Estratégias da *Química Medicinal* no planejamento de novos fármacos simbióticos

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LASSBio®
Laboratório de Avaliação e Síntese de Substâncias Bioativas

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Subcommittee Medicinal Chemistry and Drug Development

Química Medicinal

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

é uma disciplina que estuda os aspectos relacionados à descoberta, invenção e preparação de substâncias bioativas,de interesse terapêutico, i.e. ***fármacos.***

Estuda os ***fatores moleculares*** *do modo de ação dos fármacos, incluindo a compreensão da relação entre a estrutura química e a atividade terapêutica, absorção, distribuição, metabolismo, eliminação e toxicidade.*

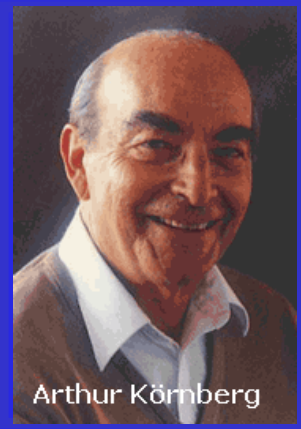
IUPAC

http://www.iupac.org

IUPAC

Chemistry and Human Health Division (VII)
Subcommittee on Medicinal Chemistry and Drug Development.

Prêmio Nobel de Fisiologia e Medicina, 1959



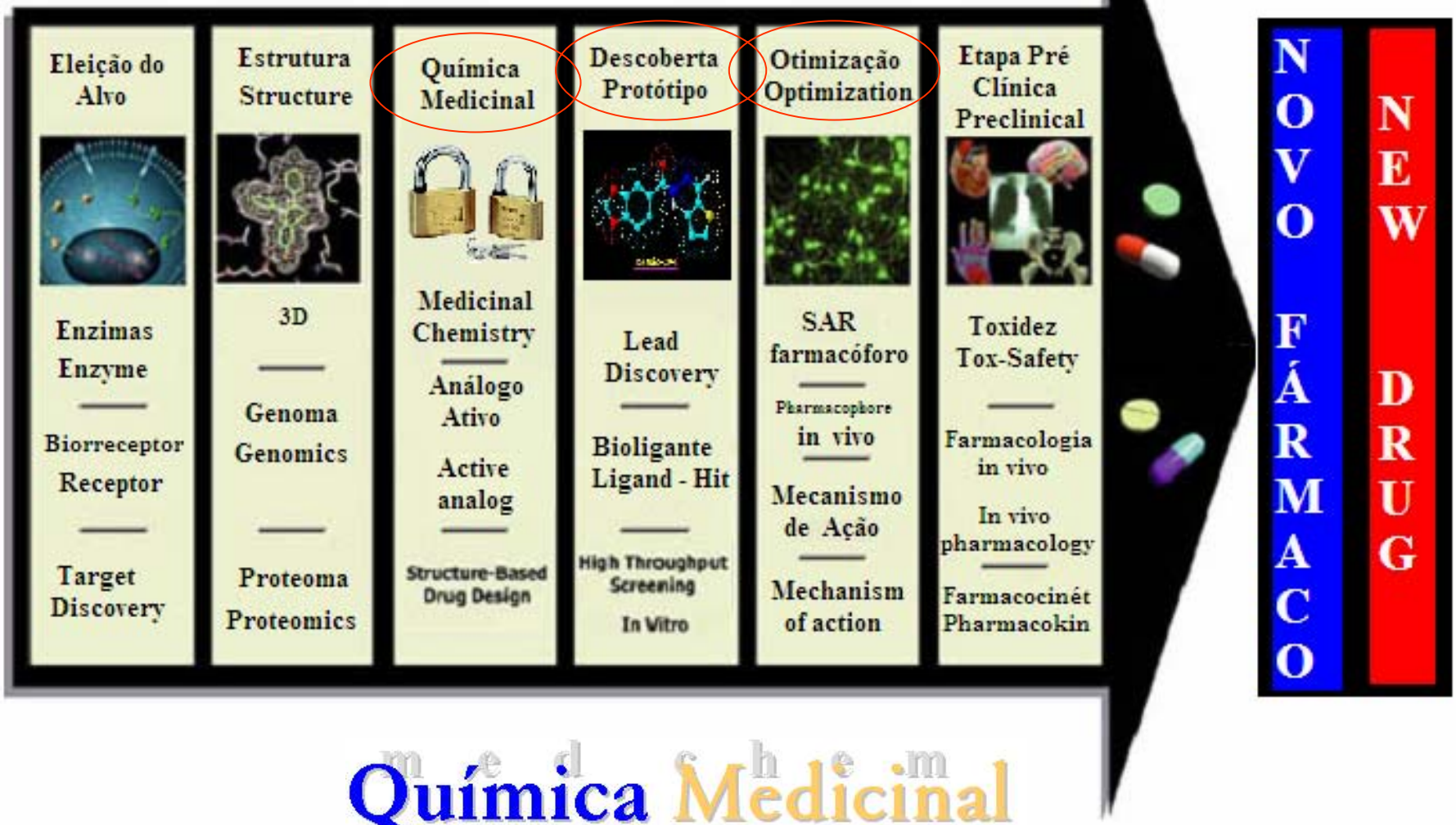
"for their discovery of the mechanisms in the biological synthesis of RNA and DNA"

"We have the paradox of the two cultures, chemistry and biology, growing further apart even as they discover more common ground. For the chemists, the chemistry of biological systems is either too mundane or too complex…"

Annual Meeting of AAAS, 1987

Química Medicinal

O paradigma da Química Medicinal para a descoberta de novos fármacos: *o composto-protótipo*



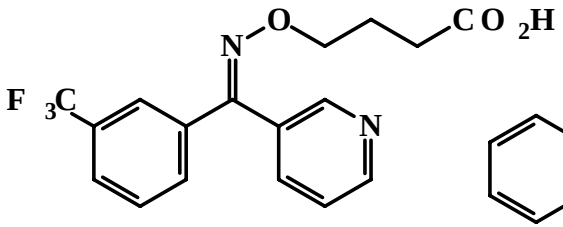
Química Medicinal

Química Medicinal

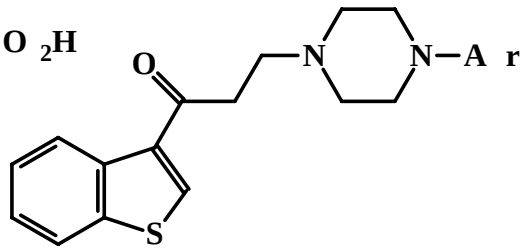
- **Modelo Chave-fechadura**: Emil Fisher

- **Abordagem "uma-doença/um ligante"**
  one-target-one-ligand approach
  one-ligand/one-disease
  Magic bullets

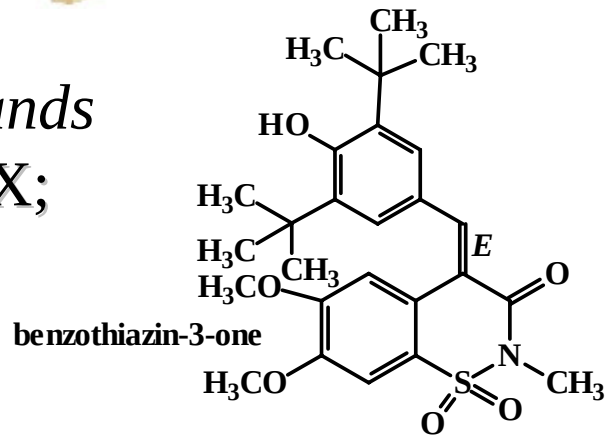
- **Ligantes duplos, para dois alvos**
  Dual, binary, dimeric, bivalent, mixed ligands
  TXS-TPant; 5-HT_{1A}Rant-SSRI; COX-LOX;



Freyne, 1987



Monge, 2001



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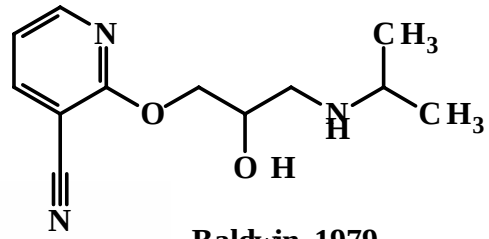
Teixeira, 1998

- **Abordagem simbiótica**

Symbiotic approach = *β-adrenoceptor blocker with vasodilatory activity not due to β-agonism* [Baldwin (MS&D),1979];



Baldwin, 1979

- **Protótipos simbióticos**

novo protótipo capaz de ser efetivo em dois distintos alvos, ambos relevantes na fisiopatologia do processo em estudo, mas pertencendo a diferentes rotas bioquímicas;

Symbiotic lead-candidates (***Multi-target lead-candidates***)

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

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

Symbiotic approach

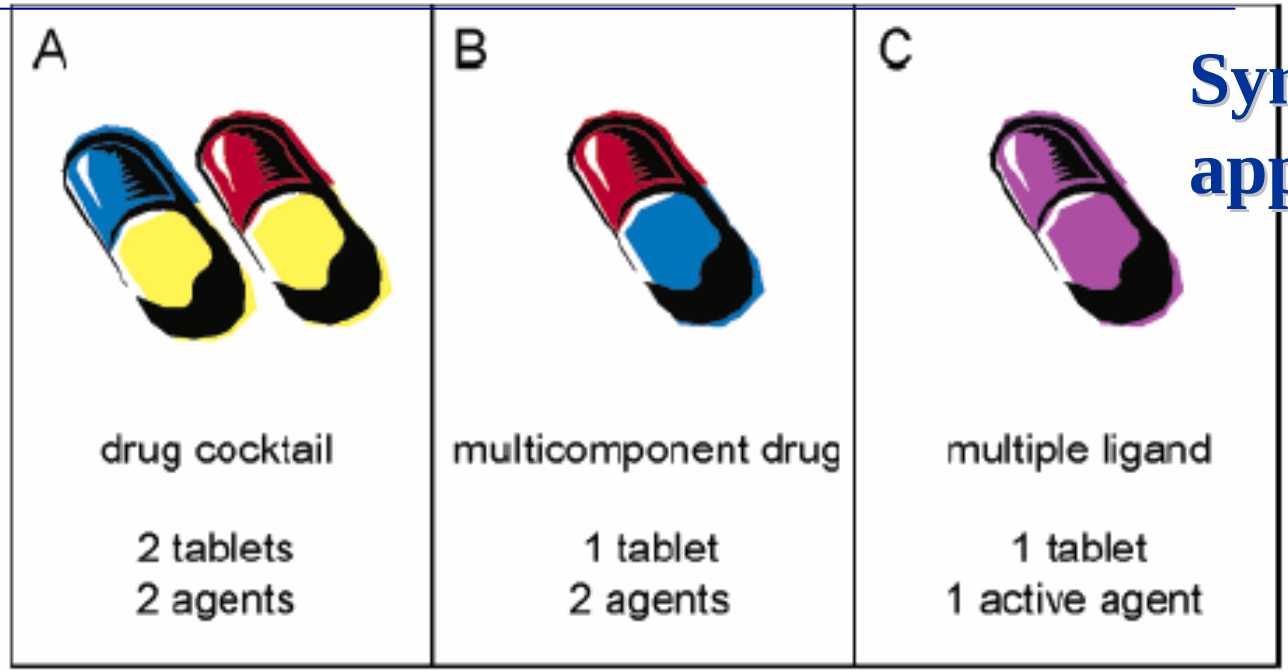


Figure 1. Three main clinical scenarios for multitarget therapy.

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.

The *magic-bullet* paradigm: *one-target, one-disease*

one component tablet

individual tablets

two one component tablet

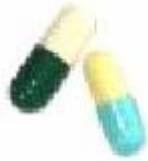
two individual tablets

two component tablet

two agents **coformulated** in a single tablet

Single chemical entity able to modulate two target simultaneously

two component tablet



two one component tablet

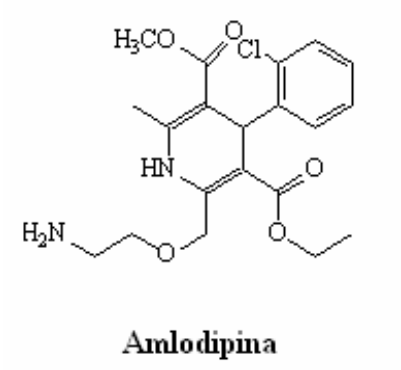
one two-target component tablet

\>

two component tablet

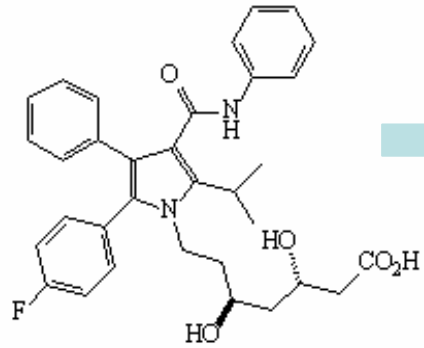
several distinct one component tablet

Symbiotic Approach



Amlodipina

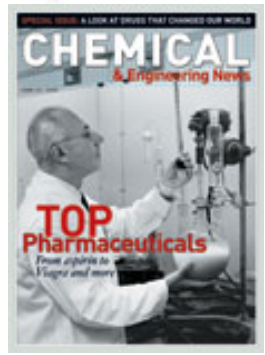
Norvasc[R]



atorvastatina

Lipitor[R]

two component tablet



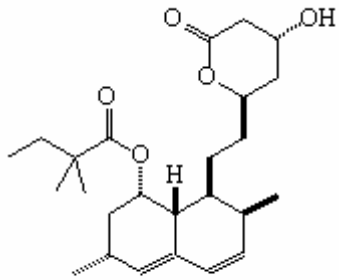
W. H. Frishman & A. L. Zuckerman, *Expert Rev. Cardiovas. Ther.* **20**

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

VYTORIN (ezetimibe/simvastatin)

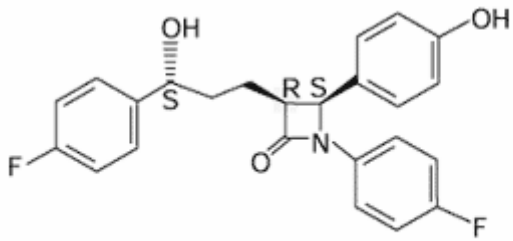
Merck/Schering-Plough

two component tablet



simvastatina

Zoccor[R]

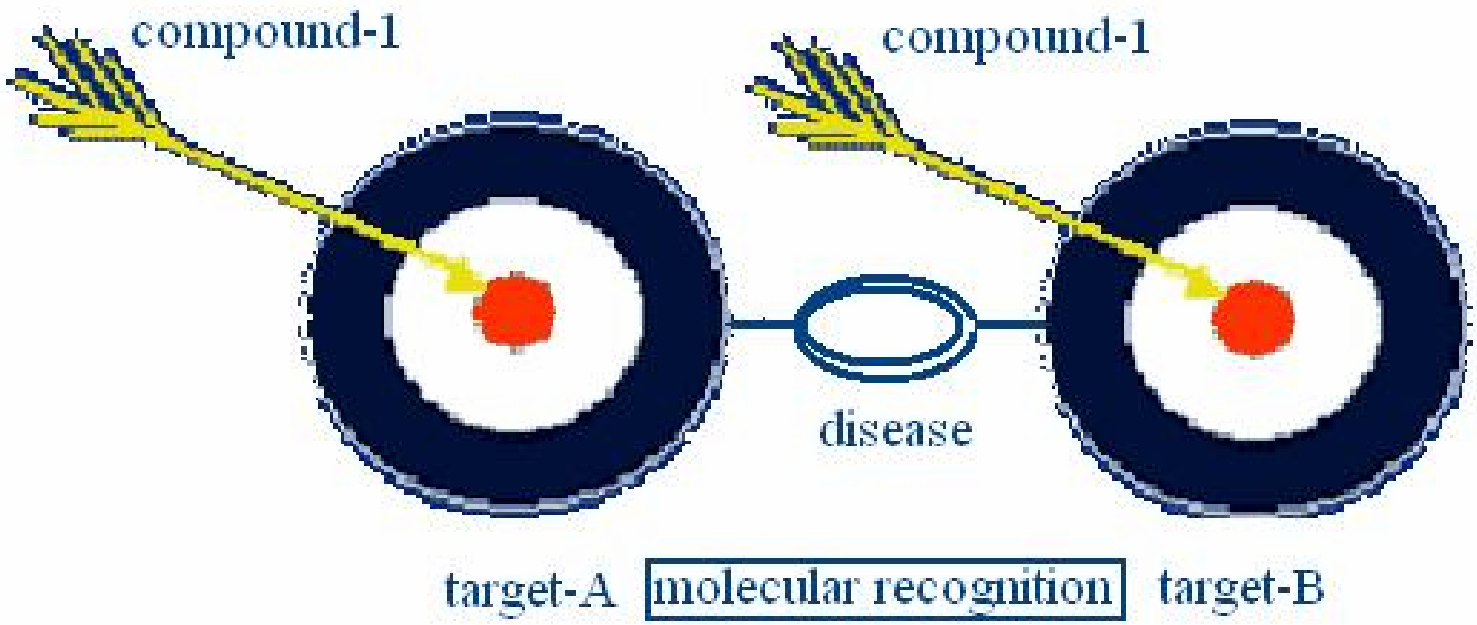


ezetimibe

Zetia[R]

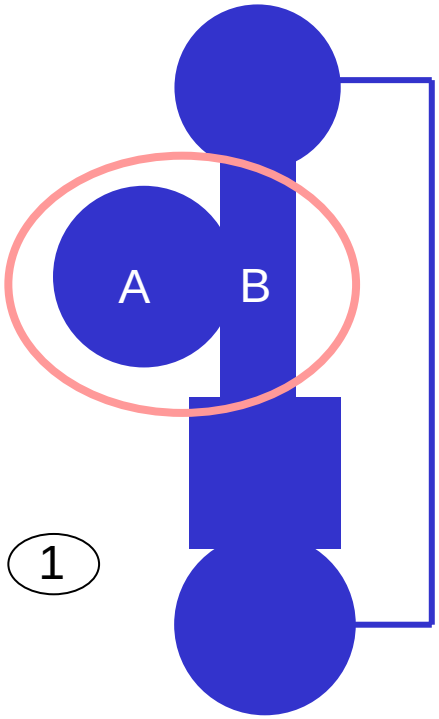
N. A. Flores, *Curr. Opin. Invest. Drugs* **2004**, *5*, 984

The symbiotic lead-candidate design

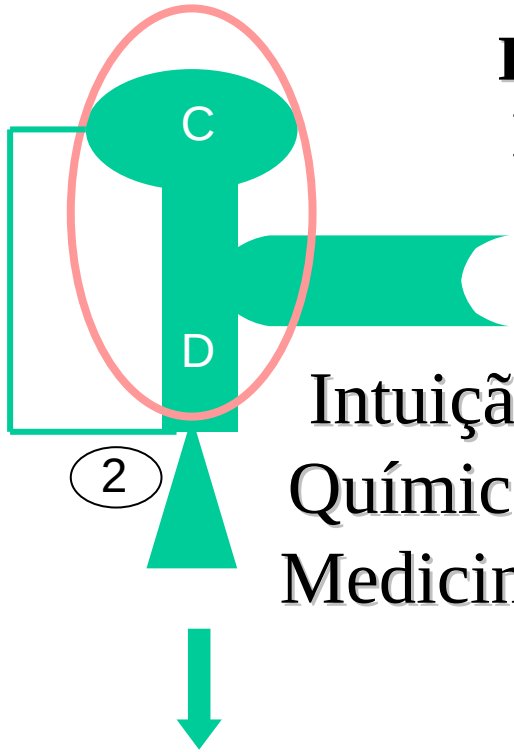


O desenho estrutural de novos candidatos a fármacos simbióticos representa uma inovação na abordagem terapêutica do tratamento de doenças crônicas que resultem, no mecanismo de sua fisiopatologia, do envolvimento de diversos e distintos biomediadores pertencentes a diferentes caminhos bioquímicos.

Unidades farmacofóricas



reconhecimento molecular pelo receptor-A



reconhecimento molecular pelo receptor-B

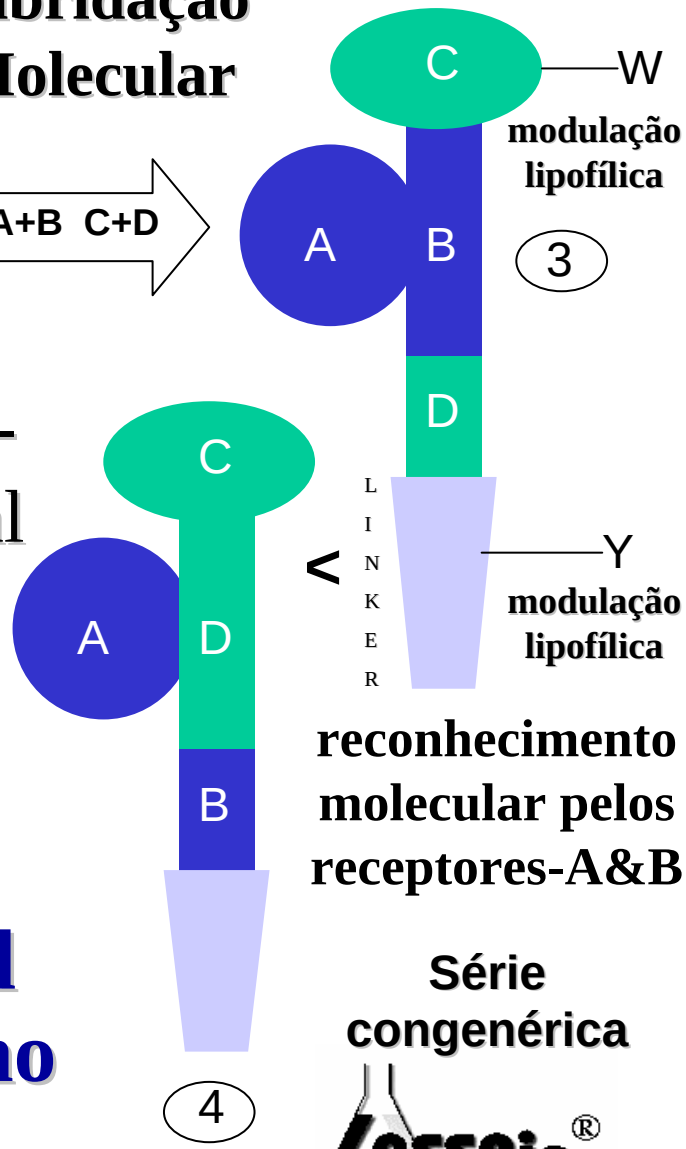
Bioisosterismo

Hibridação Molecular

Novo candidato simbiótico

Intuição Químico-Medicinal

A+B C+D



reconhecimento molecular pelos receptores-A&B

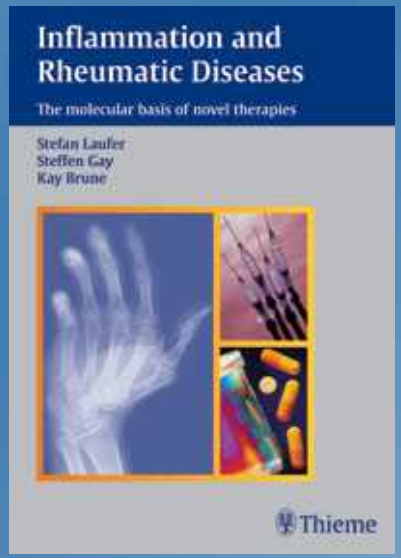
Série congenérica

Base racional para o desenho simbiótico

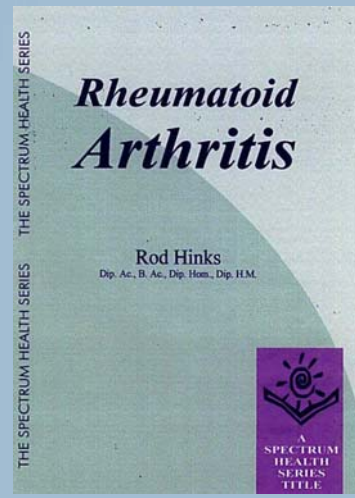
"...The genealogy of quite recently introduced drugs however provides a good illustration of the role that serendipity, ***intuition*** or even pure chance have played in drug discovery up until quite recently."

Daniel Lednicer
"On the origen of drugs"

Nova Abordagem Terapêutica para o Tratamento da Inflamação



Agentes simbióticos



Inovação terapêutica

Box 1 | Mediators of the acute inflammatory response

Mediators known to drive the acute inflammatory response

- The clotting system products (plasmin, fibrinopeptides)
- Fibrinolytic system products (fibrin)
- Kinins (bradykinin)
- Vasoactive amines (histamine and 5-hydroxytryptamine)
- Substance P
- Complement system by-products
- Eicosanoids (prostaglandins, leukotrienes and platelet activation factor)
- Cell-adhesion molecules
- Cytokines
- Chemokines
- Oxygen-derived free radicals
- Nitric oxide

Mediators recently found to be involved in pro-resolution

- Cyclopentenone prostaglandins
- Lipoxins/resolvins
- NF-κB (p50/p50)
- Mediators of apoptosis (caspases, CD44, etc.)
- Annexin-1

Nature Rev Drug Discov. 2004, 3, 401

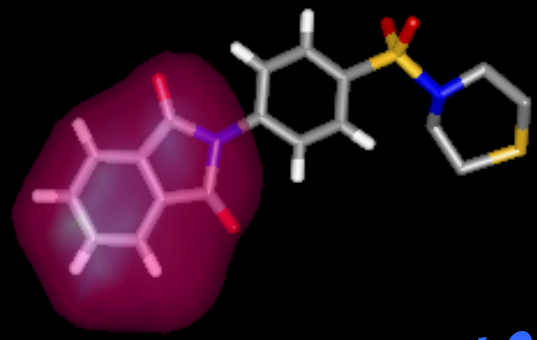
INFLAMMATORY RESOLUTION: NEW OPPORTUNITIES FOR DRUG DISCOVERY

Derek W. Gilroy, Toby Lawrence‡, Mauro Perretti* and Adriano G. Rossi§*

Treatment of inflammatory diseases today is largely based on interrupting the synthesis or action of mediators that drive the host's response to injury. Non-steroidal anti-inflammatories, steroids and antihistamines, for instance, were developed on this basis. Although such small-molecule inhibitors have provided the main treatment for inflammatory arthropathies and asthma, they are not without their shortcomings. This review offers an alternative approach to the development of novel therapeutics based on the endogenous mediators and mechanisms that switch off acute inflammation and bring about its resolution. It is thought that this strategy will open up new avenues for the future management of inflammation-based diseases.

Nature Rev Drug Discov. 2004, 3, 401

Novo protótipo de fármaco simbiótico anti-inflamatório: anti-citocina & PDEi

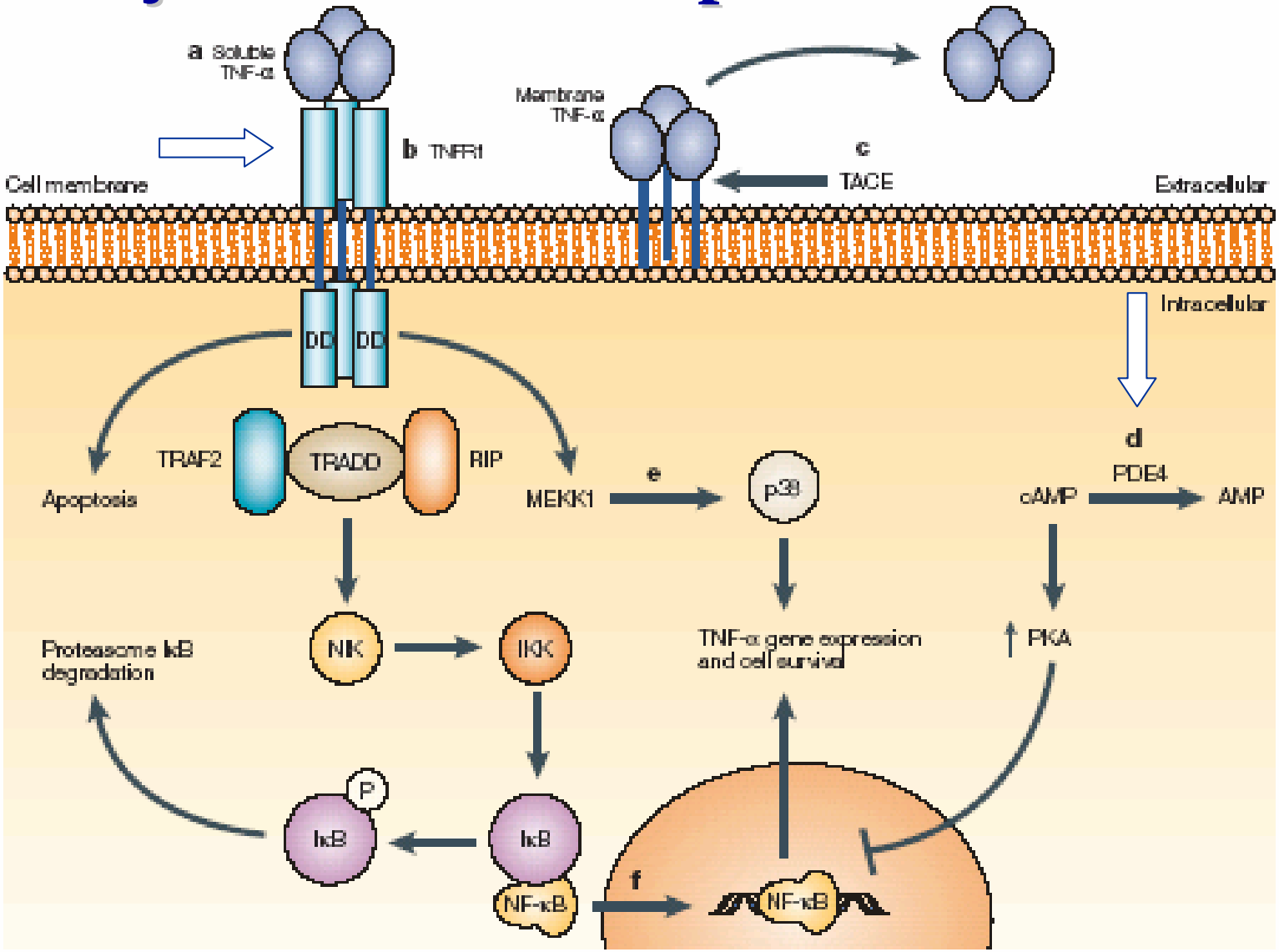


$C_{18}H_{16}N_2O_4S_2$
388.45

LASSBio-468

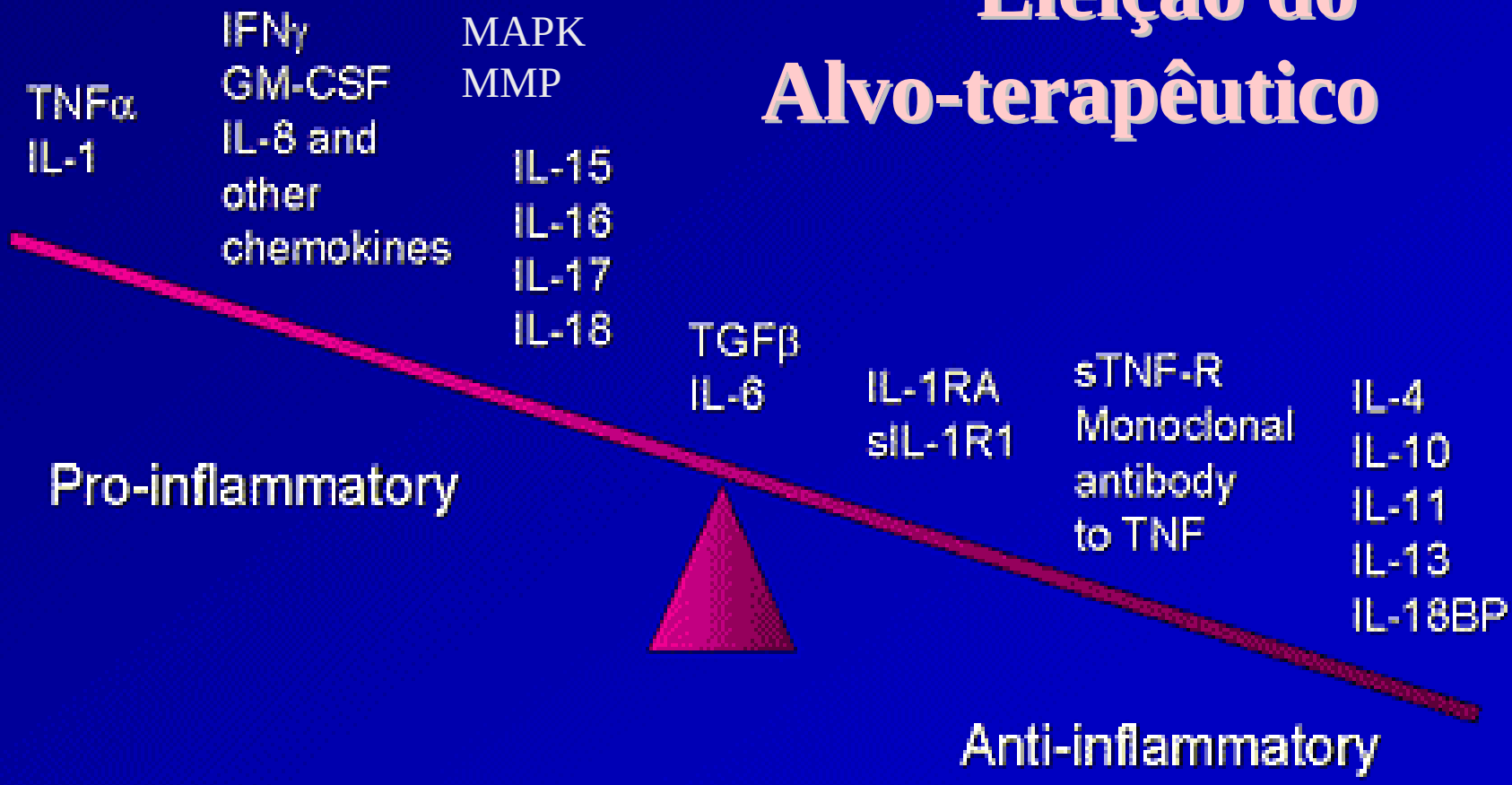
anti-TNF / PDE-4i

Eleição do Alvo-terapêutico



Role of Cytokines and Cytokine Inhibitors in Chronic Inflammation

Eleição do Alvo-terapêutico



Arend. *Arthritis Rheum* 2001.

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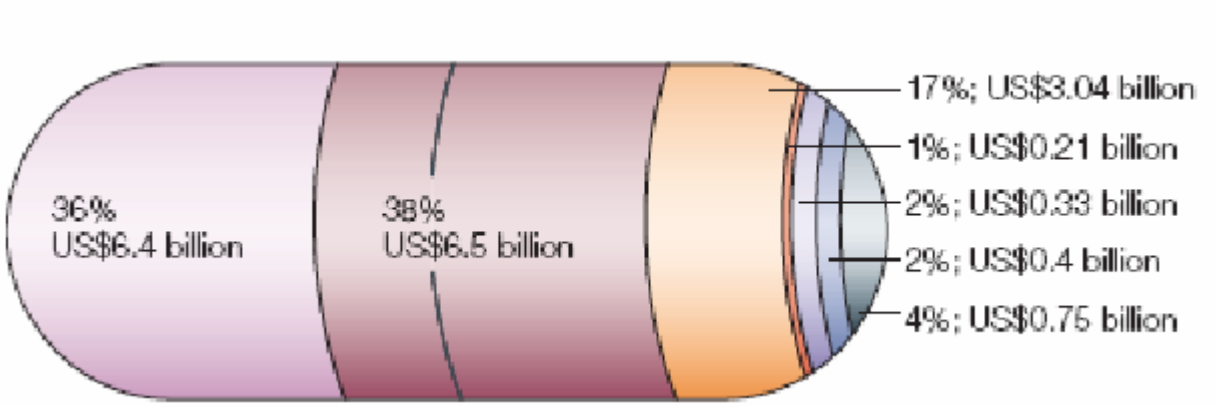
Fármacos Anti-TNF-α

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 fármacos de origem biotecnológica (injetáveis)

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.

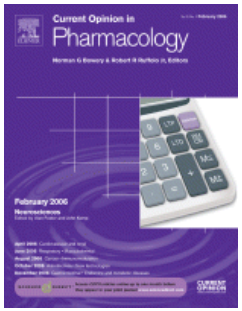
Phosphodiesterase-4 as a therapeutic target

Miles D Houslay, Peter Schafer & Kam Y J Zhang

Drug Discov Today 2005, 10, 1503,

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

Curr Op Pharmacol. 2004, 4, 276

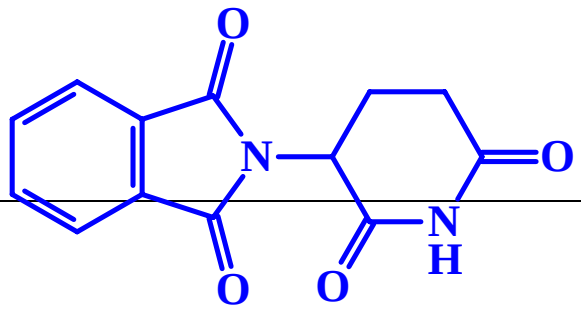


The p38 MAP kinase pathway as a therapeutic target in inflammatory disease
Jeremy Saklatvala

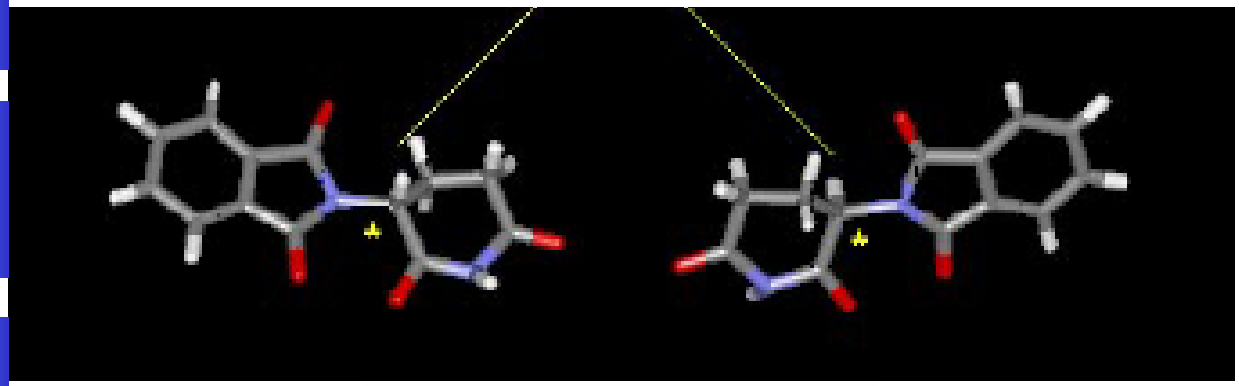
Curr Op Pharmacol. 2004, 4, 372

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



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



THALIDOMIDE

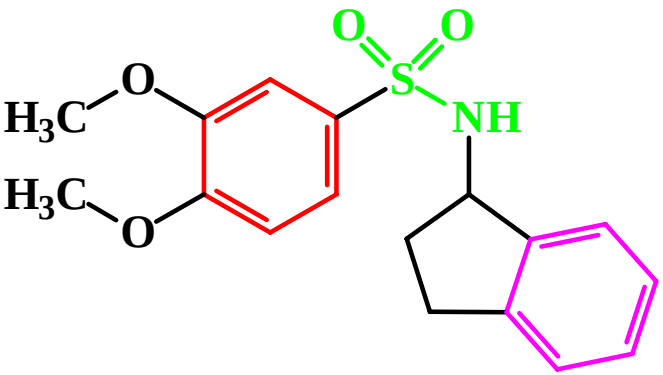
TNF-α IC_{50} = 200 μM

Thalomid^{R}, Phase III, Celgene

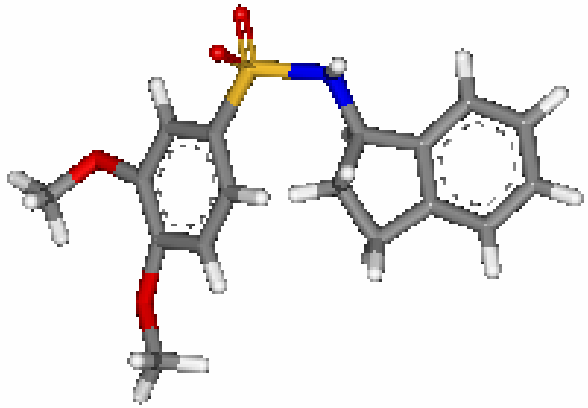
Wilhelm Kunz, 1953
Herbert Keller, 1953
CNS, 1957
Frances Kelsey, 1961
Gilla Kaplan, 1991 (TNF-α)
Elisabeth P. Sampaio,1997

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.

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



Aril-sulfonamida

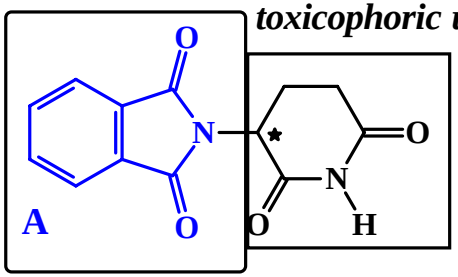


PDE-4i IC_{50} = 4.3 μM

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 do LASSBio-468, Novo Agente Simbiótico

Novo agente simbiótico com propriedades anti-TNF-a & inibidor de PDE-4

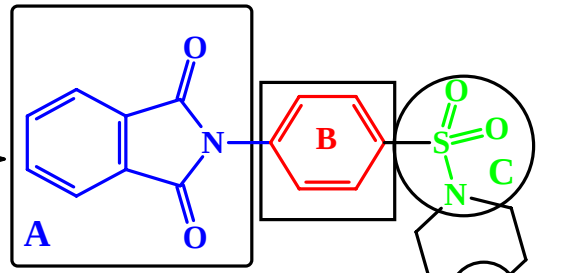


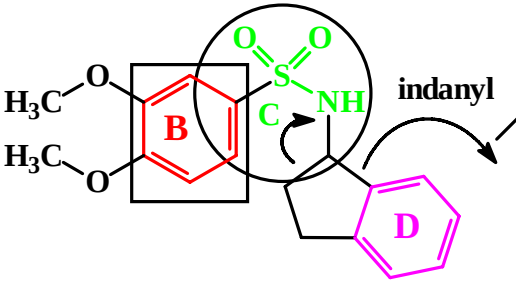
thalidomide

TNF-α IC_{50} = 200 μM

Quim. Nova 2001, **24**, 583

molecular hybridization



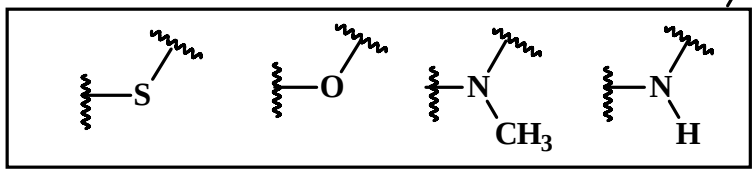


aryl sulfonamide

PDE-4i IC_{50} = 4.3 μM

isosteres

Série congênere



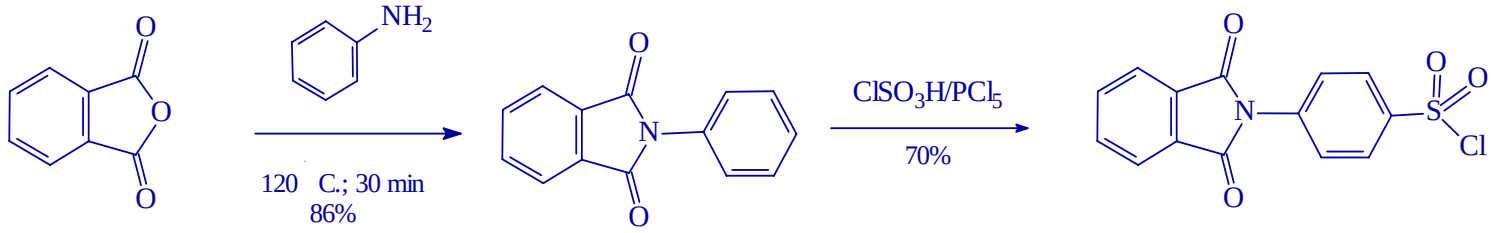
isosteres

σ, π, MR

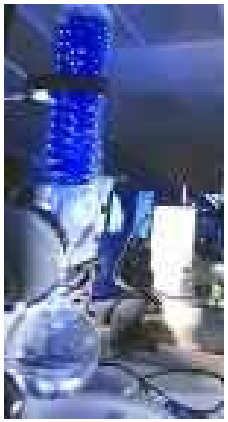
***N*-phenylpiperazinyl**

JG Montana et al., Bioorg. Med. Chem. Lett. 1998, 8, 2635

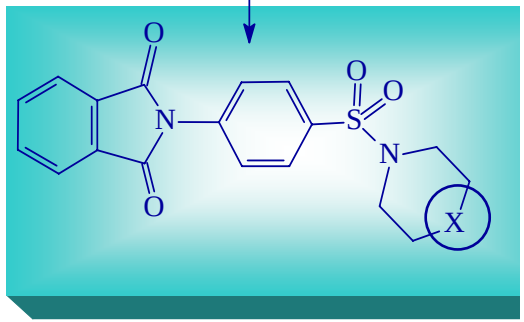
Síntese do LASSBio-468



anidrido ftálico



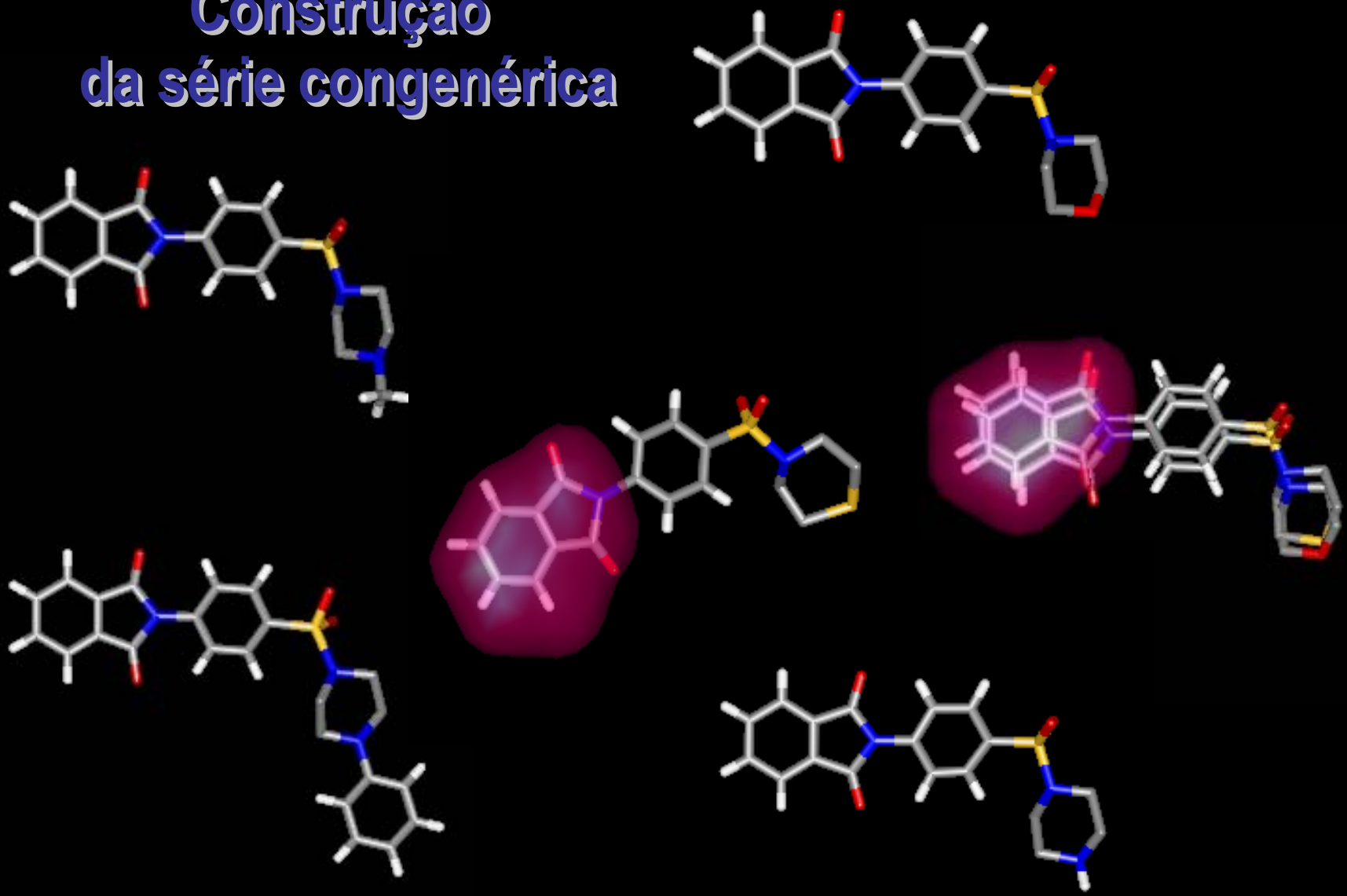
X = NMe 65%
X = NPh 67%
X = NH 58%
X = O 63%
X = S 67%



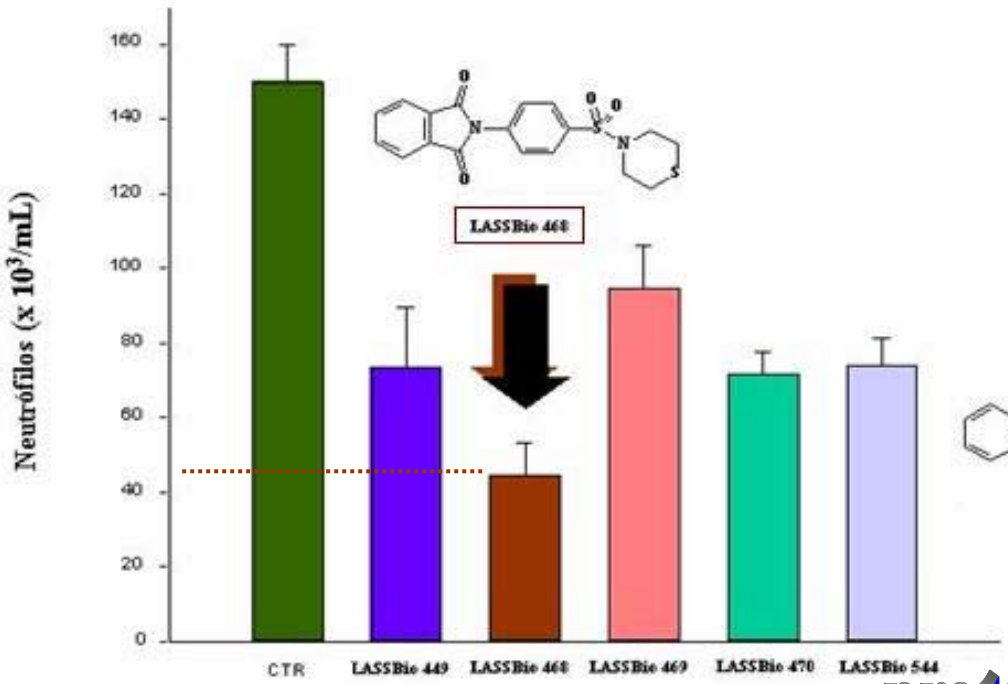
Rendimento global médio: *ca.* 20%
(escala 0.10 M *ca.* 40g)

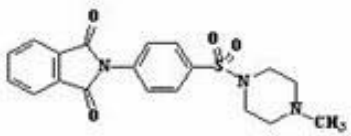
Lidia M. Lima,Tese de Doutoramento, IQ-UFRJ, Br., 2001

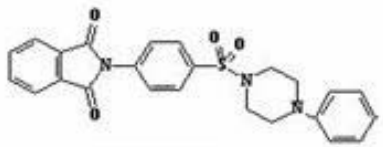
Construção da série congenérica

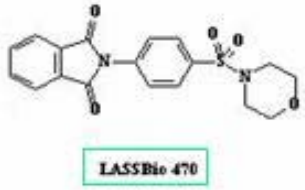


Effect of new compounds and thalidomide on neutrophil influx induced by LPS into BALB/c of mice lungs (10 mg/kg, DMSO; i.p.)



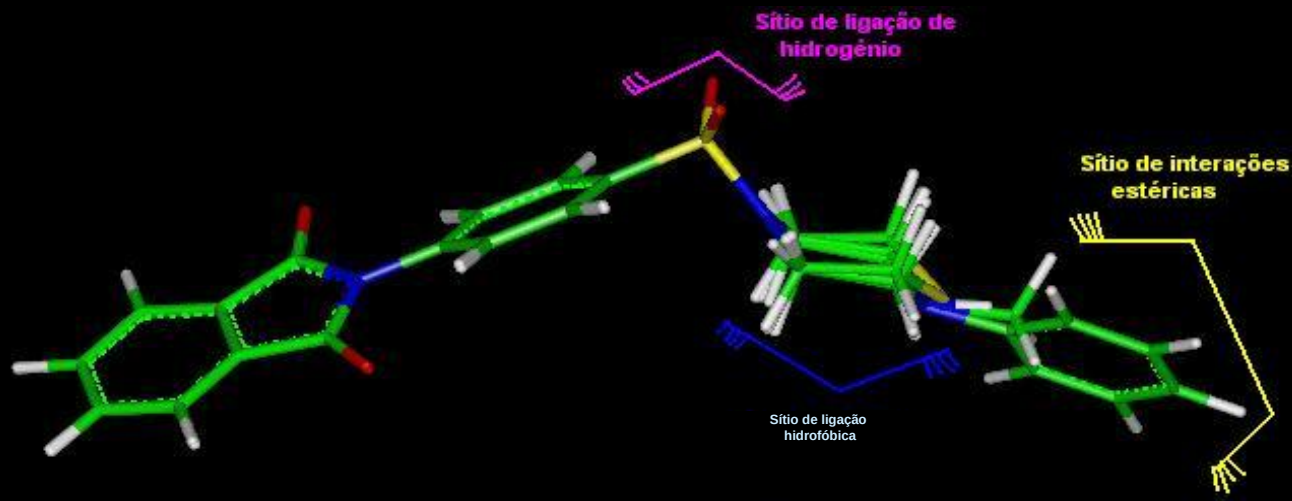


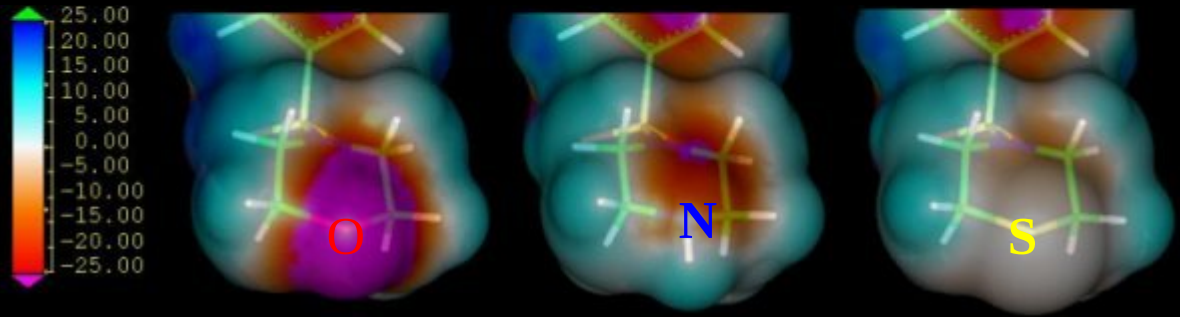




in vivo

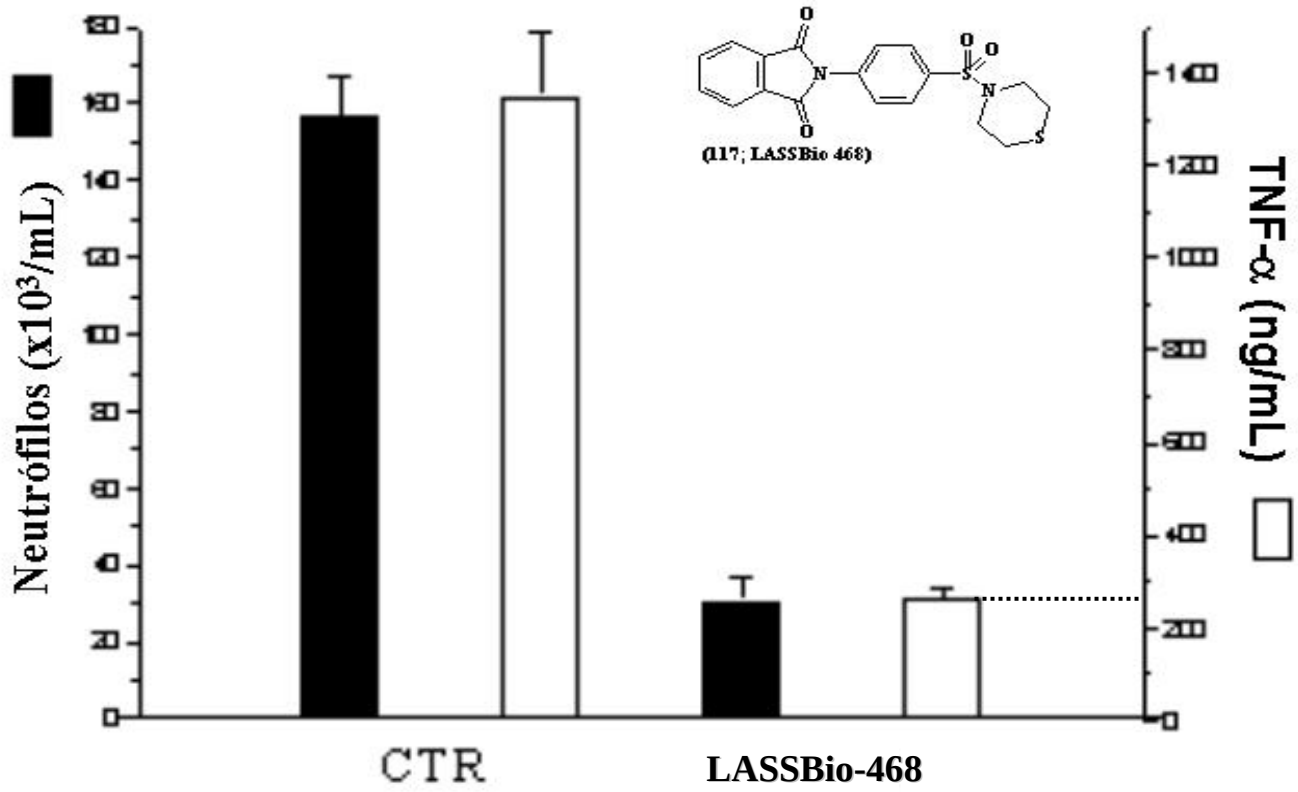
protótipo > ligante





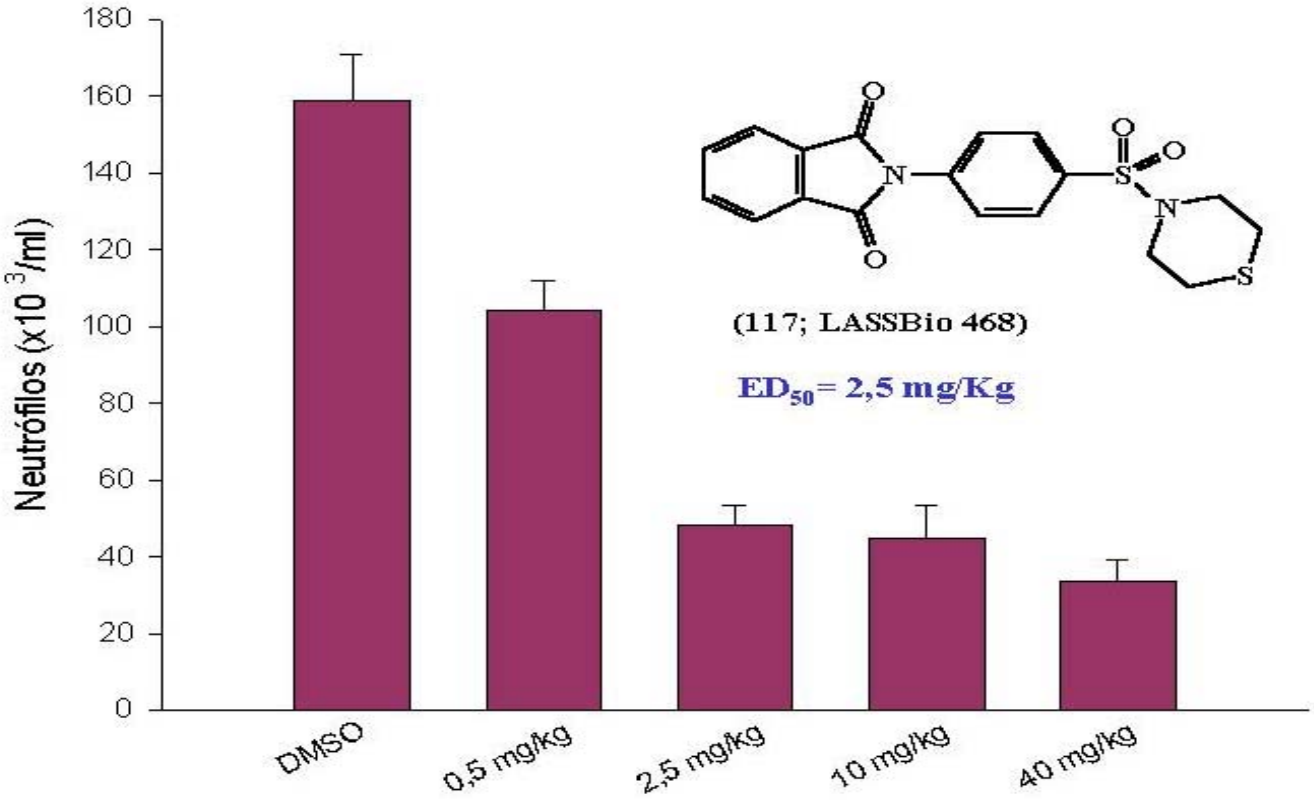
Sobreposição dos confôrmeros de menor energia dos derivados LASSBio 449, LASSBio 469 , LASSBio 468 , LASSBio 470 e LASSBio 544, calculados por métodos semiempíricos no programa Spartan 3.0.1. Mapeamento do potencial eletrostático, determinado no programa Insight II (Módulo Search Compare)

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

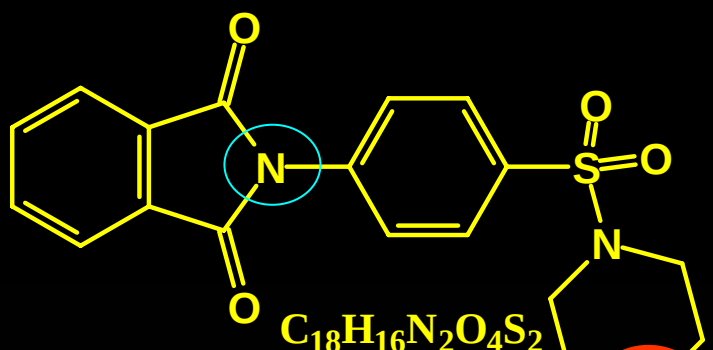


50% more active than thalidomide

ED_{50} of LASSBio-468 measured on neutrophil influx induced by LPS into BALB/c of mice lungs (DMSO; *i.p.*).



Novo Protótipo de Agente Anti-inflamatório Simbiótico



$C_{18}H_{16}N_2O_4S_2$

LASSBio 468

TNF-α ED_{50} 2,5 mg/Kg

PDE-4 inibidor

Atividade PDE-4 de foi medida em aorta bovina:

IC_{50} = 82 μM

(*cf.* PDE-1, 2, 3, 5 > 420 μM)

Dr Claire Lugnier
Université Louis Pasteur de Strasbourg
Laboratoire de Pharmacologie et de Physicochimie des Interactions Cellulaires et Moléculaires.

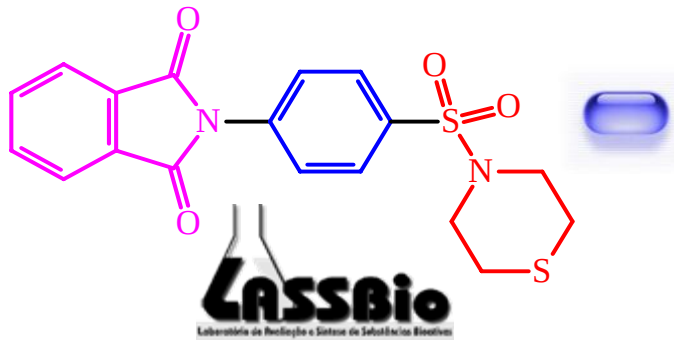
L. M. Lima, P. Castro, A. L. Machado, C. A. M. Fraga, C. Lugnier, V. L. G. Moraes, E. J. Barreiro, *Synthesis and Anti-inflammatory activity of Phthalimide Derivaatives, Designed as New Thalidomide Analogues, Bioorg. Med. Chem.* 2002, *10*, 3067.

LASSBio-468

lead compound

Novo agente anti-inflamatório simbiótico

LASSBio-468, é um novo candidato a protótipo de fármaco **AI**, desenhado por hibridação molecular com nova e original estrutura química, simples e aquiral, planejado 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.**

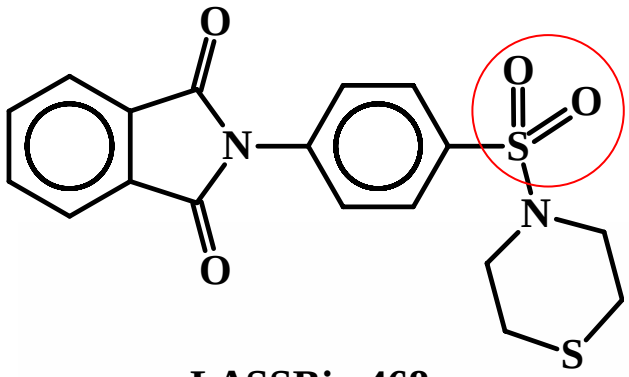


L. M. Lima *et al.*, "**Synthesis and Anti-inflammatory Activity of Phthalimide Derivatives, Designed as New Thalidomide Analogues**", *Bioorg. Med. Chem.* 2002, **10**, 3067

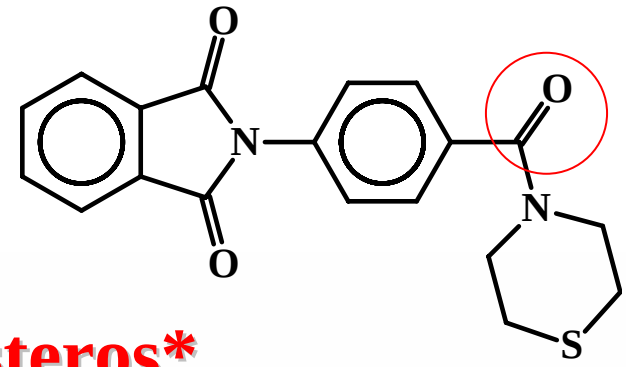
M. S. Alexandre-Moreira *et al.*, **"LASSBio-468: a New achiral Thalidomide Analogue which Modulates TNF-a and NO Production and Inhibit Endotoxic Shock and Arthritis in Animal Model",** *International Immunopharmacology 2005*, **5**, 485.

Estudos de Otimização de LASSBio-468

LEAD COMPOUND
Lead-optimization

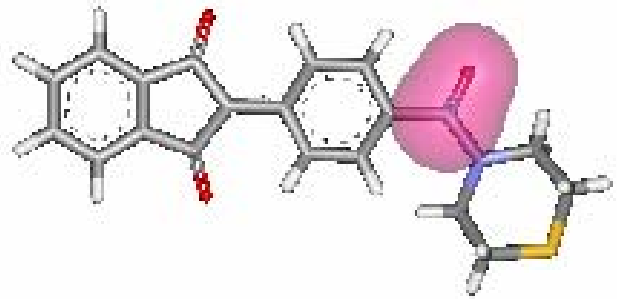


Bioisósteros*



LASSBio-595

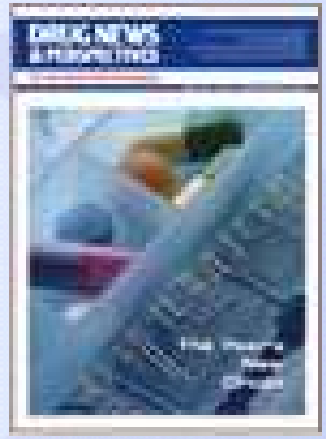
LASSBio-468



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]

LASSBIO is mentioned in the following Prous Science publications:



NME DIGEST

Drug News Perspect 1999, 12(7): 416

Drug News Perspect 2002, 15(8): 519

Drugs Fut 2002, 27(Suppl. A): 310

Drug News Perspect 2000, 13(4): 234

Respiratory Drugs

Drug Data Rep 2001, 23(10): 966

Agents Affecting blood Coagulation

Drug Data Rep 2002, 24(1): 38

Respiratory Drugs

Drug Data Rep 2002, 24(2): 125

Psychopharmacologic Drugs

Drug Data Rep 2004, 26(1): 17

John R. Proudfoot (Boehringer,Ridgefield,USA)

Drugs, Leads, and Drug-Likeness: An Analysis of Some Recently Launched Drugs

Bioorg. Med. Chem. Lett. 2002, 12, 1647

„An analysis of the origins of recently launched (2000) drugs reveals that most were derived by modification of known drug structures"

Drug Data Report

Prous Science Ed. (ES.)

Vol. 24, No. 2, 2002

New Lead-compounds:

12611 (Boehringer Ingelheim)

312652 (Bayer)

313027 (GlaxoSmithKline)

KCO-912 (Novartis)

Asthma Therapy

LASSBIO-468

Protótipos que falem português...

AGRADECIMENTOS

CNPq
Pronex
PADCT
FAPERJ
CAPES-COFECUB
FUJB
IM-INOFAR

Lidia M. Lima, Magna S. Alexandre-Moreira, Christina M. Takiya, Luciana B. de Arruda, Bernardo Pascarelli, Raquel Novaes, Hugo C.C. Faria-Neto, Vera L.G. Koatz, Alexandre Légora, Carlos A. Manssour Fraga.

"... It will be important **to integrate** new scientific advances into an environment that builds on traditional skills, fosters **multidisciplinary interactions** **between teams and individuals**, and is primed to exploit Pasteur Dictum that '**chance favours the prepared mind**' ..."

Simon F. Campbell

RSC & Pfizer Central Research

Sandwich, Kent, Inglaterra


Endereço
http://www.farmacia.ufrj.br/lassbio/
Ir
Links
www.farmacia.ufrj.br/lassbio
LASSBio
Laboratorio de Avaliação e Síntese de Substâncias Bioativas
Faculdade de Farmácia
UFRJ
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Química Farmacêutica I
Química Farmacêutica II
» Seminários e Cursos
» 2005
» 2004
» Conferências e Palestras
CONFERÊNCIAS E PALESTRAS
XIII ESCOLA DE VERÃO
em Química Farmacêutica & Medicinal
http://www.farmacia.ufrj.br/lassbio
05 a 09 de fevereiro de 2007
Inscrições a partir de agosto
<< Aula Inaugural do Curso de Pós-Graduação em Ciências Farmacêuticas
Internet

ejb@ufrj.br

Candidato a protótipo
(substância pura; bioensaios in vitro)

Quantidade de substância requerida: 1-10 µg

Candidato a protótipo
(substância pura; bioensaios in vivo)

Quantidade de substância requerida: 1-10 mg

Novo Composto-Protótipo

Quantidade de substância requerida: 1-10 g

NEQ

Ensaios Pré-clínicos

Quantidade de substância requerida: >100 g

Ensaios Clínicos (Fase 1)

Quantidade de substância requerida: > 1kg