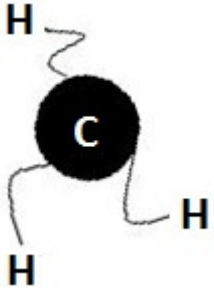
# As *incríveis façanhas* da metila na Química Medicinal





Eliezer J. Barreiro

Professor Titular

Universidade Federal do Rio de Janeiro

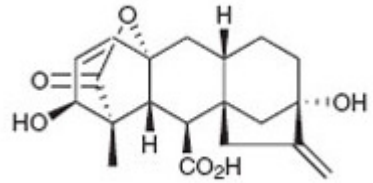
**Laboratório de Avaliação e Síntese de Substâncias Bioativas**

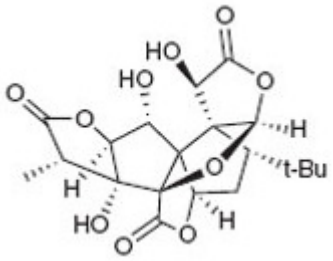
www.farmacia.ufrj.br/lassbio

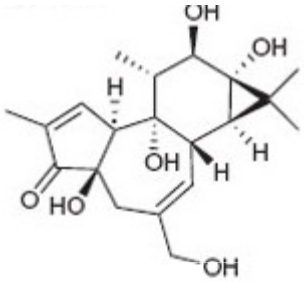
Instituto Nacional de Ciência e Tecnologia de Fármacos e Medicamentos
(INCT-INOFAR)
www.inct-inofar.ccs..ufrj.br

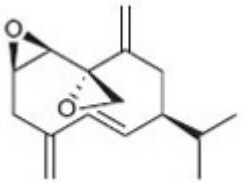
Universidade Federal do Rio de Janeiro

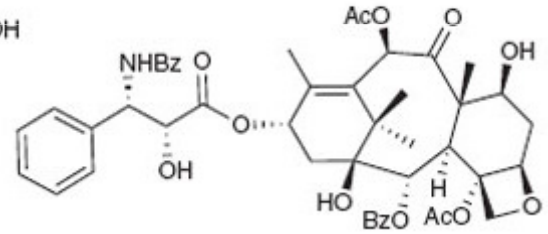
# Ao Professor Timothy John Brockson

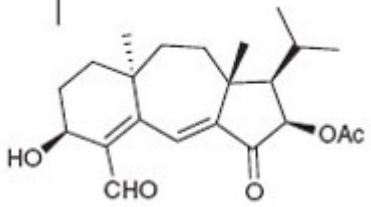


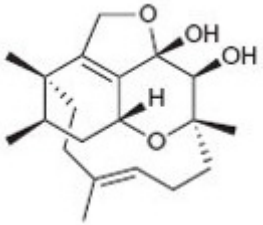



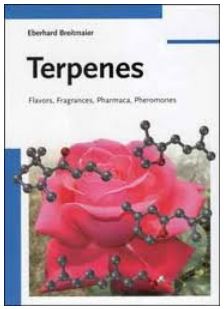



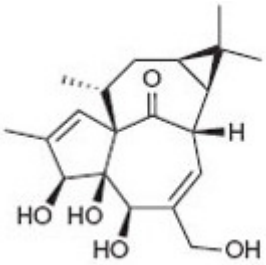




LQBO

ufrj

# Câncer

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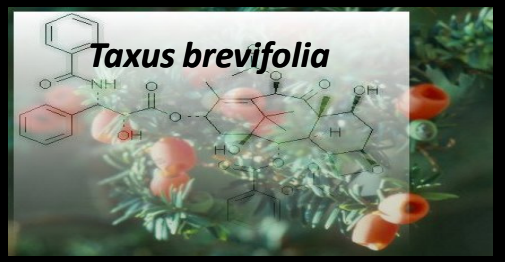
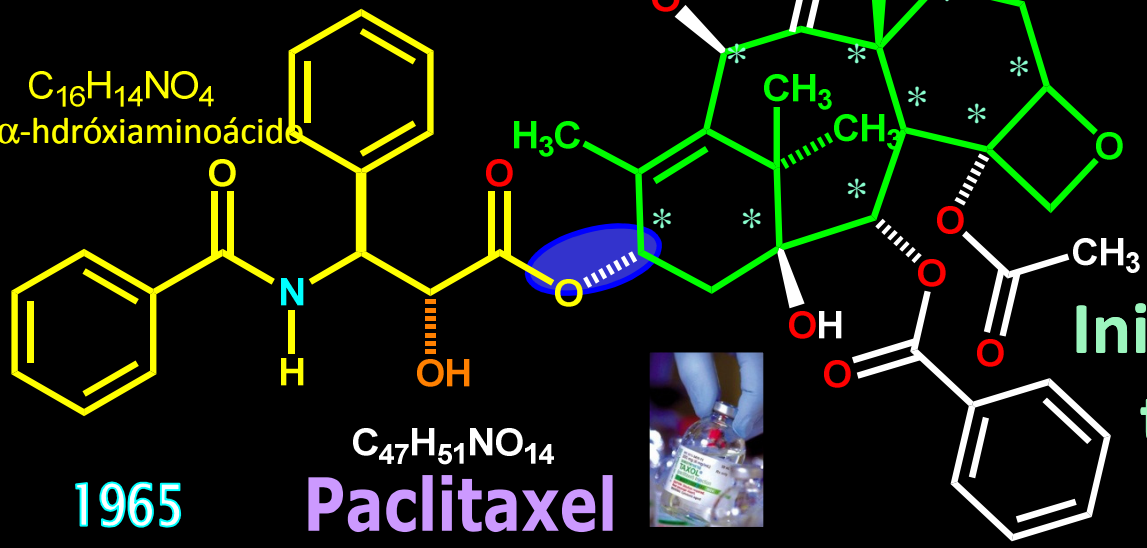



diterpeno taxano

M. E. Wall,,
"Chronicles of Drug Discovery",
D. Lednicer, vol.3, ACS, 1993,
pp. 327-348




1965



## Inibidores de tubulinas

Pierre Potier
1934-2006

M. C. Wani *et al.*, *J. Am. Chem. Soc.* **1971**, *93*, 2325

NATIONAL CANCER INSTITUTE

**Res. Triangle Park, 1967**

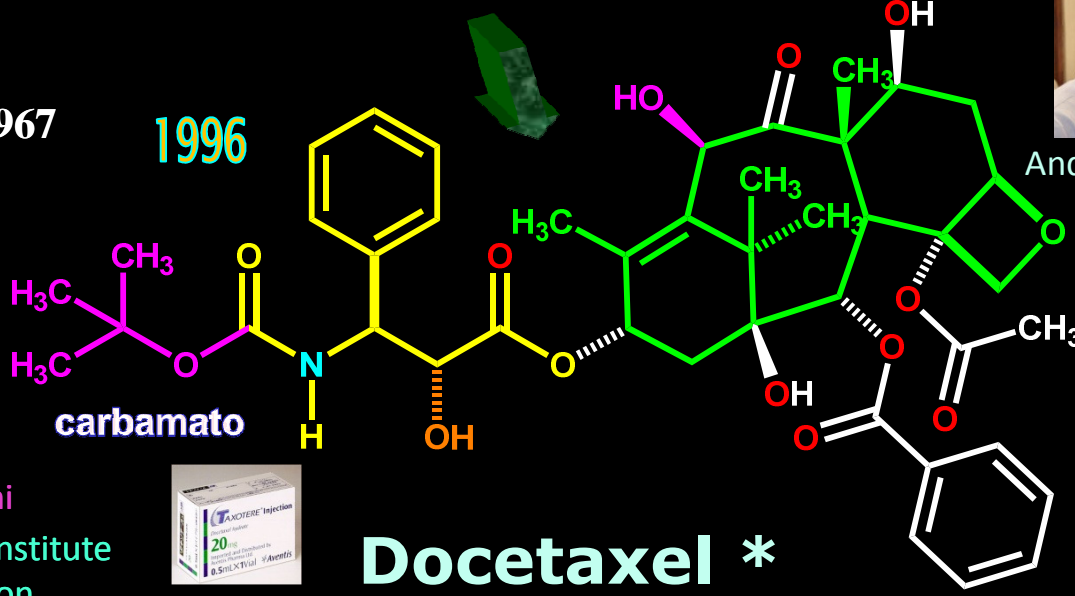
1996

*

Andy E Greene
UJF-FR

Arlene G Correa
UFSCar

M. E. Wall & M. C. Wani
1996 - National Cancer Institute
Award of Recognition







## Docetaxel *

2010
Cabazitaxel
(Jevtana$^{R}$)
Ortataxel$^{\&}$

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# Ao Professor Timothy John Brockson



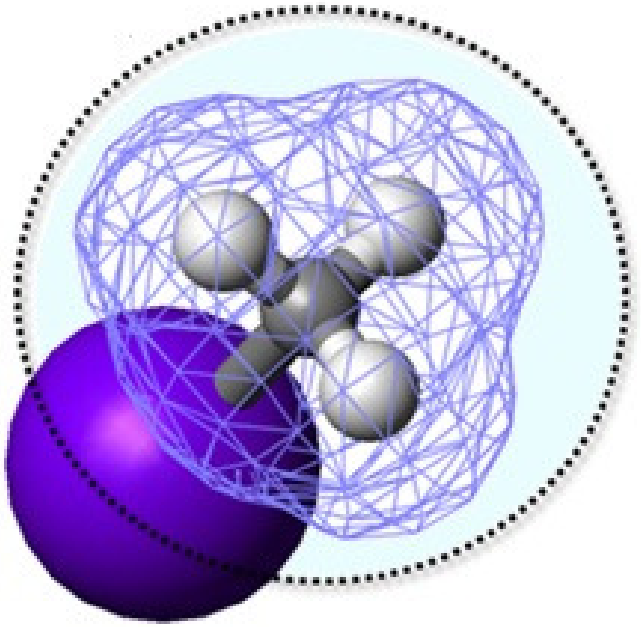

C Johnstone, *Drug Discov. Today* **2012**, *17*, 538

Universidade Federal do Rio de Janeiro

Química Medicinal

# $CH_3$

15 Da



metila

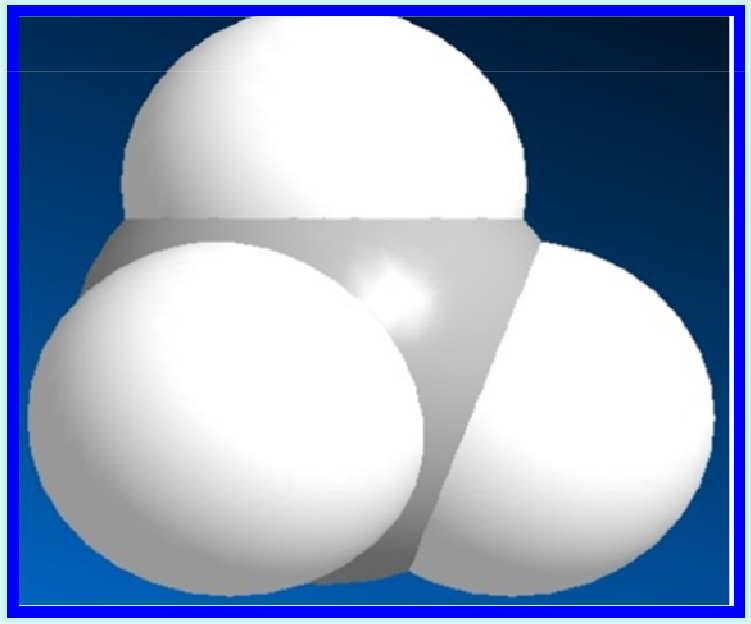
C-H $\mu$ = 0,4 D

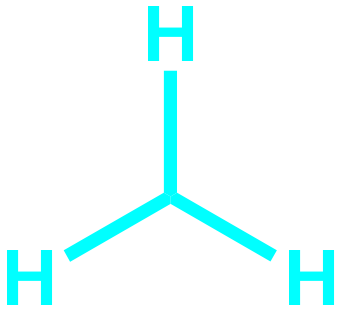
$\delta^+$ / $R^+$

P =0,22

$\sigma_{meta}$ = 0,51 / $\sigma_{para}$ = 0,52

Rekker const = 0,702






LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

Etila, propila, butila, *inutila*

UFRJ

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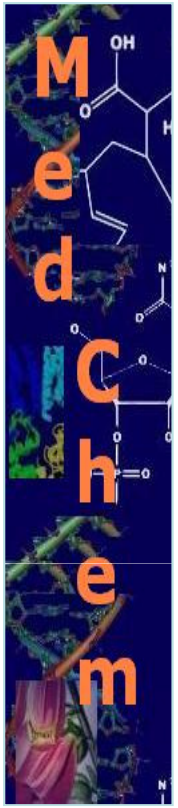
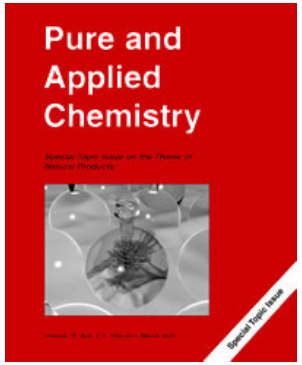



# IUPAC - Subcommittee Medicinal Chemistry & Drug Development

**Química Medicinal** é a *disciplina* que estuda aspectos **relacionados** à *descoberta* ou *invenção* de **fármacos**, seus aspectos moleculares envolvidos no mecanismo de ação e aqueles que governam a ***a****bsorção*, ***d****istribuição*, ***m****etabolismo*, ***e****liminação* e ***t****oxicidade* (ADMET), incluindo a compreensão da relação entre a estrutura química e a atividade terapêutica (REA = *SAR*).



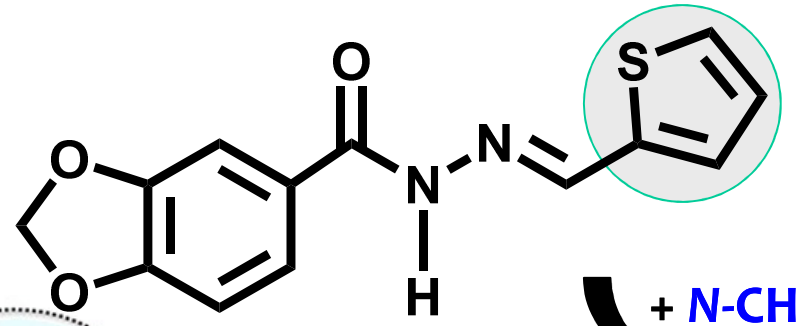

IUPAC

*Pure & Appl. Chem.*, Vol. 70, No. 5, pp. 1129–1143, 1998.
Printed in Great Britain.


**Criado em 19/04/1994**

**Laboratório de Avaliação e Síntese de Substâncias Bioativas**

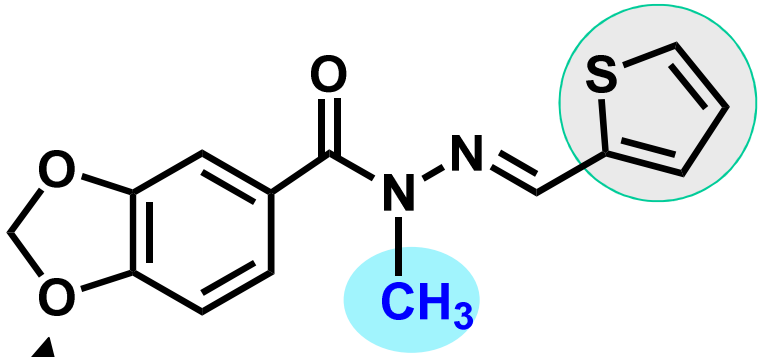
# A "*metilinha*" do LASSBio...



LASSBio-294

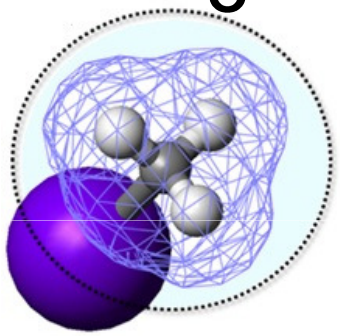
$IC_{50}$ (PDE4B) > 100 μM

+ N-$CH_3$



LASSBio-785

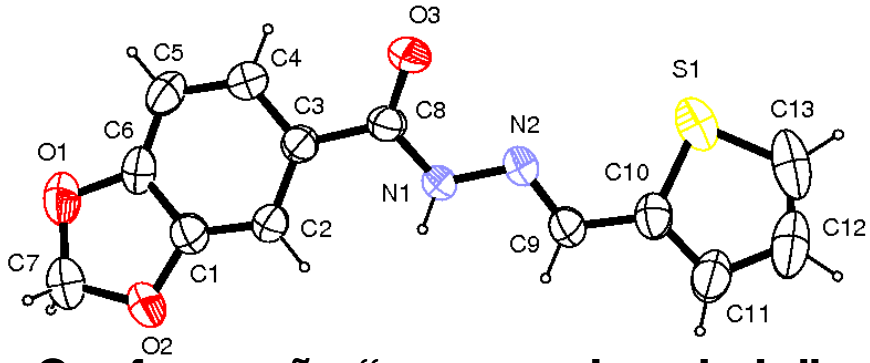
$IC_{50}$ (PDE4B) = 30 μM



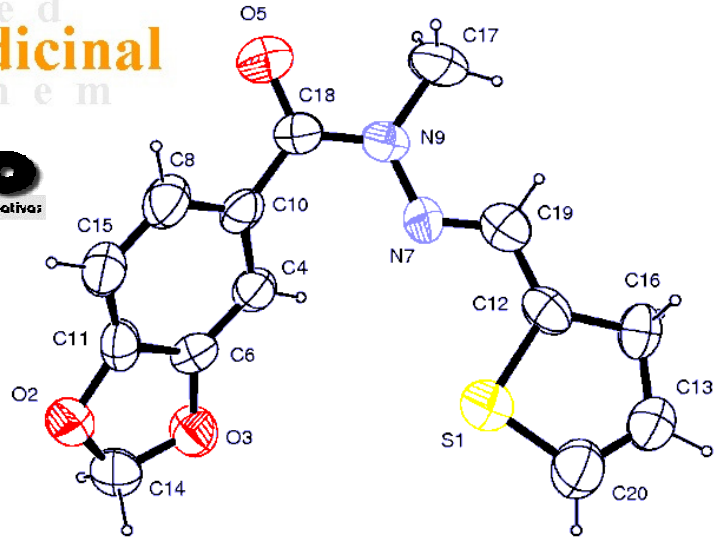
metila

Química Medicinal chem

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas



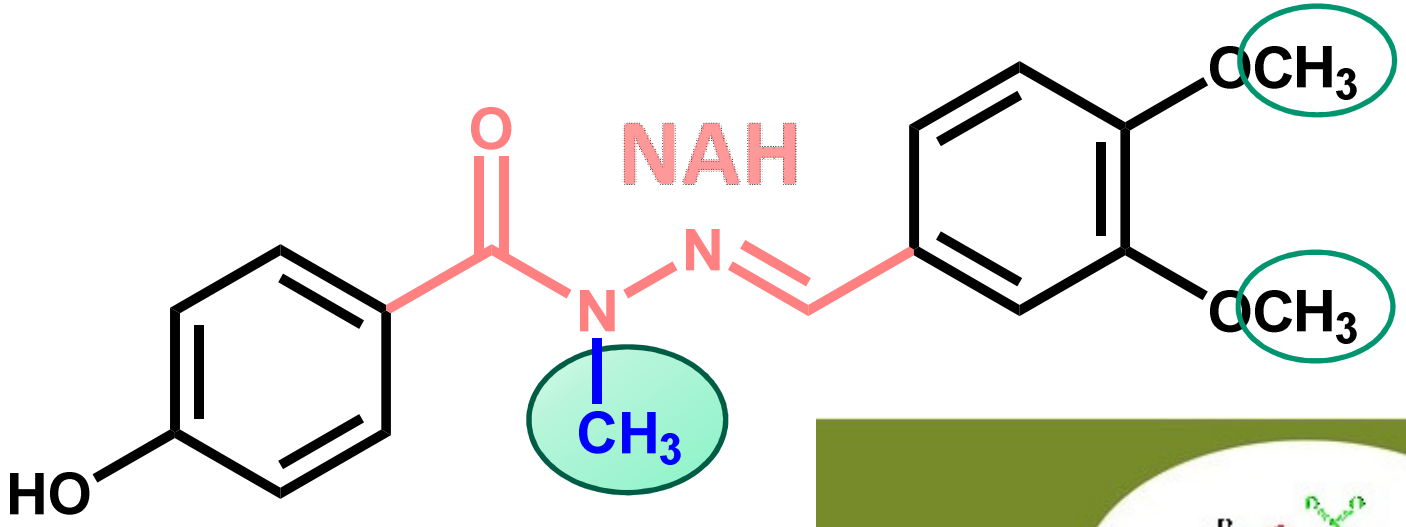

Conformação "grampo-de-cabelo"



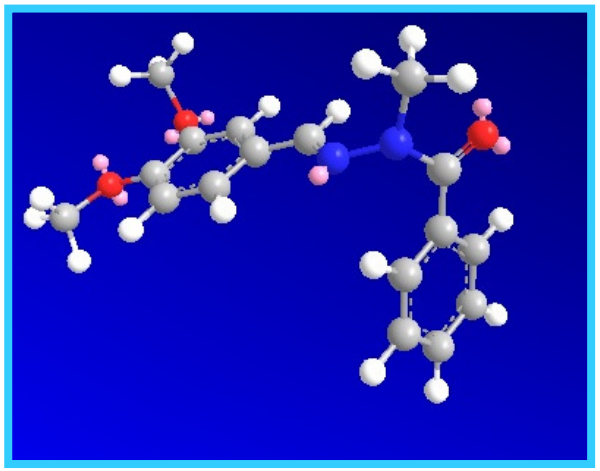

Conformação em "U"

EJ Barreiro, Estratégia de Simplificação Molecular em Química Medicinal, A Descoberta de Novo Agente Cardiotônico, *Quím Nova* **2002**, *25,* 1172

# A metilinha sabe-tudo...




Novo protótipo AI dual[b]... e metilado![a]




*In vivo*


[a] A. E. Kümmerle *et al.*, Design, Synthesis, and Pharmacological Evaluation of *N*-Acylhydrazones and Novel Conformationally Constrained Compounds as Selective and Potent Orally Active PDE-4 Inhibitors, *J Med Chem* **2012**, *55*, 7525; [b] X Jalencas & J Mestres, On the origens of polipharmacology, *MedChemComm* **2013**, *4*, 80.

# Salve, salve "*metilinha*" *poderosa* ...!

CHEMICAL REVIEWS

*Chem. Rev.* 2011, 111, 5215–5246

IF (2011) = 40,19

REVIEW

pubs.acs.org/CR

## The Methylation Effect in Medicinal Chemistry

Eliezer J. Barreiro,[*,†,‡,§] Arthur E. Kümmerle,[∥,†,§] and Carlos A. M. Fraga[†,‡,§]

[†]Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, CCS, Cidade Universitária, CP 68.006, 21941-902 Rio de Janeiro, RJ, Brazil

[‡]Programa de Pós-Graduação em Farmacologia e Química Medicinal, Instituto de Ciências Biomédicas, Universidade Federal do Rio de Janeiro, Cidade Universitária, Ilha do Fundão, Rio de Janeiro, RJ, Brazil

[§]Programa de Pós-Graduação em Química, Instituto de Química, Universidade Federal do Rio de Janeiro, Cidade Universitária, Ilha do Fundão, Rio de Janeiro, RJ, Brazil

dx.doi.org/10.1021/cr200060g

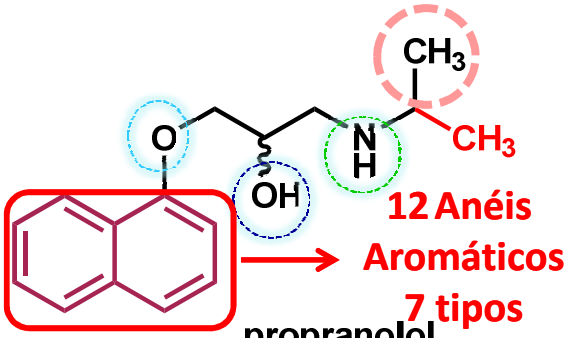
**Esta será a narrativa !**

www.uff.br/**RVQ**

# Inovações Terapêuticas

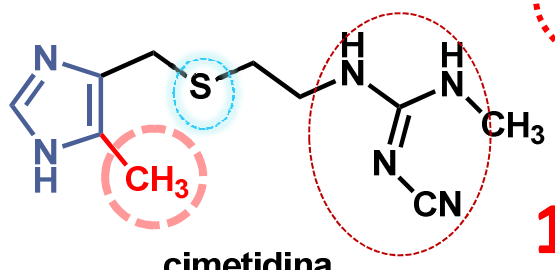
Universidade Federal do Rio de Janeiro

Química Medicinal

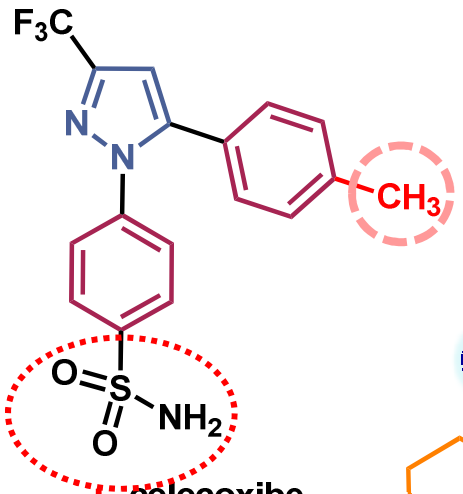



12 Anéis Aromáticos 7 tipos

propranolol
1964

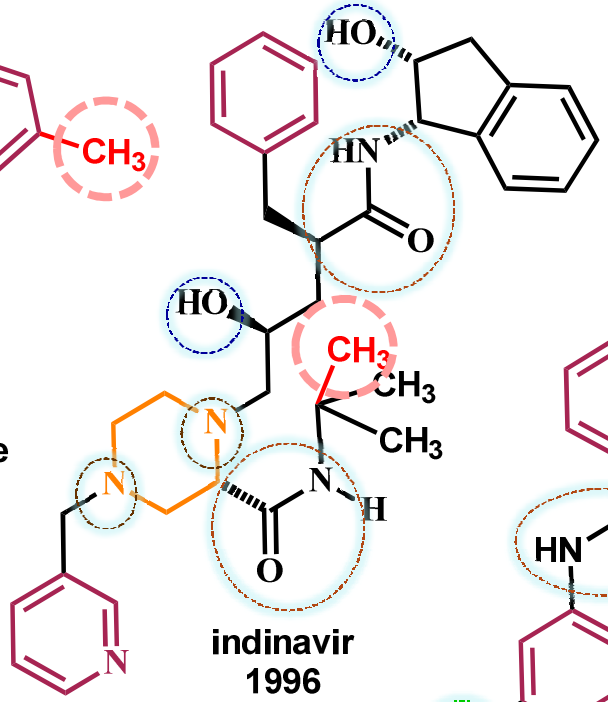



cimetidina

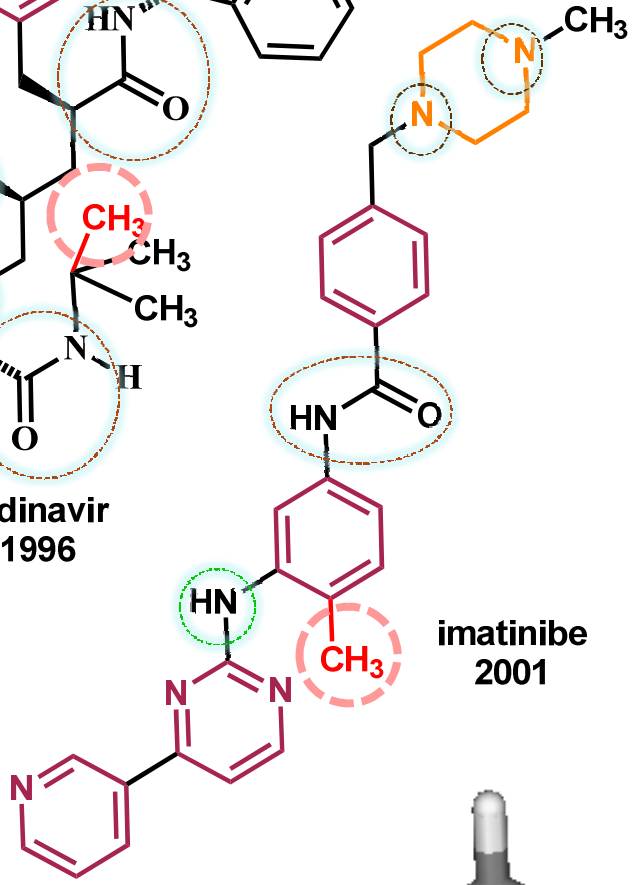



celecoxibe
1999

**12 GF's**



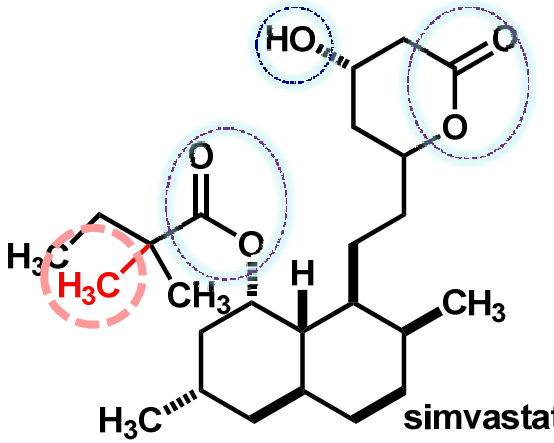

indinavir
1996



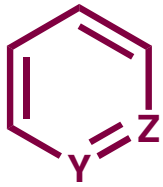

imatinibe
2001

"Fifty percent of the currently used drugs contain at least one aromatic ring that can be matter of substitution"

J Taylor




simvastatina
1986



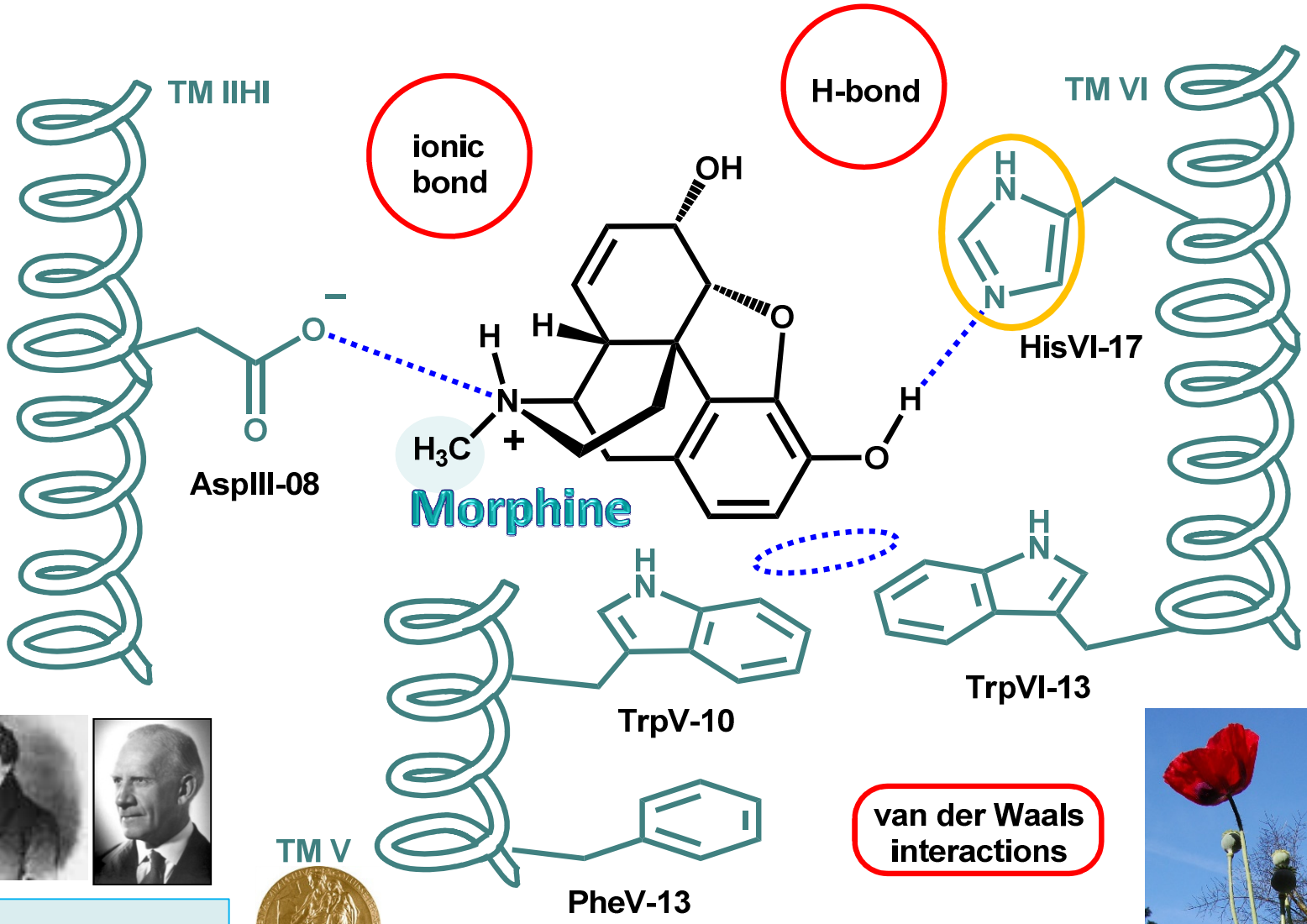

72%



100%

L Schaeffer, *The role of functional groups in D-R interactions*, em The Practice of Medicinal Chemistry, CG Wermuth Ed., Academic Press, 3rd Ed., Ch 21, p. 464

# A metila *natureba*...





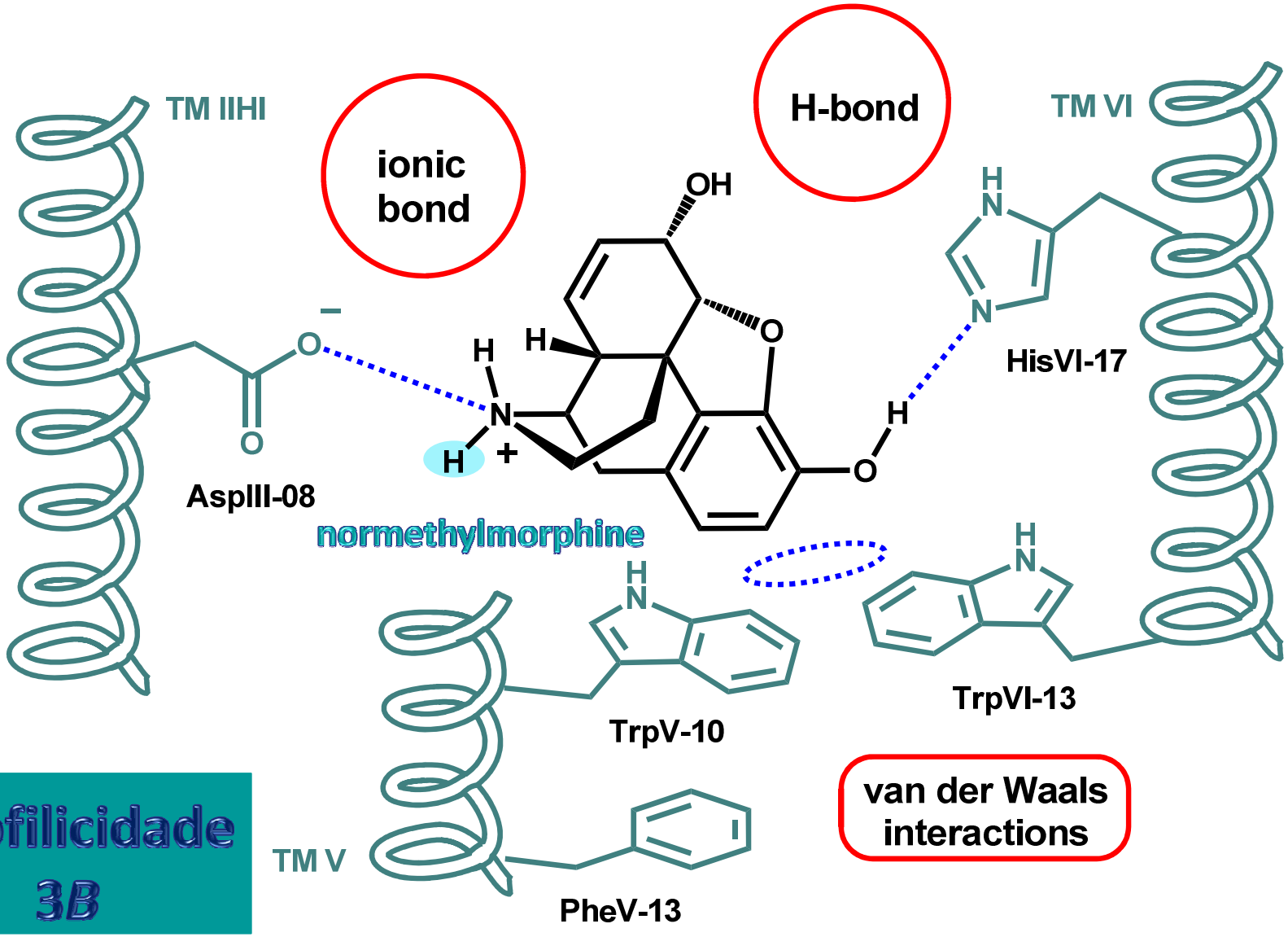

1805 - F. Setürner
1925 – R. Robinson

1947

**morphine**
$ED_{50}$ = 4.8 mg/kg

* JV Braun, *Ber. Dtsch. Bot. Ges.* **1914**, *47*, 2312

# A metila faltosa...

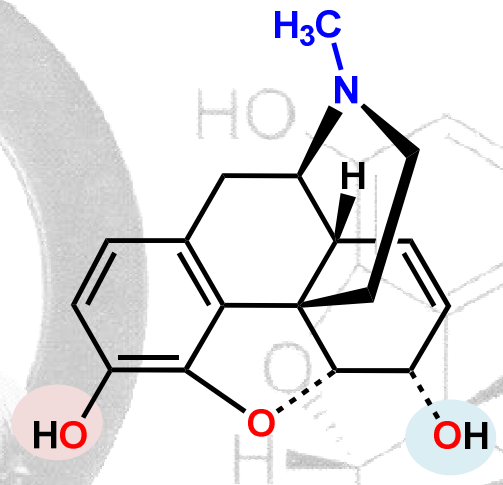



Lipofilicidade 3B

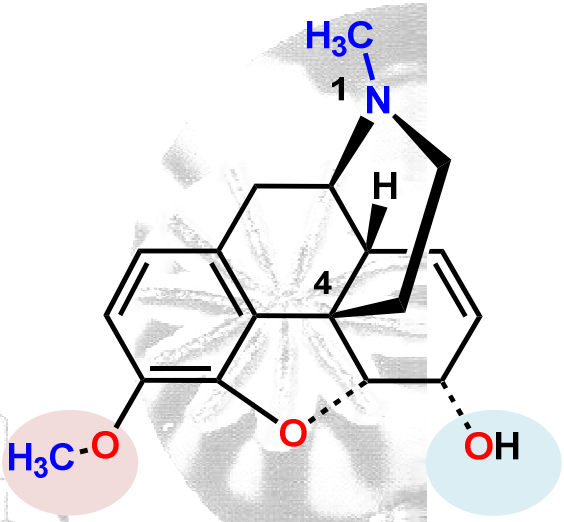
* JV Braun, *Ber. Dtsch. Bot. Ges.* **1914**, *47*, 2312

# As metilas *n*a morfina...

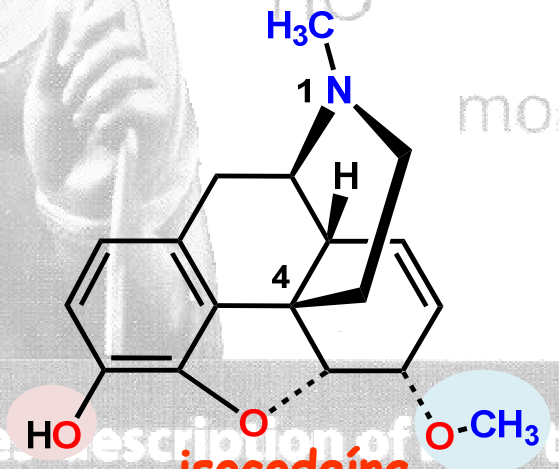
Índice de atividade analgésica



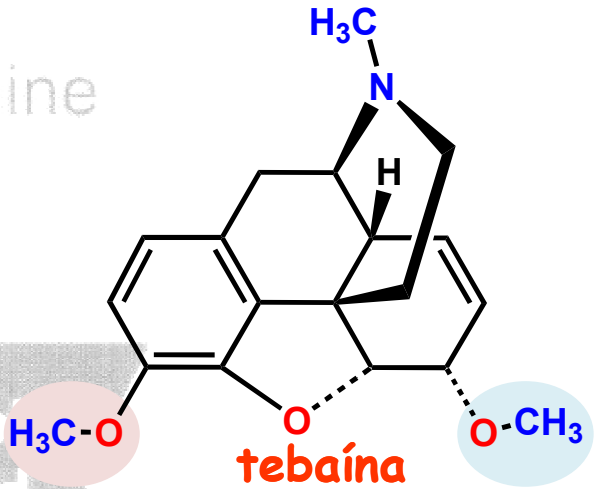

morfina
100




codeína
18




isocodeína
25




tebaína
0*

# As admiráveis metilas da floresta...

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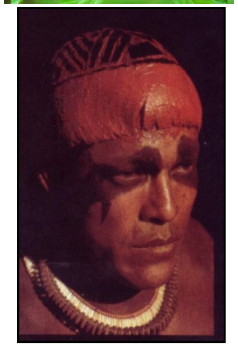
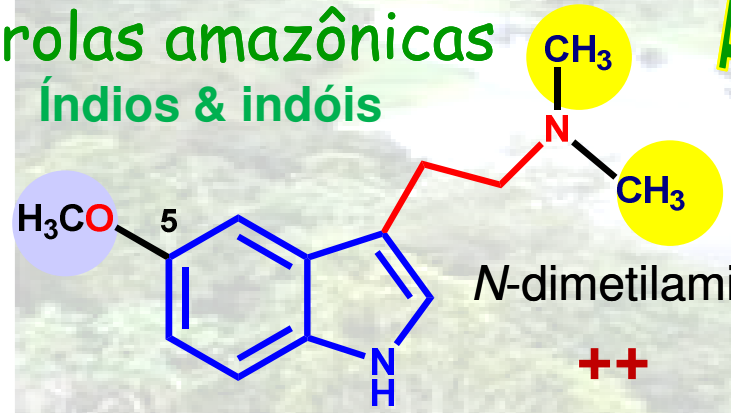


Virolas amazônicas

Índios & indóis



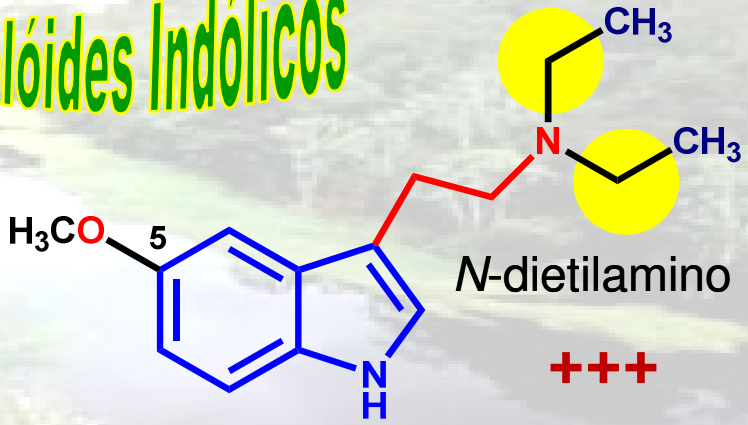

*N*-dimetilamino

++

3-indolil-etilaminas

efeitos alucinogênicos

Alcalóides Indólicos



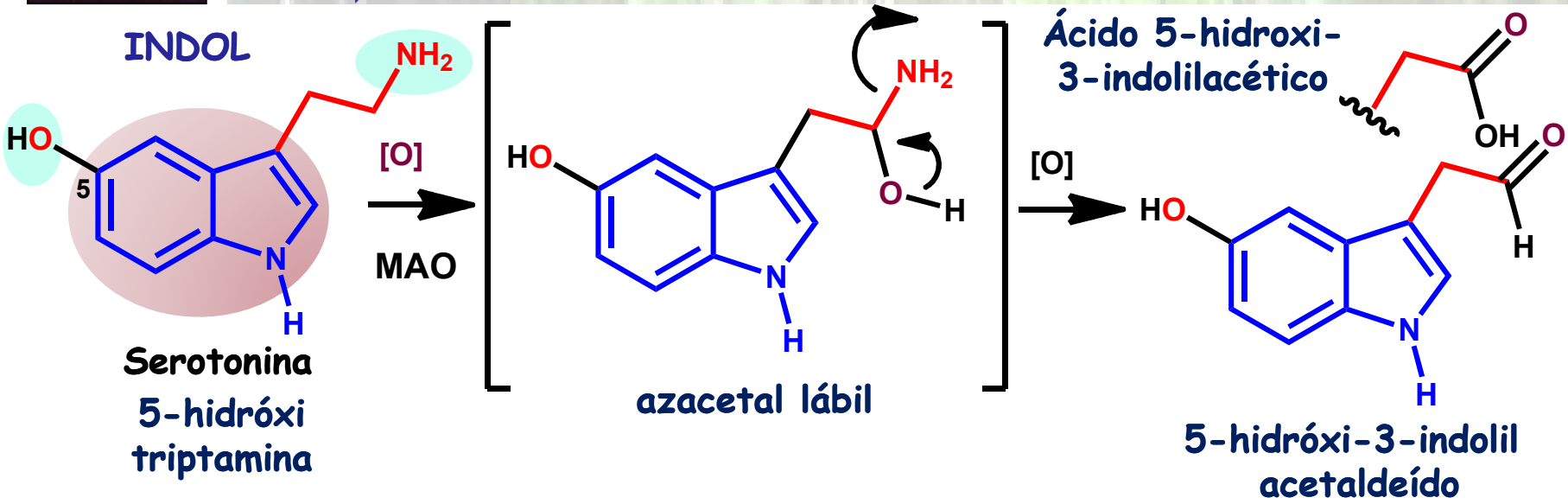

*N*-dietilamino

+++

*N*-dimetilomólogo

3 metilas

Similaridade molecular

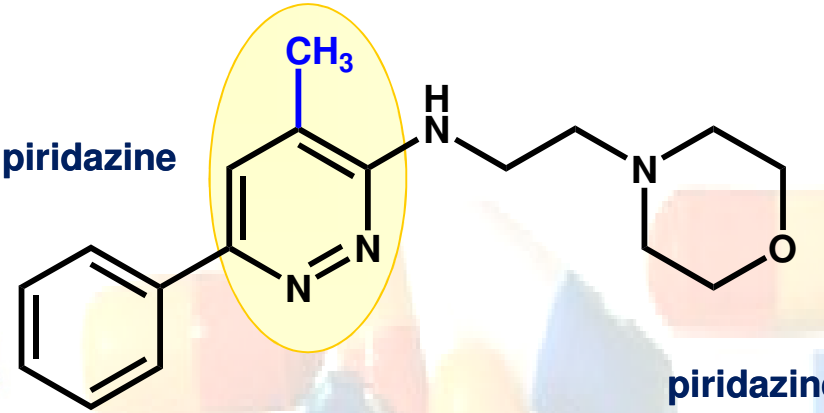


# A *incrível leveza* da metila...

Universidade Federal do Rio de Janeiro

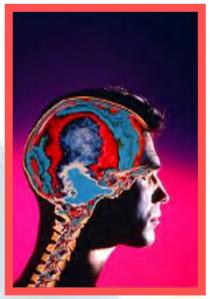
Química Medicinal

Lead Optimization

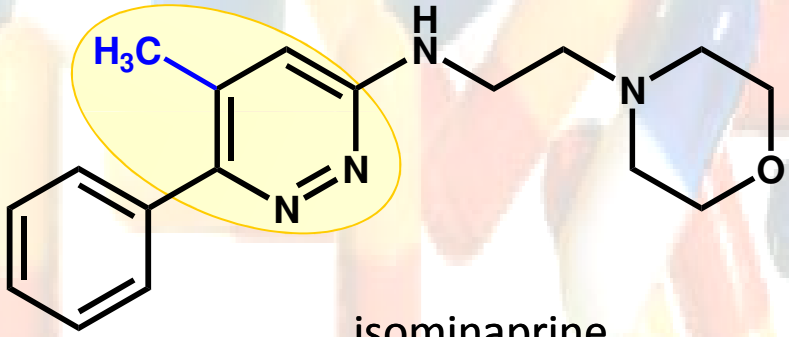




minaprine

serotonin type 2
& dopamine (D1, D2)
receptors



piridazine




isominaprine

mACh receptor (M1)

C. G. Wermuth, Aminopyridazines – an alternative route to potent muscarinic agonists with no cholinergic syndrome, *Il Farmaco* **1993**, *48*, 253-274

# A *piração* da frágil metila...

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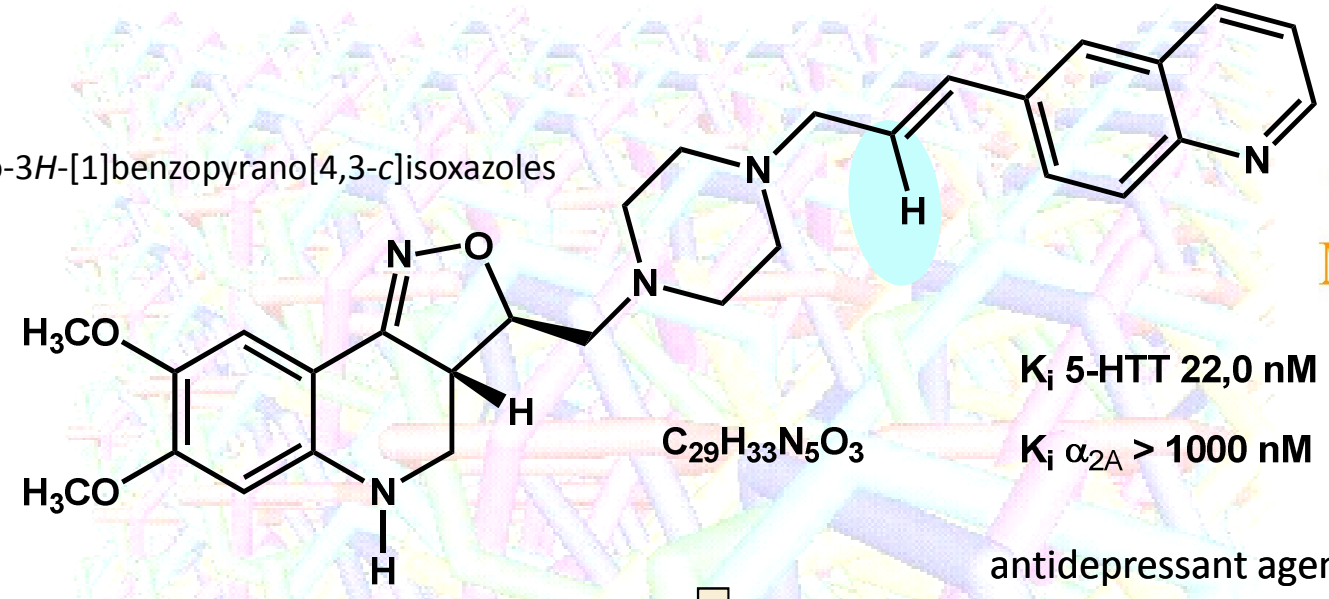
3*a*,4-dihydro-3*H*-[1]benzopyrano[4,3-*c*]isoxazoles



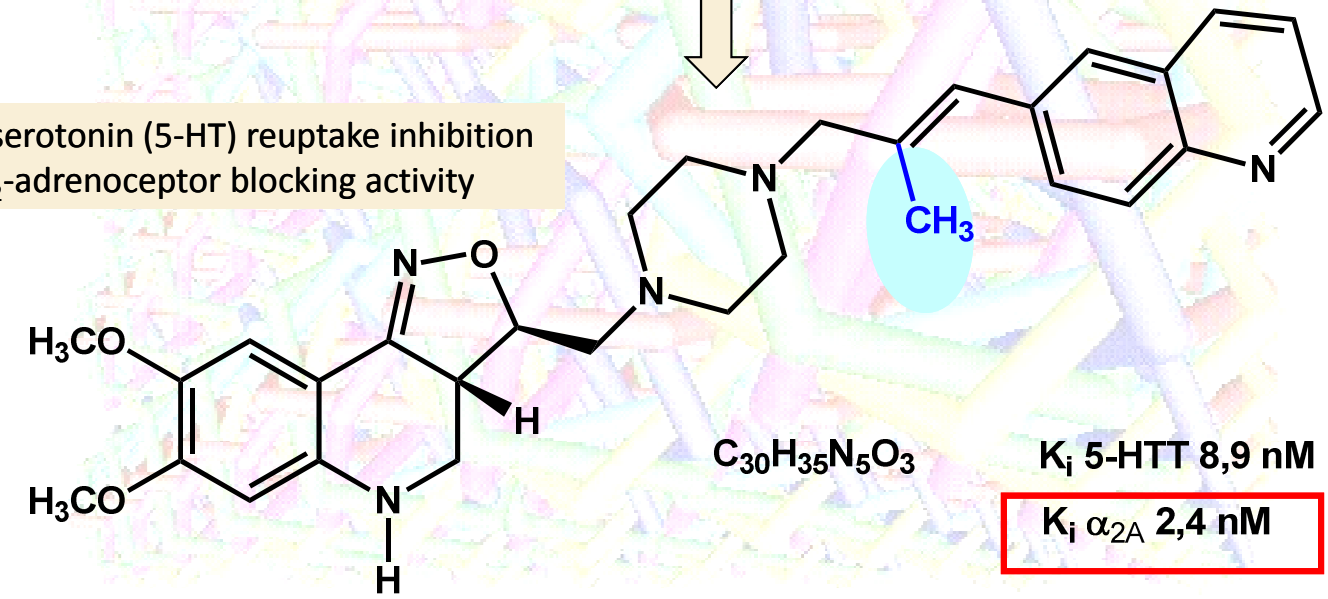
$C_{29}H_{33}N_5O_3$

$K_i$ 5-HTT 22,0 nM

$K_i$ $\alpha_{2A}$ > 1000 nM

antidepressant agent

central serotonin (5-HT) reuptake inhibition & $\alpha_2$-adrenoceptor blocking activity



$C_{30}H_{35}N_5O_3$

$K_i$ 5-HTT 8,9 nM

$K_i$ $\alpha_{2A}$ 2,4 nM


J I Andrés *et al.*, Discovery of a New Series of Centrally Active Tricyclic Isoxazoles Combining Serotonin (5-HT) Reuptake Inhibition with α2-Adrenoceptor Blocking Activity, *J Med Chem* **2005**, *48*, 2054.

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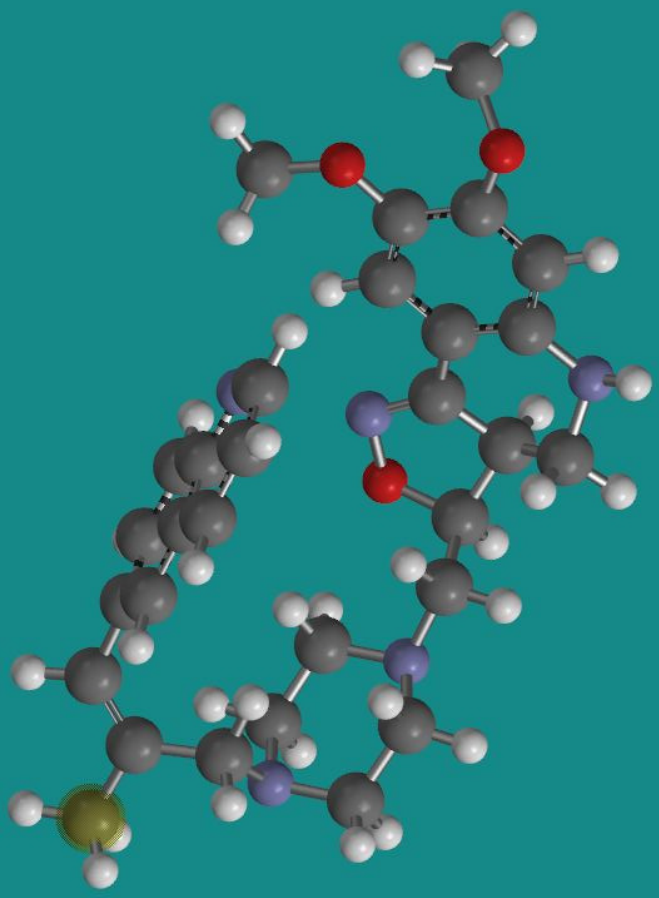
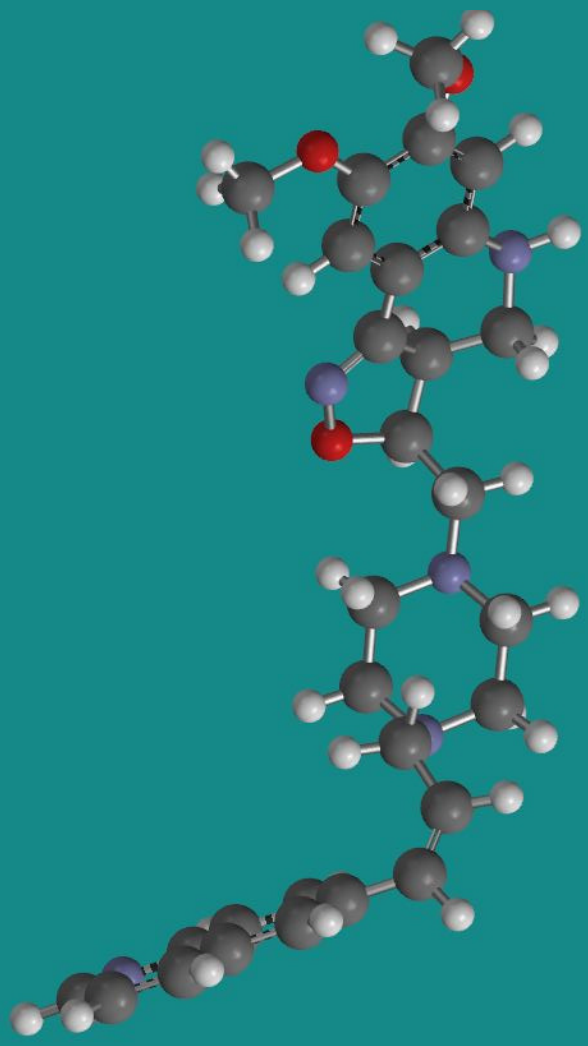
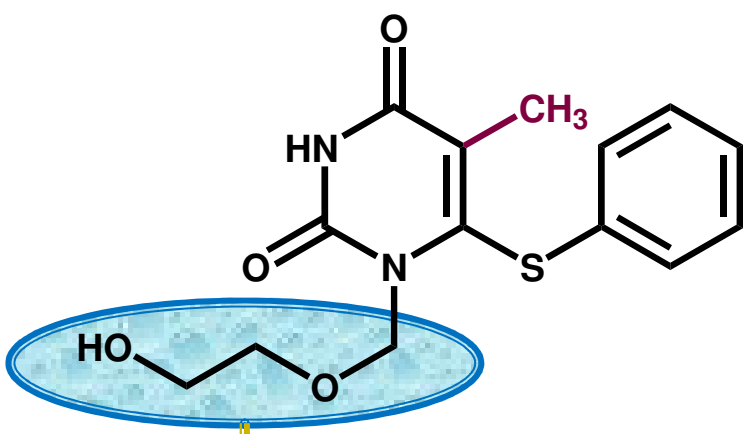


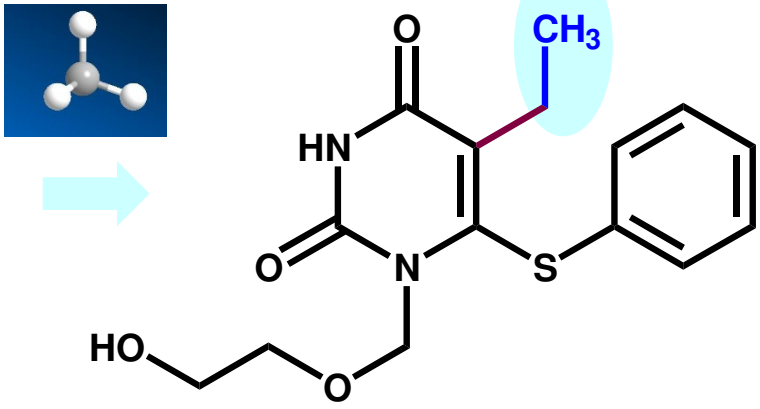


# Mais um capricho da metila ...

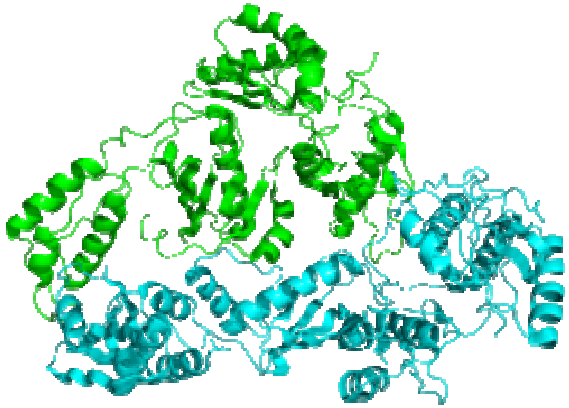



$EC_{50}$ (TR) = 6,5 µM

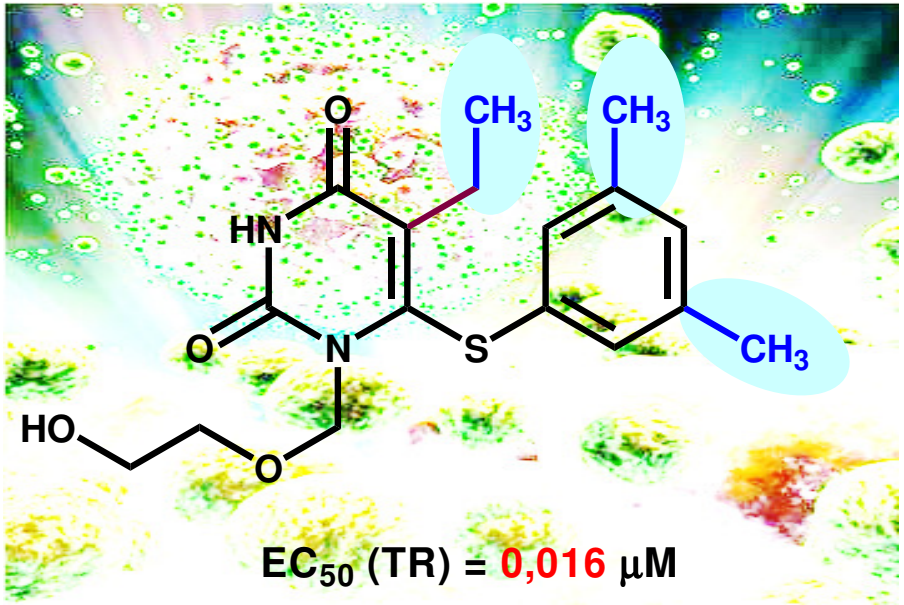
Cadeia do aciclovir




$EC_{50}$ (TR) = 0,12 µM



TR




$EC_{50}$ (TR) = 0,016 µM

# O discreto charme da metila...

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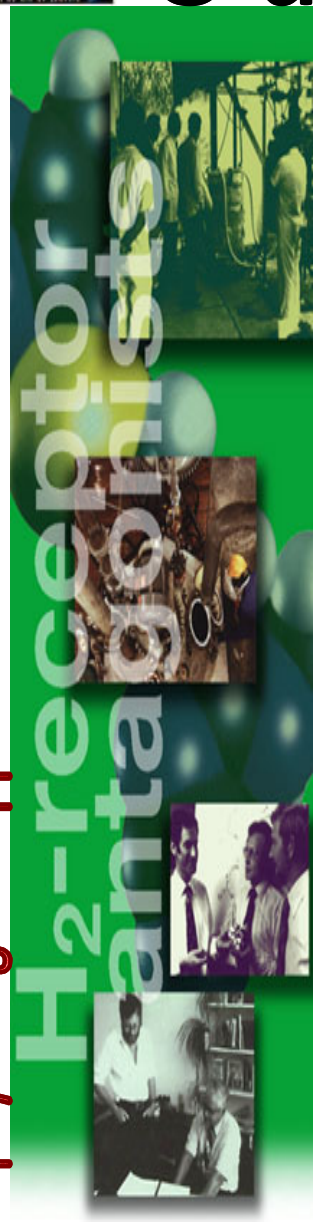


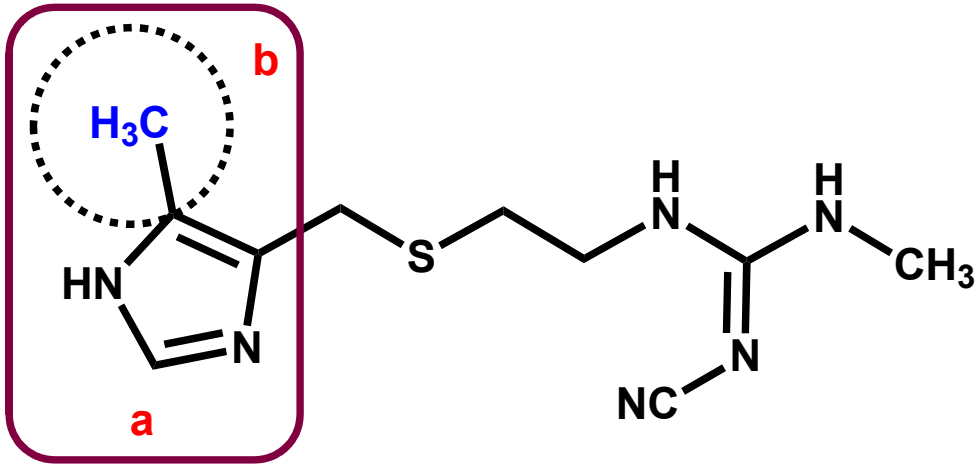

National Historic Chemical Landmarks

AMERICAN CHEMICAL SOCIETY

## A new era of logical drug design

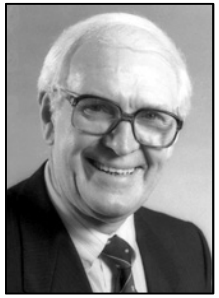
The research program leading to cimetidine also represented a revolution in the way pharmaceuticals are developed. Traditionally, the development of a new drug would often depend on the fortuitous discovery of a plant or microbial extract that showed some of the required biological activity. Using that first extract as a lead, many similar compounds would be made and tested for pharmacological effectiveness. In many cases, the researchers did not know how the drug worked, so finding an optimal compound was difficult.

The development of cimetidine was radically different: it was one of the first drugs to be designed logically from first principles. SK&F's multidisciplinary research team first looked at the physiological cause of acid secretion. They confirmed that a molecule found in the body called histamine triggers the release of acid when it binds to a specific receptor (now called the $H_2$-receptor) in the stomach lining. Their aim was to find a molecule that successfully competed with histamine in combining with the receptor, but then blocked, rather than stimulated, acid release. Such a molecule was called a histamine $H_2$-receptor antagonist and represented a new class of drugs.

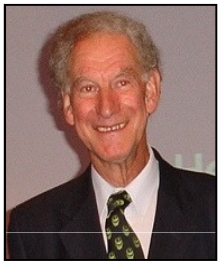



**cimetidine**

1988



James W. Black



C Robin Ganellin

John C Emmett

Graham J Durant

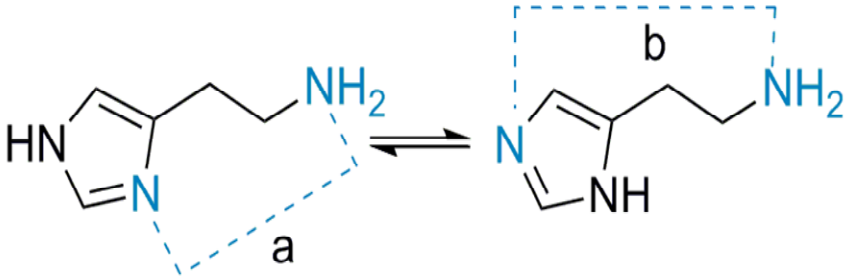
# A metila *inteligente*...

Química Medicinal

## Dois sub-tipos de $H_R$

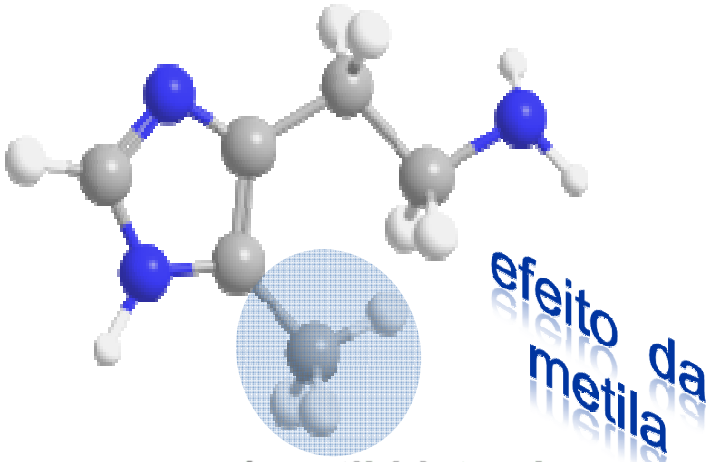
C Robin Ganellin, 1973

Interações fracas



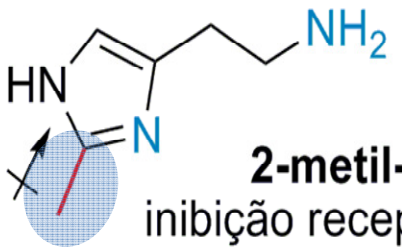

**Forma A** a = 4,83 Å b = 5,52 Å **Forma B**

**Equilíbrio tautomérico**

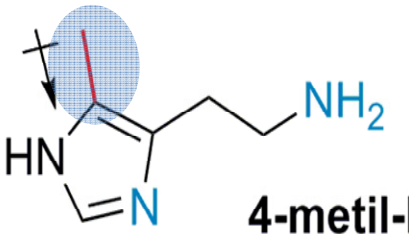



**4-metil-histamina**

**Análogo ativo**




**2-metil-histamina**
inibição receptores $H_1$ = 17%
inibição receptores $H_2$ = < 2%

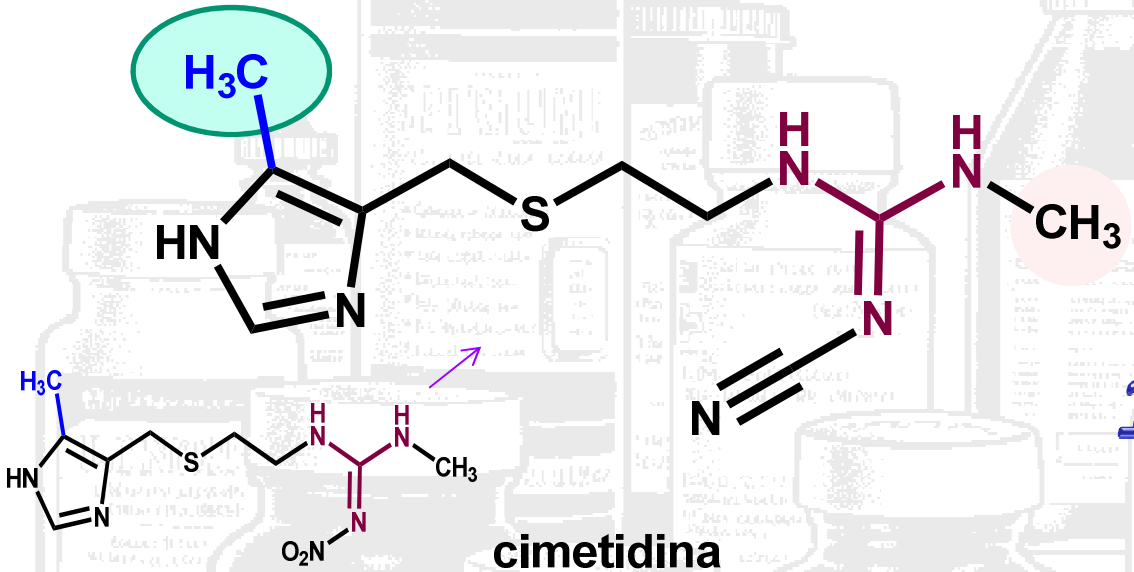



**4-metil-histamina**
inibição receptores $H_1$ = 0,2%
inibição receptores $H_2$ = 50%


S L Carney, Robin Ganellin gives his views on medicinal chemistry and drug discovery, *Drug Discov Today* **2004**, *9,* 158-160

# A primeira *metila* valiosa...

## Primeiro antagonista seletivo do receptor histaminérgico $H_2$




**cimetidina**

$C_{10}H_{16}N_6S$

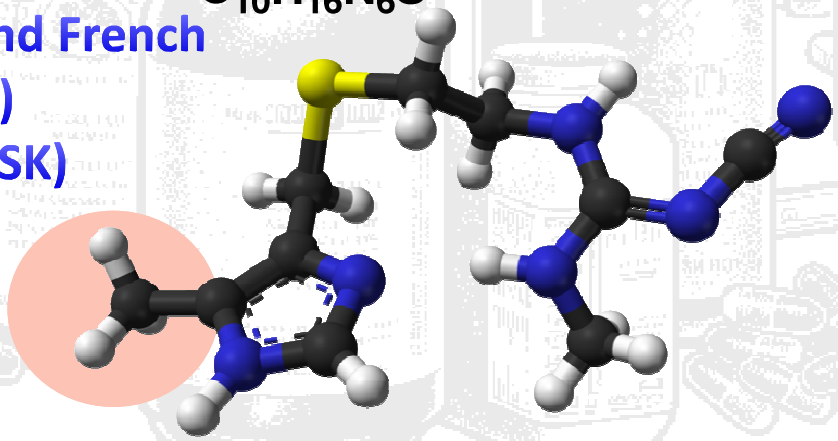
**Inovação terapêutica**

**1st blockbuster**

**1975**

**> US$ 1 bi**

**Smith, Kline and French (SK&F) (atual GSK)**



**Química Medicinal**


CR Ganellin, Cimetidine, em *Chronicles of Drug Discovery*, JS Bindra & D Lednicer Eds., Wiley, New York, pp. 1-38

# A metila *feliz*...

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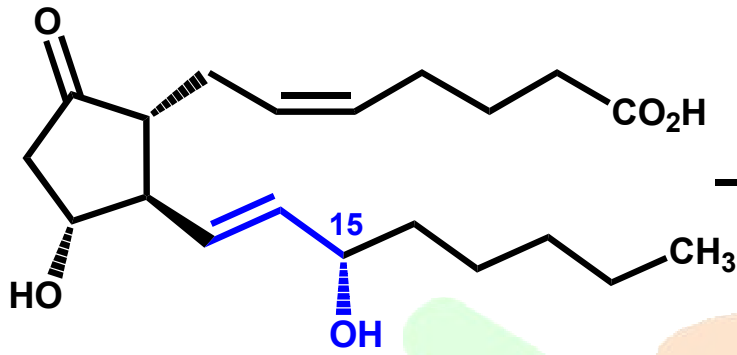
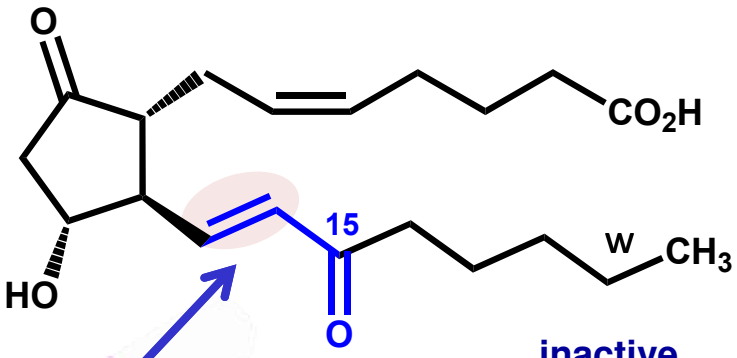



PGE$_2$

PGDH

plasma




inactive

15-ceto PGE$_2$

PG-redutase (PGR)

enhancing metabolic stability

John R. Vane

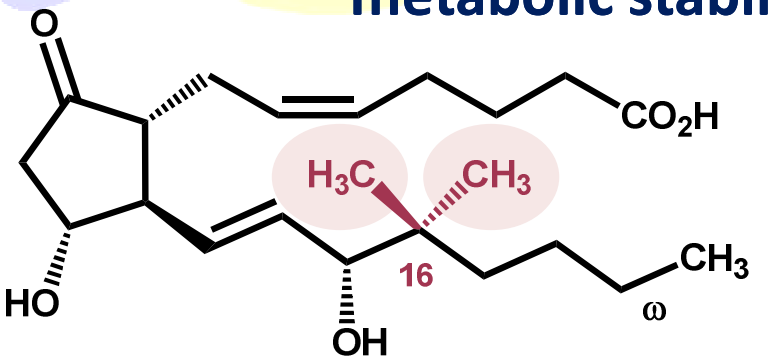
(1927-2004)

K. Sune Bergström

(1916-2004)

molecular modification

Química Medicinal



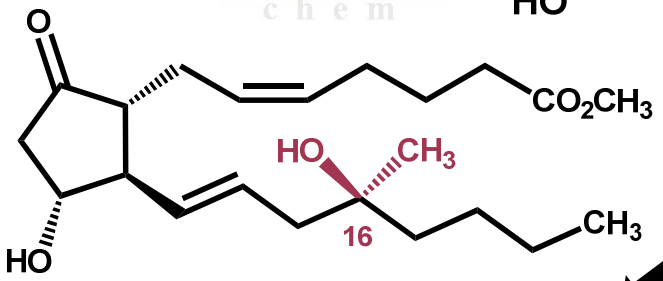

16,16-dimethyl PGE$_2$ *

EP$_2$ ag. ~ 1 nM

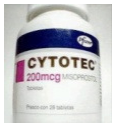
50 X PGE$_2$ (GI tract)

1982

Bengt I. Samuelsson

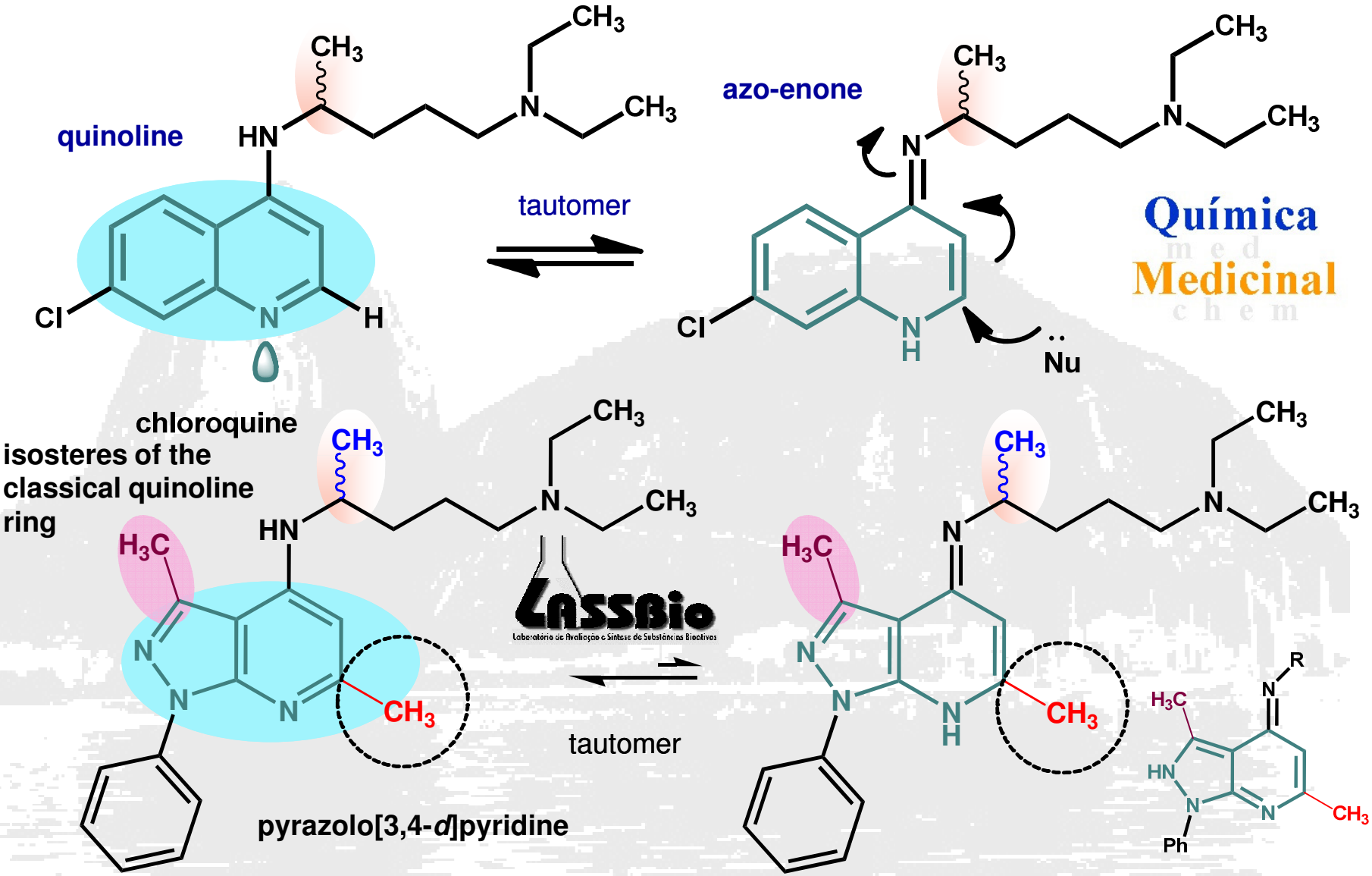



Misoprostol




* A Robert & BJ Magerlein, *Adv Biosci* **1973**, *9*, 247

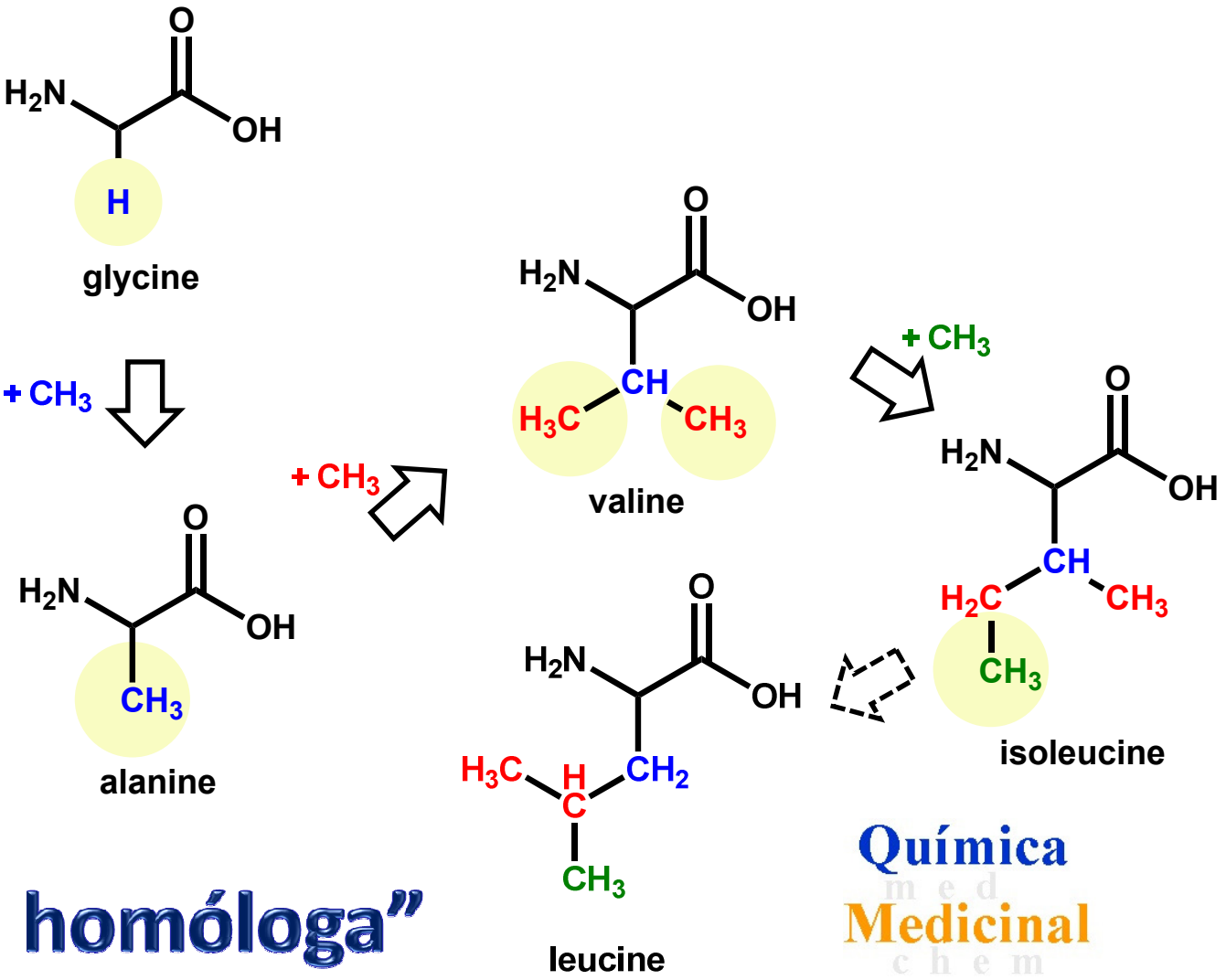
# O *fascínio* da metila...




*in vitro* antimalarial activity against chloroquine-sensitive (Sierra Leone D-6) and resistant (Indochina W-2) clones of *P. falciparum*

LRS Dias, ACC Freitas, EJ Barreiro , DK Goins, D Nanayakkara JD McChesney, Synthesis and biological activity of new potential antimalarial: 1*H*-pyrazolo[3,4-*b*]pyridine derivatives. *Boll. Chim. Farm.* **2000**, *139*, 14

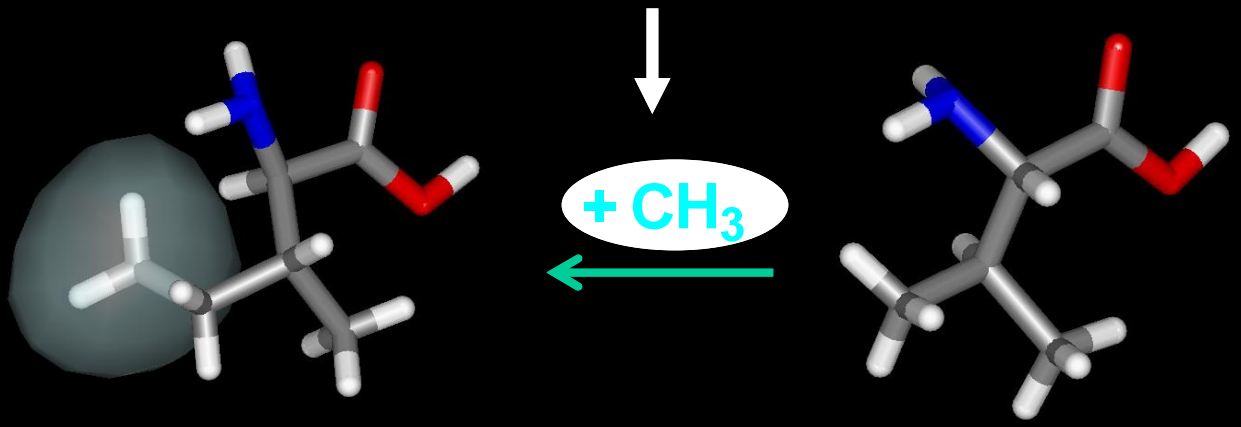
# A homologia, a metila e os *nossos* aminoácidos




**“ série homóloga”**

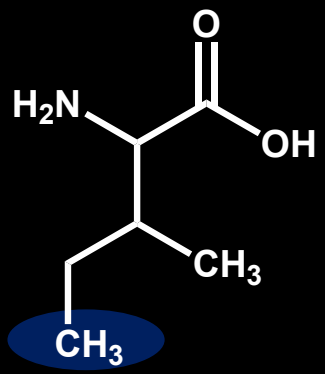
Química Medicinal

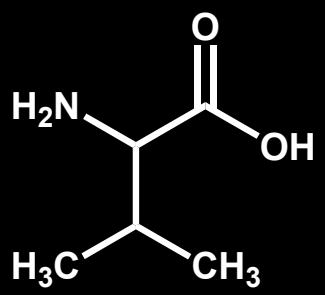
# A homologia da valina




isoleucina

valina



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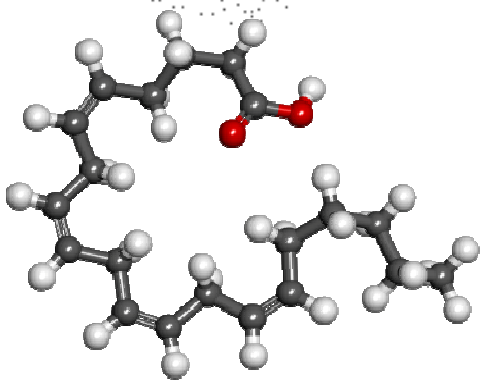
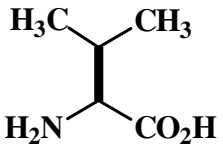
# Os amino ácidos homólogos e a COX

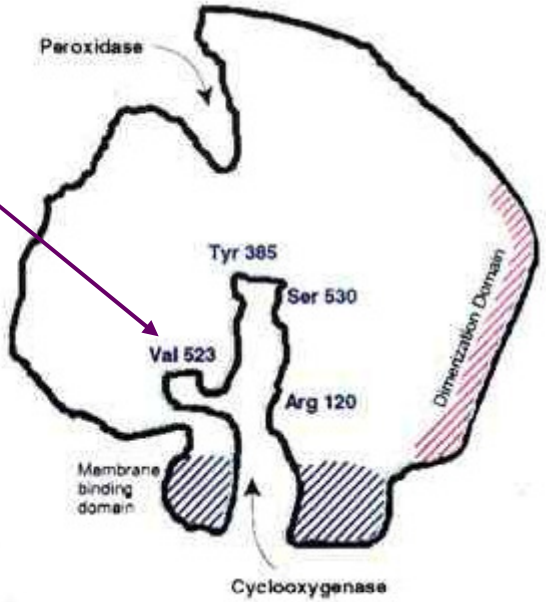


**Ácido araquidônico**
**$K_m$ = 5,6/5,4 μM**

Sítio secundário

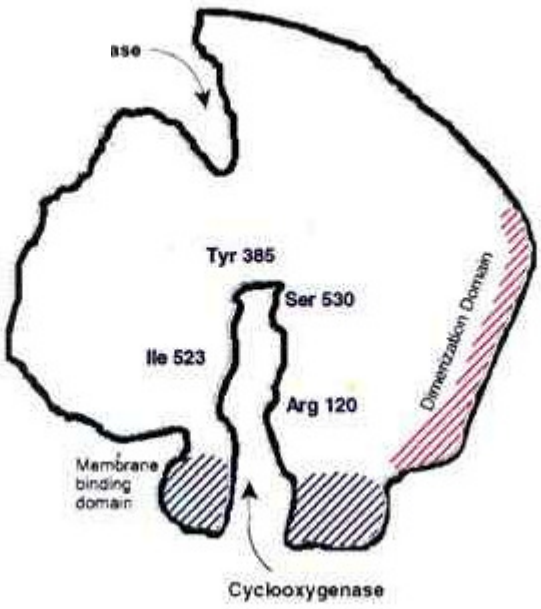


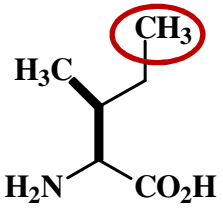
**$C_5H_{11}NO_2$**
**Valina**




## COX-2

- Inflamação
- Câncer
- Endotélio vascular
- Rins
- Cérebro



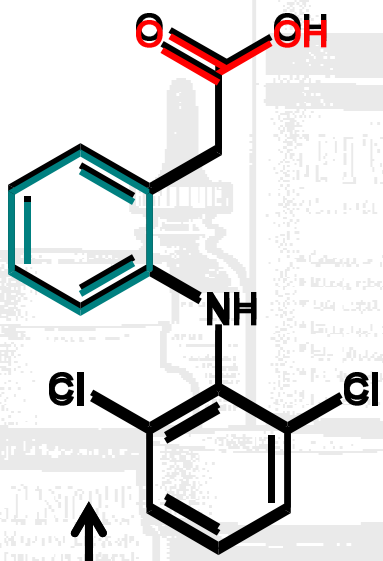



**$C_6H_{13}NO_2$**
**Isoleucina**

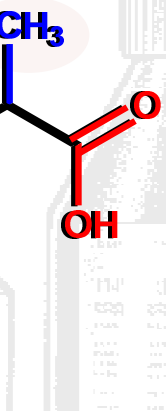
## COX-1

- Estômago
- Plaquetas
- Rins

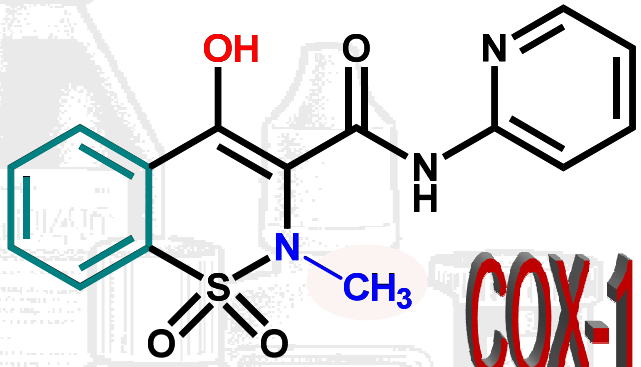
# A *genialidade* da metila ...




diclofenac



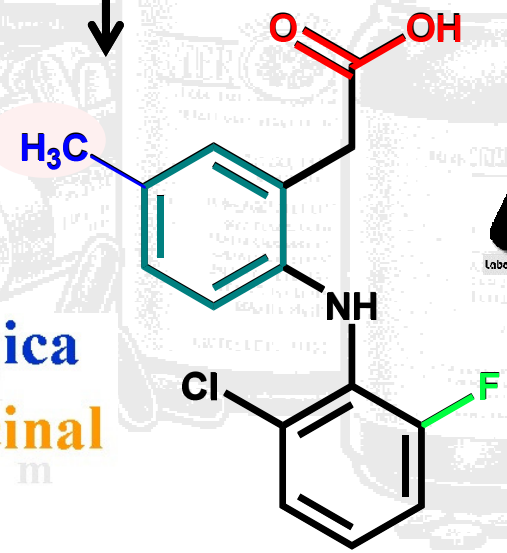

ibuprofen



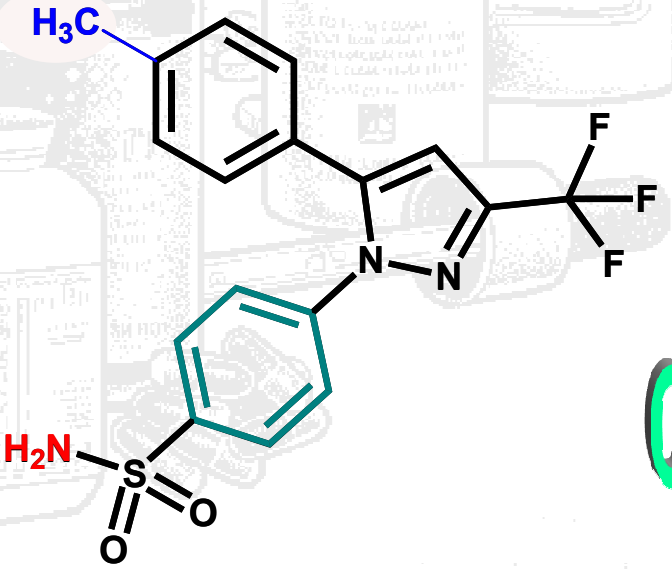

piroxicam

COX-1

Molecular similarity




lumiracoxib




celecoxib

COX-2

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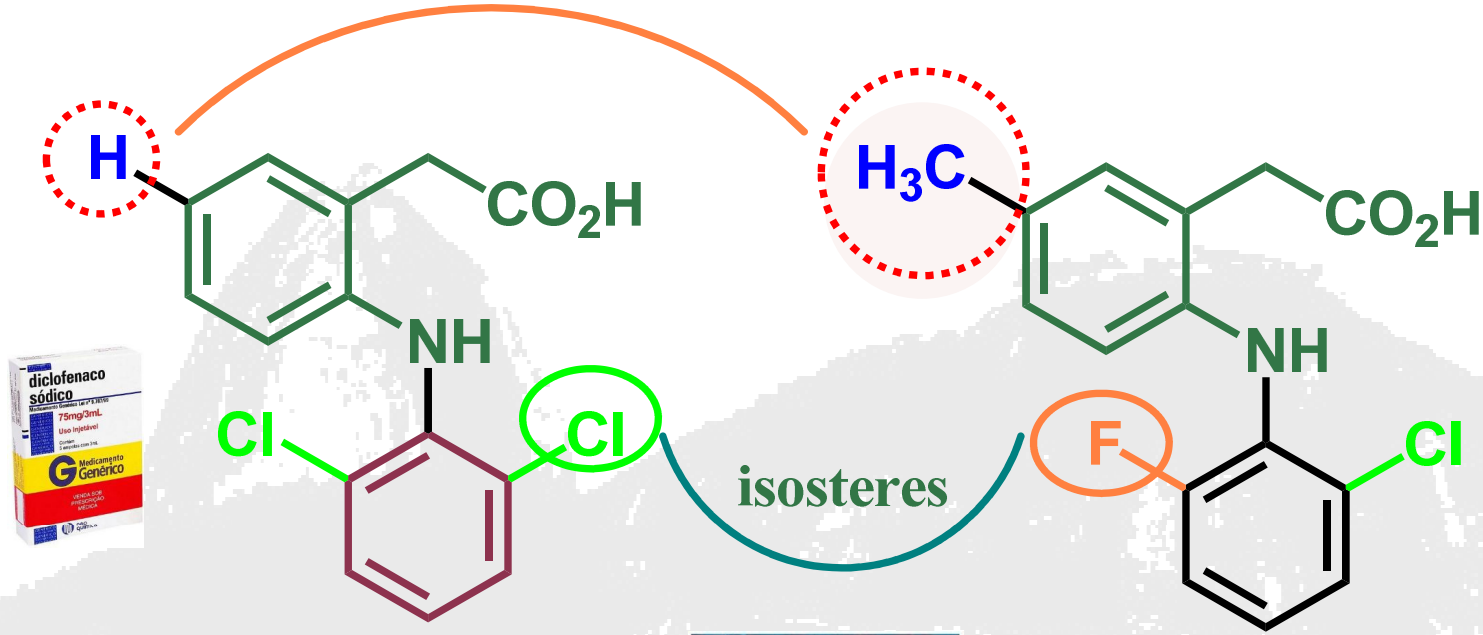
UFRJ

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

Química Medicinal
med chem

# A *genialidade* da metila ...








**DICLOFENAC**

Ki (μM) PGHS-1 = 0.010
Ki (μM) PGHS-2 = 0.018

**COX-1**

**LUMIRACOXIB**

Ki (μM) PGHS-1 = 3.2
Ki (μM) PGHS-2 = 0.06

**COX-2**

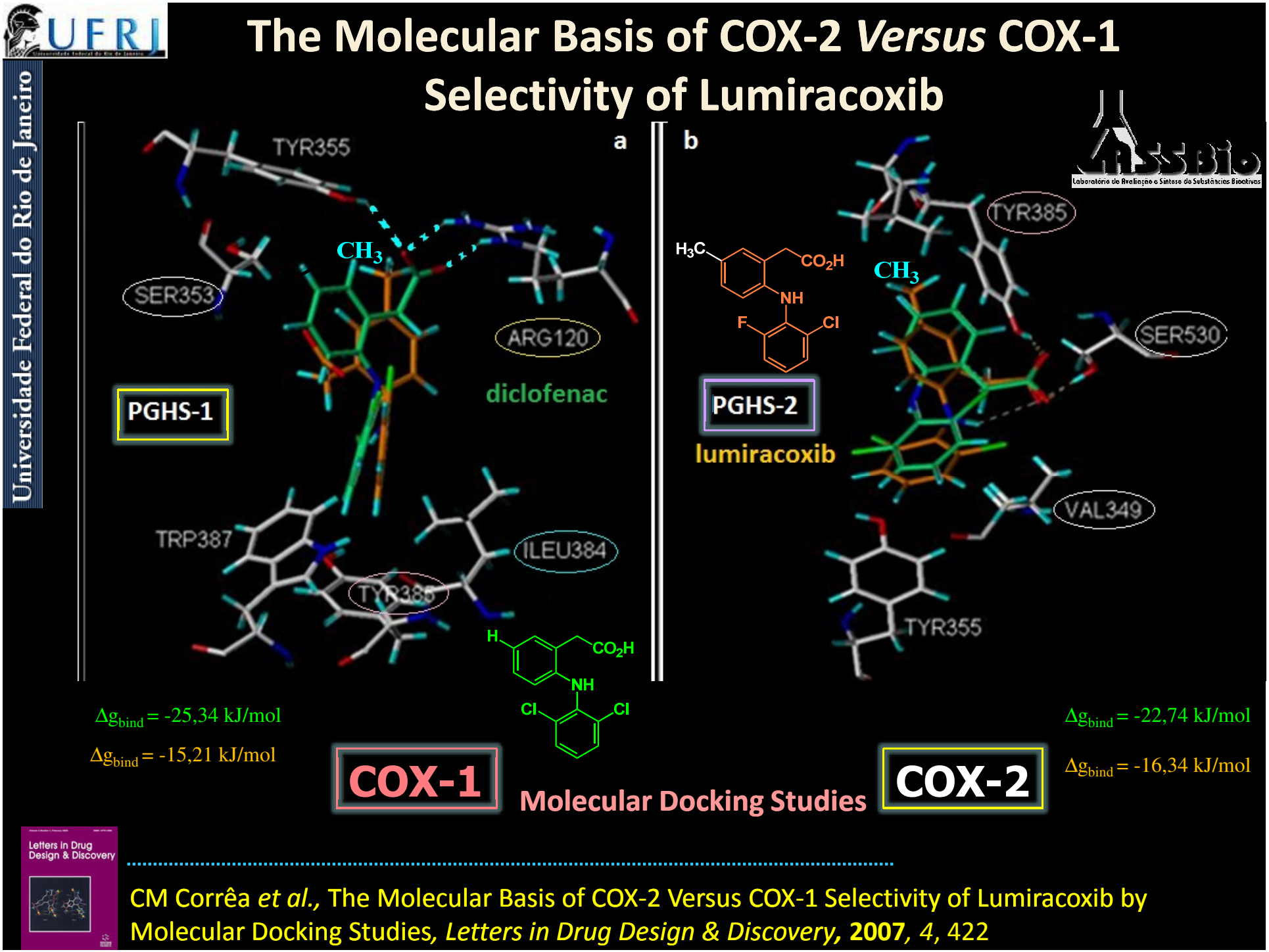
**2003 (2008)**

Química Medicinal

Lumiracoxib have one chlorine substituted by fluorine and the phenylacetic acid moiety has methyl group in *meta* position

H. Furuie et al., The evaluation of the COX-2 selective inhibition of lumiracoxib, a novel nonsteroidal anti-inflammatory drug, *Clin Pharmacol Therap* **2004**, *75*, P5

# The Molecular Basis of COX-2 *Versus* COX-1 Selectivity of Lumiracoxib







CM Corrêa *et al.*, The Molecular Basis of COX-2 Versus COX-1 Selectivity of Lumiracoxib by Molecular Docking Studies, *Letters in Drug Design & Discovery*, **2007**, *4*, 422

# O doce *fascínio* da metila...

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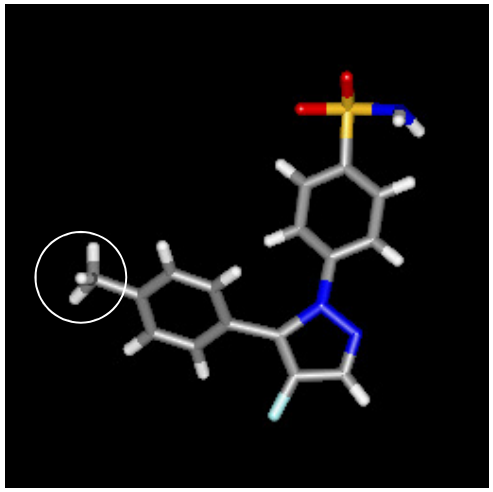
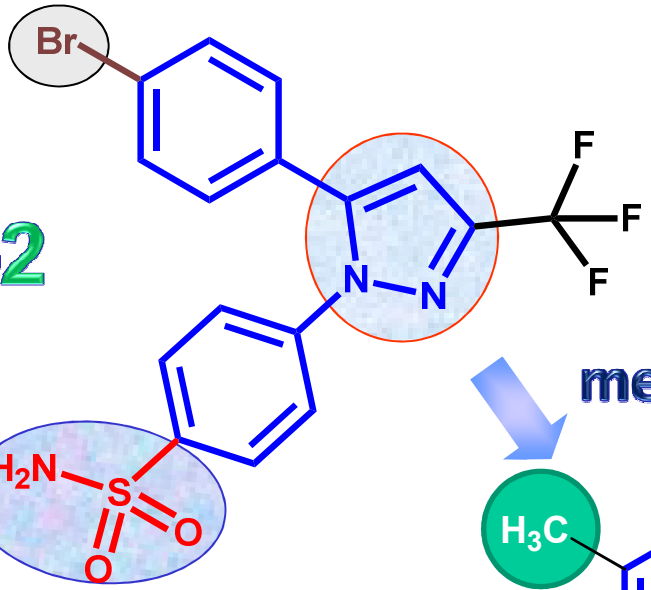
PGHS-2




TD Penning *et al., J. Med. Chem.* **1997**, *40*,1347



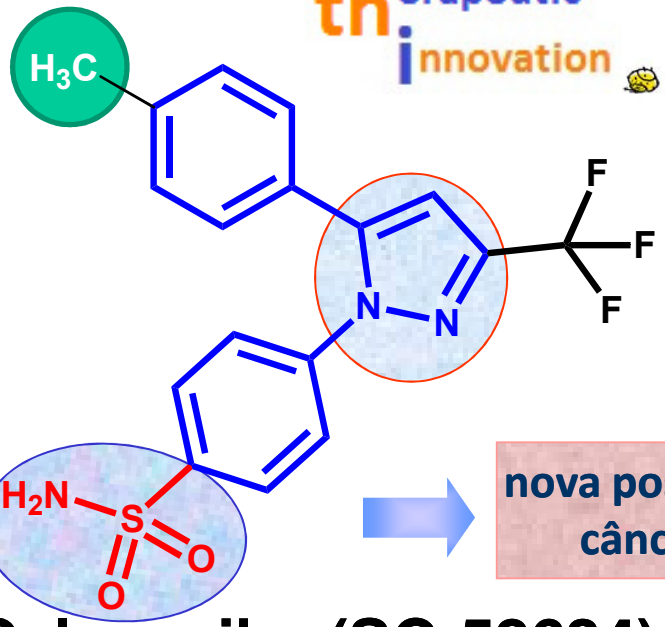

COX-2 seletivo
Searle

Vida-média = 12 dias !
(ADME)


Pfizer

metabolismo

therapeutic innovation





nova possível indicação:
câncer colo retal

**Celecoxibe (SC-58634)**

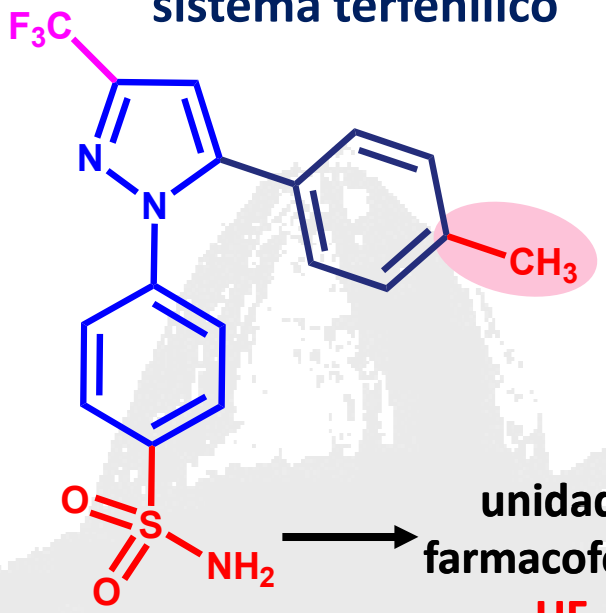
1999

**O mercado mundial de fármacos antiinflamatórios (*ca.* 50; 2012) ~ US$ 10 bi**

Universidade Federal do Rio de Janeiro

# A metila *aprontando*... [a]

sistema terfenílico

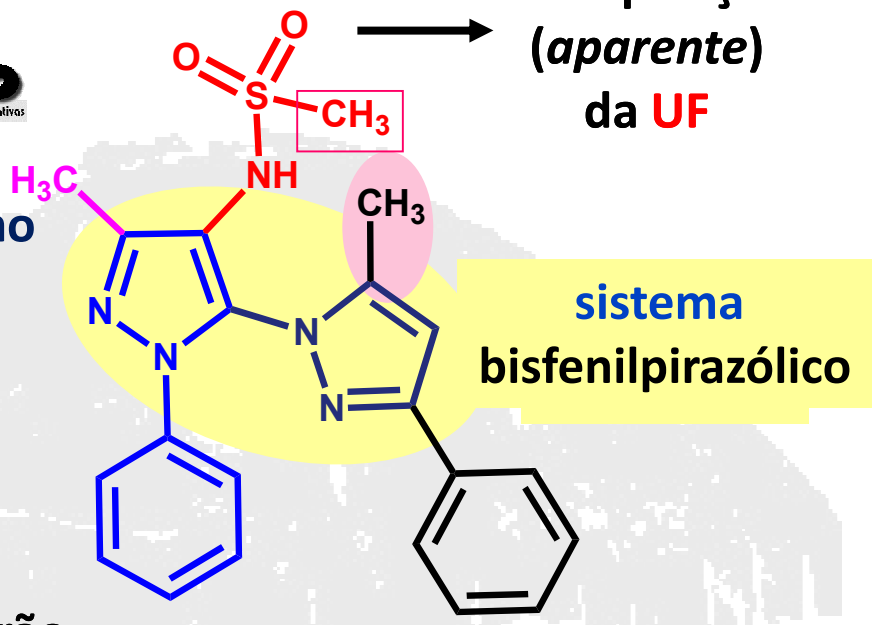



unidade farmacofórica UF

retroisosterismo

Transposição (*aparente*) da UF

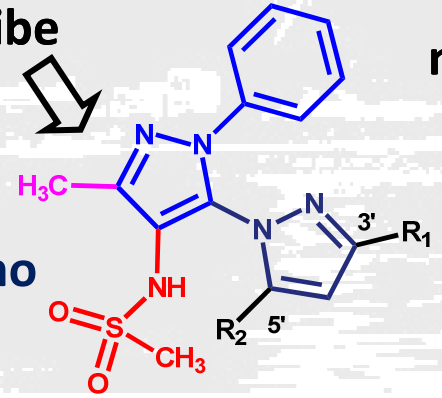
bioisosterismo




sistema bisfenilpirazólico

LASSBio-466

celecoxibe




novo padrão molecular

bispirazola

retroisosterismo

Química Medicinal

Atropoisomerismo

[a] M P Veloso, Tese de Doutoramento, Instituto de Química, UFRJ, 2000

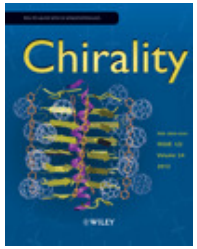
CHIRALITY 24:463–470 (2012)

Universidade Federal do Rio de Janeiro

# Synthesis and Characterization of the Atropisomeric Relationships of a Substituted *N*-Phenyl-Bipyrazole Derivative with Anti-inflammatory Properties

MARCIA P. VELOSO,[1,2,3] NELILMA C. ROMEIRO,[4] GILBERTO M. S. SILVA,[1,5,6] HÉLIO DE M. ALVES,[1] ANTONIO C. DORIGUETTO,[7] JAVIER ELLENA,[8] ANA L. P. MIRANDA,[1,5] ELIEZER J. BARREIRO[1,2,5] AND CARLOS A. M. FRAGA[1,2,5]*

[1]*Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil*
[2]*Programa de Pós-Graduação em Química, Instituto de Química, Universidade Federal do Rio de Janeiro, RJ, Brazil*
[3]*Faculdade de Ciências Farmacêuticas, Universidade Federal de Alfenas, Alfenas, MG, Brazil*
[4]*Universidade Federal do Rio de Janeiro, Macaé, RJ, Brazil*
[5]*Programa de Pós-Graduação em Farmacologia e Química Medicinal, Instituto de Ciências Biomédicas, Universidade Federal do Rio de Janeiro, RJ, Brazil*
[6]*Instituto de Pesquisa Clínica Evandro Chagas, FIOCRUZ, Rio de Janeiro, RJ, Brazil*
[7]*Instituto de Ciências Exatas, Universidade Federal de Alfenas, Alfenas, MG, Brazil*
[8]*Instituto de Física de São Carlos, Universidade de São Paulo, São Carlos, SP, Brazil*




**ABSTRACT:** This work describes the atropisomeric relationships of 3-methyl-5-(3-methyl-5-phenyl-1H-pyrazol-1-yl)-1-phenyl-1H-pyrazol-4-amine (2d), which belongs to series 4-aminobipyrazole derivatives designed as anti-inflammatory agents. The 1H-NMR spectra obtained in the presence of a chiral lanthanide shift salt associated to chiral HPLC analysis, X-ray diffraction and molecular modeling tools confirmed that ortho bis-functionalized bipyrazole 2d exists as a mixture of aR,aS-atropisomers. These results provide useful information to understand the pharmacological profile of this derivative and of other 4-aminobipyrazole analogues.

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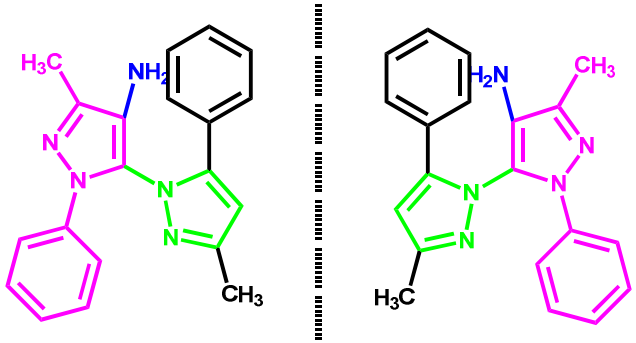
*aR*-(2d)




*aS*-(2d)

**Atropoisomerism**

# Determinação da configuração absoluta

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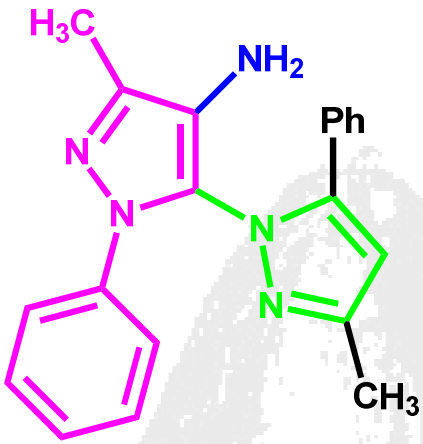
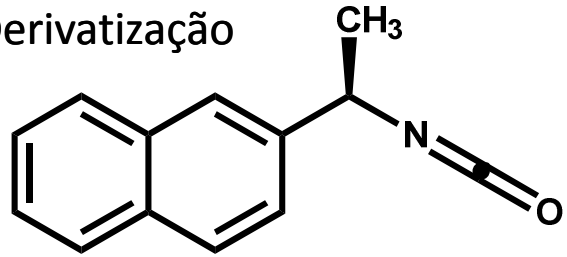


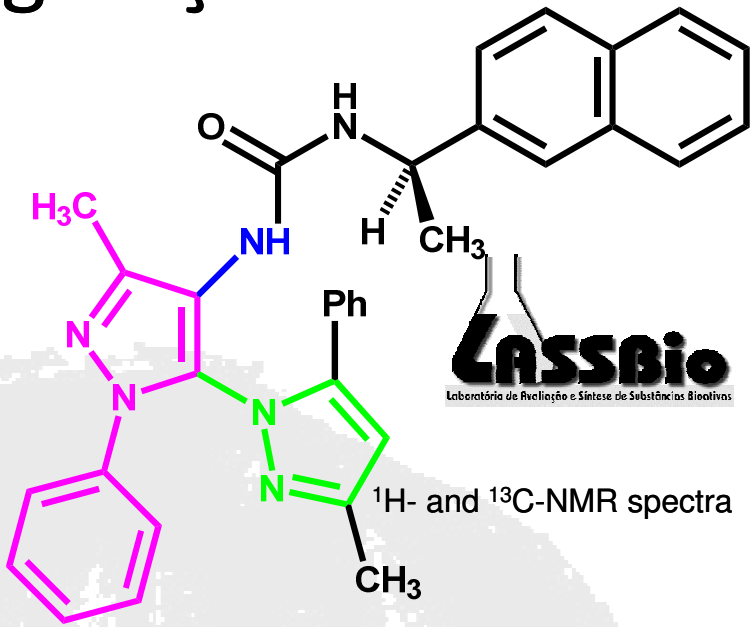

Derivatização




(*R*)-(-)-ethyl-1-(1-naphtyl)-isocyanate

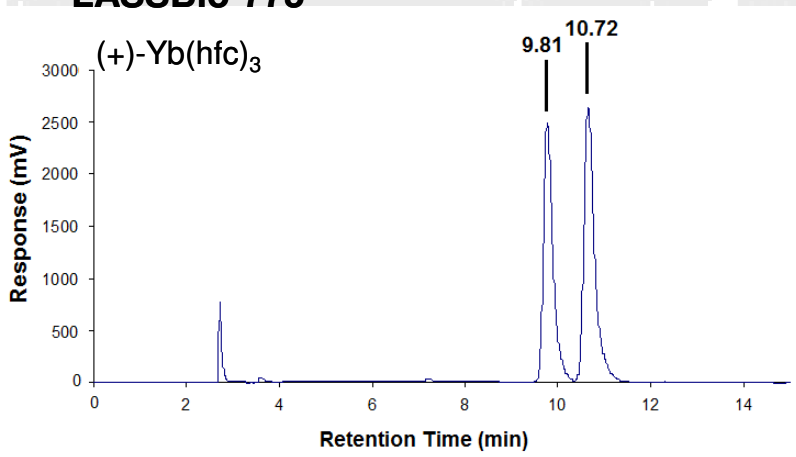
$NEt_3$, THF, rt

96%




$^1$H- and $^{13}$C-NMR spectra

**LASSBio-775**



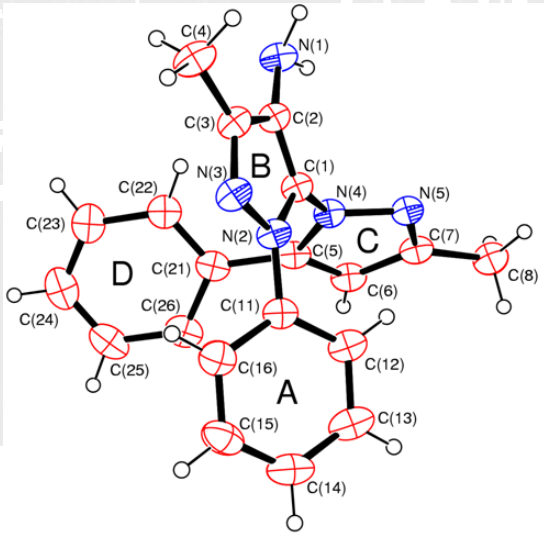

Lichosorb (N. 738342) RP-18 column (250 mm x 4 mm x 5 µm)

L-7450A diode array detector (DAD)

acetonitrile and water (adjusted to pH 3 with TFA 0.1%) gradients

[$CH_3CN$:HOH (pH 3) from 20:80 to 80:20]

**diastereomeric bipyrazole urea derivatives**

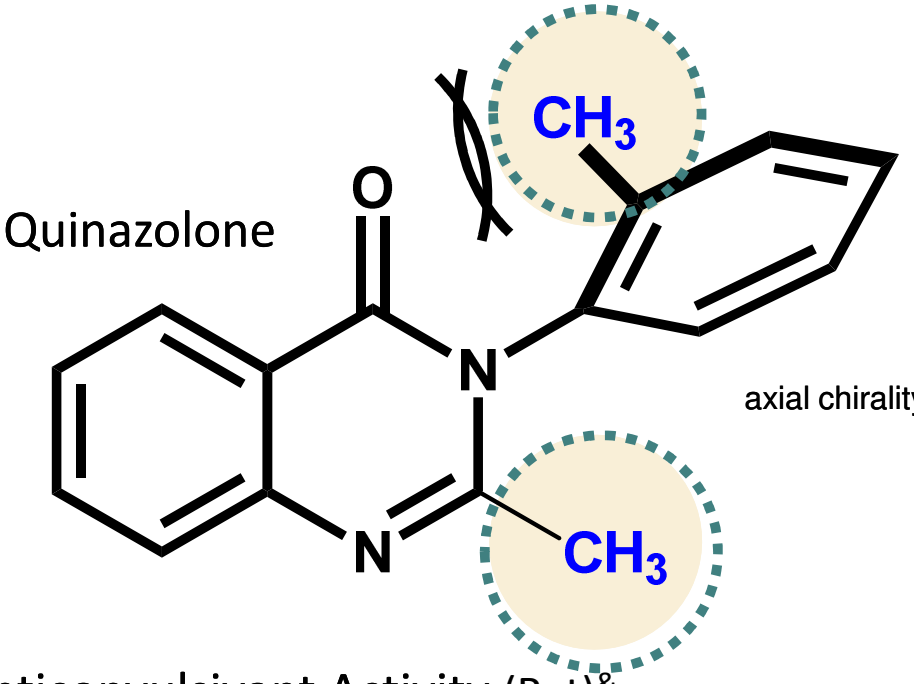



Enraf-Nonius Kappa-CCD difractometer

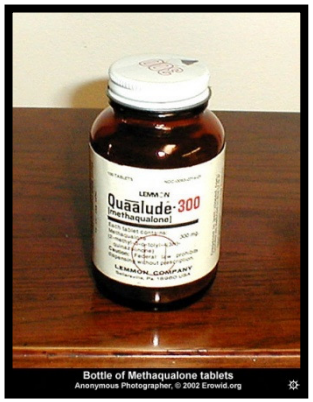
MP Veloso et al., *Chirality* **2012**, *24*, 463

# A *sofisticação* da metila...

Universidade Federal do Rio de Janeiro




Indian researchers in the 1951




Química Medicinal

methaqualone

Mandrax$^{R}$

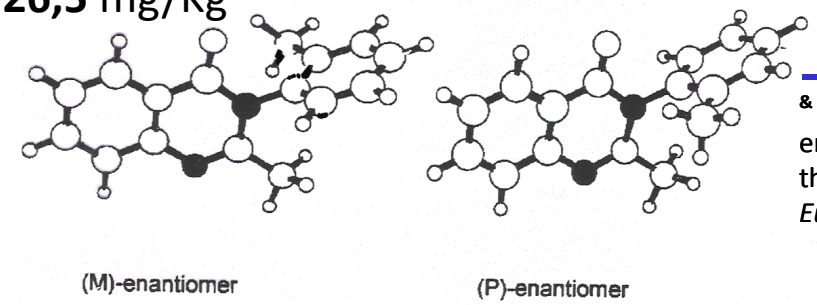
US Patent 3135659 - Hydroxy and Alkoxy Aryl Quinazolones

Anticonvulsivant Activity (Rat)[&]

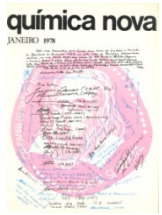
*(R)*-(+)-methaqualone $ED_{50}$= 35,7 mg/Kg

(S)-( - )-methaqualone **$ED_{50}$= 26,5** mg/Kg

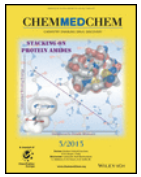
## Atropoisomerismo




[&] A. Mannschreck *et al.*, The enantiomeres of methaquolone and their unequal anticonvulsive activity, *Eur. J. Med. Chem*. **1984**, *19*, 381








AR Santos *et al*., Atropoisomerismo: o efeito da quiralidade axial em substâncias bioativas, *Quim Nova* **2007**, *30*, 125; SR LaPlante, PJ Edwards, LD Fader, A Jakalian, O Hucke, Revealing Atropisomer Axial Chirality in Drug Discovery, *ChemMedChem* **2011**, *6*, 505

# A elegante *sutileza* da metila...

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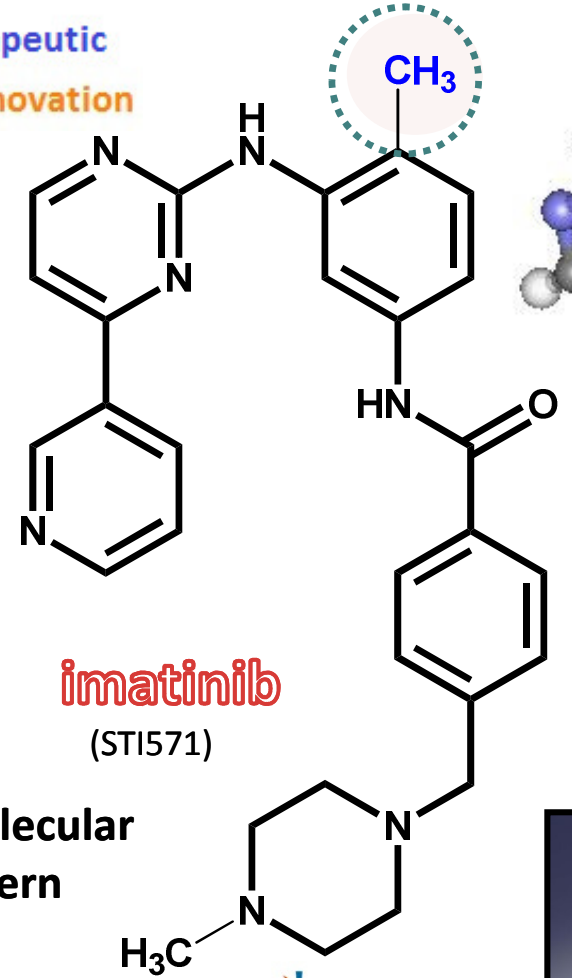
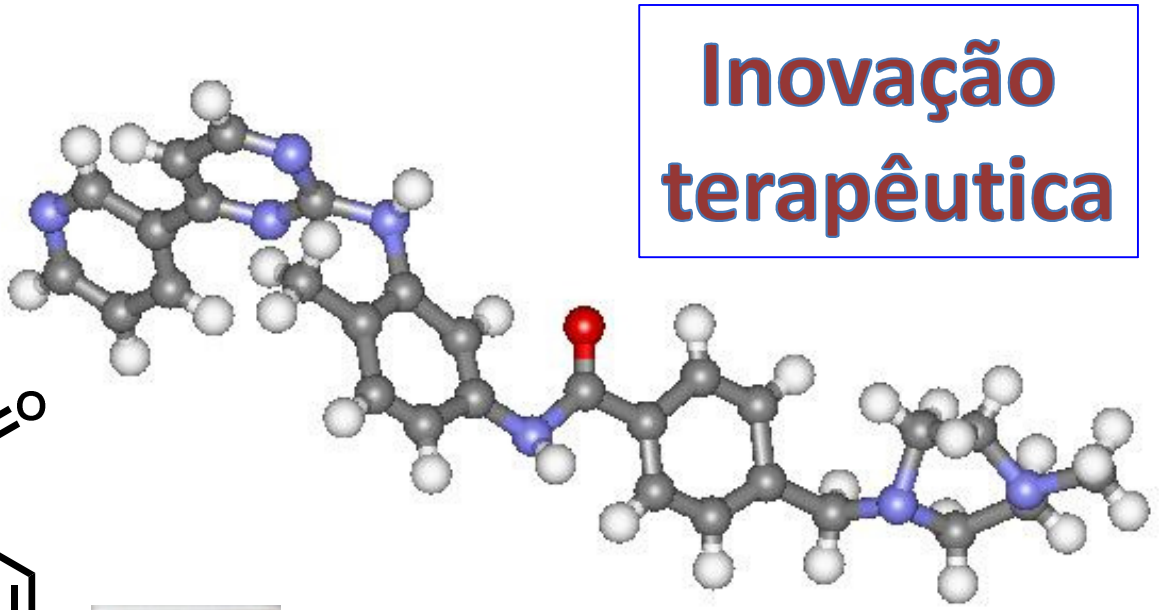
therapeutic innovation




**imatinib**

(STI571)

**New molecular pattern**



**Inovação terapêutica**


**1988 – Nicholas Lydon, Brian J. Druker & Charles L Sawyers &**
**1995 - Compound STI571 ++**
**2001 – Imatinib (Gleevec$^{R}$, Novartis)[link]**

chronic myelogenous leukemia (CML)

NOVARTIS

**imatinibe**

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**

& 2009 - Lasker Foundation Clinical Award (*J. Clin. Invest*. **2009**, *119*, 2863; DOI:10.1172/JCI41141);
* Brian J. Druker has been awarded with the 2012 Japan Prize in Healthcare and Medical Technology;
** Charles L. Sawyers was named in 2011, Thomson Reuters Citation Laureate in Medicine;

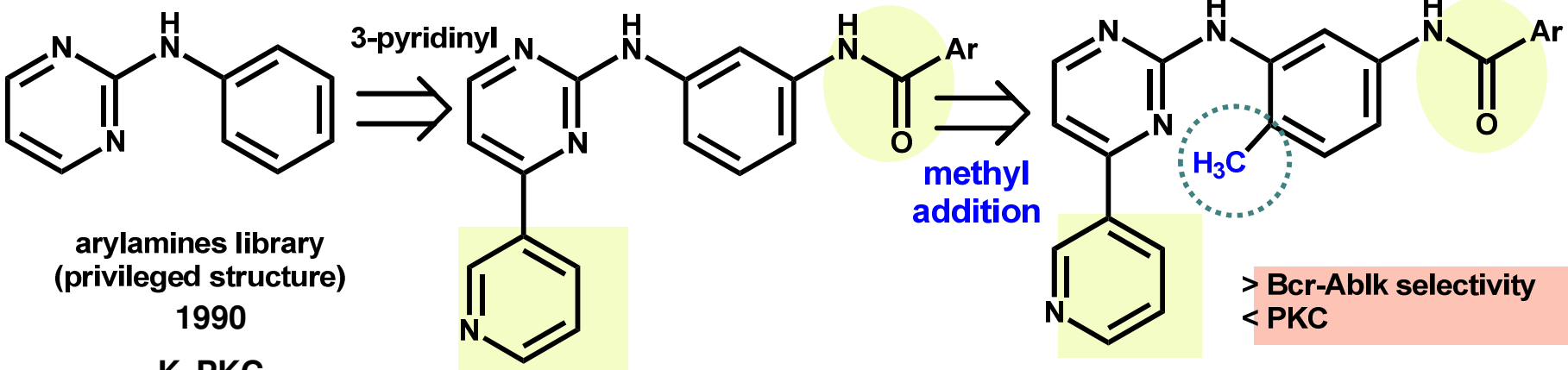
Universidade Federal do Rio de Janeiro

UFRJ

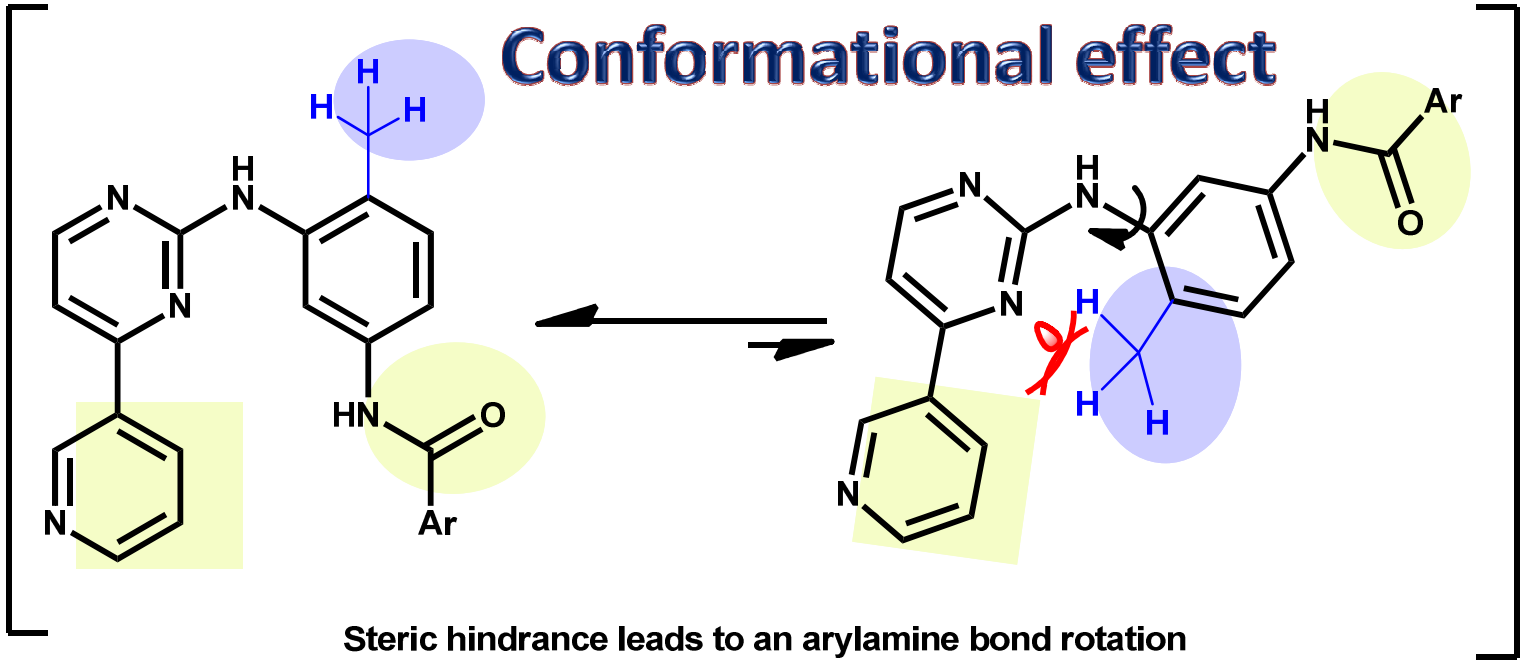
NOVARTIS

Química Medicinal

HTS




## Conformational effect

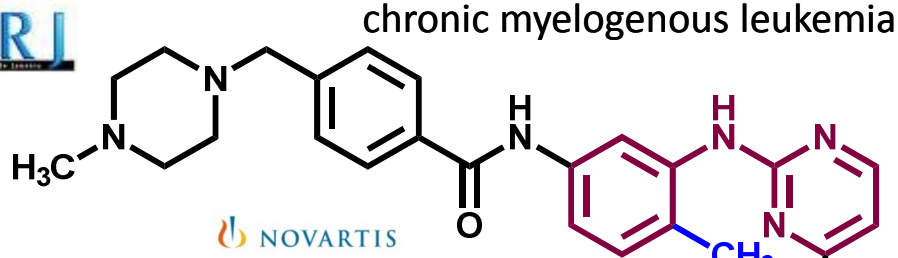



PW Manley, J Zimmermann in Case Studies in Modern Drug Discovery and Development, X Huang & RG Aslanian, Eds.,Wiley, **2012**, pp.88-102

Universidade Federal do Rio de Janeiro

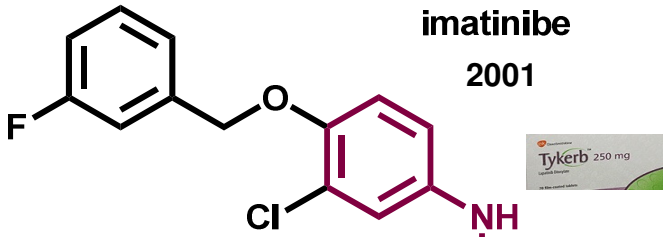
chronic myelogenous leukemia (CML)

# Tinibes

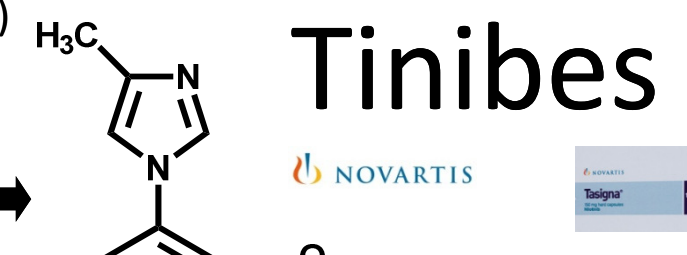


NOVARTIS

imatinibe
2001



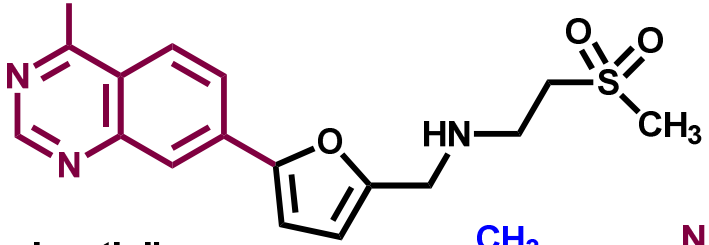




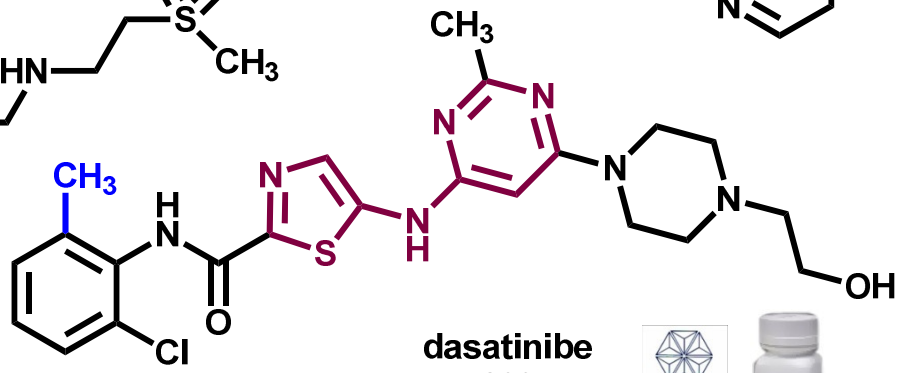
NOVARTIS



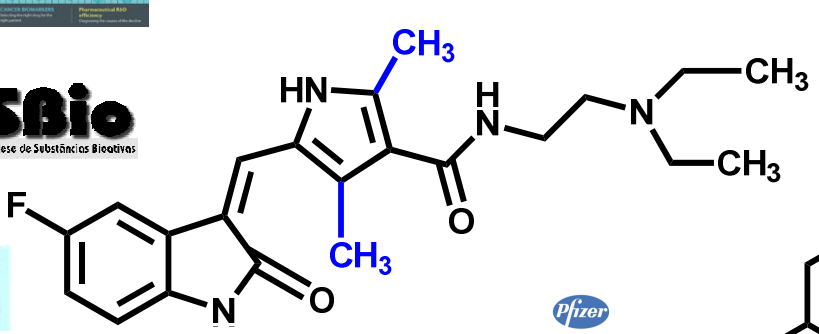
nilotinibe
2006



lapatinibe
2007

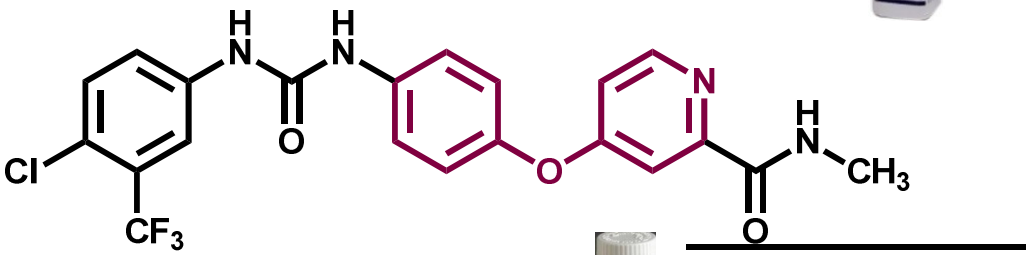


dasatinibe
2007



LASSBio-1727

sunitinibe
2006



sorafenibe
2007

2011- crisotinibe
2012- bosutinibe

TS Sampaio, 2012

- **US market in 2009: US$ 18,5 bi ***
- **Imatinibe world sales in 2009: US$ 4,0 bi***

* S Aggarwal, *Nature Rev Drug Discov* **2010**, *9*, 427

# As *metilinha$ bilionária$* ...(ah!)Final

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*Akira Endo, Sankyo Co*

## Estatinas*

***1975 – Mevastatina (ML-263b)***

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

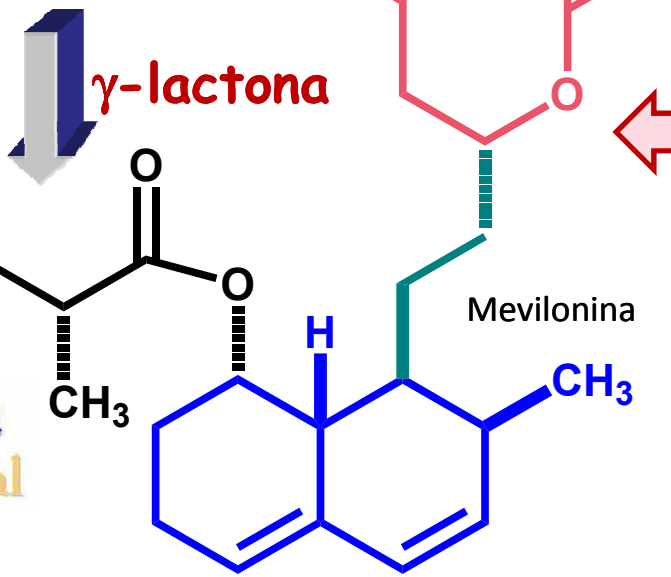
Protótipo natural

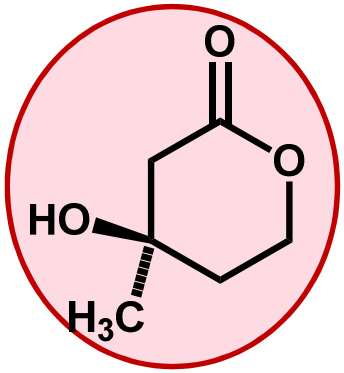
**Similaridade molecular**

A.Endo, *J. Antibiot.* **1976**, *29*, 1346
*Penicillium citrinum*
*Idem*, *Ibid*, **1979**, *32*, 852
*Monascus ruber*
(compactina)

**Mevalolactona**

**HMG-CoA redutase**




JL Goldstein

MS Brown

1985 LDL

University of Texas, Dallas

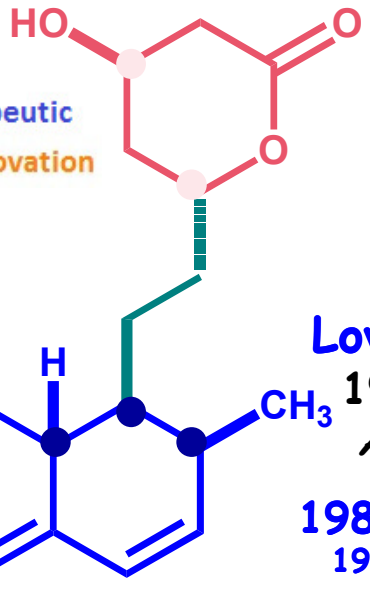
Química Medicinal

therapeutic innovation

MERCK

**Arthur A Patchett**

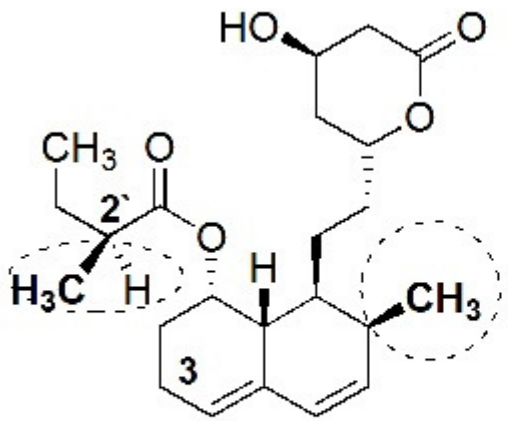
*Alfred Burger Award 2002*
*J. Med. Chem.* **1986**, *29*, 849




**Lovastatin (MK-803)**
**1978 – Merck & Co.**
***Aspergillus terreus***

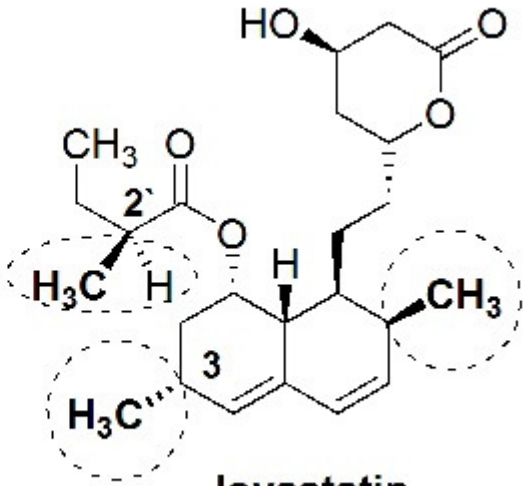
**1987 – MS&D (*Mevacor*$^{R}$)**
**1988 – *Mevacor*$^{R}$ US$ 260 mi**

# A metila *$e achando...*




mevastatin

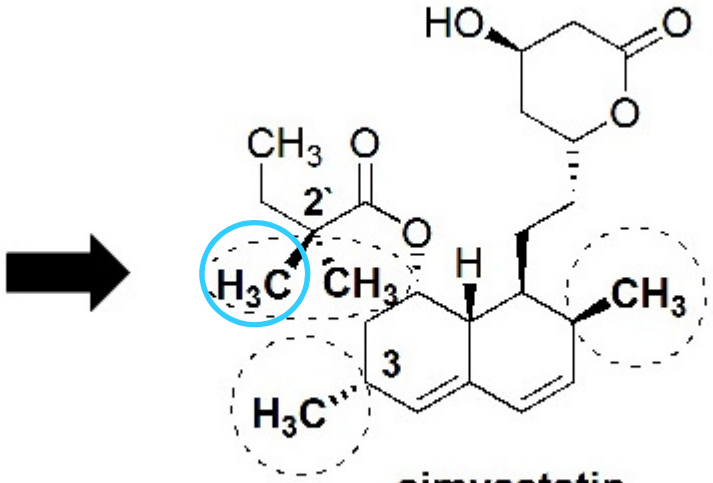
$IC_{50}$ HMG-$CoA_R$ = 5.6 nM




lovastatin

$IC_{50}$ HMG-$CoA_R$ = 2.2 nM

Química Medicinal




simvastatin

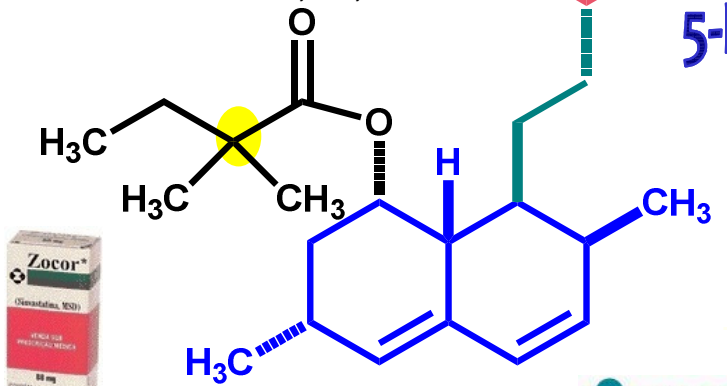
$IC_{50}$ HMG-$CoA_R$ = 0.9 nM

PS Anderson, Reflexions on medicinal chemistry at Merck, West Point, *Annu. Rept. Med. Chem*. **2012**, *47*, 3

# Estatinas

## 5-HMGCoARi

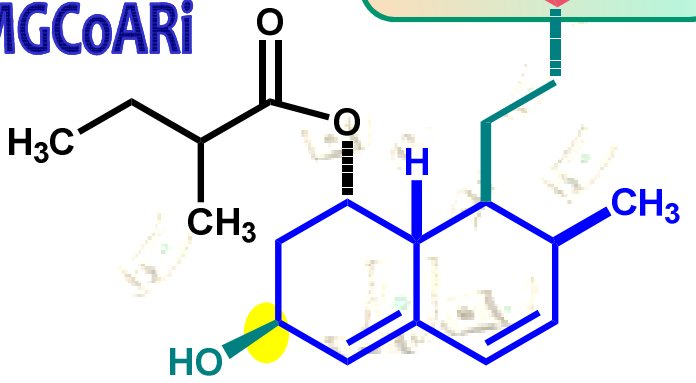
Arthur A Patchett
*J Med Chem* **2003**, *45*, 5609



simvastatina
1986




MERCK



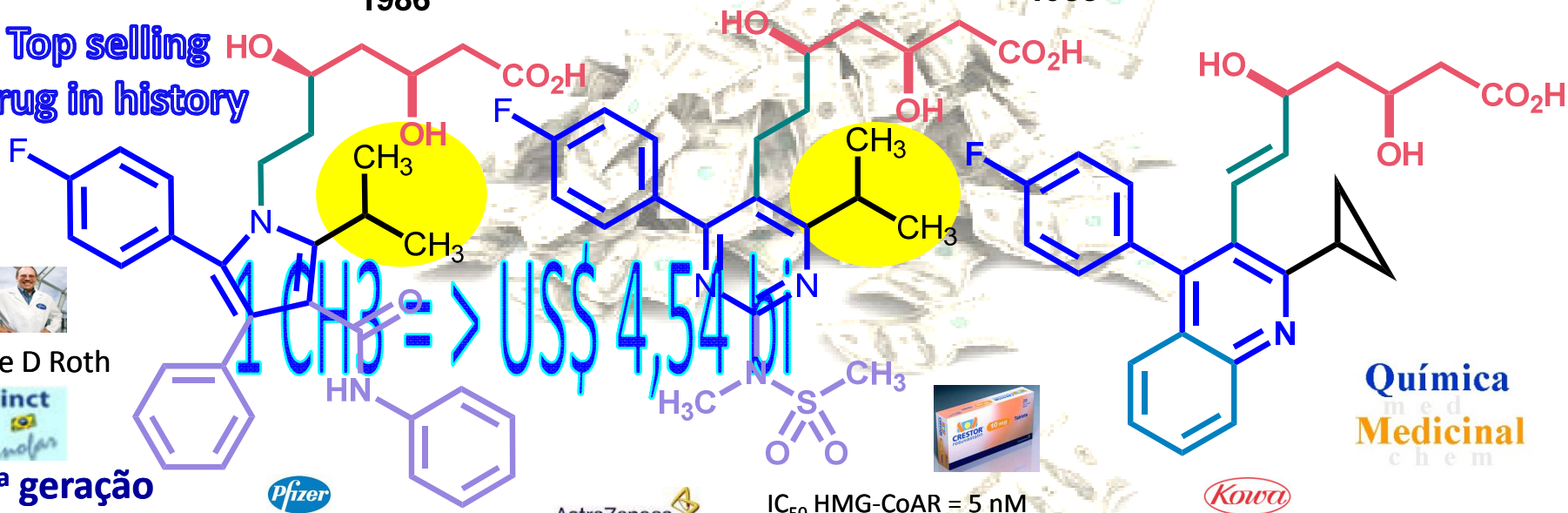
pravastatina
1988

Bristol-Myers Squibb
TEVA
(2006)


2ª geração

Universidade Federal do Rio de Janeiro

Top selling drug in history






Bruce D Roth

inct

3ª geração

Pfizer

atorvastatina
1991

"patent cliff"

AstraZeneca




IC$_{50}$ HMG-CoAR = 5 nM

rosuvastatina
2004
US$ 8,1 bi (2012)

Kowa

pitavastatina
2009

Química Medicinal

O mercado mundial de estatinas é estimado em US$ 23 bilhões (2013)

Universidade Federal do Rio de Janeiro

# De fármacos e suas descobertas

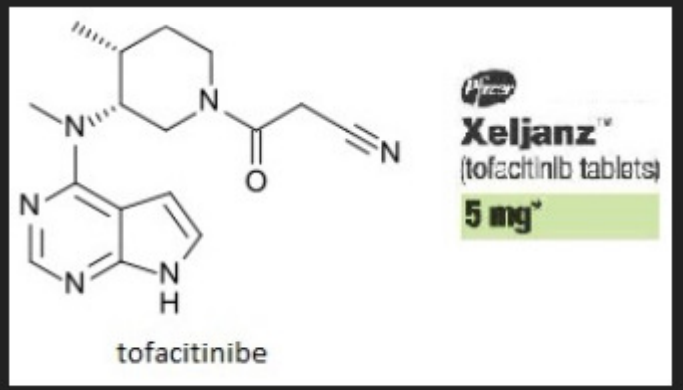
Pretende-se tratar de temas, opiniões, comentários sobre a Ciência dos Fármacos, seu uso seguro e benefícios. História da descoberta/invenção de fármacos e aspectos da formação qualificada de universitários e pós-graduandos nas Ciências dos Fármacos também são de interesse.

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

# Visite

sábado, 16 de fevereiro de 2013

## A história de uma inovação terapêutica recente: a descoberta do tofacitinibe



tofacitinibe

http://ejb-eliezer.blogspot.com


LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas
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Rio2016
http://ejb-eliezer.blogspot.com.br/
Obrigado
ejbarreiro@ccsdecania.ufrj.br
Praia do Boqueirão, Saquarema, RJ