48th Brazilian Congress of
Pharmacology & Experimental Therapeutics

SBFTE-50y

Pharmacology in Latin America:
Drug Discovery for the future

Symposia: Translational approach in Drug Development: Challenge from Medicinal Chemistry to Patient
Chair: Roberto Takashi Sudo (UFRJ)

Challenges in drug design & discovery at LASSBio-UFRJ: the first 20 years!

Eliezer J. Barreiro
ejbarreiro@ccsdecania.ufrj.br

Full Professor
Federal University of Rio de Janeiro
LASSBio, Biomedical Sciences Institute
Rio de Janeiro, R.J., Brazil

www.lassbio.icb.ufrj.br

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Medicinal chemistry

Is a chemistry-based discipline, that combines expertise from **chemistry** and **pharmacology** to **design**, **discovery**, **develop** and synthesize original chemical entities that have a therapeutic use. It includes the study of their metabolism and the interpretation of their mode of action at the molecular level, and to evaluates also the properties of existing drugs. **It is a translational discipline concerning the invention of new drugs**.

medicinal chemistry

Adapted from http://www.chem.qmul.ac.uk/iupac/medchem/

IUPAC

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THE ROLE OF THE MEDICINAL CHEMIST IN DRUG DISCOVERY — THEN AND NOW

NATURE REVIEWS | DRUG DISCOVERY VOLUME 3 | OCTOBER 2004 | 853

Joseph G. Lombardino and John A. Lowe III‡*

"As a scientist involved at the very earliest stages of drug discovery, the medicinal chemist.....

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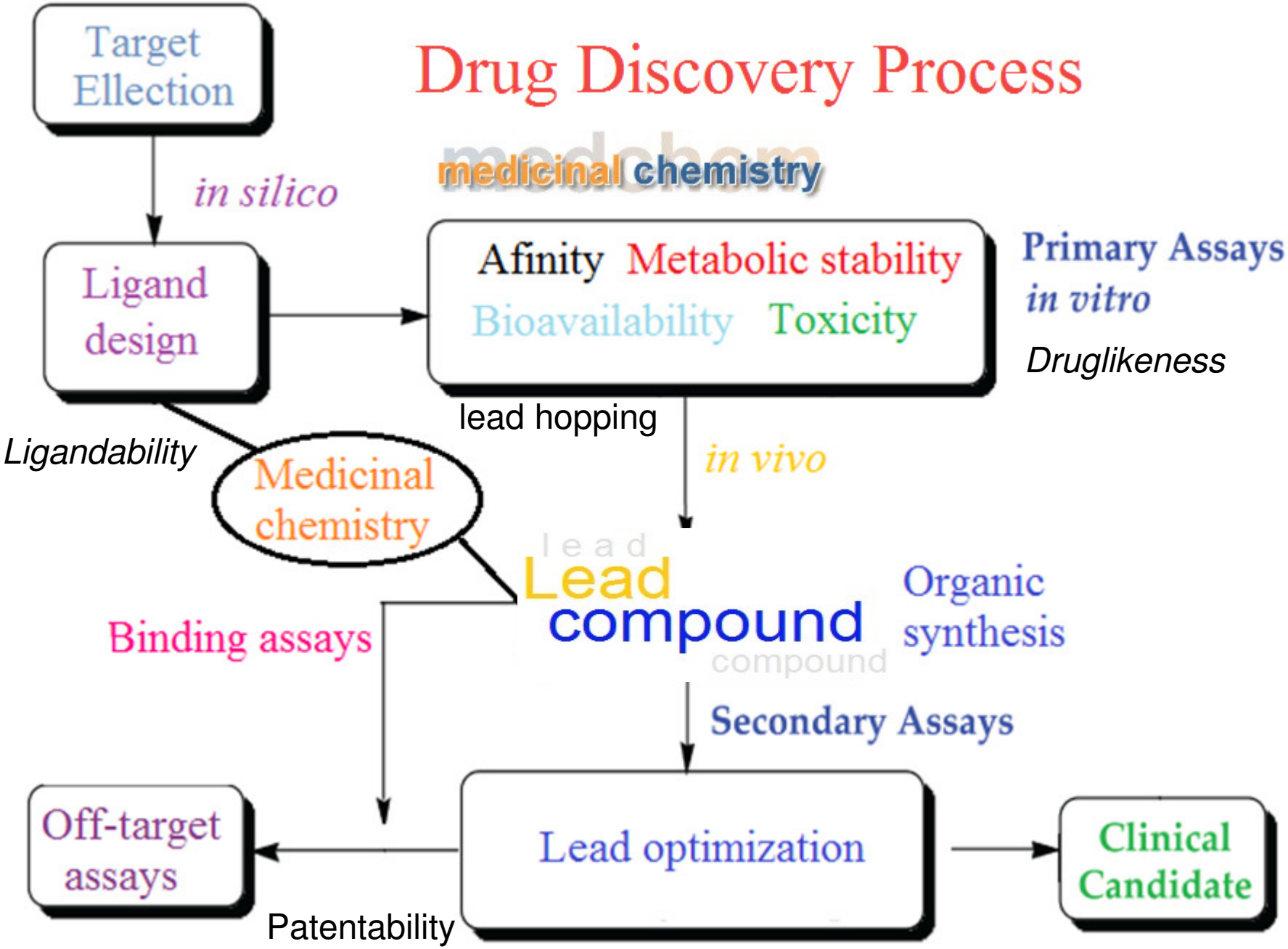
INTERDISCIPLINARY TEAMS

The role of pharmacology in drug discovery

NATURE REVIEWS | DRUG DISCOVERY VOLUME 1 | MARCH 2002 | 237

Bertil B. Fredholm, William W. Fleming, Paul M. Vanhoutte and Théophile Godfraind

"It is obvious that pharmacology is one of the most important scientific disciplines that underpin research in drug discovery."



Where we work?

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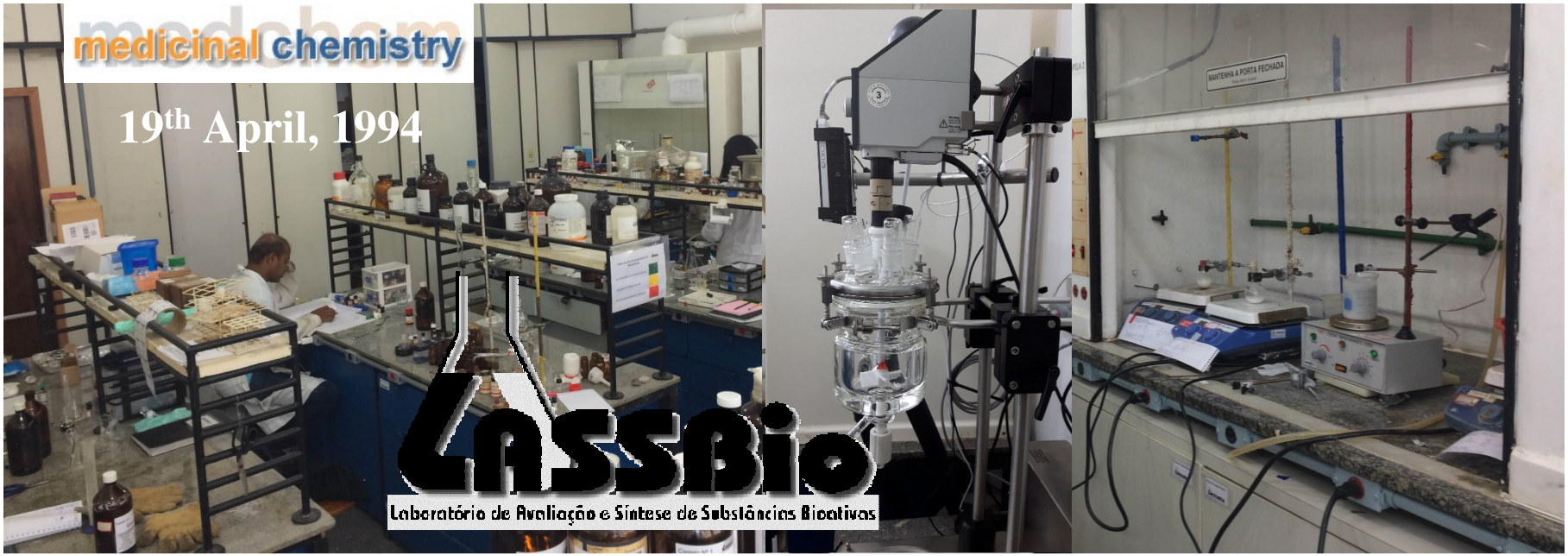
Centro de Ciências da Saúde, Federal University of Rio de Janeiro



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From abundant Brazilian natural products (biophores)

The beginning...

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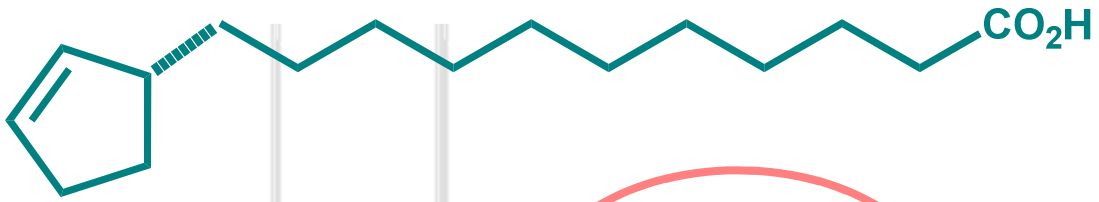
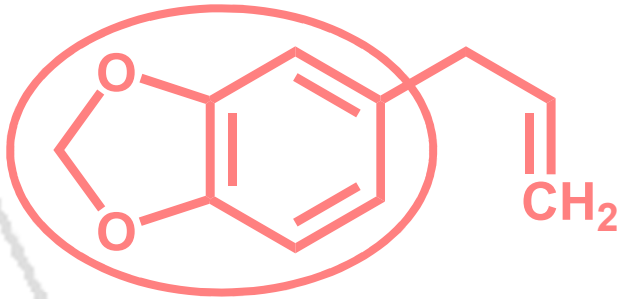


Hidnocarpic acid

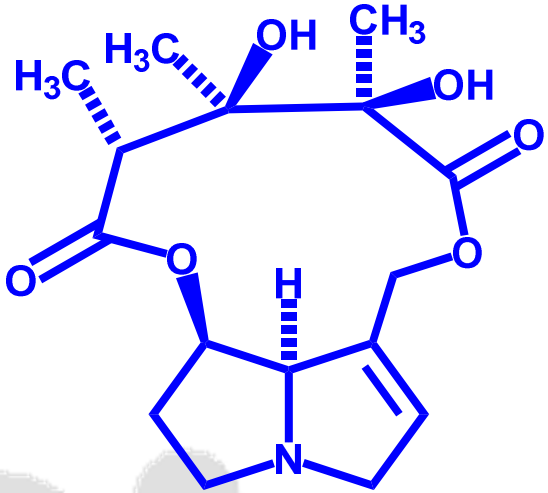
Monocrotaline

Safrole

Spectaline



Benzodioxole



helpful scaffold

1995 - Synthesis & analgesic properties of new spiro-isochromanyl acid derivatives from natural safrole; **2001** -Synthesis and non-addictive analgesic activity of novel *N*-acylarylhydrazones and isosters, derived from natural safrole; **2003** -The Medicinal Chemistry and Drug Discovery: A new cardioactive lead-compound, LASSBio-294

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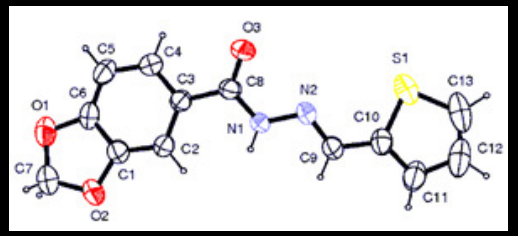
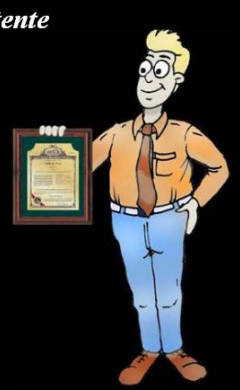
LASSBio-294

New lead of cardioactive drug with new MoA



Thienylhydrazone with digitalis-like properties (positive inotropic effects)



CAS # 314021-07-3

$C_{13}H_{10}N_2O_3S$

PM 274

*** US Patent** US7091238 15/08/2006

*** European Patent** EP1532140; WO-0078754

Pre-clinical studies completed

Inter-alia: JR Azevedo, J-J Letourneau, F Espitalier, MI Ré, Solubility of a New Cardioactive Prototype Drug in Ionic Liquids, *J. Chem. Eng. Data* **2014,** *59*, 1766; CM Leal, SL Pereira, AE Kümmerle, DM Leal, R Tesch, CMR Sant'Anna, CAM Fraga, EJ Barreiro, RT Sudo, G Zapata-Sudo, Antihypertensive profile of 2-thienyl-3,4-methylenedioxybenzoyl hydrazone is mediated by activation of the A_{2A} adenosine receptor, *Eur. J. Med. Chem.* **2012**, *55*; A G M Fraga, L L Silva, CAM Fraga, EJ Barreiro, CYP1A2-mediated biotransformation of cardioactive 2-thienylidene-3,4-methylene dioxybenzoylhydrazine (**LASSBio-294**) by rat liver microsomes and human recombinant CYP enzymes, *Eur. J. Med. Chem*. **2011**, *46* 349; EJ Barreiro, Strategy of molecular simplification in rational drug design: The discovery of a new cardioactive agent , *Quim. Nova* **2001**, *25*, 1172.

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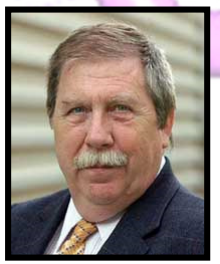
"... With the advent of *in vitro* test systems about 30 years ago, …… drug discovery schifted from animal studies to target-oriented research. This strategy works well in cases in which a certain disease is related to a unique target that can be modulated by a small molecule."



Professor Hugo Kubinyi

Universität Heidelberg
&
BASF Ludwigshafen

medicinal chemistry

H Kubinyi, Drug research: myths, hype and reality, *Nature Rev. Drug Discovery* **2003**, *2,* 665.

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Several medical problems, including not transmissible chronic diseases, do not have a single cause, they are likely associated to multiple factors, and are multifactorial diseases.

Could be effective a single target drug in the treatment of multifactorial diseases?

Current Drug Therapy, 2008

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, C.T. Bloco A, Cidade Universitária, Ilha do Fundão, 21941-590, Rio de Janeiro, RJ, Brazil.

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

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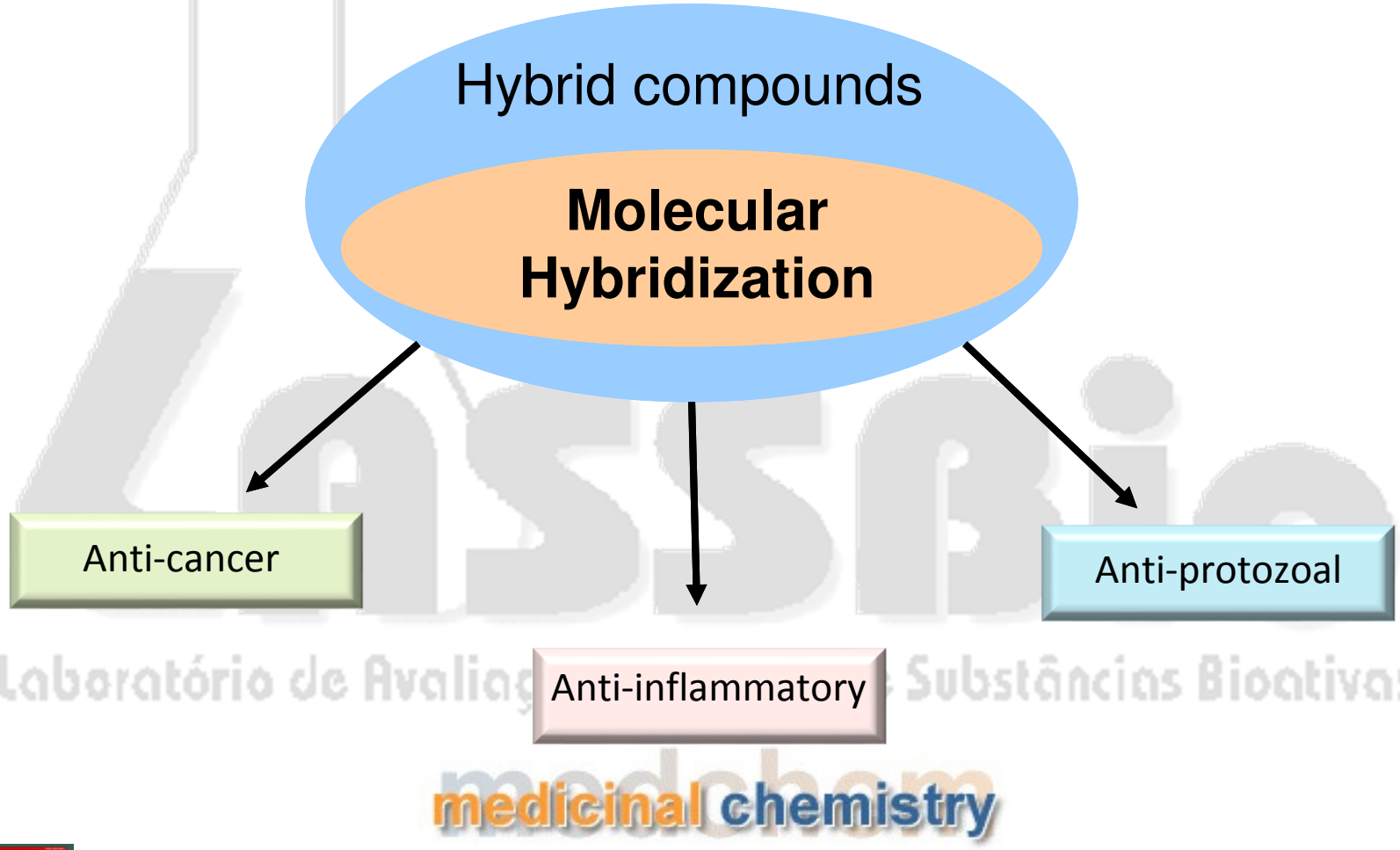
Multi-target drug candidate design



C Viegas-Jr, A Danuello, VS Bolzani, E J Barreiro, CAM Fraga, *Molecular Hybridization: A useful tool in the design of new drug prototypes, Curr Med Chem* **2007**, *14*, 1829

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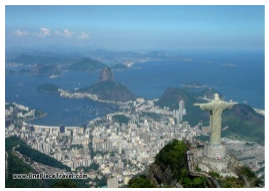
Novel 2-chloro-4-anilino-quinazoline derivatives as EGFR and VEGFR-2 dual inhibitors

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,*]

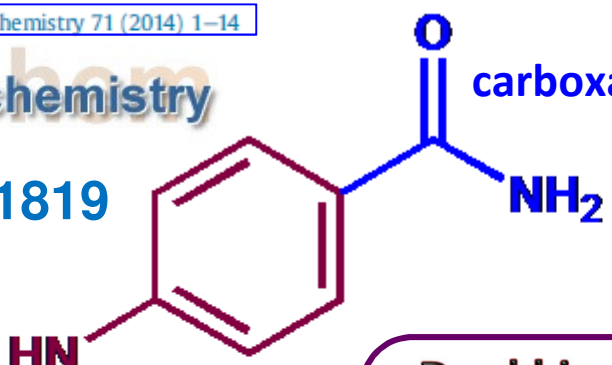
[a] Laboratory of Evaluation and Synthesis of Bioactive Substances (LASSBio), Federal University of Rio de Janeiro, P.O. Box 68024, 21944-971 Rio de Janeiro, RJ, Brazil
[b] Graduate Program of Chemistry (PGQu), Chemistry Institute, Federal University of Rio de Janeiro, Rio de Janeiro, RJ, Brazil
[c] Department of Chemistry, Federal Rural University of Rio de Janeiro (UFRRJ), Seropédica, RJ, Brazil
[d] ProQinase GmbH, Freiburg, Germany
[e] Department of Pharmaceutical/Medicinal Chemistry, Institute of Pharmacy, Eberhard-Karls-University Tübingen, Tübingen, Germany

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



medicinal chemistry

LASSBio-1819



carboxamide

Isosteric replacement

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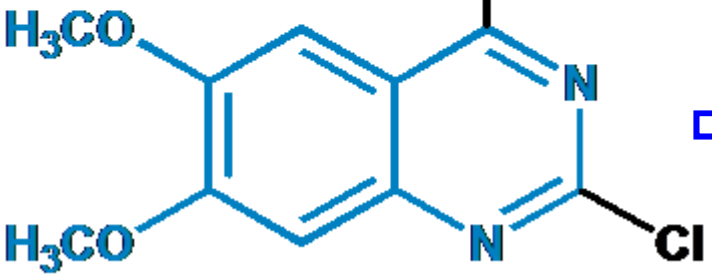
UNIVERSITÄT TÜBINGEN

Novel molecular pattern



Dual kinase activity

IC_{50} (EGFR) = 0,90 µM

IC_{50} (VEGFR) = 1,17 µM

Dual Ligand Dual

Lead Optimization

MLC Barbosa, Novos derivados quinazolínicos funcionalizados inibidores duais das tirosina cinases receptoras EGFR & VEGFR-2, PhD Thesis, Instituto de Química, UFRJ, 2013.

A new dual lead-compound

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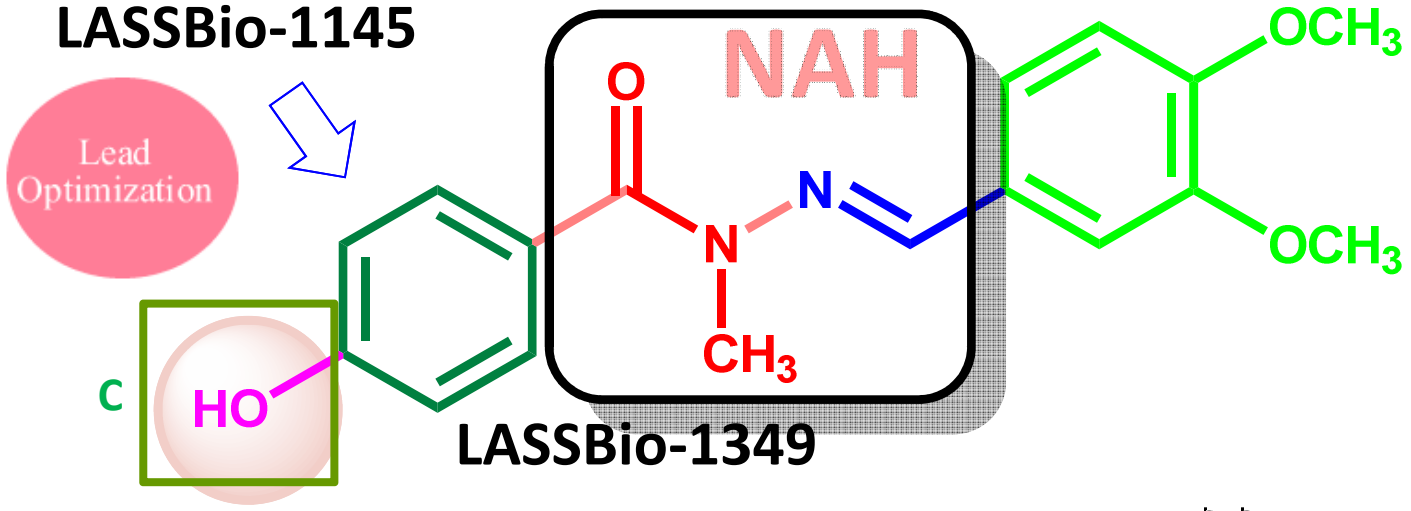
Medicinal Chemistry

LASSBio-1145

Lead Optimization



LASSBio-1349

EC_{50} TNF-α (μM) = 0.52

IC_{50} PDE4B (nM) = 47.0

SI PDEX / PDE4 (X=1, 2, 3, 5, 6) = 182

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AE Kümmerle et al. Design, Synthesis and Pharmacological Evaluation of *N*-Acylhydrazones and Novel Conformationally Constrained Compounds as Selective and Potent Orally Active PDE-4 Inhibitors, *J Med Chem* **2012**, *55*, 7525; AE Kümmerle et al. , Studies towards the identification of putative bioactive conformation of potent vasodilator arylidene *N*-acylhydrazone derivatives, *Eur J Med Chem* **2009**, *44*, 4004; EJ Barreiro, AE Kümmerle, CAM Fraga, The methylation effect in Medicinal Chemistry, *Chem. Rev*. **2011**, *111*, 5215.

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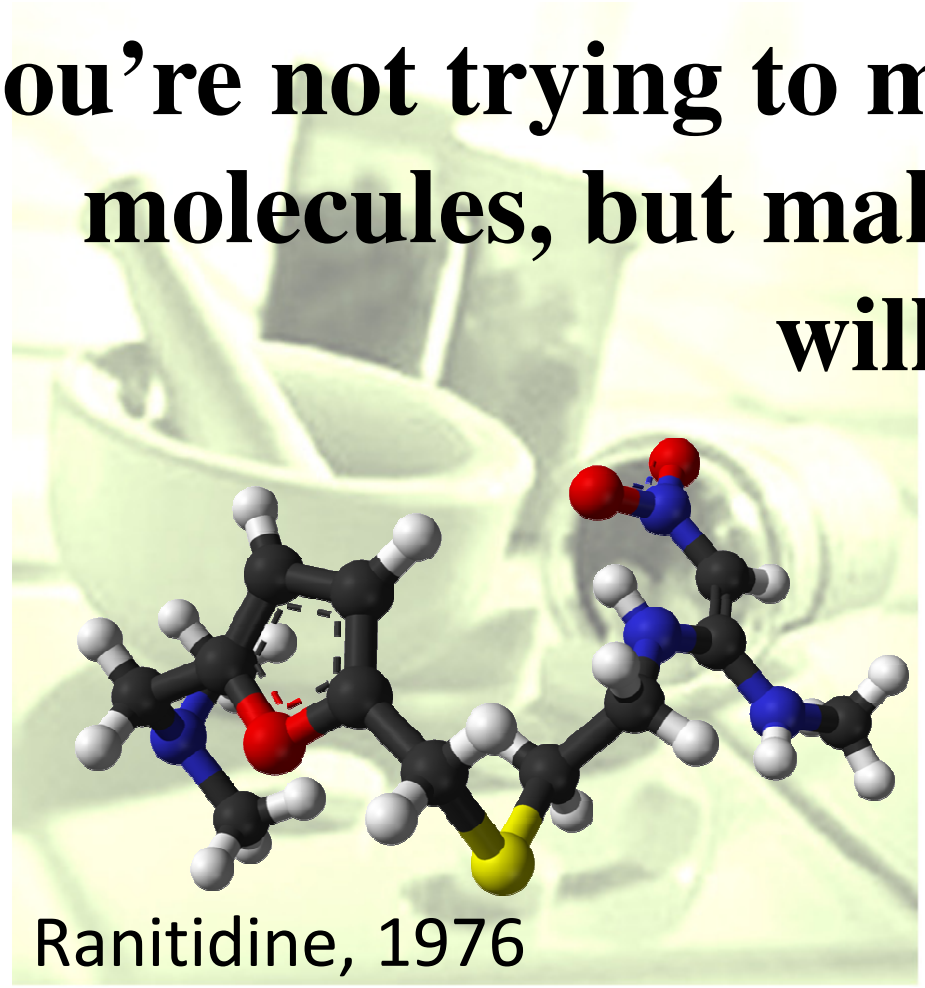
"… when it comes to drug discovery you're not trying to make complicated molecules, but make molecules that will be effective … "

Barry J. Price
Glaxo Director,
1967-1996



Ranitidine, 1976

H_2 histamine receptor antagonista
Allen & Hanburys Ltd, laboratories

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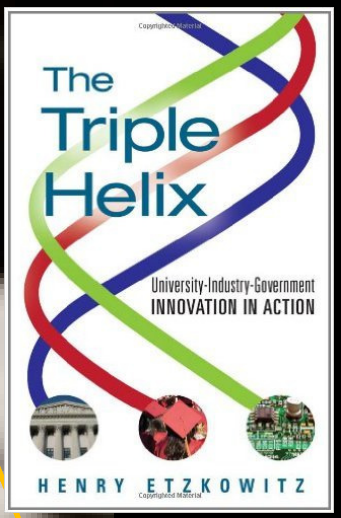
http://farmacologia.icb.ufrj.br/posgraduacao/index.html

Companies

University

Government



The current stage of *pharmaceutical radical innovation* in Brazil….

E J Barreiro, C A M Fraga, The question of innovative drugs in Brazil: Proposal of the Pronfar creation, *Quim. Nova* **2005**, *28* (*Suppl.)* S56-S63; E J Barreiro, A C Pinto, Challenges of the Brazilian pharmaceutical industry, *Quim. Nova* **2013**, *36*, 1557-1560; E J Barreiro, A C Pinto, Opportunities & Challenges for innovation in pharmaceuticals: now or never!, *Rev. Virtual Quim.* **2013**, *5*, 253.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Thank you.
ejbarreiro@ccsdecania.ufrj.br
Corcovado Hill with the Cristo Redentor statue, one of Seven Wonders of the Modern World.