



O processo de planejamento racional de novos fármacos

MC Noturno

Parte 1

Reunião Regional da SBPC em Boa Vista, RR
19 - 22 de outubro de 2010



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Professor Titular
UFRJ





Conteúdo

DEFINIÇÃO Química Medicinal; os Pioneiros (Ernest Forneau; Alfred Burger); a EVOLUÇÃO cronológica **DA** QUÍMICA Farmacêutica Medicinal; as Ciências *dos* FÁRMACOS e o prêmio **Nobel** (Emil Fischer; Paul Ehrlich; Robert KOCH; *Alexander* Fleming; **Ernest** Chain; Howard FLOREY; George *Hitchings*; Gertrude Belle ELION; *Sir James W. Black*; *bent Samuelsson*; SUNE bergstron; John VANE; A. von Szent-Györgyi; W. N. Haworth; Linus C. Pauling; Arthur Kornberg); os fármacos e suas moléculas, as PIONEIRAS; cronologia da **DESCOBERTA** de fármacos; noções sobre o **PAPEL** dos produtos **NATURAIS** na descoberta de fármacos; como *nascem* os FÁRMACOS; o **PARADIGMA** de Fischer; abordagem fisiológica; os **BIORRECEPTORES**: quantos **são?**; o *modelo* chave-fechadura; α betaS bioquímicos; bioinformática & **QUÍMICA** COMPUTACIONAL; Topografia 3D dos **BIORRECEPTORES**; **SIMILARIDADE** e dissimilaridade no *reconhecimento* MOLECULAR pelo Biorreceptor; as *fases* DA ação dos FÁRMACOS; FASE farmacocinética; *conceito* de grupamento **FARMACOFÓRICO**, *auxofórico* & *toxicofórico*; fármacos, moléculas **INTELIGENTES**; fármacos sintéticos; planejamento **RACIONAL** (propranolol; *Cimetidina*; **SILDENAFILA**; *lodenafila*; *estatinas*); considerações finais: exemplos **DE casa**, **LASSBio- UFRJ** : o início; novo COXIBE, *LASSBio-326*, *LASSBio-445* & *LASSBio-715*; candidato a fármaco cardíaco inovador, **LASSBio-294**; novo composto-protótipo de fármaco anti-asmático, *LASSBio-596*; Agradecimentos.



International Union of Pure & Applied Chemistry

Subcommittee Medicinal Chemistry & Drug Development

www.chem.qmul.ac.uk/iupac/medchem/

IUPAC

<http://www.iupac.org>



Química Medicinal é uma disciplina baseada na química, também envolvendo aspectos e conceitos de ciências biológicas, médicas e farmacêuticas. Está voltada para a invenção, descoberta, desenho, identificação e preparação de compostos bioativos, ao estudo do seu metabolismo, a interpretação molecular de seu modo de ação e à construção de relações entre a estrutura química e a atividade biológica apresentada.

Pure & Appl. Chem., Vol. 70, No. 5, pp. 1129–1143, 1998.
Printed in Great Britain.
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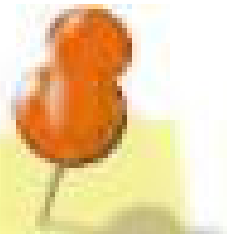
SciELO

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.

Fatos históricos:



Os pioneiros

m e d
Química
Farmacêutica
chem
Medicinal

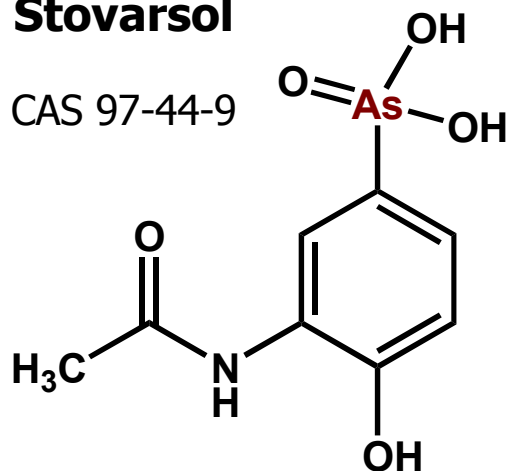
O berço da Química Medicinal



Ernest Fourneau
1872-1949

Stovarsol

CAS 97-44-9



Institut Pasteur (1887)

1911- Laboratoire de Chimie Thérapeutique

Institut Pasteur (Emile Roux)



1911-1944 – J. Tréfouël, Th. Tréfouël,
G. Benoit, D. Bovet, F. Nitti

Prontosil rubrum
(sulfonamidas)

Curare: SAR

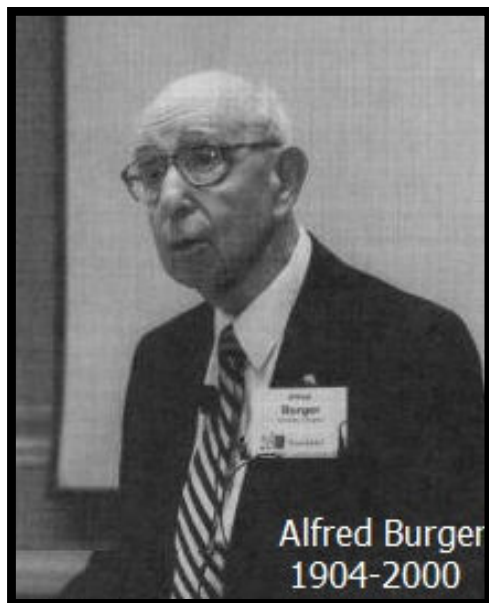


Daniel Bovet
1907-1992

Prêmio Nobel de
Fisiologia/Medicina
1957



J-P Fourneau, « Ernest Fourneau fondateur de la Chimie Pharmaceutique française », *Revue de l'Histoire de la Pharmacie*, t.XXXIV, n° 275, 335-355



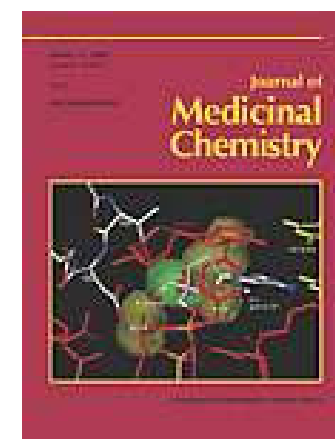
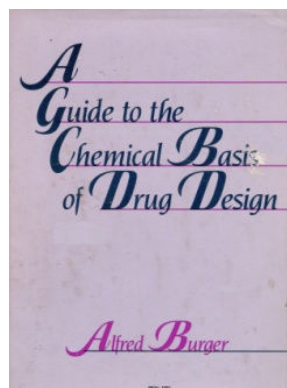
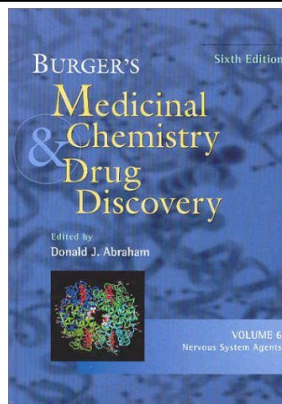
Química Medicinal

Prof. Alfred Burger

(1904-2000)

University of Virginia

EUA

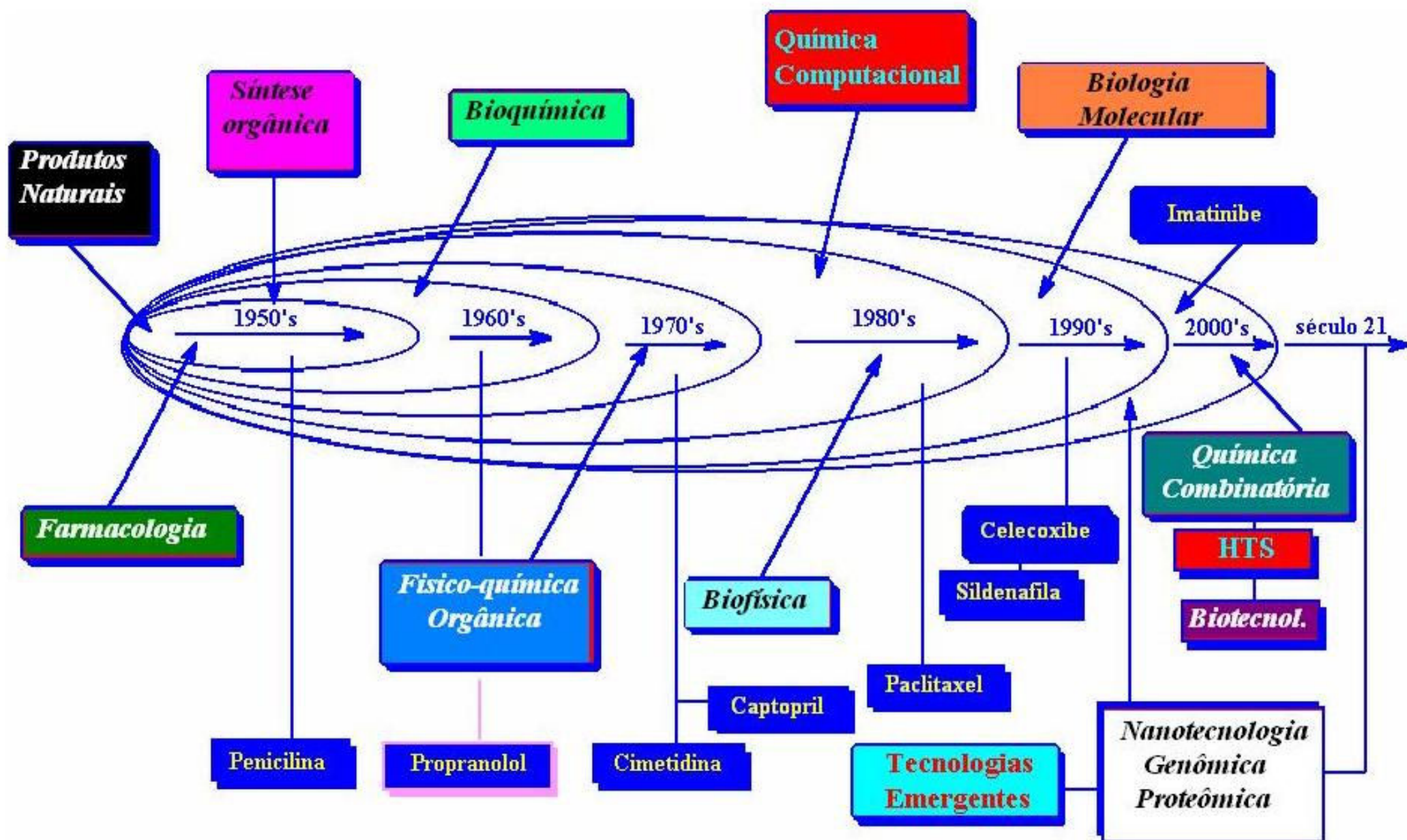


1958 – cria o Journal of the Medicinal and Pharmaceutical Chemistry → depois Journal of Medicinal Chemistry

“An Editor’s Commentary on the Birth of a Journal”
J. Med. Chem. **1991**, *34*, 2-6

1978 - GlaxoSmithKline cria com ACS o “Alfred Burger Award” em Química Medicinal
T. Y. Shen - inventor da indometacina

A evolução cronológica da Química Farmacêutica Medicinal



A química
dos
fármacos
e o prêmio
Nobel





Os fármacos e o prêmio Nobel



Emil Fischer

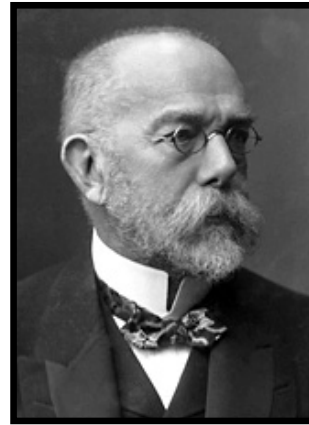
1852-1919

1902



Lock & Key

“La vie empeche la vie”



Robert Koch

1843-1910

1905



P. Ehrlich, *Chemotherapeutics: scientific principles, methods and results*. *Lancet* 1913, 2, 445

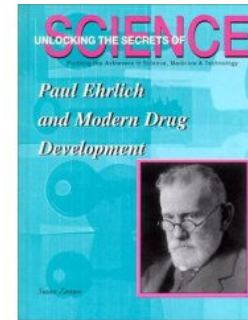
One-molecule, one-target paradigm



Paul Ehrlich

1854-1915

1908



Gerard Domagk

1895-1964

1939



Selman Waksman

1888-1973

1952

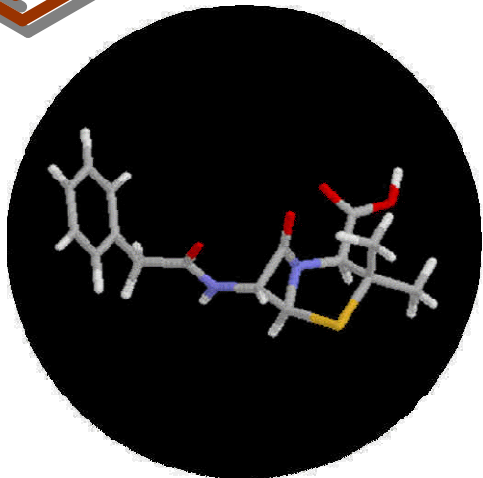
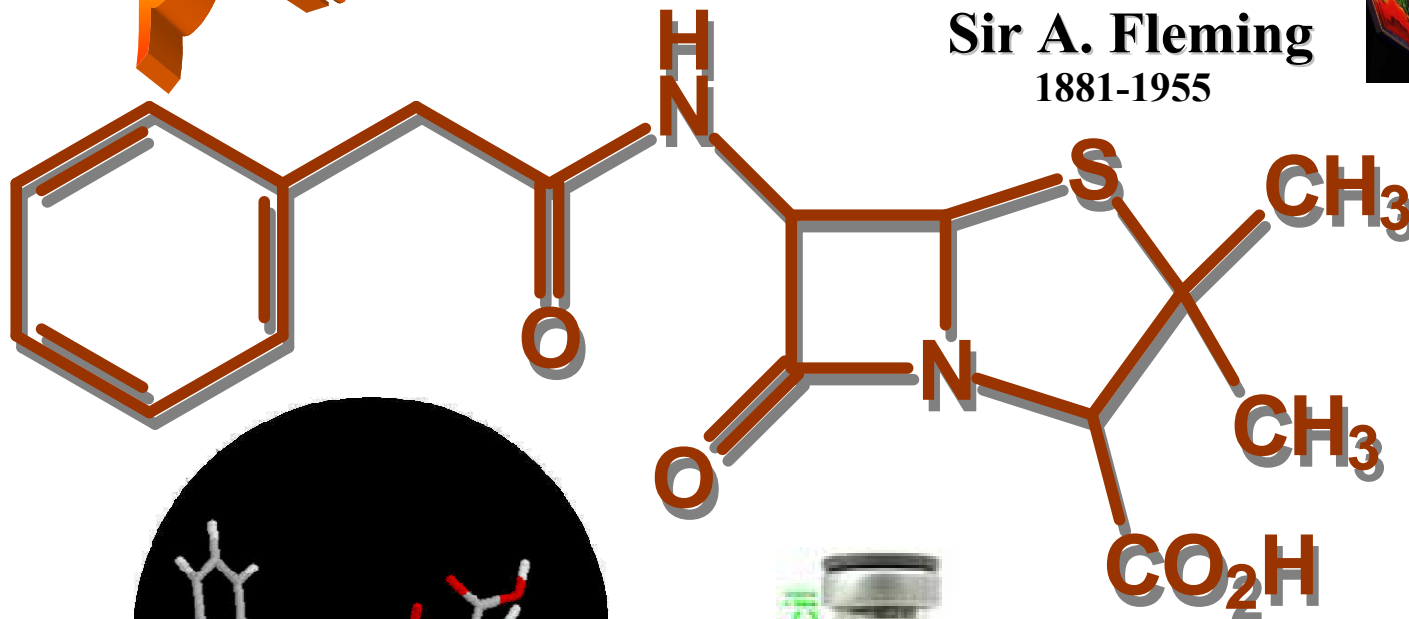


Antibioticoterapia

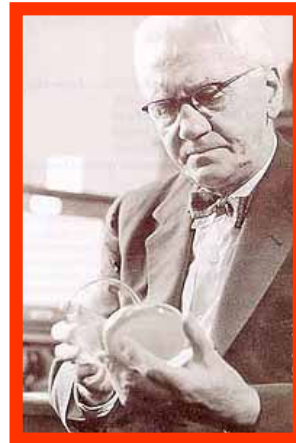
Penicilinas

Moléculas Salva-vidas

β -lactâmicos



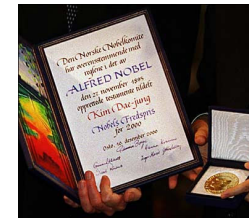
Sir A. Fleming
1881-1955



Sir H. W. Florey
1898-1968



E. B. Chain
1906-1979



1945



Penicillium notatum

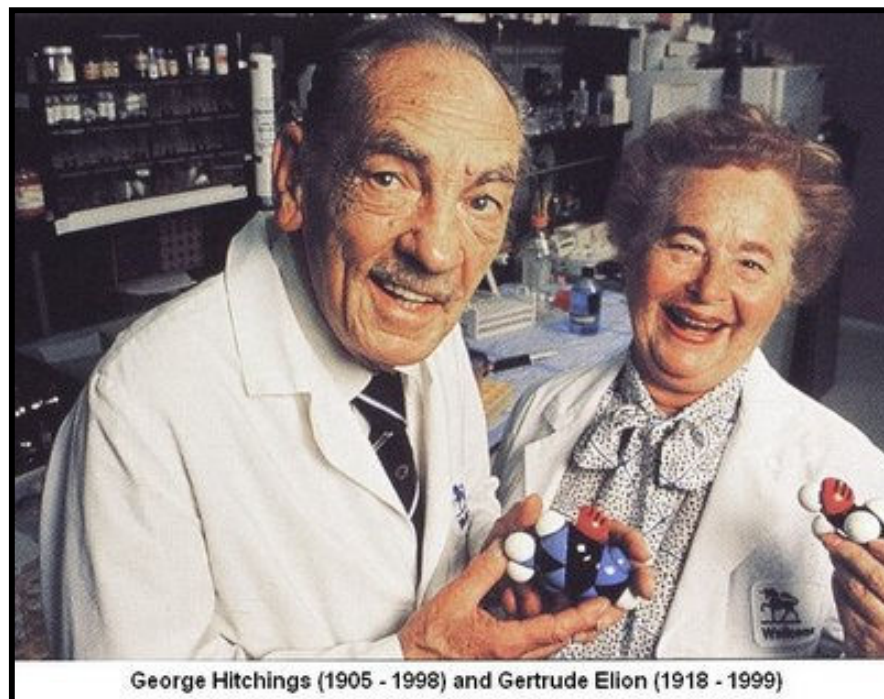
serendipidade



“for their discoveries of important principles for drug treatment”



1988 – James W. Black
(1924-2009)



George Hitchings (1905 - 1998) and Gertrude Elion (1918 - 1999)

1988



Inter-alia: Propranolol, cimetidina, *azatioprina*,
alopurinol, trimetoprim, aciclovir (AZT)



Os fármacos e o Nobel !



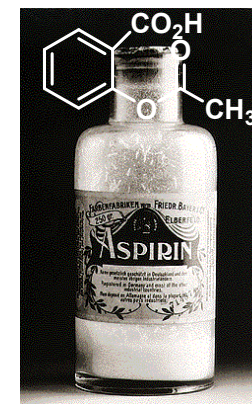
1982 – S. B. Bergstöm



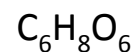
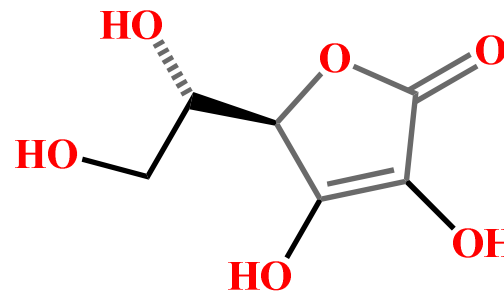
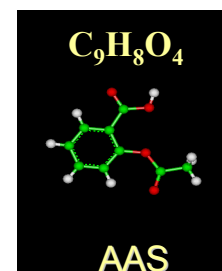
1982 – B. I. Samuelsson



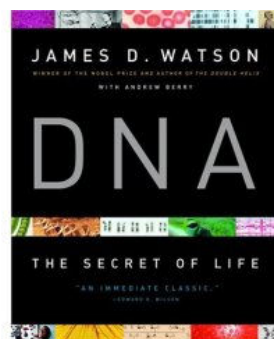
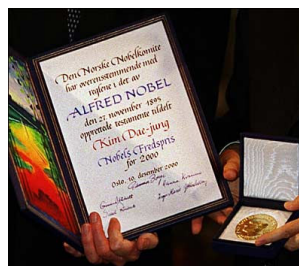
1982 – J. R. Vane



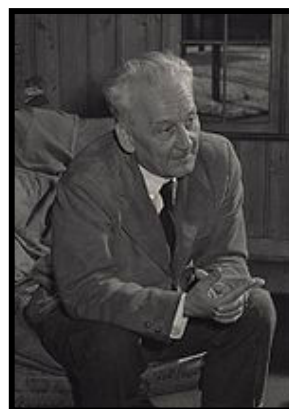
1982 – AAS



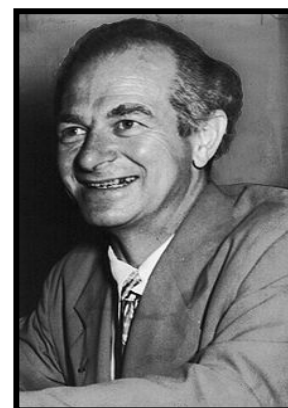
1937 – Vit C



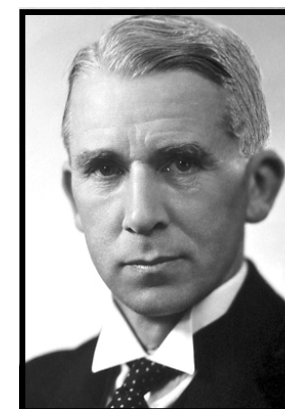
• 160 pesquisadores ganharam o Prêmio Nobel de Química desde 1901



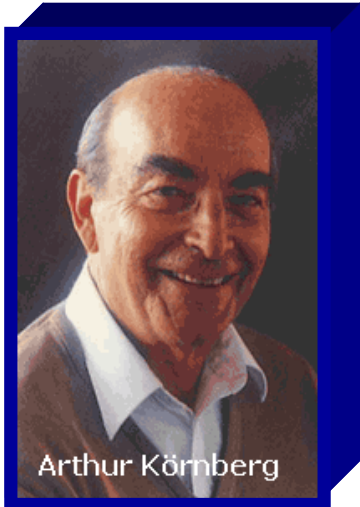
1937 – A. von Szent-Györgyi



1954 & 1962 – L. C. Pauling



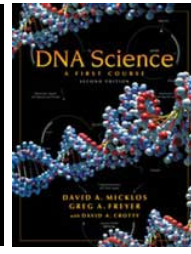
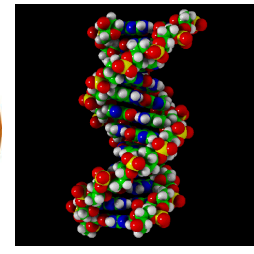
1937 – W. N. Haworth



Arthur Kornberg

Nobel Prize, 1959

“for their discovery of the mechanisms in the biological synthesis of RNA and DNA”



“We have the paradox of the two cultures,

chemistry and biology,

growing further apart even as they discover more common ground...

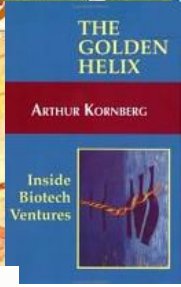
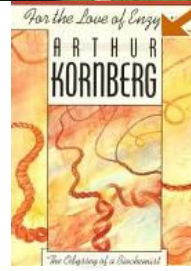
Pharmaceutical chemistry was until recently the bastion of organic chemistry...

in the search for alternative or superior drugs for the treatment of various diseases.”

Interdisciplinaridade



*Arthur Kornberg
Biochemistry 1987, 26, 6888*





m e d
Química Farmacêutica Medicinal
chem

Farmacognosia
Biofísica Bioquímica Genética
Parasitologia Síntese Orgânica Enzimologia
Química Geral Espectroscopia Computação Física
Bioinformática Toxicologia Difração R-X Fittoquímica
Farmacotécnica Química Analítica Físico-Química
Biologia estrutural Química Geral Química Orgânica
Bioinorgânica Química Inorgânica Fisiologia
Bioestatística Microbiologia Biologia molecular
Farmacogenômica Cálculo Química Computacional
Bioorgânica Farmacologia

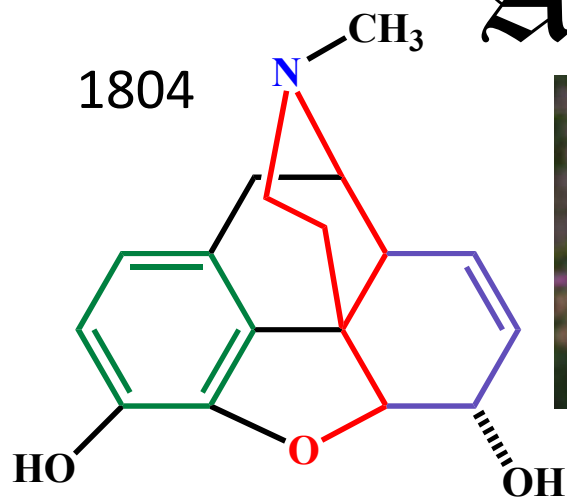


*Os fármacos
do início...*





As moléculas pioneiras...



morfina
 $C_{17}H_{19}NO_3$

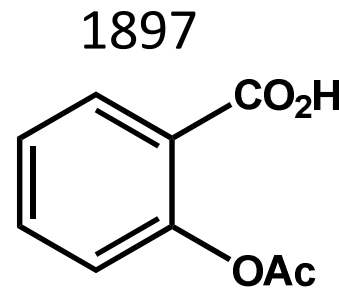
Friedrich W. A. Sertürner
1783- 1841



Henry How
1853 – *Un. Glasgow*



Sir Robert Robinson
1886-1975
Nobel 1947

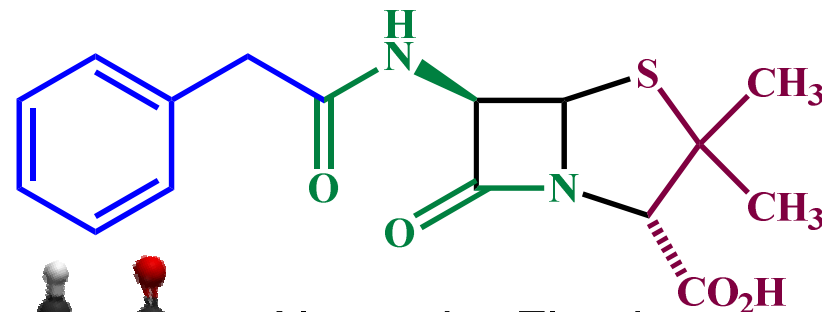


AAS
 $C_9H_8O_4$

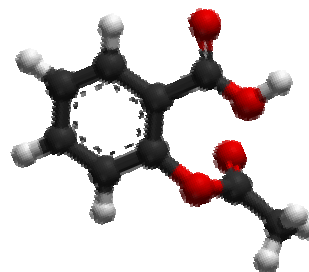
Felix Hoffman
1868- 1946



1929
penicilina
 $C_{16}H_{18}N_2O_4S$



Alexander Fleming
1881-1955
Nobel 1945



Acetylsalicylic Acid



Library of Congress

O papel dos produtos naturais





OS PRODUTOS NATURAIS e a Descoberta de NOVOS FÁRMACOS

lipstatina

paclitaxel



camptotecina

compactina

epibatidina

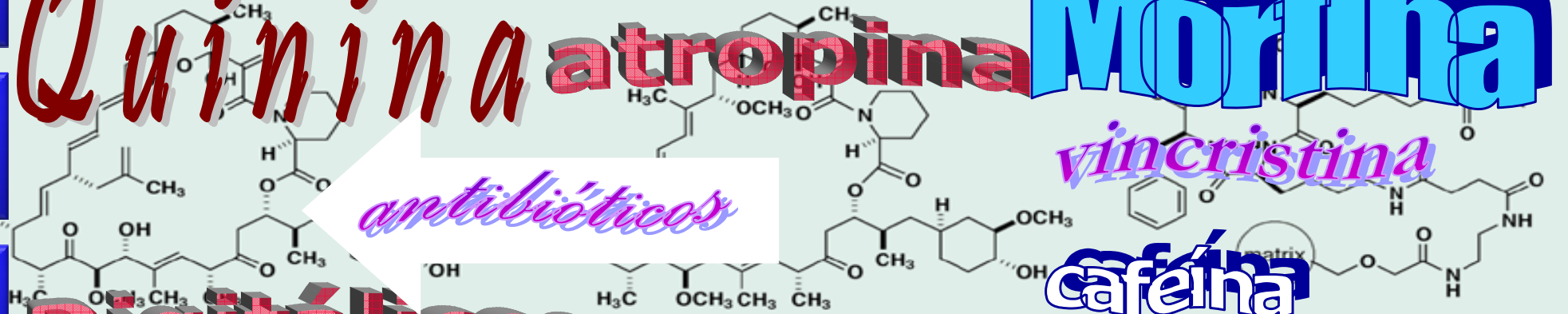
artemisinina

Prototipo Natural

Quinina

atropina

Morfina



antibióticos

Digitálicos

Vincristina

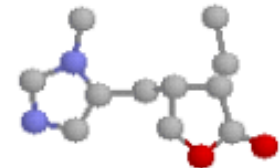
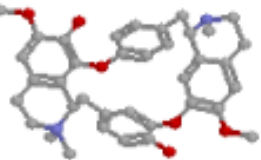
Penicilina

escopolamina

papaverina

SMALL MOLECULE PROBES
Colchicine, a probe of tubulin; spidamine, used to study glutamate receptor function; reserpine, used to discover the neuroendocrine dopaminergic system; phorbol used to study protein kinase C; pioglitazone, a peroxisome proliferator-activated receptor agonist; MK-886, used to study the physiological functions of the metabotropic glutamate receptor; 506BD, a probe of plant growth-promoting action; dimerizer (methoxyphenol), a variant of rapamycin that, by chemical modification, gained the ability to control proximal relationships between cells and animals; , a probe of the nutrient-response signaling network and of the proteins FRAP; K-trap affinity reagent (lysine derivative of trapoxin), used to discover HDAC1.

A importância dos produtos naturais



Hipocrátes ← 460-377 AC

Galeno ← 130-200 DC

Paracelsus ← 1493-1541

Fourcroy ← 1755-1809

C. Lineu ← 1753

F.W. Setürner ← 1783-1841

Pierre J. Pelletier ← 1788-1842

François Magendie ← 1783-1855

Claude Bernard ← 1813-1878

Louis Pasteur ← 1822-1895

Charles F. Gerhardt ← 1853

Hermann Kolbe ← 1874

Felix Hoffmann ← 1868-1946

cocaína ← 1860

AAS ← 1899

pilocarpina ← 1900

digitálicos ← 1905



P
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1925 →

morfina



1941 →

penicilina, cloroquina

1945 →

relaxantes musculares

1948 →

clortetraciclina

1950 →

Watson & Crick (DNA)

1951 →

esteróides

1953 →

reserpina

1964 →

zidovudina

1967 →

rifampicina



1970 →

NCI (EUA)

1971 →

Wall & Wani: *Taxus sp.*

1975 →

**Wall & Wani:
*Camptotheca sp.***

1991 →

estatinas

1993 →

Taxol[®]

2002 →

galantamina

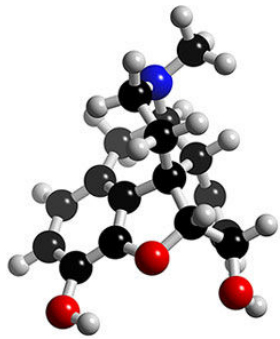


2007 →

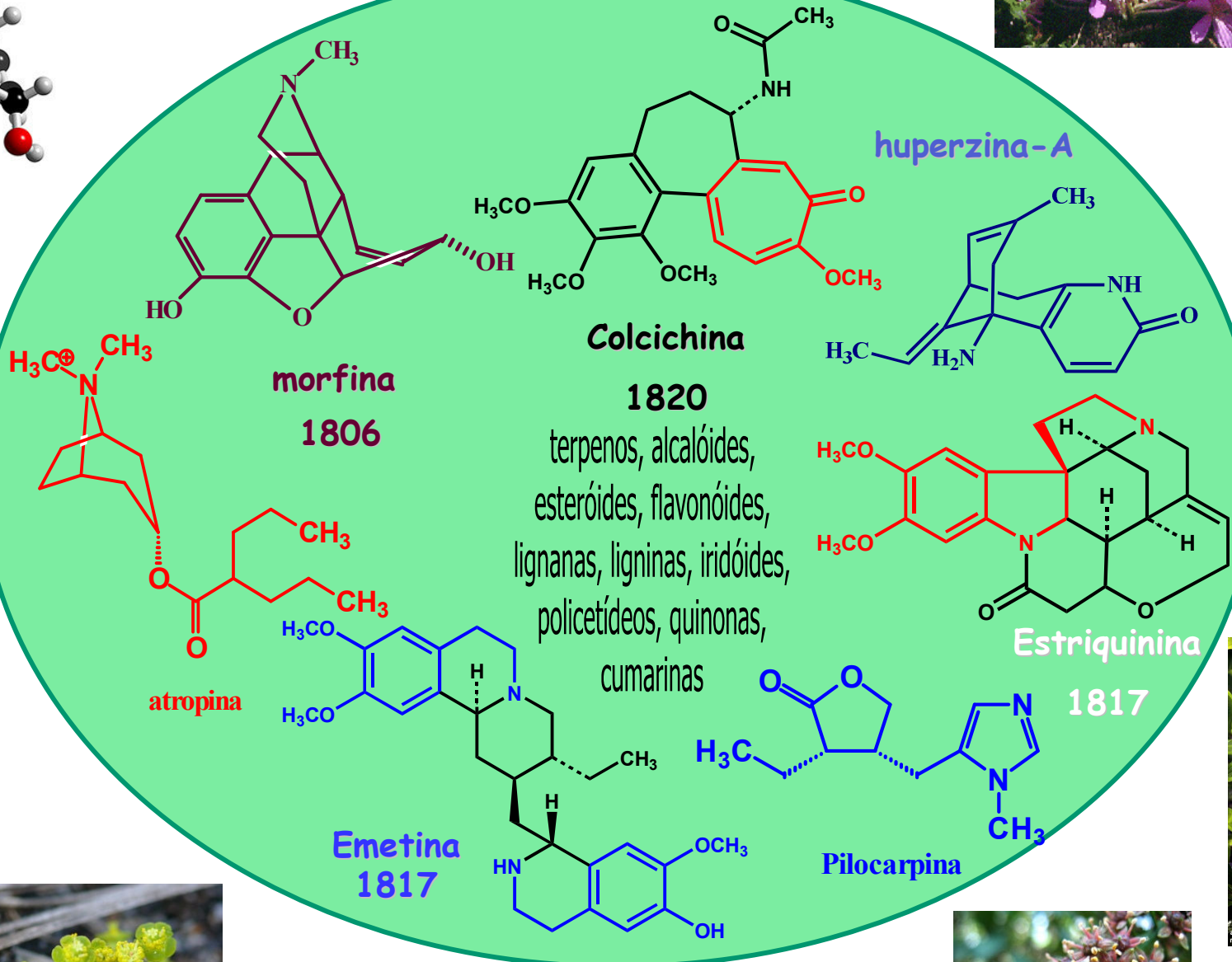
epotilonas

2009 →

ziconotido



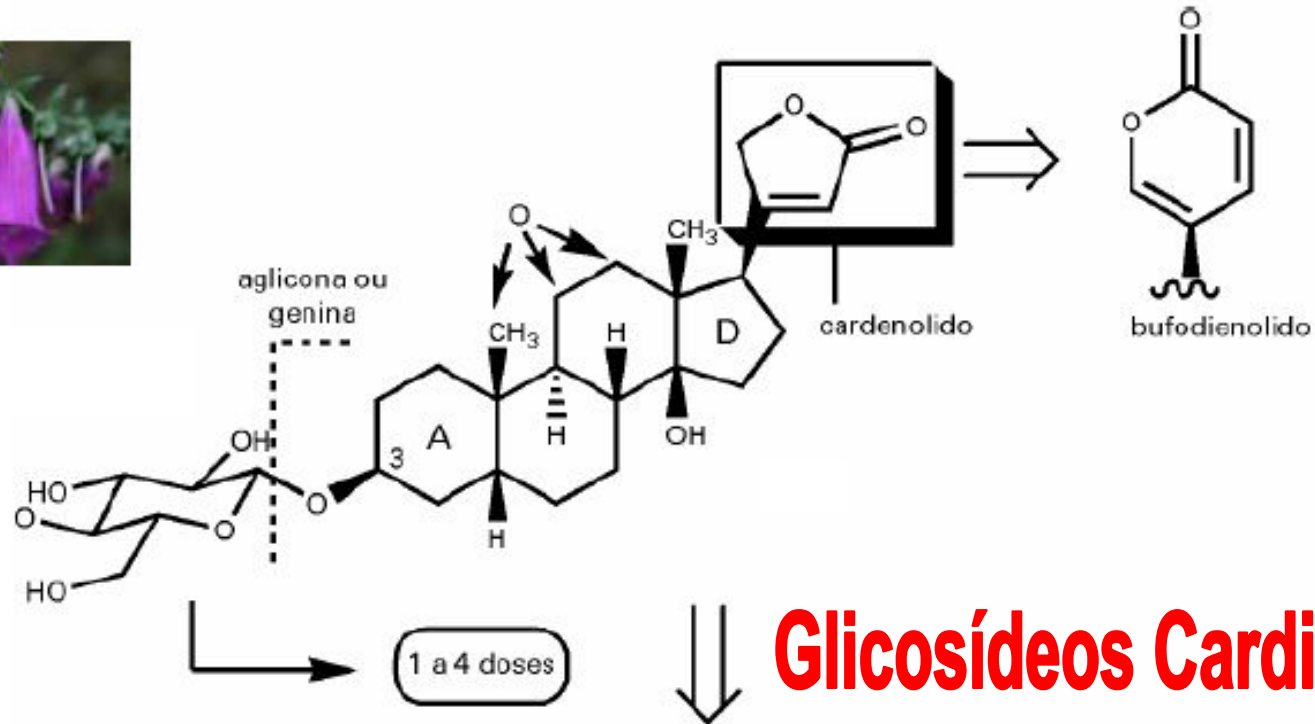
Quimiodiversidade



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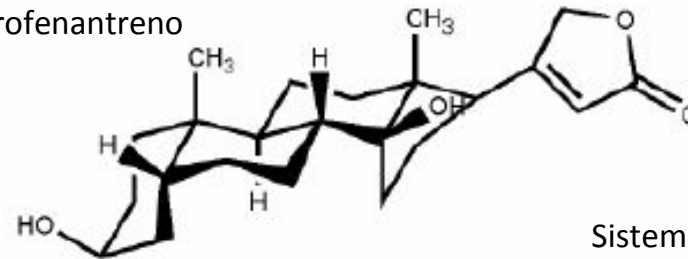
O decano dos fármacos



Glicosídeos Cardiotônicos

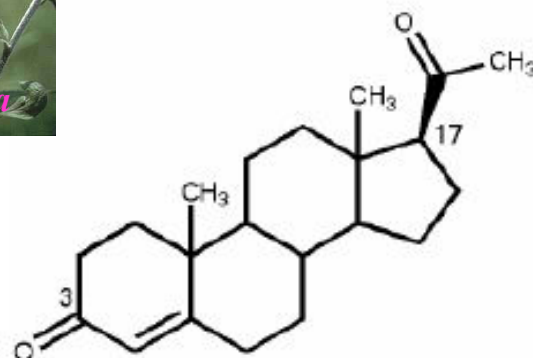


ciclopentanoperidrofenantreno

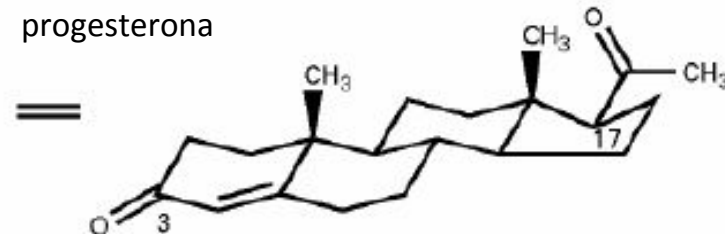


Sistema A/B-cis; B/C-trans; C/D-cis

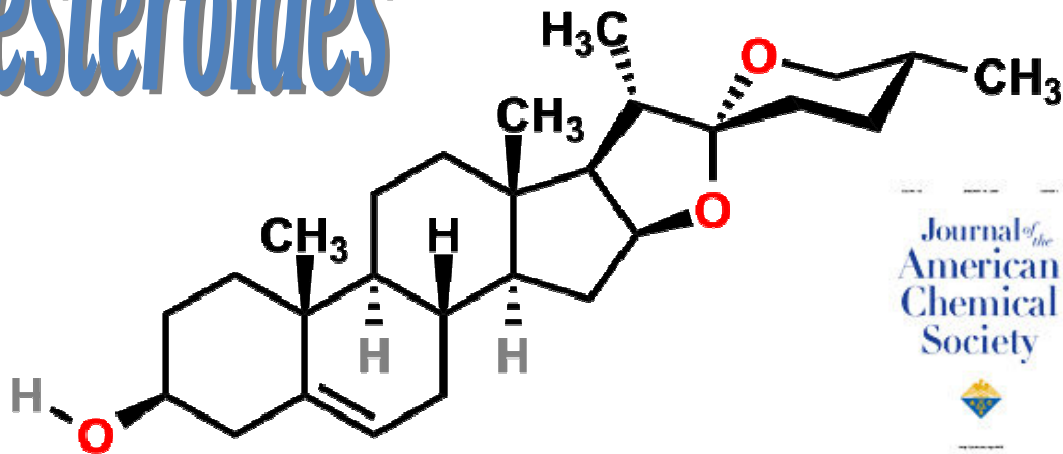
Sistema A/B-trans; B/C-trans; C/D-trans



progesterona



esteróides



diosgenina

Journal of the
American
Chemical
Society



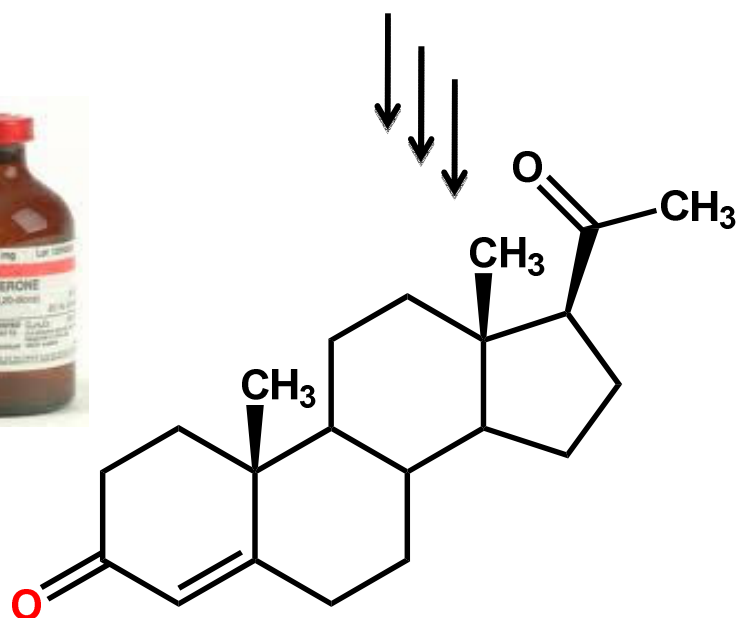
Laboratorios Syntex SA



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).



progesterona

A Pilula Contraceptiva



Carl Djerassi

Contraceptivos



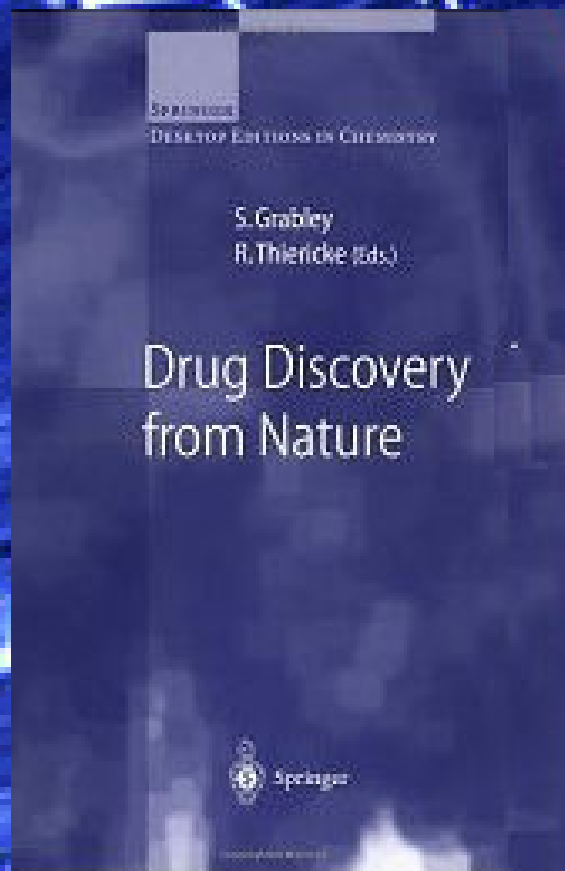


Patrimônio genético brasileiro



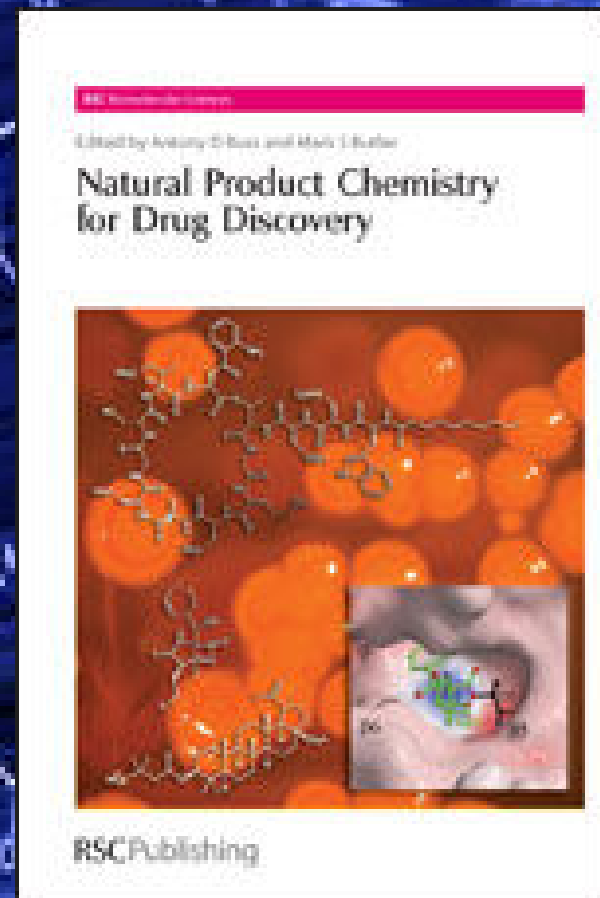


A corrida por novas moléculas...



Ewan J T Chrystal (Editor),
Stephen K Wrigley (Editor),
Robert Thomas (Editor),
Neville Nicholson (Editor),
Martin Hayes (Editor)

RSC



Antony D Buss (Editor)



Curare

Fármaco dos Índios



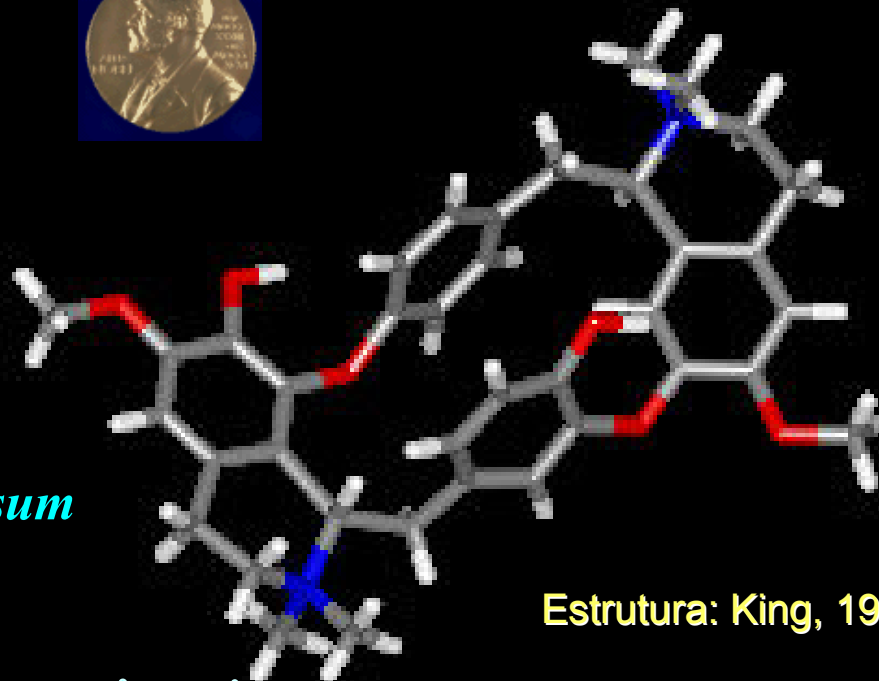
Institute Pasteur
Claude Bernard (1851)



1947 - Daniel Bovet
Institute Pasteur, FR/
Inst. Superior de Saúde
Roma, IT
Prêmio Nobel 1957



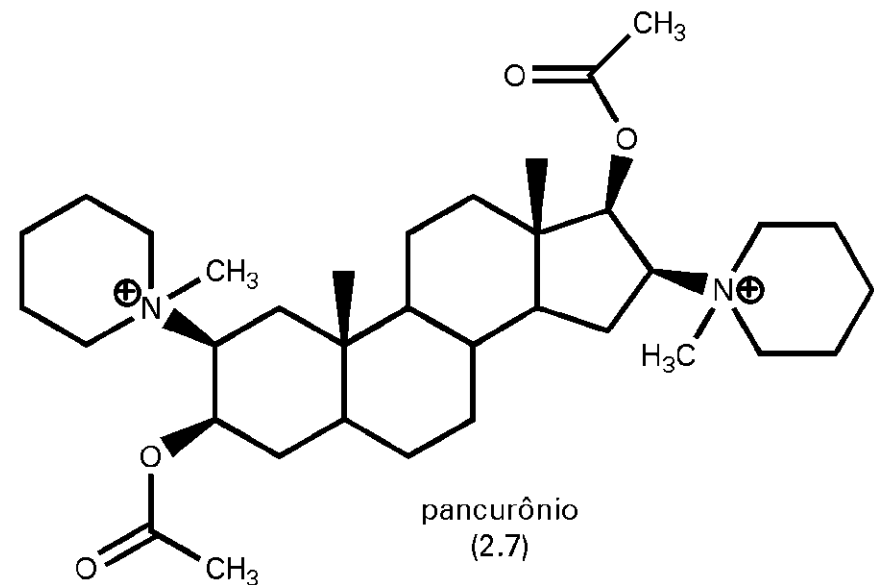
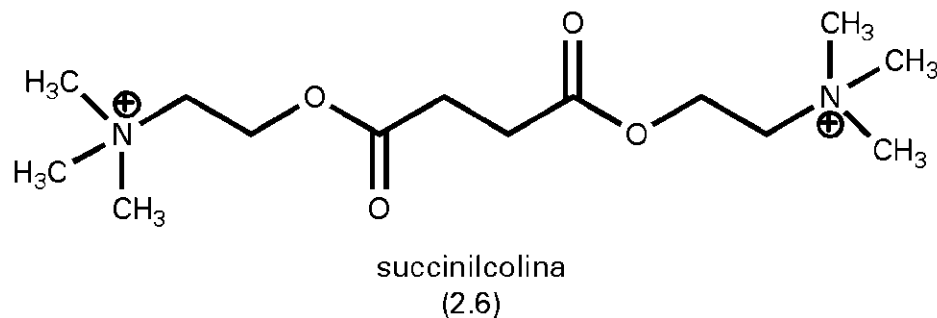
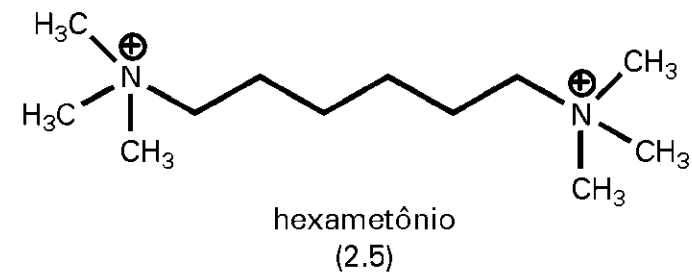
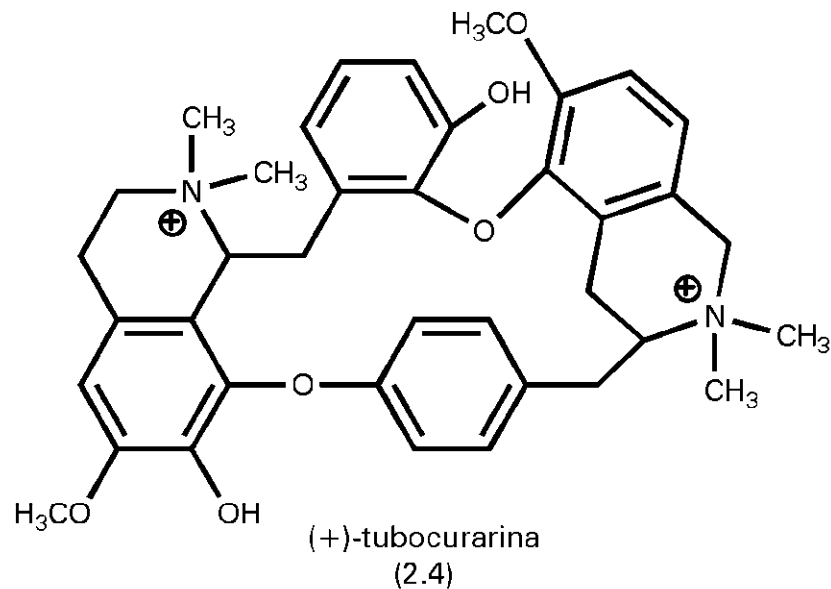
Chondrodendron tomentosum
Loganiaceae
(urari)



d-tubocurarina

Estrutura: King, 1935

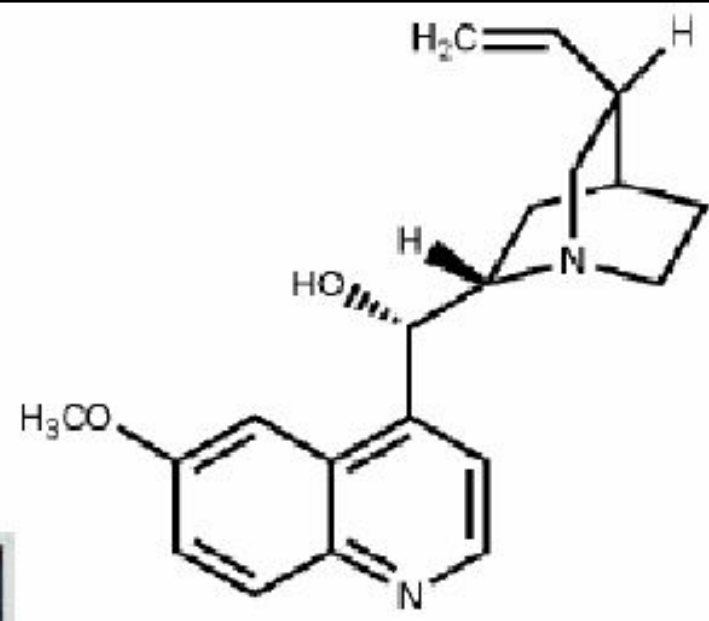
Bloqueadores ganglionares



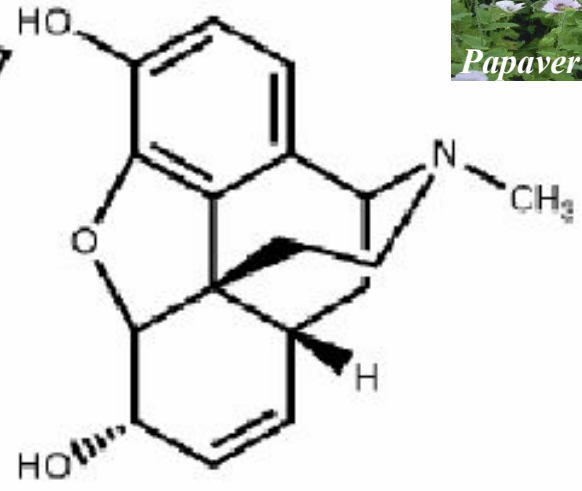
Uma classe terapêutica inovadora



Cinchona officinalis



quinina



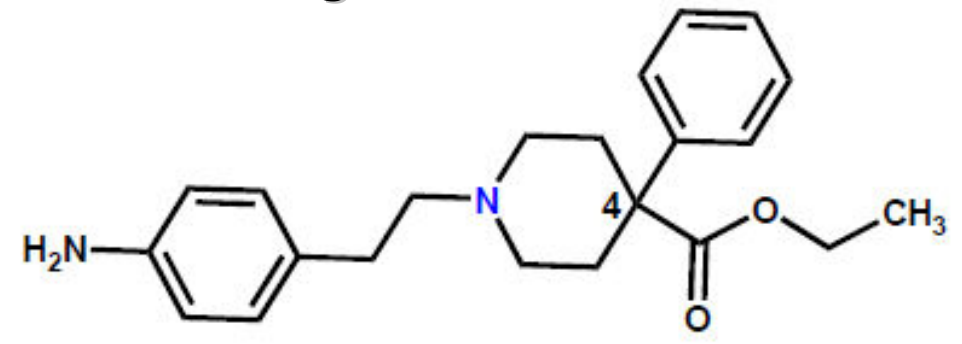
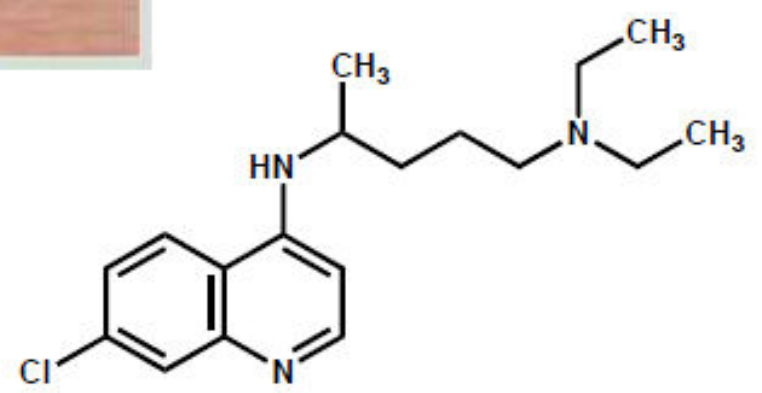
morfina



Papaver somniferum



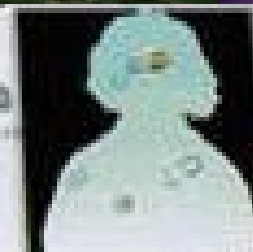
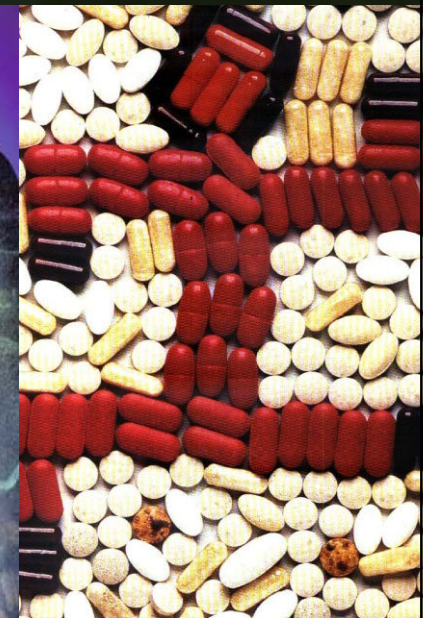
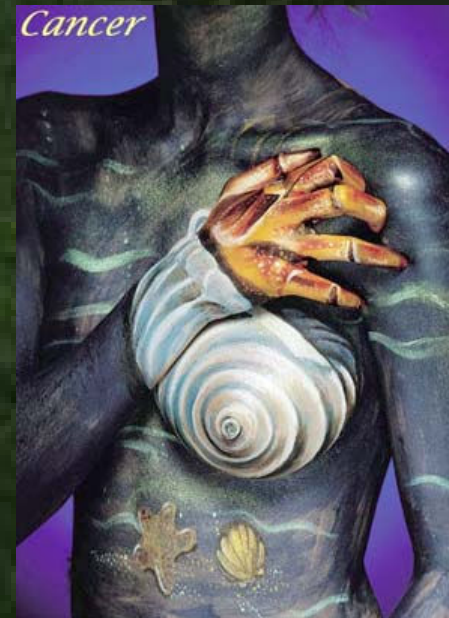
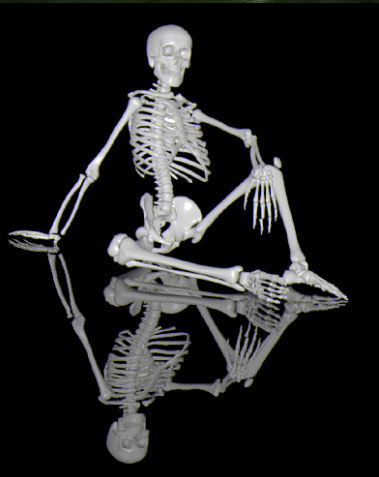
Alcalóides = alcalinos = bases nitrogenadas naturais



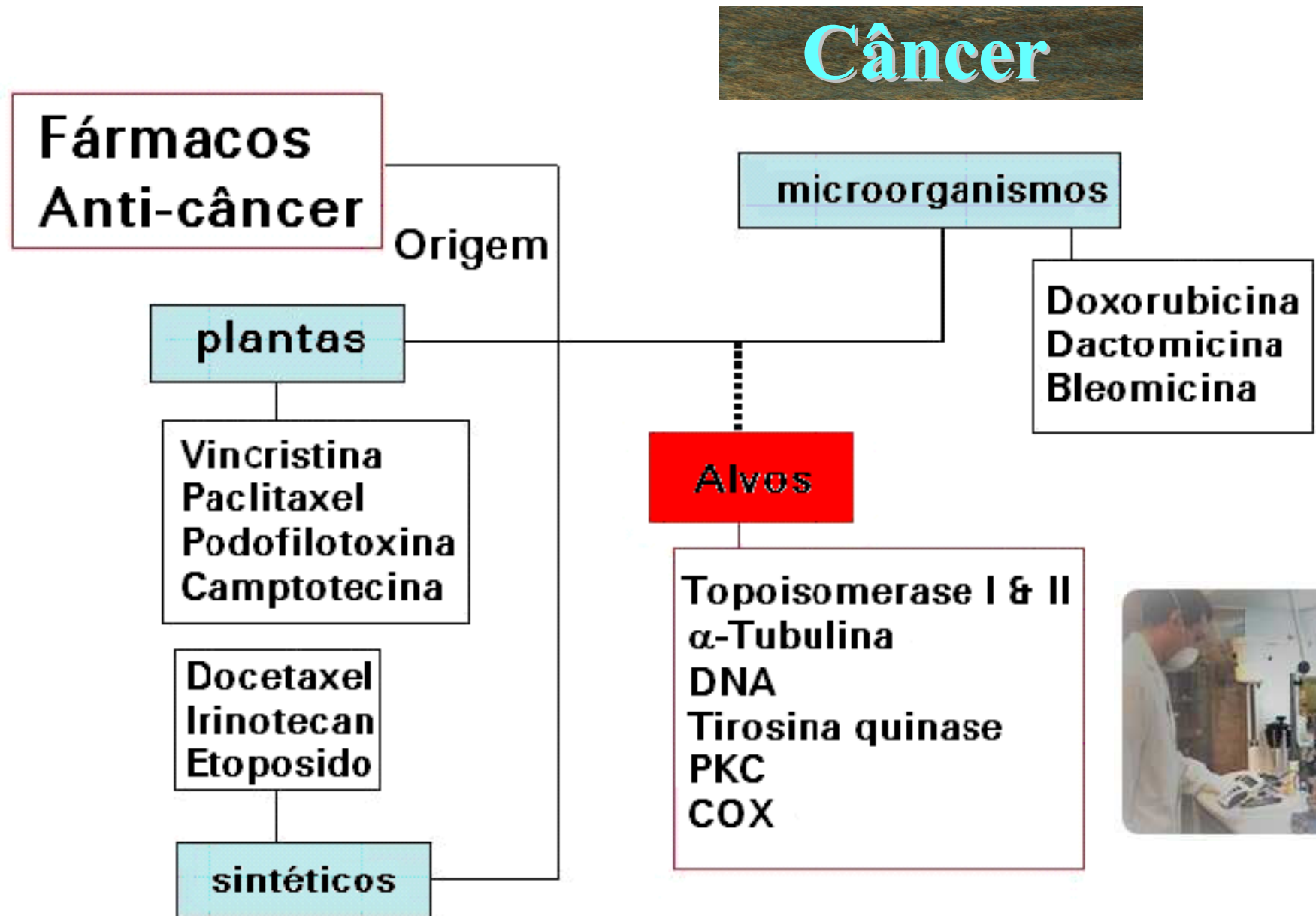
Quimioterapia do Câncer

Produtos naturais

Classes químicas
Mecanismo de ação
Protótipos naturais
Inovação terapêutica
Quimiodiversidade



Produtos naturais anti-câncer





Câncer

NATIONAL
CANCER
INSTITUTE



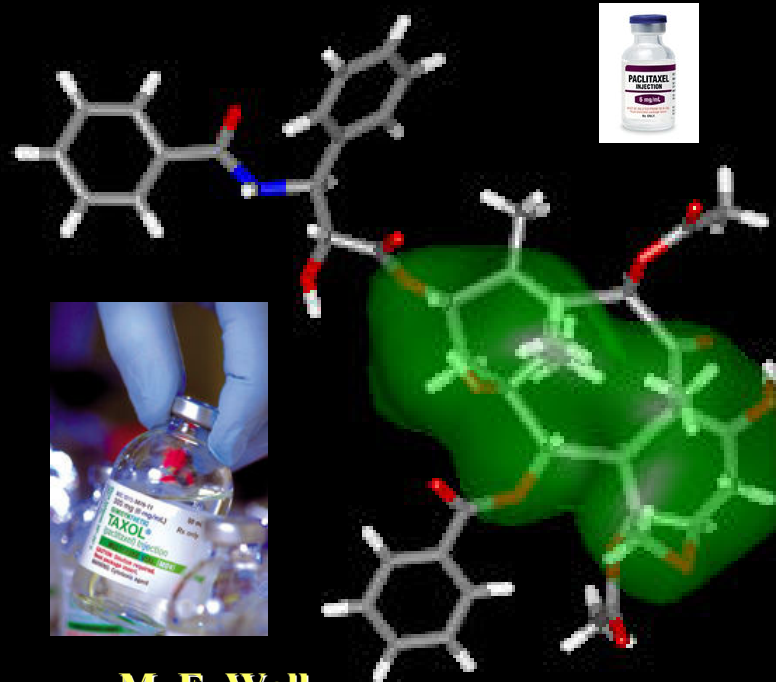
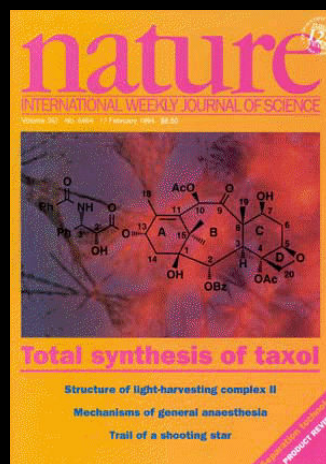
Paclitaxel

Taxol[®]

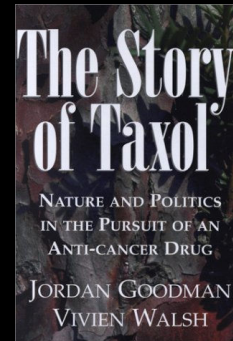
M. C. Wani *et al.*, J. Am. Chem. Soc. 1971, 93, 2325
Res. Triangle Park, 1967



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

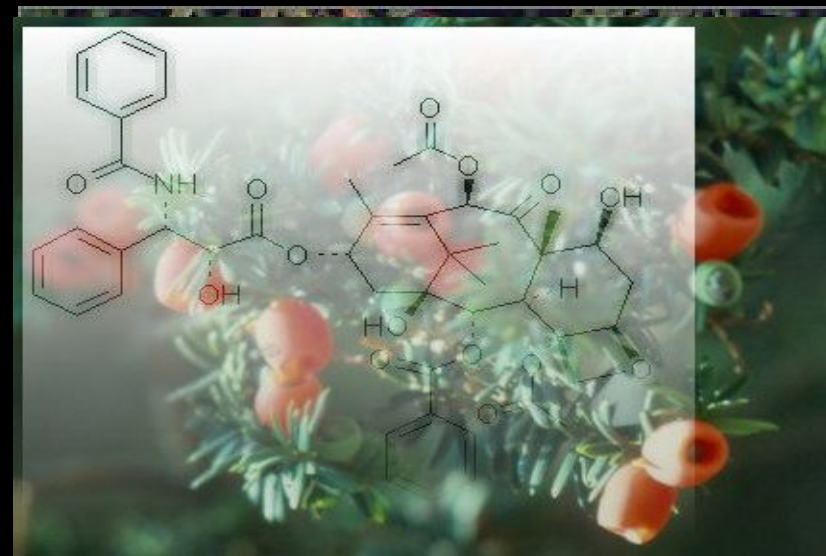


M. E. Wall,
"Chronicles of Drug Discovery",
D. Lednicer, vol.3, ACS, 1993,
pp. 327-348



TAXOL[®]
Science and
Applications

Edited by
Matthew Saffness

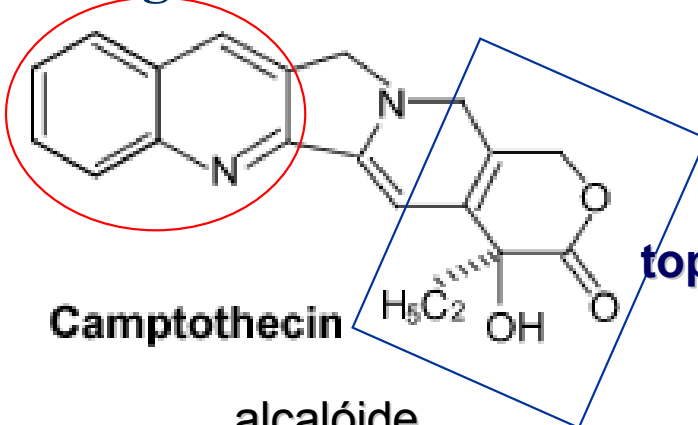


Taxus bacatta



Molécula "selvagem"

Câncer



Inibidor de topoisomerase-1

Camptothecin

alcalóide

quinolínico de biossíntese mista

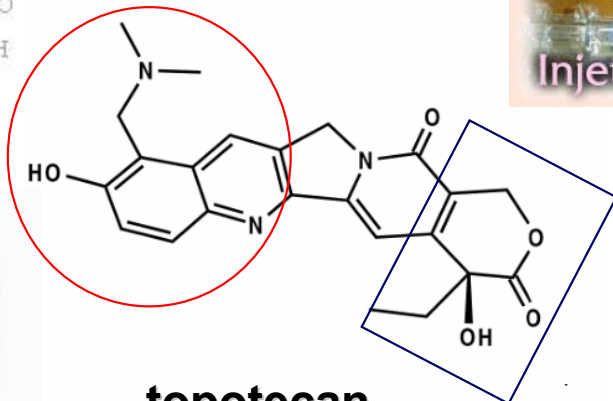


Camptotheca acuminata

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"



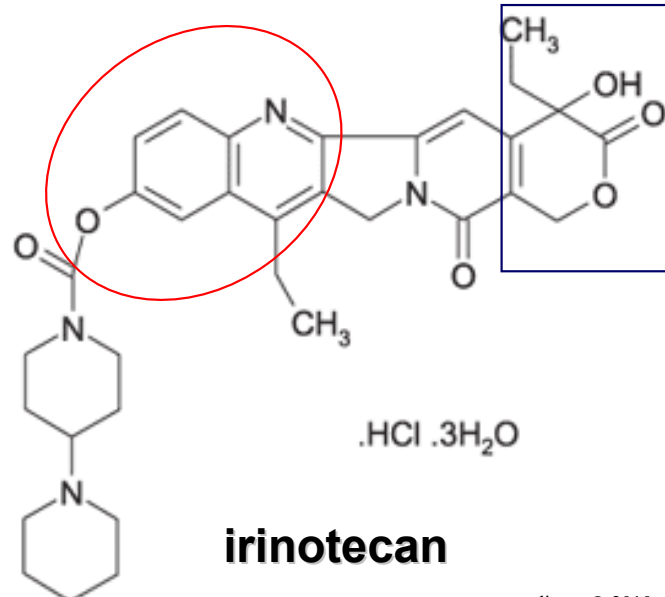
topotecan



Injetável



NDC 0009-7529-01 5 mL Vial
CAMPTOSAR
Injection
irinotecan hydrochloride injection
20 mg/mL
(on basis of trihydrate)
Caution: Federal law prohibits dispensing without prescription.
Warning: For intravenous use only—must be diluted before use.
Pharmacia & Upjohn



irinotecan

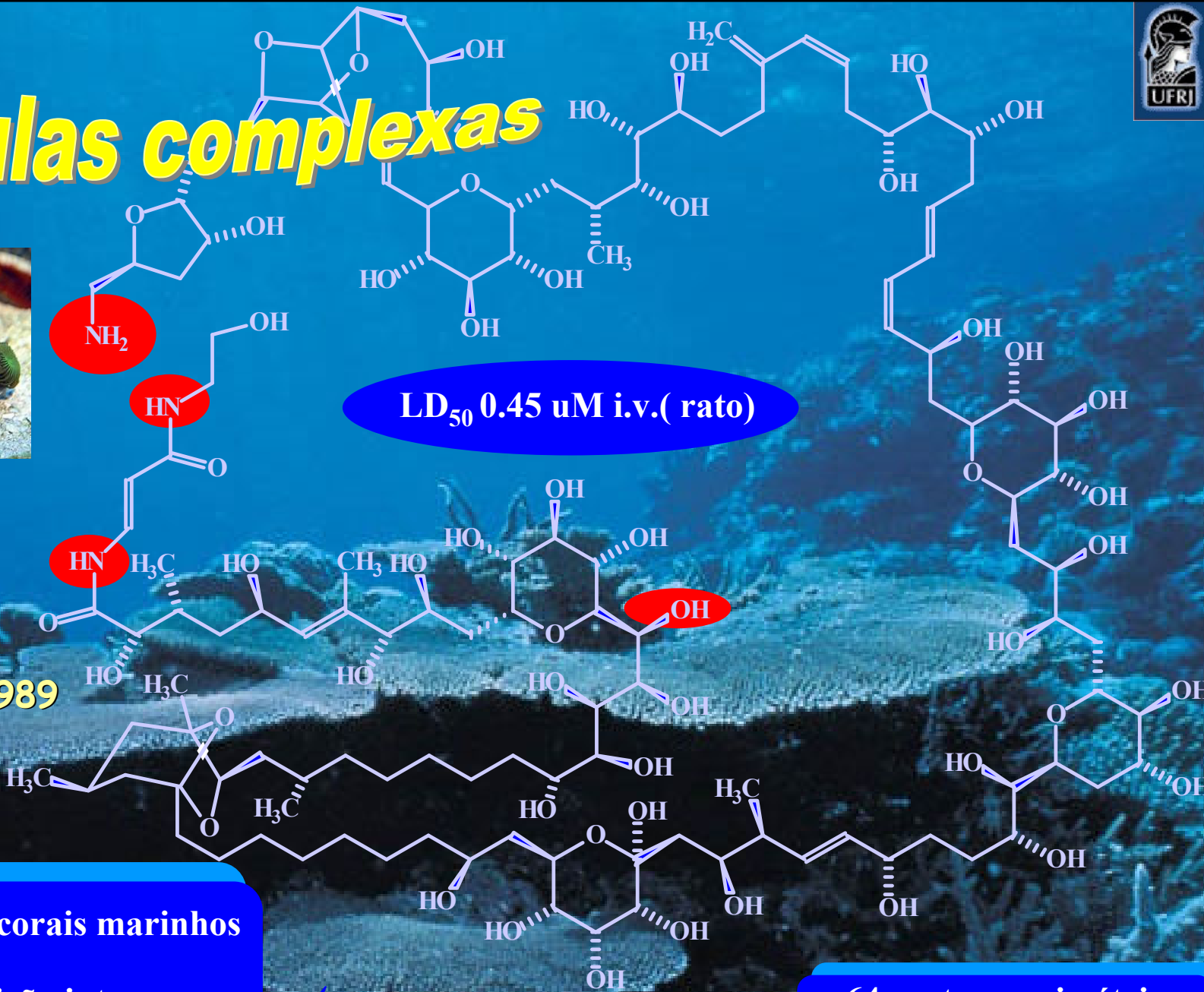
.HCl .3H₂O



Moléculas complexas



Y. Kishi *et al.*, 1989



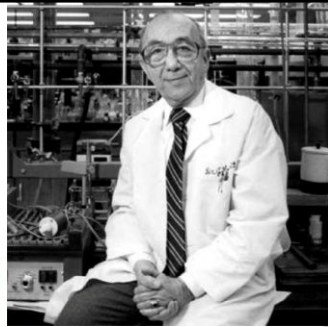
LD₅₀ 0.45 µM i.v. (rato)

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

Palitoxina
C₁₂₉H₂₂₇N₃O₅₄
PM 2684.20

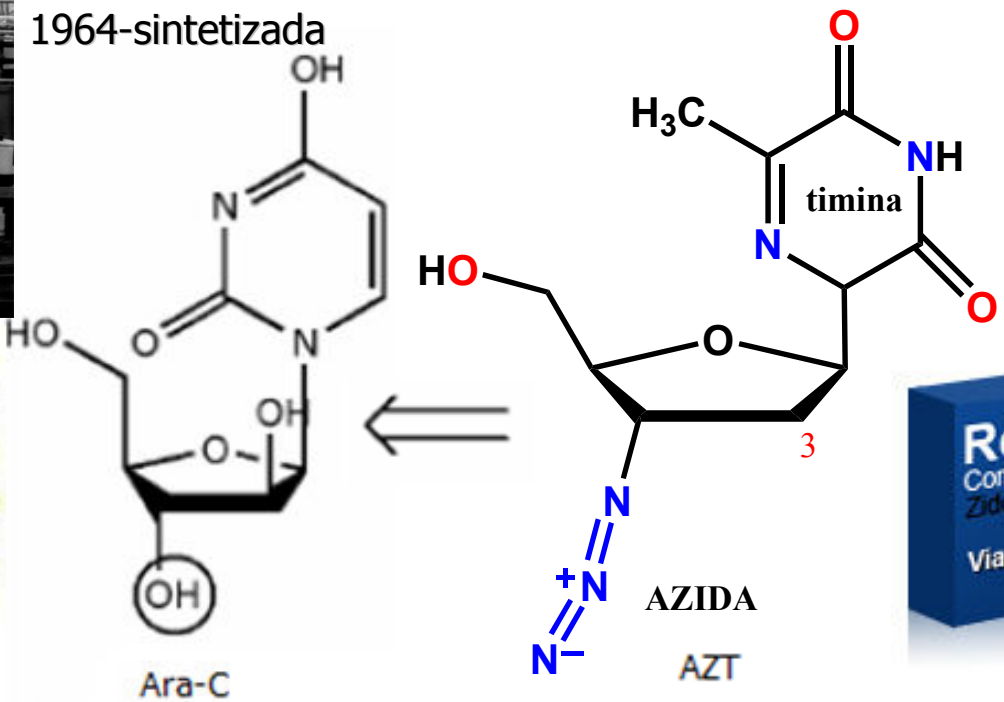
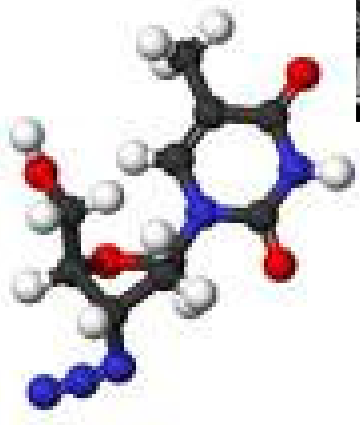
64 centros assimétricos
8 ligações duplas
42 grupos hidroxilas

2⁶⁴ isômeros



Jerome Horwitz

1964-sintetizada

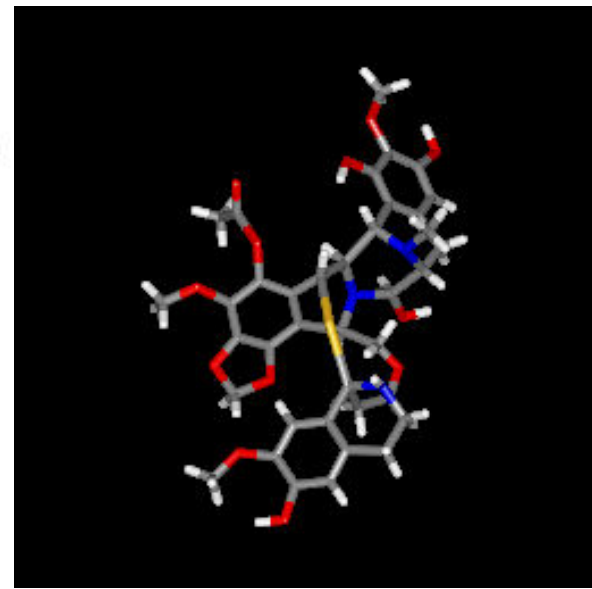
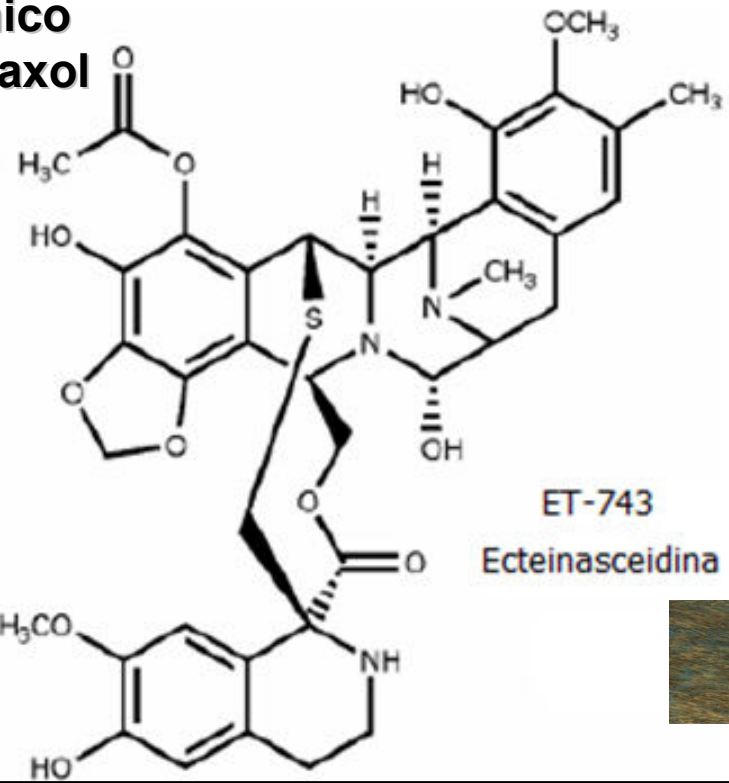


Novo Fármaco anti-câncer

Derivado tetraidroquinolínico
100 vezes mais ativo que Taxol



Yondelis™
(trabectedina)



Câncer