Princípios de Química Medicinal

MedChem

24ª Semana da Química do Instituto de Química da UFRJ
09-13 de maio de 2016

Eliezer J. Barreiro

Professor Titular

Instituto de Ciências Biomédicas

Universidade Federal do Rio de Janeiro

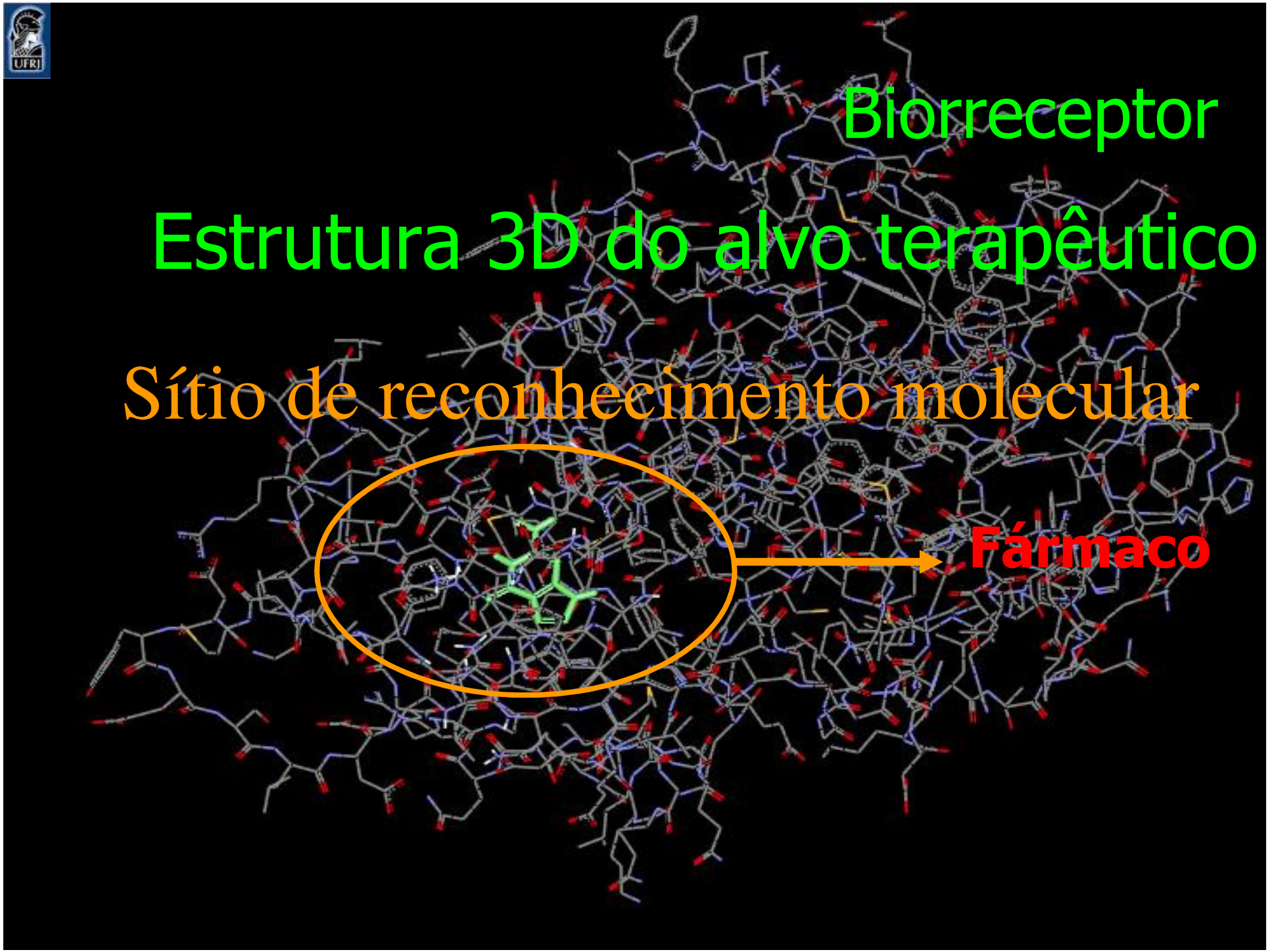
LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

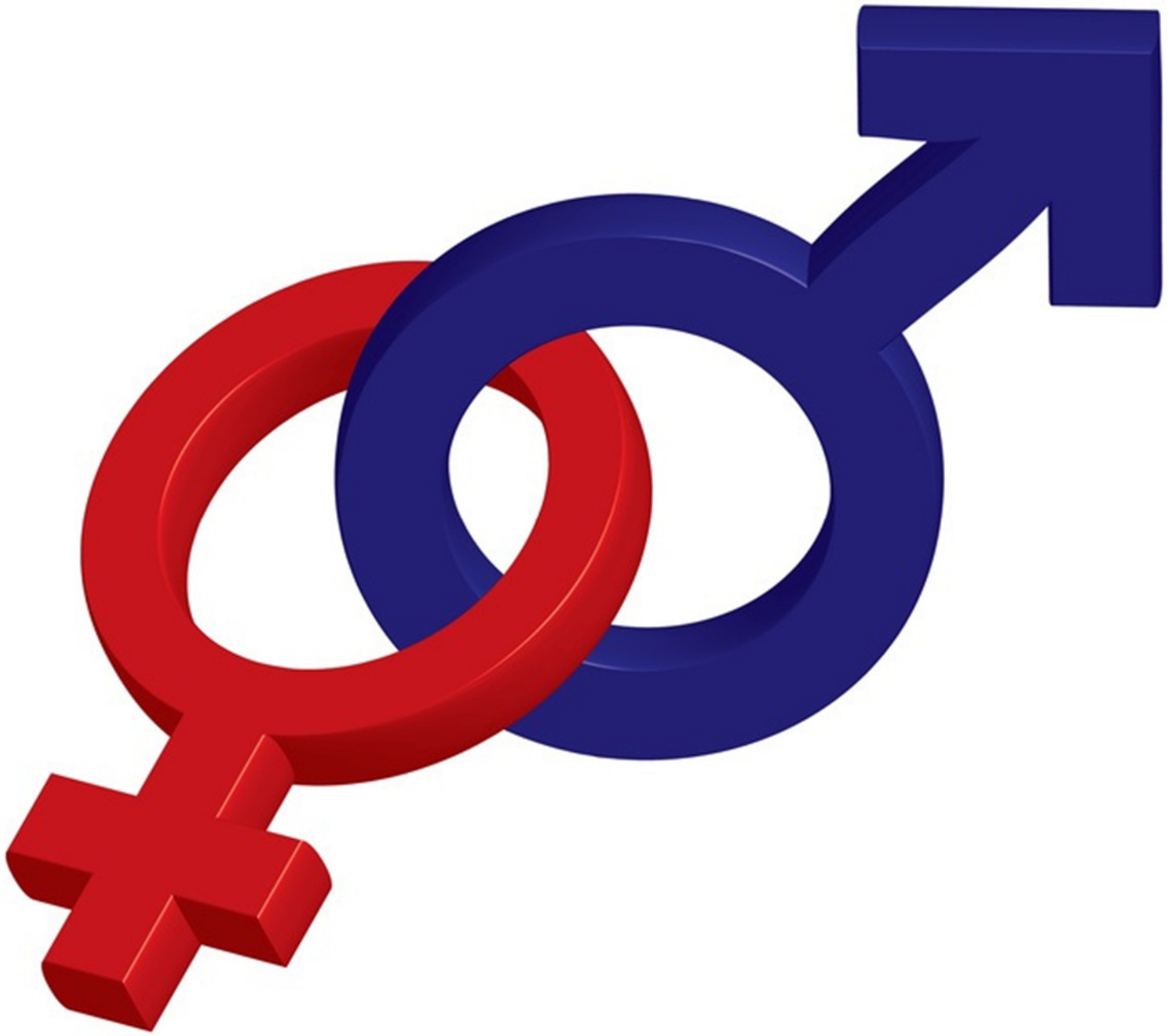
ICB
INSTITUTO DE CIÊNCIAS BIOMÉDICAS UFRJ

Parte 4

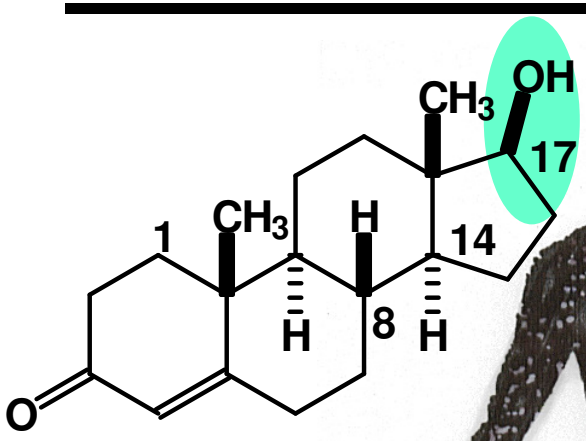
Sumário

Introdução; O processo de inovação de fármacos; O paradigma de Ehrlich & Fischer; Os alfabetos bioquímicos; As fases da ação dos fármacos; Aspectos moleculares da ação dos fármacos; Breve noção sobre o papel dos produtos naturais na descoberta de fármacos; Aspectos da química computacional: modelagem molecular; Estratégias para o desenho de novos candidatos a fármacos; Exemplos selecionados: LASSBio-294, LASSBio-349, LASSBio-445, LASSBio-1135, LASSBio-1819.


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

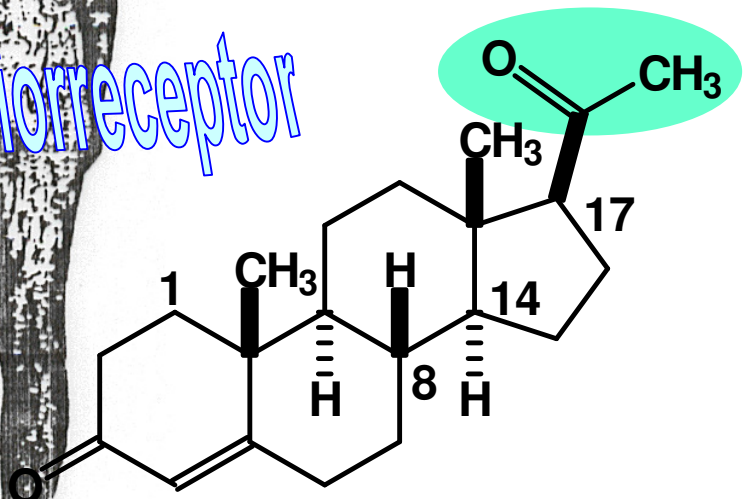


Similaridade Molecular



testosterona

no reconhecimento molecular pelo biorreceptor

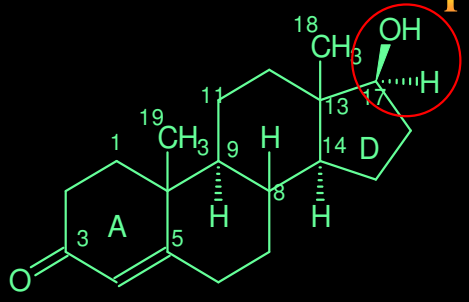


progesterona

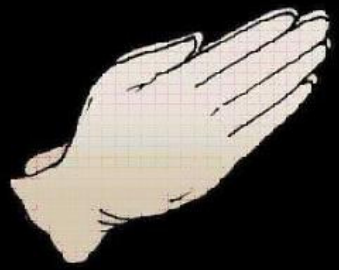
Similaridade Molecular

Biorreceptor

aceptor/doador-H

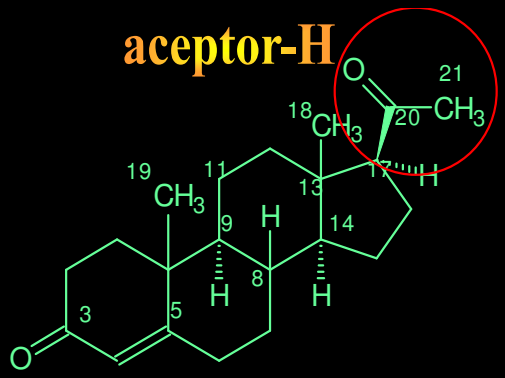


Testosterona

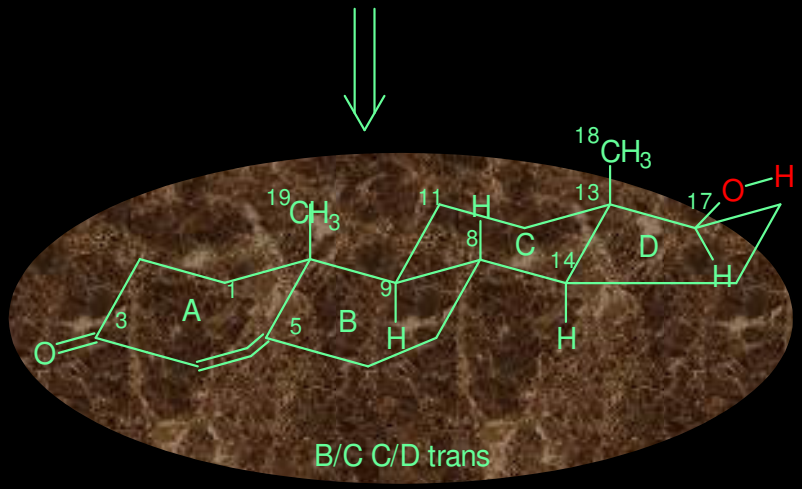


similaridade molecular

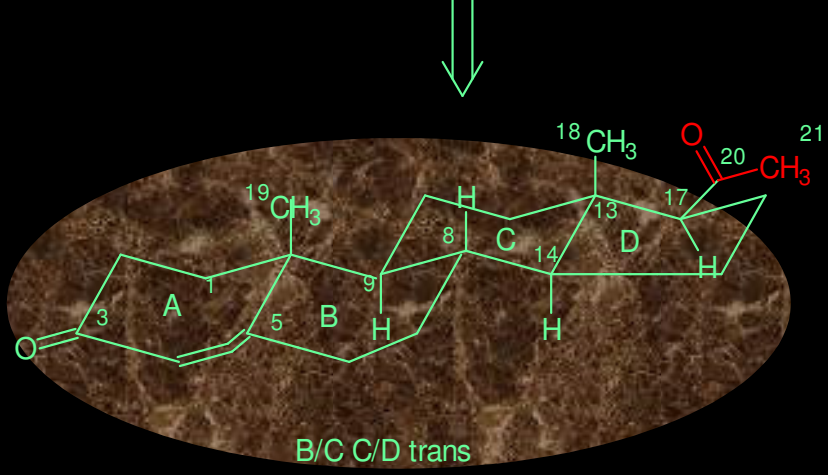
aceptor-H



Progesterona

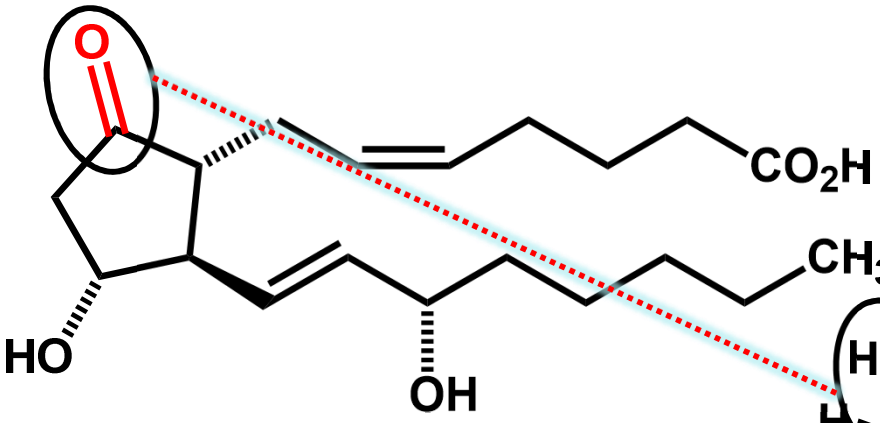


B/C C/D trans



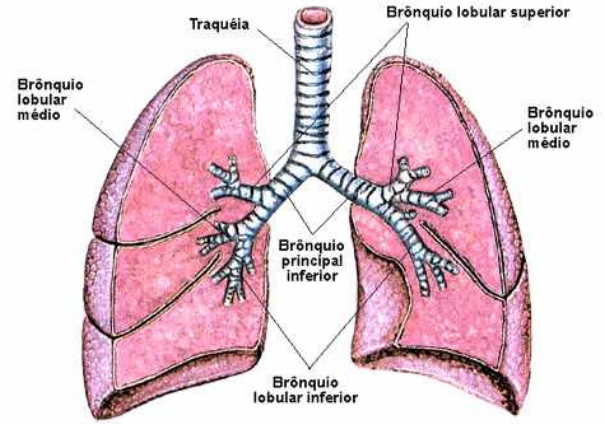
B/C C/D trans

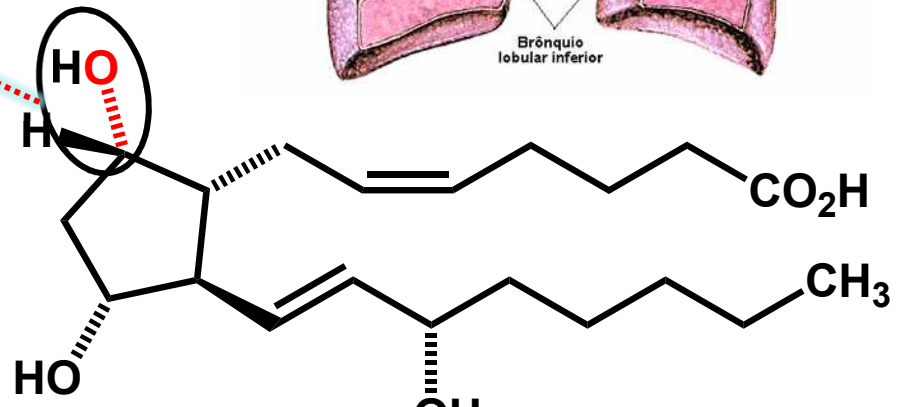
A *fidelidade* dos biorreceptores



$C_{20}H_{32}O_5$

PGE_2

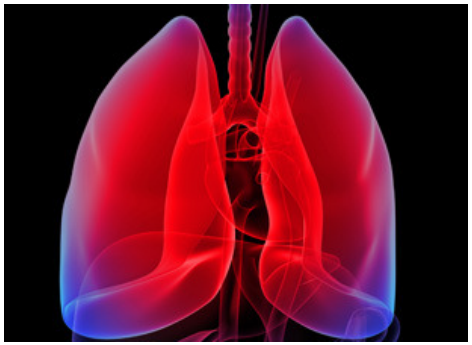




$C_{20}H_{34}O_5$

$PGF_{2\alpha}$

$PGF_{2\alpha}$ em cães provoca intensa <u>broncodilatação</u>



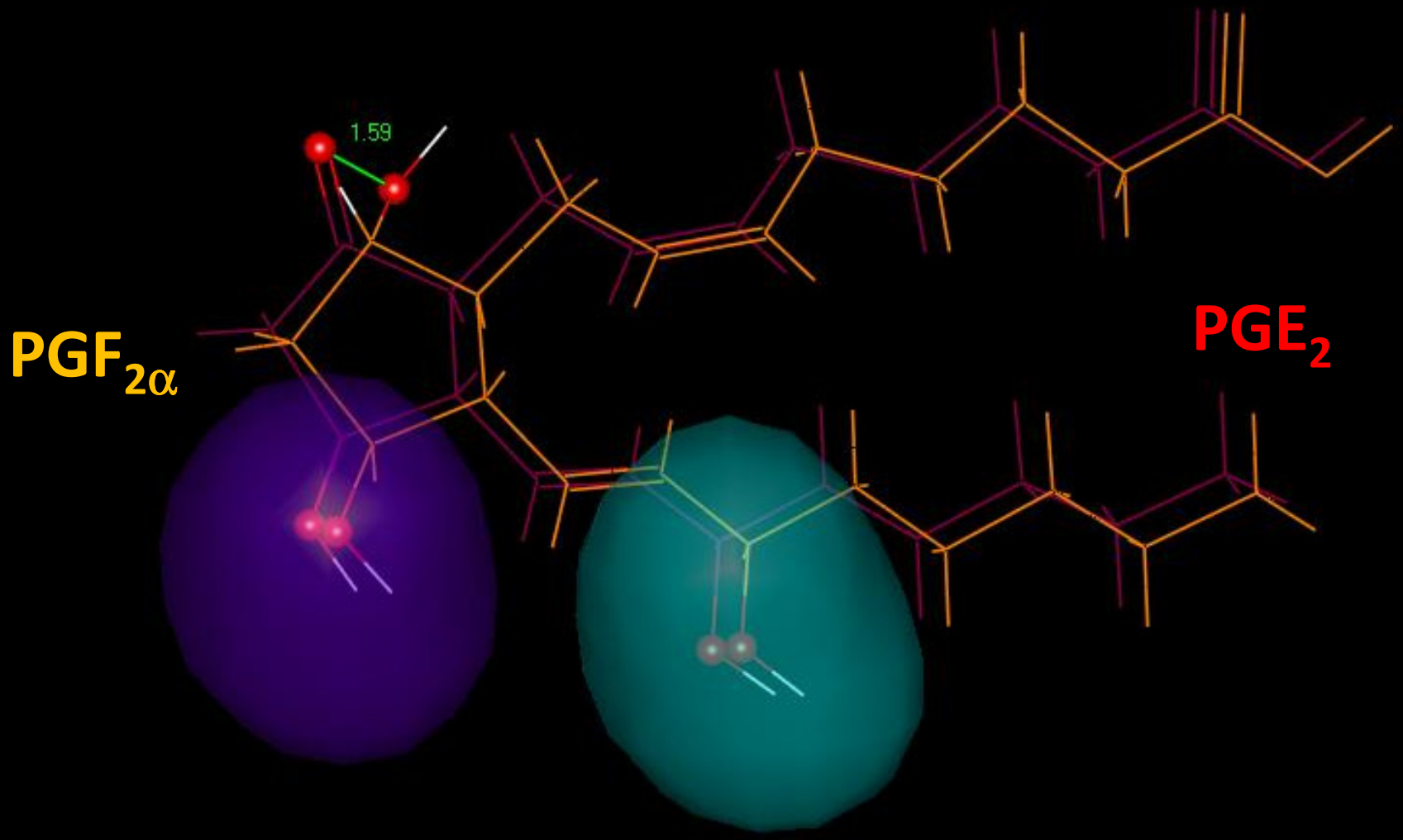
EPr

FPr

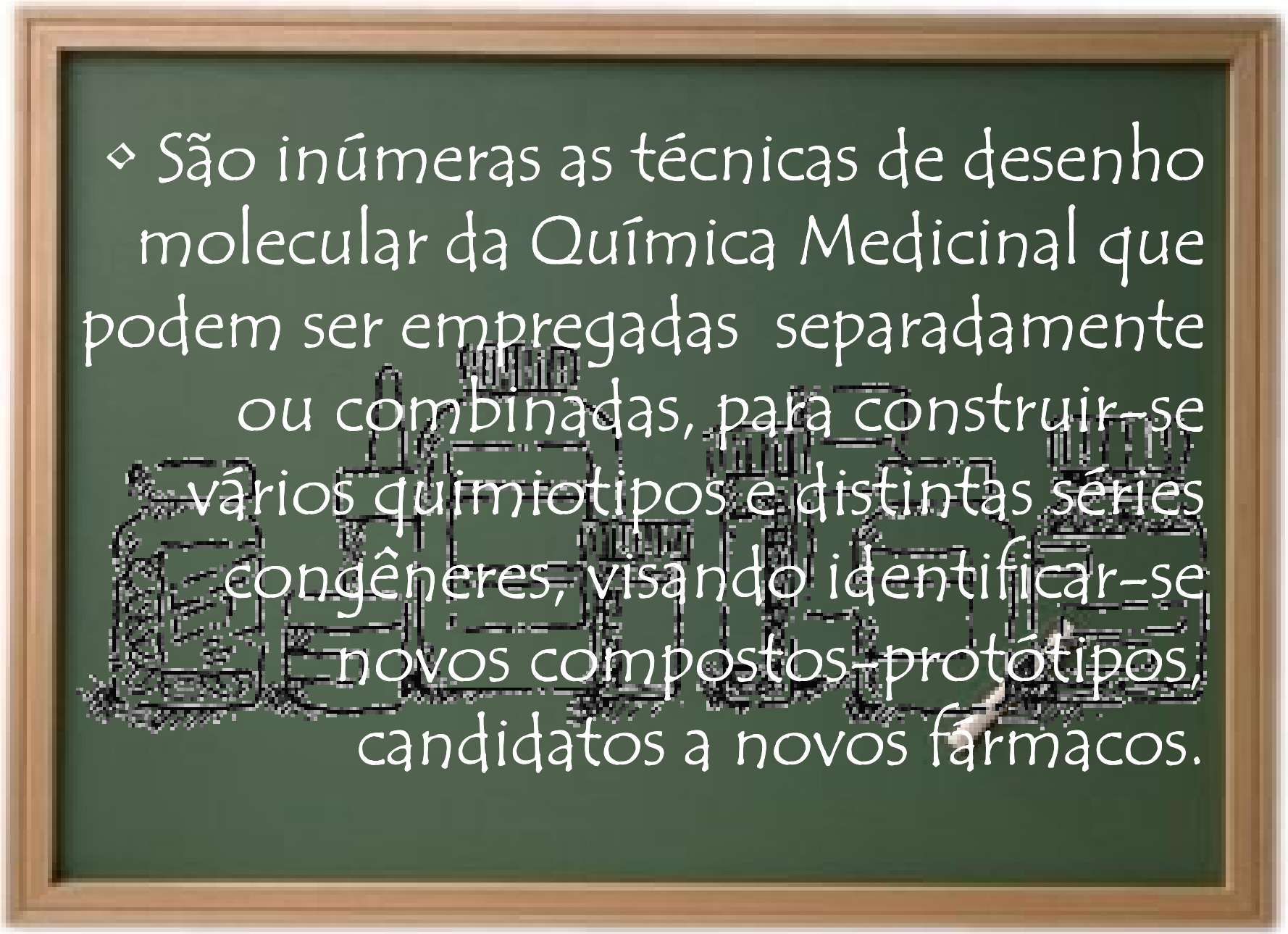
$PGF_{2\alpha}$ em cães provoca severa <u>broncoconstrição</u>

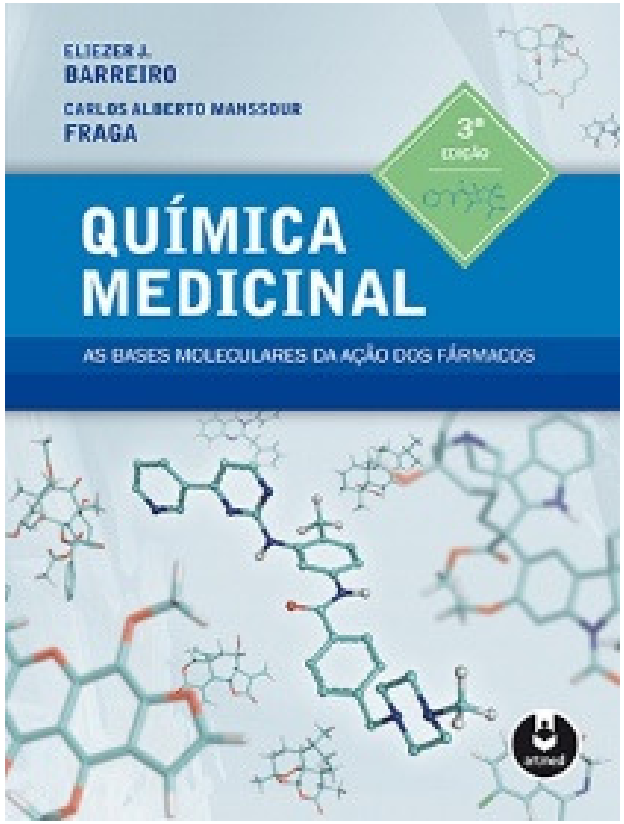
Reconhecimento Molecular Similaridade molecular

Sobreposição molecular



Ferramentas da Química Medicinal


São inúmeras as técnicas de desenho molecular da Química Medicinal que podem ser empregadas separadamente ou combinadas, para construir-se vários quimiotipos e distintas séries congêneres, visando identificar-se novos compostos-protótipos, candidatos a novos fármacos.



Química Medicinal

Cap. 5

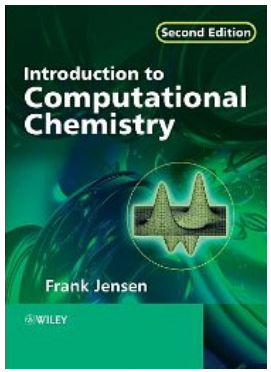
Química Computacional

2013

Ariel Warshel
(1940 -)

Michael Levitt
(1947 -)

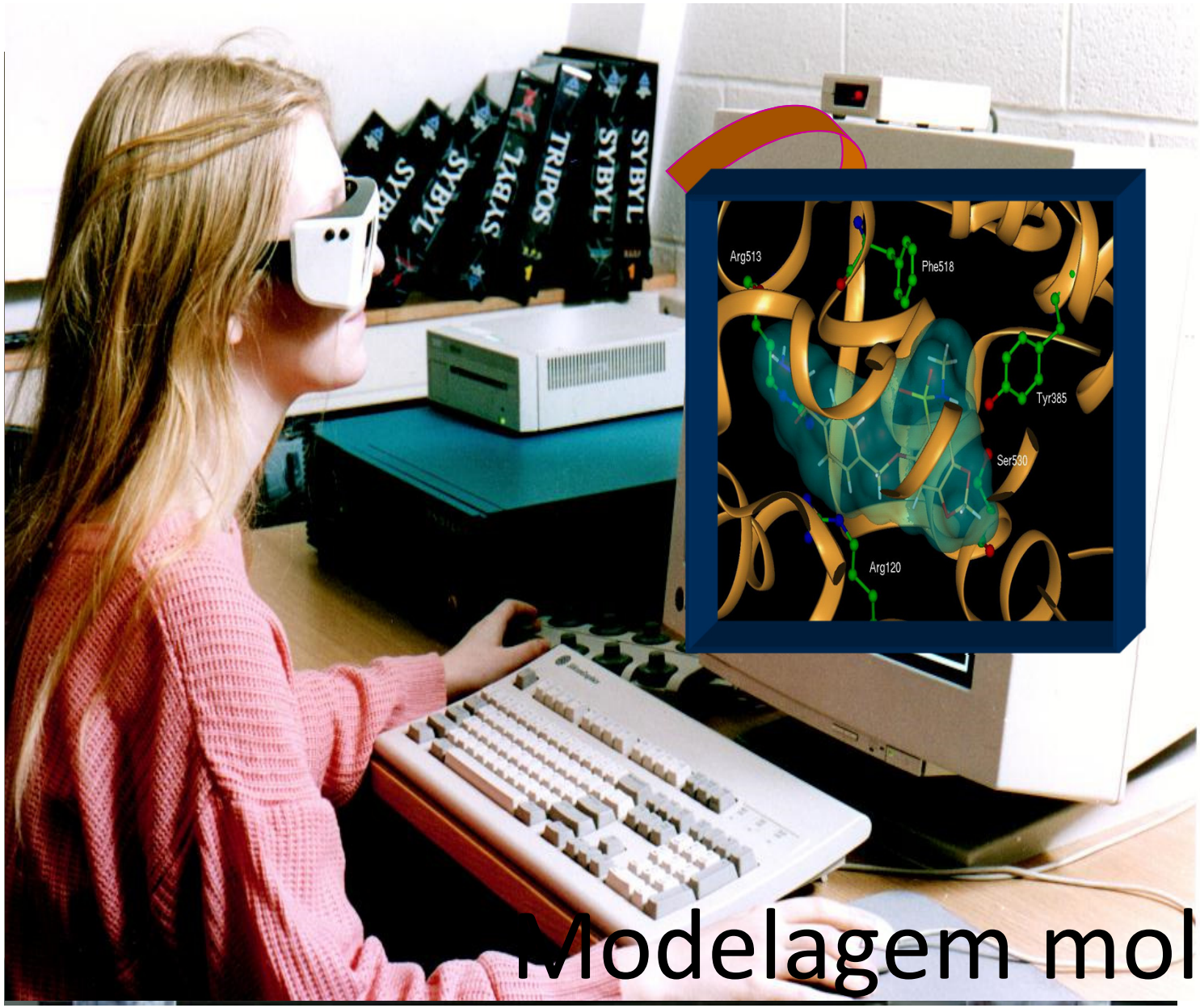
Martin Karplus
(1930 -)

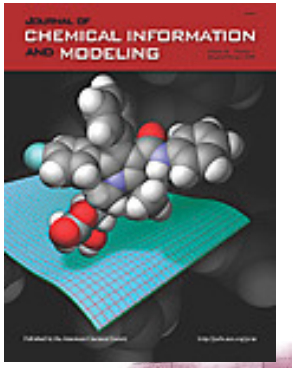


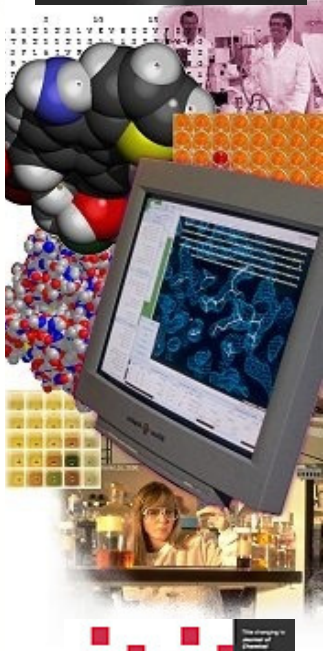
Modelagem & dinâmica molecular

"for the development of multiscale models for complex chemical systems"

Química Computacional

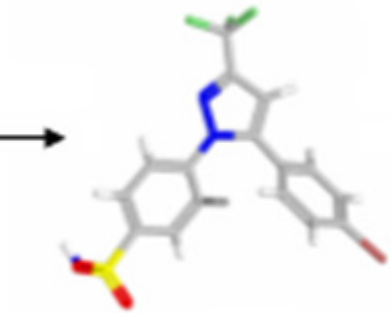




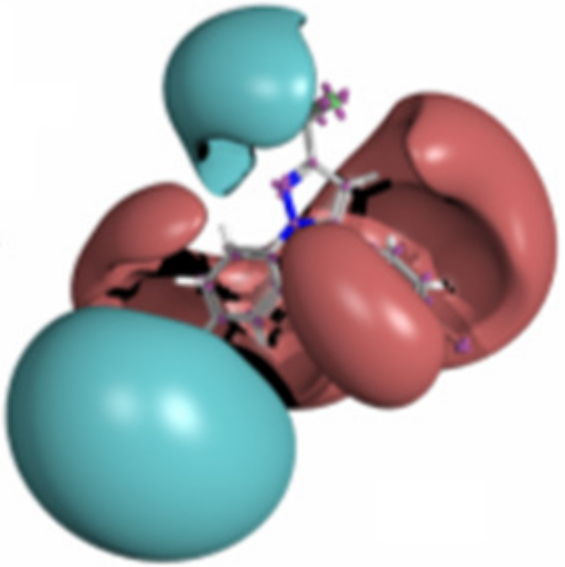


Modelagem molecular

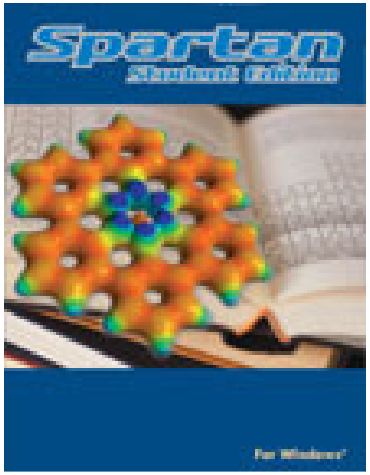
2D



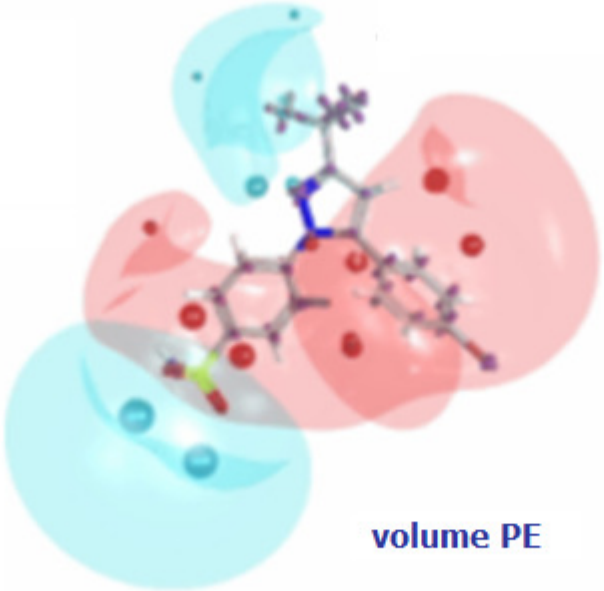
3D



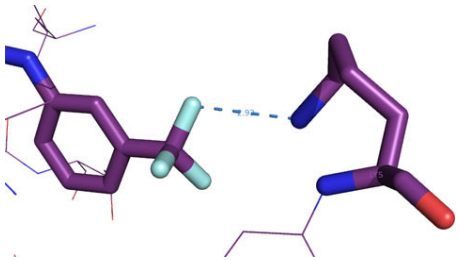
MPE

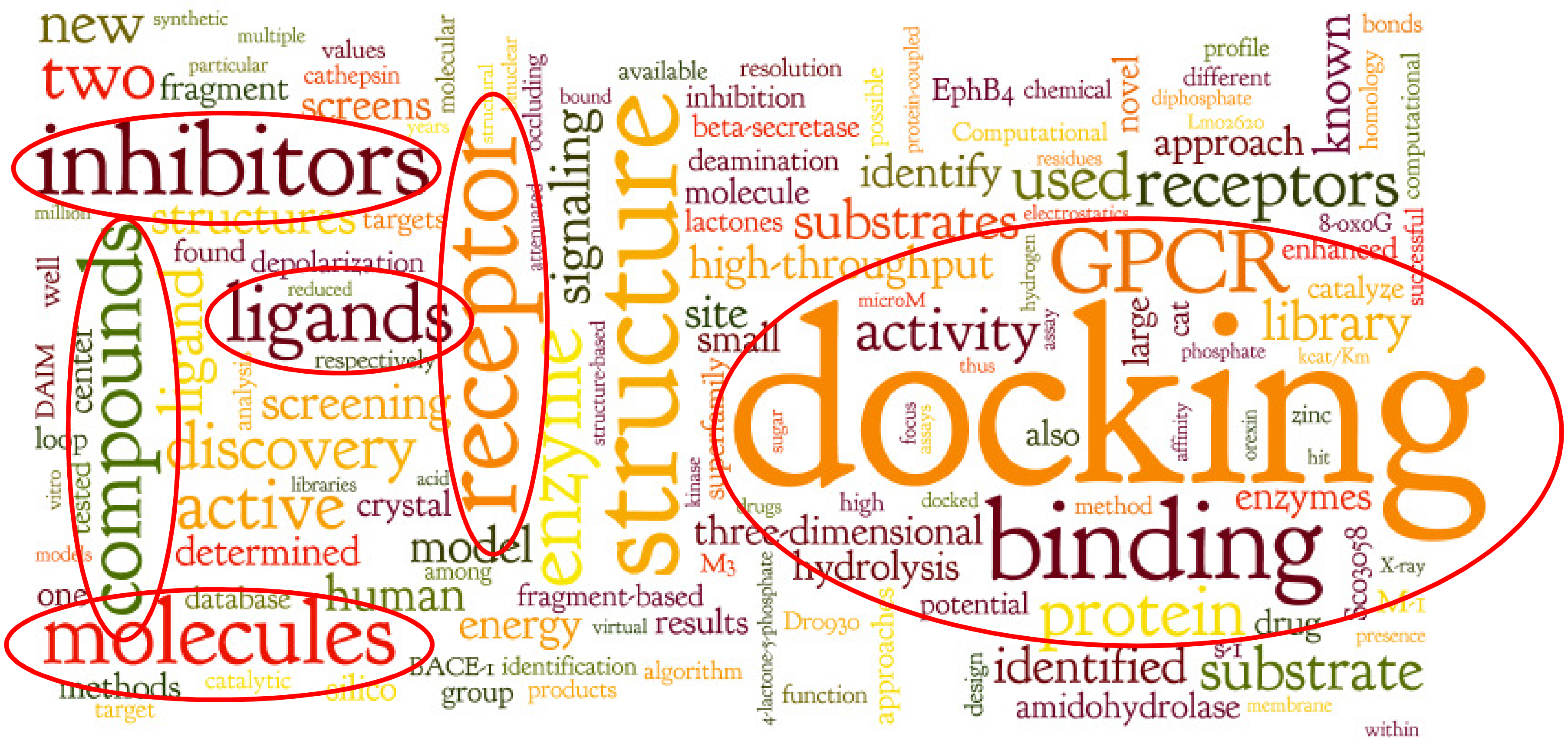


14.0



volume PE




docking
binding
inhibitors
structure
receptor
compounds
molecules
ligands
GPCR
receptors
protein
substrate
enzyme
activity
library
identified
used
substrates
high-throughput
discovery
active
ligand
structures
screening
signaling
human
model
determined
energy
identify
approach
known
two
new
fragment
screens
cathepsin
values
particular
synthetic
multiple
molecular
available
resolution
inhibition
beta-secretase
deamination
molecule
lactones
EphB4
chemical
novel
Computational
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bonds
homology
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crystal
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found
depolarization
reduced
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targets
million
well
center
tested
DAIM
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one
database
methods
catalytic
silico
target
BACE-1
identification
group
algorithm
products
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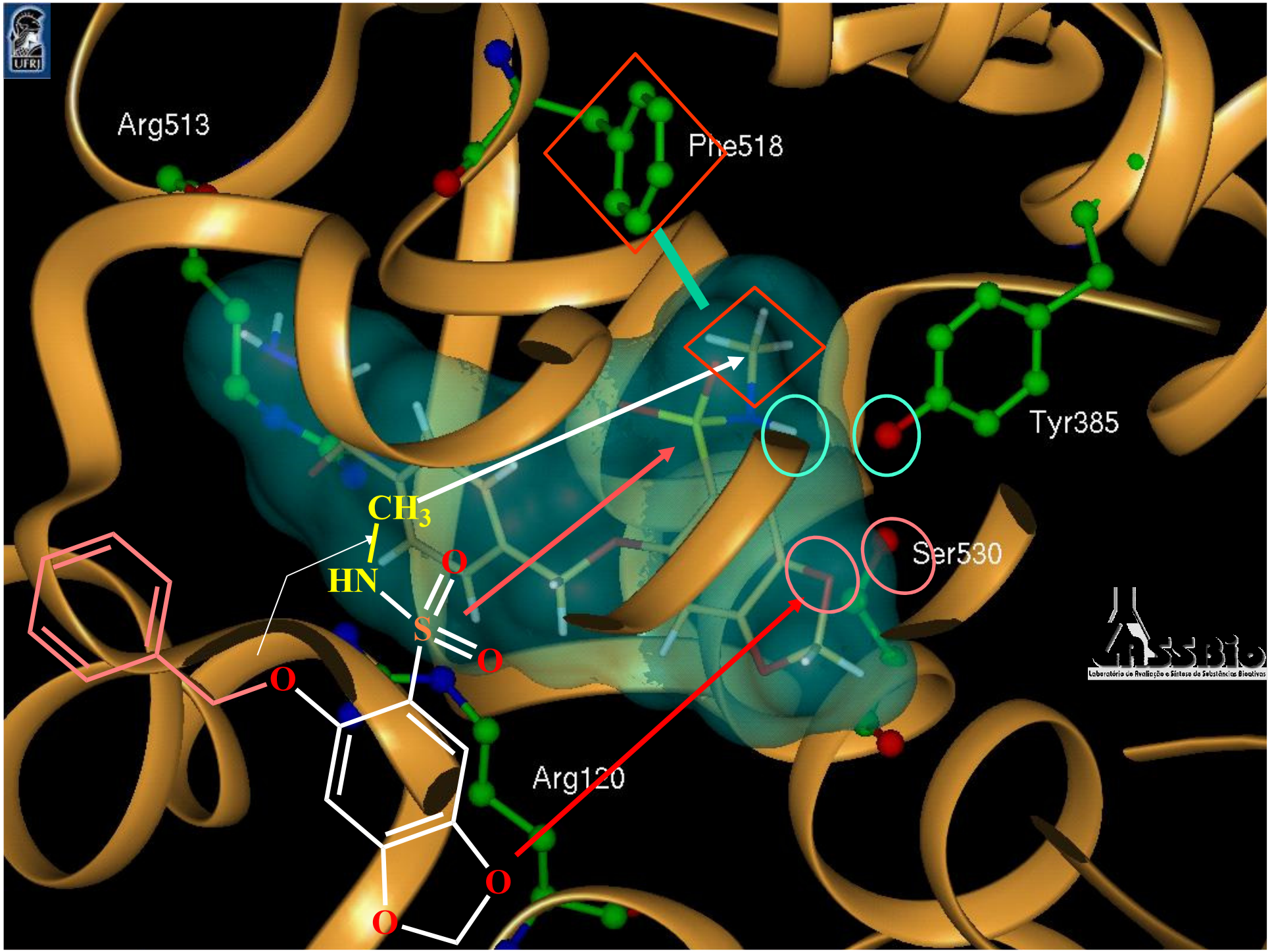
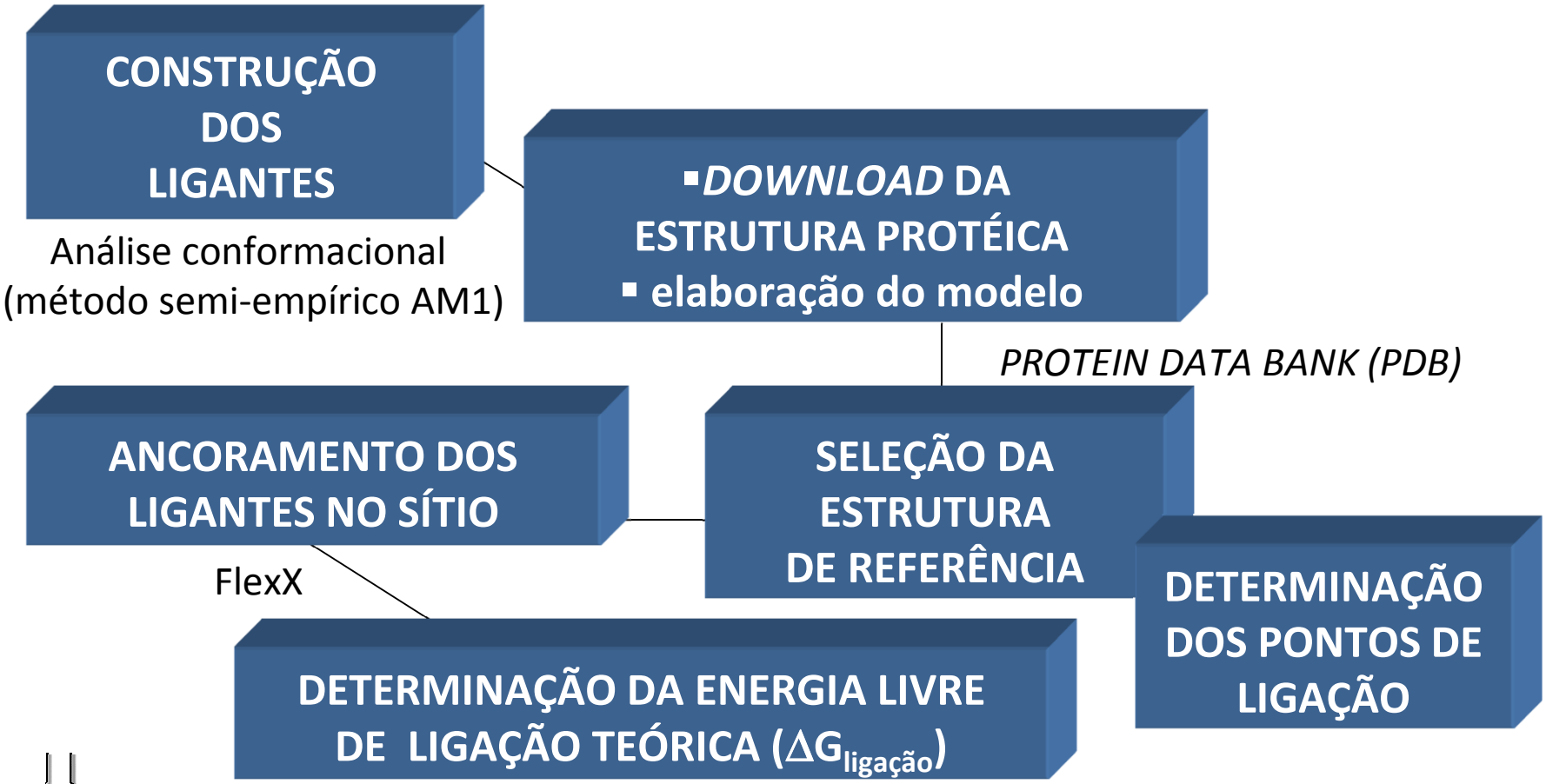
function
approaches
design
amidohydrolase
membrane
within
potential
drug
presence
X-ray
three-dimensional
hydrolysis
M3
method
enzymes
high
docked
drugs
kinase
superfamily
also
large
cat
phosphate
kcat/Km
zinc
hit
orexin
affinity
focus
assays
sugar
thus
microM
hydrogen
assay
residues
electrostatics
possible
protein-coupled
bound
occluding
structural
binuclear
attenuated
structure-based
4-lactone-5-phosphate
acid
among
years
Lm02620


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

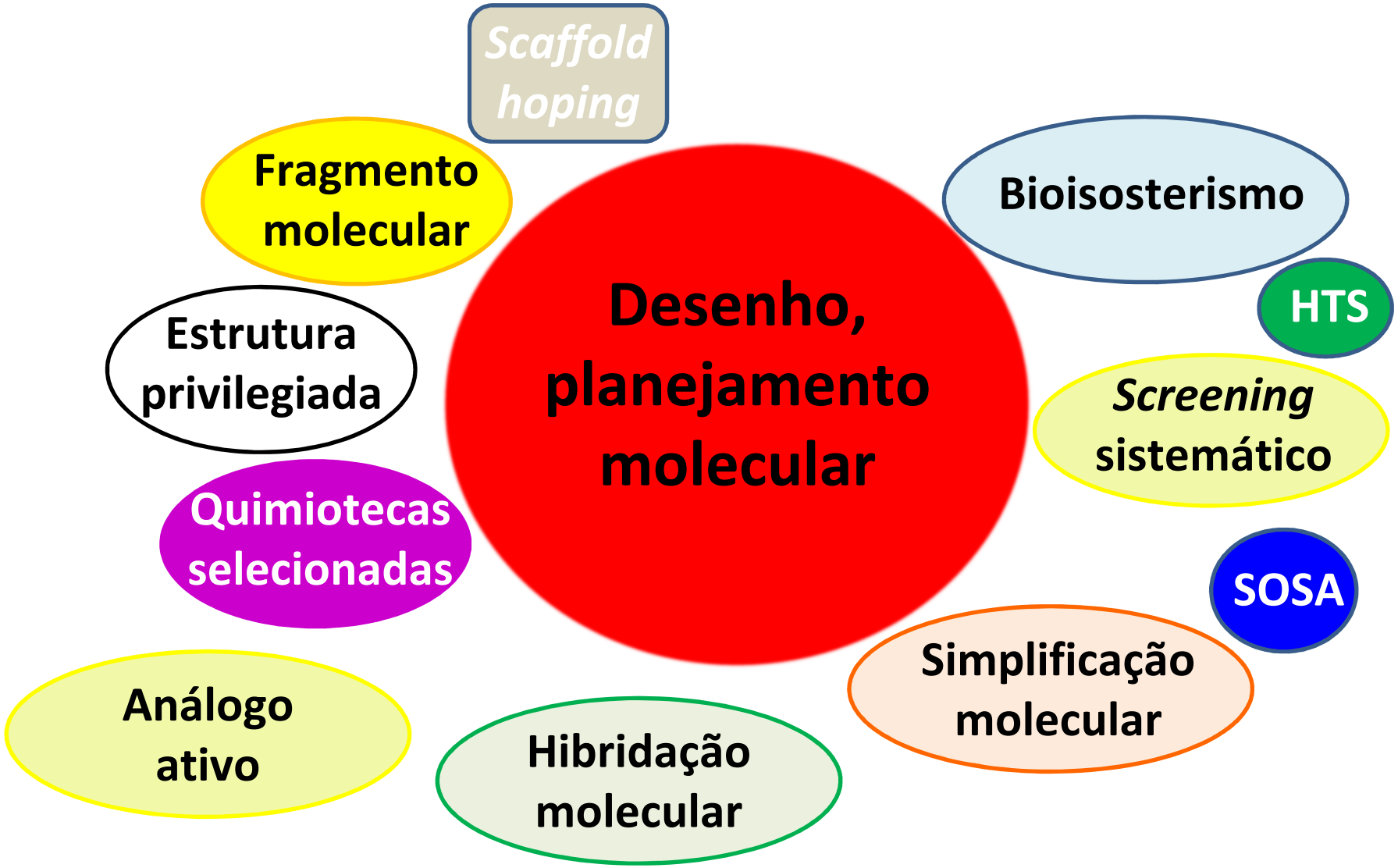
Metodologia: Estudos de *docking*



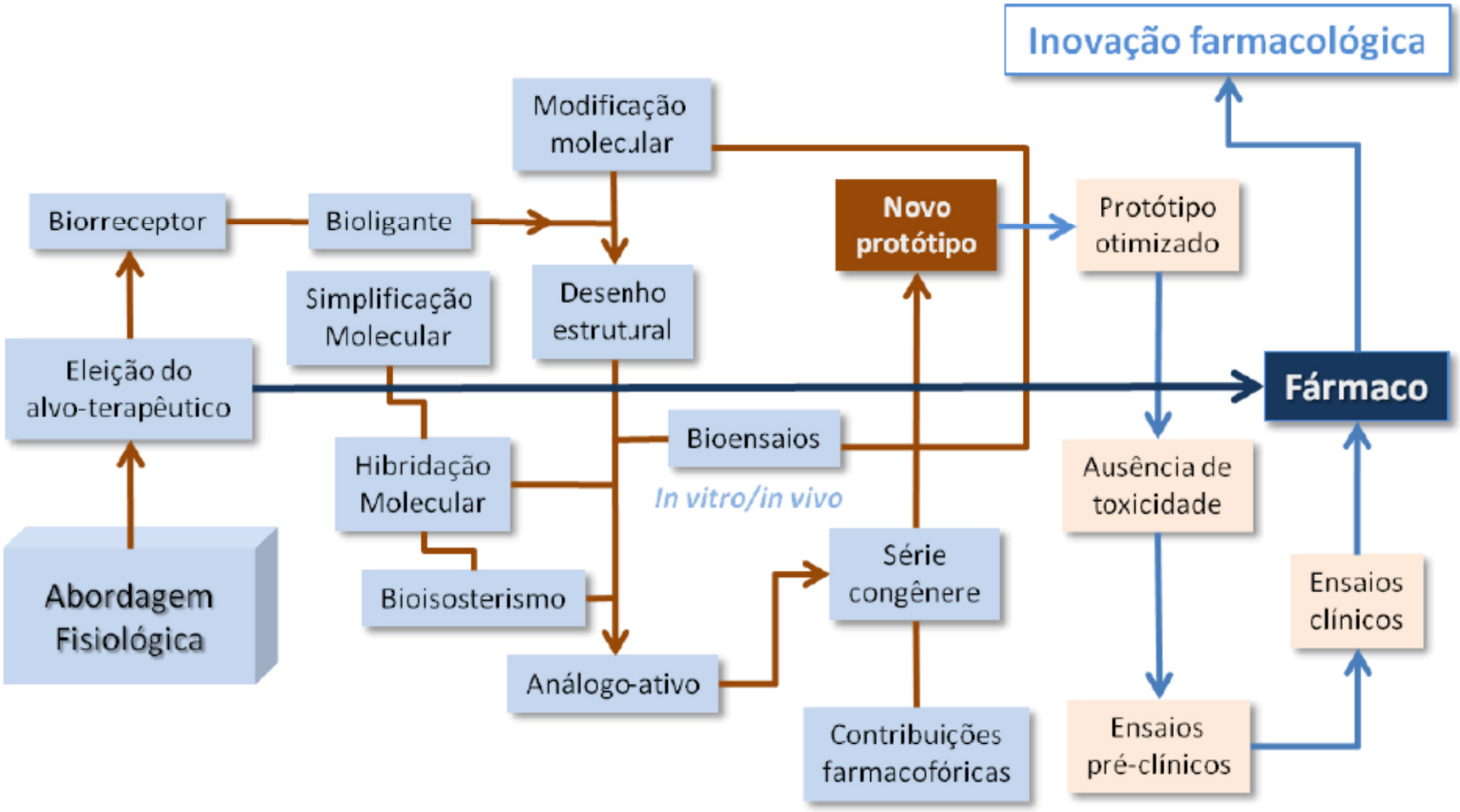
Interface gráfica GUI, Maestro, Sybyl, Accelrys, MOE, ICM

Sybyl, Version 8.0, Tripos Associates: St. Louis, MO, 2007 (**Licença # 7512**)
Spartan Pro; Wavefunction, Inc. 18401 Von Karman Avenue, Suite 370. Irvine, California 92612, USA (**Licença # 1-001259**)

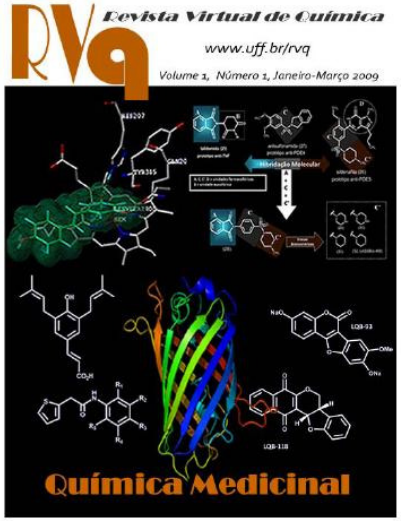
Estratégias de desenho molecular



O composto protótipo



Química Medicinal



RVq | Revista Virtual de Química

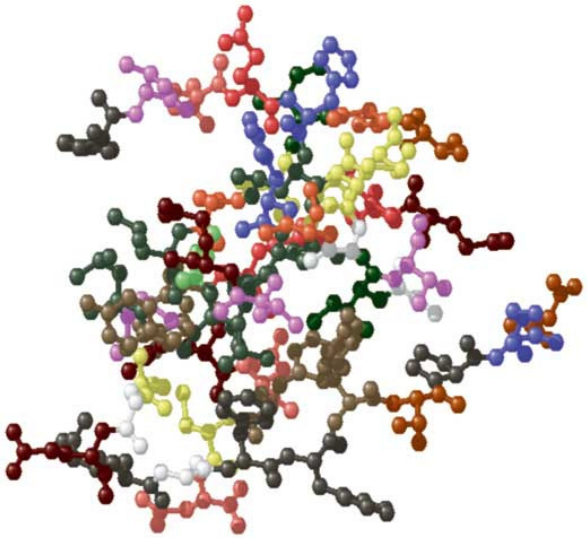
Artigo

A Química Medicinal e o paradigma do composto-protótipo

Barreiro, Eliezer J.*

Rev. Virtual Quim., 2009, 1 (1), 26-34. Data de publicação na Web: 2 de Fevereiro de 2009

http://www.uff.br/rvq



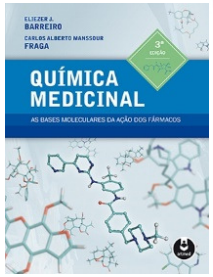
Medicinal Chemistry and the paradigm of the lead compound

Abstract: This paper briefly describes the application of the physiological approach strategy to the invention of new lead compounds, candidates for drugs from different therapeutic classes, exemplified by the discovery of some hits in the Laboratory of Synthesis and Evaluation of Bioactive Substances (LASSBio®) of the Federal University do Rio de Janeiro.

Otimização do protótipo

Química Medicinal

Lead Optimization



CAPÍTULO 4

PLANEJAMENTO RACIONAL BASEADO NO MECANISMO DE AÇÃO: FÁRMACOS INTELIGENTES 171

Características do composto protótipo

Composto inédito, original (*i.e*. patentiabilidade)

Obtido por metodologia sintética eficiente, simples, de reações clássicas, sem efluentes ambientalmente impactantes, sem purificações cromatográficas, com até 4 etapas consecutivas;

Sólido com propriedades adequadas, *i.e.* cristalino, não-higroscópico, sem polimorfismo;

Termo estável (70^{o}C), insensível à luz, estável à ácido;

Coeficiente de solubilidade em água adequado;

Biodisponibilidade oral, com dose única ao dia (5-10mg);

Estratégia do *scaffold* molecular

Drug Discovery Today: Technologies Vol. 1, No. 3 2004

Editors-in-Chief
Kelvin Lam – Pfizer, Inc., USA
Henk Timmerman – Vrije Universiteit, The Netherlands

Lead optimization

Scaffold hopping

Hans-Joachim Böhm, Alexander Flohr, Martin Stahl*

Molecular Structure and Design, Pharmaceuticals Division, F. Hoffmann-La Roche AG, PRBD-CS, Building 092/3.56B, CH-4070 Basel, Switzerland

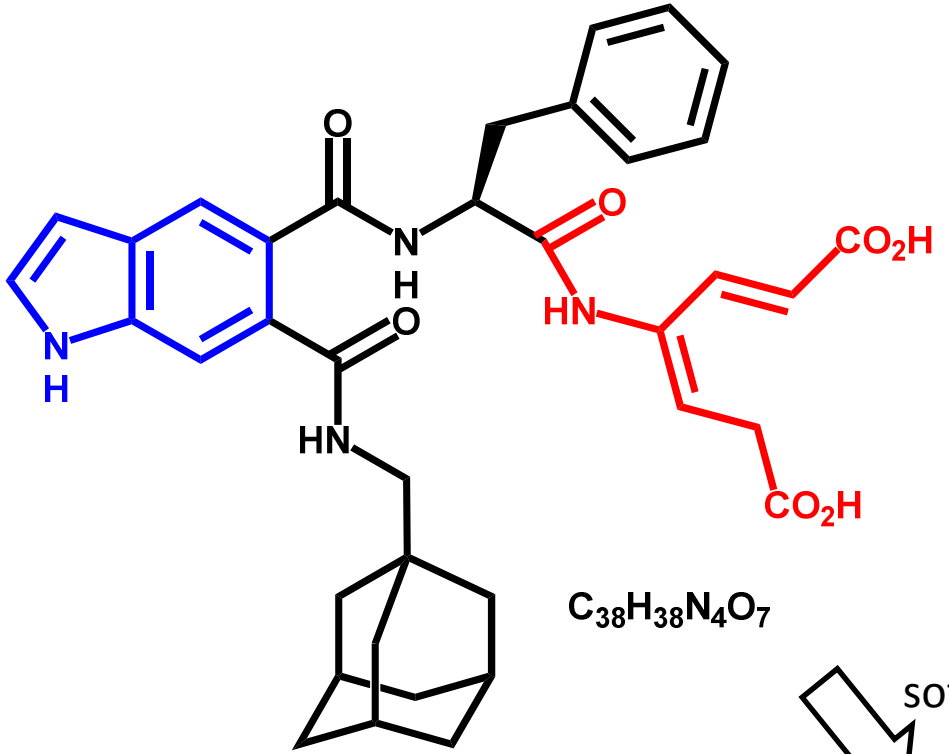
The aim of scaffold hopping is to discover structurally novel compounds starting from known active compounds by modifying the central core structure of the molecule.

Scaffold hopping is a central task of modern medicinal chemistry requiring a multitude of techniques, which are discussed in this article.

Section Editor:
Hugo Kubinyi – University of Heidelberg, Germany

In lead optimization, systematic decoration of a common scaffold and bioisosteric replacement are the predominant techniques of structural variation. Scaffold hopping is an approach to generate new chemistry, starting from any lead structure. This article describes success stories as well as computational procedures to "hop" from one scaffold to another one, to modify affinities and selectivities, to improve physicochemical and ADMET properties, and/or to arrive at patentable analogs.

Their application has led to several molecules with chemically completely different core structures, and yet binding to the same receptor. Computational approaches for scaffold hopping highlight the challenges of the field that are still unsolved.



$C_{38}H_{38}N_4O_7$

CCK2 antagonista protótipo

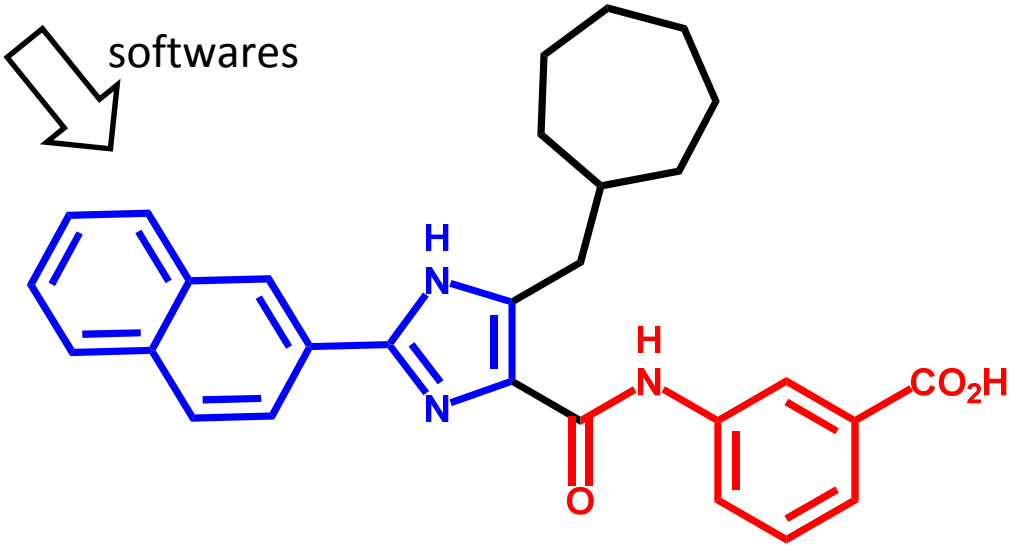
Scaffold hopping

Scaffold hunter

Scaffold search

Scaffold library

softwares



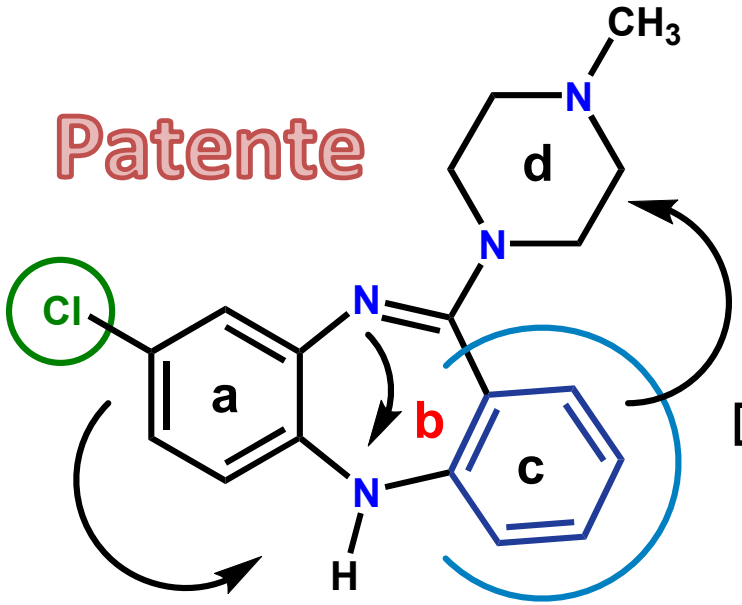
$C_{29}H_{29}N_3O_3$

CMR Low et al., *J Med Chem* **2005**, *48*, 6790

Estratégias da química medicinal

Química Medicinal

Patente

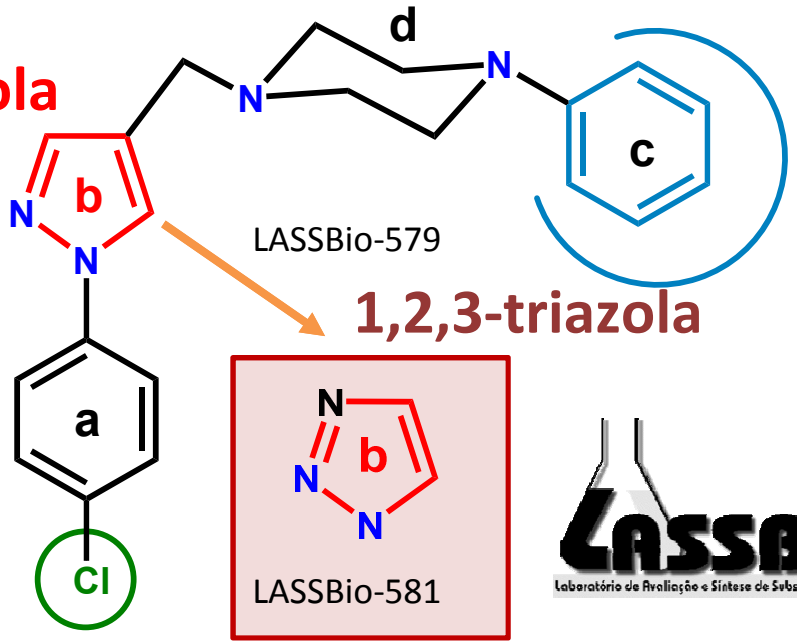


clozapina

Ki= 53,0 nM (D1)
Ki= 190,0 nM (D2)
Ki= 280,0 nM (D3)
Ki= 40,0 nM (D4)

Scaffold hoping

pirazola



LASSBio-579

1,2,3-triazola

LASSBio-581

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

Ant D2, D4, 5-HT_{1A} & 5-HT_{2A}

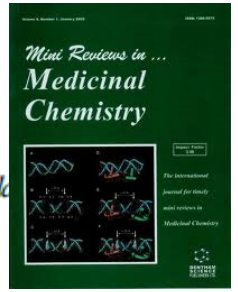
New scaffold

R. Menegatti et al., *Bioorg. Med. Chem*. **2003**, *11*, 4807

1108 *Mini-Reviews in Medicinal Chemistry*, 2007, *7*, 1108-1119

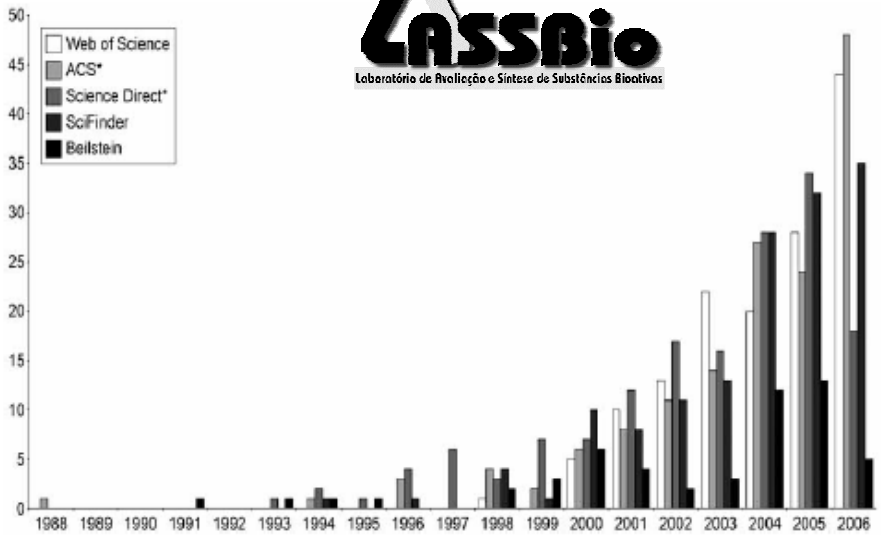
Privileged Structures: A Useful Concept for the Rational Design of New Lead Drug Candidates

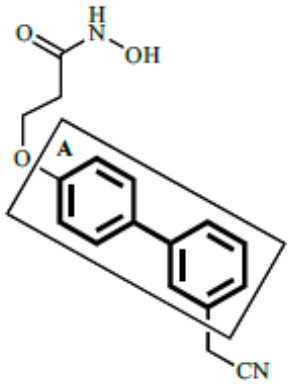
Carolina D. Duarte, Eliezer J. Barreiro and Carlos A.M. Fraga*



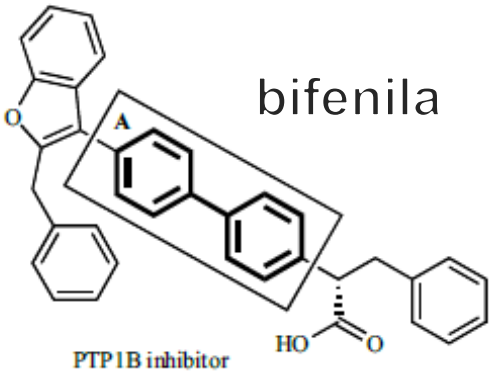
Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio, http://www.farmacia.ufrj.br/lassbio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, P.O. Box 68023, ZIP 21944-971, Rio de Janeiro, RJ, Brazil

Estruturas privilegiadas





MMP-3 inhibitor

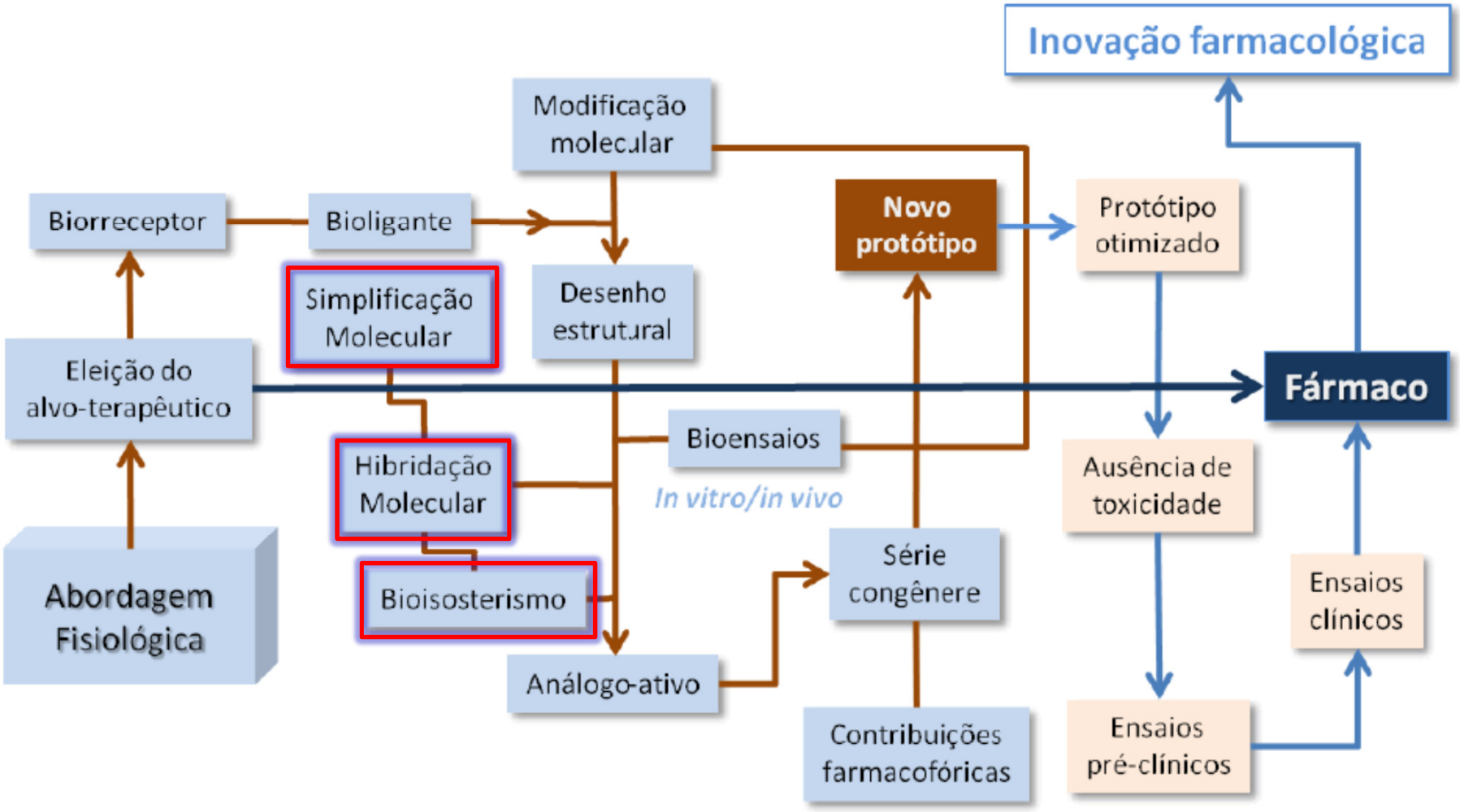


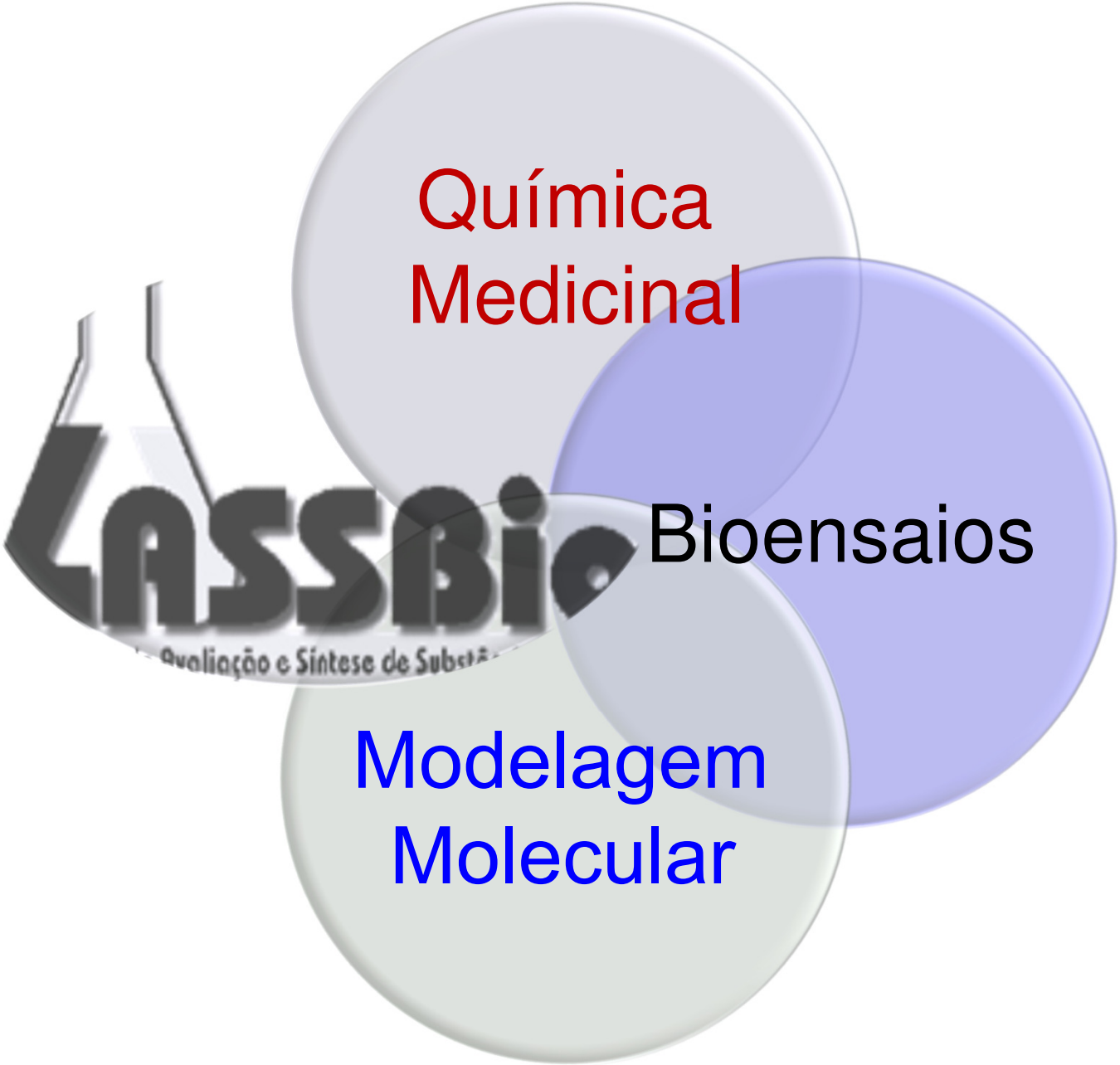
PTP1B inhibitor

D. M Schnur, M. A. Hermsmeier, A. J. Tebben, *J. Med. Chem.*, **2006**, *49*, 2000

Sub-Structures	Ligands				
	GPCRs[a]	Ionic Channels	NHR[b]	Kinase-Proteins	Serine-Proteases
GPCRs	-	26	10	11	17

Estratégias de desenho molecular




Química
Medicinal
LASSBio
Bioensaios
Modelagem
Molecular

Cidade Universitária, ilha do Fundão,
Rio de Janeiro, RJ

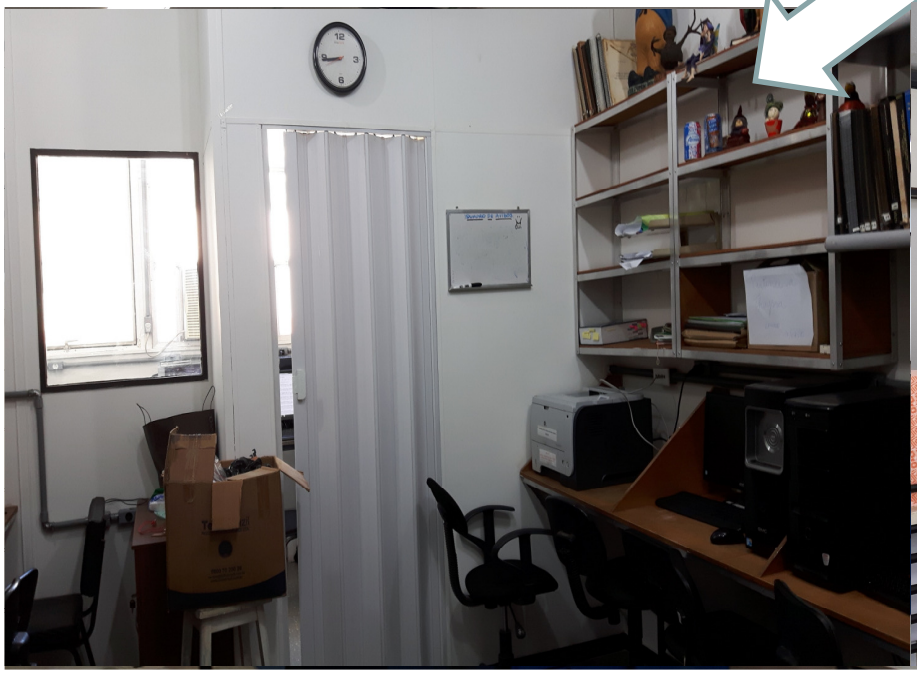
LASSBio

Laboratório de Avaliação e Síntese de Substâncias Bioativas

Química Medicinal

Desativado em 06/05/2016

Criado em 19/04/1994




Quimioteca
LASSBio
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1953 compostos*
* 06/05/2016

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

Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 183–188

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF NEW FLOSULIDE ANALOGUES, SYNTHESIZED FROM NATURAL SAFROLE

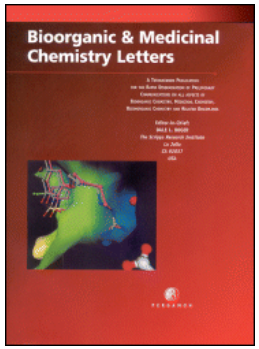
Adriana S. Lages,[a,b] Kelli C. M. Silva,[a] Ana L. P. Miranda,[a] Carlos A. M. Fraga,[a] and Eliezer J. Barreiro,[a]

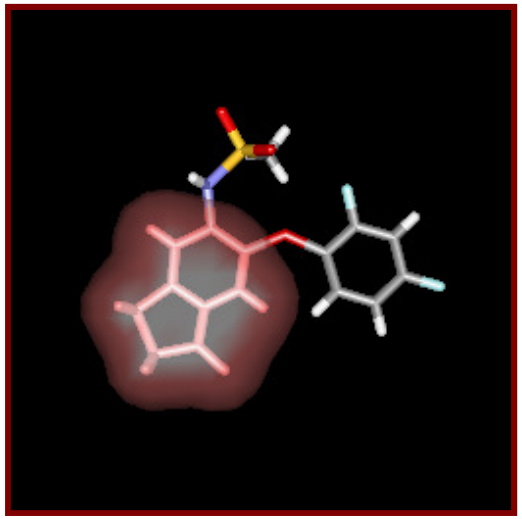
[a]*Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, CP 68006, ZIP 21944-970, Rio de Janeiro - RJ, Brazil*

[b]*Departamento de Química Orgânica, Instituto de Química, Universidade Federal do Rio de Janeiro, Rio de Janeiro - RJ, Brazil*

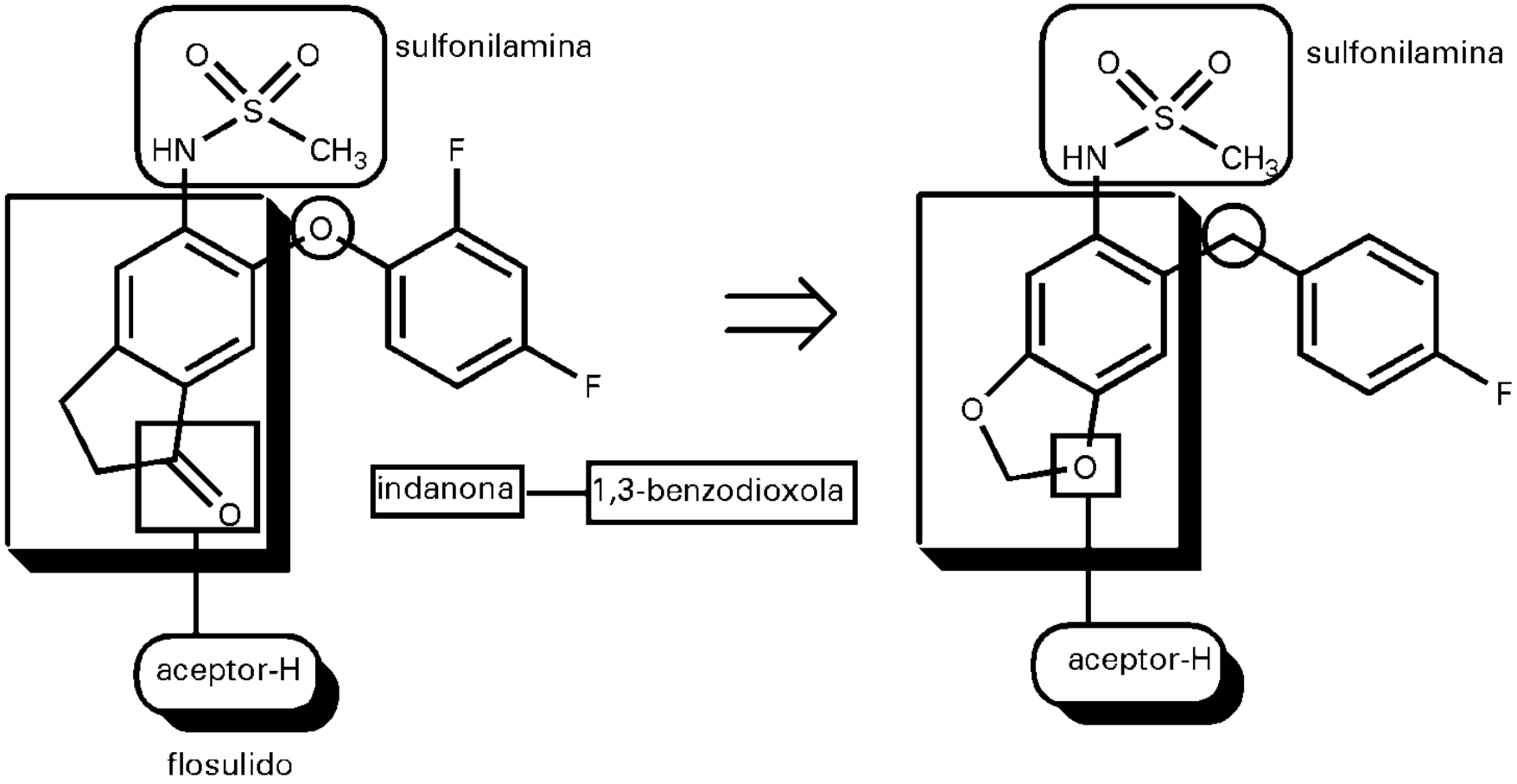
Received 27 October 1997; accepted 2 December 1997

COX - 2 Inhibitors

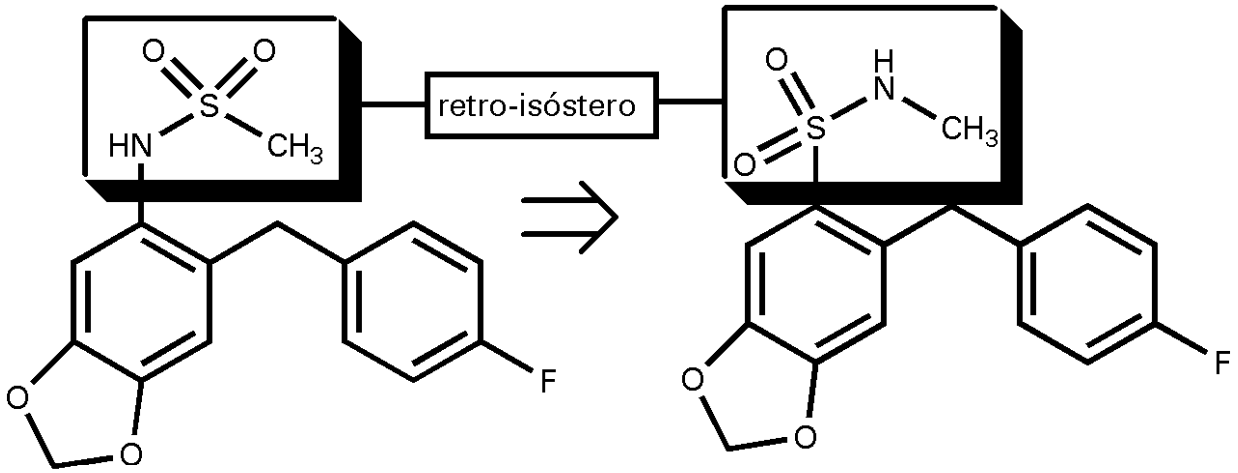


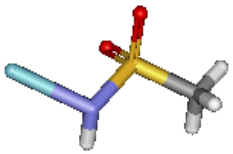


LASSBio-349: novo tipo de bioisosterismo

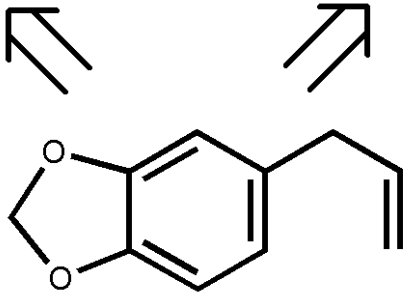


LASSBio-349: novo tipo de bioisosterismo

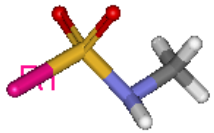




sulfonilamina



safrol



sulfonamida

Novos análogos benzílogos do LASSBio-349

J Med Chem. 2005 Jun 2;48(11):3930-4.

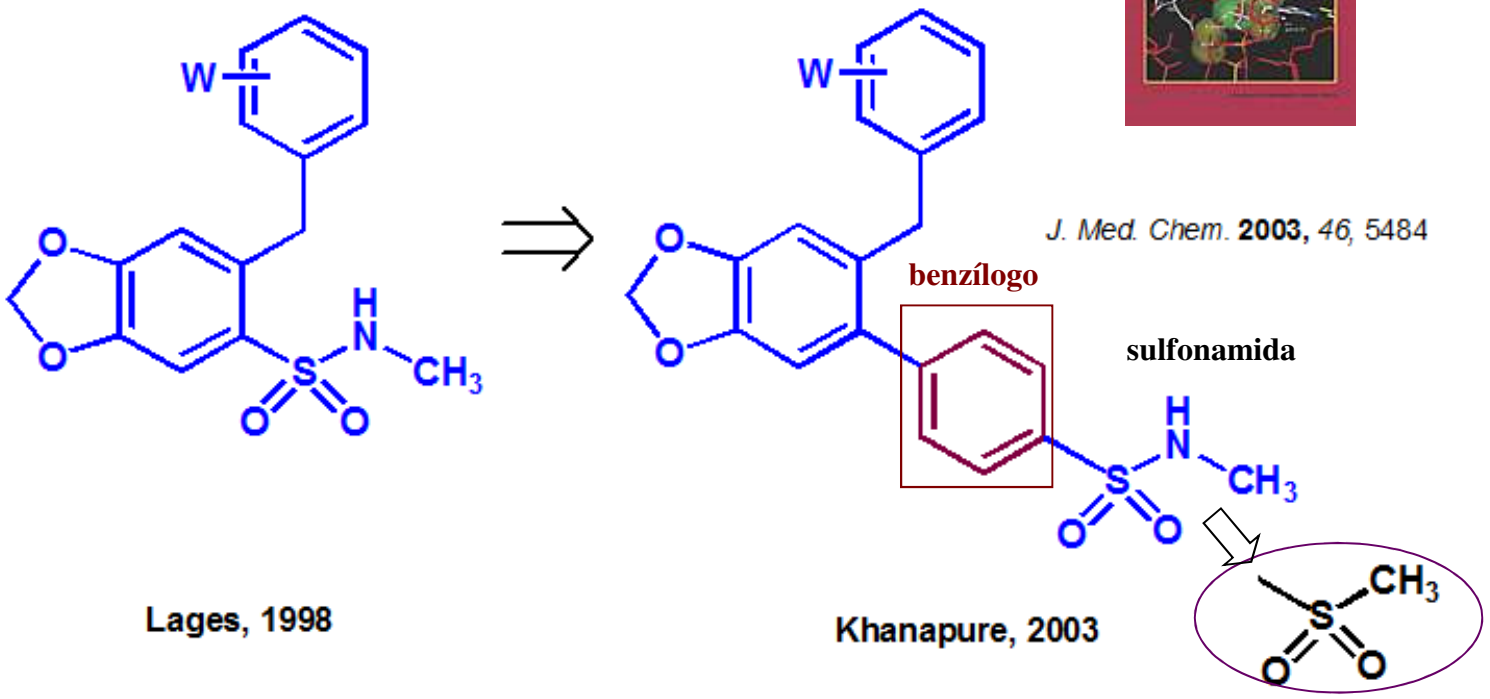
3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)(2-pyridyl) phenyl ketone as a potent and orally active cyclooxygenase-2 selective inhibitor: synthesis and biological evaluation.

Khanapure SP[1], Augustyniak ME, Earl RA, Garvey DS, Letts LG, Martino AM, Murty MG, Schwalb DJ, Shumway MJ, Trocha AM, Young DV, Zemtseva IS, Janero DR.

Author information

[1]NitroMed, Inc., 125 Spring Street, Lexington, Massachusetts 02421, USA. skhanapure@nitromed.com

J. Med. Chem., **2003**, *46* (25), pp 5484–5504
DOI: 10.1021/jm030268b
Publication Date (Web): November 7, 2003

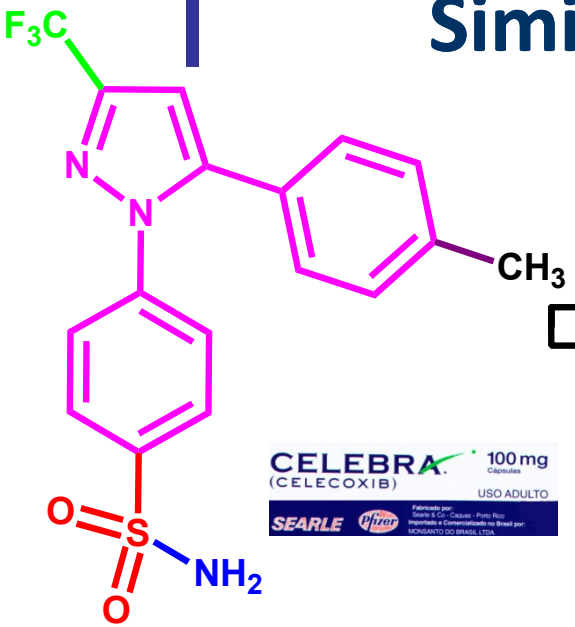


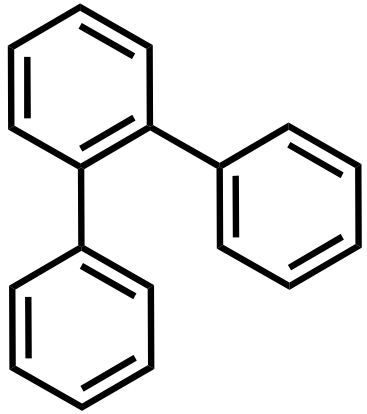
J. Med. Chem. **2003,** *46,* 5484

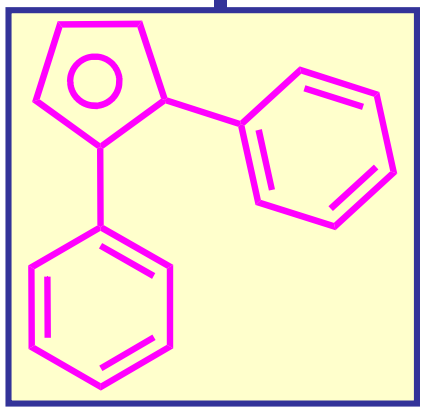
J. Med. Chem. **2005,** *48,* 3930

Desenho molecular de novos derivados antiinflamatórios bispirazólicos: LASSBio-715

Similaridade Molecular





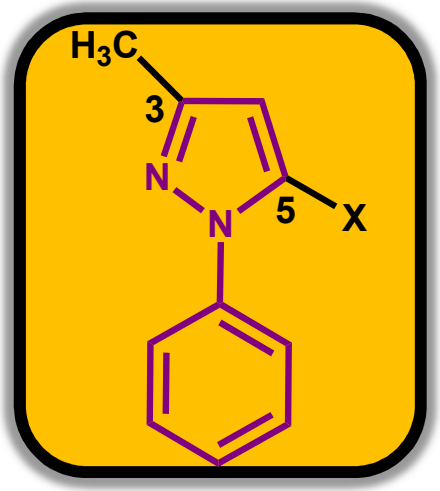


sistema terfenílico

celecoxibe
(1999)

inibidor COX-2 / COX-1

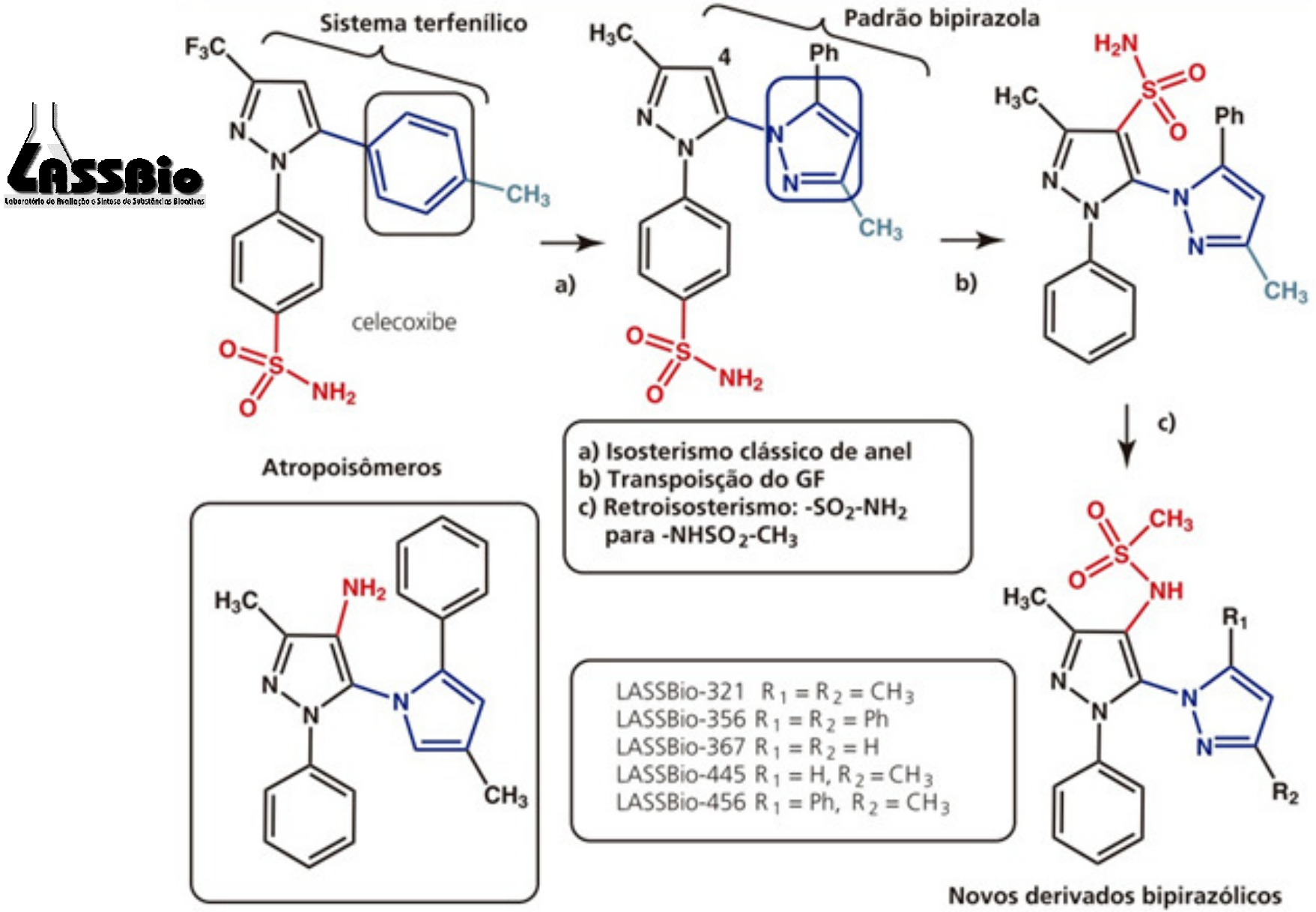
K Chun et al., Carcinogenesis 2004, 25, 713



LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

1986

Desenho estrutural dos novos derivados bispirazólicos



Novo Protótipo de Fármaco
NSAI de Segunda Geração

NSAI/2ª geração

CgIRPE*

		DI_{50}	Max. Eff.
1999	CELECOXIB	87,7 µmol/kg	35%
	LASSBio 715	44,3 µmol/kg	39%
	LASSBio 445	54,6 µmol/kg	37%

Patent: PI 9902960-0 (29/04/99)

Márcia P Veloso, PhD Thesis, Instituto de Química, UFRJ, BR, 2000

FINEP
FINANCIADORA DE ESTUDOS E PROJETOS

Ministério da Ciência e Tecnologia

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

CARTA-CONVITE MCT/MS/FINEP – Ação Transversal – Cooperação ICTs - Empresas - INOVAÇÃO EM PRODUTOS TERAPÊUTICOS E DIAGNÓSTICOS – 08/2006

PROJETOS APROVADOS

Prot. Elet.	Ref.	INTERVENIENTE CO-FINANCIADOR	Proponente/ Executor/ Projeto	Executor	
				Nome	UF Executor
1	2318/06	Laboratório Farmacoterápico Americano S/A	Pontifícia Universidade Católica do RS - PUCRS	Tecnopuc/BFR	RS
3	2303/06	Eurofarma Laboratórios S/A	FUJB	Faculdade de Farmácia	RJ

5 kg → 30.000 comprimidos

UFRJ

Licenciamento exclusivo

Eurofarma
Eurofarma Laboratórios Ltda.

PI 9902960-0 (1999) → NSAI de segunda geração*

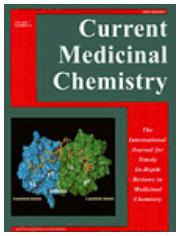
Current Medicinal Chemistry, 2007, *14*, 103-112

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]

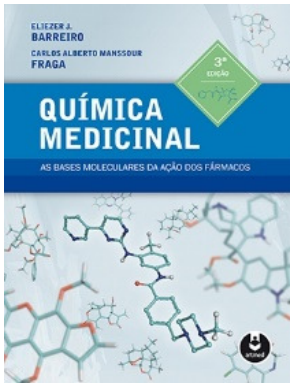
[1]*Instituto de Química, Universidade Estadual Paulista "Júlio de Mesquita Filho", P.O. Box 355, 14801-970 Araraquara, São Paulo, SP, Brazil*

[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.

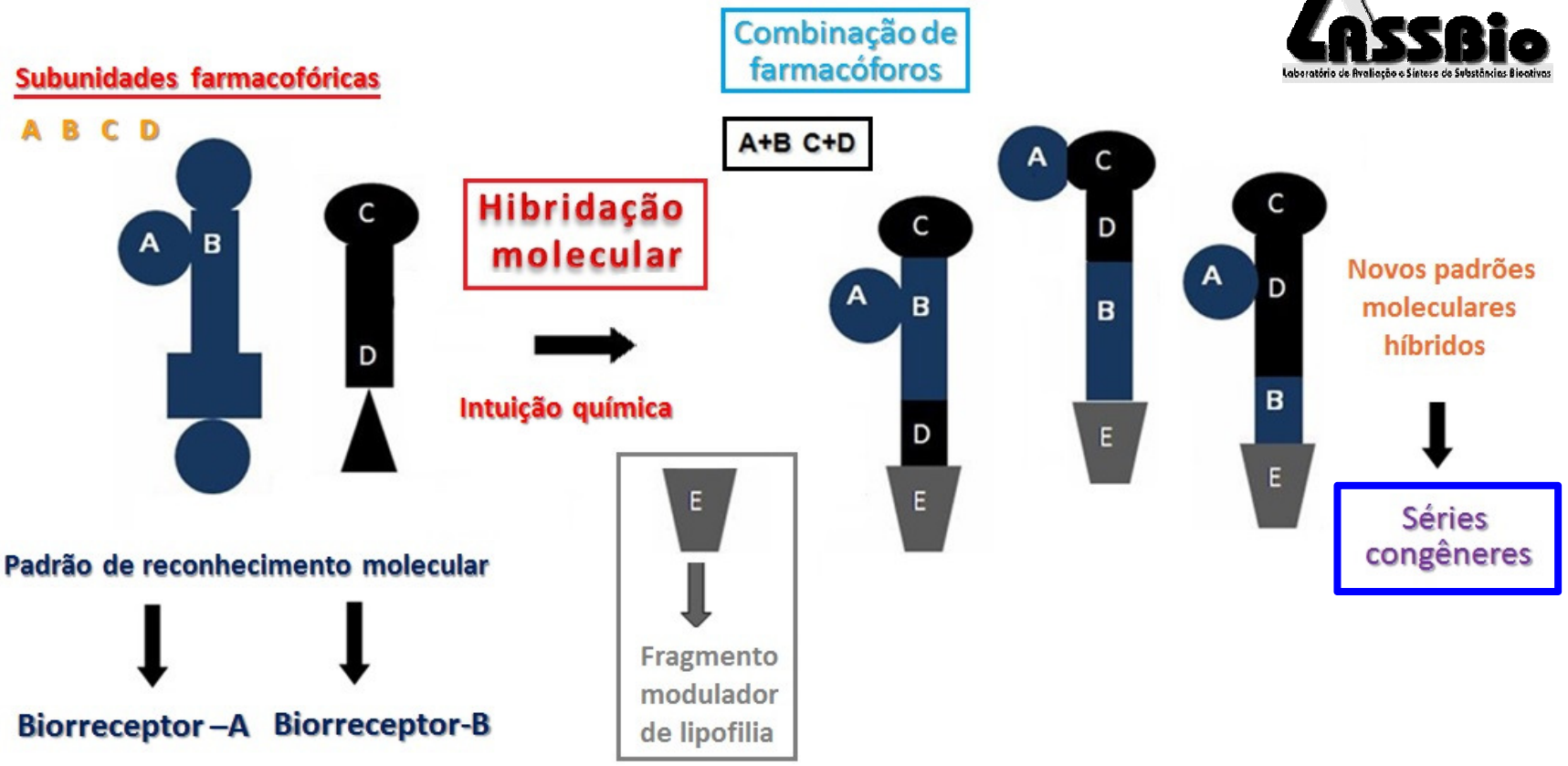
Keywords: Molecular hybridization, Drug design, Hybrid compounds, Pharmacophoric group combination.



CAPÍTULO 9

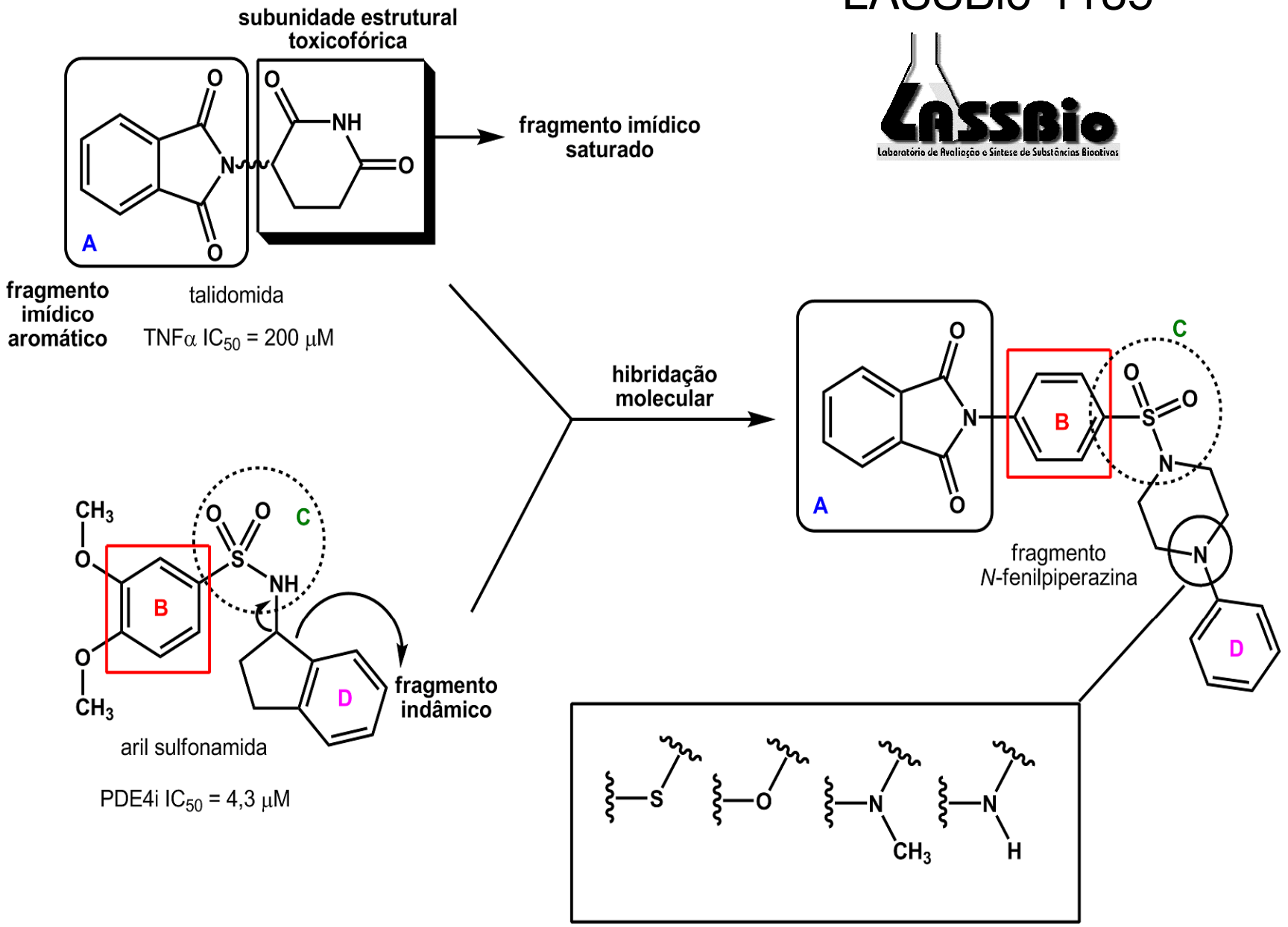
A ESTRATÉGIA DA HIBRIDAÇÃO MOLECULAR NO PLANEJAMENTO, DESENHO E MODIFICAÇÃO MOLECULAR DE LIGANTES E PROTÓTIPOS 407

Hibridação Molecular

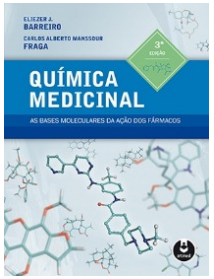


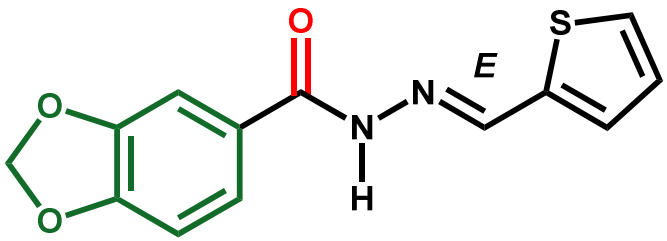
C Viegas Jr et al., *Curr Med Chem.* **2007,***14*,1829

LASSBio-1135



Simplificação Molecular





CAPÍTULO 10

SIMPLIFICAÇÃO MOLECULAR COMO ESTRATÉGIA DE MODIFICAÇÃO MOLECULAR E O PROCESSO DE OTIMIZAÇÃO DE COMPOSTOS-PROTÓTIPOS 447

Divulgação

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

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

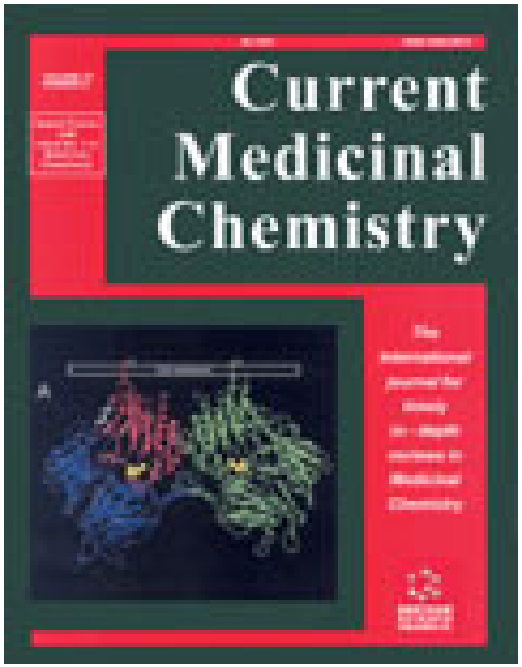
STRATEGY OF MOLECULAR SIMPLIFICATION IN RATIONAL DRUG DESIGN: THE DISCOVERY OF A NEW CARDIOACTIVE AGENT. In this article are described examples of the successful use of molecular simplification strategy in the discovery of new drugs from bioactive natural products and synthetic compounds. The discovery 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.

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

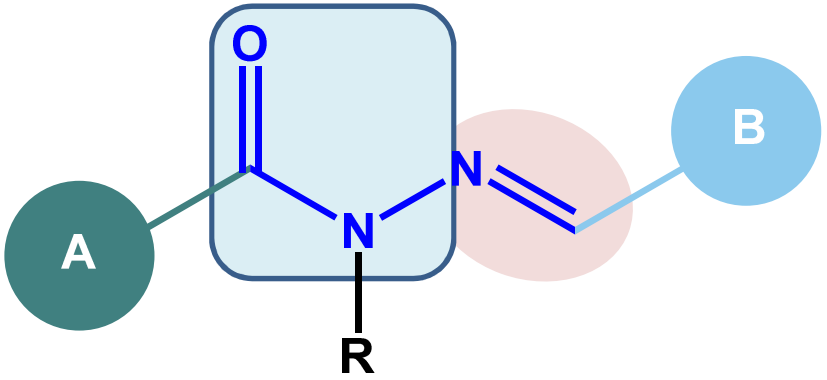
Carlos A.M. Fraga and Eliezer J. Barreiro

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.

http://dx.doi.org/10.2174/092986706775197881



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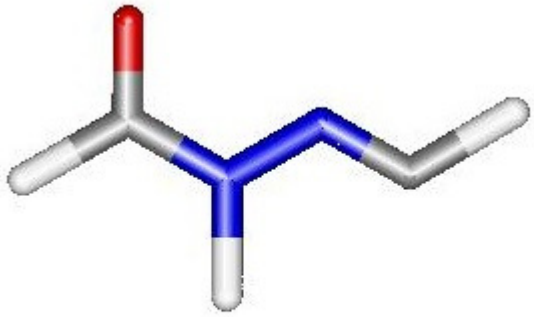


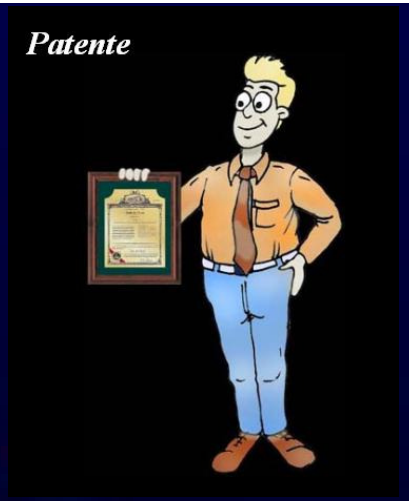
N-acylhidrazone

NAH

NAH = amide + imine

Molecular dissection

LASSBio-294



LASSBio-294 story

É intangível o capital intelectual da Universidade...

Patente obtida

Patent (USPTO) 7.091.238 (15/08/2006)

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

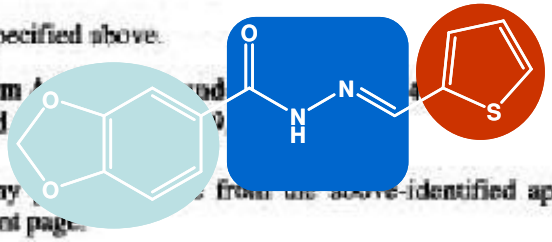
APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/020,328	Aug. 15, 2006	7,091,238	32360-178943	9681

26694 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[illegible]od
(application filed

The Patent Term Adjustment is 109 day(s). Any [illegible] 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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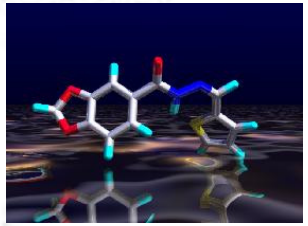
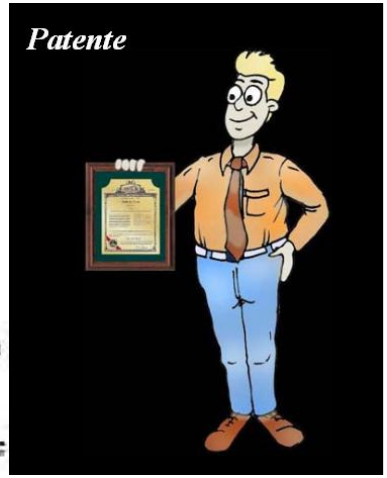
JUL 31 2006
VENABLE IP DOCKETING DEPARTMENT

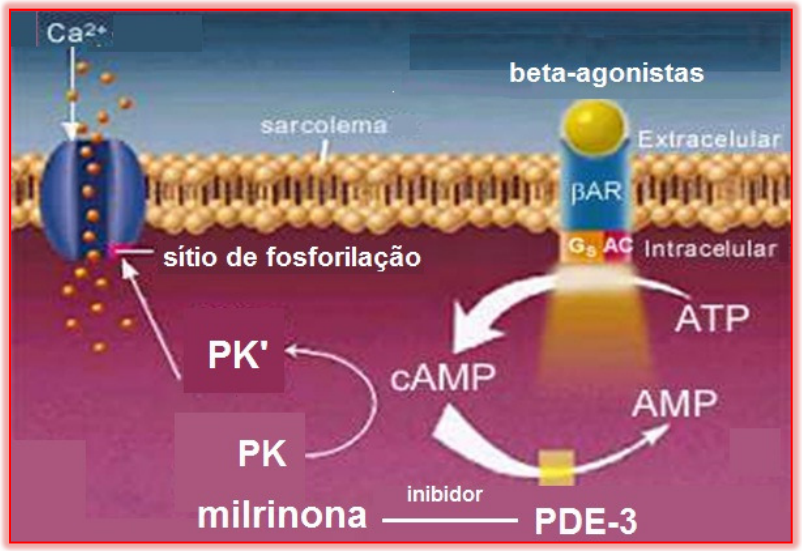
B.109 (Rev. 12/04)

Thienylhydrazone with Digitalis-like properties (positive inotropic effects)

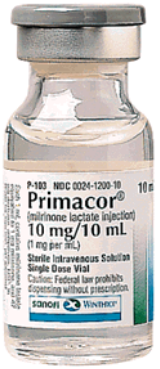


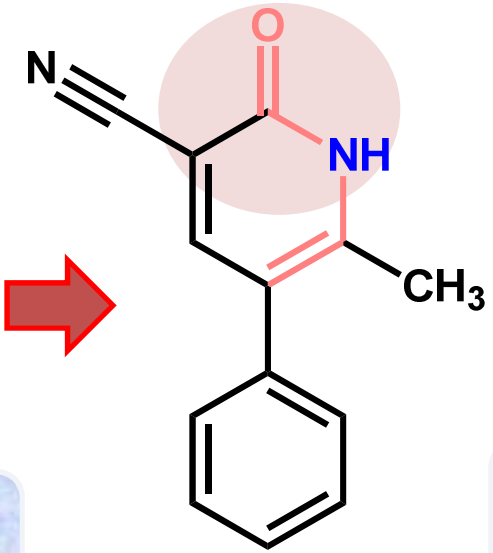


A gênese do LASSBio-294...

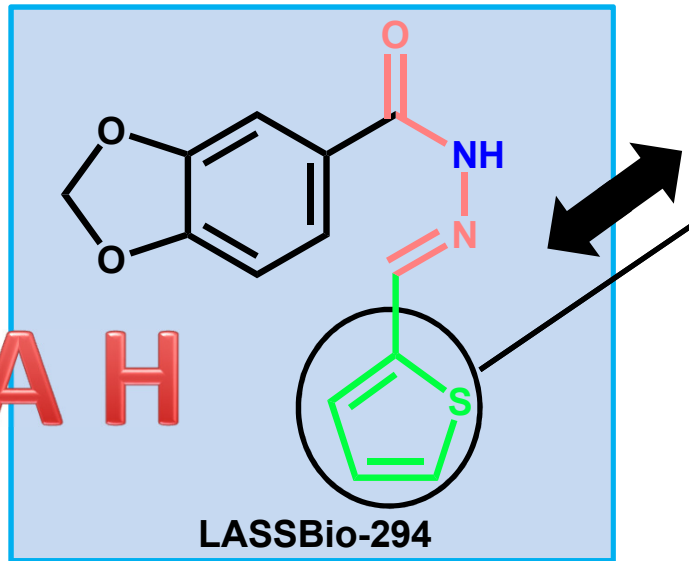


Propriedades inotrópicas,
vasodilatadoras
(arritmias ventriculares)

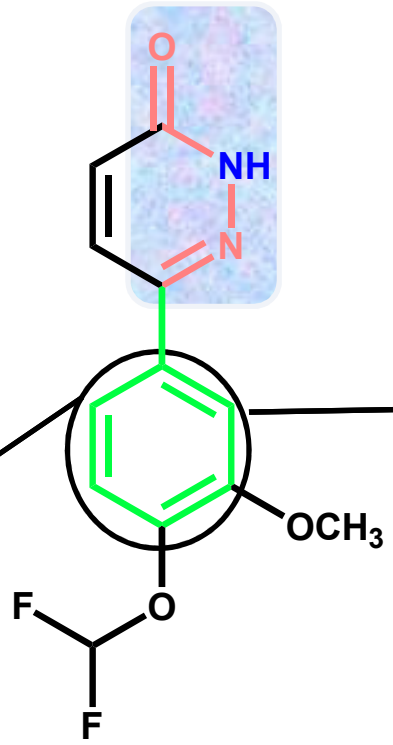




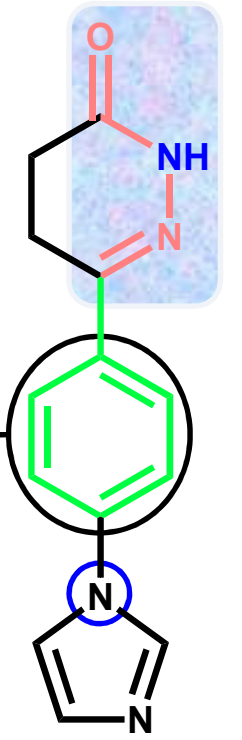
NAH



LASSBio-294

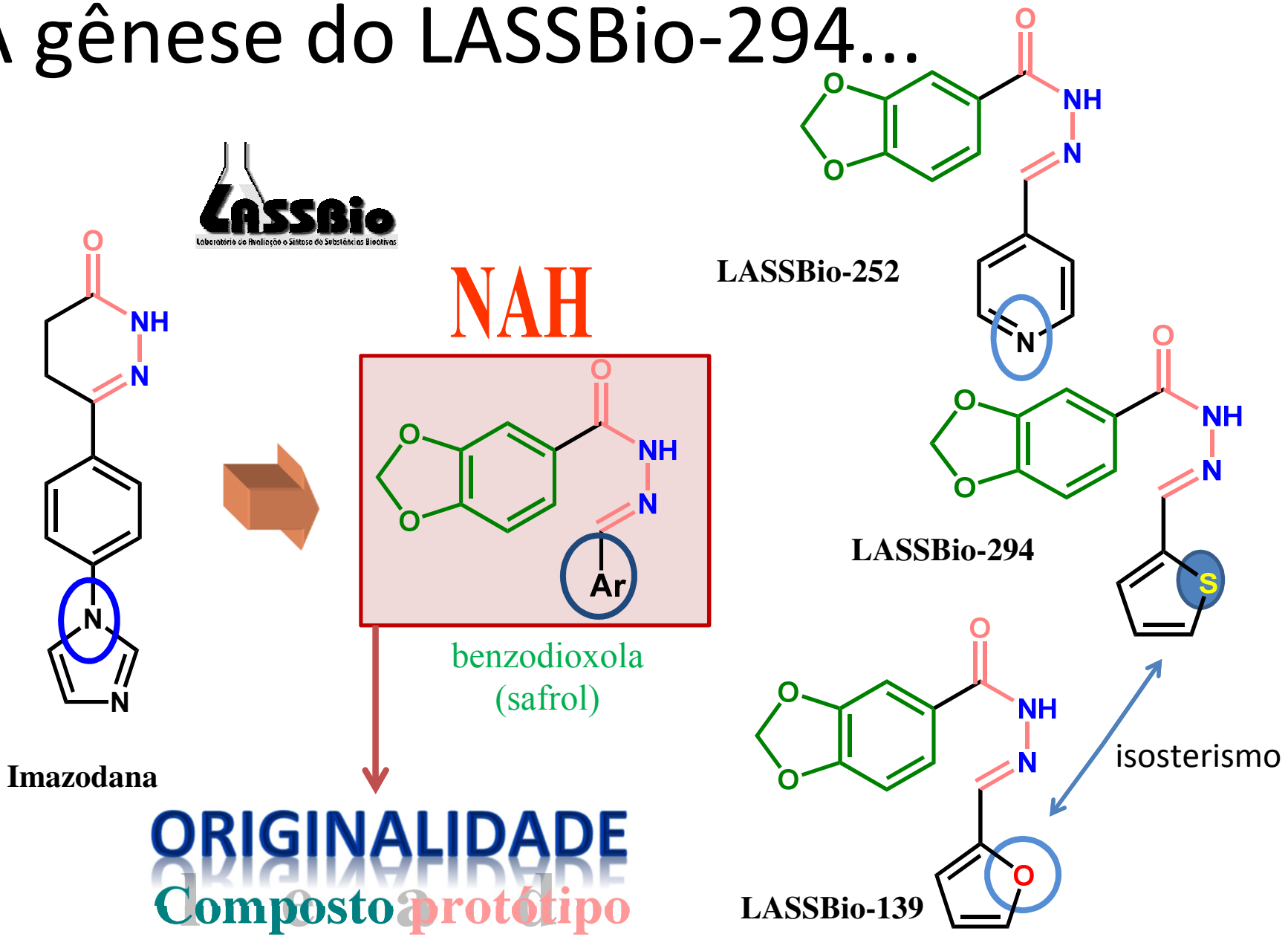


zardaverina

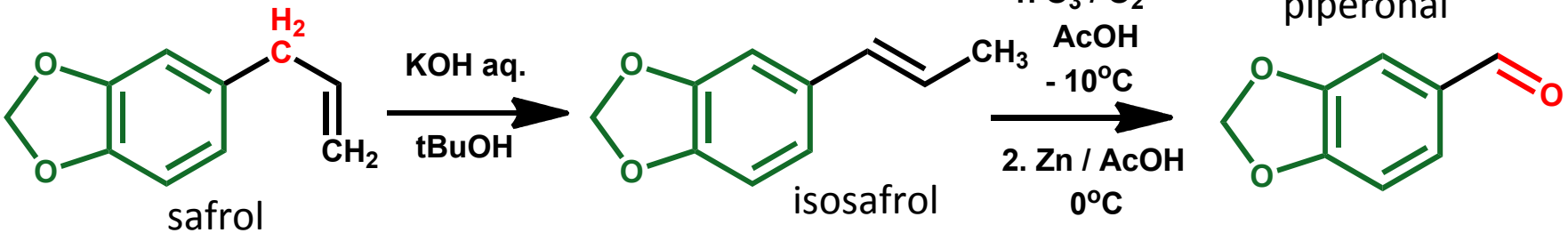


imazodana

A gênese do LASSBio-294...



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).



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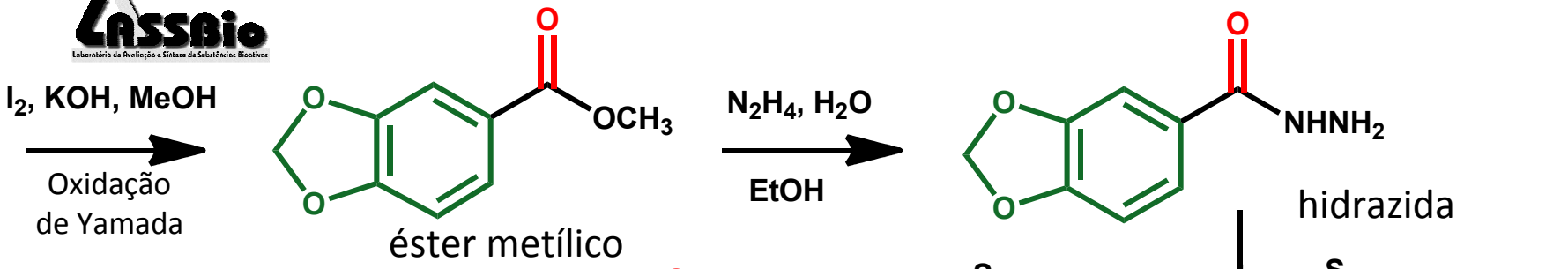

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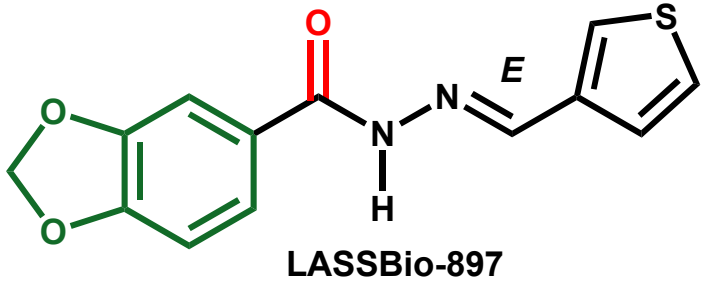

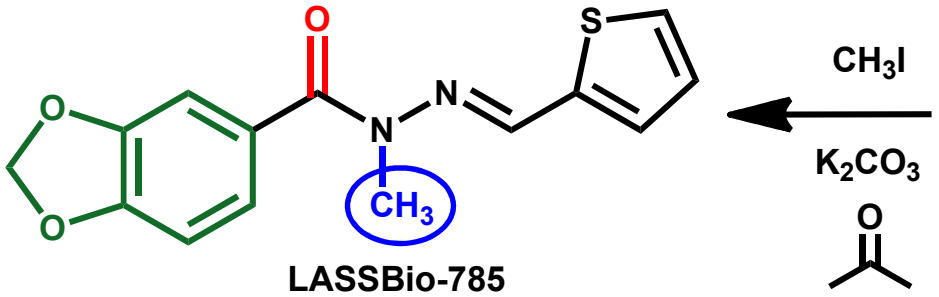

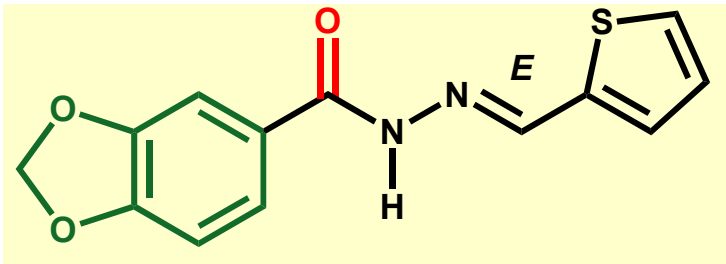

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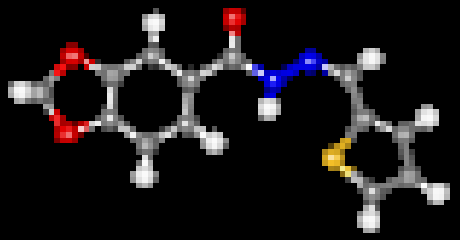
Propriedades estruturais

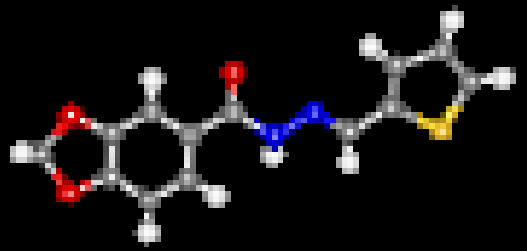
NMR ^{1}H/ ^{13}C

MS

raios-X



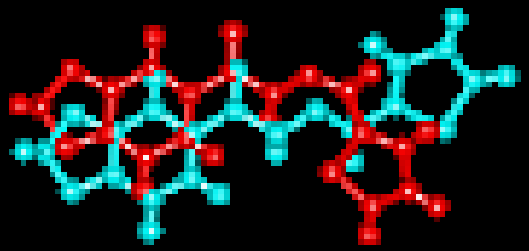
NAH



Z-isomêro

E-isomêro

LASSBio-294



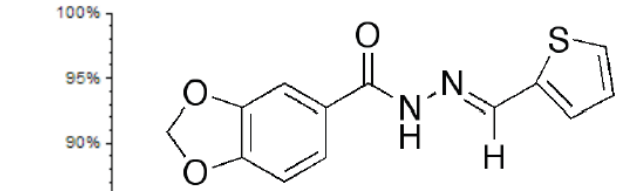
Laboratório de Avaliação e Síntese de Substâncias Bioativas

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, *et al.*, "Electron Impact Mass Spectrometry of Some 3-[3-(4-aryl)-1,2,4-oxadiazole-5-yl] acyl arylaldehyde Hydrazone derivatives", ***Spectroscopy*** 2000, **14**, 115.

L. Pol-Fachin, C. A. M. Fraga, E. J. Barreiro, H. Verli, Characterization of the conformational ensemble from bioactive *N*-acylhydrazone derivatives, ***J. Molecular. Graphics and Modelling,*** 2010, **8**, 446

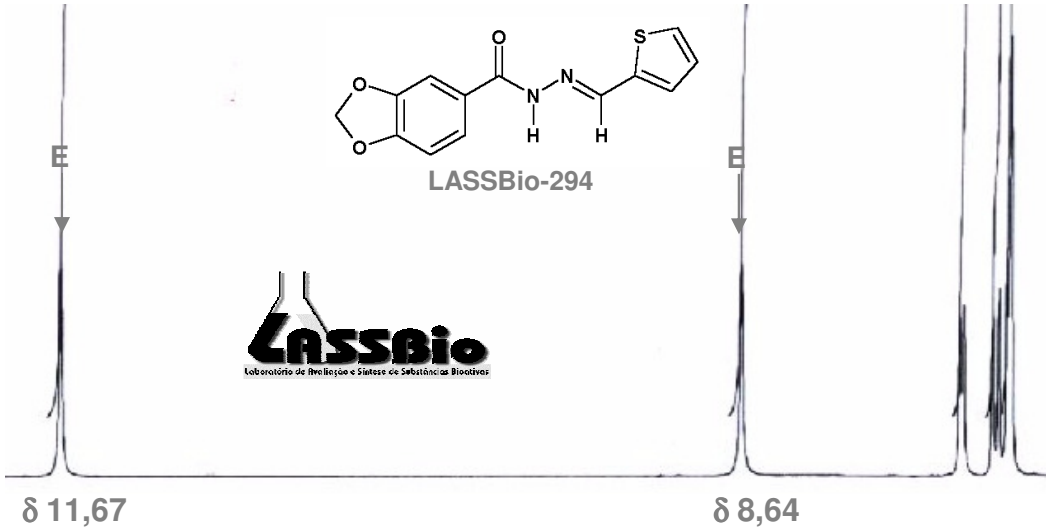
Espectrometria de Massas



Molecular Weight: 274

Análise espectroscópica e raios X

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



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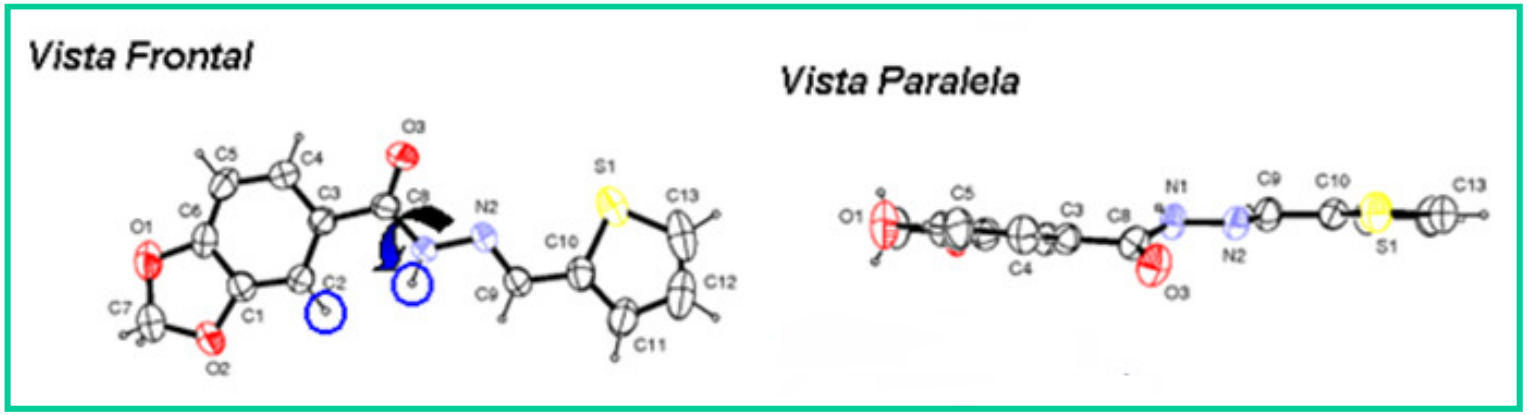
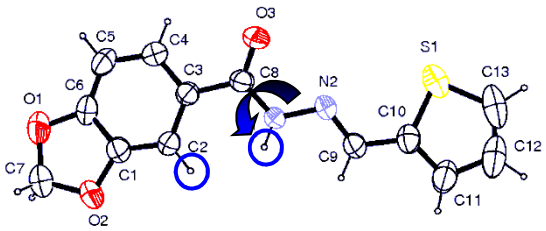


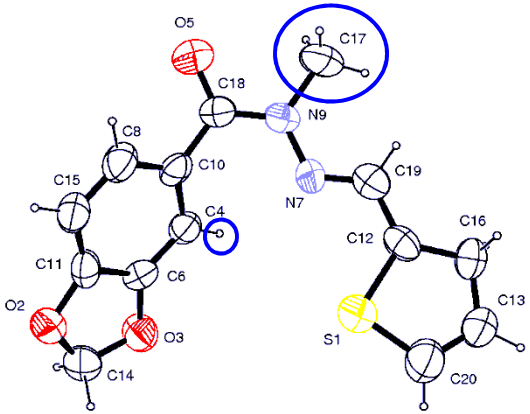
Kummerle, A. E.; Raimundo, J. M.; Leal, C. M.; Silva, G. S.; Balliano, T. A.; Pereira, M. A.; DeSimone, C. A.; Sudo, R. T.; Zapata-Sudo, G.; Fraga, C. A. M.; Barreiro, E. J. , *Eur. J. Med. Chem.* 2009, 44, 4004-4009

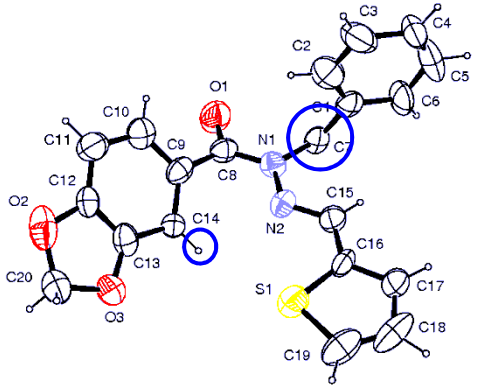
Cristalografia de Raios-X dos Compostos LASSBio-294 e LASSBio-785

LASSBio-294 ***LASSBio-785*** ***LASSBio-786***

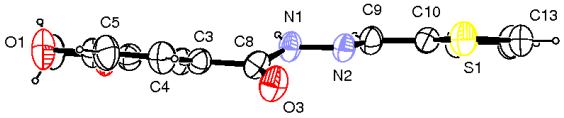
Vista Frontal

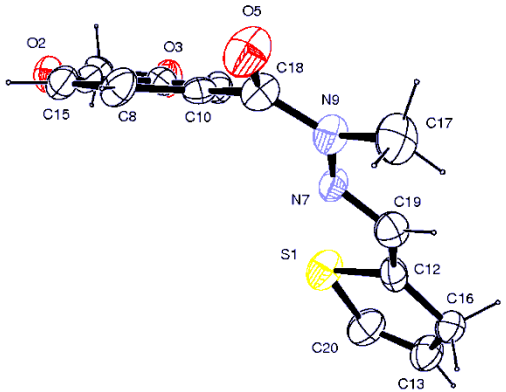


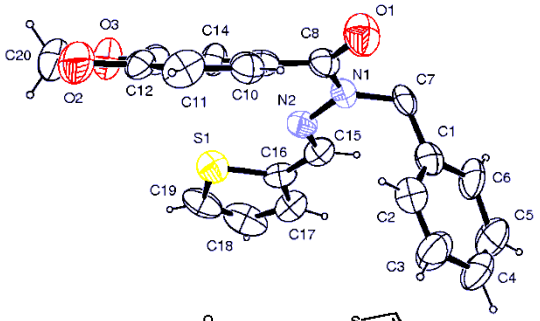


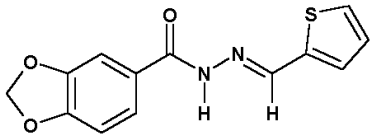


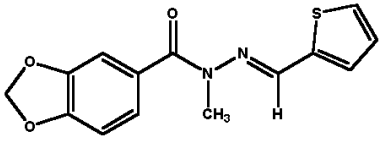
Vista Paralela

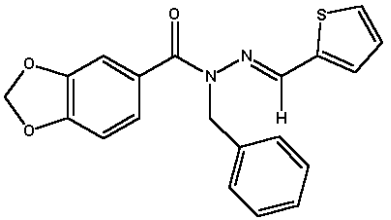




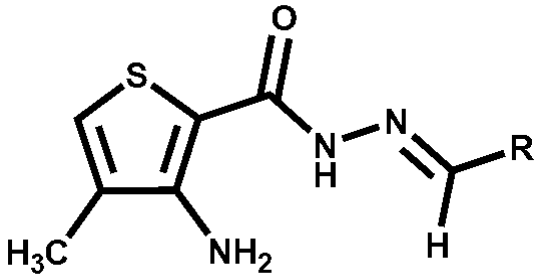




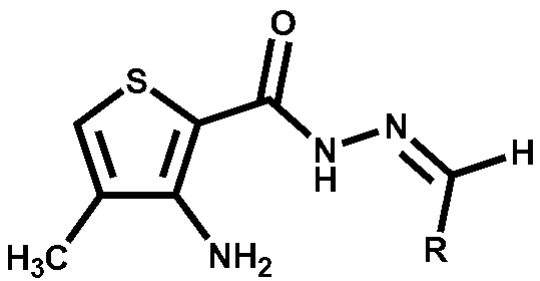




X-ray diffraction

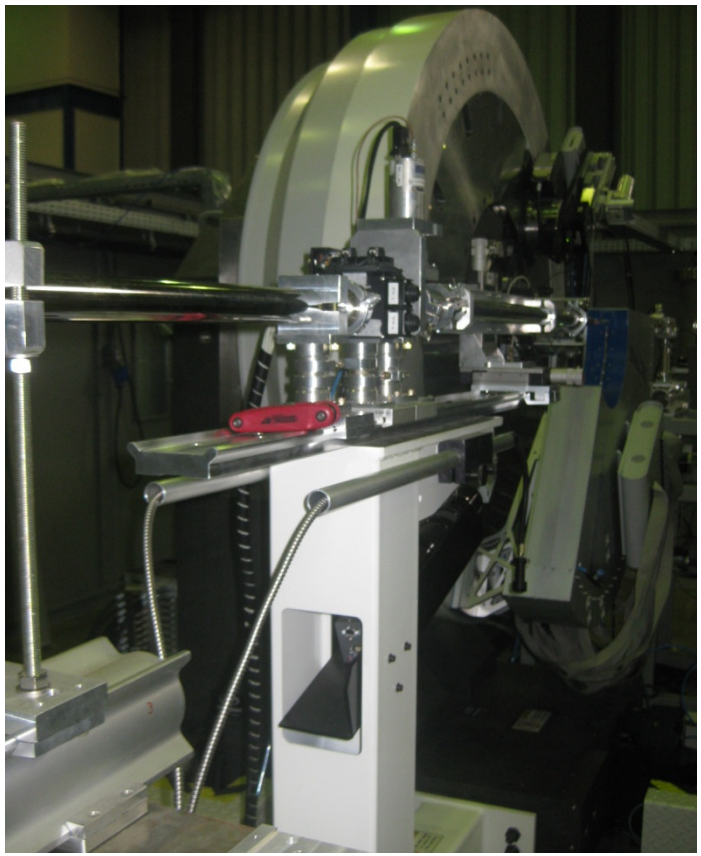


E -Isomer

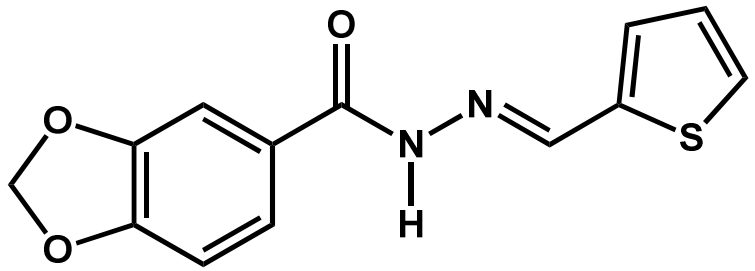


Z -Isomer

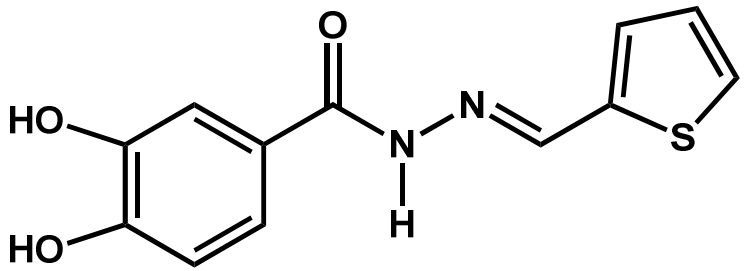
The configuration of the compounds can be analyzed via its crystal structure by powder X-ray diffraction.



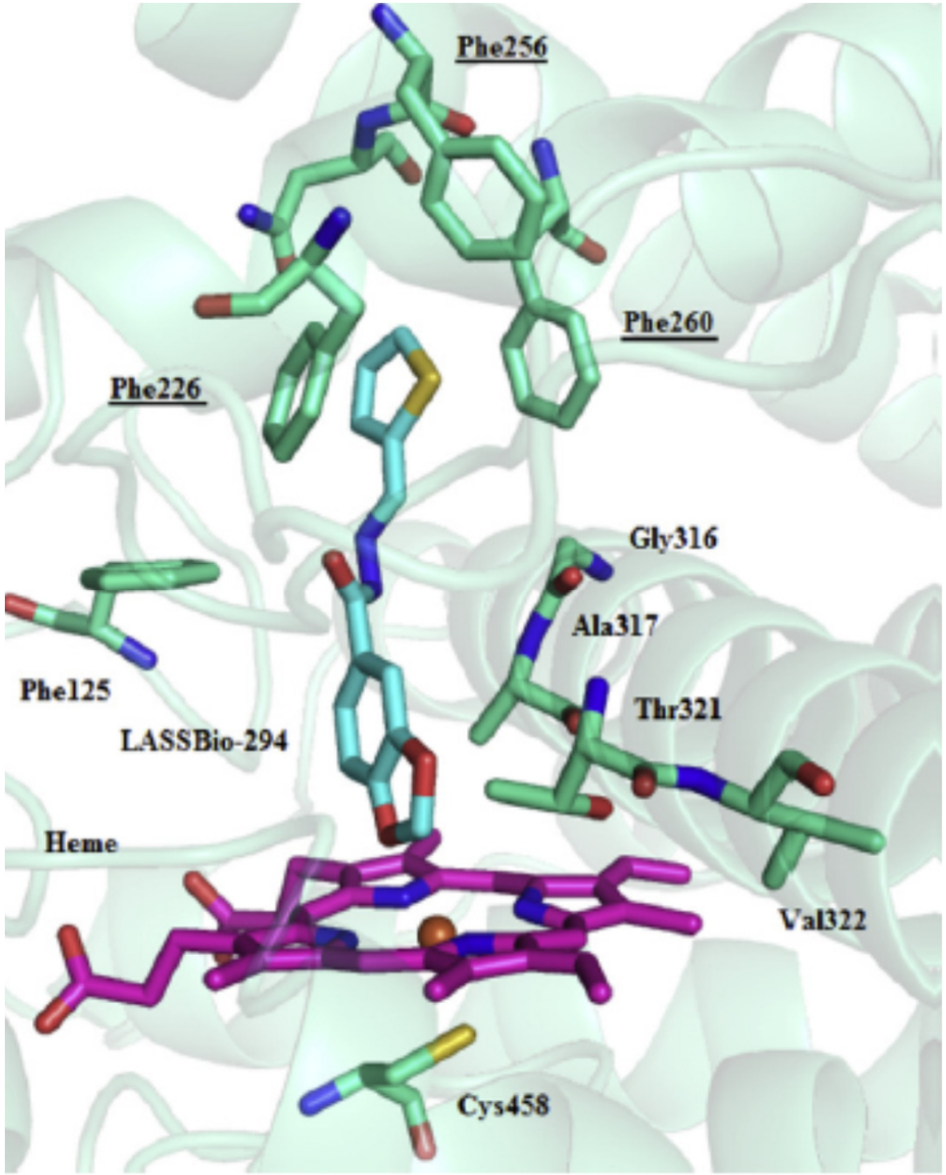
Metabolismo de LASSBio-294



CYP1A2 — In silico / *h*-microssomo

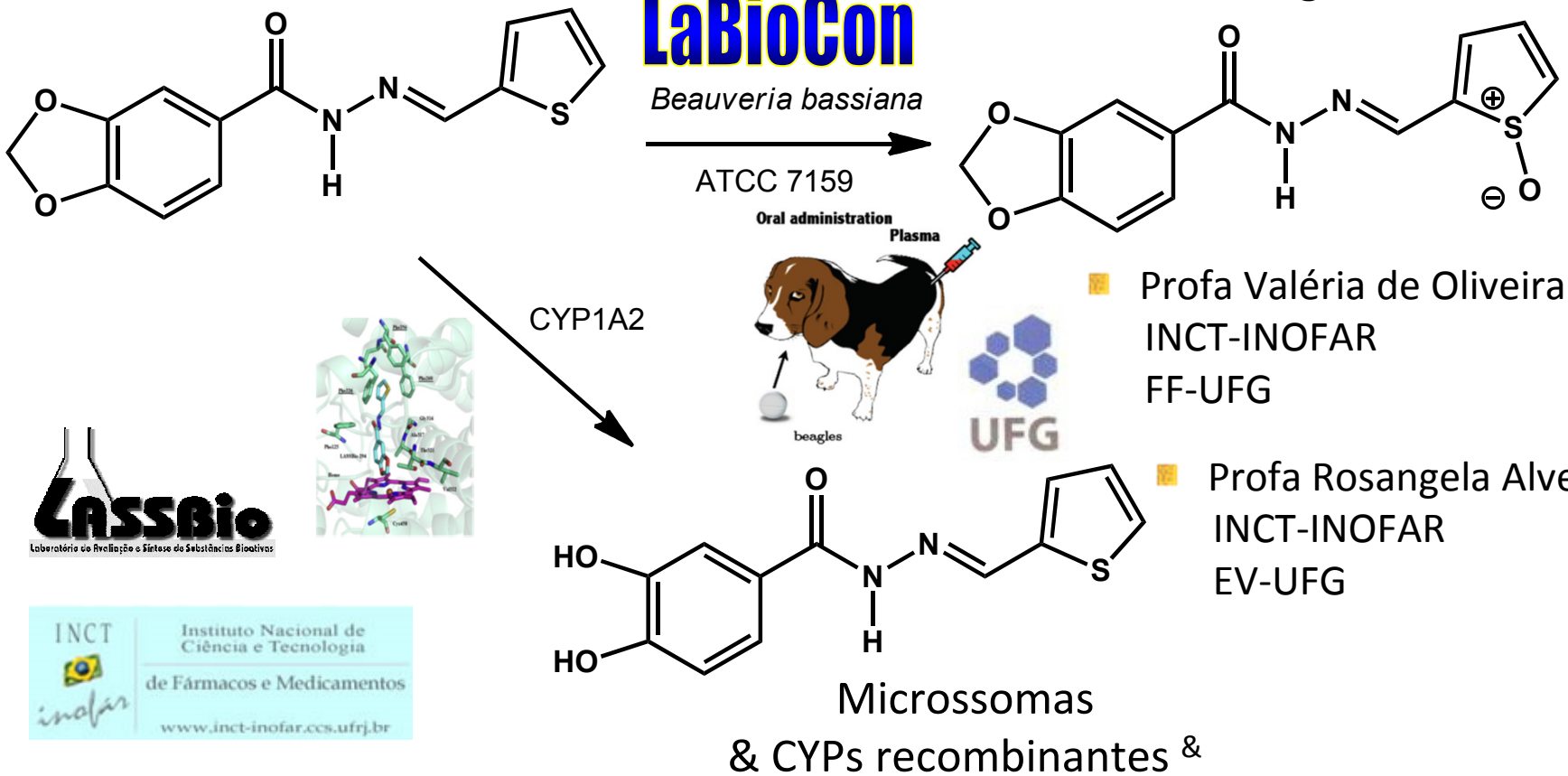


Confirmado sinteticamente



A. G. M. Fraga *et al*., "CYP1A2-mediated biotransformation of cardioactive 2-thienylidene-3,4-methylenedioxybenzoylhydrazine (LASSBio-294) by rat liver microsomes and human recombinant CYP enzymes", *Eur J. Med Chem*., **46**, 349 (2011);

Metabolismo de LASSBio-294



* E. O. Carneiro, C. H. Andrade, R. C. Braga, *et al*., Structure-based prediction and biosynthesis of the major mammalian metabolite of the cardioactive prototype LASSB io-294, *Bioorg. Med. Chem. Lett.*, **20**, 3734 (2010); R. C. Braga *et al*., "Determination of cardiactive prototype LASSBio-294 and its metabolites in dog plasma by LC-MS/MS: application for a pharmacokinetic studies", *J. Pharm. Biomed. Analysis*, **55**, 1024 (2011);

& A. G. M. Fraga *et al*., "**CYP1A2**-mediated biotransformation of cardioactive 2-thienylidene-3,4-methylenedioxybenzoylhydrazine (LASSBio-294) by rat liver microsomes and human recombinant CYP enzymes", *Eur. J. Med. Chem*., **46**, 349-355 (2011)

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2. RC Braga, ACB Tôrres, CB Persiano, RO Alves, CAM Fraga, EJ Barreiro, V de Oliveira, Determination of the cardioactive prototype LASSBio-294 and its metabolites in dog plasma by LC–MS/MS: Application for a pharmacokinetic study, *Journal of Pharmaceutical and Biomedical Analysis,* **55**, 1024-1030 (2011). (Times cited: 2)
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8. G Zapata-Sudo, SL Pereira, HJV Beiral, *et al.*, Pharmacological Characterization of (3-Thienylidene)-3,4-Methylenedioxybenzoylhydrazide: A Novel Muscarinic Agonist With Antihypertensive Profile, *Am. J.Hypertension* ,**23**, 135-141 (2010). (Times cited: 2)

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10. H Gonzalez-Serratos, EFR Pereira, RZ Chang, *et al.*, The thienylhydrazone, (2 '-thienylidene)3,4-methylenedioxvbenzoylhydrazine (LASSBio-294), develops fatigue resistance and has a positive inotropic effect in mammalian skeletal muscle, *Biophys. J.*, **86**, 225A-225A Suppl. (S 2004).
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13. CLM Silva, F Noel, EJ Barreiro, Cyclic GMP-dependent vasodilatory properties of LASSBio 294 in rat aorta, *Br. J. Pharmacol*., **135** 293-298 (2002) (Times Cited: 16)
14. H Gonzalez-Serratos , RZ Chang, EFR Pereira, *et al*., A novel thienylhydrazone, (2-thienylidene)3,4-methylenedioxybenzoylhydrazine, increases inotropism and decreases fatigue of skeletal muscle, *J. Pharmacol. Exp. Ther*., **299**, 558-566 (2001) (Times Cited: 14)
15. RT Sudo, G Zapata-Sudo, EJ Barreiro, The new compound, LASSBio 294, increases the contractility of intact and saponin-skinned cardiac muscle from Wistar rats, *Br. J. Pharmacol*., **134**, 603-613 (2001) (Times Cited: 13)
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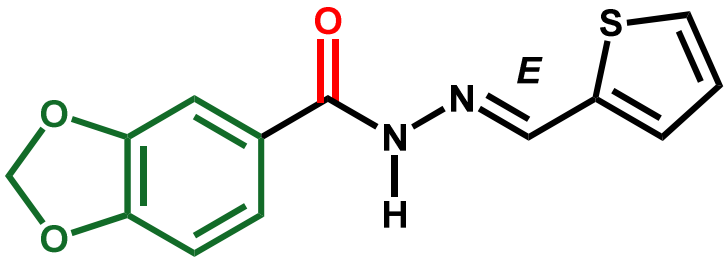

RESULTADOS RECENTES

Life Sciences 2014,

N-acylhydrazone improves exercise intolerance in rats submitted to myocardial infarction by the recovery of calcium homeostasis in skeletal muscle

Jaqueline Soares da Silva [a], Sharlene Lopes Pereira [a], Rodolfo do Couto Maia [a], Sharon Schilling Landgraf [b], Celso Caruso-Neves [b], Arthur Eugen Kümmerle [c], Carlos Alberto Manssour Fraga [a], Eliezer Jesus Barreiro [a], Roberto Takashi Sudo [a], Gisele Zapata-Sudo [a,*]

[a] *Programa de Desenvolvimento de Fármacos, Instituto de Ciências Biomédicas, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil*
[b] *Instituto de Biofísica Carlos Chagas Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil*
[c] *Departamento de Química, Instituto de Ciências Exatas, Universidade Federal Rural do Rio de Janeiro, Seropédica, RJ, Brazil*

Estudo do mecanismo de ação

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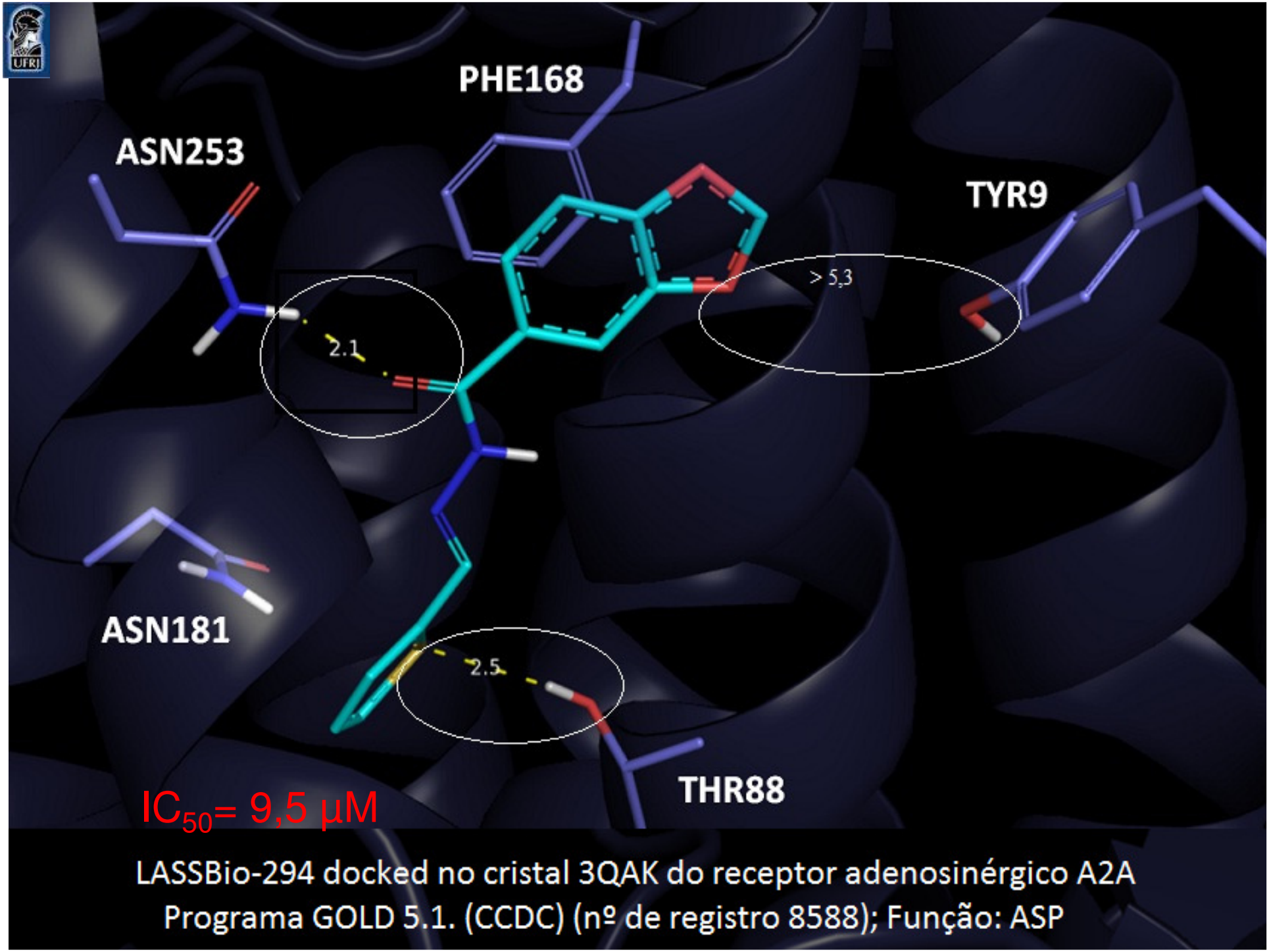
Ref.: Final Report 15180/ND

STUDY NUMBER 15180

***In Vitro* Pharmacology & ADME-Tox**
- Study of Compound LASSBio-294 -

Study Sponsor:	LASSBIO
Attention:	Pr. Carlos FRAGA
Address:	CCS - Bloco Bss - Room 16 Ilha do Fundão 68006 RIO DE JANEIRO BRAZIL
Study Director:	Jun TANG, Ph. D.
Testing Facilities:	Cerep Le Bois l'Evêque - B.P. 1 - 86600 CELLE L'EVESCAULT, FRANCE and 15318 NE 95th Street, REDMOND, WA 98052 U.S.A.
Study Period:	From August 19, 2008 to September 08, 2008
Report Version:	1
Report Date:	September 17, 2008



LASSBio-294 docked no cristal 3QAK do receptor adenosinérgico A2A
Programa GOLD 5.1. (CCDC) (nº de registro 8588); Função: ASP

Toxicidade Aguda e Sub-aguda

✓**A toxicidade sistêmica aguda e sub-aguda foi investigada em ratos, por duas vias de administração, *p.o.* e *i.p.*, nas doses de 1000 μM/kg e 73 μM/kg, respectivamente (*i.p.*, administrando-se 2 vezes ao dia, durante 15 dias seguidos: ~ 100 vezes superior à ED_{50} *in vivo*).**

Não tem efeito letal, não provoca letargia, não reduz a motilidade, nem altera o pêso dos animais.

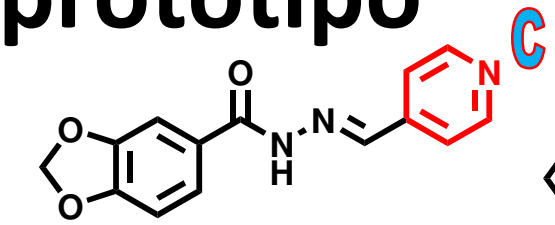
Não provoca alterações na contagem de células sanguíneas, hematócrito, nem altera a taxa de glicose, uréia, TGO, TGP, creatinina.

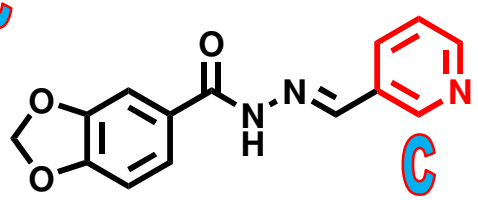
Não altera histopatologicamente orgãos vitais, tais como fígado, pulmão, SNC.

LASSBio-294

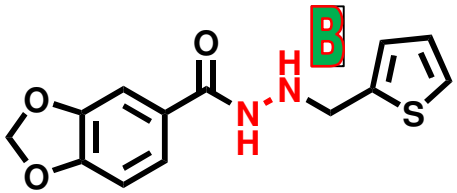
Não se observaram efeitos neurotóxicos em culturas de neurônios hipocampais de ratos, tratadas com LASSBio-294 (500 μM). Efeito neuroprotetor foi observado em < doses.

Otimização do protótipo





LASSBio-123



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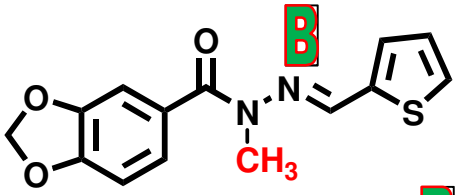
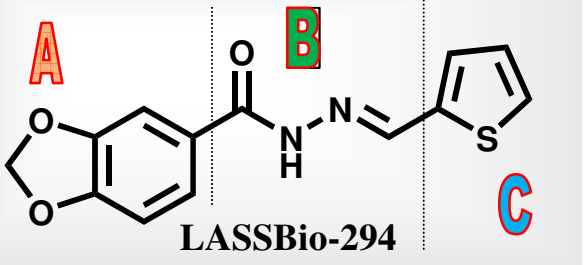


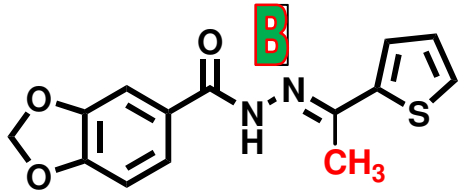
LASSBio-785
IC_{50} = 10,2 µM

Dissecação Molecular

LASSBio-129

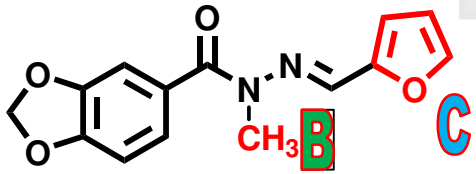


LASSBio-294
(VD) IC_{50} = 74,0 µM

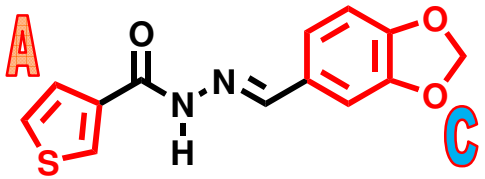


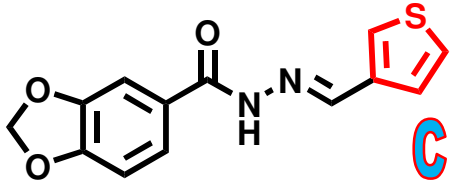
LASSBio-1029

LASSBio-787



LASSBio-1192





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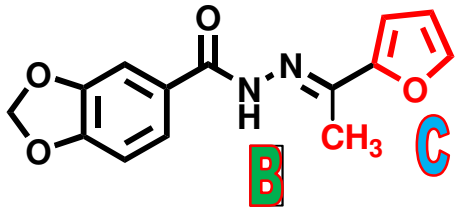

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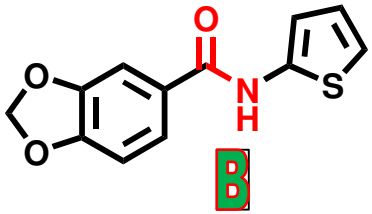

- *Bioorganic Medicinal Chemistry* 2005, **13**, 3431
  Patente BR PI0403363 9

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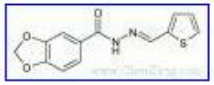

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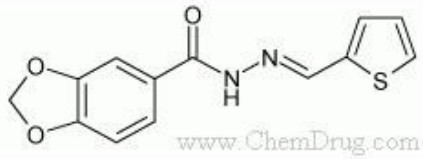
您现在的位置： >> 专业资料首页 >> 药物合成数据库 >> L-294, LASSBio-294,314021-07-3,C13-H10-N2-O3-S,(E)-N'-(Thien--药物合成数据库

【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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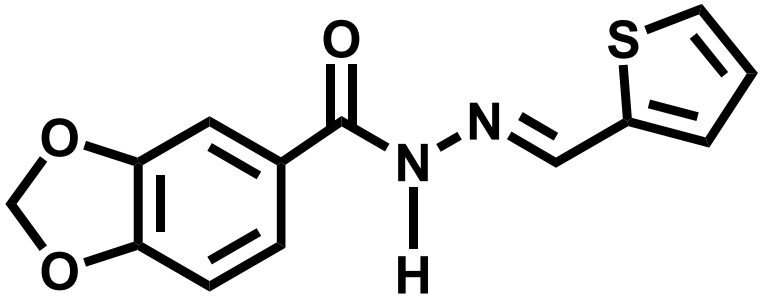
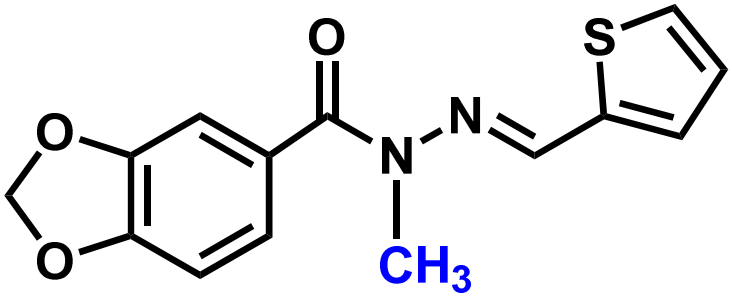


LASSBio-294



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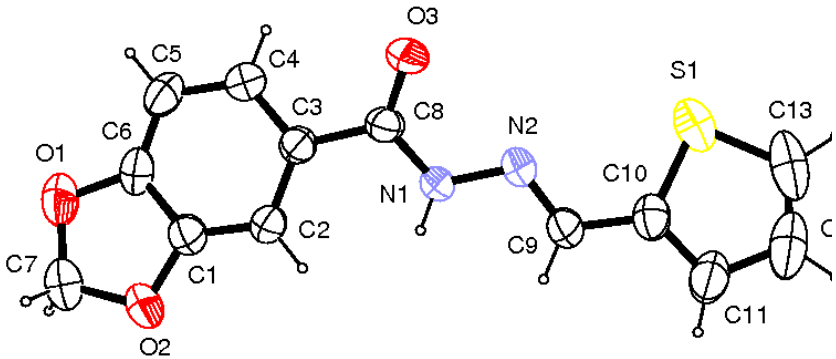
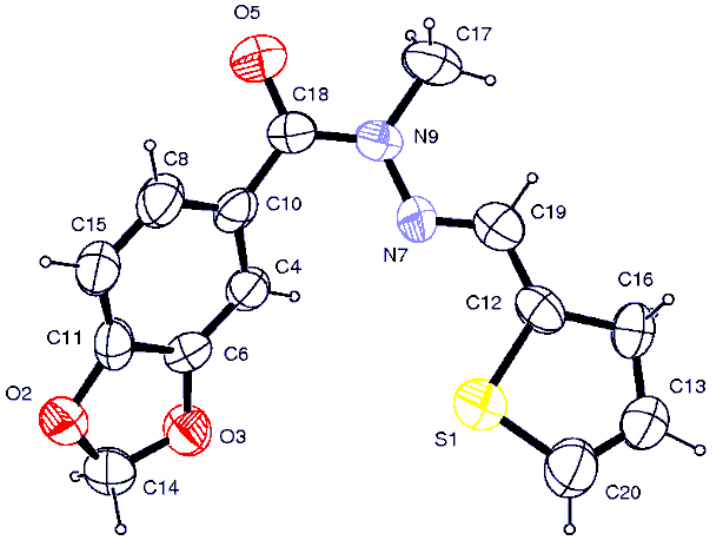
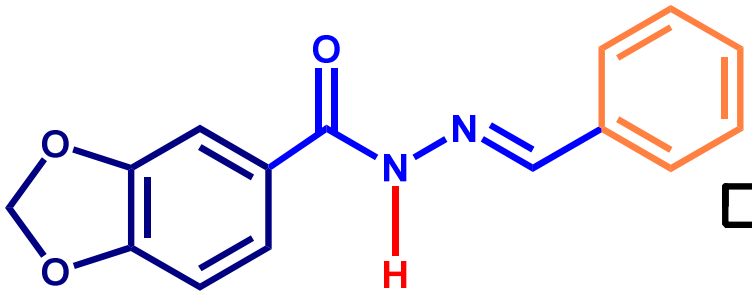




AC Dorighetto & EJ Barreiro, resultados não publicados



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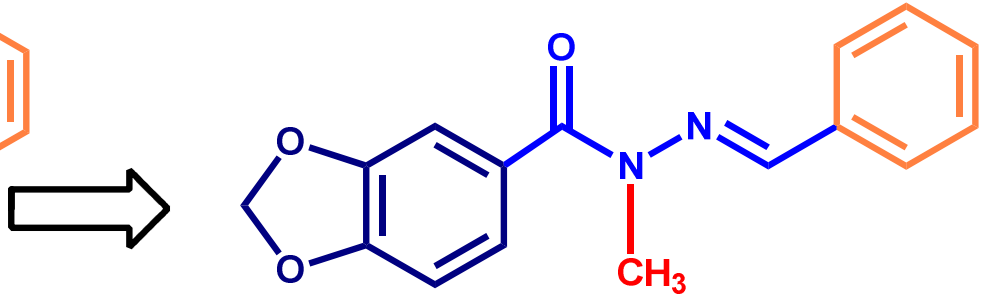

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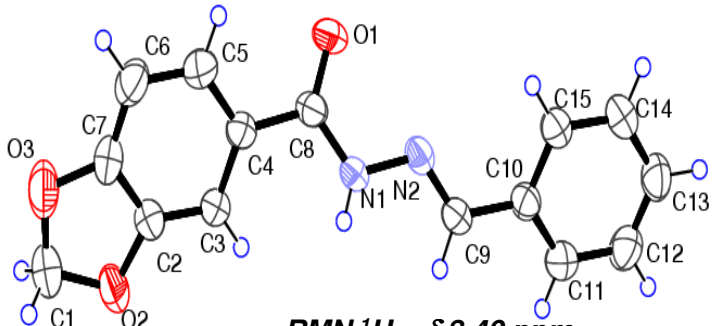
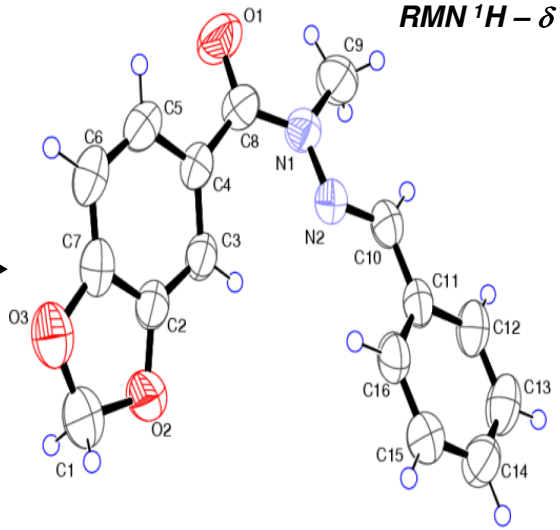


RMN ^{1}H – δ 8,40 ppm

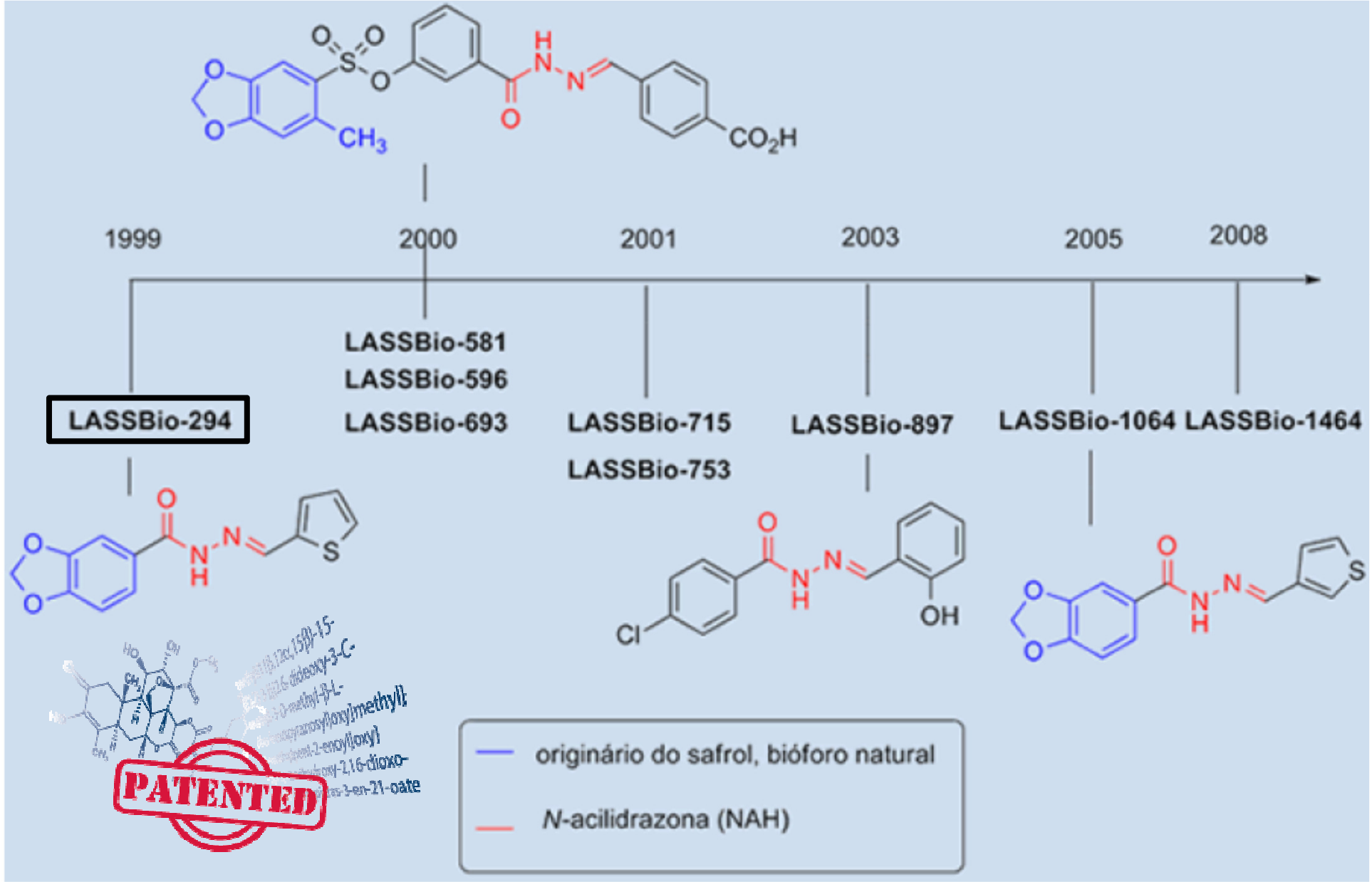
N-metilação



RMN ^{1}H – δ 3,60 ppm

LASSBio-123

LASSBio-1004


1999
2000
2001
2003
2005
2008
LASSBio-581
LASSBio-596
LASSBio-693
LASSBio-294
LASSBio-715
LASSBio-753
LASSBio-897
LASSBio-1064
LASSBio-1464
PATENTED
originário do safrol, bióforo natural
N-acilidrazona (NAH)

LASSBio-294 na Web

ChEMBL

- ChEMBL
- Downloads
- Malaria Data
- ChEMBL-NTD
- Kinase SARfari
- GPCR SARfari
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ChEMBL Statistics

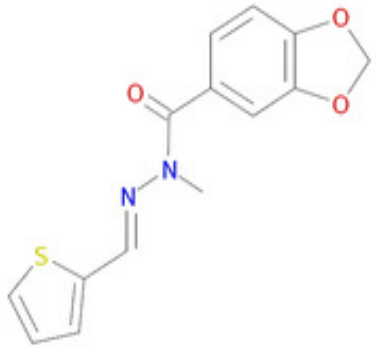
- DB: ChEMBL_17
- Targets: 9,356

EBI › Databases › Small Molecules › ChEMBL Database › Compound Search › CHEMBL573324

Compound Report Card

Compound Name and Classification

Compound ID	CHEMBL573324
Compound Name	
ChEMBL Synonyms	LASSBio-785
Max Phase	0
Trade Names	
Molecular Formula	C14H12N2O3S



CHEMBL573324

Additional synonyms for CHEMBL573324 found using NCI Chemical Identifier Resolver

ChemSpider
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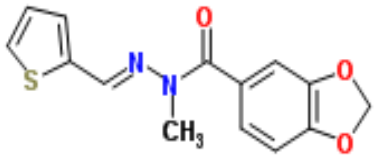
Search term: **KHKMSPFEDXGGFF-OVCLIPMQSA-N** (Found by InChIKey (full match))

N-Methyl-N'-[(E)-2-thienylmethylene]-1,3-benzodioxole-5-carbohydrazide



2D 3D Save Zoom

- *Double-bond stereo*

ChemSpider ID: **9623943**

Molecular Formula: $C_{14}H_{12}N_2O_3S$

Average mass: 288.321686 Da

Monoisotopic mass: 288.056854 Da

▼ Systematic name

N-Methyl-N'-[(E)-2-thienylmethylene]-1,3-benzodioxole-5-carbohydrazide

▶ SMILES and InChIs

▶ Cite this record

LASSBio-294

NCBI

PubChem BioAssay

PubChem BioAssay | Search

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BioActivity Analysis: 652 Bioassays (661 components), 1 Compound and 462 Protein Targets

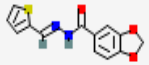
Summary | DataTable | Structure-Activity

Revise BioAssay and Compound Selection

BioAssay Summary:
Total Bioassays (652) (661 components)
MLP (629)
Defined Protein Target (550)
Summary/Confirmatory(191)
Primary (438)

Compound Summary:
Total Compound (1)
Active Compounds (1)

Structure 1 - 1 of 1

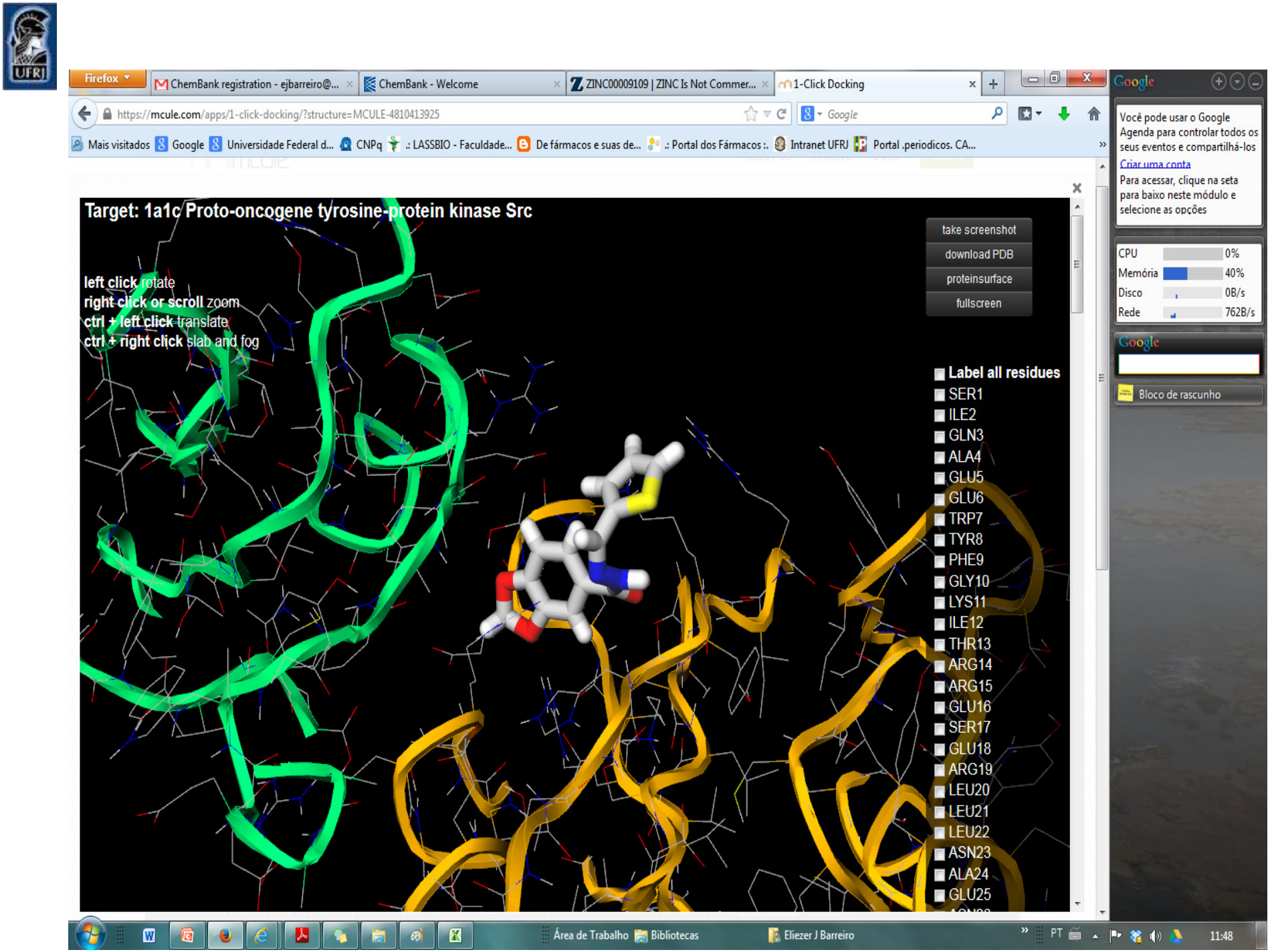


BioAssays | Targets | Compounds

Total Pages: 34 Display: 20 Go To Page 1

Sort: [Click the result table header to sort]

#	AID	Activity	AC≤1[μM]	AC≤1[nM]	AC Range	BioAssay [Outcome Type]	Protein Target
1	2288		1		0.7362 [μM]	qHTS Assay for Modulators of miRNAs and/orActivators of miR-21 [Confirmatory]	
2	2289		1		0.7362 [μM]	qHTS Assay for Modulators of miRNAs and/or Inhibitors of miR-21 [Confirmatory]	
3	485297				1.2589 [μM]	qHTS Assay for Rab9 Promoter Activators [Confirmatory]	ras-related protein Rab-9A [Homo sapiens] [gi:4759012]
4	624202				1.2589 [μM]	qHTS Assay to Identify Small Molecule Activators of BRCA1 Expression [Confirmatory]	BRCA1 [Homo sapiens][gi:1698399]
5	504832				1.6511 [μM]	Primary qHTS for delayed death inhibitors of the malarial parasite plastid, 48 hour incubation [Confirmatory]	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ChemBank registration - ejbarreiro@...
ChemBank - Welcome
ZINC00009109 | ZINC Is Not Commer...
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Target: 1a1c Proto-oncogene tyrosine-protein kinase Src
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right click or scroll zoom
ctrl + left click translate
ctrl + right click slab and fog
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Label all residues
SER1
ILE2
GLN3
ALA4
GLU5
GLU6
TRP7
TYR8
PHE9
GLY10
LYS11
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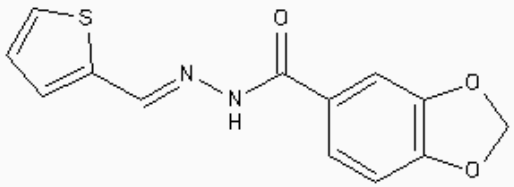
ZINC00009109

In ZINC since	Heavy atoms	Benign functionality
July 23rd, 2004	19	No



Popular Name: ***N'-[(E)-2-thienylmethylidene]-1,3-benzodioxole-5-carbohydrazide***
Find On: ***PubMed — Wikipedia — Google***

Other Names:

MFCD01425224

N-((1E)-2-(2-thienyl)-1-azavinyl)-2H-benzo[3,4-d]1,3-dioxolen-5-ylcarboxamide

Draw Identity 99% 90% 80% 70%

SMILES: c1cc(sc1)/C=N/NC(=O)c2ccc3c(c2)OCO3

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Life Chemicals	F0733-0022
Mcule	MCULE-4810413925

Annotations

ChEMBL12	CHEMBL233194, CHEMBL1428742
ChEMBL14	CHEMBL1428742
ChEMBL15	CHEMBL1428742, CHEMBL233194
ChEMBL17	CHEMBL233194, CHEMBL1428742
ChemDB	4721838
Collaborative Drug Discovery	1424725
PubChem	9579598, 667591

"...discovery *consists* of seeing

what everybody else **has seen**

***and* thinking what**

no*b*ody else

has not thought..."

***Albert Szent-Györgi* (1893-1986)**

FÁRMACOS DO SÉCULO 21

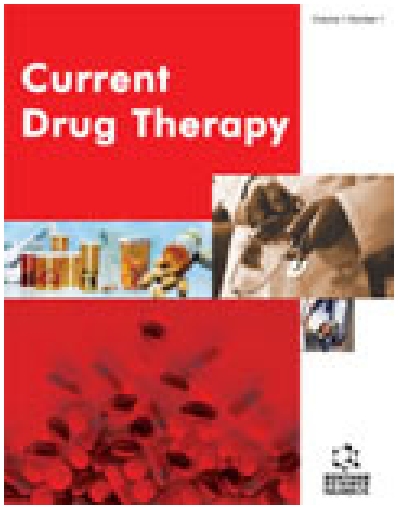
New Insights for Multifactorial Disease Therapy: The Challenge of the Symbiotic Drugs

Eliezer J. Barreiro and Carlos Alberto Manssour Fraga

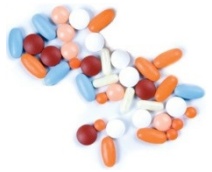
Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, P.O. Box 68023, 21944-971, Rio de Janeiro, RJ, Brazil.

Abstract: Some physiopathological processes involved in the genesis of diseases could suggest the necessity of designing bioligands or prototypes that aggregate, in only one molecule, dual pharmacodynamical properties, becoming able to be recognized by two elected bioreceptors. This approach can have distinct aspects and, when a novel ligand or a prototype acts in two elected targets belonging to the same biochemical pathway, *e.g.* arachidonic acid cascade, it receives the denomination of dual or mix agent. On the other hand, if these two targets belong to distinct biochemical routes and both are related to the same disease, we can characterize the agents able to modulate it as symbiotic ligands or prototypes. In the present work, we provide some examples and applications of the molecular hybridization concept for the structural design of new symbiotic ligands and prototypes, especially those applied in the treatment of chronic-degenerative disorders.

Key Words: Symbiotic drugs; molecular hybridization; multifactorial diseases; therapeutic innovation; drug design; dual compounds.

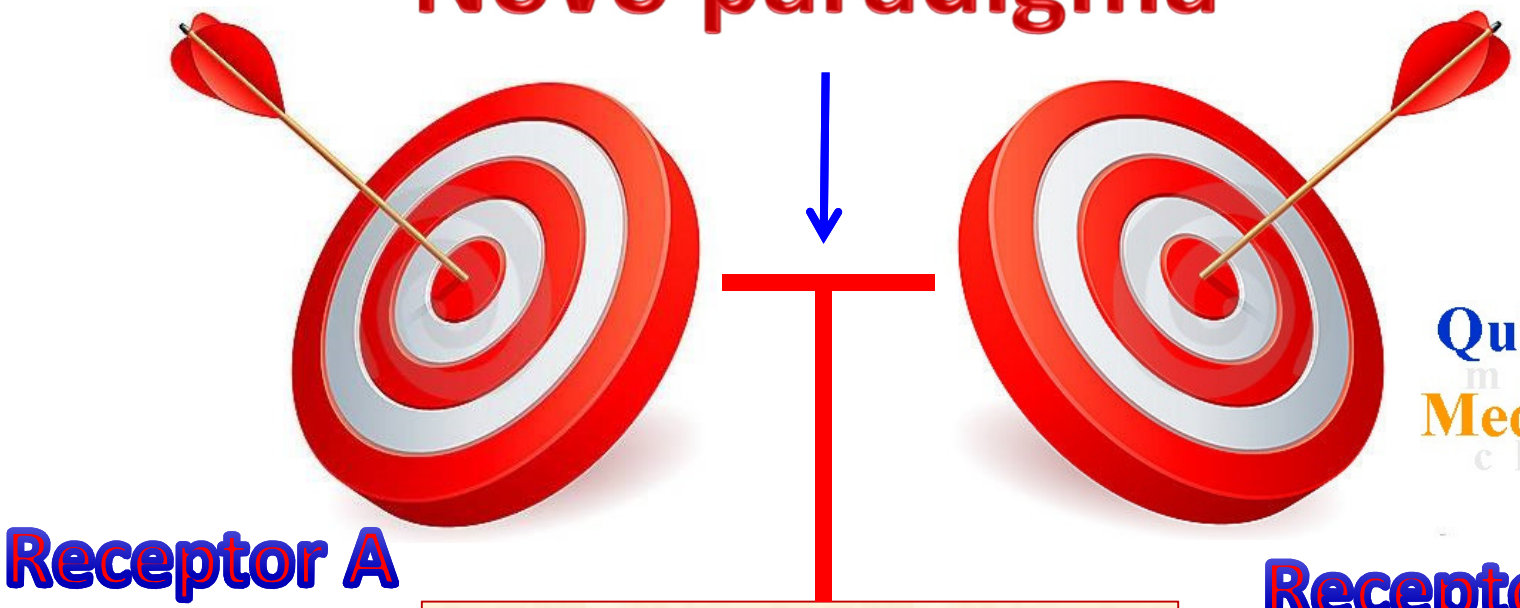


Fármacos simples não curam doenças complexas!



Fármacos do século 21

Novo paradigma



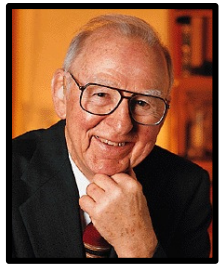
Química Medicinal

O desenho racional de fármacos *multi-alvos* depende da capacidade de se combinarem fragmentos moleculares farmacofóricos, capazes de assegurarem reconhecimento molecular pelos receptores envolvidos na patologia multifatorial

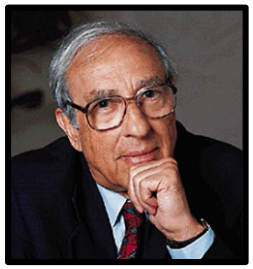
A Anighoro et al., **Polypharmacology:** challenges and opportunities in drug dsicovery, *J. Med. Chem*. **2014**, *57,* 7874; JL Medina-Franco et al. Shifting from the single to the **multitarget paradigm** in drug discovery, *Drug Discov. Today* **2013**, *18,* 495; C Hiller, J Kühhorn, P Gmeiner, Gmeiner, Class A G-Protein-Coupled Receptor (GPCR) Dimers and Bivalent Ligands, *J. Med. Chem.* **2013**, *56*, 6542; G Phillips, M Salmon, **Bifunctional compounds** for the treatment of COPD, *Annu. Rev. Med. Chem*. **2012**, *47*, 209; S Reardon, A world of chronic disease, *Science* **2011**, *333*, 558.

Tinibes: TK's inibidores

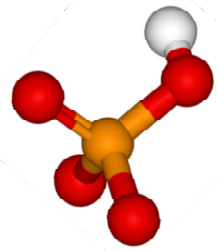
kinoma

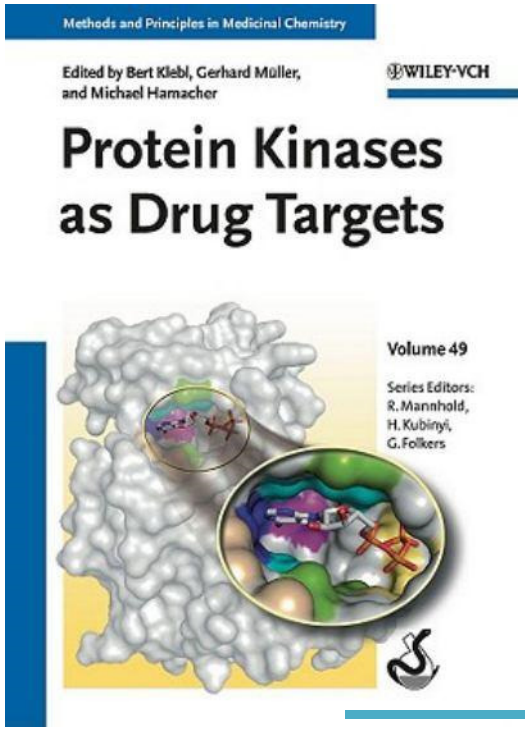


Edwin G Krebs
(1918 –2009)



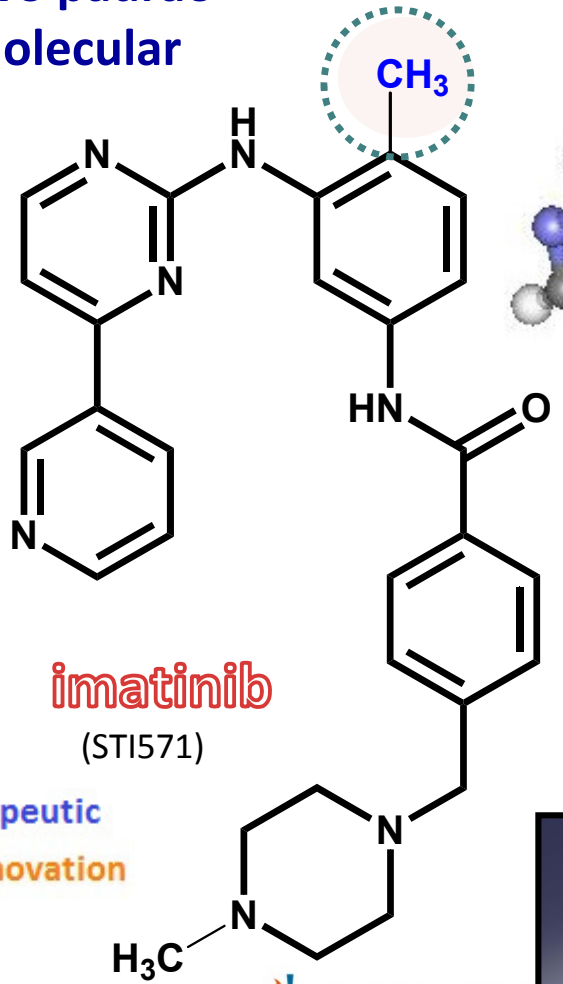
Edmond H Fischer
(1920)





S. Aggarwal, Targeted cancer therapies, *Nature Rev. Drug Discov.* **2010**, *9*, 427; P. Cohen, Timeline: Protein kinases — the major drug targets of the twenty-first century? *Nature Rev. Drug Discov.* **2002**, *1*, 309

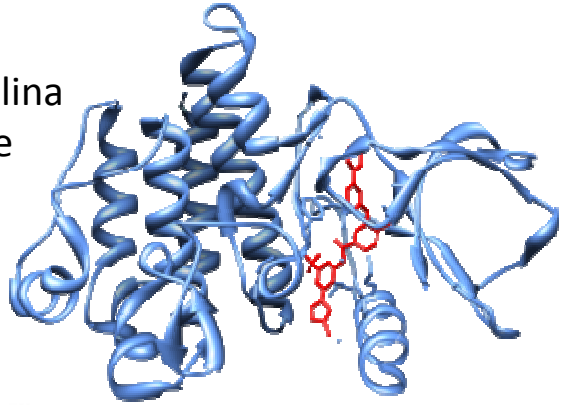
Novo padrão molecular

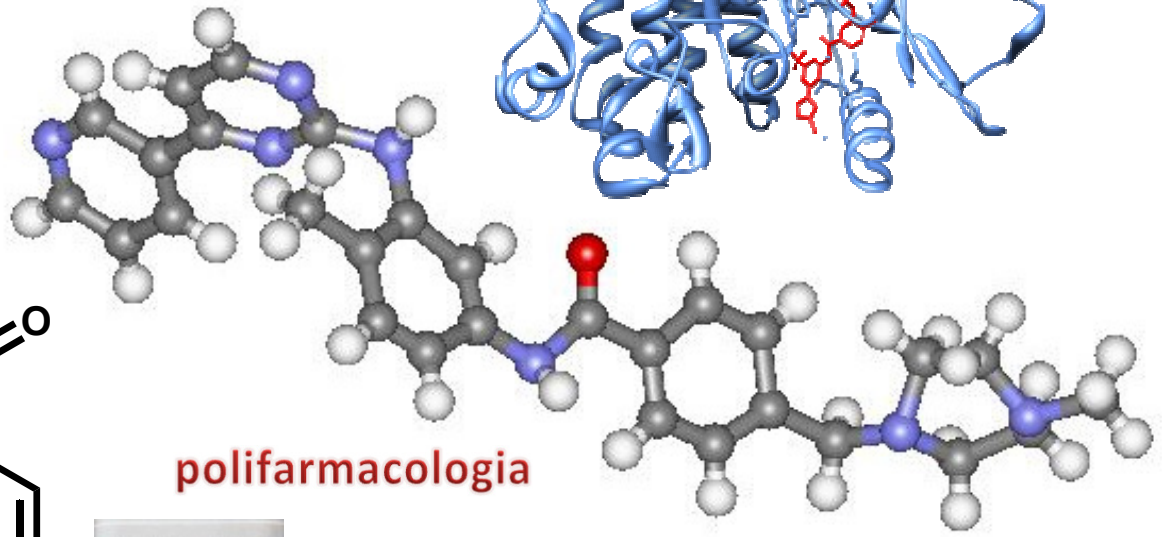


imatinib

(STI571)

Estrutura cristalina da Abl cinase





polifarmacologia

1988 – Nicholas Lydon, Brian J. Druker & Charles L Sawyers &
1995 - Compound STI571 ++
2001 – Imatinib (Gleevec^{R}, Novartis)[link]

therapeutic innovation

Leucêmia mieloide crônica (CML)

NOVARTIS

imatinibe

Nicholas B. Lydon
Blueprint Medicines Inc*

Brian J. Druker*
Blueprint Medicines Inc

Charles L. Sawyers**
Blueprint Medicines Inc

& 2009 - Lasker Foundation Clinical Award (*J. Clin. Invest*. **2009**, *119*, 2863)

* B. J. Druker has been awarded with the 2012 Japan Prize in Healthcare and Medical Technology;

** C. L. Sawyers was named in 2011, Thomson Reuters Citation Laureate in Medicine;

Novel 2-chloro-4-anilino-quinazoline derivatives as EGFR and VEGFR-2 dual inhibitors

Maria Letícia de Castro Barbosa [a,b], Lídia Moreira Lima [a,b], Roberta Tesch [a], Carlos Mauricio R. Sant'Anna [c], Frank Totzke [d], Michael H.G. Kubbutat [d], Christoph Schächtele [d], Stefan A. Laufer [e], Eliezer J. Barreiro [a,b,*]

[a] Laboratory of Evaluation and Synthesis of Bioactive Substances (LASSBio), Federal University of Rio de Janeiro, P.O. Box 68024, 21944-971 Rio de Janeiro, RJ, Brazil
[b] Graduate Program of Chemistry (PGQu), Chemistry Institute, Federal University of Rio de Janeiro, Rio de Janeiro, RJ, Brazil
[c] Department of Chemistry, Federal Rural University of Rio de Janeiro (UFRRJ), Seropédica, RJ, Brazil
[d] ProQinase GmbH, Freiburg, Germany
[e] Department of Pharmaceutical/Medicinal Chemistry, Institute of Pharmacy, Eberhard-Karls-University Tübingen, Tübingen, Germany

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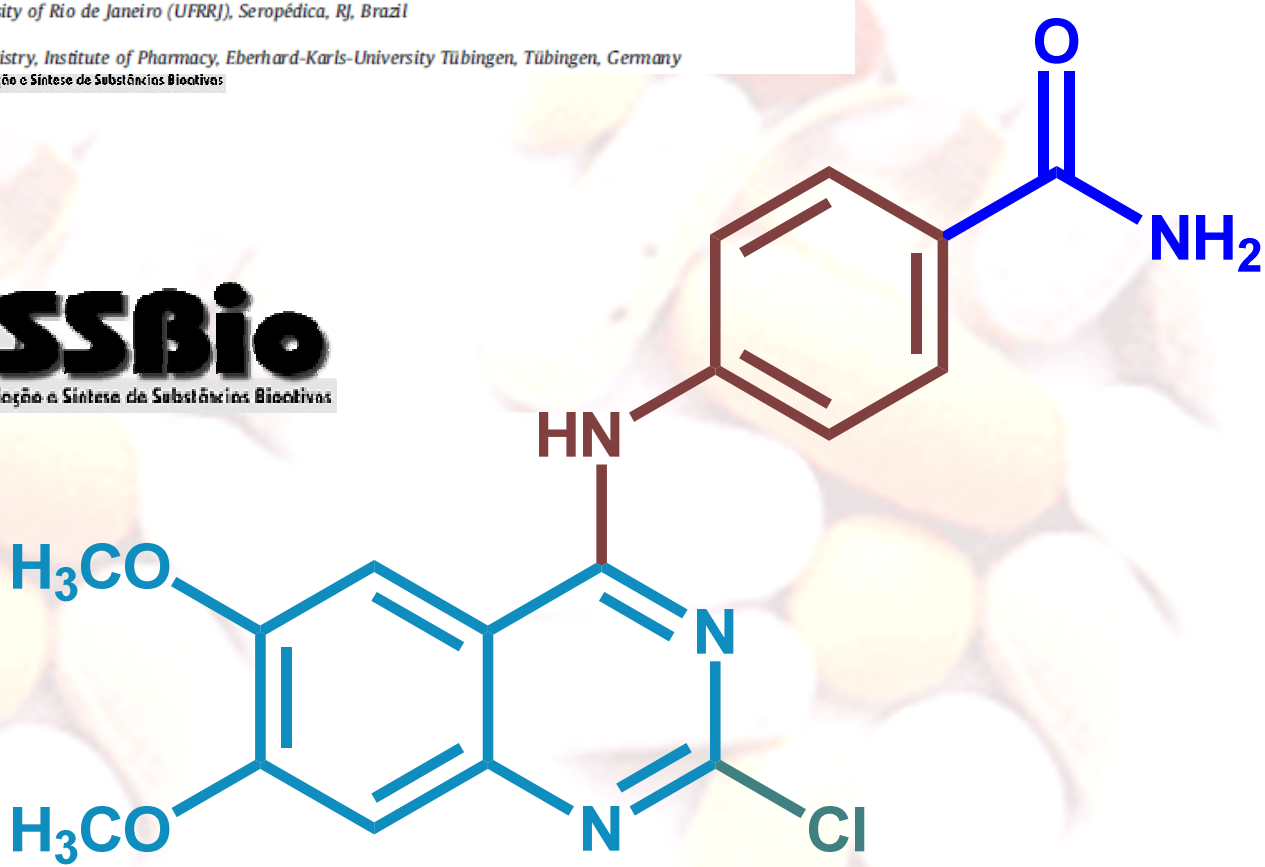

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Novel 2-chloro-4-anilino-quinazoline derivatives as EGFR and VEGFR-2 dual inhibitors

Maria Letícia de Castro Barbosa [a,b], Lídia Moreira Lima [a,b], Roberta Tesch [a], Carlos Mauricio R. Sant'Anna [c], Frank Totzke [d], Michael H.G. Kubbutat [d], Christoph Schächtele [d], Stefan A. Laufer [e], Eliezer J. Barreiro [a,b,*]

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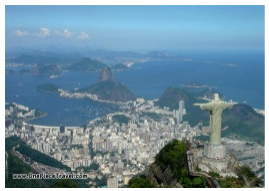
[d] ProQinase GmbH, Freiburg, Germany
[e] Department of Pharmaceutical/Medicinal Chemistry, Institute of Pharmacy, Eberhard-Karls-University Tübingen, Tübingen, Germany

European Journal of Medicinal Chemistry 71 (2014) 1–14



UNIVERSITÄT TÜBINGEN

Novel molecular pattern with EGFR/VEGFR dual activity !

LASSBio-1819

Atividade dual

IC_{50} (EGFR) = 0,90 µM

IC_{50} (VEGFR) = 1,17 µM

Depósito de patente no INPI

MLC Barbosa, Novos derivados quinazolínicos funcionalizados inibidores duais das tirosina cinases receptoras EGFR & VEGFR-2, Tese de Doutorado, Instituto de Química, UFRJ, 2013.

European Journal of Medicinal Chemistry

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3. Novel 2-chloro-4-anilino-quinazoline derivatives as EGFR and VEGFR-2 dual inhibitors

Maria Letícia de Castro Barbosa | Lídia Moreira Lima

Original article Volume 71, 7 January 2014, Pages 1–14

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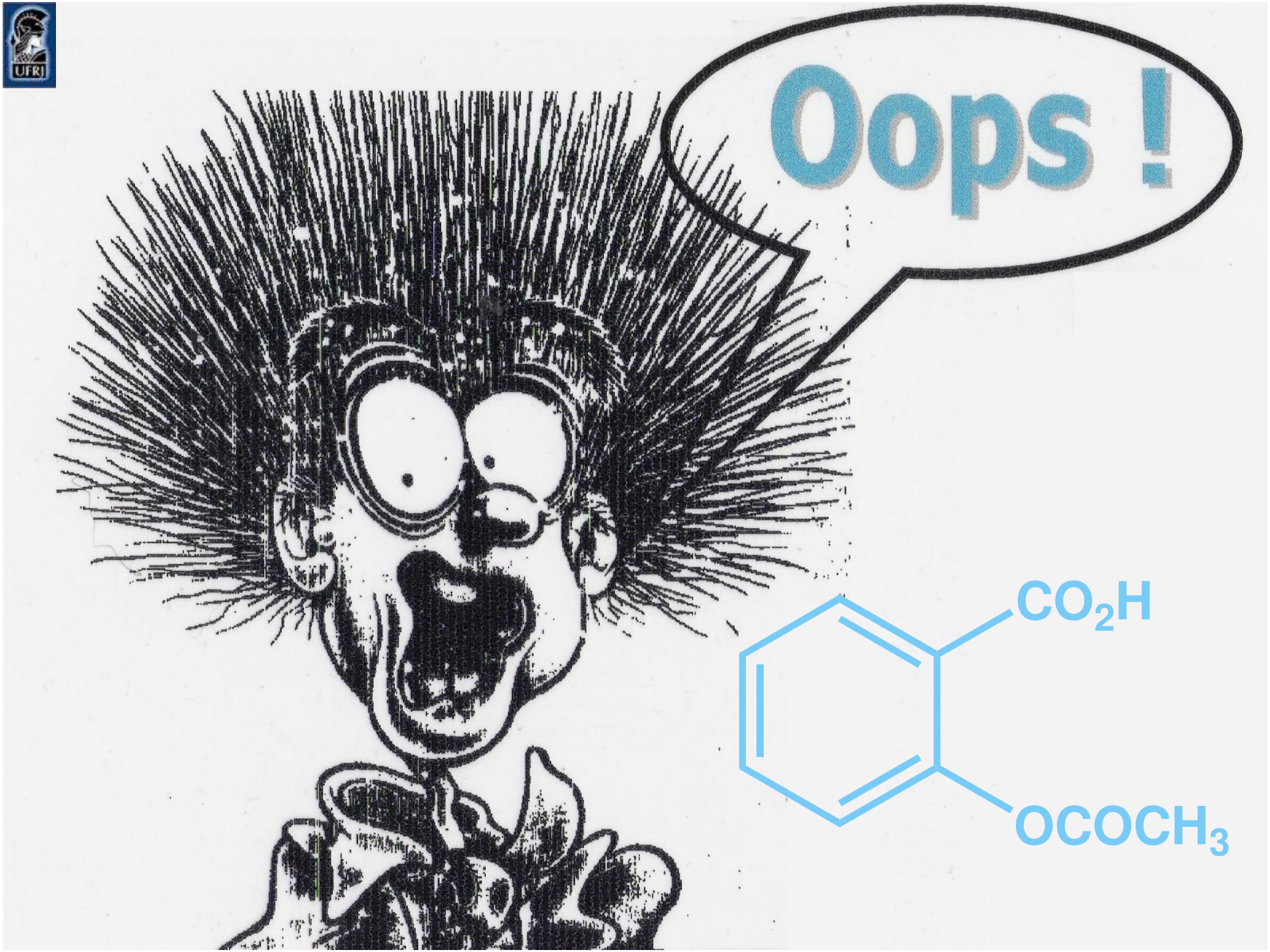
2014 - Prêmio de melhor painel no congresso **Frontiers in Medicinal Chemistry**,Tübingen,DE


Oops !
CO_2H
$OCOCH_3$


A Química
MedicInal
é simplesmente
fAscInante!
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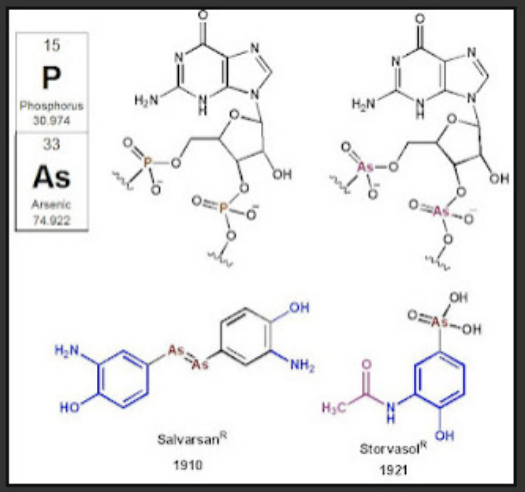
É ou não é?

De fármacos e suas descobertas

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

Convite

Sobre as moléculas dos fármacos: os acetatos famosos



Hoje me aconteceu de ler um artigo no Chemical & Engineering News (http://cen.acs.org; Chemical & Engineering News, 90, January 30, 2012) onde se comentava uma recente polêmica científica, referente à presença de arsênio (As) no DNA de organismos que vivem em ambiente rico em As, como a bactéria GFAJ-1, do lago Mono, nos EUA. Lá, pesquisadores identificaram nucleosídeos com arsênio no lugar do fósforo, em um autêntico exemplo de isosterismo na natureza. Decidi interromper a série ***Linha do Tempo da Química Medicinal****, para incluir este post em homenagem ao Carnaval 2012. Claro que continuarei*

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Presidente do STF autoriza USP a suspender 'pílula do câncer'

O presidente do STF, Ricardo Lewandowski, autorizou a USP a interromper o fornecimento da substância química fosfoetanolamina.

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Ministro sugere legalizar fosfoetanolamina como suplemento alimentar

Celso Pansera considera que a medida pode evitar que famílias e pacientes recorram a fontes desconhecidas para encontrar a pílula adotada contra o câncer.

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UFRJ
Universidade Federal do Rio de Janeiro
LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas
ejbarreiro@ccsdecania.ufrj.br
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