Universidade Federal do Rio de Janeiro

XXVIII Escola de Verão em Química Farmacêutica e Medicinal

25-28 de janeiro de 2022

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

Curso 3

Estruturas privilegiadas no desenho de fármacos

Parte 3

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Laboratório de Avaliação e Síntese de Substâncias Bioativas

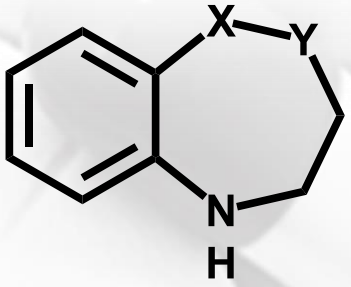
Instituto Nacional de Ciência e Tecnologia em Fármacos e Medicamentos

Programa de de Pós-Graduação em Farmacologia e Química Medicinal

www.inct-inofar.ccs.ufrj.br

www.lassbio.icb.ufrj.br

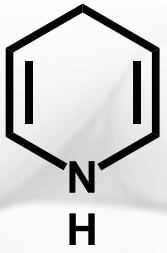
1950



$X=CH_2$ $Y=NH$ - 1,4-benzodiazepinas

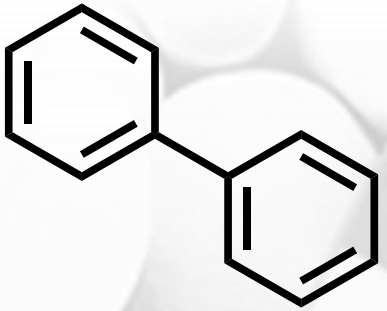
$X=NH$ $Y=CH_2$ - 1,5-benzodiazepinas

1982



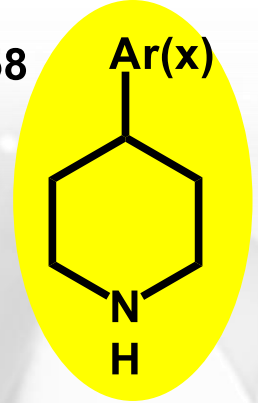
1,4-diidropiridinas

1986



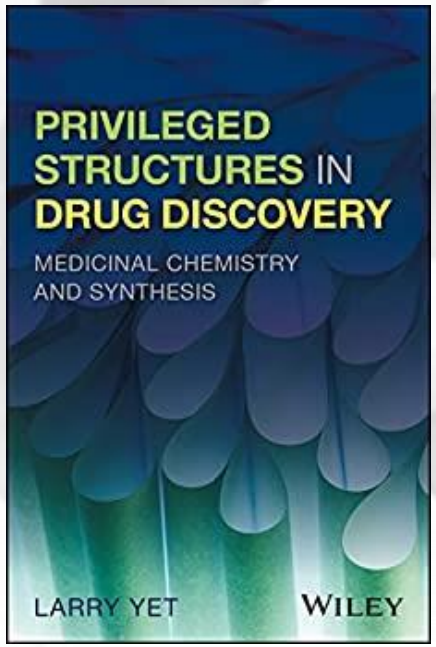
Bifenila

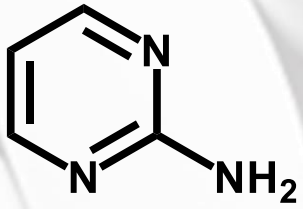
1958



4-arilpiperidinas

4-heteroarilpiperidinas

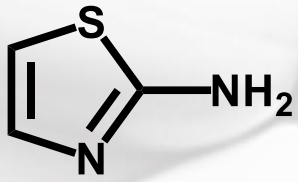




2-aminopirimidinas

crizotinibe

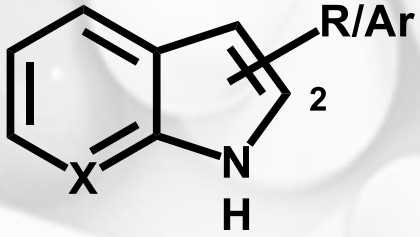
dasatinibe



2-aminotiazolas

dasatinibe

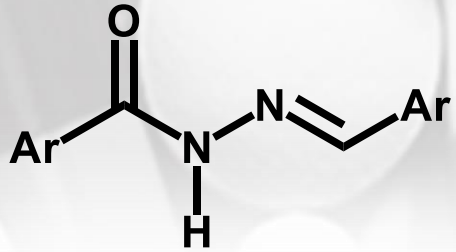
meloxicam



X=CH indol

X=N 7-azaindol

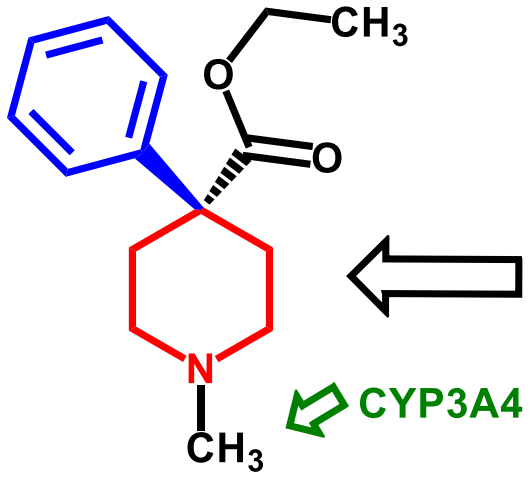
1999



N-acilidrazona

4

1943



morfina

CYP3A4

meperidina

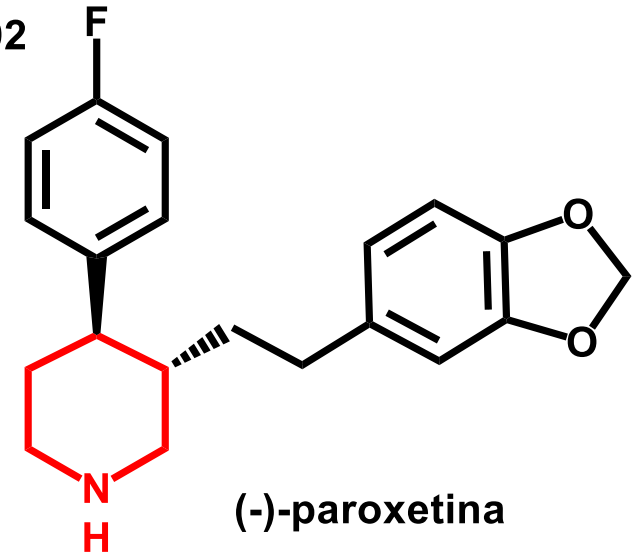
Demerol^{R}

Sanofi-Aventis

μ-opioide

morfina

1992



CYP2C19

(-)-paroxetina

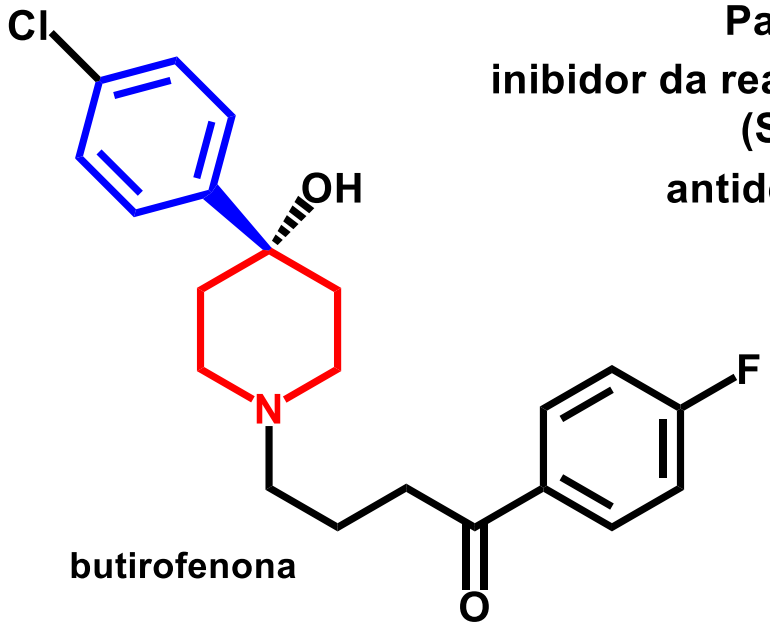
Paxil^{R}

inibidor da reabsorção de 5-HT (SSRI)

antidepressivo

GSK

1967



butirofenona

haloperidol

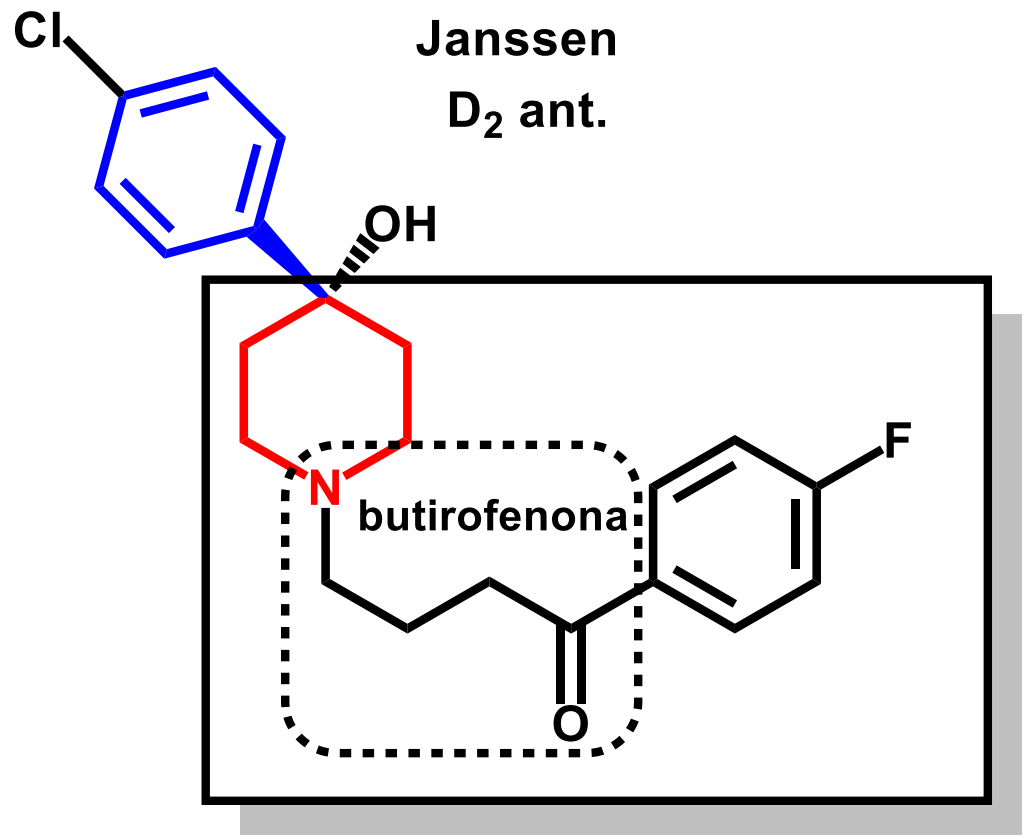
D_2 ant.

4-aril-piperidinas

1967 haloperidol

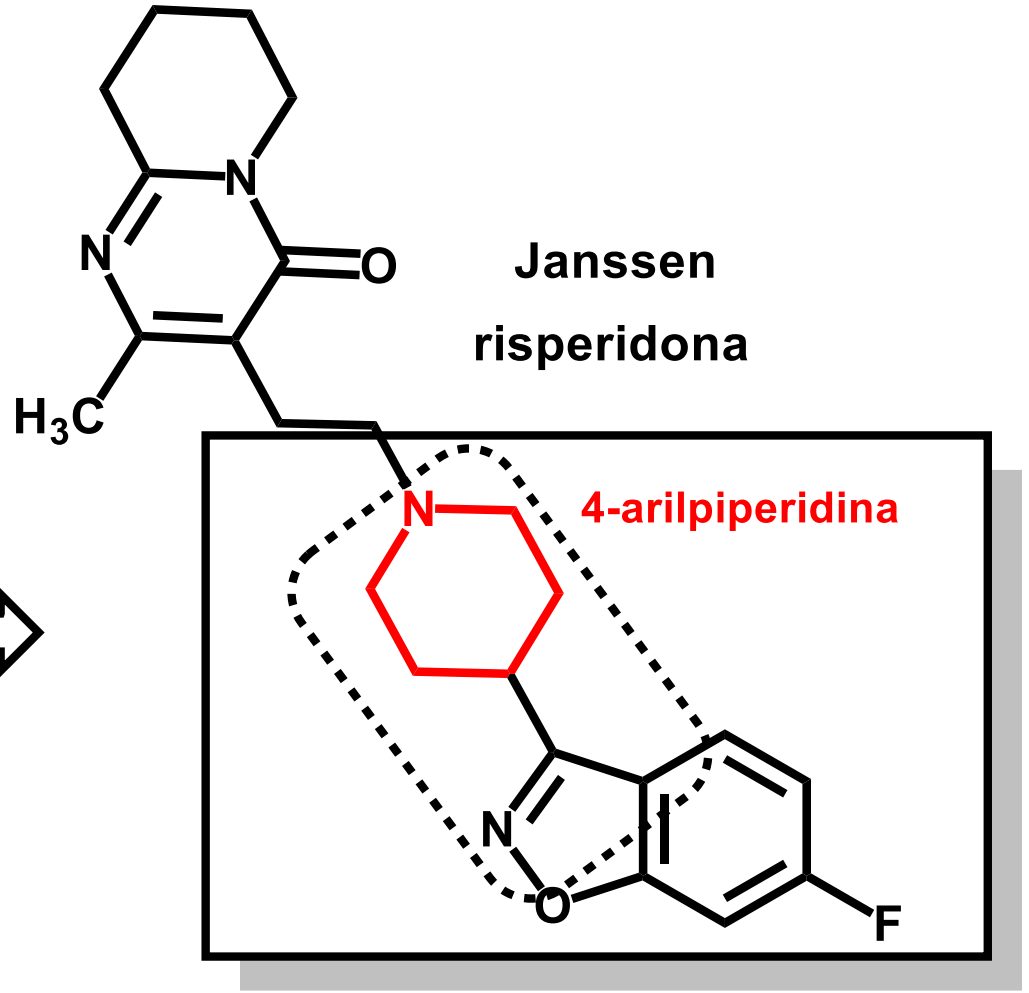
Janssen

D_2 ant.



Janssen

risperidona



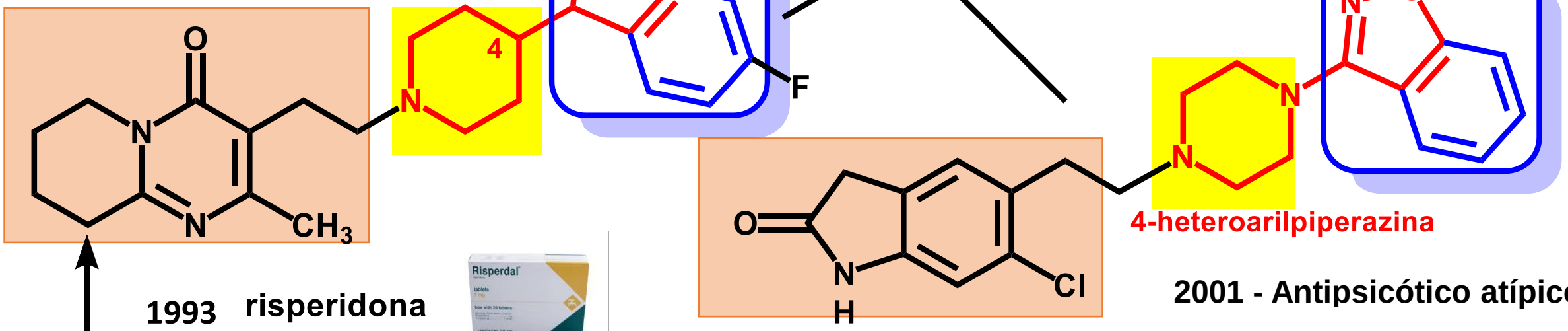
benzoisoxazola

4-heteroarilpiperidina

$D_2/5\text{-}HT_{2A}$

benzoisotiazola

4-heteroarilpiperazina



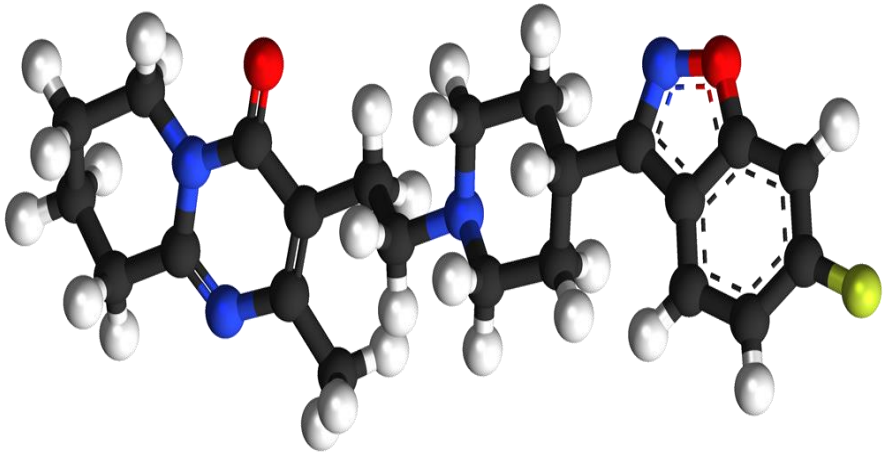
1993 risperidona Janssen

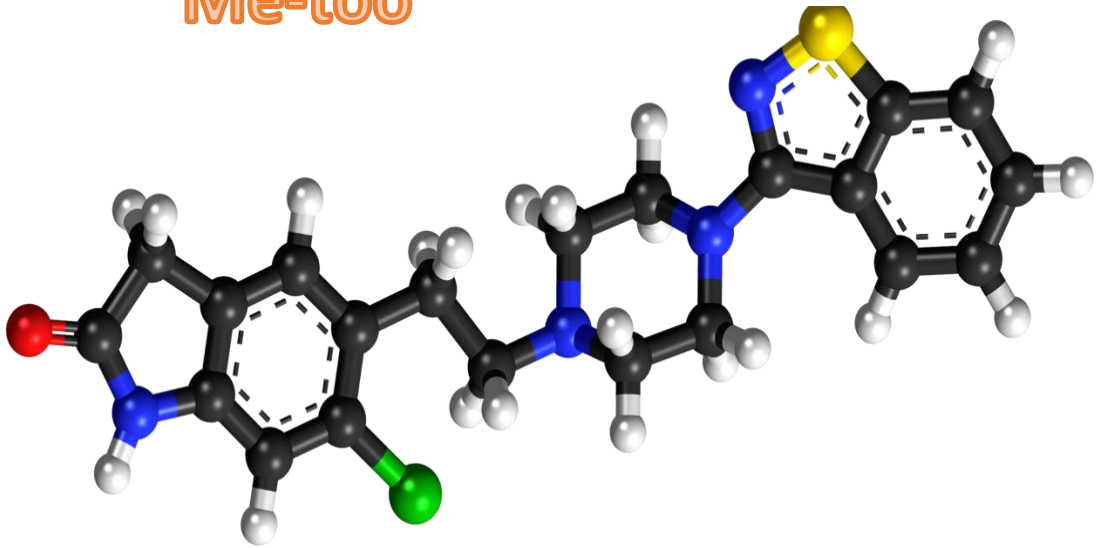
2001 - Antipsicótico atípico

ziprazidona

[O} paloperidona

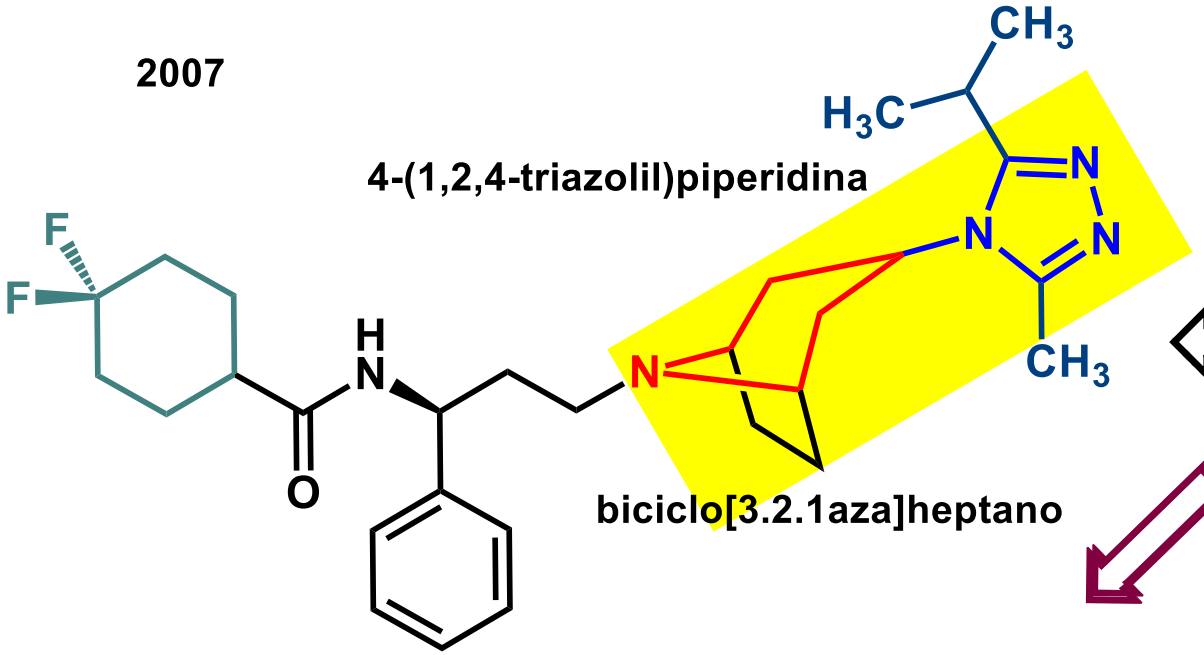
Me-too



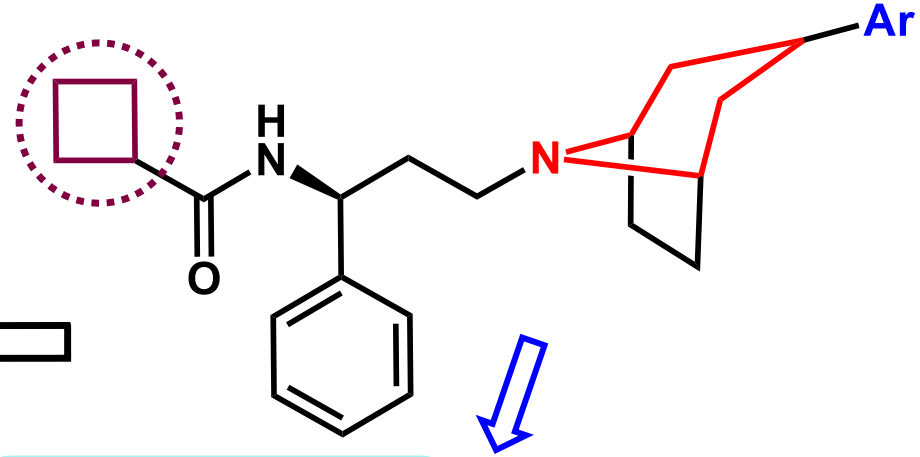


2007

4-(1,2,4-triazolil)piperidina



biciclo[3.2.1aza]heptano

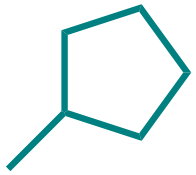


maraviroque

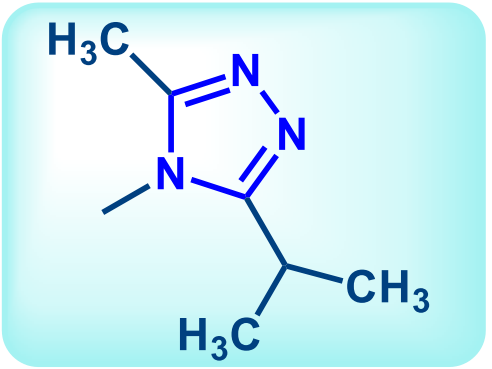
CCR5 ant.

Pfizer

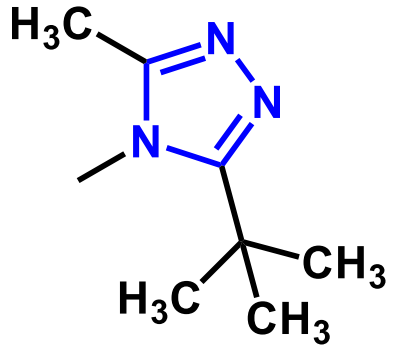
AAV = 8 nM



AAV = 2 nM



AAV = 8 nM

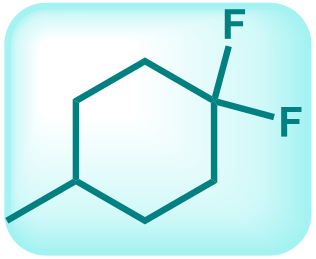


AAV = >100 nM

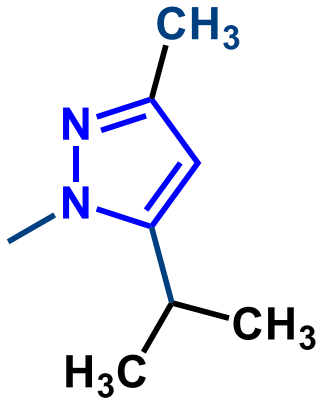
Homólogo superior

Homólogo superior

AAV = 14 nM
(<hERG %)

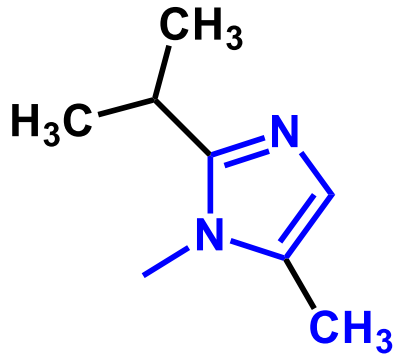


AAV = 2 nM



AAV = 29 nM

*h*ERG IC_{50} > 10 μM



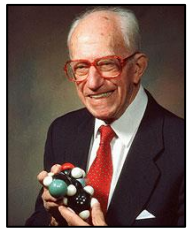
AAV = 1 nM (tóxico)

Timeline das EP´s deste curso

1942 meperidina Demerol^{R}

1945 Univ. Cracóvia benzheptoxdiazinas

1950 Hoffmann-La Roche Leo Sternbach (1908-2005) BDZ



1958 J&J haloperidol

1963 Roche diazepan

1979 Pfizer piroxicam

1982 nifedipina

Paul A. J. Janssen (1926-2003) 4-fenilpiperidinas

1986 **bifenila** losartana AT_1-ant

2000 B&I meloxicam

1999 NAH

2006 paliperidona

2007 dasatinibe BMS

2010 Novartis pazopanibe

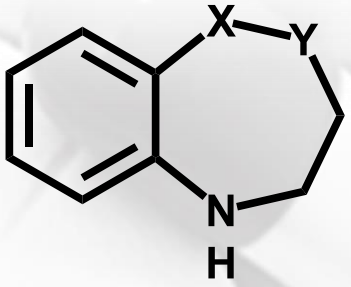
maraviroque

2011 Pfizer crizotinibe

2013 ponatinibe Ariad

Frontiers in Medcinal Chemistry

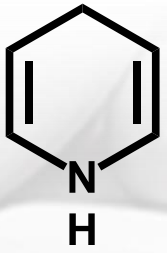
1950



$X=CH_2$ $Y=NH$ - 1,4-benzodiazepinas

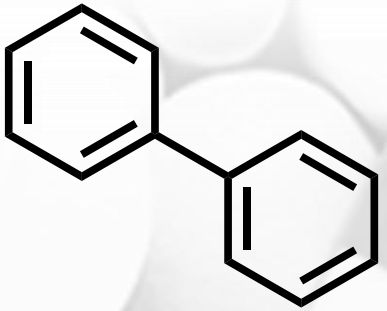
$X=NH$ $Y=CH_2$ - 1,5-benzodiazepinas

1982



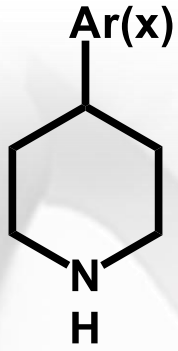
1,4-diidropiridinas

1986



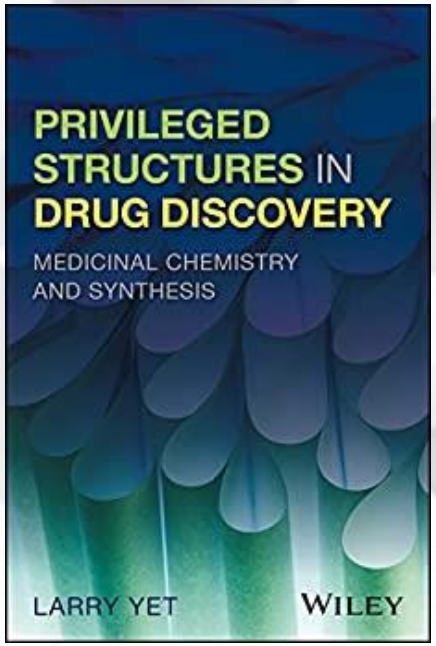
Bifenila

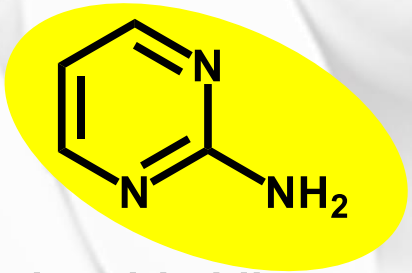
1958



4-arilpiperidinas

4-heteroarilpiperidinas

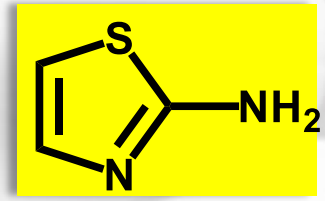




2-aminopirimidinas

crizotinibe

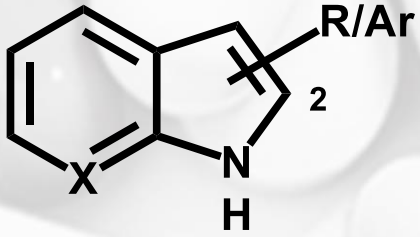
dasatinibe



2-aminotiazolas

dasatinibe

meloxicam

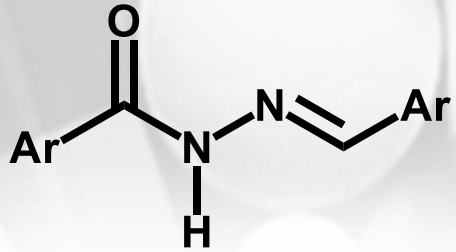


X=CH indol

X=N 7-azaindol

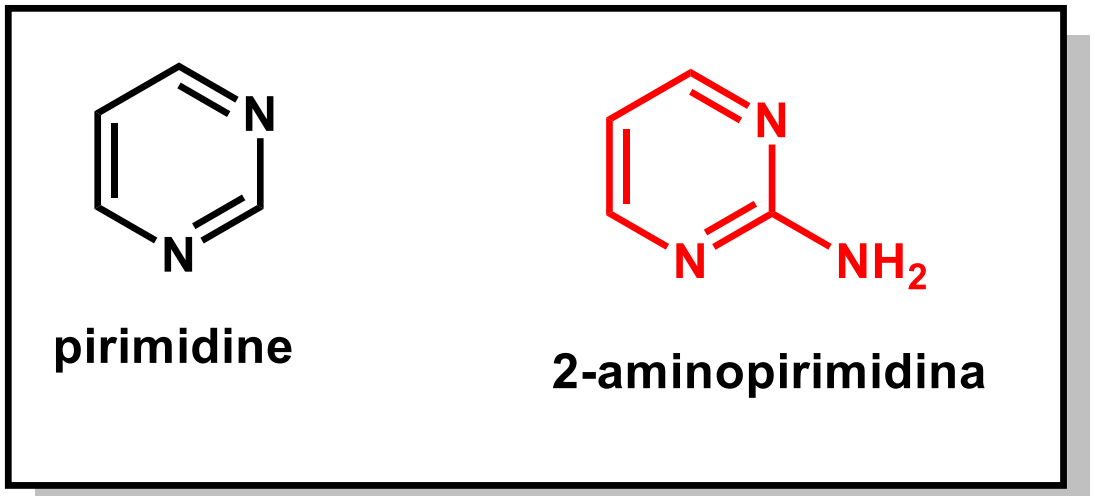
5

1999

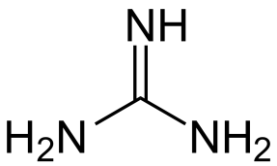


N-acilidrazona

6



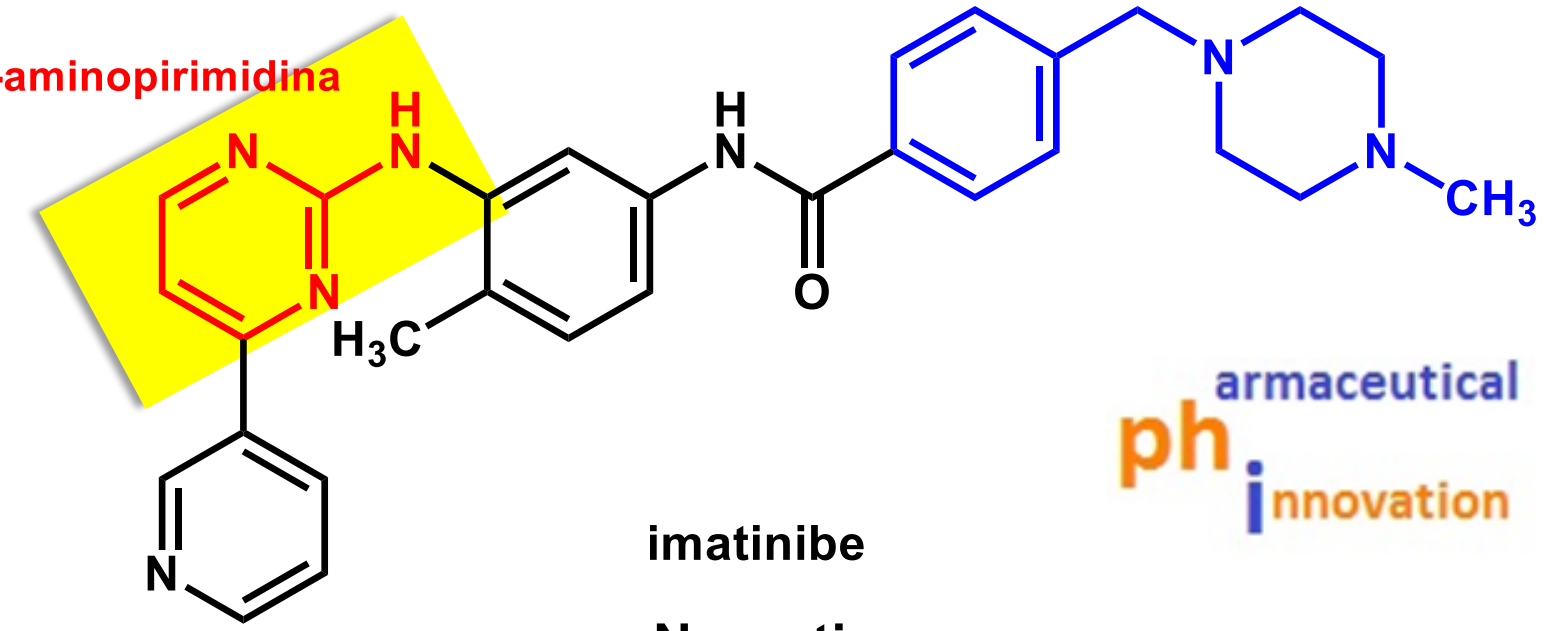
tautômeros



guanidina

2001

2-aminopirimidina



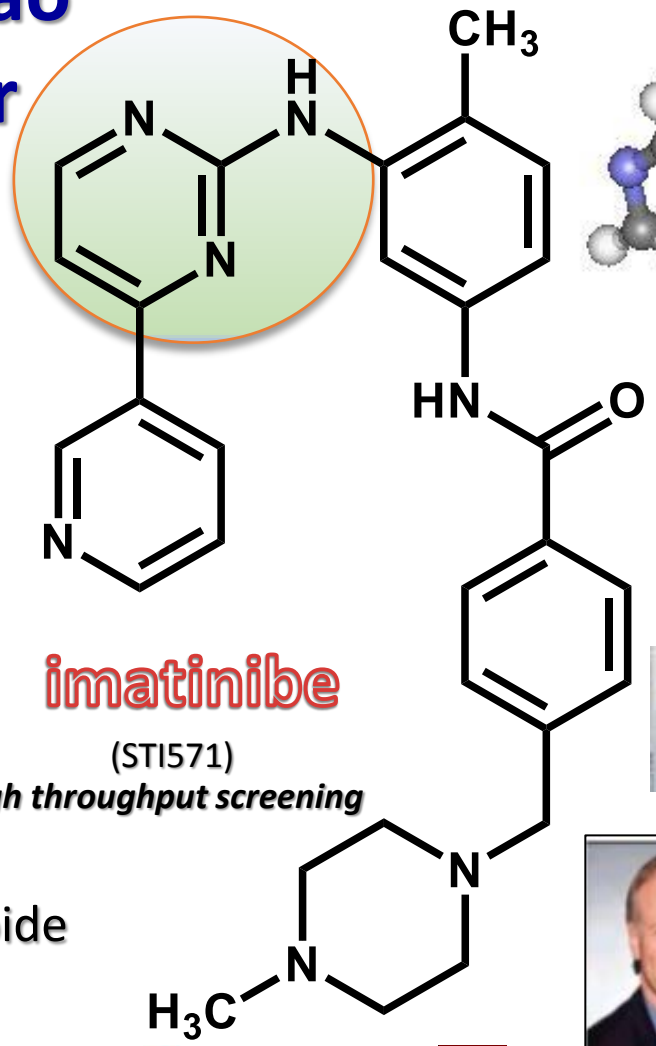
imatinibe

Novartis

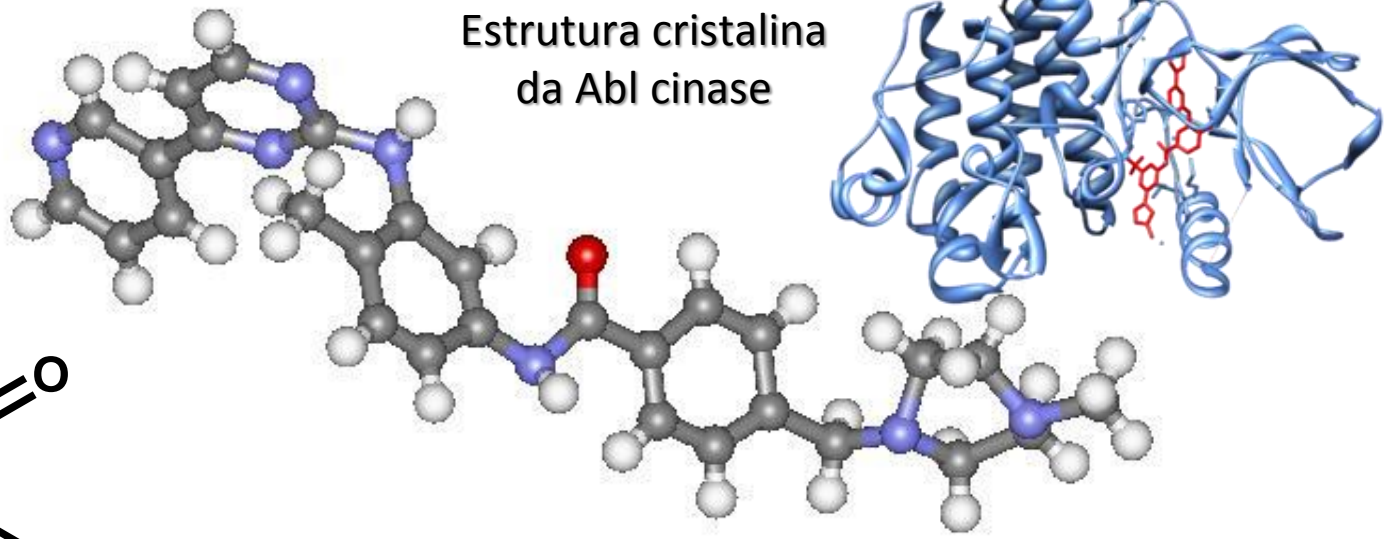
pharmaceutical innovation

Novo padrão molecular

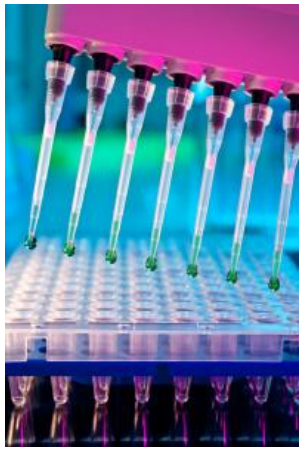
guanidina



Estrutura cristalina da Abl cinase



th erapeutic innovation



imatinibe

(STI571)

High throughput screening

1985 – Nicholas Lydon
1988 - Brian J. Druker & Charles L Sawyers&
1990 – Jurg Zimmermann
1995 - Composto STI571 ++
2001 – Imatinibe (Gleevec^{R}, Novartis)[link]

Leucemia mieloide crônica (CML)

NOVARTIS

Nicholas B. Lydon
Blueprint Medicines Inc*

Química Medicinal

OREGON HEALTH & SCIENCE UNIVERSITY

Brian J. Druker*
Blueprint Medicines Inc

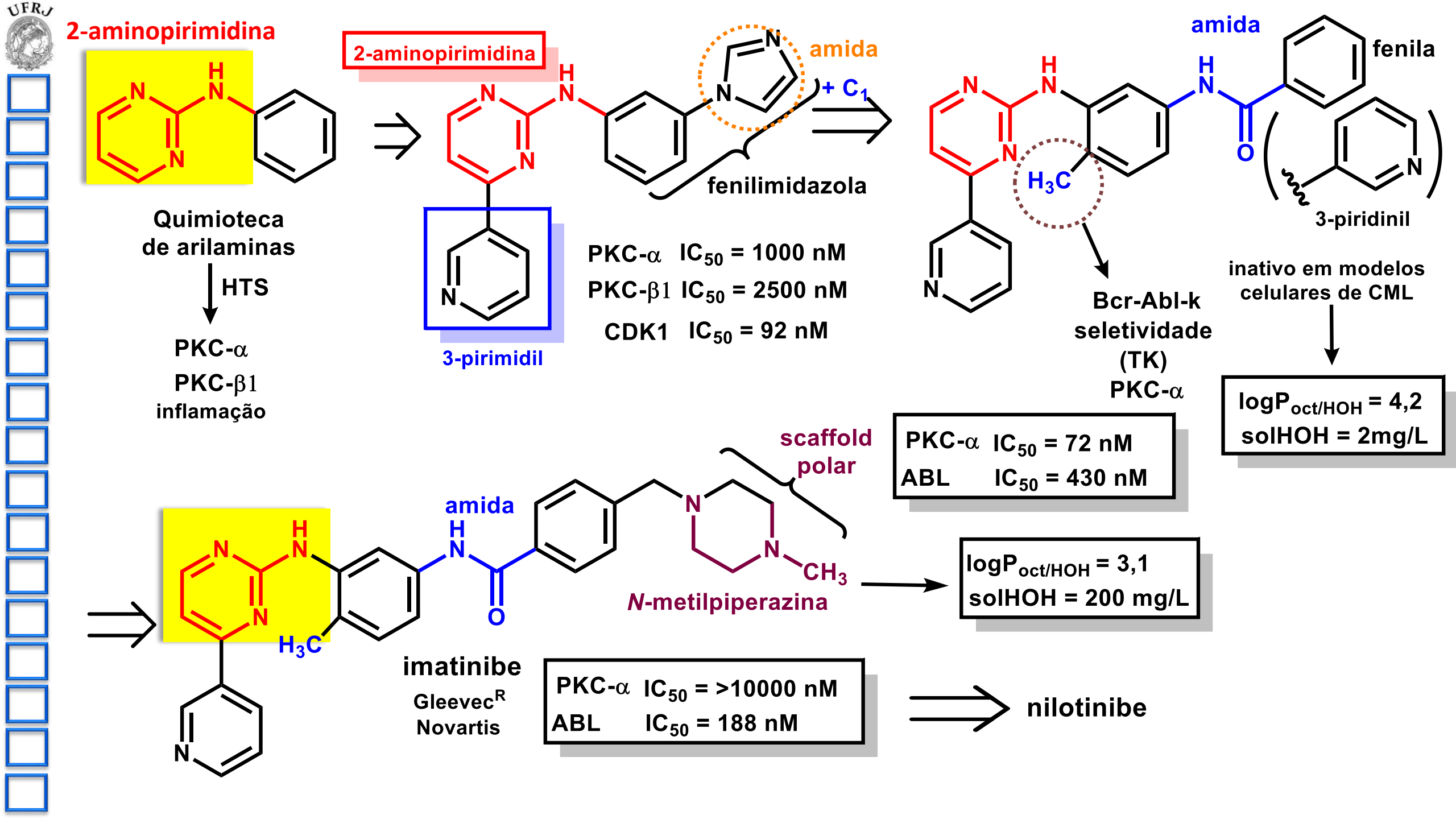
HHMI HOWARD HUGHES MEDICAL INSTITUTE

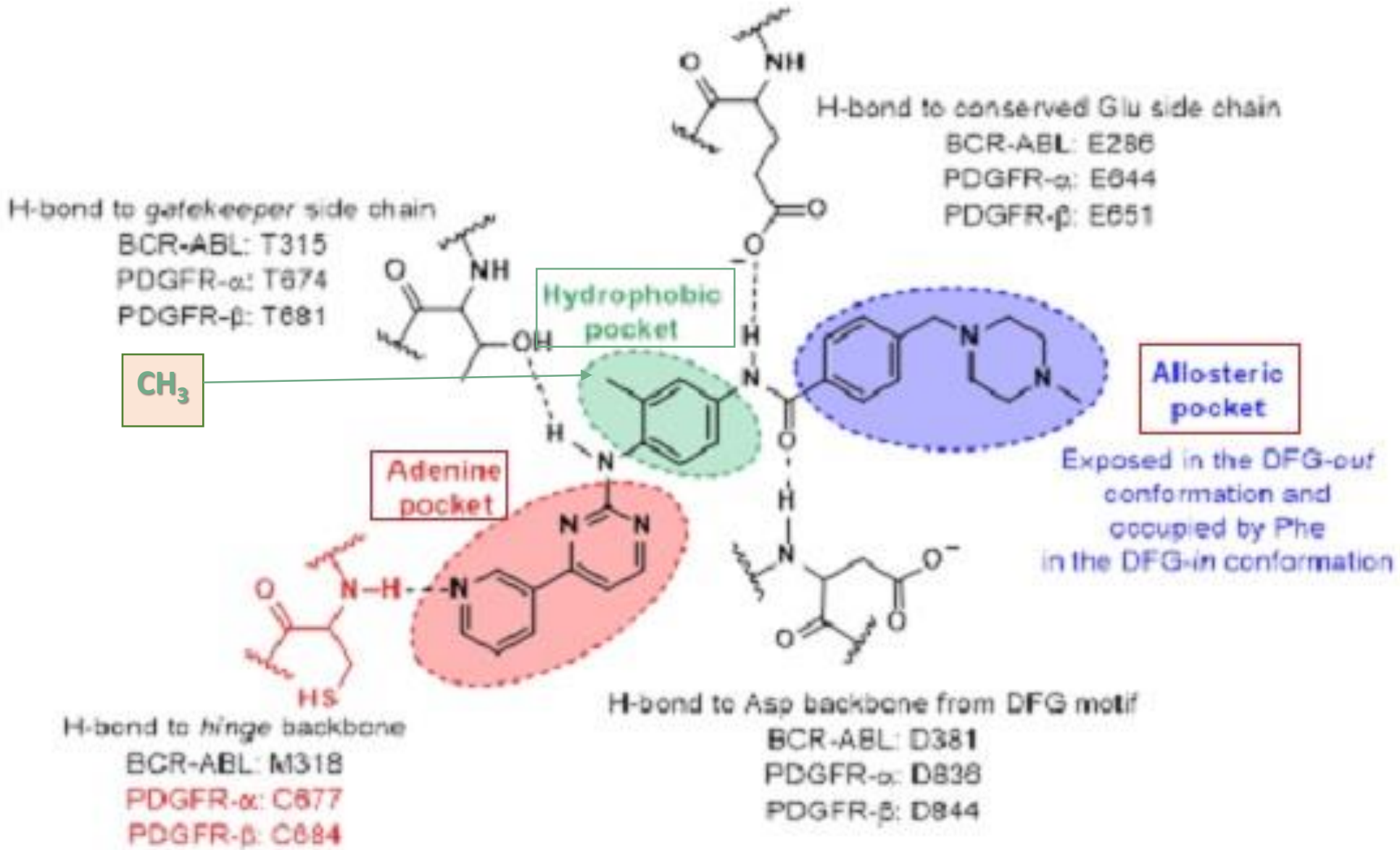
Charles L. Sawyers**
Blueprint Medicines Inc

& 2009 - Lasker Foundation Clinical Award (*J. Clin. Invest*. **2009**, *119*, 2863)

* B. J. Druker has been awarded with the 2012 Japan Prize in Healthcare and Medical Technology;

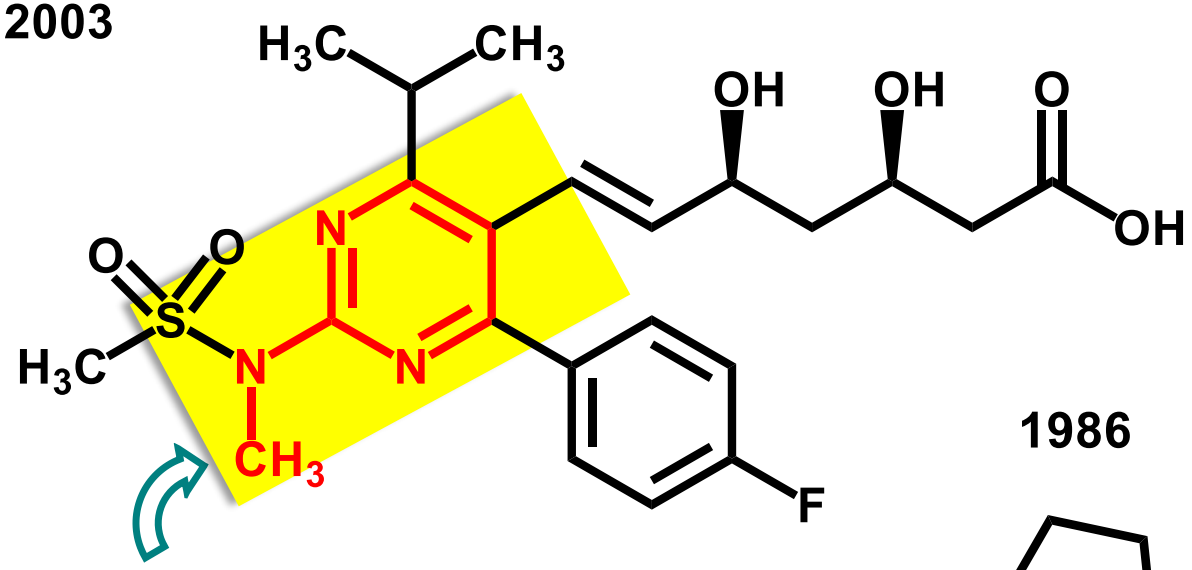
** C. L. Sawyers was named in 2011, Thomson Reuters Citation Laureate in Medicine;


2-aminopirimidina
Quimioteca
de arilaminas
HTS
PKC-α
PKC-β1
inflamação
2-aminopirimidina
3-pirimidil
amida
+ C1
fenilimidazola
PKC-α IC50 = 1000 nM
PKC-β1 IC50 = 2500 nM
CDK1 IC50 = 92 nM
amida
fenila
3-piridinil
Bcr-Abl-k
seletividade
(TK)
PKC-α
inativo em modelos
celulares de CML
logPoct/HOH = 4,2
solHOH = 2mg/L
scaffold
polar
amida
N-metilpiperazina
PKC-α IC50 = 72 nM
ABL IC50 = 430 nM
logPoct/HOH = 3,1
solHOH = 200 mg/L
imatinibe
Gleevec®
Novartis
PKC-α IC50 = >10000 nM
ABL IC50 = 188 nM
nilotinibe



L M Lima, M L C Barbosa, D N Amaral, E J Barreiro, Case study on receptor tyrosine kinases EGFR, VEGFR and PDGFR, em Proteinkinase inhibitors, AS Laufer Ed., *Top Med Chem* **2021**, *36*, 155, Springer Nature SW AG 2020

2003



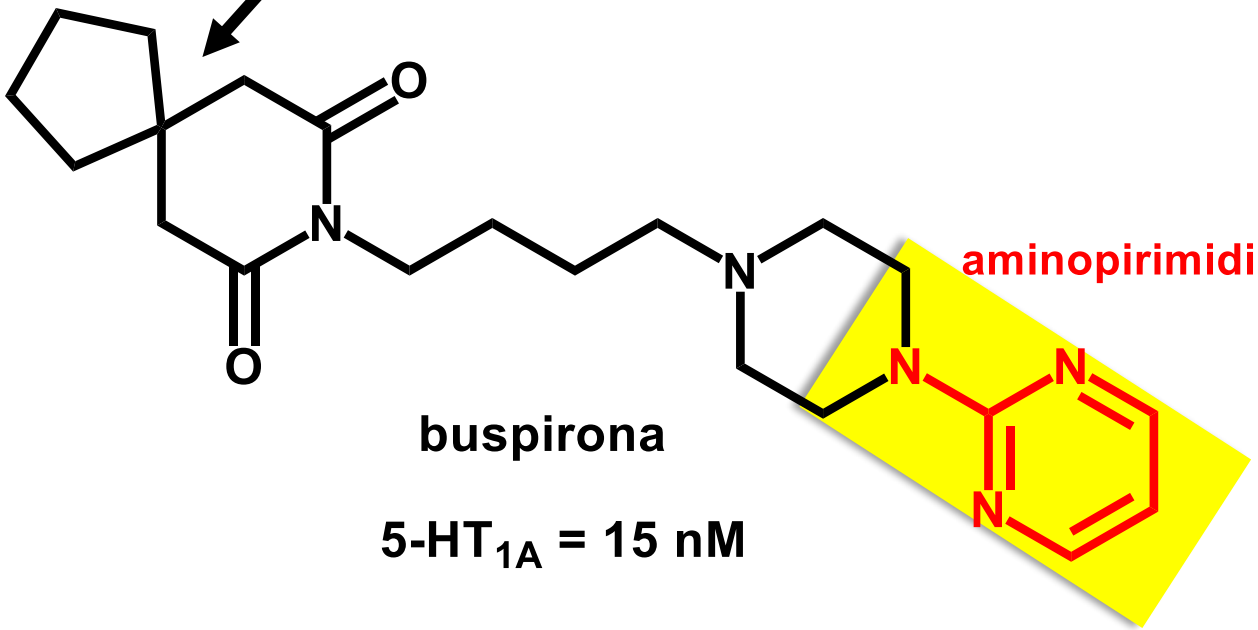
CYP2C9

rosuvastatina
AZ

HMG-CoA$_R$ IC$_{50}$ = 1,1 nM

Carbono espiro

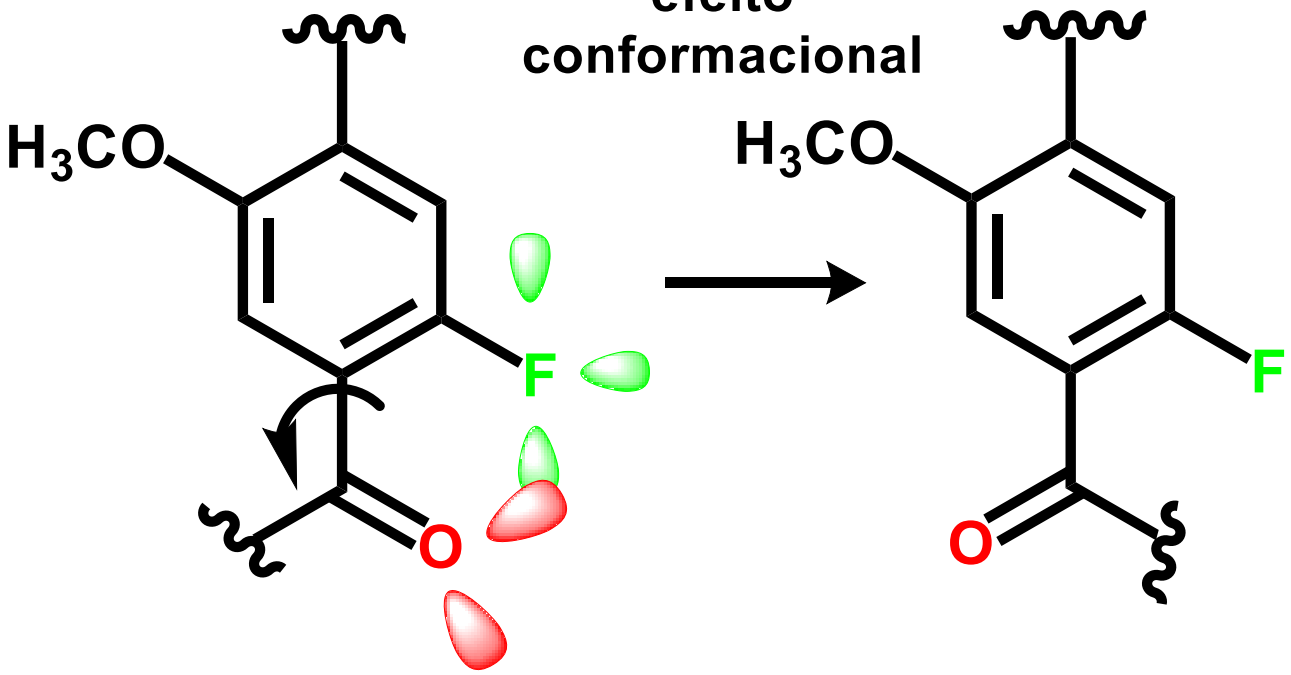
1986

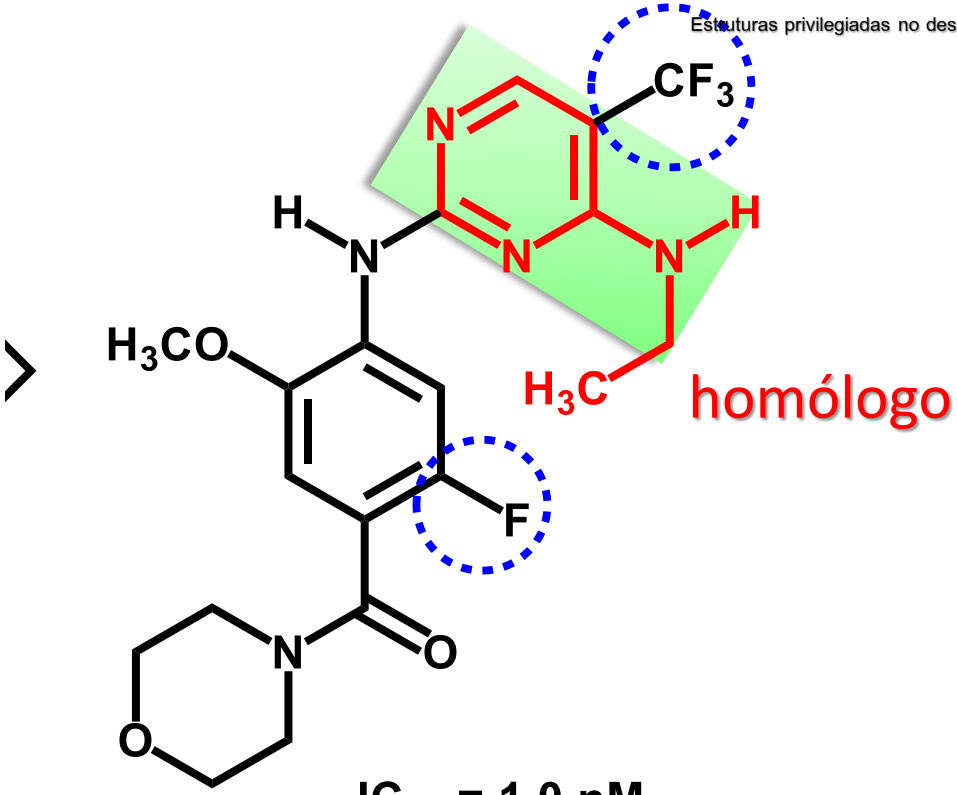


aminopirimidina

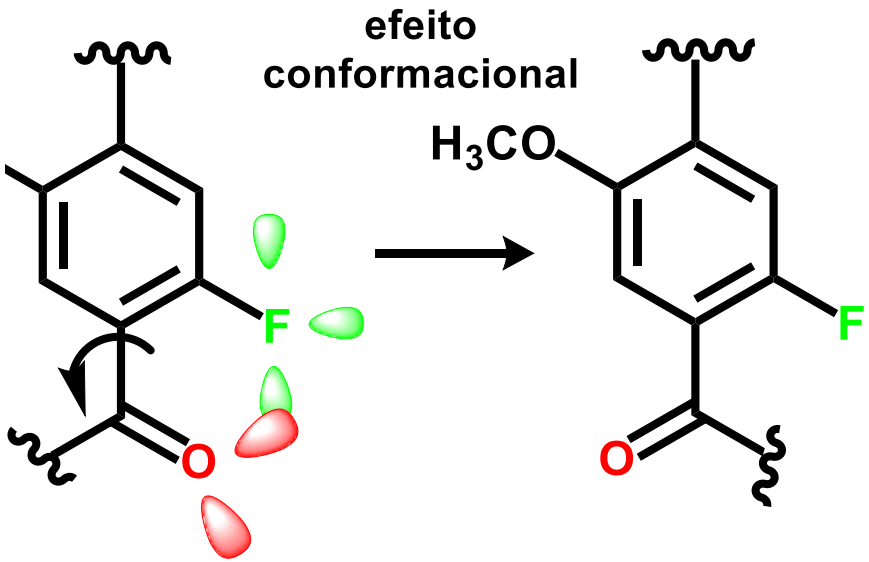
buspirona

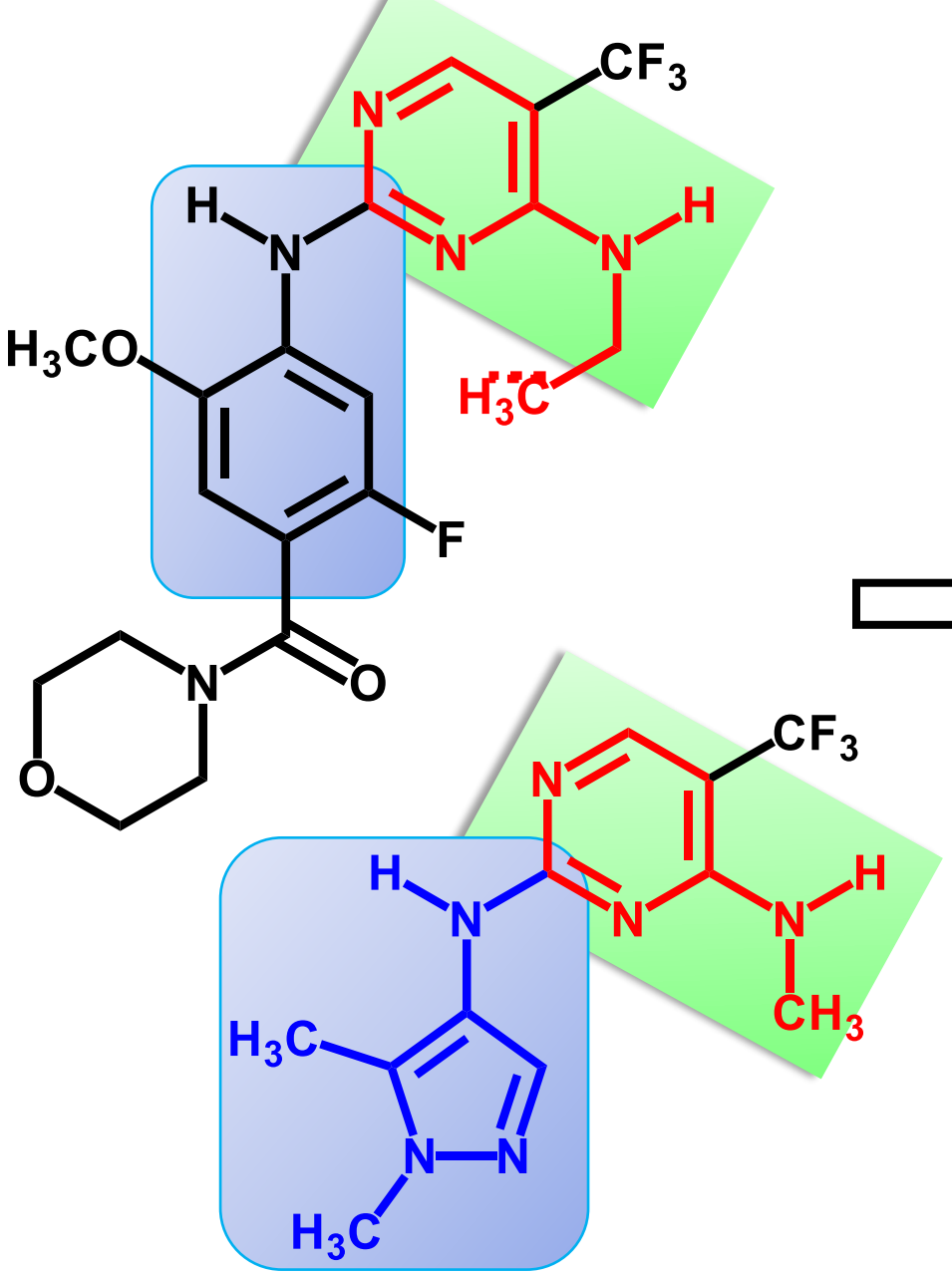
5-HT$_{1A}$ = 15 nM

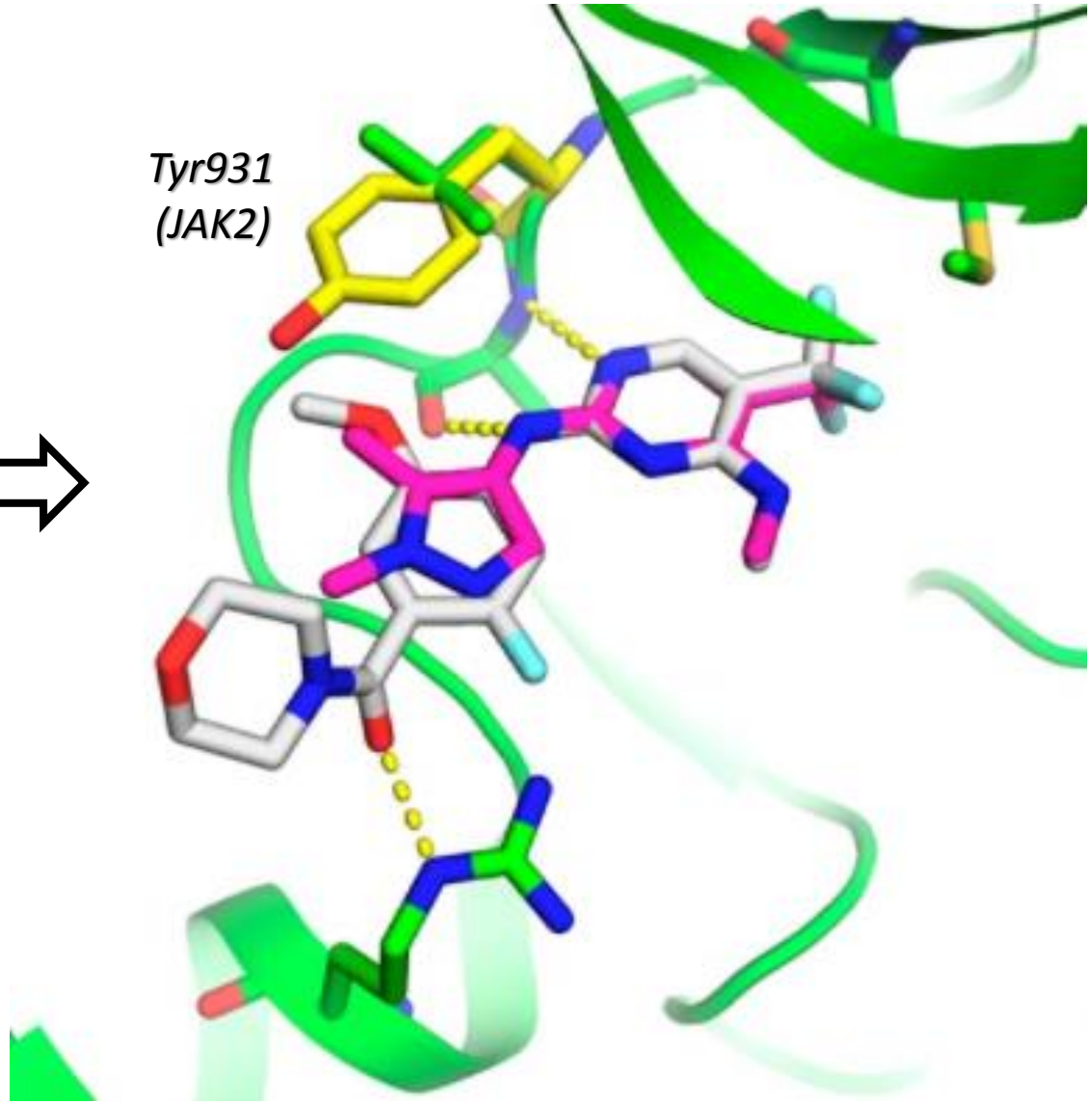

efeito
conformacional
H3CO
F
O
H3CO
F
O


CF3
N
N
N
H
H
N
H3CO
H3C
homólogo
F
N
O
O

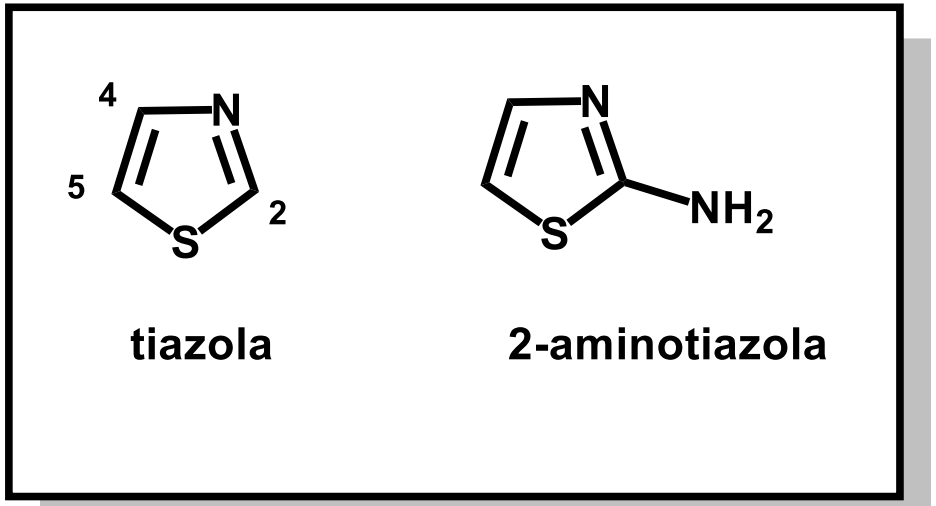
IC_{50} = 1,0 nM


efeito
conformacional
H3CO
F
O
H3CO
F
O

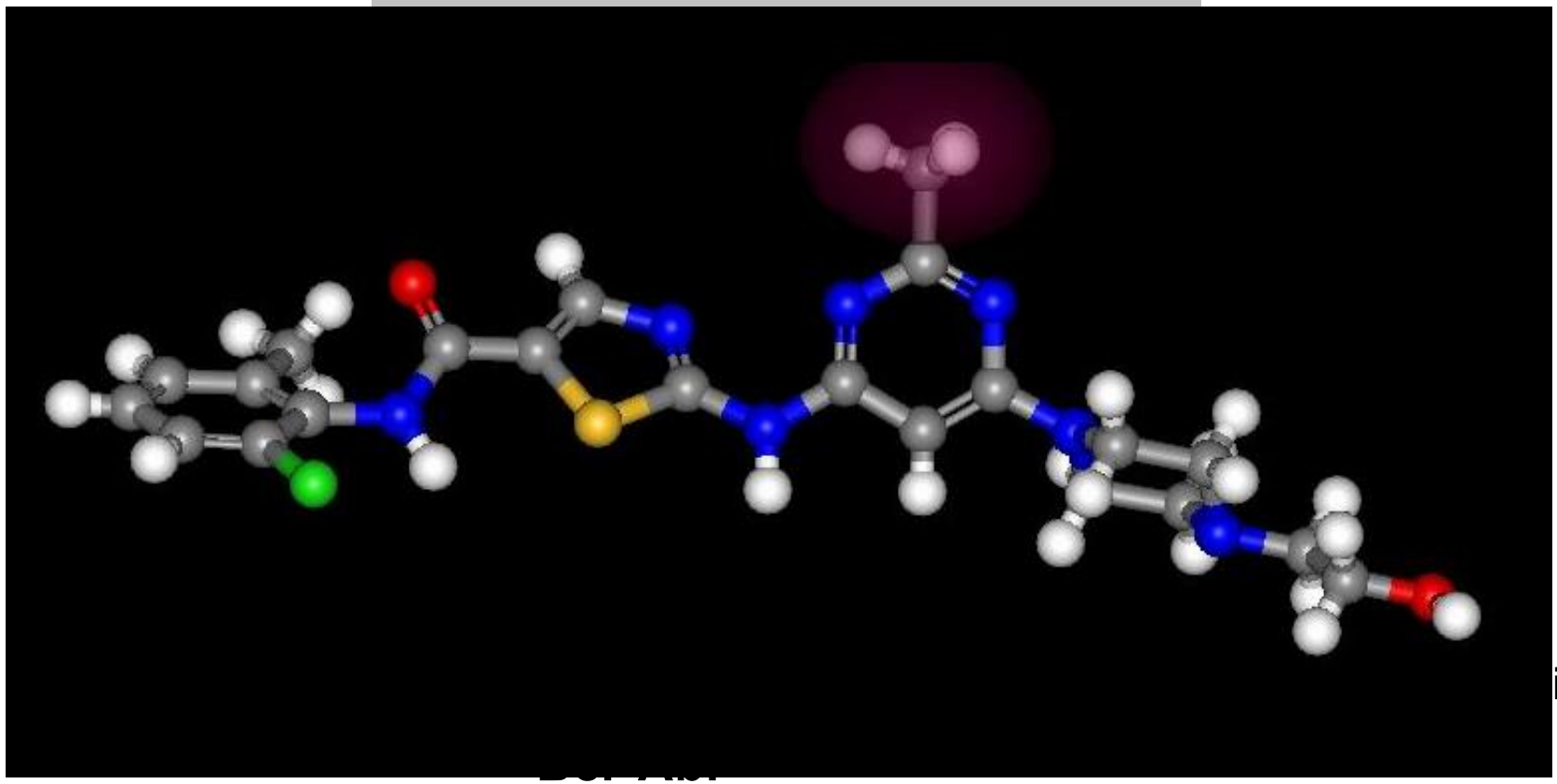




Baixa solubilidade e *soft-spots* metabólicos

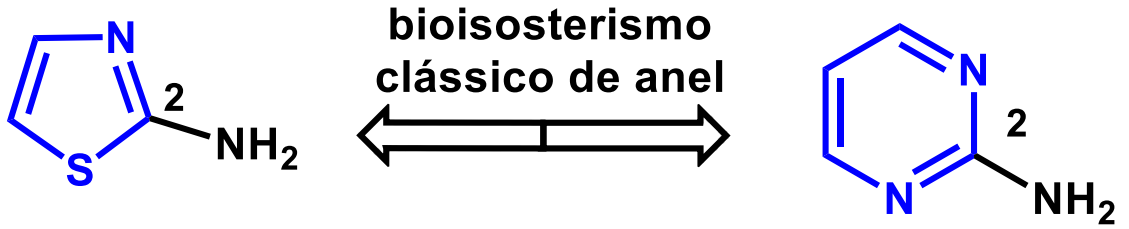


tautômeros



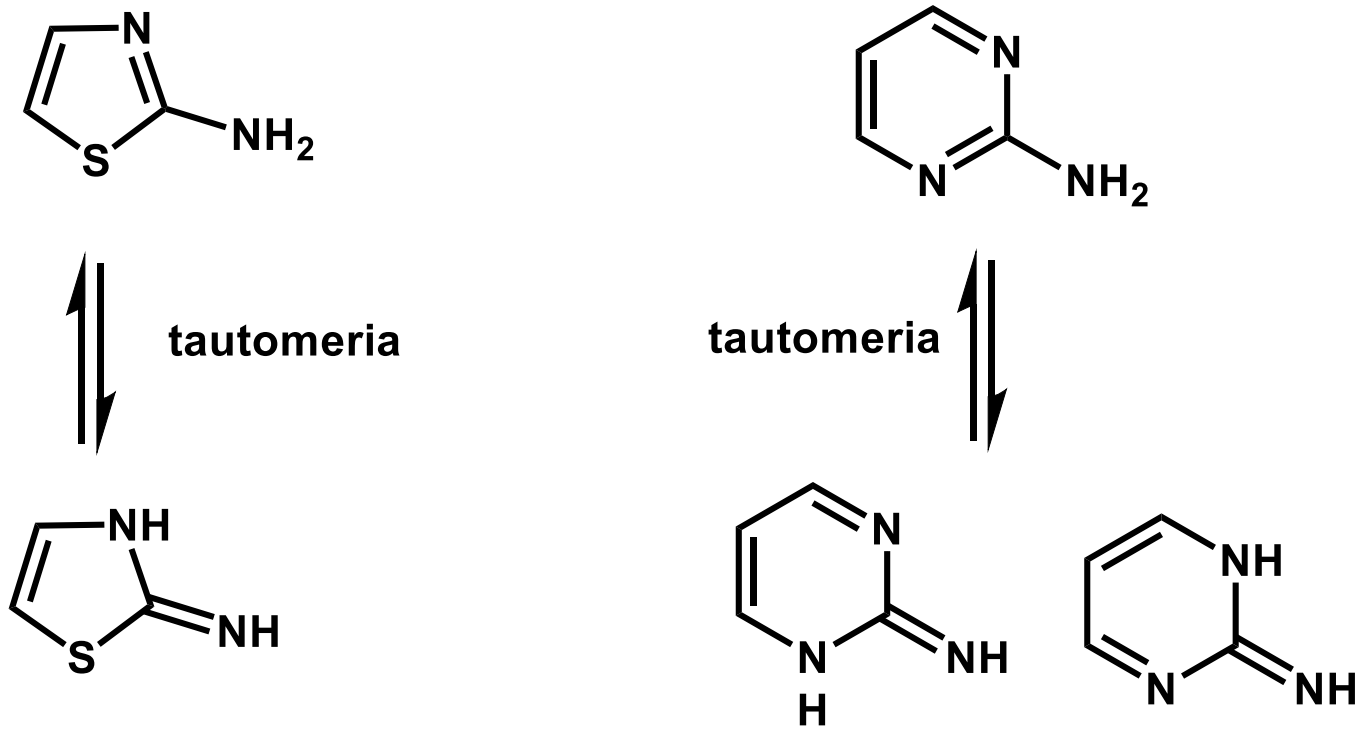
idores (CML)

J Das et al., *J. Med. Chem*. **2006**, *49*, 6819 DOI: [10.1021/jm060727j](10.1021/jm060727j)

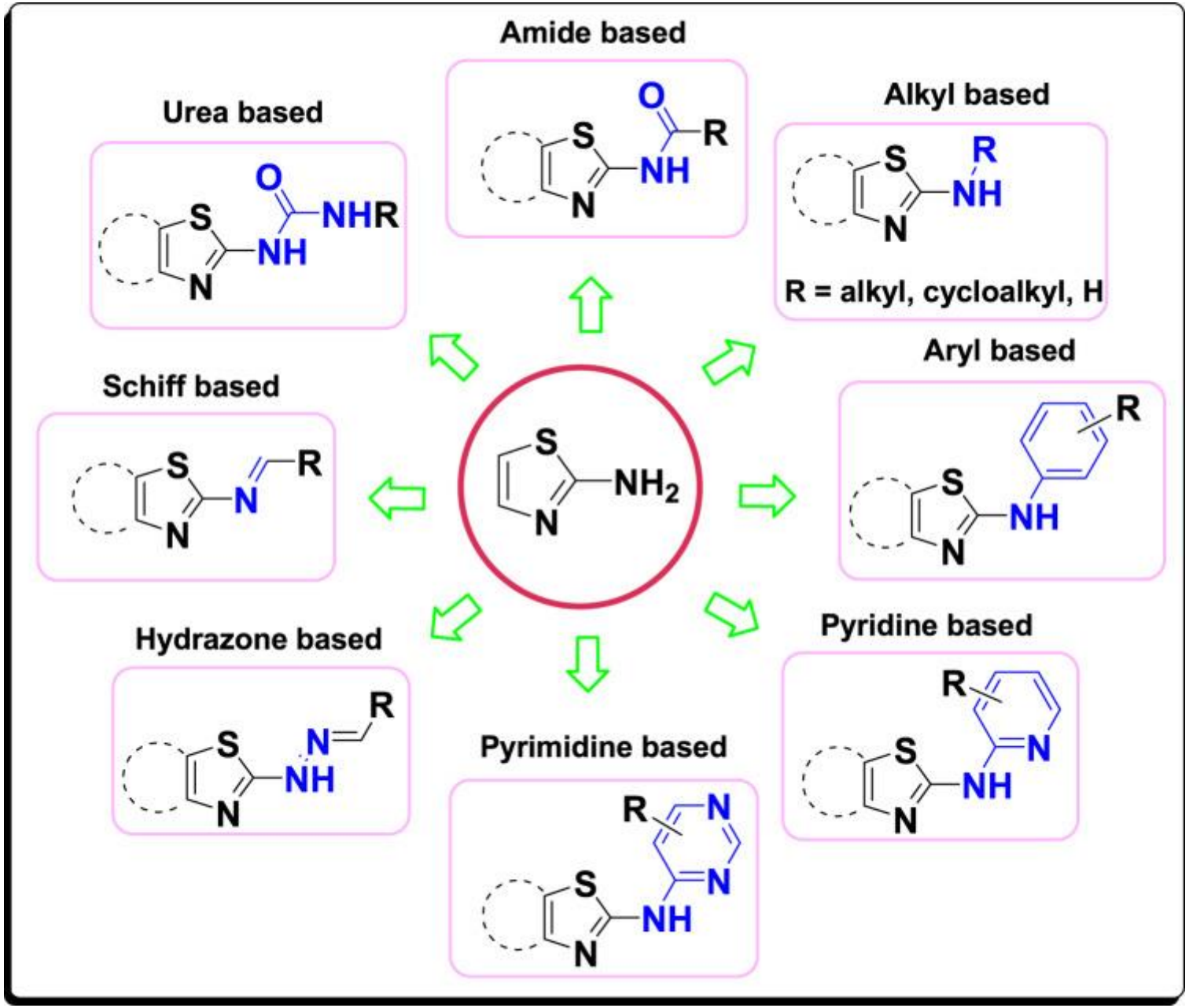


2-aminotiazola

2-aminopirimidina

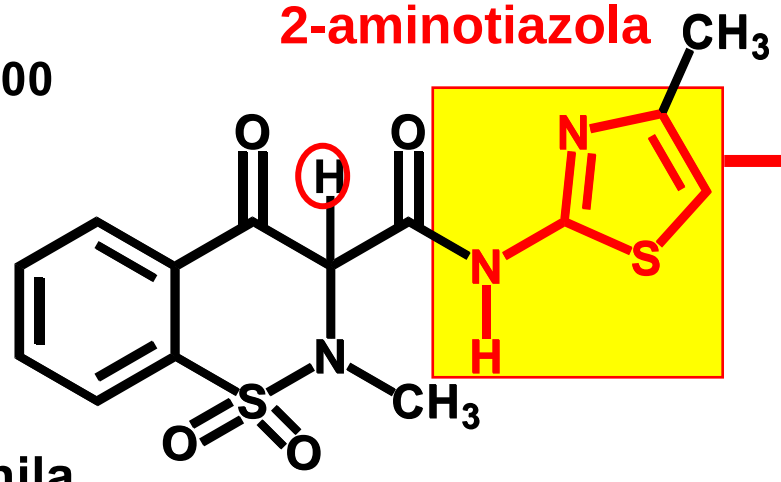


S R Alizadeh, S M Hashemi, Development and therapeutic potential of 2-aminothiazole derivatives in anticancer drug discovery, *Med Chem Res*, **2021** (Jan 15), 1; DOI: 10.1007/s00044-020-02686-2


Amide based
Urea based
Alkyl based
R = alkyl, cycloalkyl, H
Schiff based
Aryl based
Hydrazone based
Pyridine based
Pyrimidine based

2000

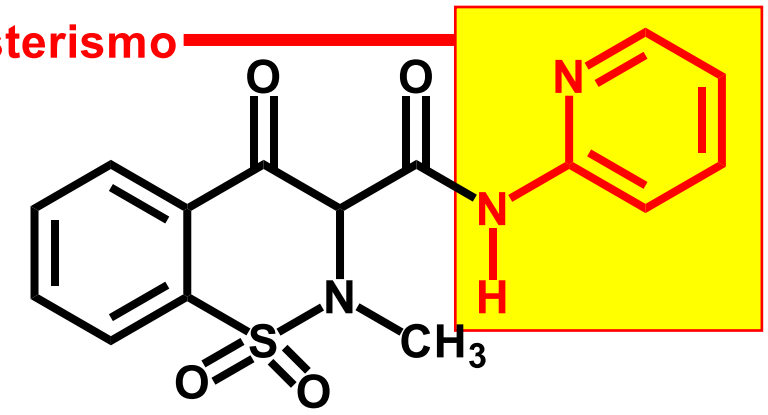
2-aminotiazola



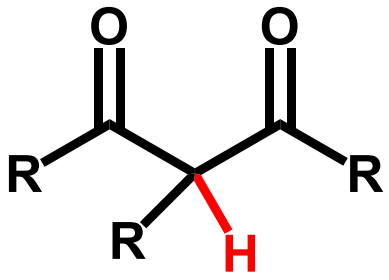
1980

2-aminopiridina

bioisosterismo



1,3-dicarbonila



meloxicam

Boehringer-Ingelheim

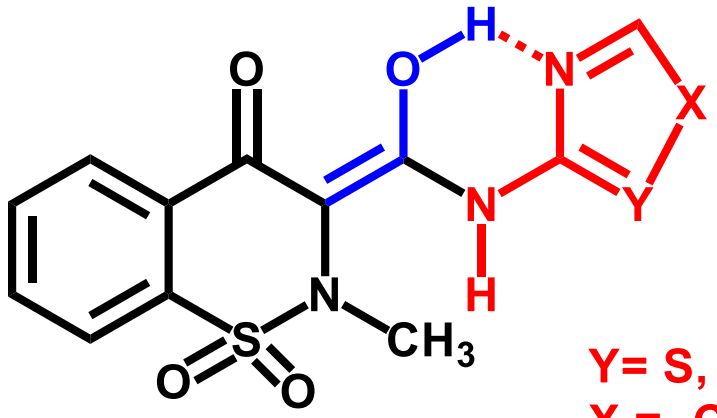
2ª da classe (me-too)

piroxicam

Pfizer

J. Lombardino

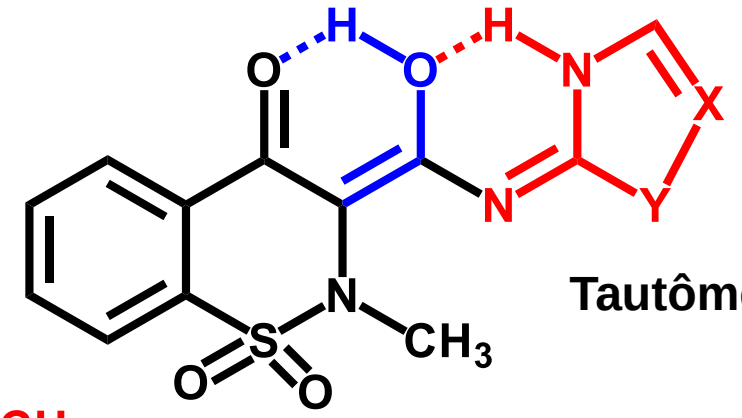
Ligação-H intramolecular



forma enólica

Y= S, =CH

X = -CH=CH-

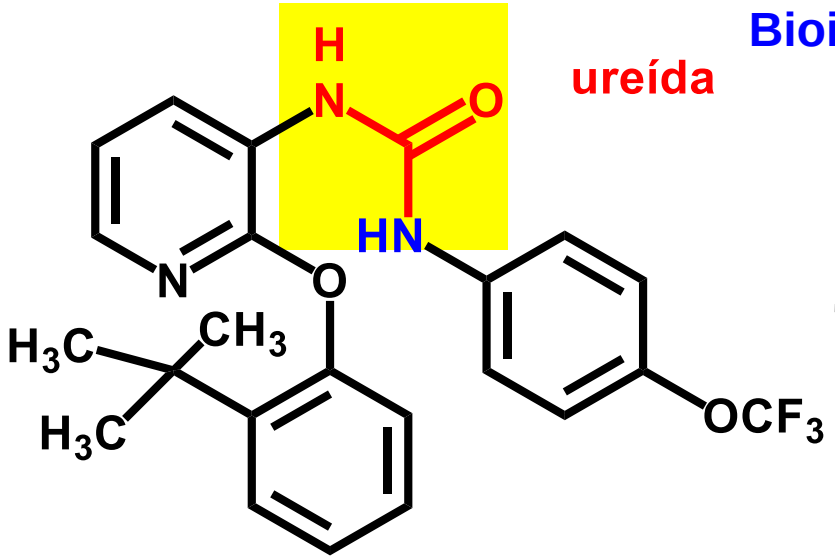


forma enólica

Tautômero

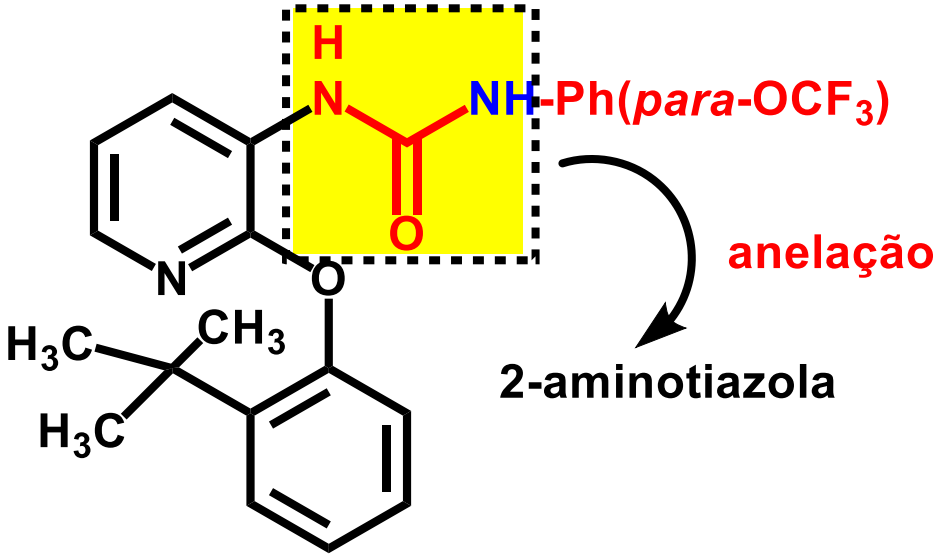
Bioisoterismo não-clássico

ureída



BMS

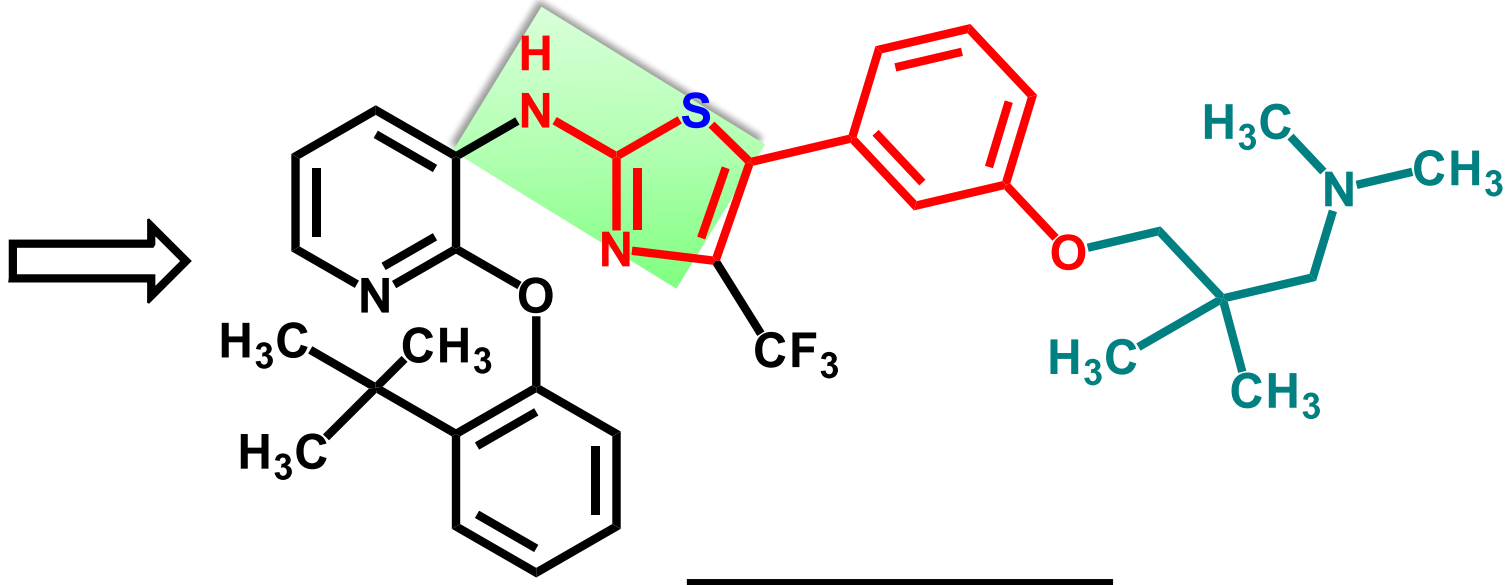
=



anelação

2-aminotiazola

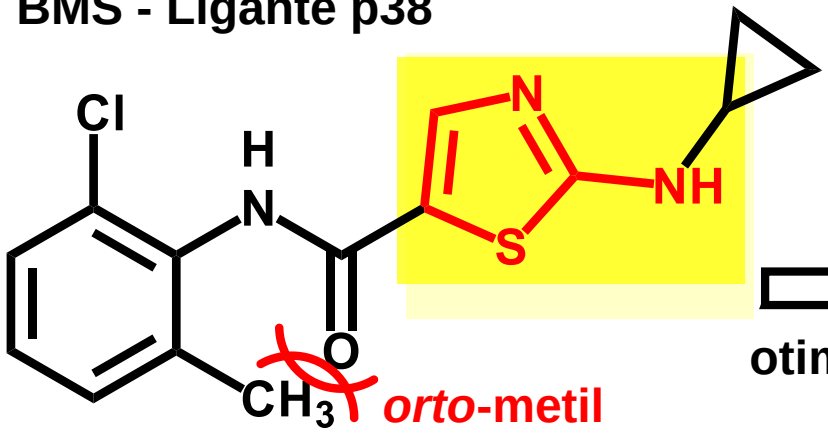
2-aminotiazola



P_2Y_1 K_i = 12 nM

Z Pi et al, *Bioorg Med Chem Lett* **2013**, *23*, 4206

BMS - Ligante p38



orto-metil

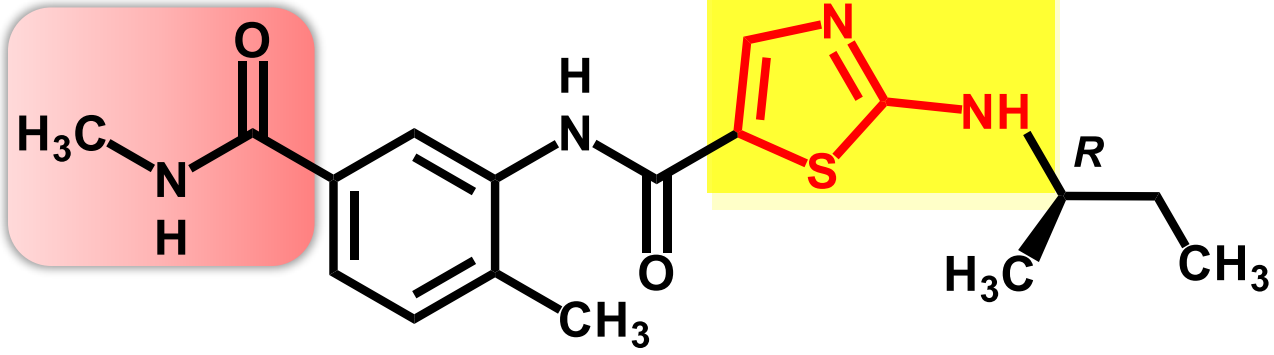
p38 IC_{50} = 39 nM

TNFα IC_{50} = 1500 nM

"open"

otimização

BMS-640994

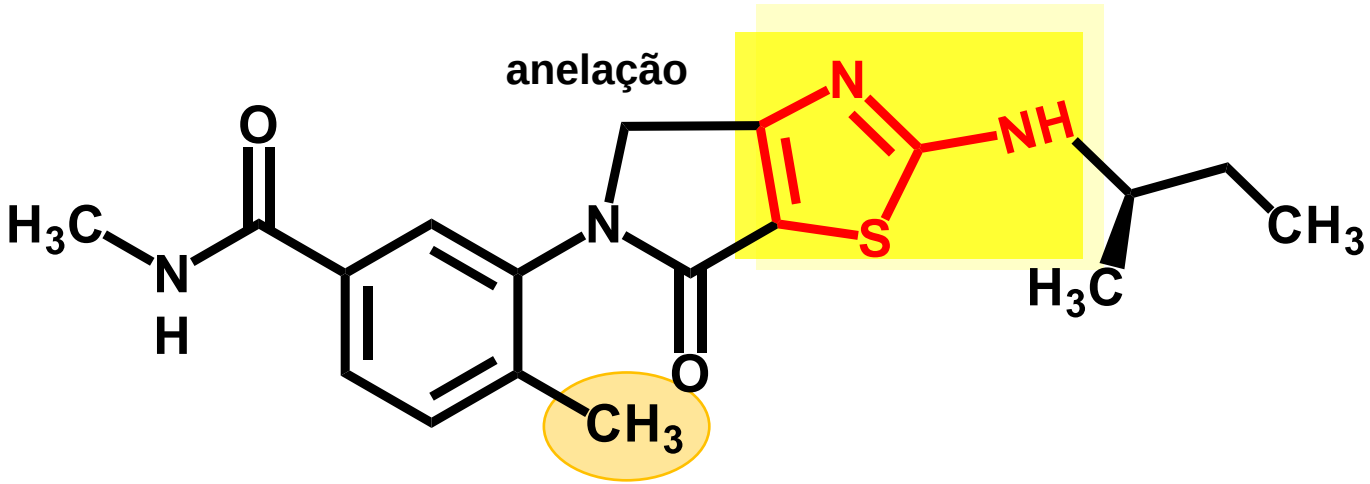


p38 IC_{50} = 3,5 nM

TNFα IC_{50} = 2,9 nM

otimização

anelação

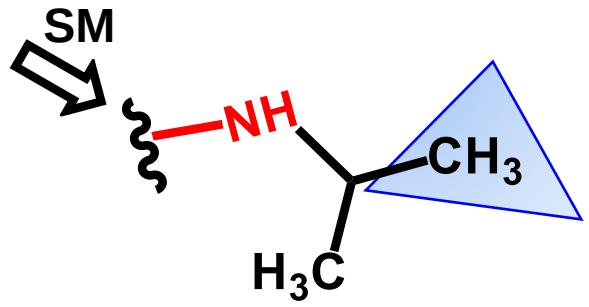


p38 IC_{50} = 110 nM

(S)-secBu

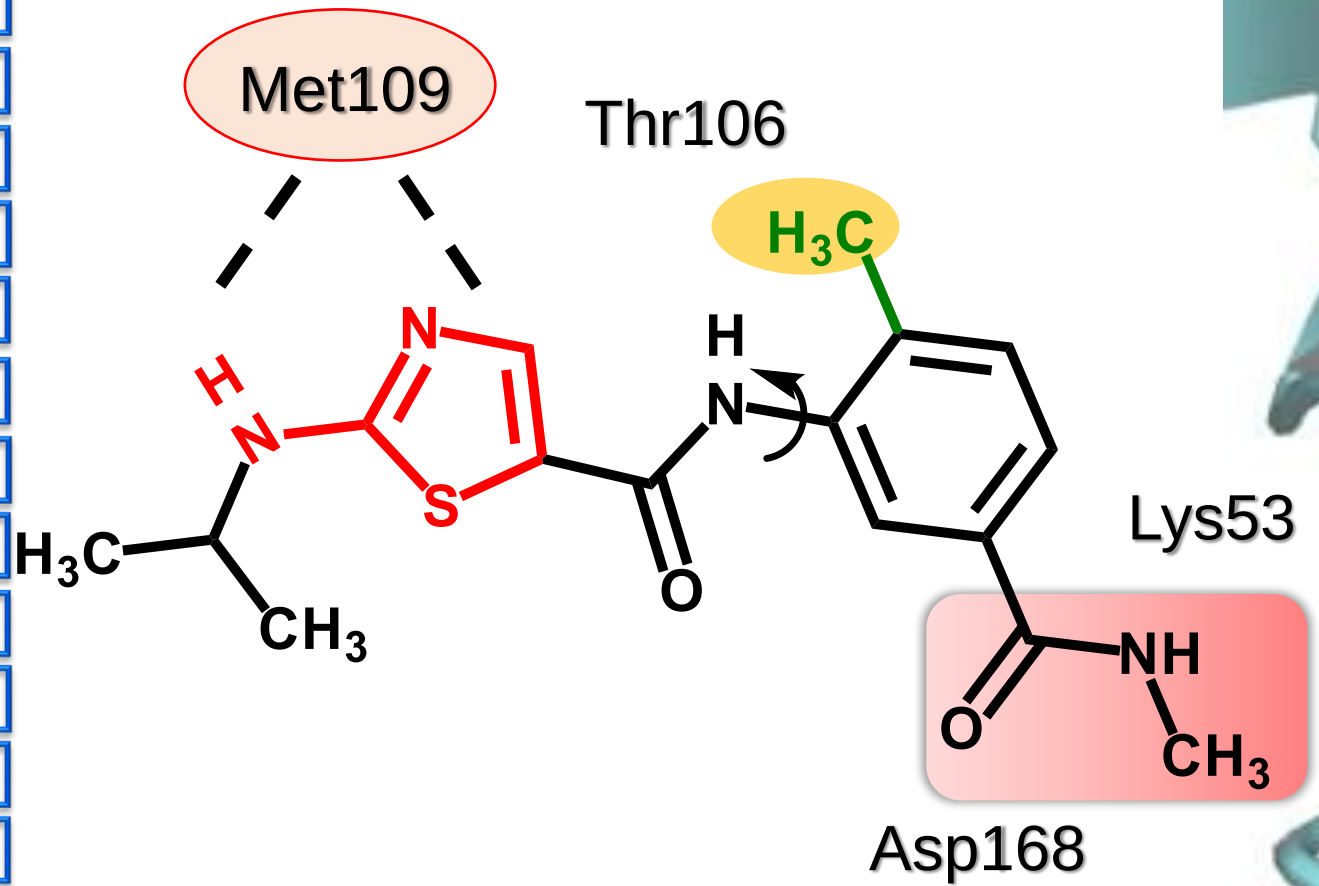
- p38 IC_{50} = 2,3 nM
- TNFα IC_{50} = 4,1 nM

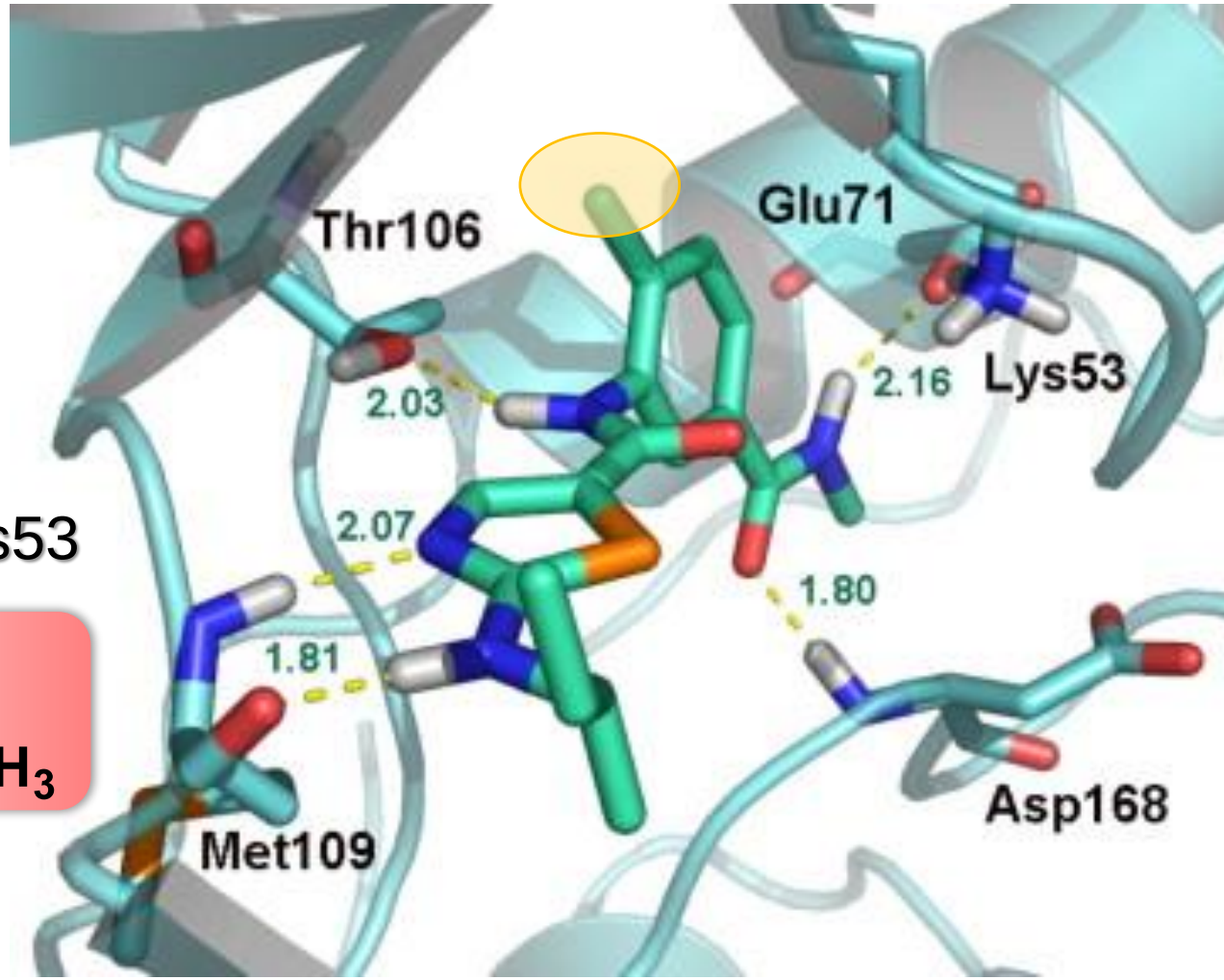
SM



p38 IC_{50} = 55 nM

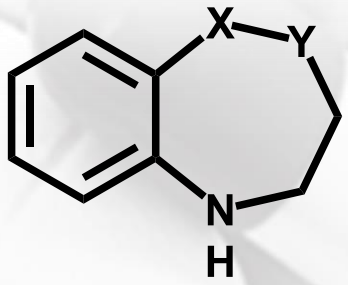
J J Hynes et al, *Bioorg Med Chem Lett* **2008**, *18*, 1762





J J Hynes et al, *Bioorg Med Chem Lett* **2008**, *18*, 1762

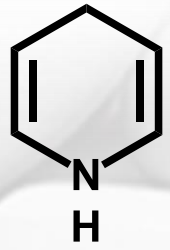
1950



X=CH_2 Y=NH - 1,4-benzodiazepinas

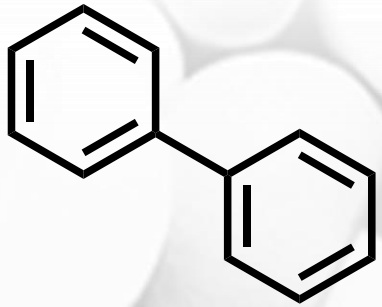
X=NH Y=CH_2 - 1,5-benzodiazepinas

1982



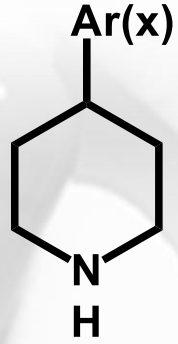
1,4-diidropiridinas

1986



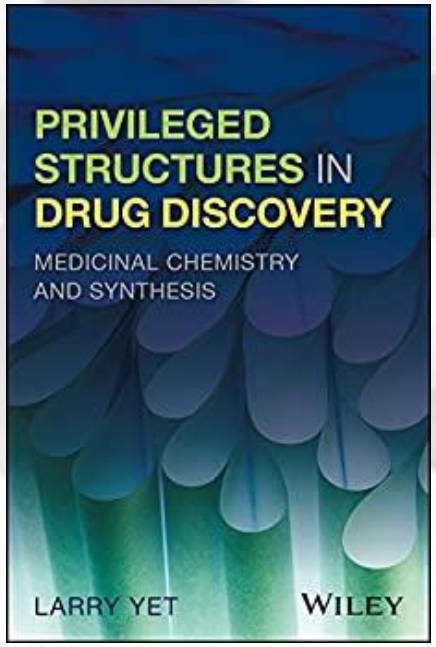
Bifenila

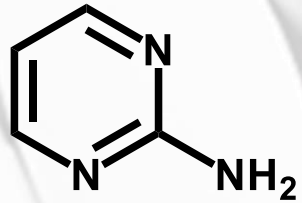
1958



4-arilpiperidinas

4-heteroarilpiperidinas

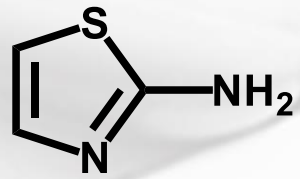




2-aminopirimidinas

crizotinibe

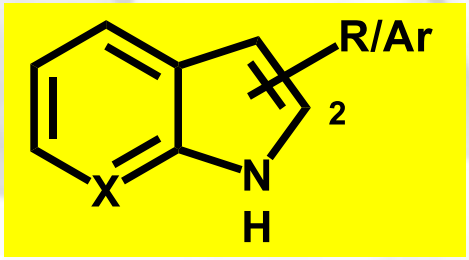
dasatinibe



2-aminotiazolas

dasatinibe

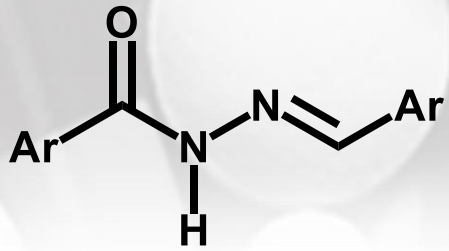
meloxicam



X=CH indol

X=N 7-azaindol

1999

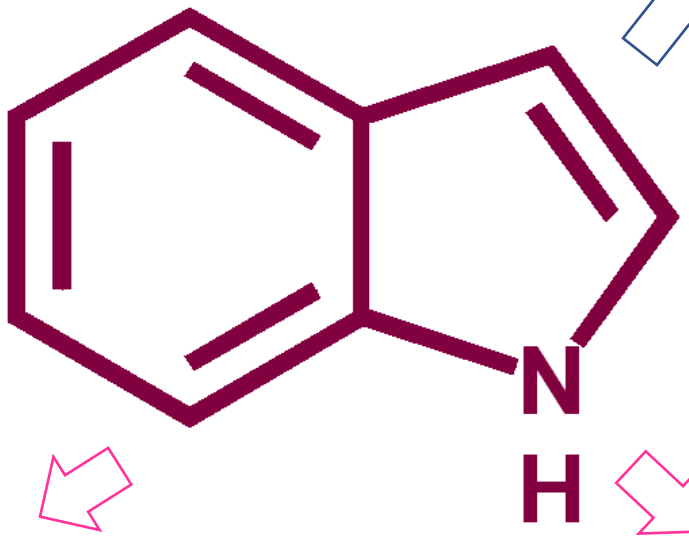


N-acilidrazona

PN´s

Síntese

Indol



Anti-hipertensivo

Reserpina

Anti-asmático

Zafirlucaste

Anti-lipêmico

Fluvastatina

Anti-viral

Delavirdina

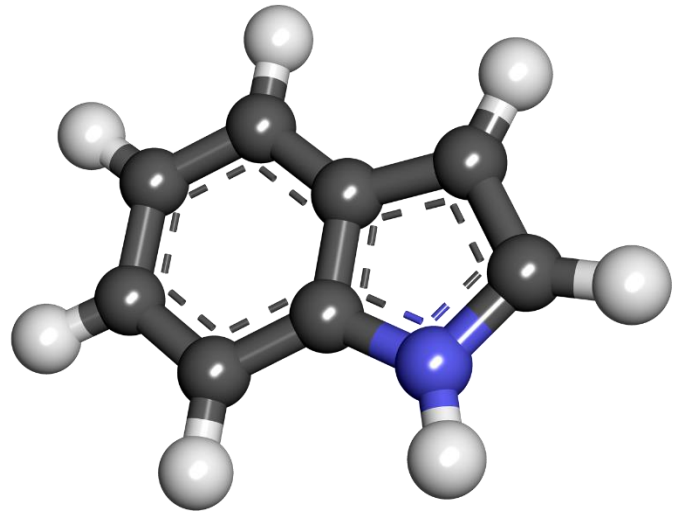
Anti-leucêmico

Vinblastina

Anti-inflamatório

Indometacina

From Nature to Drug Discovery: The Indole Scaffold as a 'Privileged Structure'

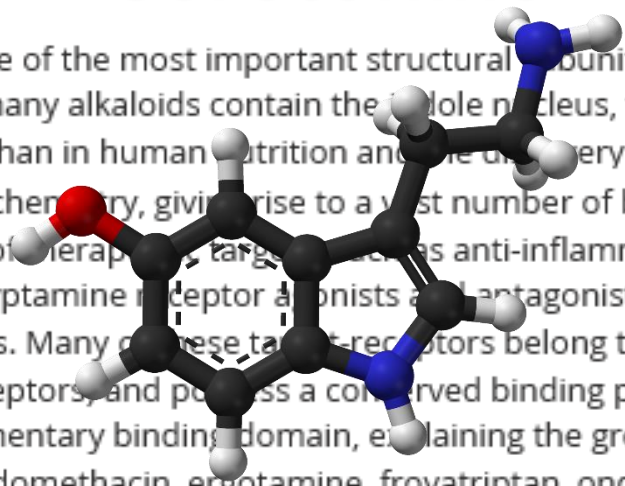


Authors: de Sa Alves, Fernando R.; Barreiro, Eliezer J.; Manssour Fraga, Carlos Alberto

Source: Mini Reviews in Medicinal Chemistry, Volume 9, Number 7, June 2009, pp. 782-793(12)

Publisher: Bentham Science Publishers

serotonine

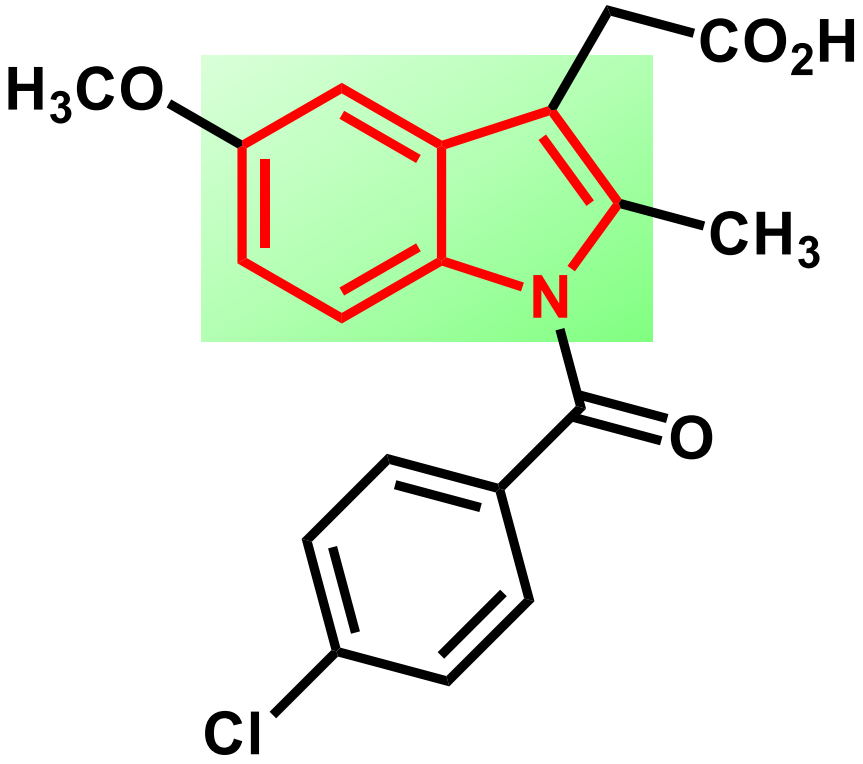


Abstract:

The indole scaffold probably represents one of the most important structural subunits for the discovery of new drug candidates. The demonstration that many alkaloids contain the indole nucleus, the recognition of the importance of essential amino acid tryptophan in human nutrition and the discovery of plant hormones served to bring about a massive search on indole chemistry, giving rise to a vast number of biologically active natural and synthetic products, with a wide range of therapeutic targets such as anti-inflammatories, phosphodiesterase inhibitors, 5-hydroxytryptamine receptor agonists and antagonists, cannabinoid receptors agonists and HMG-CoA reductase inhibitors. Many of these target-receptors belong to the class of GPCRs (integral membrane G-protein coupled receptors) and possess a conserved binding pocket that is recognized by the indole scaffold in a "common" complementary binding domain, explaining the great number of drugs that contain the indole substructure, such as indomethacin, ergotamine, frovatriptan, ondansetron, tadalafil, among many others.

FR de Sá Alves, EJ Barreiro, CA Fraga, *Mini Rev. Med. Chem.*, **2009**, *9*, 782

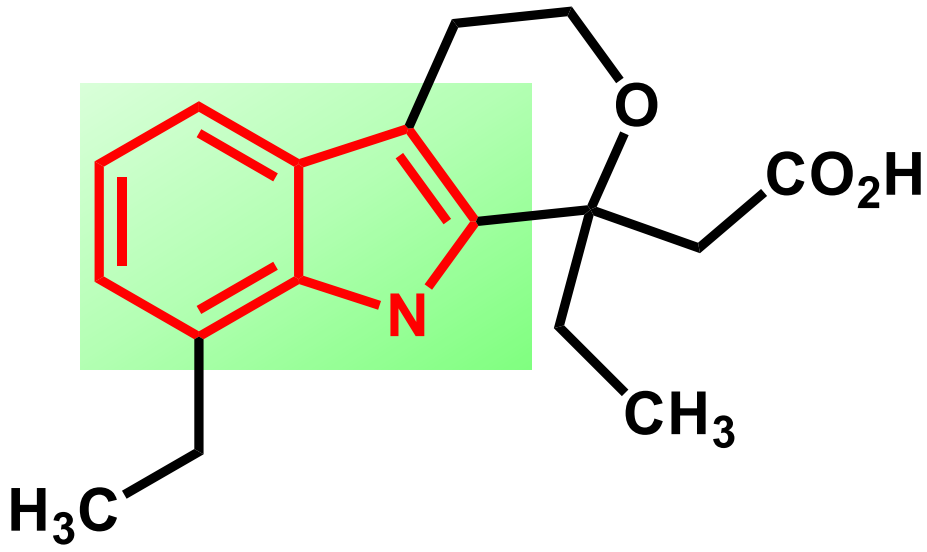
1965



indometacina

MSD

1991



etodolaco

F R S Alves, E J Barreiro, C A M Fraga, From Nature to Drug Discovery: The Indole Scaffold as a 'Privileged Structure, *Mini-Reviews Med Chem* ***20*****09**, *9*, 82;

N Chadha, O Silakari, Indoles as therapeutics of interest in medicinal chemistry: Bird's eye view, *Eur J Med Chem* **2017**, *134*, 159

1994

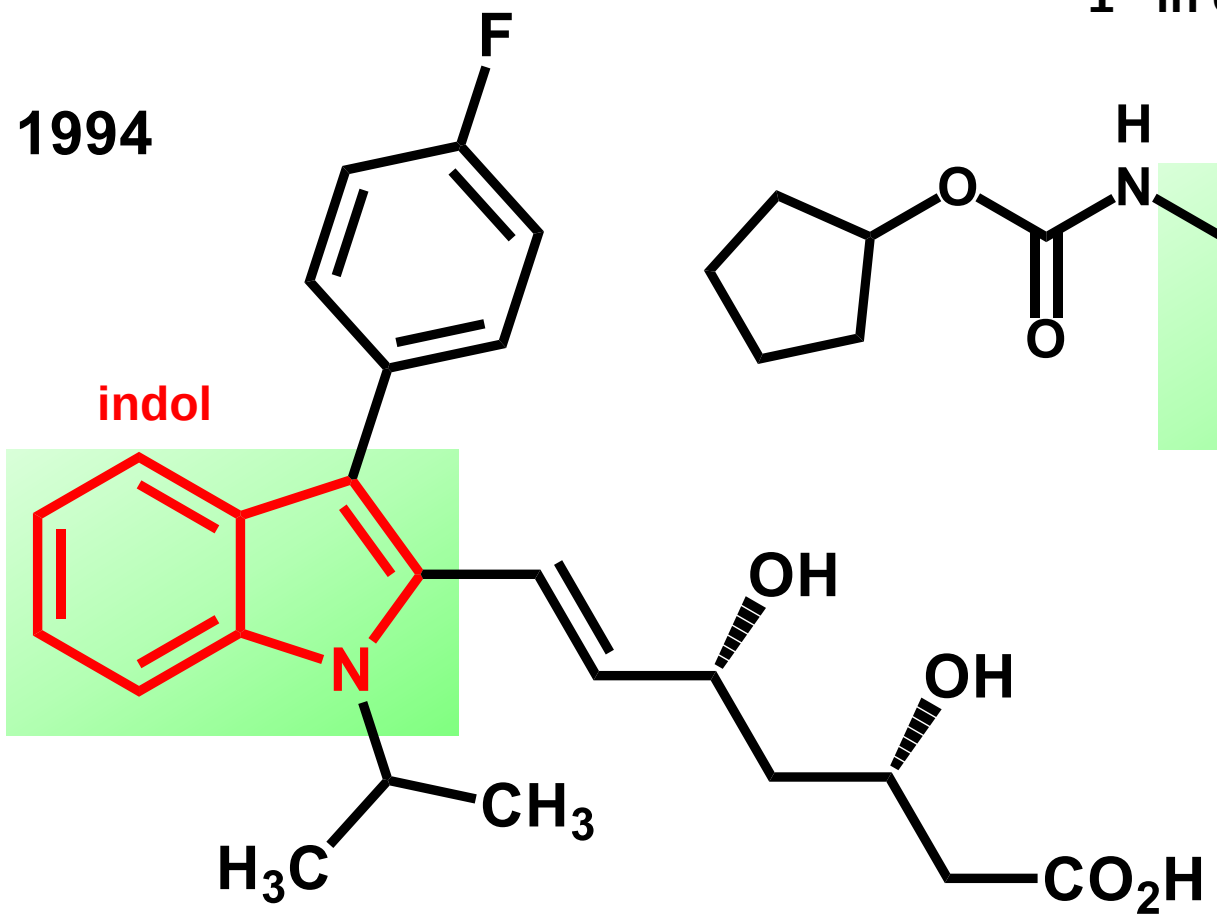
1996 (AZ)

1st in class

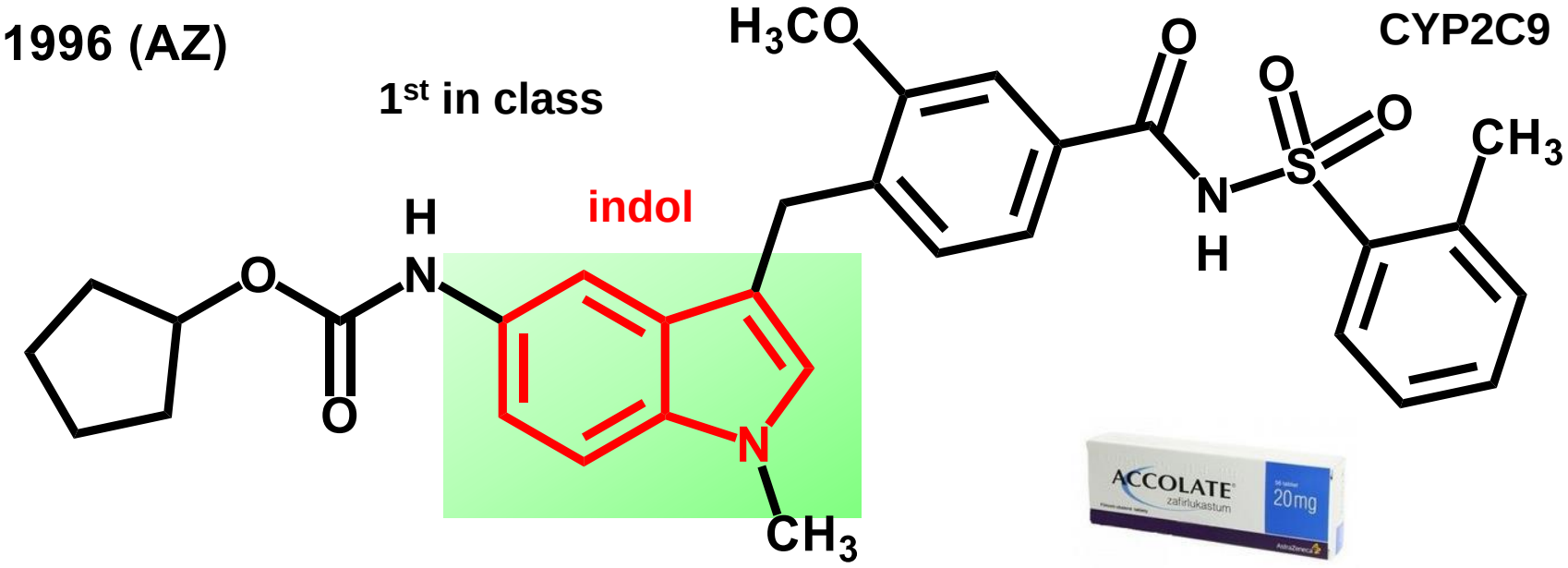
CYP2C9

indol

indol



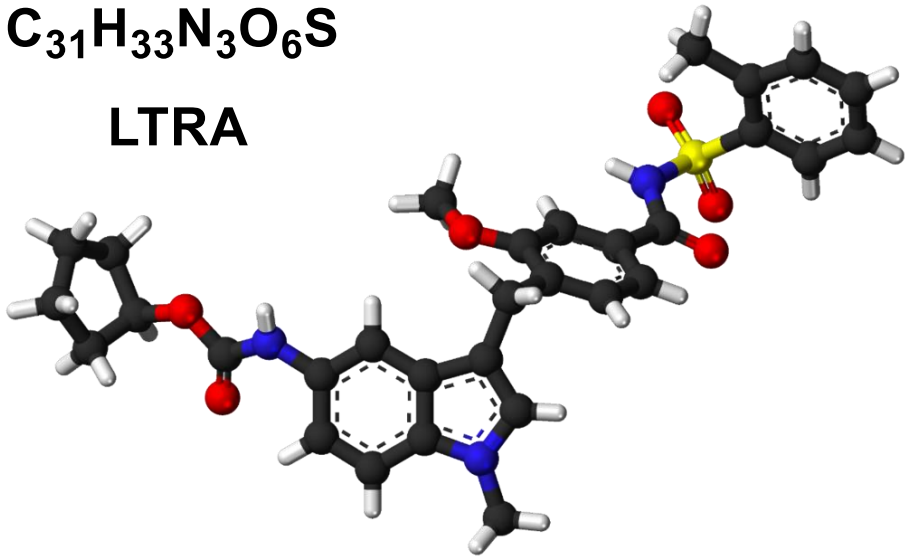
fluvastatina



zafirlucaste

$C_{31}H_{33}N_3O_6S$

LTRA



2011 - Daichi-Sankyo

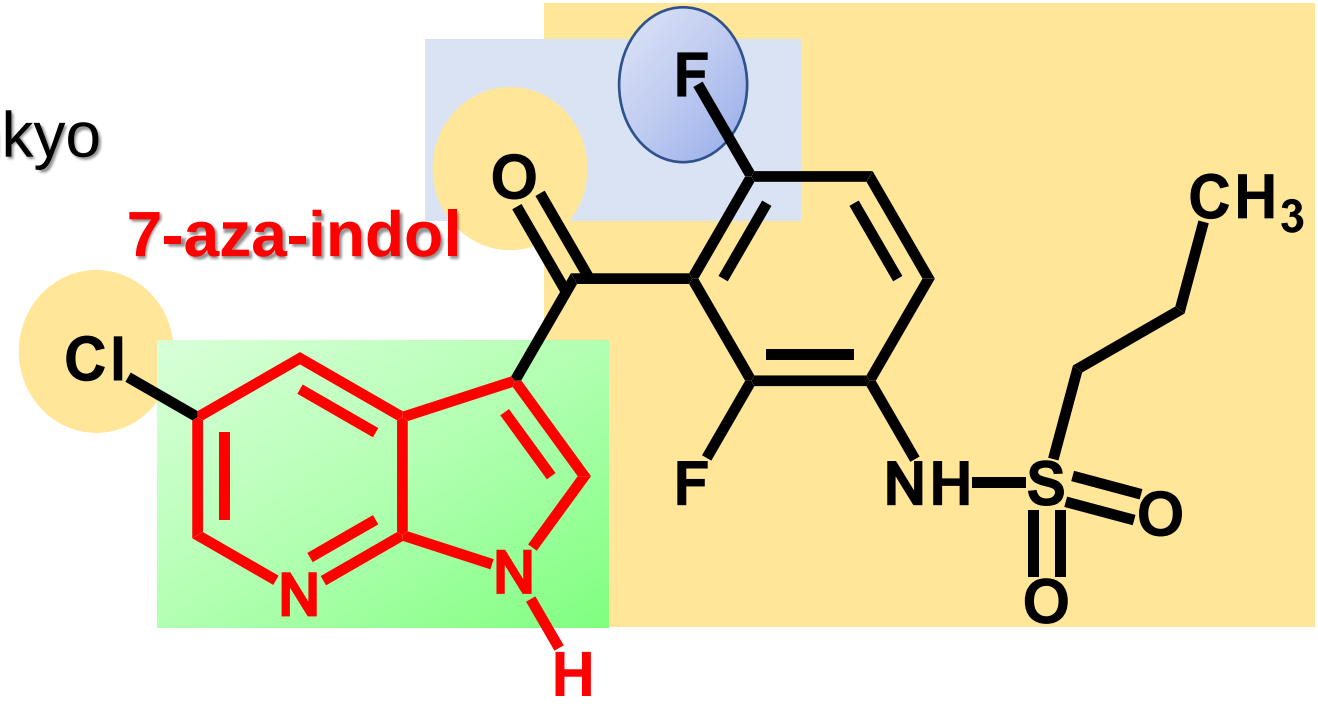
Zelboraf® vemurafenib

vemurafenibe

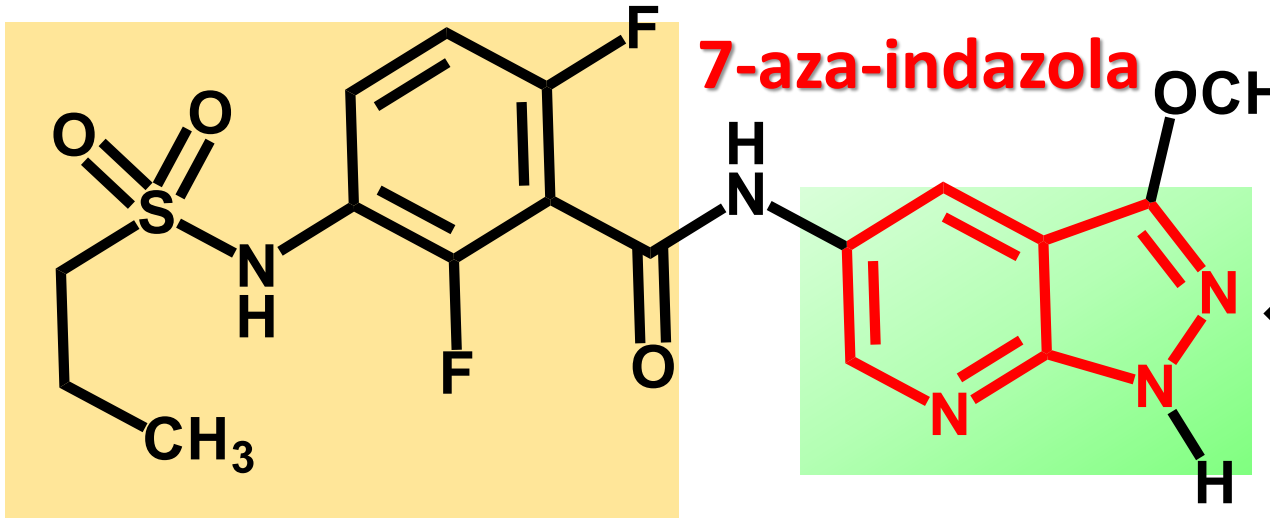
Inibidor B-Raf^{V600E}

melanoma

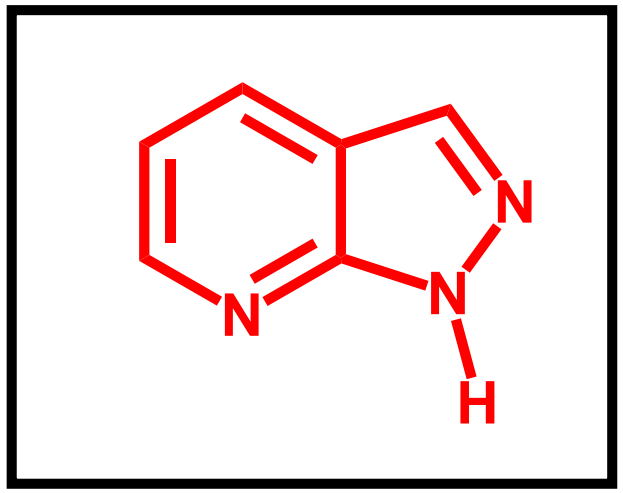
7-aza-indol



regioisômeros

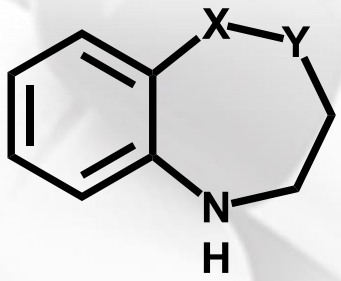


inibidor B-Raf^{V600E}



1*H*-pirazolo[3,4-*d*]piridina

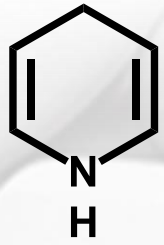
1950



X=CH_2 Y=NH - 1,4-benzodiazepinas

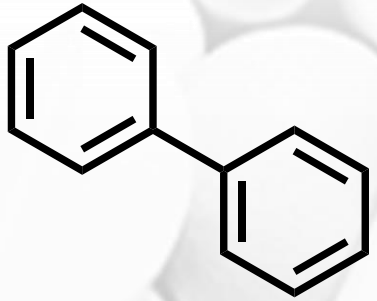
X=NH Y=CH_2 - 1,5-benzodiazepinas

1982



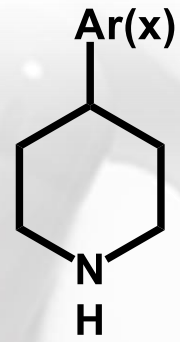
1,4-diidropiridinas

1986



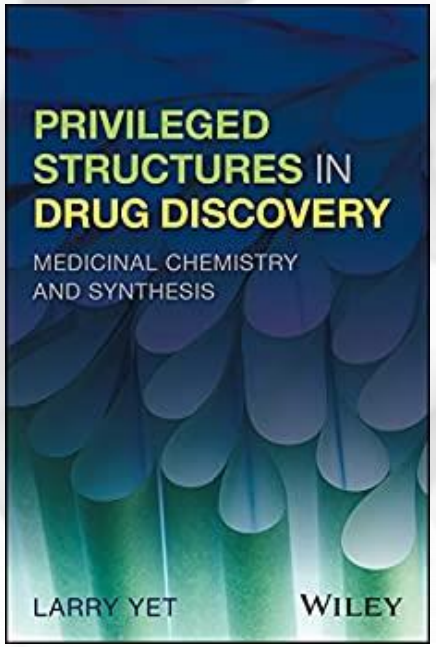
Bifenila

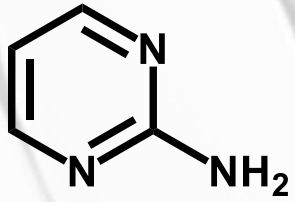
1958



4-arilpiperidinas

4-heteroarilpiperidinas

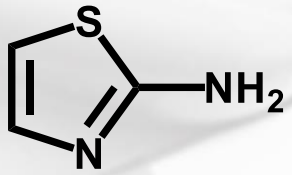




2-aminopirimidinas

crizotinibe

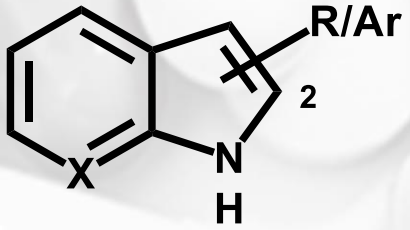
dasatinibe



2-aminotiazolas

dasatinibe

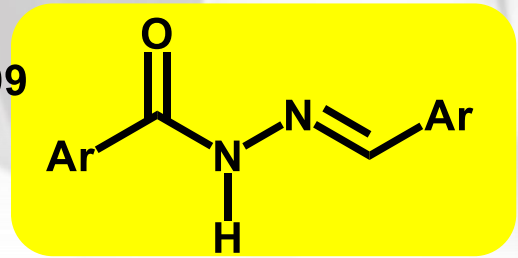
meloxicam



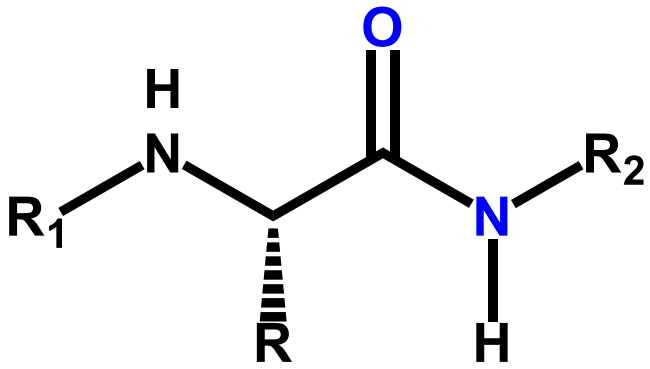
X=CH indol

X=N 7-azaindol

1999

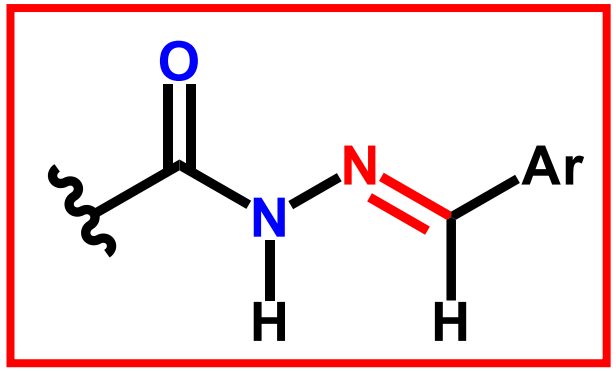


N-acilidrazona



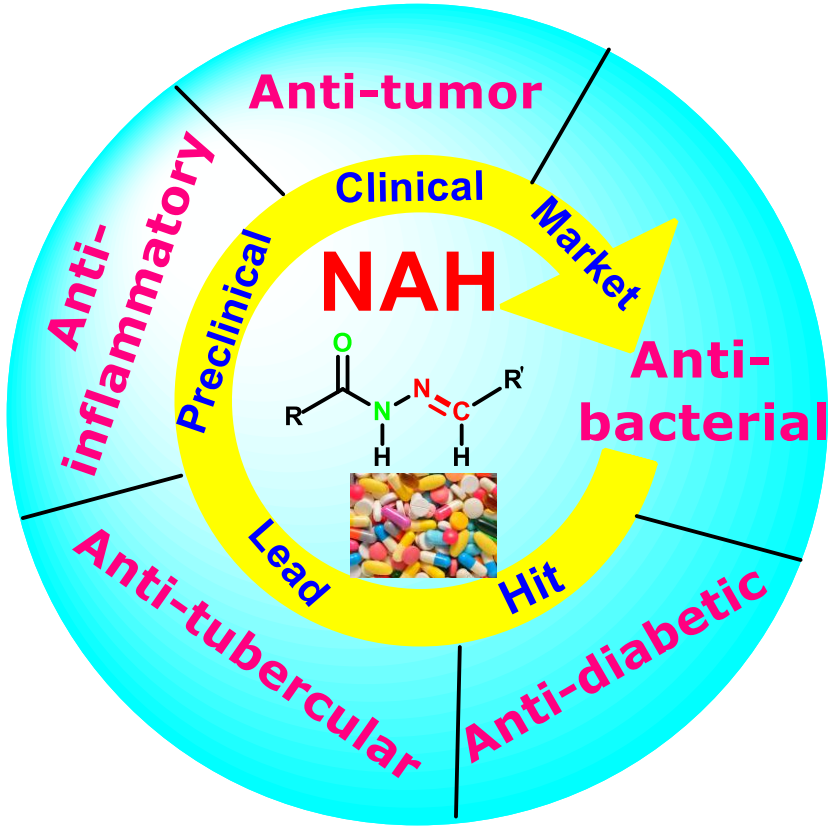
scaffold peptídico

homólogo
aza-vinilógo



N-acilidrazona

restrição conformacional >estabilidade química



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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

In this article we provide an overview on the medicinal chemistry of new bioactive *N*-acylhydrazone (NAH) derivatives designed through the structural optimization of *N*-arylhydrazone precursors, originally planned by molecular hybridization of two known 5-lipoxygenase inhibitors, *i.e*. CBS-1108 and BW-755c. The analgesic, antiedematogenic and platelet anti-aggregating profile of several isosteric NAH compounds was investigated by using classical *in vivo* and *ex-vivo* pharmacological assays, which allowed the identification of new potent centrally and peripherically-acting analgesic leads, new antiinflammatory agents and new antithrombotic prototypes. During this study, dozens of active NAH compounds were discovered, clarifying the structure-activity relationships for this series of derivatives and indicating the pharmacophoric character of the *N*-acylhydrazone moiety for its biological profile.

NAH as privileged strutures

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

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/bmcl

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,*]

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ARTICLE INFO

Keywords: *N*-Acylhydrazone
Drugs
Drug discovery
Clinical trials
Preclinical

ABSTRACT

Over the last two decades, *N*-acylhydrazone (NAH) has been proven to be a very versatile and promising motif in drug design and medicinal chemistry. Herein, we discuss the current and future challenges in the emergence of bioactive NAH-based scaffolds and to developing strategies to overcome the failures in drug discovery.

2017

Comprehensive Medicinal Chemistry III, 3rd Edition, Elsevier, 2017.

N-Acylhydrazones and related diazo structures

Fraga and coworkers have reviewed the patent literature on the acylhydrazone privileged functional group.[83] For instance, the drug dantrolene contains this privileged motif and is used to treat malignant hyperthermia. The acylhydrazone core is used in research studies for pain, inflammation, cancer, and cardiovascular targets. Fraga and coworkers[84] have combined a rational design approach using molecular modeling studies with the acylhydrazone privileged template to generate a novel IKK-β inhibitor (*E*)-*N*-(4-nitrobenzylidene)-2-naphthohydrazide. Incorporation of two lipophilic motifs around the central privileged template led to a scaffold with increased selectivity over IKK-α and CHK2. Furthermore, the privileged compound was shown to suppress arachidonic acid-induced edema formation in vivo, demonstrating an antiinflammatory mode of action.

Barreiro and coworkers[85] have designed a new class of cyclohexyl-*N*-acylhydrazones using the prototype compound, LASSBio-294 with the aim of preparing analogs with analgesic and antiinflammatory properties. The *N*-acylhydrazone motif is considered a privileged scaffold with pluripotent biological activities. Most analogs demonstrated some antiinflammatory and/or analgesic activity, and one example showed remarkable activity in a chronic neuropathic pain model.

Expert Opin. Ther. Patents (2014) 24(11):1161-1170

Review

EXPERT OPINION

Acylhydrazone derivatives: a patent review

Rodolfo do Couto Maia, Roberta Tesch & Carlos Alberto Manssour Fraga[†]

[†]*Universidade Federal do Rio de Janeiro, Instituto de Ciências Biomédicas, Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Rio de Janeiro, Brazil*

Introduction: The *N*-acylhydrazone (NAH) moiety has been characterized as a *privileged structure,* capable of providing ligands points for more than one type of bioreceptor. Modifications of the subunits bonded to its acyl and imine functions resulted in several derivatives, which modulate a great diversity of molecular targets. In this context, this patent review reflects the use of the NAH moiety in different compounds.

Keywords: analgesic drugs, anticancer drugs, anti-inflammatory drugs, *N*-acylhydrazone, privileged structure

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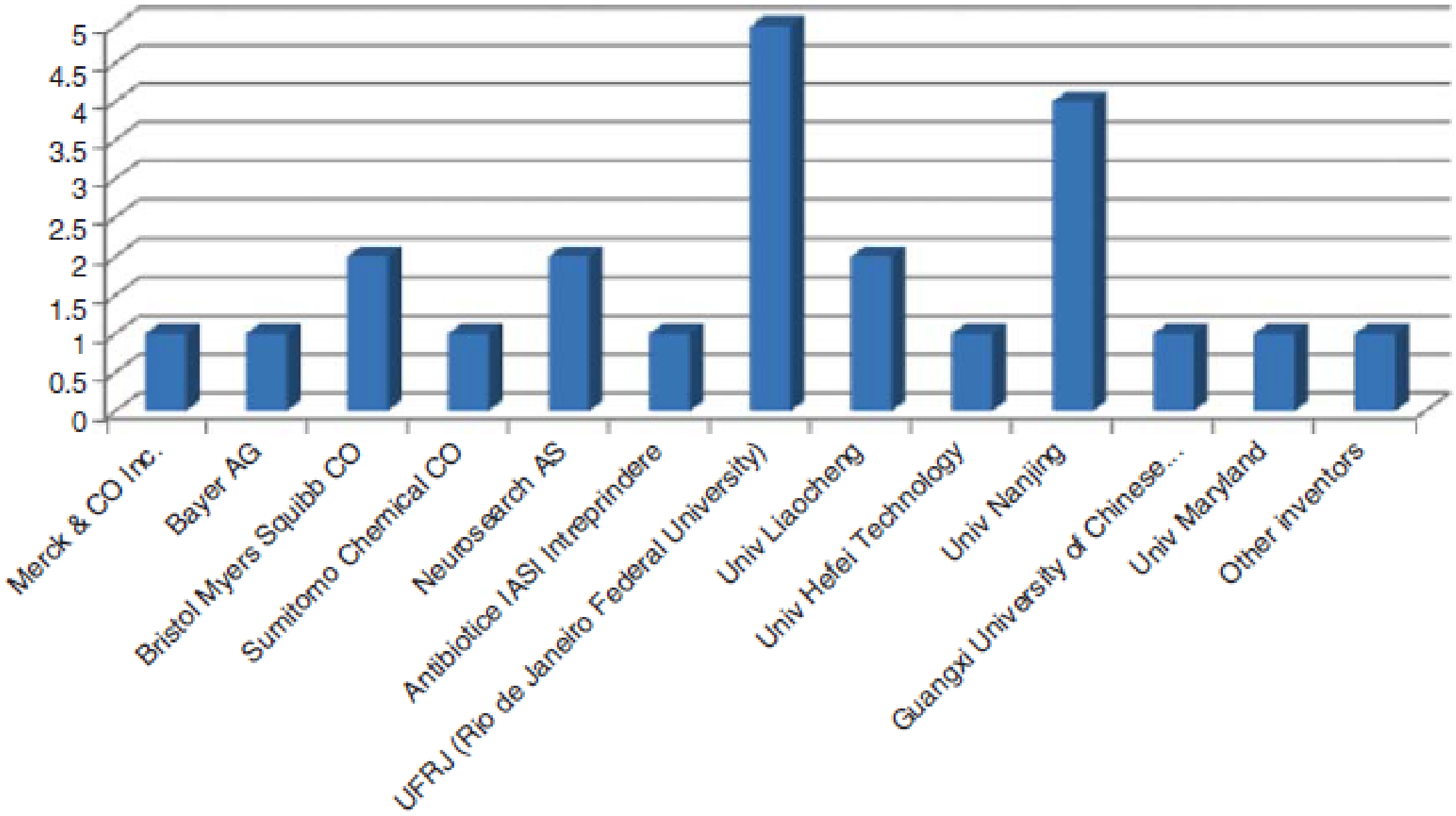
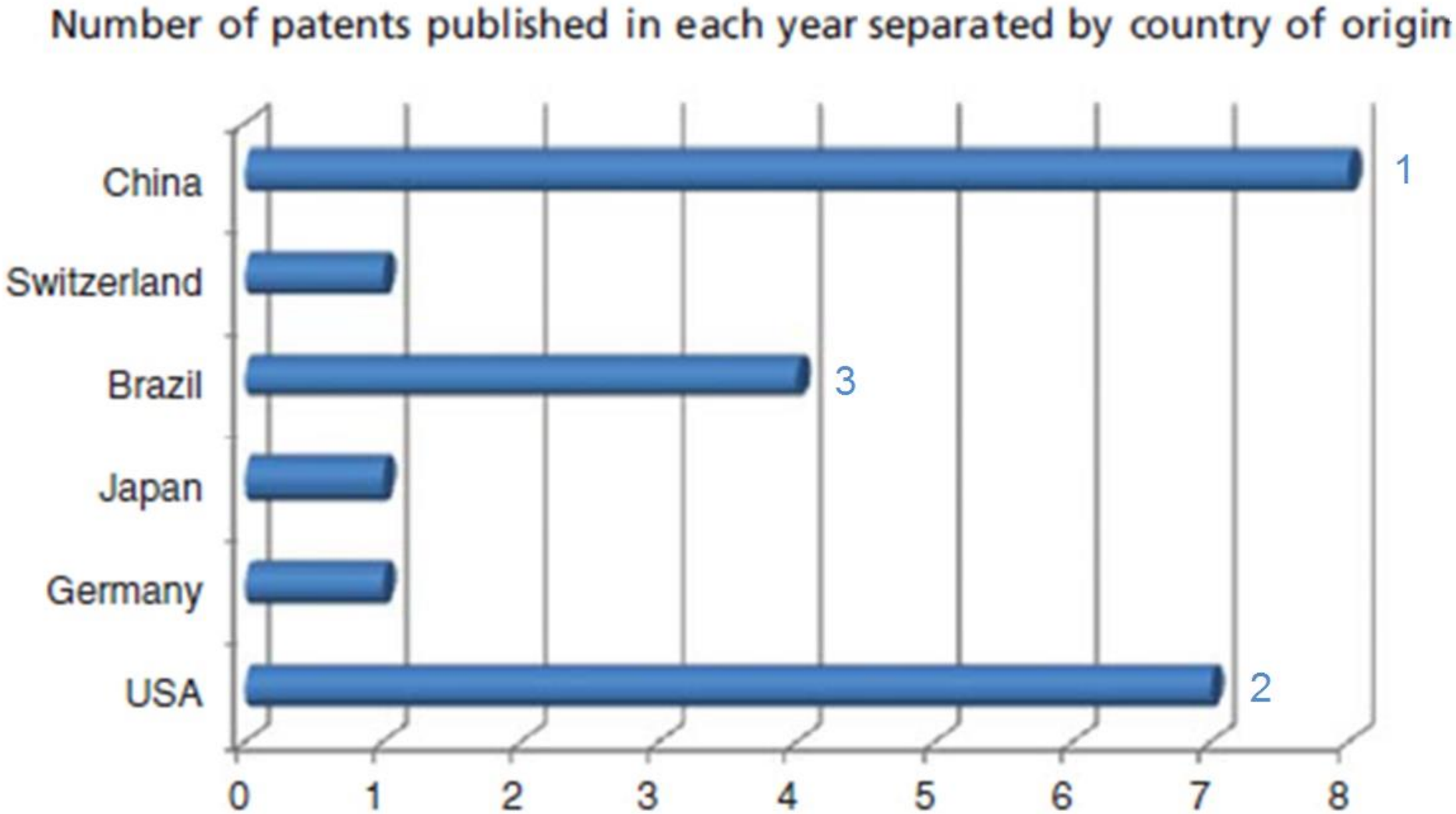
Number of patents published, separated by applicant, disclosing *N*-acylhydrazone derivatives with therapeutic uses.




Number of patents published in each year separated by country of origin
China
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Brazil
Japan
Germany
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3
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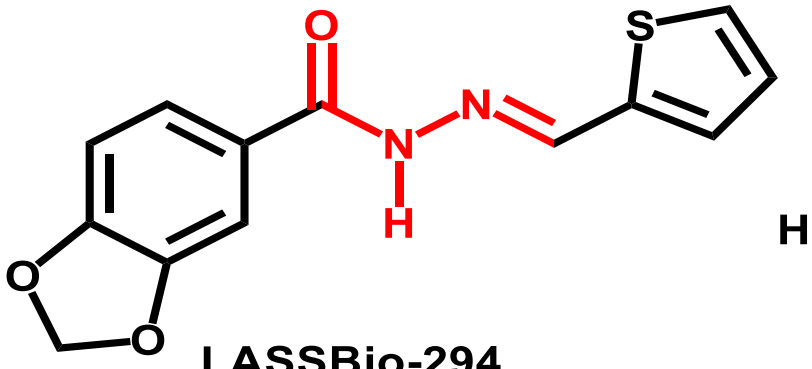
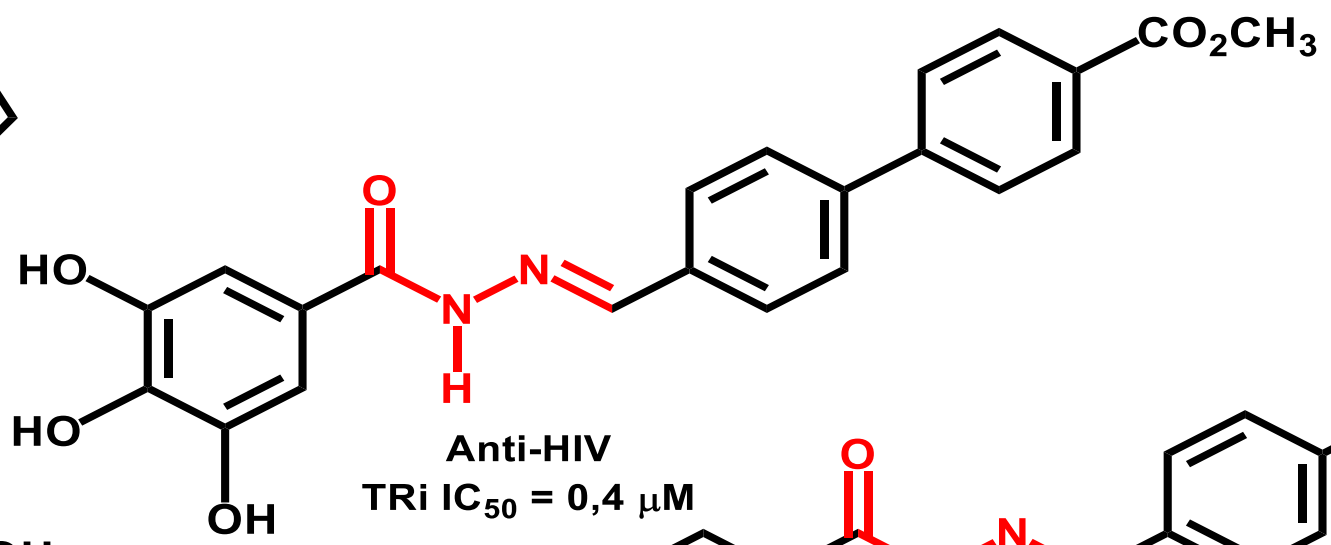
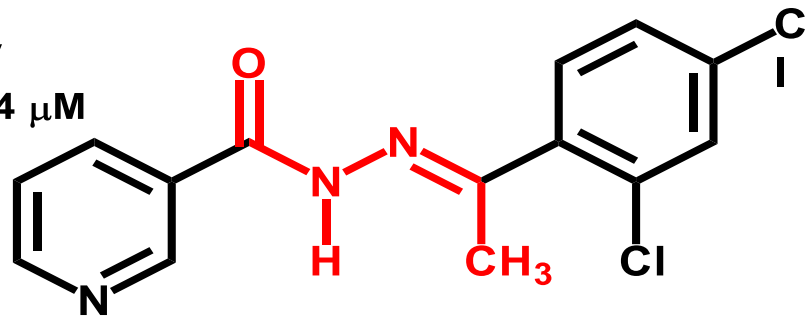


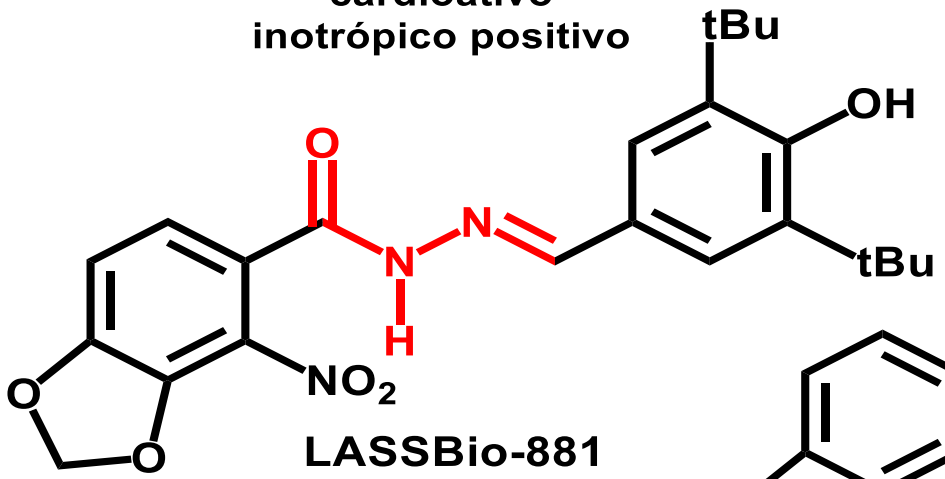
LASSBio-294
cardioativo
inotrópico positivo



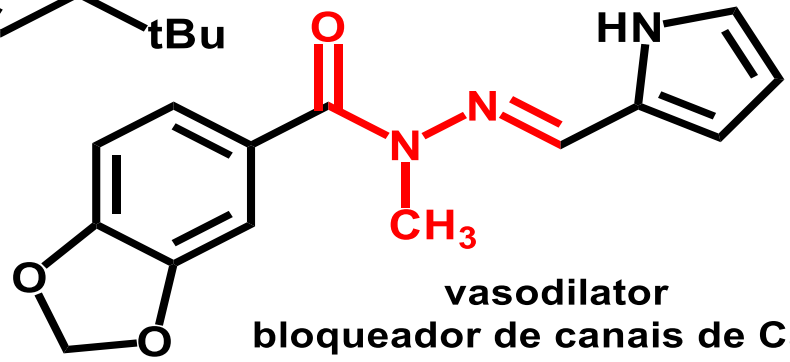
Anti-HIV
TRi IC_{50} = 0,4 μM



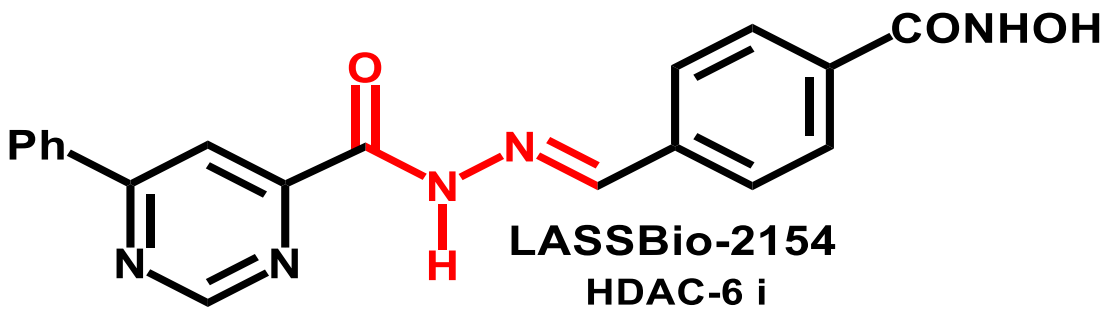
Anti-TB
MIC = 12,5 mg/ml



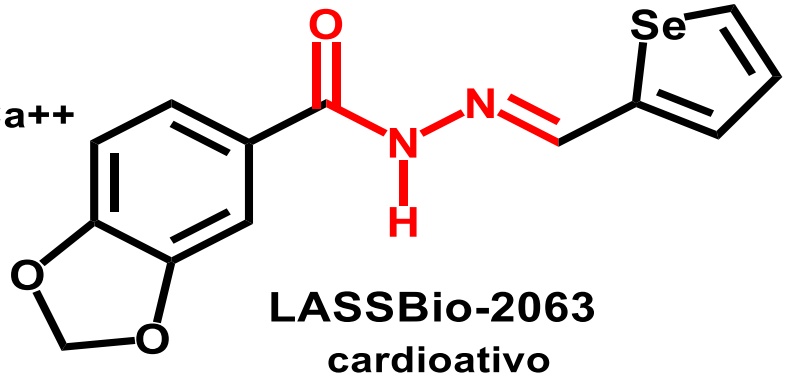
LASSBio-881
Anti-HIV
TRi IC_{50} = 0,4 μM



vasodilator
bloqueador de canais de Ca++

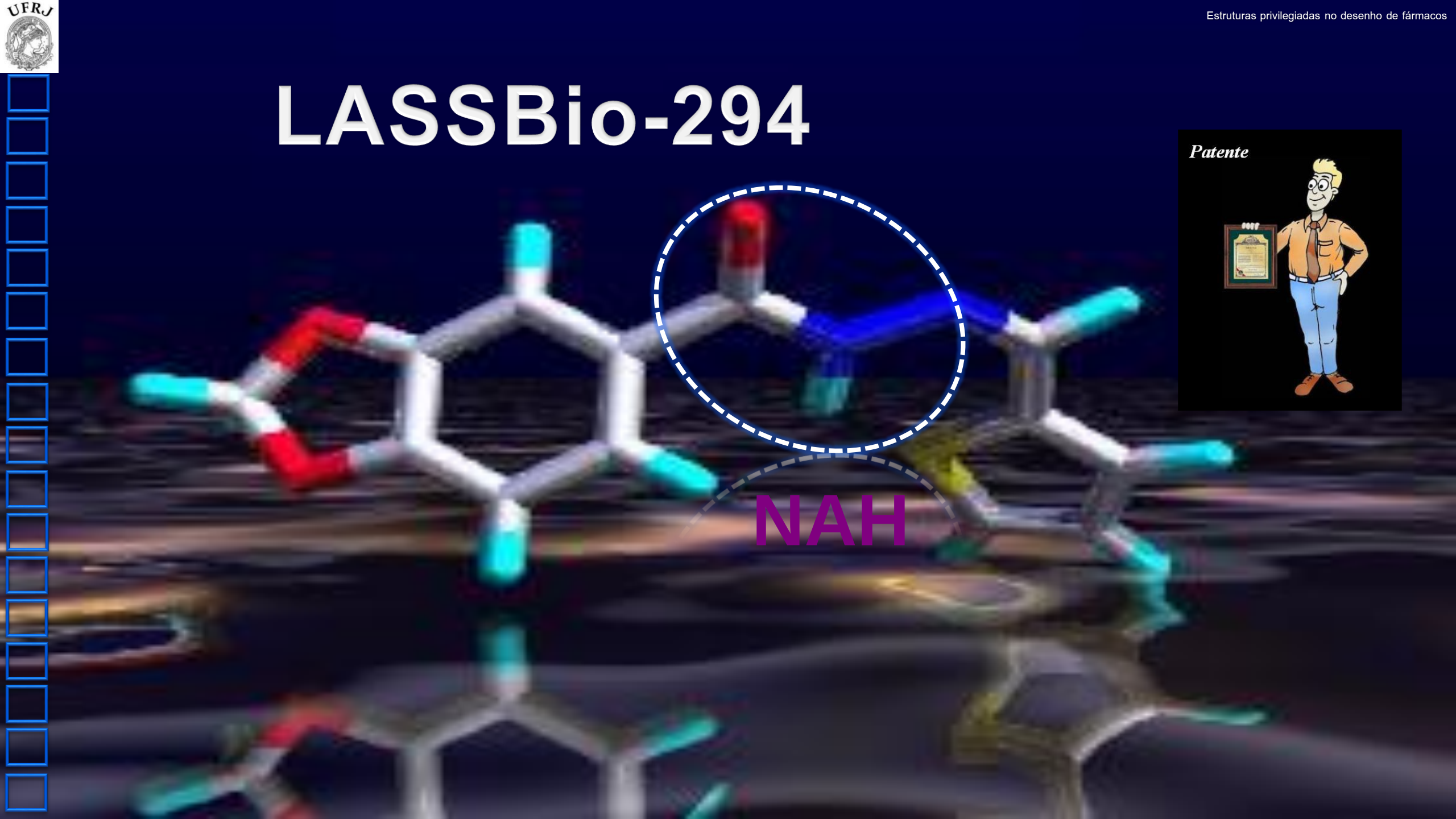


LASSBio-2154
HDAC-6 i

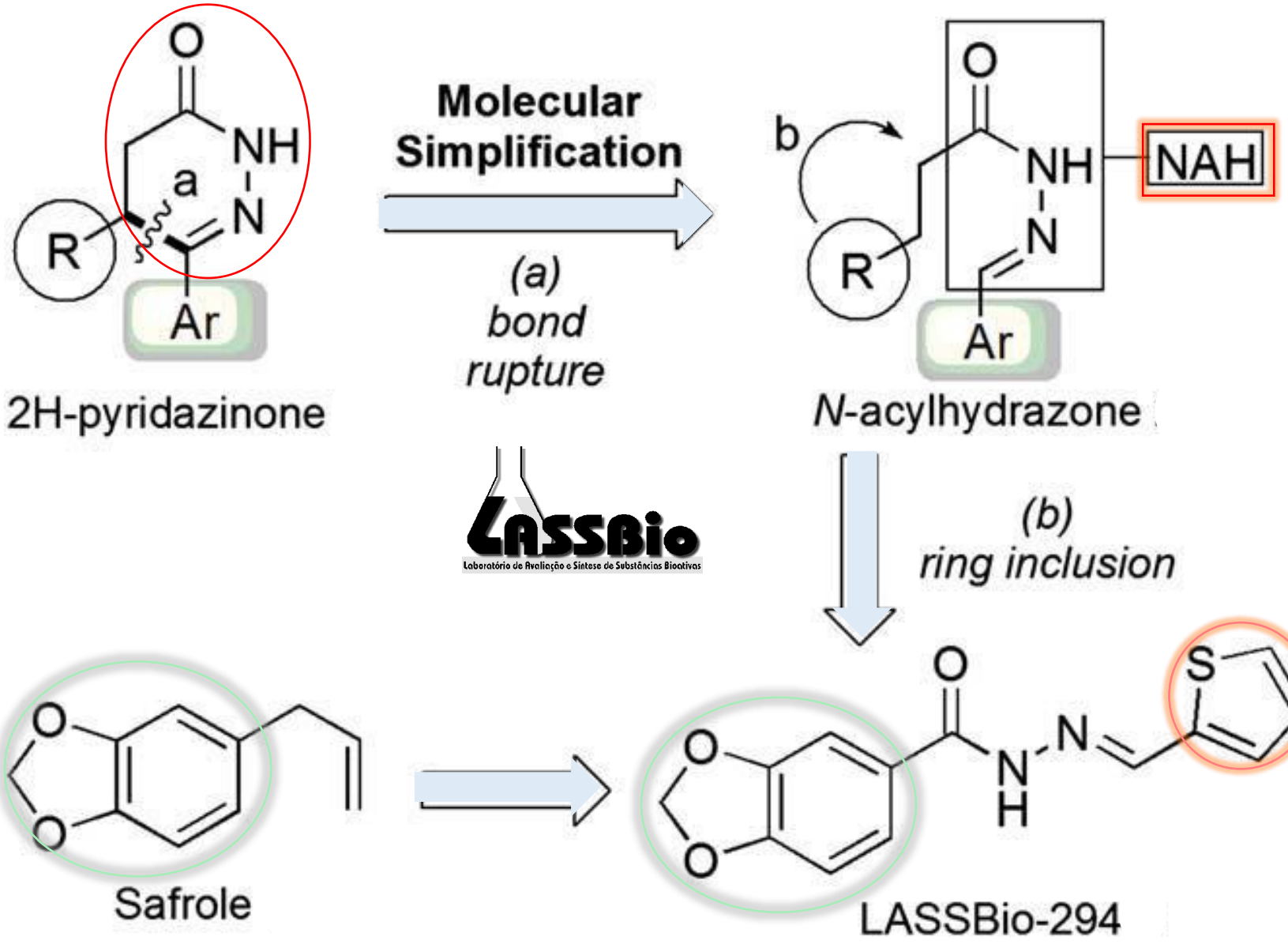


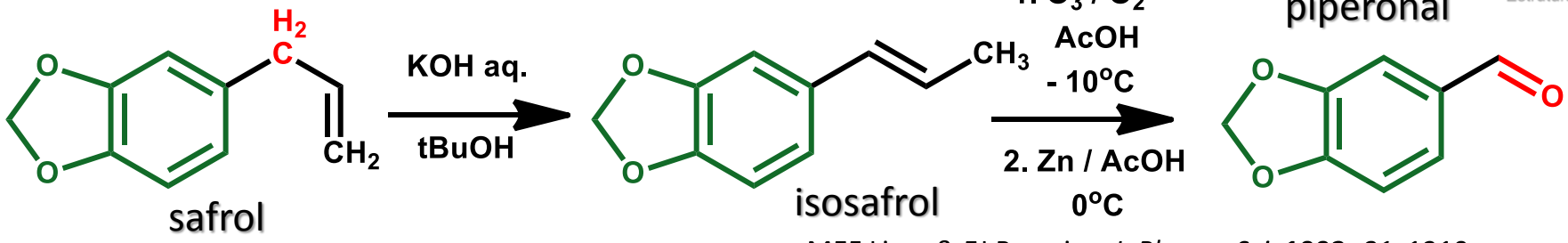
LASSBio-2063
cardioativo
inotrópico positivo

LASSBio-294



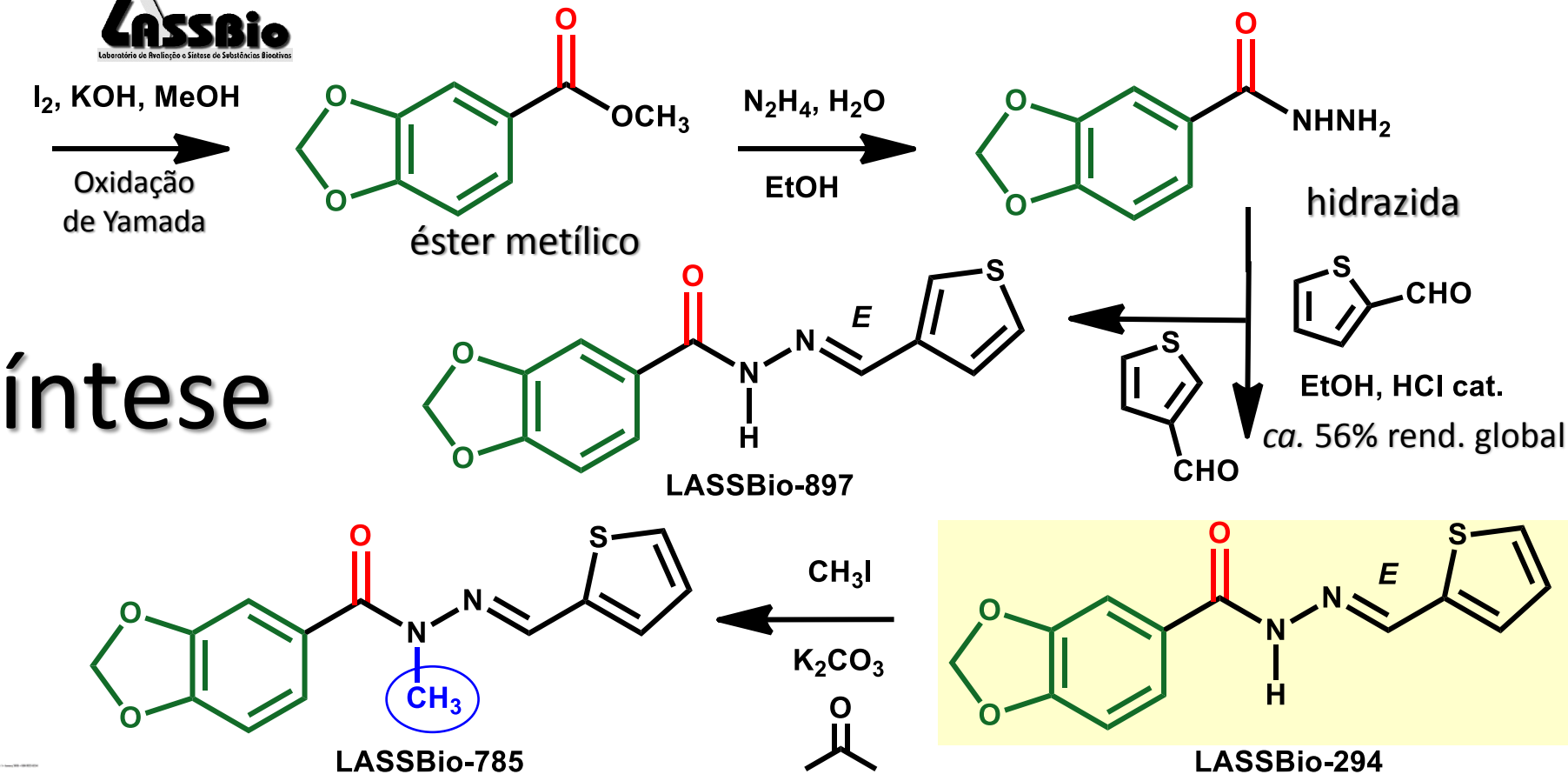
A gênese do LASSBio-294...





MEF Lima & EJ Barreiro, *J. Pharm. Sci.* **1992**, *81*, 1219

A síntese

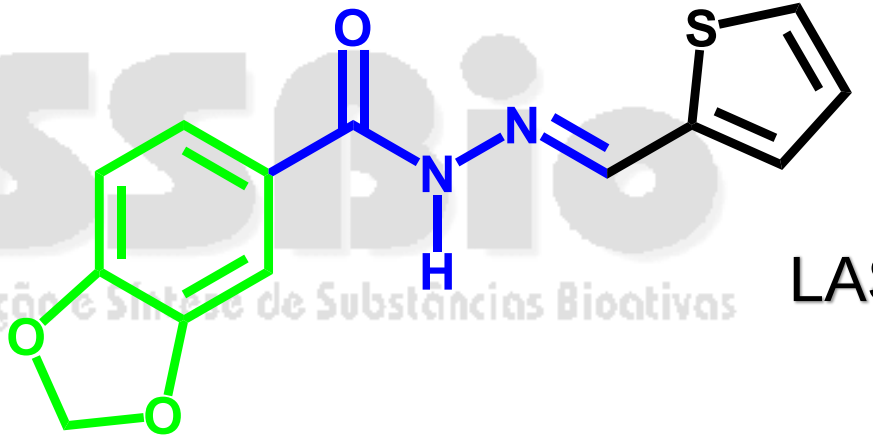


P. C. Lima et al.Synthesis and Non-addictive Analgesic Activity of Novel *N*-acylarylhydrazones and Isosters, Derived from Natural Safrole, *Eur. J. Med. Chem.* **2000,** *35*, 187.

Rota sintética escalonável

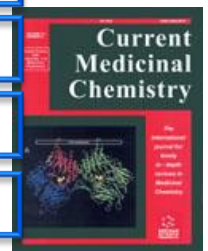
Cristália Produtos Químicos e Farmacêuticos,
Complexo Industrial de Itapira
Itapira, S.P.

CRISTÁLIA



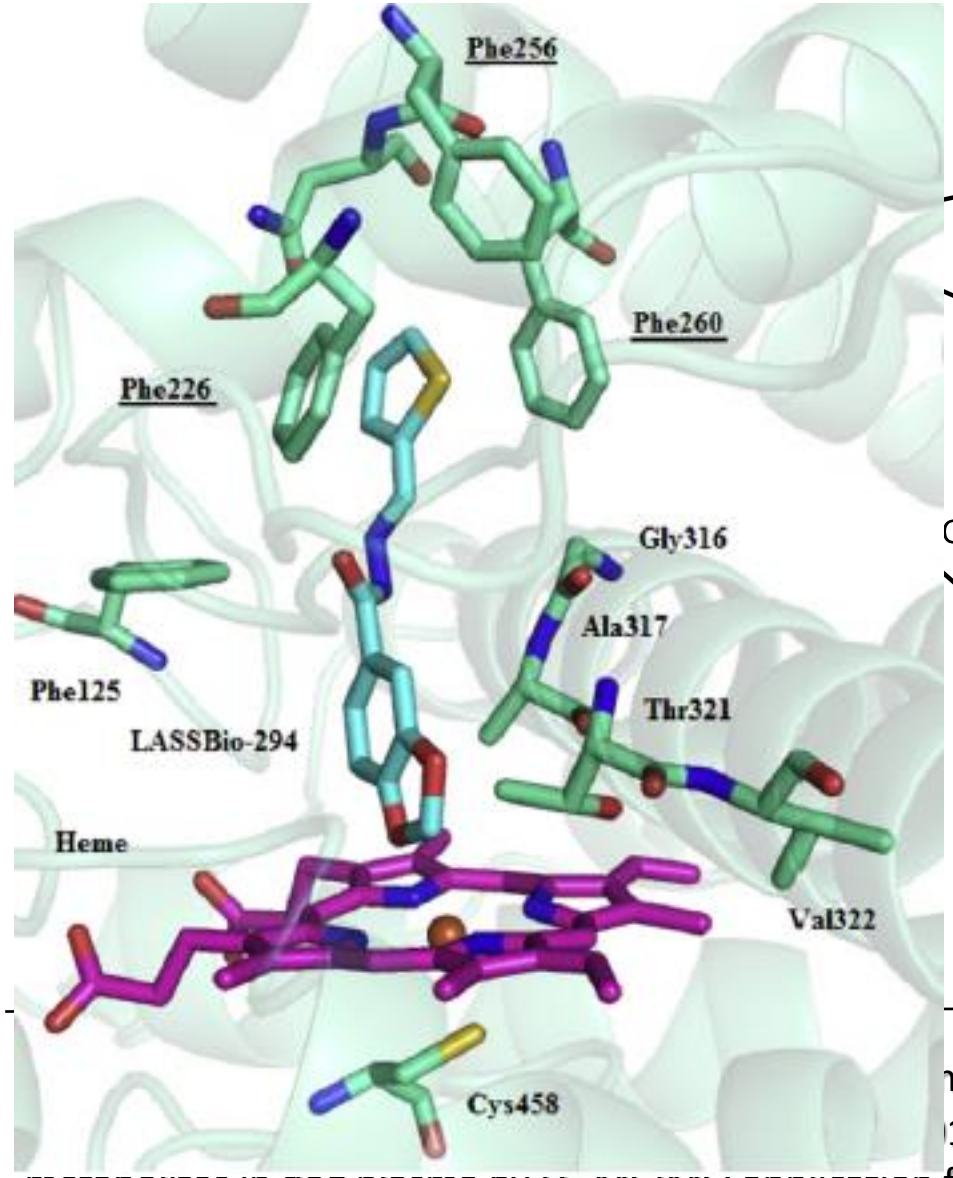
LASSBio-294

5,0 Kg = 18,2 M



CAM Fraga, EJ Barreiro, Medicinal Chemistry of *N*-Acylhydrazones: New Lead-Compounds of Analgesic, Antiinflammatory and Antithrombotic Drugs, *Curr Med Chem* **2006**, *13*, 167; RC Maia et al., Acylhydrazone Derivatives: A Patent Review, *Exp Op Ther Patents* **2014**, *24*, 1161

Metabolismo de LASSBio-294

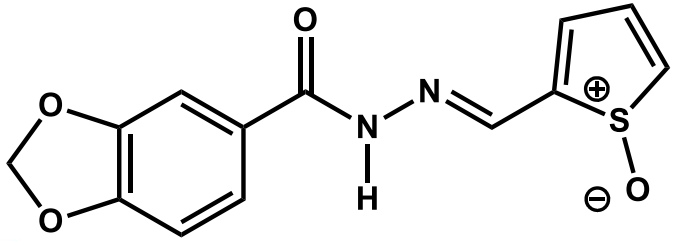


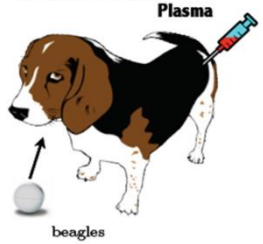
B. bassiana ATCC 7159
& Beagles*

LaBioCon

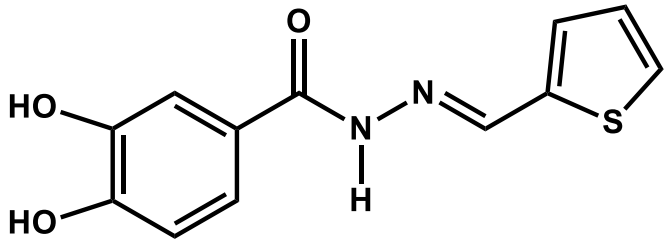
Beauveria bassiana

ATCC 7159





CYP1A2



Microssomas
& CYPs recombinantes &

- Profa Valéria de Oliveira*
  INCT-INOFAR
  FF-UFG
- Profa Rosangela Alves*
  INCT-INOFAR
  EV-UFG

nd biosynthesis of the major mammalian metabolite of the cardioactive prototype
10); R. C. Braga *et al.*, "Determination of cardiactive prototype LASSBio-294 and its metabolites in dog plasma by LC-MS/MS: application for a pharmacokinetic studies", *J. Pharm. Biomed. Analysis*, **55**, 1024 (2011);
& A. G. M. Fraga *et al.*, "**CYP1A2**-mediated biotransformation of cardioactive 2-thienylidene-3,4-methylenedioxybenzoylhydrazine (LASSBio-294) by rat liver microsomes and human recombinant CYP enzymes", *Eur. J. Med. Chem.*, **46**, 349-355 (2011)

Toxicidade Aguda e Sub-aguda

✓**A toxicidade sistêmica aguda e sub-aguda foi investigada em ratos, por duas vias de administração, *p.o.* e *i.p.*, nas doses de 1000 μM/kg e 73 μM/kg, respectivamente (*i.p.*, administrando-se 2 vezes ao dia, durante 15 dias seguidos: ~ 100 vezes superior à ED_{50} *in vivo*).**

Não tem efeito letal, não provoca letargia, não reduz a motilidade, nem altera o pêso dos animais.

Não provoca alterações na contagem de células sanguíneas, hematócrito, nem altera a taxa de glicose, uréia, TGO, TGP, creatinina.

Não altera histopatologicamente orgãos vitais, tais como fígado, pulmão, SNC.

LASSBio-294

Não se observaram efeitos neurotóxicos em culturas de neurônios hipocampais de ratos, tratadas com LASSBio-294 (500 μM). Efeito neuroprotetor foi observado em < doses.

Estudo do mecanismo de ação

Cerep

15318 NE 95th Street
Redmond, WA 98052
U.S.A.

www.cerep.com
Tel: (001) 425.895.8666
Fax: (001) 425.895.8668

Ref : Final Report 15180/ND

STUDY NUMBER 15180

***In Vitro* Pharmacology & ADME-Tox**

- Study of Compound LASSBio-294 -

Study Sponsor:	LASSBIO
Address:	CCS - Bloco Bss - Room 16 Ilha do Fundão 68006 RIO DE JANEIRO BRAZIL
Study Director:	Jun TANG, Ph. D.
Testing Facilities:	Cerep Le Bois l'Evêque - B.P. 1 - 86600 CELLE L'EVESCAULT, FRANCE and 15318 NE 95th Street, REDMOND, WA 98052 U.S.A.
Study Period:	From August 19, 2008 to September 08, 2008
Report Date:	September 17, 2008

Patent (USPTO) 7.091.238 (15/08/2006) ➡ *Cardiotônicos vasoativos*

Patente obtida

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/020,328	Aug. 15, 2006	7,091,238	32360-179943	9691

25694 7590

VENABLE LLP
P.O. BOX 34385
WASHINGTON, DC 20043-9998

Thienylhydrazone with Digitalis-like properties (positive inotropic effects)

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term A **od**

(application filed

LASSBio-294

The Patent Term Adjustment is 109 day(s). Any **from the above-identified application** include an indication of the adjustment on the front pag

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571) 272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at (703) 305-8283.

Roberto Takashi Sudo, Rio de Janeiro, BRAZIL;
Edson X. Albuquerque, Baltimore, MD;
Eliezer J. Barreiro, Rio de Janeiro, MD;
Carlos Alberto Manssour Fraga, Rio de Janeiro, BRAZIL;
Ana Luisa Palhares De Miranda, Petropolis, BRAZIL;

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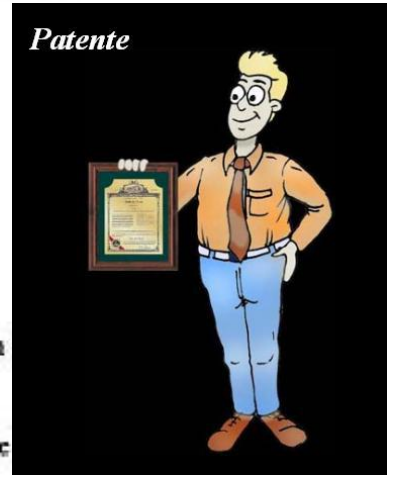

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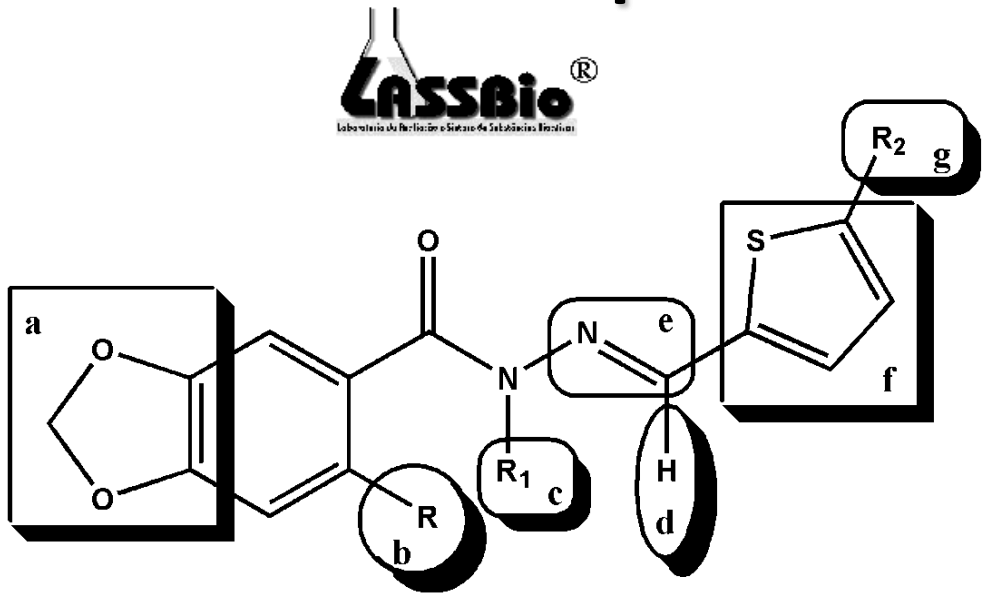
> 500 citações

Dissertações, teses ⇩ Análogos de LASSBio-294

A.P.A. Costa, *Ação do LASSBio-294 sobre os parâmetros cardiovasculares em modelo experimental de cardiomiopatia dilatada em coelhos*. Tese Doutorado em Ciência Animal, Universidade Federal de Goiás, Goiânia, 2016.

Etapa de otimização



"lead optimisation is defined as those activities that are required to optimise a screening hit to a pre-clinical candidate. Thus, lead optimisation invariably comprises synthetic and medicinal chemistry, biochemical and functional screening, computer-aided drug design, *in vitro* and *in vivo* pharmacokinetic studies and physicochemical (e.g. solubility, partition coefficient and acidity) studies"
Baxter, A. D. & Lockey, P. M. (2001) *Drug Discov. World* 2, 9–15.

a = Introdução de grupos com diferente perfil de contribuição estereoeletrônica;

b = Substituinte R na posição 6 do anel benzodioxola – efeitos estereoeletrônicos;

c = Alquilação do grupamento farmacofõrico – Modificação da habilidade como doador de ligação de H; Alterações conformacionais;

d = Introdução de substituintes alquila – Efeitos estéricos e/ou conformacionais;

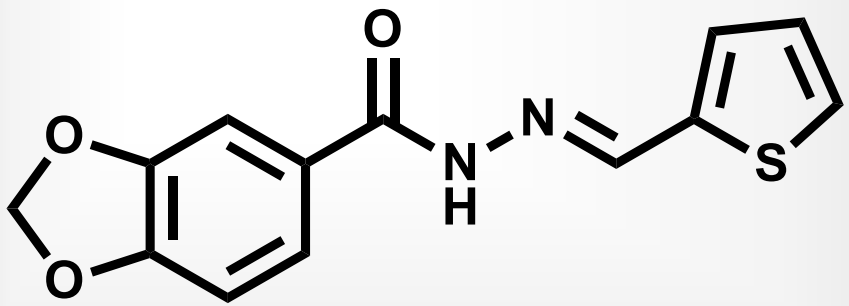
e = Redução da dupla ligação imínica – Modificação da extensão de conjugação do grupamento farmacofórico; aumento da liberadade conformacional;

f = Troca do anel tiofeno por núcleos isostéricos com diferentes contribuições eletrônicas;

g = Introdução de grupos com diferente perfil de contribuição estereoeletrônica.

Etapa de otimização

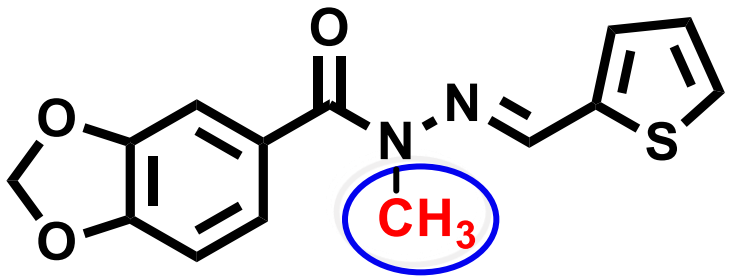
lead compound



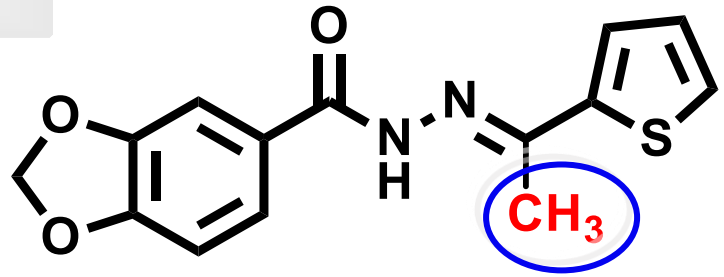
LASSBio-294

(VD) IC_{50} = 74,0 µM
IC_{50} (A_{2A}) = 9,5 µM

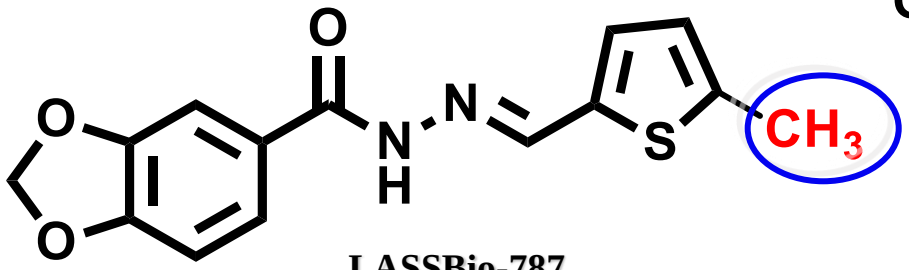
Lead Optimization



LASSBio-785
IC_{50} = 10,2 µM



LASSBio-1099



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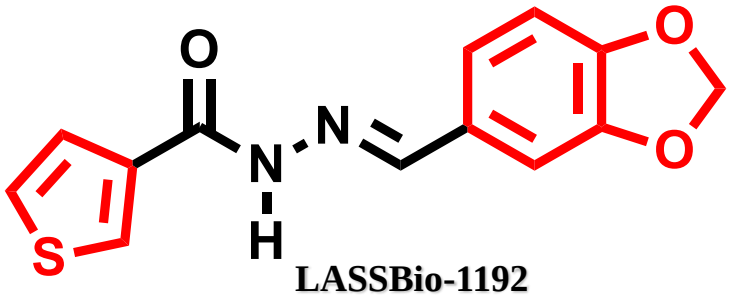
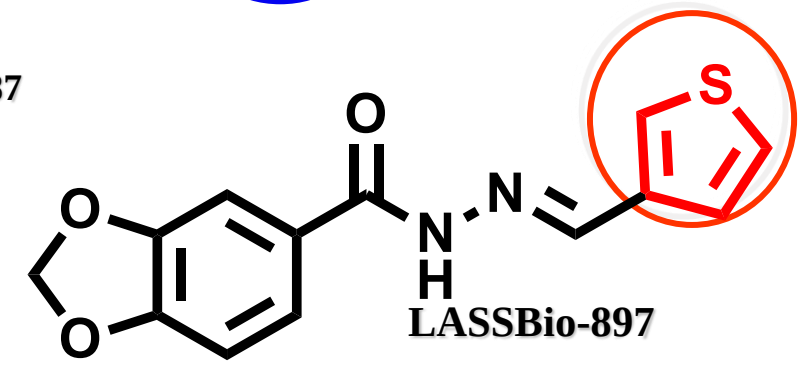


LASSBio-1192

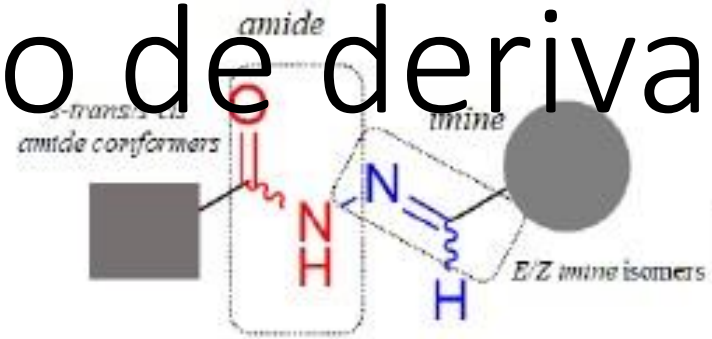


LASSBio-897

Bioorganic Medicinal Chemistry 2005, **13**, 3431

Patente BR PI0403363 9

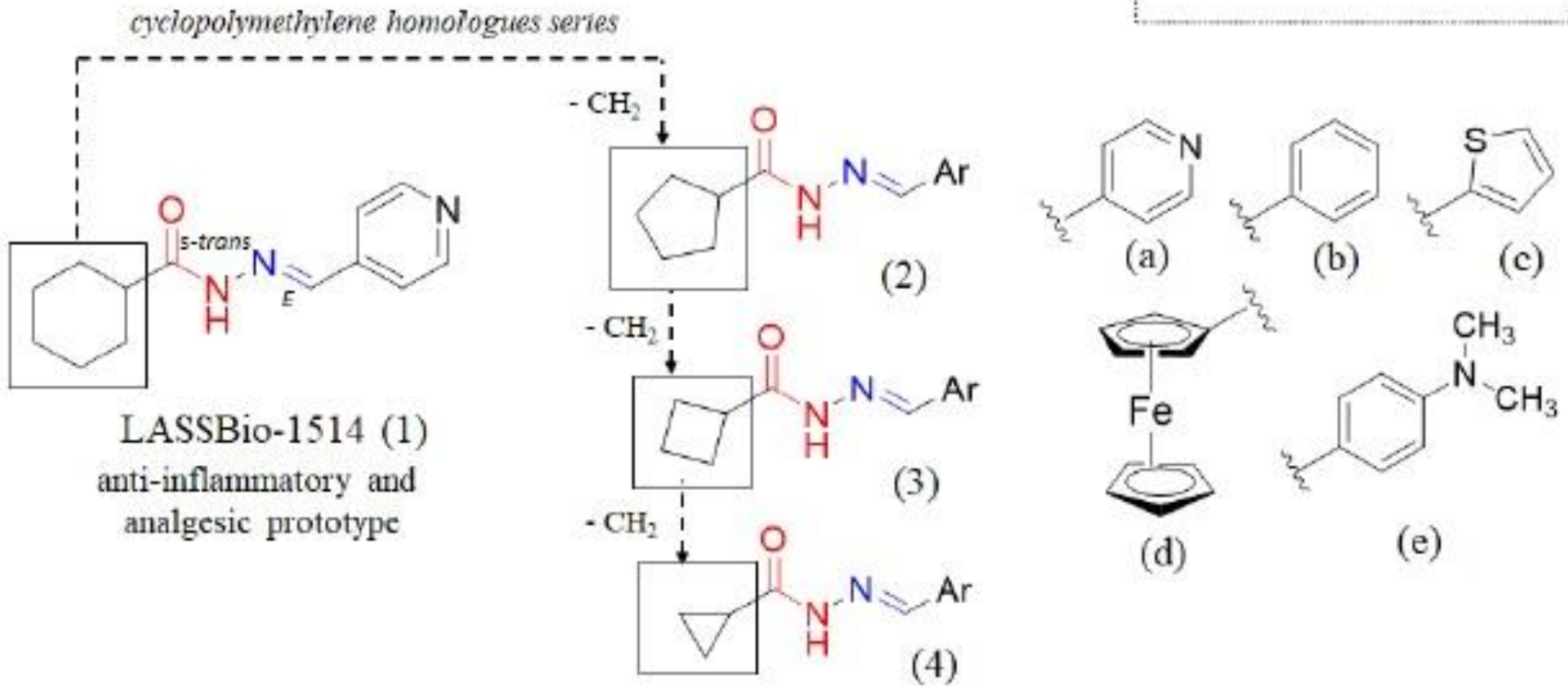
Otimização de derivados NAH



Acylhydrazone framework

- Anti-inflammatory
- Analgesic
- Antiviral
- Antiprotozoa
- Anti-diabetes
- Antitumoral
- Antioxidant

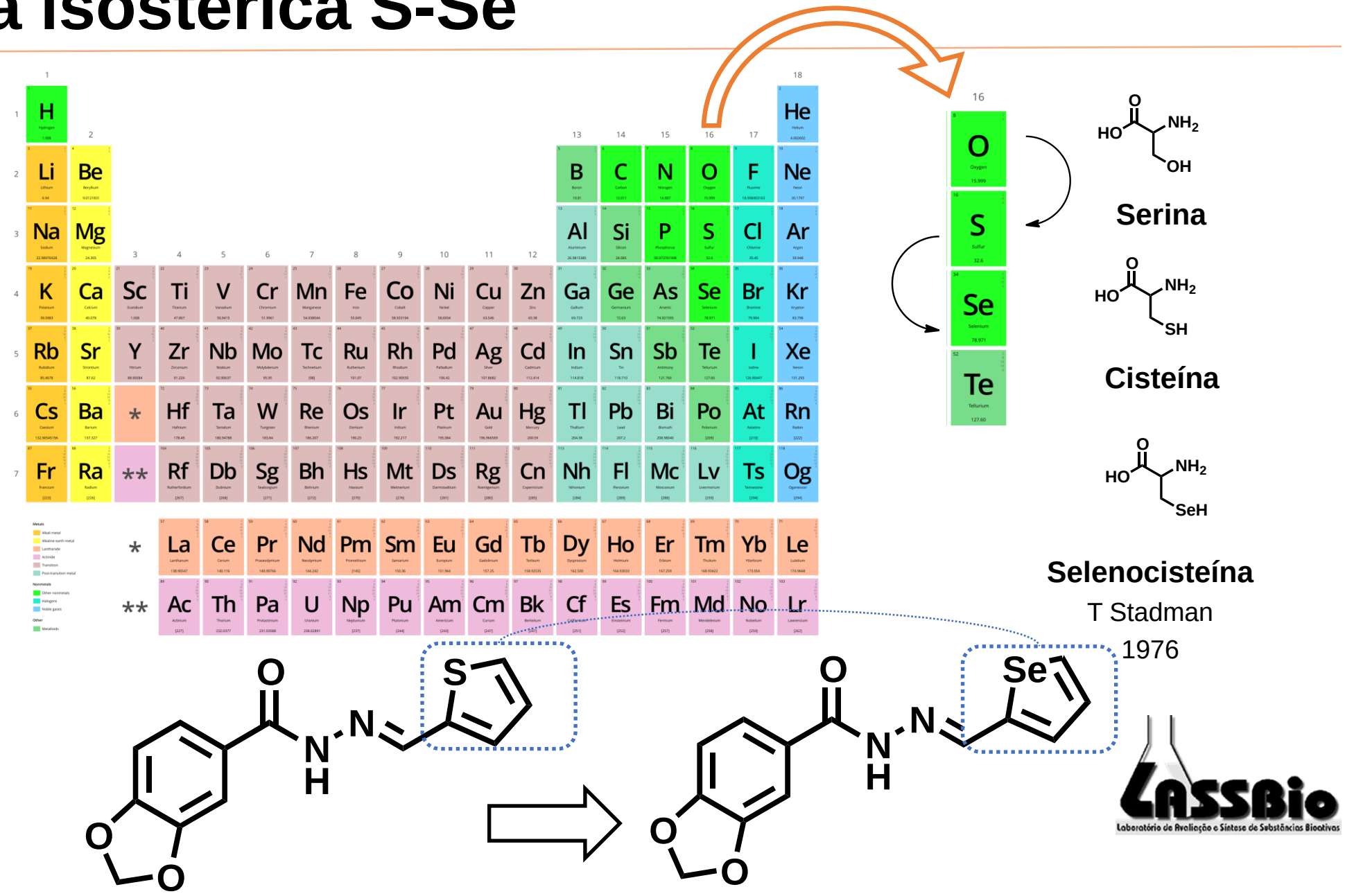
Estrutura privilegiada



LASSBio-1514 (1)
anti-inflammatory and analgesic prototype

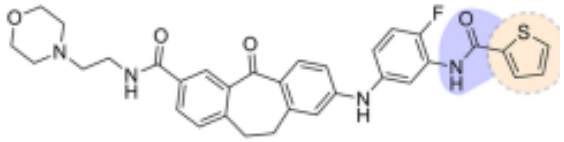
L M Lima et al., Design and Synthesis In Silico Drug-like Prediction and Pharmacological Evaluation of Cyclopolymethylenic Homologous of LASSBio-1514, *Molecules* **2021**, *26*, 4868.

Troca isostérica S-Se

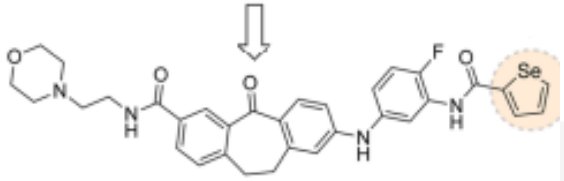


Parnham, Kindt, ***Biochem. Pharmacol.***,1984 33, 3247, Wessjohann et. al., ***Biol. Chem.***, 388, 2007, 997, Cone, ***Proc. Natl. Acad. Sci,*** 1976, 8, 2659

Resultados Recentes



skepinone



isóstero selenofênico

Journal of Medicinal Chemistry

pubs.acs.org/jmc 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 Read Online

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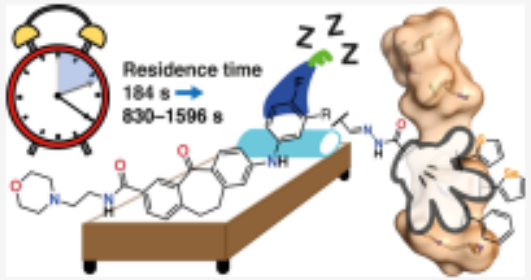
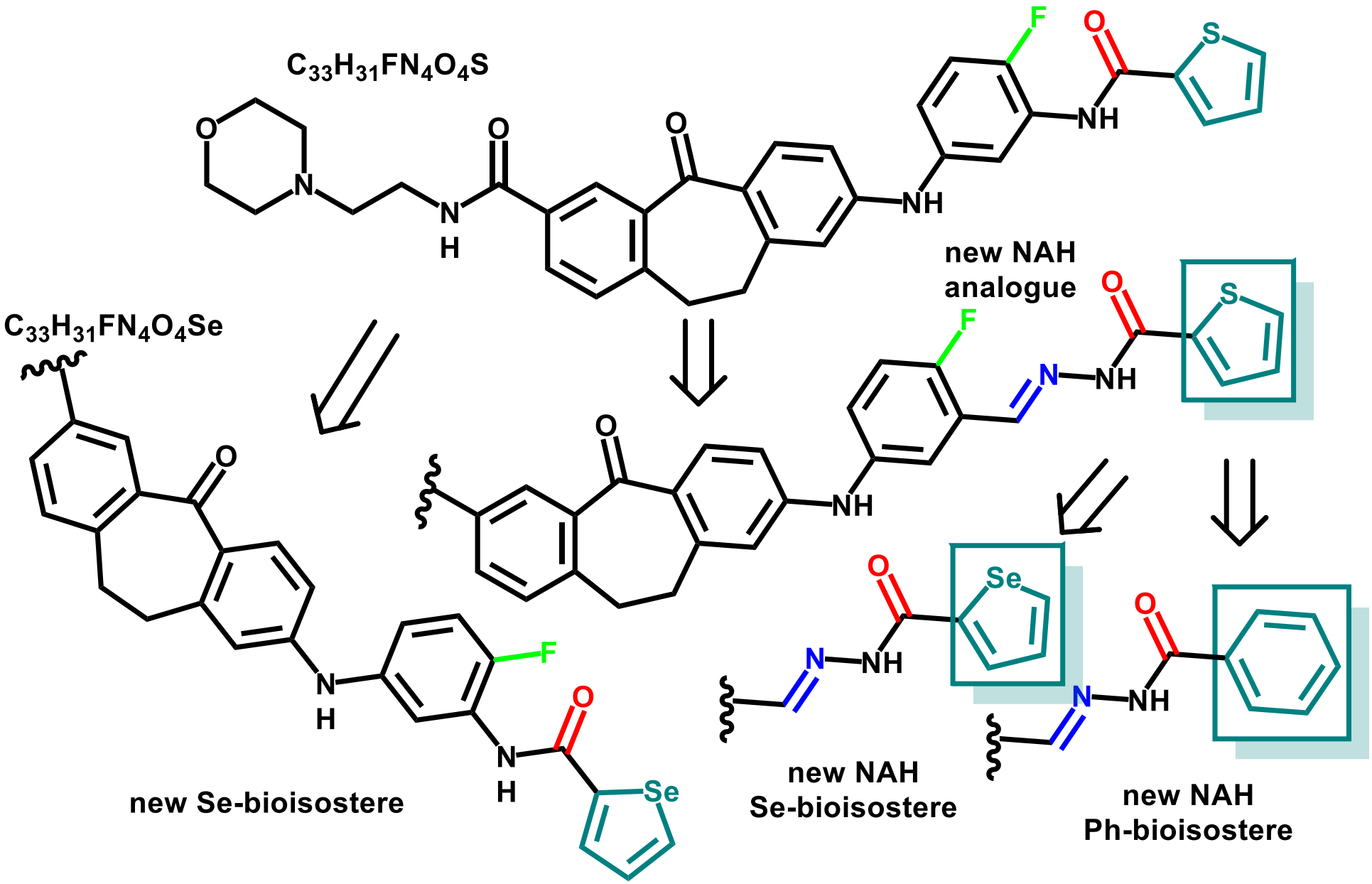
ABSTRACT: The recent disclosure of type I 1/2 inhibitors for p38α MAPK demonstrated how the stabilization of the R-spine can be used as a strategy to greatly increase the target residence time (TRT) of inhibitors. Herein, for the first time, we describe *N*-acylhydrazone and selenophene residues as spine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





J G B Pedreira, PhD Thesis, IQ-UFRJ/BR & Un Tuebingen/Al, 2020

Effect of S–Se Bioisosteric Exchange on Affinity and Intrinsic Efficacy of Novel *N*-acylhydrazone Derivatives at the Adenosine A_{2A} Receptor

by Júlia Galvez Bulhões Pedreira [1,2,†], Rafaela Ribeiro Silva [3,†], François G. Noël [3,4] and Eliezer J. Barreiro [1,2,4,*]

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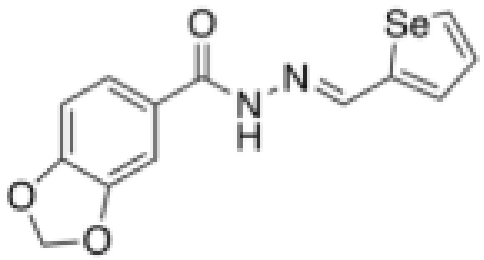
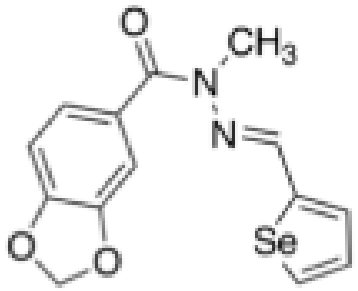
[4] Nacional Institute of Science & Technology in Drugs and Medicines (INCT-INOFAR), Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro 21944-971, Brazil

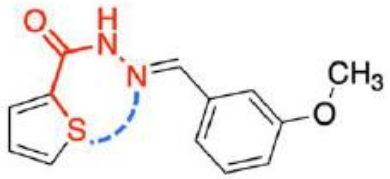
[*] Author to whom correspondence should be addressed.

[†] These authors contributed equally to this work.

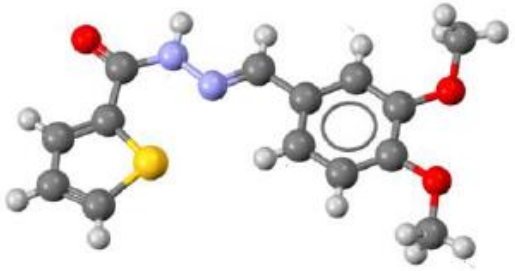
Molecules **2021**, *26*(23), 7364; https://doi.org/10.3390/

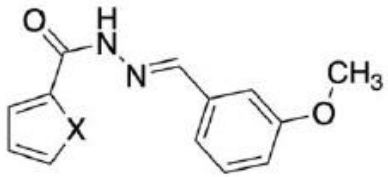






LASSBio-1834
(12)





13 (X = S)
14 (X = Se)

Red shado


A Química Medicinal
é simplesmente
fascinante!

De fármacos e suas descobertas

Convite

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

Química Medicinal

domingo, 25 de julho de 2021

As estruturas privilegiadas e o desenho de novos fármacos...

Há pouco tempo, precisamente em 2019, publiquei um artigo com dois orientandos como coautores (e.g. Lucas Franco e Júlia Pedreira), sobre o papel da intuição em química medicinal. Foi uma ótima experiência em que o "produto final" foi fruto do trabalho de 6 mãos e 3 cabeças...! Mas só uma "branquinha"...!!!! (Veja: JGB Pedreira, LS Franco, EJ Barreiro, Chemical Intuition in Drug Design and Discovery, Curr Top Med Chem 2019, 19, 1679).

www.ejb-eliezer.blogspot.com

Obrigado.

UFRJ XXVIII Escola de Verão em Química Farmacêutica e Medicinal LASSBio