O efeito da metila na Química Medicinal

DQ - Universidade de Aveiro – 12 de setembro de 2012

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www.farmacia.ufrj.br/lassbio

Instituto Nacional de Ciência e Tecnologia de Fármacos e Medicamentos

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Rio de Janeiro, BR

LASSBio

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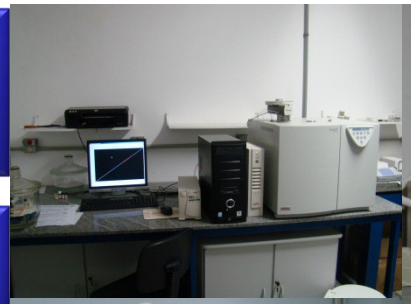
Laboratório de Avaliação e Síntese de Substâncias Bioativas

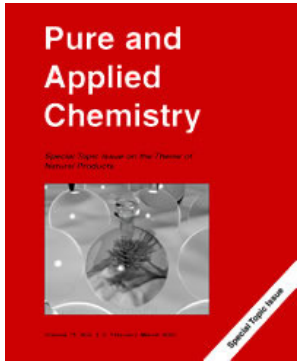


medchem Química Medicinal

Criado em 19/04/1994

IUPAC - Subcommittee Medicinal Chemistry & Drug Development

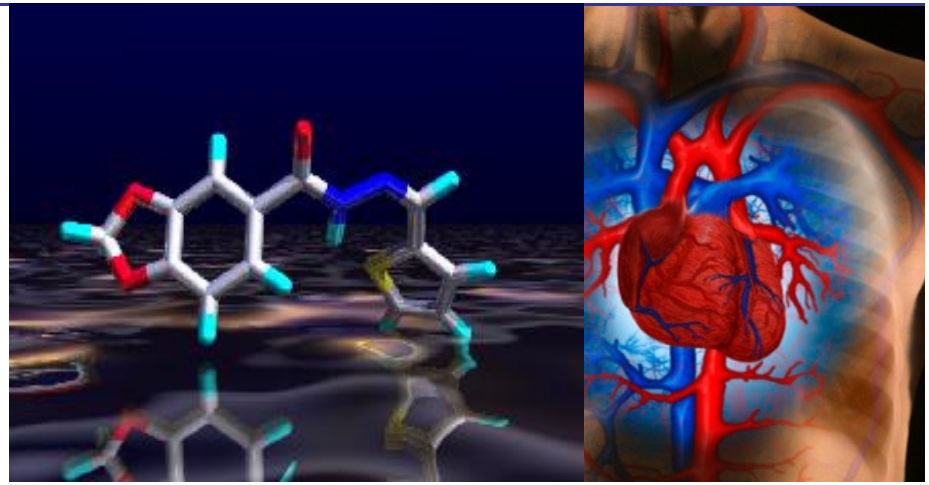
Química Medicinal é a *disciplina* que estuda aspectos **relacionados** à *descoberta* ou *invenção* de **fármacos**, seus aspectos moleculares envolvidos no mecanismo de ação e aqueles que governam a ***a**bsorção*, ***d**istribuição*, ***m**etabolismo*, ***e**liminação* e ***t**oxicidade* (ADMET),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

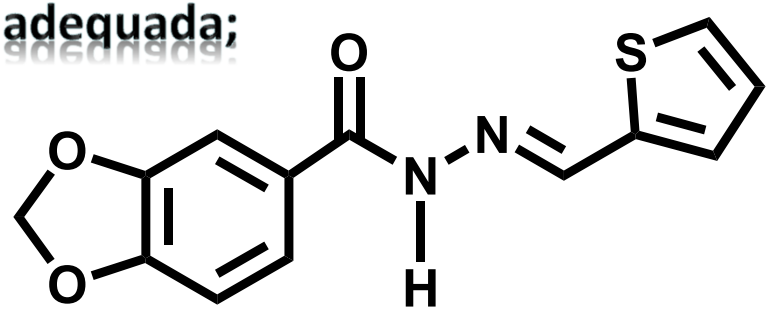


IUPAC

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

Derivado estruturalmente simples; sinteticamente acessível em ótimos rendimentos e em escala 20 M, a partir de matéria-prima natural sustentável & acessível; com estabilidade química e metabólica; com biodisponibilidade adequada;





LASSBio-294

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Protótipo de fármaco cardioativo, com potentes propriedades inotrópicas, vasodilatadoras & neuroprotetoras;

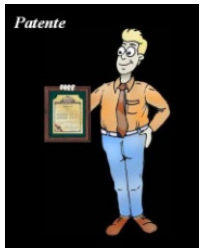
Ativo *p.o.* por <u>novo mecanismo de ação</u>;

Sem cito-, embrio- & genotoxicidade.

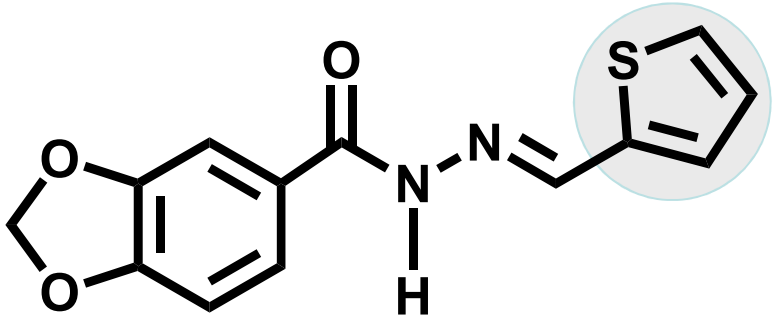
Possíveis indicações terapêuticas

Cardiopatias c/ hipertensão

US Pat. 7,091,238 (15 de agosto de 2006)



LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas



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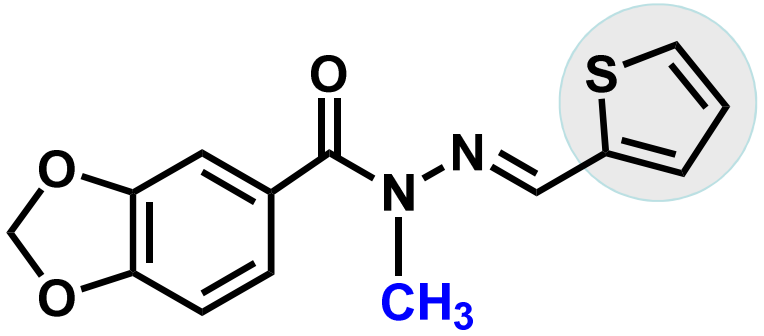
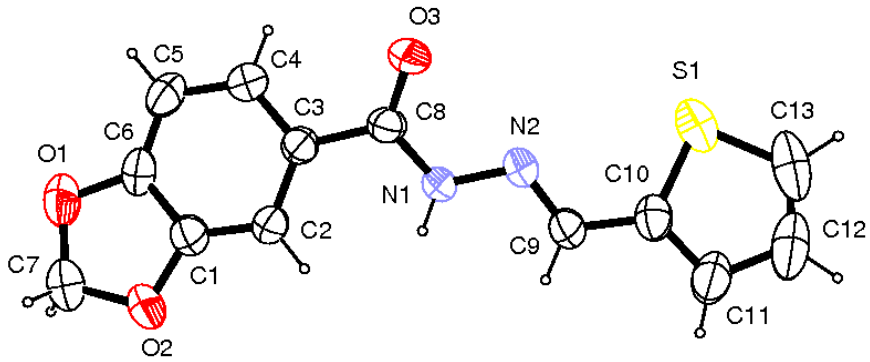
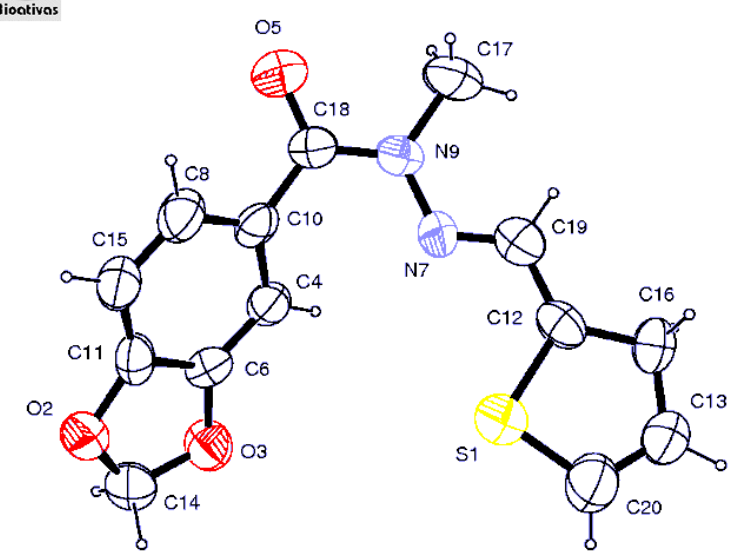


LASSBio-785

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

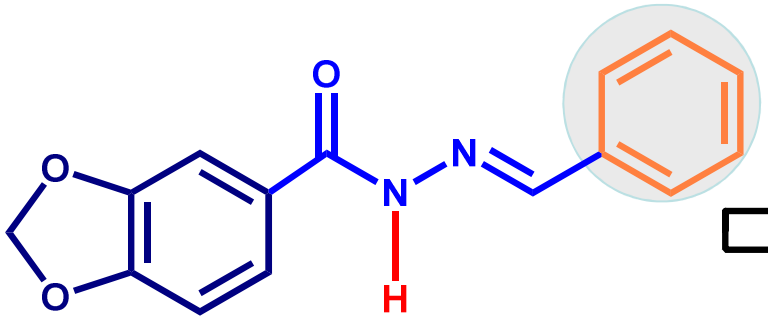


Conformação "grampo-de-cabelo"

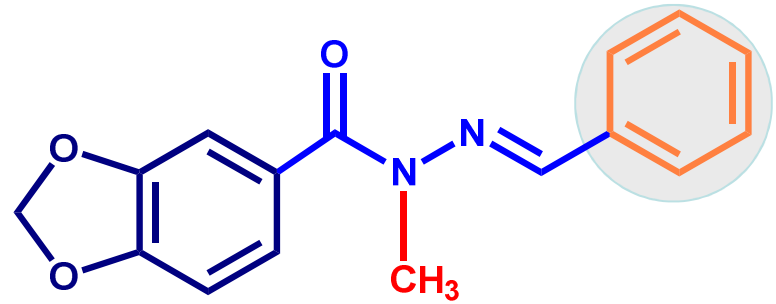


Conformação em "U"

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas



LASSBio-123



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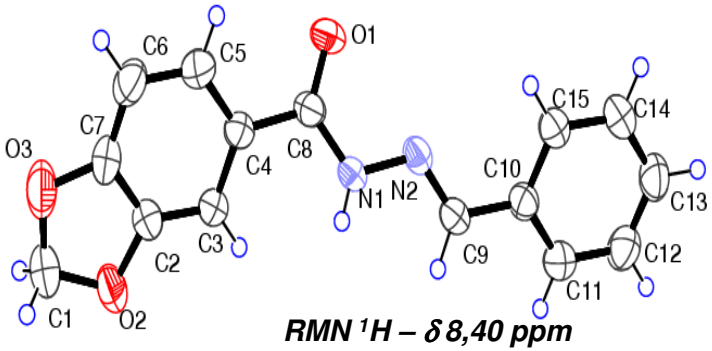
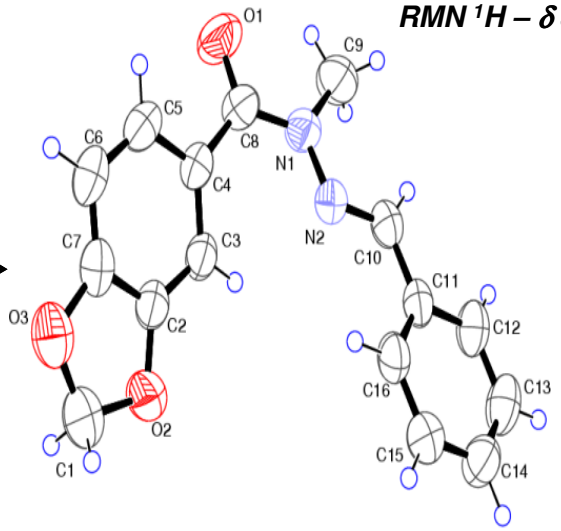


RMN ^1H – δ 8,40 ppm

N-metilação



RMN ^1H – δ 3,60 ppm

LASSBio-123

LASSBio-1004

Conformação "grampo-de-cabelo"

Conformação em "U"

CH_3

15 Da

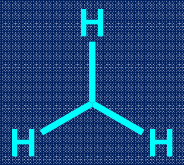
C-H μ = 0,4 D

δ^+ / R^+

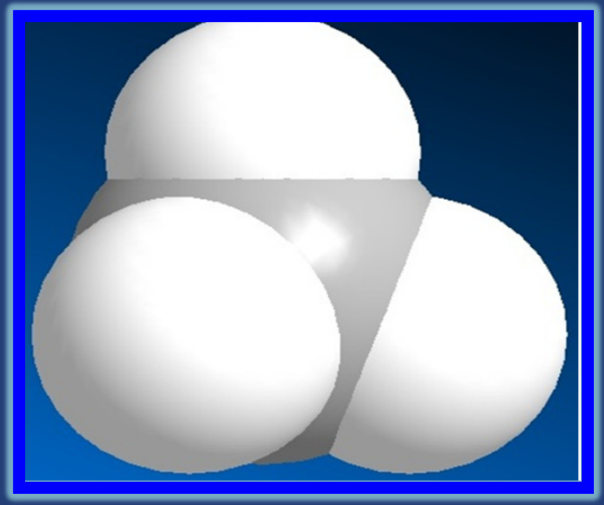
P =0,22

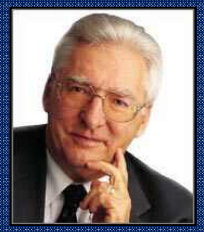
σ_{meta} = 0,51 / σ_{para} = 0,52

Rekker const = 0,702

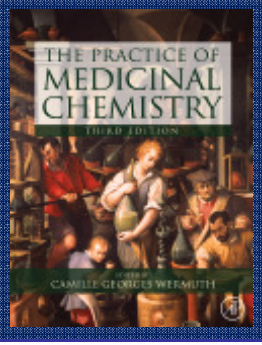


"The methyl group, so often considered as chemically inert, is able to alter deeply the pharmacological properties of a molecule."





Camille G. Wermuth



CHEMICAL REVIEWS

Chem. Rev. 2011, 111, 5215–5246

REVIEW

pubs.acs.org/CR

The Methylation Effect in Medicinal Chemistry

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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

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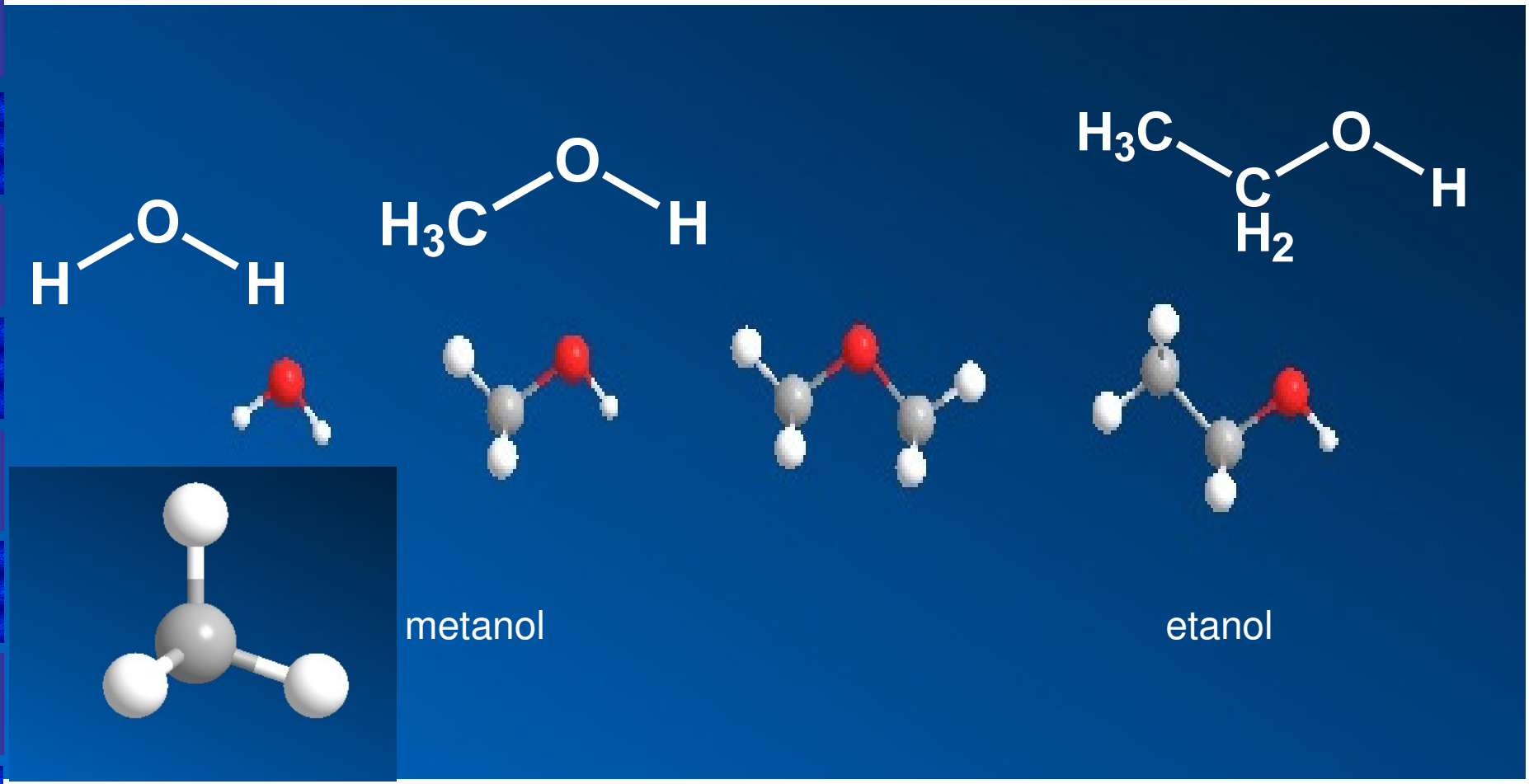
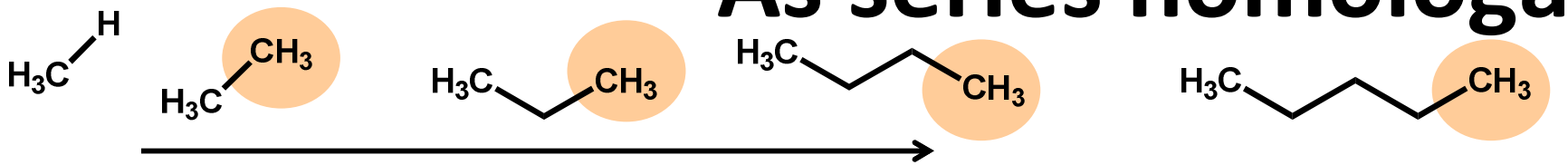
dx.doi.org/10.1021/cr200060g

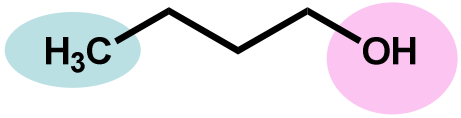
A homologia do carbono...



As séries homólogas

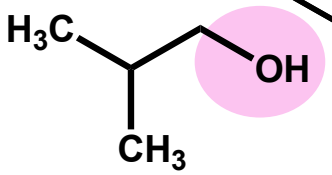


Lipofilicidade



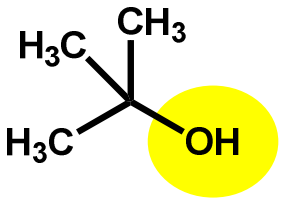
n-butanol

solubility in water
8.2g/100g



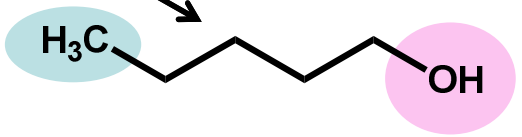
*iso*butanol

solubility in water
12,5 g/100g



tert-butanol

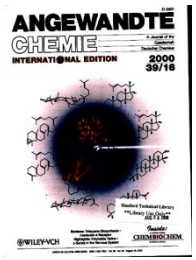
solubility in water
miscible

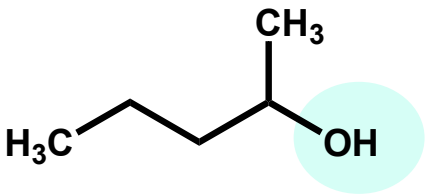


n-pentanol

solubility in water
2.4g/100g

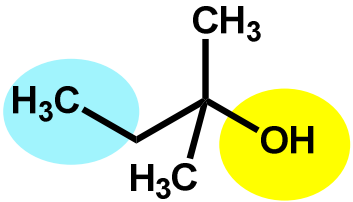
G Némethy, *Angew Chem Int Ed Engl* **1967**, *6*, 195





2-pentanol

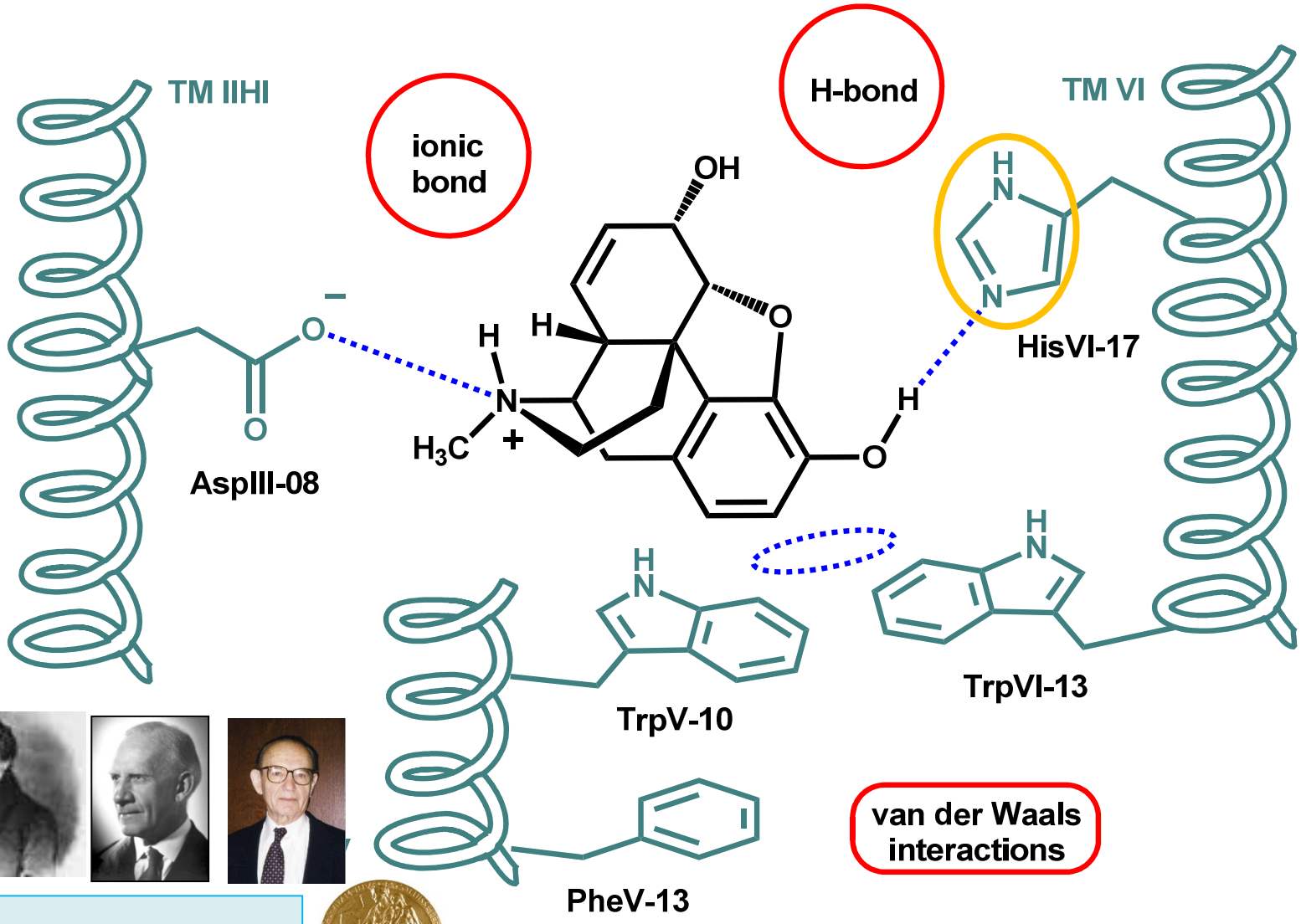
solubility in water
4.9g/100g



*neo*pentanol

solubility in water
12.2g/100g

A *metila* e a morfina...



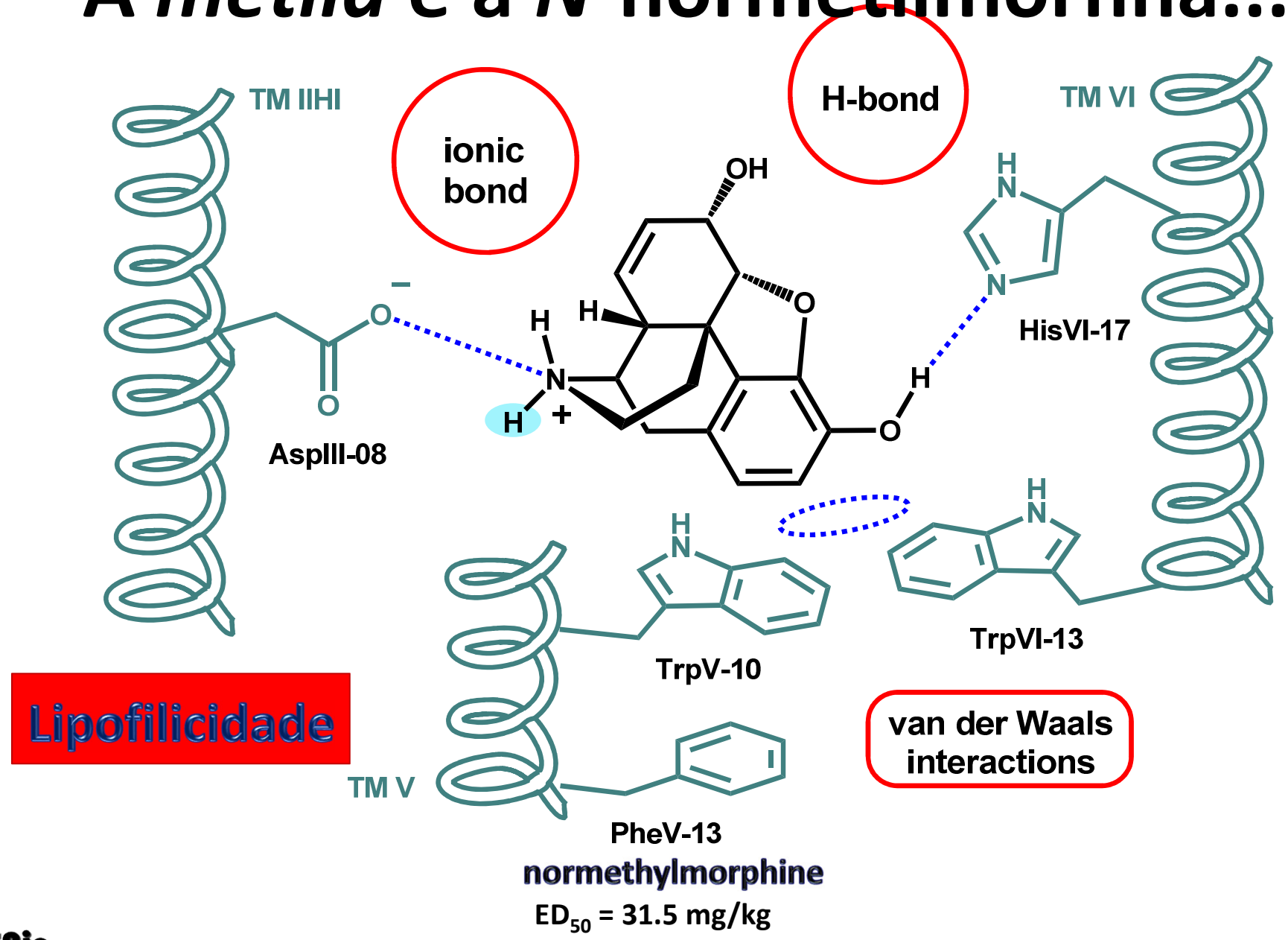
1805 - F. Setürner
1925 – R. Robinson
2001 – G. Stork

1947

Morphine

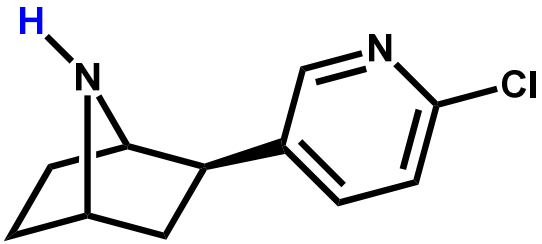
ED_{50} = 4.8 mg/kg

A *metila* e a *N*-normetilmorfina...



O *charme* da *metila* na *epi*batidina...

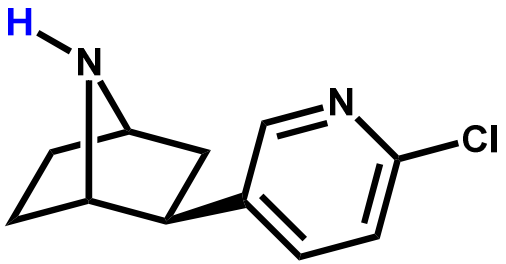
***Epi**pedobates tricolor*



(-)-epibatidina (natural)

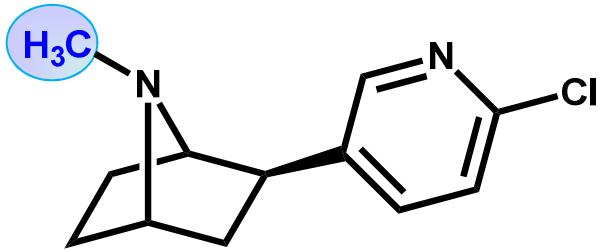
+

nAChR



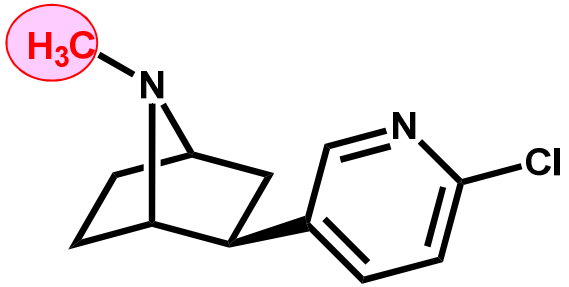
(+)-epibatidina

+



(-)-*N*-metilepibatidina (natural)

+



(+)-*N*-metilepibatidina

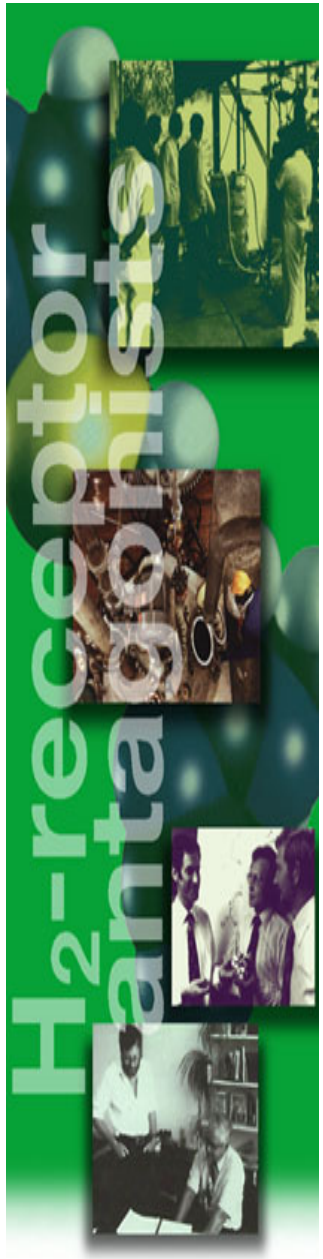
-

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

John W. Daly

Un. Maryland, Baltimore, EUA



National Historic Chemical Landmarks

AMERICAN CHEMICAL SOCIETY

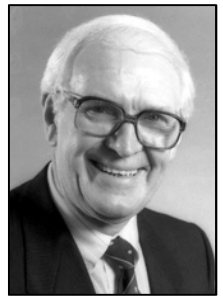
A new era of logical drug design

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.

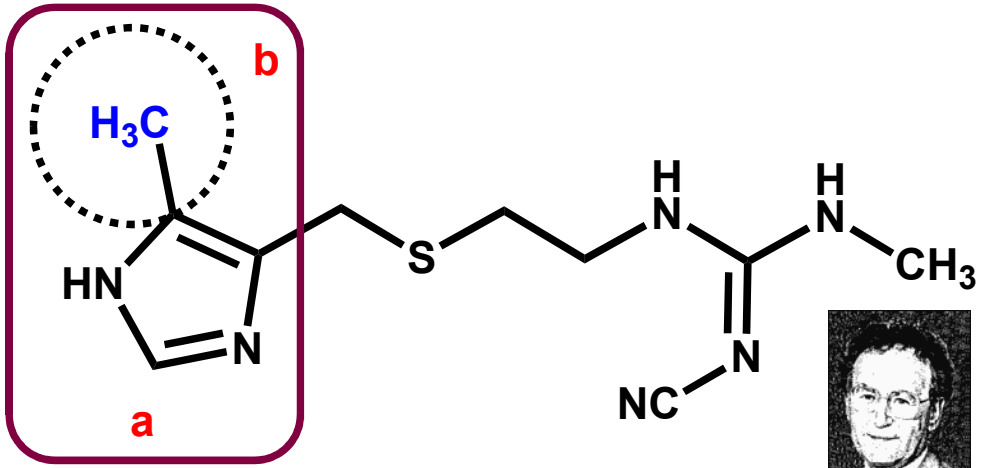
Inovação terapêutica

1988



James W. Black

C Robin Ganellin



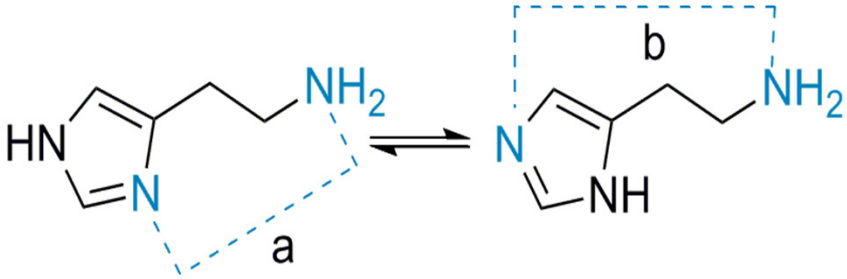
cimetidine

John C Emmett

Graham J Durant

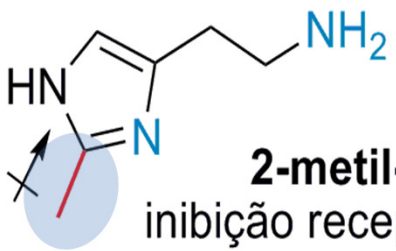
Dois sub-tipos de H_R

Interações fracas

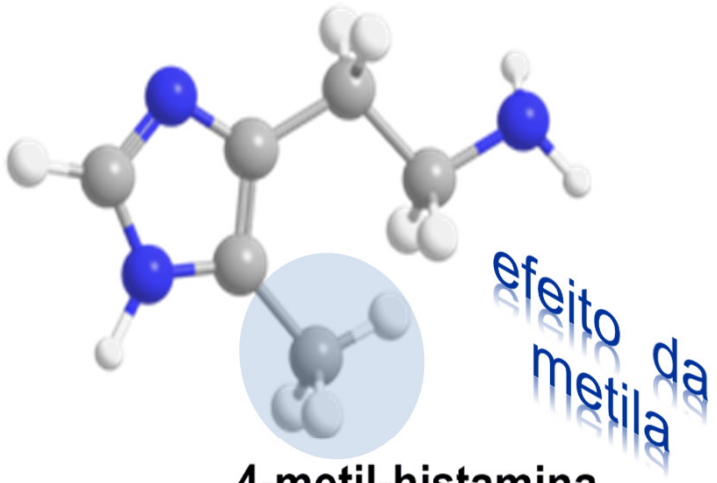


Forma A a = 4,83 Å b = 5,52 Å **Forma B**

Equilíbrio tautomérico

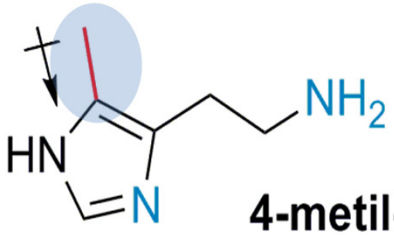


2-metil-histamina
inibição receptores H_1 = 17%
inibição receptores H_2 = < 2%



4-metil-histamina

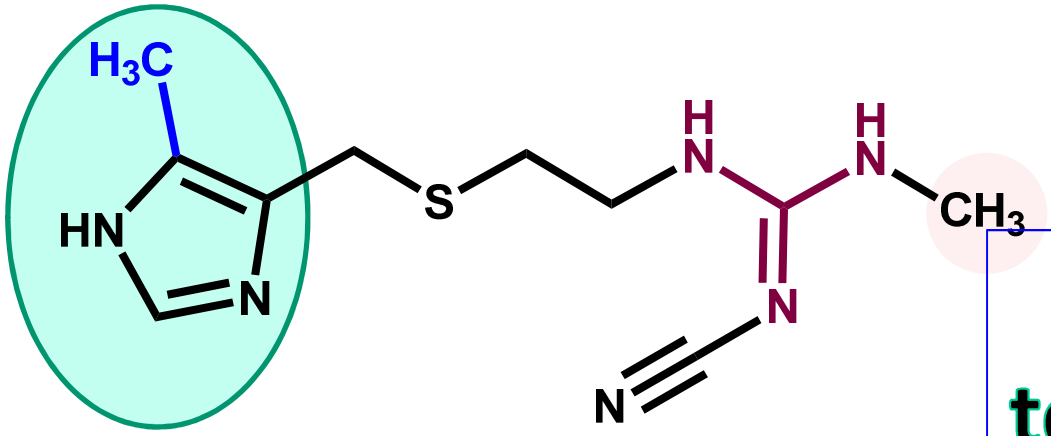
Análogo ativo



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

CR Ganellin, *Drug Discov Today* **2004**, *9*, 158

A *metila* e a invenção da cimetidina



Inovação terapêutica

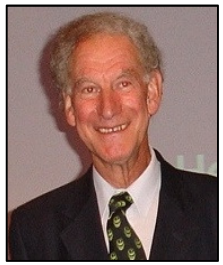
cimetidina

$C_{10}H_{16}N_6S$

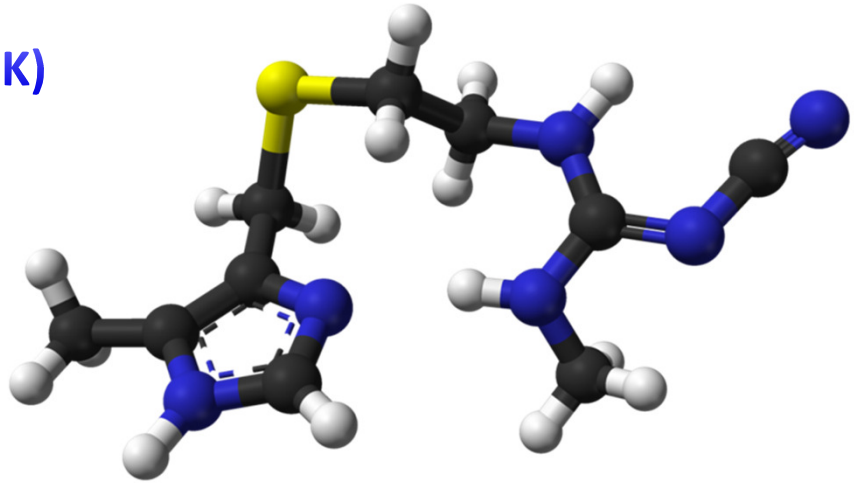
Smith, Kline and French

(SK&F)

(atual GSK)



C Robin Ganellin



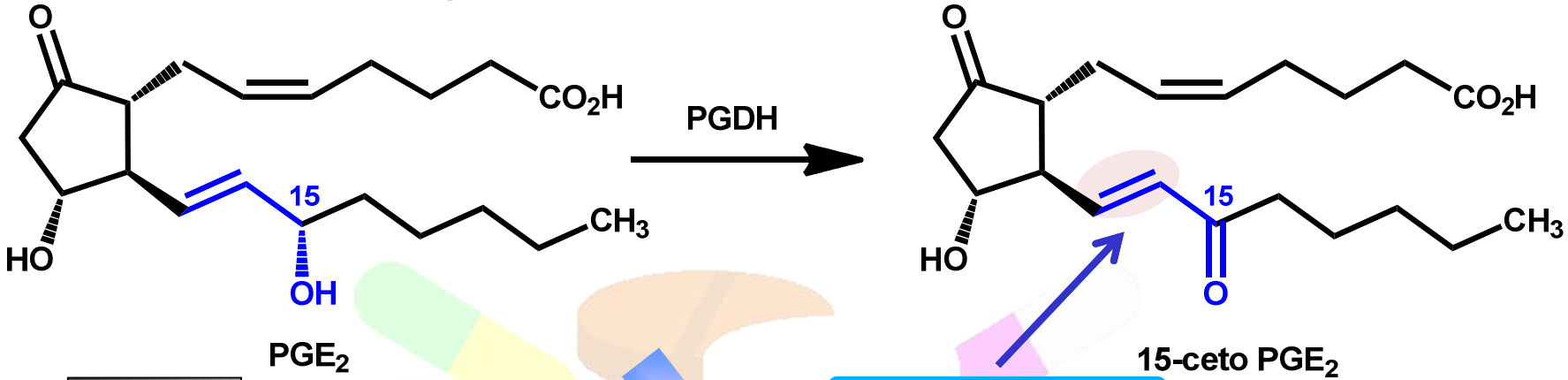
1st blockbuster

1975

> US$ 1 bi

Antagonista seletivo de receptor histaminérgico H_2

A *metila* previnindo o metabolismo



PGE_2

15-ceto PGE_2

PG-redutase (PGR)

John R. Vane

(1927-2004)

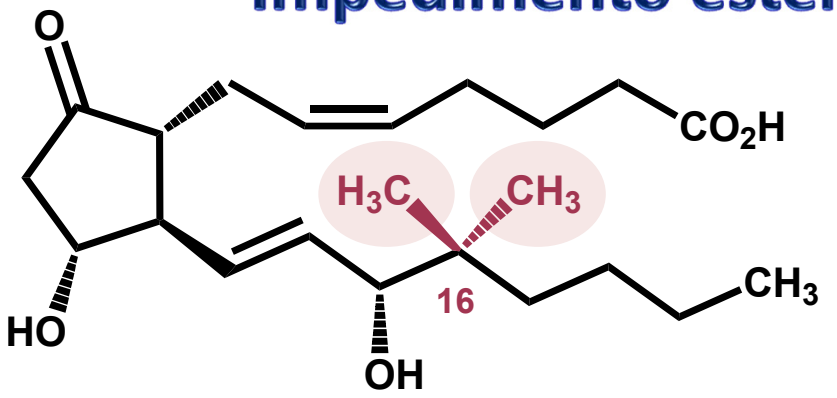
Sune K. Bergström

(1916-2004)

1982

Bengt I. Samuelsson

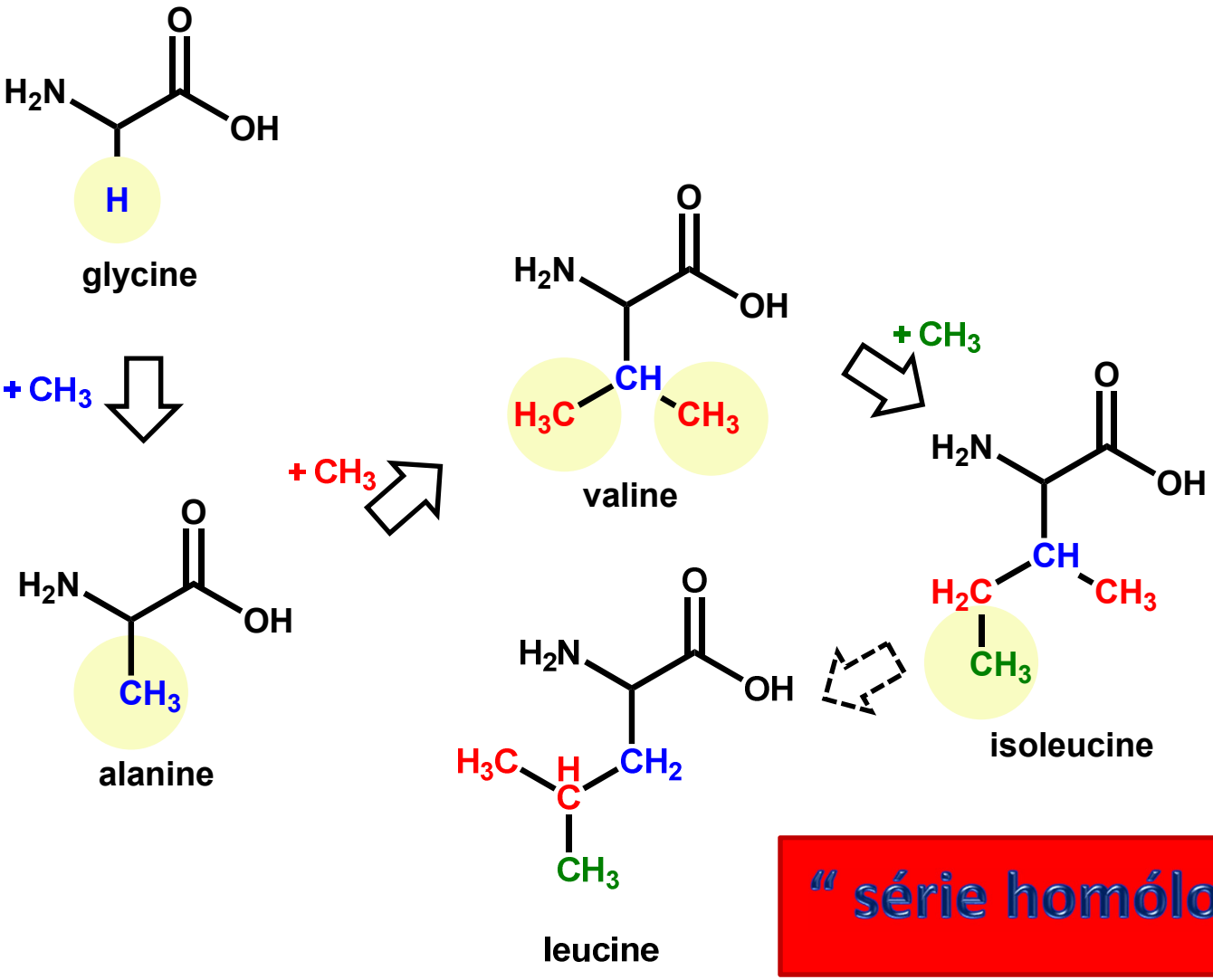
Impedimento estérico



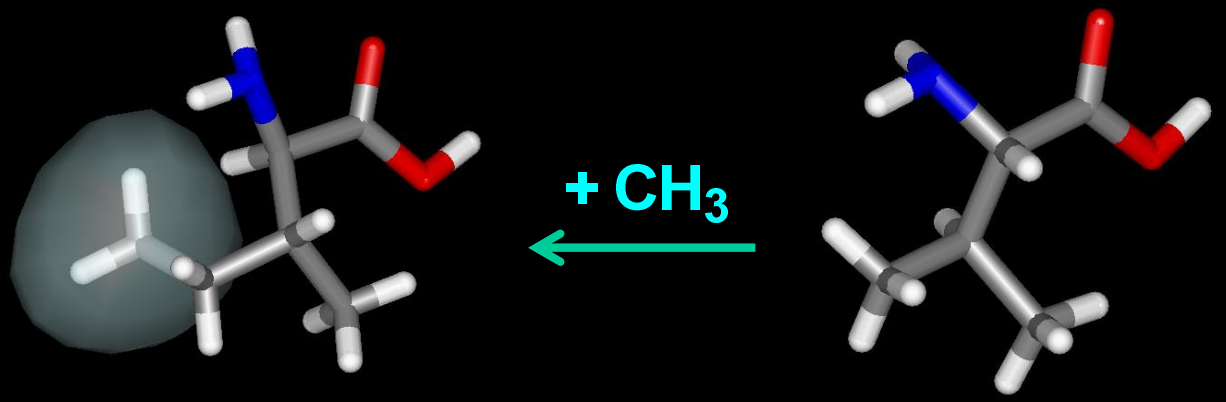
16,16-dimethyl PGE_2

EP_2 ag (1 nM)

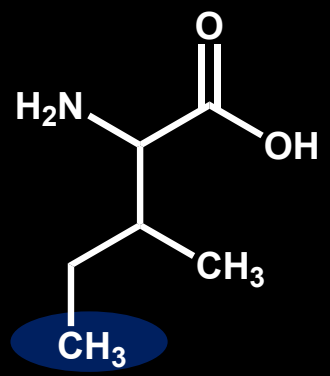
A homologia e os aminoácidos



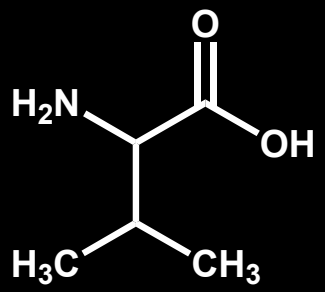
A homologia e os aminoácidos



isoleucina

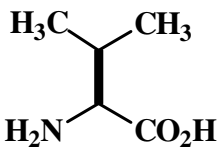


valina

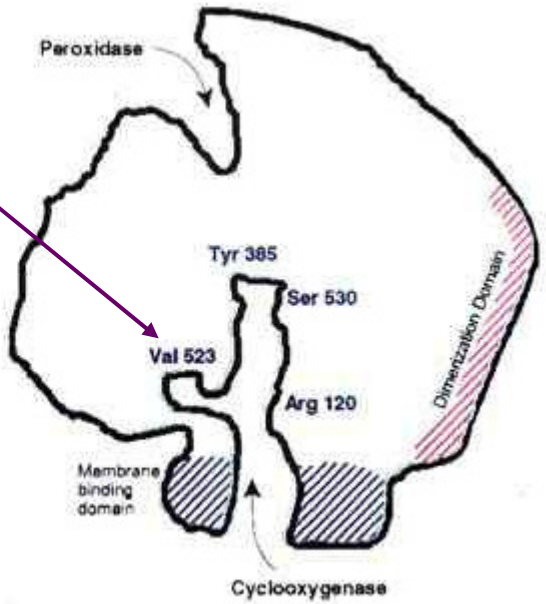


Os amino ácidos homólogos e a COX

Sítio secundário

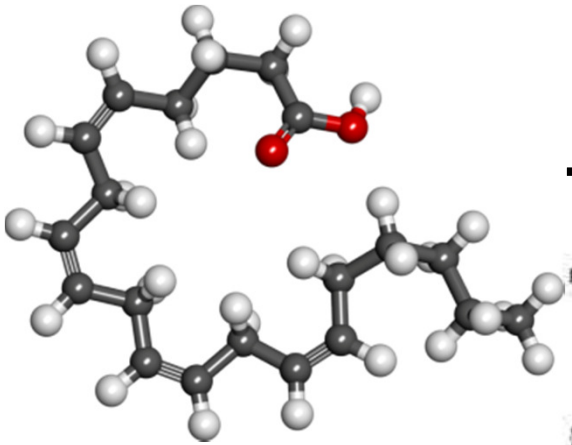


$C_5H_{11}NO_2$
Valina

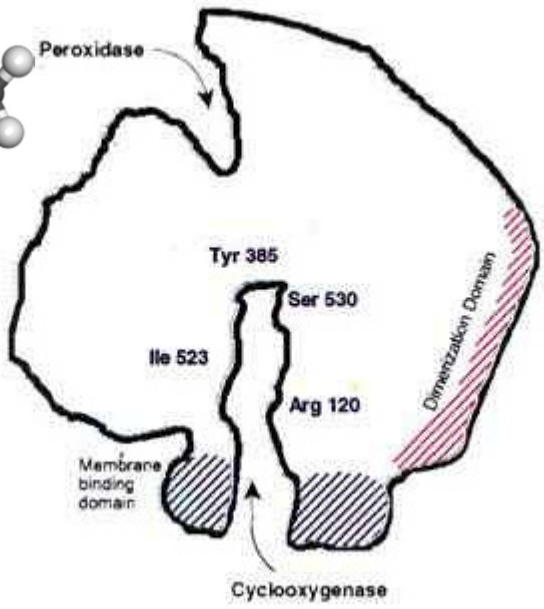


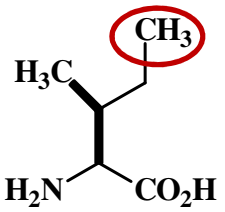
COX-2

- Inflamação
- Câncer
- Endotélio vascular
- Rins
- Cérebro



Ácido araquidônico
K_m = 5,6/5,4 µM



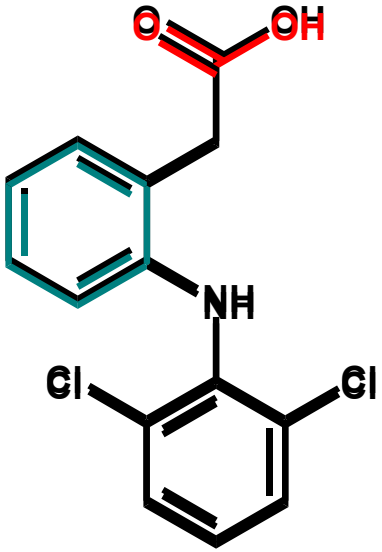


$C_6H_{13}NO_2$
Isoleucina

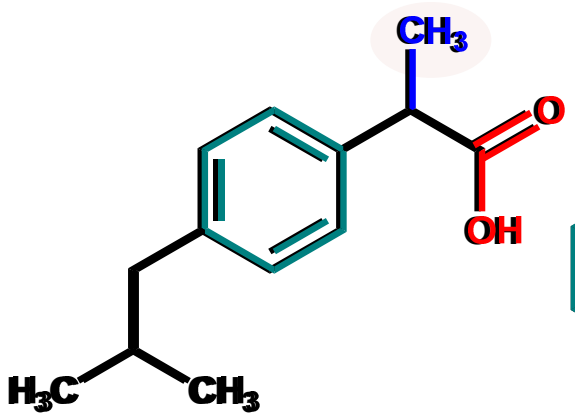
COX-1

- Estômago
- Plaquetas
- Rins

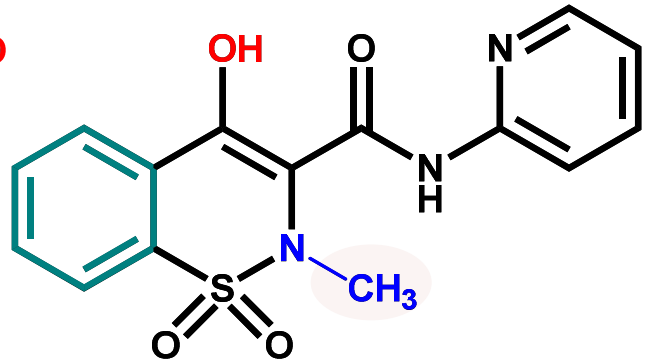
Antiinflamatórios não esteróides



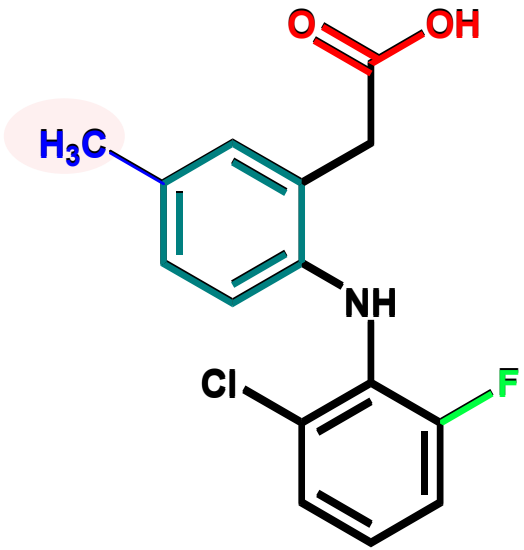
diclofenac



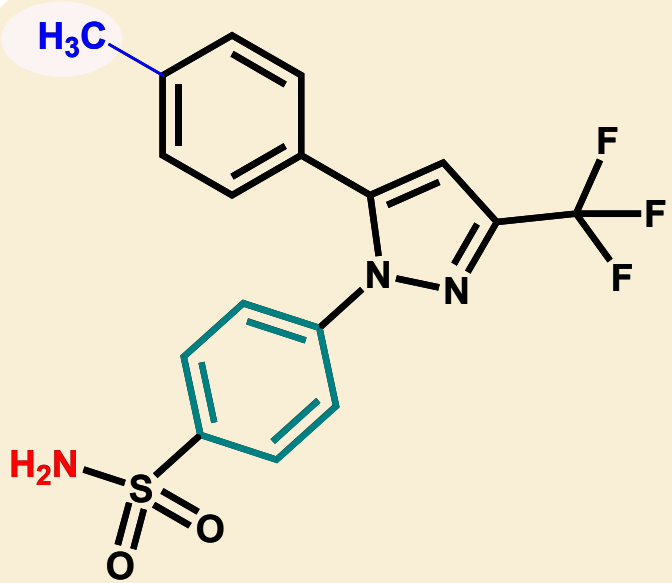
ibuprofen



piroxicam

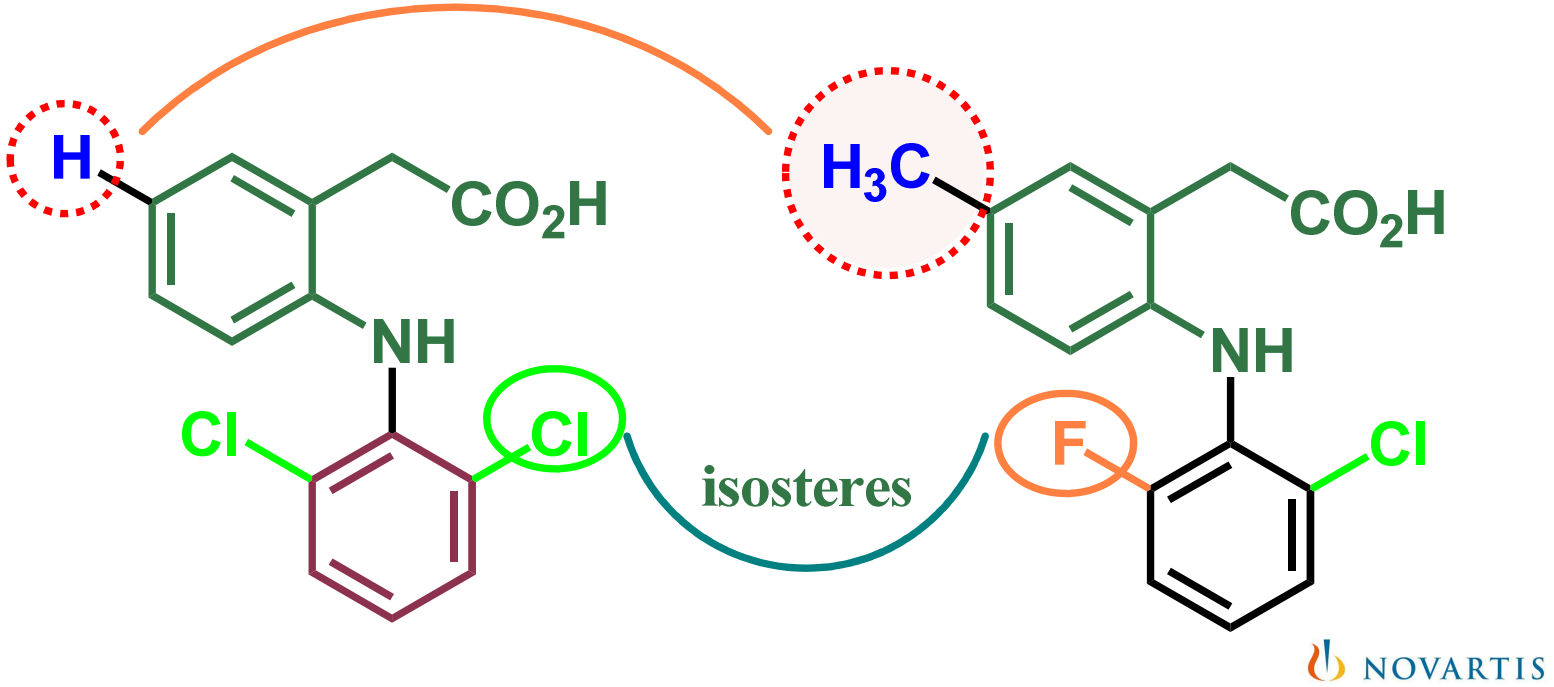


lumiracoxib



celecoxib

O *charme* da metila...



DICLOFENAC

COX-1

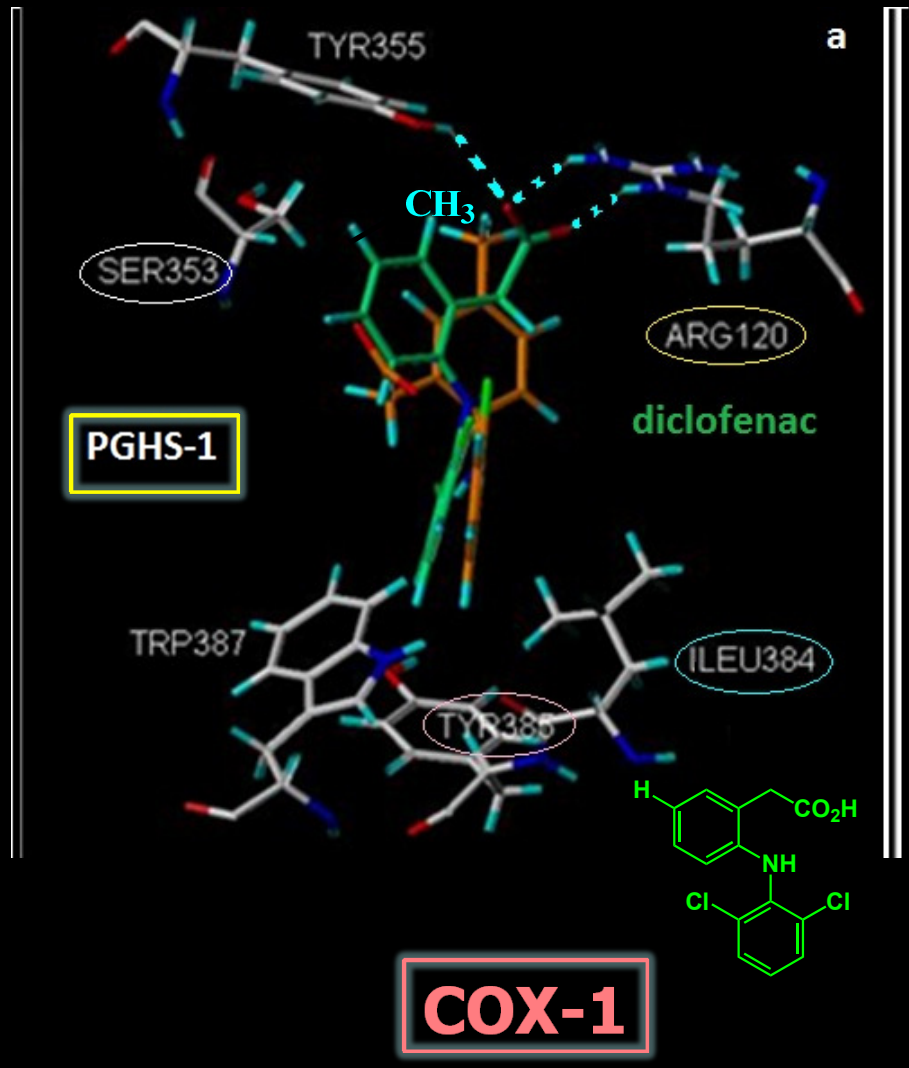
LUMIRACOXIB

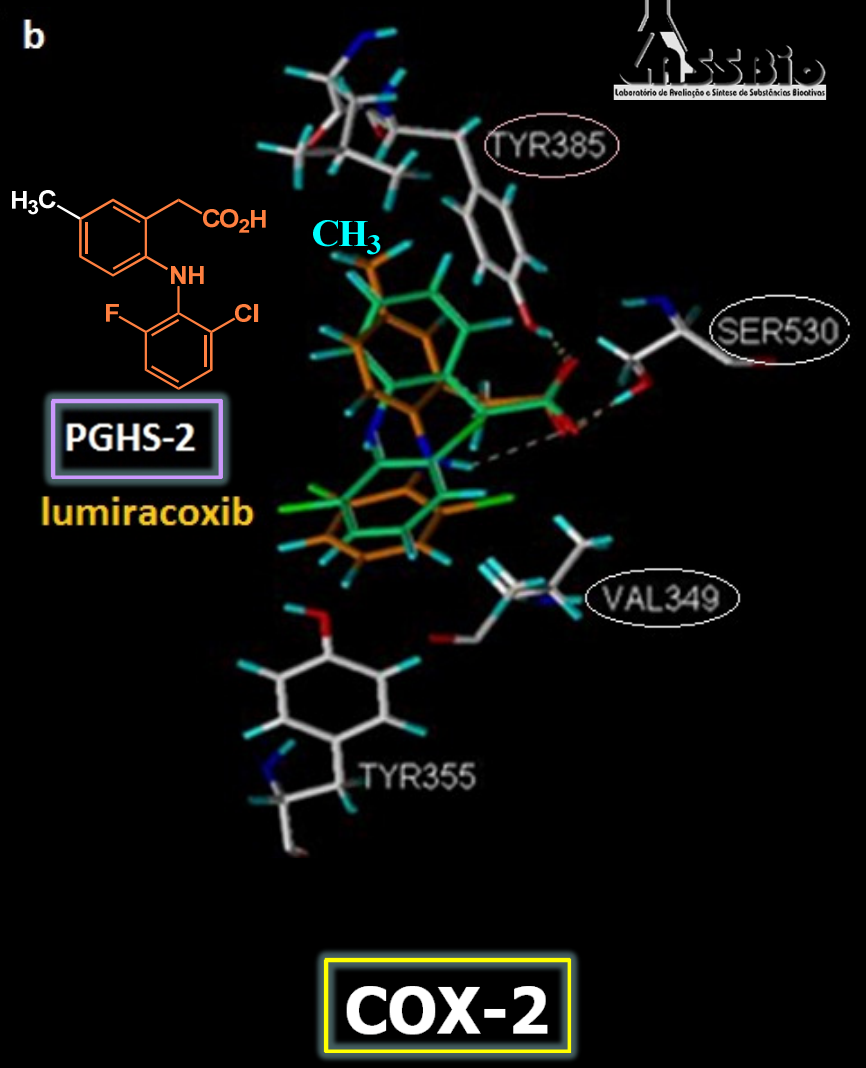
COX-2

2006 (2007)

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

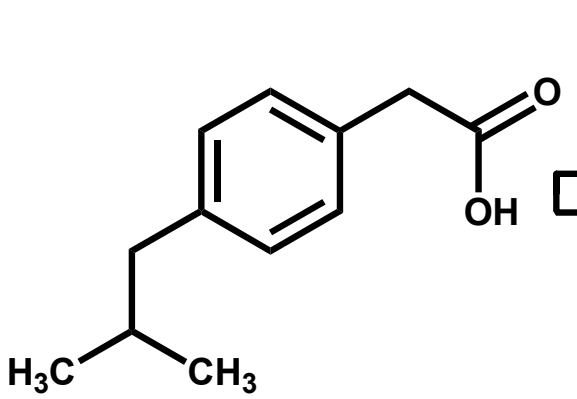
A seletividade entre COX-1 e COX-2





CM Corrêa *et al.*, *Letters in Drug Design & Discovery*, 2007, *4*, 422

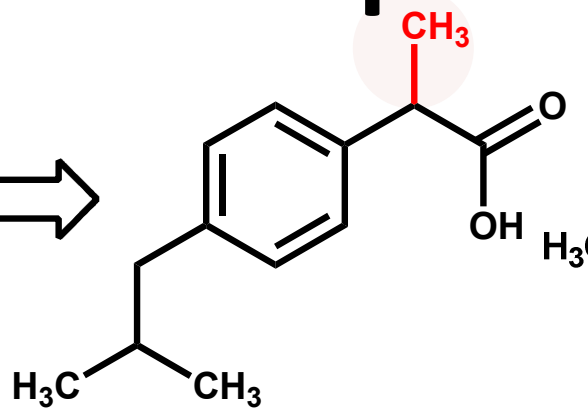
A metila e a quiralidade



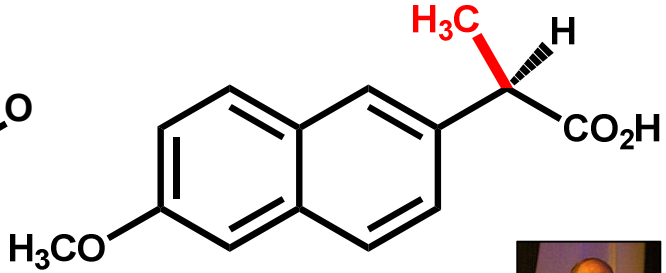
ibufenac

S Adams

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



ibuprofen
(1961)

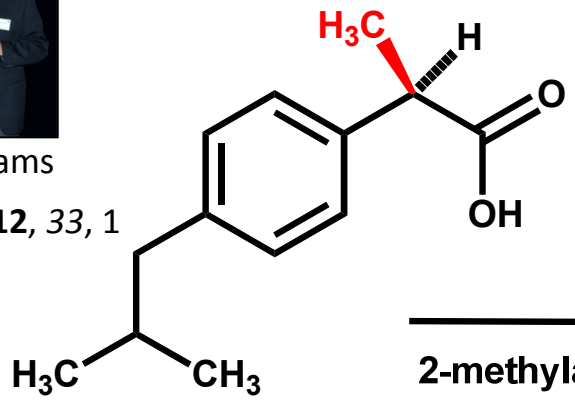


naproxen
(1976)
S(uper)-Naprosin^{R}

IT Harrison, *J Med Chem* **1970**, *13*, 203

R Noyori

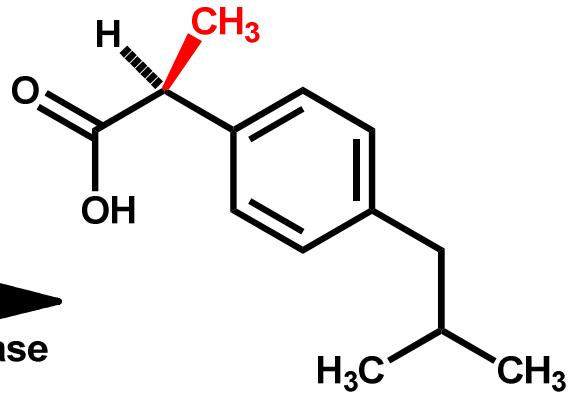
2001



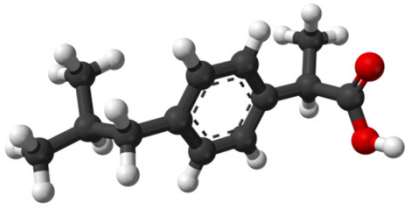
liver

2-methylacyl-CoA 2-epimerase

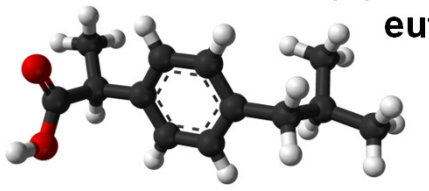
in vivo



(*R*)-ibuprofen

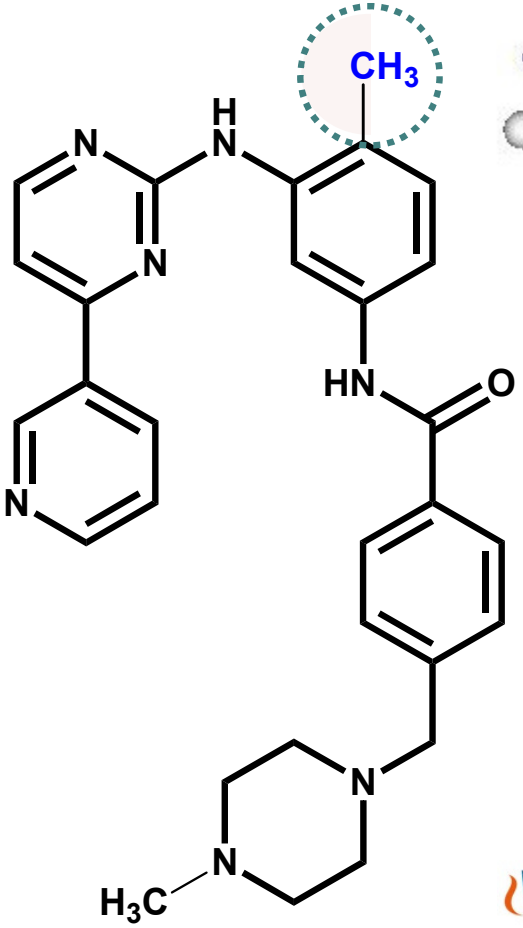


σ



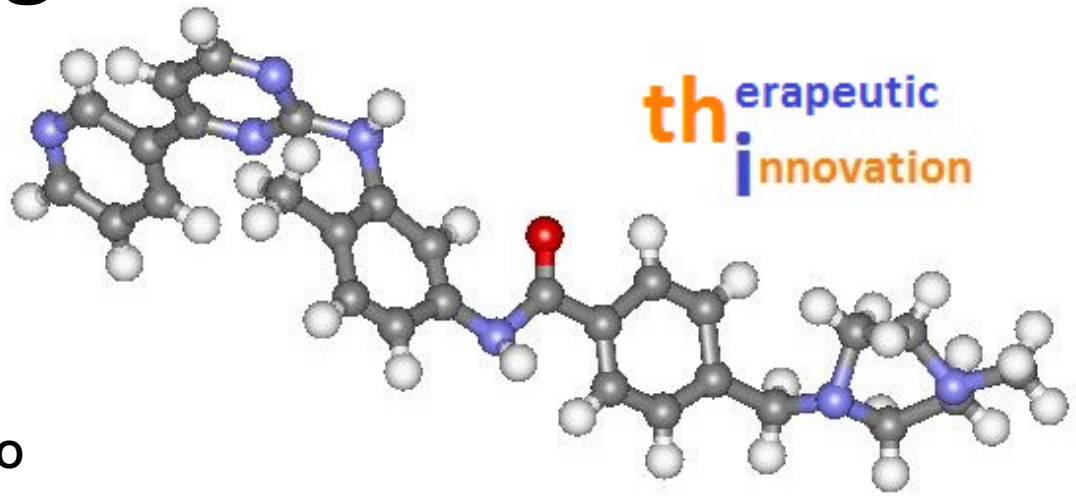
(*S*)-ibuprofen
eutômero

A metila e a gênese do imatinibe



imatinibe

2001



th erapeutic
i nnovation

NOVARTIS

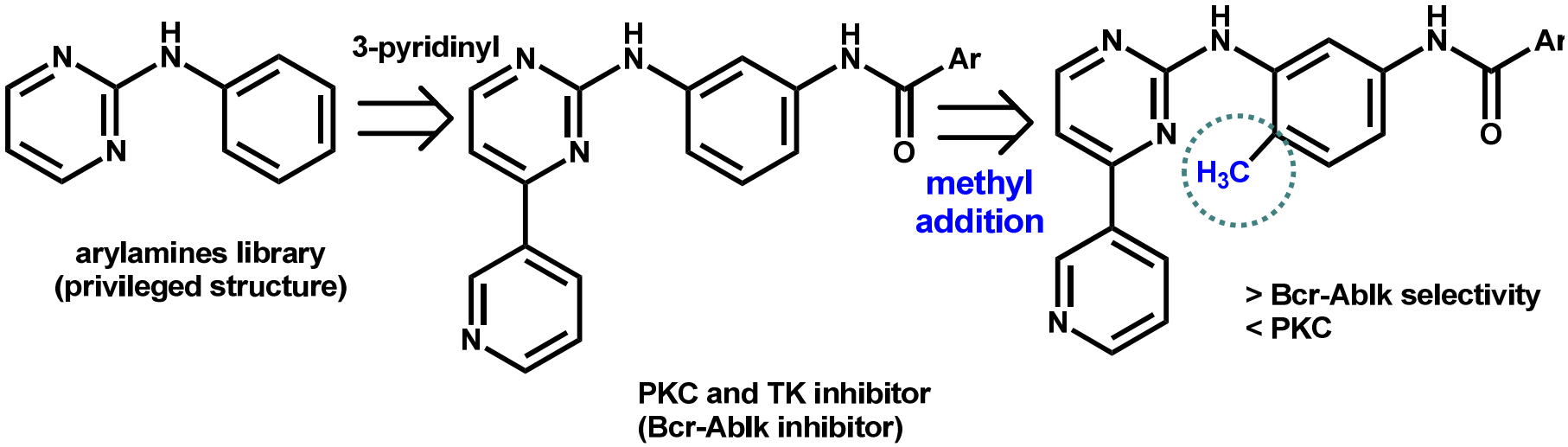
Jürg Zimmermann

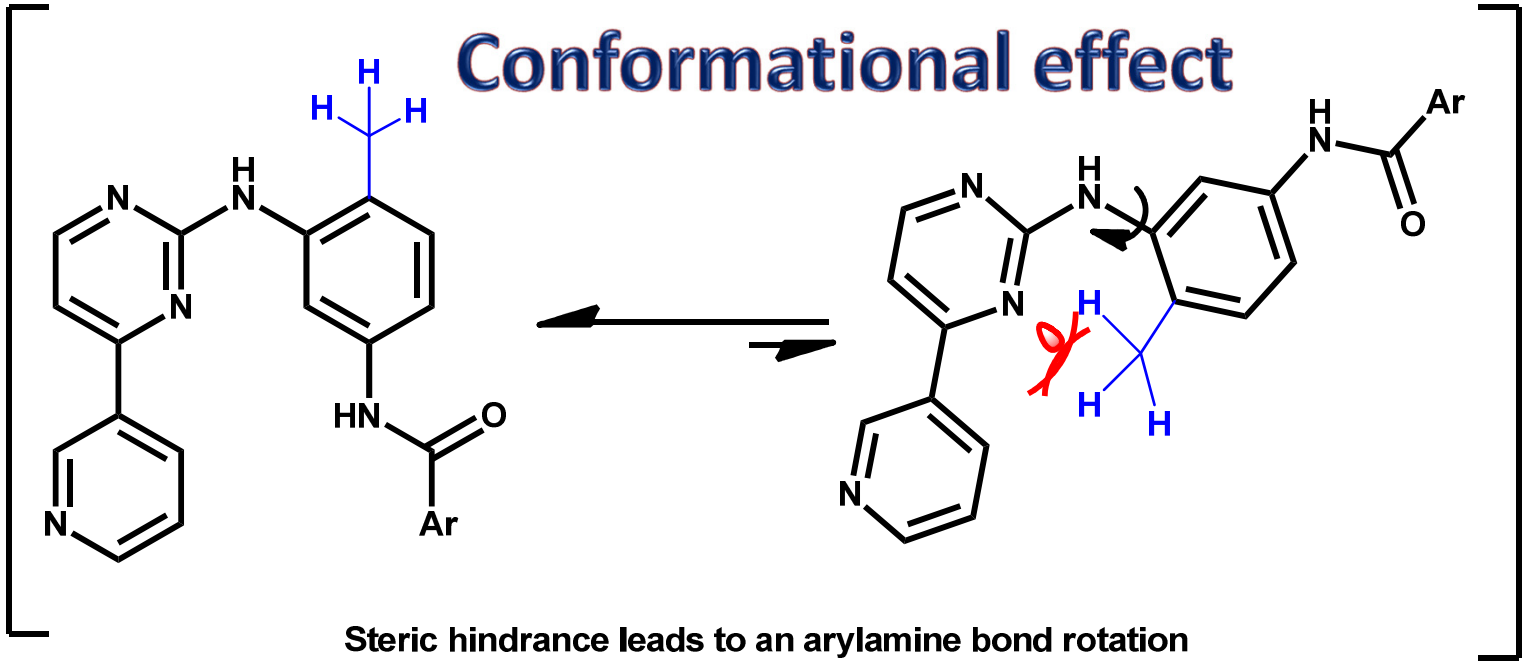
Elisabeth Buchdunger

OREGON HEALTH & SCIENCE UNIVERSITY

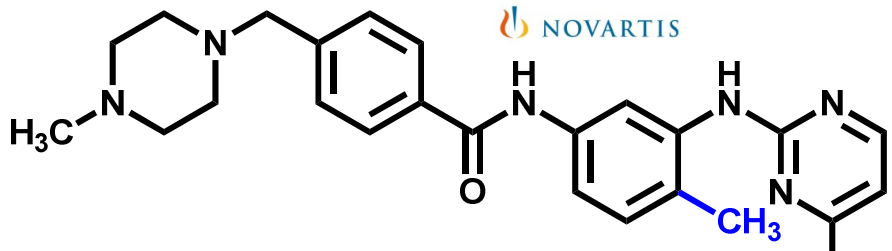
Brian J. Druker

A metila e a gênese do imatinibe



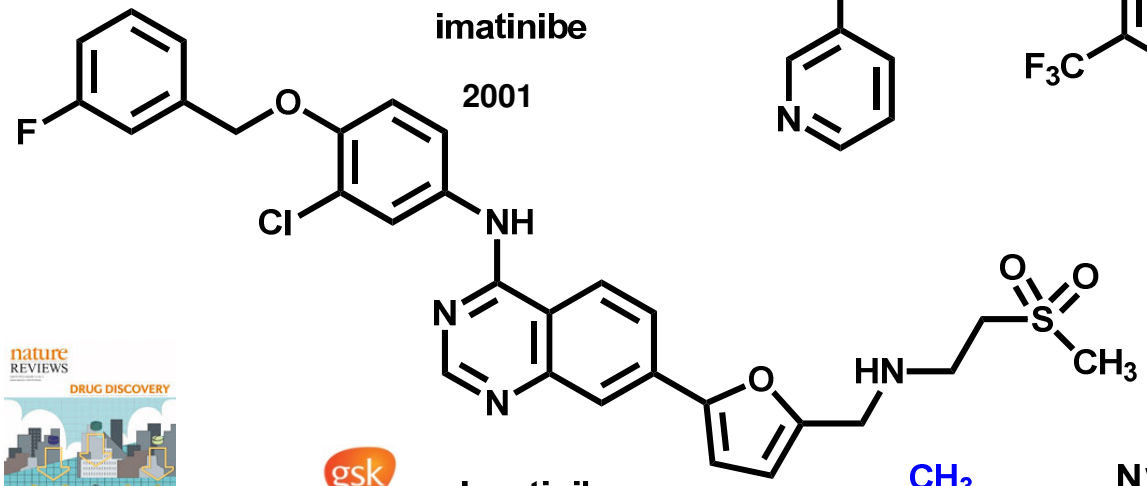


Tinibes



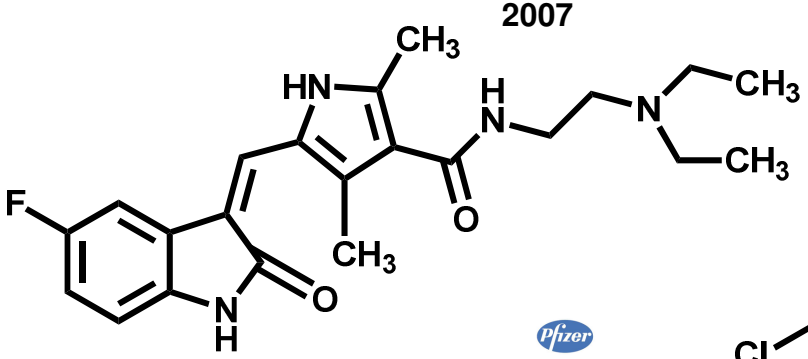
imatinibe

2001



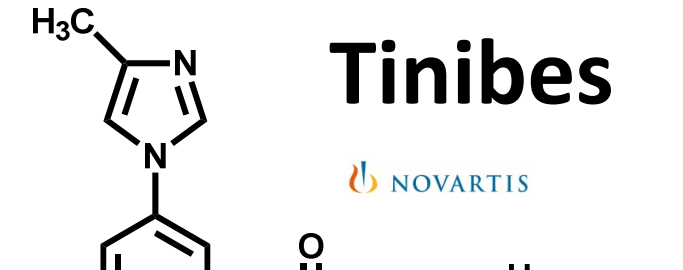
lapatinibe

2007



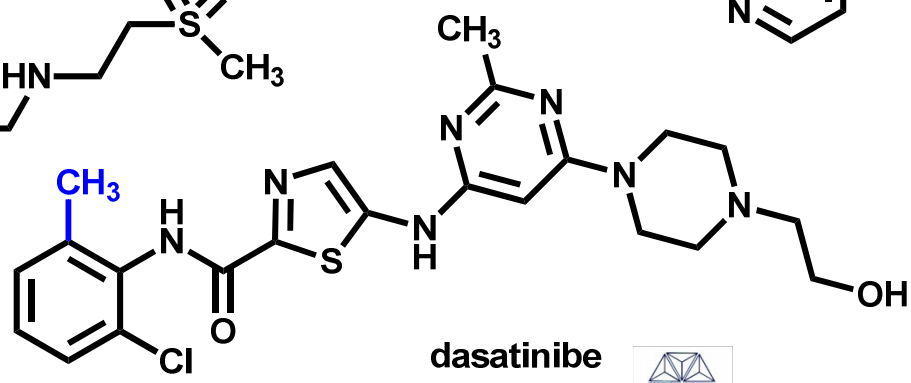
sunitinibe

2006



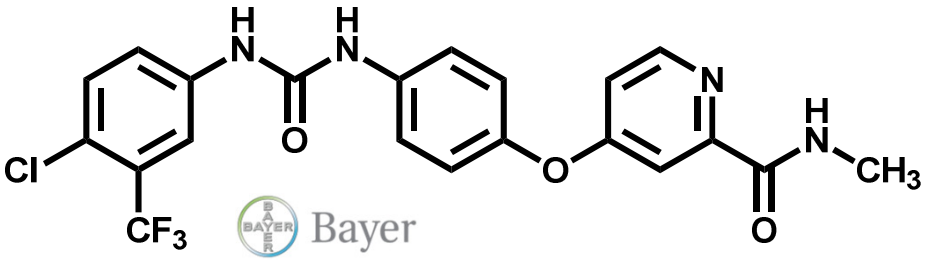
nilotinibe

2006



dasatinibe

2007



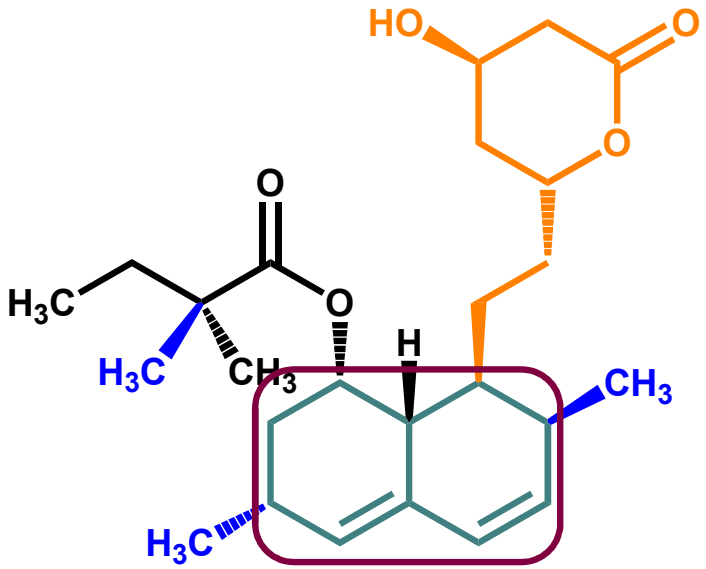
sorafenibe

2007

- 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

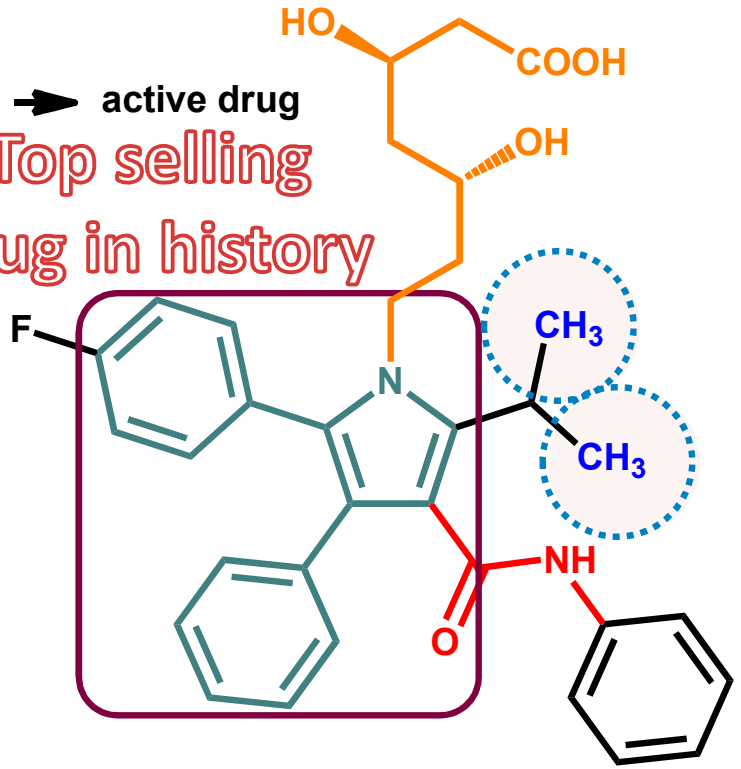
As *metilinhas* bilionárias...



simvastatin

prodrug-like → active drug

Top selling drug in history



atorvastatin

A Endo

A A Patchett

MERCK

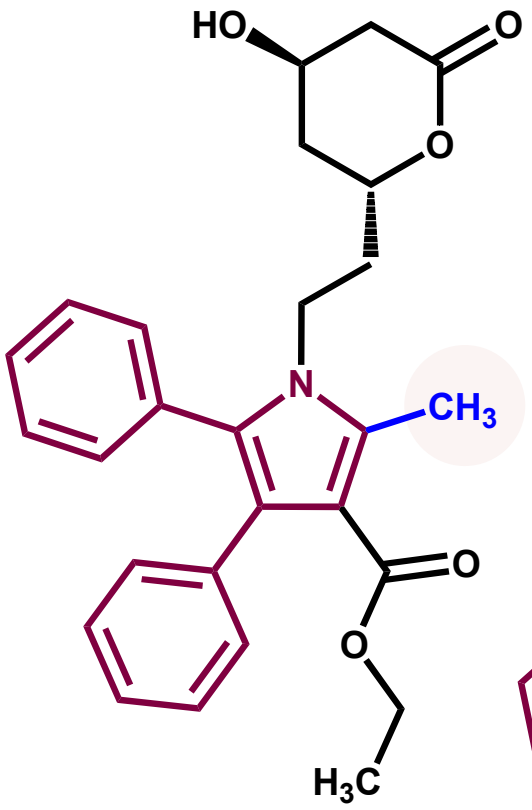
B D Roth

BD Roth, *Prog Med Chem* **2002**, *40*, 1

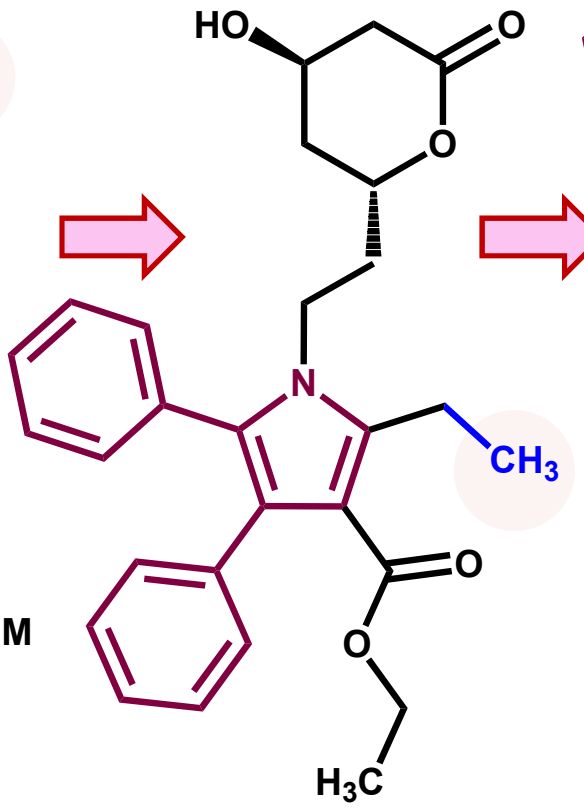
IC_{50} HMG-CoAR = 8 nM

Pfizer *blockbuster = > US$ 150 bi*

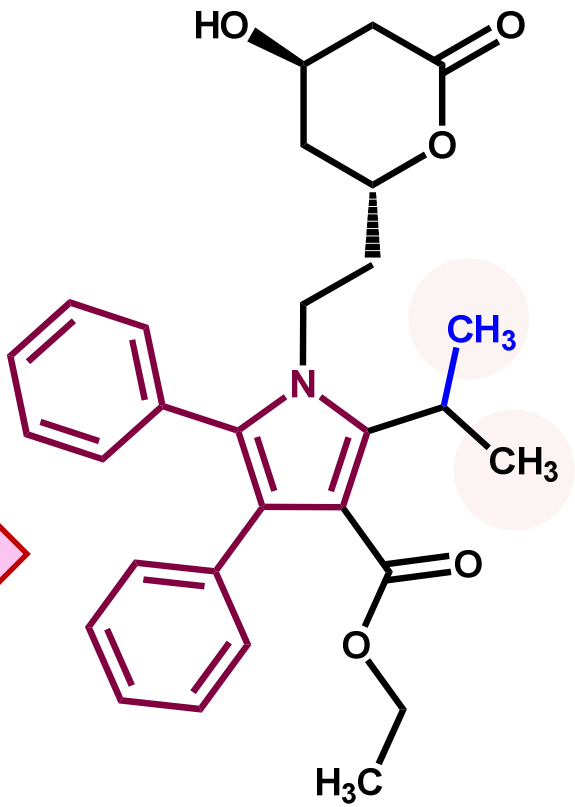
1991-2011



IC_{50} HMG-CoAR = 4000 nM



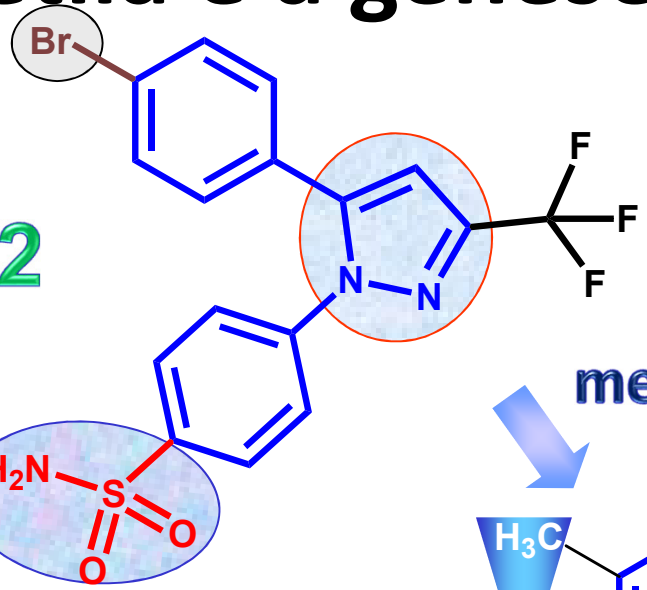
IC_{50} HMG-CoAR = 890 nM



IC_{50} HMG-CoAR = 170 nM

1 CH_3 = > US$ 4,54 bi

A metila e a gênese do celecoxibe



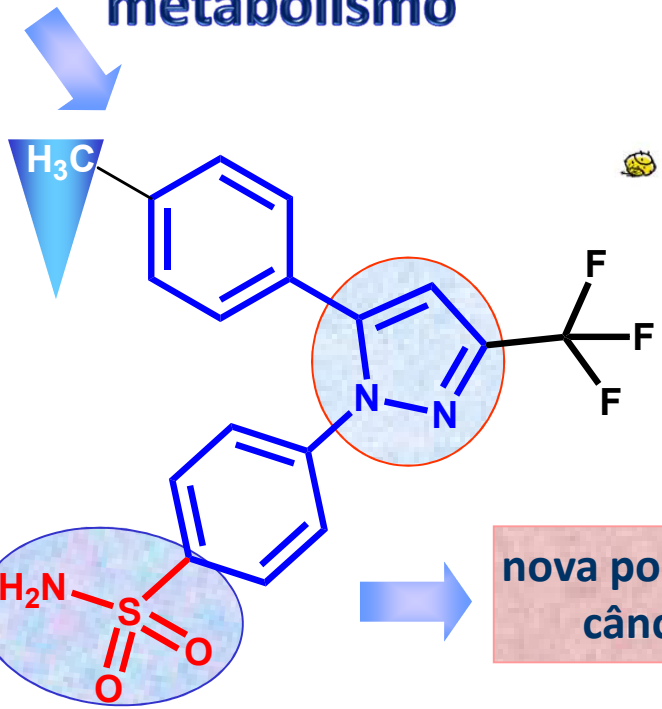
COX-2 seletivo
Searle

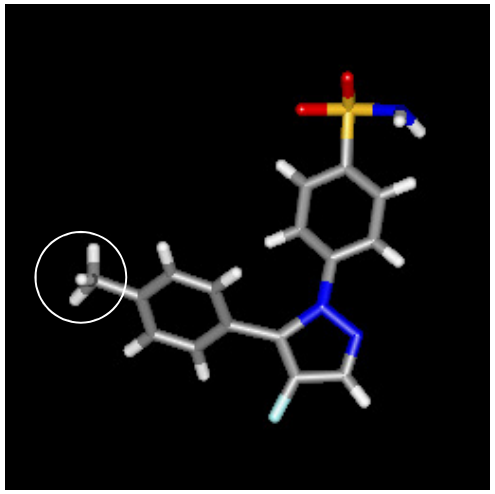
Vida-média = 12 dias !
(ADME)

Pfizer

PGHS-2

metabolismo





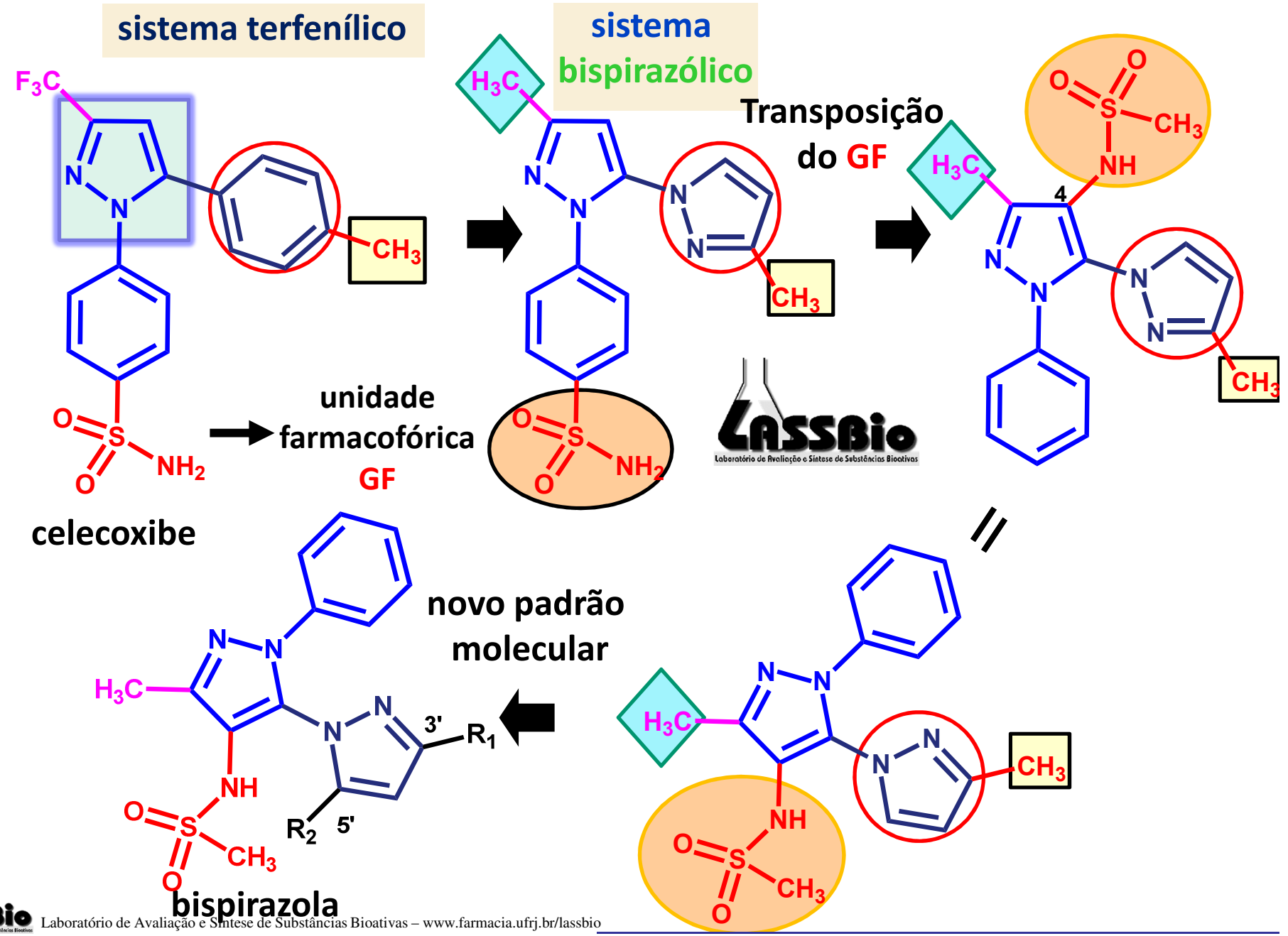
TD Penning *et al., J. Med. Chem.* **1997**, *40*,1347

Celecoxibe (SC-58634)
1999

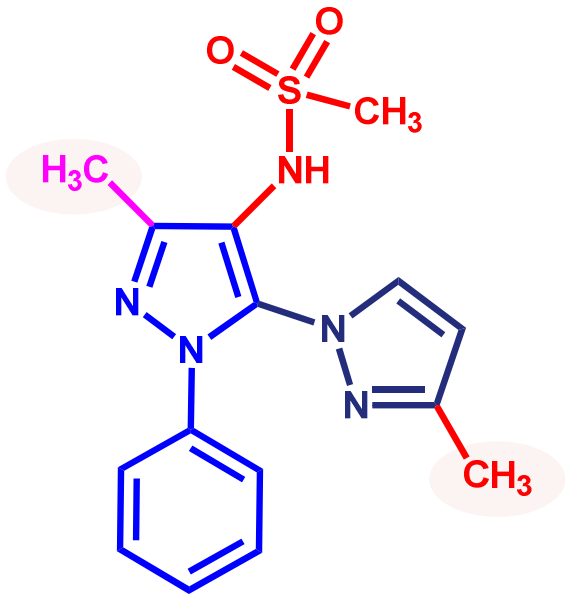
nova possível indicação: câncer coloretal

O mercado mundial de fármacos antiinflamatórios (2008) = *ca.* US$ 32 bi

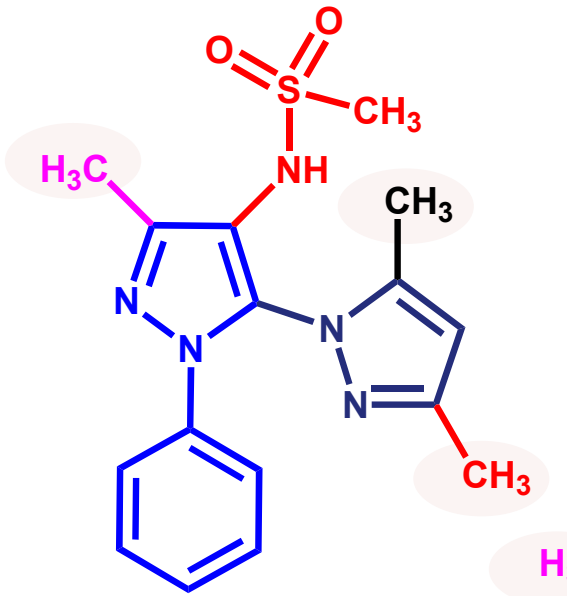
Desenho estrutural de novos COX-2i bispirazólicos

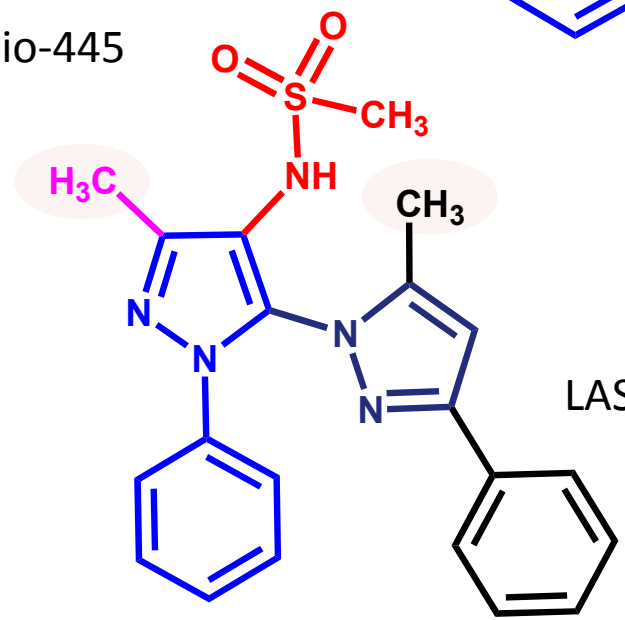


Série congênere dos novos COX-2i bispirazólicos

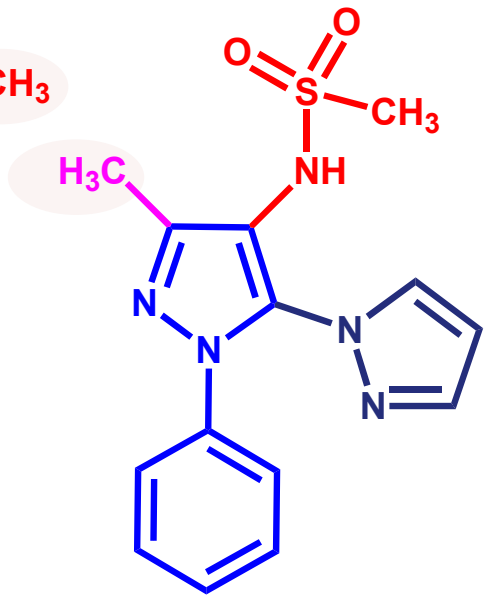


LASSBio-445



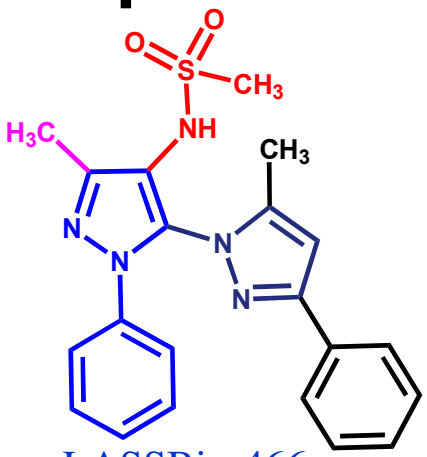


LASSBio-466

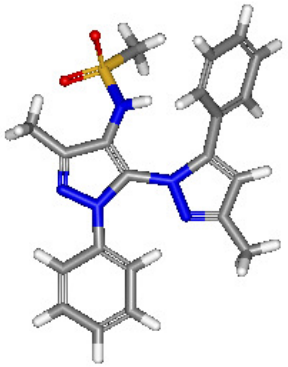


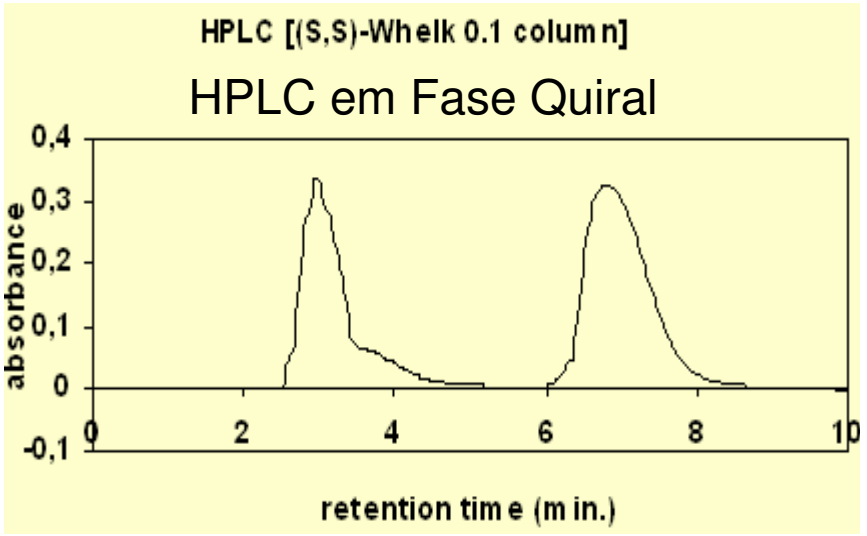
MP Veloso, Tese de Doutoramento, Instituto de Química, UFRJ, 2000

Atropoisomerismo de Derivados Bispirazólicos



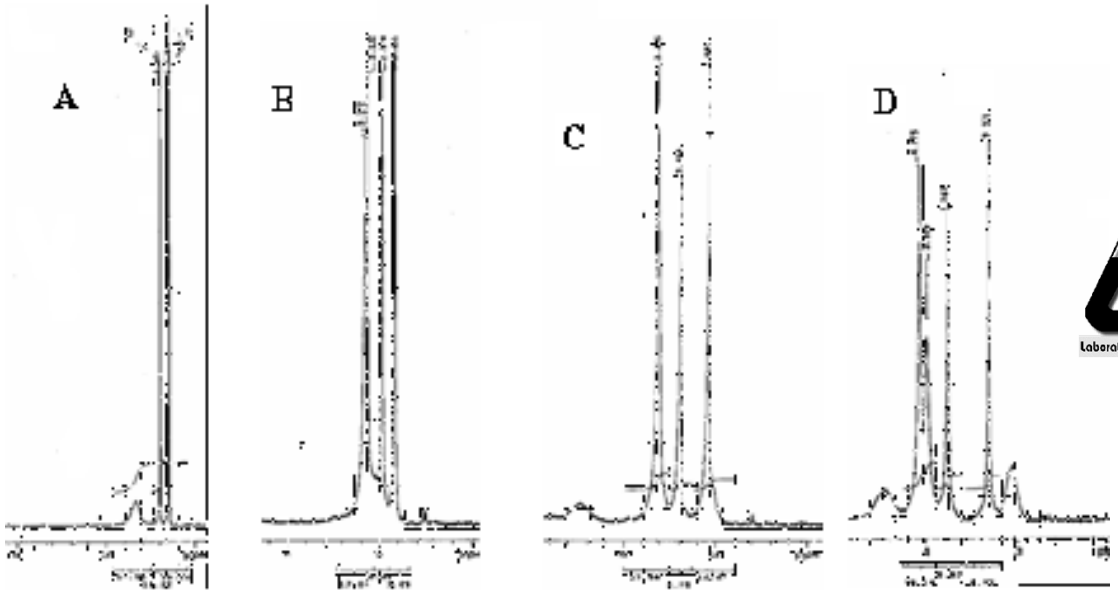
LASSBio-466





Prof. Helio M. Alves (FF-UFRJ)

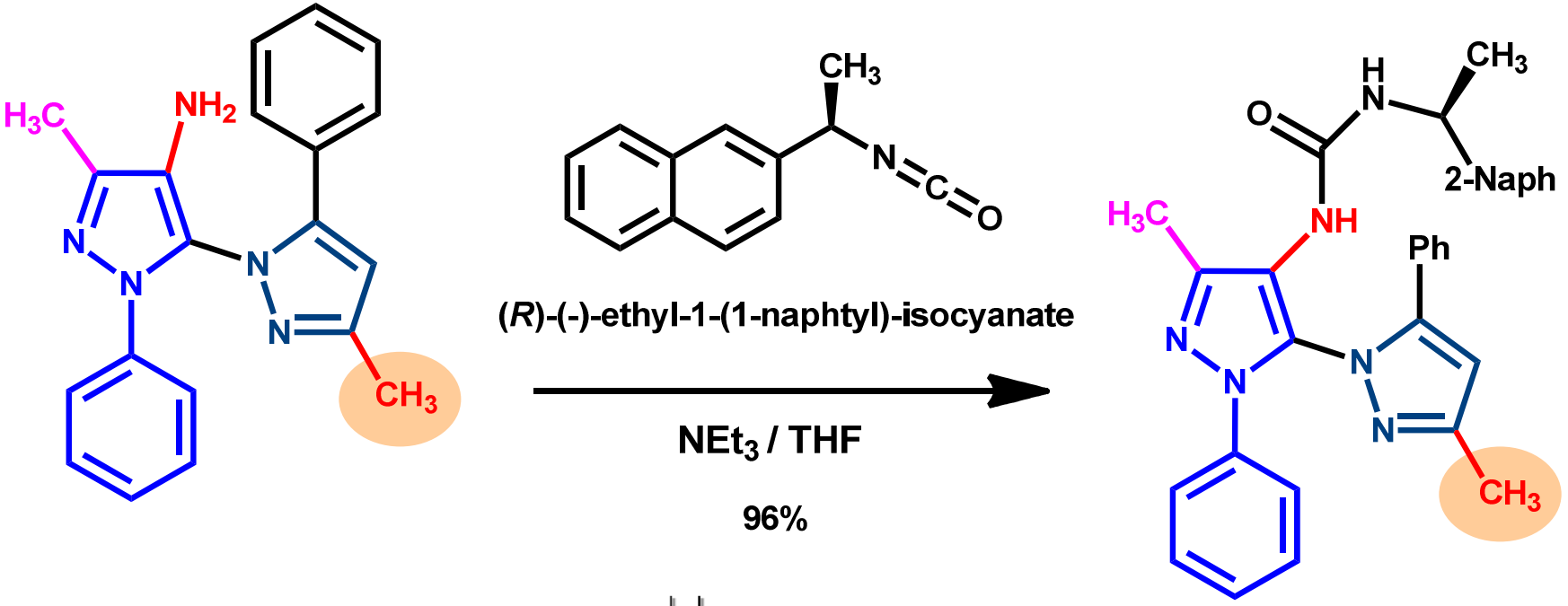
Espectro da ^{1}H-NMR na presença de concentração variável de Yb(thc)3: A = sem adição; B = adição 1; C = adição 2; D = adição 3 (concentrações crescentes)



Veloso, M. P. (2000) Tese de Doutorado, IQ-UFRJ

E. J. Barreiro *et al.* (1999) INPI PI9902960-0

Derivatização a partir da amina



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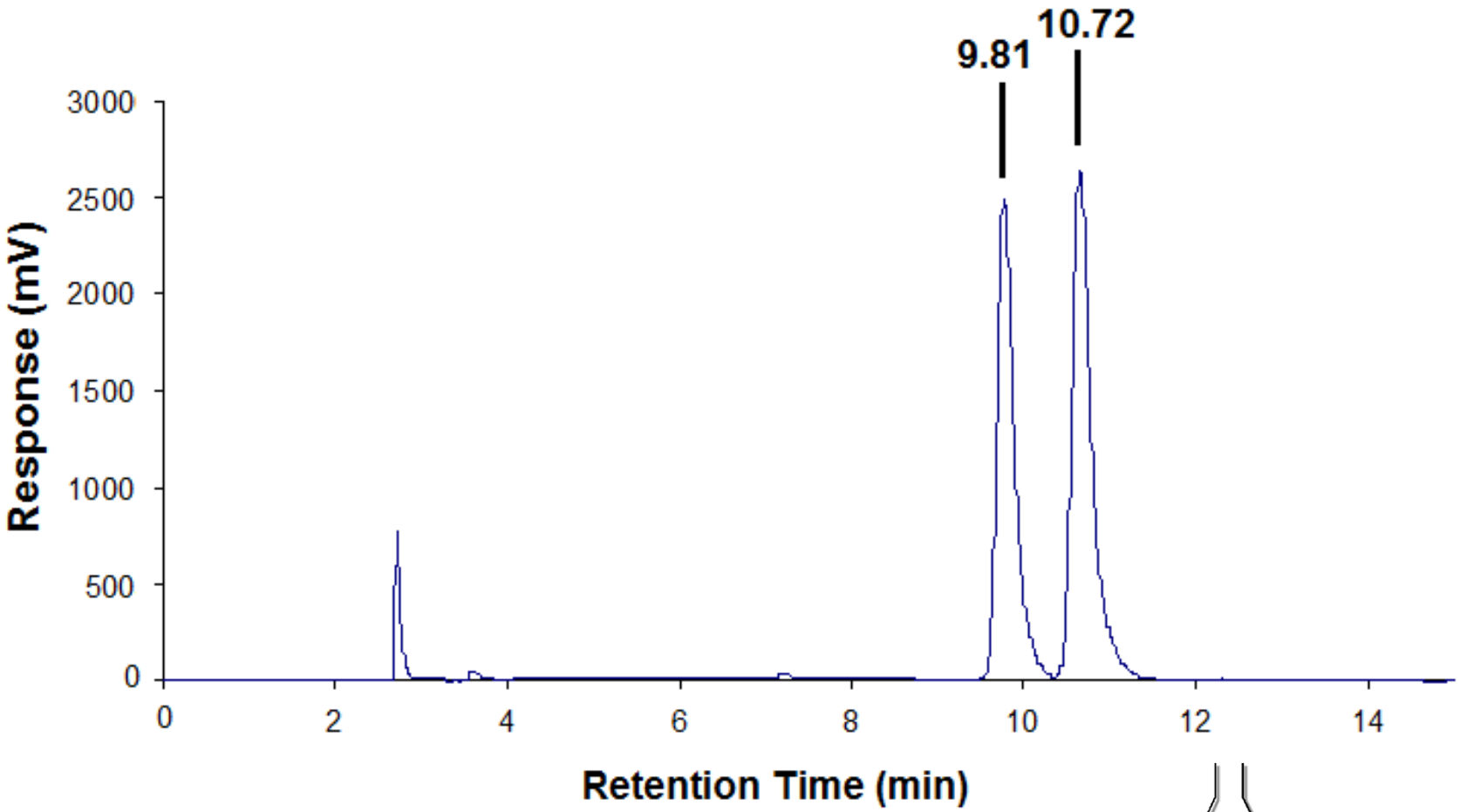
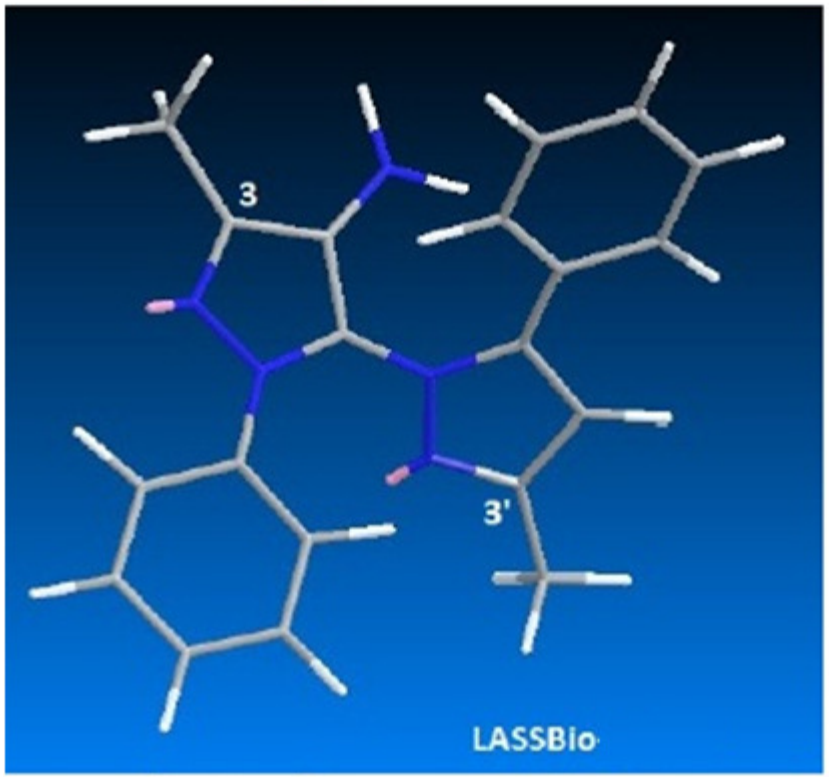
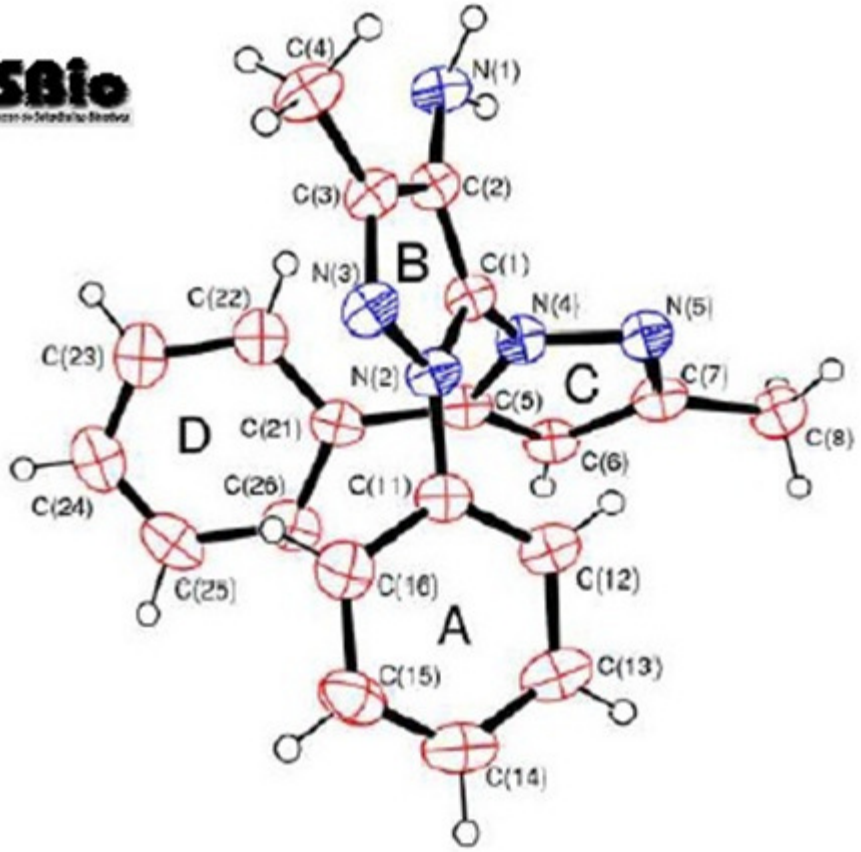


Lichosorb (N. 738342) RP-18 column (250 mm x 4 mm x 5 µm)
L-7450A diode array detector (DAD)
acetonitrile and water (adjusted to pH 3 with TFA 0.1%) gradients

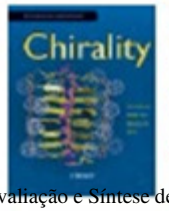
Atropoisomerismo em bispirazóis antiinflamatórios

quiral





ORTEP view of ***P***-atropisomer



MP Veloso *et al.*, Synthesis and characterization of the atropisomeric relationships of a substituted *N*-phenyl-bipyrazole derivative with Antiinflammatory properties, *Chirality* **2012**, *00*, 000.

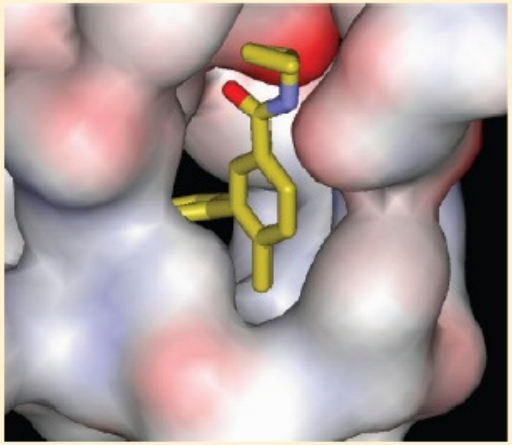
Journal of Medicinal Chemistry

Methyl Effects on Protein–Ligand Binding

Cheryl S. Leung, Siegfried S. F. Leung, Julian Tirado-Rives, and William L. Jorgensen*
Department of Chemistry, Yale University, New Haven, Connecticut 06520, United States

J. Med. Chem. **2012**, *55*, 4489

ABSTRACT: The effects of addition of a methyl group to a lead compound on biological activity are examined. A literature analysis of >2000 cases reveals that an activity boost of a factor of 10 or more is found with an 8% frequency, and a 100-fold boost is a 1 in 200 event. Four cases in the latter category are analyzed in depth to elucidate any unusual aspects of the protein–ligand binding, distribution of water molecules, and changes in conformational energetics. The analyses include Monte Carlo/free-energy perturbation (MC/FEP) calculations for methyl replacements in inhibitor series for p38α MAP kinase, ACK1, PTP1B, and thrombin. Methyl substitutions *ortho* to an aryl ring can be particularly effective at improving activity by inducing a propitious conformational change. The greatest improvements in activity arise from coupling the conformational gain with the burial of the methyl group in a hydrophobic region of the protein.



The importance of methyl groups in modulating biological activity for small molecules is well documented.[1] Consistent with this, the most fundamental change in structure–activity studies is replacement of a hydrogen atom by a methyl group.

(1) Barreiro, E. J.; Kummerle, A. E.; Fraga, C. A. M. The Methylation Effect in Medicinal Chemistry. *Chem. Rev.* **2011**, *111*, 5215–5246.

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