New Challenge in Drug Discovery

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III International Symposium on Drug Discovery

24 – 26th JULY 2013

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LASSBio®

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Instituto Nacional de Ciência e Tecnologia em Fármacos e Medicamentos

INCT-INOFAR

Projeto CNPq nº 573.564/2008-6 « » FAPERJ nº E-26/170.020/2008

Summary

- Introduction
  - The Fischer-Ehrlich paradigm of *MedChem*: 20th century
  - The present *MedChem* paradigm of drug discovery: 21th century
  - The mutitarget contemporary challenge
- *Rational Design of New Dual Lead-candidates*:
  - The design & discovery of LASSBio-468
  - LASSBio-596, LASSBio-1349
  - Novel dual antiinflammatory lead-compound
- Aknowledgements

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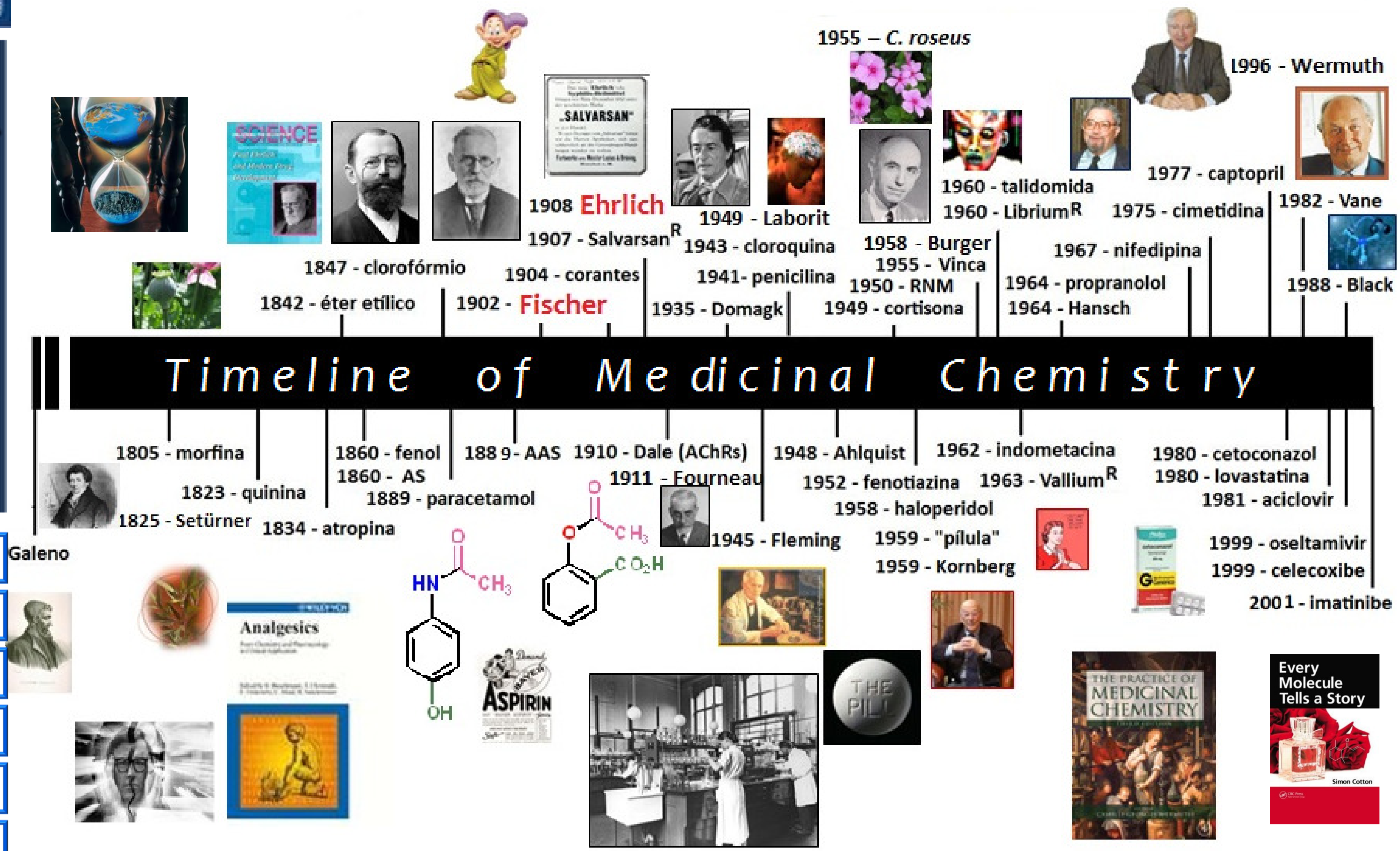


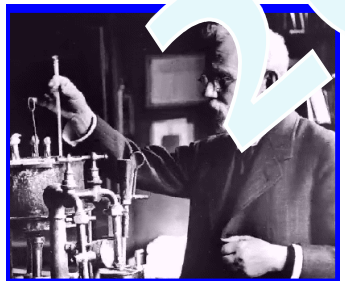
http://ejb-eliezer.blogspot.com

The Fischer-Ehrlich paradigm

Emil Fischer
1852-1919
1902

1908

Paul Ehrlich
1854-1915



LOCK & KEY
CONCEPT

+

1900

postulated the existence of specific receptors,
ociated with cells or distributed in the blood

K Strebhardt & A Ullrich, Paul Ehrlich magic bullet concept: 100 years of progress, *Nature Rev. Cancer* **2008**, *8*, 473

One-molecule, one-target

Receptor

Macromolecule

Structure-based DD

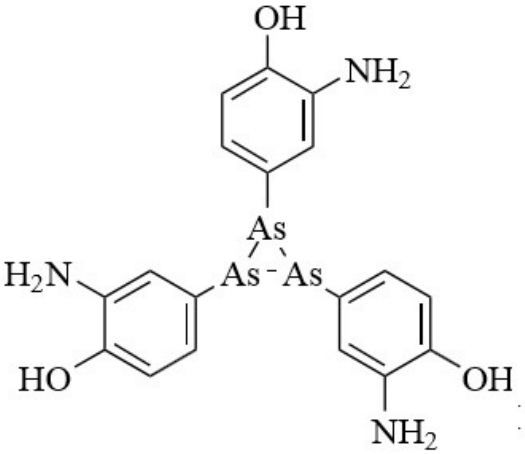
Rational Drug Design (20th century)

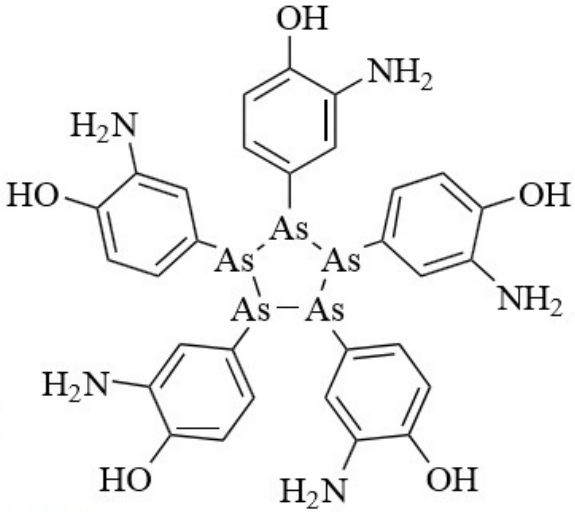
Drug

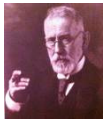
Small molecule

Ligand-based DD

Drug Innovation during 20th Century







Salvarsan
1909
Ehrlich & Hata

NC Lloydet al., *The composition of Ehrlich's salvarsan: resolution of a century-old debate, Angew. Chem. Int. Ed. Engl.* ***2005****, 44,* 941.

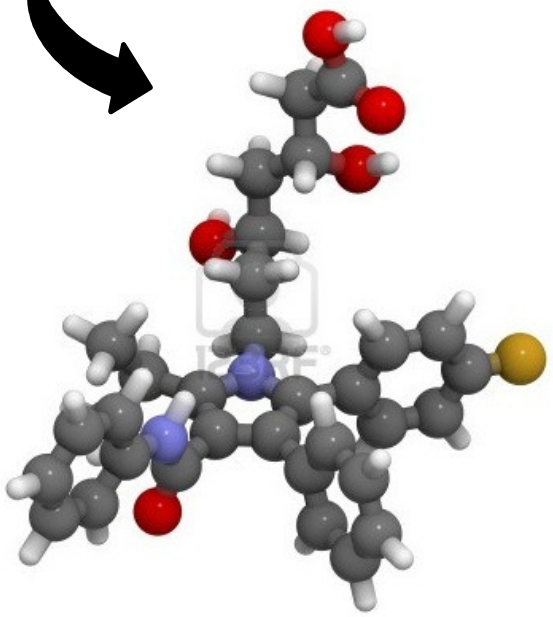
Innovation

1910 – Introduced
1912 – the leading drug
Arsenic-containing drug
~1.5 year

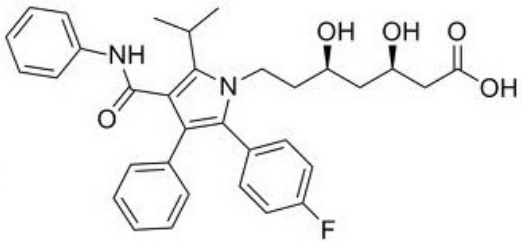
translational

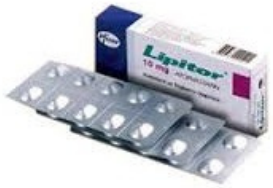
~100y

translational



Atorvastatina
1991
B Roth





Top-seiling drug of all time
1991–2011 - patent
Total world sales: US$ 140bi
~8-10 year

Innovation

Drug Innovation during 20th Century

1964

propranolol
cimetidine
captopril
omeprazole

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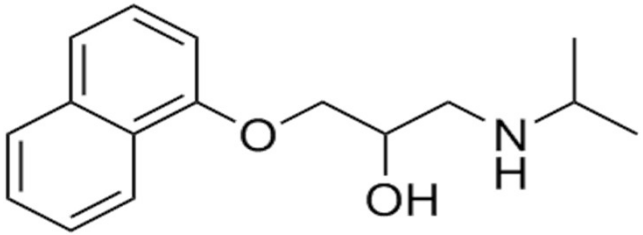
paclitaxel
lovastatin
penicillin

1942



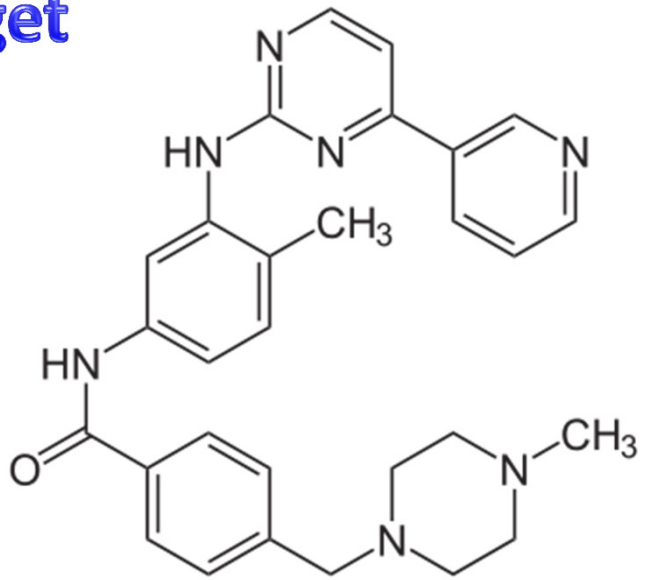
Mono-target

2001

imatinib

Multi-target

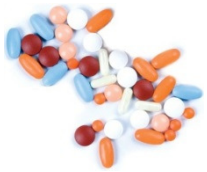
Therapeutic innovations



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

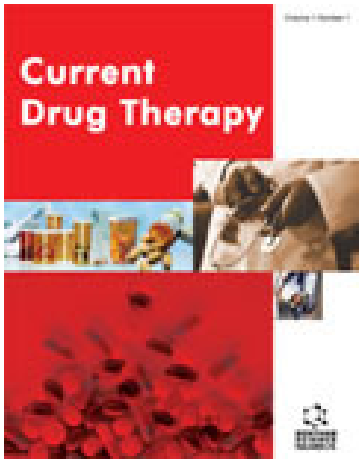
Eliezer J. Barreiro and Carlos Alberto Manssour Fraga

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.



& "WHO has recently recognized that noncommunicable diseases such as cardiovascular, diabetes, cancer, respiratory and neurological disorders are now also a great emerging epidemic *among the poor*"

& AB Reitz, Future horizons in drug discovery research, *ACS Med. Chem. Lett.* **2012**, *3*, 80

JL Medina-Franco, MA Giulianotti, GS Welmaker, RA Houghten, Shifting from the single to the multitarget paradigm in drug discovery, *Drug Discov Today* **2013**, *18,* 495; S Reardon, A world of chronic disease, *Science* **2011**, *333*, 558.

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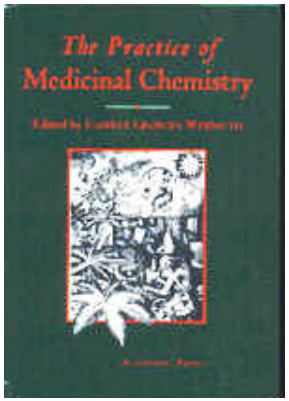
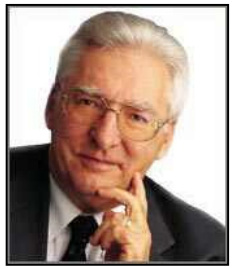
The modern MedChem paradigm

" ... the preparation of dual- or multiple-ligands on an almost rational basis is now conceivable and it can be expected that many of these molecules will yield drugs of superior clinical value compared with monotarget formulations"





Camille G. Wermuth

Drug Discov. Today 2004, **9**, 826

medicinal chemistry

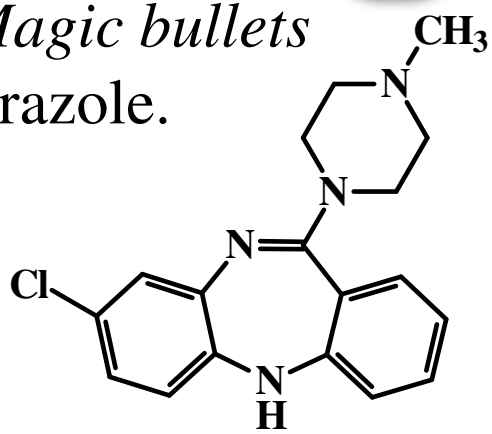
medicinal chemistry

- **One-target-one-ligand: the 20th century paradigm**

  One-ligand / one-disease – *Lock & Key & Magic bullets*

  e.g. propranolol, cimetidine, captopril, omeprazole.

  Clozapine, an "*atypical*" neuroleptic drug has affinity for the D_4 central receptor & D_2, D_3, 5-HT_{2A}, 5-HT_3, α1 and 2 - is an exception considered as "*promiscous*" drug.



Clozapine

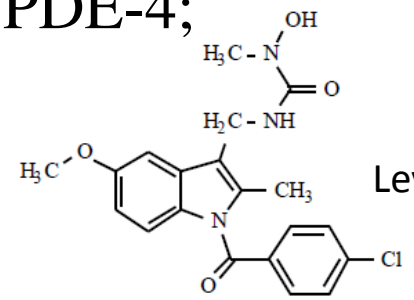
- **Ligands for <u>multi-target</u>: the 21th paradigm**

  Dual, binary, dimeric, bivalent, symbiotic = multi ligands:

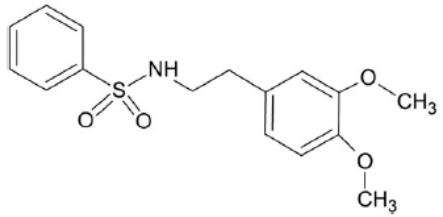
  5-LOX/COX-2 ; TXS/TP_{ant}; COX-1/LTA_4 hydrolase;

  5-$HT_{1A}R_{ant}$/SSRI; TP_{ant}/IP_{ag}; SSRI/PDE-4; PDE-3/PDE-4

  TNFα/PDE-4;

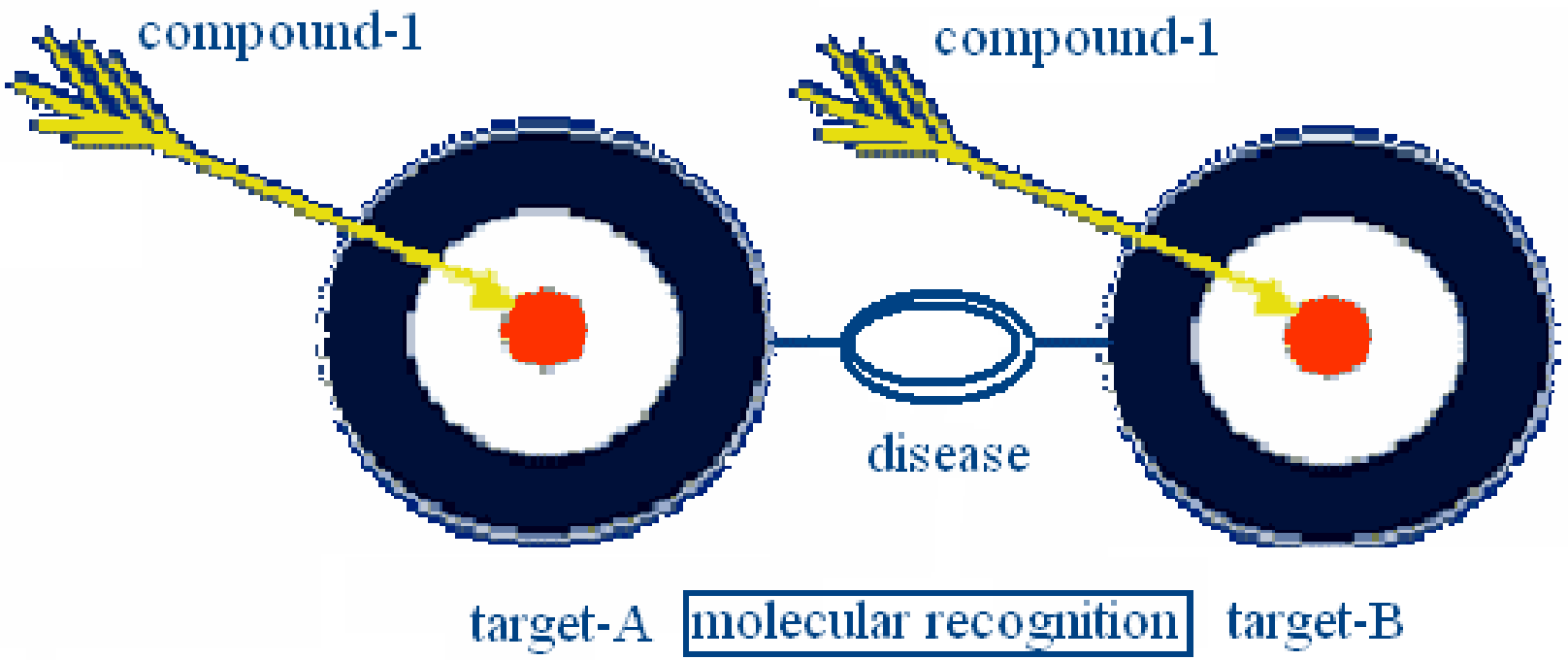


Leval, 2002



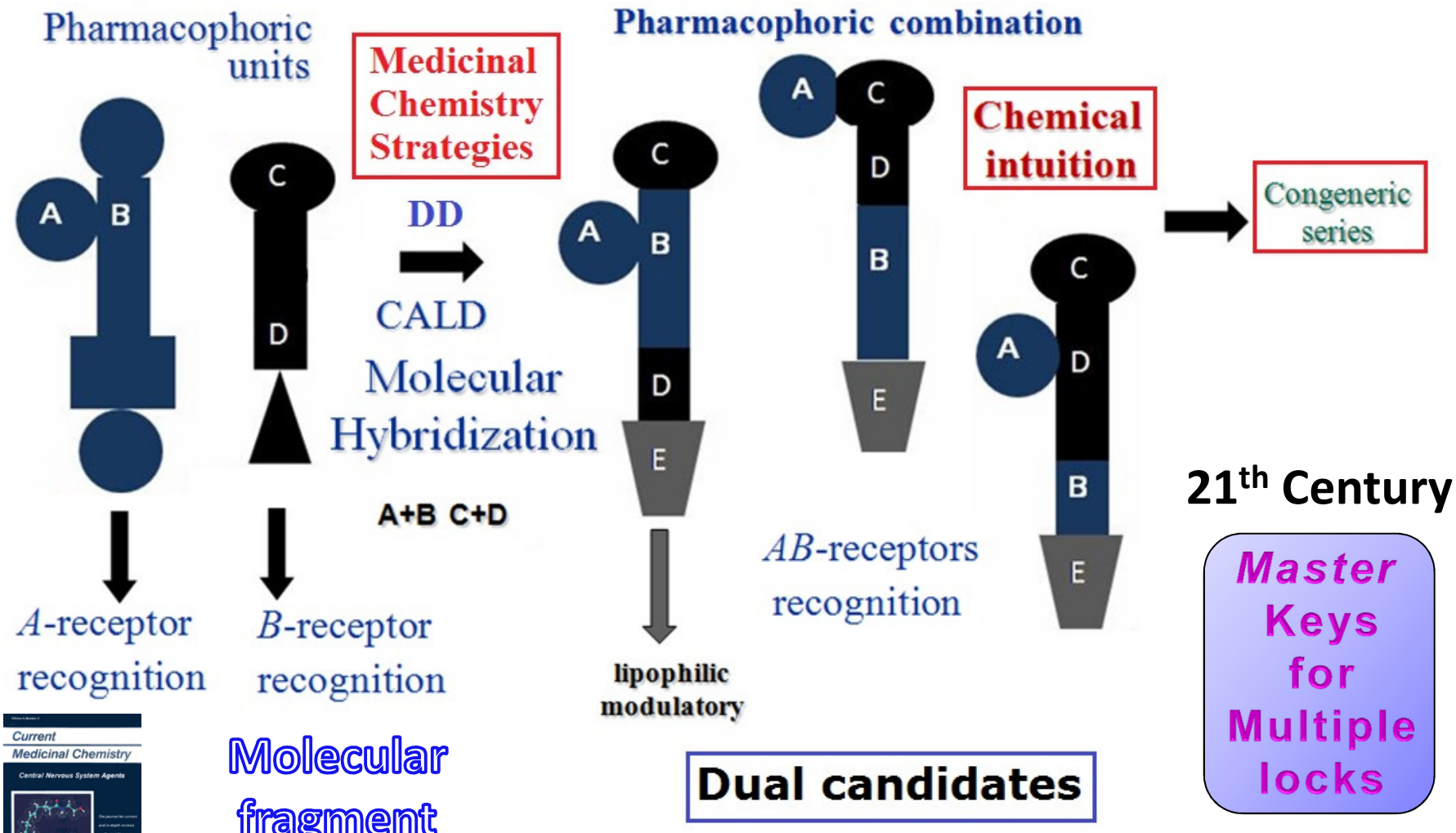
Zapata-Sudo, 2012

The symbiotic lead-candidate design



The symbiotic approach is concerned to a new lead-compound with multiple-target recognition pattern, where the receptors are involved with a complex disease pathology, but belonging to different biochemical pathways. A dual agent with this profile can be structuraly designed by combining molecular pharmacophoric fragments for each target.

The rational-based dual ligand design



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

G Nicola et al., *Public domain databases for medicinal chemistry, J Med Chem* **2012**, *55*, 6987

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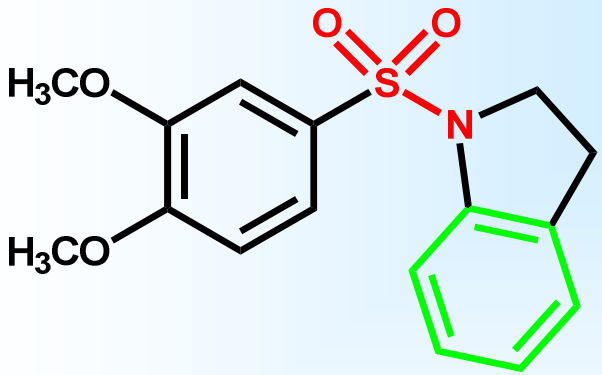
Rational Design of New Symbiotic Lead-candidates:

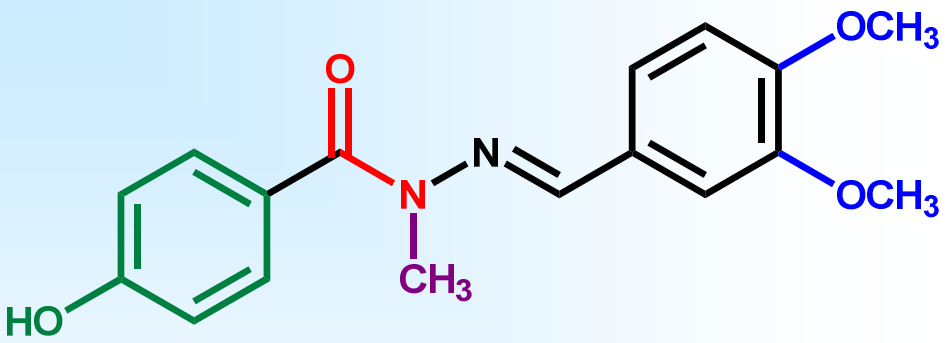
The discovery of LASSBio-468, 596 & 1349 as novel dual antiinflammatory drug candidates

sulfonamide



Montana, 1998

LASSBio-1349



***N*-methyl-*N*-acylhydrazone**

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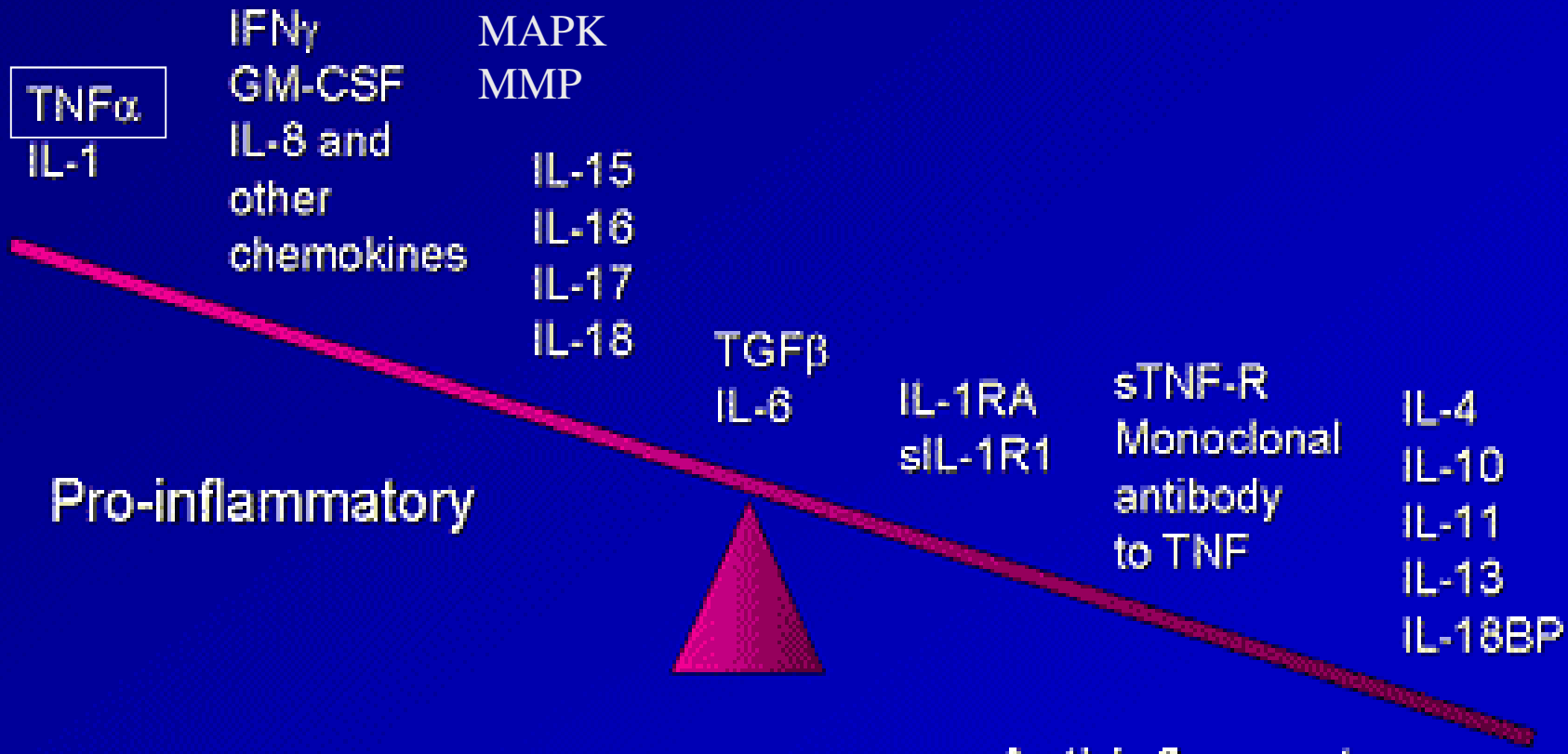
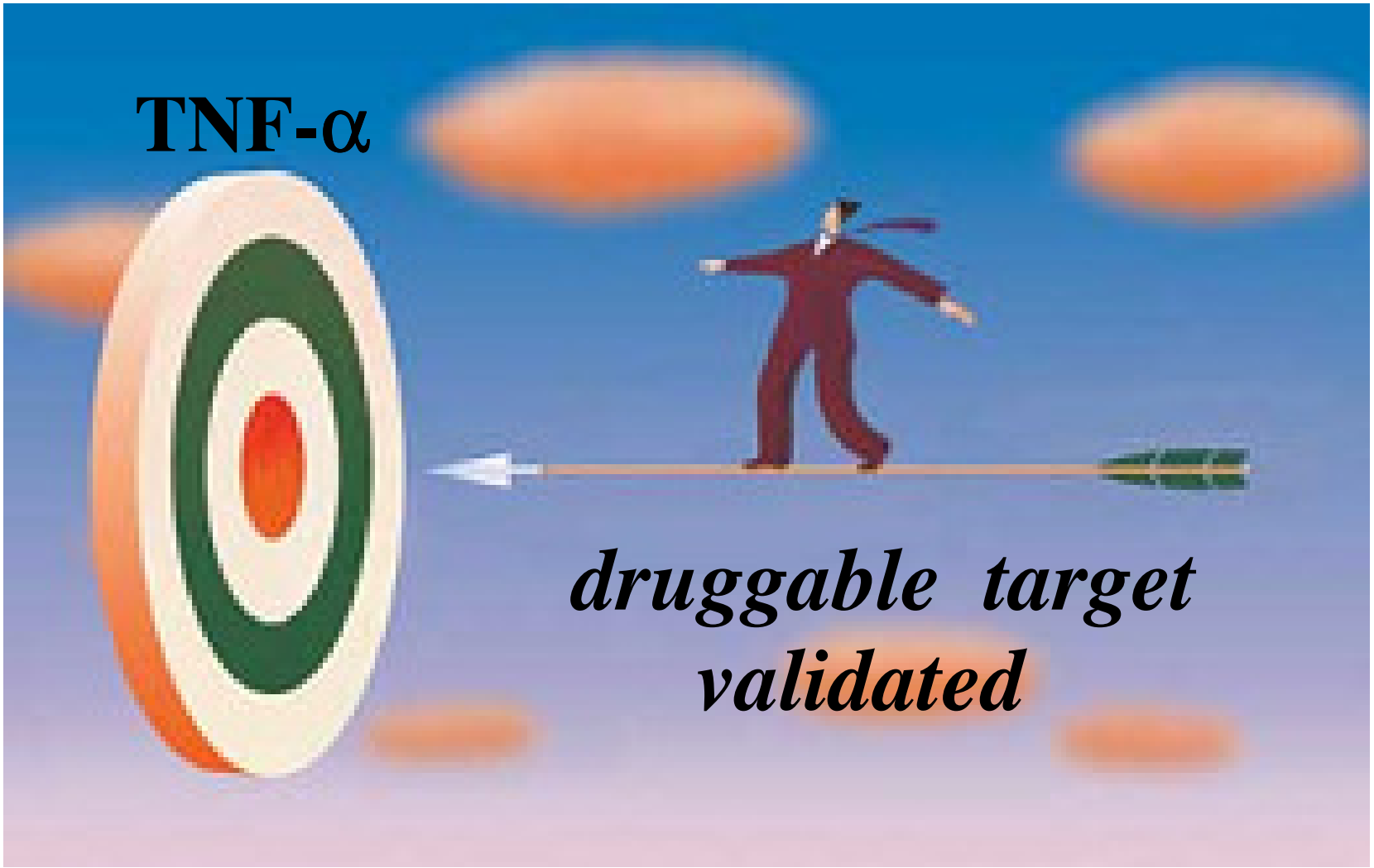
Role of Cytokines and Cytokine Inhibitors in Chronic Inflammation



Arend. *Arthritis Rheum* 2001.

* TNF-α = Tumor necrosis factor-alpha

The Target Election: TNF-α



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

PC Taylor, Pharmacology of TNF blockde in RA and other chronic inflammatory diseases, *Curr. Op. Pharmacol.* **2010**, *10*, 308; MLC Barbosa et al., Therapeutic approaches for tumor necrosis factor inhibition, *Braz. J. Pharm. Sci.* **2011**, *47*, 427.

Anti-TNFα Therapies

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

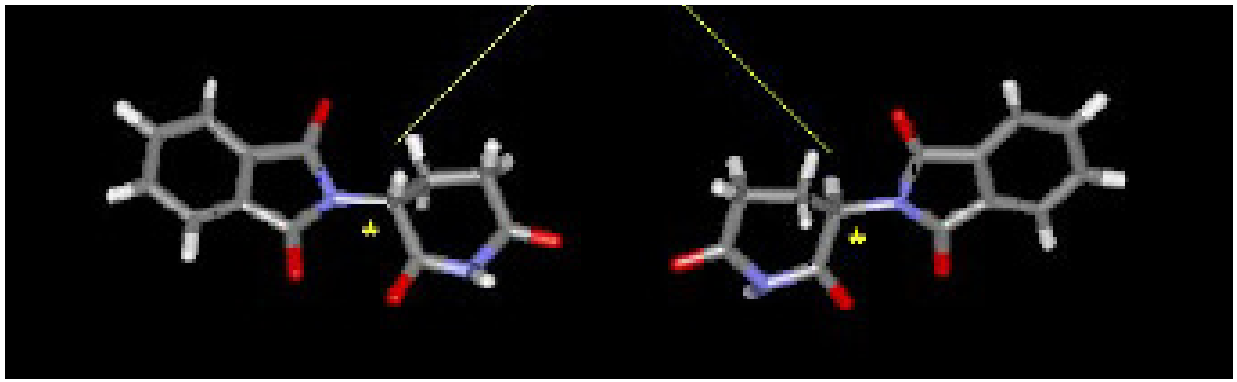
Drug	Status	Biological Form
Etanercept	approved	soluble TNFR2 coupled to Fc portion of IgG
Infliximab	approved	chimeric anti-human TNF antibodie
Adalimumab	approved	anti-human TNF antibodie
ISIS 104838	clinical	TNF anti-sense
Onercept	clinical	soluble p55 TNFR
Humicade	clinical	anti-TNF humanised IgG4

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

* protein-based injectable anti-TNFα therapies

The first pharmacophoric identity

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

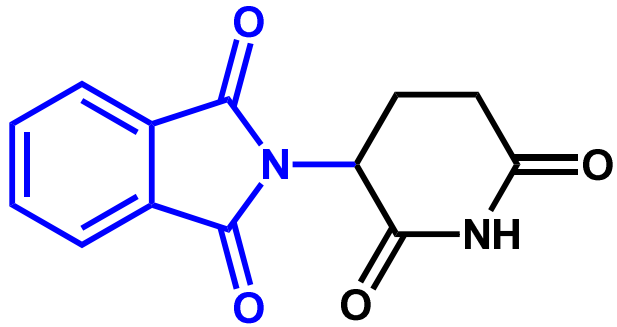


Thalidomide

Anti-TNF

TNF-α IC_{50} = 200 μM

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



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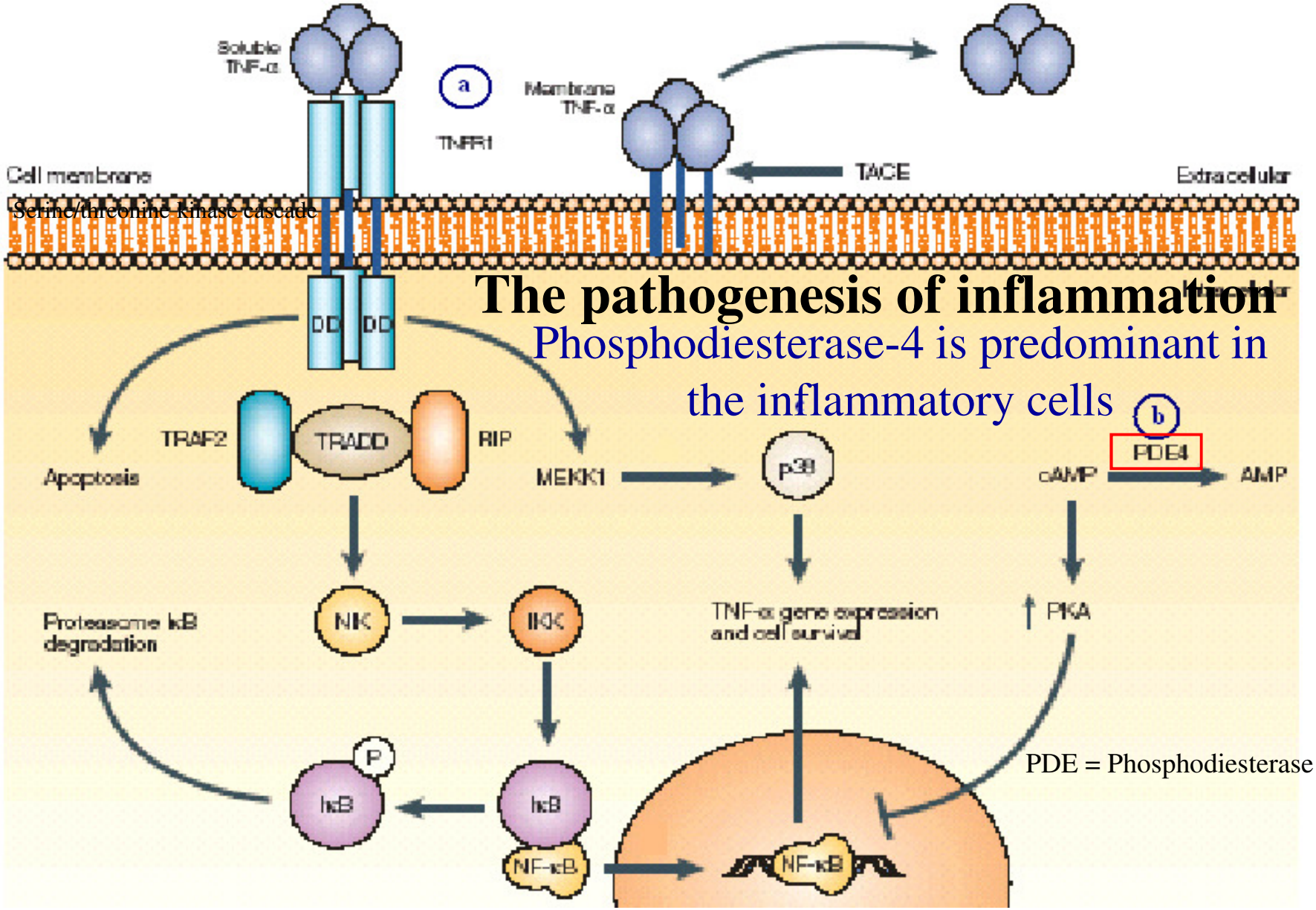
Second Target Election:PDE



The pathogenesis of inflammation

Phosphodiesterase-4 is predominant in the inflammatory cells

PDE = Phosphodiesterase

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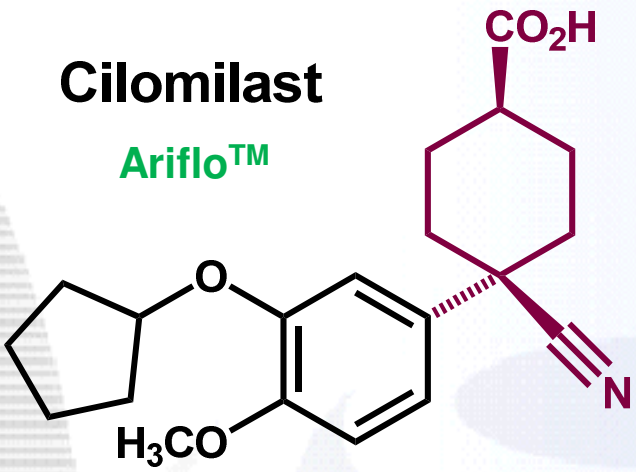
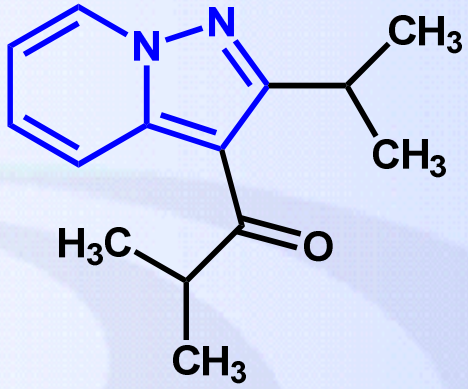
Cilomilast

Ariflo™



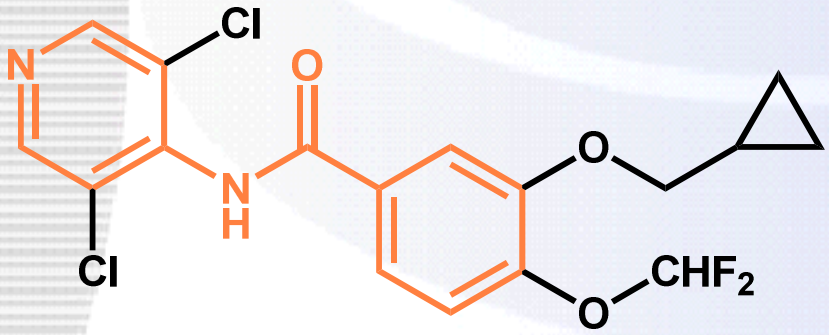
4-cyano-cyclohexyl carboxylic acid

Ibudilast



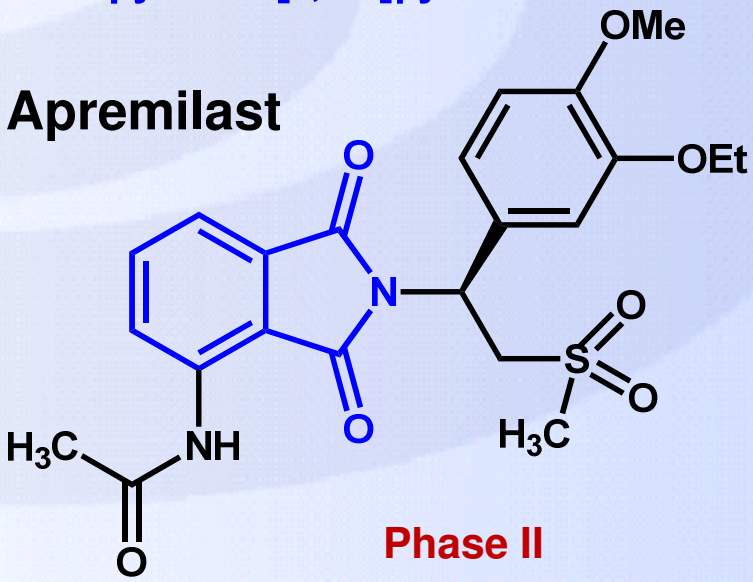
pyrazolo[1,5-*a*]pyridine

Ruflomilast



pyridine-benzamide

Apremilast



Phase II

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

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

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

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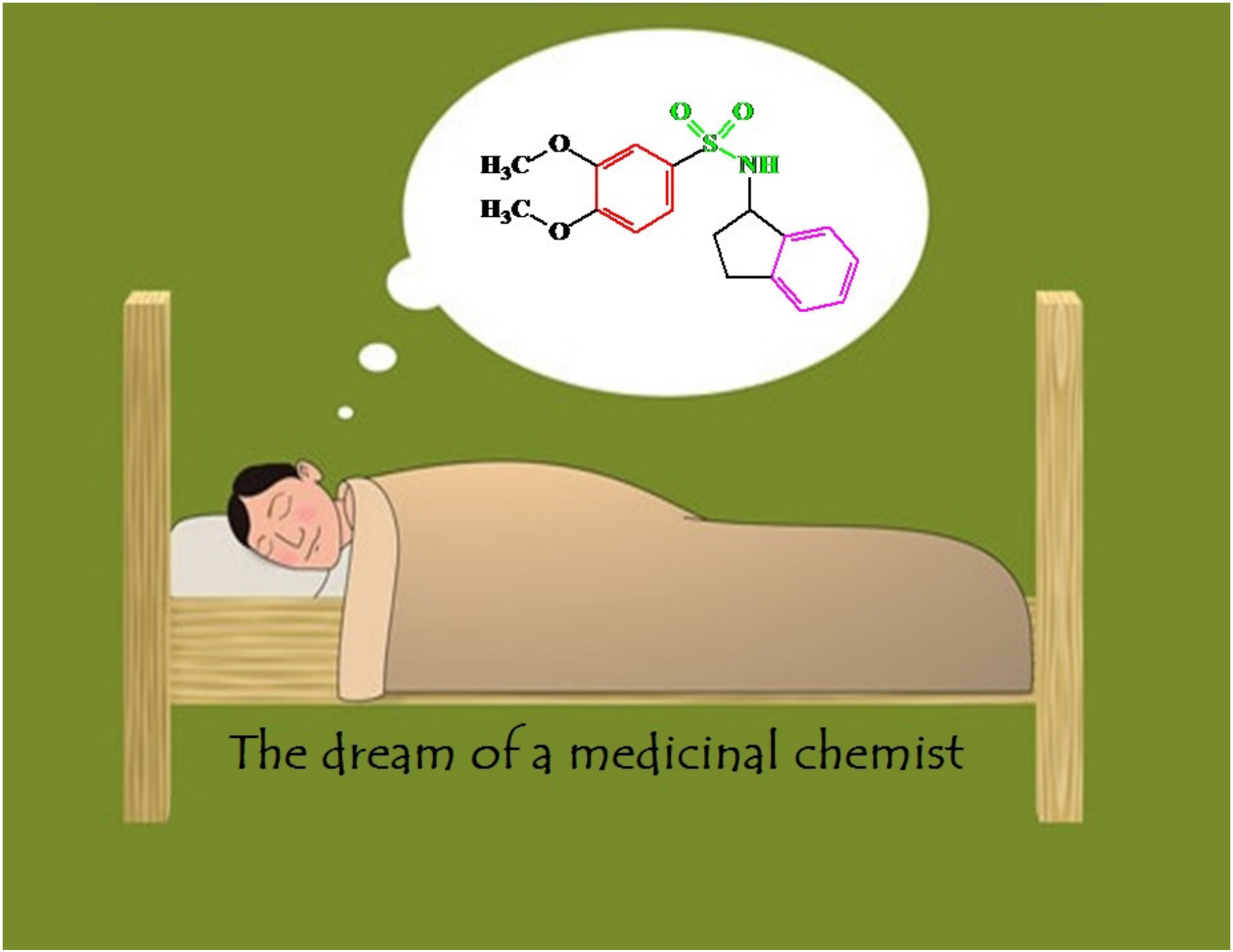
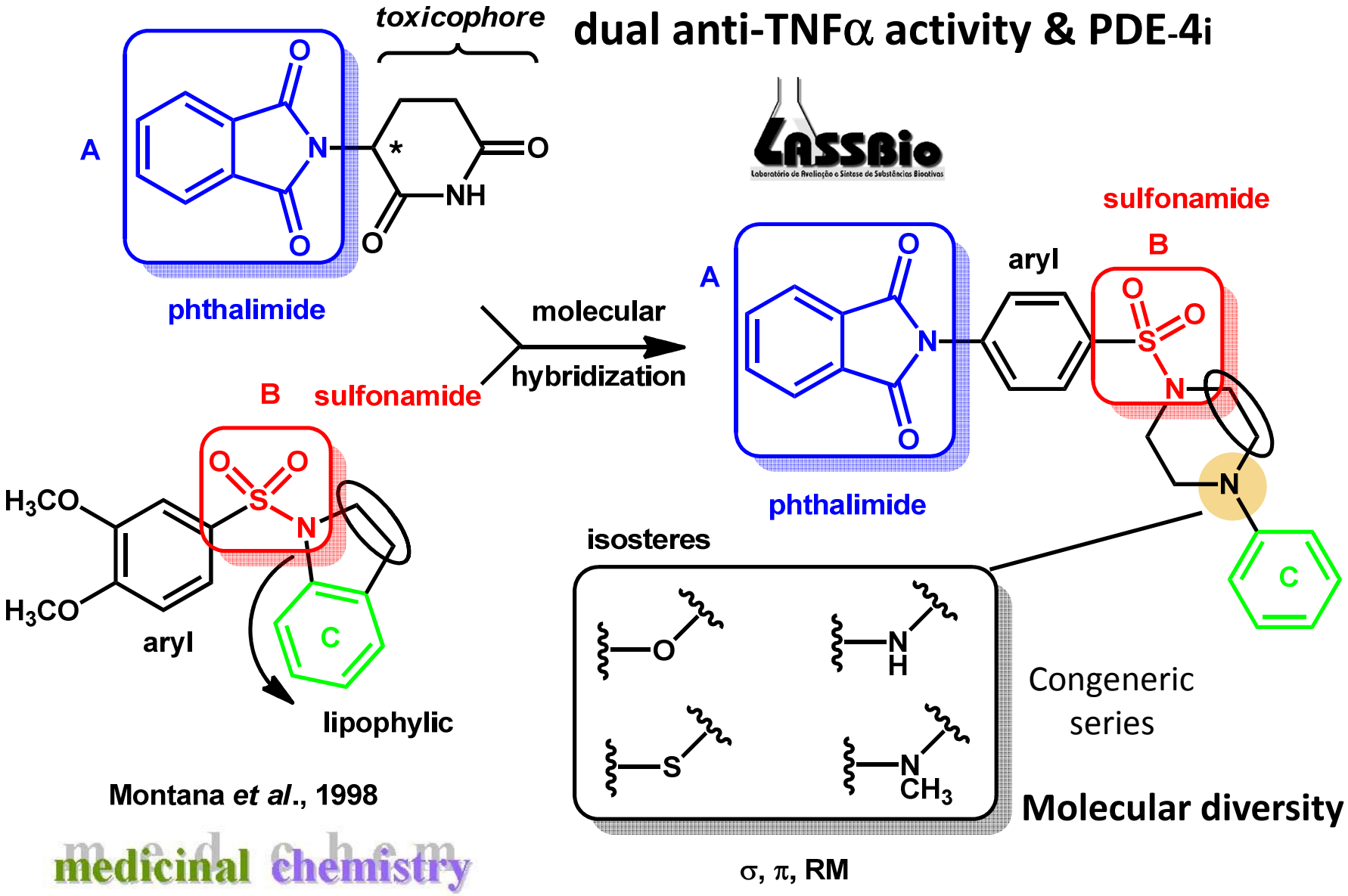


Drug Design

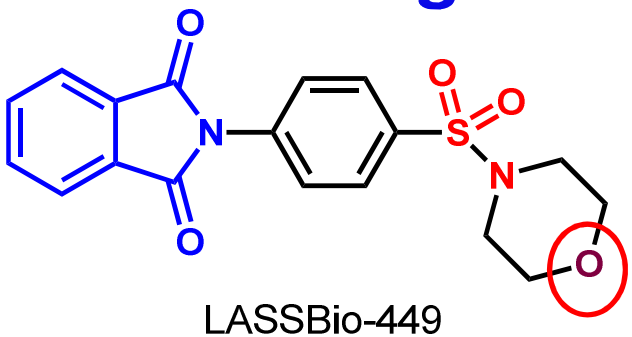
The molecular design of new agent with dual anti-TNFα activity & PDE-4i



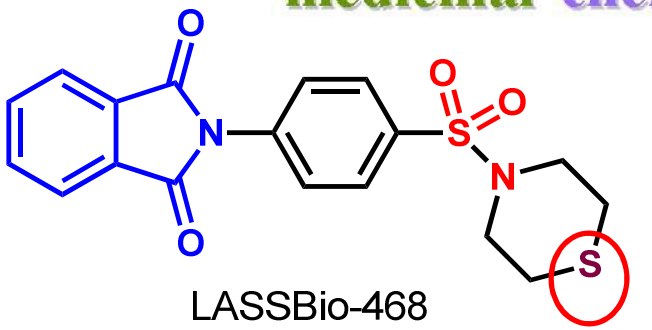
C Viegas Jr, A Danuello, VS Bolsani, EJ Barreiro, CAM Fraga, Molecular Hybridization: A useful tool in the design of new drug prototypes, *Curr Med Chem* **2007**, *14*, 1829

Congeneric series

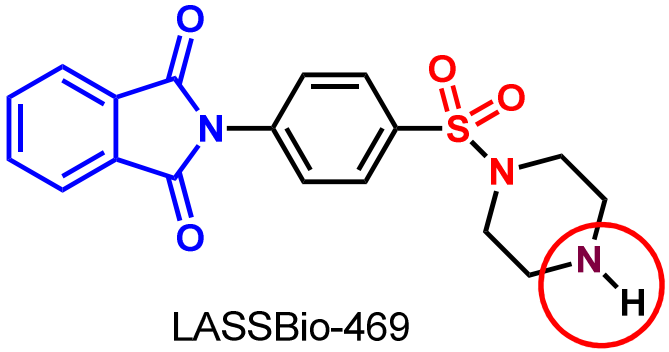
medicinal chemistry



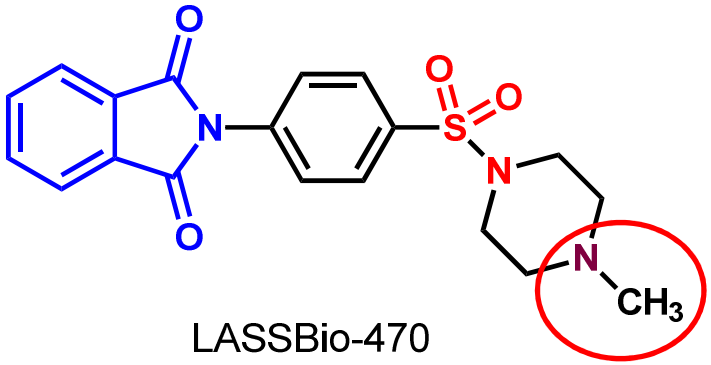
LASSBio-449



LASSBio-468

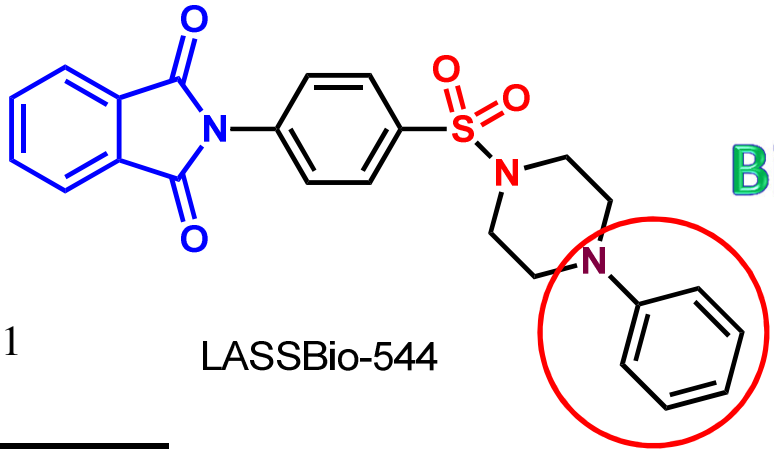


LASSBio-469



LASSBio-470

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



LASSBio-544

Bioisosterism

LM Lima, EJ Barreiro, Bioisosterism an useful strategy for molecular modification and drug design, *Curr.Med.Chem.***2005**, *12*, 23

Synthesis of congeneric series

phthalic anhydride
$C_8H_4O_3$

120°C
1 hr
2.0 M

$C_{14}H_9NO_2$

$ClSO_3H$
0°C to rt, then 60°C
1 hr
1.0 M

$C_{14}H_8ClNO_4S$

NEt_3
CH_2Cl_2
1 hr
0.4 M

LASSBio-544
69%

LASSBio-469
58%

LASSBio-449
65%

67%
LASSBio-470

LASSBio-468
72%

Overall yield: *ca.* 25%
(~ 0.5 M, 200 g)

$C_{18}H_{16}N_2O_4S_2$
M.W. = 388.45

Lidia M. Lima, PhD Thesis, IQ-UFRJ,2001

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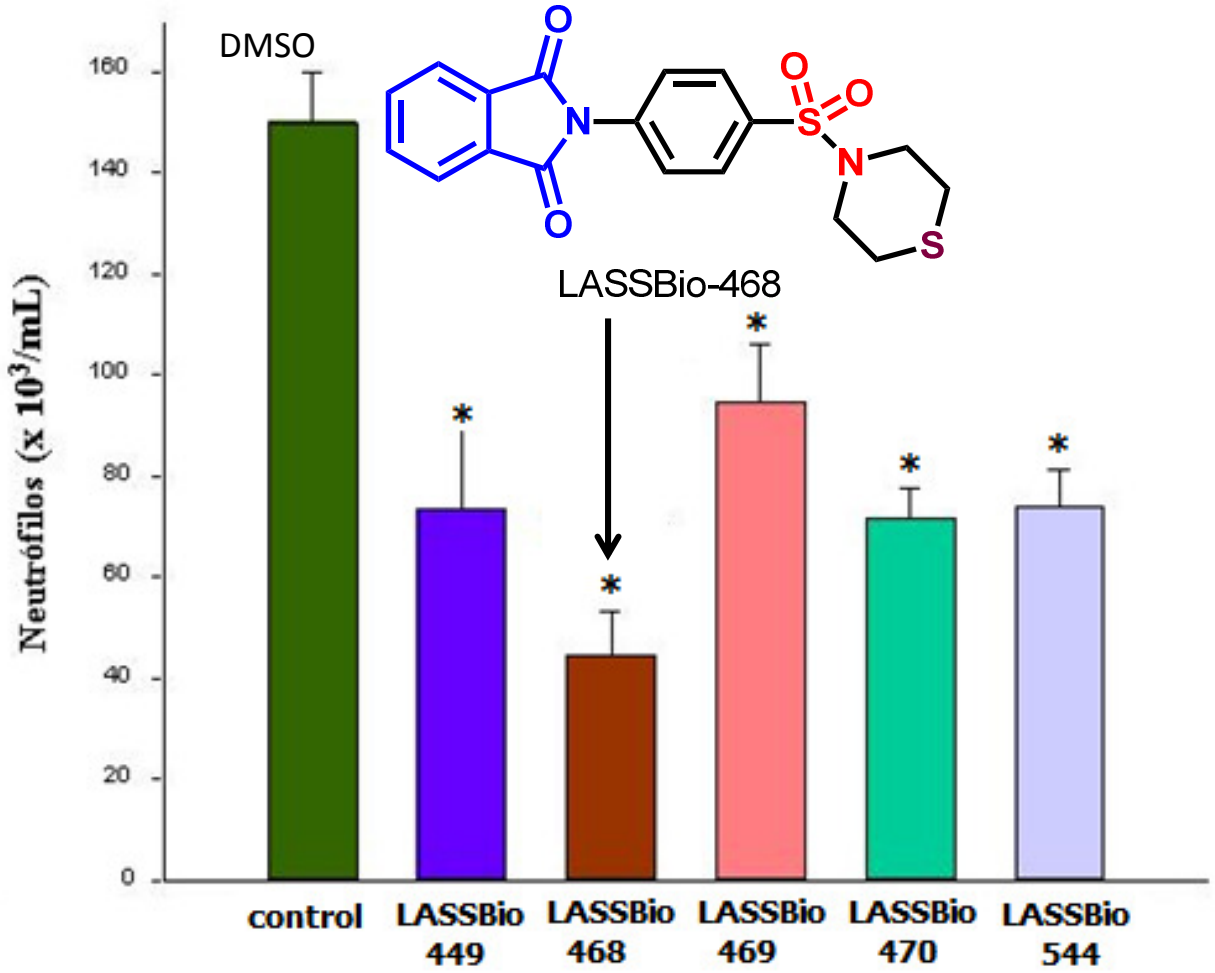
Effect of new compounds and thalidomide on neutrophils influx, induced by *LPS* into BALB/c of mice lungs (10 mg/kg, DMSO; *ip*)

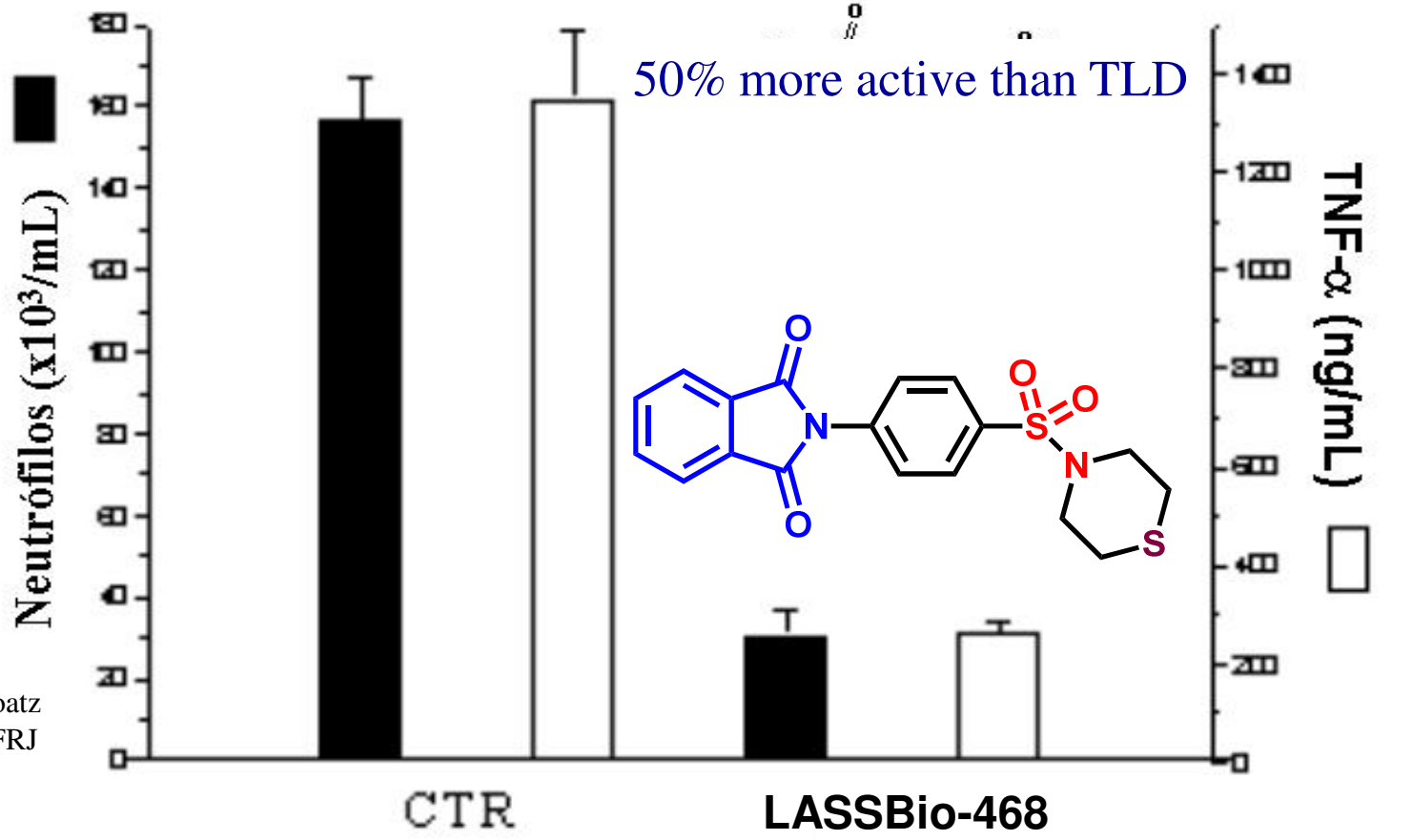
in vivo



Results are expressed as means SEM of seven animals.

Vera G Koatz
IBqM, Universidade Federal do Rio de Janeiro

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



Vera G Koatz
IBqM, UFRJ

inhibition of the production of TNF-α promote the elevation of intracellular levels of cyclic 3',5'-adenosine monophosphate (cAMP) in leukocytes, associated with inhibition of PDE-4 activity.*

* DO Procopio, MM Teixeira, MM Camargo, LR Travassos, MA Ferguson, IC Almeida, RT Gazzinelli, Differential inhibitory mechanism of cyclic AMP on TNF- and IL-12 synthesis by macrophages exposed to microbial stimuli. *Br. J. Pharmacol.***1999**, *127*, 1195

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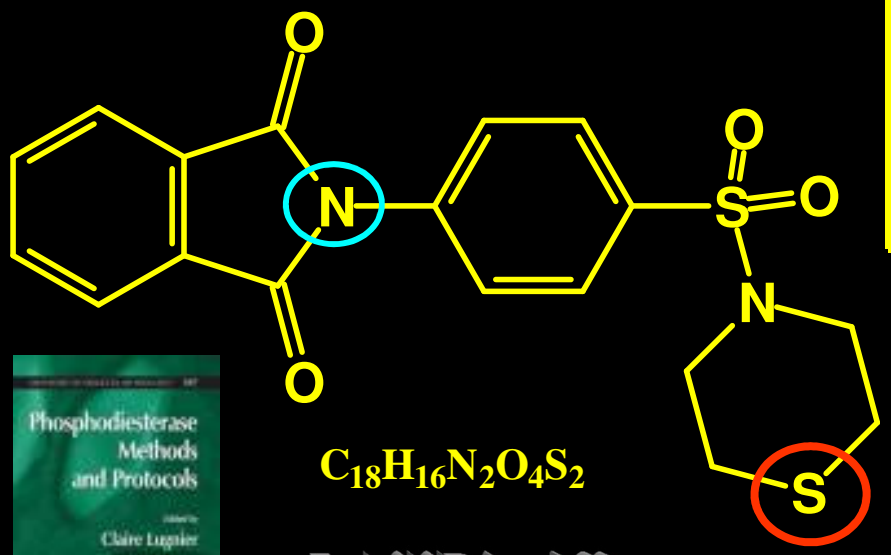
LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas



$C_{18}H_{16}N_2O_4S_2$

LASSBio 468

TNF-α ED_{50} 2.5 mg/Kg

lead compound

PDE-4 inhibitor

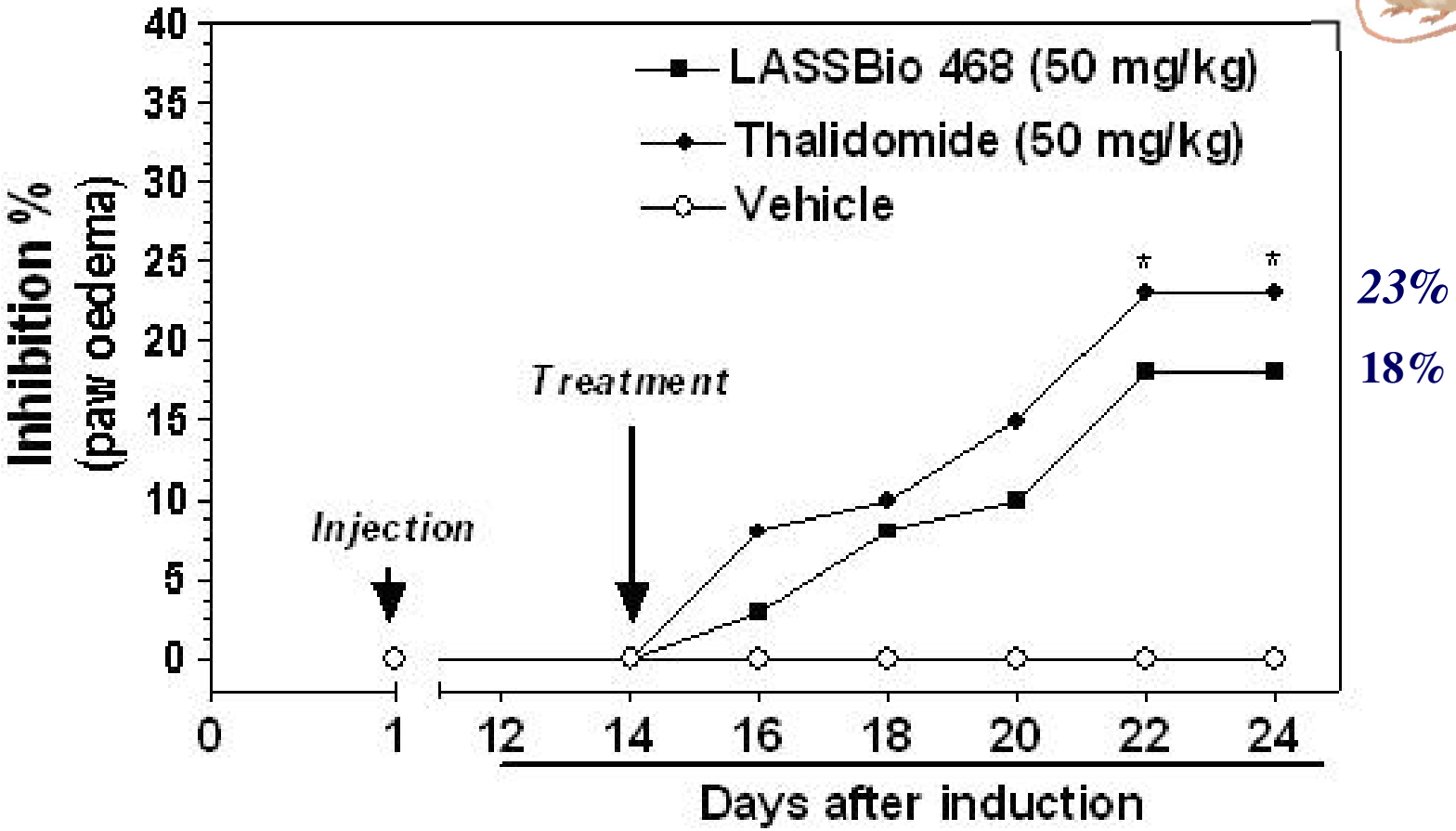
Dr Claire Lugnier (CAPES-COFECUB; LASSBio-Strasbourg)
Université Louis Pasteur, Strasbourg, FR.
Laboratoire de Pharmacologie et de Physicochimie des Interactions Cellulaires et Moléculaires.

IC_{50} = 30.3 μM

cf. PDE-1, 2, 3, > 150 μM;

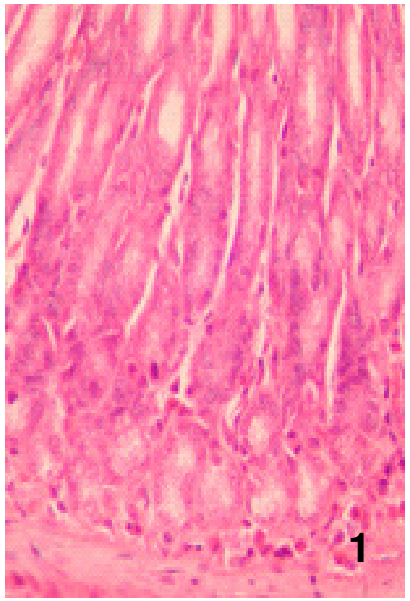
L M Lima et al., Synthesis and Anti-inflammatory Activity of Phthalimide Derivatives, Designed as New Thalidomide Analogues, *Bioorg. Med. Chem.* **2002**, *10*, 3067; M S Alexandre-Moreira et al., LASSBio-468: a New achiral Thalidomide Analogue which Modulates TNF-α and NO Production and Inhibit Endotoxic Shock and Arthritis in Animal Model, *International Immunopharmacology* **2005**, *5*, 485; LM Lima, CAM Fraga, VLG Koatz, EJ Barreiro, Thalidomide and Analogs as Anti-Inflammatory and Immunomodulator Drug Candidates, *Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry*, **2006**, *5*, 79; L M Lima, N M de Lima, *Rev. Virtual Quim.* **2009**, *1*, 35;

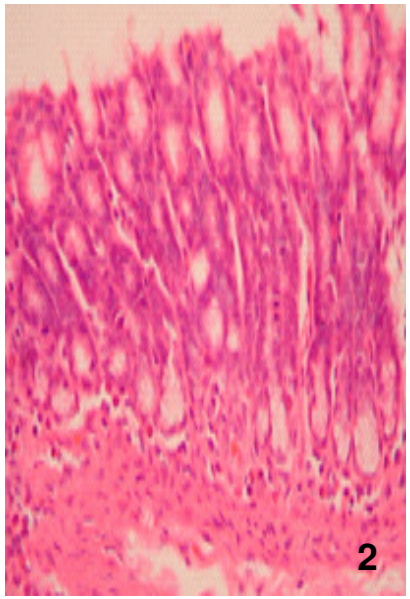
Effect of the treatment with LASSBio-468 (50 mg/kg *po*) on hind paw edema in adjuvant-induced arthritis (*AiA*-model) (*Mycobacterium tuberculosis*) in rats

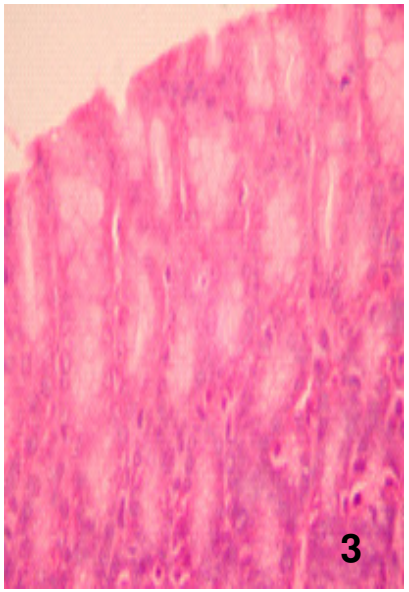


Magna Suzana Alexandre-Moreira
LASSBio, Universidade Federal do Rio de Janeiro

Histopathological results







(1) Photomicrography of granulomatous hepatitis in the control animals (HE – 100X);
(2) Animals treated with thalidomide (HE – 100X);
(3) Animals treated with LASSBio 468 (HE – 200X);

*** A positive control was performed *M. tuberculosum*.**

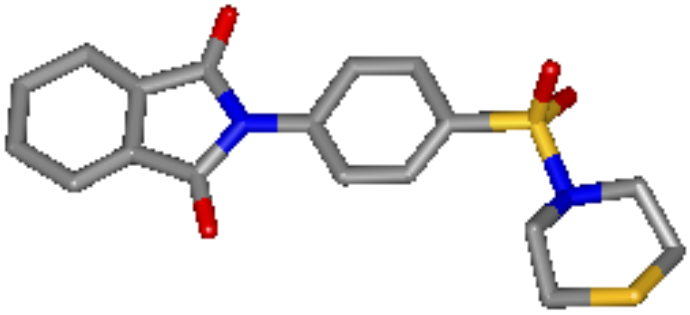
LASSBio-468 has a protective effect on inflamation development mediated by immunomodulatory macrophage activity

Christina M Takyia
ICB, Universidade Federal do Rio de Janeiro

LASSBio-468

A new symbiotic anti-inflammatory agent

LASSBio-468 is a new dual antiinflammatory agent (DMARD), active at TNF-α production with inhibitory activity on PDE-4.



This new achiral compound is an immunomodulator lead, without proliferative activity in the concavalin-A mitogen assay, in contrast to TLD. It is an useful lead to therapy of rheumatoid arthritis & shock septic syndrome.

L. M. Lima *et al*., Synthesis and Anti-inflammatory Activity of Phthalimide Derivatives, Designed as New Thalidomide Analogues, *Bioorg. Med. Chem*. 2002, *10,* 3067; AL Machado *et al.*, Design, Synthesis and anti-inflammatory activity of novel phthalimide derivatives, structurally related to thalidomide, *Bioorg. Med. Chem. Lett*. 2005*, 15*, 1169.

Universidade Federal do Rio de Janeiro

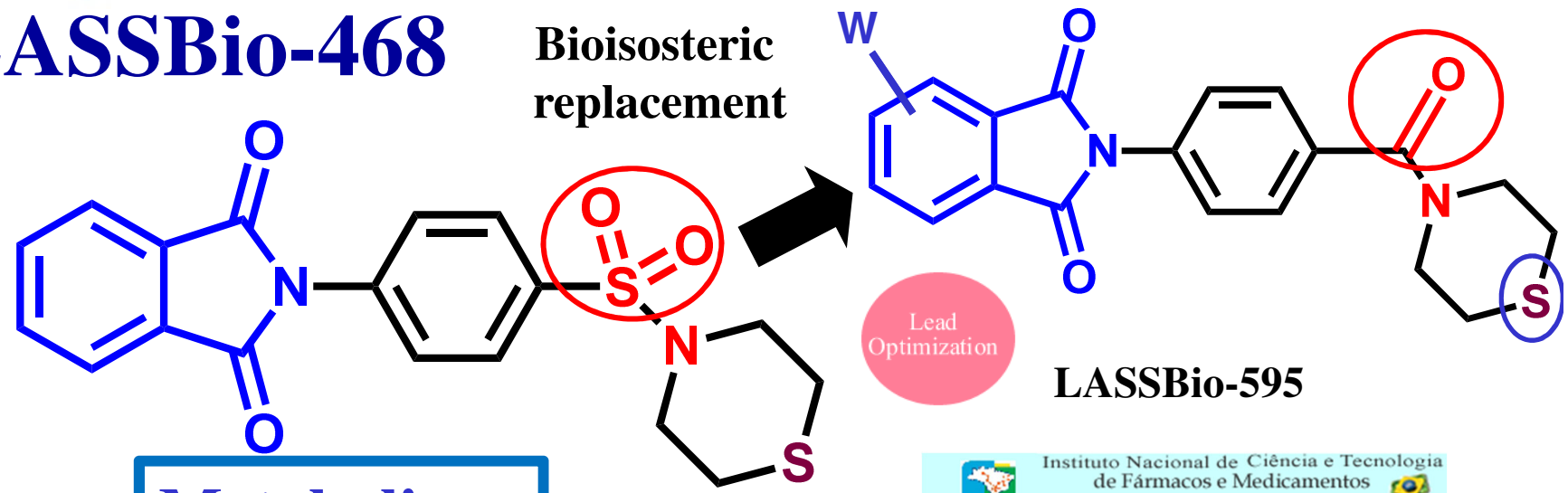
Lead optimization

Phthalimide Derivatives as TNF-α Inhibitor

medicinal chemistry

LASSBio-468

Bioisosteric replacement



Lead Optimization

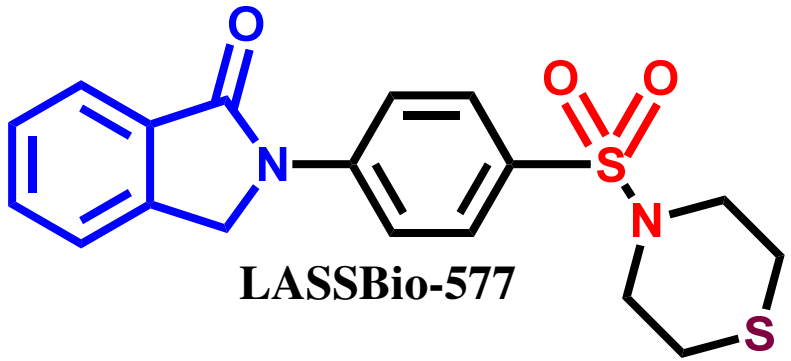
LASSBio-595

Instituto Nacional de Ciência e Tecnologia de Fármacos e Medicamentos

inofar

www.inct-inofar.ccs.ufrj.br

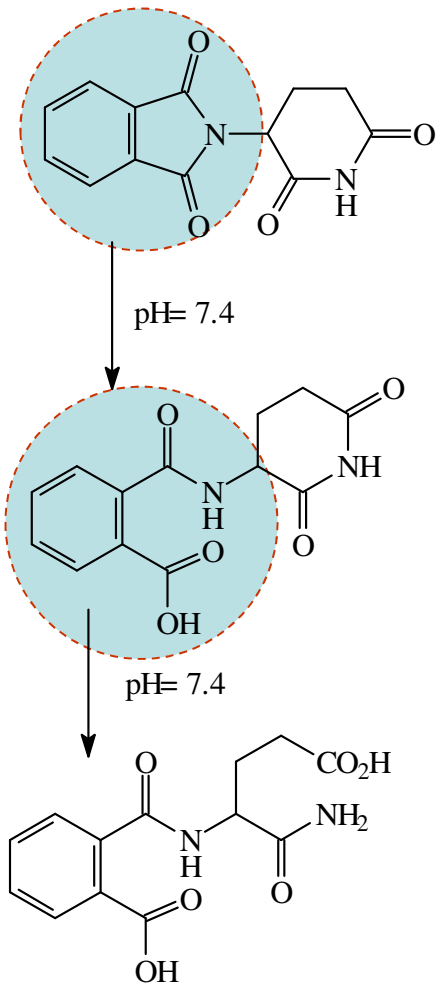
Metabolism studies



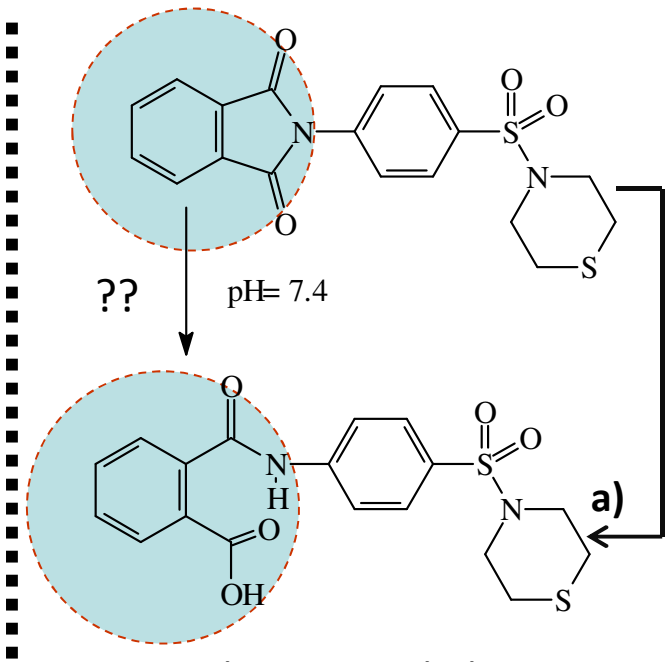
LASSBio-577

LM Lima, EJ Barreiro, "Bioisosterism: A Useful Strategy for Molecular Modification and Drug Design, *Curr. Med. Chem*. **2005**, *13*, 23

Metabolic & chemical stability of LASSBio-468

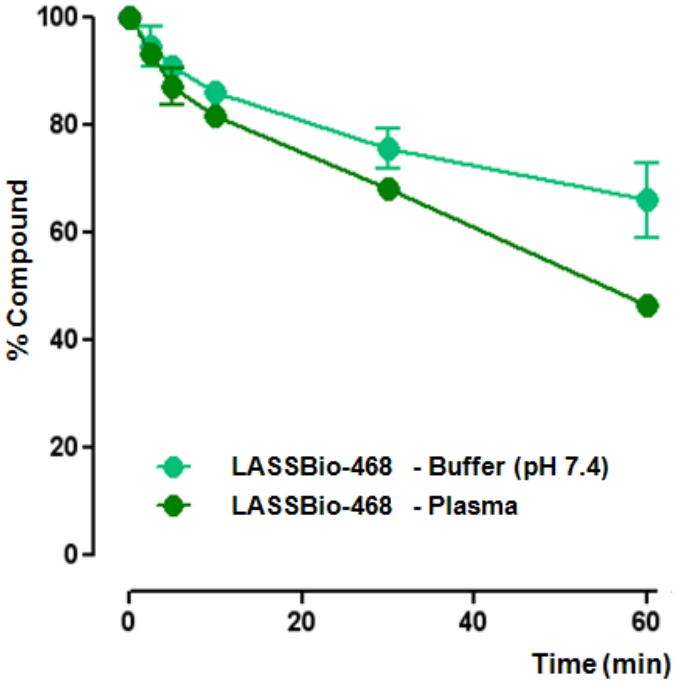


***in vivo* plasma metabolites of TLD**



in vivo plasma metabolite of LASSBio-468 (**596**)

a) KOH,MeOH/H_2O, 0°C, 1h, 91%



Chemical stability at pH 7.4 and plasma stability of LASSBio-468. The points represent the mean of the percentage of compound remaining at each time point. **P<0,01 Student's t-test.

Schumacher, H.; Smith, R. L. & Williams, R. T. (1965) *Brit. J. Pharmacol.*, **1965**, *25*, 324

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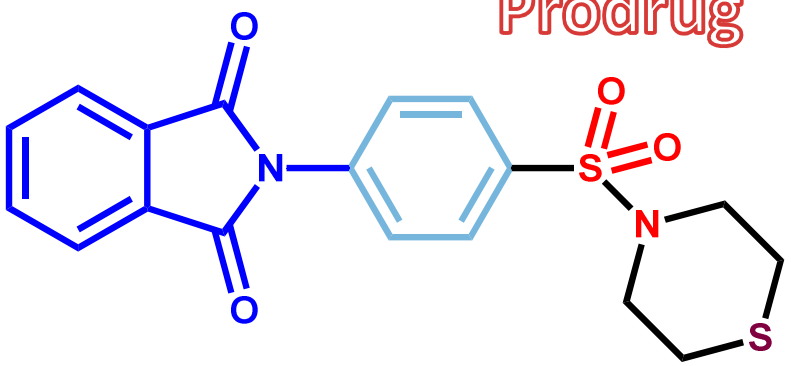
Prodrug



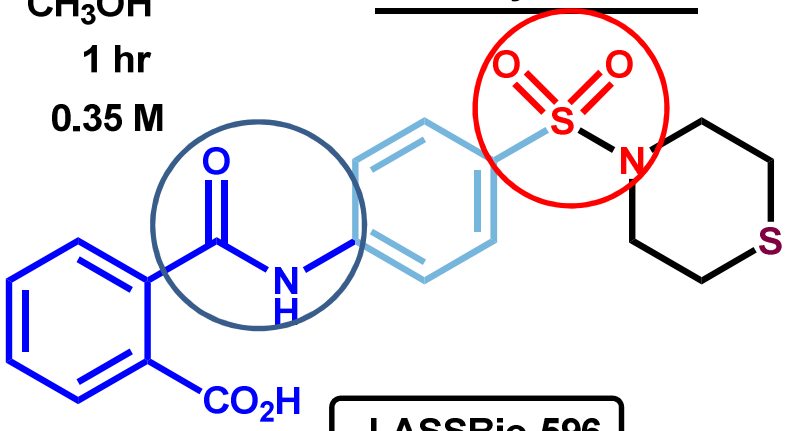
KOH / HOH

CH_3OH

1 hr

0.35 M

Overall yield: 29%



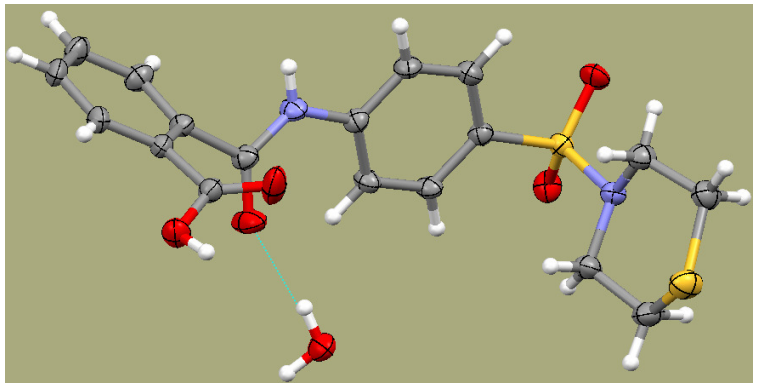
LASSBio-468

$C_{18}H_{16}N_2O_4S_2$

LASSBio-596

$C_{18}H_{18}N_2O_5S_2$

x-ray diffraction



^{13}C, ^{1}H NMR / IR / UV / MS
HPLC / CHN
differential scanning calorimetry (DSC)
X-ray

Ames Test

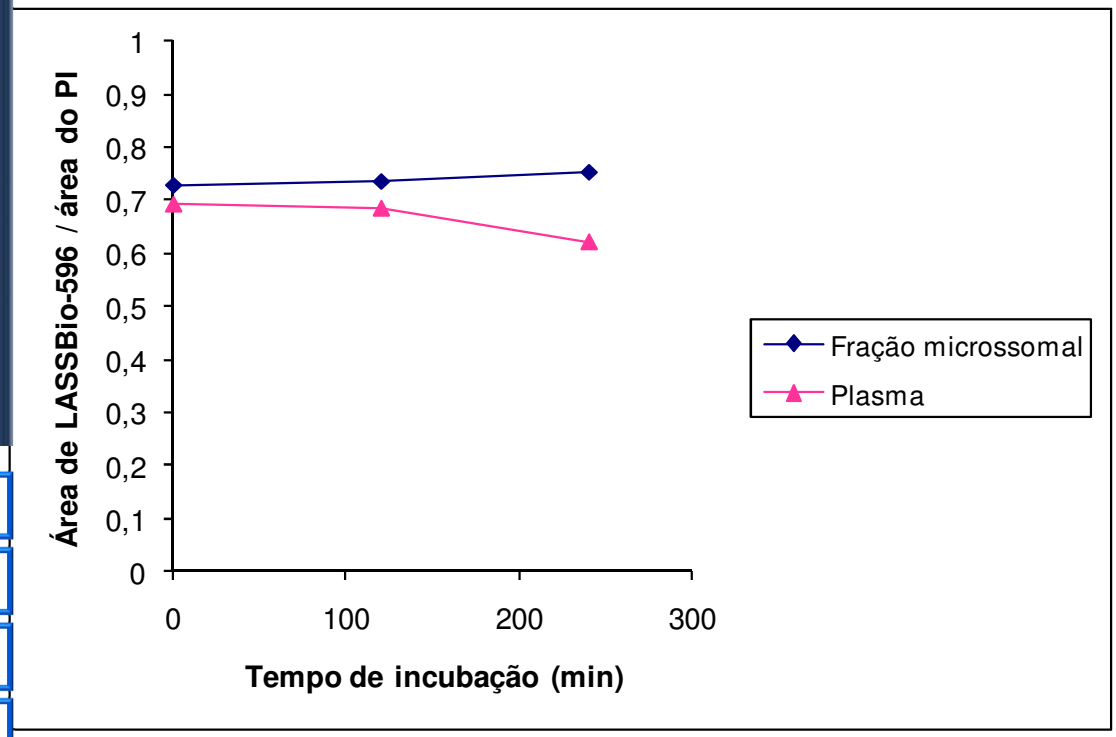
The bacteria reversed mutation assay : in the presence or absence of liver S9 fraction ⇒ **LASSBio-596 (625-3125 µg/plate) not presented carcinogenic potential**

Micronucleus Test

Used to quantify chromosomal damage in eukaryotic cell : in the presence or absence of liver S9 fraction ⇒ **LASSBio-596 (153-768 µM) not presented genotoxic potential**

Metabolism profile & toxicity in animals (rodents)

LASSBio-596



Metabolism profile of LASSBio-596 in rat liver microsomes in the presence of cofactors (blue) and in plasma of rats (in pink). Chart obtained from the ratio of the area LASSBio-596 and the area of internal standard methyl-biphenyl-4-carboxylate *vs.* incubation time.

✓**Acute Toxicity (14 days):**

LD_{50} = 150-200mg (iv)

LD_{50} > 2000 mg (po)

✓**Subchronic Toxicity (90 days)**:

Dose = 10, 50 and 250 mg/Kg

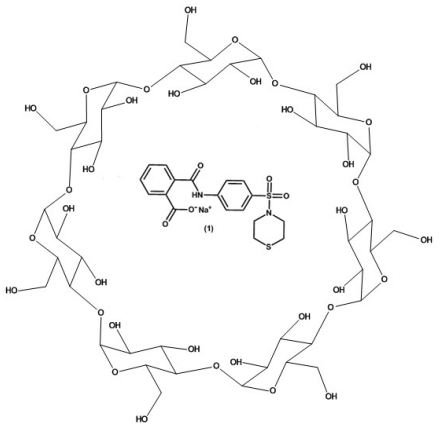
Not induce death;
some hematological
and few histopathological
changes were observed,
without clinical significance.

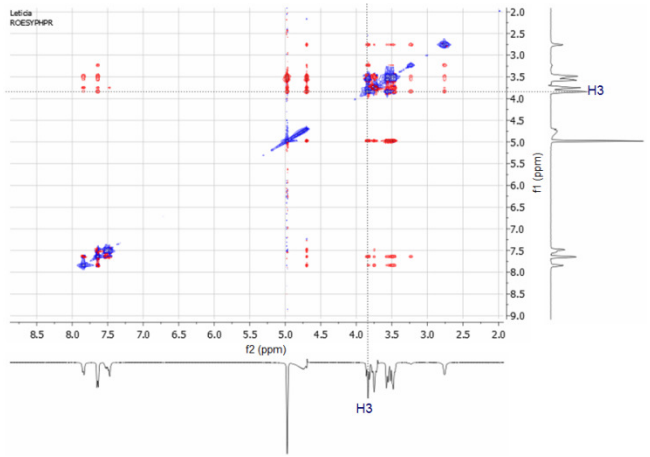
Pharmacokinetic Parameters

PK	LASSBio-596
t½ (h)	2.0 ± 0.4*
CL (L/h/kg)	0.22 ± 0.05
C_{max} (µg/mL)	0.61 ± 0.16
Bioavailability (%) (p.o)	3.6
Bioavailability (%) (ip)	96

* Significantly different with respect to the parameters after ip dose (a = 0.05)

ß-Cyclodextrin Inclusion complex





ROESY spectra (D_2O)

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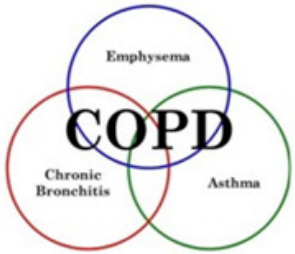
a s t h m a

LASSBio-596

Antifibrinogenic
Antiasthmatic
Antiinflammatory



$C_{18}H_{18}N_2O_5S_2$

406,4

Log P = 2 / CLogP = 1,80

MR = 103,02

medicinal chemistry

RVq Revista Virtual de Química

Volume 2, Número 1 Janeiro-Março 2010

INCT Instituto Nacional de Ciência e Tecnologia de Fármacos e Medicamentos inofar www.inct-inofar.ccs.ufrj.br

Lead Optimization

PIBR 0208767-7 - 08/11/2002

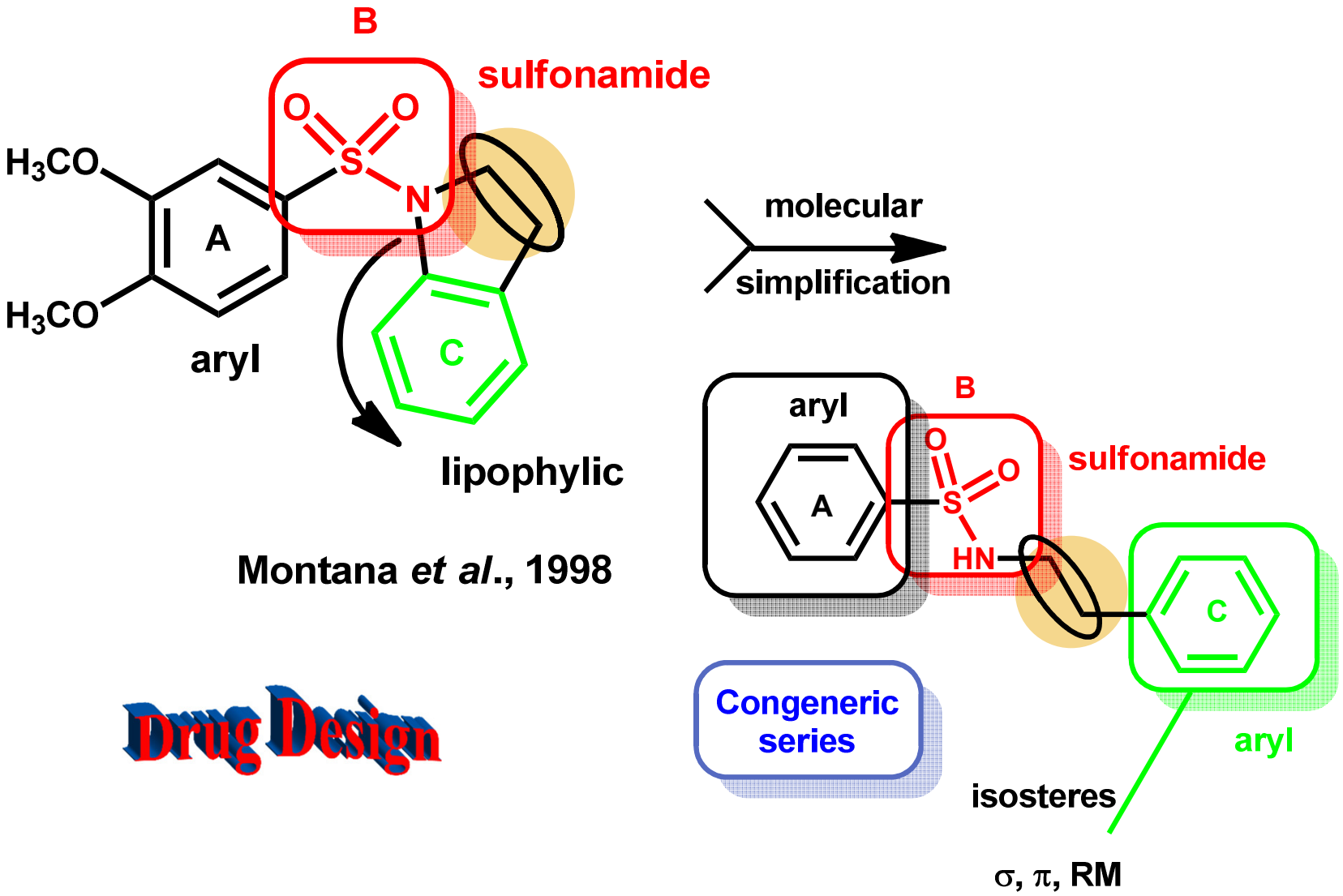
PIBR 0401660-2 - 27/04/2004

Pre-clinic studies

lead compound 2012

L. M. Lima *et al*., Synthesis and Anti-inflammatory Activity of Phthalimide Derivatives, Designed as New Thalidomide Analogues, *Bioorg. Med. Chem*. **2002**, *10,* 3067; A. L. Machado *et al.*, Design, Synthesis and anti-inflammatory activity of novel phthalimide derivatives, structurally related to thalidomide, *Bioorg. Med. Chem. Lett***. 2005***, 15***,*** 1169; 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*, Internat. Immunopharmacol.* **2005**, *5*, 485; L. M. Lima, N. M. de Lima, Contribuição do LASSBio no desenvolvimento de novos candidatos a protótipos de fármacos antiasmáticos*, Rev. Virtual Quim*. **2009**, *1*, 35; R.M.P. Rocco *et al*., LASSBio-596: da descoberta aos ensaios pré-clínicos, *Rev. Virtual Quim*. **2010**, *2*, 10; G.M.C. Carvalho *et al*., Can LASSBio-596 and dexamethasone treat acute lung and liver inflammation induced by microcystin-LR?, *Toxicon* **2010**, *56*, 604; N.V. Casquilho *et al*., LASSBio-596 *per os* avoids pulmonary and hepatic inflammation induced by microscystin-LR, *Toxicon* **2011**, *58*, 195;JCML Ribeiro, FVFechine, MZML Ribeiro, EJ Barreiro et al.,Potential Inhibitory Effect of LASSBio-596, a New Thalidomide Hybrid, on Inflammatory Corneal Angiogenesis in Rabbits, *Ophthalmic Res* **2012**, *48*, 177.

Molecular Diversity



Montana *et al*., 1998

Drug Design

M. L. C. Barbosa, T. J. F. Ramos, et al., Synthesis and pharmacological evaluation of novel phenyl sulfonamide derivatives designed as modulators of pulmonary inflammatory response, *Molecules* **2013**, *17,* 14651.

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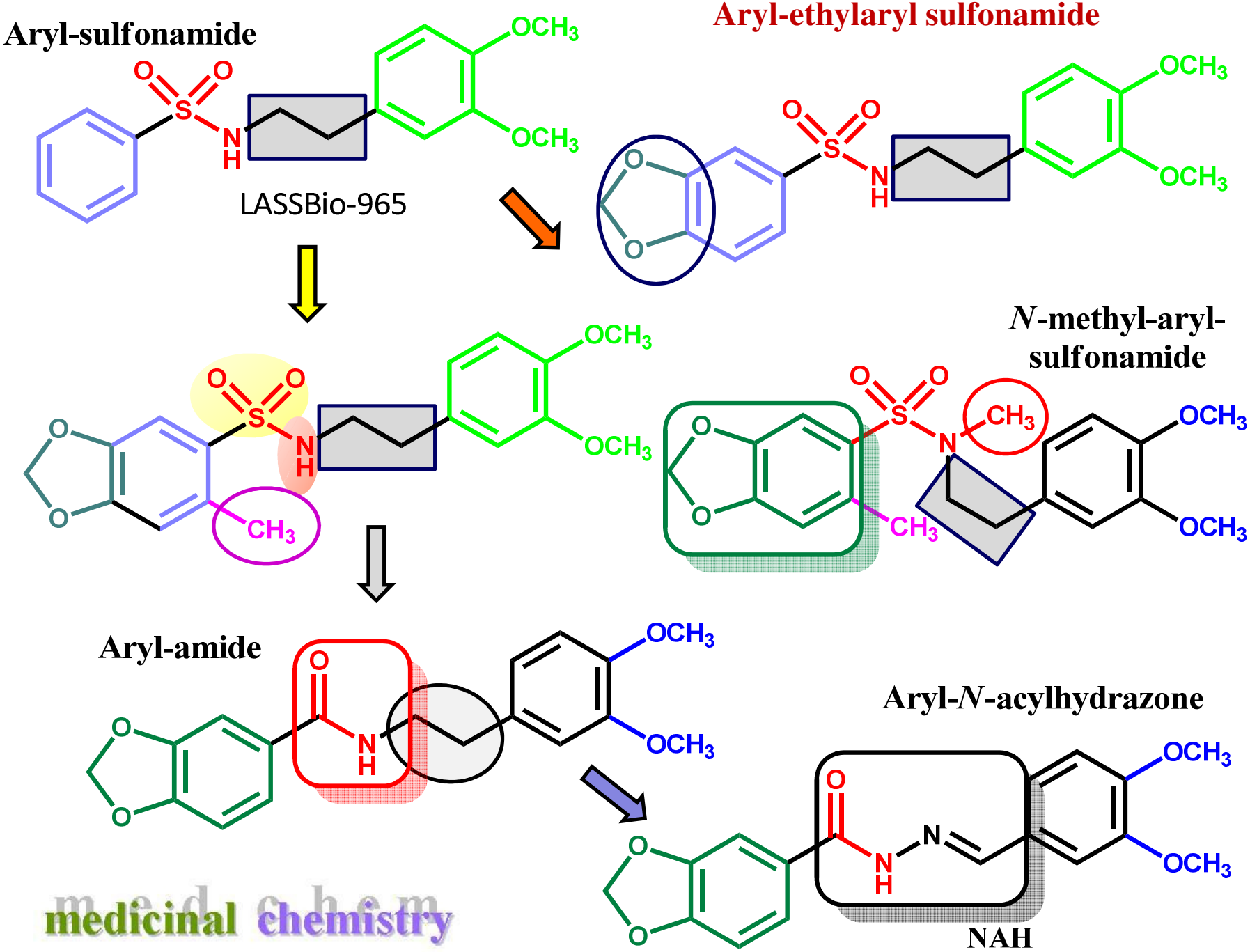
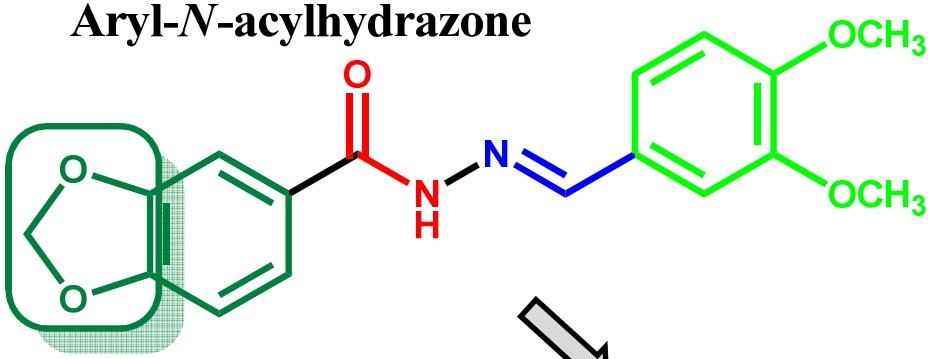
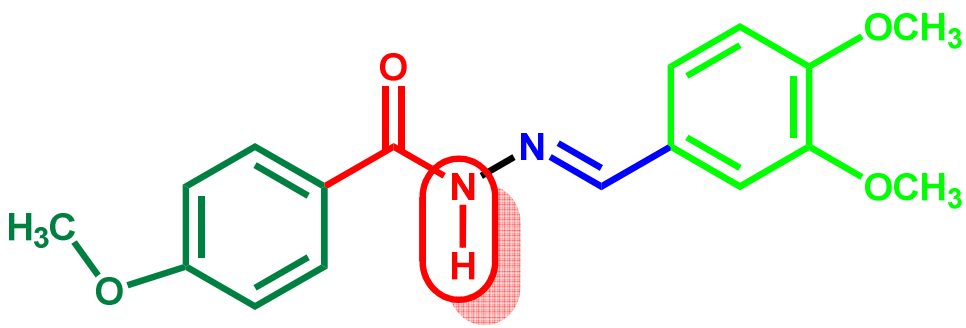
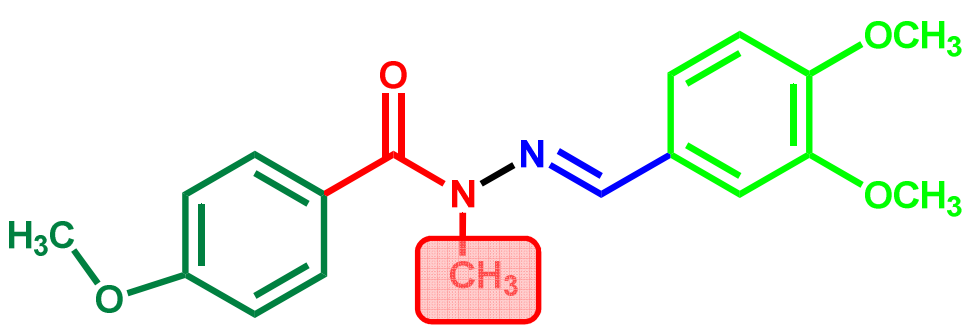


Aryl-*N*-acylhydrazone







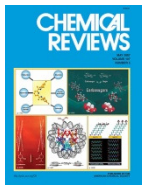
LASSBio-1145

IC_{50} PDE4 (nM) = 105.0

EC_{50} TNF-α (μM) = 1.45 ± 2.1

Lead Optimization

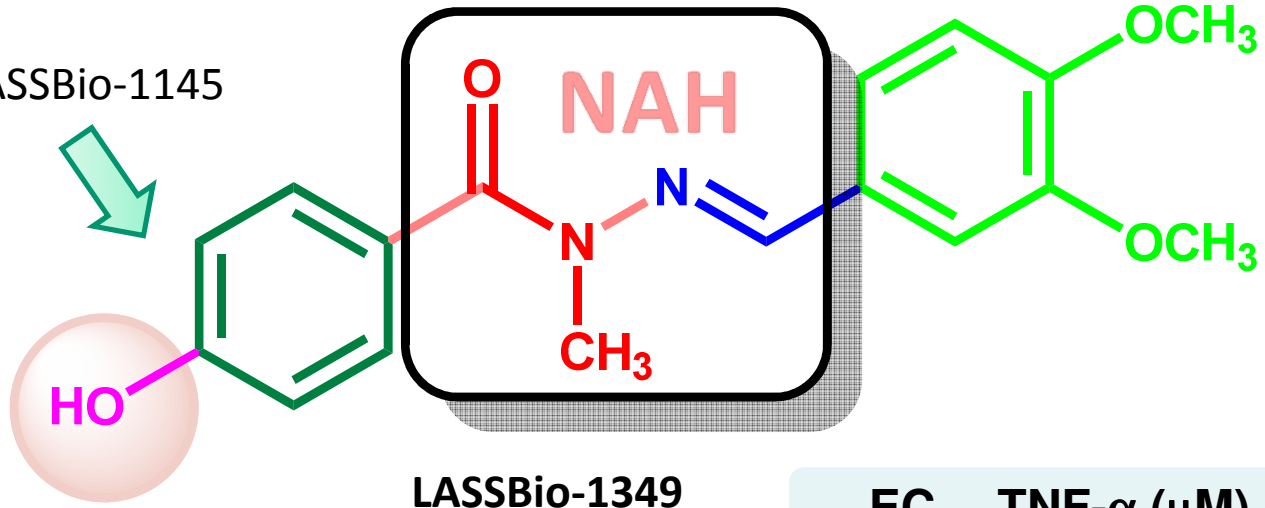
LASSBio-1349



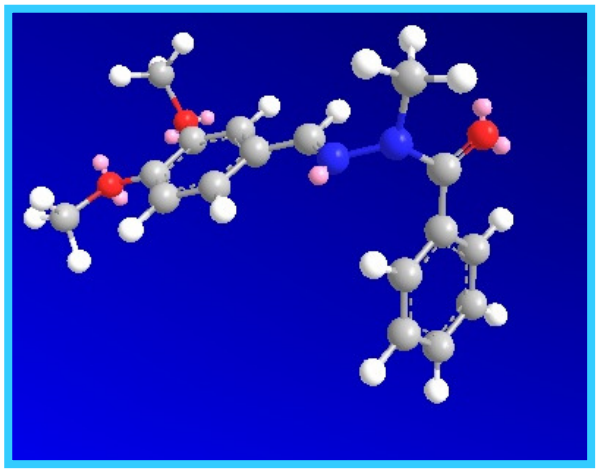
EJ Barreiro, AE Kümmerle, CAM Fraga, The methylation effect in Medicinal Chemistry, *Chem. Rev*. **2011**, *111*, 5215

New Dual AI-DMARD Lead-candidate

LASSBio-1145



LASSBio-1349



EC_{50} TNF-α (μM) = 0.52

IC_{50} PDE4 (nM) = 50.0

IC_{50} PDE4A (nM) = 64

IC_{50} PDE4B (nM) = 47

IC_{50} PDE4C (nM) = 206

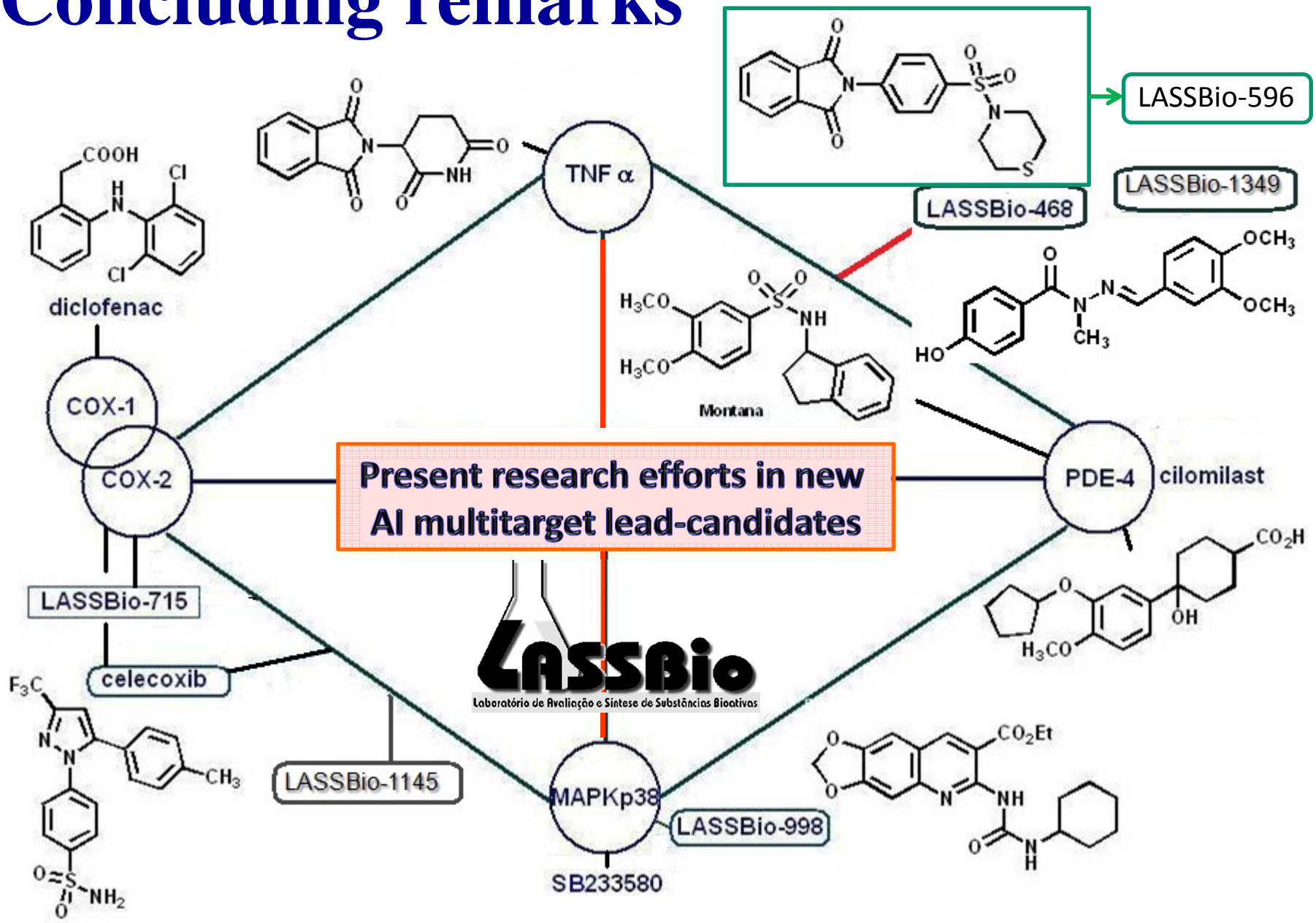
IC_{50} PDE4D (nM) = 31.0

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

In vivo

AE Kümmerle *et al*. Design, Synthesis and Pharmacological Evaluation of *N*-Acylhydrazones and Novel Conformationally Constrained Compounds as Selective and Potent Orally Active PDE-4 Inhibitors, *J Med Chem* **2012**, *55*, 7525.

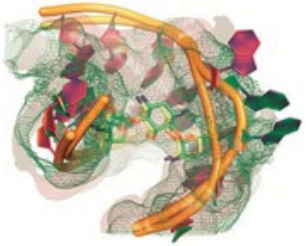
Concluding remarks



RB Lacerda, LL da Silva, et al.,Discovery of Novel Orally Active Anti-Inflammatory *N*-Phenylpyrazolyl-*N*-Glycinyl Hydrazone Derivatives That Inhibit TNF-α Production." PLoS ONE 2013, *7* (10).

Concluding remarks

ACS Medicinal Chemistry Letters



Drug Discovery in an Academic Setting: Playing to the Strengths

Donna M. Huryn*

Department of Pharmaceutical Sciences, University of Pittsburgh, 712 Salk Hall, 3501 Terrace Street, Pittsburgh, Pennsylvania 15261, United States

The Penn Center for Molecular Discovery

medicinal chemistry

" Without a doubt, a university has a number of unique characteristics that could contribute to making it an ideal enviroment where drug discovery & medicinal chemistry activities can thrive....There is no doubt that academia can play an important role in drug discovery"

ACS Med. Chem. Lett. **2013**, *4*, 313

Universidade Federal do Rio de Janeiro

http://ejb-eliezer.blogspot.com

De fármacos e suas descobertas

Pretende-se tratar de temas, opiniões, comentários sobre a Ciência dos Fármacos, seu uso seguro e benefícios. Aspectos da formação qualificada de universitários e pós-graduandos nas Ciências dos Fármacos também são de interesse.

sábado, 6 de julho de 2013

As estruturas químicas e os recursos para desenhá-las

*Relendo um artigo de divulgação científica publicado este ano, me deparei com alguns argumentos centrais do autor, sobre o avanço tecnológico que se observou na difusão da informação, com inúmeros novos recursos, além das redes sociais, capazes de distribuí-la eficiente e rapidamente. Não sei bem porque, fiz um link com a evolução que acompanhei no desenho das estruturas químicas de compostos orgânicos desde aquelas dos triterpenos tetracíclicos do tipo damarano de minha dissertação de mestrado, concluída em 1973, até as últimas, representadas em recente publicação oriunda do **LASSBio**. Achei que poderia ser interessante como leitura, o registro da evolução dos recursos para o desenho das estruturas químicas dos compostos orgânicos, que testemunhei, daquela época até hoje.*

Total de visualizações de página

27,632

www.ejb-eliezer.blogspot.com

Universidade Federal do Rio de Janeiro

Acknowledgements

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Instituto Nacional de Ciência e Tecnologia de Fármacos e Medicamentos

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LASSBio

Laboratório de Avaliação e Síntese de Substâncias Bioativas

Thank You