



**UFRJ**

Universidade Federal do Rio de Janeiro

# Noções básicas de Química Medicinal na descoberta de fármacos



Laboratório de Avaliação e Síntese de Substâncias Bioativas

<http://www.farmacia.ufrj.br/lassbio>

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Parte 2

Professor Titular

([ejbarreiro@ccsdeqania.ufrj.br](mailto:ejbarreiro@ccsdeqania.ufrj.br))

Universidade Federal do Rio de Janeiro

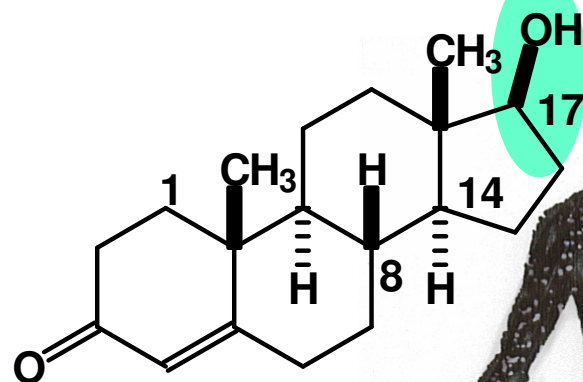
Departamento de Fármacos  
Faculdade de Farmácia



Universidade Federal de Goiás, junho de 2008

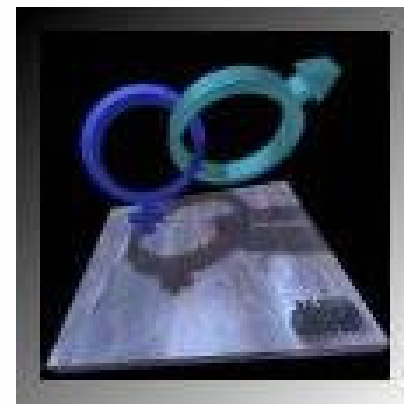


# Similaridade & Dissimilaridade Molecular

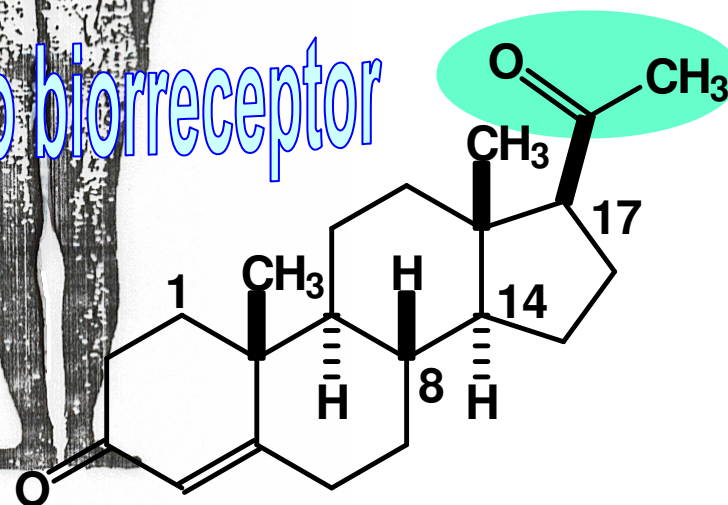


testosterona

no reconhecimento molecular do biorreceptor



similaridade molecular

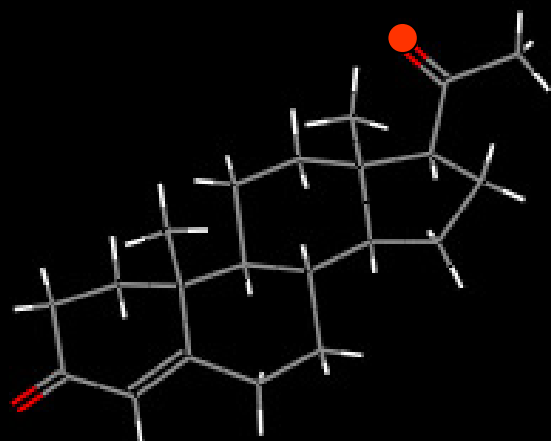


progesterona

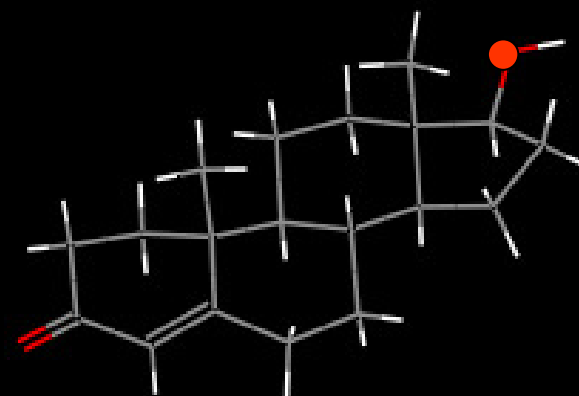
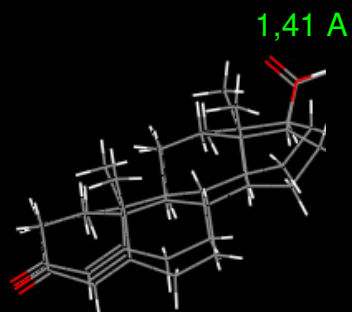


# Biorreceptor

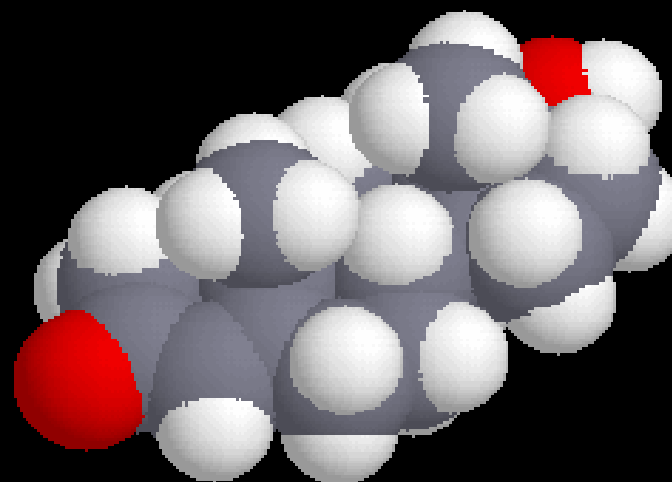
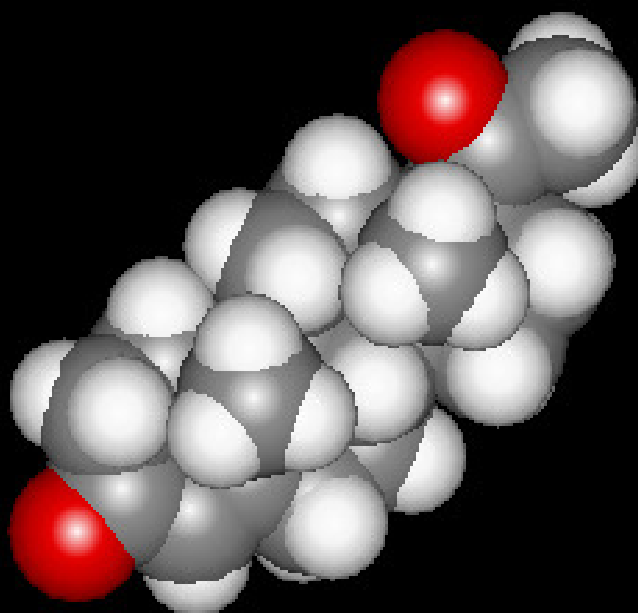




progesterona



testosterona

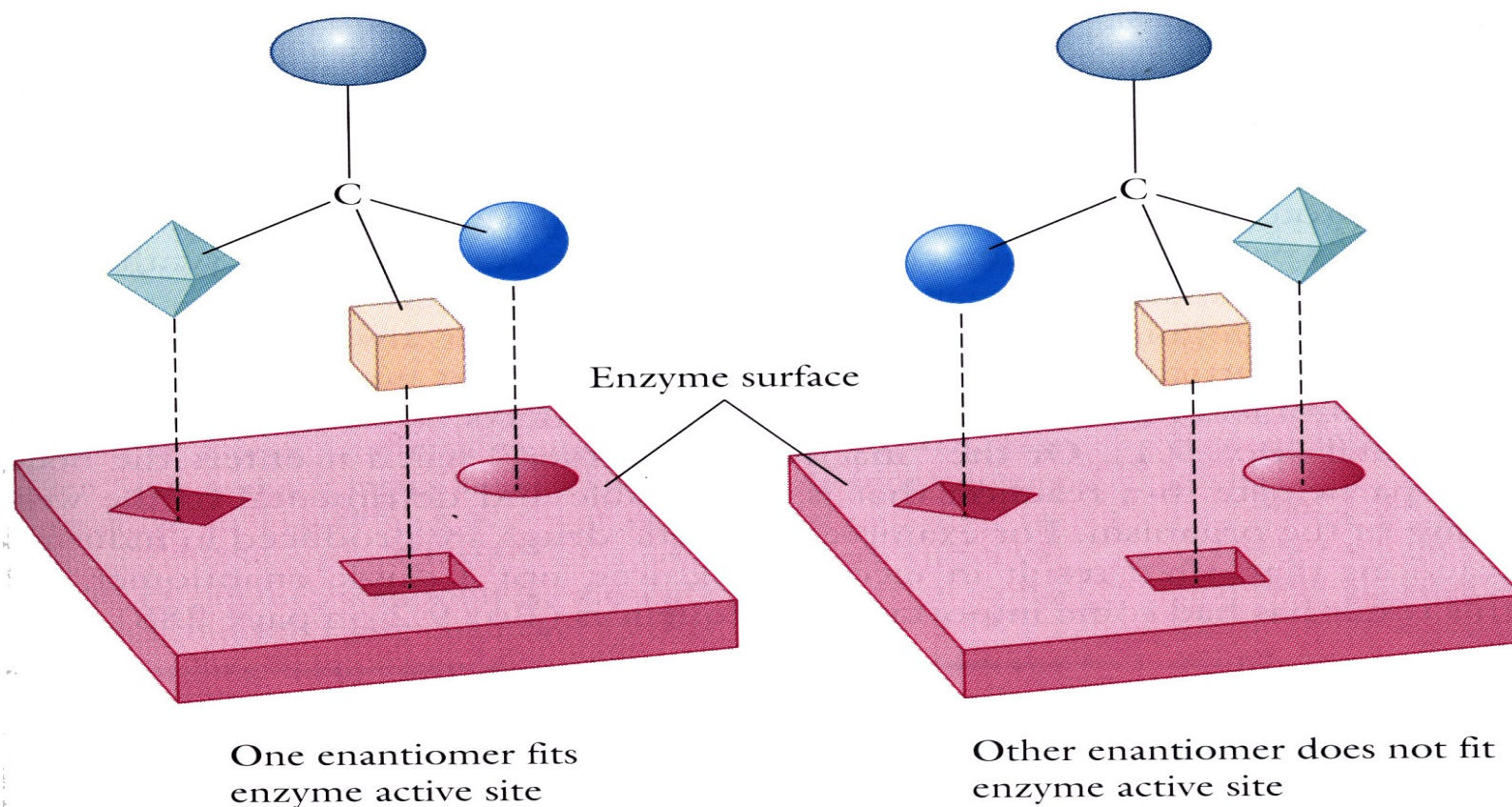




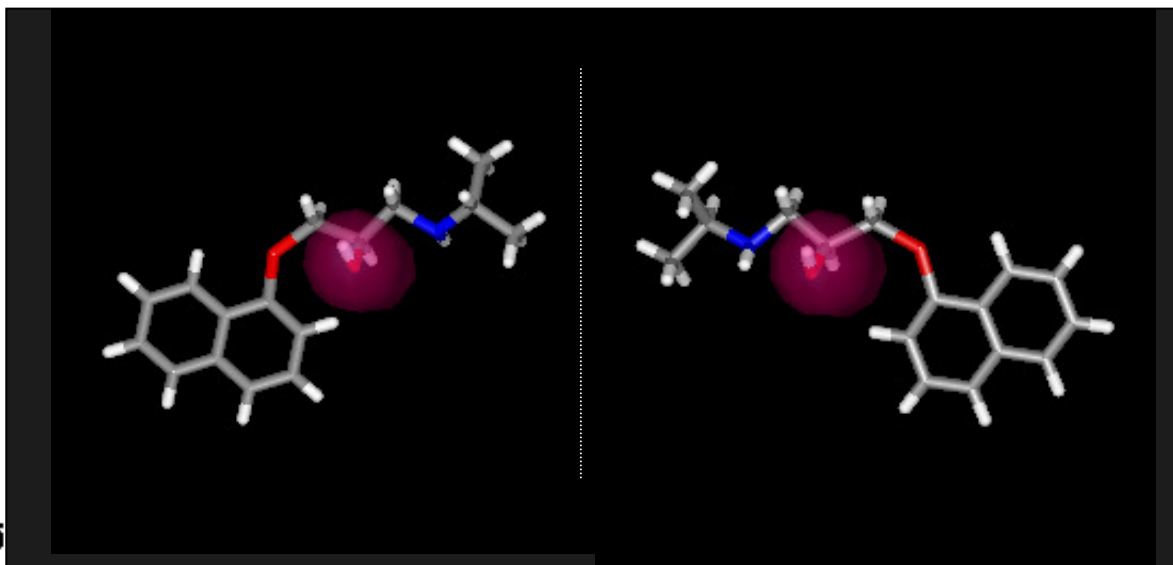


# Modelo dos três pontos

Modelo de Easson-Stedman

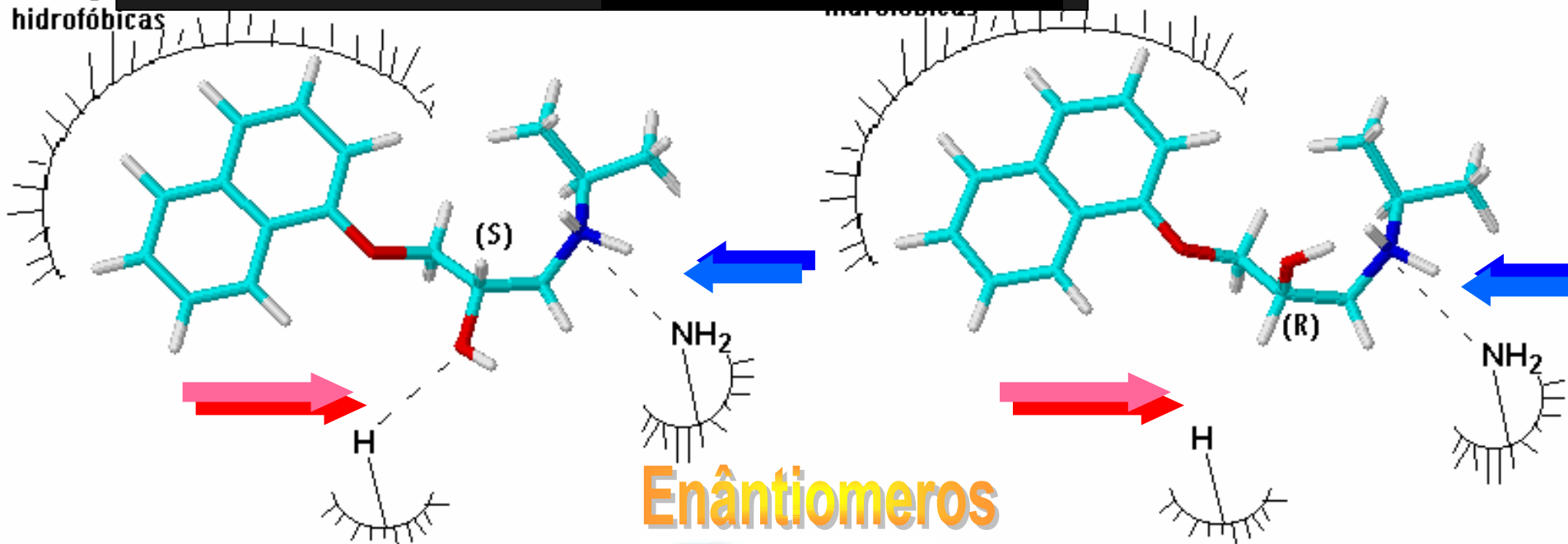


## A quiralidade e os fármacos...



**Eutômero**  
**Distômero**

Interação  
hidrofóbicas



**A quiralidade da vida e os fármacos...**





# Descoberta de Fármacos: O Papel dos Produtos Naturais

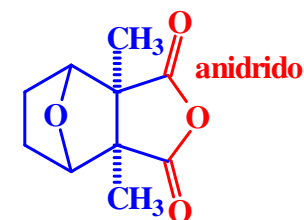
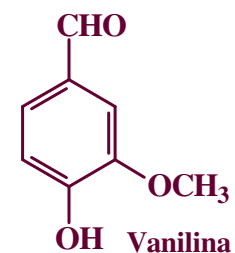


# Produtos Naturais Afrodisíacos

*J. Chem. Ed.* 1980, 57, 341

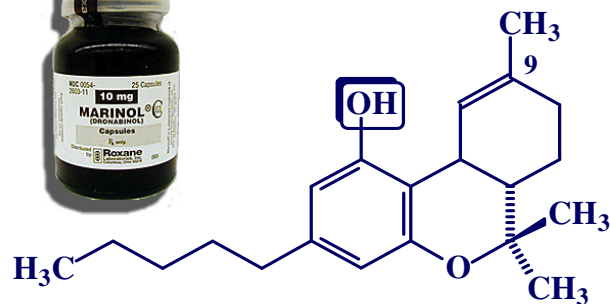
T. G. Waddell, H. Jones & A.L. Keith

“... the well known flavoring substances which has unquestionable aphrodisiac qualities...”. In: *Herbal Aphrodisiacs*, Cal., USA, 1971



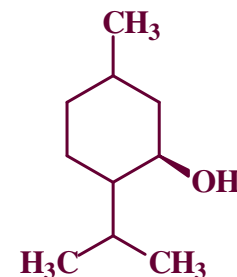
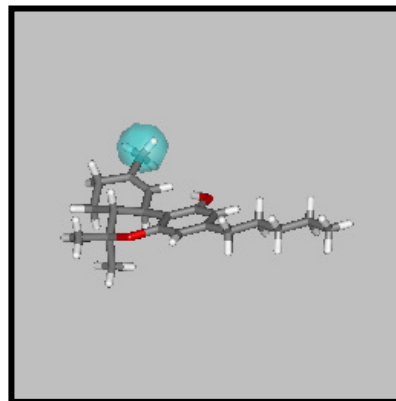
Cantaridina

*Cantharis vesicatorica*



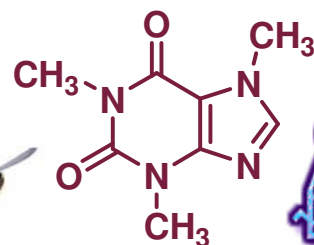
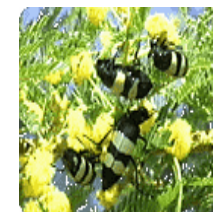
THC

*Canabis sativa*



Mentol

Volátil



cafeína



# AFRODISÍACOS





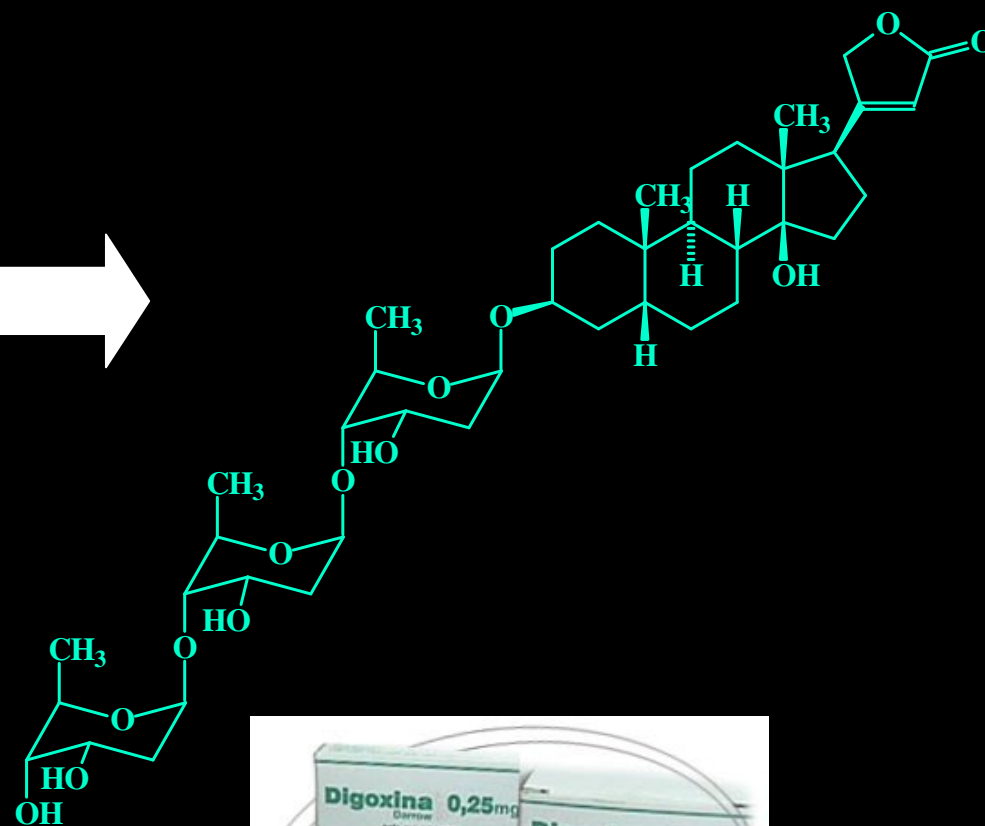
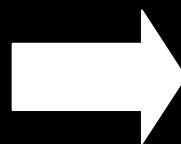
Photo Henriette Kress



terpenos, alcalóides,  
esteróides, flavonóides

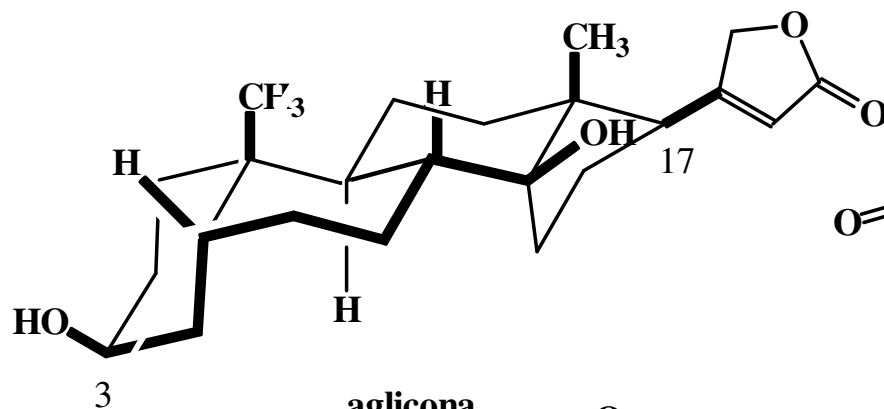
*Digitalis purpurea*

# Glicosídeos Cardiotônicos

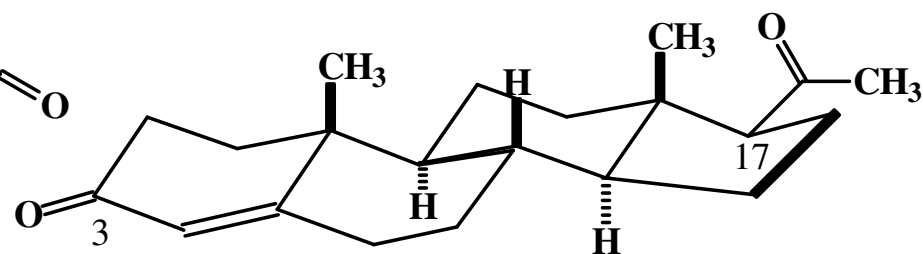


## Decano dos Fármacos

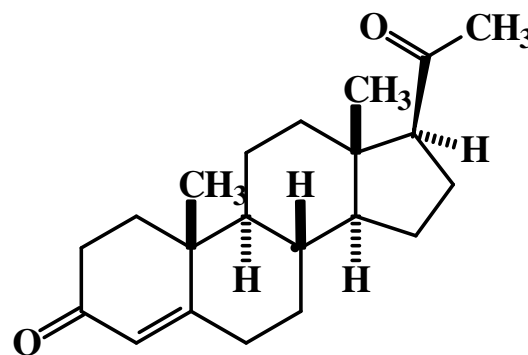
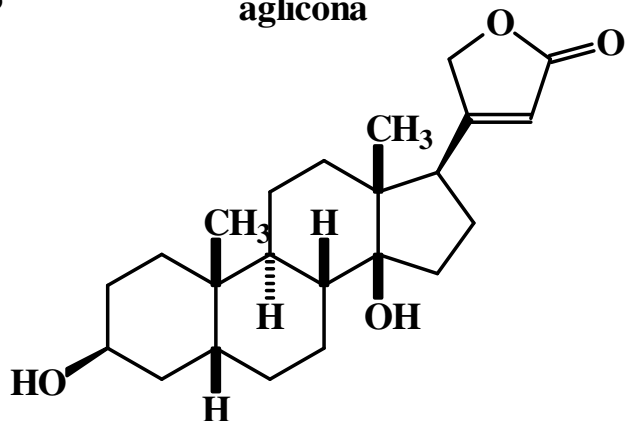




aglicona



progesterona



# A Importância da Conformação



# Curare

## Fármaco dos Índios



*Chondrodendron tomentosum*

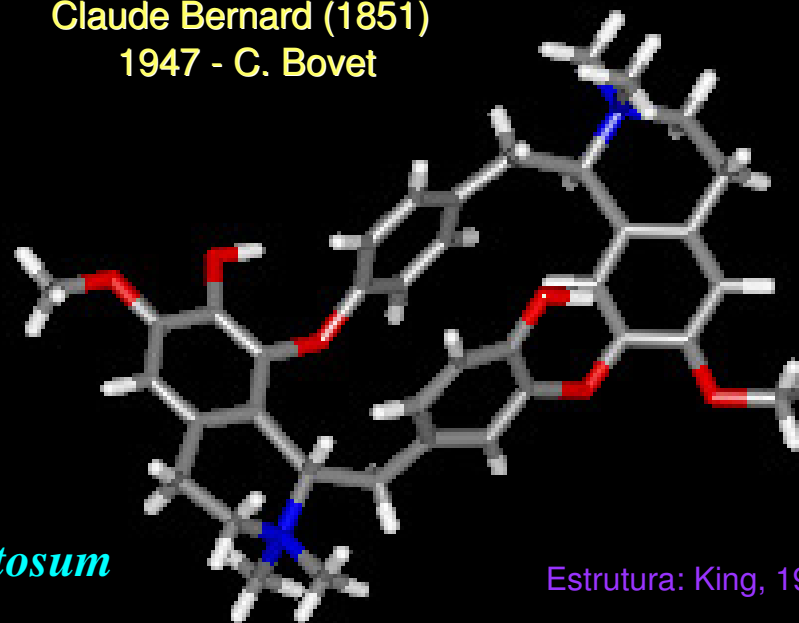
## Bloqueadores ganglionares



Institute Pasteur

Claude Bernard (1851)

1947 - C. Bovet

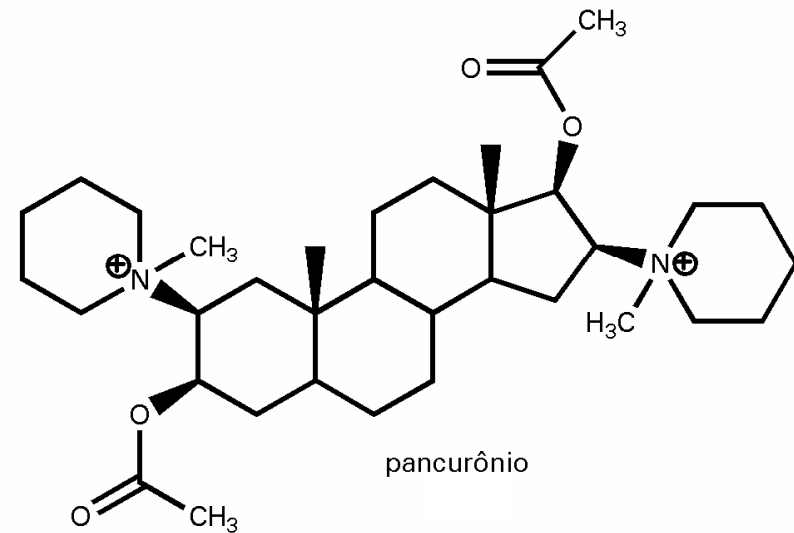
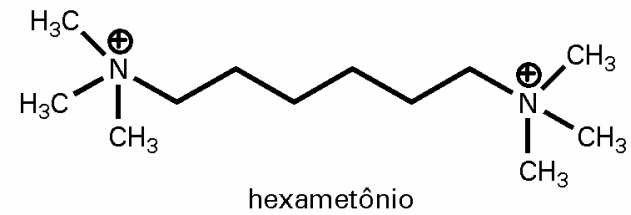
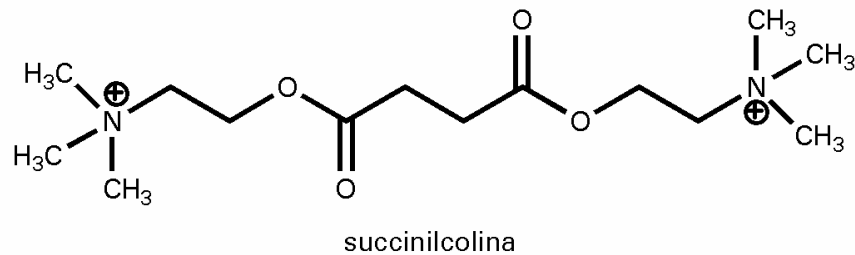
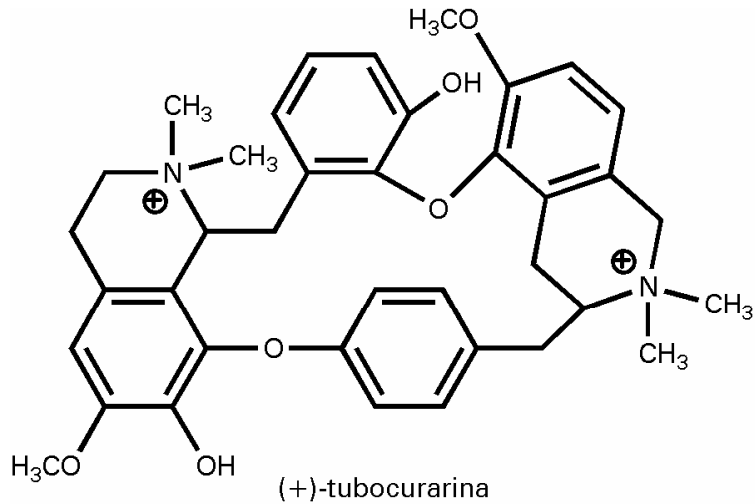


Estrutura: King, 1935

## d-tubocurarina



# Bloqueadores ganglionares





# Índios & indóis

Virolas amazônicas



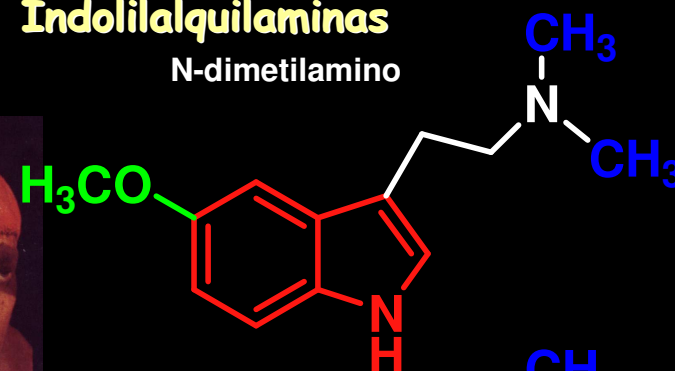
Virola spp

## Alcalóides Indólicos

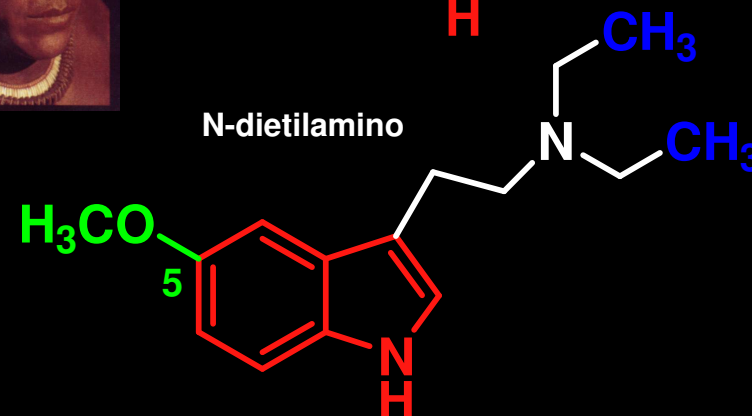


Indolilalquilaminas

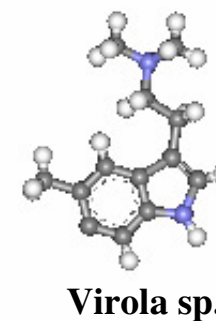
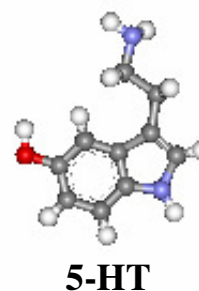
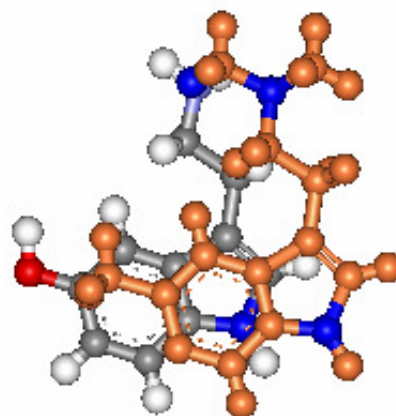
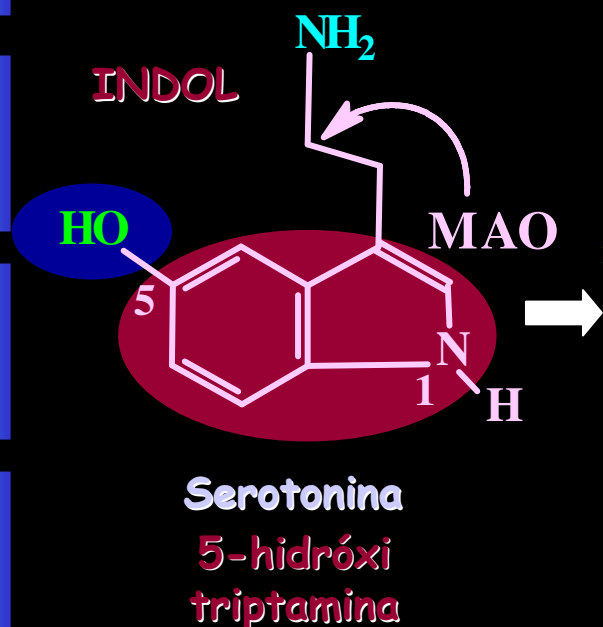
N-dimetilamino



N-dietilamino



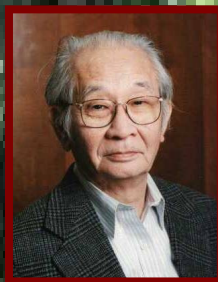
## Compostos Alucinogênicos





**“*Específico Pessoa*”,** criado pelo farmacêutico  
José Torquato Pessoa, de Camocim, Ceará, BR,  
como preparado antiofídico.  
(Francisco José de Abreu Matos)

Koji Nakanishi

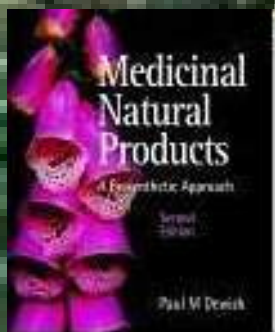


ACS, 1991

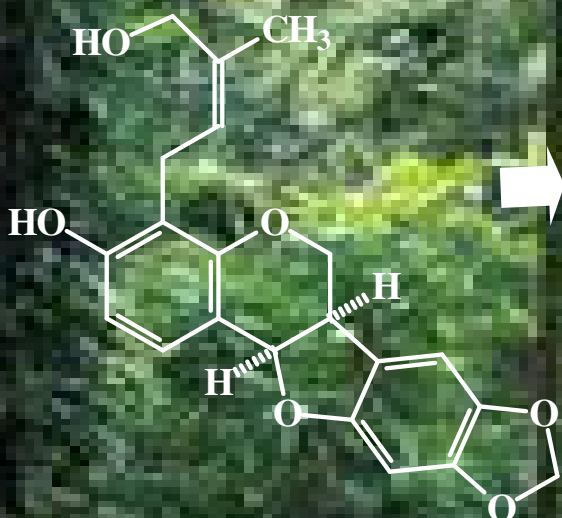
Un. Columbia EUA

“A Wandering Natural Products Scientist”

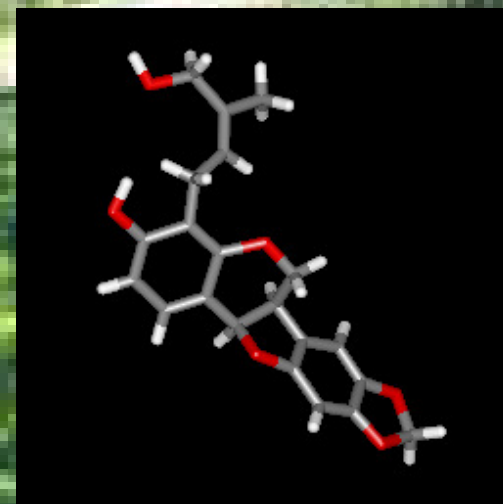
Cabenegrina-A



Medicinal Natural Products:  
A Biosynthetic Approach  
Paul M. Dewick,  
Wiley, 1997.



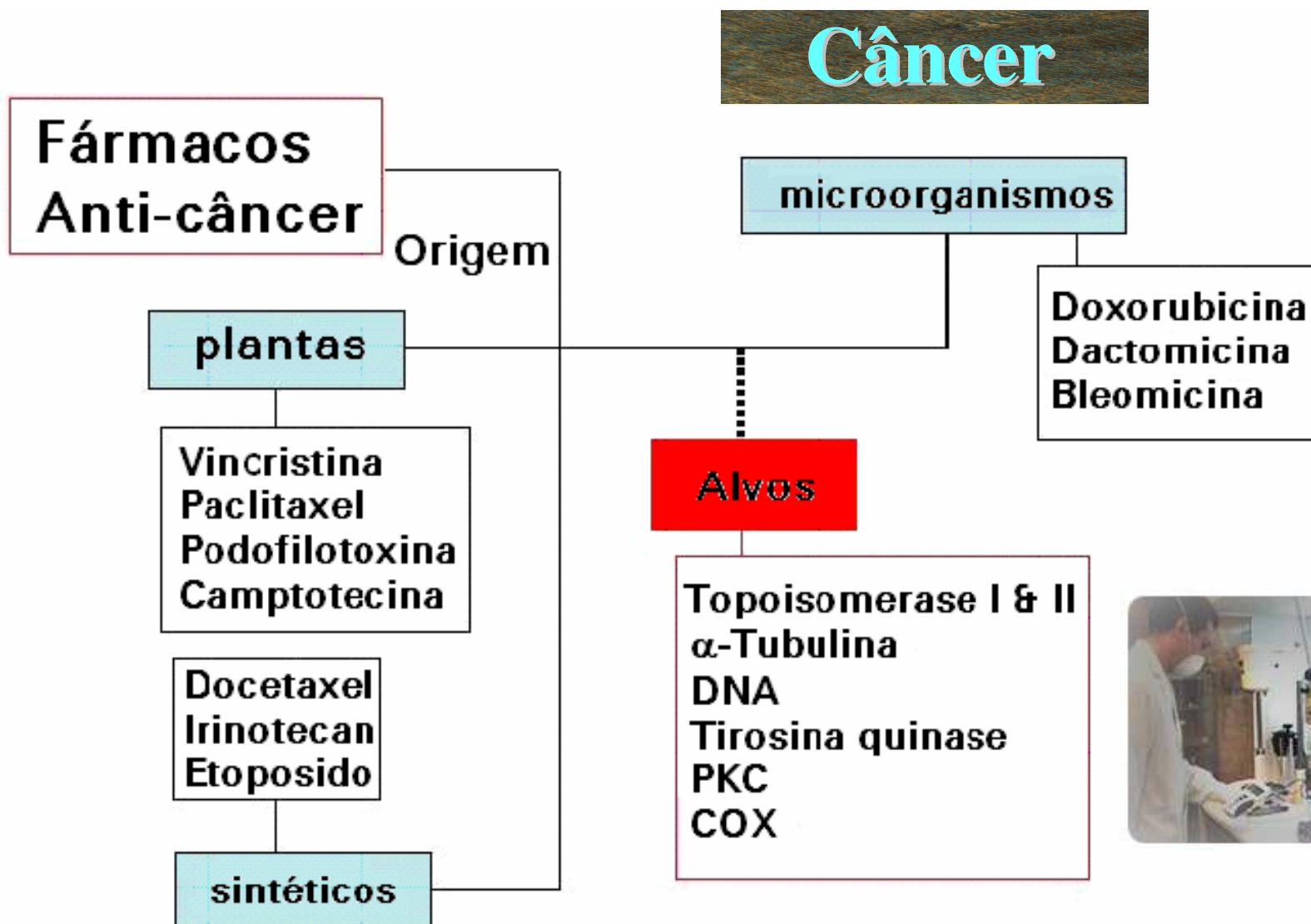
*Tetrahedron Lett.* 1982, 23, 3855







# Produtos naturais com propriedades anti-câncer

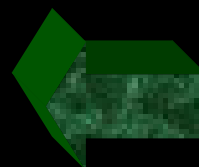




# Agentes Anti-câncer de Origem Natural

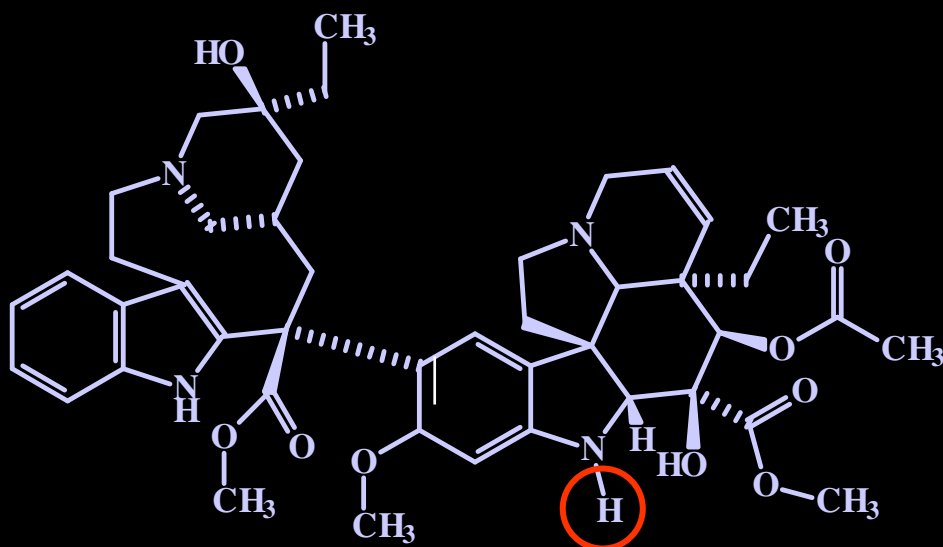


*Vinca sp.*



*Catharanthus roseus*

Câncer



## Alcalóides

E. Wenkert, 1955

Inibidor mitótico ( metafase)

## Alcalóides bis-indólicos

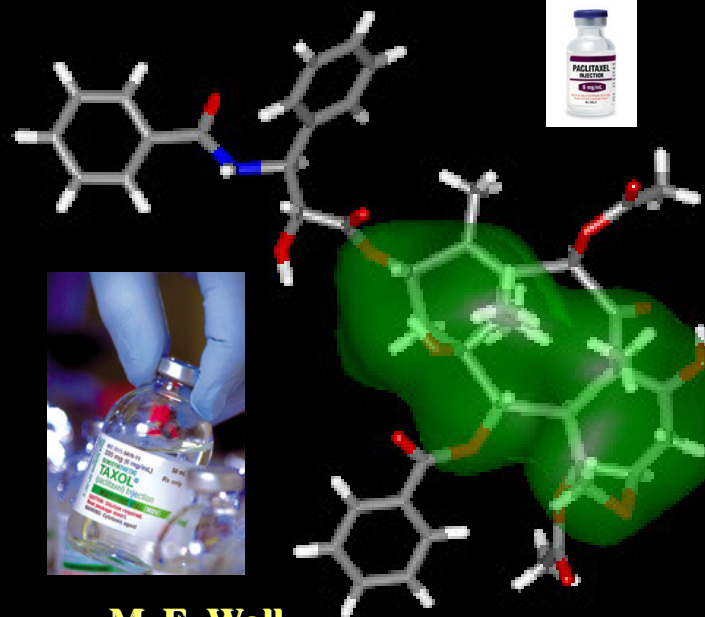
vincristina R= H  
vinblastina R= CHO




**M. C. Wani *et al.*, J. Am. Chem. Soc. 1971, 93, 2325**  
**Res. Triangle Park, 1967**



**1996 - National Cancer Institute  
Award of Recognition**



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



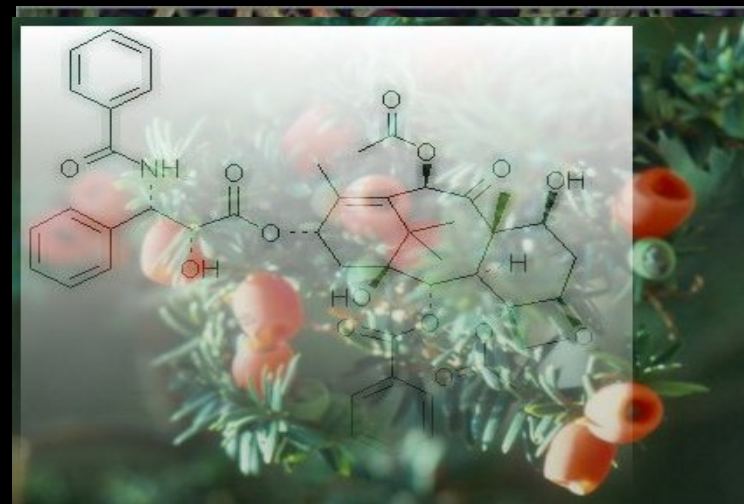
# The Story of Taxol

NATURE AND POLITICS  
IN THE PURSUIT OF AN  
ANTI-CANCER DRUG

JORDAN GOODMAN  
VIVIEN WALSH

**TAXOL®**  
*Science and  
Applications*

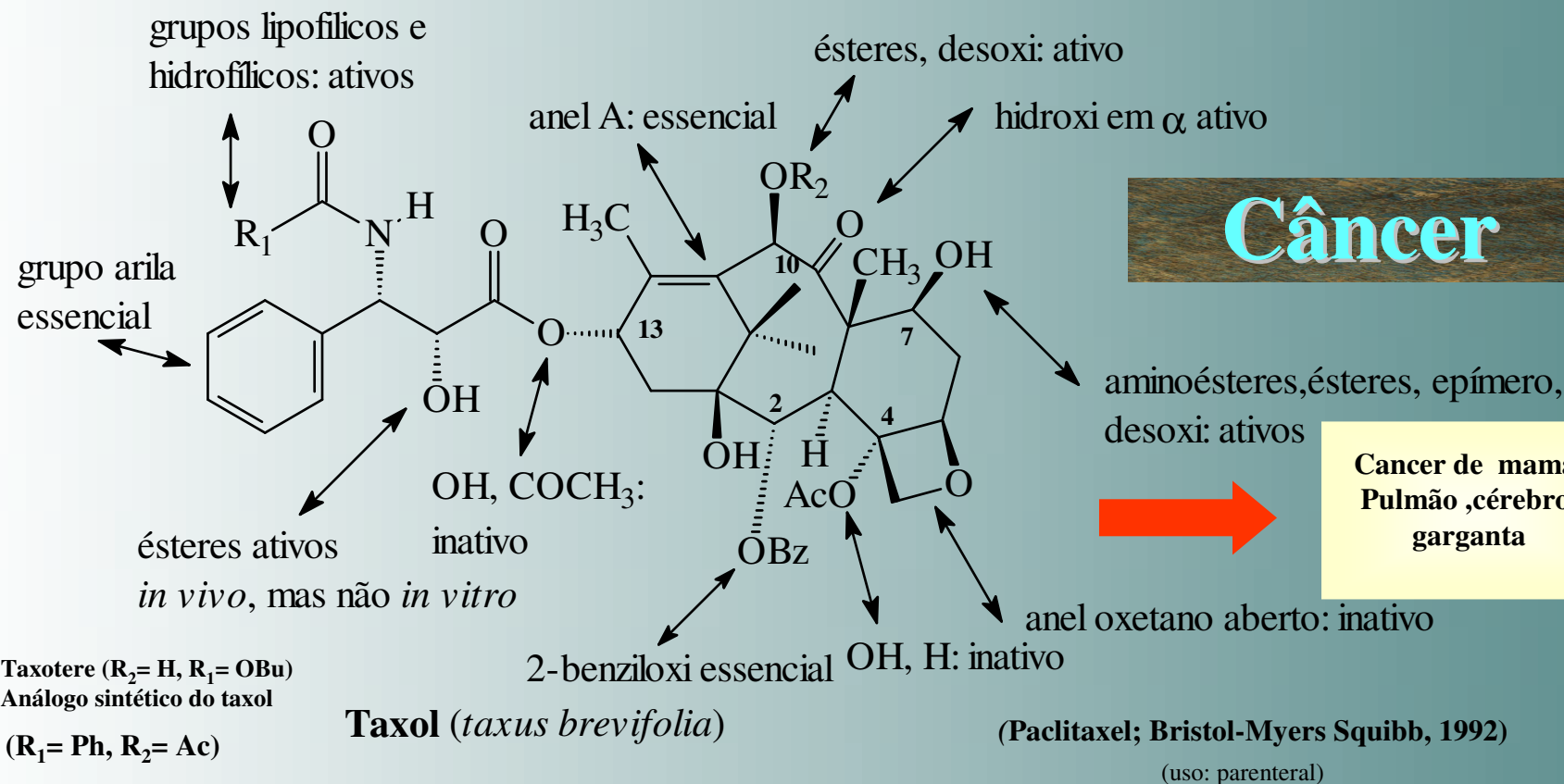
*Edited by*  
**Matthew Saffness**



*Taxus bacatta*



# SAR dos taxóides



**Baixa biodisponibilidade**

Toxicidade: Medula óssea  
Neutropenia

“Natural Compounds in Cancer Therapy: Promising Nontoxic Antitumor Agents from Plants and Other Natural Sources”, J. Boik, Medical Press, Princeton, 2001.

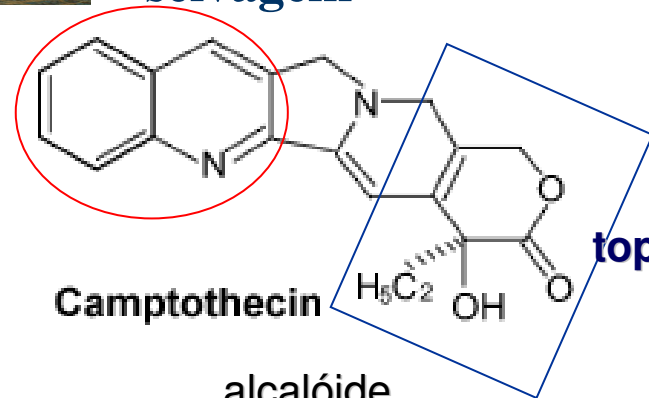




# Câncer

Molécula  
“selvagem”

Baixa biodisponibilidade



Camptothecin

Inibidor de  
topoisomerase-1

alcalóide  
quinolínico de biossíntese mista

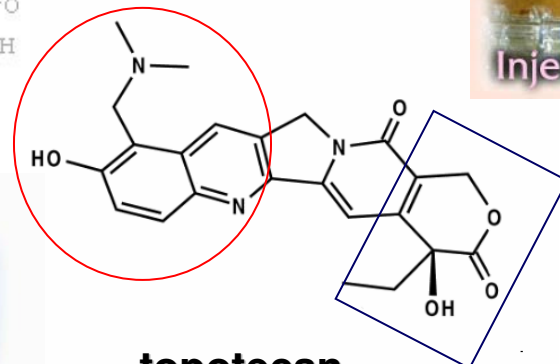
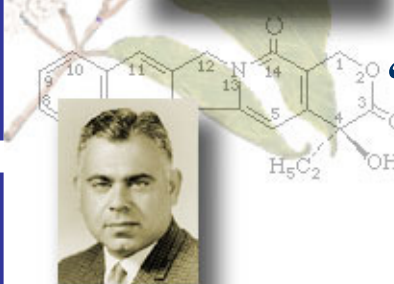


*Camptotheca  
acuminata*

Wall, ME & Wani, MC “**Camptothecin: Discovery to Clinic**”  
*Annals of the New York Academy of Sciences* 1996, 803, 1

Wall, ME, MC Wani, CE Cook, KH Palmer, AT McPhail, GA Sim, “Plant antitumor agents. 1. The isolation and structure of camptothecin, a novel alkaloidal leukemia and tumor inhibitor from *Camptotheca acuminata*” *J. Am. Chem. Soc.* 1966, 88, 3888.

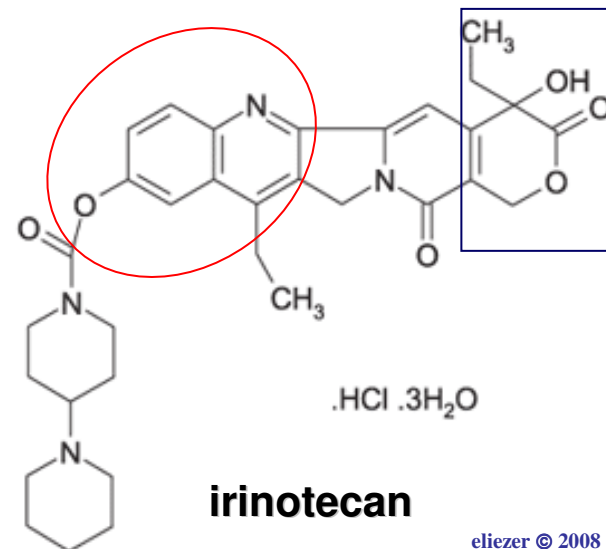
Molécula  
“domesticada”



topotecan



Injetável

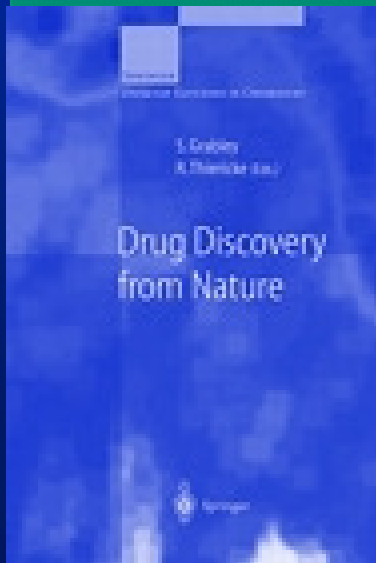


irinotecan





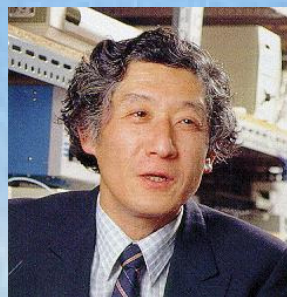
# Patrimônio genético brasileiro



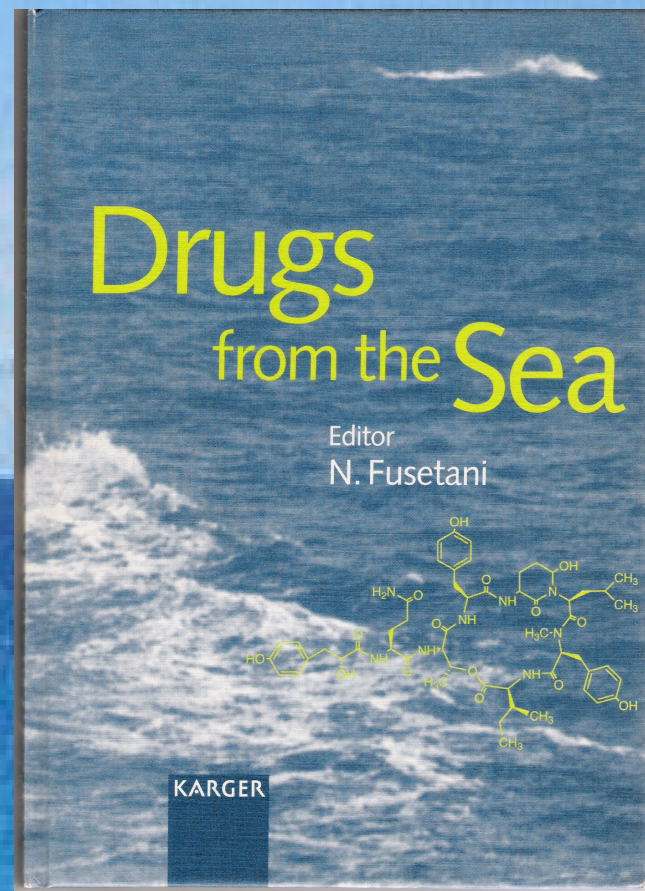
C Viegas Jr, V S Bolzani, EJ Barreiro, *Quim Nova* 2006, 29, 326-337



# Produtos Naturais do Mar



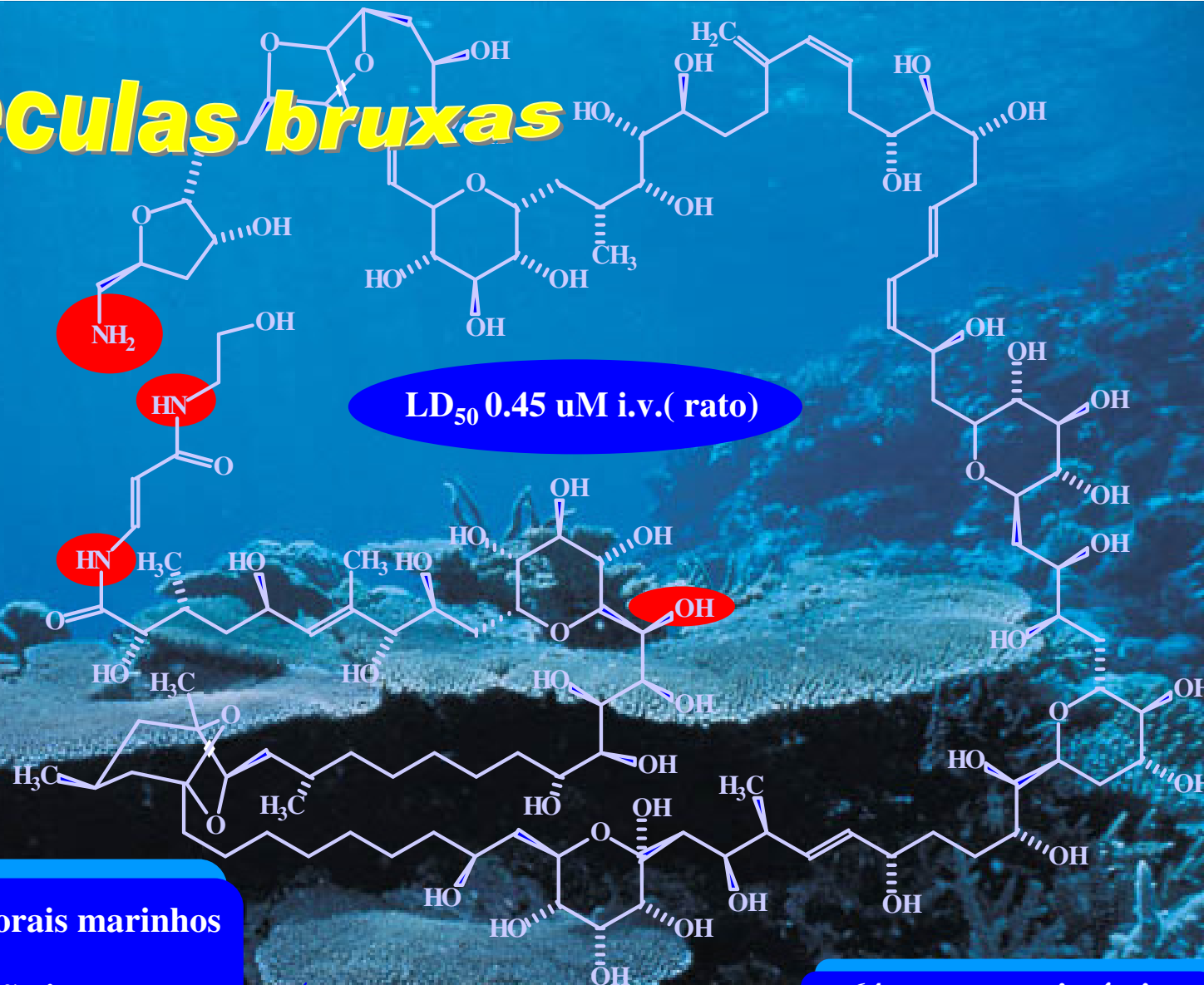
**N. Fusetani**







# Moléculas bruxas



LD<sub>50</sub> 0.45 uM i.v. (rato)

1971 - Isolada de corais marinhos do gen. *Palythoa*  
1982 - vasoconstrição intensa  
1983 - estrutura elucidada  
1989 - síntese total estereosseletiva

Y. Kishi *et al.*, 1989

Palitoxina

C<sub>129</sub>H<sub>227</sub>N<sub>3</sub>O<sub>54</sub>  
PM 2684.20

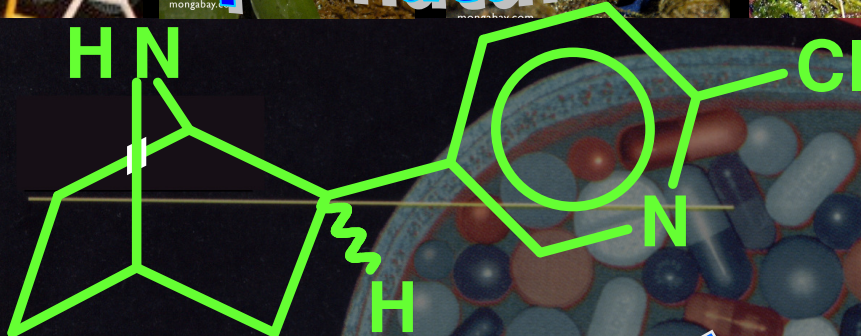
64 centros assimétricos  
8 ligações duplas  
42 grupos hidroxilas

2<sup>64</sup> isômeros





protótipo natural



**Epibatidina**

200-400 vezes mais  
potente  
que a morfina

IT baixo



1992

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

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



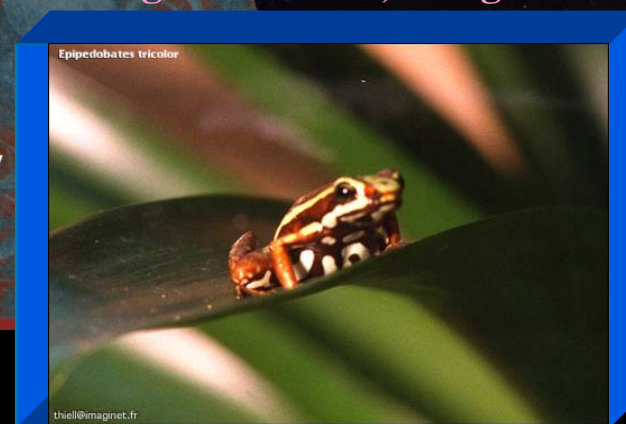
John W. Daly

Un. Maryland, EUA



Primeiro PN com quimiotipo  
7-azabicyclo[2.2.1]heptano

Primeiro alcalóide não-opiíode,  
organo-clorado, analgésico.



**Epipedobates tricolor**





# Inovação terapêutica



M. O. Rocha e Silva  
1910-1983



jararacá

## Fármacos Inteligentes

Bradicinina

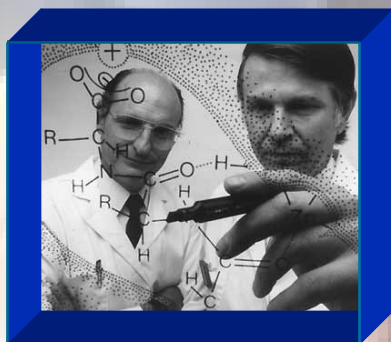
(W. Beraldo, 1949)



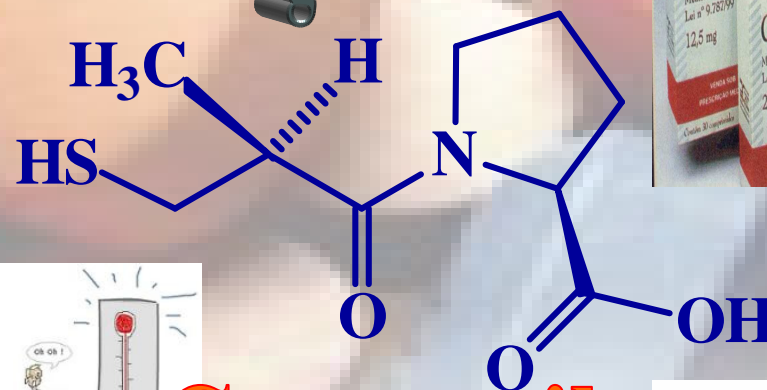
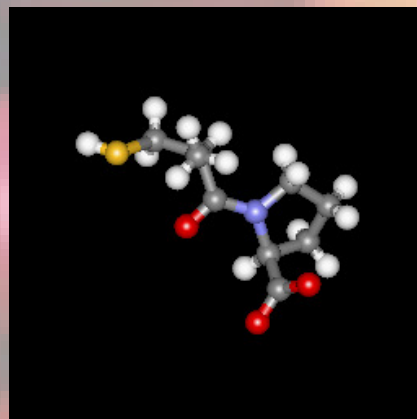
S. H. Ferreira  
1934-

S.H. Ferreira, A Bradykinin-potentiating factor (BFP) present in the venom 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





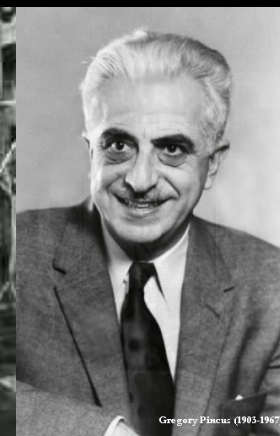
# esteróides



Moléculas revolucionárias



Russell Marker

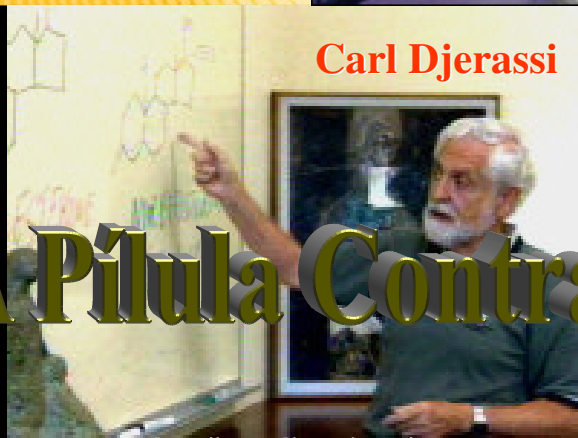


Gregory Pincus (1903-1967)

Russell E. Marker & Gregory Pincus

(*J. Chem. Educ.* 1973, 50, 195).

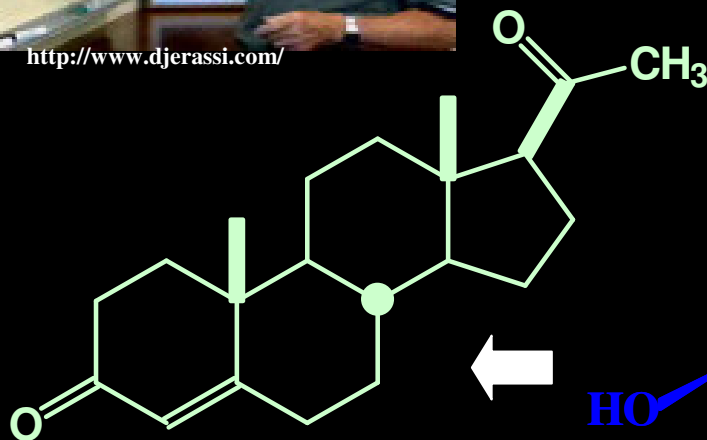
Em 1937 no “Pond Laboratory” da Universidade da Pensilvânia, EUA, Marker concluiu a primeira síntese da progesterona a partir da diosgenina



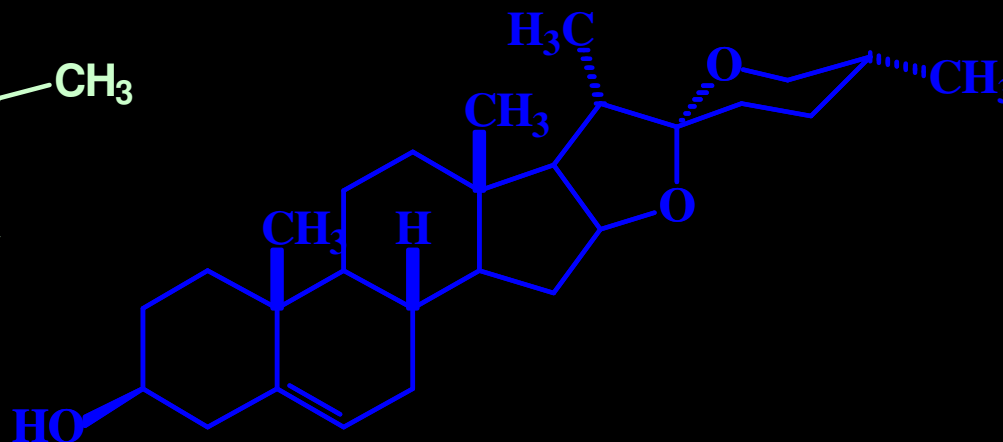
Carl Djerassi

## A Pílula Contraceptiva

<http://www.djerassi.com/>



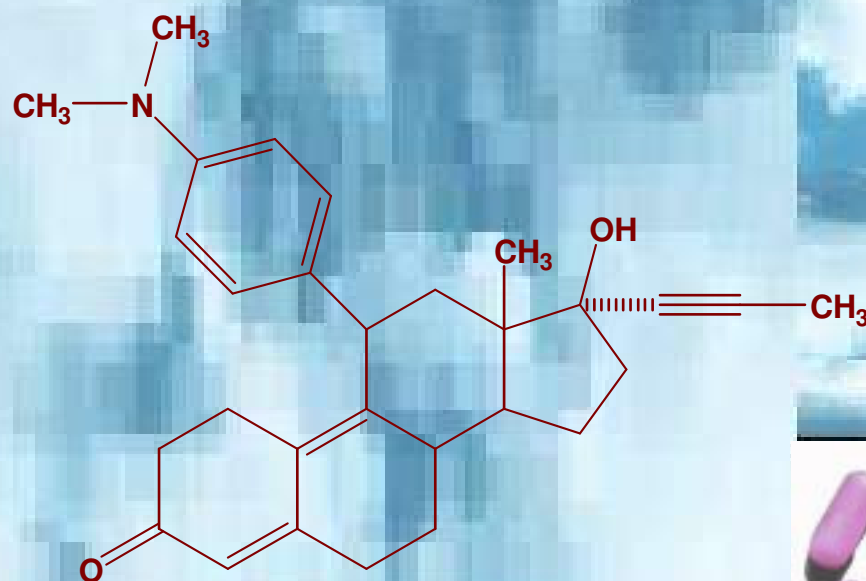
progesterona



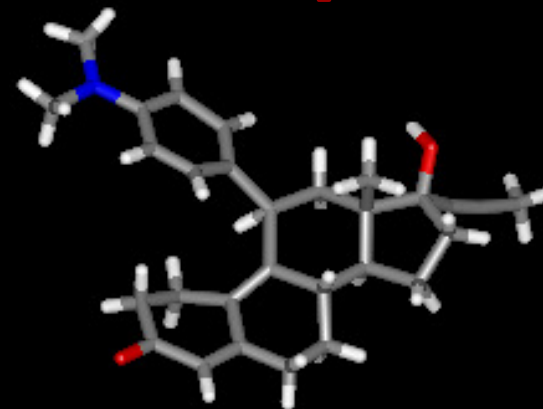
diosgenina



# *mifepristona*



## Mifepristona



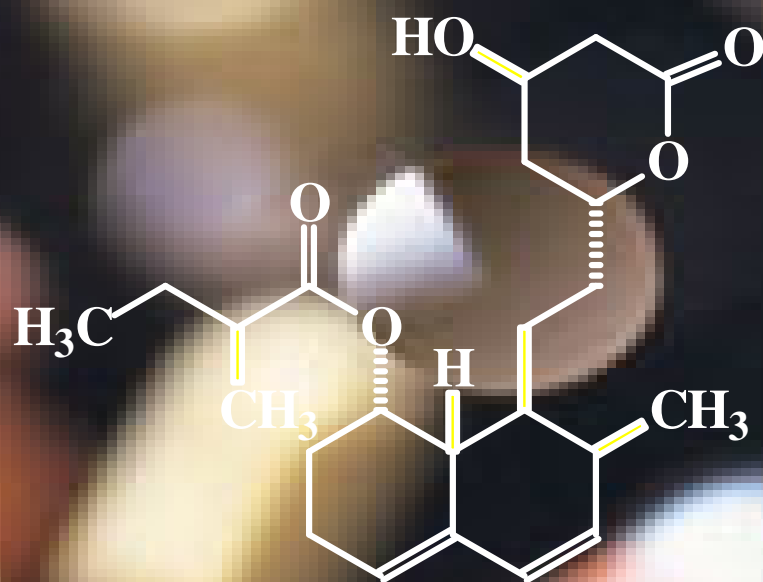
**RU 486**

*Pílula do dia seguinte*





# ...do protótipo natural ao super-fármaco...



*mevastatina*



*atorvastatina*





# Metabólito de Fungo

Protótipo natural

1975 - Mevastatina

A.Endo, J. Antibiot.

1976, 29, 1346

*Penicillium citrinum*

Idem, Ibid, 1979, 32, 852

*Monascus ruber*

(*compactina*)

A.Endo, J. Med. Chem. 1985, 28, 01



Arthur A. Patchett

J. Med. Chem.

2002, 45, 5609.

$\gamma$ -lactona

Similaridade molecular

Mevilonina

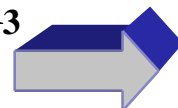
Lovastatina (MK-803)

1980 - Merck & Co.

*Aspergillus terreus*

1987 - MS&D (Mevacor<sup>R</sup>)

US\$ 5,5 bi  
(2007)



IC<sub>50</sub> = 11,2 nM

Pró-fármaco

Simvastatin

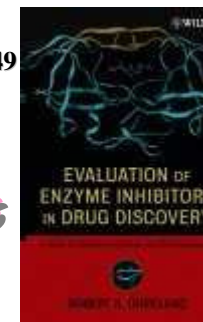
(Zocor<sup>R</sup>)

MK-733

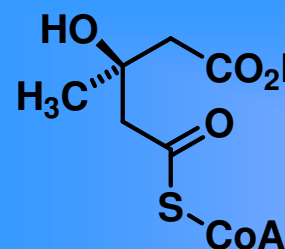
1988

J. Med. Chem. 1986, 29, 849

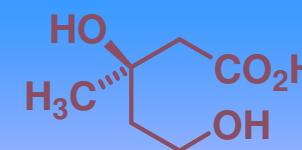
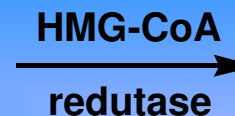
Fármacos Inteligentes



Biossíntese do colesterol



3-hidróxi-3-metil-glutaril-CoA

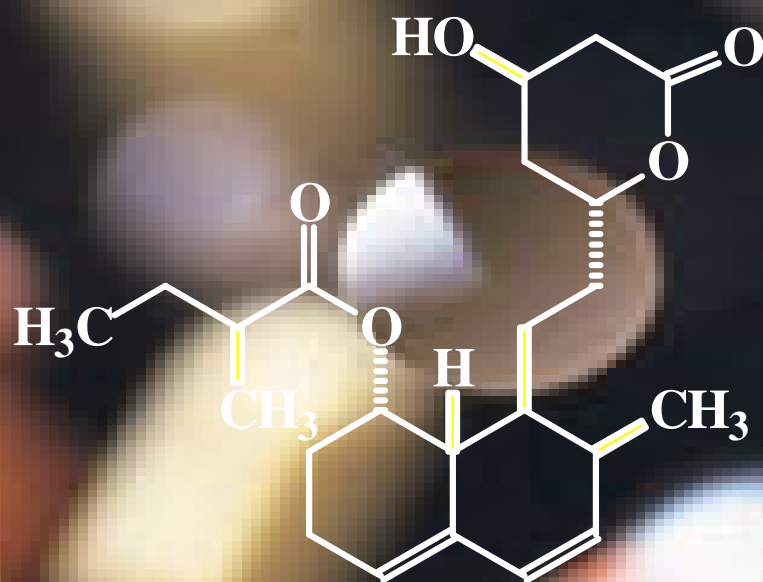


ácido mevalônico





# ...do protótipo natural ao super-fármaco...



**mevastatina**



**atorvastatina**

2007: US\$ > 13,5 bi

\* CE&N, Dec, 2007

eliezer © 2008



....o acaso....



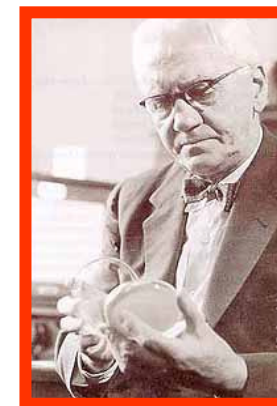
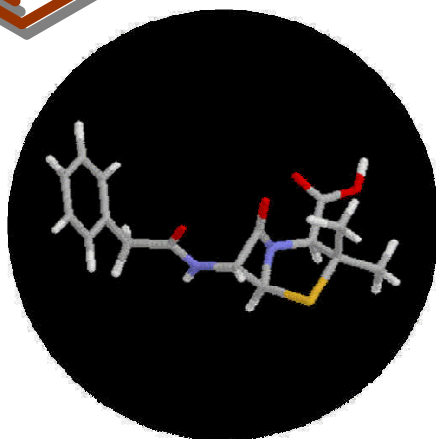
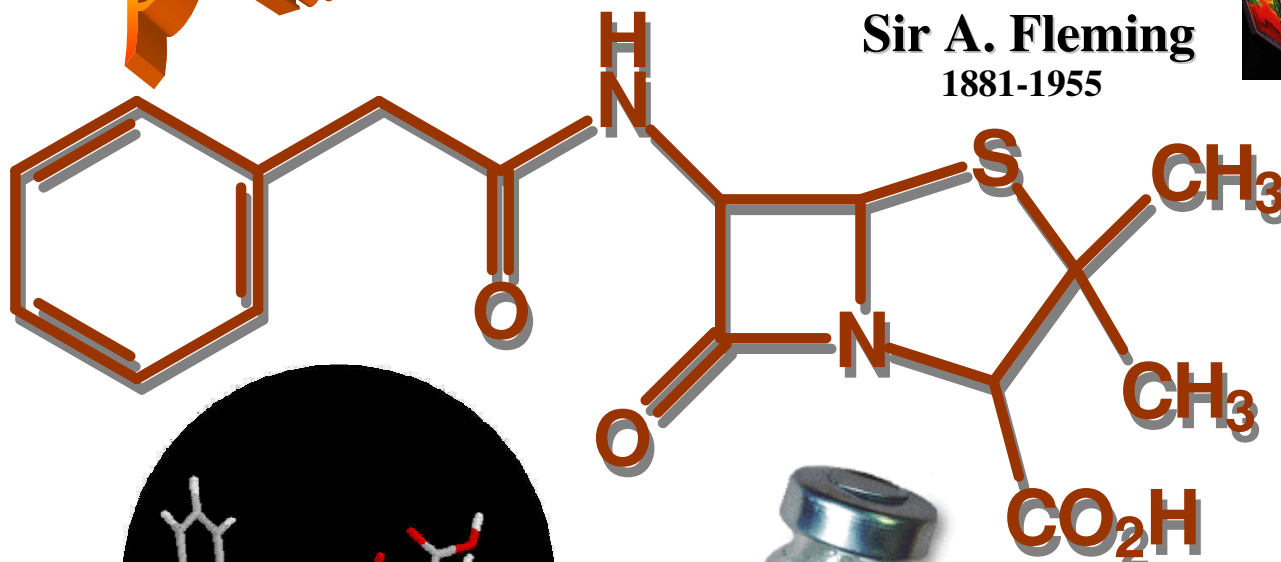


# Antibioticoterapia

## Penicilinas

### Moléculas Salva-vidas

$\beta$ -lactâmicos



Sir A. Fleming  
1881-1955

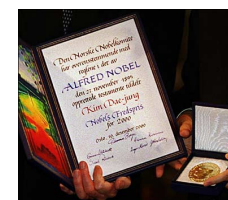


Sir H. W. Florey  
1898-1968

*serendipidade*



E. B. Chain  
1906-1979



1945



*Penicillium notatum*

## Cefalosporinas





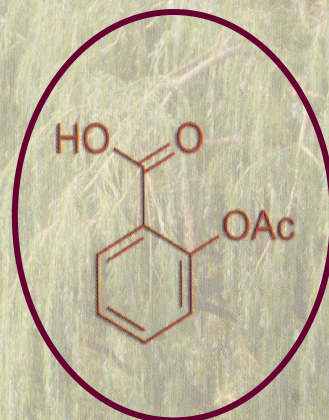
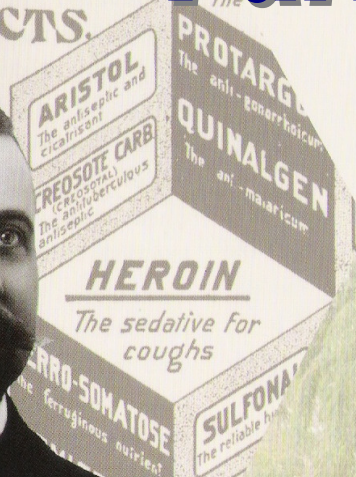
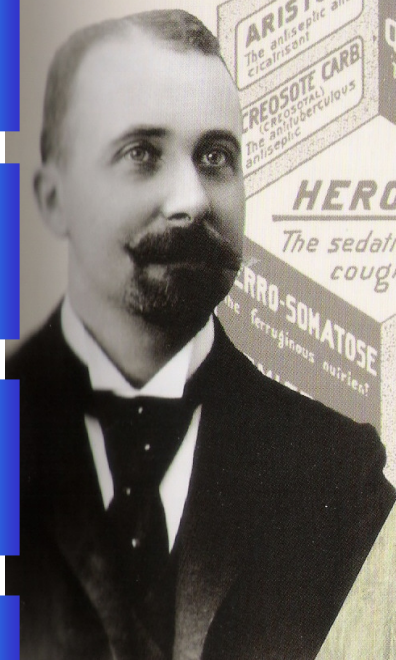


BAYER  
PHARMACEUTICAL  
PRODUCTS.

# Fármacos Sintéticos

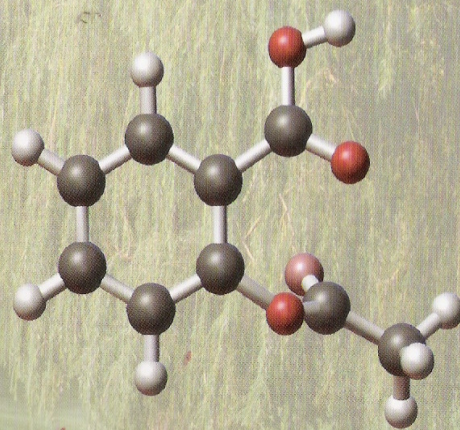
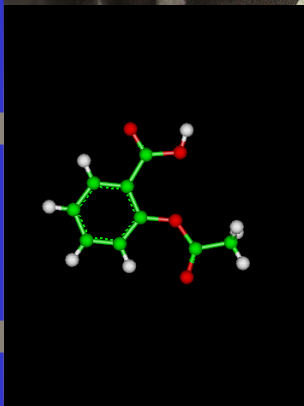


## ácido acetilsalicílico



Organic  
Chemistry  
of Drug  
Synthesis  
Volume 1

Daniel Lednicher  
Lester A. Mitscher



1897

Aspirin®

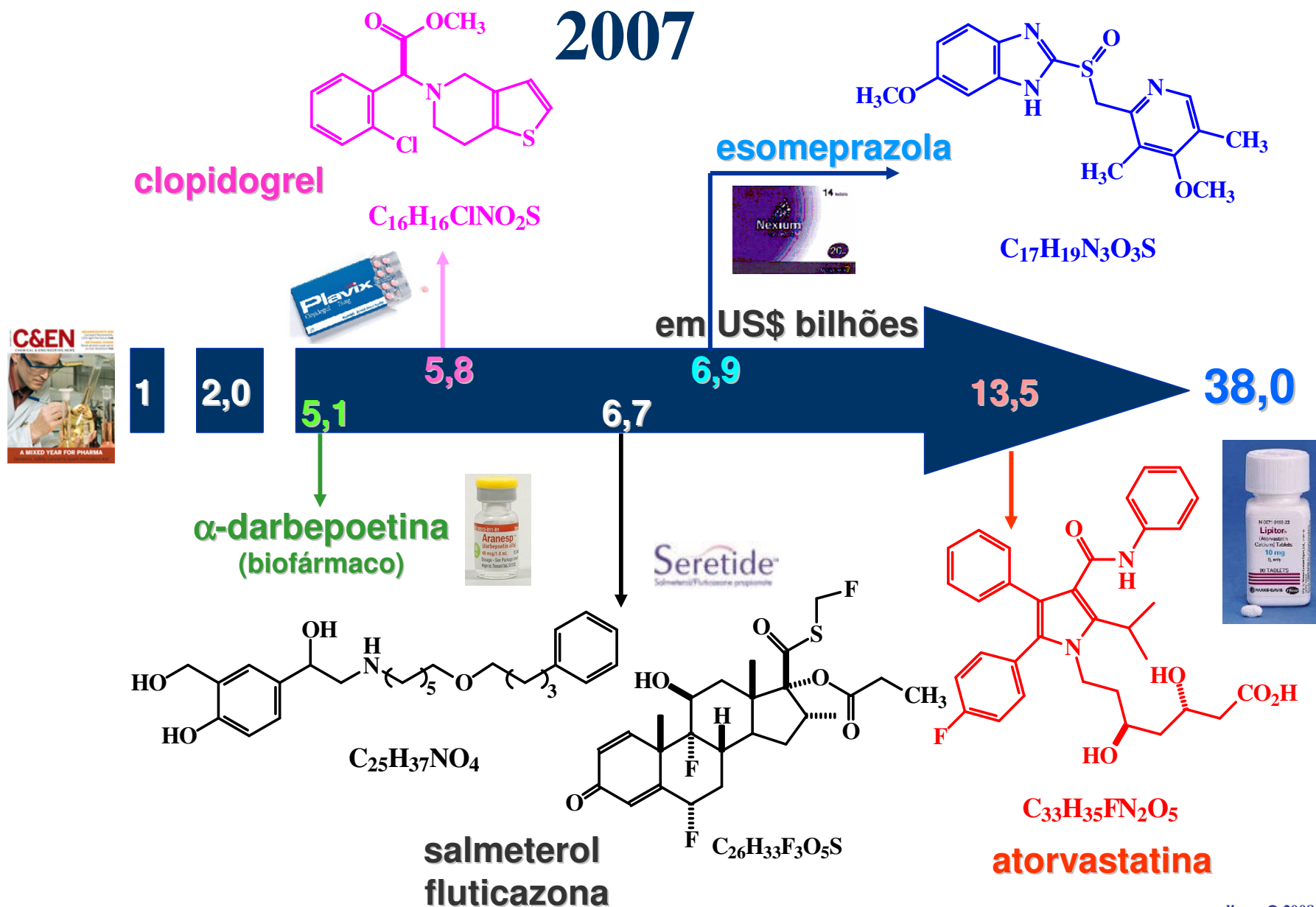


Spirea sp





# Os *top-5* fármacos no mercado mundial





# Características estruturais comuns aos cinco fármacos mais vendidos no mundo em 2007:

- Possuem apenas 7 elementos químicos: C,H,O,N,S,F,Cl;

*São moléculas de quimiodiversidade singela !*

- 80% têm unidades aromáticas;
- 02 podem ser considerados me-too;
- 01 representa uma inovação incremental;
- 01 é um biofármaco indicado para anemia (Amgen);
- pertencem a apenas 04 classes terapêuticas distintas;
- possuem uma tímida diversidade química;
- são responsáveis por US\$ 38,0 bilhões em vendas;
- pequenas moléculas, grandes negócios;





# *O processo da descoberta racional...*



*... o paradigma do composto-protótipo.*



# Química Medicinal



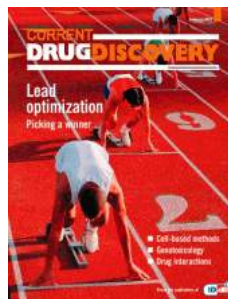
*Lead compound*  
**Composto-protótipo**





# Composto-protótipo

“ O composto-protótipo é o primeiro derivado puro, identificado em uma série congênere de novas substâncias, bioensaiadas em modelos animais padronizados, relacionados à patologia a ser tratada ”



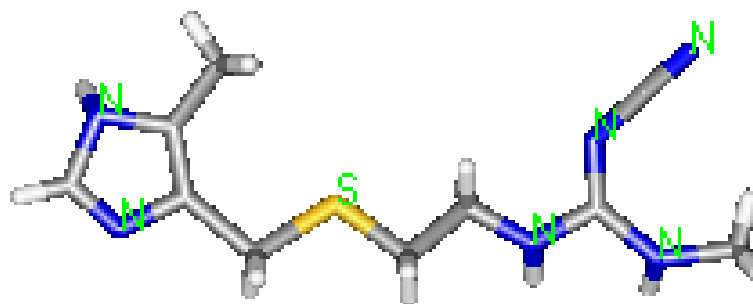
Otimização  
do  
Protótipo





**Cimetidina**

# Inovação terapêutica



Os descobridores da cimetidina: Ganellim, Emmet, Durant & Black, da esquerda para a direita,



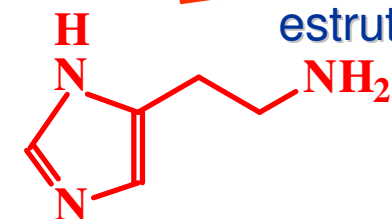
# Inovação terapêutica

## Abordagem Fisiológica

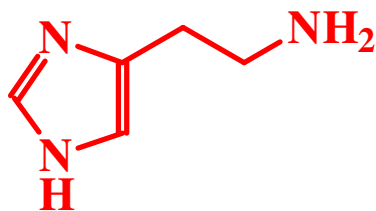
Análogo ativo

Ligações  
frágeis

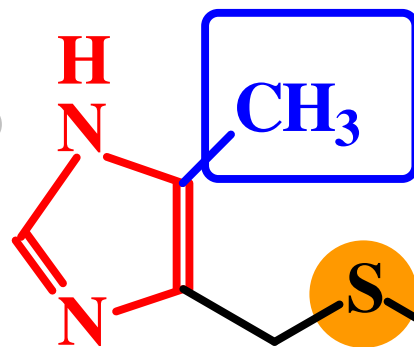
Propriedades  
estruturais



Agonista natural



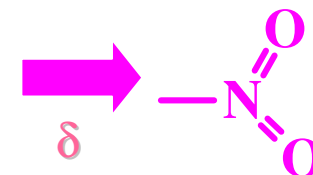
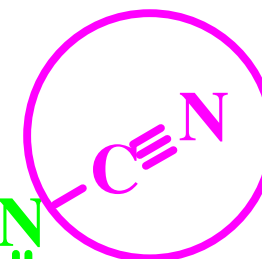
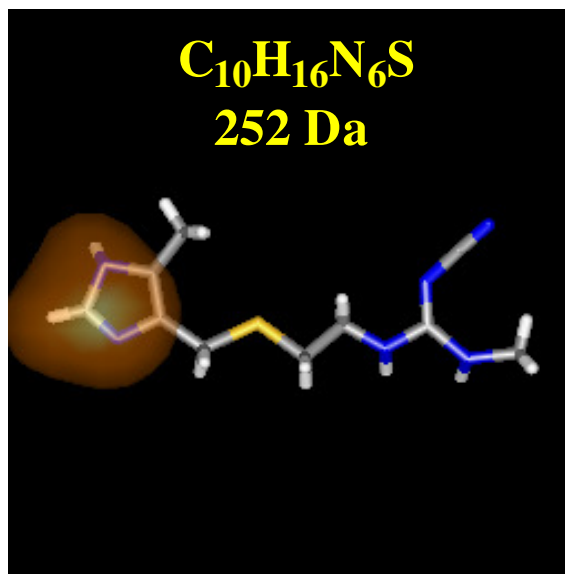
histamina



linker

cimetidina

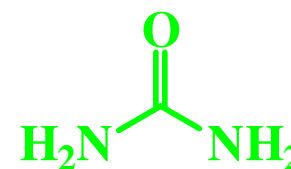
$C_{10}H_{16}N_6S$   
252 Da



nitro



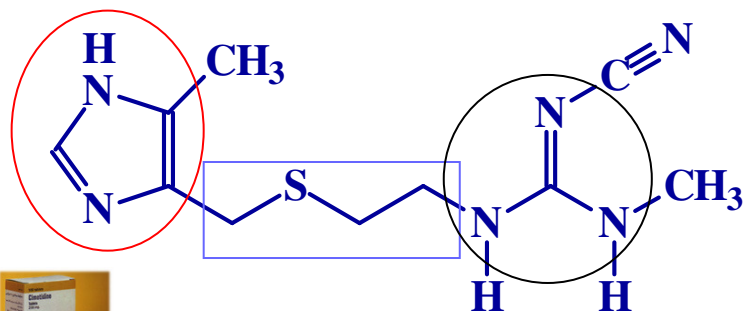
amidina



uréia

Retro-dissecação  
molecular

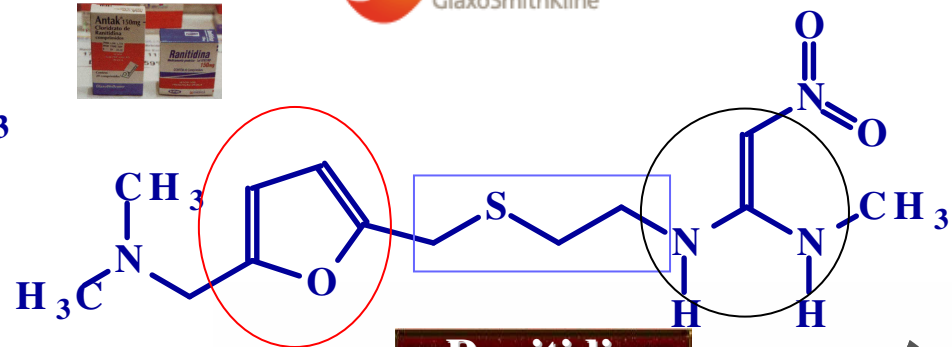
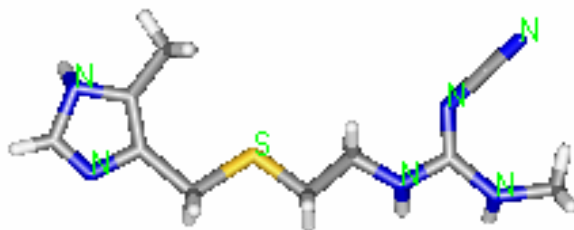
Fragmentos moleculares



**Cimetidina**

Robin Ganellin *et al.*, 1974  
US 3950333 1974, 1976 - SK&F  
*Brit. J. Pharmacol.* **53**, 435 (1975).

*similaridade  
molecular*



**Ranitidina**

Barry J. Price *et al.*, 1978  
US 4128658 1978 - Allen & Hanburys  
*Brit. J. Pharmacol.* **66**, 464 (1979)

