Tópicos (Avançados)
em Química Medicinal
Código: **BMF-777**
Carga Horária: 45 horas
Créditos: 3 créditos

Dr Eliezer J. Barreiro
Professor Titular - UFRJ

Dra Lidia M Lima
Professor Associado - UFRJ

2017

Química Medicinal

Aula 2

Química Medicinal

Programa Tentativa BMF-777 / 2017-1:

- Breve histórico: origem da disciplina, definição & bibliografia
- A origem dos fármacos: QM & PN´s
- Paradigma de Erhlich & Fischer

  Interação F-R (micro- macromoléculas)

  Reconhecimento molecular (RM)

  Fatores estruturais essenciais para o RM

  O(s) caminho(s) até os R´s

  Fases do estudo dos fármacos: PD/PK

  ADME(T)

  Fatores estruturais e metabolismo dos F´s

  Estratégias de desenho molecular

    Análogo-ativo

    Hibridação molecular

    Bioisosterismo

    Combinadas

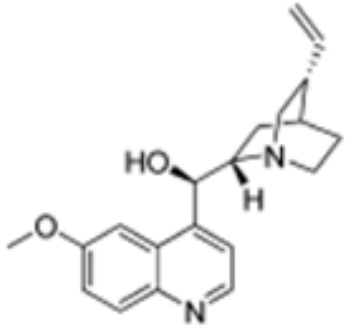
  Estudos de casos (*in-house*)

Bibliografia

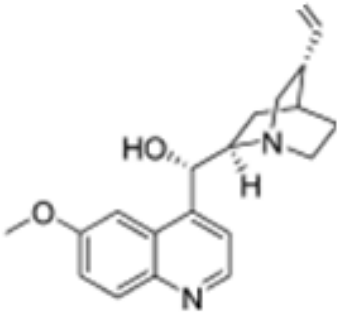
Avaliação final

---

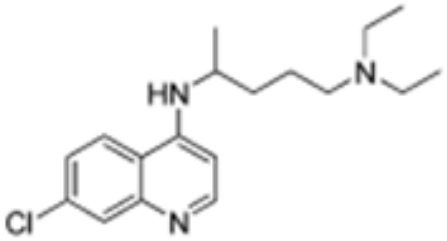
* QM = Química Medicinal
PN = Produtos Naturais
F-R = Fármacos – Receptores
R´s = Receptores ou biorreceptores
PD = Fase farmacodinâmica
PK = Fase farmacocinética
ADME(T) = abosorção/distribuição/metabolismo/eliminação(toxicidade)
F´s = Fármacos



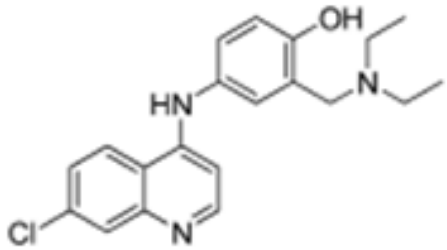
Quinine



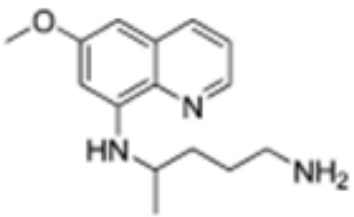
Quinidine



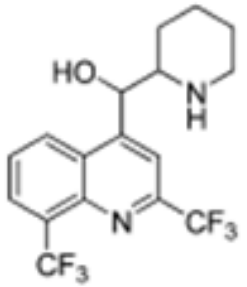
Chloroquine



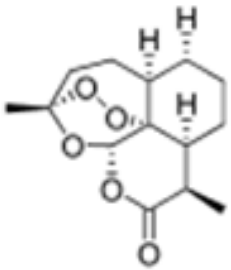
Amodiaquine



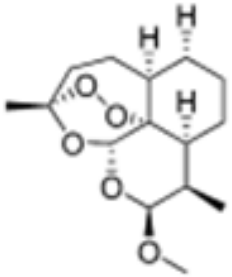
Primaquine



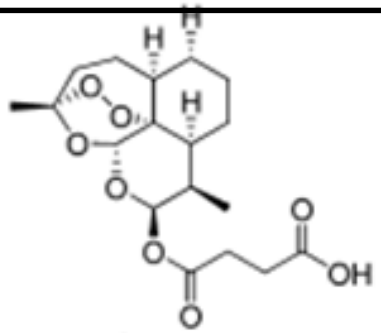
Mefloquine



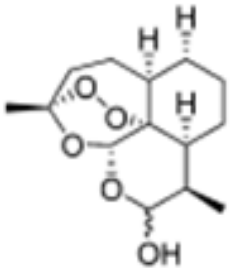
Artemisinin



Artemether



Artesunate

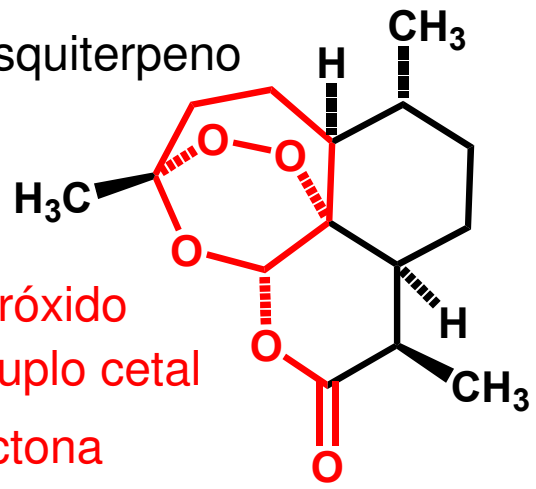


Dihydroartemisinin

Molécula fascinante

Antimalariais originados de PN´s

Sesquiterpeno



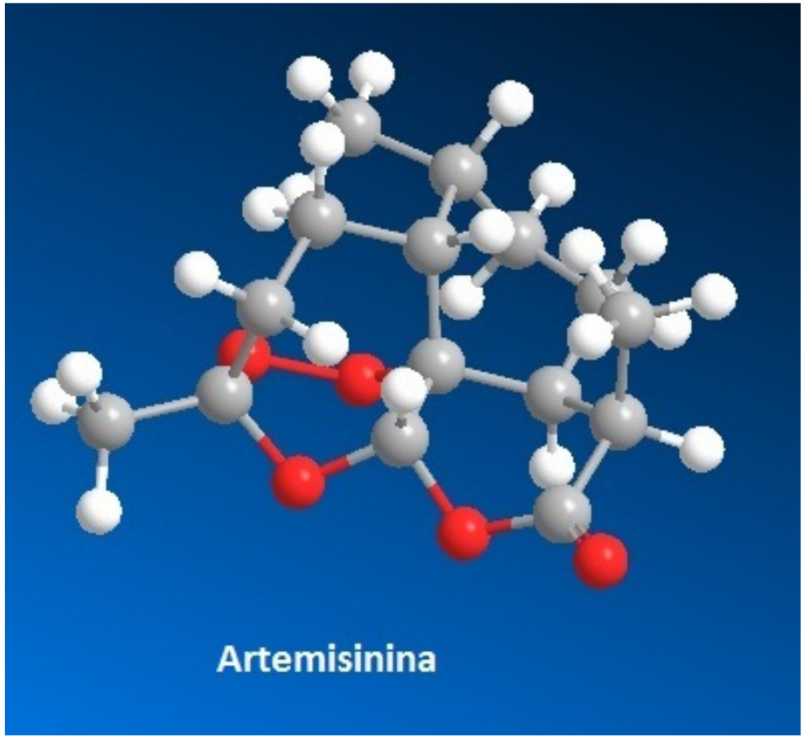
peróxido

duplo cetal

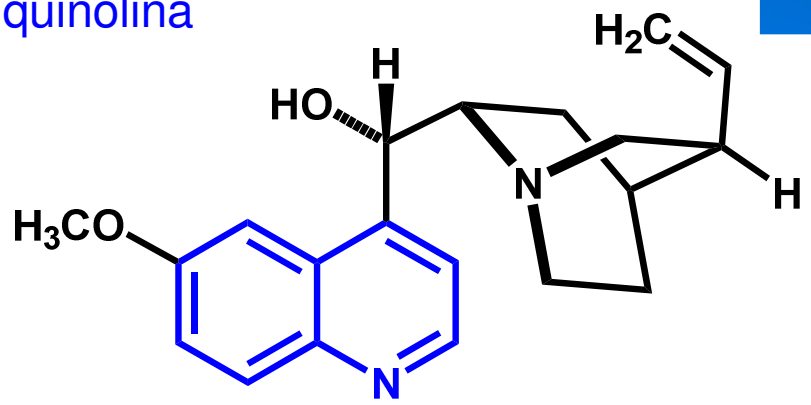
lactona

artemisinina

$C_{15}H_{22}O_5$

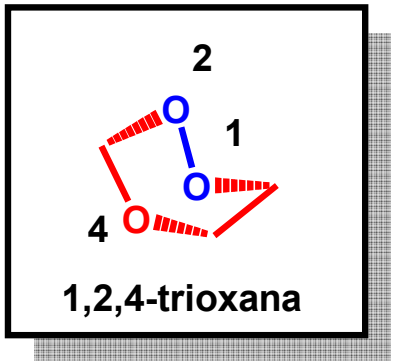


quinolina



quinina

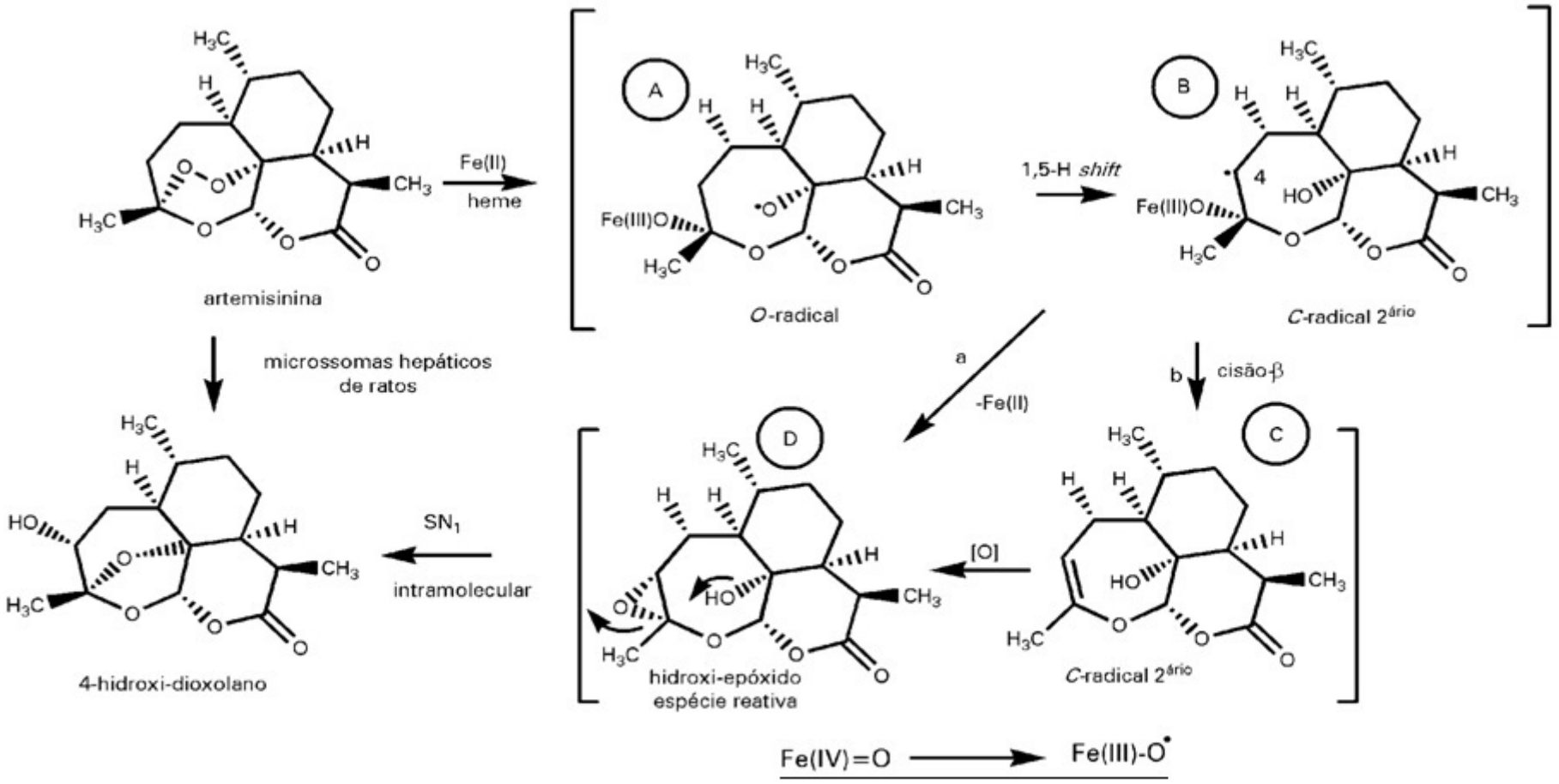
$C_{20}H_{24}N_2O_2$



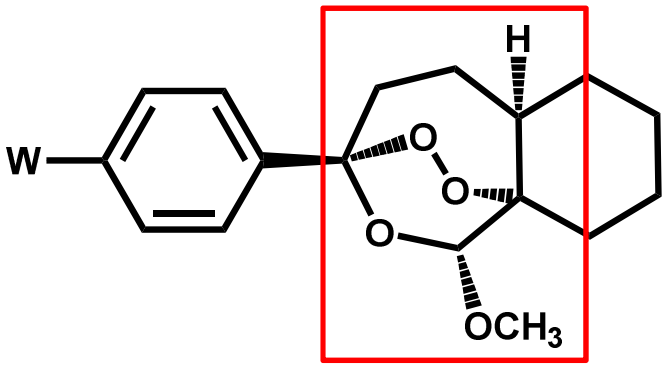
1,2,4-trioxana

Grupos essenciais à atividade?

Mecanismo molecular de ação da artemisinina

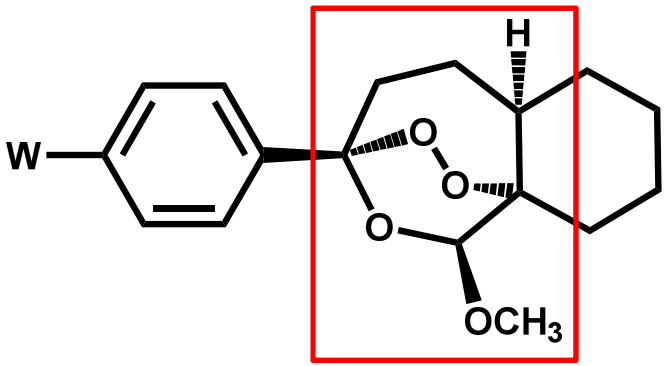


Para identificarem-se os grupamentos farmacofóricos de uma substância, é necessário conhecer o mecanismo molecular de ação...



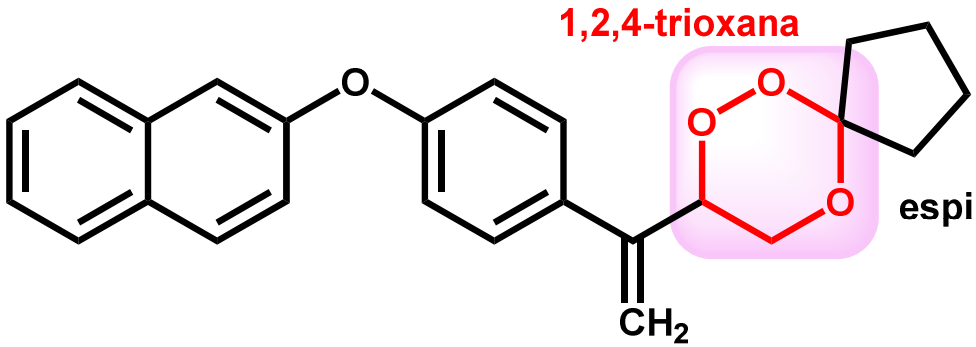
W = H IC_{50} = 100nM

W = F IC_{50} = 65nM



W = H IC_{50} = 38nM

W = F IC_{50} = 30nM



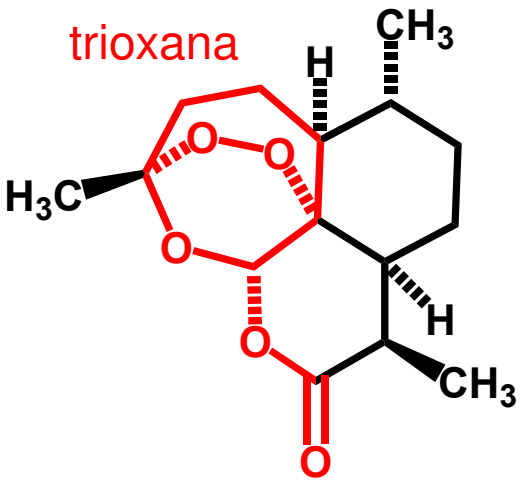
espirociclopentano

J Med Chem 2010, 53, 7587

1994 (Ro 42-1116)

Simplificação molecular

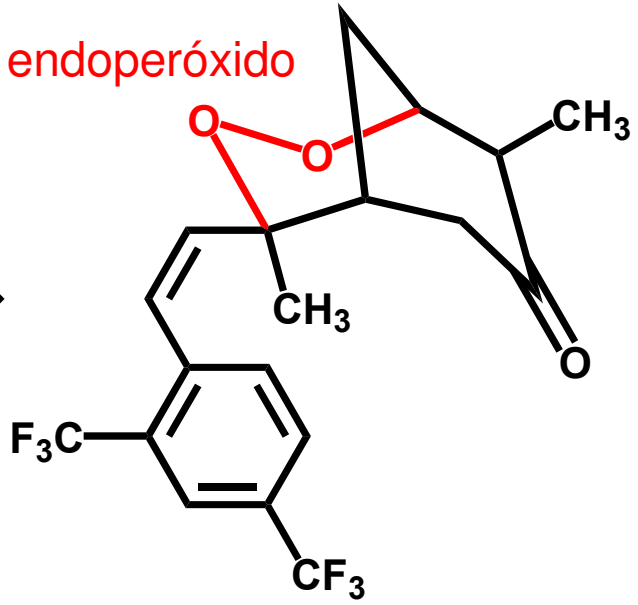
trioxana



artemisinina

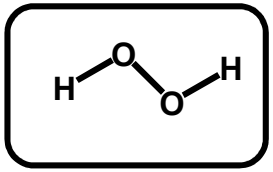
$C_{15}H_{22}O_5$

endoperóxido

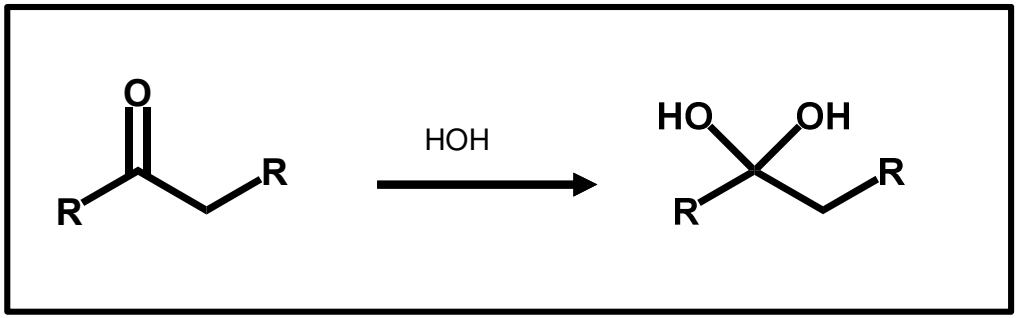


arteflene

$C_{19}H_{18}F_6O_3$



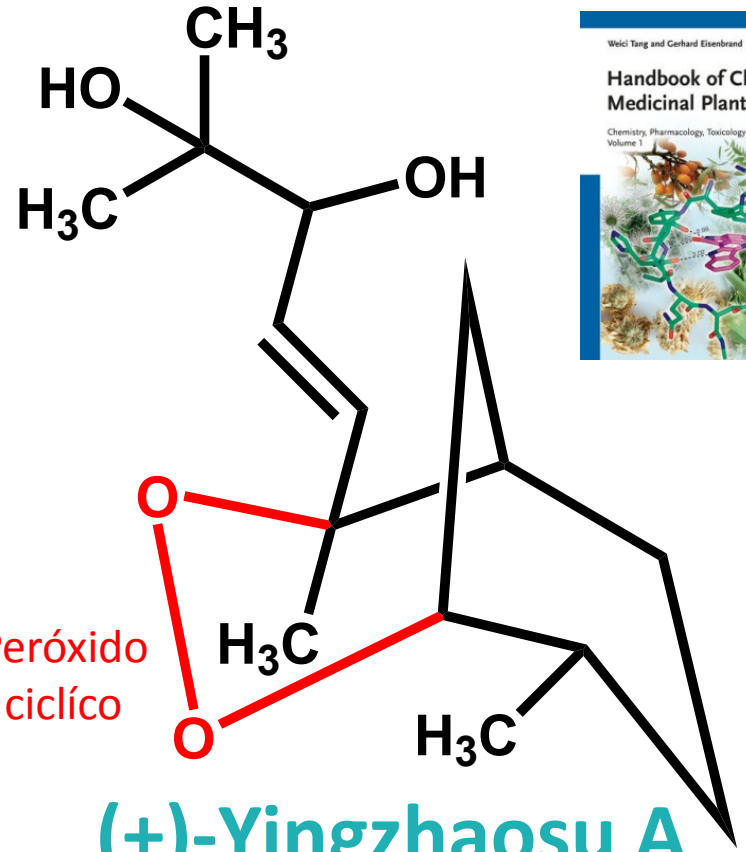
Peróxido de hidrogênio



hidrato

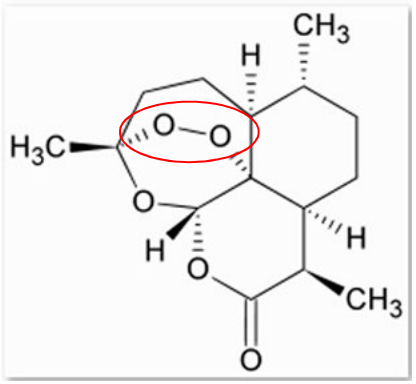
Mais produtos naturais e malária...

Natural products and malaria



(+)-Yingzhaosu A

Artabotrys uncinatus (L.) Merr

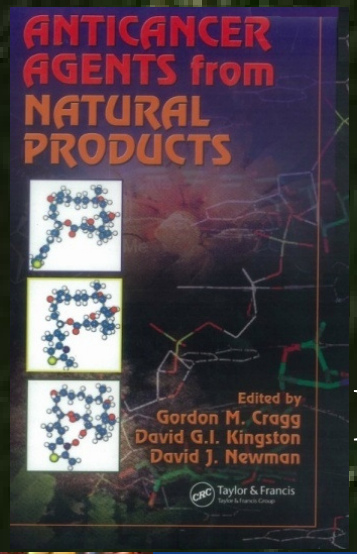


artemisinina

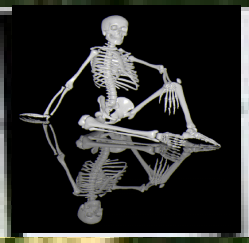
K Borstnik, I-H Paik, T A Shapiro, G H Posner, Antimalarial chemotherapeutic peroxides: artemisinin, yingzhaosu A and related compounds, *Internat J Parasitol* **2001**, *32*, 1661; X-X Xu et al, Total synthesis of (+)-yingzhaosu A, *Tetrahedron Lett.* **1991**, *32*, 5785

Quimioterapia do Câncer

Produtos naturais vegetais

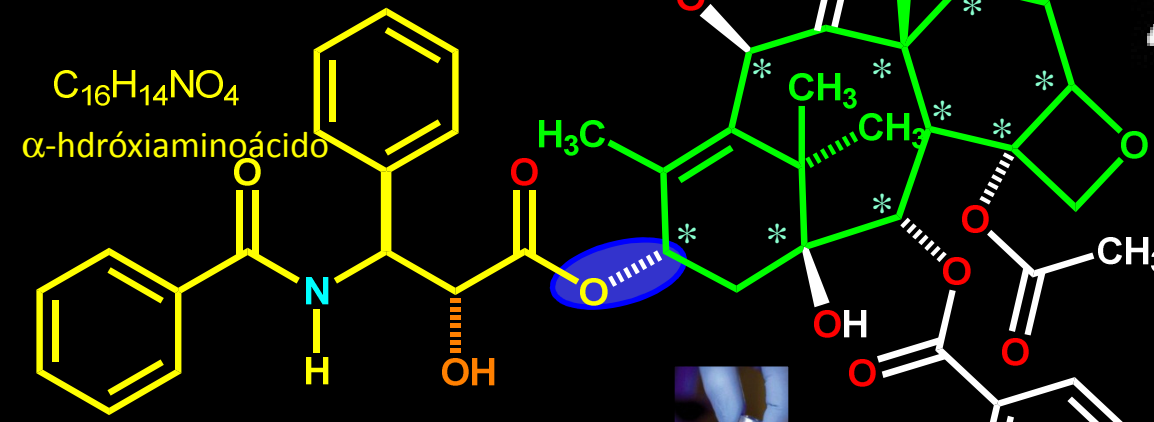


Quimiodiversidade
Estruturas originais
Mecanismo de ação inovadores
Inovações terapêuticas
Moléculas otimizadas



Inter-alia: Alcaloides da Vinca, podofilotoxina

Câncer

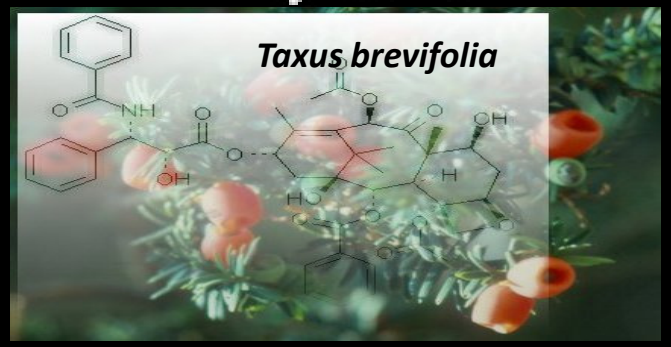


diterpeno
taxano

1965 **Paclitaxel**

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

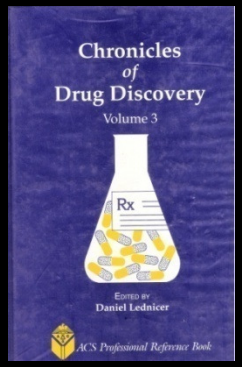
Inibidores de tubulinas



Res. Triangle Park, 1967

M. E. Wall & M. C. Wani

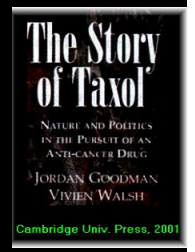
1996 - National Cancer Institute
Award of Recognition



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

blockbuster
2010

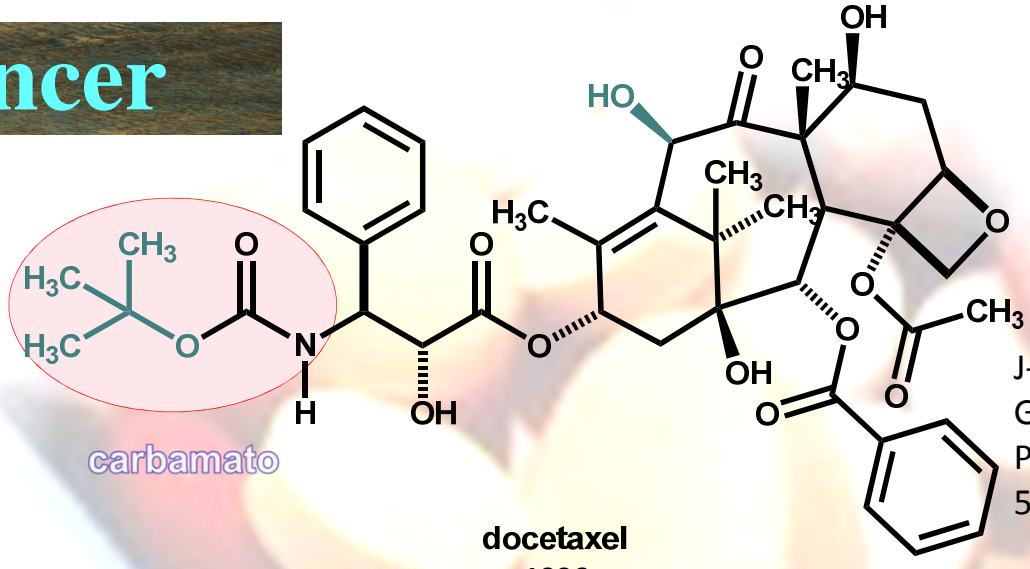
Docetaxel*
Cabazitaxel (Jevtana^{R})
Ortataxel$^{\&}$



A família dos taxanos cresceu

Câncer

sanofi aventis



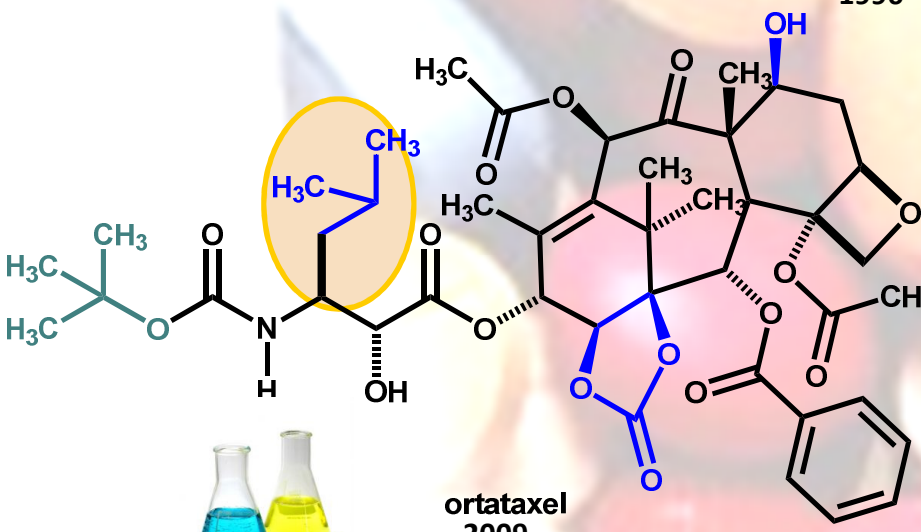
docetaxel
1996

Pierre Potier
1934-2006

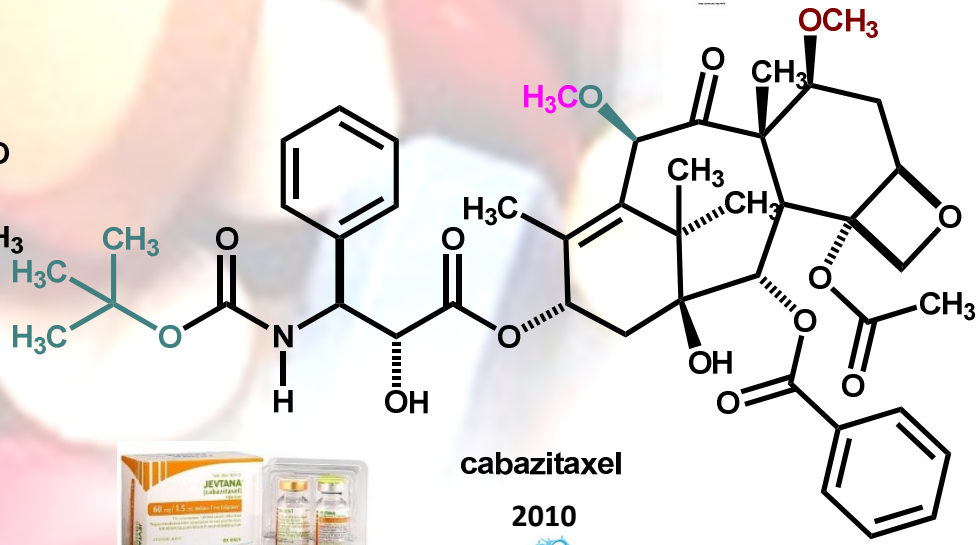
Andy E Greene
UJF-FR

J-N Denis, AE Greene, D Guénard, F Guerite-Voegelein, L Mangatal, P Potier, *J. Am. Chem. Soc.* **1988**, *110*, 5917

Journal of the American Chemical Society



ortataxel
2009



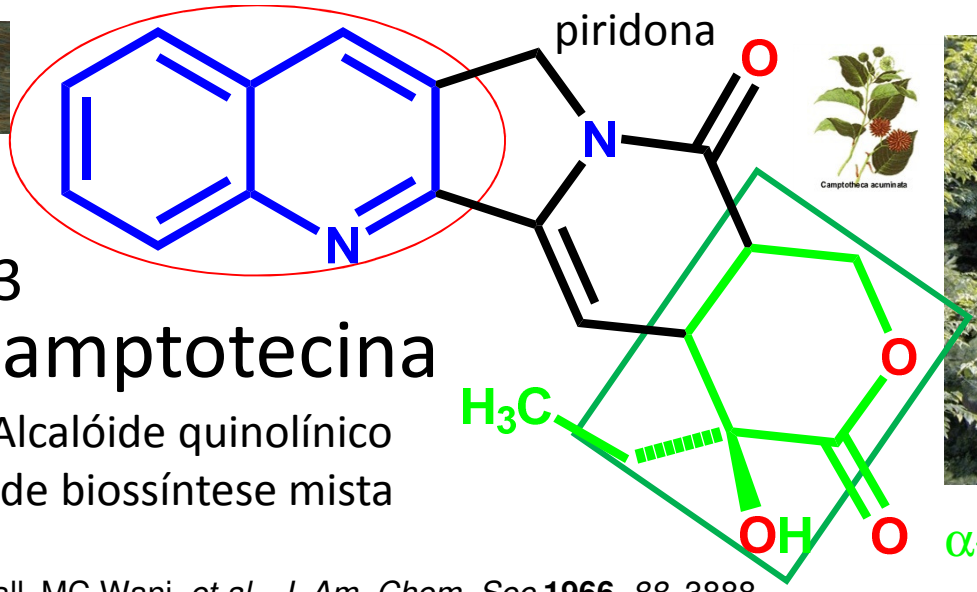
cabazitaxel
2010

sanofi aventis

AL Demain, P Vaishnav, Natural products for cancer chemotherapy, *Microbial Biotechnology* **2011**, *6*, 687

Câncer

piridona



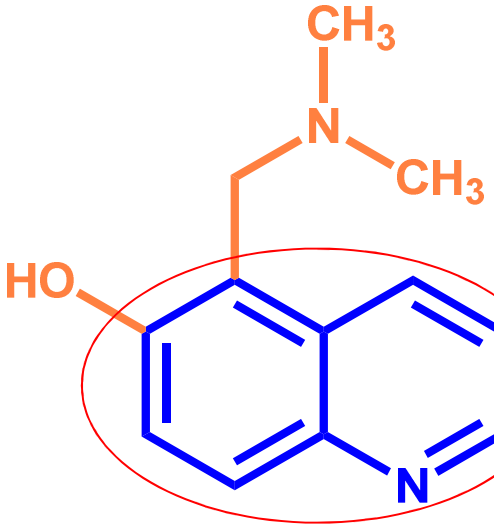
1963

camptotecina

Alcalóide quinolínico
de biossíntese mista

α-hidróxilactona

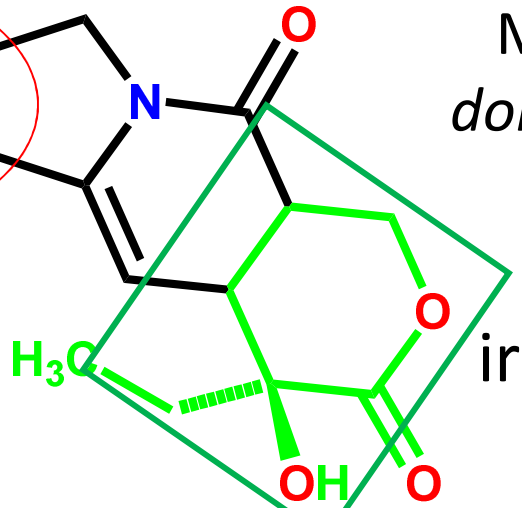
ME Wall, MC Wani, *et al.*, *J. Am. Chem. Soc.***1966**, *88*, 3888
ME Wall, MC Wani, "Camptothecin: Discovery to Clinic" *Ann. NY Acad. Sci* .**1996,** *803*,1



topotecan

Inibidores de
topoisomerase-1

Grupamento farmacofórico



Molécula
domesticada

irinotecan

1996

Molécula
domesticada

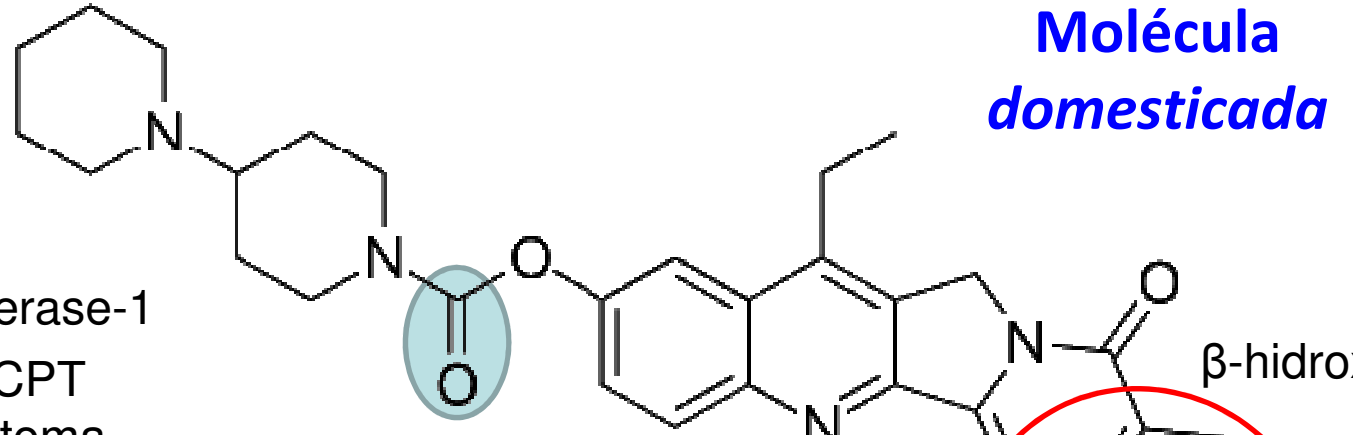
Topoisomerase-1

1000 X CPT

glioblastoma

1996

β-hidroxilactona



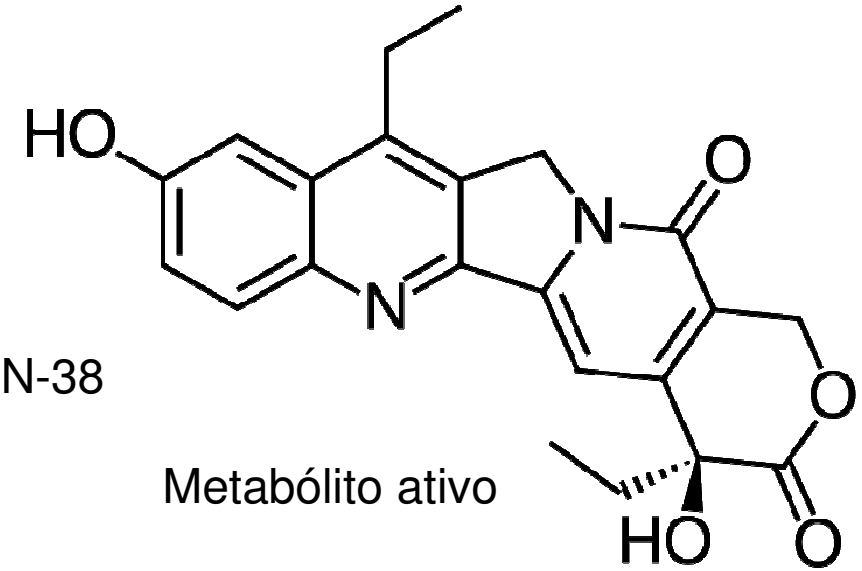
irinotecan

(Camptosar^{R})

Pró-fármaco

carboxilesterases

In vivo



SN-38

Metabólito ativo

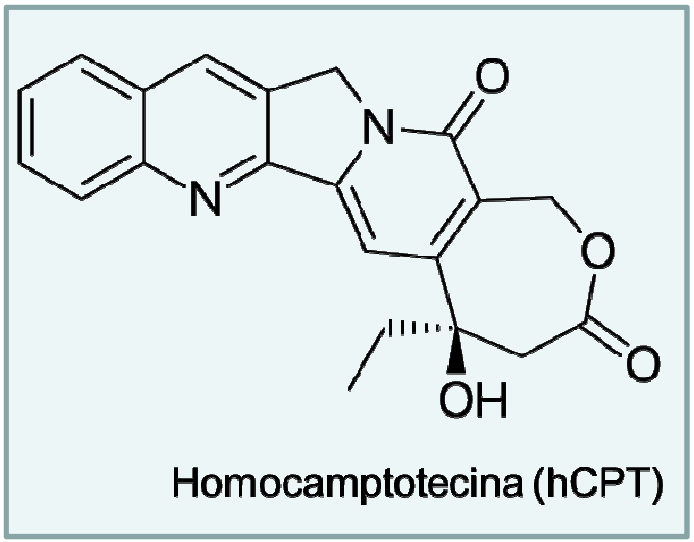
GF

Topoisomerase-1

Arg364

Camptotecina

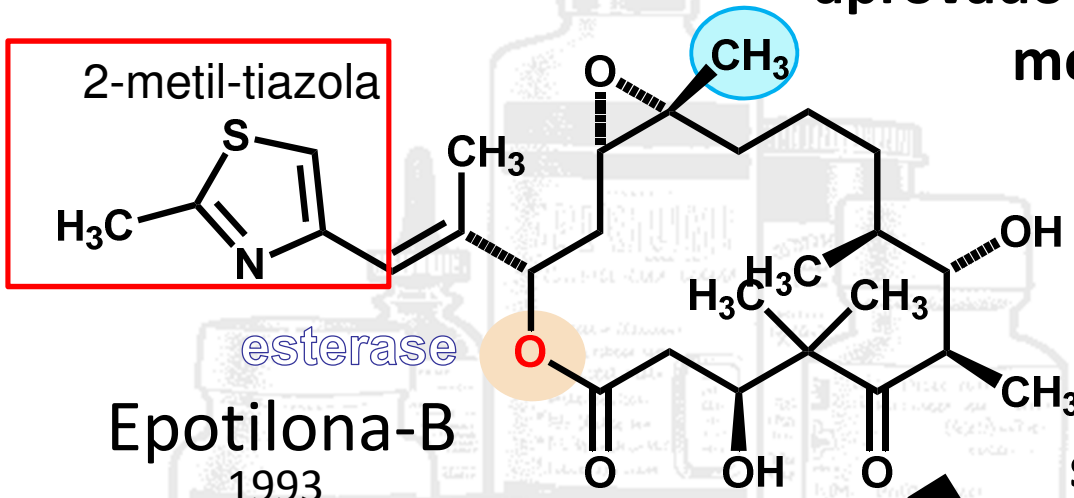
Asp533



Câncer

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

2-metil-tiazola



Inibidor de microtúbulo

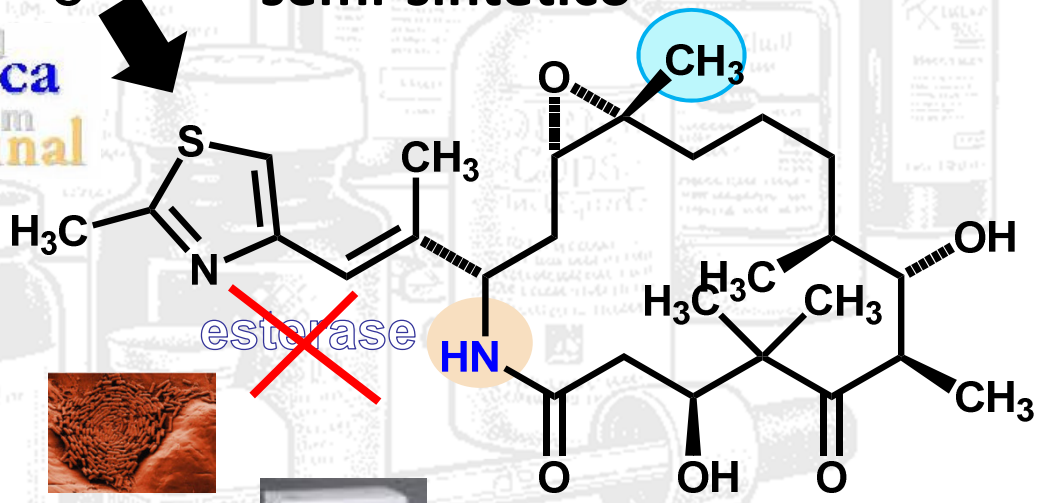
Epotilona-B

1993

Análogo semi-sintético

Mixobacteria

Química Medicinal



Isolada de *Sorangium cellulosum*

Via fermentativa bacteriana, ativo em células taxano-R

Ixabepilona

Ixempra^{R}

BMS, 2007

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

Análogos de Epotilonas

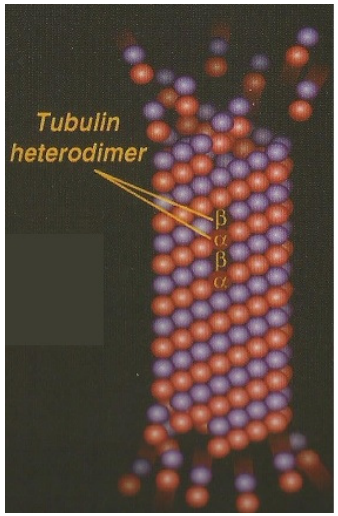
Analogs of Epothilones

X = NH, NCH_3, O, S, CH=CH

hetero-arila

homologue

R = H, CH_3



Química Medicinal

Isosteres

lactona

Professor Dieter Schinzer
University of Magdeburg

BRAZMEDCHEM 2016 NOVEMBER 27-30
8TH Brazilian Symposium in Medicinal Chemistry

D Schinzer, A Bauer, Total Synthesis of (–)-Epothilone A, *Eur J Chem.* **1999**, *5*, 2483

Câncer

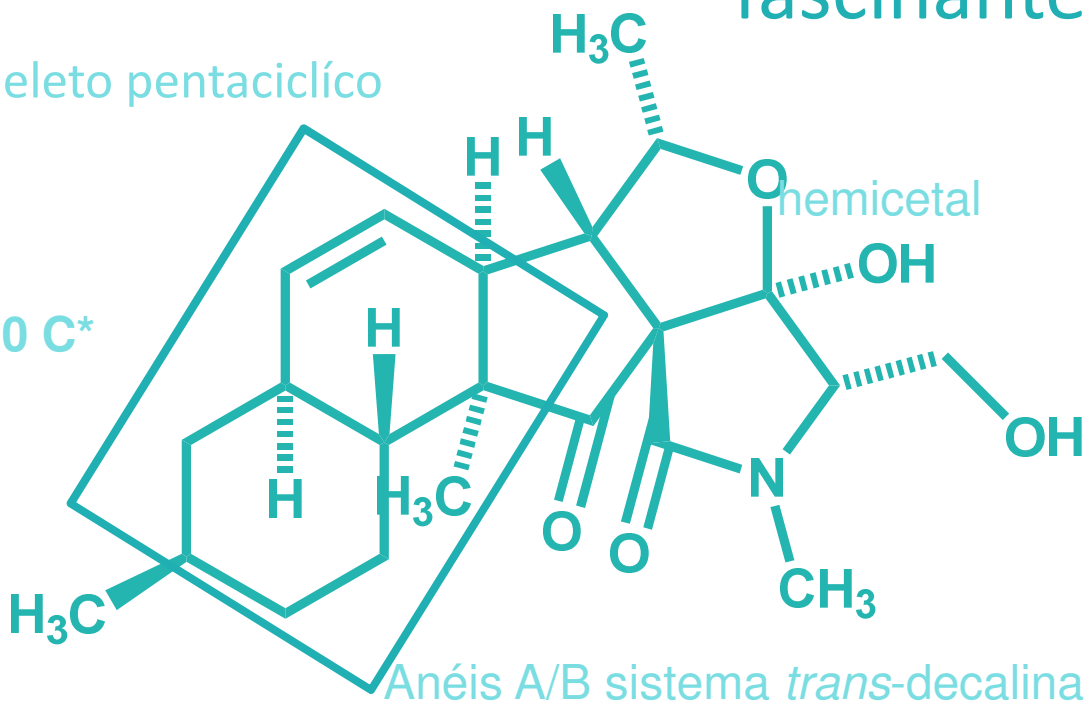
Estrutura fascinante

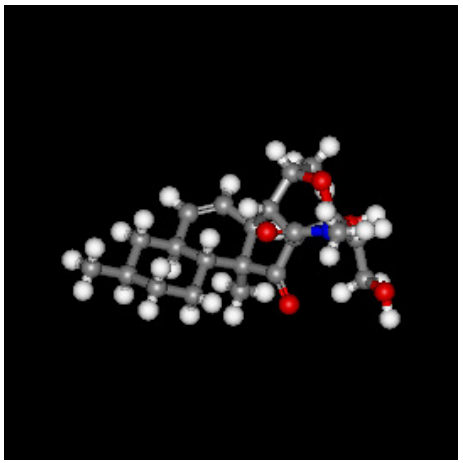
Esqueleto pentaciclíco

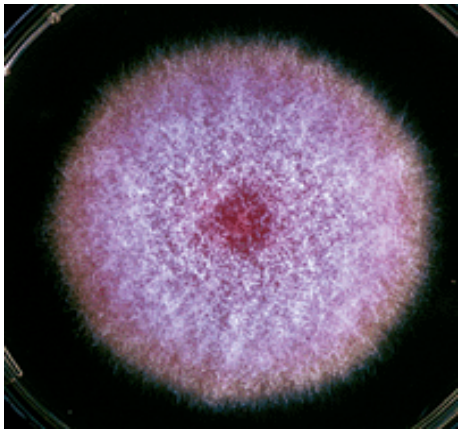
10 C*

hemicetal

Anéis A/B sistema *trans*-decalina







Fusarium sp

(+)-fusarisetina*

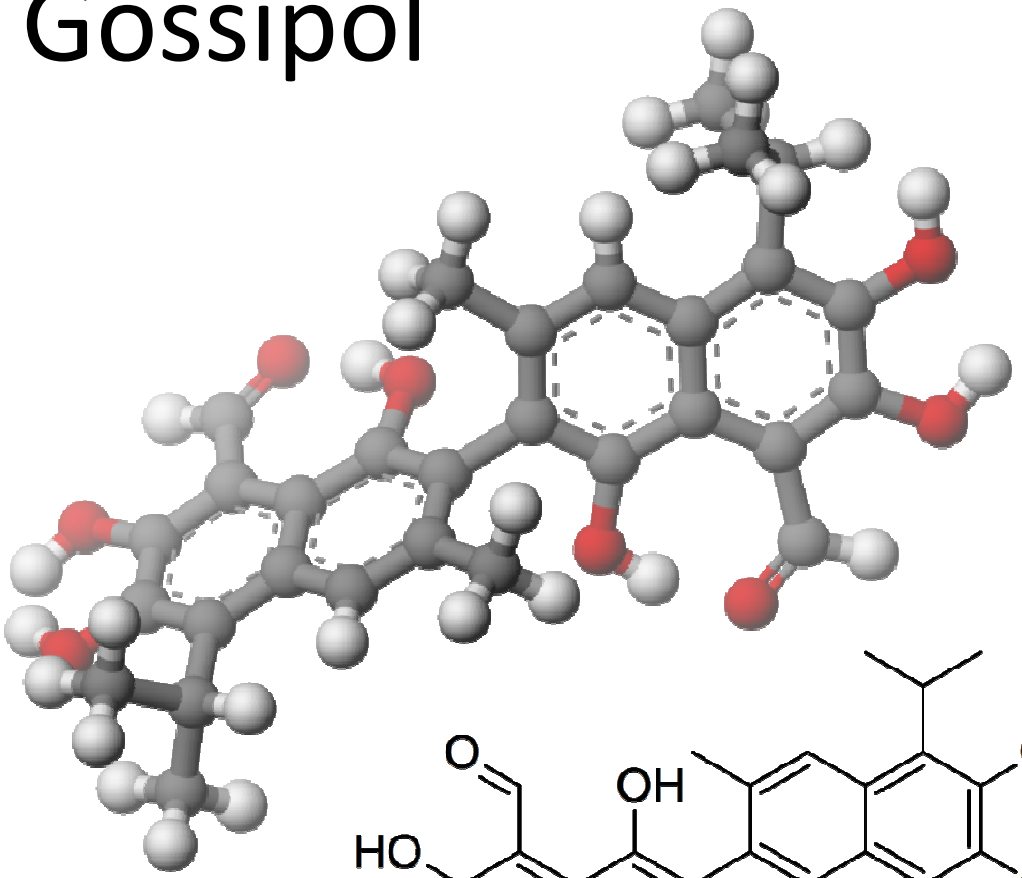
Inibe a migração e metastase de células cancerosas

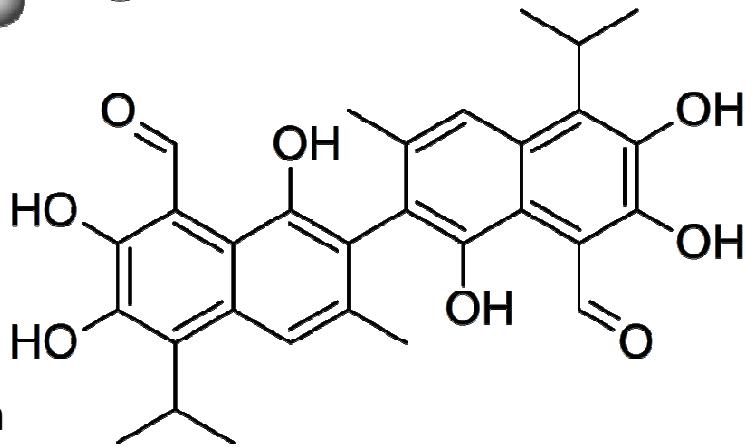
* Isolamento: J-H Jang, Y Asami, J-P Jang, S-O Kim, DO Moon, K-S Shin, D Hashizume, M Muroi, T Saito, H Oh, BY Kim, H Osada, JS Ahn, *J. Am. Chem. Soc.* **2011**, *133*, 6865.

* Síntese: J Xu, EJE Caro-Diaz, L Trzoss, EA Theodorakis, *J. Am. Chem. Soc.* **2012**, *134*, 5072; J Deng, B Zhu, Z-Y Lu, H-X Yu, A Li, *J. Am. Chem. Soc.* **2012**, *134*, 920.

Gossipol

Gossypium hirsutum



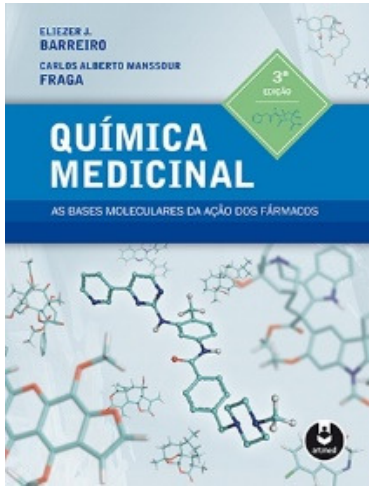


Prof. Stephen A. Matlin

Institute of Global Health Innovation,
Imperial College London, UK;
Head of Strategic Development for the International Organization for Chemical Sciences in Development.

CAPÍTULO 7

A IMPORTÂNCIA DOS FATORES ESTRUTURAIS NA ATIVIDADE DOS FÁRMACOS 285



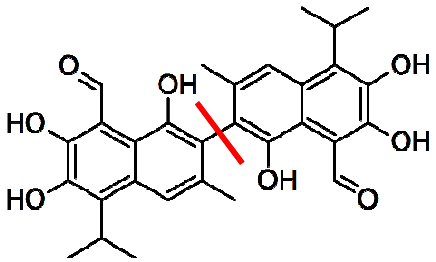
LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

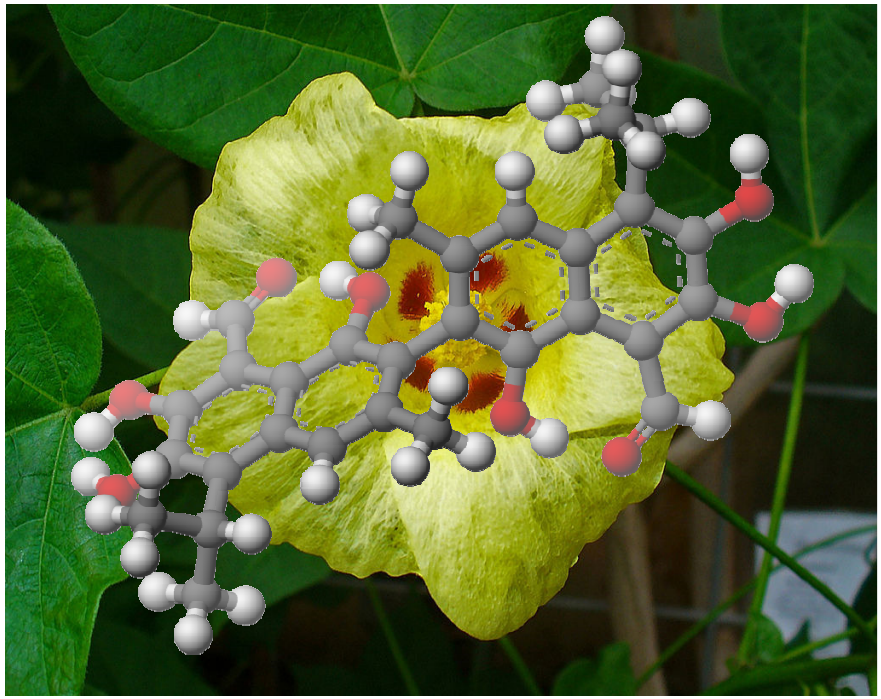
Quim. Nova, Vol. 30, No. 1, 125-135, 2007

ATROPOISOMERISMO: O EFEITO DA QUIRALIDADE AXIAL EM SUBSTÂNCIAS BIOATIVAS

Anderson Rouge dos Santos, Alessandra Campbell Pinheiro, Ana Carolina Rennó Sodero, Andréa Sousa da Cunha, Monica Costa Padilha, Priscila Mesquita de Sousa e Silvia Paredes Fontes
Departamento de Química Orgânica, Instituto de Química, Universidade Federal do Rio de Janeiro, 21941-972 Rio de Janeiro – RJ, Brasil
Márcia Paranho Veloso
Universidade Federal de Alfenas, 37130-000 Alfenas – MG, Brasil
Carlos Alberto Manssour Fraga*
Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, CP 68023, 21944-270 Rio de Janeiro – RJ, Brasil

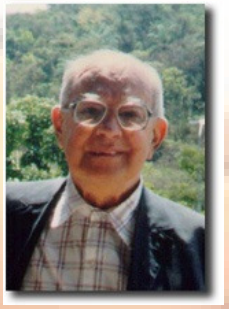
Recebido em 26/9/05; aceito em 30/3/06; publicado na web em 26/9/06



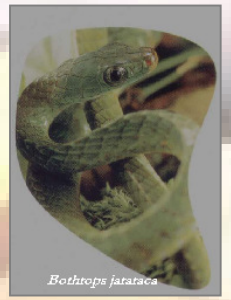


Inovação terapêutica

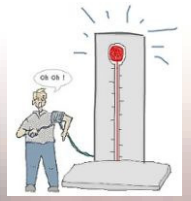
MO Rocha e Silva
1910-1983



WT Beraldo
1917-1998



jararacá



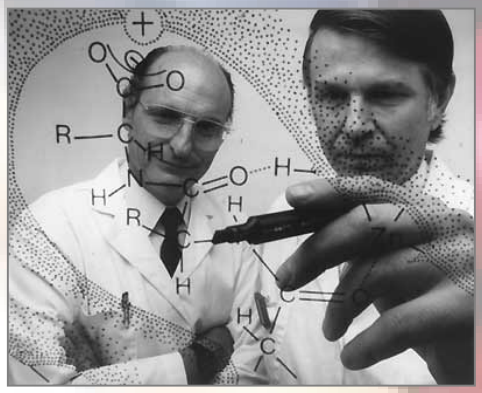
Bradicinina
1949

SH Ferreira
1934-2016

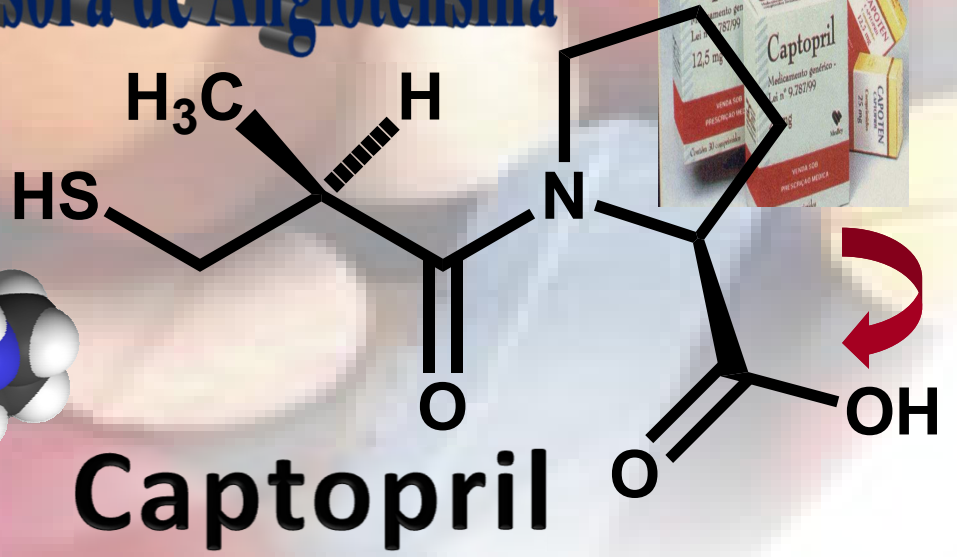
M Rocha e Silva, WT Beraldo, G Rosenfeld, Bradykinin, a hypotensive and smooth muscle stimulating factor released from plasma globulin by snake venoms and by trypsin. *Am J Physiol.* **1949,**156,261

S.H. Ferreira, A Bradykinin-potentiating factor (BFP) present in the venon of *Bothrops jararaca, Brit. J. Pharmacol.* **1965**, *24*, 163.

Inibidores da Enzima Conversora de Angiotensina



D W Cushman & M A Ondetti



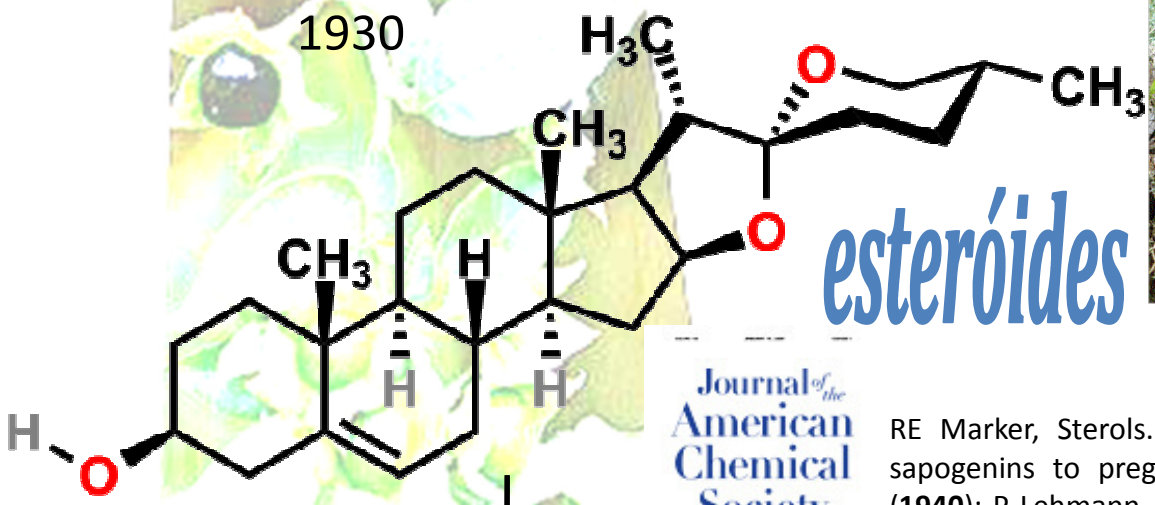
Captopril

M. A. Ondetti, D. W. Cushman & B. Rubin, *Chronicles of Drug Discovery*, vol. 2, J.S. Bindra & D. Lednicer, Eds., Wiley, Nova Iorque, 1983, p. 1-32

Diosgenina

Degradação de Marker

1930



esteróides

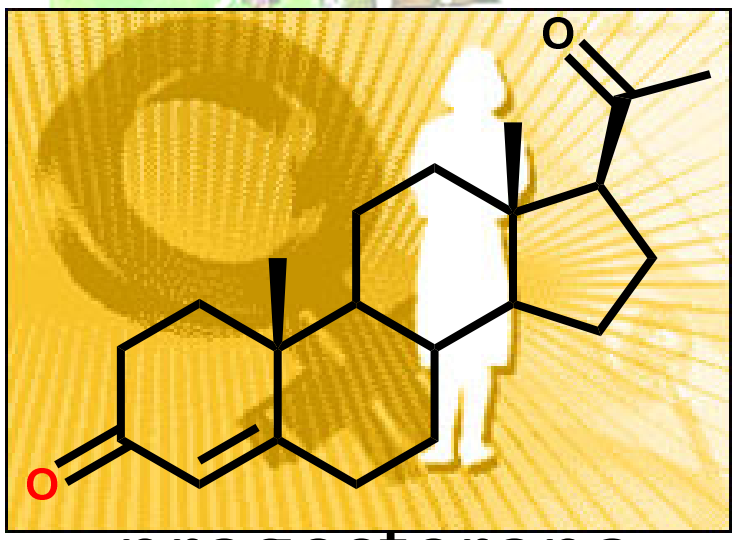
Laboratorios Syntex SA

Dioscorea mexicana Scheidw

Russell E Marker

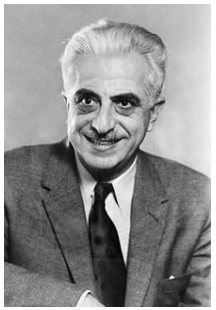
RE Marker, Sterols. CXIII. Sapogenins. XLII. The conversion of the sapogenins to pregnenolones". *J. Am. Chem. Soc.*, **62** 3350–3352 (**1940**); P Lehmann, A Bolivar, R Quintero, Russell E. Marker - Pioneer of the Mexican steroid industry, *J. Chem. Ed.*, **50**, 195–9 (**1973**).

Journal of the American Chemical Society

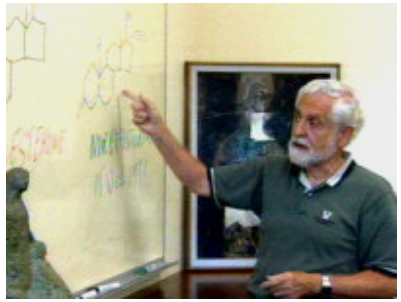


progesterona

Contraceptivos

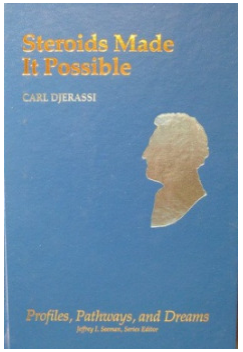


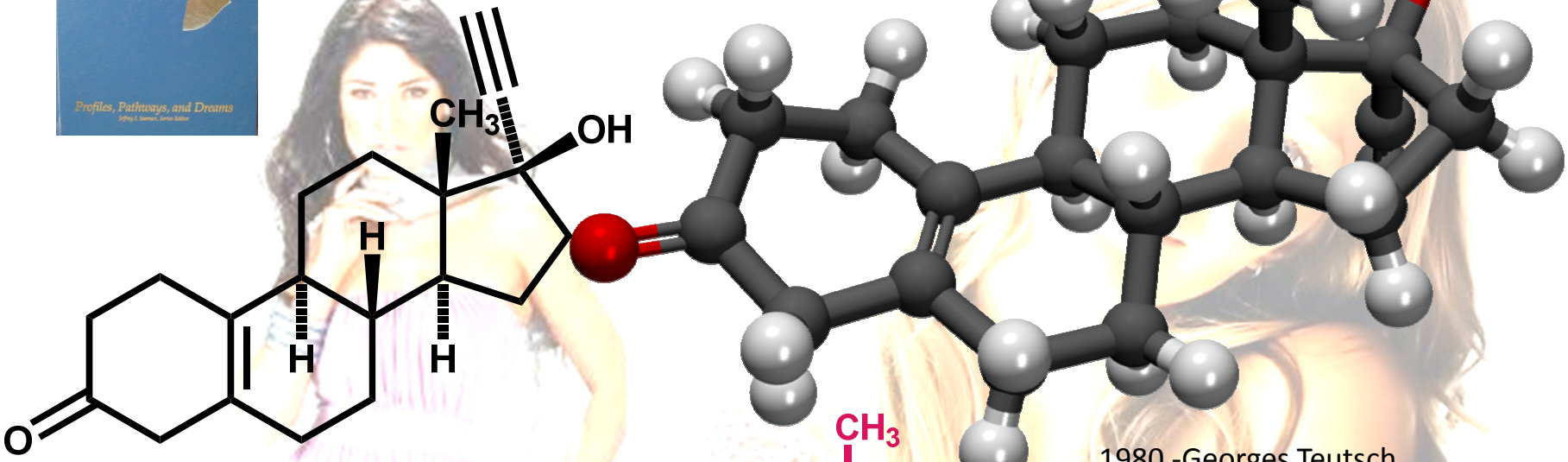
Gregory Pinkus



Carl Djerassi

A pílula





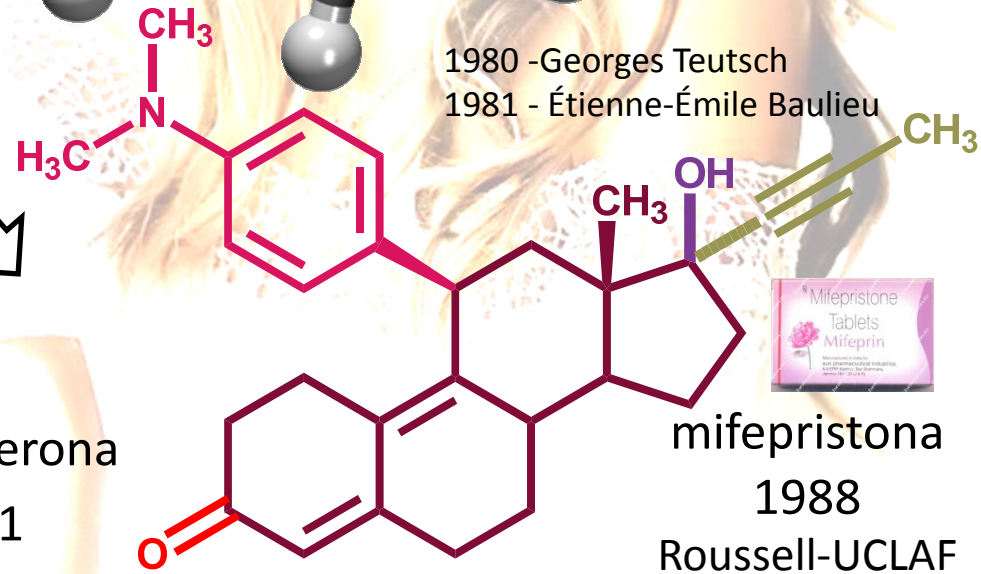
noretinodrel

1980 -Georges Teutsch
1981 - Étienne-Émile Baulieu

1951
Searle

noretisterona

1951
Syntex



mifepristona
1988
Roussell-UCLAF
RU-486

Mais de 140 milhões de mulheres utilizaram a pílula contraceptiva até *ca.* 2009

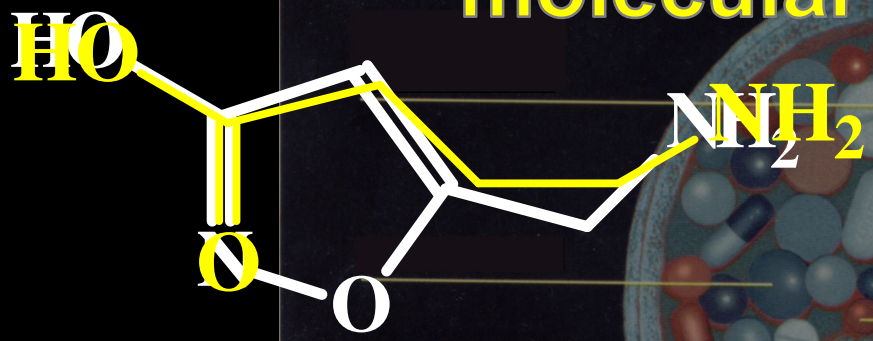
Substâncias ativas no SNC

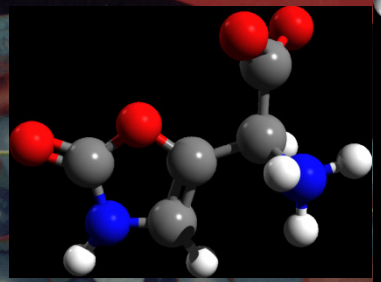
alucinogêno

Zé Ramalho

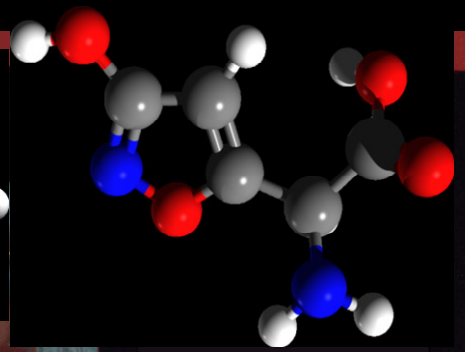
Amanita muscaria

Similaridade molecular





muscazona

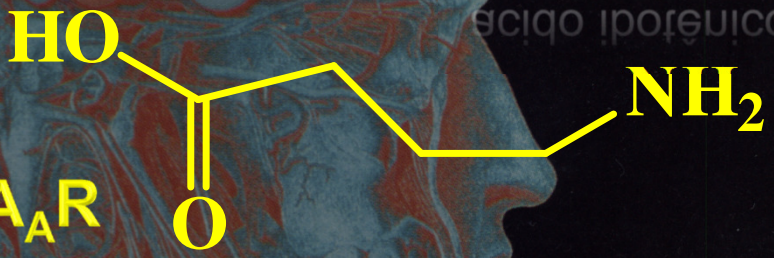


ácido ibotênico

ALCALOIDE

Muscimol

PSICOATIVA

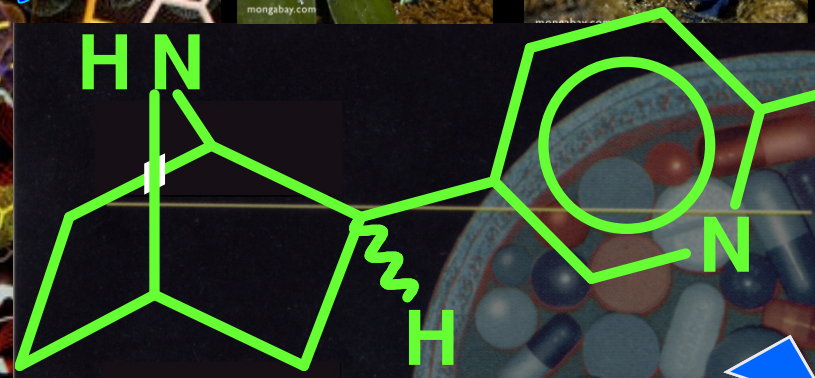


GABA$_A$R

Ácido γ-aminobutírico

X. Chen, M. Decker, Multi-Target Compounds Acting in the Central Nervous System Designed From Natural Products, *Curr Med Chem* **2013**, *20*, 1673.

protótipo natural



Un. Maryland, EUA

Primeiro quimiotipo natural:
7-azabiciclo[2.2.1]heptano

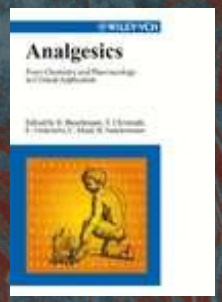
John W Daly
1933-2008

Epibatidina

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

analgésico

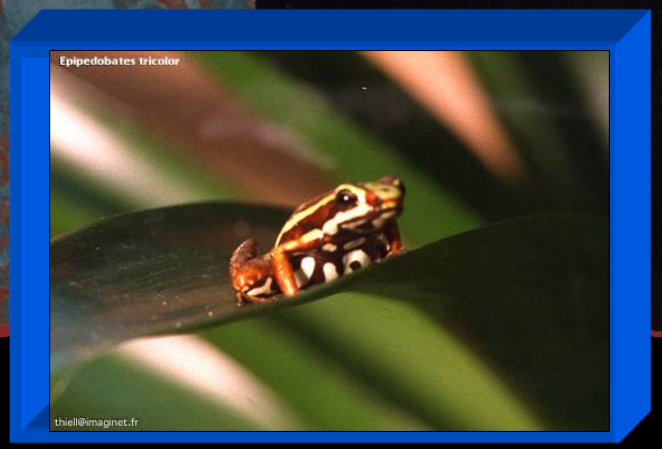
200-400 vezes mais potente que a morfina



Primeiro alcalóide não-opióide, organo-clorado.

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

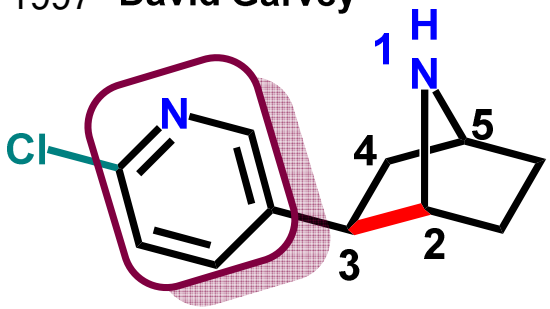
1992



Epipadobates tricolor

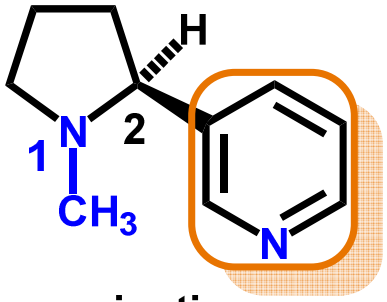
J W Daly, "Thirty Years of Discovering Arthropod Alkaloids in Amphibian Skin", *J. Nat. Prod.* 1998, *61*, 162-172

1997 **David Garvey**



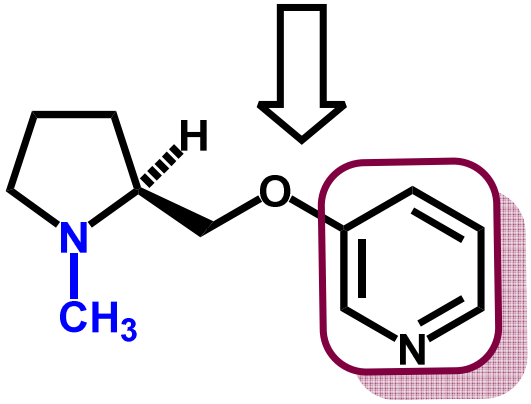
epibatidina

Similaridade melecular

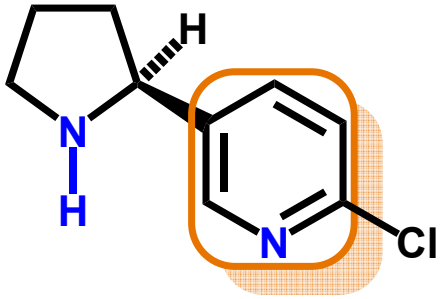


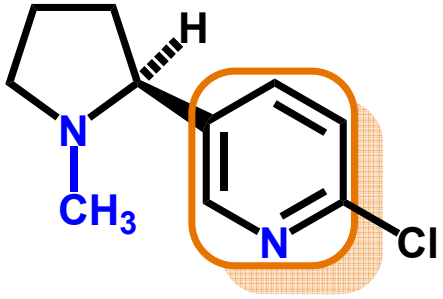
nicotina

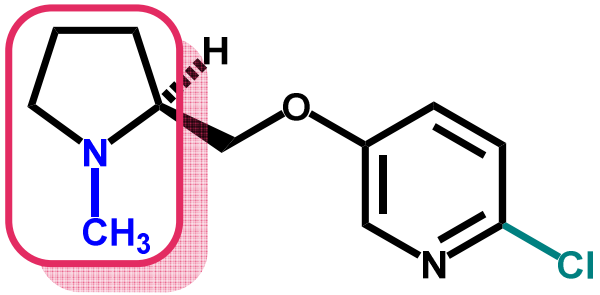
nAChR = 1,0 nM



nAChR = 0,15 nM

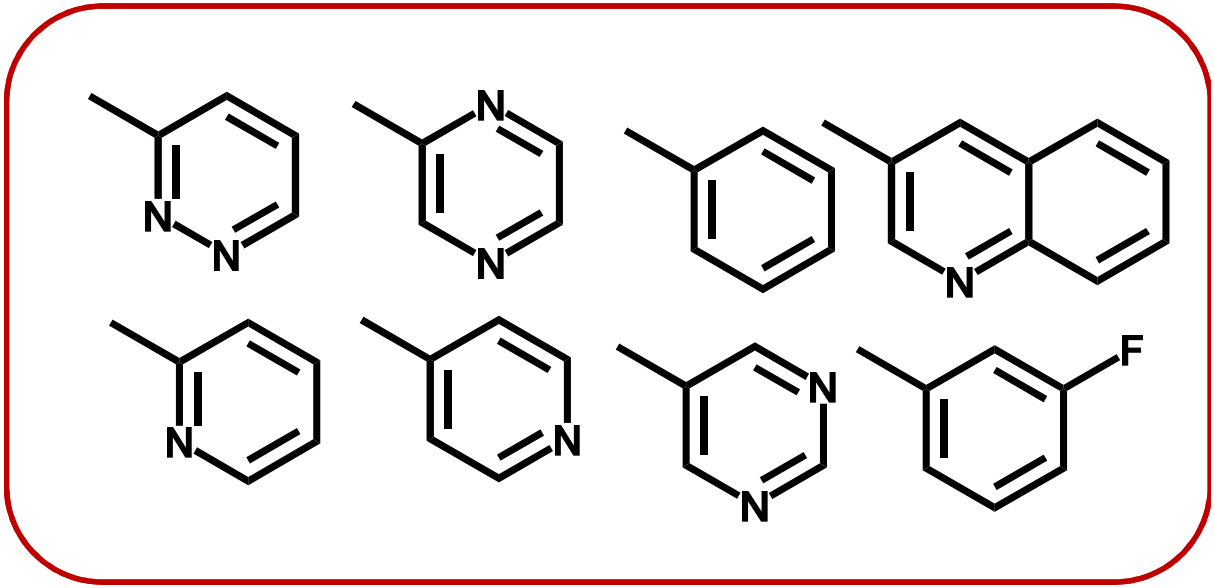




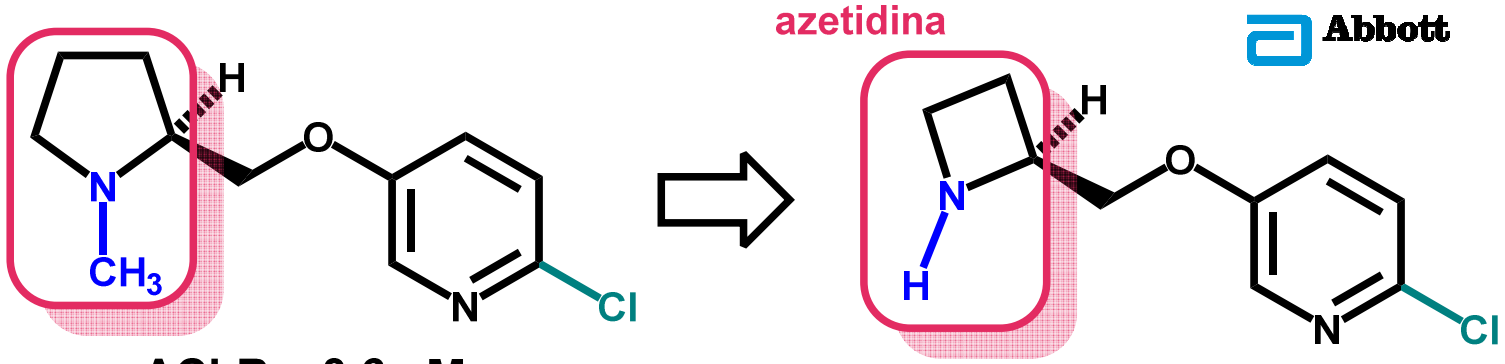


nAChR = 0,6 nM

ABT-594



Domesticando produtos naturais



nAChR = 0,6 nM

nAChR = 0,04 nM

ABT-594

1998 - Mark W. Holladay

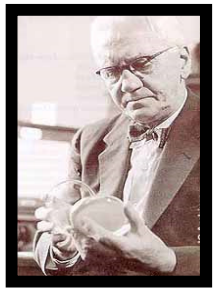
30X > morfina

MW Holladay & MW Decker, Medicinal Chemistry and Biology of ABT-594, *Adv Med Chem* 2000, 5, 85

Do *bolor* às moléculas salva-vidas...

Antibióticos β-lactâmicos

1877 – L. Pasteur
1897 - Ernest Duchesne, Lyon
1928 – A Fleming, Londres
1939 – Florey & Chain
1943 – RB Woodward, R Robinson
1945 - Dorothy C. Hodgkin
1948 – Patente de processo
1957 –John Sheehan, MIT



Alexander Fleming
1881-1955

Howard W. Florey
1898-1968

Dorothy C. Hodgkin
1910-1994

antibioticoterapia

O acaso ajuda a sorte

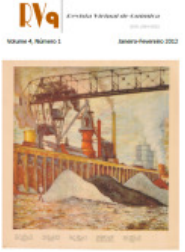
E. Boris Chain
1906-1979

1945

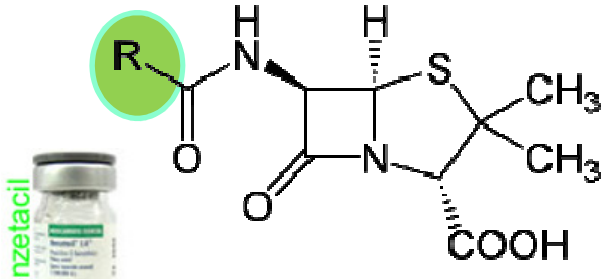
Fungos

EB Chain *et al.*, *Lancet* **1940**, *2*, 226

1964

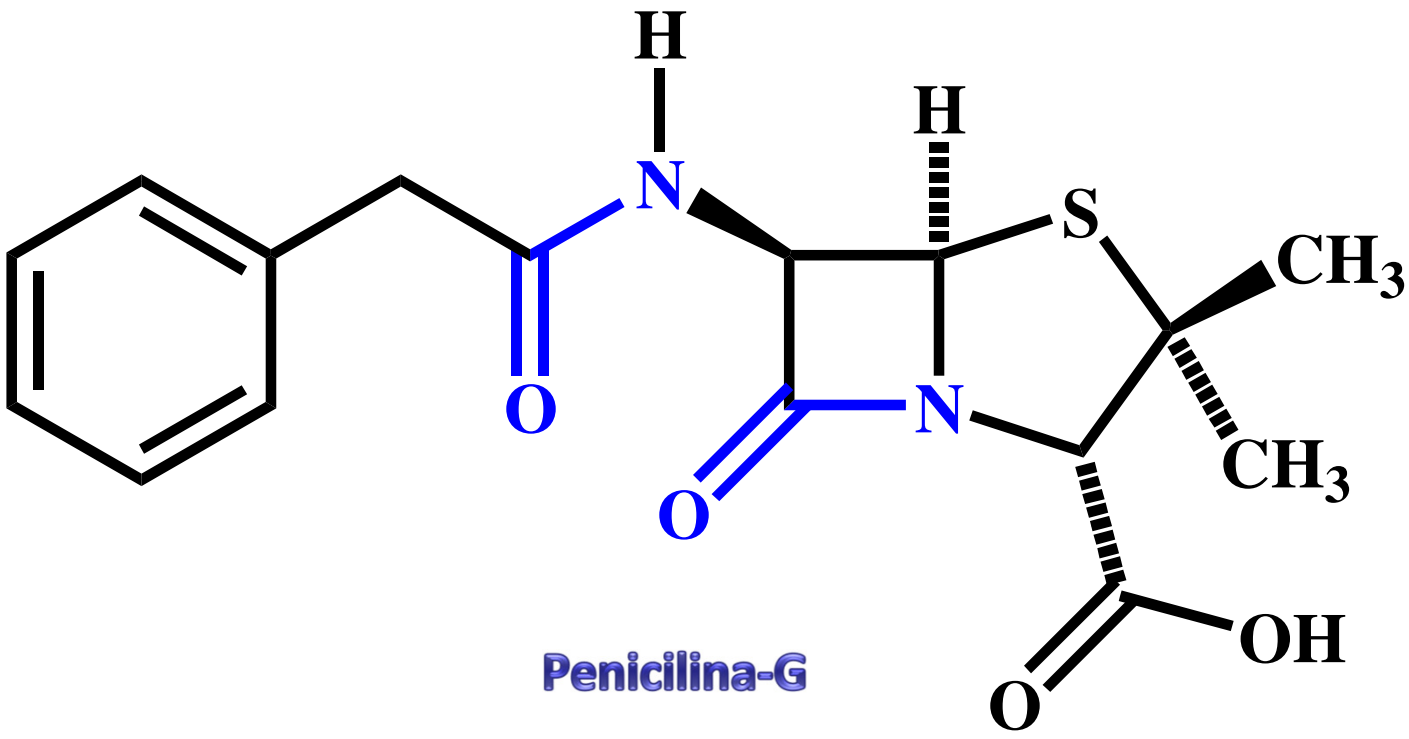


MD Vargas, *Rev Virtual Quim* **2012**, *4*, 85



Penicilina

Quantos grupos funcionais?



Penicilina-G

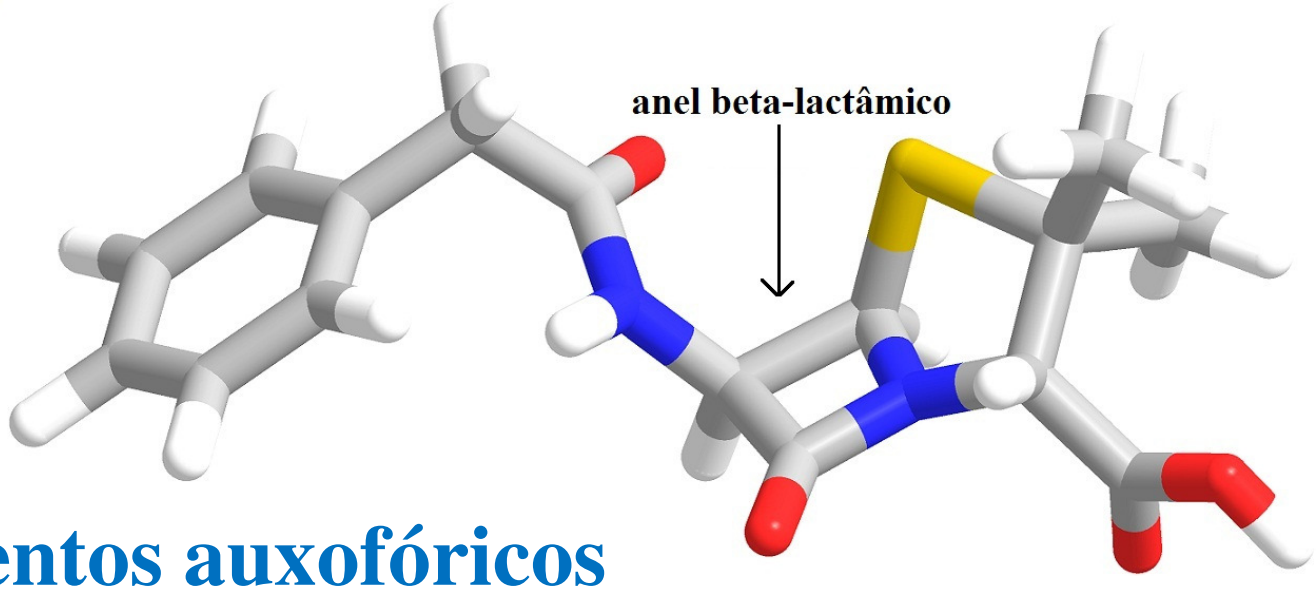
São todos equivalentes?

Quais são bioequivalentes?

O sistema β-lactâmico

anel beta-lactâmico de conformação piramidal definida

Grupamento farmacofórico



Grupamentos auxofóricos

A evolução dos β-lactâmicos...

1928

tiazolidina

azetidin-2-ona

penicilina G

1976 - carbapeneno

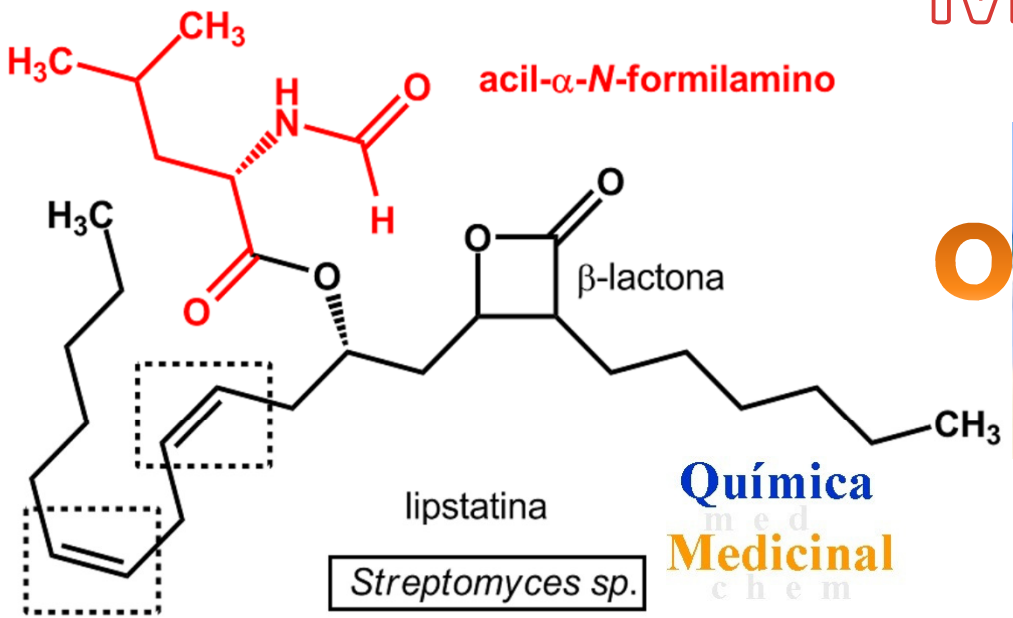
tienamicina

1980 - Monobactama

nocardicina

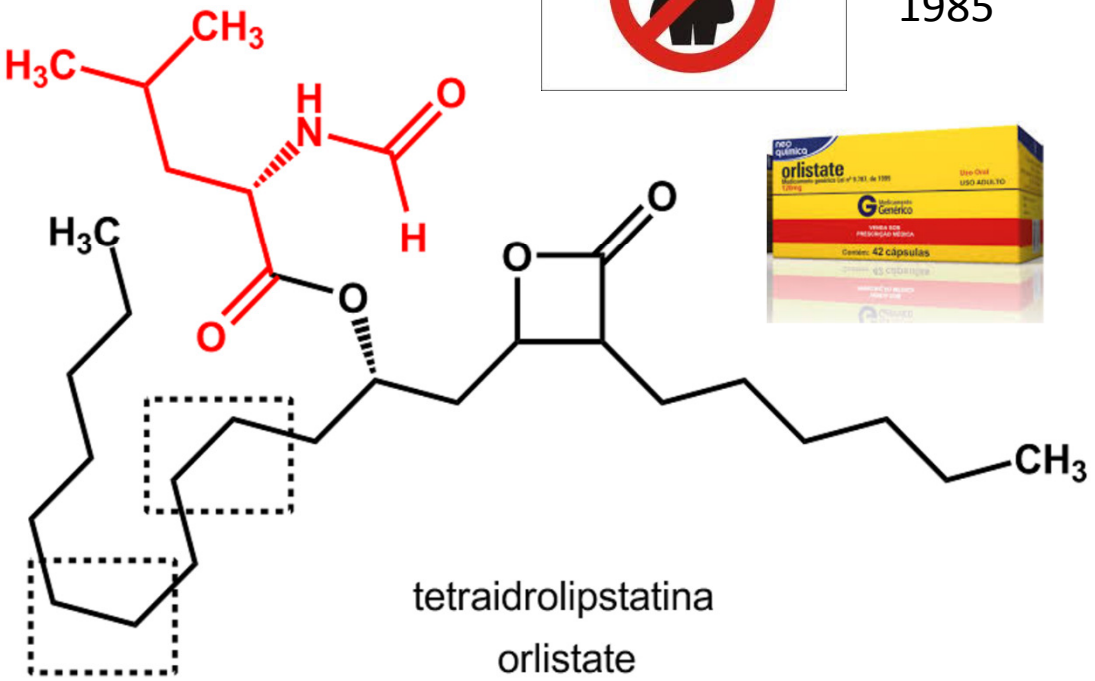
Nocardia uniformis

Mais *bolor*....

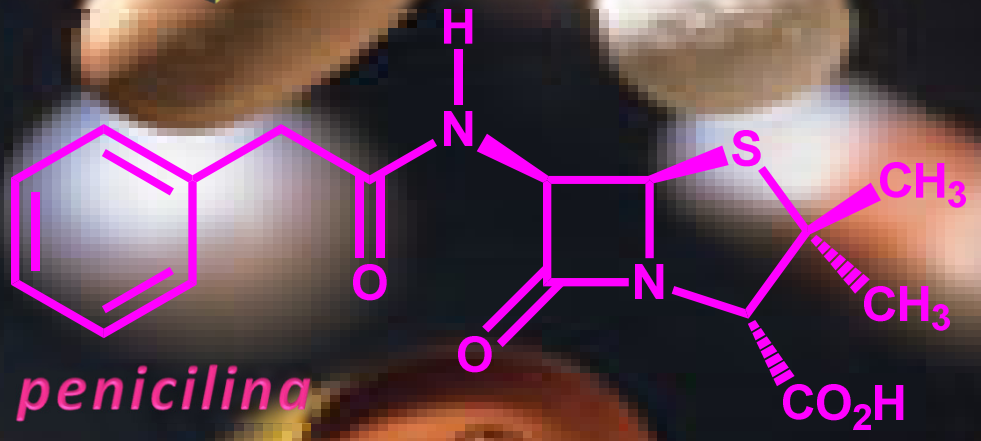


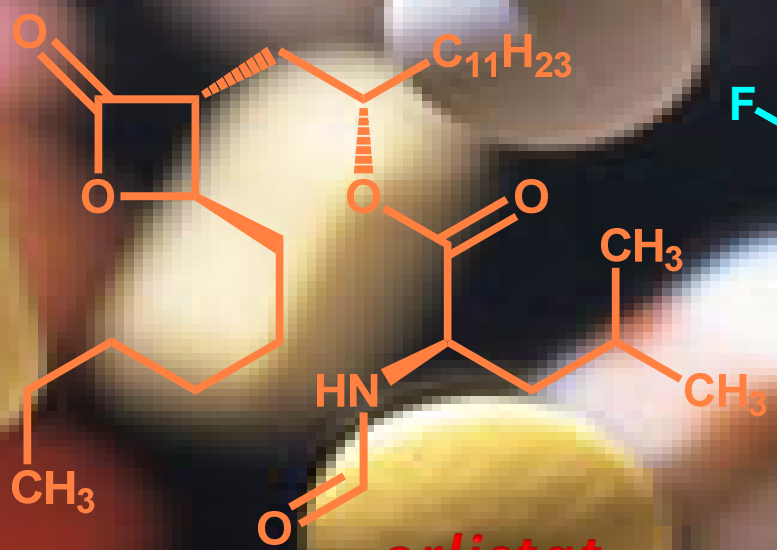
Química Medicinal

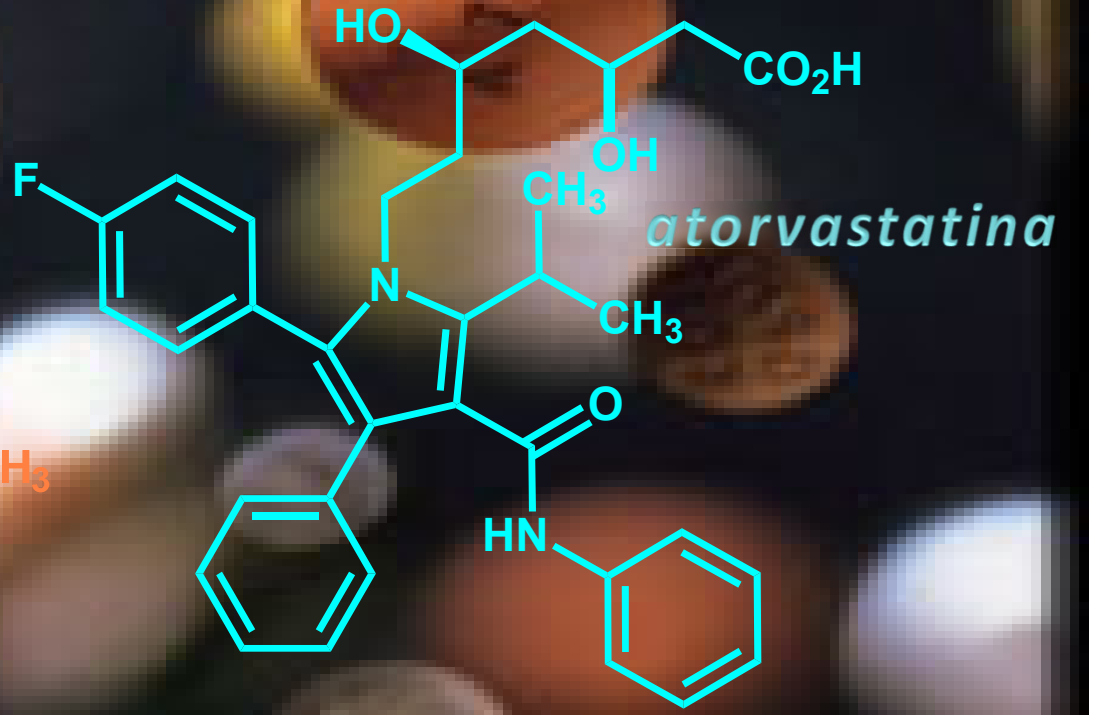
1985



Moléculas diferentes, mas semelhantes!







C Viegas Jr, V S Bolzani, E J Barreiro, Os produtos naturais e a química medicinal moderna, *Quim Nova* **2006**, *29*, 326

Metabólito de Fungo

Estatinas

Akira Endo, Sankyo Co

1975 – Mevastatina (ML-263b)

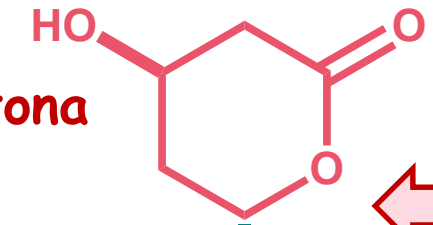
A.Endo, *J. Med. Chem*. **1985**, *28*, 1

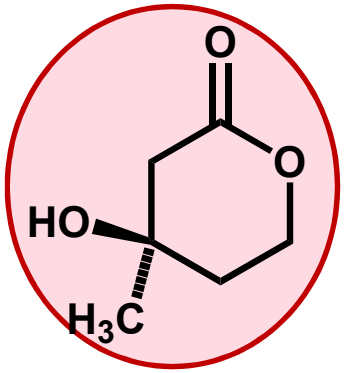
A.Endo, *J. Antibiot.* **1976**, *29*, 1346
Penicillium citrinum
Idem, *Ibid*, **1979**, *32*, 852
Monascus ruber
(compactina)

Protótipo natural

Similaridade molecular

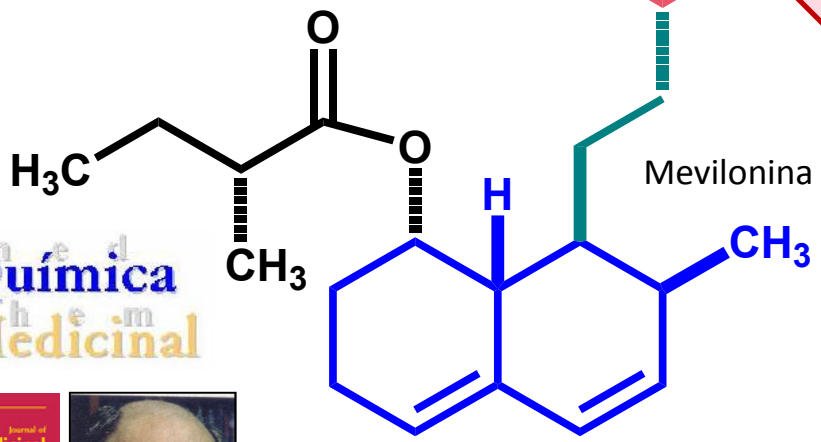
γ-lactona





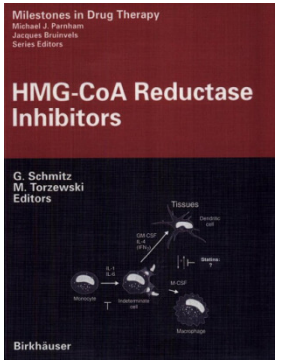
Mevalolactona

HMG-CoA redutase

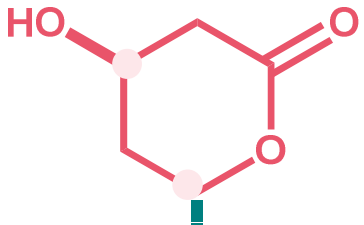


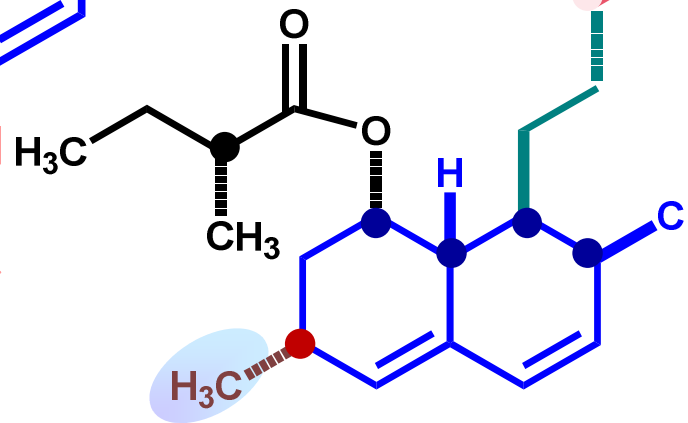
Mevilonina

Química Medicinal



MERCK





Lovastatin (MK-803)

1980 – Merck & Co.

Aspergillus terreus

1987 – MS&D (*Mevacor*^{R})

Arthur A Patchett

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

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

MERCK

simvastatina
1986

2ª geração

Bristol-Myers Squibb

TEVA
(2006)

pravastatina
1988

3ª geração

Pfizer

atorvastatina
1991

AstraZeneca

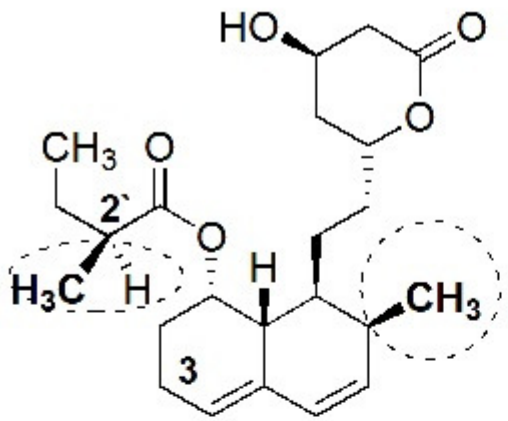
rosuvastatina
2004

Kowa

pitavastatina
2009

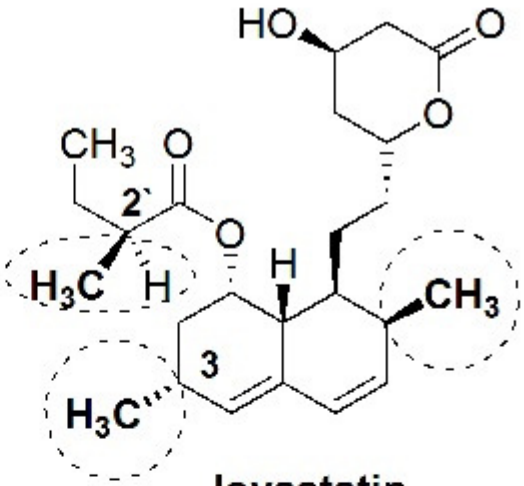
Statins
The HMG CoA Reductase Inhibitors in Perspective
Edited by Allan Gaw, Christopher J Packard, James Shepherd
Martin Dunitz

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



mevastatin

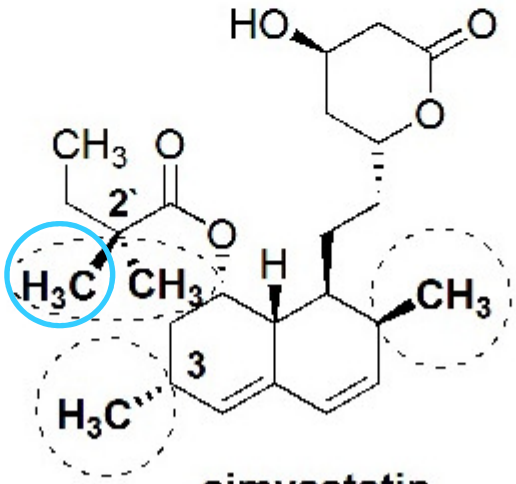
IC_{50} HMG-CoA_R = 5.6 nM



lovastatin

IC_{50} HMG-CoA_R = 2.2 nM

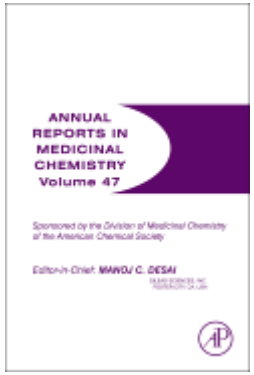
Química
Medicinal

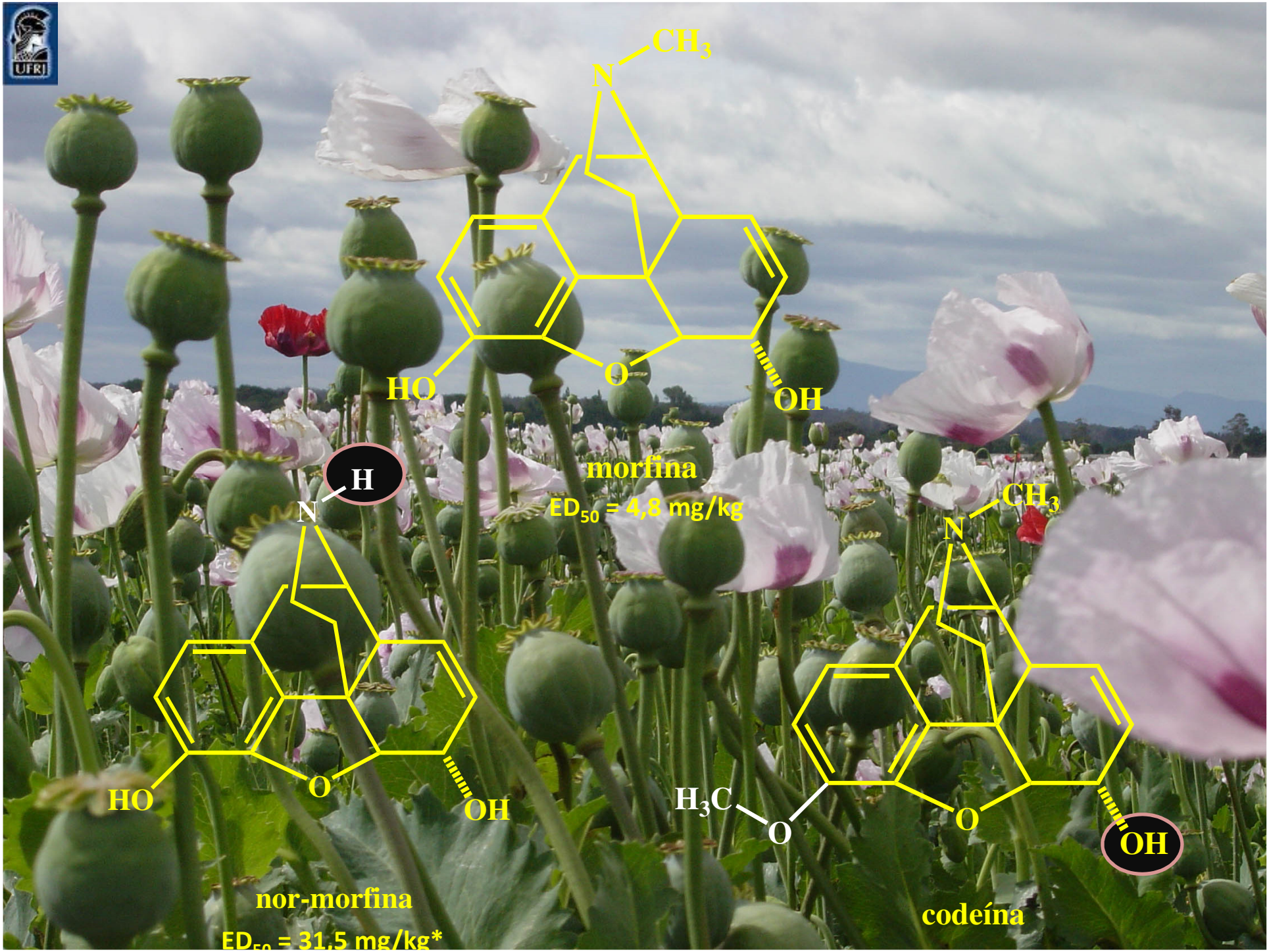


simvastatin

IC_{50} HMG-CoA_R = 0.9 nM

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




CH3
N
HO
O
OH
morfina
ED50 = 4,8 mg/kg
H
N
HO
O
OH
nor-morfina
ED50 = 31,5 mg/kg*
CH3
N
H3C
O
O
OH
codeína

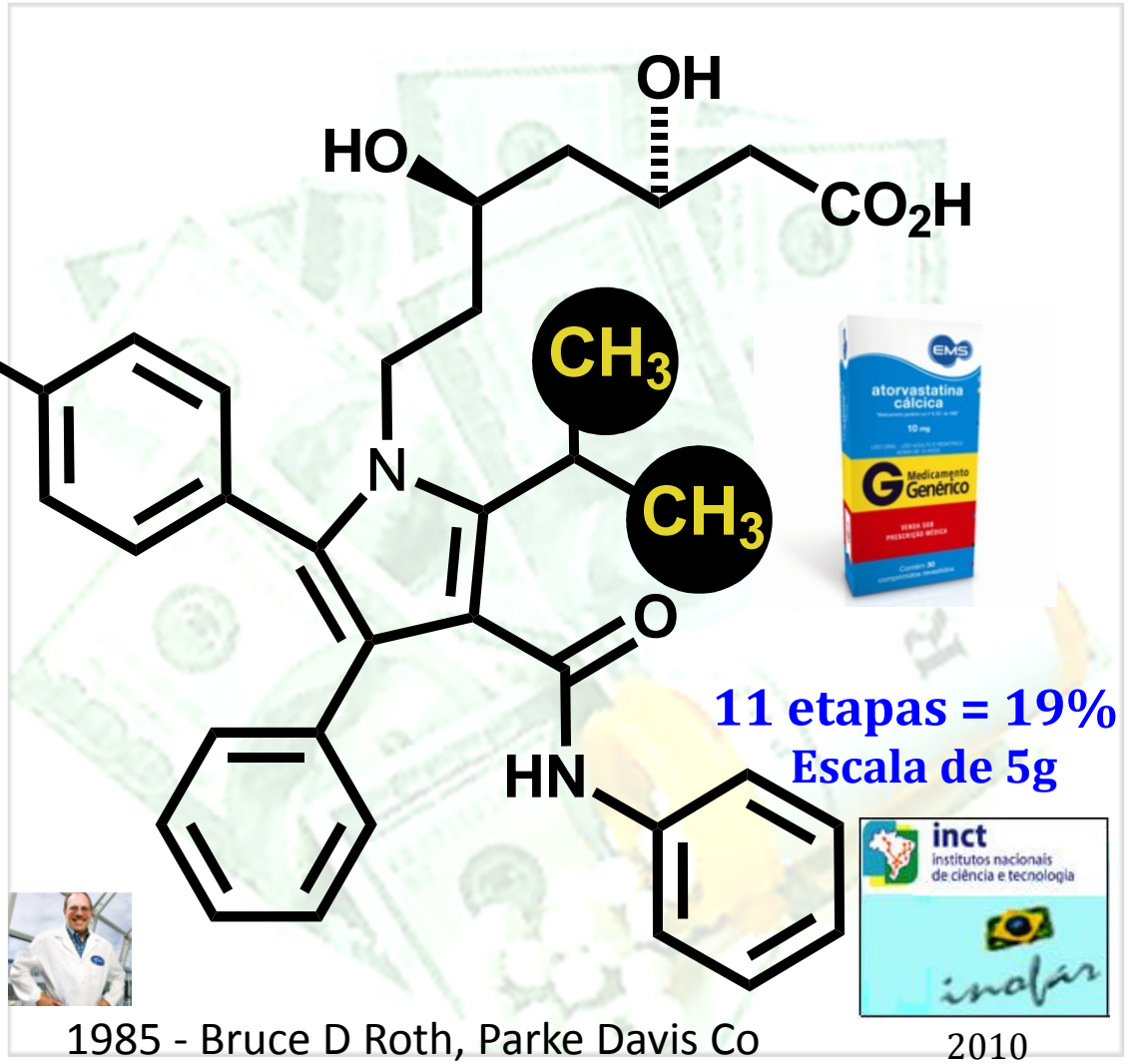
A molécula mais valiosa da história

1991-2011

- Total de vendas mundiais da **atorvastatina**

ca. >US$ **150** bi !

- 41 milhões de pessoas.

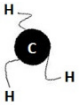


1985 - Bruce D Roth, Parke Davis Co

2010

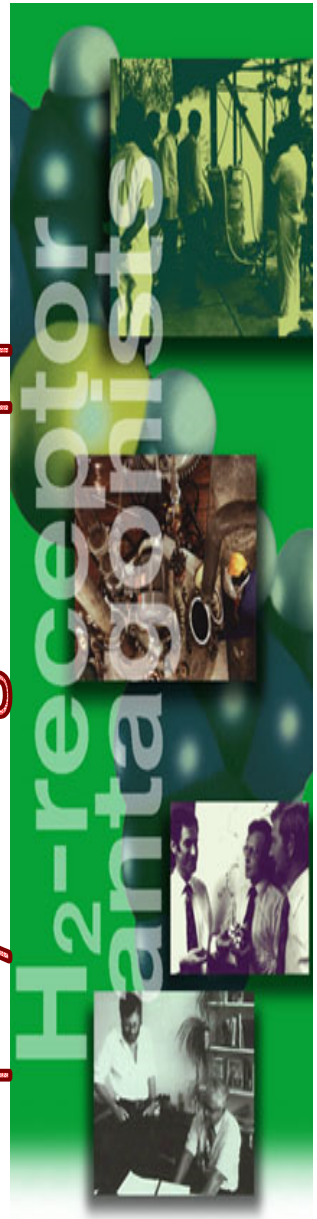
LC Dias, AS Vieira, EJ Barreiro, Processo de obtenção de atorvastatina cálcica utilizando novos intermediários *PI 018110015039* (protocolado no INPI, em 25/04/2011) PCT dezembro de 2011

a metila ...



the physiological approach

H_2-receptor antagonist



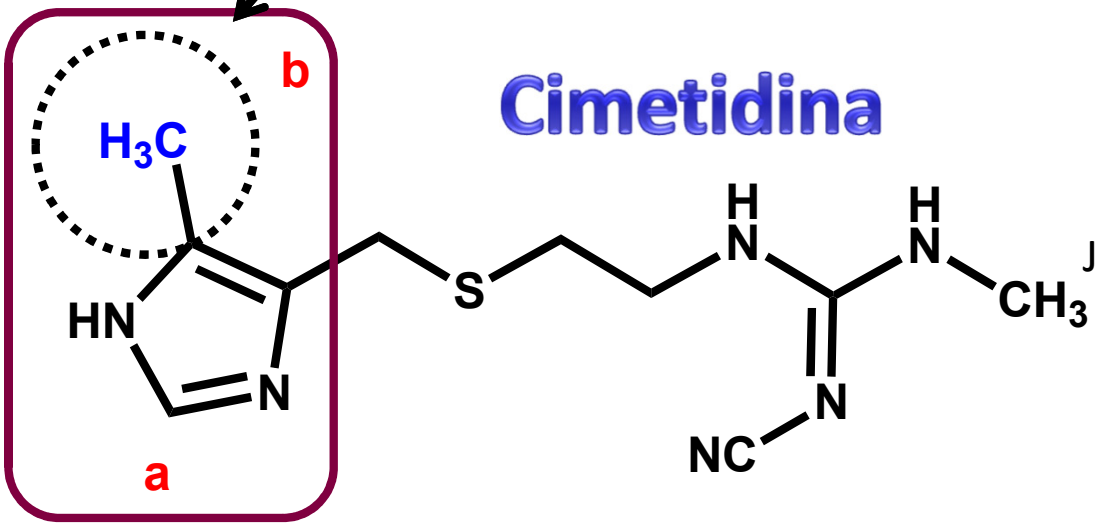
National Historic Chemical Landmarks

AMERICAN CHEMICAL SOCIETY

A new era of logical drug design

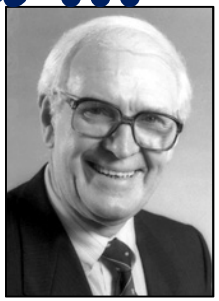
The research program leading to cimetidine also represented a revolution in the way pharmaceuticals are developed. Traditionally, the development of a new drug would often depend on the fortuitous discovery of a plant or microbial extract that showed some of the required biological activity. Using that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

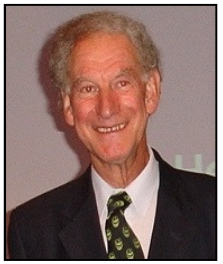


Cimetidina

1988



James W. Black



C Robin Ganellin

John C Emmett

Graham J Durant

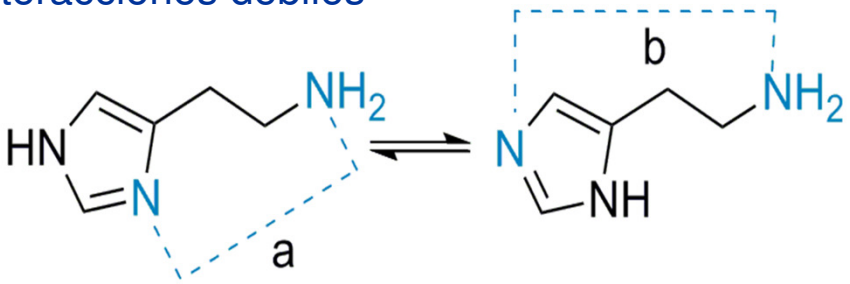
A metila valiosa...

Química Medicinal

Dos subtipos de H_R

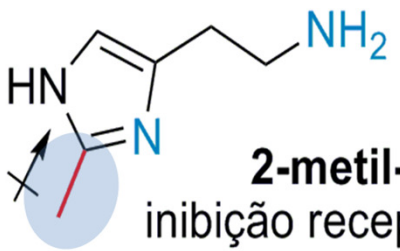
C. Robin Ganellin, 1973

Interacciones débiles

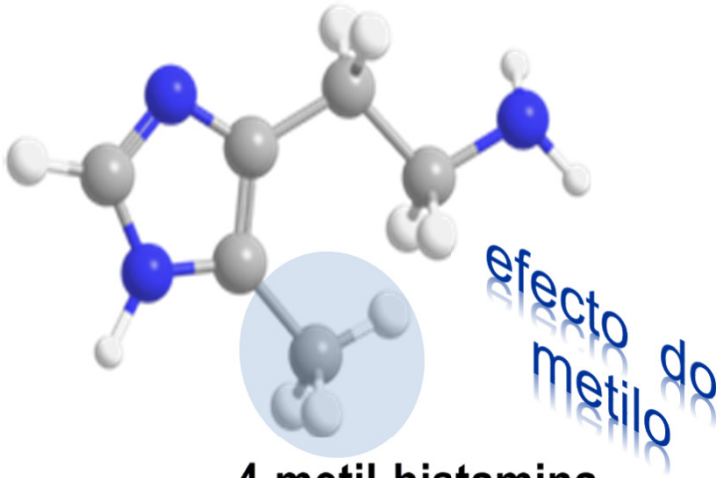


Forma A a = 4,83 Å b = 5,52 Å **Forma B**

Equilibrio tautomérico

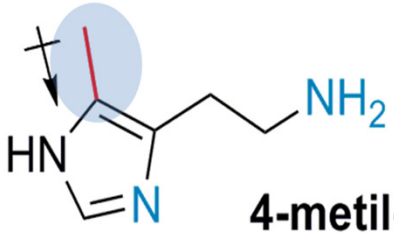


2-metil-histamina
inibição receptores H_1 = 17%
inibição receptores H_2 = < 2%



4-metil-histamina

Analog ativa



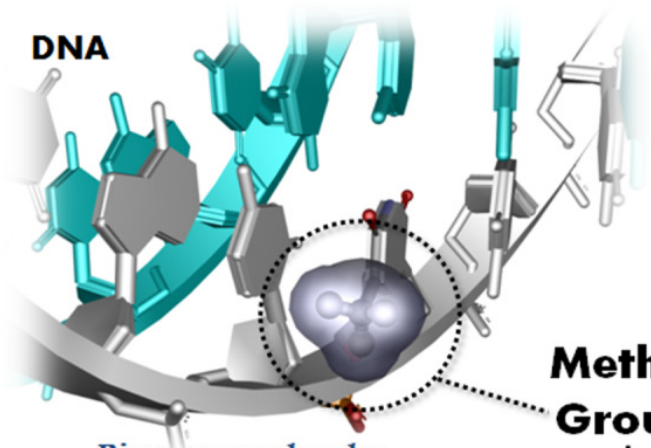
4-metil-histamina
inibição receptores H_1 = 0,2%
inibição receptores H_2 = 50%

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

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

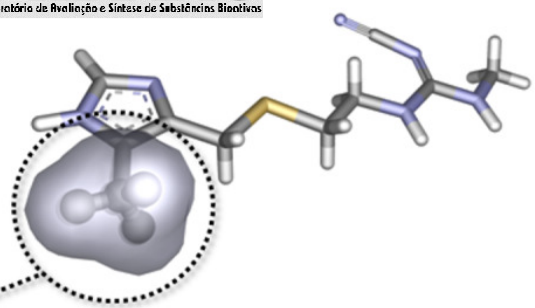
The Methylation Effect in Medicinal Chemistry

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



LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

Química Medicinal



Methyl Group

Biomacromolecules

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

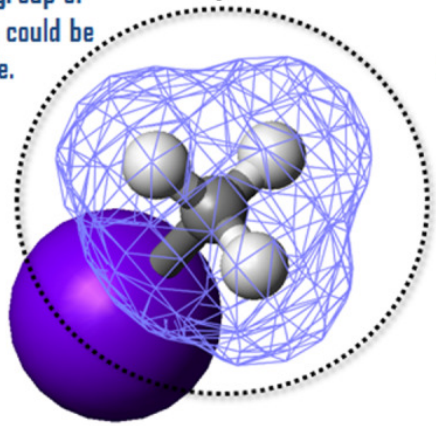
Micromolecules

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

CH_3

15 Da

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

The Methylation Effect in Medicinal Chemistry

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

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

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

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

CONTENTS

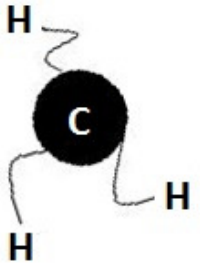
1. INTRODUCTION: THE METHYL GROUP AND ITS BIOLOGICAL INTERACTIONS

The monovalent methyl group is derived from methane through the removal of a hydrogen atom,[1] and its etymology is directly related to the discovery of methanol.[2] The first reports of the use of methanol were from ancient Egyptians. In their embalming process, they used a mixture of substances obtained from the pyrolysis of wood shards that contained a significant amount of methyl alcohol.[2] Pure methanol was first isolated and described in 1661 by Robert Boyle, who called it "*spirit of box*," as it is the product of the distillation of "*Boxwood*," the generic name given to ca. 70 types of trees from the *Buxaceae* family. In 1834, the French chemists Jean-Baptiste Dumas and Eugene Peligot determined its elementary composition as CH_4O through combustion analysis. They introduced the term methyl to organic chemistry through a mistranslation from the Greek, *methy* = "wine" + *hȳlē* = wood (wood bark), when the intention was to define "wood alcohol" or methanol.[2]

The methyl group is very important in the molecular recognition of endogenous and exogenous organic compounds by bioreceptors. Although it only participates in London dispersion interactions, which are the weakest of all intermolecular interactions,[3] methyl groups have stereoelectronic effects[4] on micromolecules and biomacromolecules, thereby leading to diverse biological effects, including selectivity among bioreceptors, increased potency, and protection against enzyme metabolism.[5] Cognizant of the methyl group's importance in molecular recognition, Wermuth wrote:[5]

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

Received: February 18, 2011
Published: June 01, 2011



CH_3

甲基在药物分子设计中的应用

连 捷[1,2], 王 江[2], 孙海峰[2], 林岱宗[2], 柳 红[1,2*]

(1. 中国药科大学药学院, 江苏 南京 210009; 2. 中国科学院上海药物研究所, 新药研究国家重点实验室, 上海 201203)

摘要: 甲基在药物分子的合理设计中起到重要作用, 如何巧妙地在分子中引入甲基已成为先导化合物结构优化的重要改造策略之一。本文综述了在药物分子设计中一些合理引入甲基的应用实例。将甲基引入小分子中通过影响脂溶性和水溶性改变药物的理化性质; 通过诱导效应、改变分子构象以及改变蛋白−配体相互作用影响药物的药效性质; 通过邻位效应、弱代谢作用以及增加稳定性来影响药物的代谢性质; 同时, 甲基在 me-too 药物研发以及老药新用研发策略中也起到重要作用。

关键词: 甲基; 药物设计; 结构优化; 空间电子效应; 脂溶性

中图分类号: R916 **文献标识码**: A **文章编号**: 0513-4870 (2013) 08-1195-14

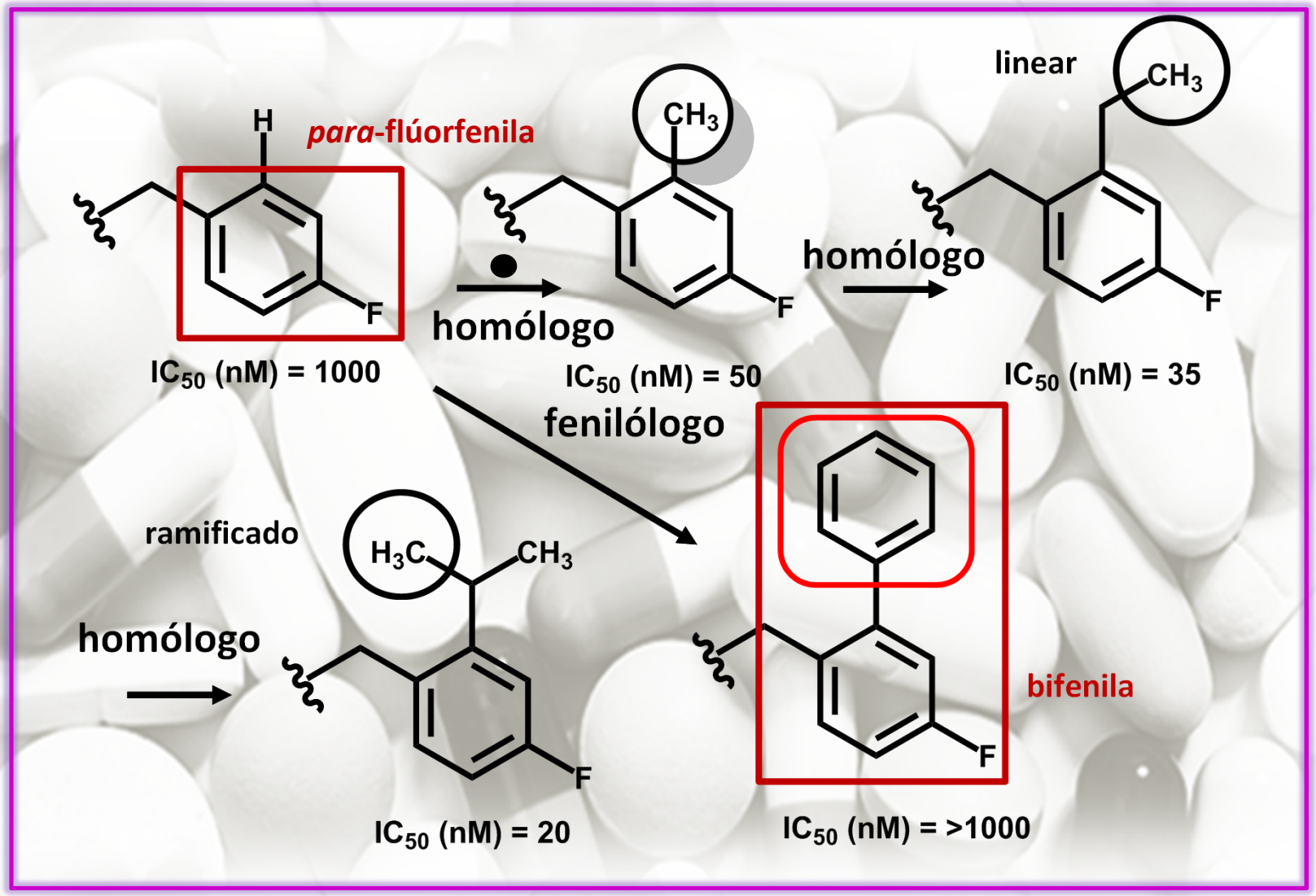
Application of methyl in drug design

LIAN Jie[1,2], WANG Jiang[2], SUN Hai-feng[2], LIN Dai-zong[2], LIU Hong[1,2*]

(*1. School of Pharmacy, China Pharmaceutical University, Nanjing 210009, China; 2. State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China*)

Abstract: The methyl group plays an important role in the rational drug design. Introducing methyl into small molecules has become an important strategy of lead compound optimization. The application of methyl in drug design is reviewed in this paper. Methyl can modulate the physicochemical, pharmacodynamic, and pharmacokinetic properties by ortho effect, inductive effect, and conformational effect. It also improves the metabolic stability as a soft metabolic point. In addition, introducing methyl into drug molecules can also be applied as a strategy in new uses of old drugs and generate me-too drugs.

Exercício 1



Conceito de *scaffold* (andaime): sistema cíclico; anel; núcleo;
(core, framework, ring, nucleous)