



Universidade Federal do Rio de Janeiro

Princípios de Química Medicinal



Parte 1

30ª Semana Acadêmica de Farmácia da Faculdade de Farmácia da UFBA

"Saúde, Educação e Interdisciplinaridade: Inserção no Mercado de Trabalho e Transformação da Sociedade"

13-17 de setembro de 2010

Salvador, BA



Eliezer J. Barreiro

Professor Titular

UFRJ





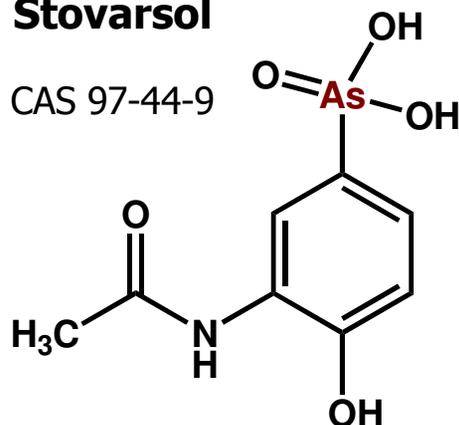
O berço da Química Medicinal



Ernest Fourneau
1872-1949

Stovarsol

CAS 97-44-9



Institut Pasteur (1887)

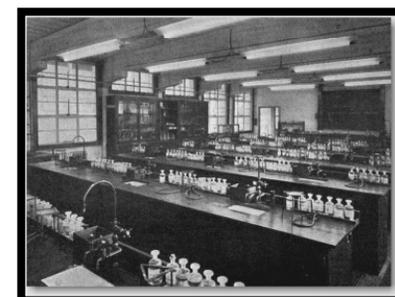
1911- Laboratoire de Chimie Thérapeutique

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



Conteúdo

DEFINIÇÃO; os Pioneiros; Ernest forneau; Alfred Burger; a **EVOLUÇÃO** cronológica **DA QUÍMICA Medicinal**; os **FÁRMACOS** e o **Nobel**; Emil Fischer; Paul Ehrlich; Robert KOCH/louis Pasteur; *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; a **INTERDISCIPLINARIDADE**; as **MOLÉCULAS** dos *fármacos*; as *moléculas* PIONEIRAS; cronologia da **DESCOBERTA** de *fármacos*; os produtos **NATURAIS** e a *descoberta* de *fármacos*; a cadeia da *descoberta* dos **FÁRMACOS**; como nascem os **FÁRMACOS**; o **PARADIGMA** de Fischer; abordagem fisiológica; os **BIORRECEPTORES**; o modelo chave-fechadura; α betos *bioquímicos*; bioinformática & **QUÍMICA COMPUTACIONAL**; Topografia 3D dos **BIORRECEPTORES**; as **CHAVES**; **TIPOS** de interações **FÁRMACOS**-biorreceptores; **SIMILARIDADE** e dissimilaridade **MOLECULAR**; *reconhecimento* **MOLECULAR**; as *fases* DA ação dos **FÁRMACOS**; FASE farmacocinética; *metabolismo* dos *fármacos*; CYP450; **RATO** transgênico *humanizado*; *conceito* de grupamento **FARMACOFÓRICOS**, *auxofóricos*; *conceito* de **COMPOSTO**-protótipo; *moléculas* **INTELIGENTES**; *fármacos* sintéticos; *planejamento* **RACIONAL**; *Cimetidina*; **SILDENAFILA**; *lodenafila*; *estatinas*; **ORLISTAT**; novos *fármacos*; *rimonabanto*; *ziconotídeo*; *considerações* finais; *mercado* **FARMACÊUTICO**; **MOLÉCULAS** bilionárias; **LASSBio**; exemplos DE *casa*; **COXIBES**; *LASSBio-294 & 596*; **BIBLIOGRAFIA**; convite; agradecimentos.



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Chemistry

Special Topic: Issues on the Theme of
Natural Products



IUPAC - Subcommittee Medicinal Chemistry & Drug Development

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

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.
© 1998 IUPAC

Eur. J. Med. Chem., 31, 747 (1996)



Quim. Nova, Vol. 25, No. 3, 505-512, 2002.

GLOSSÁRIO DE TERMOS USADOS NO PLANEJAMENTO DE FÁRMACOS (RECOMENDAÇÕES DA IUPAC PARA 1997)

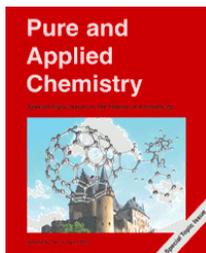
Carlos Mauricio R. Sant'Anna*

Departamento de Química, Universidade Federal Rural do Rio de Janeiro, 23851-970 Seropédica - RJ; Departamento de Fármacos, Universidade Federal do Rio de Janeiro, 21949-910 Rio de Janeiro - RJ

Recebido em 13/12/01



*O presente glossário é uma tradução para o português (aprova-
da pelo Comitê Brasileiro para Assuntos de Química junto à IUPAC)
do artigo Glossary of Terms Used in Computational Drug Design
publicado em Pure Appl. Chem. 1997, 69, 1137, preparado por H.
van de WaterBeemd, M. S. Tute, R. E. Carter, G. Grassy, H. Kubinyi,
Y. C. Martin e P. Willet.*



Pure & Appl. Chem. 1998, 70, 1129-1143



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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.



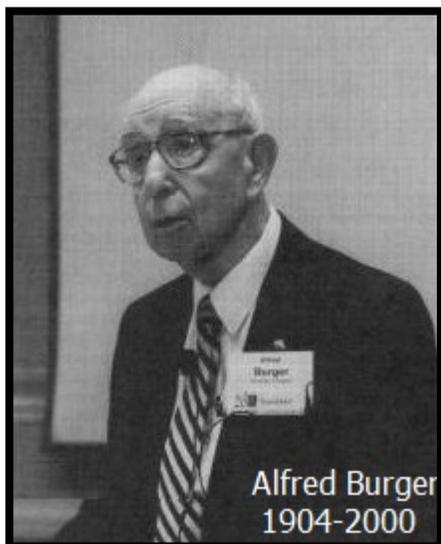


Fatos históricos:



Os pioneiros

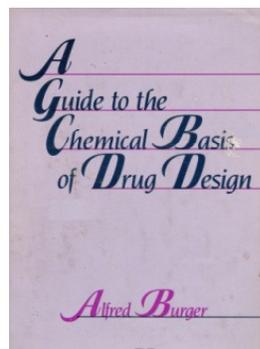
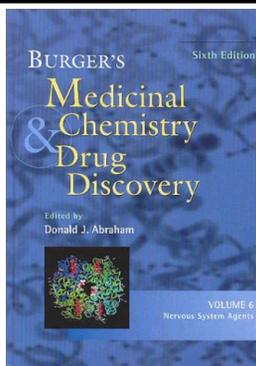
Química
Medicinal



Química Medicinal Prof. Alfred Burger

(1904-2000)

University of Virginia
EUA



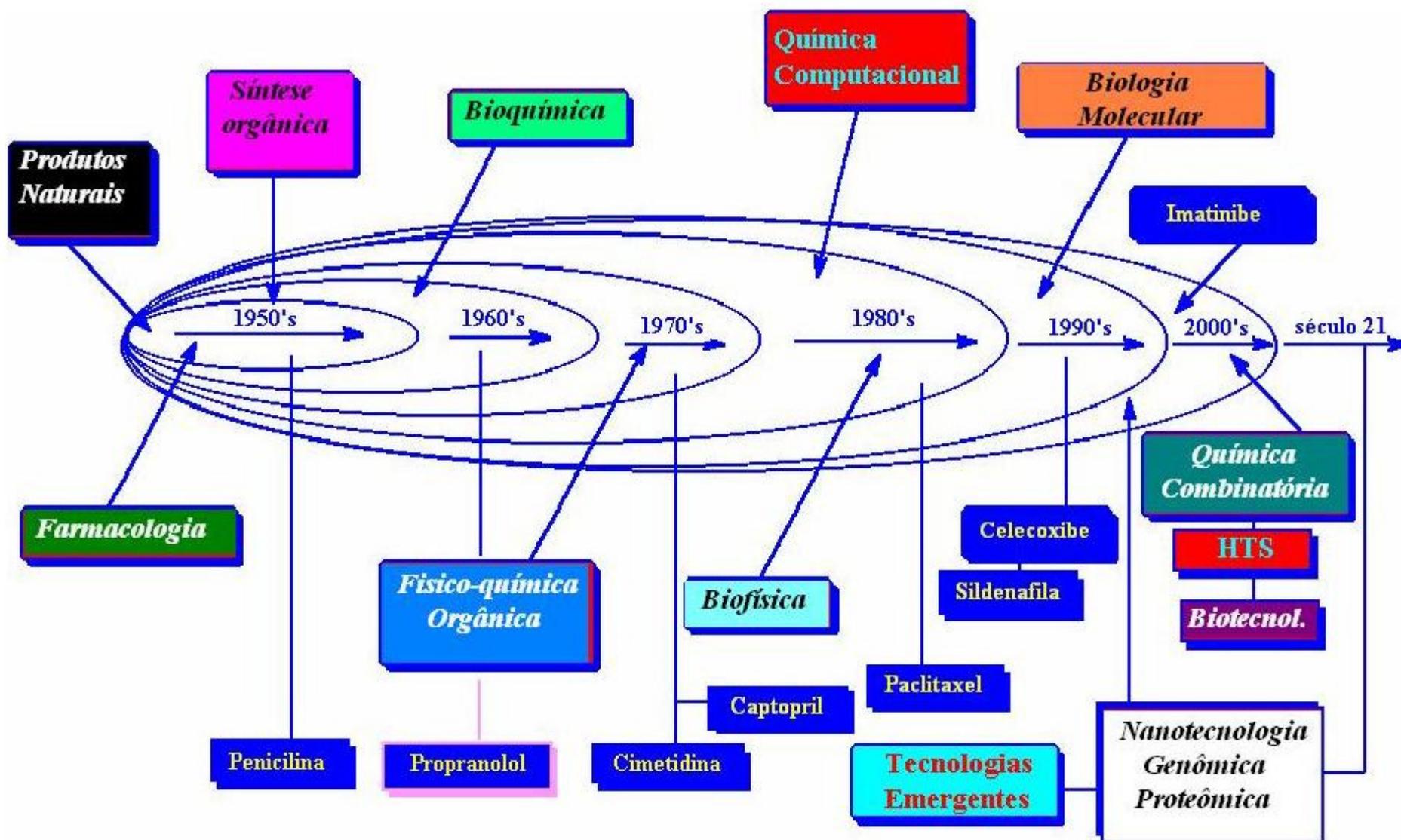
1958 – cria o Journal of the Medicinal and Pharmaceutical Chemistry → depois Journal of Medicinal Chemistry

“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





Os *Fármacos* e o *Prêmio* *Nobel*



Os fármacos e o Prêmio Nobel



Louis Pasteur

1822-1895

“La vie empeche la vie”

“L’hazard ne favorisée que les sprits preparées”



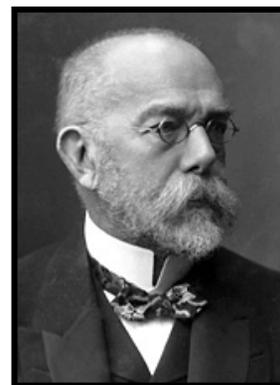
Emil Fischer

1852-1919

1902



Lock & Key



Robert Koch

1843-1910

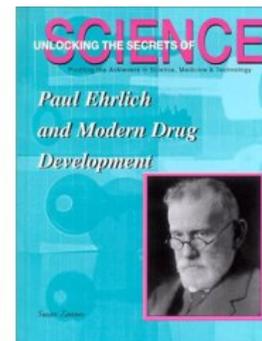
1905



Paul Ehrlich

1854-1915

1908



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

One-molecule, one-target paradigm



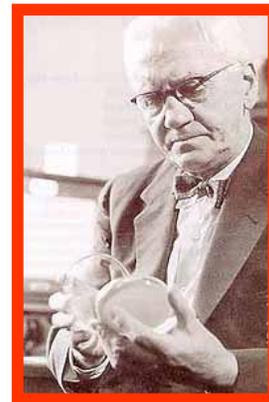
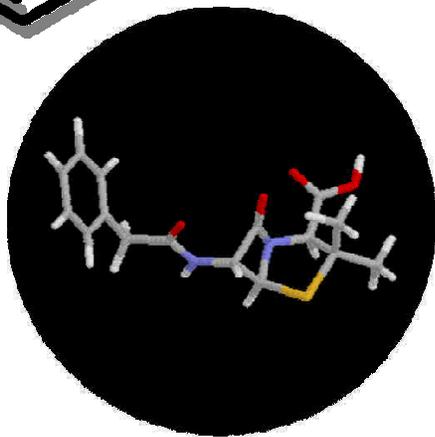
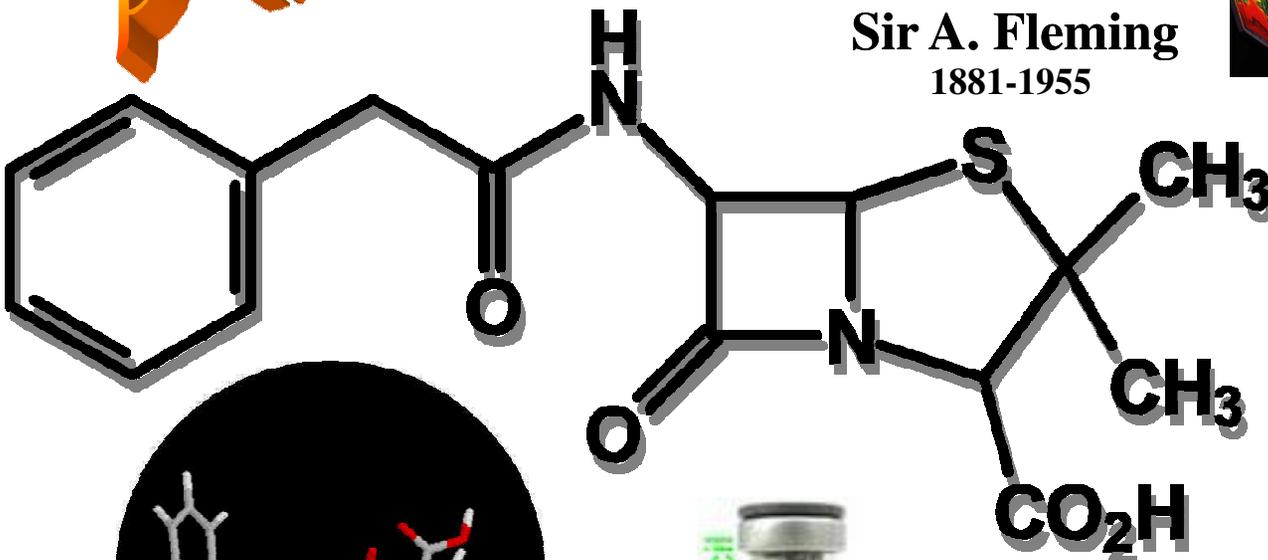


Antibioticoterapia

Penicilinas

Moléculas Salva-vidas

β -lactâmicos



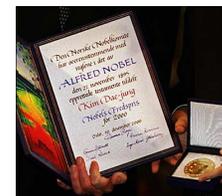
Sir A. Fleming
1881-1955



Sir H. W. Florey
1898-1968



E. B. Chain
1906-1979



1945



Penicillium notatum

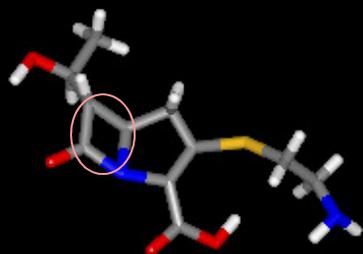
serendipidade





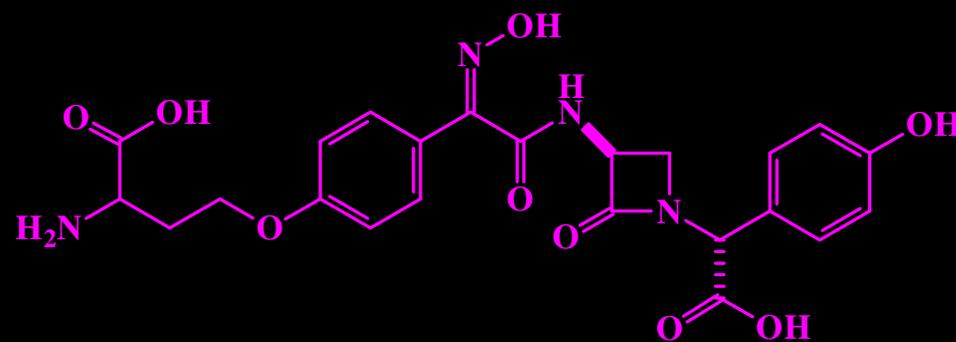
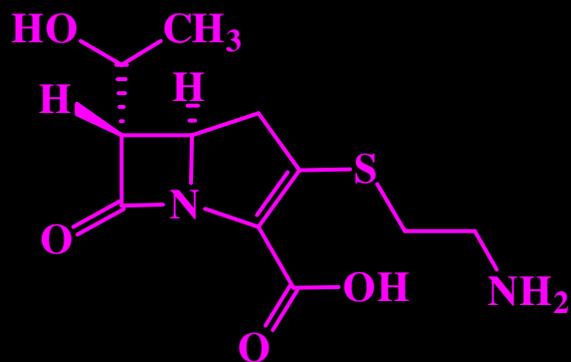
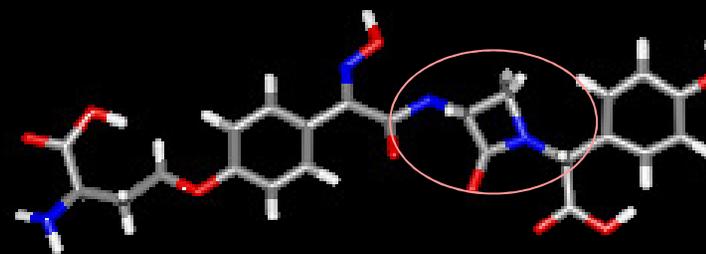
Novas Gerações de Antibióticos

**Antibiótico β -lactâmico
do grupo dos carbapenenos**
Resistente à β -lactamases



tienamicina

Antibiótico β -lactâmico monocíclico
Nocardia uniformis
Ativo via Oral
azetidionas
(Sintético)



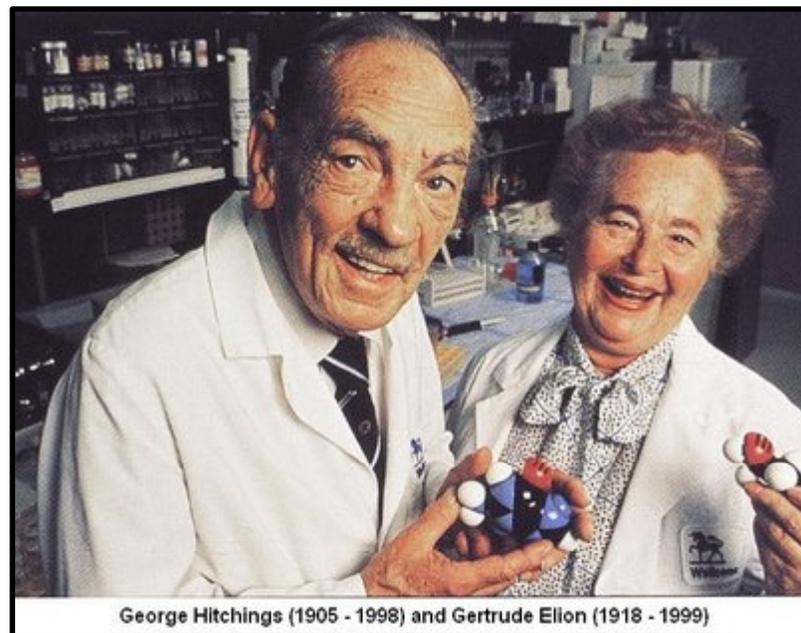
nocardicina



“for their discoveries of important principles for drug treatment”



1988 – James W. Black
(1924-2009)



1988



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



Os fármacos e o Nobel !



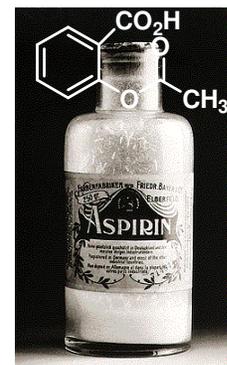
1982 – S.B. Bergström



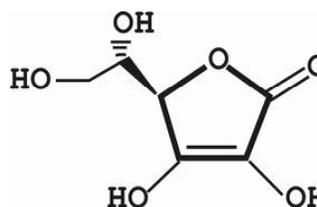
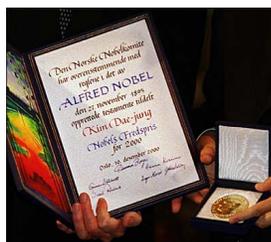
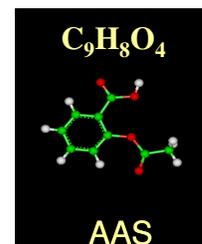
1982 – B.I. Samuelsson



1982 – J.R. Vane



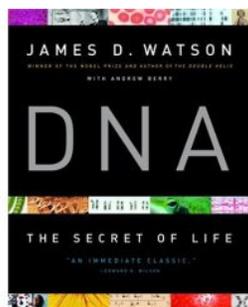
1982 – AAS



1937 – Vit C



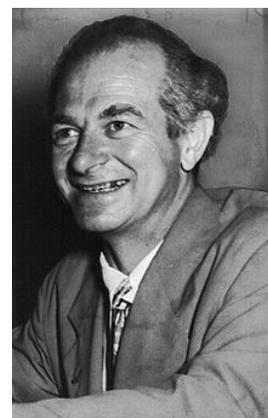
1937 – W. N. Haworth



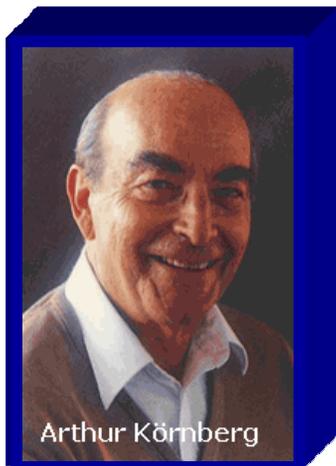
• 157 pesquisadores ganharam o Prêmio Nobel de Química desde 1901



1937 – A. von Szent-Györgyi

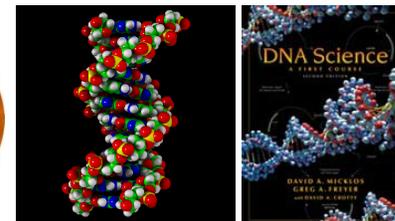


1954 & 1962 – L. C. Pauling



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,

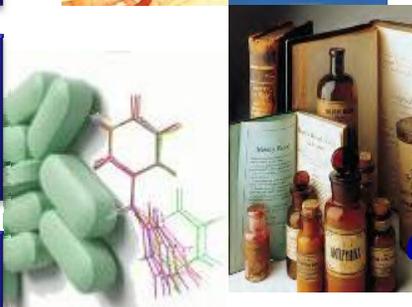
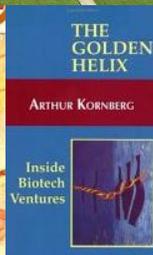
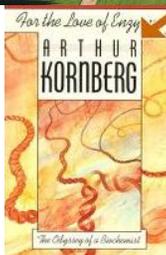
growing further apart even as they discover more common ground....

Pharmaceutical chemistry was until recently the bastion of organic chemistry... in the search for alternative or superior drugs for the treatment of various diseases.”

Arthur Kornberg

Biochemistry 1987, 26, 6888-6891

Interdisciplinaridade



Diapositivo 16

EJB1

Kornberg definiu as bases da interdisciplinaridade das ciências dos fármacos quando antecipou a necessidade de aproximar-se a Química e a Biologia.

Eliezer J Barreiro; 27/08/2010



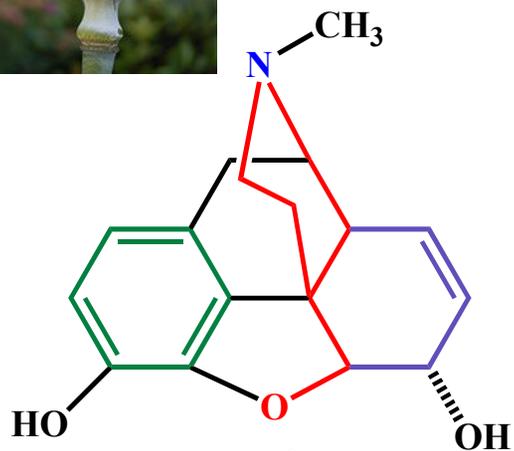
Interdisciplinaridade

A yellow sticky note is pinned to the white background with an orange pushpin. The text on the note is written in a blue, italicized font.

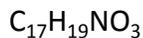
As moléculas dos fármacos



As moléculas pioneiras...



morfina



Henry How

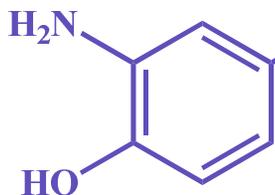
1853 – Un. Glasgow



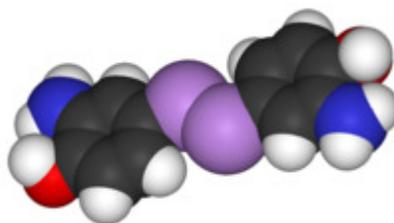
Sir Robert Robinson

1886-1975

Nobel 1947



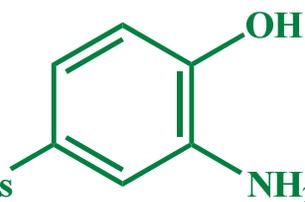
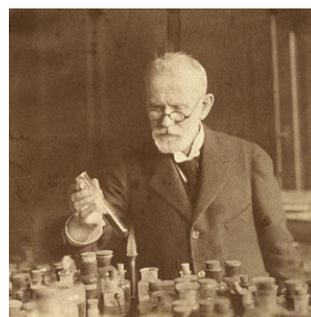
arsrfenafina



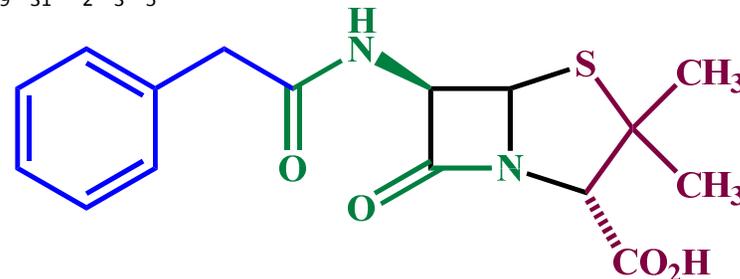
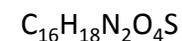
Paul Ehrlich

1854-1915

Nobel 1908



penicilina



Alexander Fleming

1881-1955

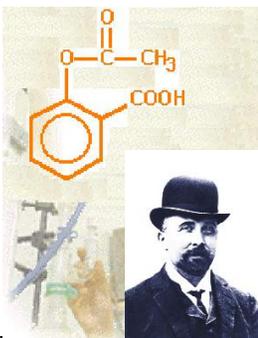
Nobel 1945



Library of Congress

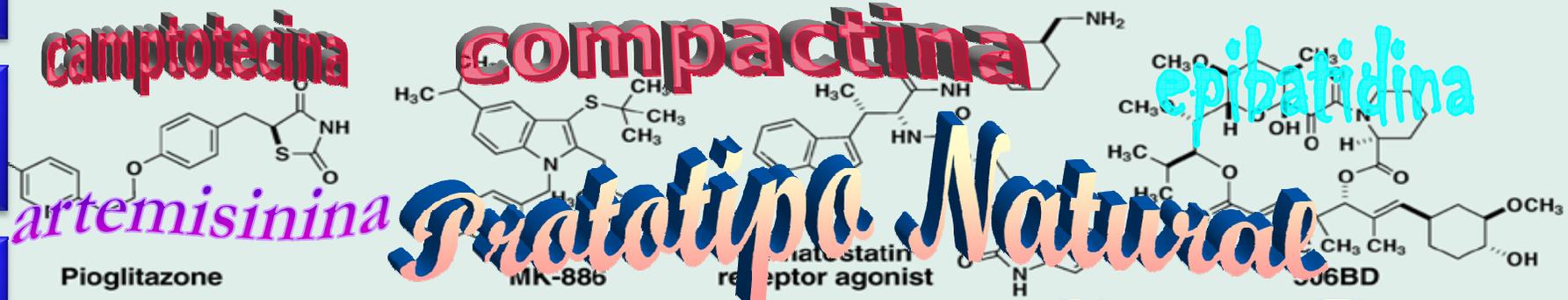


Cronologia da descoberta de fármacos



AAS *	1889	1986	ciprofloxacina fluoxetina
barbitúricos	1923	1987	zidovudina lovastatina
cloroquina	1934	1988	cetirizina, enalapril
sulfonamidas	1935	1989	ozagrel mifepristona
penicilina	1942	1990	salmeterol, amlodipina
nitrofurano	1952	1991	alpidem, paroxetina
progesterona	1953	1992	paclitaxel
talidomida	1954	1993	tacrina, fanciclovir
haloperidol	1958	1994	irinotecan, pimobendano
verapamil	1962	1995	indinavir, losartano
indometacina	1963	1996	docetaxel, atorvastatina
propranolol	1964	1997	zafirlukast, montelukast
salbutamol	1968	1998	infiximabe sildenafil efavirenz
prostaglandinas	1970	1999	celecoxibe orlistate oseltamivir
oxamniquina	1970	2000	galantamina rofecoxibe
cimetidina nifedipina	1975	2001	imatinibe <i>rosiglitazona</i>
atenolol	1976	2002	voriconazola, etoricoxibe
captopril	1977	2003	gefitinibide, aripiprazola
tamoxifeno	1978	2004	rosuvastatina, rofecoxibe
praziquantel	1979	2005	pregabalina, Caduet [®]
oxicams	1980	2006	risperidona, erlotinibe
ranitidina aciclovir	1981	2007	maraviroc*, ambrisentam
mefloquina misoprostol	1985	2008	etravirina
		2009	pitavastatina





SMALL-MOLECULE PROBES

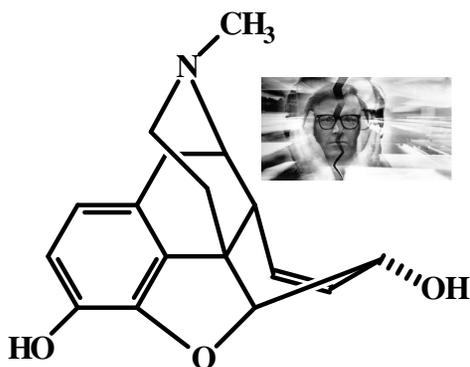
Colchicine, a probe of tubulin; spidamine, used to study glutamate receptor function; reserpine, used to discover the neurotransmitter dopamine; phorbol used to study protein kinase C; pioglitazone (act on the transcription factor PPAR-γ); MK-886, used to study the function of the G-protein-coupled receptor's physiological functions; 506BD, a probe of human opium action; dimerizer (methallylamine), a variant of rapamycin that, by chemical modification, gained the ability to control proximal relations 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.

Penicilina

escopolamina

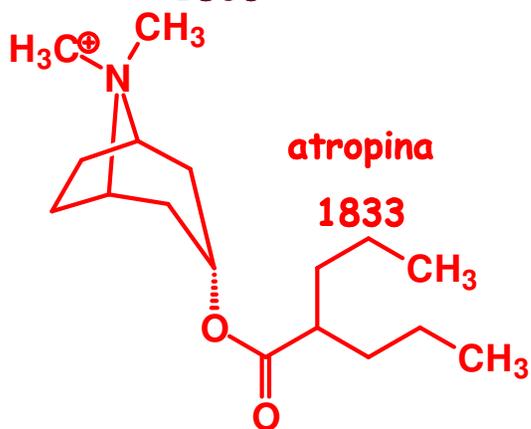
papaverina





morfina

1806

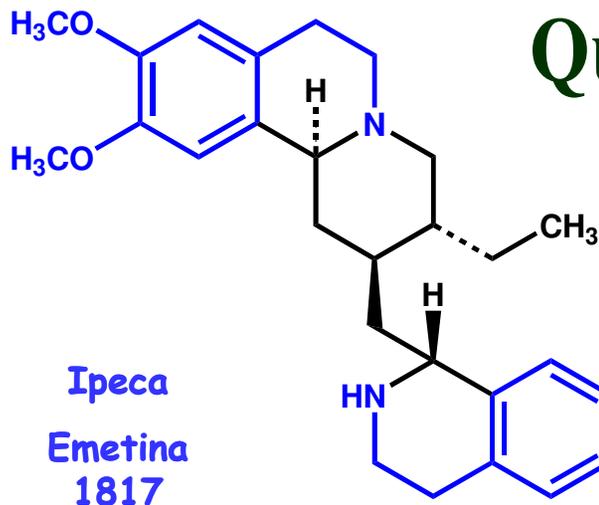


atropina

1833

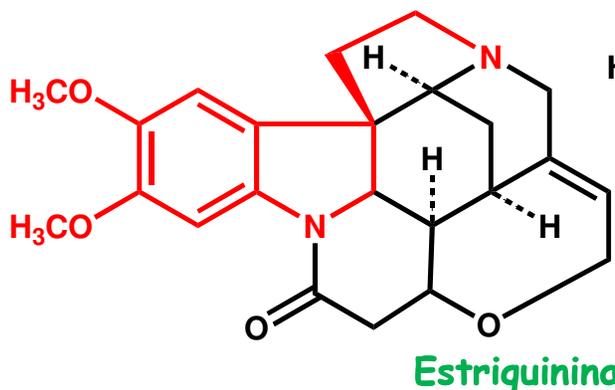
terpenos, alcalóides,
 esteróides, flavonóides,
 lignanas, ligninas, iridóides,
 policetídeos, quinonas,
 cumarinas

Quimiodiversidade



Ipeca

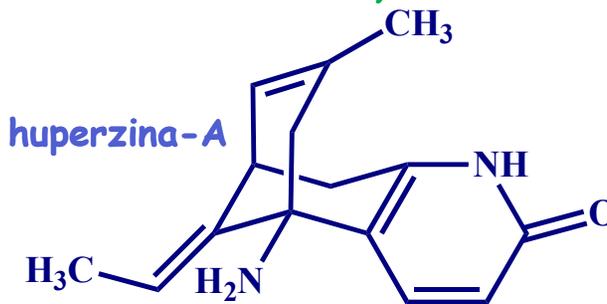
Emetina
1817



Estriquinina

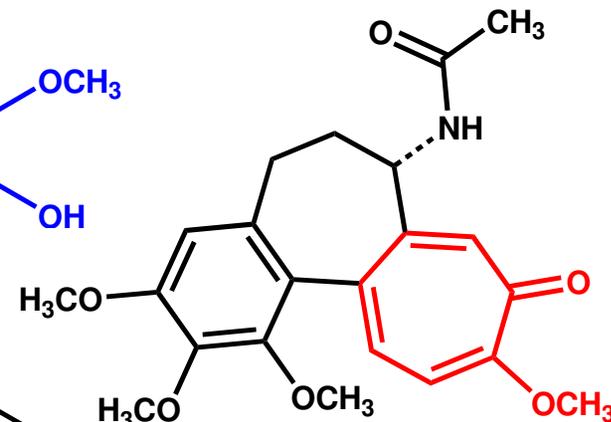
1817

Strychnos nux vomica



huperzina-A

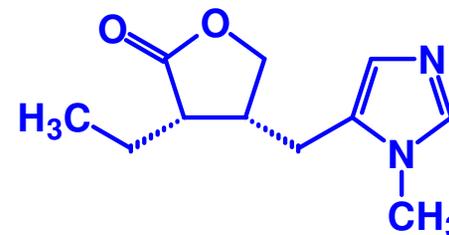
Huperzia serrata.



Colchicina

1820

Colchicum autumnale

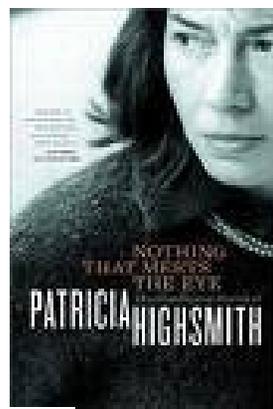
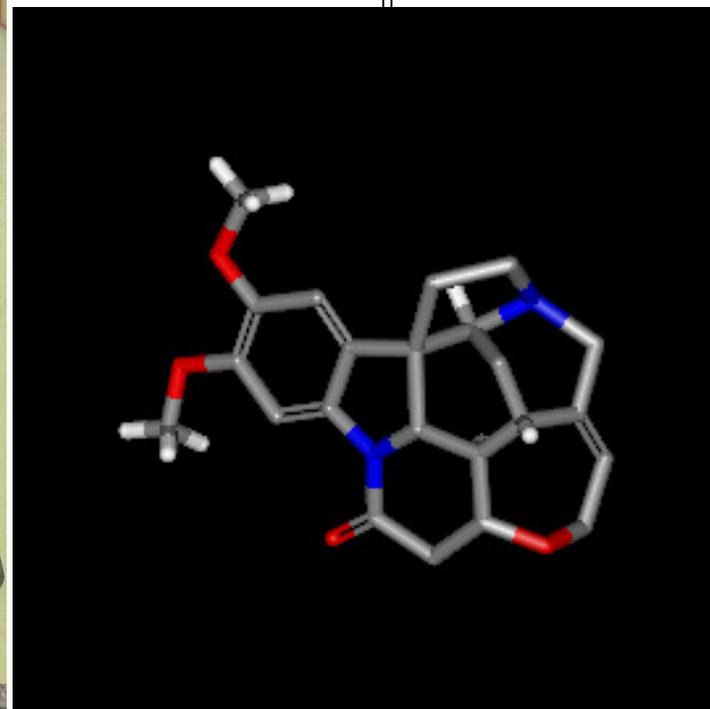


Pilocarpina



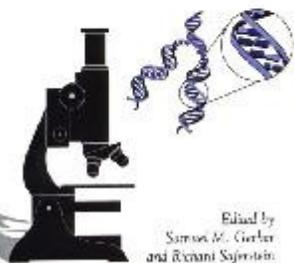
Strychnos nux vomica

Estriquinina



MORE CHEMISTRY AND CRIME

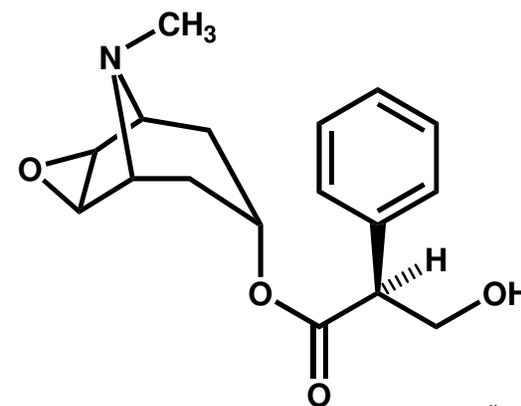
From Marsh Ascetic Test to DNA Profile



Edited by
Samson W. Garber
and Robert Szejtli

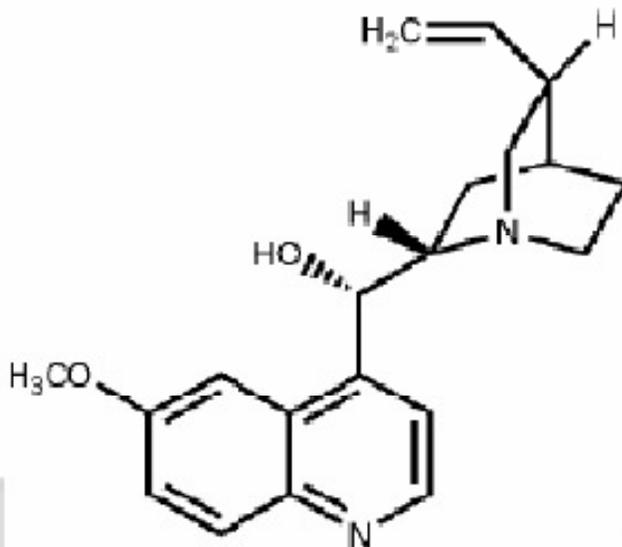


Escopolamina

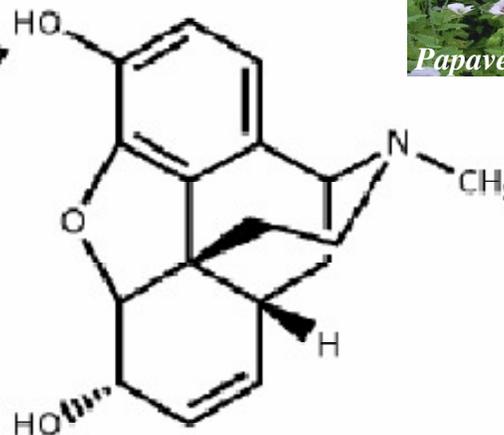




Cinchona officinalis



quinina



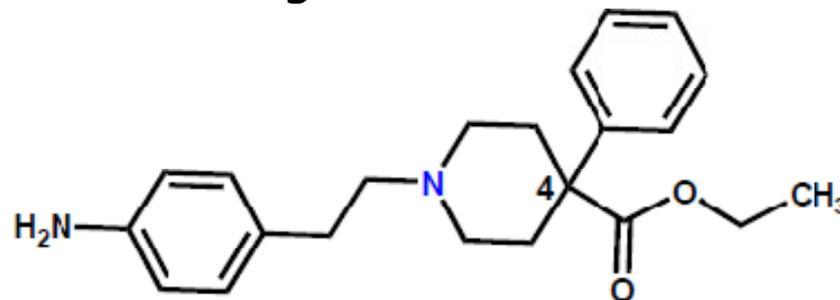
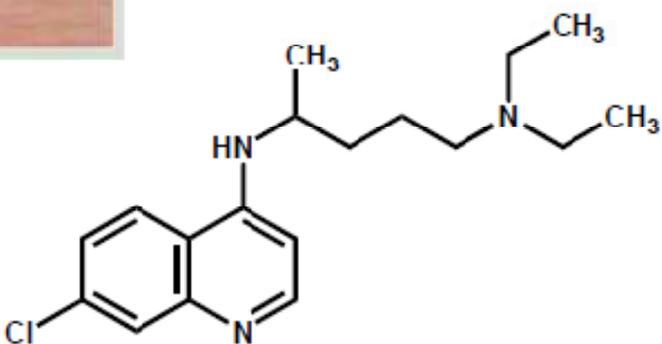
morfina



Papaver somniferum



Alcalóides = alcalinos = bases nitrogenadas naturais

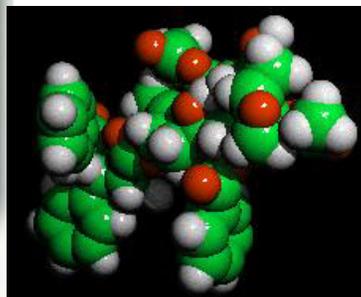




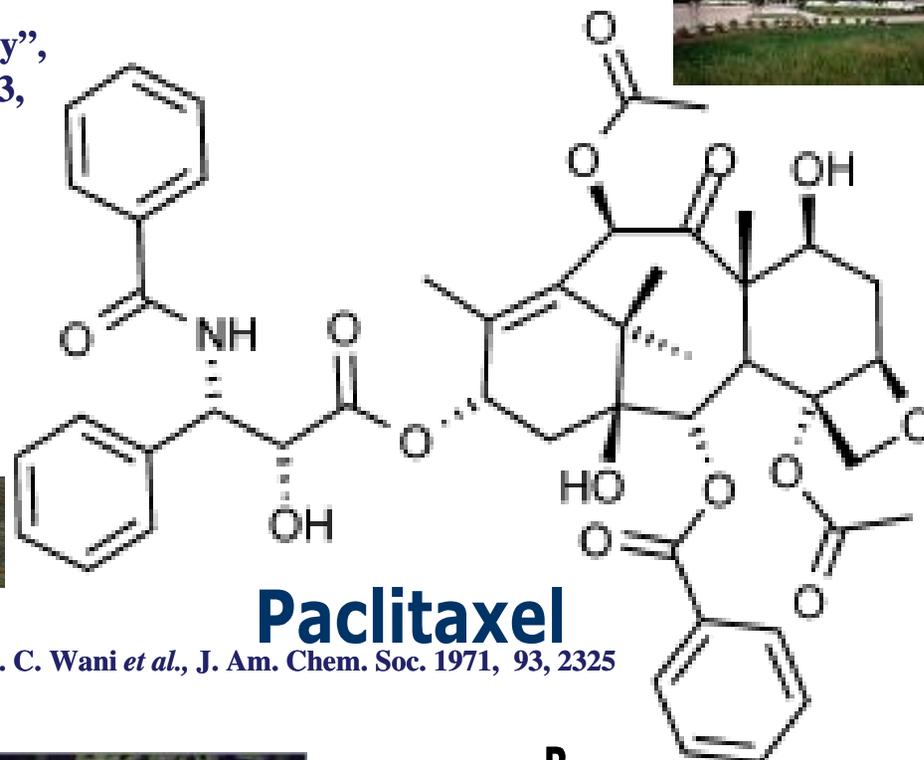
Uma descoberta...

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

NATIONAL
CANCER
INSTITUTE



Câncer



Paclitaxel

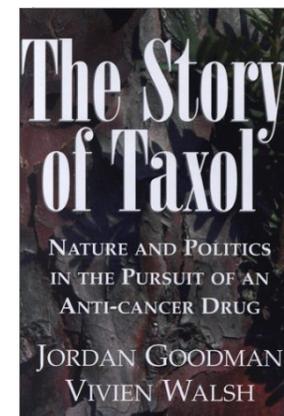
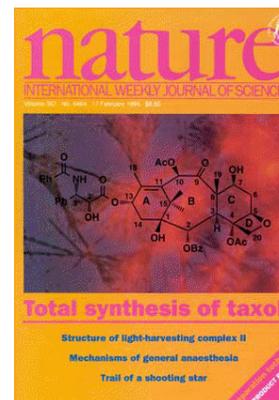
M. C. Wani *et al.*, *J. Am. Chem. Soc.* 1971, 93, 2325

Taxol^R

taxo

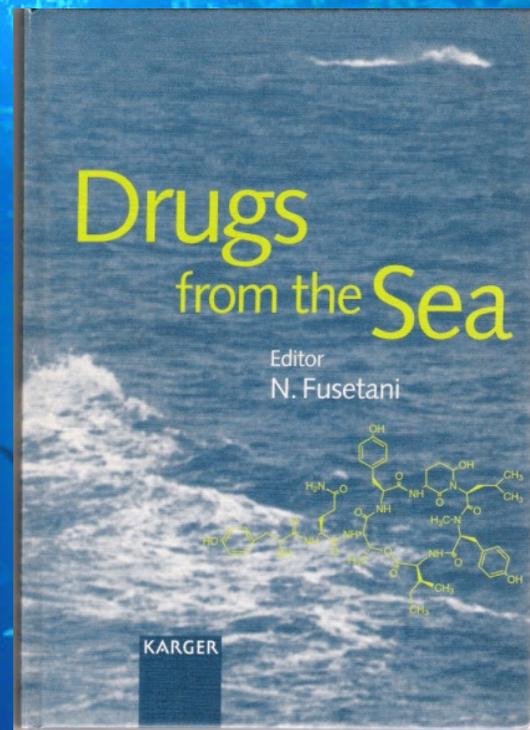


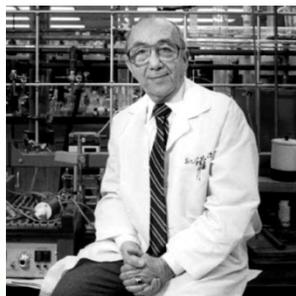
RM Mohammad, *J. Nat. Prod.* 2008, 71, 492



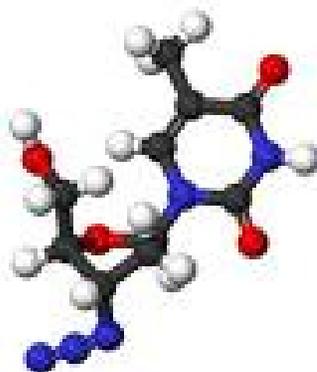


Produtos Naturais do Mar

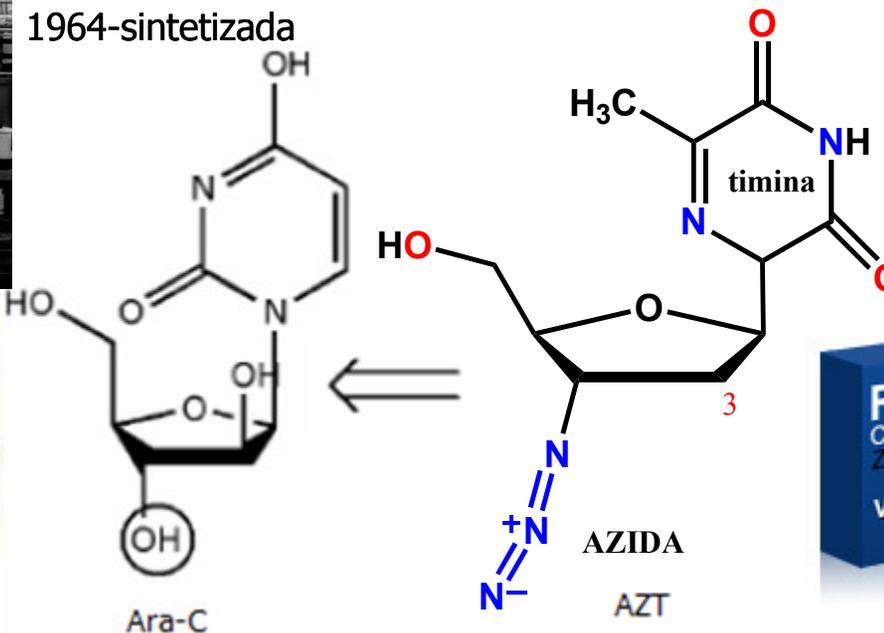




Jerome Horwitz

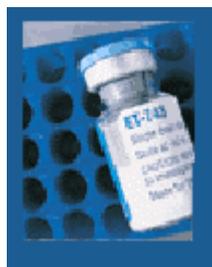


1964-sintetizada

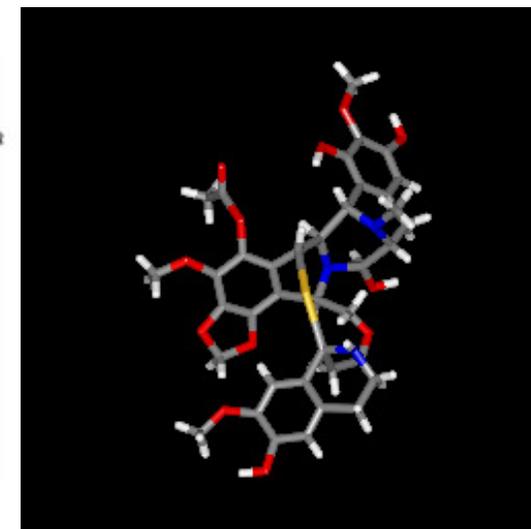
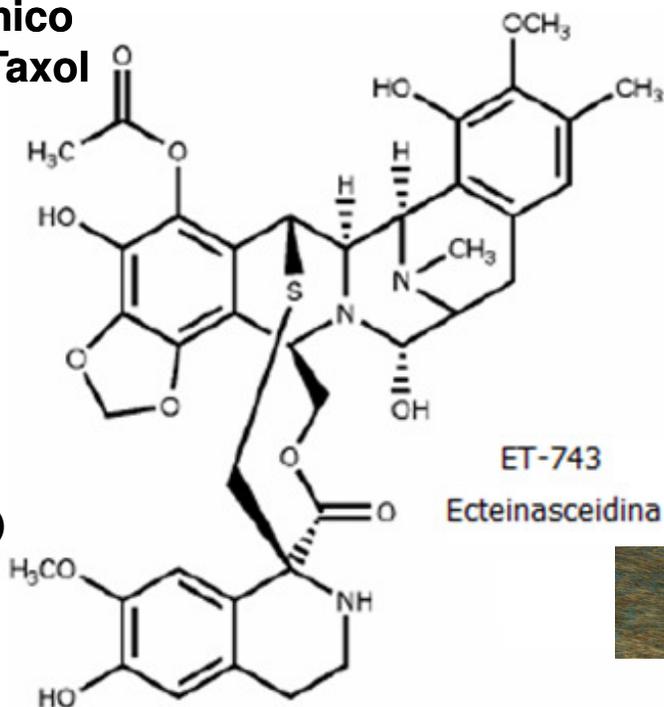


Novo Fármaco anti-câncer

Derivado tetraidroquinolínico
100 vezes mais ativo que Taxol



Yondelis™
(trabectedina)



Câncer



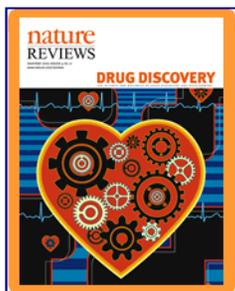


Produtos Naturais Marinhos em Ensaios Clínicos

Composto	Organismo	Fase	Doença
KRN7000	Porifera	I	câncer
IPL-567	Porifera	I	inflamação
methopetrosin	Celenterata	I	inflamação
GST-21	nemertea	I	Alzheimer
Dolastatina 10	molusco	II	câncer
LU-103793	molusco	I	câncer
Ziconotido (SNX-111)*	molusco	III	dor crônica
Briostatina	Briozoa	II	câncer
Didemnina B	Urocordata	II	câncer
<i>Ecteinascidina</i> (ET-743)	Urocordata	II	câncer
Esqualamina	Cordata	I	câncer



Peptídeo-conotoxina (Prialt[®]) aprovado pelo FDA para uso em dor neuropática por injeção intratecal em 2008



Drug development from marine natural products

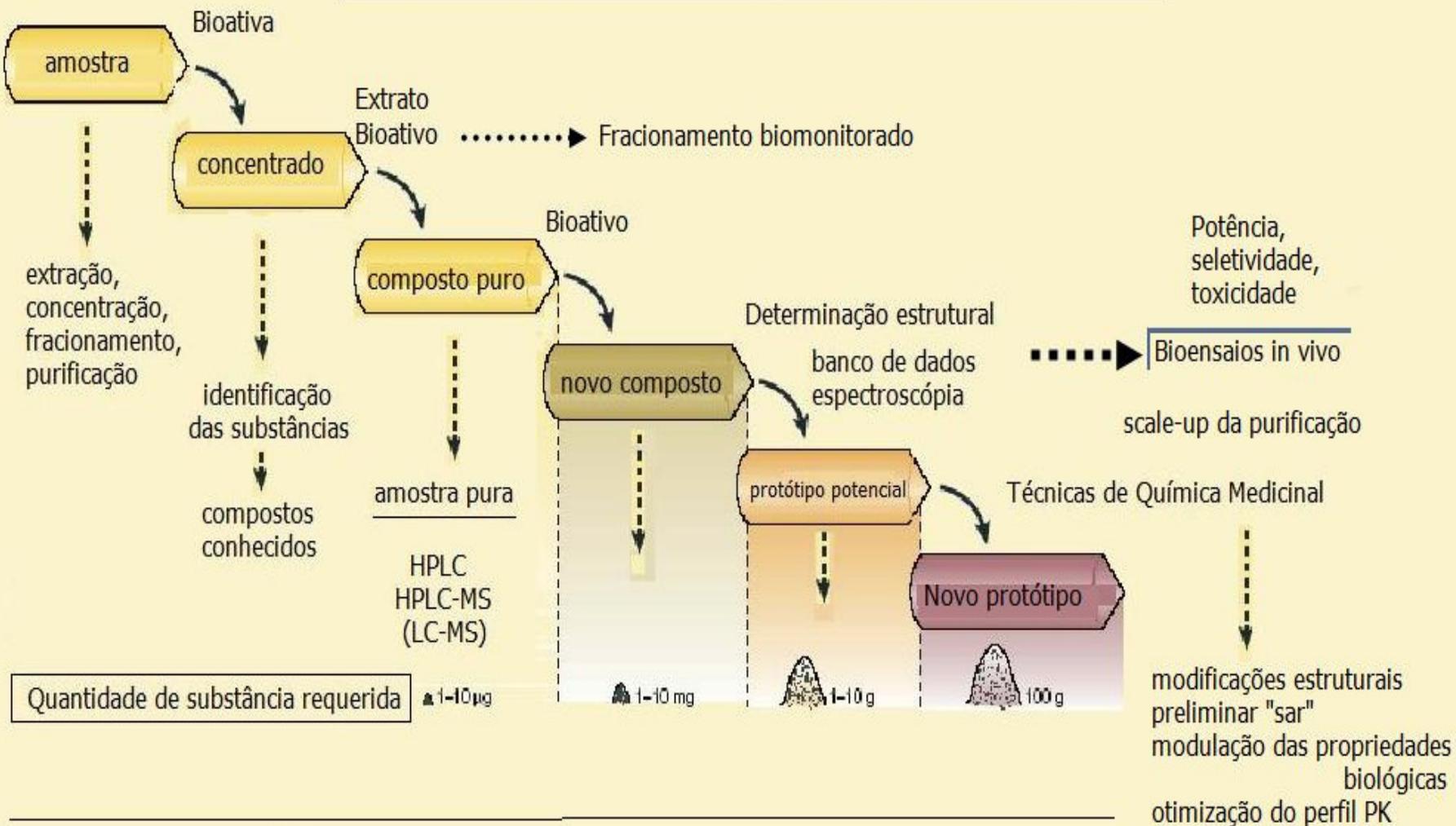
*Tadeusz F. Molinski**, *Doralyn S. Dalisay**, *Sarah L. Lievens*‡* and *Jonel P. Saludes*‡*

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.

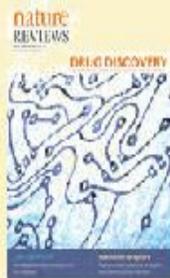
Nat. Rev. Drug Discov. **2009**, *8*, 69



Processo de descoberta de novos hits-naturais



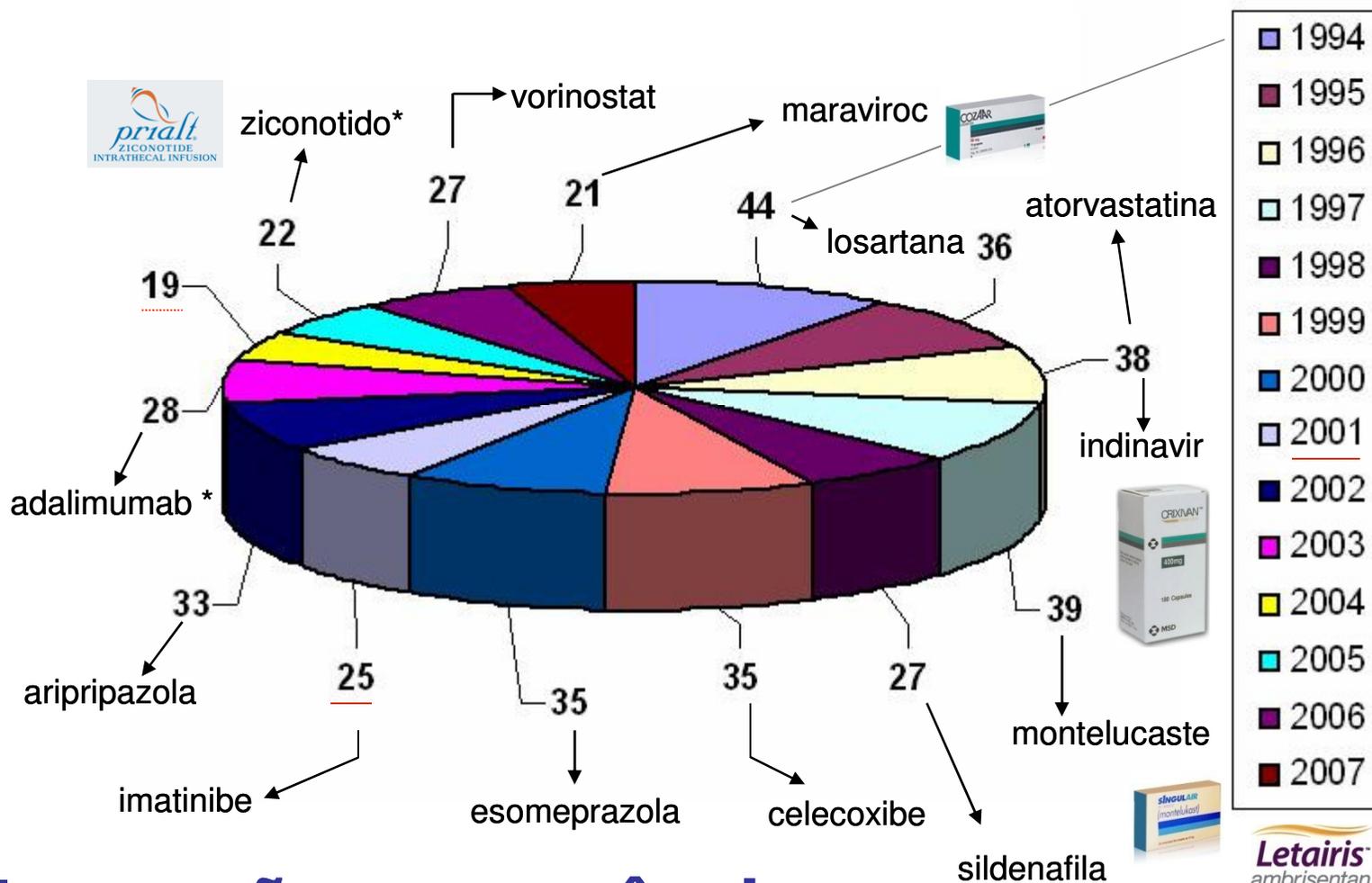
Adaptado de



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



Novos fármacos lançados por ano / 1994 - 2007



Inovações terapêuticas

ca. 30 novos fármacos lançados / ano



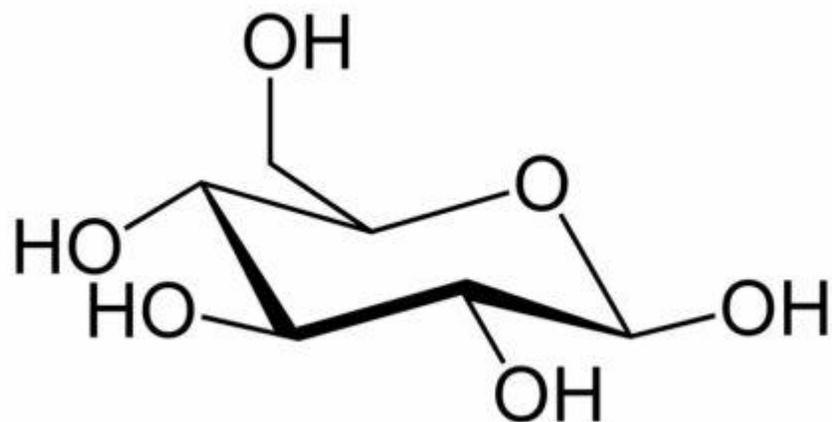




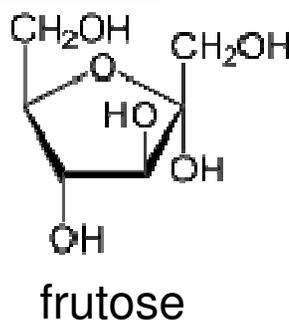
*Como nascem os
fármacos*



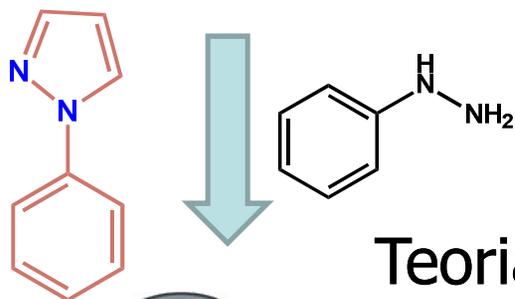
The Nobel Prize in Chemistry 1902
Emil Fischer



Glicose



Emil Fischer
1852-1919

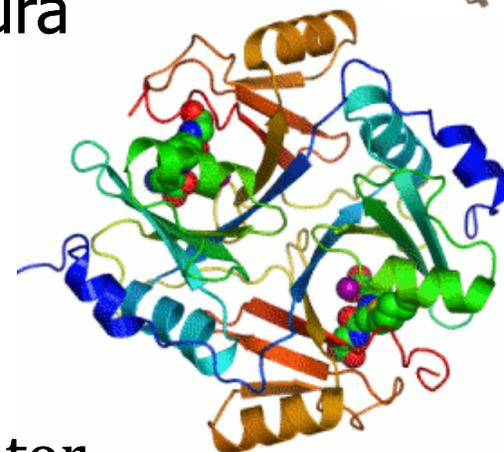


Teoria da chave-fechadura

Complementaridade
molecular

Reconhecimento
molecular

Interação fármaco-receptor





Emil Fischer

1852-1919

1902



O paradigma de Fischer

LOCK & KEY
CONCEPT



Biorreceptor

macromolécula

baseado no sítio de reconhecimento

Planejamento racional

Fármaco

micromolécula

baseado no ligante / análogo-ativo



Robin Ganellin gives his views on medicinal chemistry and drug discovery

Interview by Stephen L. Carney

C. Robin Ganellin, FRS, Smith Kline & French Professor
Medicinal Chemistry, University College London

Physiologic
A abordagem
approach
fisiológica