



XXVI ESCOLA DE VERÃO EM QUÍMICA FARMACÊUTICA MEDICINAL



Química
m e d
Medicinal
c h e m

CCS, Cidade Universitária, Rio de Janeiro, RJ
27-31 de janeiro de 2020

Curso 3

Bioisosterismo



XXVI Escola
de Verão
em Química Farmacêutica
Medicinal
Professor Eliezer Barreiro



Eliezer J. Barreiro Parte 3

<https://www.evqfm-ufri.org/>

Professor Titular

Laboratório de Avaliação e Síntese de Substâncias Bioativas

Instituto de Ciências Biomédicas

Universidade Federal do Rio de Janeiro

Instituto Nacional de Ciência e Tecnologia em Fármacos e Medicamentos

Programa de Pesquisas em Desenvolvimento de Fármacos – ICB/UFRJ



Laboratório de Avaliação e Síntese de Substâncias Bioativas

www.lassbio.icb.ufri.br

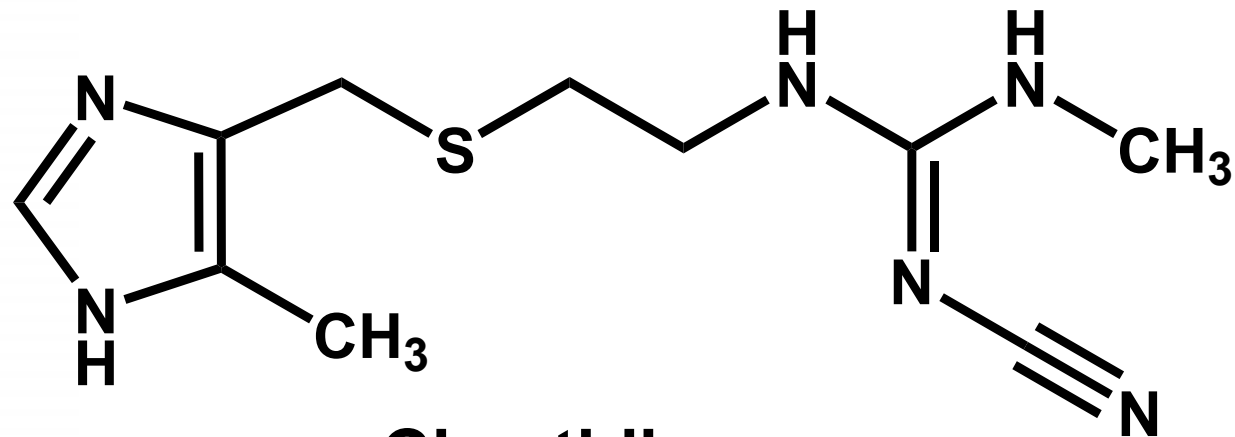
www.inct-inofar.ccs.ufri.br



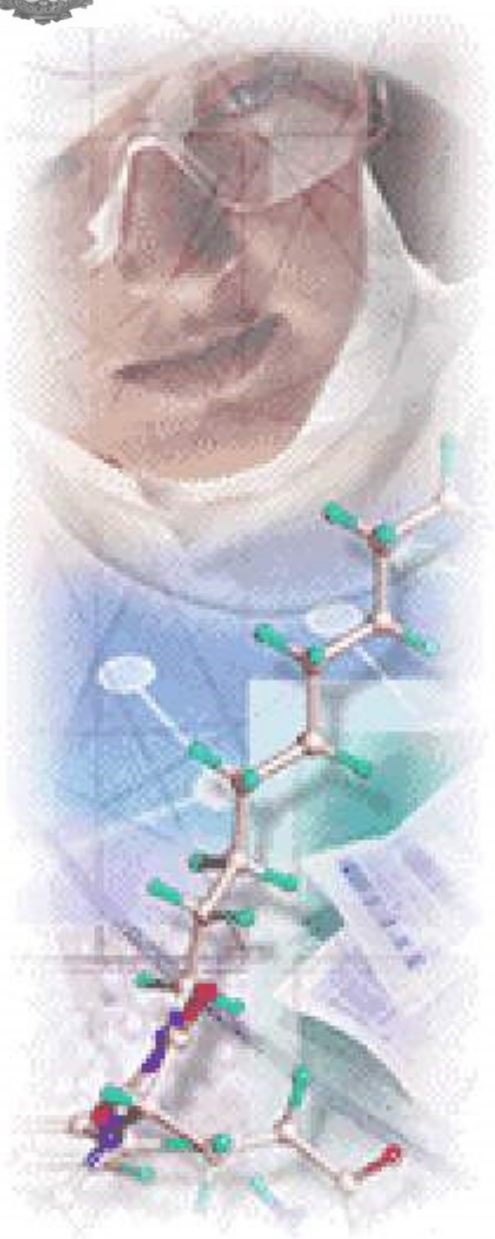
Bioisosterismo

Química
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Medicinal
chem

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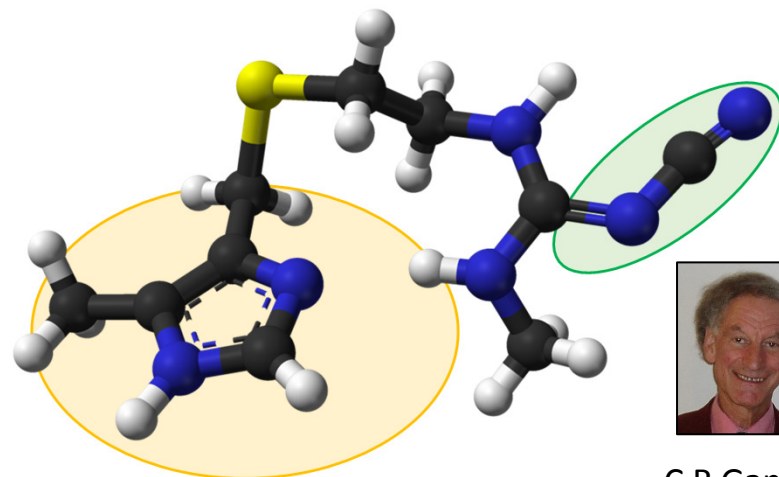


Cimetidina





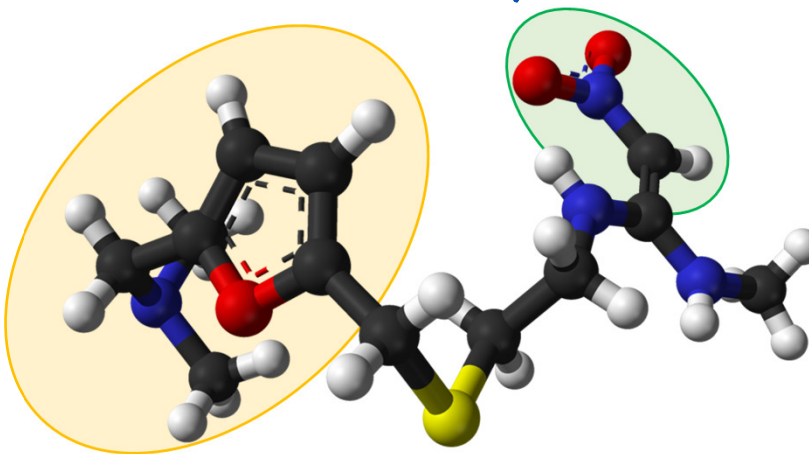
Cimetidina & Ranitidina



C R Ganellin



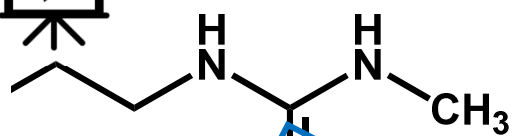
2005 - XI EVQFM



Química medicinal

Ranitidina

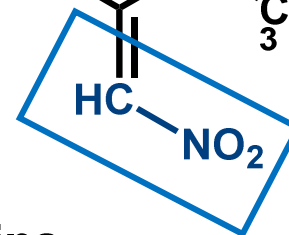
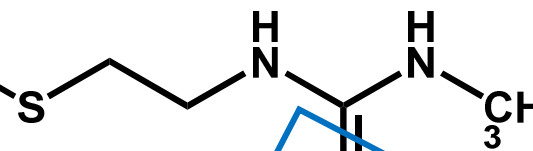
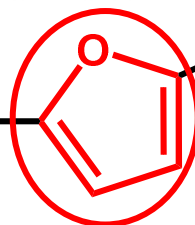
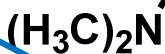
Cimetidina



Cimetidina

ant. (1st)

Ganellin, SKF



1981 - Ranitidina

J Bradshaw & B Price, Allen & Hanburys, UK

2019 - N-nitrosodimethylamine (NDMA)



BLOCK-BUSTER DRUGS

THE RISE AND DECLINE OF THE PHARMACEUTICAL INDUSTRY
JIE JACK LI

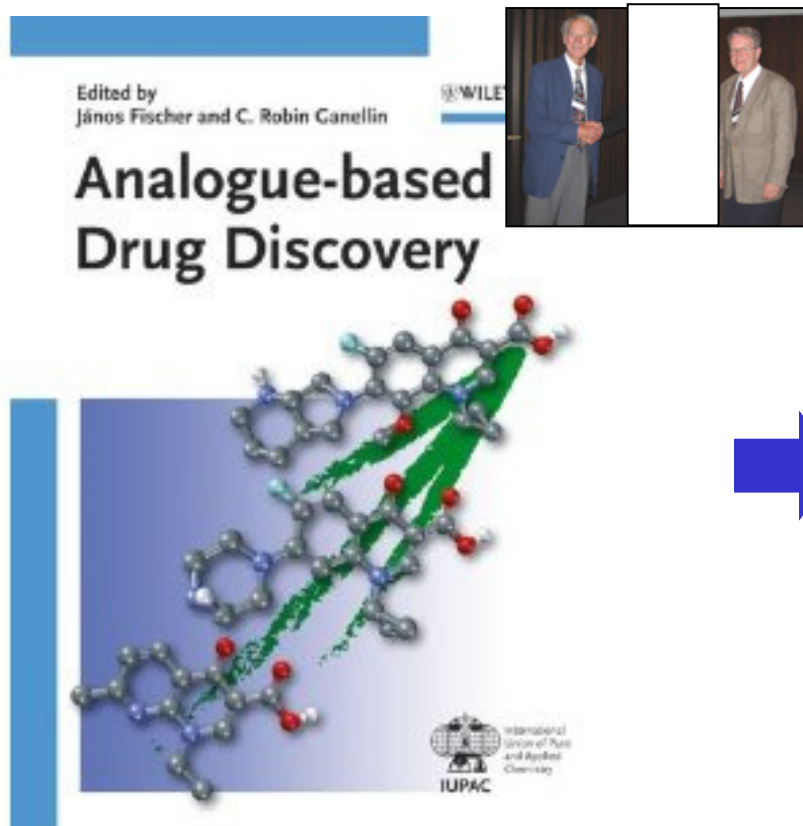
Blockbusters drugs (Me-too)



Janos Fischer is research laboratory head at Richter Ltd., Budapest, Hungary.

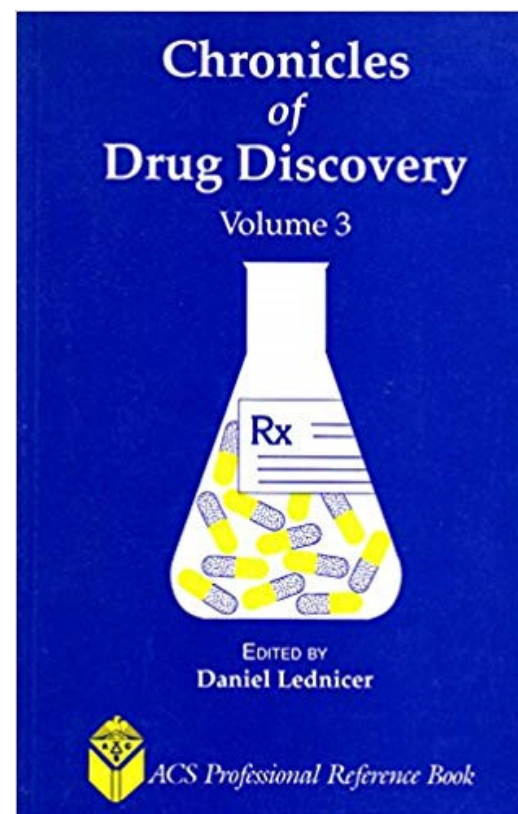
Robin Ganellin is Emeritus Professor of Medicinal Chemistry at University College London, UK.

Daniel Lednicer, Medicinal chemist, National Institute of Health, Bethesda, Maryland, US



CR Ganellin Development of
Anti-ulcer, H-2 antagonists, p.72

ISBN-10 3527325492
April 2006

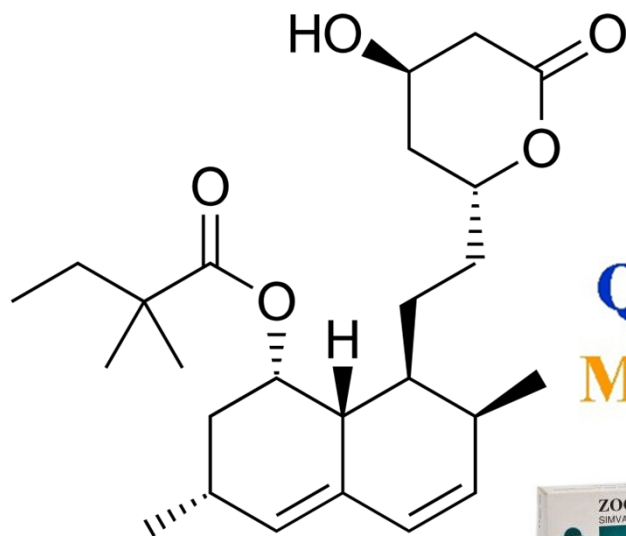


J Bradshaw, Ranitidine, p.45

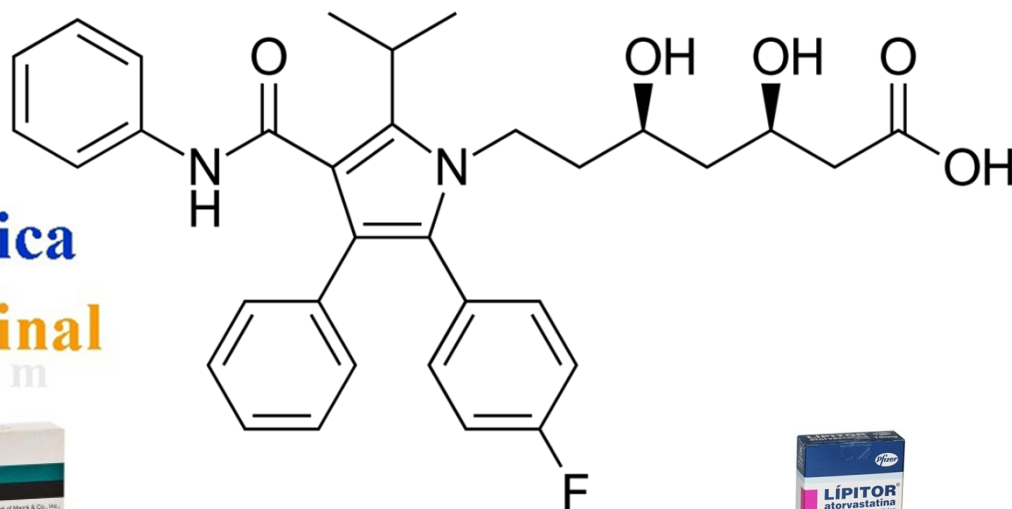
ISBN-0-8412-2733-0
Setembro de 1993



Estatinas



1992 - Simvastatina



1996 - Atorvastatina

- 1950 – biossíntese do colesterol
- 1959 – HMGCoAR
- 1976 – A Endo (Daiichi Sankyo, Jpn)
- 1980 – MK-733 (A Patchett, R Vagelos)

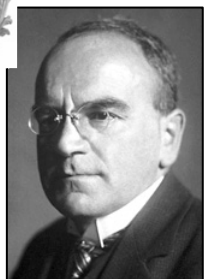
- 1982 – Bruce Roth (Warner-Lambert)
- 1985 – Fase Clínica
- 1996 – Lançamento (Co-share WL-Pfizer)
- 2000 – Pfizer compra WL (US\$ 90,7 bi)
- 2011 – Fim da proteção patentária

A descoberta da lovastatina



Desde o início...9 Nobelistas!

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Heinrich Wieland
1877-1957



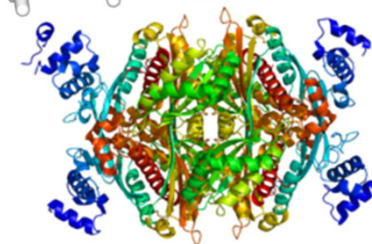
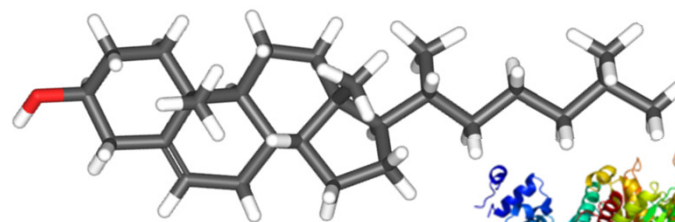
1927



Adolf Windaus
1876-1959

1928

colesterol



HMGCoAR

1947



Robert Robinson
1886-1975

1965



Robert B. Woodward
1917-1979



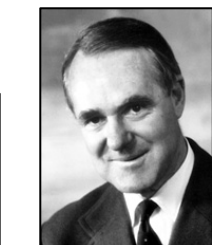
1964



Konrad Bloch
1912-2000

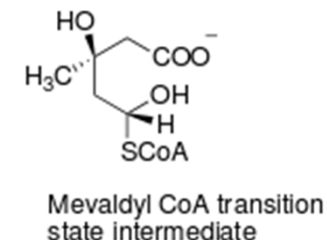
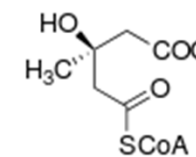
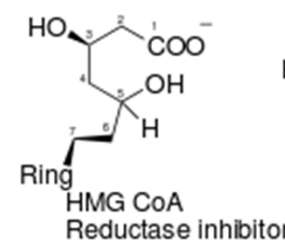


Feodor Lynen
1911-1979

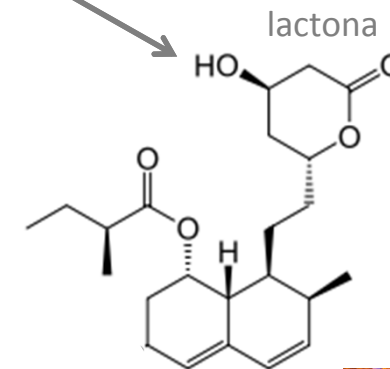


John Cornforth
1917-2013

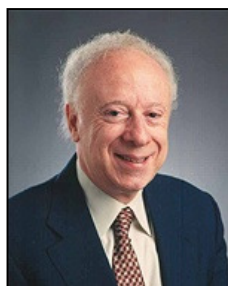
1975



A.Endo, *J Med Chem*
1985, 28, 1



mevilonina



Joseph L. Goldstein
1940-
University of Texas, Dallas

1985

LDL



Michael S. Brown
1941-



Akira Endo
1933-

Albert Lasker Award
for Clinical
Medical Research, 2008*

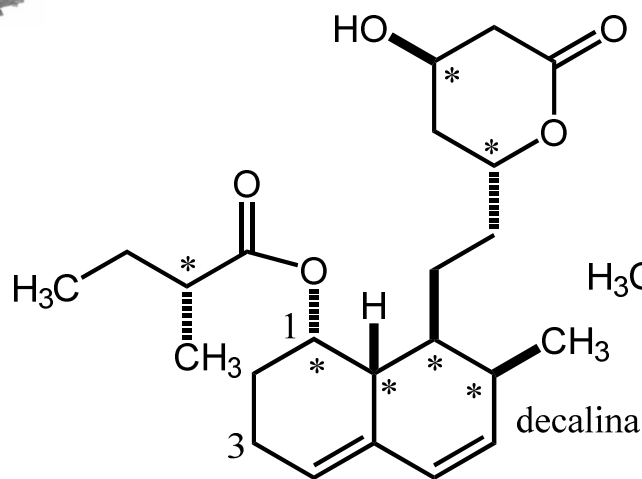
* A Endo, A gift from nature: the birth of the statins, *Nature Medicine* 2008, 14, 26



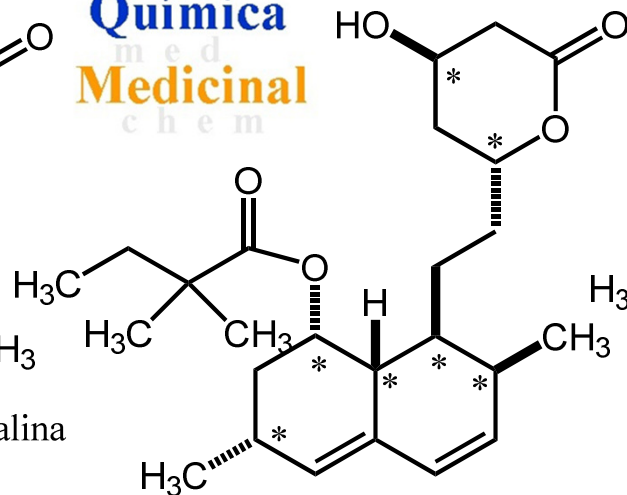
Estatinas & Bioisosterismo

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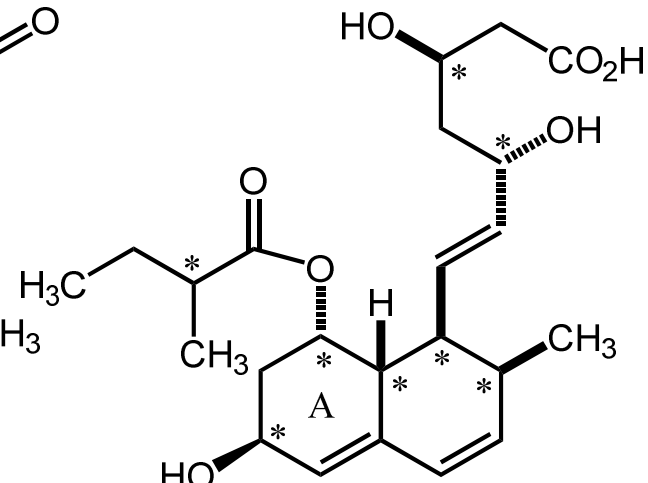
Química
med
Medicinal
chem



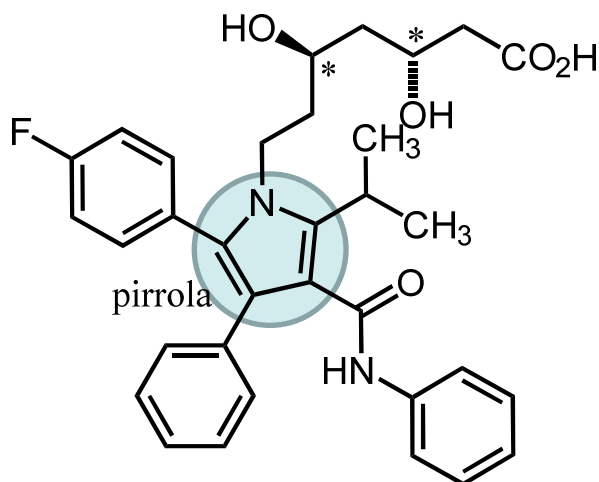
compactina
1976



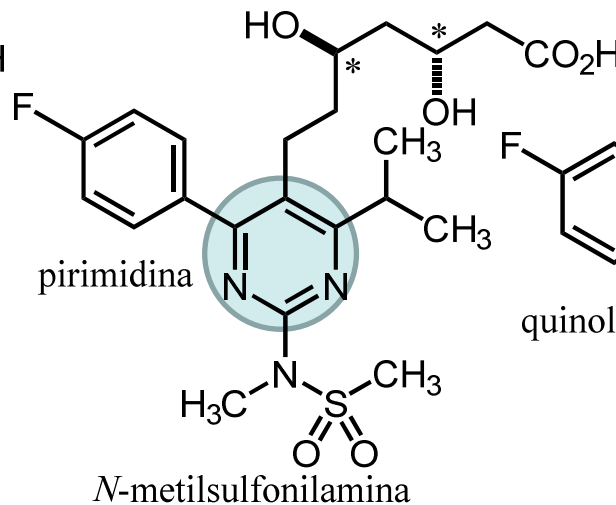
simvastatina
1986



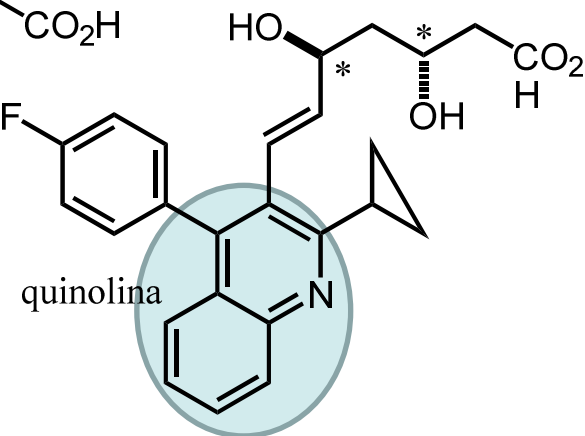
álcool alílico **pravastatina**
1988



atorvastatina
1991



N-metilsulfonilamina
rosuvastatina
2004



pitavastatina
2009



1 February 2011




Pfizer to close UK research site

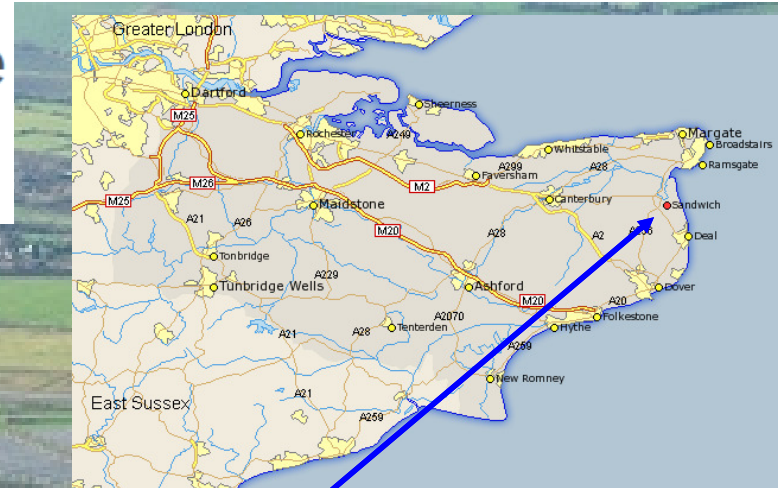
Drug maker Pfizer is to close its research and development (R&D) facility in Kent, which employs 2,400 people.

C&EN
CHEMICAL & ENGINEERING NEWS

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Particles probe materials
in unique ways P36
COPYRIGHT FIRST
College course website
sparkle fractal P41



TURNING TO TEAMWORK
Drug firms huddle on intractable diseases P12



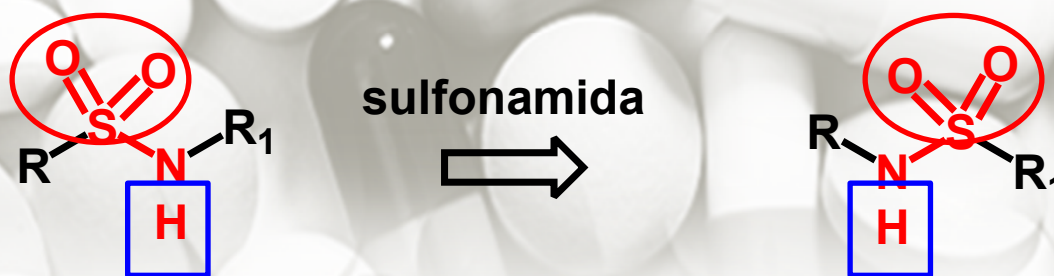
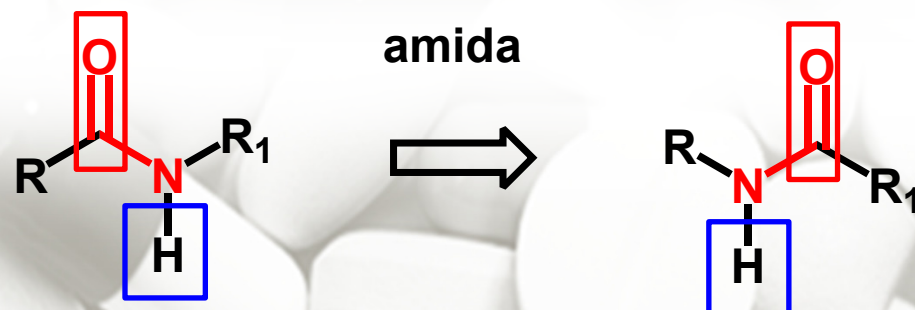
<http://www.bbc.co.uk/news/business-12335801>

Pfizer Co., Sandwich, UK



Retroisosterismo

Inversão de grupo funcional



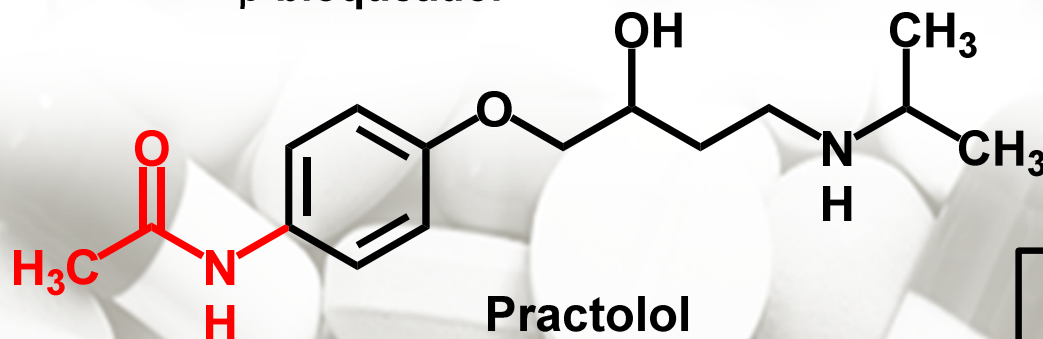
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Medicinal
chem



Exemplo de Retroisosterismo

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β -bloqueador

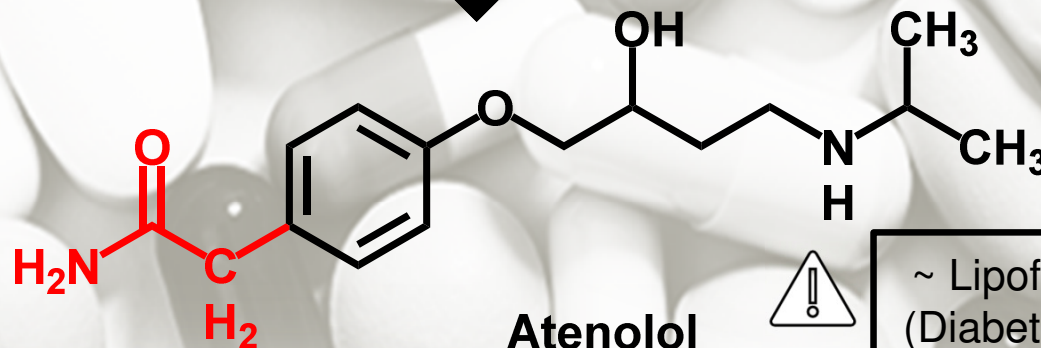


> Lipofílico
> Seletivo β_1

1970 - ICI Pharmaceuticals Division
University of Leeds

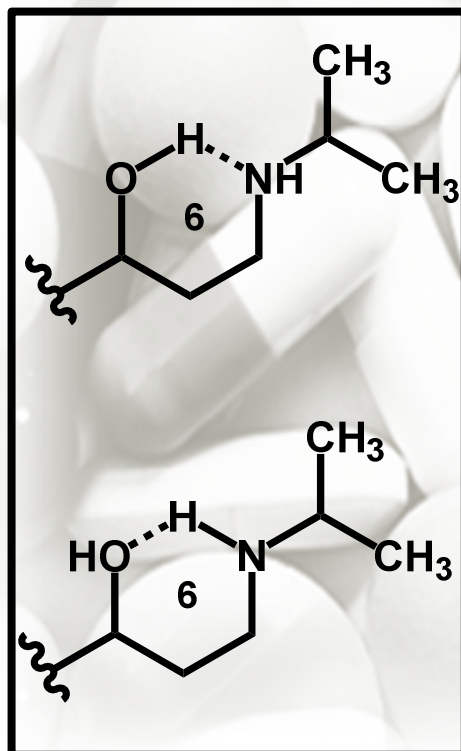
AM Barrett et al. *Br J Pharmacol.* 1973, 48, 340

β -bloqueador



~ Lipofílico
(Diabetes-2)

1975 - ICI Pharmaceuticals Division

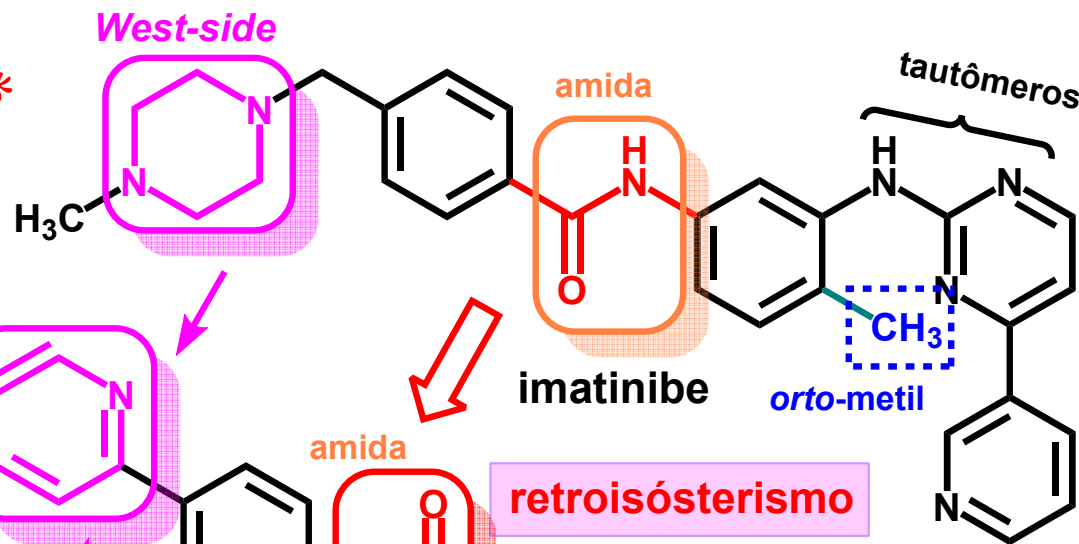




Aplicação do retroisosterismo

Tinibes*

2001



th^eerapeutic
iⁿnovation

PM= 493 (<500)
cLogP = 3,5 (<5)
H-acceptor 6 (<10)
H-doador 2 (<5)

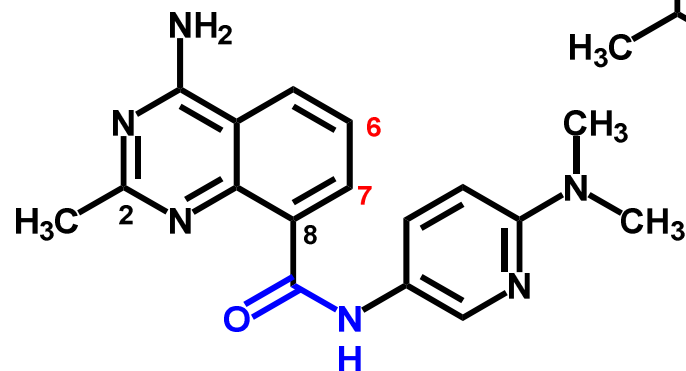
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chem

* The global 27 cancer blockbuster drugs market size is set to surpass US\$ 120 billion by **2025**

* R Capdeville et al. *Nat Rev Drug Discov* 2002, 1, 493

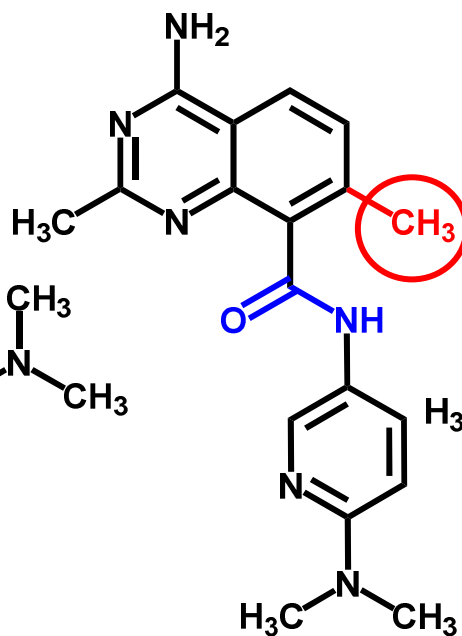


Homologação & amida



PI3K α IC₅₀ = 54 nM

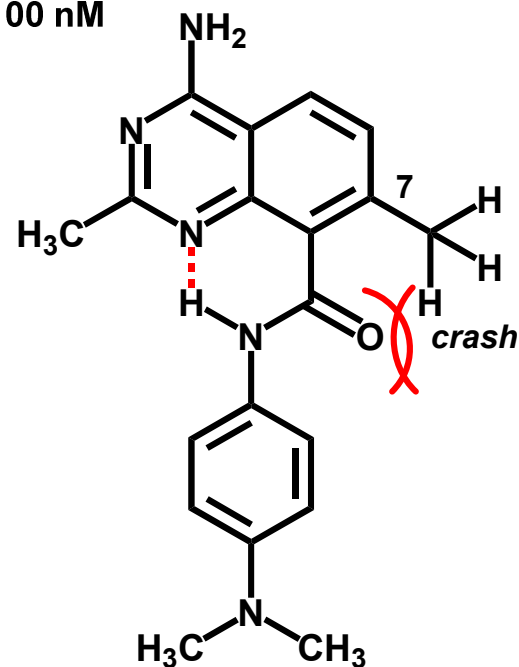
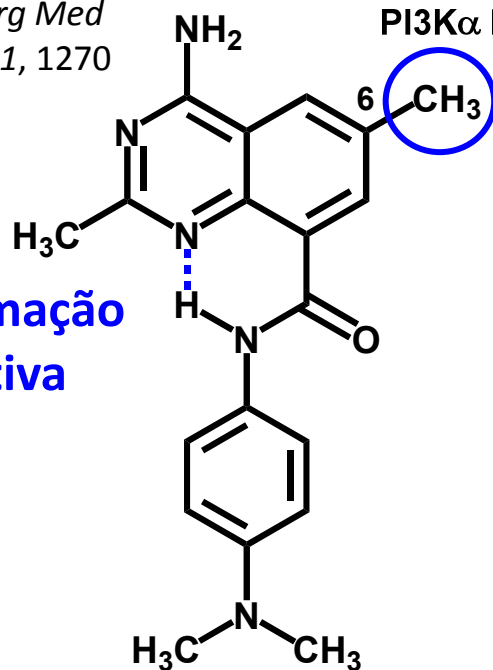
KKC Liu et al, *Bioorg Med Chem Lett* **2011**, *21*, 1270



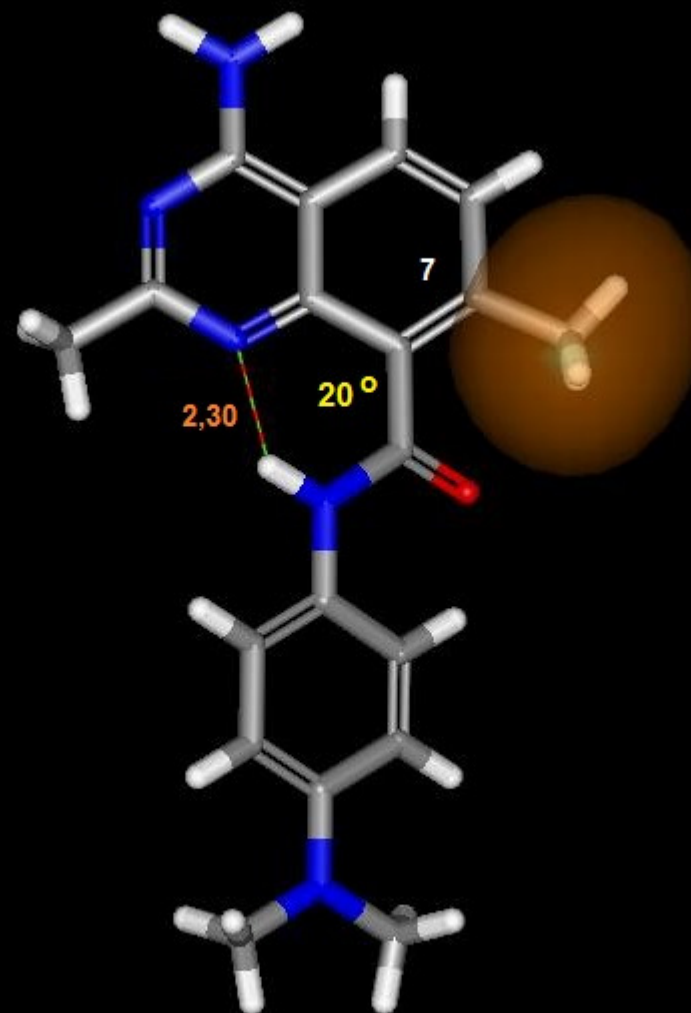
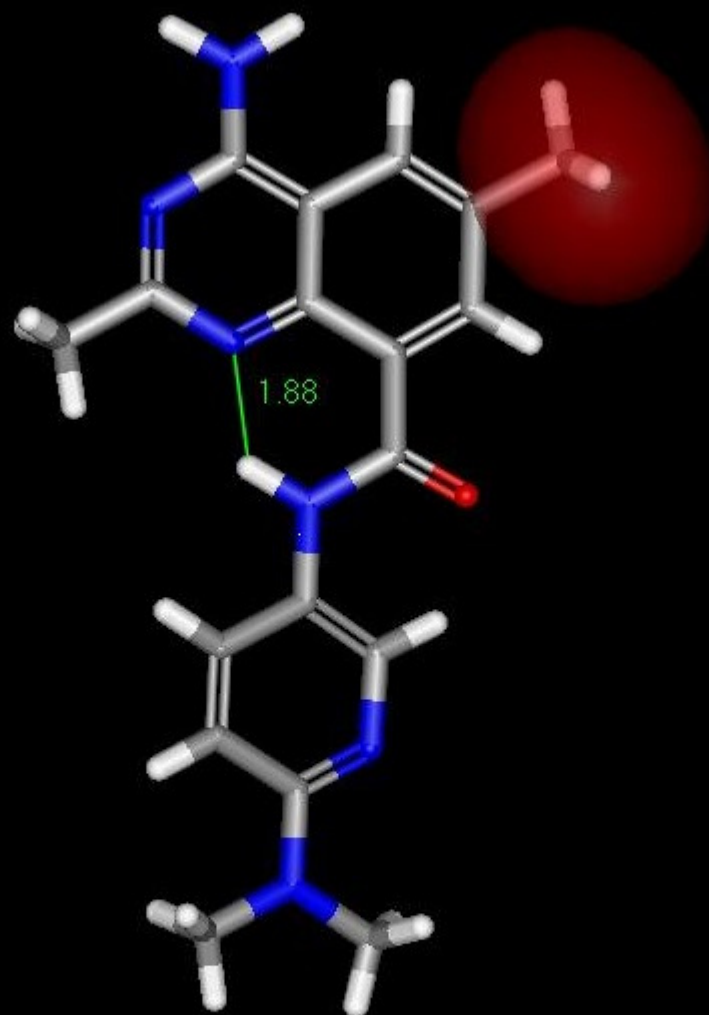
PI3K α IC₅₀ = 12 nM

PI3K α IC₅₀ >> 100 nM

Conformação bioativa



A Chaikuad, P Koch, AS Laufer, S Knapp, *Angew Chem* **2018**, *57*, 4372



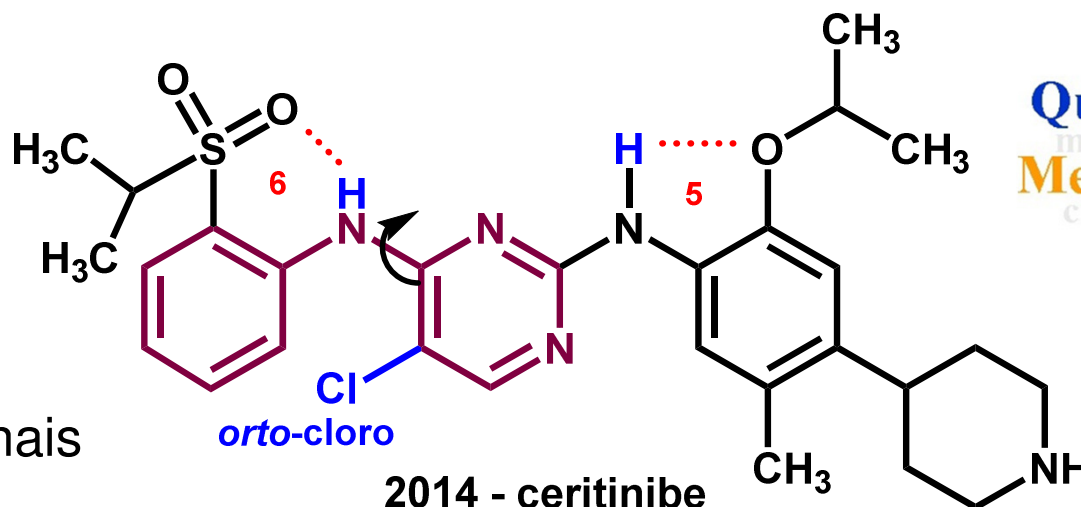


Ceritinibe

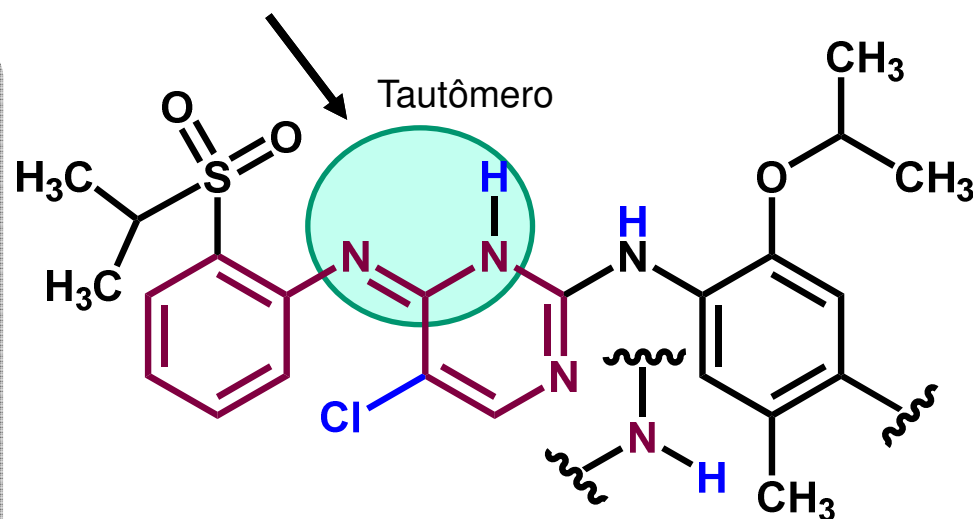
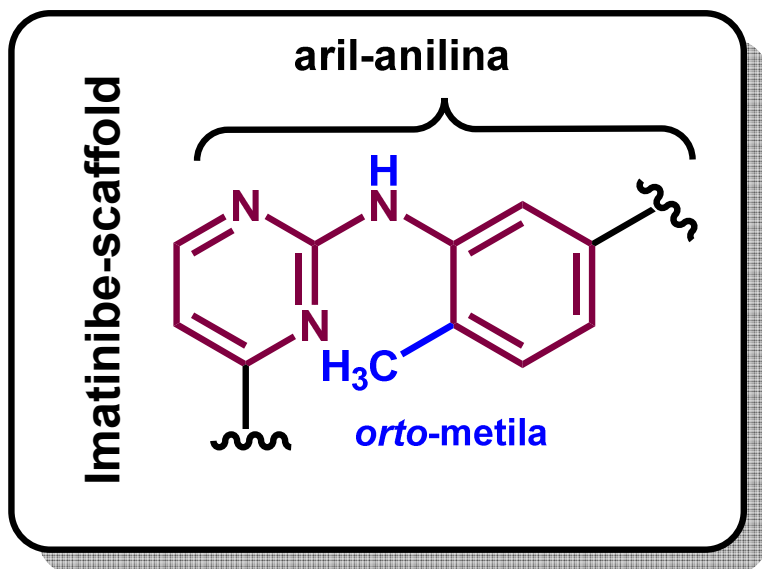


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Aspectos
Conformacionais



2014 - ceritinibe
ALK-inhibitor



Polimorfismo (cristalino/amorfo); Hidrato (solubilidade);



Bioisosterismo funcional clássico



Raio de Van der Waals (A)

1,20

1,35

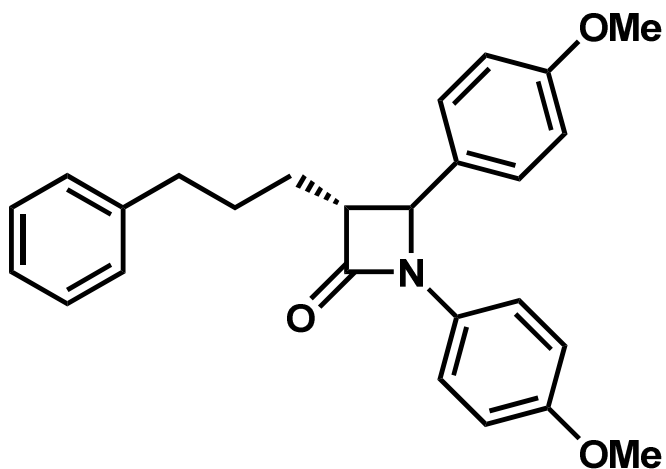
25% dos fármacos contém F*

* EP Gillis et al. Applications of fluorine in medicinal chemistry, *J Med Chem* **2015**, 58, 8315



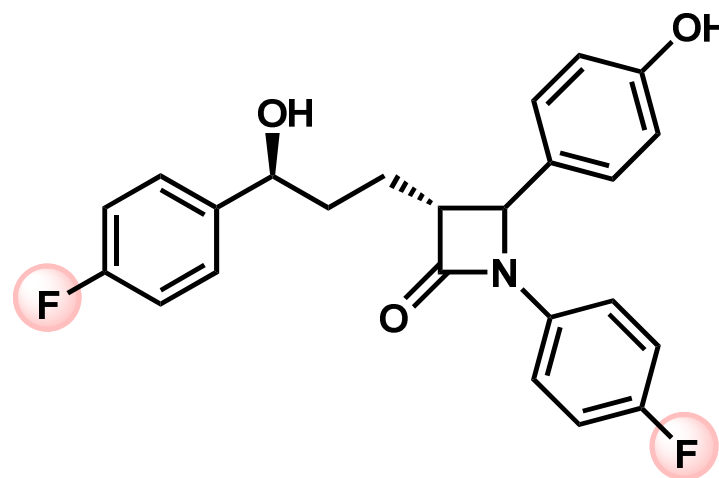
Bioisosterismo funcional clássico

Cholesterol absorption inhibitor (Hyperlipidemia)



Lead compound

ED₅₀ (hamster) = 2.2 mg/kg



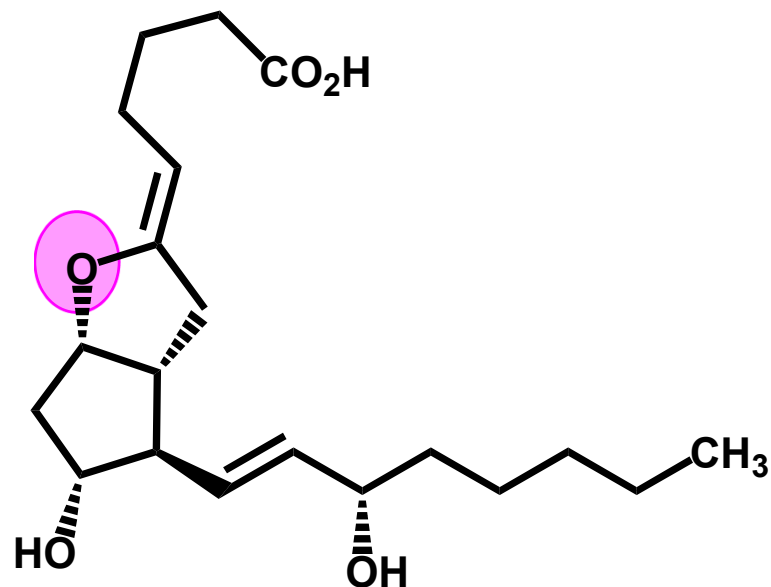
Ezetimib

ED₅₀ (hamster) = 0.04 mg/kg

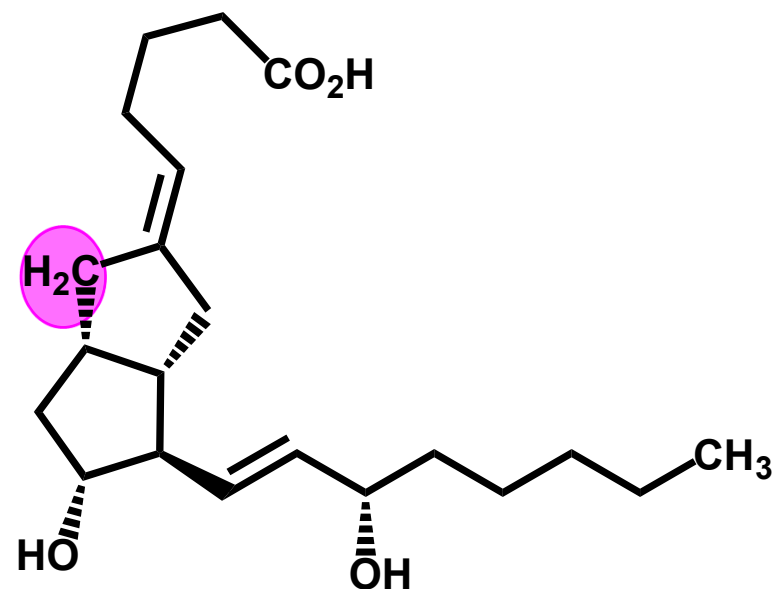


Bioisosterismo clássico

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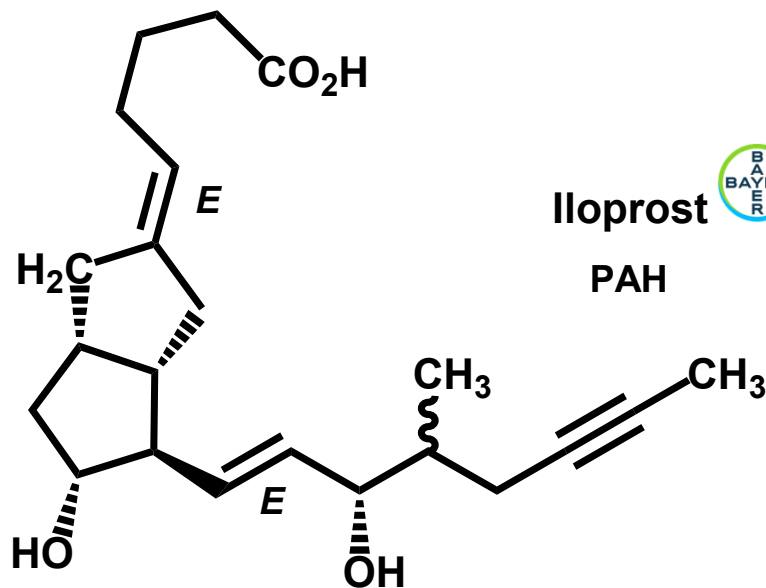
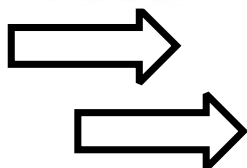


Prostaciclina



Carbaciclina

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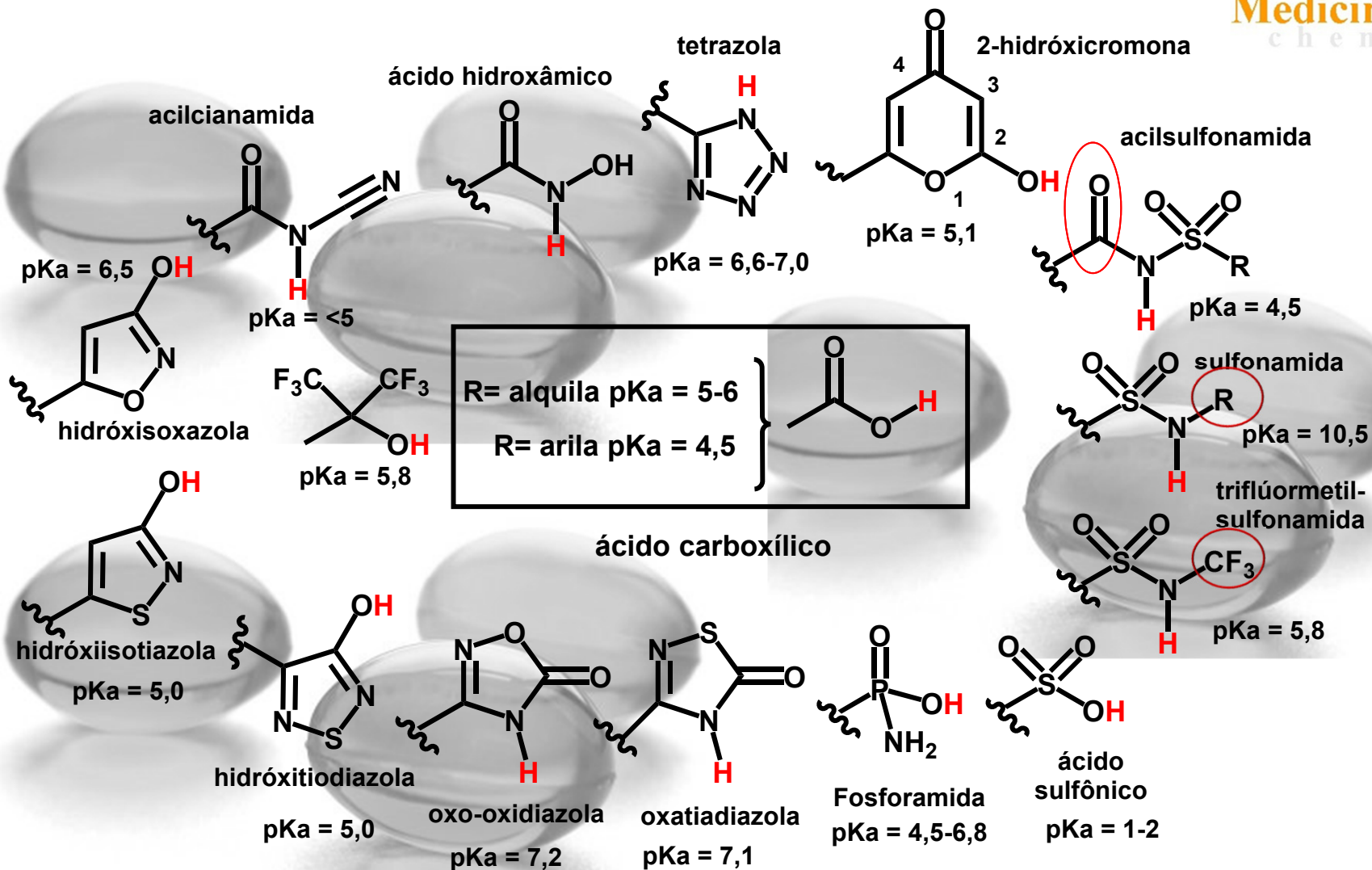
Iloprost
PAH





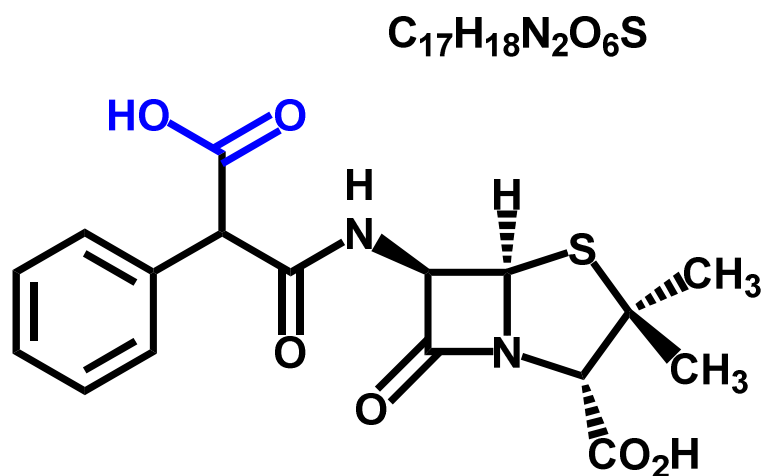
Distinção Funcional

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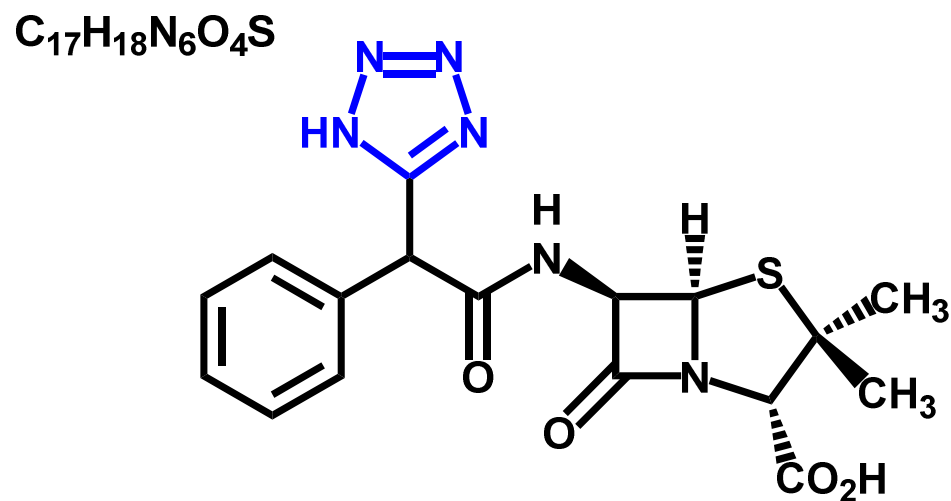




Bioisosterismo funcional não-clássico



Carbenicilina



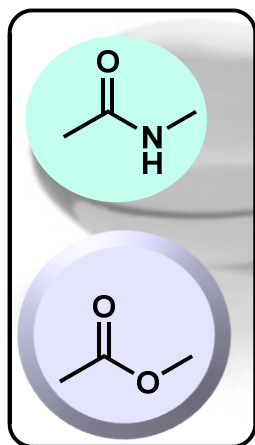
Carbenicilina-tetrazola análogo

>> estabilidade química

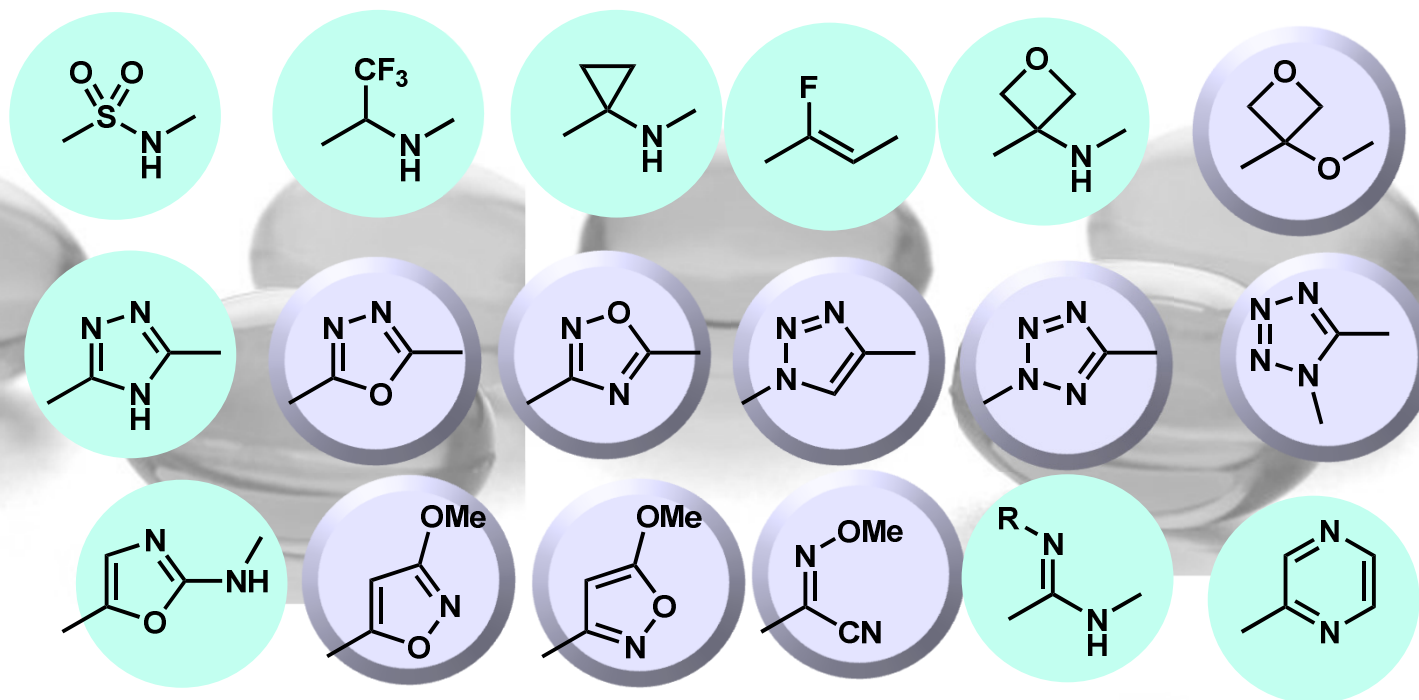
JM Essery et al. *J Med Chem* **1969**, 12, 703



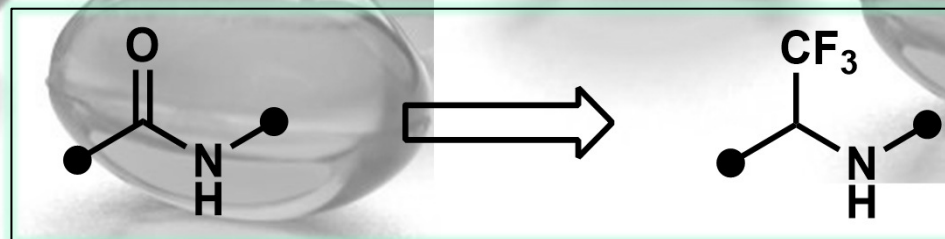
Bioisosterismo funcional, amida & éster



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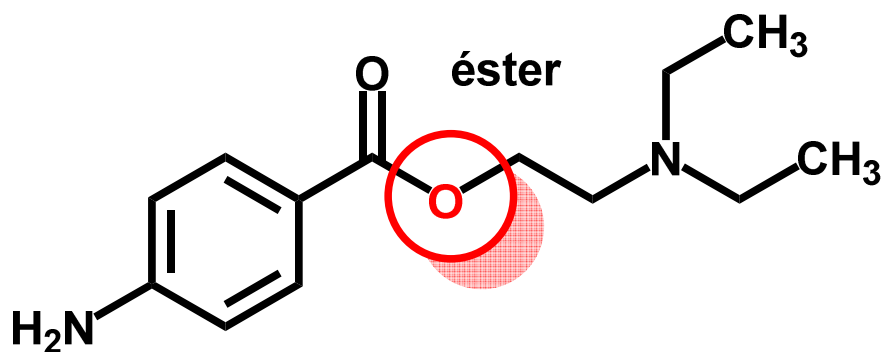


Os isómeros de amida servem para melhorar a biodisponibilidade, enquanto o dos ésteres podem ser mais rápidos.



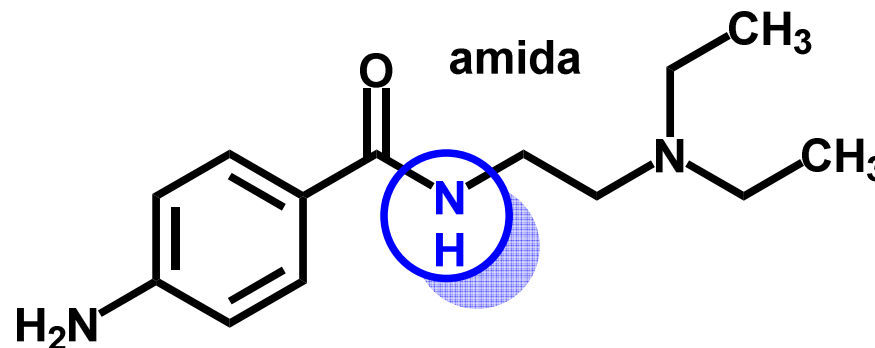


Bioisosterismo funcional: amida & éster



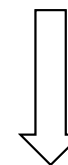
1905- procaina
Canaís Na⁺

anestésico tópico/
usado com Pen im
& odontologia



1950 - procainamida (BMS)
Canaís Na⁺
antiarrítmico oral

Química
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Medicinal
chem

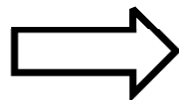
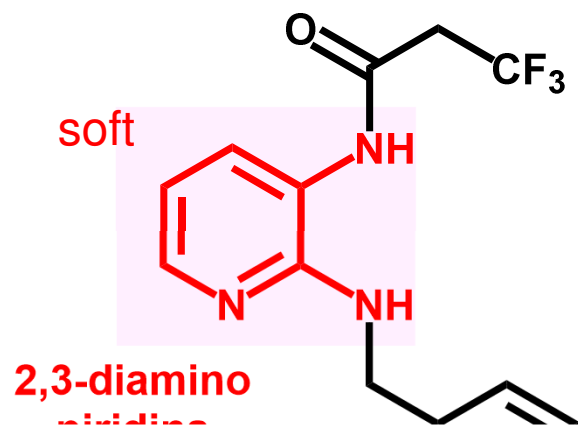


Metabolicamente + estável

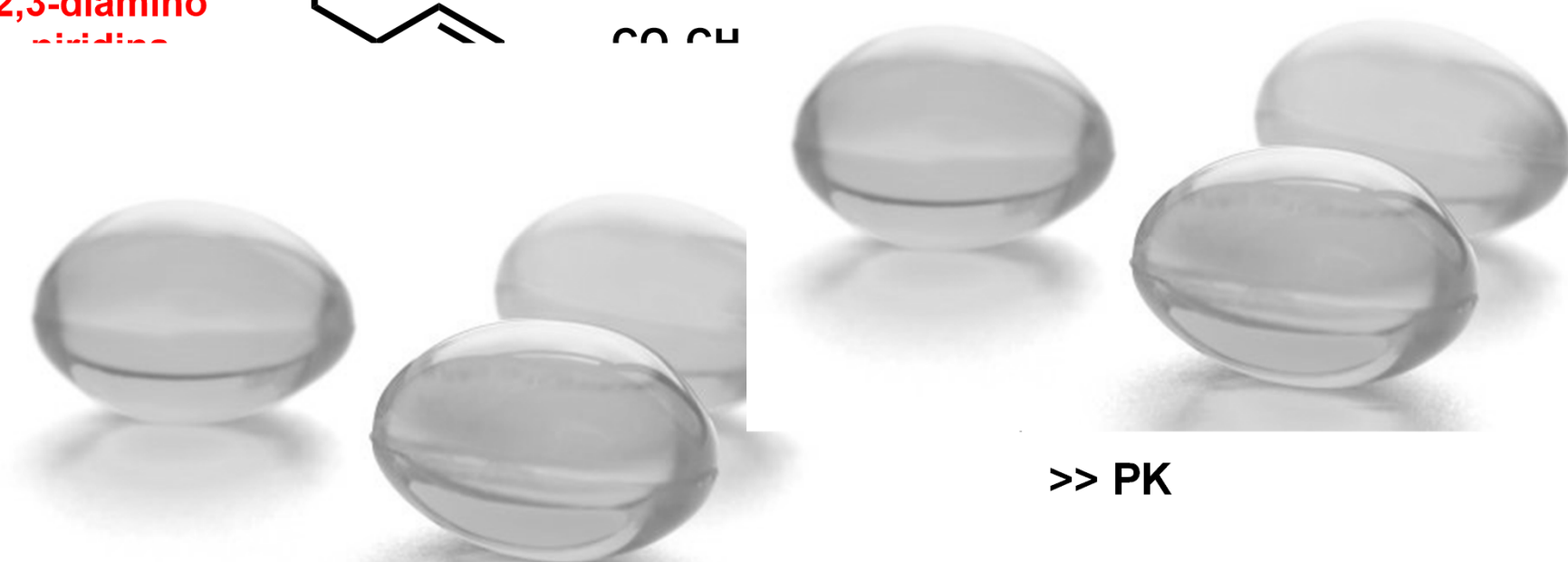
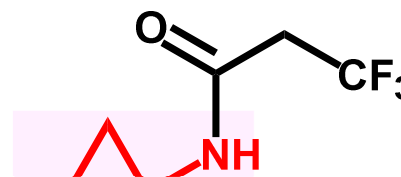


Aplicação do bioisosterismo funcional não-clássico

Química
med
Medicinal
chem



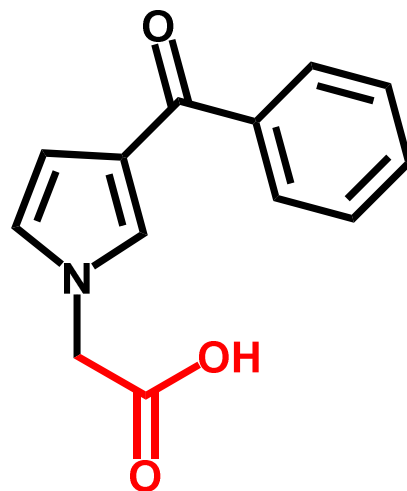
CO CH



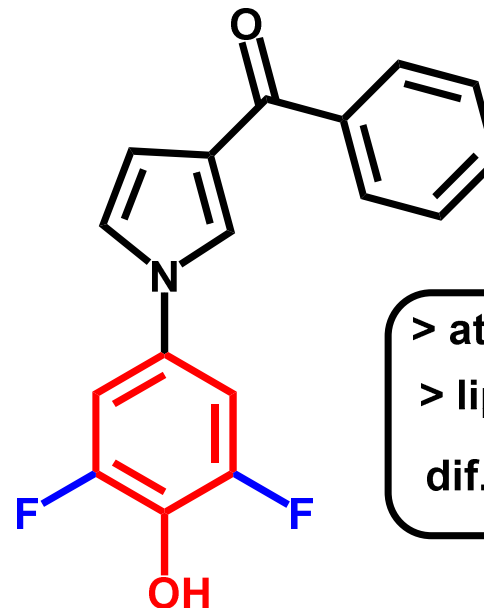
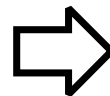
>> PK



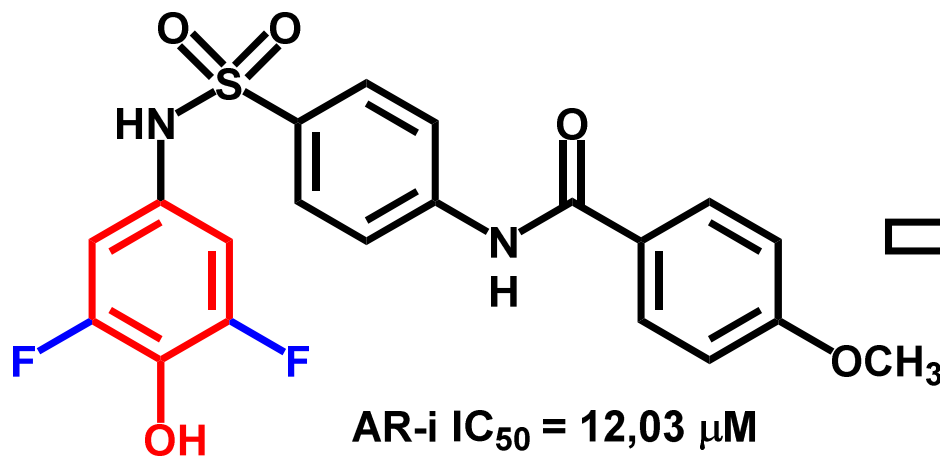
Aplicação do bioisosterismo funcional não-clássico



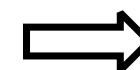
AR-i IC₅₀ = 2,4 μM



> atividade
> lipofilicidade
dif. metabolismo



AR-i IC₅₀ = 12,03 μM

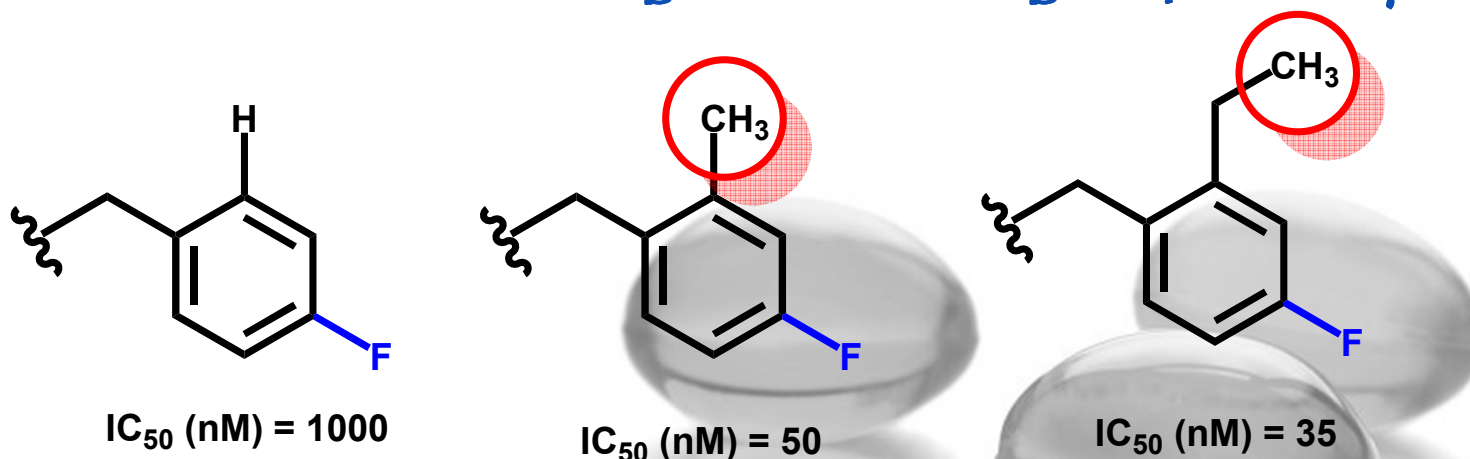


Otimização

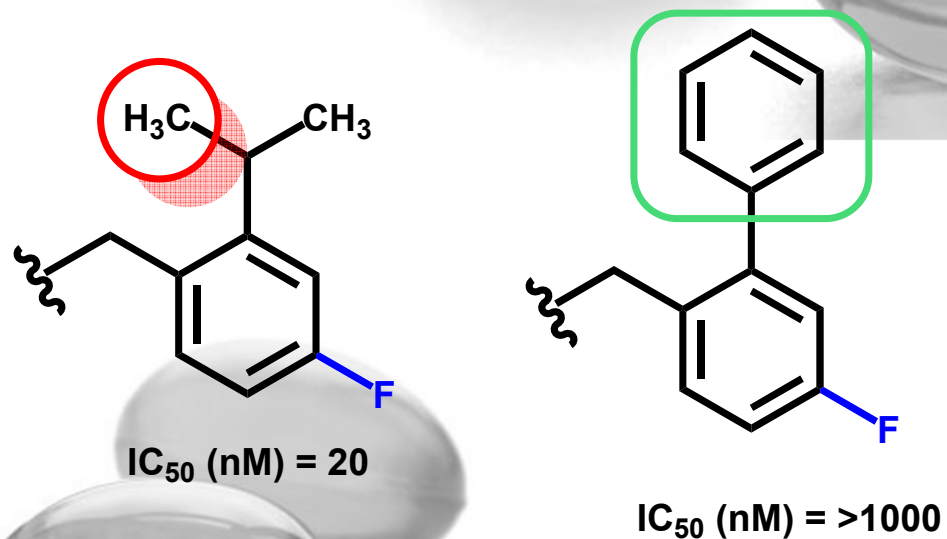
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Efeitos da homologação do grupo alquila



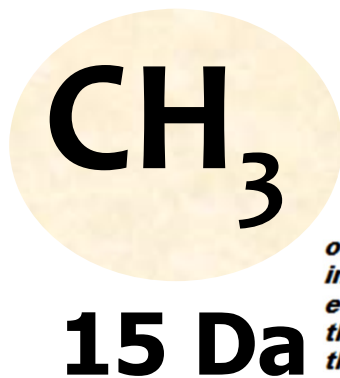
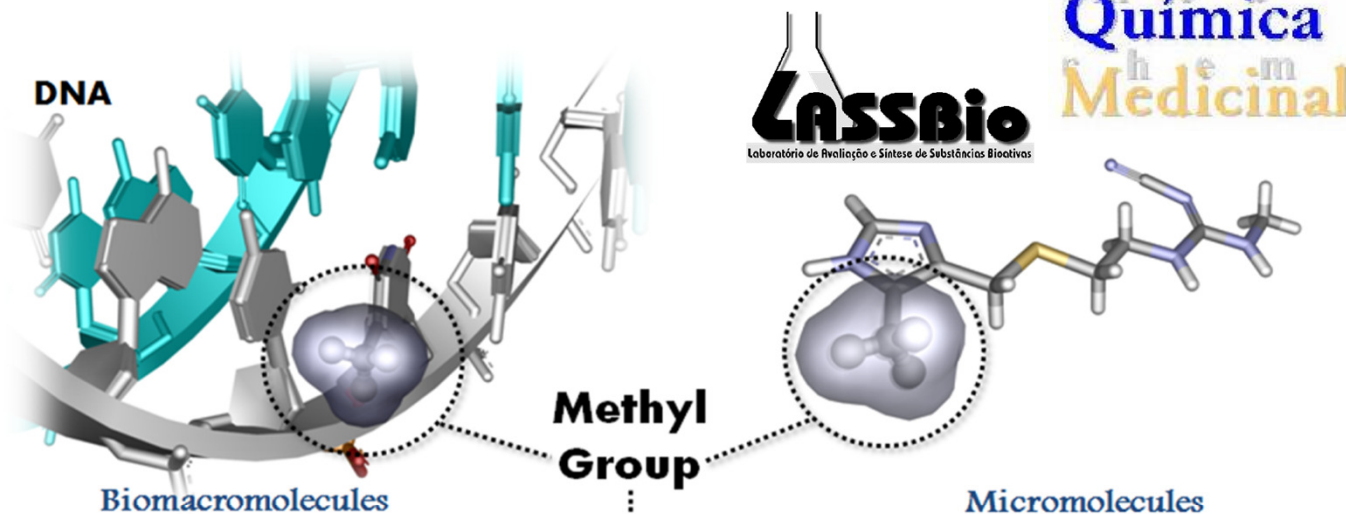
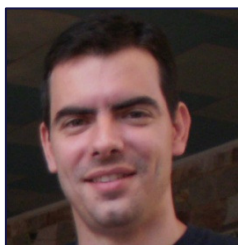
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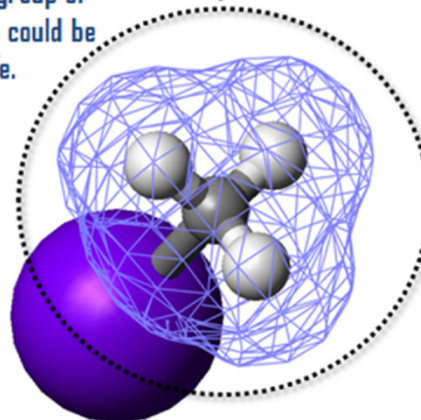
The Methylation Effect in Medicinal Chemistry

E. J. Barreiro, A. E. Kümmerle and C. A. M. Fraga



CH/ π interactions from the methyl group of timine. Conformational changes, wich could be involved on maintenance of life.

The stereoelectronic effects of the methyl group have great importance on biological events and are widely used by the Medicinal Chemistries in the development of new drugs.



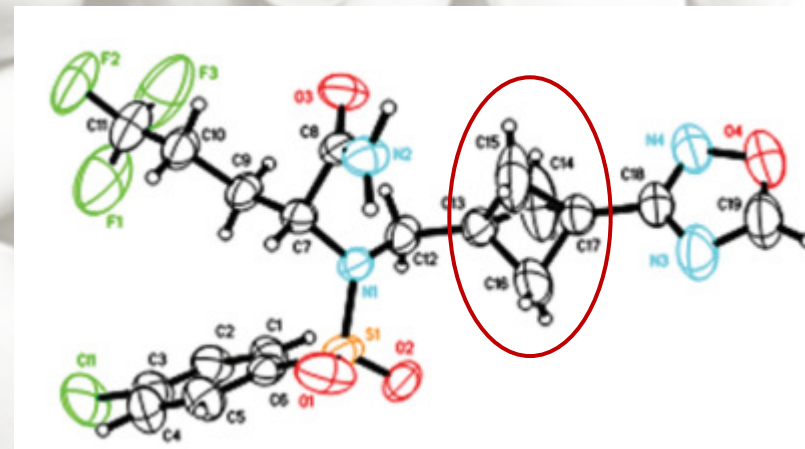
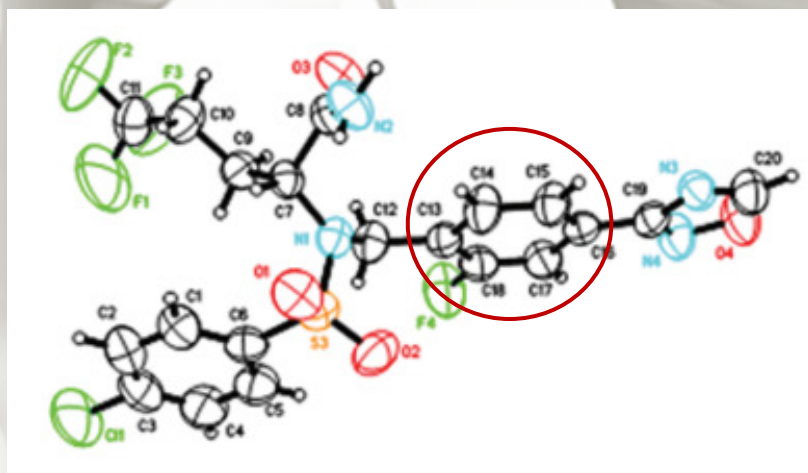
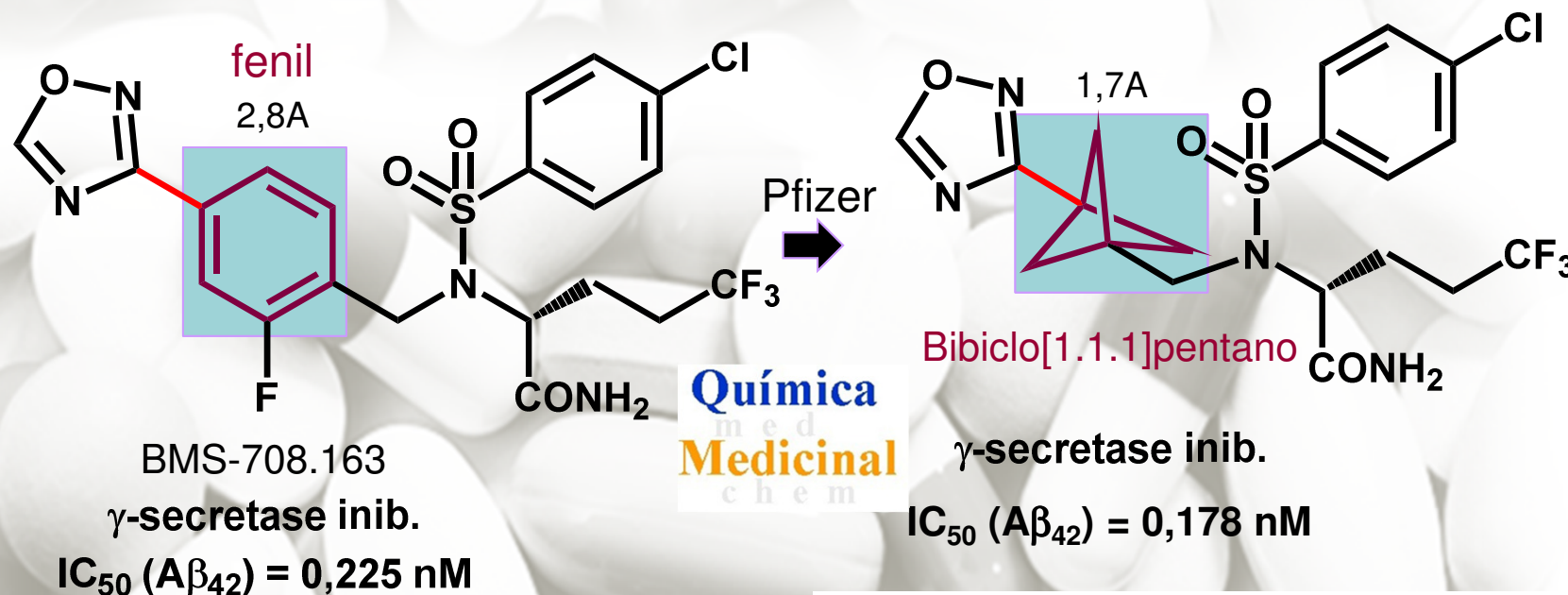
The inductive eletronic effect of the methyl group is the responsible for the subtype receptors selectivity (H₂x H₁) on cimetidine

Stereoelectronic Properties

MW = 15,03
MR = 5,65 cm³/mol
 π hansch = 0,56
 σ hammett = -0,17

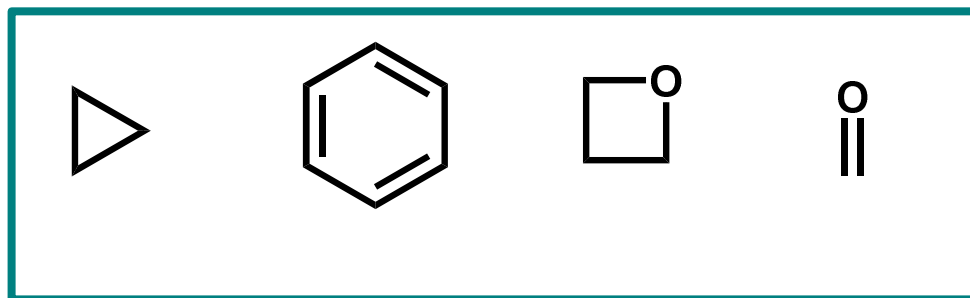


Bioisosterismo funcional não-clássico

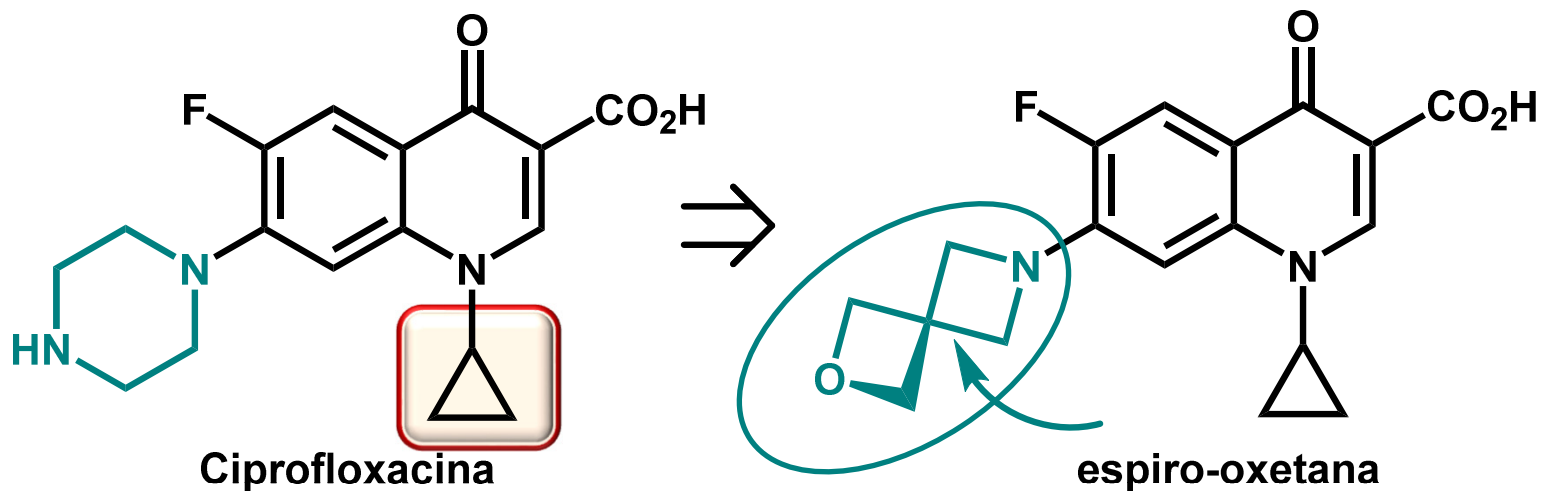


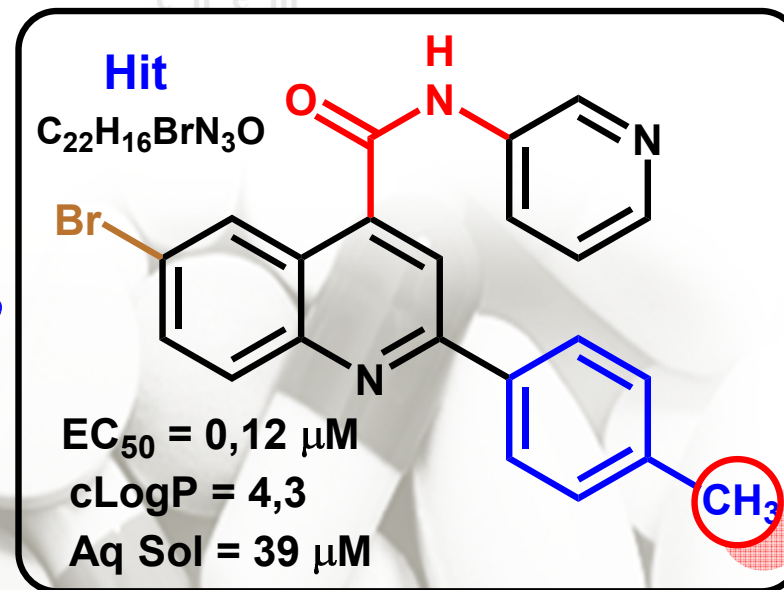
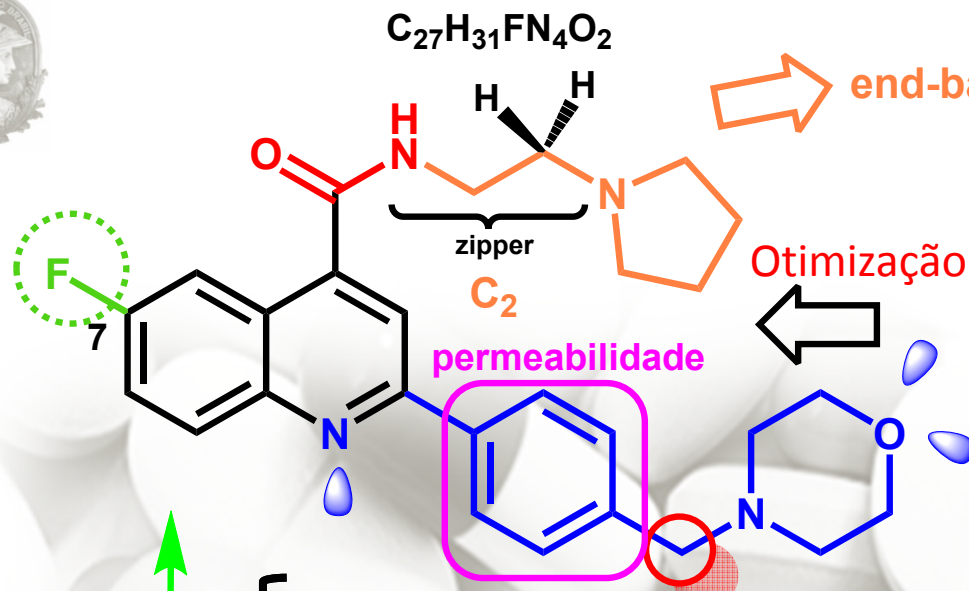


Bioisosterismo funcional não-clássico



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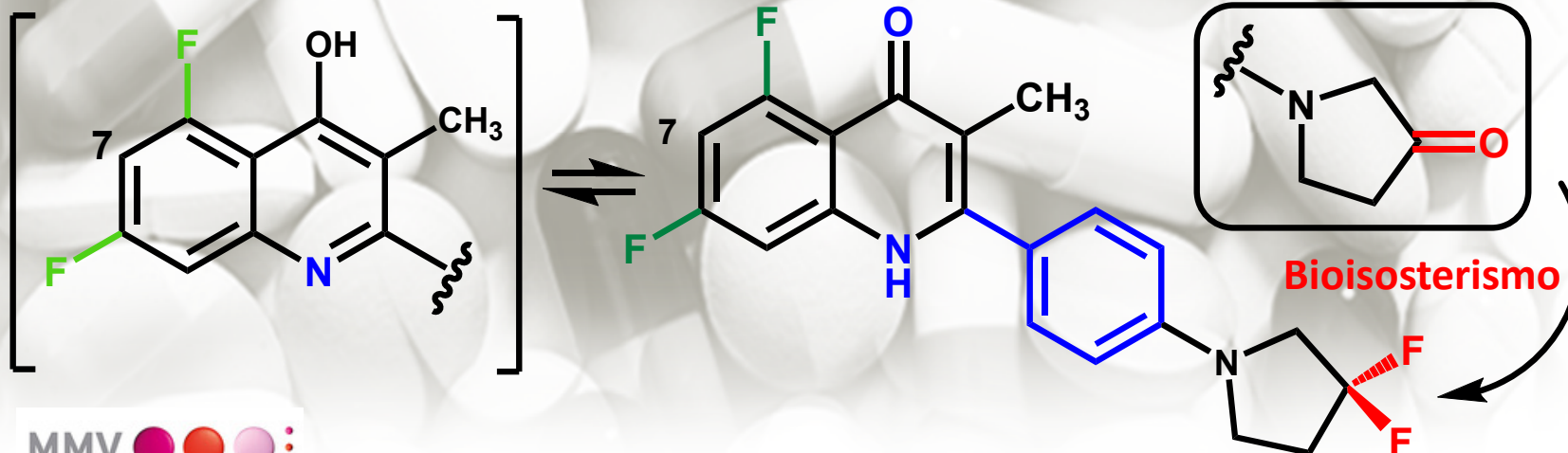


EC₅₀ = 0,001 μM

cLogP = 3,2

Aq Sol = 216 μM

Campbell, Willis et al, 2016
J Med Chem 2016, 59, 9672

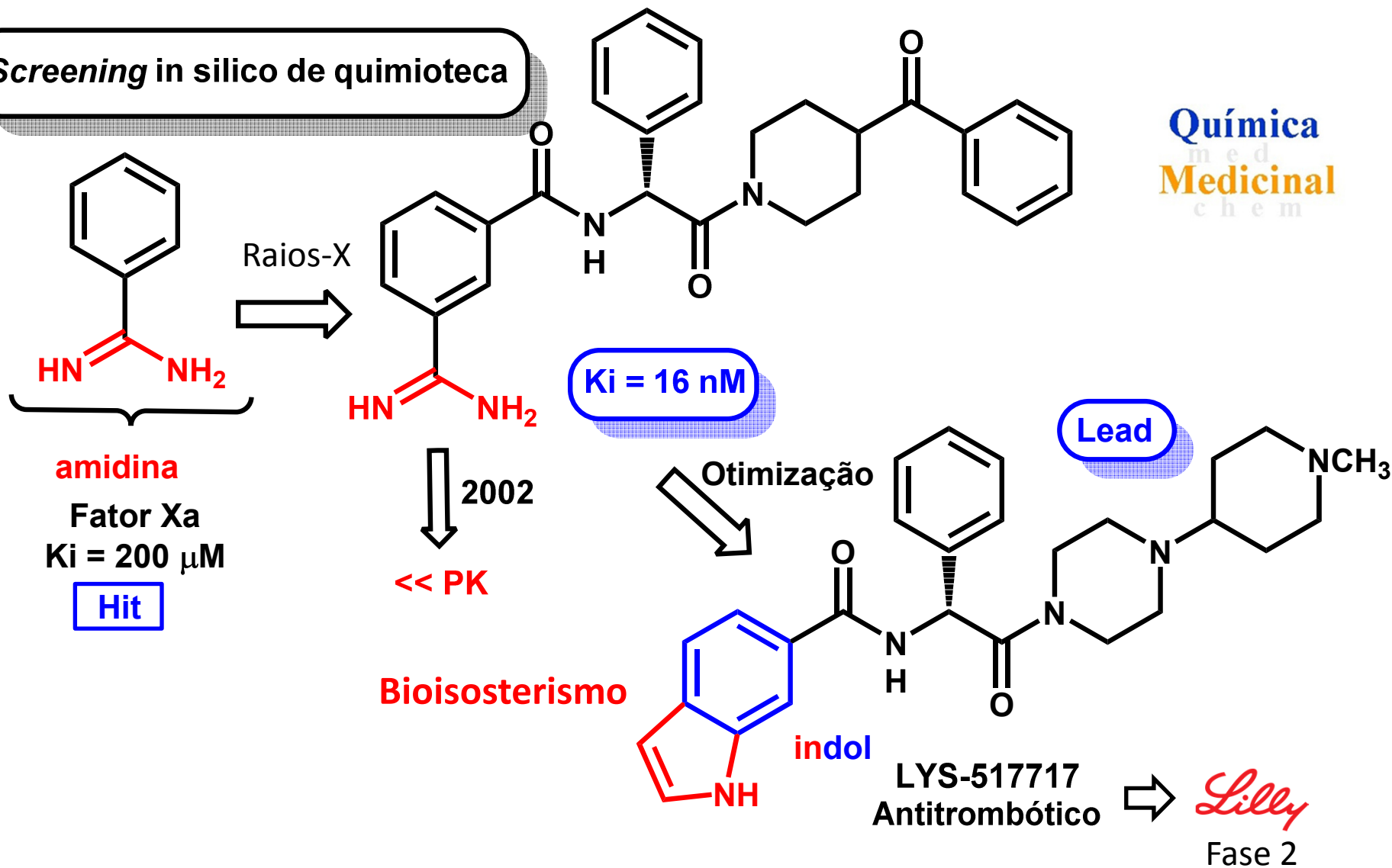





Exemplos da Aplicação do Bioisosterismo (III)

Screening in silico de quimioteca

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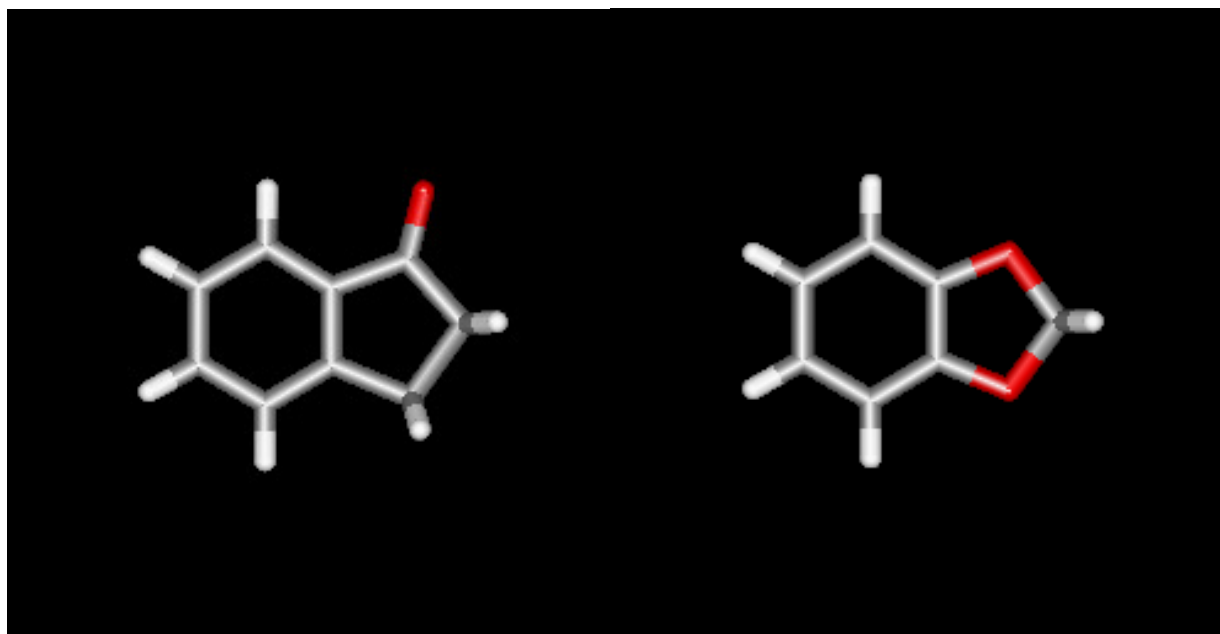




Bioisosterismo no 

Indanona - Benzodioxola

1998



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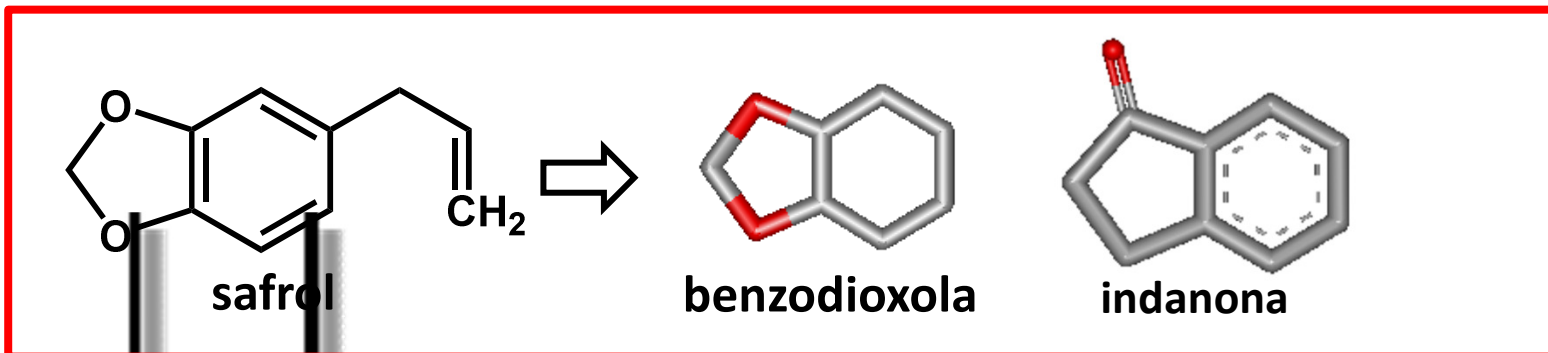
A S Lages et al. Synthesis and pharmacological evaluation of new flosulide analogues, synthesized from natural safrole, *Bioorg Med Chem Lett* **1998**, 8, 183-188



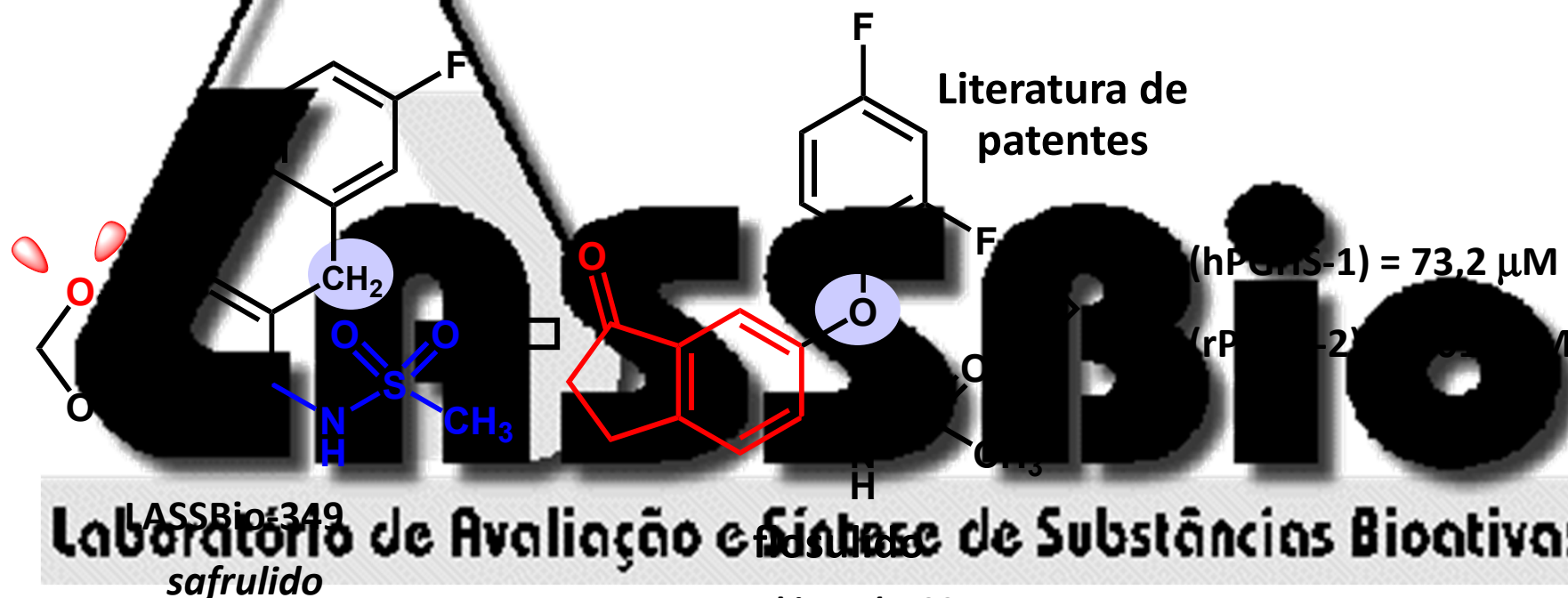
Bioisosterismo no LASSBio

XXVI EVQFM - Curso 3 "Bioisosterismo"

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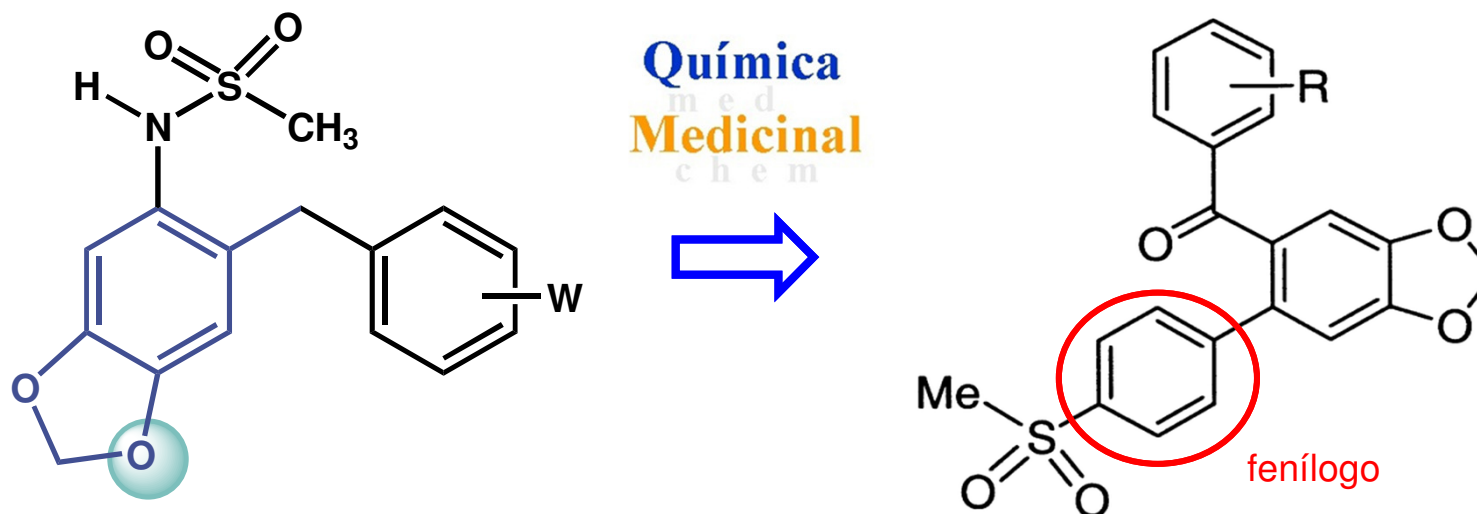


Nova relação bioisostérica





Bioisosterismo no LASSBio



AS Lages, et al. *Bioorg Med Chem Lett* 1998, 8, 183

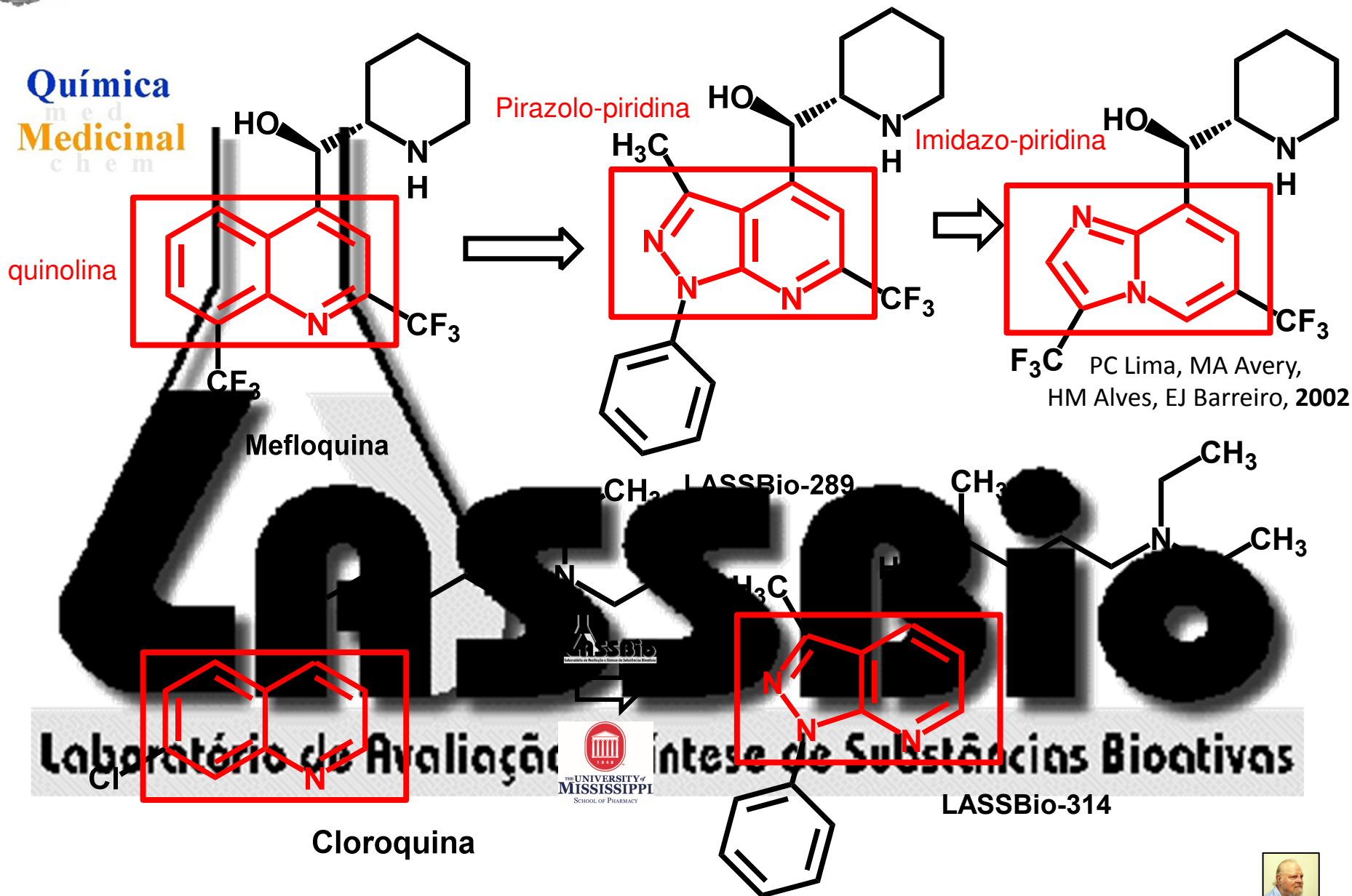


a) Khanpure SP et al., Synthesis and structure-activity relationship of novel, highly potent methyl and methcycloalkyl cyclooxygenase-2 (COX-2) selective inhibitors, *J Med Chem.* **2003**, 46, 5484 (A)

b) Khanpure SP et al., 3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl) (2-pyridyl) phenyl ketone as a potent and orally active cyclooxygenase-2 selective inhibitor: synthesis and biological evaluation, *J Med Chem.* **2005**, 48, 3930 (B)

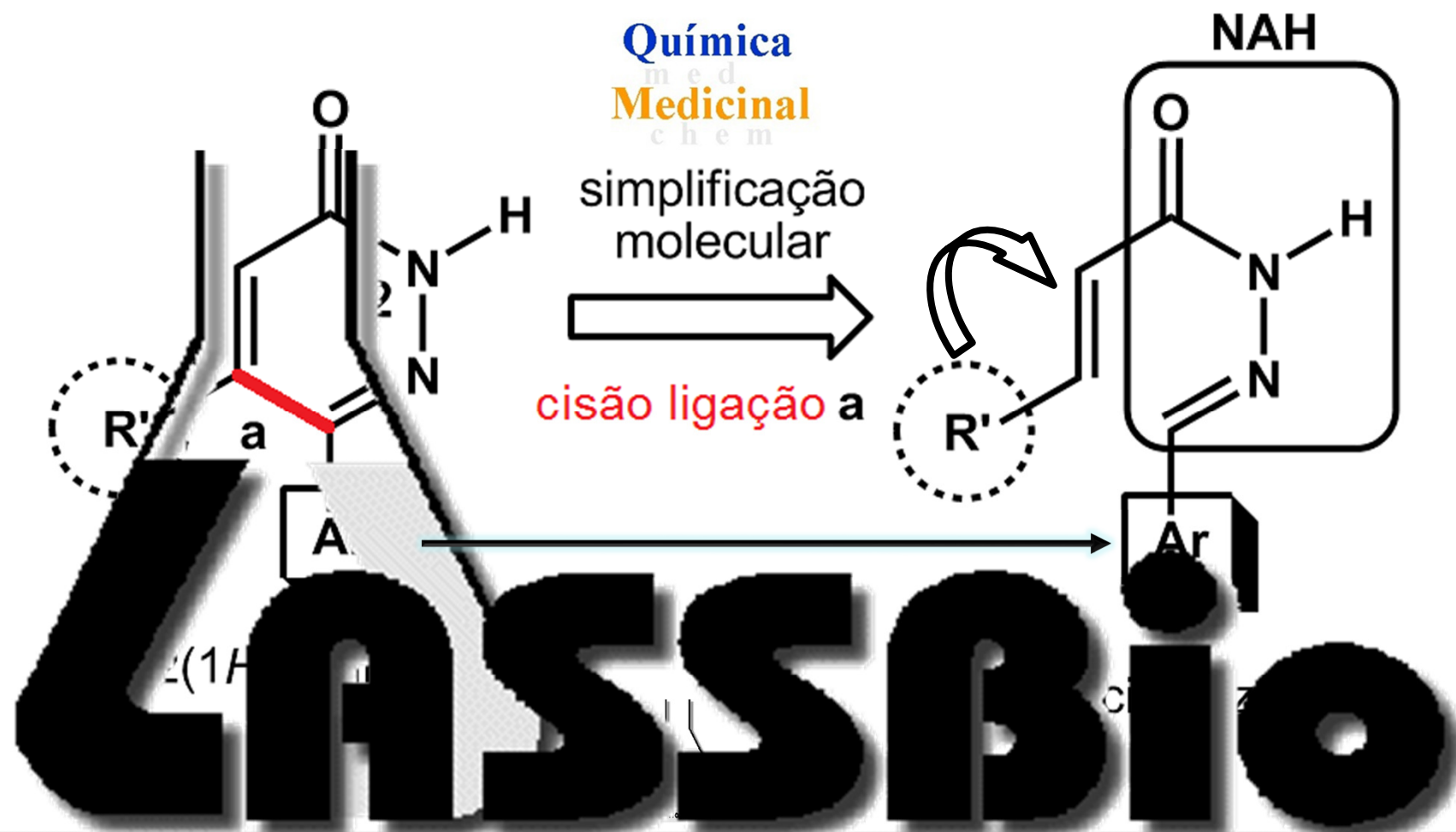


Bioisosterismo no LASSBio (II)





Bioisosterismo no LASSBio (IV)



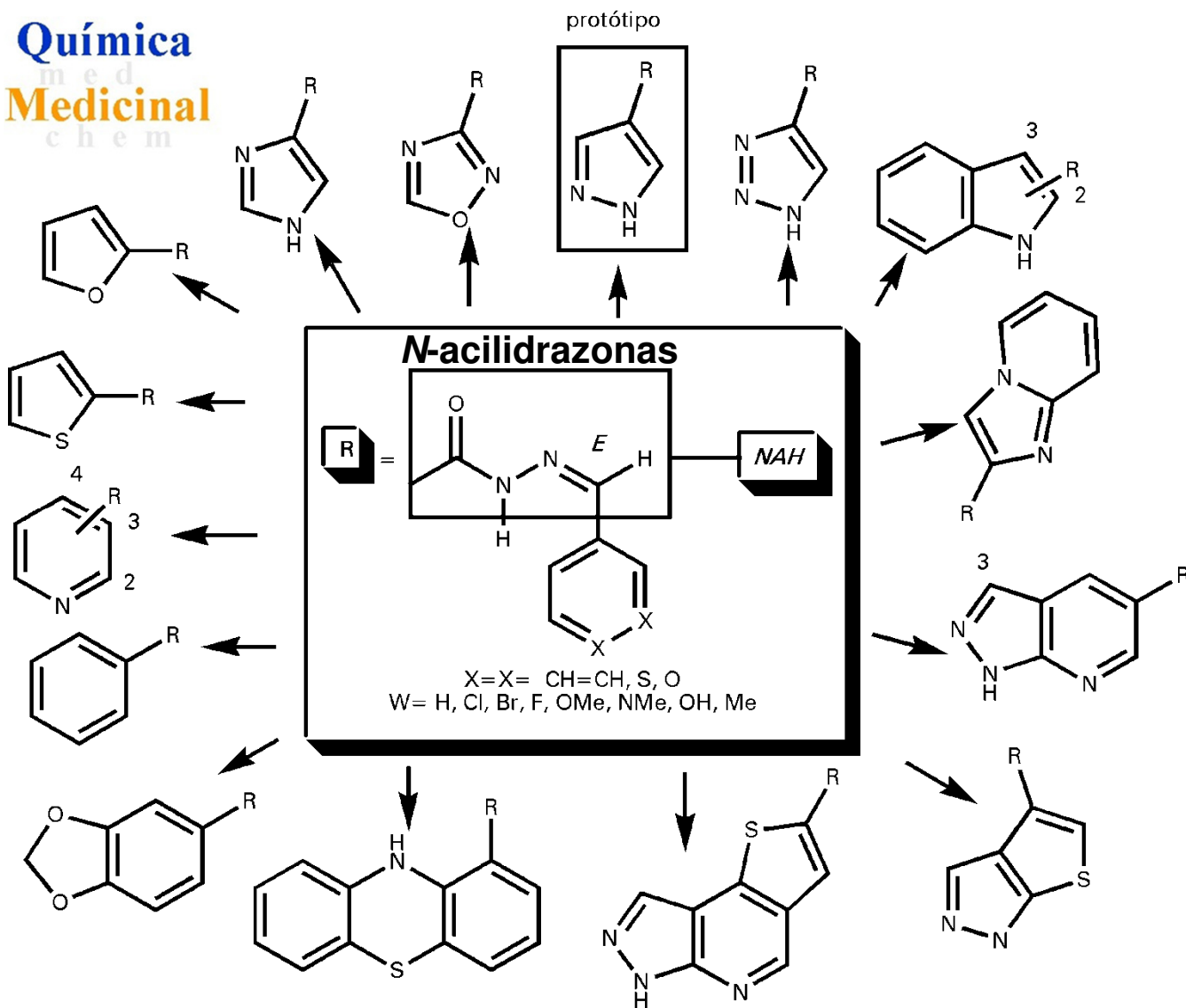
Laboratório de Avaliação e Síntese de Substâncias Bioativas



Bioisosterismo clássico de anéis

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MEDICINAL CHEMISTRY OF *N*-ACYLHYDRAZONES: NEW LEAD-COMPOUNDS OF ANALGESIC, ANTIINFLAMMATORY AND ANTITHROMBOTIC DRUGS

Carlos A.M. Fraga and Eliezer J. Barreiro

Volume 13, 167-198, 2006

Citações: 97 (21/01/2020)



Bioorganic & Medicinal Chemistry Letters 28 (2018) 2797–2806



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N-Acylhydrazones as drugs

Citações: 93 (21/01/2020)

Sreekanth Thota^{a,b,*}, Lídia M. Lima^{b,*} ... Carlos A.M. Fraga^{b,*}, Eliezer J. Barreiro^{b,*}

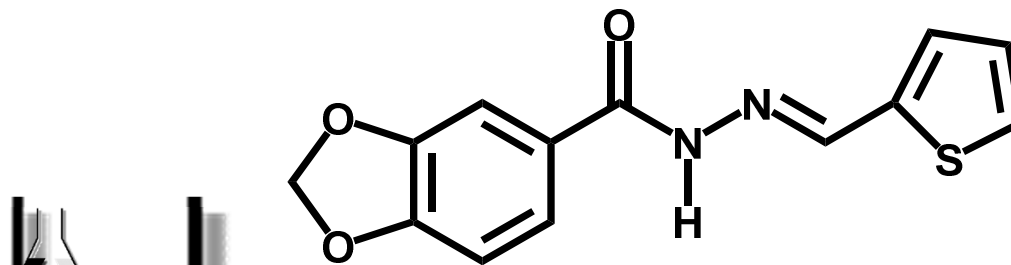
^a National Institute for Science and Technology on Innovation on Neglected Diseases (INCT/IDN), Center for Technological Development in Health (CDTS), Fundação Oswaldo Cruz – Ministério da Saúde, Av. Brasil 4036 – Prédio da Expansão, 8º Andar – Sala 814, Mangueiras, 21040-361 Rio de Janeiro, RJ, Brazil

^b Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Institute of Biomedical Sciences, Federal University of Rio de Janeiro (UFRJ), PO Box 68023, 21941-902 Rio de Janeiro, RJ, Brazil

Ru(II) Compounds: Next-Generation Anticancer Metallotherapeutics?

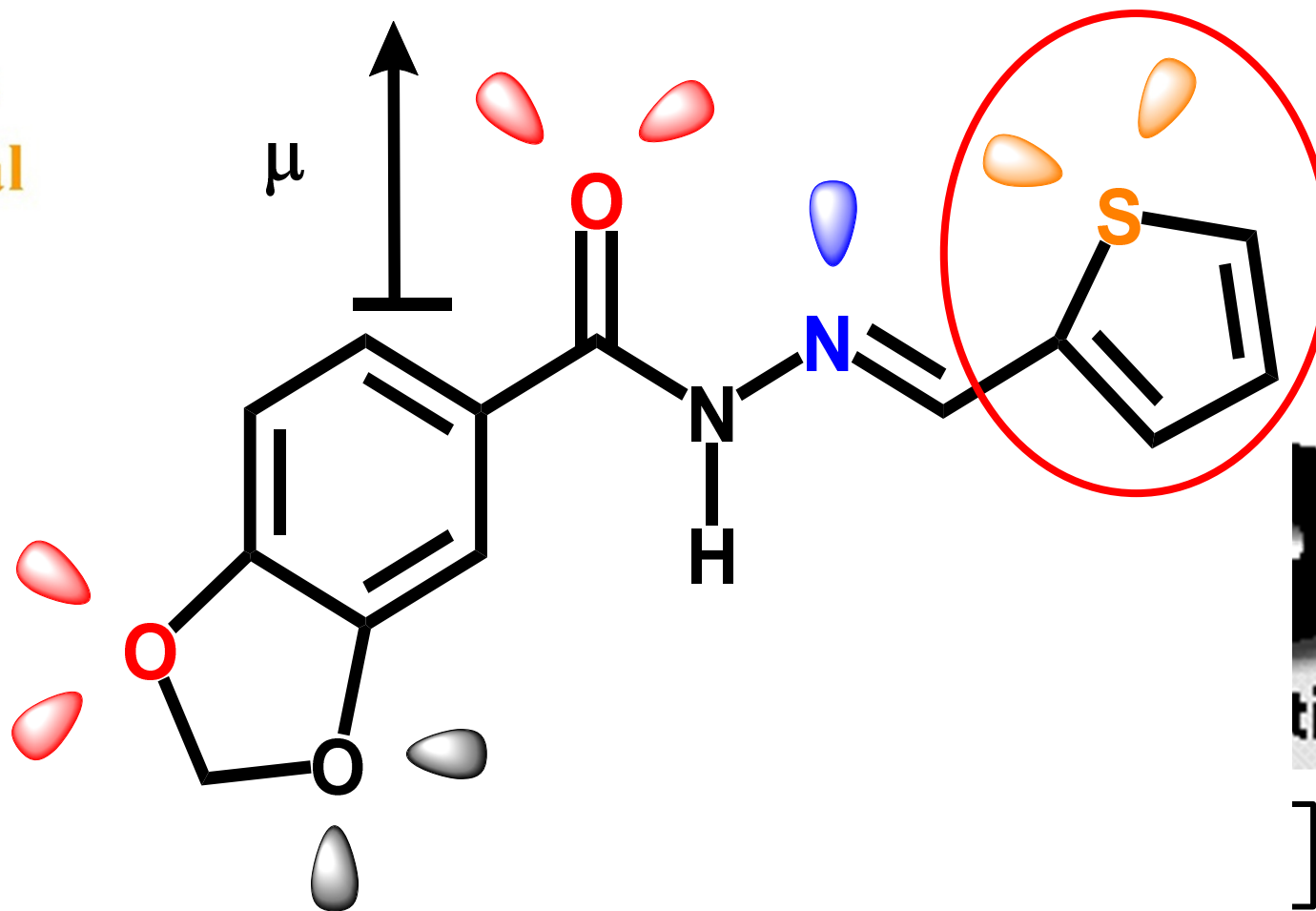
Citações: 88 (21/01/2020)

S Thota, DA Rodrigues, DC Crans, EJ Barreiro, *J Med Chem* **2018**, *61*, 5805



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A *Química* *Medicinal* é simplesmente *fascinante!*

LM Lima, Química Medicinal Moderna: desafios e contribuição brasileira, *Quím Nova* 2007, 30, 1456

AT Amaral et al, A evolução da química medicinal no Brasil: ...nos 40 anos da SBQ, *Quim Nova* 2017, 40, 694

CH Andrade et al, Perspectivas da QM para o século XXI: desafios e oportunidades, *Quim Nova* 2018, 41, 476



Obrigado pela
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e pela
atenção!



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