



XXVIII Escola de Verão em Química Farmacêutica e Medicinal
25-28 de janeiro de 2022

Curso 3

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



Estruturas privilegiadas no desenho de fármacos

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Instituto Nacional de Ciência e Tecnologia em Fármacos e Medicamentos

Programa de Pós-Graduação em Farmacologia e Química Medicinal



www.inct-inofar.ccs.ufrj.br



Laboratório de Avaliação e Síntese de Substâncias Bioativas

www.lassbio.icb.ufrj.br



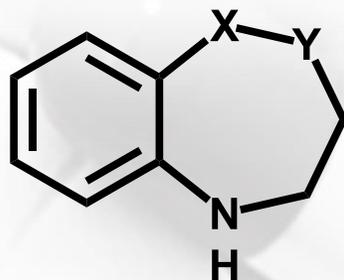
Parte 2

Química
med
Medicinal
chem





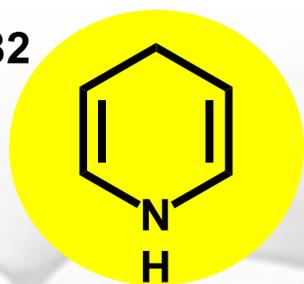
1950



X=CH₂ Y=NH - 1,4-benzodiazepinas

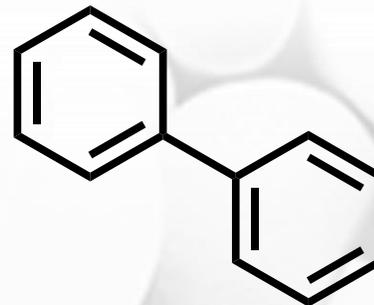
X=NH Y=CH₂ - 1,5-benzodiazepinas

1982



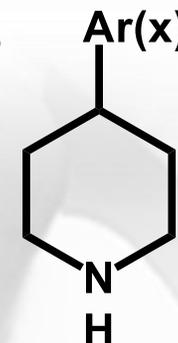
1,4-diidropiridinas

1986



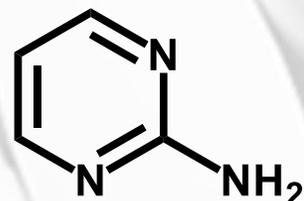
Bifenila

1958



4-arilpiperidinas

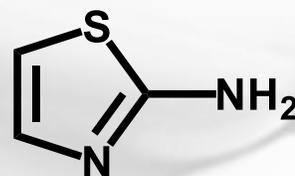
4-heteroarilpiperidinas



2-aminopirimidinas

crizotinibe

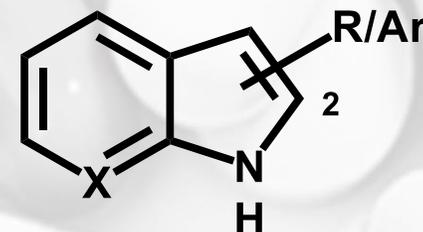
dasatinibe



2-aminotiazolas

dasatinibe

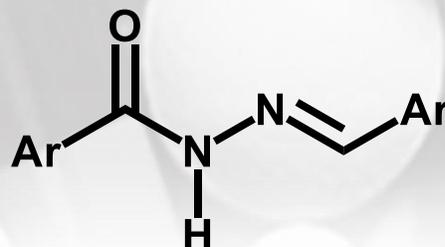
meloxicam



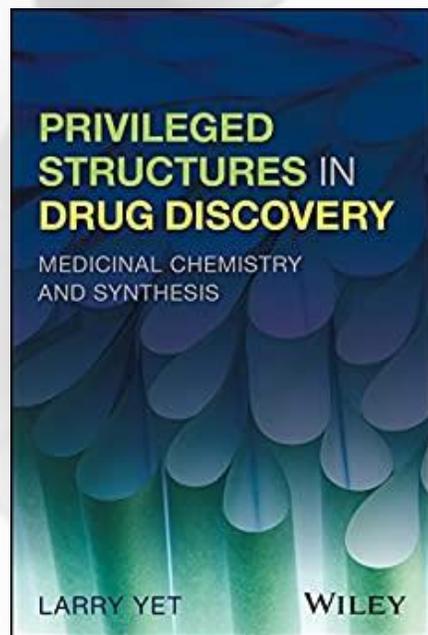
X=CH indol

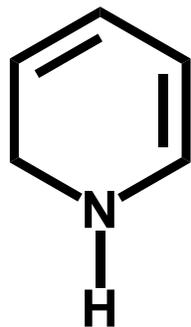
X=N 7-azaindol

1999

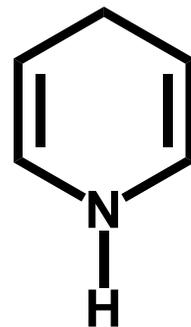


N-acilidrazona

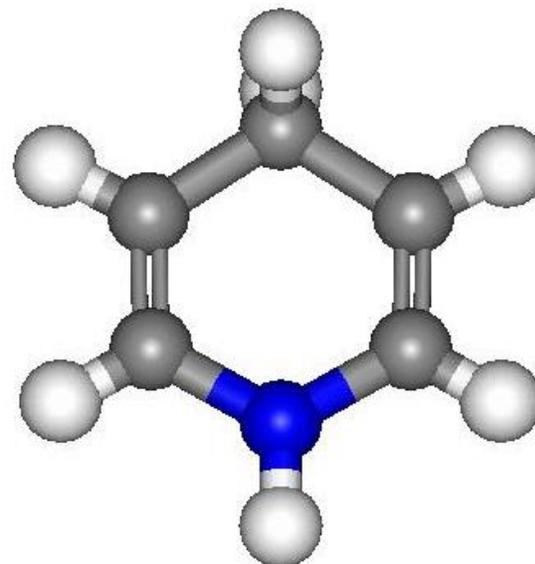
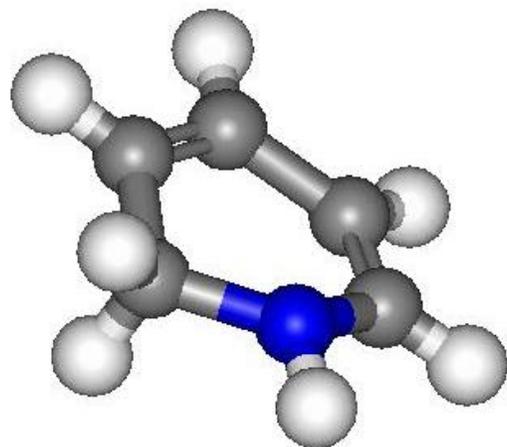




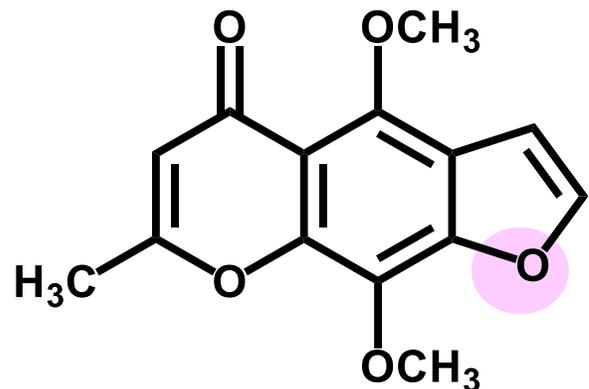
1,2-diidropiridine



1,4-diidropiridina



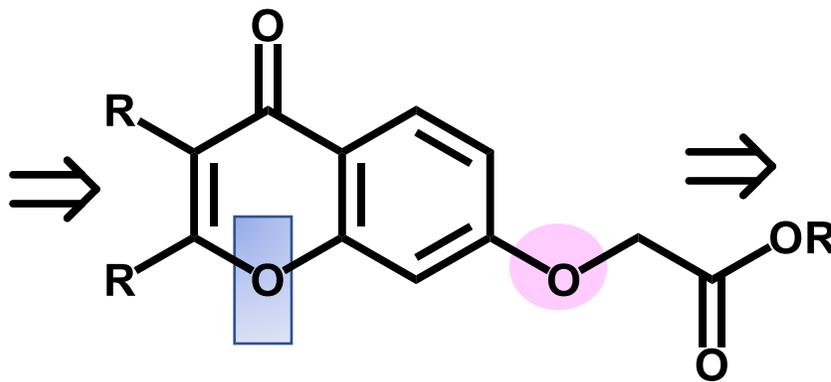
Gênese do sistema 1,4-diidropiridina



khelina

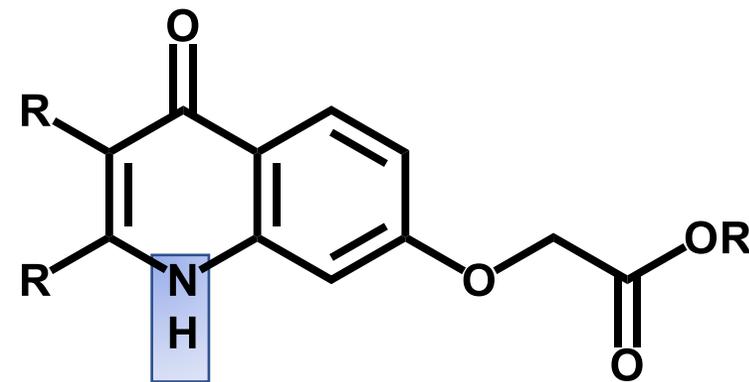
Furocromona natural

CP Hutterer, E Dale, *Chem.Rev.* 1951, 48, 543

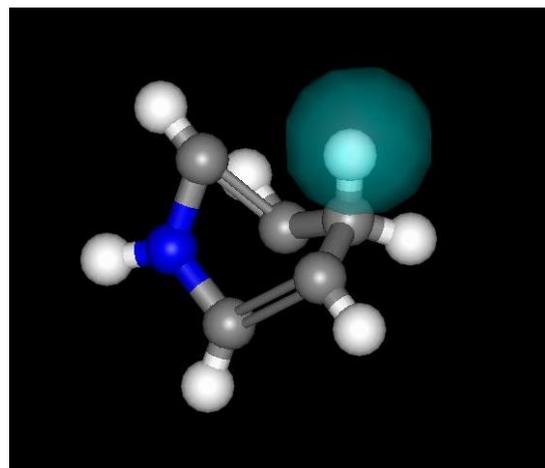


1950 - Bayer

1,4-diidropiridina



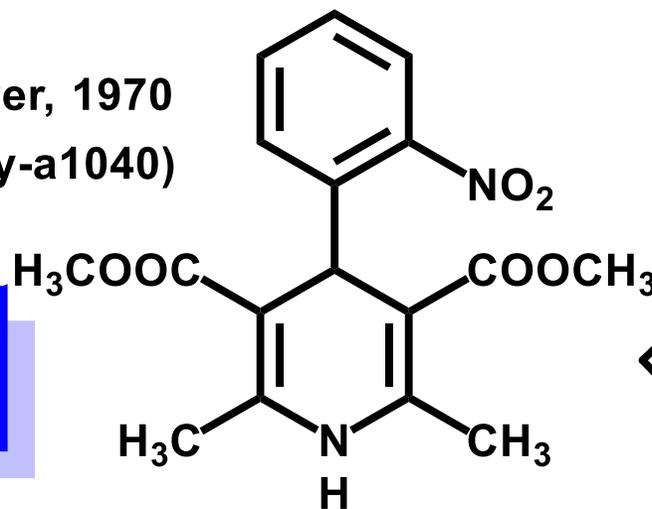
1970 - Bayer



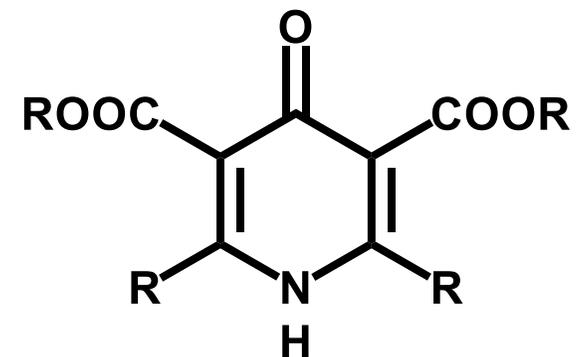
Conformação

Bayer, 1970
(Bay-a1040)

Adalat^R
1st-in-class



nifedipina



inativos



CCB

Produto Natural

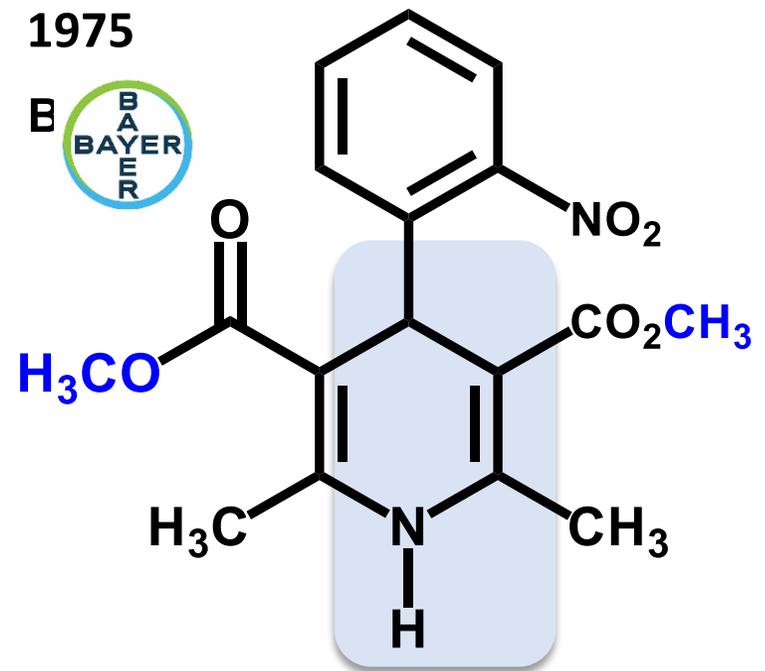
Composto Protótipo



Otimização



1975



nifedipina
1st in class



- Cilnidipine
- Felodipine
- Lacidipine
- Nilvadipine
- Nimodipine

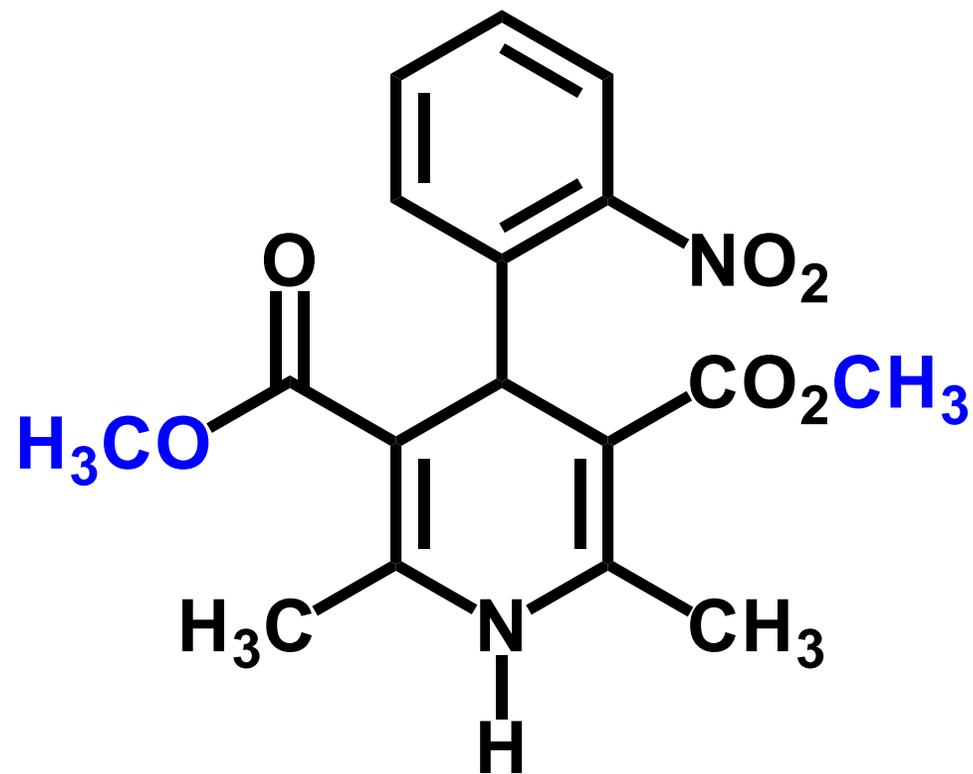


- Obesidade
- Hiperplasia prostática benigna (BPH)
- Glicoproteína-P

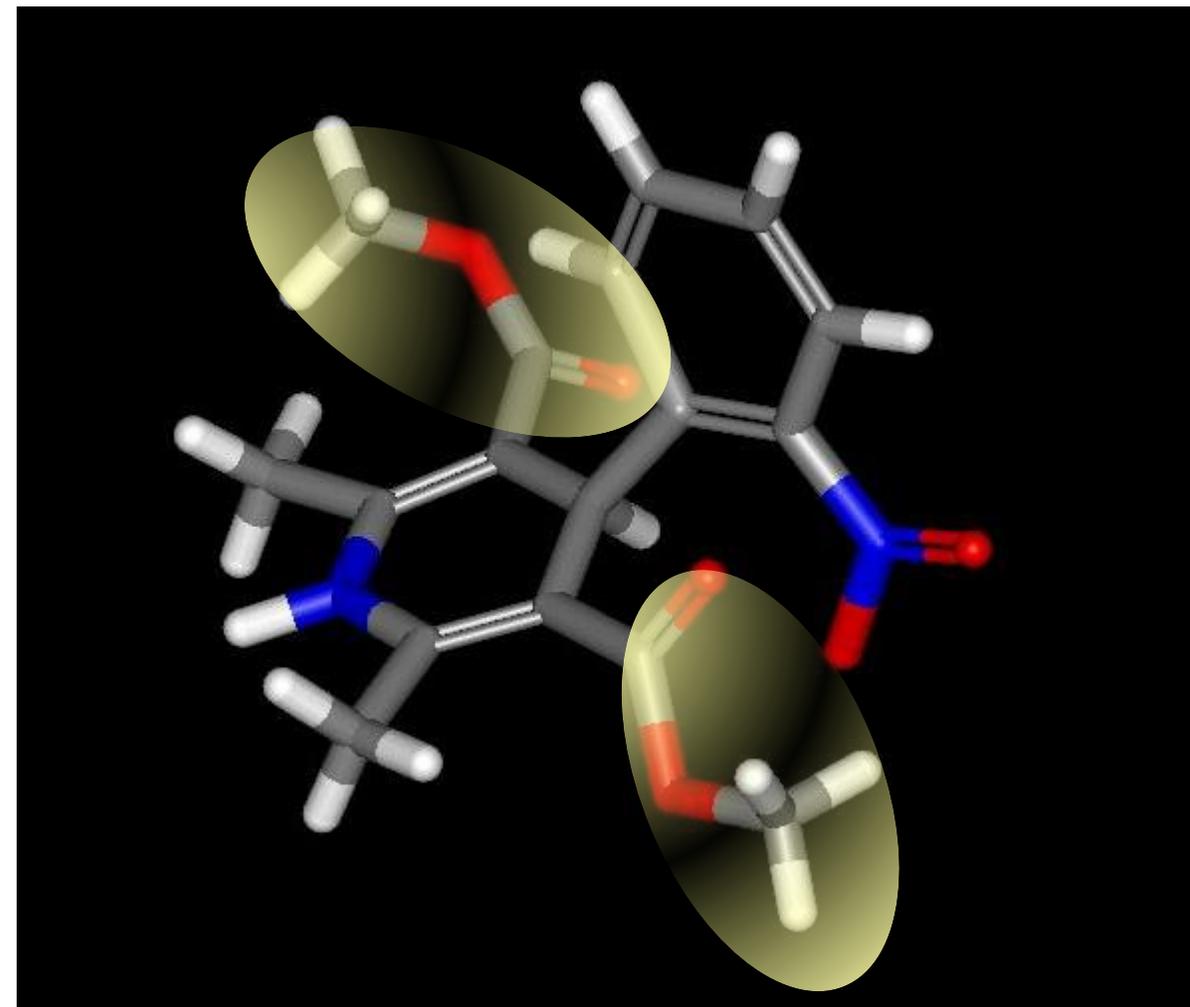
Conformação da nifedipina

Estereoquímica dinâmica

1975 – Bayer (1970)



nifedipina

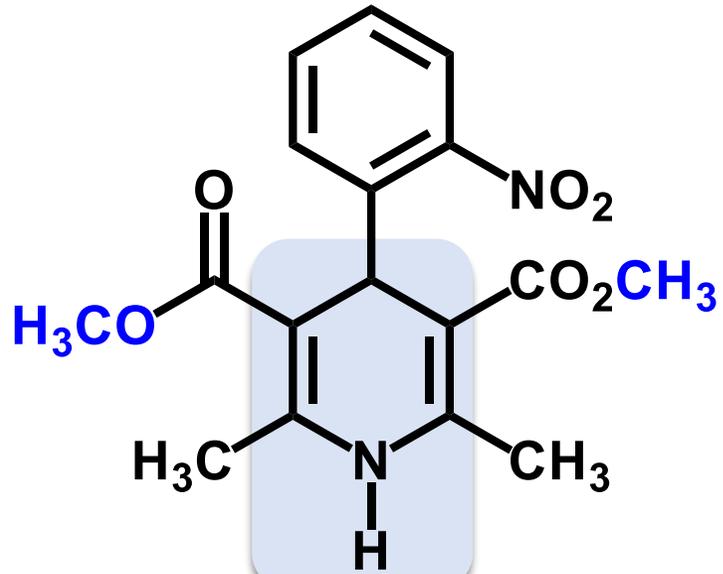


1981 - Bayer (CCB)

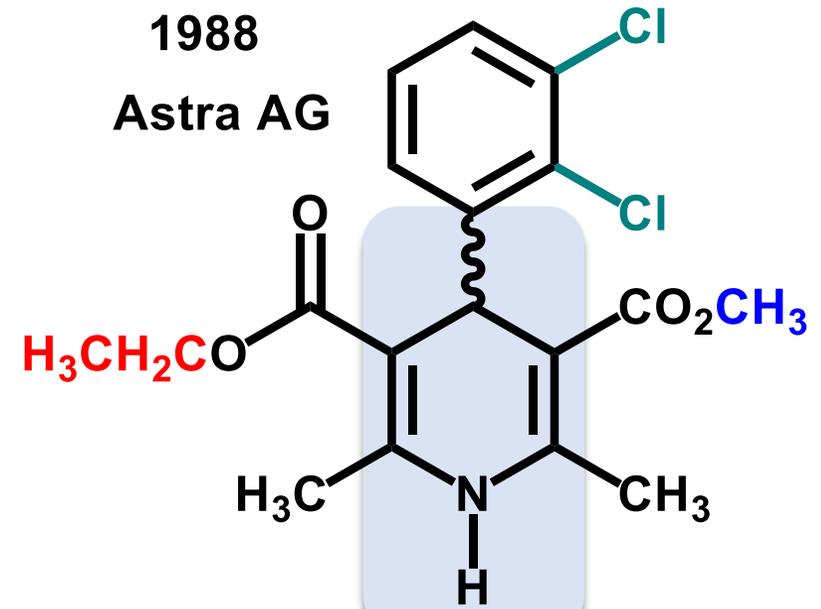
Ahmed G. Hegazy



1939-2021

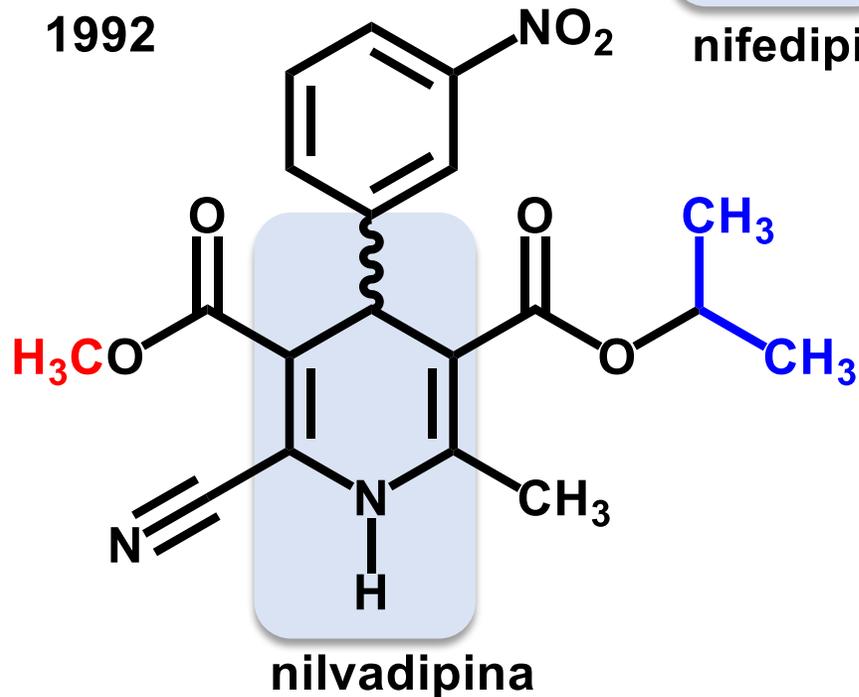


nifedipina

 1988
Astra AG


filodipina

1992



nilvadipina

1,4-diidropiridinas são exemplos clássicos da quiralidade no efeito farmacológico (ésteres distintos)

A quiralidade e os fármacos

Reconhecimento molecular

Methods and Principles in Medicinal Chemistry

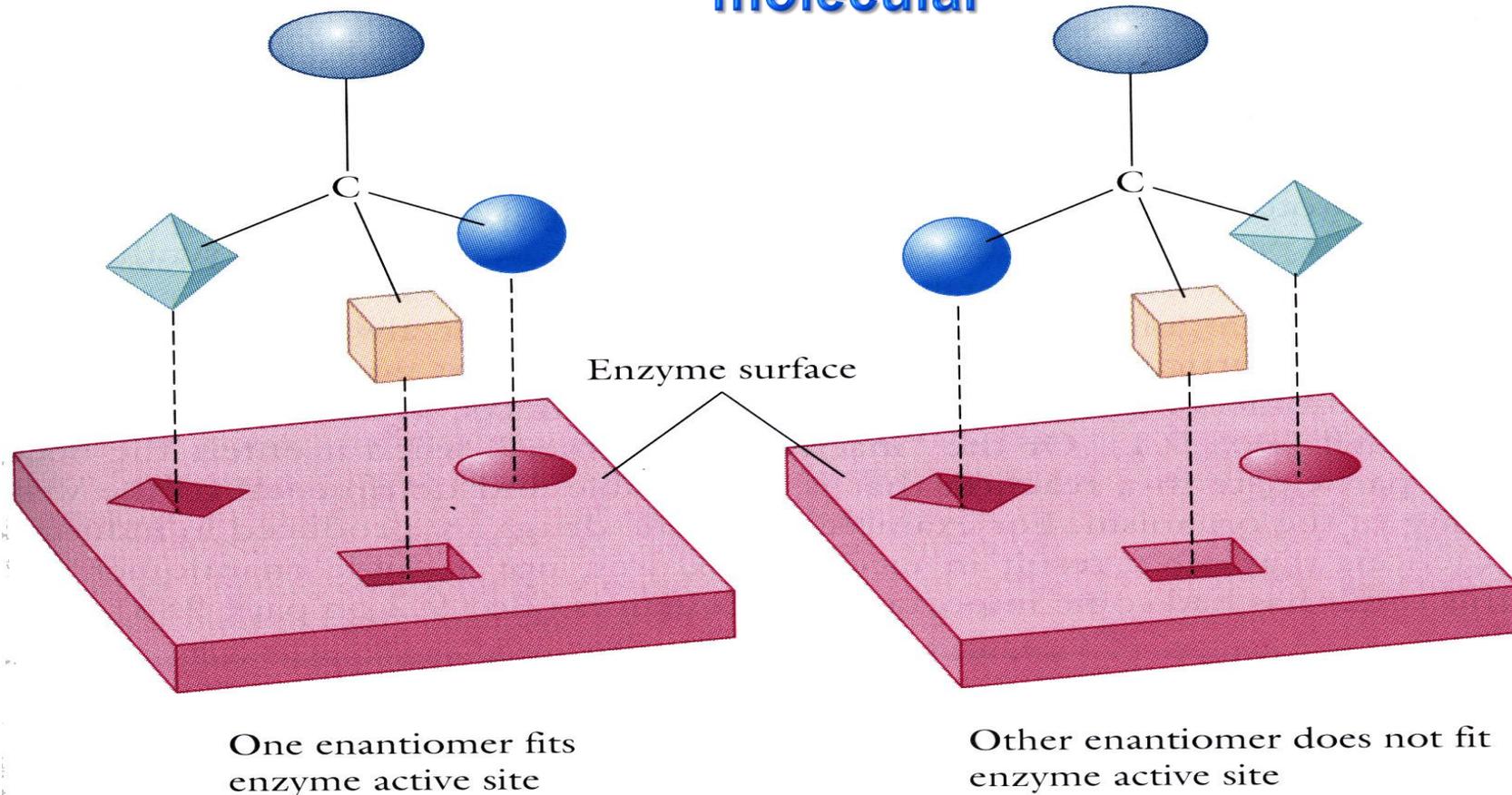
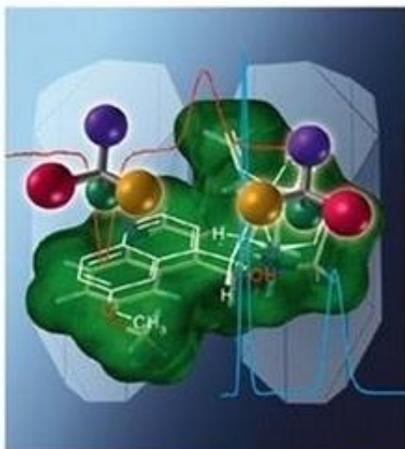
Edited by
Eric Francotte and Wolfgang Lindner

WILEY-VCH

Chirality in Drug Research

Volume 33

Series Editors:
R. Mannhold,
H. Kubinyi,
G. Folkers

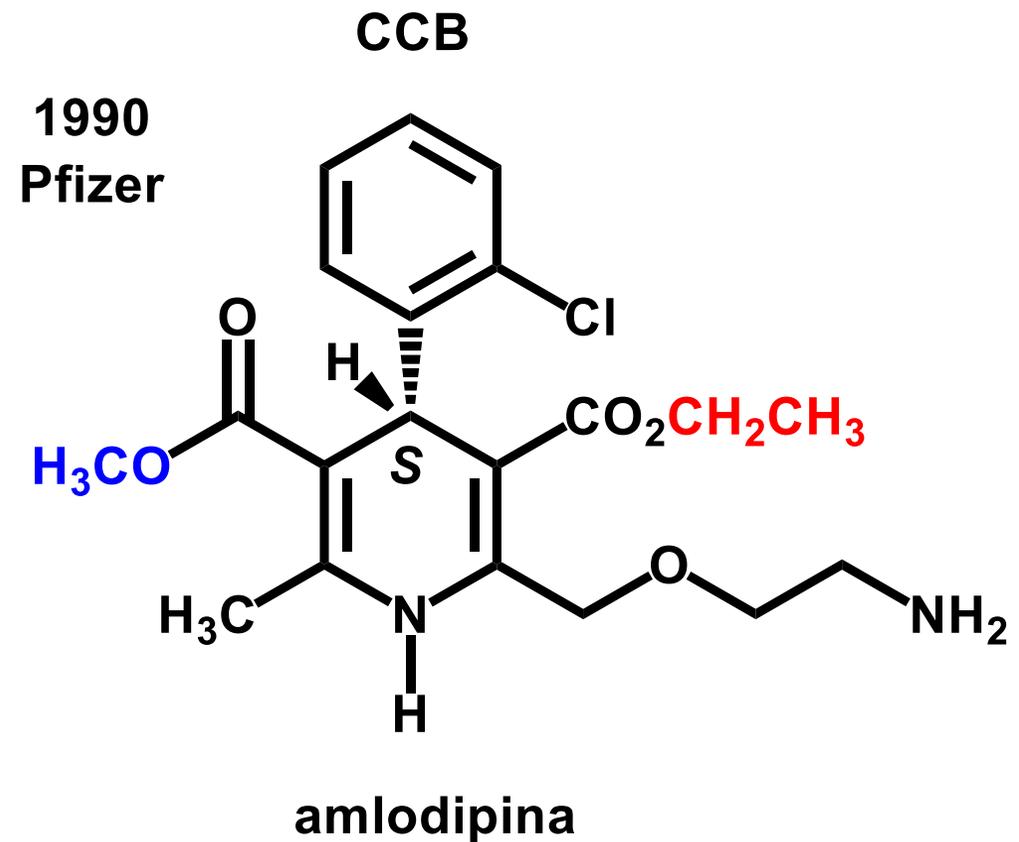
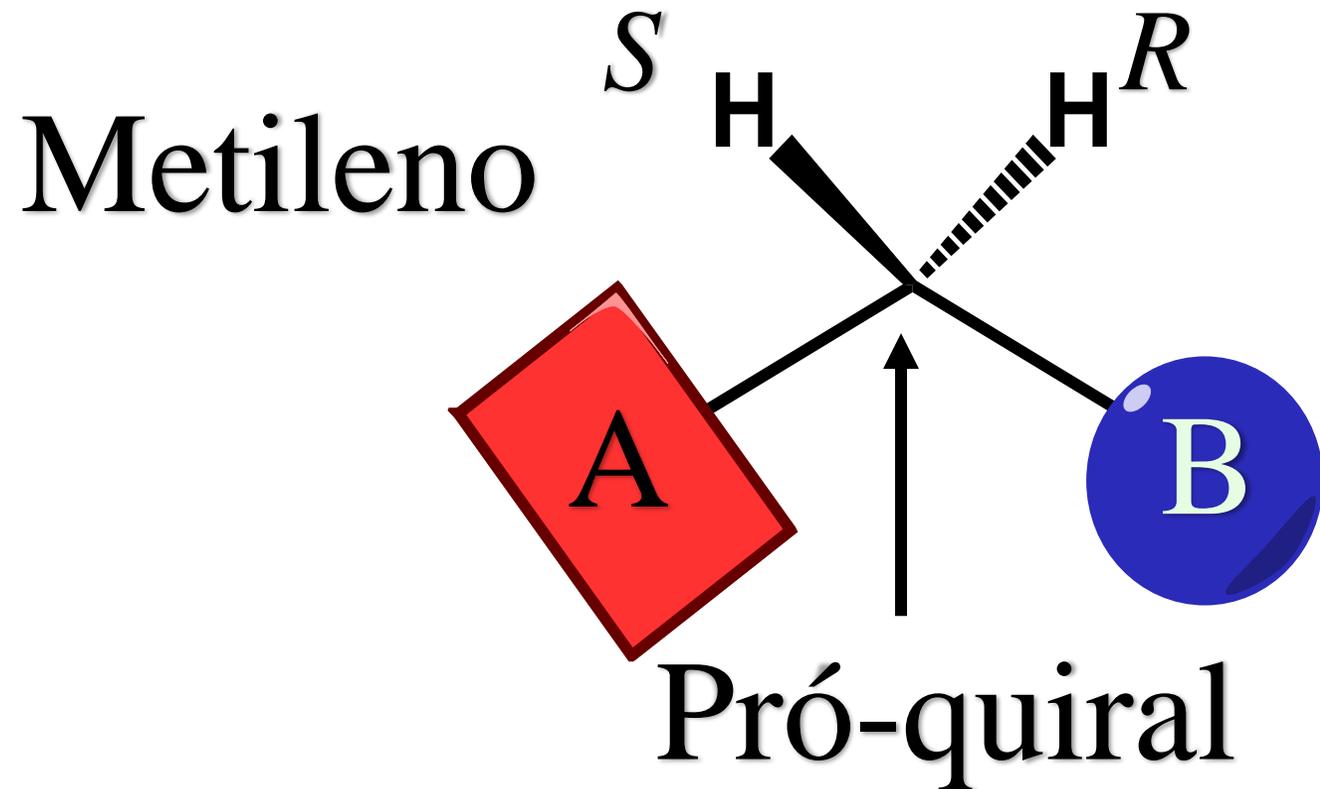


Modelo dos três pontos

Modelo de Easson-Stedman

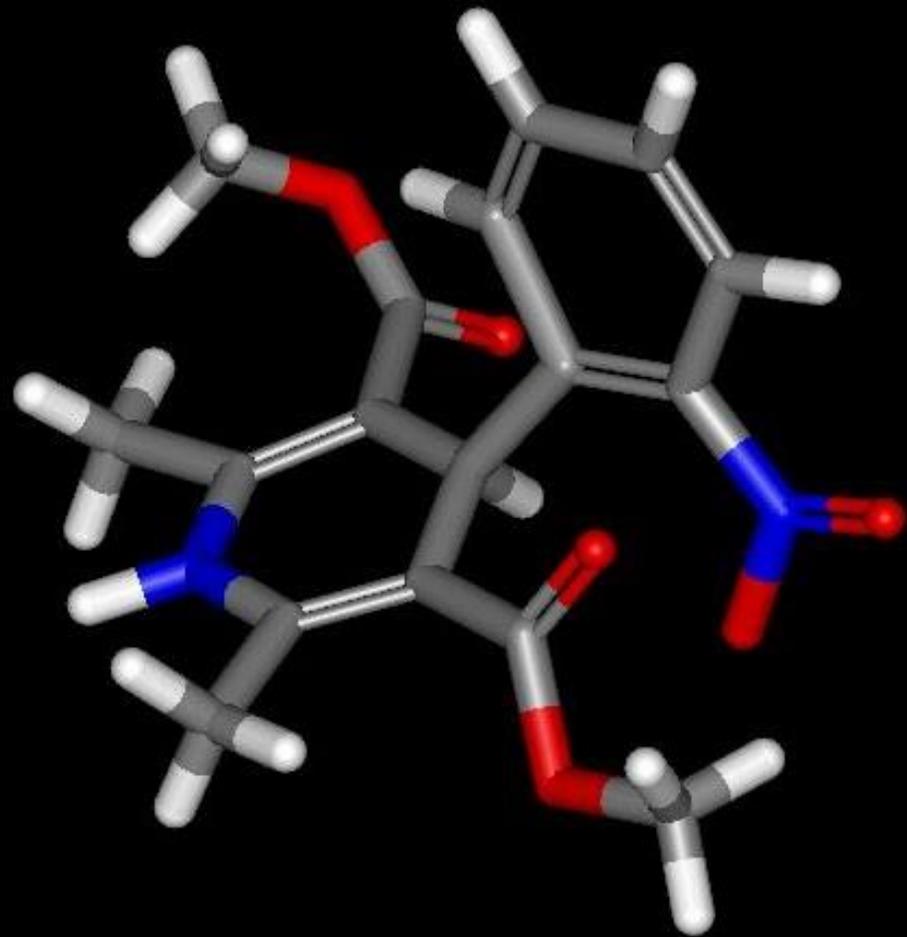
Efeito da configuração

Estereoquímica estática

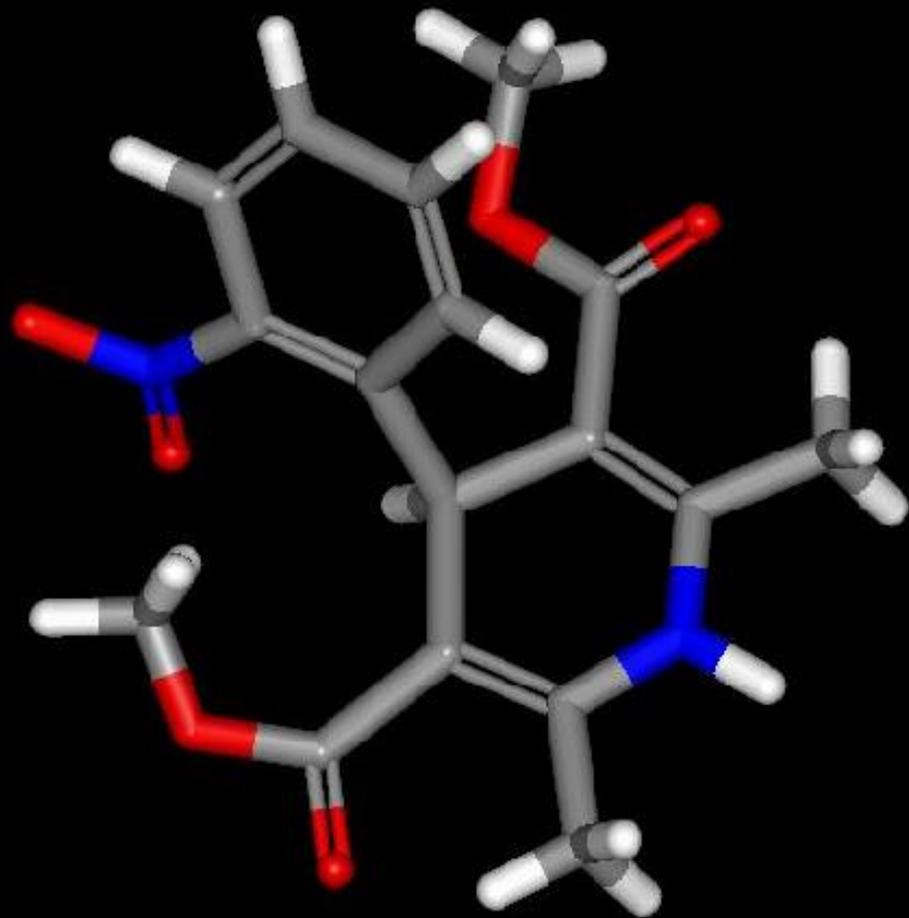


Eutômero / Distômero

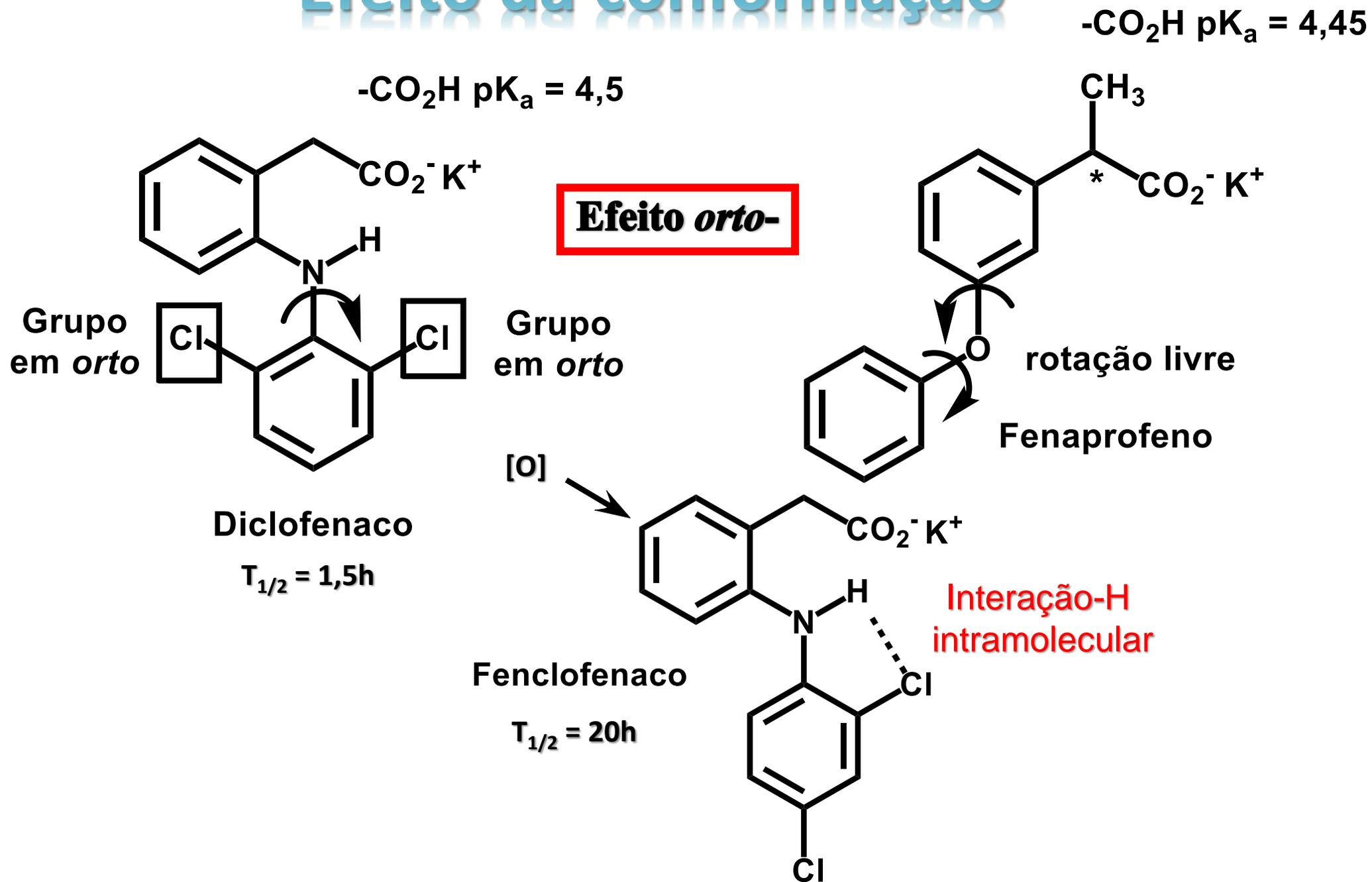




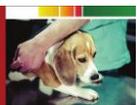
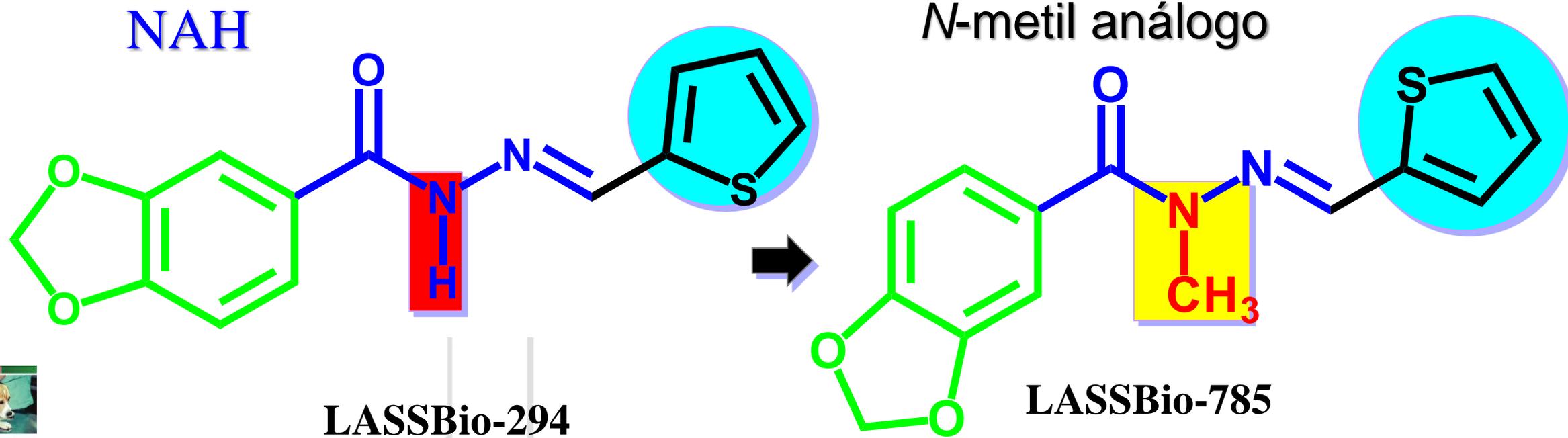
espelho



Efeito da conformação



Efeito conformacional



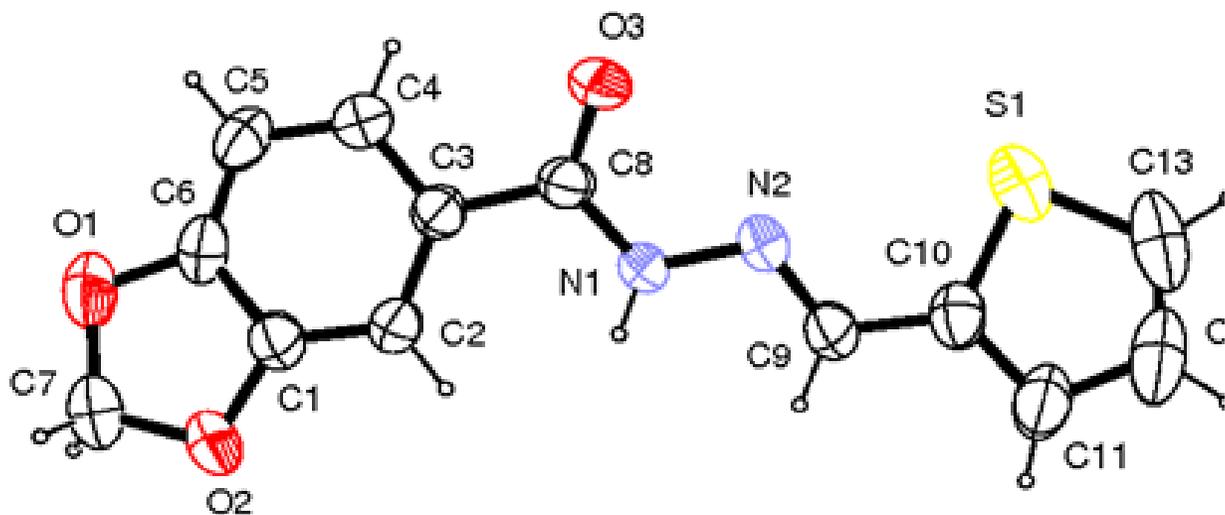
Ação do protótipo anti-hipertensivo LASSBio 897

*D. D. Viveiros, Efeito do derivado *N*-acilidrazônico LASSBio-897 sobre a resposta inflamatória pulmonar na asma e silicose experimentais, Tese Doutor (Biologia Celular e Molecular) – FIOCRUZ, IOC, Rio de Janeiro, RJ, **2014**;

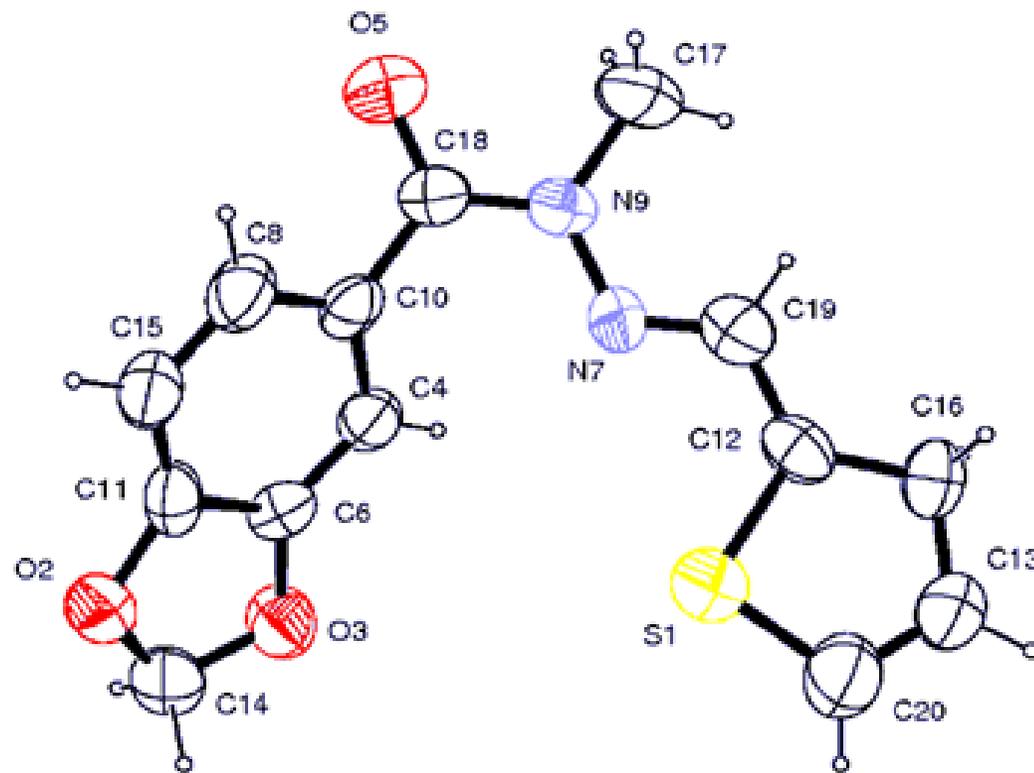
*P R Nasciutti, R Oliveira, E J Barreiro, Efeitos do LASSBio-897 sobre o sistema cardiovascular de cães hípidos da raça Beagle, Novas Edições Acadêmicas, **2016**, ISBN 978-3-330-73277-3;

&G Zapata-Sudo et al., *Am J. Hypertens.* **2010**, 23, 135; GAP Silva et al., *Braz. J. Med. Biol. Res.* **2013**, 46, 263; E B Marques et al., *Int. J. Cardiol.* **2015**, 201, 282.

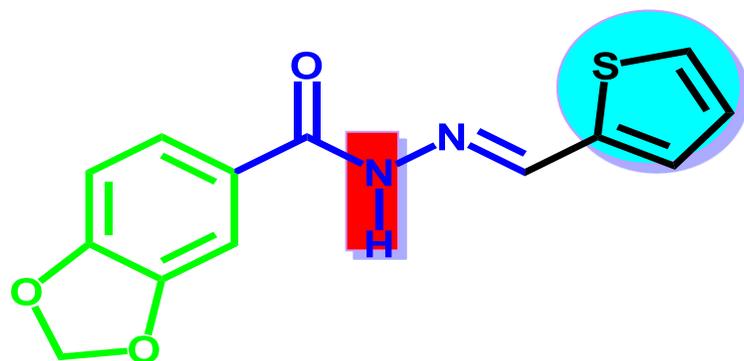
Difração de raios-X



LASSBio-294

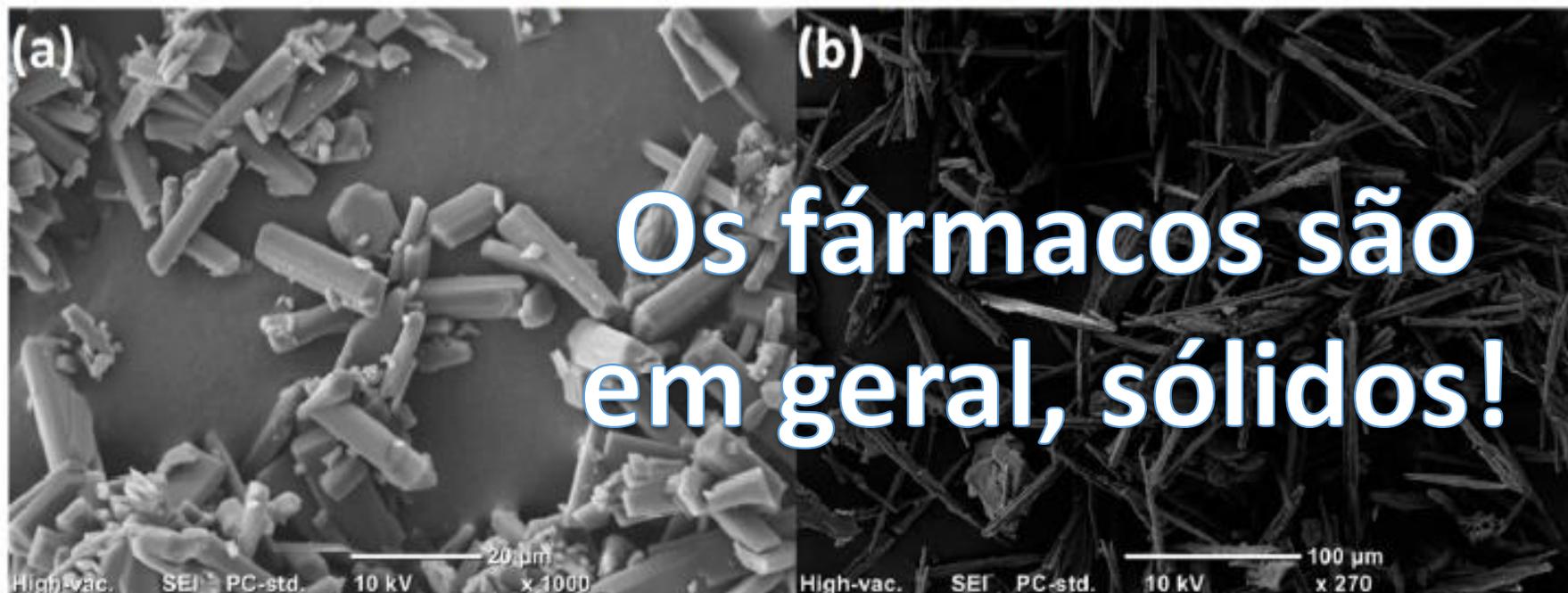


LASSBio-785

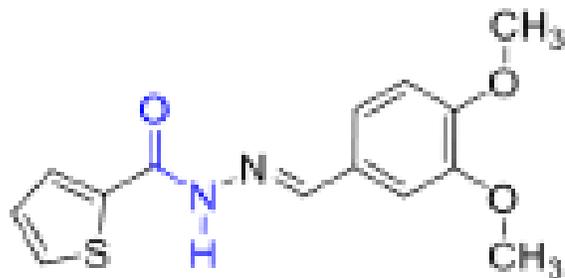


Conformação & solubilidade

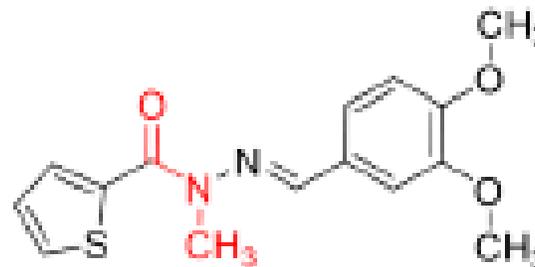
Scanning electron microscopy (SEM) image



Os fármacos são em geral, sólidos!



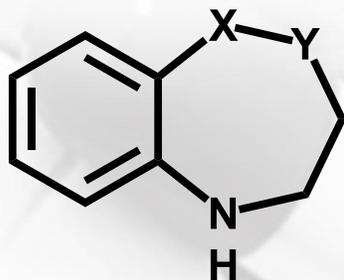
LASSBio-1834



LASSBio-1835



1950



X=CH₂ Y=NH - 1,4-benzodiazepinas

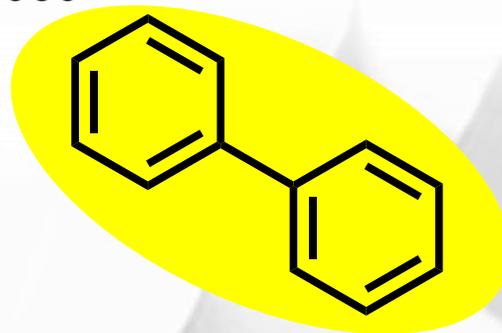
X=NH Y=CH₂ - 1,5-benzodiazepinas

1982



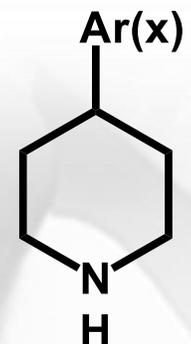
1,4-diidropiridinas

1986



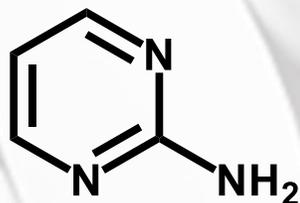
Bifenila

1958



4-arilpiperidinas

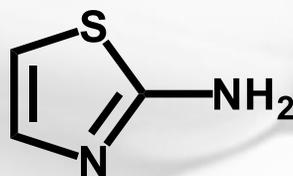
4-heteroarilpiperidinas



2-aminopirimidinas

crizotinibe

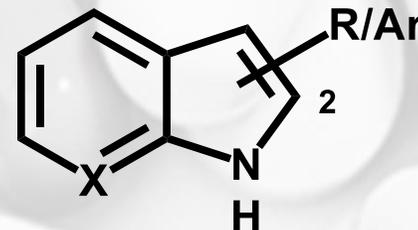
dasatinibe



2-aminotiazolas

dasatinibe

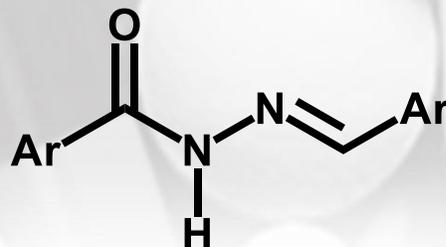
meloxicam



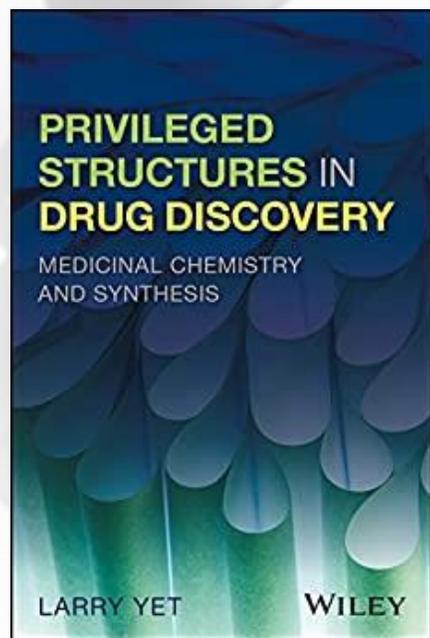
X=CH indol

X=N 7-azaindol

1999



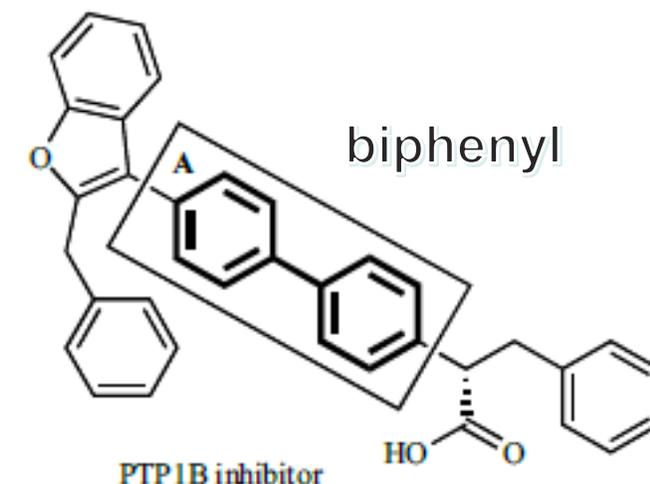
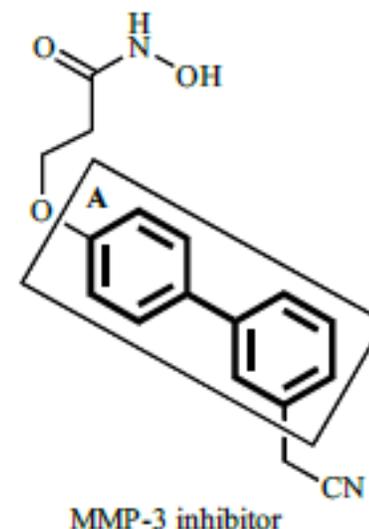
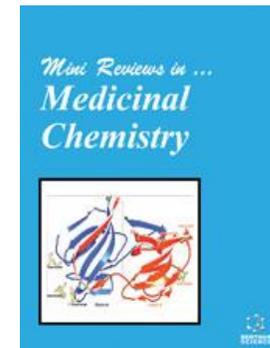
N-acilidrazona



Privileged Structures: A Useful Concept for the Rational Design of New Lead Drug Candidates

Carolina D. Duarte, Eliezer J. Barreiro and Carlos A.M. Fraga*

Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio, <http://www.farmacia.ufrj.br/lassbio>), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, P.O. Box 68023, ZIP 21944-971, Rio de Janeiro, RJ, Brazil



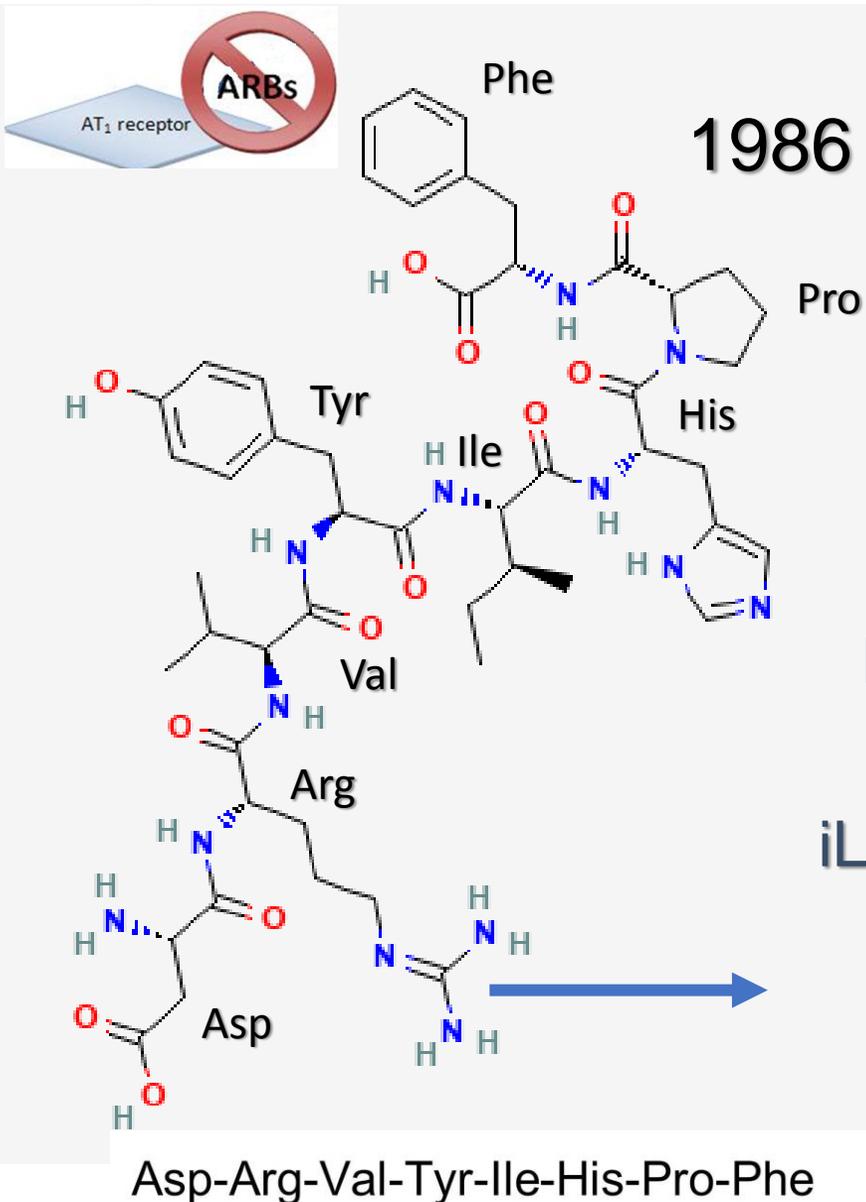
D. M Schnur, M. A. Hermsmeier, A. J. Tebben, *J. Med. Chem.*, 2006, 49, 2000

Sub-Structures	Ligands				
	GPCRs ^a	Ionic Channels	NHR ^b	Kinase-Proteins	Serine-Proteases
GPCRs	-	26	10	11	17

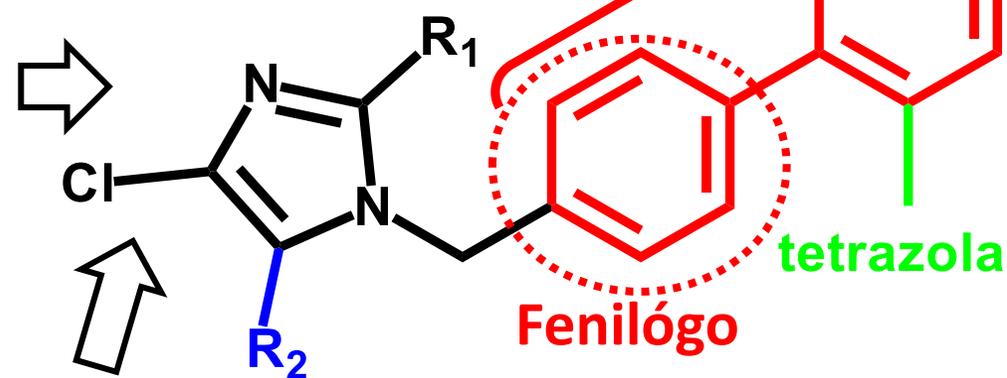
B E Evans, et al. *J Med Chem*, 1988, 31, 2235; AA Patchett, R P Nargund, *Annu Rep Med Chem*, 2000, 35, 289.

Angiotensina-II

SBDD

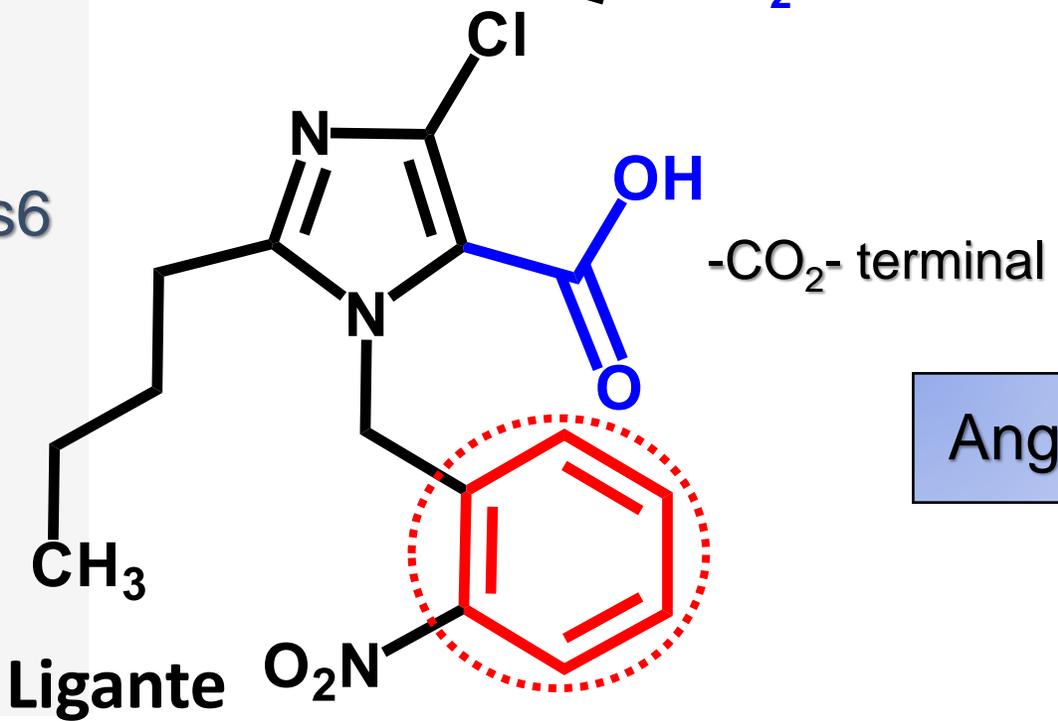


John Duncia
David Carini



His6

iLe



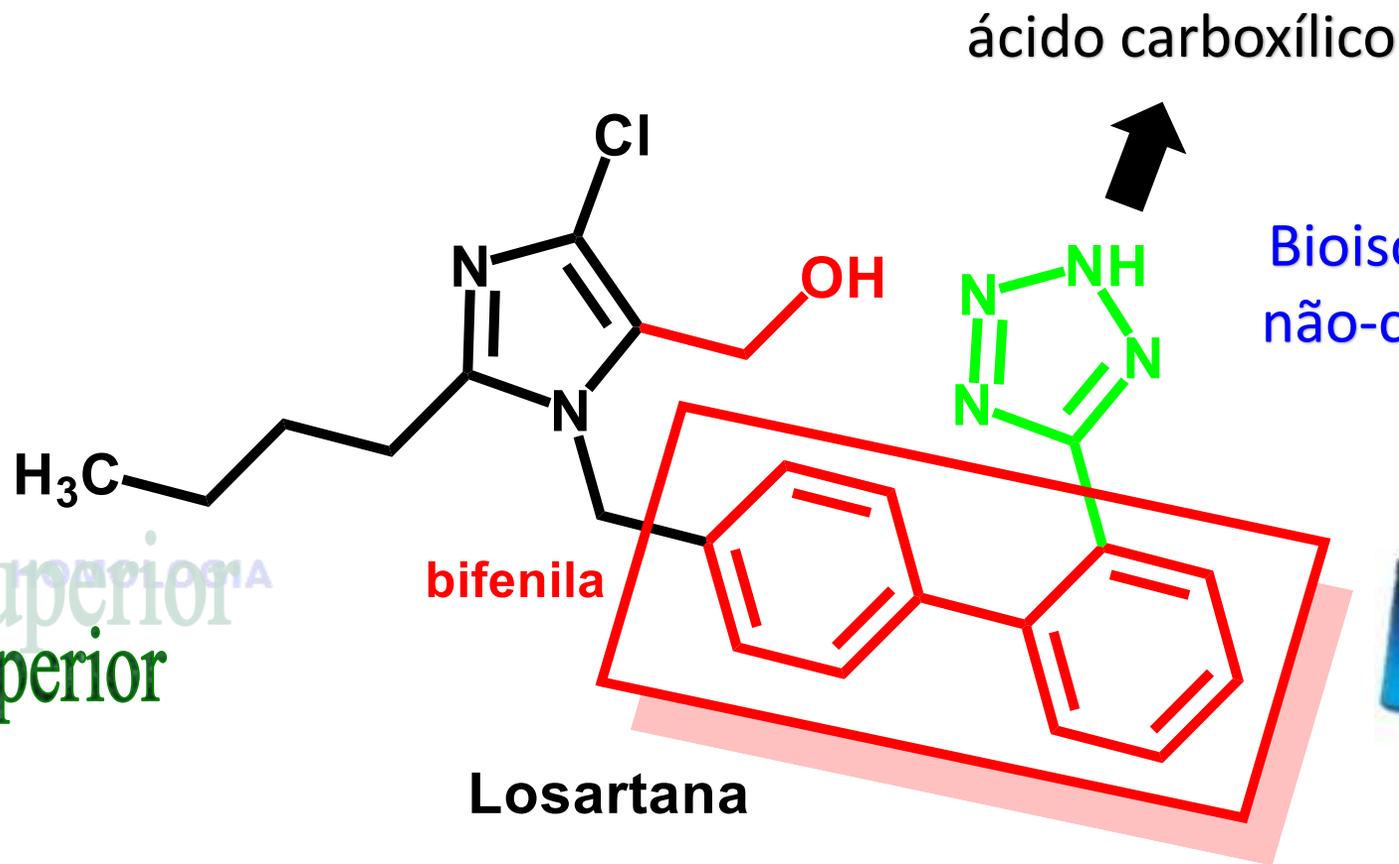
Angiotensina-II

S-8308



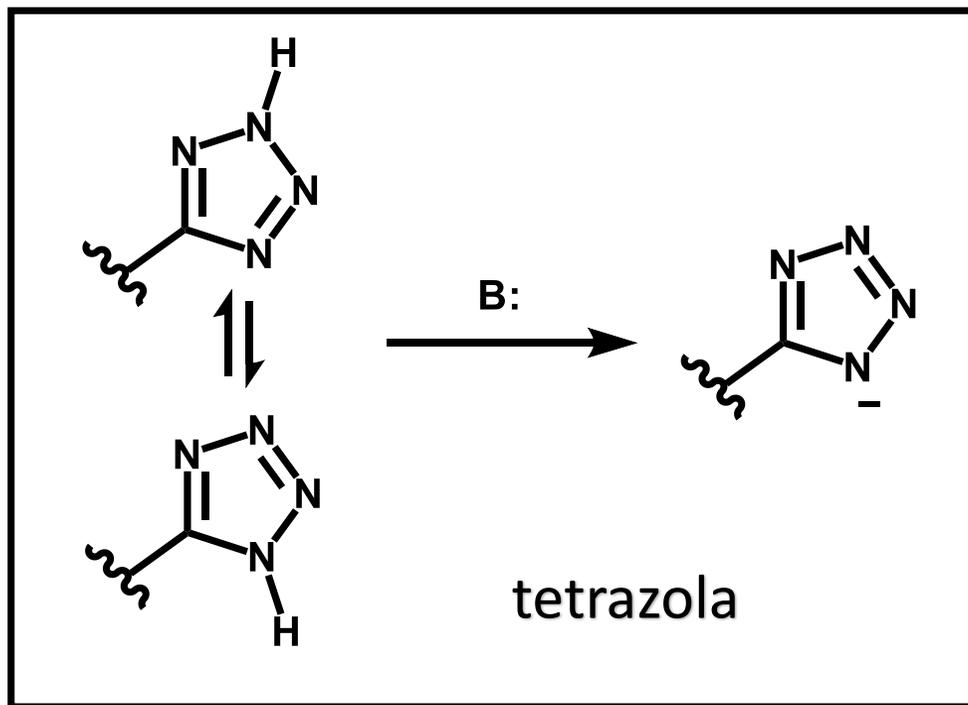
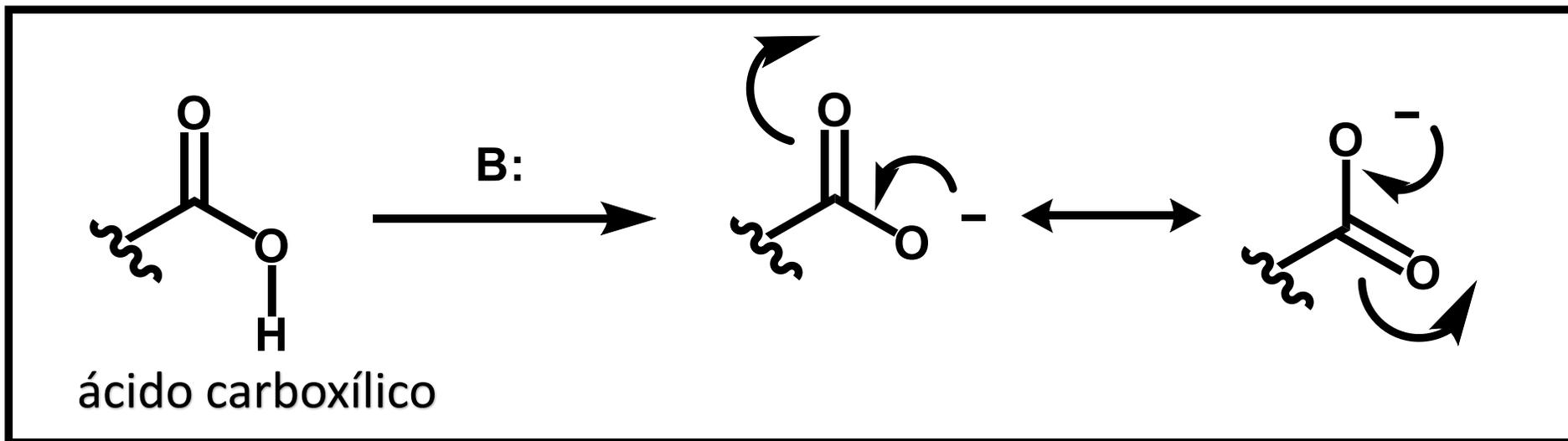


1986

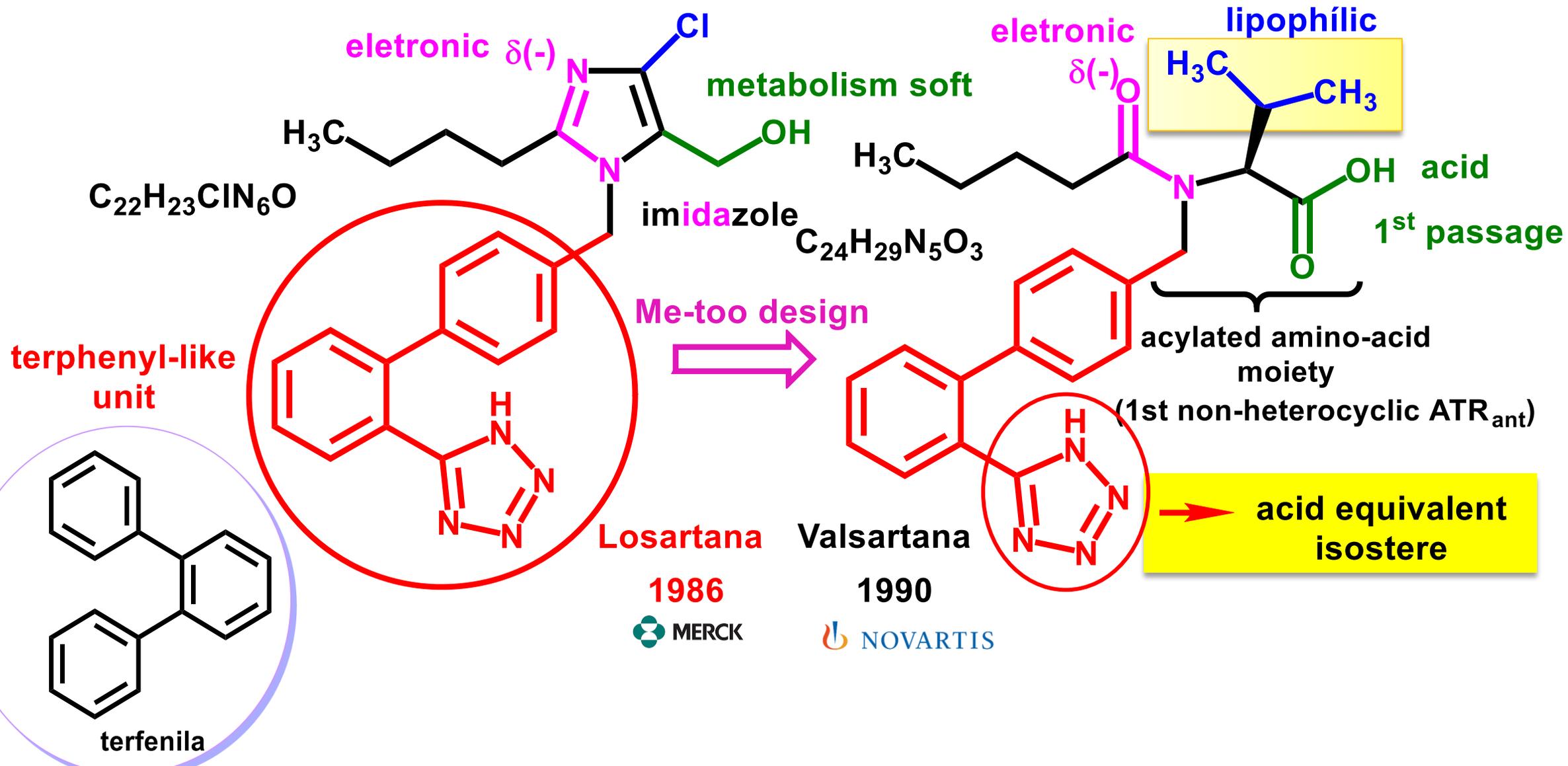


Homólogo superior
 Homólogo superior

primeiro agonista não-peptídico de AT₁R



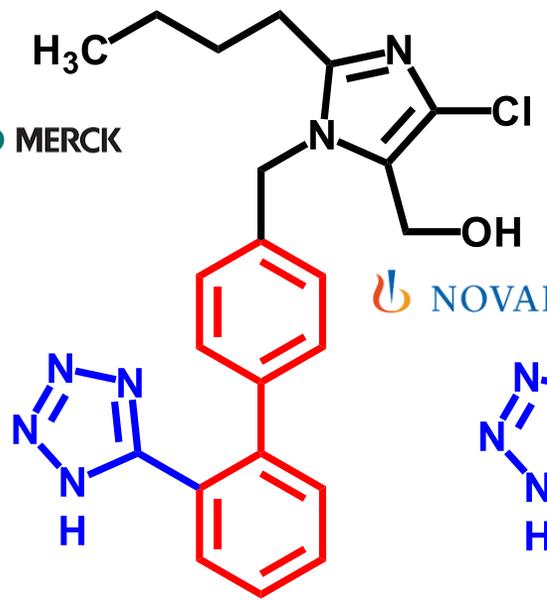
Me-too drug design





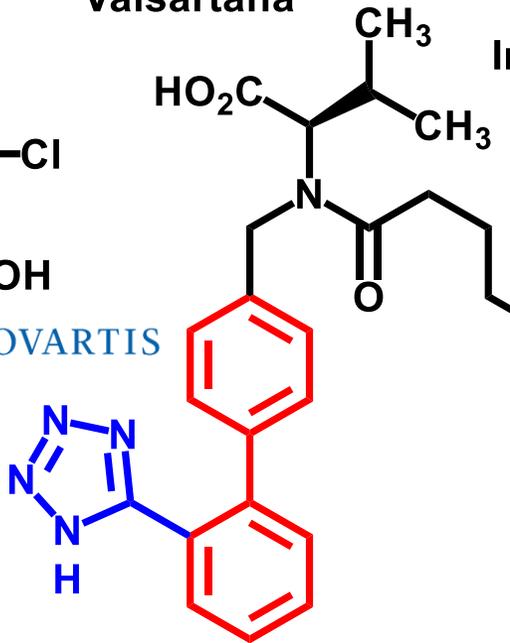
Losartana

MERCK

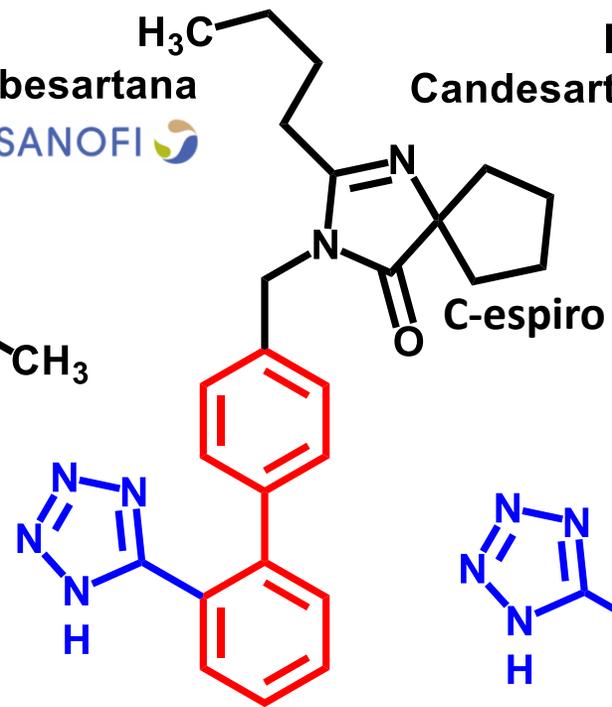


Valsartana

NOVARTIS

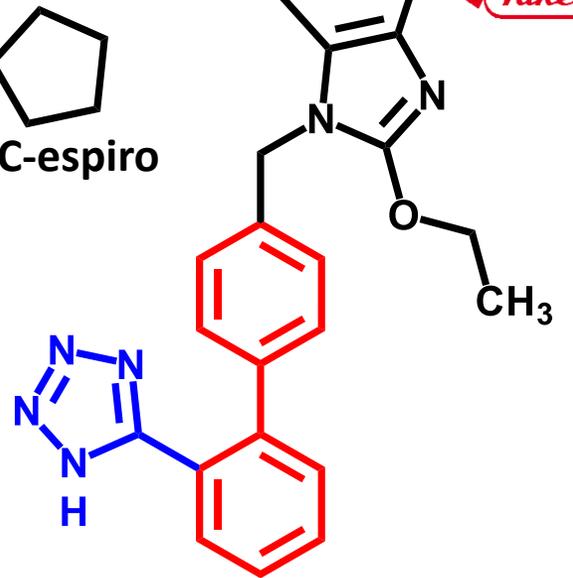


Irbesartana
SANOFI



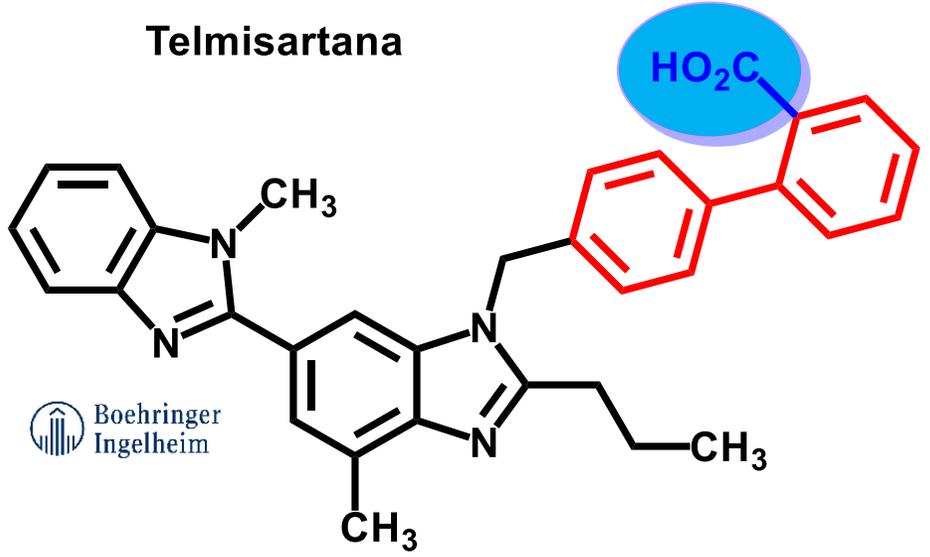
Candesartana

Takeda



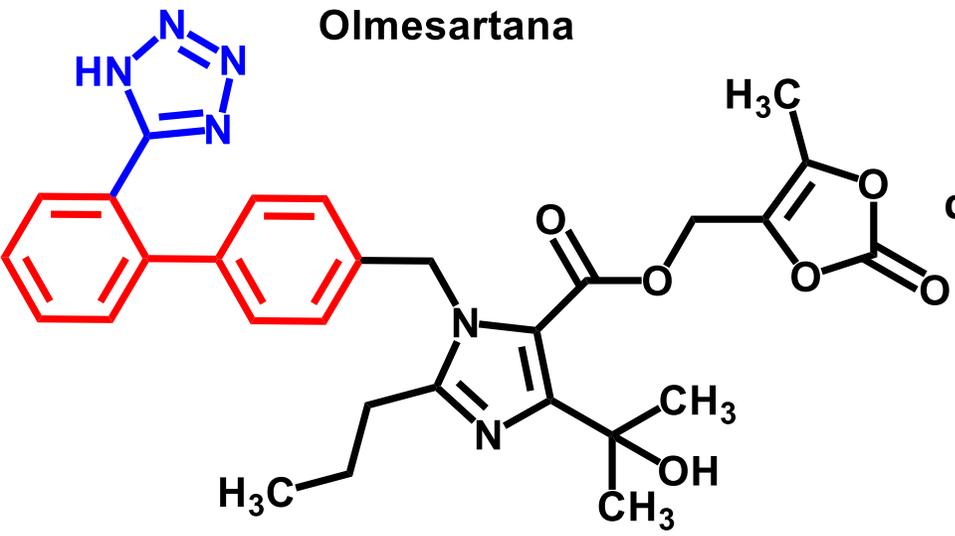
Telmisartana

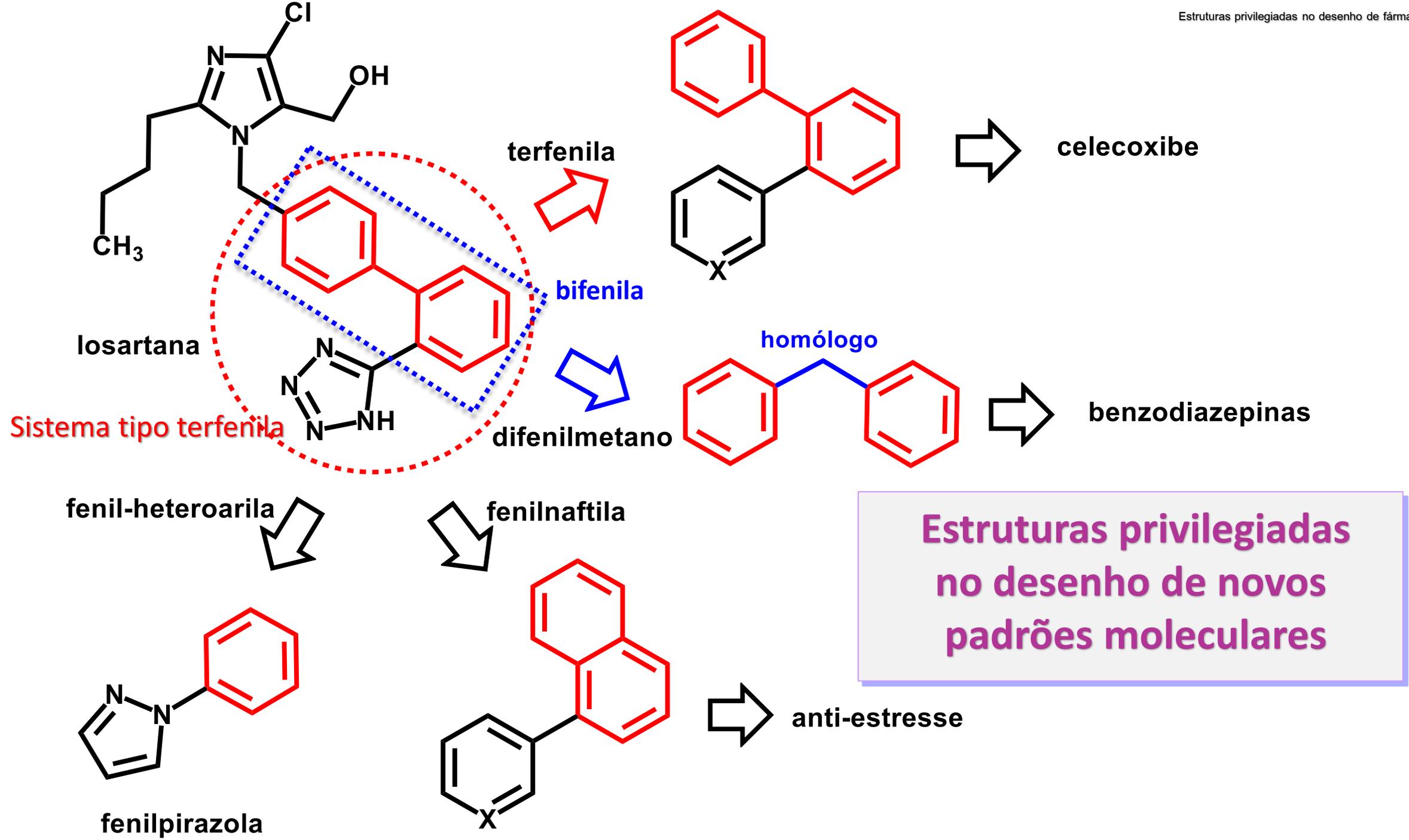
Boehringer
Ingelheim



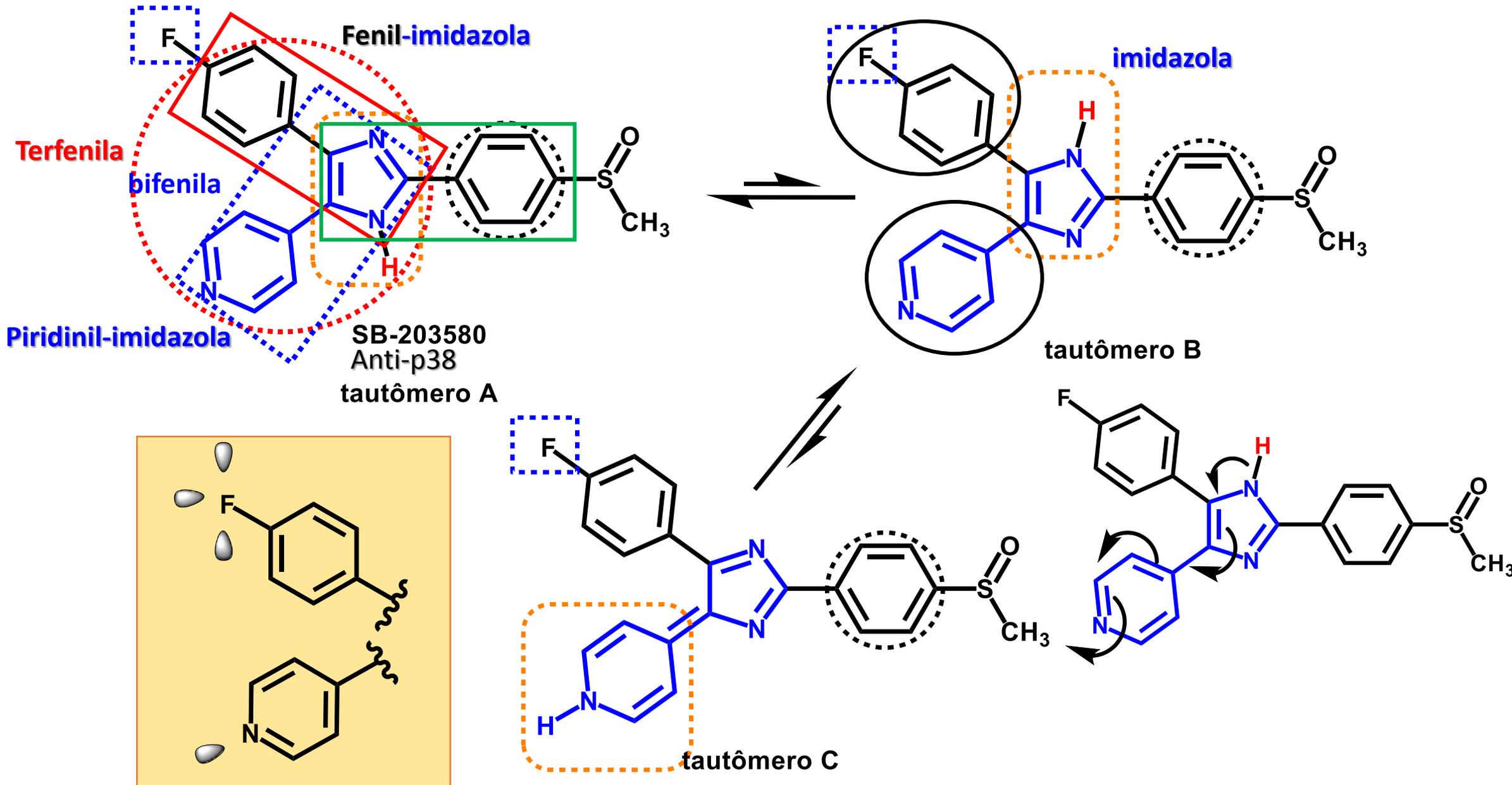
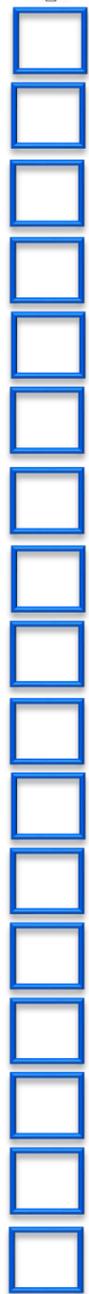
Olmesartana

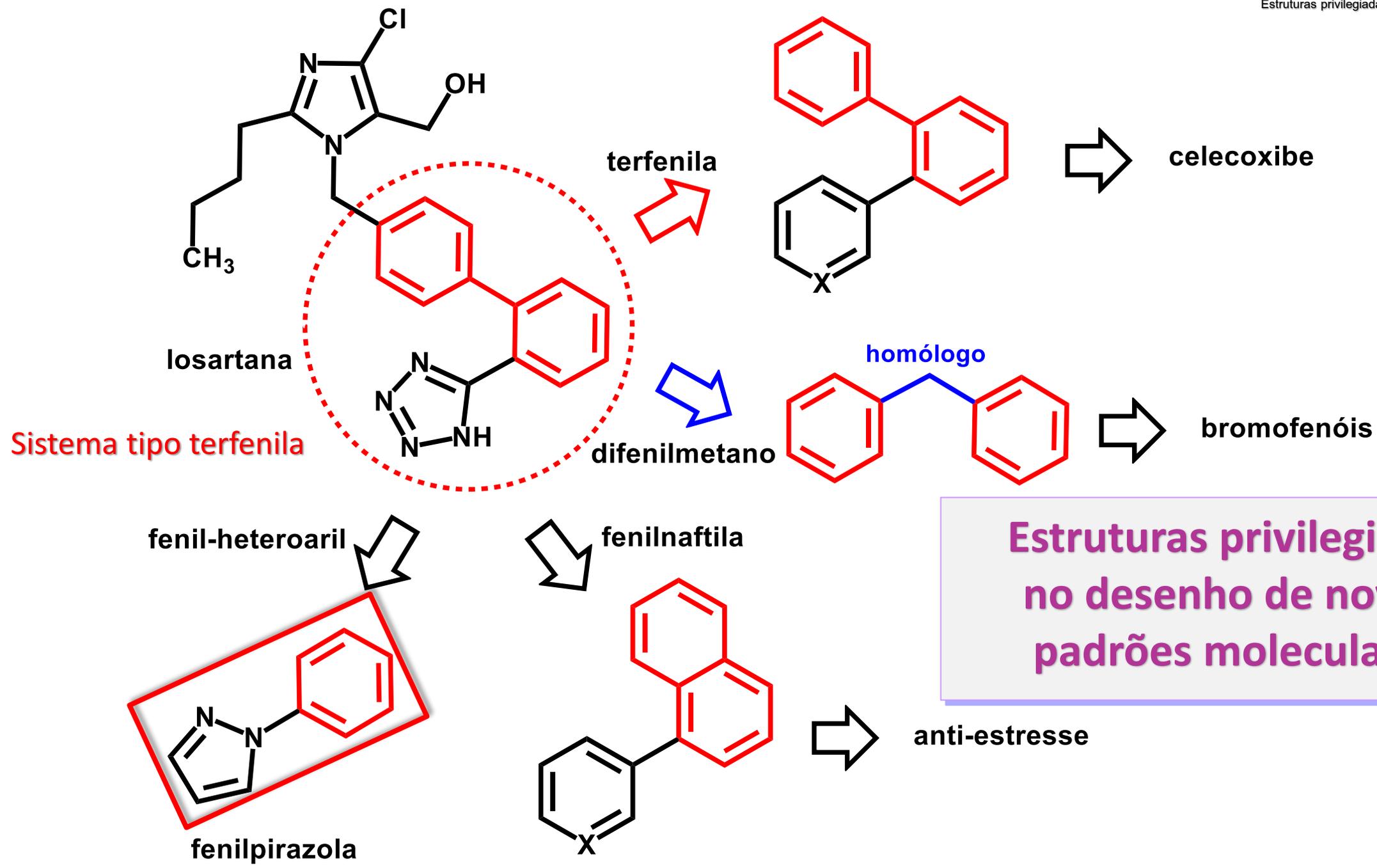
carbonato
Daiichi-Sankyo



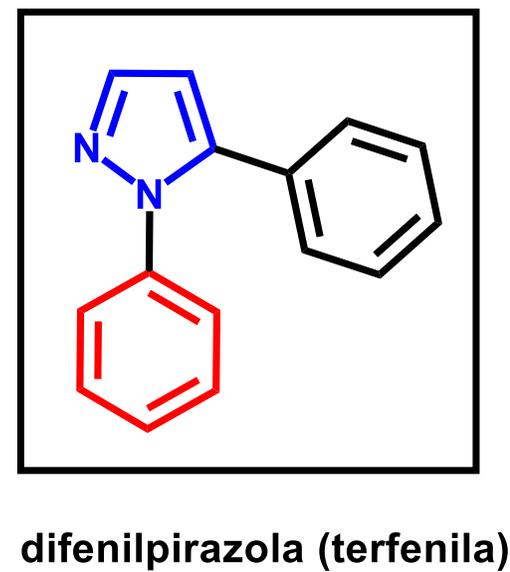
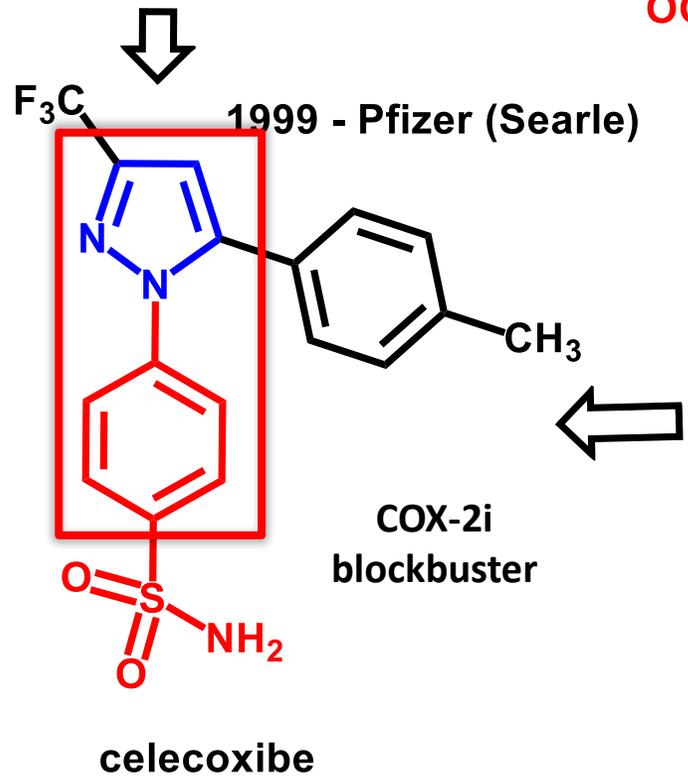
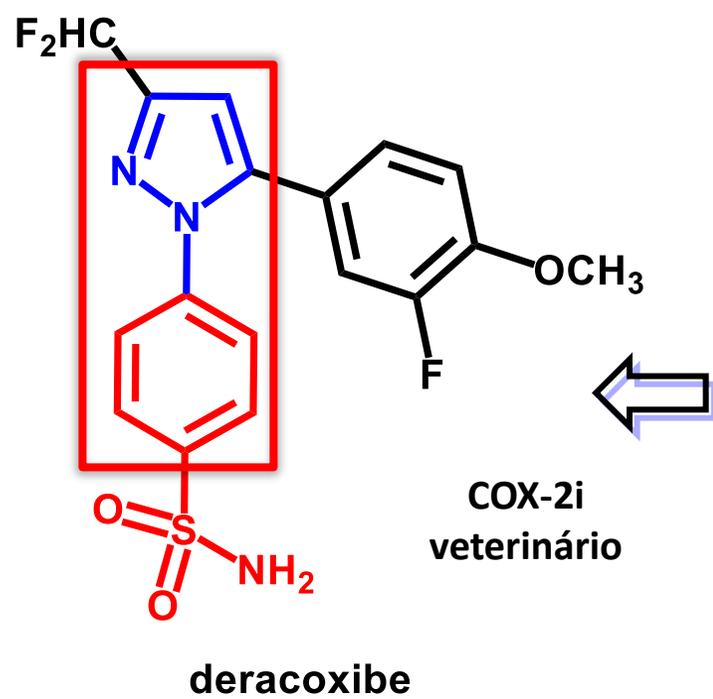
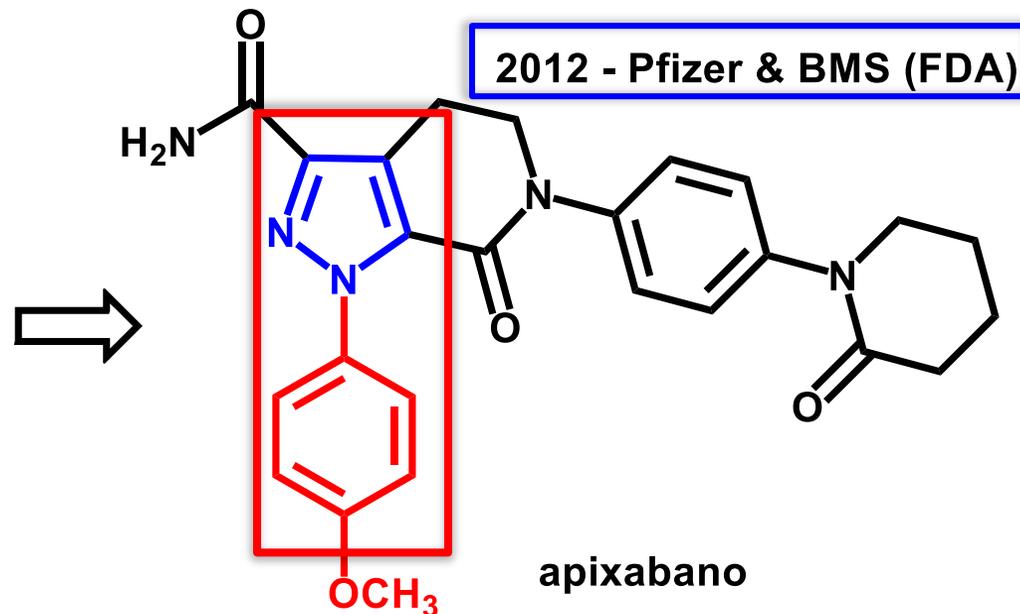
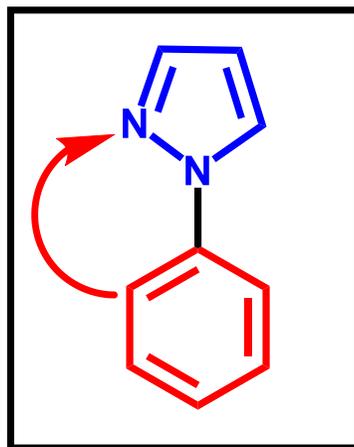
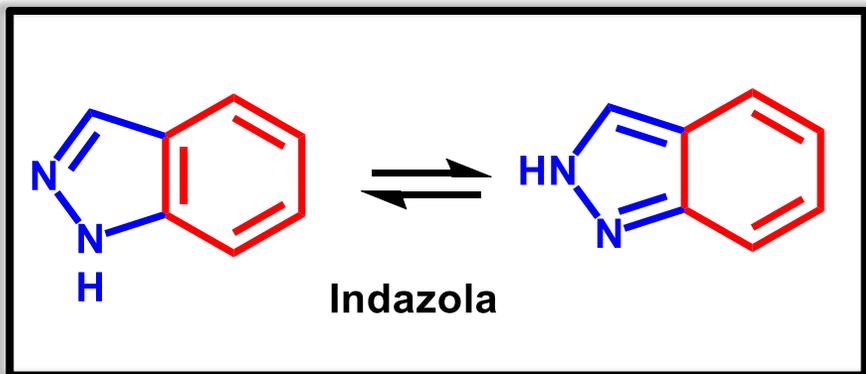


Prototropia aza-heterociclos & amino-heterociclos



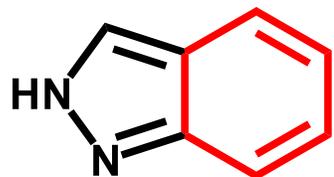


**Estruturas privilegiadas
no desenho de novos
padrões moleculares**



Estruturas privilegiadas no desenho de novos padrões moleculares

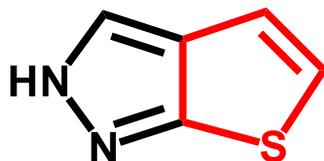
Indazola



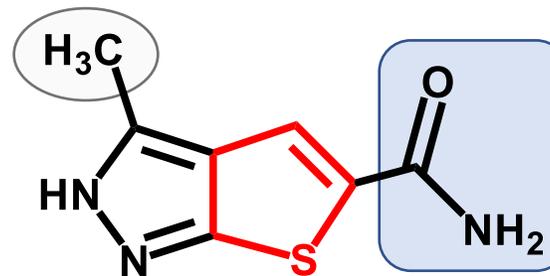
Sci Finder 2043 patentes
220 kinases pat

isósteros

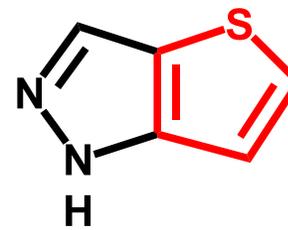
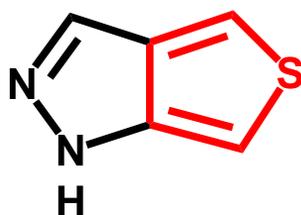
Tieno-pirazola



Sci Finder 20 patentes
15 kinases



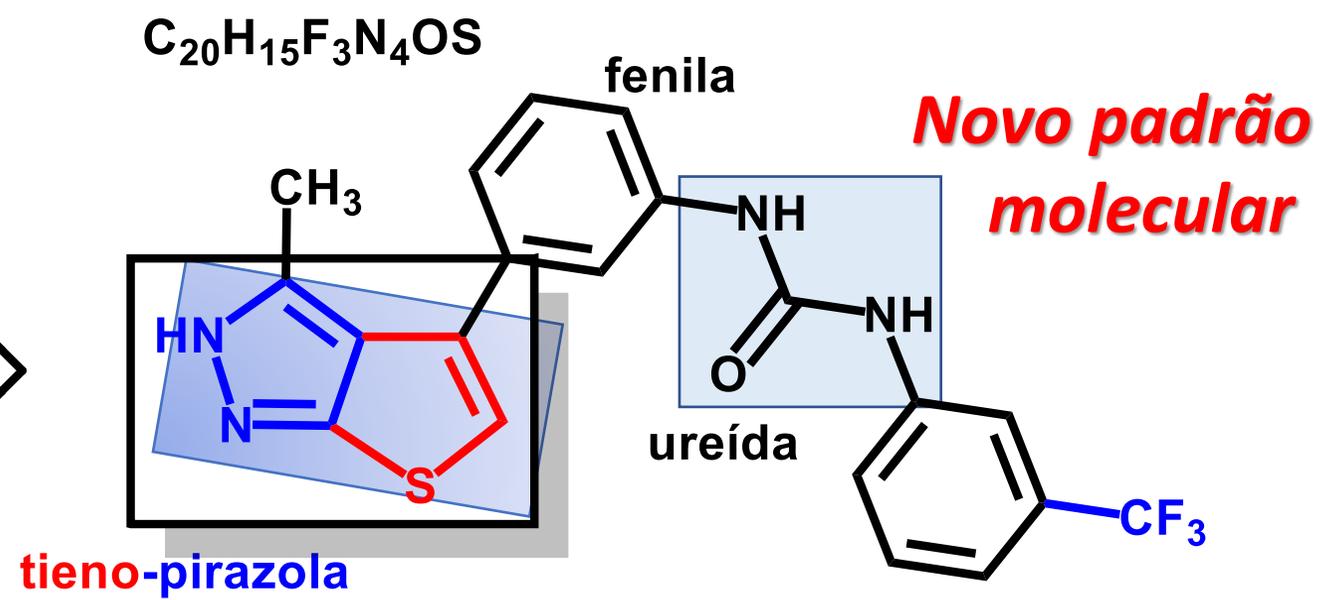
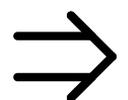
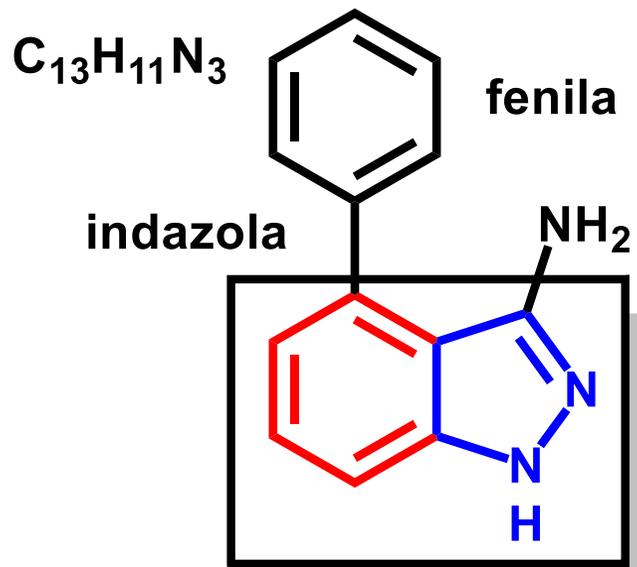
K_i (KDR) = 23 μ M



regioisômeros

isósteros

ORIGINALIDADE



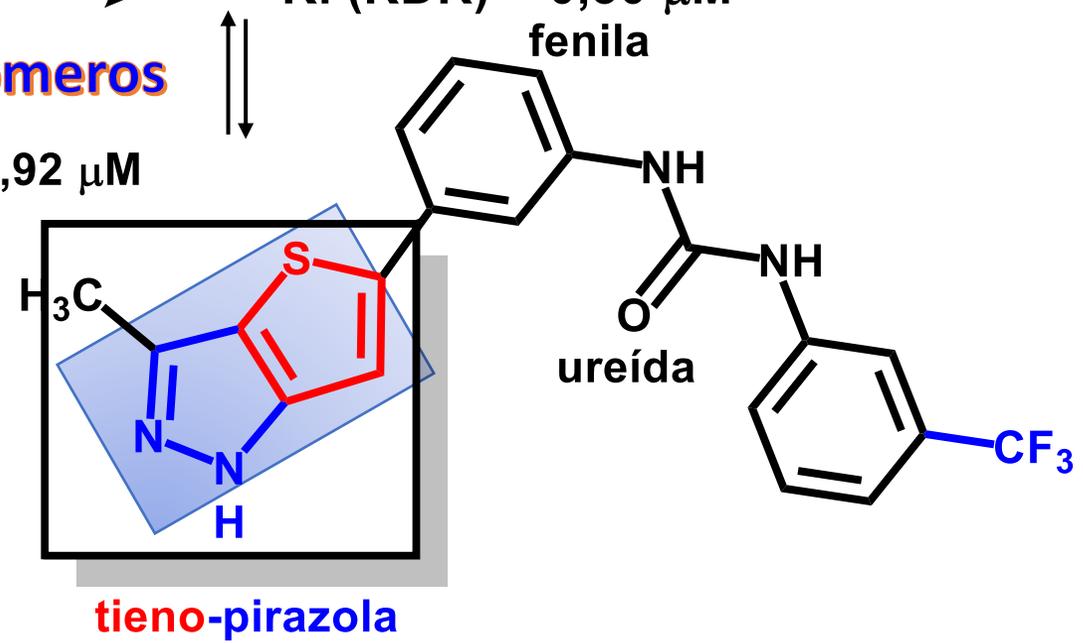
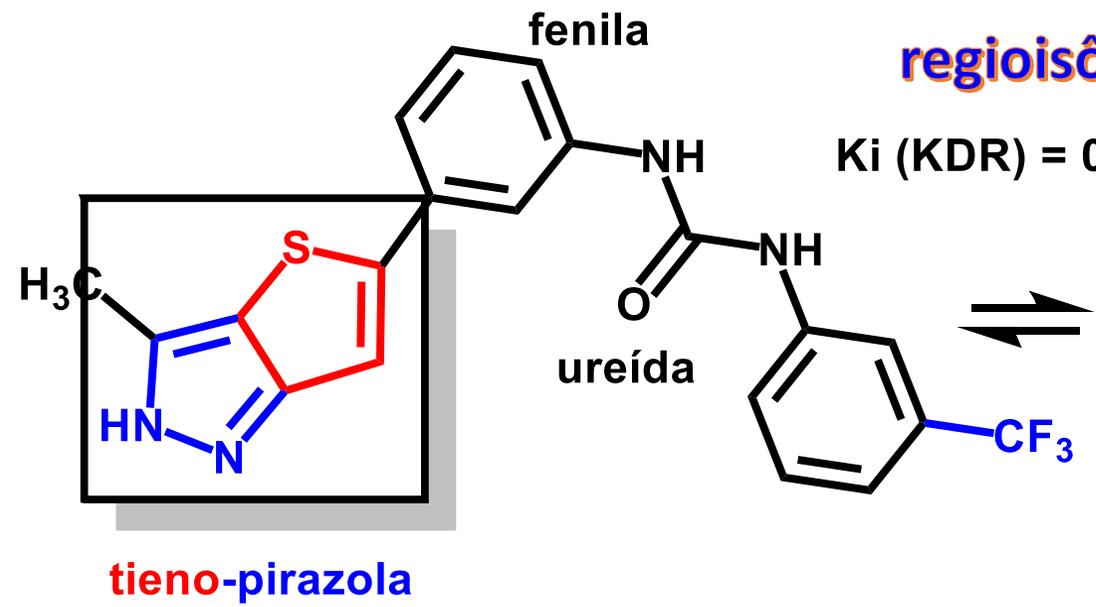
K_i (KDR) = 5,0 μM



K_i (KDR) = 0,30 μM

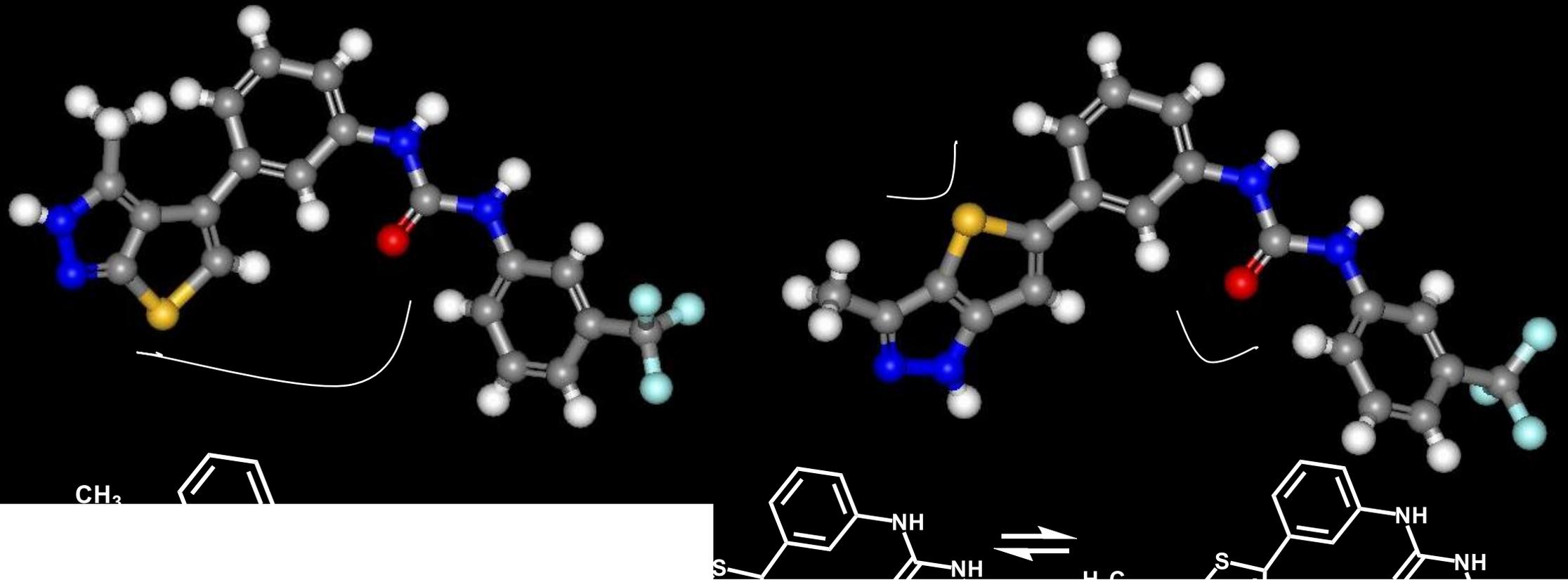
regioisômeros

K_i (KDR) = 0,92 μM

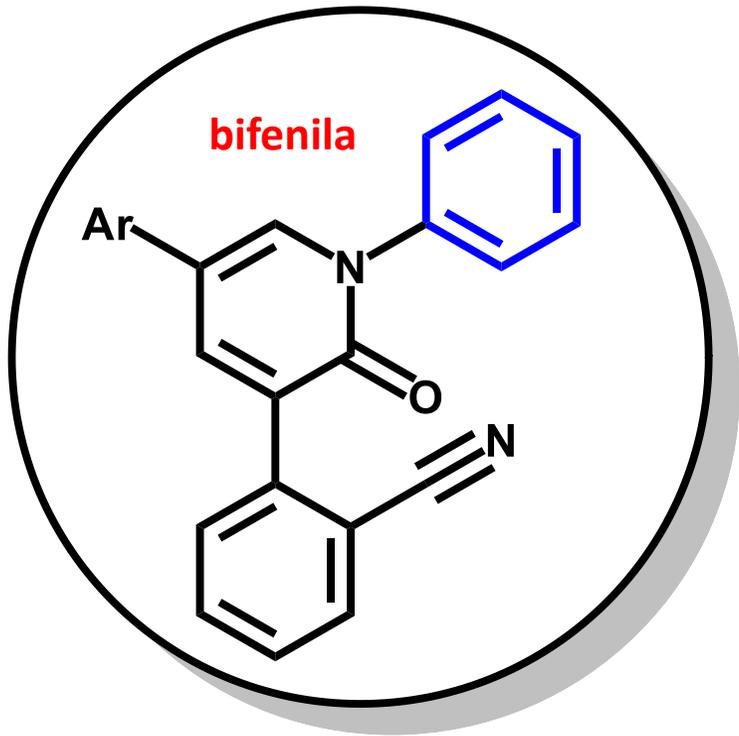


Regioisômeros

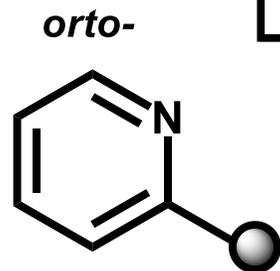
Tieno-pirazola



Regioisômeros

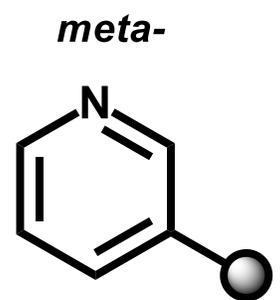


AMPA- induced Ca⁺⁺ assay

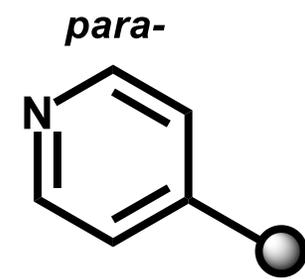


IC₅₀ = 0,06 μM

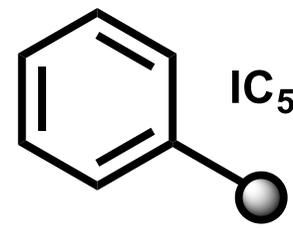
perampanel
Anti-epiléptico



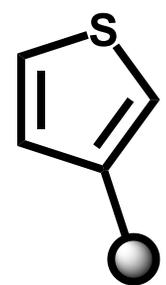
IC₅₀ = 4,02 μM



IC₅₀ = 5,53 μM



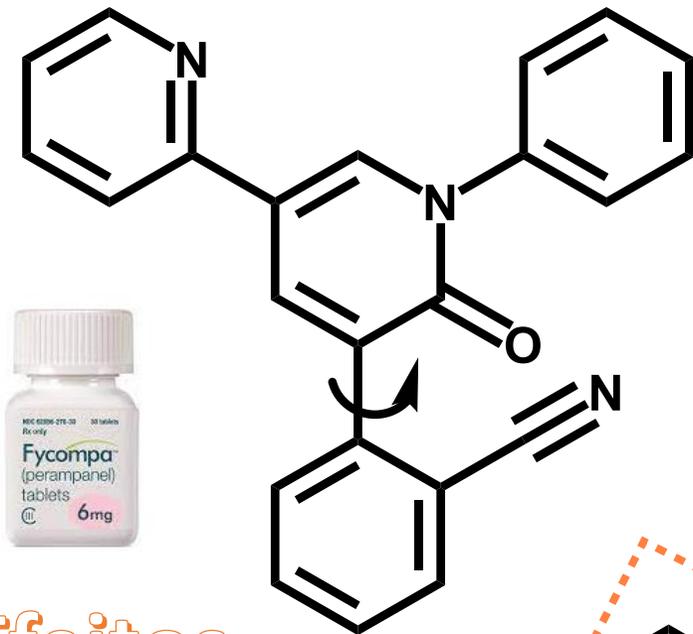
IC₅₀ = 0,33 μM



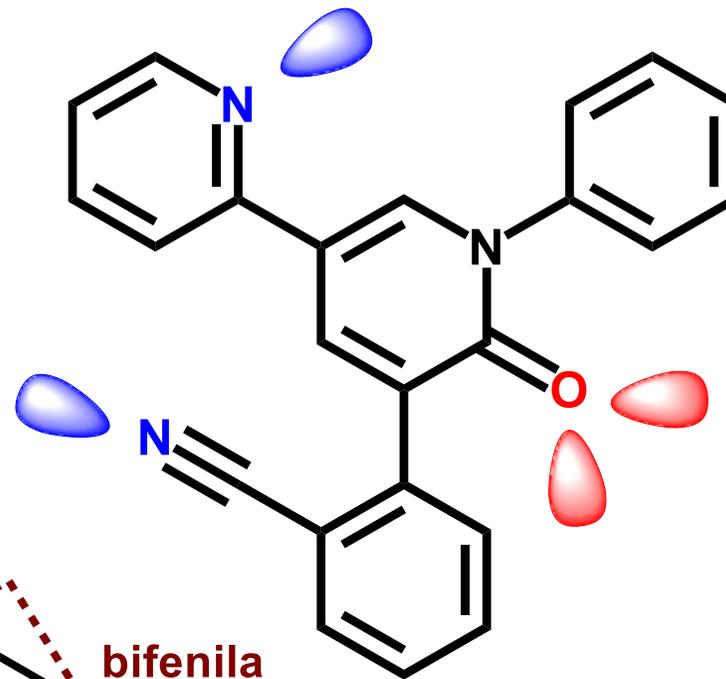
IC₅₀ = 0,14 μM

regioisômeros

bioisosteros



180°
efeito conformacional



Efeitos conformacionais

