Estratégias para obtenção de substâncias bioativas a partir da biodiversidade

VII Simpósio Iberoamericano de Plantas Medicinais

I Simpósio Iberoamericano de Investigação em Câncer

Centro de Convenções do Hotel Praia do Sol

27-30 de outubro de 2014

Ilhéus, BA

Eliezer J. Barreiro

Professor Titular

Universidade Federal do Rio de Janeiro

Laboratório de Avaliação e Síntese de Substâncias Bioativas

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

BIODIVERSIDADE: FONTE POTENCIAL PARA A DESCOBERTA DE FÁRMACOS

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

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


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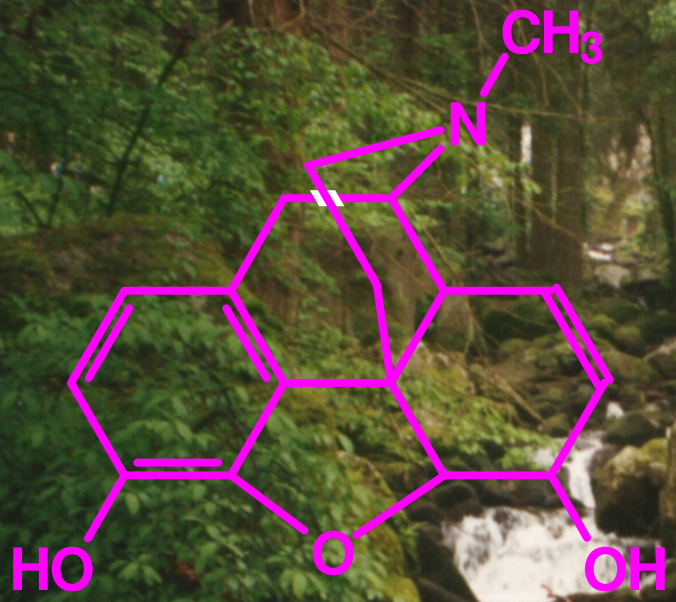
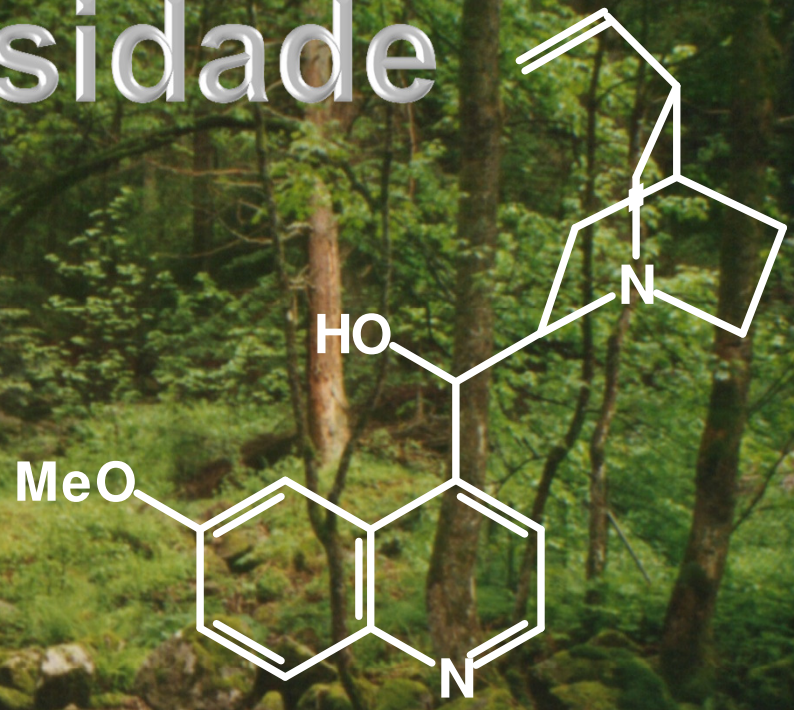
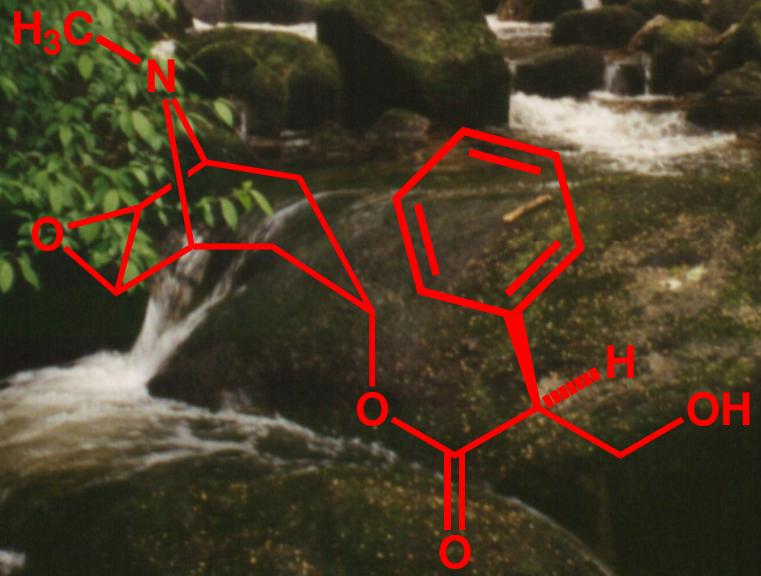
UFRJ
captopril
lipstatina
paclitaxel
Vincristina
compactina
estatinas
escopolamina
epibatidina
artemisinina
Protótipo Natural
Pioglitazone
Reserpine
Phorbol
Quinina
atropina
Morfina
vincristina
antibióticos
Digitálicos
camptotecina
Cafeína
Analgésicos
Penicilina
escopolamina
papaverina
matrix
K-trap affinity reagent
SMALL-MOLECULE PROBES
S. L. Schreiber, C&EN 2003, 81(03 de março)51.

Quimiodiversidade







alcaloides, terpenos,
esteroides, flavonoides,
lignanas, ligninas, iridoides,,
policetídeos, quinonas,
cumarinas, ...

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Do produto natural ao fármaco sintético

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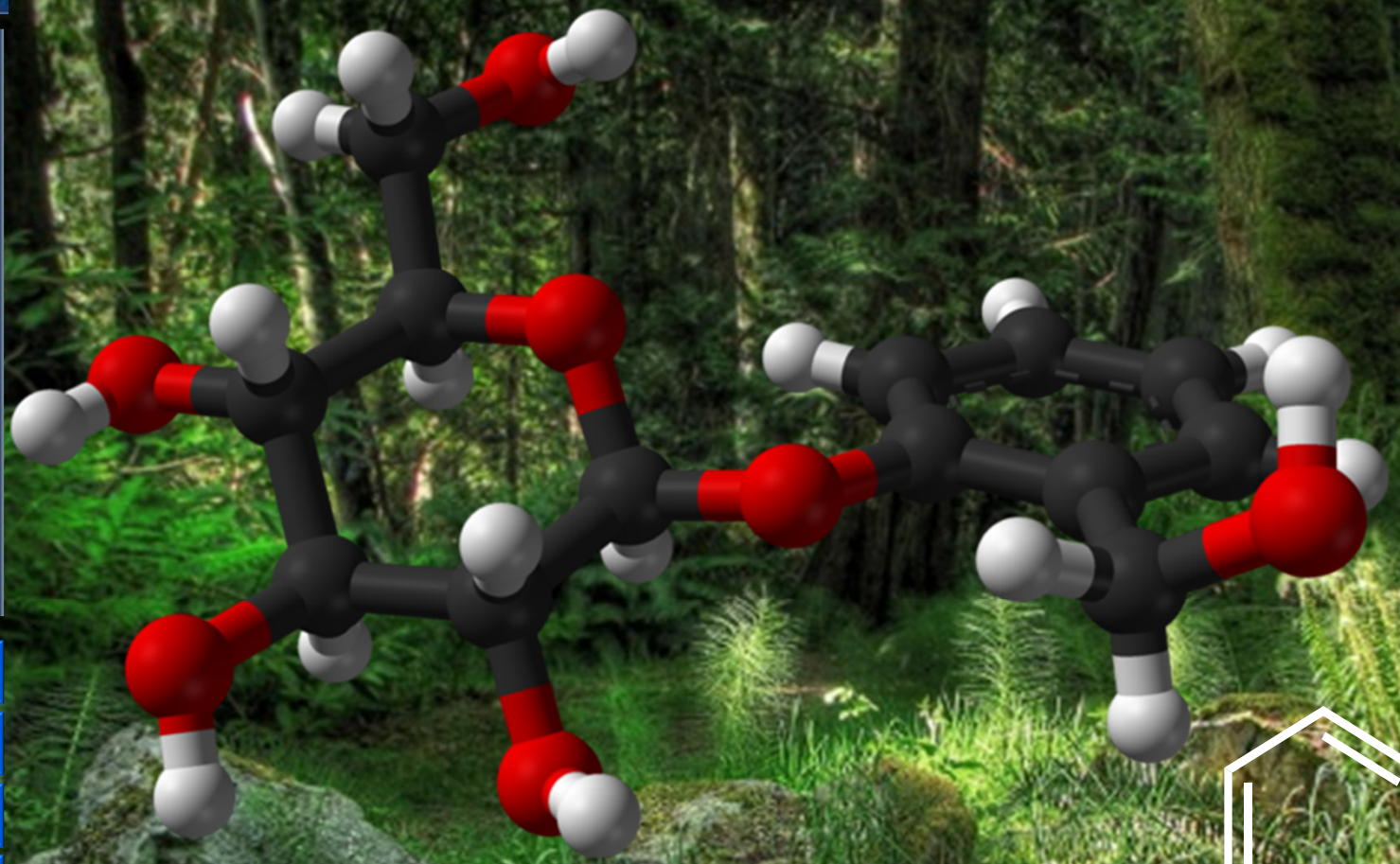
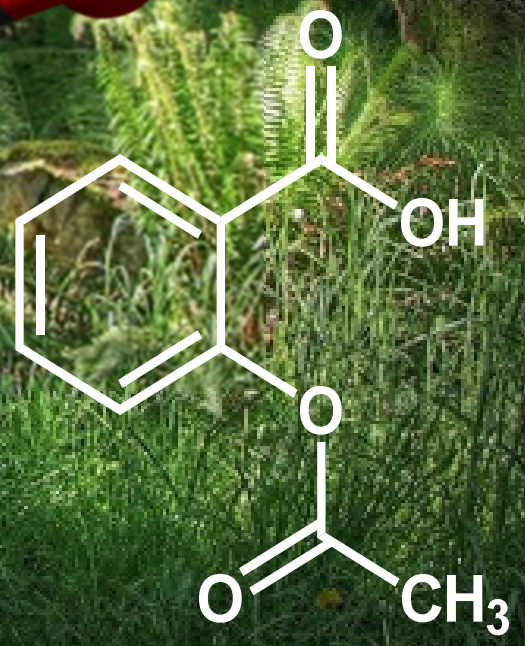


salicina

AAS



Vane, Bergstron, Samuelsson, 1982

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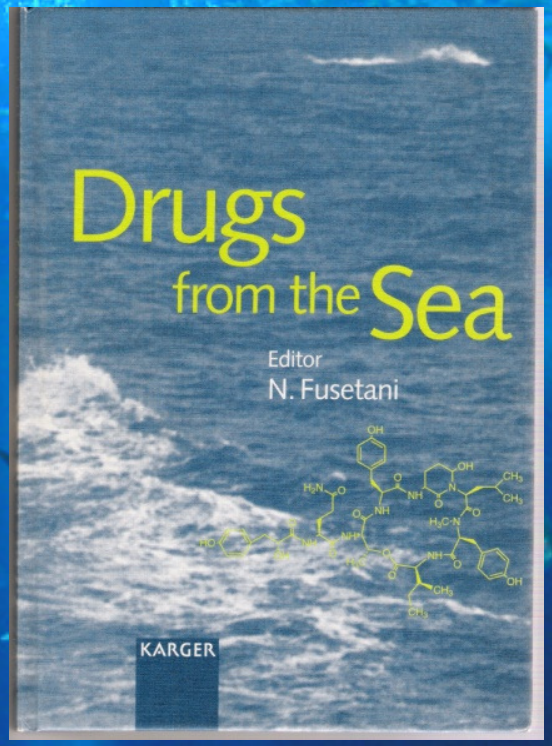
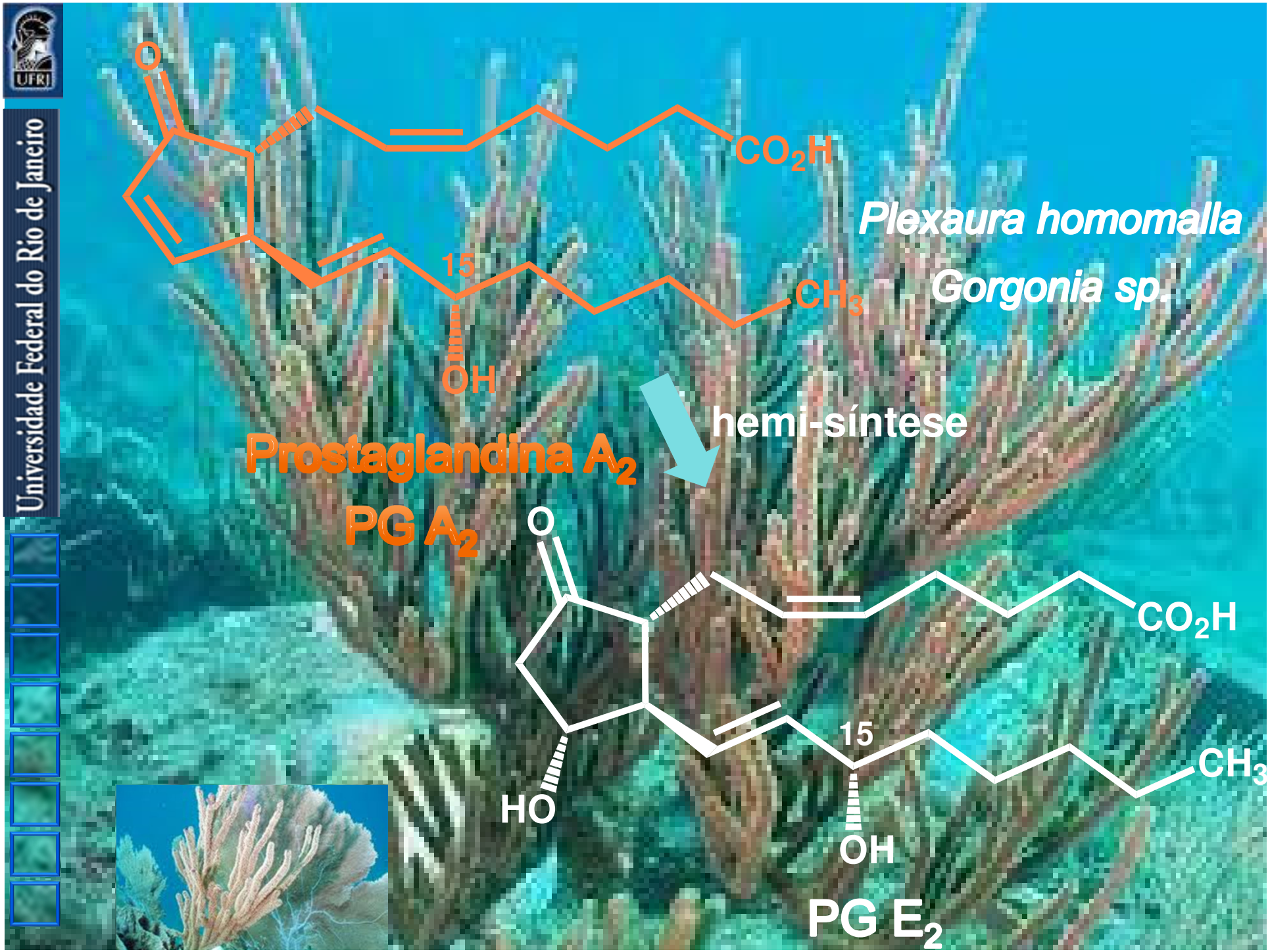
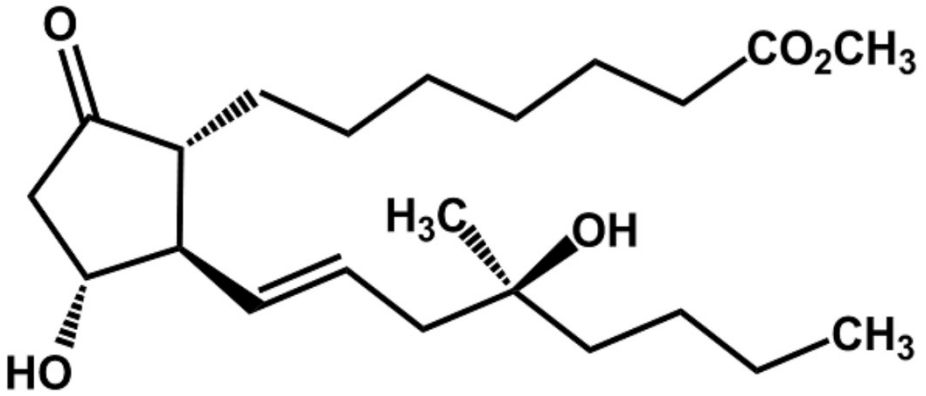
Produtos Naturais do Mar




Universidade Federal do Rio de Janeiro
UFRJ
O
CO_2H
15
CH_3
OH
Plexaura homomalla
Gorgonia sp.
hemi-síntese
Prostaglandina A_2
PG A_2
O
CO_2H
15
CH_3
HO
OH
PG E_2

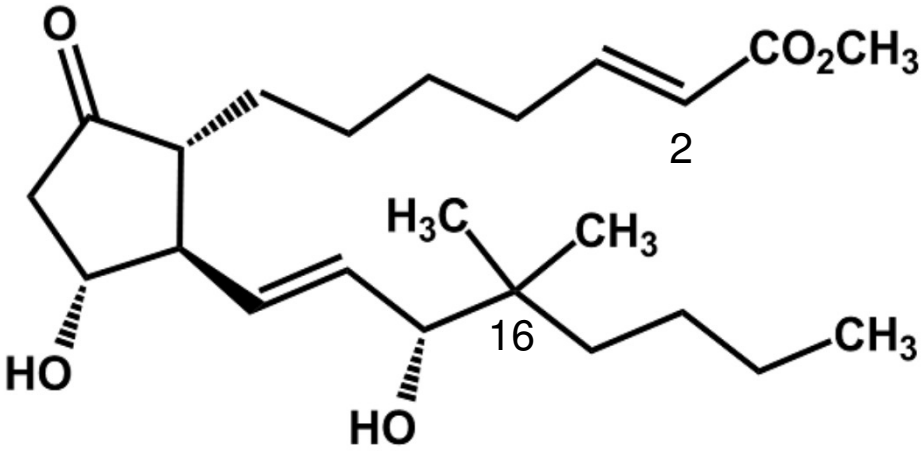


misoprostol
(pró-fármaco)

1984

Química Medicinal

1992



gemeprost
(pró-fármaco)

1980 - Michael McIntosh & Baldomero Olivera

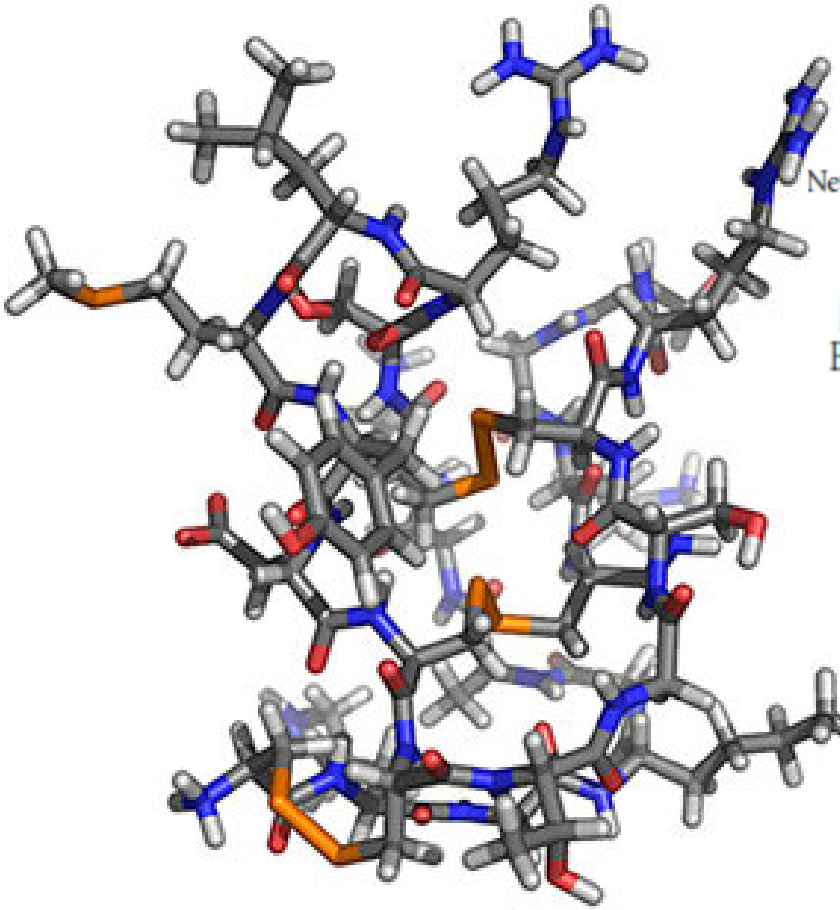
Ziconotido

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

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

Uso intratecal

Conus magus



élan

SNX-111

Neurex (Menlo Park, CA)

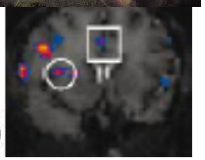
prialt

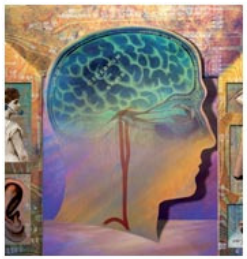
ZICONOTIDE

INTRATHECAL INFUSION

Elan Pharmaceuticals

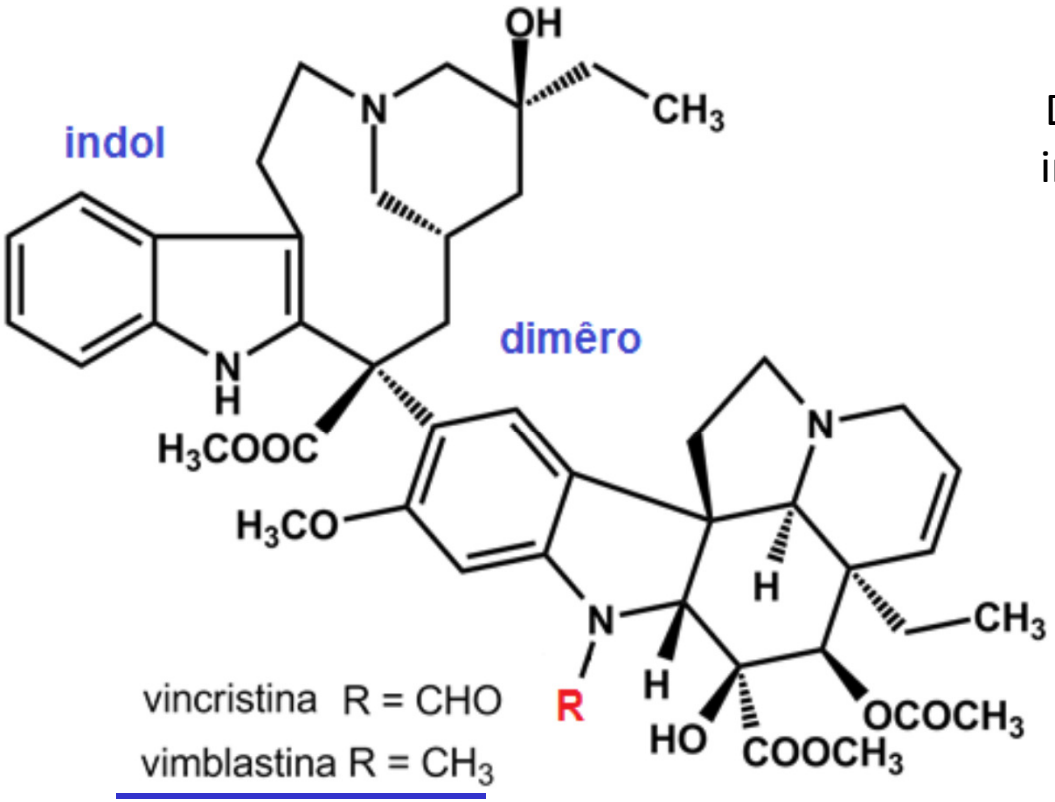
(Dublin, Ireland





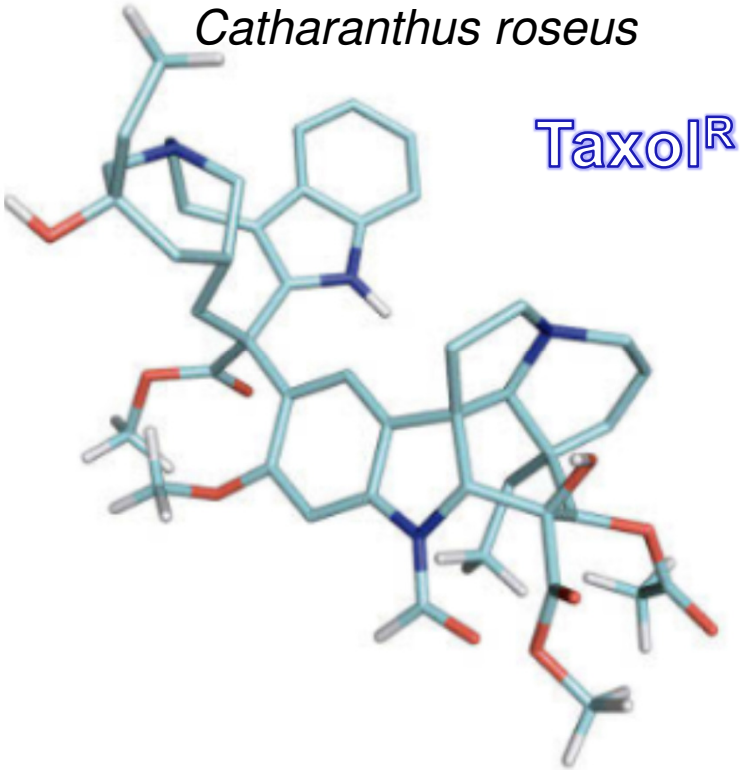
Antagonista de canais Ca^{++} voltagem dependentes tipo-N

Alcaloides da Vinca



Dimêro indólicol

Catharanthus roseus



1950 - Robert Noble & Charles T. Beer
1958 – NY Academy of Sciences Congress
Noble descreve vinblastina
1958 - NY Academy of Sciences Congress
Gordon Svoboda Eli Lilly vincristina
1963 – Eli Lilly (Oncovin®)[FDA]

Do *bolor* às moléculas salva-vidas...

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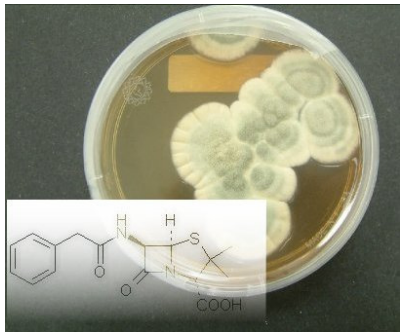
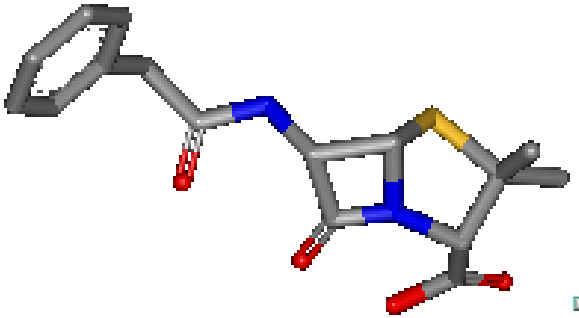


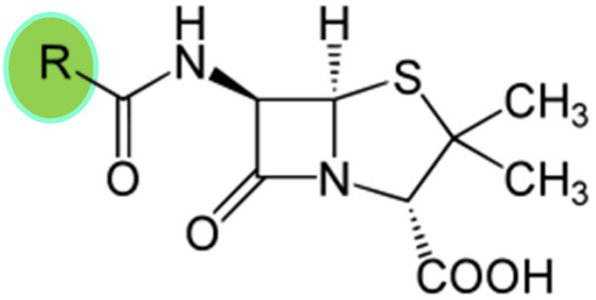
Alexander Fleming
1881-1955



Penicilina

Fungos

antibioticoterapia



Howard W. Florey
1898-1968

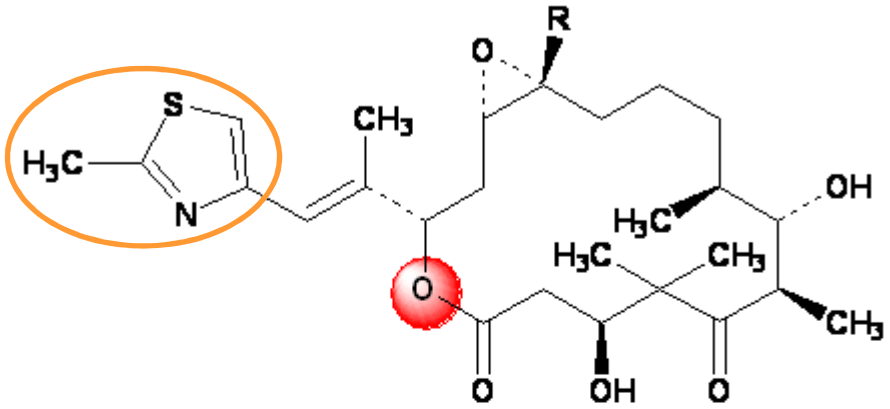
1945

Ernest B. Chain
1906-1979

Antibióticos β-lactâmicos ⇨ **4ª geração**

Outras fontes....

Isolada de Sorangium cellulosum em 1993

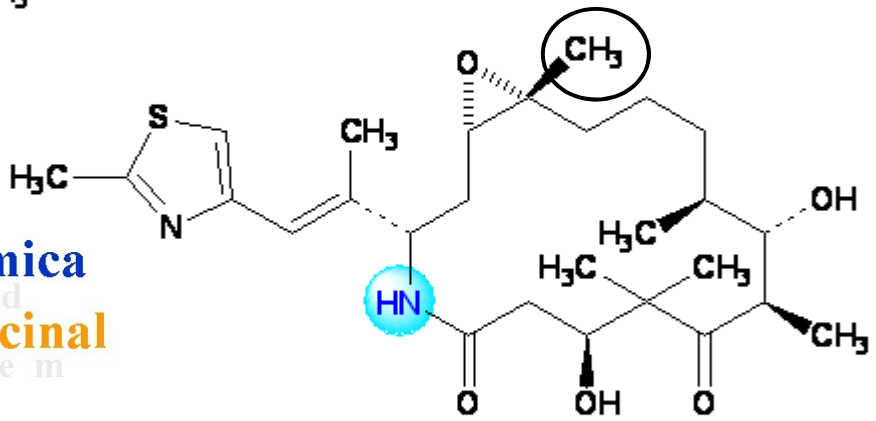


Epotilona A R = H

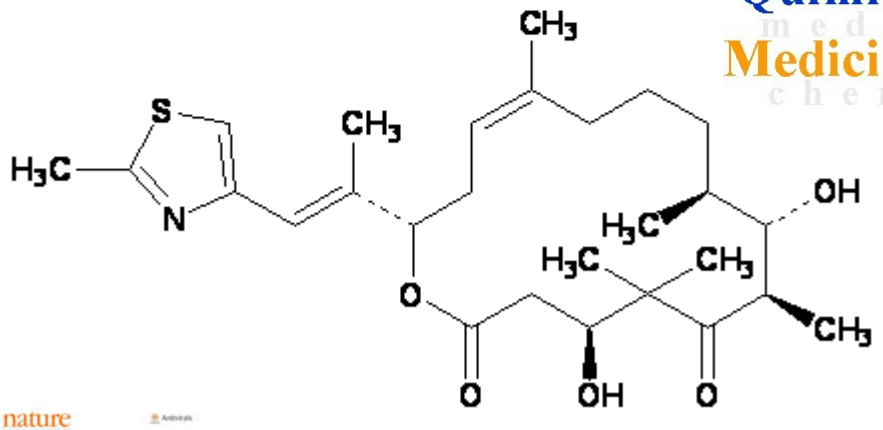
Epotilona B R = CH_3

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

Análogo semi-sintético



Química Medicinal



Epotilona D

Ixabepilona

Ixempra^{R}

BMS, Out. 2007

Via fermentativa bacteriana, ativo em células taxano-R

Bactéria Gram- do grupo Myxobacteria

A Conlin, M Fornier, C Hudiis, S Kar, P. Kirkpatrick, *Nat. Rev. Drug Discov*. **2007**, *6*, 953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UFRJ
Produtos naturais abundantes...
+
=
LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas
Química
med
Medicinal
chem

Universidade Federal do Rio de Janeiro

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

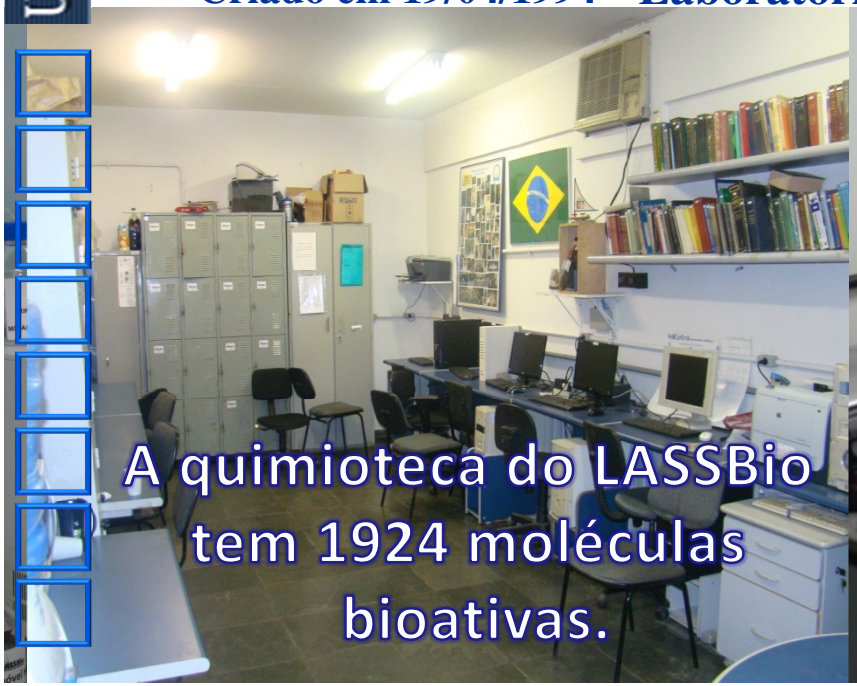
LASSBio

Laboratório de Avaliação e Síntese de Substâncias Bioativas

Química Medicinal

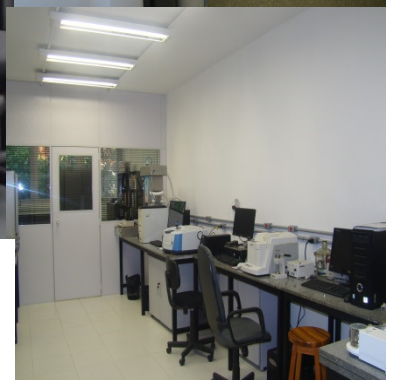
Bioensaios

Criado em 19/04/1994 Laboratório de Avaliação e Síntese de Substâncias Bioativas



A quimioteca do LASSBio tem 1924 moléculas bioativas.

Molecular Modelagem



Produtos naturais como blocos moleculares

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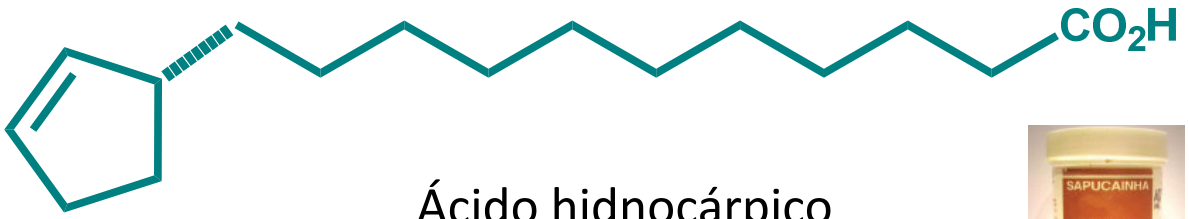

Ácido hidnocárpico

1982

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Primeiras prostaglandinas brasileiras

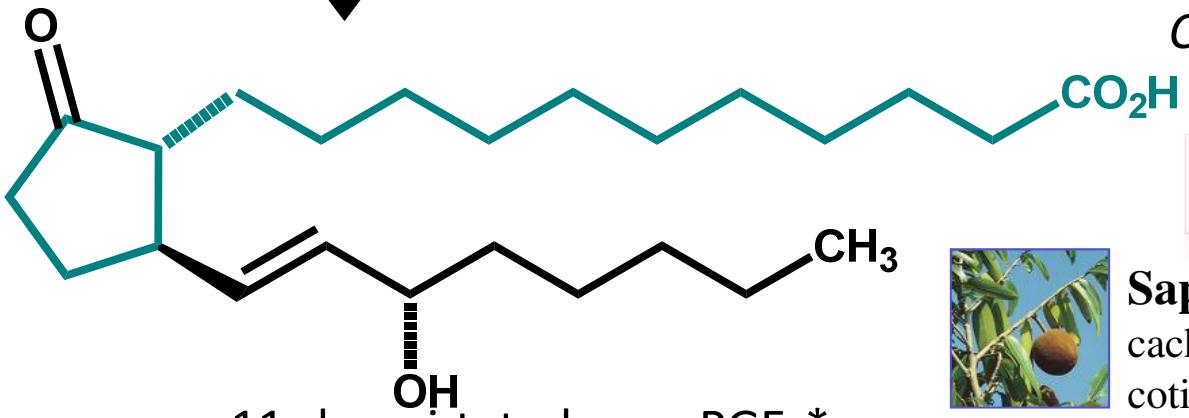
Óleo de Sapucainha

Cole & Cardoso, 1938

Carpotroche brasiliensis, Endl

Flacourtiácea

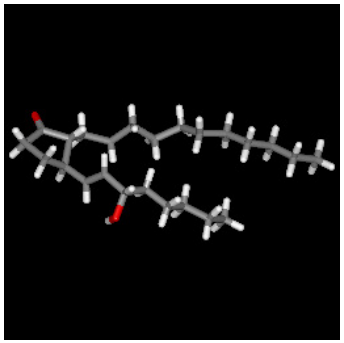
AS Oliveira, JA Lima, CM Rezende, AC Pinto, *Quim. Nova* **2009**, *32*, 139



11-desoxi-tetrahomo PGE_1*

Sapucainha, Papo de anjo, Pau de cachimbo, Canudo de pito, Fruta de cotia, Fruta de Macaco.

EJ Barreiro, LNLF Gomes, Prostaglandin Analogues. Synthesis of Tetrahomoprostaglandin Derivatives From Natural Hydnocarpic Acid Isolated From Sapucainha Oil, *J. Chem. Res*. **1983**, 2701;



*EJ Barreiro, LNLF Gomes, Novo Método de Síntese de Prostaglandinas Modificadas da Série 11-desoxi PG E1". **INPI, PI 38201866, 02/04/1982** ; *Chem. Abstr.*, **100**, 17452lu (**1984**)

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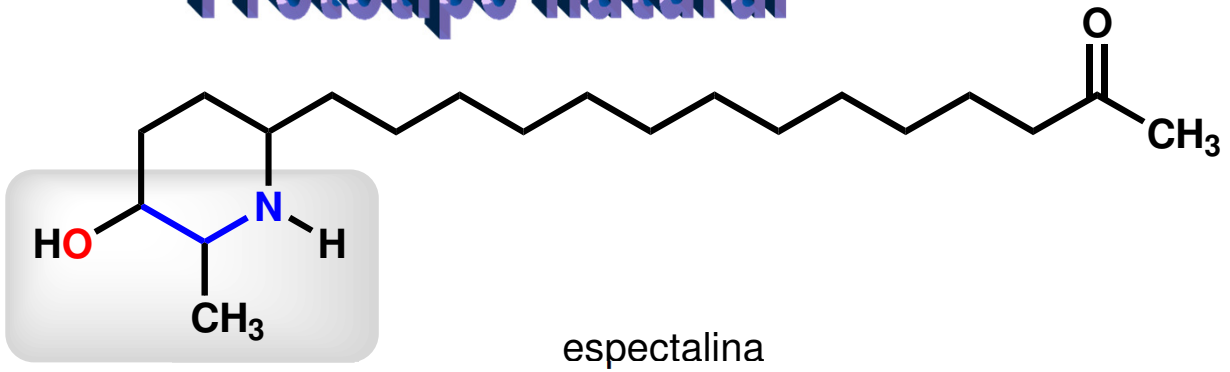
Cassia leptophylla

Leguminosa

8%

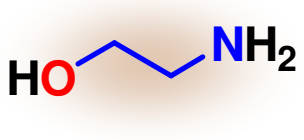
Protótipo natural



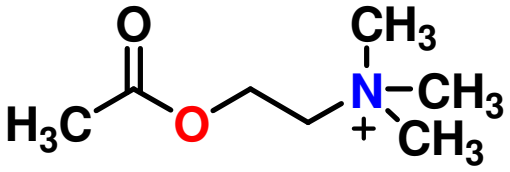
espectalina

2002 ⇩ Similaridade Molecular

Bióforo etanol-amina



etanol-amina

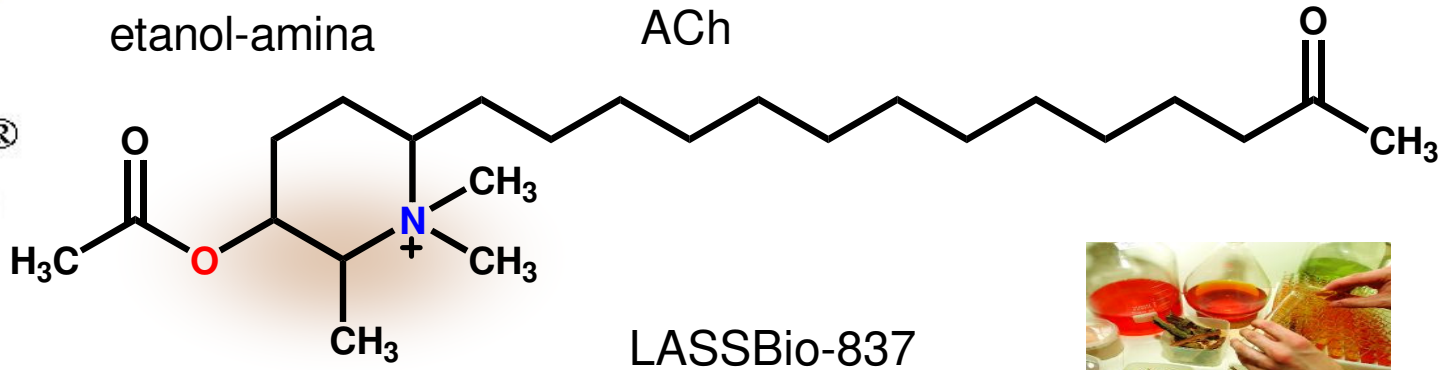


ACh

Química Medicinal

LASSBio®

NuBBE



LASSBio-837

MS Alexandre-Moreira, C Viegas Jr, VS Bolzani, EJ Barreiro, *Planta Med*. **2003**, *69*, 795-9

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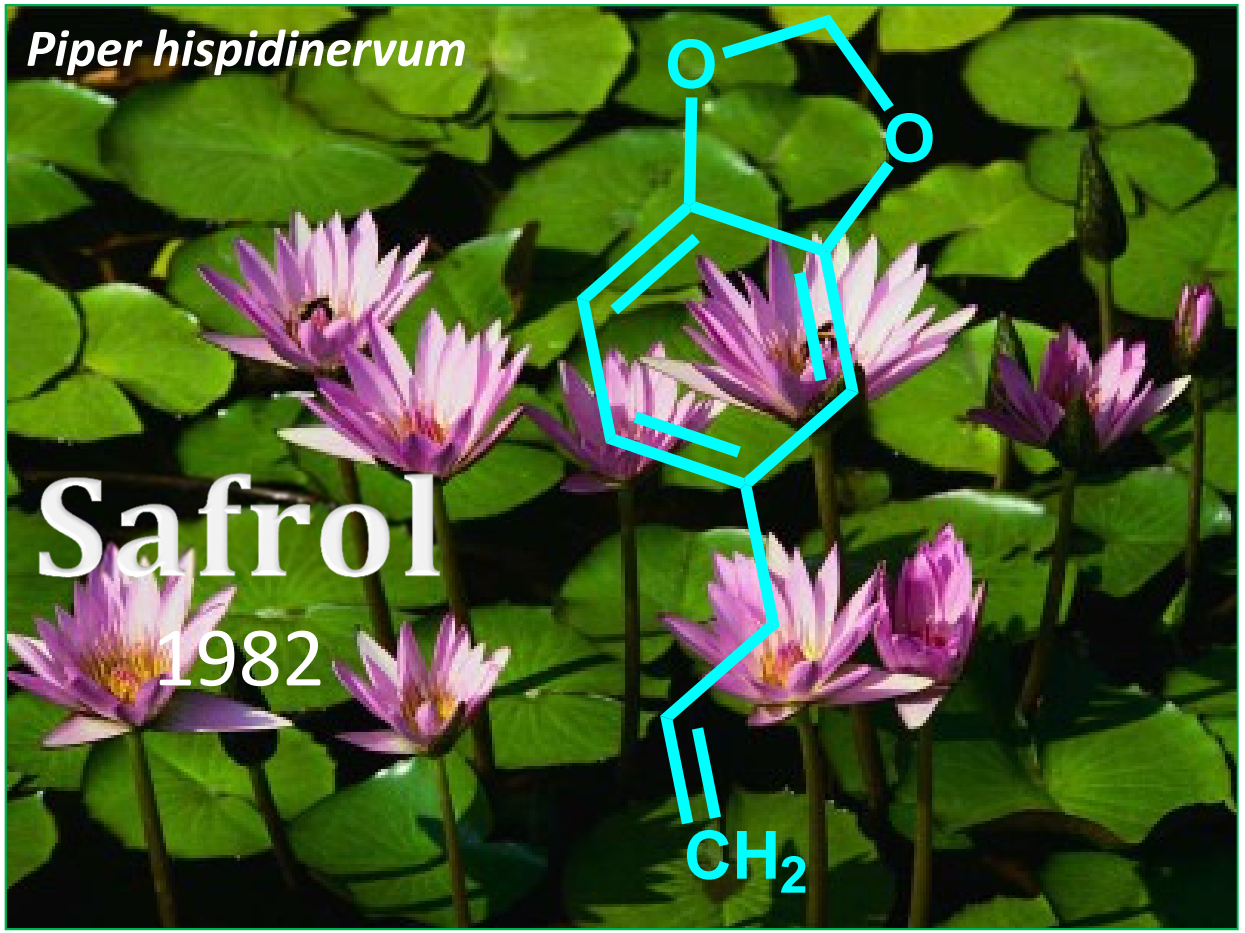

1982

5% oléo

82% safrol

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Laboratório de Avaliação e Síntese de Substâncias Bioativas

D Riva *et al.*, *Acta Amazonica* **2011**, *41*, 297

Oléo de Sassafrás ⟶ *Ocotea pretiosa*

E. J. Barreiro, P. R. R. Costa, P. R. V. R. Barros e W. M. Queiroz, "An Improved Synthesis of Indole Derivatives Related to Indomethacin from Natural Safrole", **Journal of Chemical Research (S)**, 102-103; (M) 1142-1165, (1982)

E. J. Barreiro & C. A. M. Fraga, "A Utilização do Safrol, Principal Componente Químico do Óleo de Sassafrás, na Síntese de Substâncias Bioativas na Cascata do Ácido Araquidônico: Anti-inflamatórios, Analgésicos e Anti-trombóticos", **Química Nova, 22**, 744-759 (1999)

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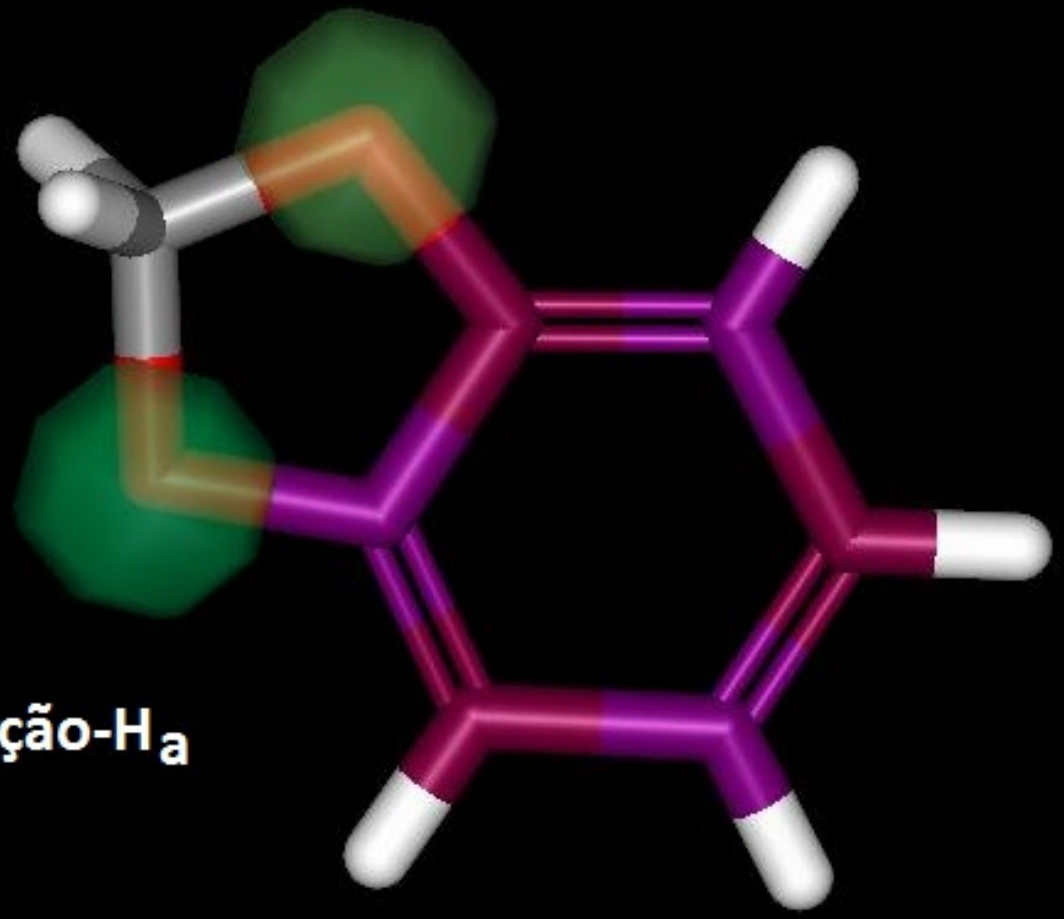
SAFROL

Benzodioxola



Química med Medicinal chem

Fragmento molecular natural privilegiado

Interação hidrofóbica

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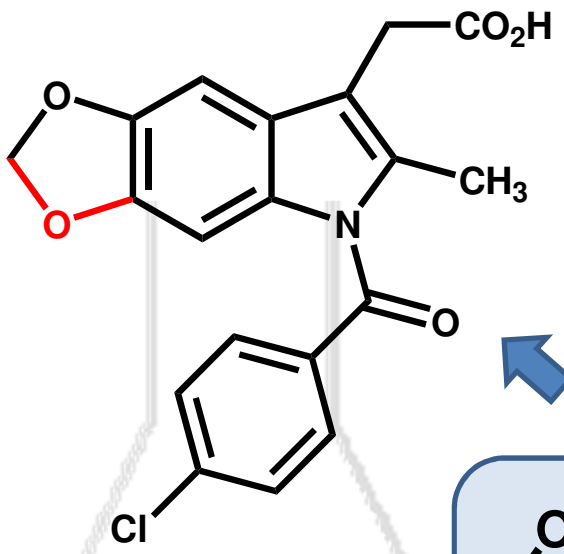
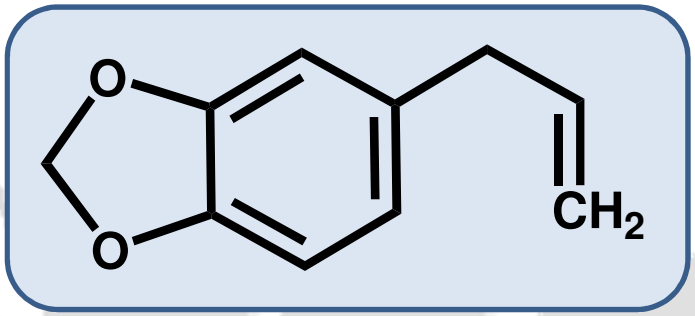
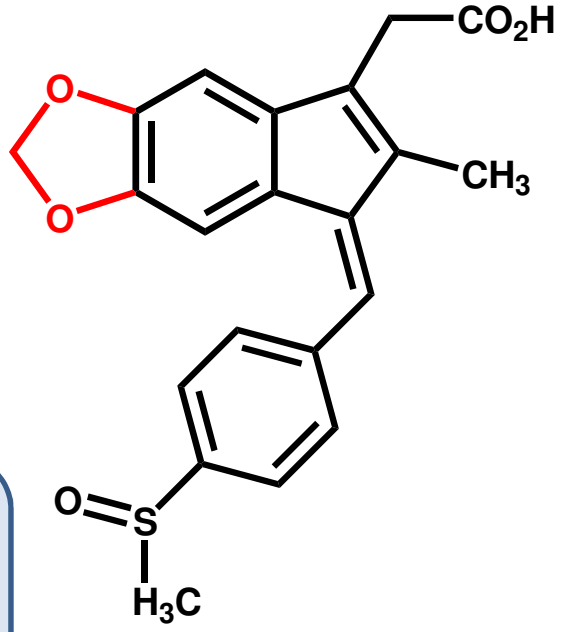
Análogos de AINE´s a partir do safrol

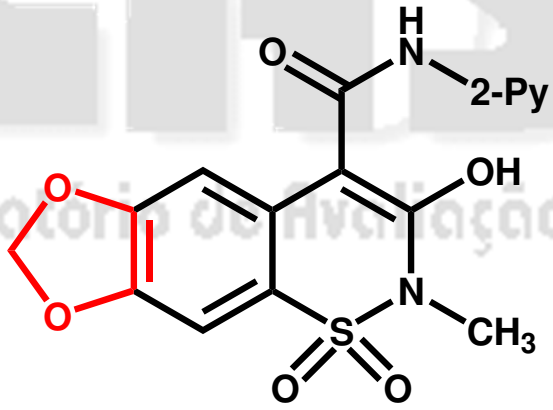


EFR Pereira, 1989

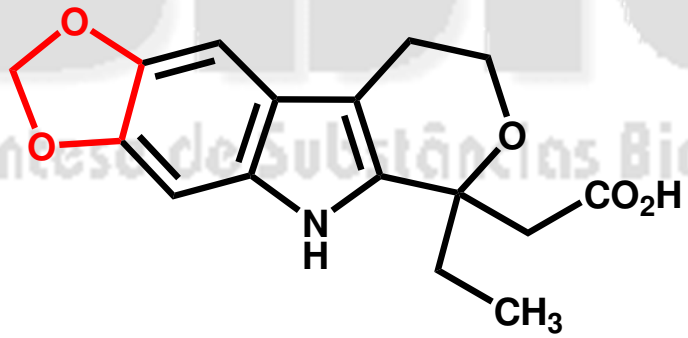




MEF Lima, 1992

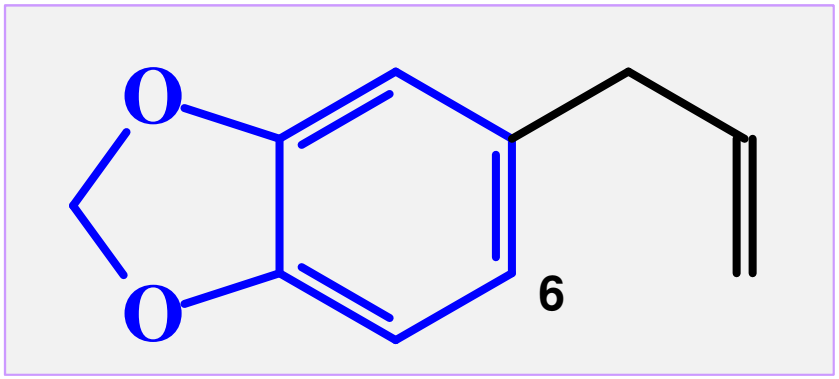


CAM Fraga, 1992



LM Cabral, 1995

Nova relação bioisostérica



1998

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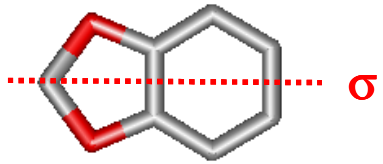
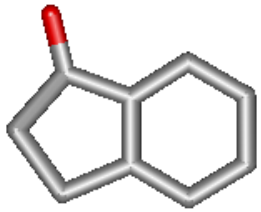
benzodioxola

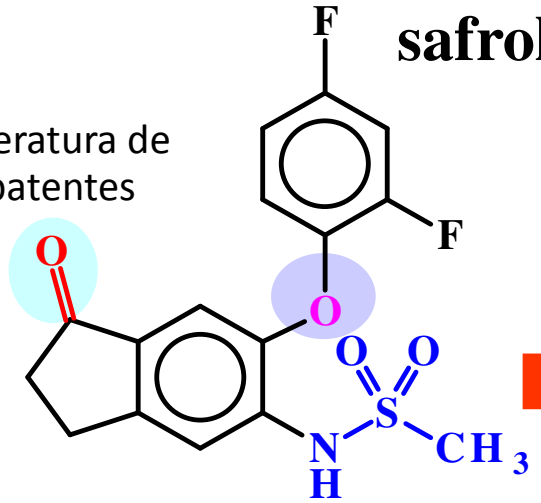




indanona

Literatura de patentes

safrol

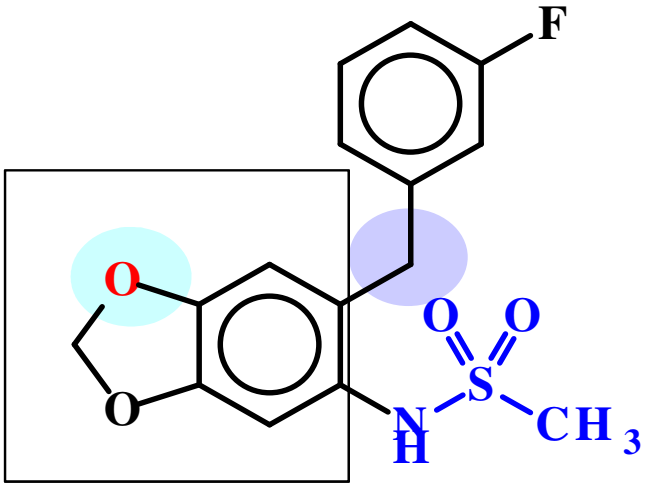


Flosulido

IC_{50} (hPGHS-1) = 73,2 μM

IC_{50} (rPGHS-2) = 0,015 μM

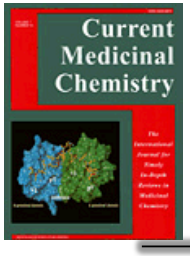
Futaki *et al*, 1995



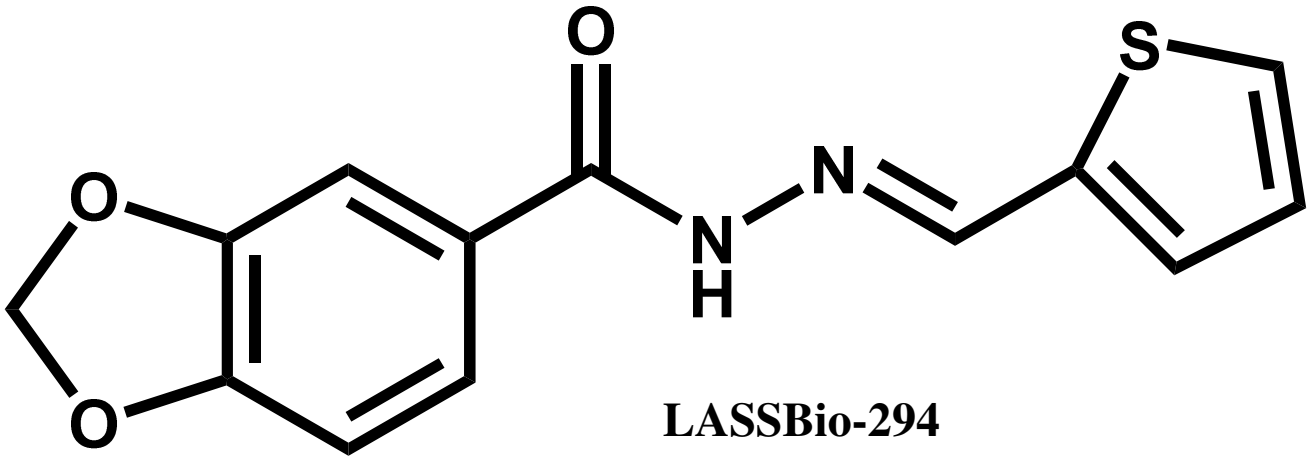
safrolido

AS Lages, KC Silva, CAM Fraga, EJ Barreiro,

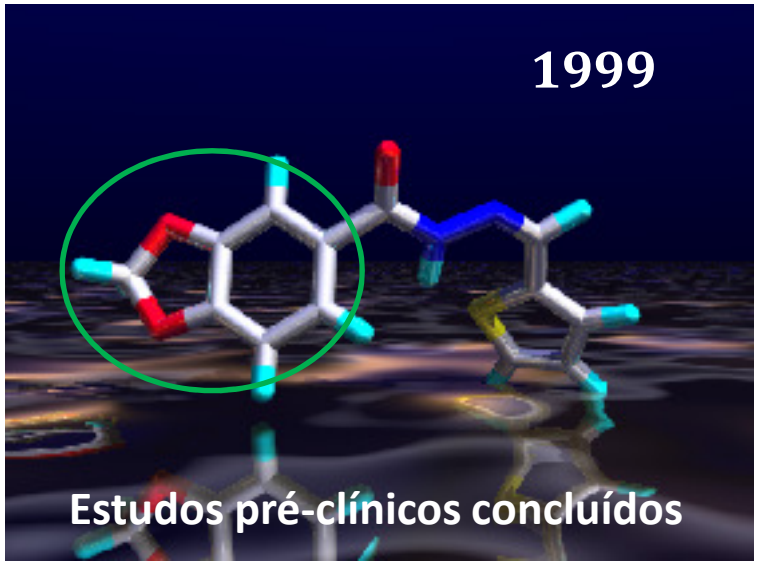
***Bioorg. Med. Chem. Lett*. 1998, *8*, 183**



LM Lima, EJ Barreiro, Bioisosterism: a useful strategy for molecular modification in drug design, *Curr. Med. Chem*. **2005**, *12*, 23.



LASSBio-294



Novo protótipo de fármaco cardioativo

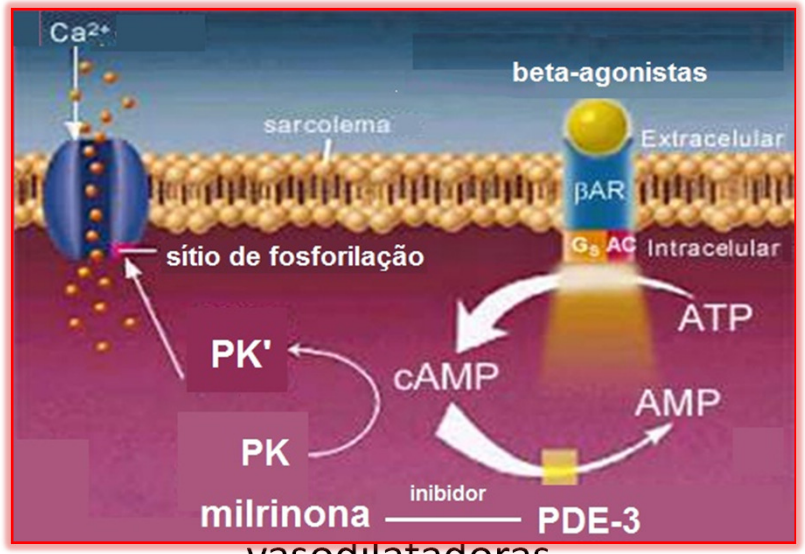
***US Patent** US7091238-15/08/2006

European Patent EP1532140; WO-0078754

EJ Barreiro, "Estratégia de Simplificação Molecular em Química Medicinal, A Descoberta de Novo Agente Cardiotônico", *Química Nova* **2002**, *25*, 1172

A gênese do LASSBio-294...

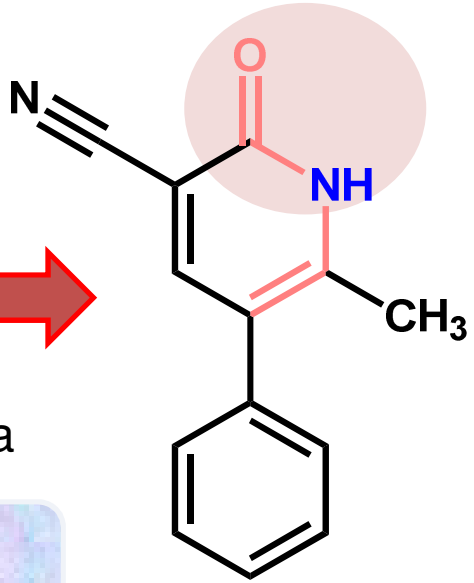
Inibidores de PDE-3



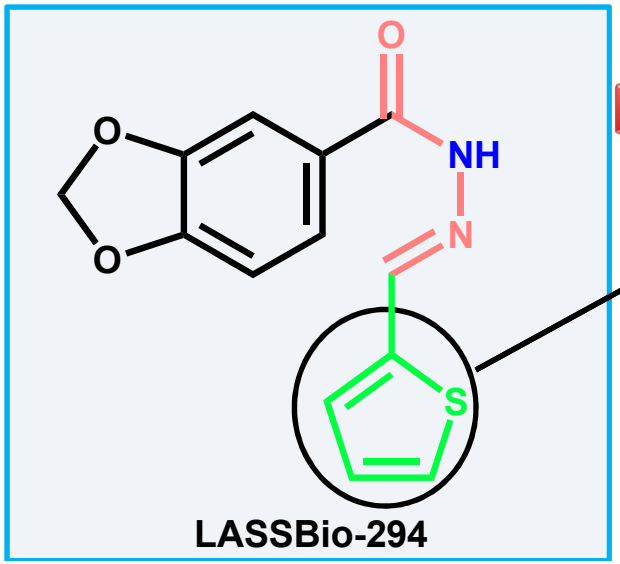
vasodilatadoras

(arritmias ventriculares)

milrenona



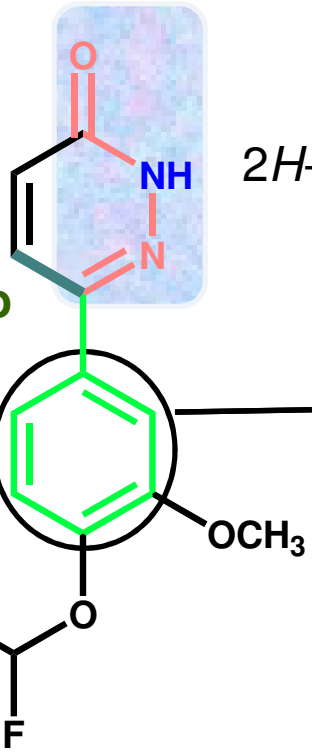
2*H*-piridazinona



LASSBio-294

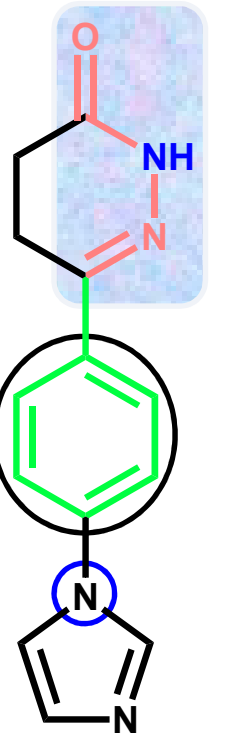
cisão

N A H



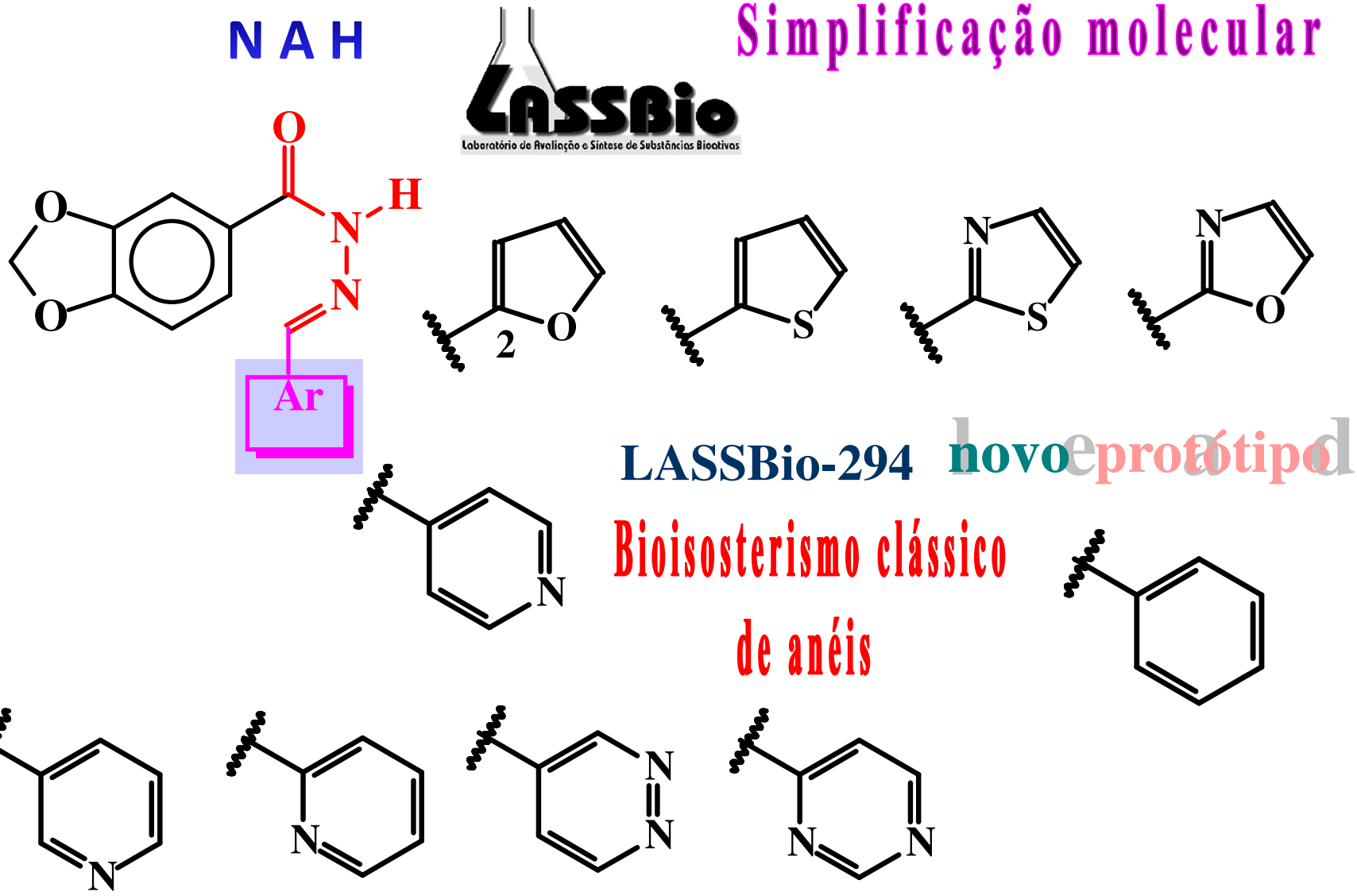
zardaverina

PDE-I



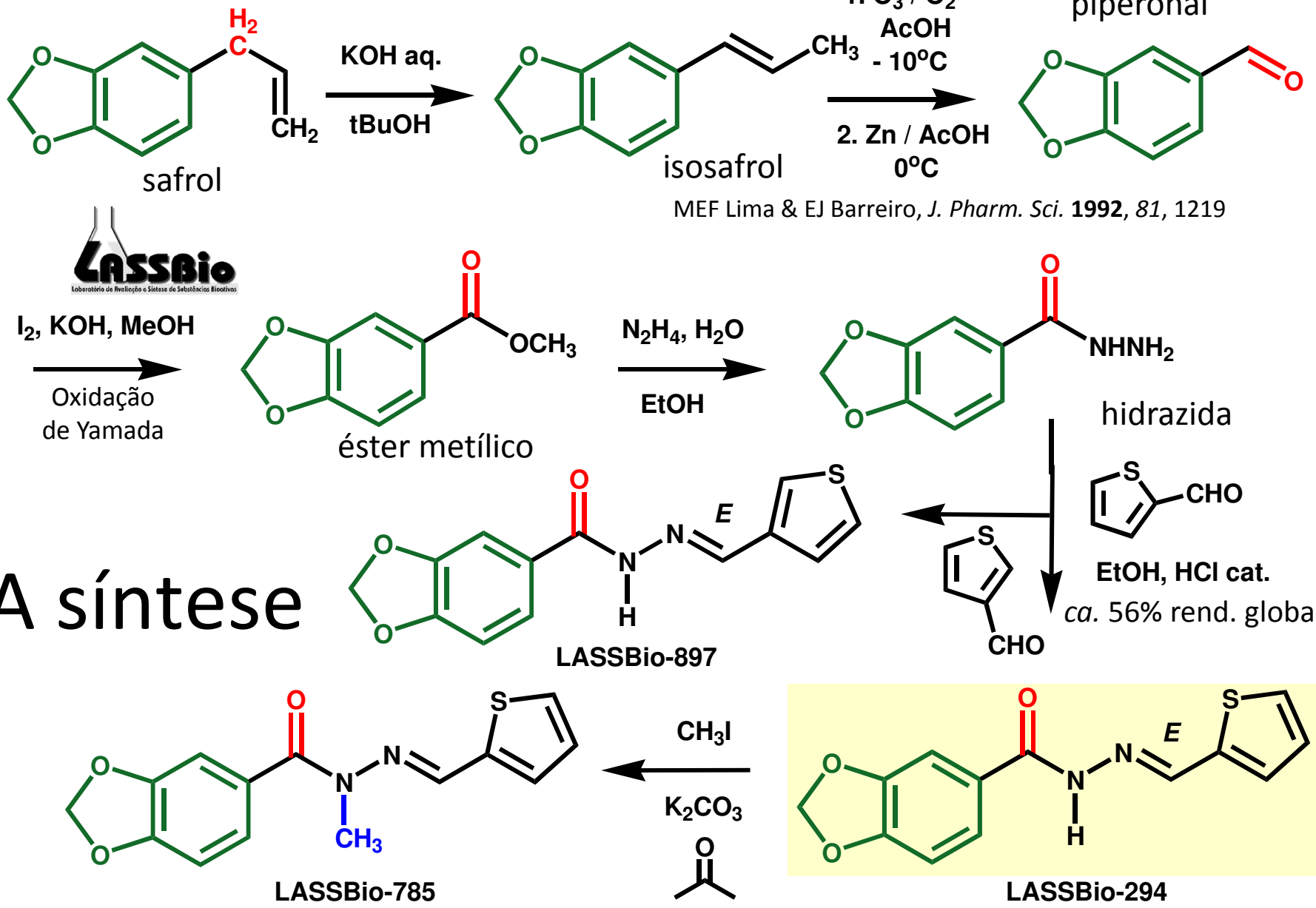
imazodana

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).

A síntese



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).

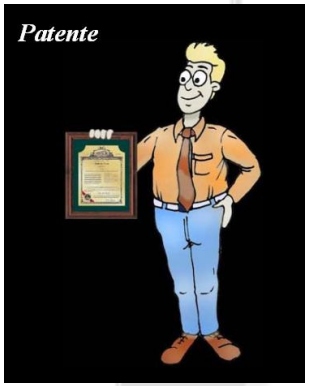
LASSBio-294

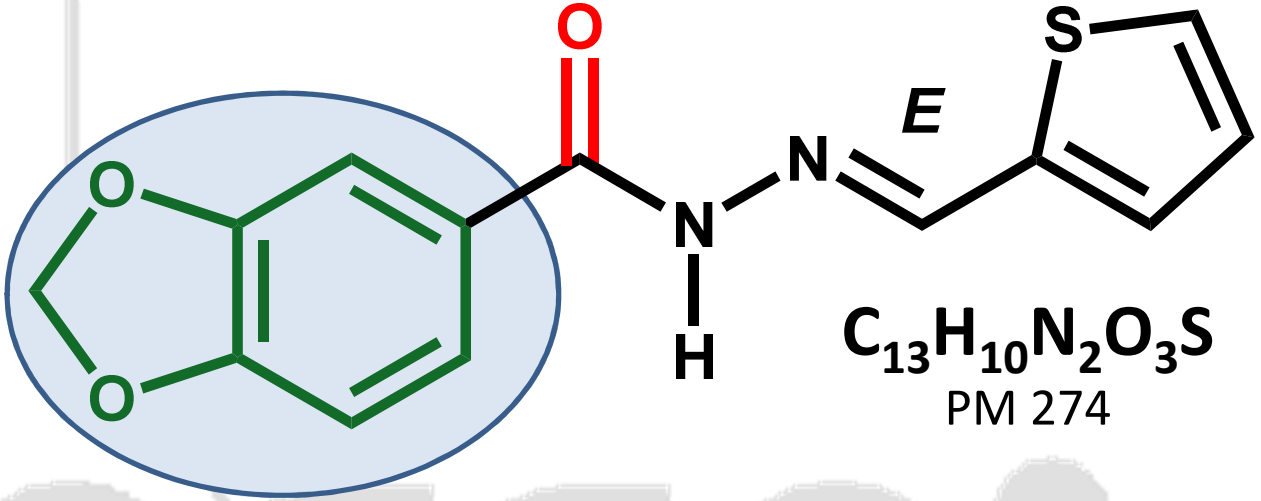
Novo protótipo de fármaco cardioativo*

***US Patent** US7091238-15/08/2006

***European Patent** EP1532140; WO-0078754

Thienylhydrazone with digitalis-like properties (positive inotropic effects)





$C_{13}H_{10}N_2O_3S$

PM 274

✓ **Estruturalmente simples; rota de síntese com >55% de rendimento global, empregando matéria-prima acessível; escalonável até 5,0 kg (18,2 M);**

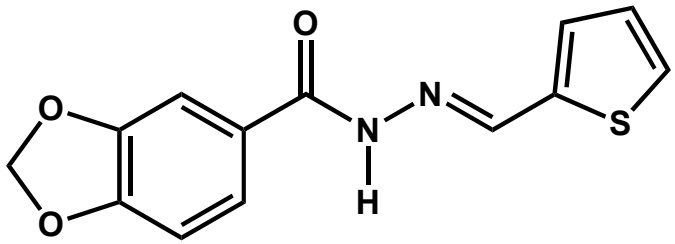
✓ **Potentes propriedades inotrópicas positivas & vasodilatadoras & também neuroprotetoras; ativo por via oral com boa biodisponibilidade;**

✓ **Novo mecanismo farmacológico de ação: ligante de receptores adenosinérgicos A_{2A};**

✓**Sem citotoxicidade, genotoxicidade, nem toxicidade sistêmica (aguda e sub-aguda) em duas vias de administração (*p.o.* e *i.p.**) nas doses 1000 μM/kg e 73 μM/kg, respectivamente; sem toxiddade crônica;**

****i.p.*= 2 vezes ao dia, durante 15 dias seguidos: ~100 vezes ED_{50} *in vivo*.**

Metabolismo de LASSBio-294

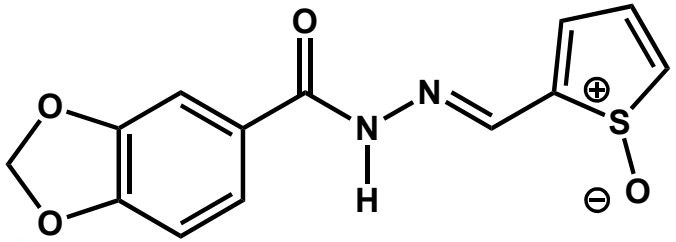


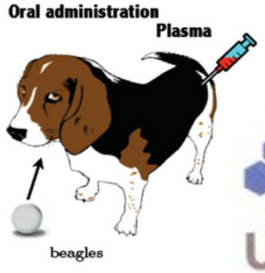
B. bassiana ATCC 7159
& Beagles*

LaBioCon

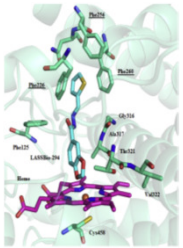
Beauveria bassiana

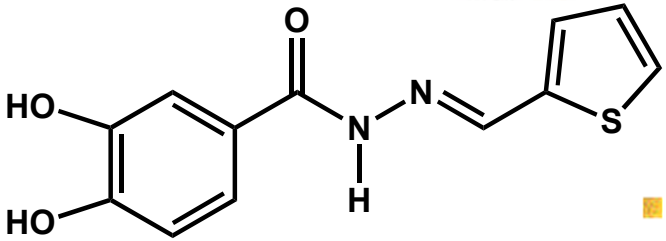
ATCC 7159





CYP1A2





Microssomas
& CYPs recombinantes&

- Profa Valéria de Oliveira*
  INCT-INOFAR
  FF-UFG
- Profa Rosangela Alves*
  INCT-INOFAR
  EV-UFG
- Profa Carolina H Andrade*
  FF-UFG

* 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 LASSBio-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)

European Journal of Medicinal Chemistry 46 (2011) 349–355

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European Journal of Medicinal Chemistry

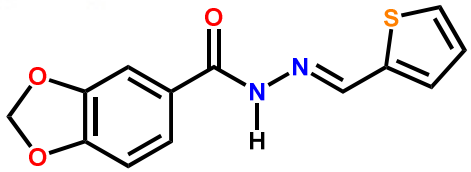
journal homepage: http://www.elsevier.com/locate/ejmech

Original article

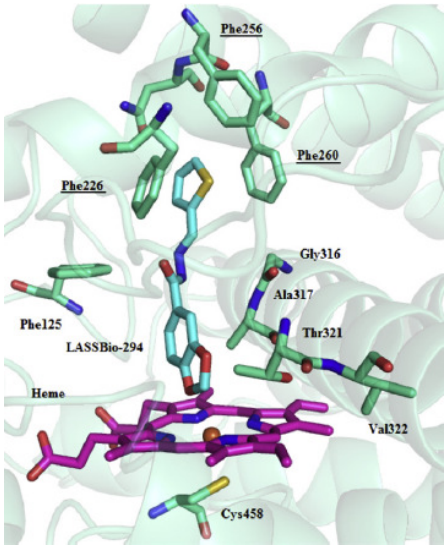
CYP1A2-mediated biotransformation of cardioactive 2-thienylidene-3,4-methylenedioxybenzoylhydrazine (LASSBio-294) by rat liver microsomes and human recombinant CYP enzymes

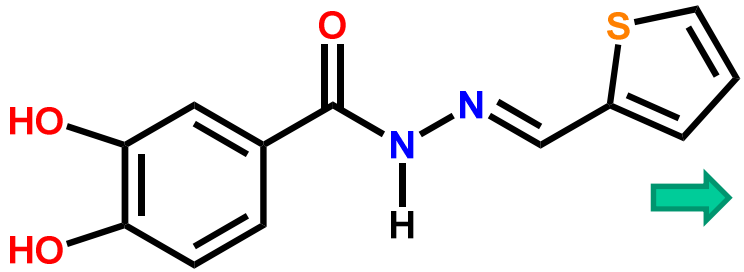
Aline Guerra M. Fraga [a,b], Leandro Louback da Silva [a,c], Carlos Alberto Manssour Fraga [a,b,c], Eliezer J. Barreiro [a,b,c,*]

[a] Laboratório de Avaliação e Síntese de Substâncias Bioativas[1], Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, RJ 21941-902, PO Box [illegible], Brazil
[b] Programa de Pós-Graduação em Química, Instituto de Química, Universidade Federal do Rio de Janeiro, RJ 21949-900, Brazil
[c] Programa de Pós-Graduação em Farmacologia e Química Medicinal, Instituto de Ciências Biomédicas, Universidade Federal do Rio de Janeiro, RJ 21941-590, Brazil



LASSBio-294





rat liver microsomes

síntese

Estudos do mecanismo de ação

CEREP

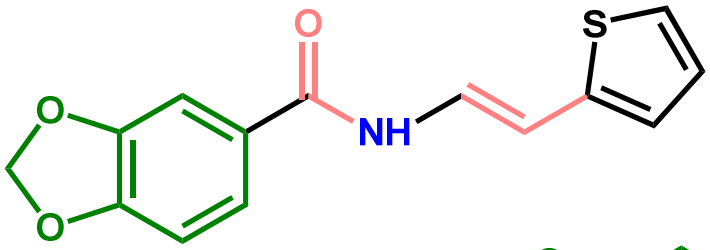
"Diversity Profile" 101 Alvos Moleculares

Receptores de Adenosina A_{2A}

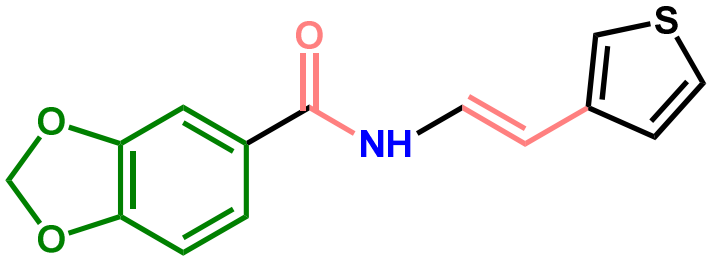
IC_{50}= 9,5 µM

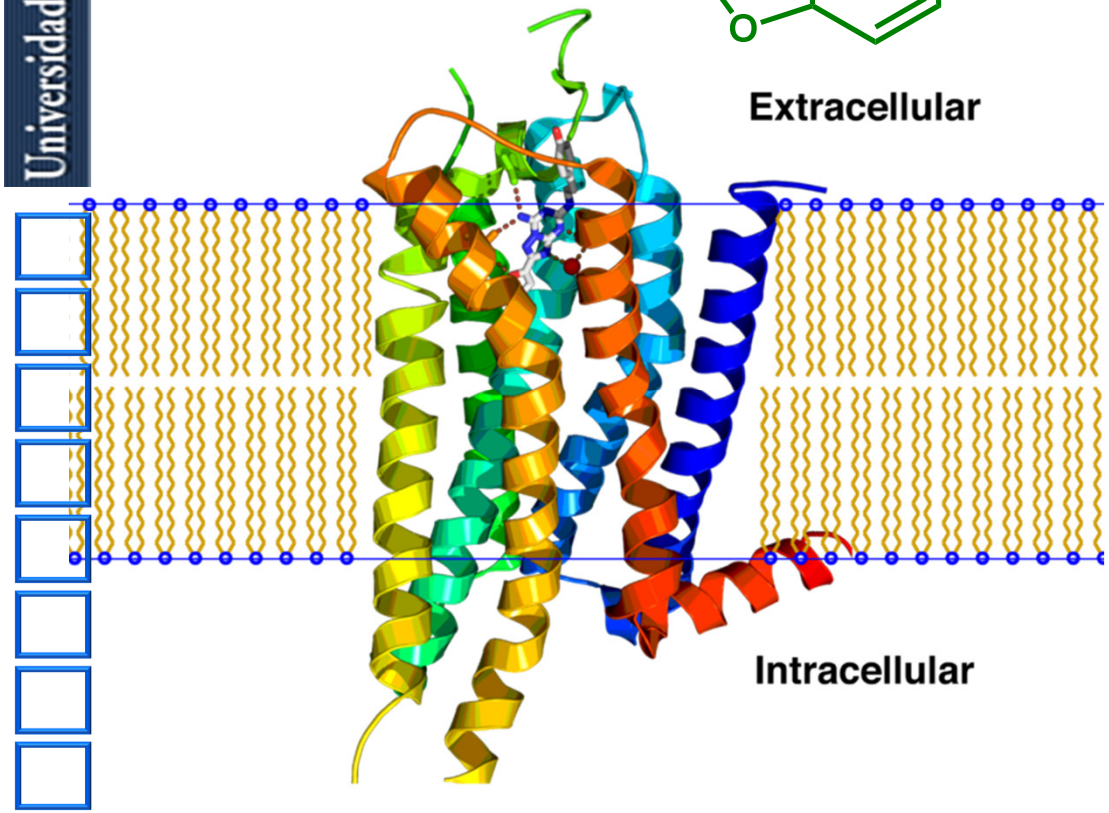
IC_{50}= 4,6 µM

LASSBio-294



LASSBio-897

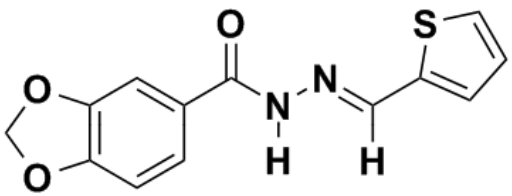




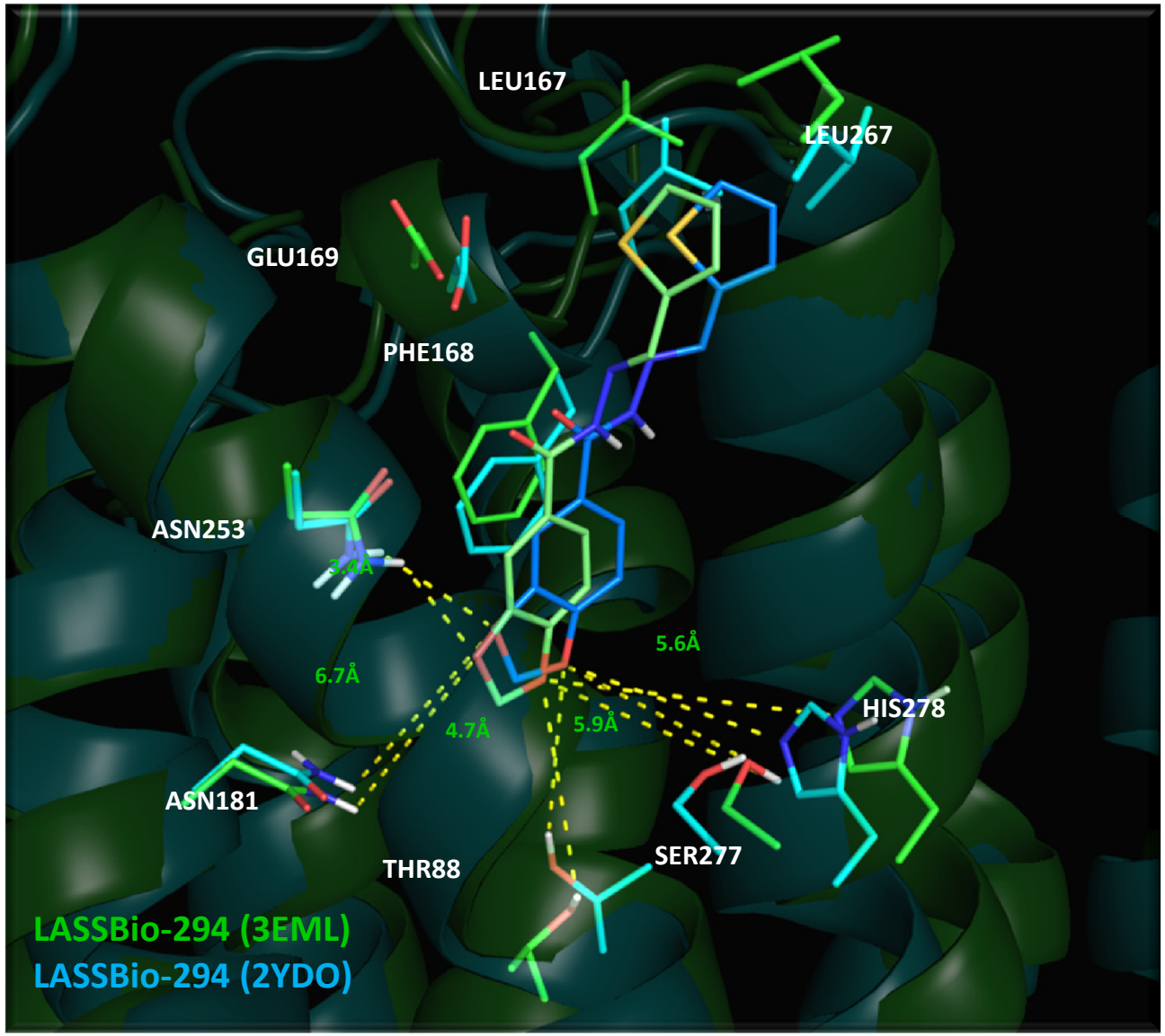
Receptor A_{2A}
PDB 3EML

V. Jaakola et al., *Science* **2008,** *322,* 1211

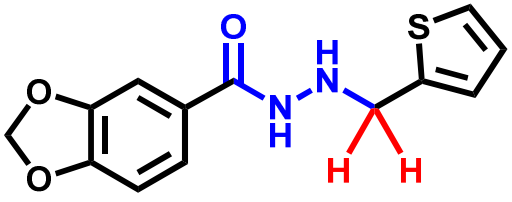
Análise do LASSBio-294 com receptores de adenosina



LASSBio-294



Otimização do protótipo



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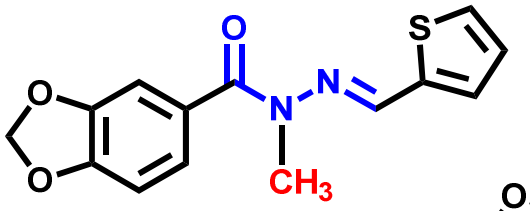
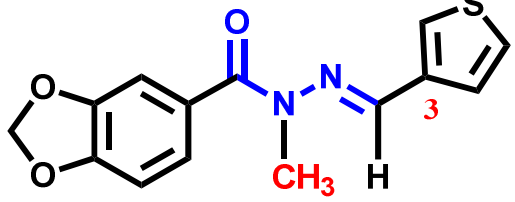


LASSBio-785



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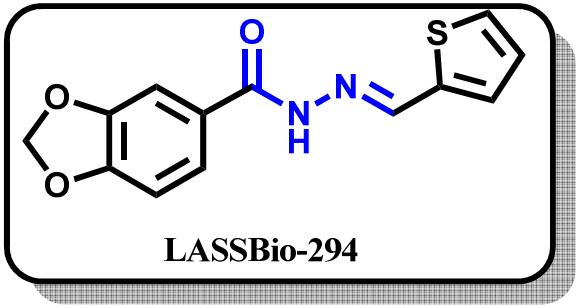

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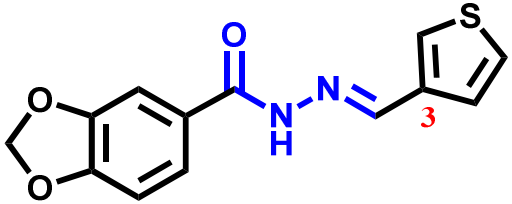

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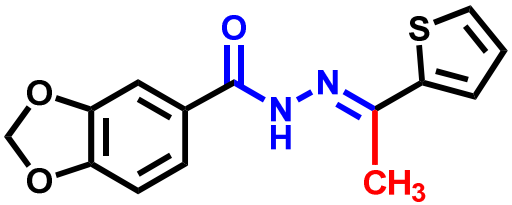

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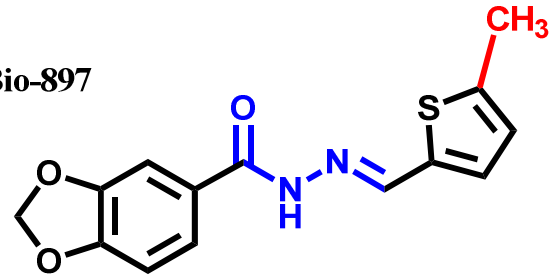

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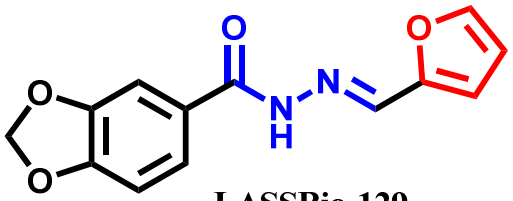
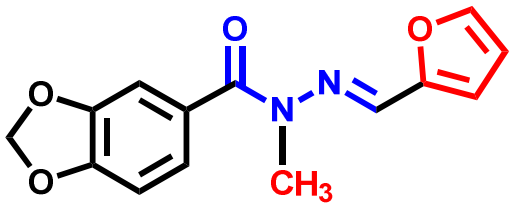


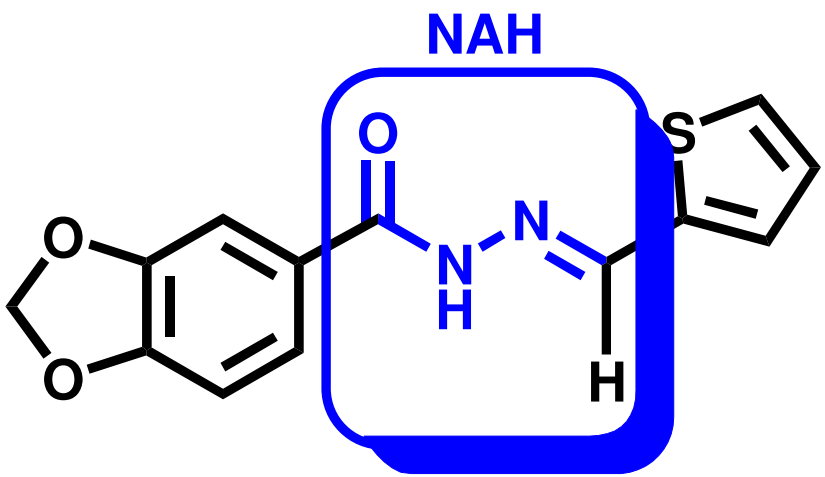
LASSBio-129

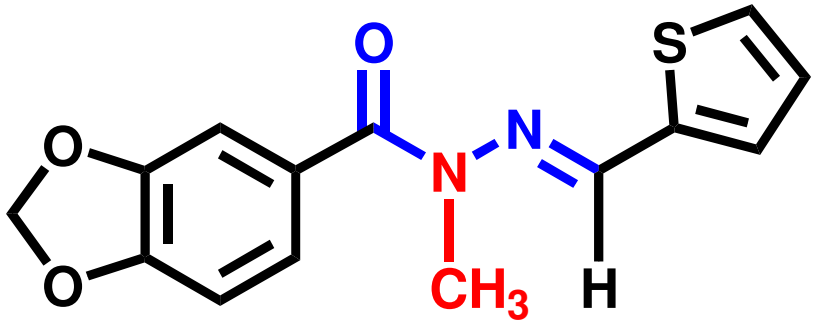


LASSBio-785

Silva, A.G. et al., *Bioorg. Med. Chem*. **2005**, *13*, 3431; Zapata-Sudo, G. et al., *Am. J. Hypertens.* **2010**, *23*, 135

Otimização do protótipo





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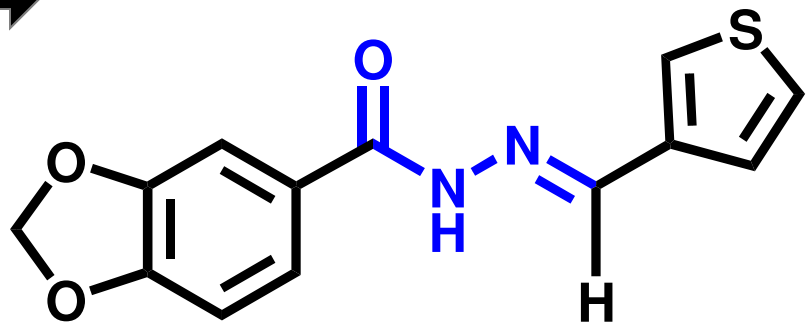

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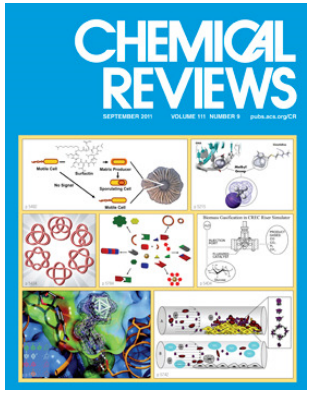
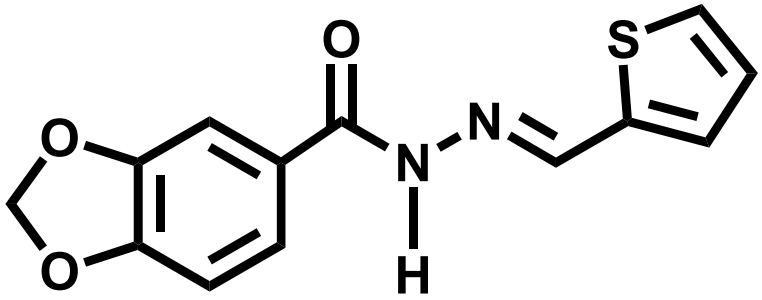


EJ Barreiro, AE Kummerle, CAM Fraga, The methylation effect in medicinal chemistry, *Chem. Rev.* **2011**, *111*, 5215



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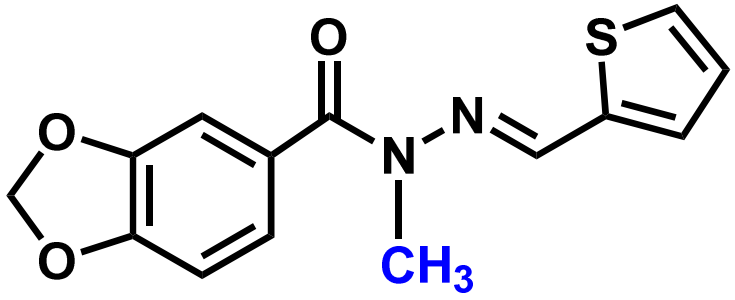

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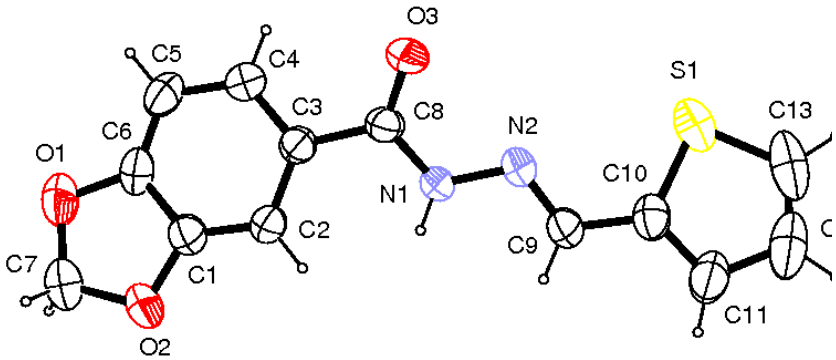
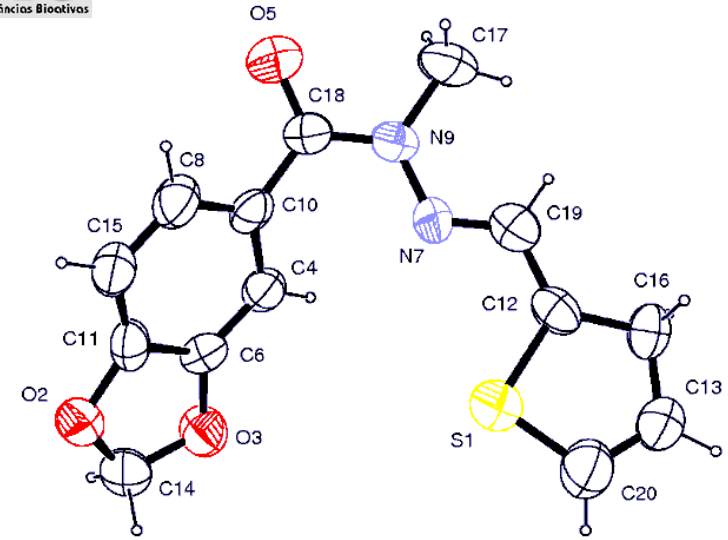
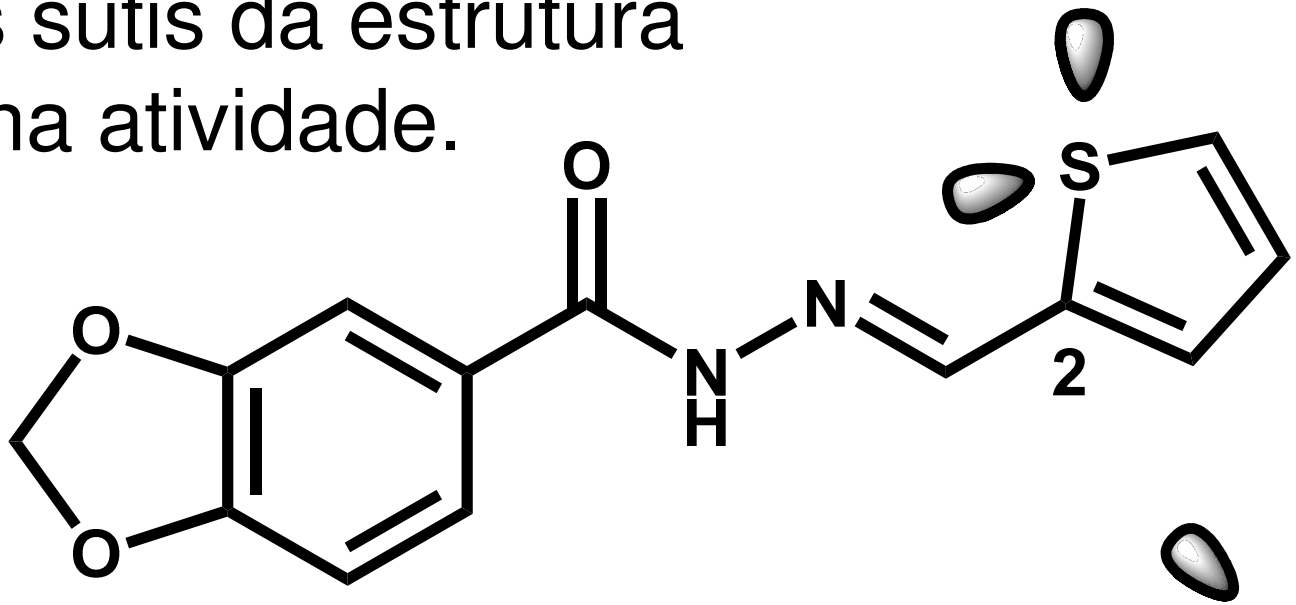




…mais um exemplo dos efeitos sutis da estrutura na atividade.



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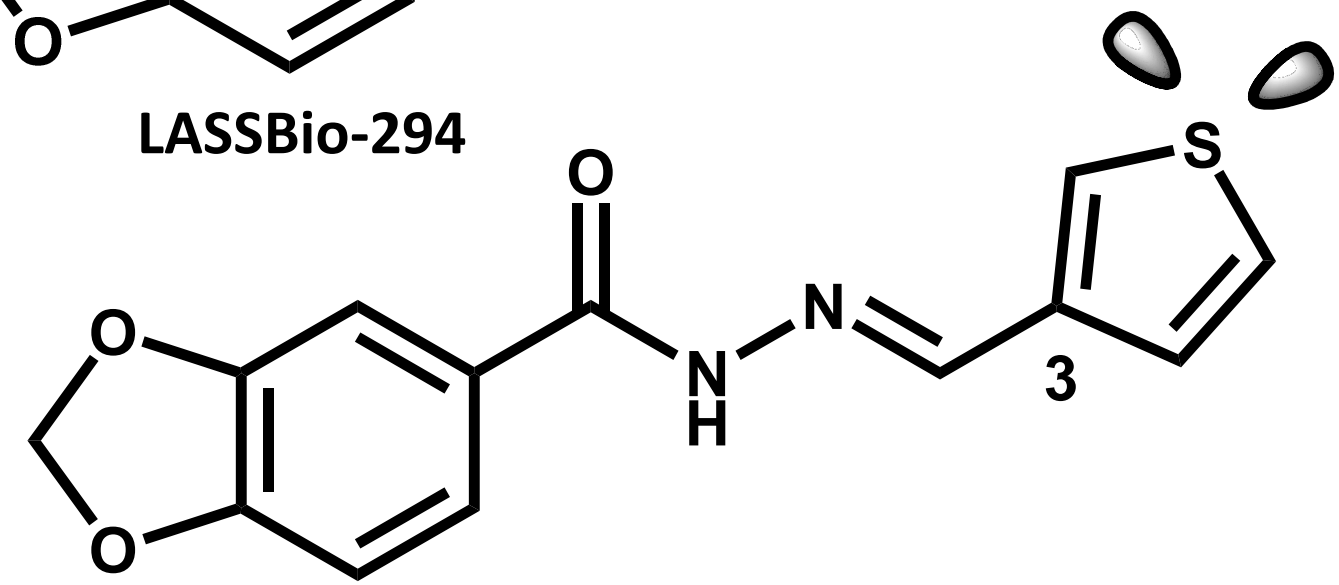


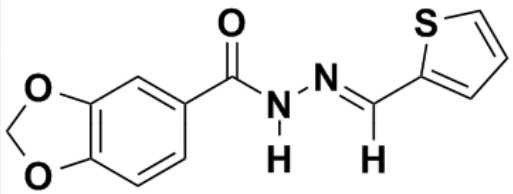
LASSBio-897

Δ C=S ~1.57 A

LASSBio-294 e LASSBio-897 são ligantes de receptores de adenosina A_{2A}

Universidade Federal do Rio de Janeiro

LASSBio-294



A_{2A} IC_{50} = 9,5 µM

British Journal of Pharmacology (2001) 134, 603–613
www.nature.com/bjp

The new compound, LASSBio 294, increases the contractility of intact and saponin-skinned cardiac muscle from Wistar rats

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A Novel Thienylhydrazone, (2-Thienylidene)3,4-methylenedioxybenzoylhydrazine, Increases Inotropism and Decreases Fatigue of Skeletal Muscle

HUGO GONZALEZ-SERRATOS, RUZHANG CHANG, EDNA F. R. PEREIRA, NEWTON G. CASTRO, YASCO ARACAVA, PAULO A. MELO, PATRÍCIA C. LIMA, CARLOS A. M. FRAGA, ELIEZER J. BARREIRO, and EDSON X. ALBUQUERQUE

Departments of Physiology (H.G.-S., R.C.) and Pharmacology and Experimental Therapeutics (E.F.R.P., E.X.A.), University of Maryland School of Medicine, Baltimore, Maryland; and Departamento de Farmacologia Básica e Clínica (E.X.A., N.G.C., Y.A., P.A.M.), Instituto de Ciências Biomédicas, and Departamento de Fármacos (P.C.L., C.A.M.F., E.J.B.), Faculdade de Farmácia, Centro de Ciências da Saúde, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

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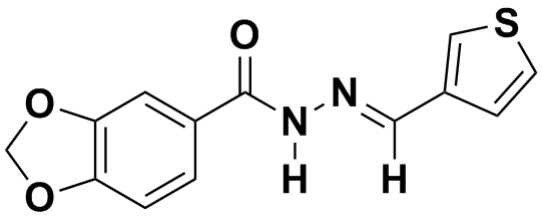
LASSBio-897

A_{2A} IC_{50} = 4,6 µM



American Journal of Hypertension 2010; **23** 2, 135–141. doi:10.1038/ajh.2009.238

Pharmacological Characterization of (3-Thienylidene)-3,4-Methylenedioxybenzoylhydrazide: A Novel Muscarinic Agonist With Antihypertensive Profile

Gisele Zapata-Sudo[1], Sharlene L. Pereira[1], Hellen J.V. Beiral[1], Arthur E. Kummerle[2,3], Juliana M. Raimundo[1], Fernanda Antunes[4], Roberto T. Sudo[1], Eliezer J. Barreiro[2,3] and Carlos A.M. Fraga[2,3]

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CEREP STUDY NUMBER 18080 / FINAL REPORT

European Journal of Medicinal Chemistry 55 (2012) 49–57

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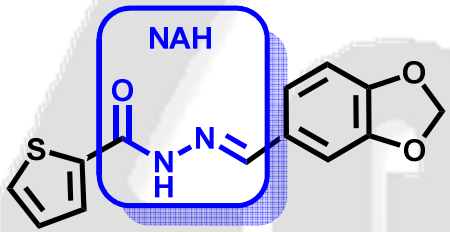
journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Antihypertensive profile of 2-thienyl-3,4-methylenedioxybenzoylhydrazone is mediated by activation of the A_{2A} adenosine receptor

Carla Moreira Leal [a,1], Sharlene Lopes Pereira [a,1], Arthur Eugen Kümmerle [b,2], Daniella Moreira Leal [a,1], Roberta Tesch [c,3], Carlos M.R. de Sant'Anna [b,2], Carlos Alberto M. Fraga [a,c,1,3], Eliezer Jesus Barreiro [a,c,1,3], Roberto Takashi Sudo [a,c,1,3], Gisele Zapata-Sudo [a,c,*,1,3]



LASSBio-1027

European Journal of Medicinal Chemistry 54 (2012) 264–271

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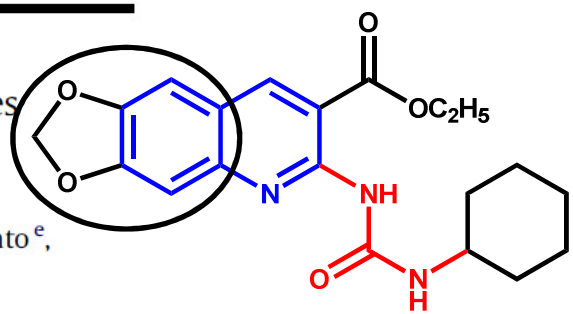
Original article

Docking, synthesis and pharmacological activity of novel urea-derivatives designed as p38 MAPK inhibitors

Raquel de Oliveira Lopes [a,b], Nelilma Correia Romeiro [a,b], Cleverton Kleiton F. de Lima [a,c], Leandro Louback da Silva [a,c], Ana Luisa Palhares de Miranda [a,c], Paulo Gustavo B.D. Nascimento [e], Fernando Q. Cunha [d], Eliezer J. Barreiro [a,b,c], Lídia Moreira Lima [a,b,c,*]



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Química med Medicinal chem

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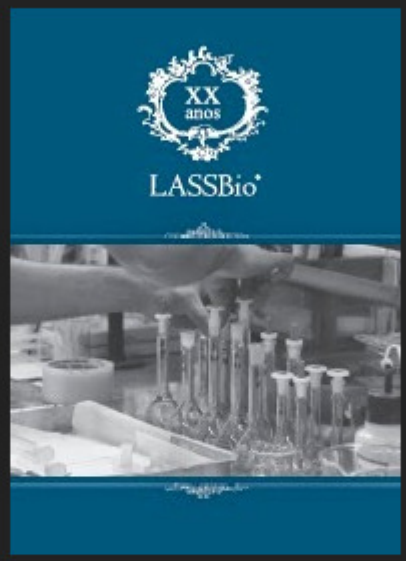
Os 20 Anos do LASSBio!



O registro da história é sempre necessário para garantirmos a construção de uma memória fiel. Na verdade, estas palavras, além de rimarem, referem-se ao passado, ao que já vivemos, ao que já foi vivido. Entretanto, se sob esta ótica podem sugerir apenas lembranças, documenta-las representa o cumprimento e o exercício de cidadania, sobretudo quando dizem respeito a realizações coletivas, assegurando a

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