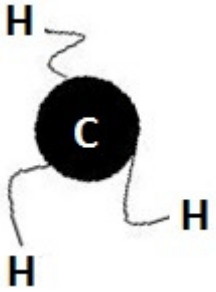
As peripécias da metila na Química Medicinal



Universidade Federal do Rio de Janeiro

Farmácia

XII Encontro Nacional de Professores de Química Farmacêutica
"A Química Farmacêutica Medicinal no Brasil: Novas Perspectivas no Ensino e Pesquisa"
27 de fevereiro a 01 de março de 2013

Química Medicinal

A Química Farmacêutica Medicinal no Brasil: Novas Perspectivas no Ensino e Pesquisa

Eliezer J. Barreiro

Professor Titular

Universidade Federal do Rio de Janeiro

Laboratório de Avaliação e Síntese de Substâncias Bioativas

www.farmacia.ufrj.br/lassbio

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Minha homenagem aos Professores de Química Farmacêutica Medicinal

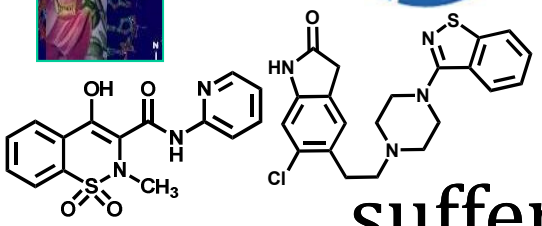
THE ROLE OF THE MEDICINAL CHEMIST IN DRUG DISCOVERY — THEN AND NOW

Joseph G. Lombardino and John A. Lowe III‡*

Química Medicinal

2011- ACS Award in Industrial Chemistry (ziprasidone)

Pfizer



" ...medicinal chemists today live in exciting times... their work can have a beneficial effect on millions of suffering patients – surely an important motivating factor for any scientist..."

The Role of the Medicinal Chemist in Drug Discovery – Then and Now, *Nature Rev. Drug Disc.* **2004**, *3*, 853.

Inovações Terapêuticas

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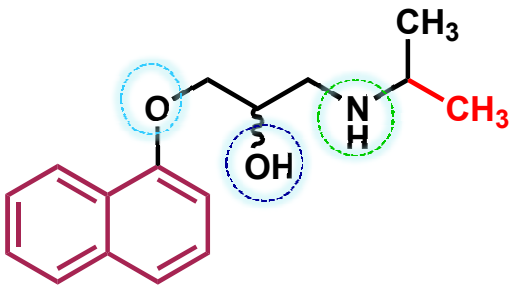
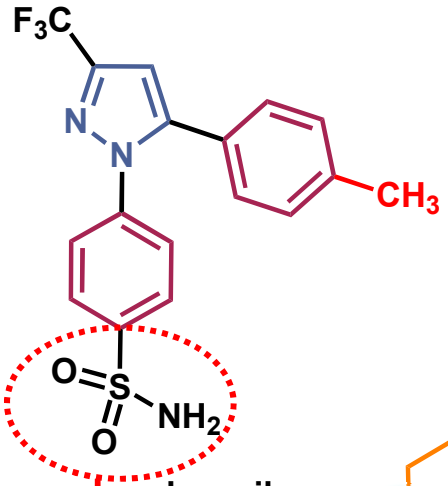
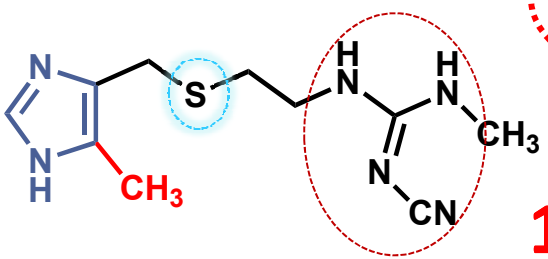
Química Medicinal



propranolol
1964

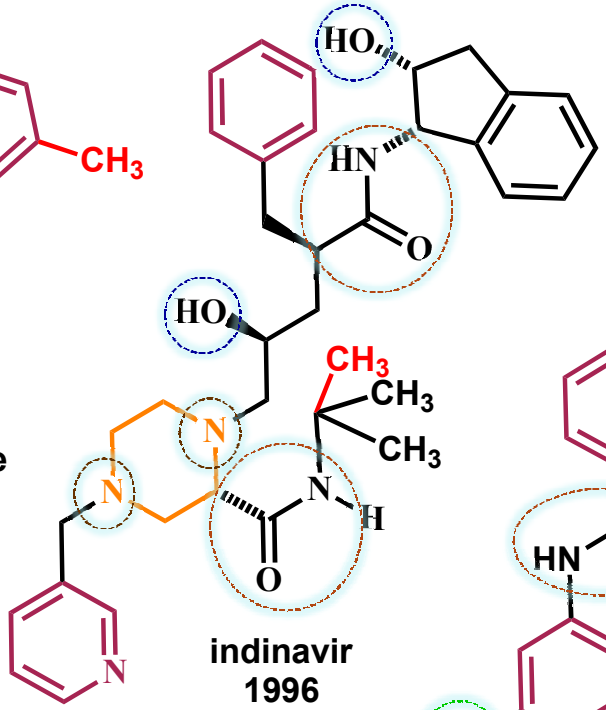


celecoxibe
1999

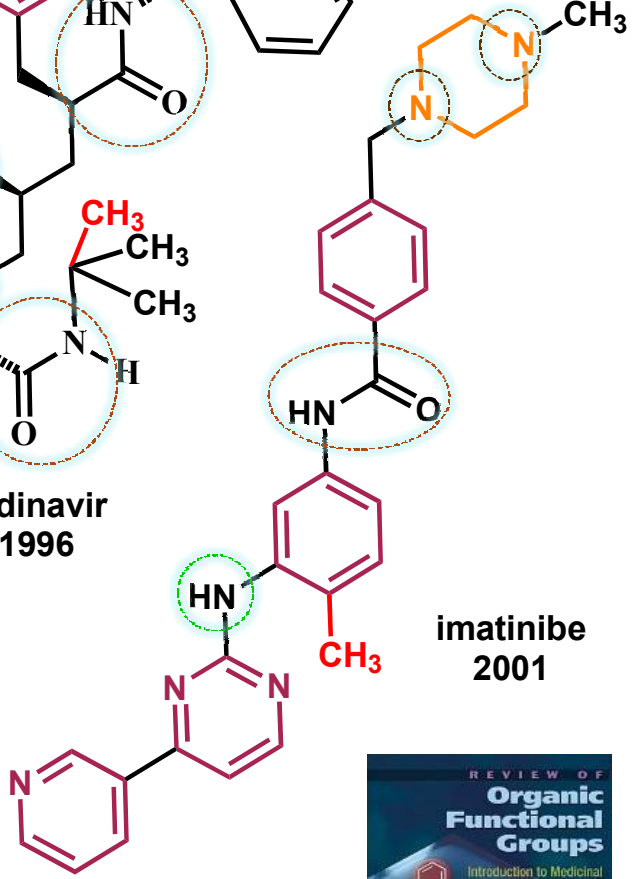


cimetidina
1975

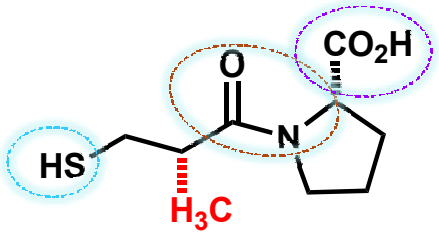
12 GF's



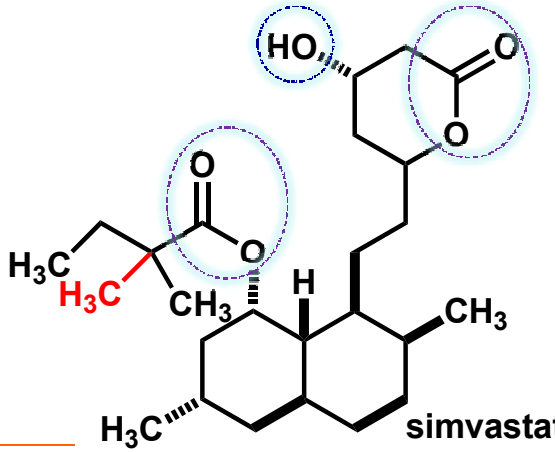
indinavir
1996



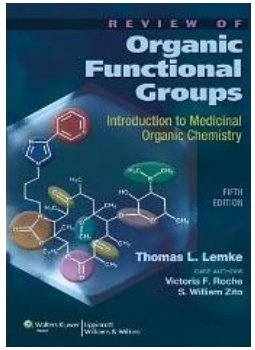
imatinibe
2001



captopril
1987



simvastatina
1986

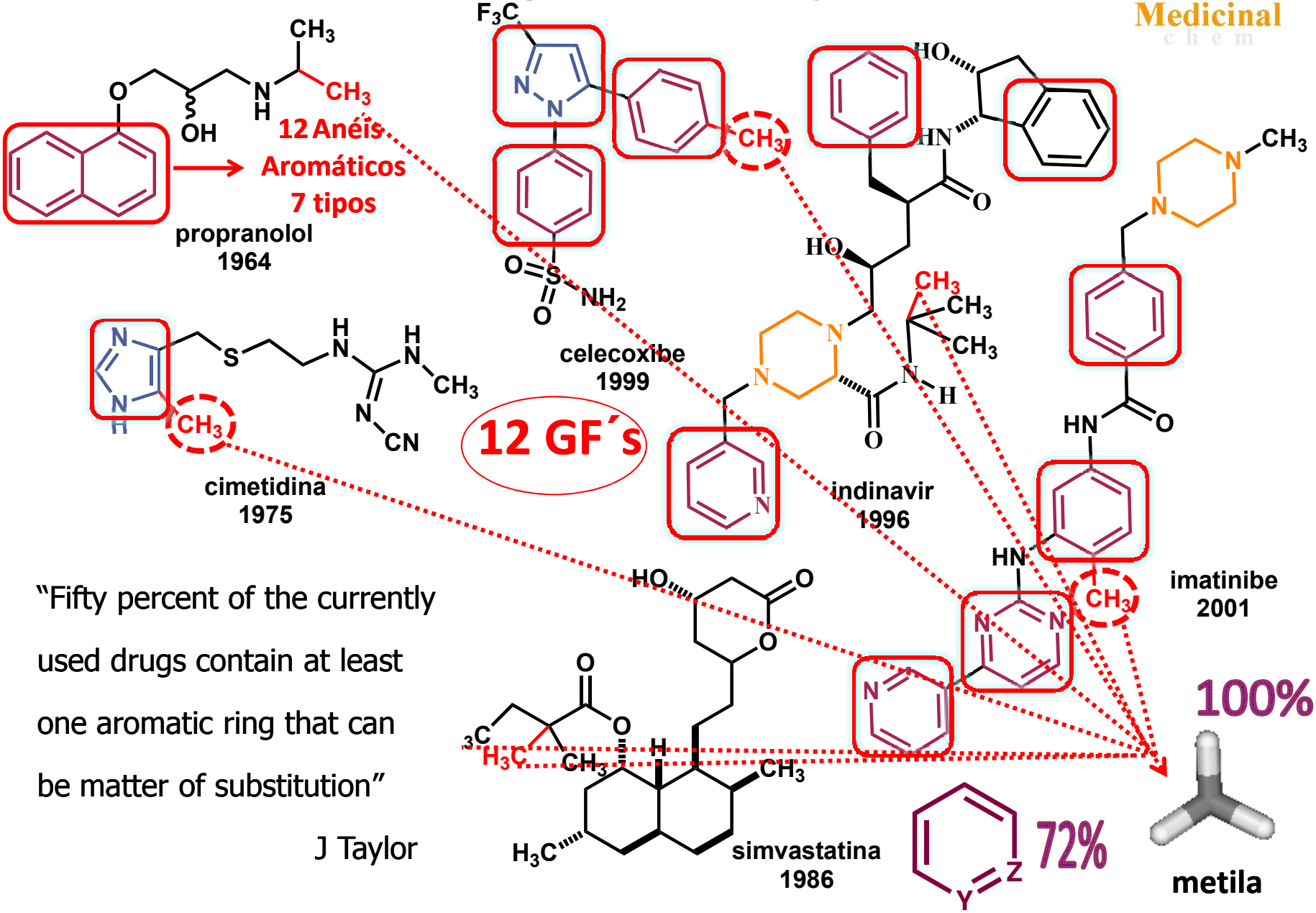


L Schaeffer, *The role of functional groups in D-R interactions*, em The Practice of Medicinal Chemistry, CG Wermuth Ed., Academic Press, 3rd Ed., Ch 21, p. 464

Inovações Terapêuticas

Universidade Federal do Rio de Janeiro

Química Medicinal



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

J Taylor

As séries homólogas

Universidade Federal do Rio de Janeiro

Alquila: metila, etila, propila, *inutila*

Química Medicinal

miscível em água

Lipofilicidade

n-butanol
solubilidade em água 8,2g/100g

*iso*butanol
solubilidade em água 12,5g/100g

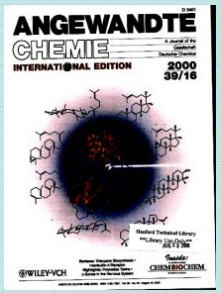
tert-butanol
miscível em água

n-pentanol
solubilidade em água 2,4g/100g

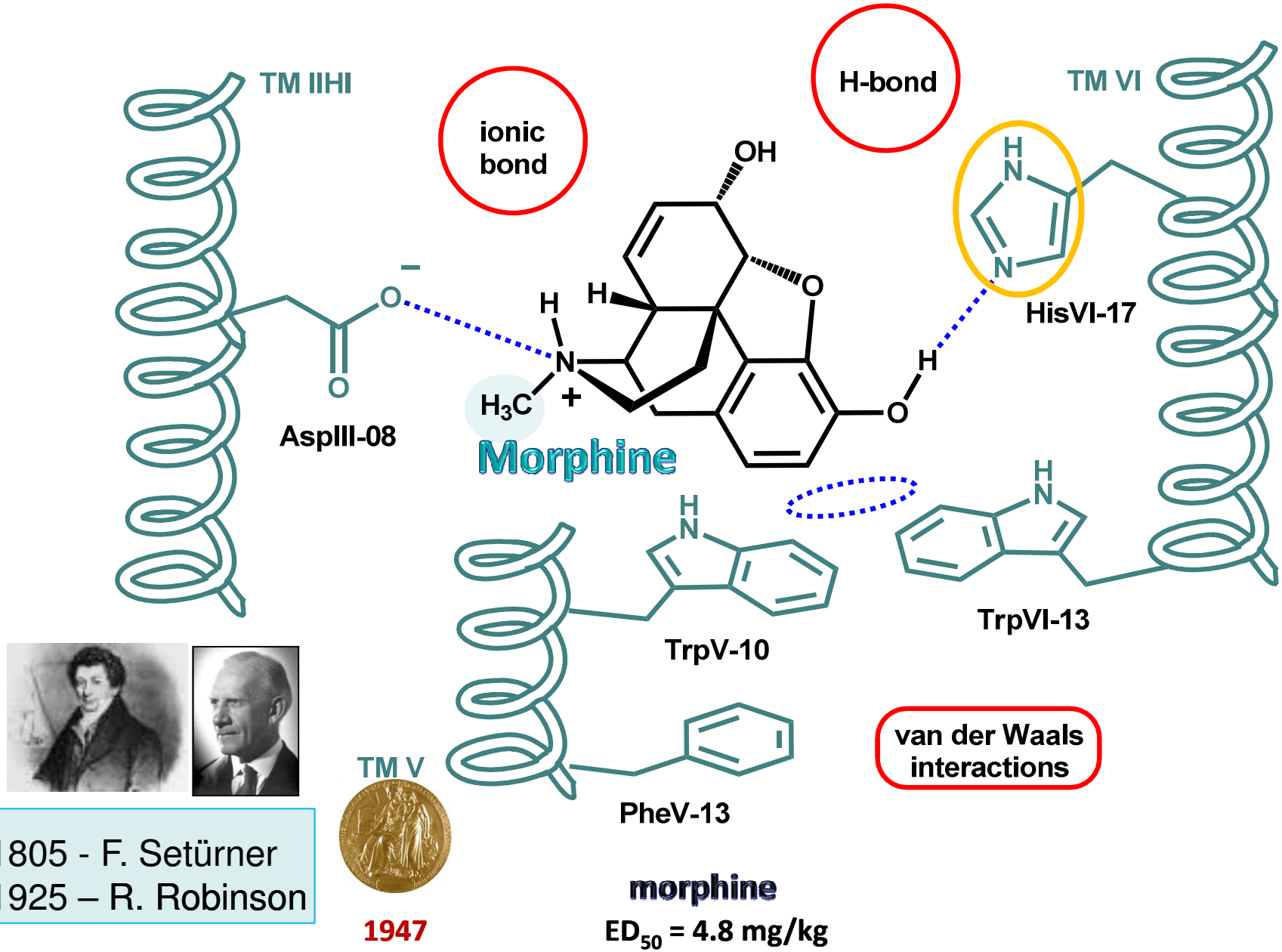
2-pentanol
solubilidade em água 4,9g/100g

*neo*pentanol
solubilidade em água 12,2g/100g

G Némethy, *Angew Chem Int Ed Engl* **1967**, *6*, 195
10.1002/anie.196701951



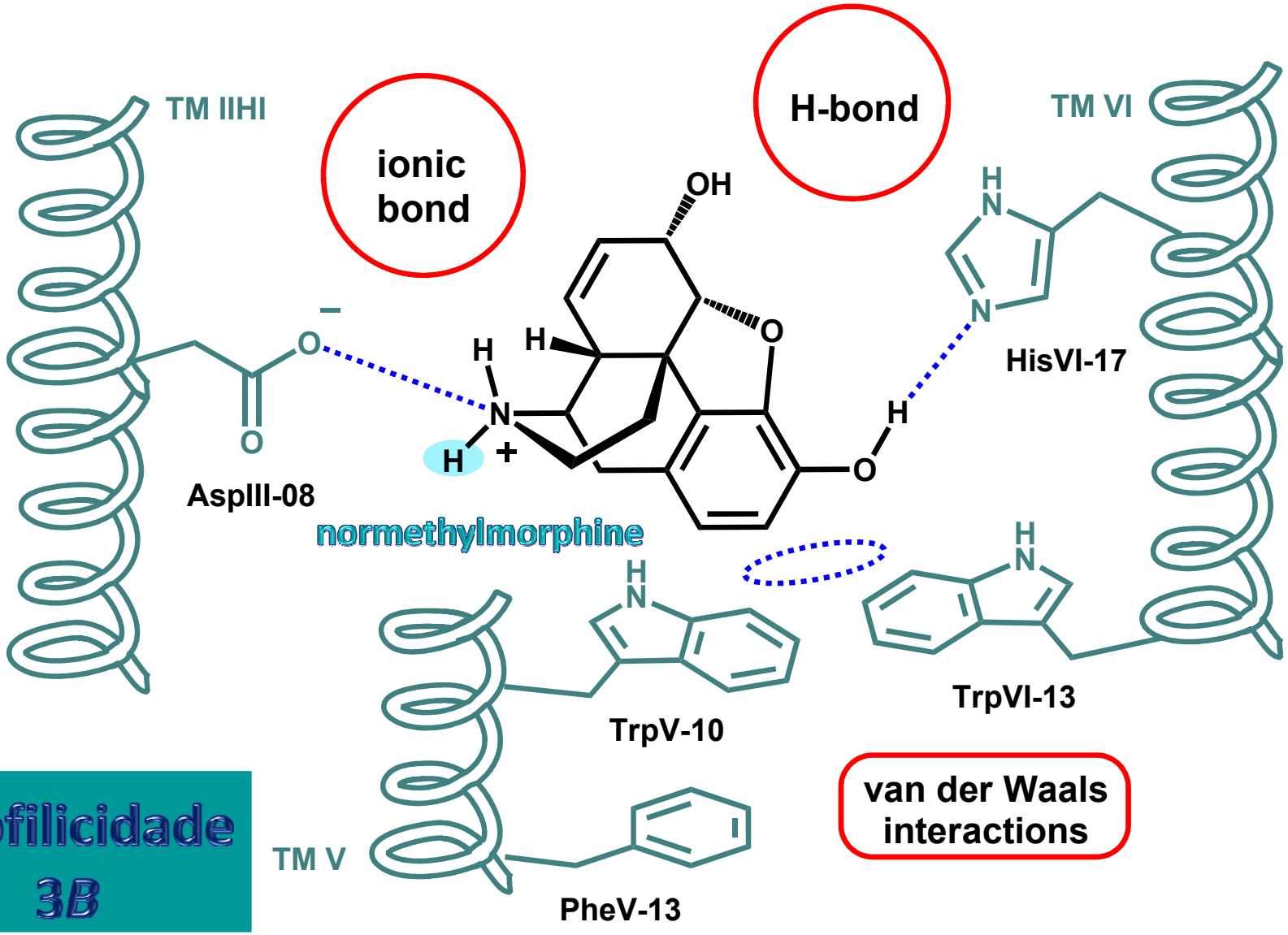
A metila *natureba*...



1805 - F. Setürner
1925 – R. Robinson

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

A ausência da metila...



Lipofilicidade 3B

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

As metilas *n*a morfina...

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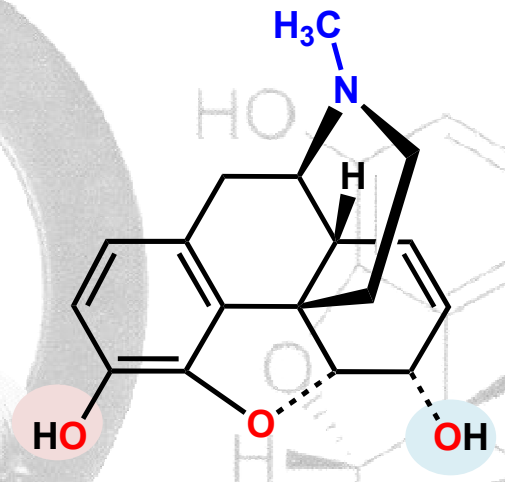
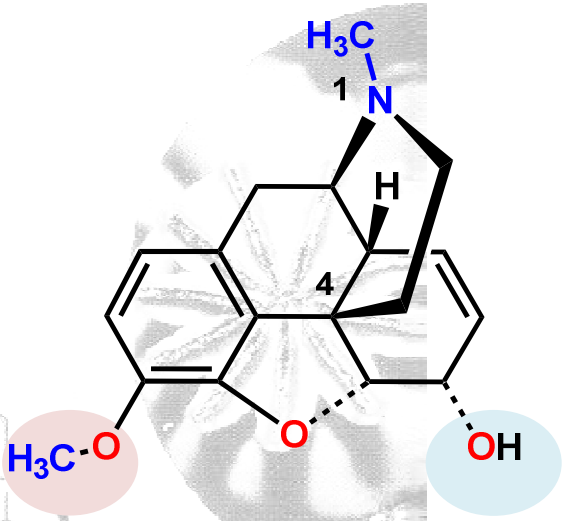
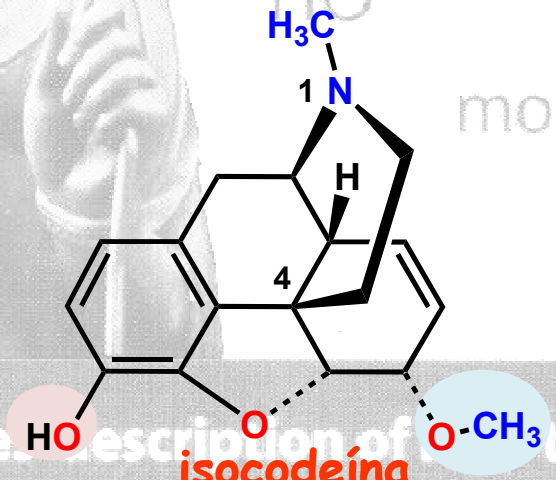
Índice de atividade analgésica



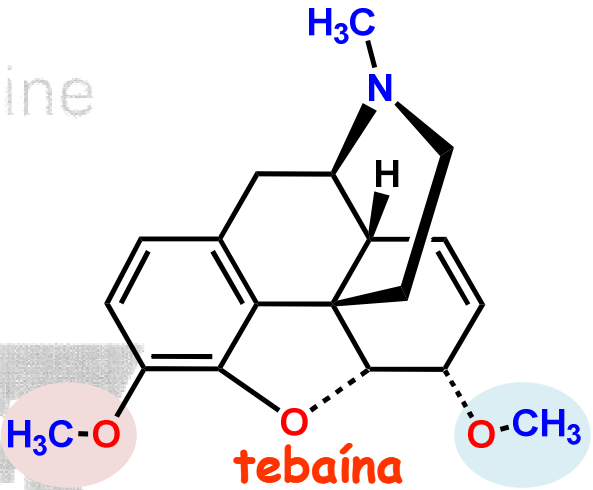
morfina
100



codeína
18



isocodeína
25



tebaína
0*

As admiráveis metilas da floresta...

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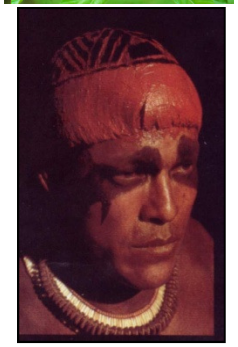
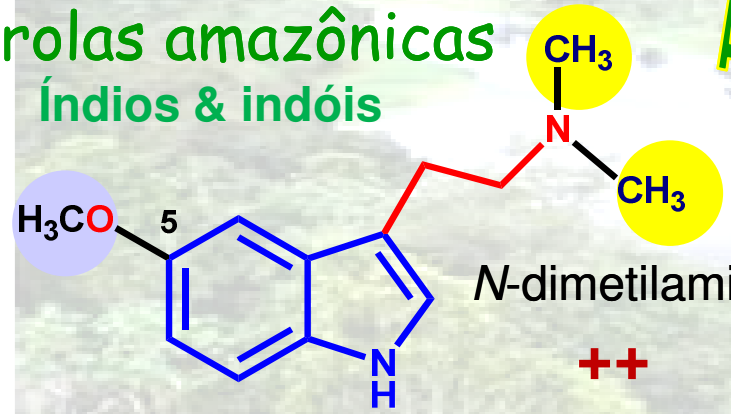


Virolas amazônicas

Índios & indóis

Alcalóides Indólicos

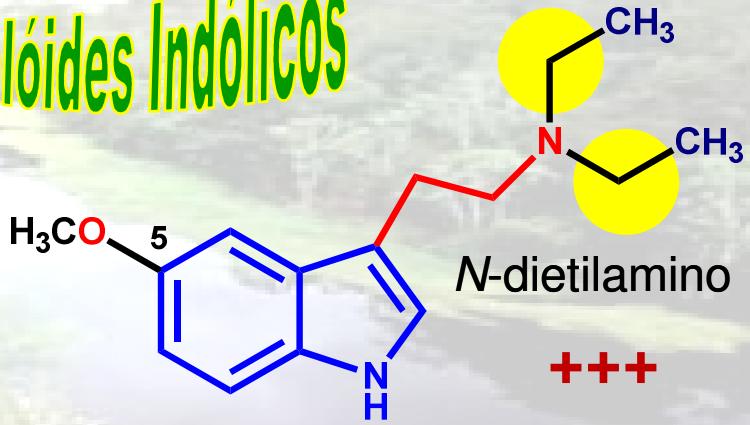


N-dimetilamino

++

3-indolil-etilaminas

efeitos alucinogênicos



N-dietilamino

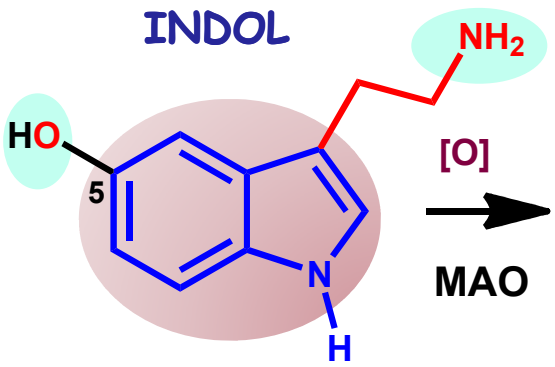
+++

N-dimetilomólogo

3 metilas

Similaridade molecular

INDOL

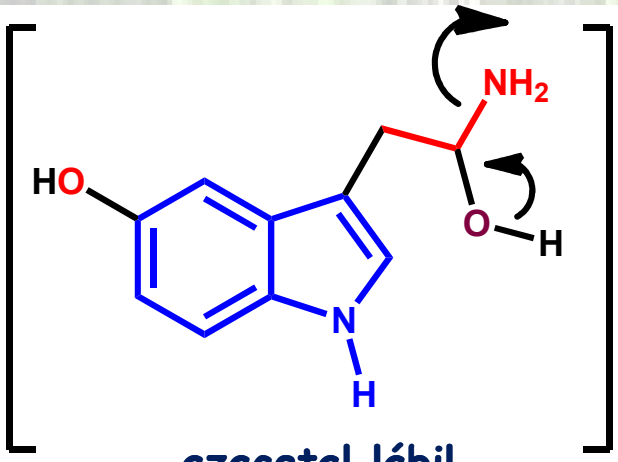


Serotonina

5-hidróxi triptamina

[O]

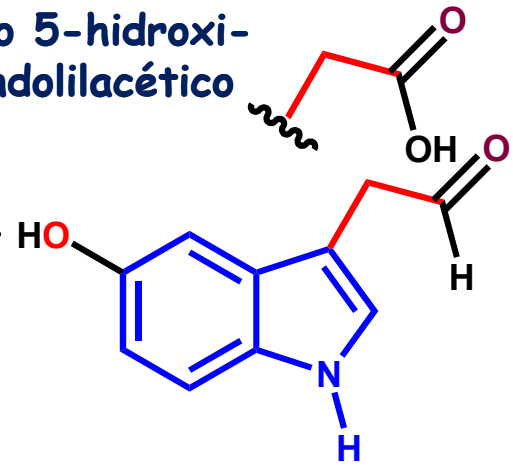
MAO



azacetal lábil

[O]

Ácido 5-hidroxi-3-indolilacético



5-hidróxi-3-indolil acetaldeído

A *extravagância da* metila...

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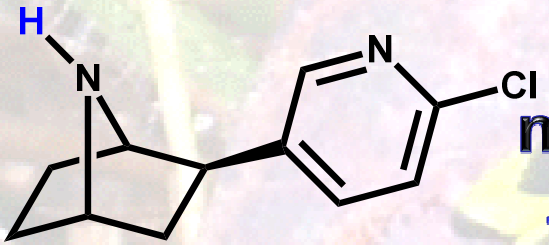
Epipedobates tricolor

John W. Daly
1933-2008
Un. Maryland, EUA

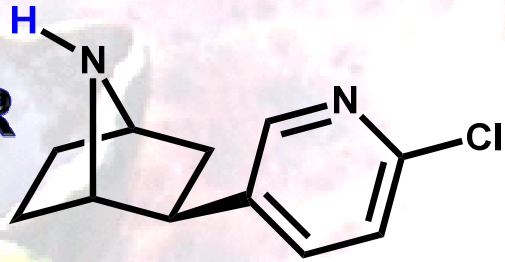


(-)-epibatidine (natural)

First natural chemotype: 7-azabicyclo[2.2.1]heptane

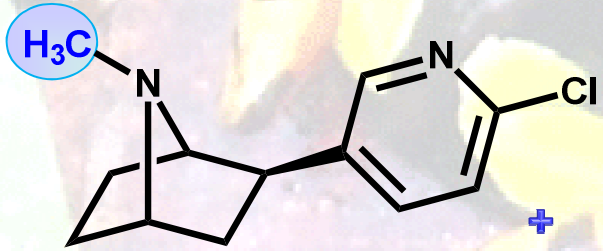
nAChR

organochloride alkaloid



(+)-epibatidine

Molecular similarity



(-)-*N*-methylepibatidine (natural)

(+)-*N*-methylepibatidine

J W Daly, " Ernest Guenther Award in Chemistry of Natural Products. Amphibian Skin: A Remarkable Source of Biologically Active Arthropod Alkaloids", *J. Med. Chem.* **2003,** *46,* 445-452

J W Daly, "Thirty Years of Discovering Arthropod Alkaloids in Amphibian Skin", *J. Nat. Prod.* **1998**, *61*, 162-172

Editorial, *J Nat Prod* **2010**, *73*, 300

A *incrível leveza* da metila...

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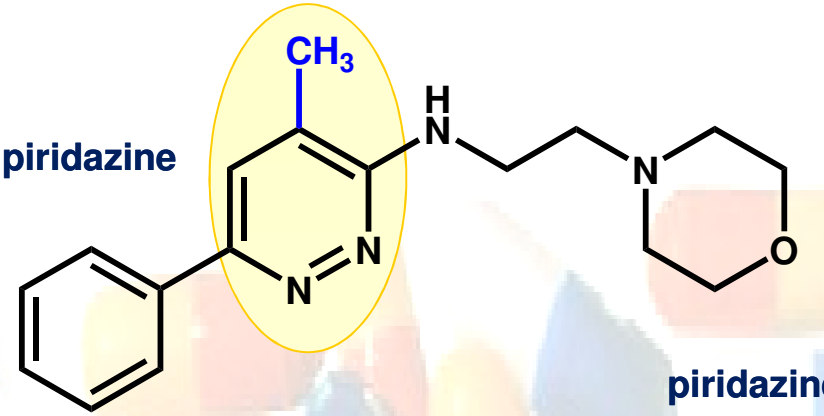
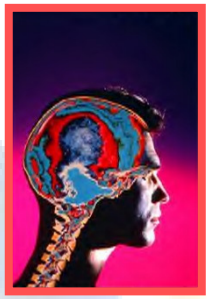
Química Medicinal

Lead Optimization

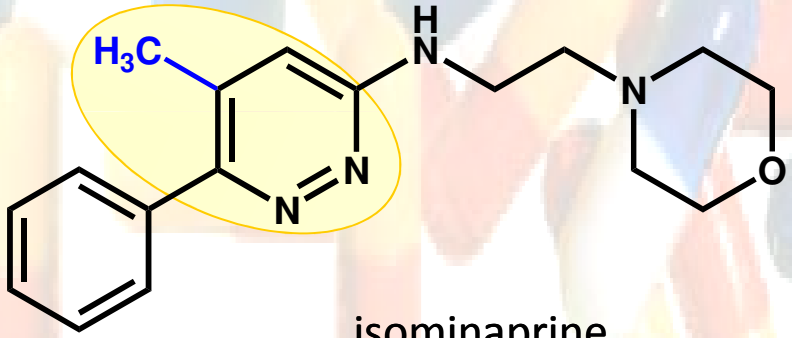


minaprine

serotonin type 2
& dopamine (D1, D2)
receptors



piridazine



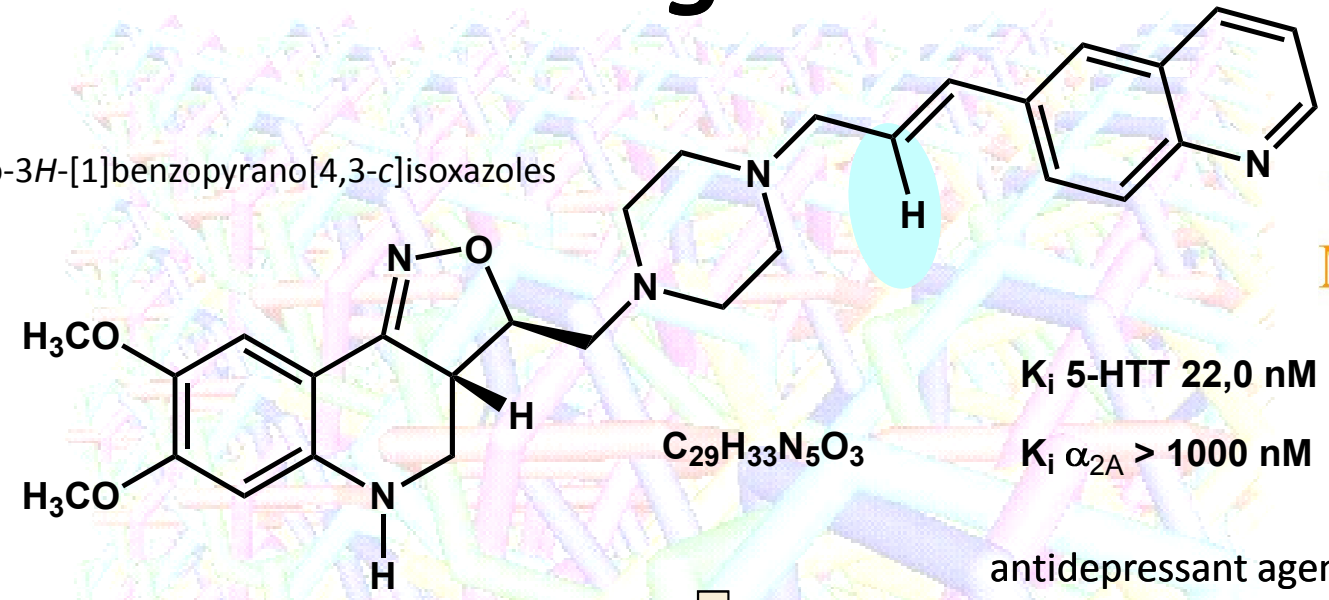
isominaprine

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 metila *enigmática*...

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



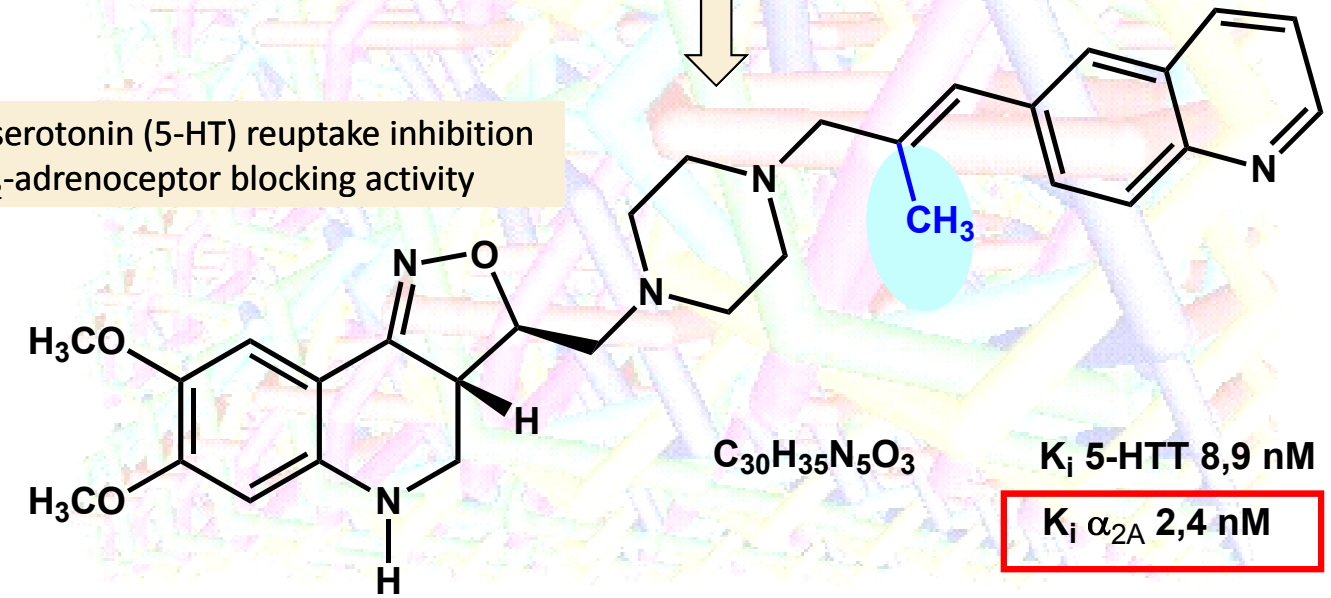
$C_{29}H_{33}N_5O_3$

K_i 5-HTT 22,0 nM

K_i α_{2A} > 1000 nM

antidepressant agent

central serotonin (5-HT) reuptake inhibition
& α_2-adrenoceptor blocking activity



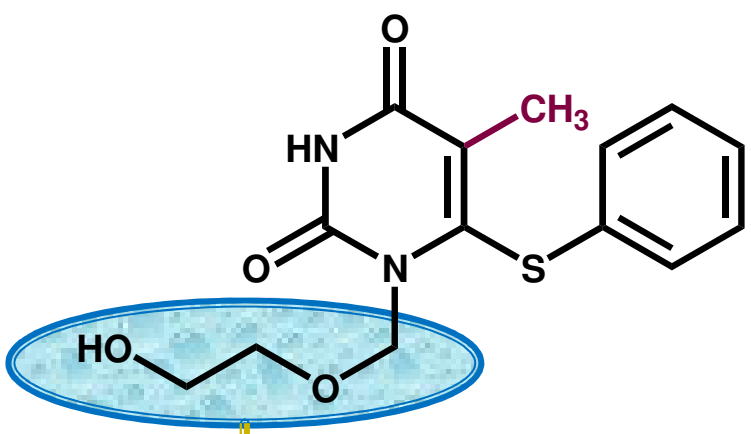
$C_{30}H_{35}N_5O_3$

K_i 5-HTT 8,9 nM

K_i α_{2A} 2,4 nM

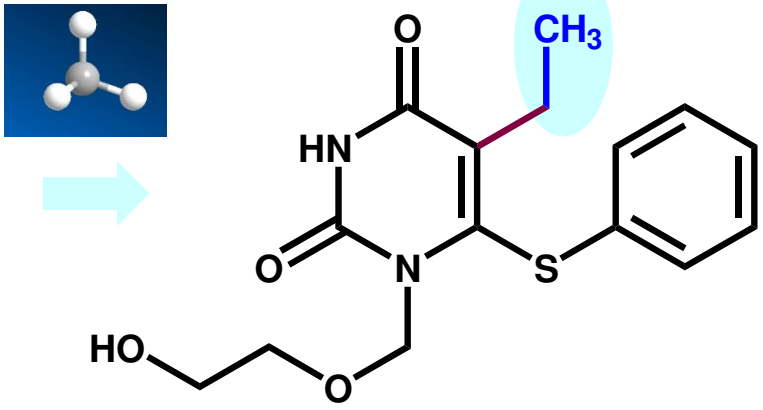
J I Andrés *et al.*, Discovery of a New Series of Centrally Active Tricyclic Isoxazoles Combining Serotonin (5-HT) Reuptake Inhibition with α2-Adrenoceptor Blocking Activity, *J Med Chem* **2005**, *48*, 2054.

Mais um capricho da metila ...

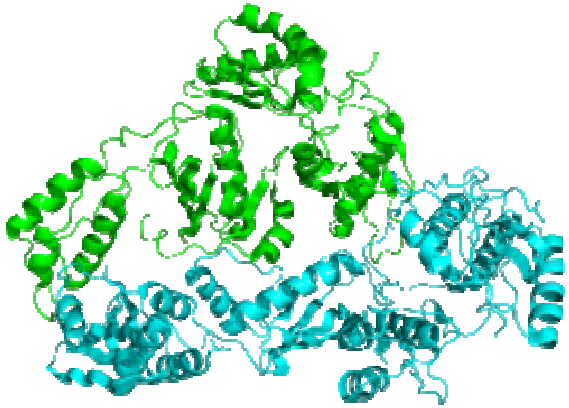


EC_{50} (TR) = 6,5 µM

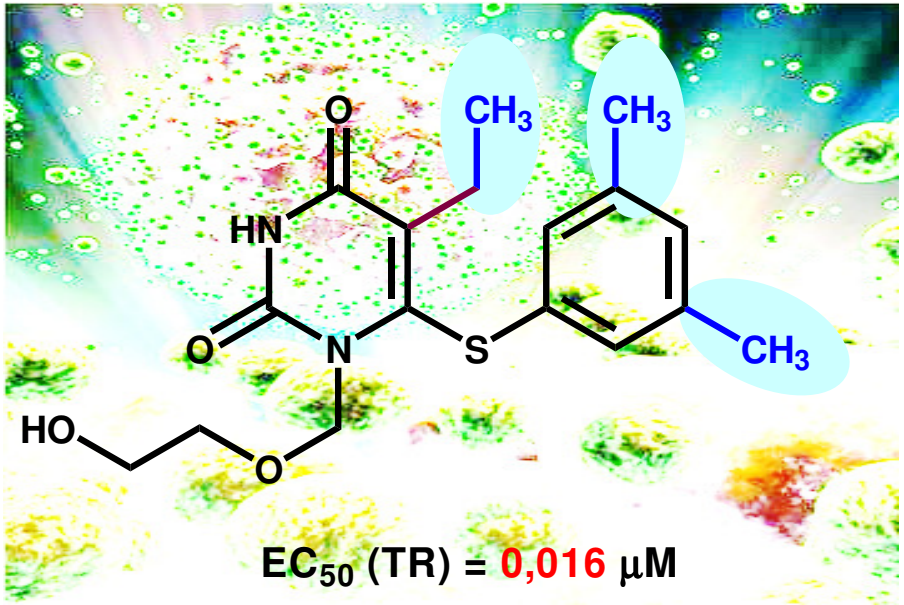
Cadeia do aciclovir



EC_{50} (TR) = 0,12 µM



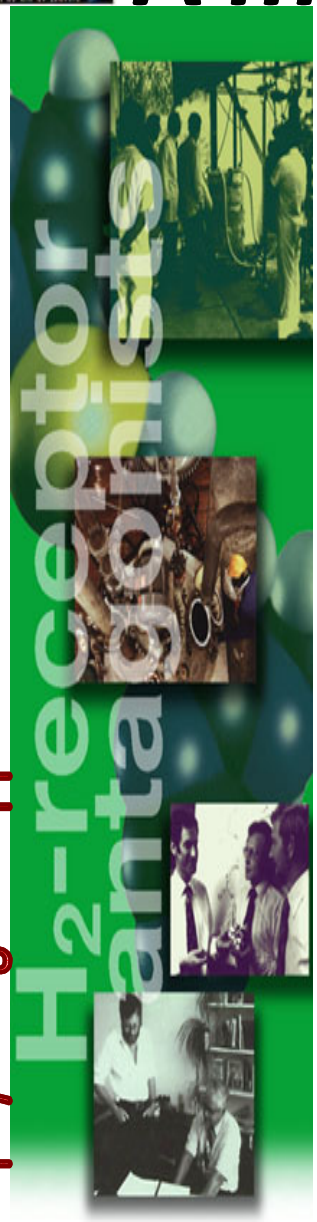
TR



EC_{50} (TR) = 0,016 µM

A *metila* que não podia faltar...

Universidade Federal do Rio de Janeiro



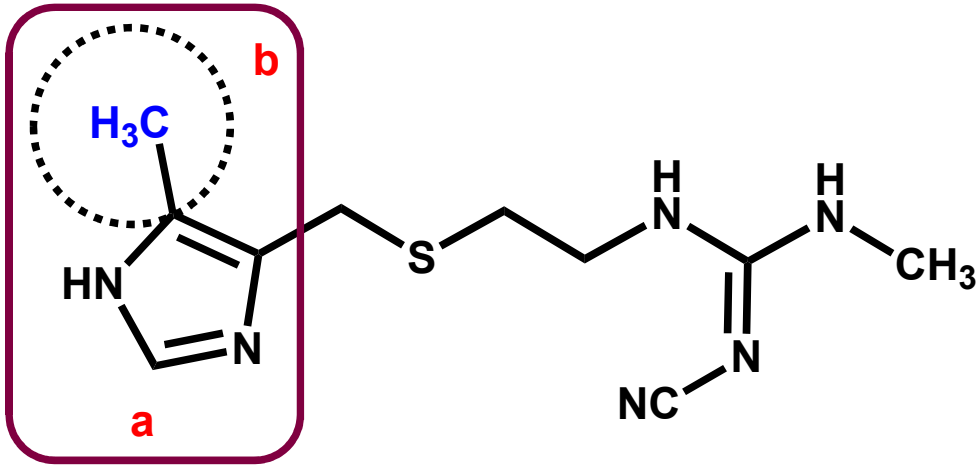
National Historic Chemical Landmarks

AMERICAN CHEMICAL SOCIETY

A new era of logical drug design

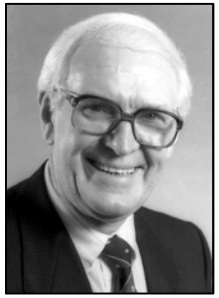
The research program leading to cimetidine also represented a revolution in the way pharmaceuticals are developed. Traditionally, the development of a new drug would often depend on the fortuitous discovery of a plant or microbial extract that showed some of the required biological activity. Using that 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.

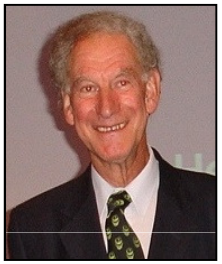


cimetidine

1988



James W. Black



C Robin Ganellin

John C Emmett

Graham J Durant

A metila muito *inteligente*...

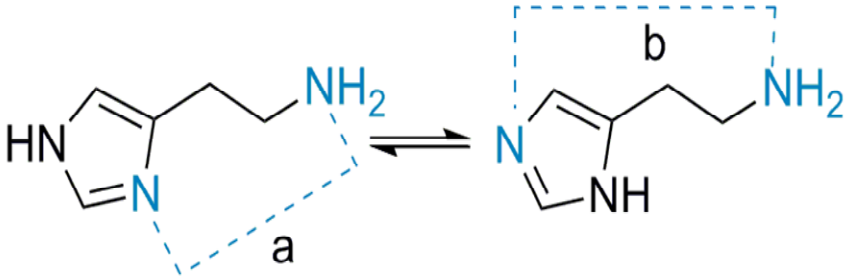
Universidade Federal do Rio de Janeiro

Química Medicinal

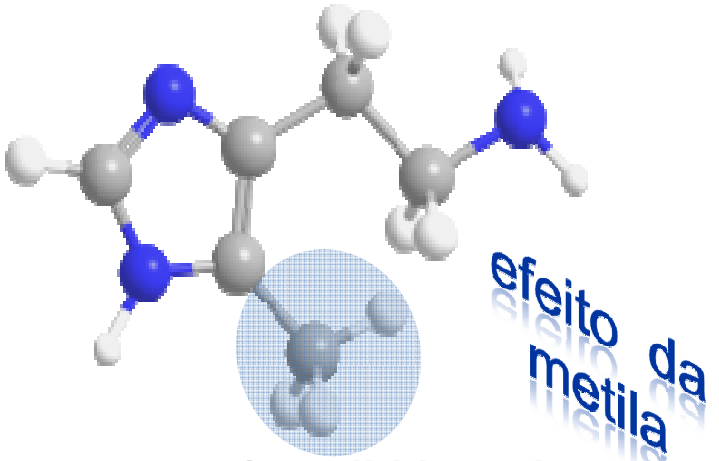
Dois sub-tipos de H_R

C Robin Ganellin, 1973

Interações fracas

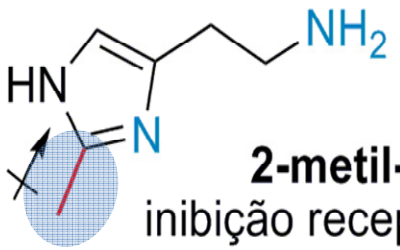


Forma A a = 4,83 Å b = 5,52 Å **Forma B**

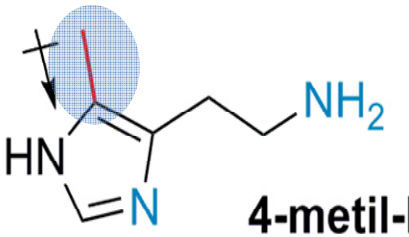


4-metil-histamina

Equilíbrio tautomérico



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



Análogo ativo

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 *sagacidade* da suave metila...

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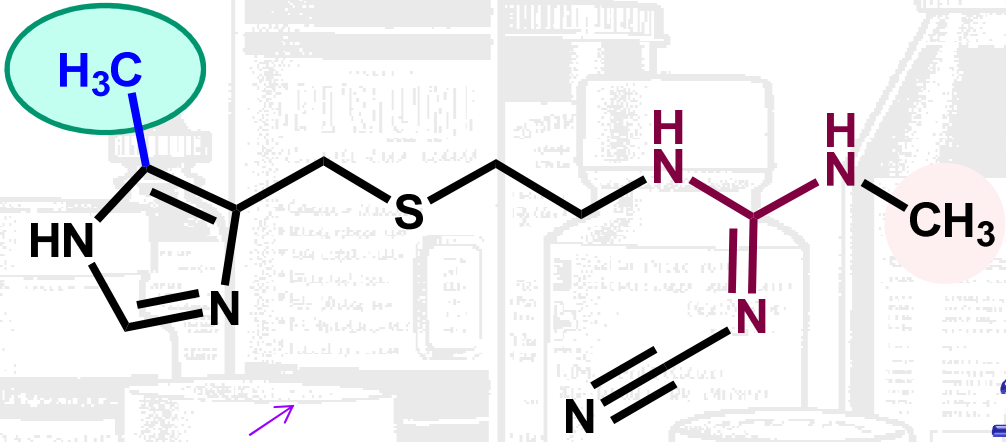
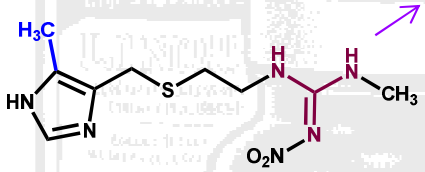
Primeiro antagonista seletivo do receptor histaminérgico H_2



Inovação terapêutica



cimetidina

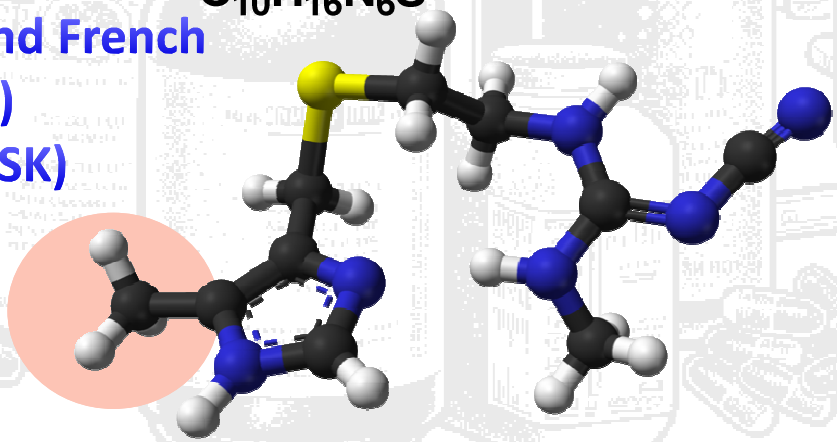
$C_{10}H_{16}N_6S$

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 (*bis*)metila *astuta*...

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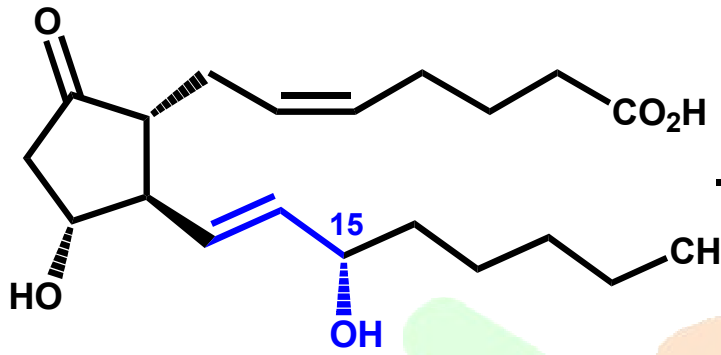
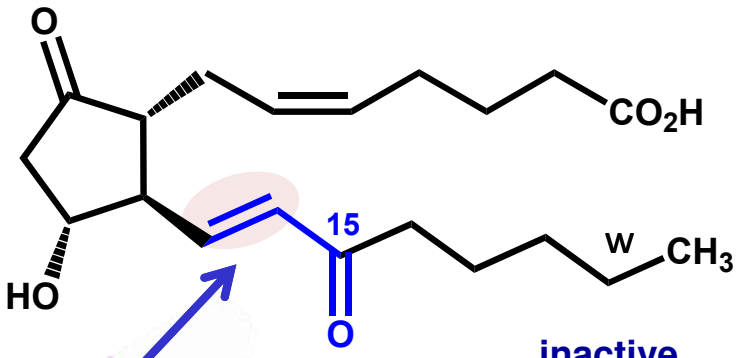


PGE$_2$

PGDH

plasma



inactive

15-ceto PGE$_2$

PG-redutase (PGR)

enhancing metabolic stability

John R. Vane

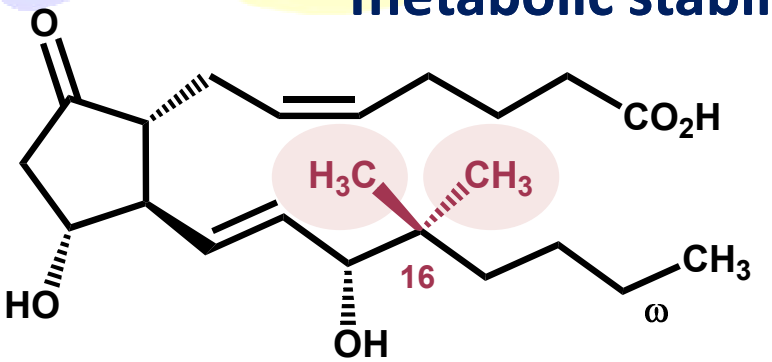
(1927-2004)

K. Sune Bergström

(1916-2004)

molecular modification

Química Medicinal



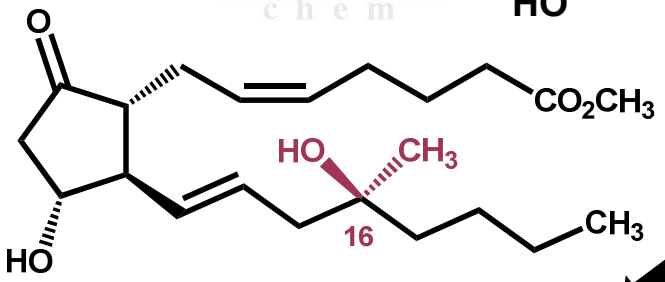
16,16-dimethyl PGE$_2$ *

EP$_2$ ag. ~ 1 nM

50 X PGE$_2$ (GI tract)

1982

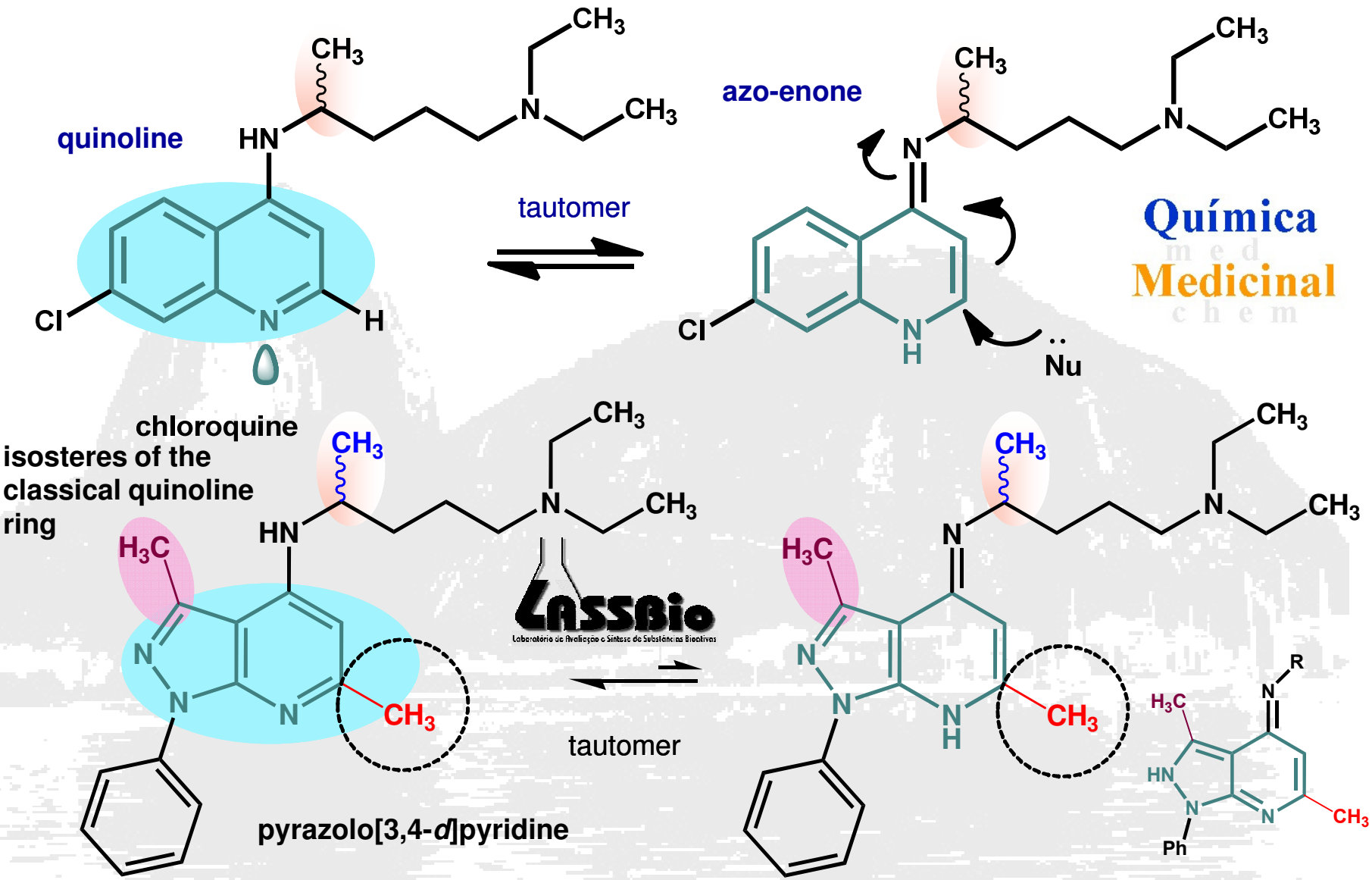
Bengt I. Samuelsson



Misoprostol

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

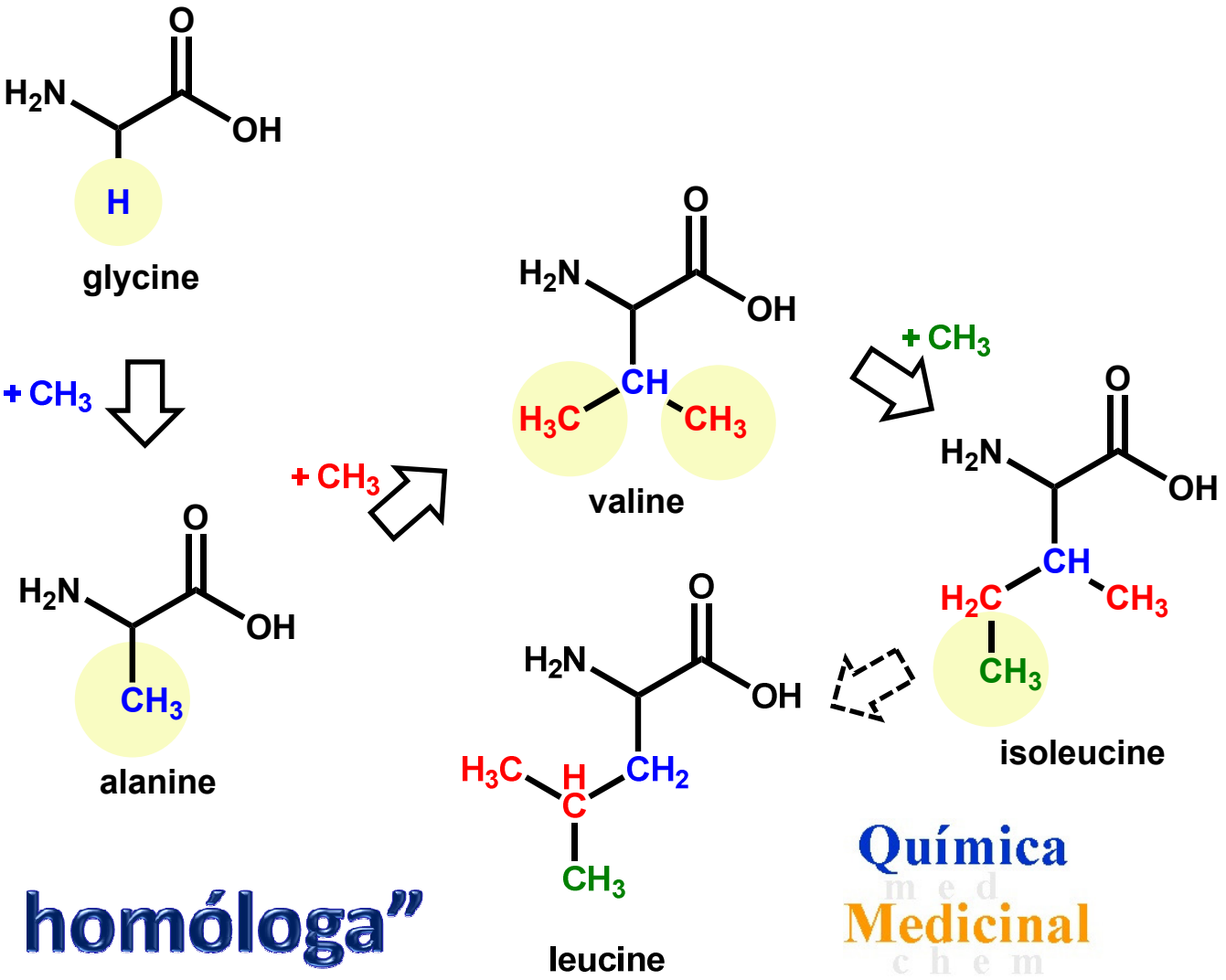
A metila *entrona*...



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

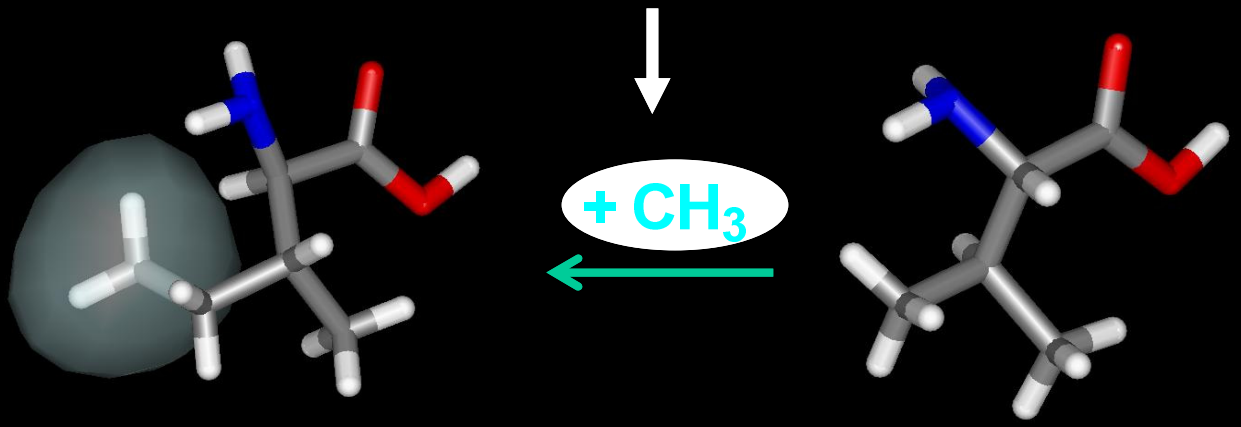
A homologia, a metila e os *nossos* aminoácidos



“ série homóloga”

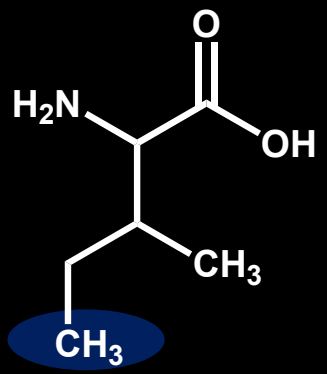
Química Medicinal

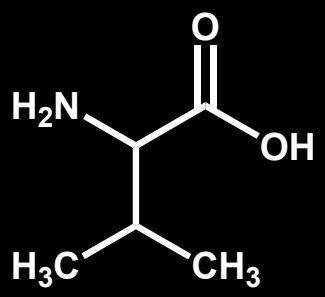
A homologia da valina



isoleucina

valina





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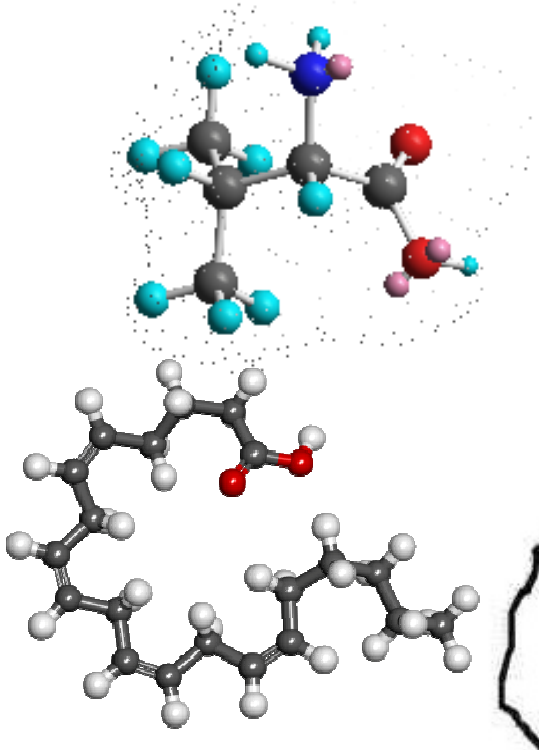
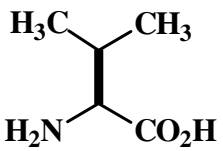
Os amino ácidos homólogos e a COX

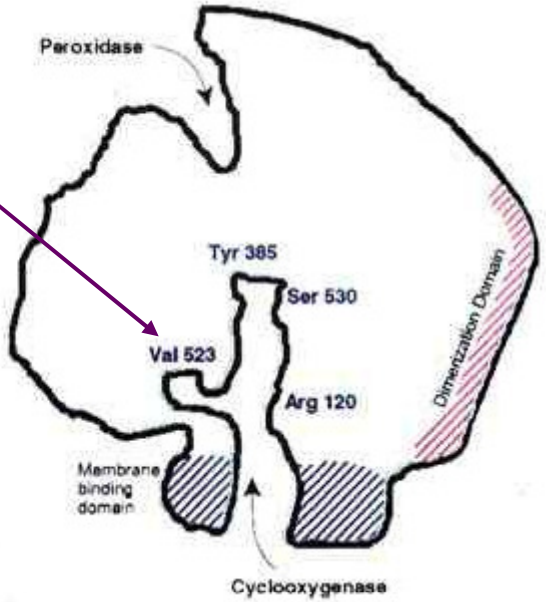


Ácido araquidônico
K_m = 5,6/5,4 μM

Sítio secundário

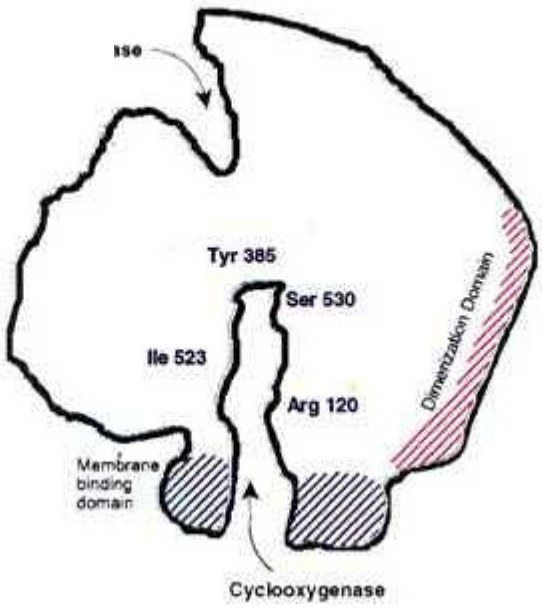


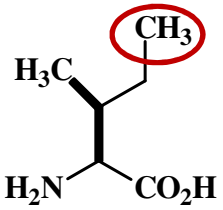
$C_5H_{11}NO_2$
Valina



COX-2

- Inflamação
- Câncer
- Endotélio vascular
- Rins
- Cérebro



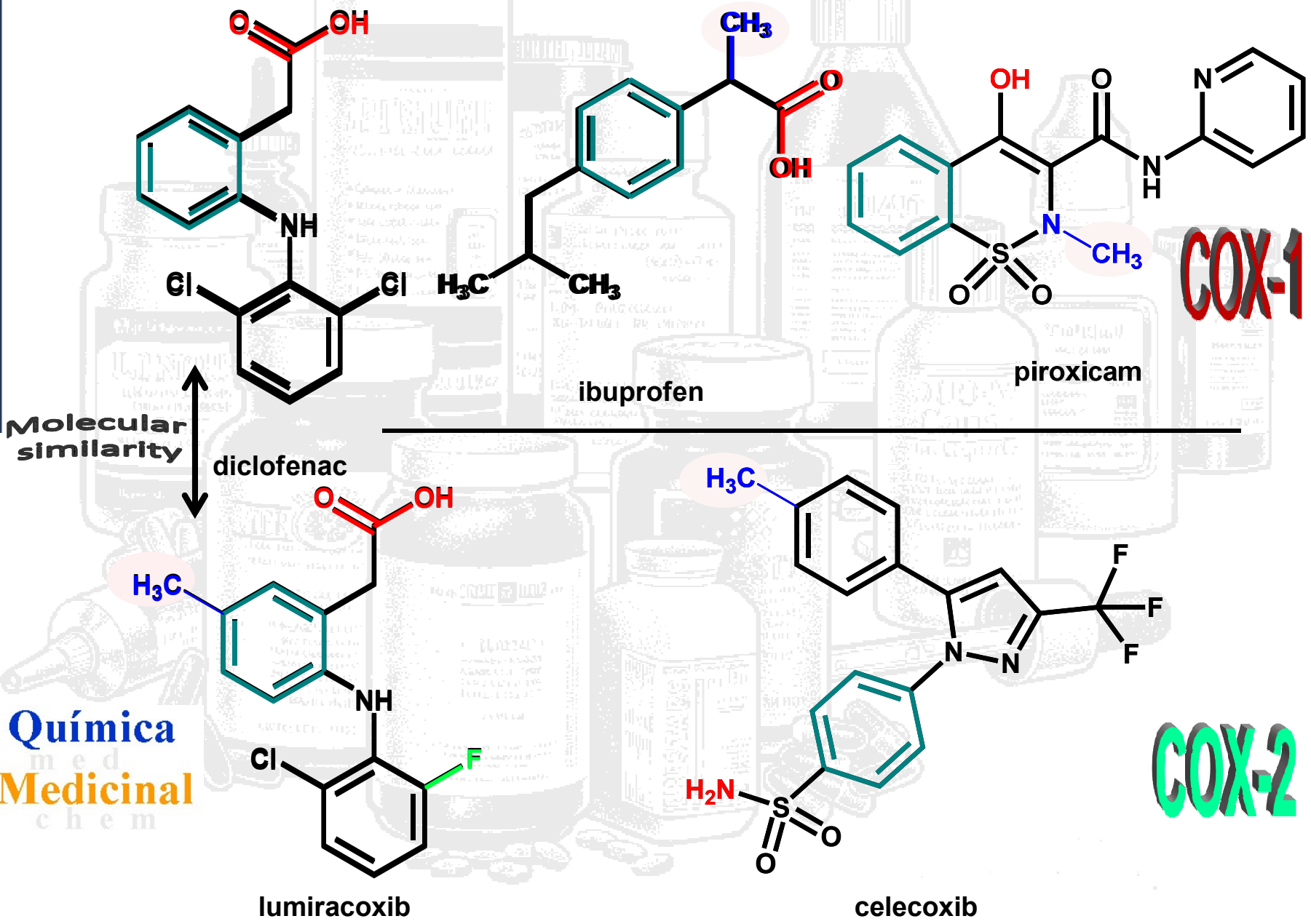


$C_6H_{13}NO_2$
Isoleucina

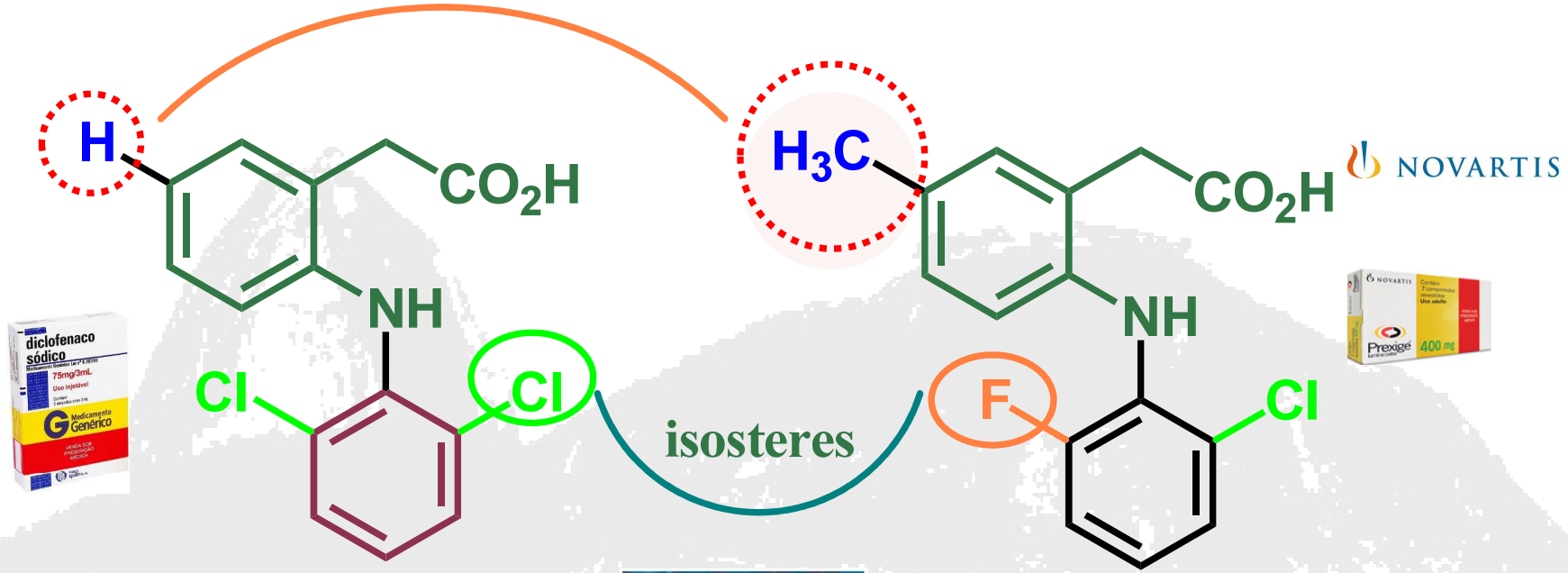
COX-1

- Estômago
- Plaquetas
- Rins

A metila *mágica*...(*the magic methyl*)



A *genialidade* da metila *mágica* ...



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

DICLOFENAC

COX-1

LUMIRACOXIB

COX-2

2003 (2008)

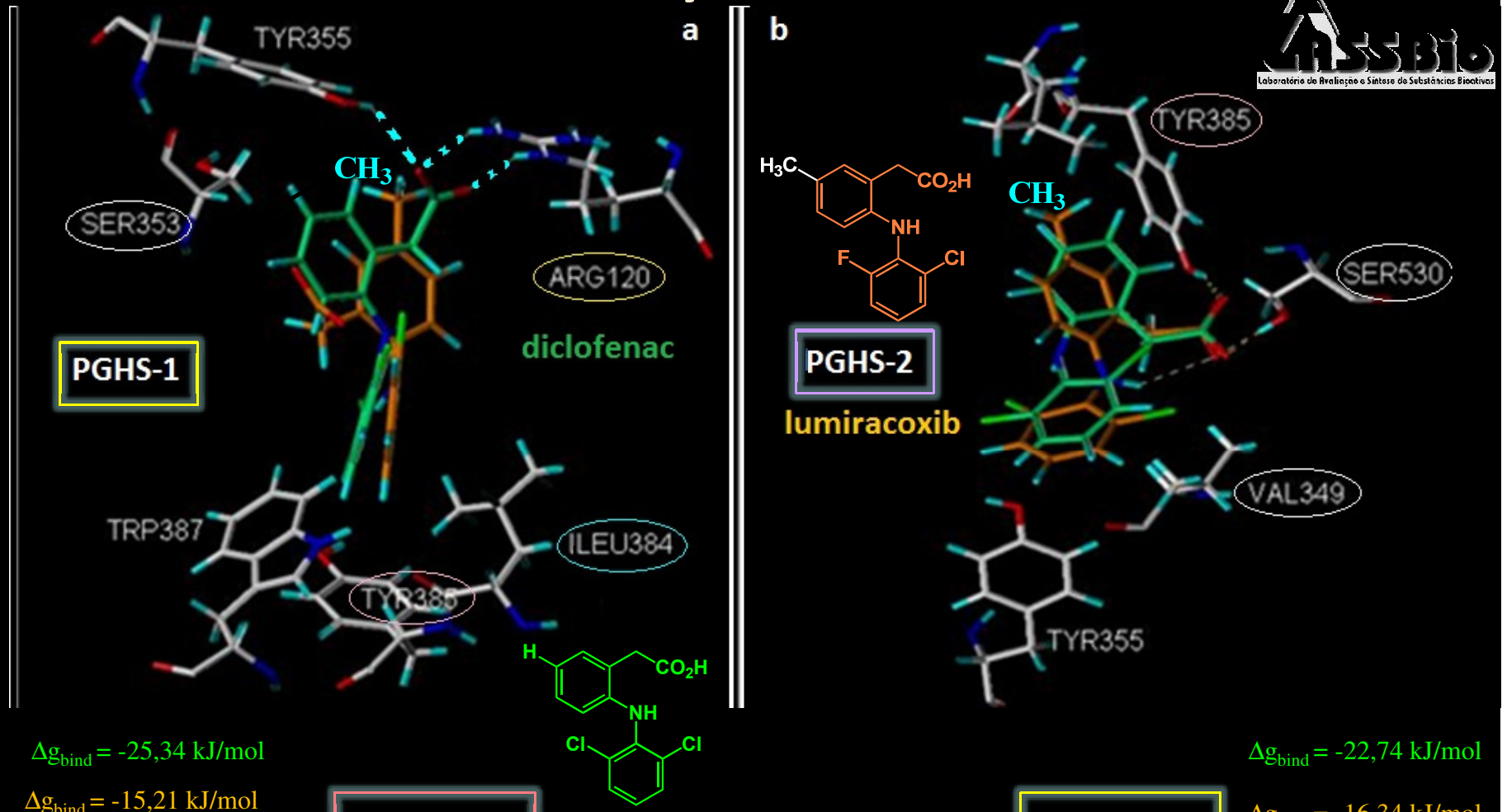
Ki (μM) PGHS-1 = 3.2
Ki (μM) PGHS-2 = 0.06

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



Δg_{bind} = -25,34 kJ/mol

Δg_{bind} = -15,21 kJ/mol

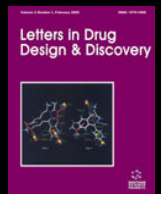
COX-1

Molecular Docking Studies

COX-2

Δg_{bind} = -22,74 kJ/mol

Δg_{bind} = -16,34 kJ/mol



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 discreto *charme* da metila...

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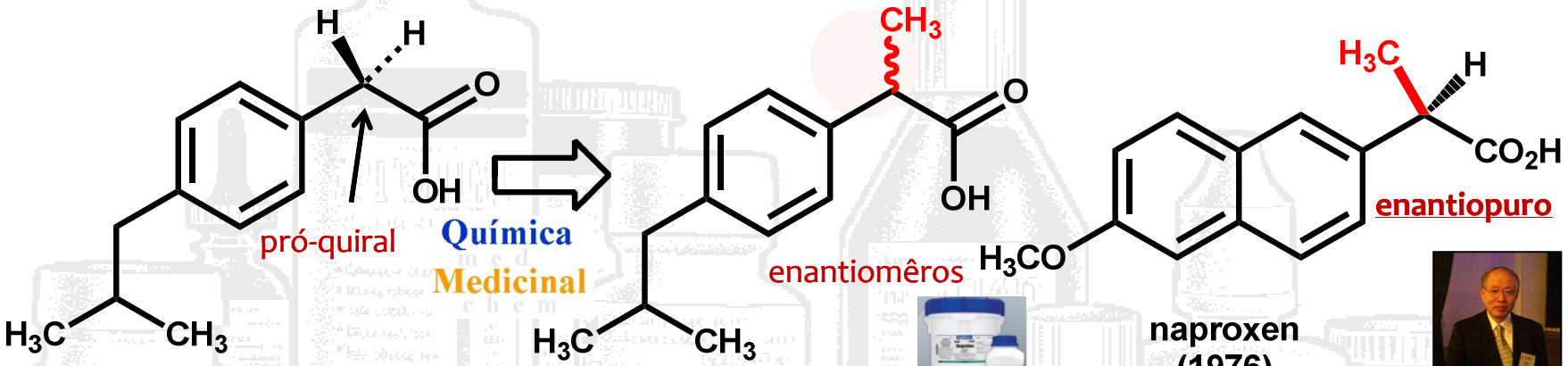


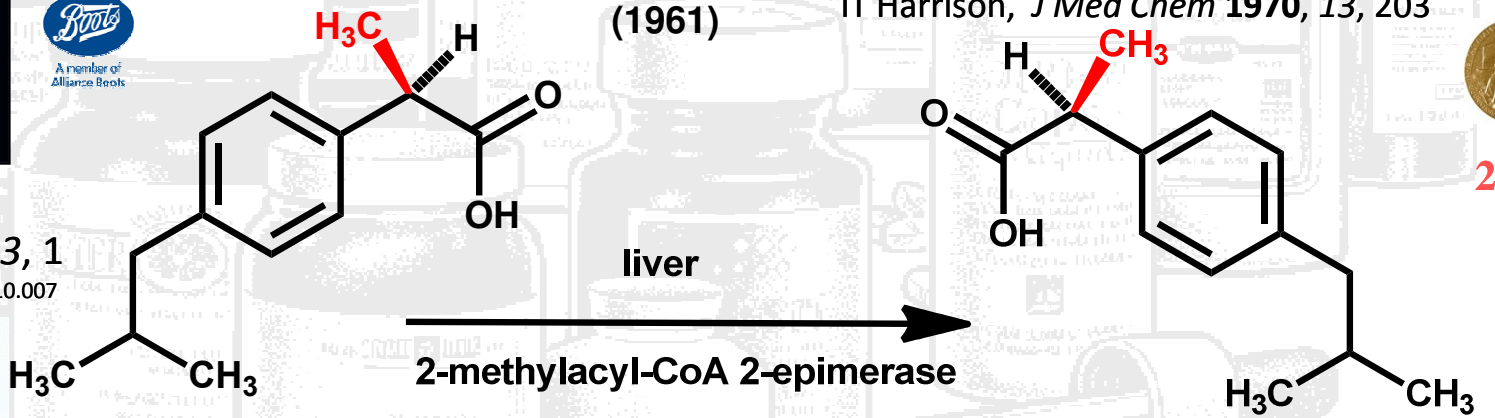
S S Adams*

TiPS **2012**, *33*, 1

10.1016/j.tips.2011.10.007

R Noyori

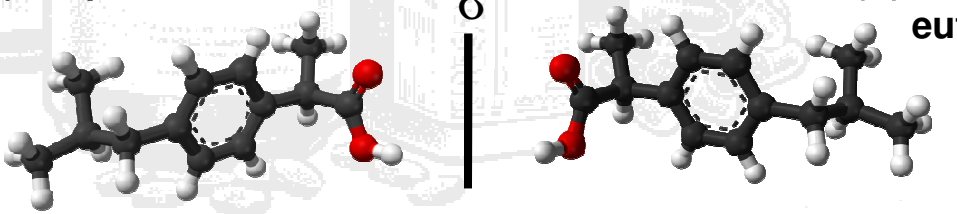
2001



(*R*)-ibuprofen

σ

(*S*)-ibuprofen
eutômero



*S S Adams, The propionic acids: A personal perspective", *Journal of Clinical Pharmacology* **1992**, *32*, 317–323.

& V L E Lima, Os fármacos e a quiralidade: uma breve abordagem, *Quim Nova* **1997**, *20*, 657-663.

O doce *fascínio* da metila...

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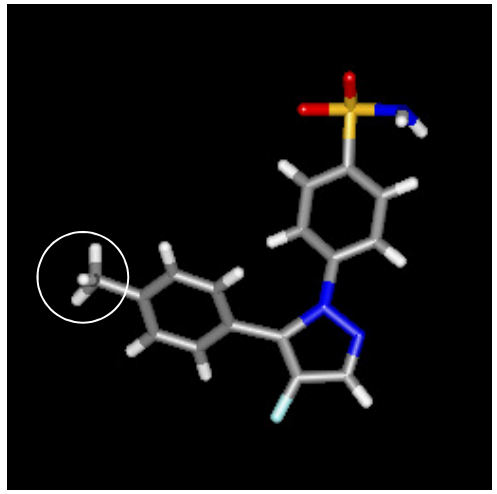
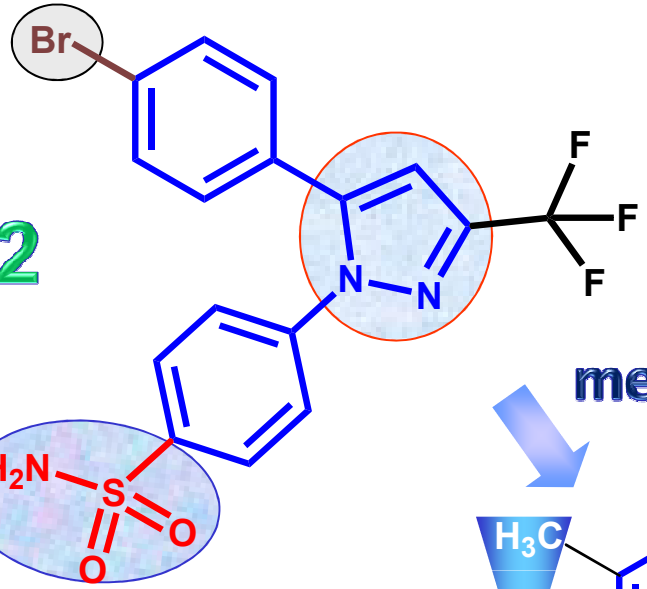
Química Medicinal

PGHS-2



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



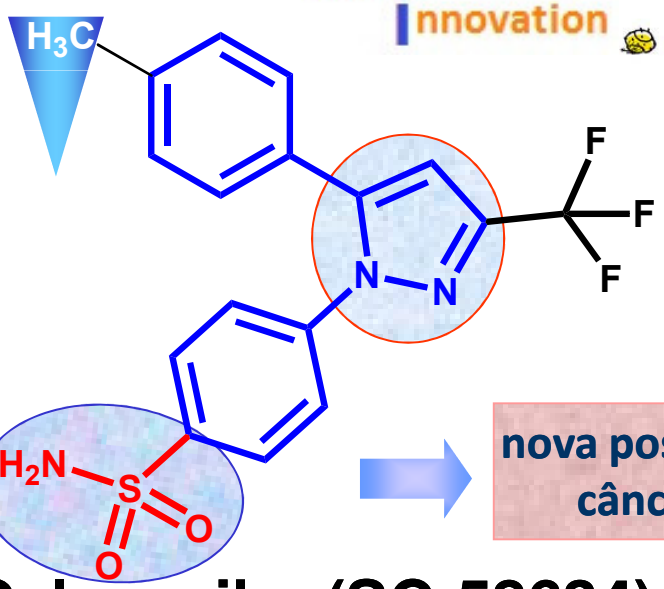
COX-2 seletivo
Searle

Vida-média = 12 dias !
(ADME)

Pfizer

metabolismo

therapeutic innovation



nova possível indicação:
câncer colo retal

Celecoxibe (SC-58634)

1999 [1998 - Dr Mario G Cardozo (na USP)]

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

A *sofisticação* da metila...

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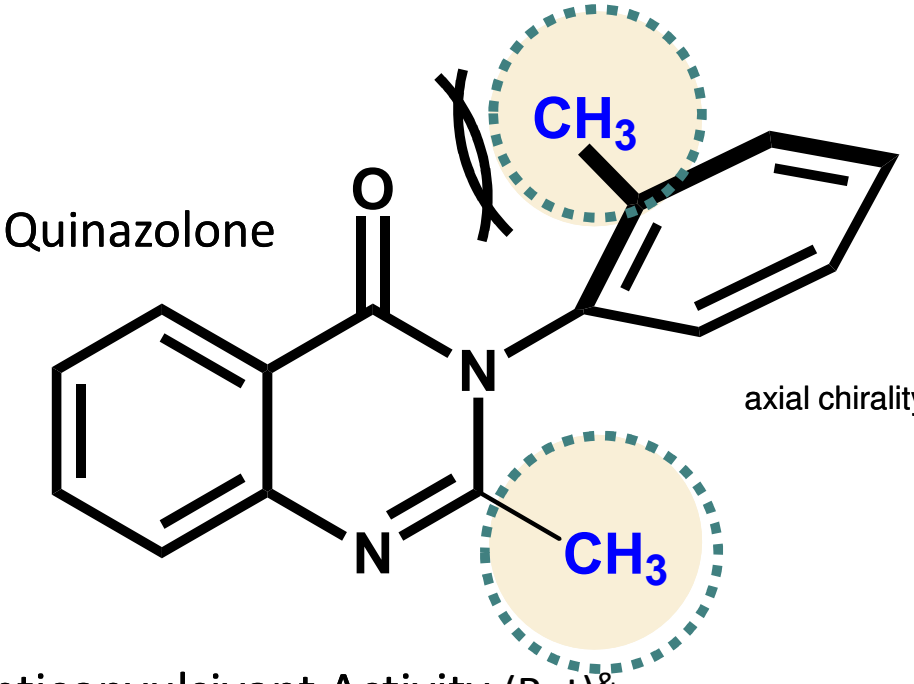


Indian researchers in the 1951

Química Medicinal

methaqualone

Mandrax^{R}

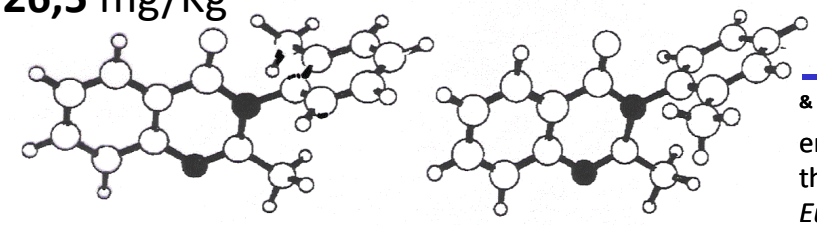
US Patent 3135659 - Hydroxy and Alkoxy Aryl Quinazolones

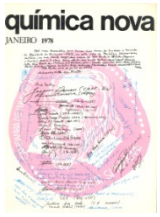
Anticonvulsivant Activity (Rat)[&]

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

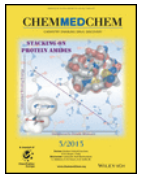
(S)-(-)-methaqualone **ED_{50}= 26,5** mg/Kg

Atropoisomerismo





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

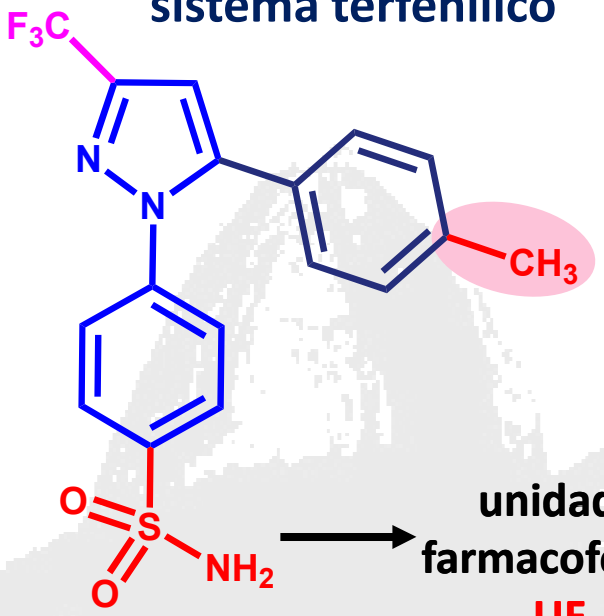


AR Santos *et al*., Atropoisomerismo: o efeito da quiralidade axial em substâncias bioativas, *Quim Nova* **2007**, *30*, 125; SR LaPlante, PJ Edwards, LD Fader, A Jakalian, O Hucke, Revealing Atropisomer Axial Chirality in Drug Discovery, *ChemMedChem* **2011**, *6*, 505

Universidade Federal do Rio de Janeiro

Novos inibidores da COX-2 bispirazólicos[a)]

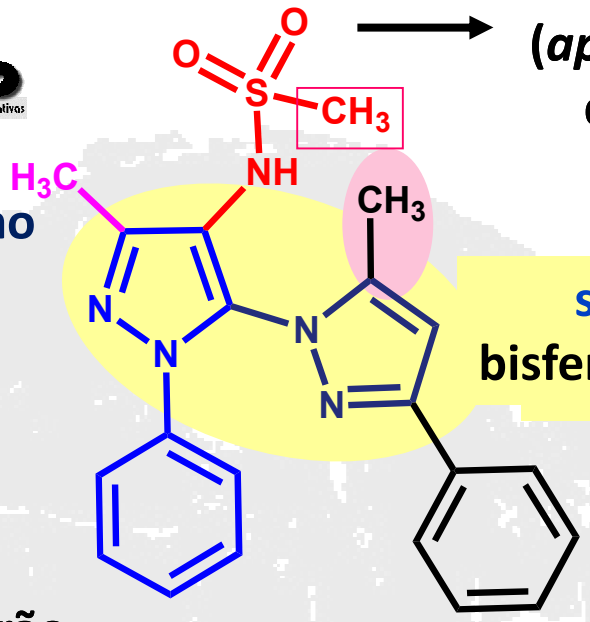
sistema terfenílico



unidade farmacofórica UF

bioisosterismo

retroisosterismo



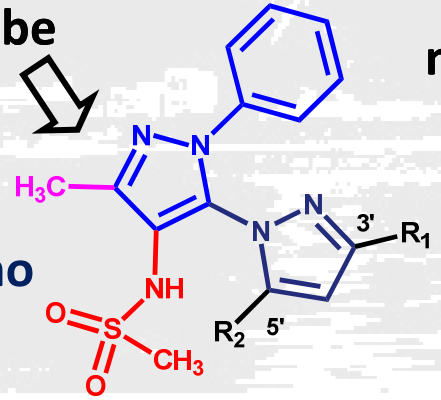
Transposição (*aparente*) da UF

sistema bisfenilpirazólico

LASSBio-466

novo padrão molecular

celecoxibe



bispirazola

retroisosterismo

Química Medicinal

Atropoisomerismo

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

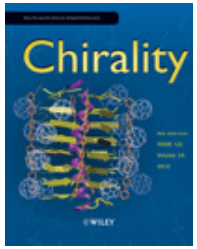
CHIRALITY 24:463–470 (2012)

Universidade Federal do Rio de Janeiro

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

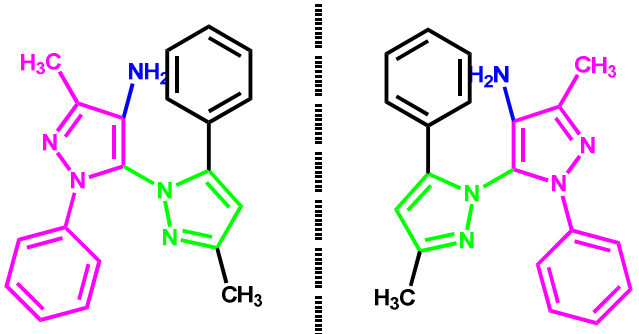
MARCIA P. VELOSO,[1,2,3] NELILMA C. ROMEIRO,[4] GILBERTO M. S. SILVA,[1,5,6] HÉLIO DE M. ALVES,[1] ANTONIO C. DORIGUETTO,[7] JAVIER ELLENA,[8] ANA L. P. MIRANDA,[1,5] ELIEZER J. BARREIRO[1,2,5] AND CARLOS A. M. FRAGA[1,2,5]*

[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.

aR-(2d)



aS-(2d)

Atropoisomerism

Determinação da configuração absoluta

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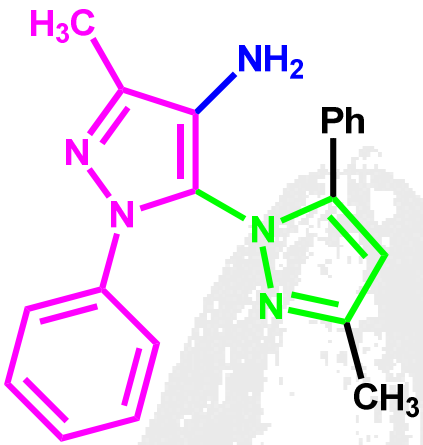
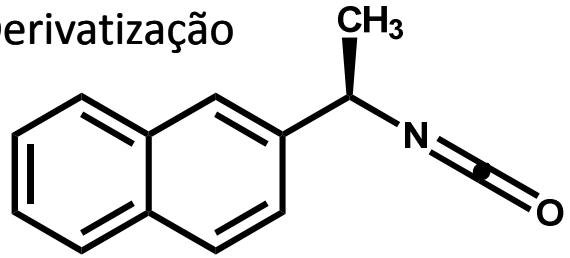


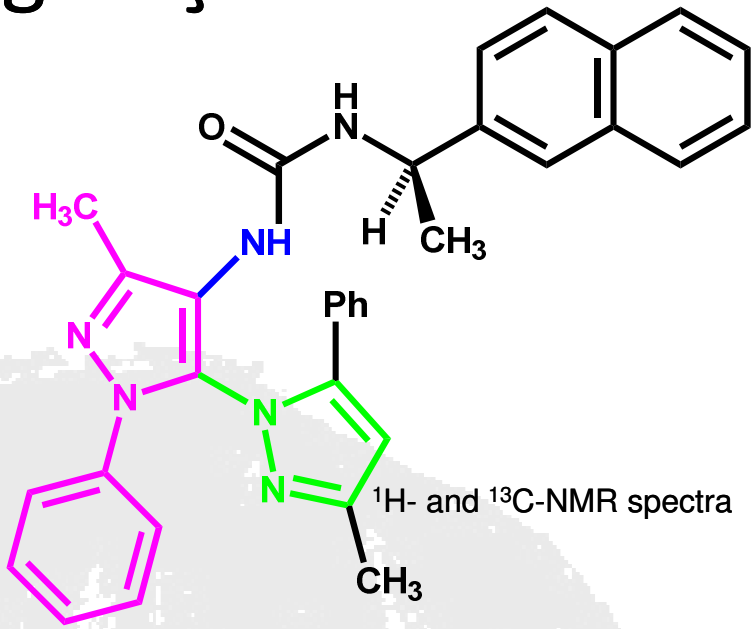
Derivatização



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

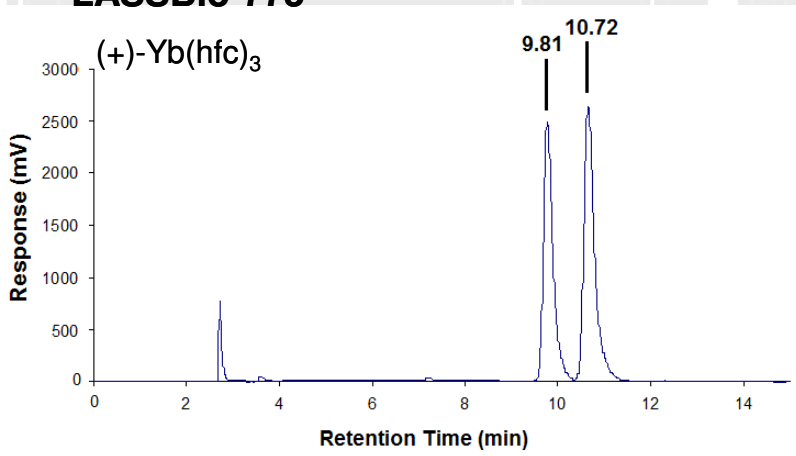
NEt_3, THF, rt

96%



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

LASSBio-775



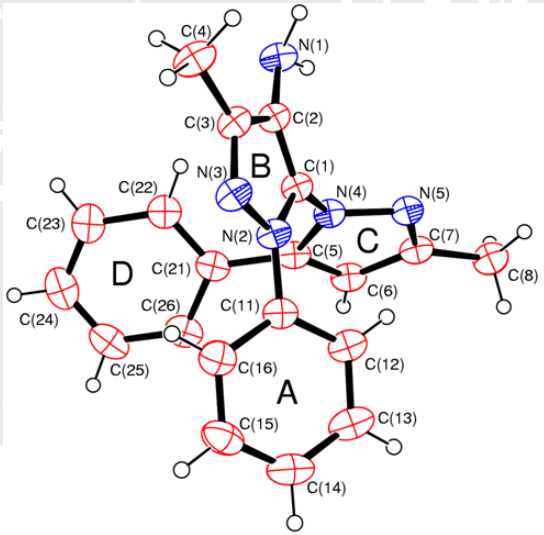
Lichosorb (N. 738342) RP-18 column (250 mm x 4 mm x 5 µm)

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 elegante *sutileza* da metila...

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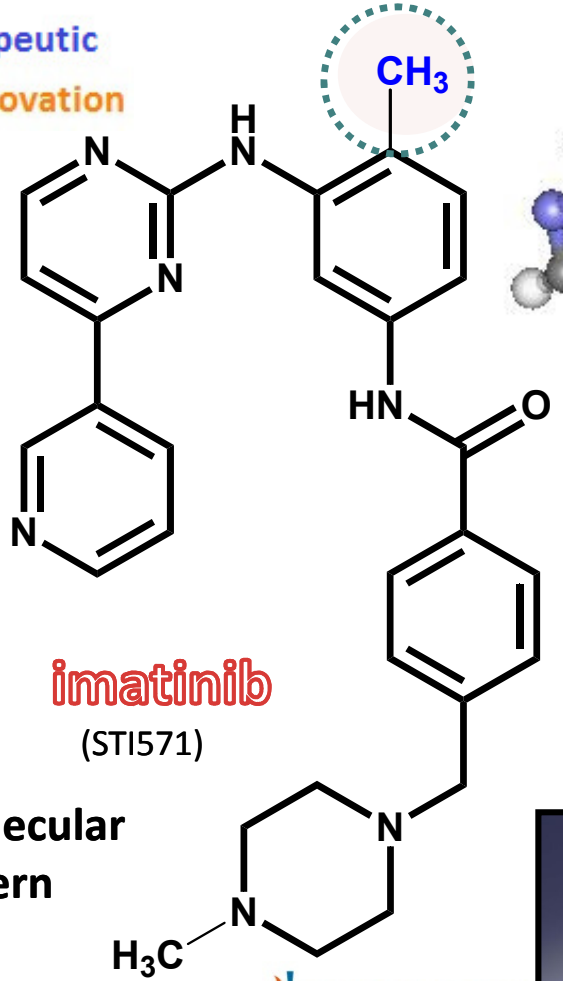
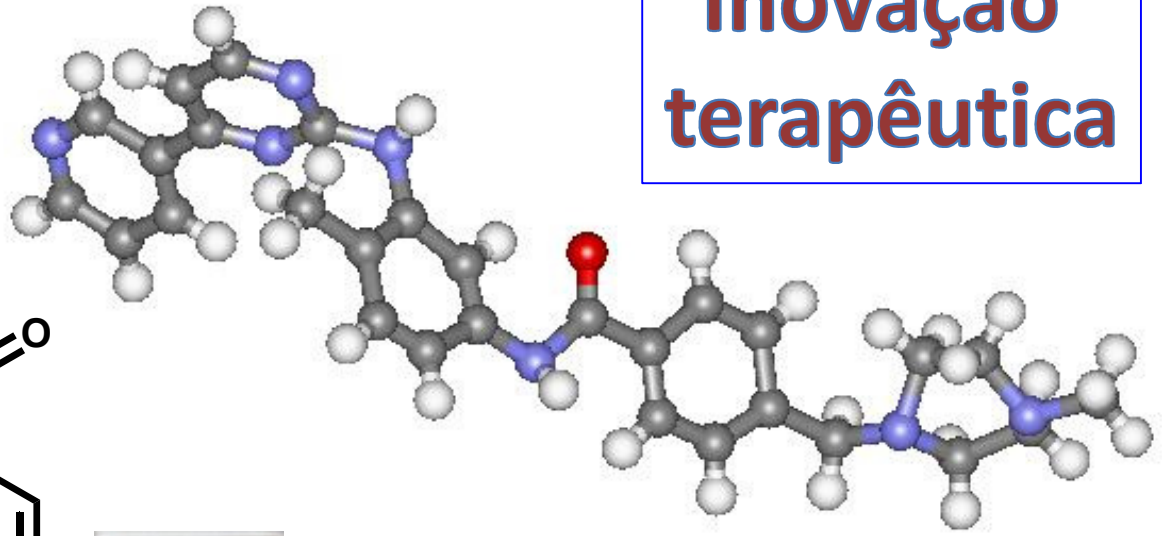
therapeutic innovation

Inovação terapêutica





imatinib

(STI571)

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

New molecular pattern

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;

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UFRJ

NOVARTIS

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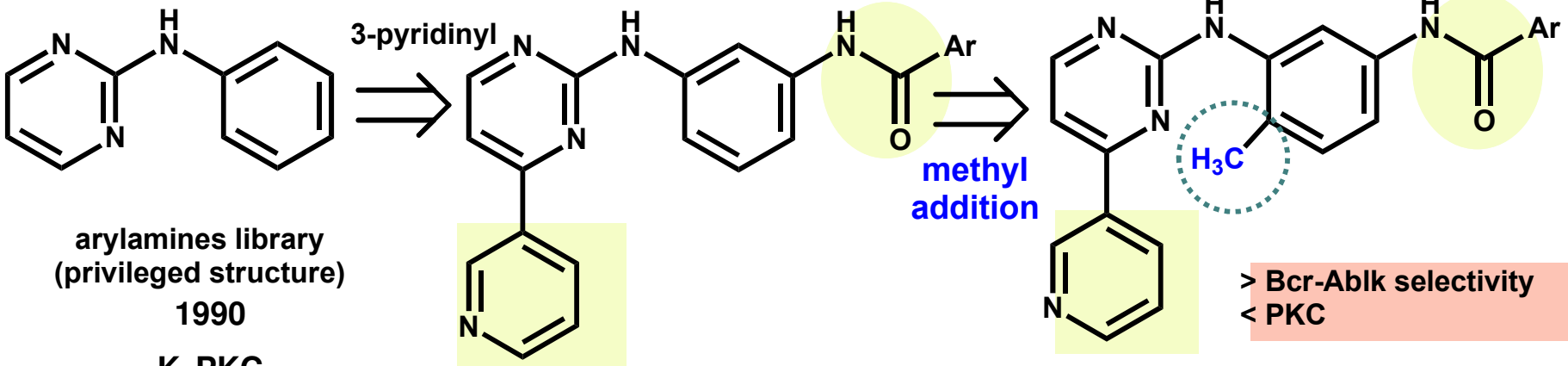
HTS



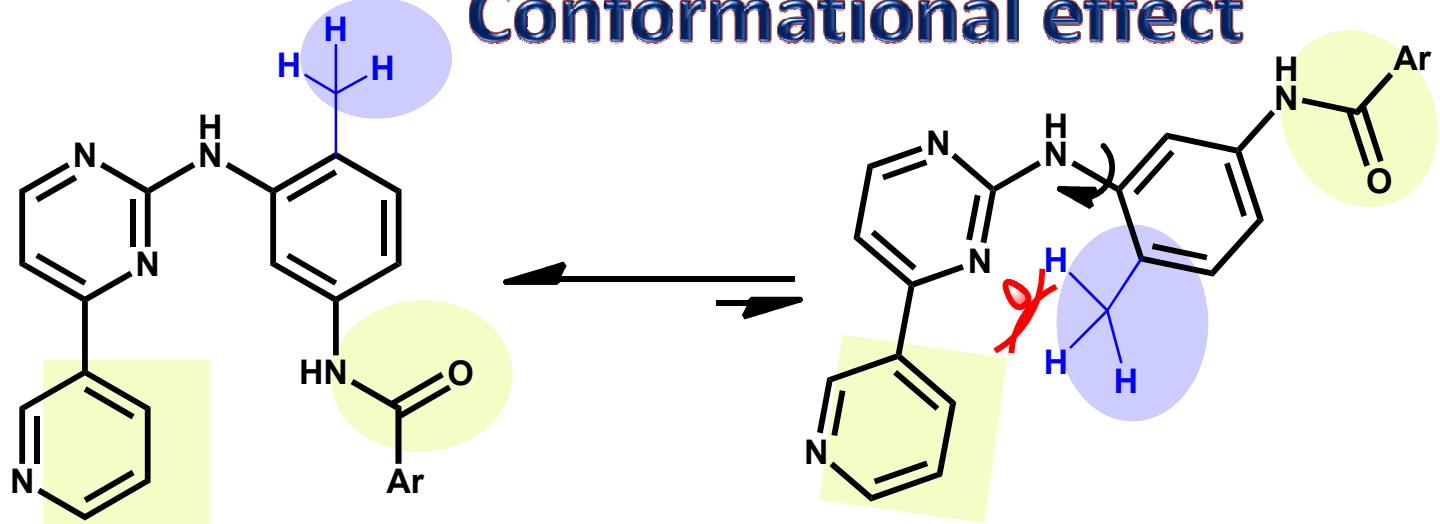
arylamines library
(privileged structure)
1990

K_i PKC

PKC and TK inhibitor
(Bcr-Ablk inhibitor)

> Bcr-Ablk selectivity
< PKC

Conformational effect



Steric hindrance leads to an arylamine bond rotation

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

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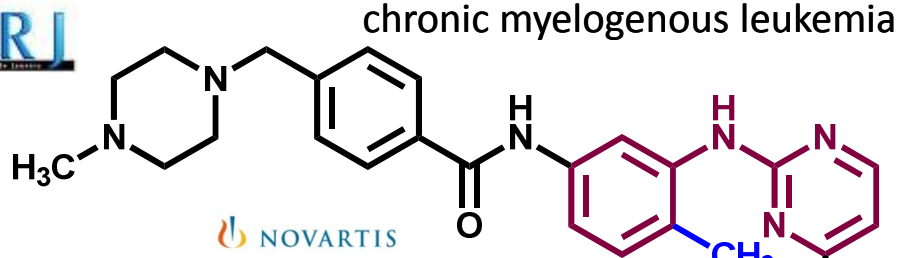
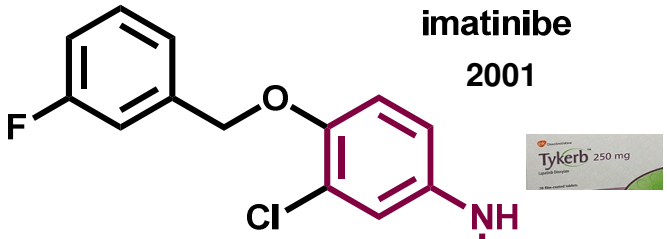
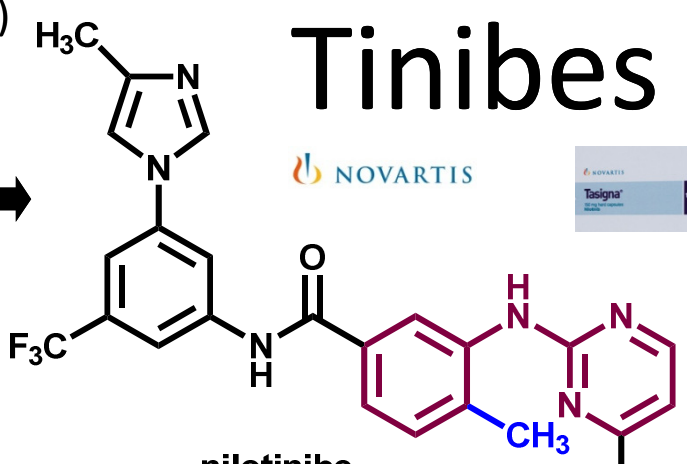
chronic myelogenous leukemia (CML)

Tinibes

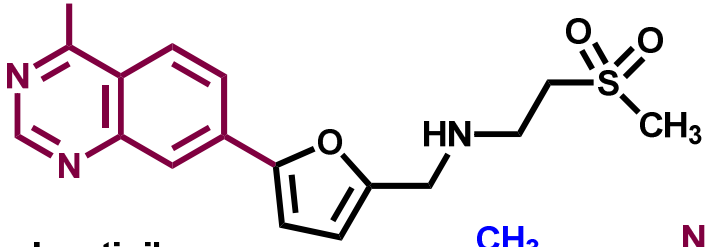


imatinibe
2001

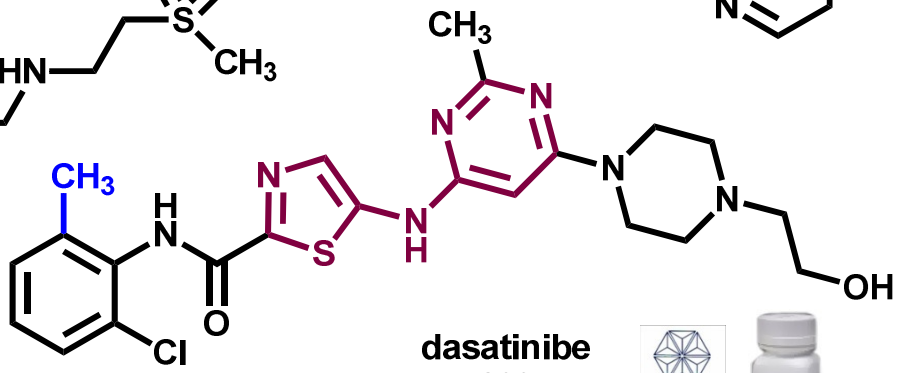




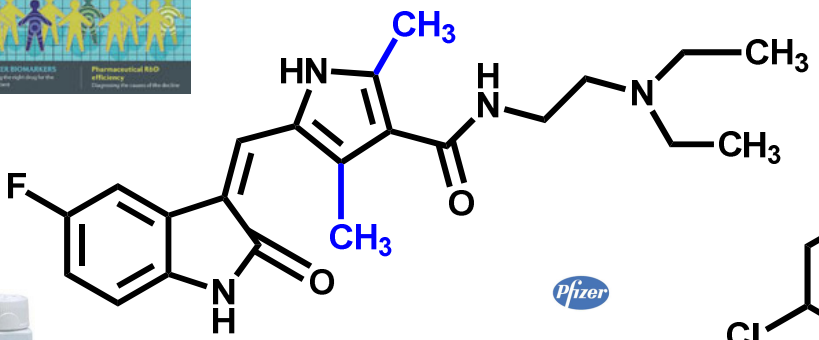
nilotinibe
2006



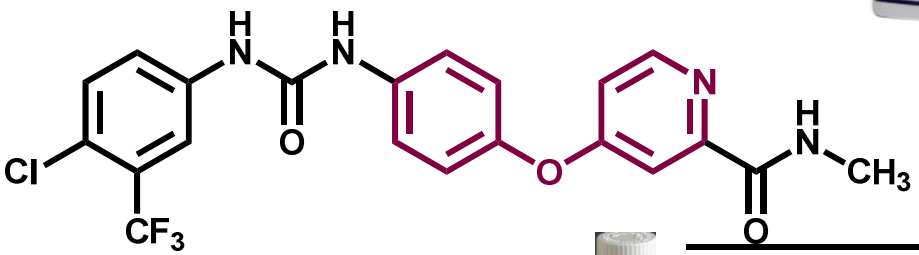
lapatinibe
2007



dasatinibe
2007



sunitinibe
2006



sorafenibe
2007

2011- crisotinibe
2012- bosutinibe

- 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$...*

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Akira Endo, Sankyo Co

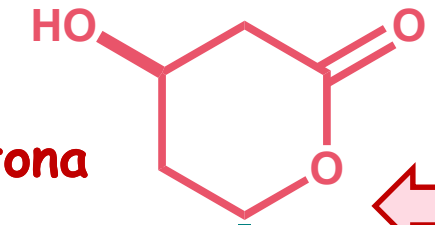
Estatinas*

1975 – Mevastatina (ML-263b)

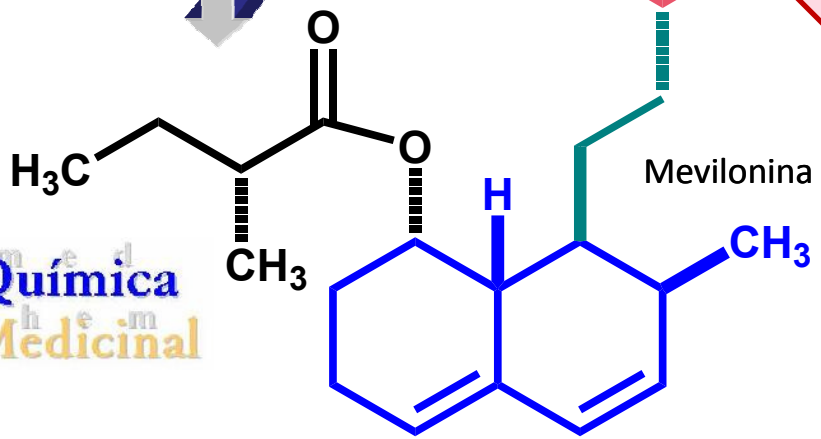
A.Endo, *J. Med. Chem*. **1985**, *28*, 1

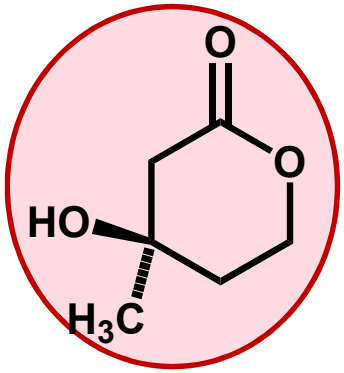
Protótipo natural

Similaridade molecular



γ-lactona

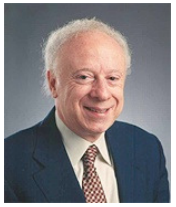




Mevalolactona

HMG-CoA redutase

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



JL Goldstein

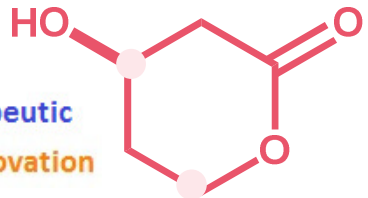
MS Brown

1985 LDL

University of Texas, Dallas

Química Medicinal

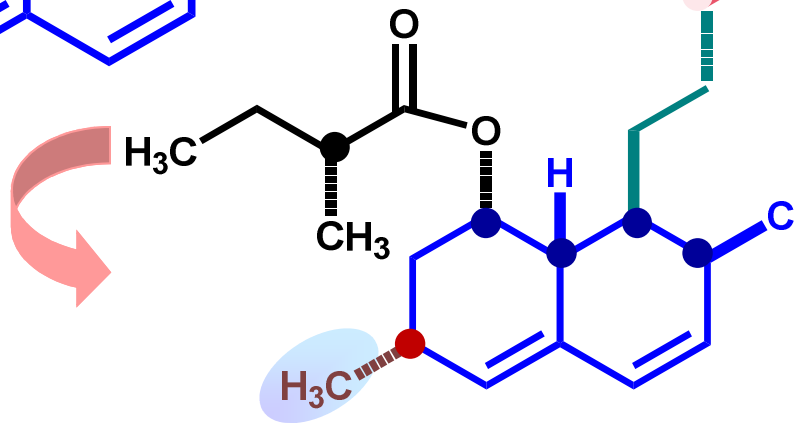
therapeutic innovation



MERCK

Arthur A Patchett

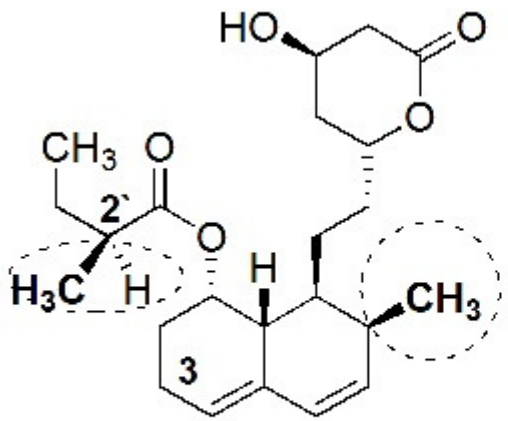
Alfred Burger Award 2002
J. Med. Chem. **1986,** *29*, 849



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

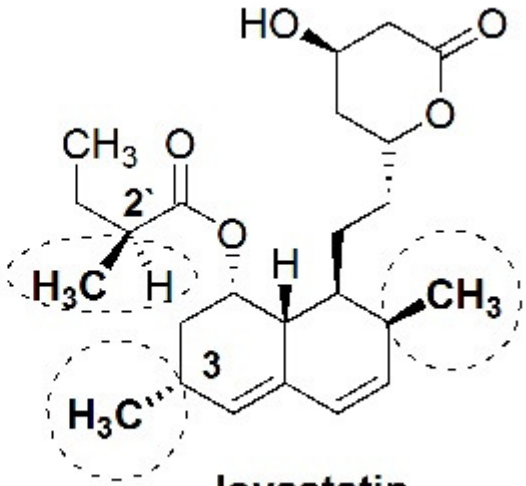
1987 – MS&D (*Mevacor*^{R})
1988 – *Mevacor*^{R} US$ 260 mi

A metila *$e achando...*



mevastatin

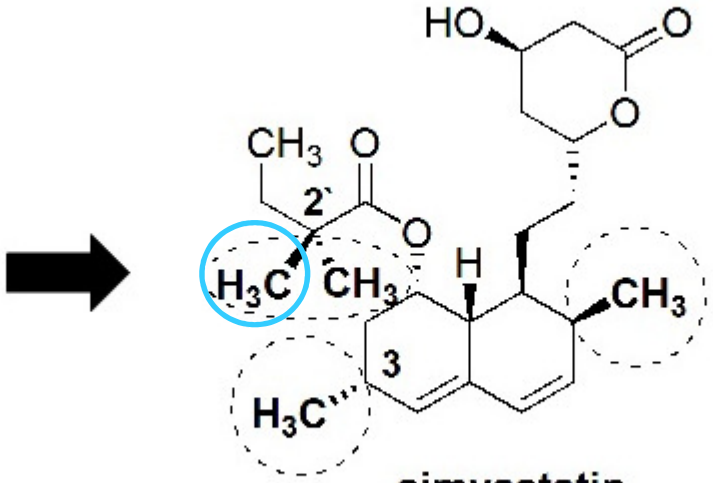
IC_{50} HMG-CoA_R = 5.6 nM



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

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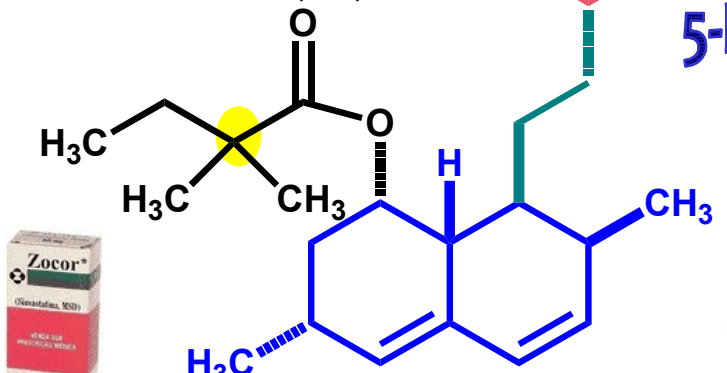
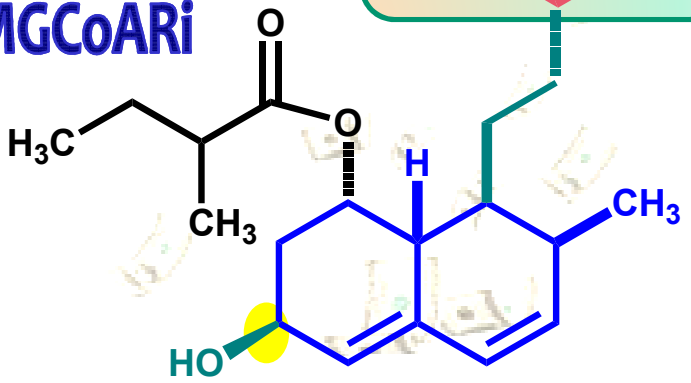
Arthur A Patchett
J Med Chem **2003**, *45*, 5609



simvastatina
1986

MERCK



pravastatina
1988

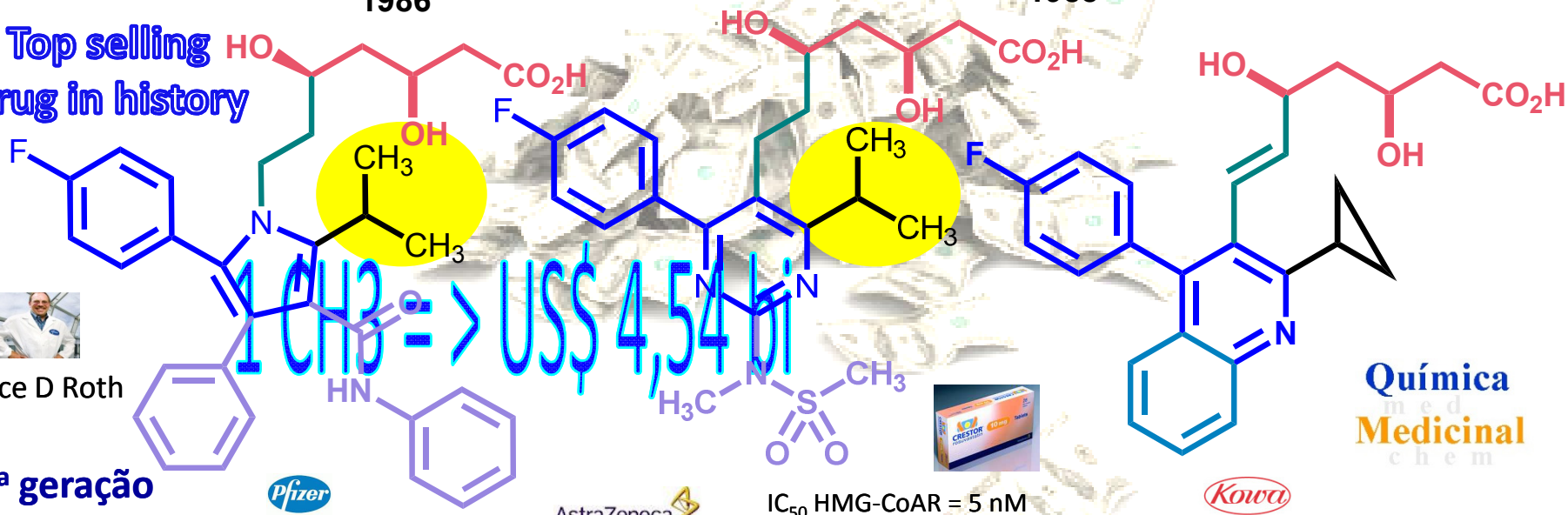
Bristol-Myers Squibb

TEVA

(2006)

2ª geração

Top selling drug in history



Bruce D Roth

3ª geração

Pfizer

atorvastatina
1991

"patent cliff"

AstraZeneca

rosuvastatina
2004
US$ 8,1 bi (2012)

IC_{50} HMG-CoAR = 5 nM

Kowa

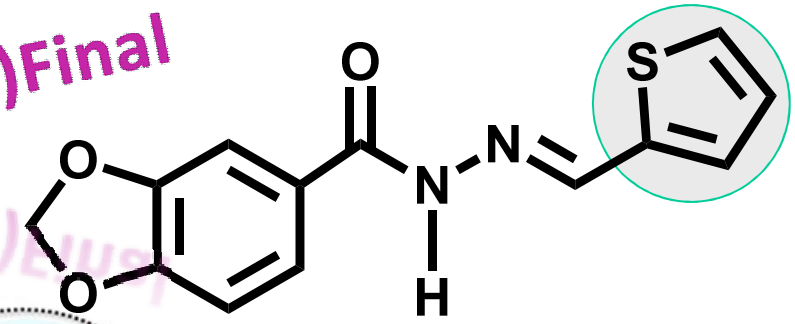
pitavastatina
2009

Química Medicinal

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

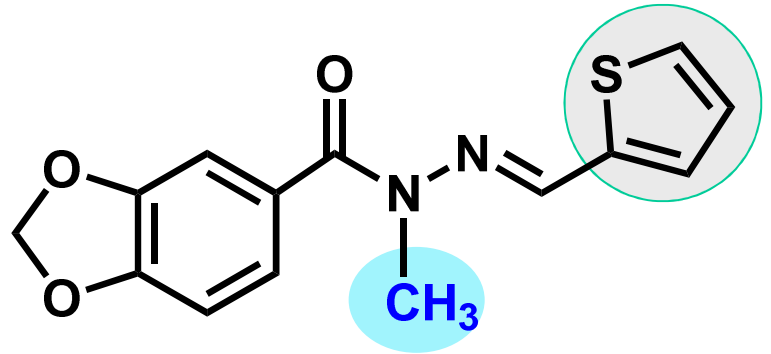
A "*metilinha*" do LASSBio...

(ah!)Final



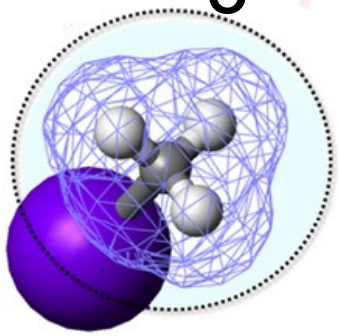
LASSBio-294

IC_{50} (PDE4B) > 100 µM



LASSBio-785

IC_{50} (PDE4B) = 30 µM

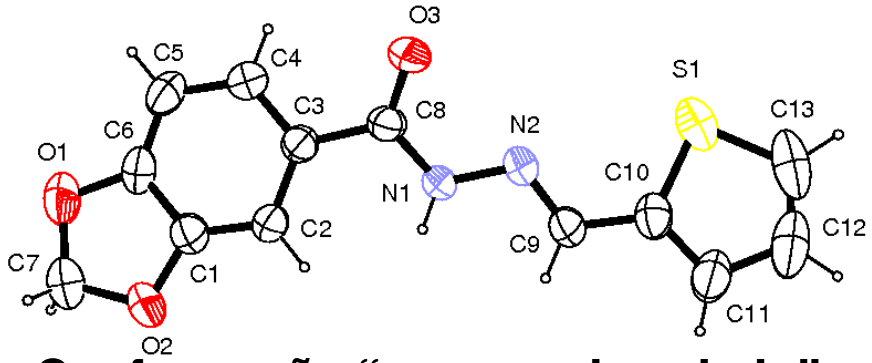


metila

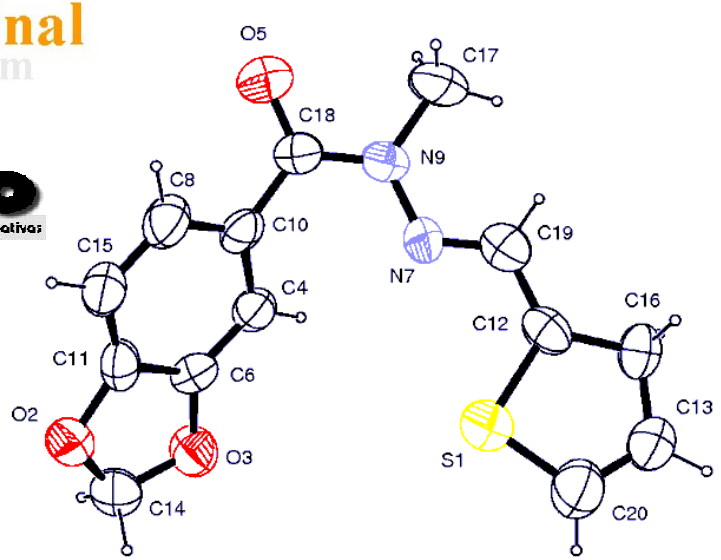
Química Medicinal

LASSBio

Laboratório de Avaliação e Síntese de Substâncias Bioativas



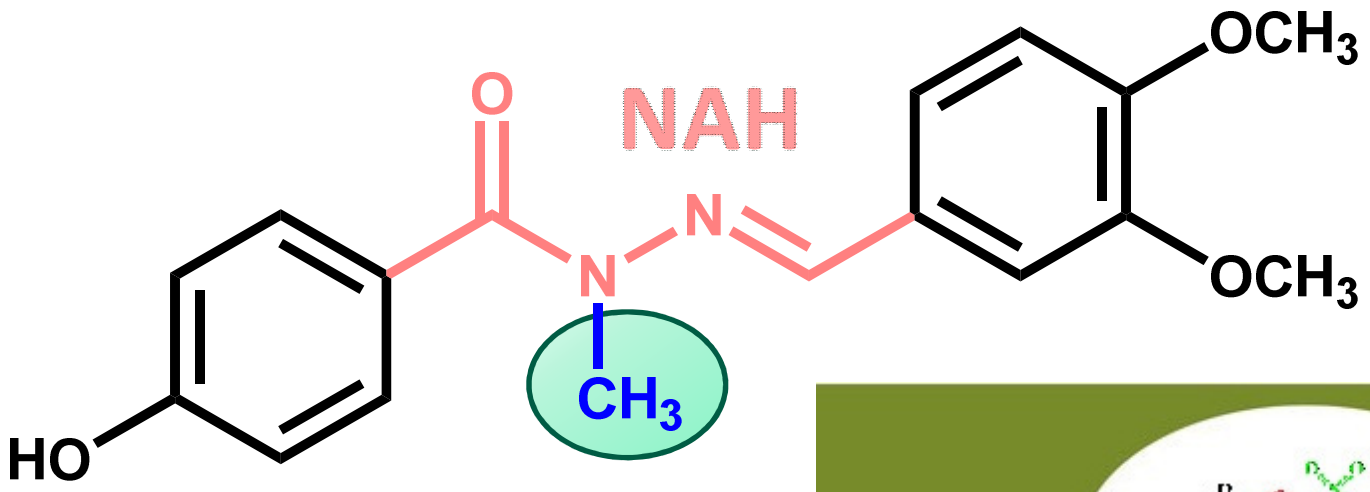
Conformação "grampo-de-cabelo"



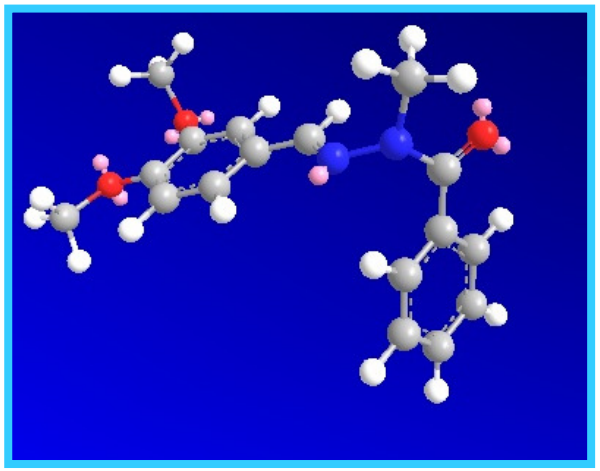
Conformação em "U"

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.

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CH_3

15 Da

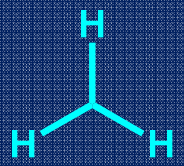
C-H μ = 0,4 D

δ^+ / R^+

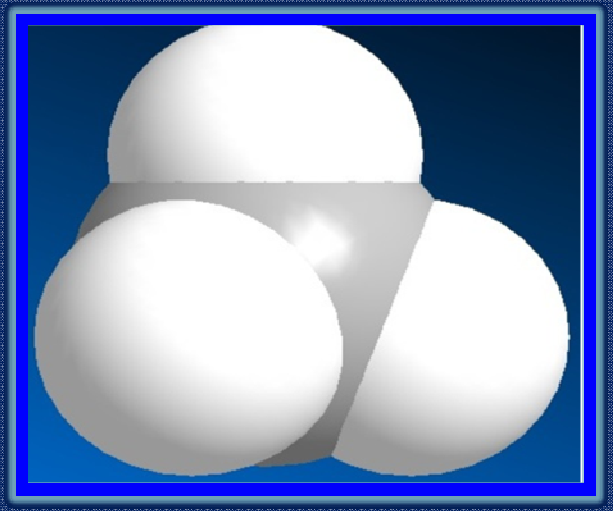
π =0,22

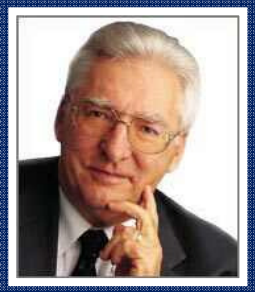
σ_{meta} = 0,51 / σ_{para} = 0,52

Rekker const = 0,702

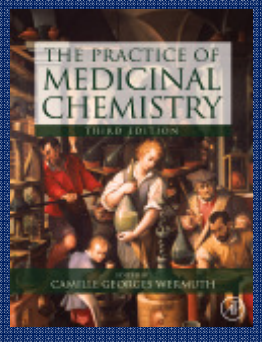


"The methyl group, so often considered as chemically inert, is able to alter deeply the pharmacological properties of a molecule."





Camille G. Wermuth



Química Medicinal

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[†,‡,§]

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[‡]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

*www.uff.br/**RVQ***

AS de Miranda, *Rev. Virtual Quim*. 2011, 3, 228


LASSBio
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