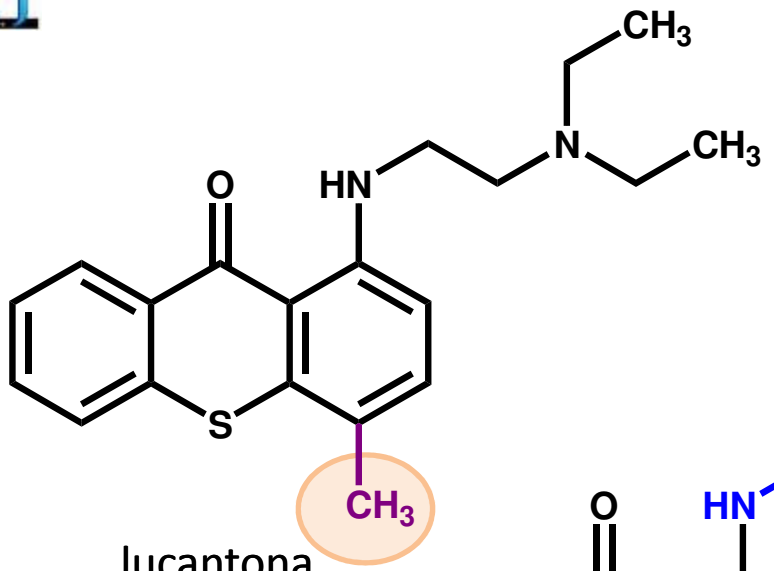
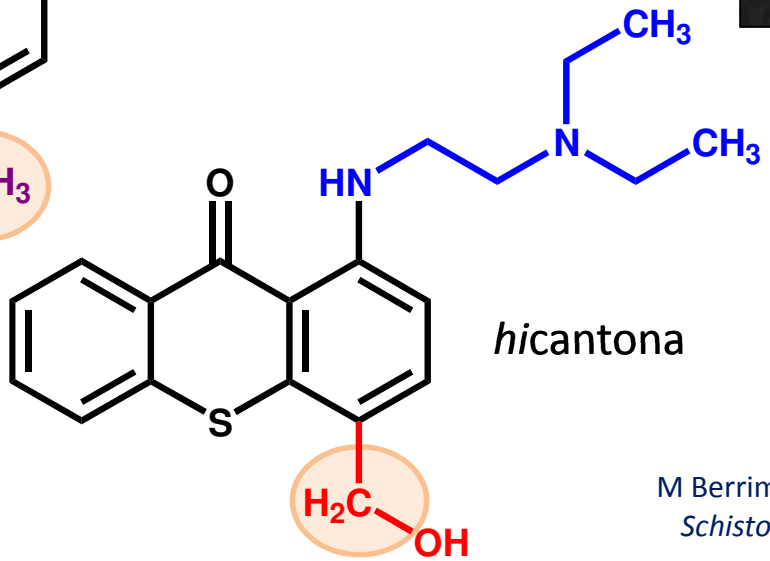
UFRJ





lucantona

Miracil B



*hi*cantona

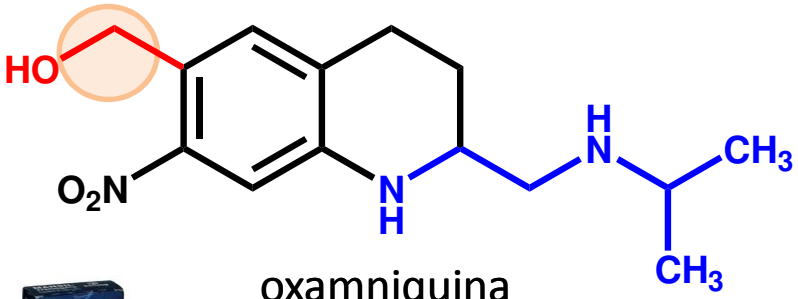
Schistosoma mansoni

140 - 60 µm

nature

M Berriman et al., The genome of the blood fluke *Schistosoma mansoni*, *Nature* **2009**, *460*, 352.

Química
m e d
Medicinal
c h e m

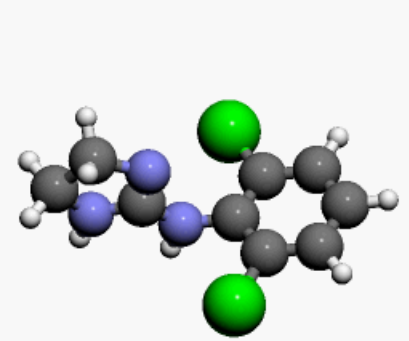


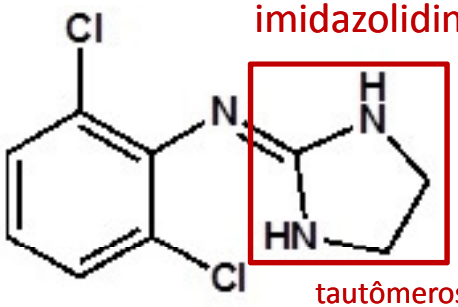
oxamniquina

Kaye & Woolhouse, 1972
Pfizer, Sandwich, UK

Efeito-*orto* na clonidina

agonista α-$_{2A}$ adrenérgico



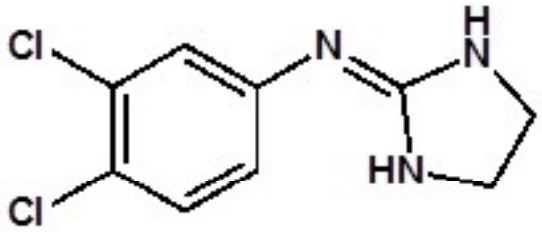


imidazolidina

tautômeros

clonidina

1961



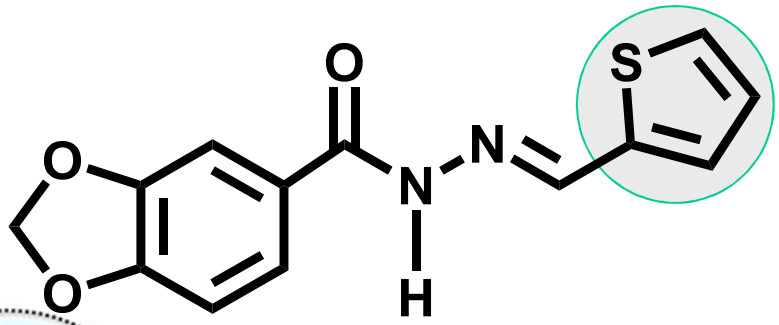
regioisômero

Atividade hipotensora	clonidina	*meta-para*-regio-isômero
ED_{50}	0,1 mg/Kg	3,0 mg/Kg

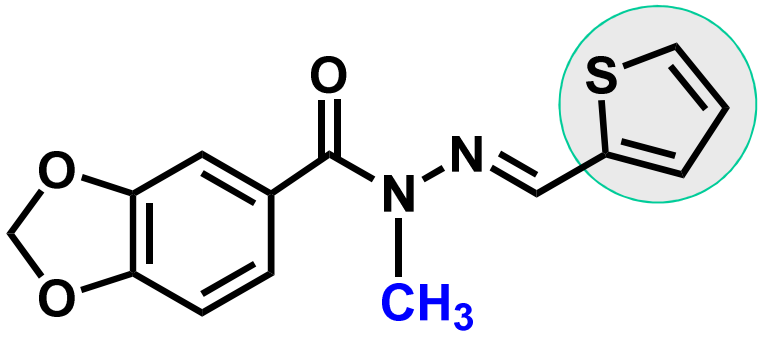
Receptor	K_i (nM)
α_{1A}	>300
α_{1B}	>300
α_{1D}	>100
α_{2A}	42,92
α_{2B}	106,31
α_{2C}	233,1

ED_{50} indica atividade *in vivo*

A *metilinha* do LASSBio...



LASSBio-294



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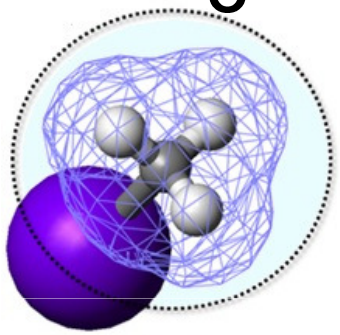
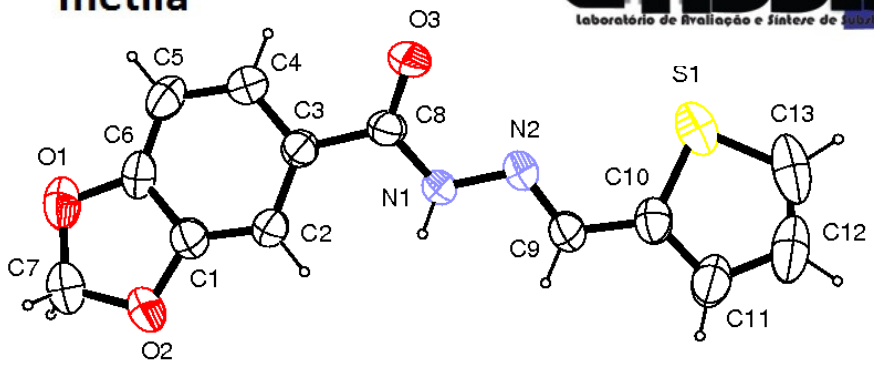
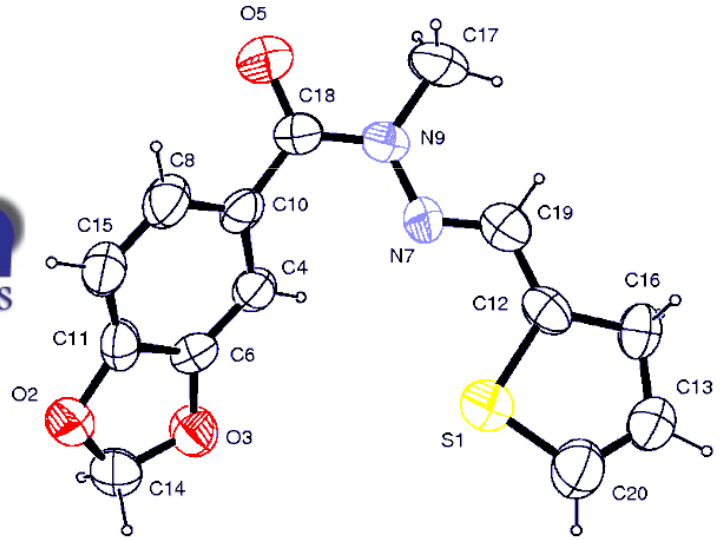


metila



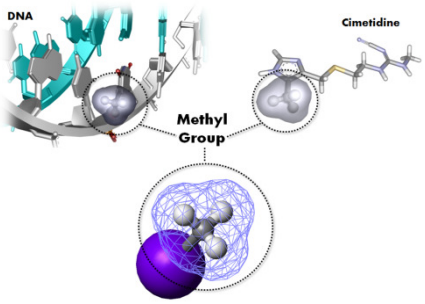
Conformação "grampo-de-cabelo"



Conformação em "U"

* PDE4i IC_{50}=190nM
anti-TNF-α EC_{50}=1.30μM
orally active anti-inflamatory

* A. E. Kümmerle *et al.*, Design, Synthesis, and Pharmacological Evaluation of *N*-Acylhydrazones and Novel Conformationally Constrained Compounds as Selective and Potent Orally Active PDE-4 Inhibitors, *J Med Chem* **2012**, *55*, 7525



CHEMICAL REVIEWS

Chem. Rev. 2011, 111, 5215–5246

F I (2011) = 40,19

REVIEW

pubs.acs.org/CR

The Methylation Effect in Medicinal Chemistry


Eliezer J. Barreiro,*[,†,‡,§] Arthur E. Kümmerle,[||,†,§] and Carlos A. M. Fraga[†,‡,§]

[†]Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, CCS, Cidade Universitária, CP 68.006, 21941-902 Rio de Janeiro, RJ, Brazil

[‡]Programa de Pós-Graduação em Farmacologia e Química Medicinal, Instituto de Ciências Biomédicas, Universidade Federal do Rio de Janeiro, Cidade Universitária, Ilha do Fundão, Rio de Janeiro, RJ, Brazil

[§]Programa de Pós-Graduação em Química, Instituto de Química, Universidade Federal do Rio de Janeiro, Cidade Universitária, Ilha do Fundão, Rio de Janeiro, RJ, Brazil

dx.doi.org/10.1021/cr200060g

www.uff.br/rvq

Química Medicinal

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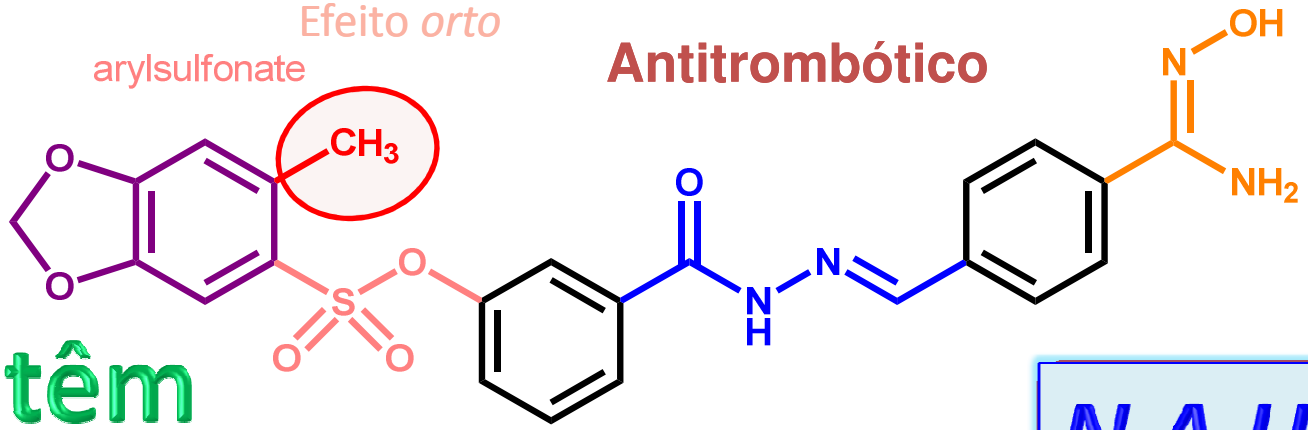
O quê têm em comum?

Efeito *orto*

arylsulfonate

Antitrombótico

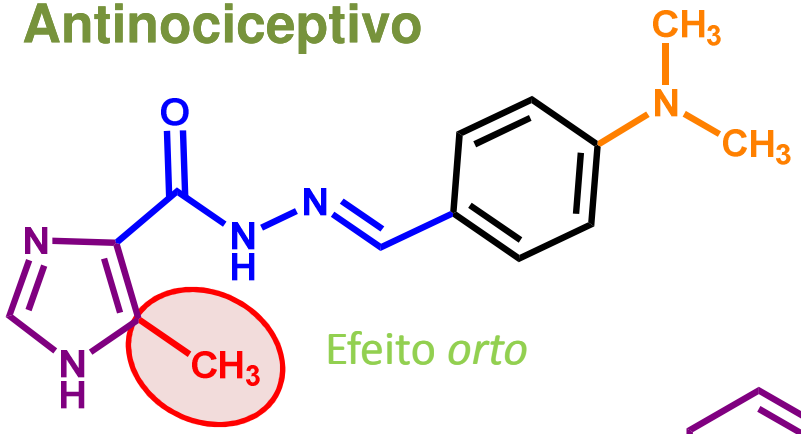


LASSBio-770

LM Lima *et al*., *Eur. J. Med. Chem*. **2008**, 43, 348

N A H

Antinociceptivo



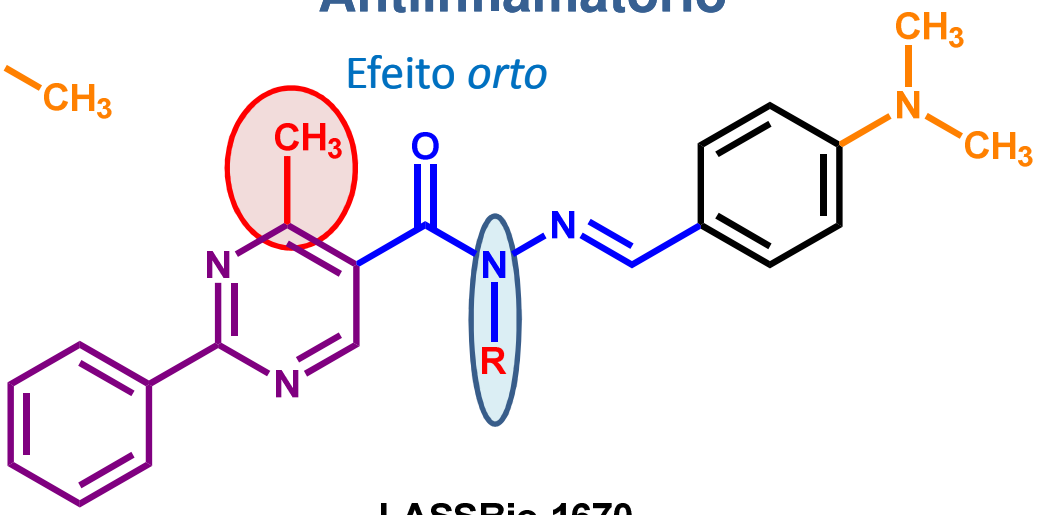
Efeito *orto*

LASSBio-456

JM Figueiredo *et al*., *Bioorg. Med. Chem*. **2008**, *43*, 187

Antiinflamatório

Efeito *orto*



LASSBio-1670

AB Lopes, Diss. Mestrado, Instituto de Química/UFRJ 2011

A B Lopes et al., *Molecules* **2013**, *18*, 11683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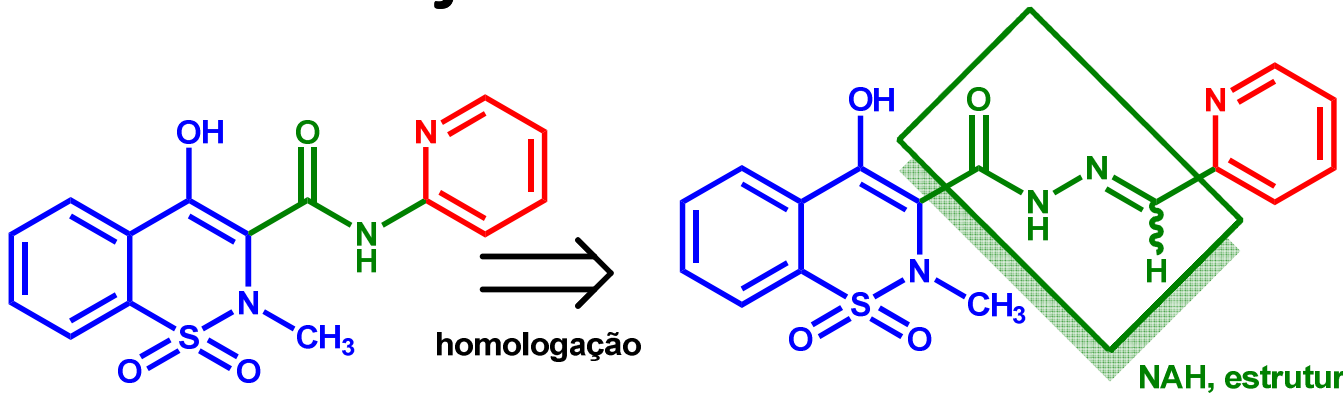
Quimioteca com 1871 compostos*
* 07/03/2014

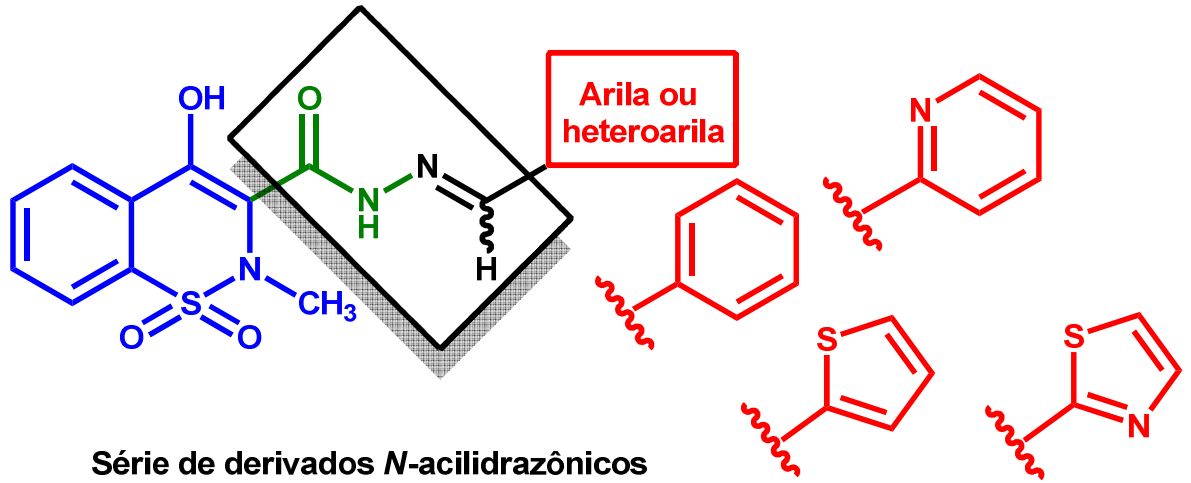
Planejamento estrutural



piroxicam

Inibidor de COX-1 / COX-2

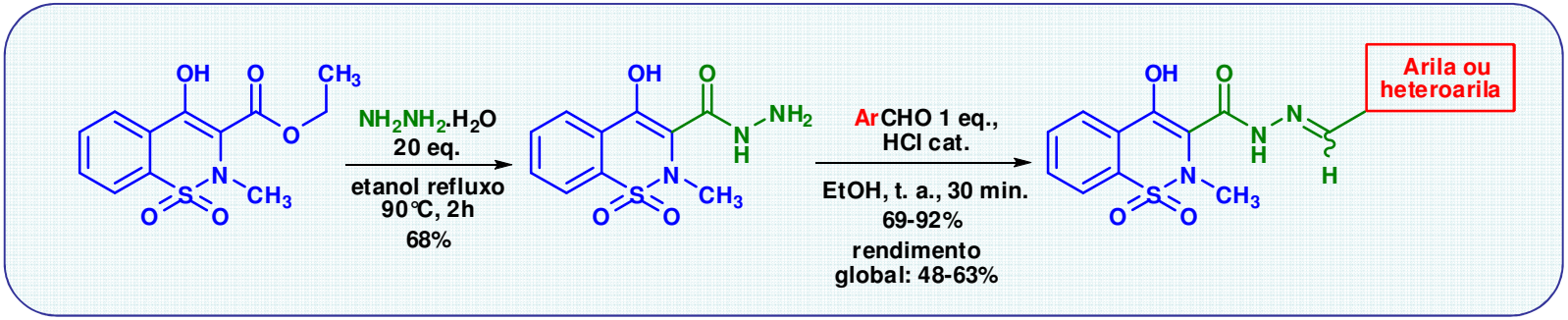
derivado aza-vinílogo

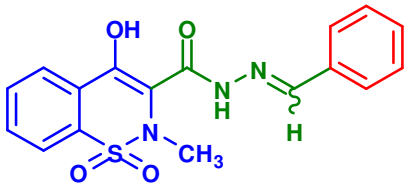


Série de derivados *N*-acilidrazônicos análogos ao piroxicam

de Miranda, A. S. et al., *Molecules* **2012,** *17*(12): e14126

Síntese dos novos derivados *N*-acilidrazônicos análogos ao piroxicam

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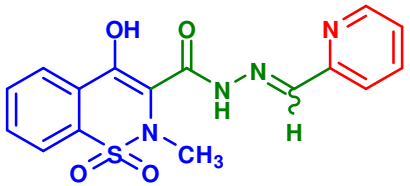
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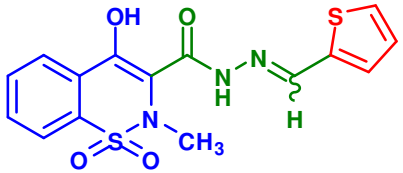
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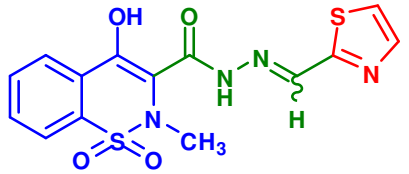
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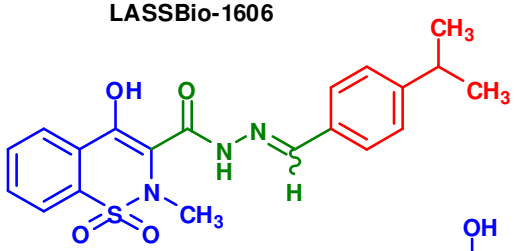
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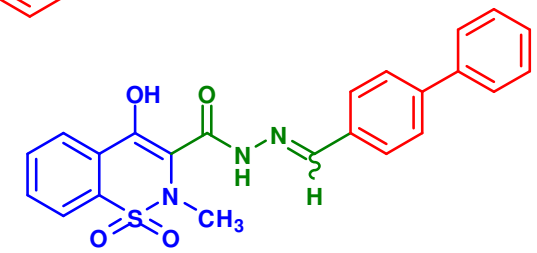
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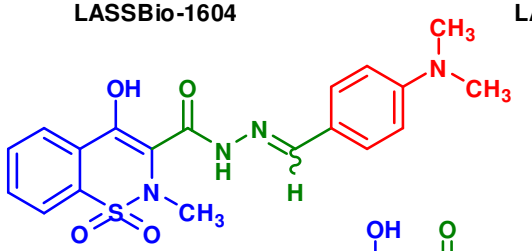
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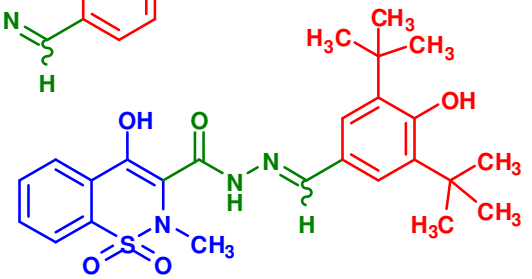

LASSBio-1639

molecules

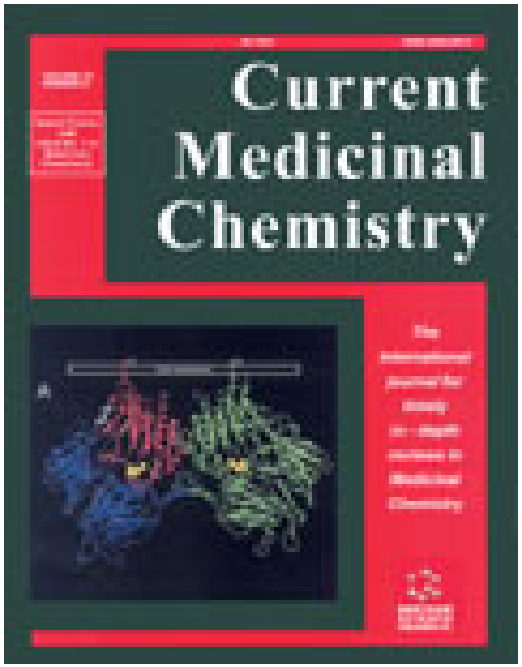
AS de Miranda et al., *Molecules* **2012**, *17*, 14126

Universidade Federal do Rio de Janeiro

MEDICINAL CHEMISTRY OF *N*-ACYLHYDRAZONES: NEW LEAD-COMPOUNDS OF ANALGESIC, ANTIINFLAMMATORY AND ANTITHROMBOTIC DRUGS

Carlos A.M. Fraga and Eliezer J. Barreiro

Volume 13, 167-198, 2006



In this article we provide an overview on the medicinal chemistry of new bioactive *N*-acylhydrazone (NAH) derivatives designed through the structural optimization of *N*-arylhydrazone precursors, originally planned by molecular hybridization of two known 5-lipoxygenase inhibitors, *i.e*. CBS-1108 and BW-755c. The analgesic, antiedematogenic and platelet anti-aggregating profile of several isosteric NAH compounds was investigated by using classical *in vivo* and *ex-vivo* pharmacological assays, which allowed the identification of new potent centrally and peripherically-acting analgesic leads, new antiinflammatory agents and new antithrombotic prototypes. During this study, dozens of active NAH compounds were discovered, clarifying the structure-activity relationships for this series of derivatives and indicating the pharmacophoric character of the *N*-acylhydrazone moiety for its biological profile.

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HIBRIDAÇÃO

Bioorganic & Medicinal Chemistry 20 (2012) 2158–2171

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

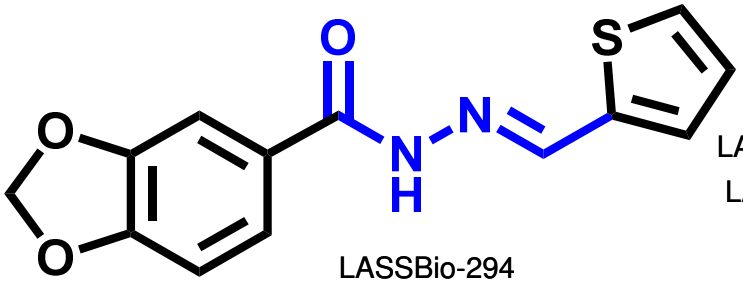
journal homepage: www.elsevier.com/locate/bmc

Discovery of new orally effective analgesic and anti-inflammatory hybrid furoxanyl *N*-acylhydrazone derivatives

Paola Hernández [a], Mauricio Cabrera [a], María Laura Lavaggi [a], Laura Celano [b], Inés Tiscornia [c], Thiago Rodrigues da Costa [d], Leonor Thomson [b], Mariela Bollati-Fogolín [c], Ana Luisa P. Miranda [d], Lidia M. Lima [d], Eliezer J. Barreiro [d,*], Mercedes González [d,*], Hugo Cerecetto [d,*]

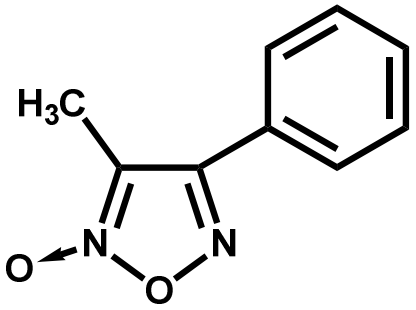
[a] Grupo de Química Medicinal, Laboratorio de Química Orgánica, Facultad de Ciencias-Facultad de Química, Uruguay
[b] Laboratorio de Enzimología, Facultad de Ciencias, Universidad de la República, Montevideo, Uruguay
[c] Cell Biology Unit, Institut Pasteur de Montevideo, Uruguay
[d] LASSBio-Laboratório de Avaliação e Síntese de Substâncias Bioativas, Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas



LASSBio-294

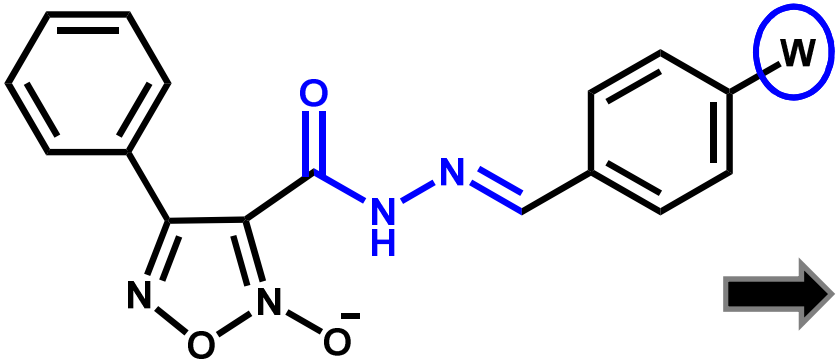
LASSBio-206
LASSBio-246



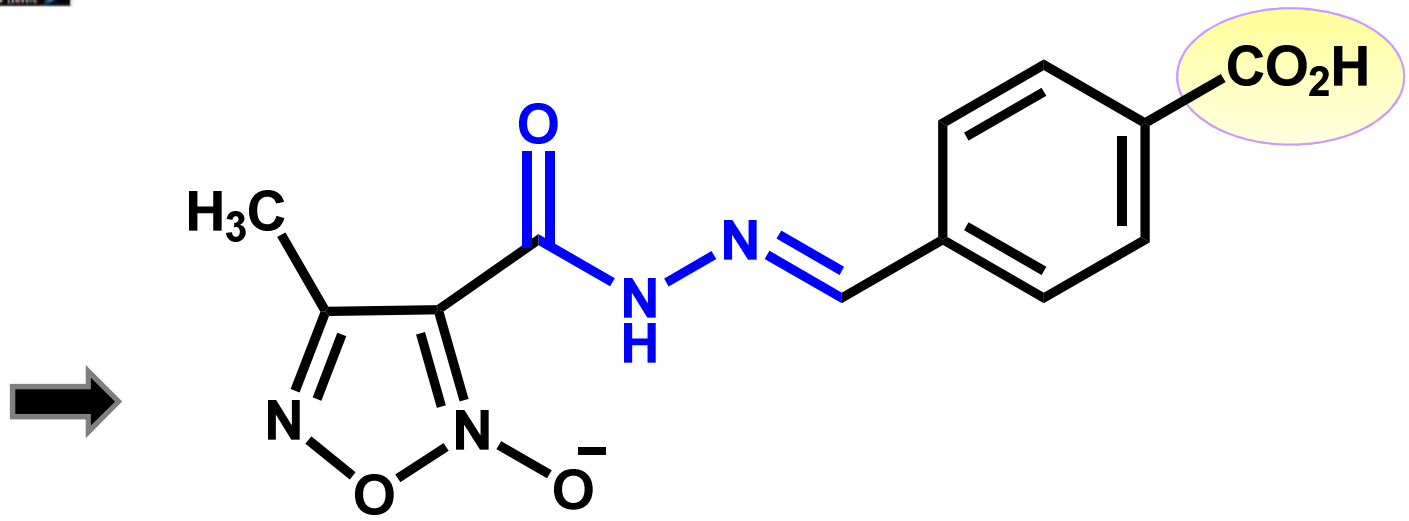
furoxana

Hibridação Molecular

Furoxanyl-*N*-acylhydrazones



42 new compounds



Novo derivado furoxanil-*N*-acilidrazônico

H Cerecetto

Atividade AI no CIRPE

IC_{50} (LOX) 35,0 µM
IL-8 < 50% (300µM)

P. Hernandez et al., Discovery of new orally effective analgesic and anti-inflammatory hybrid furoxanyl *N*-acylhydrazones derivatives, *Bioorg Med Chem* **2012**, *20*, 2158

Química Medicinal na Web

Banco de Dados (finalidade)[&]	Hyperlink
ChEBI (Estruturas químicas de interesse biológico)	http://www.ebi.ac.uk/chebi/
ChemBank (Quimioinformática)	http://chembank.broadinstitute.org/
ChemSpider (RSC; estruturas químicas e propriedades)	http://www.chemspider.com/*
ChEMBL (banco de dados de moléculas bioativas)	https://www.ebi.ac.uk/chembl/*
DISEASOME (Variações genéticas em doenças;109715 registros)	http://diseasome.kobic.re.kr/
PubChem/PubMed (Banco de dados de moléculas pequenas)[a)]	http://www.ncbi.nlm.nih.gov/pubmed*
2P2Is (informações estruturais sobre PPI's)	http://2p2idb.cnrs-mrs.fr/
STITCH (prediz interações entre estruturas)	http://stitch.embl.de/
IniPro (sequência de proteínas & classificação)	http://www.ebi.ac.uk/interpro/

[&] Outros sites uteis: PDB; IUPHAR; Zinc;* REACTOME; Supertarget; Sideeffects; WikiPathways (Beta); MetaCyc;
* Exemplos

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RVq Revista Virtual de Química

ISSN 1984-6835

Artigo

As Longas Pernas do Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio®; http://www.farmacia.ufrj.br/lassbio): Histórico e Perspectivas

Barreiro, E. J.

Rev. Virtual Quim., **2013**, *5* (2), 266-282. Data de publicação na Web: 19 de janeiro de 2013

http://www.uff.br/rvq

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Química Medicinal

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Revista Virtual de Química

Artigo

A química medicinal brasileira de 1998 a 2008 nos periódicos *Journal of Medicinal Chemistry, Bioorganic and Medicinal Chemistry, Bioorganic and Medicinal Chemistry Letters* e *European Journal of Medicinal Chemistry*

Bastos, Renato S.*; Silva, Bárbara V.; Pinto, Angelo C.

Rev. Virtual Quim., **2009**, 1 (1), 67-86. Data de publicação na Web: 2 de Fevereiro de 2009

http://www.uff.br/rvq

UFRJ

Universidade Federal do Rio de Janeiro

Química Medicinal

Química

med

Medicinal

chem

Farmacologia

LASSBio

Laboratório de Avaliação e Síntese de Substâncias Bioativas

Anos

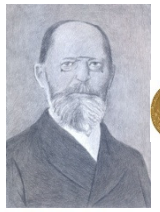
Parcerias

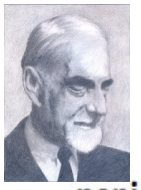
Interdisciplinaridade

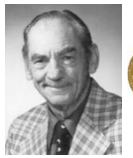
Universidade Federal do Rio de Janeiro

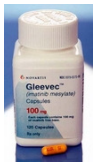
Linha do tempo...

Química Medicinal









Galeno

Fischer

Salvarsan^{R}

Fourneau

penicilina

Fleming

Bovet

indometacina

cimetidina

lovastatina

aciclovir

Elion

Hitchings

Black

imatinibe

estatina

indinavir

150 | 1902 | 1907 | 1911 | 1941 | 1945 | 1957 | 1962 | 1975 | 1980 | 1981 | 1987 | 1988 | 1996 | 2001

500aC | 1889 | 1908 | 1935 | 1943 | 1948 | 1959 | 1964 | 1982 | 1985 | 1991 | 2013

Hipocrates

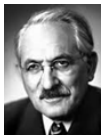
Paracelso

AAS

Ehrlich

Domagk

estreptomicina



Ahlquist

Kornberg

propranolol

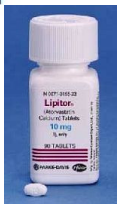
Hodgkin

Vane

Goldstein

Brown

atorvastatina



ponatinibe

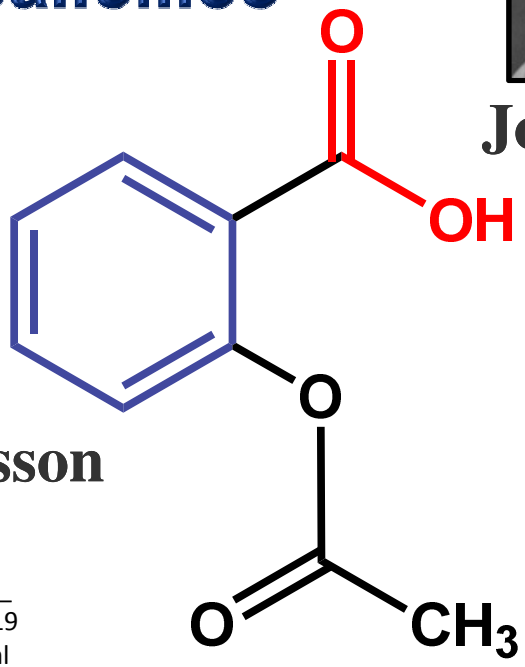
AAS

Os fármacos e o Nobel ! 1982

Ácido acetilsalicílico

Sune K. Bergström
(1916-2004)
http://nobelprize.org/nobel_prizes/medicine/laureates/1982/bergstrom-autobio.html

Bengt I. Samuelsson
(1934-)
http://nobelprize.org/nobel_prizes/medicine/laureates/1982/samuelsson-autobio.html

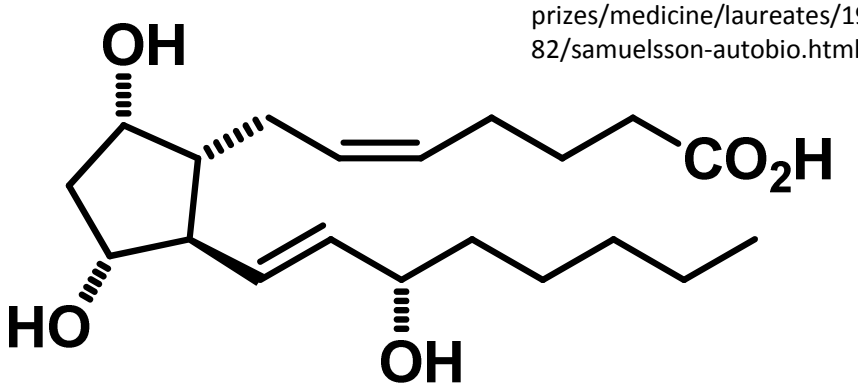


John R. Vane
(1927-2004)
http://nobelprize.org/nobel_prizes/medicine/laureates/1982/vane-autobio.html

$C_9H_8O_4$

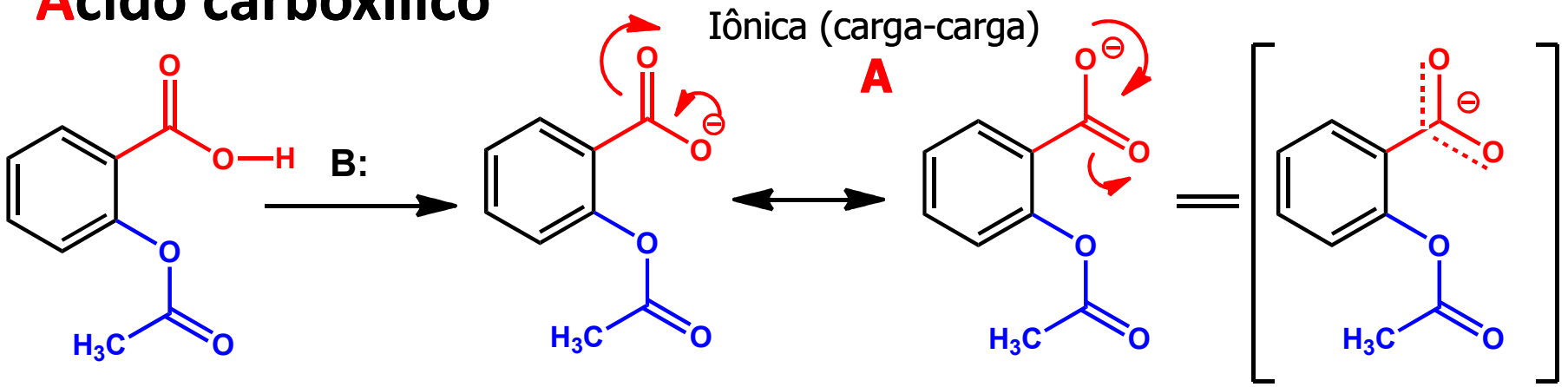
AAS

1889 ➡ 1982



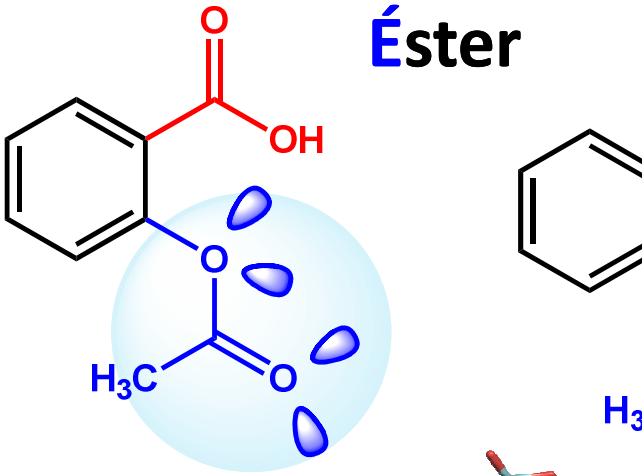
Prostaglandina $F_{2\alpha}$

Ácido carboxílico

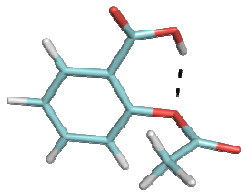


Dissecação molecular

Éster

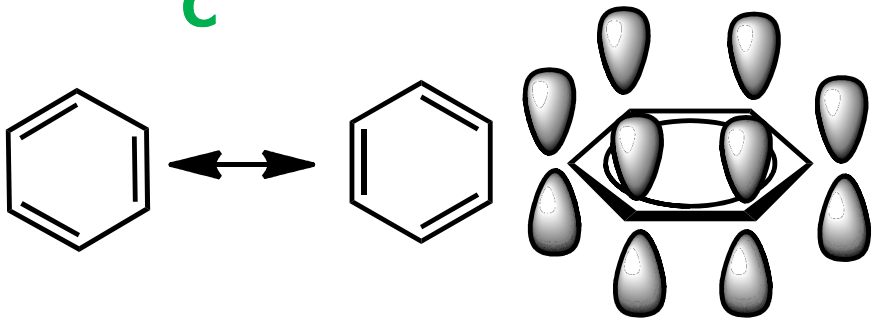


Ligação-H
B



Fenila

Interações π-π
C

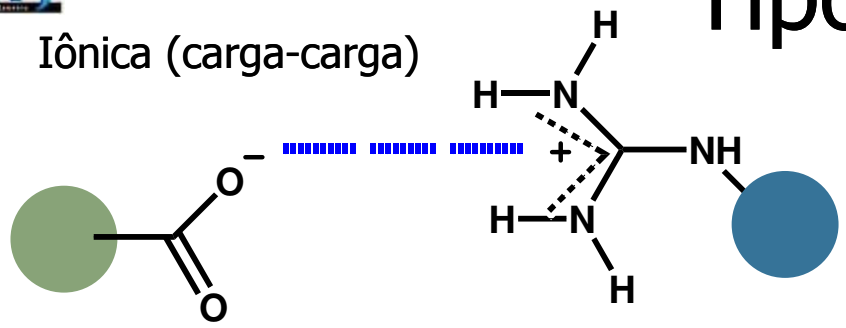


E_{int} =A >B >> C

***Pontos* farmacofóricos**

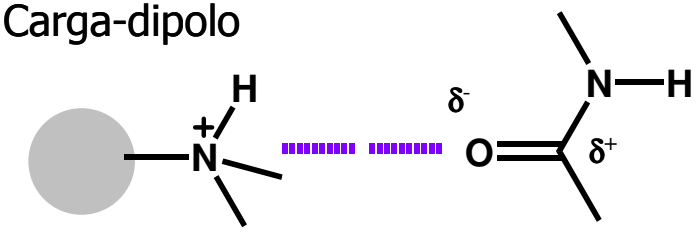
Tipos de interações F-R

Iônica (carga-carga)



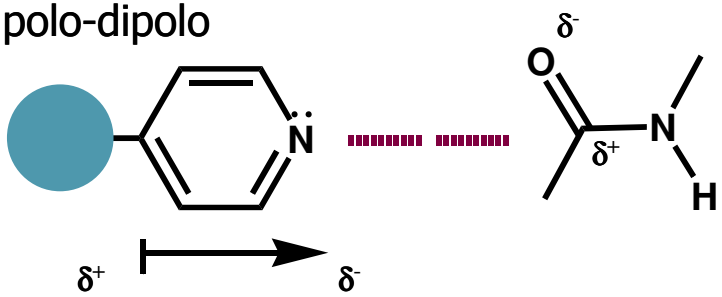
ΔG = 20-40kJ/mol

Carga-dipolo



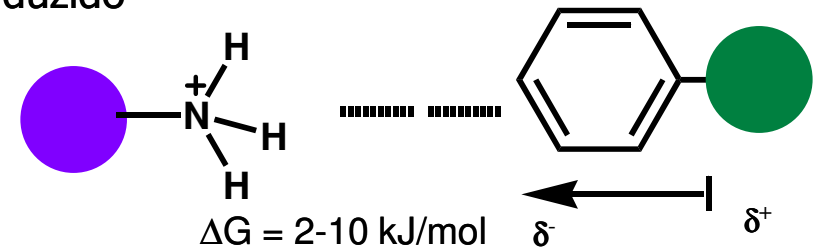
ΔG = 12-20kJ/mol

Dipolo-dipolo



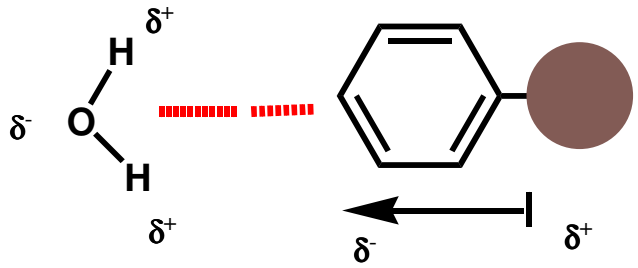
ΔG = 4-12 kJ/mol

Carga-dipolo induzido



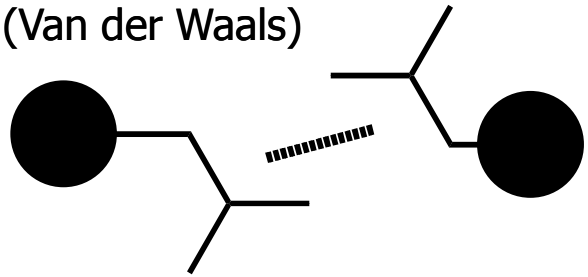
ΔG = 2-10 kJ/mol

Dipolo induzido-dipolo



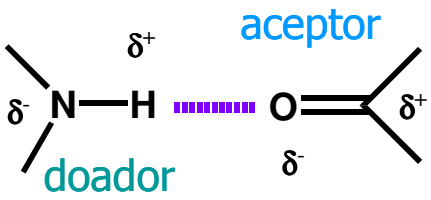
ΔG = 2 kJ/mol

Dispersão (Van der Waals)



ΔG = 2-4 kJ/mol

Ligação-H



ΔG = 4-30 kJ/mol

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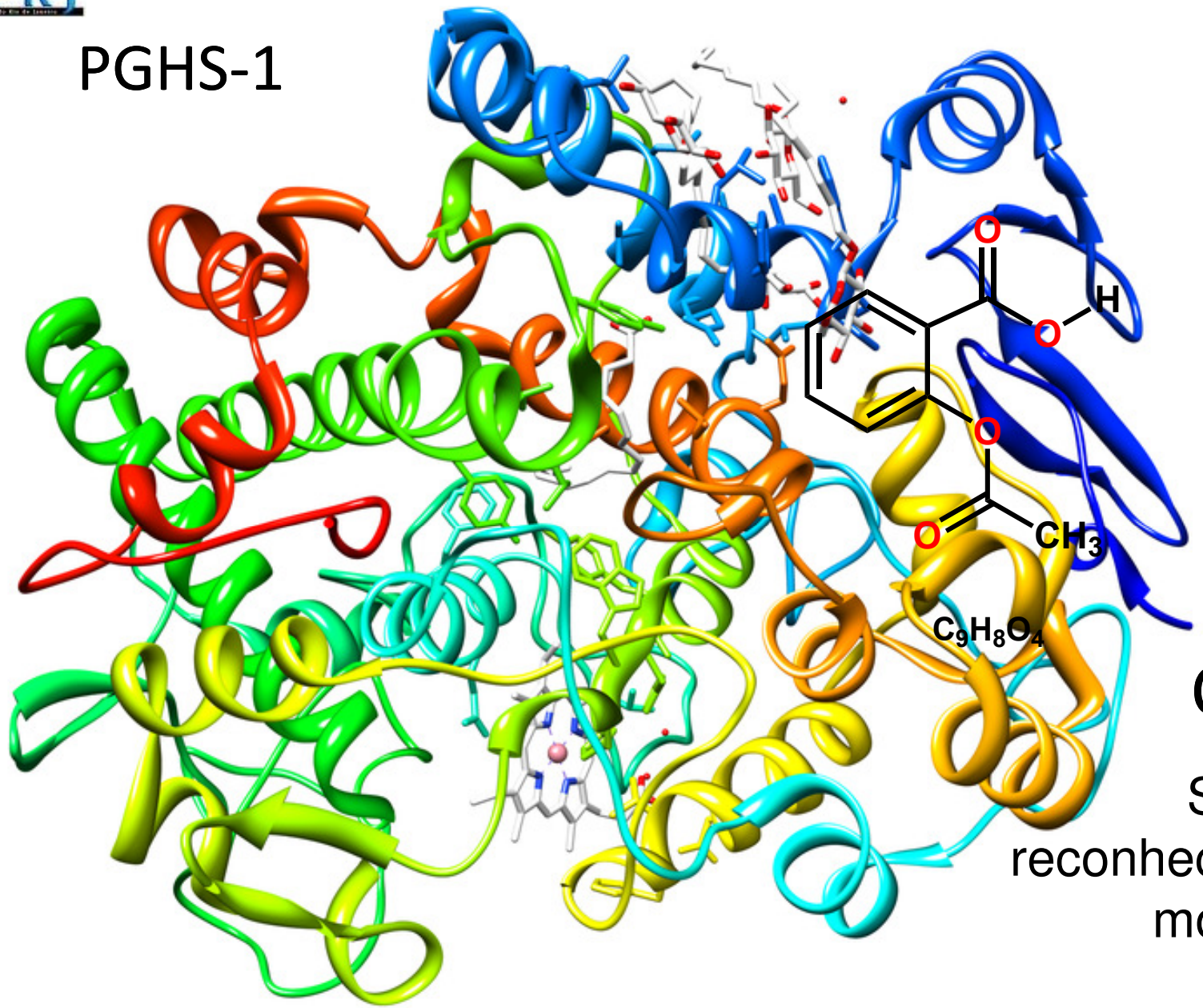
PGHS-1



COX-1

Sítio de reconhecimento molecular

PGHS-2 (COX-2): Kurumbail, R. G. *et. al.,* *Nature* **1996**, *384,* 644

Alvo terapêutico dos AINE´s (NSAI´s)

Cascata do AA