Universidade Federal do Rio de Janeiro

Programa de Seminários

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

[0] [1] [11] [2] [3] [4] [5] [581] [6] [acylhydrazone]
[acylhydrazone derivatives]
[allyl] [anti] [farmacológica de novos derivados] [inflamatórios] [inibidores seletivos de pghs]
[pyridine derivatives] [structures of pyrazole derivatives] [synthesis and analgesic properties]
[synthesis and anti]
[synthesis and pharmacological evaluation]
[synthesized from natural safrole] [síntese e avaliação farmacológica]

2012

Pot-pourri de QuimMed

Eliezer J. Barreiro

Professor Titular

Universidade Federal do Rio de Janeiro

Laboratório de Avaliação e Síntese de Substâncias Bioativas

http://www.farmacia.ufrj.br/lassbio

Instituto Nacional de Ciência e Tecnologia de Fármacos e Medicamentos – INCT-INOFAR

Programa de Desenvolvimento de Fármacos - ICB

Química Medicinal

THE ROLE OF THE MEDICINAL CHEMIST IN DRUG DISCOVERY — THEN AND NOW

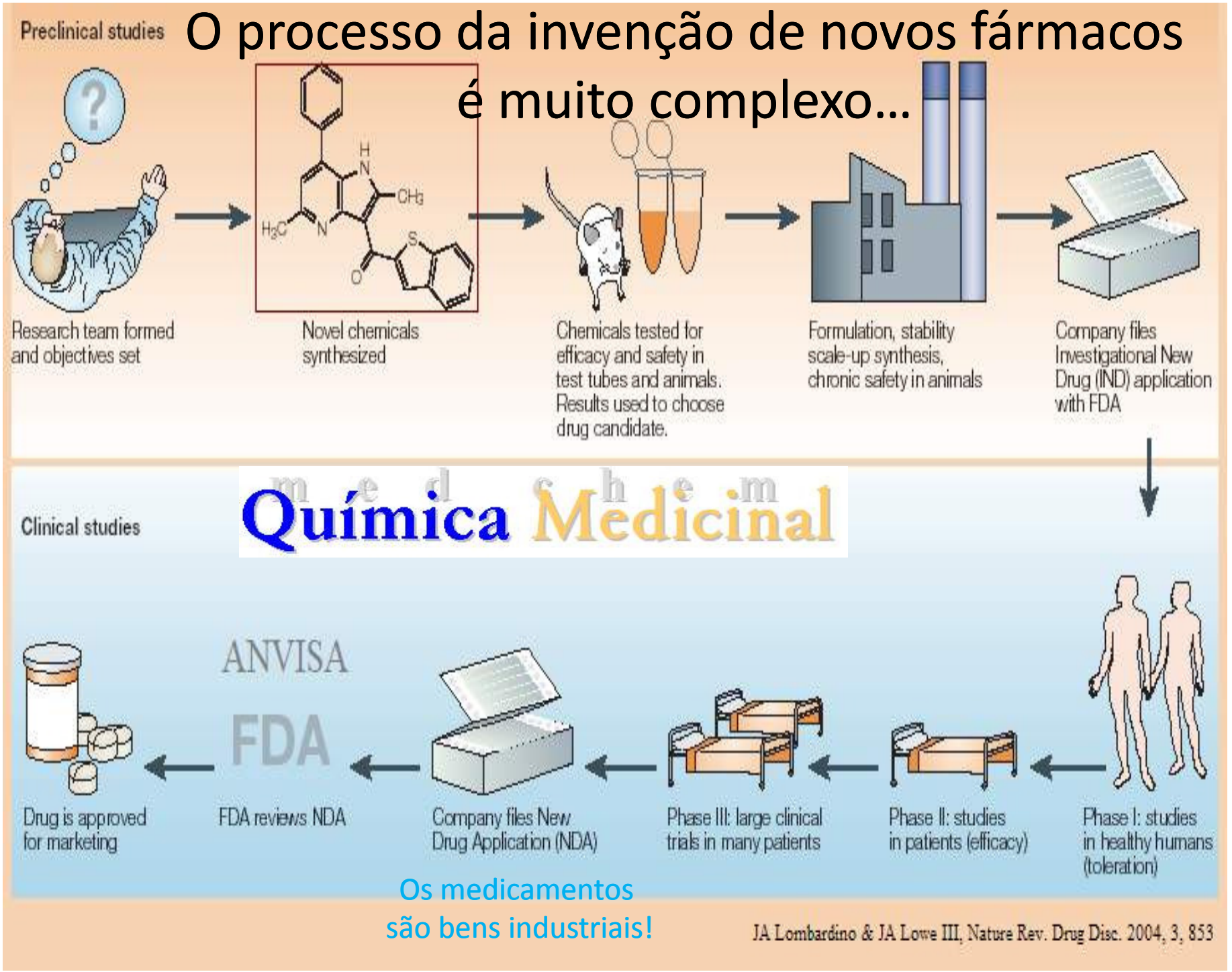
Joseph G. Lombardino and John A. Lowe III‡*

Pfizer

" ...medicinal chemists today live in exciting times... their work can have a beneficial effect on millions of suffering patients – surely an important motivating factor for any scientist..."

The Role of the Medicinal Chemist in Drug Discovery – Then and Now, *Nature Rev. Drug Disc.* **2004**, *3*, 853.

O processo da invenção de novos fármacos é muito complexo...



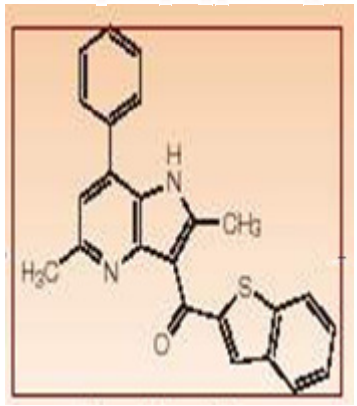
Química Medicinal

idéia

" Success isn't about finding the best idea.
It's about doing something with it. "

Abstração

materialização



Método Científico

Criatividade

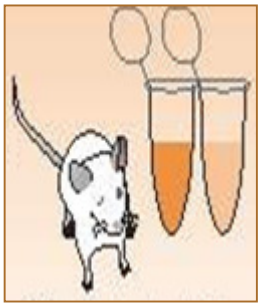
H

C

N O F

S Cl

Intuição

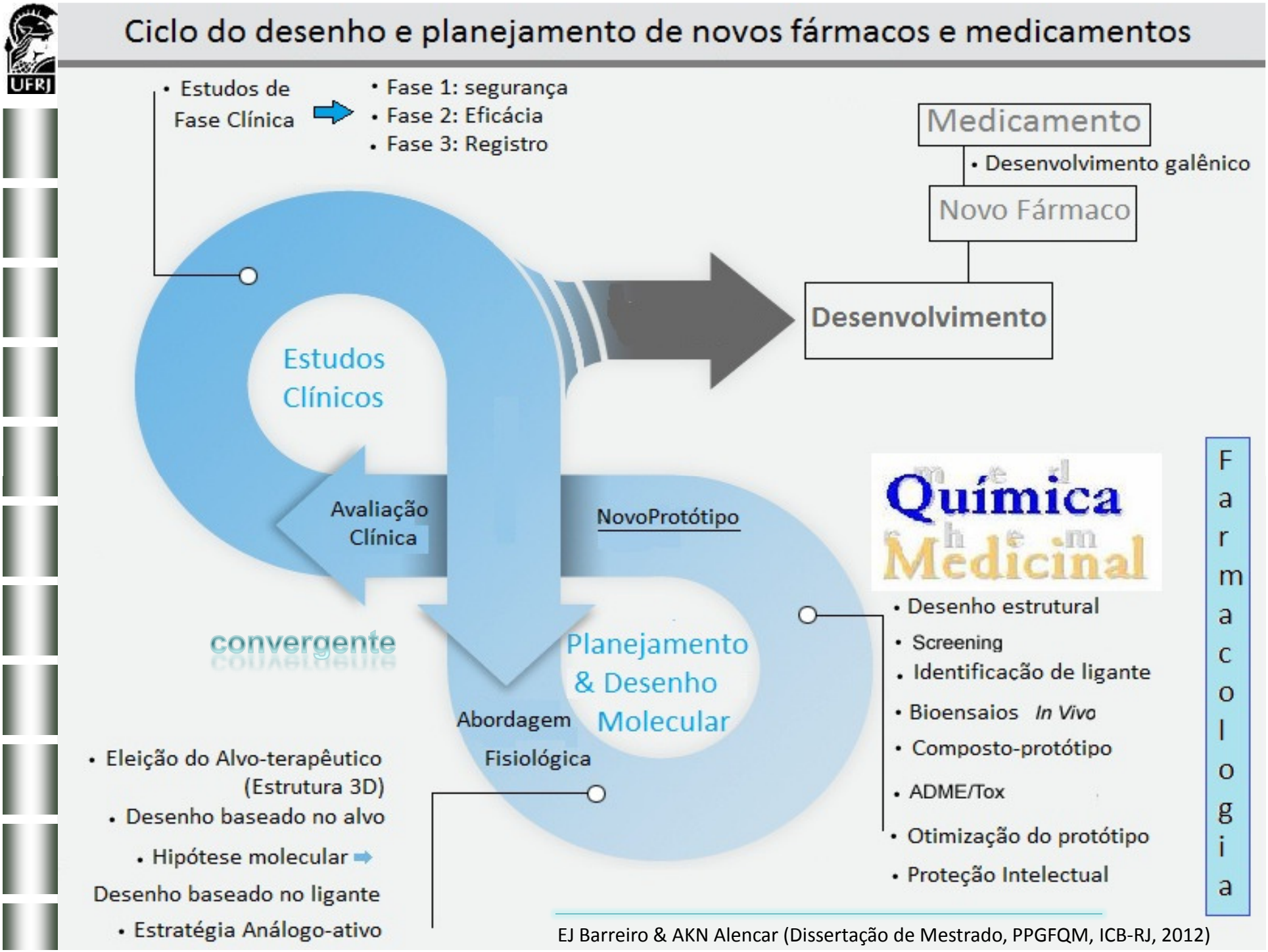


idéias inovadoras

acerto

comprometimento

Ciclo do desenho e planejamento de novos fármacos e medicamentos



EJ Barreiro & AKN Alencar (Dissertação de Mestrado, PPGFQM, ICB-RJ, 2012)


O sonho do Químico Medicinal

Conceito de composto-protótipo

É a primeira substância de uma série congênere – *i.e.* estruturalmente relacionada – que apresentou perfil terapêutico adequado – *i.e.* ativo em modelos farmacológicos validados *in vivo* - que pode ser subsequentemente otimizado por modificações moleculares racionais.

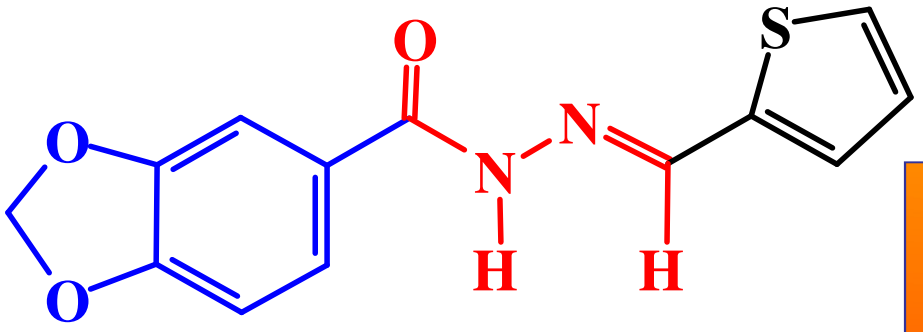
A Química Medicinal e o paradigma do composto-protótipo

E. J. Barreiro *Rev. Virtual Quim.*, **2009**, 1 (1), 18-26.

http://www.uff.br/rvq

Novo Protótipo de Fármaco Cardioativo

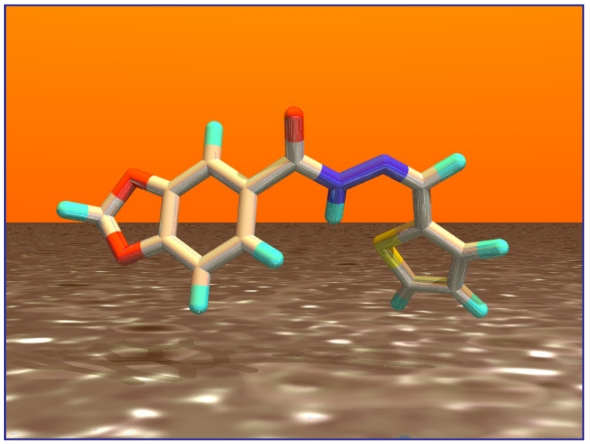
Simplificação molecular



$C_{13}H_{10}N_2O_3S$

MW 274

LASSBio-294



Patente obtida

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,328	Aug. 15, 2006	7,091,238	32360-178943	9681

26694 7590

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

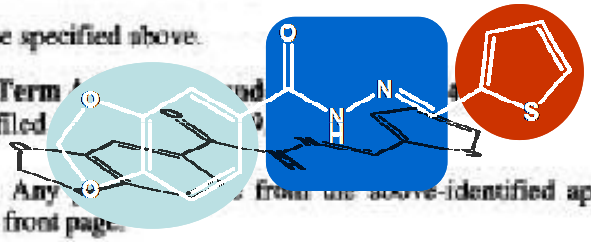
Thienylhydrazone with Digitalis-like properties (positive inotropic effects)

LASSBio-294

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term A[illegible]od
(application filed [illegible]



The Patent Term Adjustment is 109 day(s). Any [illegible] from the above-identified application include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date determines Patent Term Adjustment is the filing date of the most recent CPA.

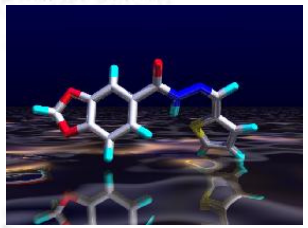
Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571) 272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at (703) 305-8283.

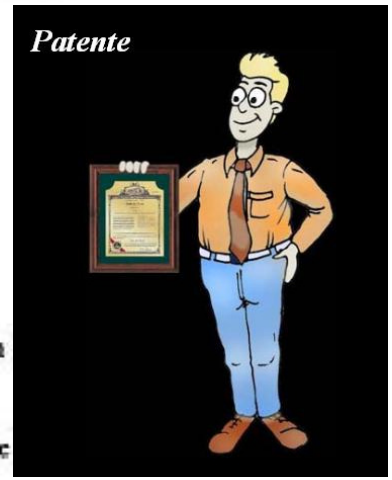
Roberto Takashi Sudo, Rio de Janeiro, BRAZIL;
Edson X. Albuquerque, Baltimore, MD;
Eliezer J. Barreiro, Rio de Janeiro, MD;
Carlos Alberto Manssour Fraga, Rio de Janeiro, BRAZIL;
Ana Luiza Palhares De Miranda, Petropolis, BRAZIL;

Thienylhydrazone with Digitalis-like properties (positive inotropic effects)

RECEIVED
JUL 31 2006
VENABLE IP DOCKETING DEPARTMENT

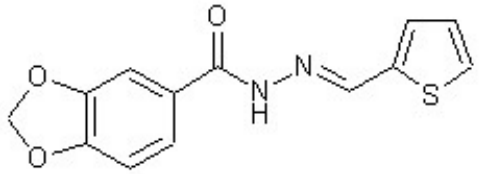


B100 (Rev. 12/04) **WO 00/78754 A1**

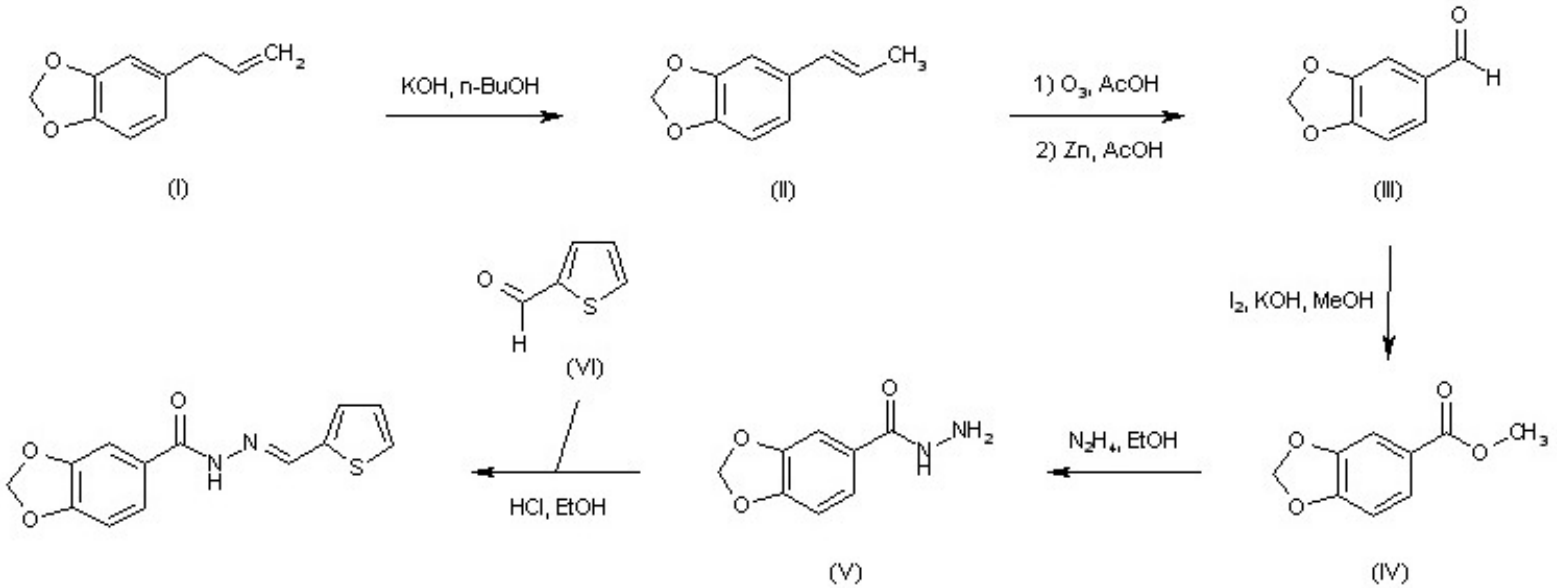


【药物名称】L-294, LASSBio-294

化学结构式(Chemical Structure):



参考文献No.	52092
标题:	Thienylhydrazon with digitalis-like properties (positive inotropic effects)
作者:	Sudo, R.T.; Alburquerque, E.X.; De Barreiro, E.J.
来源:	WO 0078754



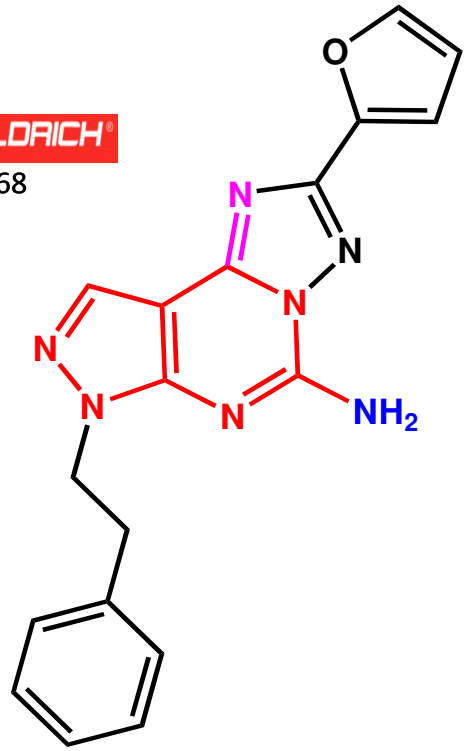
合成路线图解说明:

Isosafrole (II) was obtained by isomerization of safrole (I) under basic conditions. Ozonolysis of (II), followed by reductive decomposition of the intermediate ozonide with Zn, furnished piperonal (III). Oxidation of aldehyde (III) with methanolic iodine produced the methyl ester (IV), which was converted to the corresponding hydrazide (V) upon treatment with hydrazine in refluxing EtOH. Finally, condensation of (V) with thiophene-2-carboxaldehyde (VI) yielded the title hydrazone.

Similaridade molecular & mecanismo de ação

SIGMA-ALDRICH®

S4568



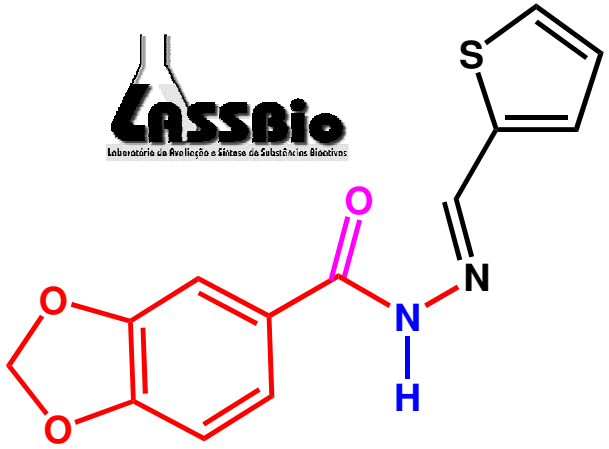
SCH-58261

Antagonista competitivo de A2A
Ki = 1,3 nM

7-(2-phenylethyl)-5-amino-2-(2-furyl)-pyr
[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine

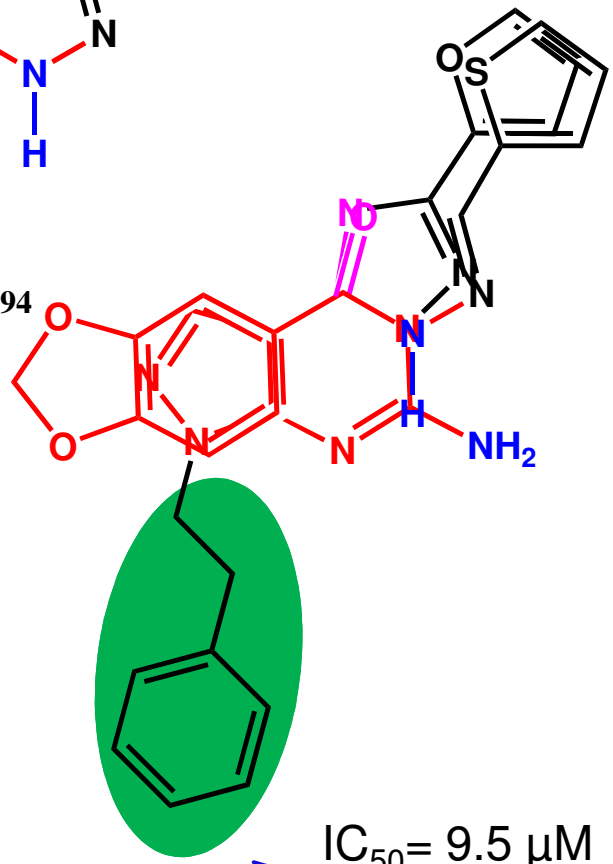
LASSBio-294
E
LASSBio-897

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas



LASSBio-294

1999



Cerep

101
Alvos Moleculares

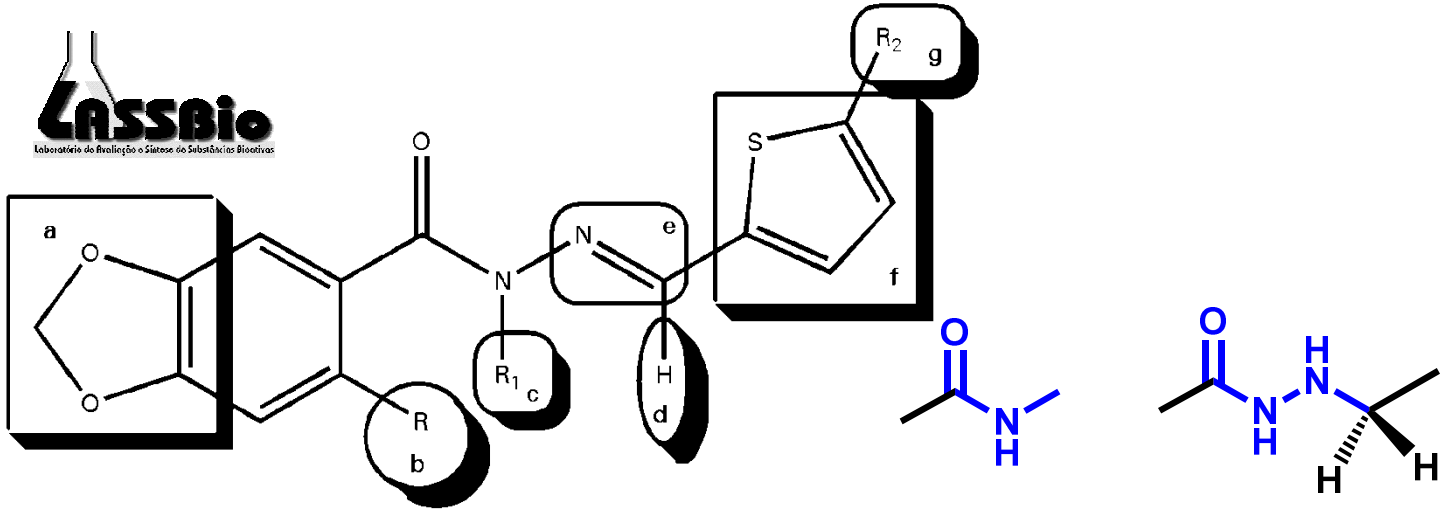
Receptores de Adenosina A_{2A}

2009

IC_{50}= 9.5 µM

IC_{50}= 4.6 µM

Estudos de otimização do protótipo



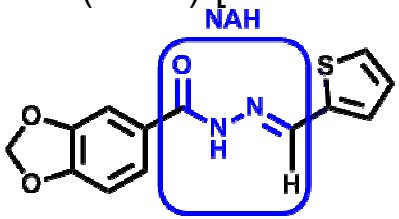
a= Introdução de grupos com diferente perfil de contribuição estereoeletrônica;
b= Substituinte R na posição 6 do anel benzodioxola- efeitos estereoeletrônicos;
c= Alquilação do grupamento farmacofórico- Modificação da habilidade como doador de ligação de H, Alterações conformacionais;
d= Introdução de substtuintes alquila- Efeitos estéricos e/ou conformacionais;
e= Redução da dupla ligação imínica- Modificações da extensão de conjugação do grupamento farmacofórico; aumento da liberdade conformacional;
f= Troca do anel tiofeno por núcleos isostéricos om diferentes contribuições eletrônicas;
g= Introdução de grupos com diferente perfil de contribuição estereoeletrônica.

Dissecação molecular;

Preservar o grupamento farmacofórico (GrF);

1. RT Sudo, G Zapata-Sudo, EJ Barreiro, The new compound, LASSBio 294, increases the contractility of intact and saponin-skinned cardiac muscle from Wistar rats, *Br. J. Pharmacol*., **134**, 603-613 (2001) (Times Cited: 14)
2. H Gonzalez-Serratos *et al*., A novel thienylhydrazone, (2-thienylidene)3,4-methylenedioxybenzoylhydrazine, increases inotropism and decreases fatigue of skeletal muscle, *J. Pharmacol. Exp. Ther*., **299**, 558-566 (2001) (Times Cited: 13)
3. CLM Silva, F Noel, EJ Barreiro, Cyclic GMP-dependent vasodilatory properties of LASSBio 294 in rat aorta, *Br. J. Pharmacol*., **135**, 293-298 (2002) (Times Cited: 16)
4. EJ Barreiro, Strategy of molecular simplification in rational drug design: The discovery of a new cardioactive agent, *Quim. Nova*, **25**, 1172-1180 (2002) (Times Cited: 15)
5. G Zapata-Sudo *et a*l., Thienylhydrazone derivative increases sarcoplasmic reticulum Ca2+ release in mammalian skeletal muscle, *Eur. J. Pharmacol*., **470**, 79-85 (2003) [Times Cited: 3]
6. H Gonzalez-Serratos *et al.,* The thienylhydrazone, (2 '-thienylidene)3,4-methylenedioxvbenzoylhydrazine (LASSBio-294), develops fatigue resistance and has a positive inotropic effect in mammalian skeletal muscle, *Biophys. J*., **86**, 225A-225A Suppl. S (2004) [Times Cited: 0]
7. AG Silva, G Zapata-Sudo, AE Kummerle *et al*., Synthesis and vasodilatory activity of new *N*-acylhydrazone derivatives, designed as LASSBio-294 analogues, *Bioorg. Med. Chem*., **13**, 3431-3437 (2005) [Times Cited: 33]
8. AE Kummerle et al., Studies towards the identification of putative bioactive conformation of potent vasodilator arylidene *N*-acylhydrazone derivatives, *Eur. J. Med. Chem*., **44**, 4004-4009 (2009) [Times Cited: 14]

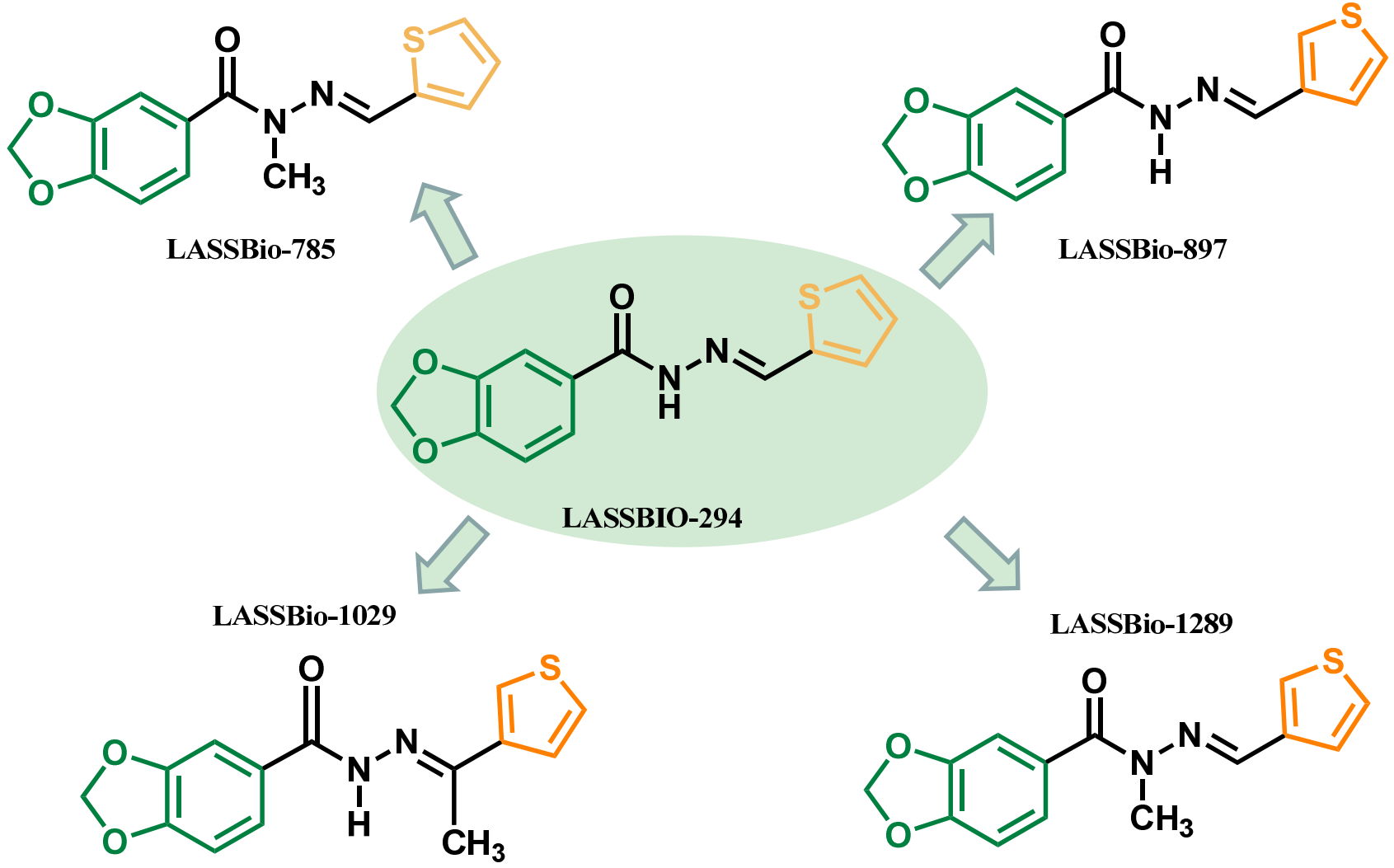
9. G Zapata-Sudo *et al*., Pharmacological Characterization of (3-Thienylidene)-3,4-Methylenedioxybenzoylhydrazide: A Novel Muscarinic Agonist With Antihypertensive Profile, *Am. J. Hypert.,* **23**, 135-141 (2010) [Times Cited: 1]
10. L Pol-Fachin *et al*., Characterization of the conformational ensemble from bioactive *N*-acylhydrazone derivatives, *J. Mol. Graph. Model.,* **28**, 446-454 (2010) [Times Cited: 0]
11. EO Carneiro *et al*., Structure-based prediction and biosynthesis of the major mammalian metabolite of the cardioactive prototype LASSBio-294, *Bioorg. Med. Chem. Lett.,* **20**, 3734-3736 (2010) [Times Cited: 3]
12. FCF Brito *et al* Novel thienylacylhydrazone derivatives inhibit platelet aggregation through cyclic nucleotides modulation and thromboxane A(2) synthesis inhibition, *Eur. J. Pharmacol*., **638** , 5-12 (2010) [Times Cited: 3]
13. AE Kummerle *et al*., LASSBio-294, A Compound With Inotropic and Lusitropic Activity, Decreases Cardiac Remodeling and Impro, oves Ca2+ Influx Into Sarcoplasmic Reticulum After Myocardial Infarction, *Am. J. Hypert*., **23**, 1220-1227 (2010) [Times Cited: 2]
14. AGM Fraga, LL Silva, CAM Fraga, EJ Barreiro, 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) [Times Cited: 1]
15. RC Braga, ACB Tôrres, CB Persiano, RO Alves, CAM Fraga, EJ Barreiro, V Oliveira, Determination of the cardioactive prototype LASSBio-294 and its metabolites in dog plasma by LC–MS/MS: Application for a pharmacokinetic study, *J. Pharm. Biomed. Anal*., **55**, 1024–1030 (2011) [Times Cited: 1]



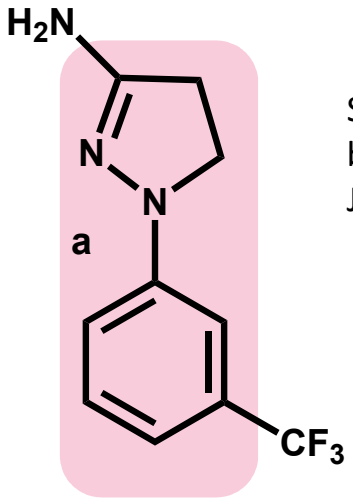
LASSBio

LO

LASSBio-785
LASSBio-897
LASSBio-1029
LASSBio-1289

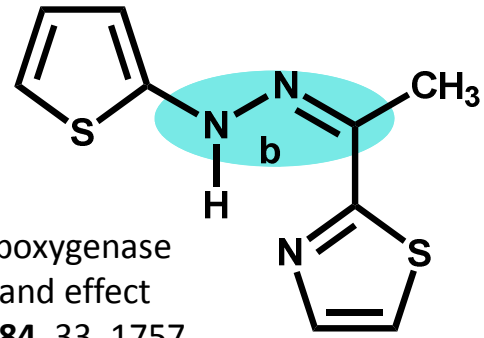

LASSBio-785
LASSBio-897
LASSBIO-294
LASSBio-1029
LASSBio-1289

Como chegamos às NAH?



BW-755c

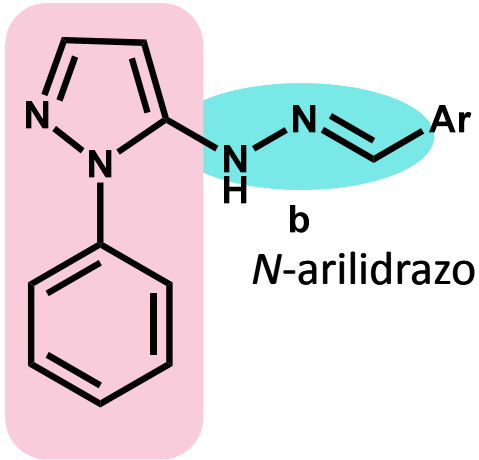
SP Janssens *et al*, Cyclooxygenase and lipoxygenase inhibition by BW-755C reduces acrolein smoke-induced acute lung injury, Journal of Applied Physiology **1994**, 77, 888



C Bertez *et al.*, Dual inhibition of cyclooxygenase and lipoxygenase by 2-acetylthiophene 2-thiazolylhydrazone (CBS-1108) and effect on leukocyte migration in vivo, *Biochem Pharmacol*. **1984**, 33, 1757

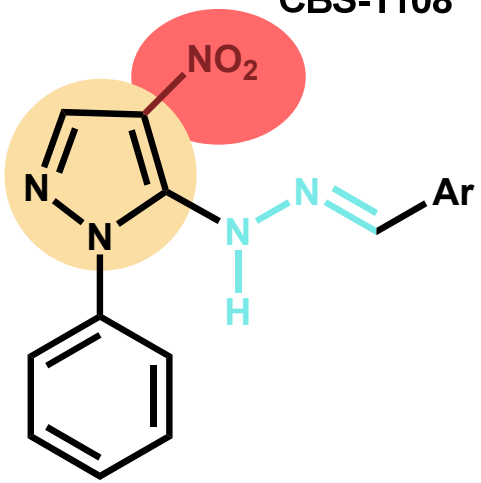
Hibridação molecular [a]

a + b

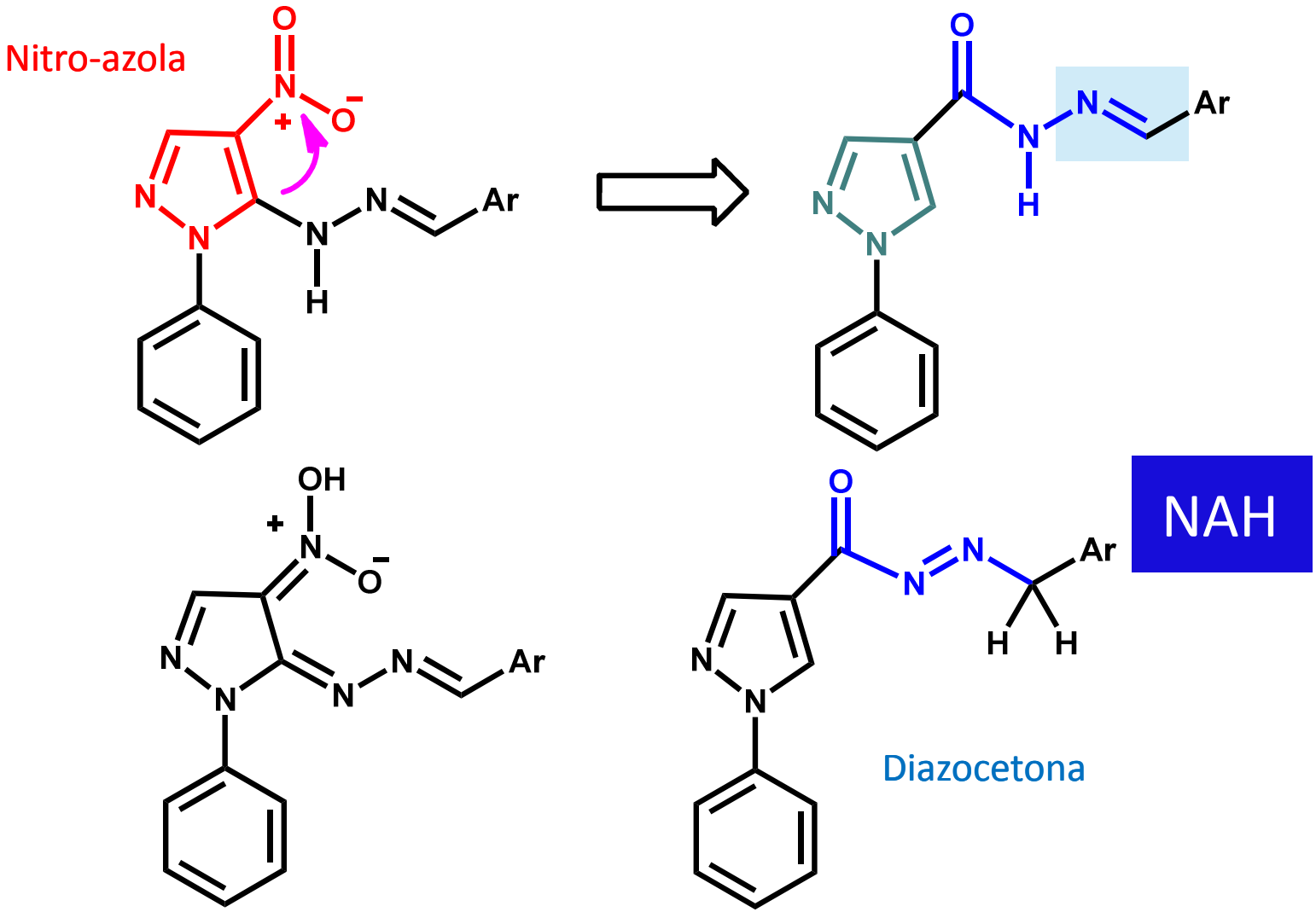


N-arilidrazona

CBS-1108

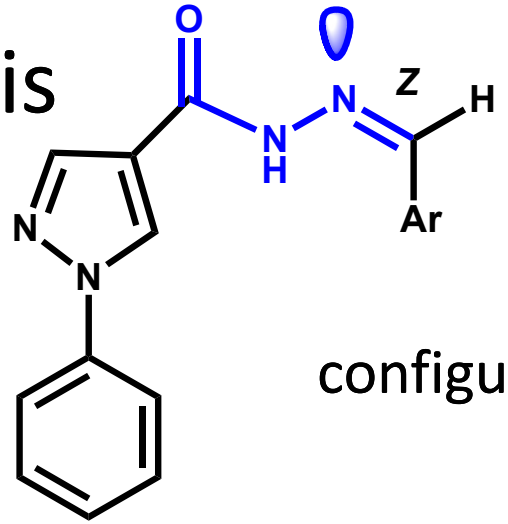


C Viegas-Jr, A Danuello, VS Bolzani, EJ Barreiro, CAM Fraga, Molecular hybridization: a useful tool in the design of new drug prototypes, *Curr. Med. Chem.* **2007**, *14*, 103 [46 citações]

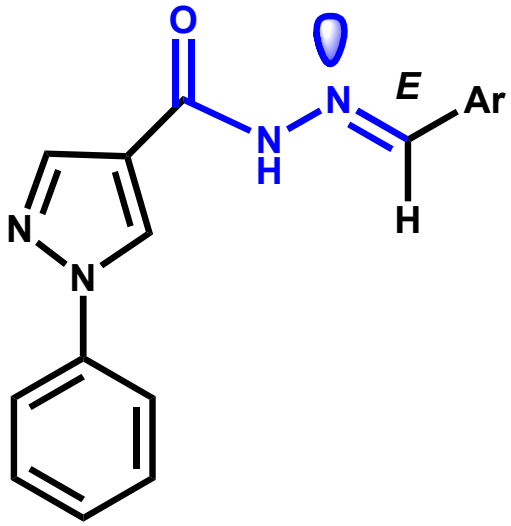


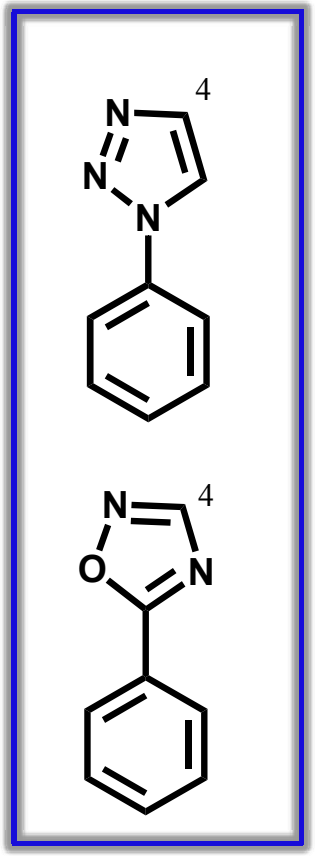
EJ Barreiro *et al.*, A química medicinal de *N*-acilidrazonas: novos compostos protótipos de fármacos analgésicos, antiinflamtórios e anti-trombóticos, Q*uim. Nova* **2002**, *25*, 129 [20 citações]

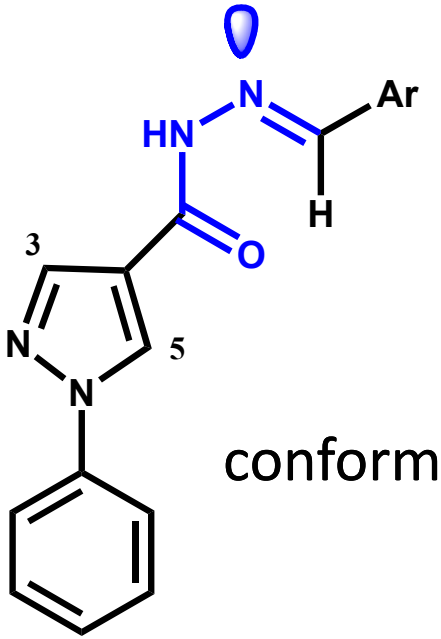
Propriedades estruturais



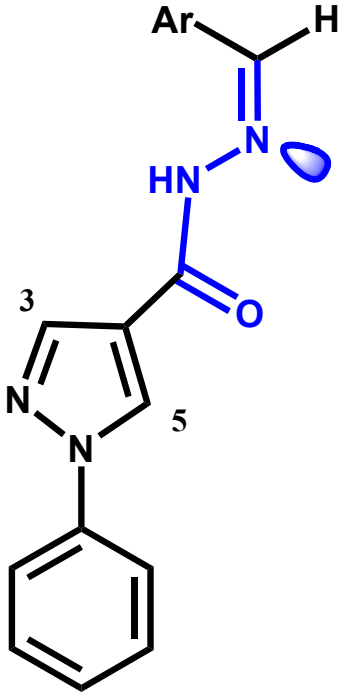
configuração







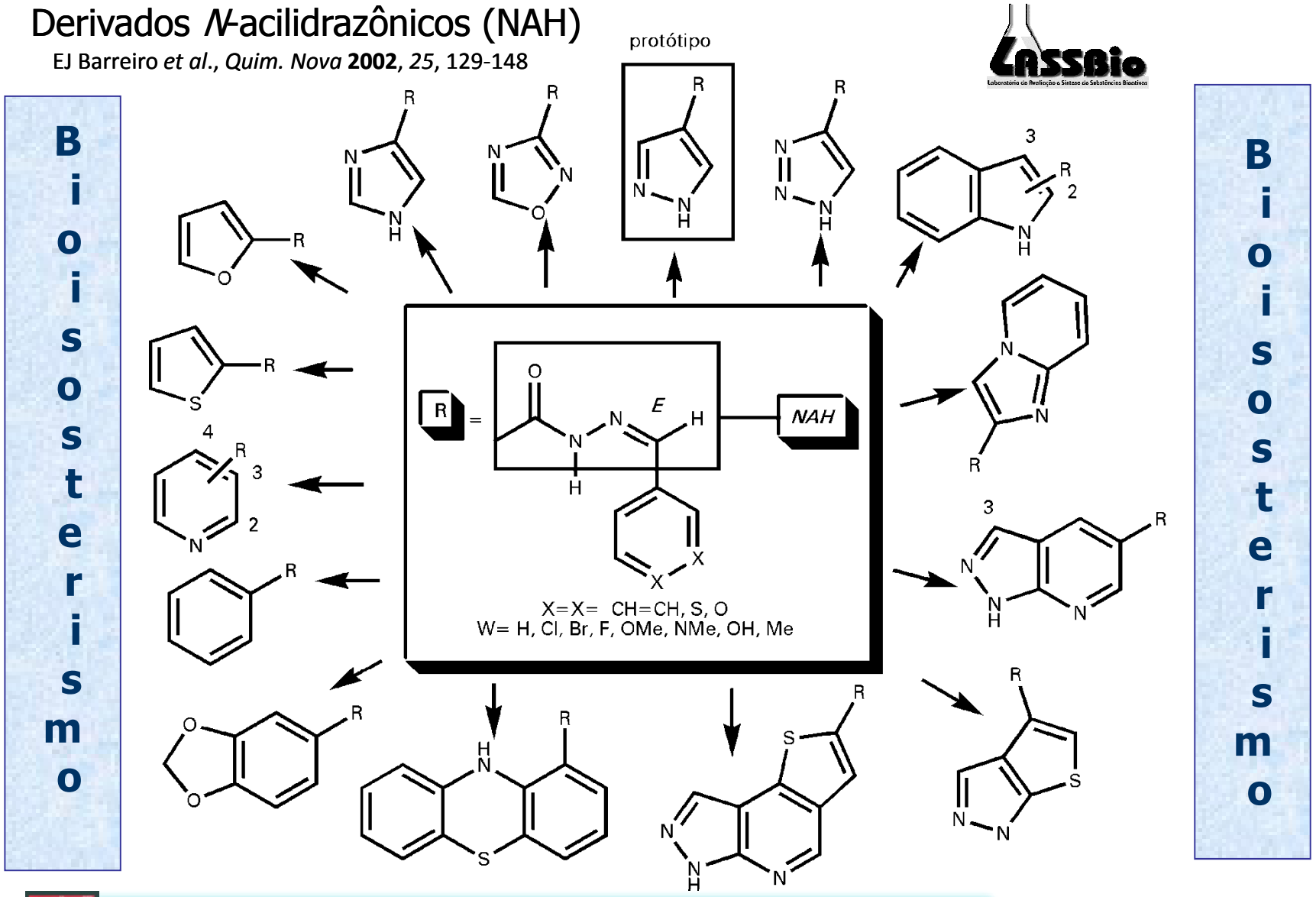
conformação

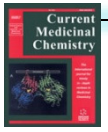


Bioisosterismo & quimiodiversidade

Derivados *N*-acilidrazônicos (NAH)

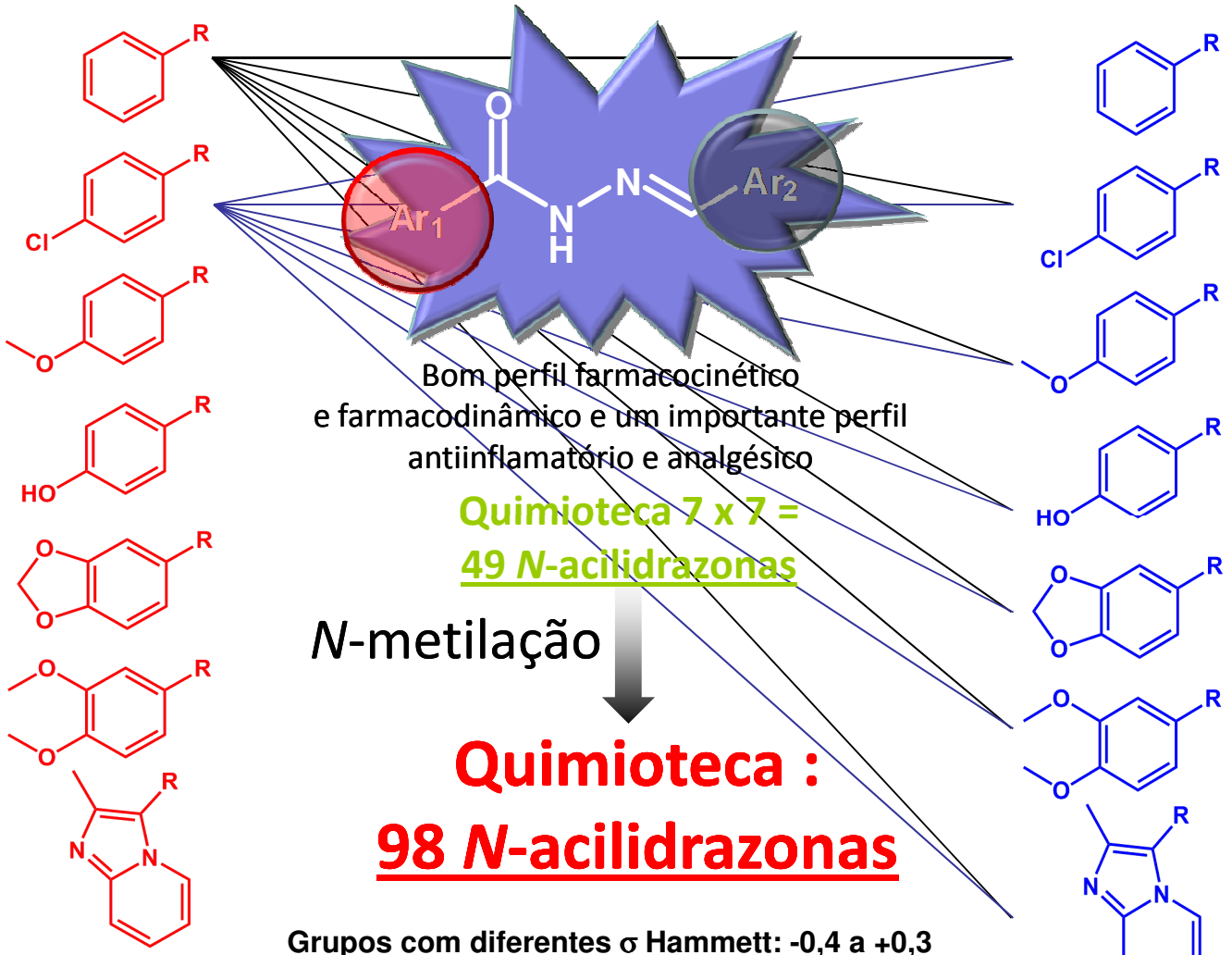
EJ Barreiro *et al.*, *Quim. Nova* **2002**, *25*, 129-148





LM Lima, EJ Barreiro, Bioisosterism: a useful strategy for molecular modification and drug design, *Curr. Med. Chem*. **2005**, *12*, 23 [161 citações]

Quimioteca “combinatória”de NAH



Bom perfil farmacocinético e farmacodinâmico e um importante perfil antiinflamatório e analgésico

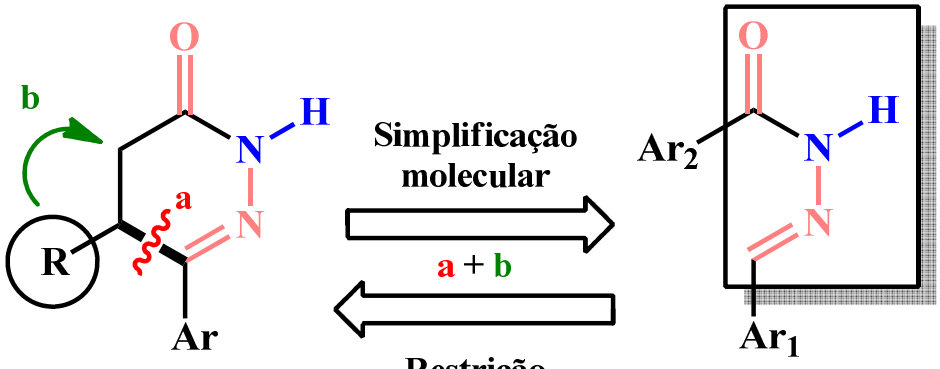
Quimioteca 7 x 7 = 49 *N*-acilidrazonas

N-metilação

Quimioteca : 98 *N*-acilidrazonas

Grupos com diferentes σ Hammett: -0,4 a +0,3
Refratividade molar: 25 a 39 cm^3/mol
Grupos aceptores ou doadores de ligação hidrogênio
Grupos com diferentes perfis de hidrofilicidade

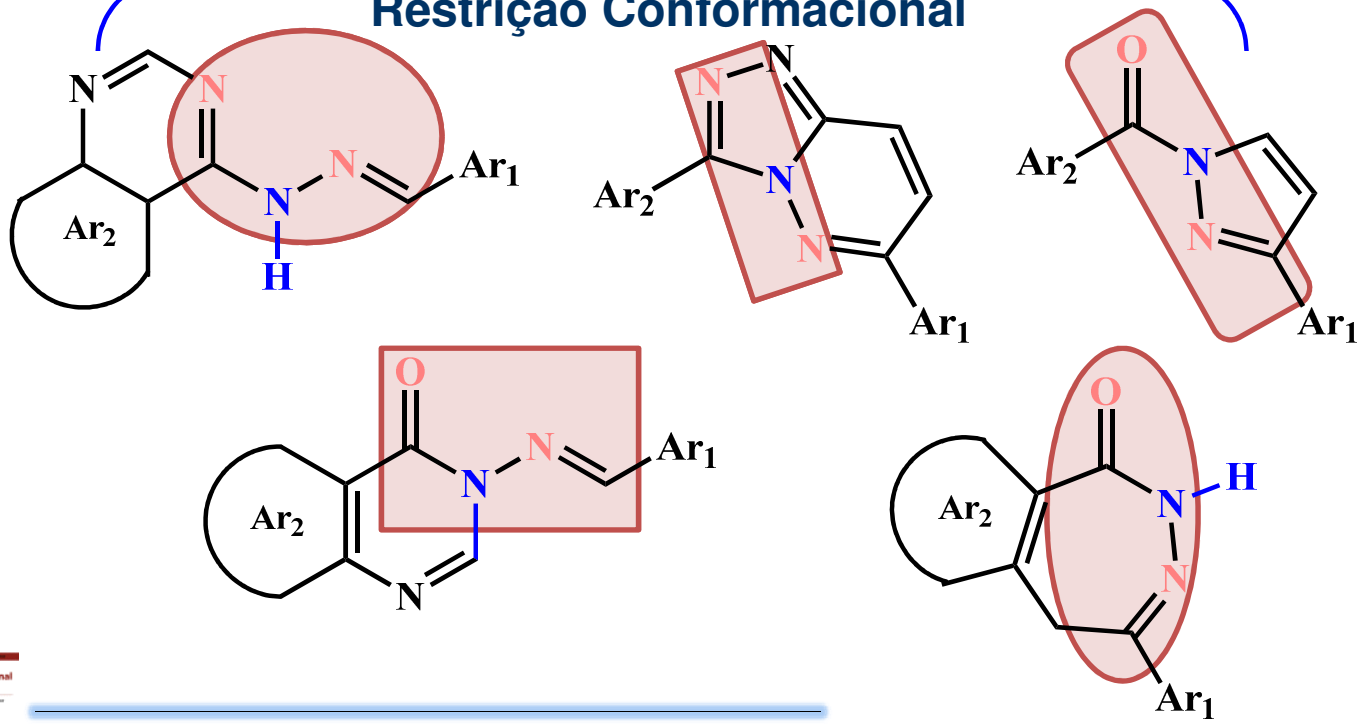
AE Kummerle, Tese de Doutoramento, Instituto de Química, UFRJ, 2009



Diversidade química

C

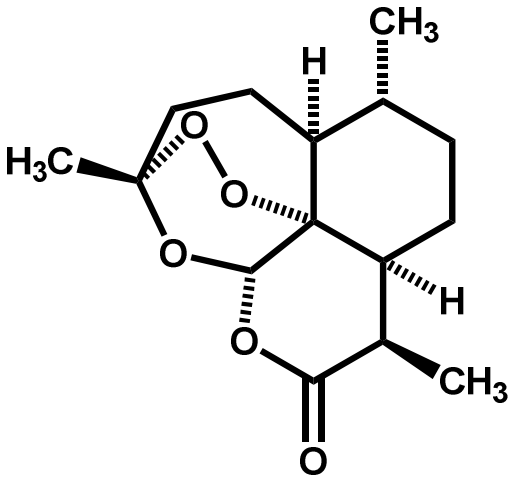
Restrição Conformacional



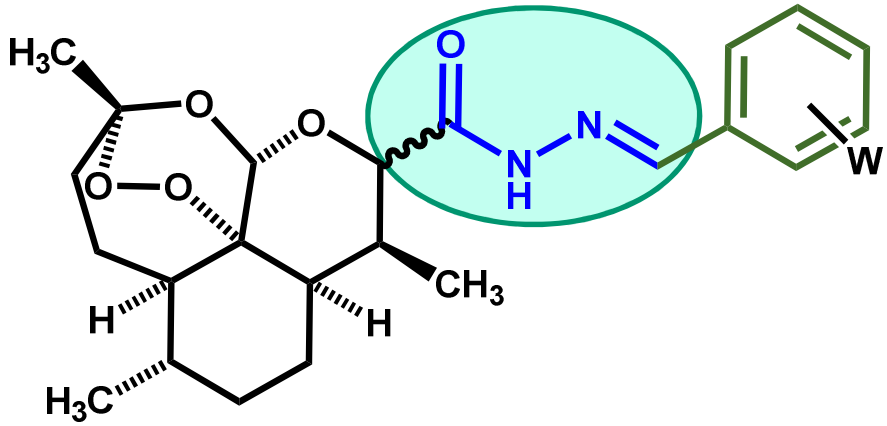
AE Kummerle, MV Martins, M Schmitt, ALPMiranda, CAM Fraga, J-J Bourguignon, EJ Barreiro, Design, synthesis and analgesic properties of novel conformationally-restricted *N*-acylhydrazones, *Bioorg.Med.Chem.Lett.* **2009**, *19*, 4963 [3 citações]

NAH antimalárico

Un Miss



artemisinina



NAH-artemisinina

M J Alvim-Gaston, M A Avery, E J Barreiro, 1999 (resultados não publicados)

Bioorg. Med Chem. **2012**, *20*, 2158-2171

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Bioorganic & Medicinal Chemistry

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

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

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

LASSBio-294

LASSBio-206

LASSBio-246

Furoxanyl-*N*-acylhydrazones

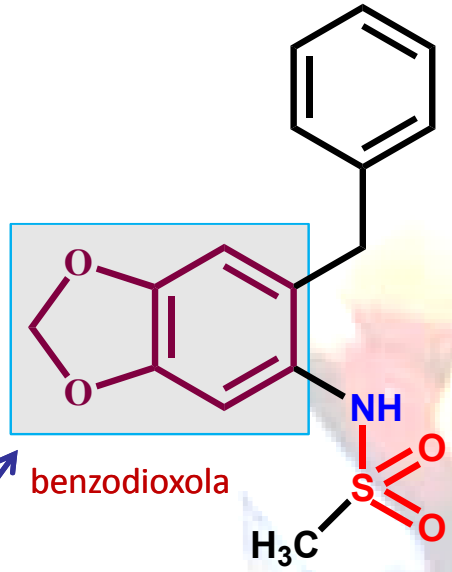
42 new compounds

furoxanas

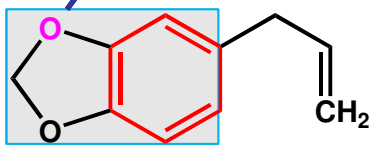
Molecular hybridization

Do LASSBio-259 ao LASSBio-445...

Bióforo natural

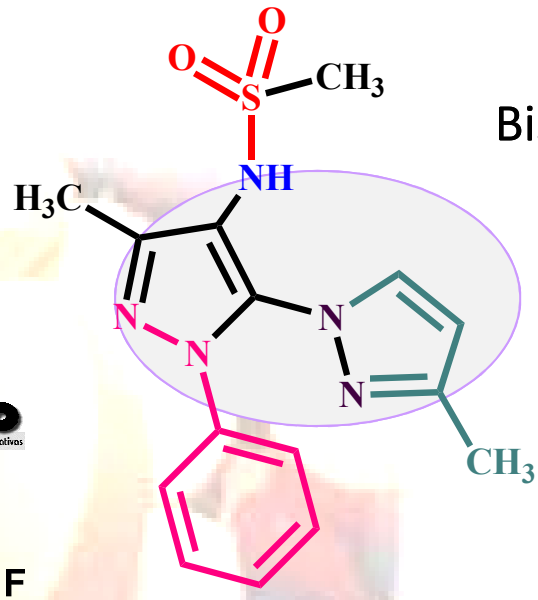


benzodioxola



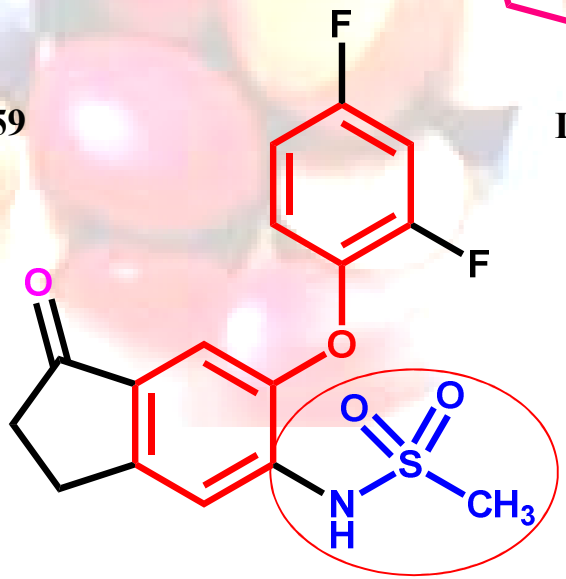
1982-safrol

LASSBio-259
1996 *



Bispirazola

LASSBio-445
2000



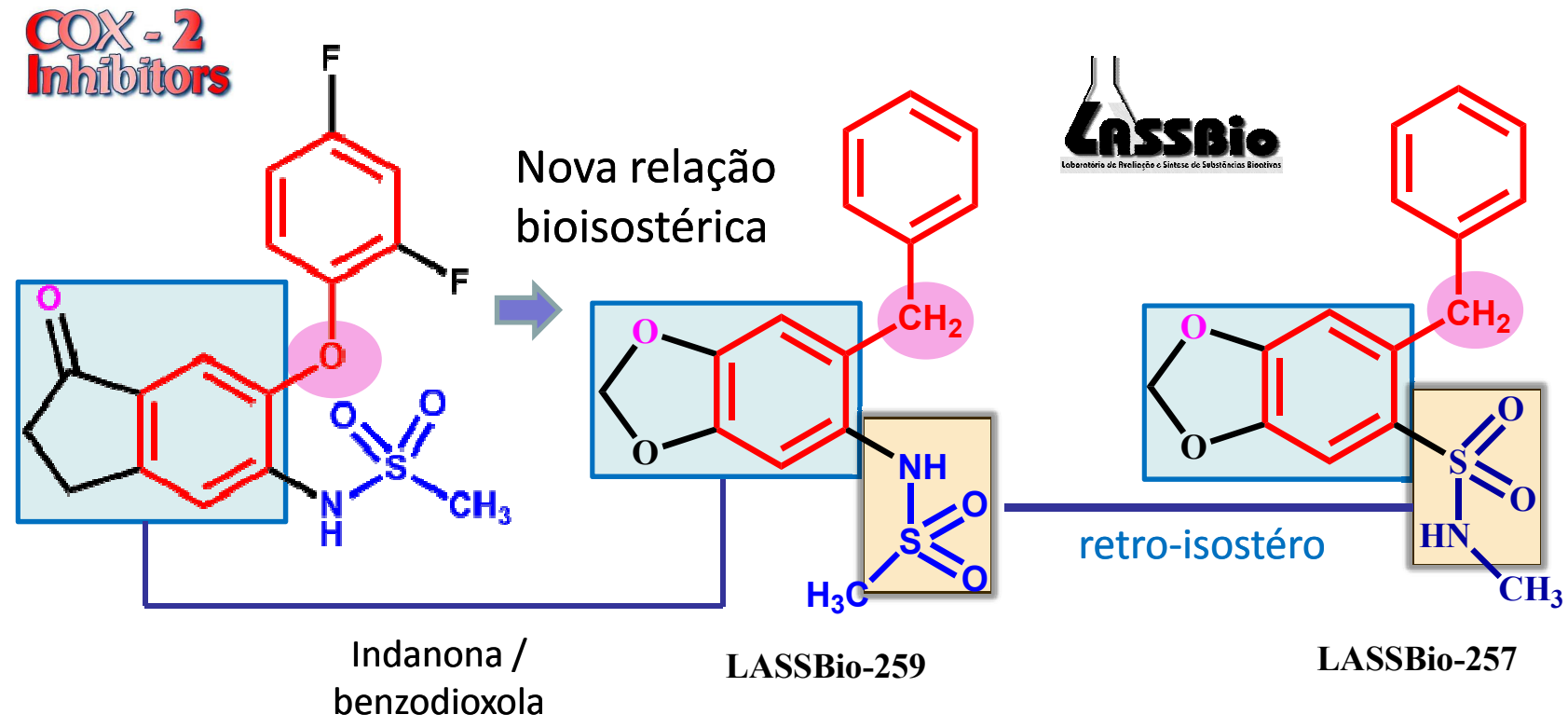
1995-flosulido

Literatura de patentes

COX - 2 Inhibitors

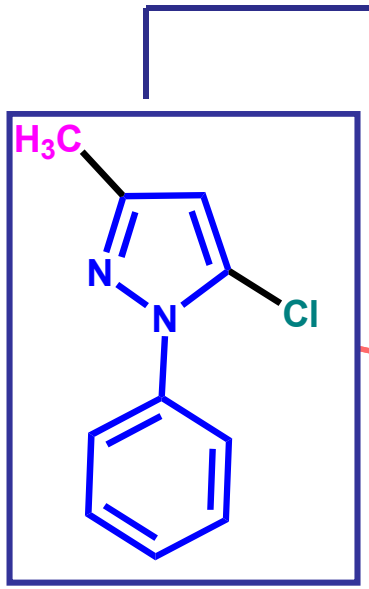
* AS Lages, 23 de setembro de 1996

Desenho molecular de derivados bispirazólicos

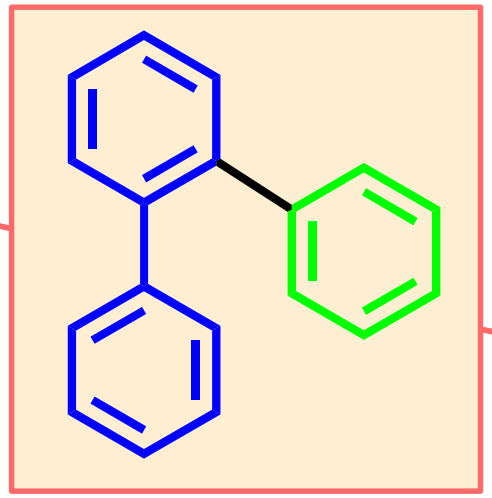


* A.S. Lages, K. C. M. da Silva, A. L. P. Miranda, C. A. M. Fraga & E. J. Barreiro, "Synthesis and Pharmacological Evaluation of New Flosulide Analogues, Synthesized from Natural Safrole", *Bioorganic Medicinal Chemistry Letters*, **8,** 183-188 (1998) [21 citações]

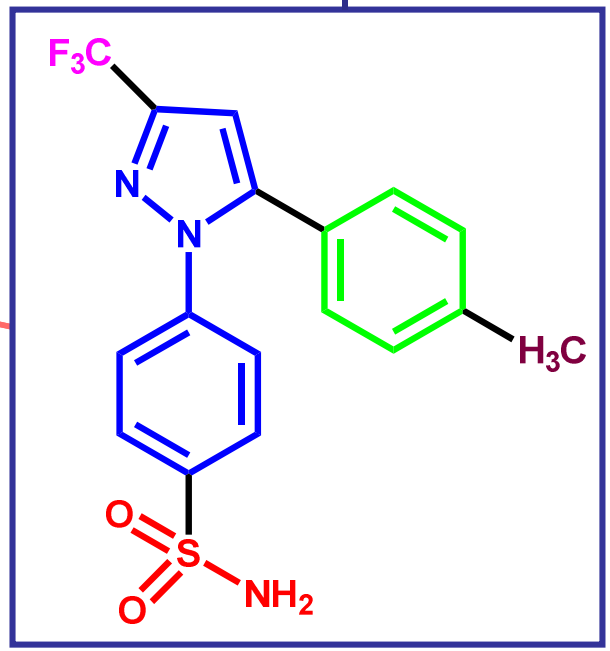
Desenho molecular de derivados bispirazólicos



3-metil-5-cloro-
N-fenilpirazola

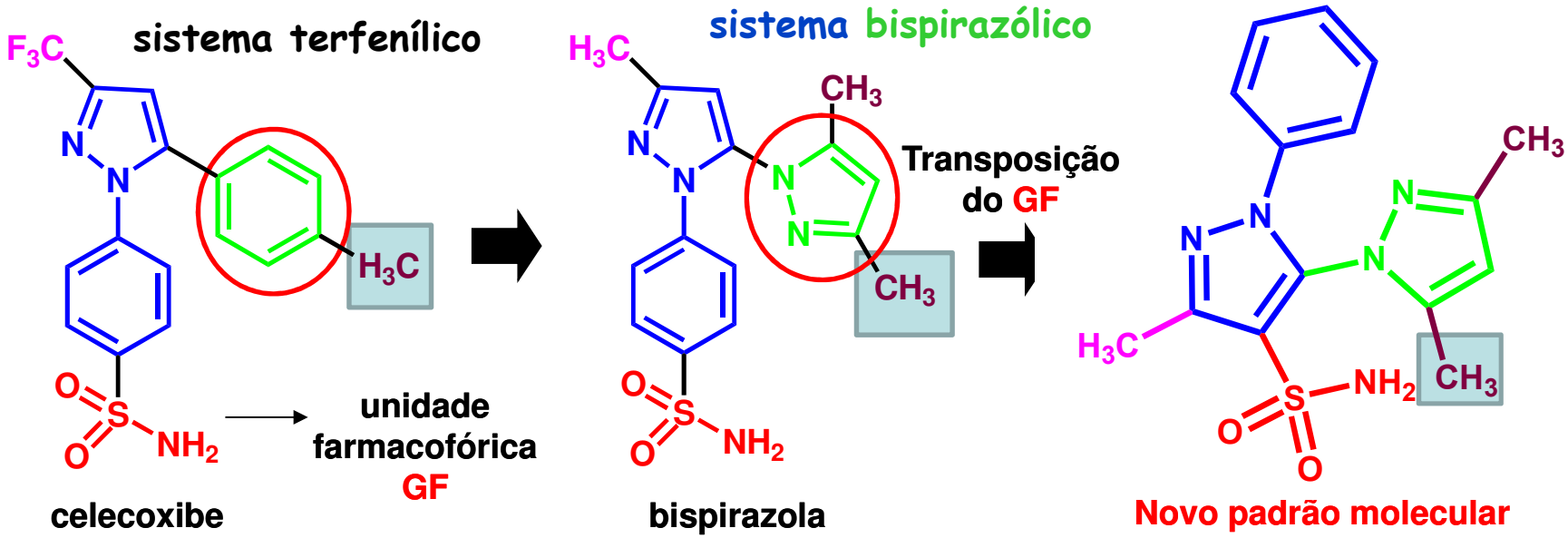


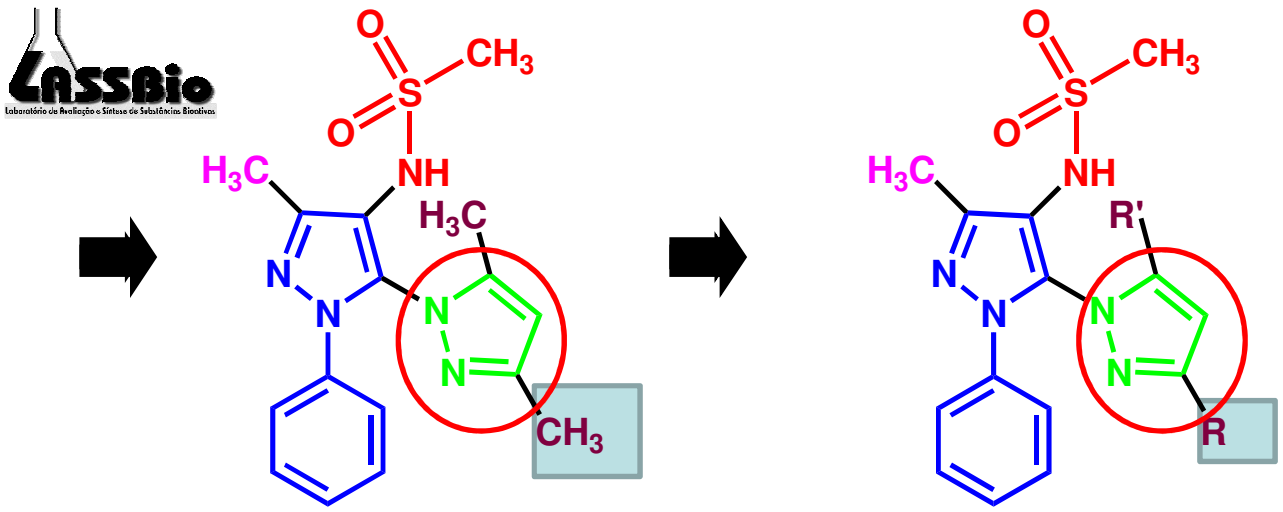
sistema terfenílico

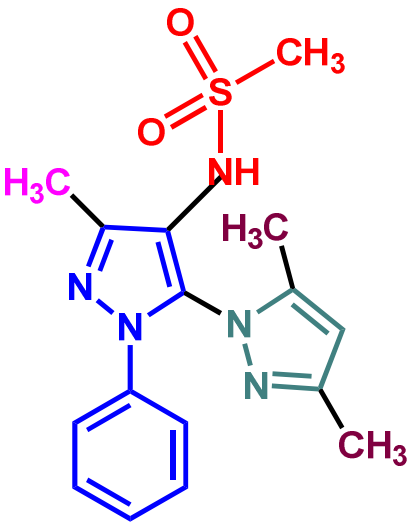


1995-Celecoxibe
1999 - Celebra^{R}

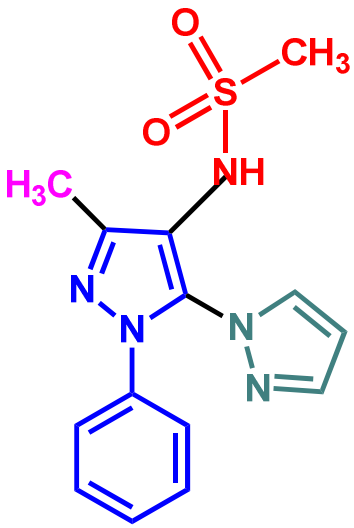
Desenho molecular de derivados bispirazólicos







LASSBio-321



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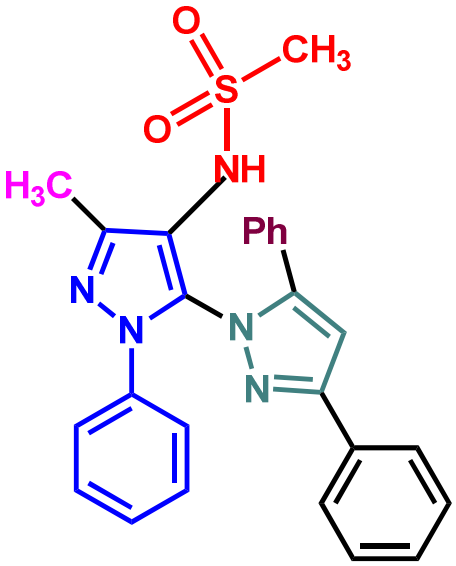

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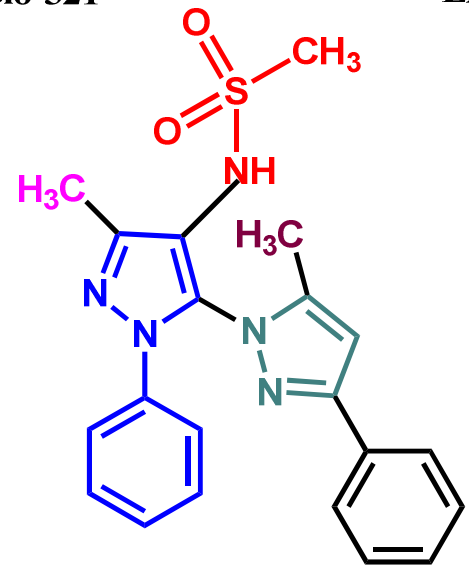

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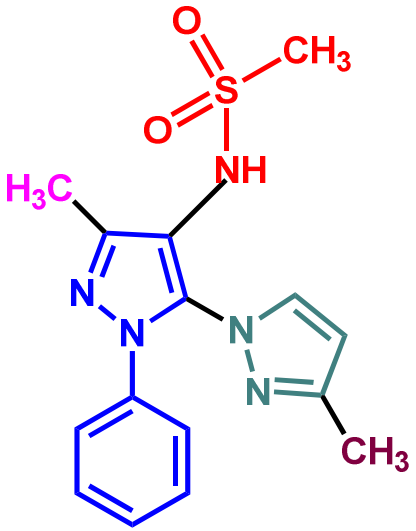
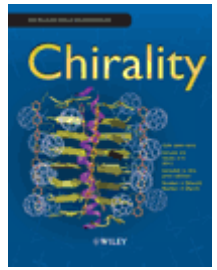


LASSBio-445

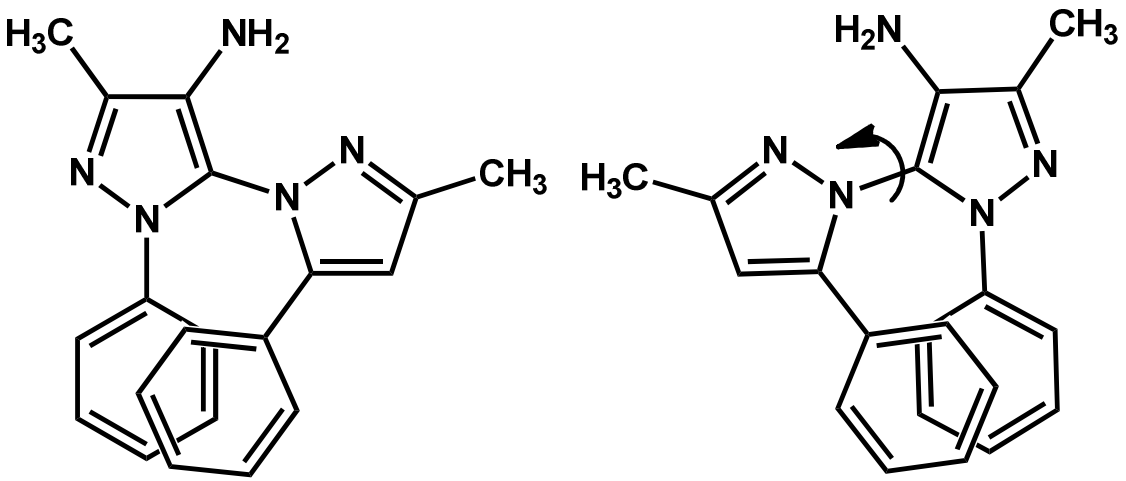
M. P. Veloso, Tese Doutorado, Instituto de Química, UFRJ, 2000

Chirality 2012 24, 000

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

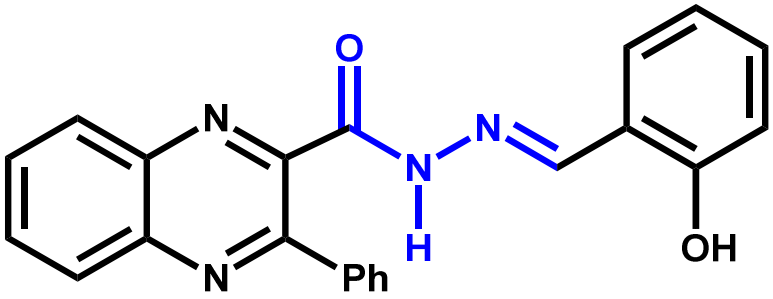


MARCIA P. VELOSO, NELILMA C. ROMEIRO, GILBERTO M. S. SILVA, HÉLIO DE M. ALVES, ANTONIO C. DORIGUETTO, JAVIER ELLENA. ANA L. P. MIRANDA, ELIEZER J. BARREIRO CARLOS A. M. FRAGA

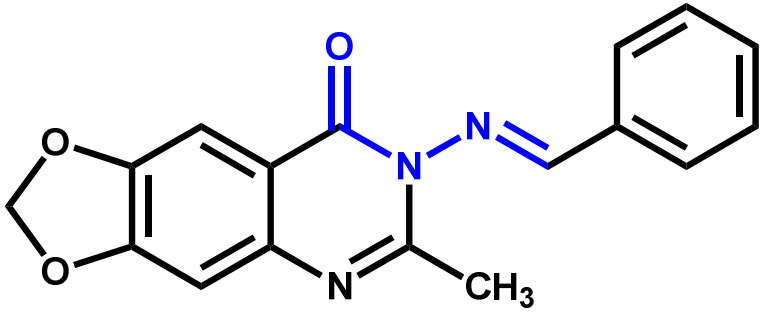


AR dos Santos *et al*., Atropoisomerismo: o efeito da quiralidade axial em substâncias bioativas, *Quim. Nova* **2007**, *30*, 125

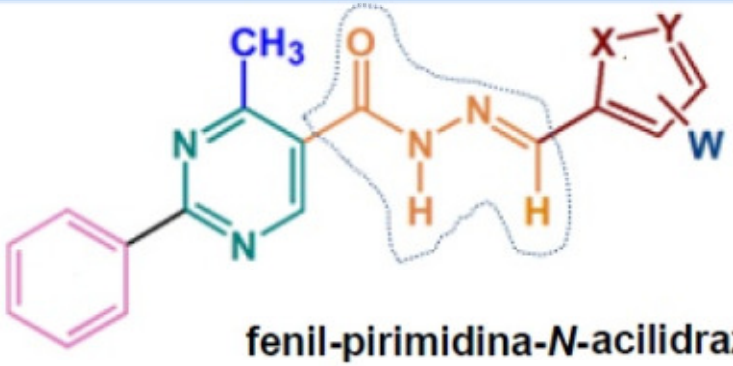
A busca por novos *simbióticos*...



NC Romeiro, G Aguirre, P Hernándeb, M González, H Cerecetto, I Aldana, S Pérez-Silanes, A Monge, EJ Barreiro, LM Lima, *Bioorg Med Chem* **2009**, *17*, 641



RC Maia, LL Silva, EF Mazzeu, MM Fumian, CM Rezende, AC Doriguetto, RS Corrêa, ALP Miranda, E J Barreiro, CAM Fraga. *Bioorg Med Chem* **2009**, *17*, 6517



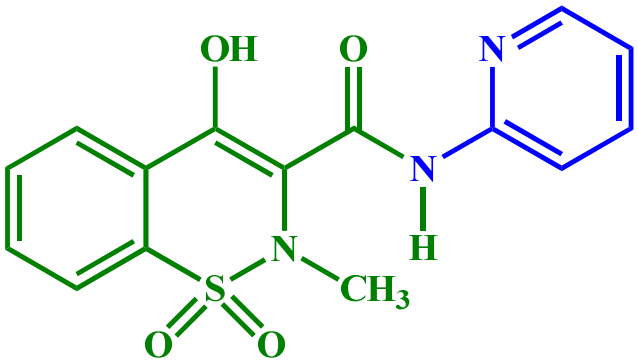
X = O, S, N
Y = CH, $(CH)_2$

fenil-pirimidina-*N*-acilidrazona

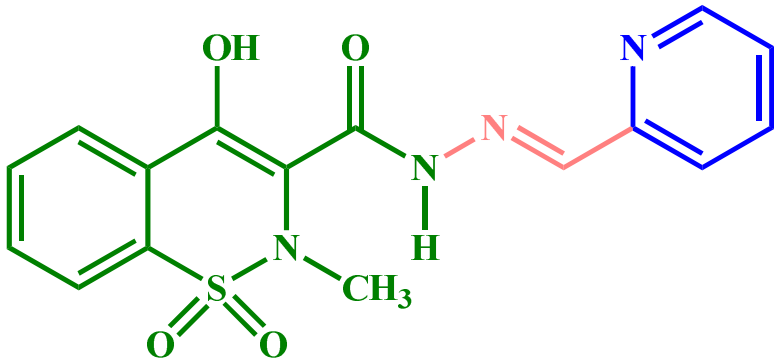
LASSBio 1079-1090

LASSBio 1118-1121

AB Lopes, "Síntese e avaliação das atividades antinociceptiva e anti-inflamatória de compostos fenil-pirimidina-*N*-acilidrazonas planejados a partir de derivados imidazo[1,2*a*]piridina-*N*-acilidrazonas, Dissertação de Mestrado, Instituto de Química, UFRJ, 2010

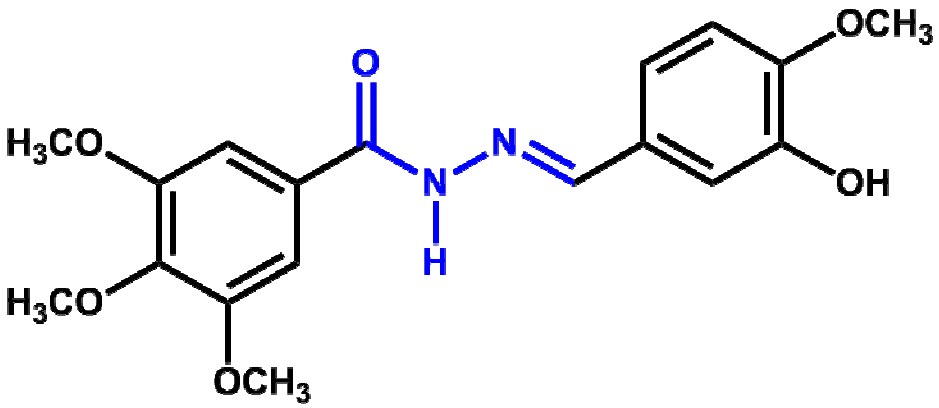


Piroxicam



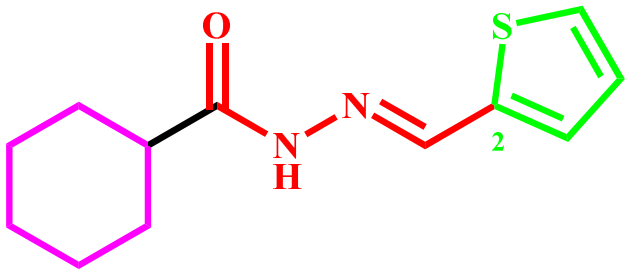
Análogo NAH do piroxicam

AS de Miranda, "Síntese, caracterização e avaliação farmacológica de novos derivados *N*-acilidrazônicos análogos ao piroxicam", Dissertação de Mestrado, Instituto de Química, UFRJ, 2011



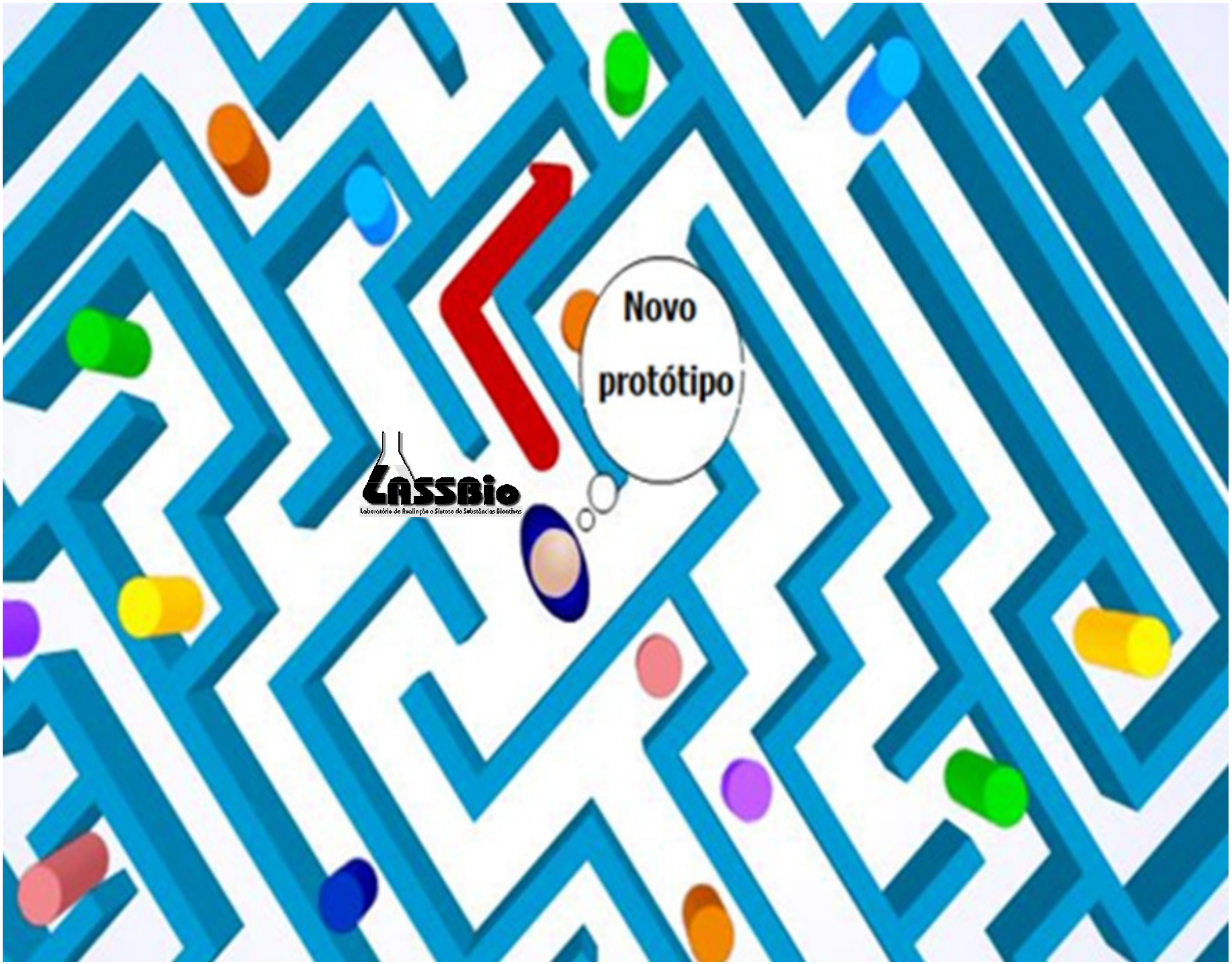
Daniel Nascimento do Amaral, resultados não publicados (2012)

Em 26/03



Tiago Fernandes da Silva, resultados não publicados (2011)

Em 11/06


Novo
protótipo
LASSBio
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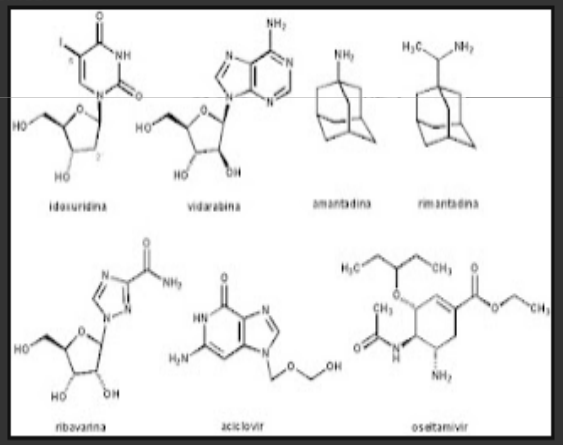
De fármacos e suas descobertas

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

SÁBADO, 17 DE MARÇO DE 2012

Linha do Tempo da Química Medicinal: assim nascem os fármacos - Parte IX

Entramos na nona parte desta **Linha do Tempo da Química Medicinal** e vamos tratar agora dos fármacos anti-virais que durante muitos anos foram considerados ineficazes, quando pouco se conhecia sobre o ciclo evolutivo destes microrganismos.



http://ejb-eliezer.blogspot.com

Obrigado