Universidade Federal do Rio de Janeiro

XXV Encontro Regional da SBQ-MG

12-14 de novembro de 2011
Universidade Federal de Lavras

"A QUÍMICA MEDICINAL E A DESCOBERTA DE NOVOS FÁRMACOS:

o exemplo do INCT- INOFAR"

Eliezer J. Barreiro

Professor Titular

U F R J

Laboratório de Avaliação e Síntese de Substâncias Bioativas

Instituto Nacional de Ciência e Tecnologia
de Fármacos e Medicamentos
INCT-INOFAR

Universidade Federal do Rio de Janeiro

Química Medicinal

Definição

*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.*

IUPAC
http://www.iupac.org
Chemistry and Human Health Division (VII)
Subcommittee on Medicinal Chemistry and Drug Development.

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

C. R. Ganellin et al., Eur. J. Med. Chem. 2000, 35, 163; A. Monge et al., Eur. J. Med. Chem. 2000, 35, 1121

Química Medicinal

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

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

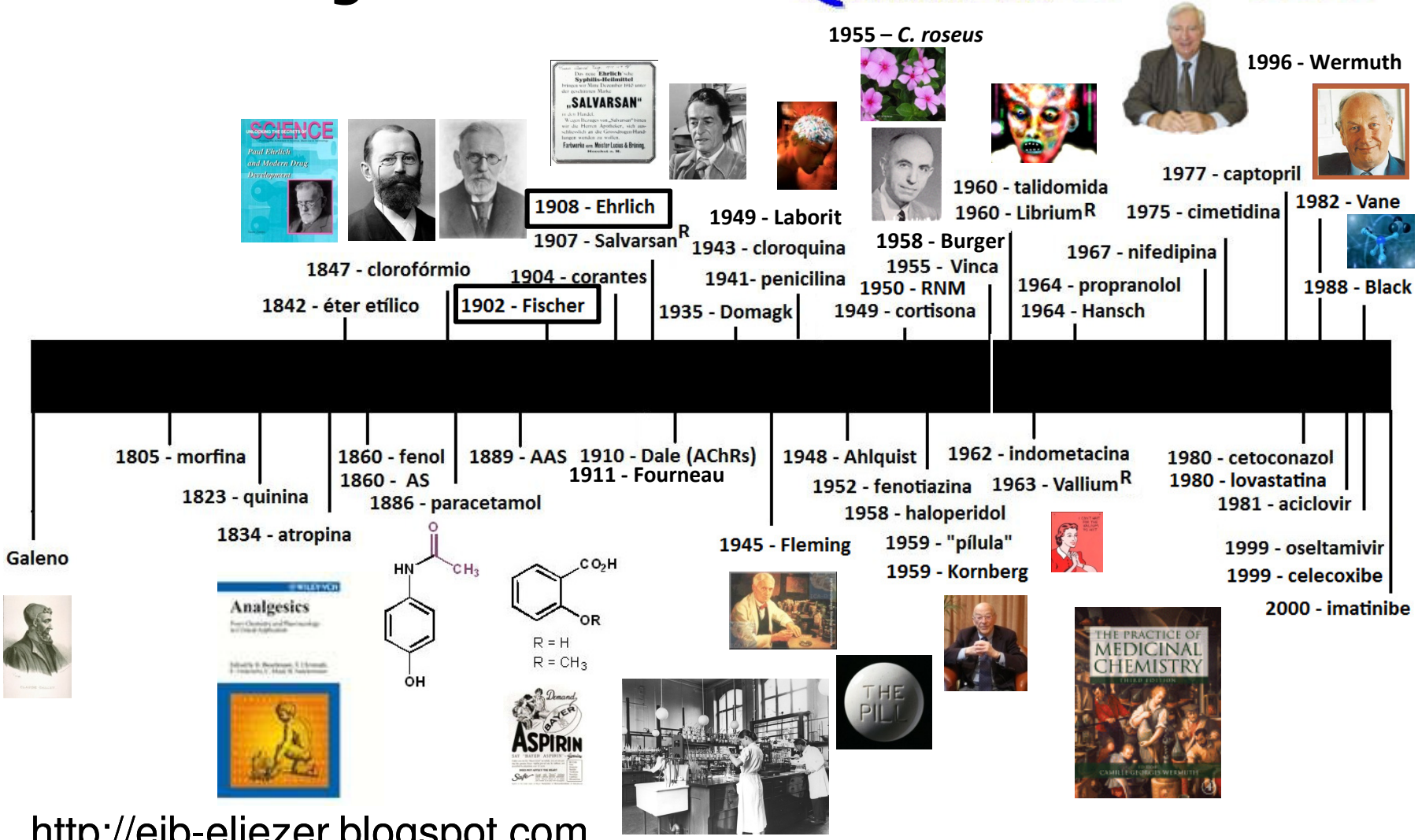
Pfizer

" ...medicinal chemists today live in exciting times... their work can have a beneficial effect on millions of suffering patients – surely an important motivating factor for any scientist..."

The Role of the Medicinal Chemist in Drug Discovery – Then and Now, *Nature Rev. Drug Disc.* **2004**, *3*, 853.

Universidade Federal do Rio de Janeiro

Cronologia histórica da Química Medicinal

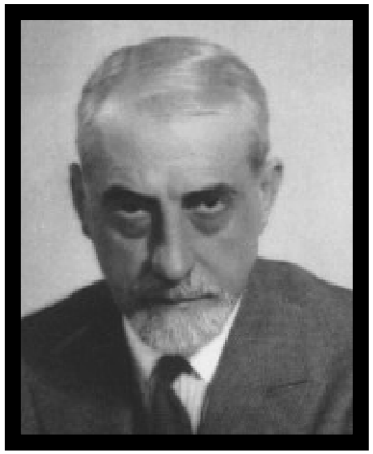


http://ejb-eliezer.blogspot.com

Paradigma de Ehrlich & Fischer, Primeiro Paradigma da Química Medicinal

LASSBio®

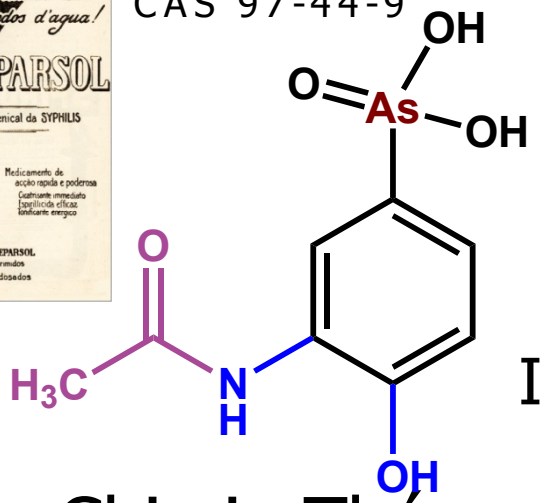
O berço da Química Medicinal



Ernest Fourneau
1872-1949

Stovarsol

CAS 97-44-9

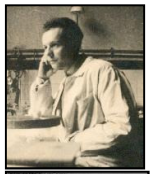


Institut Pasteur (1887)

1911- Laboratoire de Chimie Thérapeutique

Diretor: Emile Roux

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



Daniel Bovet
1907-1992 *

*Farmacêutico suiço
Doutor *h.c.* UFRJ

Prêmio Nobel de Fisiologia/Medicina 1957

Sulfonamidas, anti-histamínicos.

Curare: SAR

J-P Fourneau, « Ernest Fourneau foundateur de la Chimie Pharmaceutique française », *Revue de l´Histoire de la Pharmacie*, t.XXXIV, nº 275, 335-355

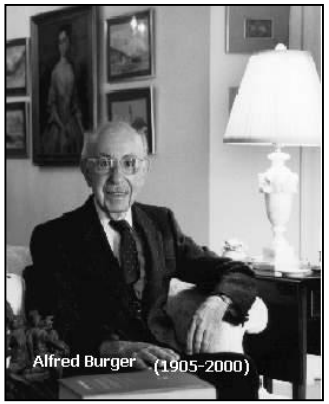
Drug Design and Development. A Realistic Appraisal*

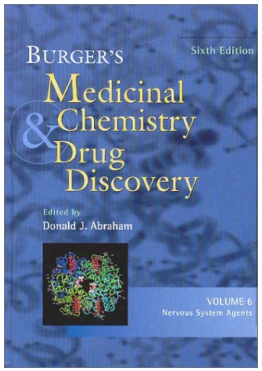
Alfred Burger

J. Med Chem. **1978**, *21*, 1

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901. *Received December 29, 1976*

The discovery of new biologically–therapeutically active structures continues to depend on screening and on isolated observations of unexpected drug metabolites and drug activities. The selection of therapeutically improved and useful chemicals requires molecular modification. Refinements in intuitive and physicochemical methodology can provide shortcuts in random choices and permit extrapolations of some facets of activity with a variable degree of accuracy. The final decisions concerning the usefulness of a drug remain in the domain of experimental and clinical pharmacology.





Prof. Alfred Burger

(1904-2000)

University of Virginia

EUA

1958 – fundou o Journal of the Medicinal and Pharmaceutical Chemistry → depois Journal of Medicinal Chemistry

---

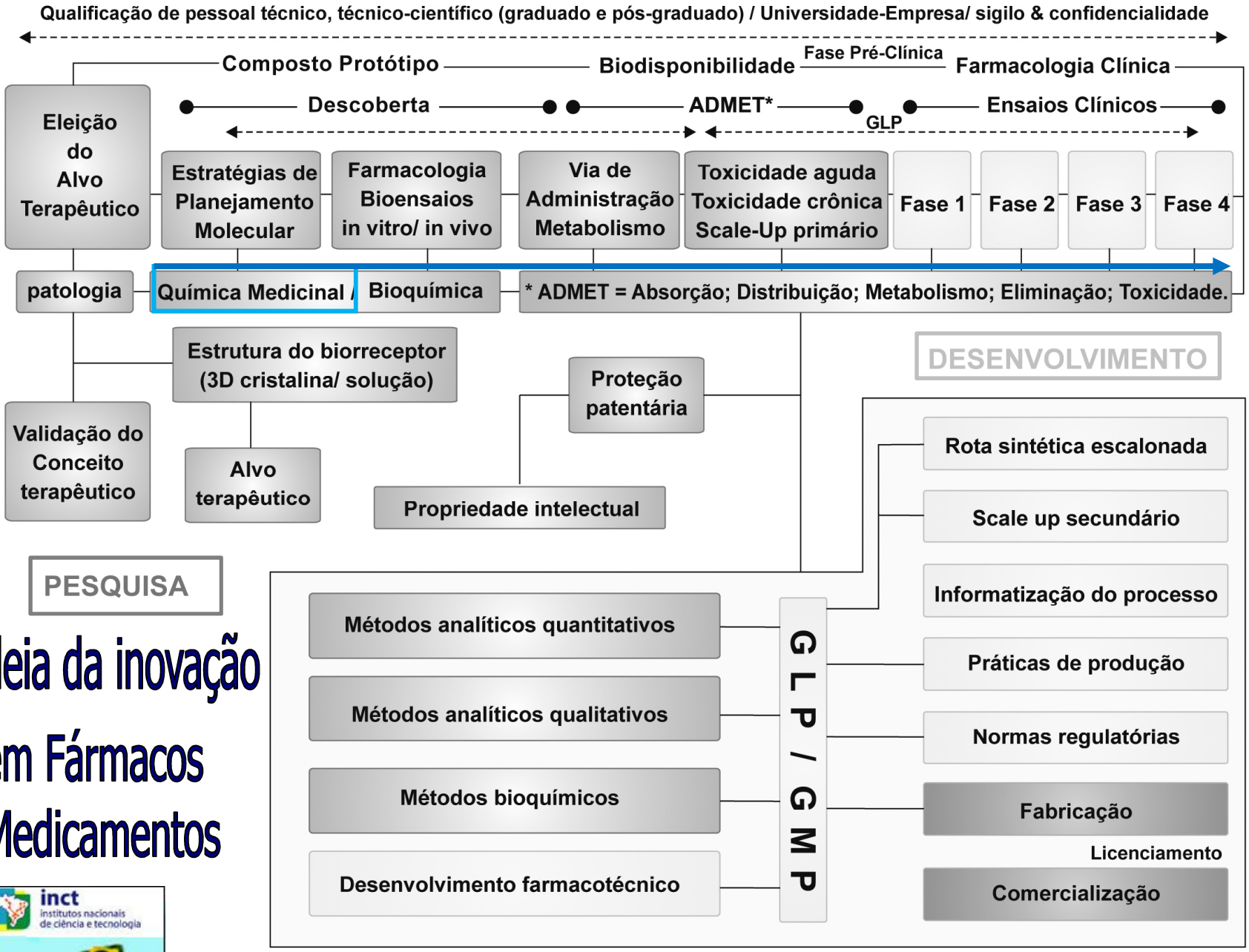
"An Editor's Commentary on the Birth of a Journal", *J. Med. Chem.* **1991**,*34*, 2-6

O processo da descoberta/invenção de fármacos …

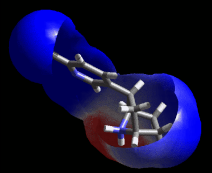
Interdisciplinar

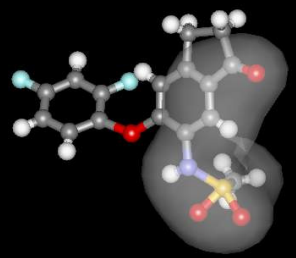
Complexo

Cadeia da inovação em Fármacos e Medicamentos



Atualmente, os novos fármacos, capazes de atuarem em qualquer alvo-terapêutico, são *descobertos/inventados* por planejamento racional.



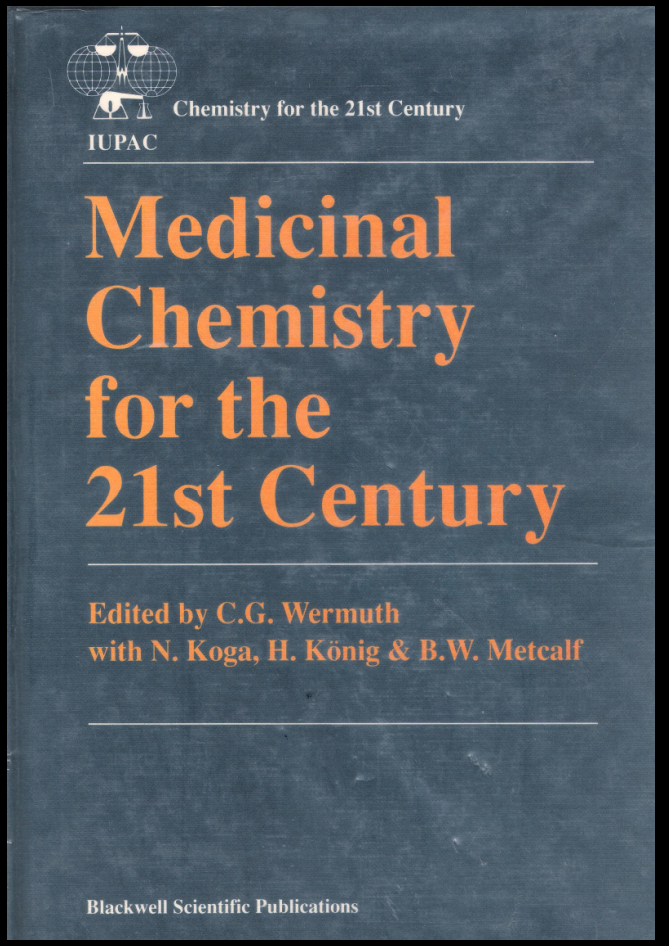


Química Medicinal

EJ Barreiro, CAM Fraga, ALP Miranda, Estratégias em Química Medicinal para o Planejamento de Fármacos, *Braz. J. Pharm. Sc., 37*, 269-292 (2001).

A Química Medicinal

Século 21
Siglo 21
21st Century
Siécle 21



Segundo paradigma da *QuimMed*

Current Drug Therapy, 2008, *3*, 000-000

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

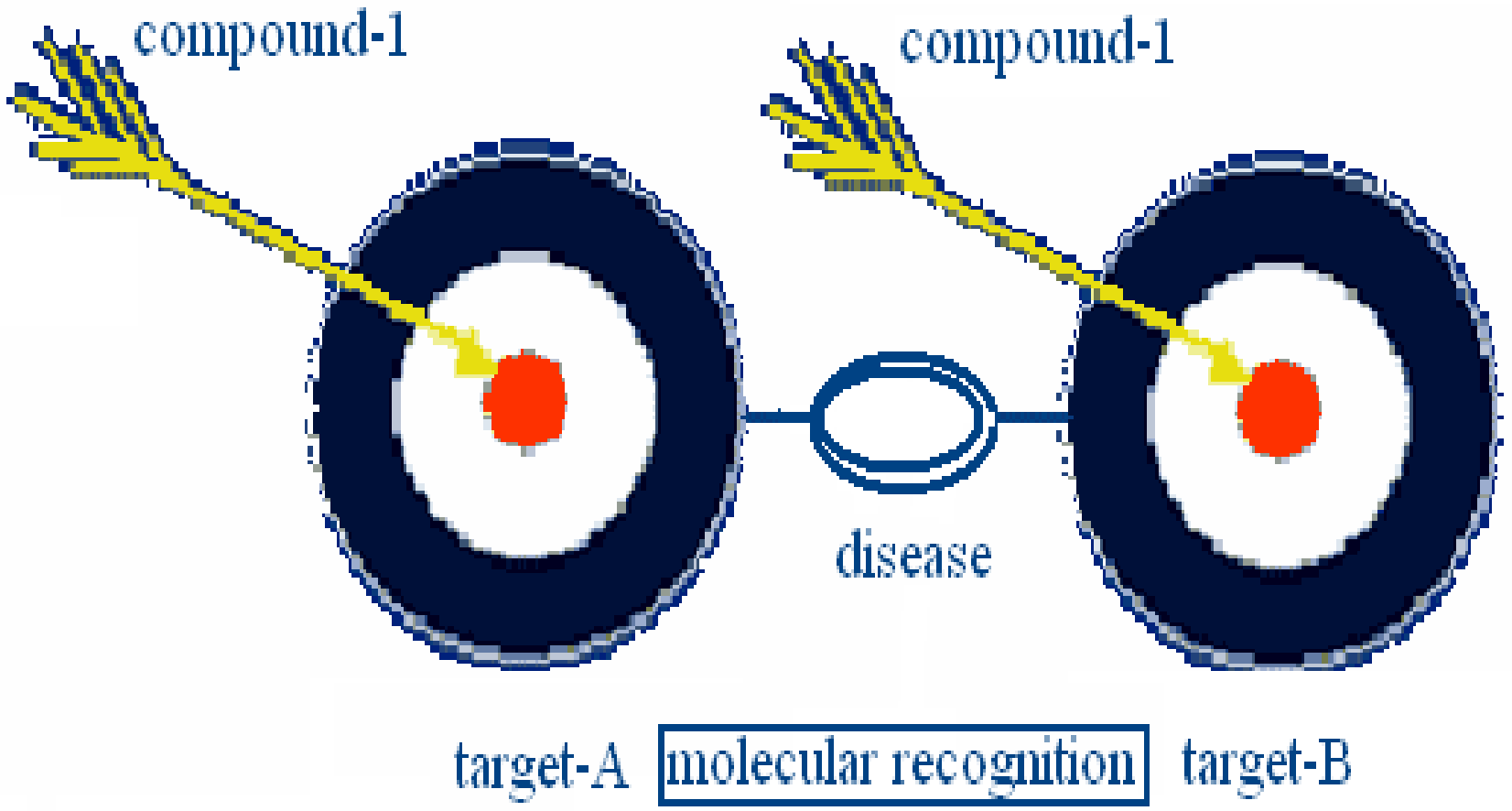
Eliezer J. Barreiro and Carlos Alberto Manssour Fraga

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.

Química Medicinal

O tratamento de uma patologia multifatorial (*e.g.* doenças crônicas não transmissíveis, câncer, metabólicas, etc) com fármacos planejados para *alvos terapêuticos únicos* (*Primeiro paradigma da Química Medicinal* ou *Paradigma de Ehrlich & Fischer*) será sempre paliativo! Estas patologias requerem fármacos multi-alvos, *i.e.* duplos, mixtos, múltiplos ou simbióticos.

The multiple-target lead design



Segundo paradigma da Química Medicinal

Universidade Federal do Rio de Janeiro

Química Medicinal

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

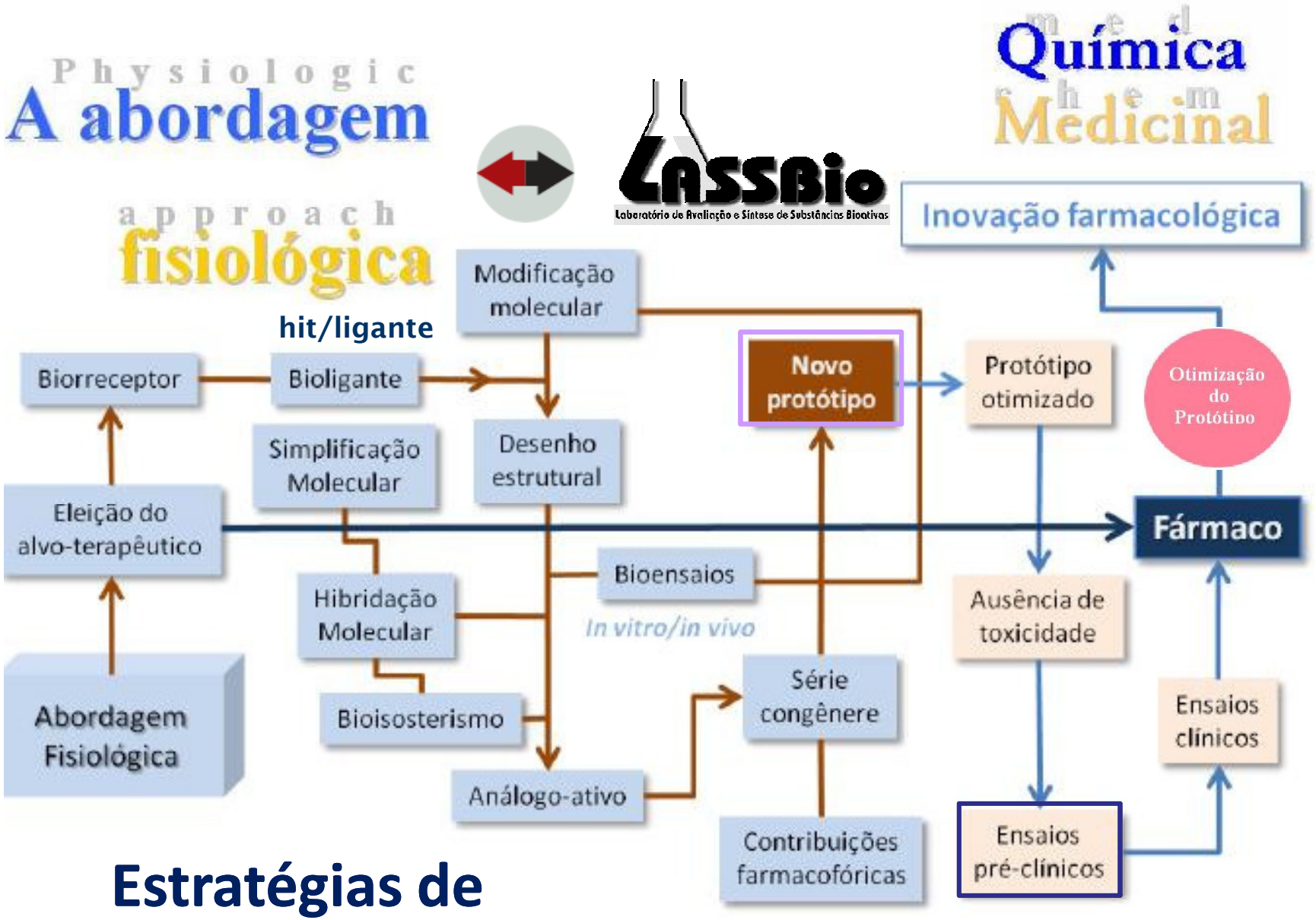
LASSBio

Laboratório de Avaliação e Síntese de Substâncias Bioativas

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

Pharmacology
Farmacologia

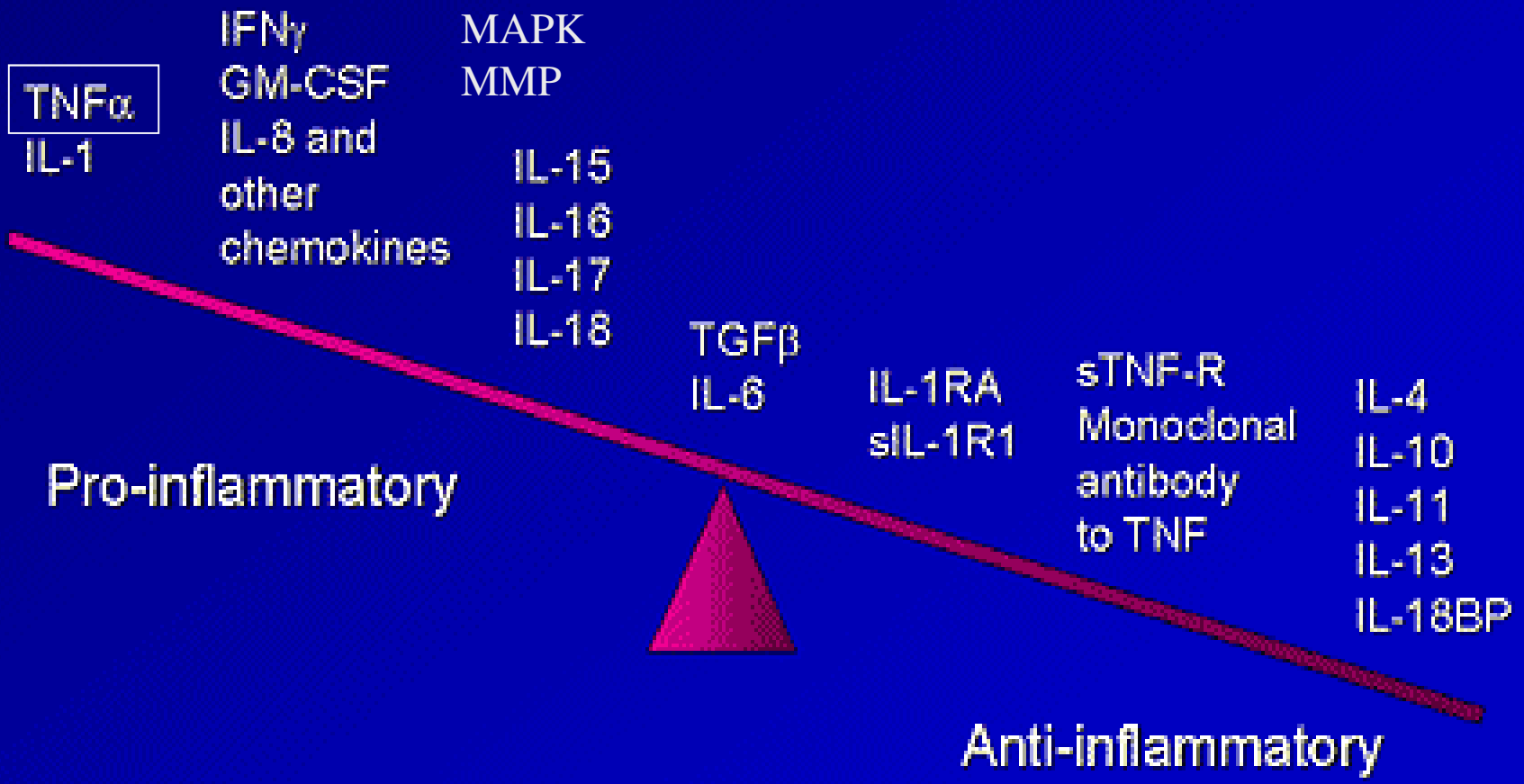
Molecular
Modelagem
Modeling
Molecular



Estratégias de *desenho* molecular

validação precoce do alvo-terapêutico

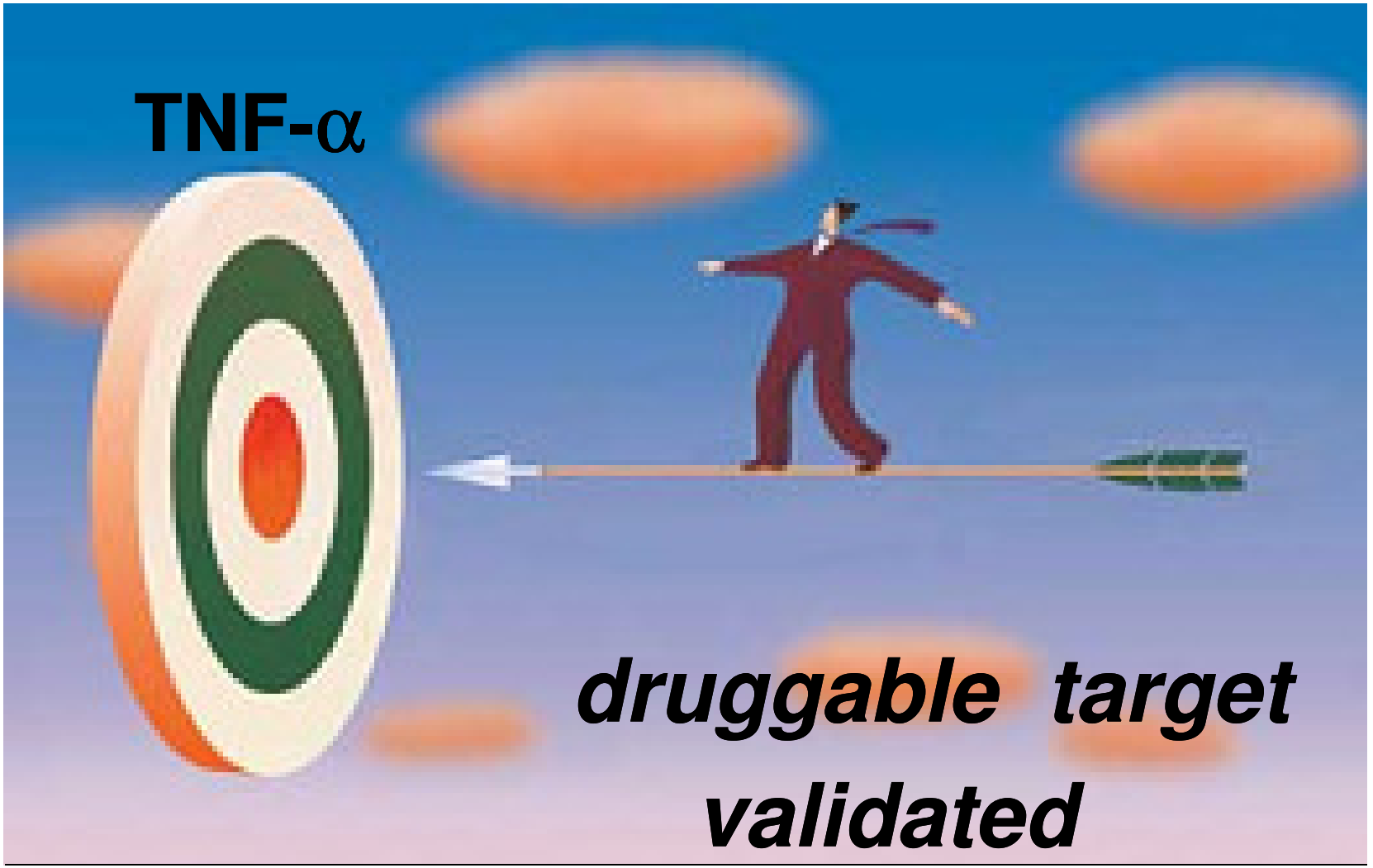
Role of Cytokines and Cytokine Inhibitors in Chronic Inflammation



Arend. *Arthritis Rheum* 2001.

* TNF-α = Tumor necrosis factor-alpha

The Target Election: TNF-α



TNF-α is a cytokine that appears rapidly in response to inflammatory injury

PC Taylor, Pharmacology of TNF blockde in RA and other chronic inflammatory diseases, *Curr. Op. Pharmacol.* **2010**, *10*, 308

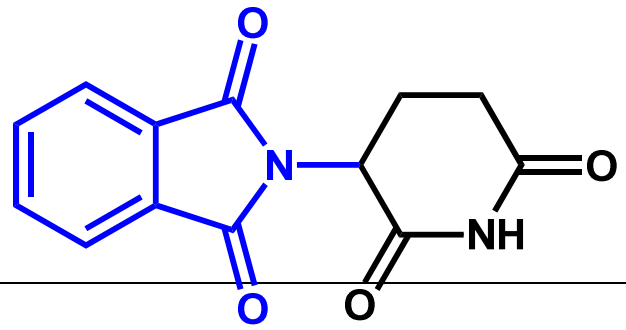
Anti-TNFα Therapies

*Protein-based anti-TNF-alpha Therapies in Clinical Use**

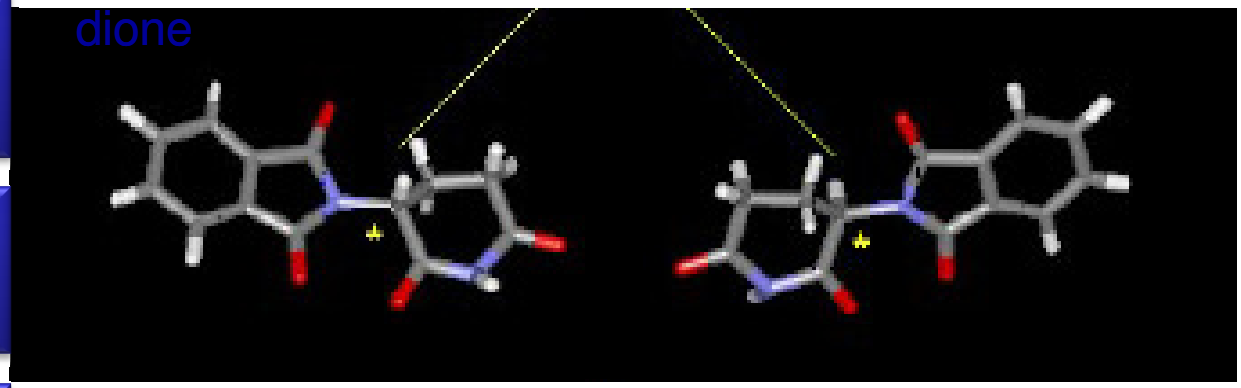
Drug	Status	Biological Form
Etanercept	approved	soluble TNFR2 coupled to Fc portion of IgG
Infliximab	approved	chimeric anti-human TNF antibodie
Adalimumab	approved	anti-human TNF antibodie
ISIS 104838	clinical	TNF anti-sense
Onercept	clinical	soluble p55 TNFR
Humicade	clinical	anti-TNF humanised IgG4

PC Taylor, Pharmacology of TNF blockade in rheumatoid arthritis and other chronic inflammatory diseases, *Curr. Op. Pharmacol*. **2010**, *10*, 308

* protein-based injectable anti-TNFα therapies



2-(2,6-Dioxo-3-piperidinyl)-1*H*-isoindole-1,3(2*H*)-dione

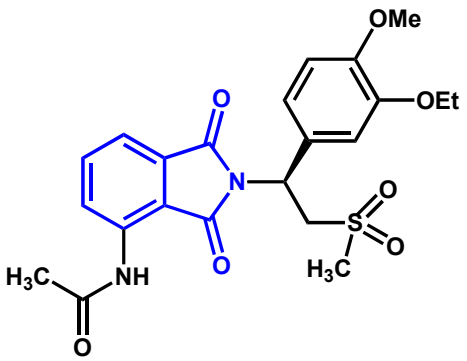


Thalidomide

Anti-TNF

TNF-α IC_{50} = 200 μM

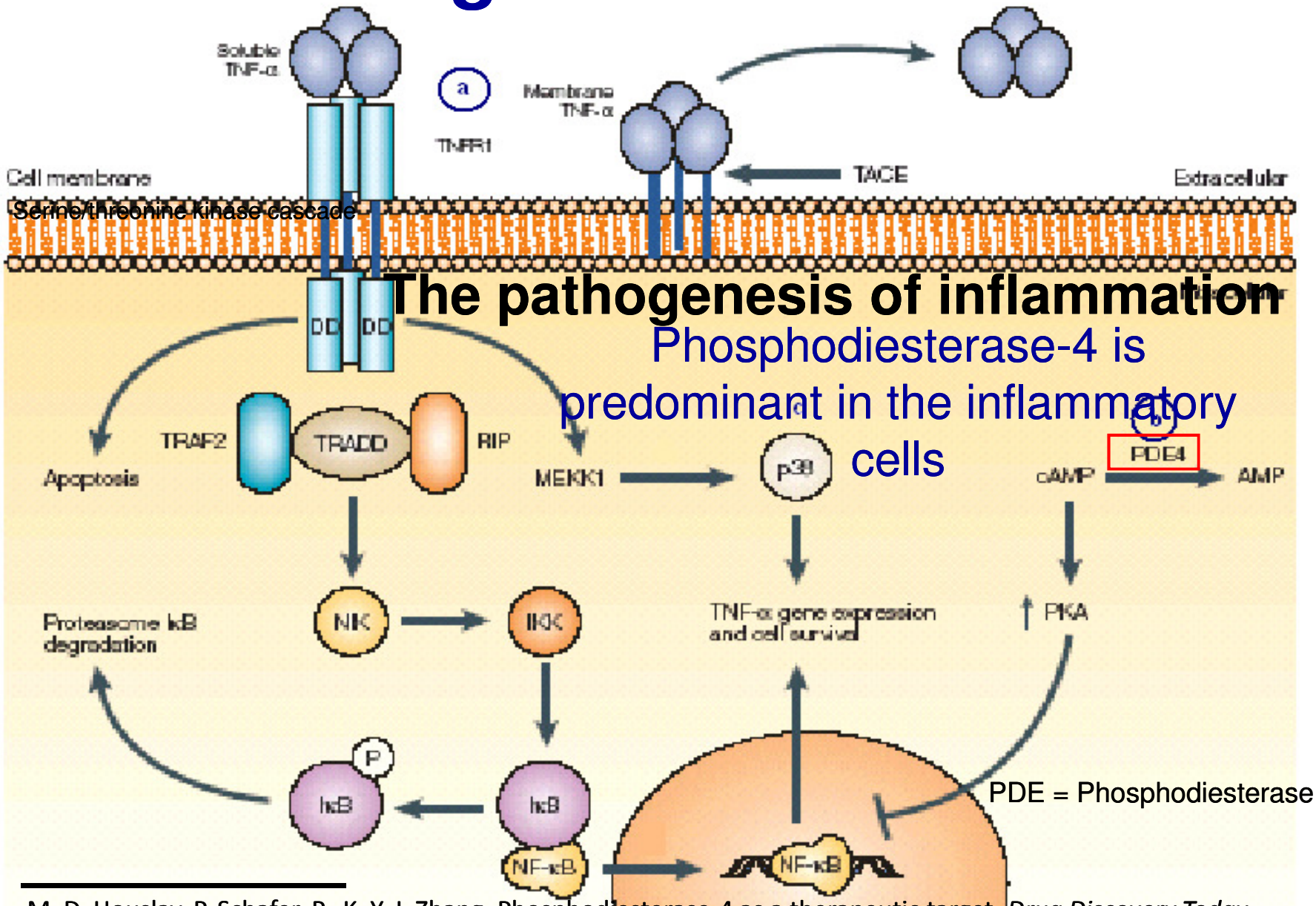
Wilhelm Kunz, 1953
Herbert Keller, 1953
CNS, 1957
Frances Kelsey, 1961
Gilla Kaplan, 1991 (TNF-α)
Elisabeth Sampaio,1997



Apremilast, Phase II, Celgene (2009)

H-W Man *et al.*, *J. Med. Chem.* **2009,** *52,* 1522

Second Target Election:PDE-4



The pathogenesis of inflammation

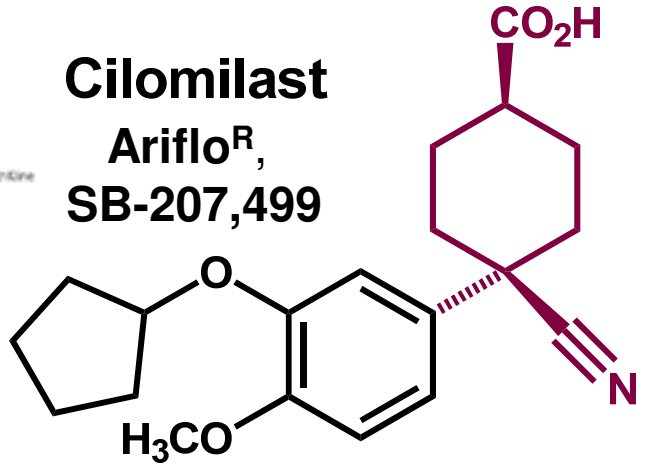
Phosphodiesterase-4 is predominant in the inflammatory cells

PDE = Phosphodiesterase

M. D. Houslay, P. Schafer, P.; K. Y. J. Zhang, Phosphodiesterase-4 as a therapeutic target, *Drug Discovery Today* **2005**, *10,* 1503; B. J. Lipworth, Phosphodiesterase-4 inhibitors for asthma and chronic obstructive pulmonary disease, *Lancet* **2005**, *365*, 167

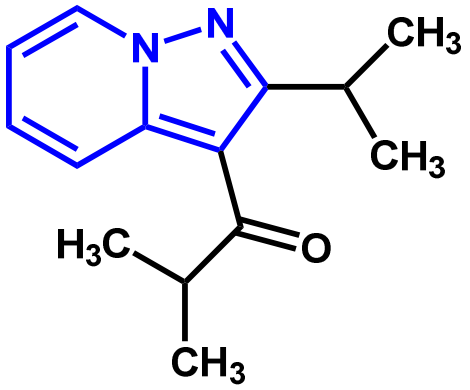
Alvo terapêutico validado

Cilomilast
Ariflo^{R},
SB-207,499



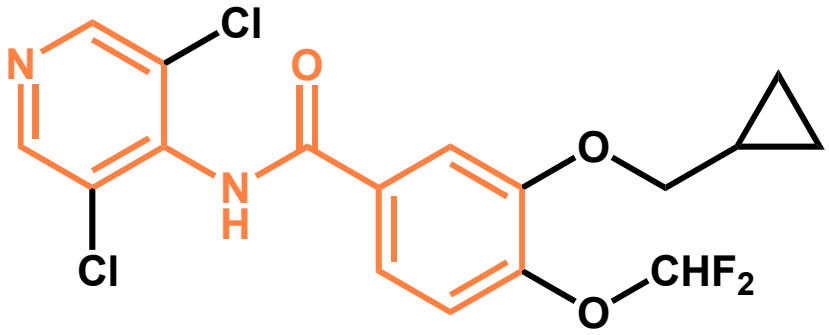
4-cyano-cyclohexyl carboxylic acid

Ibudilast



pyrazolo[1,5-*a*]pyridine

Ruflomilast



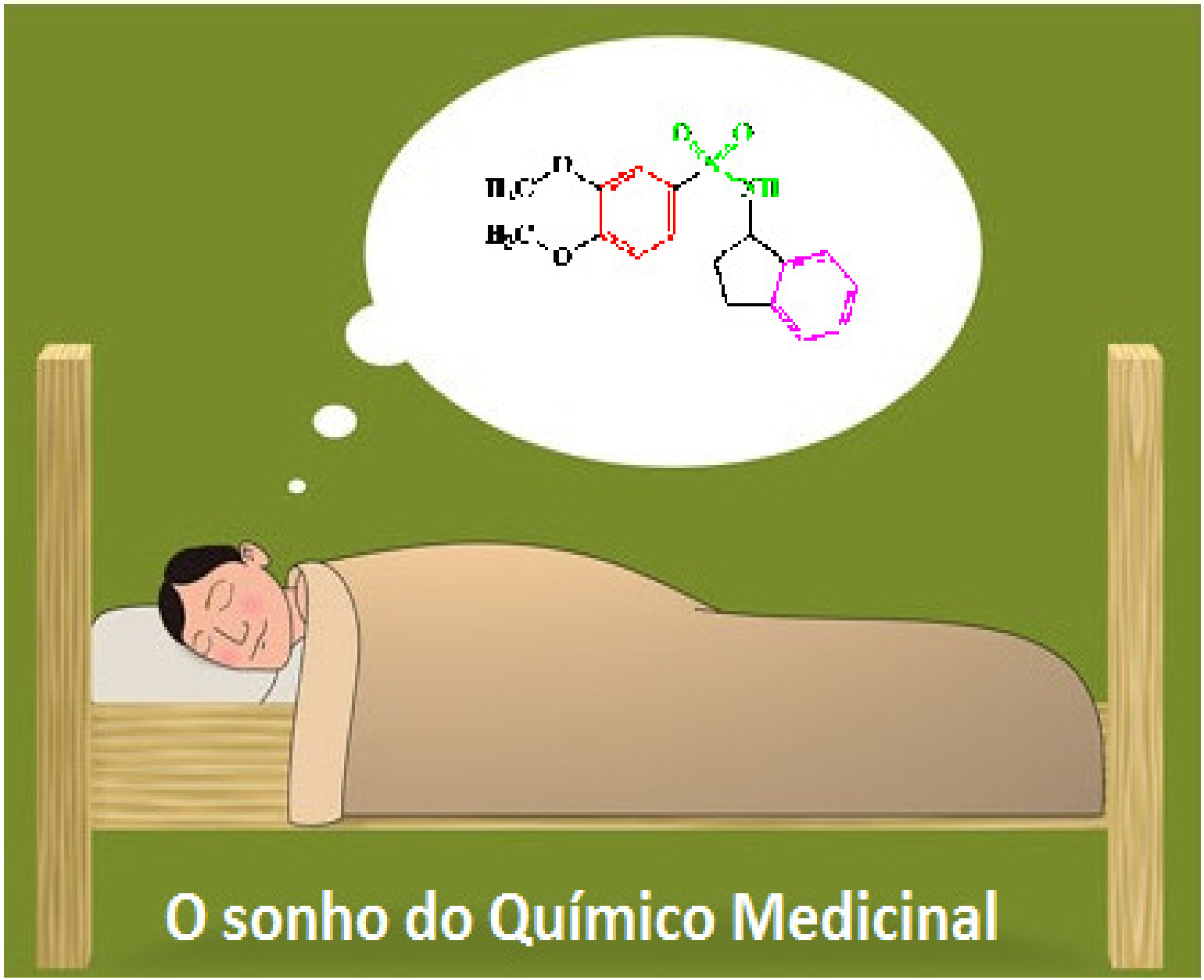
pyridine-benzamide

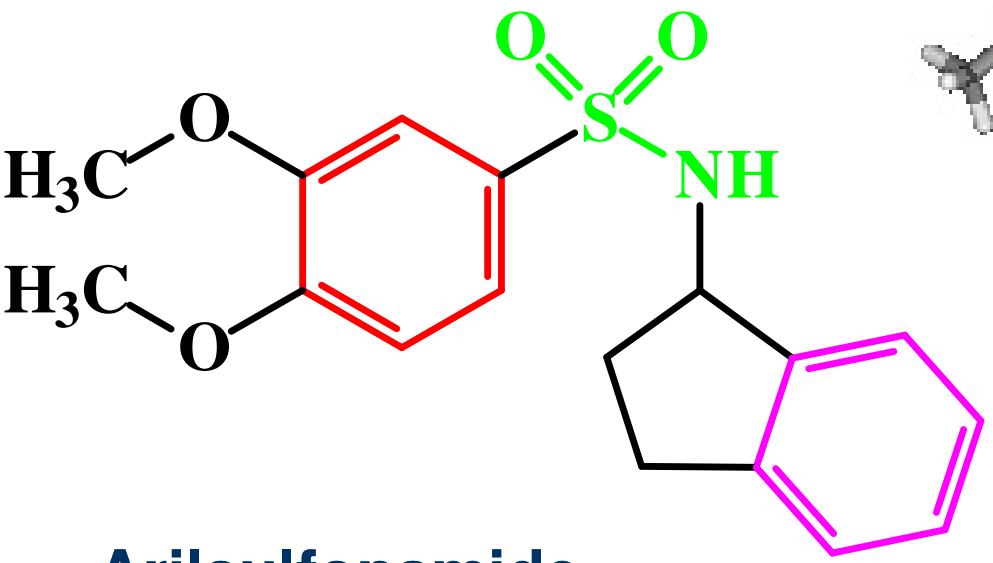
Daxas^{R}
Aprovado
2011

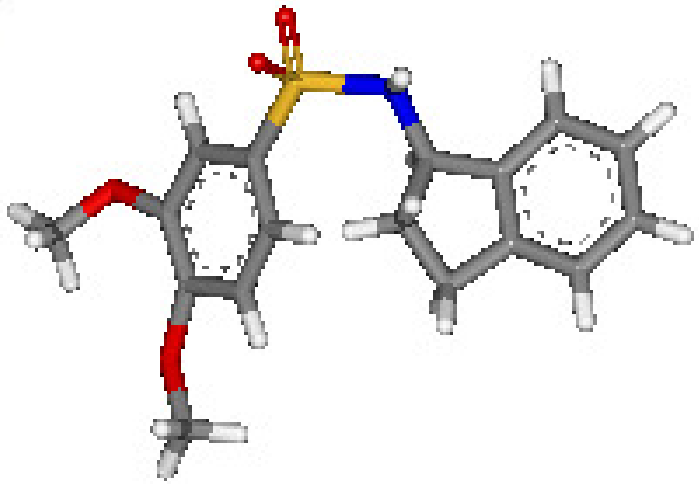
Recent advances on phosphodiesterase 4 inhibitors for the treatment of asthma and chronic obstructive pulmonary disease

A. Kodimuthali, S. S. L. Jabaris, M. Pal

J. Med. Chem. **2008**, *51*, 5471


O sonho do Químico Medicinal





Arilsulfonamide

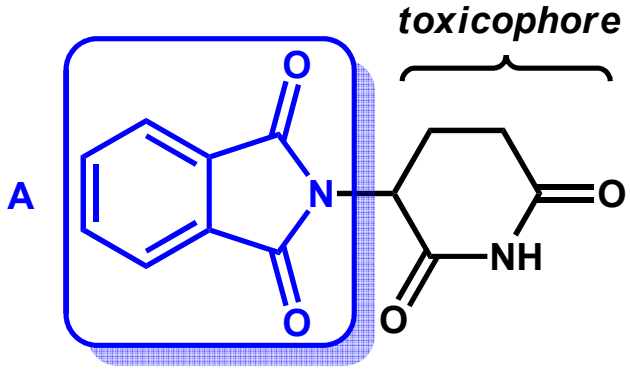
PDE-4i IC_{50} = 4.3 μM

Patent US 5728712 , Application Number US/08/650672; 20 May, 1996

J. G. Montana *et al.**, “Arylsulfonamides as selective PDE-4 inhibitors”, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2635

* Chiroscience Ltd, Cambridge Science Park, Cambridge, UK

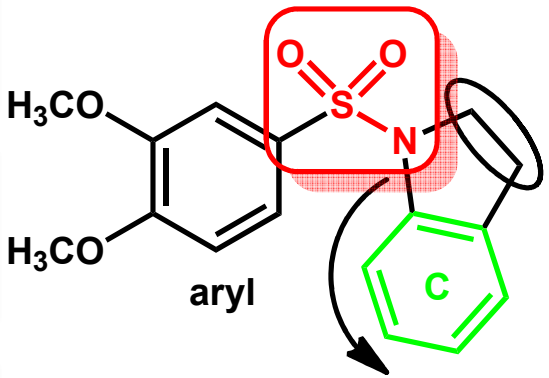
The design of new dual agent with anti-TNFα activity & PDE-4i



phthalimide

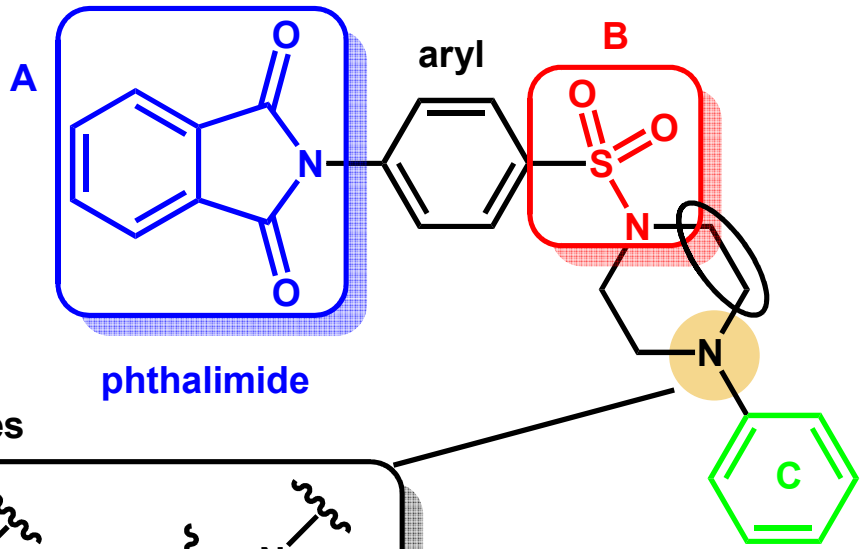
molecular hybridization

B sulfonamide



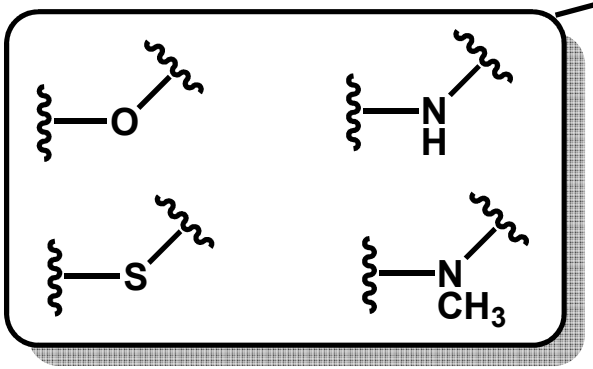
lipophylic

Montana *et al*., 1998



phthalimide

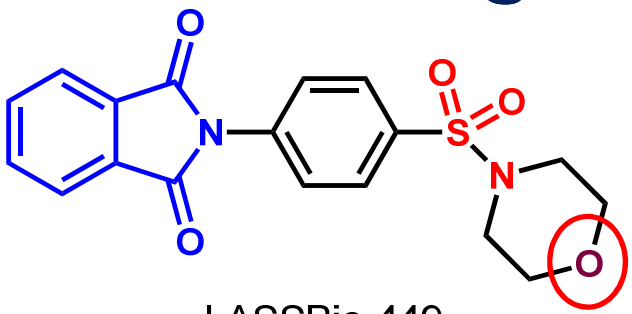
isosteres



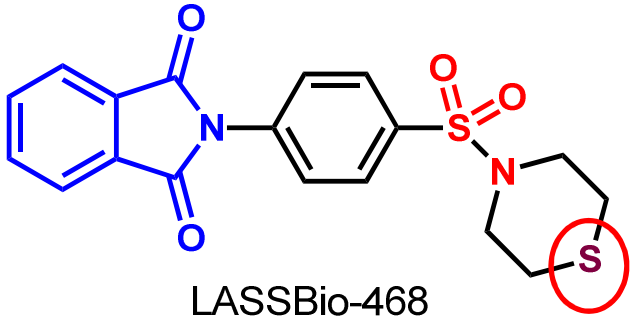
σ, π, RM

Drug Design

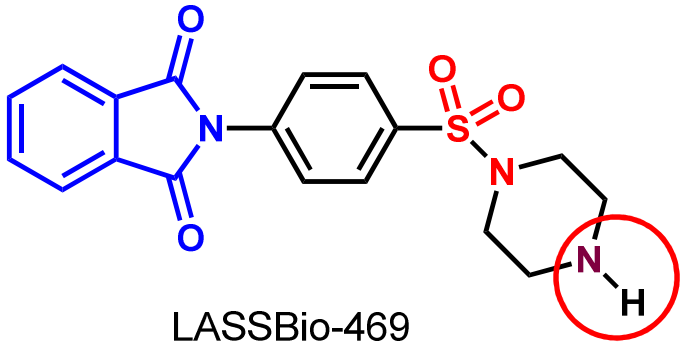
Série Congênere



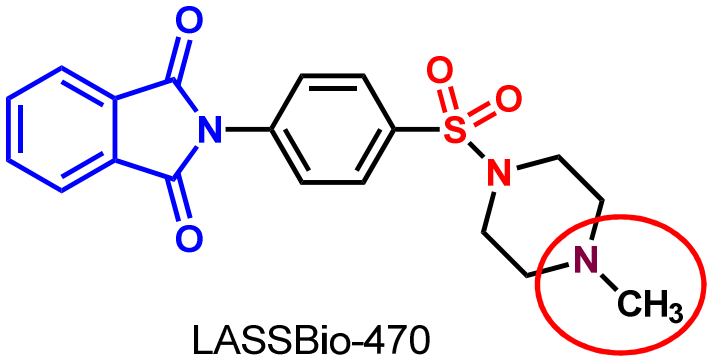
LASSBio-449



LASSBio-468

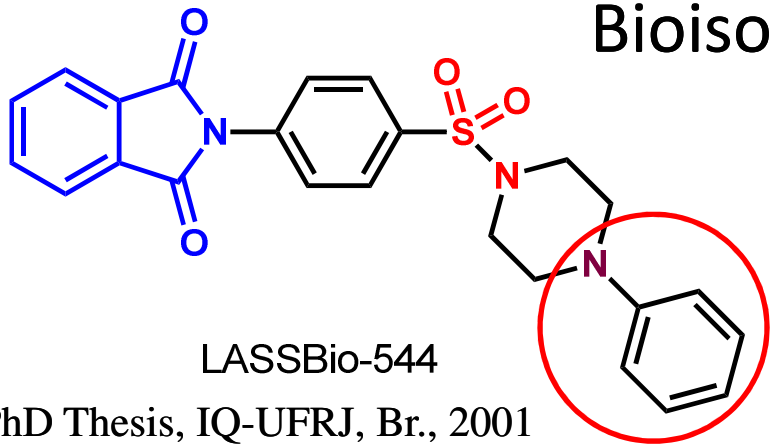


LASSBio-469



LASSBio-470

Bioisosterismo



LASSBio-544

Lidia M. Lima (LASSBio), PhD Thesis, IQ-UFRJ, Br., 2001

Effect of compound LASSBio 468 (50 mg/kg, i.p.) on TNF-α levels and neutrophils influx (BALB/c of mice lungs)

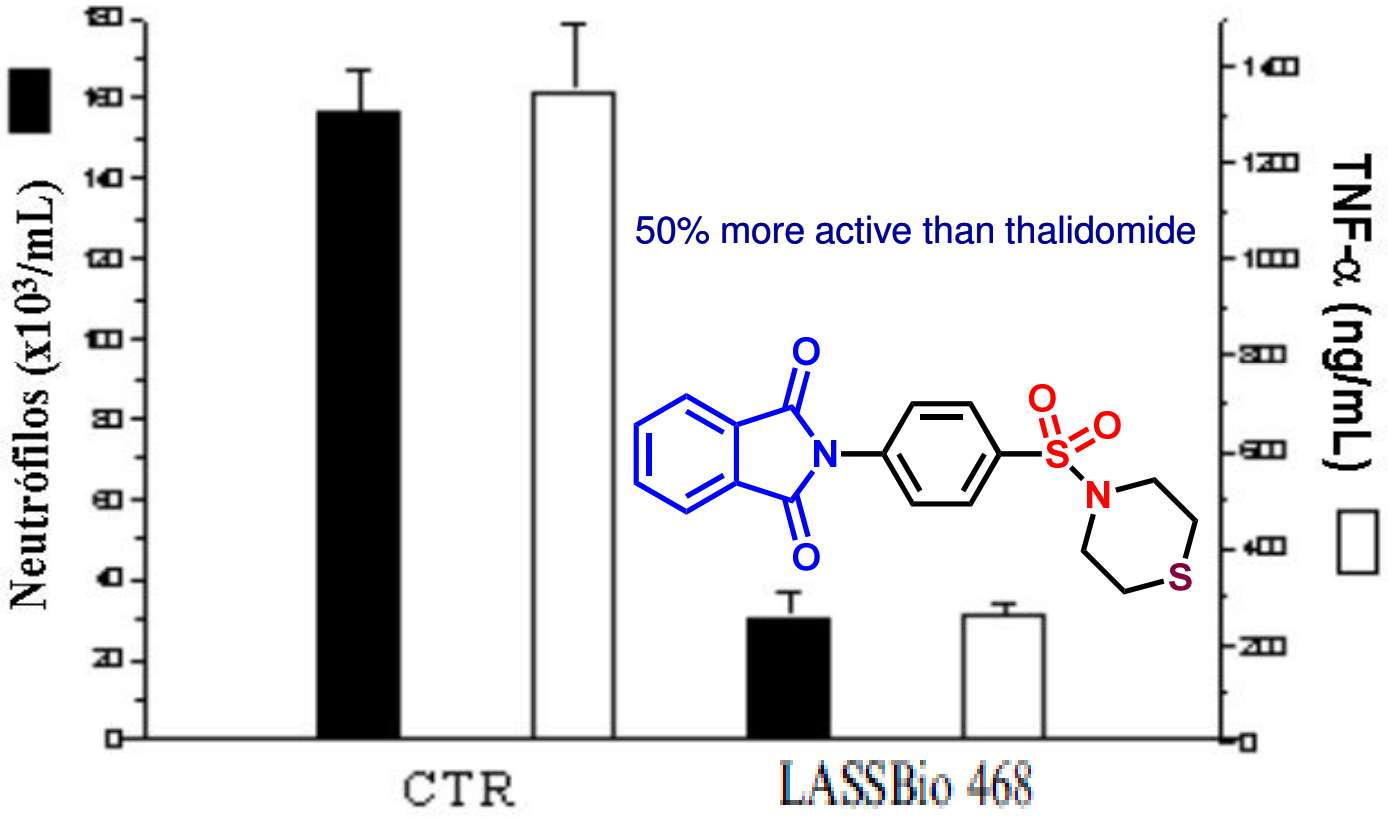
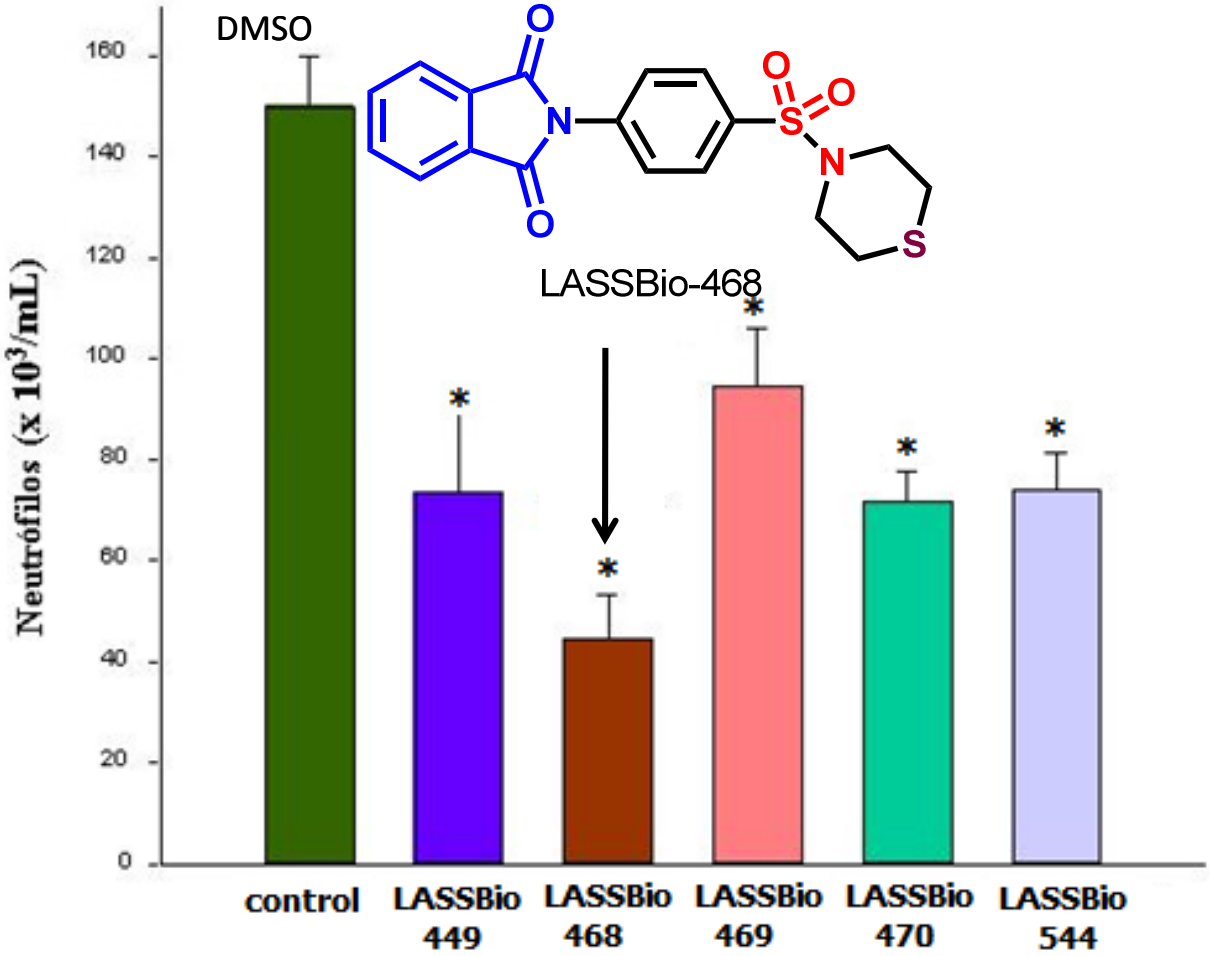


Fig. . Effect of LASSBio-468, thalidomide and pentoxifylline on survival BALB/c mice after LPS (500 µg/mice) administration.

Vera G Koatz
IBqM, Universidade Federal do Rio de Janeiro

Effect of new compounds and thalidomide on neutrophils influx, induced by LPS into BALB/c of mice lungs (10 mg/kg, DMSO; i.p.)

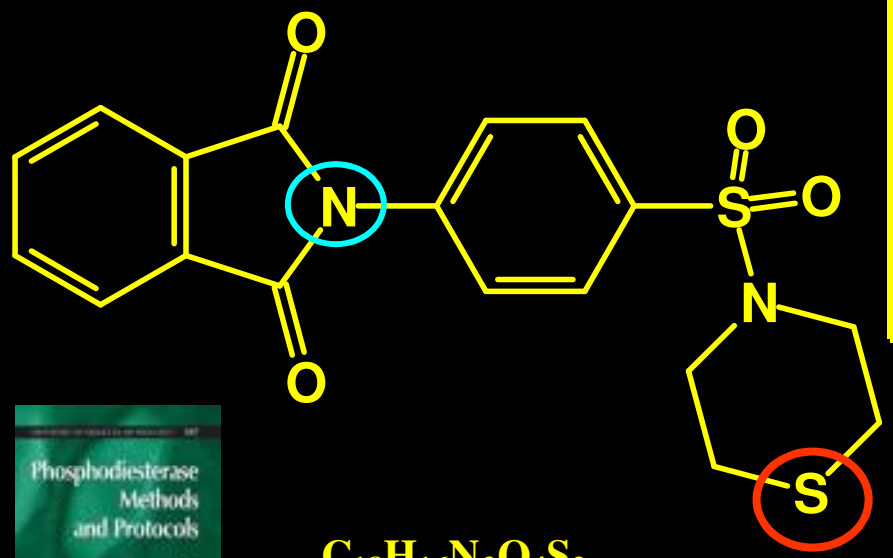
in vivo

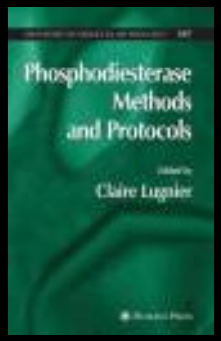


Results are expressed as means SEM of seven animals.

Vera G Koatz
IBqM, Universidade Federal do Rio de Janeiro

Universidade Federal do Rio de Janeiro





$C_{18}H_{16}N_2O_4S_2$

LASSBio 468

TNF-α ED_{50} 2,5 mg/Kg

lead compound

PDE-4 inhibitor

Dr **Claire** **Lugnier** (CAPES-COFECUB; LASSBio-Strasbourg)
Université Louis Pasteur, Strasbourg, FR.
Laboratoire de Pharmacologie et de Physicochimie des Interactions Cellulaires et Moléculaires.

IC_{50} = 13,5μM

cf. PDE-1, 2, 3, > 150 μM;

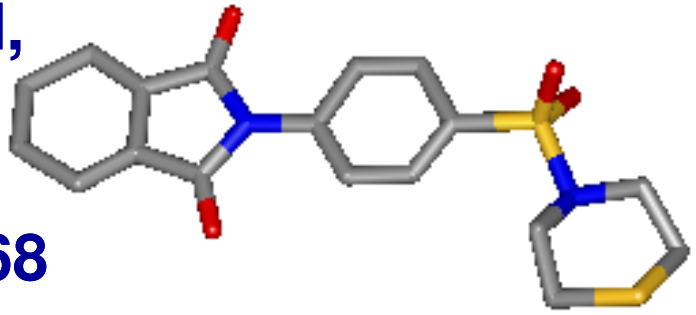
a) L. M. Lima *et al.*, "Synthesis and Anti-inflammatory Activity of Phthalimide Derivatives, Designed as New Thalidomide Analogues", *Bioorg. Med. Chem.* 2002, 10, 3067;

b) M. S. Alexandre-Moreira *et al.*, "LASSBio-468: a New achiral Thalidomide Analogue which Modulates TNF-α and NO Production and Inhibit Endotoxic Shock and Arthritis in Animal Model", *International Immunopharmacology* 2005, 5, 485.

LASSBio-468

A new symbiotic anti-inflammatory agent

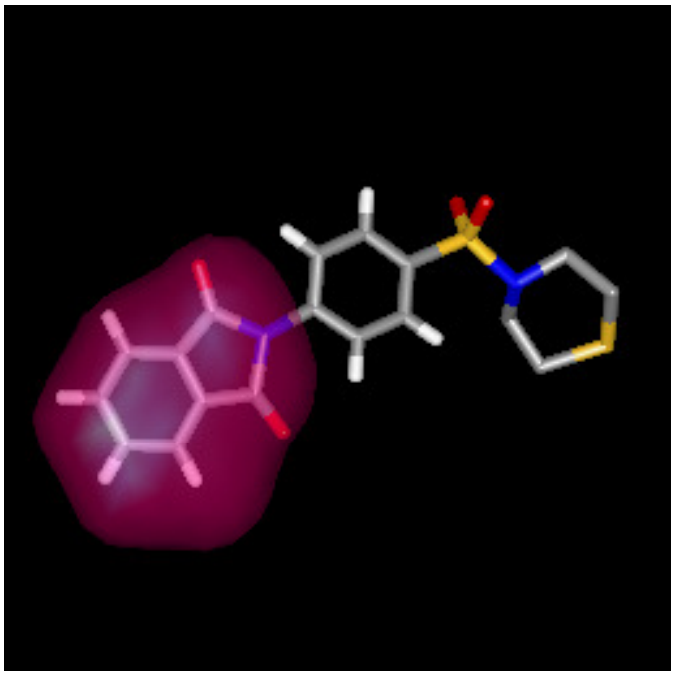
LASSBio-468 is a new dual-target anti-inflammatory lead-compound, active at TNF-α production and with inhibitory activity on PDE-4, as originally planned. LASSBio-468 is structurally simple derivative, easy to synthesized at good overall yield and 0.5 M scale. This new achiral compound presents immunomodulatory activity without anti-proliferative effect, in contrast to THLD. LASSBio-468 is an useful lead-compound to treatment of chronicle inflammatory disorders as rheumatoid arthritis and shock septic syndrome.



L. M. Lima *et al.*, "Synthesis and Anti-inflammatory Activity of Phthalimide Derivatives, Designed as New Thalidomide Analogues", *Bioorg. Med. Chem.* 2002, *10,* 3067

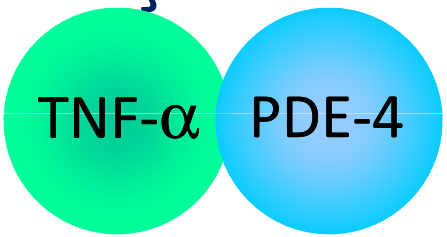
A. L. Machado *et al.*, "Design, Synthesis and anti-inflammatory activity of novel phthalimide derivatives, structurally related to thalidomide", *Bioorg. Med. Chem. Lett.* 2005, *15*, 1169

The discovery of new dual lead-compounds



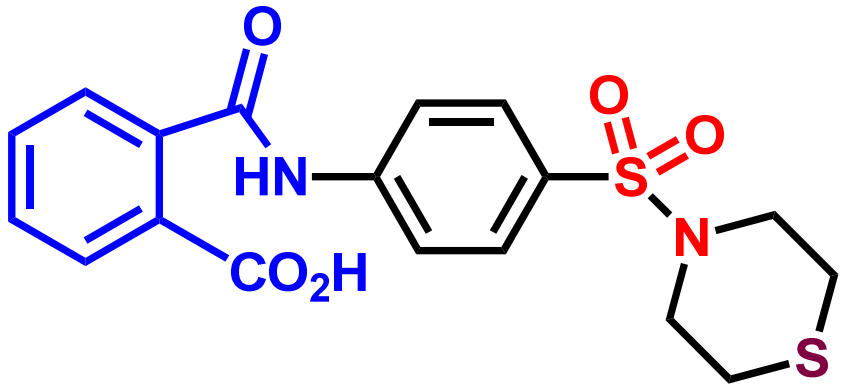
LASSBio-468

Desenhado por hibridação molecular



TNF-α ED_{50} 2,5 mg/Kg

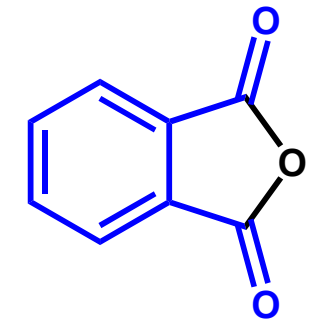
PDE-4 IC_{50} = 13,6 µM



Metabolism studies

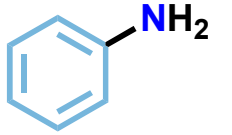
LASSBio-596

L. M. Lima, P. Castro, A. L. Machado, C. A. M. Fraga, C. Lugnier, V. L. G. Moraes, E. J. Barreiro, *Synthesis and Anti-inflammatory activity of Phthalimide Derivaatives, Designed as New Thalidomide Analogues, Bioorg. Med. Chem*. 2002, *10,* 3067.



anidrido ftálico

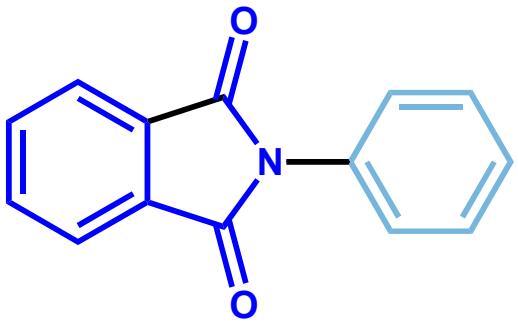
$C_8H_4O_3$



120°C

1h

(2M)



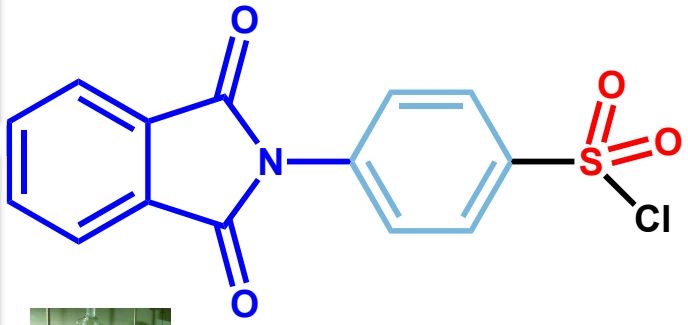
$C_{14}H_9NO_2$

$ClSO_3H$

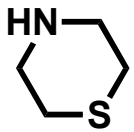
0°C a t.a. até 60°C

1h

(1M)



$C_{14}H_8ClNO_4S$

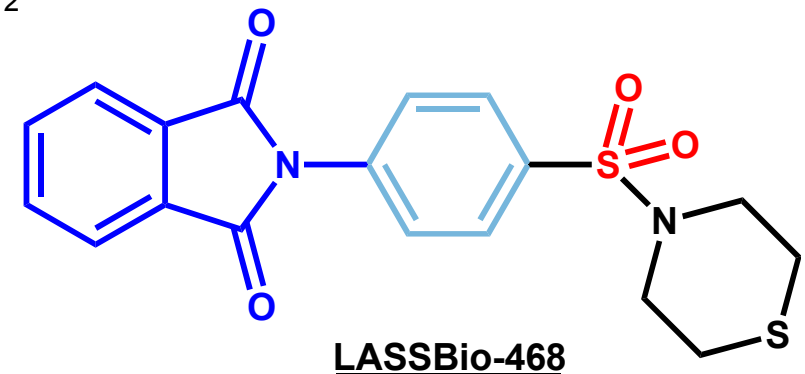


NEt_3

CH_2Cl_2

1h

0,4M



LASSBio-468

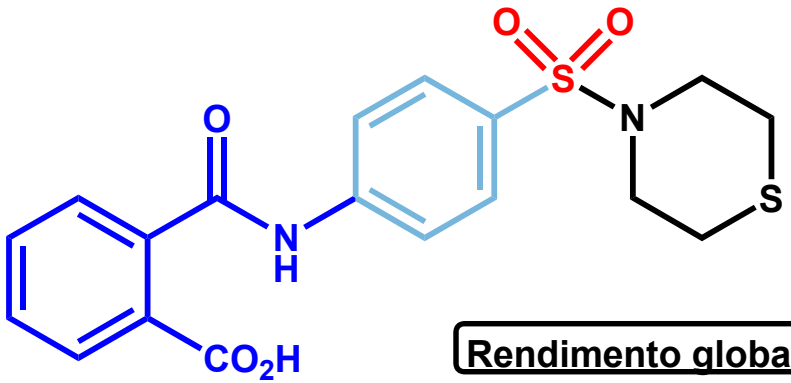
$C_{18}H_{16}N_2O_4S_2$

KOH / HOH

CH_3OH

1h

0,35M



LASSBio-596

$C_{18}H_{18}N_2O_5S_2$

Rendimento global: 29%

^{13}C, ^{1}H RMN / IV / UV / EM

HPLC

calorimetria diferencial de varredura (DSC)

CHN

Difração de Raios-X

RVq Revista Virtual de Química

ISSN 1984-6835

LASSBio-596: da descoberta aos ensaios pré-clínicos

Rocco, Patricia R. M.;[a] Xisto, Debora G.;[a] Silva, J. D.;[a] Diniz, Magareth F. F. M.;[b] Almeida, Reinaldo N.;[b] Luciano, Melissa N.;[b] Medeiros, Isac A.;[b] Cavalcanti, Bruno C.;[c] Ferreira, José R. O.;[c] de Moraes, Manoel O.;[c] Costa-Lotufo, Letícia V.;[c] Pessoa, Claudia do Ó;[c] Dalla-Costa, T.;[d]* Cattani, Vitória B.;[d] Barreiro, Eliezer J.[e], Lima, Lidia M.[e]

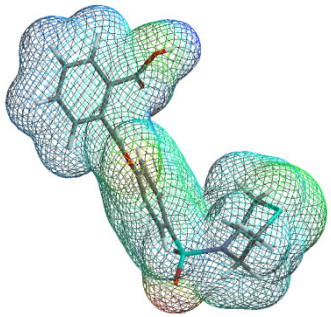
Rev. Virtual Quim., **2010**, *2* (1), 10-27. Data de publicação na Web: 30 de agosto de 2010

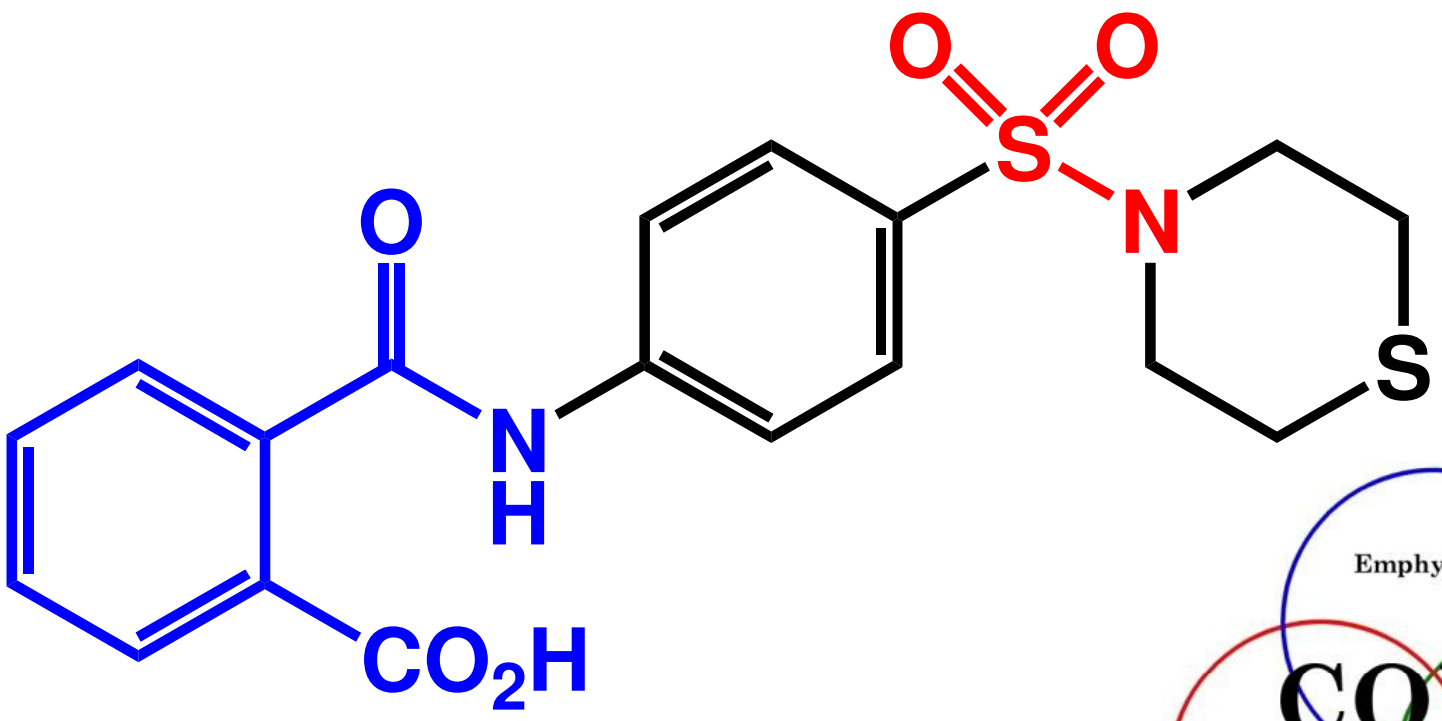
http://www.uff.br/rvq

Resumo

Neste artigo é revisado a trajetória que vai da descoberta de um novo candidato a fármaco antiasmático, o ácido 2-[4-(1,4-tiazinan-4-ilsulfonil)fenilcarbamoil]benzoico (LASSBio-596), à realização dos primeiros ensaios pré-clínicos, com enfoque nos efeitos de LASSBio-596 em modelo murino de asma aguda e crônica, estudos farmacocinéticos e toxicológicos em roedores e determinação do seu potencial genotóxico e mutagênico.

LASSBio-596

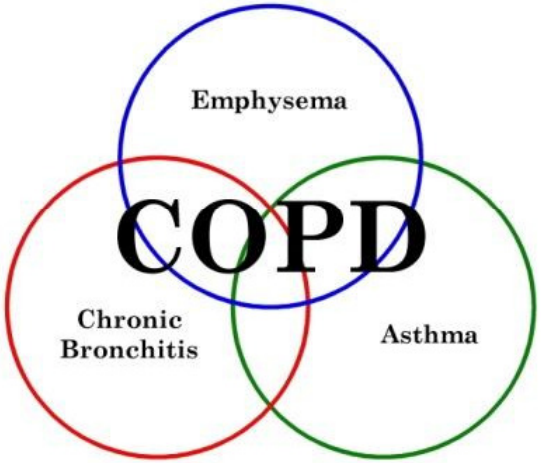




a s t h m a

LASSBio-596

Scale-up



anti-fibrogenic

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Project CNPq 573.564/2008-6

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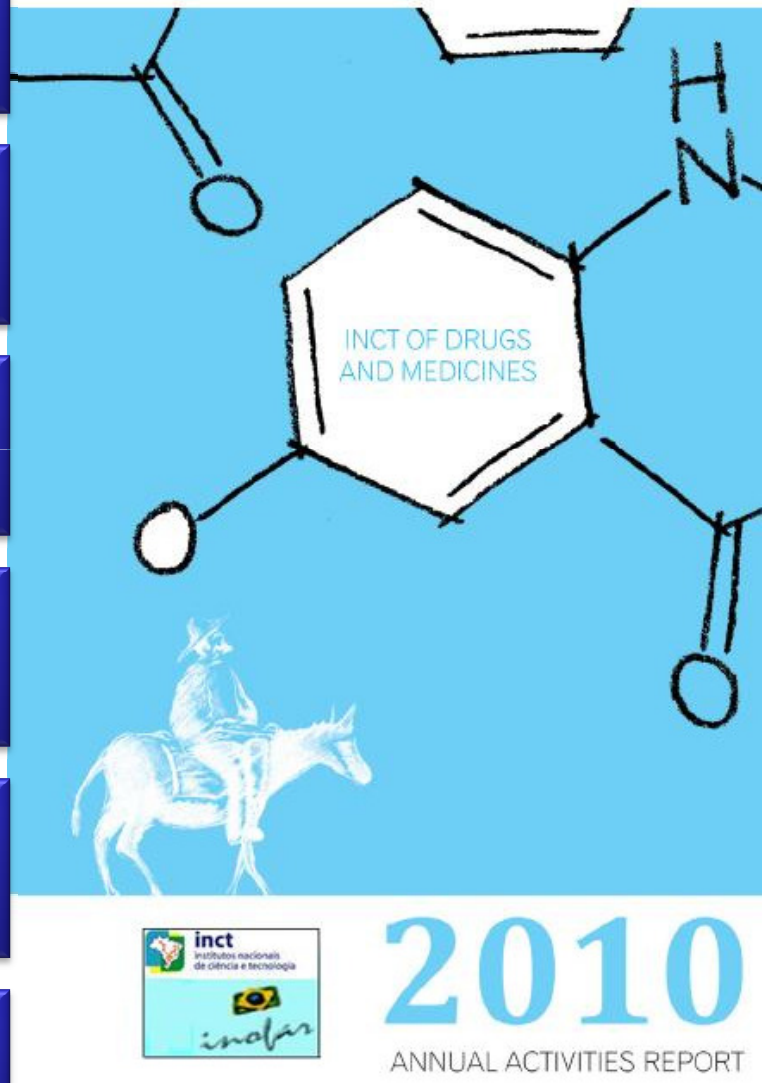
- Research groups
- Research people
- Useful articles
- Publications
- Meetings
- Videos

A missão do INCT-INOFAR

- Organizar as competências científicas nacionais em uma rede efetiva de pesquisa em fármacos;
- Apoiar projetos de pesquisa científica multi-institucionais voltados para novos fármacos;
- Contribuir para a inovação incremental e radical em novos fármacos e genéricos;
- Estudar e desenvolver a síntese total de genéricos, intermediários avançados e matérias-primas;
- Contribuir para a formação científica qualificada de pessoal em química medicinal & farmacologia;
- Promover a divulgação das ciências dos fármacos e dos medicamentos, assim como seu uso racional e seguro;

Annual Activities Report



Interdisciplinar & multi-team research projects

- **Radical innovation**
  pain, inflammation, asthma, CNS, neglected diseases, cardiovascular system, anticancer
- **Incremental innovation**
  SUS (BR healthcare)
  new generic drugs

www.inct-inofar.ccs.ufrj.br/download/aar/2010.pdf

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Dr Camile G Wermuth (França)
Dr Simon Campbell

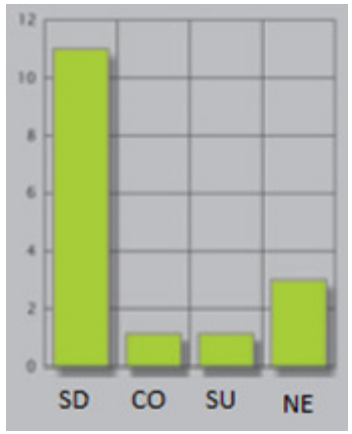
Foreign scientific consultants

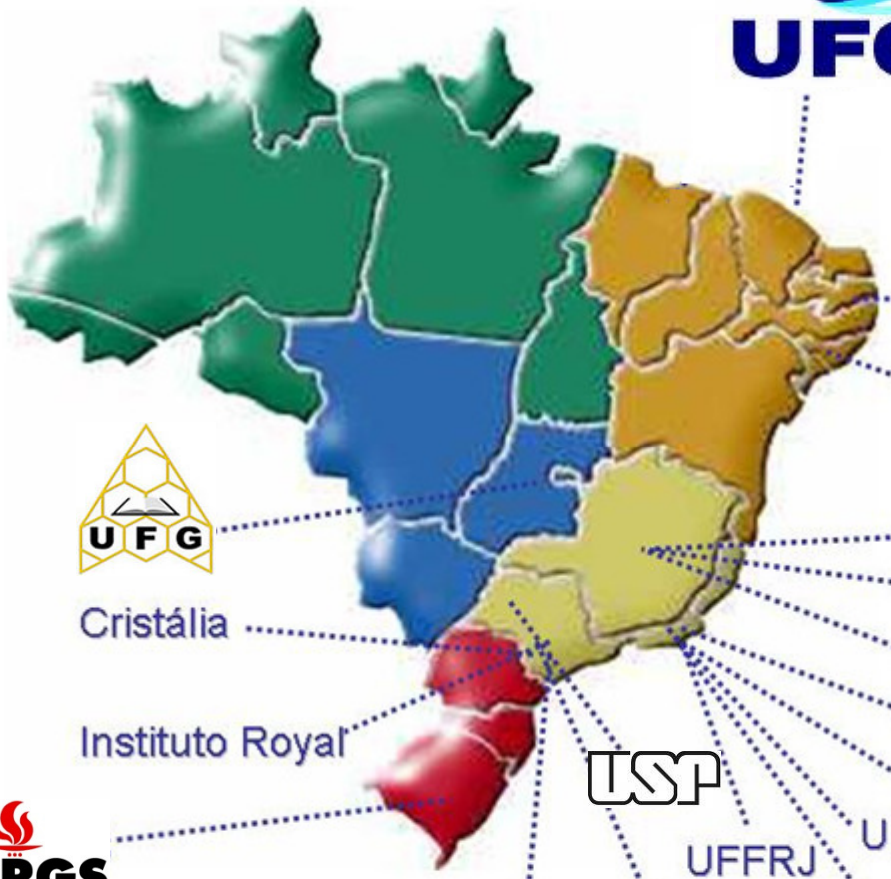


Antonio Monge, Universidad de Navarra,ES
Camille G. Wermuth, Prestwick Co., Ilkirch, FR
Simon Campbell, ex-Pfizer Major Scientist UK

Research partners

INCT-INOFAR





UFC

UFPB

UFAL

UNIFAL-MG

In Vitro Cells

UFMG

FIOCRUZ

UFMG

UFG

Cristália

Instituto Royal

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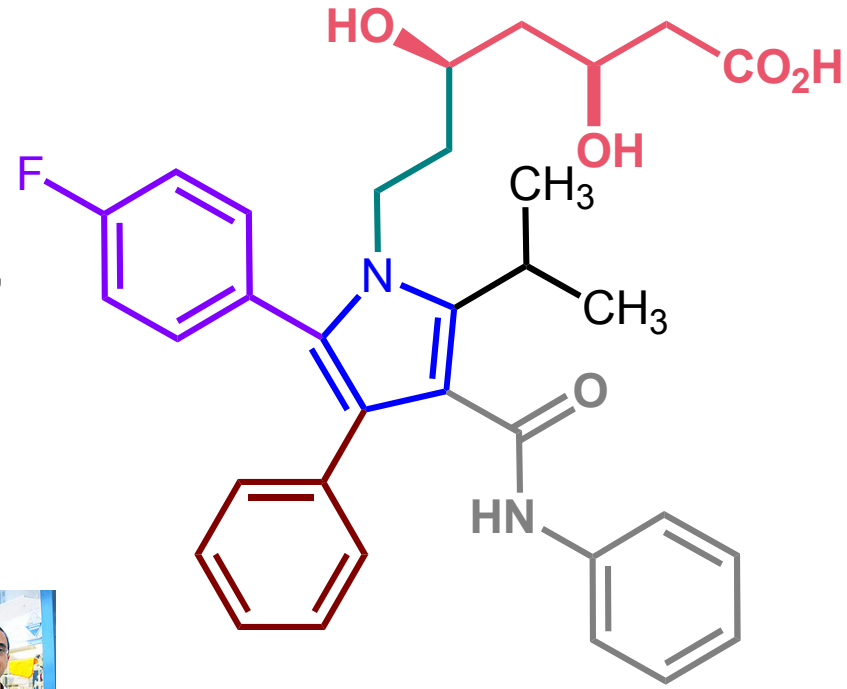
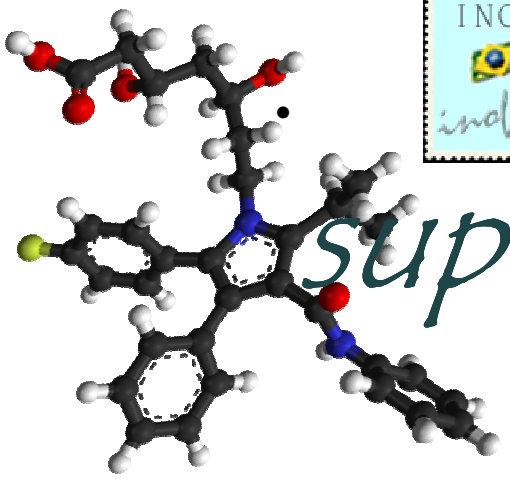
Atorvastatina

Incremental *In*novation

1991

- Sintetizada, em 1985, por Bruce Roth
[B. D. Roth, "The discovery and development of atorvastatin, a potent novel hypolipidemic agent", Prog. Med. Chem. **2002**, *40*, 1–22]
Patente US 5273995 Pfizer (1991):
12 etapas = 4,2%
- Nova síntese Prof. **Luiz Carlos Dias** & Dr **Adriano S Vieira**, IQ-UNICAMP, em **2010**, pelo **INCT-INOFAR:**






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

11 etapas = 19,3%

super blockbuster-drug

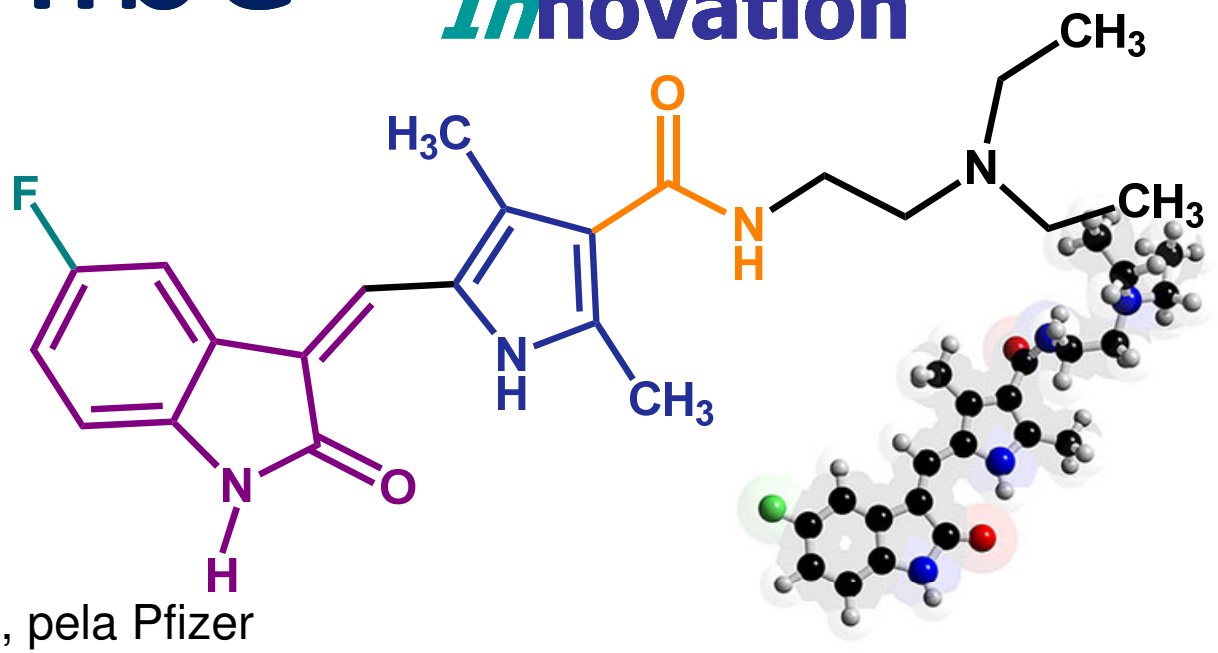
LC Dias, A S Vieira, EJ Barreiro, Processo de obtenção de atorvastatina cálcica utilizando novos intermediários
*PI 018110015039 (*protocolado no INPI, em 25/04/2011)

Sunitinibe

Incremental *In*novation

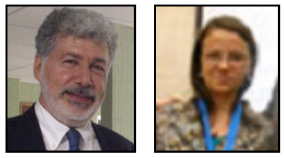
2006

Sutent^{R}



- Sintetizado, em 1999, pela Pfizer
- Patente de 2001 (US)
- Inibidor BCR–ABL Tyr-quinase
- Indicado para Ca-estômago/rim
- Nova síntese Prof. **Angelo da Cunha Pinto** & Dr **Bárbara Vasconcellos da Silva**, IQ-UFRJ, **em 2011**, pelo INCT-INOFAR

50 mg / 28 caps *ca.* R$ 20.837,90



Vendas de tinibes no mercado norte-americano:

US$ 18,5 bi (2009)

Importações

ca. US$ 3 milhões/ano

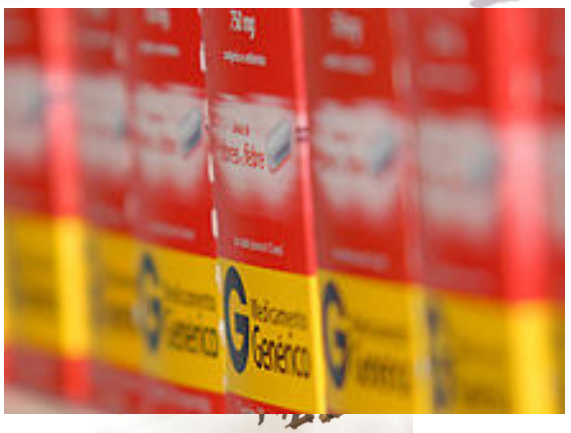
S Aggarwal, *Nature Rev Drug Discov* **2010**, *9*, 427

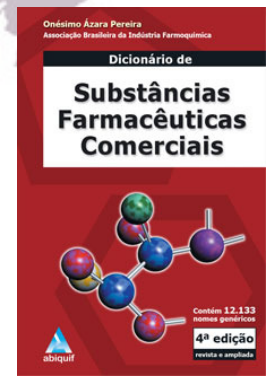
O "*Caminho das Índias*" dos nossos fármacos (genéricos!)

Precisamos resolver, com urgência, a grave situação de dependência das importações de fármacos, invertendo o sentido do *atual Caminho das Índias*...

Inovação incemental

Biolab Sanus Farmaceutica Ltda
Cristália Produtos Químicos Farmacêuticos Ltda
EMS - Sigma Pharma
Eurofarma Laboratórios Ltda
Genom Farmacêutica Ltda
Laboratórios BIOSINTÉTICA
Laboratório Neo Química Indústria Farmacêutica Ltda
Laboratório Teuto Brasileiro
LIBBS Farmacêutica
Medley S/A Indústria Farmacêutica
Mantecorp
Zambon Laboratórios Farmacêuticos Ltda





Universidade Federal do Rio de Janeiro

A equipe do INCT-INOFAR

Universidade Federal do Rio de Janeiro, março 2011

Primeira reunião de avaliação e acompanhamento de 2011

Universidade Federal do Rio de Janeiro

Considerações Finais

"For all the efforts to industrialize and automate discovery, history suggests drug discovery is art as well as science and relies heavily on the skill of experienced drug hunters..."

Charles H. Reynolds

J&J Pharmaceutical Research and Development, Spring House, Pa

em *Pharma's Road Ahead* , C&EN, Volume 84, Issue 25, June 19, 2006

Universidade Federal do Rio de Janeiro

Drug Discovery Today • Volume 14, Numbers 1/2 • January 2009 07 October 2009 vol 1, issue 1, 95-101 REVIEWS

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Drug discovery: new models for industry–academic partnerships

Cathy J. Tralau-Stewart, Colin A. Wyatt, Dominique E. Kleyn and Alex Ayad

Drug Discovery Centre and Business Development, Imperial College London SW7 2AZ, UK

The re-focusing of pharmaceutical industry research away from early discovery activities is stimulating the development of novel models of drug discovery, notably involving academia as a 'front end'. In this article the authors explore the drivers of change, the role of new entrants (universities with specialised core facilities) and novel partnership models. If they are to be sustainable and deliver, these new models must be flexible and properly funded by industry or public funding, rewarding all partners for

Reviews • POST SCREEN

MR Barnes *et al.*, Lowering industry firewalls: pre-competitive informatics iniciatives in drug discovery, *Nature Rev. Drug Discov.* **2009**, *8*, 701; PG Wyatt, The emerging academic drug-discovery sector. *Future Med. Chem.* **2009**, *1*, 1013; R Kneller, The importance of new companies for drug discovery: origins of a decade of new drugs. *Nature Rev. Drug Discov.* **2010**, *9*, 867; AJ Stevens *et al.*, The role of public-sector research in the discovery of drugs and vaccines. *N. Engl. J. Med.* **2011**, *364*, 535.

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Obrigado

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2011
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Rio de Janeiro, BR


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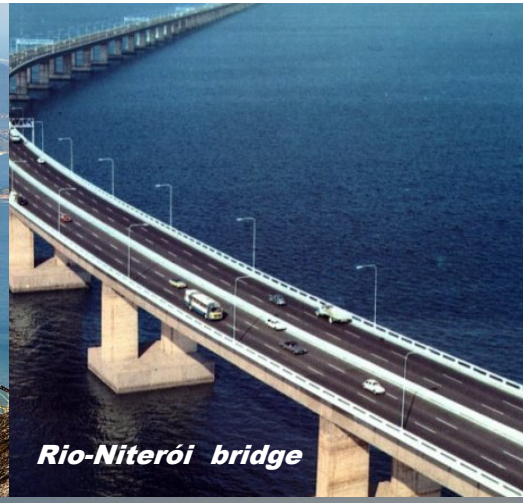
Sugar Loaf


Rio-Niterói bridge


Copacabana Beach


Copacabana beach view from Sugar Loaf


Sunset at Arpoador Beach


Maracanã stadium

Rio2016


Botanic gardem