Aula 13 – 19/08

Tópicos Especiais em Química Medicinal

Tópicos Especiais
em Química Medicinal
Código: **BMF-777**
Carga Horária: 45 horas
Créditos: 3 créditos

Bioisosterismo

L.M. Lima & E. J. Barreiro

"Bioisosterism: A Useful Strategy for Molecular Modification and Drug Design"

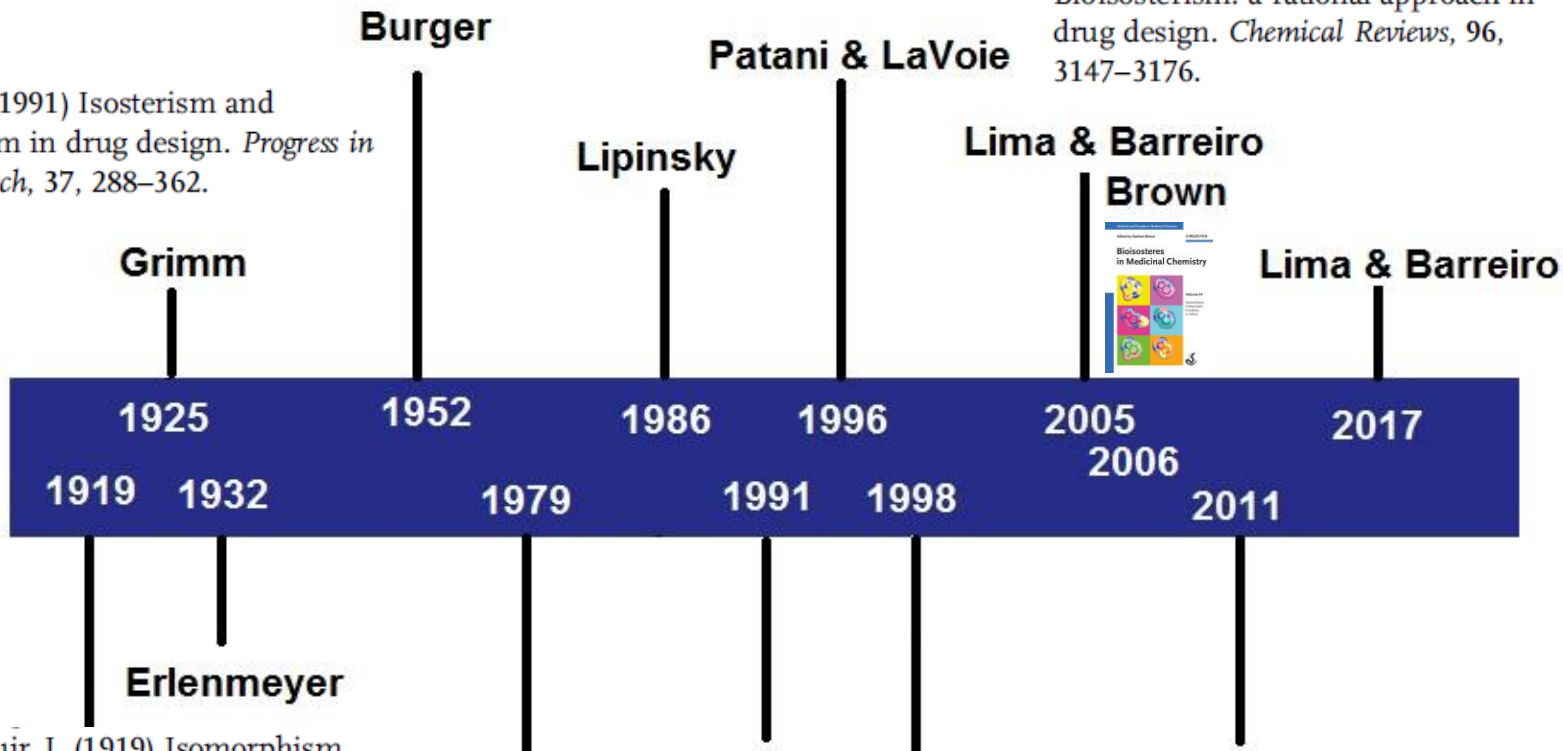
Current Medicinal Chemistry **2005,** *12*, 23-49

775 citações
(18.08.21)

Bioisosterism

Patani, G.A. and LaVoie, E.J. (1996) Bioisosterism: a rational approach in drug design. *Chemical Reviews*, 96, 3147–3176.

Burger, A. (1991) Isosterism and bioisosterism in drug design. *Progress in Drug Research*, 37, 288–362.

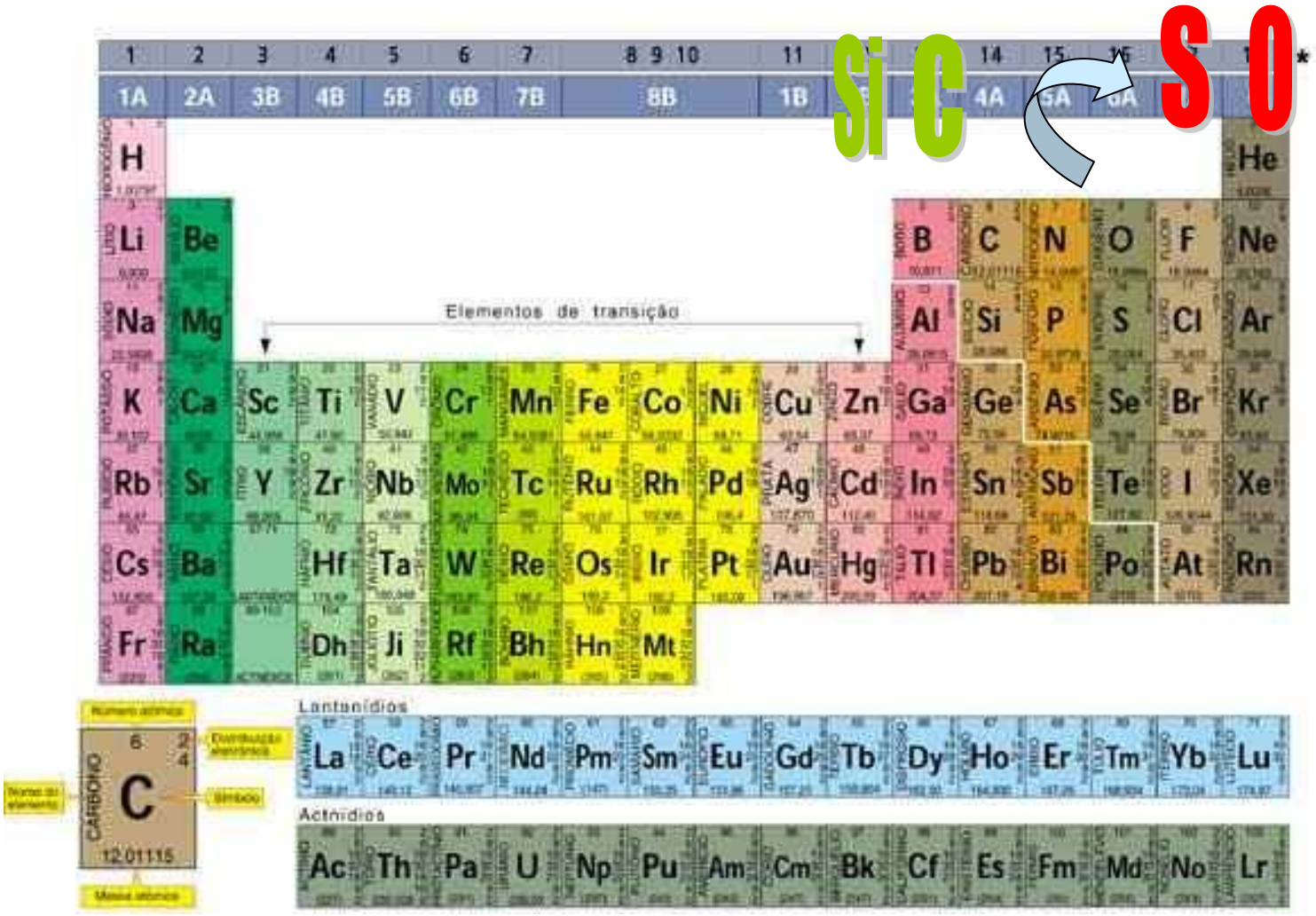


Langmuir, I. (1919) Isomorphism, isosterism and covalence. *Journal of the American Chemical Society*, 41, 1543–1559.

Thornber, C.W. (1979) Isosterism and molecular modification in drug design. *Chemical Society Reviews*, 8, 563–580.

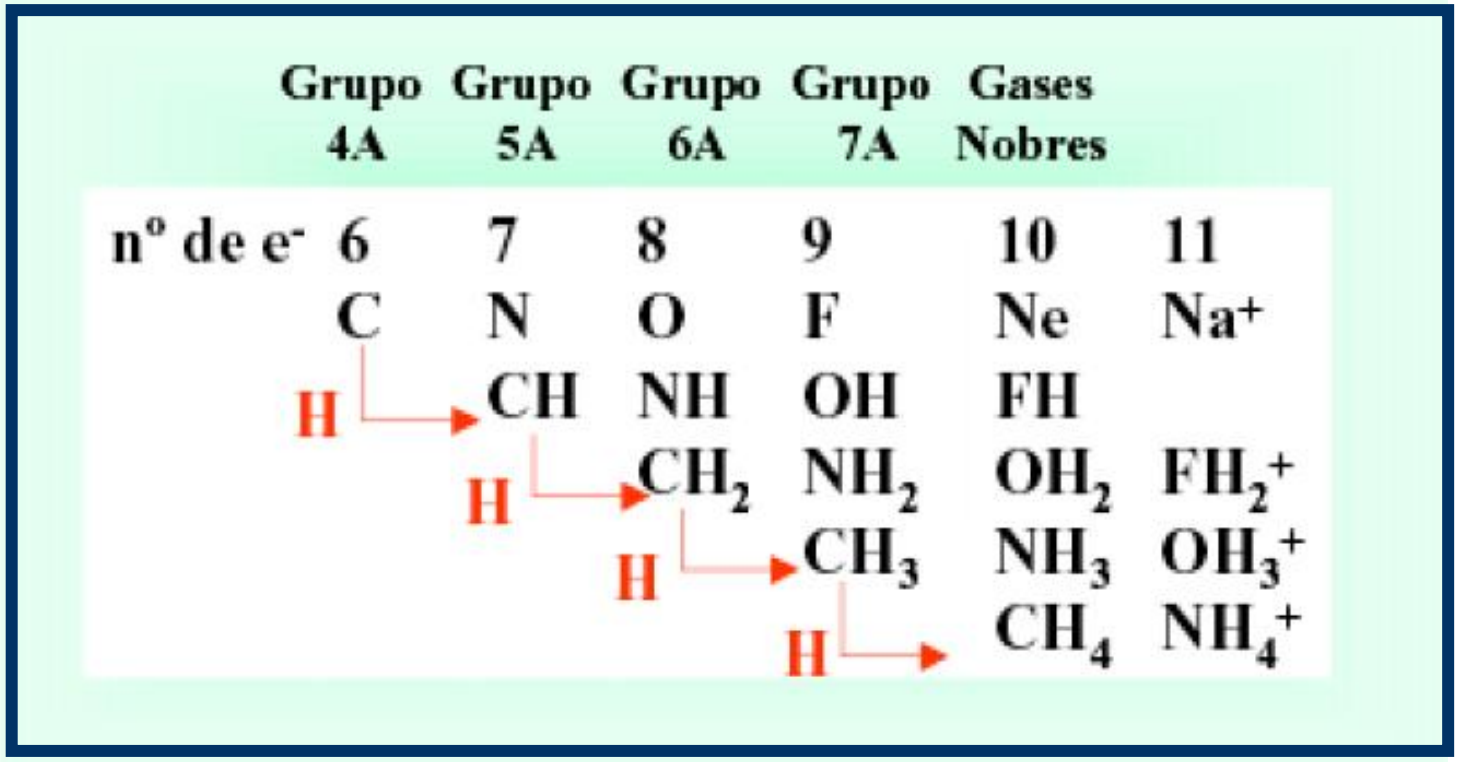
Meanwell, N.A. (2011) Synopsis of some recent tactical application of bioisosteres in drug design. *Journal of Medicinal Chemistry*, 54, 2529–2591.

Os elementos da Tabela Periódica



bioisosterismo

Regra do *hidreto* de Grimm



Bioisosterismo

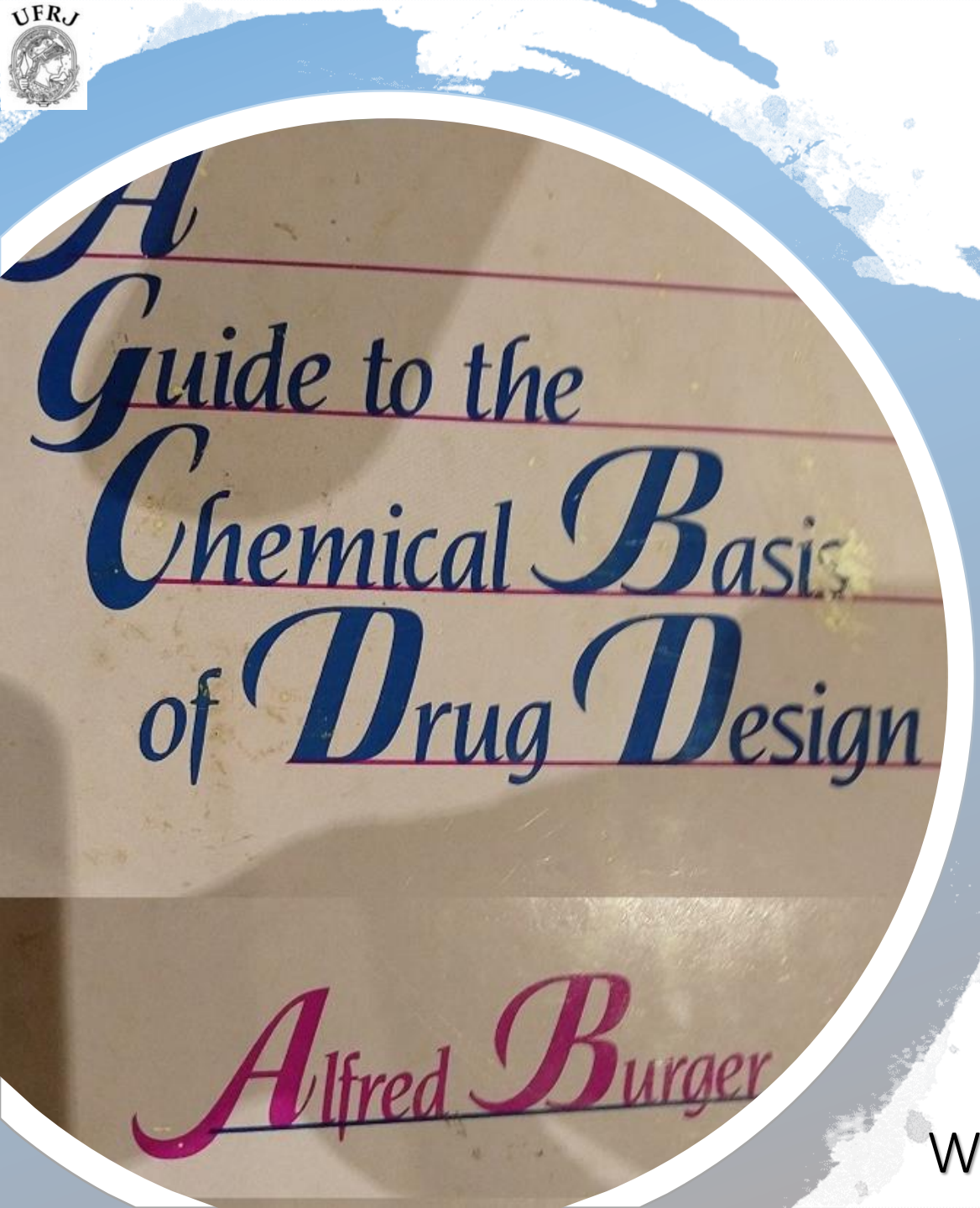
Alfred Burger em 1970, classificou:

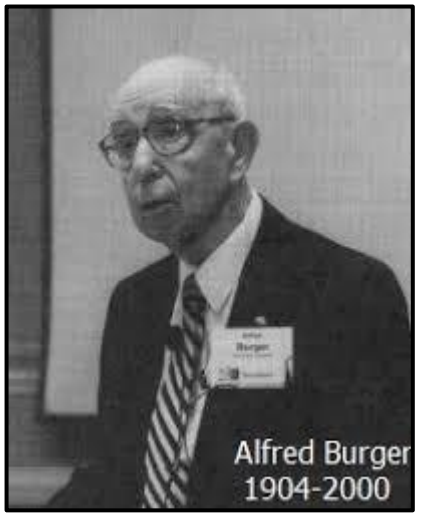
1 Classic Bioisosteres

- 1.1 Monovalent atoms or groups
- 1.2 Divalent atoms or groups
- 1.3 Trivalent atoms or groups
- 1.4 Tetrasubstituted atoms
- 1.5 Ring equivalents

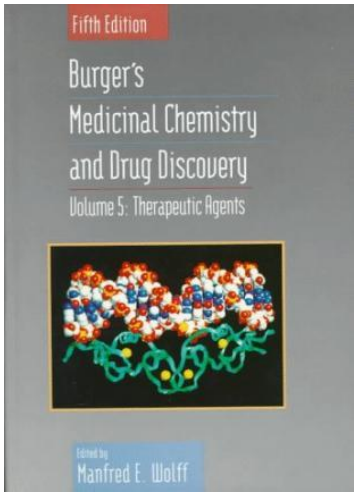
Non-Classic Bioisosteres

- 2.1 Cyclic vs Noncyclic
- 2.2 Functional groups
- 2.3 Retroisosterismz



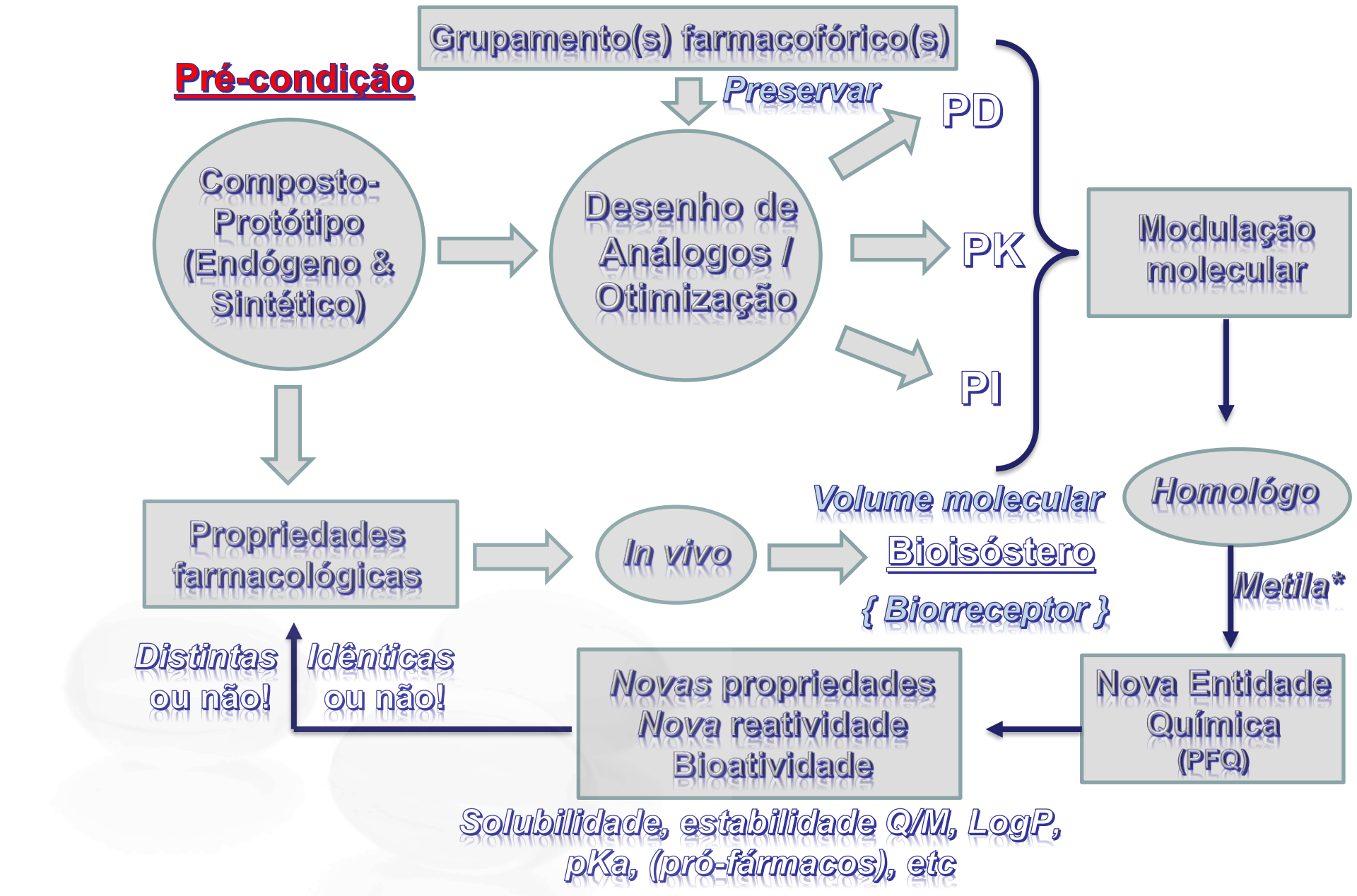


Medicinal Chemistry



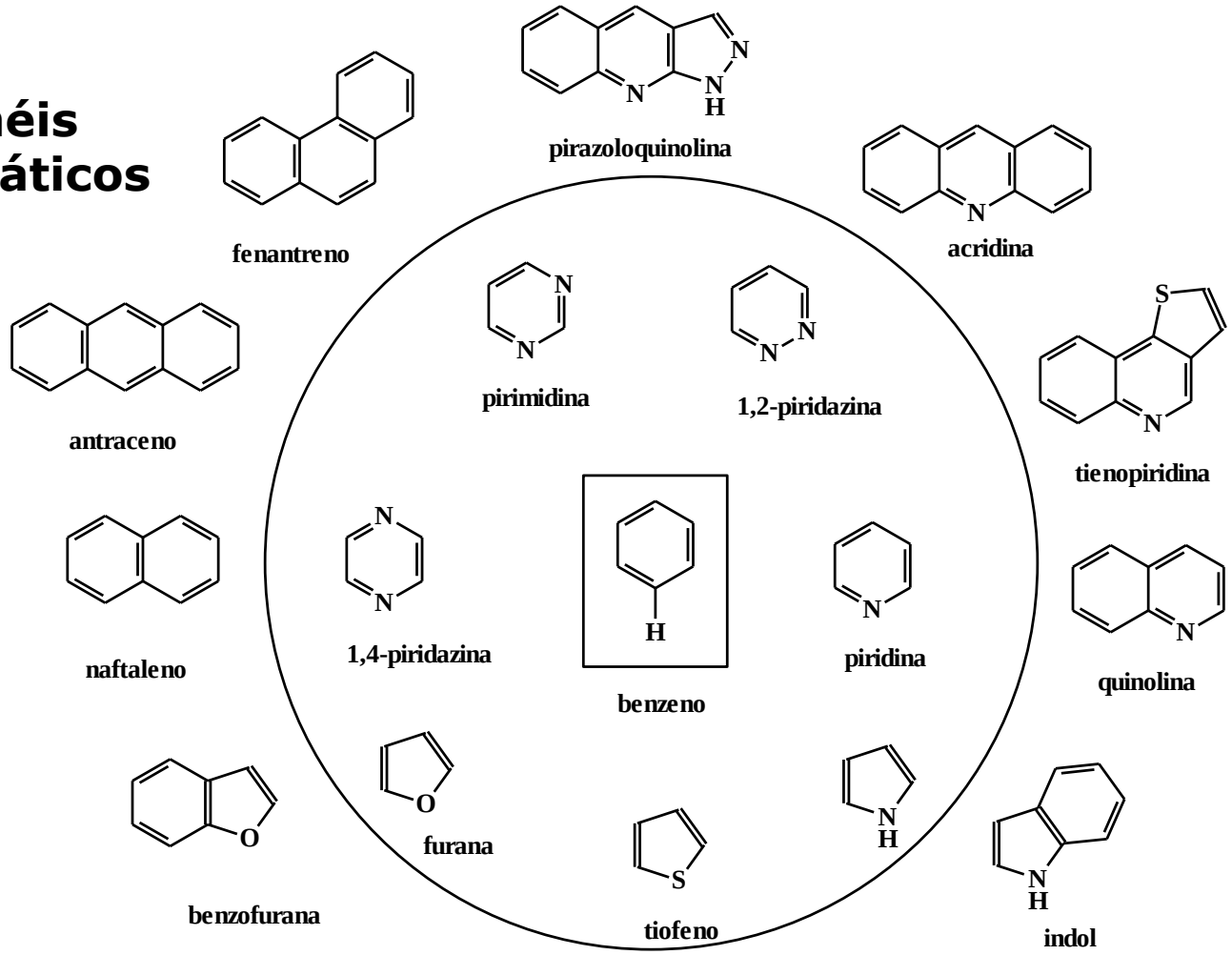
Wiley, 1983

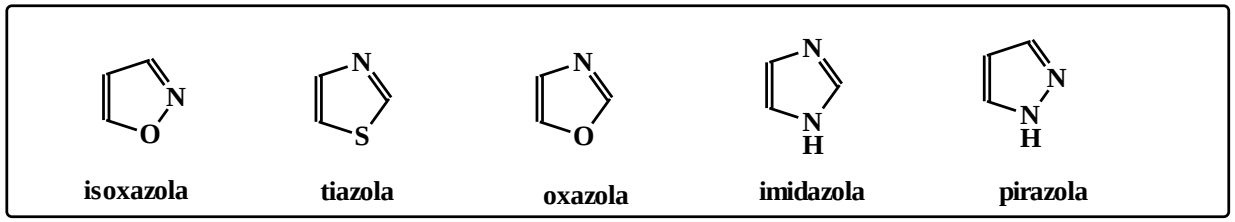
Bioisosterismo



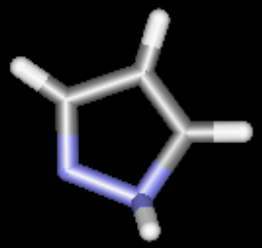
Bioisosterismo clássico de anéis

Anéis aromáticos

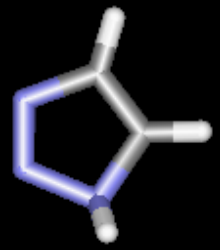




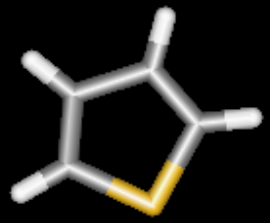
Bioisosterismo Clássico de Anel



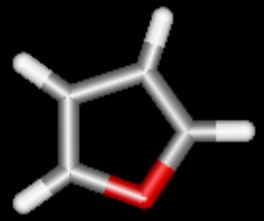
pirazola



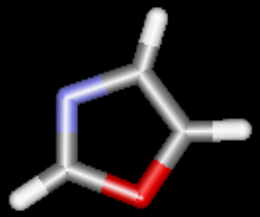
1,2,3-triazola



tiofeno



furana



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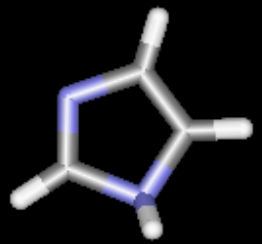
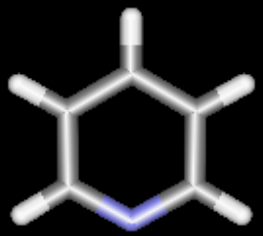
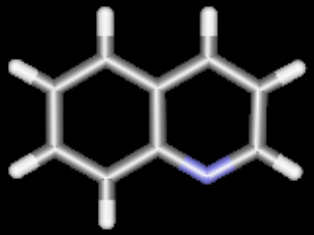


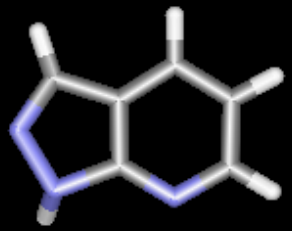
imidazola



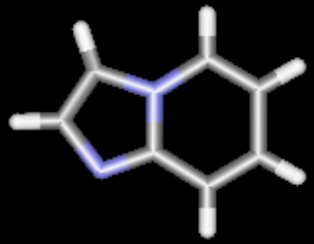
piridina



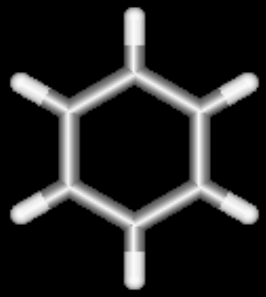
quinolina



pirazolo-piridina

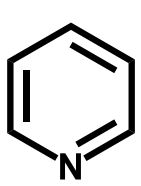


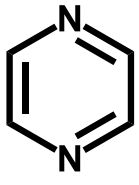
Imidazo-piridina



benzeno

Isósteros *N*-heterocíclicos


Piridina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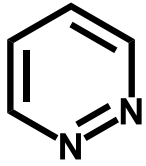
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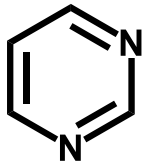
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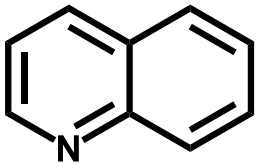
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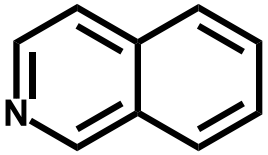
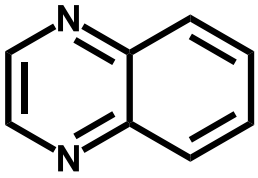

Isoquinolina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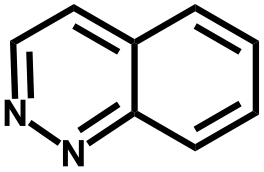
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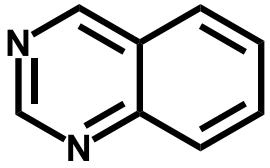
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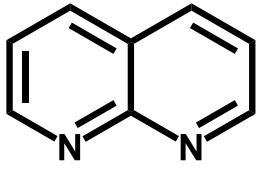
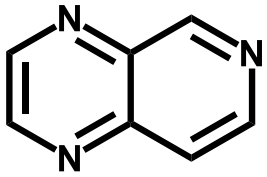
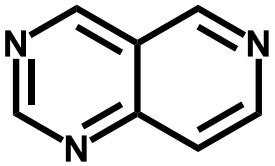
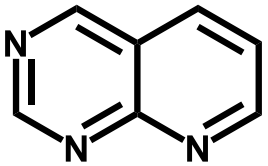

1,8-Diazanaftaleno


Pirido[4,3-*b*]pirazina


Pirido[4,3-*d*]pirimidina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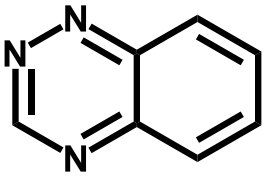
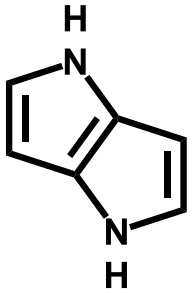
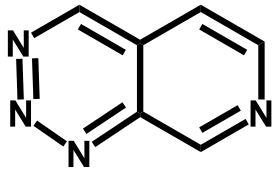
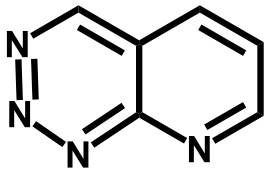

1,2,4-Benzotriazina


1,4-Diidropirrolo[3,2-*b*]pirrola


Pirido[3,4-*d*]-[1,2,3]-triazina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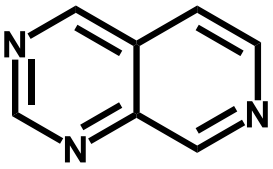
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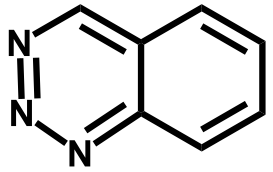
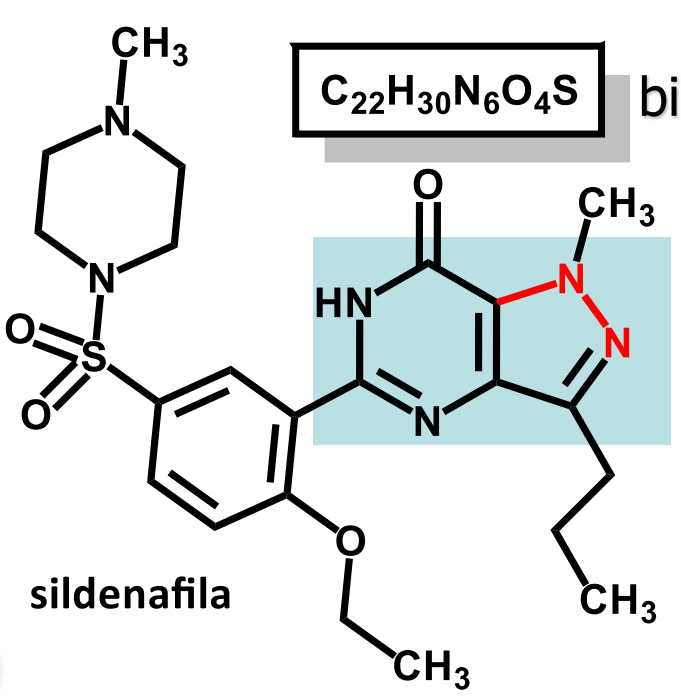

1,2,3-Benzotriazina

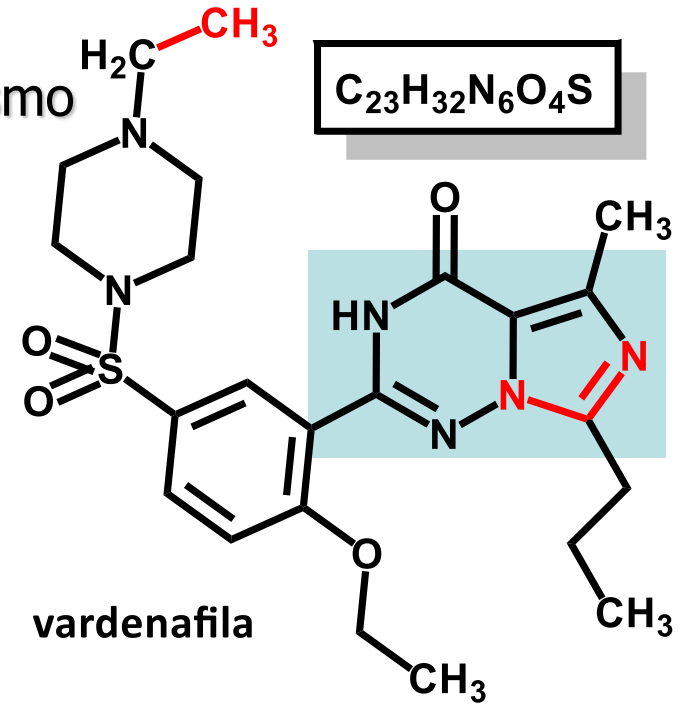
1197 estruturas de fármacos no mercado (FDA) até 2013 → **351** sistemas cíclico

7-1*H*-pirazolo[4,3-*d*]pirimidinona

4-imidazo[5,1-*f*][1,2,4]triazinona

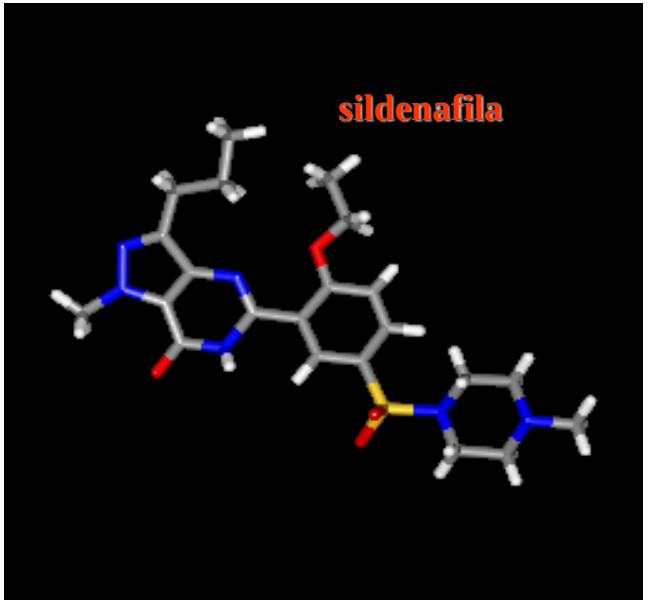


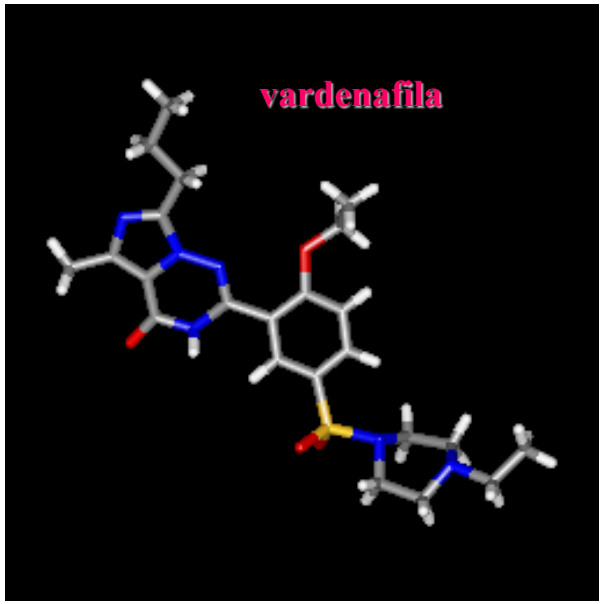
bioisosterismo



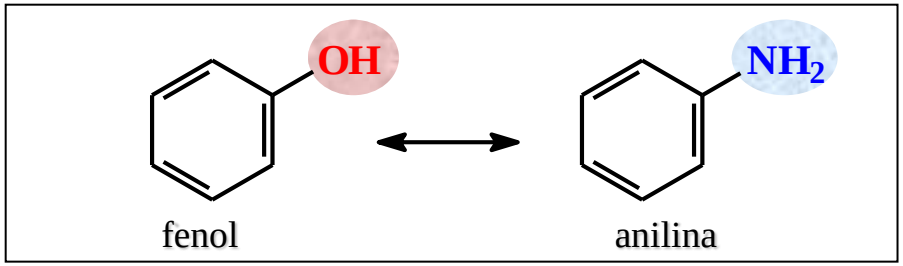
sildenafila

vardenafila

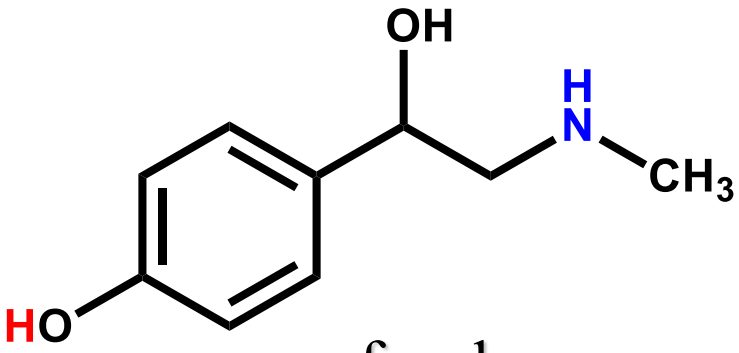




Bioisosterismo funcional

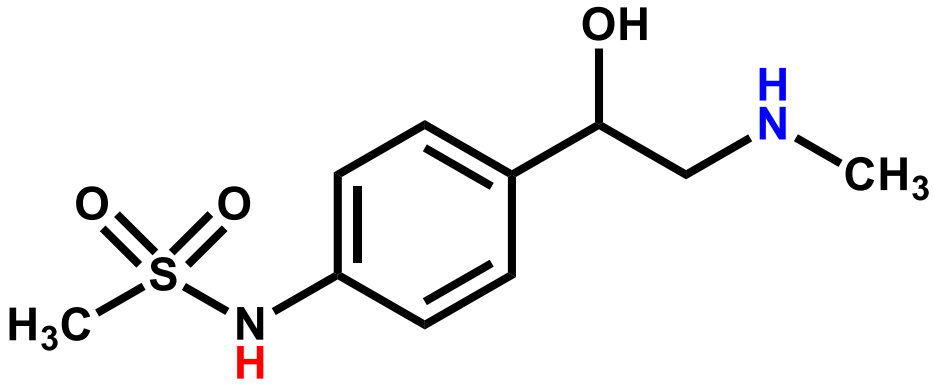


Pontos farmacofóricos monovalentes



fenol

pK_a 9,1



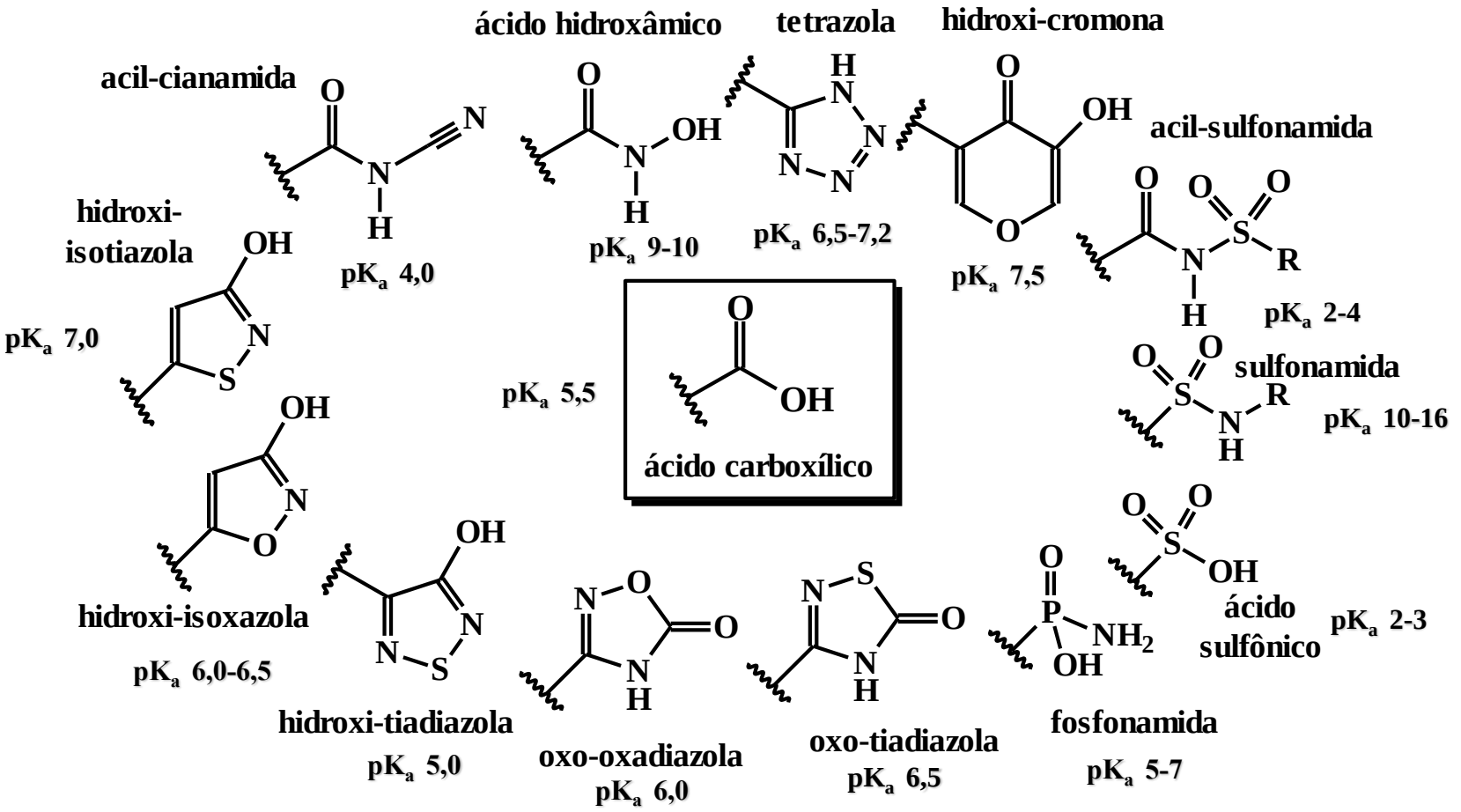
Aril-sulfonilamina

pK_a 9,6

AA Larsen & PM Lisch, *Nature* **1964**, *203*, 1283

Bioisosterismo funcional

Isósteros do ácido carboxílico

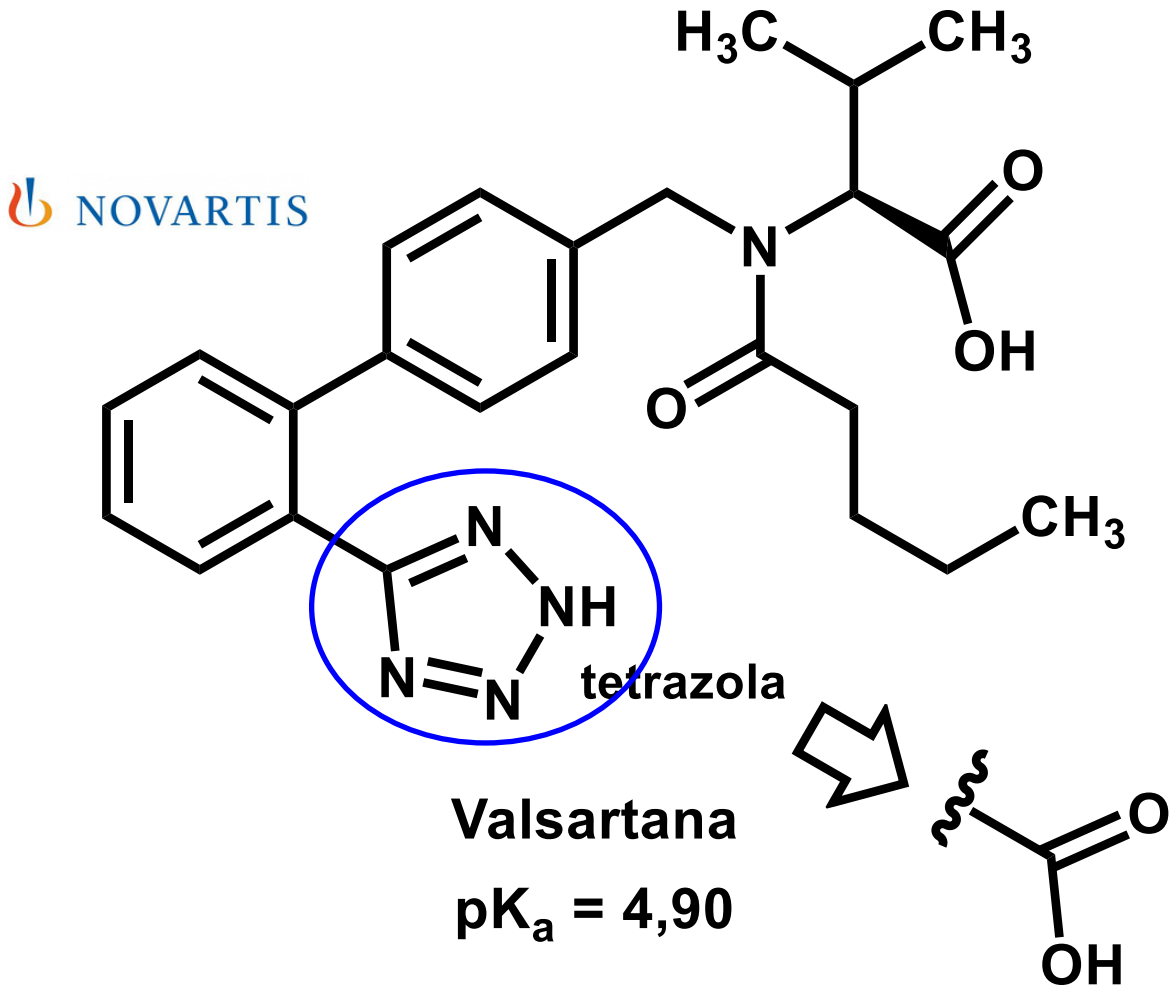


evans.harvard.edu/pdf/evans_pka_table.pdf

Todas as funções orgânicas têm a mesma diversidade de isósteros ?

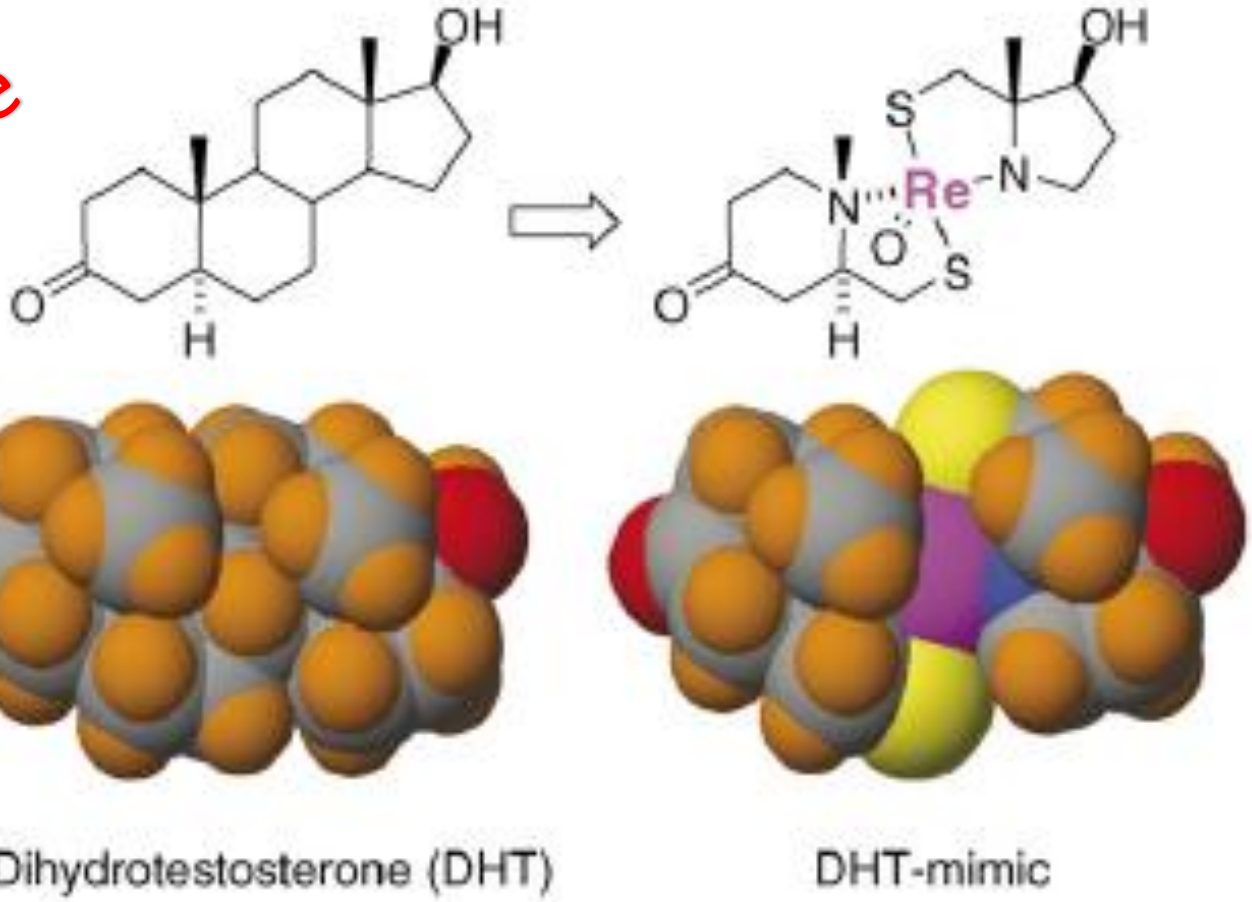
Fármaco tetrazólico

Fármaco tetrazólico: bioisóstero de ácido



Exploring biologically relevant chemical space (metal complexes)

Curiosidade

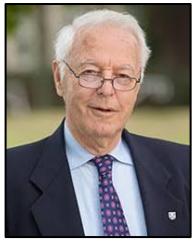


E. Meggers, Curr Op Chem Biol 2007, 11, 287

Adaptado da conferência da Profª H. O. Beraldo, 31ª RASBQ, Águas de Lindóia, SP, 26-29/06/2008.

Chaveiro molecular

J. L. Neumeyer, A Tribute to Joseph G. Cannon,
J. Med. Chem. **2012**, *55*, 1423



John L. Neumeyer
(1935-)

Joseph G. Cannon
(1926–2011)

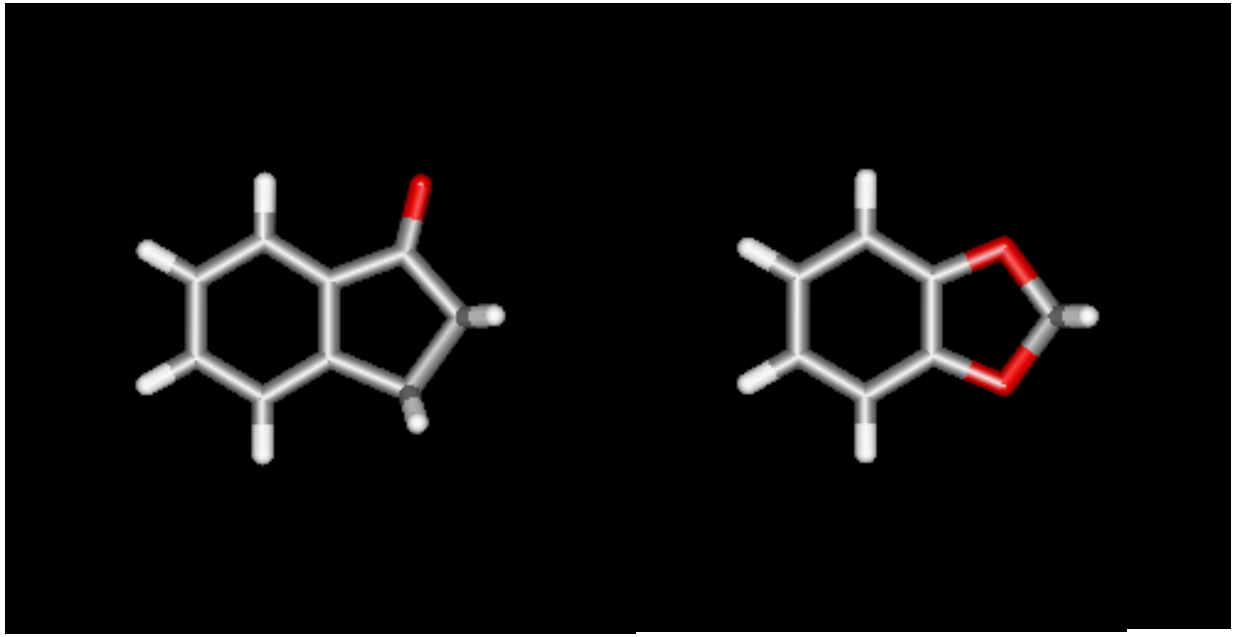
"...there no absolute rules for designing new drugs... the knowledge, imagination, and intuition of the Medicinal Chemist are the most important factor of success..."

J. G. Cannon*

* em *Analog Desig*n, Chapter 19, Burger´s Medicinal Chemistry and Drug Discovery, 5th Ed., Vol 1: Principles and Practice, ME Wolf Editor, Wiley, 1995, pp. 783-802.

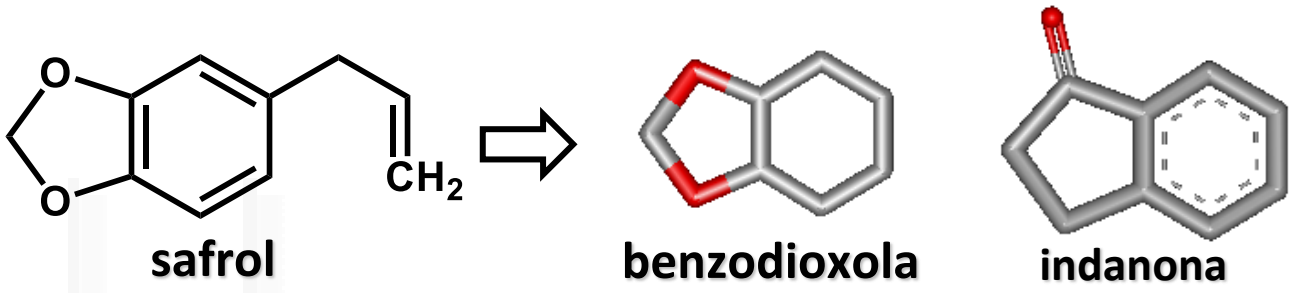
Bioisosterismo no LASSBio

Indanona - Benzodioxola

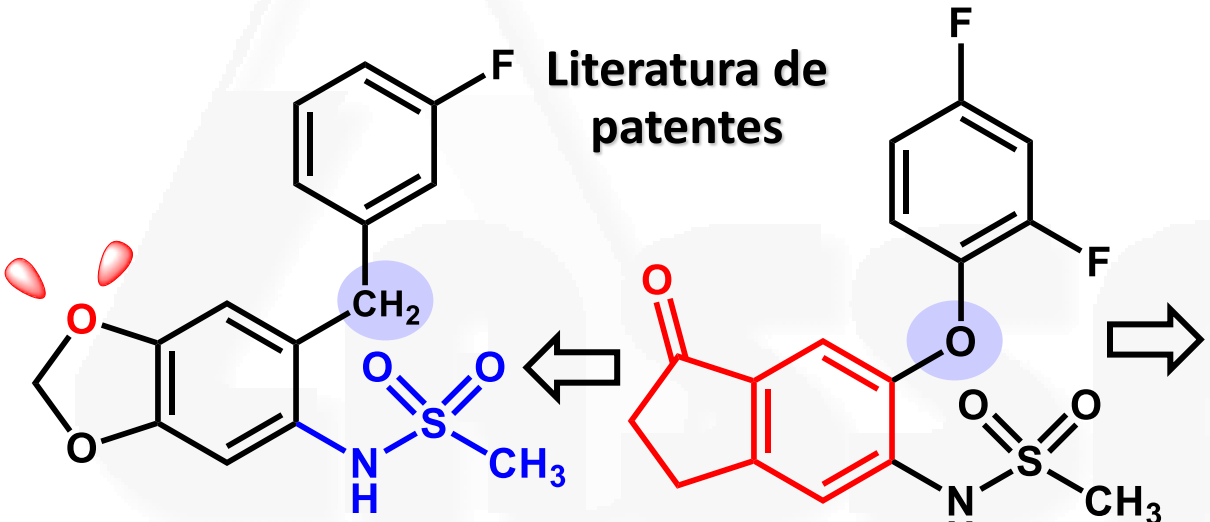


A S Lages et al. Synthesis and pharmacological evaluation of new flosulide analogues, synthesized from natural safrole, *Bioorg Med Chem Lett* **1998**, *8*, 183-188

Bioisosterismo no LASSBio



Nova relação bioisostérica



LASSBio-349

safrulido

Literatura de patentes

flosulido

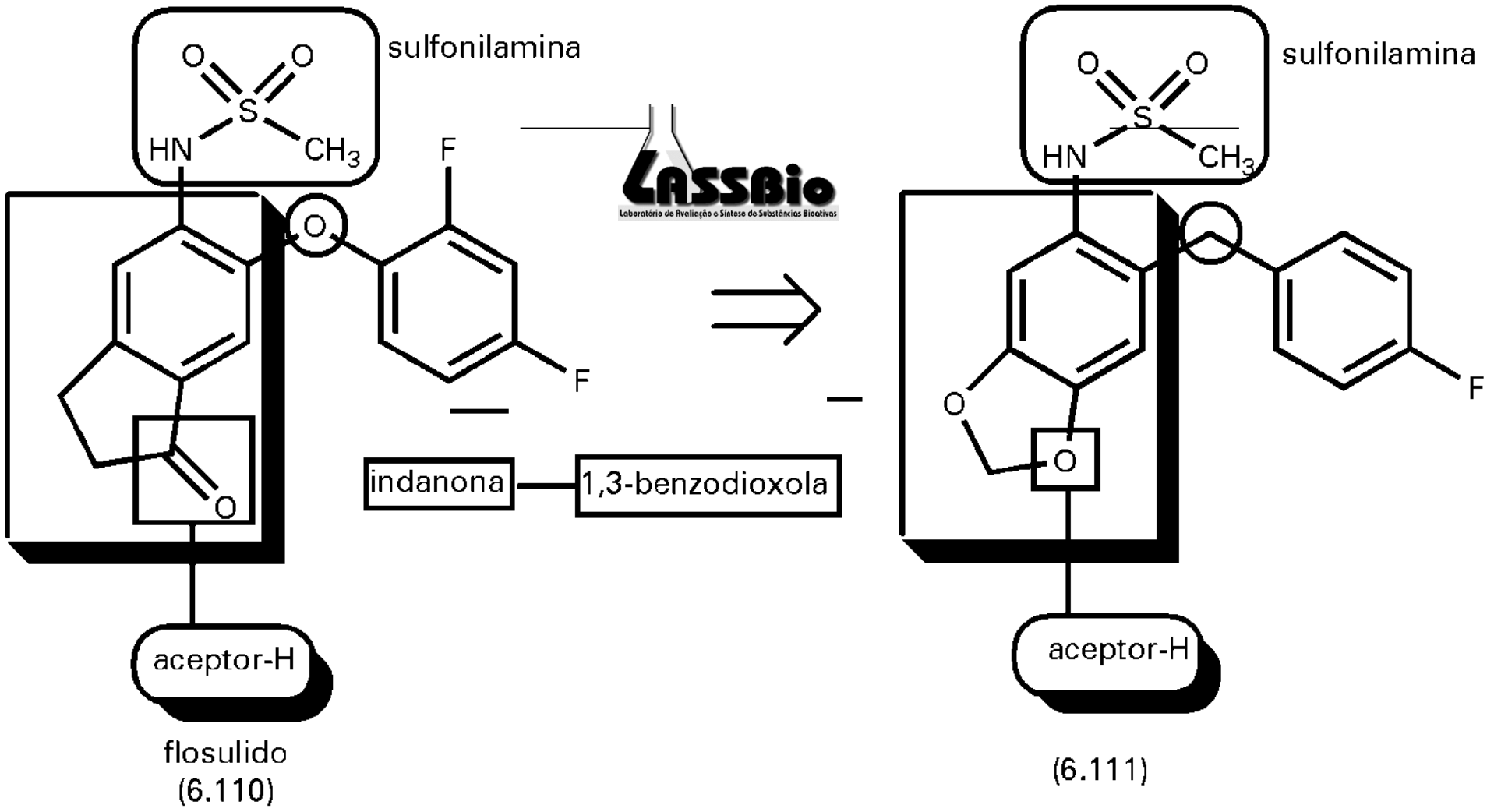
Futaki *et al*, 1995

IC_{50} (hPGHS-1) = 73,2 μM

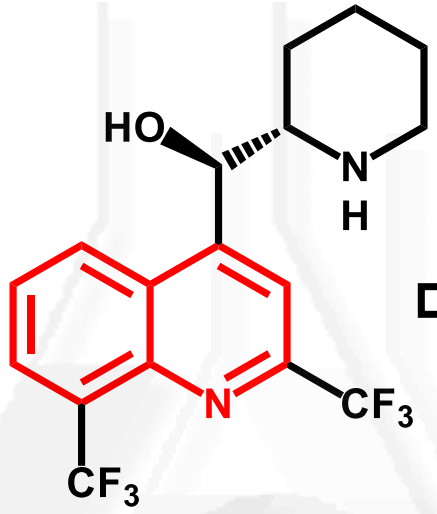
IC_{50} (rPGHS-2) = 0,015 μM

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

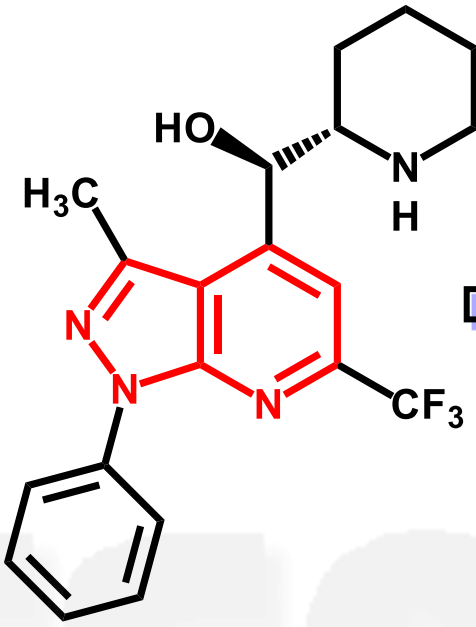
LASSBio-349: novo tipo de bioisosterismo



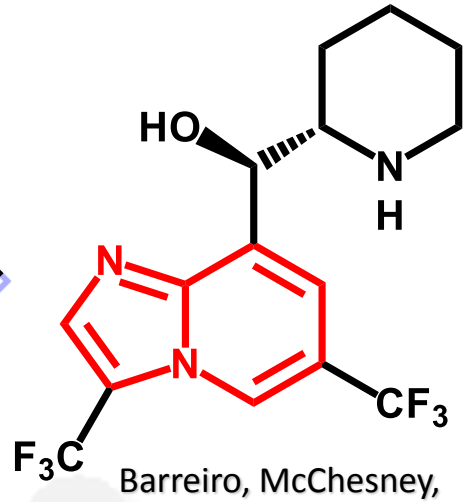
Bioisosterismo no LASSBio



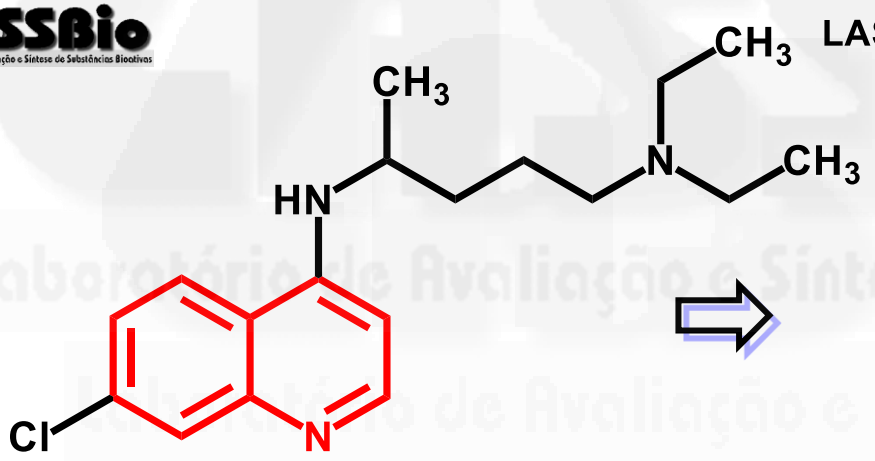
Mefloquina



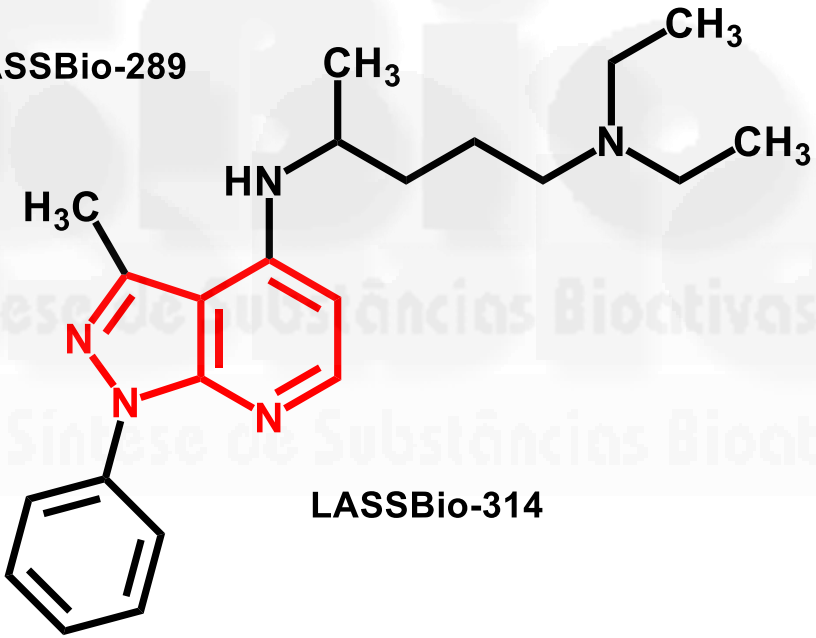
LASSBio-289



Barreiro, McChesney, Dias, Nanayakkara, 1997

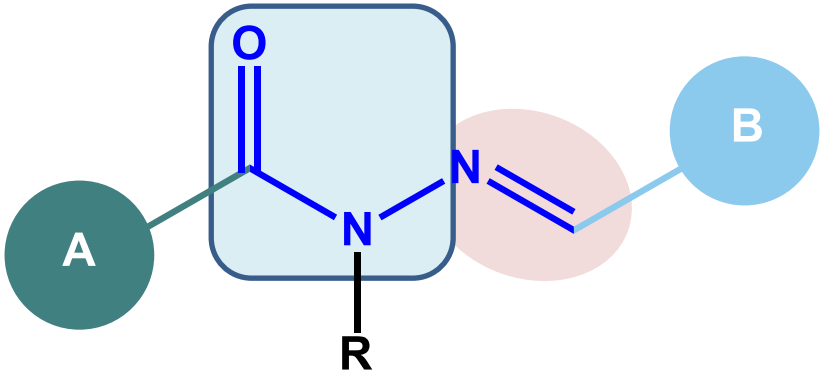


Cloroquina



LASSBio-314

RS Dias, ACC Freitas, EJ Barreiro, DK Goins, D Nanayakkara, JD McChesney, *Boll. Chim. Farm.* **2000**, *139*, 14



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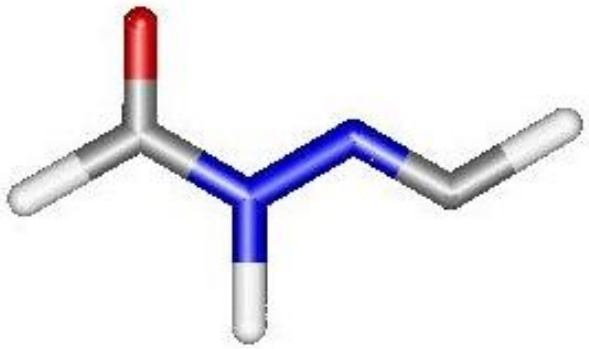


N-acilidrazona

NAH

Peptide-like scaffold

NAH = amida + imina

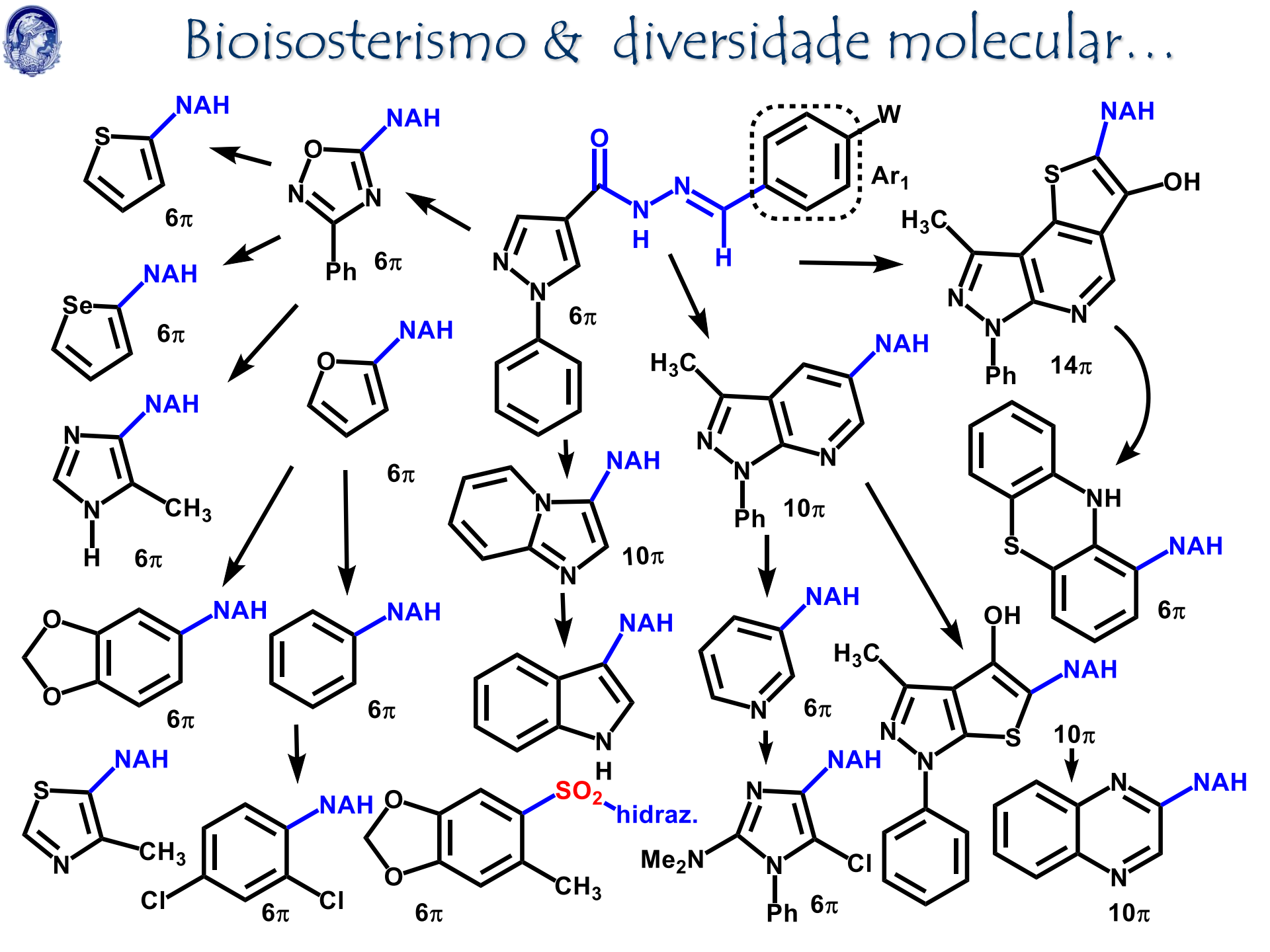
CAPÍTULO 10

SIMPLIFICAÇÃO MOLECULAR COMO ESTRATÉGIA DE MODIFICAÇÃO MOLECULAR E O PROCESSO DE OTIMIZAÇÃO DE COMPOSTOS-PROTÓTIPOS 447

As propriedades farmacológicas de derivados NAH foram descobertas no

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

Bioisosterismo & diversidade molecular...



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

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Digest

N-Acylhydrazones as drugs

Sreekanth Thota[a,b,*], Daniel A. Rodrigues[b], Pedro de Sena Murteira Pinheiro[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. Brazil 4036 – Prédio da Expansão, 8° Andar – Sala 814, Manguinhos, 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

Journal of Medicinal Chemistry

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Article

Bioisosteric Replacement of Arylamide-Linked Spine Residues with *N*-Acylhydrazones and Selenophenes as a Design Strategy to Novel Dibenzosuberone Derivatives as Type I 1/2 p38α MAP Kinase Inhibitors

Júlia G. B. Pedreira, Philipp Nahidino, Mark Kudolo, Tatu Pantsar, Benedict-Tilman Berger, Michael Forster, Stefan Knapp, Stefan Laufer,* and Eliezer J. Barreiro*

Cite This: *J. Med. Chem.* 2020, 63, 7347−7354

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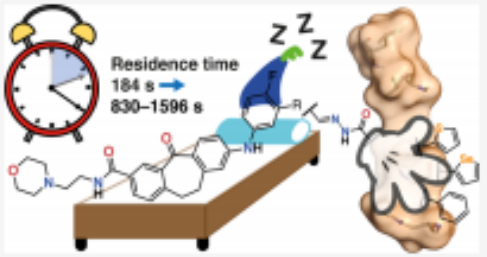
ABSTRACT: The recent disclosure of type I 1/2 inhibitors for p38α MAPK demonstrated how the stabilization of the R-spine can be used as a strategy to greatly increase the target residence time (TRT) of inhibitors. Herein, for the first time, we describe *N*-acylhydrazone and selenophene residues as spine motifs, yielding metabolically stable inhibitors with high potency on enzymatic, NanoBRET, and whole blood assays, improved metabolic stability, and prolonged TRT.



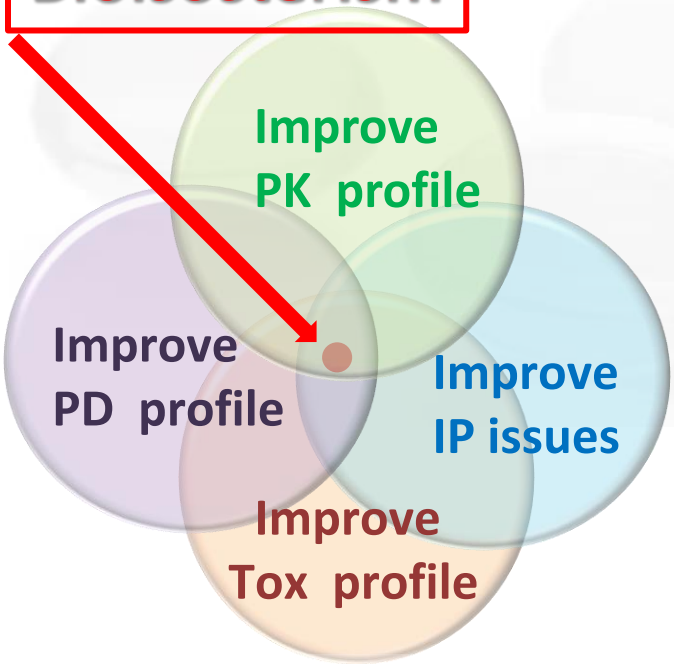
"...discovery *consists* of seeing what everybody else **has seen** ***and*** **thinking what nobody else has not thought..."**

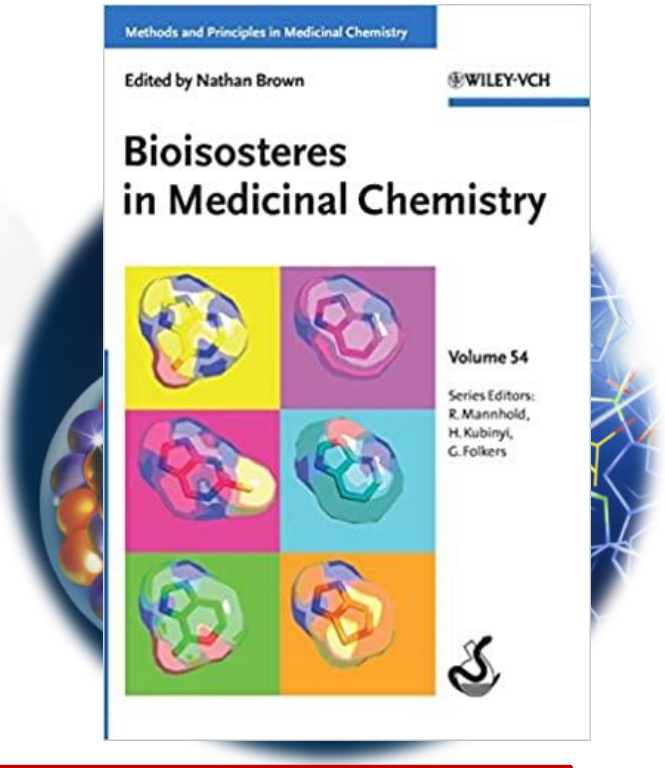
1937

Albert Szent-Györgi (1893-1986)

DRUG DISCOVERY

Bioisosterism





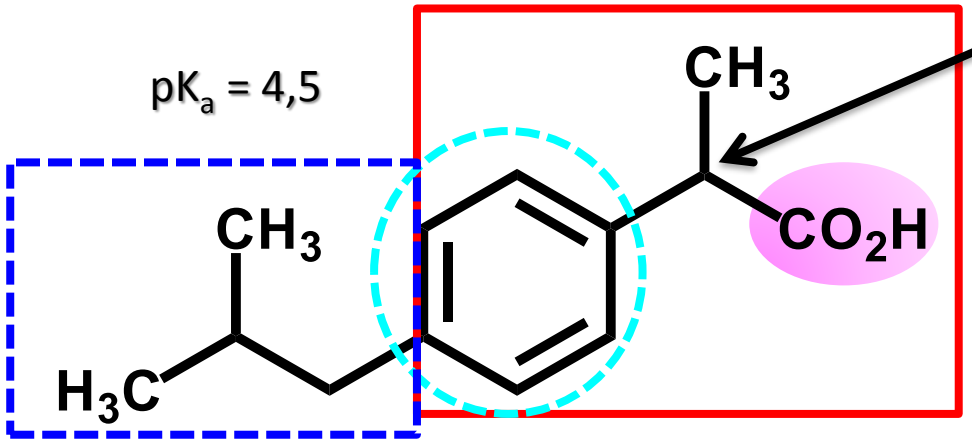
New Drug Candidate

Drug design
SBDD/LBDD

Lead optimization

- To remove side effects & toxicity
- To improve ADME (PK)
- To improve selectivity/potency/activity (PD)
- To synthesize easier compounds
- To avoid patent constraints
- To enhance the chemical space

Anelação molecular



NSAI's

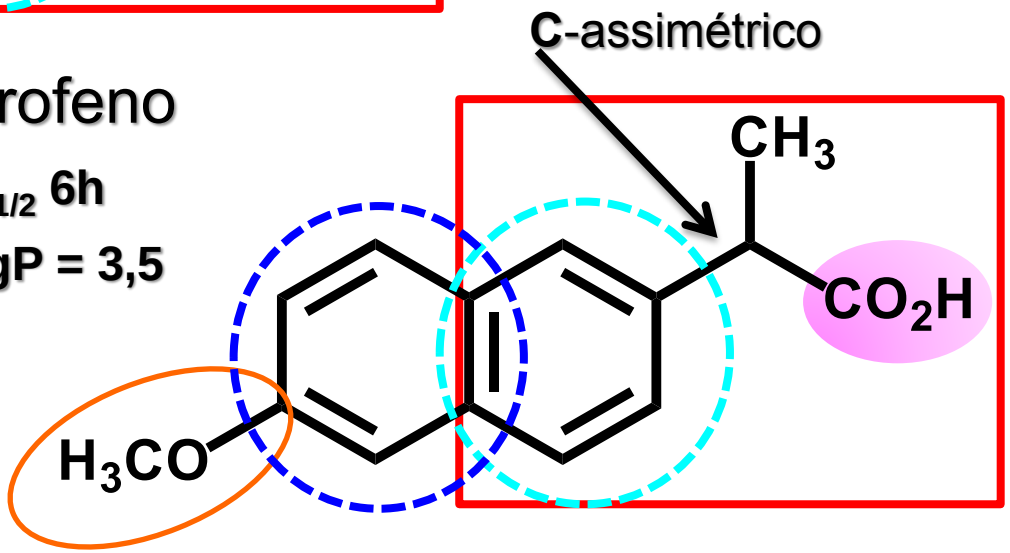
Ácido carboxílico α-metilado

ibuprofeno

T$_{1/2}$ 6h

LogP = 3,5

Similaridade molecular



naproxeno

T$_{1/2}$ 12h

LogP = 2,9

Química Medicinal