

# A descoberta de novos protótipos de fármacos antiinflamatórios simbióticos

IIIEIQ - FURB – julho de 2008



**Eliezer J. Barreiro**

**Professor Titular - UFRJ**

**Laboratório de Avaliação e Síntese de Substâncias Bioativas**



**Universidade Federal do Rio de Janeiro**



**Louis Pasteur**

1822-1895

“La vie empeche la vie”

Química  
Medicinal



**Emil Fisher**

1852-1919

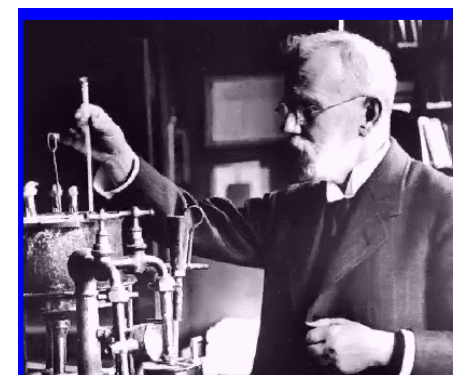
**1902**



**Robert Koch**

1843-1910

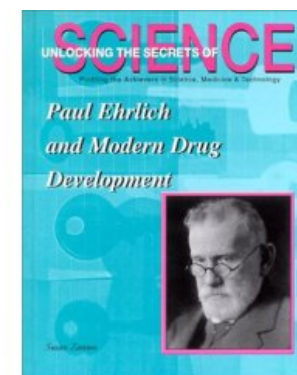
**1905**



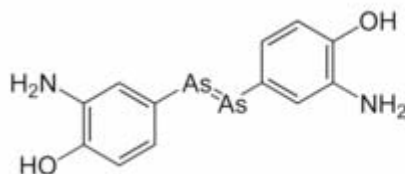
**Paul Ehrlich**

1854-1915

**1908**



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



Paul Ehrlich

1854-1915

Nobel 1908



**Arsfenamina**



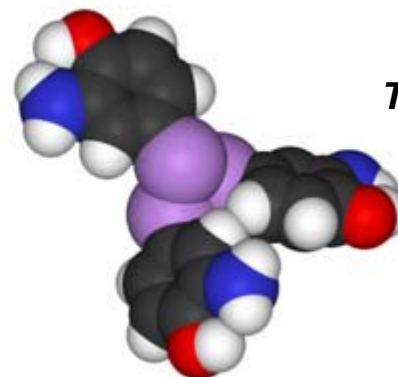
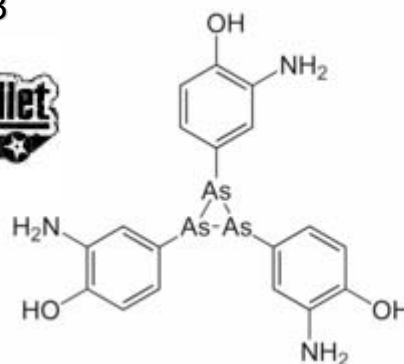
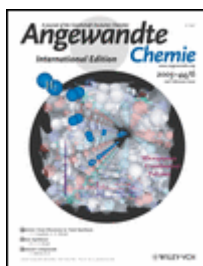
## Dr. Ehrlich's Magic Bullet

SCIENCE IN THE CINEMA

*Dr. Ehrlich's  
Magic Bullet*

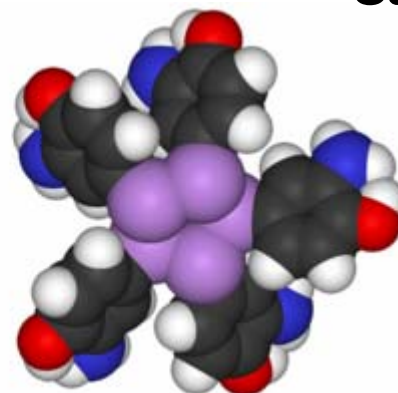
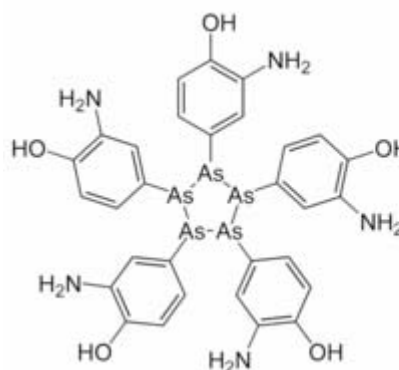
Thursday ■ July 31 ■ 7:00 p.m.

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



Trimêro

**Salvarsan<sup>R</sup>**



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)



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



Paul Ehrlich in his office, Frankfurt 1914.

F. Wnau, O. Westphal F. Wnau, Microbes & Infection 2004, 6, 706.

- ***“Balas mágicas”***

Magic bullets

Paul Ehrlich (1854-1915)



- ***Segundo paradigma da descoberta 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 “new-magic bullets”*

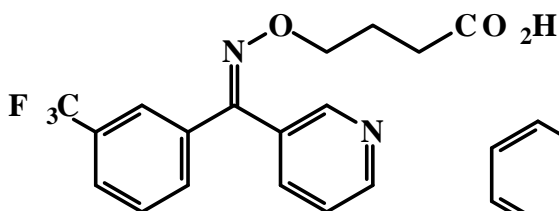
coxibes

• *Ligantes duplos, para dois alvos*

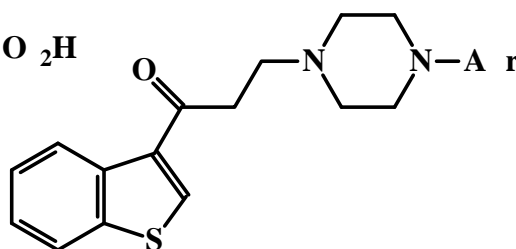
dual, binary, dimeric, bivalent, mixed ligands  
TXS-TPant; 5-HT1ARant-SSRI;

• *Desenho racional de ligantes múltiplos*

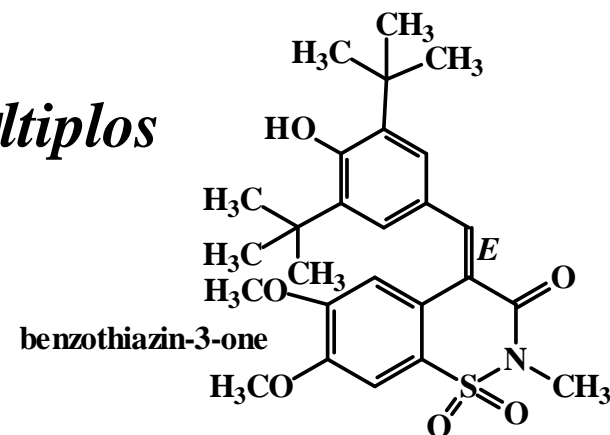
inibidores duplos COX-2 & 5-LOX



Freyne, 1987

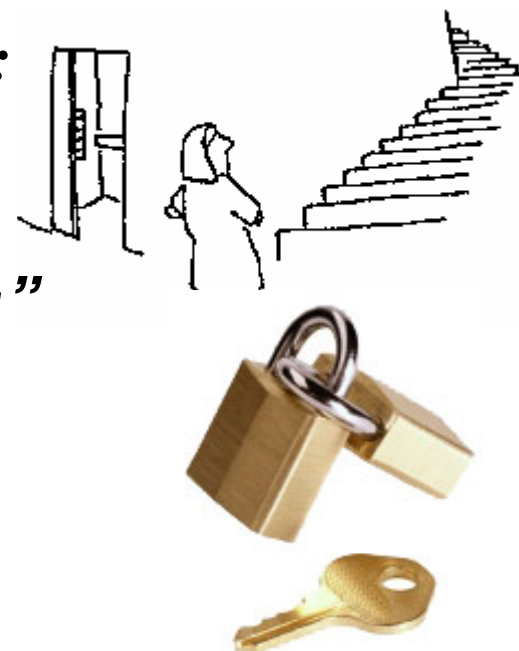


Monge, 2001



LASSBio-272

Teixeira, 1998





# • Ligantes duplos/duais/mistos/bivalentes para dois alvos (*Dual, binary, dimeric, bivalent, mixed ligands, multi-target*)

*novos compostos-protótipos, 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



multi-alvos

1 cápsula  
1 única EQ





**“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.”**



prescrição dupla

2 cápsulas  
2 fármacos



*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
<b>Drug combinations</b>					
Vytorin <sup>®</sup>	Hyperlipidemia	Ezetimibe	Simvastatin	Dietary cholesterol	HMG-CoA reductase
Caduet <sup>®</sup>	CHD	Amlodipine	Atorvastatin	Calcium-channel antagonist	HMG-CoA reductase
Lotrel <sup>®</sup>	Hypertension	Amlodipine	Benzapril	Calcium-channel antagonist	ACE inhibitor
Glucovance <sup>®</sup>	T2DM	Metformin	Glyburide	Gluconeogenesis	Insulin secretagogue
Avandamet <sup>®</sup>	T2DM	Metformin	Rosiglitazone	Gluconeogenesis	PPAR $\gamma$ agonist
Truvada <sup>®</sup>	Antiviral (HIV)	Emtricitabine	Tenofovir	RT inhibitor	RT inhibitor
Kaletra <sup>®</sup>	Antiviral (HIV)	Lopinavir	Ritonavir	Protease inhibitor	Protease inhibitor
Rebetron <sup>®</sup>	Antiviral (Hepatitis C)	PEG-interferon	Ribavirin	Interferon- $\alpha$ 2B	Antimetabolite
Bactrim <sup>®</sup>	Antibacterial	Trimethoprim	Sulfamethoxazole	DHFR	DHPS
Advair <sup>®</sup>	Asthma	Fluticasone	Salmeterol	Glucocorticoid receptor	$\beta$ 2-Adrenergic



combinação

1 cápsula  
2 EQ's







Endereço: <http://www.centerwatch.com/patient/drugs/dru847.html>

Google caduet Search 3 blocked ABC Check AutoLink AutoFill Options caduet Web assistant

THOMSON CENTERWATCH **CenterWatch** Clinical Trials Listing Service™

Industry Professionals Books & Publications

Trial Listings Notification Services Patient's Bookstore About Research Drug Directories Additional Resources

### Drugs Approved by the FDA

**Drug Name: Caduet (amlodipine/atorvastatin)**

The following information is obtained from various newswires, published medical journal articles, and medical conference presentations.

**Description of Medical Areas**

**About the FDA Approved Listings**


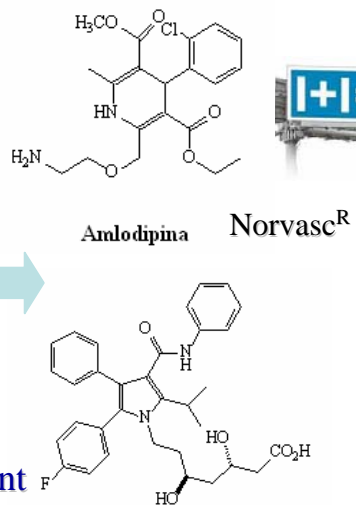
Company: Pfizer  
Approval Status: Approved January 2004  
Treatment for: Hypertension/Angina

**General Information**

Caduet combines the drugs amlodipine (Norvasc, Lotrel) and atorvastatin (Lipitor), two widely prescribed cardiovascular medications. It's the first medicine to treat two different conditions, high blood pressure and high cholesterol.

It is indicated for the treatment of hypertension, chronic stable angina and vasospastic angina (Prinzmetal's or variant angina). It is also indicated for primary dysbetalipoproteinemia, elevated serum TG levels.

Back to Drug Listing

 → 

**two component tablet**

Amlodipina Norvasc<sup>®</sup>

atorvastatina Lipitor<sup>®</sup>



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

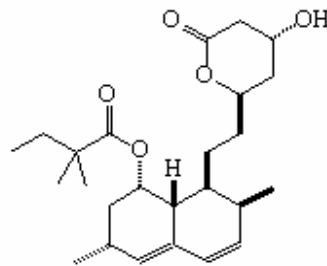
O setor de medicamentos cardiovasculares movimentou em 2005 *ca.* US\$ 72 bilhões



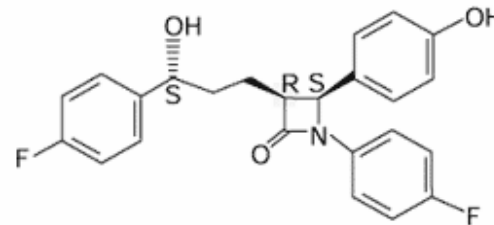
**VYTORIN**  
(ezetimibe/simvastatin)

**Merck/Schering-Plough**

two component tablet  
(estatin & vastatin)



simvastatina  
Zoccor<sup>®</sup>



ezetimibe  
Zetia<sup>®</sup>

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

# Multi-target therapeutics

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Vytorin <sup>®</sup>	Hyperlipidemia	Ezetimibe	Simvastatin	Dietary cholesterol
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Glucovance <sup>®</sup>	T2DM	Metformin	Glyburide	Gluconeogenesis
Avandamet <sup>®</sup>	T2DM	Metformin	Rosiglitazone	Gluconeogenesis
Truvada <sup>®</sup>	Antiviral (HIV)	Emtricitabine	Tenofovir	RT inhibitor
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Rebetron <sup>®</sup>	Antiviral (Hepatitis C)	PEG-interferon	Ribavirin	Interferon- $\alpha$ 2B
Bactrim <sup>®</sup>	Antibacterial	Trimethoprim	Sulfamethoxazole	DHFR
Advair <sup>®</sup>	Asthma	Fluticasone	Salmeterol	Glucocorticoid receptor



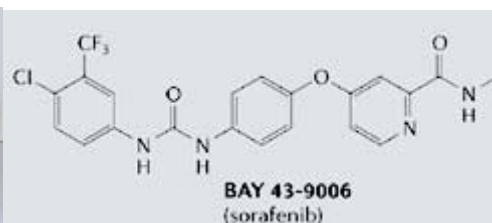
**multi-alvos**

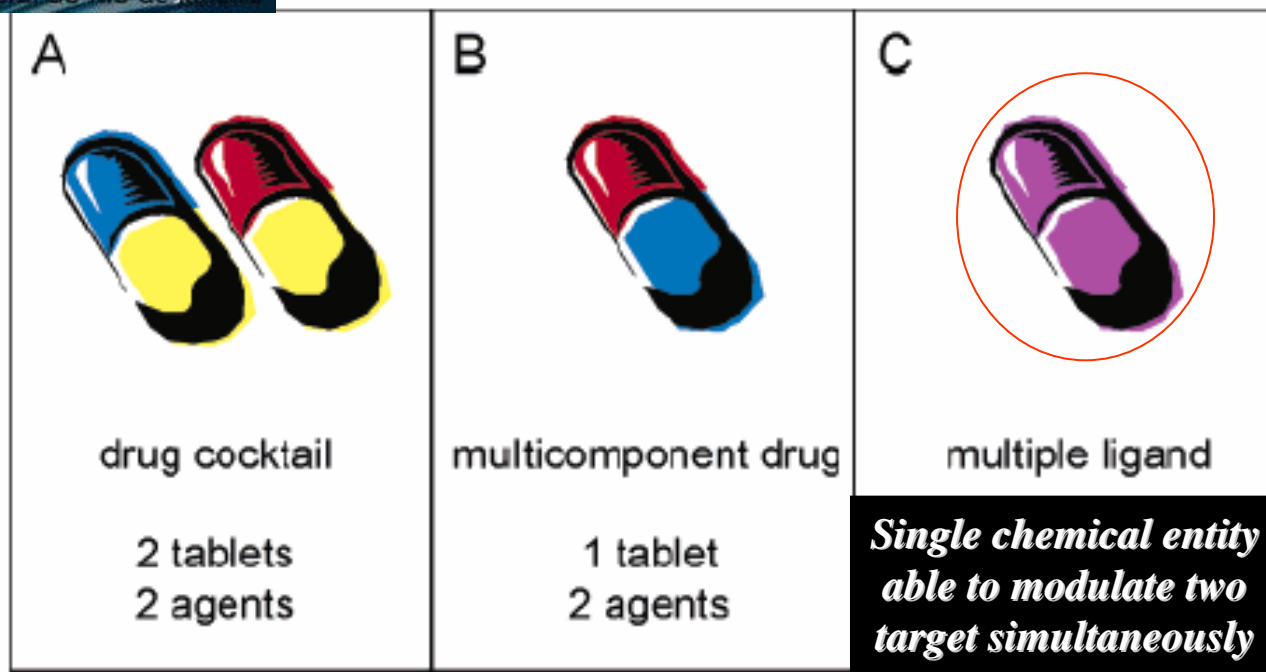
**1 cápsula  
1 única EQ**

## Multi-target drugs

Cymbalta <sup>®</sup>	Depression	Duloxetine	NA	SRI	NRI
Sutent <sup>®</sup>	Cancer	Sunitinib	NA	PDGFR	VEGFR
Nexavar <sup>®</sup>	Cancer	Sorafenib	NA	BRAF	VEGFR
Sprycel <sup>®</sup>	Cancer	Dasatinib	NA	BCR-ABL	SRC
Tykerb <sup>®</sup>	Cancer	Lapatinib	NA	EGFR (ErbB1)	HER-2 (ErbB2)

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 growth factor receptor 2; NA, not applicable.





**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.



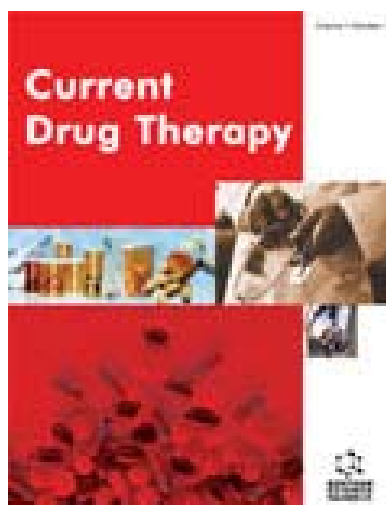
# New Insights for Multifactorial Disease Therapy: The Challenge of the Symbiotic Drugs

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.





# • 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

*J. Med. Chem.* **2004**, 47, 550

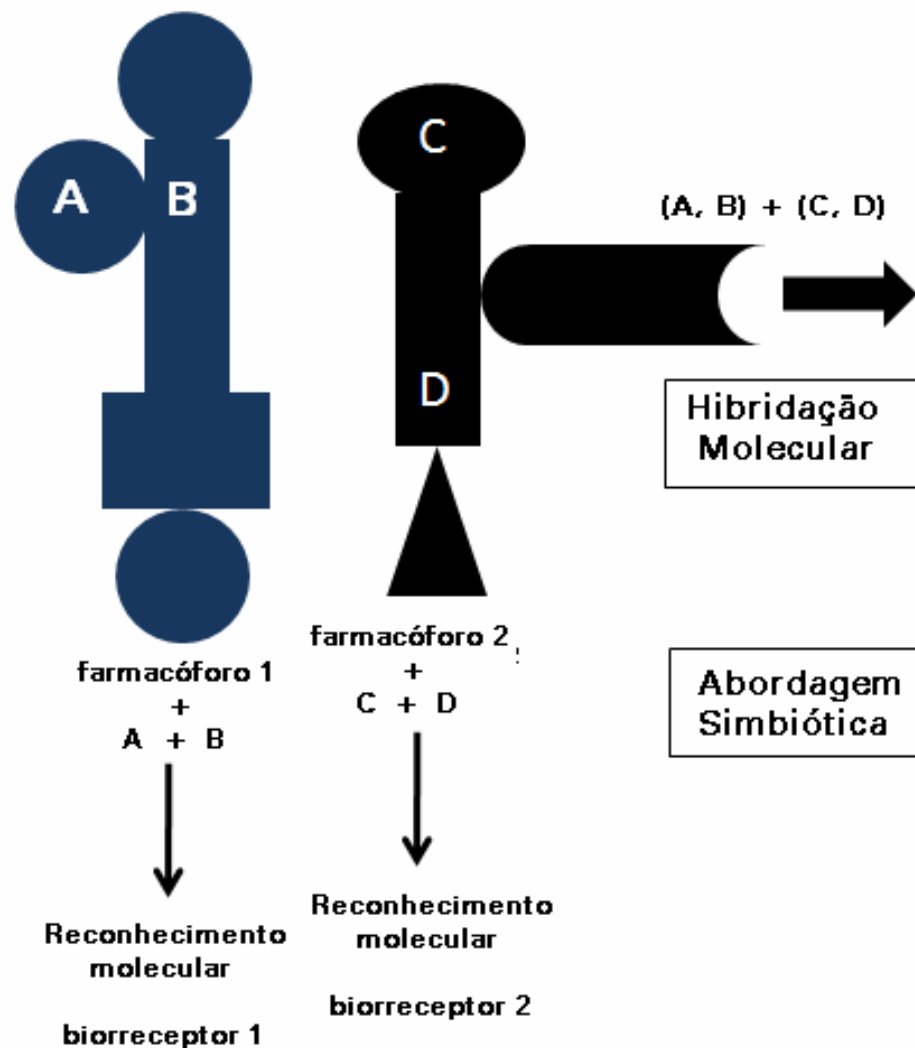
RTi/integrase

*J. Med. Chem.* **2007**, 50, 3416

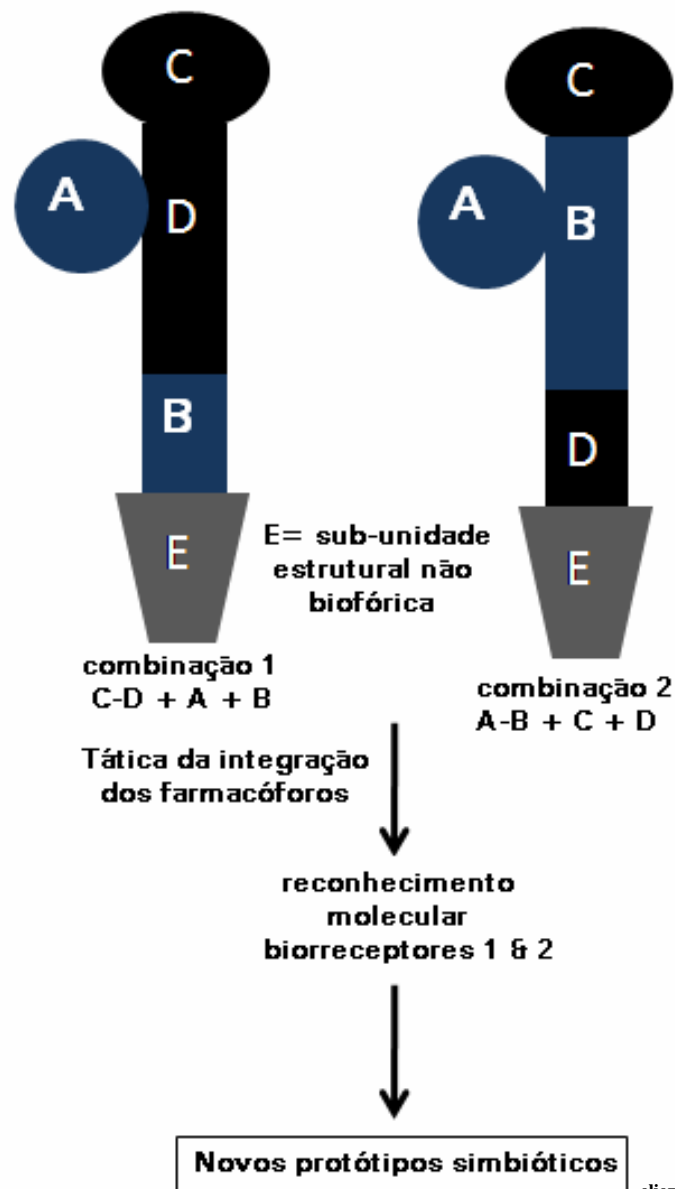
TACE-MMP's

*J. Med. Chem.* **2002**, 45, 2289

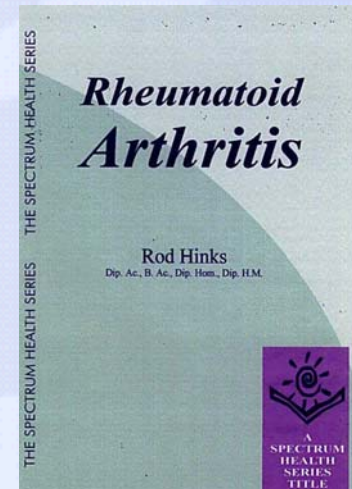
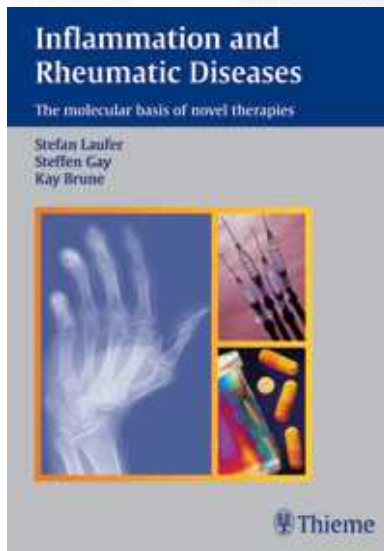
## Precusores (análogos ativos; substratos naturais)



## Novos padrões moleculares híbridos



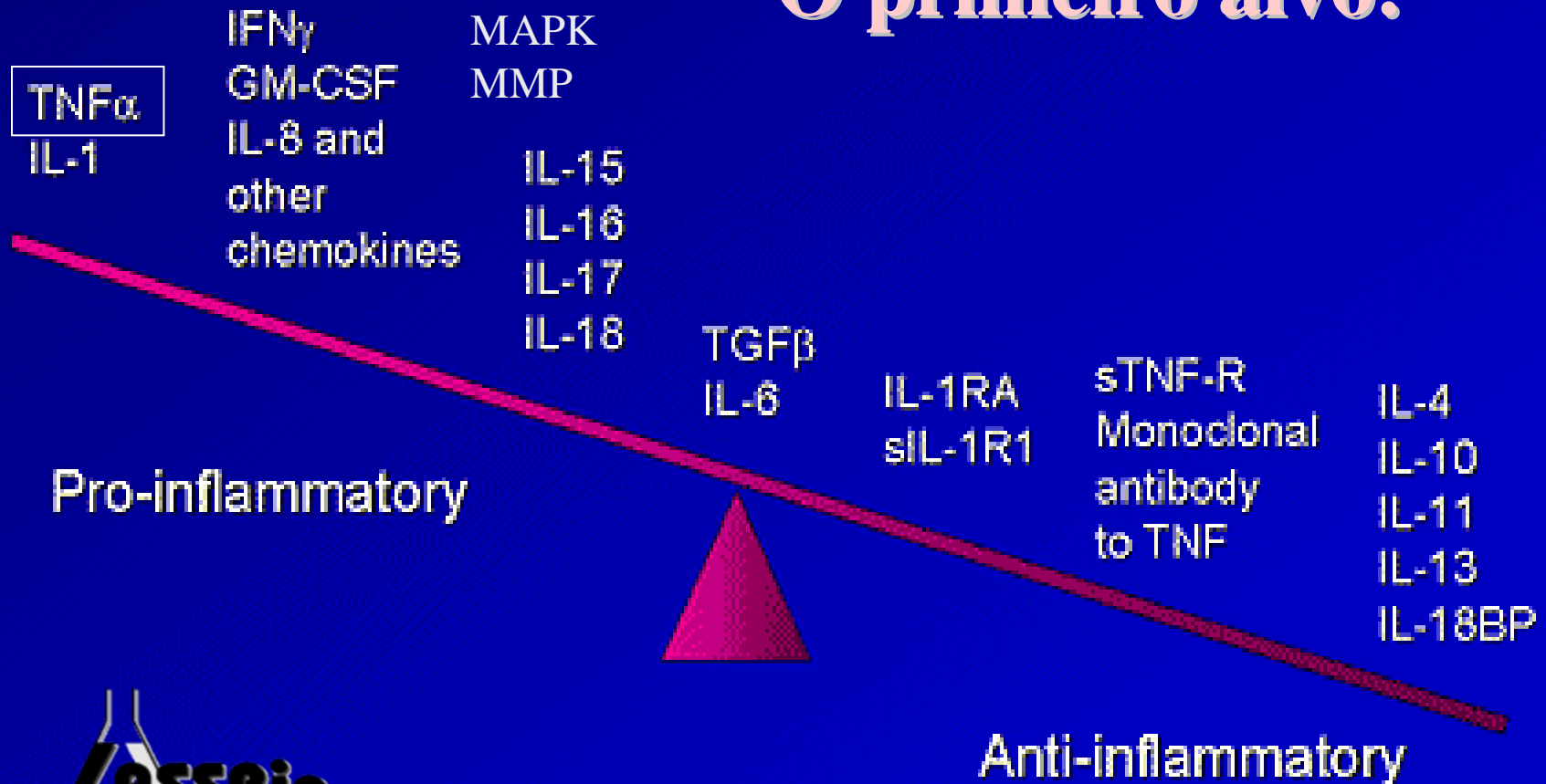
# Novas Abordagens Terapêuticas para o Tratamento da Inflamação



## Inovação terapêutica

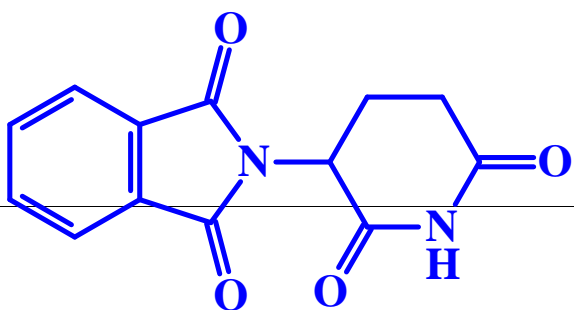
# Role of Cytokines and Cytokine Inhibitors in Chronic Inflammation

O primeiro alvo:

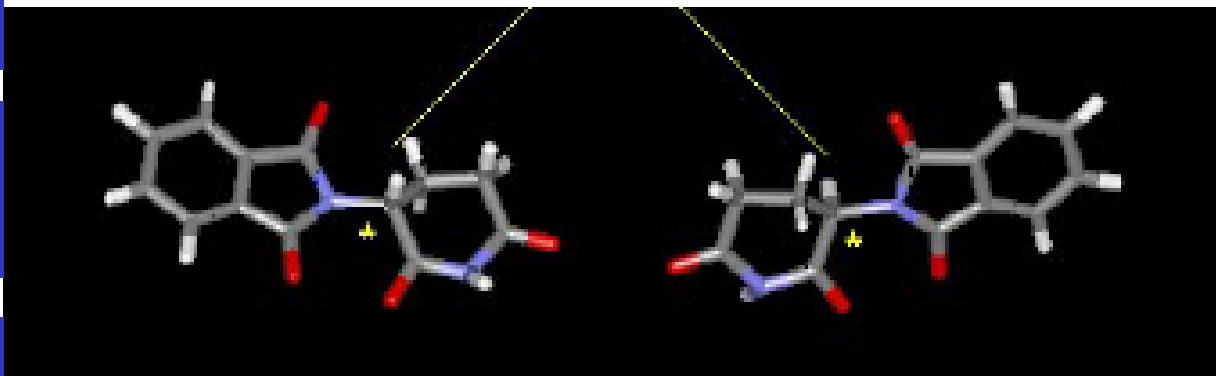


Arend. *Arthritis Rheum* 2001.





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



**THALIDOMIDE**

**TNF- $\alpha$  IC<sub>50</sub> = 200  $\mu$ M**

**Thalomid<sup>®</sup>, Phase III, Celgene**

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

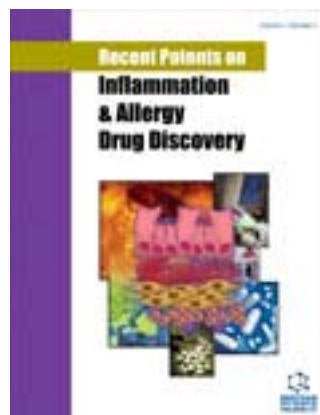
*L.M. Lima et al., O Renascimento de um Fármaco: Talidomida, Quim. Nova 2001, 24, 683; (www.scielo.br); E.P. Sampaio, D.S. Carvalho, J.A.C. Nery, U.G. Lopes, E.N. Sarno, "Thalidomide: An Overview of its Pharmacological Mechanisms of Action" Anti-inflammatory & Anti-allergy Agents in Medicinal Chemistry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

# Thalidomide and Analogs as Anti-Inflammatory and Immunomodulator Drug Candidates

Lídia Moreira Lima<sup>1</sup>, Carlos Alberto Manssour Fraga<sup>1</sup>, Vera Lucia Gonçalves Koatz<sup>2</sup>, and Eliezer J. Barreiro<sup>1,\*</sup>




<sup>1</sup>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; <sup>2</sup>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- $\alpha$

*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 antibody
 Adalimumab	approved	anti-human TNF antibody
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<sup>®</sup>), leflunomide (Arava<sup>®</sup>), cyclosporine (Neoral<sup>®</sup>), chlorambucyl (Leukeran<sup>®</sup>), penicilamine (Cuprimine<sup>®</sup>), hidroxychloroquine, Gold salt, azathioprine (Imuran<sup>®</sup>)

### anti-tumor necrosis factor (TNF) drugs:

etanercepte (Enbrel<sup>®</sup>), infliximabe (Remicade<sup>®</sup>), adalimumabe (Humira<sup>®</sup>)  
tocilizumabe [Actemra<sup>®</sup>]

methotrexate + sulfasalazine + hydrochloroquine



R\$7.057,77\*



R\$7.082,39\*



R\$3.668,79\*

\* Consulta em 15/07/2008: <http://www.consultaremedios.com.br/>



Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

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Bioorganic &  
Medicinal  
Chemistry

Bioorganic & Medicinal Chemistry xxx (2006) xxx–xxx



# Development of new CoMFA and CoMSIA 3D-QSAR models for anti-inflammatory phthalimide-containing TNF $\alpha$ modulators

Carolina Martins Avila,<sup>a</sup> Nelilma Correia Romeiro,<sup>a</sup> Gilberto M. Sperandio da Silva,<sup>a</sup>  
Carlos M. R. Sant'Anna,<sup>a,b</sup> Eliezer J. Barreiro<sup>a</sup> and Carlos A. M. Fraga<sup>a,\*</sup>

<sup>a</sup>*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*

<sup>b</sup>*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

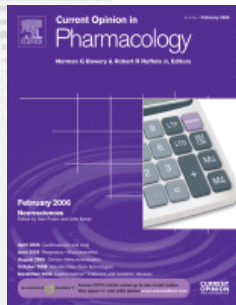
**Abstract**—In the present study, we describe a new 3D-QSAR analysis of 42 previously reported thalidomide analogues, with the ability to modulate the pro-inflammatory cytokine TNF $\alpha$ , by using comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (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.

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## 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,

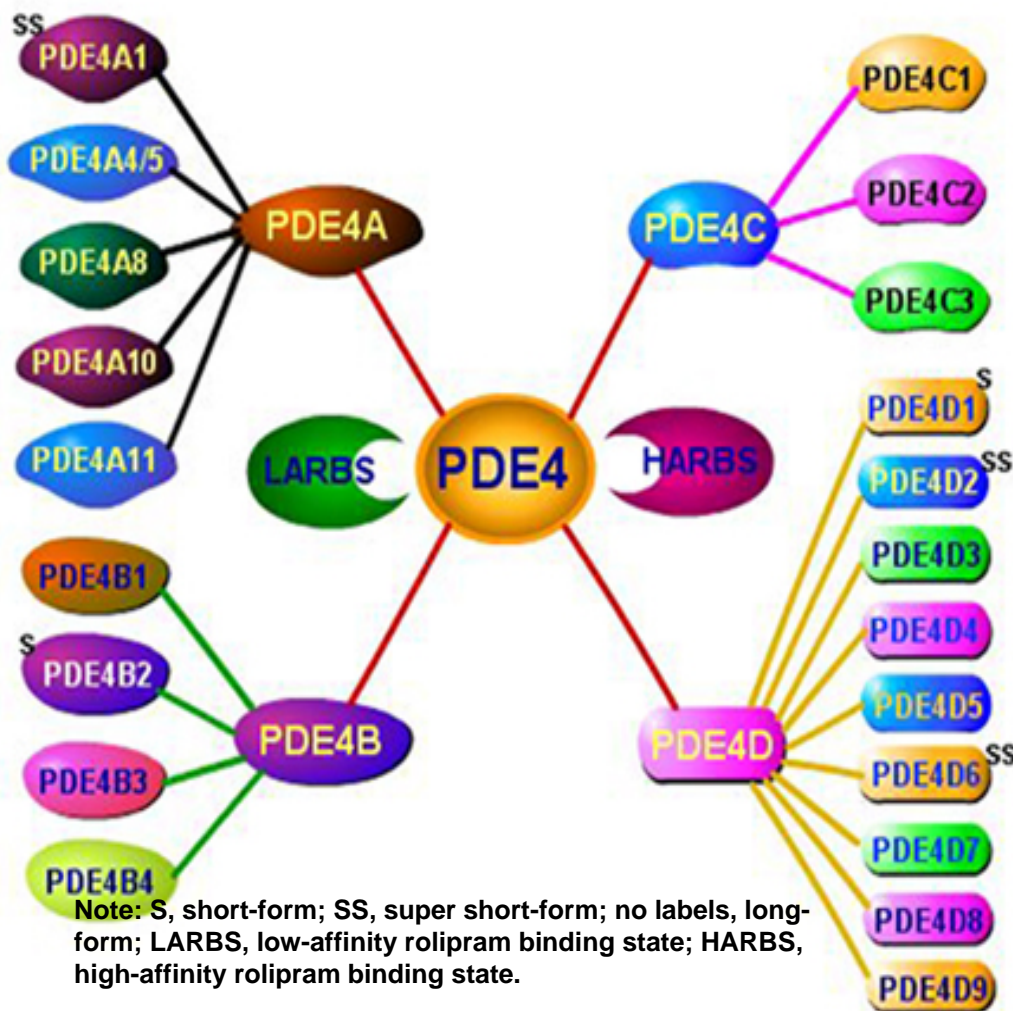


## Matrix metalloproteinases in asthma and COPD

Ingel K Demedts, Guy G Brusselle, Ken R Bracke, Karim Y Vermaelen and Romain A Pauwels

*Curr Op Pharmacol.* 2005, 5, 257

## PDE4 subtypes and splice variants



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.





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Bioorganic & Medicinal Chemistry xxx (2006) xxx–xxx

Bioorganic &  
Medicinal  
Chemistry

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

Fernanda G. Oliveira,<sup>a</sup> Carlos M. R. Sant'Anna,<sup>b</sup> Ernesto R. Caffarena,<sup>c</sup>  
Laurent E. Dardenne<sup>d</sup> and Eliezer J. Barreiro<sup>a,\*</sup>

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<sup>b</sup>Departamento de Química, ICE, Universidade Federal Rural do Rio de Janeiro (UFRRJ), Seropédica, RJ 23851-970, Brazil

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<sup>d</sup>Laboratório Nacional de Computação Científica—LNCC/MCT, Quitandinha, Petrópolis, RJ 25651-075, Brazil

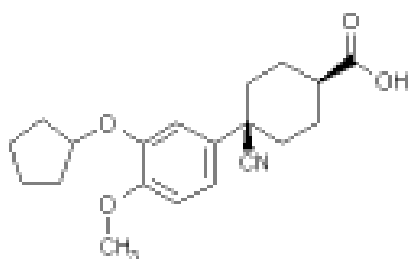
Received 8 November 2005; revised 10 May 2006; accepted 10 May 2006

**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.

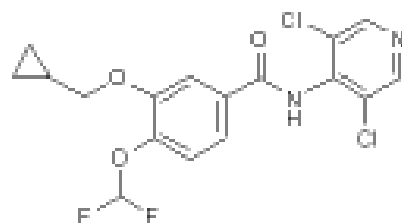
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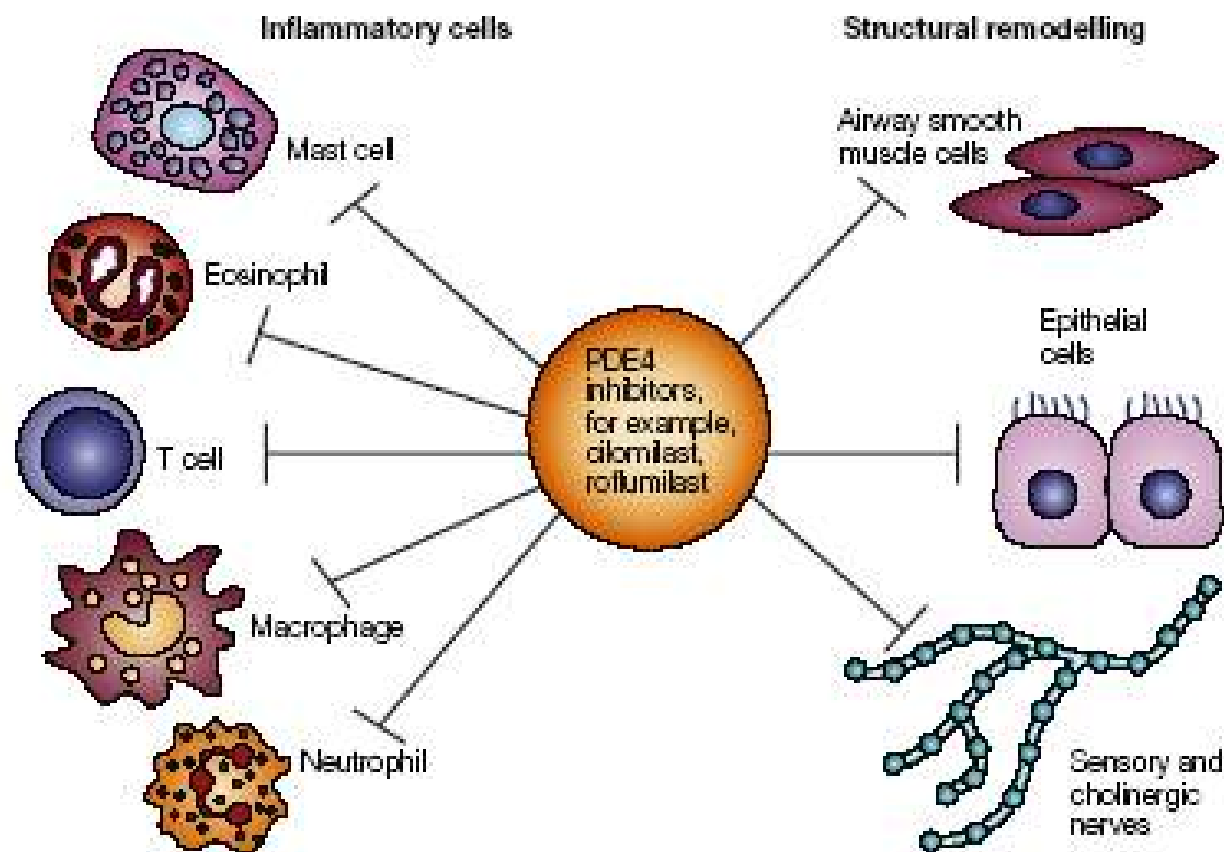


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GSK



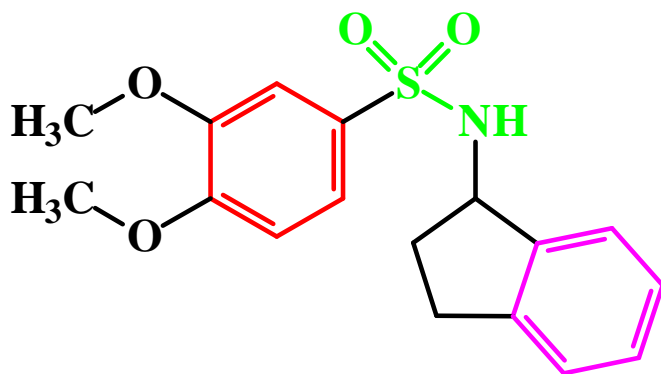
Roflumilast (Daxas<sup>®</sup>)  
Altana Pharma AG  
& Pfizer Inc

Daxas®

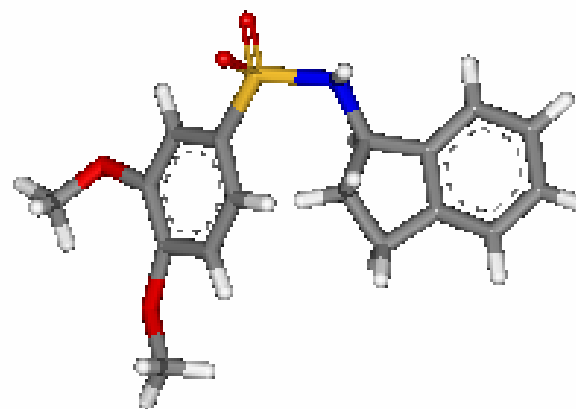


Phosphodiesterase-4 inhibitors have a broad spectrum of anti-inflammatory effects in asthma. Phosphodiesterase-4 (PDE4) inhibitors inhibit the recruitment and activation of key inflammatory cells, including mast cells, eosinophils, T lymphocytes, macrophages and neutrophils, as well as the hyperplasia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

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

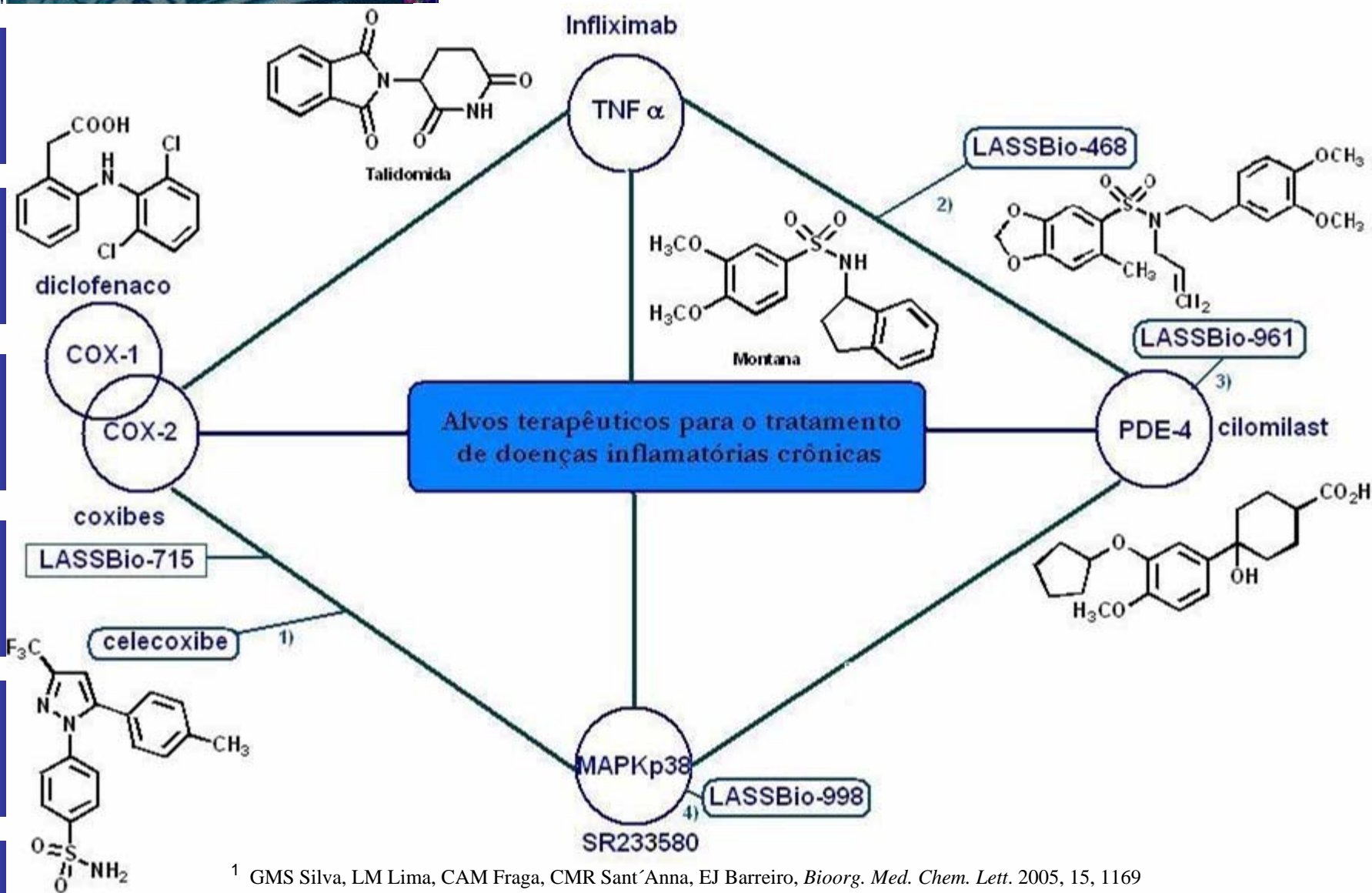


**Aryl-sulfonamida**



$$\text{PDE-4i IC}_{50} = 4.3 \mu\text{M}$$

**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.



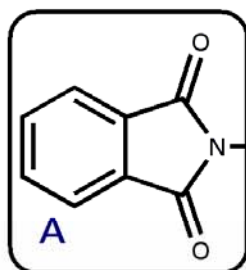
<sup>1</sup> GMS Silva, LM Lima, CAM Fraga, CMR Sant'Anna, EJ Barreiro, *Bioorg. Med. Chem. Lett.* 2005, 15, 1169

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

<sup>3</sup> LM Lima & EJ Barreiro, resultados não publicados

<sup>4</sup> BR-0502016-6 03/06/2005

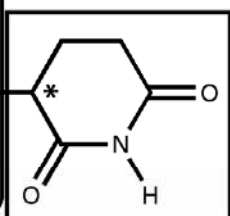
fragmento  
imídico  
aromático



talidomida  
(7.92)

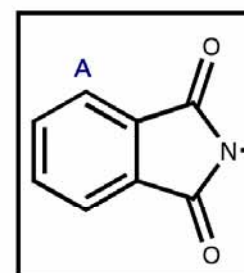
TNF- $\alpha$  IC<sub>50</sub> = 200  $\mu$ M

Sub-unidade estrutural  
toxicofórica



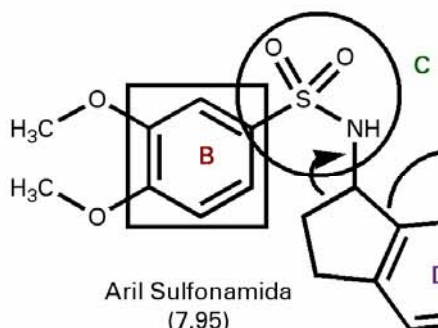
fragmento imídico saturado

Hibridação  
Molecular



(7.96)

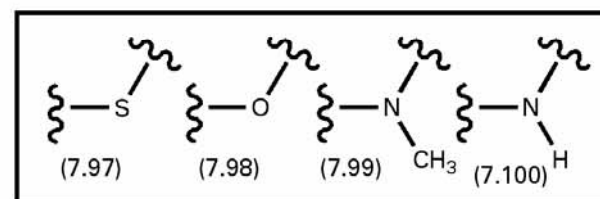
fragmento  
N-fenilpiperazina



Aril Sulfonamida  
(7.95)

PDE-4i IC<sub>50</sub> = 4,3  $\mu$ M

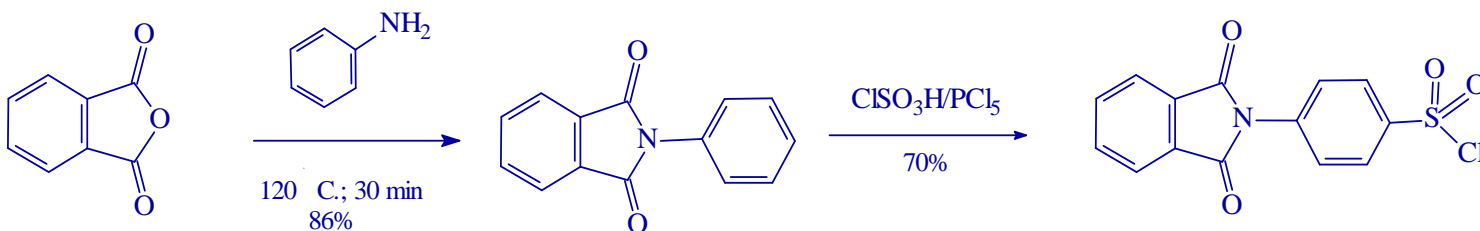
fragmento indânico



série congênere (isósteros)



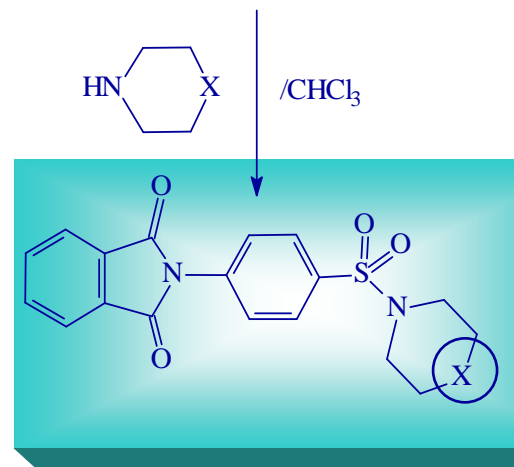
# Synthesis of LASSBio-468



anidrido ftálico

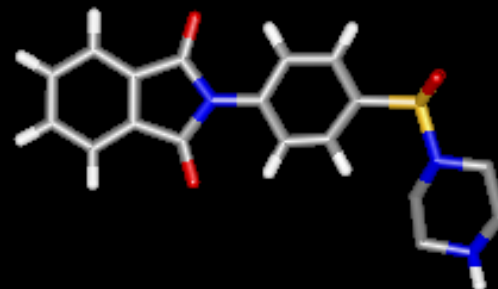
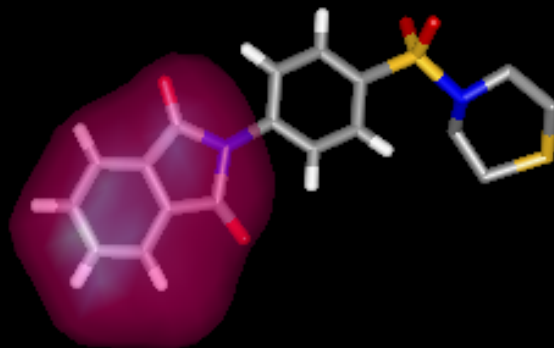
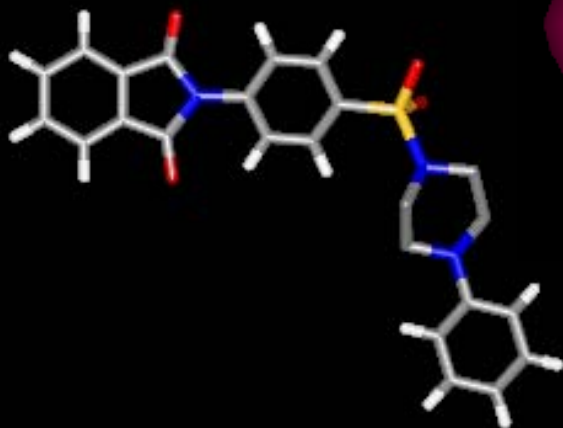
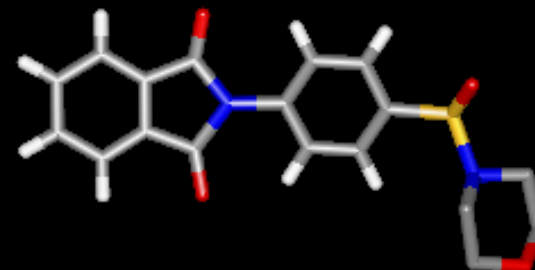


X = NMe 65%  
 X = NPh 67%  
 X = NH 58%  
 X = O 63%  
 X = S 67%

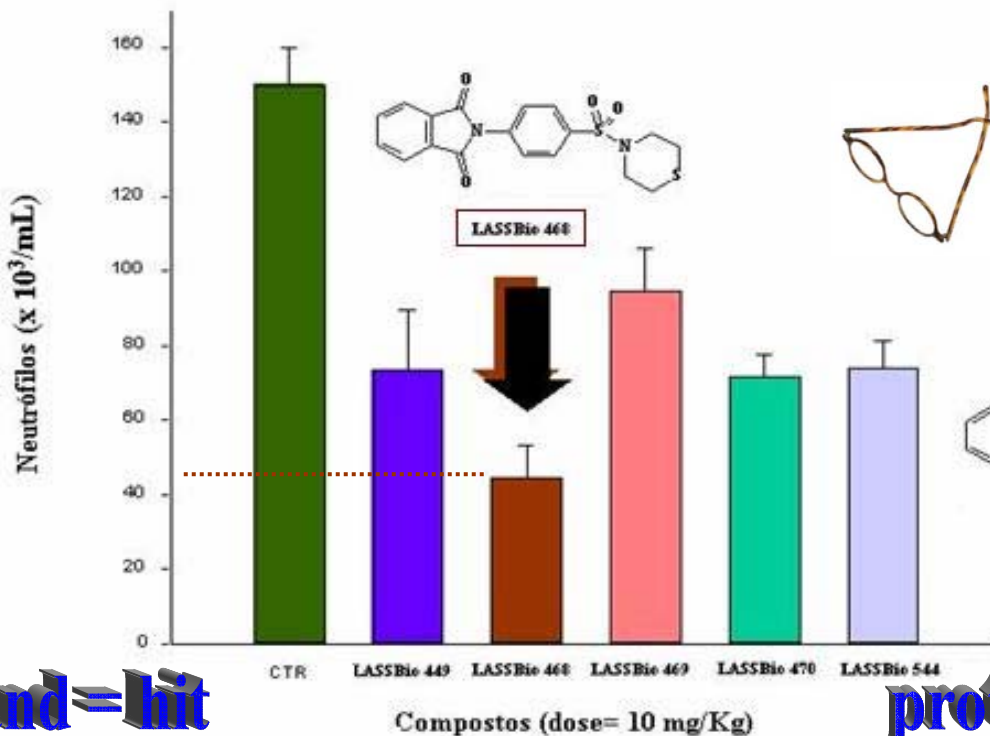


**Overall yield: *ca.* 20%**  
**(0.35 M, *ca.* 150g)**

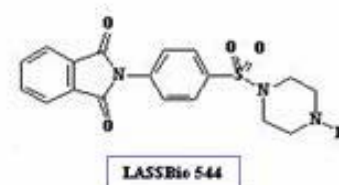
## Congeneric Series



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

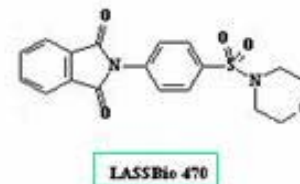
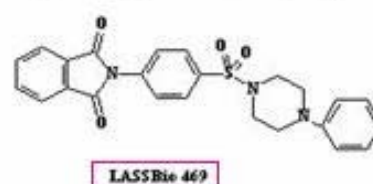
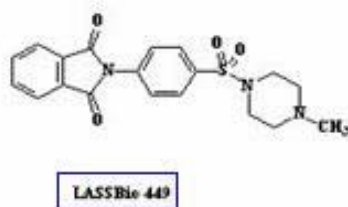


*in vivo*



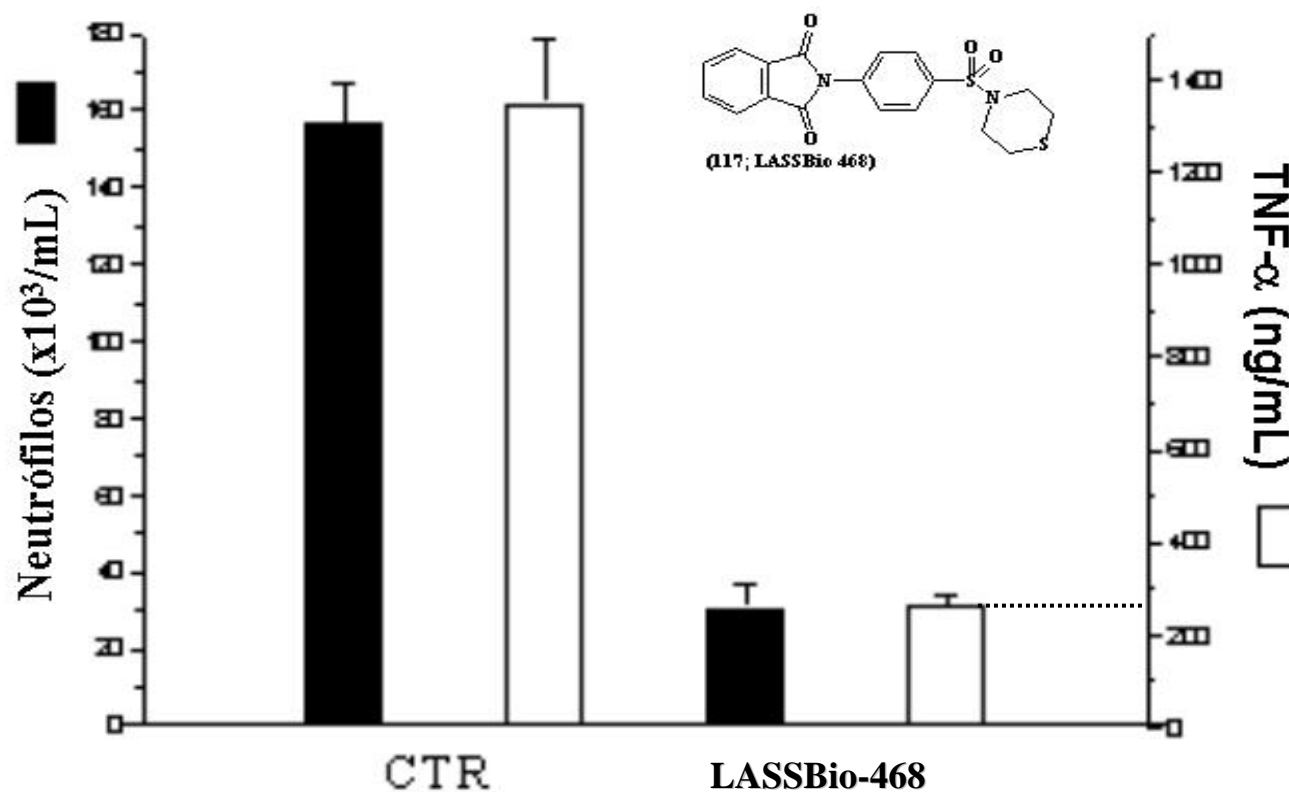
lead >> ligand = hit

protótipo > ligante

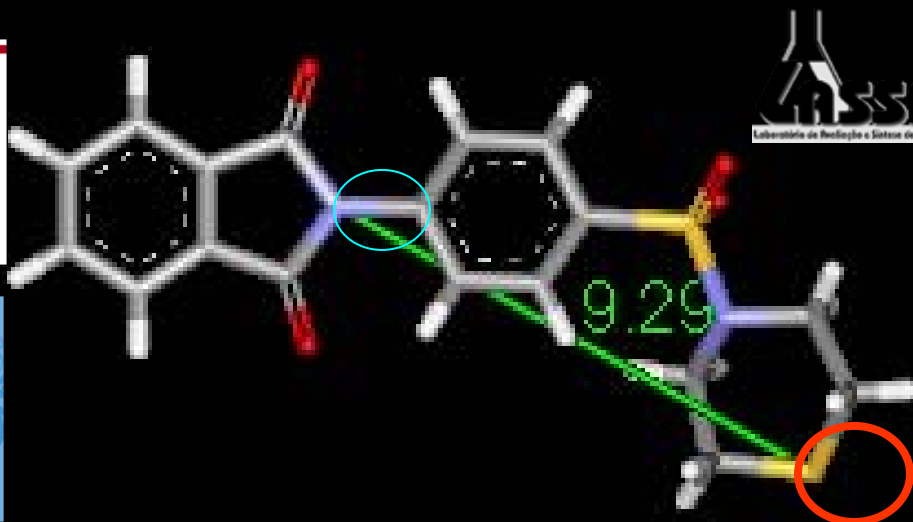
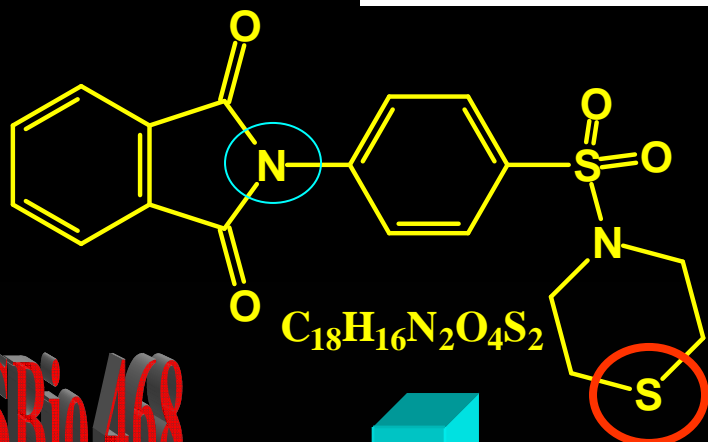




## Effect of compound LASSBio 468 on TNF- $\alpha$ levels and neutrophil influx into the BALB/c of mice lungs



50% more active than thalidomide



**TNF- $\alpha$  ED<sub>50</sub> 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<sub>50</sub> = 32,6 $\mu$ M**  
(cf. PDE-1, 2, 3, > 420  $\mu$ M; 5)



# LASSBio-468

lead compound

## Novo agente anti-inflamatório simbiótico

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- $\alpha$**  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- $\alpha$  and NO Production and Inhibit Endotoxic Shock and Arthritis in Animal Model", *International*

*Immunopharmacology* 2005, **5**, 485.







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  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

### ANALGESIC AND ANESTHETIC DRUGS

Full Text: PDF (72 Kb)

#### ANALGESIC DRUGS

306339 (Euroceltique)  
306344 (Euroceltique)  
306935 (Ono)  
307215 (Meiji Seika)  
307485 (AstraZeneca)  
307488 (AstraZeneca)  
GRT-1539R (Grünenthal)  
REN-1869 (Novo Nordisk; ReNeuron)

### RESPIRATORY DRUGS

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#### ASTHMA THERAPY

305505 (Merck KGaA)  
305527 (Boehringer Ingelheim)  
305570 (Euroceltique)  
306350 (Advanced Medicine)  
307151 (Protherics)  
307296 (Nikken Chemicals)  
307455 (Ube)  
307490 (Icos)  
307517 (Byk Gulden)  
307521 (Byk Gulden)  
307617 (Merck Frosst)  
307627 (Celgene)  
307629 (Celgene)  
307841 (Bayer)  
307866 (Celltech Group)

### DERMATOLOGIC DRUGS

Full Text: PDF (35 Kb)

#### ANTIPSORIATICS

305669 (Fournier)

#### WOUND-HEALING AGENTS

307736 (Pfizer)

### CARDIOVASCULAR DRUGS

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#### ANTIHYPERTENSIVE DRUGS

307618 (Actelion)  
308603 (Kirin Brewery)  
Bay-41-8543 (Bayer)

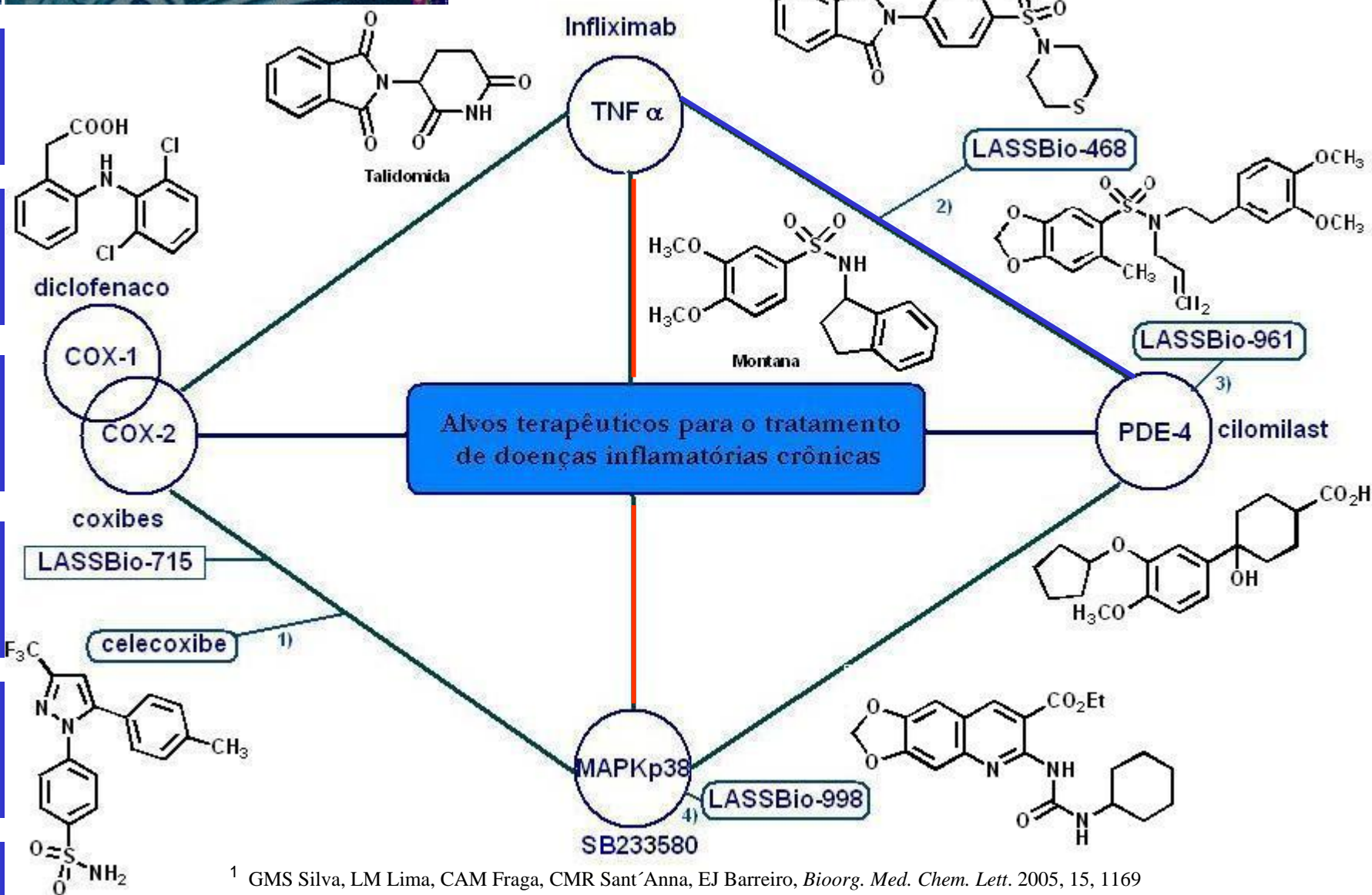
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308145 (Pfizer)  
308151 (Pfizer)  
308641 (Teijin)  
308677 (Bayer)  
CALP2 (University of Alabama at Birmingham; Janssen; Utrecht University)  
LASSBio-468 (Universidade Federal do Rio de Janeiro)

#### AGENTS FOR RESPIRATORY DISTRESS SYNDROME

305451 (Shionogi)

**TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASES (COPD)**  
308751 (Bristol-Myers Squibb)





<sup>1</sup> GMS Silva, LM Lima, CAM Fraga, CMR Sant'Anna, EJ Barreiro, *Bioorg. Med. Chem. Lett.* 2005, 15, 1169

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

<sup>3</sup> LM Lima & EJ Barreiro, resultados não publicados

<sup>4</sup> BR-0502016-6 03/06/2005

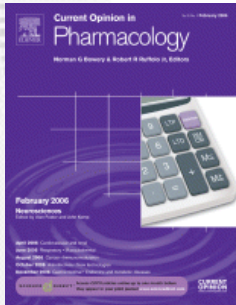


# O terceiro alvo:

## What next for rheumatoid arthritis therapy?

Simon M Blake\* and Barbara A Swift

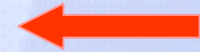
*Curr Op Pharmacol.* 2004, 4, 276



## 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

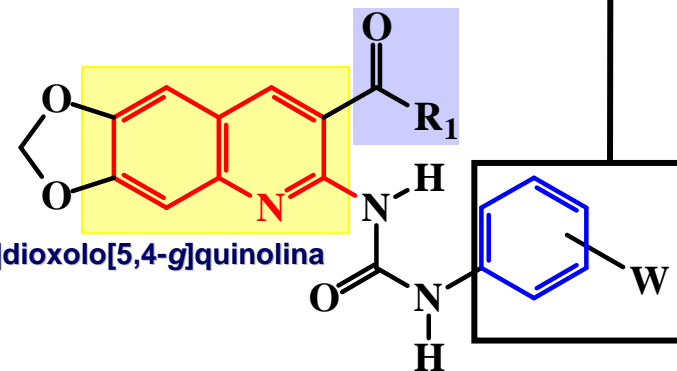




# Desenho Estrutural & Planejamento Molecular

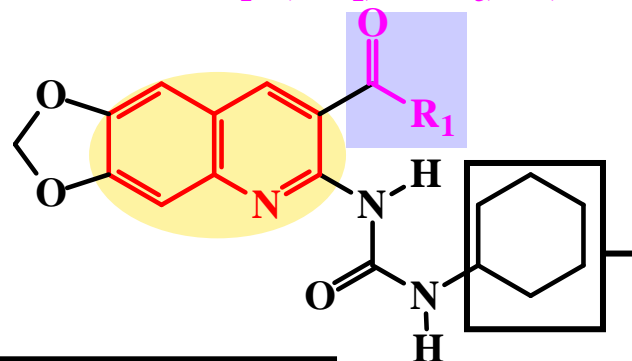
*Inter-alia:* 2-Py, 3-Py, 4-Py, a-naftila, 2-tiofeno, 2-furano, tiazola, isoxazola, tiadiazola, pirimidina, pirrola, oxazola, piridazina, triazina, imidazola;

## LASSBio-998

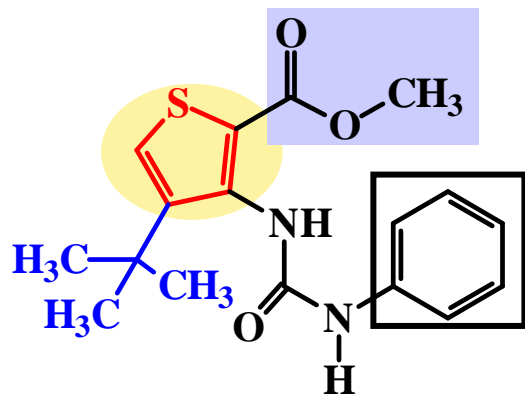


W = *orto*, *meta*, *para*: H; F; Cl; Br; CH<sub>3</sub>; CH<sub>2</sub>CH<sub>3</sub>; CF<sub>3</sub>; OCH<sub>3</sub>; OCF<sub>3</sub>; NO<sub>2</sub>; NH<sub>2</sub>; NHCH<sub>3</sub>; NHC(=O)CH<sub>3</sub>; NHSO<sub>2</sub>CH<sub>3</sub>

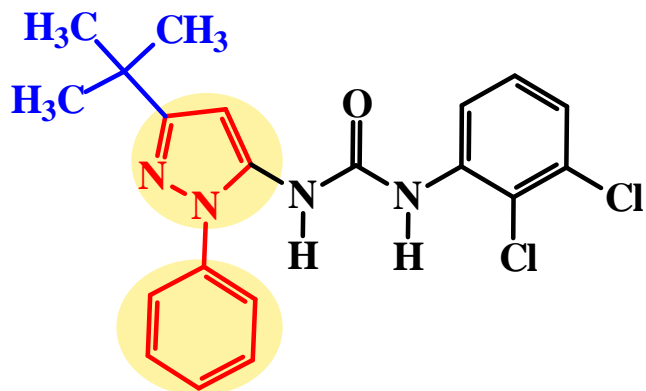
R<sub>1</sub> = OMe; OEt; OPr; OiPr; OPh, OCH<sub>2</sub>Ph; NH<sub>2</sub>, NHCH<sub>3</sub>, OH, NHNH<sub>2</sub>



CH<sub>3</sub>; (CH<sub>2</sub>)<sub>n</sub>CH<sub>3</sub>; alquila ramificados; ciclopropila; ciclopentila, cicloeptila.



GSK 00687

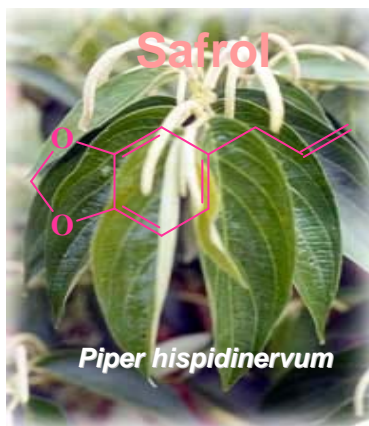


Literatura de patentes:  
Anti MAPKp38

**Hibridação molecular**



**Bioisosterismo**



*Piper hispidinervum*


Volume 15  
No. 1, 2005

# The molecular basis for coxib inhibition of p38 $\alpha$ MAP kinase

Gilberto M. Sperandio da Silva,<sup>a,b</sup> Lidia M. Lima,<sup>a</sup> Carlos A. M. Fraga,<sup>a</sup>  
Carlos M. R. Sant'Anna<sup>a,c</sup> and Eliezer J. Barreiro<sup>a,b,\*</sup>

<sup>a</sup>*Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, PO Box 68006, RJ 21944-971, Brazil*

<sup>b</sup>*Departamento de Farmacologia Básica e Clínica, Instituto de Ciências Biomédicas, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, RJ, 21941-590, Brazil*

<sup>c</sup>*Departamento de Química, ICE, Universidade Federal Rural do Rio de Janeiro (UFRRJ), Seropédica, RJ 23851-970, Brazil*

Received 11 April 2005; revised 20 May 2005; accepted 26 May 2005

**Abstract**—In this work, we present the results of two combined approaches, molecular docking and comparative molecular field analysis (CoMFA), to propose how the selective cyclooxygenase-2 inhibitor celecoxib could act as a p38 mitogen-activated protein (MAP) kinase inhibitor. The docking analysis revealed why celecoxib has a less favorable binding energy ( $\Delta G = -12.4$  kcal/mol) than the selective p38 MAP kinase (p38 MAPK) inhibitor, SB203580 ( $\Delta G = -22.2$  kcal/mol). The CoMFA results revealed unfavorable steric effects that can be related to the predicted lower p38 MAP kinase inhibitory activity of celecoxib. Additionally, FlexX and CoMFA results also suggested that etoricoxib, another selective COX-2 inhibitor, could inhibit p38 MAP kinase.

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*Bioorganic & Medicinal Chemistry Letters*, Volume 12, Issue 16, 1 August 2002, Pages 2237-2240  
Shi, T.; Rabenstein, D.L.
2. Structural biology of G protein-coupled receptors • Short communication  
*Bioorganic & Medicinal Chemistry Letters*, Volume 15, Issue 16, 1 August 2005, Pages 3654-3657  
Lundstrom, K.
13. The molecular basis for coxib inhibition of p38 $\alpha$  MAP kinase • Short communication  
*Bioorganic & Medicinal Chemistry Letters*, Volume 15, Issue 15, 1 August 2005, Pages 3506-3509  
Sperandio da Silva, G.M.; Lima, L.M.; Fraga, C.A.M.; Sant'Anna, C.M.R.; Barreiro, E.J.

# Modelo CoMFA – Mapa de contorno eletrostático & estérico

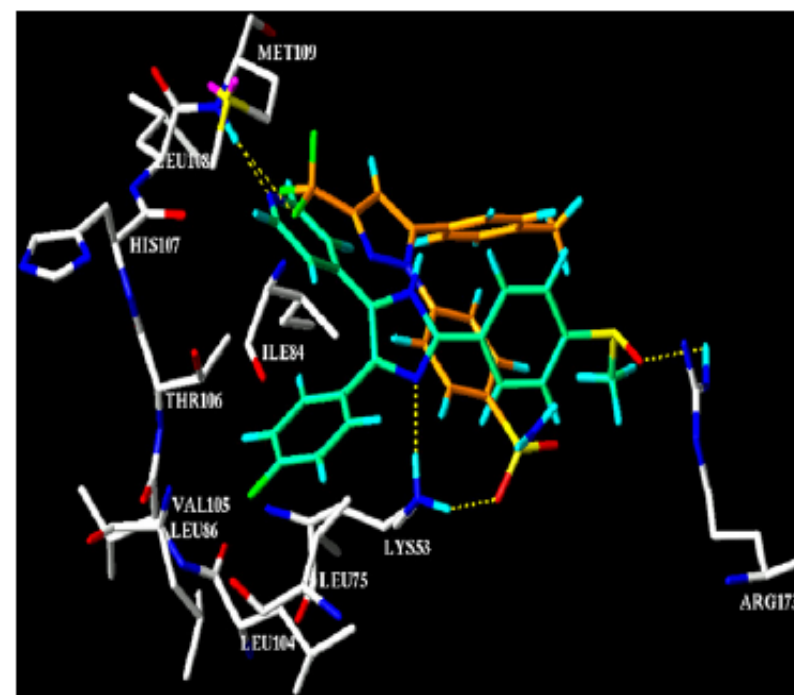
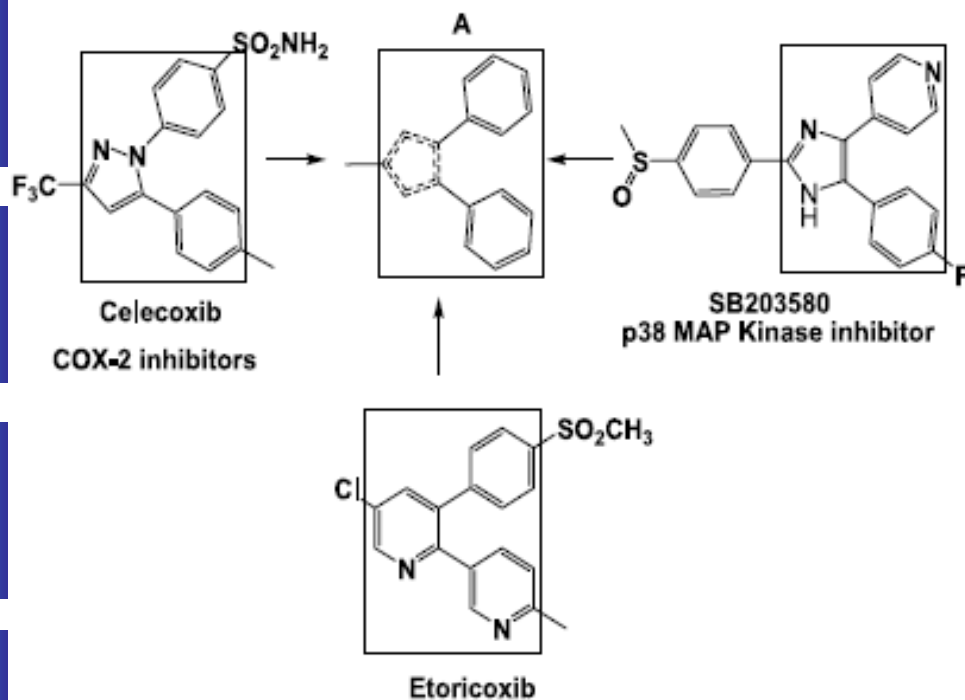
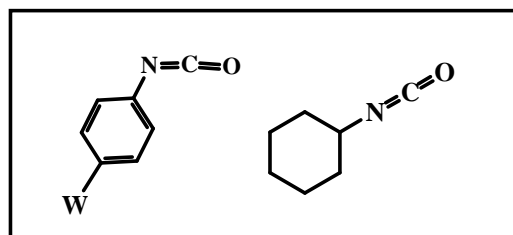
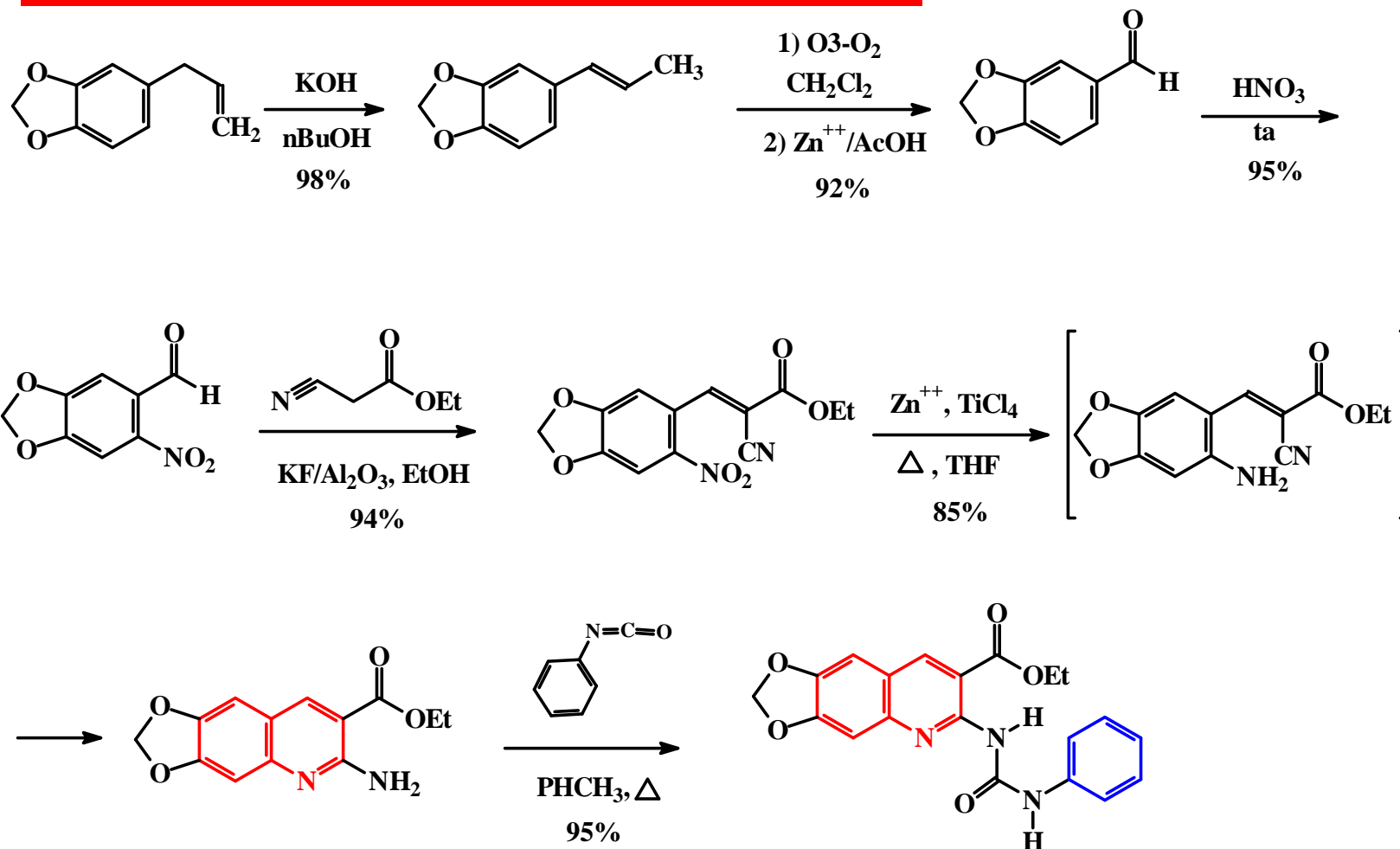


Figure 2. Probable binding conformation of celecoxib and its alignment in the binding site of p38 MAPK. FexX docking shows most important amino acid of p38 MAPK to interact with celecoxib. For celecoxib the carbon atoms are shown in orange (C), blue (N), red (O), and green (halogen). For SB203580, the carbon atoms are shown in green-blue (C), blue (N), red (O), and green (halogen).

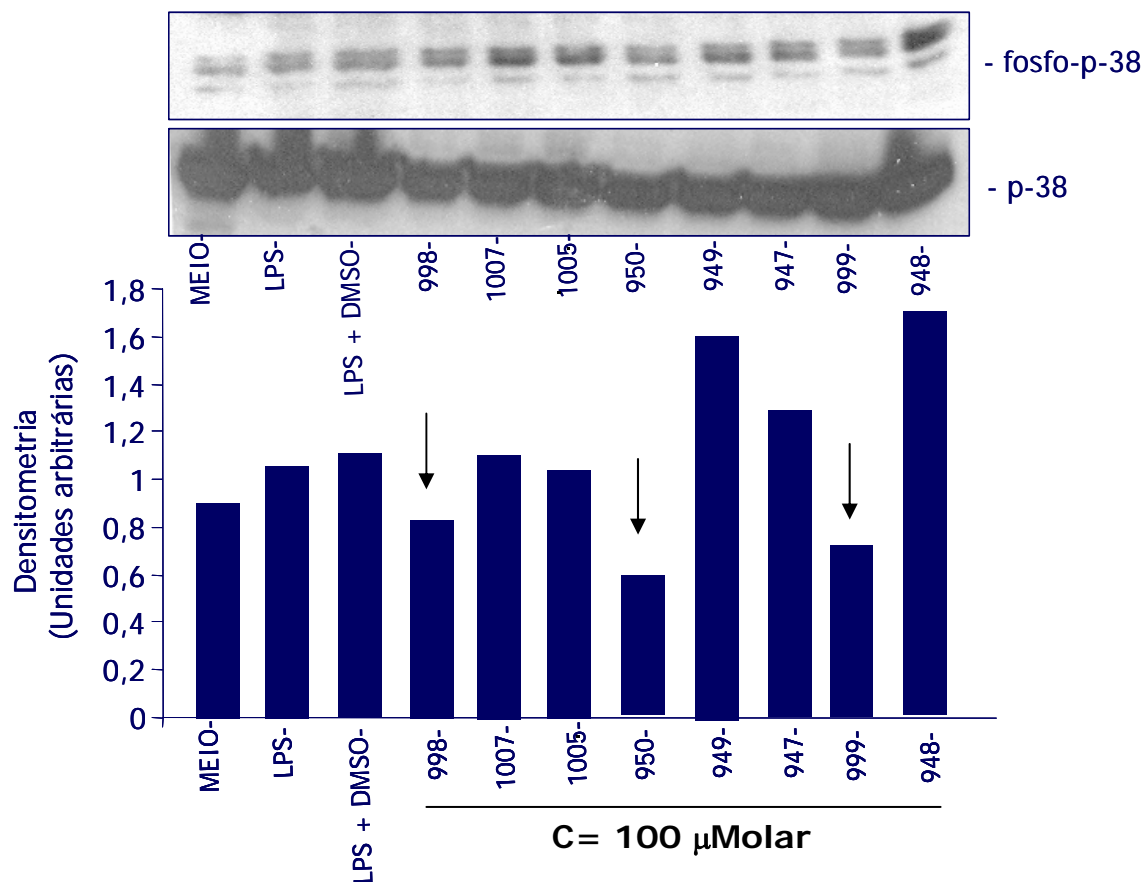


# Síntese dos compostos-alvo



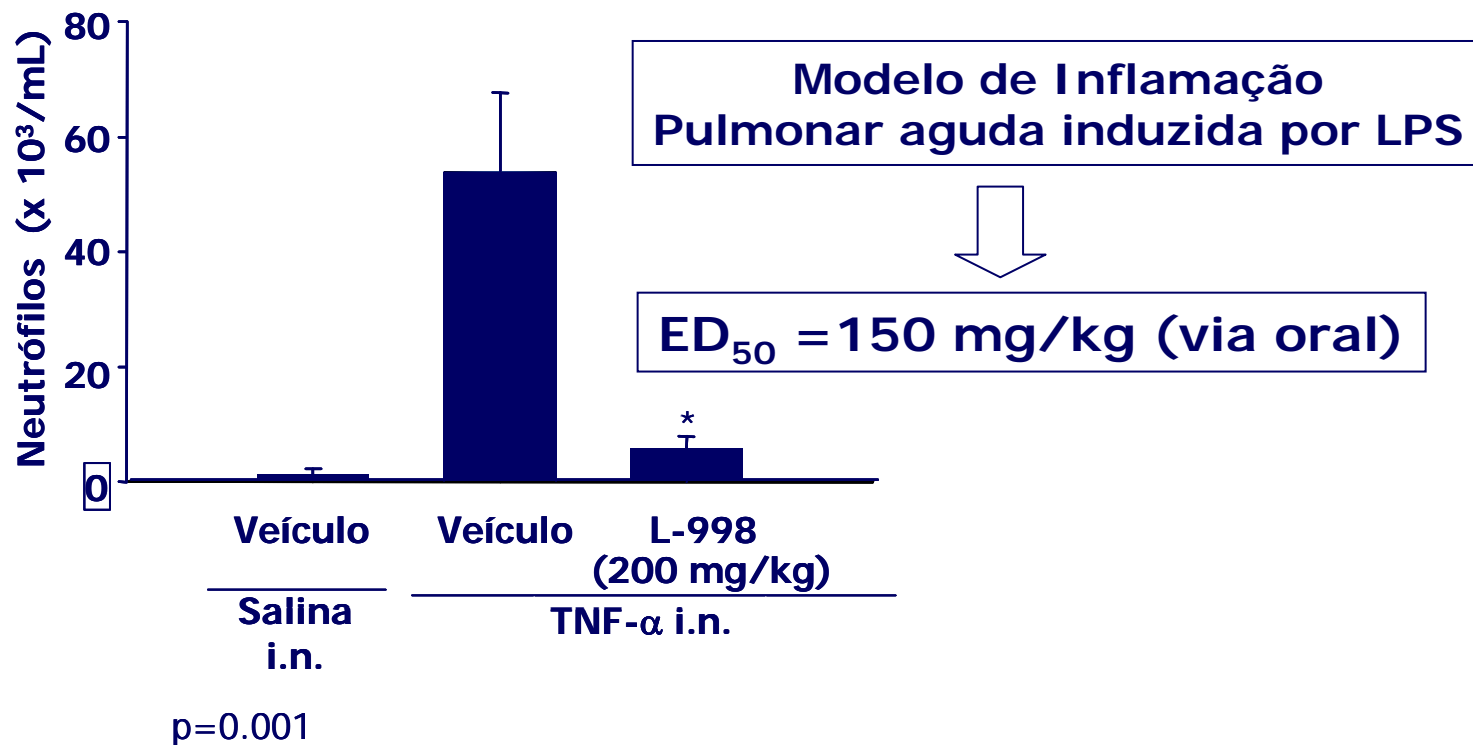
# Perfil Farmacológico

**EFEITOS DOS COMPOSTOS INIBIDORES DE p38 SOBRE A FOSFORILAÇÃO DA MAP KINASE p38 EM PBMC INDUZIDA POR LPS (Western-Blot)**



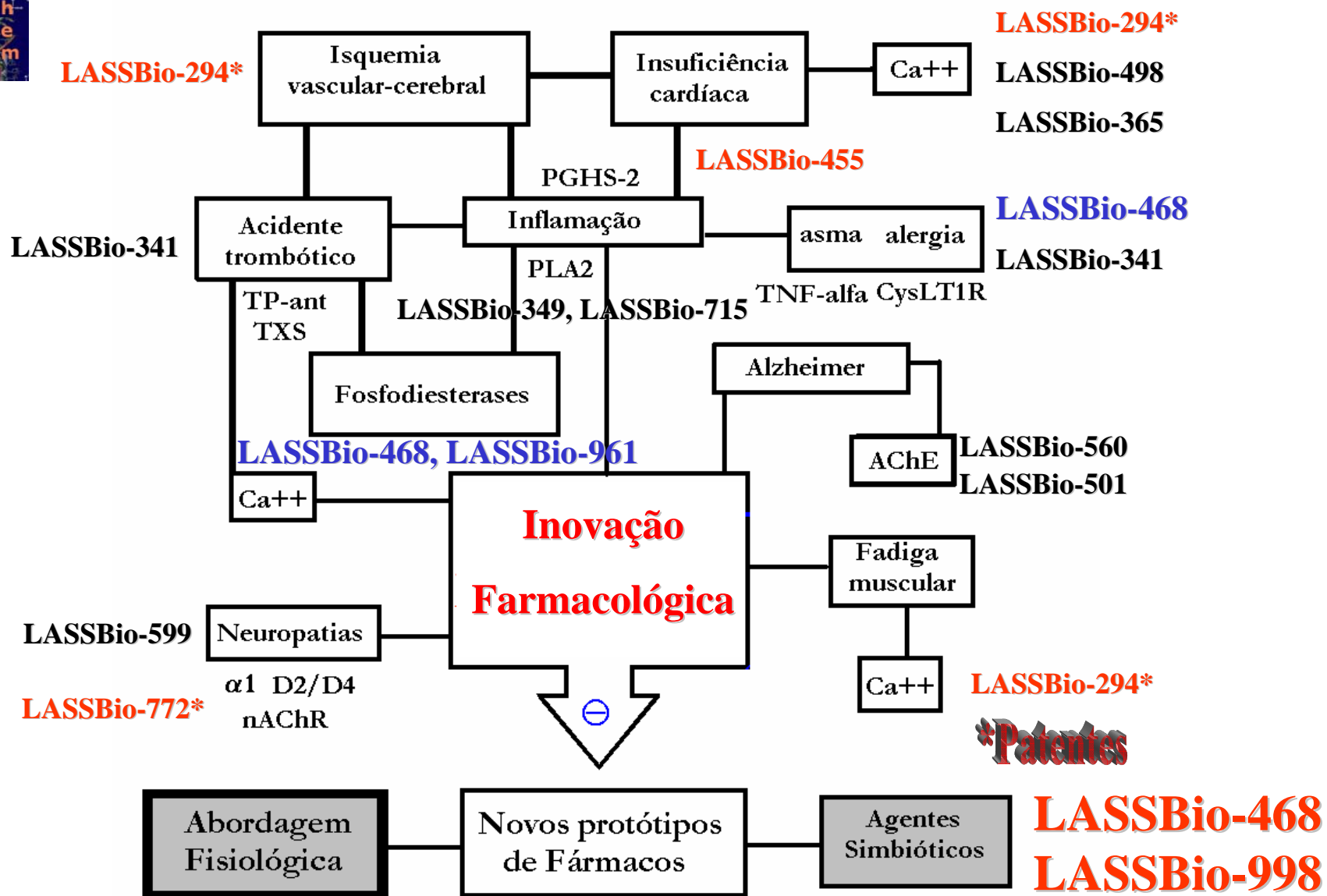
## Perfil Farmacológico 2

### EFEITO DE TRATAMENTO COM L-998 NO INFLUXO DE NEUTRÓFILOS APÓS INSTILAÇÃO INTRANASAL DE TNF- $\alpha$



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.

# Novos Protótipos Descobertos no LASSBio





- ✦ Prof. Dr Fernando Queiroz Cunha (FM, USP-RP)
- ✦ Profa. Dra Vera L. G. Koatz (in memoriam IBqM, UFRJ)
- ✦ Profa Dra Magna Suzana Alexandre Moreira (ICBS, UFAL)
- ✦ Dr Paulo Barboni (FM-USP-RP)
- ✦ Dra Aline Brando Lima (IBqM, UFRJ)
- ✦ Dr Gilberto Marcelo Sperandio da Silva (FIOCRUZ, RJ)
- ✦ Dra Claire Lugnier, (Faculté de Pharmacie, Université Louis Pasteur, Strasbourg, França.

**LASSBio, UFRJ:**

**Prof. Dra Lidia M. Lima**

**Prof. Dr Carlos A. M. Fraga, Prof. Dra Ana L. P. Miranda**

**Apoio financeiro: IM-INOVAR, Pronex, FAPERJ, CNPq, CAPES.**

# Agradecimentos