O que pode fazer uma *metilinha* na Química Medicinal...

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www.farmacia.ufrj.br/lassbio

http://ejb-eliezer.blogspot.com.br

Química Medicinal

Definição

estuda os fatores moleculares relacionados ao modo de ação dos fármacos, a compreensão da relação entre a estrutura química e a atividade (SAR), incluindo a absorção, distribuição, metabolismo, eliminação (ADME) e toxicidade (STR).

IUPAC
http://www.iupac.org

Chemistry and Human Health Division (VII)
Subcommittee on Medicinal Chemistry and Drug Development.

CR Ganellin *et al.*, *Eur. J. Med. Chem.* **2000**, *35*, 163; A Monge *et al.*, *Eur. J. Med. Chem.* **2000**, *35*, 1121

Complexity in Biological Signaling Systems

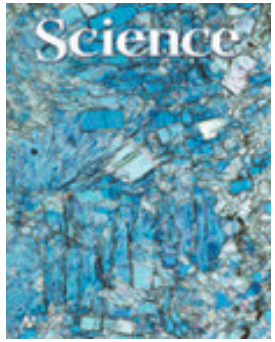
Gezhi Weng

Upinder S. Bhalla

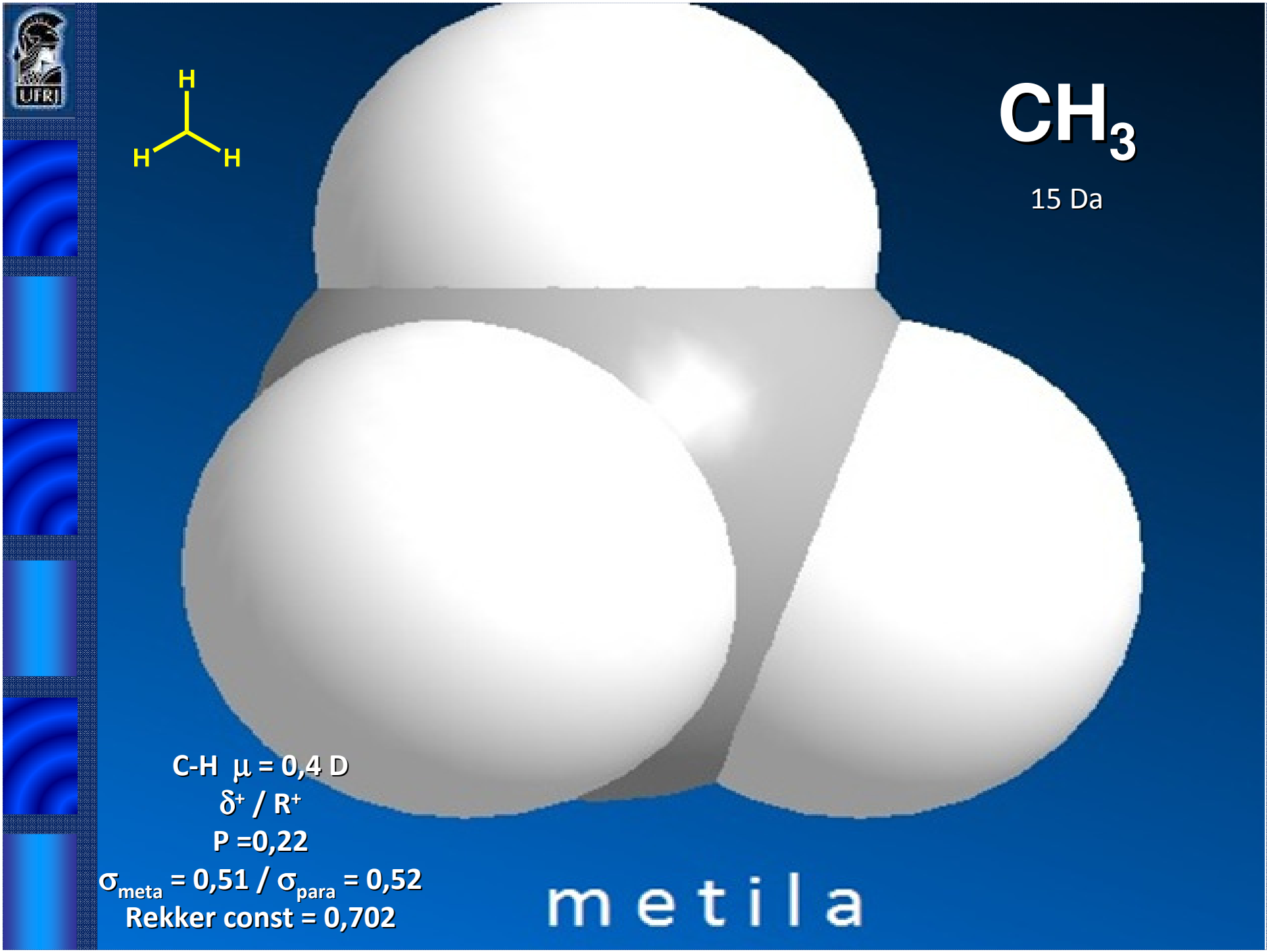
Ravi Iyengar

Science **1999**, *284*, 92

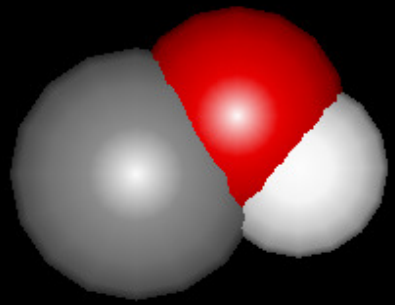
DOI: 10.1126/science.284.5411.92

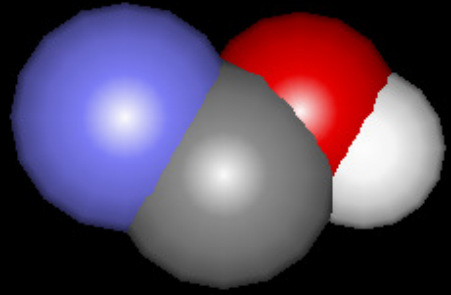


Biological signaling pathways interact with one another to form complex networks. Complexity arises from the large number of components, many with isoforms that have partially overlapping functions; from the connections among components; and from the spatial relationship between components.

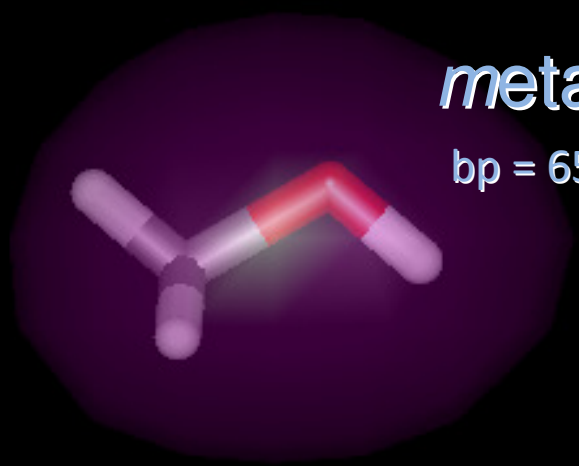

H
H
H
CH_3
15 Da
C-H μ = 0,4 D
δ+ / R+
P =0,22
σ_{meta} = 0,51 / σ_{para} = 0,52
Rekker const = 0,702
metila

O sutil efeito da *metilinha*...



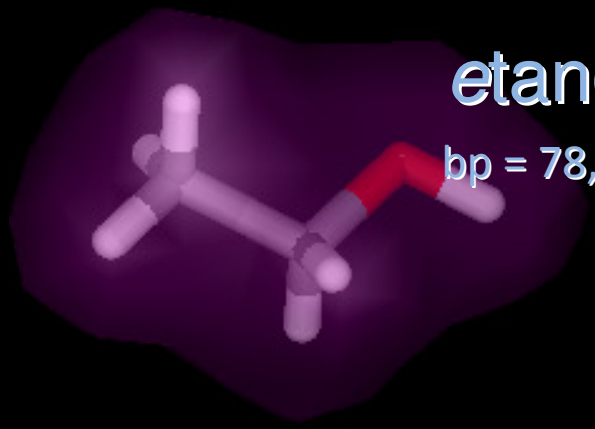


H-O-H **H_3C-O-H** **H_3C-CH_2-O-H**



*m*etanol

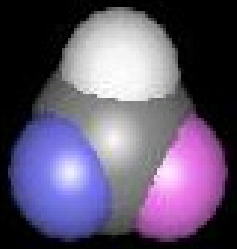
bp = 65,5°C



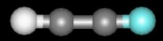
etanol

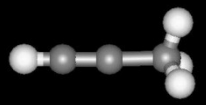
bp = 78,3°C

canais iônicos = $GABA_A$ (Dose ! ? ? ?)



metila





acetilenos

álcool

éter

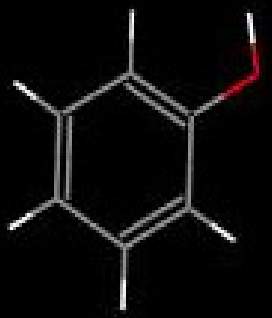
aminas

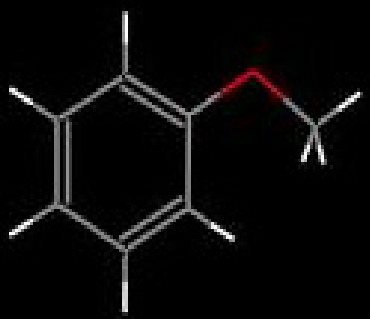
fenol

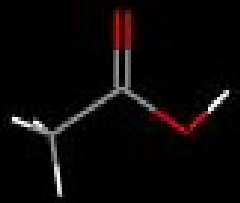
metil-éter

ácido

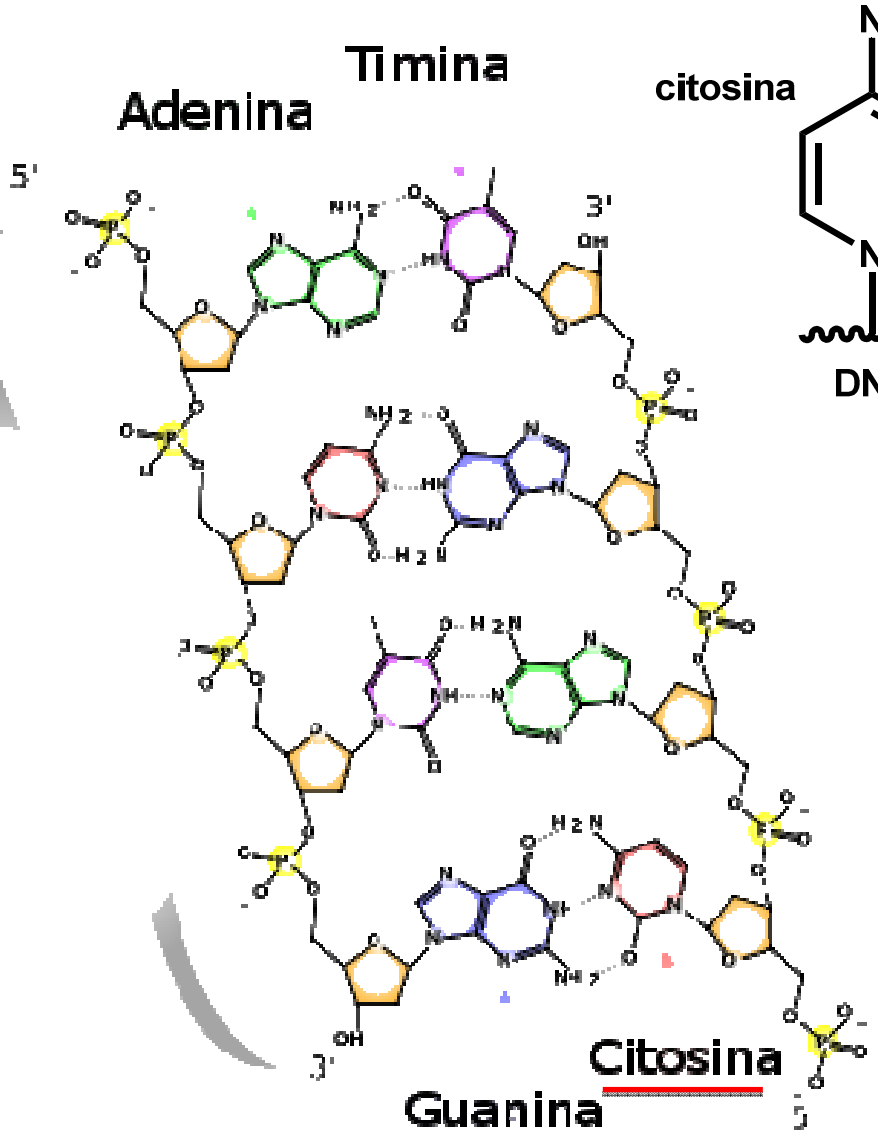
éster

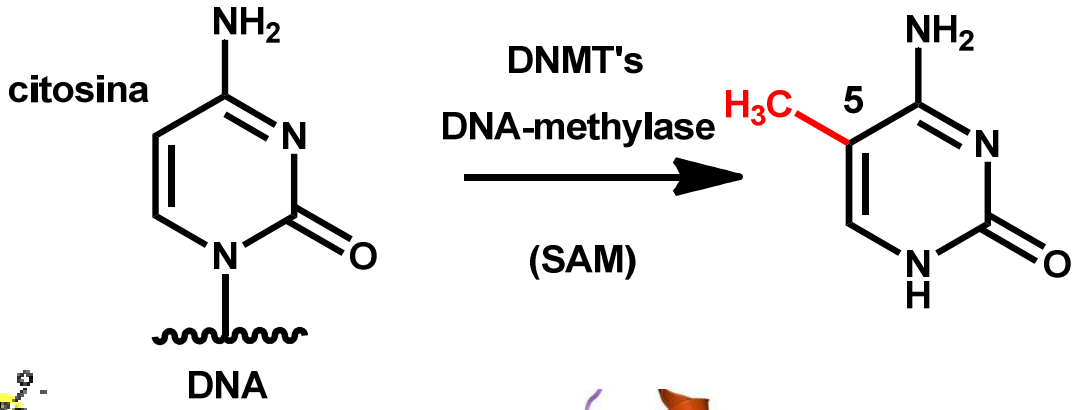


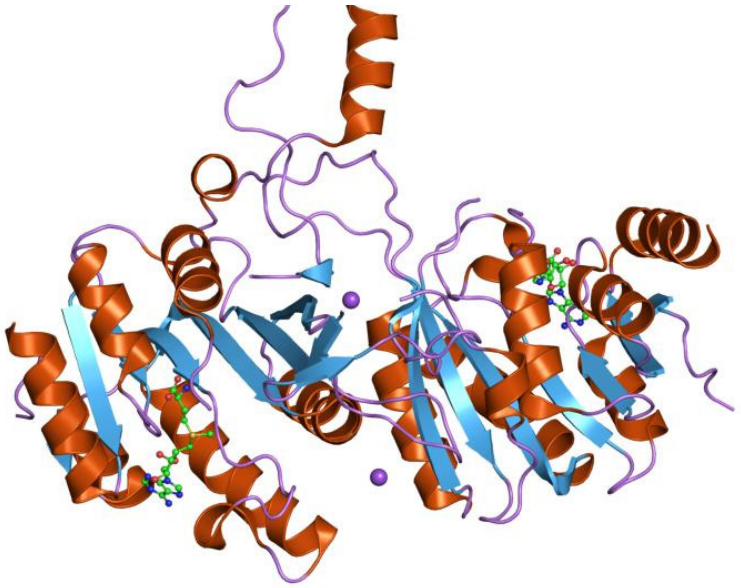




A importância da metilação...

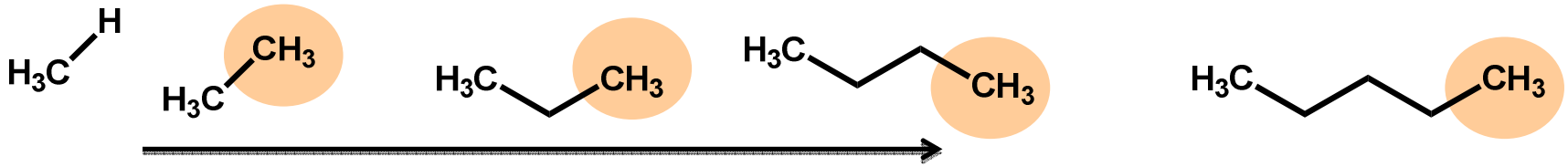




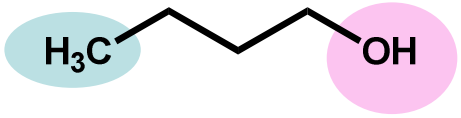


DNA-methylase

As séries homólogas

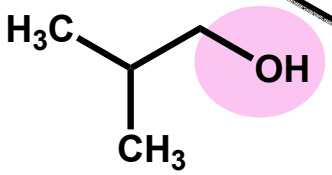


Lipofilicidade



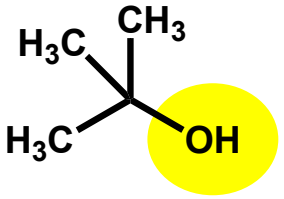
n-butanol

solubility in water
8.2g/100g



*iso*butanol

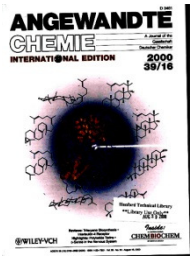
solubility in water
12,5 g/100g

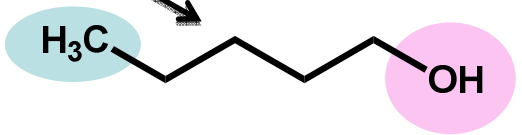


tert-butanol

solubility in water
miscible

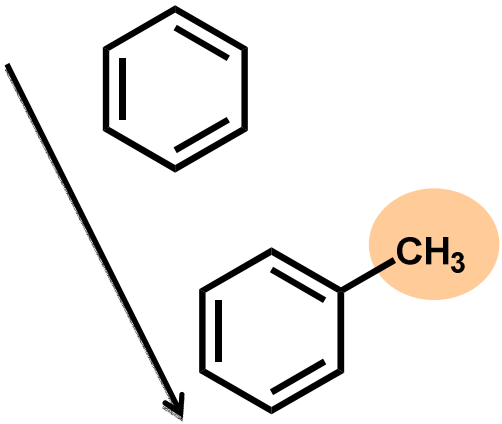
G Némethy, *Angew Chem Int Ed Engl* **1967**, *6*, 195

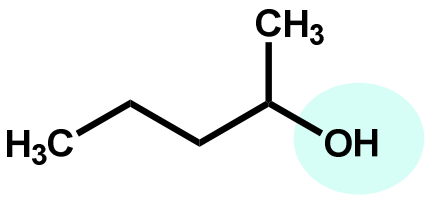




n-pentanol

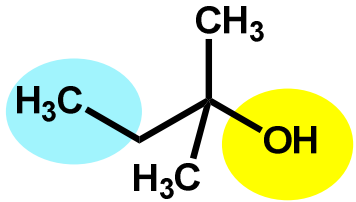
solubility in water
2.4g/100g





2-pentanol

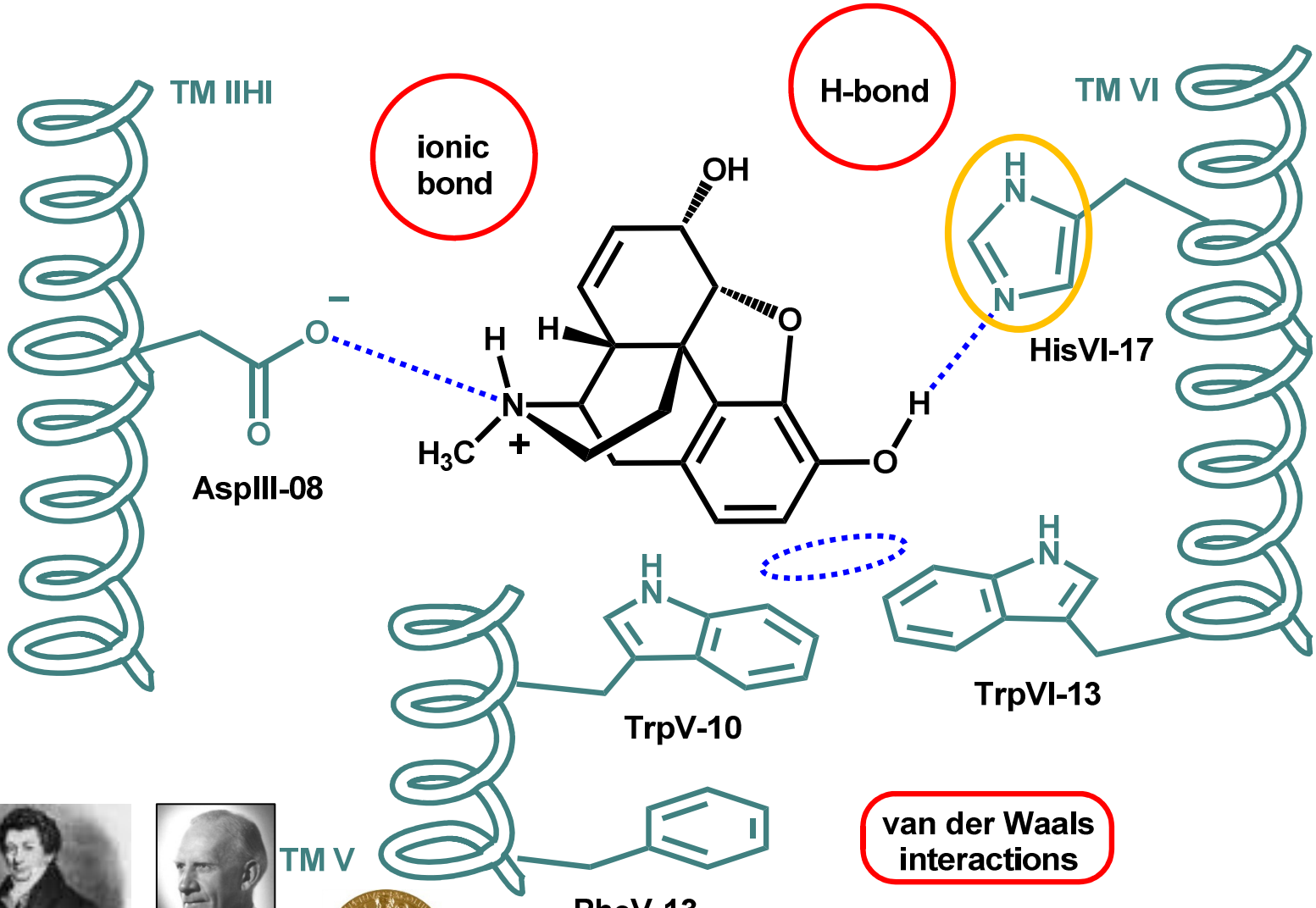
solubility in water
4.9g/100g



*neo*pentanol

solubility in water
12.2g/100g

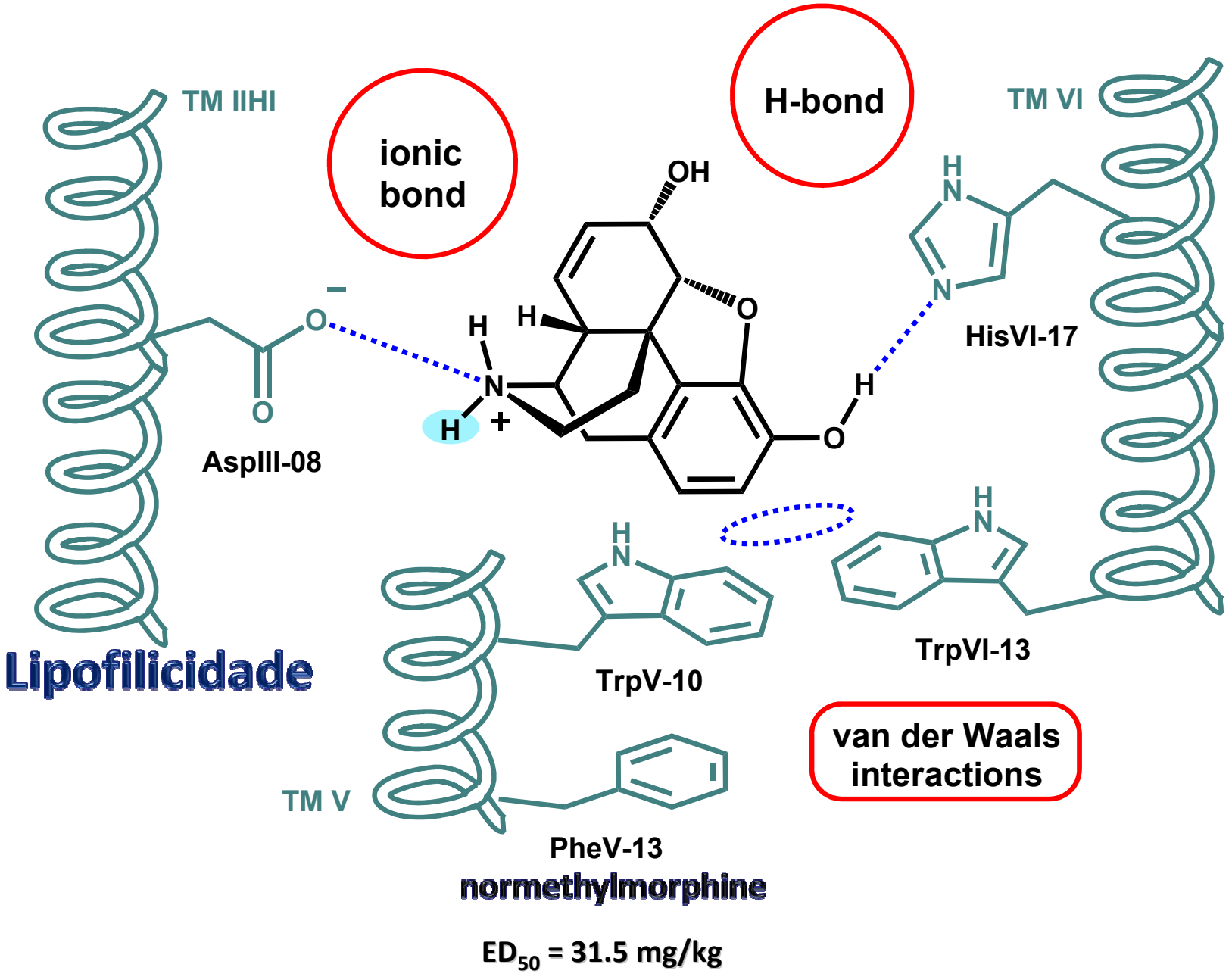
A *metila* e os Produtos Naturais



1805 - F. Setürner
1925 – R. Robinson

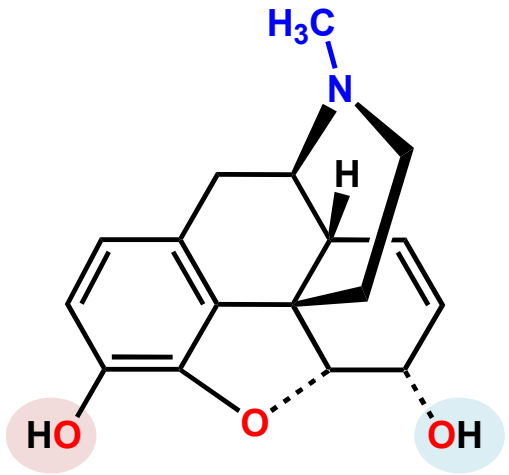
1947

A *metila* e os Produtos Naturais



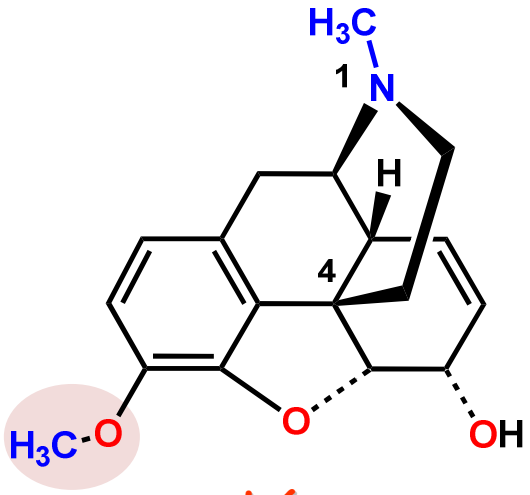
A *metila* e a morfina...

Índice de atividade analgésica



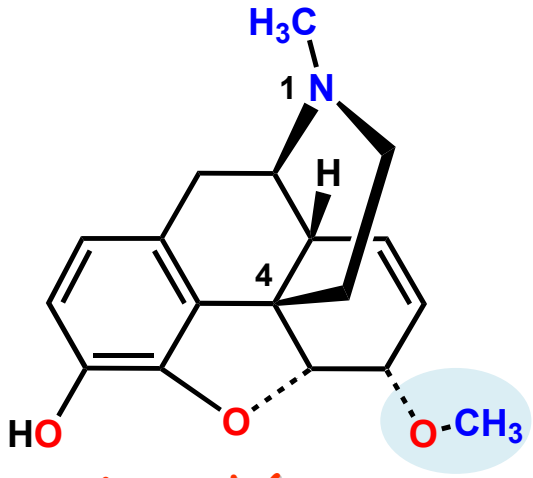
morfina

100



codeína

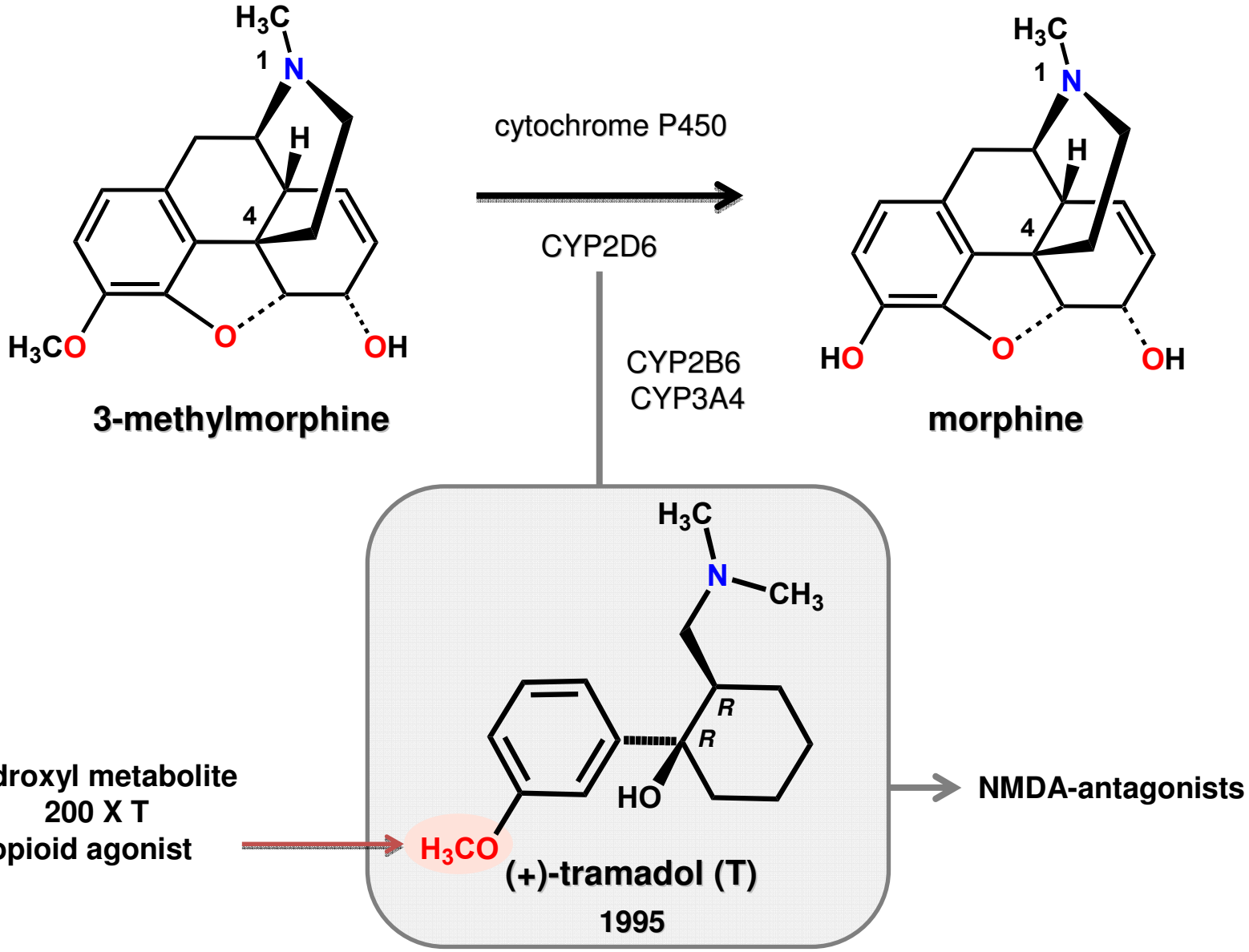
18



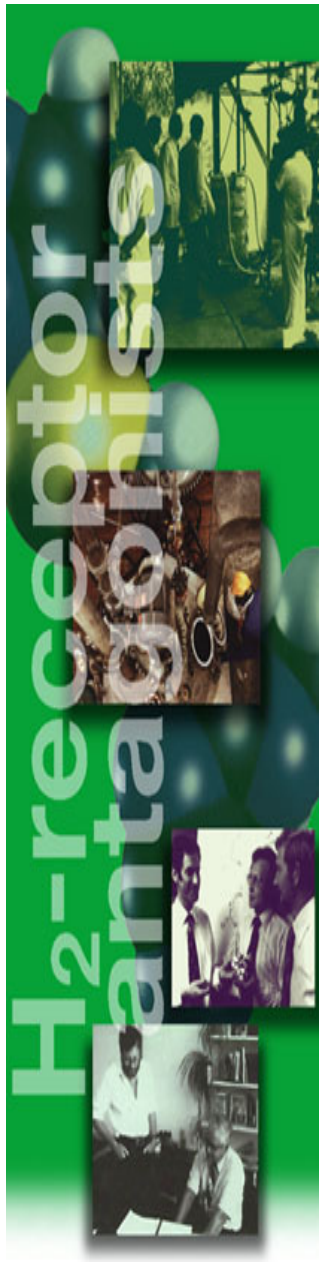
isocodeína

25

Quimiosseletividade metabólica



Inovação terapêutica



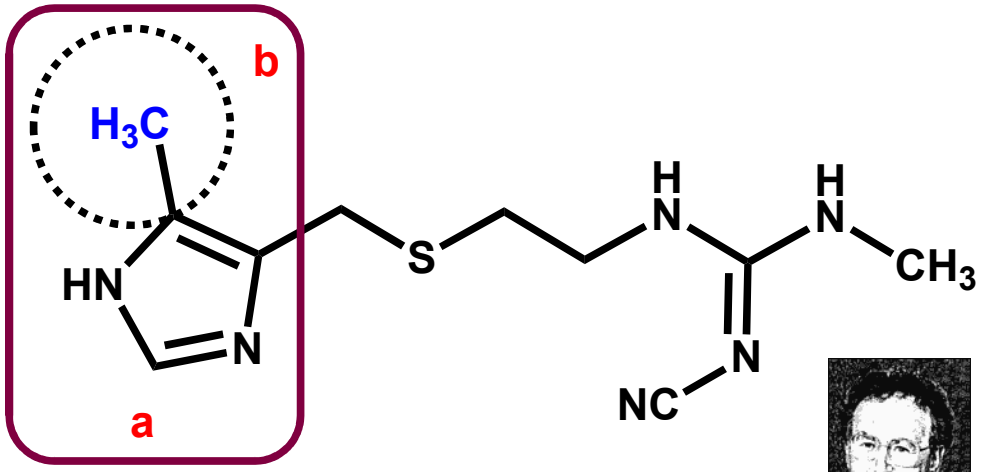
National Historic Chemical Landmarks

AMERICAN CHEMICAL SOCIETY

A new era of logical drug design

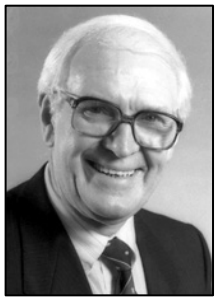
The research program leading to cimetidine also represented a revolution in the way pharmaceuticals are developed. Traditionally, the development of a new drug would often depend on the fortuitous discovery of a plant or microbial extract that showed some of the required biological activity. Using that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

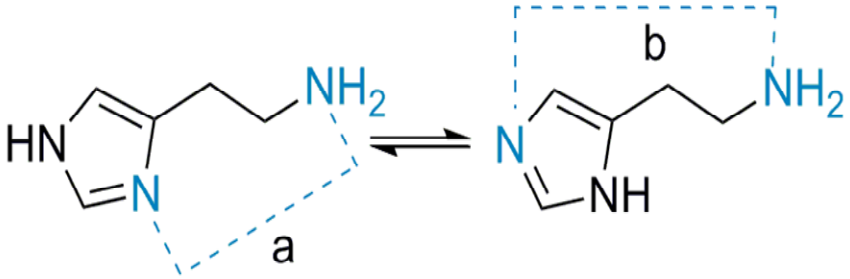
John C Emmett

Graham J Durant

A *metila* na descoberta da cimetidina

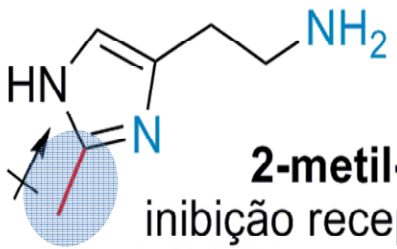
Dois sub-tipos de H_R

Weak interactions

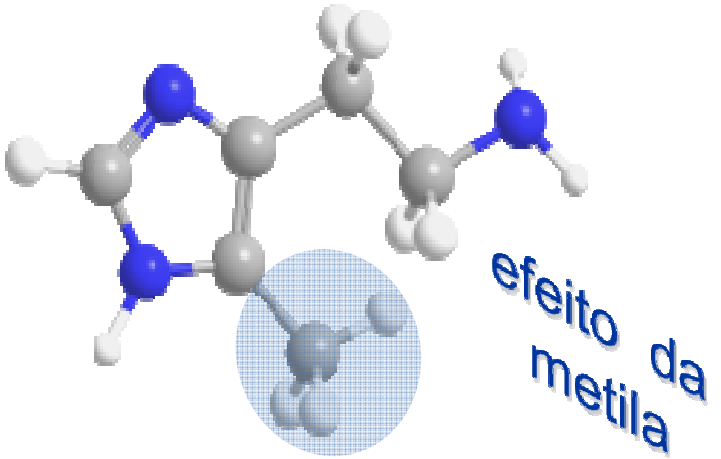


Forma A a = 4,83 Å b = 5,52 Å **Forma B**

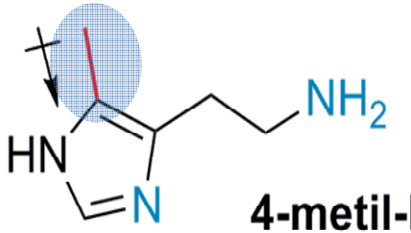
Tautomere equilibrium



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



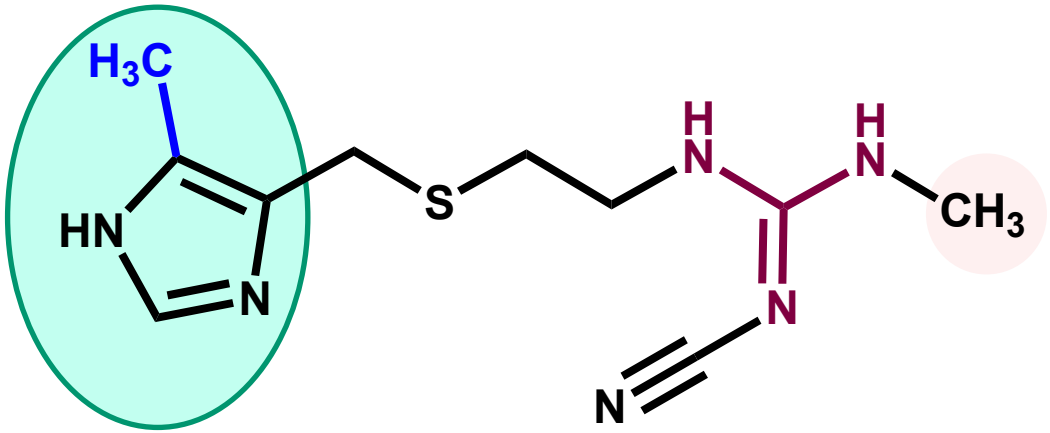
4-metil-histamina



Active analog

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

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



cimetidina

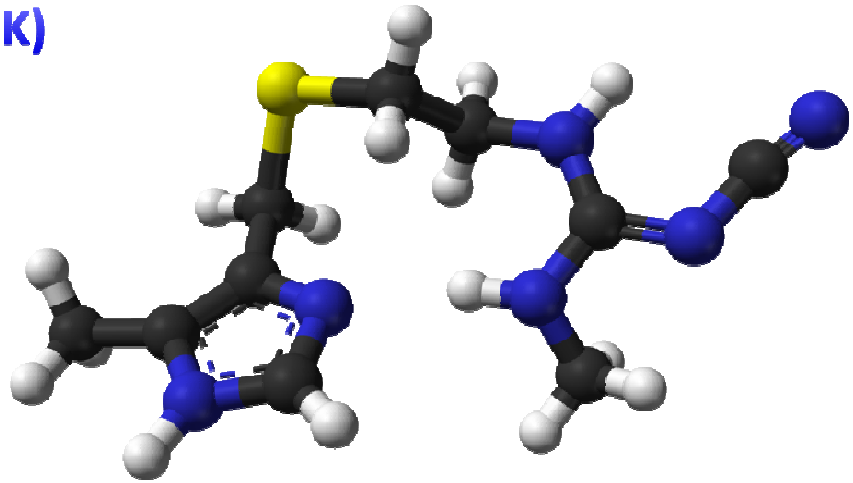
$C_{10}H_{16}N_6S$

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

1st blockbuster

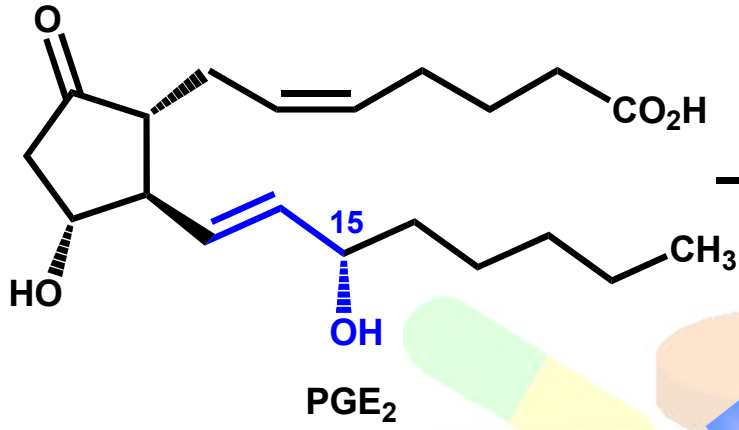
1975

> US$ 1 bi



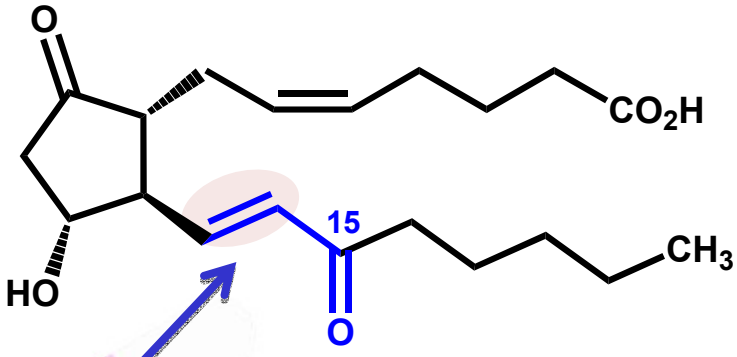
Selective H_2-receptor antagonist

A metila previnindo o metabolismo



PGE$_2$

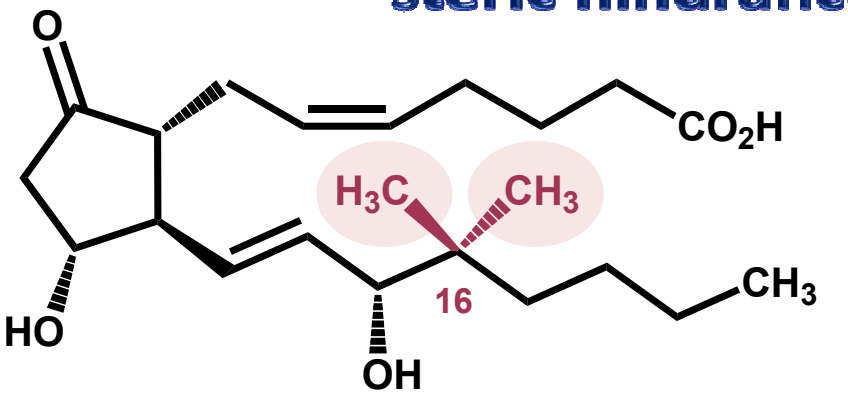
PGDH



15-ceto PGE$_2$

PG-redutase (PGR)

steric hindrance



16,16-dimethyl PGE$_2$

EP$_2$ ag (1 nM)

John R. Vane

(1927-2004)

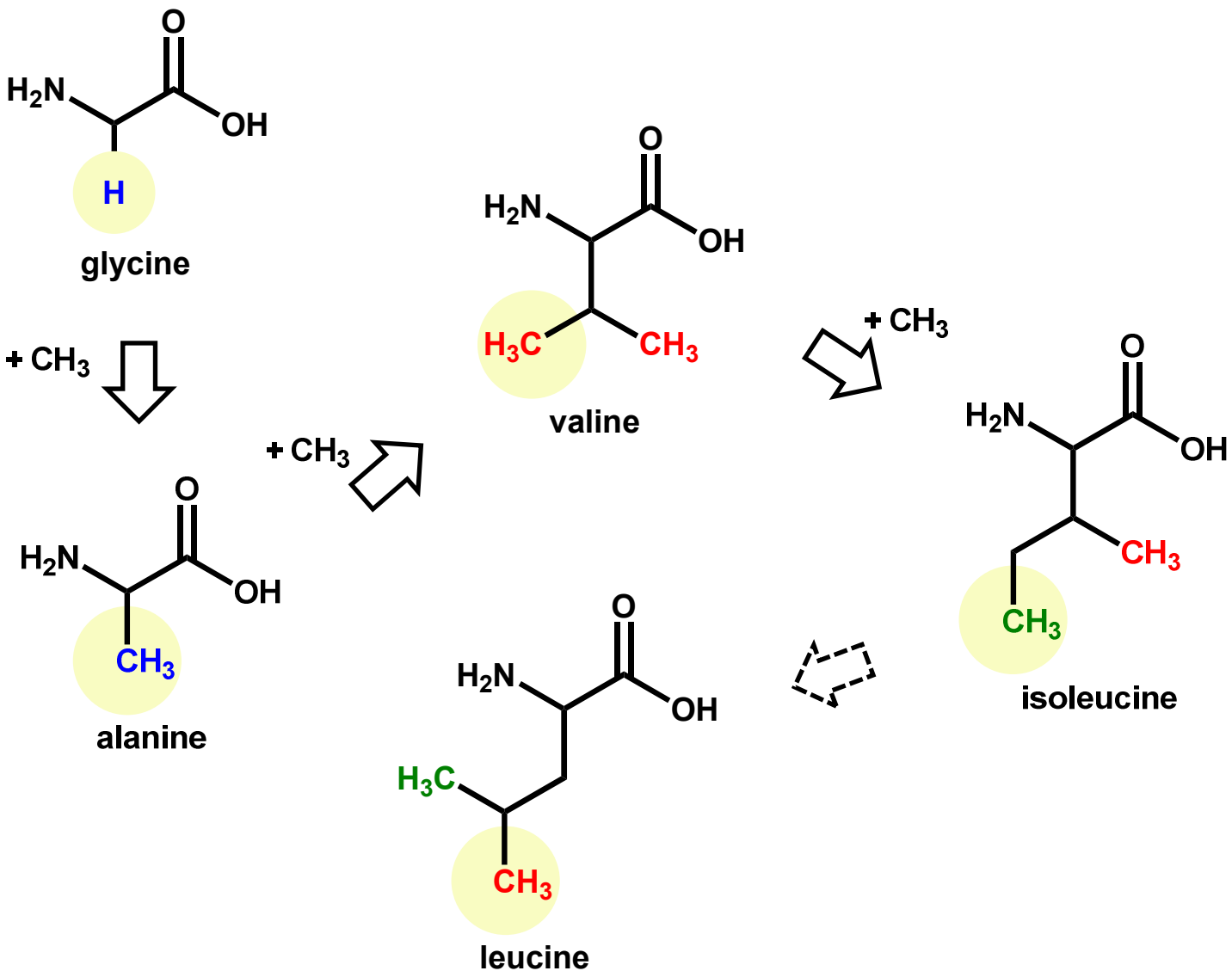
Sune K. Bergström

(1916-2004)

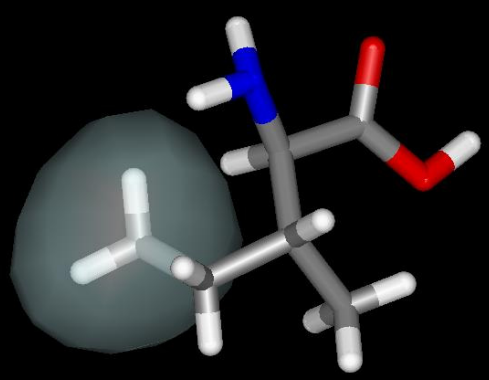
1982

Bengt I. Samuelsson

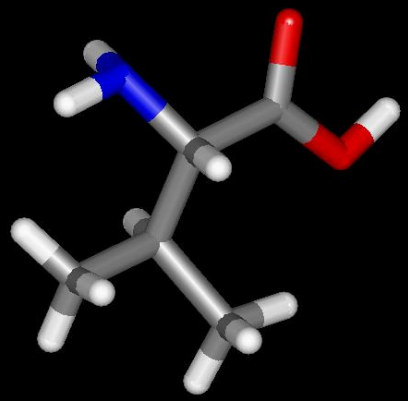
A homologia da metila e os AA´s



A homologia da metila e os AA´s

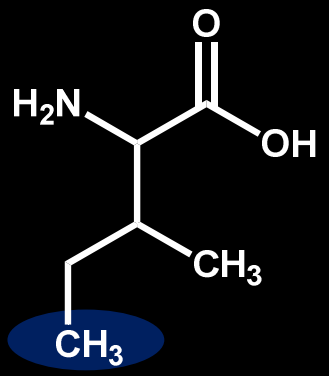


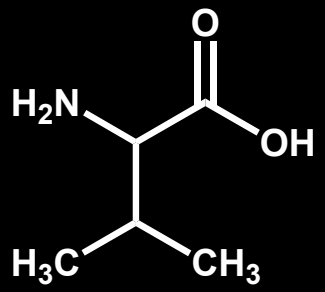
+ CH_3



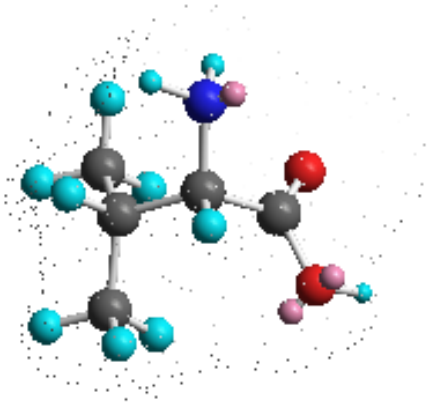
isoleucina

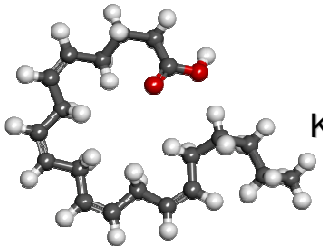
valina





Os AA homólogos e a COX

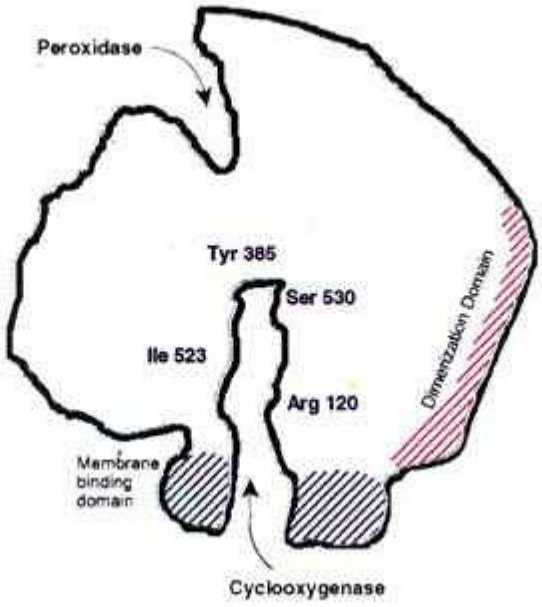




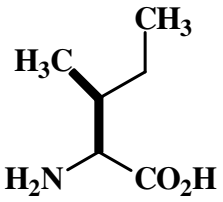
Arachidonic acid
K_m = 5,6/5,4 µM

COX-1

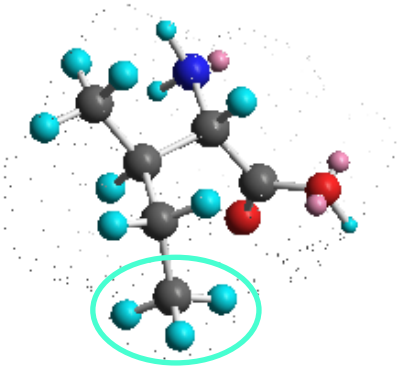
- Estômago
- Plaquetas
- Rins



c.



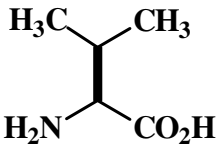
$C_6H_{13}NO_2$
Isoleucina



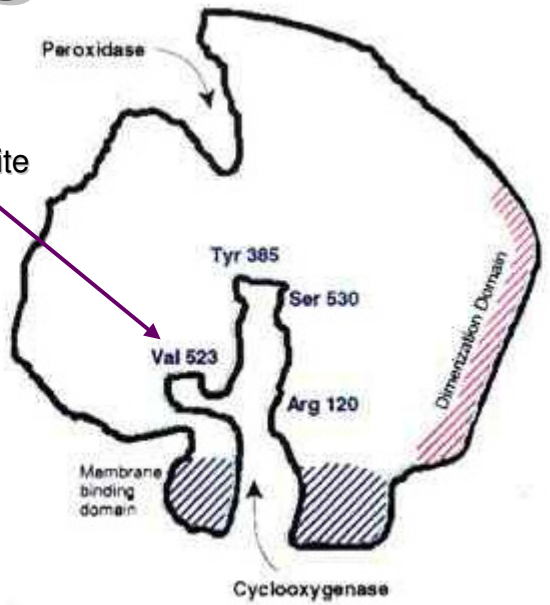
COX-2

- Inflamação
- Câncer
- Endotélio vascular
- Rins
- Cérebro

Secundary pocket site

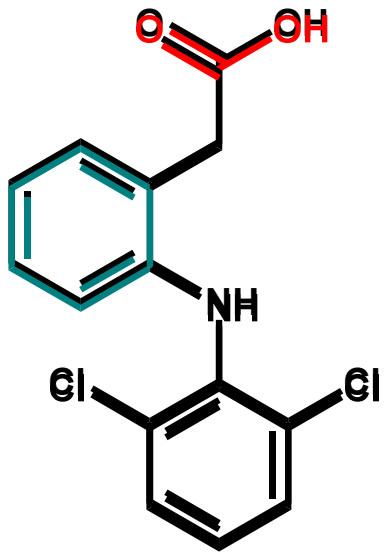


$C_5H_{11}NO_2$
Valina

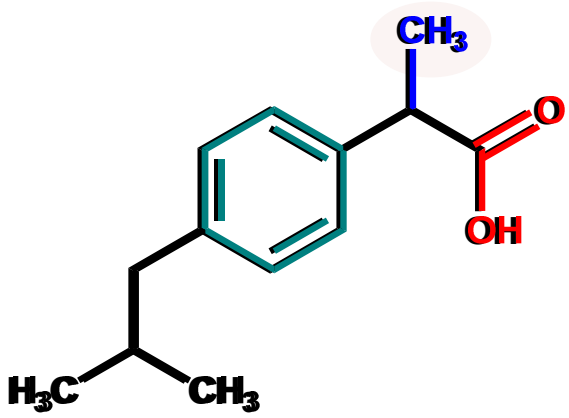


b.

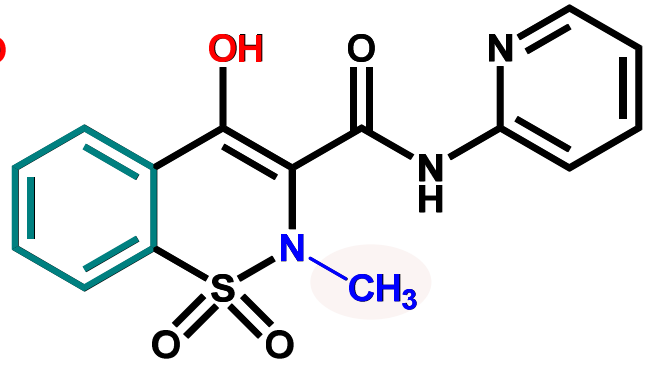
Antiinflamatórios não esteróides



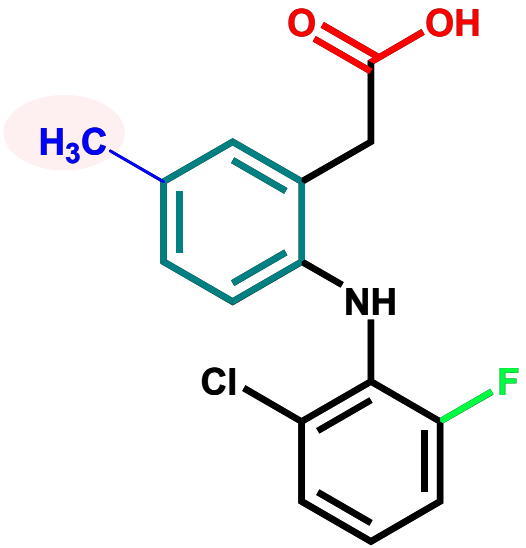
diclofenac



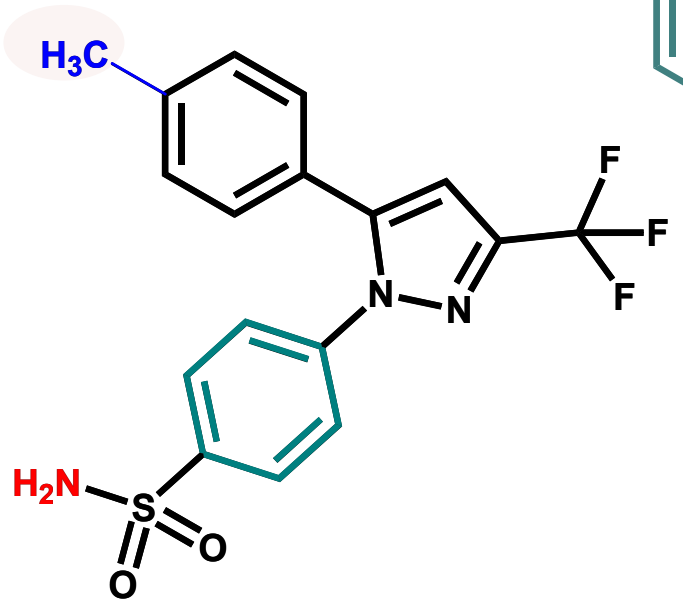
ibuprofen



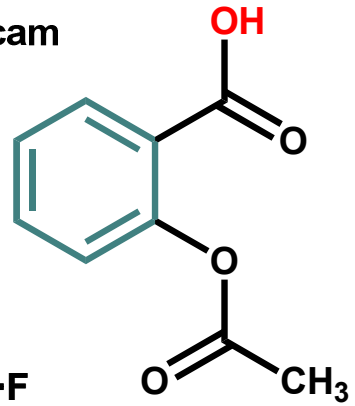
piroxicam



lumiracoxib



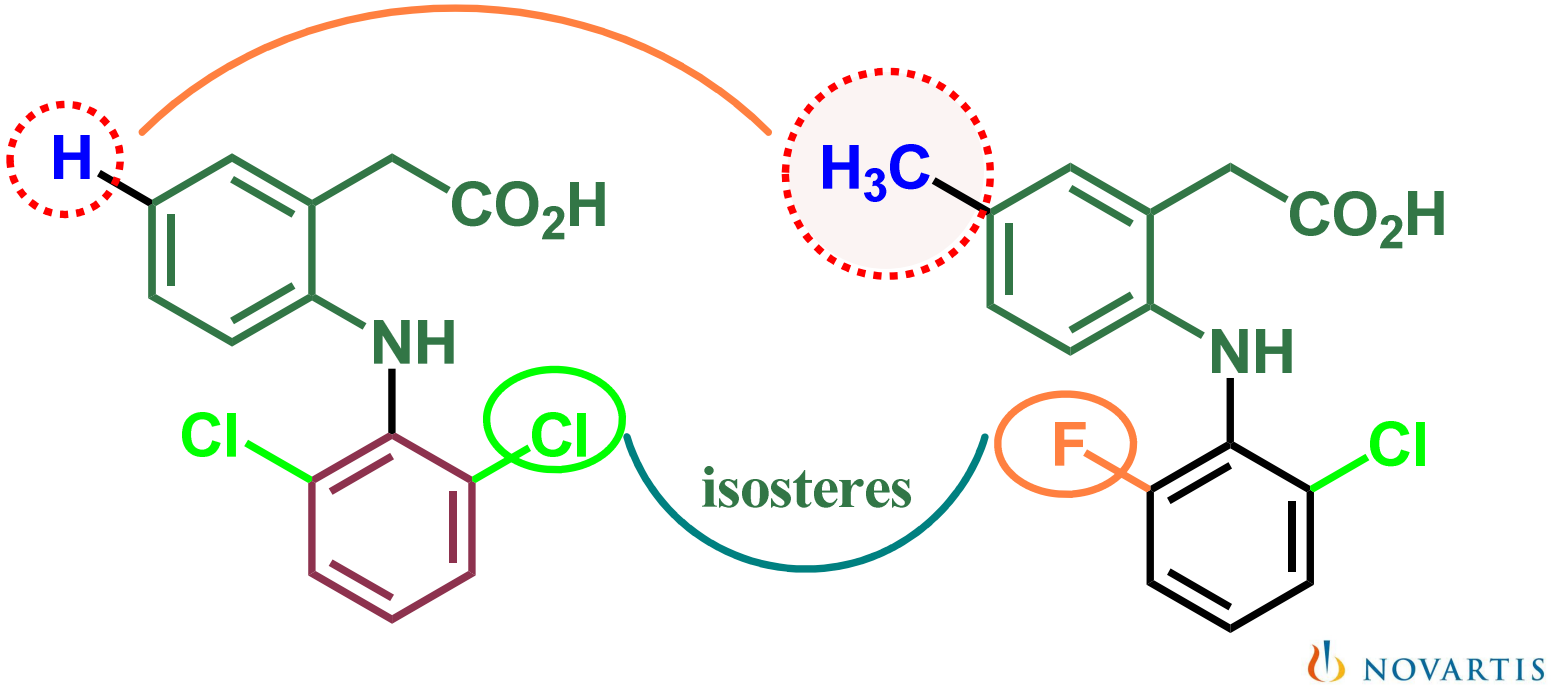
celecoxib



AAS

Top star of bioactive acetates

O charme da metila...



DICLOFENAC

COX-1

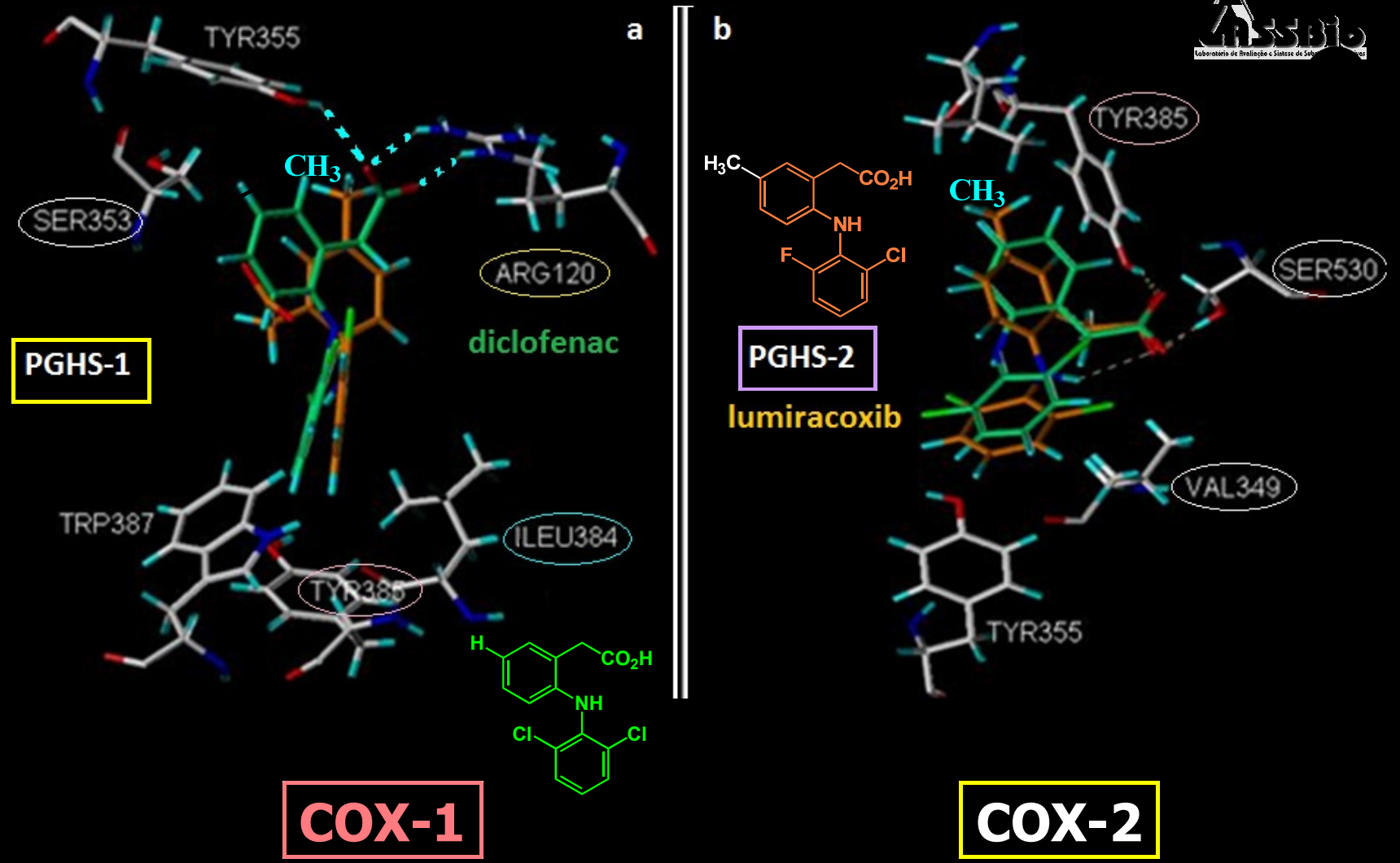
LUMIRACOXIB

COX-2

2006 (2007)

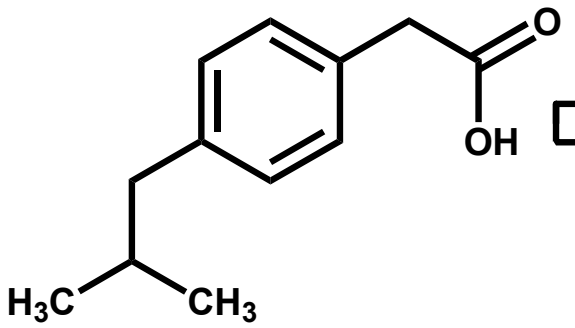
Lumiracoxib have one chlorine substituted by fluorine and the phenylacetic acid moiety has methyl group in meta position

A seletividade entre COX-1 e COX-2



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

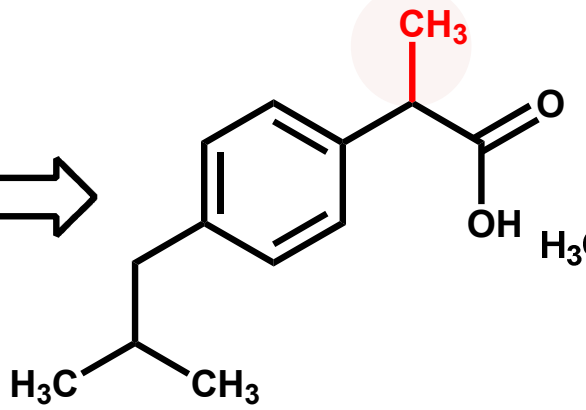
A metila e a quiralidade



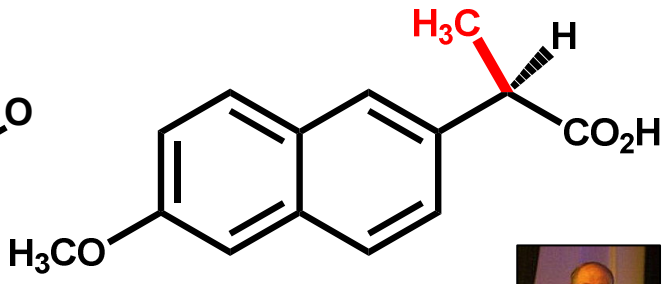
ibufenac

S Adams

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



ibuprofen
(1961)

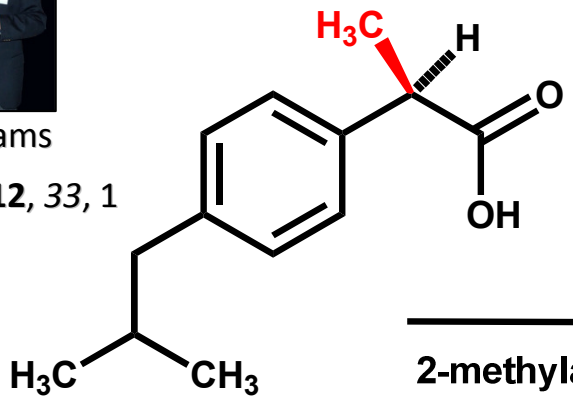


naproxen
(1976)
S(uper)-Naprosin^{R}

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

R Noyori

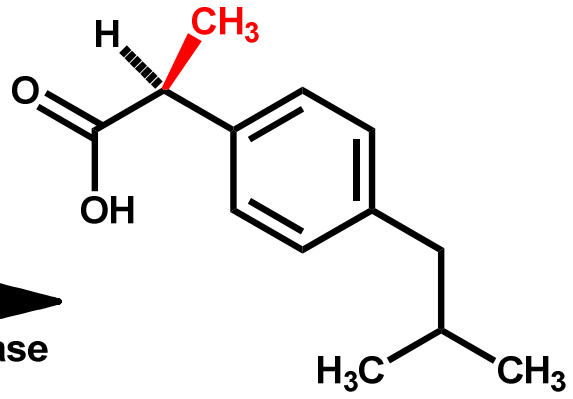
2001



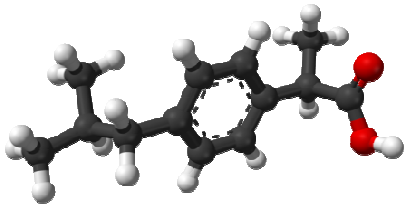
liver

2-methylacyl-CoA 2-epimerase

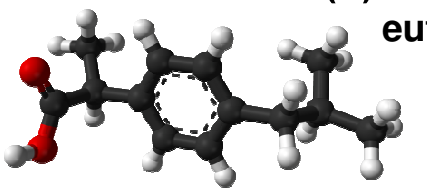
in vivo



(*R*)-ibuprofen

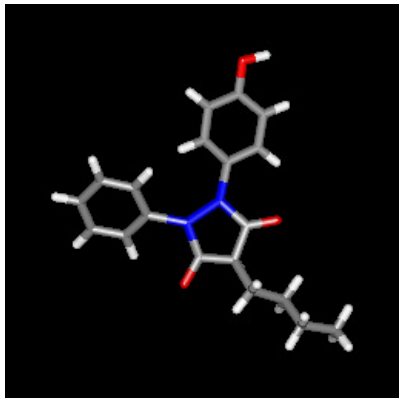


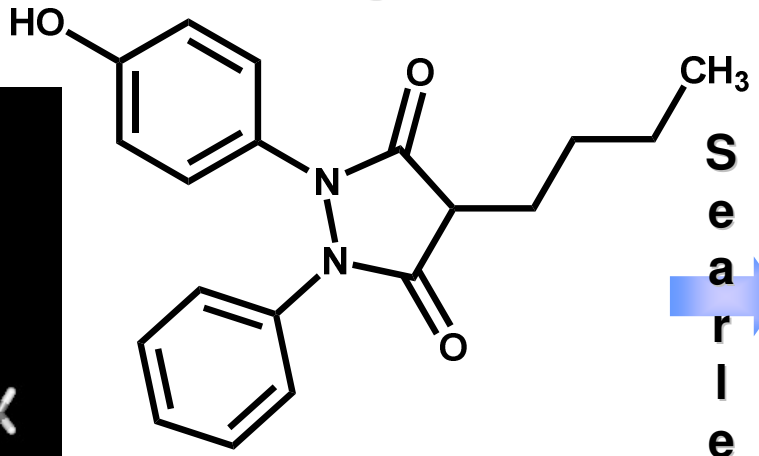
σ



(*S*)-ibuprofen
eutômero

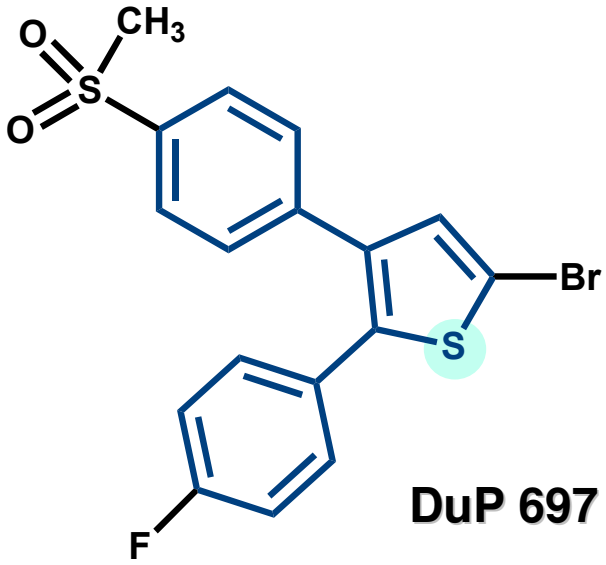
A metila e a gênese do celecoxibe





1956 – Oxifenilbutazona

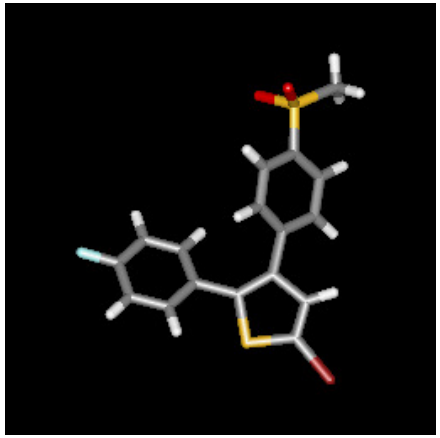
Searle

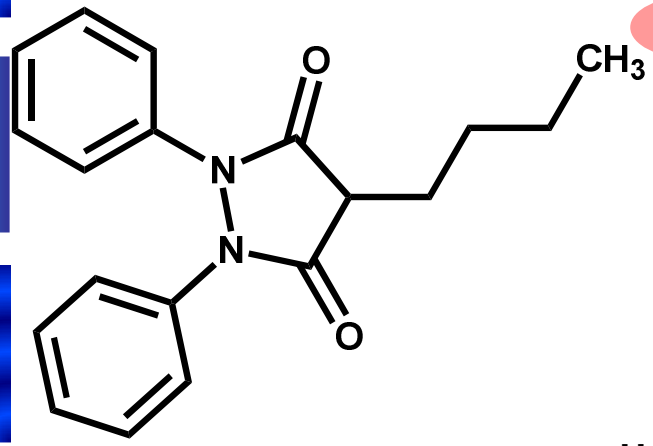


DuP 697

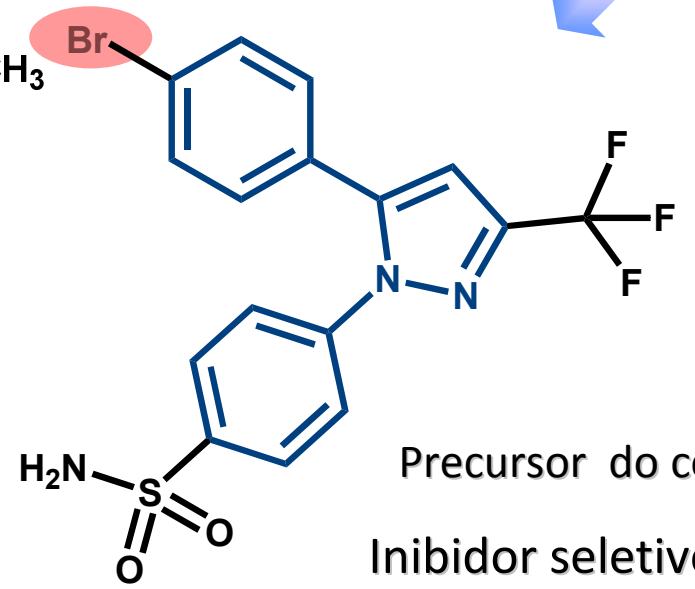
Geigy

estudos de metabolismo





1951 – fenilbutazona

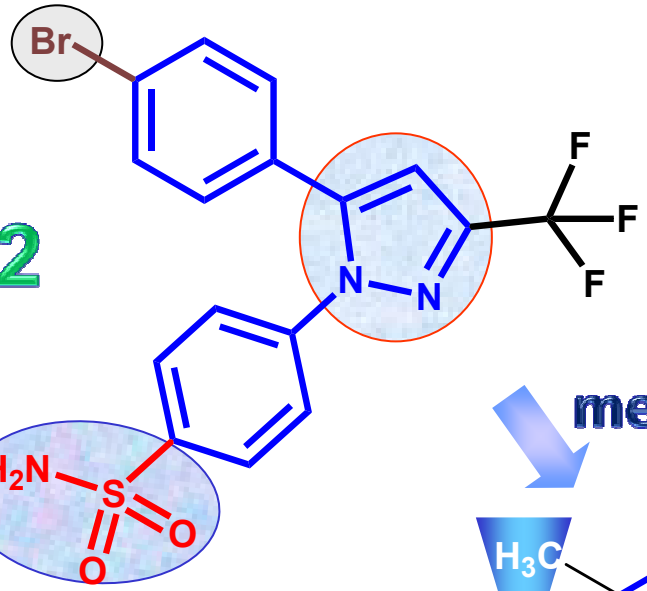


Precursor do celecoxibe

Inibidor seletivo de COX-2

A metila e a gênese do celecoxibe

PGHS-2

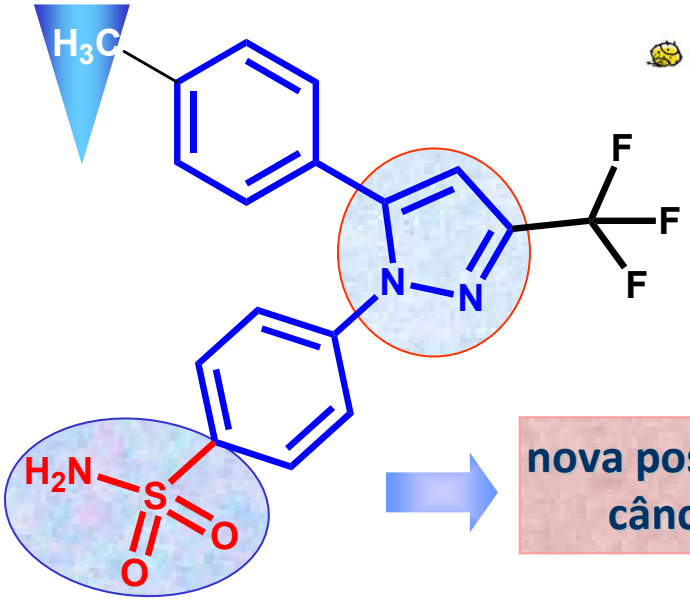


COX-2 seletivo
Searle

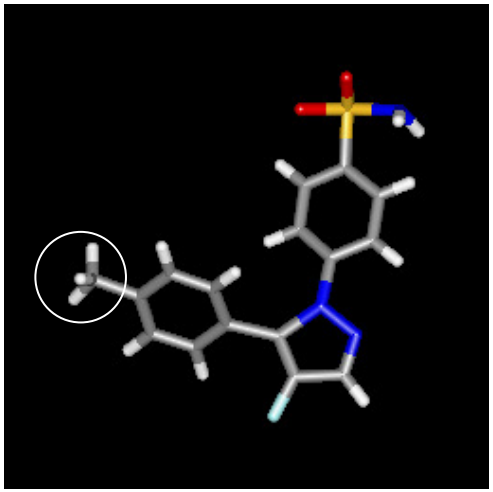
Vida-média = 12 dias !
(ADME)

Pfizer

metabolismo



nova possível indicação:
câncer coloretal

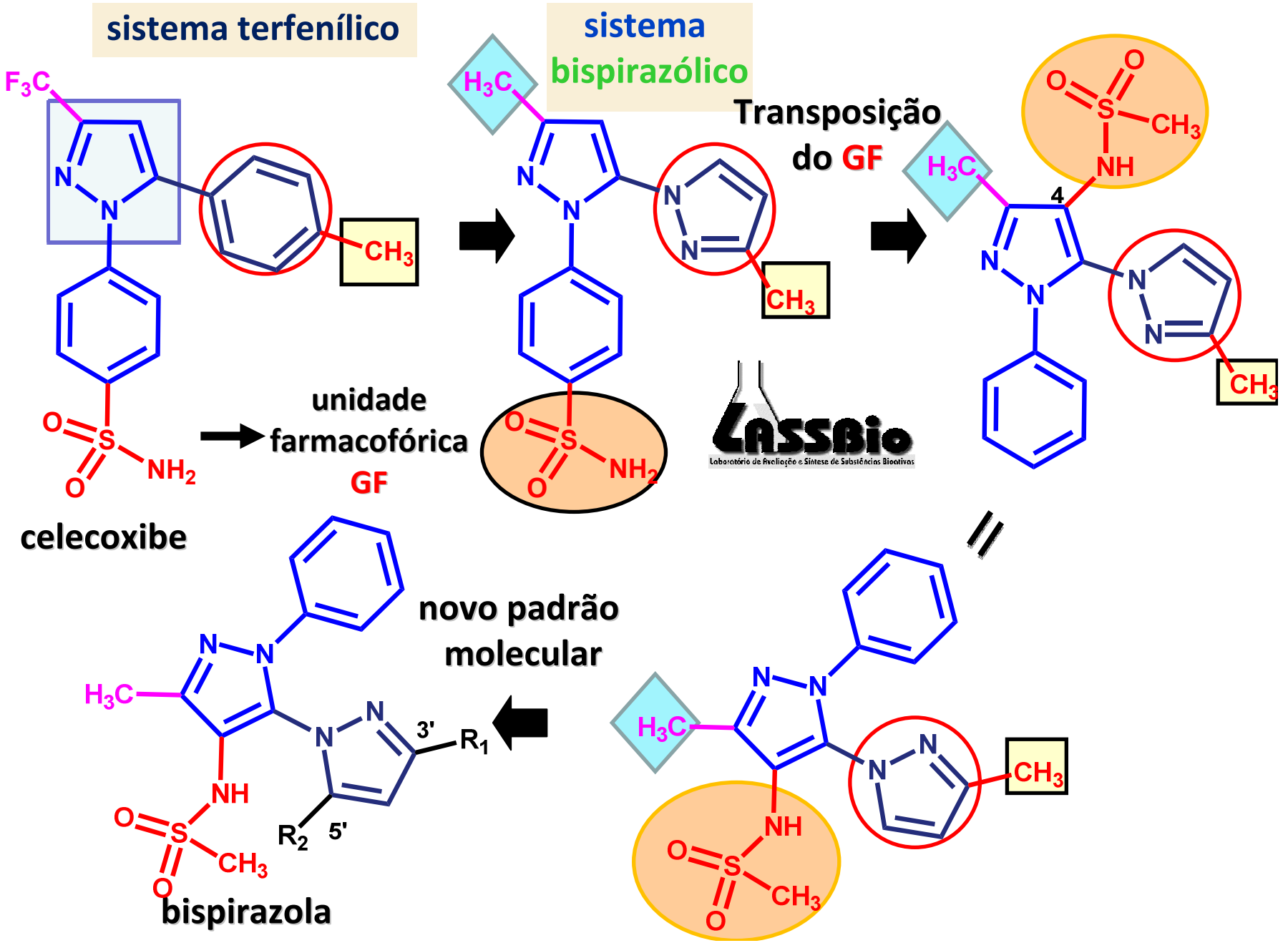


TD Penning *et al., J. Med. Chem.* **1997**, *40*,1347

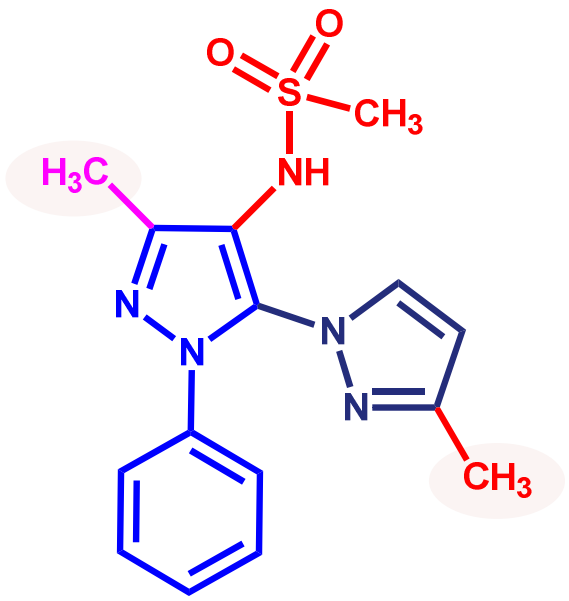
Celecoxibe (SC-58634)
1999

The global market for arthritis drugs was *ca.* US$ 32 billion (in 2008)

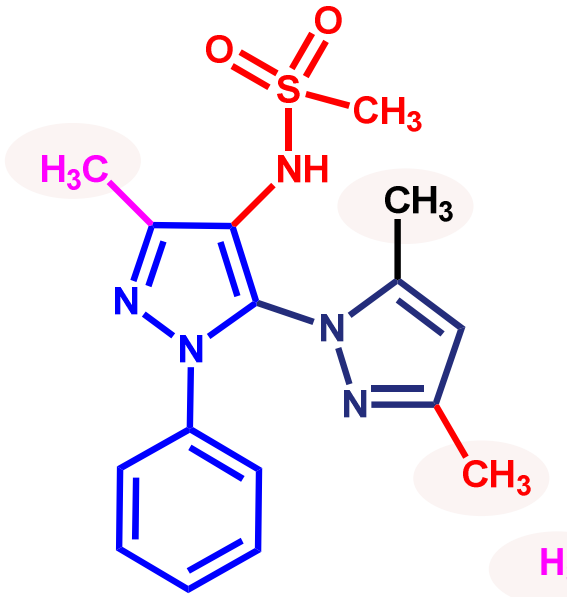
Desenho estrutural de novos COX-2i bispirazólicos

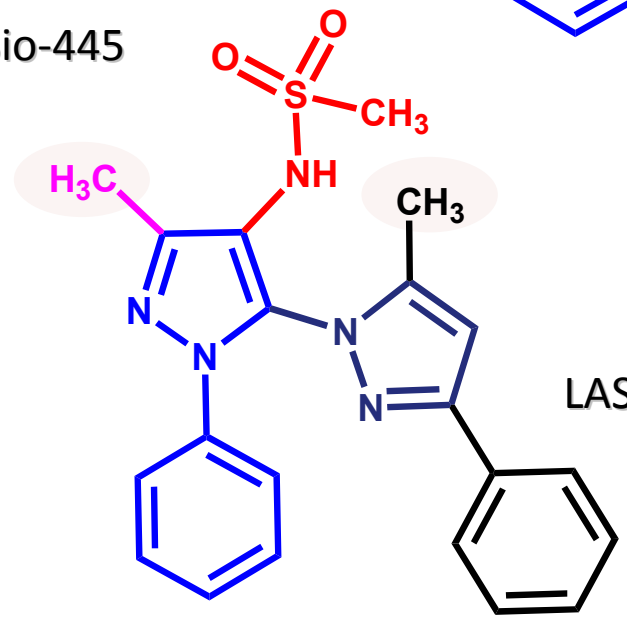


Série congênere dos novos COX-2i bispirazólicos

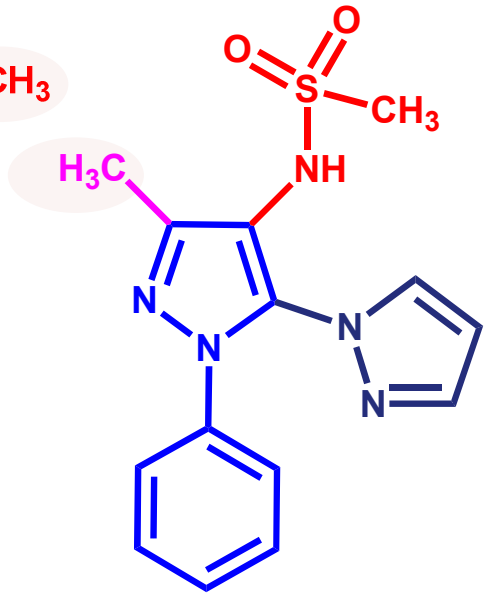


LASSBio-445





LASSBio-466

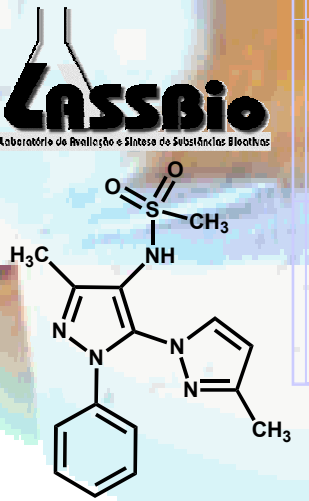


MP Veloso, Tese de Doutoramento, Instituto de Química, UFRJ, 2000

Novo protótipo de COX-2i

CgIRPE*

		DI_{50}	Max. Eff.
1999	CELECOXIB 	87,7 µmol/kg	35%
	LASSBio 715	44,3 µmol/kg	39%
	LASSBio 445	54,6 µmol/kg	37%

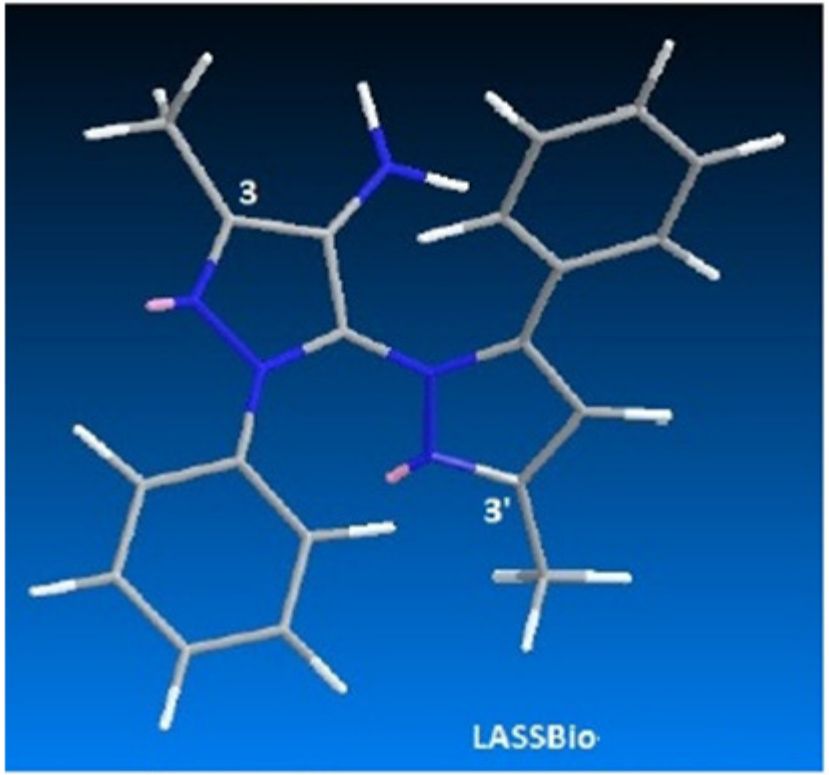


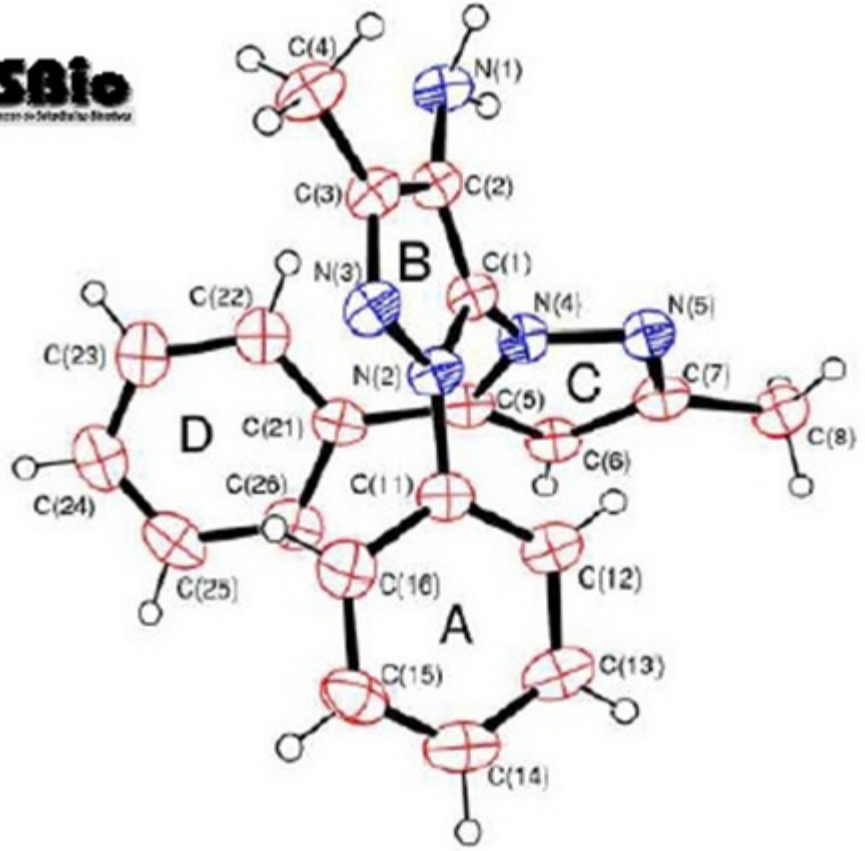
Patent: PI 9902960-0 (29/04/99)

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

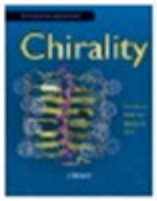
Atropoisomerismo em bispirazóis bioativos

quiral



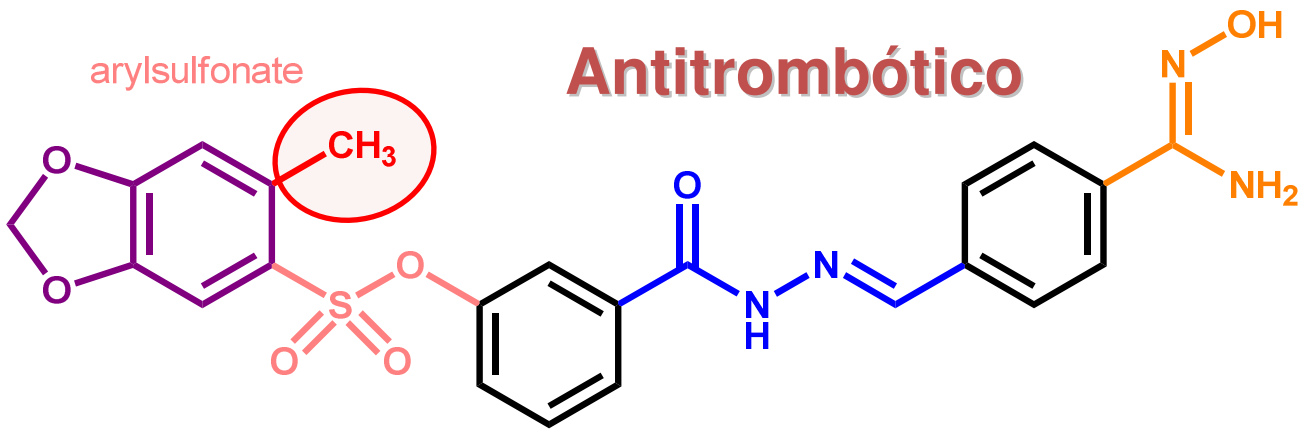


ORTEP view of ***P***-atropisomer



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.

Antitrombótico

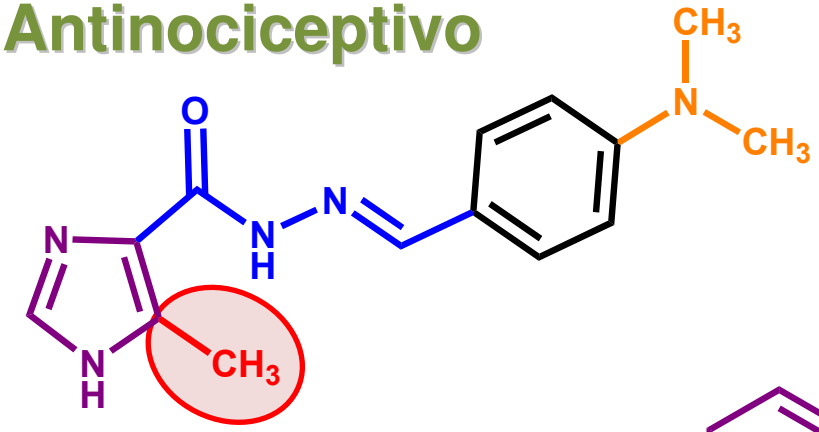


LASSBio®

LASSBio-770

LM Lima *et al*., *Eur. J. Med. Chem*. **2008**,

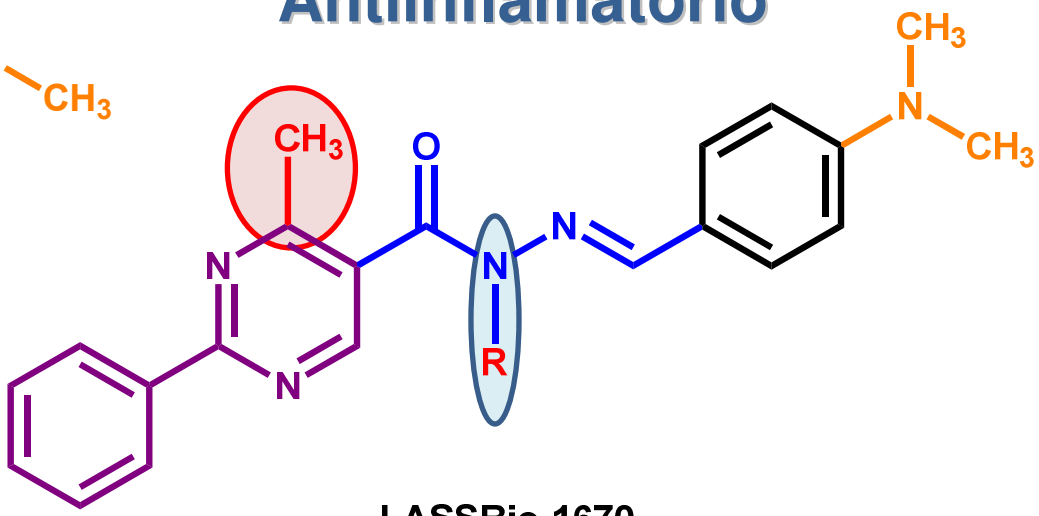
Antinociceptivo



LASSBio-456

JM Figueiredo *et al*., *Bioorg. Med. Chem*. **2008**, *43*, 187

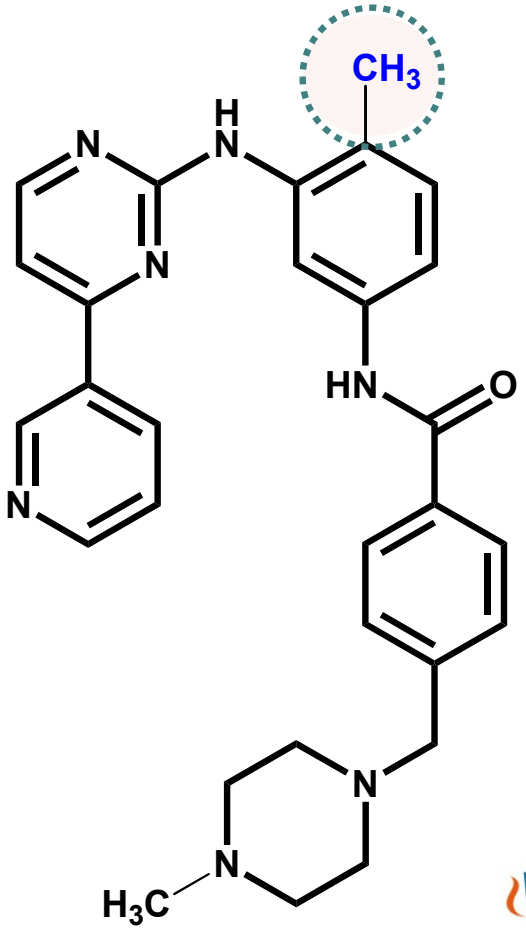
Antiinflamatório



LASSBio-1670

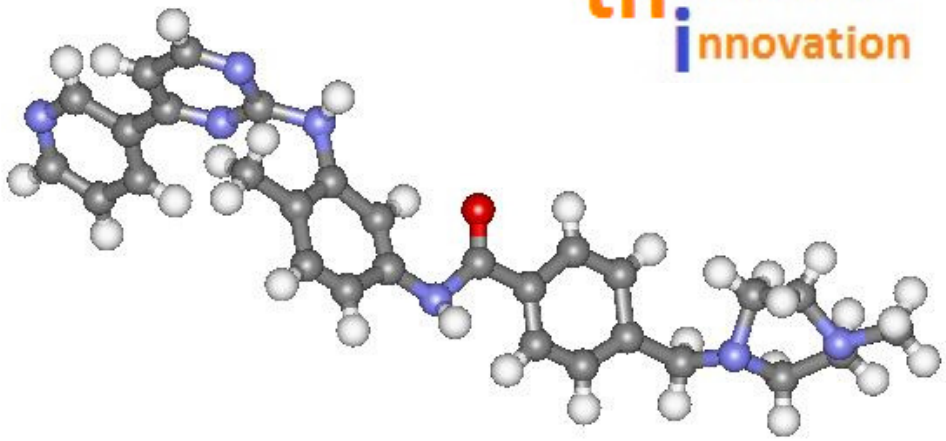
AB Lopes, Diss. Mestrado, Instituto de Química, 2011

A metila e a gênese do imatinibe



imatinibe

2001



NOVARTIS

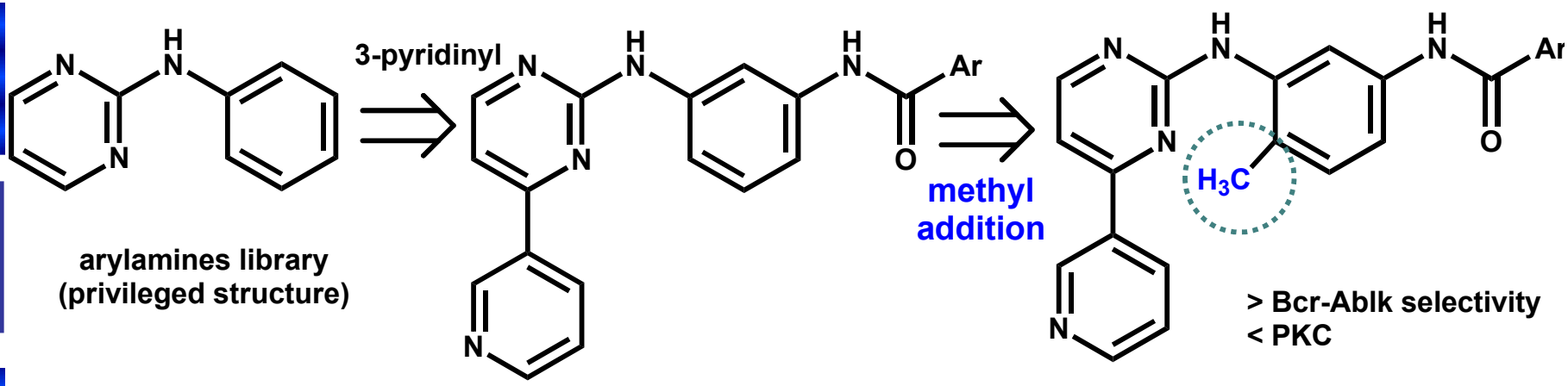
Jürg Zimmermann

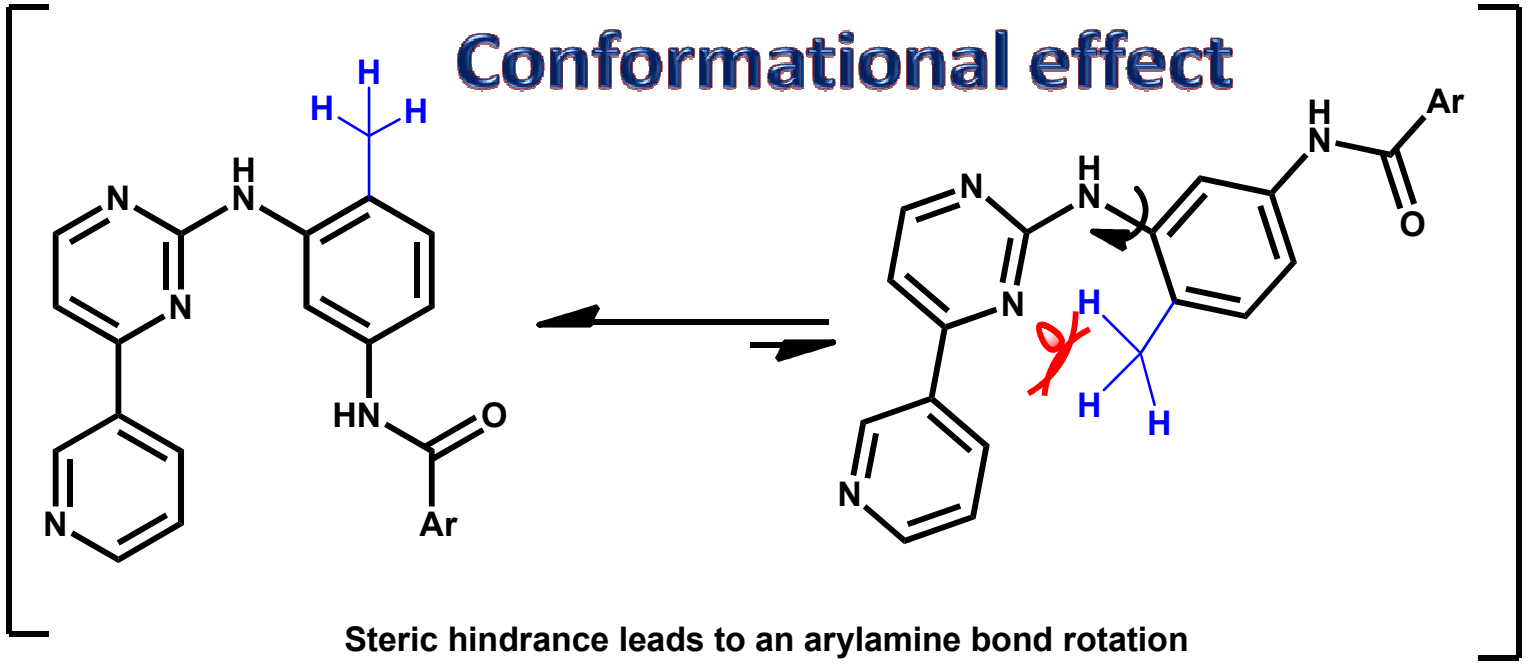
Elisabeth Buchdunger

Brian J. Druker

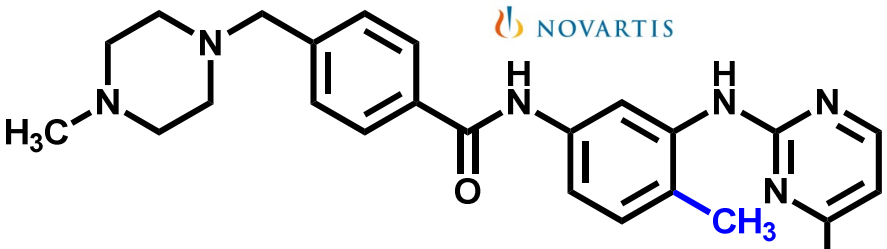
OREGON HEALTH & SCIENCE UNIVERSITY

A metila e a gênese do imatinibe





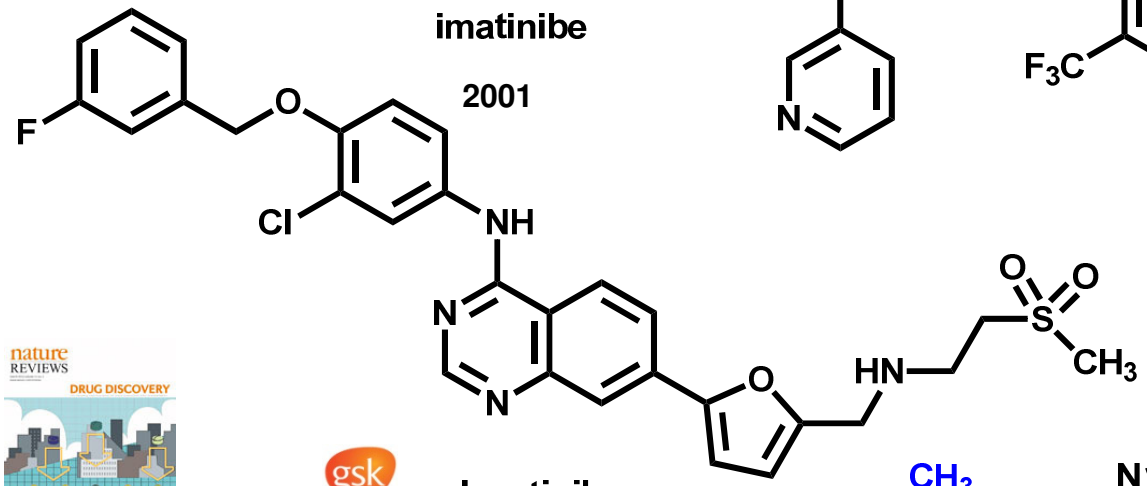
Tinibes



NOVARTIS

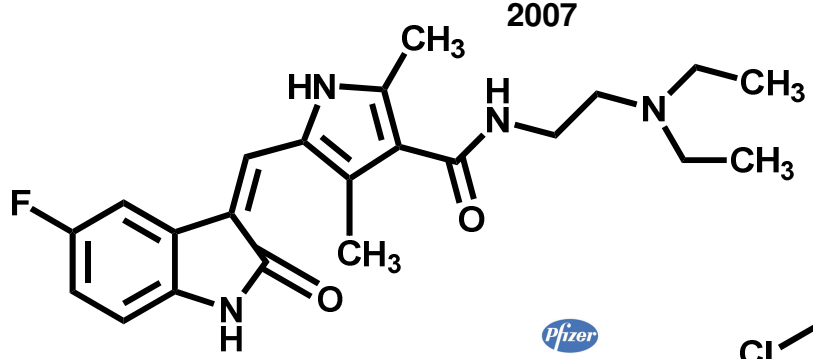
imatinibe

2001



lapatinibe

2007



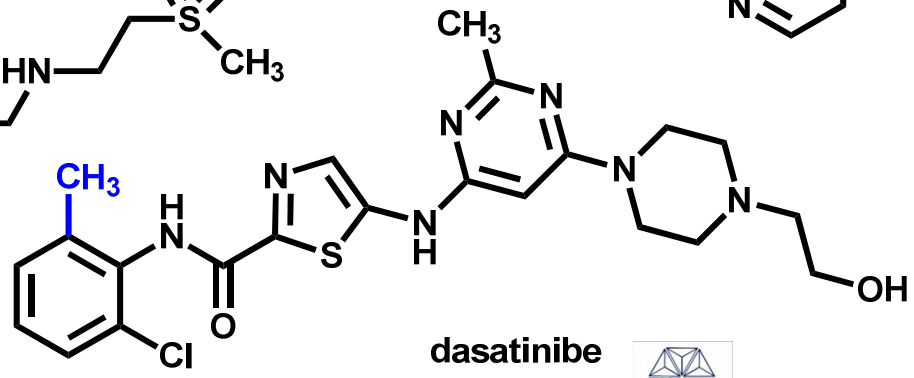
sunitinibe

2006

NOVARTIS

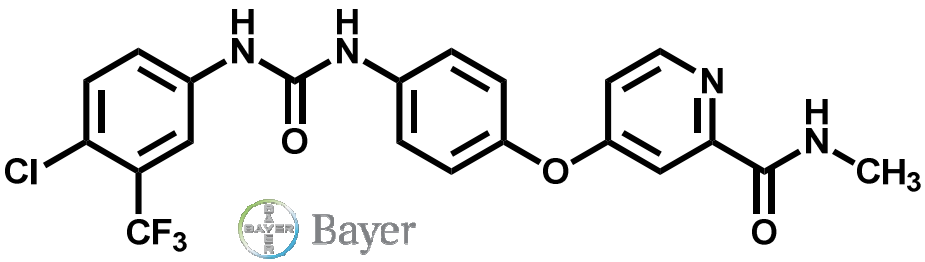
nilotinibe

2006



dasatinibe

2007



Bayer

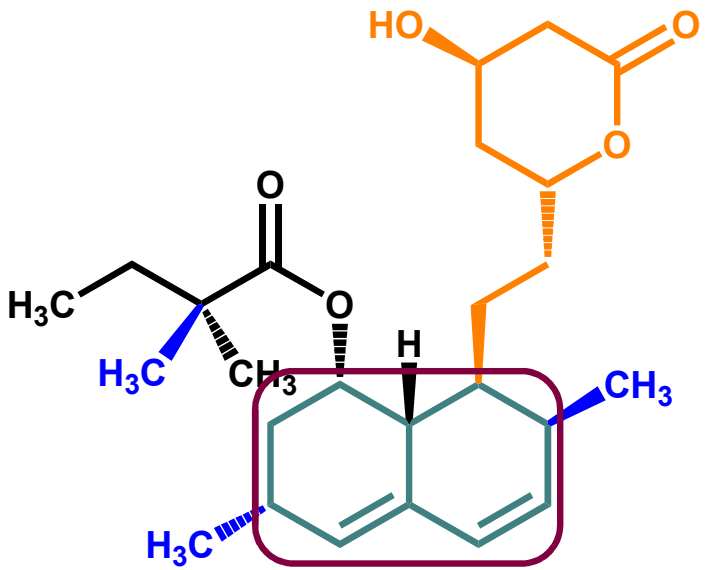
sorafenibe

2007

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

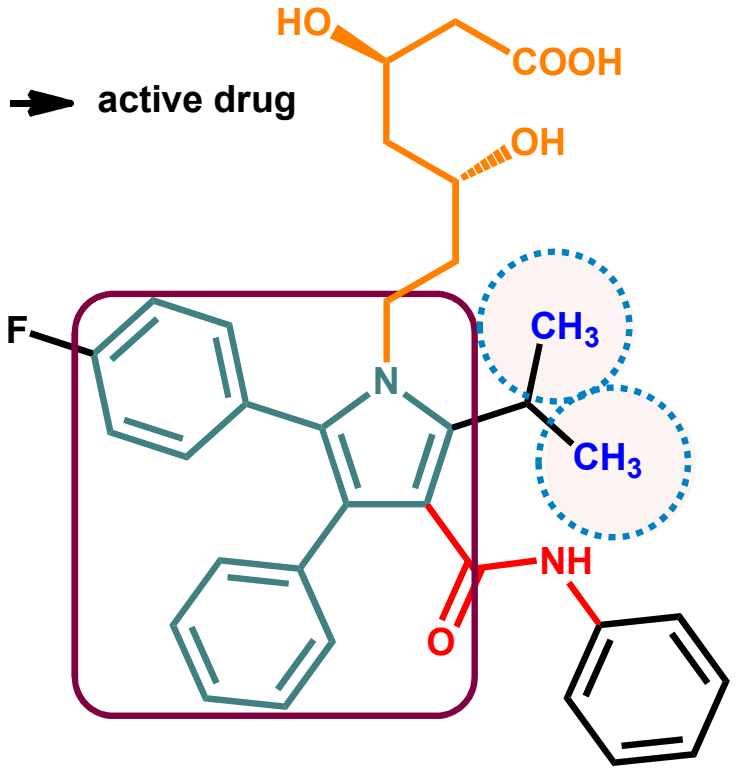
* S Aggarwal, *Nature Rev Drug Discov* **2010**, *9*, 427

As *metilinhas* bilionárias…



simvastatin

prodrug-like → active drug



atorvastatin

B D Roth

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

A Endo

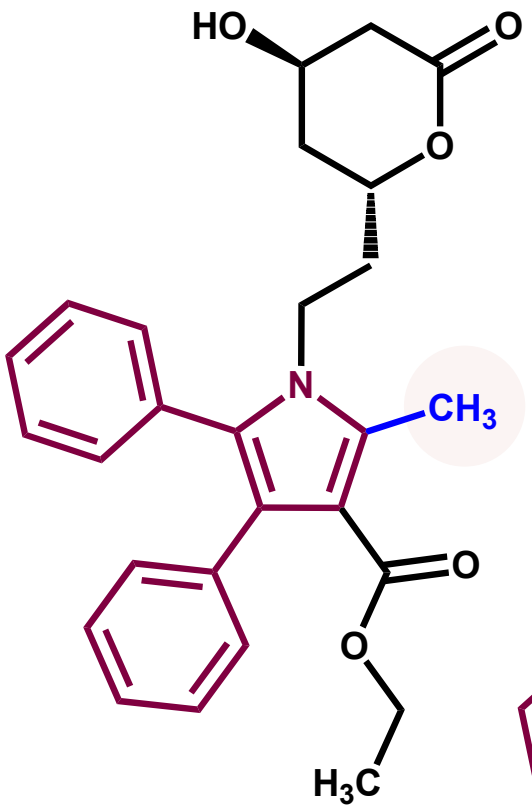
A A Patchett

MERCK

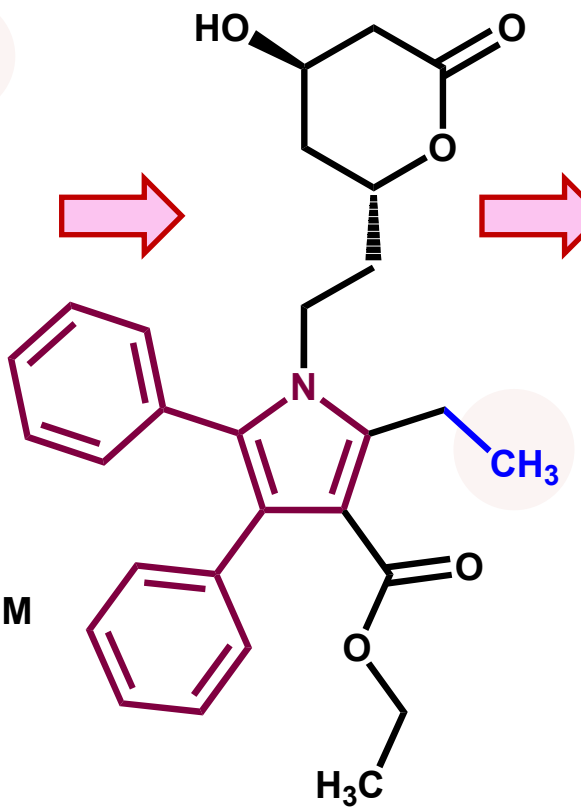
IC_{50} HMG-CoAR = 8 nM

Pfizer *blockbuster = > US$ 120 bi*

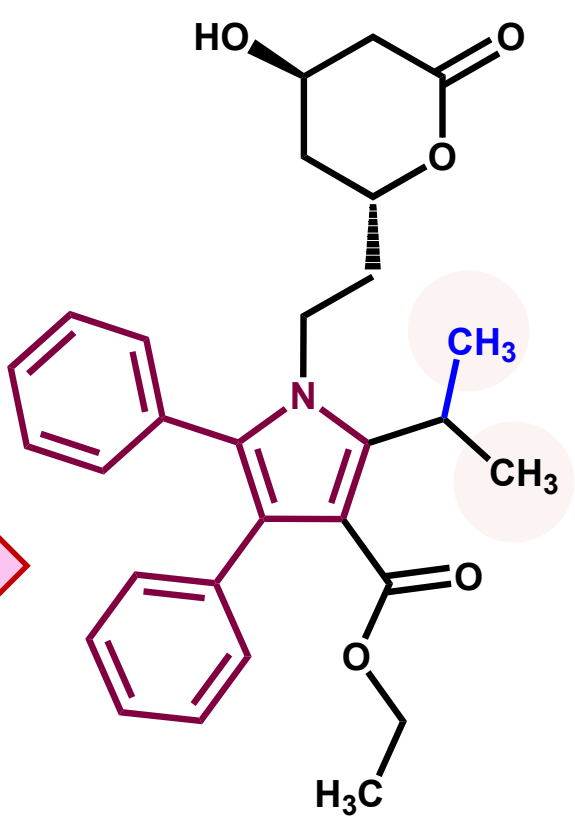
www.wikipedia.org



IC_{50} HMG-CoAR = 4000 nM



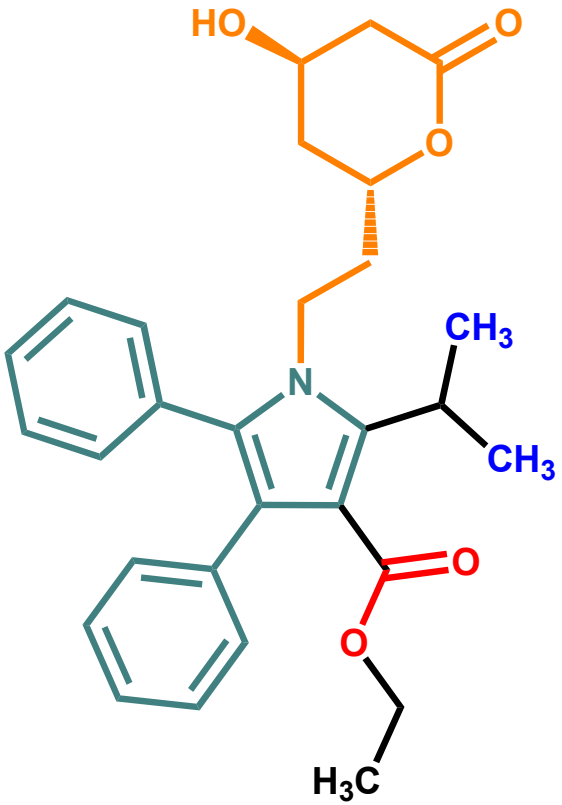
IC_{50} HMG-CoAR = 890 nM



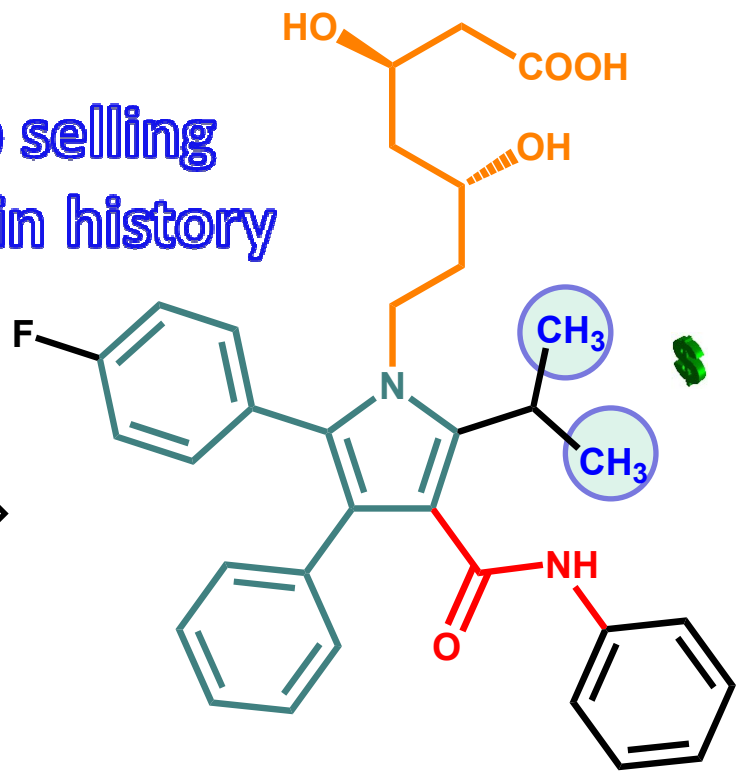
IC_{50} HMG-CoAR = 170 nM

As *metilinhas* bilionárias…

1 CH_3 = > US$ 3,6 bilhões



Top selling drug in history



IC_{50} HMG-CoAR = 170 nM

atorvastatin

IC_{50} HMG-CoAR = 8 nM

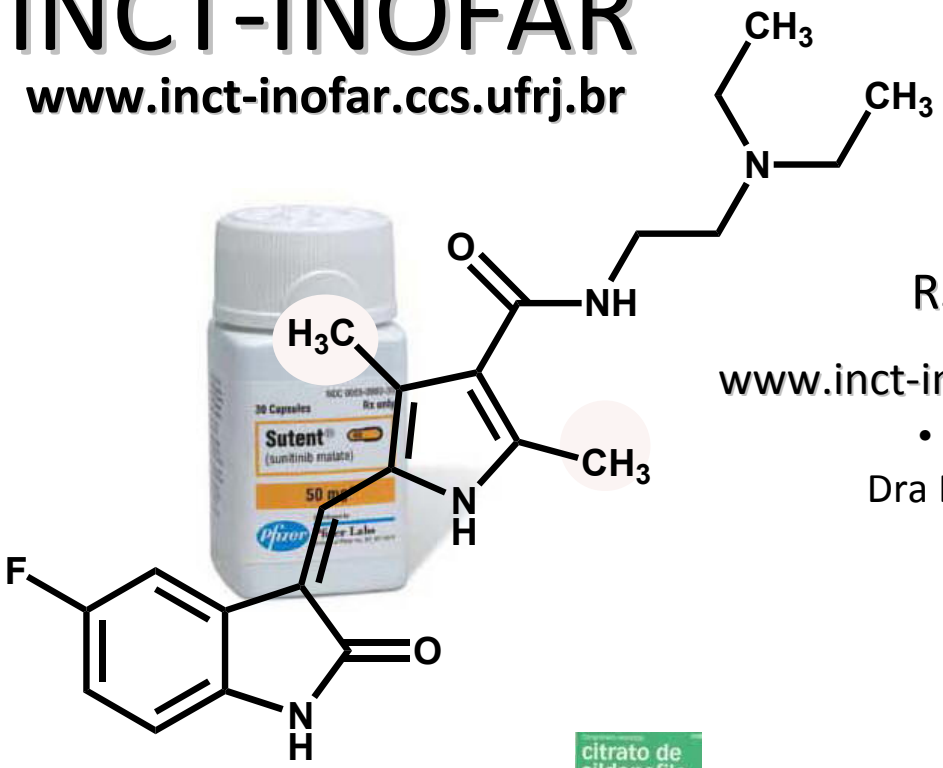
Biodisponibilidade = 12%

Patente venceu em novembro 2011 = US$ 13,3 bi

1 CH_3 = *ca*. US$ 403 mi

INCT-INOFAR

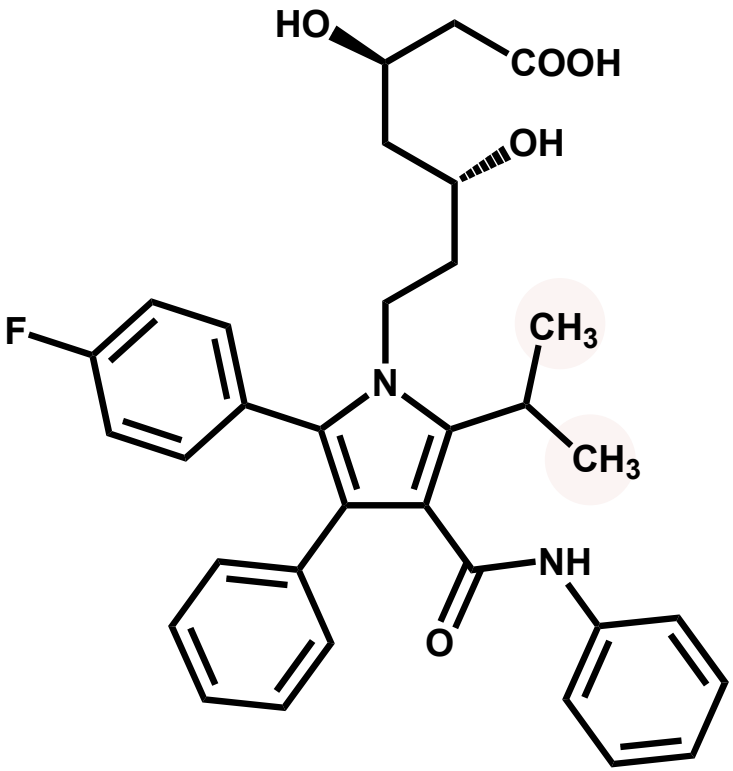
www.inct-inofar.ccs.ufrj.br



R$ 17.378,20 (1 cx. c/ 30 compr.)

www.inct-inofar.ccs.ufrj.br/release_sunitinibe.html

• Síntese Prof. Angelo da Cunha Pinto &
Dra Bárbara Vasconcelos Silva IQ-UFRJ (2011)

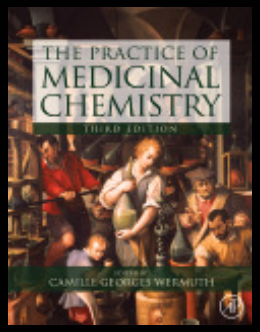


• Síntese Prof. Luiz Carlos Dias &
Dr Adriano Vieira Siqueira IQ-UNICAMP
(2010)

LC Dias, AV Siqueira, EJ Barreiro, Processo de obtenção de atorvastatina cálcica utilizando novos intermediários *PI 018110015039* (protocolado no INPI, em 25/04/2011)

Universidade Federal do Rio de Janeiro

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



Camille G. Wermuth

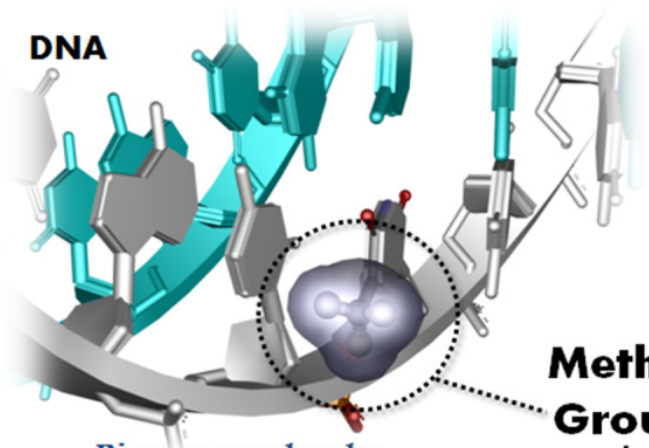
CHEMICAL REVIEWS
Chem. Rev. 2011, 111, 5215-5246
REVIEW
dx.doi.org/10.1021/cr200060g

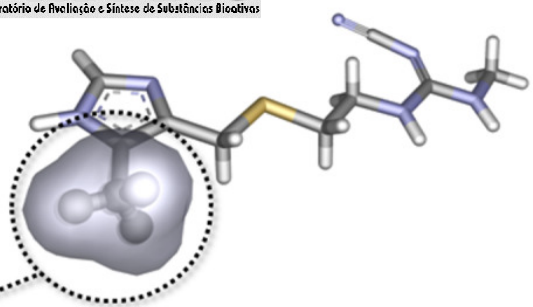
The Methylation Effect in Medicinal Chemistry

E. J. Barreiro, A. E. Kümmerle and C. A. M. Fraga

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

Química Medicinal





Methyl Group

CH_3

15 Da

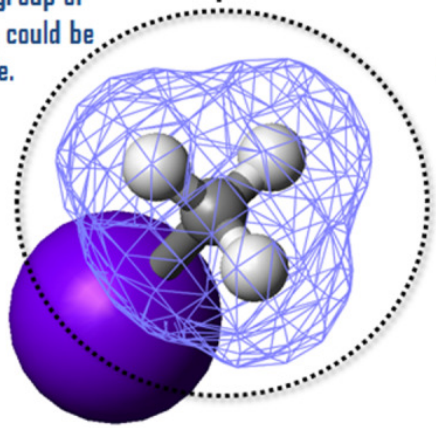
Biomacromolecules

CH/π interactions from the methyl group of timine. Conformational changes, wich could be involved on maintenance of life.

Micromolecules

The inductive eletronic effect of the methyl group is the responsible for the subtype receptors selectivity (H_2x H_1) on cimetidine

The stereoelectronic effects of the methyl group have great importance on biological events and are widely used by the Medicinal Chemistries in the development of new drugs.



Stereoelectronic Properties

MW = 15,03
MR = 5,65 cm³/mol
π hansch = 0,56
σ hammett = -0,17

Obrigado

Praia do Boqueirão, Saquarema, RJ

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