Multi-target drug design
(MTDD)

Eliezer J. Barreiro

Professor

Universidade Federal do Rio de Janeiro

Laboratório de Avaliação e Síntese de Substâncias Bioativas

http://www.farmacia.ufrj.br/lassbio

Instituto Nacional de Ciência e Tecnologia em Fármacos e Medicamentos

INCT-INOFAR

http://www.inct-inofar.ccs.ufrj.br/

Universidade Federal do Rio de Janeiro

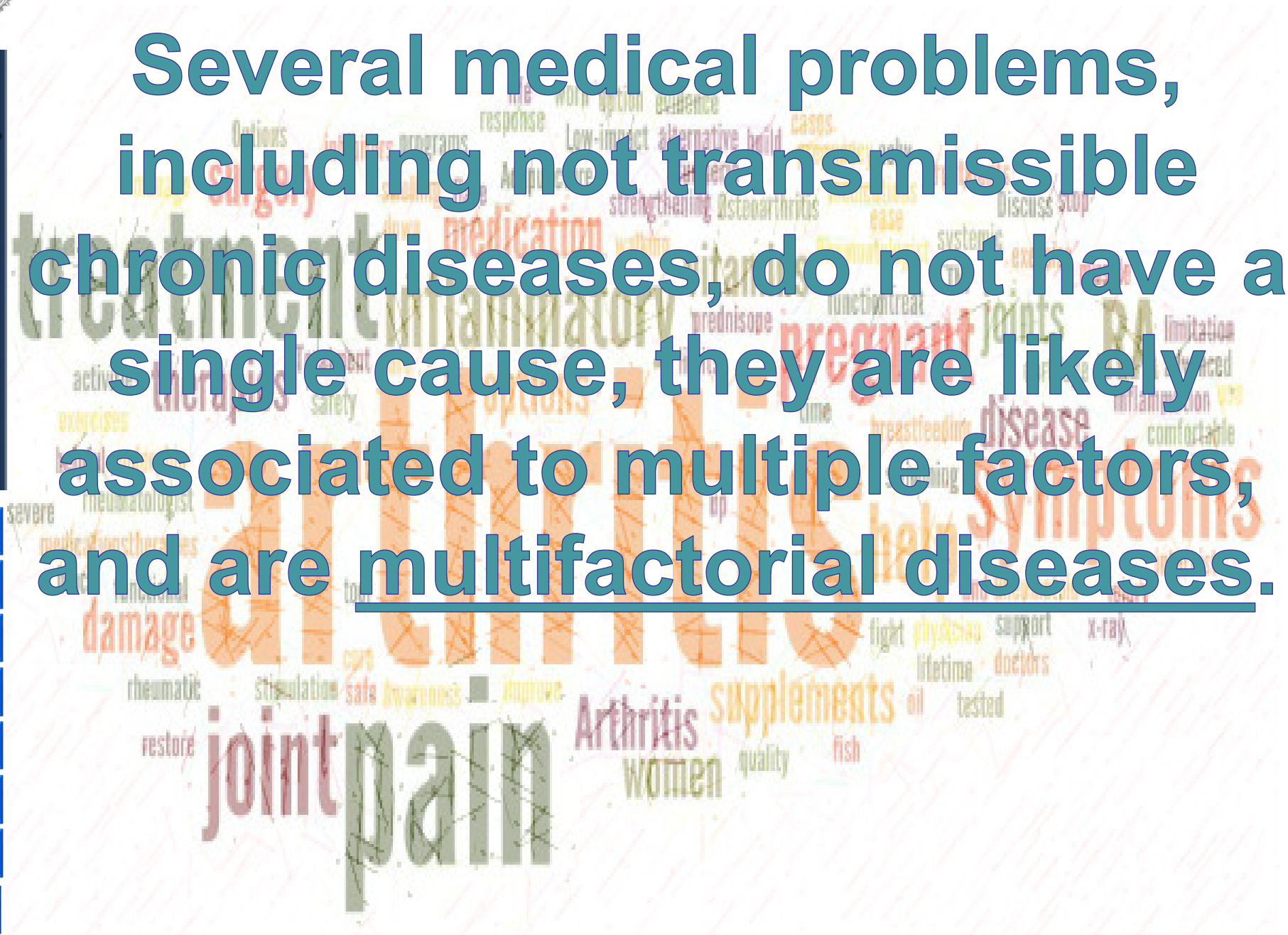
Summary

- Non-transmissible Multifactorial Chronical Diseases (NTMCD´s);
- Rational Multi-target Drug Design (RMTDD);
- LASSBio-UFRJ/BR & **MTDD** candidates:
  - New anti-inflammatory dual drug candidates;
- Concluding remarks;
- Acknowledgments.

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

Universidade Federal do Rio de Janeiro

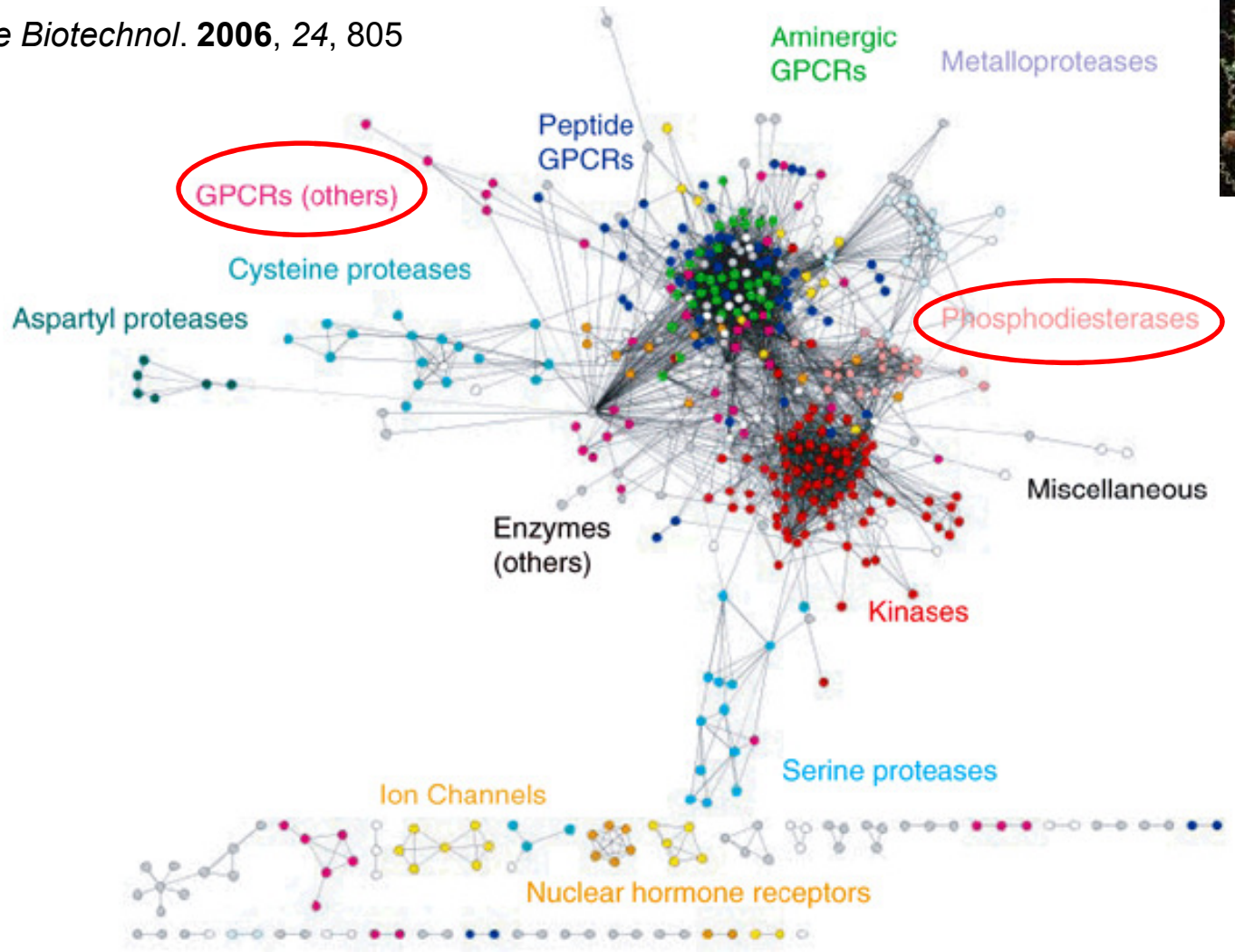
Several medical problems, including not transmissible chronic diseases, do not have a single cause, they are likely associated to multiple factors, and are multifactorial diseases.



Global mapping of pharmacological space

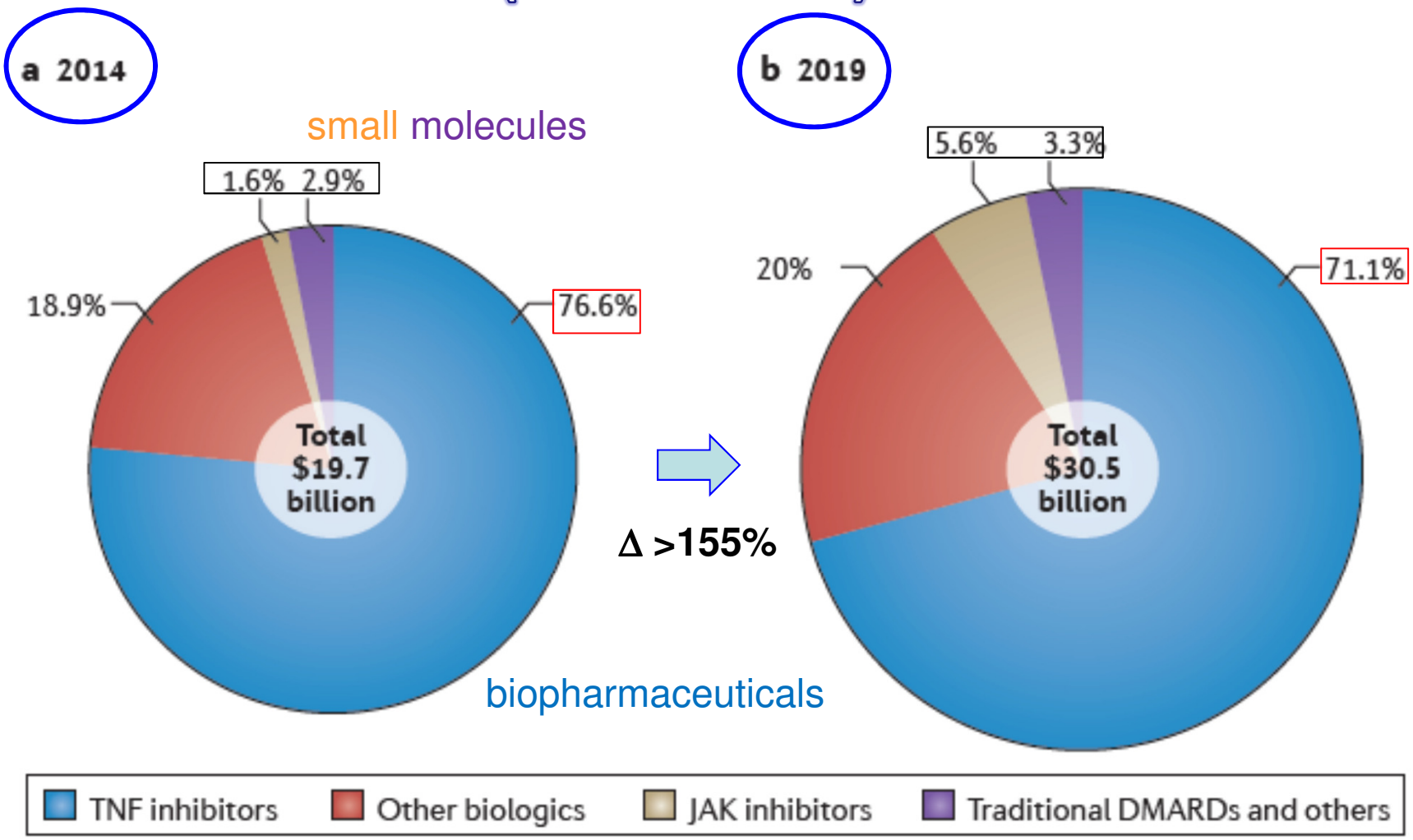
Gaia V Paolini[1,3,7], Richard H B Shapland[1,4,5], Willem P van Hoorn[2,3], Jonathan S Mason[3,6] & Andrew L Hopkins[1,3,7]

Nature Biotechnol. **2006**, *24*, 805



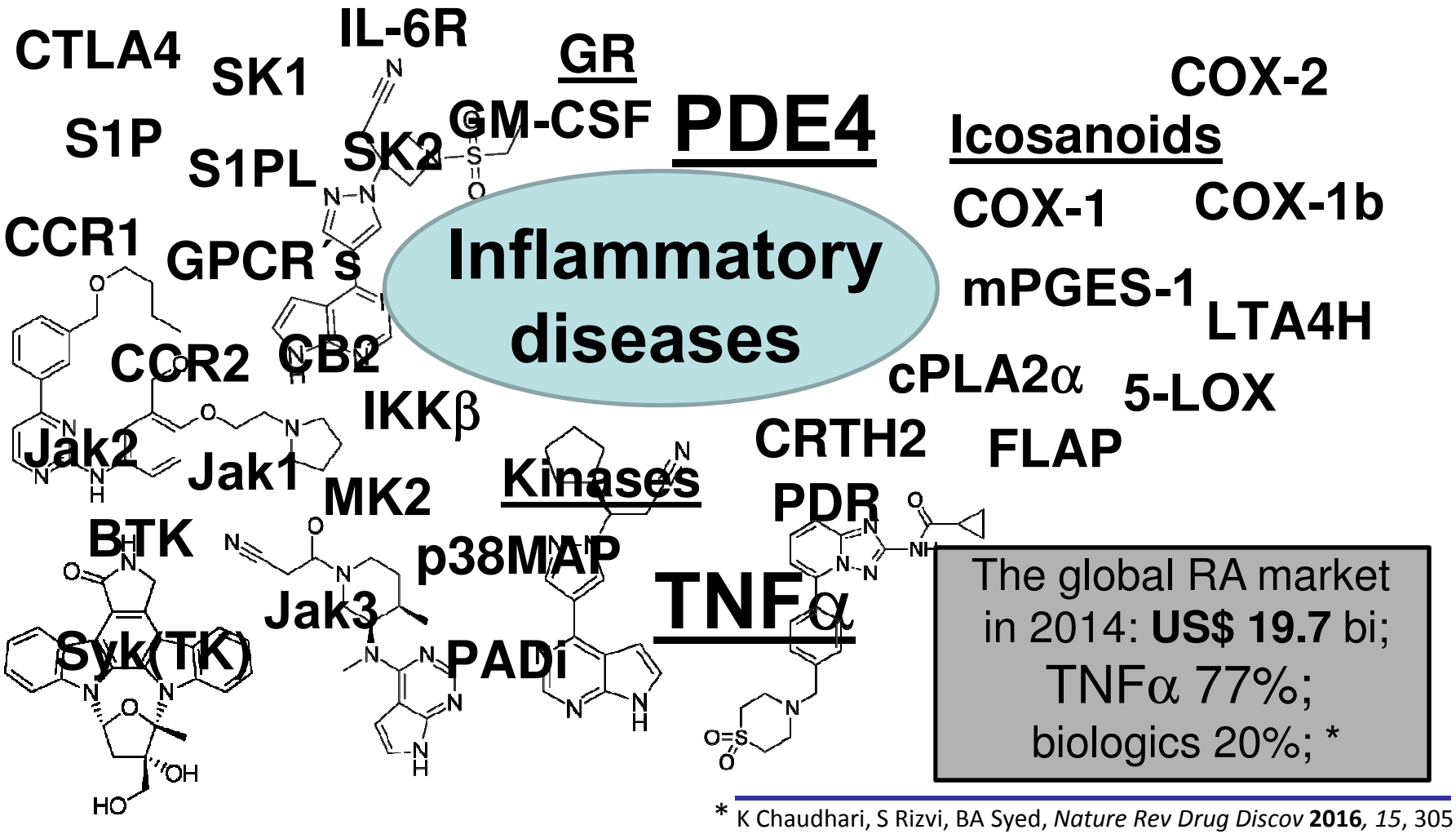
R. O. Dror et al. Structural basis for modulation of a G-protein coupled receptor by allosteric drugs, *Nature* **2013**, *503*, 295.

Global sales of drugs to rheumatoid arthritis ($ US) (2014 & 2019)



K Chaudhari, S Rizvi, B. A. Syed, *Nature Rev Drug Discovery* **2016**, *35*, 305;

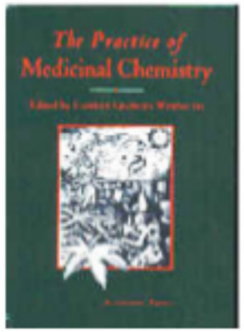
Inflammation = Non-transmissible Multifactorial Chronical Diseases



* K Chaudhari, S Rizvi, BA Syed, *Nature Rev Drug Discov* **2016**, *15*, 305

Universidade Federal do Rio de Janeiro

" ... 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

A Anighoro et al., **Polypharmacology:** challenges and opportunities in drug dsicovery, *J. Med. Chem*. **2014**, *57,* 7874; K Li et al., Multitarget drug discovery for tuberculosis and other infectious diseases, *J Med Chem* **2014**, *57*, 3126; JL Medina-Franco et al. Shifting from the single to the **multitarget paradigm** in drug discovery, *Drug Discov. Today* **2013**, *18,* 495; C Hiller, J Kühhorn, P Gmeiner, Class A G-Protein-Coupled Receptor (GPCR) Dimers and Bivalent Ligands, *J. Med. Chem.* **2013**, *56*, 6542; G Phillips, M Salmon, **Bifunctional compounds** for the treatment of COPD, *Annu. Rev. Med. Chem*. **2012**, *47*, 209; S Reardon, A world of chronic disease, *Science* **2011**, *333*, 558.

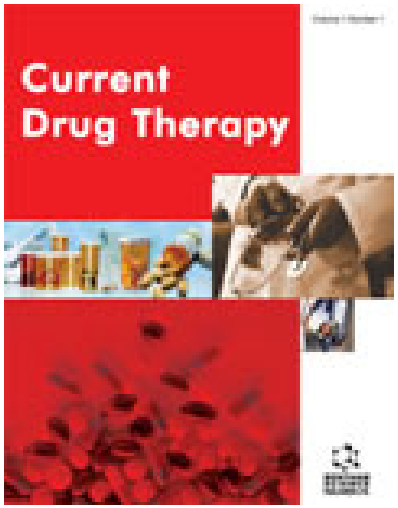
New Insights for Multifactorial Disease Therapy: The Challenge of the Symbiotic Drugs

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.

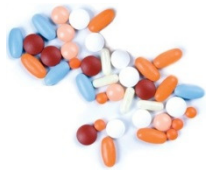
Abstract: Some physiopathological processes involved in the genesis of diseases could suggest the necessity of designing bioligands or prototypes that aggregate, in only one molecule, dual pharmacodynamical properties, becoming able to be recognized by two elected bioreceptors. This approach can have 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.

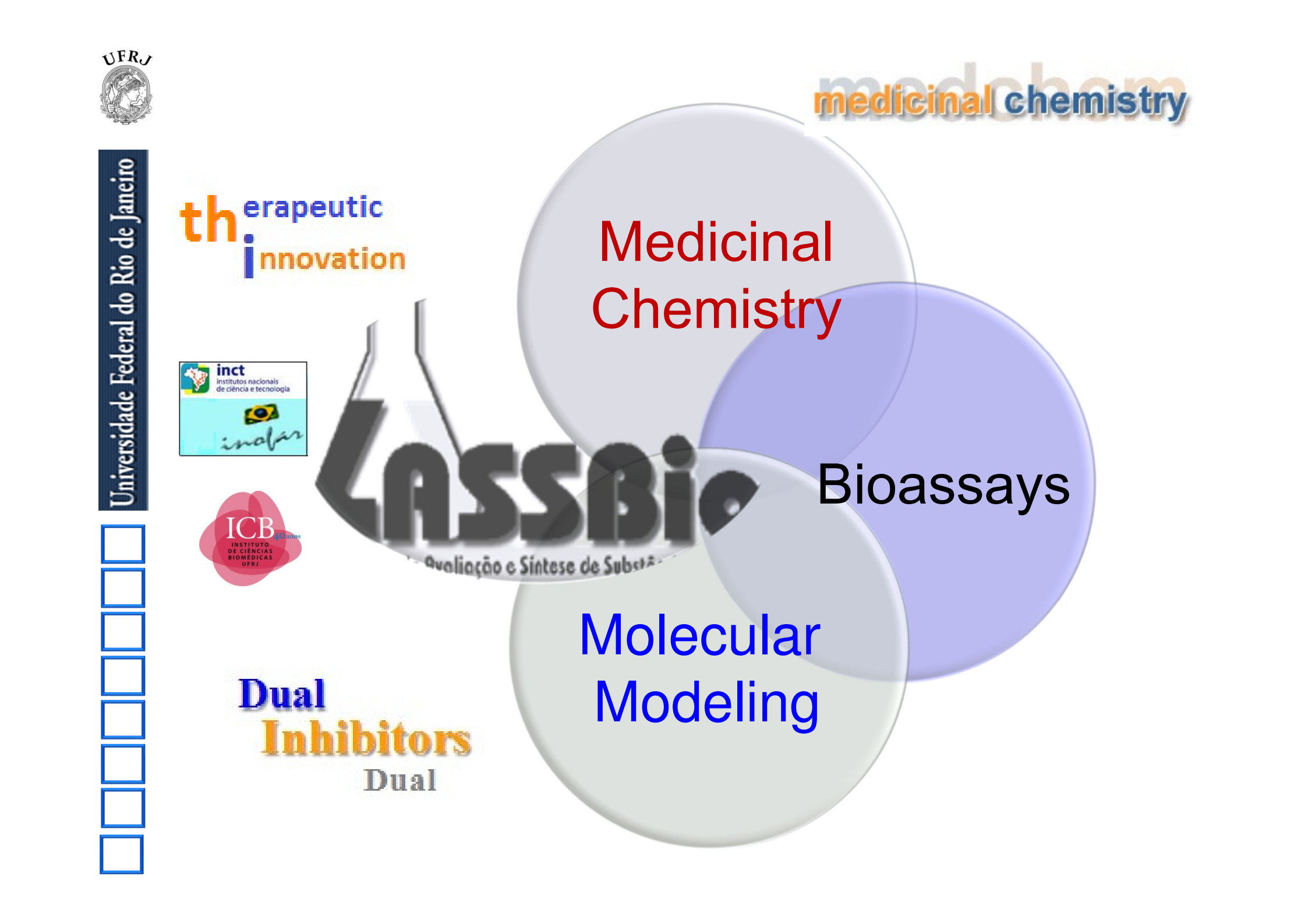
Key Words: Symbiotic drugs; molecular hybridization; multifactorial diseases; therapeutic innovation; drug design; dual compounds.



Could be effective a single target drug in the treatment of multifactorial diseases?

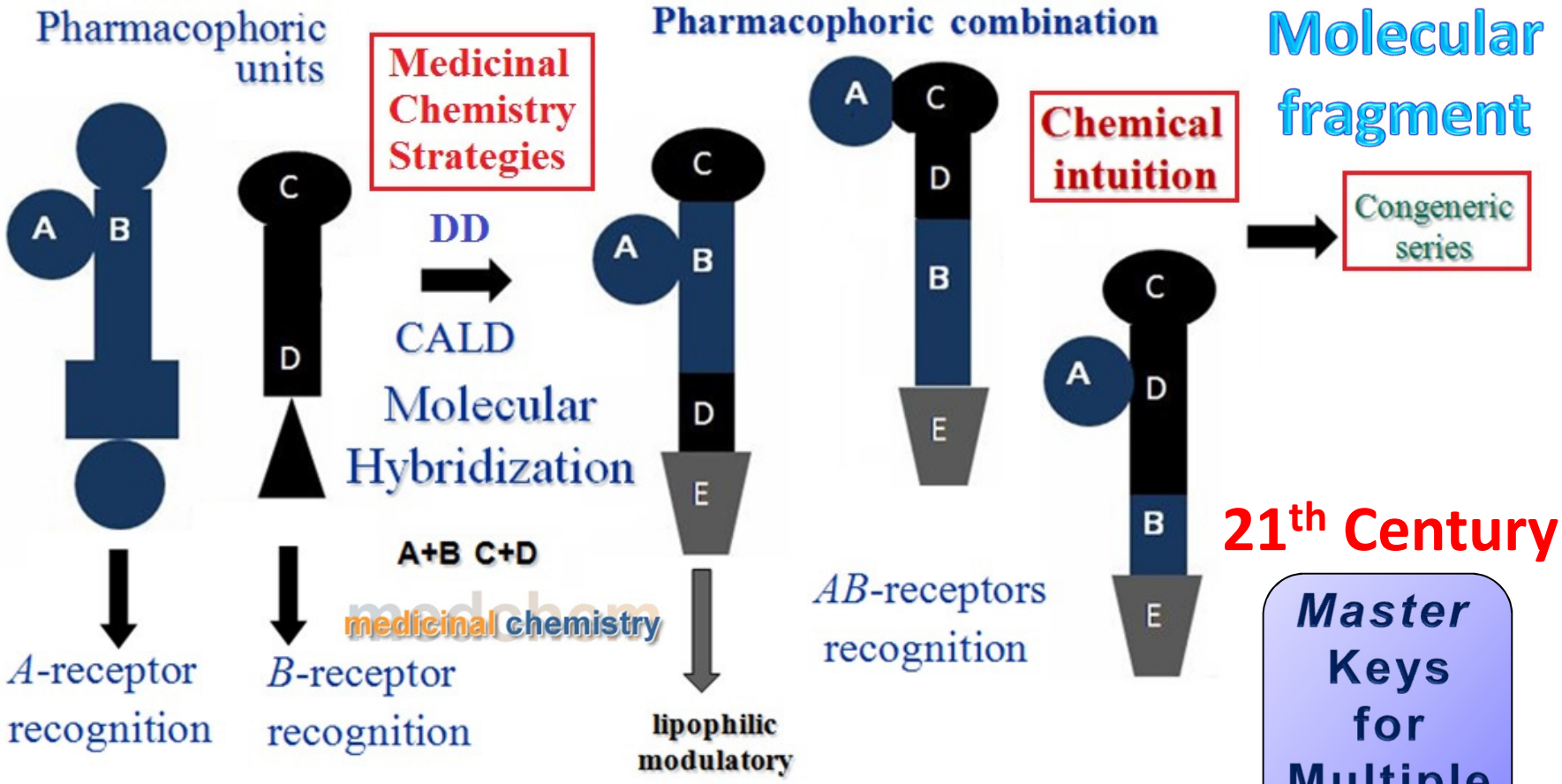
medicinal chemistry




UFRJ
Universidade Federal do Rio de Janeiro
medicinal chemistry
therapeutic innovation
inct
institutos nacionais de ciência e tecnologia
inofar
ICB
INSTITUTO DE CIÊNCIAS BIOMÉDICAS UFRJ
LASSBio
Medicinal Chemistry
Bioassays
Molecular Modeling
Dual Inhibitors
Dual

The rational-based MTD design

Universidade Federal do Rio de Janeiro



21th Century

Master Keys for Multiple locks

Pharmacophoric contribution
Chemical libraries

Dual candidates

Cocktail = multicomponent therapy

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

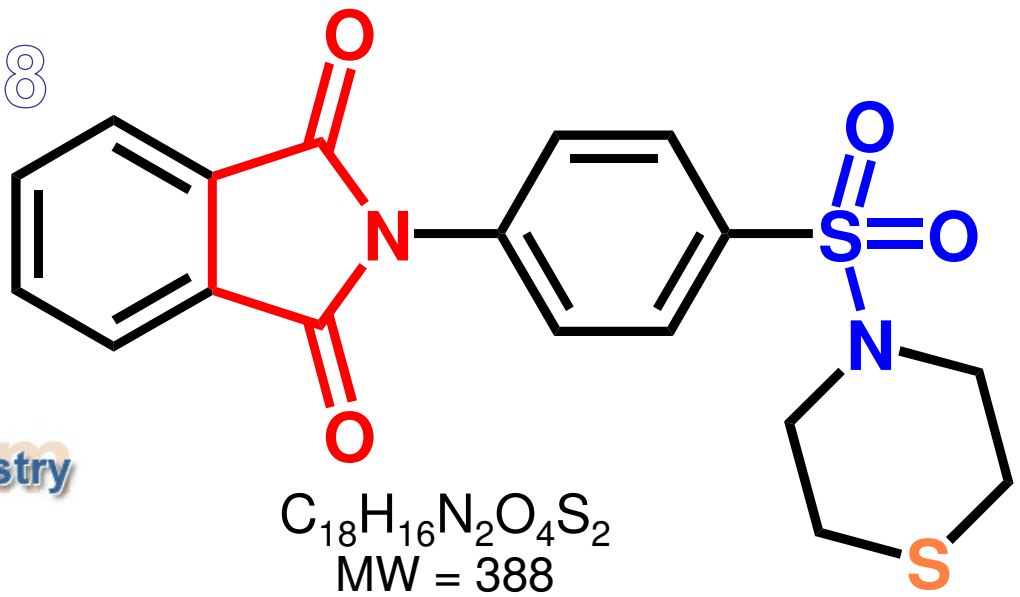
New achiral dual anti-inflammatory drug candidate.

A new TNF-α modulator & PDE-4 inhibitor

LASSBio-468

2002

medicinal chemistry



$C_{18}H_{16}N_2O_4S_2$

MW = 388

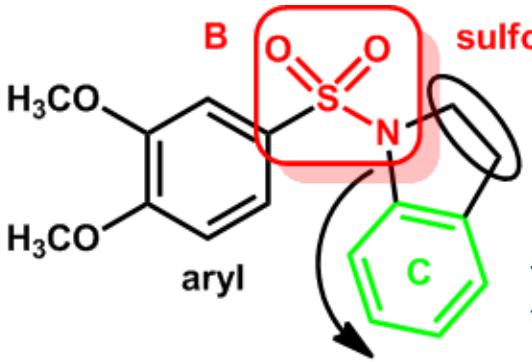
cLog P = 2,3

MR = 100 [cm^3/mol]

Lima, L. M.; Castro, Paulo ; Machado, A. L.; Fraga, C. A. M. ; Lugnier, C. ; Koatz, V. L. G.; Barreiro, E. J. *Bioorg. Med. Chem*. **2002**, *10*, 3067; Alexandre-Moreira, M. S.; Takiya, C. M.;Arruda, L.B.P.; Pascarelli, B.; Gomes, R. N.; Faria-Neto, H. C. C.; Lima, L. M.; Barreiro, E. J., *Internat. Immunopharmacol*. **2005**, *5*, 485; Lima, L. M.; Fraga, C. A. M.; Koatz, Vera Lucia G.; Barreiro, E. J. *Anti-Inflamm. Anti-Allergy Agents Med. Chem*. **2006**, *5*, 79; Lima, L M.; Lima, N M, *Rev. Virtual Quim.,* **2009,** *1*, 35.

The molecular design of the *new* agent

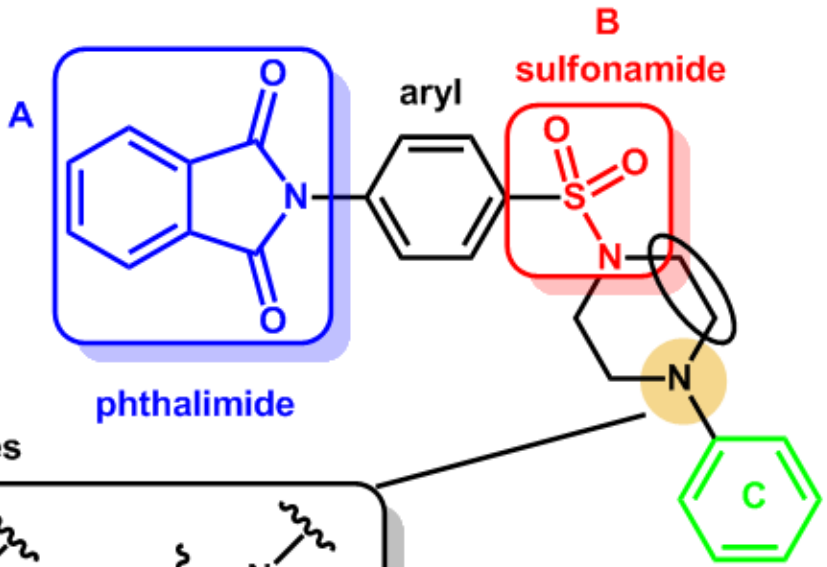
anti-TNFα activity & PDE-4i



lipophylic

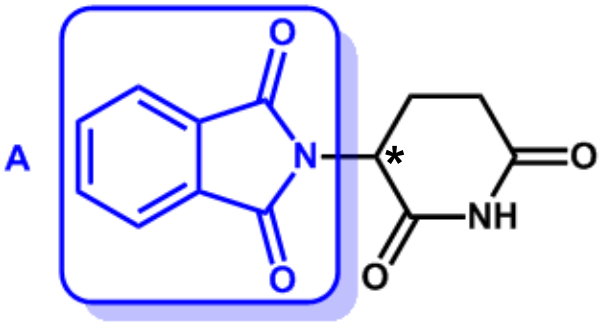
Montana *et al*., 1998

molecular hybridization



phthalimide

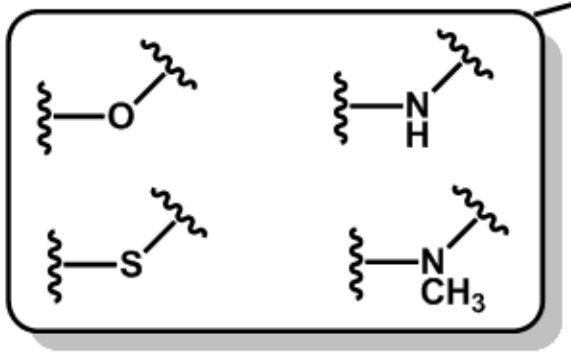
"The medicinal chemist dream molecule"



phthalimide

Thalidomide (1957)

isosteres

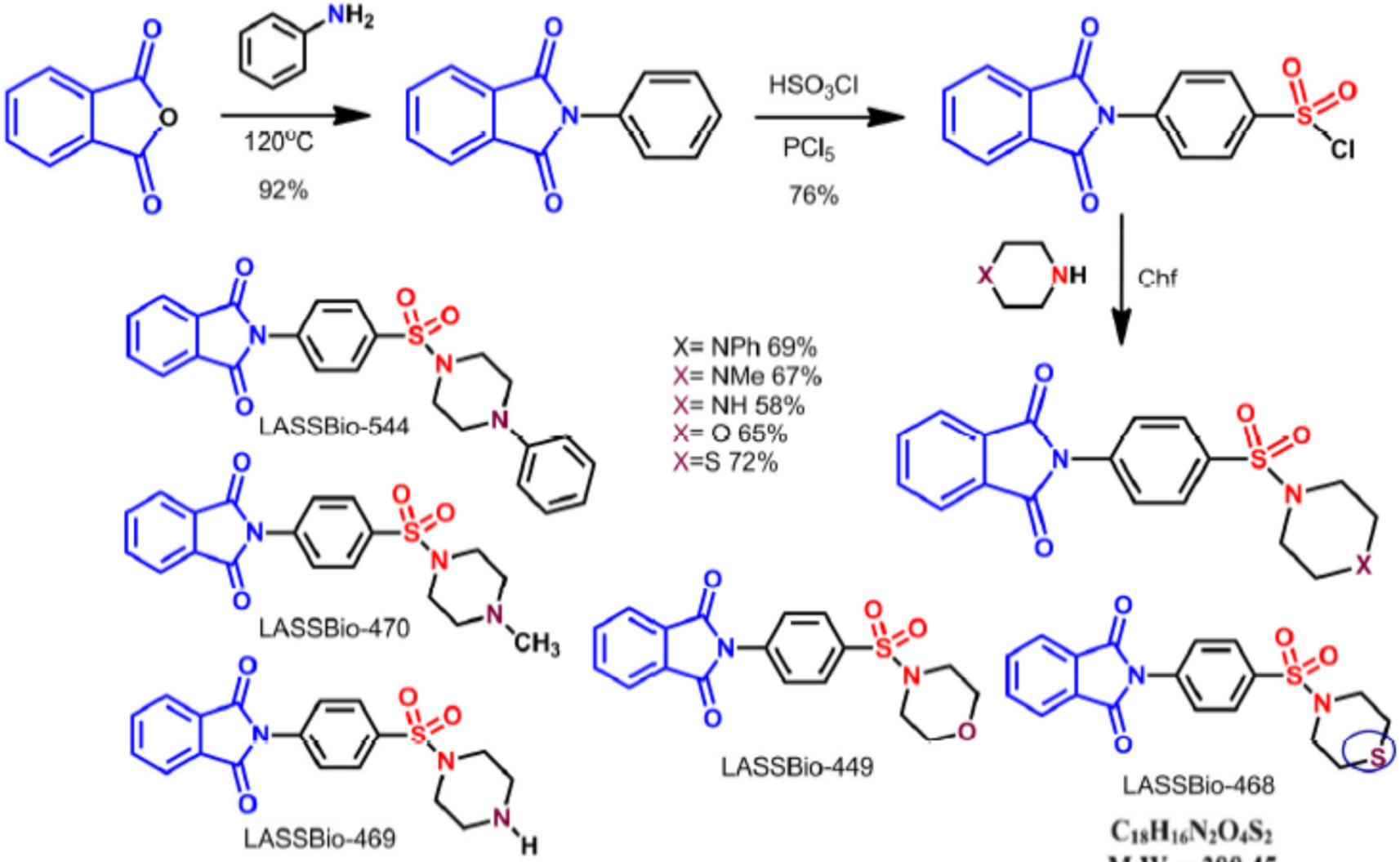


Molecular diversity

σ, π, RM

C Viegas Jr, A Danuello, VS Bolsani, EJ Barreiro, CAM Fraga, Molecular Hybridization: An useful tool in the design of new drug prototypes, *Curr Med Chem* **2007**, *14*, 1829; LM Lima & EJ Barreiro, Bioisosterism: A Useful Strategy for Molecular Modification and Drug Design, *Curr. Med. Chem.* **2005**, *12*, 23.

Synthesis of LASSBio-468 & isosteres



Overall yield: *ca.* 20%

(~ 0.5 M, 200 g)

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

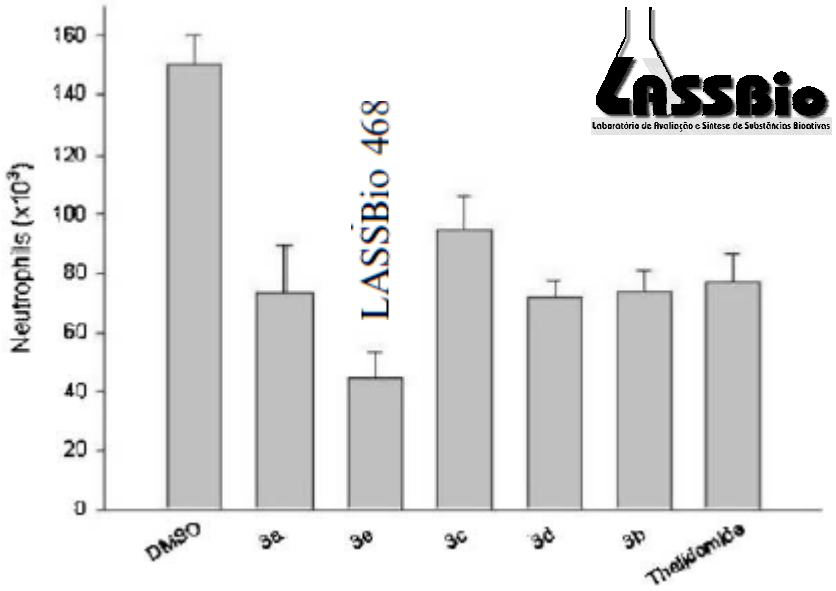


Figure 1. Effect of compounds **3a–e** and thalidomide on neutrophil influx induced by LPS into BALF of mice lungs.

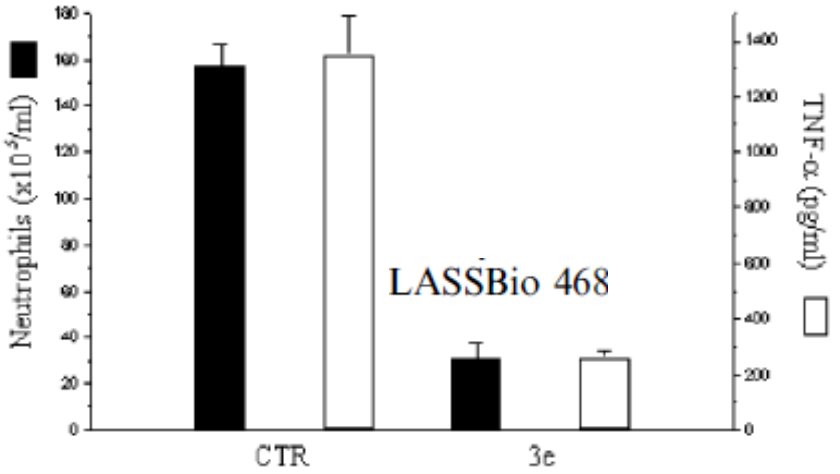
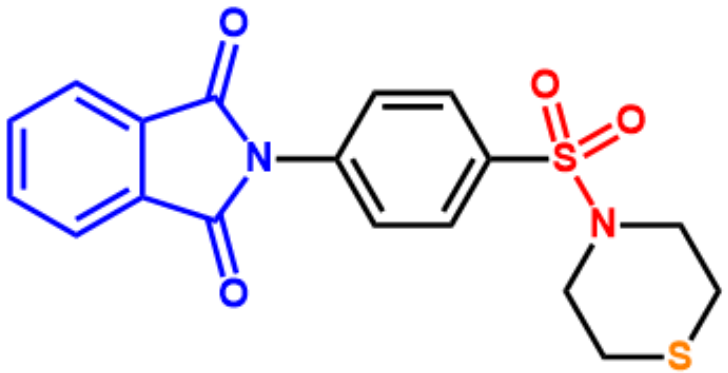


Figure 2. Effect of compound **3e** (LASSBio 468) on TNF-α levels and neutrophil influx into the BALF of mice lungs.



LASSBio-468

Bioorganic & Medicinal Chemistry
Volume 10, Issue 9, September 2002, Pages 3067–3073

Synthesis and anti-inflammatory activity of phthalimide derivatives, designed as new thalidomide analogues

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

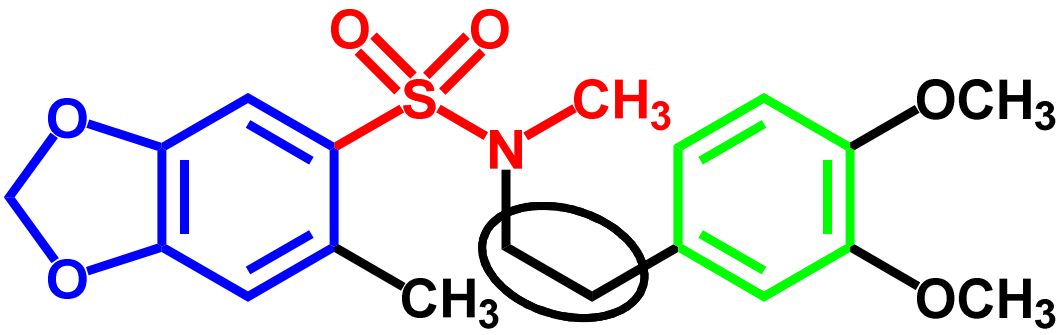
TNF-α ED_{50} = 2.5 mg/Kg

PDE-4 IC_{50} = 29.4 μM

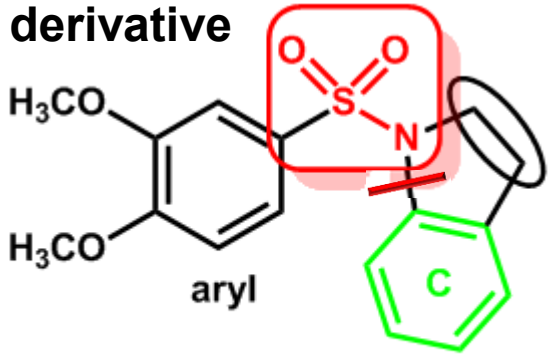
PDE-4/TNF-α

Universidade Federal do Rio de Janeiro

Sulfonamide derivative



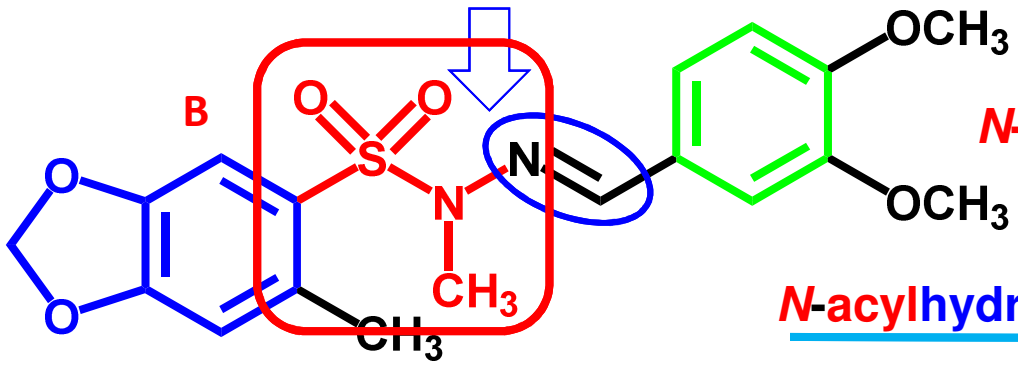
Sulfonamide derivative



Montana *et al.*, 1998

"The medicinal chemist dream molecule"

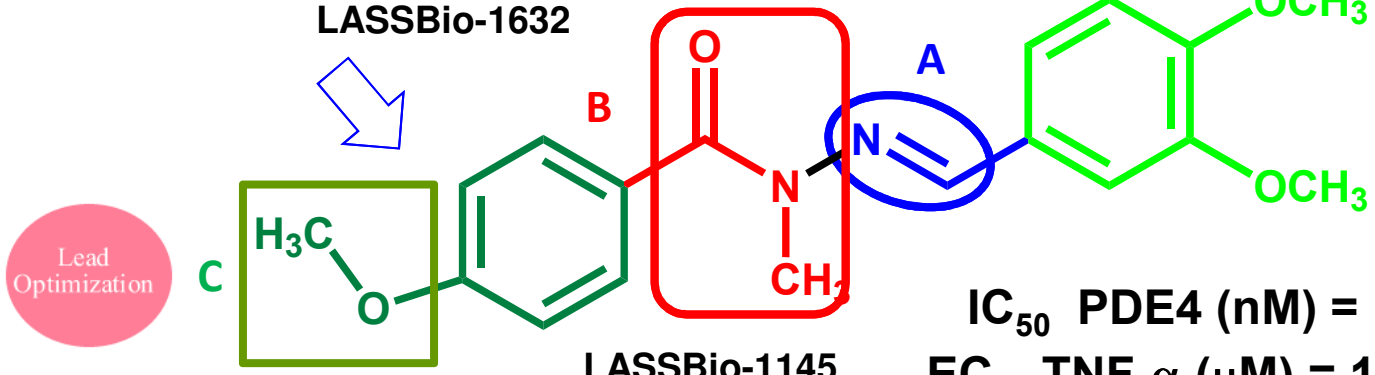
LASSBio-448



***N*-sulfonylhydrazone derivative**

***N*-acylhydrazone derivative**

LASSBio-1632



LASSBio-1145

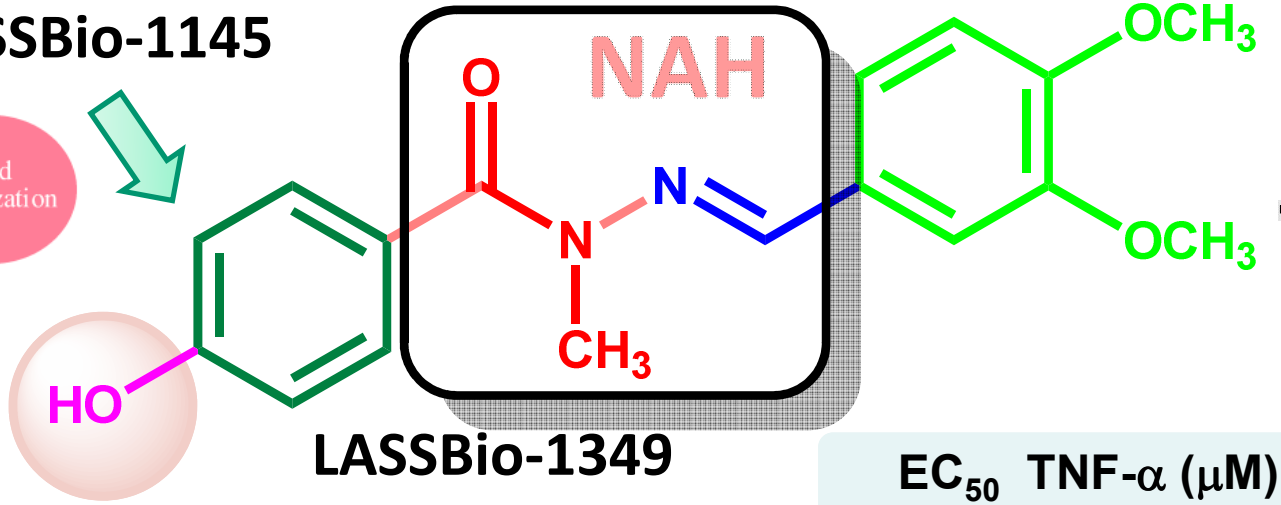
IC_{50} PDE4 (nM) = 105

EC_{50} TNF-α (μM) = 1.45 ± 1.1

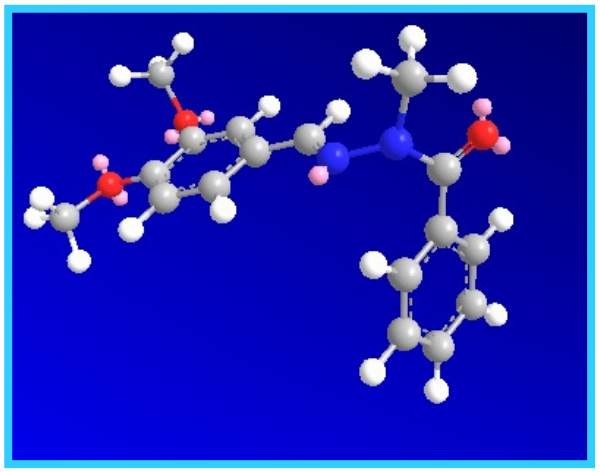
A new dual lead-compound

LASSBio-1145

Lead Optimization



LASSBio-1349



EC_{50} TNF-α (μM) = 0.52

IC_{50} PDE4B (nM) = 47.0

IC_{50} PDE4A (nM) = 64

IC_{50} PDE4C (nM) = 206

IC_{50} PDE4D (nM) = 31

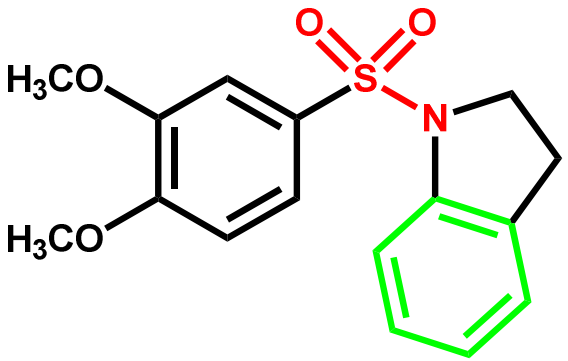
SI PDEX / PDE4 (X=1, 2, 3, 5, 6) = 182

Universidade Federal do Rio de Janeiro

Medicinal Chemistry

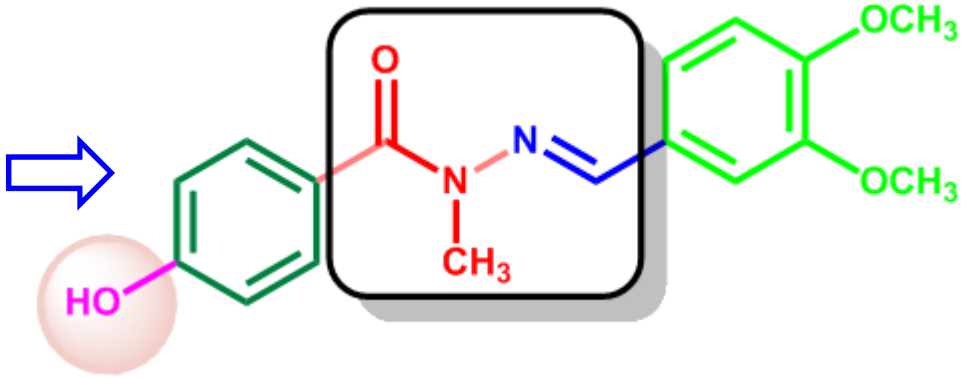
AE Kümmerle et al. Design, Synthesis and Pharmacological Evaluation of *N*-Acylhydrazones and Novel Conformationally Constrained Compounds as Selective and Potent Orally Active PDE-4 Inhibitors, *J Med Chem* **2012**, *55*, 7525; AE Kümmerle et al. , Studies towards the identification of putative bioactive conformation of potent vasodilator arylidene *N*-acylhydrazone derivatives, *Eur J Med Chem* **2009**, *44*, 4004EJ Barreiro, AE Kümmerle, CAM Fraga, The methylation effect in Medicinal Chemistry, *Chem. Rev*. **2011**, *111*, 5215.

From the "*medicinal chemist dream molecule*" to a new multi-target anti-inflammatory drug candidate



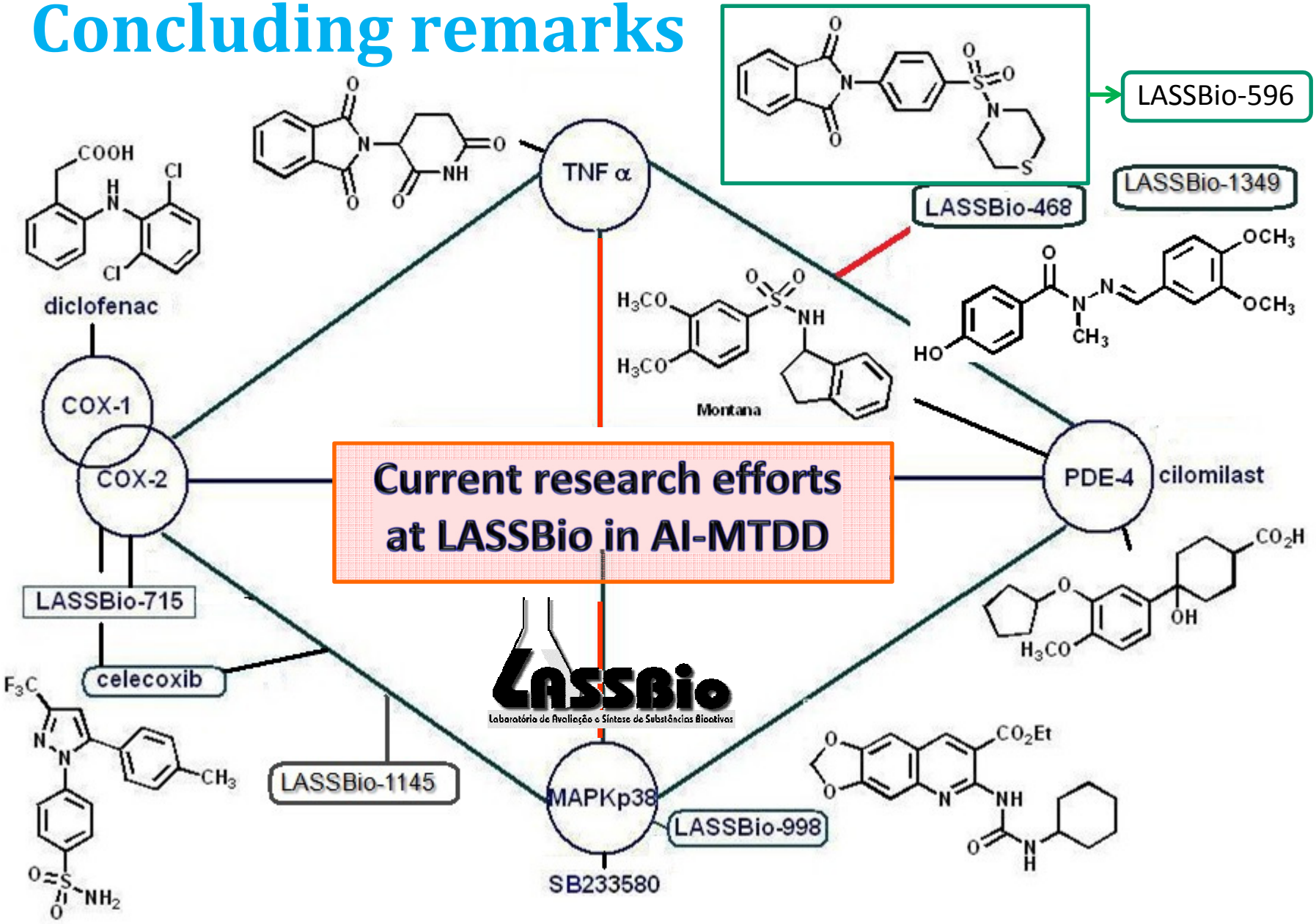
$C_{16}H_{17}NO_4S$

Montana et al., 1998



LASSBio-1349

Concluding remarks



Universidade Federal do Rio de Janeiro

Acknowledgements

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

Thank you very much for your attention.