Química Medicinal

Mini-curso 17

62a Reunião Anual SBPC - UFRN

27-30 julho de 2010

LASSBio

UFRJ

Eliezer j. Barreiro

Professor Titular

Parte 3

Farmácia

Química Medicinal

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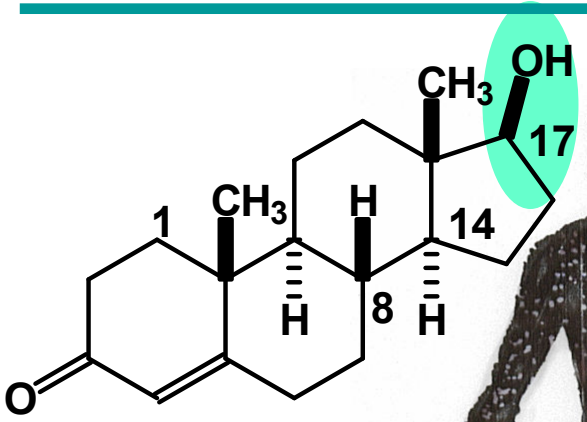
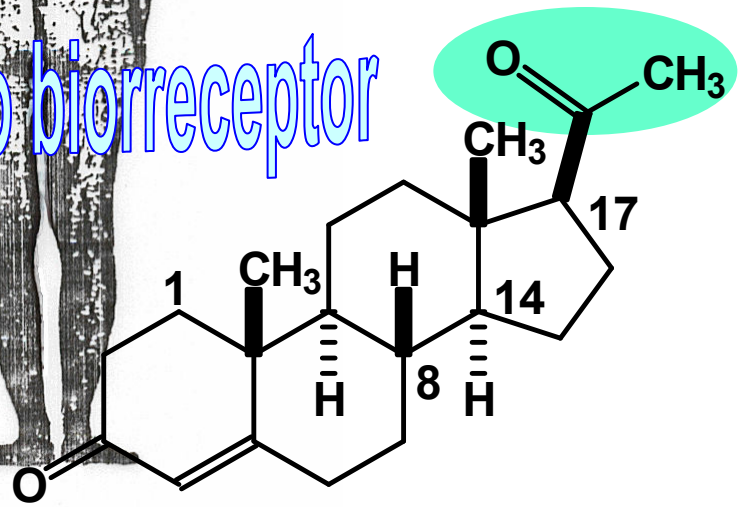
Similaridade & Dissimilaridade Molecular



testosterona

no reconhecimento molecular do biorreceptor



progesterona

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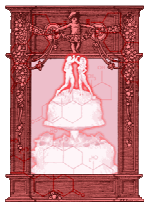
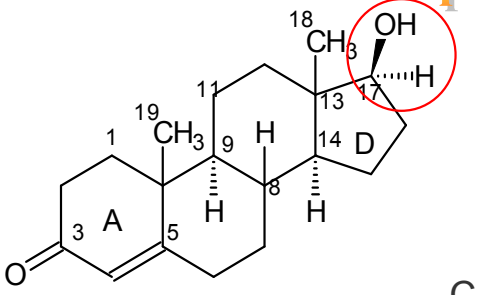
Similaridade & Dissimilaridade Molecular

Biorreceptor

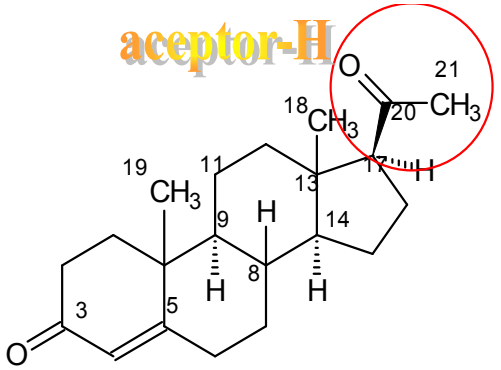


aceptor/doador-H



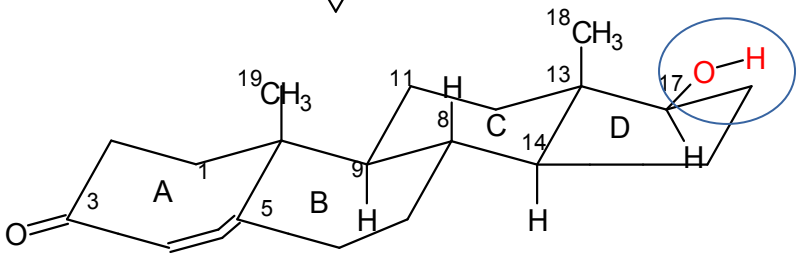
Esqueleto ciclopentano
peridrofenantreno

aceptor-H

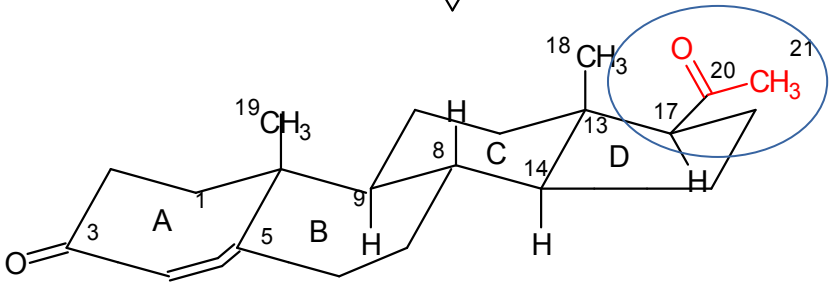


C_{19} C_{21}

Testosterona — similaridade molecular — Progesterona



B/C C/D trans



B/C C/D trans

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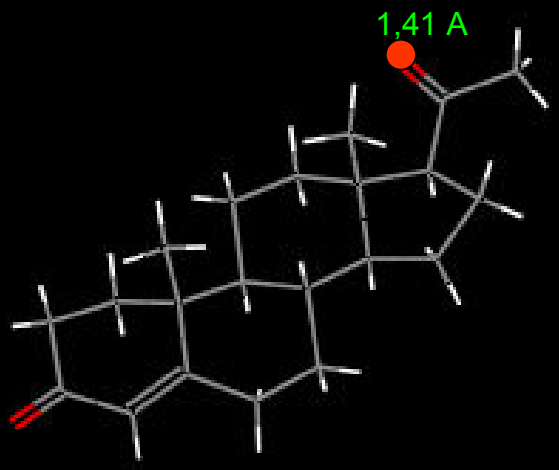
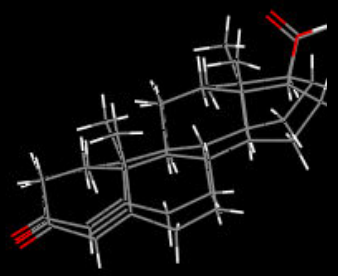
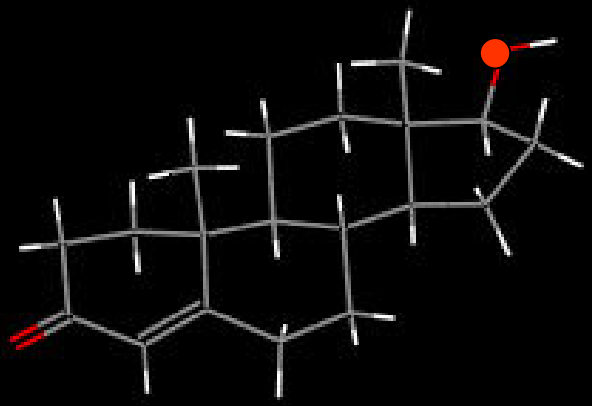
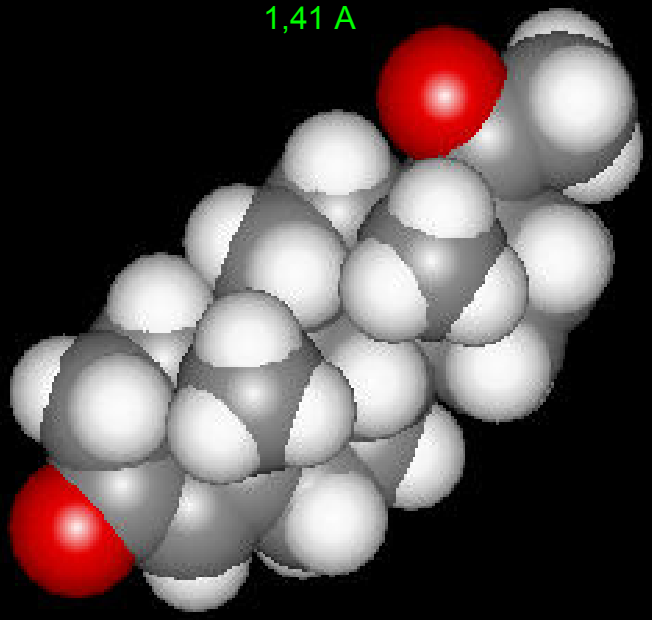


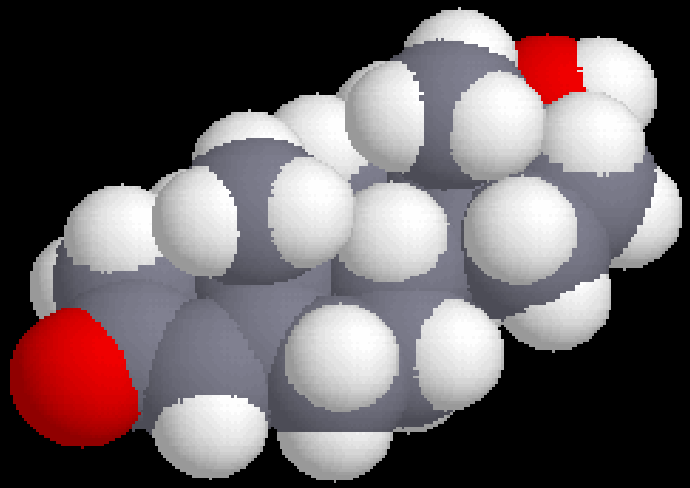




progesterona

testosterona





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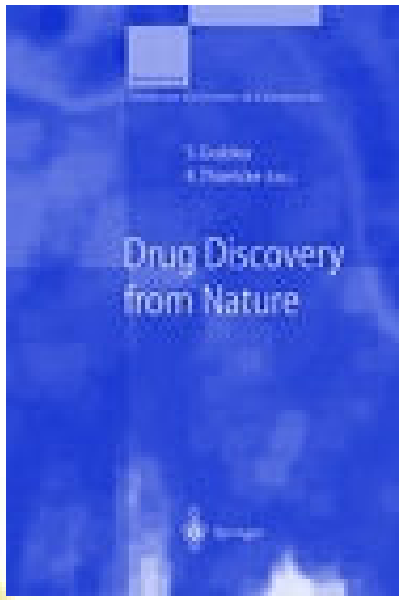
O início...

Química Medicinal



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Origem dos Fármacos

85%

propranolol

cimetidina

atorvastatina

Produtos Naturais

Sintéticos

Fármacos

Novos

marinhos

AZT, ziconotido

CALD

sulfas diuréticas

microorganismos, fungos estatinas antibióticos

vegetais

Taxol^{R}

camptotecina

Estudo do metabolismo

penicilinas

Acaso

hicantona

oxifenilbutazona

benzodiazepínicos

Processo de descoberta de novos hits-naturais

amostra

Bioativa

concentrado

Extrato Bioativo ⋯⋯▶ Fracionamento biomonitorado

composto puro

Bioativo

novo composto

Determinação estrutural

banco de dados espectroscópia

protótipo potencial

Novo protótipo

Técnicas de Química Medicinal

extração, concentração, fracionamento, purificação

identificação das substâncias

compostos conhecidos

amostra pura

HPLC
HPLC-MS
(LC-MS)

toxicidade

Bioensaios in vivo

scale-up da purificação

modificações estruturais
preliminar "sar"
modulação das propriedades biológicas
otimização do perfil PK

Quantidade de substância requerida

1-10 µg | 1-10 mg | 1-10 g | 100 g

Adaptado de

F. E. Koehn & G. T. Carter, The evolving role of natural products in drug discovery, Nature Review Drug Discovery, 2005, 4, 206-220

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Química Medicinal

Os índios e os indóis...

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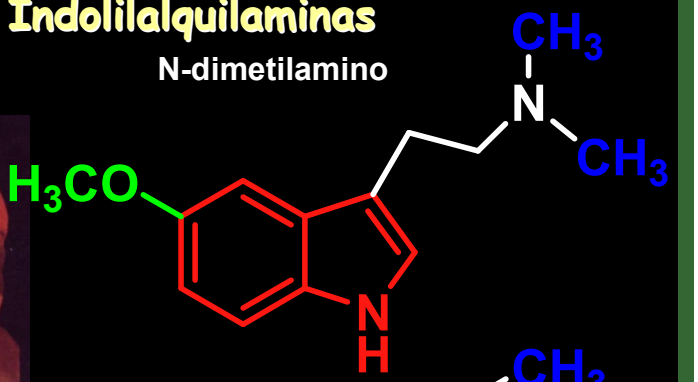
Índios & indóis

Virolas amazônicas

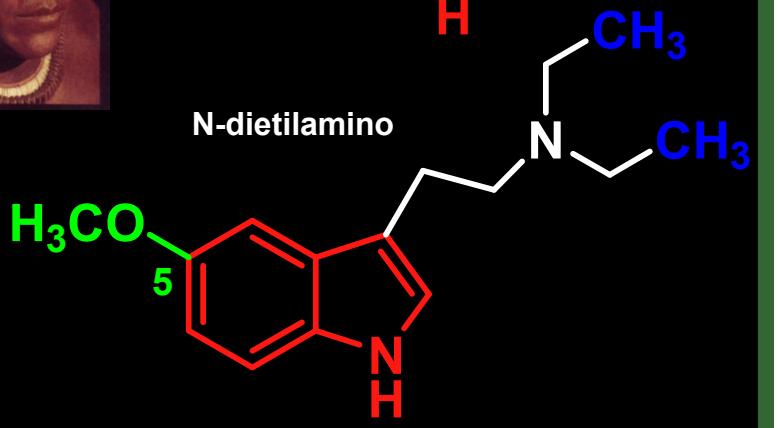
Alcalóides Indólicos

Indolilalquilaminas

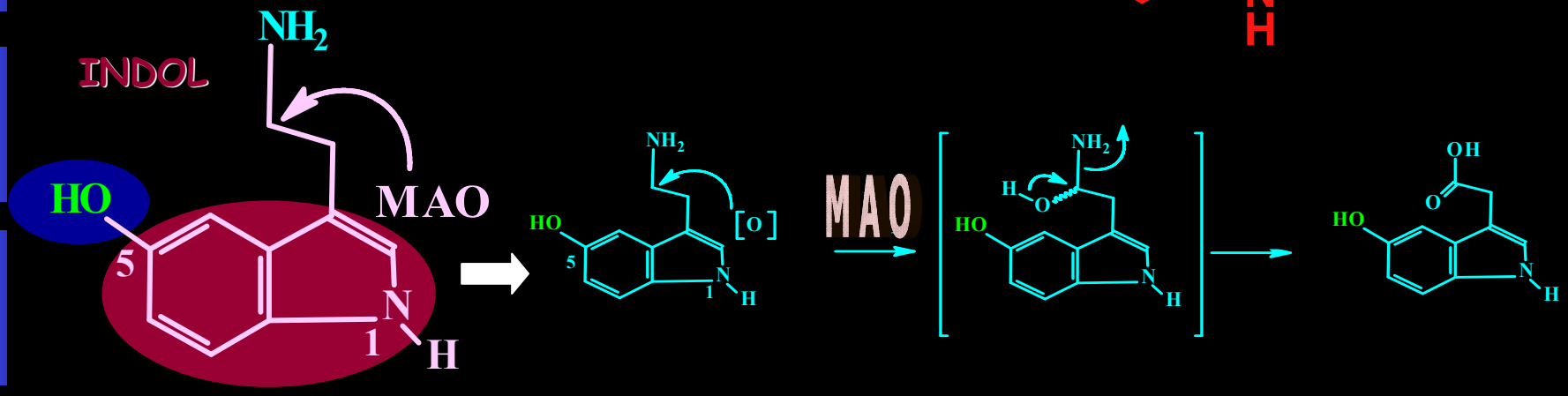
N-dimetilamino



N-dietilamino



Compostos Alucinogênicos



Serotonina

5-hidróxi triptamina

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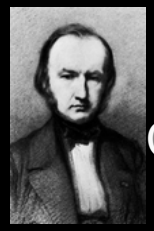
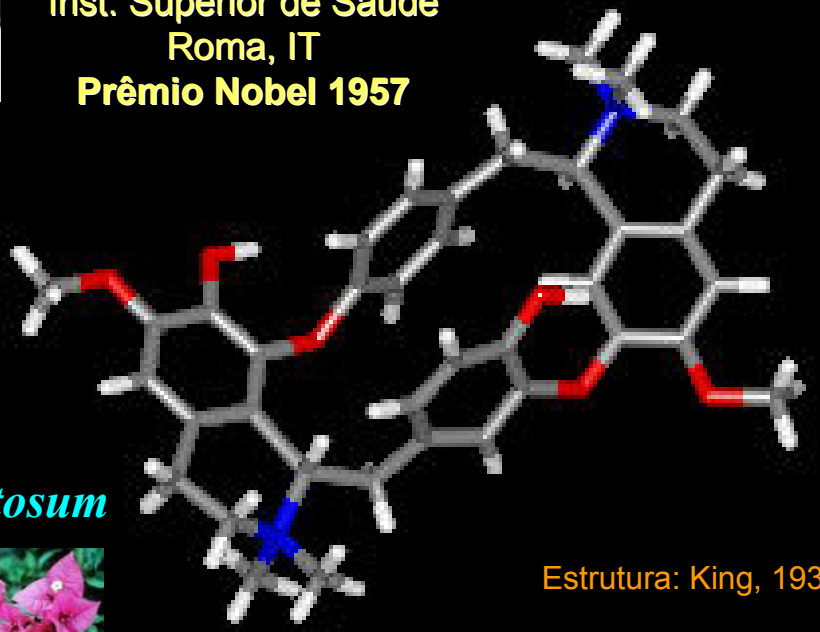
Bloqueadores ganglionares

Curare

Fármaco dos Índios



1947 - Daniel Bovet
Inst. Superior de Saúde
Roma, IT
Prêmio Nobel 1957



Estrutura: King, 1935

Chondrodendron_tomentosum
Loganiaceae
(urari)

d-tubocurarina

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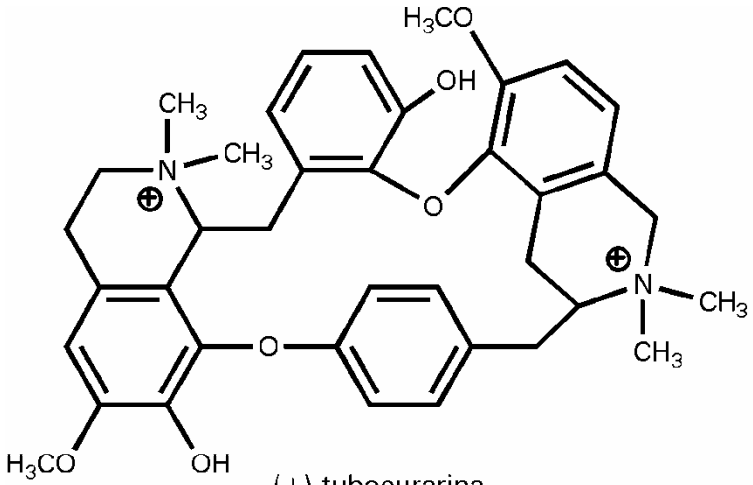
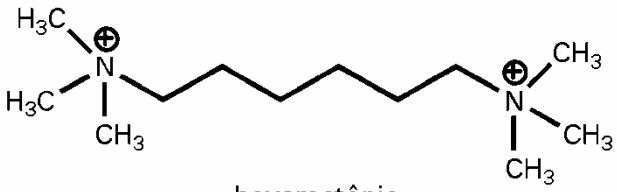
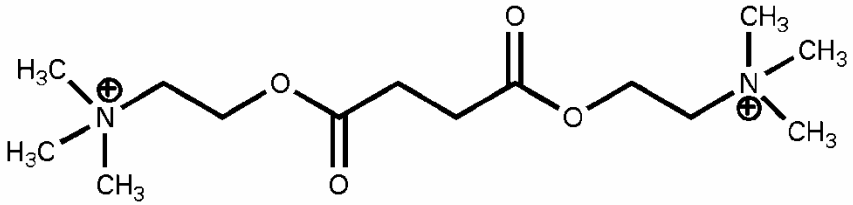
Bloqueadores ganglionares



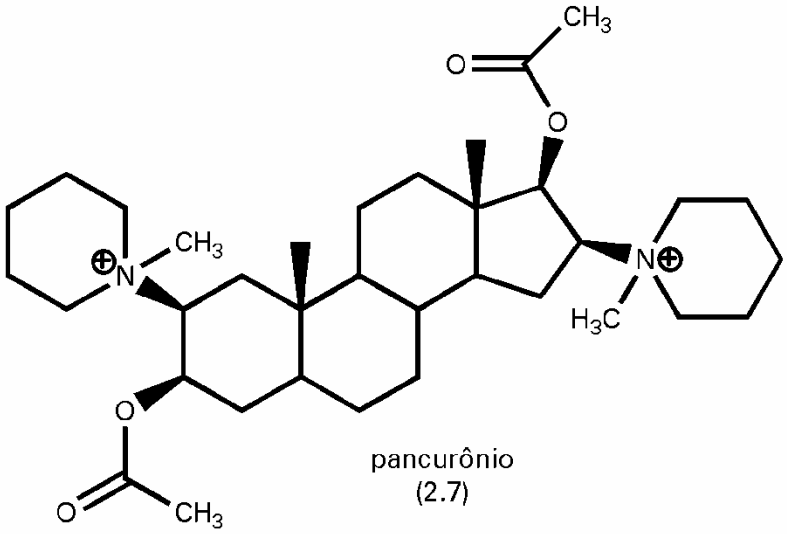
(+)-tubocurarina
(2.4)



hexametônio
(2.5)



succinilcolina
(2.6)



pancurônio
(2.7)

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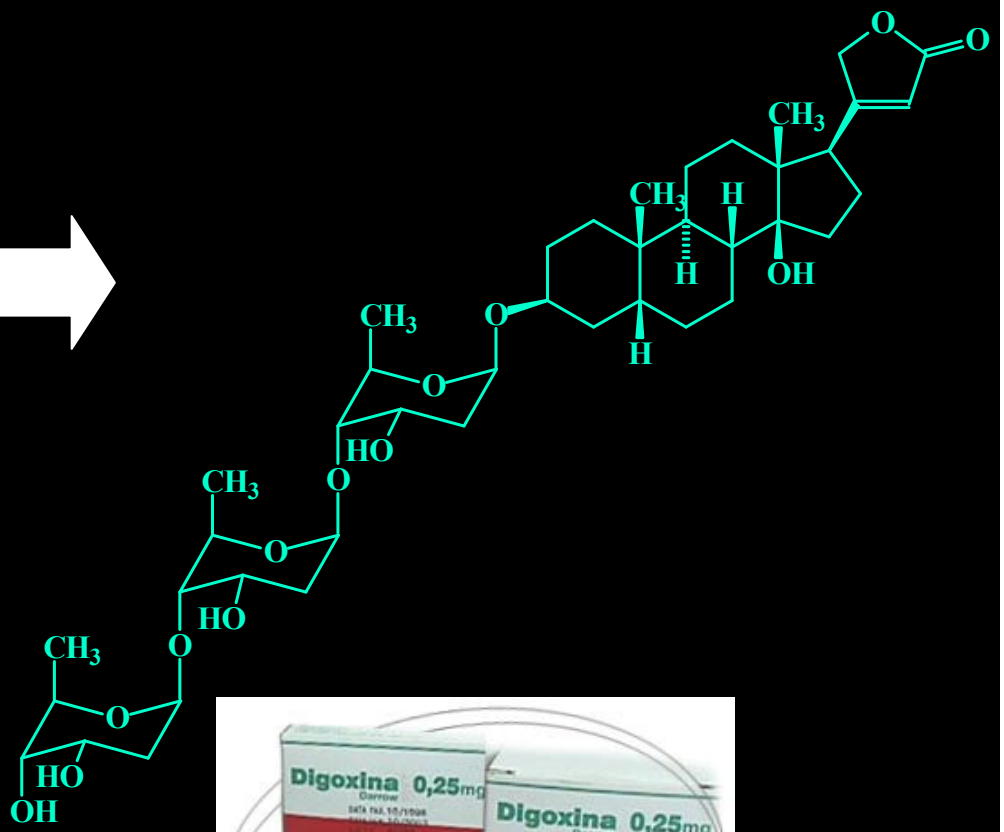
Glicosídeos Cardiotônicos



Decano dos Fármacos

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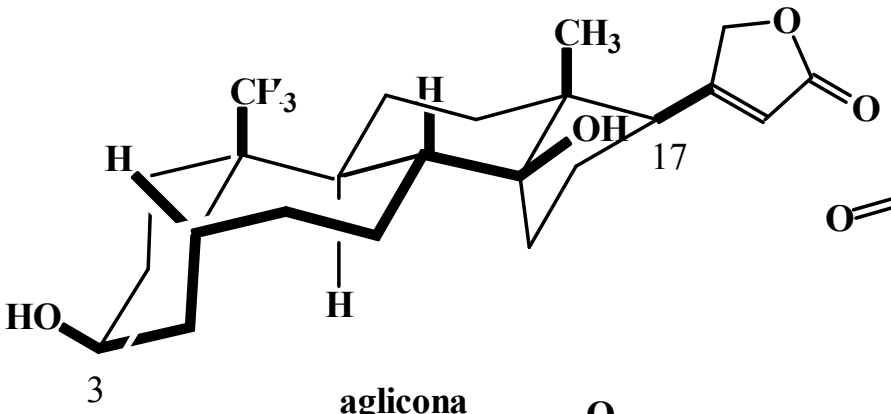
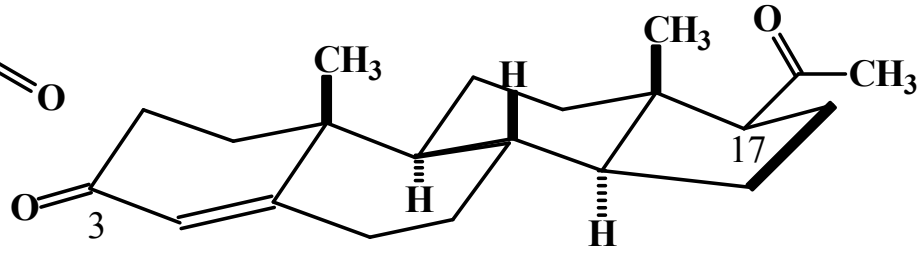
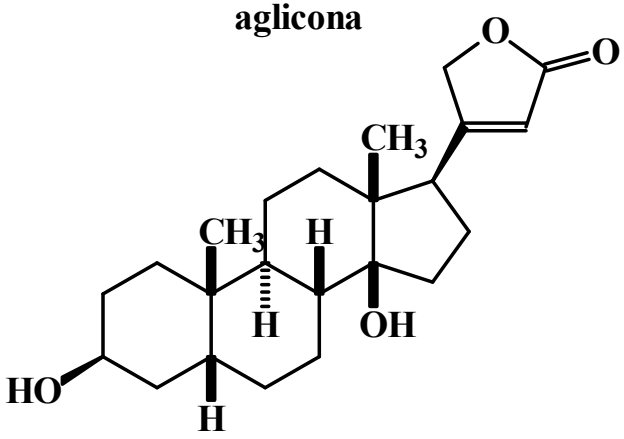
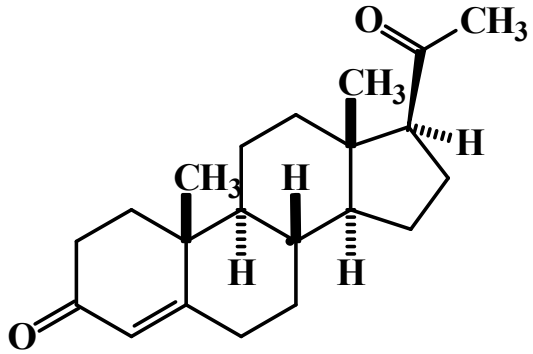




aglicona



progesterona



A Importância da Conformação

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Química Medicinal

O streptease molecular

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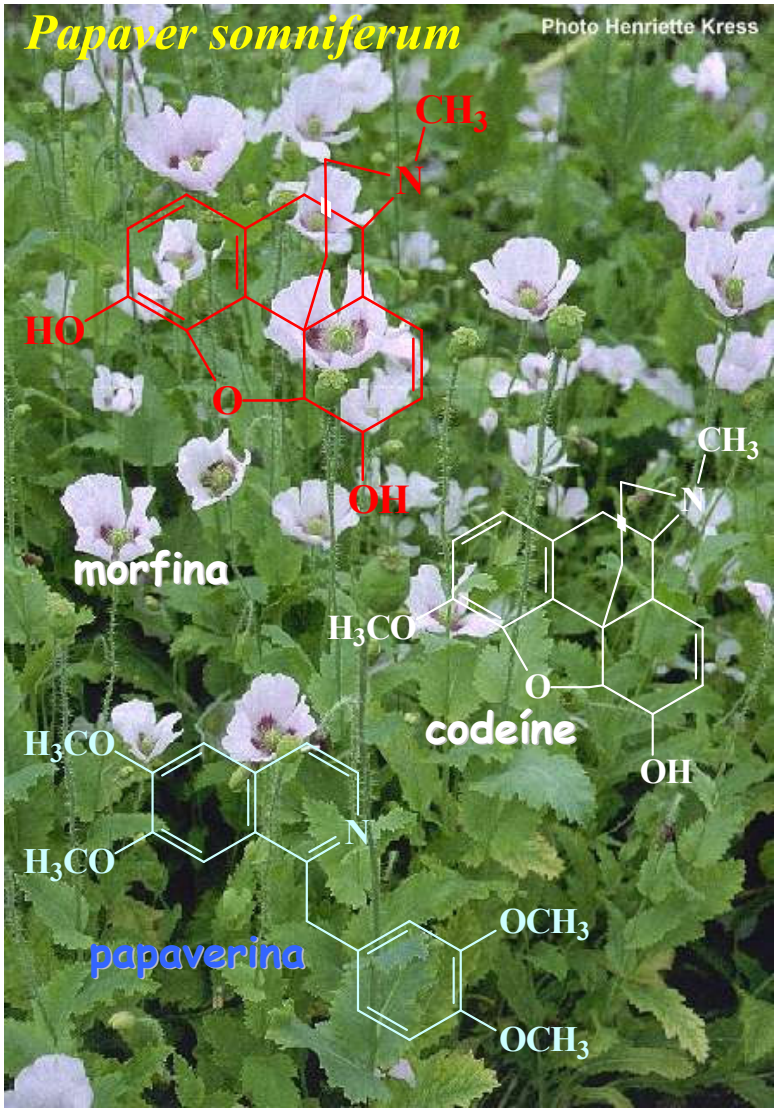
Produtos Naturais: Morfina

Alcalóides fenantrênicos e benzilisoquinolínicos (papaverina 0,2%)



1493-1541 Marco Polo (Veneza) ⇒ Ópio

1806 ⇒ Friedrich Sertürner isola a morfina ("Morpheus") ⇒ hipno-analgesia

1954 - Beckett & Casey, Un. London

opiate effects were receptor mediated

Sub-tipos de receptores centrais: δ, κ, μ

P. W. Schiller, ***Progr. Med. Chem.*** *1991*, **28,** 301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analgesia central; tolerância; dependência química; síndrome de abstinência

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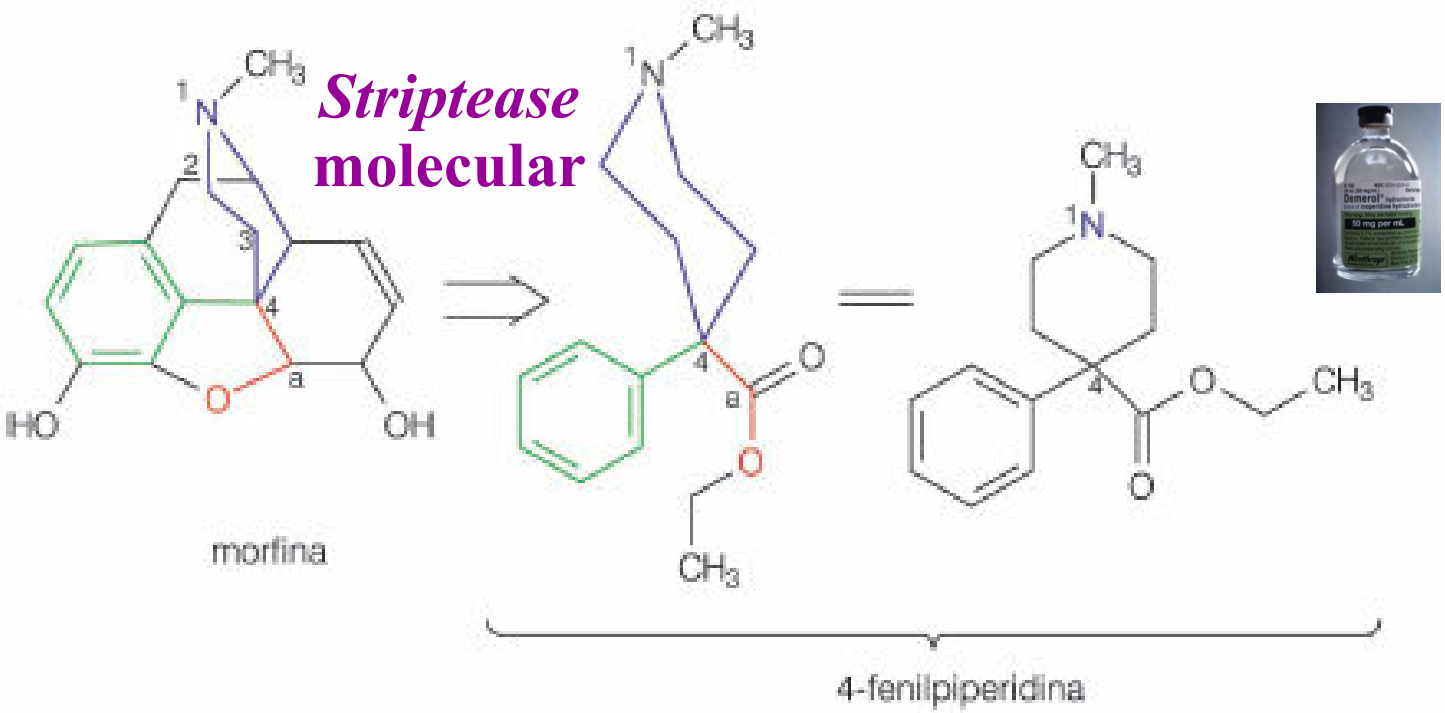
Domesticando produtos naturais



A origem dos analgésicos 4-fenilpiperidíncos a partir da estrutura da morfina: o anel piperidínico, em azul, substituído em C-4 no alcalóide por uma unidade fenila (verde) e um átomo de carbono quaternário oxigenado (a, em vermelho).

Produto natural como protótipo

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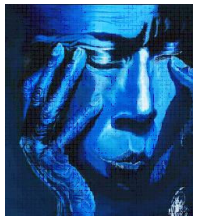
Domesticando produtos naturais



Streptease molecular

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Produtos naturais com propriedades anti-câncer

Câncer

Fármacos Anti-câncer

Origem

- plantas
  - Vincristina
  - Paclitaxel
  - Podofilotoxina
  - Camptotecina
- sintéticos
  - Docetaxel
  - Irinotecan
  - Etoposido
- microorganismos
  - Doxorubicina
  - Dactomicina
  - Bleomicina

Alvos

- Topoisomerase I & II
- α-Tubulina
- DNA
- Tirosina quinase
- PKC
- COX

NATIONAL CANCER INSTITUTE

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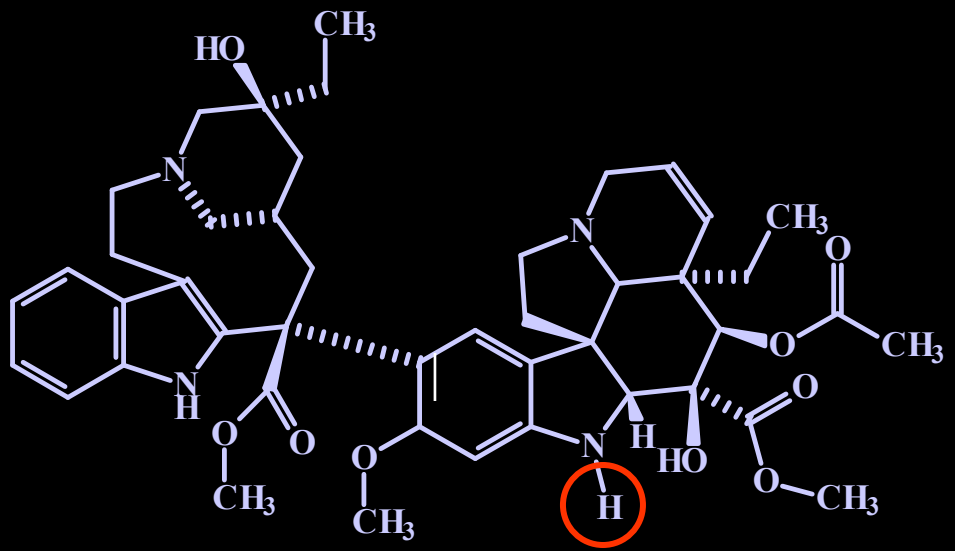
Agentes Anti-câncer de Origem Natural

Câncer

Vinca sp.

Catharanthus roseus



Alcalóides

E. Wenkert, 1955

Inibidor mitótico (metafase)

Alcalóides bis-indólicos

vinc ristina R= H
vim bla stina R= CHO

eliezer © 2010

Câncer

Paclitaxel

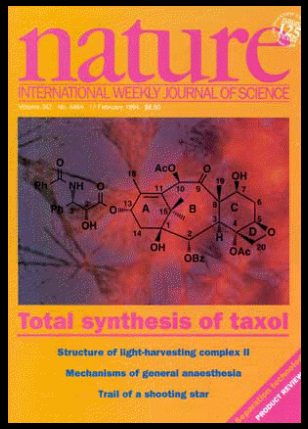
Taxol®

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

Res. Triangle Park, 1967

M. E. Wall & M. C. Wani

1996 - National Cancer Institute Award of Recognition



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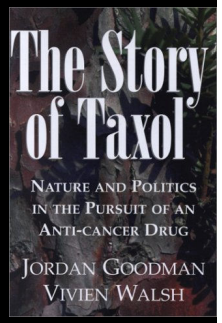
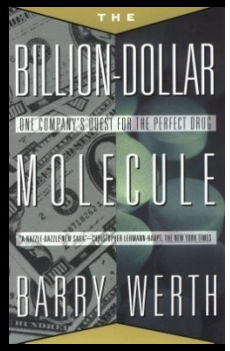
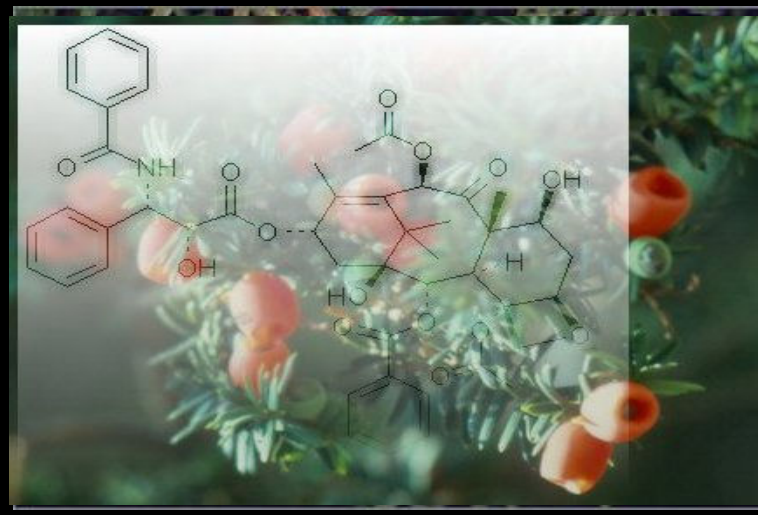
M. E. Wall,,
"Chronicles of Drug Discovery",
D. Lednicer, vol.3, ACS, 1993,
pp. 327-348







Taxus bacatta

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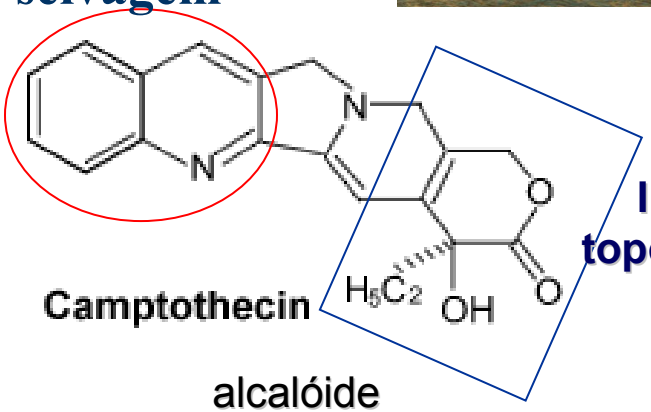
Câncer

Molécula "selvagem"



Camptothecin

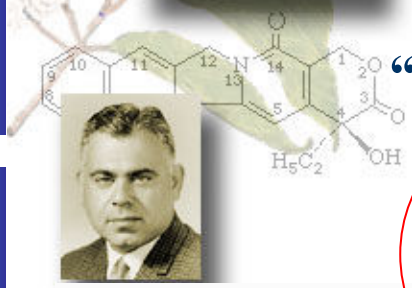
Inibidor de topoisomerase-1

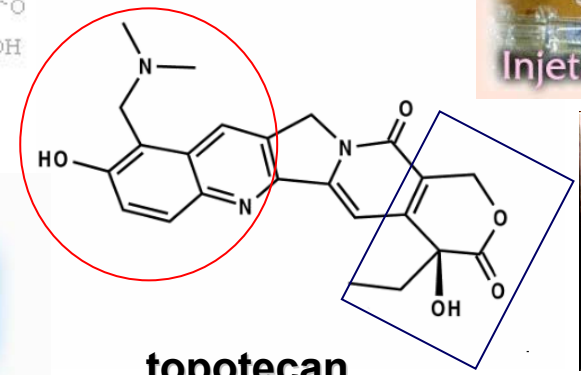
alcalóide
quinolínico de biossíntese mista

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

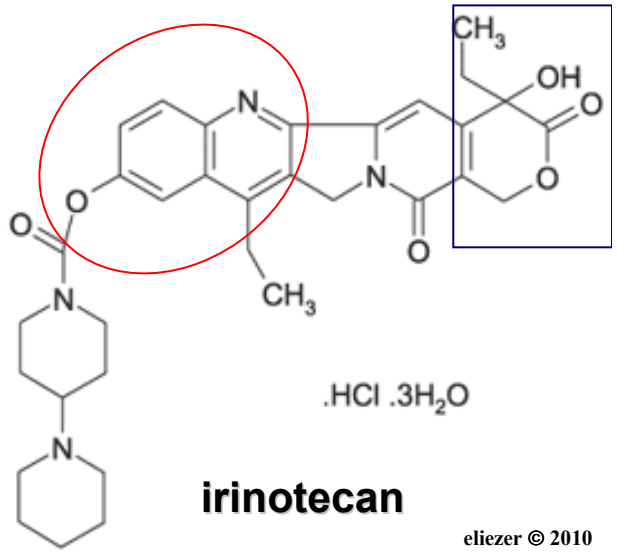
Wall, ME, MC Wani, CE Cook, KH Palmer, AT McPhail, GA Sim, "Plant antitumor agents. 1. The isolation and structure of camptothecin, a novel alkaloidal leukemia and tumor inhibitor from *Camptotheca acuminata*" *J. Am. Chem. Soc.*1966, 88, 3888.

Molécula "domesticada"





topotecan



irinotecan

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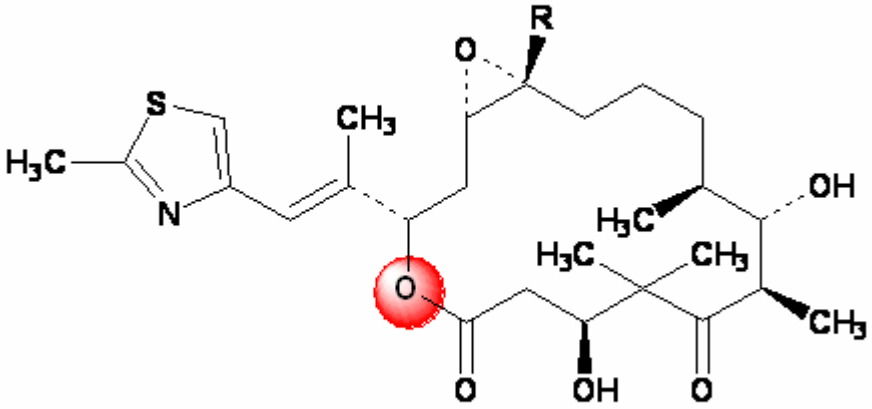
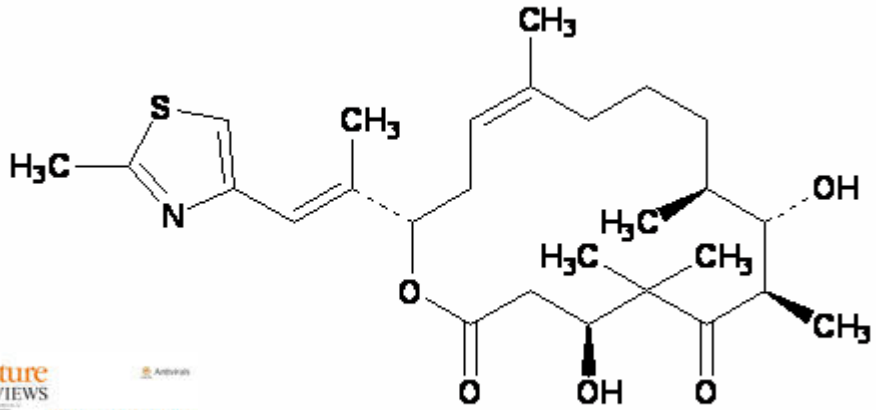
Isolada de Sorangium cellulosum em 1993



Epotilona A R = H

Epotilona B R = CH_3

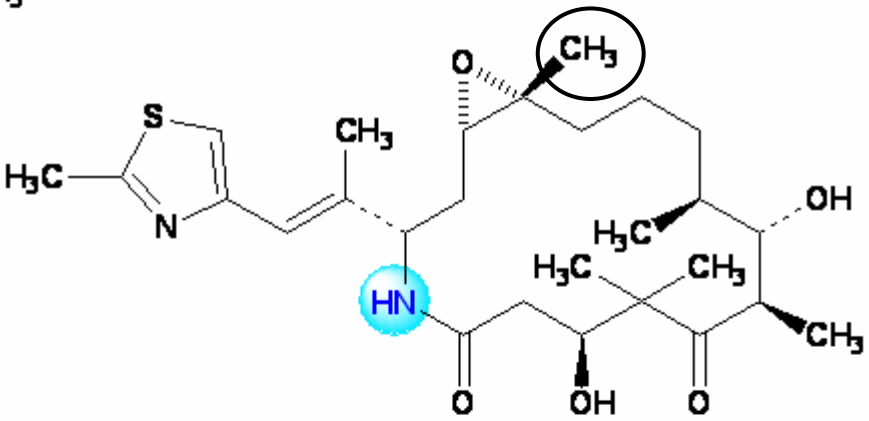


Epotilona D

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

2007 - Primeiro membro da classe dos macrociclos de 16 membros (epotilonas) a ser aprovado pelo FDA para tratamento do câncer metastático de mama, atuando como inibidor de microtúbulos

Análogo semi-sintético



Ixabepilona

Ixempra^{R}

BMS, 0ut. 2007

Via fermentativa bacteriana, ativo em células taxano-R

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

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Drug development from marine natural products

Tadeusz F. Molinski, Doralyn S. Dalisay*, Sarah L. Lievens*‡ and Jonel P. Saludes*‡*

Abstract | Drug discovery from marine natural products has enjoyed a renaissance in the past few years. Ziconotide (Prialt; Elan Pharmaceuticals), a peptide originally discovered in a tropical cone snail, was the first marine-derived compound to be approved in the United States in December 2004 for the treatment of pain. Then, in October 2007, trabectedin (Yondelis; PharmaMar) became the first marine anticancer drug to be approved in the European Union. Here, we review the history of drug discovery from marine natural products, and by describing selected examples, we examine the factors that contribute to new discoveries and the difficulties associated with translating marine-derived compounds into clinical trials. Providing an outlook into the future, we also examine the advances that may further expand the promise of drugs from the sea.

Nat. Rev. Drug Discov. **2009**, *8*, 69

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timina

AZT

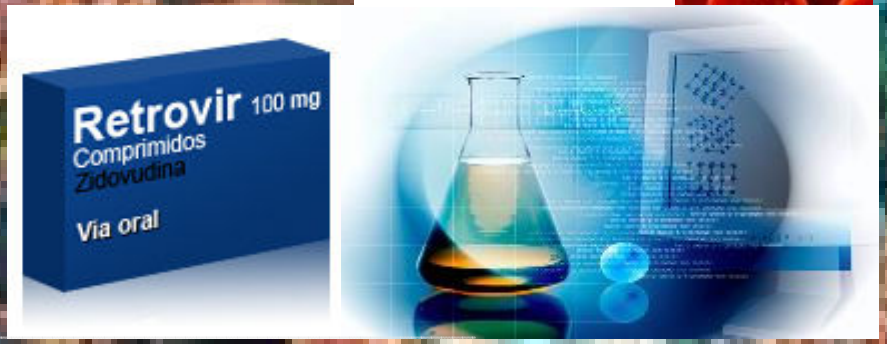
desoxi-ribose

AZIDA

ZIDOVUDINA

TIMIDINA

Primeiro anti-HIV inibidor da transcriptase-reversa



Simpósio: PN de organismos marinhos: fonte potencial de bioprodutos
28/08, 15h30 – Escola de C&T – sala 3 (SBQ)

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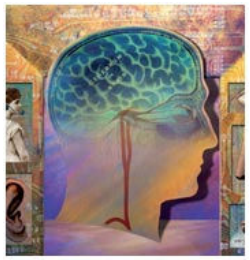
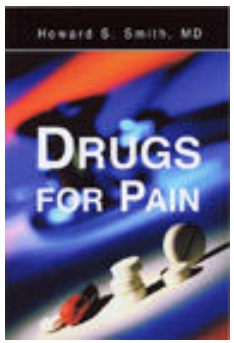




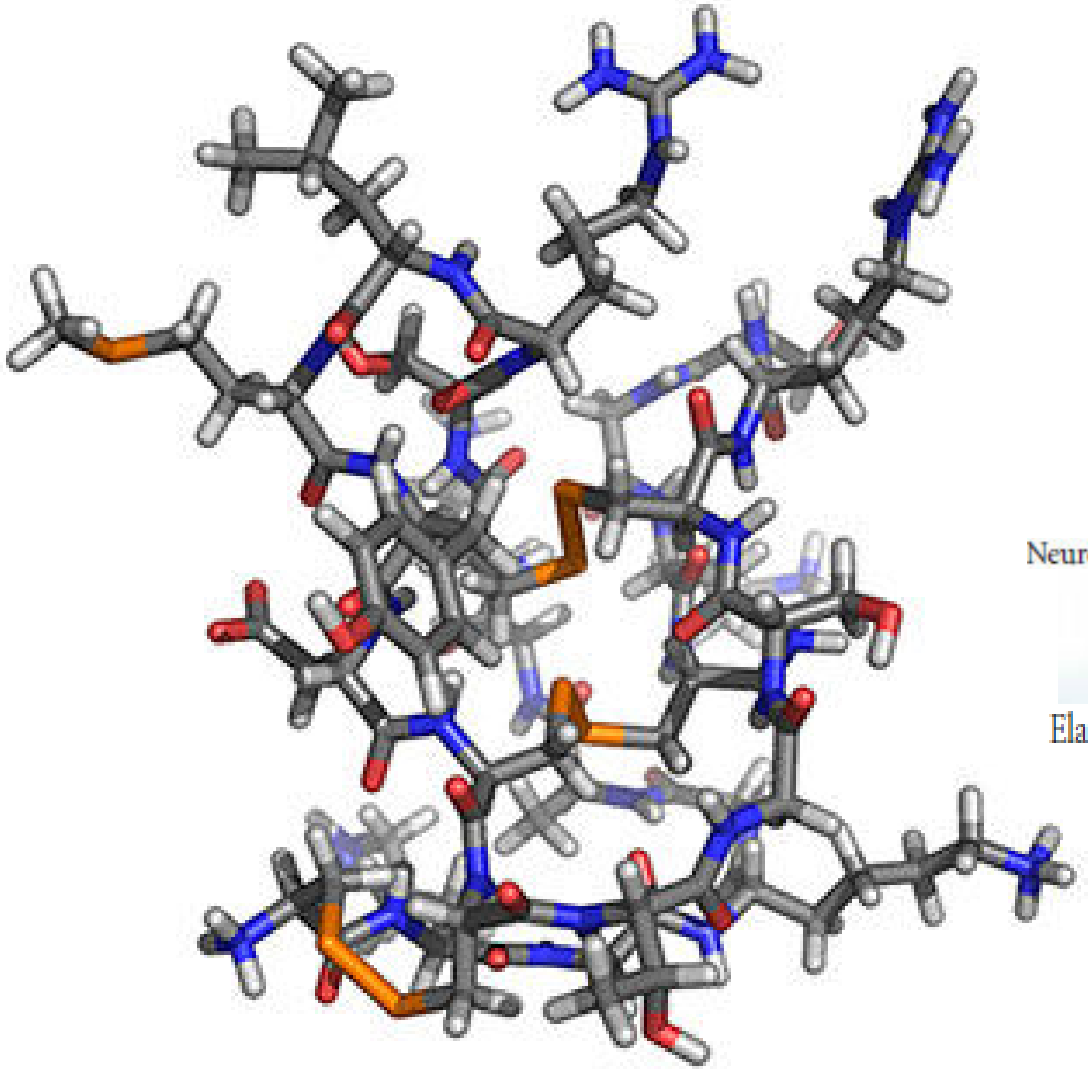
1980 - Michael McIntosh & Baldomero Olivera

Ziconotídeo

$C_{102}\ H_{172}\ N_{36}\ O_{32}\ S_7$

FDA em 28/12/2004; Eur Comm. em 22/02/2005

Uso intratecal



25 aa

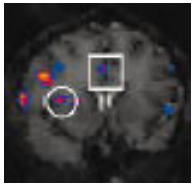
Conus magus

SNX-111

Neurex (Menlo Park, CA)

Elan Pharmaceuticals

(Dublin, Ireland



Antagonista de canais Ca^{++} voltagem dependentes tipo-N

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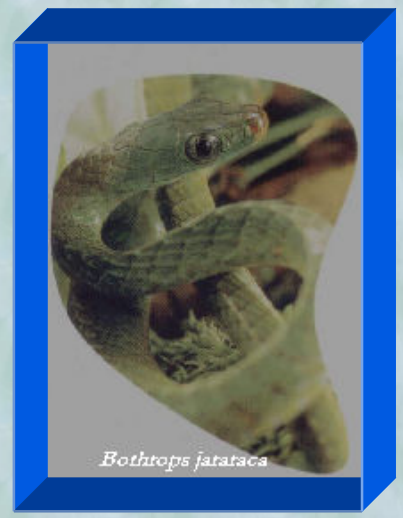
Produtos naturais de...



....cobras & lagartos !

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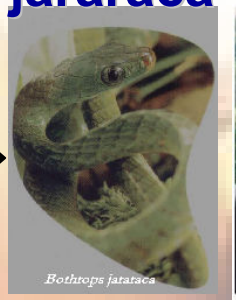
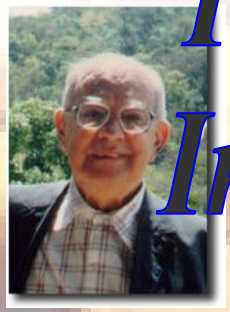
Inovação terapêutica

Fármacos Inteligentes

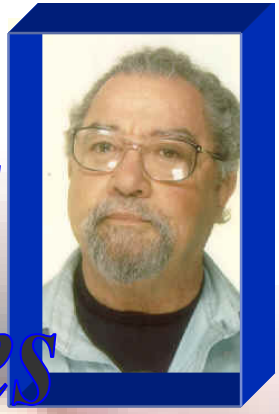
M. O. Rocha e Silva
1910-1983

jararacá





W. T. Beraldo

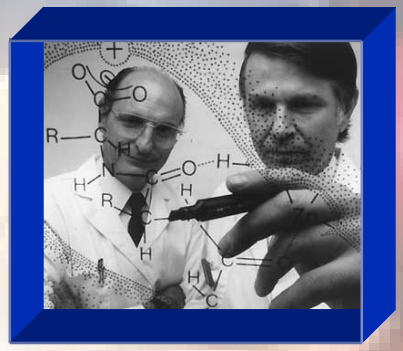


S. H. Ferreira
1934-

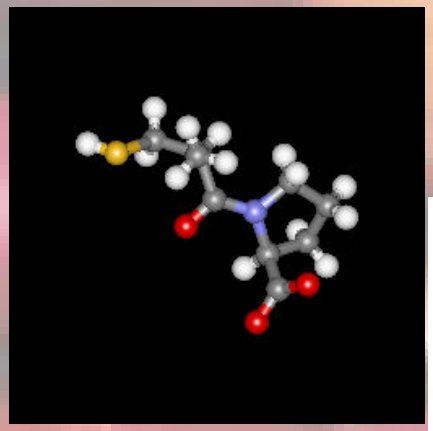
S.H. Ferreira, A Bradykinin-potentiating factor (BFP) present in the venon of *Bothrops jararaca, Brit. J. Pharmacol.* 1965, *24*, 163.

Bradicinina

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

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Sistema Renina-Angiotensina

Angiotensinogênio

fígado

inibidores

renina

Asp-protease

rins

REDUÇÃO DA PRESSÃO ARTERIAL

Angiotensina I

Asp-Arg-Val-Tyr-Ile-His-Pro-Phe—His-Leu-OH

Bradicinina

inibidores

E C A

Zn-metalopeptidase

E C A

inibidores

Feedback Negativo

Angiotensina II

peptídeo inativo

Asp-Arg-Val-Tyr-Ile-His-Pro-Phe- OH

antagonistas

1934 – Harry Goldblat (EUA)
1940 – Bruno Menendez (ARG)
1949 – Maurício Rocha e Silva (BR)
1965 – Sérgio H. Ferreira (BR)

Receptores de Angiotensina II

Vasoconstrição

AUMENTO DA PRESSÃO ARTERIAL

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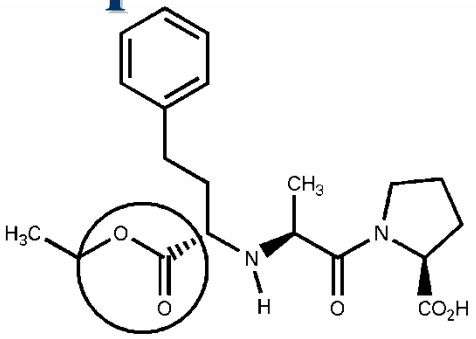
Anti-hipertensivos inibidores da enzima conversora

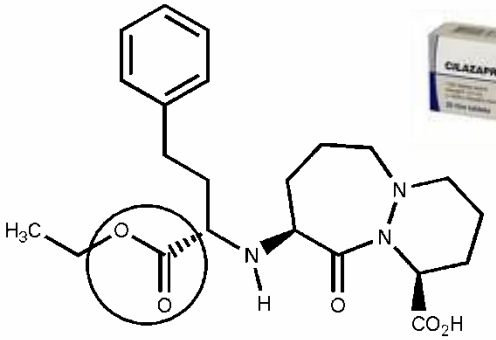


enalapril

MERCK

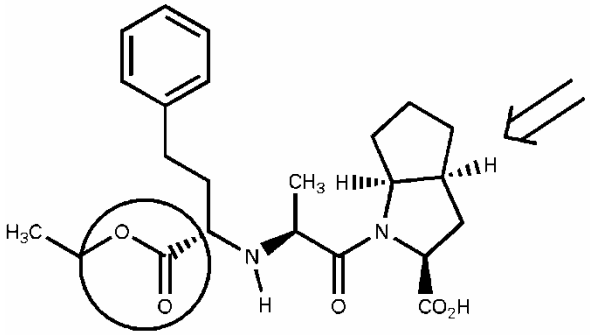
Bristol-Myers Squibb Company

captopril



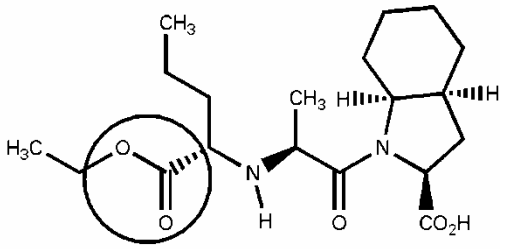
cilazapril

Roche



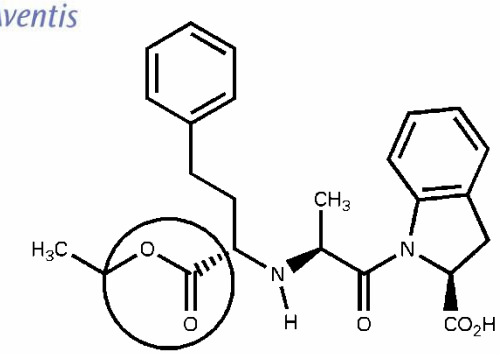
ramipril

Aventis



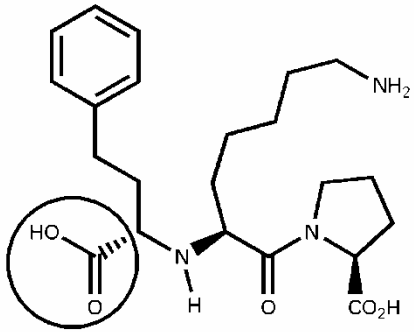
perendopril

SOLVAY



quinapril

Pfizer



lisinopril

AstraZeneca

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Drug development from marine natural products

Tadeusz F. Molinski*, Doralyn S. Dalisay*, Sarah L. Lievens*‡ and Jonel P. Saludes*‡

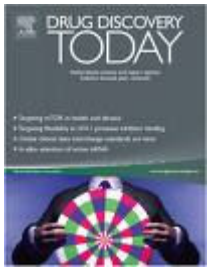
NATURE REVIEWS | DRUG DISCOVERY VOLUME 8 | JANUARY 2009 | 69

REVIEWS Drug Discovery Today • Volume 13, Numbers 19/20 • October 2008

Natural products in drug discovery

Alan L. Harvey

Strathclyde Institute of Pharmacy & Biomedical Sciences, University of Strathclyde, 27 Taylor Street, Glasgow G4 0NR, UK



J. Nat. Prod. **2008**, *71*, 492–496

Efficacy of Selected Natural Products as Therapeutic Agents against Cancer⊥

Sanjeev Banerjee,† Zhiwei Wang,† Mussop Mohammad,‡ Fazlul H. Sarkar,† and Ramzi M. Mohammad*,‡

Department of Pathology and Division of Hematology and Oncology, Barbara Ann Karmanos Cancer Institute, School of Medicine, Wayne State University, Detroit, Michigan 48201

J. Nat. Prod. **2007**, *70*, 461–477

Natural Products as Sources of New Drugs over the Last 25 Years⊥

David J. Newman* and Gordon M. Cragg

Natural Products Branch, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute-Frederick, P.O. Box B, Frederick, Maryland 21702

REVIEW www.rsc.org/npr | Natural Product Reports

The value of natural products to future pharmaceutical discovery

Dwight D. Baker,* Min Chu, Uma Oza and Vineet Rajgarhia†

Nat. Prod. Rep., 2007, **24**, 1225–1244 | 1225

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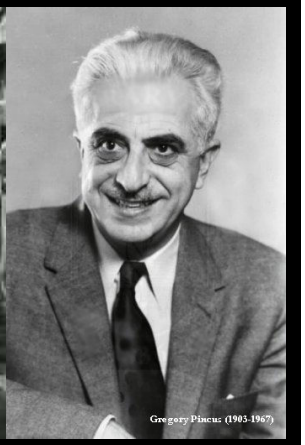
esteróides



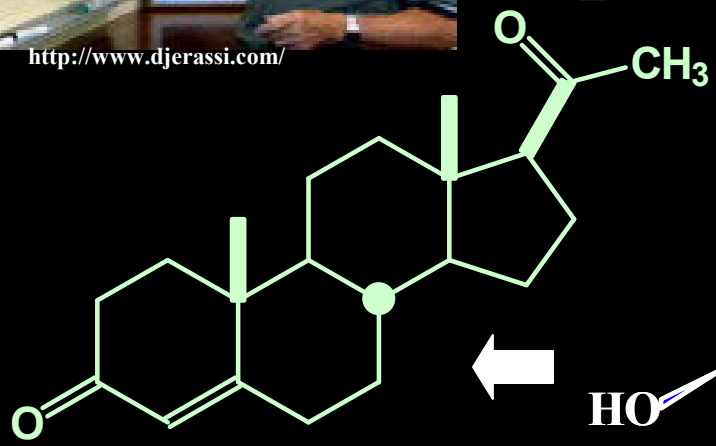
Russell E. Marker & Gregory Pincus

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

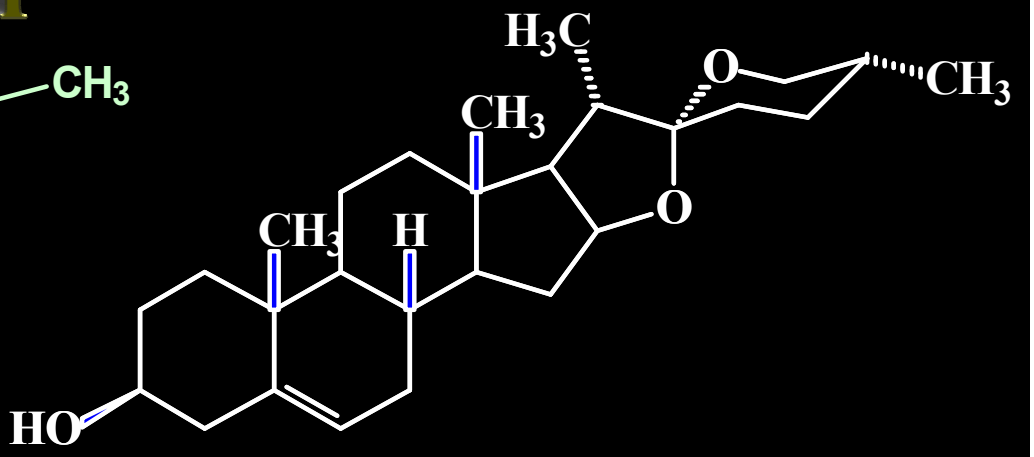
Em 1937 no " Pond Laboratory" da Universidade da Pensilvania, EUA, Marker concluiu a primeira síntese da progesterona a partir da diosgenina

A Pílula Contraceptiva

http://www.djerassi.com/



progesterona



diosgenina

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Contraceptivos

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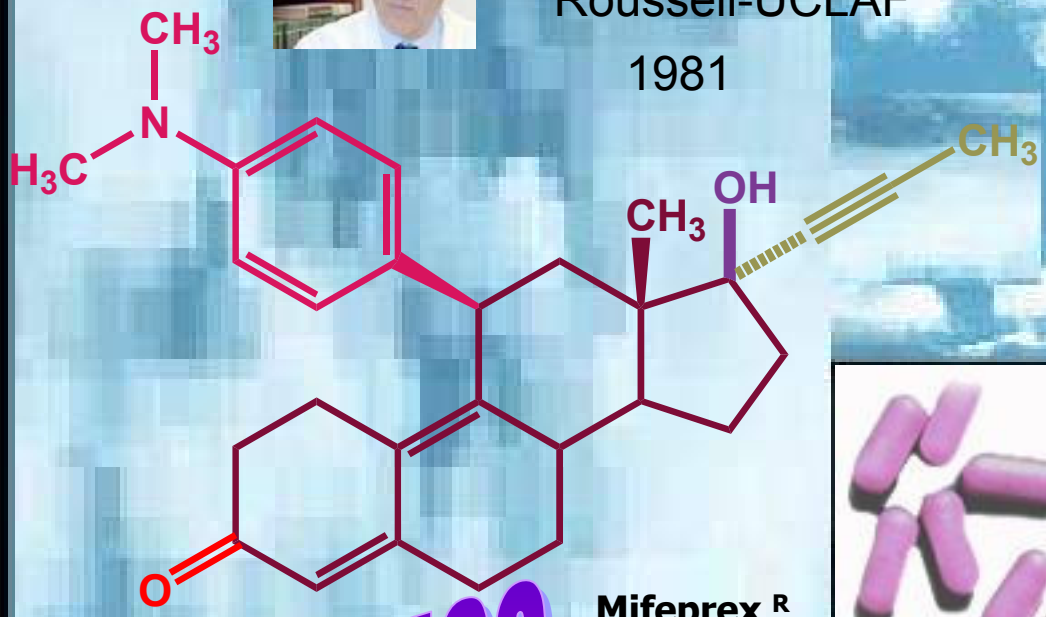
mifepristona

Etienne-Emile Beaulieu
Roussell-UCLAF

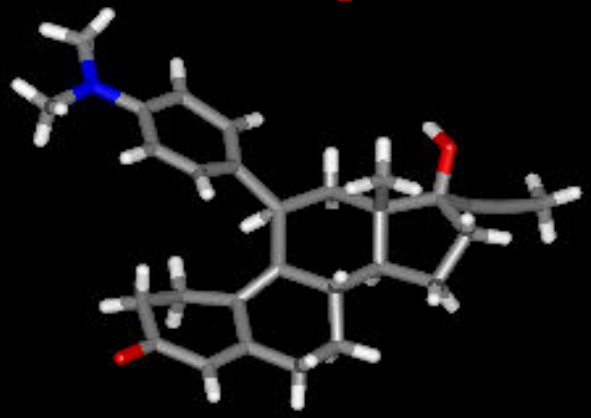
1981



RU 486

Mifeprex R

Mifepristona



Pílula do dia seguinte

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