FUNDAMENTOS DE QUÍMICA MEDICINAL -

Parte 4

COMO NASCEM OS FÁRMACOS

26ª Semana da Química do Instituto de Química da UFRJ

09-13 de abril de 2018

Eliezer J. Barreiro

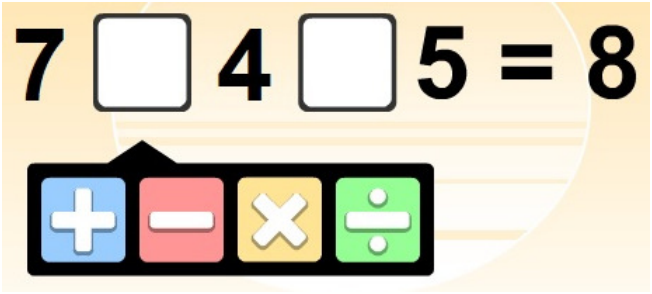
Professor Titular

Universidade Federal do Rio de Janeiro

Resumo

Neste curso-curto apresentaremos os fundamentos da **Química Medicinal**, para o desenho molecular de novos candidatos a fármacos. A introdução abordará o histórico e a cronologia da disciplina, com ênfase ao seu caráter interdisciplinar. O processo de descoberta de fármacos ilustrará como "nascem" os fármacos. Apresentaremos alguns aspectos da inovação farmacêutica radical, em especial para os fármacos sintéticos. Em conclusão, alguns exemplos selecionados do trabalho realizado no Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio) do ICB da UFRJ, criado e coordenado pelo apresentador, serão apresentados.

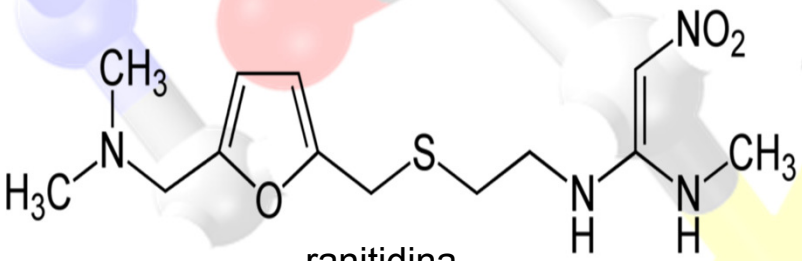
Ferramentas da química medicinal




O “enigma” do química medicinal!

Química Medicinal

"… when it comes to drug discovery you're not trying to make complicated molecules, but make molecules that will be effective …"



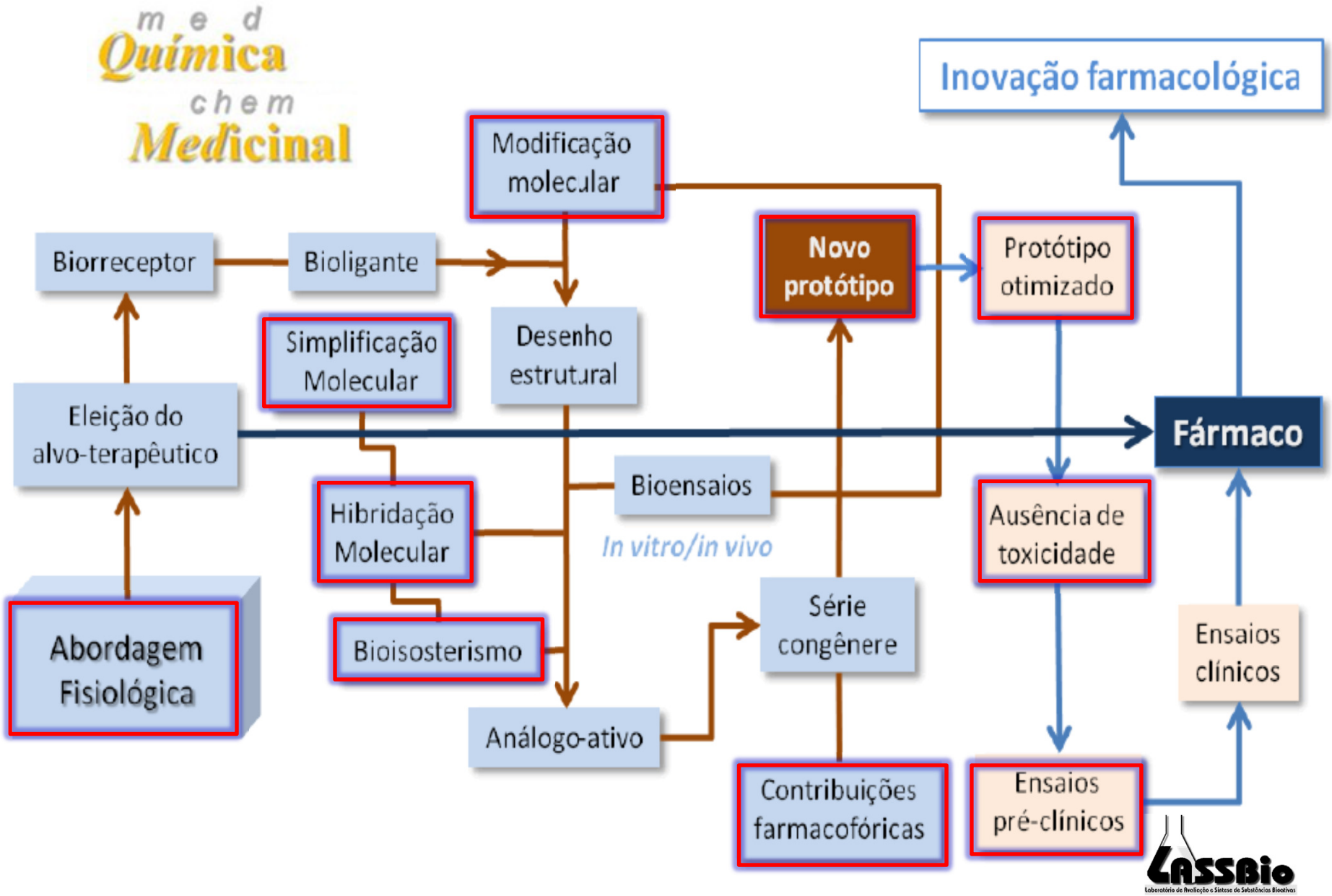
ranitidina

Barry J. Price

Research Director Glaxo (1967-1995)

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

O processo da Química Medicinal



Laboratório de Avaliação e Síntese de Substâncias Bioativas

UFRJ

Cidade Universitária
Ilha do Fundão,
Rio de Janeiro, R.J.

ICB,
Centro de Ciências da Saúde, Bloco F, sala 12
& Bloco B, sala 14

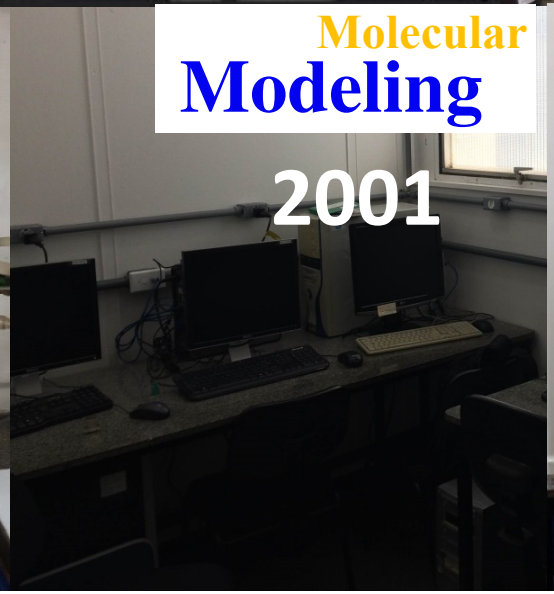
Criado em 19 de abril de 1994

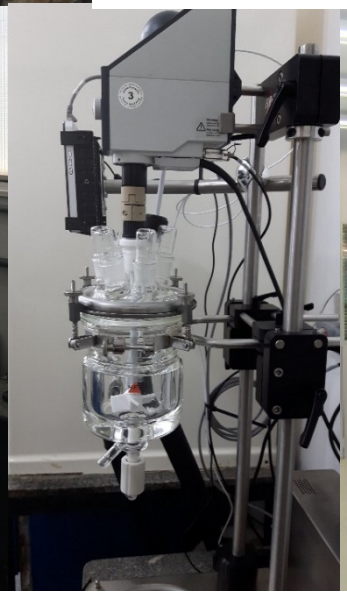
Centro de Ciências da Saúde, Universidade Federal do Rio de Janeiro

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

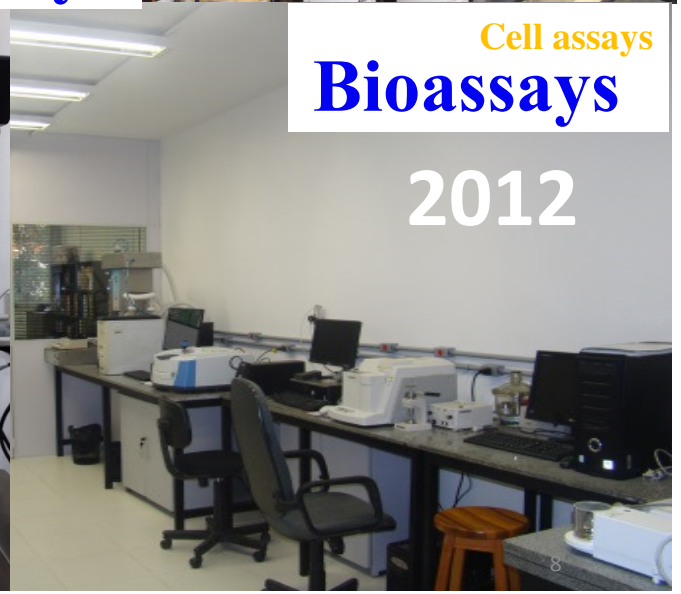
Medicinal
Chemisty

Molecular
Modeling
2001





Cell assays
Bioassays
2012




LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

RVq | Revista Virtual de Química

ISSN 1984-6835

Artigo

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

Barreiro, E. J.

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

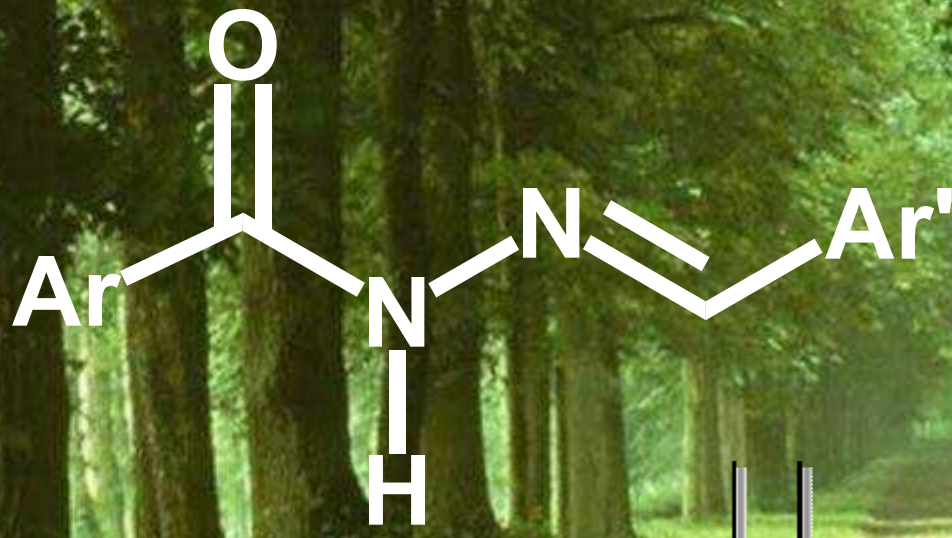
http://www.uff.br/rvq

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

Química Medicinal


Quimioteca
LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas
2117 compostos*
* 06/04/2018

A classe das NAH bioativas



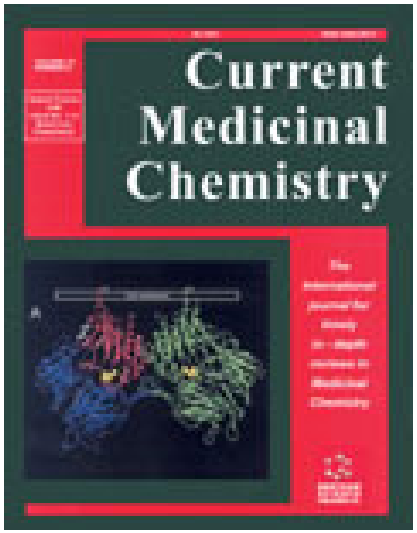
LASSBio

Laboratório de Avaliação e Síntese de Substâncias Bioativas

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

Carlos A.M. Fraga and Eliezer J. Barreiro

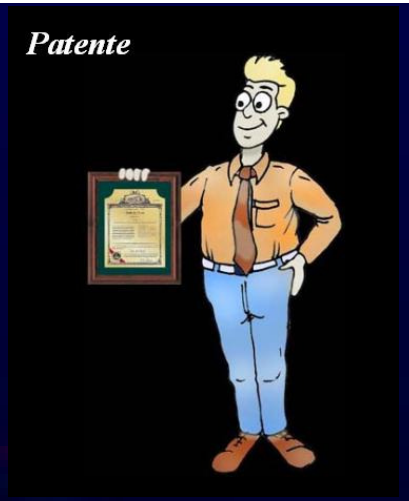
Volume 13, 167-198, 2006



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.

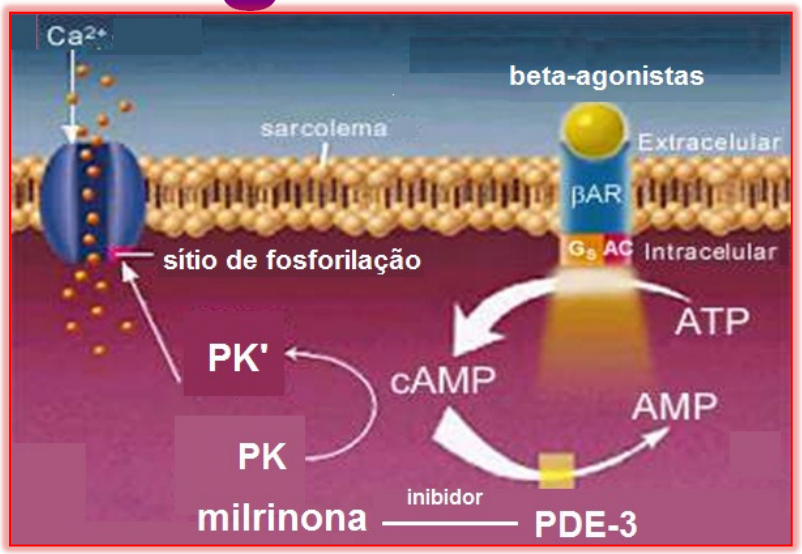
http://dx.doi.org/10.2174/092986706775197881

LASSBio-294

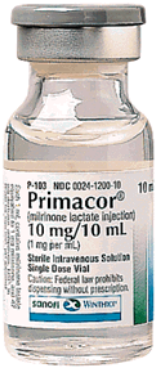


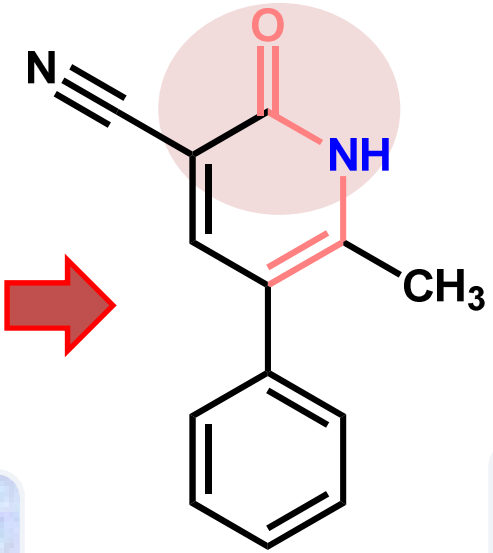
NAH

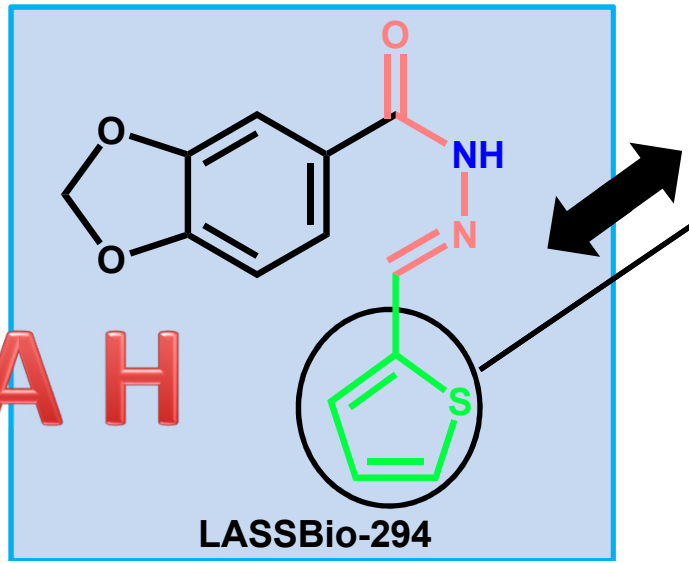
A gênese do LASSBio-294...



Propriedades inotrópicas,
vasodilatadoras
(arritmias ventriculares)

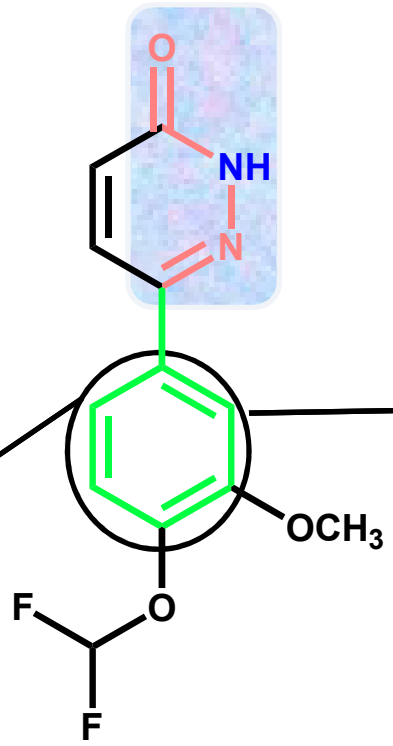




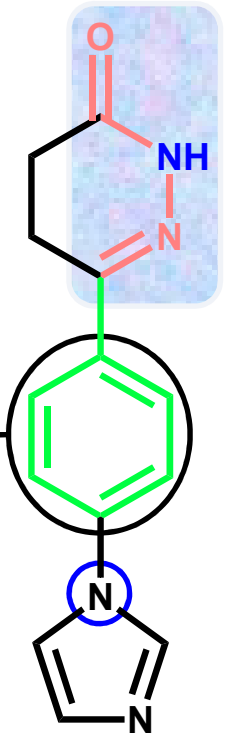


NAH

LASSBio-294

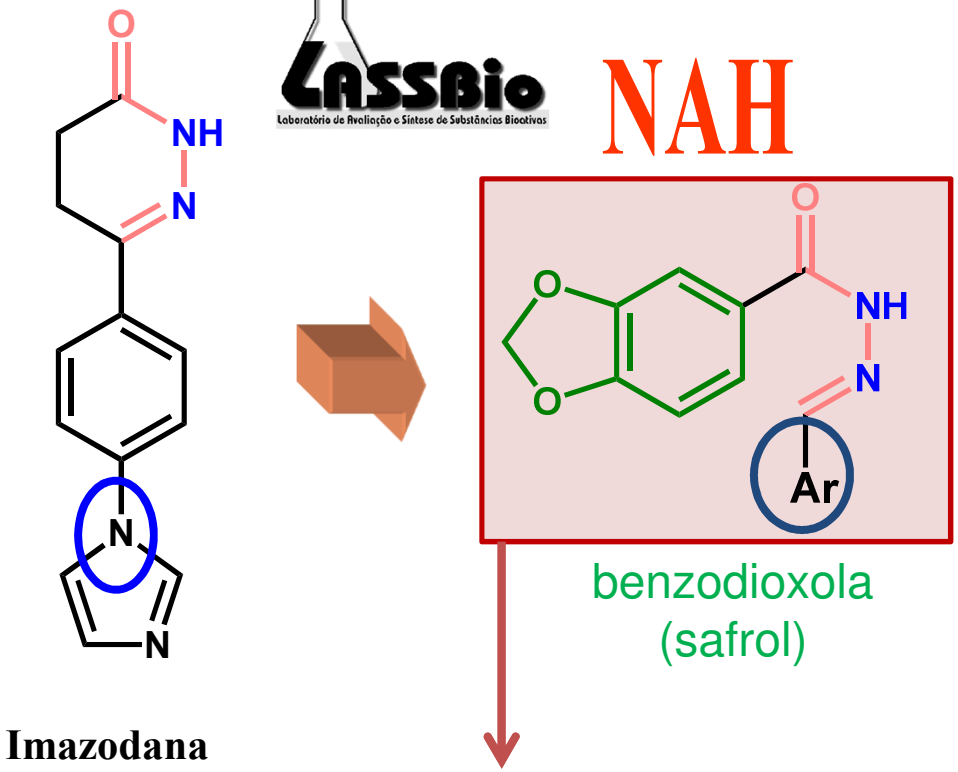


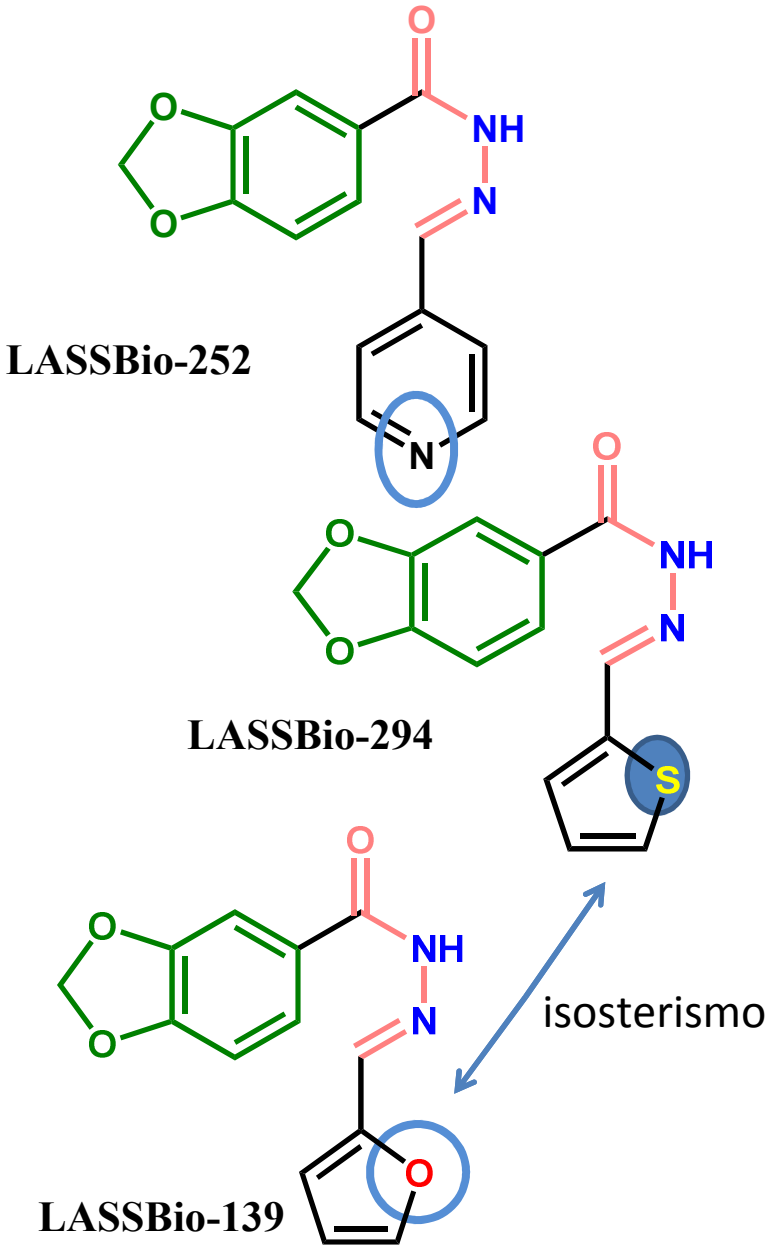
zardaverina



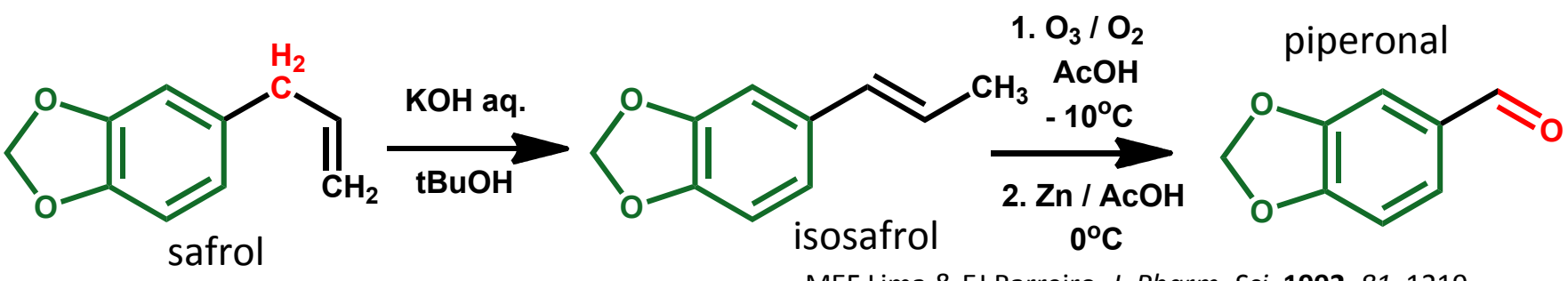
imazodana

A gênese do LASSBio-294...

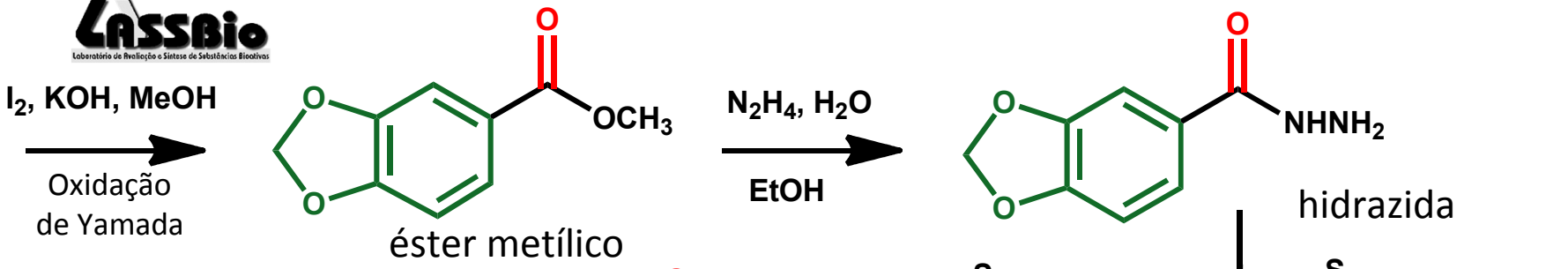




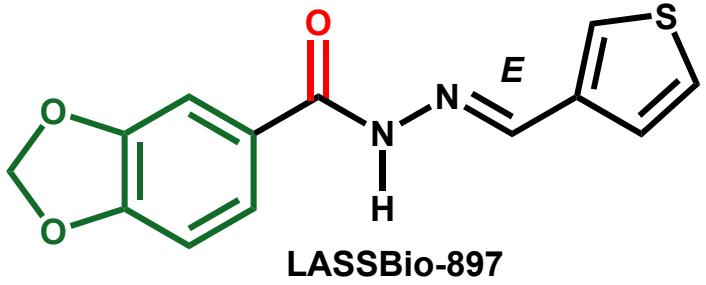
P. C. Lima, L. M. Lima, K. C. M. da Silva, P. H. O. Léda, A. L. P. Miranda, C. A. M. Fraga & E. J. Barreiro, "Synthesis and Non-addictive Analgesic Activity of Novel *N*-acylarylhydrazones and Isosters, Derived from Natural Safrole", ***Eur. J. Med. Chem.*, *35***, 187 (2000).

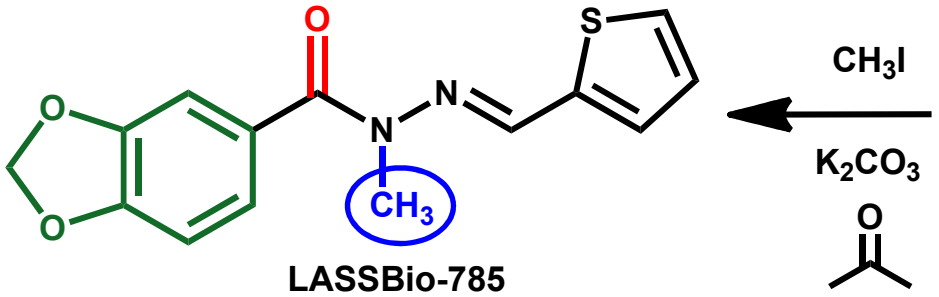


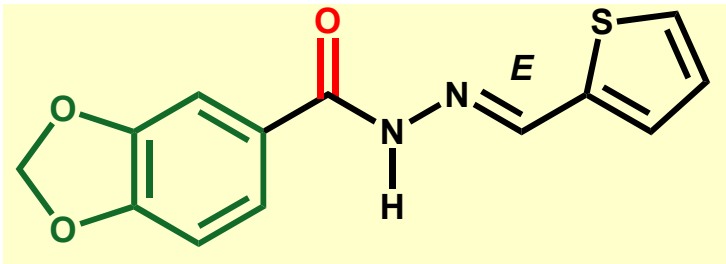
MEF Lima & EJ Barreiro, *J. Pharm. Sci.* **1992**, *81*, 1219



A síntese







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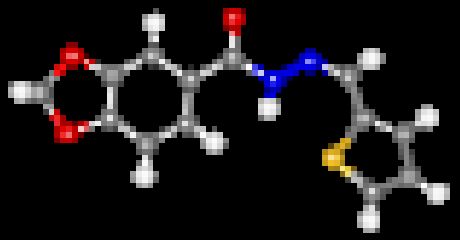
Propriedades estruturais

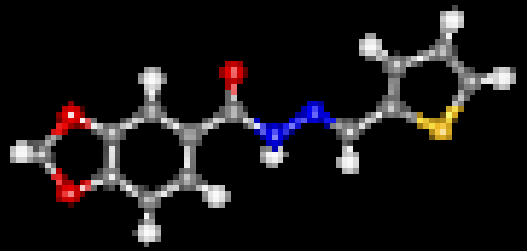
NMR ^{1}H/ ^{13}C

MS

raios-X



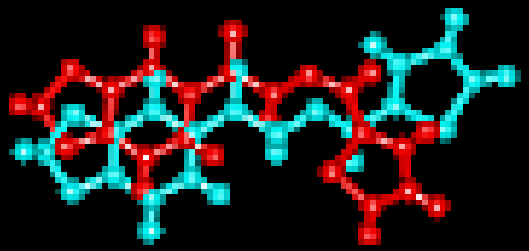
NAH



Z-isomêro

E-isomêro

LASSBio-294



Laboratório de Avaliação e Síntese de Substâncias Bioativas

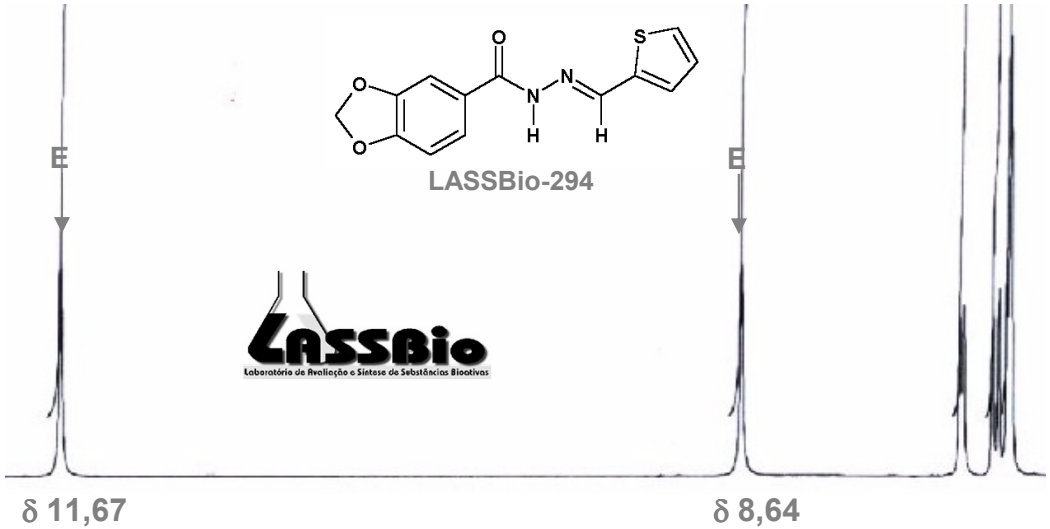
M. R. L. Santos, M. G. de Carvalho, R. Bráz-Filho, **E. J. Barreiro**, "^{1}H and ^{13}C of New Bioactive Isochromanylactylarylhydrazone Derivatives", ***Magn. Reson. Chem.*** **1998, 36,** 533.

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.

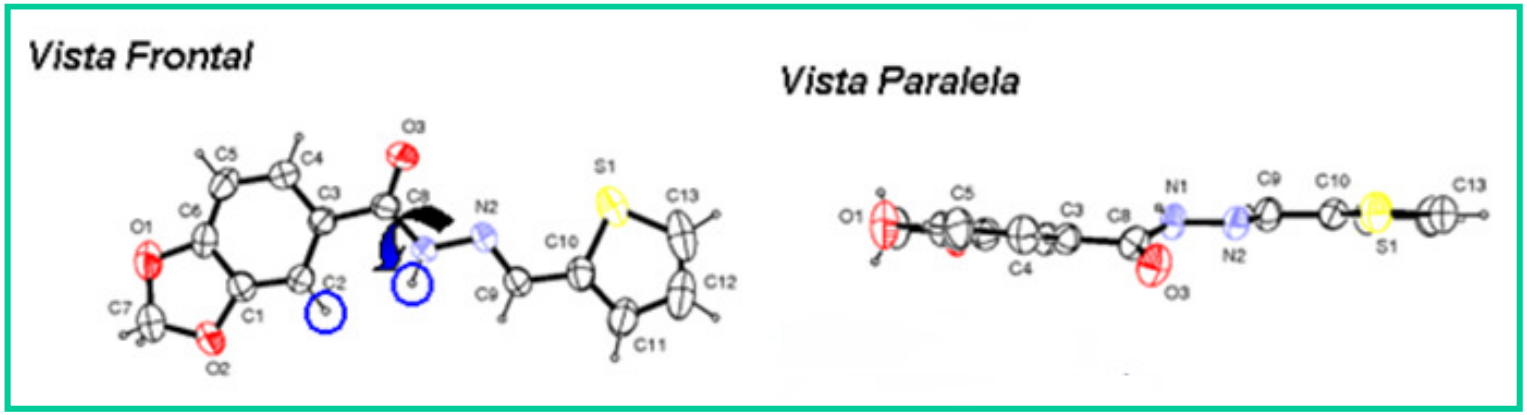
L. Pol-Fachin, C. A. M. Fraga, E. J. Barreiro, H. Verli, Characterization of the conformational ensemble from bioactive *N*-acylhydrazone derivatives, ***J. Molecular. Graphics and Modelling,*** 2010, **8**, 446

Análise espectroscópica e raios X

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

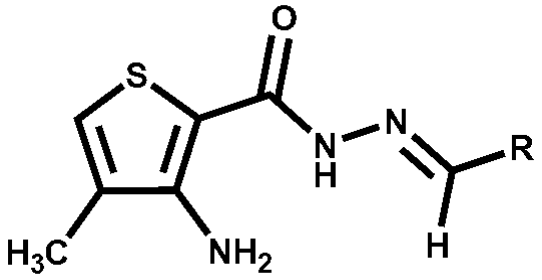


Karabatsos, G.J., *et al.* (1964) *J. Am. Chem. Soc.,* 86, 3351; Karabatsos, G.J., *et al.* (1967) *Tetrahedron*, 24, 3907; ibid (1967) *Tetrahedron*, 24, 3361.

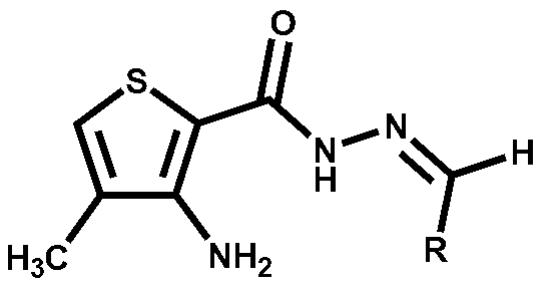


Kummerle, A. E.; Raimundo, J. M.; Leal, C. M.; Silva, G. S.; Balliano, T. A.; Pereira, M. A.; DeSimone, C. A.; Sudo, R. T.; Zapata-Sudo, G.; Fraga, C. A. M.; Barreiro, E. J. , *Eur. J. Med. Chem.* 2009, 44, 4004-4009

X-ray diffraction

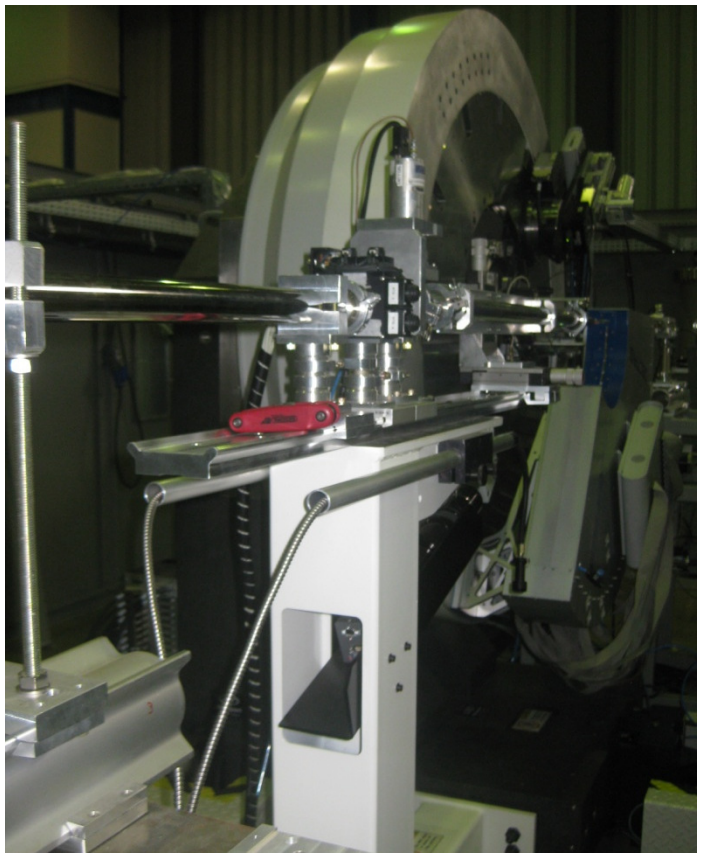


E -Isomer

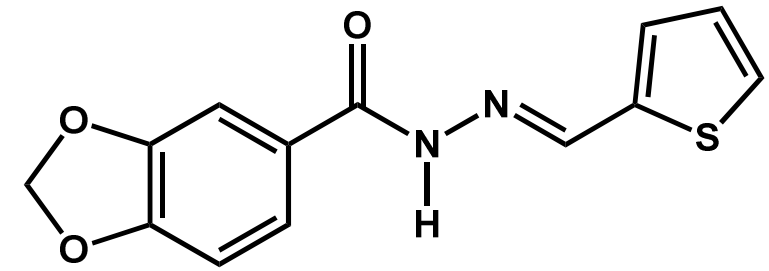


Z -Isomer

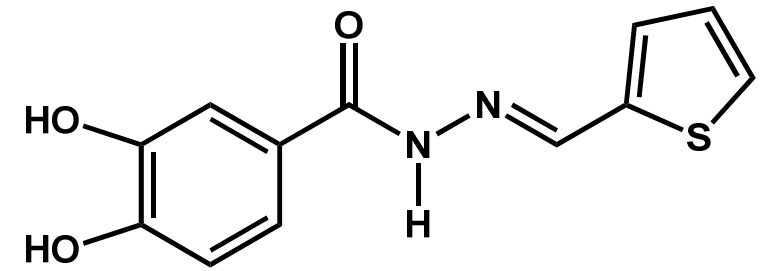
The configuration of the compounds can be analyzed via its crystal structure by powder X-ray diffraction.



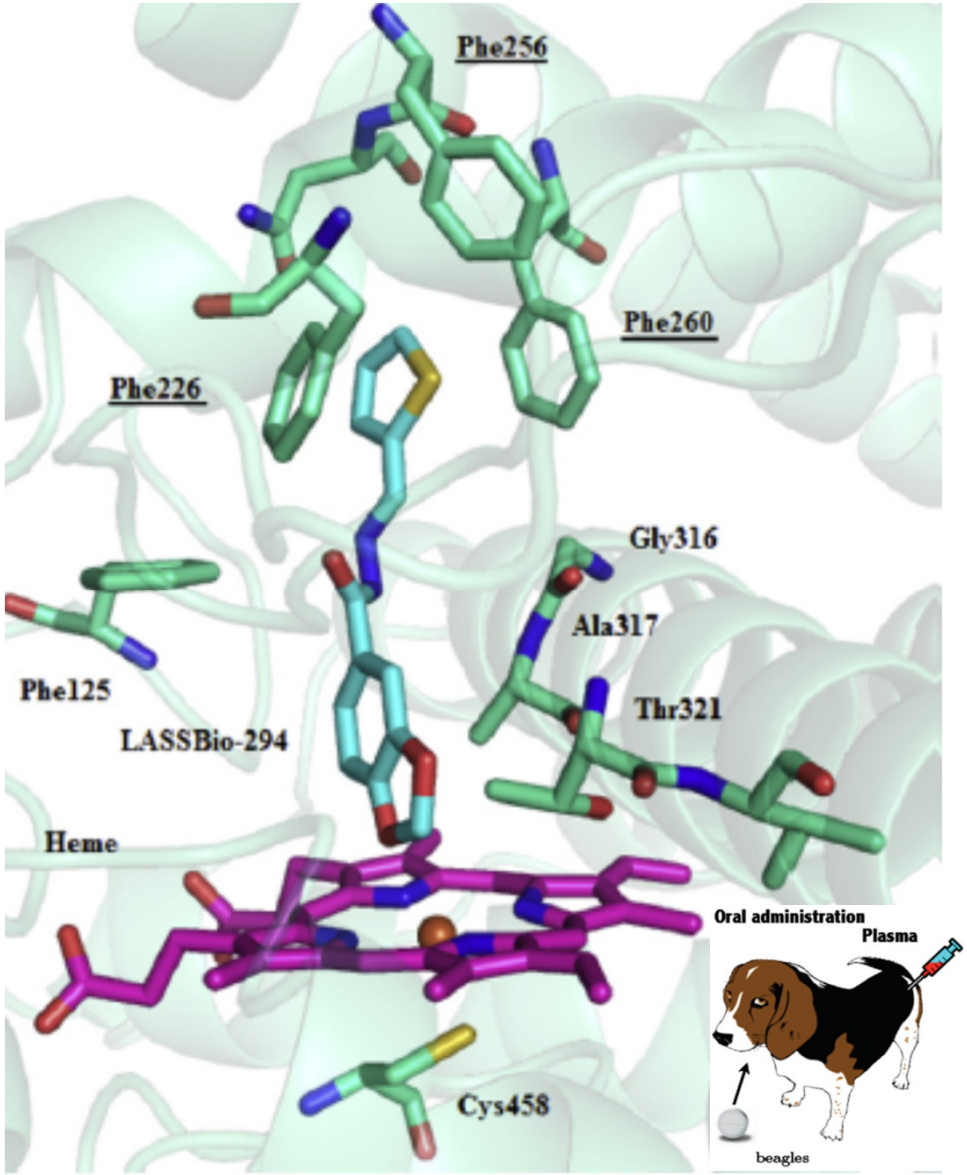
Metabolismo de LASSBio-294



CYP1A2 — In silico / *h*-microssomo



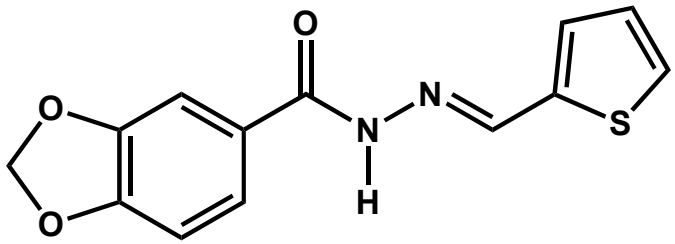
Confirmado sinteticamente



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

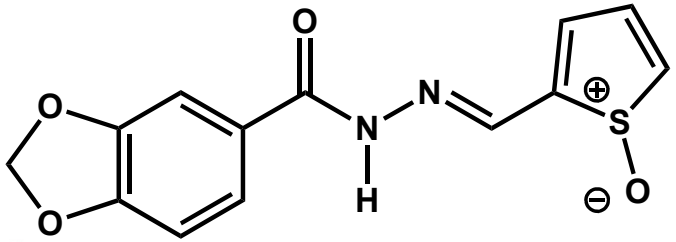
B. bassiana ATCC 7159
& Beagles*

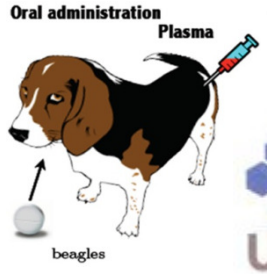


LaBioCon

Beauveria bassiana

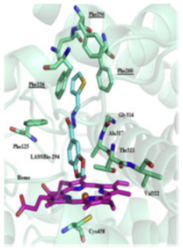
ATCC 7159





Profa Valéria de Oliveira*
INCT-INOFAR
FF-UFG

CYP1A2



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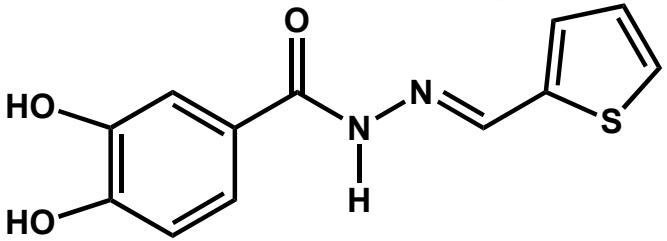

Profa Rosangela Alves*
INCT-INOFAR
EV-UFG

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

Microssomas
& CYPs recombinantes &

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* 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)

1. JS Silva, D Gabriel-Costa, RT Sudo, H Wang, L Groban, EB Ferraz, JHM Nascimento, CAM Fraga, EJ Barreiro, G Zapata-Sudo, Adenosine A_{2A} receptor agonist prevents cardiac remodeling and dysfunction in spontaneously hypertensive male rats after myocardial infarction, *Drug Design, Development and Therapy*, **11**, 553-562 (2017).
2. JR Azevedo, J-J Letourneau, F Espitalier, MI Ré, Solubility of a New Cardioactive Prototype Drug in Ionic Liquids, *J. Chem. Eng. Data*, **59**, 1766–1773 (2014). (Times cited: 10)
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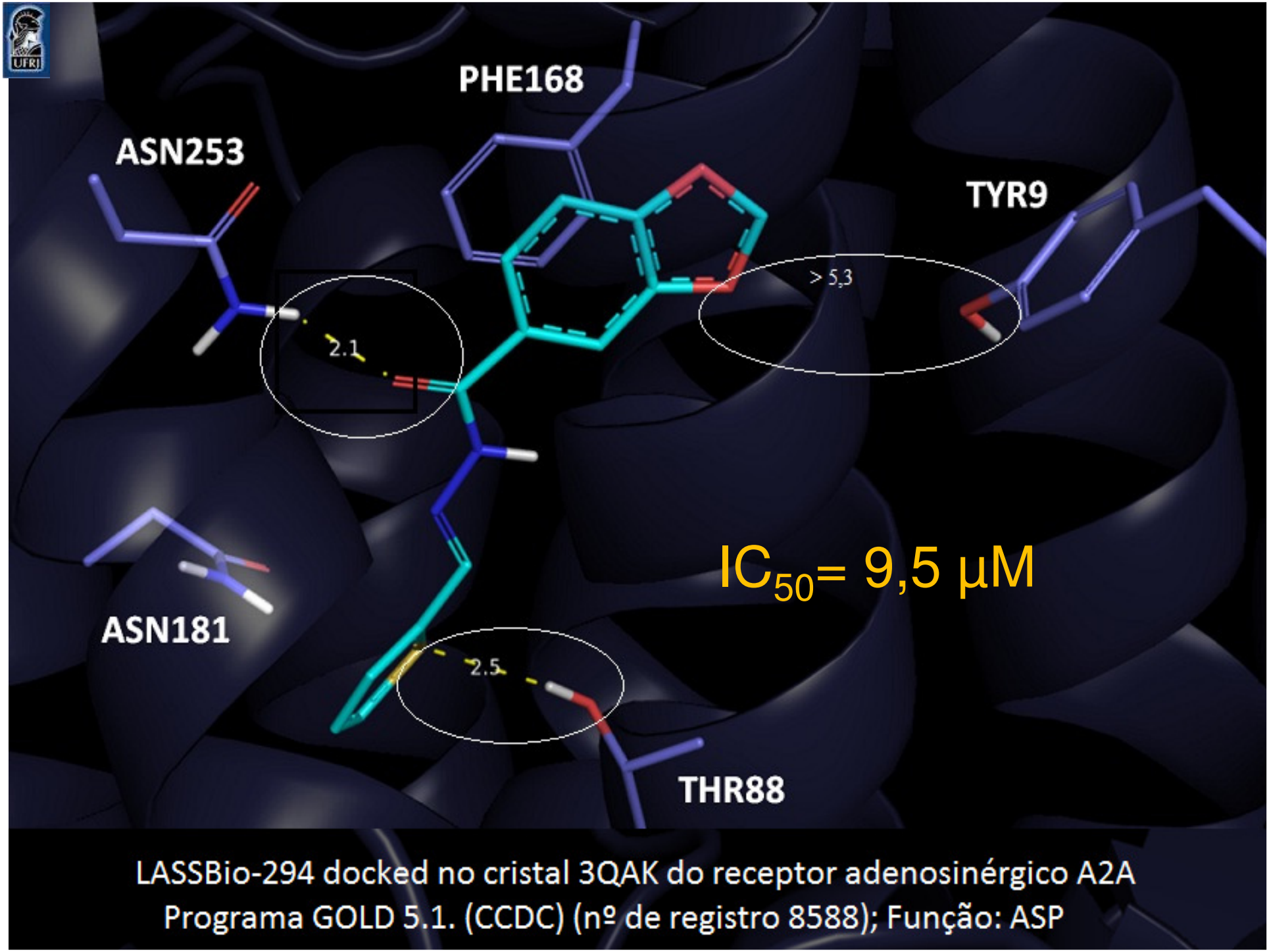
> 500 citações

Dissertações, teses ⇩ Análogos

A P A Costa, *Ação do LASSBio-294 sobre os parâmetros cardiovasculares em modelo experimental de cardiomiopatia dilatada em coelhos*. Tese Doutorado em Ciência Animal, Universidade Federal de Goiás, Goiânia, 2016.



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

Rota sintética escalonável

CRISTÁLIA

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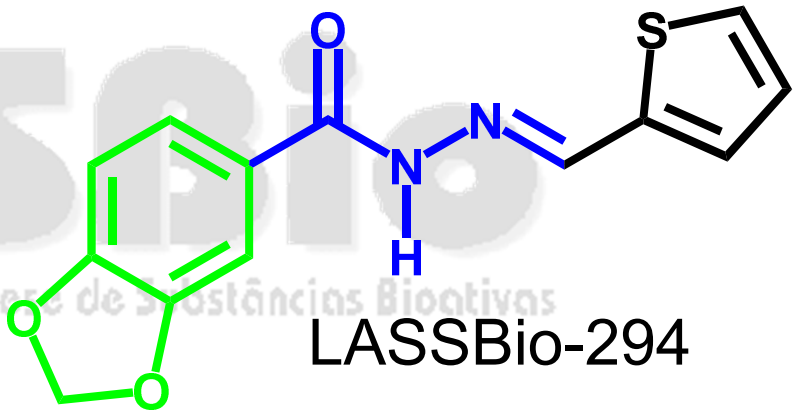

LASSBio-294

CAM Fraga, EJ Barreiro, Medicinal Chemistry of *N*-Acylhydrazones: New Lead-Compounds of Analgesic, Antiinflammatory and Antithrombotic Drugs, *Curr. Med. Chem.* **2006**, *13*, 167; RC Maia et al., Acylhydrazone Derivatives: A Patent Review, *Exp. Op. Ther. Patents* **2014**, *24*, 1161

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.

Patente obtida

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

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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

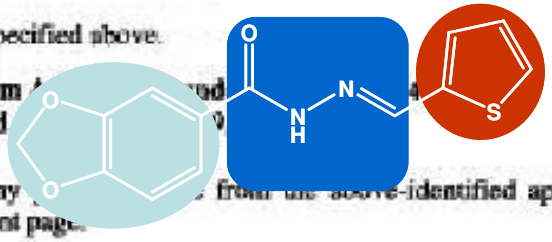
VENABLE LLP
P.O. BOX 34385
WASHINGTON, DC 20043-9998

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 od
(application filed

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Roberto Takashi Sudo, Rio de Janeiro, BRAZIL;
Edson X. Albuquerque, Baltimore, MD;
Eliezer J. Barreiro, Rio de Janeiro, MD;
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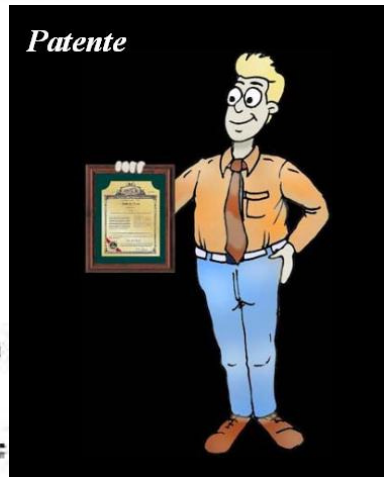
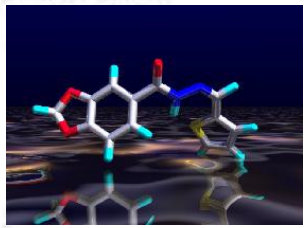


Thienylhydrazone with Digitalis-like properties (positive inotropic effects)



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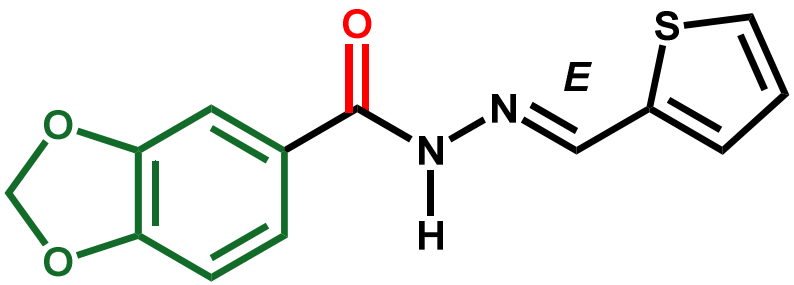

Quim. Nova, Vol. 25, No. 6B, 1172-1180, 2002

Divulgação

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

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

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

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

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

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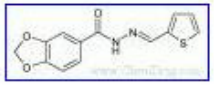

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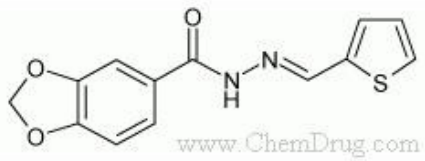
您现在的位置： >> 专业资料首页 >> 药物合成数据库 >> L-294, LASSBio-294,314021-07-3,C13-H10-N2-O3-S,(E)-N'-(Thien--药物合成数据库

【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

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ZINC00257502	MLS000716050,BAS 078671
STK138182,ZINC00302421,	IUPAC Name: (3E)-3-[(4-etho
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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
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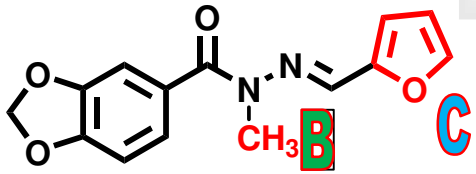
Otimização do protótipo

LASSBio-123

LASSBio-129



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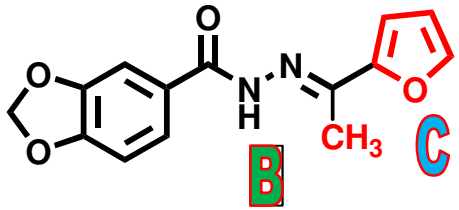

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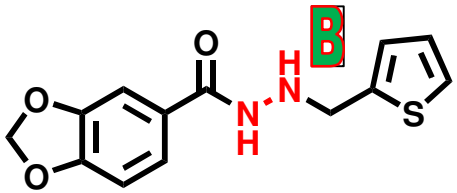

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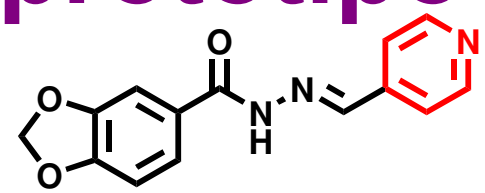
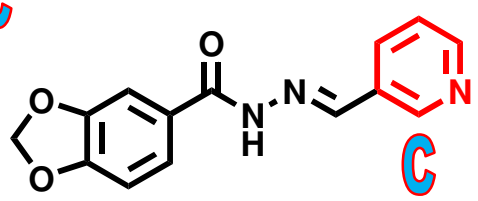
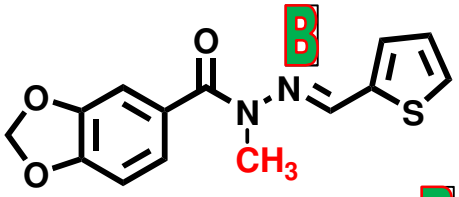
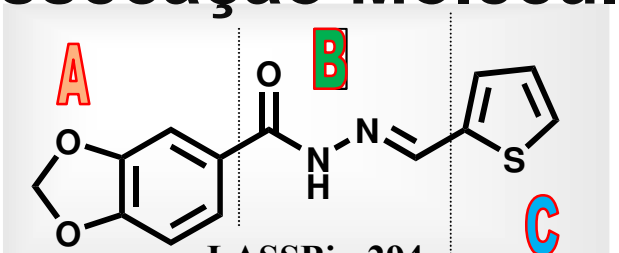




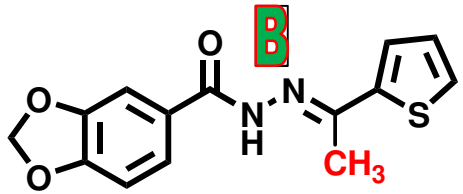


LASSBio-785
IC_{50} = 10,2 μM

Dissecação Molecular

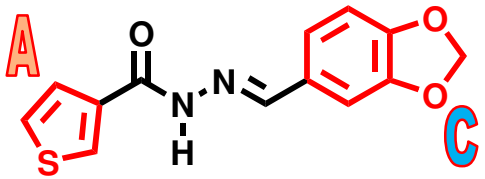


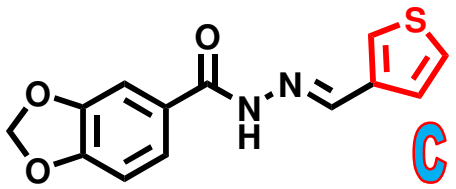
LASSBio-294
(VD) IC_{50} = 74,0 μM



LASSBio-1029

LASSBio-787





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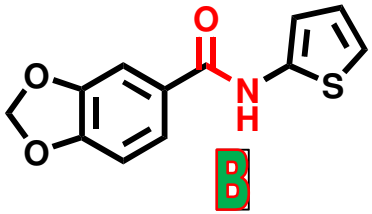

Bioorganic Medicinal Chemistry 2005, **13**, 3431
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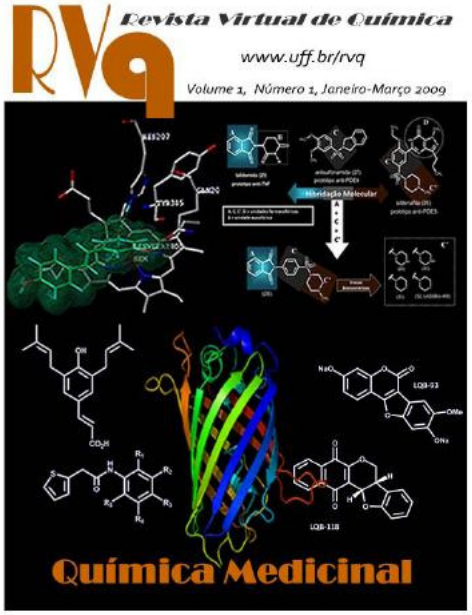

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Artigo

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

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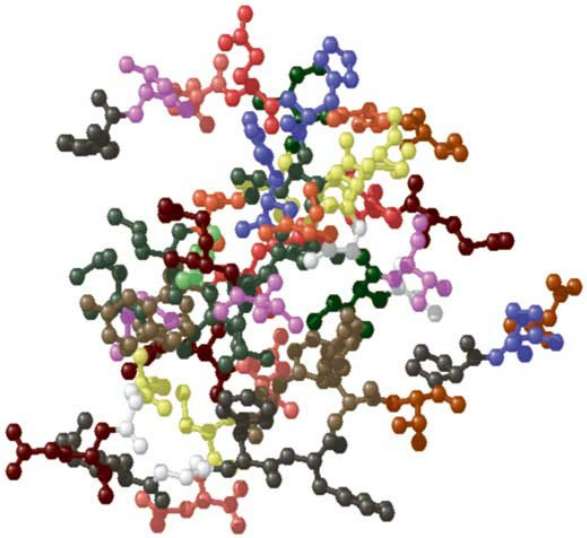

ledicinal Chemistry and the paradigm of the lead compound

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

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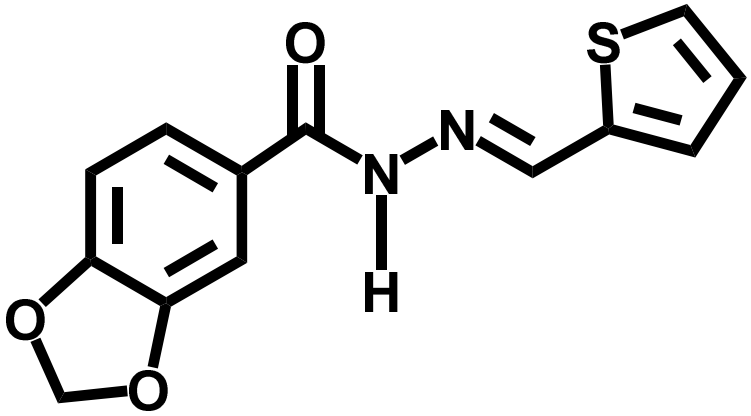

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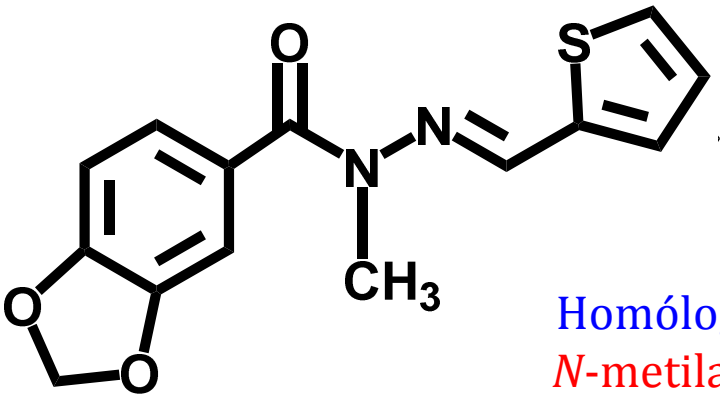
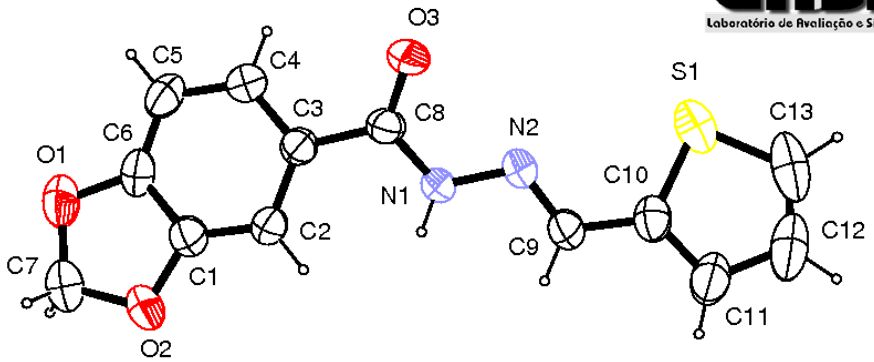
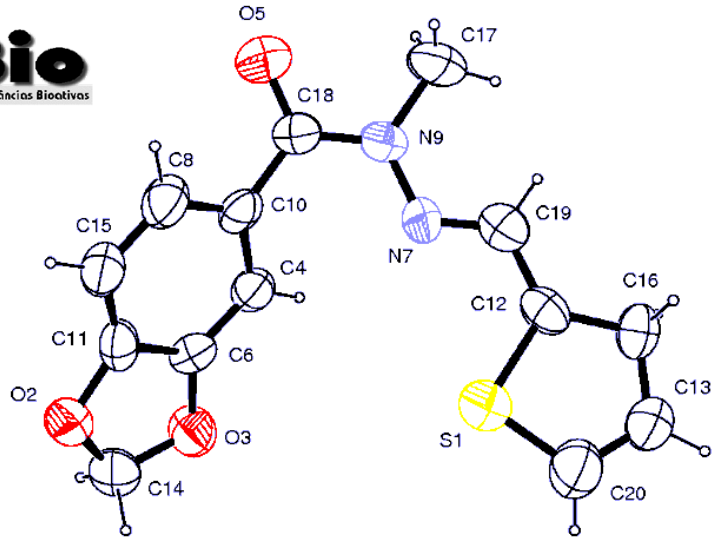


LASSBio-785

Homólogo
N-metilado



Conformação "grampo-de-cabelo"



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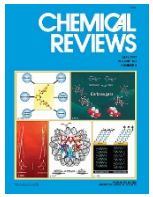

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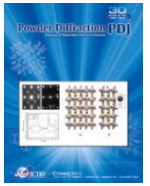

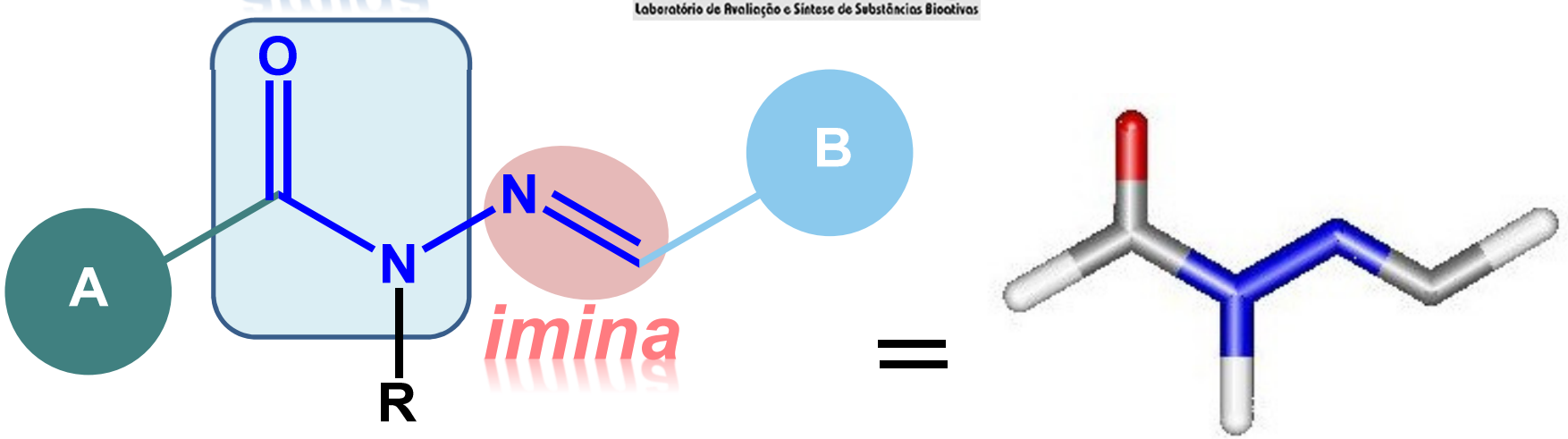

N-acilidrazona **NAH**

NAH = amida + imina

As propriedades biológicas das NAH foi descoberta no LASSBio!

"...discovery *consists* of seeing

what everybody else **has seen**

***and* thinking what**

no*b*ody else

has not thought..."

***Albert Szent-Györgi* (1893-1986)**

LASSBio-1819

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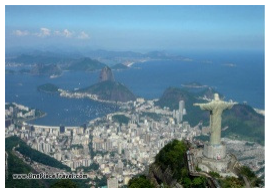
European Journal of Medicinal Chemistry 71 (2014) 1–14



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Laboratório de Avaliação e Síntese de Substâncias Bioativas

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.

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

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A Química
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