34ª Reunião Annual da SBQ
Química para um mundo melhor

26.05.2011 - Sessão Temática

FÁRMACOS E MEDICAMENTOS

Ronaldo A. Pilli - UNICAMP
Adriano Lisboa Monteiro – UFRGS

O paradigma de Fischer & Ehrlich na Química Medicinal moderna

Eliezer J. Barreiro
Professor Titular – U F R J

Laboratório de Avaliação e Síntese de Substâncias Bioativas
LASSBio[R]

Instituto Nacional de Ciência e Tecnologia em Fármacos e Medicamentos
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Química Medicinal

2011 AIQ Ano Internacional da Química

O quê podemos considerar como *conhecimento* em Química Medicinal ?

O Químico Medicinal

O **Químico Medicinal** utiliza conhecimento híbrido da **Q**uímica e da **B**iologia, integrando equipe interdisciplinar, *na busca de novos fármacos*, em atividade interativa contínua de otimização de inúmeras variáveis moleculares dos novos compostos-protótipos que inventa!

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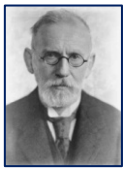
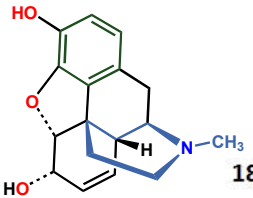
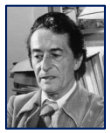
Cronologia histórica da Química Medicinal







1955 – *C. roseus*

1996 - Wermuth

1977 - captopril

1982 - Vane

1988 - Black

1960 - talidomida

1960 - Librium®

1975 - cimetidina

1967 - nifedipina

1964 - propranolol

1964 - Hansch

1908 - Ehrlich

1907 - Salvarsan®

1949 - Laborit

1943 - cloroquina

1941- penicilina

1935 - Domagk

1958 - Burger

1955 - Vinca

1950 - RNM

1949 - cortisona

1847 - clorofórmio

1842 - éter etílico

1902 - Fischer

1904 - corantes

1805 - morfina

1823 - quinina

1834 - atropina

1860 - fenol

1860 - AS

1886 - paracetamol

1889 - AAS

1910 - Dale (AChRs)

1911 - Fourneau

1948 - Ahlquist

1952 - fenotiazina

1958 - haloperidol

1962 - indometacina

1963 - Vallium®

1980 - cetoconazol

1980 - lovastatina

1981 - aciclovir

1999 - oseltamivir

1999 - celecoxibe

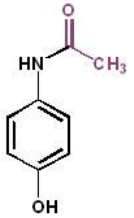
2000 - imatinibe

1945 - Fleming

1959 - "pílula"

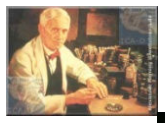
1959 - Kornberg

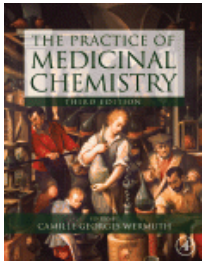
Galeno



R = H

R = CH_3





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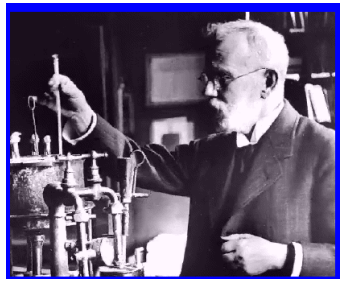
O paradigma de Fischer-Ehrlich

Emil Fischer

1852-1919

1902

1908



Paul Ehrlich

1854-1915

LOCK & KEY CONCEPT

http://nobelprize.org/nobel_prizes/chemistry/laureates/1902/fischer-lecture.pdf

The Magic Bullet Theory

One-molecule, one-target paradigm

Biorreceptor

macrobiomolécula

baseado no sítio de reconhecimento

Planejamento racional

Química Medicinal

Fármaco

micromolécula

baseado no ligante / análogo-ativo

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

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Os fármacos atuam em alvos terapêuticos...

... os biorreceptores

Estima-se que hoje sejam 483 os biorreceptores envolvidos na resposta terapêutica de todos os fármacos contemporâneos.

J.Drews & S.Ryser, The classical drug targets, *Nature Biotechnol*. **1997**, *15*, 1350; P. Imming, C. Sinning, A. Meyer, *Nature Rev. Drug Discov*. **2006**, *5*, 821.

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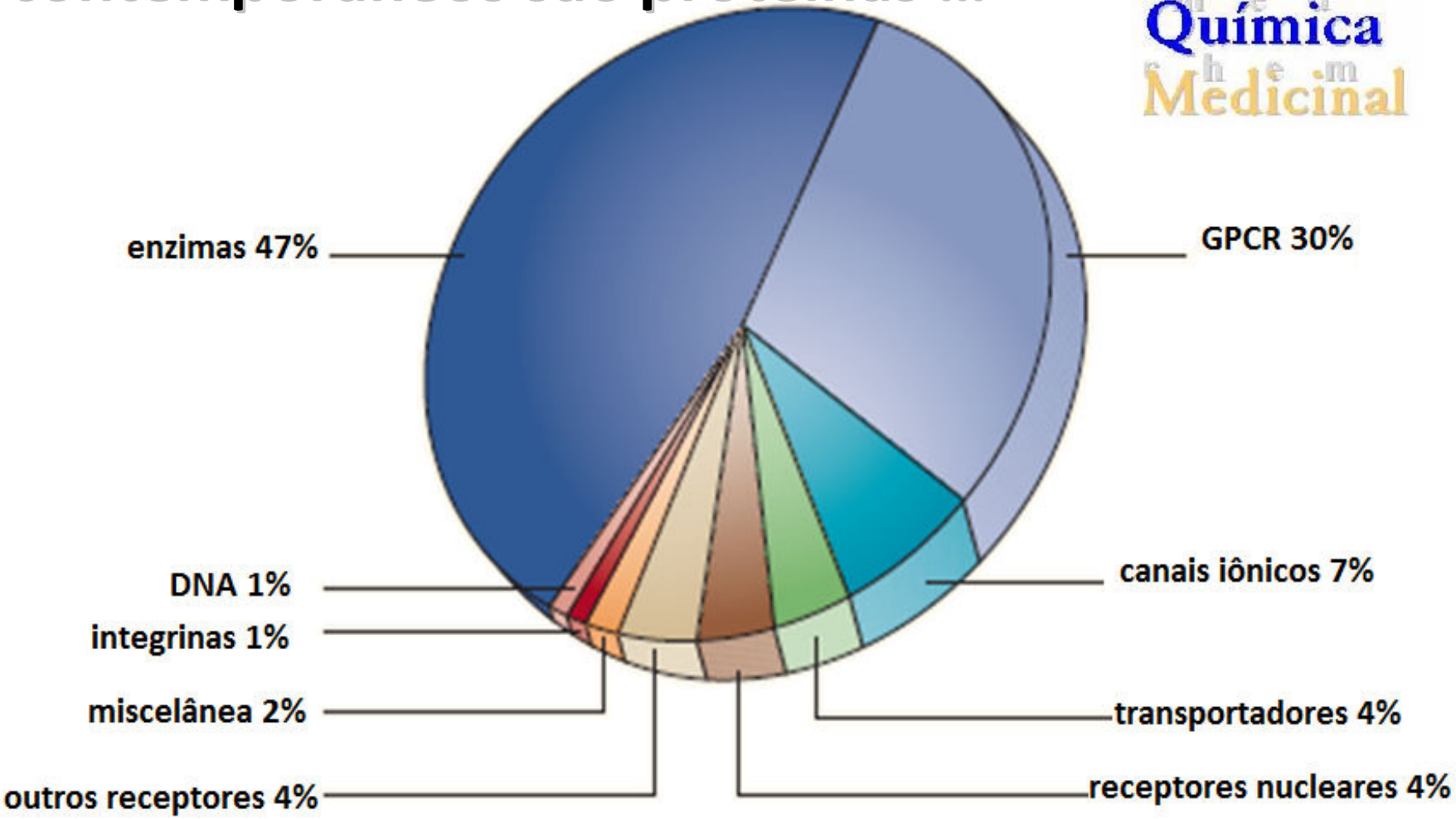
A maioria dos biorreceptores dos fármacos contemporâneos são proteínas ...



A.L. Hopkins & C.R. Groom, The Drugable genome, *Nature Rev. Drug Discov*. **2002**, *1*, 727

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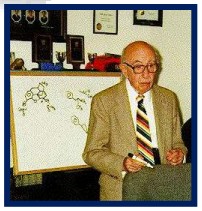
"...The unprecedented increase in human life expectancy, which has almost doubled in a hundred years, is mainly due to drugs and to those who discovered them."



Alfred Burger

em "The practice of medicinal chemistry", Wiley, 1970, p. 4.

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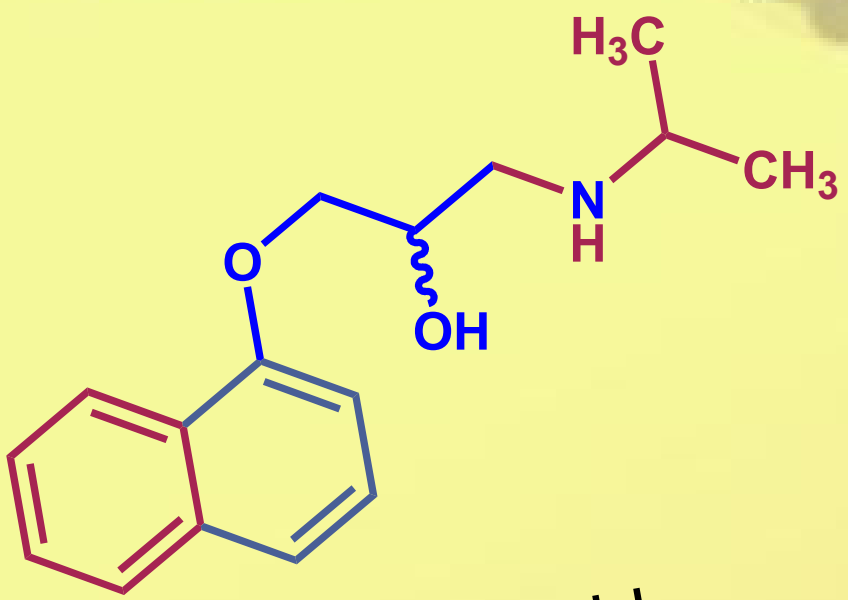
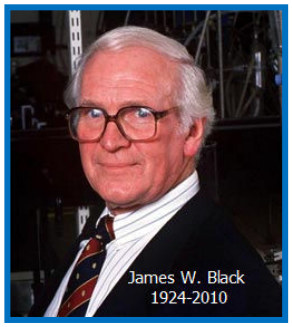


propranolol
1964



James W. Black

1988

J.W. Black & J. S. Stephenson, *Lancet* **1962**, *280*, 311.

M.J.A. Walker, The major impacts of James Black's drug discoveries on medicine and pharmacology, *Trends in Pharmacological Sciences* **2011**, *32*, 183.

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Am J Physiol 1948, 153, 586

A STUDY OF THE ADRENOTROPIC RECEPTORS

RAYMOND P. AHLQUIST

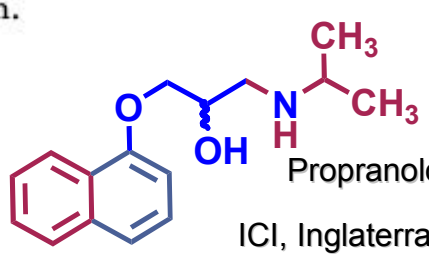
From the Department of Pharmacology, University of Georgia School of Medicine

AUGUSTA, GEORGIA

Received for publication May 10, 1948.

THE adrenotropic receptors are those hypothetical structures or systems located in, on or near the muscle or gland cells affected by epinephrine. The concept of a receptive mechanism was introduced by Langley (1, 2) to explain the action of curare on skeletal muscle. Dale was probably the first to make significant use of the receptor concept in connection with the sympathetic nervous system. In his classical paper (3) on the sympatholytic action of the ergot alkaloids, he recognized that what he called the sympathetic myoneural junction could also be called 'the receptive mechanism for adrenaline'; and he used this mechanism to explain the fact that the ergot alkaloids prevented only the motor (excitatory) actions of epinephrine and had no effect on the inhibitory actions of epinephrine or on the excitatory actions of barium or pituitrin.

1988 - James W. Black



Propranolol (inderal^{R})

ICI, Inglaterra (1965)

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

Barry J. Price, Glaxo, 1989

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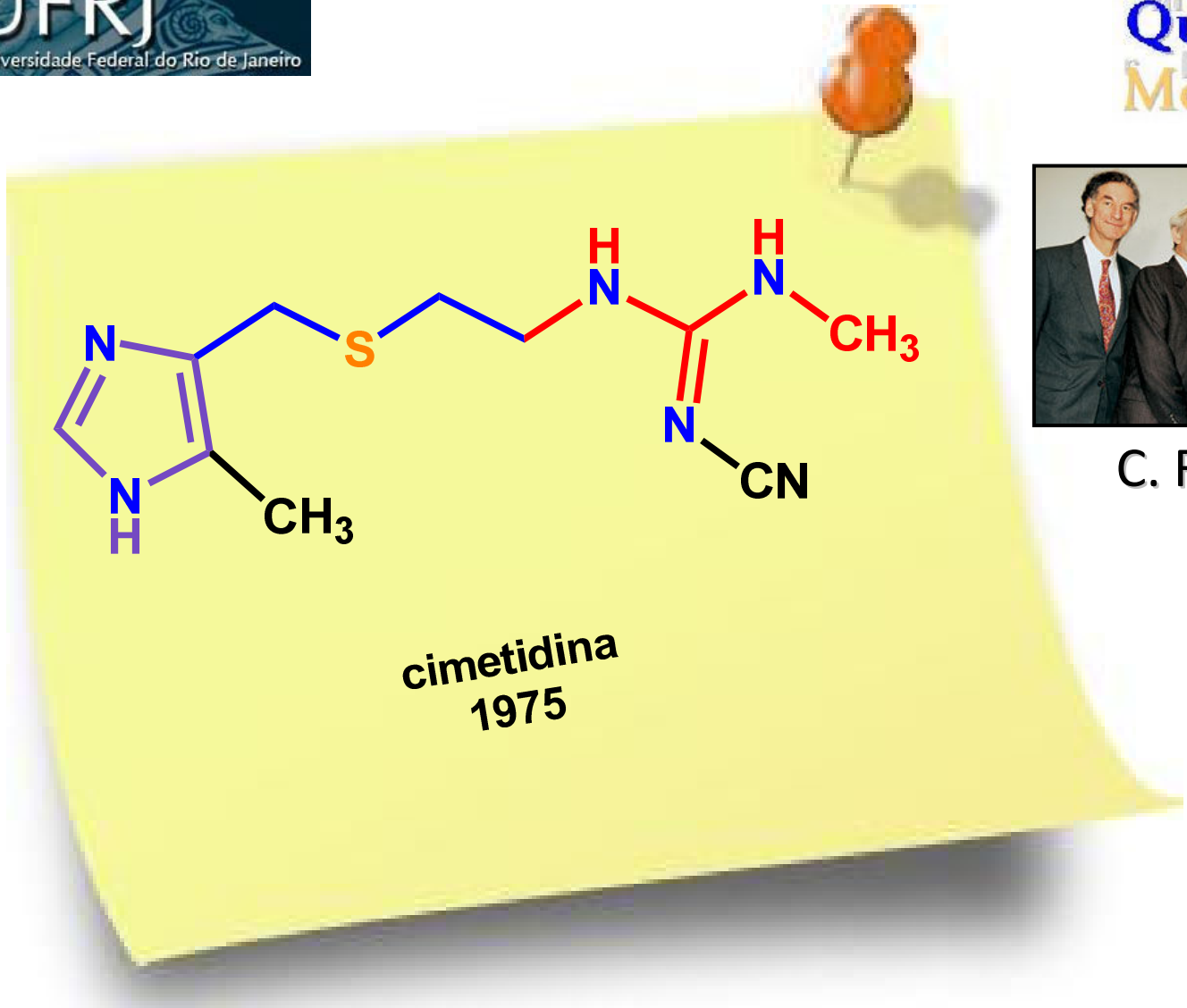

C. Robin Ganellin
JW Black
GJ Durant
JC Emmett
SK&F

1975

J.W. Black, G.J. Durant, J.C. Emmett, C.R. Ganellin, *Nature* 1974, *248*, 65

C.R. Ganellin, Cimetidine, *em Chronicles of Drug Discovery*, JS Bindra & D Lednicer Eds., Wiley, Nova Iorque, Vol. 1, p. 1-38.

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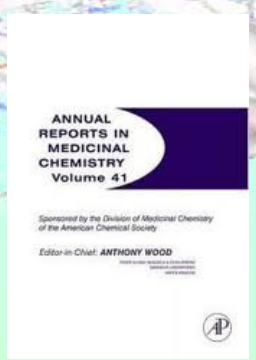
"Considering the vast size of chemical space to be explored,* it is not surprising that <u>experience</u> and <u>intuition</u> are the characteristics that distinguish the most successful medicinal chemists."

A. L. Hopkins & A. Polinsky

Knowledge and Intelligence in Drug Design,

Annu. Rept. Med.Chem. 2006, *41*, 425.



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* Número de possíveis moléculas com propriedades farmacêuticas = *ca.* 10^{60}

J-L Reymond, R van Deursen, L C Blum, L Ruddigkeit, *Med.Chem.Commun.* **2010**, *1*, 30

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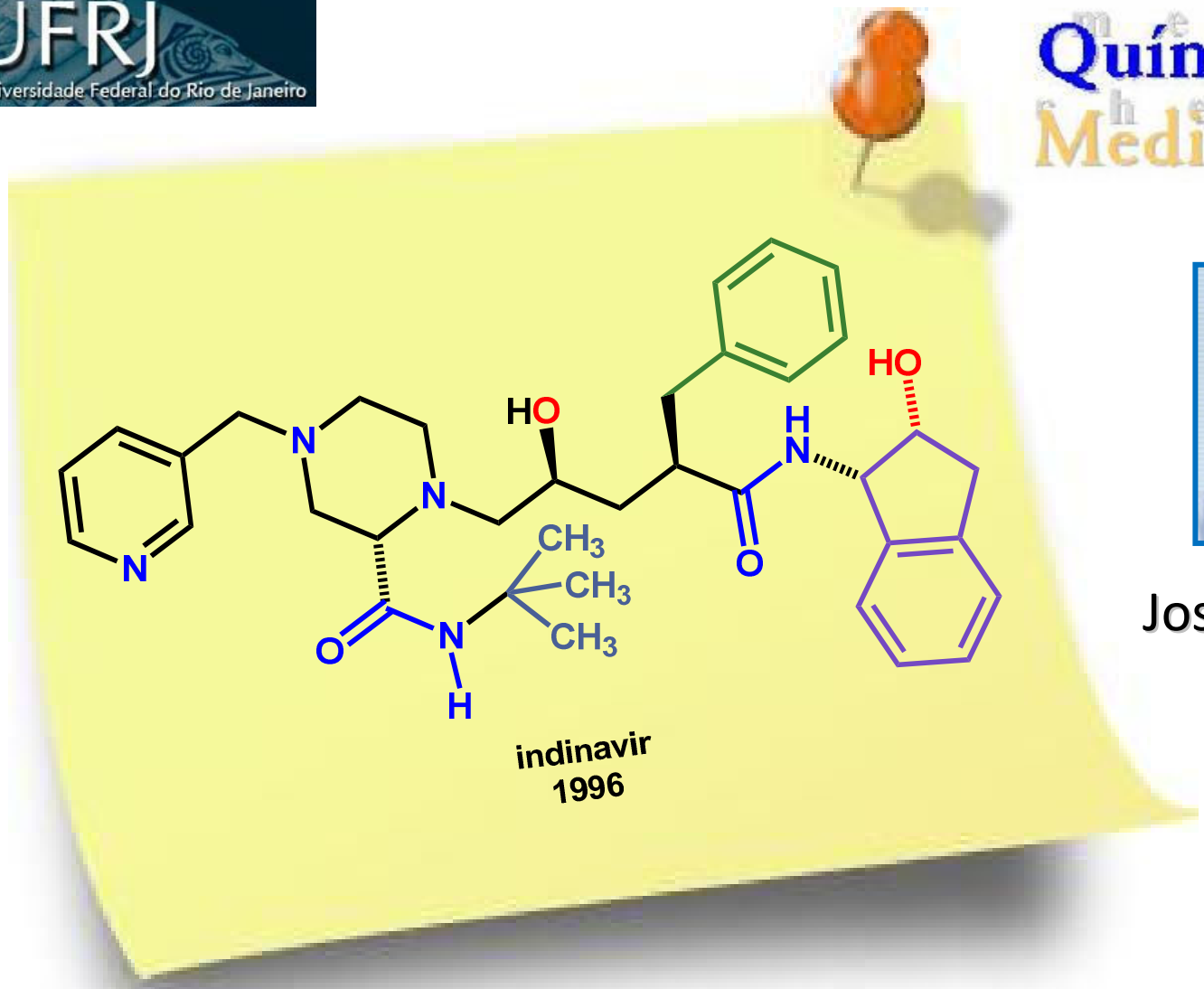

Joseph P. Vacca
Merck

1996

J. P. Vacca *et al.*, *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 4096; B. D. Dorsey *et al.*, *J. Med. Chem.* **1994**, *37*, 3443; J. H. Lin, D. Ostovic, J. P. Vacca, The integration of medicinal chemistry, drug metabolism, and pharmaceutical research and development in drug discovery and development, em *Integration of Pharmaceutical Discovery and Development, Case Histories*, R.T. Borchardt, R.M. Freidinger, T.K. Sawyer & P.L. Smith Eds, Plenum Press, Nova Iorque, 1998, p. 233-255.

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"… success (*in drug discovery*) depends on the proper integration of new promising technologies with the experience and strategies of classical medicinal chemistry."

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Hugo Kubinyi, 2003

H. Kubinyi, *Nature Rev. Drug Discov*. **2003**, *2*, 667

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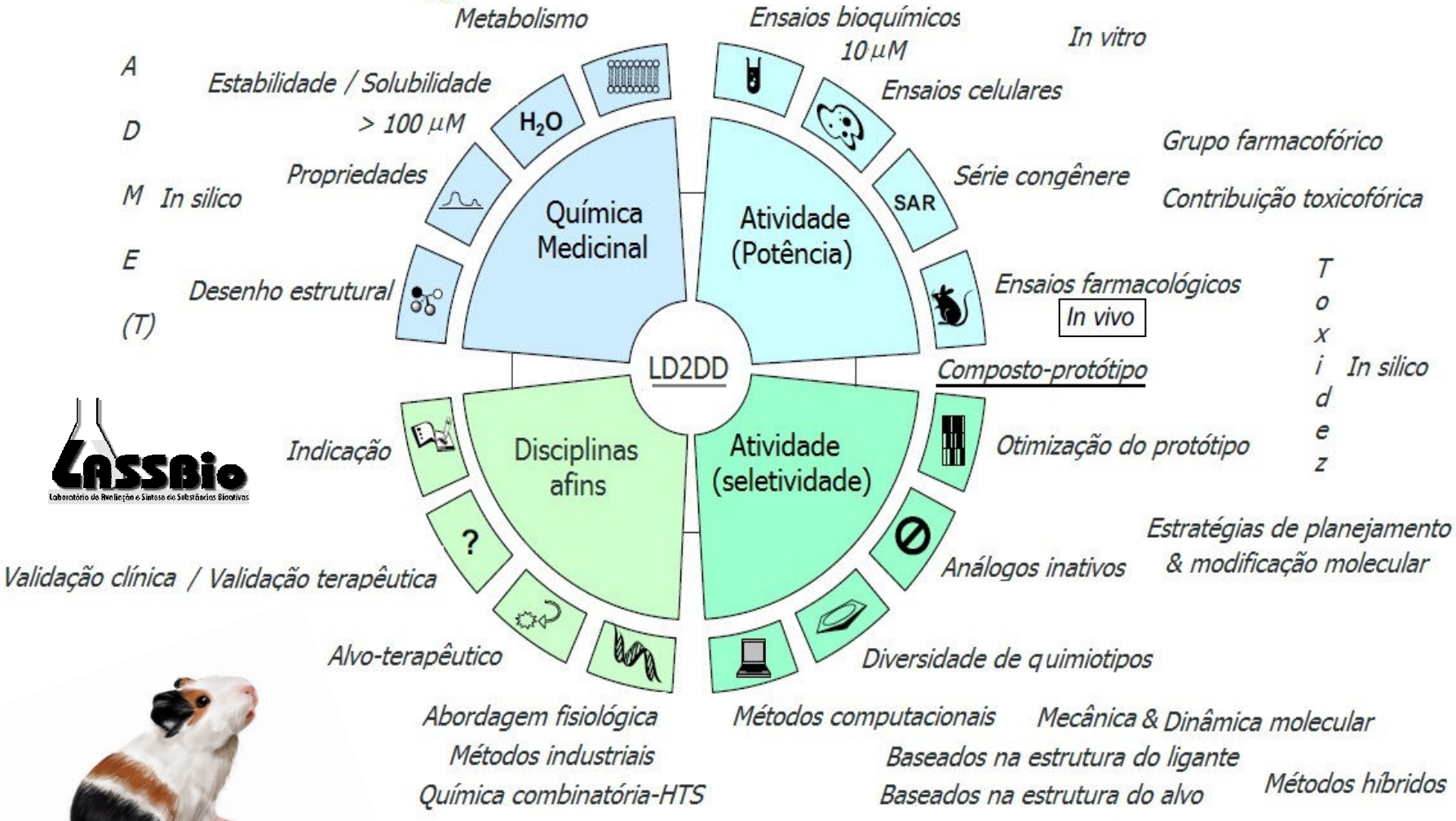

O **composto-protótipo** é um autêntico candidato a nova entidade química, *i.e.* um novo fármaco, portanto é muito mais valioso do que um mero ligante (>>*hit*) !

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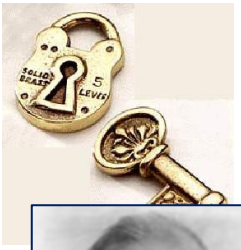
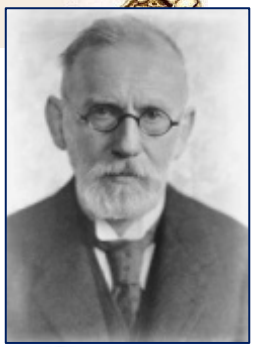
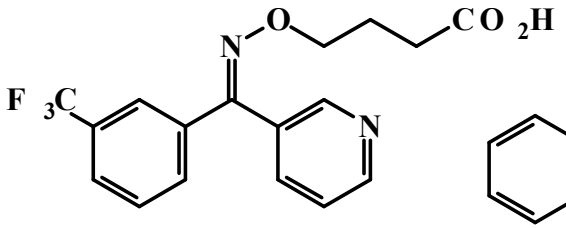




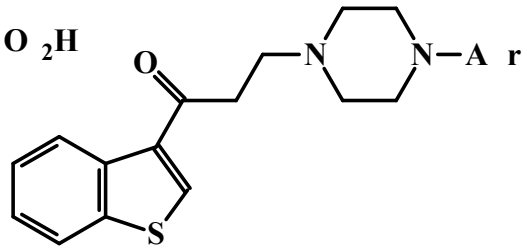
- **Lock-key concept**: Emil Fischer

- **One-target-one-ligand approach**
  One-ligand/one-disease
  Paul Ehrlich & magic bullets

- **Ligands for two targets**
  Dual, binary, dimeric, bivalent, mixed ligands
  TXS-TPant; 5-HT_{1A}Rant-SSRI; COX-LOX;



Freyne, 1987



Monge, 2001

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Teixeira, 1998

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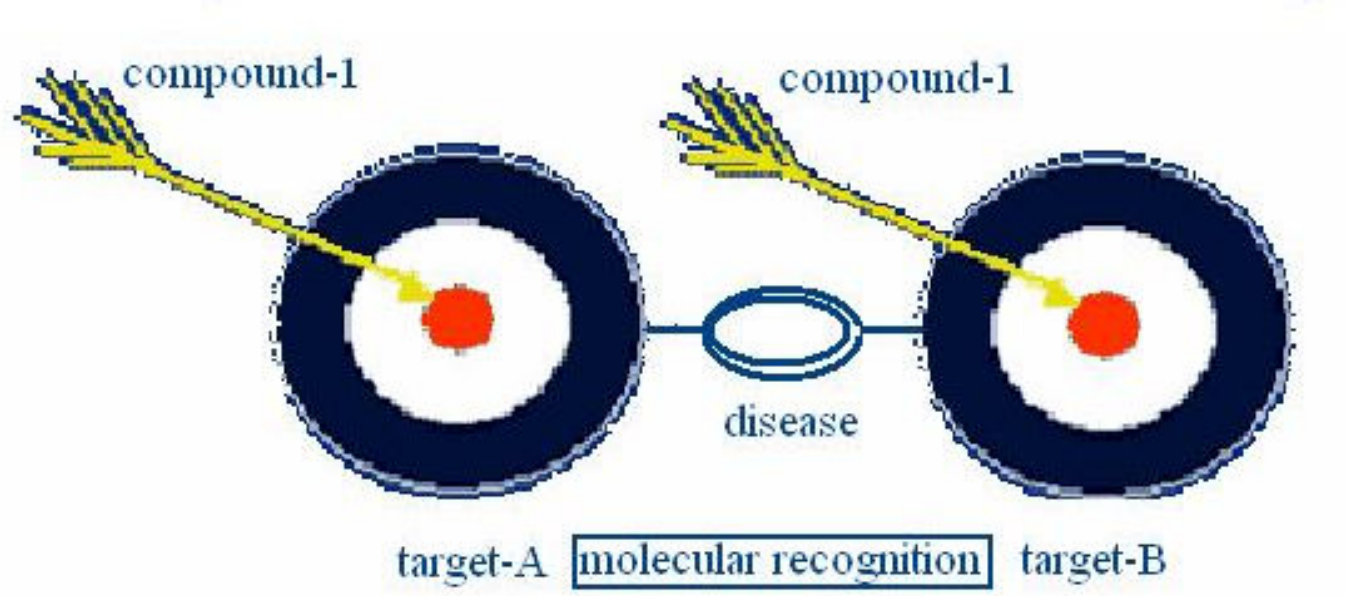
Symbiotic lead-candidates

*compound able to be effective in **two** differents targets, both relevant to disease, belonging to distinct biochemical pathway;*



The symbiotic-lead candidate design

E.J. Barreiro & C.A.M. Fraga, New insighths for multifactorial disese therapy: the challenge of the symbiotic drugs, *Current Drug Therapy* **2008**, *3*, 1.

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www.inct-inofar.ccs.ufrj.br

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Química Medicinal

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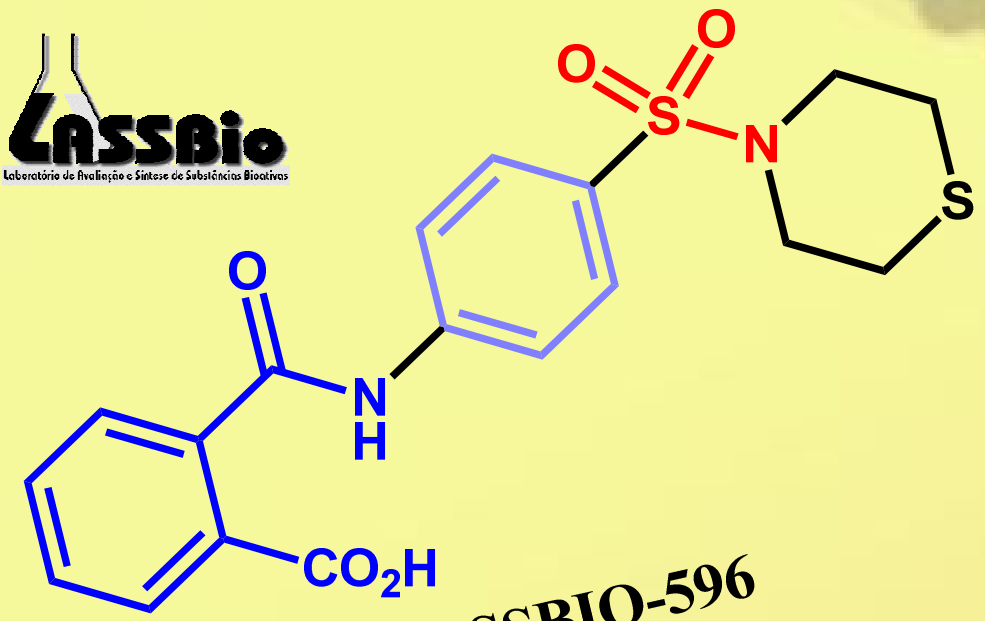

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2005

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INCT inofar

Novo candidato a fármaco anti-asmático

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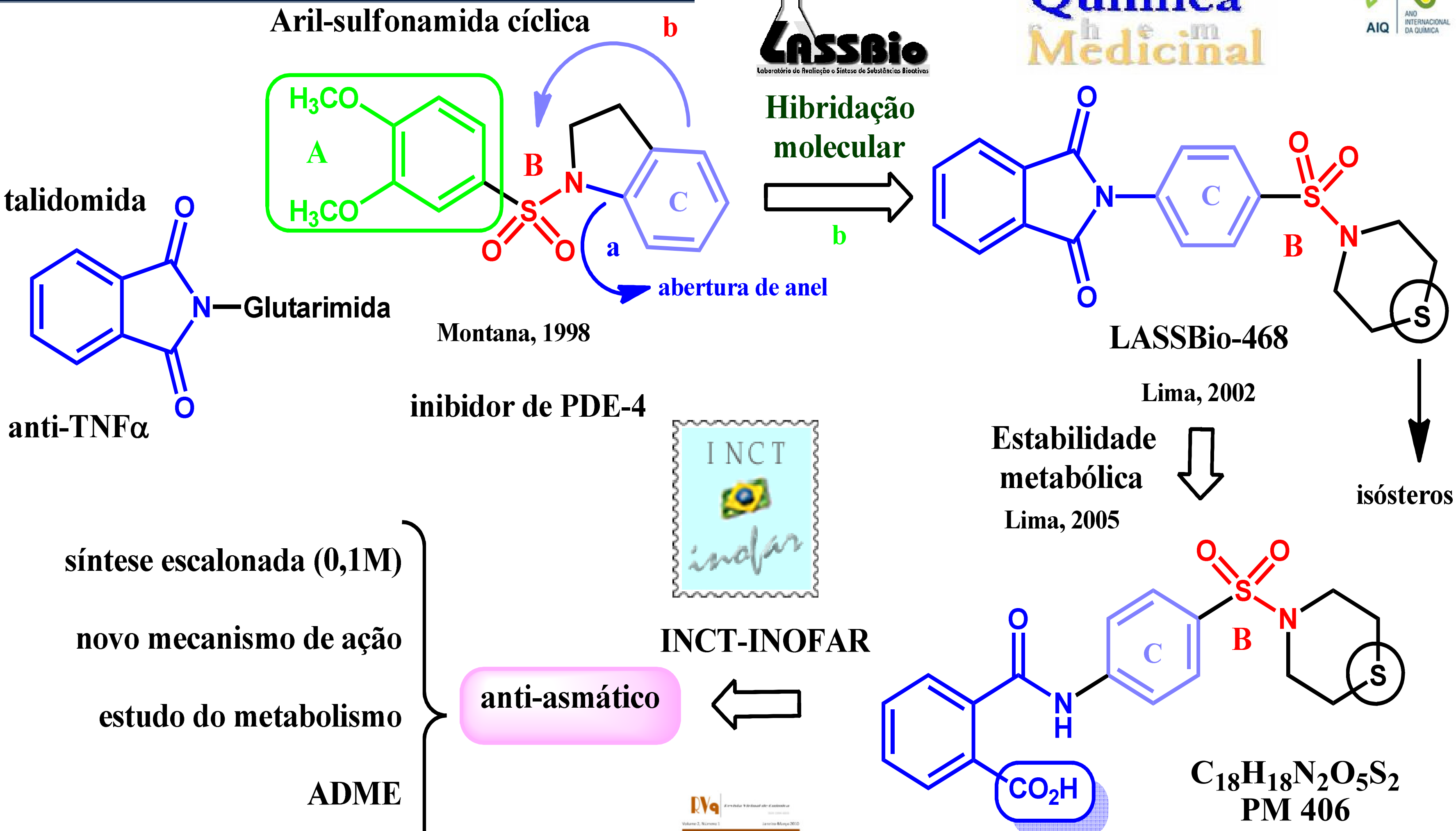

Os efeitos sutis da estrutura na atividade farmacológica!

PR Rocco *et al.*, *Rev. Virtual Quim.* **2010**, *2*, 10-17

H. S. Campos *et al.*, Protective Effects of Phosphodiesterase Inhibitors on Lung Function and Remodeling in a Murine Model of Chronic Asthma, *Braz. J. Med. Biol. Res.* **2006**, *39*, 283

M. S. Alexandre-Moreira *et al.* LASSBio-468: a New achiral thalidomide analogue which modulates TNF-α and NO production and inhibits endotoxic shock and arthritis in an animal model, *Int. Immunopharmacol.* **2005**, *5*, 485

symbiotic prototypes, *Bioorg. Med. Chem.* **2009**, *17*, 74

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CHEMICAL REVIEWS

Impact Index = 35,95

REVIEW

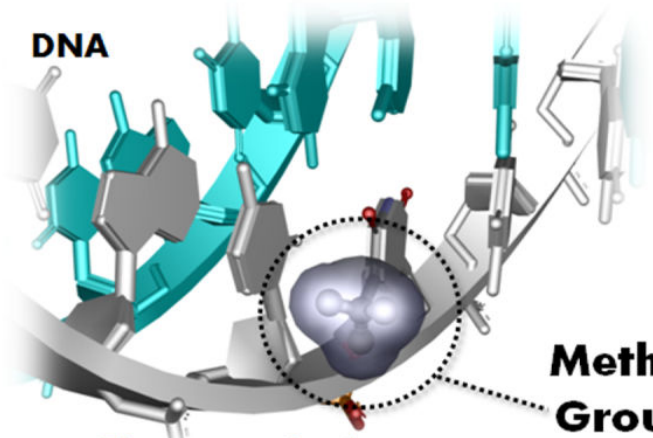
Chem. Rev. 2011, *111*, 000 (in press)

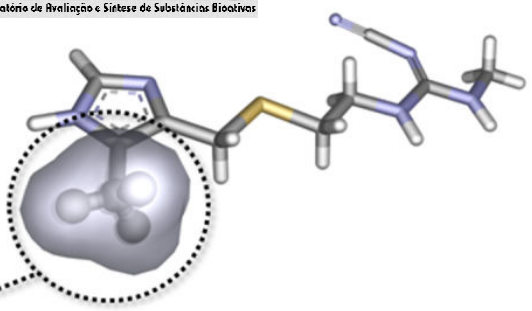
The Methylation Effect in Medicinal Chemistry

E. J. Barreiro, A. E. Kümmerle and C. A. M. Fraga

CH_3

15 Da





Methyl Group

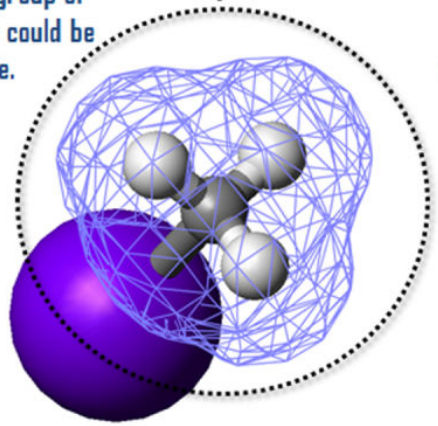
Biomacromolecules

CH/π interactions from the methyl group of timine. Conformational changes, wich could be involved on maintenance of life.

Micromolecules

The inductive eletronic effect of the methyl group is the responsible for the subtype receptors selectivity (H_2x H_1) on cimetidine

The stereoelectronic effects of the methyl group have great importance on biological events and are widely used by the Medicinal Chemistries in the development of new drugs.



Stereoelectronic Properties

MW = 15,03
MR = 5,65 cm³/mol
π hansch = 0,56
σ hammett = -0,17

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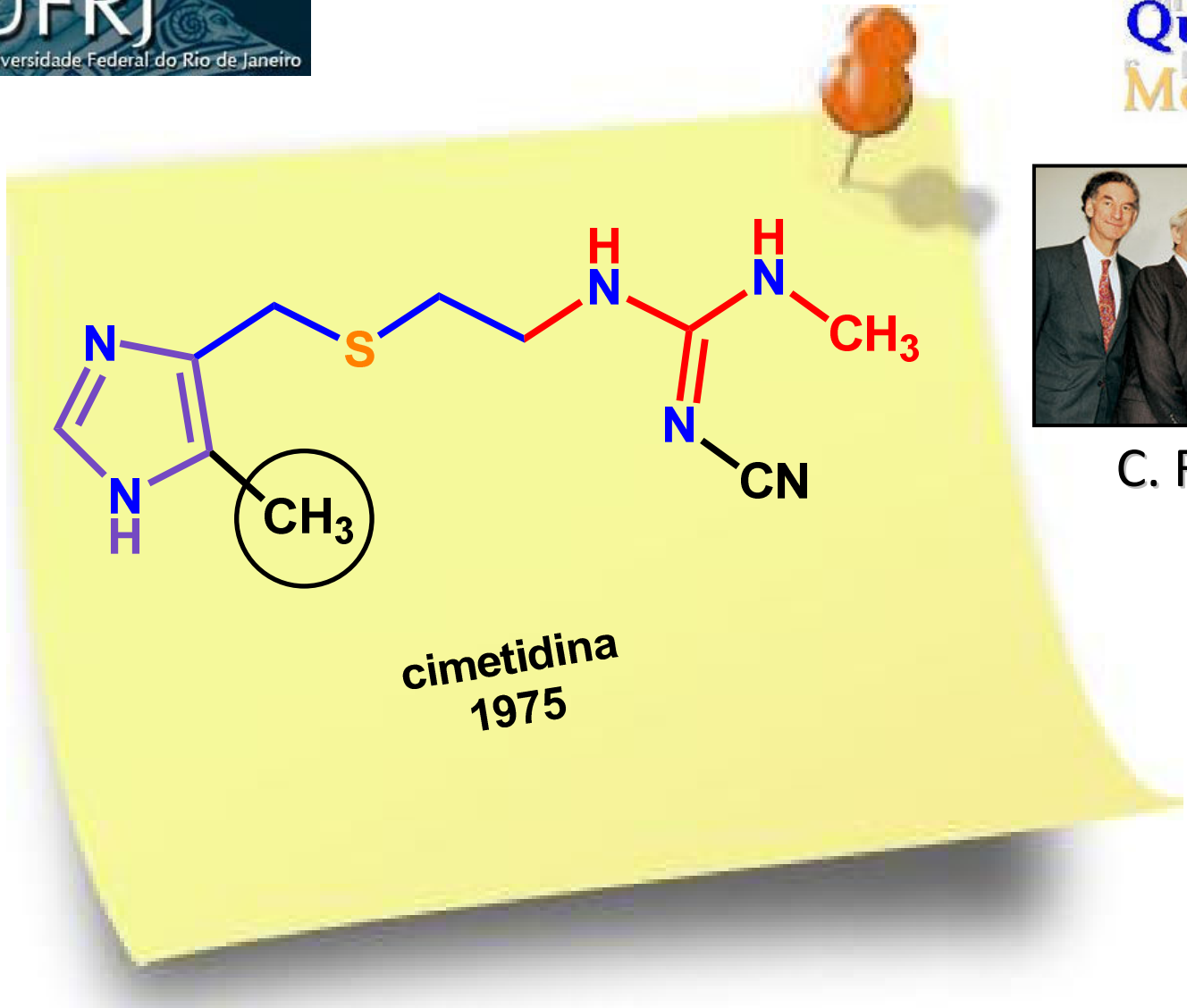

cimetidina
1975

C. Robin Ganellin
JW Black
GJ Durant
JC Emmett
SK&F

1975

J.W. Black, G.J. Durant, J.C. Emmett, C.R. Ganellin, *Nature* 1974, *248*, 65

C.R. Ganellin, Cimetidine, *em Chronicles of Drug Discovery*, JS Bindra & D Lednicer Eds., Wiley, Nova Iorque, Vol. 1, p. 1-38.

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ICB Instituto de Ciências Biomédicas

Da molécula ao corpo

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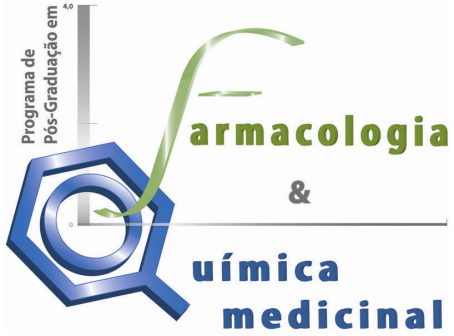
Programa de Pós Graduação em Farmacologia e Química Medicinal 2006

29 de abril de 2008

"Medicinal chemistry is a discipline at the intersection of chemistry and pharmacology involved with discovery of new drugs."

Interface Química-Biologia em Química Medicinal



Único programa de pós-graduação (M/D) com este perfil na América Latina (2011) !

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