



Universidade Federal do Rio de Janeiro

A importância da Química Medicinal no desenvolvimento de fármacos



Eliezer J. Barreiro

Professor Titular - UFRJ



Laboratório de Avaliação e Síntese de Substâncias Bioativas
Instituto Nacional de Ciência e Tecnologia de Fármacos e Medicamentos
INCT-INO FAR



Programa de Desenvolvimento de Fármacos - ICB



Laboratório de Avaliação e Síntese de Substâncias Bioativas

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





Fármacos e medicamentos são instrumentos essenciais à atenção farmacêutica, eficiente e segura , sendo, portanto, imprescindíveis nas políticas de saúde, promovendo a inclusão social e a cidadania.

Sumário

- Definição da Química Medicinal (QM)
 - Breve histórico da QM
 - Os fármacos e o prêmio Nobel
 - A interdisciplinaridade da QM
- O desenvolvimento de fármacos & a pesquisa científica
 - *A mais valia* dos fármacos
- O LASSBio-UF RJ sede do INCT-INO FAR



Definição:

Química Medicinal

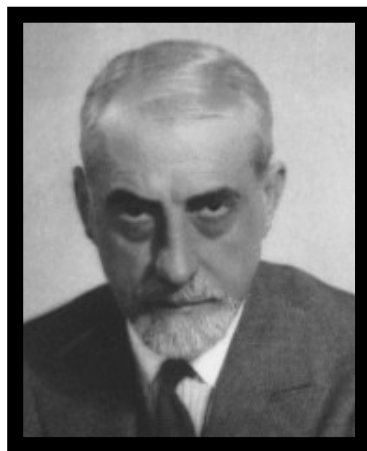
estuda os fatores moleculares relacionados ao modo de ação dos fármacos, incluindo a compreensão da relação entre a estrutura química e a atividade (SAR), além das propriedades que governam sua absorção, distribuição, metabolismo, eliminação (ADME) e toxicidade.

Química Medicinal

Eur. J. Med. Chem., 31, 747 (1996)



O berço da Química Medicinal

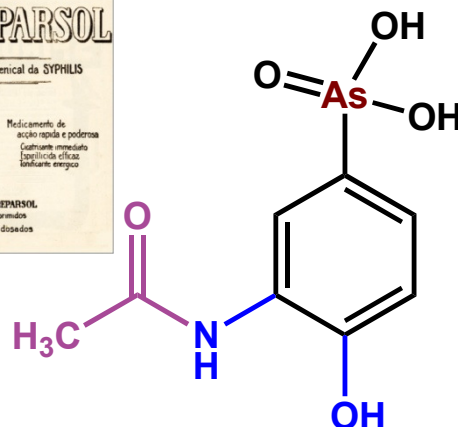


Ernest Fourneau
1872-1949



Stovarsol

CAS 97-44-9



Institut Pasteur (1887)

1911- Laboratoire de Chimie Thérapeutique

Institut Pasteur (Emile Roux)

1911-1944 – Jacques Tréfouël (1897-1977)
 Thérèse Tréfouël (1892-1978)
 Germaine Benoit (1901-1983)
 Federico Nitti (1903-1947)



Daniel Bovet
1907-1992 *

*Farmacêutico suíço
Doutor *h.c.* UFRJ

Prêmio Nobel de
Fisiologia/Medicina
1957



Sulfonamidas,
anti-histamínicos.
Curare: SAR

J-P Fourneau, « Ernest Fourneau fondateur de la Chimie Pharmaceutique française », *Revue de l'Histoire de la Pharmacie*, t.XXXIV, nº 275, 335-355



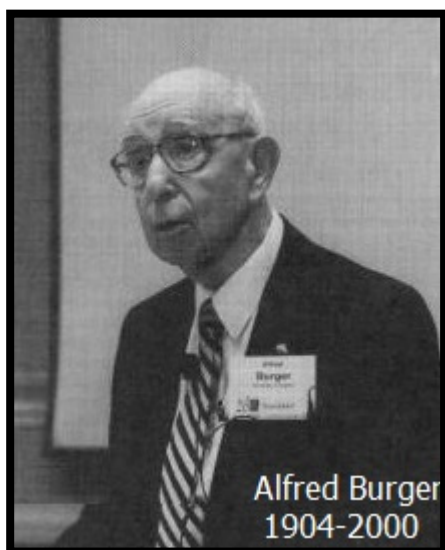
Química Medicinal

Prof. Alfred Burger

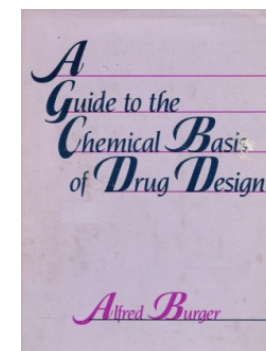
(1904-2000)

University of Virginia

EUA



Alfred Burger
1904-2000



1929 – Emigra para EUA (SW)
University of Virginia

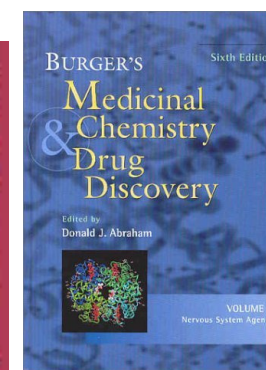
1952 – Professor of Medicinal Chemistry

1953 - Pasteur Medal by the Pasteur Institute in Paris

1958 – cria o Journal of the Medicinal and Pharmaceutical Chemistry → depois Journal of Medicinal Chemistry
"An Editor's Commentary on the Birth of a Journal"

J. Med. Chem. **1991**, *34*, 2-6

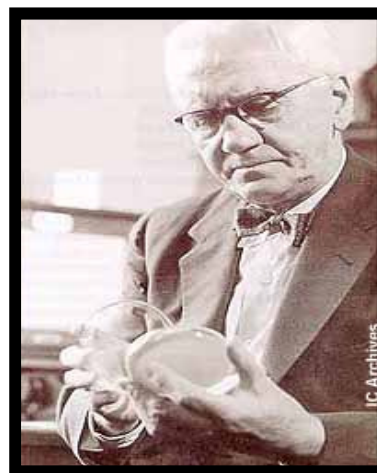
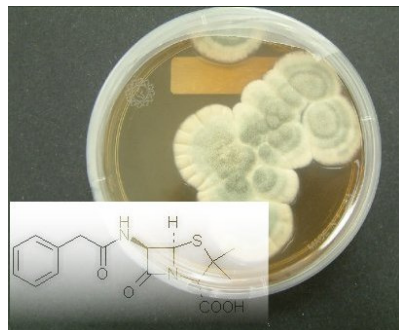
1978 - GlaxoSmithKline cria com ACS o "Alfred Burger Award" em Química Medicinal
T. Y. Shen - inventor da indometacina



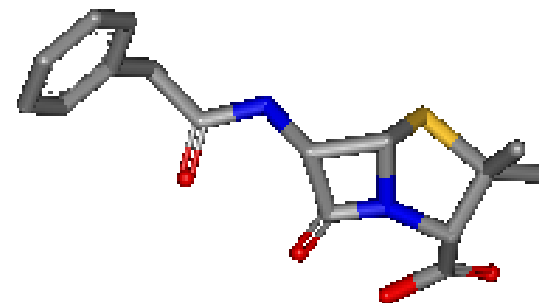
1979 – Congresso Brasileiro de Farmacologia, São Paulo, SP



Os fármacos e o Nobel !



Alexander Fleming
1881-1955



Penicilina

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



Howard W. Florey
1898-1968



<http://nobelprize.org>

1945



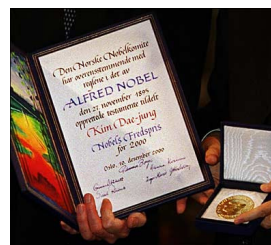
Ernest B. Chain
1906-1979



Os fármacos e o Nobel !



1982



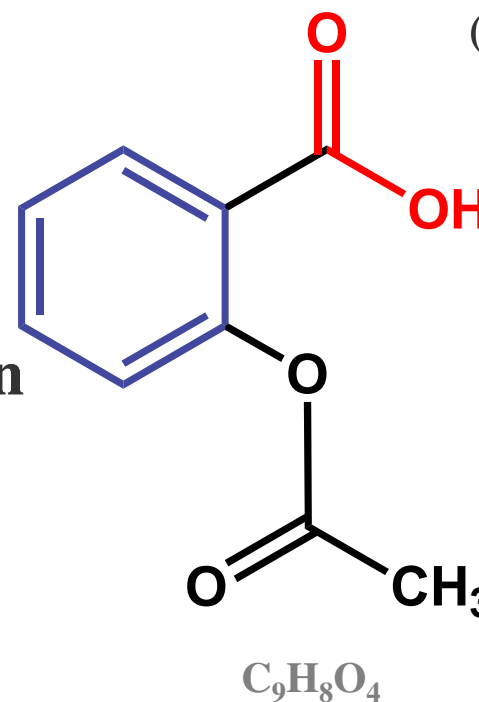
John R. Vane
(1927-2004)



Sune K. Bergström
(1916-2004)

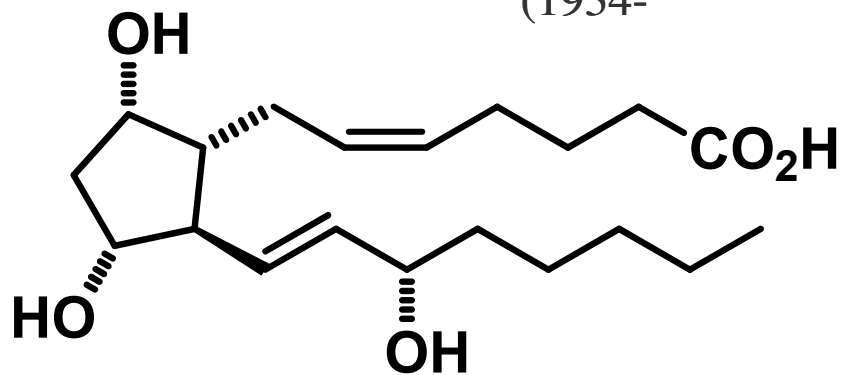


Bengt I. Samuelsson
(1934-

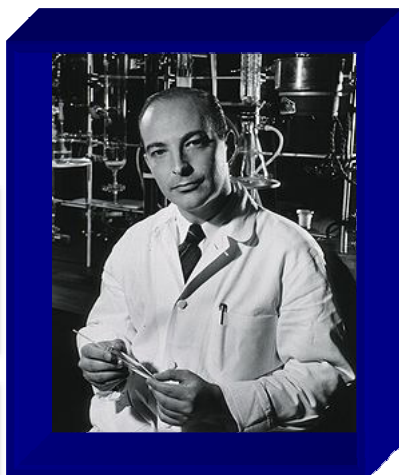


Ácido acetil salicílico

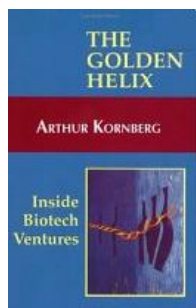
10 de agosto de 1897



Prostaglandina $F_{2\alpha}$



Arthur Kornberg
1918-2007



University of Stanford

Prêmio Nobel, 1959



The Two Cultures: Chemistry and Biology¹

Arthur Kornberg

Department of Biochemistry, Stanford University, Stanford, California 94305

Received July 14, 1987

1987
“Much of life can be understood in rational terms if expressed in the language of chemistry... the

historical roots of chemistry and biology

are intertwined in many places...



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

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



Biochemistry 1987, 26, 6888-6891

Química Medicinal

Diapositivo 9

EJB6

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

Eliezer J. Barreiro; 04/03/2010

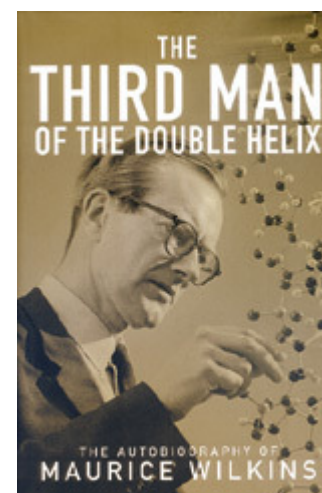
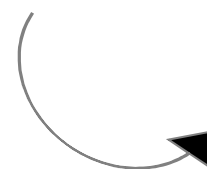
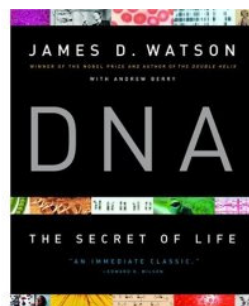
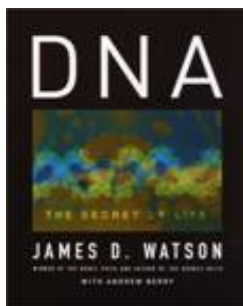
A importância da interdisciplinaridade



O físico Crick & biólogo Watson

The Nobel Prize in Physiology or Medicine 1962

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



O biofísico Maurice Hugh Frederick Wilkins



Interdisciplinaridade

Síntese Orgânica

Bioinorgânica

Química Orgânica

Bioinformática

Bioquímica

Farmacologia

Toxicologia

Interdisciplinaridade

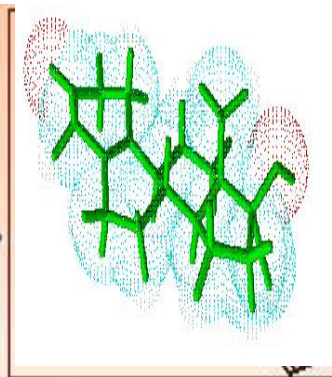


Preclinical studies

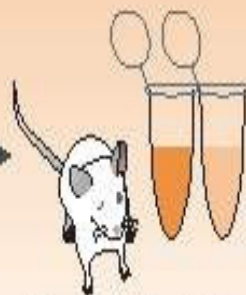
Química Medicinal



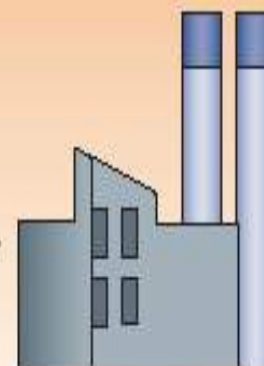
Research team formed and objectives set



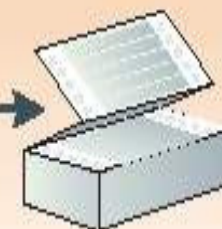
Novel chemicals synthesized



Chemicals tested for efficacy and safety in test tubes and animals. Results used to choose drug candidate.

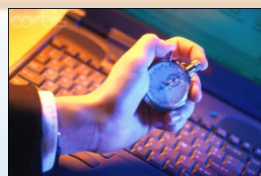


Formulation, stability scale-up synthesis, chronic safety in animals



Company files Investigational New Drug (IND) application with FDA

Clinical studies



O processo de desenvolvimento de novos fármacos



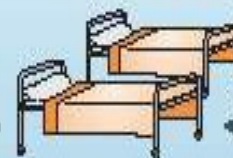
Drug is approved for marketing

ANVISA
FDA

FDA reviews NDA



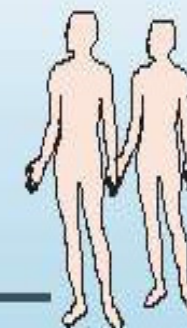
Company files New Drug Application (NDA)



Phase III: large clinical trials in many patients



Phase II: studies in patients (efficacy)



Phase I: studies in healthy humans (toleration)



JA Lombardino & JA Lowe III, Nature Rev. Drug Disc. 2004, 3, 853



O desenvolvimento de fármacos ...



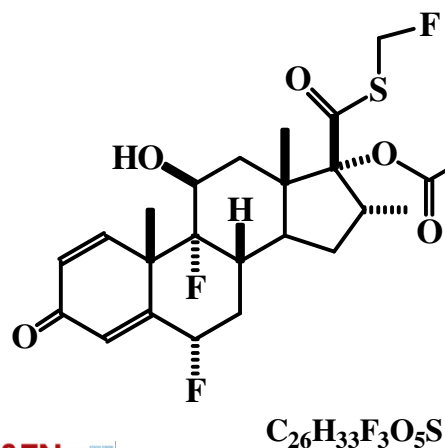
- *Science* **2000**, 287, 1951 (J.Uppenbrink, J.Mervis)

Índice de impacto (2009) = 29,747

depende da pesquisa científica

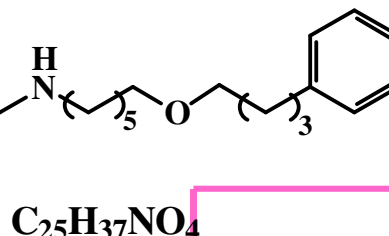


Os fármacos *best-seller* em 2010*

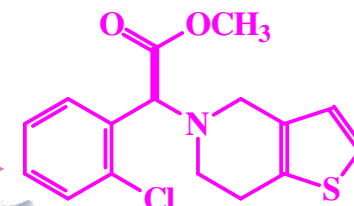


Seretide

fluticazona salmeterol (GSK, 2012)



Clopidogrel (BMS, 2011)



C16H16ClNO2S



1

2,0

5,6-6,2 6,5

8,4 8,4

9,1

13,3

45,7



Rosuvastatina (Crestor[®], AZ)



Etanercept (Enbrel[®], biofármaco)

Infliximab (Remicade[®], biofármaco)

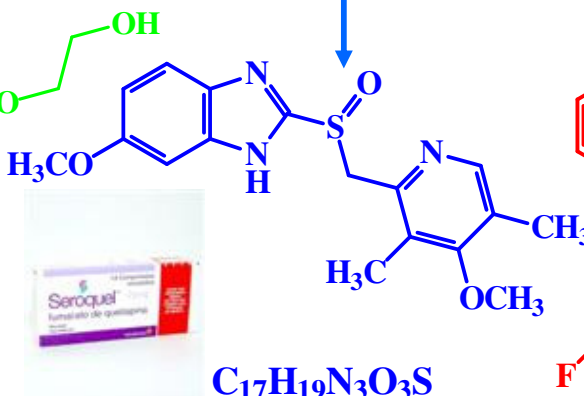
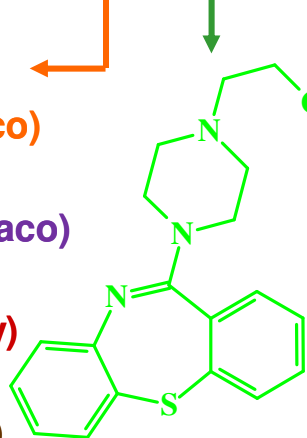
Olanzapina (Zyprexa[®], Ely Lilly)

Adalimumab (Humira[®], Abbott)

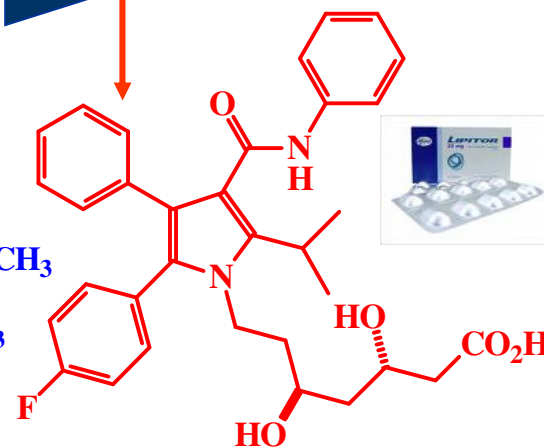
75,0 (8,7%)

Quetiapina (AZ, 2012)

em US\$ bilhões



C17H19N3O3S



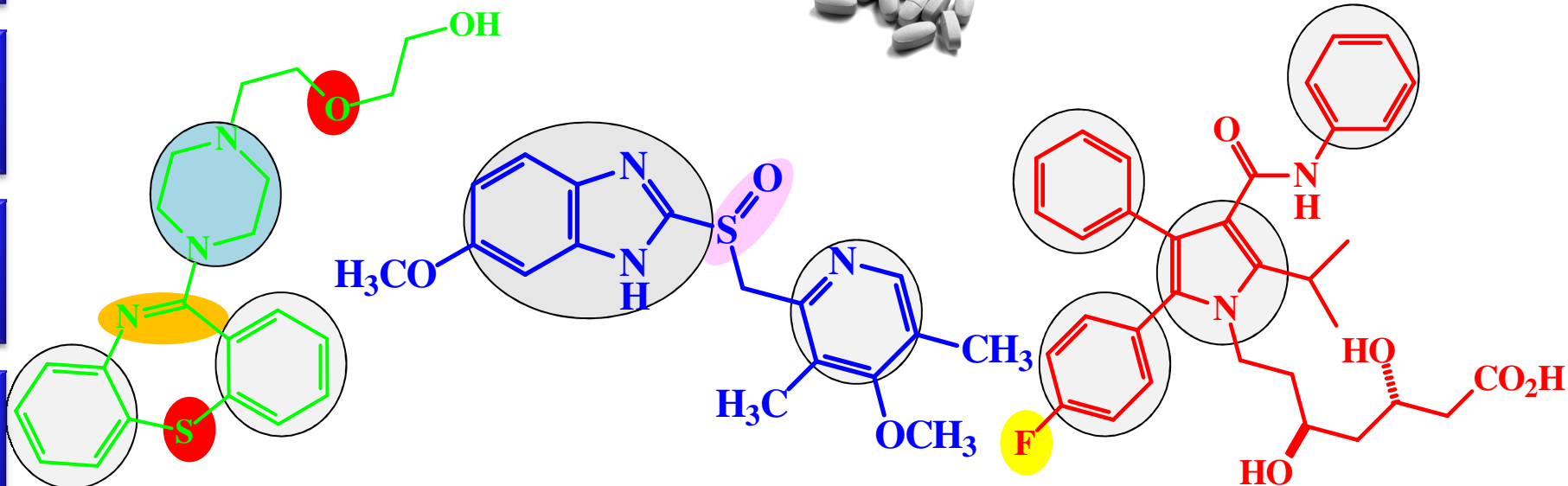
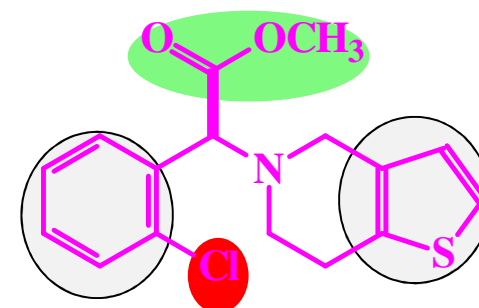
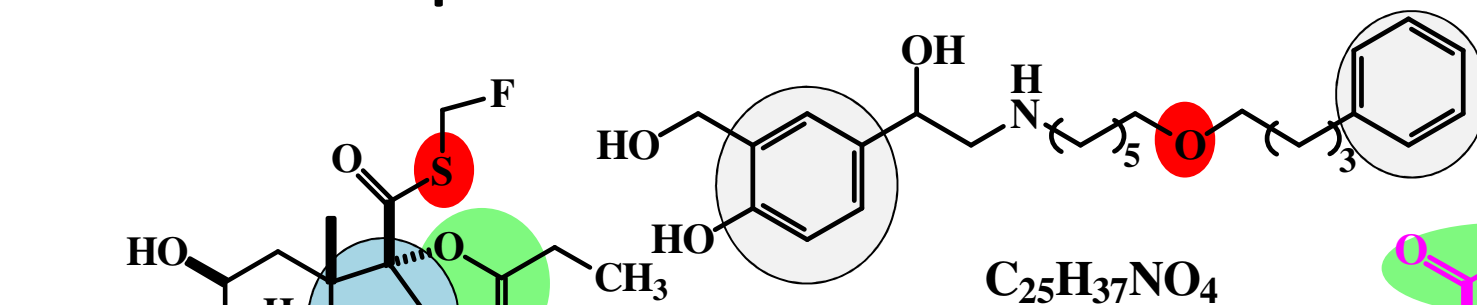
Atorvastatina (Pfizer; 06/2011)



C33H35FN2O5

* R Mullin, *C&EN* 2010 (06/12) 14-21

Sobre a quimiodiversidade dos fármacos

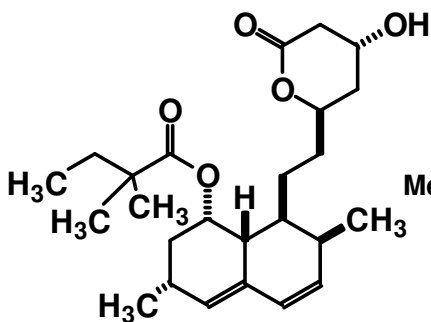


➤ **São moléculas pequenas mas muito valiosas!**

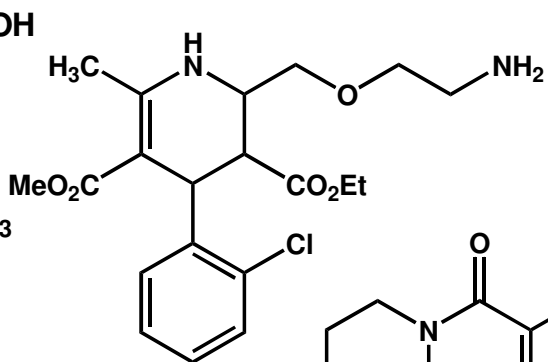


Valor de mercado de alguns fármacos ao final de suas patentes

2013

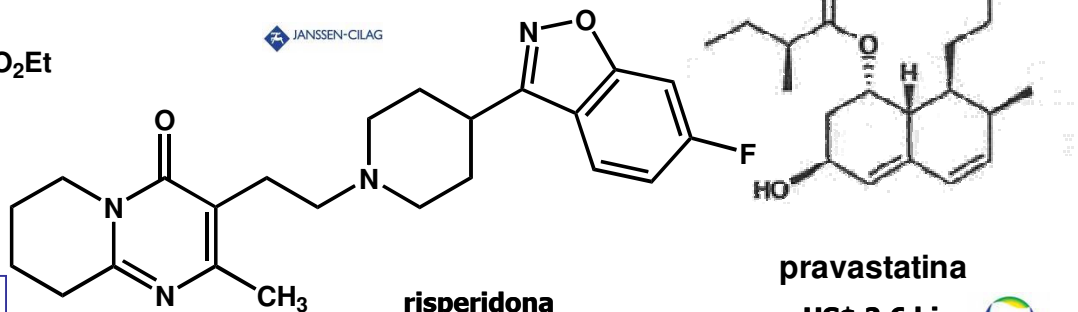


MERCK **simvastatina**
US\$ 5,6 bi

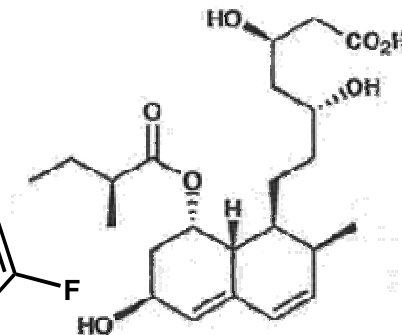


Pfizer **amlodipina**

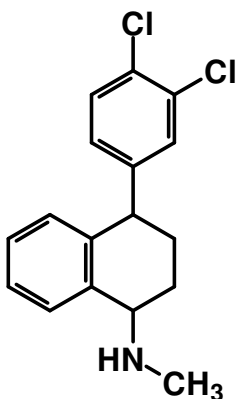
JANSSEN-CILAG



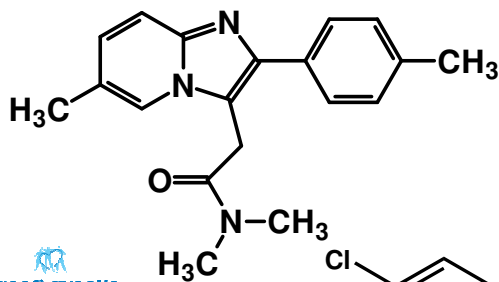
risperidona
US\$ 4,3 bi



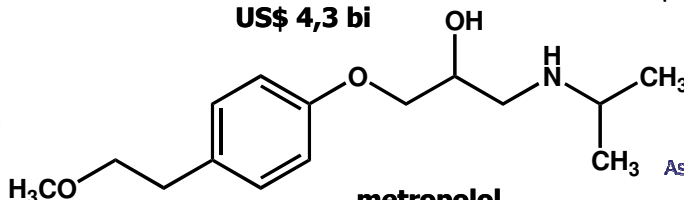
pravastatina
US\$ 2,6 bi



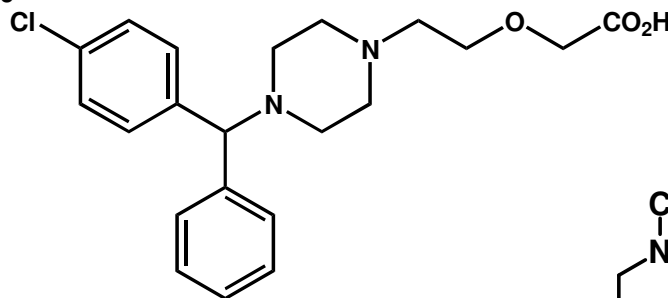
sertralina
US\$ 3,7 bi



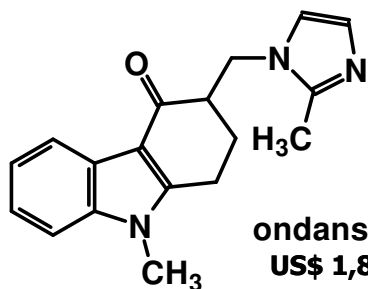
zolpidem
US\$ 2,3 bi



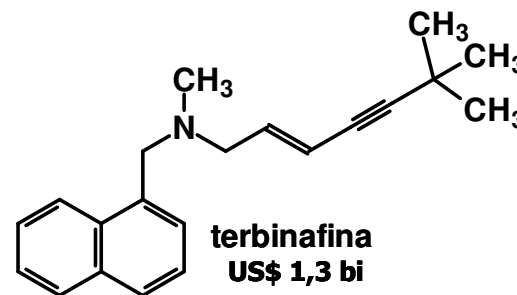
metoprolol
US\$ 1,9 bi



cetirizina
US\$ 1,5 bi



ondansetron
US\$ 1,8 bi



terbinafina
US\$ 1,3 bi





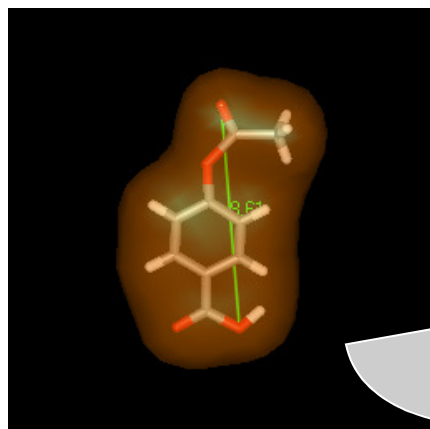
Todos procuram moléculas...



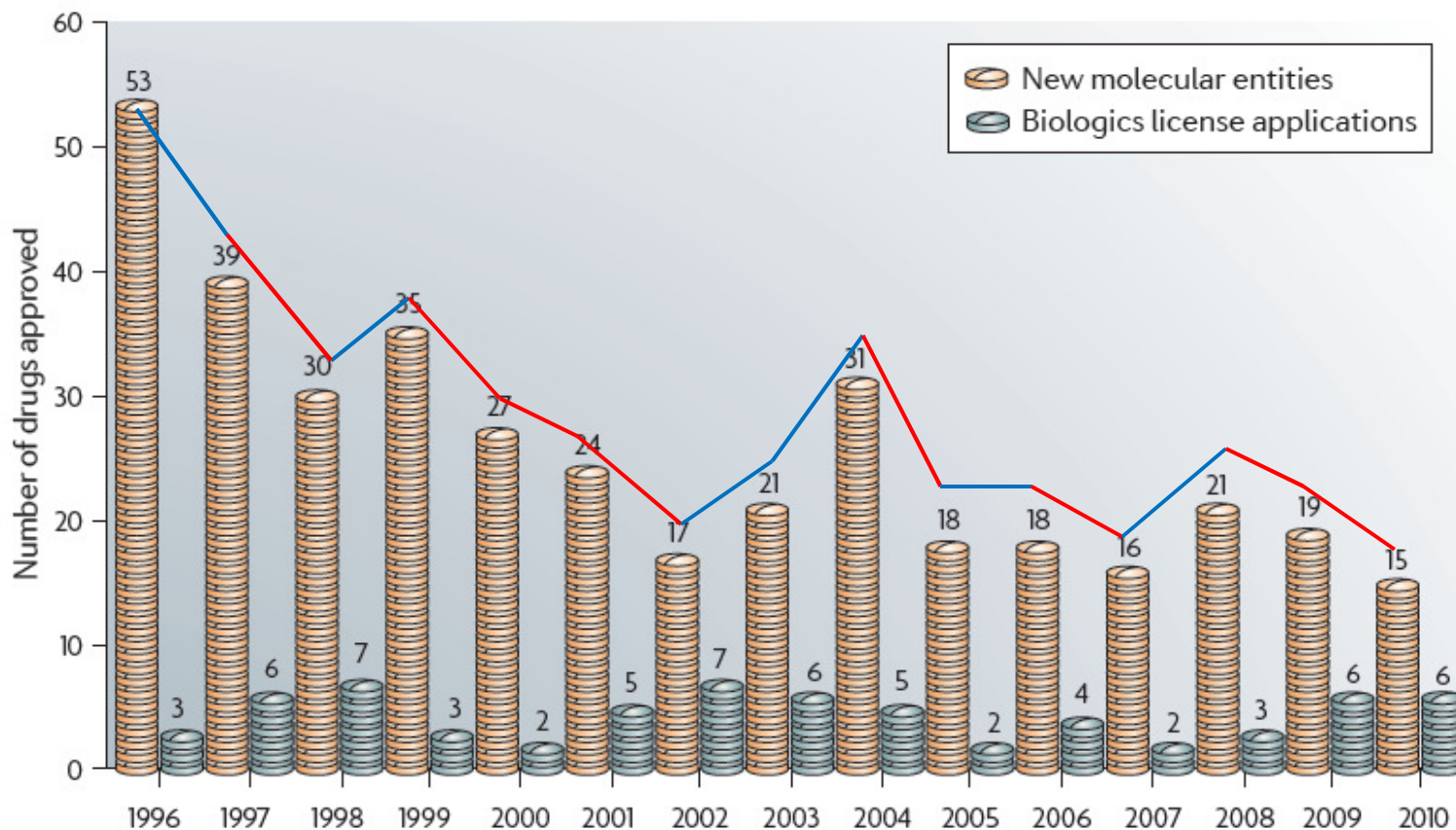
Editorial overview
Alan Cuthbert

Current Opinion in Pharmacology 2004, 4, 487

**Big-pharma
&
moléculas**



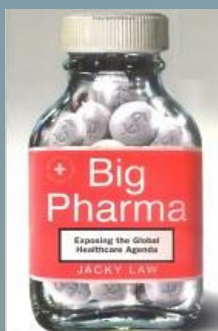
Os fármacos inovadores estão mais raros...



A. Mullard, 2010 FDA drug approvals, *Nature Rev. Drug Discov.* **2011**, 10, 82

...as inovações já não são assim tão inovadoras !

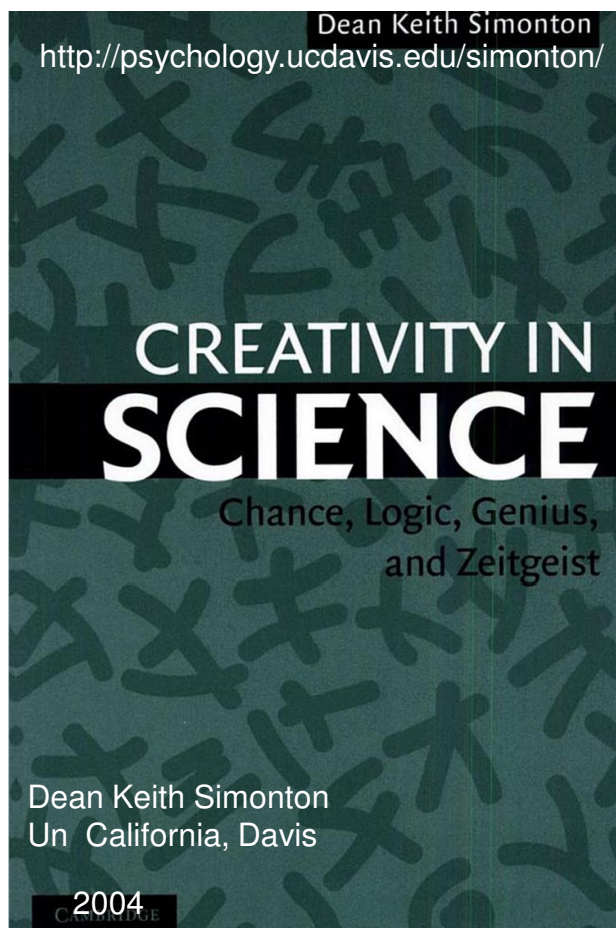
A IF encontra-se na era *Pharma1.0* ➡ *Pharma 2.0*



Minha visão da indústria farmacêutica mundial...

Invenção & Criatividade

Trabalhar em colaboração



“discoveries and inventions become virtually inevitable (1) as prerequisite kinds of knowledge accumulate in man’s cultural store; (2) as the attention of a sufficient number of investigators is focused on a problem – by emerging social needs, or by developments internal to the particular science, or by both”

Robert K. Merton (1961)

The role of genius in scientific advance. *New Scientist*, 12, 306-308

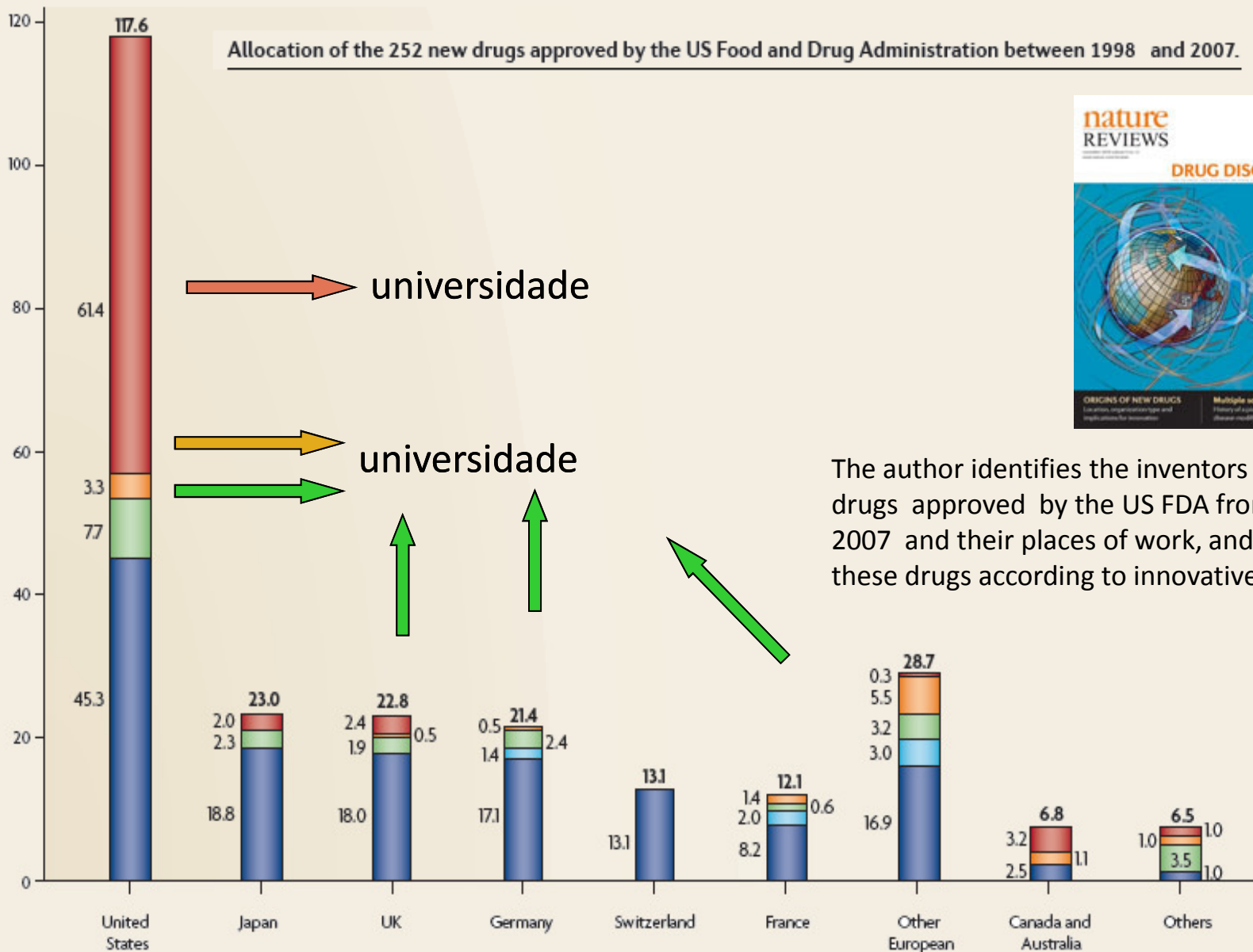
A ecônomia do conhecimento



Allocation of the 252 new drugs approved by the US Food and Drug Administration between 1998 and 2007.



Number of whole drug equivalents



The author identifies the inventors of 252 new drugs approved by the US FDA from 1998 to 2007 and their places of work, and classifies these drugs according to innovativeness

■ Large pharmaceutical company
 ■ University-discovered, transferred to pharmaceutical company
 ■ Biotechnology company; or university-discovered, transferred to biotechnology company in the same region
■ Small pharmaceutical company
 ■ University-discovered, transferred to biotechnology company in a different region





Universidade Federal do Rio de Janeiro

Química Medicinal



LASSBio

Laboratório de Avaliação e Síntese de Substâncias Bioativas

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

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



LASSBio Pharmacology
Farmacologia

Molecular
Modelagem
Modeling
Molecular



Novos Compostos-Protótipos Descobertos no LASSBio

Biochem. Eng. J., 21, 103 (2004)

Bioorg. Med. Chem. Lett, 15, 1169 (2005)

Applied Biochem. Biotechnol., 121, 117 (2005)

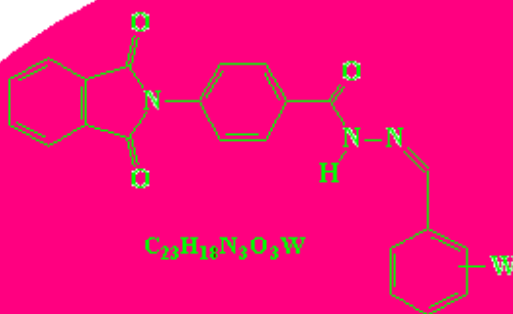
Eur. J. Pharmacol., 511, 219 (2005)

INPI # 0401660-2 de 09/04/2004

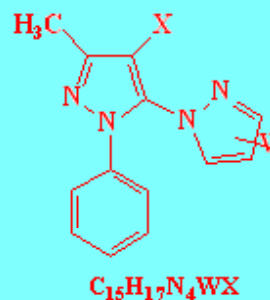
LASSBio-881

INPI # 38201866 de 29/04/1999

LASSBio-552

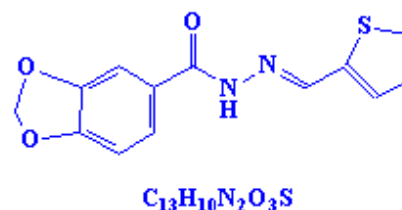
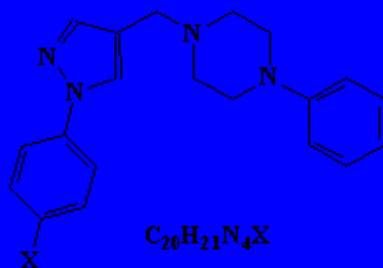


LASSBio-715



LASSBio-596

LASSBio-581



LASSBio-294

USPTO Patent # 7.091.238
August 15, 2006

INPI # 0303465-8 de 05/09/2003

Braz. J. Biol. Med. Res., 36, 625 (2003)

Bioorg. Med. Chem., 11, 4807 (2003)

J. Pharm. Biomed. Anal., 33, 1127 (2003)

Quim. Nova, 27, 949 (2004)

Ass Spectrometry, 40, 815-820, (2005)

J. Pharmacol. Exper. Therap., 299, 558 (2001)

Br. J. Pharmacol., 134, 603 (2001)

Br. J. Pharmacol., 135, 293 (2002)

Quim. Nova, 25, 1172 (2002)

Eur. J. Pharmacol., 470, 79 (2003)

INPI # 0403363-9 de 20/08/2004



LASSBio LLDB LIGAND DATA BANK

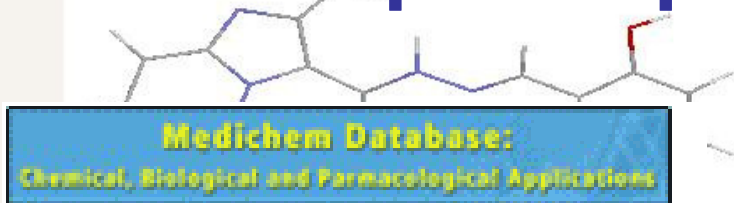
L. E. Dardenne, LNCC GRUPO DE MODELAGEM MOLECULAR DE SISTEMAS BIOLÓGICOS LNCC/MCT



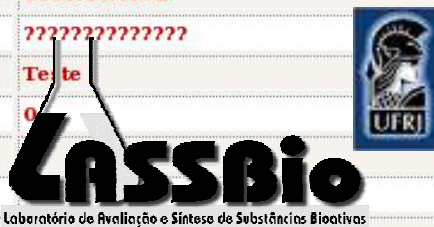
Search Register Ligand Help Logout

Banco de dados de moléculas =

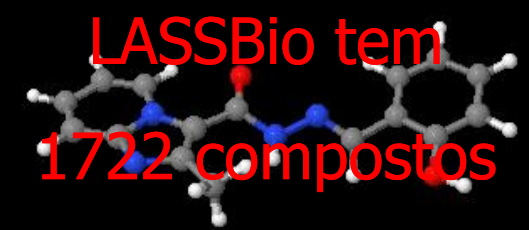
Novos protótipos



Molecular Form:	C16H14N4O2
IUPAC Nomenclature :	????????????
Fantasy Name :	Te te
Number of Quiral Centers :	0
Number of H-Bond Donors	
Number of H-Bond Acceptors	
Number of Free Bonds	4
Log P	2.0
Fusion Point	100
Functional Group:	Acylhydrazone

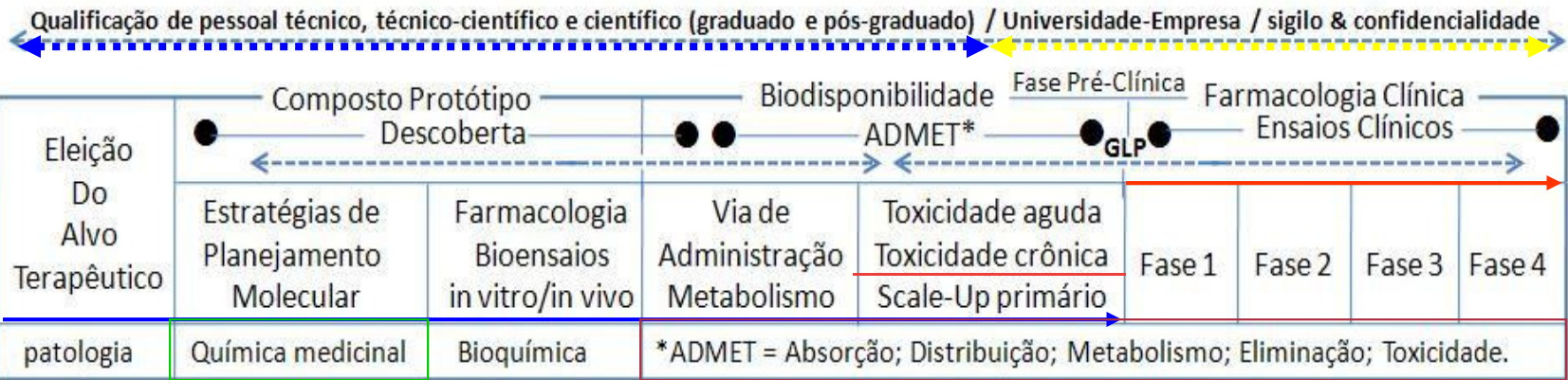


A quimioteca do LASSBio tem 1722 compostos originais e ativos

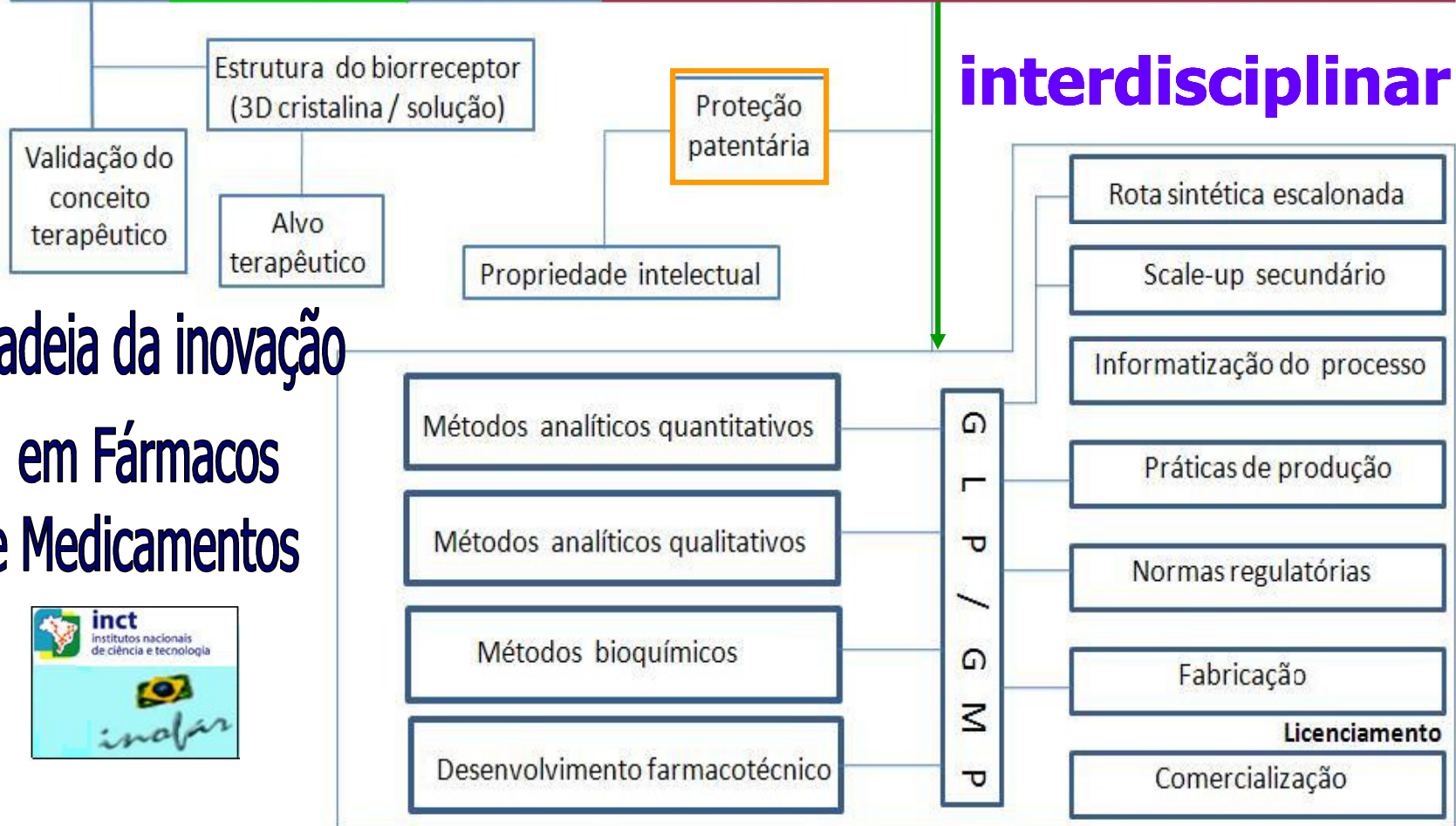


Jmol

Wireframe Ball-and-Stick Space Fill
To return for initial orientation
Rotacionar



Cadeia da inovação em Fármacos e Medicamentos



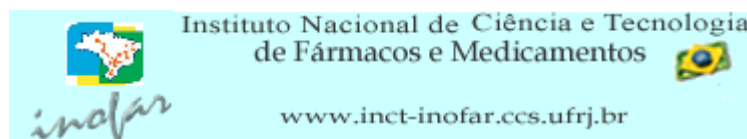
interdisciplinar



INCT de Fármacos e Medicamentos INCT-INO FAR



Proc. CNPq 573.564/2008-6/
FAPERJ E-26/170.020/2008



Coordenador Vice-Coordenador
Eliezer J. Barreiro Fernando Q. Cunha
UFRJ USP



INTITUIÇÃO SEDE





Missão do INCT-INOVAR

- Organizar as competências científicas nacionais em rede de pesquisa em fármacos e medicamentos;
- Estudar projetos de inovação radical em fármacos ;
- Contribuir para a inovação incremental em fármacos;
- Estudar rotas de síntese total de novos fármacos genéricos, intermediários avançados e estratégicos;
- Contribuir para a formação qualificada e continuada de pessoal, especialmente em química medicinal e farmacologia;
- Identificar e definir soluções para os eventuais *gargalos* na cadeia de inovação em fármacos;
- Promover ações de aproximação entre ICT's e empresas do setor, visando a transferência da tecnologia desenvolvida;
- Zelar e proteger o conhecimento novo de valia, acumulado;
- Promover e divulgar as ciências dos fármacos e medicamentos;
- Contribuir para o uso seguro e racional dos medicamentos.



Universidade Federal do Rio de Janeiro

Distribuição regional





Áreas de interesse

Research Interest

- ⊕ Inflamação
- ⊕ Asma
- ⊕ Dor
- ⊕ CNS
- ⊕ Sistema cardiovascular
- ⊕ Quimioterapia do câncer & antiparasitária



- Descoberta e ensaio pré-clínico de novo candidato a fármaco anti-asmático (LASSBio-596)

Profa. Patrícia M. R. Rocco & Profa. Lidia Moreira Lima
Instituto de Biofísica Carlos Chagas Filho & LASSBio –
Universidade Federal do Rio de Janeiro

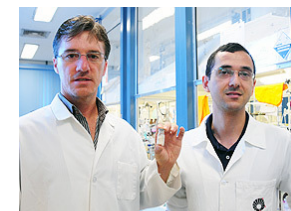
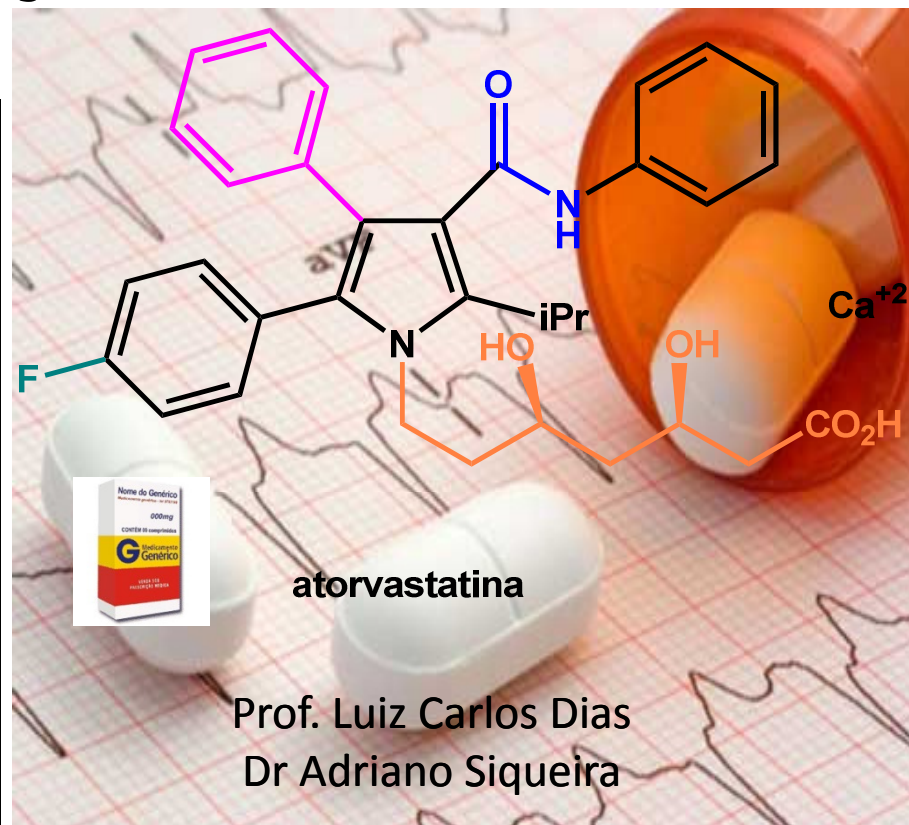


Inovação incremental

Estudo de rotas de síntese, a partir de intermediários primários de menor custo, de novos fármacos genéricos de interesse para o SUS e empresas:
Estatina & Tinibe.



Prof. Ângelo da Cunha Pinto



O professor Luiz Carlos Dias e o pós-doutorando Adriano Siqueira Vieira: nova rota é mais barata e eficiente

Obrigado



Corcovado mountain with the statue of Cristo Redentor
one of the new seven wonders of the world.