



Mini Curso - 004

Planejamento de candidatos a novos fármacos

Parte 3

Eliezer J. Barreiro

Professor Titular - UFRJ



Ementa

Breve introdução histórica da Química Medicinal; O papel dos pioneiros; Os fármacos e os produtos naturais; Estratégias de desenho molecular de novos candidatos a fármacos; Considerações finais.

64ª Reunião Anual da SBPC

22 a 27 de Julho de 2012 | UFMA | São Luís, MA

CIÊNCIA, CULTURA E SABERES TRADICIONAIS PARA ENFRENTAR A POBREZA.

SB
PC



www.scielo.br



Scientific Electronic Library Online

Free sign up

SciELO.org
journals evaluation

português
español

help
about this site
SciELO news
SciELO team

serial browsing

alphabetic list
subject list
search form

article browsing

author index
subject index
search form

reports

site usage
journal citation
co-authors

www.scielo.br

SciELO

The Scientific Electronic Library Online - SciELO is an electronic library covering a selected collection of Brazilian scientific journals.

The library is an integral part of a project being developed by FAPESP - Fundação de Amparo à Pesquisa do Estado de São Paulo, in partnership with BIREME - the Latin American and Caribbean Center on Health Sciences Information. Since 2002, the Project is also supported by CNPq - Conselho Nacional de Desenvolvimento Científico e Tecnológico.

The Project envisages the development of a common methodology for the preparation, storage, dissemination and evaluation of scientific literature in electronic format.

Revista Virtual de Química = www.uff.br/rvq



Laboratório de Avaliação e Síntese de Substâncias Bioativas

Faculdade de Farmácia
UFRJ



Área de Atuação [links](#) [Equipe](#) [Contato](#) [Home](#)

LASSBio, interesses de pesquisa

Publicações Selecionadas

Teses e Dissertações

Escolas de Verão

Projetos de Pesquisa em Andamento

Tópicos de Interesse em Química Farmacêutica Medicinal

Cursos → 2012

Conferências



28 de janeiro a 01 de fevereiro

INSCRIÇÕES:
a partir de 01 de setembro 2012

[Certificados da XVIII EVQFM disponíveis para download](#)

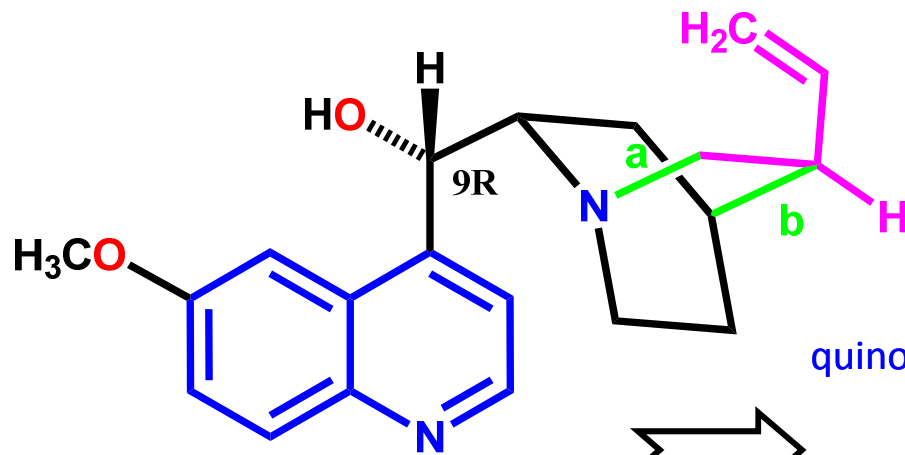
5 VISÕES DA QUÍMICA FARMACÊUTICA MEDICINAL

XVIII Escola de Verão em Química Farmacêutica Medicinal traz especialistas do Brasil e do exterior para participar de Ciclo de Conferências na área.

[Leia mais](#)

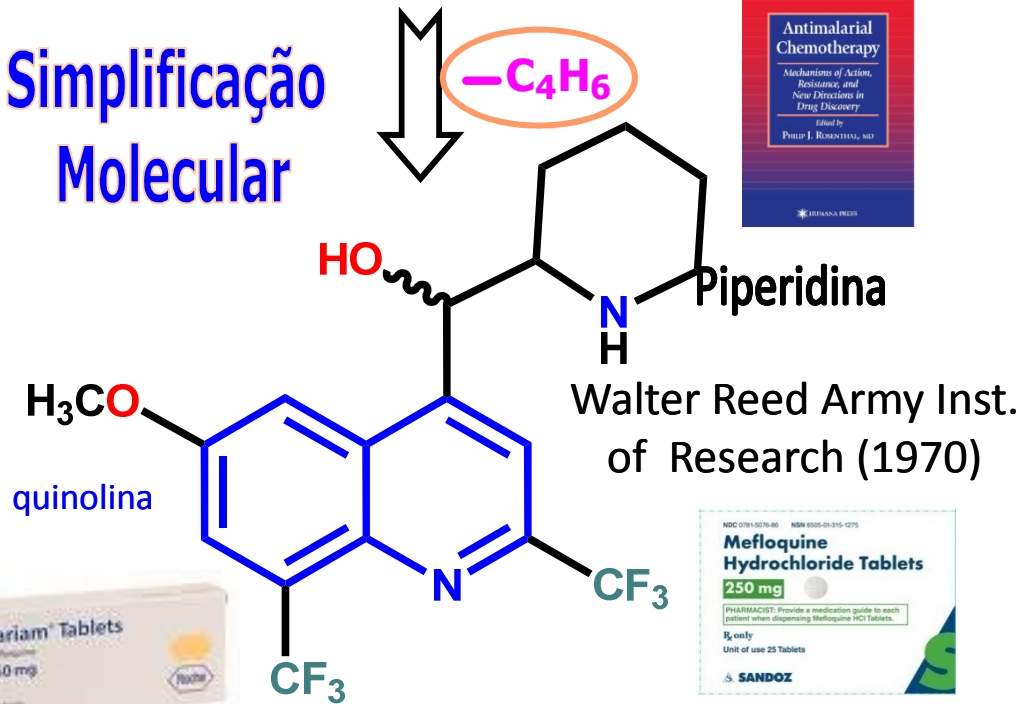


www.farmacia.ufrj.br/lassbio



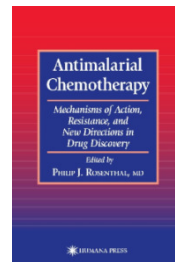
Quinina

Simplificação Molecular



Mefloquina

T_{1/2} = 16d

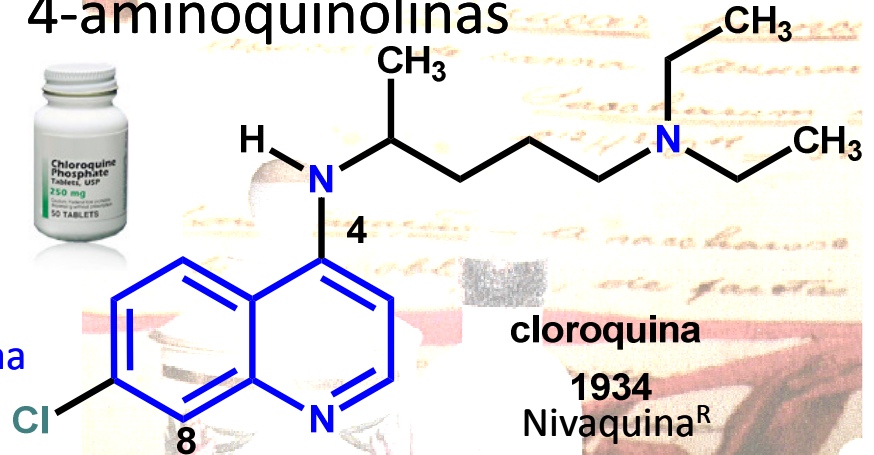


Walter Reed Army Inst. of Research (1970)



1989 - FDA

4-aminoquinolinas



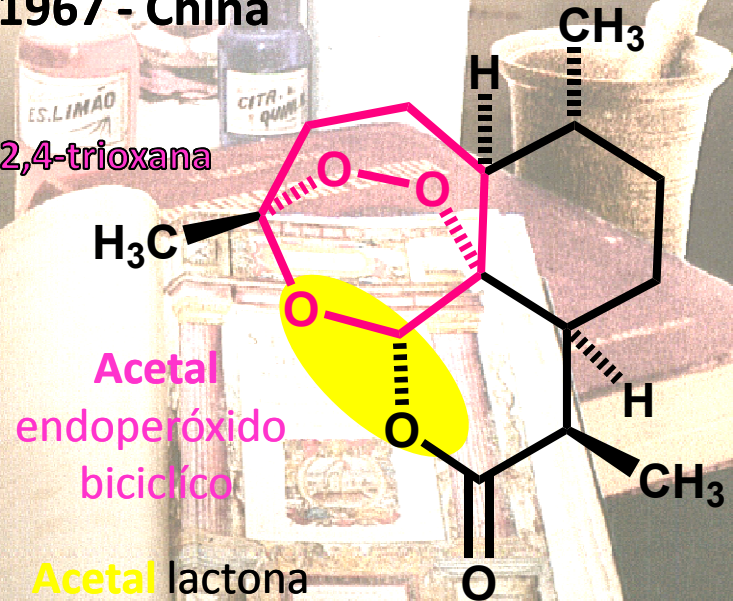
cloroquina

1934 Nivaquina^R

De volta ao Oriente...

1967 - China

1,2,4-trioxana



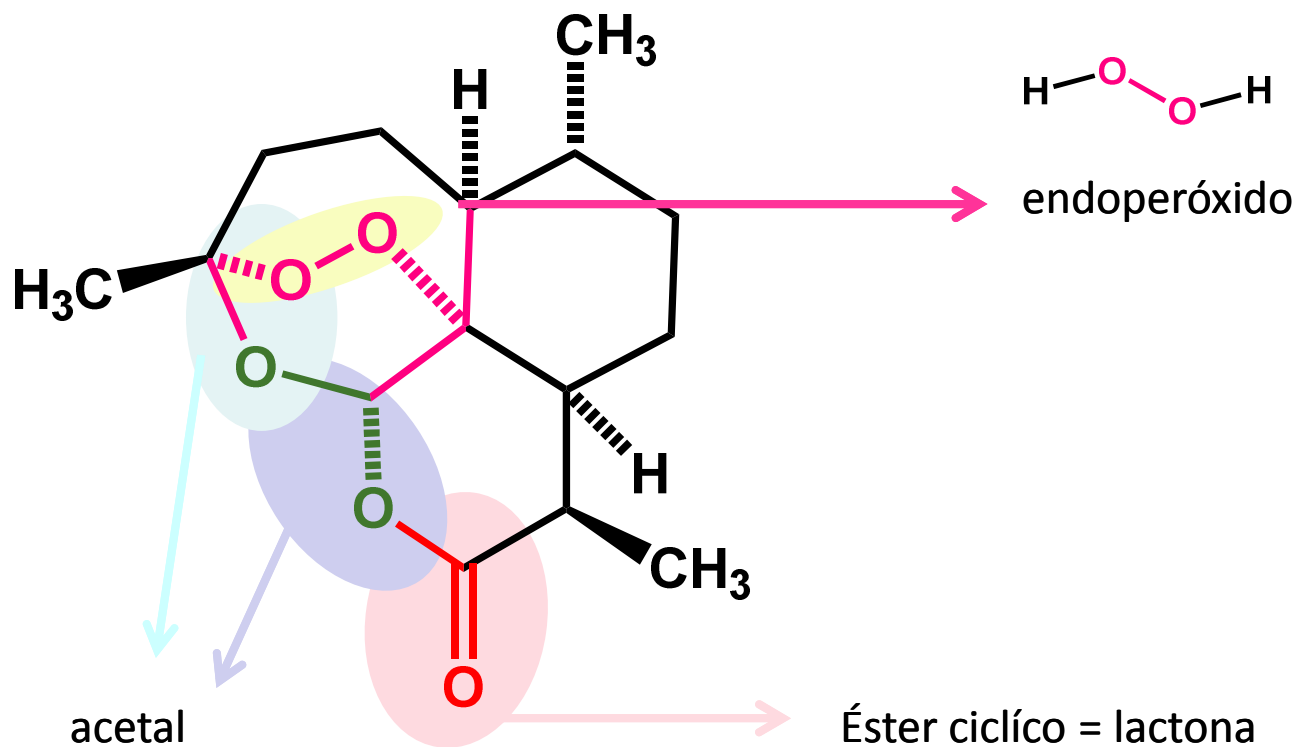
artemisinina

sesquiterpeno C₁₅H₂₂O₅





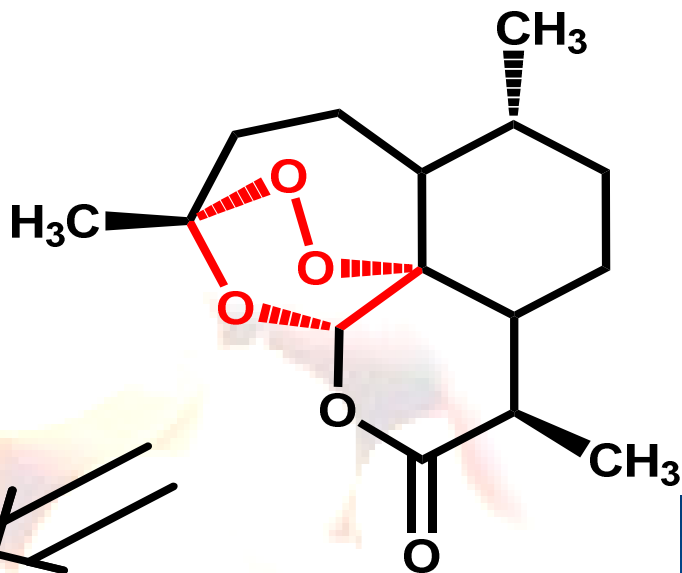
Originalidade molecular dos produtos naturais



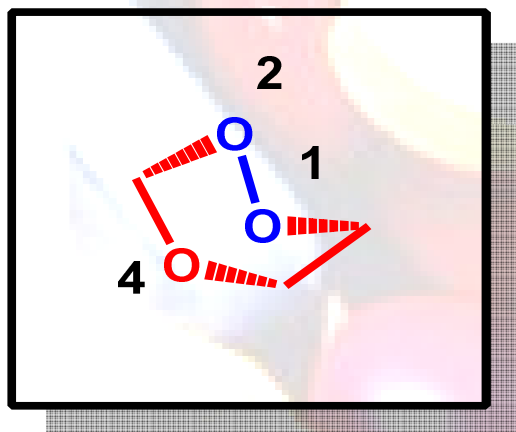
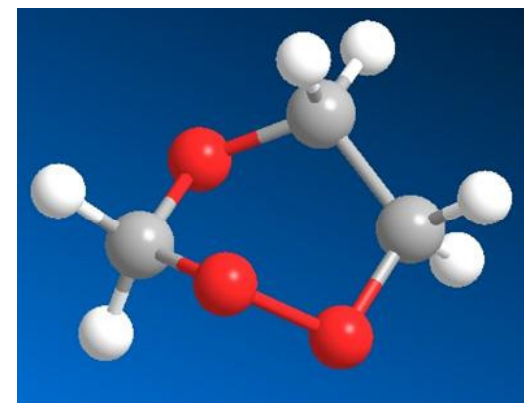
Grupamento farmacofórico



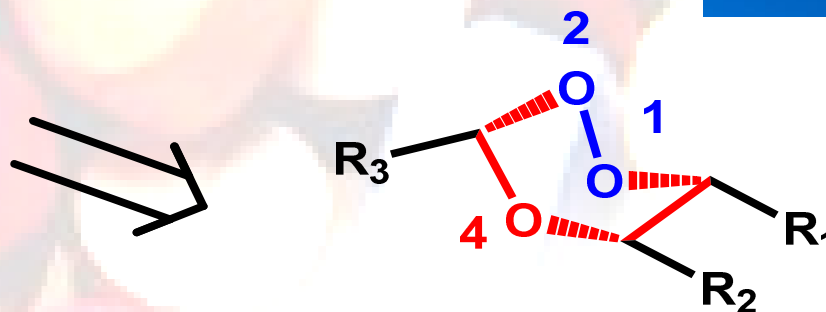
Simplificação molecular



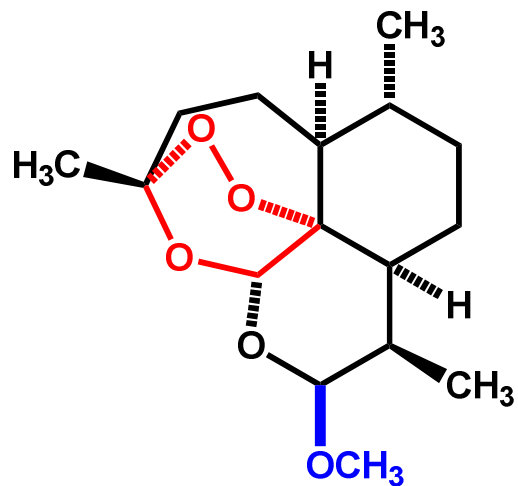
artemisina



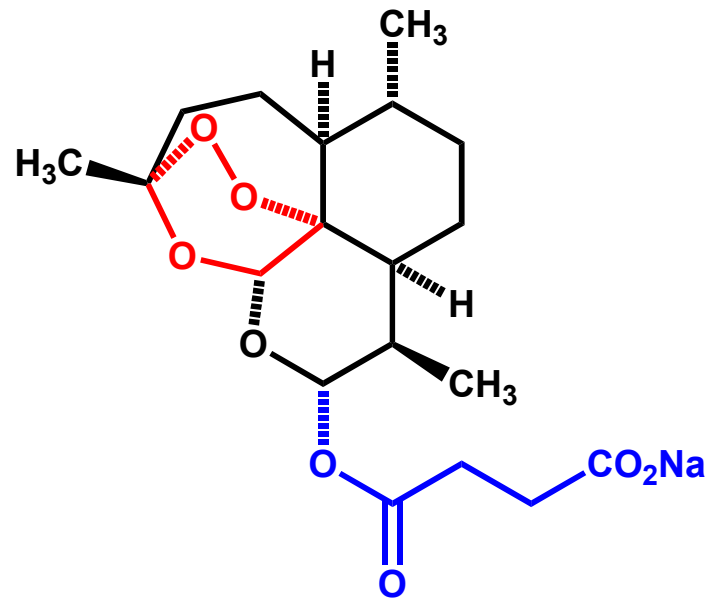
1,2,4-trioxana



derivados 1,2,4-trioxana



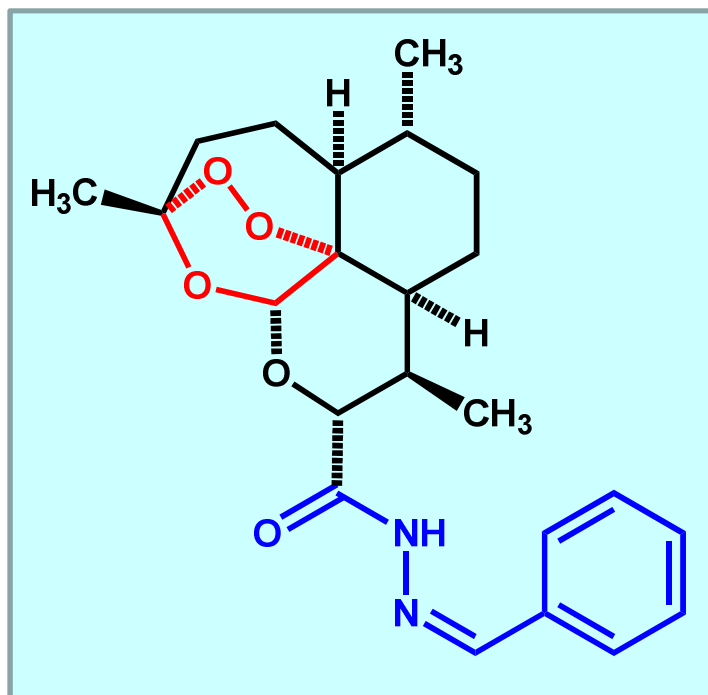
arteméter



artesanato de sódio



M A Avery, Olemiss



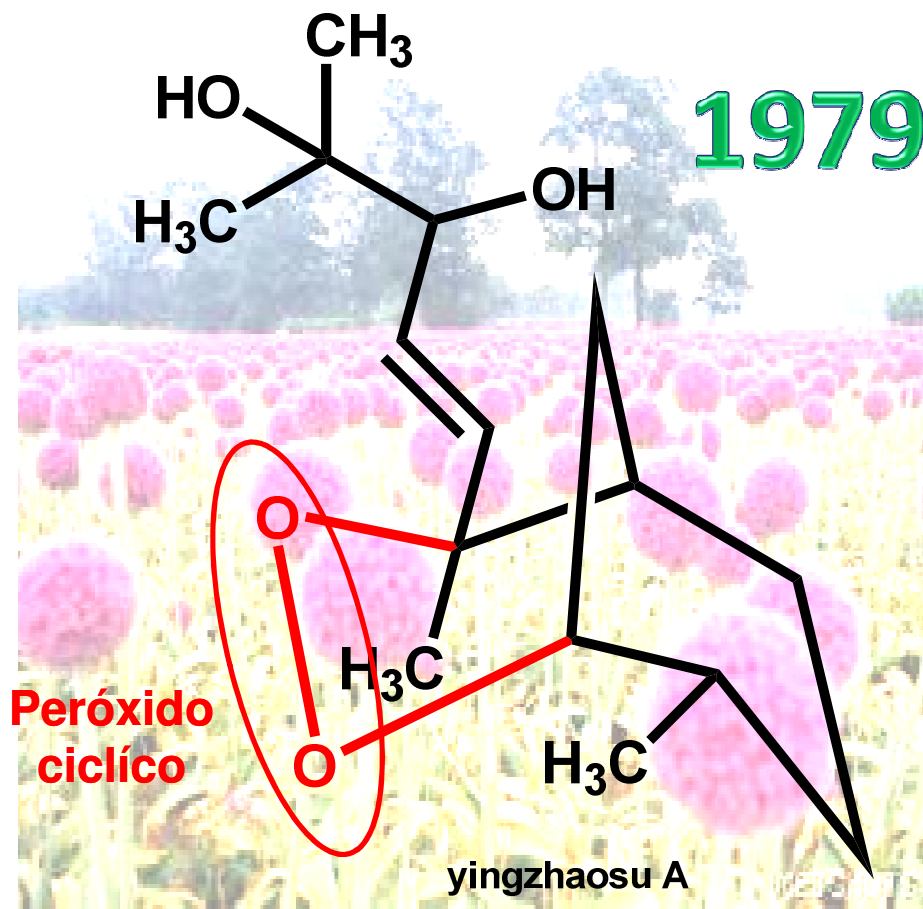
Mitchell A Avery, EJ Barreiro
M Alvim-Gaston, 2001

Senior Research Scientist
Eli Lilly Co., EUA

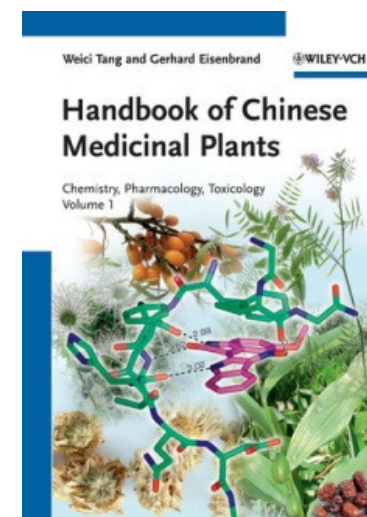
Lilly



Produtos naturais e malária



Artabotrys unciatus (L.) Meer.



Similaridade Molecular



Bloqueadores ganglionares

Universidade Federal do Rio de Janeiro

Curare



WWW.AMAZON-INDIAN.ORG



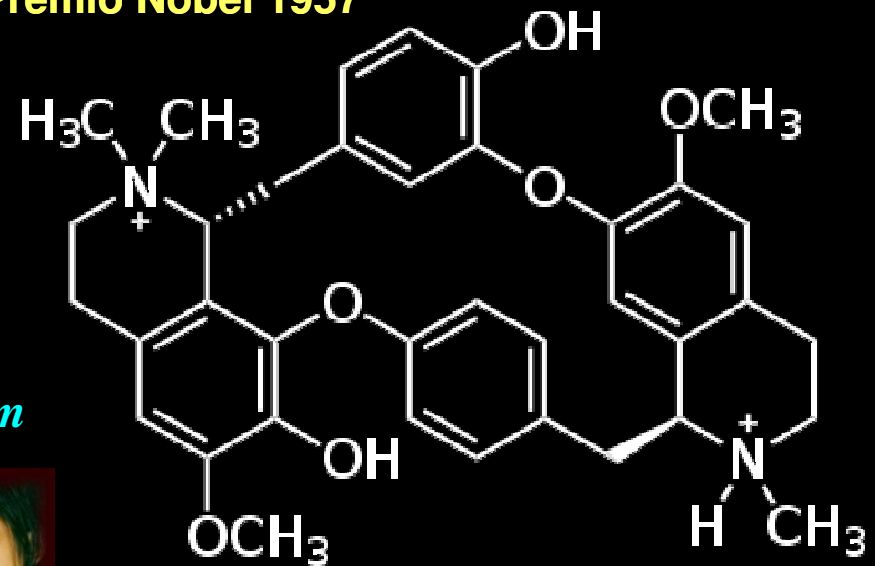
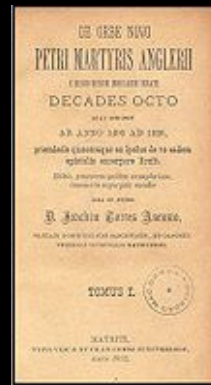
Museu Etnológico de Berlim

1947 - Daniel Bovet

Institute Pasteur

Prêmio Nobel 1957

Estrutura: King, 1935



(D)-tubocurarina

Molécula amazônica

Chondrodendron tomentosum

Loganiaceae

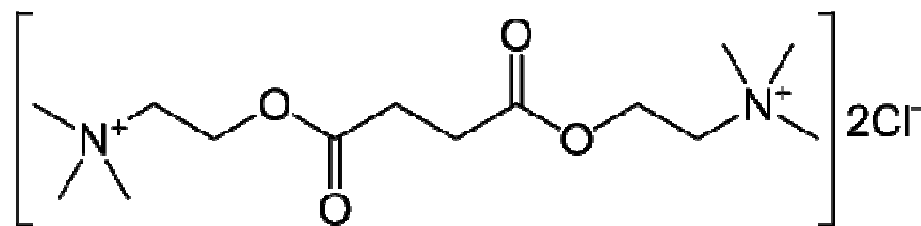
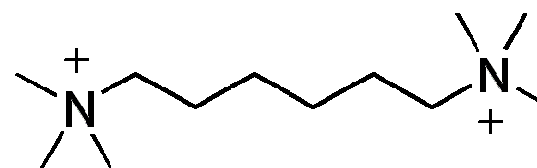
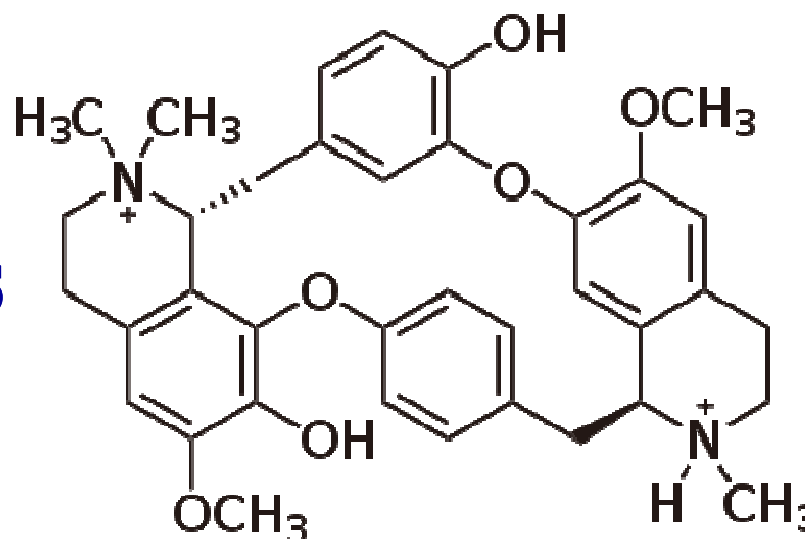
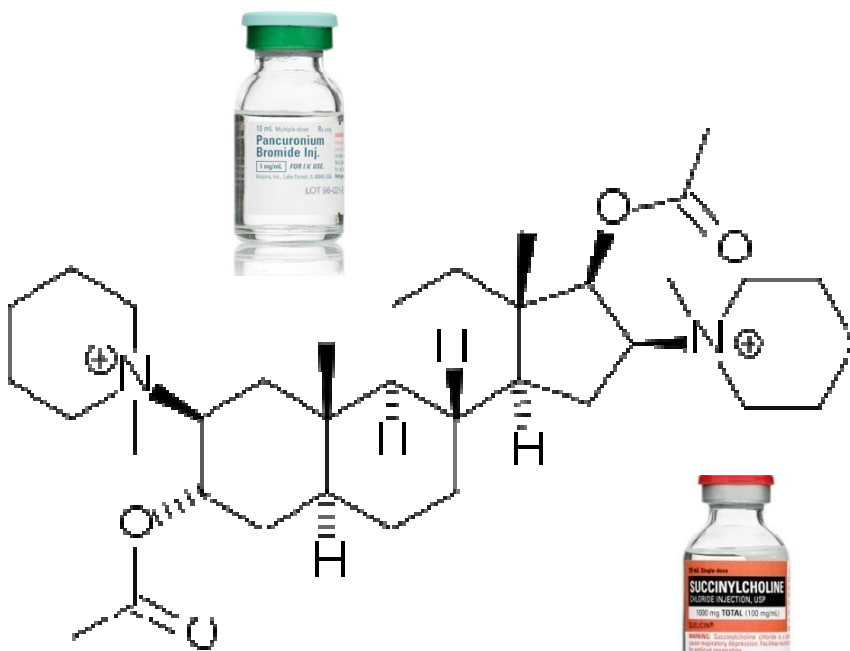
(urari)





Bloqueadores ganglionares

Fármaco dos Ameríndios



R. Bade, H.-F. Chan, J. Reynisson, Characteristics of known drug space. Natural products, their derivatives and synthetic drugs. *European Journal of Medicinal Chemistry* **2010**, *45*, 5646-5652



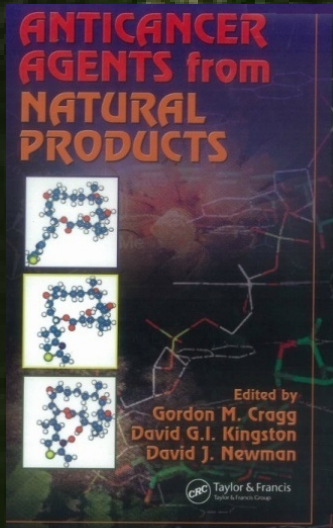
Universidade Federal do Rio de Janeiro



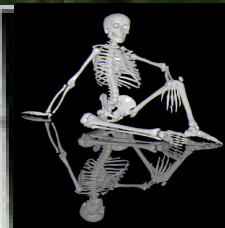
Quimioterapia do Câncer



Produtos naturais vegetais



Quimiodiversidade
Estruturas originais
Mecanismo de ação inovadores
Inovações terapêuticas
Moléculas otimizadas

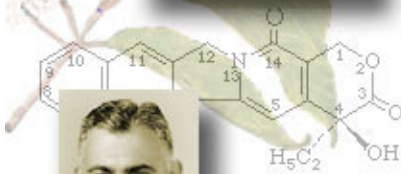


Inter-alia: Alcalóides da Vinca, podofilotoxina



Câncer

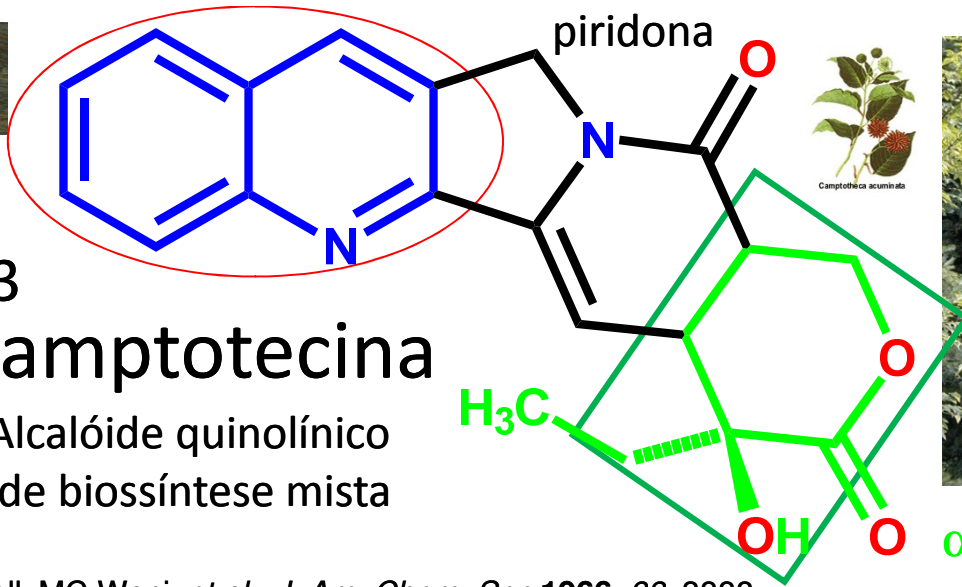
Universidade Federal do Rio de Janeiro



1963

camptotecina

Alcalóide quinolínico de biossíntese mista

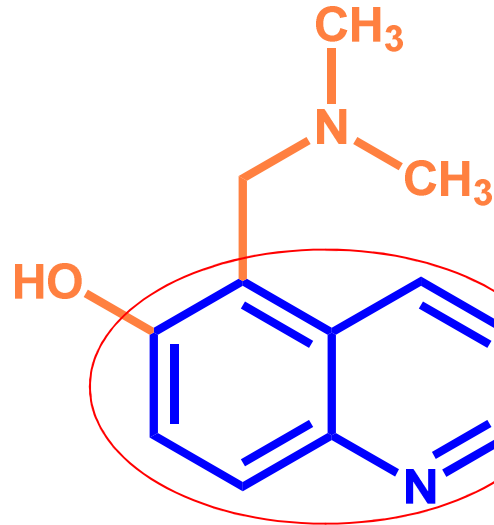


ME Wall, MC Wani, et al., *J. Am. Chem. Soc.* 1966, 88, 3888

ME Wall, MC Wani, "Camptothecin: Discovery to Clinic" *Ann. NY Acad. Sci.* 1996, 803,1



Inibidores de topoisomerase-1

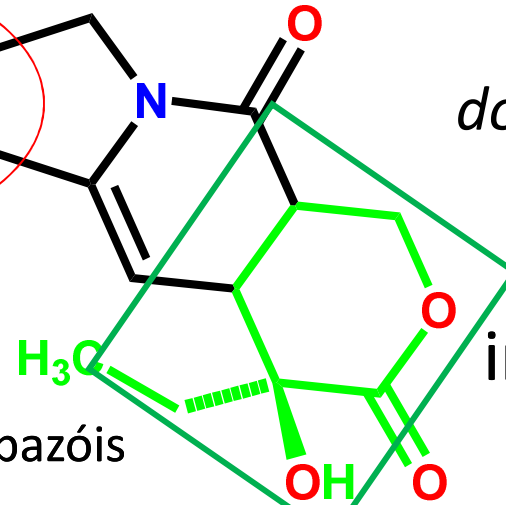


topotecan

piridocarbazóis



Molécula domesticada



irinotecan

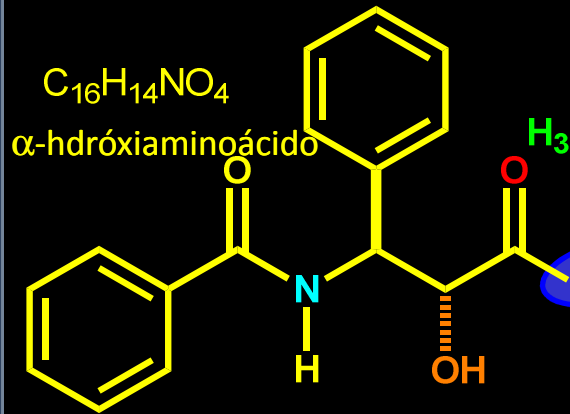
1996





Universidade Federal do Rio de Janeiro

Câncer

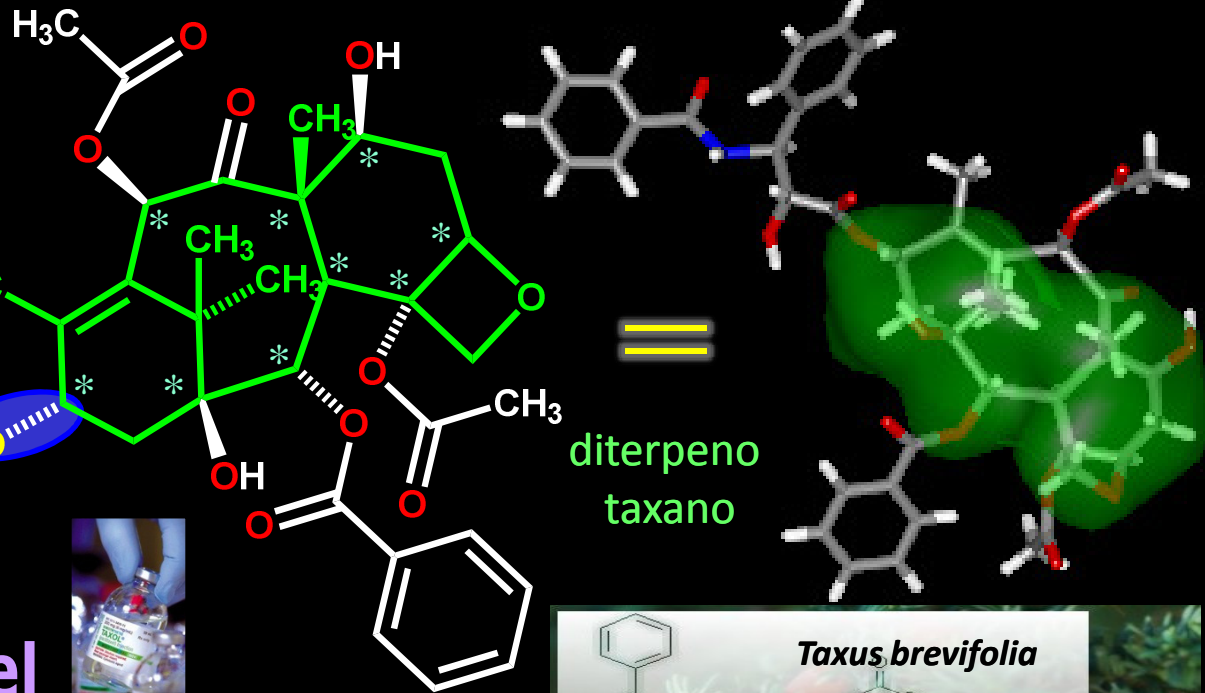


1965

Paclitaxel

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

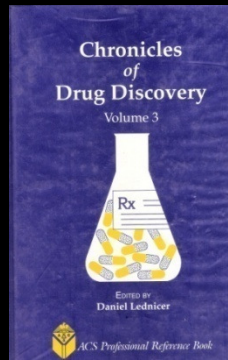
Inibidores de tubulinas



Res. Triangle Park, 1967



M. E. Wall & M. C. Wani
 1996 - National Cancer Institute
 Award of Recognition



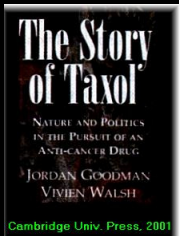
M. E. Wall,,
 "Chronicles of Drug Discovery",
 D. Lednicer, vol.3, ACS, 1993,
 pp. 327-348

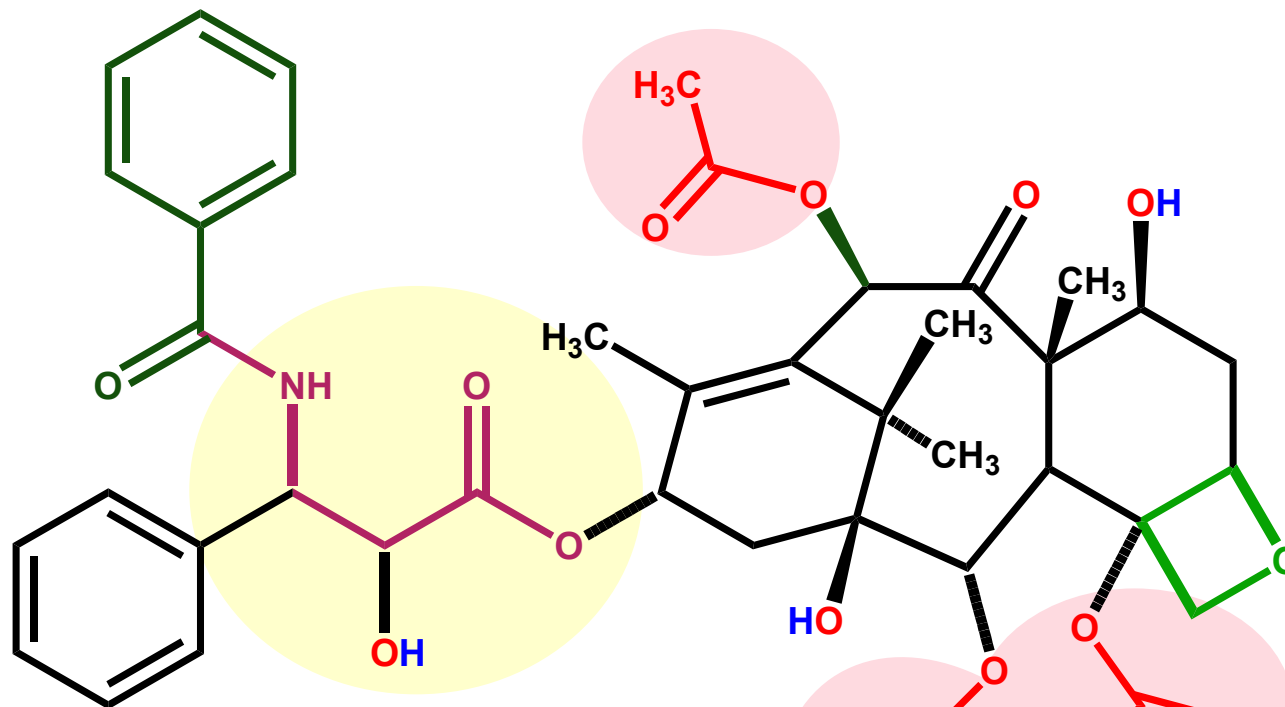


blockbuster
2010

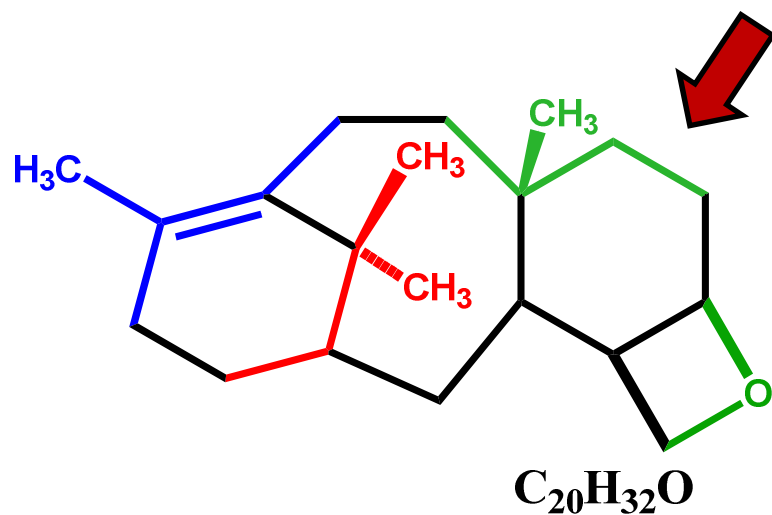


Docetaxel*
 Cabazitaxel (Jevtana[®])
 Ortataxel[&]

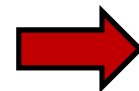




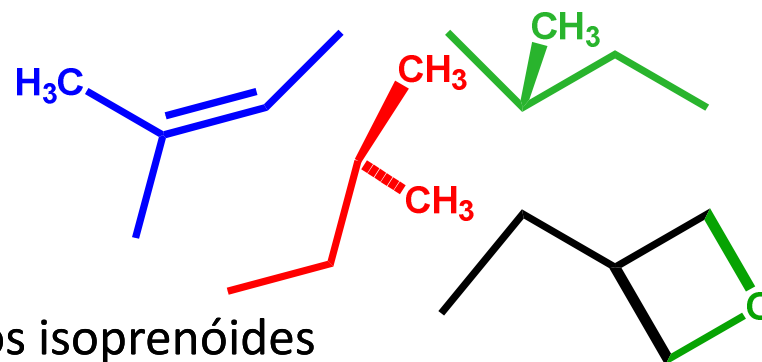
paclitaxel



taxano = diterpeno



Fragmentos isoprenóides



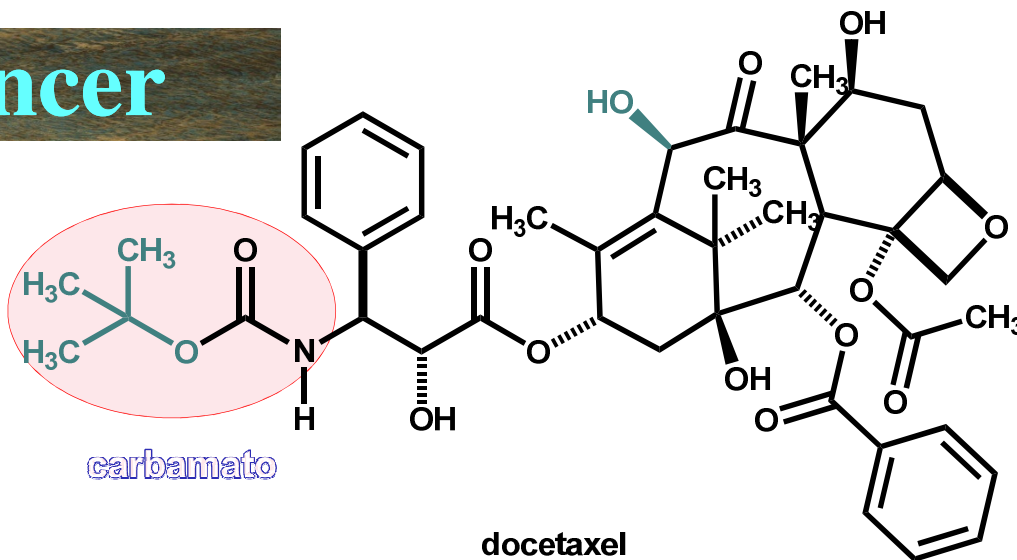
Farmacognosia



Universidade Federal do Rio de Janeiro

A família dos taxanos cresceu...

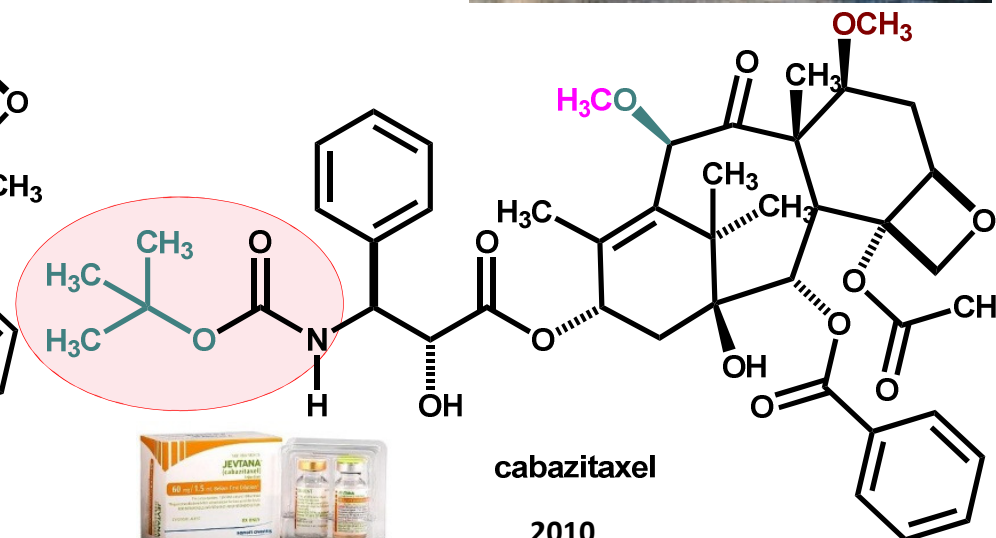
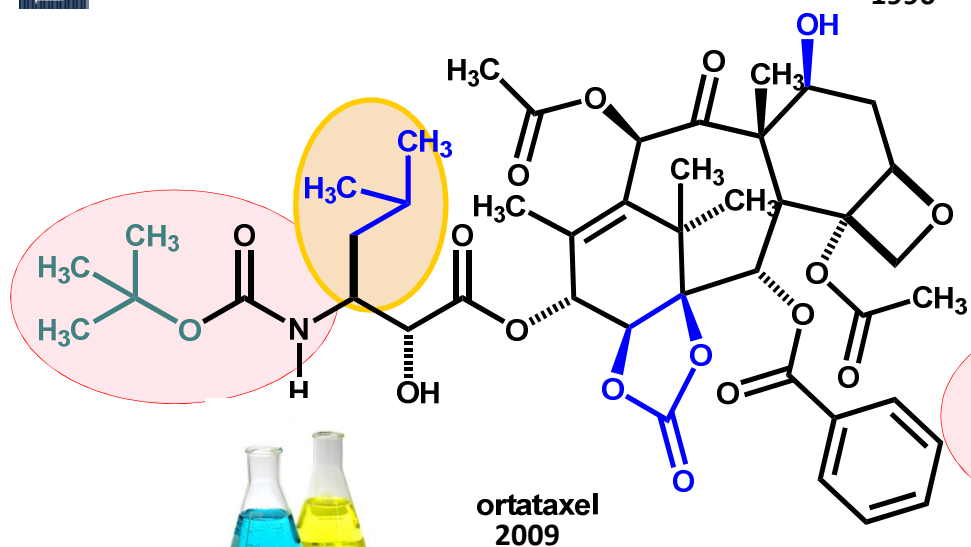
Câncer



Pierre Potier
1934-2006



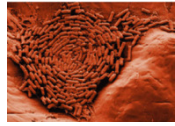
Andy E Greene
UJF-FR





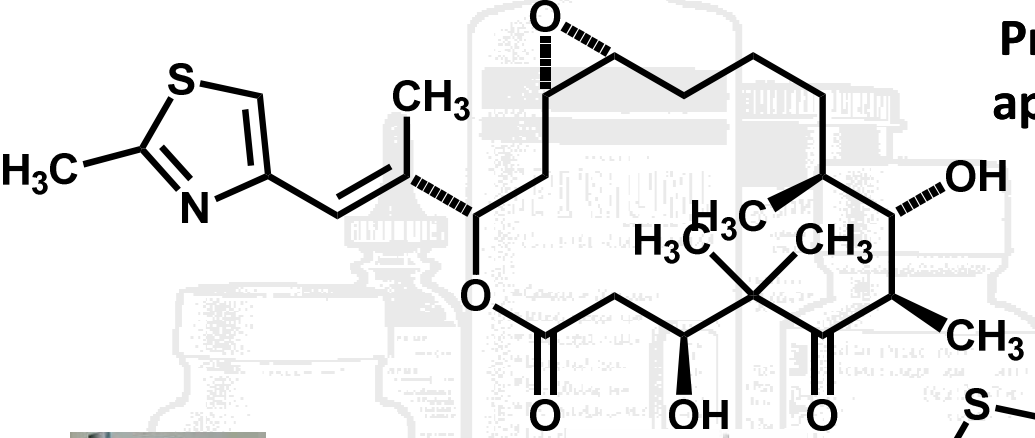
Câncer

Isoladas de *Sorangium cellulosum*



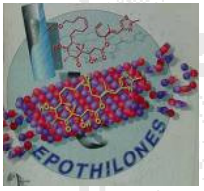
Primeiro macrociclo de 16 membros
aprovado para tratamento do câncer
metástatico de mama

Inibidor de microtúbulo



Epotilona-A

1993

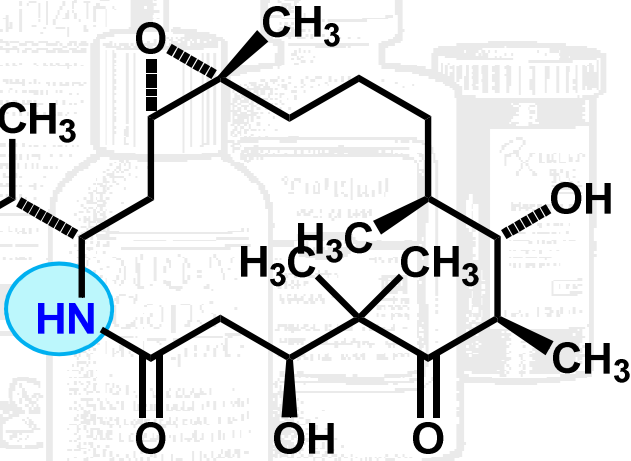
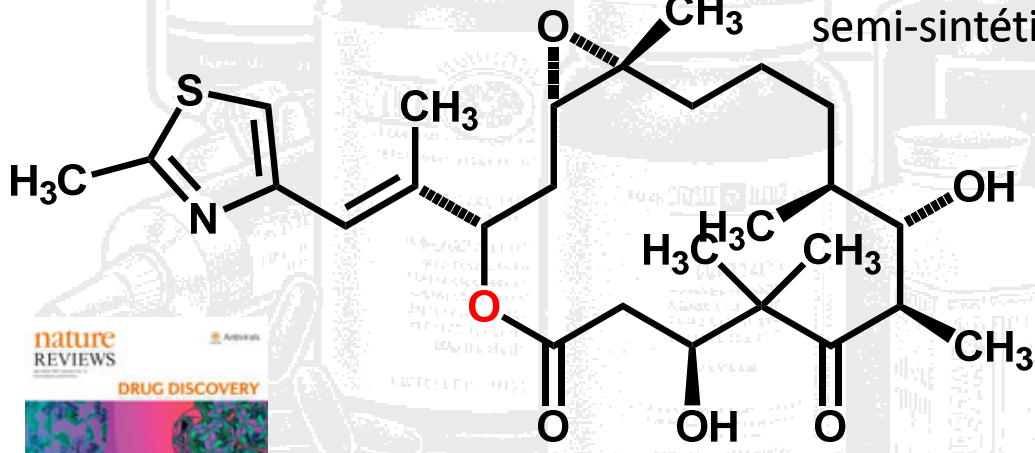


Epotilona-B

Química Medicinal



Análogo semi-sintético



Ixabepilona

Ixempra^R

BMS, 2007



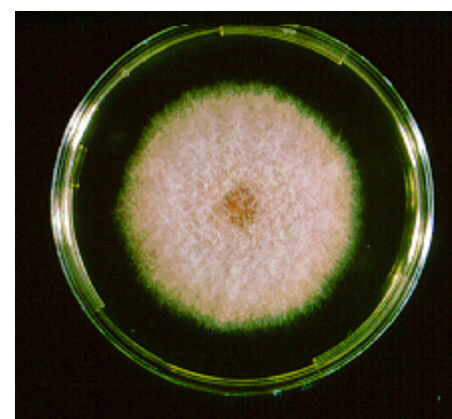
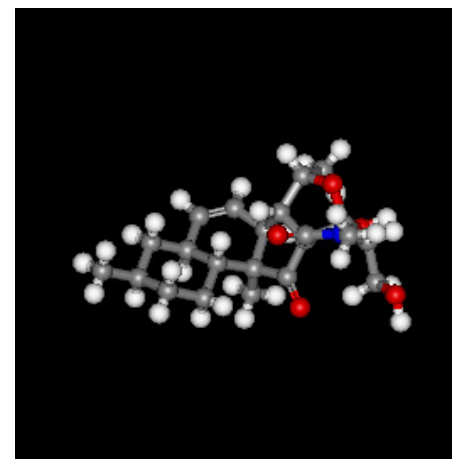
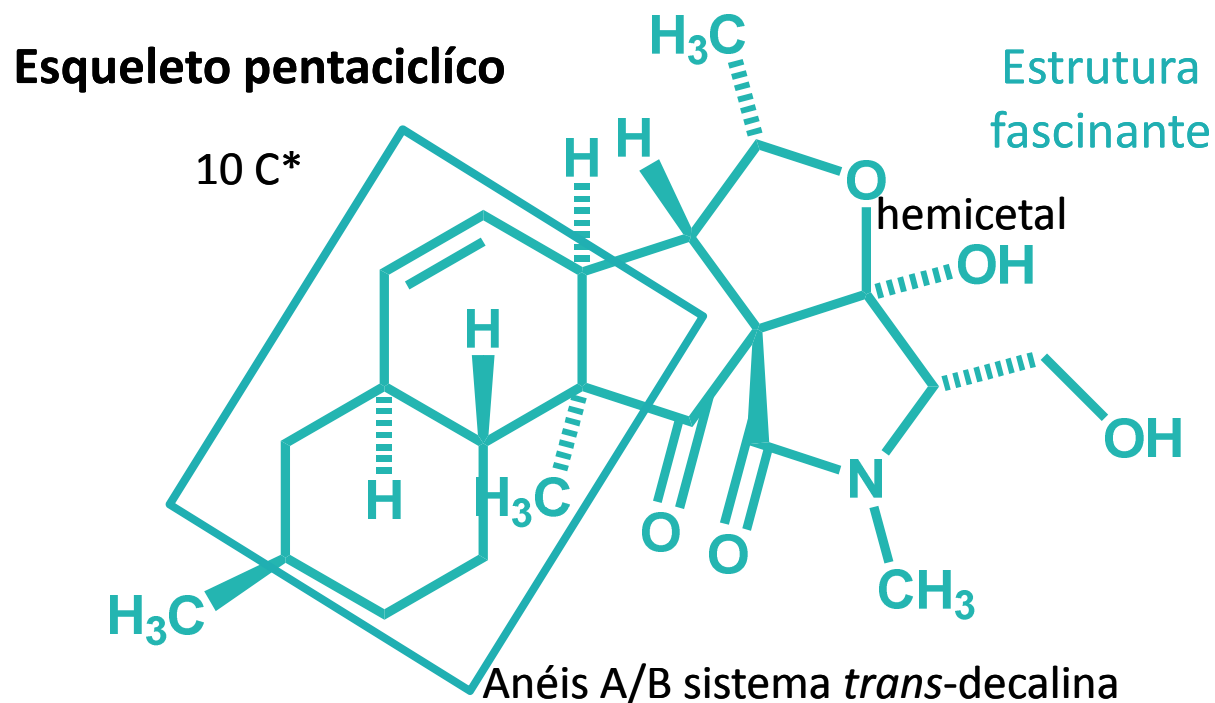
Via fermentativa bacteriana,
ativo em células taxano-R



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



Produtos naturais & câncer



Fusarium sp

(+)-fusarisetina*

Inibe a migração e metastase
de células cancerosas

2011

* 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.



Universidade Federal do Rio de Janeiro

Os fármacos e o comportamento social...



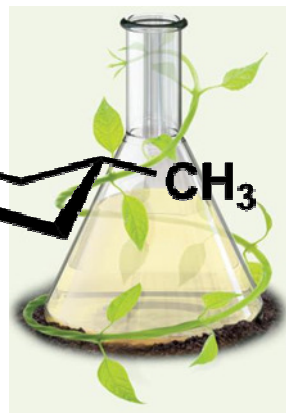
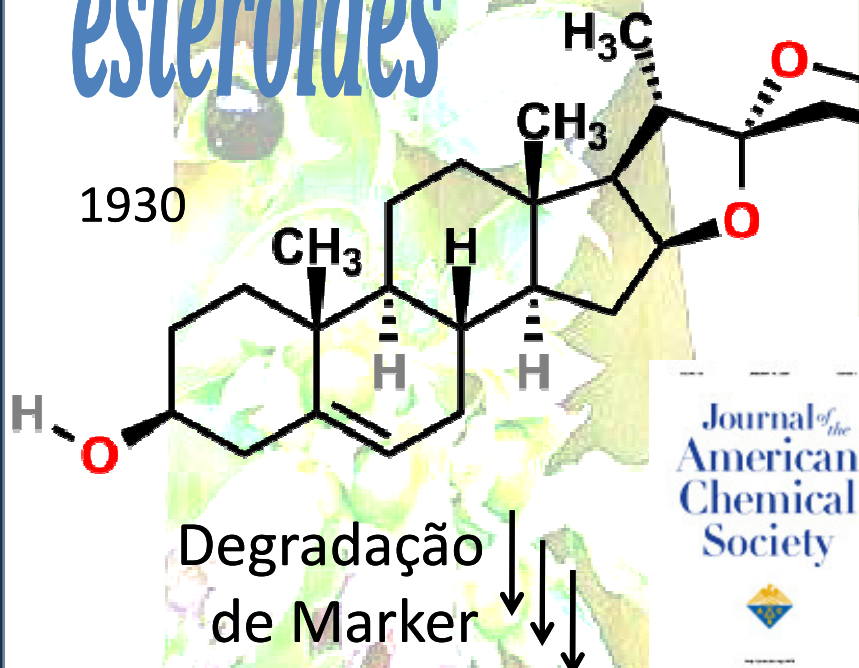
Química Medicinal



Universidade Federal do Rio de Janeiro

esteróides

1930



Laboratorios Syntex SA

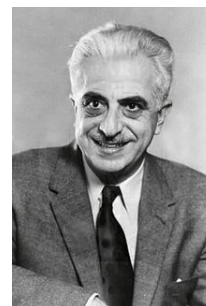
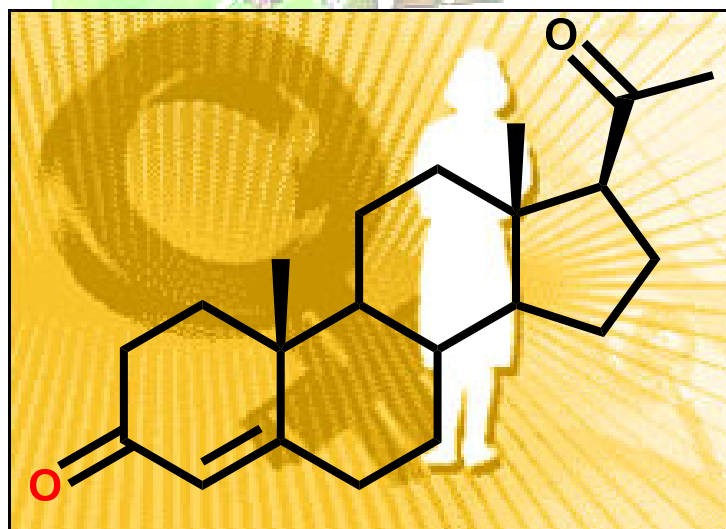


Russell Marker 1902-1995

Dioscorea mexicana Scheidw

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).

Contraceptivos



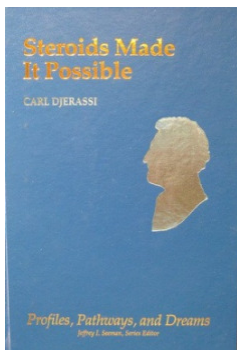
Gregory Pinkus



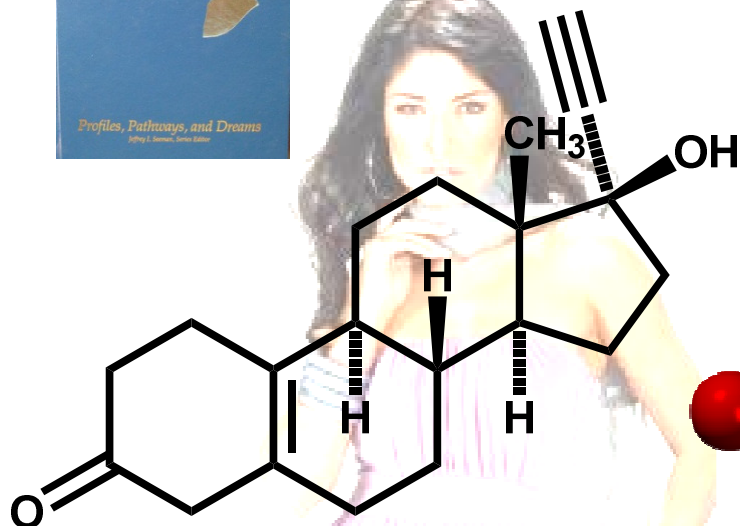
Carl Djerassi



Universidade Federal do Rio de Janeiro

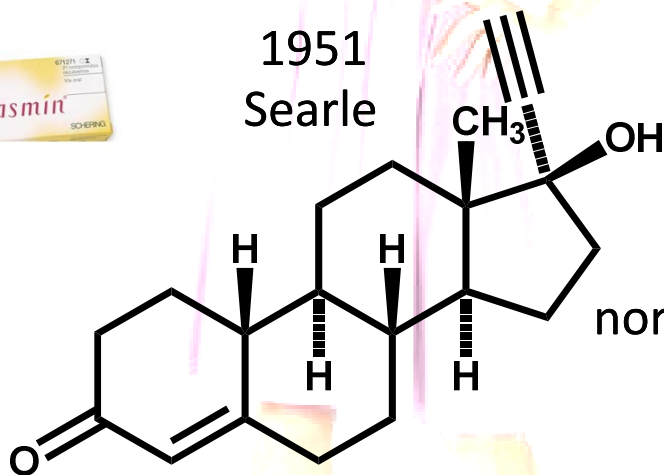


A pílula



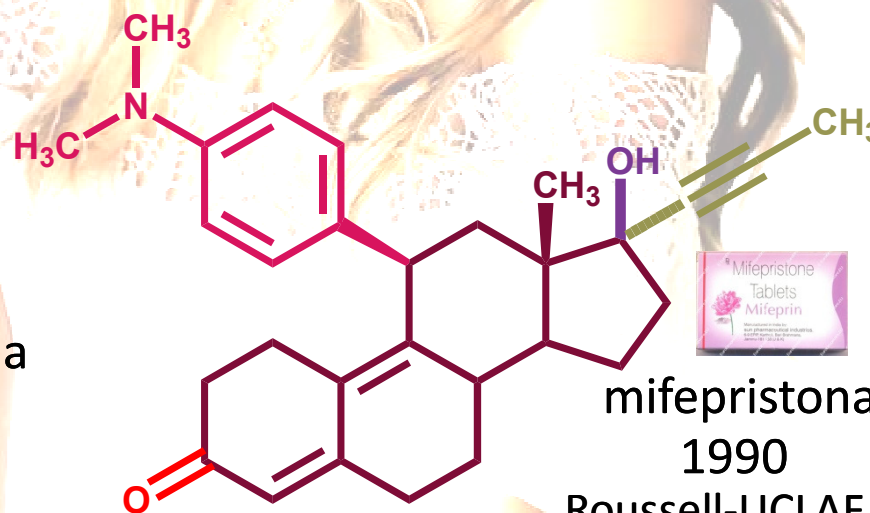
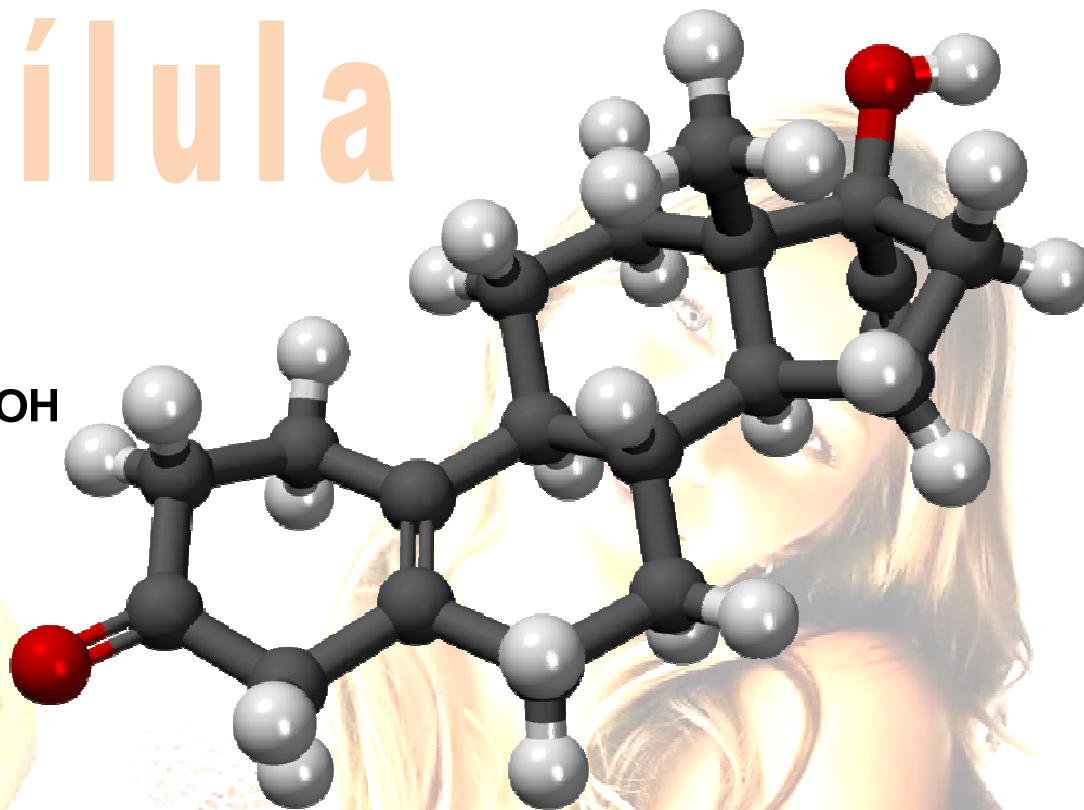
noretinodrel

1951
Searle



noretisterona

1951
Syntex



mifepristona

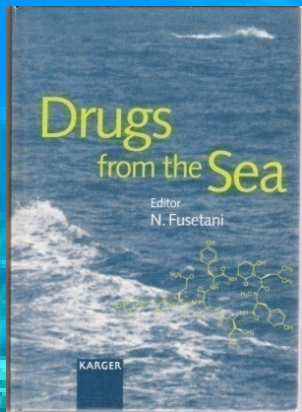
1990
Russell-UCLAF



Mais de 120 milhões de mulheres utilizaram a pílula contraceptiva (2009)



Universidade Federal do Rio de Janeiro



N Fusetani



Produtos naturais marinhos

L V Costa-Lotufo, D V Wilke, P C Jimenez, R A Epifanio, *Quím. Nova* 2009, 32, 703

T F Molinsky *et al.*, *Nat. Rev. Drug Discov.* 2009, 8, 69

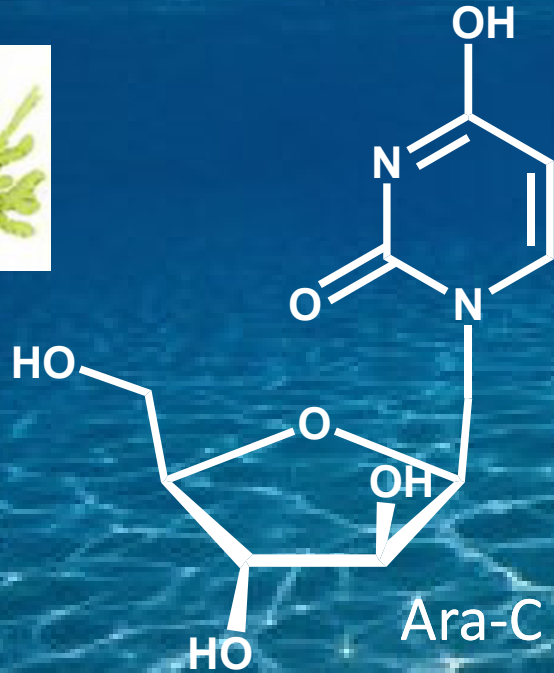


Universidade Federal do Rio de Janeiro

Produtos Naturais do Mar



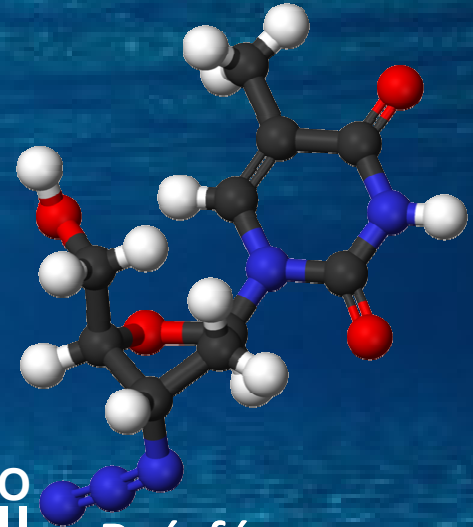
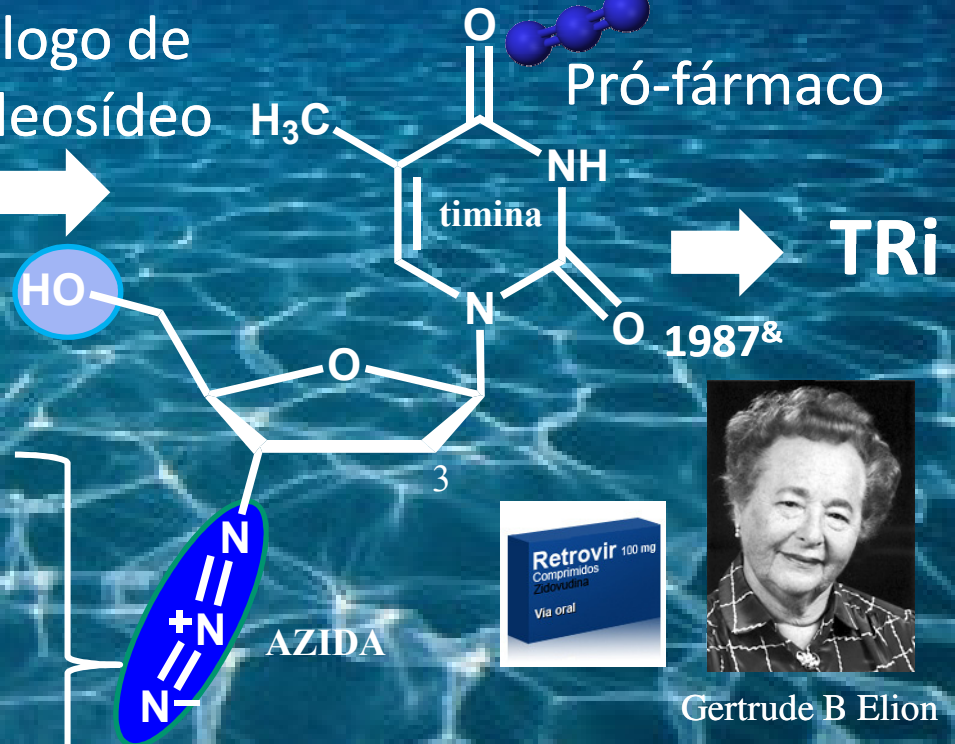
algas



Ara-C

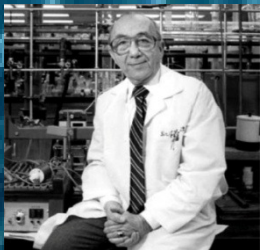


Análogo de nucleosídeo



TRi

1964-sintetizada*
 1984- Burroughs Wellcome
 1987- H Mitsuya & S Broder,
Nature 1987, 325, 773&



Jerome Horowitz



Gertrude B Elion

Zidovudina (AZT)

* J Horowitz et al., *J Org Chem* 1964, 29, 2076



Câncer

Ecteinascidina

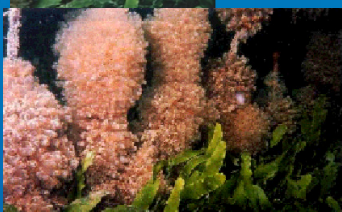


Yondelis^R (ET-743)

Alcalóide tetraidroisoquinolínico de origem marinha
Sarcoma avançado de tecidos moles

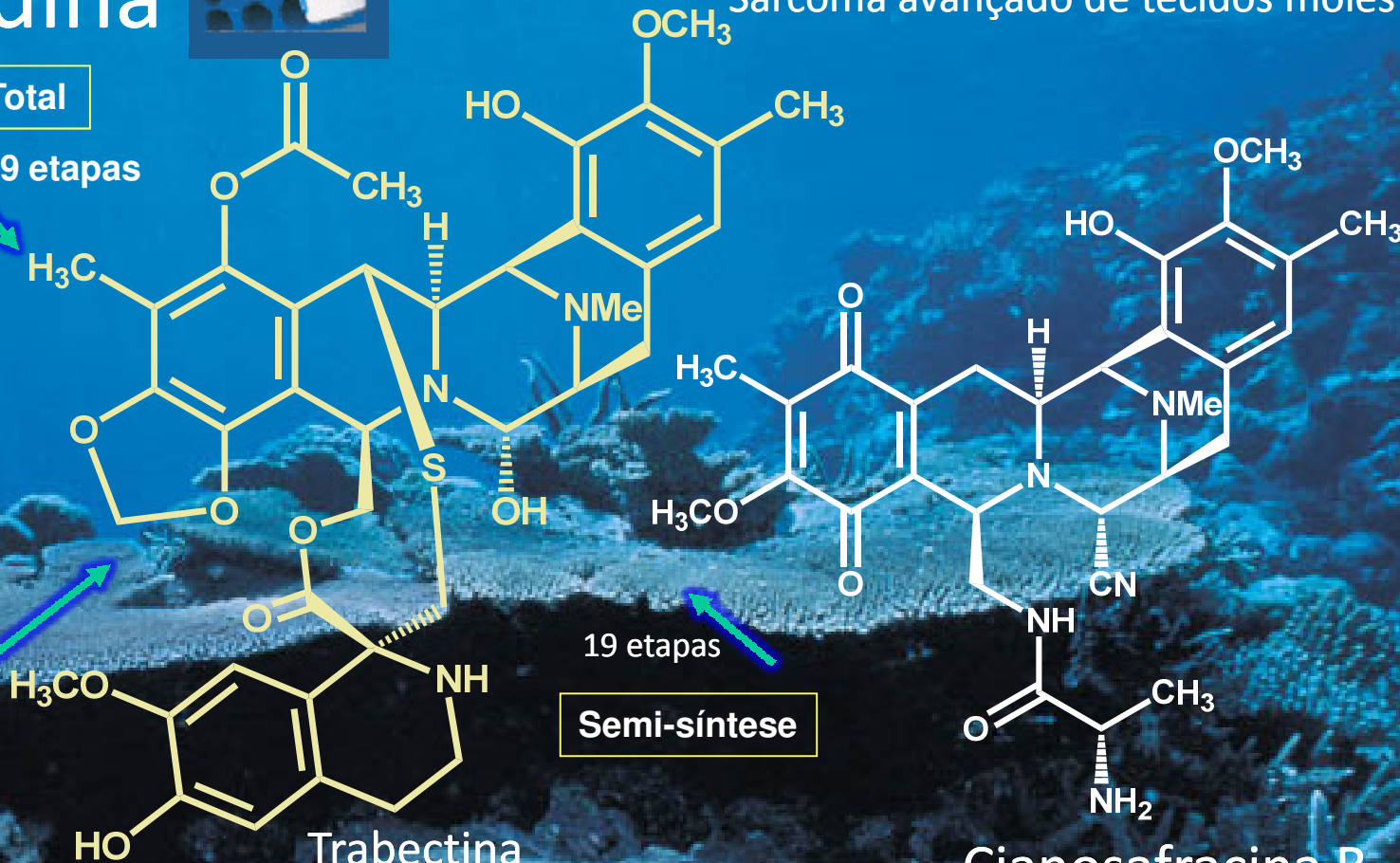
Síntese Total

49 etapas



Ecteinascidia turbinata

Marinocultura



100 vezes mais ativo que Taxol^R

C Cuevas, A Franchesch, *Nat. Prod. Rep.* **2009**, 26, 322

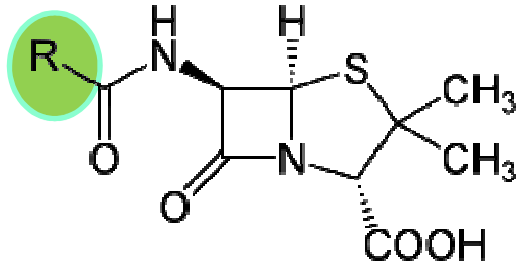
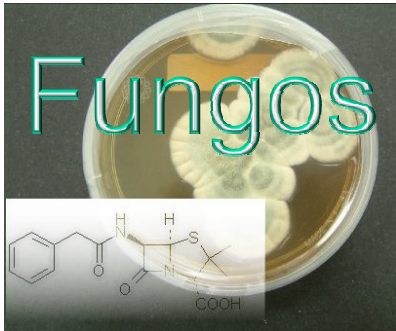
- ✓ **Natural:** KL Rinehart *et al*, *J. Nat. Prod.* **1990**, 53, 771
- ✓ **Síntese:** EJ Corey *et al*, *J. Am. Chem. Soc.* **1996**, 118, 9202
- ✓ **Hemi-síntese:** I Manzanares *et al*, *Org Lett.* **2000**, 2, 2545





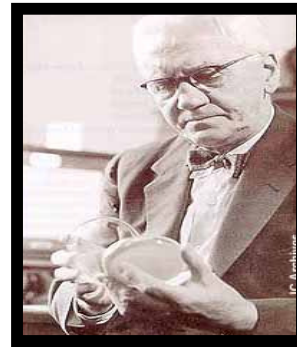
Universidade Federal do Rio de Janeiro

Penicilina



- 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

antibioticoterapia



Alexander Fleming
1881-1955



Howard W. Florey
1898-1968



1965

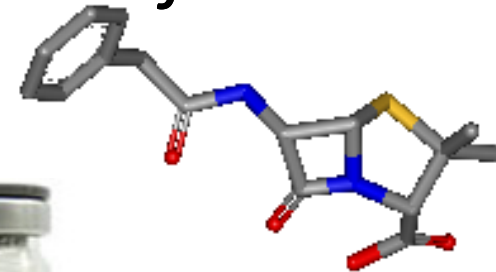
1947

Dorothy C. Hodgkin
1910-1994

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

Antibióticos β -lactâmicos

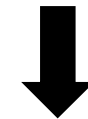
O acaso ajuda a sorte



E. Boris Chain
1906-1979



1964



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



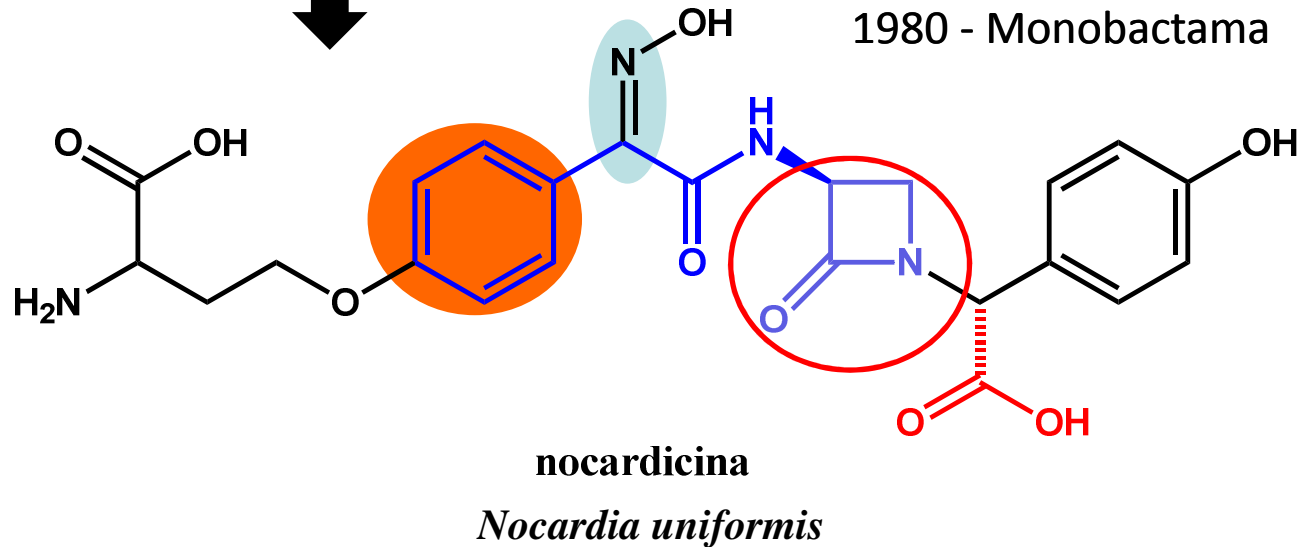
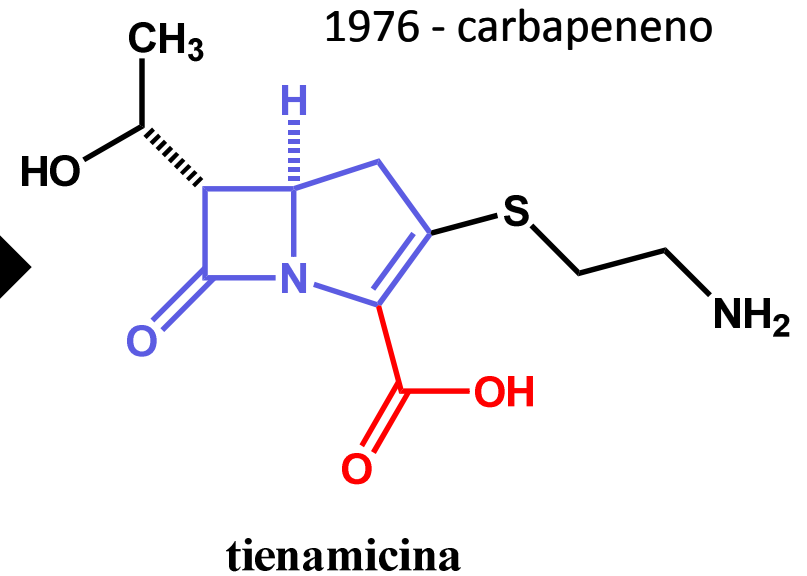
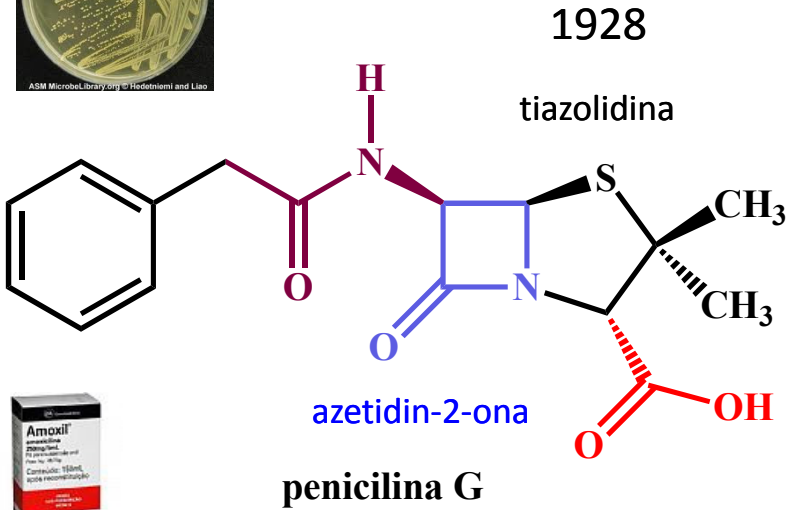


Universidade Federal do Rio de Janeiro

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



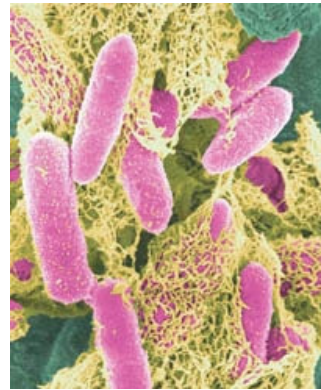
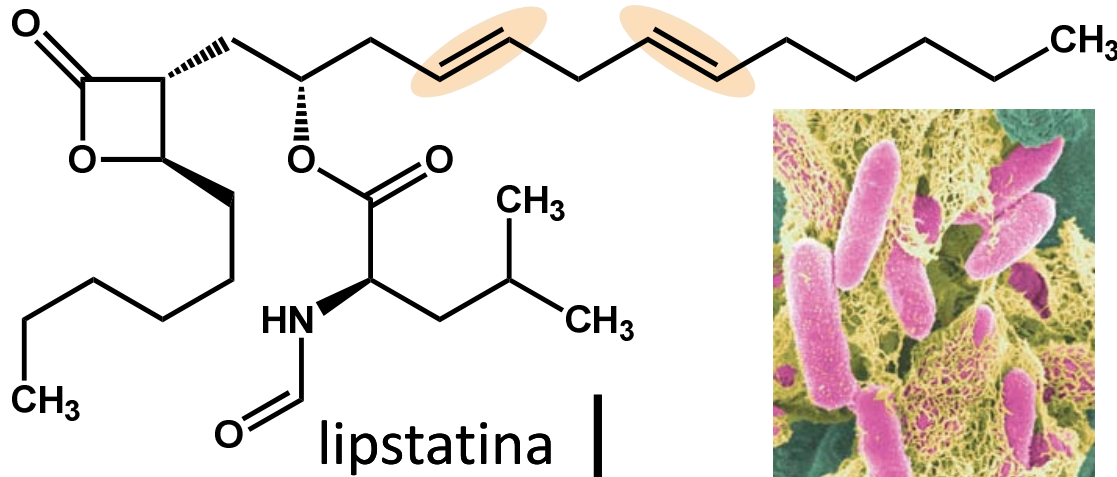
ASM Microbial Library.org - Hechtmi and Liao



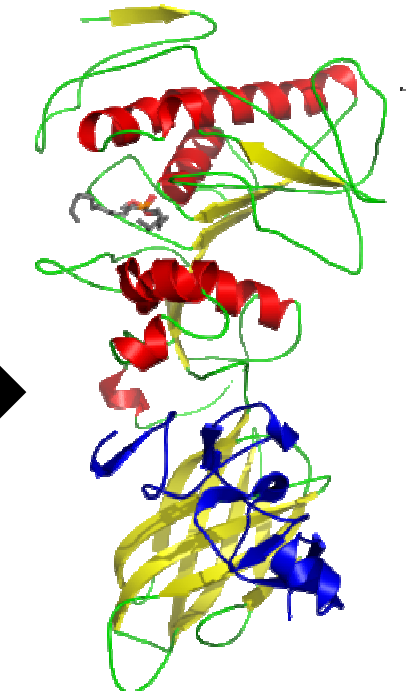
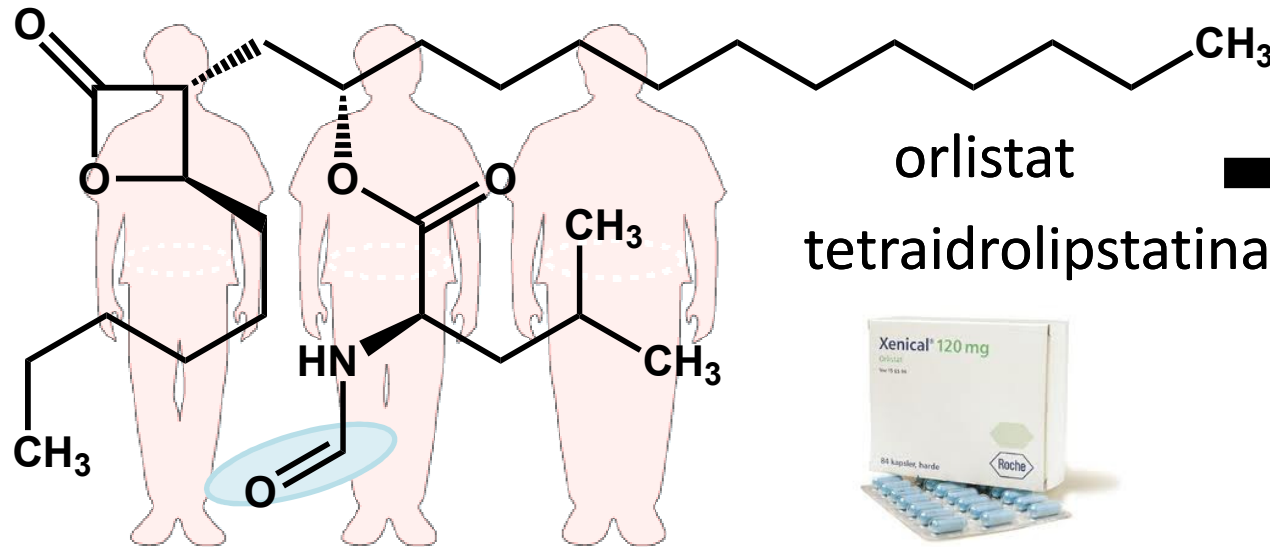
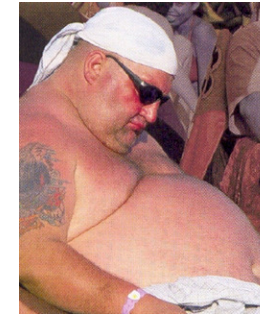


Universidade Federal do Rio de Janeiro

Dos fungos para combater a obesidade



Streptomyces toxytricini



Triacilglicerol lipase pancreática



Universidade Federal do Rio de Janeiro

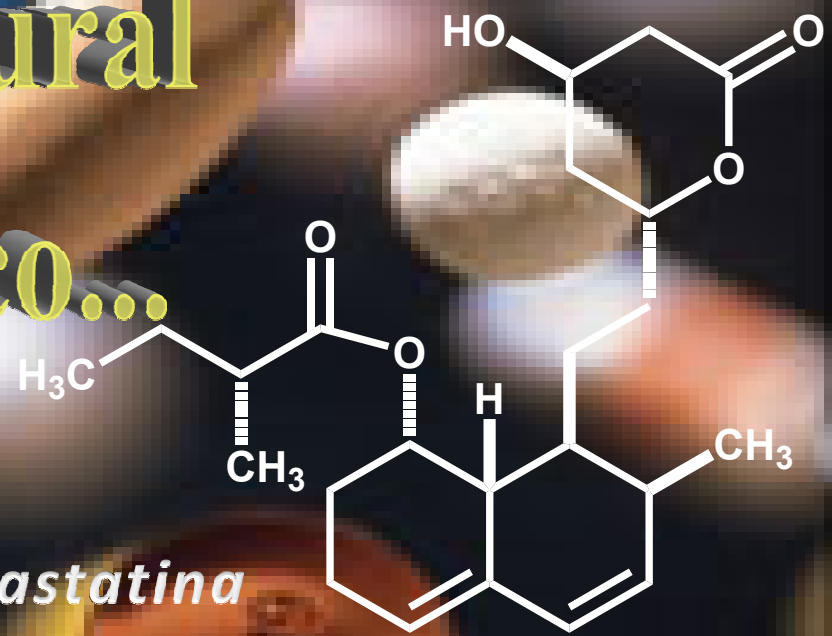
Do protótipo natural ao Super-fármaco...



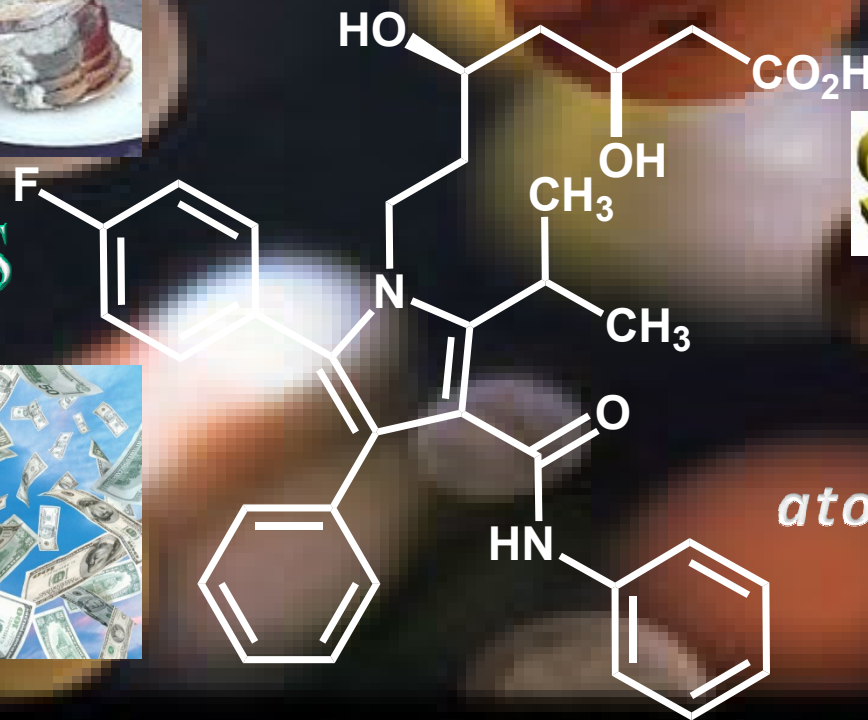
Fungos



mevastatina



atorvastatina





Quim. Nova, Vol. 32, No. 3, 679-688, 2009

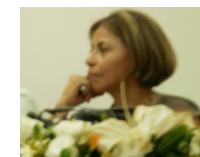
BIODIVERSIDADE: FONTE POTENCIAL PARA A DESCOBERTA DE FÁRMACOS

Eliezer J. Barreiro*

Departamento de Fármacos, Faculdade de Farmácia, Centro de Ciências da Saúde, Universidade Federal do Rio de Janeiro, CP 68006, 21944-910 Rio de Janeiro - RJ, Brasil

Vanderlan da Silva Bolzani**

Instituto de Química, Universidade Estadual Paulista, Rua Francisco Degni, s/n, 14800-900, Araraquara - SP, Brasil



Recebido em 16/1/09; aceito em 6/4/09; publicado na web em 9/4/09

BIODIVERSITY: POTENTIAL SOURCE FOR DRUG DISCOVERY. In economic terms, biodiversity transcends the boundaries usually given to conventional industries because it is a valuable source of biological and chemical data of great use to drug discovery. Certainly, the use of natural products has been the single most successful strategy in the discovery of novel medicines, and most of the medical breakthroughs are based on natural products. Half of the top 20 best-selling drugs are natural products, and their total sales amounted to US\$ 16 billions shows the importance of natural products, which is evidenced by the new chemical entities (NCE) approved by regulatory authorities around the world in the past decade. Recently, the approval of the alkaloid galanthamine as a medicine to treat Alzheimer's disease shows that natural compounds from plants will continue to reach the market. The huge biological diversity of the Brazilian biomes, by its ability to generate new knowledge and technological innovation can be a fantastic alternative as raw material for drug discovery.





*“Quem é pequeno
vê no maior apenas
o que um pequeno
é capaz de perceber.”*

Hermann Hesse