A *Química Medicinal* na descoberta de fármacos Parte IV

60ª Reunião Anual da SBPC
Energia Ambiente Tecnologia
13 a 18 de julho de 2008
Unicamp – Campinas, SP
realização SBPC UNICAMP

Farmácia

Dr Eliezer J. Barreiro
Professor Titular - UFRJ

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas
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A Química Medicinal na descoberta de fármacos -IV

- Primeiro paradima da descoberta de fármacos
- Paradigma de Ehrlich
- O paradigma atual
- Fármacos como ligantes de receptores múltiplos
- LASSBio-468 & 998: Protótipos simbióticos

Louis Pasteur

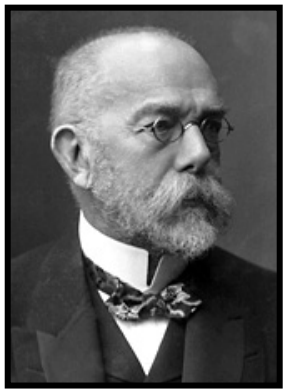
1822-1895

‘La vie empeche la vie”

Emil Fisher

1852-1919

1902



Robert Koch

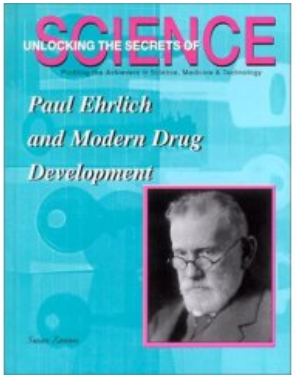
1843-1910

1905

Paul Ehrlich

1854-1915

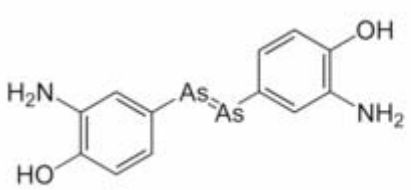
1908



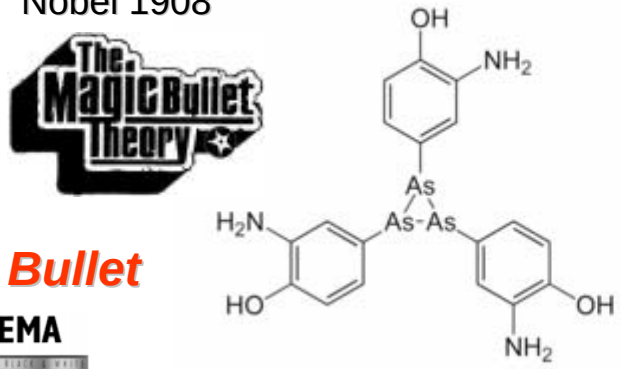
Química Medicinal

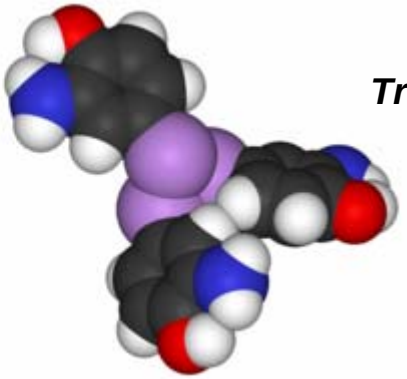
P. Ehrlich, *Chemotherapeutics: scientific principles, methods and results*. *Lancet* 1913, **2**, 445

Paul Ehrlich
1854-1915
Nobel 1908



Arsfenamina





Trimêro

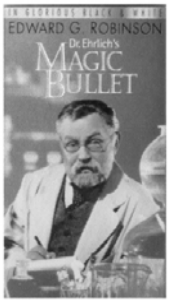
Dr. Ehrlich's Magic Bullet

SCIENCE IN THE CINEMA

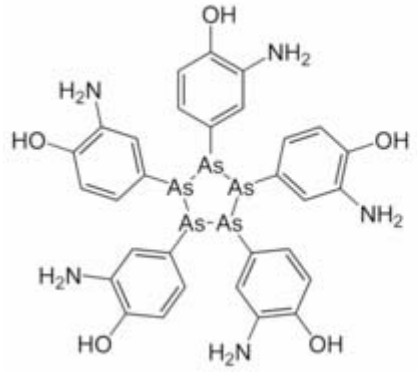
Dr. Ehrlich's Magic Bullet

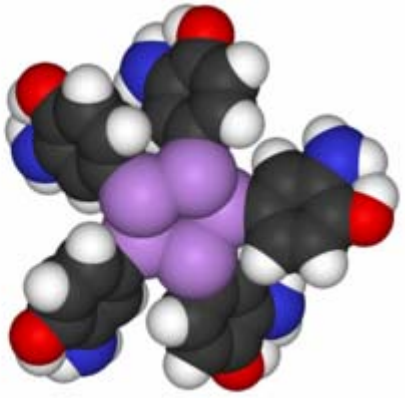
Thursday ■ July 31 ■ 7:00 p.m.

Starring
EDWARD G. ROBINSON (Dr. Paul Ehrlich)
RUTH GORDON (Mrs. Ehrlich)
OTTO KRUGER (Dr. Emil Von Behring)
DONALD CRISP (Minister Althoff)
MARIA OUSPENSKAYA (Franziska Speyer)
MONTAGU LOVE (Prof. Hartmann)
Directed by WILLIAM DIETERLE
Written by JOHN HUSTON, HEINZ HERALD, and NORMAN BURNSIDE

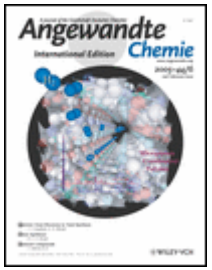


Salvarsan^R





Pentâmero



Lloyd NC, Morgan HW, Nicholson BK, Ronimus RS "The composition of Ehrlich's salvarsan: resolution of a century-old debate". Angew. Chem. Int. Ed. Engl. 2005, 44, 941.

Química Medicinal

- ***Modelo Chave-fechadura***
  Lock-Key Concept : Emil Fisher
  (1852-1919)

Paul Ehrlich in his office, Frankfurt 1914.

F.Winau, O. Westphal, R. Winau, Microbes & Infection 2004, 6, 786.

- ***Primeiro paradigma da descoberta de fármacos***
  (first drug discovery paradigm)
  abordagem caixa-preta ('black box' approach)

- ***"Balas mágicas"***
  Magic bullets
  Paul Ehrlich (1854-1915)

- ***Segundo paradigma da descobrta de fármacos:***
  'one-target one-disease' approach
  abordagem "uma-doença/um ligante"

- ***O paradigma atual: o composto-protótipo:***

  lead-compound discovery

  'one-target one-disease'

- ***Recentes sucessos das "magic bullets"***

  coxibes

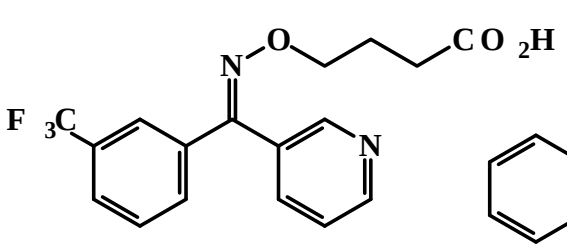
- ***Ligantes duplos, para dois alvos***

  dual, binary, dimeric, bivalent, mixed ligands

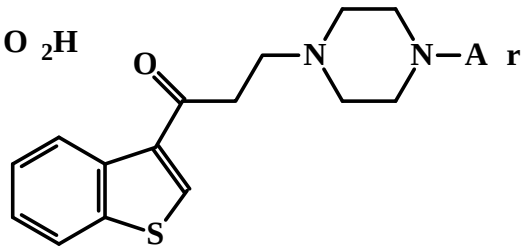
  TXS-TPant; 5-HT1ARant-SSRI;

- ***Desenho racional de ligantes múltiplos***

  inibidores duplos COX-2 & 5-LOX

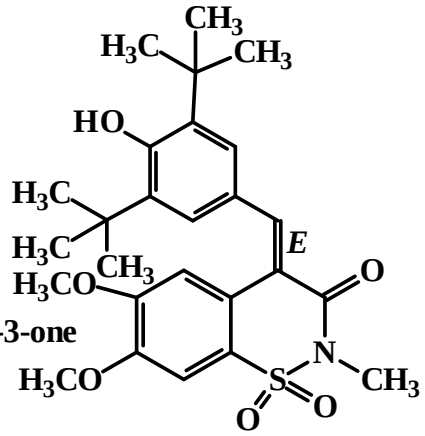


Freyne, 1987



Monge, 2001

benzothiazin-3-one



LASSBio-272

Teixeira, 1998

• Ligantes duplos/duais/mistos/bivalentes para dois alvos

(Dual, binary, dimeric, bivalent, mixed ligands, multi-target)

novos compostos-protótipos com afinidade (SAfiR) relativa semelhantes, capazes de serem reconhecidos molecularmente por dois alvos-terapêuticos distintos da mesma cadeia bioquímica, envolvidos na mesma patologia.

- **COX-LOX**

J. Med. Chem. **2006**, *49*, 1668 *(1/2COX - 5/15LOX)*
Bioorg.Med.Chem.Lett. **2005**, *15*, 4842 (COX – LOX)

- **Ser-Treo quinase Akt1/2 (PKB)**

Bioorg. Med. Chem. Lett. **2008**, *18,* 3178

- **Trombina &Fator Xa**

Bioorg. Med. Chem. Lett. **2007**, *17*, 3322
Bioorg. Med. Chem. Lett. **2007**, *17*, 2927

- **TXS-TPant**

Bioorg.Med.Chem.Lett. **2001**,*11,* 1019 (BM-567)

- **Fibroblast Growth Factor R-1/Vascular Endothelial Growth FR-2**

J. Med. Chem. **2005**, *48,* 4628

- **Proteínas anti-apoptóticas Bcl-2 & Bcl-xL**

J. Med. Chem. **2007**, *50,* 641

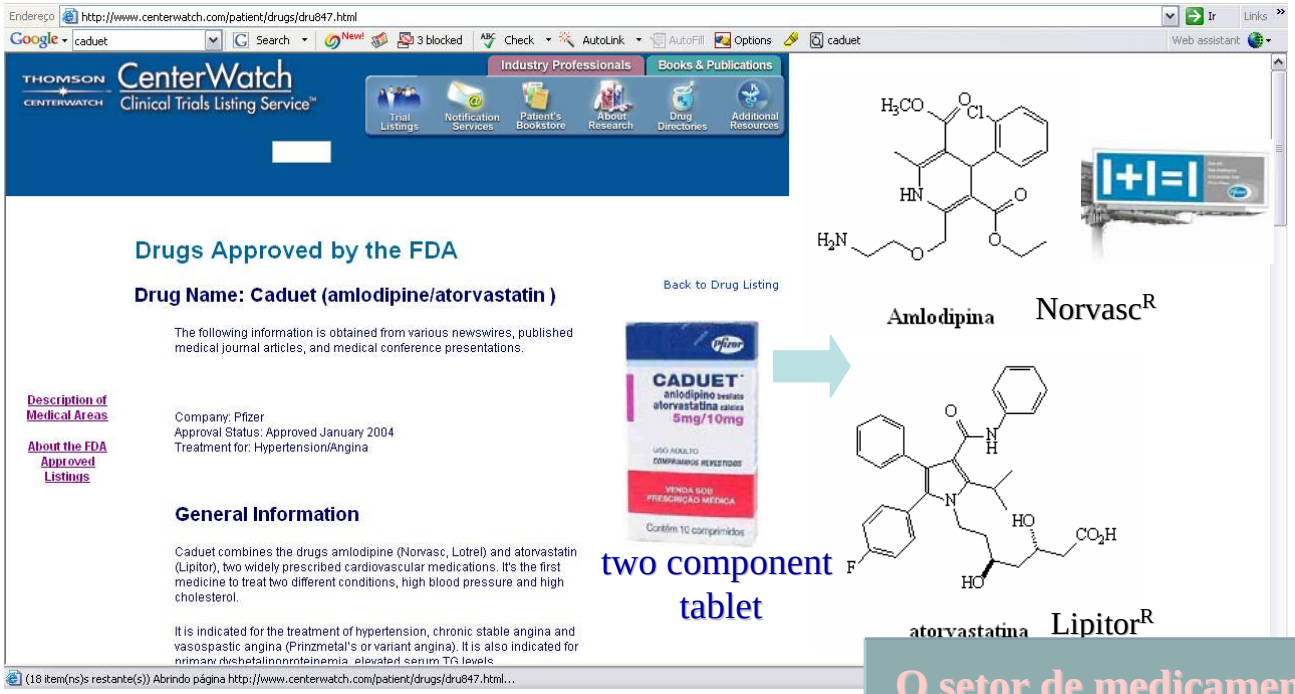
"Therapeutic regimens that comprise more than one active ingredient are commonly used in clinical. Despite this, most drug discovery efforts search for drugs that are composed of a single chemical entity."

C.T. Keith, A.A. Borisy, B.R. Stockwell, Multicomponent therapeutics for networked systems Nature Rev. Drug Discov. 2005, **4**, 1

Multi-target therapeutics

Examples of combination-drug products or candidates

Trade name	Indication	Compound 1	Compound 2	Target or mechanism 1	Target or mechanism 2
Drug combinations					
Vytorin®	Hyperlipidemia	Ezetimibe	Simvastatin	Dietary cholesterol	HMG-CoA reductase
Caduet®	CHD	Amlodipine	Atorvasatin	Calcium-channel antagonist	HMG-CoA reductase
Lotrel®	Hypertension	Amlodipine	Benezapril	Calcium-channel antagonist	ACE inhibitor
Glucovance®	T2DM	Metformin	Glyburide	Gluconeogenesis	Insulin secretagogue
Avandamet®	T2DM	Metformin	Rosiglitasone	Gluconeogenesis	PPARγ agonist
Truvada®	Antiviral (HIV)	Emtricitabine	Tenofovir	RT inhibitor	RT inhibitor
Kaletra®	Antiviral (HIV)	Lopinavir	Ritonavir	Protease inhibitor	Protease inhibitor
Rebetron®	Antiviral (Hepatitis C)	PEG–interferon	Ribavirin	Interferon-α2B	Antimetabolite
Bactrim®	Antibacterial	Trimethoprim	Sulfamethoxazole	DHFR	DHPS
Advair®	Asthma	Fluticasone	Salmeterol	Glucocorticoid receptor	β2-Adrenergic



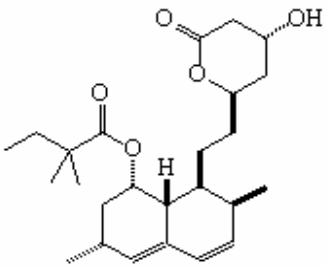
W. H. Frishman & A. L. Zuckerman, *Expert Rev. Cardio*

O setor de medicamentos cardiovasculares movimentou em 2005 *ca.* US$ 72 bilhões

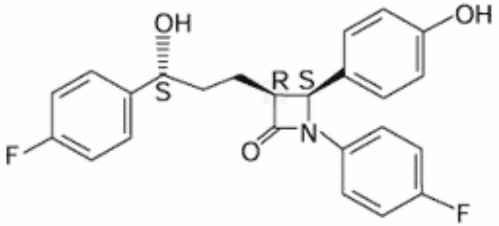
VYTORIN (ezetimibe/simvastatin)

Merck/Schering-Plough

two component tablet



simvastatina
Zocor®



ezetimibe
Zetia®

N. A. Flores, *Curr. Opin. Invest. Drugs* **2004**, *5*, 984

Multi-target therapeutics

Examples of combination-drug products or candidates

Trade name	Indication	Compound 1	Compound 2	Target or mechanism 1	
Drug combinations					
Vytorin®	Hyperlipidemia	Ezetimibe	Simvastatin	Dietary cholesterol	
Caduet®	CHD	Amlodipine	Atorvasatin	Calcium-channel antagonist	
Lotrel®	Hypertension	Amlodipine	Benezapril	Calcium-channel antagonist	
Glucovance®	T2DM	Metformin	Glyburide	Gluconeogenesis	
Avandamet®	T2DM	Metformin	Rosiglitasone	Gluconeogenesis	
Truvada®	Antiviral (HIV)	Emtricitabine	Tenofovir	RT inhibitor	
Kaletra®	Antiviral (HIV)	Lopinavir	Ritonavir	Protease inhibitor	
Rebetron®	Antiviral (Hepatitis C)	PEG–interferon	Ribavirin	Interferon-α2B	
Bactrim®	Antibacterial	Trimethoprim	Sulfamethoxazole	DHFR	
Advair®	Asthma	Fluticasone	Salmeterol	Glucocorticoid receptor	
Multi-target drugs					
Cymbalta®	Depression	Duloxetine	NA	SRI	NRI
Sutent®	Cancer	Sunitinib	NA	PDGFR	VEGFR
Nexavar®	Cancer	Sorafenib	NA	BRAF	VEGFR
Sprycel®	Cancer	Dasatinib	NA	BCR–ABL	SRC
Tykerb®	Cancer	Lapatinib	NA	EGFR (ErbB1)	HER-2 (ErbB2)

multi-alvos

1 cápsula
1 única EQ

Abbreviations. HMG-CoA reductase, hydroxymethylglutaryl-coenzyme A reductase; CHD, coronary heart disease; ACE, angiotensin-converting enzyme; T2DM, type 2 diabetes mellitus; PPAR, peroxisome proliferative activated receptor; RT, reverse transcriptase; DHFR, dihydrofolate reductase; DHPS, dihydropteroate synthase; SRI, serotonin reuptake inhibitor; NRI, norepinephrine reuptake inhibitor; VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; BCR–ABL, breakpoint cluster region–abelson kinase; SRC, sarcoma virus kinase; EGFR, epidermal growth factor receptor; PEG, polyethylene glycol; BRAF, v-raf murine sarcoma viral oncogene homolog B1; HER-2, human epidermal growtgh factor receptor 2; NA, not applicable.

Journal of
Medicinal
Chemistry

Volume 48, Number 21

October 20, 2005

Perspective

Designed Multiple Ligands. An Emerging Drug Discovery Paradigm

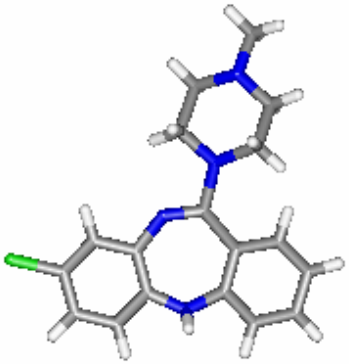
Richard Morphy* and Zoran Rankovic

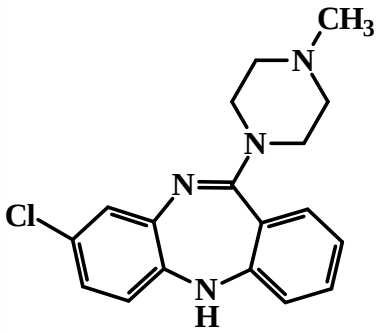
Medicinal Chemistry Department, Organon Laboratories, Newhouse, Lanarkshire, ML1 5SH, U.K.

Received May 3, 2005

•*Antagonistas duplos serotonina–dopamina*

(antipsicóticos)

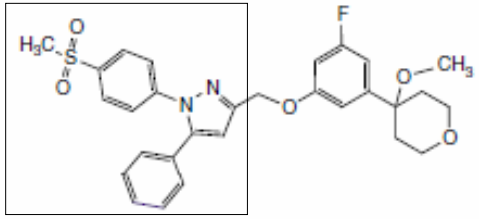




Clozapine

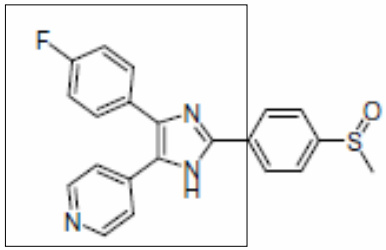
• *Abordagem dos farmacóforos integrados*

(rational design of multiple-action (DM) ligands)



IC_{50} = 50 nM (COX-2)
IC_{50} = 3 nM (5-LOX)
IC_{50} >10 μM (COX-1)

Drug Discovery Today



SB203580

TNF-α IC_{50} = 72 nM
p38 kinase IC_{50} = 136 nM

Imidazole-based pro-inflammatory cytokine inhibitor.

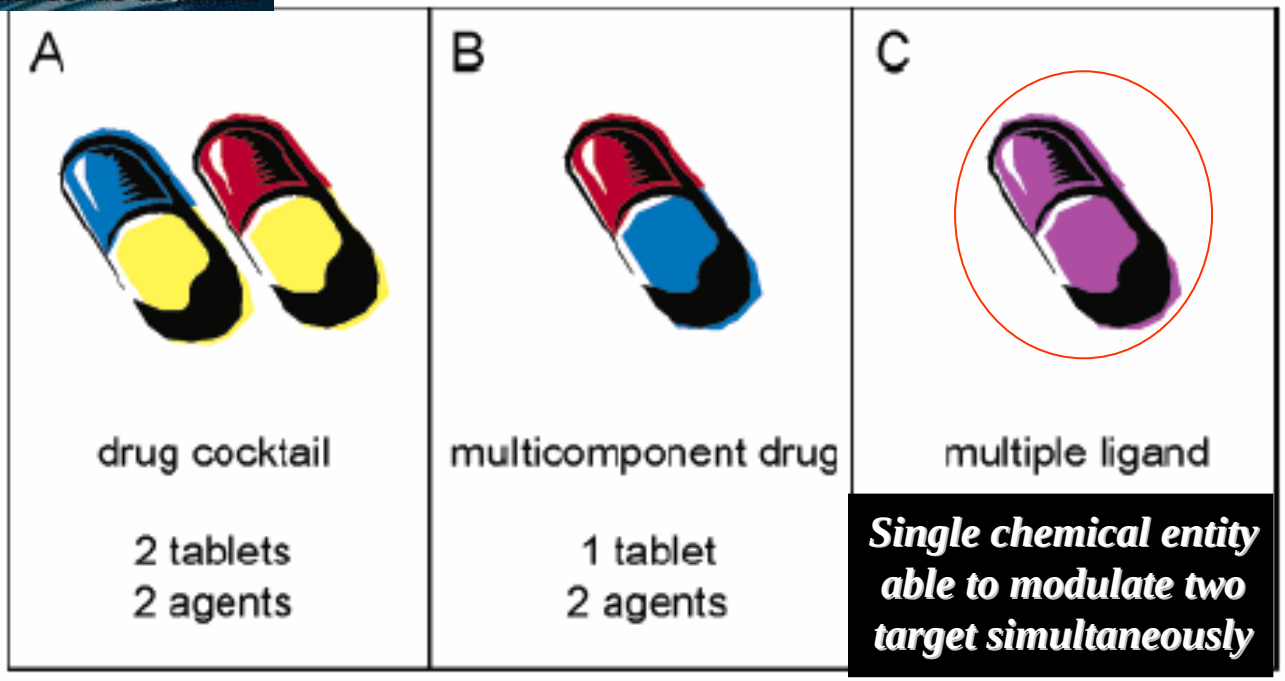
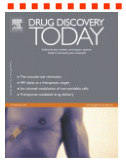


Figure 1. Three main clinical scenarios for multitarget therapy.

B: "...*there are significant risks involved in the development of multicomponent drugs*..."

C: "... **there has been growing interest in the (..) rational design of ligands acting specifically on multiple targets**..." *Morphy & Rankovic, J. Med. Chem. 2005*, **48**, 6523



Inter-alia: G. Glass, "*Cardiovascular combinations*" *Nat. Rev. Drug Discovery* **2004**, *3*, 731; R. Morphy, C. Kay, Z. Rankovic, "*From magic bullets to designed multiple ligands*" *Drug Discovery Today* **2004**, *9*, 641.

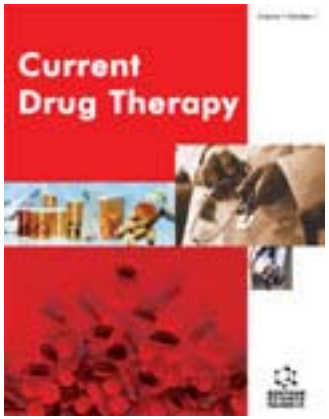
New Insights for Multifactorial Disease Therapy: The Challenge of the Symbiotic Drugs

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.

Abstract: Some physiopathological processes involved in the genesis of diseases could suggest the necessity of designing bioligands or prototypes that aggregate, in only one molecule, dual pharmacodynamical properties, becoming able to be recognized by two elected bioreceptors. This approach can have distinct aspects and, when a novel ligand or a prototype acts in two elected targets belonging to the same biochemical pathway, *e.g.* arachidonic acid cascade, it receives the denomination of dual or mix agent. On the other hand, if these two targets belong to distinct biochemical routes and both are related to the same disease, we can characterize the agents able to modulate it as symbiotic ligands or prototypes. In the present work, we provide some examples and applications of the molecular hybridization concept for the structural design of new symbiotic ligands and prototypes, especially those applied in the treatment of chronic-degenerative disorders.

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



Journal of Medicinal Chemistry

Volume 51, Number 3 February 14, 2008

Perspective

Multi-target-Directed Ligands To Combat Neurodegenerative Diseases

Andrea Cavalli,* Maria Laura Bolognesi,* Anna Minarini, Michela Rosini, Vincenzo Tumiatti, Maurizio Recanatini, and Carlo Melchiorre*

Department of Pharmaceutical Sciences, Alma Mater Studiorum, University of Bologna, Via Belmeloro 6, 40126 Bologna, Italy

Received July 31, 2007

•Fármacos simbióticos

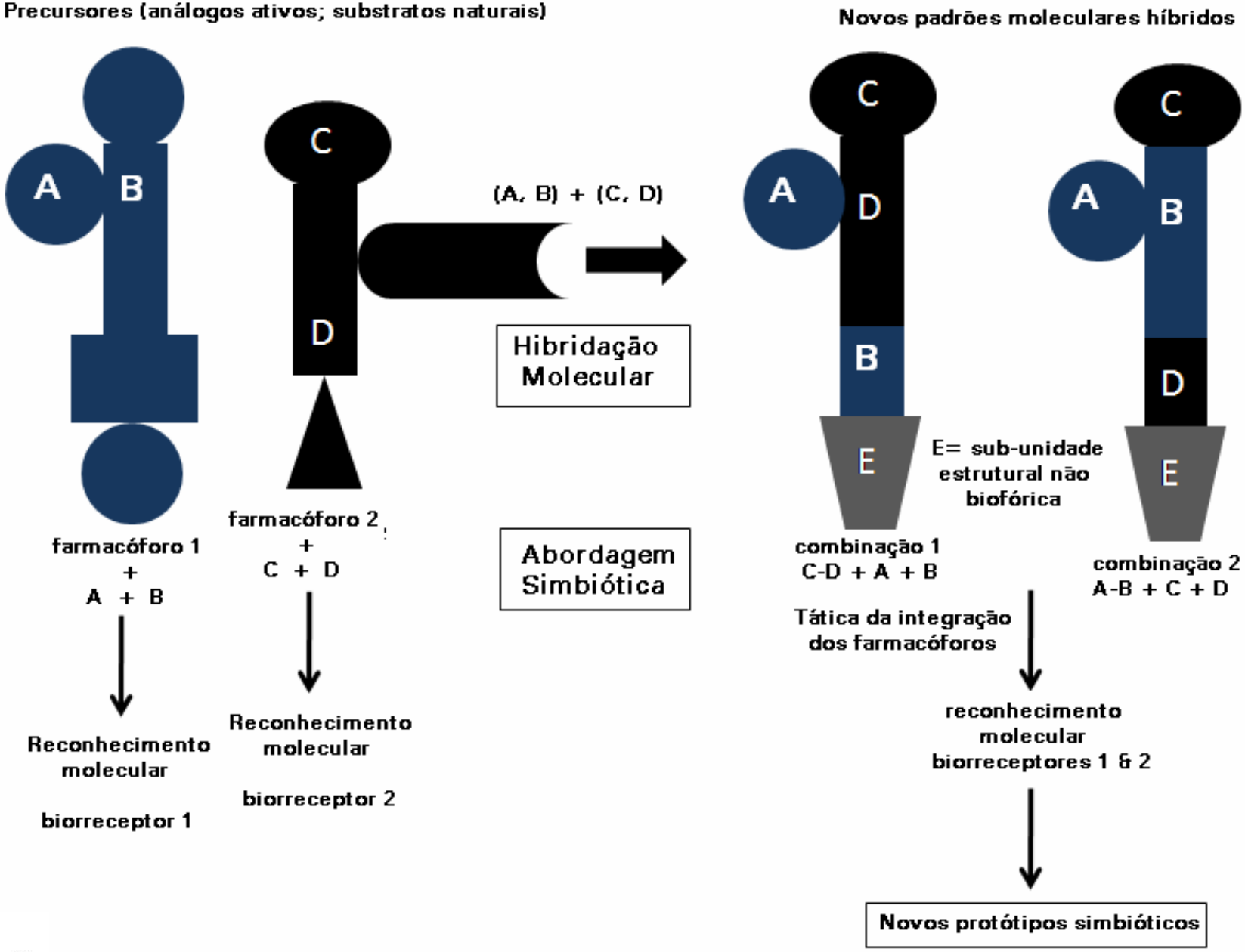
novos compostos-protótipos com afinidade (SAfiR) relativa próxima capazes de serem reconhecidos molecularmente por dois alvos-terapêuticos distintos de diferentes cascatas bioquímicas, envolvidos na mesma fisiopatologia.

Symbiotic approach to new lead-candidates

(***Multi-target-based new lead-candidates discovery***)

*a new compound able to be effective in **two** different target, both relevant to disease but belonging to distinct biochemical pathway;*

COX-2/CA	RTi/integrase	TACE-MMP's
J. Med. Chem. **2004**, *47*, 550	*J. Med. Chem.* **2007**, *50*, 3416	*J. Med. Chem.* **2002**, *45*, 2289



UFRJ
Universidade Federal do Rio de Janeiro

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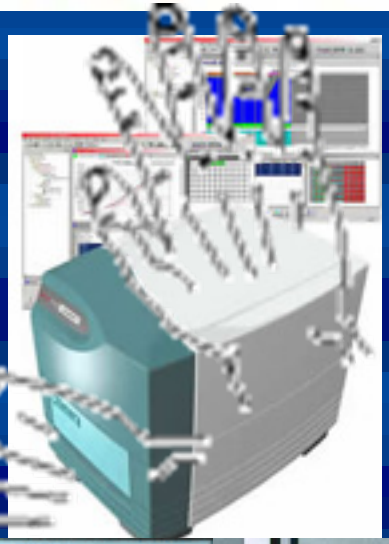
Química Medicinal

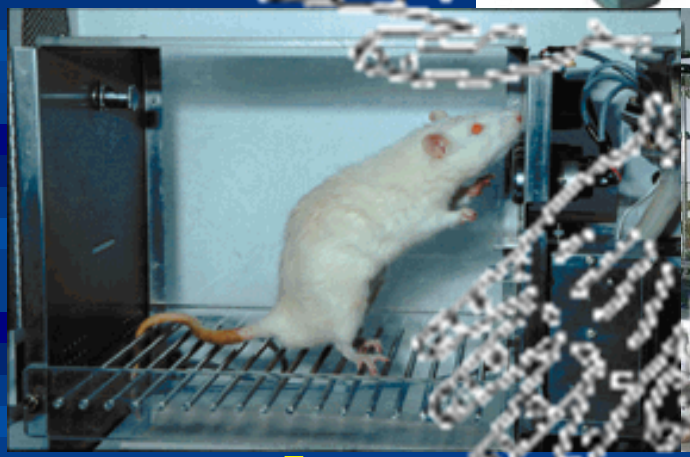
LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas



Bioinformática

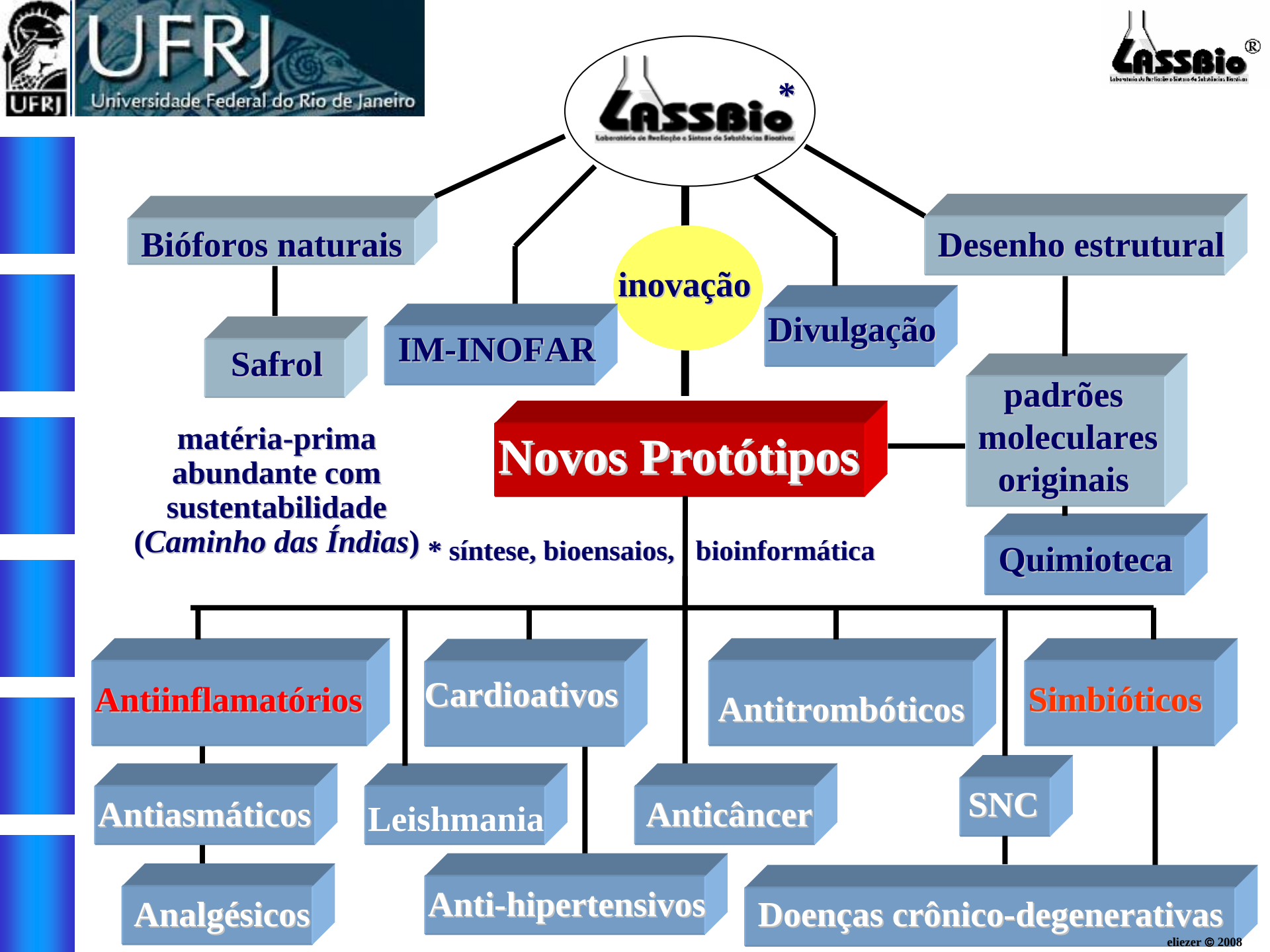
Química

Bioensaios



Biologia

Síntese Orgânica Medicinal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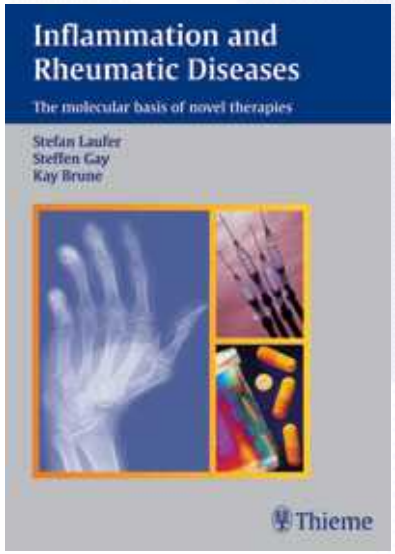
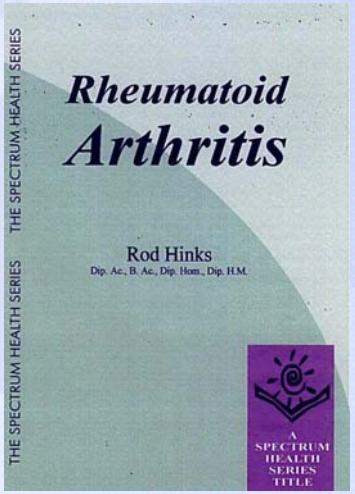
Safrol
IM-INOFAR
inovação
Divulgação
Desenho estrutural
padrões moleculares originais
Quimioteca
matéria-prima abundante com sustentabilidade (Caminho das Índias)
Novos Protótipos
* síntese, bioensaios, bioinformática
Antiinflamatórios
Antiasmáticos
Analgésicos
Cardioativos
Leishmania
Anti-hipertensivos
Antitrombóticos
Anticâncer
Simbióticos
SNC
Doenças crônico-degenerativas
eliezer © 2008

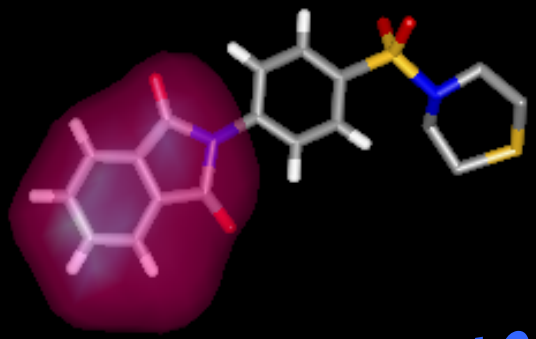
Novas Abordagens Terapêuticas para o Tratamento da Inflamação





Inovação terapêutica

Novo protótipo de fármaco antiinflamatório simbiótico



$C_{18}H_{16}N_2O_4S_2$
388.45

LASSBio-468

Agentes simbióticos

Bioorganic & Medicinal Chemistry 10 (2002) 3067–3073

BIOORGANIC & MEDICINAL CHEMISTRY

Synthesis and Anti-Inflammatory Activity of Phthalimide Derivatives, Designed as New Thalidomide Analogues

Lídia M. Lima,[a,b] Paulo Castro,[c] Alexandre L. Machado,[c] Carlos Alberto M. Fraga,[a,b] Claire Lugnier,[d] Vera Lúcia Gonçalves de Moraes[c] and Eliezer J. Barreiro[a,b,*]

[a]*Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio, http://www.farmacia.ufrj.br/lassbio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, Brazil*

[b]*Instituto de Química, Universidade Federal do Rio de Janeiro, Brazil*

[c]*Departamento de Bioquímica Médica, Universidade Federal do Rio de Janeiro, Brazil*

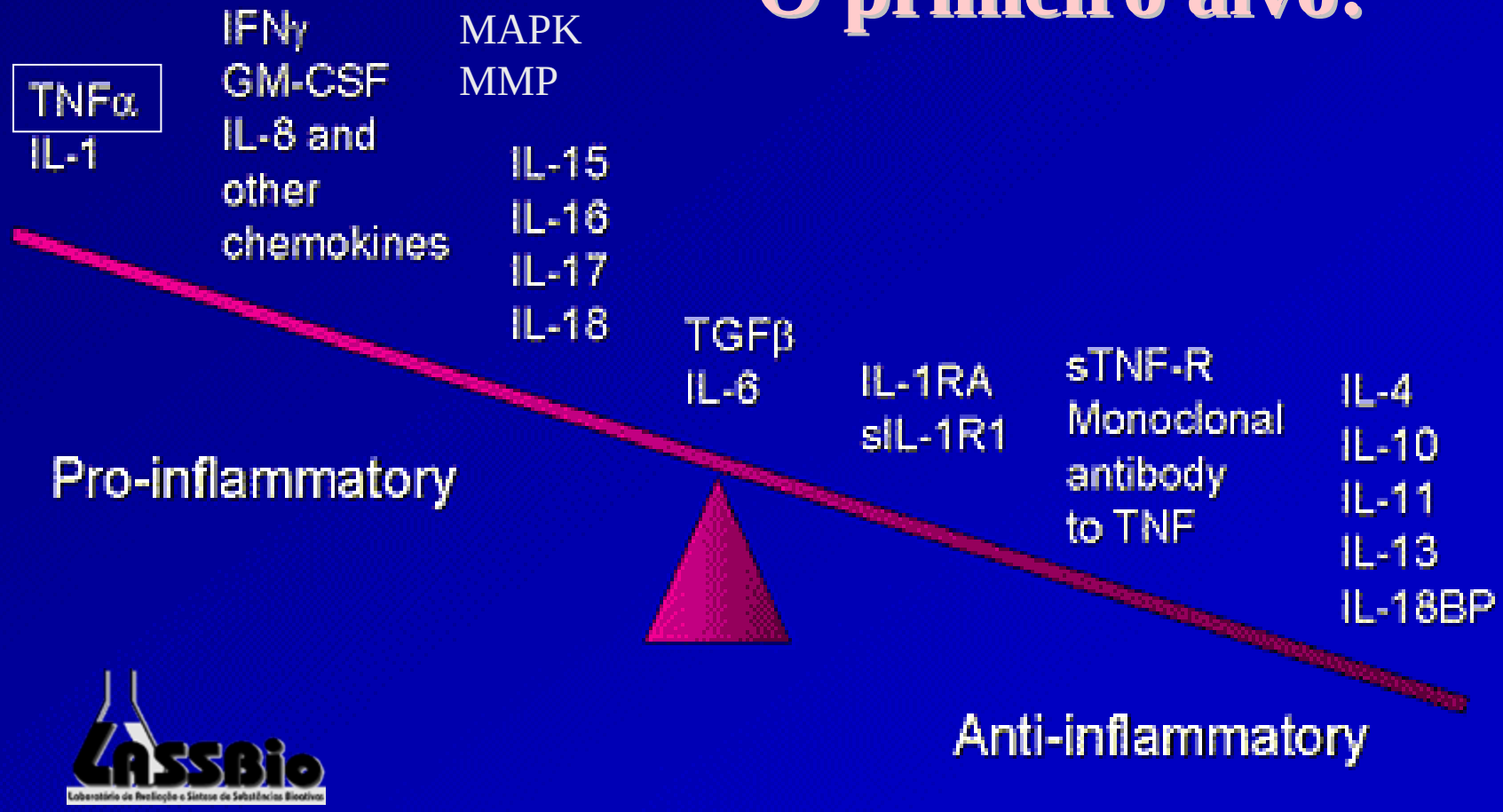
[d]*CNRS URA 600, IllKirch, France*

Received 3 December 2001; accepted 16 January 2002

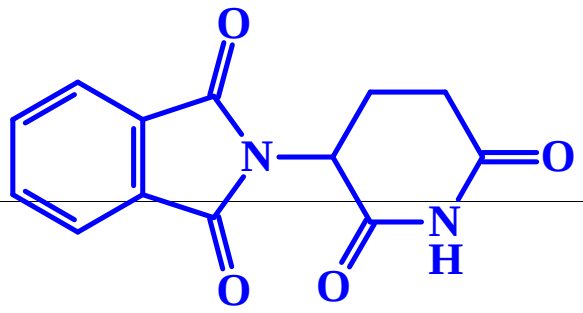
Abstract—This paper describes the synthesis and anti-inflammatory activity of new *N*-phenyl-phthalimide sulfonamides (**3a–e**) and the isosters *N*-phenyl-phthalimide amides (**4a–e**), designed as hybrids of thalidomide (**1**) and aryl sulfonamide phosphodiesterase inhibitor (**2**). In these series, compound **3e** (LASSBio 468), having a sulfonyl-thiomorpholine moiety, showed potent inhibitory activity on LPS-induced neutrophil recruitment with $ED_{50} = 2.5\,mg\,kg^{-1}$, which was correlated with its inhibitory effect on TNF-α level.

Role of Cytokines and Cytokine Inhibitors in Chronic Inflammation

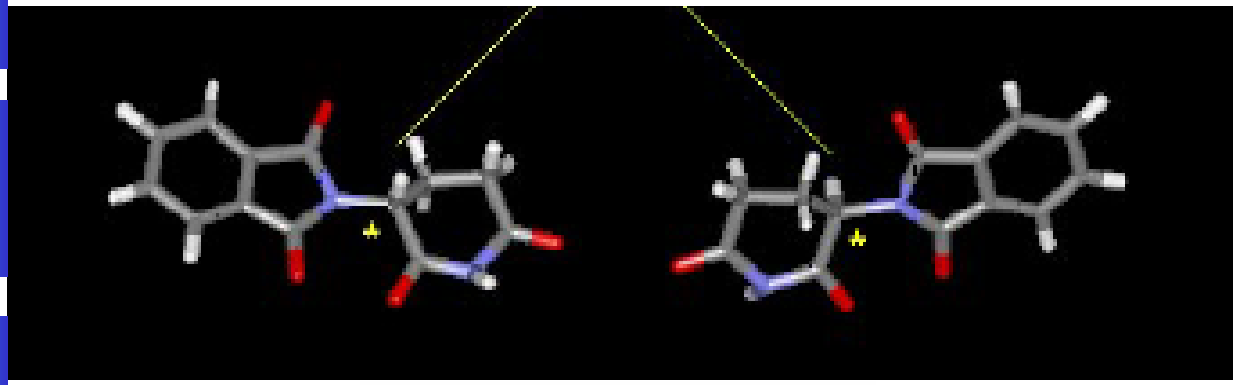
O primeiro alvo:



Arend. *Arthritis Rheum* 2001.



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



THALIDOMIDE

TNF-α IC_{50} = 200 μM

Thalomid^{R}, Phase III, Celgene

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

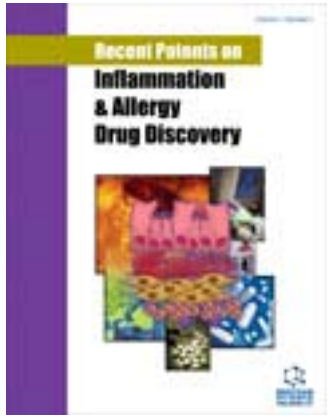
L.M. Lima et al., O Renascimento de um Fármaco: Talidomida, Quim. Nova **2001, 24, 683; (www.scielo.br);** ***E.P. Sampaio, D.S. Carvalho, J.A.C. Nery, U.G. Lopes, E.N. Sarno,"Thalidomide: An Overview of its Pharmacological Mechanisms of Action"Anti-inflammatory & &anti-alergy Agents in Medicinal Chemistry 2006, 5, 71; L.M. Lima, C.A.M. Fraga, V.L.G. Koatz, E.J. Barreiro, "Thalidomide and Analogs as Anti-inflammatory and Immunomodulator Drug Candidates", Anti-inflammatory & &anti-alergy Agents in Medicinal Chemistry 2006, 5,79.***

Thalidomide and Analogs as Anti-Inflammatory and Immunomodulator Drug Candidates

Lídia Moreira Lima[1], Carlos Alberto Manssour Fraga[1], Vera Lucia Gonçalves Koatz[2], and Eliezer J. Barreiro[1,*]

[1]*Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), CP 68.006, 21944-190, Rio de Janeiro, RJ, Brazil), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, RJ, Brazil;* [2]*Instituto de Bioquímica Médica, Universidade Federal do Rio de Janeiro, RJ, Brazil.*

Abstract: Thalidomide ([2-(2,6-dioxo-hexahydro-3-(*R,S*)-pyridinyl)-1,3-isoindolinedione]), well known by its teratogenic effect, caused birth defects in up to 12,000 children in the 1960s. More recently, this drug was approved by the US Food and Drug Administration for the treatment of erythema nodosum leprosum, under restricted-use program, and a variety of new possible therapeutic applications have been described. This article will accomplish a review of medicinal chemistry aspects of thalidomide and state of the art in the development of new anti-inflammatory and immunomodulator drug candidates designed using thalidomide as lead-compound.



Biofármacos Anti-TNF-α

*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

JD Gale, KF McClure, N Pullen, *Annu.Rept. Med. Chem*. 2003, **38**, 141;
B Bain, M Brazil, *Nature Rev. Drug Disc*. 2003, **2**, 693;

* Terapias com biofármacos injetáveis.

DMARD (*disease-modifying antirheumatic drug*)

methotrexate, sulfasalazine (Azulfidine^{R}), leflunomide (Arava^{R}), cyclosporine (Neoral^{R}), chlorambucyl (Leukeran^{R}), penicilamine (Cuprimine^{R}), hidroxychloroquine, Gold salt, azathioprine (Imuran^{R})

anti-tumor necrosis factor (TNF) drugs:

etanercept (Enbrel^{R}), infliximab (Remicade^{R}), adalimunab (Humira^{R}) tocilizumab [Actemra^{R}]

methotrexate + sulfasalazine + hydrochloroquine

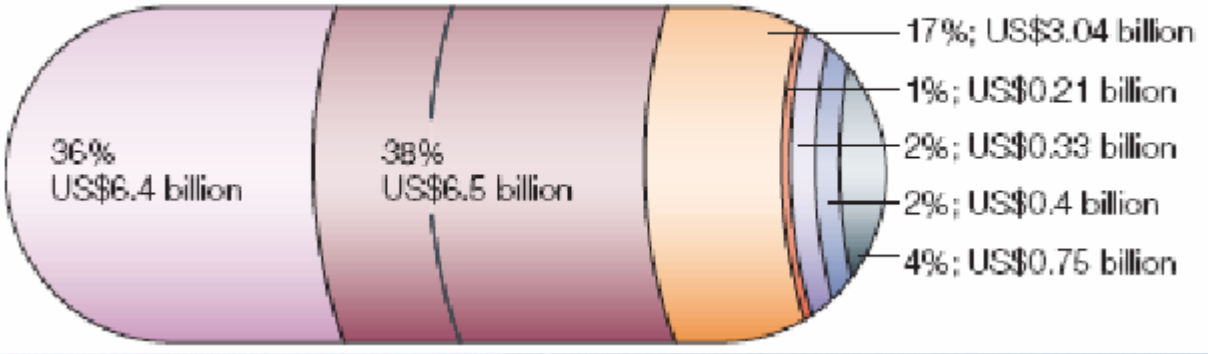
R$4.599,00*

R$6.924,00*

R$3.587,00*

* Consulta em 12/08/2007: http://www.consultaremedios.com.br/

2004 Worldwide sales of arthritis drugs



- TNF inhibitors
- COX2 inhibitors
- NSAID
- Biologics
- DMARD
- Muscle relaxants
- Other therapies

TNF, tumour-necrosis factor
NSAID, non-steroidal anti-inflammatory drug
DMARD, disease-modifying antirheumatic drug

I Melnikova, *Nature Rev. Drug Discov.* 2005, **4**, 453.

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Bioorganic & Medicinal Chemistry xxx (2006) xxx–xxx

Development of new CoMFA and CoMSIA 3D-QSAR models for anti-inflammatory phthalimide-containing TNFα modulators

Carolina Martins Avila,[a] Nelilma Correia Romeiro,[a] Gilberto M. Sperandio da Silva,[a] Carlos M. R. Sant'Anna,[a,b] Eliezer J. Barreiro[a] and Carlos A. M. Fraga[a,*]

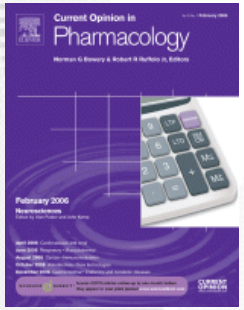
[a]*Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, PO Box 68023, RJ 21944-970, Brazil*
[b]*Departamento de Química, ICE, Universidade Federal Rural do Rio de Janeiro (UFRRJ), Seropédica, RJ 23851-970, Brazil*

Received 8 May 2006; revised 15 June 2006; accepted 19 June 2006

Abstract—In the present study, we describe a new 3D-QSAR analysis of 42 previously reported thalidomide analogues, with the ability to modulate the pro-inflammatory cytokine TNFα, by using comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA). Three statistically significant models were obtained. The best resulting CoMFA and CoMSIA models have conventional r^2 values of 0.996 and 0.983, respectively. The cross-validated q^2 values are 0.869 and 0.868, respectively. The analysis of CoMFA and CoMSIA contour maps provided insight into the possible sites for structural modification of the thalidomide analogues for better activity and reduced toxicity.

What next for rheumatoid arthritis therapy?
Simon M Blake* and Barbara A Swift

Curr Op Pharmacol. 2004, 4, 276



The p38 MAP kinase pathway as a therapeutic target in inflammatory disease
Jeremy Saklatvala

Curr Op Pharmacol. 2004, 4, 372

Phosphodiesterase-4 as a therapeutic target

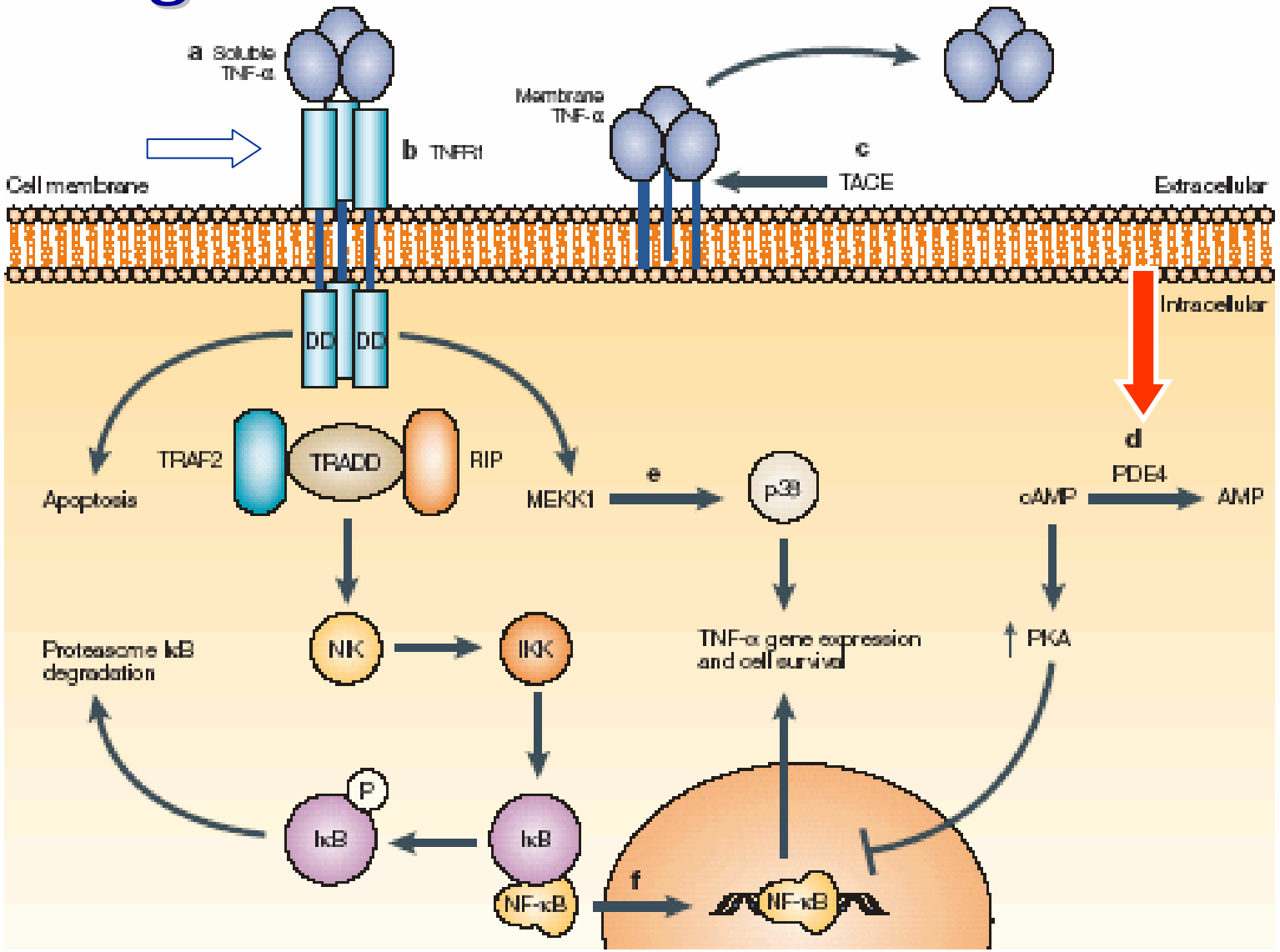
Miles D Houslay, Peter Schafer & Kam Y J Zhang

Drug Discov Today 2005, 10, 1503,

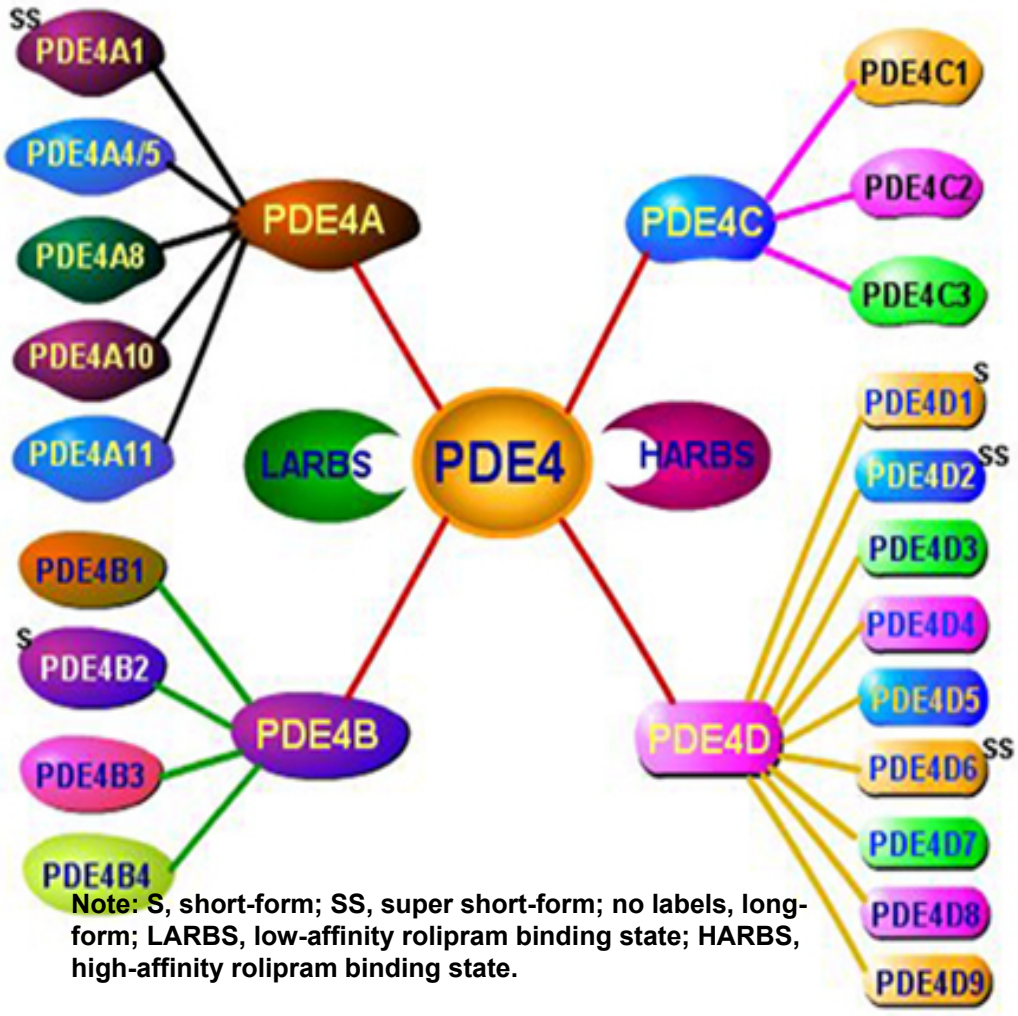
Matrix metalloproteinases in asthma and COPD
Ingel K Demedts, Guy G Brusselle, Ken R Bracke, Karim Y Vermaelen and Romain A Pauwels

Curr Op Pharmacol. 2005, 5, 257

O segundo alvo:



PDE4 subtypes and splice variants



Note: S, short-form; SS, super short-form; no labels, long-form; LARBS, low-affinity rolipram binding state; HARBS, high-affinity rolipram binding state.

The phosphodiesterase 4 (PDE4) is the most important PDE family in the control of intra-cellular cAMP. PDE4 is encoded by four separate genes (PDE4A, 4B, 4C, and 4D). The PDE4 subtypes are differentially distributed in brain regions, indicating that they may exert different CNS activity. Our preliminary studies supported the idea that PDE4D plays a critical role in the mediation of memory. Using gene knockout and gene silencing techniques, we are determining the roles of PDE4D and its splice variants in memory processes and in other aspects of behavior. Hopefully, this will help guide the chemical syntheses of potent, selective inhibitors of individual PDE4 subtypes.

www.hsc.wvu.edu/wvucn/People/Zhang/research.html

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Bioorganic & Medicinal Chemistry xxx (2006) xxx–xxx

Molecular docking study and development of an empirical binding free energy model for phosphodiesterase 4 inhibitors

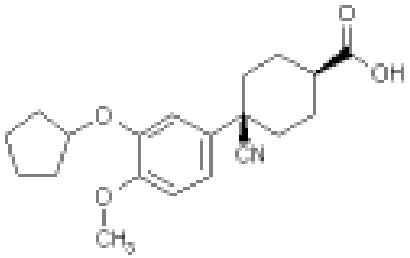
Fernanda G. Oliveira,[a] Carlos M. R. Sant'Anna,[b] Ernesto R. Caffarena,[c] Laurent E. Dardenne[d] and Eliezer J. Barreiro[a,*]

[a]*LASSBio, Laboratório de Avaliação e Síntese de Substâncias Bioativas, Faculdade de Farmácia and Instituto de Química, Universidade Federal do Rio de Janeiro, PO Box 68006, Rio de Janeiro, RJ 21944-910, Brazil*
[b]*Departamento de Química, ICE, Universidade Federal Rural do Rio de Janeiro (UFRRJ), Seropédica, RJ 23851-970, Brazil*
[c]*Programa de Computação Científica—Fundação Oswaldo Cruz (FIOCRUZ/MS)—Manguinhos, RJ 21045-900, Brazil*
[d]*Laboratório Nacional de Computação Científica—LNCC/MCT, Quitandinha, Petrópolis, RJ 25651-075, Brazil*

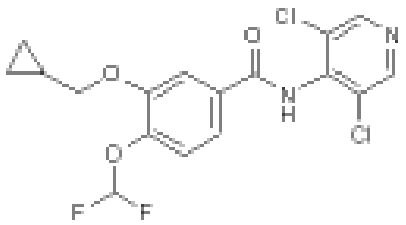
Received 8 November 2005; revised 10 May 2006; accepted 10 May 2006

Abstract—In the present work, several computational methodologies were combined to develop a model for the prediction of PDE4B inhibitors' activity. The adequacy of applying the ligand docking approach, keeping the enzyme rigid, to the study of a series of PDE4 inhibitors was confirmed by a previous molecular dynamics analysis of the complete enzyme. An exhaustive docking procedure was performed to identify the most probable binding modes of the ligands to the enzyme, including the active site metal ions and the surrounding structural water molecules. The enzyme–inhibitor interaction enthalpies, refined by using the semiempirical molecular orbital approach, were combined with calculated solvation free energies and entropy considerations in an empirical free energy model that enabled the calculation of binding free energies that correlated very well with experimentally derived binding free energies. Our results indicate that both the inclusion of the structural water molecules close to the ions in the binding site and the use of a free energy model with a quadratic dependency on the ligand free energy of solvation are important aspects to be considered for molecular docking investigations involving the PDE4 enzyme family.

Ariflo ®

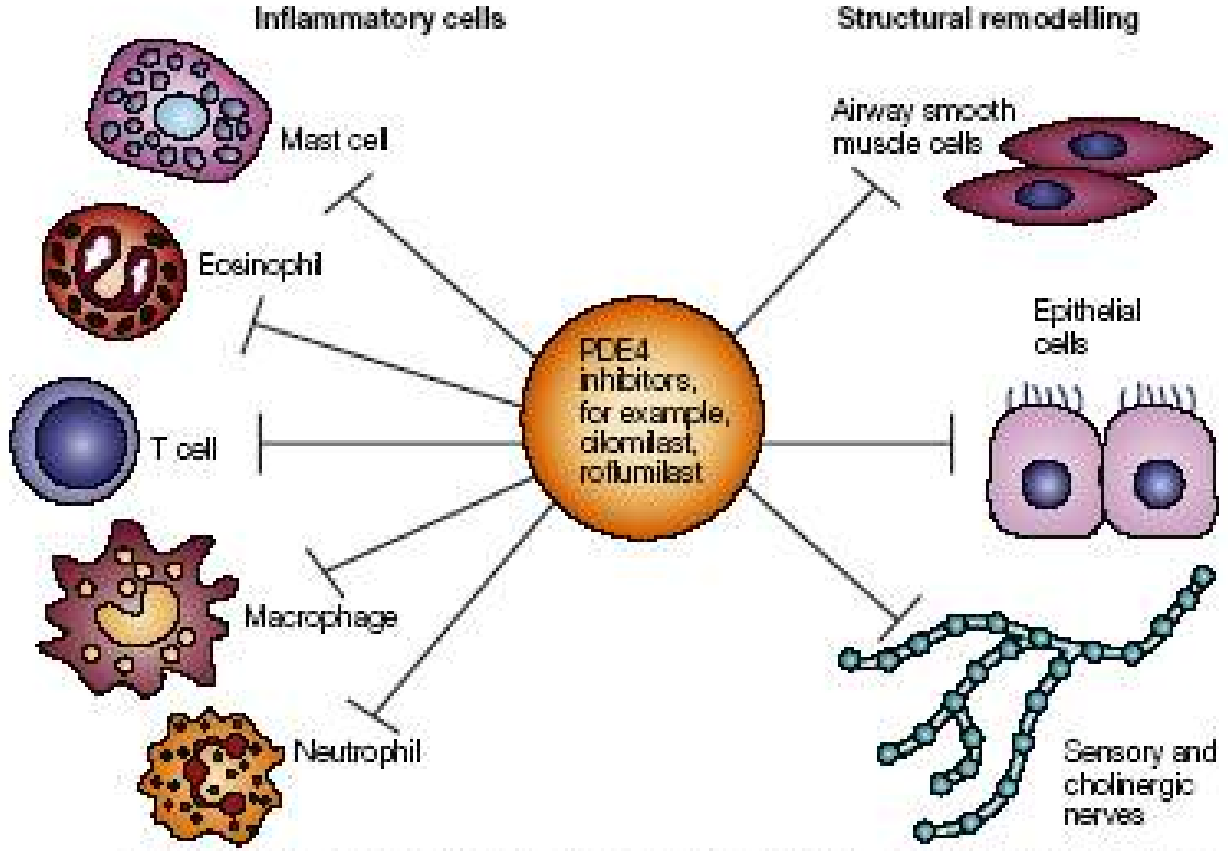


Cilomilast (Ariflo^{R})
GSK



Roflumilast (Daxas^{R})
Altana Pharma AG
& Pfizer Inc

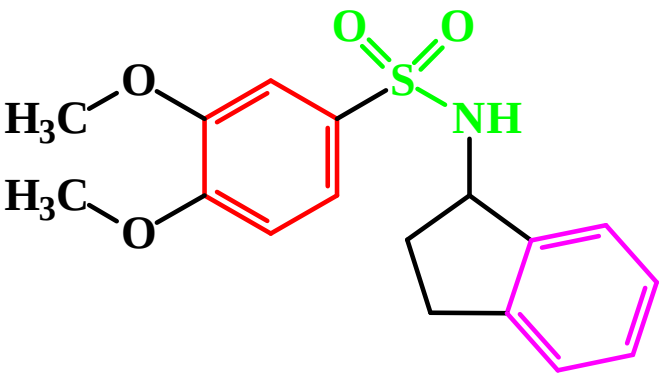
Daxas ®



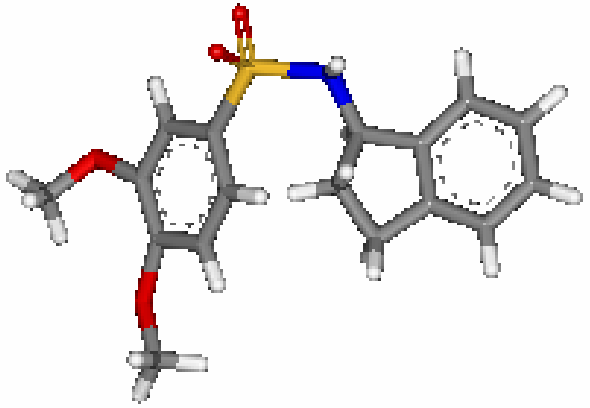
Phosphodiesterase-4 inhibitors have a broad spectrum of anti-inflammatory effects in asthma. Phosphodiesterase-4 (PDE4) inhibitors inhibit the recruitment and activation of key inflammatory cells, including mast cells, eosinophils, T lymphocytes, macrophages and neutrophils, as well as the hyperplasia and hypertrophy of structural cells, including airway smooth-muscle cells, epithelial cells and sensory and cholinergic nerves.

P. J. Barnes, Nature Review Drug Discovery 2004, 3, 931.

Chiroscience Ltd, Cambridge Science Park, Milton Road, Cambridge, UK
(Celltech Chiroscience Ltd)



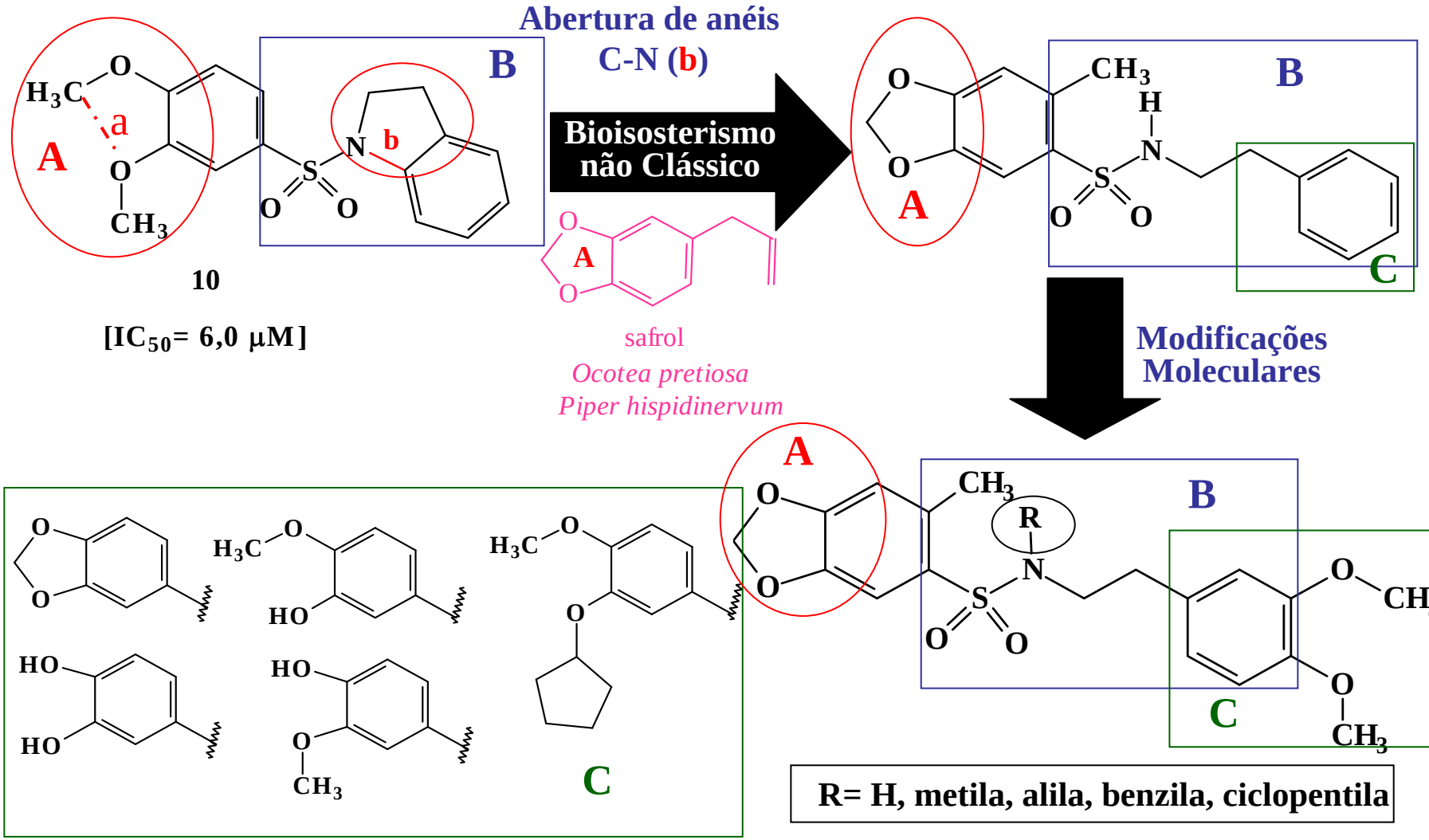
Aril-sulfonamida

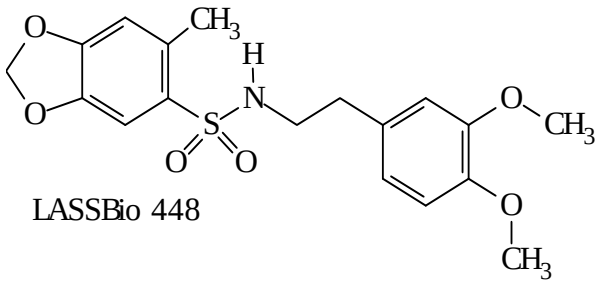


PDE-4i IC_{50} = 4.3 μM

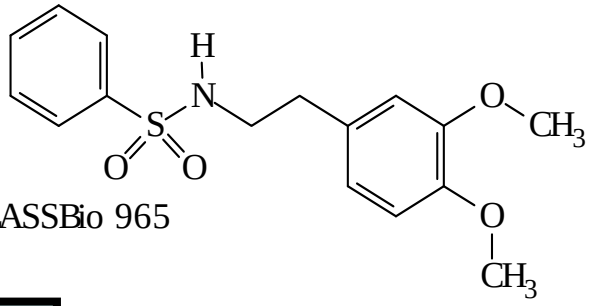
J. G. Montana, G. M. Buckley, N. Cooper, H. J. Dyke, L. Gowers, J. P. Gregory, P. G. Hellewell, H. J. Kendall, C. Lowe, R. Maxey, L. Miotla, R. J. Naylor, K. A. Runcie, B. Tuladhar, J. B. H. Warneck, "Aryl sulfonamides as selective PDE-4 inhibitors" , *Bioorg. Med. Chem. Lett.* 1998, **8**, 2635.

Gênese dos novos candidatos a fármacos antiinflamatórios, planejados como inibidores da PDE-4.



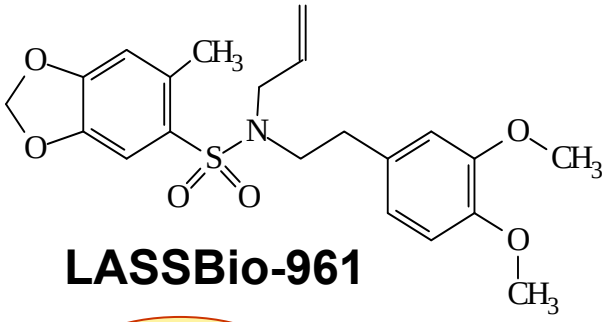


LASSBio 448



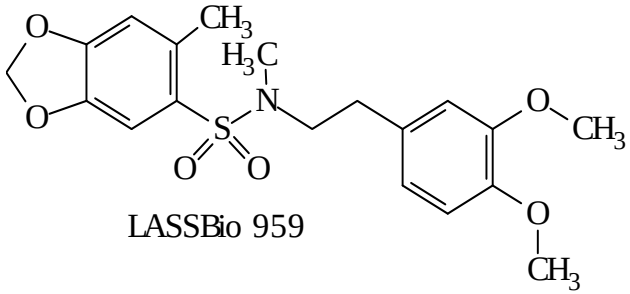
LASSBio 965

PDE-4, IC_{50}, µM



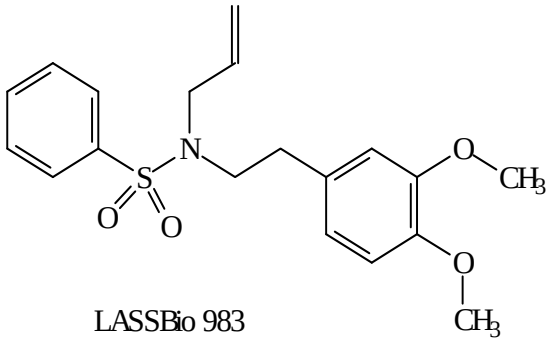
LASSBio-961

2,1 ± 0,6



LASSBio 959

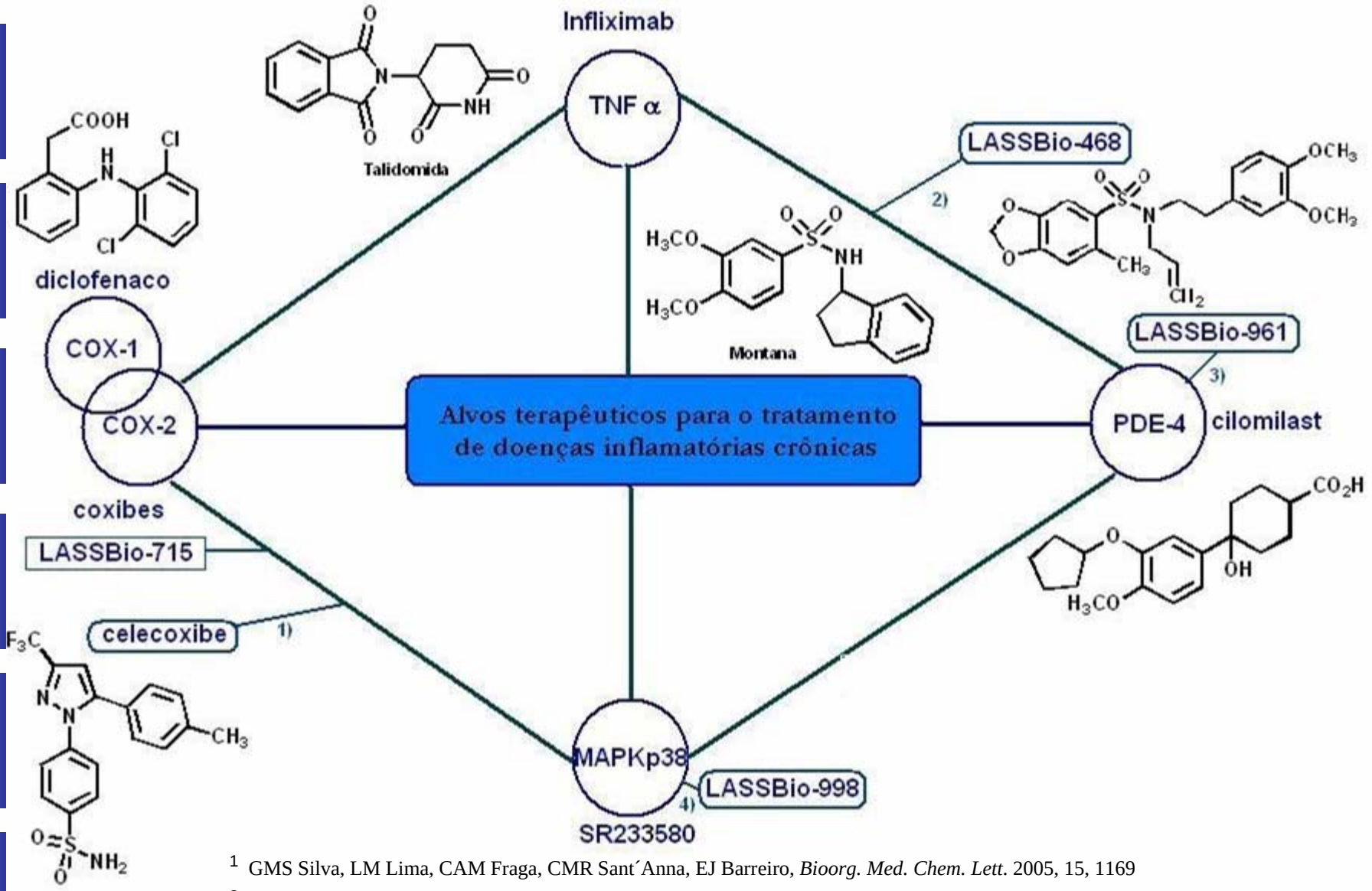
6,7



LASSBio 983

2,4

Dra Claire Lugnier, ULP, CNRS UMR 7175

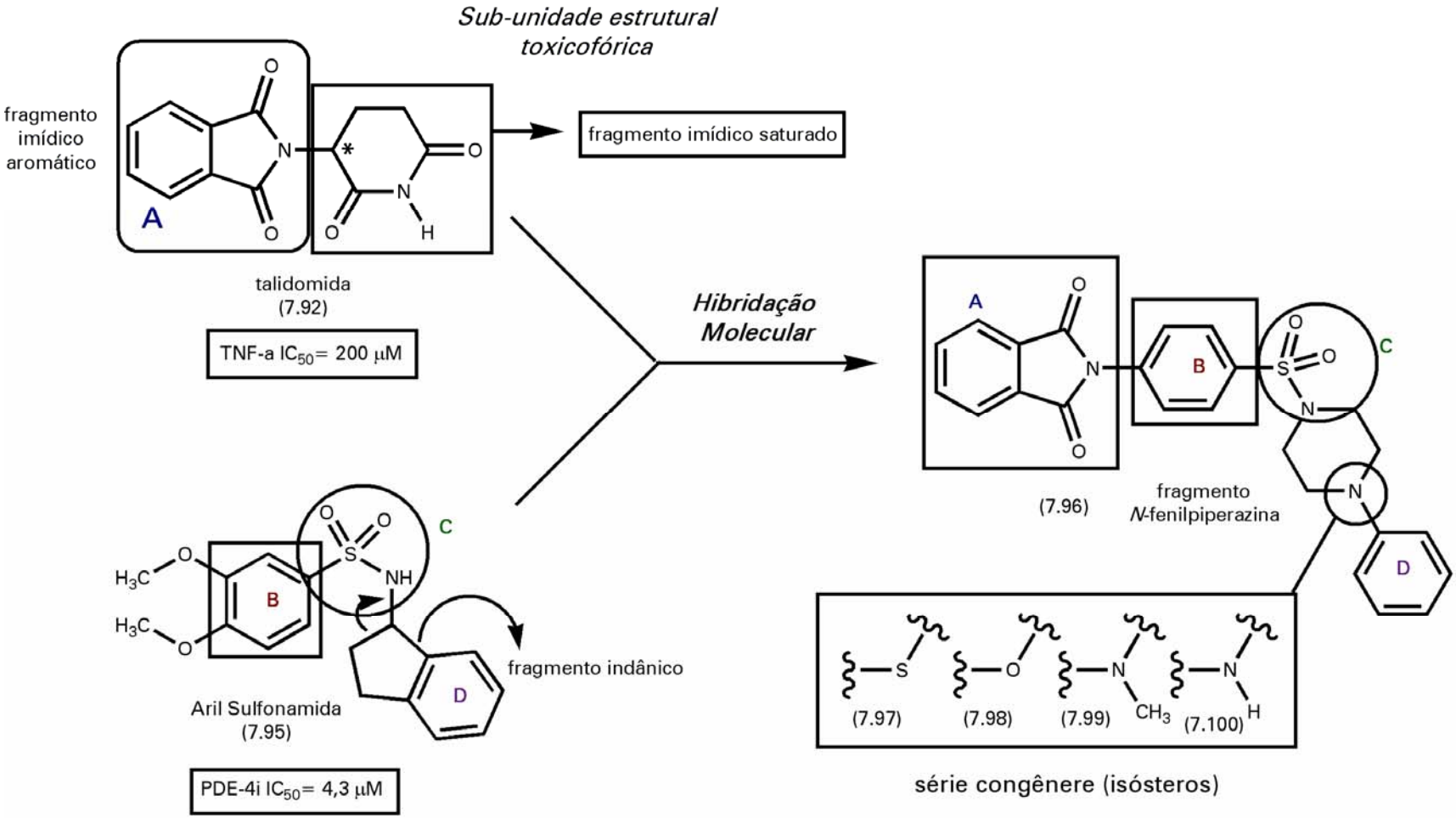


1 GMS Silva, LM Lima, CAM Fraga, CMR Sant´Anna, EJ Barreiro, *Bioorg. Med. Chem. Lett*. 2005, 15, 1169

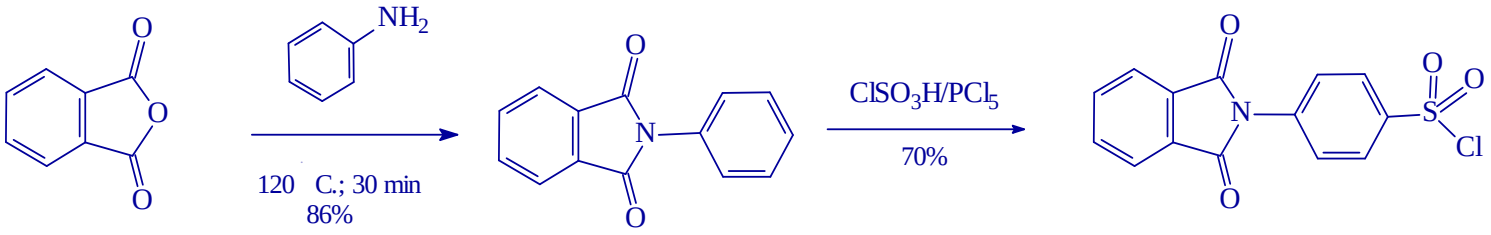
2 LM Lima, P Castro, AL Machado, CAM Fraga, *Bioorg. Med. Chem*. 2002, 10, 3067

3 LM Lima & EJ Barreiro, resultados não publicados

4 BR-0502016-6 03/06/2005



Synthesis of LASSBio-468

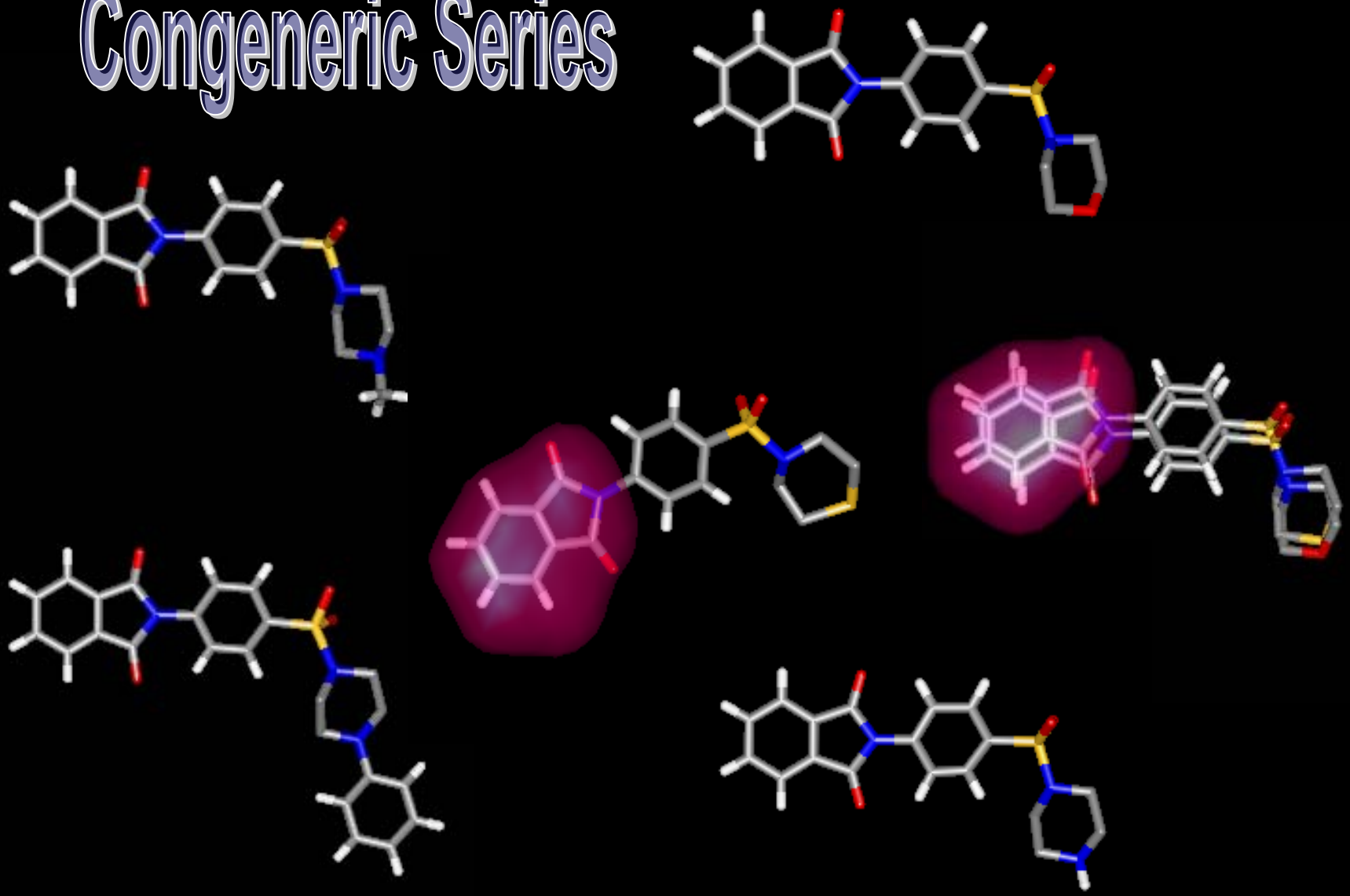


X = NMe 65%
X = NPh 67%
X = NH 58%
X = O 63%
X = S 67%

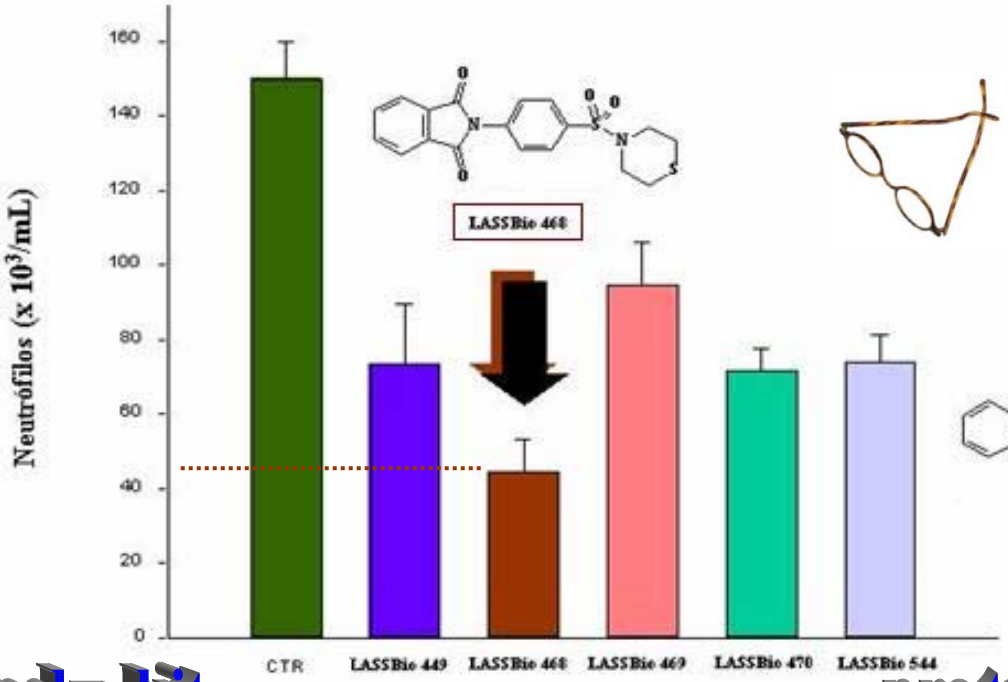
Overall yield: *ca.* 20%
(0.10 M *i.e. ca.* 40g)

Lidia M. Lima,Tese de Doutoramento, IQ-UFRJ, Br., 2001

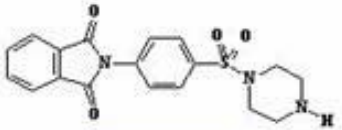
Congeneric Series



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

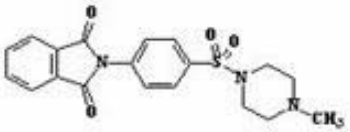


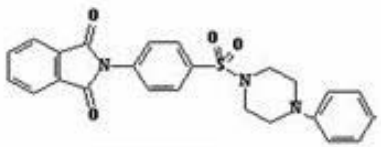
in vivo

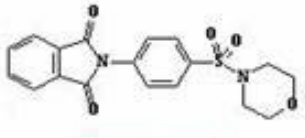


lead >> ligand = hit

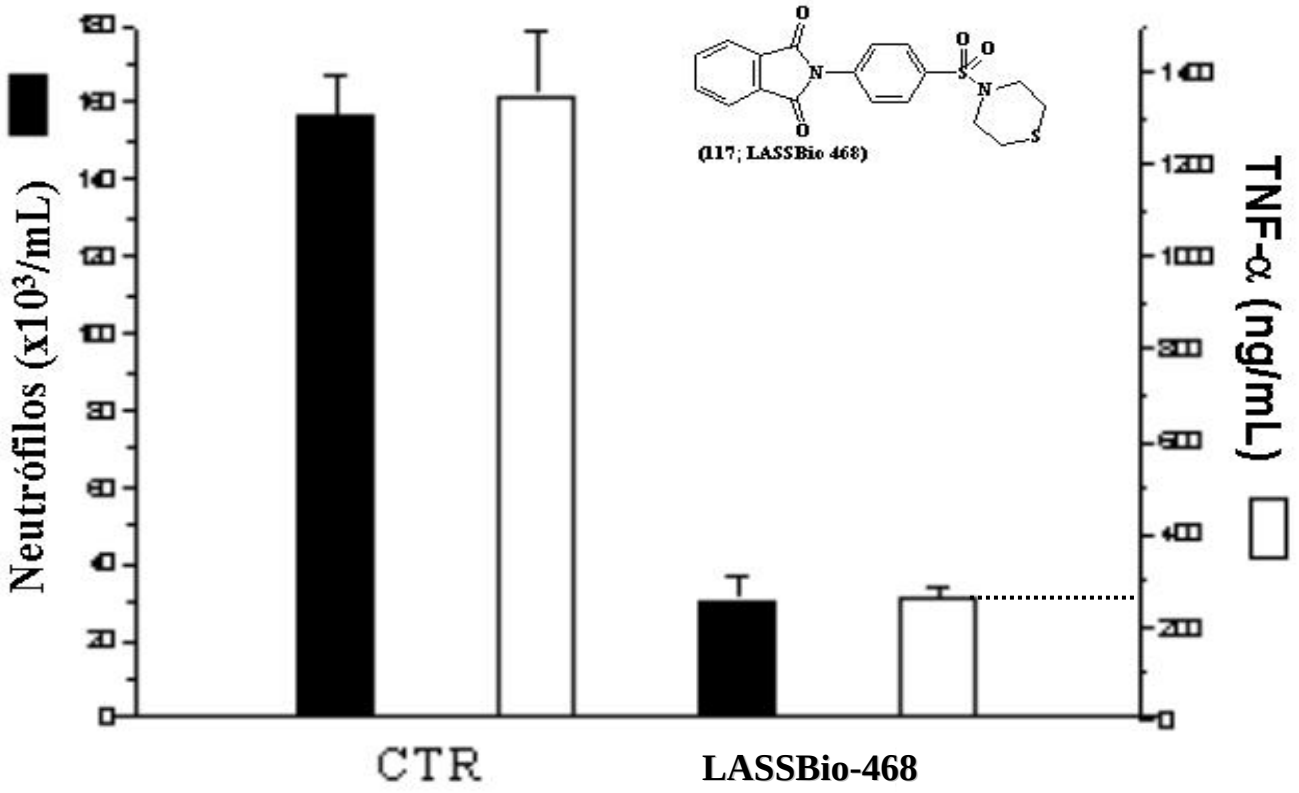
protótipo > ligante







Effect of compound LASSBio 468 on TNF-α levels and neutrophil influx into the BALB/c of mice lungs



50% more active than thalidomide

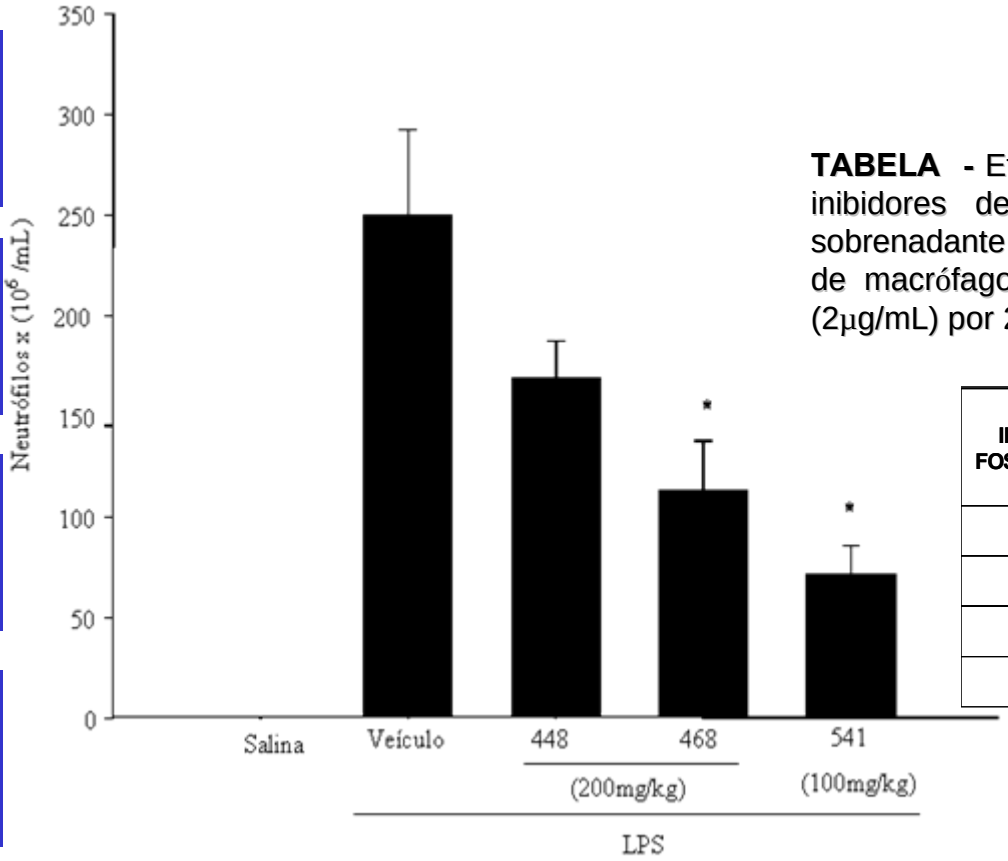
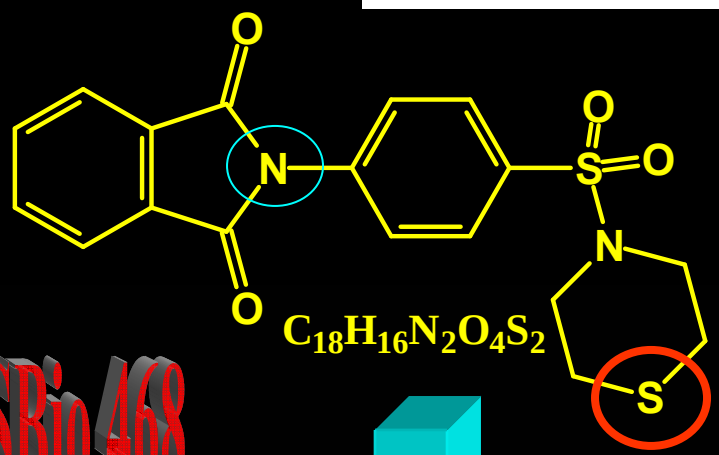


TABELA - Efeito dos compostos LASSBio (100 µM) da família dos inibidores de fosfodiesterase na produção de TNF-α em sobrenadante de células mononucleares de sangue humano (PBL) e de macrófagos alveolares de camundongo estimulados com LPS (2µg/mL) por 2 horas.

COMPOSTOS INIBIDORES DE FOSFODIESTERASE	INIBIÇÃO EM PBL	INIBIÇÃO EM Mϕ ALVEOLAR
Talidomida	54 %	21,4 %
468	41 %	32%
541	36 %	25,3%
448	28 %	Sem Inibição

FIGURA - Tratamento com compostos inibidores de PDE4 reduz o número de neutrófilos no LBA após a inalação de LPS. Os camundongos BALB/c foram pré-tratados com veículo (carboximetilcelulose) ou os compostos por v.o 4 h antes e o LBA foi realizado 3 h após a inalação de aerossóis de uma suspensão de 2mL de LPS (0,5 mg/mL). Os animais controle inalaram salina. Os resultados são expressos como média ± erro padrão da média de 2 a 3 experimentos com 5-7 animais. *p<0,05 em comparação ao grupo LPS

lead compound



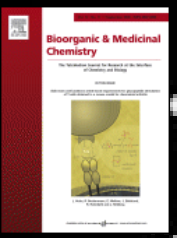
$C_{18}H_{16}N_2O_4S_2$

LASSBio 468

TNF-α ED_{50} 2,5 mg/Kg

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

PDE-4 inibidor



Atividade PDE-4 de foi medida em aorta bovina:

IC_{50} = 62,6μM

(*cf.* PDE-1, 2, 3, > 420 μM; 5)

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

lead compound

Novo agente anti-inflamatório simbiótico

Universidade Federal do Rio de Janeiro

LASSBio-468, é um novo candidato a protótipo de fármaco **AI**, (DMARD) estruturalmente planejado por hibridação molecular, com novo e original padrão molecular, estruturalmente simples, aquiral, desenhado como candidato a **fármaco simbiótico**, útil para o tratamento da **artrite reumatóide** e da **doença de Crohn**, com atividade protetora no **choque séptico** e na resposta granulomatosa em modelo de artrite reumatóide em camundongos, **sem efeito imunossupressor**. Possui **novo mecanismo de ação**, original, inibindo a resposta ao **TNF-α e** a atividade **PDE-4**, como desejado quando de seu planejamento estrutural. **Representa uma autêntica inovação terapêutica.**

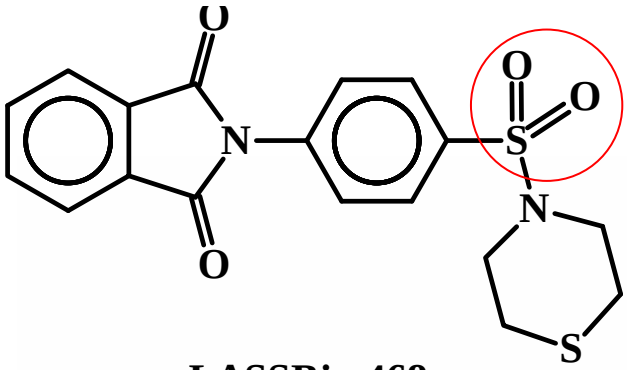
L. M. Lima *et al.*, "**Synthesis and Anti-inflammatory Activity of Phthalimide Derivatives, Designed as New Thalidomide Analogues**", *Bioorg. Med. Chem.* 2002, **10**, 3067

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

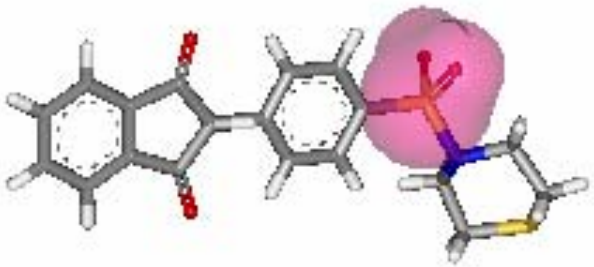
LASSBio-468 Optimization

LEAD COMPOUND

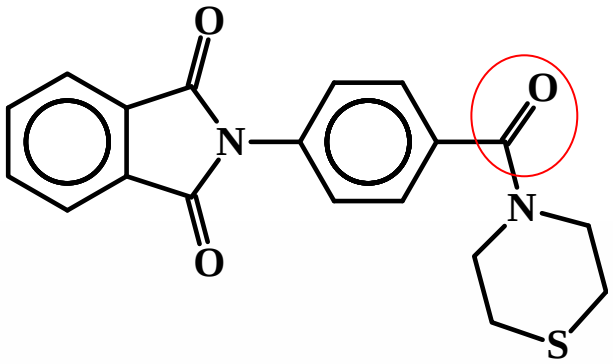
Lead-optimization



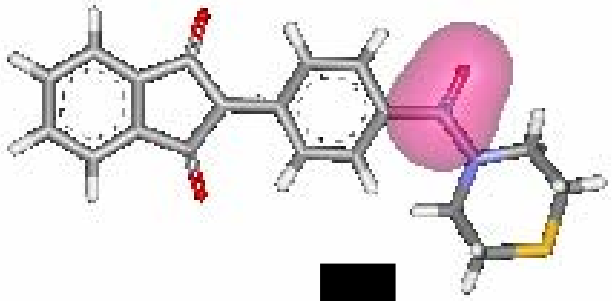
LASSBio-468



Bioisosteres*



LASSBio-595



LASSBio-596

* L. M. Lima & E. J. Barreiro, "Bioisosterism: A Useful Strategy for Molecular Modification and Drug Design", *Curr. Med.Chem.* 2005, **13,** 23; [http://www.bentham.org/cmc/samples/cmc12-1/0002C.pdf]

International Immunopharmacology 5 (2005) 485–494

International
Immunopharmacology

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LASSBio-468: a new achiral thalidomide analogue which modulates TNF-α and NO production and inhibits endotoxic shock and arthritis in an animal model

Magna S. Alexandre-Moreira[a,b], Christina M. Takiya[c], Luciana B. de Arruda[d], Bernardo Pascarelli[c], Raquel N. Gomes[e], Hugo C. Castro Faria Neto[e], Lídia M. Lima[a], Eliezer J. Barreiro[a,*]

[a]*LASSBio-Laboratório de Avaliação e Síntese de Substâncias Bioativas, Departamento de Fármacos, Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, CP 68.006, ZIP 21944-910, Rio de Janeiro, R.J., Brazil*
[b]*Departamento de Fisiologia, Universidade Federal de Alagoas, Al., Brazil*
[c]*Departamento de Histologia e Embriologia ICB, Universidade Federal do Rio de Janeiro, R.J., Brazil*
[d]*Instituto de Microbiologia Prof. Paulo de Góes, Universidade Federal do Rio de Janeiro, R.J., Brazil*
[e]*Departamento de Farmacodinâmica IOC-FIOCRUZ, Rio de Janeiro, Brazil*

Received 19 April 2004; received in revised form 13 May 2004; accepted 20 October 2004

Note: Performing your original search, ***LASSBio-468***, in PubMed will retrieve *2* citations.

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1: Int Immunopharmacol. 2005 Mar;5(3):485-94. Related Articles, Links

ELSEVIER FULL-TEXT ARTICLE

LASSBio-468: a new achiral thalidomide analogue which modulates TNF-alpha and NO production and inhibits endotoxic shock and arthritis in an animal model.

Alexandre-Moreira MS, Takiya CM, de Arruda LB, Pascarelli B, Gomes RN, Castro Faria Neto HC, Lima LM, Barreiro EJ.

LASSBio-Laboratorio de Avaliacao e Sintese de Substancias Bioativas, Departamento de Farmacos, Faculdade de Farmacia, Universidade Federal do Rio de Janeiro, CP 68.006, ZIP 21944-910, Rio de Janeiro, R.J., Brazil.

As part of a program researching the synthesis and immunopharmacological evaluation of novel synthetic compounds, we have described the immune modulatory profile of the new achiral thalidomide analogue LASSBio-468 in the present work. This compound was planned as an N-substituted phthalimide derivate, structurally designed as a hybrid of thalidomide and aryl sulfonamides, which were previously described as tumor necrosis factor-alpha (TNF-alpha) and PDE4 inhibitors. LASSBio-468 was recently demonstrated to inhibit the TNF-alpha production induced by lipopolysaccharide (LPS), in vivo. Here, we investigated whether this compound would affect chronic inflammation processes associated with the production of this pro-inflammatory cytokine. Treatment with LASSBio-468 before a lethal dose injection of LPS in animals greatly inhibited endotoxic shock. This effect seems to be mediated by a specific down regulation of TNF-alpha and nitric oxide production, regulated mainly at the RNA level. In another model, histopathological analysis indicated that this compound also inhibited adjuvant-induced arthritis in rats. Taken together, our data demonstrated a potent anti-inflammatory effect of LASSBio-468, suggesting its use as a potential drug against chronic inflammatory diseases.

PMID: 15683845 [PubMed - indexed for MEDLINE]

Lassbio-468: A New Achiral Thalidomide Analogue Which Modulates Tnf-Alpha And No Production And Inhibits Endotoxic Shock And Arthritis In An Animal Model

As part of a program researching the synthesis and immunopharmacological evaluation of novel synthetic compounds, we have described the immune modulatory profile of the new achiral thalidomide analogue LASSBio-468 in the present work. This compound was planned as an N-substituted phthalimide derivate, structurally designed as a hybrid of thalidomide and aryl sulfonamides, which were previously described as tumor necrosis factor-alpha (TNF-alpha) and PDE4 inhibitors. LASSBio-468 was recently demonstrated to inhibit the TNF-alpha production induced by lipopolysaccharide (LPS), in vivo. Here, we investigated whether this compound would affect chronic inflammation processes associated with the production of this pro-inflammatory cytokine. Treatment with LASSBio-468 before a lethal dose injection of LPS in animals greatly inhibited endotoxic shock. This effect seems to be mediated by a specific down regulation of TNF-alpha and nitric oxide production, regulated mainly at the RNA level. In another model, histopathological analysis indicated that this compound also inhibited adjuvant-induced arthritis in rats. Taken together, our data demonstrated a potent anti-inflammatory effect of LASSBio-468, suggesting its use

PUBLICAÇÕES & PATENTES LASSBio-468

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2. ALEXANDREMOREIRA, Magna S; TAKIYA, Christina M; ARRUDA, Luciana B de; PASCARELLI, Bernardo; GOMES, Raquel N; FARIA NETO, Hugo C Castro; LIMA, L. M.; BARREIRO, E.J. LASSBio-468: a new achiral thalidomide analogue which modulates TNF-alfa and NO production and inhibits endotoxic shock and arthritis in a animal model. ***International immunopharmacology, 5***, 485-494, **2005.**
3. ROCCO, P. R M; LIMA, L. M.; MACHADO, A. L.; GONÇALVES DE MORAES, V. L.; BARREIRO, E. J; ZIN, W. A. The therapeutic potential of a new phosphodiesterase inhibitor in acute respiratory distress syndrome. ***Eur. Respir. J., 22***, 20-27, **2003**.
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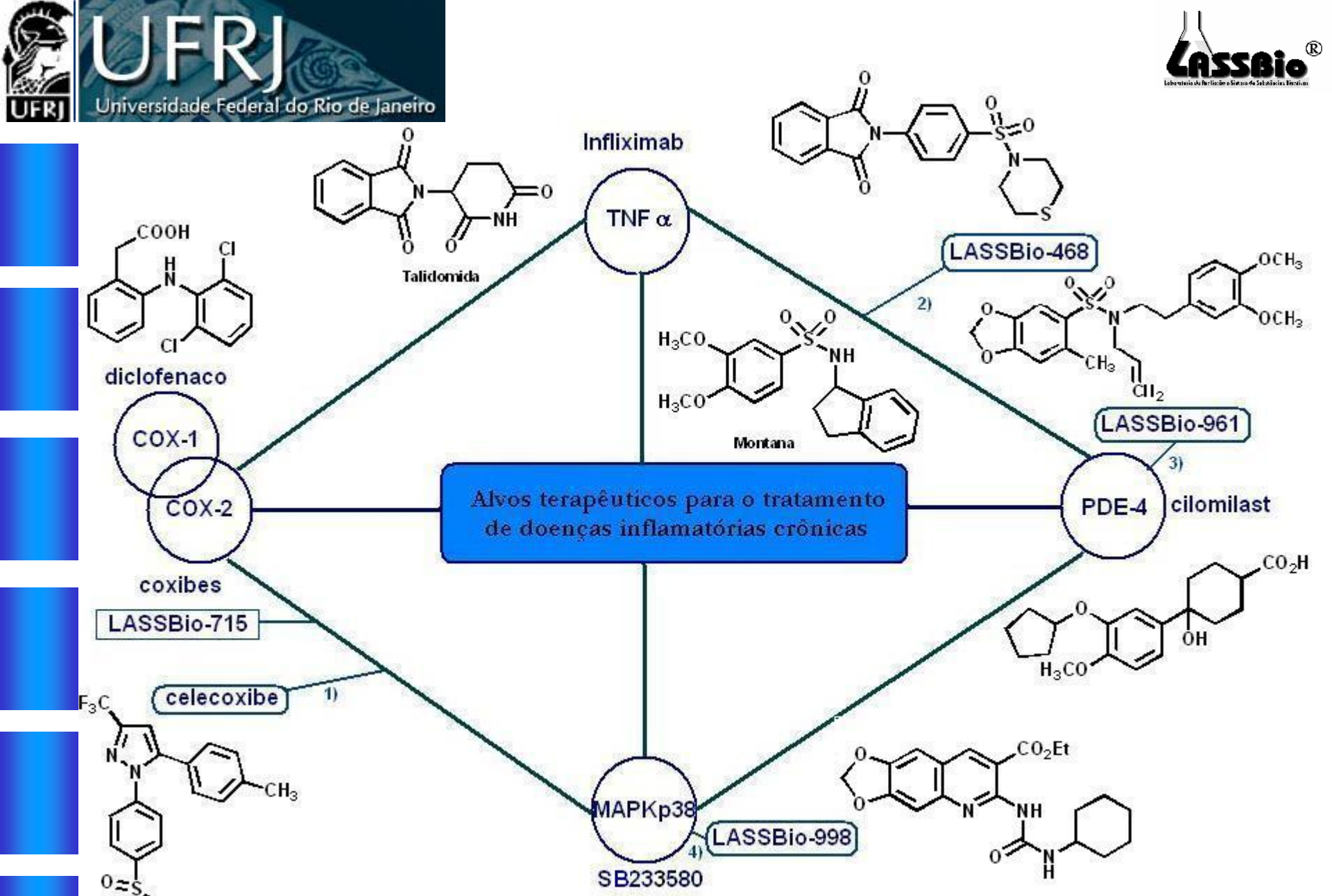
1. BARREIRO, E. J.; ROCCO, P.R. M.; ZIN, W. A.; LIMA, L. M., FRAGA, C.A. M.; KOATZ, V. L. G.. USO DO COMPOSTO LASSBio 596 E CONGÊNERES, E COMPOSIÇÕES FARMACÊUTICAS CONTENDO OS MESMOS, NO TRATAMENTO DA SÍNDROME DO DESCONFORTO RESPIRATÓRIO AGUDO. **2002 [INPI#0208667-7]**
2. BARREIRO, E.J.; ROCCO, P. R. M.; ZIN, W. A.; LIMA, L. M., FRAGA, C. A. M. DERIVADOS N-FENILFTALIMÍDICOS E CARBAMOILBENZÓICOS FUNCIONALIZADOS, PROCESSOS PARA SUA PREPARAÇÃO E COMPOSIÇÕES FARMACÊUTICAS CONTENDO OS MESMOS, **2003 [INPI#0401660-2]**

Drug Data Report

Volume 23, Issue 10, 2001, Pages 949-1034



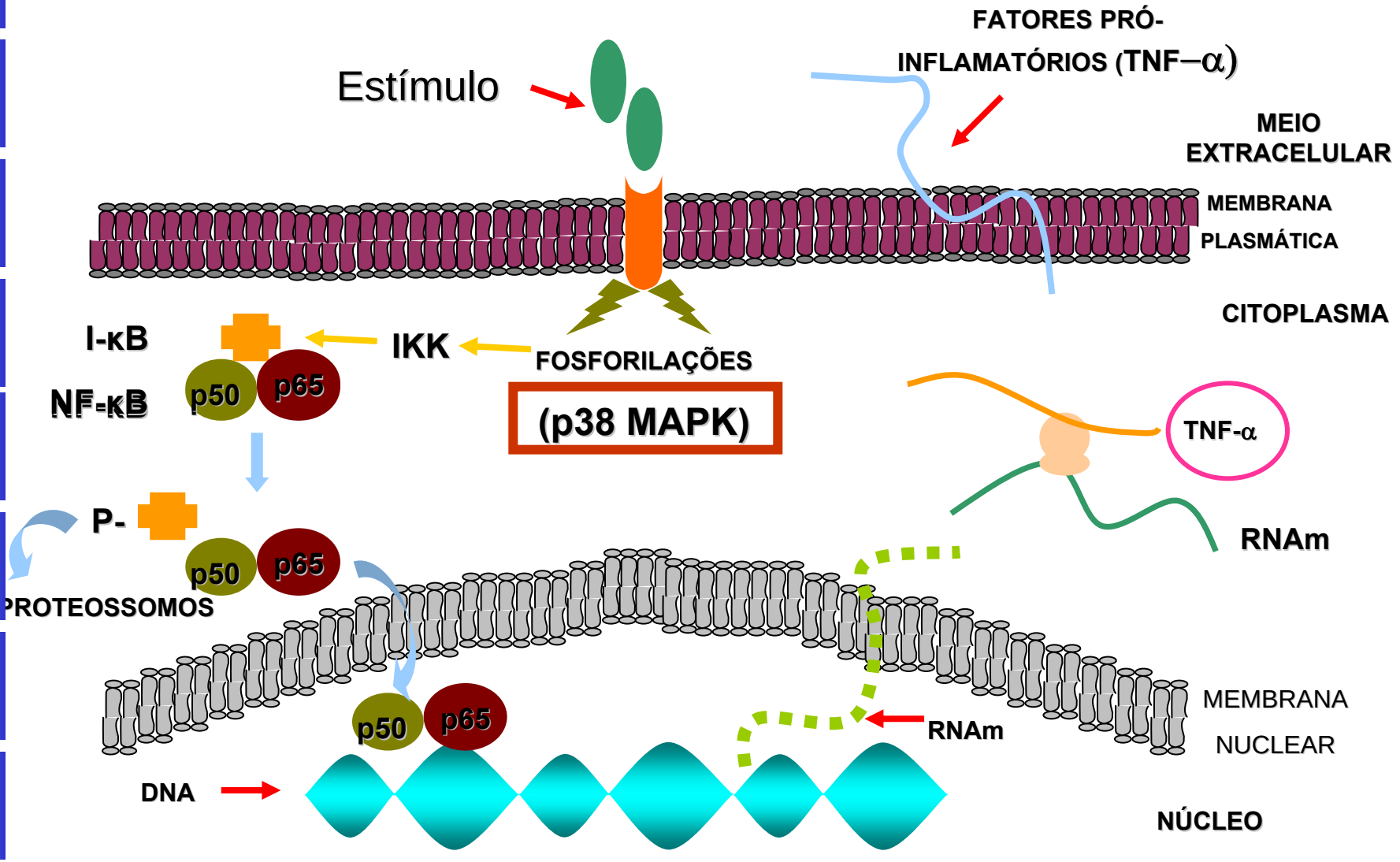
1 GMS Silva, LM Lima, CAM Fraga, CMR Sant´Anna, EJ Barreiro, *Bioorg. Med. Chem. Lett*. 2005, 15, 1169

2 LM Lima, P Castro, AL Machado, CAM Fraga, *Bioorg. Med. Chem*. 2002, 10, 3067

3 LM Lima & EJ Barreiro, resultados não publicados

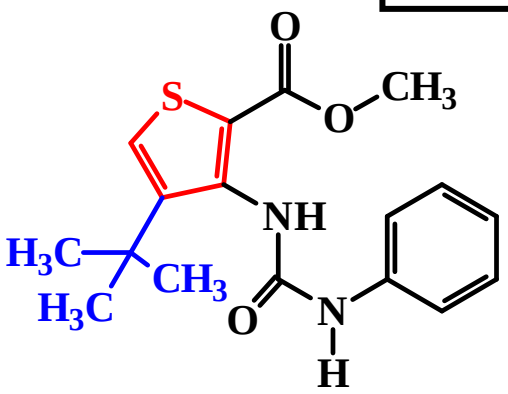
4 BR-0502016-6 03/06/2005

ALVO TERAPÊUTICO



Desenho Estrutural & Planejamento Molecular

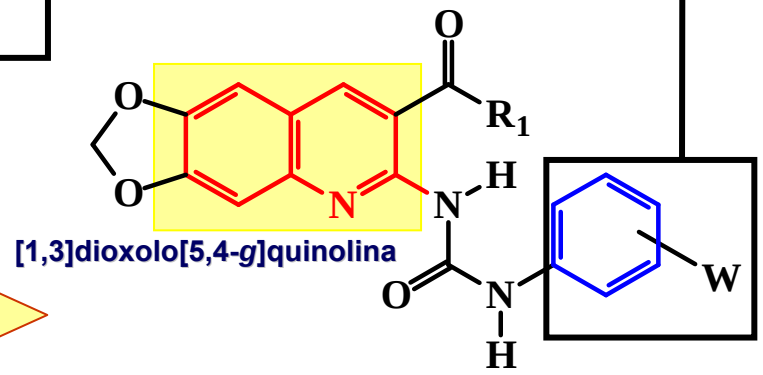
Inter-alia: 2-Py, 3-Py, 4-Py, a-naftila, 2-tiofeno, 2-furano, tiazola, isoxazola, tiadiazola, pirimidina, pirrola, oxazola, piridazina, triazina, imidazola;



GK 00687

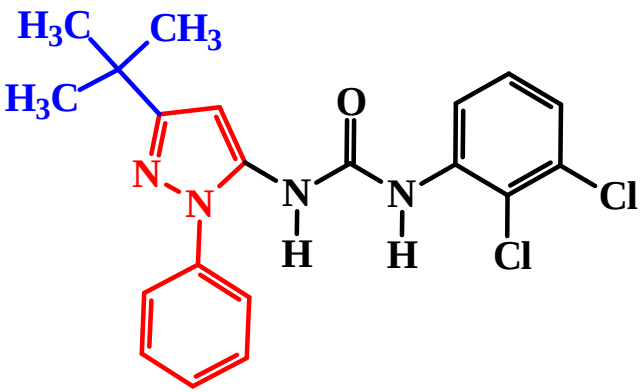
Bioisosterismo

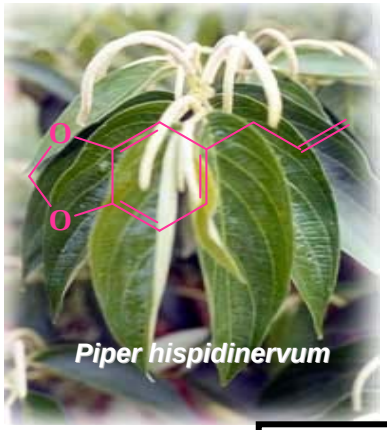
LASSBio-998



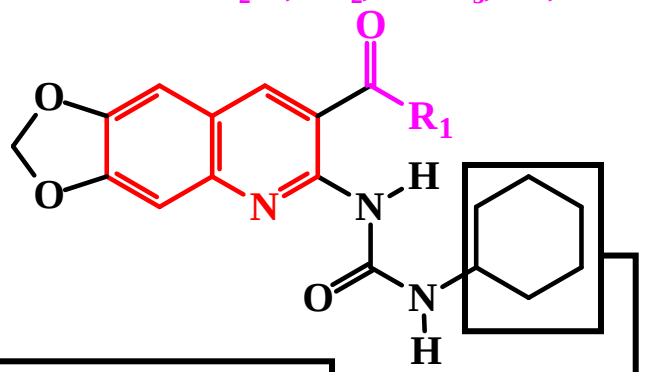
[1,3]dioxolo[5,4-*g*]quinolina

W = *orto*, *meta*, *para*: H; F; Cl; Br; CH_3; CH_2CH_3; CF_3; OCH_3; OCF_3; NO_2; NH_2; $NHCH_3$; $NHCOCH_3$; $NHSO_2CH_3$



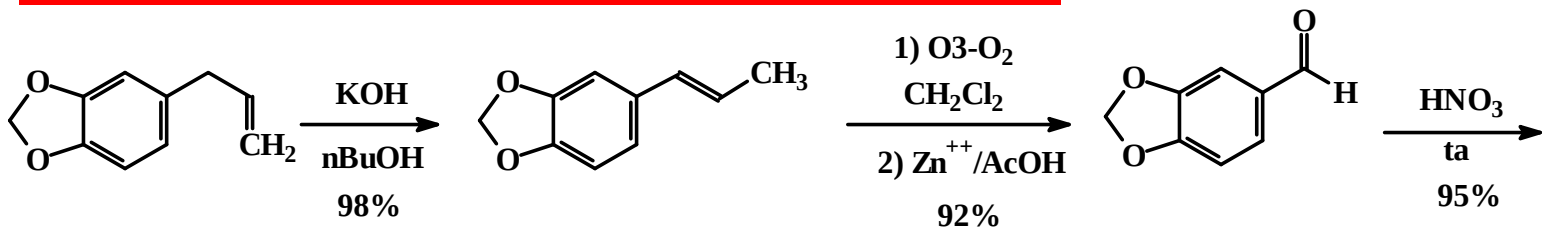


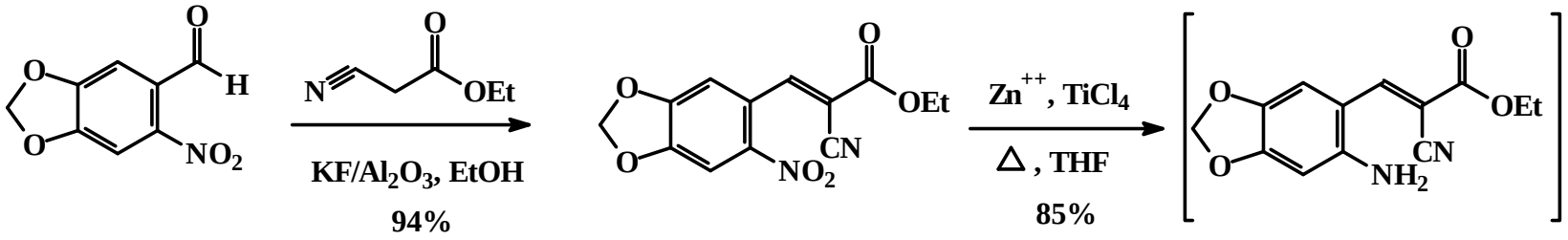
R_1 = OMe; OEt; OPr; OiPr; OPh, OCH_2Ph; NH_2, $NHCH_3$, OH, $NHNH_2$

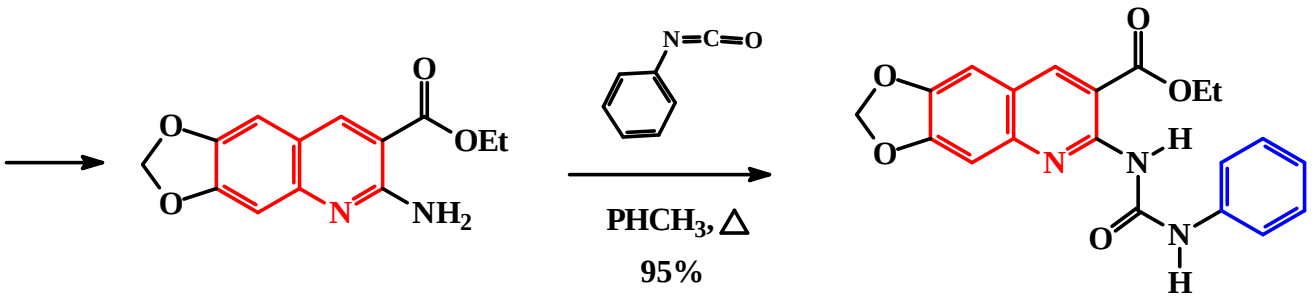


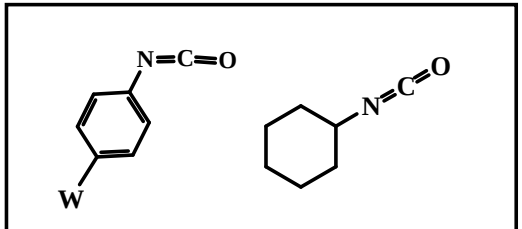
CH_3; $(CH_2)nCH_3$; alquila ramificados; ciclopropila; ciclopentila, cicloeptila.

Síntese dos compostos-alvo



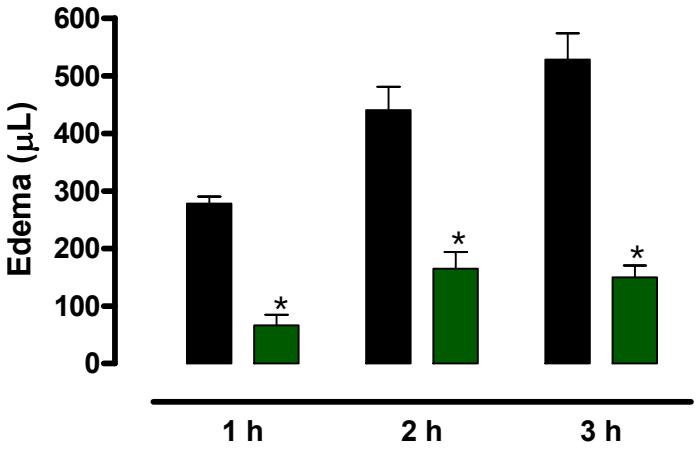






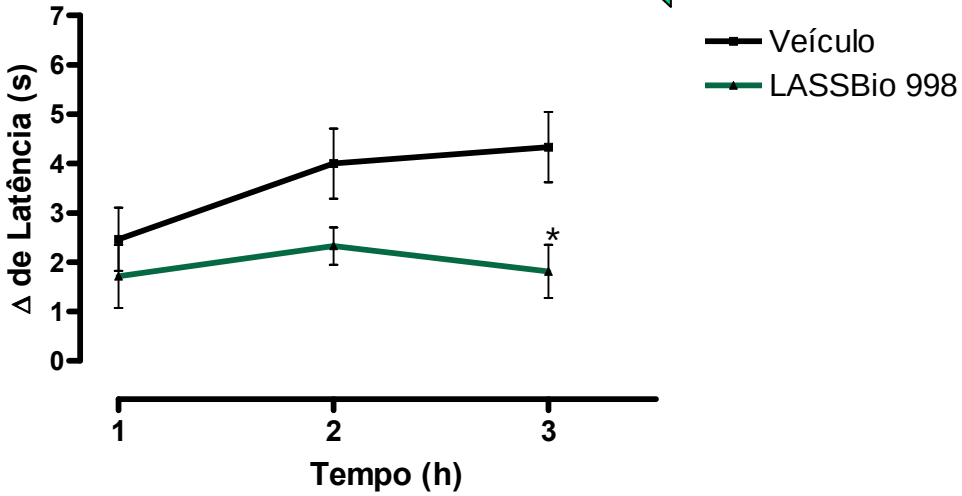
Edema de Pata de Rato Induzido por Carragenina 1%

- administração v.o. 3 hs antes da indução do edema;
- veículo: goma arábica 5%;
- dose: 100 μmol/kg;
- n = 7 animais



Edema

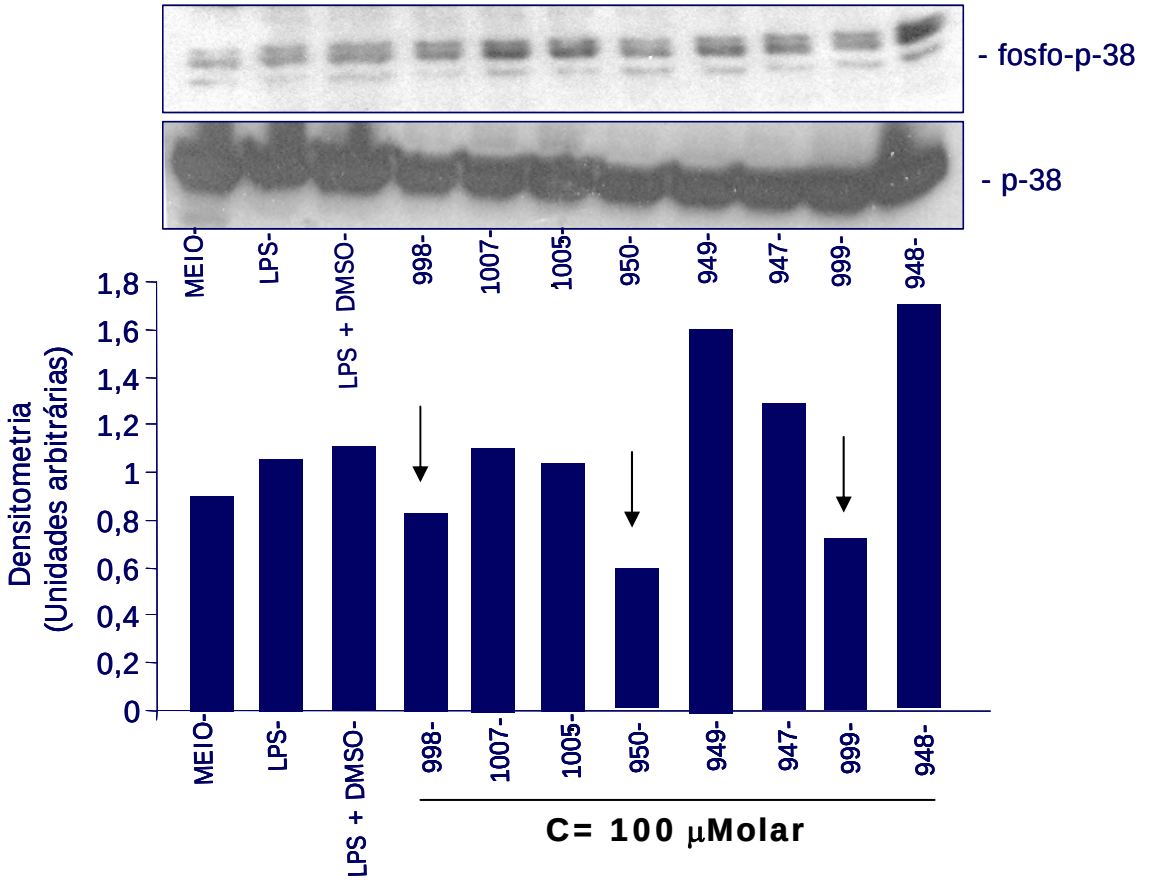
Hiperalgesia



Perfil Farmacológico

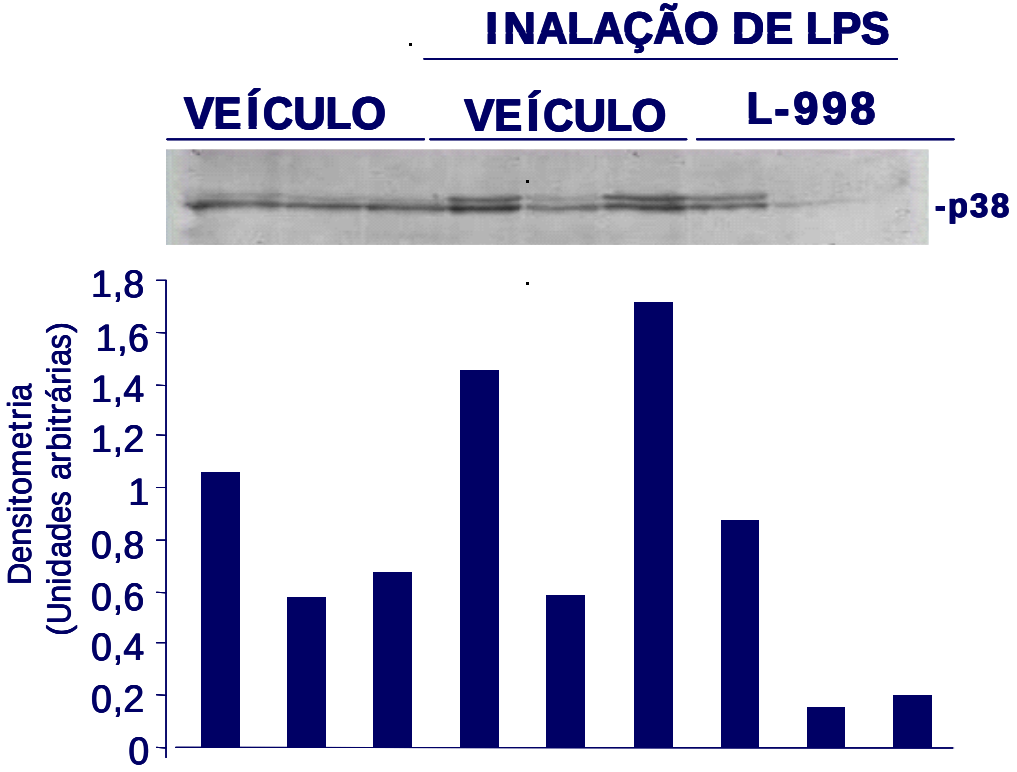
EFEITOS DOS COMPOSTOS INIBIDORES DE p38 SOBRE A FOSFORILAÇÃO DA MAP KINASE p38 EM PBMC INDUZIDA POR LPS

(Western-Blot)



Perfil Farmacológico

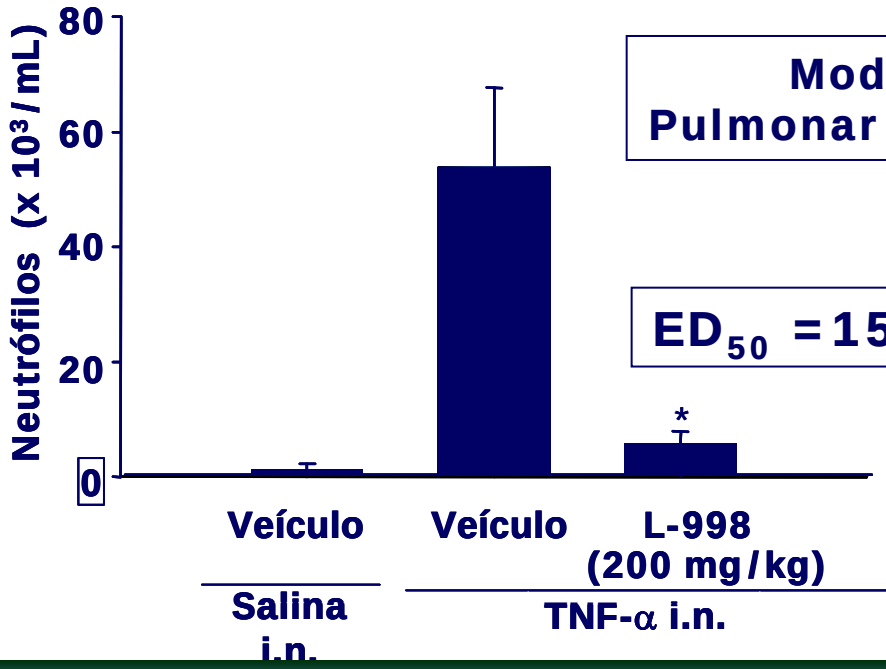
INIBIÇÃO DA FOSFORILAÇÃO DA MAPK p38 NO PULMÃO DE CAMUNDONGOS TRATADOS COM L-998



A figura mostra um experimento representativo com n=3 animais em cada grupo. A p38 fosforilada foi medida 3h após a inalação de LPS (0,5 mg/mL) por western blotting em homogenado de pulmão de animais pré-tratados com LASSBio-998 p.o. 4h antes da inalação.

Perfil Farmacológico 2

EFEITO DE TRATAMENTO COM L-998 NO INFLUXO DE NEUTRÓFILOS APÓS INSTILAÇÃO INTRANASAL DE TNF-α

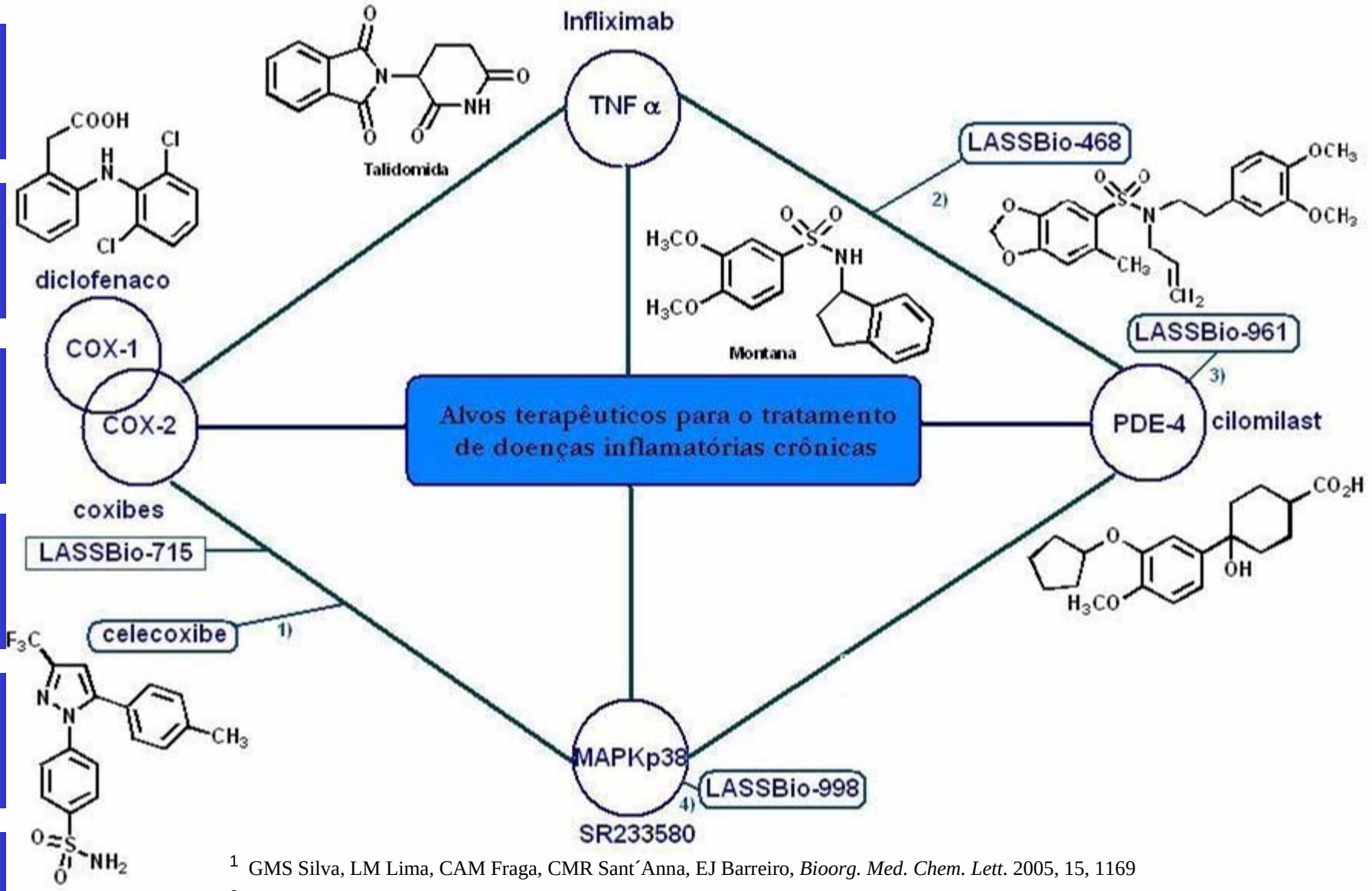


Modelo de Inflamação Pulmonar aguda induzida por LPS

ED_{50} = 150 mg/kg (via oral)

PI-0502016-6 03/06/2005 → Inibidores de MAPKp38 como AI

Os animais foram pré-tratados com LASSBio-998 p.o., 4h antes da inalação de LPS (0,5 mg/mL) e a contagem de neutrófilos foi efetuada após 3h.



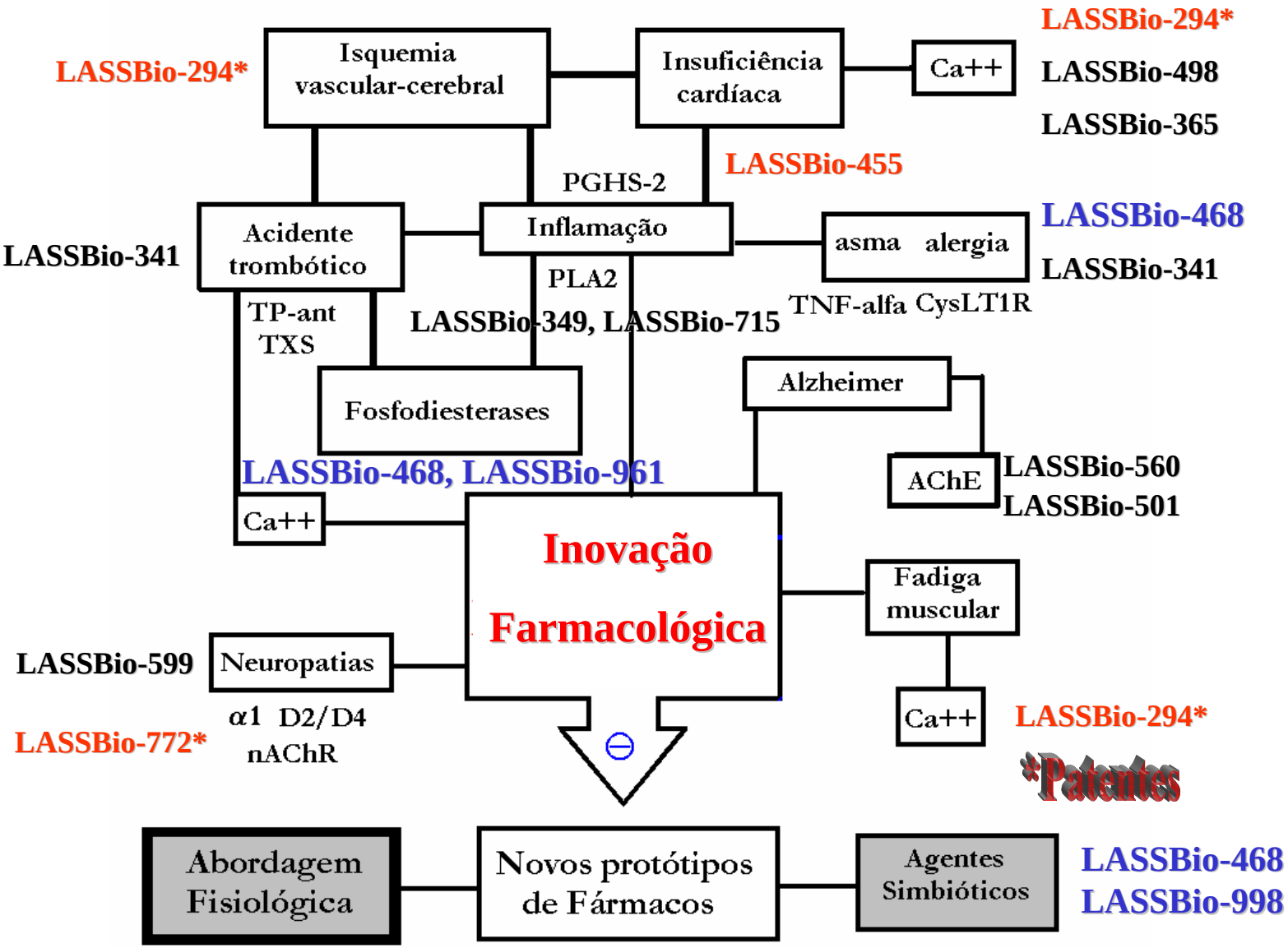
1 GMS Silva, LM Lima, CAM Fraga, CMR Sant´Anna, EJ Barreiro, *Bioorg. Med. Chem. Lett*. 2005, 15, 1169

2 LM Lima, P Castro, AL Machado, CAM Fraga, *Bioorg. Med. Chem*. 2002, 10, 3067

3 LM Lima & EJ Barreiro, resultados não publicados

4 BR-0502016-6 03/06/2005

Novos Protótipos Descobertos no LASSBio



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