A Química Medicinal no âmbito do Laboratório de Avaliação no Síntese de Substâncias Bioativas (LASSBio) e do INCT-INOFAR

23 de setembro de 2016 Estácio Petrópolis, Bingen - RJ

Eliezer J. Barreiro

Professor Titular

Laboratório de Avaliação e Síntese de Substâncias Bioativas

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

Instituto Nacional de Ciência e Tecnologia de Fármacos e Medicamentos

http://www.inct-inofar.ccs.ufrj.br/

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Universidade Federal do Rio de Janeiro

Quem somos?

Onde estamos?

Universidade Federal do Rio de Janeiro

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

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Universidade Federal do Rio de Janeiro

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

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

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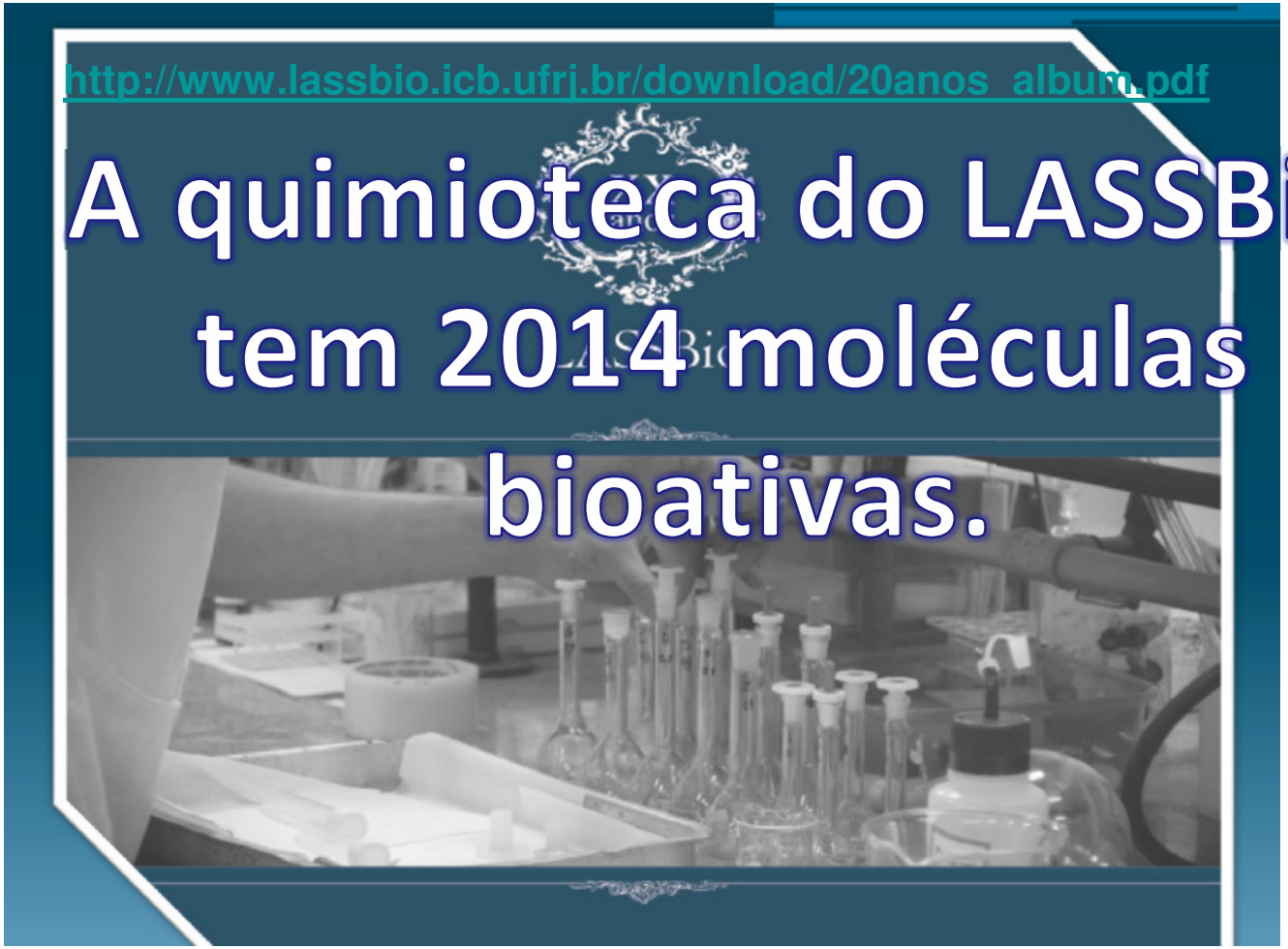
Química Medicinal

Livro Comemorativo dos 20 anos

www.lassbio.icb.ufrj.br

http://www.lassbio.icb.ufrj.br/download/20anos_album.pdf

A quimioteca do LASSBio tem 2014 moléculas bioativas.



www.scielo.br

E. J. Barreiro, As Longas Pernas do Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio®): Histórico e Perspectivas, *Rev Virtual Quim* **2013**, *5*, 266-282 [http://rvq.sbq.org.br/index.php/rvq]

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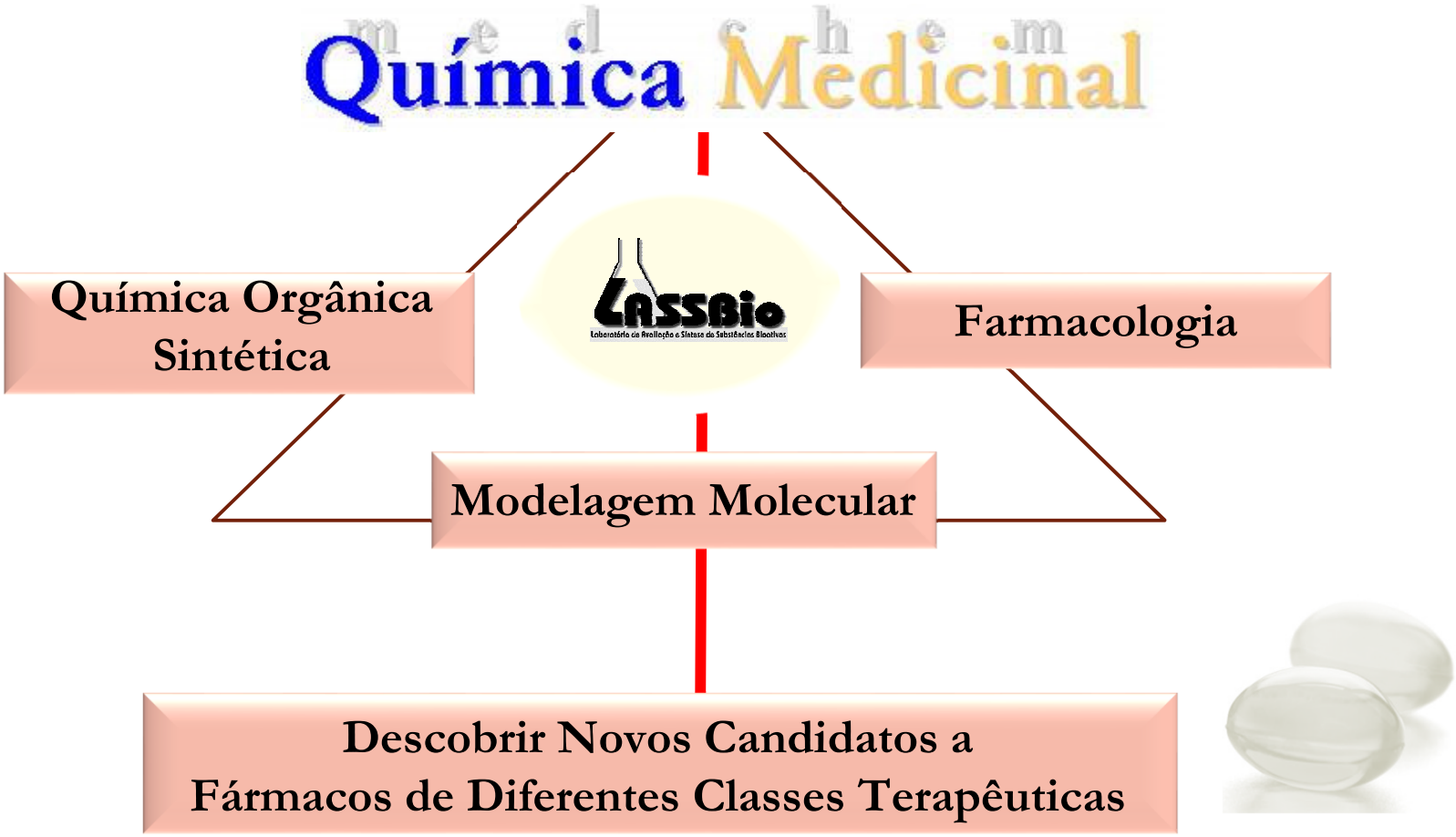
O que fazemos?



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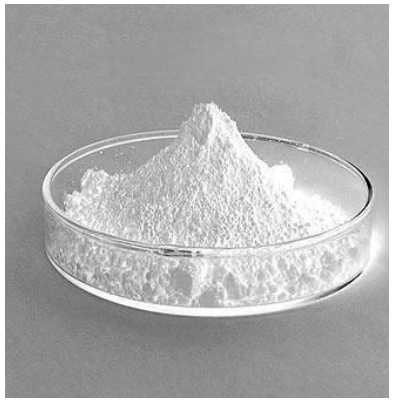
Fármaco...

Formas Farmacêuticas

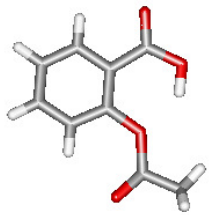
Farmoquímico

IFA



Pureza farmacopêica

Tecnologia Farmacêutica



Princípio ativo

IFA= insumo farmacêutico ativo

ácido acetilsalicílico

.... & medicamento.

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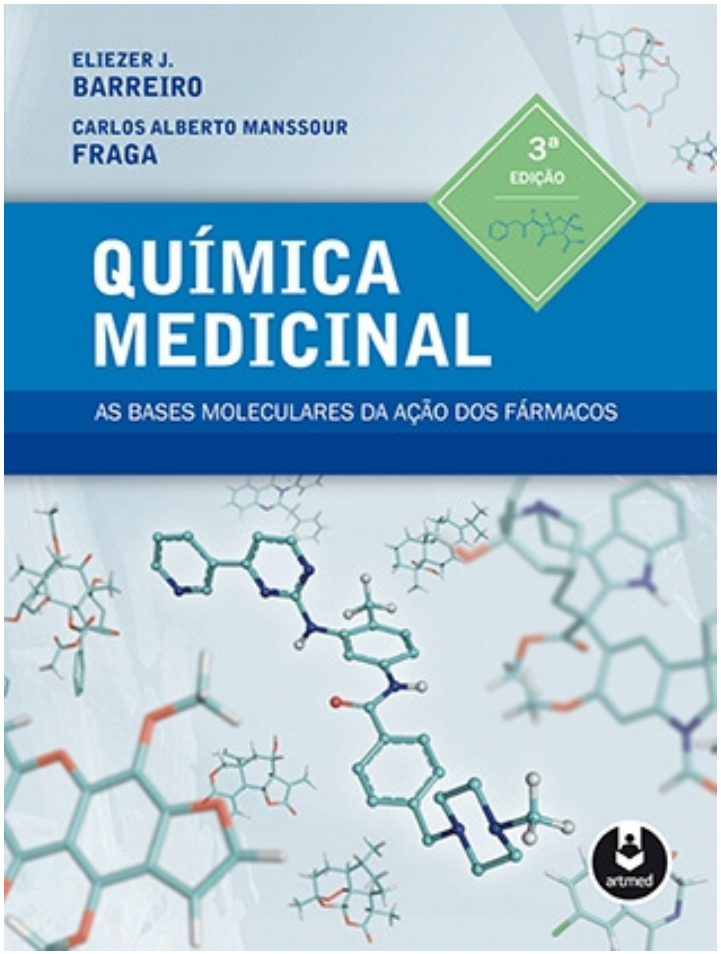
Definição & bibliografia

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

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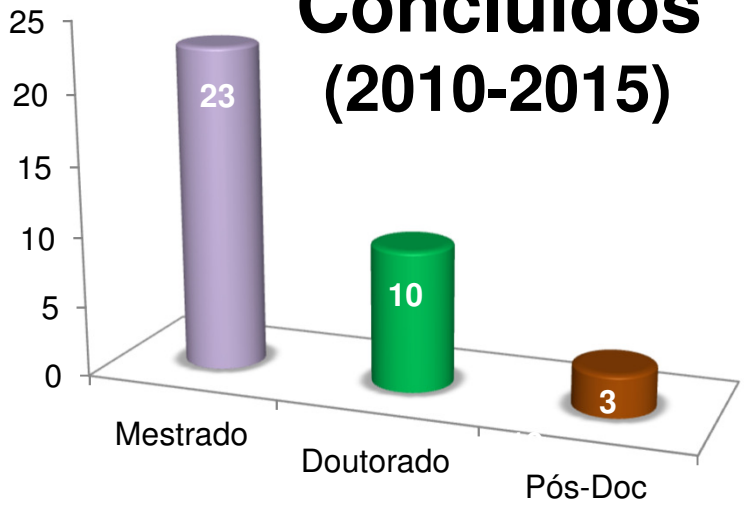
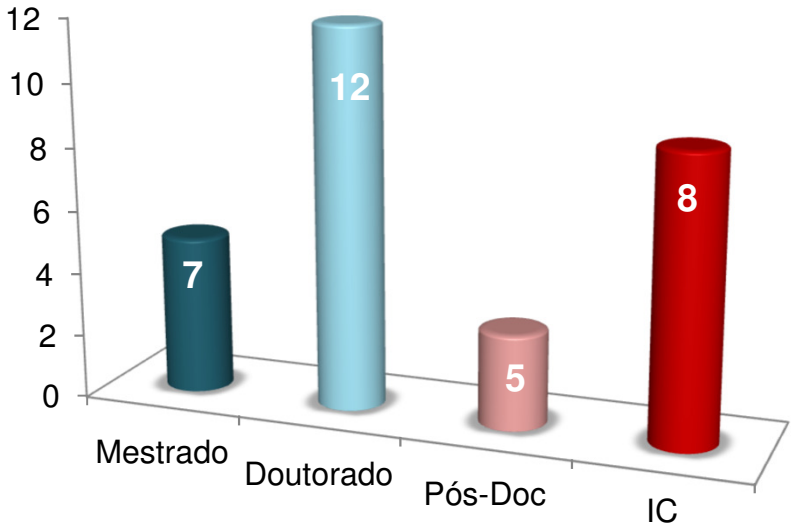
Mestrados e Doutorados Concluídos (2010-2015)



Período: 2010-2015
Total = **97** artigos

Mestrados e Doutorados em Andamento (2016)



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2016

International Journal of Cardiology 202 (2016) 497–499

Contents lists available at ScienceDirect

International Journal of Cardiolog

journal homepage: www.elsevier.com/locate/ij

Correspondence

LASSBio-1425, an analog of thalidomide, decreases triglycer increases HDL cholesterol levels by inhibition of TNF-α pro

Milla Machado Fumian [a], Nadia Alice Vieira da Motta [a], Rodolfo Maia [b], Carlo Eliezer Jesus Barreiro [b], Fernanda Carla Ferreira de Brito [a,*]

Cell Physiol Biochem 2016;38:821-835
(DOI:10.1159/000443037)

Respiratory and Systemic Effects of LASSBio596 Plus Surfactant in Experimental Acute Respiratory Distress Syndrome

Silva J.D.[a] · de Oliveira G.P.[a] · Samary C.S.[a] · Araujo C.C.[a] · Padilha G.A.[a] · e Silva Filho F.C.[b] · da Silva R.T.[c] · Einicker-Lamas M.[c] · Morales M.M.[d] · Capelozzi V.L.[e] · da Silva V.M.[e] · Lima L.M.[f] · Barreiro E.J.[f] · Diaz B.L.[g] · Garcia C.S.N.B.[a,i] · Rocco P.R.M.[a]

[a]Laboratory of Pulmonary Investigation, Carlos Chag Biophysics, Federal University of Rio de Janeiro, Rio of Biophysics, Carlos Chagas Filho Institute of Biophy Rio de Janeiro, Rio de Janeiro, [c]Laboratory of Physica Carlos Chagas Filho Institute of Biophysics, Federal U Janeiro, Rio de Janeiro, [d]Laboratory of Cellular and N Carlos Chagas Filho Institute of Biophysics, Federal U Janeiro, Rio de Janeiro

PLOS ONE

RESEARCH ARTICLE

PLoS ONE 2016, 11(5):e0156271.
doi:10.1371/journal.pone.0156271

Discovery of Novel Orally Active Tetrahydro-Naphthyl-*N*-Acylhydrazones with *In Vivo*

Paper

Non-competitive Inhibitor of Nucleoside Hydrolase from Leishmania donovani Identified by Fragment-based Drug Discovery

Marina Amaral Alves, Charlotte Nirma, Mayara M. Moreira, Rosemberg O. Soares, Pedro G. Pascutti, F Noel, Paulo Costa, Carlos Sant'Anna, Eliezer J. Barreiro, Lídia Moreira Lima and Luzineide Tinoco

RSC Adv., 2016, Accepted Manuscript
DOI: 10.1039/C6RA15143D
Received 10 Jun 2016, Accepted 30 Aug 2016
First published online 31 Aug 2016

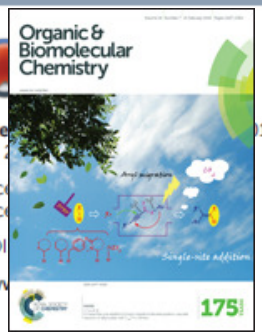
Article

Synthesis, Cytotoxic Activity and Docking Studies of LASSBio-1586 Isosteres

Teiliane Rodrigues Carneiro[1,2], Daniel Nascimento do Amaral[1], Maria Luisa Gomez Porras[1], Augusto César Aragão Oliveira[2], Bruno Coêlho Cavalcanti[2], Cláudia Pessoa[2,3], Eliezer J. Barreiro[1], Lídia Moreira Lima[1]*

[1]Instituto Nacional de Ciência e Tecnologia de Fármacos e Medicamentos (INCT-INOFAR; http://www.inct-inofar.ccs.ufrj.br/), Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio®, http:// www.lassbio.icb.ufrj.br) . Box 68006, ZIP: 21941-902, Rio de Ja

PAPER



The total synthesis of calcium atorvastatin†

Luiz C. Dias,*[a] Adriano S. Vieira[a] and Eliezer J. Barreiro[b]

A practical and convergent asymmetric route to calcium atorvastatin (**1**) is reported. Th calcium atorvastatin (**1**) was performed using the remote 1,5-*anti* asymmetric induction mediated aldol reaction of β-alkoxy methylketone (**4**) with pyrrolic aldehyde (**3**) as a key atorvastatin was obtained from aldehyde (**3**) after 6 steps, with a 41% overall yield.

Journal of Medicinal Chemistry

Article

J. Med. Chem. 2016, 59, 655−670

pubs.acs.org/jmc

Design, Synthesis, and Pharmacological Evaluation of Novel *N*-Acylhydrazone Derivatives as Potent Histone Deacetylase 6/8 Dual Inhibitors

Daniel A. Rodrigues,[†,‡] Guilherme À. Ferreira-Silva,[⊥] Ana C. S. Ferreira,[#] Renan A. Fernandes,[#] Jolie K. Kwee,[#] Carlos M. R. Sant'Anna,[†,∥] Marisa Ionta,[⊥] and Carlos A. M. Fraga[*,†,‡,§]

[†]Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Instituto de Ciências Biomédicas, [‡]Programa de Pós-Graduação em Química, Instituto de Química, and [§]Programa de Pós-Graduação em Farmacologia e Química Medicinal, Instituto de Ciências Biomédicas, Universidade Federal do Rio de Janeiro, P.O. Box 68023, 21941-902 Rio de Janeiro, Rio de Janeiro, Brazil

[∥]Departamento de Química, Instituto de Ciências Exatas, Universidade Federal Rural do Rio de Janeiro, 23970-000 Seropédica, Rio de Janeiro, Brazil

[⊥]Laboratório de Biologia Animal Integrativa, Departamento de Biologia Celular e do Desenvolvimento, Instituto de Ciências Biomédicas, Universidade Federal de Alfenas, 37130-000 Alfenas, Minas Gerais, Brazil

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Definição da Doença-Alvo *e.g.* Asma

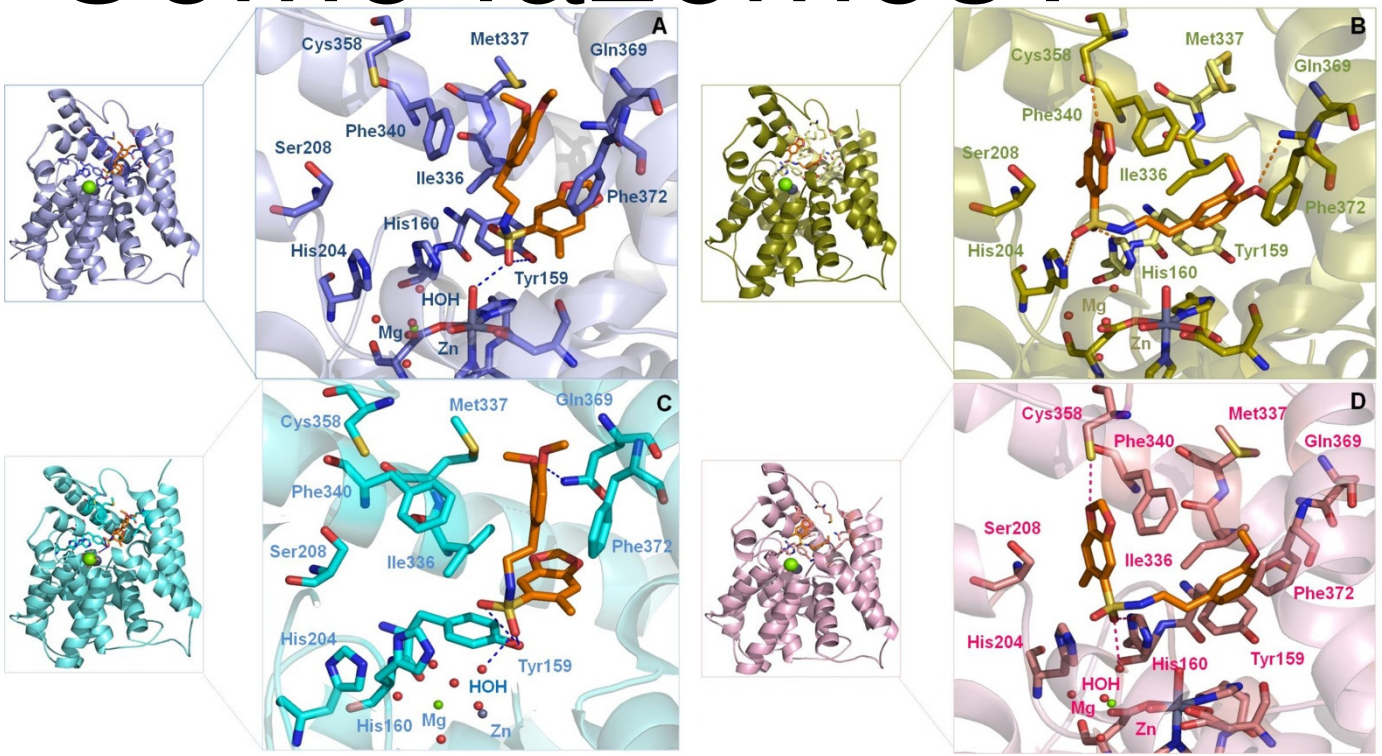
Definição da Alvo Molecular (receptor) *e.g.* PDE-4

Planejamento Baseado em Estrutura (*SBDD*) = PDB PDE4A-D

Docking Molecular

Estrutura de Novos Ligantes

Como fazemos?



Top poses of **LASSBio-448** (orange carbon atoms) with PDE4A (A), PDE4B (B), PDE4C (C) and PDE4D (D) obtained with GOLD 5.2 software.

Hydrogen atoms have been omitted for clarity. Hydrogen bonds are in dashed lines. PDE4D numbering has been used

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Definição da Doença-Alvo *e.g.* Asma

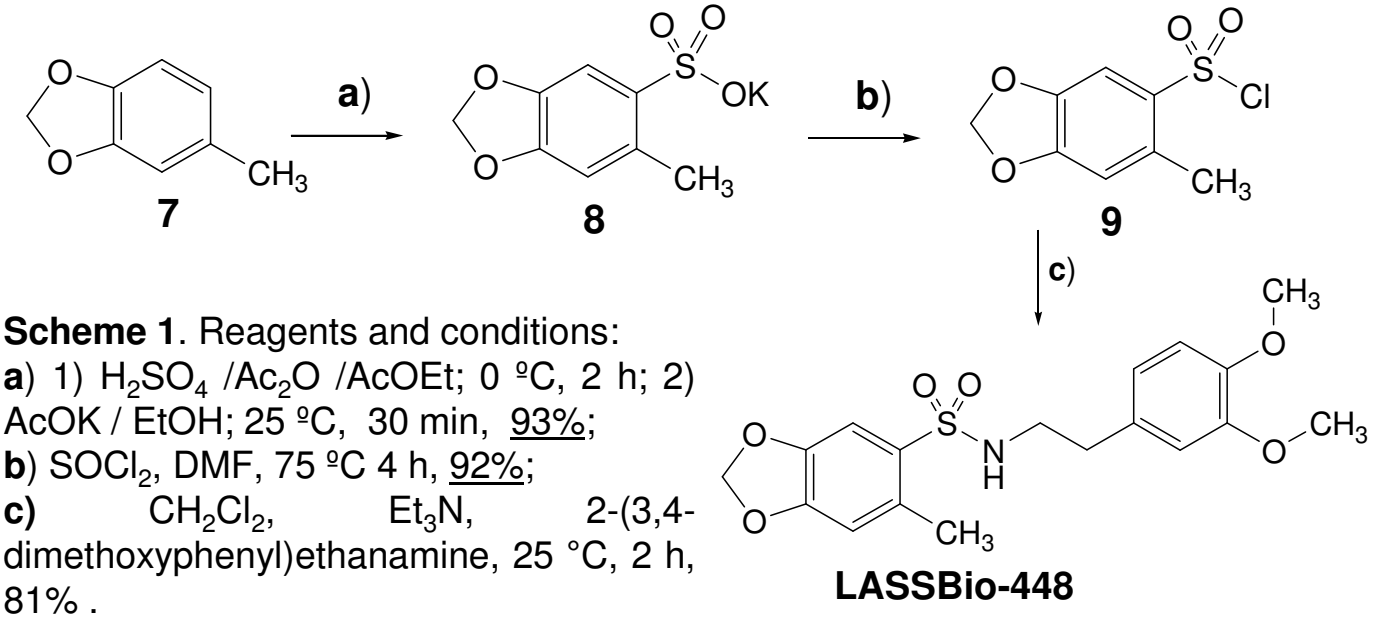
Definição da Alvo Molecular (receptor) *e.g.* PDE-4

Planejamento Baseado em Estrutura (SBDD) = PDB PDE4A-D

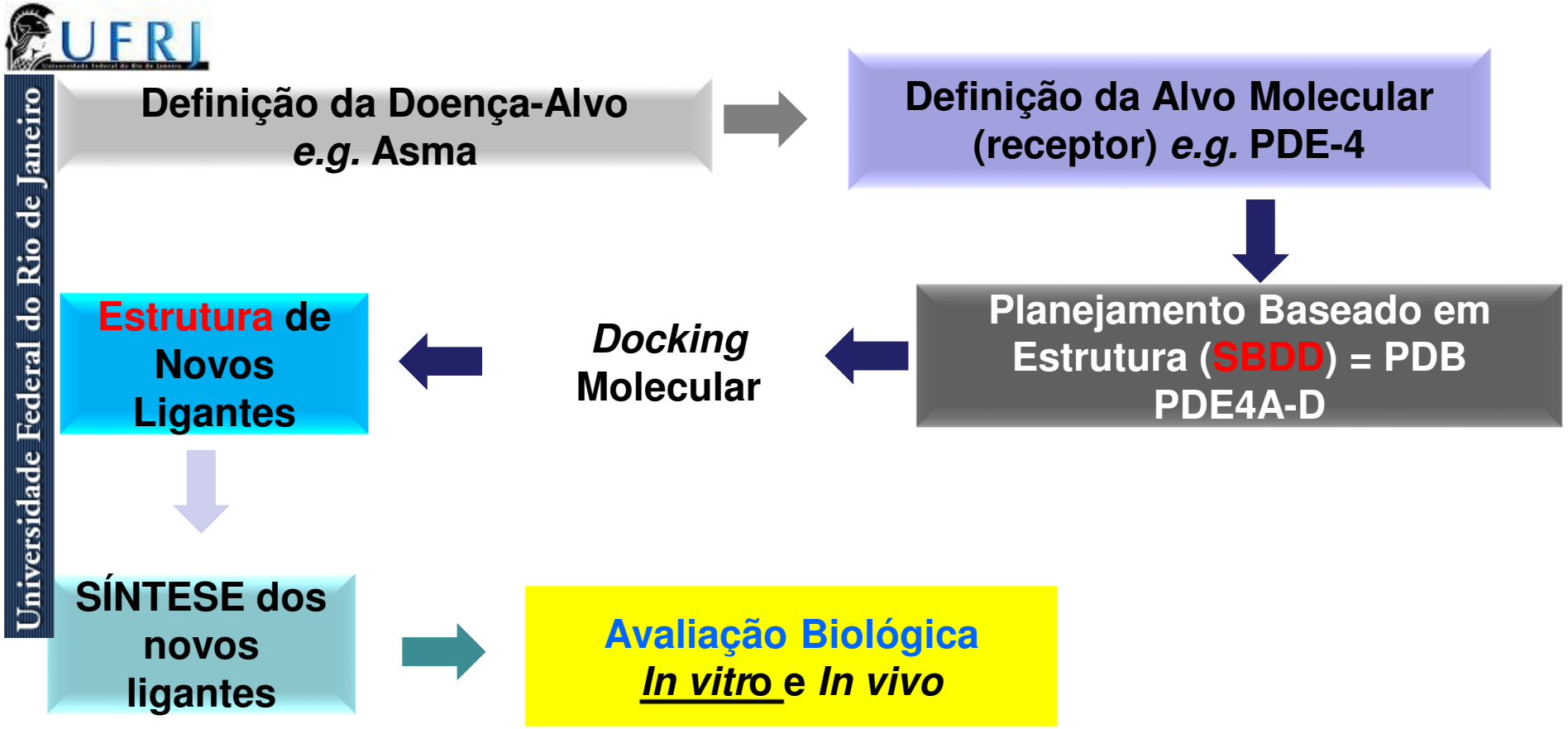
***Docking* Molecular**

Estrutura de Novos Ligantes

SÍNTESE dos novos ligantes



Scheme 1. Reagents and conditions:
a) 1) H_2SO_4 /Ac_2O /AcOEt; 0 ºC, 2 h; 2) AcOK / EtOH; 25 ºC, 30 min, 93%;
b) $SOCl_2$, DMF, 75 ºC 4 h, 92%;
c) CH_2Cl_2, Et_3N, 2-(3,4-dimethoxyphenyl)ethanamine, 25 °C, 2 h, 81% .



PDE4 recombinant isoform inhibition (IC_{50}, µM) for sulfonamide LASSBio-448 & rolipram

Recombinant enzyme	LASSBio-448 IC_{50}[a] (µM ± S. D.)	Rolipram IC_{50}[a] (µM± SEM)
PDE4A	0.7 ± 0.13	0.3 ± 0.03
PDE4B	1.4 ± 0.14	0.9 ± 0.04
PDE4C	1.1 ± 0.13	0.9 ± 0.02
PDE4D	4.7 ± 0.10	0.6 ± 0.10

[a]The IC_{50} was calculated by nonlinear regression and represents the mean value of three measurements.

ENSAIO EM MODELO MURINO DE ASMA CRÔNICA (CAMUNDONGOS A/J).

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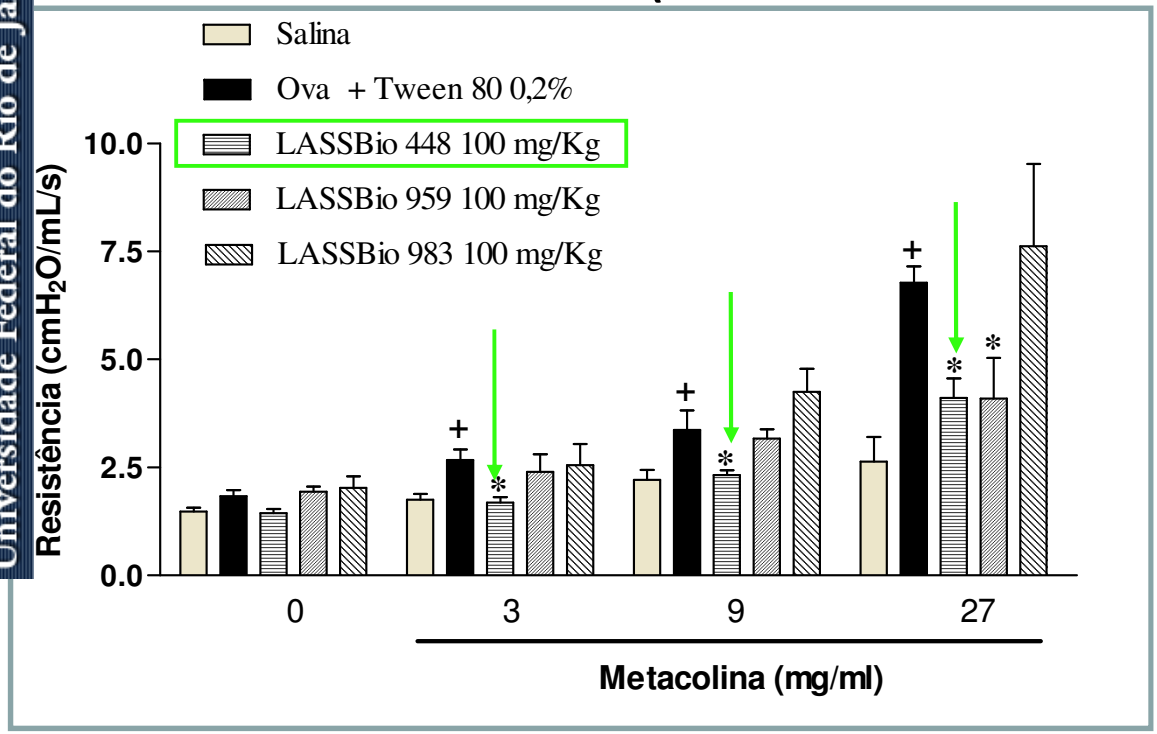
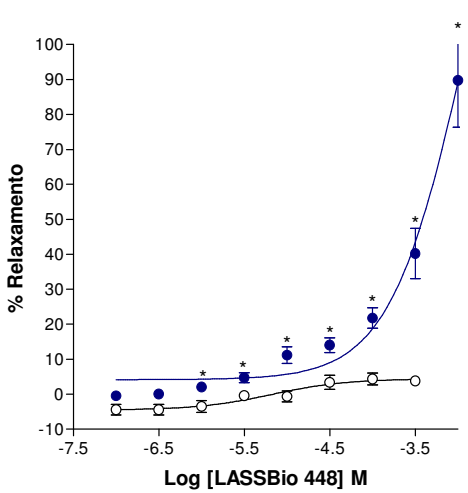
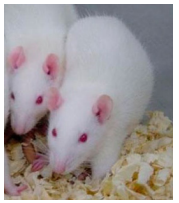
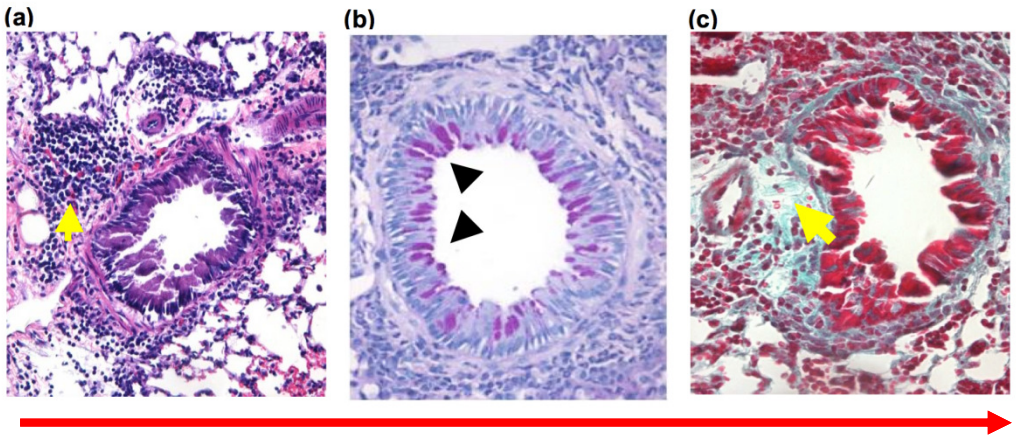




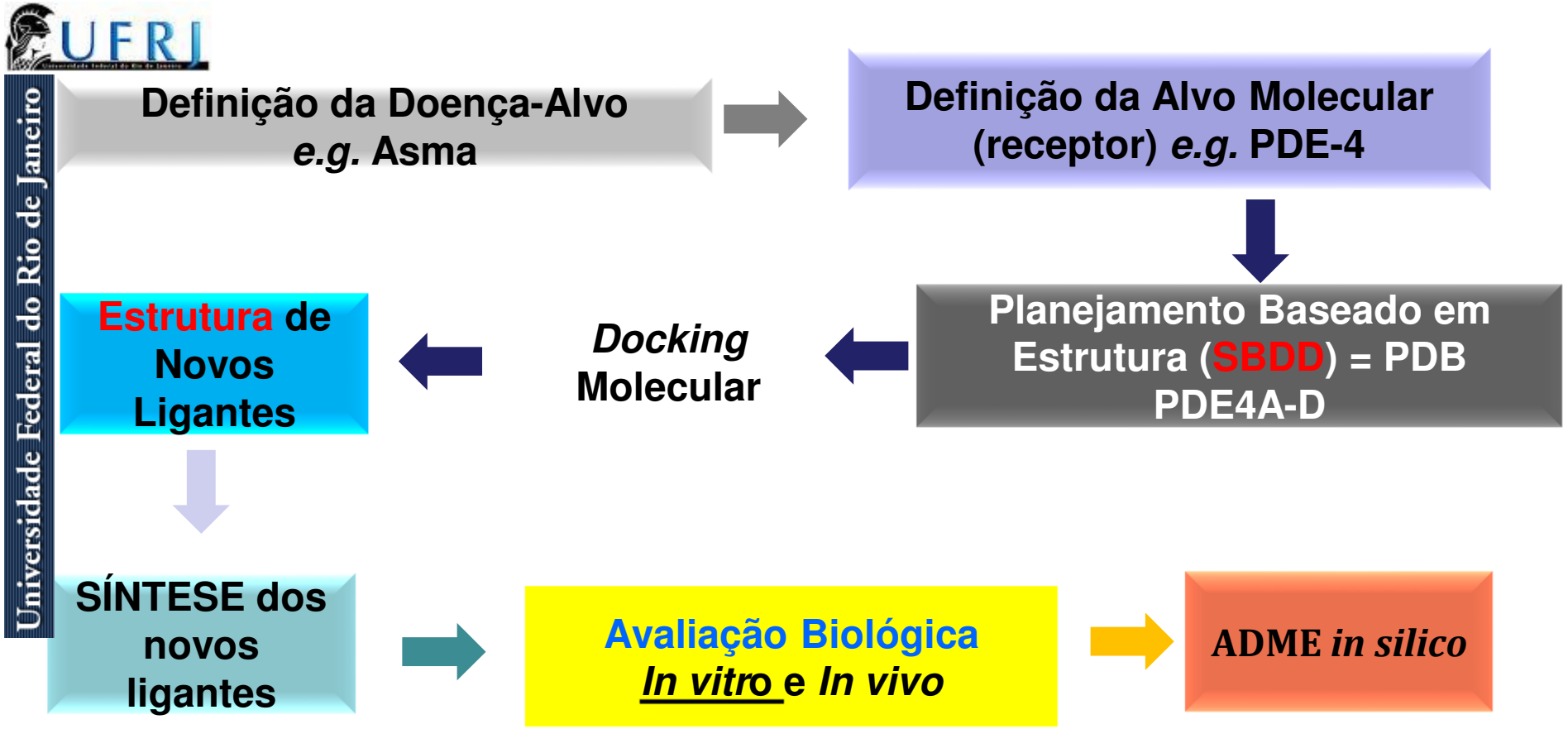
In vivo



Efeito relaxante de LASSBio-448 (em diferentes concentrações: 10^{-7} a 10^{-2}M) sobre traquéias de ratos pré-contraídas com carbacol (2,5 µM). Cada ponto representa a média ± erro padrão da média de valores obtidos em 5 experimentos .

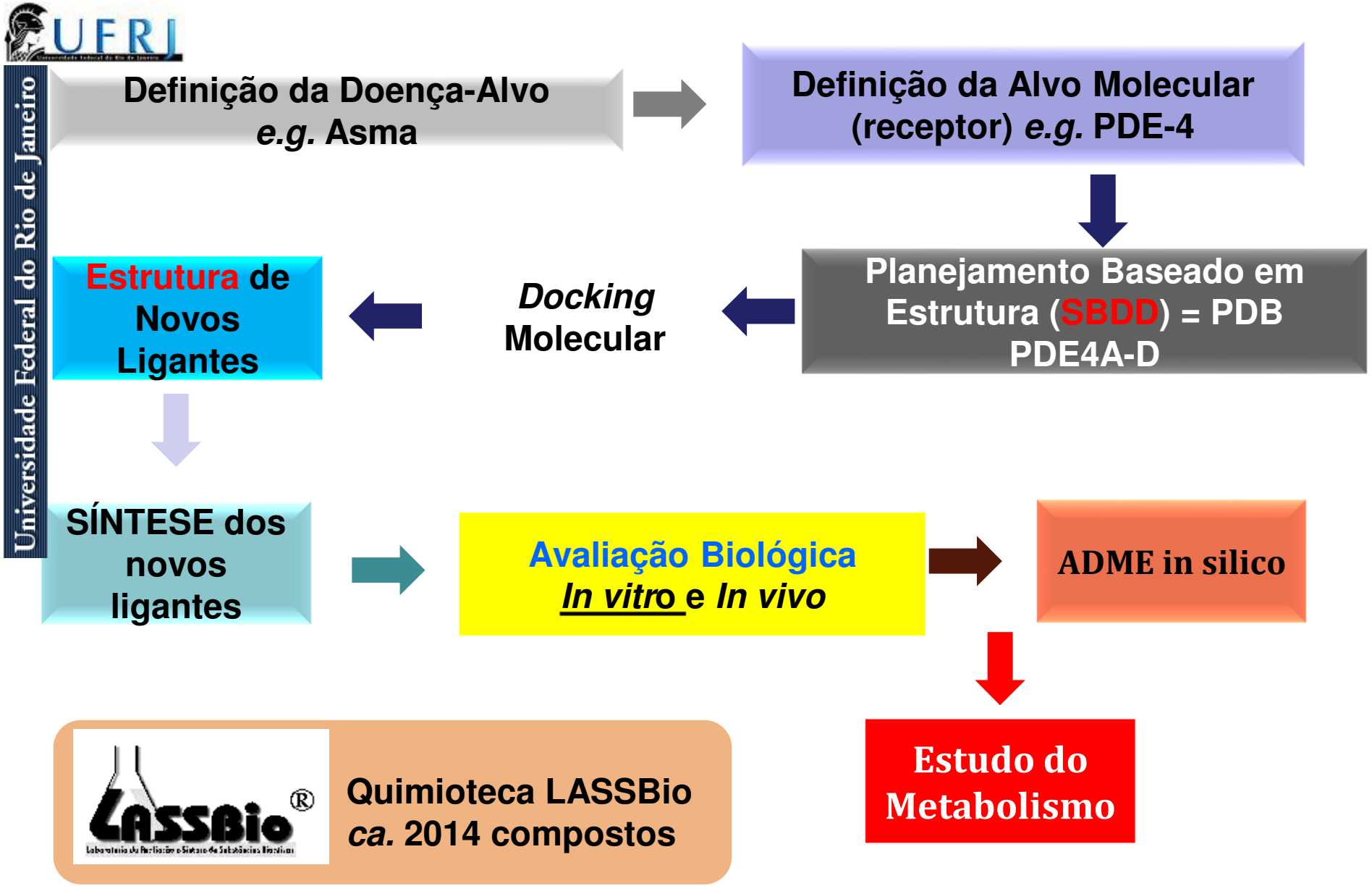


Representative histological changes noted 24 h after the series of three **ovalbumin** challenges, done at days 14, 21 and 28 post-sensitization. (**a**) Photomicrograph of paraffin-embedded lung section stained by hematoxilin-eosin indicating peribronchial **inflammatory infiltrate;** (**b**) Photomicrograph taken of representative airways showing goblet-cell hyperplasia and **mucus production** (purple color, arrowheads), and (**c**) Photomicrograph of representative lung histologic section stained with Gomori trichrome revealing **peribronchial fibrosis**. Original magnifications of x400



Comparative ADME properties of rolipram (**1**) and LASSBio-448 predicted *in silico* using the **Program ACD/Percepta 14.0**

Compounds	Caco-2	HIA(%)	F% (oral)	Vd	PPB(%)	CNS
Rolipram	P_e = 180 x10^{-6} cm/s	100	99%	1.4 L/Kg	63	-2.06
LASSBio-448	P_e = 211x10^{-6} cm/s	100	99%	1.8 L/Kg	87	-2.54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Definição da Doença-Alvo
e.g. Asma
Definição da Alvo Molecular
(receptor) e.g. PDE-4
Planejamento Baseado em
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PDE4A-D
Docking
Molecular
Estrutura de
Novos
Ligantes
SÍNTESE dos
novos
ligantes
Avaliação Biológica
In vitro e In vivo
ADME in silico
Estudo do
Metabolismo
LASSBio®
Quimioteca LASSBio
ca. 2014 compostos

ESTUDOS DO METABOLISMO

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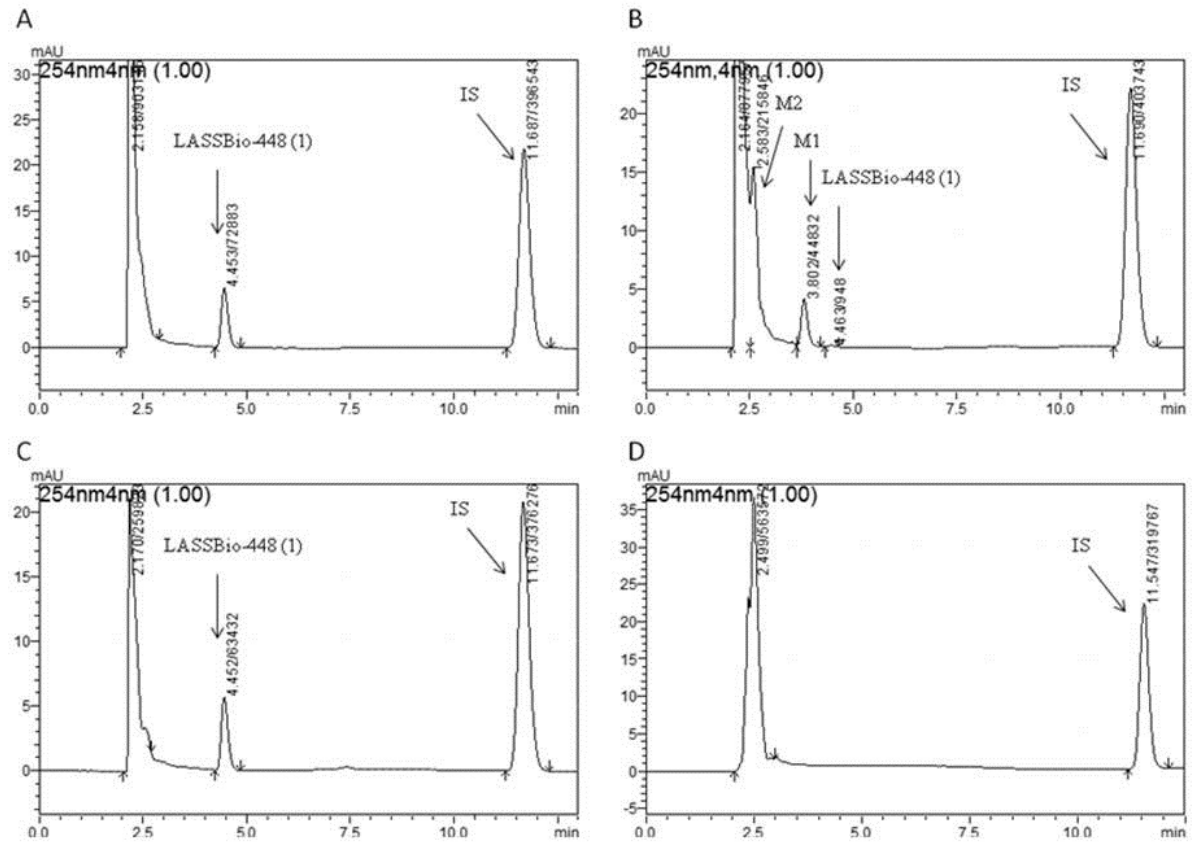
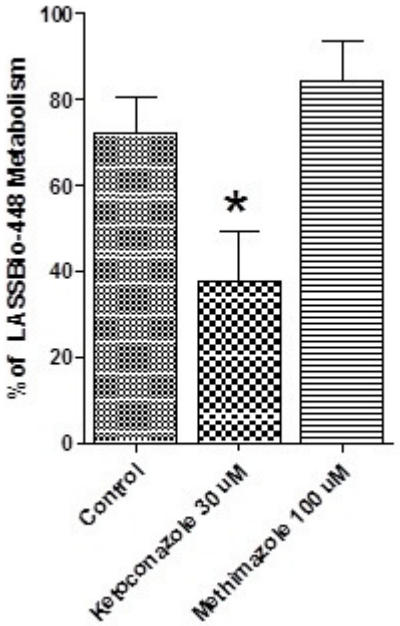


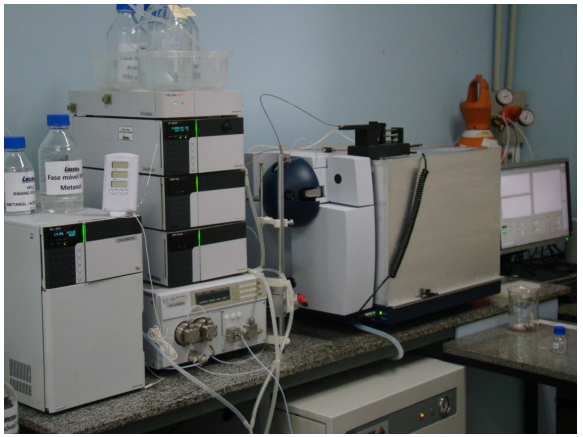
HPLC chromatograms of LASSBio-448 and its metabolites formed by incubation with rat liver microsomes (1mg/mL). **A**) Incubation in the presence of NADPH generating system at time = 0 min; **B**) Incubation in the presence of NADPH generating system and the formation of **LASSBio-448**-related metabolites at time = 120 minutes; **C**) Incubation in the absence of NADPH generating system at time = 120 minutes;

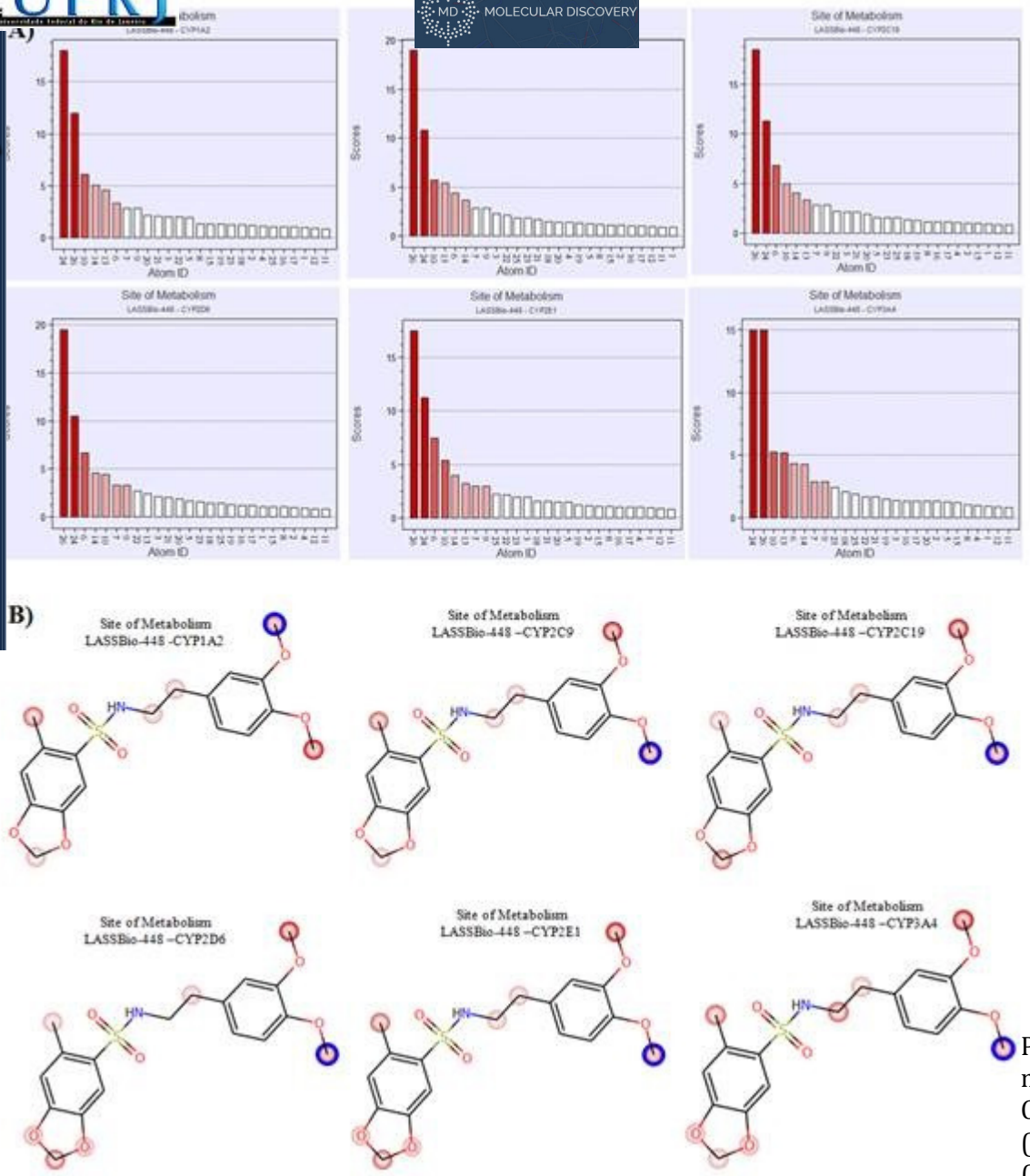
D) Blank test: 1mg/mL microsomes proteins from rat liver, in addition to NADPH generating system and in the absence of **LASSBio-448**.

IS = internal standard (*e.g*. biphenyl-4-carboxylate Methyl, C=20 µM). Apparatus: Shimadzu - LC20AD, column: Kromasil 100-5 C18 250 to 4.6 mm; Mobile phase: 70% ACN, 30% water, 0.1% TFA, flow: 1mL/min; Detector: SPD-M20A (Diode array); Wavelength: 254 nm.

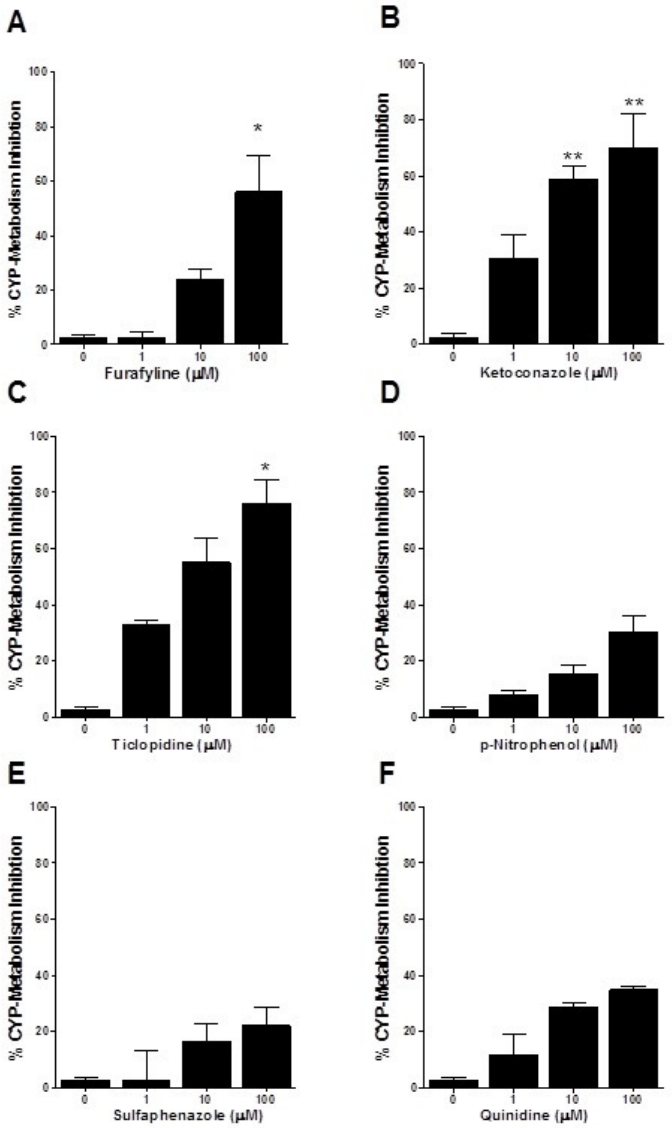


Percentage of *in vitro* microsomal hepatic metabolism of **LASSBio-448** in the presence of CYPs and FMO inhibitors (ketoconazole and methimazole, respectively).





The *in silico* predition of the site of metabolism for **LASSBio-448** using several CYP's in program MetaSite



Percentage inhibition of *in vitro* microsomal hepatic metabolism of **LASSBio-448** by selective inhibitors of CYPs isoenzymes: furafylline (CYP1A2), ketoconazole (**CYP3A4**), ticlopidine (**CYP2C19**), *p*-nitrophenol (CYP2E1), sulfaphenazole (CYP2C9) and quinidine (CYP2D6).

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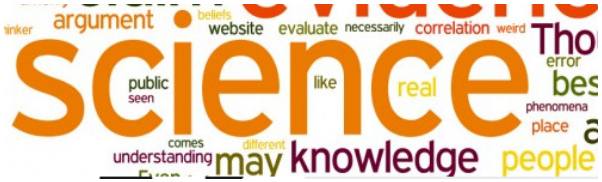
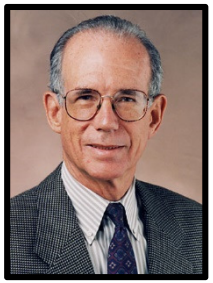


A descoberta de fármacos é baseada em Ciência!



OnLine

- *Science* **2004**, *303*, 1713 (Donald Kennedy)
- *Science* **2000**, *287*, 1951 (Julia Uppenbrink, J. Mervis)
- *Science* **2005**, *309*, 728 (Jeffrey Mervis)

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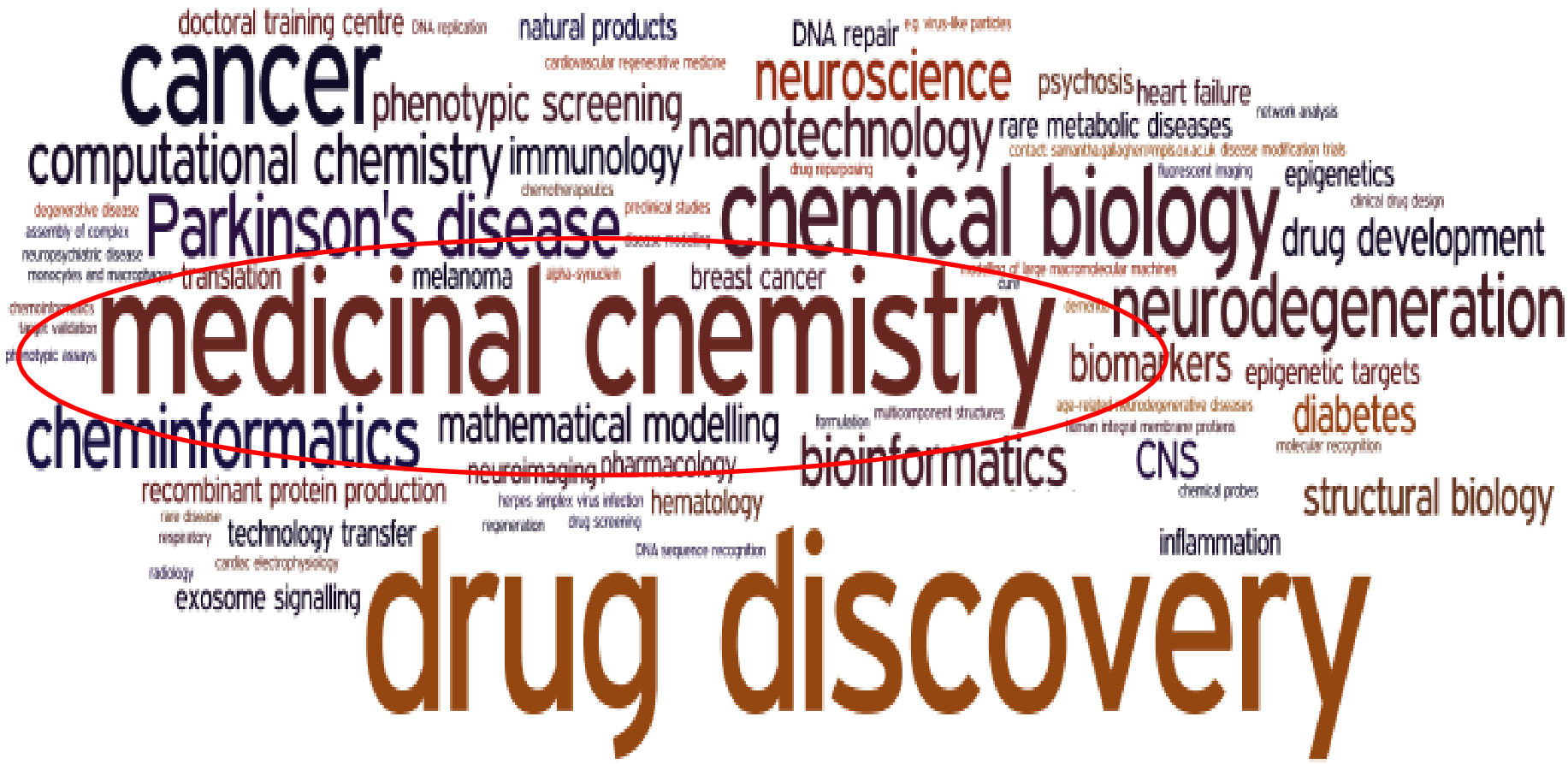
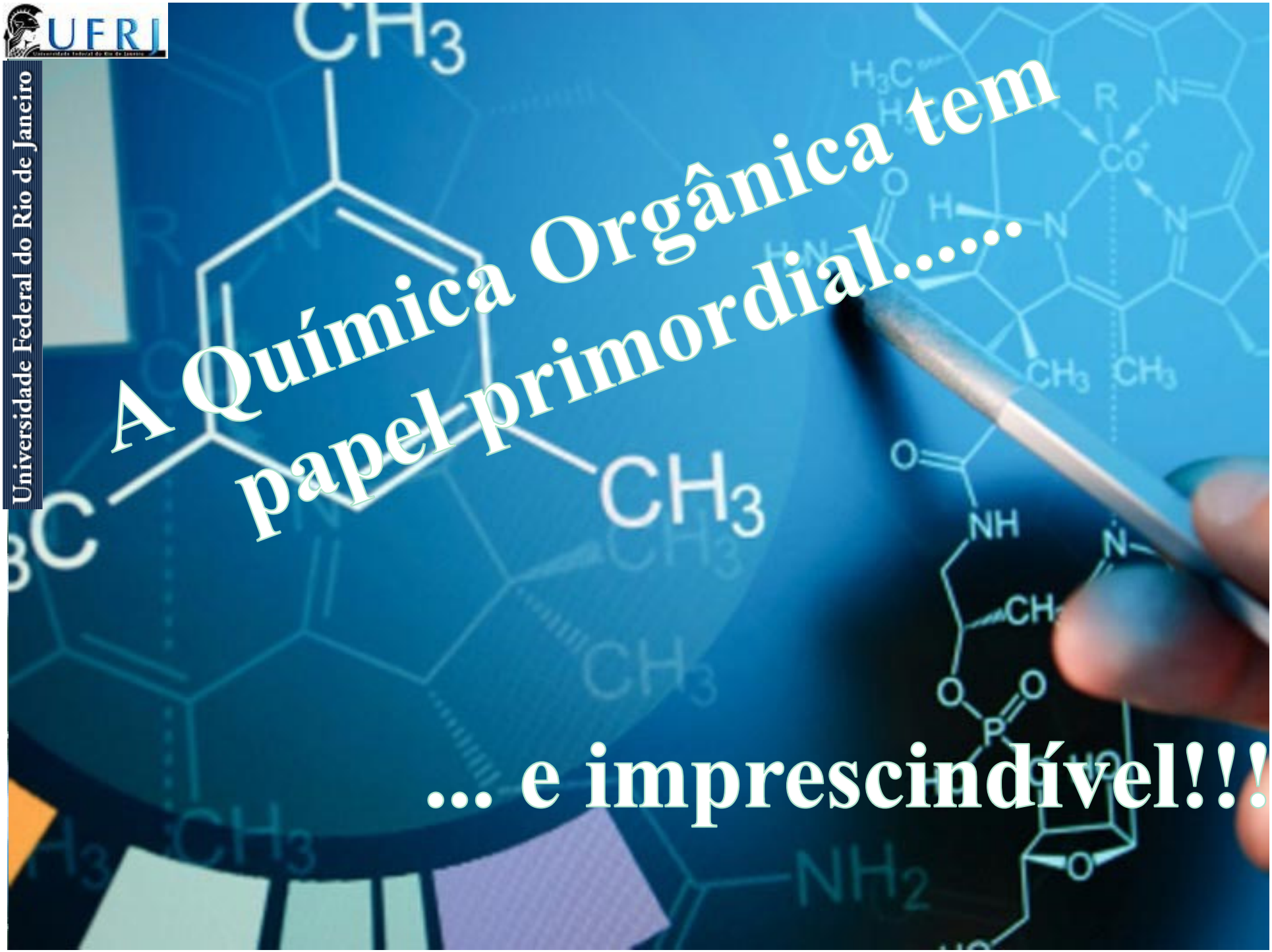
O processo de *drug discovery*

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A Química Orgânica tem papel primordial.....
... e imprescindível!!!


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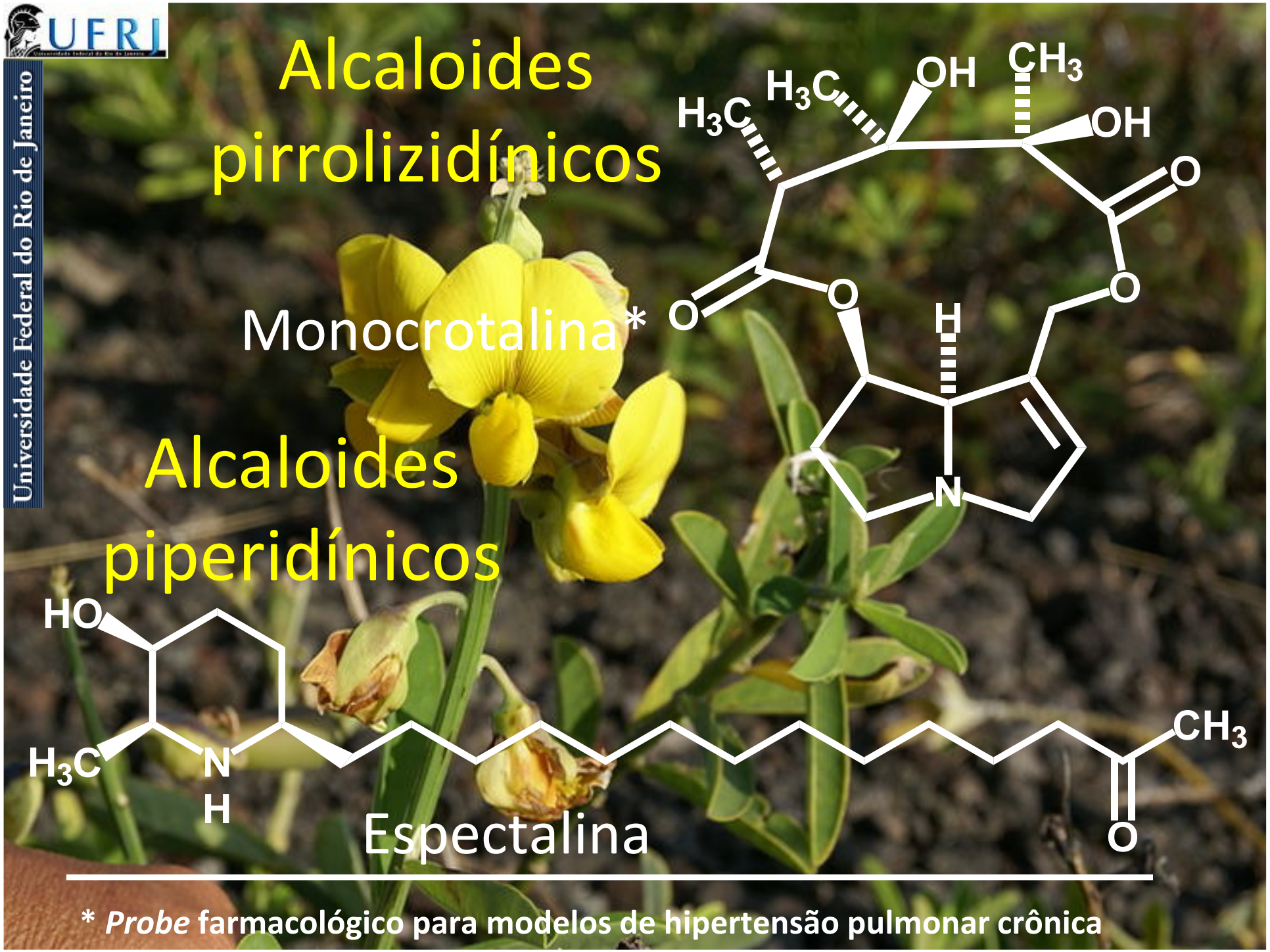
The Beginning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Alcaloides pirrolizidínicos
Monocrotalina*
Alcaloides piperidínicos
Espectalina
* Probe farmacológico para modelos de hipertensão pulmonar crônica

Instituto Nacional de Ciência e Tecnologia de Fármacos e Medicamentos

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Protótipo natural

Bióforo etanol-amina incluso

espectalina

2002

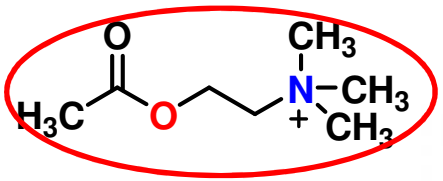
Sociedade Brasileira de Química

Química Medicinal

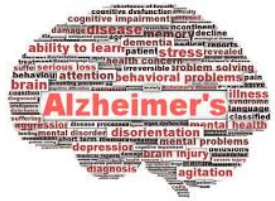
fragmento biofórico

Similaridade molecular

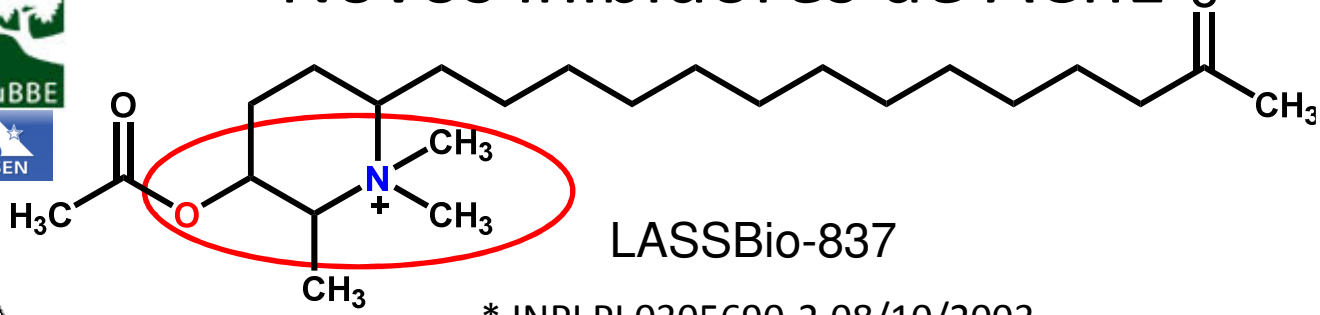
etanol-amina



ACh



Novos inibidores de AChE*



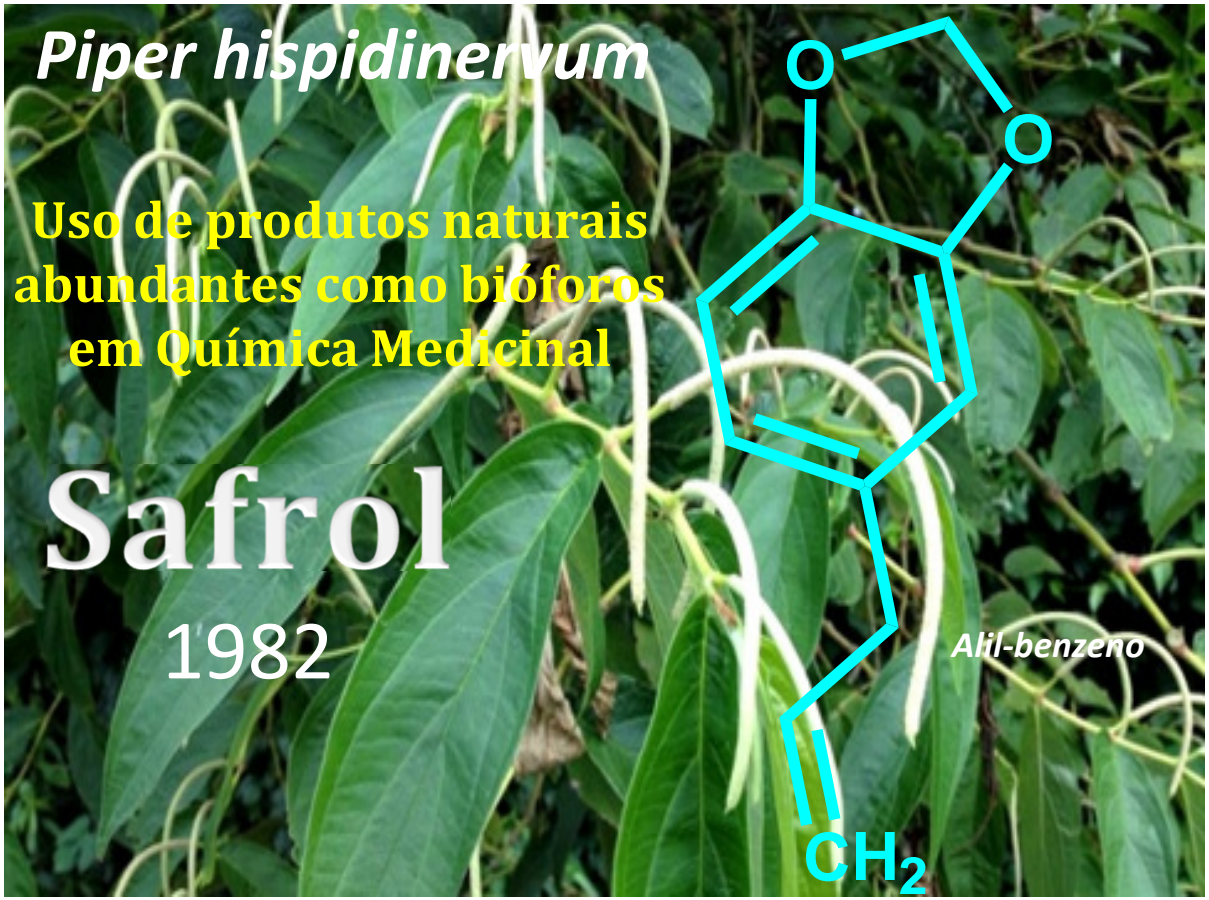
LASSBio-837

* INPI PI 0305690-2 08/10/2003
* Patent NZ554392 (15/10/2004)

Cassia leptophylla

Leguminosa

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



1982

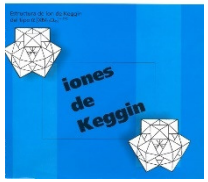
5% oléo

82% safrol

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

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

química nova



Oléo de Sassafrás ⟶ *Ocotea pretiosa*

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

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

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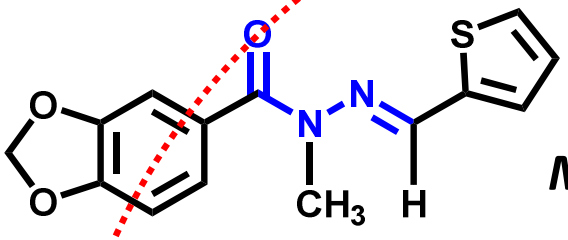
Estudos de otimização

Molécula vedete



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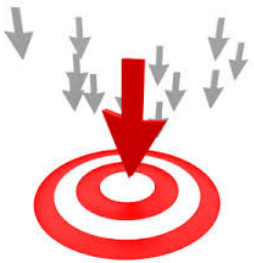
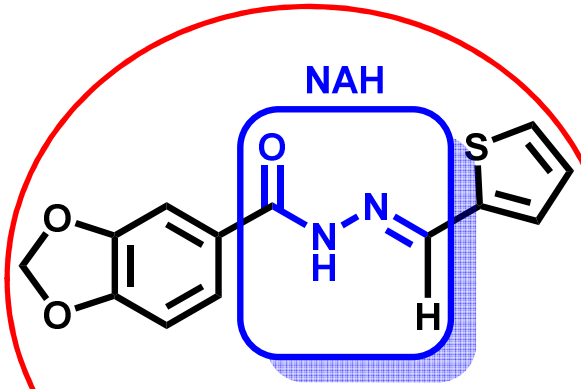
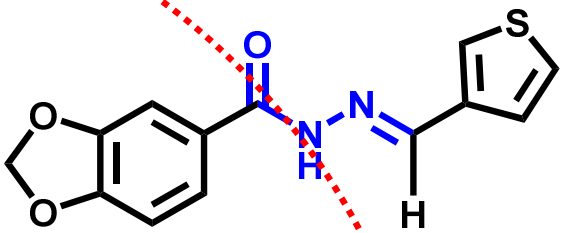




LASSBio-294
1999



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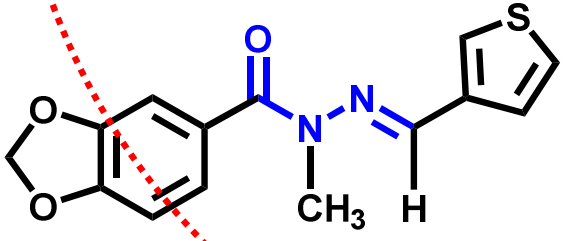

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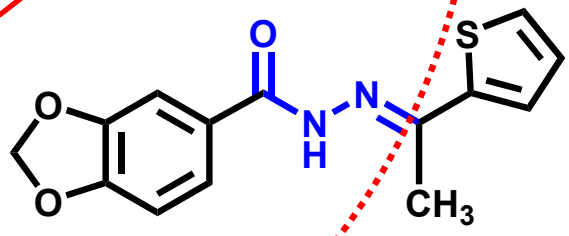

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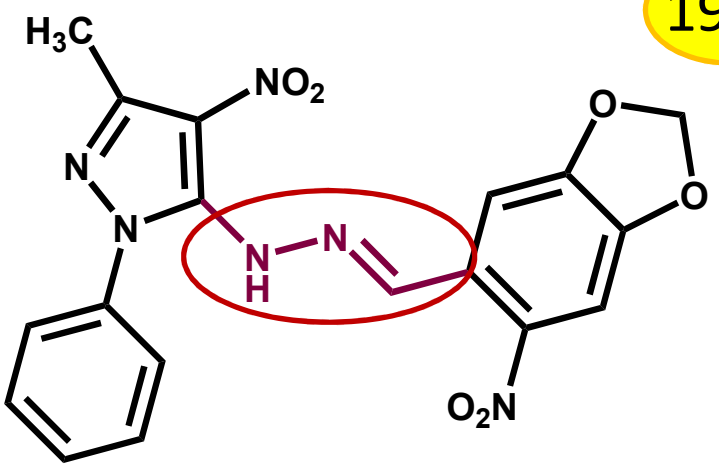
Novas hidrazonas

1994



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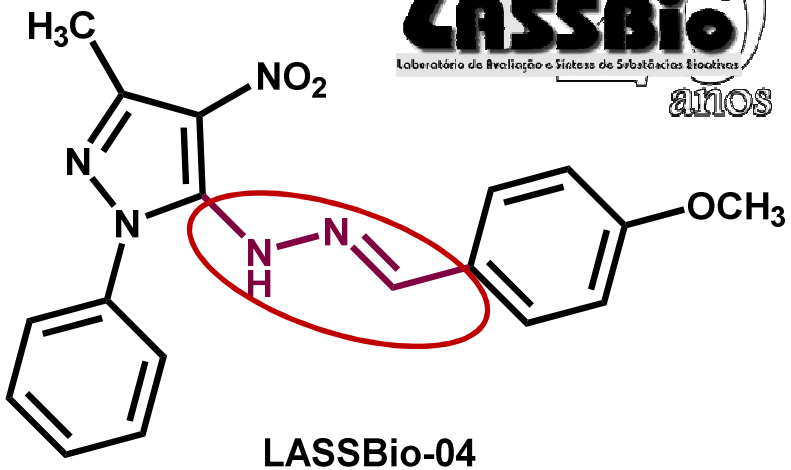

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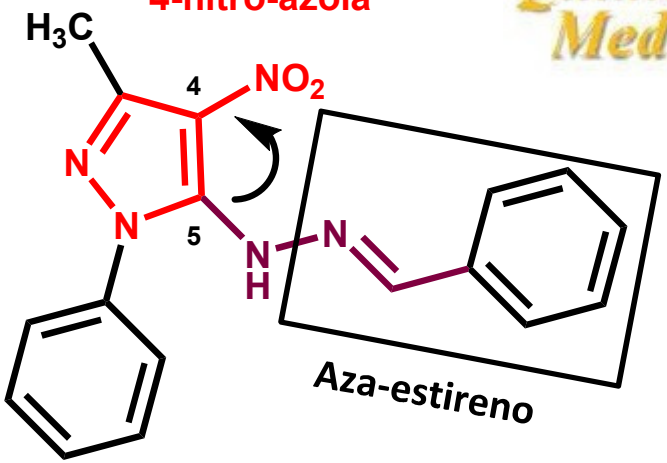

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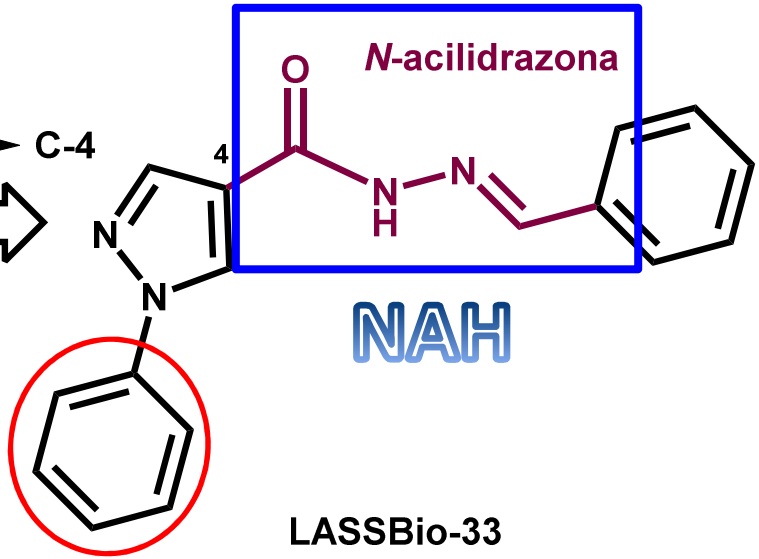
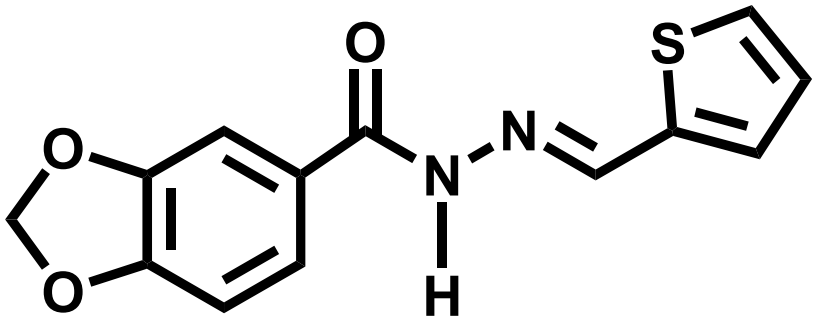
C-5 → C-4



LASSBio-33

Novas acilidrazonas

Universidade Federal do Rio de Janeiro



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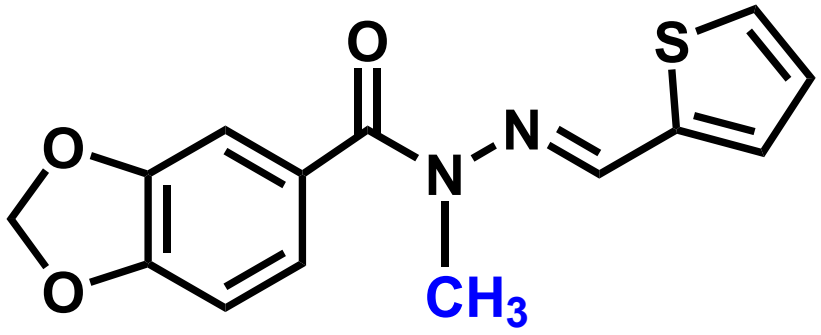

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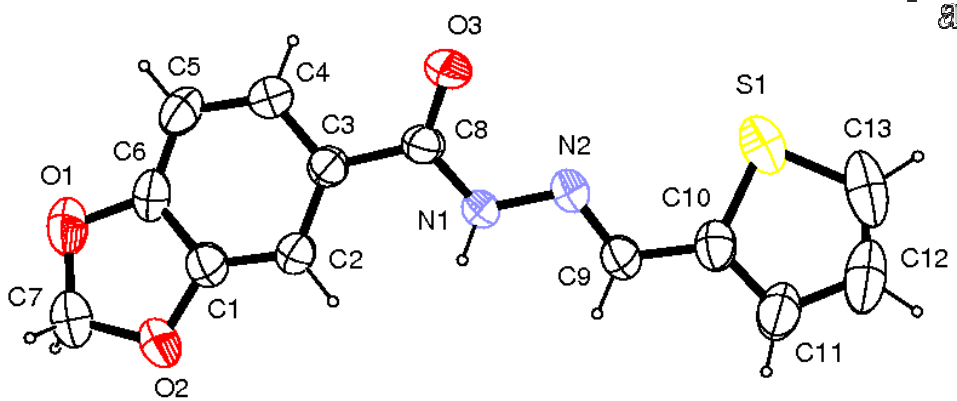

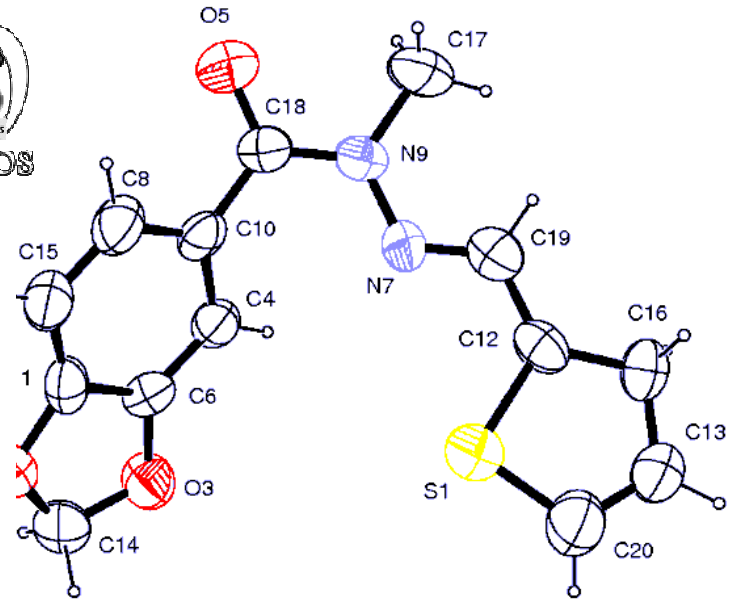

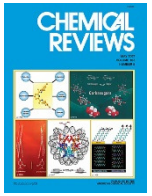

EJ Barreiro, AE Kümmerle, CAM Fraga, The methylation effect in medicinal chemistry, *Chem Rev*. **2011**, *111*, 5215

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Universidade Federal do Rio de Janeiro

Patente obtida

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

UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/020,328	Aug. 15, 2006	7.091.238	32360-178943	9681

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
(application filed

The Patent Term Adjustment is 109 day(s). Any
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;

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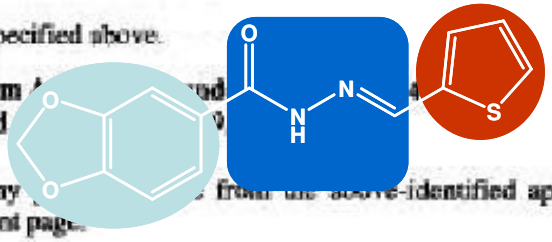
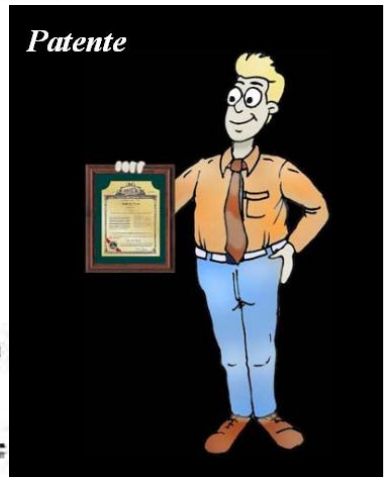
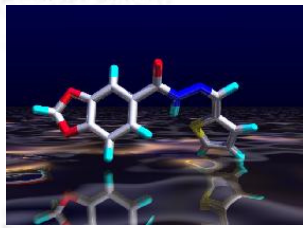




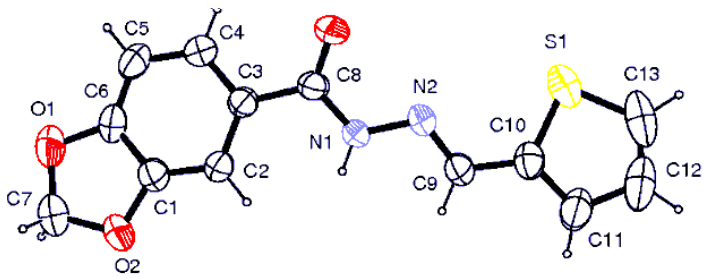
Thienylhydrazone with Digitalis-like properties (positive inotropic effects)



1. 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).&
2. JS da Silva, SL Pereira, RC Maia, SS Landgraf, C Caruso-Neves, AE Kümmerle, CAM Fraga, EJ Barreiro, RT Sudo, G Zapata-Sudo, *N*-acylhydrazone improves exercise intolerance in rats submitted to myocardial infarction by the recovery of calcium homeostasis in skeletal muscle, *Life Sciences*, **94**, 30–36 (2014).
3. SL Pereira, AE Kümmerle, CAM Fraga, EJ Barreiro, RT Sudo, G Zapata-Sudo, Vasodilator and antihypertensive effects of a novel *N*-acylhydrazone derivative mediated by the inhibition of L-type Ca2+ channels, *Fundamental & Clinical Pharmacology*, **28**, 29–41 (2014).
4. FN Costa, FF Ferreira, TF da Silva, EJ Barreiro, LM Lima, D Braza, RC Barroso, Structure Re-determination of LASSBio-294 – a cardioactive compound of the *N*-acylhydrazone class – using X-ray powder diffraction data, *Powder Diffraction,* **28**, S491-S509 (2013).
5. CM Leal, SL Pereira, AE Kümmerle, DM Leal, R Teschc, CMR Sant'Anna, CAM Fraga, EJ Barreiro, RT Sudo, G Zapata-Sudo, Antihypertensive profile of 2-thienyl-3,4-methylenedioxybenzoylhydrazone is mediated by activation of the $A2_A$ adenosine receptor, *Eur. J. Med. Chem*., **55**, 49–57 (2012).#
6. RC Braga, VM Alves, CAM Fraga, EJ Barreiro, V de Oliveira, CH Andrade, Combination of docking, molecular dynamics and quantum mechanical calculations for metabolism prediction of 3,4-methylenedioxybenzoyl-2-thienylhydrazone, *J. Mol. Model*., **18**, 2065–2078 (2012).
7. RC Braga, ACB Tôrres, CB Persiano, RO Alves, CAM Fraga, EJ Barreiro, V de Oliveira, Determination of the cardioactive prototype LASSBio-294 and its metabolites in dog plasma by LC–MS/MS: Application for a pharmacokinetic study, *Journal of Pharmaceutical and Biomedical Analysis,* **55**, 1024-1030 (2011). (Times cited: 2)
8. A G M Fraga, L L da 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, *European Journal of Medicinal Chemistry* ,**46** 349-355 (2011). (Times cited: 1)

9. DG Costa , JS da Silva, AE Kummerle et al., LASSBio-294, A Compound With Inotropic and Lusitropic Activity, Decreases Cardiac Remodeling and Improves Ca2+ Influx Into Sarcoplasmic Reticulum After Myocardial Infarction, *Am. J.Hypertension*, **23**, 1220-1227 (2010). (Times cited:3)
10. FCF Brito, AE Kummerle, C Lugnier 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: 4)
11. EO Carneiro, CH Andrade, RC Braga et al., Structure-based prediction and biosynthesis of the major mammalian metabolite of the cardioactive prototype LASSBio-294, *Bioorg. Med. Chem. Lett*., **20**, 3734-3736 (2010). (Times cited:4)
12. L Pol-Fachin, CAM Fraga, EJ Barreiro et al., Characterization of the conformational ensemble from bioactive *N*-acylhydrazone derivatives , *J. Mol. Graphics & Modelling*, **28**, 446-454 (2010).
13. G Zapata-Sudo, SL Pereira, HJV Beiral et al., Pharmacological Characterization of (3-Thienylidene)-3,4-Methylenedioxybenzoylhydrazide: A Novel Muscarinic Agonist With Antihypertensive Profile, *Am. J.Hypertension*, **23**, 135-141 (2010). (Times cited: 2)
14. FCF Brito, AE Kummerle, C Lugnier et al. Novel thienylacylhydrazone derivatives inhibit platelet aggregation through cyclic nucleotides modulation and thromboxane A2 synthesis inhibition, *Eur. J. Pharmacol*., **638**, 5–12 (2010).
15. AE Kummerle, JM Raimundo, CM Leal *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: 16)
16. 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: 44)
17. H Gonzalez-Serratos, EFR Pereira, RZ Chang *et al.*, The thienylhydrazone, (2 '-thienylidene)3,4-methylenedioxvbenzoylhydrazine (LASSBio-294), develops fatigue resistance and has a positive inotropic effect in mammalian skeletal muscle, *Biophys. J.*, **86**, 225A-225A Suppl. (S 2004).

18. G Zapata-Sudo, RT Sudo, PA Maronas et al., Thienylhydrazone derivative increases sarcoplasmic reticulum Ca2+ release in mammalian skeletal muscle, Eur. J. Pharmacol., 470, 79-85 (2003) (Times Cited: 4)
19. 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: 14)
20. 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)
21. H Gonzalez-Serratos , RZ Chang, EFR Pereira et al., A novel thienylhydrazone, (2-thienylidene)3,4-methylenedioxybenzoylhydrazine, increases inotropism and decreases fatigue of skeletal muscle, *J. Pharmacol. Exp. Ther*., **299**, 558-566 (2001) (Times Cited: 14)
22. RT Sudo, G Zapata-Sudo, EJ Barreiro, The new compound, LASSBio 294, increases the contractility of intact and saponin-skinned cardiac muscle from Wistar rats, *Br. J. Pharmacol*., **134**, 603-613 (2001) (Times Cited: 13)
23. PC Lima, LM Lima, KCM Silva et al., Synthesis and analgesic activity of novel *N*-acylarylhydrazones and isosters, derived from natural safrole, *Eur. J. Med. Chem*., **35**, 187−203 (2000). (Times cited: 70)



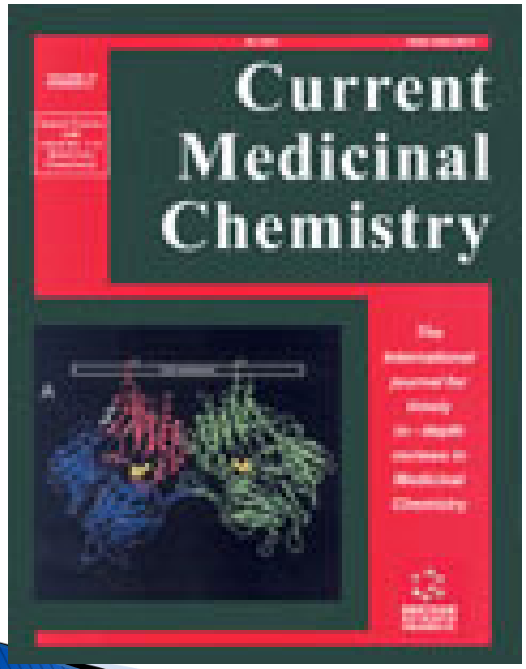
CAS # 314021-07-3

Universidade Federal do Rio de Janeiro

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

Carlos A.M. Fraga and Eliezer J. Barreiro

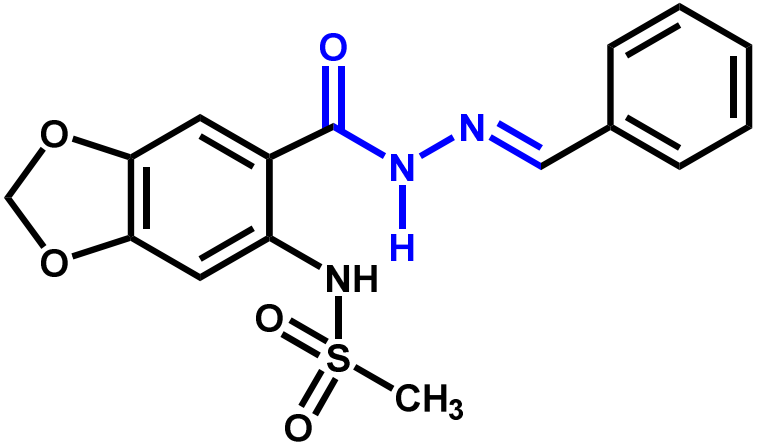
Volume 13, 167-198, 2006



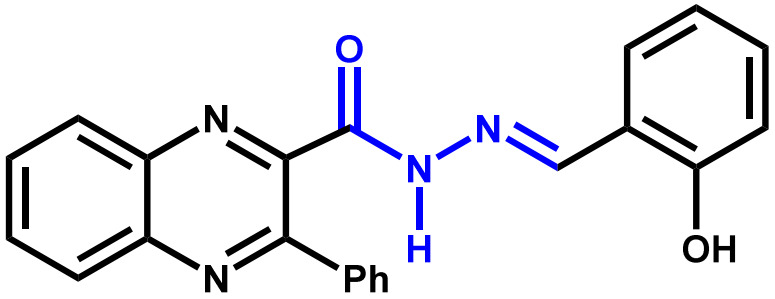
In this article we provide an overview on the medicinal chemistry of new bioactive *N*-acylhydrazone (NAH) derivatives designed through the structural optimization of *N*-arylhydrazone precursors, originally planned by molecular hybridization of two known 5-lipoxygenase inhibitors, *i.e*. CBS-1108 and 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.

Quim Nova, 2002.

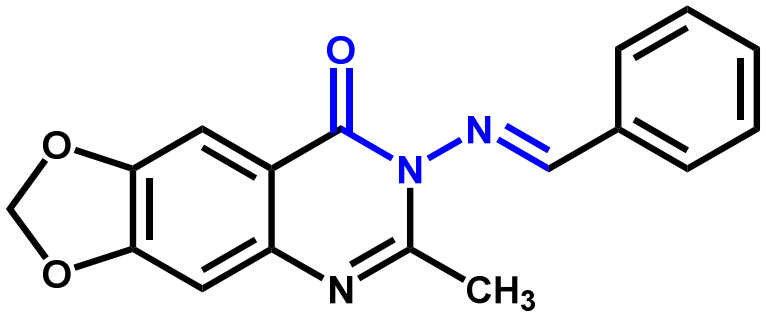
Quimiodiversidade NAH



JLM Tributino, CD Duarte, RS Corrêa, AC Doriguetto, J Ellena, NC Romeiro, NG Castro, ALP Miranda, EJ Barreiro, CAM Fraga, *Bioorg Med Chem* **2007**, *15*, 2421



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



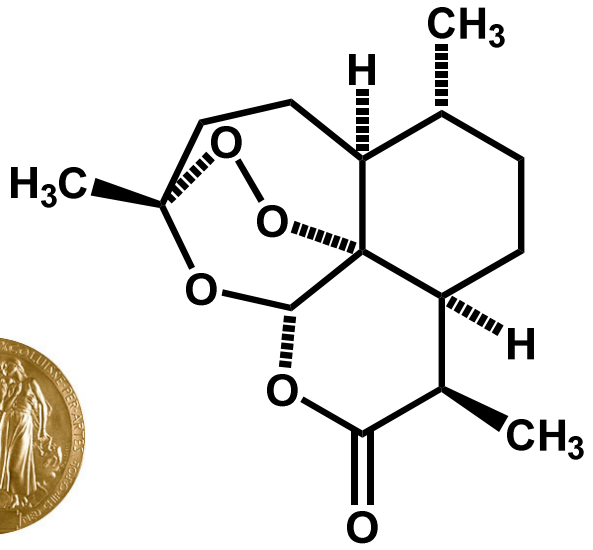
RC Maia, LL Silva, EF Mazzeu, MM Fumian, CM Rezende, AC Doriguetto, RS Corrêa, ALP Miranda, E J Barreiro, CAM Fraga. *Bioorg Med Chem* **2009**, *17*, 6517

http://www.lassbio.icb.ufrj.br/publicacoes.html

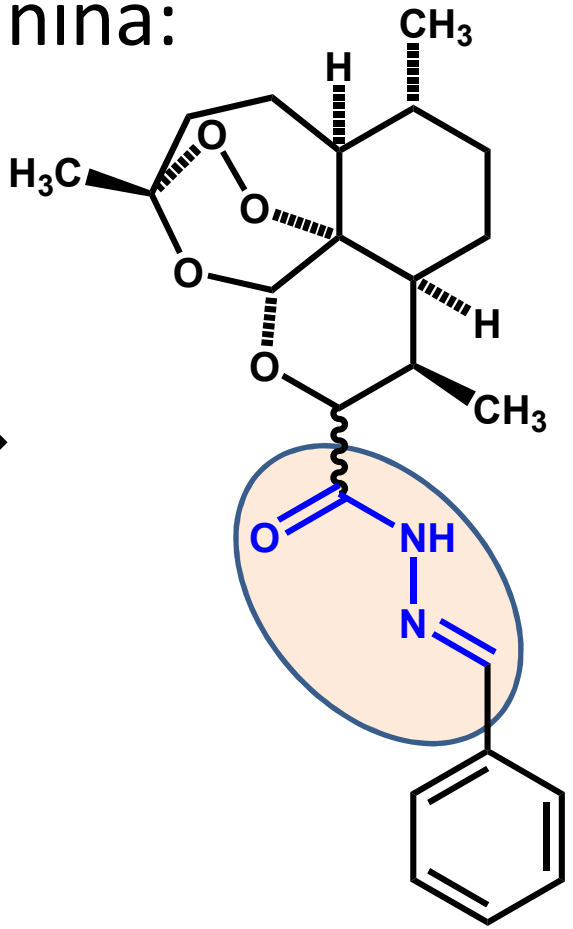
Derivados NAH da artemisinina:

Tu Youyou
(1930-)

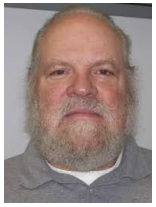
2015



artemisinina



NAH-artemisinina



J McChesney, MA Avery, MJF Alvim, EJ Barreiro, 2002

Senior Research Scientist
Eli Lilly

MA Avery, M Alvim-Gaston, EJ Barreiro, FE Cohen, YA Sabnis, JR Woolfrey, Structure-activity relationships of the antimalarial agent artemisinin. 6. The development of predictive in vitro potency models using CoMFA and HQSAR methodologies, *J Med Chem* **2002**, *45*, 292-303.

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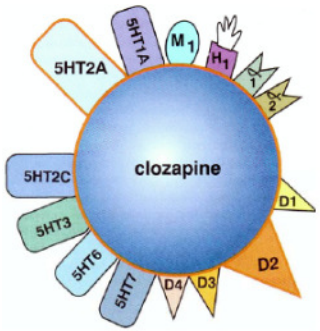
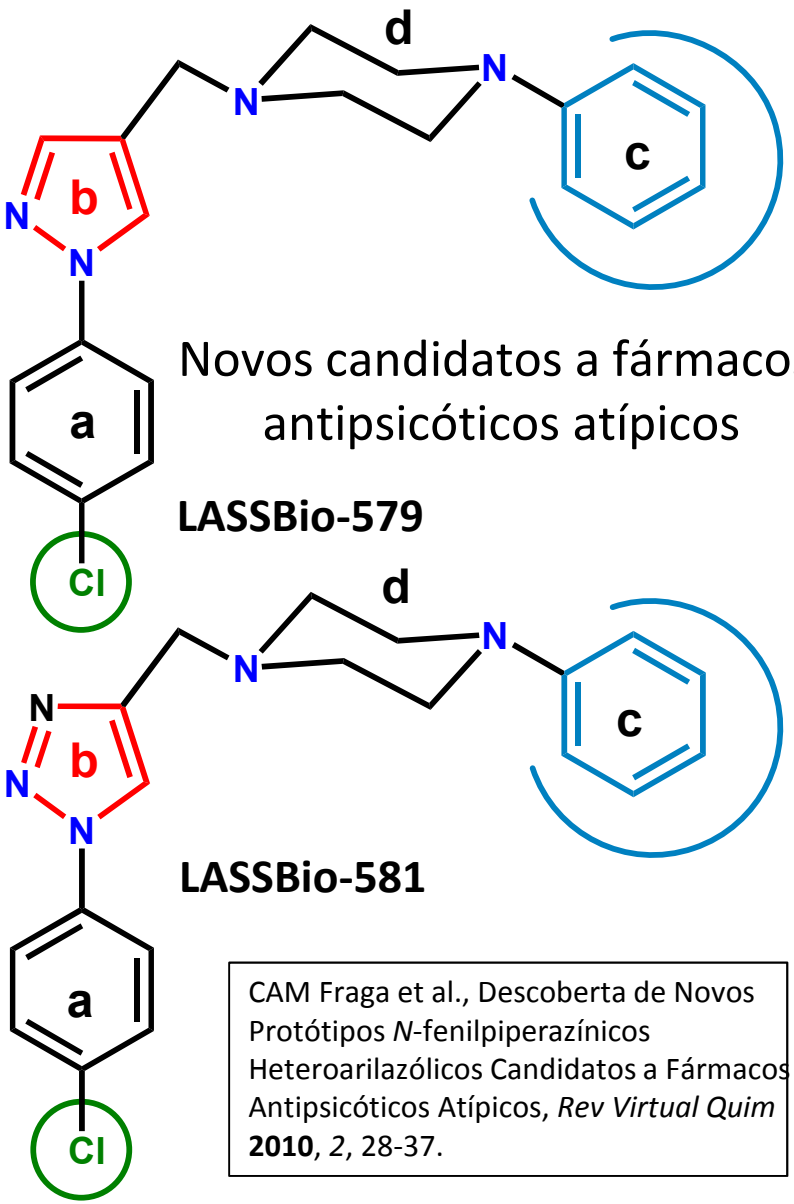
Scaffold hopping

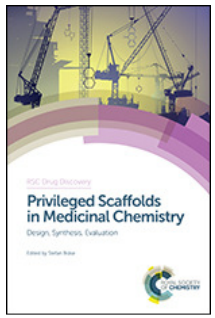
clozapina



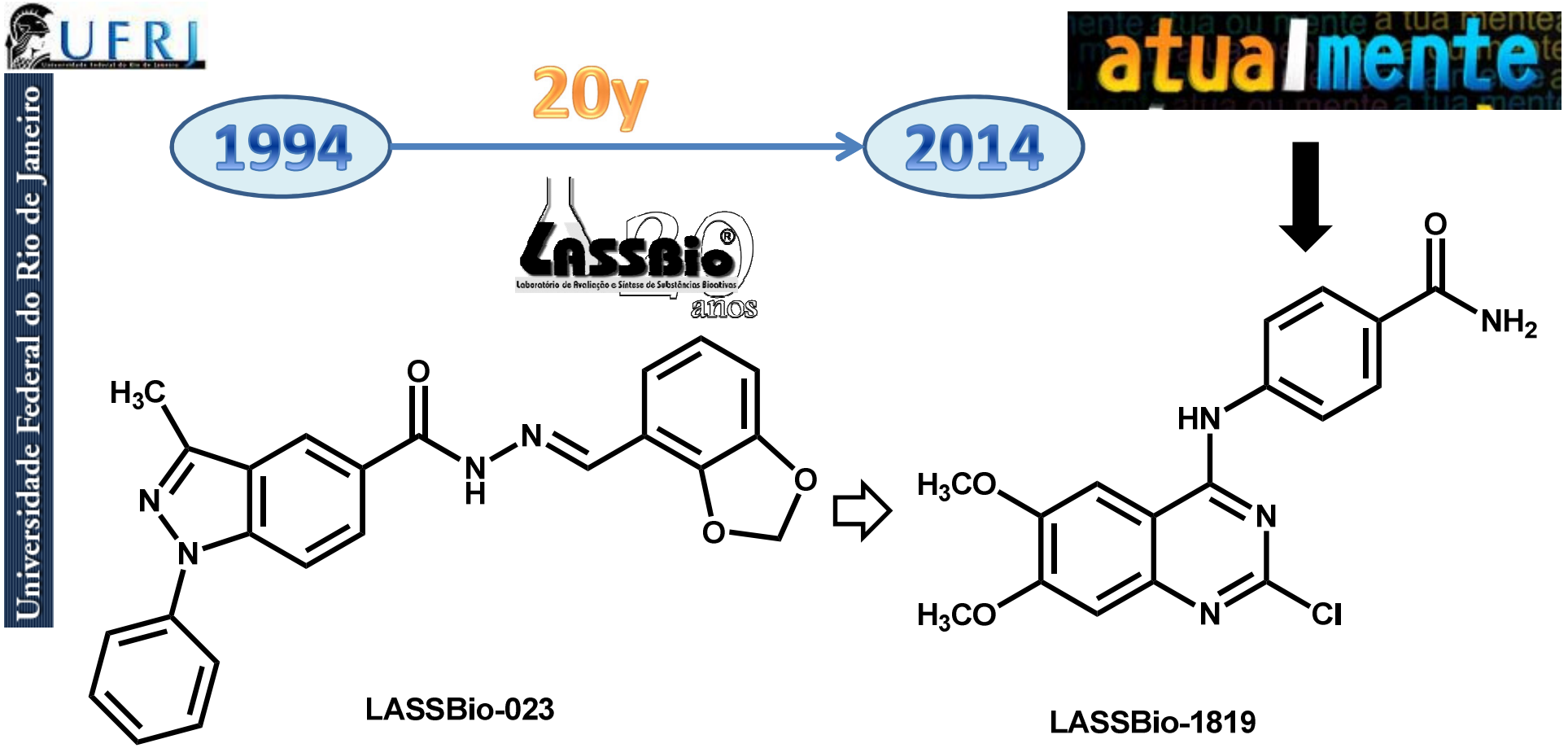


Novos candidatos a fármacos antipsicóticos atípicos

CAM Fraga et al., Descoberta de Novos Protótipos *N*-fenilpiperazínicos Heteroarilazólicos Candidatos a Fármacos Antipsicóticos Atípicos, *Rev Virtual Quim* **2010**, *2*, 28-37.



EJ Barreiro, Privileged Scaffolds in Medicinal Chemistry: An Introduction, em Privileged Scaffolds in Medicinal Chemistry : Design, Synthesis, Evaluation, S Bräse Ed., Royal Society of Chemistry **2015**, Chapter 1, pp. 1-15.[10.1039/9781782622246-00001]

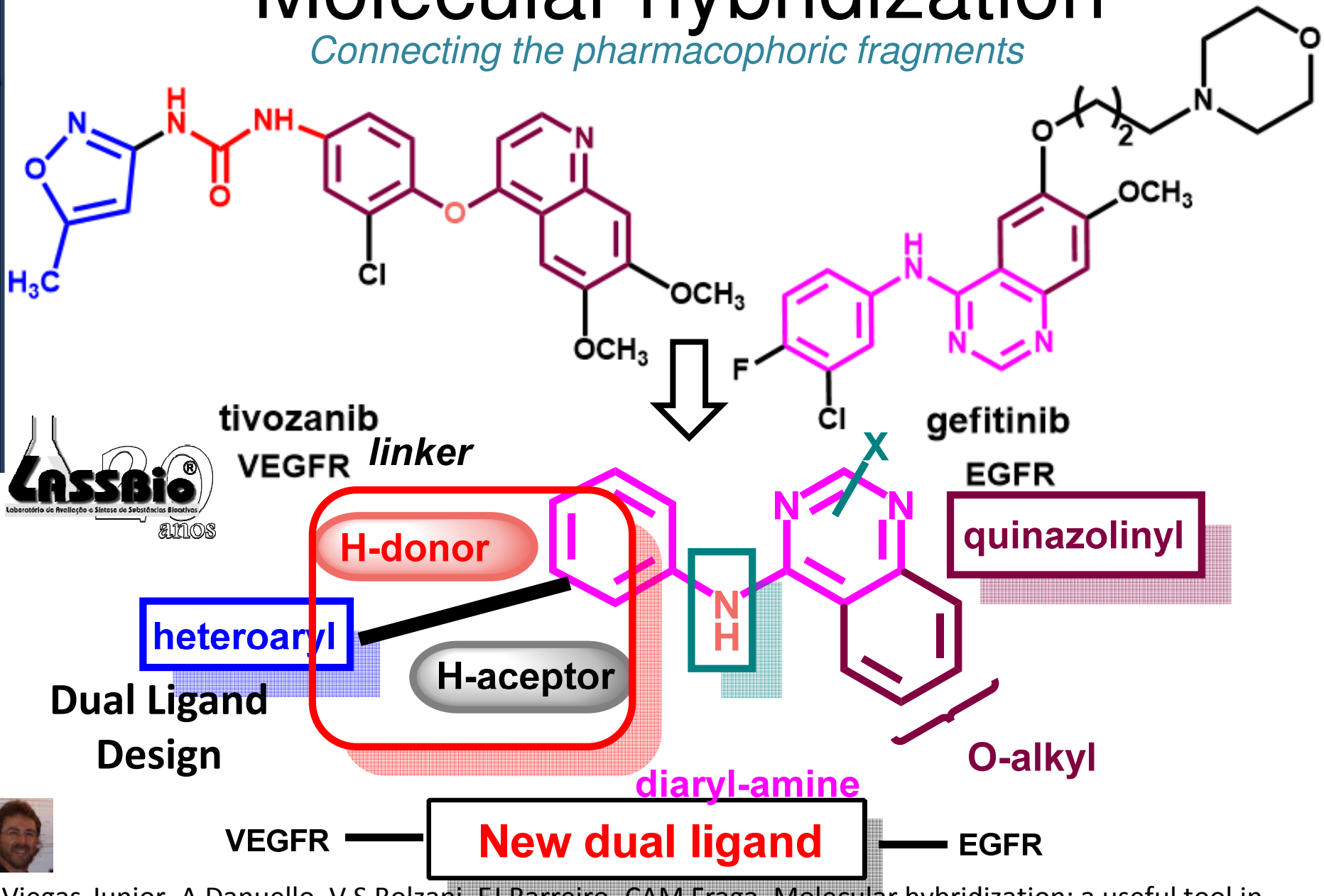


L R S Dias, M J F Alvim, A C C Freitas, E J Barreiro, Synthesis and analgesic properties of 5-acyl-aryl hydrazone 1-*H* pyrazolo [3,4-*b*] pyridine derivatives, *Pharm Acta Helvetiae* **1994**, *69*, 163-169

MLC Barbosa, LM Lima, R Tesch, CMR Sant'Anna, F Totzke, MH Kubbutat , C Schächtele, SA Laufer, EJ Barreiro, Novel 2-chloro-4-anilino-quinazoline derivatives as EGFR and VEGFR-2 dual inhibitors, *Eur J Med Chem*. **2014**, *71*, 1-15.

Molecular hybridization

Connecting the pharmacophoric fragments



C Viegas-Junior, A Danuello, V S Bolzani, EJ Barreiro, CAM Fraga, Molecular hybridization: a useful tool in the design of new drug prototypes, *Curr Med Chem* **2007**, *14*, 1829.

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Dual Inhibitor

Dual Ligand

Isosteric replacement

carboxamide

medicinal chemistry

Dual kinase activity

EGFRwt IC_{50} = 0,90 μM

VEGFR-2 IC_{50} = 1,17 μM

$C_{17}H_{15}ClN_4O_3$

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Novel molecular pattern

Lead Optimization

M. L. C. Barbosa, *Novos derivados quinazolínicos funcionalizados inibidores duais das tirosina cinases receptoras EGFR & VEGFR-2*, Tese Dr, Instituto de Química, UFRJ, 2013.

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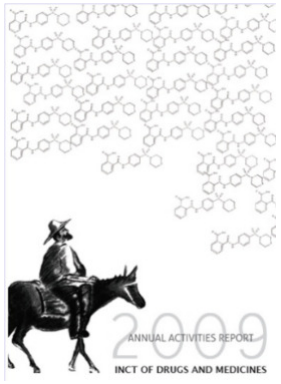

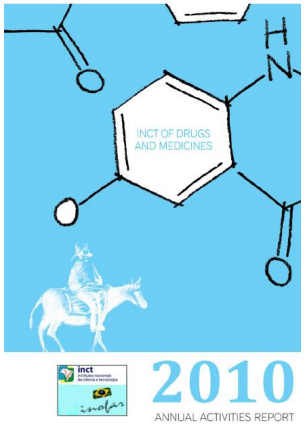

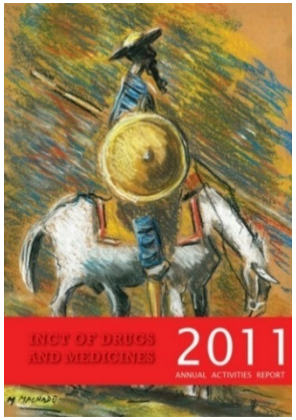

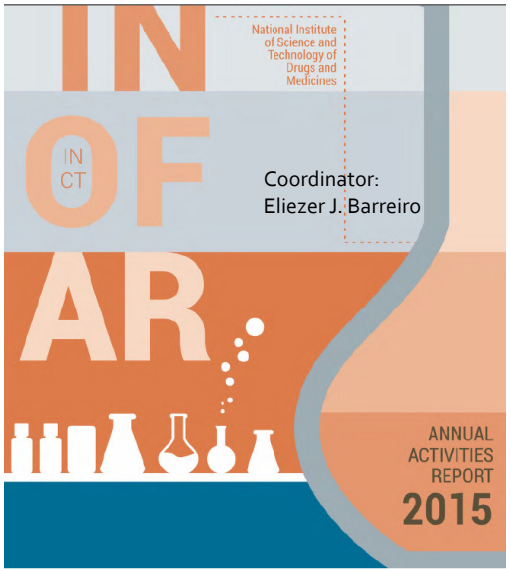

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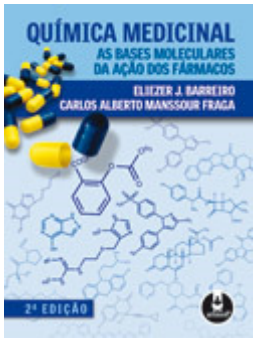

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