

Universidade Federal do Rio de Janeiro

Horizontes e Fronteiras da Interdisciplinaridade da Química Medicinal



UFRJ

Eliezer j. Barreiro

Professor Titular



Instituto Nacional de
Ciência e Tecnologia
de Fármacos e Medicamentos

www.inct-inofar.ccs.ufrj.br



Resumo

Definição de Química Medicinal: o início

Os fármacos e o prêmio Nobel

As moléculas dos fármacos e sua diversidade

O paradigma de Fischer e a Química Computacional

A contribuição das interações frágeis

A fase farmacocinética da ação dos fármacos

Feito em casa: LASSBio-294, novo agente cardioativo

Perspectivas



Definição:

Química Medicinal

estuda os fatores moleculares relacionados ao modo de ação dos fármacos, incluindo a compreensão da relação entre a estrutura química e a atividade (SAR), além das propriedades que governam sua absorção, distribuição, metabolismo, eliminação (ADME) e toxicidade.

Química Medicinal



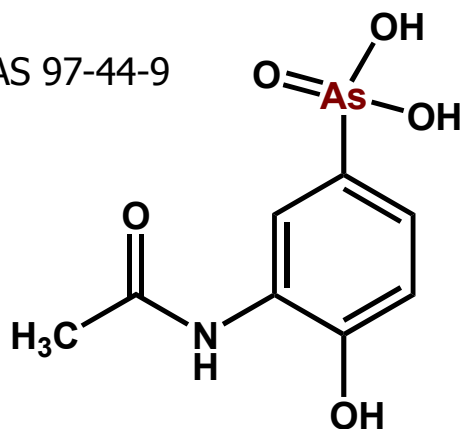
O berço da Química Medicinal



Ernest Fourneau
1872-1949

Stovarsol

CAS 97-44-9



Institut Pasteur (1887)

1911- Laboratoire de Chimie Thérapeutique

Institut Pasteur (Emile Roux)

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

Prontosil rubrum
(sulfonamidas)

Curare: SAR



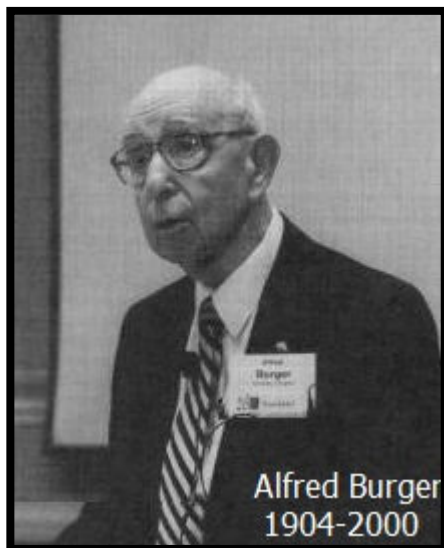
Daniel Bovet
1907-1992



Prêmio Nobel de
Fisiologia/Medicina

1957





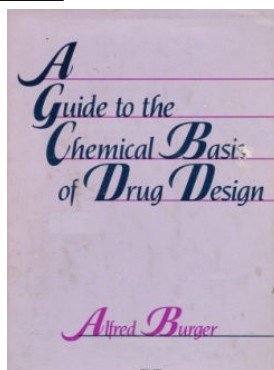
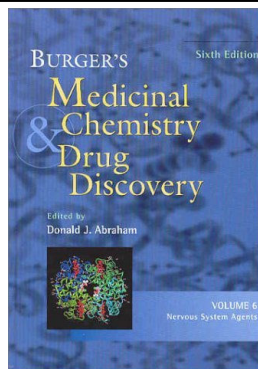
Química Medicinal

Prof. Alfred Burger

(1904-2000)

University of Virginia

EUA



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

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

1978 - GlaxoSmithKline cria com ACS o “Alfred Burger Award”
em Química Medicinal



Emil Fischer

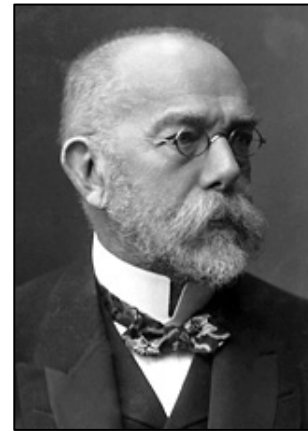
1852-1919

1902

http://nobelprize.org/nobel_prizes/chemistry/laureates/1902/fischer-bio.html



Lock & Key

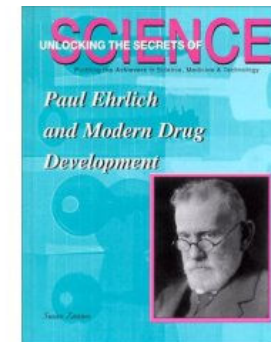


Robert Koch

1843-1910

1905

http://nobelprize.org/nobel_prizes/medicine/laureates/1905/koch-bio.html



Paul Ehrlich

1854-1915

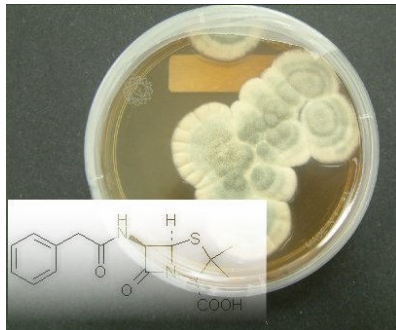
1908

http://nobelprize.org/nobel_prizes/medicine/laureates/1908/ehrlich-bio.html

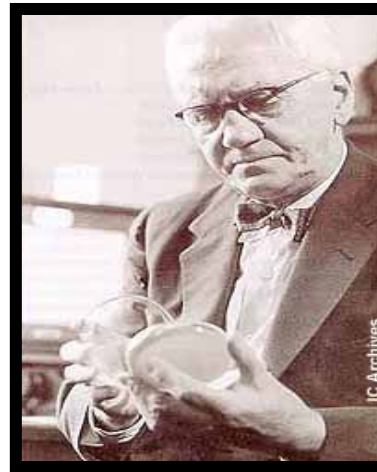
P. Ehrlich, *Chemotherapeutics: scientific principles, methods and results. Lancet* 1913, **2**, 445



Os fármacos e o Nobel !



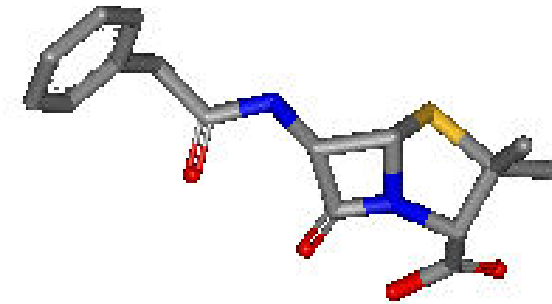
196 pesquisadores ganharam o Prêmio Nobel de Medicina (1901-2010)



Alexander Fleming

1881-1955

http://nobelprize.org/nobel_prizes/medicine/laureates/1945/fleming-bio.html



Penicilina



Howard W. Florey

1898-1968

http://nobelprize.org/nobel_prizes/medicine/laureates/1945/florey-bio.html



<http://nobelprize.org>

1945



Ernest B. Chain

1906-1979

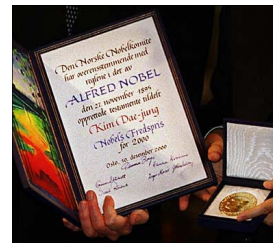
http://nobelprize.org/nobel_prizes/medicine/laureates/1945/cchain-bio.html



Os fármacos e o Nobel !



1982



John R. Vane
(1927-2004)

http://nobelprize.org/nobel_prizes/medicine/laureates/1982/vane-autobio.html



Sune K. Bergström

(1916-2004)

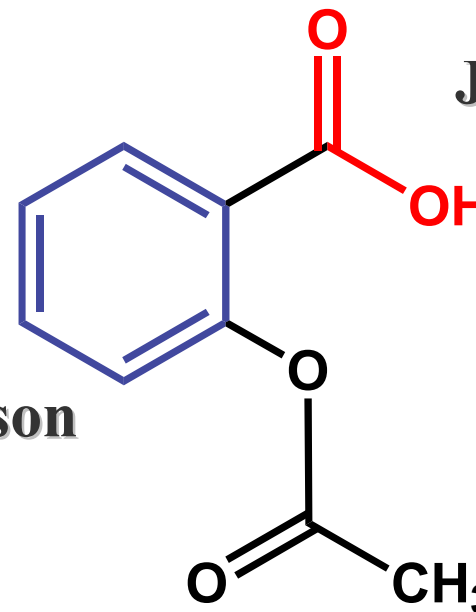
http://nobelprize.org/nobel_prizes/medicine/laureates/1982/bergstrom-autobio.html



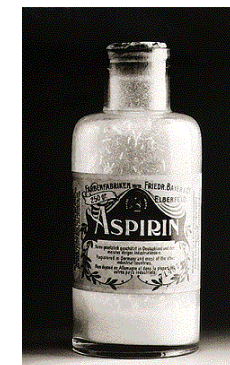
Bengt I. Samuelsson

(1934-

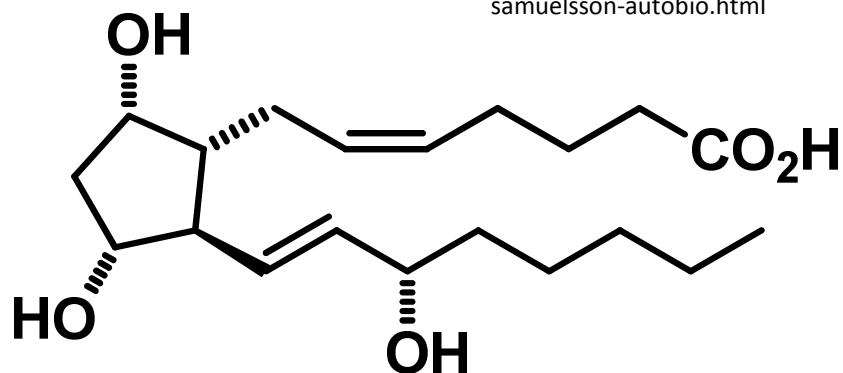
http://nobelprize.org/nobel_prizes/medicine/laureates/1982/samuelsson-autobio.html



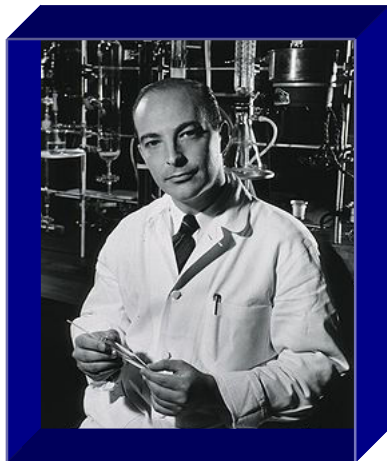
$C_9H_8O_4$



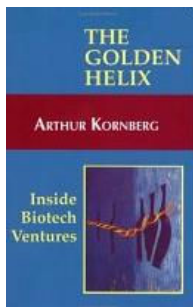
1982 – AAS



Prostaglandina $F_{2\alpha}$



Arthur Kornberg
1918-2007



University of Stanford

Prêmio Nobel, 1959



The Two Cultures: Chemistry and Biology¹

1997

Arthur Kornberg

Department of Biochemistry, Stanford University, Stanford, California 94305

Received July 14, 1987

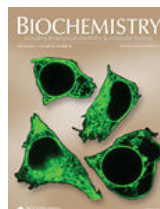
“Much of life can be understood in rational terms if expressed in the language of chemistry... the

historical roots of chemistry and biology are intertwined in many places...



Pharmaceutical chemistry was until recently the bastion of organic chemistry... in the search for alternative or superior drugs for the treatment of various diseases...”

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



Biochemistry 1987, 26, 6888-6891

Química Medicinal

Slide 9

EJB3

Kornberg definiu as bases da interdisciplinaridade das ciências dos fármacos quando antecipou a necessidade de aproximar-se a Química e a Biologia.

Eliezer J. Barreiro; 4/3/2010



The American Chemical Society, Division of Medicinal Chemistry

Vision Statement and Strategic Initiatives

1. Provide, support and advocate education in medicinal chemistry.
2. Be a strong advocate for interdisciplinary, cutting edge research as reflected in our programming, policy and global outreach.

- * Symposia that provide medicinal chemists with advances in the basic understanding of interdisciplinary core concepts in drug discovery.

Increase collaboration with international societies to become more global in outlook.

Enhance national meeting content to provide a forum for people who work in related areas to meet and interact.

Sponsor or organize a newly emerging therapeutic target conference.

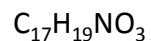
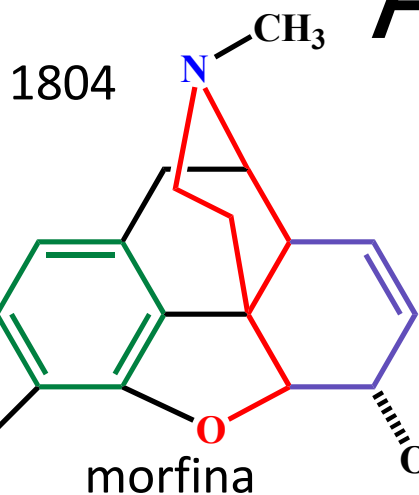
Get involved with ACS Previews at the planning level (or develop our own workshops).

3. Increase communication by targeting:
4. Enhance communication by targeting:

Interdisciplinaridade



As moléculas pioneiras.



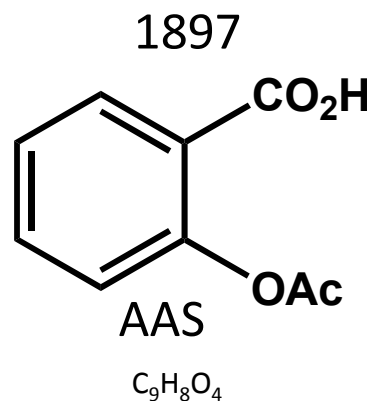
Friedrich W. A. Sertürner
1783- 1841



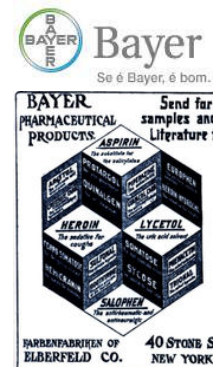
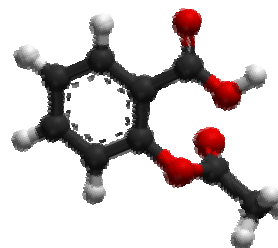
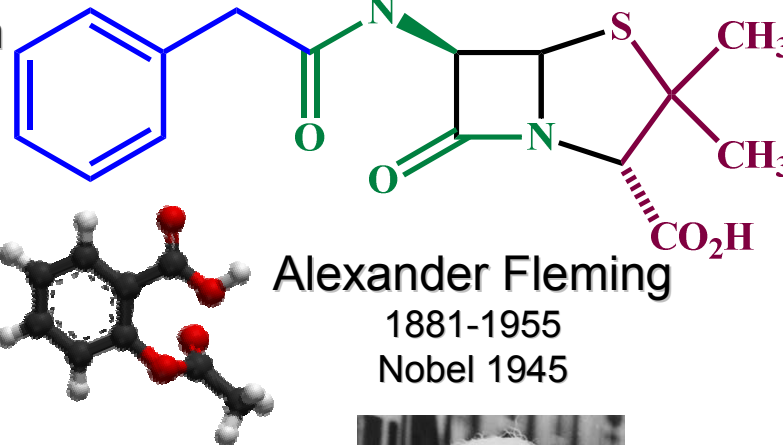
Henry How
1853 – *Un. Glasgow*



Sir Robert Robinson
1886-1975
Nobel 1947



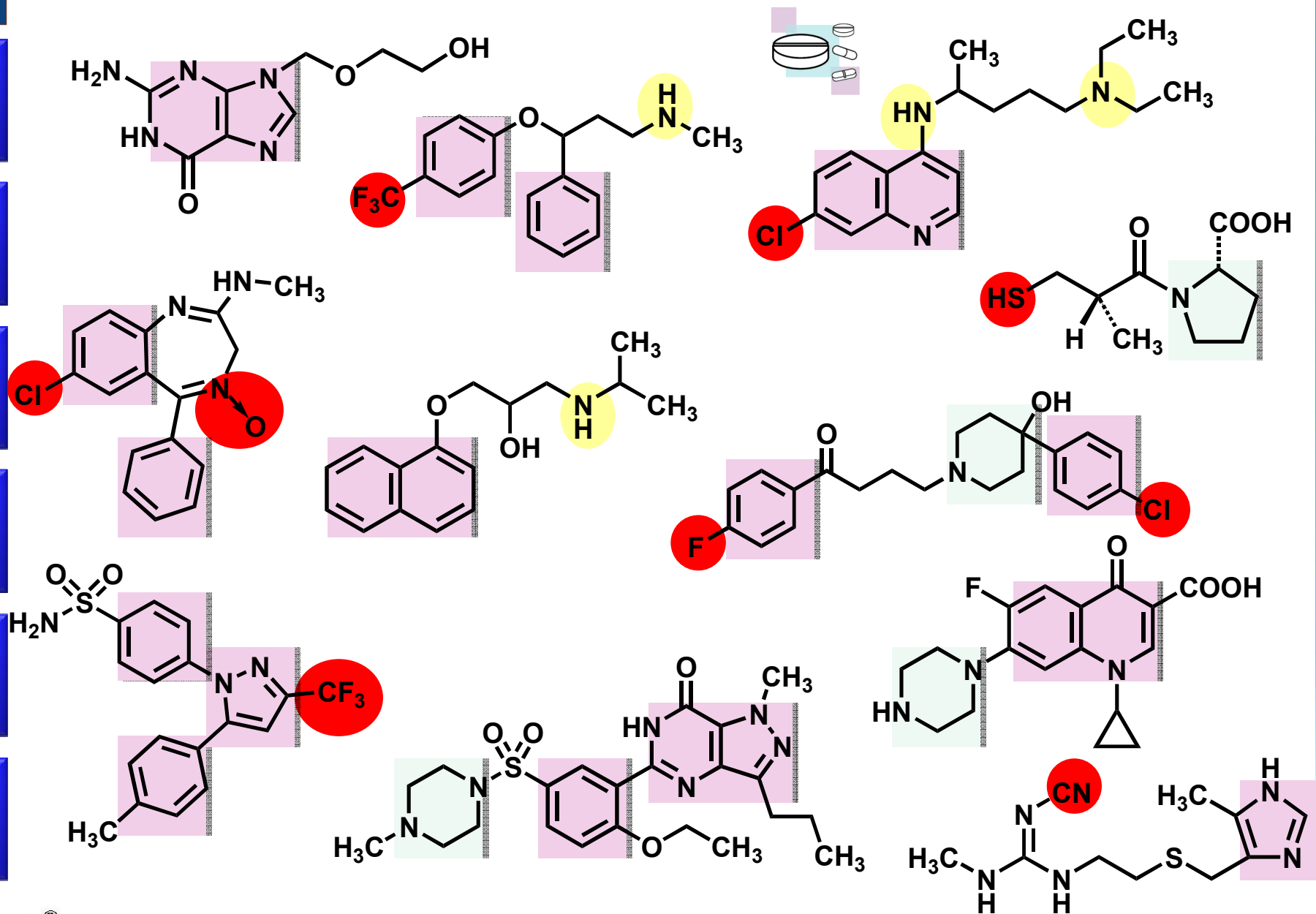
Felix Hoffman
1868- 1946



Library of Congress



A quimiodiversidade dos fármacos...é singela!





O paradigma de Fischer



Emil Fischer
1852-1919
1902



LOCK & KEY
CONCEPT



Biorreceptor

macromolécula

baseado no sítio de reconhecimento

Planejamento racional

Fármaco

micromolécula

baseado no ligante / análogo-ativo



Robin Ganellin gives his views on medicinal chemistry and drug discovery

Interview by Stephen L. Carney

C. Robin Ganellin, FRS, Smith Kline & French Professor
Medicinal Chemistry, University College London

Physiologic
A abordagem
approach
fisiológica



C. Robin Ganellin, *Drug Discovery Today* 2004, 9, 158



Journal of
Medicinal Chemistry

Subscriber access provided by UNIV FED DO RIO DE JANEIRO UFRJ

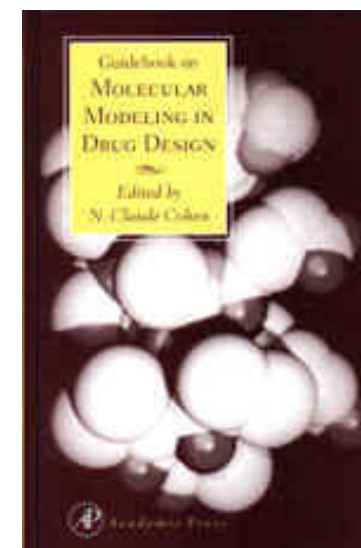
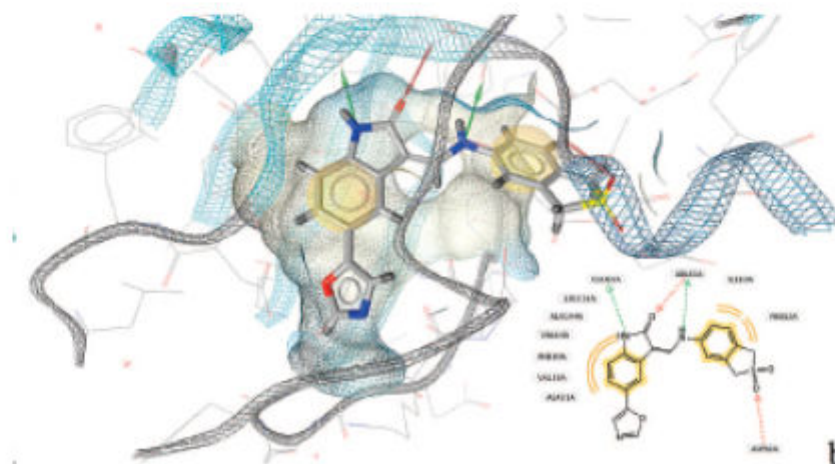
Perspective

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

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

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

Journal of Medicinal Chemistry, 2008, Vol. 51, No. 22 7027





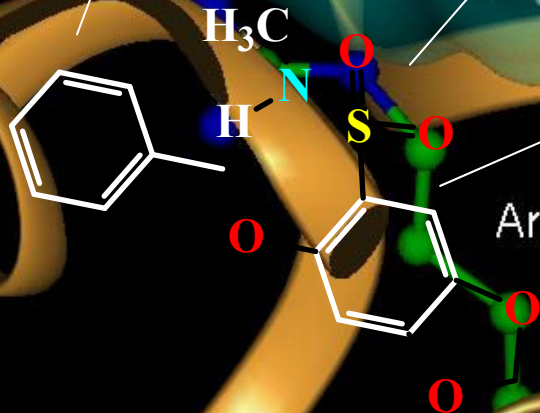
Arg513

Phe518

Tyr385

Ser530

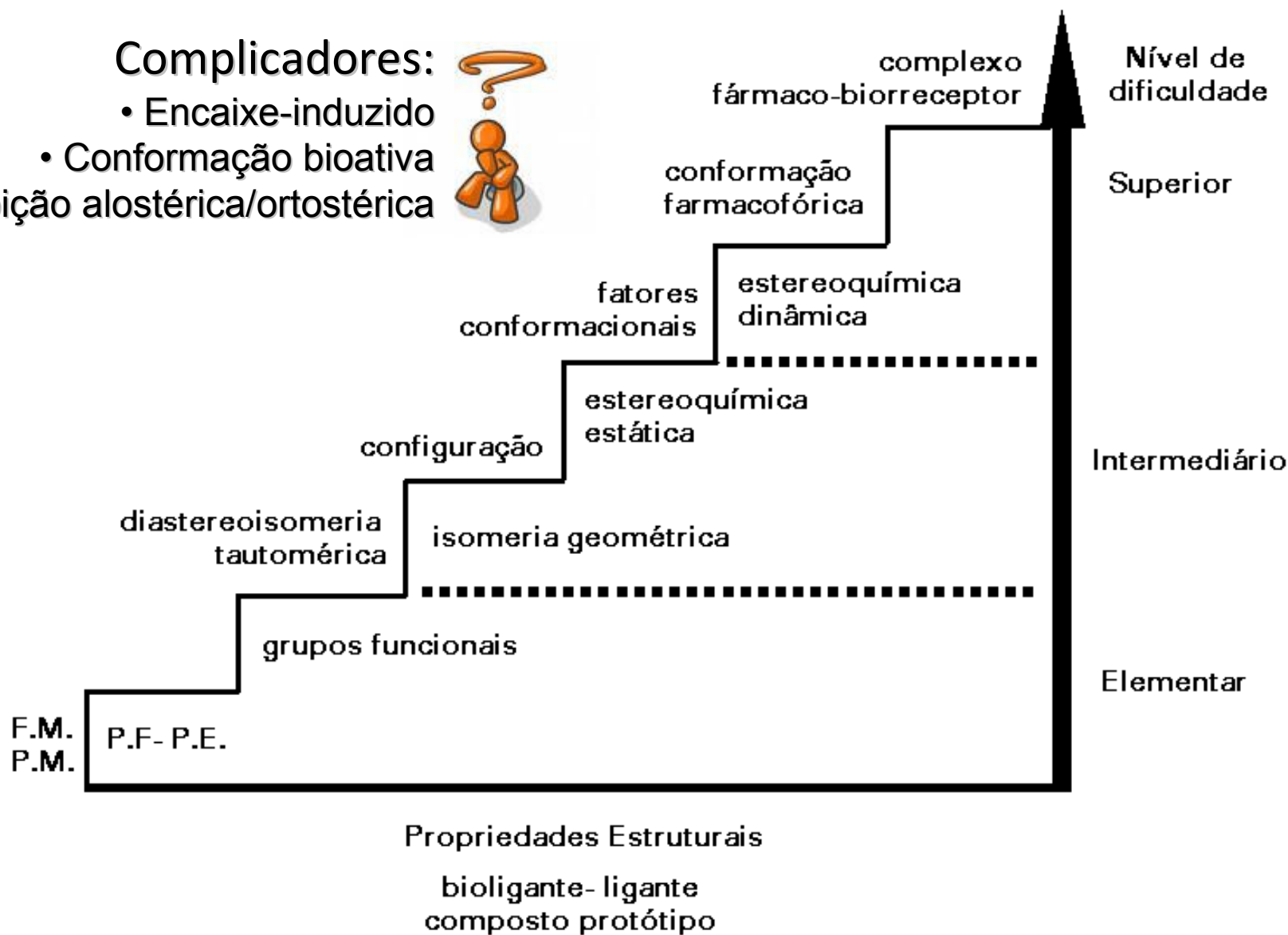
Arg120





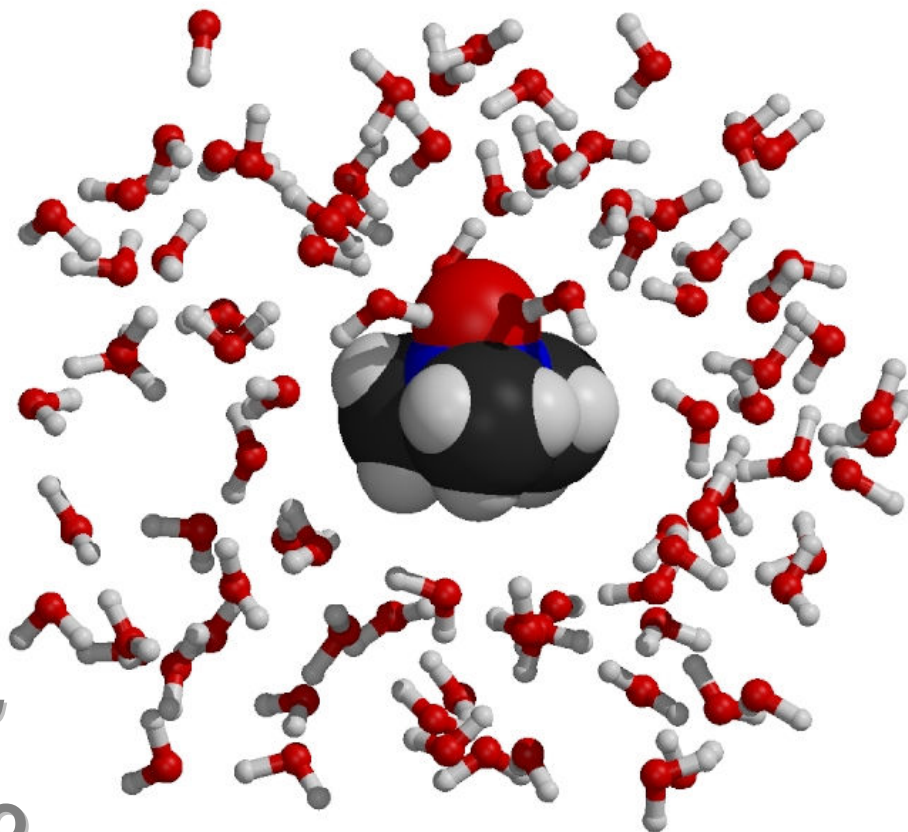
Nível hierárquico da descrição da complementaridade F-R

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

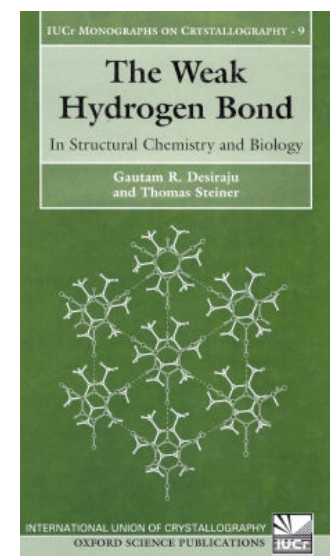




A importância das “ligações” frágeis...



“ligações”
de hidrogênio ...



Linus C. Pauling, 1954 & 1963



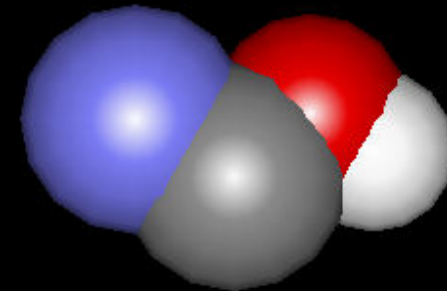
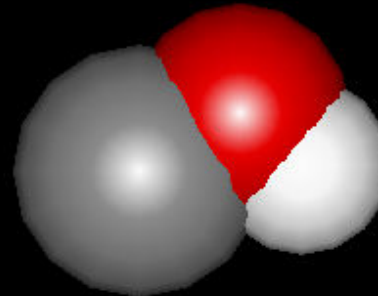
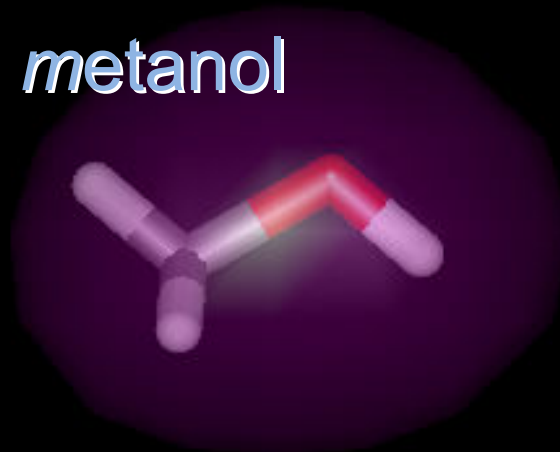


Fatores estruturais

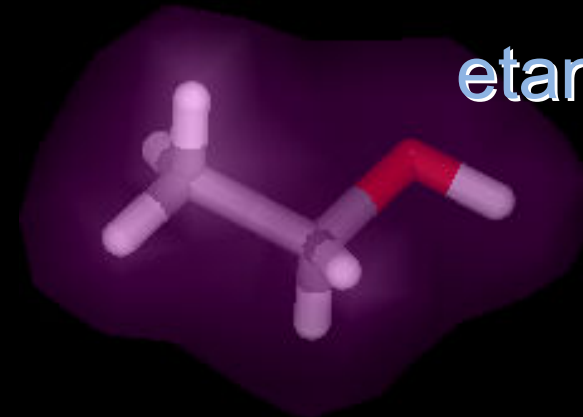
Como atua o álcool ?



metanol



etanol

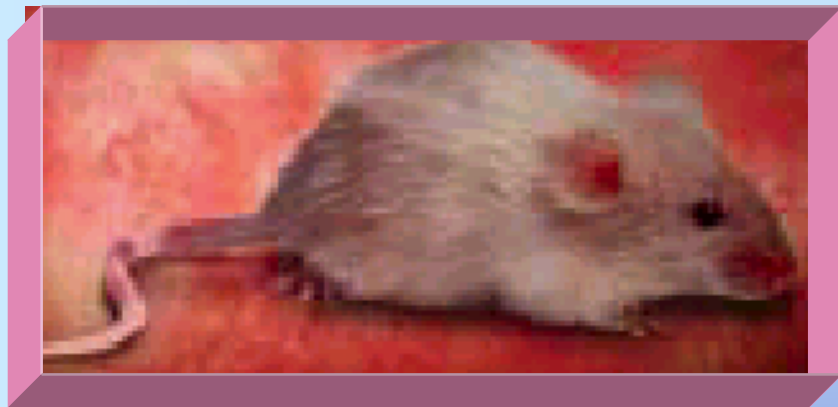


Dose ! canais iônicos = GABA_A (? ? ?)



Rato Transgênico Humanizado

Humanized mouse model



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

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



Animal transgênico com mesmo perfil de resposta à ação fármacos que humanos.

Possui como majoritária a isoforma **CYP3A** com alta homologia à forma-*h* que permite o estudo do metabolismo.

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



Universidade Federal do Rio de Janeiro

Química Medicinal



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



LASSBio

Laboratório de Avaliação e Síntese de Substâncias Bioativas

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



Pharmacology
Farmacologia



Molecular
Modelagem
Modeling
Molecular



© 2010



Abordagem Fisiológica



Síntese orgânica medicinal

Princípio de Price

Química Medicinal

Pharmacology
Farmacologia

Efeito porta-a-lado

Molecular
Modelagem
Modeling
Molecular

Química
Medicinal

Química
computacional

Bioensaios



in vivo / in vitro

modelagem molecular





Novos Compostos-Protótipos Descobertos no



LASSBio-585

LASSBio-294



USPTO Patent # 7.091.238
August 15, 2006
2nd license agreement
ORD, Un Maryland,
Baltimore, USA

LASSBio-579

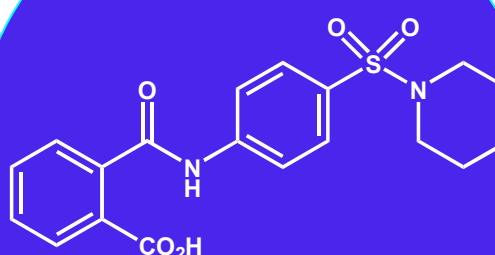


INPI # 0303465-8 de 05/09/2003

LASSBio-581

*Thienylhydrazone with digitalis-like properties
(positive inotropic effects)*
August 15, 2006
Publication Number: 07091238

LASSBio-596



Sob contrato c/ empresa
farmacêutica nacional



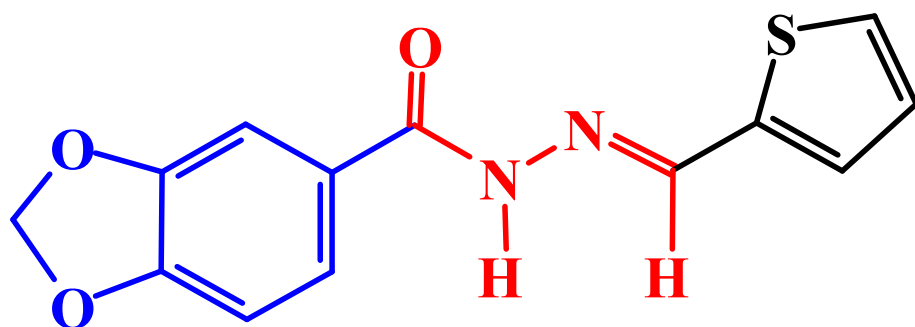
Otimização do protótipo
Otimização do protótipo Otimização do protótipo





Universidade Federal do Rio de Janeiro

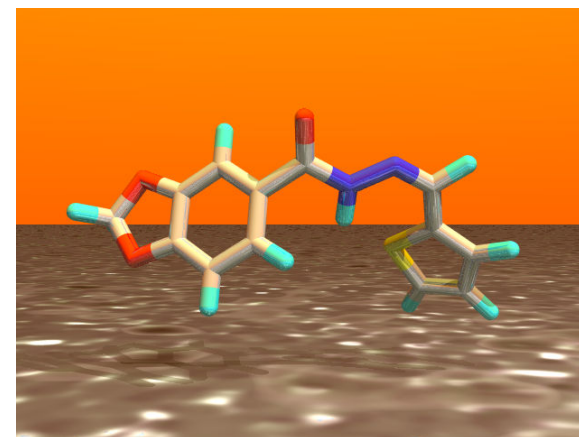
Novo Protótipo de Fármaco Cardioativo



$C_{13}H_{10}N_2O_3S$

MW 274

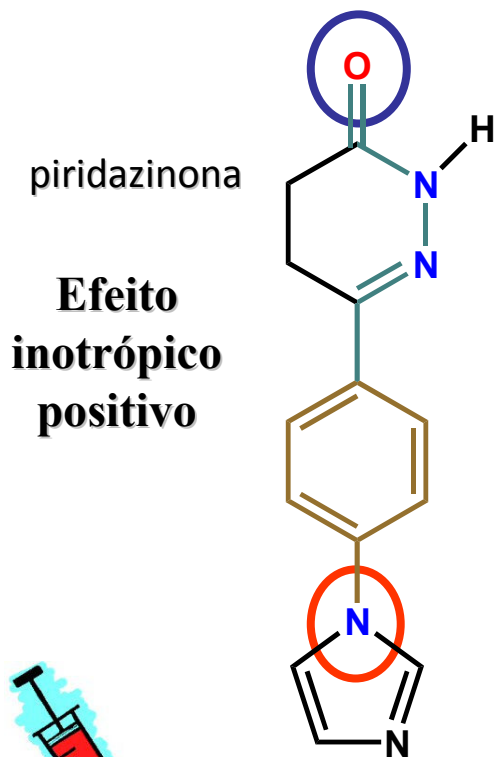
LASSBio-294



LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

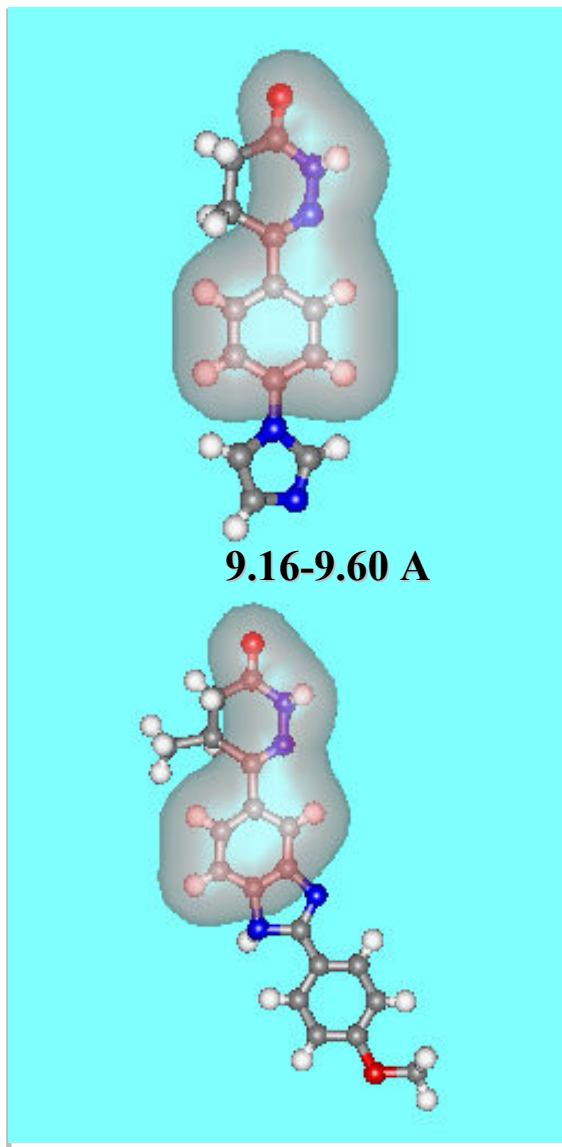


Inibidores de PDE-3

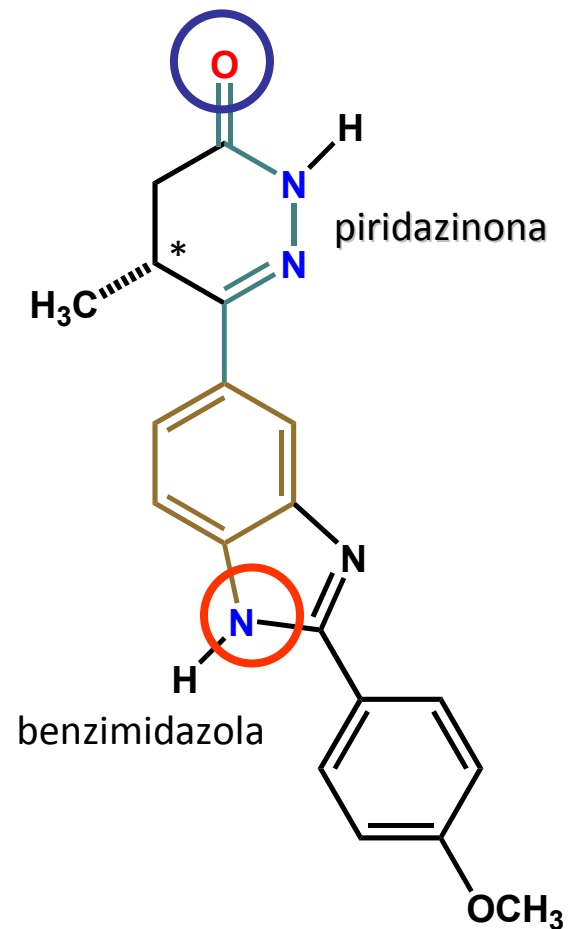


imazodana

JA Bristol et al., *J Med Chem* 1984, 27, 1099



9.16-9.60 Å

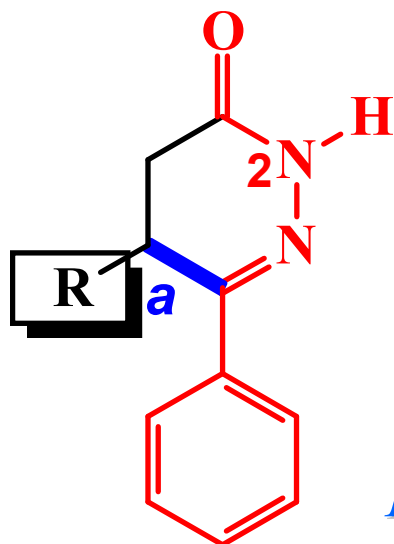


pimobendana
5-metil-3(2H)-piridazinona

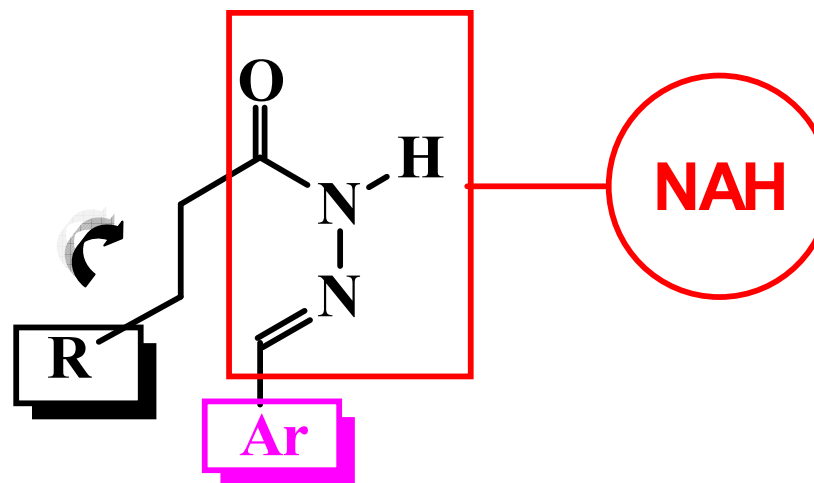
I Sircar et al., *J Med Chem* 1985, 28, 1405



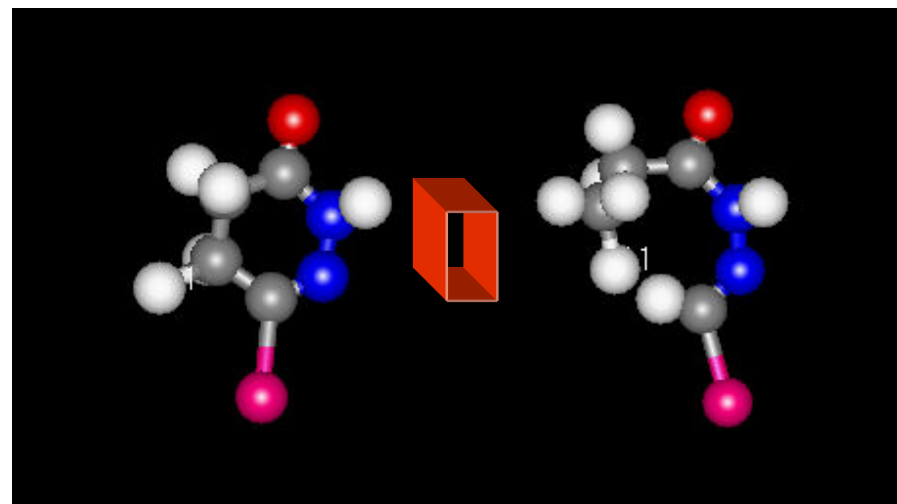
2H-piridazinonas & NAH



*Abertura
Ligação a*

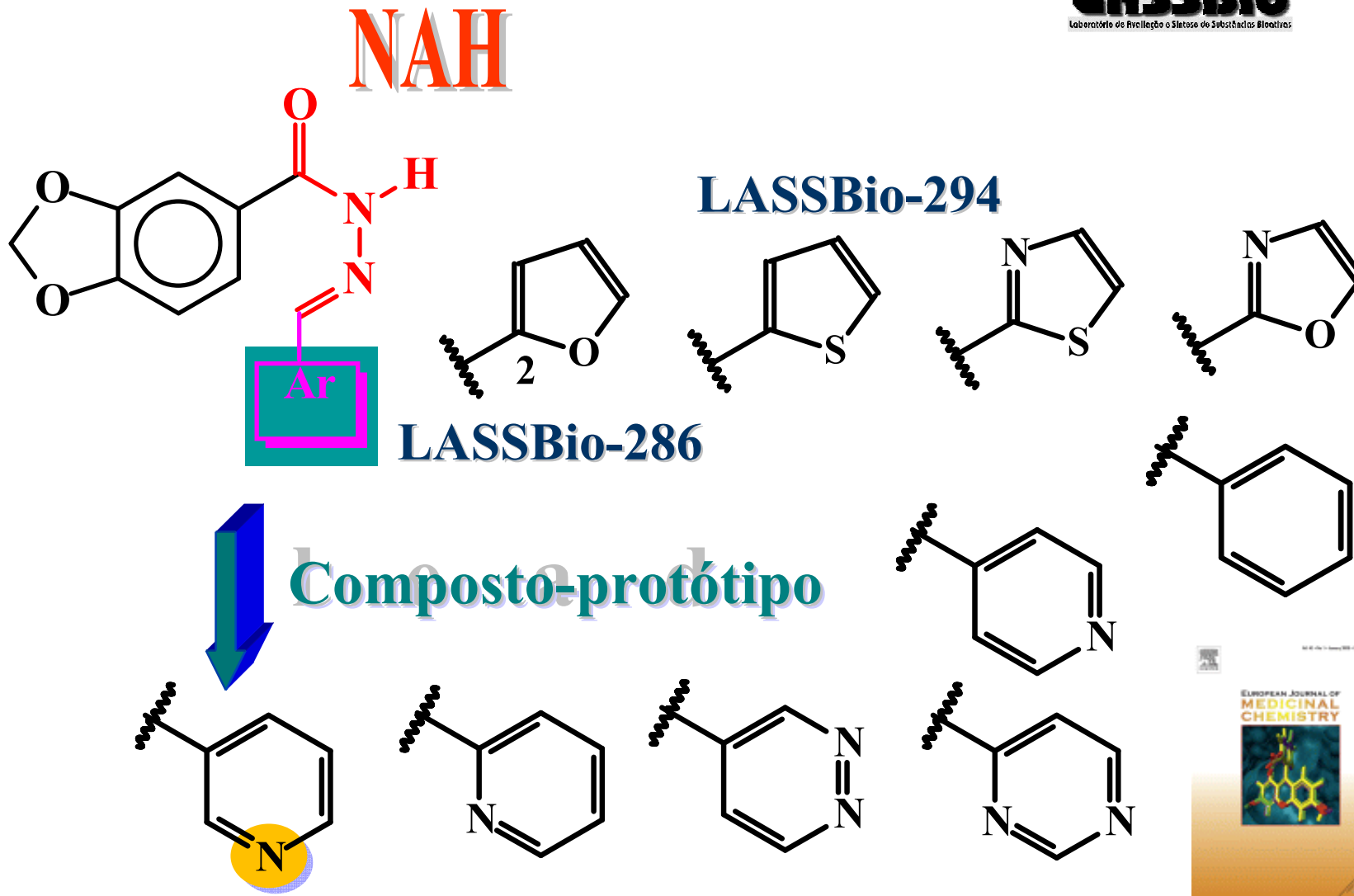


Similaridade molecular





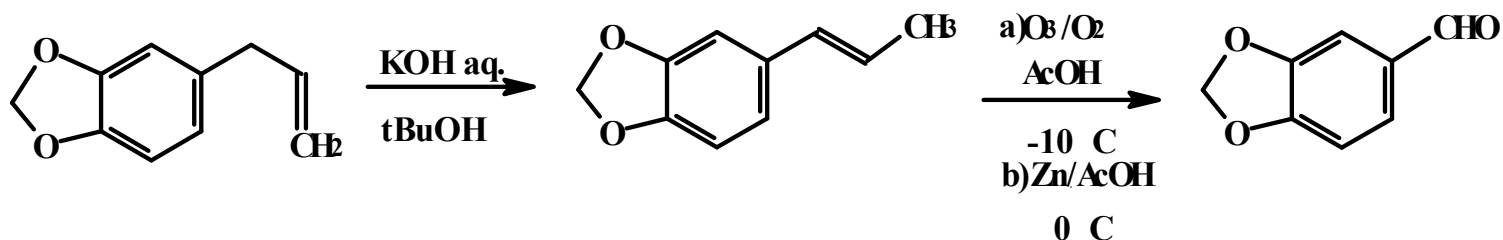
Similaridade molecular



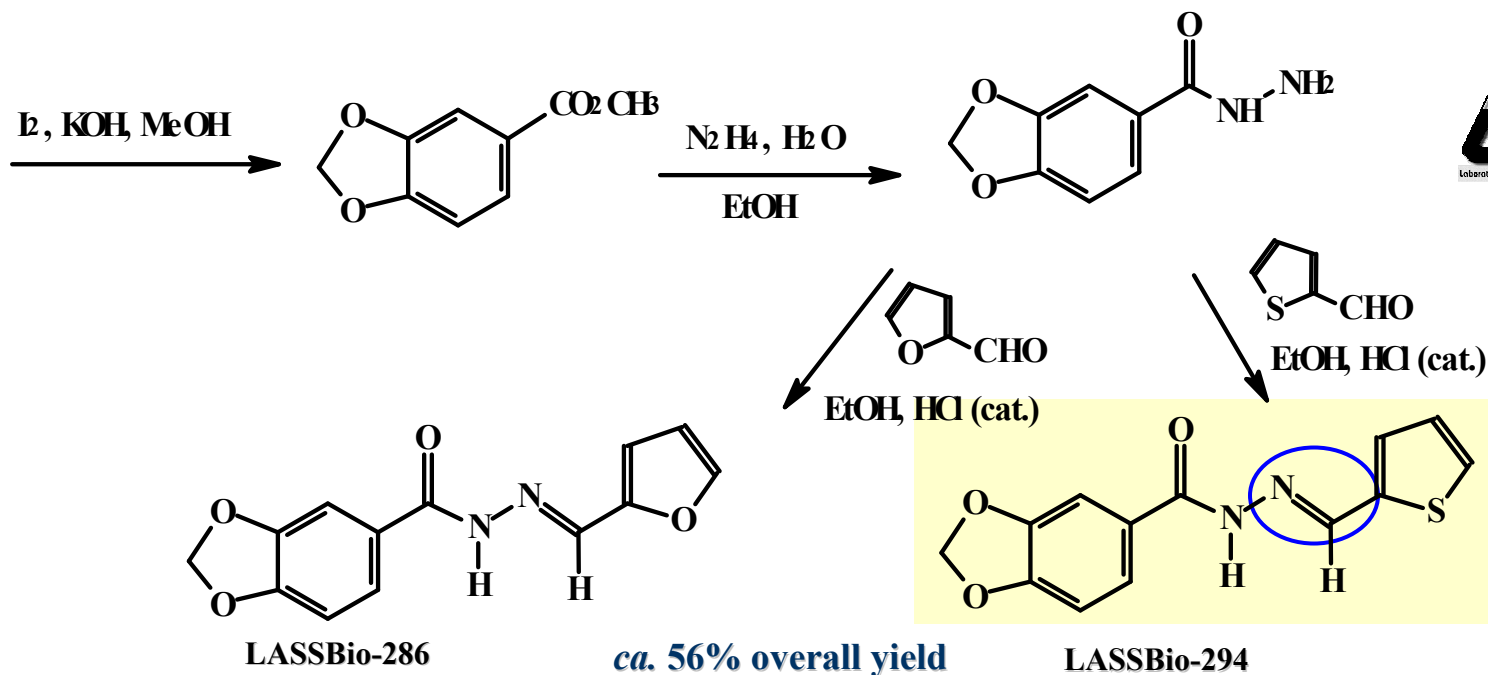
P. C. Lima, L. M. Lima, K. C. M. da Silva, P. H. O. Léda, A. L. P. Miranda, C. A. M. Fraga & E. J. Barreiro, "Synthesis and Non-addictive Analgesic Activity of Novel *N*-acylarylhydrazones and Isosters, Derived from Natural Safrole", *Eur. J. Med. Chem.*, **35**, 187



Síntese do LASSBio-294



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



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

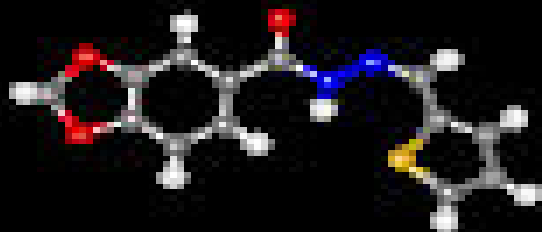


Propriedades estruturais

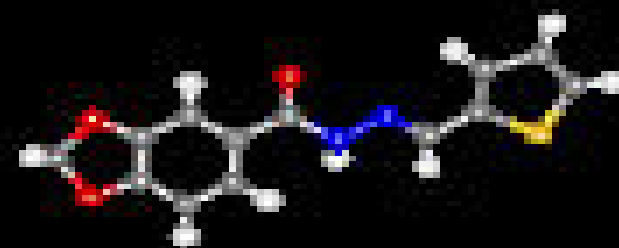
NMR ^1H / ^{13}C

MS

raios-X



Z-isomêro



E-isomêro

NAH

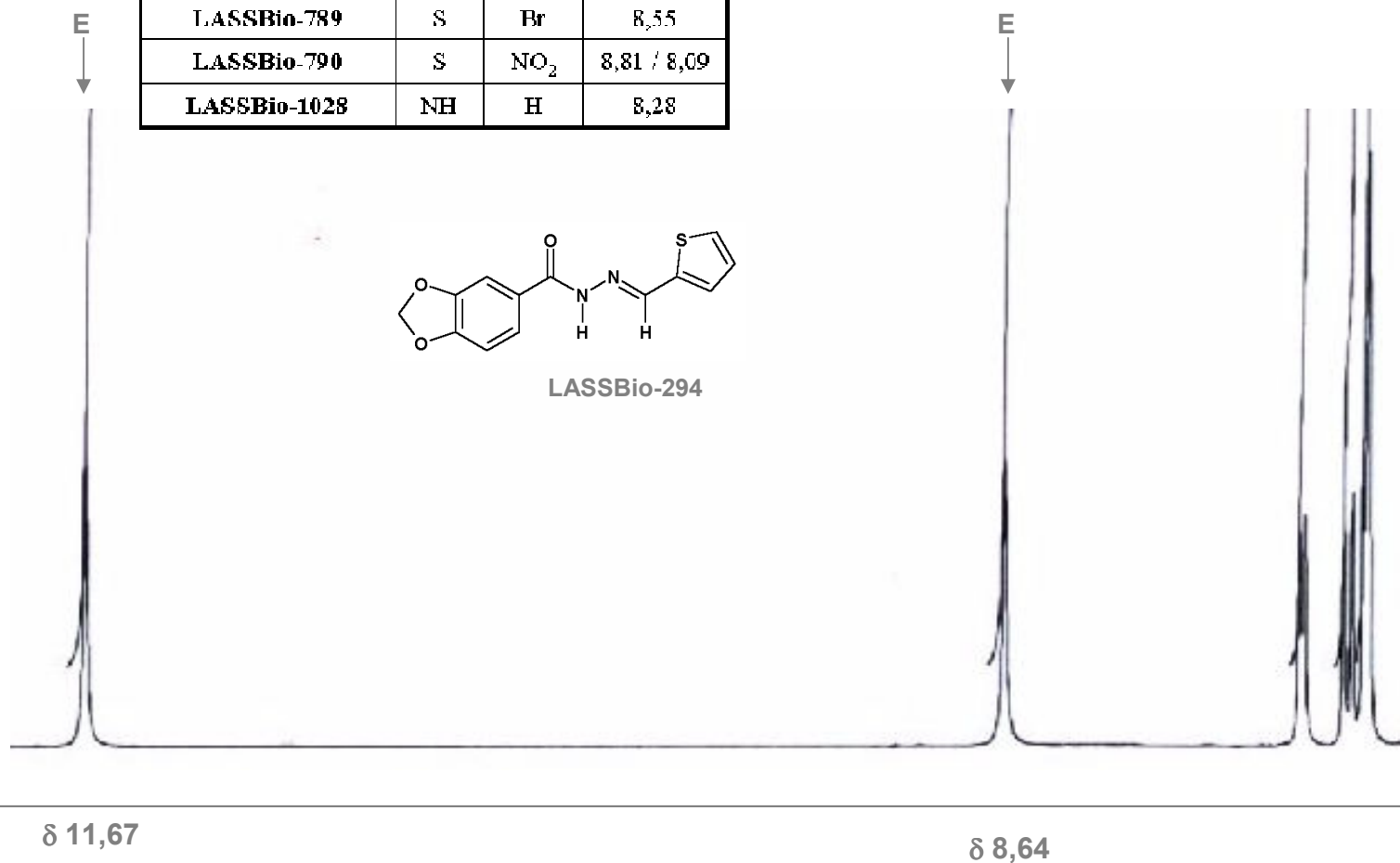


M. R. L. Santos, M. G. de Carvalho, R. Bráz-Filho, E. J. Barreiro, " ^1H and ^{13}C of New Bioactive Isochromanylactylaryldiazone Derivatives", *Magn. Reson. Chem.* 1998, 36, 533.

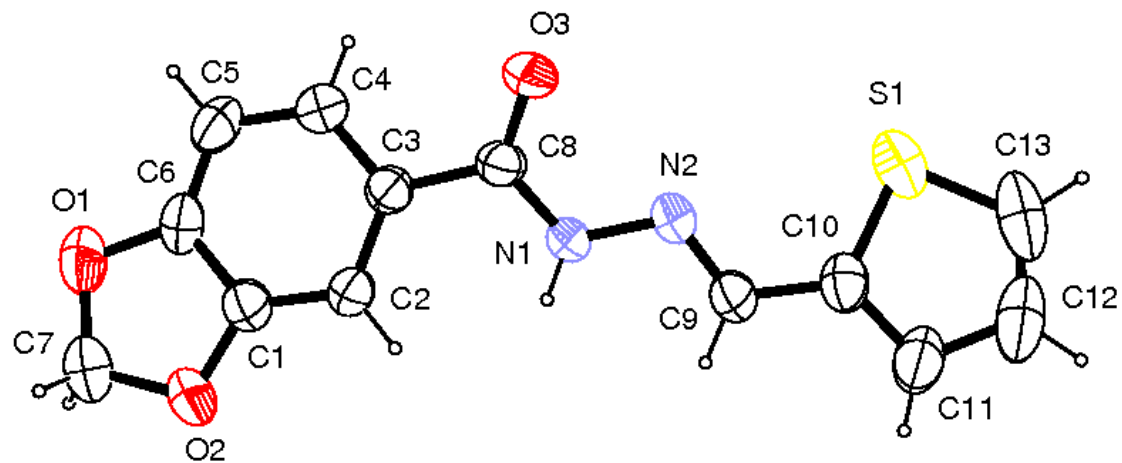
L. F. C. C. Leite, E. J. Barreiro, M. N. Ramos, J. B. P. da Silva, S. L. Galdino & I. R. Pitta, "Electron Impact Mass Spectrometry of Some 3-[3-(4-aryl)-1,2,4-oxadiazole-5-yl] acyl arylaldehyde Hydrazone derivatives", *Spectroscopy* 2000, 14, 115.



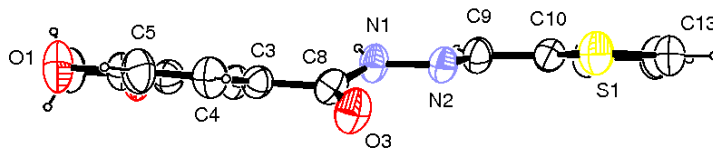
Composto	X	R	δ^1H
LASSBio-129	O	II	8,32
LASSBio-294	S	H	8,64
LASSBio-787	S	CH ₃	8,58
LASSBio-789	S	Br	8,55
LASSBio-790	S	NO ₂	8,81 / 8,09
LASSBio-1028	NH	H	8,28



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



LASSBio-294

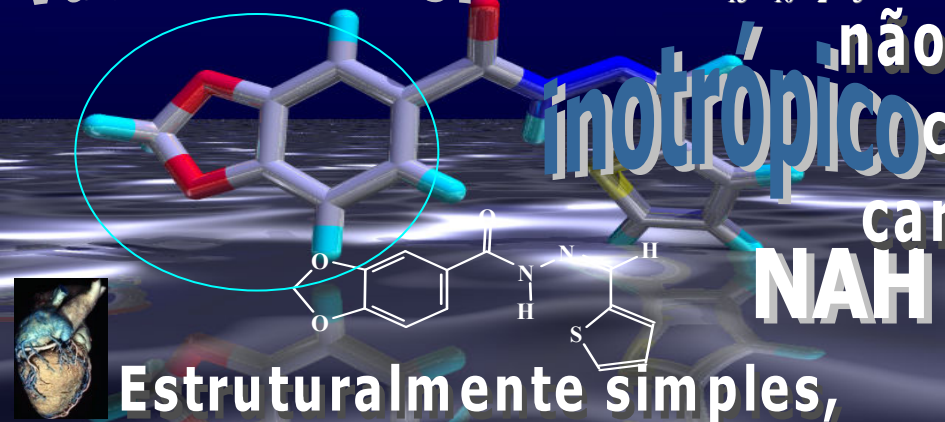




Novo Protótipo de Fármaco Cardioativo

LASSBio-294

vasodilatador

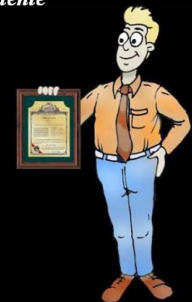


Estruturalmente simples,
 sinteticamente acessível
 em ótimos rendimentos,
 através de metodologia
 clássica, escalonada (1,0 M),
 a partir de produto natural
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 Ativo por via oral;
 Sem toxicidade aguda,
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Patente



“Thienylhydrazon with digitalis-like properties (positive inotropic effects) - **Patente 07091238 (USPTO), 15 de agosto de 2006;**

WO 2000-078754 (65 países) .

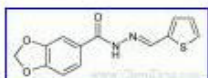




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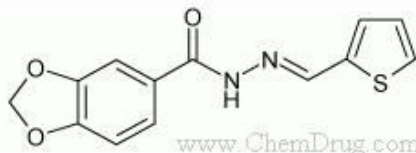
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【药物名称】 L-294, LASSBio-294

【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-Amidinoj
Zonampanel, YM-872,21024 SB-221284,196965-14-7,5-(0

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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-mett
IUPAC Name: (1R,,6R)-6-[(2- Oprea1_406105
IUPAC Name: 6-hydroxy-1-(2- ZINC00081150
STOCK2S-20570,ZINC00266 ZINC00214910
ZINC00230690 Oprea1_042214,CBDivE_01

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

A. L. Hopkins & A. Polinsky

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Editor in Chief: ANTHONY WOOD



Knowledge and Intelligence in Drug Design,

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

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

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



O perfil da pesquisa científica...



Galileo, Newton, Darwin, & Einstein

...contemporânea!



O físico Crick & biólogo Watson

J. D. Watson & F. H. C. Crick,
Nature 1953, **171**, 737-738



Sequenciamento do genoma humano

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The Sequence of the Human Genome

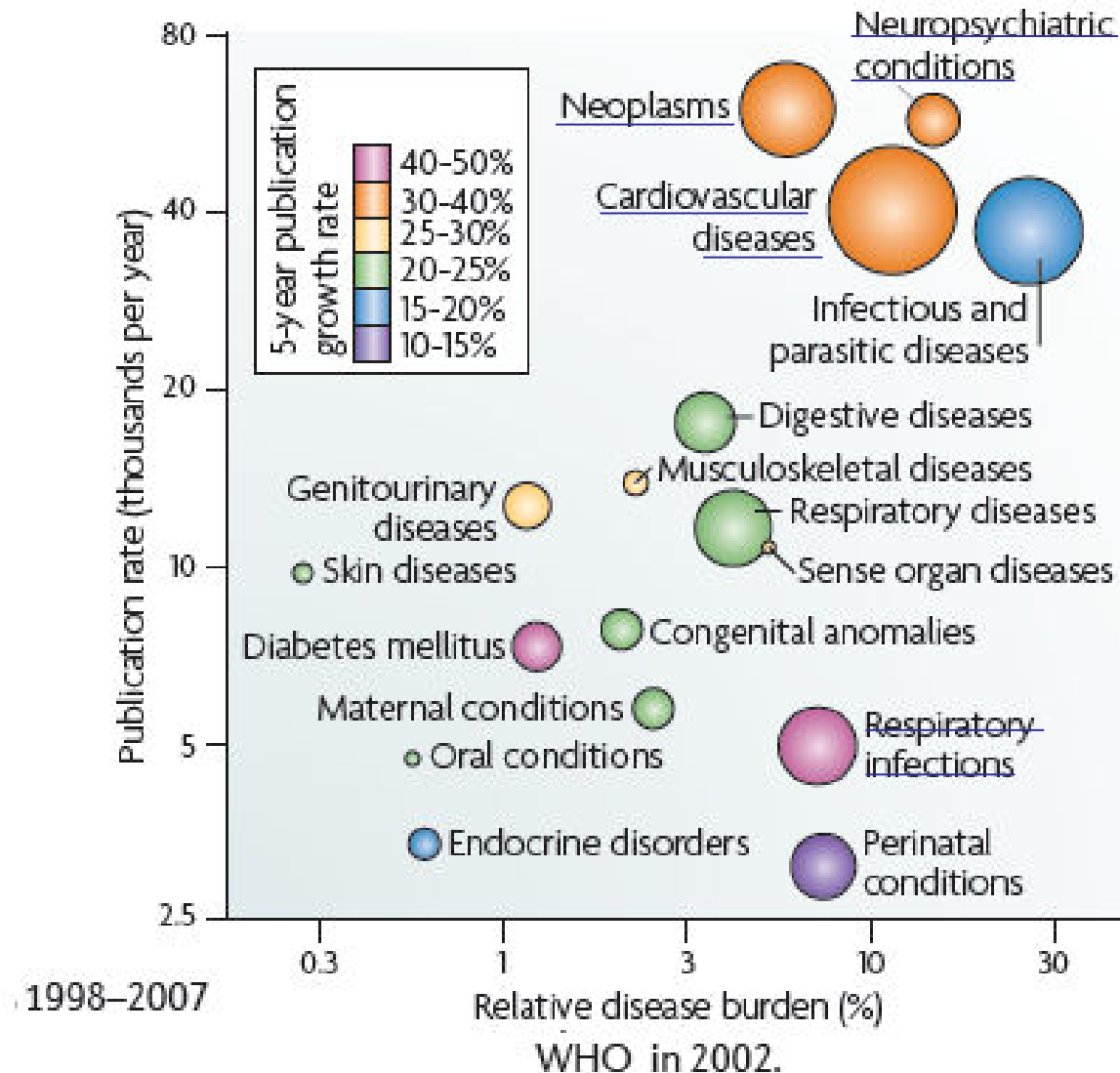
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Science 2001 291, 1304-1351 [DOI: 10.1126/science.1058040]



Rate of scientific publication versus relative disease burden for key therapeutic areas.



P Agarwal & DB Searls, Can literature analysis identify innovation drivers in drug discovery?, Nature Rev. Drug Discov. 2010, 9, 865.



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sem participação IF?**

**Atrofia da atividade
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29 de abril de 2008

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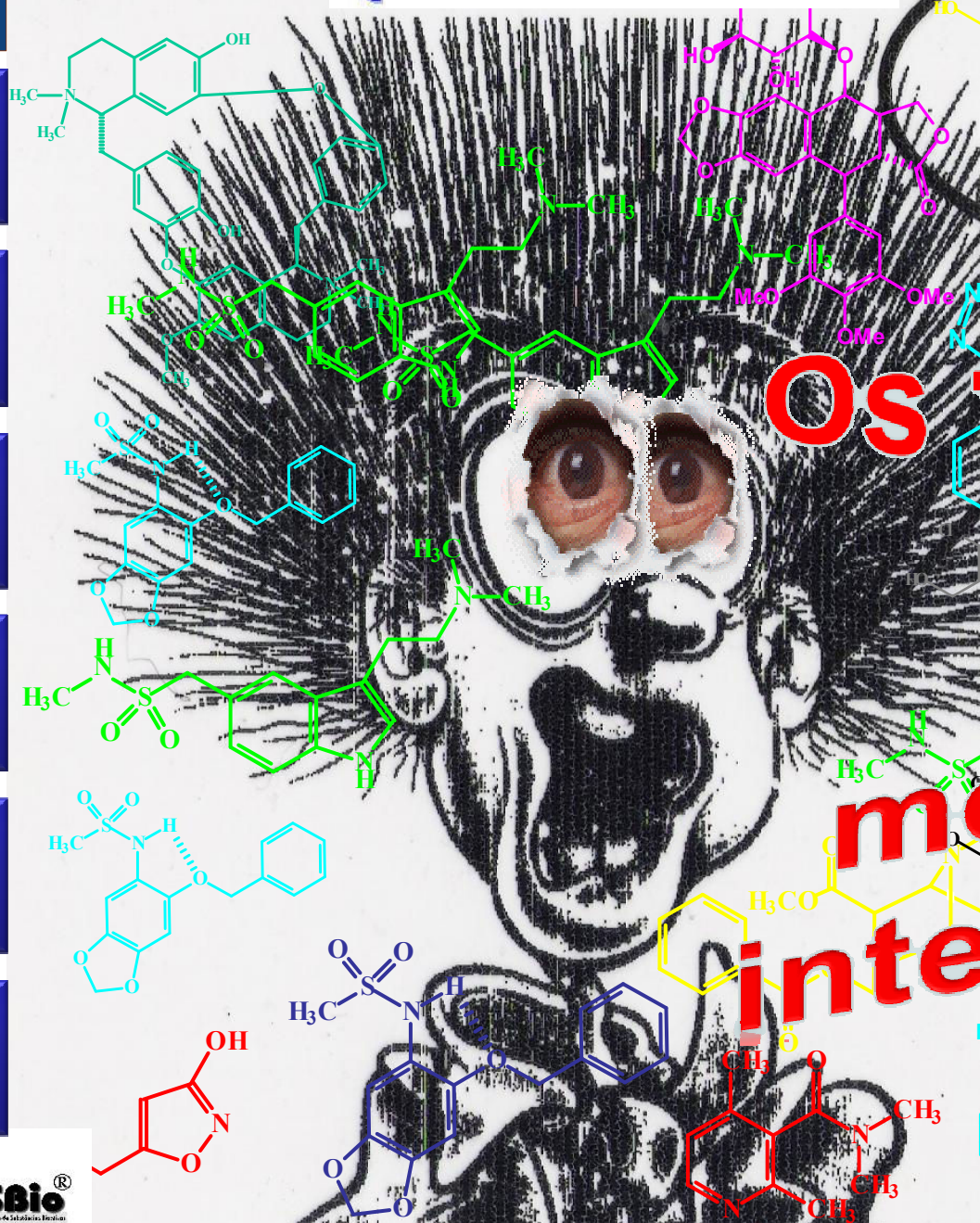
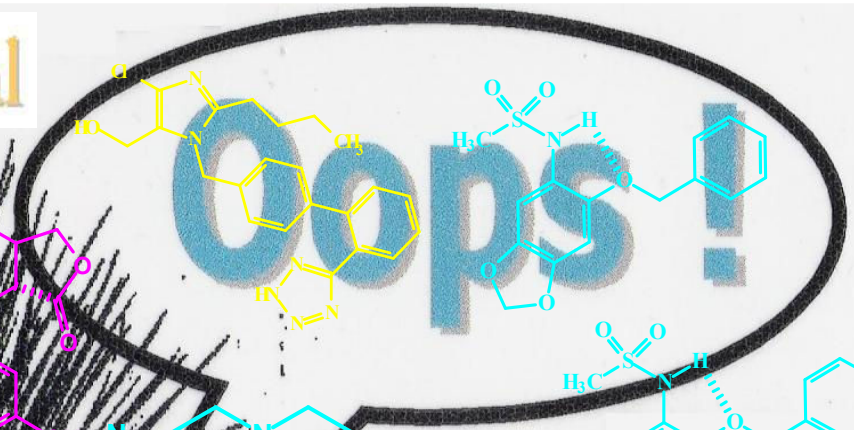
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Eliezer J. Barreiro; 4/3/2010



Química Medicinal



Os fármacos =

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Volume 1, Número 1, Janeiro-Março 2009

Química Medicinal

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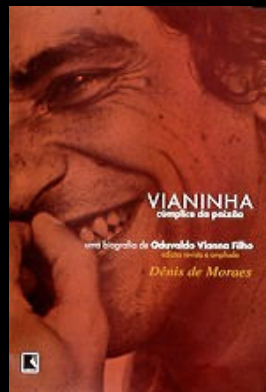


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“...Para achar água é preciso
descer terra adentro,
encharcar-se no lodo.

Mas há os que preferem
olhar os céus,
e esperar pelas chuvas...”

Oduvaldo Vianna Filho



(em “Cúmplice da Paixão”, Dênis de Moraes
Ed. Nórdica, RJ, 1990; Ed. Record, RJ, 2001).



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