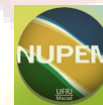




# *O processo de invenção/ descoberta de fármacos*

NUPEM, UFRJ, Junho 2013



***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>

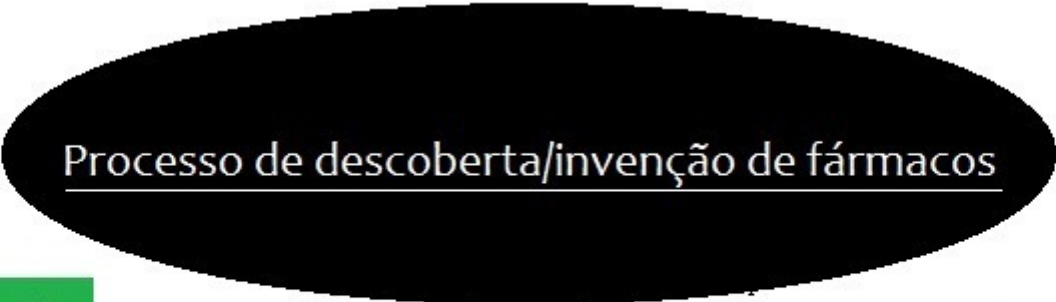
**Instituto Nacional de Ciência e Tecnologia de Fármacos e Medicamentos  
(INCT-INO FAR)**

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





# Sumário



Descoberta

Invenção

Ciência dos fármacos

Inovação



Saúde

promoção

manutenção

preservação

Fármacos  
Medicamentos



Fármacos e o prêmio Nobel

Novas moléculas

Ciência & Criatividade

Inventar moléculas

LASSBio-294

Expectativa de vida

Interdisciplinaridade

Fármacos sintéticos

INCT-INOVAR

Inovação radical & incremental





Universidade Federal do Rio de Janeiro



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Antes de mais nada...



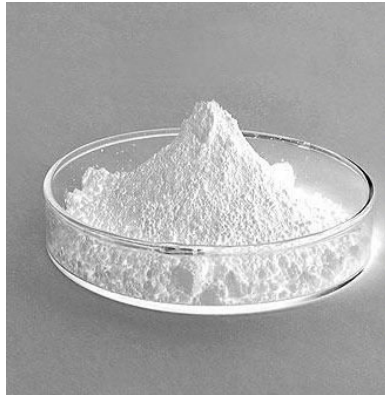


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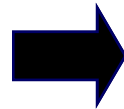
# Fármaco...

## Formas Farmacêuticas



Princípio ativo

Pureza farmacopêica



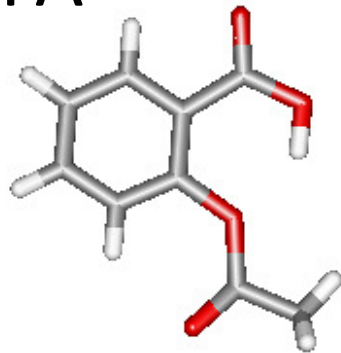
Tecnologia Farmacêutica



# & medicamento

Farmoquímico

IFA



ácido acetilsalicílico





**Fármacos são instrumentos de promoção da Saúde...**

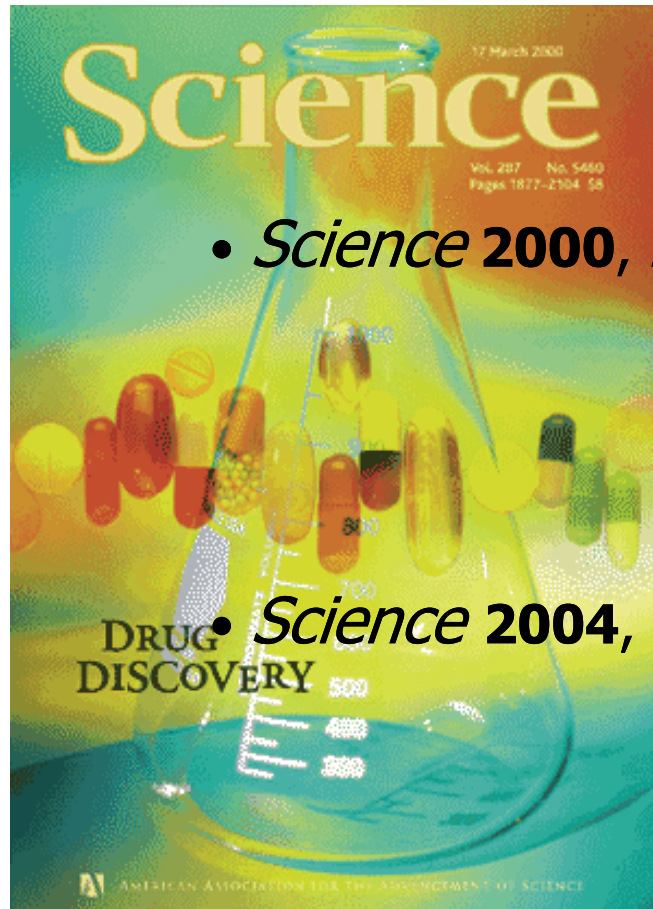
**... contribuem para melhoria da qualidade e expectativa de vida !**

**Fármacos = recuperam, corrigem, preservam mantem o estado de Saúde**





# Os (novos) fármacos ...



• *Science* **2000**, 287, 1951 (J. Uppenbrink, J. Mervis)



• *Science* **2004**, 303, 1713 (D. Kennedy)



...dependem da pesquisa científica!

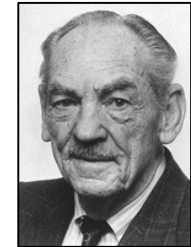
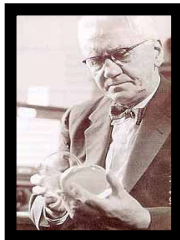
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# Os fármacos e o prêmio Nobel



Penicilina

AAS

Propranolol

Aciclovir

Cimetidina

Captopril



# O paradigma de Ehrlich & Fischer



**Emil Fischer**  
1852-1919  
**1902**



**Paul Ehrlich**  
1854-1915  
**1908**



**LOCK & KEY**  
CONCEPT

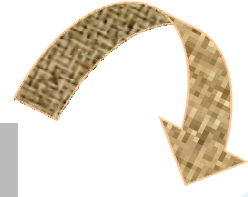
He postulated the existence of specific receptors, associated with cells distributed in the blood

K Stürzbecher & A Ullrich, Paul Ehrlich magic bullet concept: 100 years of progress, *Nature Rev. Cancer* **2008**, 8, 473

LANCET

"In patients with locally advanced or high-risk local prostate cancer, addition of local radiotherapy to endocrine treatment halved 10-year prostate-cancer-specific mortality."

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



Biorreceptor  
macrobiomolécula  
baseado no sítio de reconhecimento

Planejamento racional

BSRM  
BL-AA

Fármaco  
micromolécula

baseado no ligante / análogo-ativo





Physiologic  
**A abordagem**  
approach  
fisiológica

# A eleição do alvo-terapêutico



# Conhecimento da fisiopatologia

**Doenças multifatoriais**

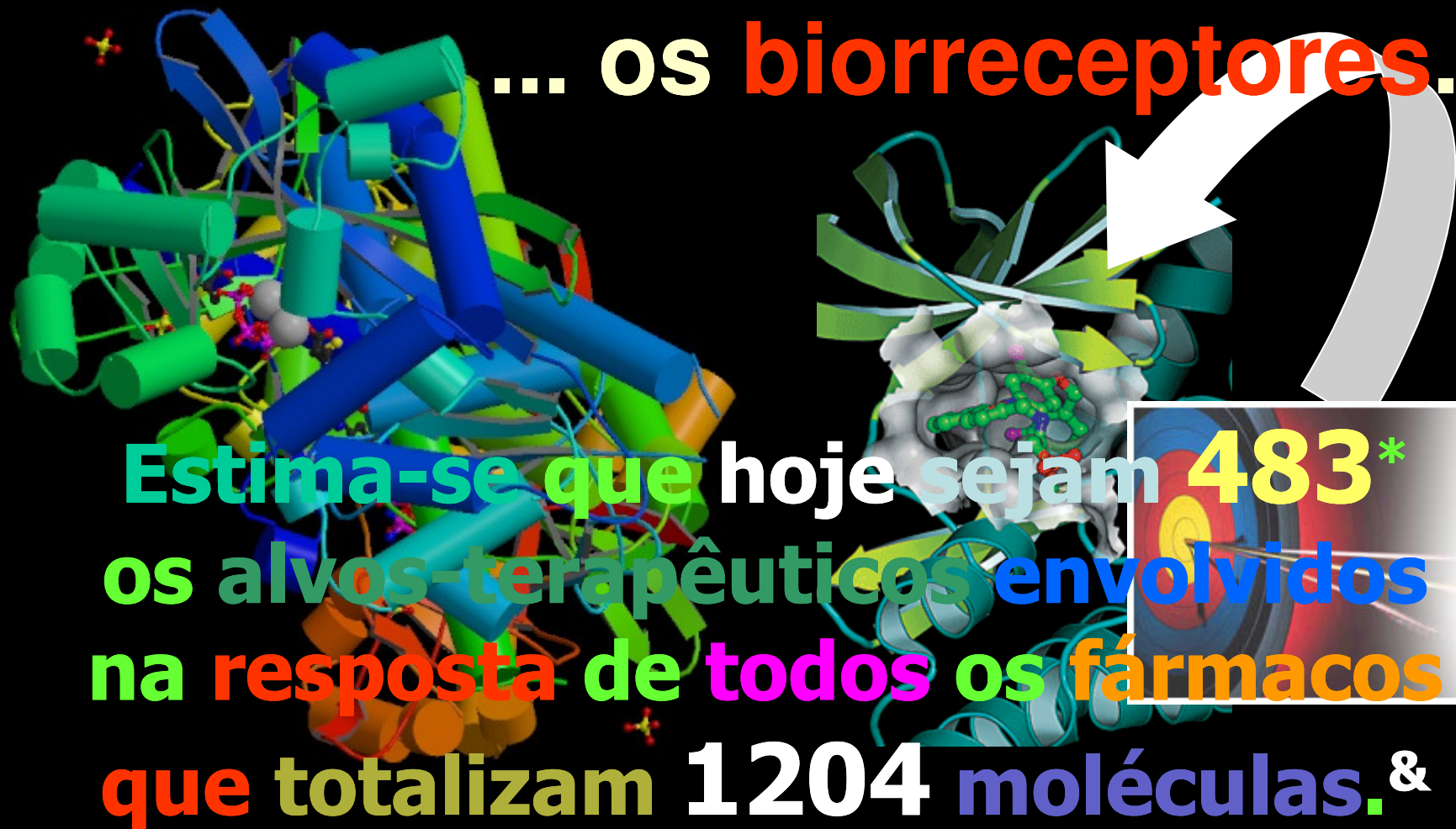
**Quimioterapia  
SNC  
Doença crônica**



# Os fármacos atuam em alvos terapêuticos...

Química Medicinal

## ... os biorreceptores.

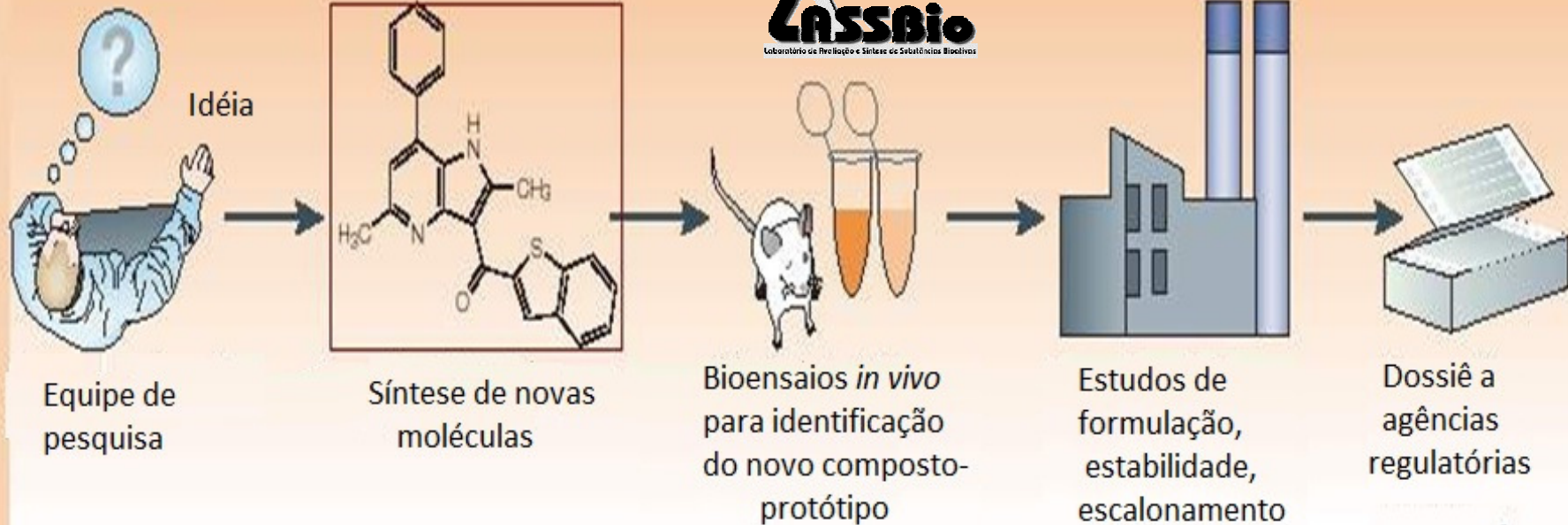


\* J. Drews, "Editorial: What's in a number?", *Nature Rev. Drug Discov.* **2006**, *5*, 975;  
J. Drews & S. Ryser, Classic drug targets, *Nature Biotechnol.* **1997**, *15*, 1318;  
& J.P. Overington, A-L Bissan & A.L. Hopkins, *Nature Rev. Drug Discov.* **2006**, *5*, 993;  
Estes autores estimam em 324 os biorreceptores de todos os fármacos contemporâneos.



### Fase pré-clínica

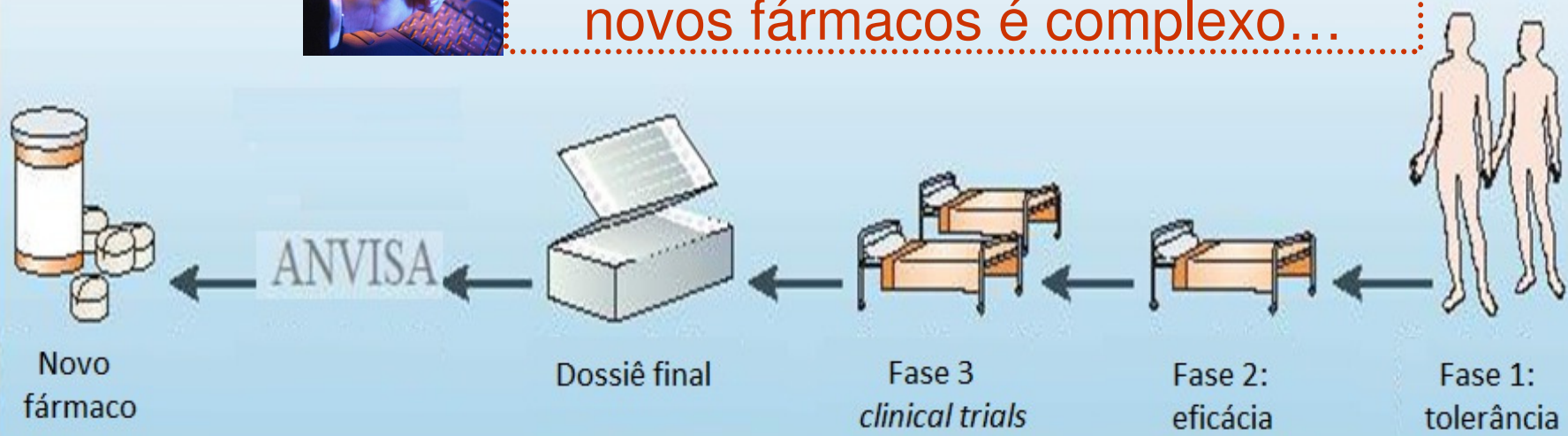
Química Medicinal



### Estudos clínicos



O processo do desenvolvimento de novos fármacos é complexo...





**O mercado farmacêutico**

**mundial atingiu**

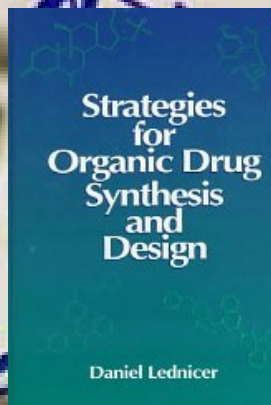
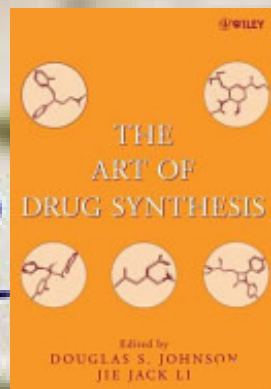
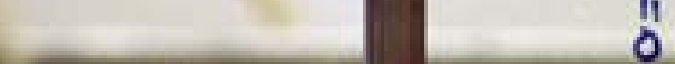
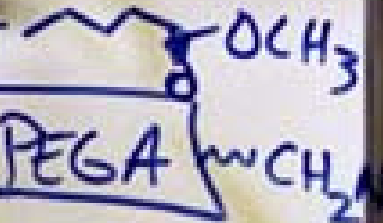
**US\$ 860 bilhões**

**em 2012.**





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>> 85% do arsenal terapêutico

São fármacos sintéticos



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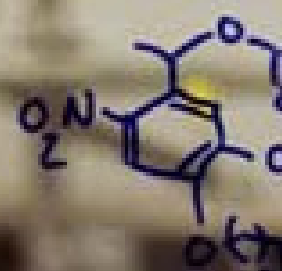
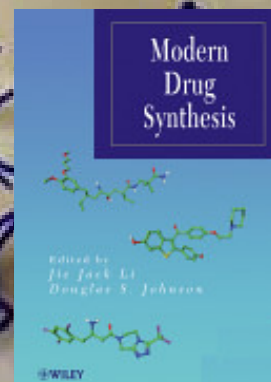
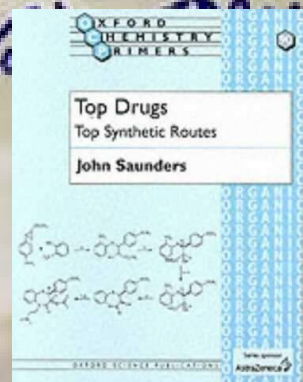
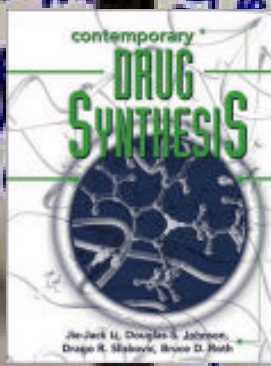
MeOH/CH<sub>2</sub>Cl<sub>2</sub>

MeOH/CH<sub>2</sub>Cl<sub>2</sub>

CHCl<sub>3</sub>/A

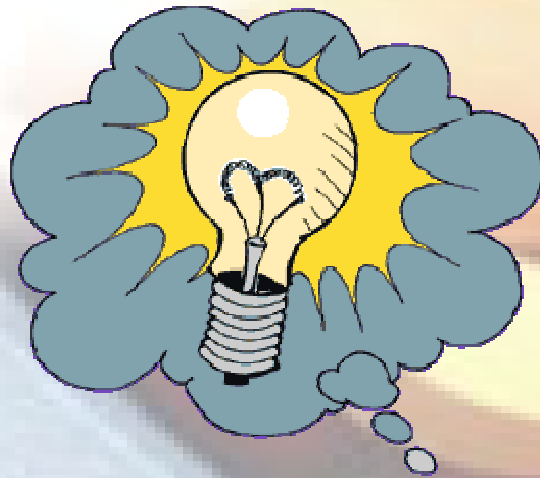
86% CHCl<sub>3</sub>, 14% MeOH

12% CHCl<sub>3</sub>, 20%





desCo**bert**A



i**N**vençã**o**

...e assim nascem os fármacos!



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# Uma descoberta marcante...



**Ernest Duchesne**  
(1874 – 1912)

1896 - Médico na *Ecole du Service de Santé Militaire de Lyon*, com tese intitulada "*Contribution à l'étude de la concurrence vitale chez les micro-organismes: antagonisme entre les moisissures et les microbes*", 1897

*Penicillium glaucum*



**Howard Florey**  
(1898 – 1968)

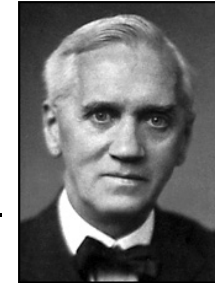


**Ernst B Chain**  
(1906 – 1979)

**Norman G Heatley**  
(1911 – 2004)

1928 - St. Mary's Hospital em King's Cross, Londres  
Prêmio Nobel de Medicina em 1945

1939 – Un Oxford equipe envolvida nos estudos de substâncias antibacterianas de fungos  
Prêmio Nobel de Medicina em 1945



**Alexander Fleming**  
(1881 – 1955)

1942 – Un Oxford elucidada a estrutura por difração de raios-X

Prêmio Nobel de Química em 1964



**Dorothy C Hodgkin**  
(1910 – 1995)

**Andrew J Moyer** (1899 – 1959) - Microbiologista norte-americano  
descobriu o crescimento de fungos.



**John C Sheehan** (1915 – 1992) – Produção industrial da penicilina (1944)  
Síntese total da penicilina (MIT, 1957)

Molécula Salva-Vidas!



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# Uma invenção

## Inibidor da ECA



David Cushman  
Bristol-Myers Squibb  
Pharmaceutical Research  
Institute



Miguel Ondetti  
Bristol-Myers Squibb  
Pharmaceutical Research  
Institute



John R Vane

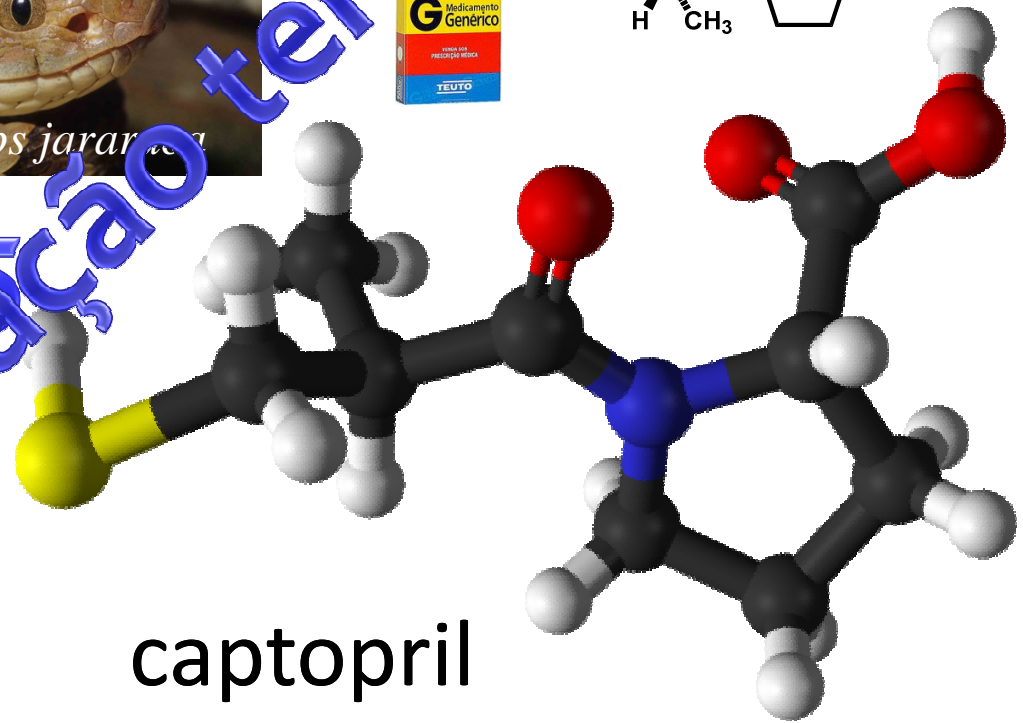
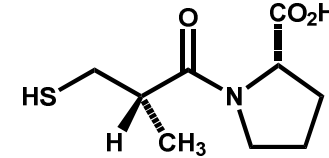


*Bothrops jararaca*



1975 Inovação Terapêutica

- 1939 - Oscar M. Rocha e Silva
- 1948 - Wilson Teixeira Beraldo e Gastão Rosenfeld = bradisinina
- 1960 - Sérgio H. Ferreira = BPF
- 1967 - Royal College of Surgeons of England, John Vane = ECA
- 1970 - Squibb (enalapril)
- 1975 - Bernard Rubin, Miguel Ondetti, David Cushman = captopril



captopril





# Processo de invenção de fármacos





## Artigo

A química medicinal brasileira de 1998 a 2008 nos periódicos *Journal of Medicinal Chemistry*, *Bioorganic and Medicinal Chemistry*, *Bioorganic and Medicinal Chemistry Letters* e *European Journal of Medicinal Chemistry*

Bastos, Renato S.\*; Silva, Bárbara V.; Pinto, Angelo C.

*Rev. Virtual Quim.*, 2009, 1 (1), 67-86. Data de publicação na Web: 2 de Fevereiro de 2009

<http://www.uff.br/rvq>

# Interdisciplinaridade



Universidade Federal do Rio de Janeiro

# Usina de Invenção de moléculas...



Laboratório de Avaliação e Síntese de Substâncias Bioativas

Criado em 19/04/1994

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

Química  
med  
Medicinal  
chem

Pharmacology  
Farmacologia

Molecular  
Modelagem  
Modeling  
Molecular



Artigo

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

**Barreiro, E. J.**

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



<http://www.uff.br/rvq>



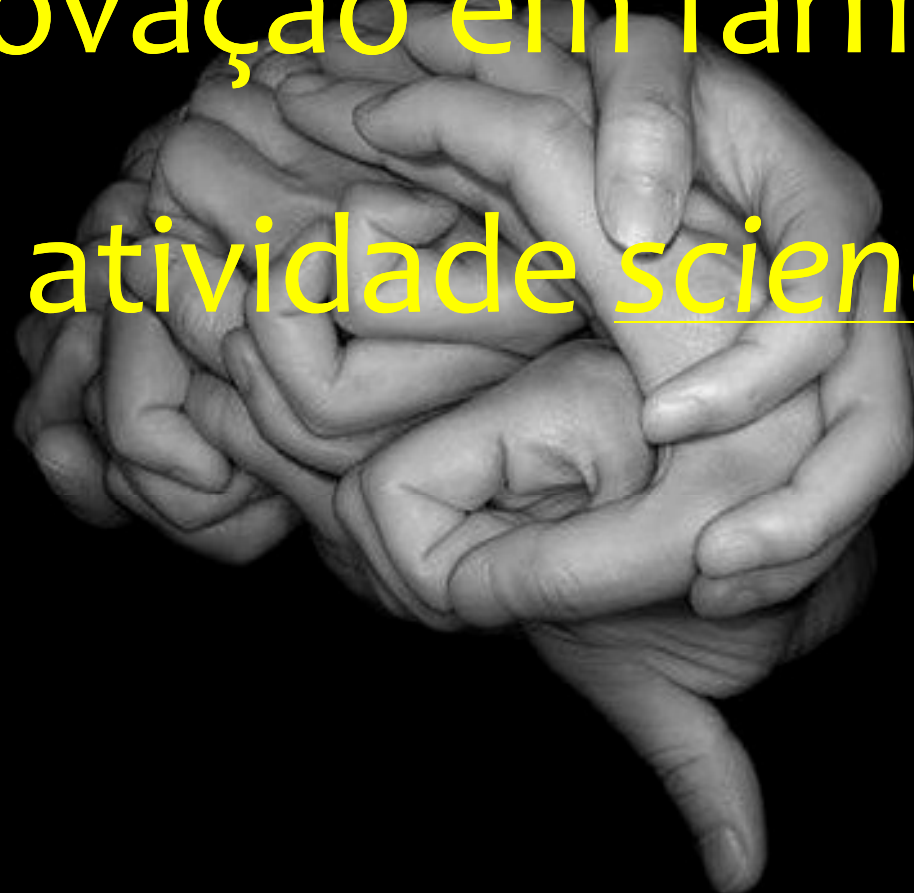
[www.uff.br/rvq](http://www.uff.br/rvq)



Química  
med  
Medicinal  
chem



# A inovação em fármacos é uma atividade science-based



Laboratório de Avaliação e Síntese de Substâncias Bioativas

INCT



*inofar*

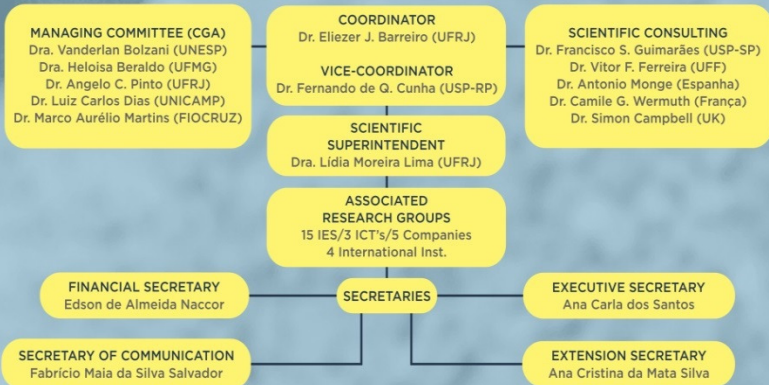
Instituto Nacional de  
Ciência e Tecnologia

de Fármacos e Medicamentos

[www.inct-inofar.ccs.ufrj.br](http://www.inct-inofar.ccs.ufrj.br)



## ORGANIZATION STRUCTURE



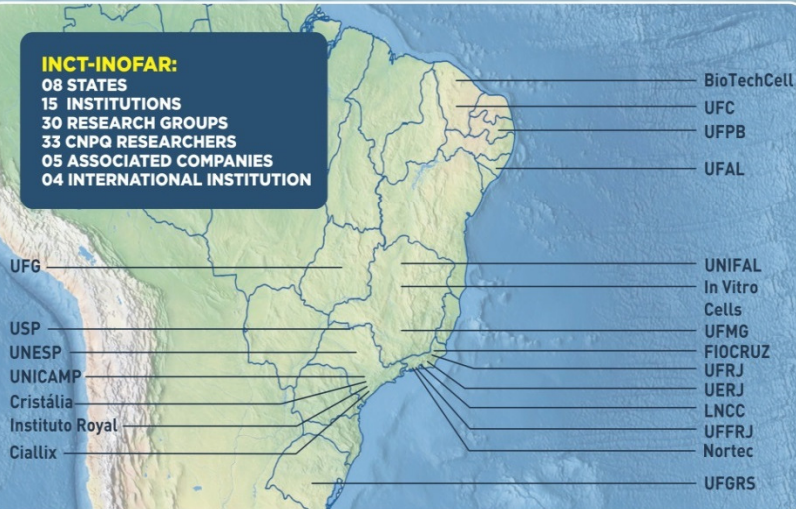
## SCIENTIFIC TEAM

INCT-INOVAR has a multidisciplinary staff of experts in several areas such as medicinal chemistry, pharmacology, organic chemistry, toxicology, organic synthesis, biochemistry, computational chemistry, spectroscopy, natural products chemistry, among others.

The network of scientific expertise that comprises INCT-INOVAR is made up of 30 research groups located in 15 teaching and research institutions in 8 Brazilian states.

The pharmaceutical innovation process has clear interdisciplinary and multidisciplinary characteristics that demand competences in distinct areas of health sciences. INCT-INOVAR is aware of this, and, therefore, coordinates a network of research groups with scientifically standard and academically distributed in different areas, and that have a history of previous results that makes them qualified to carry out successfully the several stages of the rational drug discovery process.

**INCT-INOVAR:**  
08 STATES  
15 INSTITUTIONS  
30 RESEARCH GROUPS  
33 CNPQ RESEARCHERS  
05 ASSOCIATED COMPANIES  
04 INTERNATIONAL INSTITUTION



## OUTREACH ACTIVITIES

**INCT-INOVAR BOOKLET 2009-2011**  
([www.inct-inovar.ccs.ufrj.br/revista](http://www.inct-inovar.ccs.ufrj.br/revista))



The complete portfolio of INCT-INOVAR actions developed to publicize and popularize science, including the production of events and the publicizing of its research in the media is in the "INCT-INOVAR Booklet 2009-2011: Scientific Awareness and Health Education". The booklet is available in a bilingual edition, in English and Portuguese, both in print and online.

## CONTINUING EDUCATION



To contribute to the process of continuing education, the INCT-INOVAR supports the achievement of the Summer School on Medicinal and Pharmaceutical Chemistry, which always happens in the first months of the school year, during the holiday period and aims to collaborate update undergraduate, graduate, professional pharmacists, chemists, engineers, chemists, biologists and the like, on issues related to drugs and medicines.

**THE PORTAL DOS FÁRMACOS**  
([www.portaldosfarmacos.ccs.ufrj.br](http://www.portaldosfarmacos.ccs.ufrj.br))



The Portal dos Fármacos is the INCT-INOVAR website for the publicizing and popularization of Pharmaceutical Sciences. Through this portal, INCT-INOVAR publicizes its research activities, in language accessible to laypeople, and makes its Health Education materials available.

## PARTNERSHIPS



**CRISTÁLIA** Cristália Produtos Químicos Farmacêuticos Ltda.

**NORTEQUÍMICA** Nortec Química S.A.

**In Vitro Cells** In Vitro Cells - Pesquisa Toxicológica S.A.

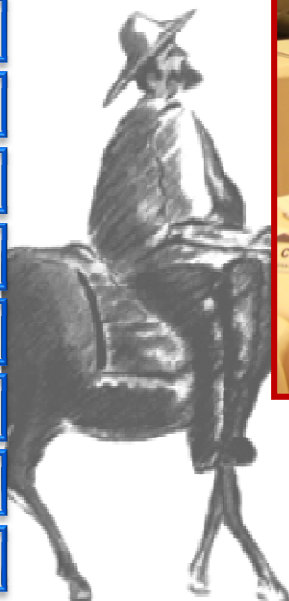
**bio TECHCELL** BioTechCell

**Ciallix** CIALLYX Laboratório e Consultoria

**icepha** Interfaculty Center for Pharmacogenomics and Pharma Research



Universidade Federal do Rio de Janeiro



# VII Workshop de Acompanhamento & Avaliação / INCT-INO FAR



INCT DE FARMACOS E MEDICAMENTOS

INCT-INO FAR

Rio de Janeiro, 24-25 abril de 2013.

# A equipe

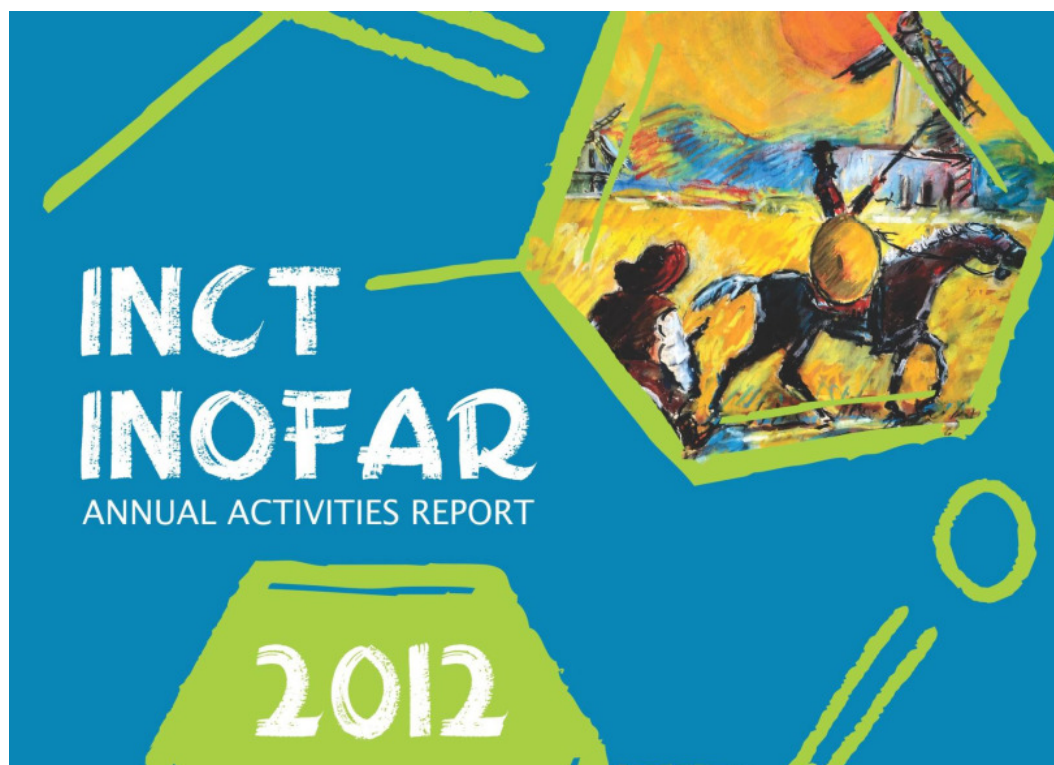
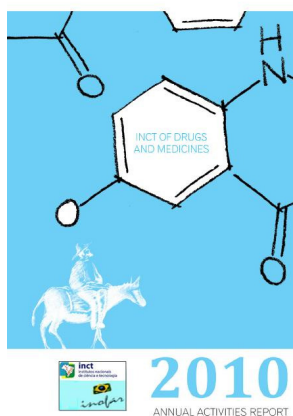
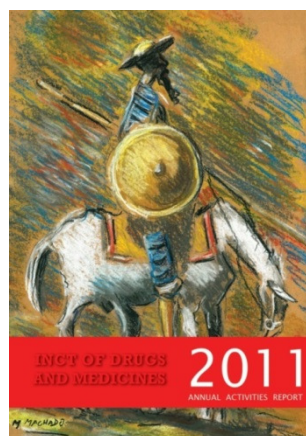
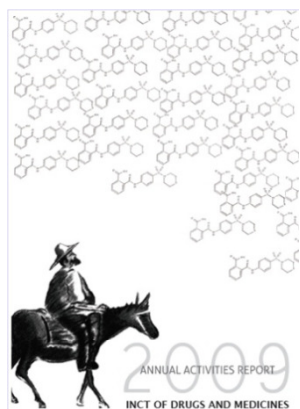


Universidade Federal do Rio de Janeiro



# Instituto Nacional de Ciência e Tecnologia em FÁRMACOS e MEDICAMENTOS (INCT-INO FAR)

## Annual Activities Report



[www.inct-inofar.ccs.ufrj.br/download/aar/2012.pdf](http://www.inct-inofar.ccs.ufrj.br/download/aar/2012.pdf)





Universidade Federal do Rio de Janeiro

# LASSBio

Laboratório de Avaliação e Síntese de Substâncias Bioativas

Quimioteca com  
1855 compostos  
inovação



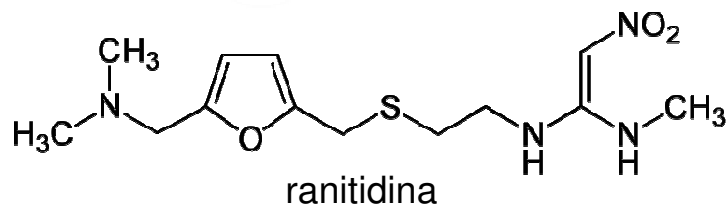
# Química Medicinal

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



**Barry J. Price**

**Research Director Glaxo (1967-1995)**



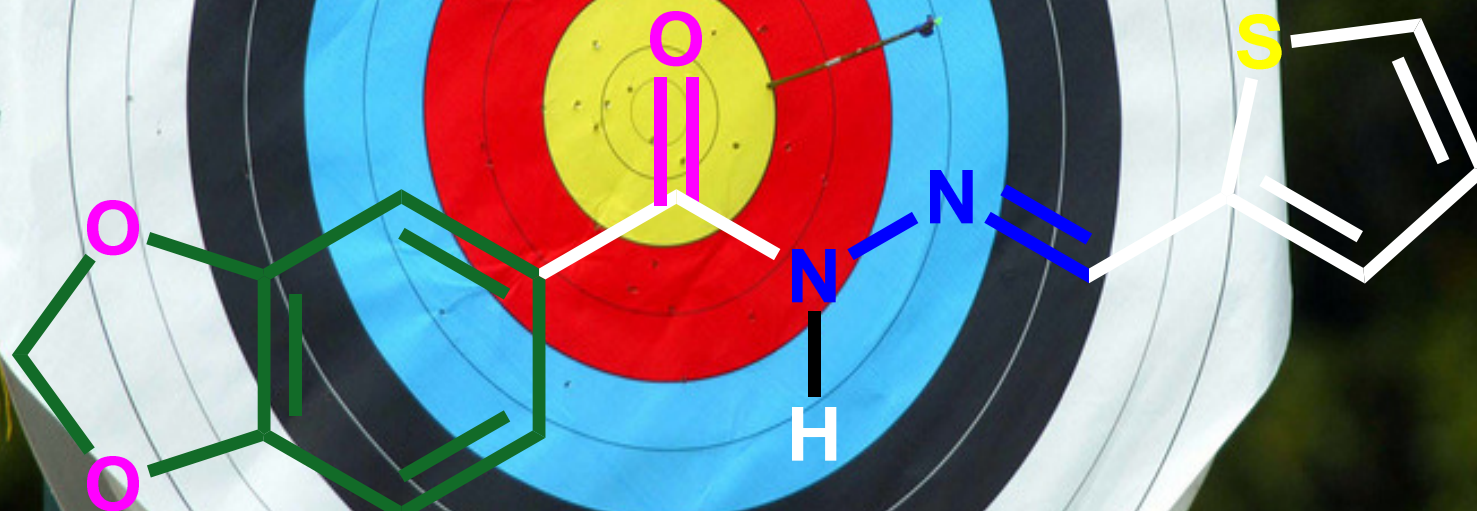


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# LASSBio

Laboratório de Avaliação e Síntese de Substâncias Bioativas



LASSBio-294



INPI

Instituto Nacional da Propriedade Industrial



Consulta à Base de Dados do INPI

# Patentes

» Consultar por: Base Patentes | Finalizar Sessão

RESULTADO DA PESQUISA (18/05/2013 )

Pesquisa por:

Todas as palavras: 'ELIEZER JESUS DE LACERDA BARREIRO no inventor' \ Foram encontrados 15 processos que satisfazem à pesquisa.



Processo	Depósito	Título
PI0806985-9	16/10/2008	DERIVADOS N-ACILIDRAZÔNICOS, PROCESSO DE PRODUÇÃO DE COMPOSTOS N-ACILIDRAZÔNICOS, COMPOSIÇÕES FARMACÊUTICAS CONTENDO OS MESMOS, USOS E MÉTODOS DE TRATAMENTO
PI0711519-9	20/09/2007	DERIVADOS IMIDAZO [1,2-a] PIRIDÍNICOS, COMPOSIÇÕES FARMACÊUTICAS COMPREENDENDO OS MESMOS E PROCESSOS PARA SUA PREPARAÇÃO
PI0705051-8	31/05/2007	USO DE COMPOSTOS QUINOXALÍNICOS ACILIDRAZÔNICOS, E COMPOSIÇÕES FARMACÊUTICAS CONTENDO OS MESMOS, NO TRATAMENTO DE QUADROS INFLAMATÓRIOS, DOR AGUDA E CRÔNICA
PI0601885-8	15/05/2006	COMPOSIÇÃO FARMACÊUTICA ANTIINFLAMATÓRIA E ANALGÉSICA CONTENDO DERIVADOS N-ACILIDRAZÔNICOS DO SAFROL, USO, E PROCESSO PARA SUA PREPARAÇÃO
PI0502016-6	03/06/2005	COMPOSTO UREÍDICOS, COMPOSIÇÕES FARMACÊUTICAS CONTENDO OS MESMOS E SEU USO NO TRATAMENTO DE DOENÇAS INFLAMATÓRIAS
PI0500727-5	03/03/2005	DERIVADOS 1-METIL-3,6,7,8 - TETRAHIDROPIRAZOLO [3,4,-B] PIRROLO [4,3-D] PIRIDINA-6,8-DIONA, PROCESSO DE PREPARAÇÃO, COMPOSIÇÕES FARMACÊUTICAS CONTENDO OS MESMOS E USOS RELACIONADOS
PI0405418-0	02/09/2004	USO DE DERIVADOS N-FENILPERAZÍNICOS E COMPOSIÇÕES FARMACÊUTICAS CONTENDO OS MESMOS
PI0403363-9	20/08/2004	RELAXANTES MUSCULARES SELETIVOS E COMPOSIÇÕES FARMACÊUTICAS
PI0401797-8	20/05/2004	USO DE ANTAGONISTAS A-ADRENÉRGICOS N-FENILPIPERAZÍNICOS, COMPOSIÇÕES FARMACÊUTICAS CONTENDO OS MESMOS E PROCESSOS PARA SUA PREPARAÇÃO
PI0401660-2	27/04/2004	DERIVADOS N-FENILFTALIMÍDICOS E CARBAMOILBENZÓICOS FUNCIONALIZADOS, PROCESSOS PARA SUA PREPARAÇÃO E COMPOSIÇÕES FARMACÊUTICAS CONTENDO OS MESMOS
PI0305690-2	08/10/2003	NOVOS DERIVADOS PIPERIDÍNICOS, COMPOSIÇÕES FARMACÊUTICAS CONTENDO OS MESMOS E PROCESSOS PARA SUA PREPARAÇÃO
PI0303465-8	05/09/2003	NOVOS DERIVADOS N-FENILPIPERAZÍNICOS E COMPOSIÇÕES FARMACÊUTICAS CONTENDO OS MESMOS
PI0202025-4	20/05/2002	- ADRENÉRGICOS N-FENILPIPERAZÍNICOS DERIVADOS DO SAFROL, COMPOSIÇÕES FARMACÊUTICAS CONTENDO OS MESMOS E PROCESSOS PARA SUA PREPARAÇÃO
PI9902960-0	29/04/1999	NOVOS COMPOSTOS BI-PIRAZÓLICOS FUNCIONALIZADOS, NOVA CLASSE DE AGENTES ANTI-INFLAMATÓRIOS NÃO-ESTERÓIDES SINTÉTICOS
PI8201868-5	31/03/1982	SÍNTESE DE PROSTAGLANDINAS DA SÉRIE DESOXI-11-PGE



# Patente obtida



United States Patent 7,091,238

August 15, 2006

Thienylhydrazon with digitalis-like properties (positive inotropic effects)

## Abstract

The invention discloses a compound having the formula (I) wherein R.sub.1 is selected from the group consisting of hydrogen, alkyl of 1 to 6 carbon atoms, unsubstituted phenyl, and substituted phenyl; R.sub.2 is selected from the group consisting of H, alkene, un-substituted phenol, and substituted phenyl; and pharmaceutically acceptable salts thereof, having digitalis-like properties. The invention further discloses a novel method to synthesize 3,4-methylenedioxybenzoyl-2-thienylhydrazone (LASSBio-294). LASSBio-294 produces positive inotropic effect on cardiac and skeletal muscle. The invention is useful for the treatment of congestive heart failure and muscle fatigue. It lacks toxic effects seen in digitalis glycosides.

**Inventors:** Sudo; Roberto Takashi (Rio de Janeiro, BR), Albuquerque; Edson X. (Baltimore, MD), Barreiro; Eliezer J. (Rio de Janeiro, BR)

**Filed:** June 21, 2000

**PCT Filed:** June 21, 2000

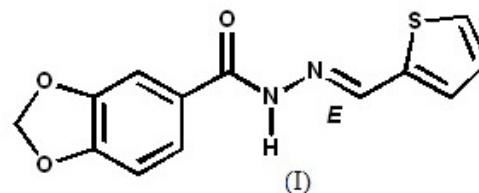
**PCT No.:** PCT/US00/17024

**371(c)(1),(2),(4) Date:** April 08, 2004

**PCT Pub. No.:** WO00/78754

**PCT Pub. Date:** December 28, 2000

The invention includes the novel chemical compound having the formula (I)



$C_{13}H_{10}N_2O_3S$

## SUMMARY OF THE INVENTION

There is a great medical need for drugs to treat congestive heart failure. Congestive heart failure is an important cause of mortality and morbidity in the U.S.: over 2.5 million patients are currently diagnosed. Compounds derived from digitalis, which are in the class of cardiac glycosides, are the primary drugs used in the treatment of congestive heart failure, particularly systolic dysfunction. However, digitalis ameliorates congestive heart failure by producing a positive inotropic effect. A positive inotropic agent strengthens the contractility of muscular tissue. Digitalis-derived drugs have the defect of being cardio-toxic and neuro-toxic at doses just above their therapeutic range (Hardman, J. G. and Limbird, L. E., The Pharmaceutical Basis of Therapeutics, 9.sup.th ed. McGraw-Hill New York, 1996, chapter 34). There is a need for drugs that can treat congestive heart failure and are less toxic near their therapeutic range.



Google

LASSBio-294



Web Imagens Shopping Mais Ferramentas de pesquisa



Aproximadamente 12.800 resultados (0,28 segundos)

### [LASSBio-294 - Redetec](#)

[www.redetec.org.br/inventabrasil/barreiro.htm](http://www.redetec.org.br/inventabrasil/barreiro.htm)

Estamos falando do **LASSBio-294**, um fármaco desenvolvido pelo Laboratório de Avaliação de Substâncias Bioativas (LASSBio) da Universidade Federal do ...

### [CYP1A2-mediated biotransformation of cardioactive 2-thienylidene ...](#)

[www.sigmaaldrich.com/catalog/papers/21144625](http://www.sigmaaldrich.com/catalog/papers/21144625)

The identification of this isoform in the **LASSBio-294** in the clearance of **LASSBio-294** (4) oxidation was performed by the use of selective CYP inhibitors or ...

### [The new compound, \*\*LASSBio 294\*\*, increases the contractility of ...](#)

[www.ncbi.nlm.nih.gov/pubmed/11588115](http://www.ncbi.nlm.nih.gov/pubmed/11588115)

de RT Sudo - 2001 - Citado por 18 - Artigos relacionados

A new compound designated as **LASSBio 294** (L-294), 3,4-methylenedioxybenzoyl-2-thienylhydrazone, was synthesized as an alternative therapeutic for ...

### [Braga RC. Determination of the cardioactive prototype \*\*LASSBio-294\*\* ...](#)

[pubget.com/paper/21440401](http://pubget.com/paper/21440401)

Braga RC. Determination of the cardioactive prototype **LASSBio-294** and its metabolites in dog plasma by LC-MS/MS: Application for a pharmacokinetic study.

### [LASSBio-294. A Compound With Inotropic and Lusitropic Activity ...](#)

[ajh.oxfordjournals.org/content/23/11/1220.abstract](http://ajh.oxfordjournals.org/content/23/11/1220.abstract)

de DG Costa - 2010 - Citado por 3 - Artigos relacionados

Methods **LASSBio-294** (2mg/kg) or vehicle (dimethyl sulfoxide) was administered ... **LASSBio-294** treatment also reduced the nuclear density, collagen volume ...

### [Cyclic GMP-dependent vasodilatory properties of \*\*LASSBio 294\*\* in ...](#)

[onlinelibrary.wiley.com](http://onlinelibrary.wiley.com)

de CLM Silva - 2002 - Citado por 24 - Artigos relacionados

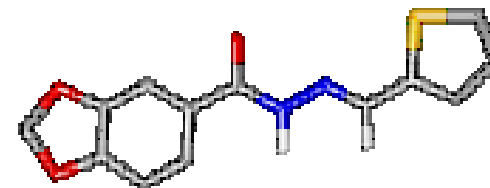
29/01/2009 – Cyclic GMP-dependent vasodilatory properties of **LASSBio 294** in rat aorta ... **LASSBio 294** induced a concentration-dependent relaxation of ...

### [Full Article - Wiley Online Library](#)

[onlinelibrary.wiley.com](http://onlinelibrary.wiley.com)

de RT Sudo - 2001 - Citado por 18 - Artigos relacionados

29/01/2009 – A new compound designated as **LASSBio 294** (L-294), ... Figure 1. Retrosynthetic analysis for preparation of **LASSBio-294** (L-294) from safrole.





# Catalog Name: ChemDiv, Inc. Product Library

Publication Date: 25 Apr 2003

Order Number: 2358-0022

Chemical Name: 1,3-Benzodioxole-5-carboxylic acid, (2-thienylmethylene)hydrazide

Registry Number: 314021-07-3

Pricing: Quantity : milligram quantities

Price: contact supplier

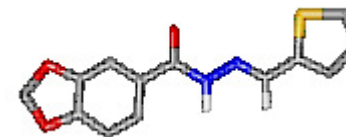
Company Info: ChemDiv, Inc.

11575 Sorrento Valley Road; San Diego, CA, 92121USA

Phone: +1-858-794-4860

Fax: +1-858-794-4931

Web: <http://www.chemdiv.com>



The screenshot shows the ChemDiv website homepage. At the top left is the ChemDiv logo with the tagline "The chemistry of cures<sup>SM</sup>". To the right of the logo is a navigation menu with links for "PRODUCTS AND SERVICES", "RESOURCES", "CUSTOMER AREA", "COMPANY", and "CONTACT US". Above the navigation menu is a search bar with a "SEARCH" button and a "SUBSCRIBE" link. Below the navigation menu is a main banner area with the heading "Target to Proof of Concept" and a photo of Dr. Frederic Cren, Head of Research at Solvay Pharmaceuticals. The banner text reads: "We are very happy to consolidate a portion of our external research activities that are currently being outsourced to several different contract research organizations as this we believe will shorten development timeline. Moreover we are pleased to have found a partner that shares our business model approach." Below the banner is a sidebar with a list of categories: "TARGET TO PROOF OF CONCEPT DEVELOPMENT", "CLINICAL DEVELOPMENT", "PRE-CLINICAL DEVELOPMENT", "DRUG DISCOVERY", and "DISCOVERY TOOLS. CHEMISTRY". At the bottom of the page are three columns of news and information: "WHAT'S NEW?" with a news item dated 04.24.2013, "SHOP ONLINE" with a link to "Visit ChemistryOnDemand eShop", and "BLOG" with a link to "FDA Will Monitor Japanese-Made Drugs as Well as Food for Radiation".



Contents lists available at ScienceDirect

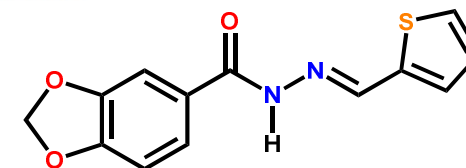
European Journal of Medicinal Chemistry

journal homepage: <http://www.elsevier.com/locate/ejmech>

Original article

## CYP1A2-mediated biotransformation of cardioactive 2-thienylidene-3,4-methylenedioxybenzoylhydrazine (LASSBio-294) by rat liver microsomes and human recombinant CYP enzymes

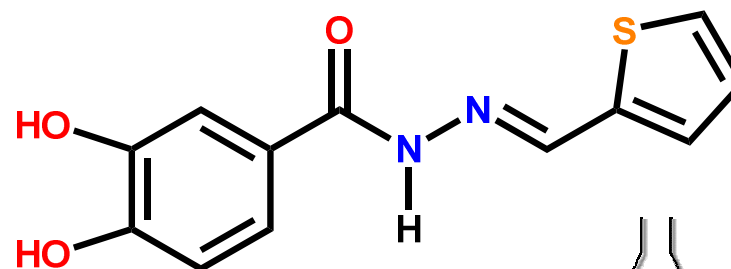
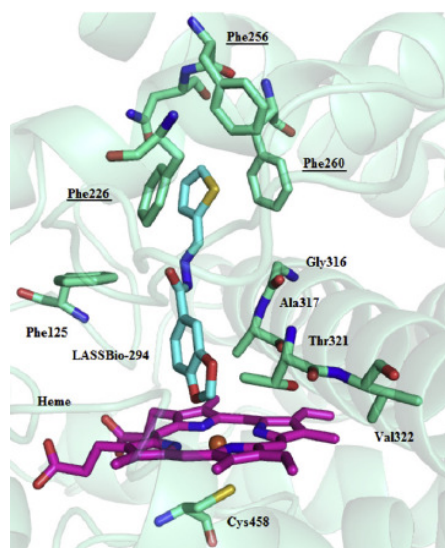
Aline Guerra M. Fraga<sup>a,b</sup>, Leandro Louback da Silva<sup>a,c</sup>,  
Carlos Alberto Manssour Fraga<sup>a,b,c</sup>, Eliezer J. Barreiro<sup>a,b,c,\*</sup>



<sup>a</sup> Laboratório de Avaliação e Síntese de Substâncias Bioativas<sup>1</sup>, Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, RJ 21941-902, PO Box 680, LASSBio-294

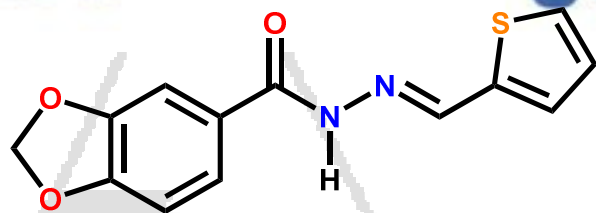
<sup>b</sup> Programa de Pós-Graduação em Química, Instituto de Química, Universidade Federal do Rio de Janeiro, RJ 21949-900, Brazil

<sup>c</sup> Programa de Pós-Graduação em Farmacologia e Química Medicinal, Instituto de Ciências Biomédicas, Universidade Federal do Rio de Janeiro, RJ 21941-590, Brazil



**LASSBio**  
Laboratório de Avaliação e Síntese de Substâncias Bioativas





LASSBio-294

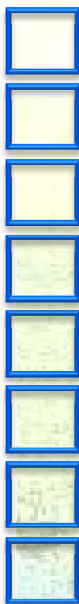


Laboratório de Avaliação e Síntese de Substâncias Bioativas

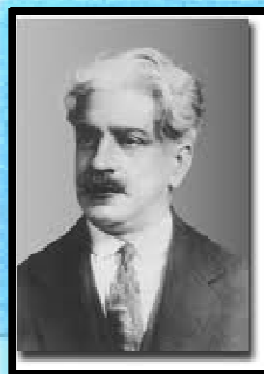
Química Medicinal

# Conclusões

LASSBio-294 é um novo candidato a fármaco cardiovascular, com mecanismo de ação farmacológico original, inédito, **duplo**, ativo p.o., com biodisponibilidade adequada para uso continuado, sem toxicidade crônica, apresentando potentes efeitos inotrópicos positivos e vasodilatadores.



**"Meditai se só as nações  
fortes podem fazer Ciência  
ou se é a Ciência  
que as fazem fortes"**



Walter Oswaldo Cruz

(1910 -1967)



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Conferências



Cursos

27-31 de janeiro de 2014

Inscrições a partir de 01/09/2013

[www.farmacia.ufrj.br/lassbio](http://www.farmacia.ufrj.br/lassbio)



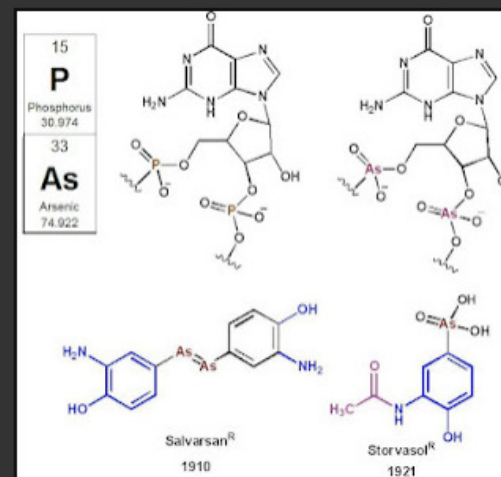


# De fármacos e suas descobertas

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.

## Convite

Sobre as moléculas dos fármacos: os acetatos famosos



Hoje me aconteceu de ler um artigo no *Chemical & Engineering News* (<http://cen.acs.org>; *Chemical & Engineering News*, 90, January 30, 2012) onde se comentava uma recente polêmica científica, referente à presença de arsênio (As) no DNA de organismos que vivem em ambiente rico em As, como a bactéria GFAJ-1, do

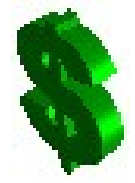
lago Mono, nos EUA. Lá, pesquisadores identificaram nucleosídeos com arsênio no lugar do fósforo, em um autêntico exemplo de isostemismo na natureza. Decidi interromper a série *Linha do Tempo da Química Medicinal*, para incluir este post em homenagem ao Carnaval 2012. Claro que continuarei

<http://ejb-eliezer.blogspot.com>



Universidade Federal do Rio de Janeiro

# Obrigado



XX Reunião Anual de Avaliação LASSBio, Barra Nova, Saquarema, RJ, dez 2012.