Desafios no planejamento & inovação em fármacos no LASSBio/UFRJ: os primeiros 20 anos.

II Encontro em Química Medicinal e Desenvolvimento de Fármacos

Importância, perspectivas e inovações no planejamento de fármacos

28 de setembro de 2016

Eliezer J. Barreiro

Professor Titular - UFRJ

Laboratório de Avaliação e Síntese de Substâncias Bioativas

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

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Quem Somos?

Onde estamos?

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Química Medicinal

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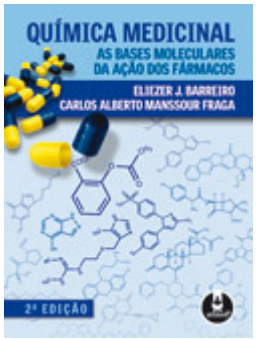

Portal dos Fármacos
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Livro Comemorativo dos 20 anos

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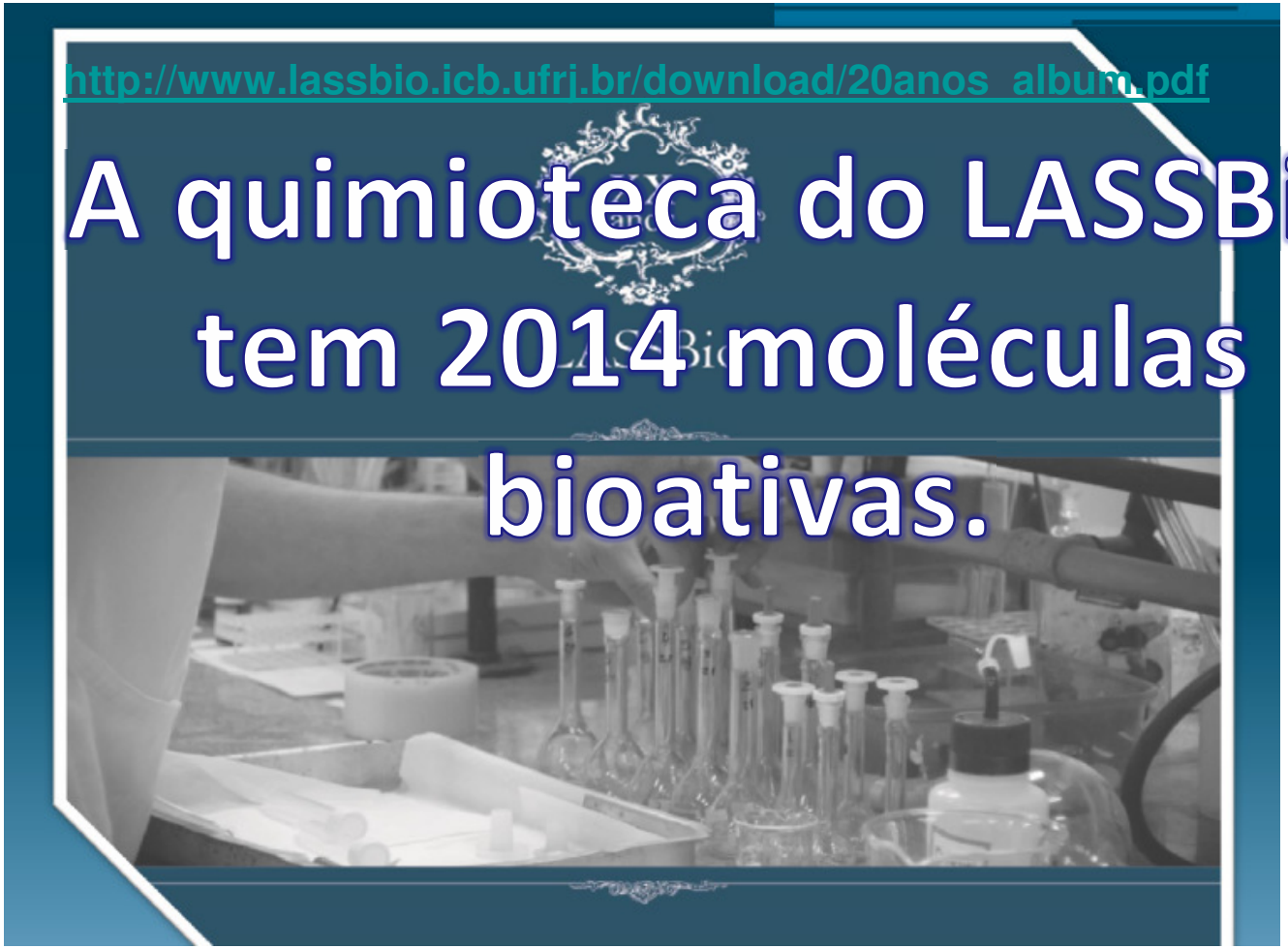
A quimioteca do LASSBio tem 2014 moléculas bioativas.



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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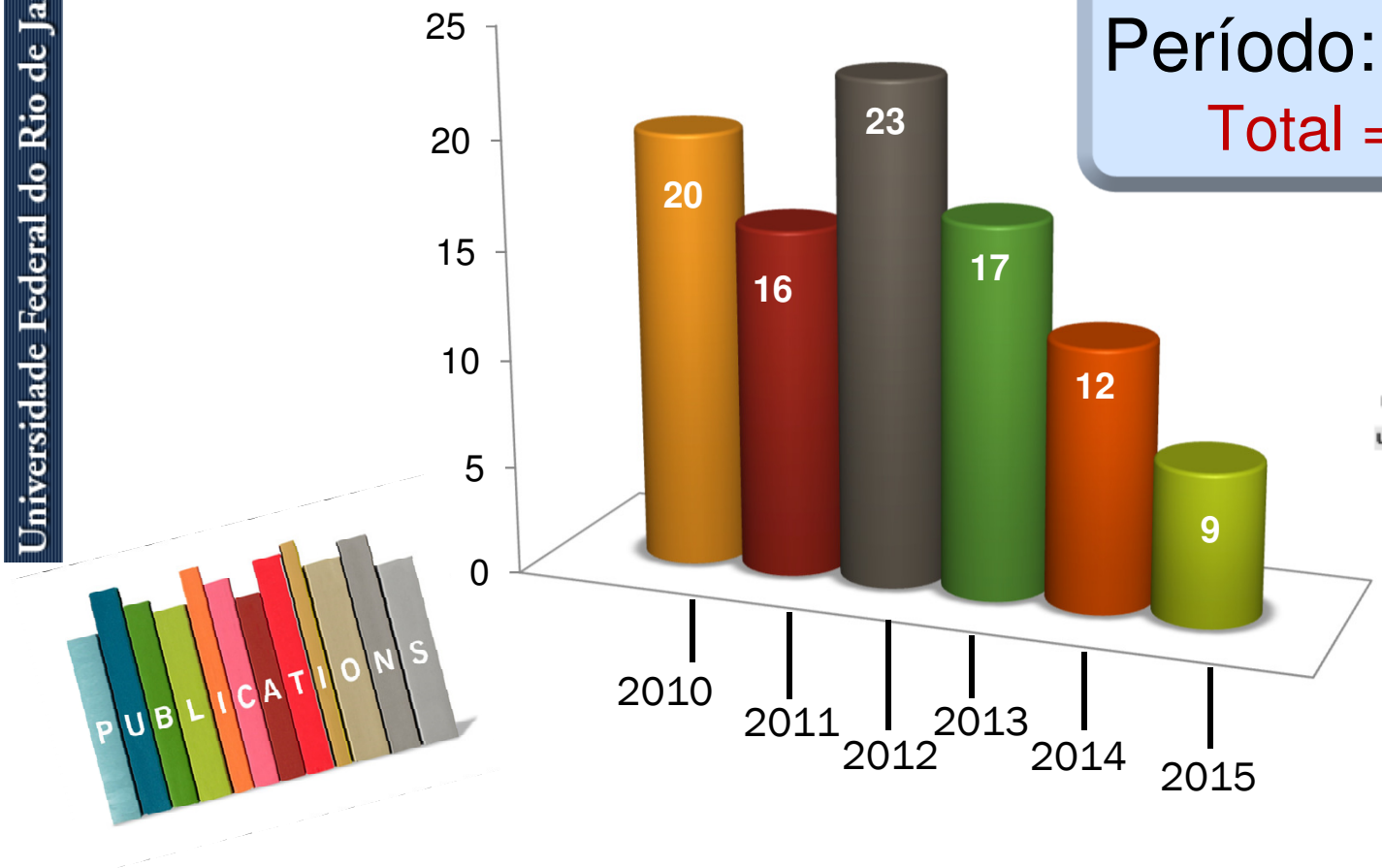

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Fonte: Base Scopus (acesso em 08/06/2015)

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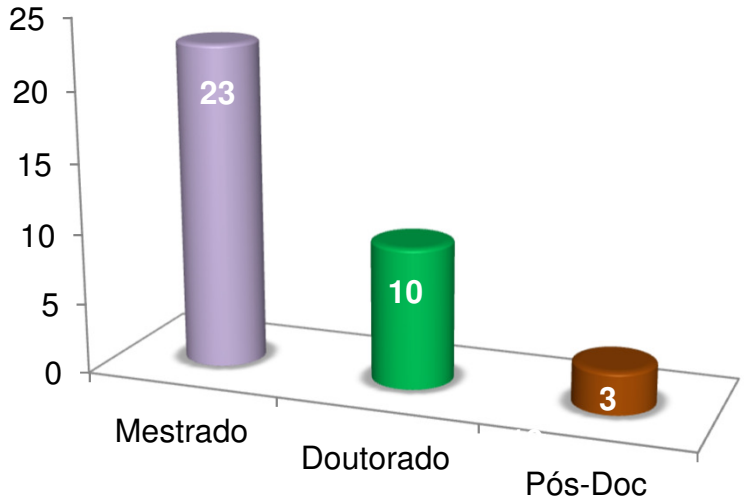
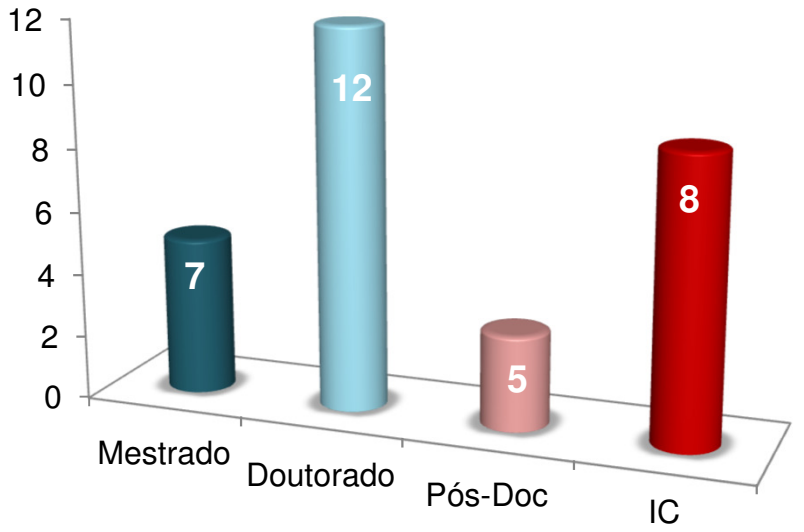
Mestrados e Doutorados Concluídos (2010-2015)



Mestrados e Doutorados em Andamento (2016)



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2016

International Journal of Cardiology 202 (2016) 497–499

Contents lists available at ScienceDirect

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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

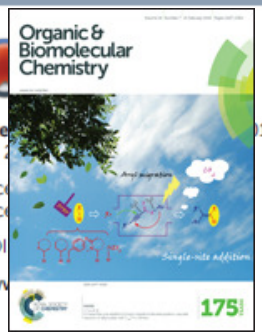
Article

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**

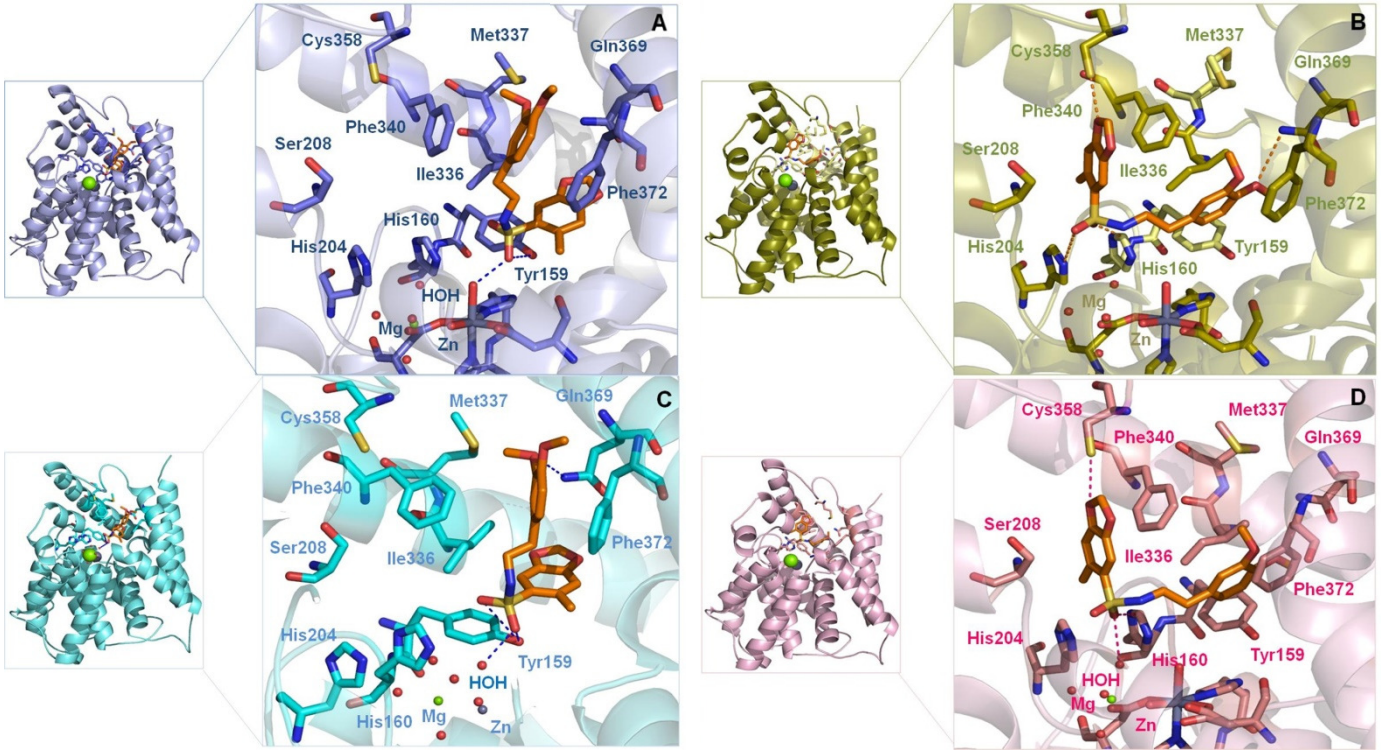
Eleição do Alvo Molecular (receptor) ***e.g.*** **PDE-4**

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

Docking **Molecular**

Estrutura de Novos Ligantes

Como fazemos?



Poses de **LASSBio-448** (laranja) com as 4 isoformas de PDE: PDE4A (A), PDE4B (B), PDE4C (C), PDE4D (D). 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

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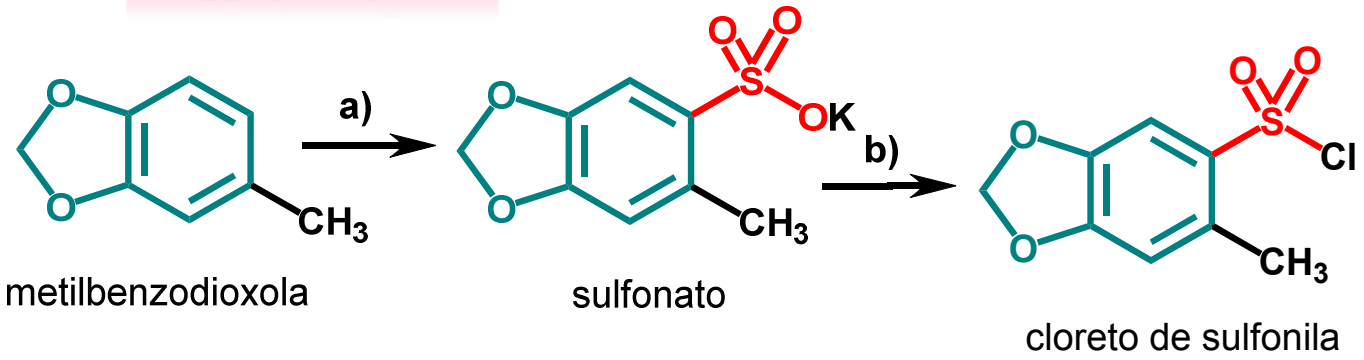
***Docking* Molecular**

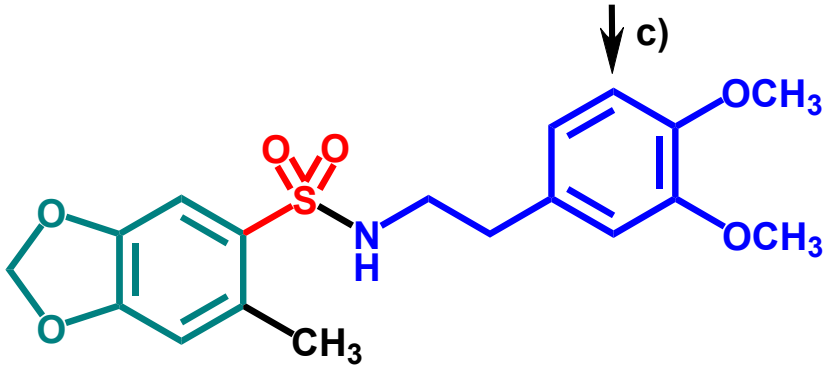
Estrutura de Novos Ligantes

SÍNTESE dos novos ligantes

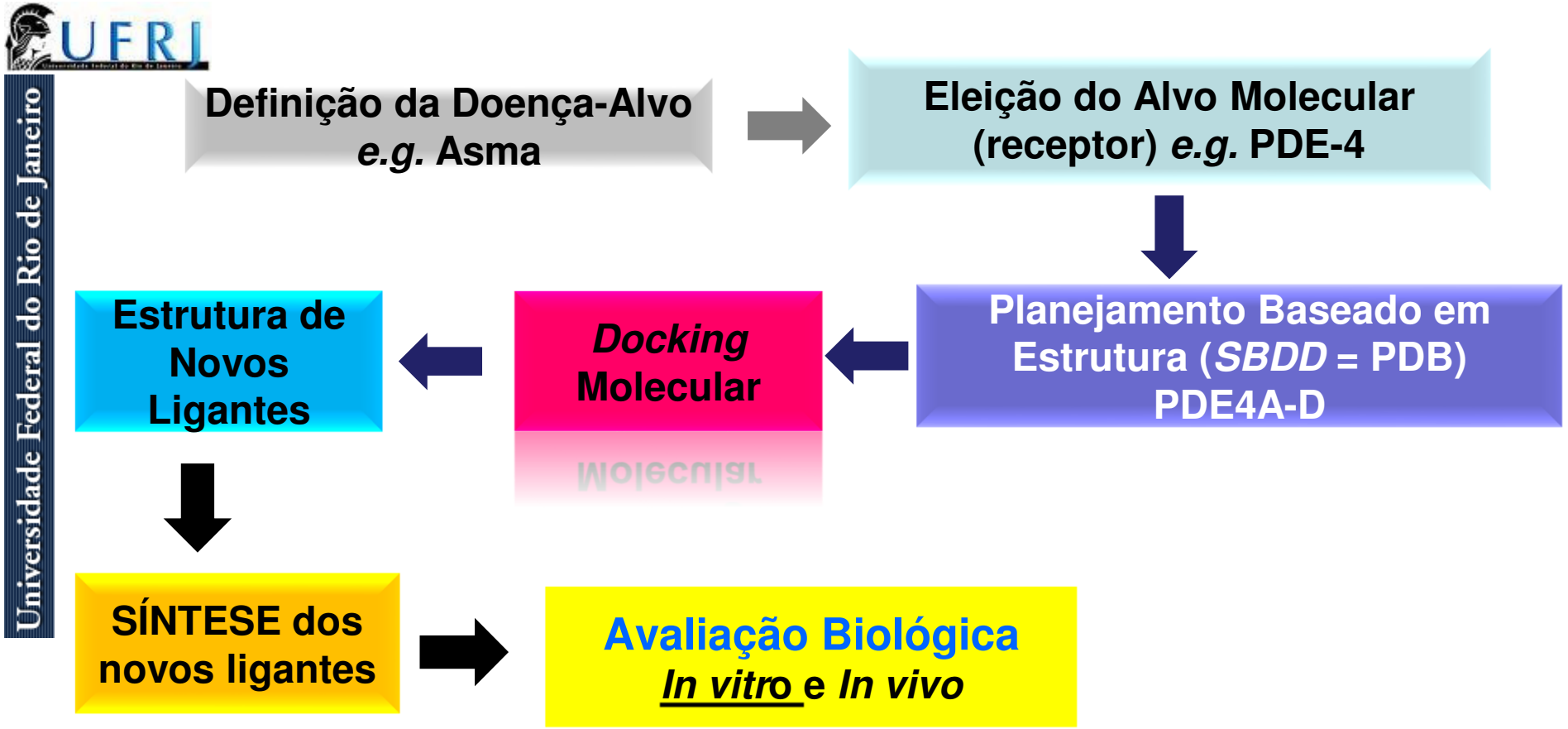


Reagentes & condições:
a) 1) H_2SO_4 /Ac_2O /AcOEt; 0 ºC, 2 h;
2) AcO**K** / EtOH; 25 ºC, 30 min, 93%;
b) SO**Cl**$_2$, DMF, 75 ºC 4 h, 92%;
c)CH_2Cl_2,Et_3N,2-(3,4-dimetoxifenil) etanolamina, 25 °C, 2 h, 81% .

65% rendimento global



LASSBio-448



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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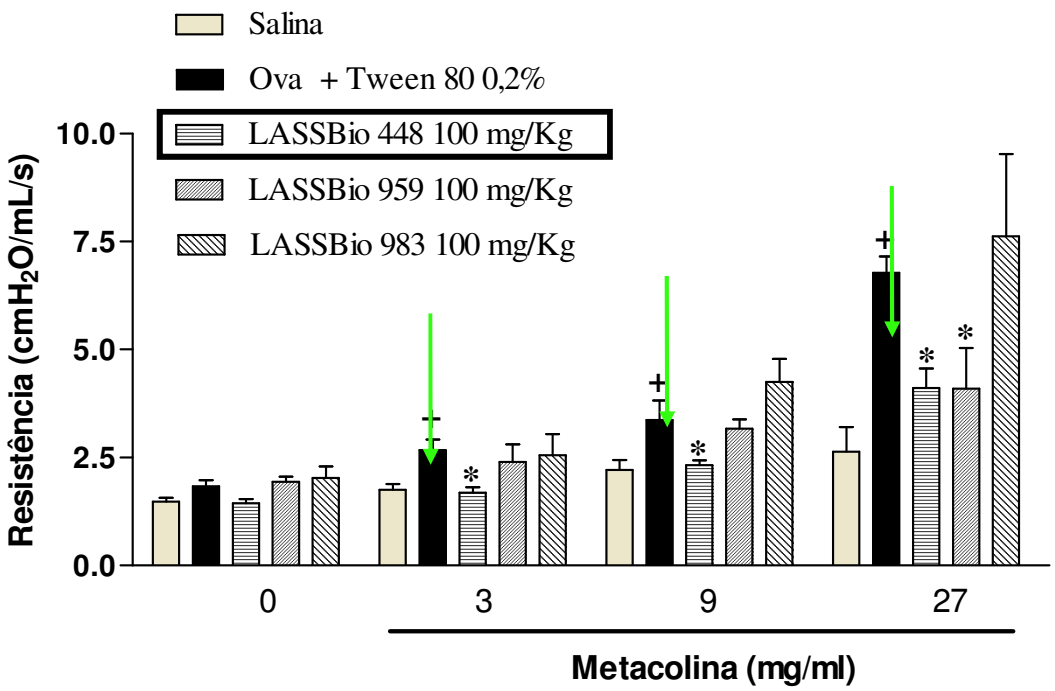
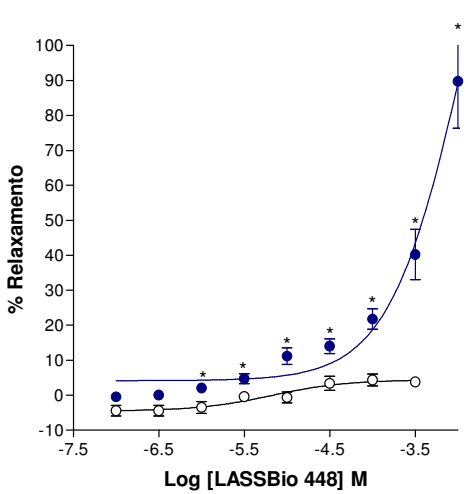
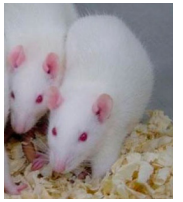
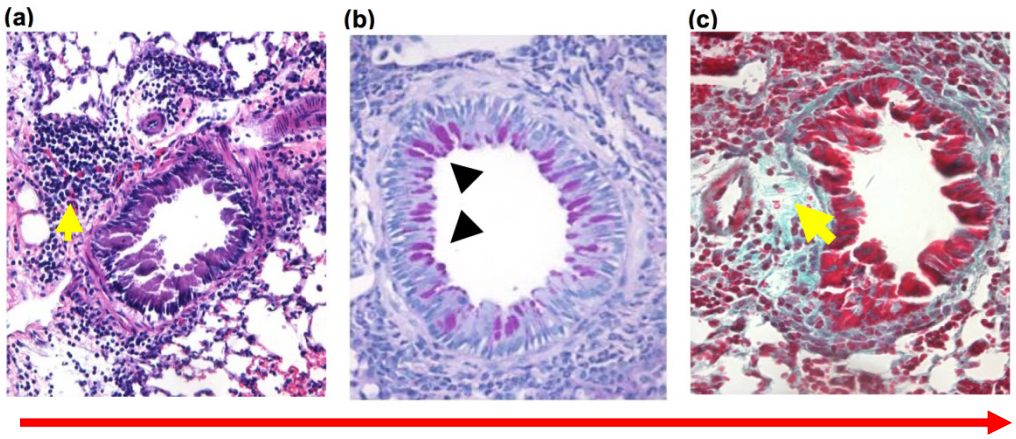




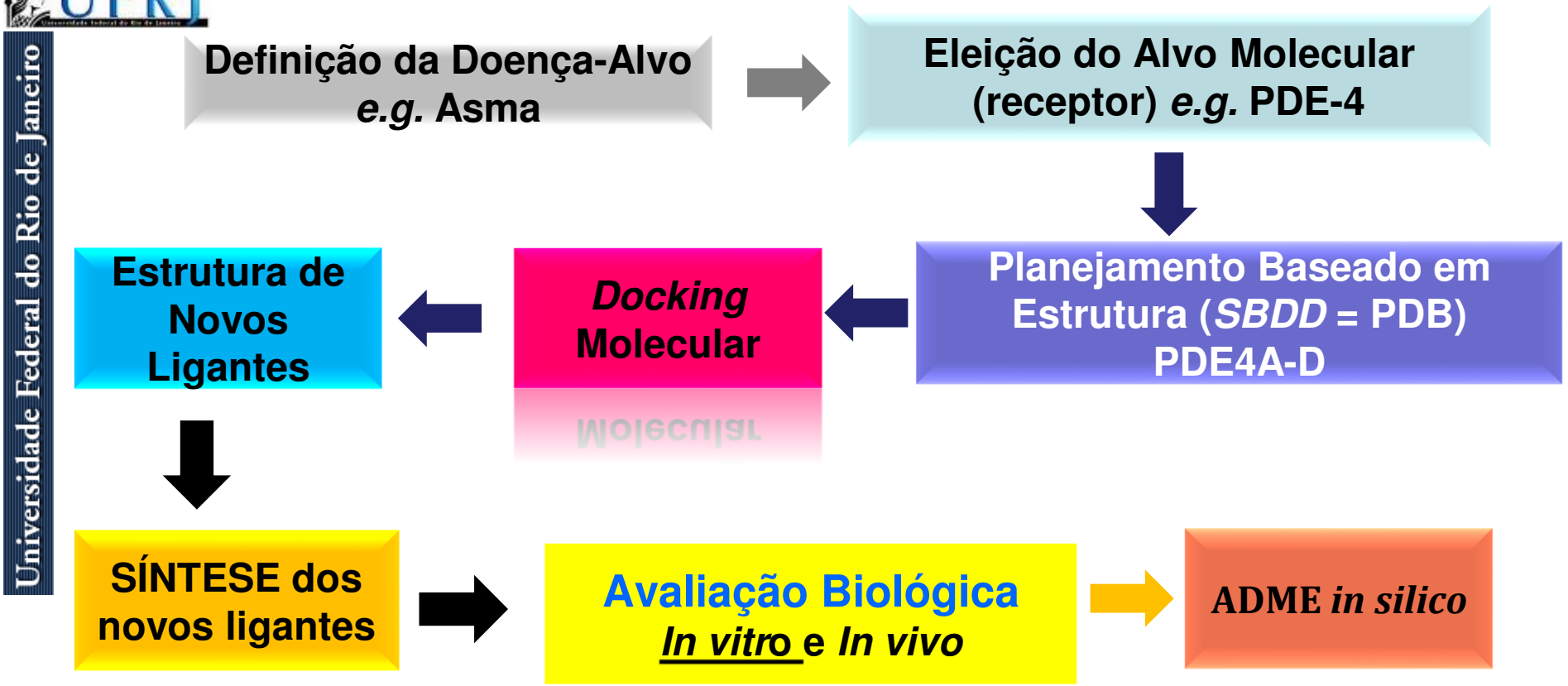
In vivo



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 & 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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***Docking* Molecular**

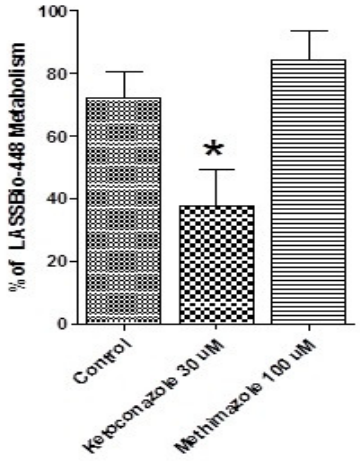
Estrutura de Novos Ligantes

SÍNTESE dos novos ligantes

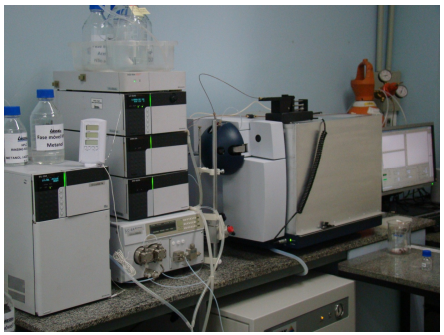
Avaliação Biológica
In vitro* e *In vivo

ADME *in silico*

Estudo do Metabolismo



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



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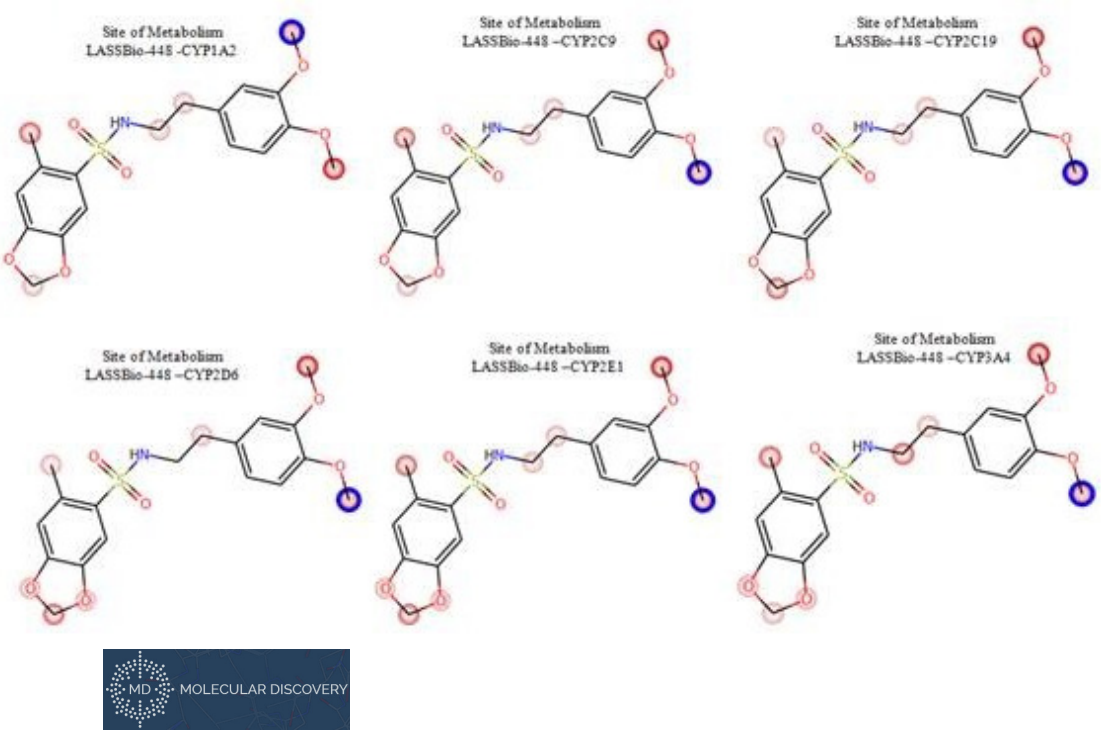
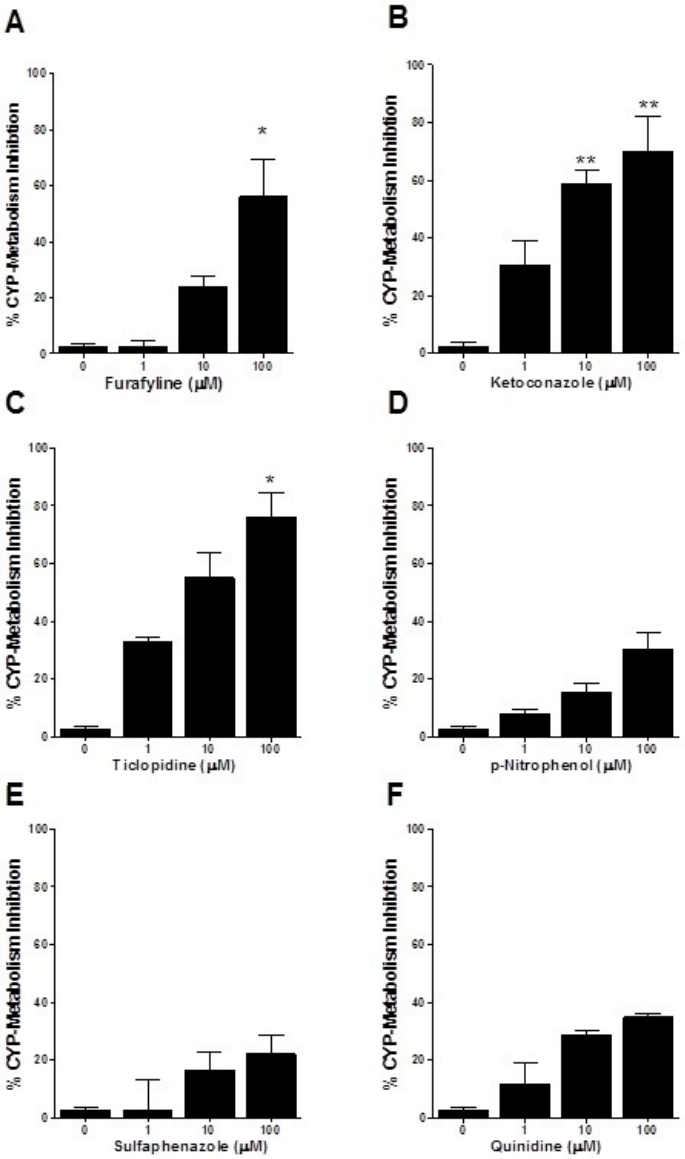
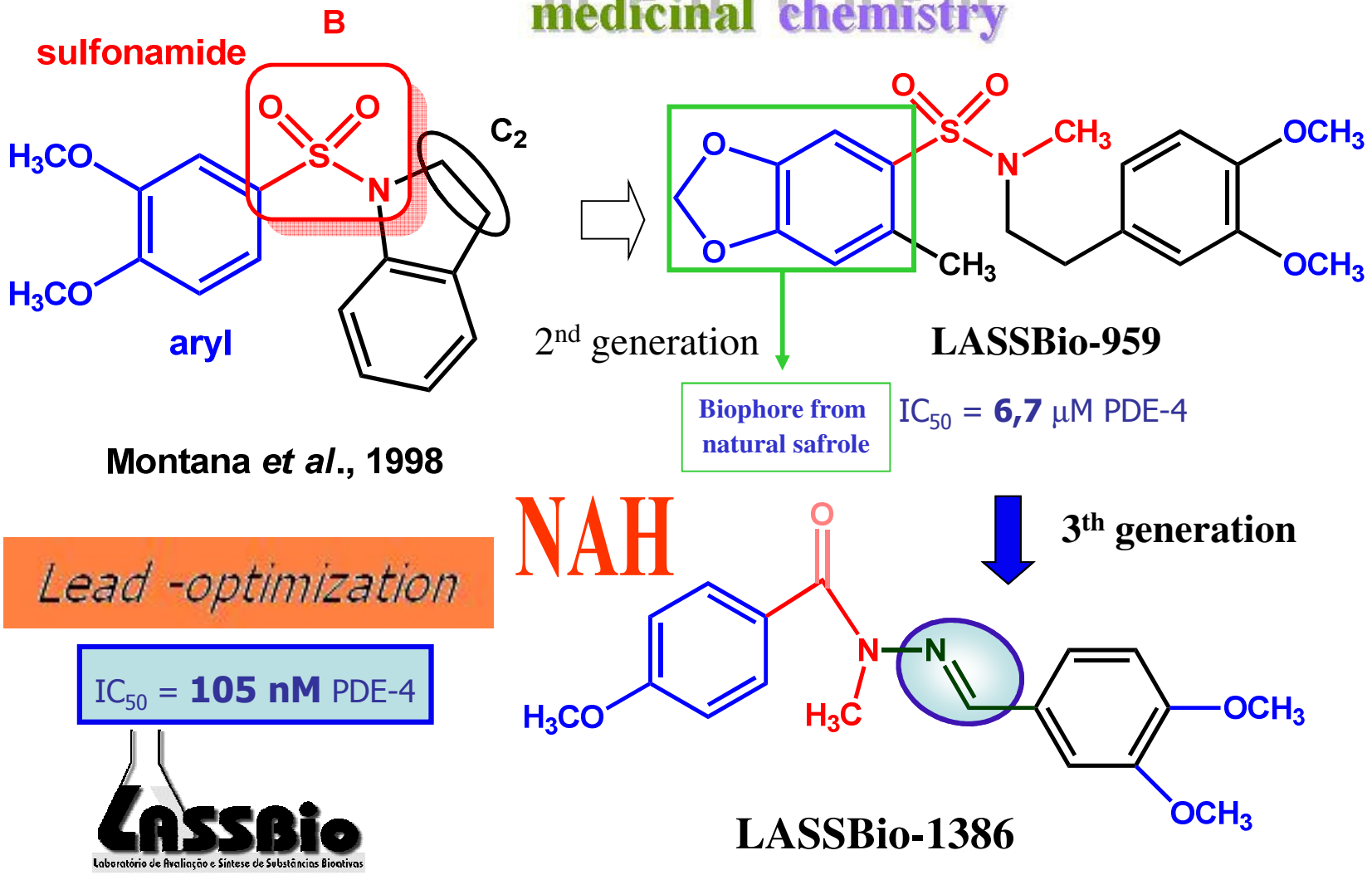
The *in silico* predition of the site of metabolism for **LASSBio-448** using several CYP's in program MetaSite





Percentage inhibition of *in vitro* microsomal hepatic metabolism of **LASSBio-448** by selective inhibitors of CYPs isoenzymes: furafylline (**CYP1A2; A**), ketoconazole (**CYP3A4; B**), ticlopidine (**CYP2C19; C**), *para*-nitrophenol (**CYP2E1; D**), sulfaphenazole (**CYP2C9; E**) and quinidine (**CYP2D6**; **F**).

Otimização do composto-protótipo



AE Kümmerle, et al., Design, synthesis, and pharmacological evaluation of *N*-acylhydrazones and novel conformationally constrained compounds as selective and potent orally active phosphodiesterase-4 inhibitors , *J. Med.Chem*. **2012**, *55*, 7525

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O processo de *drug discovery*

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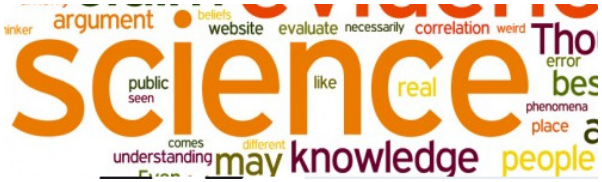
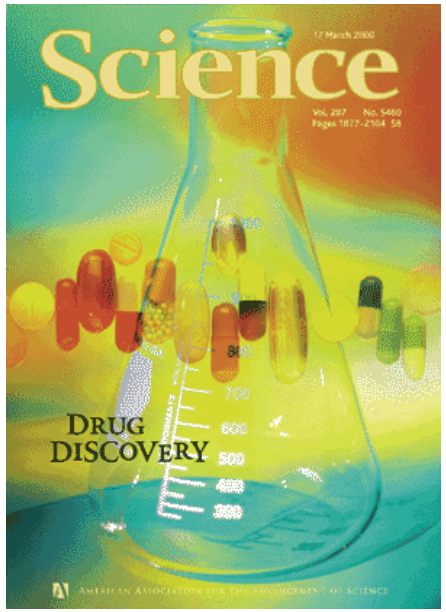
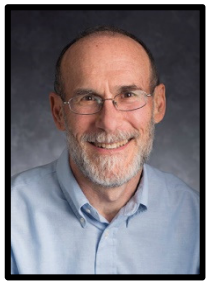
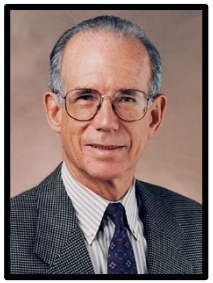






- *Science* **2000**, *287*, 1951

(Julia Uppenbrink, J. Mervis)



OnLine

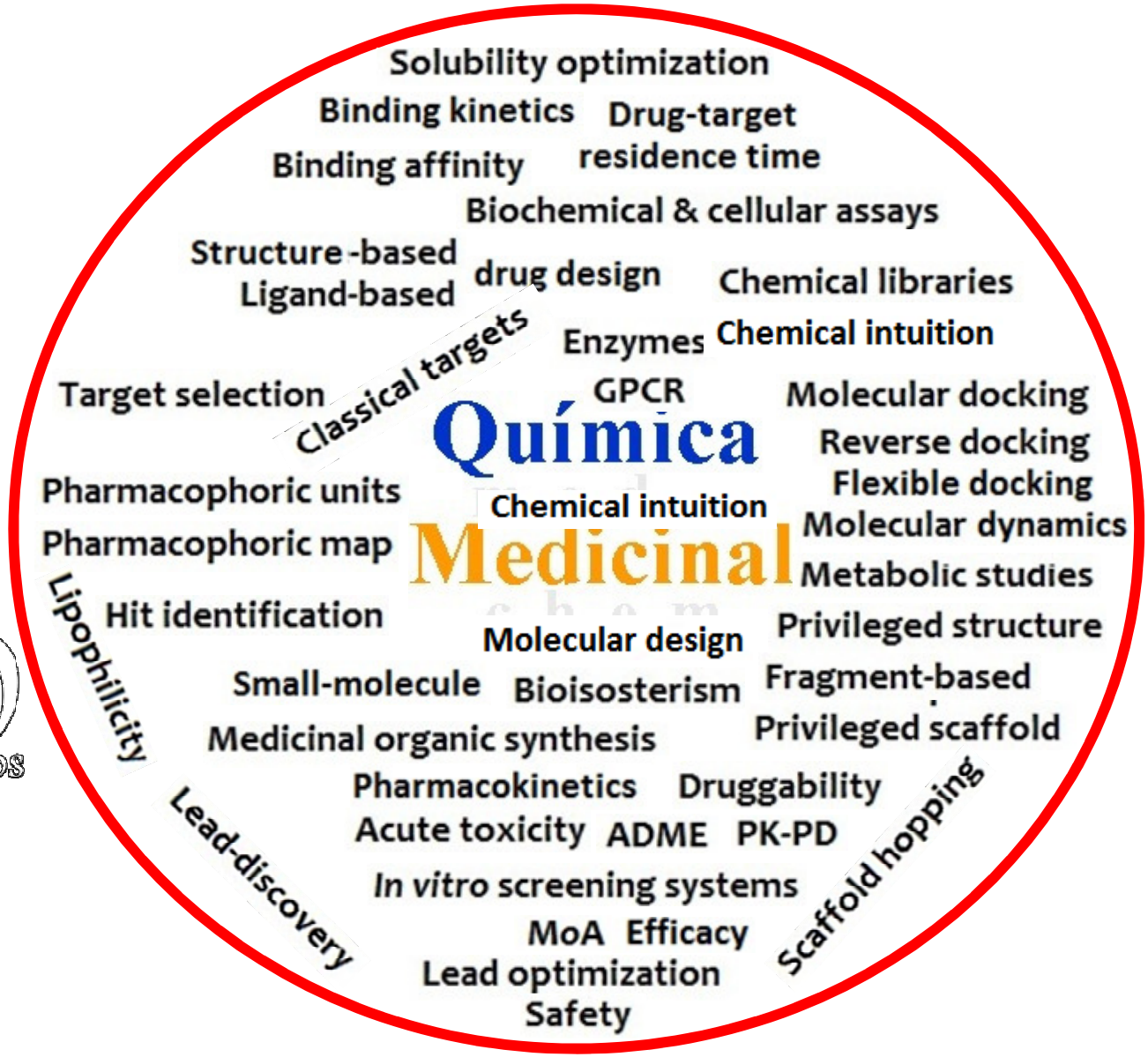
- *Science* **2004**, *303*, 1713

(Donald Kennedy)

- *Science* **2005**, *309*, 721

(Jeffrey Mervis)

O processo de *drug discovery*



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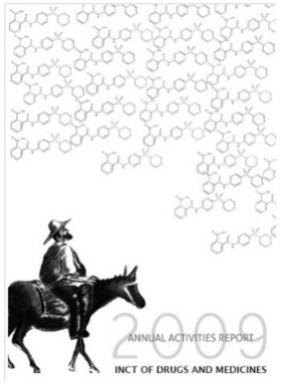

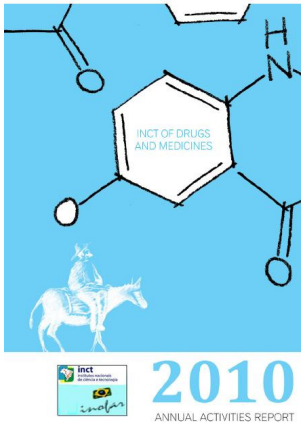

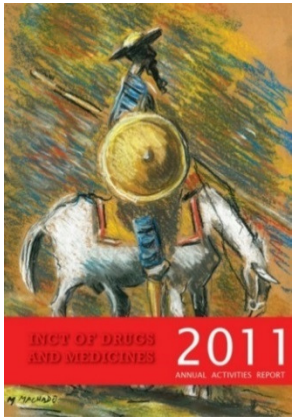

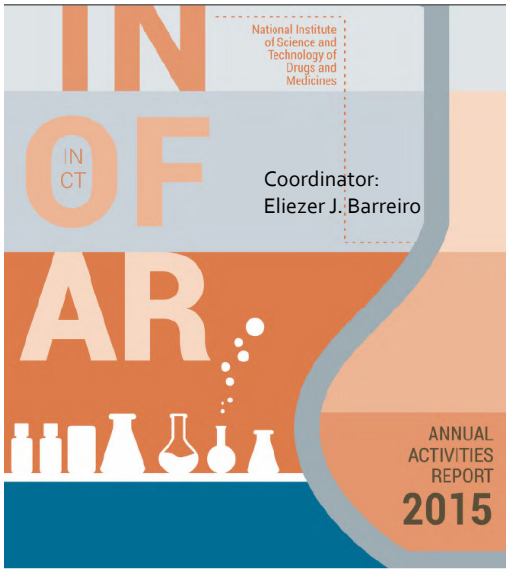

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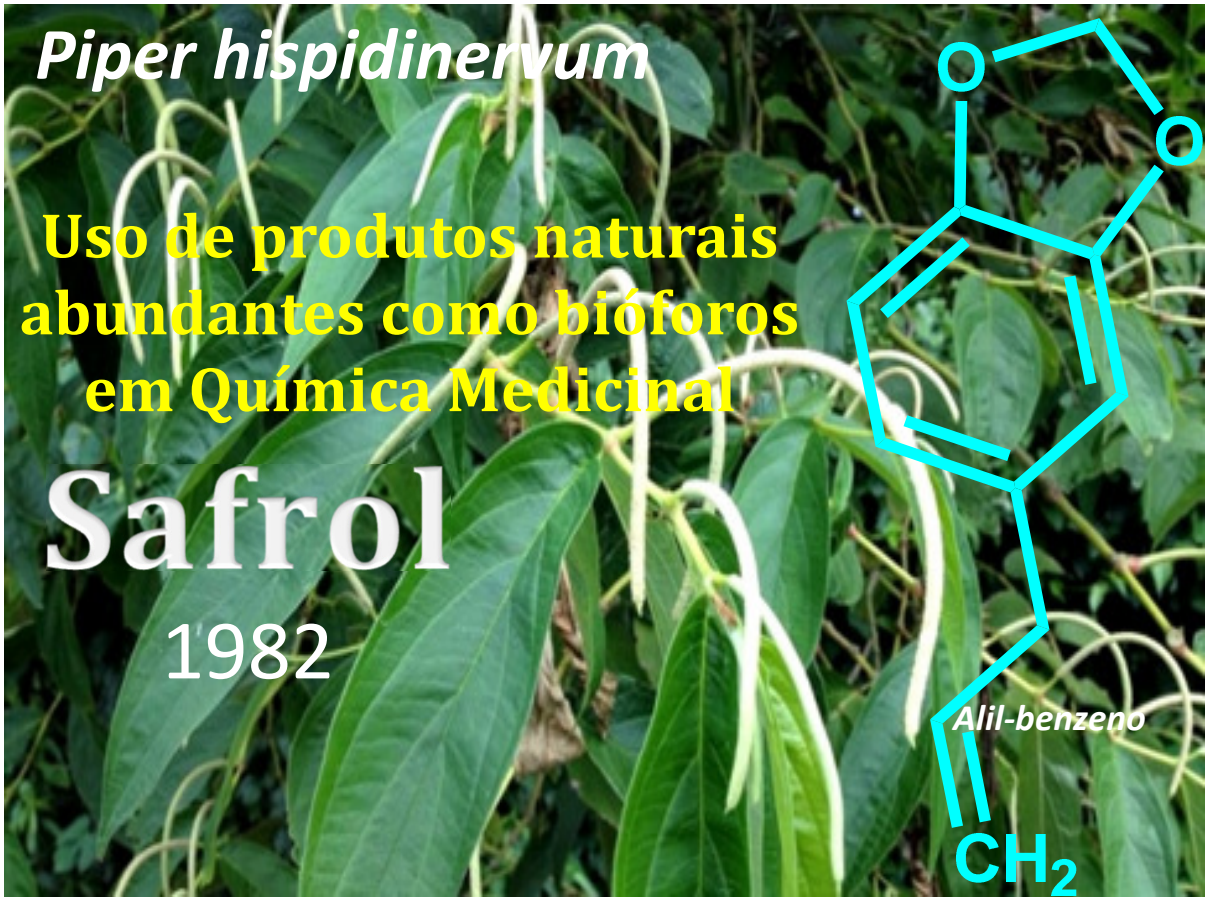
The Beginning



1982

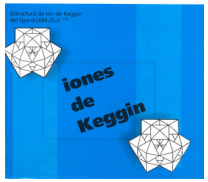
5% oléo

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)* **1982**, 102-103; (*M*) 1142-1165

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,* **1999**, *22*, 744-759.

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Patente obtida

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

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/020,328	Aug. 15, 2006	7,091,238	32360-178943	9681

20874 7590

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

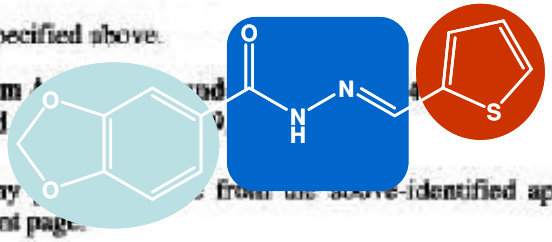
Thienylhydrazone with Digitalis-like properties (positive inotropic effects)

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.

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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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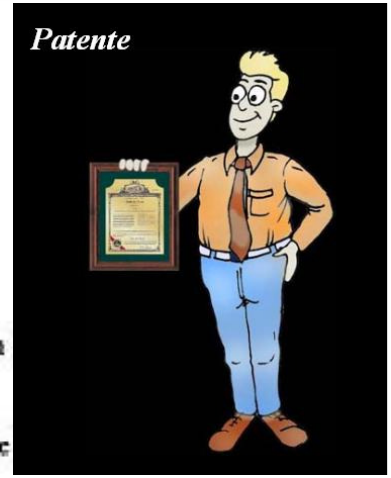
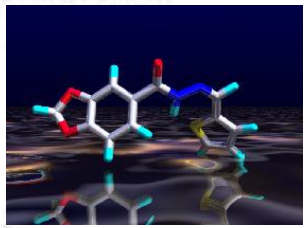
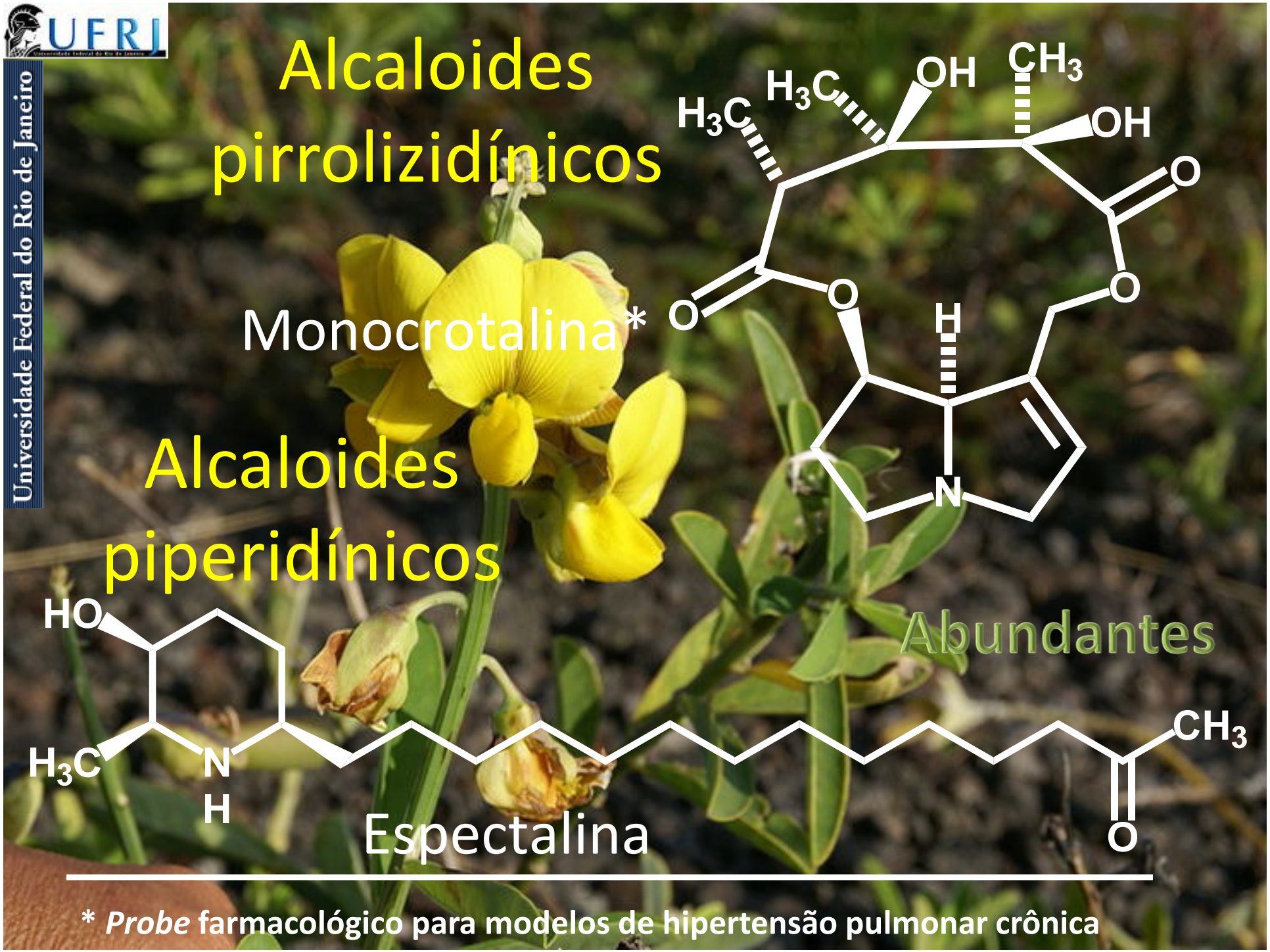


Thienylhydrazone with Digitalis-like properties (positive inotropic effects)

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

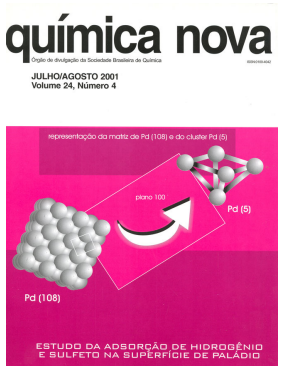
Universidade Federal do Rio de Janeiro

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

www.periodicos.capes.gov.br

Volume 13, 167-198, 2006 *CAM Fraga, EJ Barreiro*

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.



www.scielo.br

In this article are described new bioactive *N*-acylhydrazone (NAH) derivatives, structurally designed as optimization of aryl hydrazones precursors planned by molecular hybridization of two 5-lipoxigenase inhibitors, e.g. CBS-1108 and BW-755c. The analgesic, antiedematogenic and anti-platelet aggregating profile of several isosteric compounds was investigated by using classic pharmacological assays in vivo and ex-vivo, allowing to identify new potent peripheric analgesic lead, a new anti-inflammatory and an antithrombotic agent. During this study was discovered dozen of active NAH compounds clarifying the structure-activity relationship for this series of NAH derivatives, indicating the pharmacophore character of the *N*-acylhydrazone functionality.

Eliezer J. Barreiro et al., **A química medicinal de *N*-acilidrazonas: novos compostos-protótipos de fármacos analgésicos, antiinflamatórios e anti-trombóticos**. *Quím. Nova* **2002**, *25*, 129-148

Novas hidrazonas analgésicas

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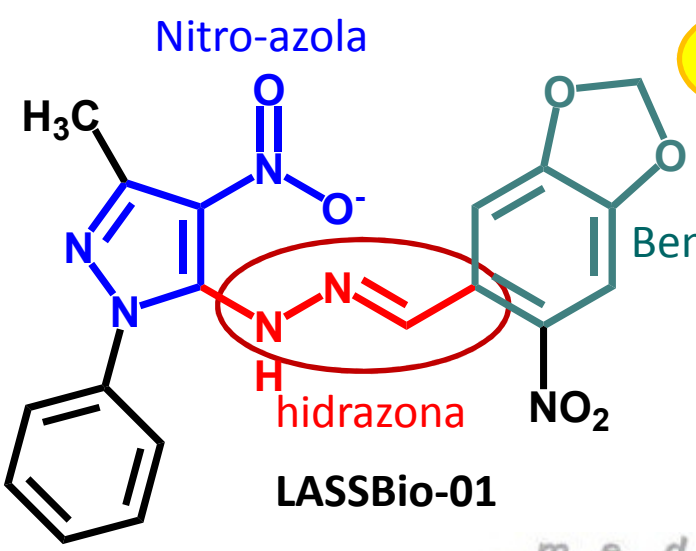
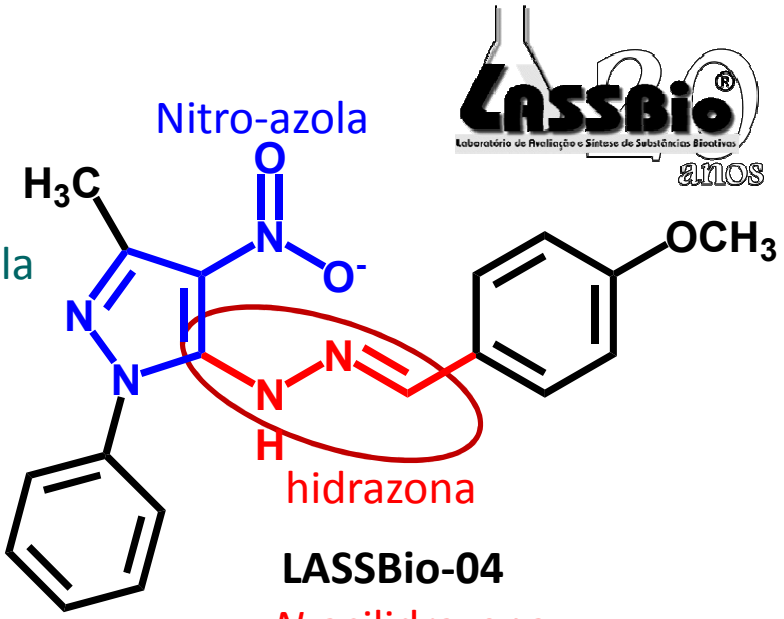


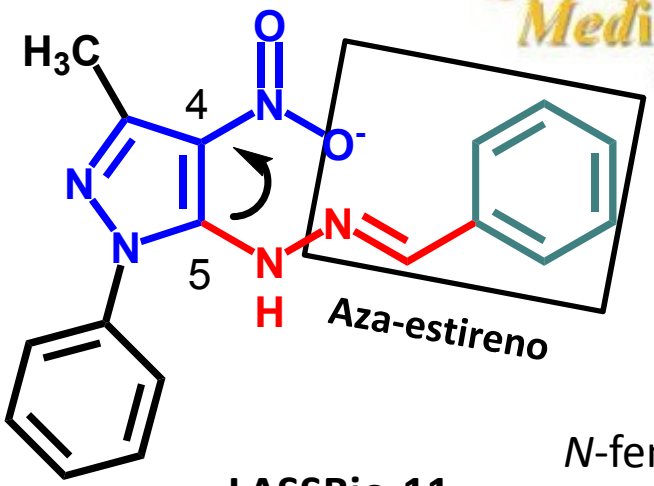
1994

LASSBio-01



LASSBio-04

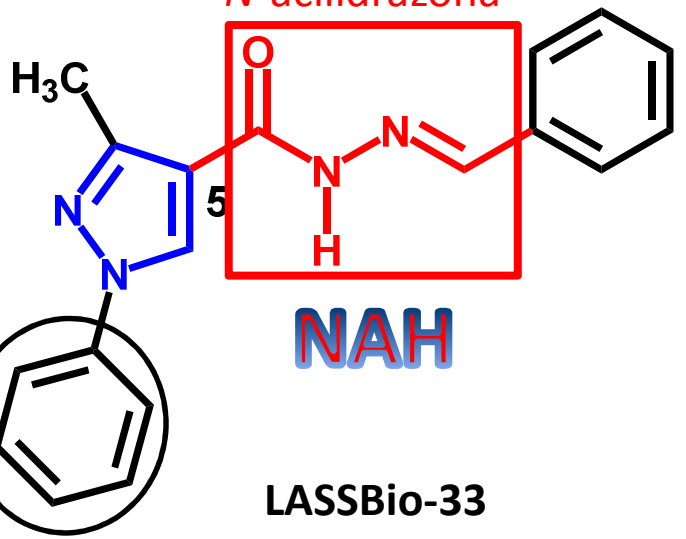
med Química Medicinal chem



LASSBio-11

C4 → C5

N-acilidrazona



N-fenilpirazola

LASSBio-33

Novas acilidrazonas

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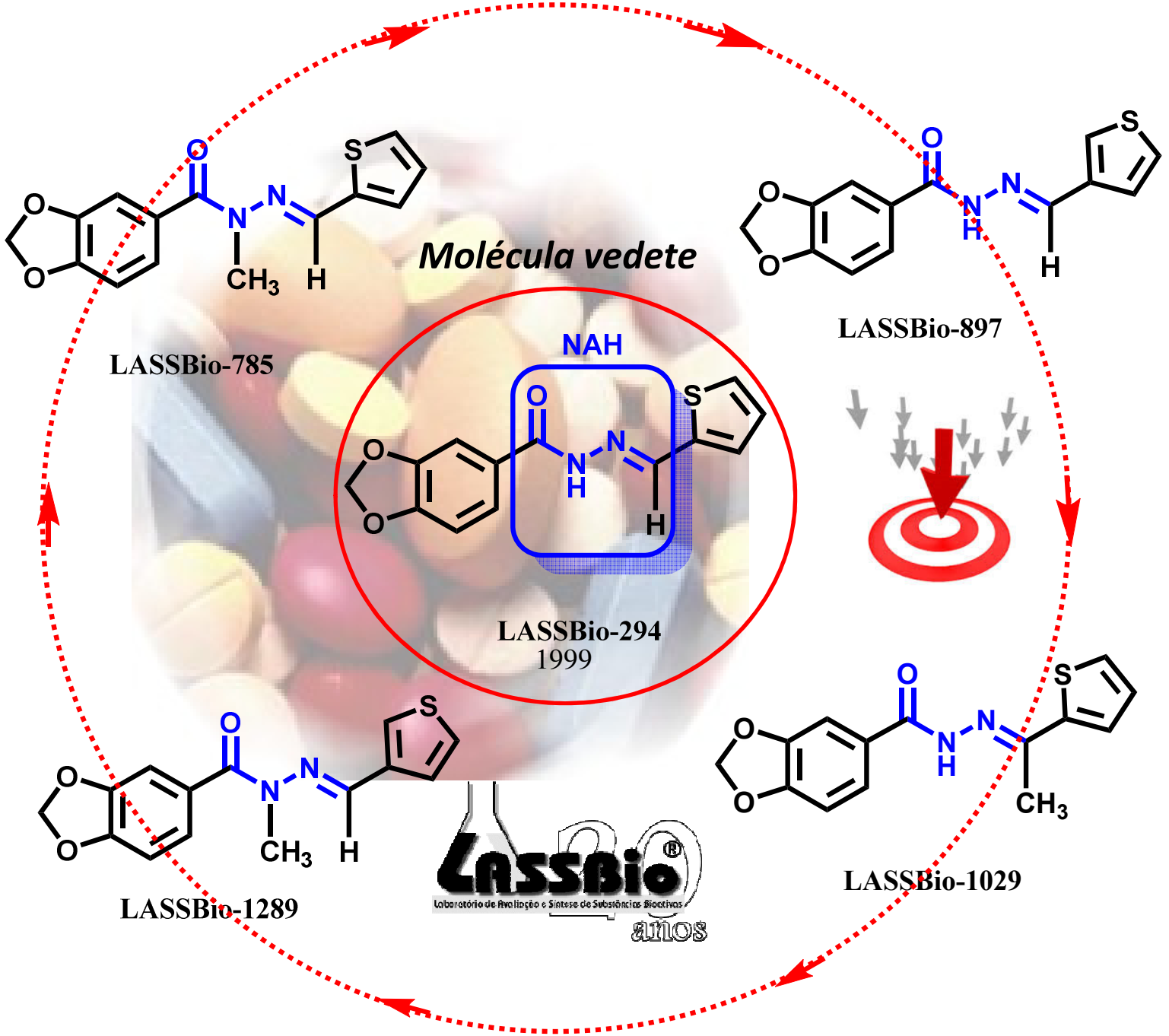
Estudos de otimização



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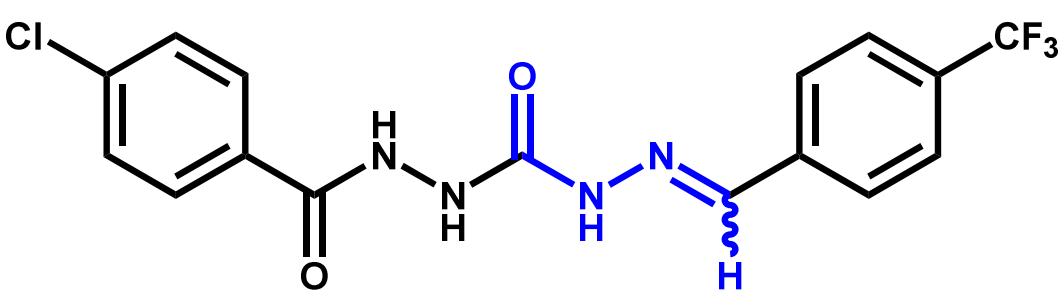
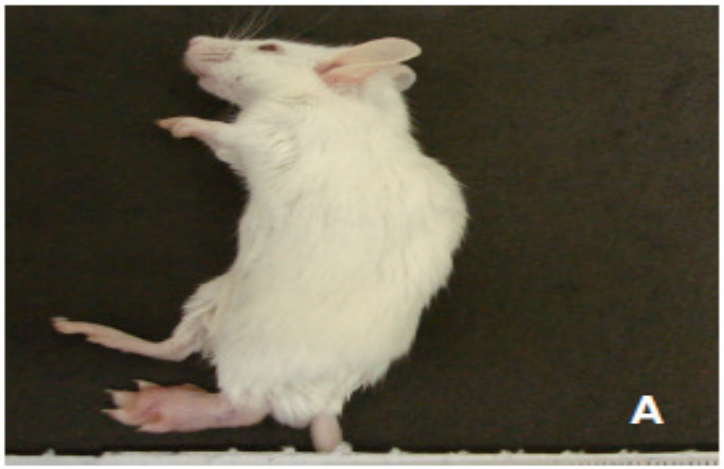
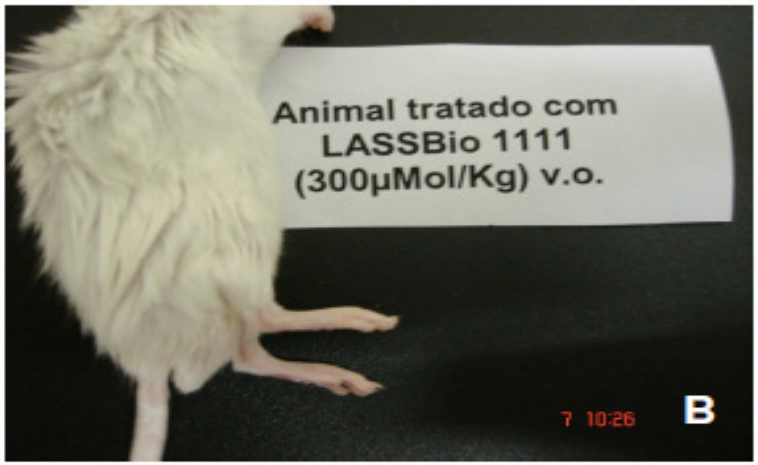


Camundongo BALB/c: Injeção de 2 X 10^6 *L. amazonensis* na pata esquerda→ tratamento diário (via oral) com os compostos testes → Medida das patas esquerda e direita com o paquímetro 2 vezes por semana por 30 dias.

"Leishpaína" ?





Tamanho das lesões.
(A) animal sem tratamento.
(B) animal tratado com LASSBio 1111 (300 µmol/kg/ via oral) após o período de 30 dias.

LASSBio-1491

FQ Cunha, LM Lima, H Cerecetto, M Gonzalez, MS Alexandre-Moreira, MV Martins, MP Nunes, EJ Barreiro, resultados não publicados.

R. E. Silva-López, Leishmania proteases:new targets for rational drug development, *Quim Nova* **2010**, *33*, 1541.

Universidade Federal do Rio de Janeiro

New Insights for Multifactorial Disease Therapy: The Challenge of the Symbiotic Drugs

Eliezer J. Barreiro and Carlos Alberto Manssour Fraga

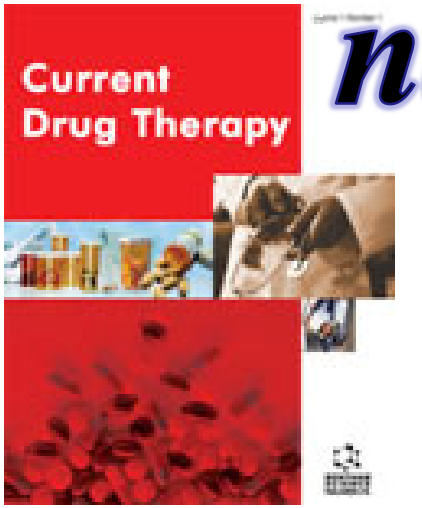
Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, P.O. Box 68023, 21944-971, Rio de Janeiro, RJ, Brazil.

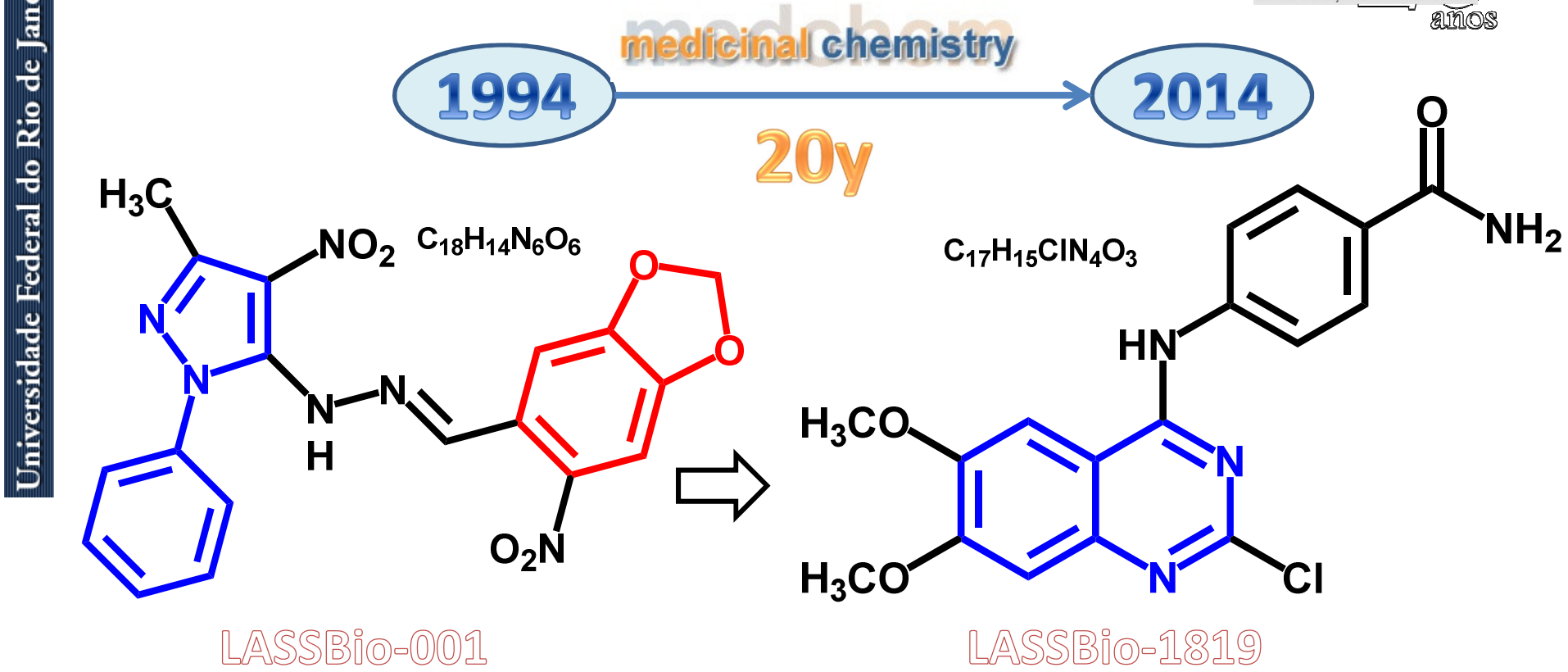
Abstract: Some physiopathological processes involved in the genesis of diseases could suggest the necessity of designing bioligands or prototypes that aggregate, in only one molecule, dual pharmacodynamical properties, becoming able to be recognized by two elected bioreceptors. This approach can have distinct aspects and, when a novel ligand or a prototype acts in two elected targets belonging to the same biochemical pathway, *e.g.* arachidonic acid cascade, it receives the denomination of dual or mix agent. On the other hand, if these two targets belong to distinct biochemical routes and both are related to the same disease, we can characterize the agents able to modulate it as symbiotic ligands or prototypes. In the present work, we provide some examples and applications of the molecular hybridization concept for the structural design of new symbiotic ligands, [illegible] applied to the treatment of [illegible] diseases.

Key Words: Symbiotic drugs; molecular hybridization; multifactorial diseases; therapeutic innovation; drug design; dual compounds.

Química Medicinal

Fármacos simples, não curam doenças complexas!





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, *Pharmaceutica Acta Helvetiae* **1994**, *69*, 163

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*, 1-14.

Dual Ligand Design

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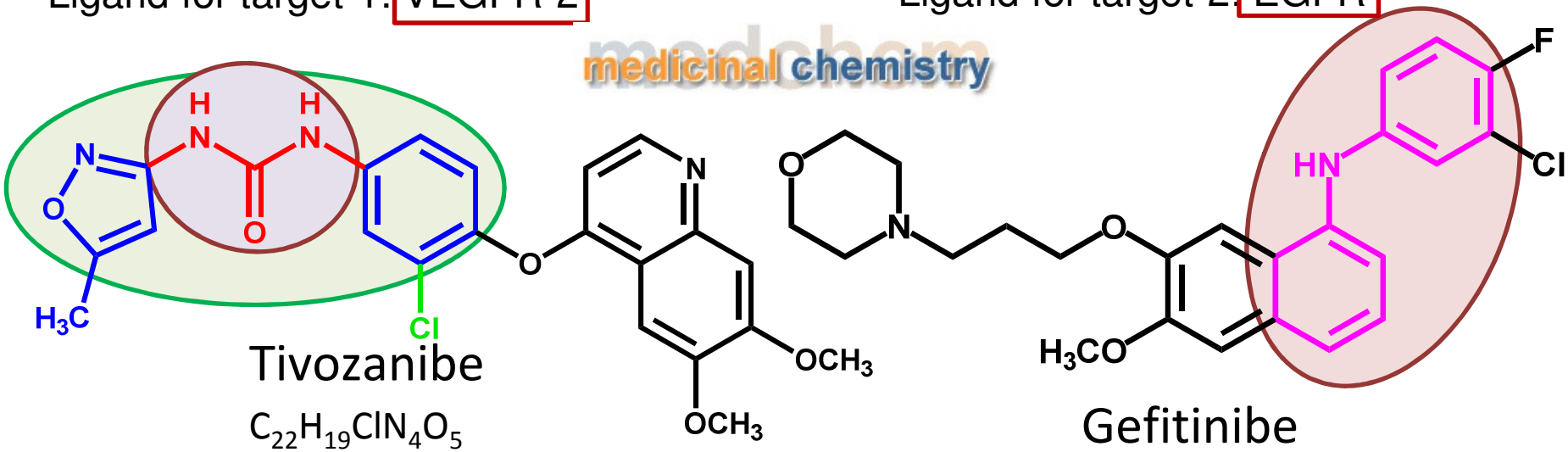
Ligand for target-1: VEGFR-2

Ligand for target-2: EGFR



Tivozanibe

$C_{22}H_{19}ClN_4O_5$

VEGFR-1 = 30 nM

VEGFR-2 = 6,5 nM

VEGFR-3 = 15 nM

VEGFR tyrosine kinase inhibitor

2016

Gefitinibe

$C_{22}H_{24}ClFN_4O_3$

EGFR = 33 nM

2003

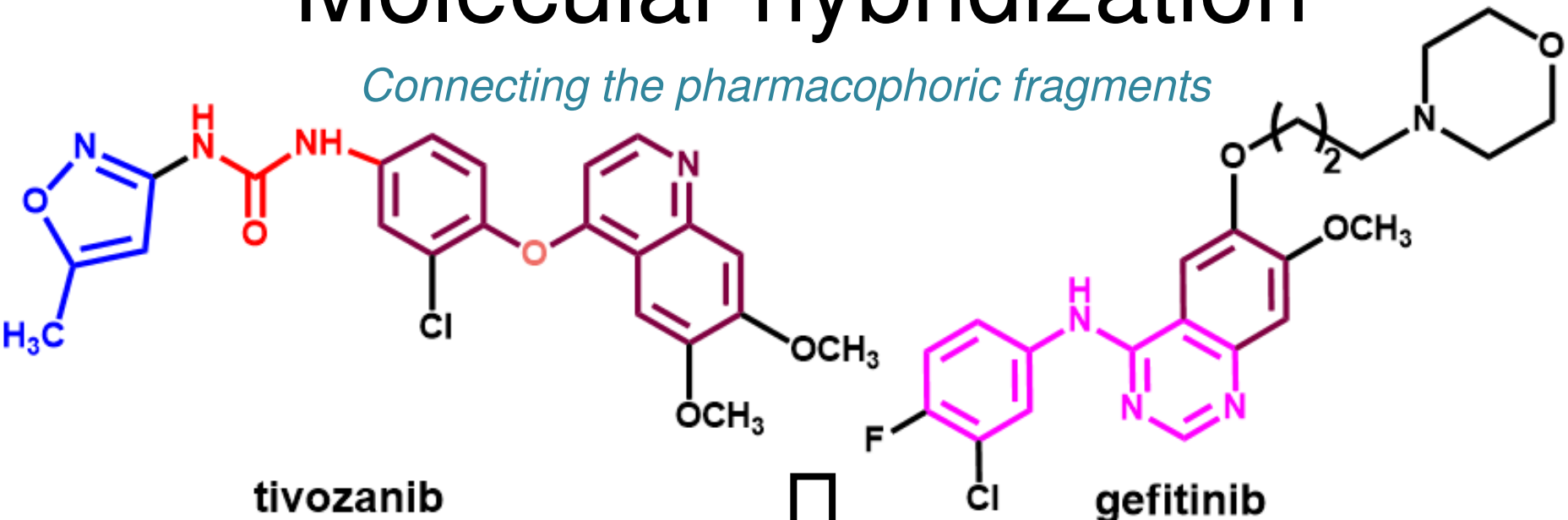
Originalidade

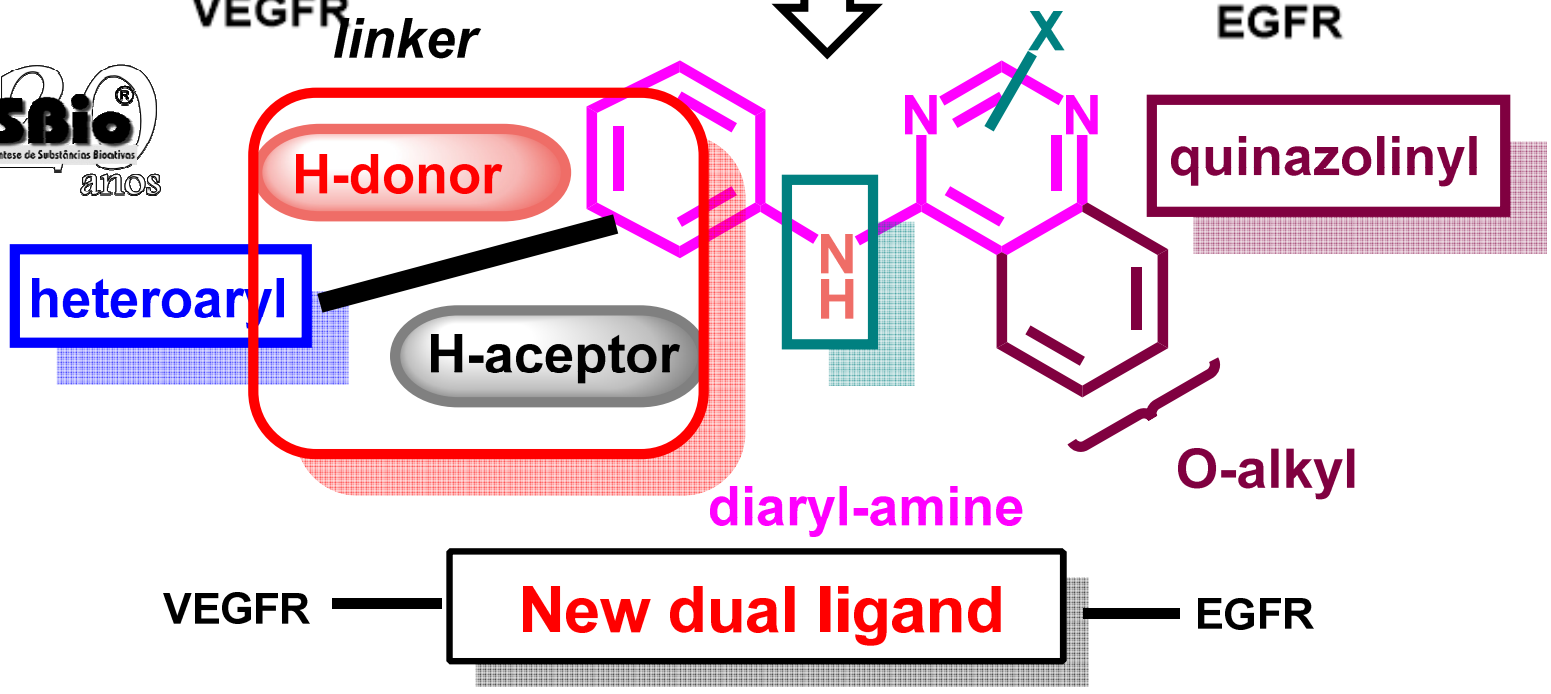
Hibridação Molecular: identificação de fragmentos farmacofóricos

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.

Molecular hybridization

Connecting the pharmacophoric fragments





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(19) Organização Mundial da Propriedade Intelectual
Secretaria Internacional

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(71) Requerente : UNIVERSIDADE FEDERAL DO RIO DE JANEIRO [BR/BR]; Av. Pedro Calmon, 550 - Prédio Reitoria - 2° andar, Ilha do Fundão, CEP-21941-901 Rio de Janeiro - RJ (BR).

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(81) Estados Designados *(sem indicação contrária, para todos os tipos de proteção nacional existentes)* : AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW,

Novel 2-chloro-4-a
VEGFR-2 dual inhi

Maria Letícia de Castro Barbosa [a,b], Lídia Moreira Lima [a,b], Roberta Tesch [a], Carlos Mauricio R. Sant'Anna [c], Frank Totzke [d], Michael H.G. Kubbutat [d], Christoph Schächtele [d], Stefan A. Laufer [e], Eliezer J. Barreiro [a,b,*]

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[e] Department of Pharmaceutical/Medicinal Chemistry, Institute of Pharmacy, Eberhard-Karls-University Tübingen, Tübingen, Germany

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

, 2013.

vel molecular pattern

Lead Optimization


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Cardioativos
Anticâncer
Neuroativos
Antiparasitários
Analgésicos
Anti-inflamatórios
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ejbarreiro@ccsdecania.ufrj.br
Obrigado
Morro do Corcovado com a estátua do Cristo Redentor, uma das sete maravilhas do mundo moderno.