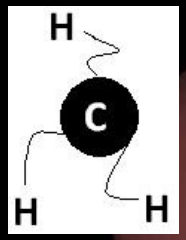
As *peripécias* do grupamento metila na Química Medicinal



Dr 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

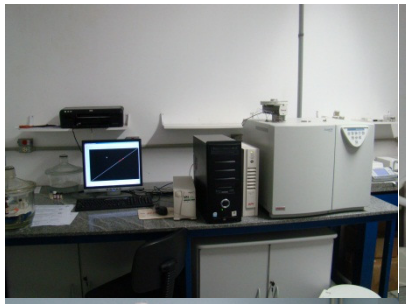
(INCT-INOFAR)

www.inct-inofar.ccs..ufrj.br

Universidade Federal do Rio de Janeiro

Cidade Universitária, ilha do Fundão,
Rio de Janeiro, BR

Laboratório de Avaliação e Síntese de Substâncias Bioativas



LASSBio Criado em 19/04/1994; Vide a história em http://eib-eliezer.blogspot.com.br

Peripécias

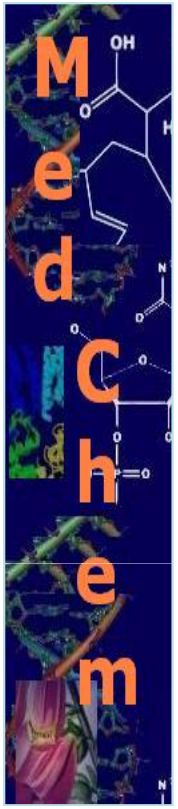
Grande Dicionário
Houaiss
da língua portuguesa

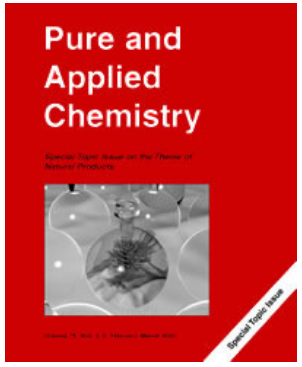
Subst. fem.

- que altera o curso dos acontecimentos, de maneira inesperada,
- modifica a situação e o modo de agir dos personagens ;

Uso informal:
acontecimento inesperado, imprevisto

IUPAC - Subcommittee Medicinal Chemistry & Drug Development

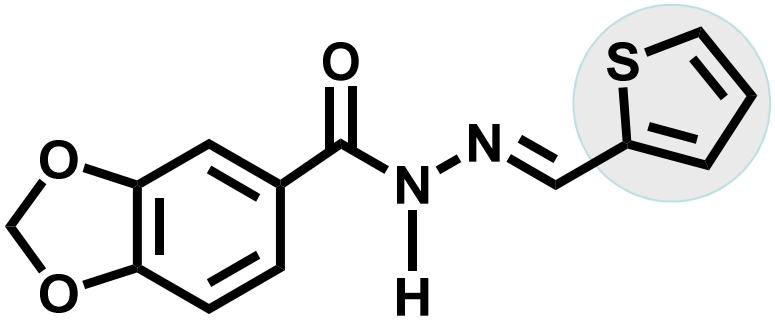




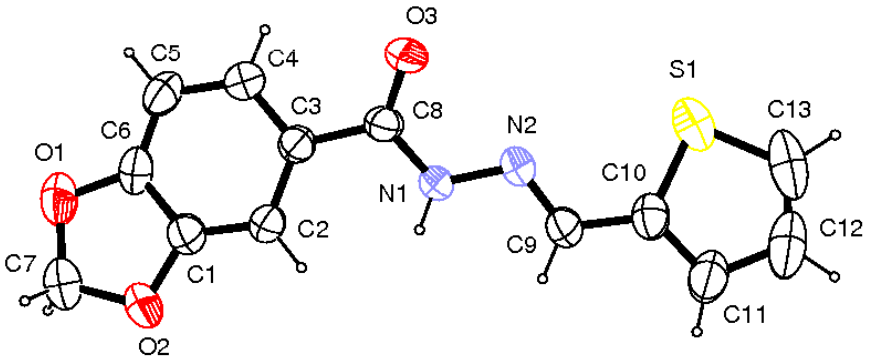
Química Medicinal é a *disciplina* que estuda aspectos **relacionados** à *descoberta* ou *invenção* de **fármacos**, seus aspectos moleculares envolvidos no mecanismo de ação e aqueles que governam a ***a****bsorção*, ***d****istribuição*, ***m****etabolismo*, ***e****liminação* e ***t****oxicidade* (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.



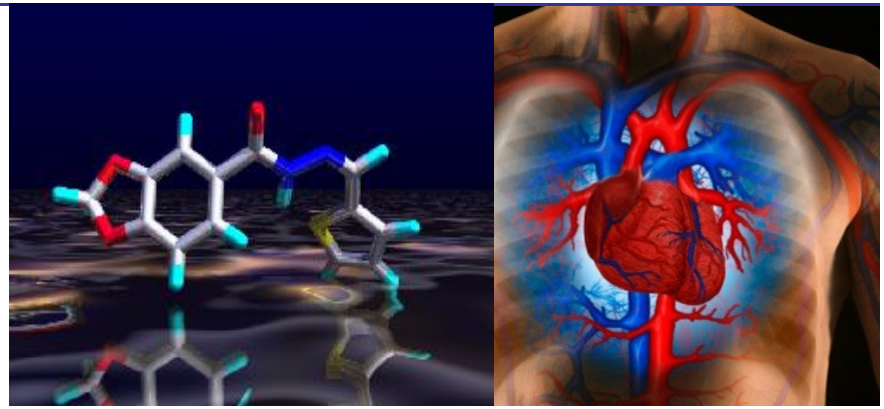
LASSBio-294

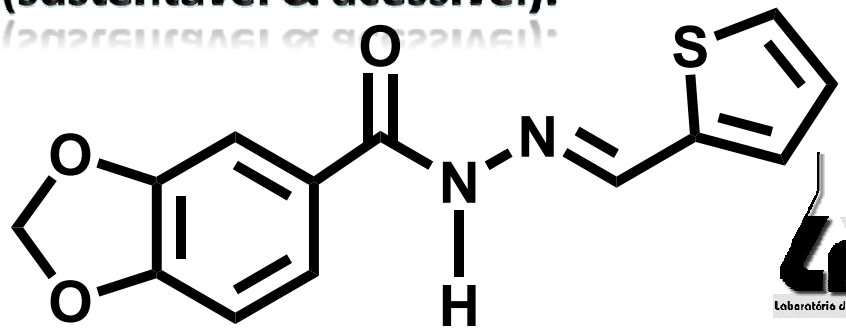


Conformação “grampo-de-cabelo”

Representa uma inovação terapêutica no tratamento de insuficiência cardíaca;

Derivado estruturalmente simples, sinteticamente acessível em ótimos rendimentos , em escala 20 M, a partir de matéria-prima natural abundante (sustentável & acessível).





LASSBio-294

Autêntico protótipo de fármaco cardioativo, com potentes propriedades inotrópicas, vasodilatadoras & neuroprotetoras; estabilidade química e metabólica & biodisponibilidade adequada;

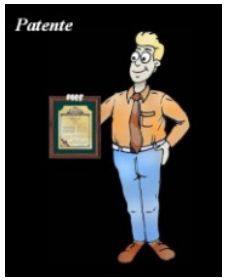
Ativo *p.o.* por novo mecanismo de ação;

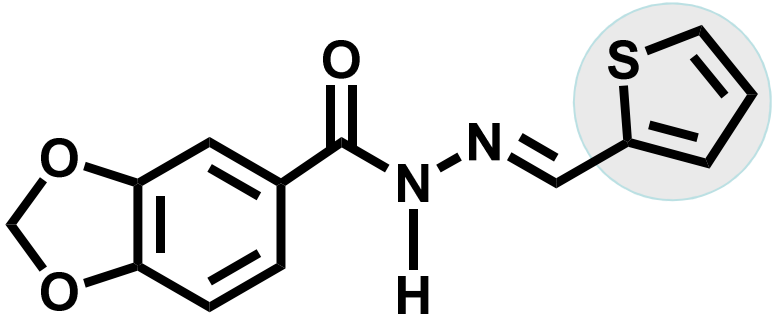
sem cito-, embrio- & genotoxicidade.

Possíveis indicações terapêuticas

Cardiopatias severas; hipertensão

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





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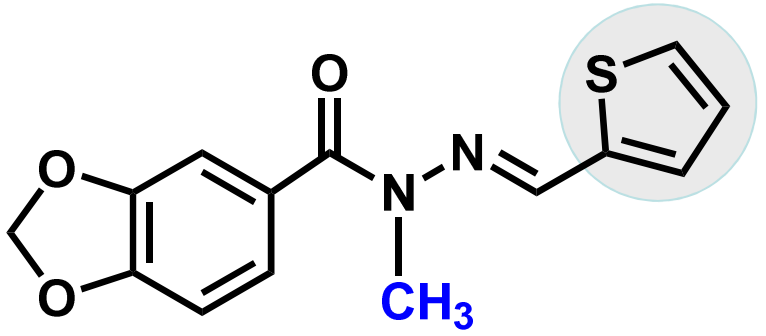
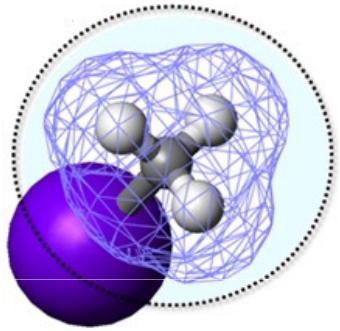


LASSBio-785

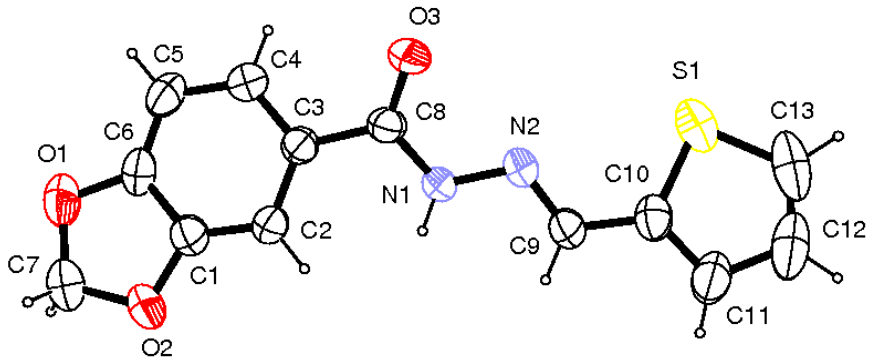


metila

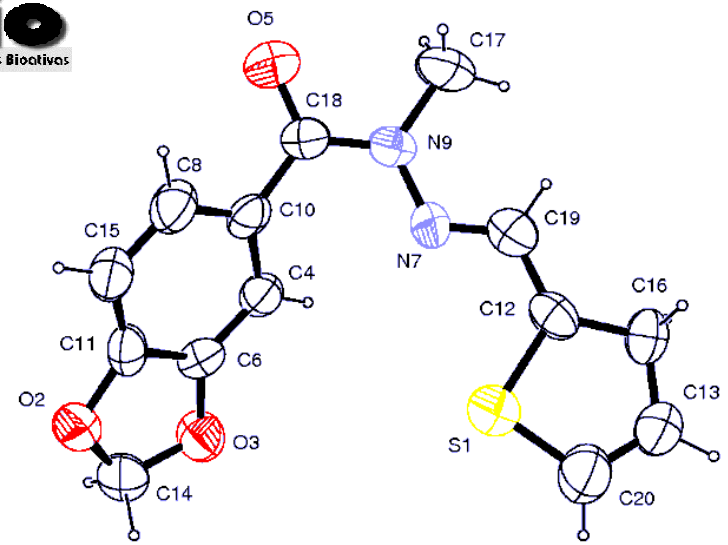
+ *N*-CH_3

Química Medicinal

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas



Conformação "grampo-de-cabelo"



Conformação em "U"

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CH_3

15 Da

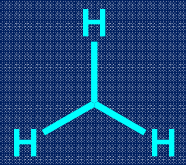
C-H μ = 0,4 D

δ^+ / R^+

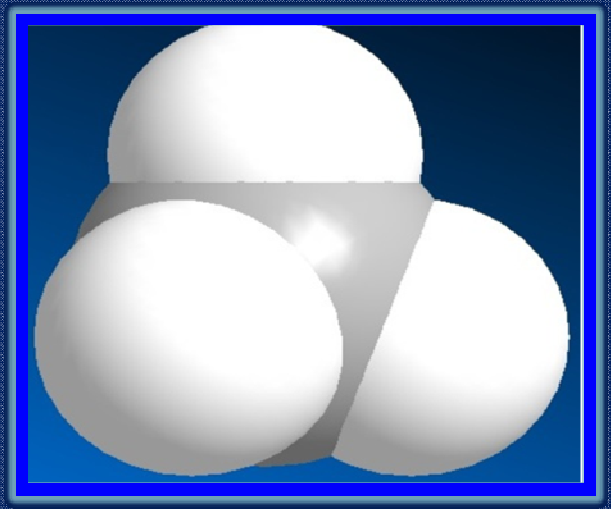
P =0,22

σ_{meta} = 0,51 / σ_{para} = 0,52

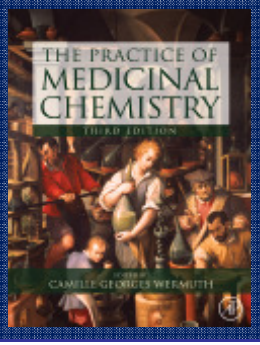
Rekker const = 0,702



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



Camille G. Wermuth



Química Medicinal

CHEMICAL REVIEWS

Chem. Rev. 2011, 111, 5215–5246

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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dx.doi.org/10.1021/cr200060g

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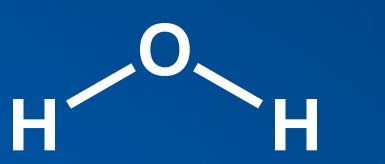
Laboratório de Avaliação e Síntese de Substâncias Bioativas

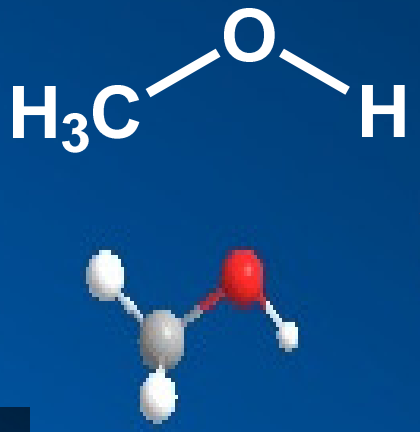
Esta será a narrativa...

Série homóloga

água

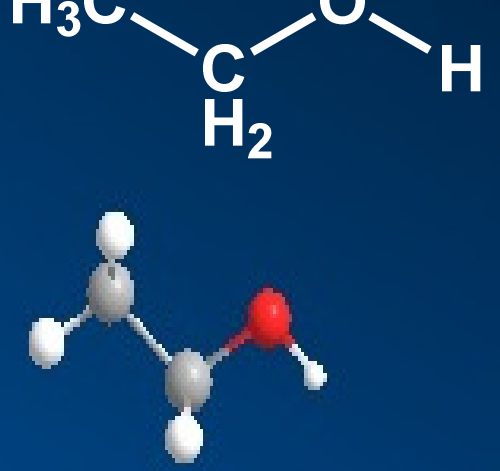


metila



metanol

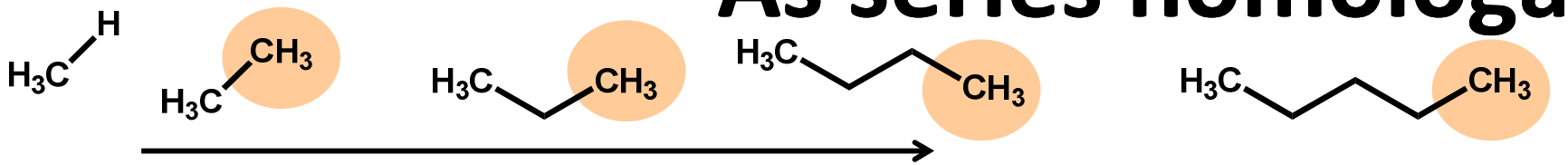
éter metílico



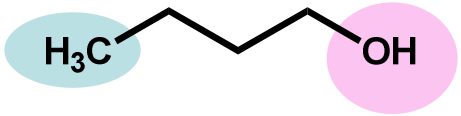
etanol

A homologia do carbono...

As séries homólogas

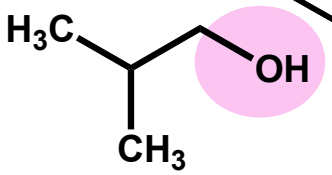


Lipofilicidade



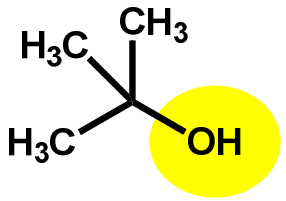
n-butanol

solubility in water
8.2g/100g



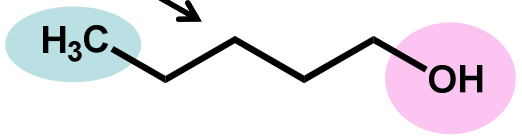
*iso*butanol

solubility in water
12,5 g/100g



tert-butanol

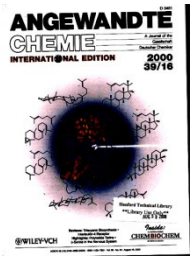
solubility in water
miscible

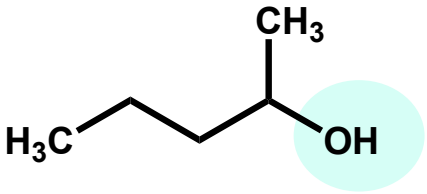


n-pentanol

solubility in water
2.4g/100g

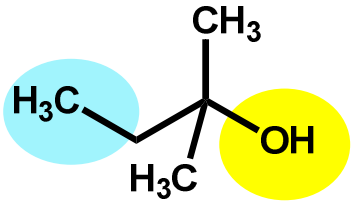
G Némethy, *Angew Chem Int Ed Engl* **1967**, *6*, 195





2-pentanol

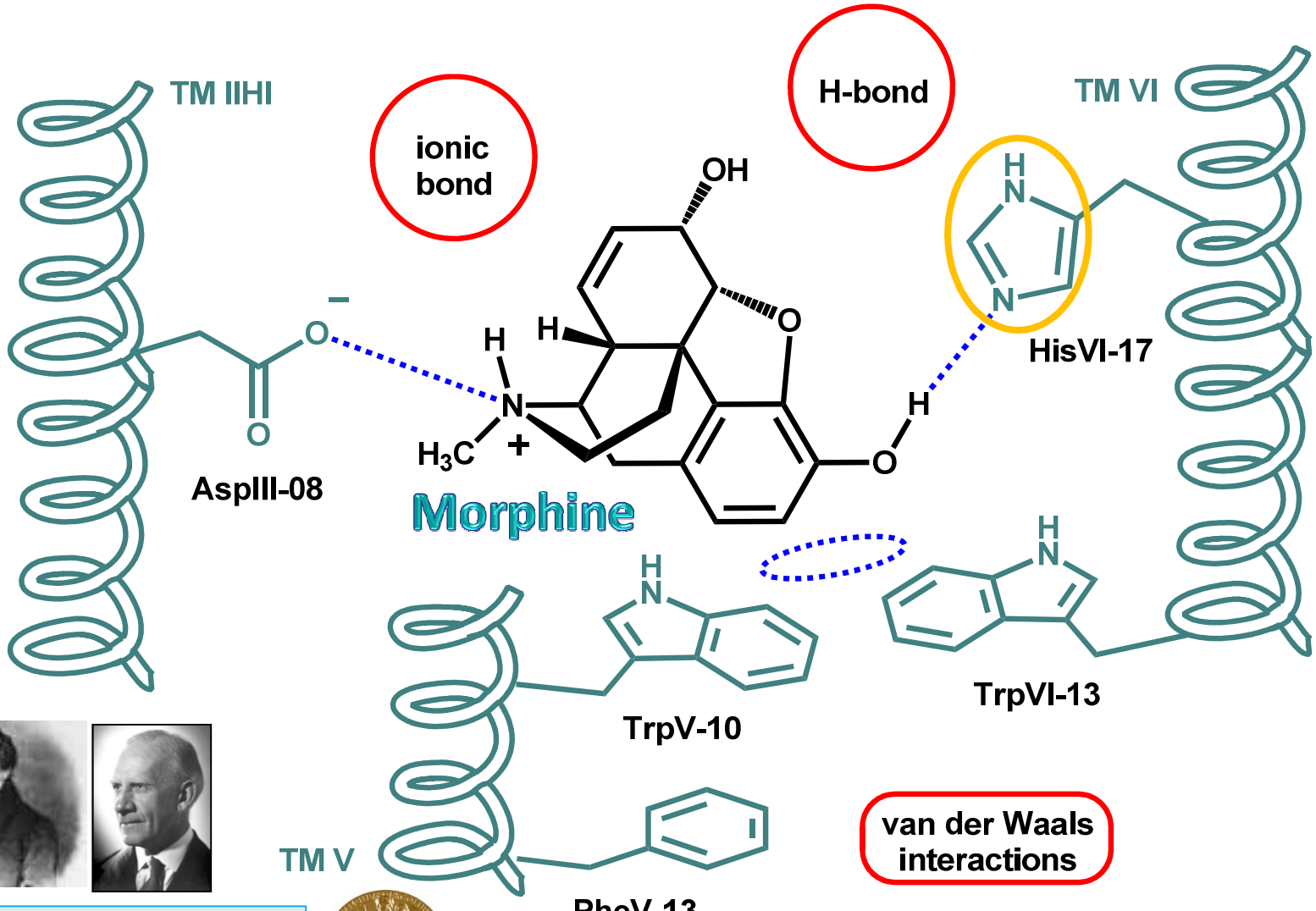
solubility in water
4.9g/100g



*neo*pentanol

solubility in water
12.2g/100g

A *metila* na natureza...



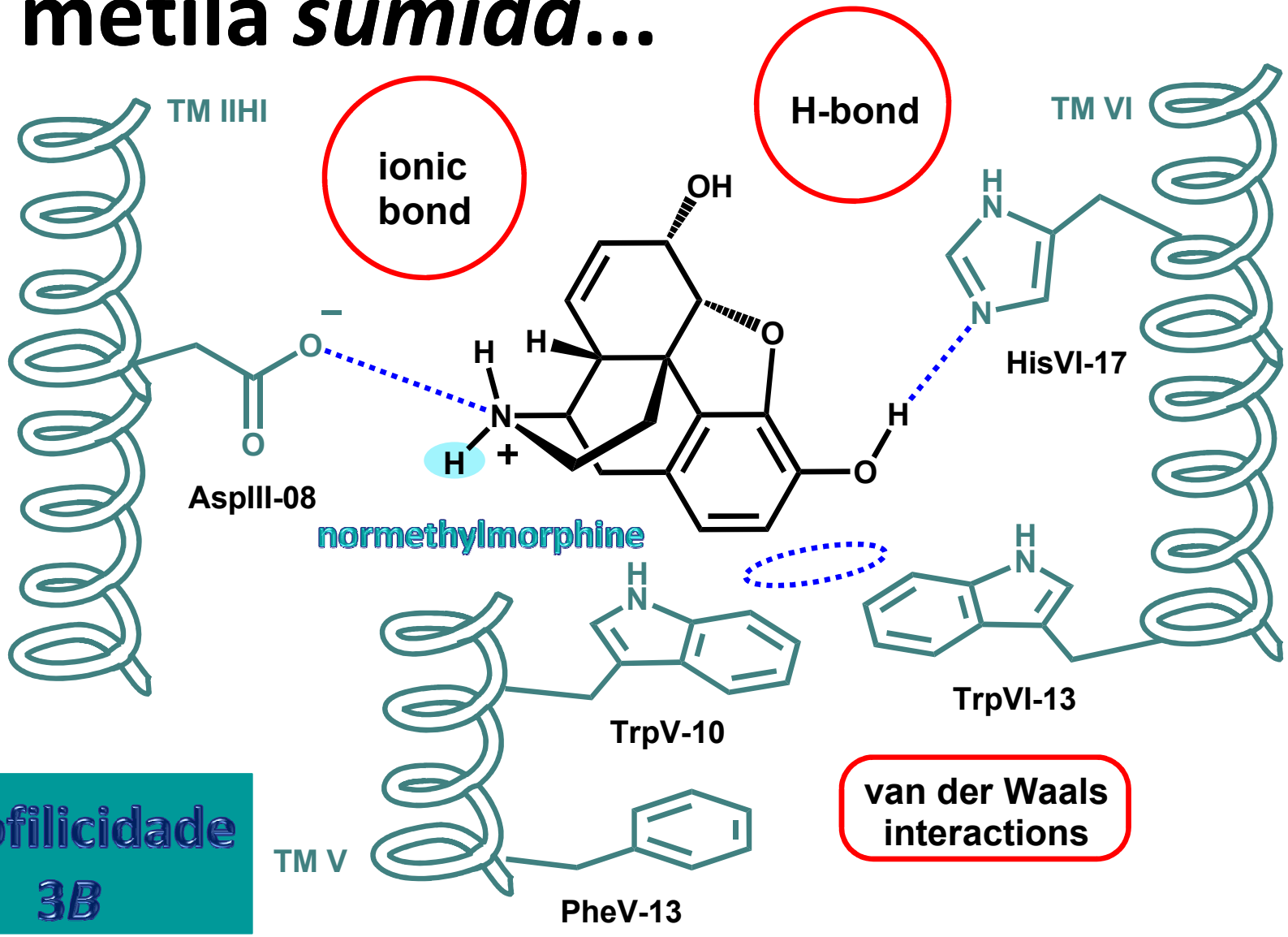
1805 - F. Setürner
1925 – R. Robinson

1947

morphine

ED_{50} = 4.8 mg/kg

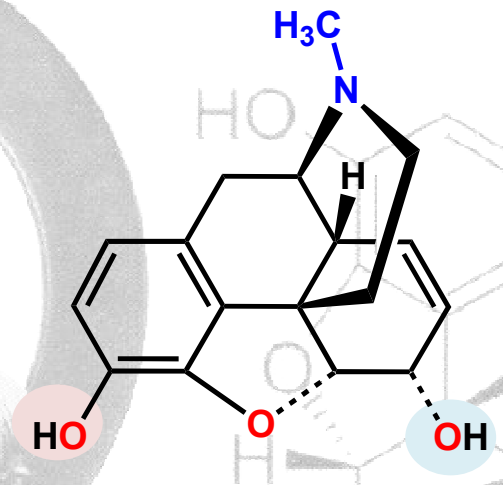
A metila *sumida*...



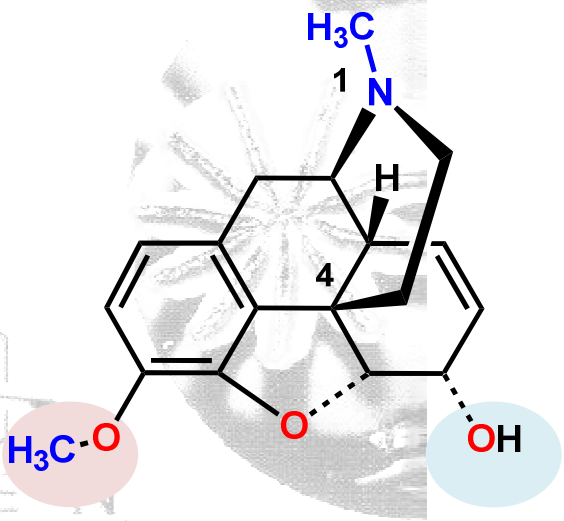
Lipofilicidade 3B

As *travessas* metilas *na* morfina...

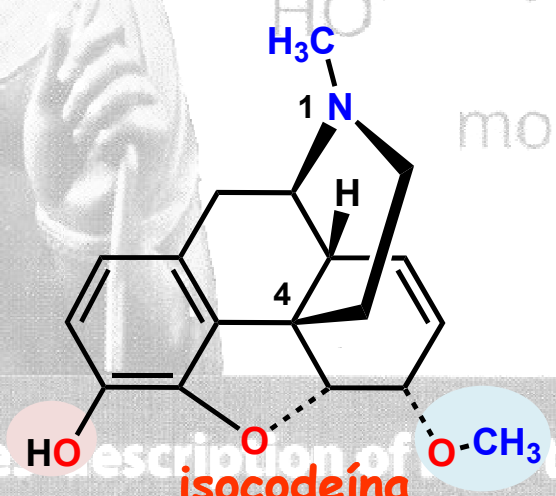
Índice de atividade analgésica



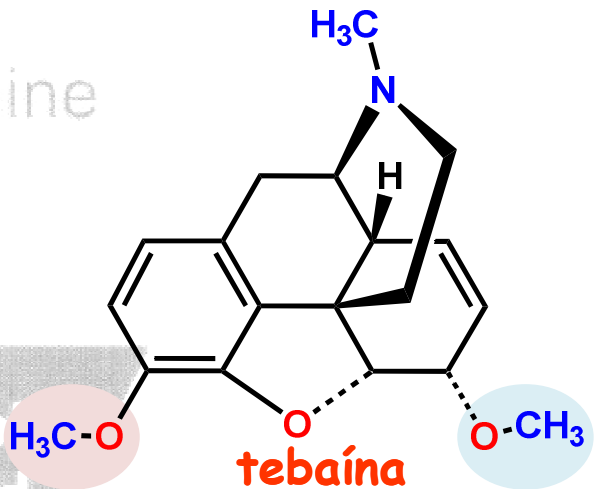
morfina
100



codeína
18



isocodeína
25

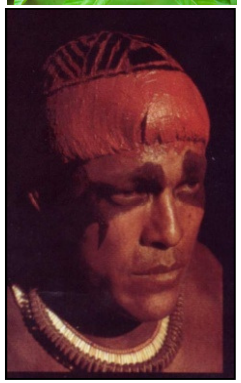


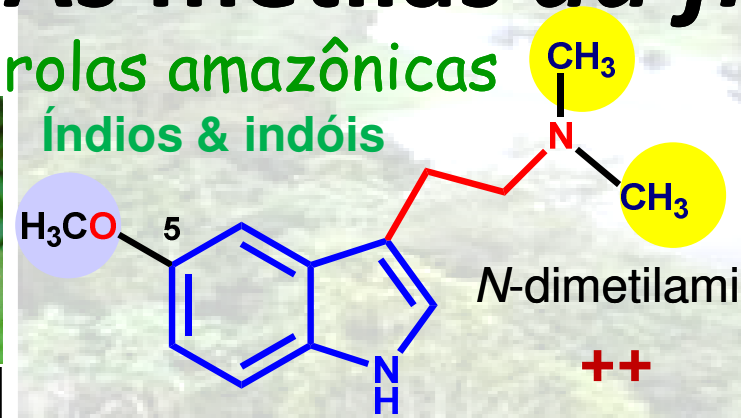
tebaína
0*

As metilas *da floresta*...

Virolas amazônicas

Índios & indóis

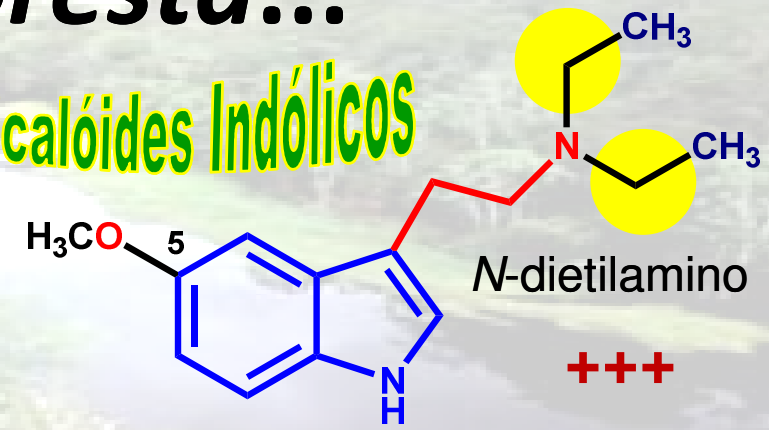




N-dimetilamino

++

Alcalóides Indólicos



N-dietilamino

+++

Indolil-alquilaminas

efeitos alucinogênicos

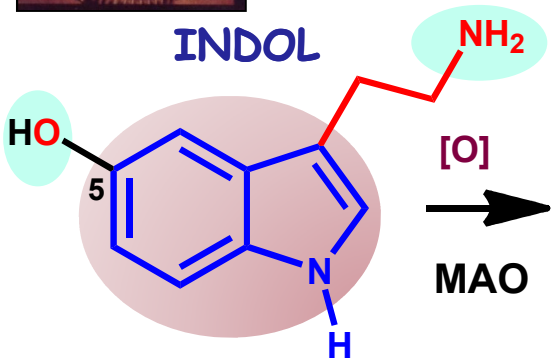
3 metilas

Similaridade molecular

N-dimetilomólogo

Ácido 5-hidroxi-3-indolilacético

INDOL

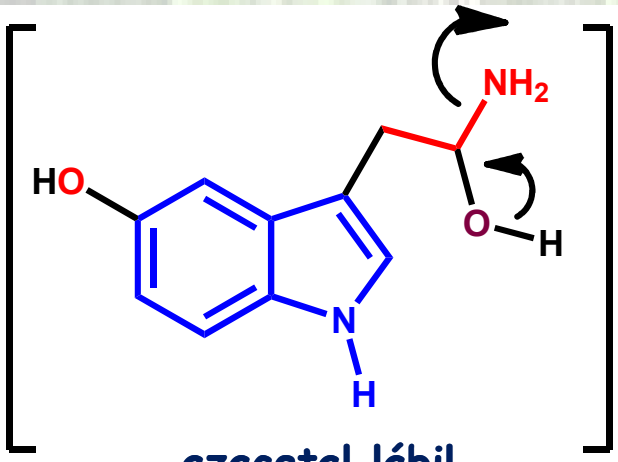


Serotonina

5-hidróxi triptamina

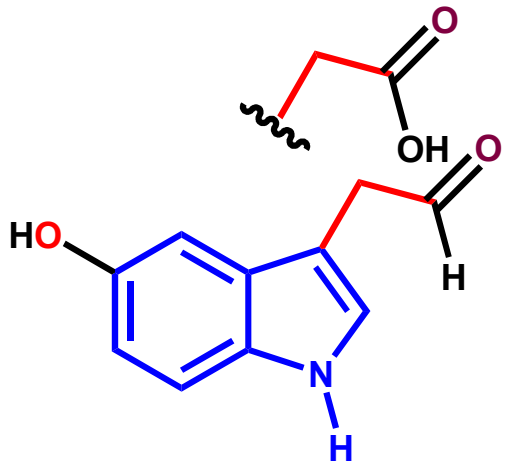
[O]

MAO



azacetal lábil

[O]

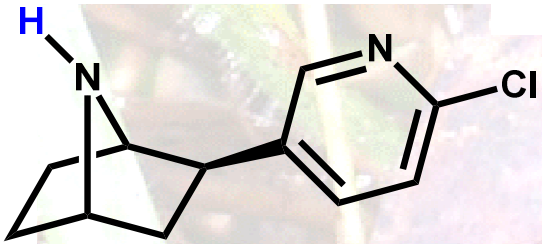


5-hidróxi-3-indolil acetaldeído

A metila *temperamental*...

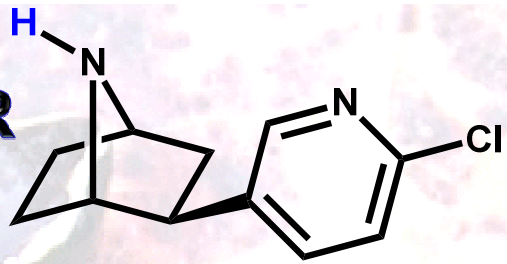
Epipedobates tricolor

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



(-)-epibatidina (natural)

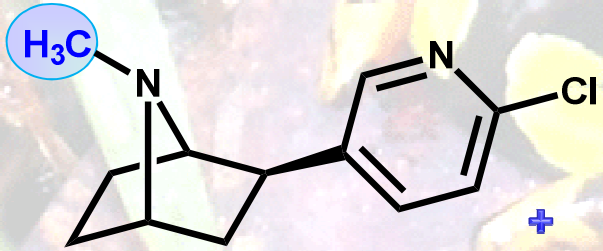
nAChR



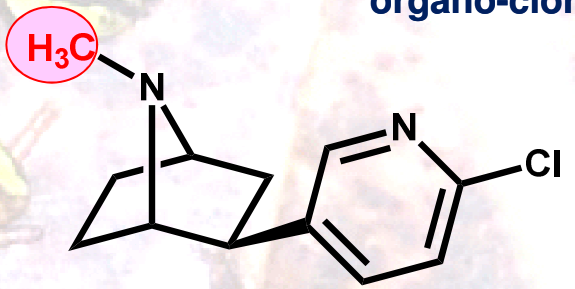
(+)-epibatidina

Primeiro quimiotipo natural: 7-azabiciclo[2.2.1]heptano

Primeiro alcalóide organo-clorado.



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



(+)-*N*-metilepibatidina

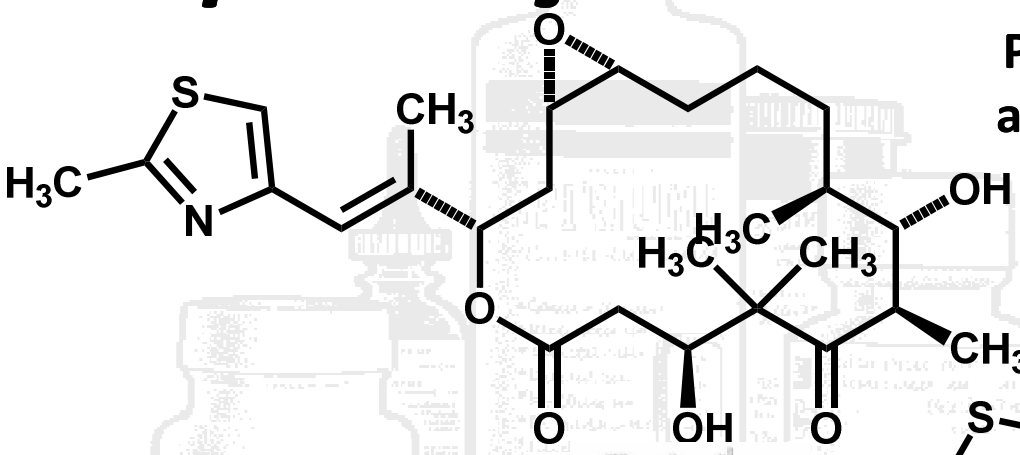
100-200 X mais analgésico que a morfina!

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

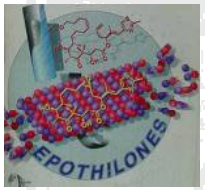
Editorial, *J Nat Prod* **2010**, *73*, 300

A *presença* da metila...



Primeiro macrociclo de 16 membros aprovado para tratamento do câncer metástatico de mama

Inibidor de microtúbulo

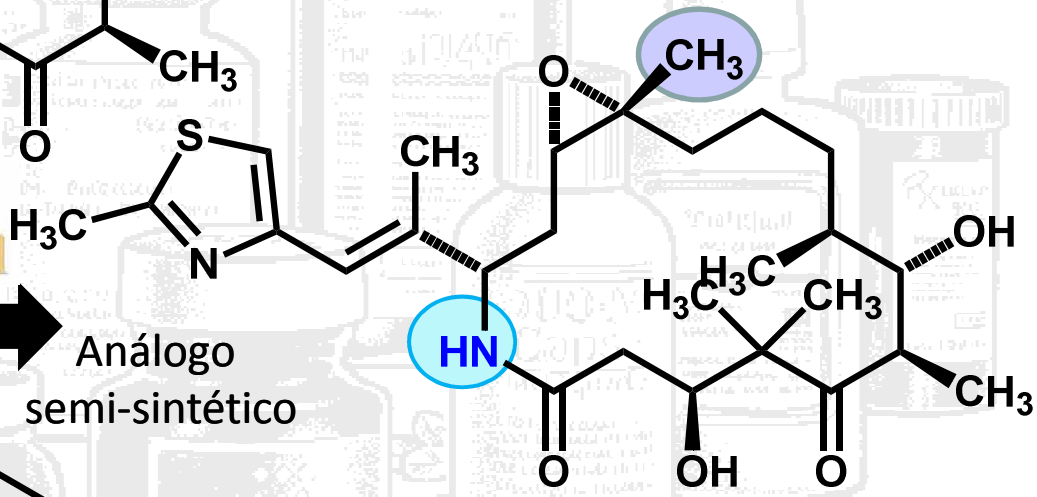


Epotilona-A

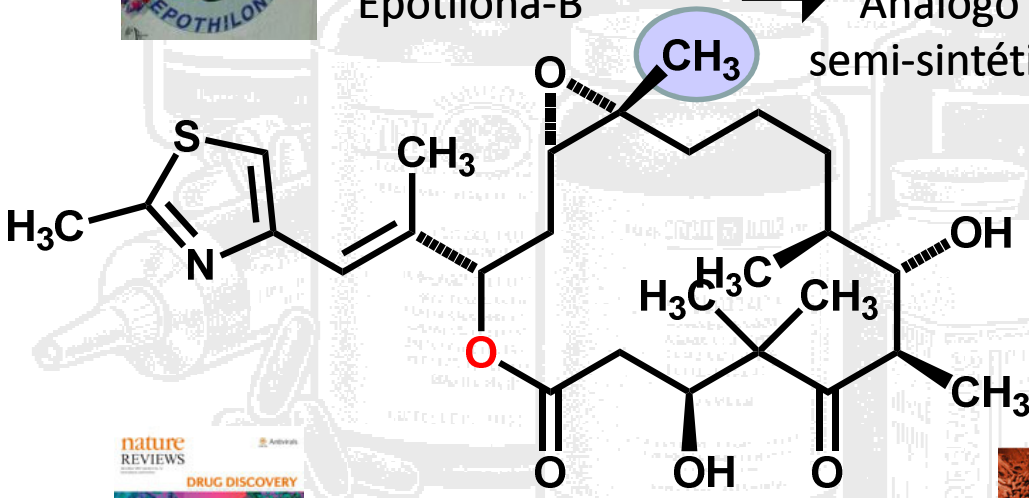
1993

Epotilona-B

Química Medicinal



Análogo semi-sintético

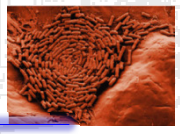


Ixabepilona

Ixempra^{R}

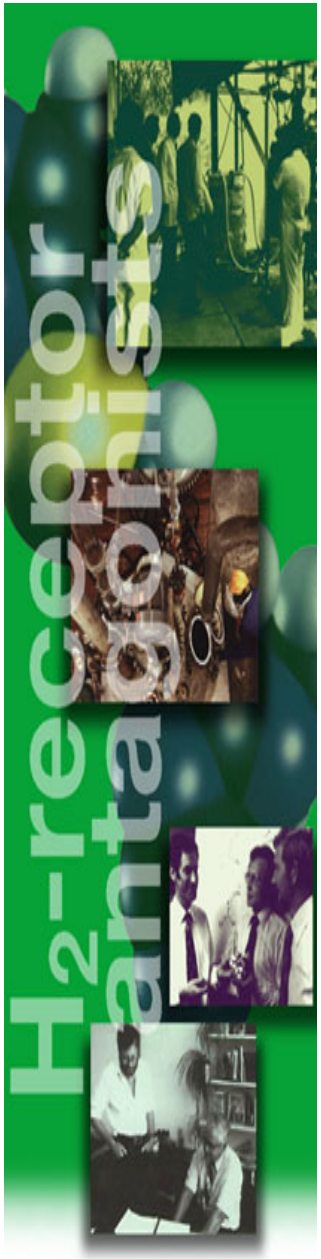
BMS, 2007

Isoladas de *Sorangium cellulosum*



Via fermentativa bacteriana, ativo em células taxano-R

A Conlin, M Fornier, C Hudiis, S Kar, P. Kirkpatrick, *Nat. Rev. Drug Discov.* **2007**, *6*, 953



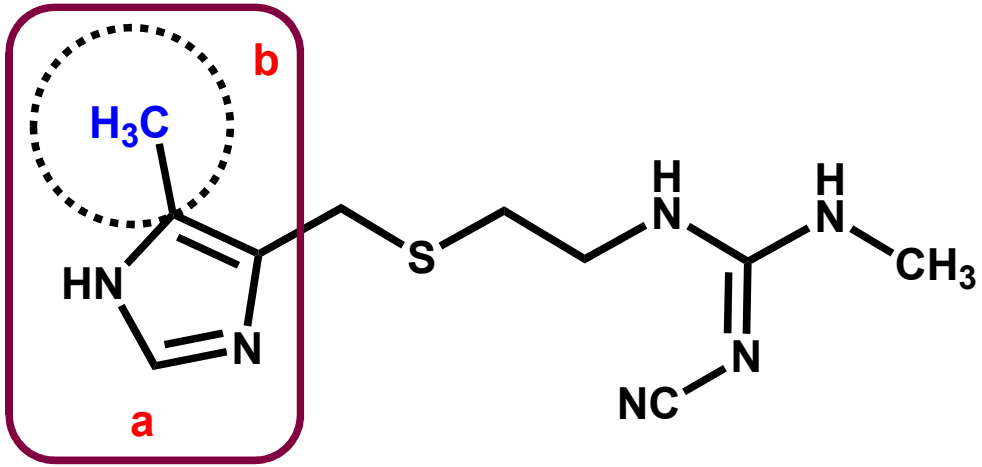
National Historic Chemical Landmarks

AMERICAN CHEMICAL SOCIETY

A new era of logical drug design

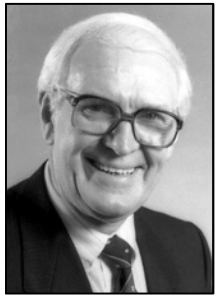
The research program leading to cimetidine also represented a revolution in the way pharmaceuticals are developed. Traditionally, the development of a new drug would often depend on the fortuitous discovery of a plant or microbial extract that showed some of the required biological activity. Using that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

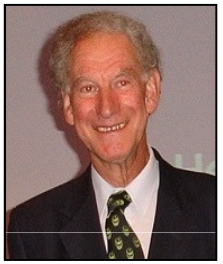


cimetidine

1988



James W. Black



C Robin Ganellin

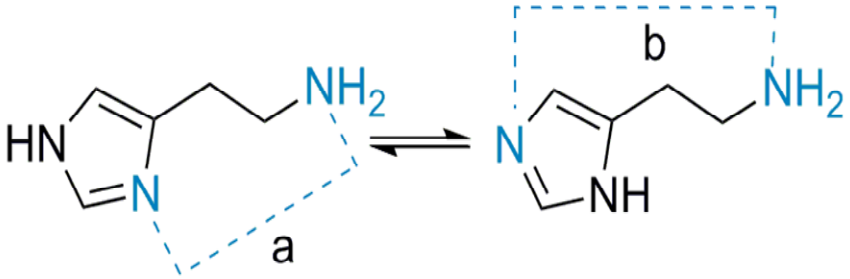
John C Emmett

Graham J Durant

A *metila* na invenção da cimetidina

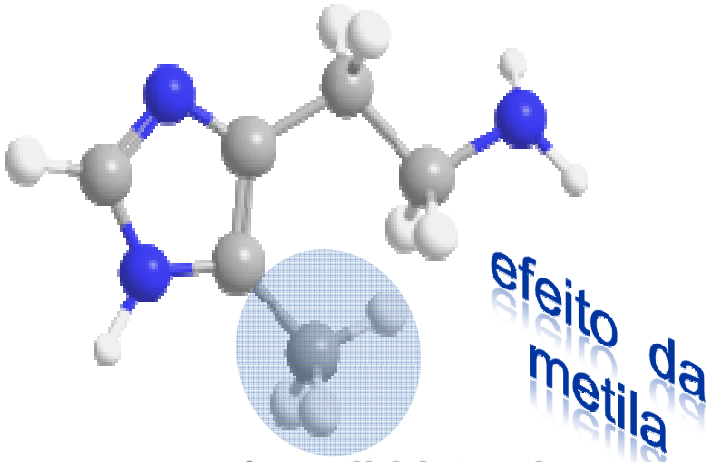
Dois sub-tipos de H_R

Interações fracas



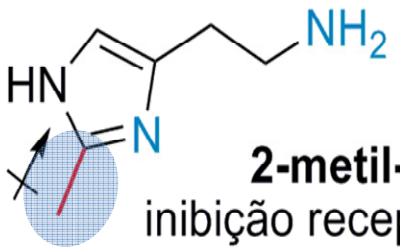
Forma A a = 4,83 Å b = 5,52 Å **Forma B**

Equilíbrio tautomérico

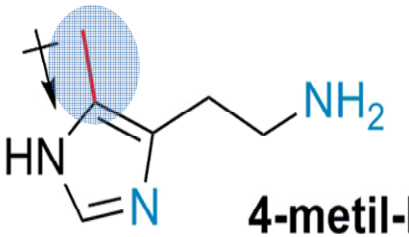


4-metil-histamina

Análogo ativo



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



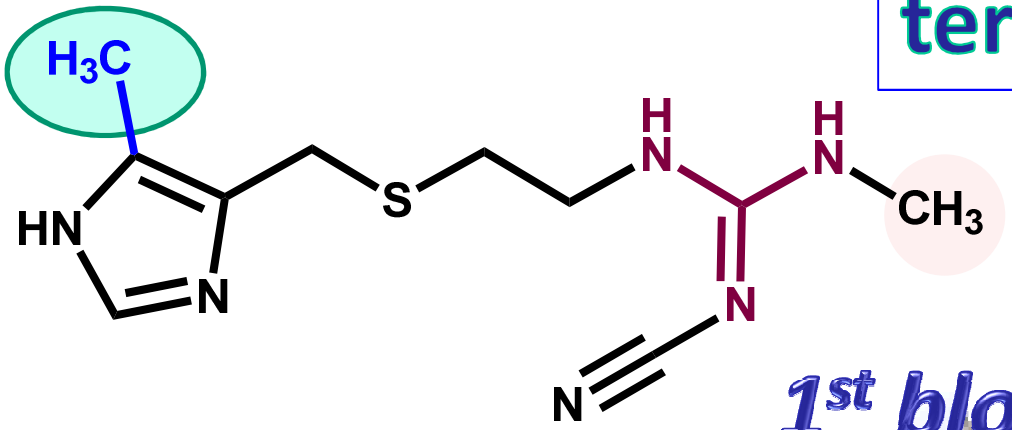
4-metil-histamina
inibição receptores H_1 = 0,2%
inibição receptores H_2 = 50%

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

Química Medicinal

A primeira *metila* valiosa...

Inovação terapêutica

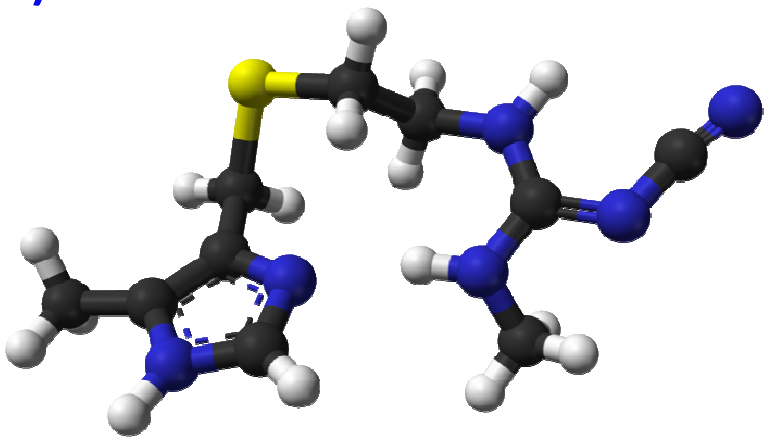


1st blockbuster

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

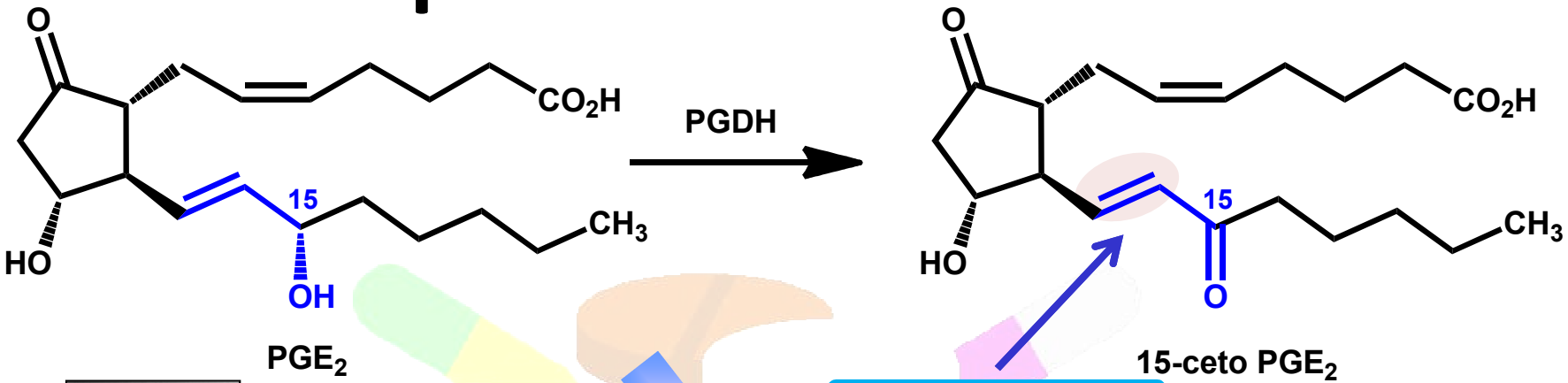
cimetidina

$C_{10}H_{16}N_6S$



Primeiro antagonista seletivo do receptor histaminérgico H_2

A metila prevenindo o metabolismo



PGE_2

15-ceto PGE_2

PG-redutase (PGR)

John R. Vane

(1927-2004)

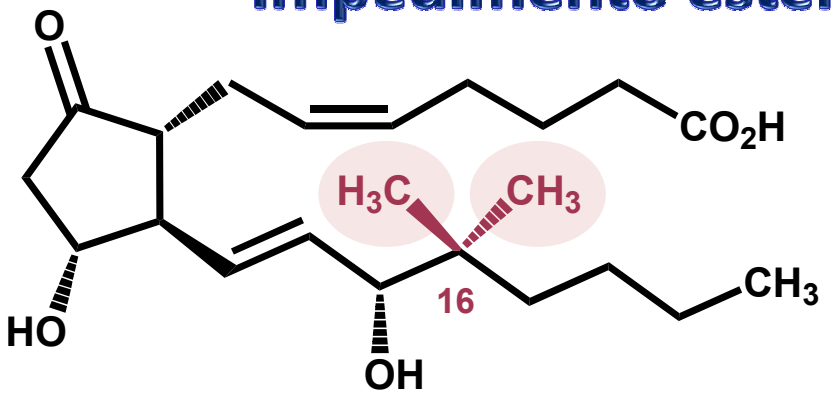
Sune K. Bergström

(1916-2004)

1982

Bengt I. Samuelsson

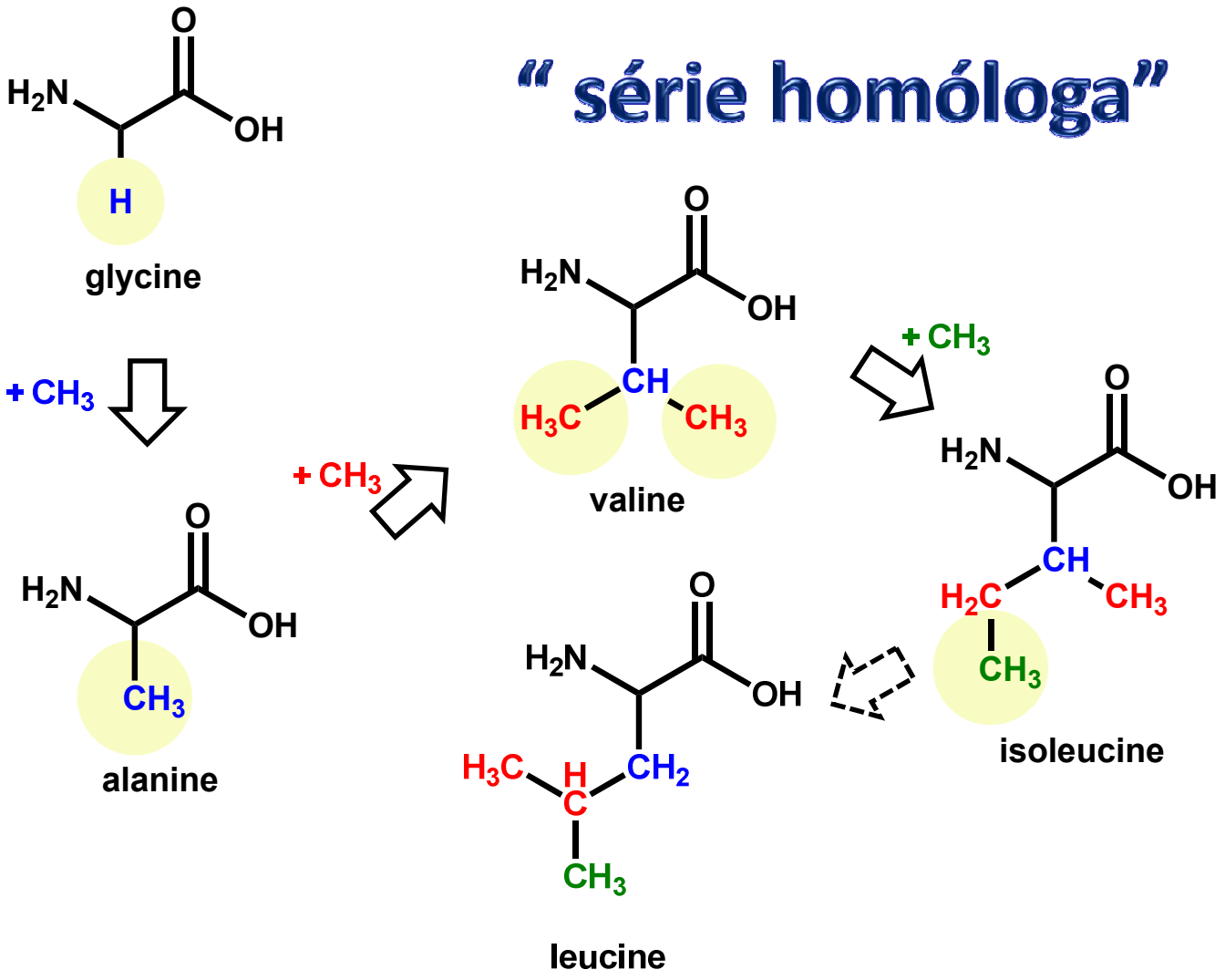
Impedimento estérico



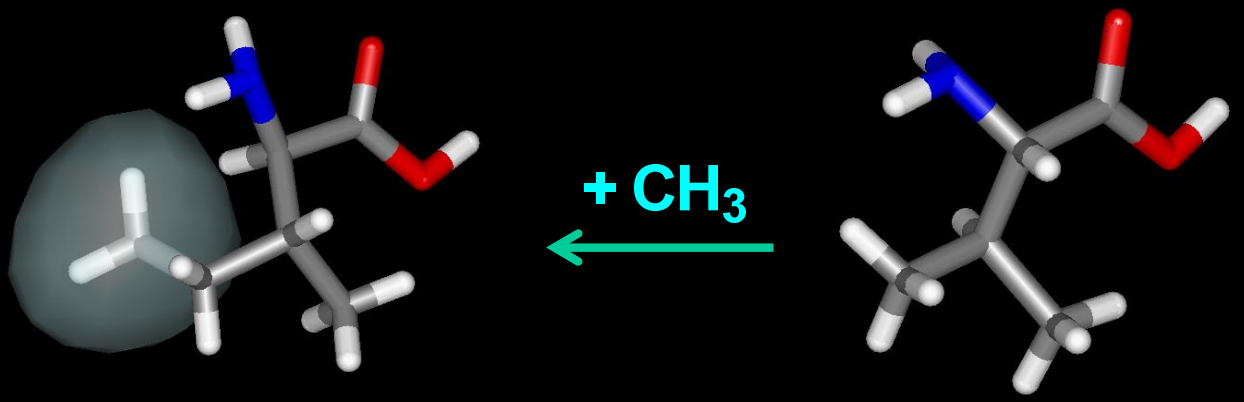
16,16-dimethyl PGE_2

EP_2 ag (1 nM)

A homologia, a metila e os aminoácidos

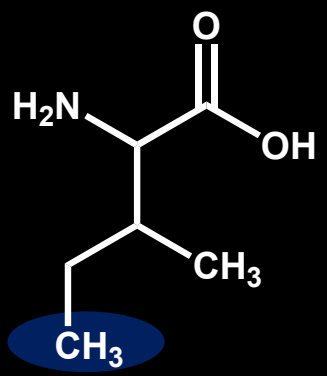


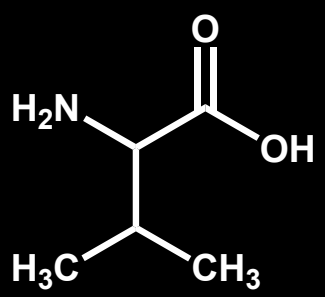
A metila e os aminoácidos



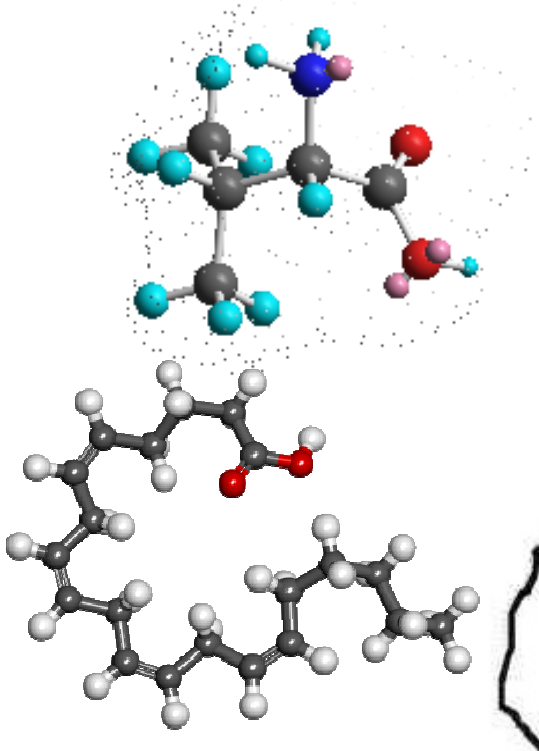
isoleucina

valina



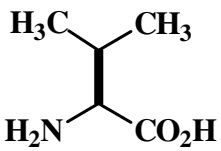


Os amino ácidos homólogos e a COX

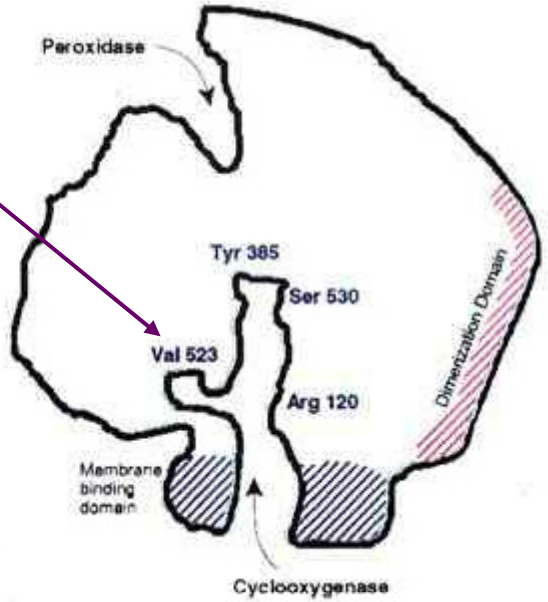


Ácido araquidônico
K_m = 5,6/5,4 μM

Sítio secundário

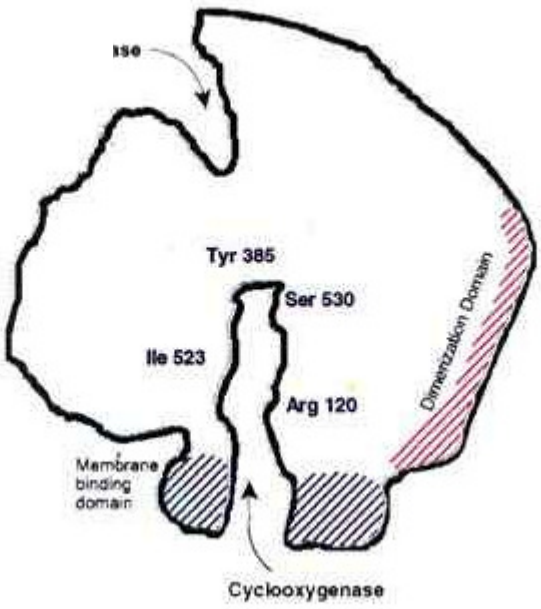


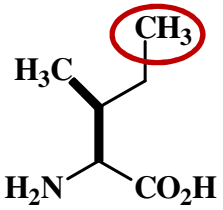
$C_5H_{11}NO_2$
Valina



COX-2

- Inflamação
- Câncer
- Endotélio vascular
- Rins
- Cérebro





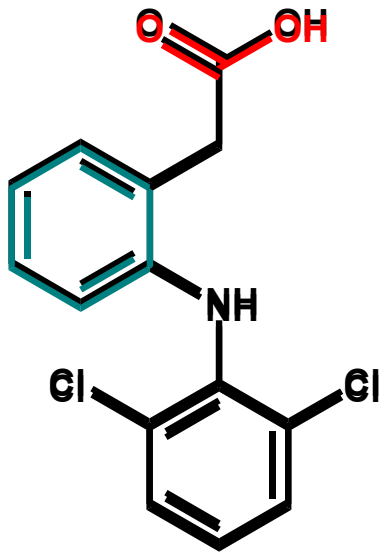
$C_6H_{13}NO_2$
Isoleucina

COX-1

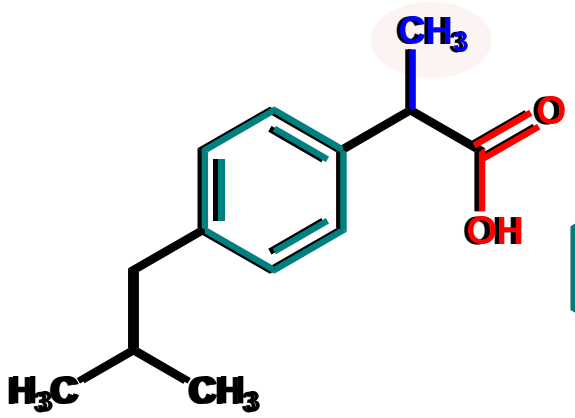
- Estômago
- Plaquetas
- Rins

A metila e os antiinflamatórios não esteróides

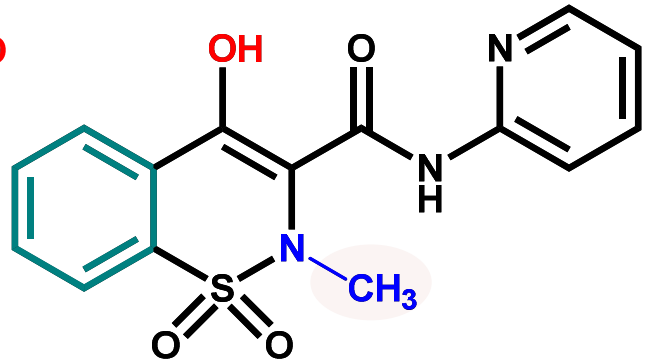
COX - 1



diclofenac

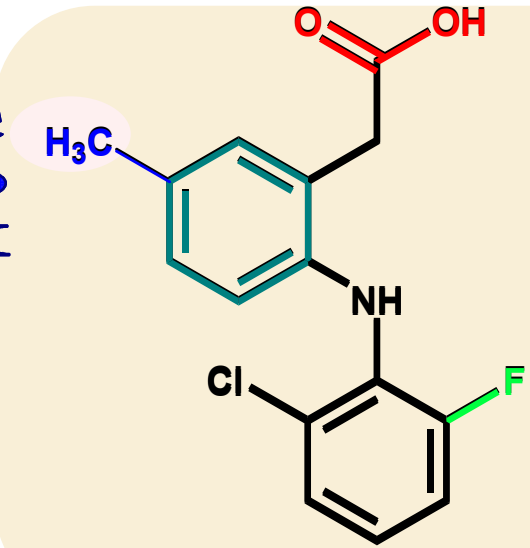


ibuprofen

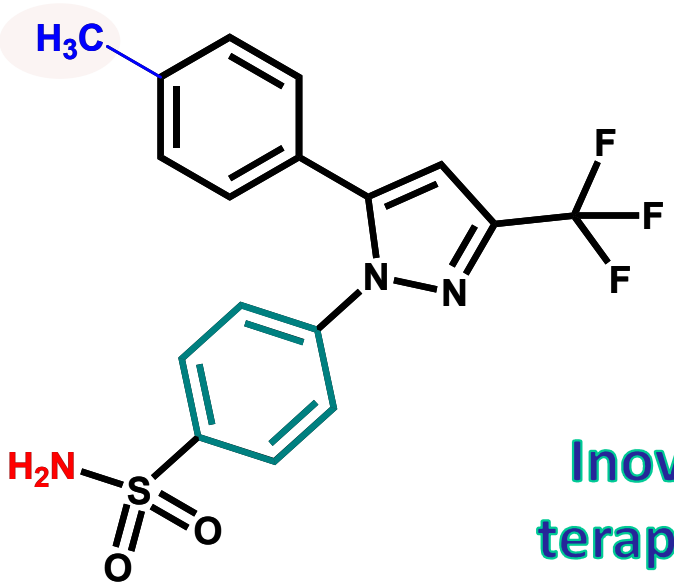


piroxicam

COX - 2



lumiracoxib

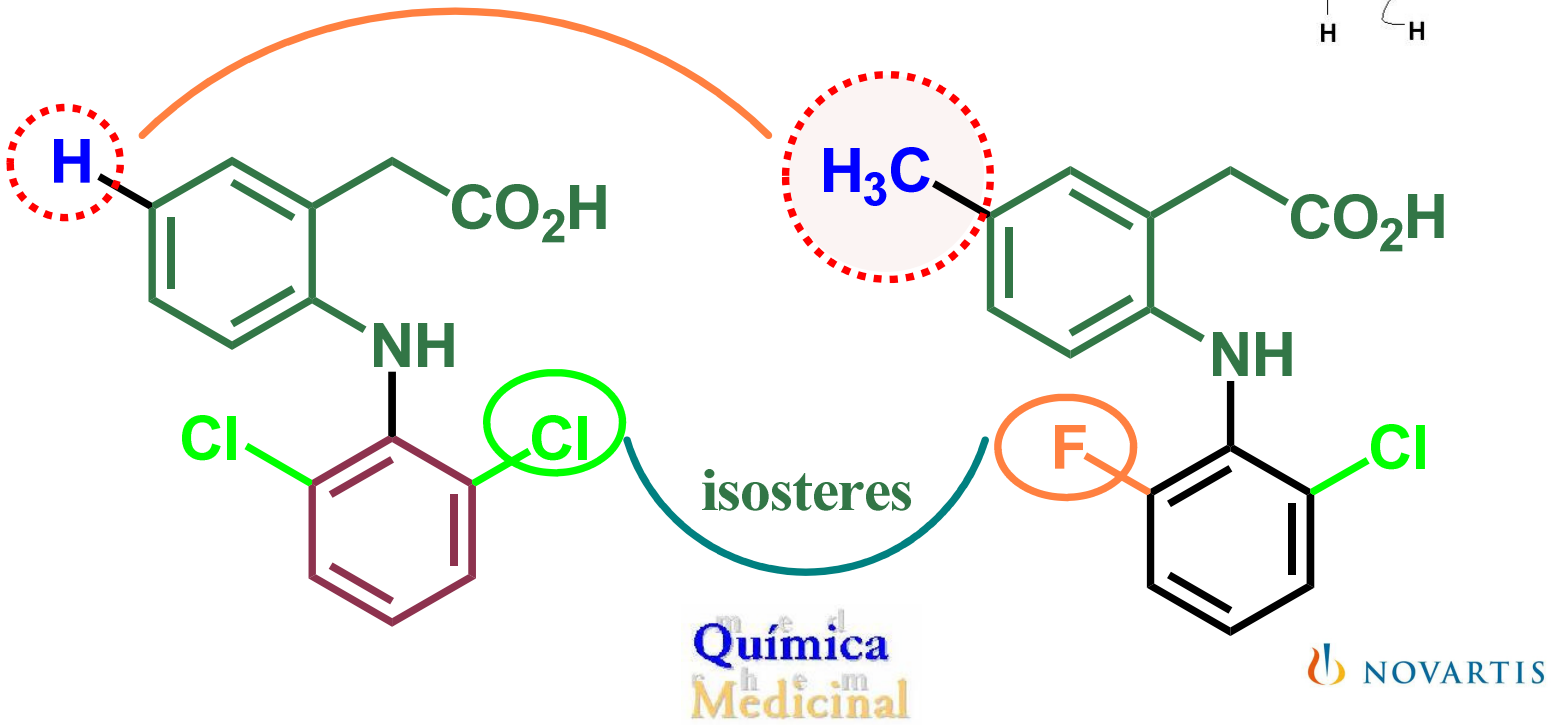


celecoxib

Inovação terapêutica

LASSBio

O *fascínio* da metila...



DICLOFENAC

COX-1

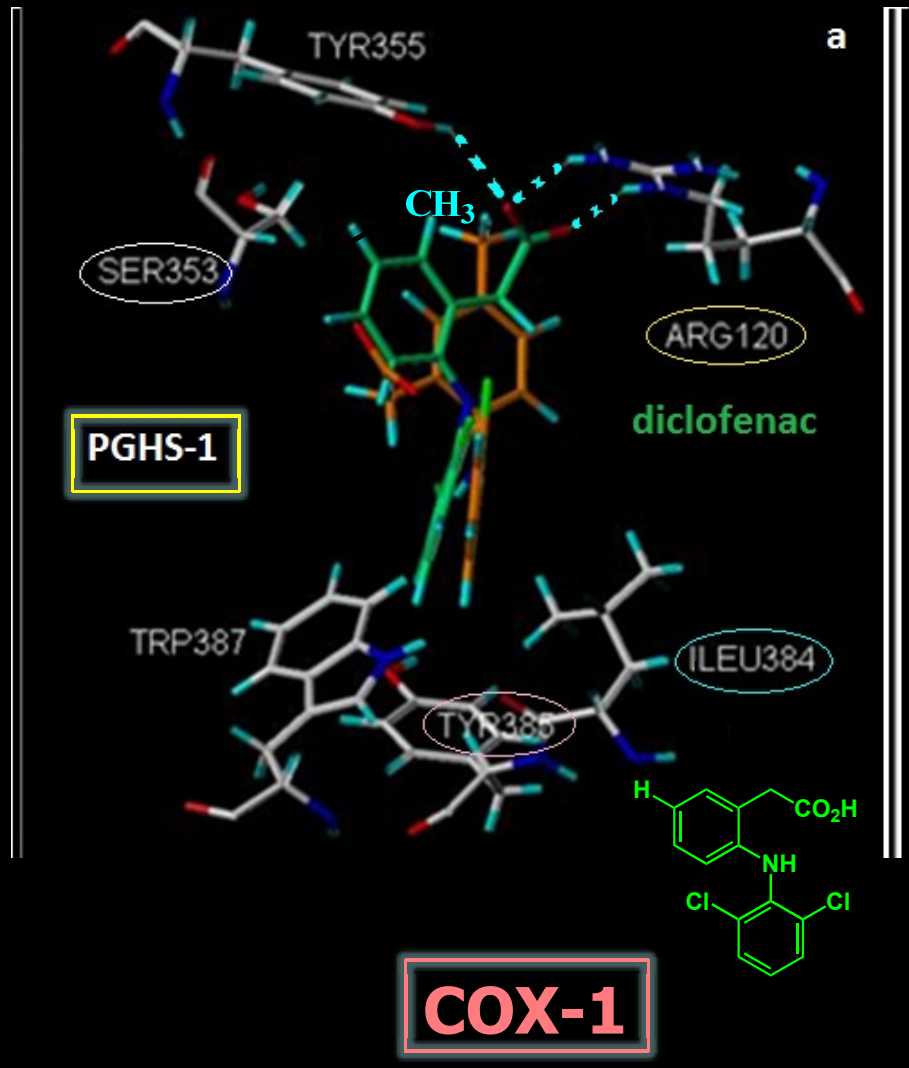
LUMIRACOXIB

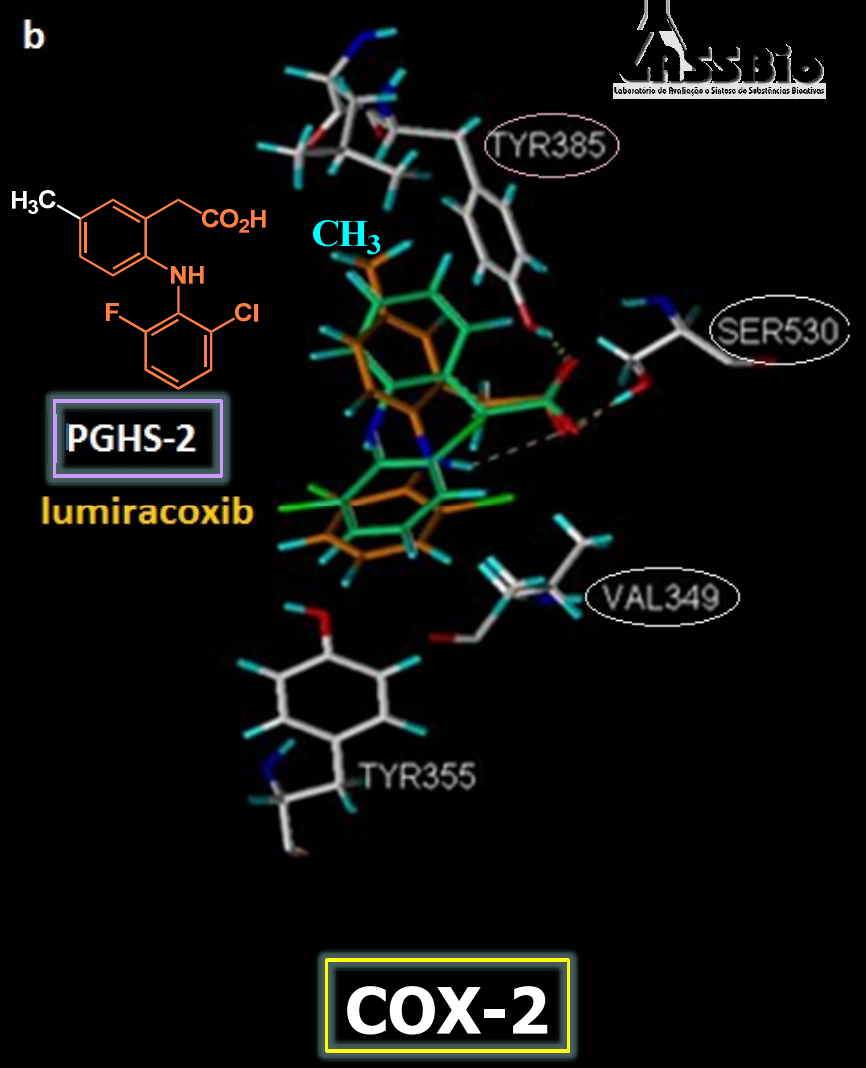
COX-2

2006 (2007)

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

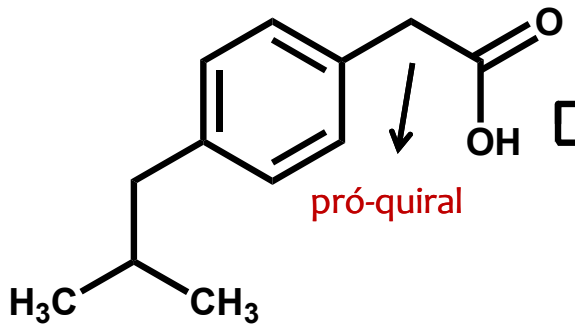
A seletividade entre COX-1 e COX-2

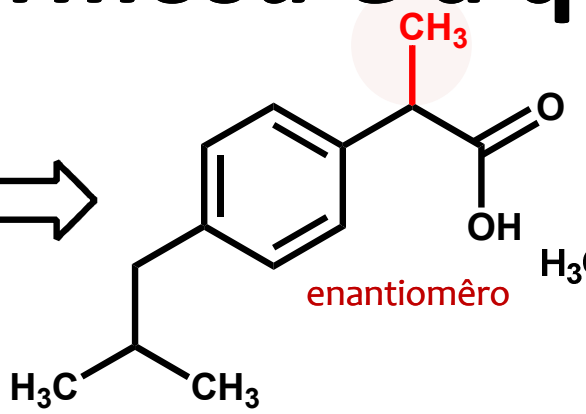


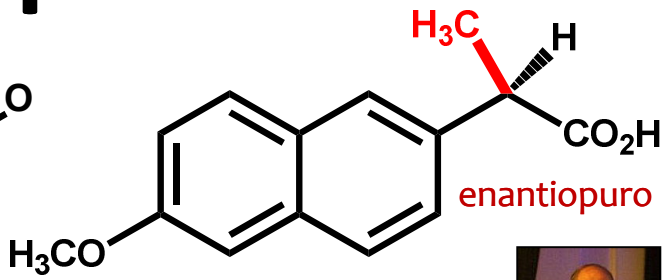


CM Corrêa *et al.*, *Letters in Drug Design & Discovery*, 2007, *4*, 422

A metila *charmosa* e a quiralidade







ibufenac

ibuprofen
(1961)

naproxen
(1976)
***S*(uper)-Naprosin^R**

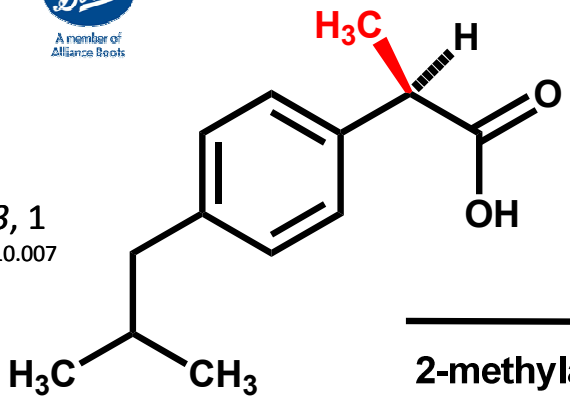
IT Harrison, *J Med Chem* **1970**, *13*, 203

R Noyori

2001

SS Adams*

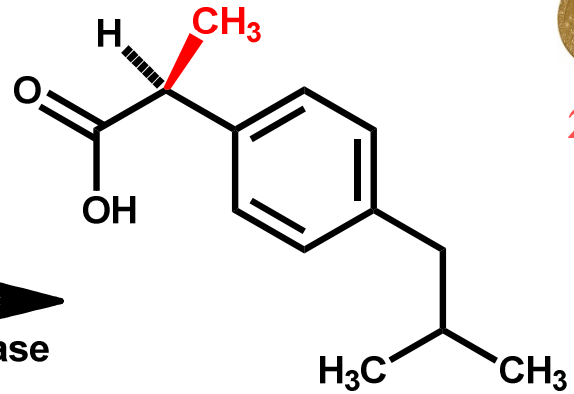
TiPS **2012**, *33*, 1
10.1016/j.tips.2011.10.007



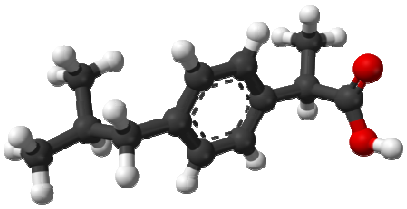
liver

2-methylacyl-CoA 2-epimerase

in vivo

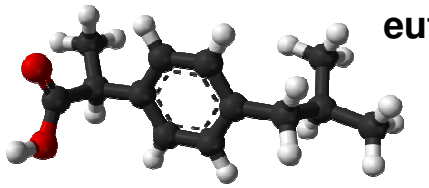


(*R*)-ibuprofen



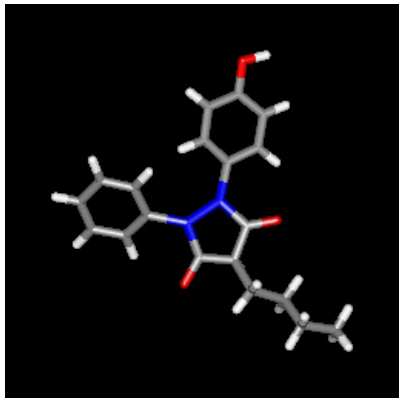
σ

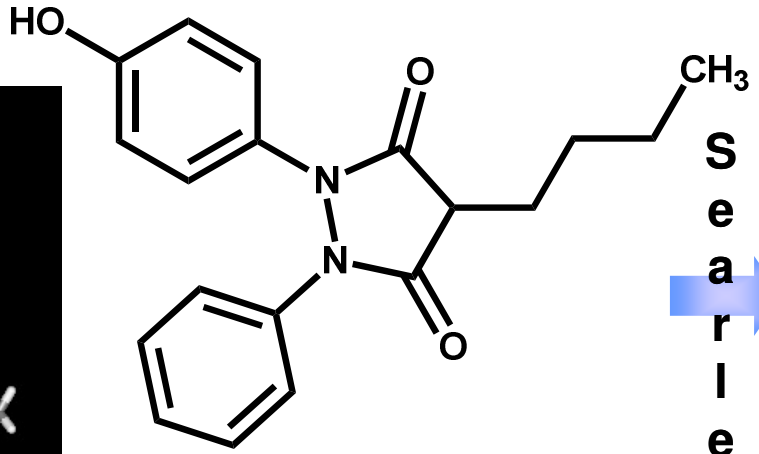
(*S*)-ibuprofen
eutômero



*SS Adams, The propionic acids: A personal perspective". *Journal of clinical pharmacology* **1992**, *32*, 317–323.

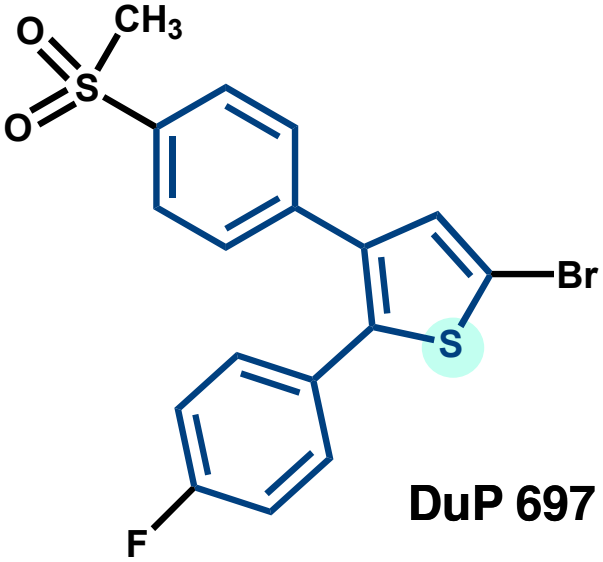
A metila e a gênese do celecoxibe





1956 – Oxifenilbutazona

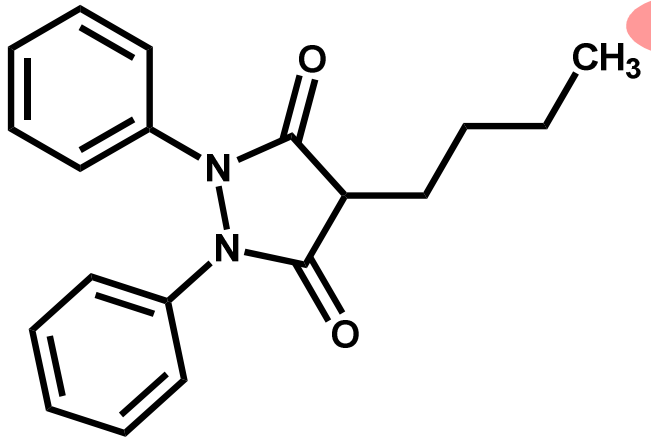
Searle



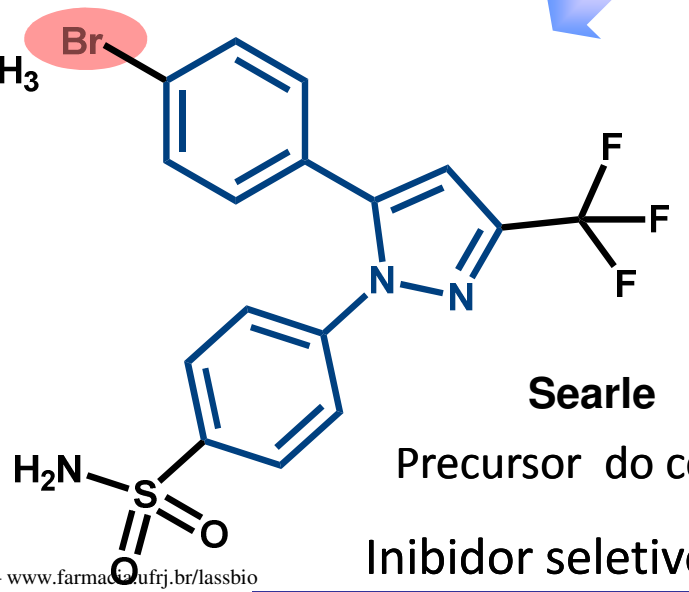
DuP 697

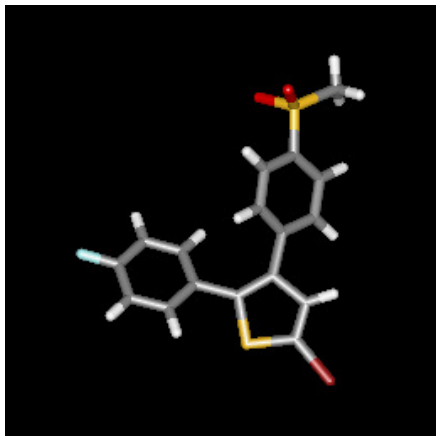
Geigy

estudos de metabolismo



1951 – fenilbutazona





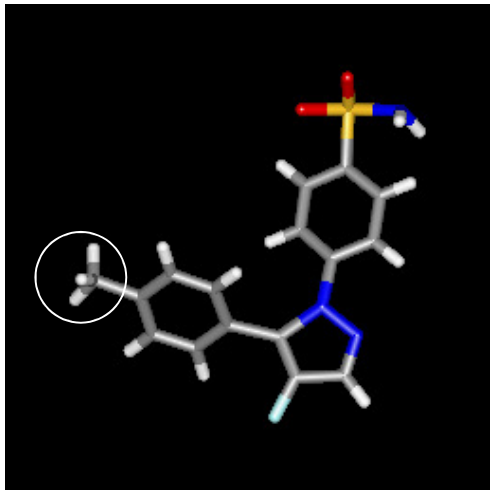
Searle

Precursor do celecoxibe

Inibidor seletivo de COX-2

A metila ativando o metabolismo

PGHS-2



SC-558

COX-2 seletivo
Searle

Vida-média = 12 dias !
(ADME)
metabolismo

Pfizer

Química Medicinal

therapeutic innovation

CYP2C9
CYP3A4

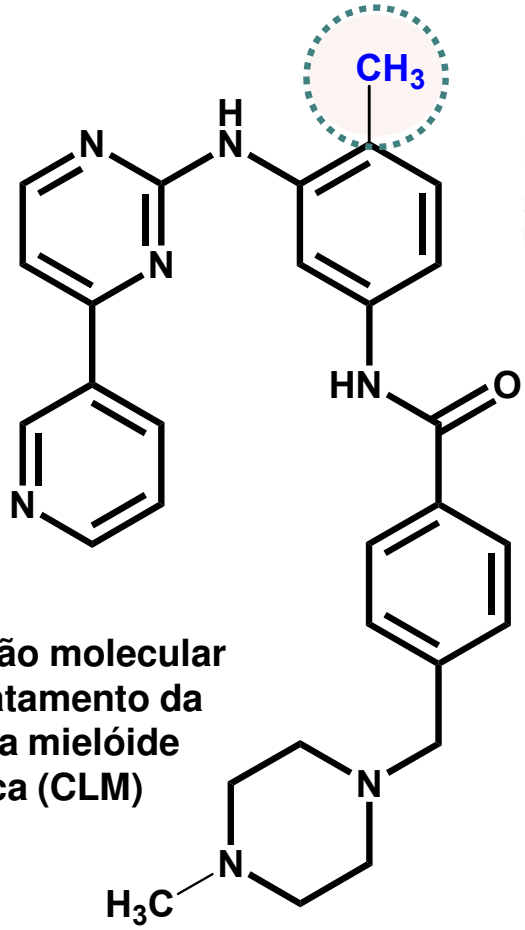
nova possível indicação:
câncer coloretal

Celecoxibe (SC-58634)
1999

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

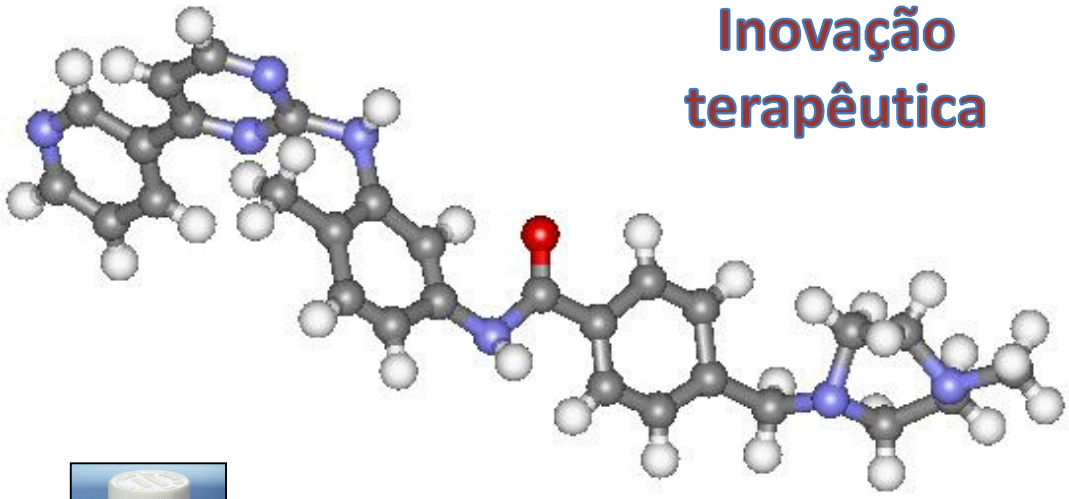
O mercado mundial de fármacos antiinflamatórios (2008) = *ca.* US$ 32 bi

A metila e a gênese do imatinibe



Novo padrão molecular para o tratamento da leucemia mielóide crônica (CLM)

imatinibe



Inovação terapêutica

1990 – Nicholas Lydon & Brian J Druker
2001 - Imatinibe

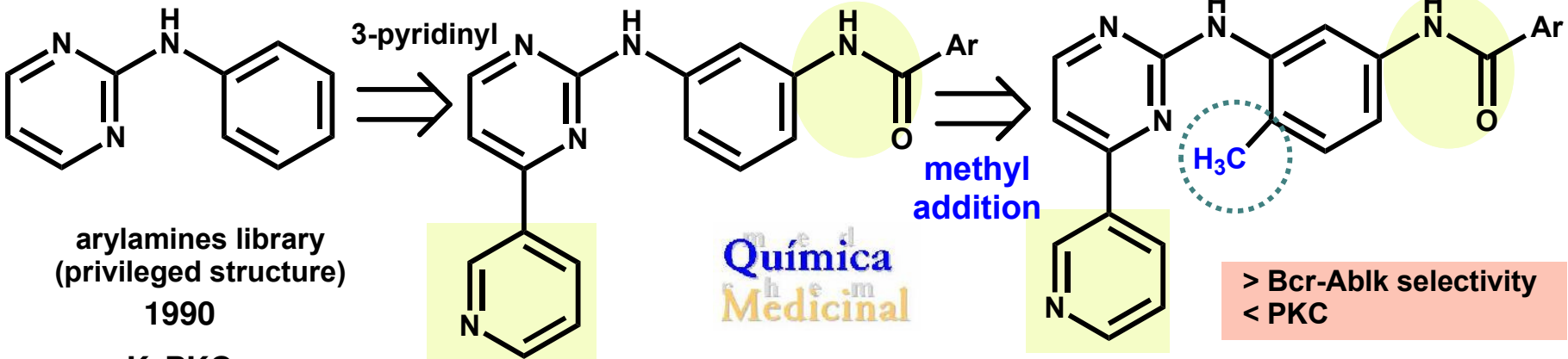
Nicholas Lydon

Brian J. Druker

A metila e a gênese do imatinibe

NOVARTIS

HTS



arylamines library
(privileged structure)
1990

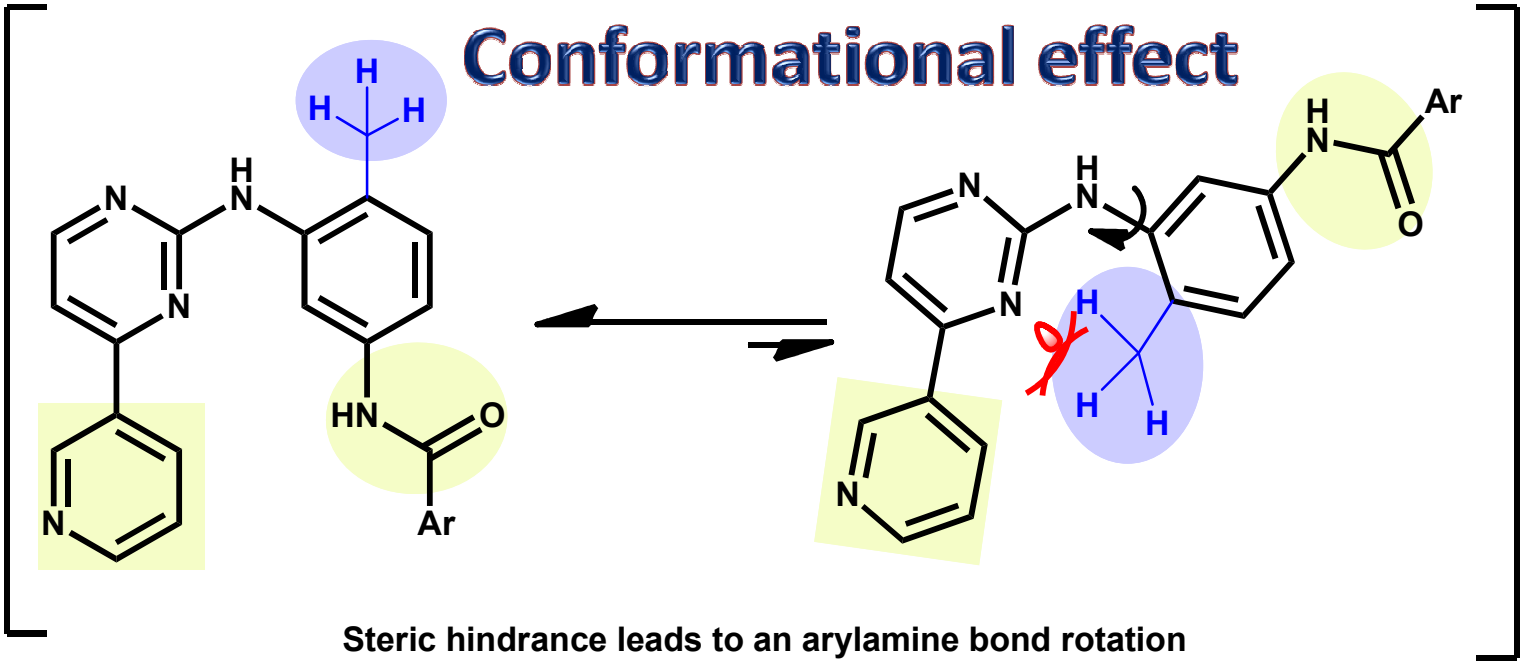
K_i PKC

Química Medicinal

PKC and TK inhibitor
(Bcr-Ablk inhibitor)

> Bcr-Ablk selectivity
< PKC

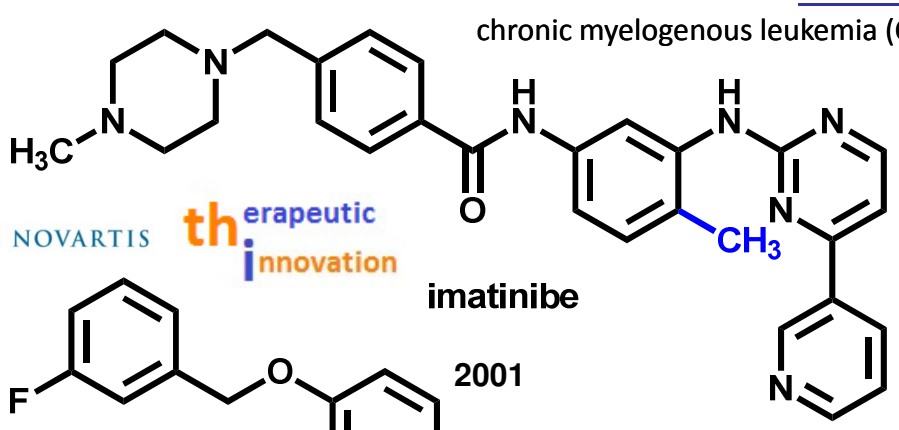
Conformational effect



Steric hindrance leads to an arylamine bond rotation

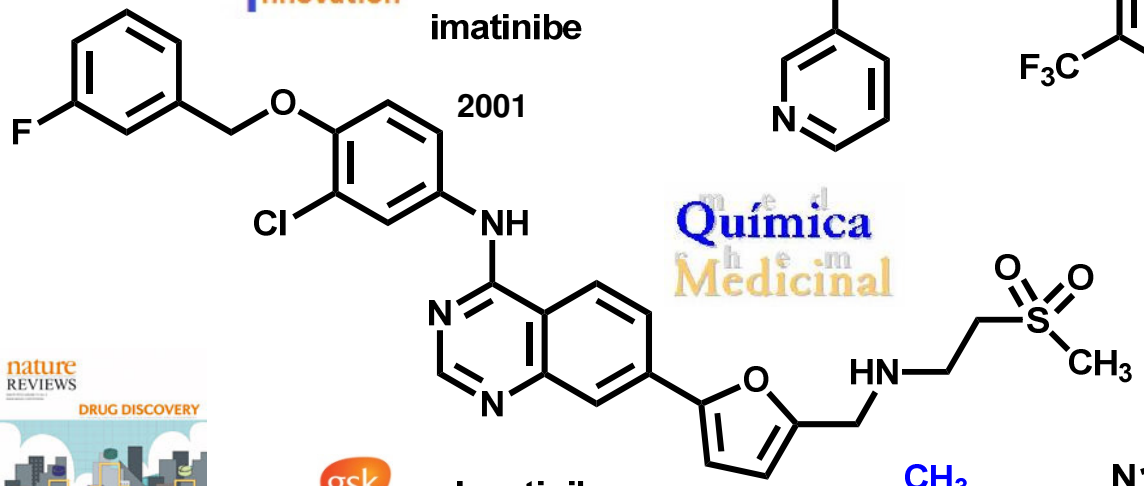
chronic myelogenous leukemia (CML)

Tinibes



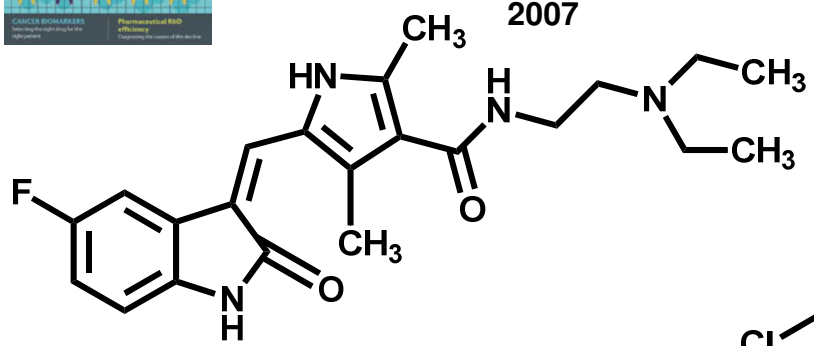
imatinibe

2001



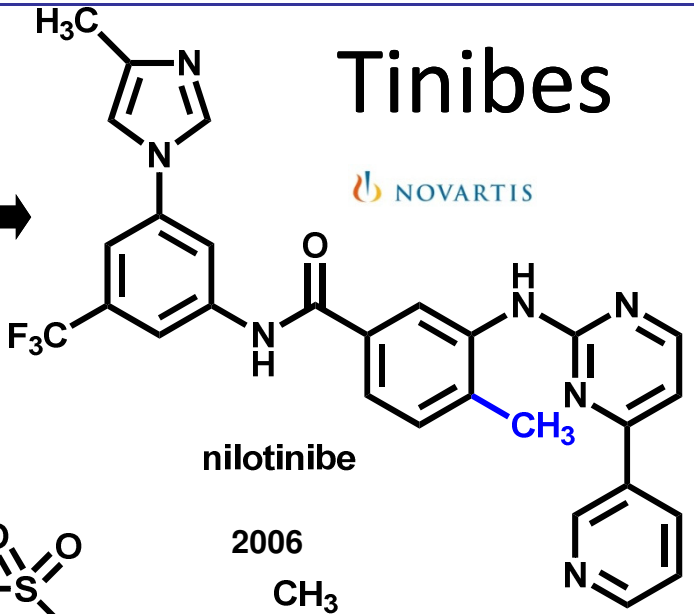
lapatinibe

2007



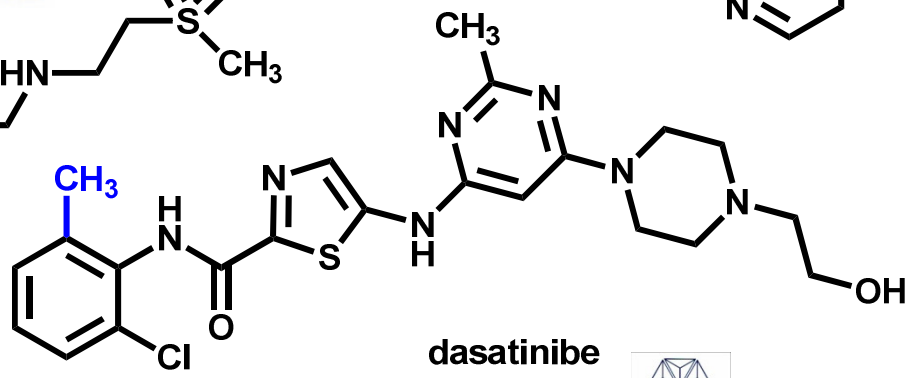
sunitinibe

2006



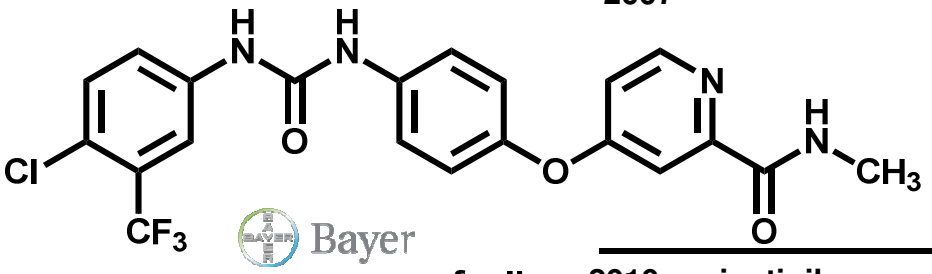
nilotinibe

2006



dasatinibe

2007



sorafenibe

2007

2010- crisotinibe

2011 - bosutinibe

- Tinib´s 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...*

Akira Endo, Sankyo Co

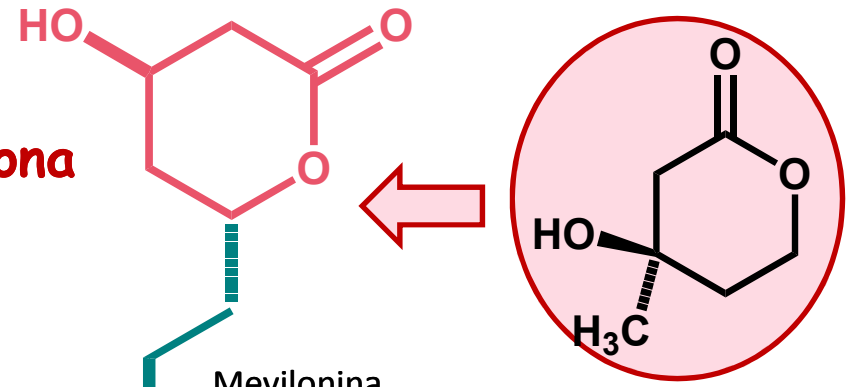
Estatinas

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

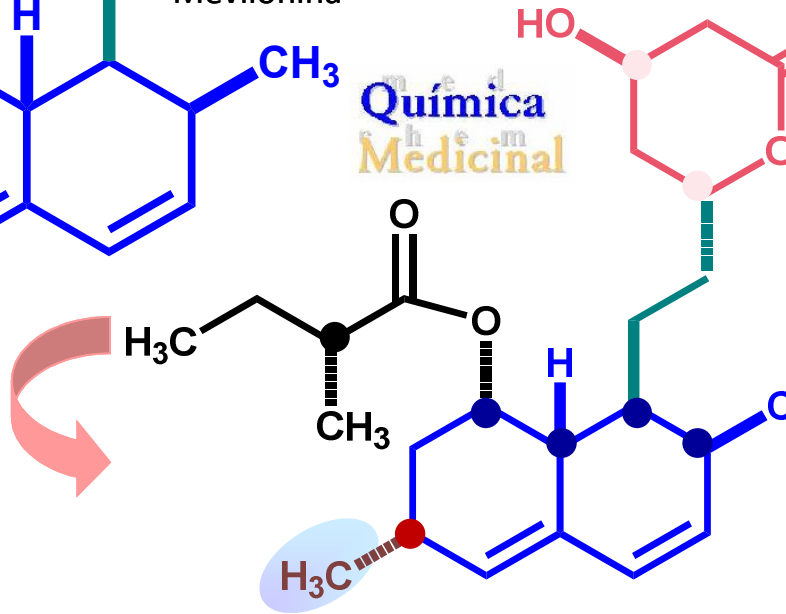
1985

WHAT STARTS HERE CHANGES THE WORLD
THE UNIVERSITY OF TEXAS AT AUSTIN

MERCK

Arthur A Patchett

J. Med. Chem. **1986,** *29*, 849



Química Medicinal

Lovastatin (MK-803)

1978 – Merck & Co.

Aspergillus terreus

1987 – MS&D (*Mevacor*^{R})

1988 – *Mevacor*^{R} US$ 260 mi

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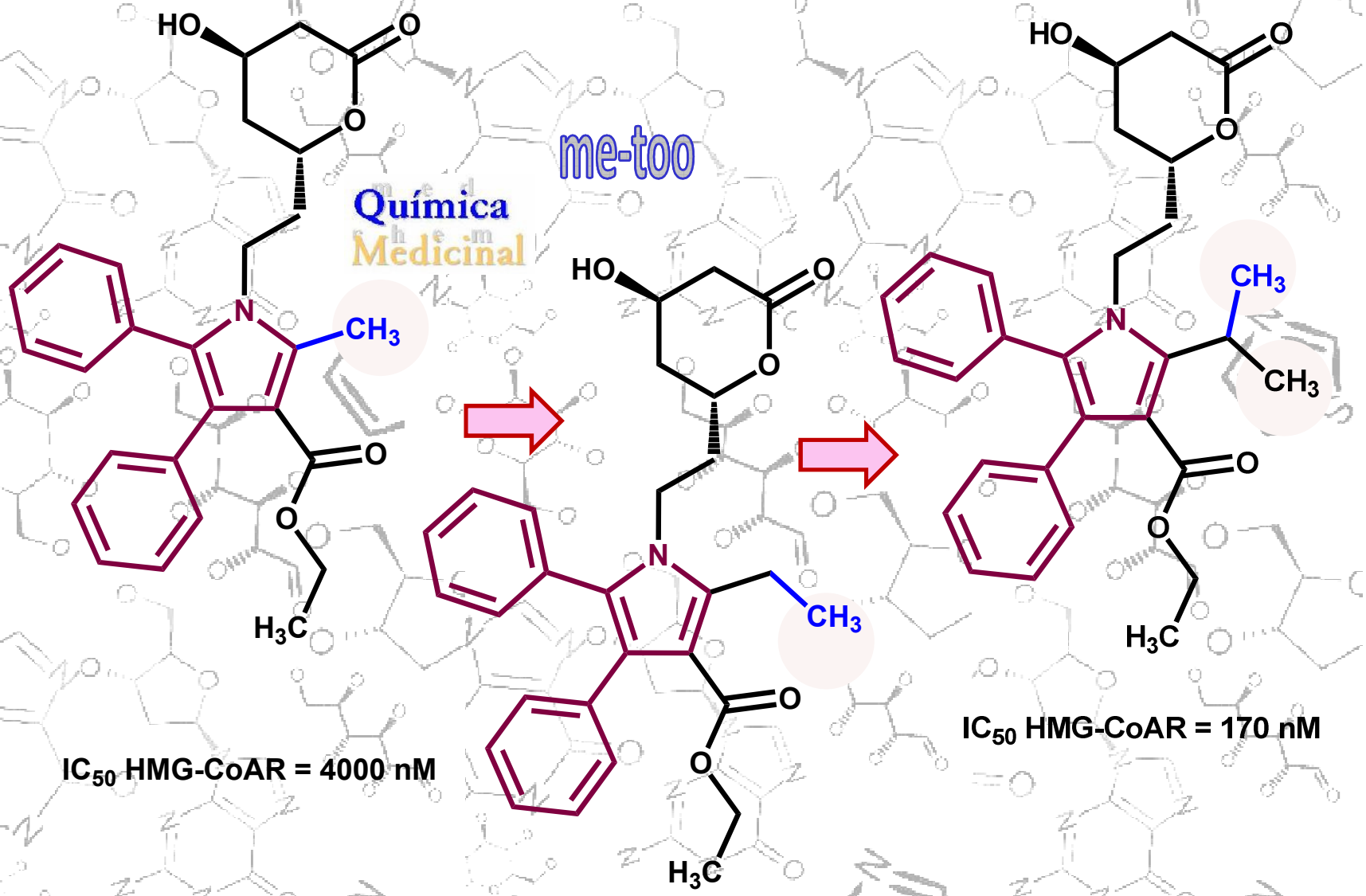

me-too
Química
Medicinal
HO
O
O
N
CH3
O
O
H3C
IC50 HMG-CoAR = 4000 nM
IC50 HMG-CoAR = 890 nM
IC50 HMG-CoAR = 170 nM

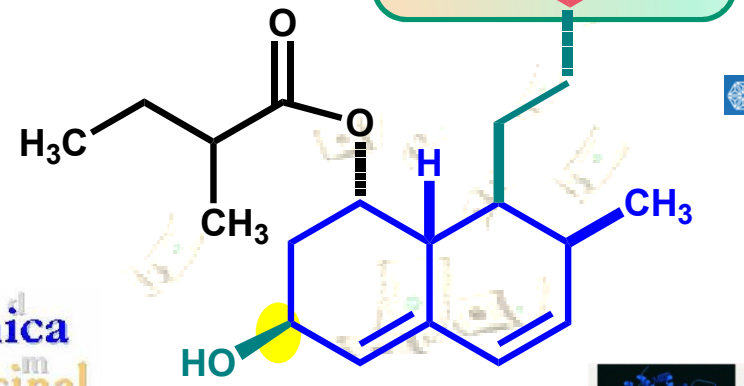
Estatinas

Arthur A Patchett
Alfred Burger Award 2002
J Med Chem **2003**, *45*, 5609

simvastatina
1986

MERCK

Química Medicinal

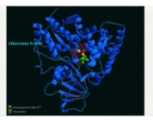


pravastatina
1988

Bristol-Myers Squibb

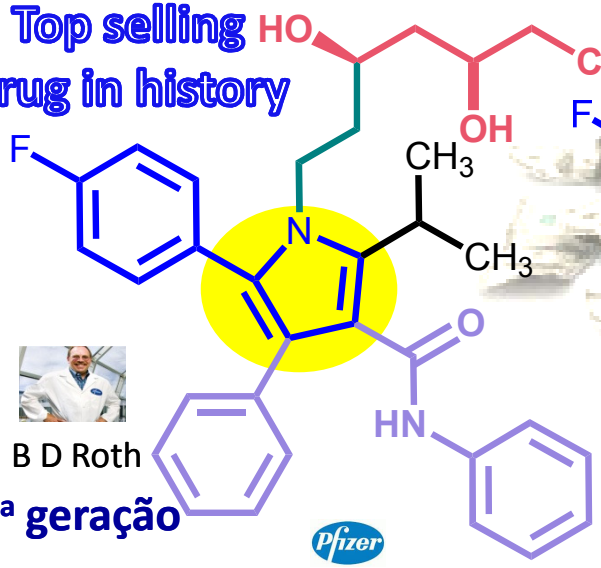
TEVA

(2006)



2ª geração

Top selling drug in history

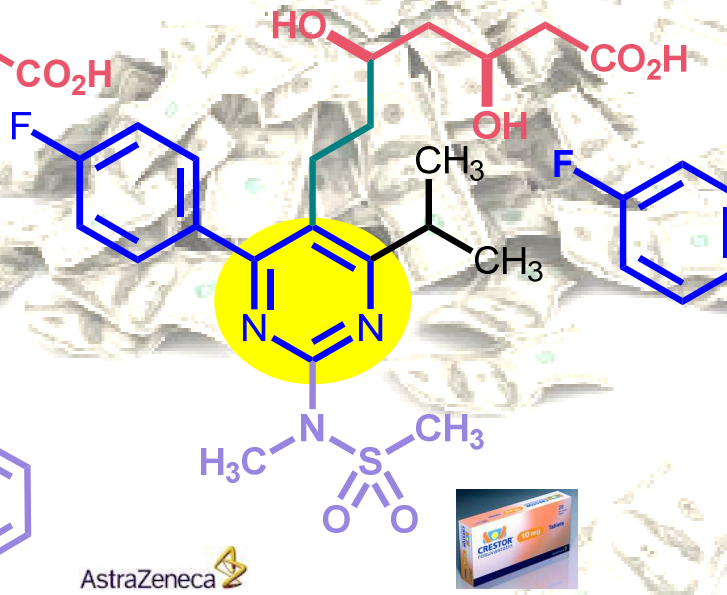


B D Roth

3ª geração

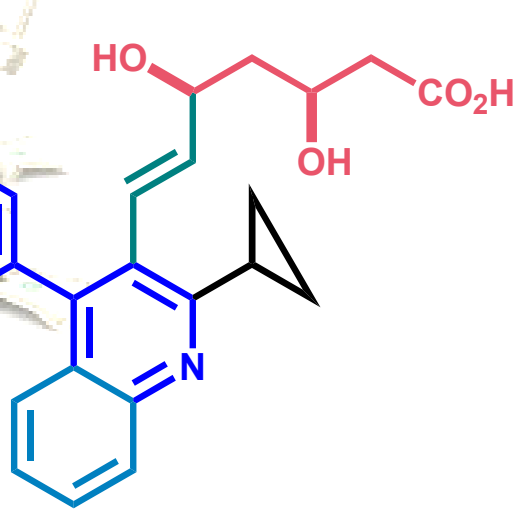
atorvastatina
1991

Pfizer



AstraZeneca

rosuvastatina
2004



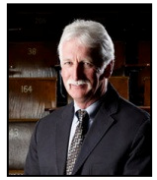
Kowa

pitavastatina
2009

1 CH_3 = > US$ 4,54 bi

O mercado mundial de estatinas foi estimado em US$ 22 bilhões (2011)

Journal of Medicinal Chemistry

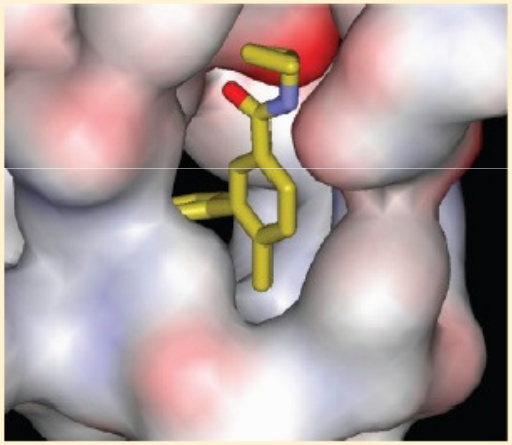


Methyl Effects on Protein–Ligand Binding

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.

Universidade Federal do Rio de Janeiro

Obrigado

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ejb-eliezer.blogspot.com.br

Uma das sete maravilhas do mundo moderno!