



Universidade Federal do Rio de Janeiro

Tópicos de Interesse Farmacêutico

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Professor Titular

Universidade Federal do Rio de Janeiro

LASSBio - Faculdade de Farmácia



1ª Jornada de Ciências Farmacêuticas

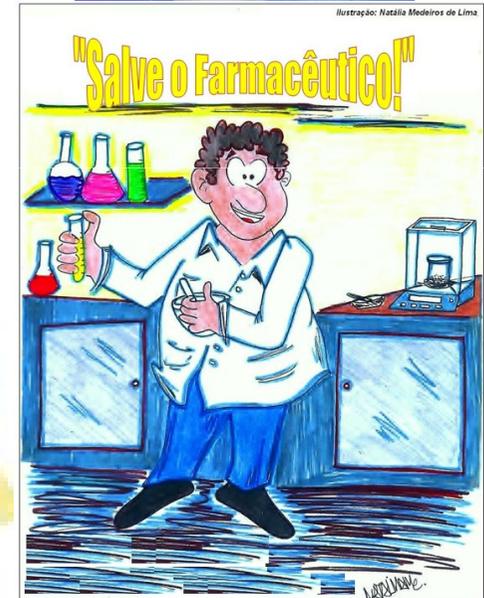
Centro Universitário Estadual da Zona Oeste

01-03 de junho de 2011



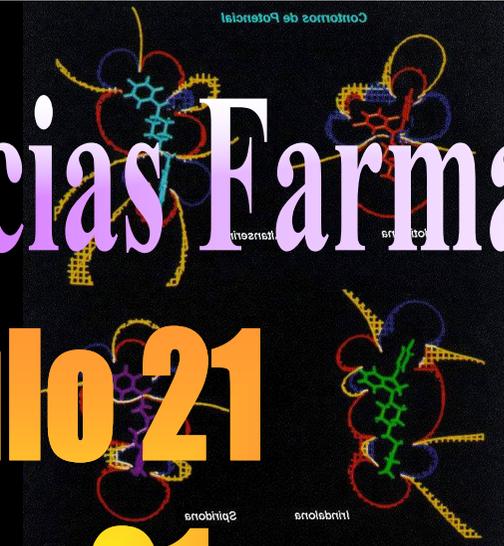
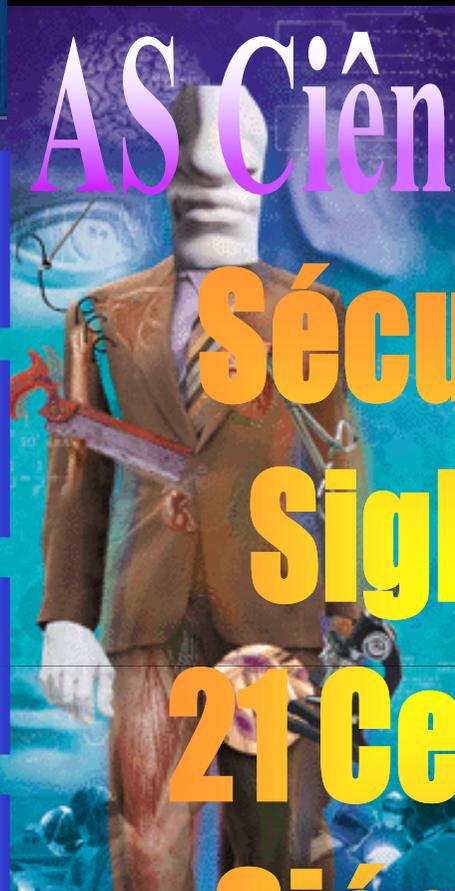


As Ciências Farmacêuticas

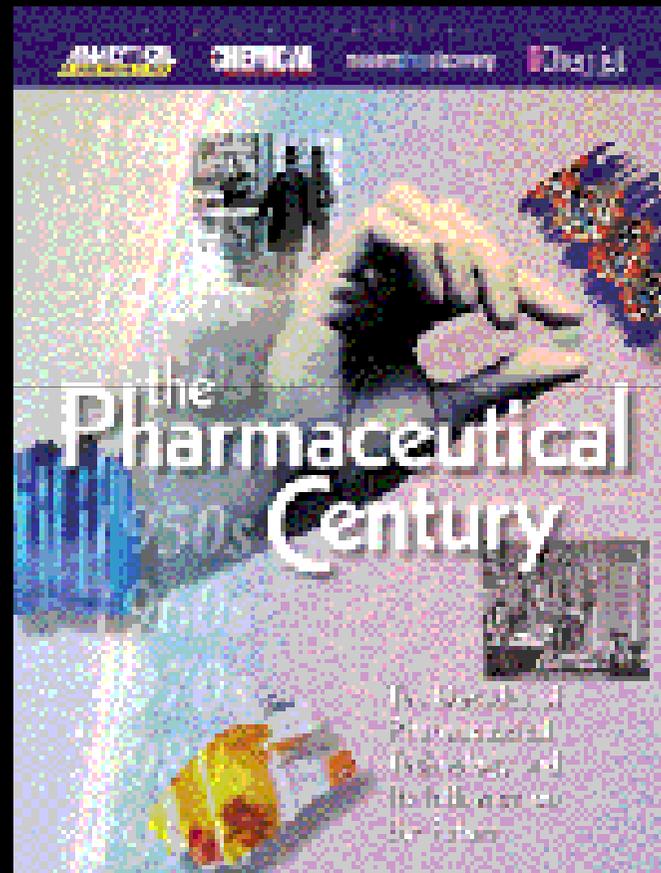




AS Ciências Farmacêuticas



Século 21
Siglo 21
21 Century
Siécle 21





Galeno



Obras de Galeno, 1556

Botica



Cosme e Damião

Litografia de Jean Chissé (1939) [Corbis]



José de Anchieta



"primeiro farmacêutico do Brasil..." (! ?)



São Cosme & São Damião

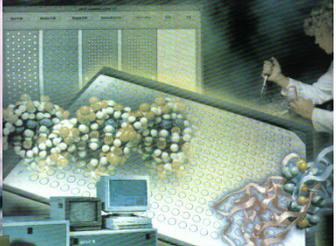




Dos tempos da botica...



"The Apothecary", A.C. Wootton
(Chronicles of Pharmacy Vol II 1910)



Fármaco

Medicamento



... à Farmácia Moderna.



Século 21

Nível Técnico

Nível Superior

CPA Ciências Farmacêuticas

Âmbito profissional

Interdisciplinaridade

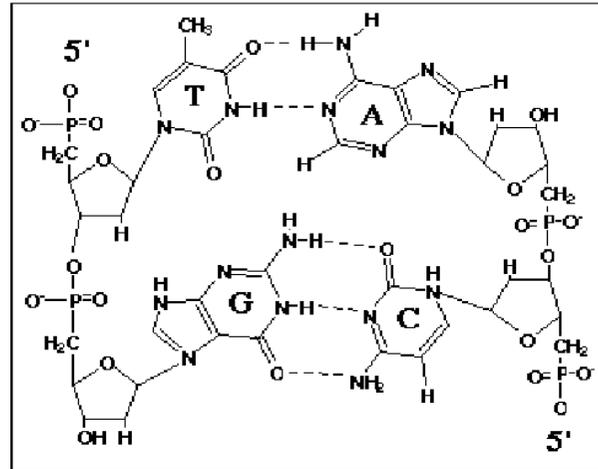


“for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material“
Prêmio Nobel de Medicina e Fisiologia 1962

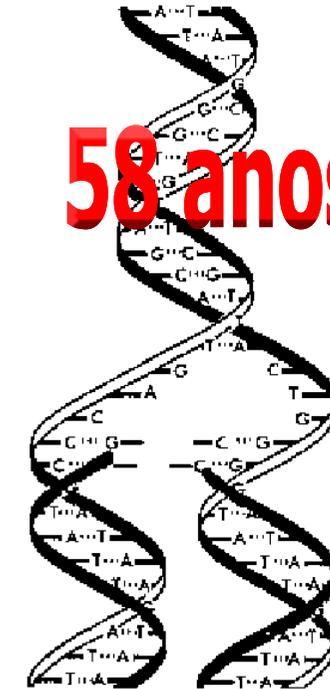


J. D. Watson & F. H. C. Crick

Molecular structure of Nucleic Acids,
Nature **171**, 737-738 (1953)



Ligações de Hidrogênio entre
 Guanina (G) / Citosina (C) e
 Adenina (A) / Timidina (T)

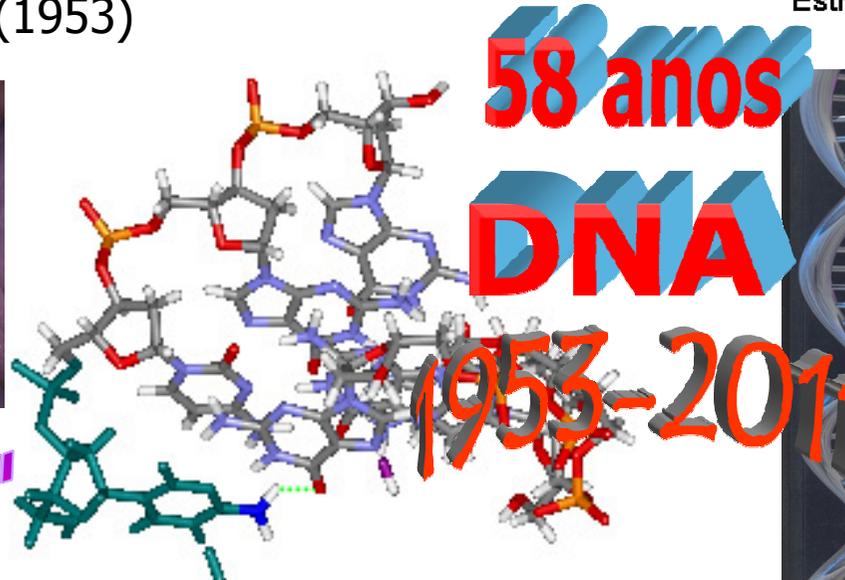


58 anos

Estrutura α -hélice do
 DNA



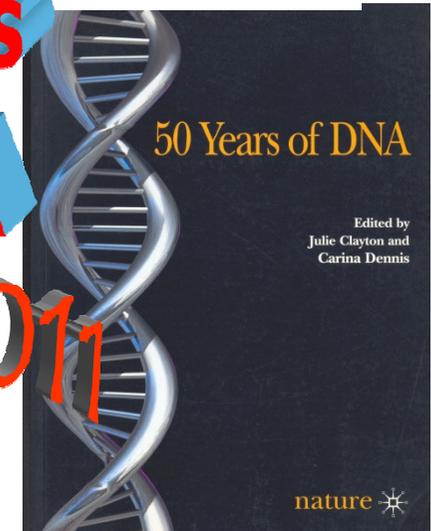
Molécula da vida



58 anos

DNA

1953-2011



50 Years of DNA

Edited by
 Julie Clayton and
 Carina Dennis

nature

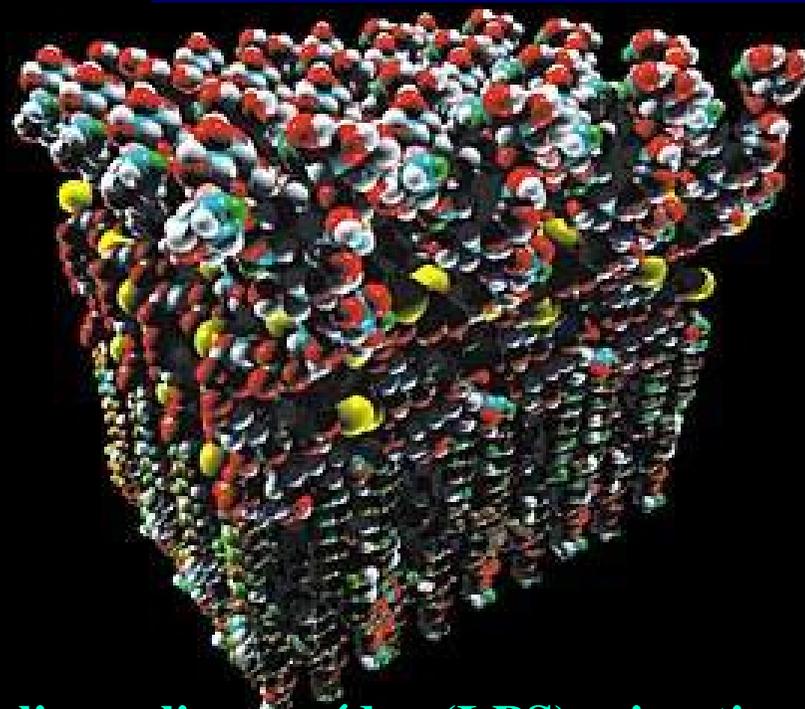
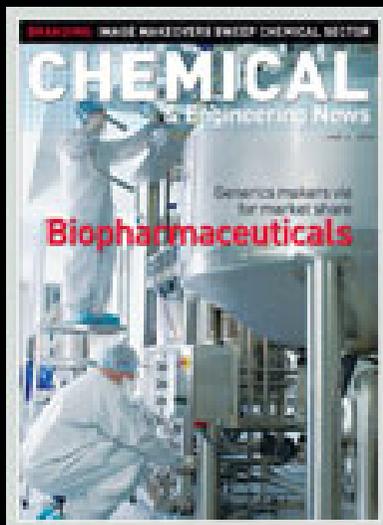
J. Clayton & C. Dennis, Eds., “50 Years of DNA”, Nature Pub. 2003.
 CSW Koehler, “Watson & Crick – Beyond the double helice”, DDT 2003, 6, 21



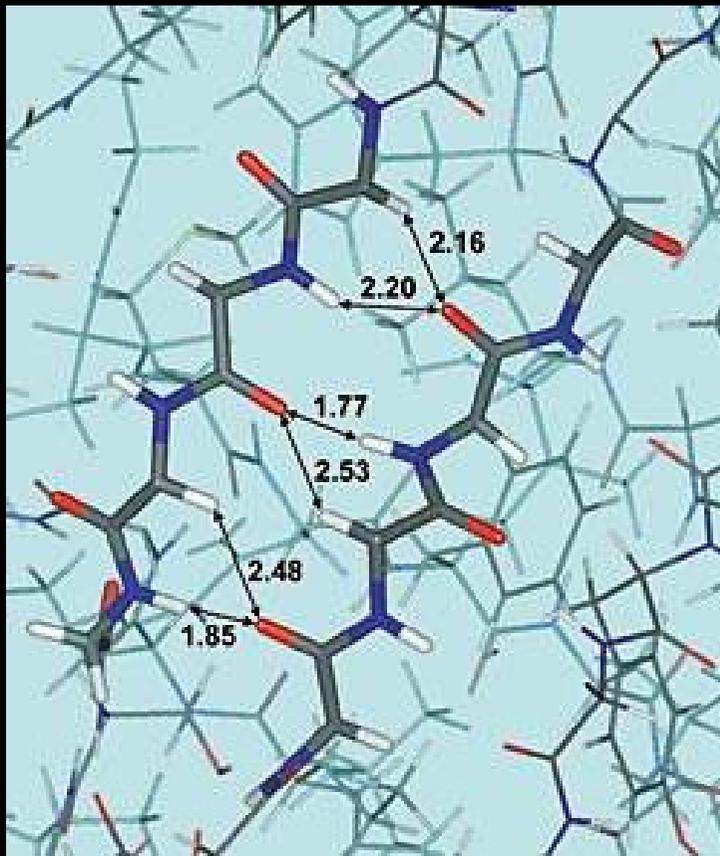
A Inovação Farmacêutica



Controle de fatores entrópicos e eletrostáticos permitiu a construção de cápsulas tubulares com estruturas similares àquela da parede celular das bactérias. { Science, 288, 2035 (2000) }

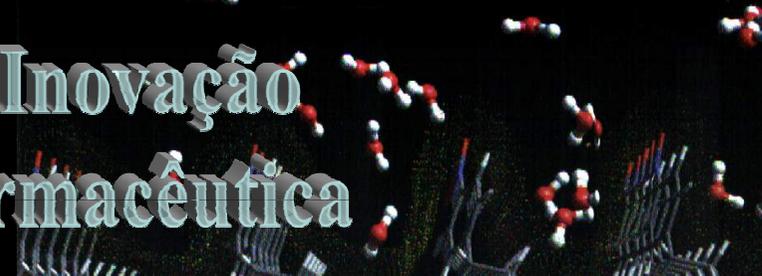


Modêlo lipopolissacarídeo (LPS) mimetizando a membrana de *Pseudomonas aeruginosa*, constituído de 16 lipopolissacarídeos (em cima) e 48 moléculas de fosfolípídeo-etilamina (em baixo). Este modelo possui 104 contra-ions Ca^{2+} . Cálculos de dinâmica molecular demonstraram a afinidade desta membrana sintética no processo de “metal-ion uptake”

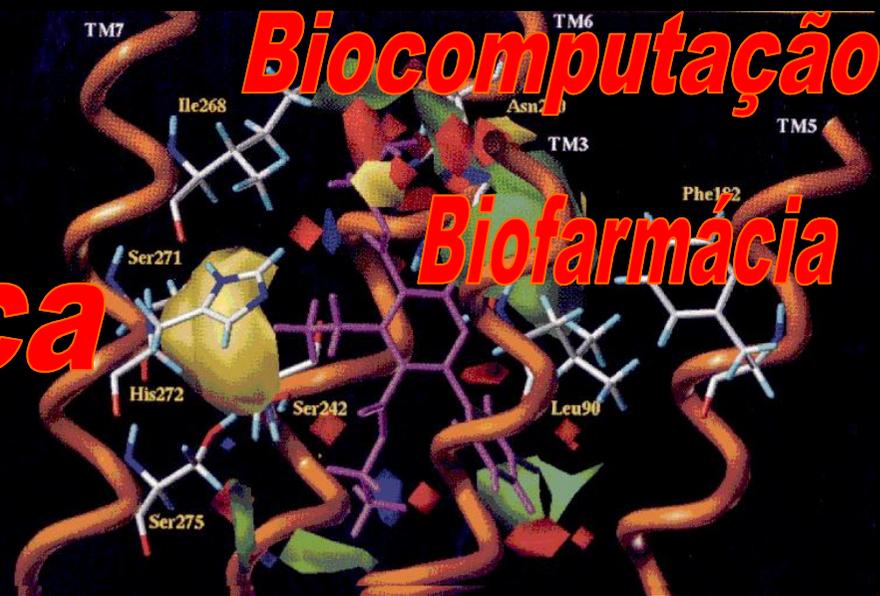
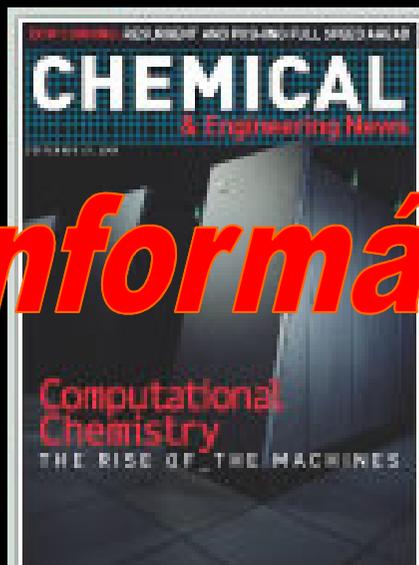


A detecção de ligações-H no sítio ativo de protease-I de *Achromobacter* envolvendo os resíduos treonina-99 e glicina-102 de uma banda da fita com e tirosina-72 e isoleucina-69 expande a possibilidade de construir-se racionalmente inibidores seletivos.

A Inovação
Farmacêutica

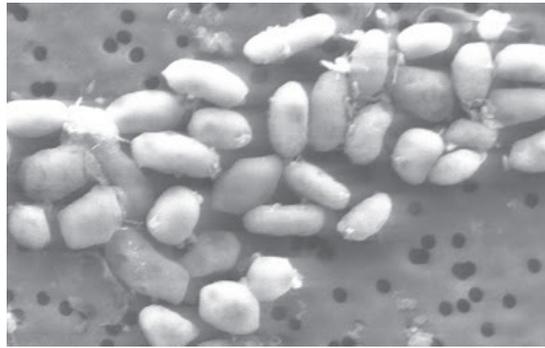


Bioinformática



Biocomputação

Biofarmácia



GFAJ-1

Halomonadaceae

Felisa Wolfe-Simon *et al.*
astrobióloga

NASA Astrobiology Institute

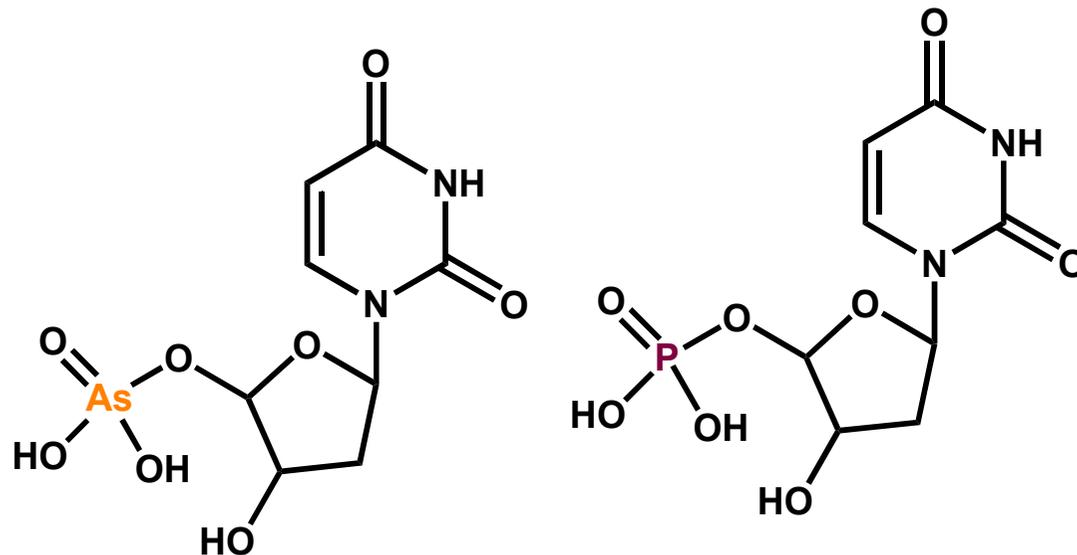


F. Wolfe-Simon, J. S. Blum, T. R. Kulp, G.W. Gordon, S.E. Hoefft, J. Pett-Ridge, J.F. Stolz, S.M. Webb, P.K. Weber, P.C. W. Davies, A. D. Anbar, R.S. Oremland
A Bacterium That Can Grow by Using Arsenic Instead of Phosphorus,
Science (DOI: 10.1126/science.1197258), 2 December 2010

Lago Mono, Cal., EUA



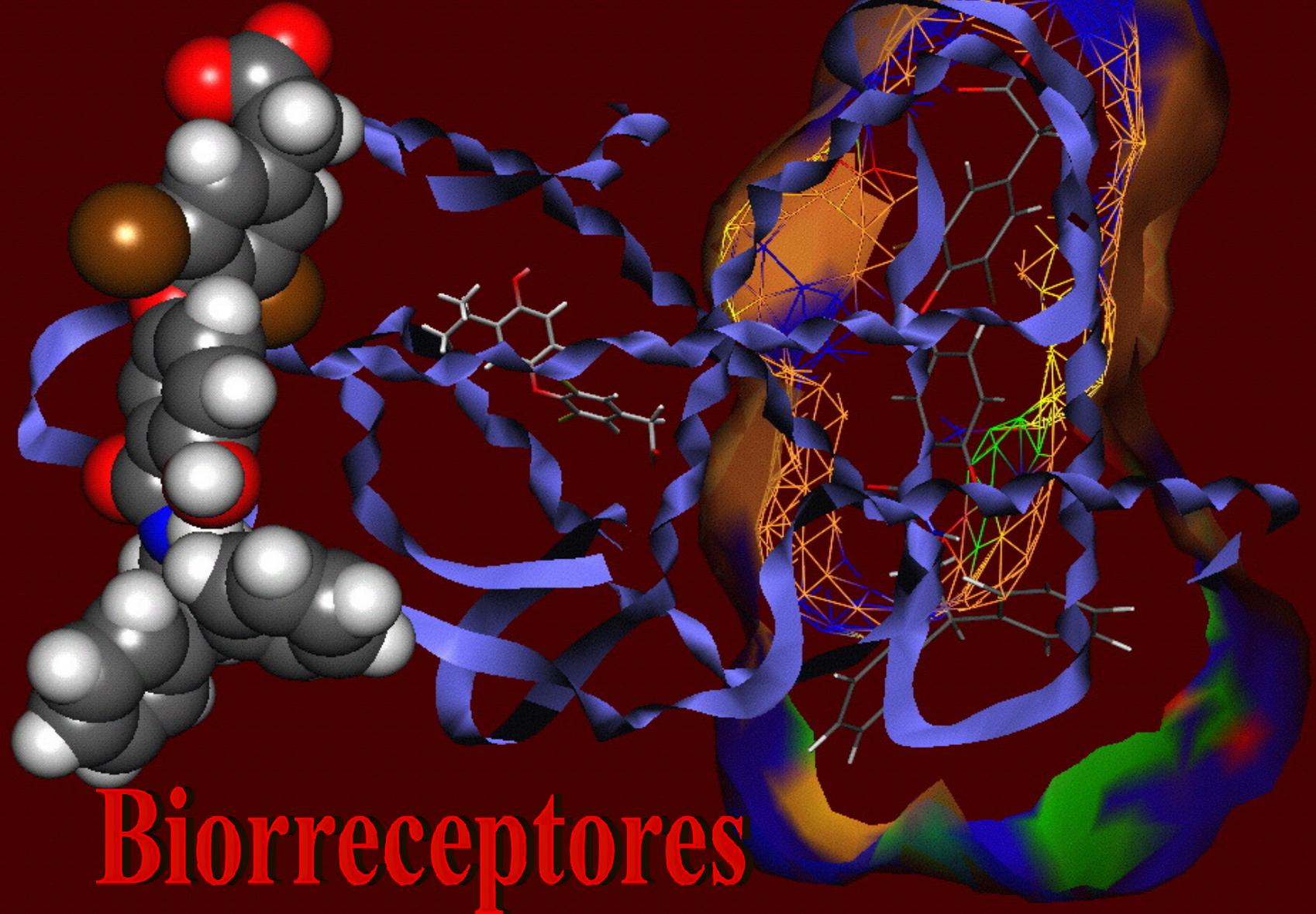
Similaridade Molecular



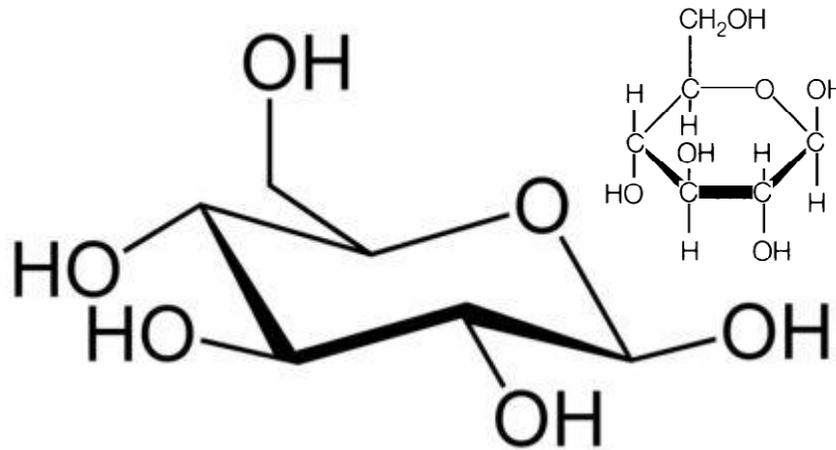
15	16	17	18
5A	6A	7A	0
			He
N	O	F	Ne
P	S	Cl	Ar
As	Se	Br	Kr
Sb	Te	I	Xe
Bi	Po	At	Rn



Agora....



Biorreceptores

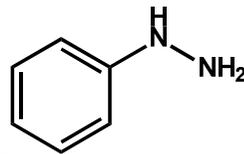
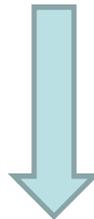
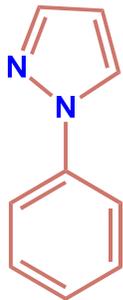
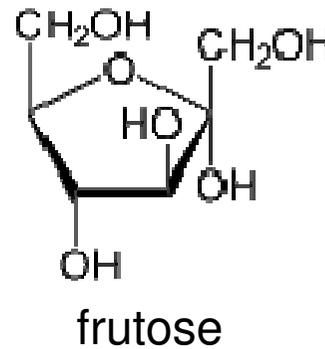


The Nobel Prize in Chemistry 1902
Emil Fischer



Emil Fischer
1852-1919

Glicose



Teoria da chave-fechadura

Complementaridade
molecular

Reconhecimento
molecular

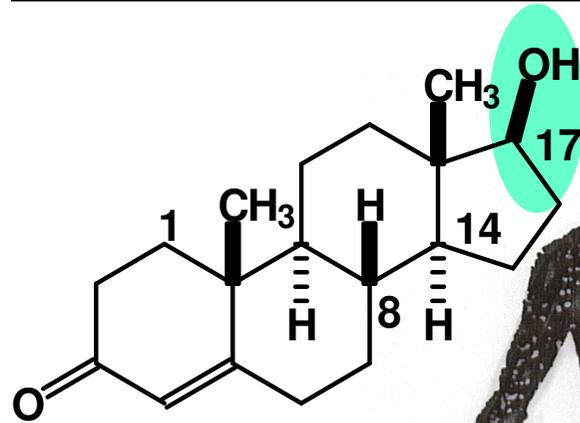
Interação fármaco-biorreceptor



Química
Medicinal



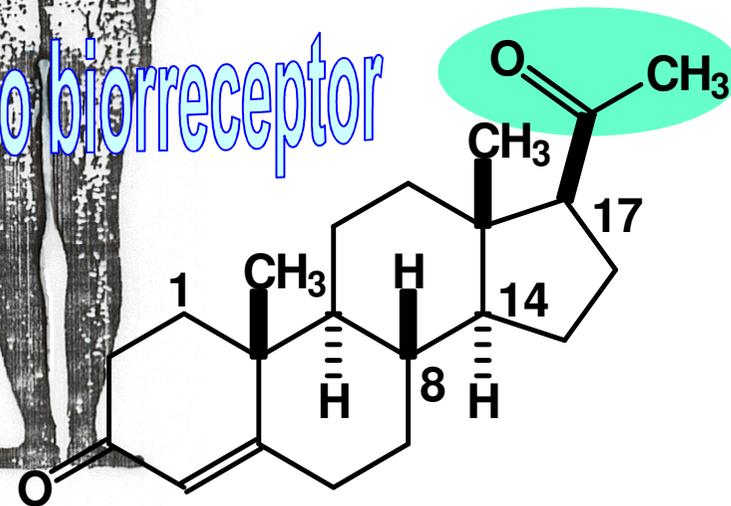
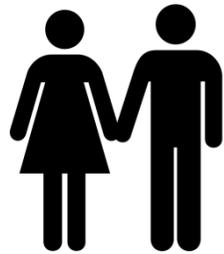
Similaridade & Dissimilaridade Molecular



testosterona



no reconhecimento molecular pelo biorreceptor



progesterona

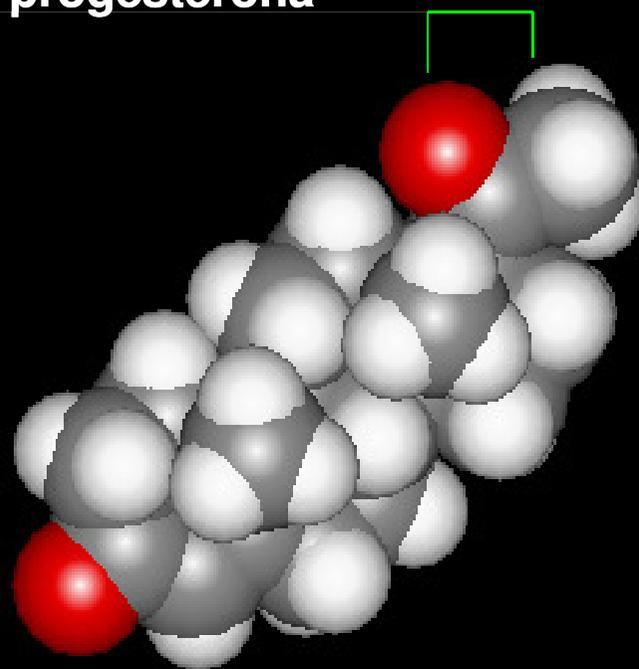
Biorreceptores



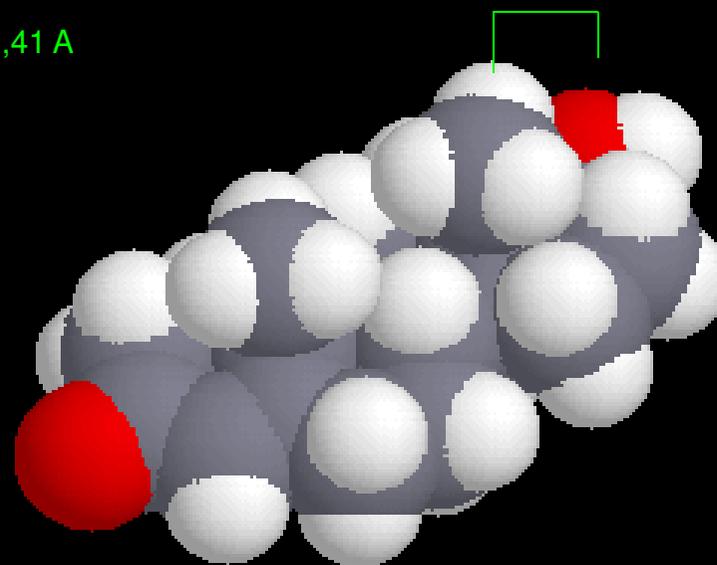
progesterona

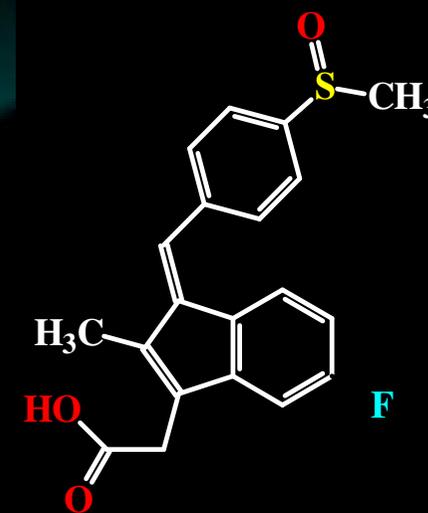
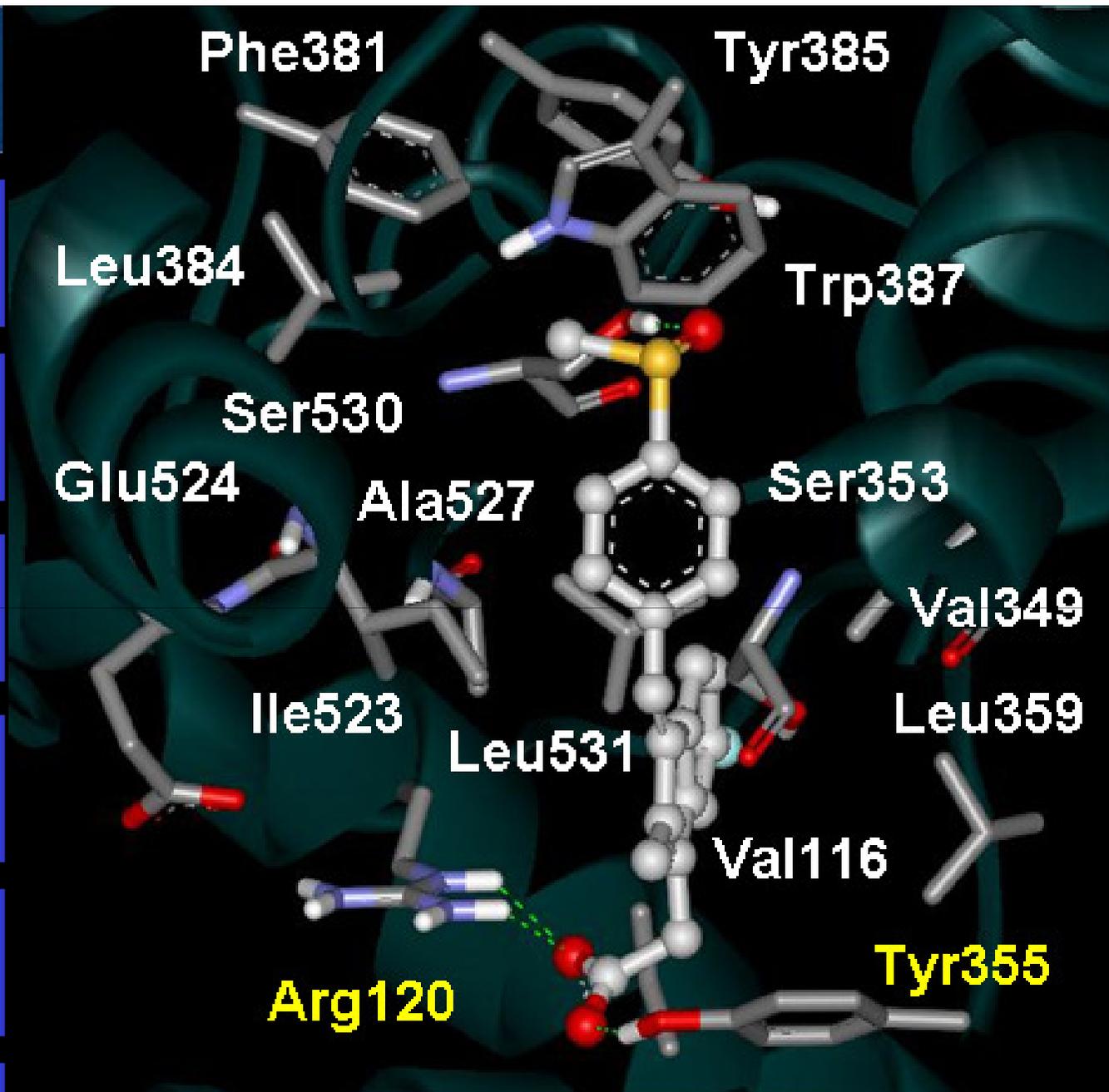
testosterona

Biorreceptores



1,41 A



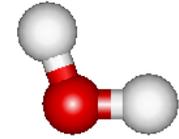
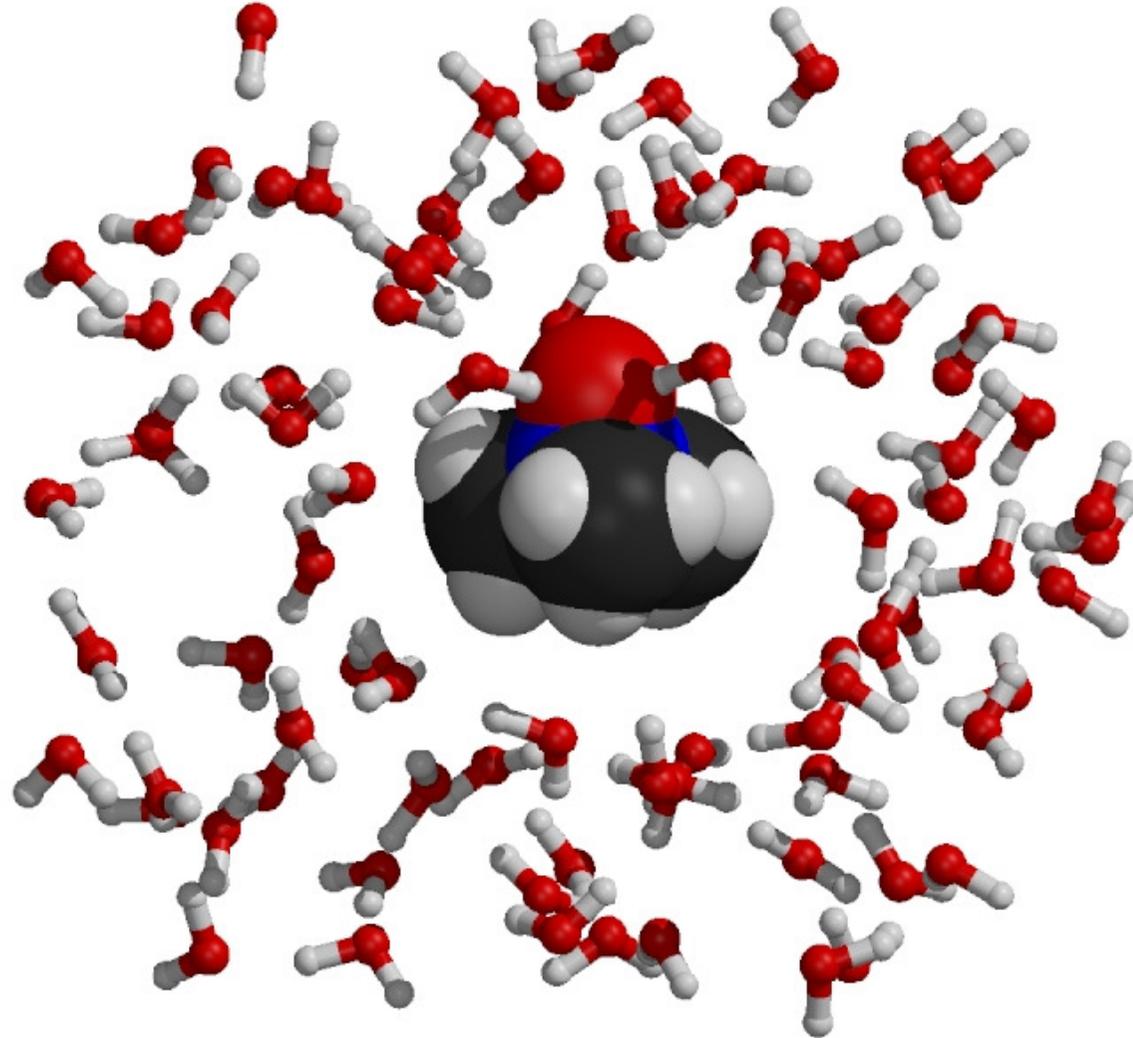


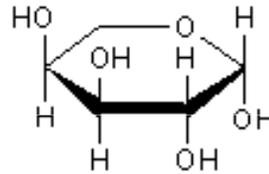
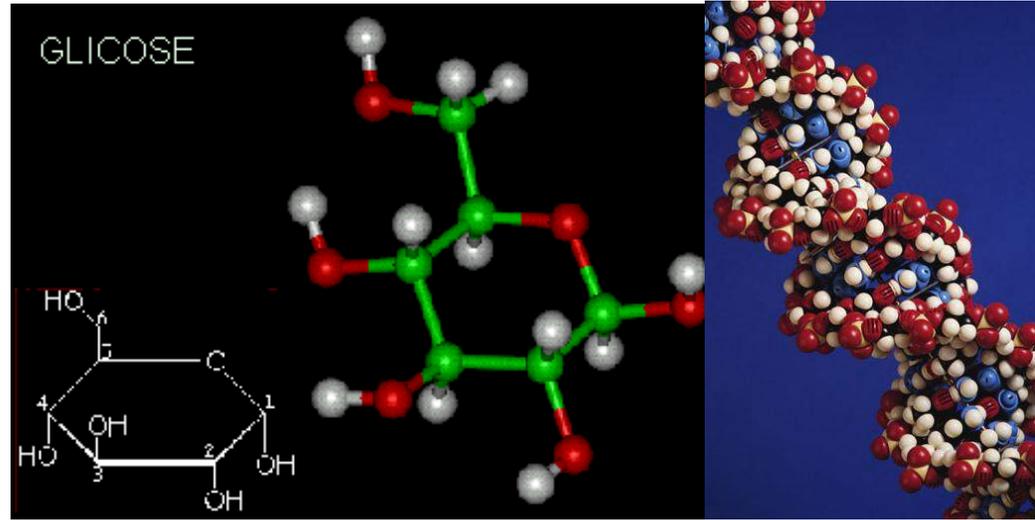
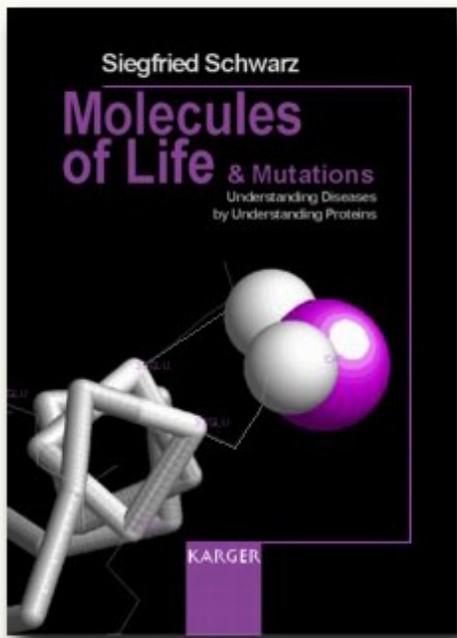
Interações do sulindaco com COX-1



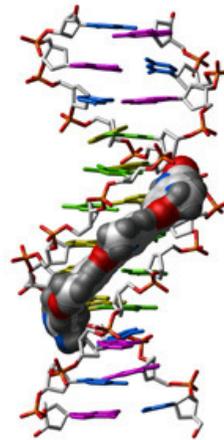
A importância das “ligações” frágeis...

Moléculas da vida...





β-L-Arabinose



Model Compound Bound to the Minor Groove of a DNA Molecule

Carboïdratos

Lipídeos

ácidos nucleïcos

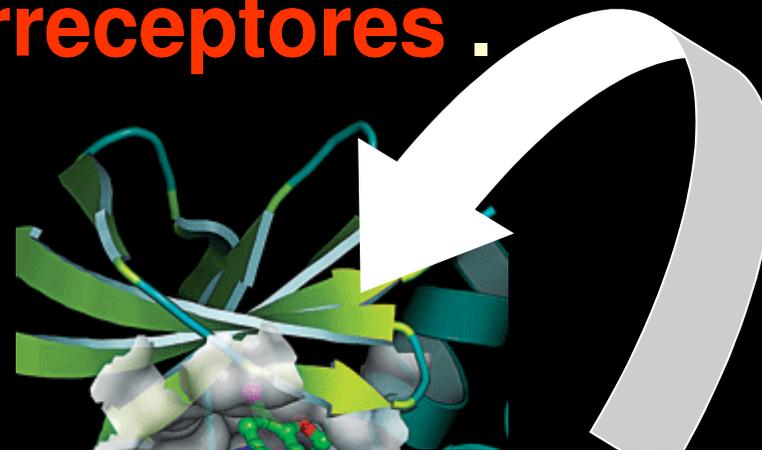
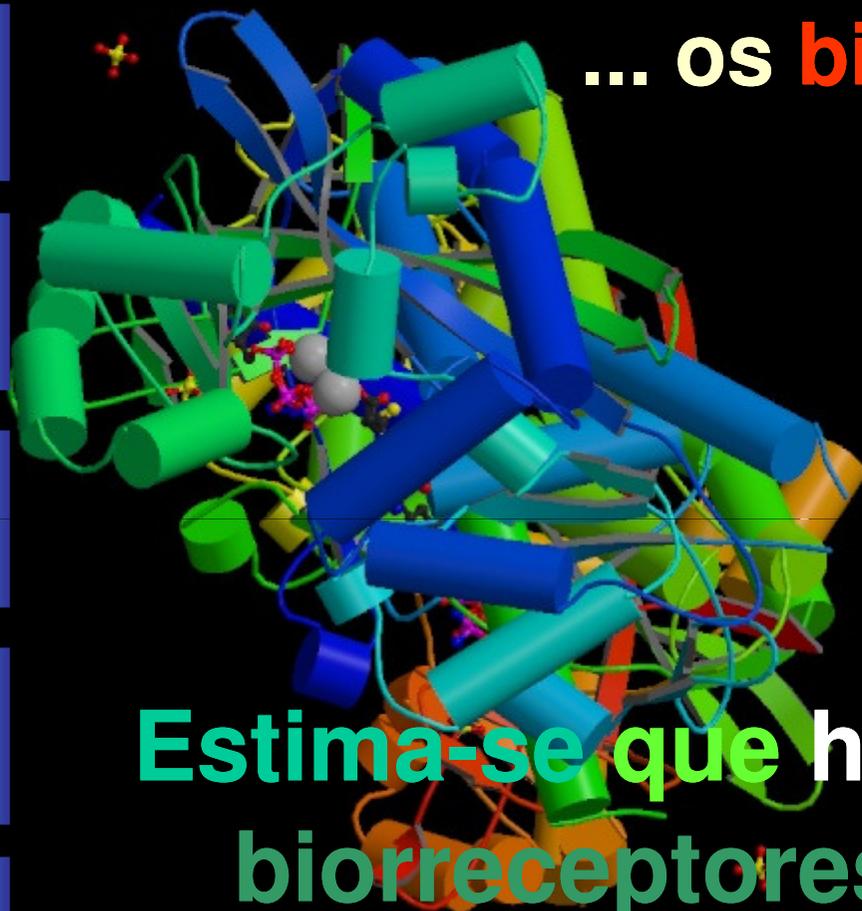
proteínas





Os fármacos atuam em alvos terapêuticos...

... os **biorreceptores**.



Estima-se que hoje sejam **483** os biorreceptores envolvidos na resposta terapêutica de todos os fármacos contemporâneos.



Os biorreceptores...

McKemy, D.D.; Neuhauser, W.M.; Julius D.;

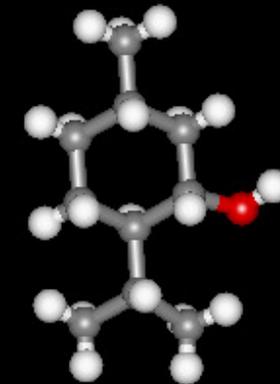
Identification of a cold receptor reveals a general role for TRP channels in thermosensation



Nature 2002, 416, 52.

CMR1 (*cold-menthol receptor type 1*)

Farmácia

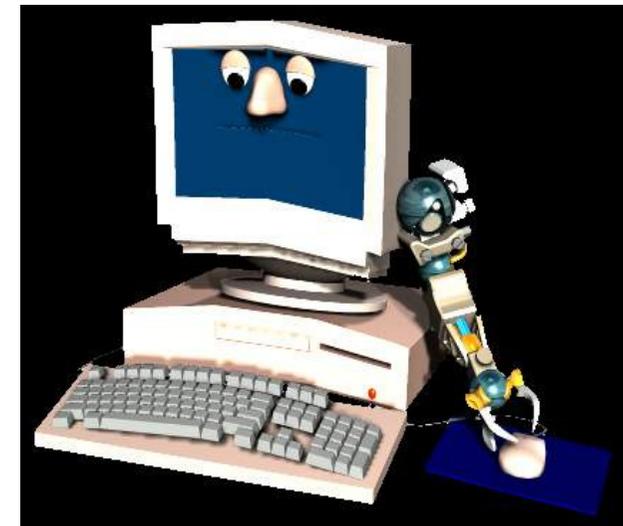
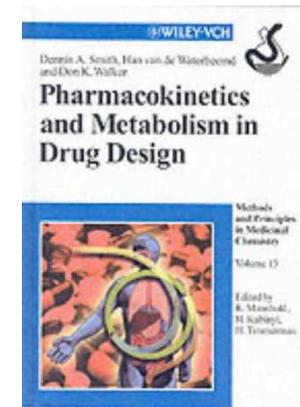
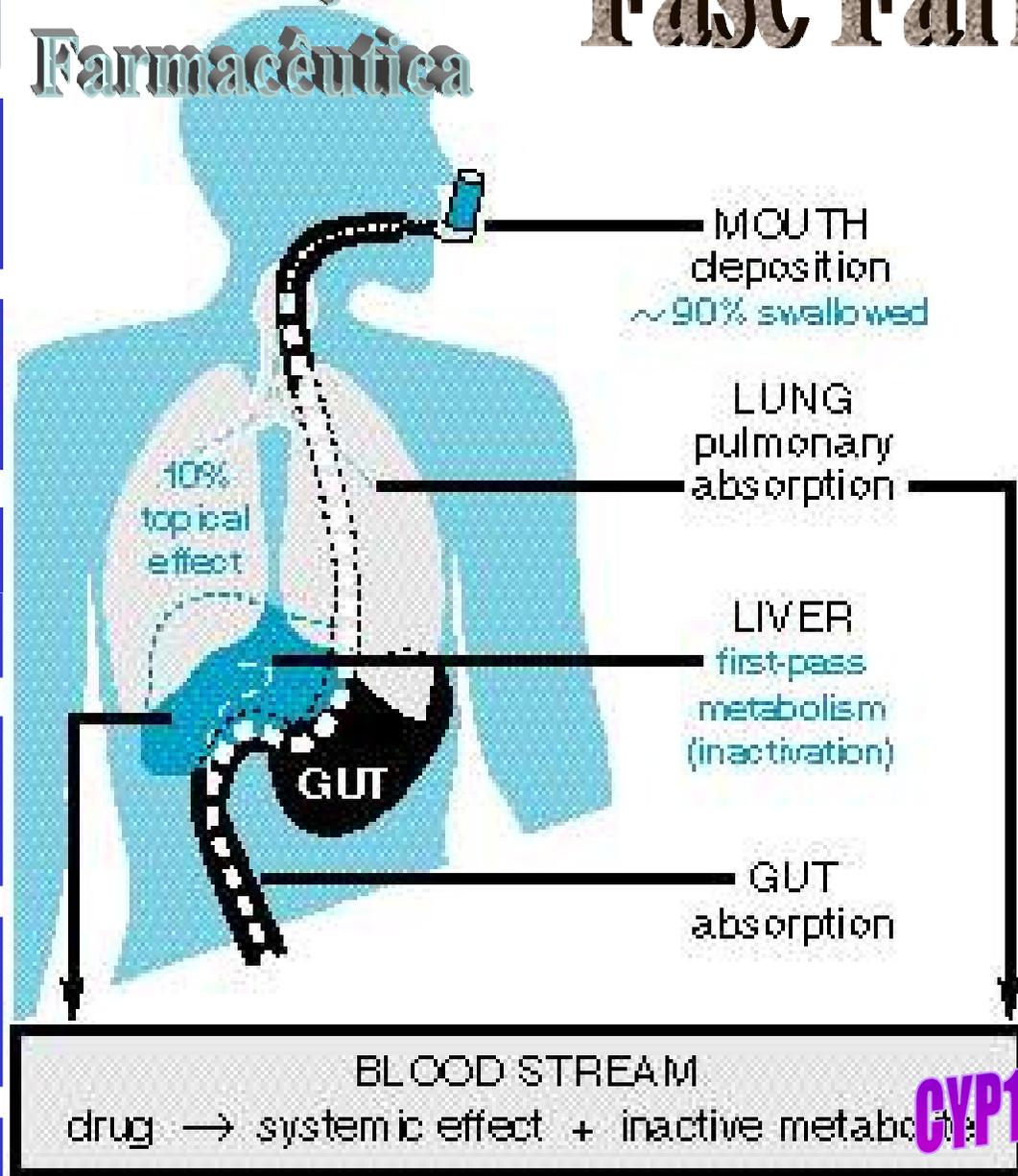


mentol



A Inovação Farmacêutica

Fase Farmacocinética



**CYP1A2, CYP2C9, CYP2C19, CYP2D6
and CYP3A4**

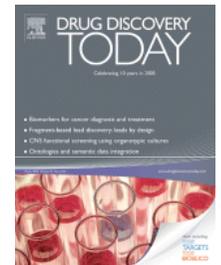


Rato Transgênico Humanizado



*This mouse is a xeno-sensor
allows the investigation of
drug-drug interactions .*

W. Xie & R. M. Evans, *Drug Discovery Today* 2002, 7, 509-515

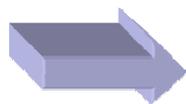


Animal transgênico com mesmo perfil de resposta à ação de fármacos que humanos. Possui **CYP3A isoenzimas** (*xeno-sensor*) que permite o estudo de interações de fármacos, simulando o estudo em humanos.

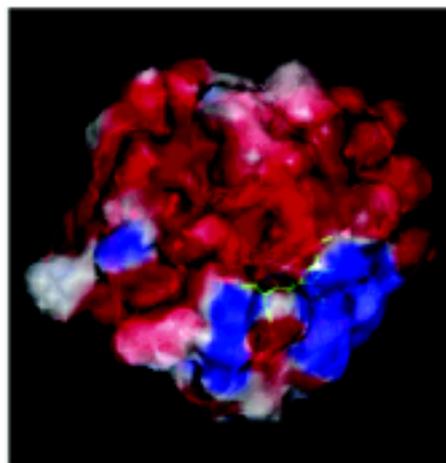
Humanized mouse model



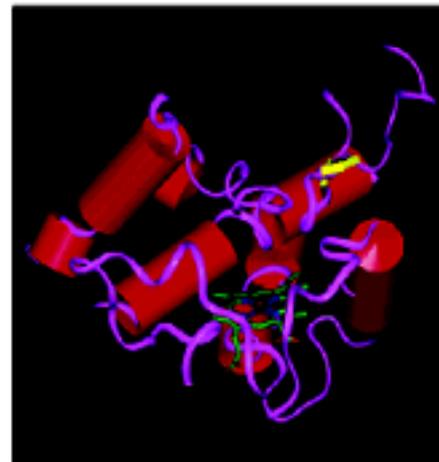
**Modelagem por homologia das isoformas
do CYP2D6 humano e do rato
e subsequente racionalização computadorizada
das interações com ligantes
permitiu esclarecer as especificidades
moleculares destas interações.**



a)



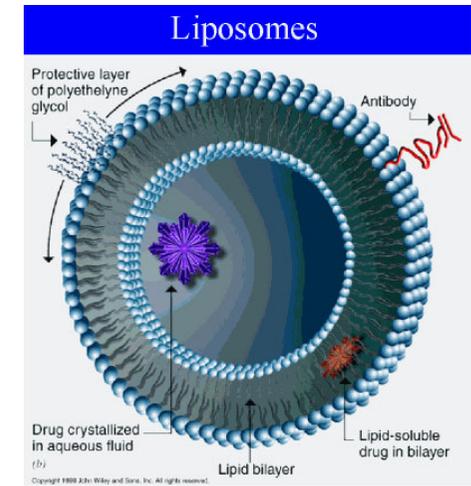
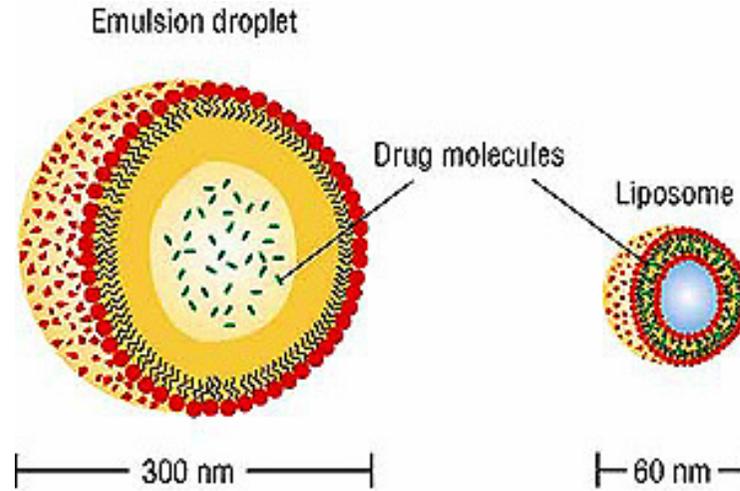
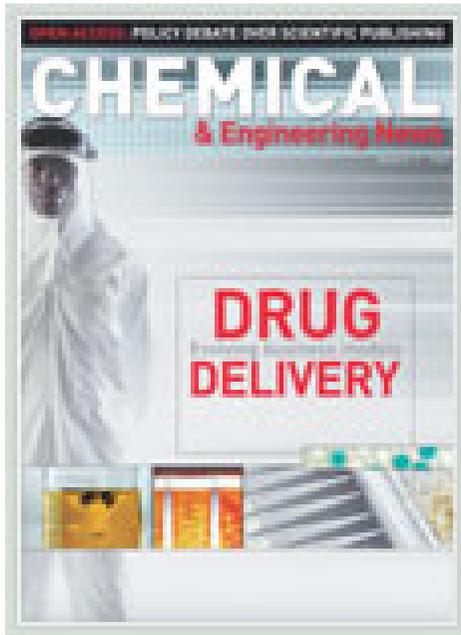
b)



a) Potencial eletrostático no sítio-ativo de CP2D6; b) sítio-ativo, contendo o grupo heme (verde) ao fundo.

NPE Vermeulen et al., J. Med. Chem. 2003, 46, 74.





Pharmacotecnia

The Multifunctional BIOCHIP

Microarrays and biosensors represent the potential for high-throughput, high-resolution analysis of a large number of samples.

Biotechnology and Biosensors

Biosensors and biosensors represent the potential for high-throughput, high-resolution analysis of a large number of samples.

The BIOCHIP

The BIOCHIP has the following characteristics:

- High resolution and high throughput
- High resolution and high throughput
- High resolution and high throughput

Medical Diagnostics

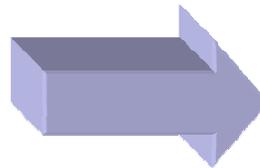
The multifunctional capabilities of the BIOCHIP can be used for a wide range of applications, including:

- High resolution and high throughput
- High resolution and high throughput
- High resolution and high throughput

Drug Development

The multifunctional capabilities of the BIOCHIP can be used for a wide range of applications, including:

- High resolution and high throughput
- High resolution and high throughput
- High resolution and high throughput



the
Pharmaceutical
Century

CONTRACT RESEARCH: CHEMISTRY OPTIONS GO GLOBAL

CHEMICAL & Engineering News

NANOTECH
Drexler & Smalley square off



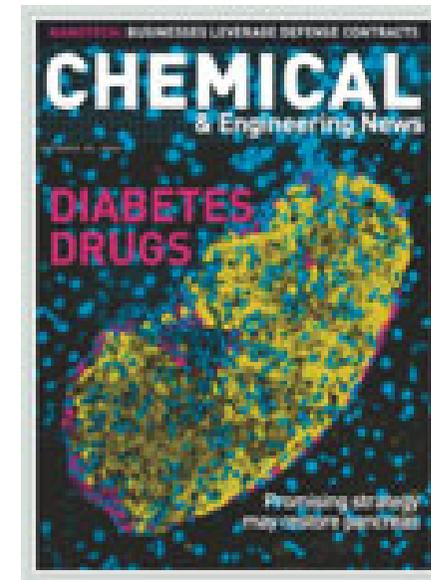
Novas formulações

Exubera^R

Insulina para inalação:
diabetes tipo 1 e 2.

Pfizer
Exubera[®]

18/10/2007 suspendeu a
comercialização mundial!

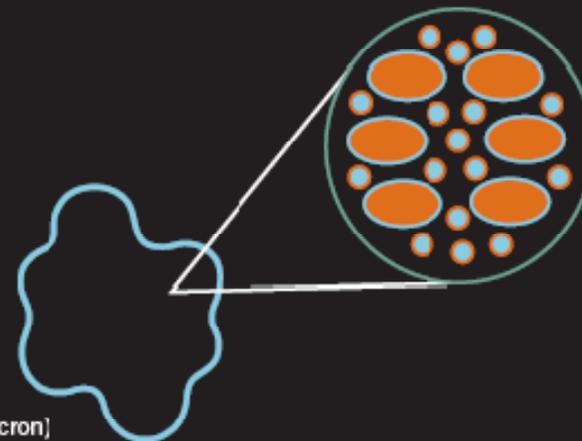


Nektar Pulmonary Particle Technology

- Insulin molecule
- Glass stabilizer

One aerosol insulin particle
contains approximately 300
million insulin molecules
stabilized with glass formers.

Aerosol particle
(diameter: 1 micron)



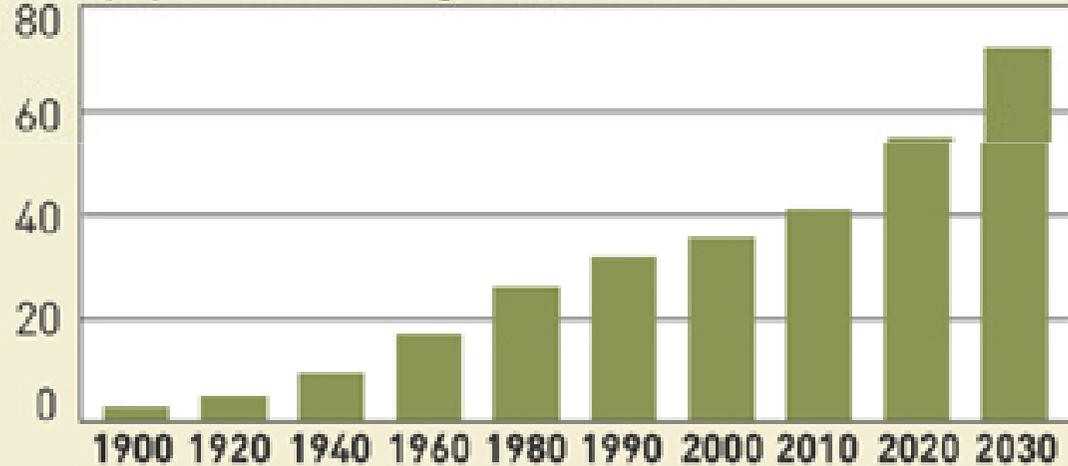


"New style drugs"

ELDER BOOM

Thanks to baby boomers, the U.S. population over 65 will swell between 2010 and 2030

U.S. population over age 65, millions



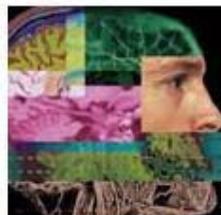
SOURCE: Census Bureau



À esquerda rato transgênico "envelhecido" (equivalente a 100 anos humanos).

the **Pharmaceutical Century**

TEN DECADES OF DRUG DISCOVERY



the Pharmaceutical Century

TEN DECADES OF DRUG DISCOVERY

[Analytical Chemistry](#) | [Chemical & Engineering News](#) | [Modern Drug Discovery](#)
[Today's Chemist at Work](#) | [E-Mail Us](#) | [Electronic Readers Service](#)

1800s to 1919

We live today in a world of drugs. Drugs for pain, drugs for disease, drugs for allergies, drugs for pleasure, and drugs for mental health. Drugs that have been rationally designed; drugs that have been synthesized in the factory or purified from nature. Drugs fermented and drugs engineered. Drugs that have been clinically tested. Effective. Safe.



zoom



*"We live today in a world of **drugs**.* Drugs for **pain**, drugs for **disease**, drugs for **allergies**, drugs for **pleasure**, and drugs for **mental health**. Drugs that have been **rationally designed**; drugs that **have been synthesized** or **purified from nature**. Drugs **fermented** and drugs **engineered**. Drugs that have been clinically tested. Effective. Safe."



Século 21

O conhecimento é instrumento de ascensão social !



Estamos vivendo a Era do Conhecimento





**"Se o conhecimento pode
criar problemas,
não é através da ignorância
que podemos solucioná-los."**

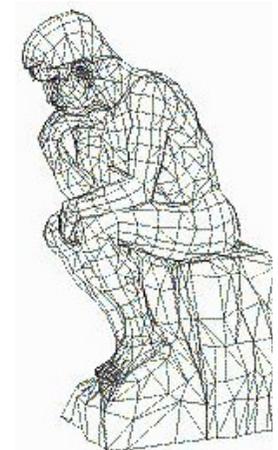


Isaac Asimov

(1920-1992)



Cuidados com a modernidade

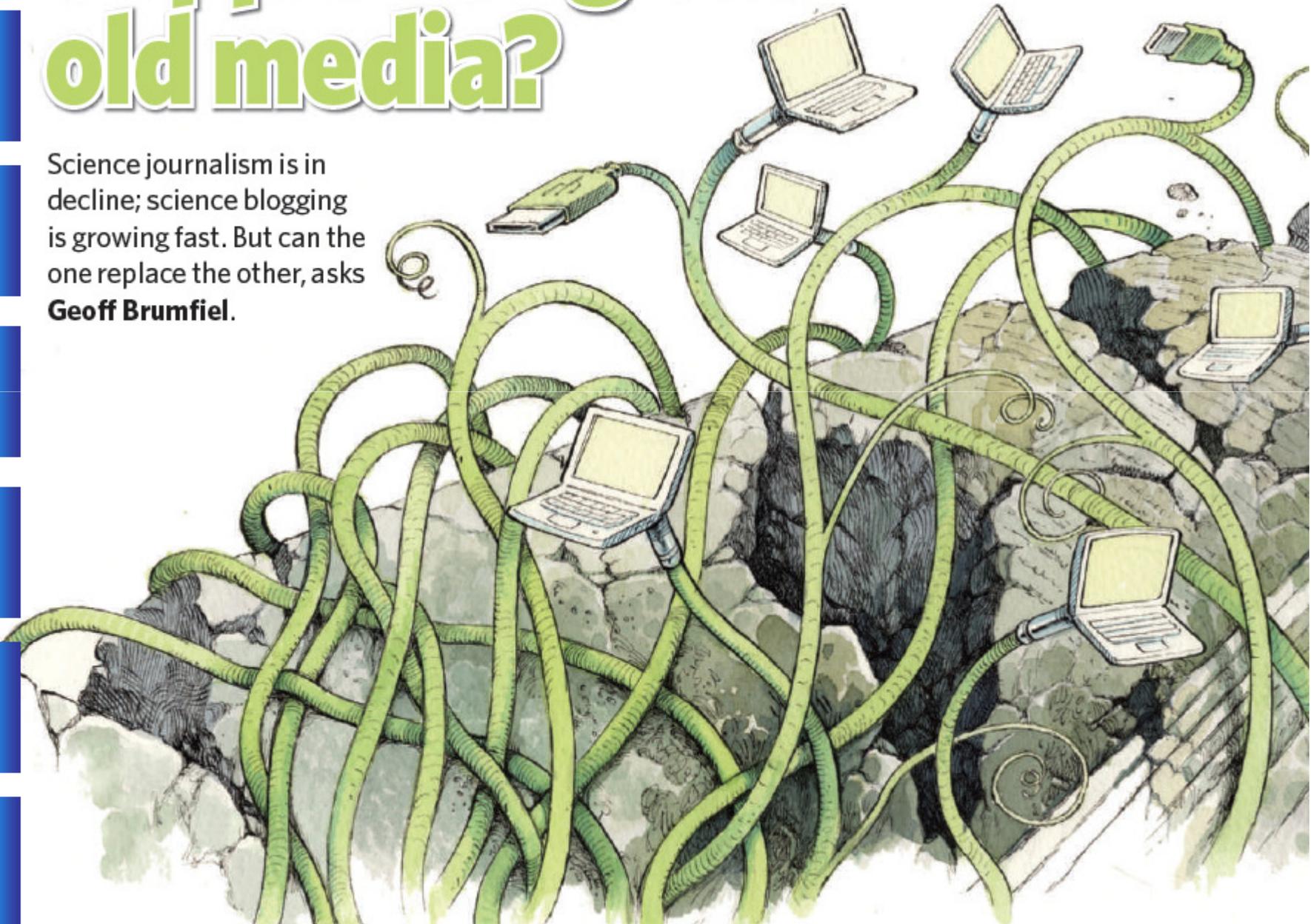




Supplanting the old media?

Nature **2009**, 458, 274

Science journalism is in decline; science blogging is growing fast. But can the one replace the other, asks **Geoff Brumfiel**.





A descoberta de fármacos ...



- *Science* **2000**, 287, 1951 (J.Uppenbrink, J.Mervis)

Índice de impacto (2009) = 29,747



depende da pesquisa científica

“Science is made of facts, just as houses are made of stones; but a mere collection of facts is no more science than a pile of stones a house”

Henri Poincaré, 1902



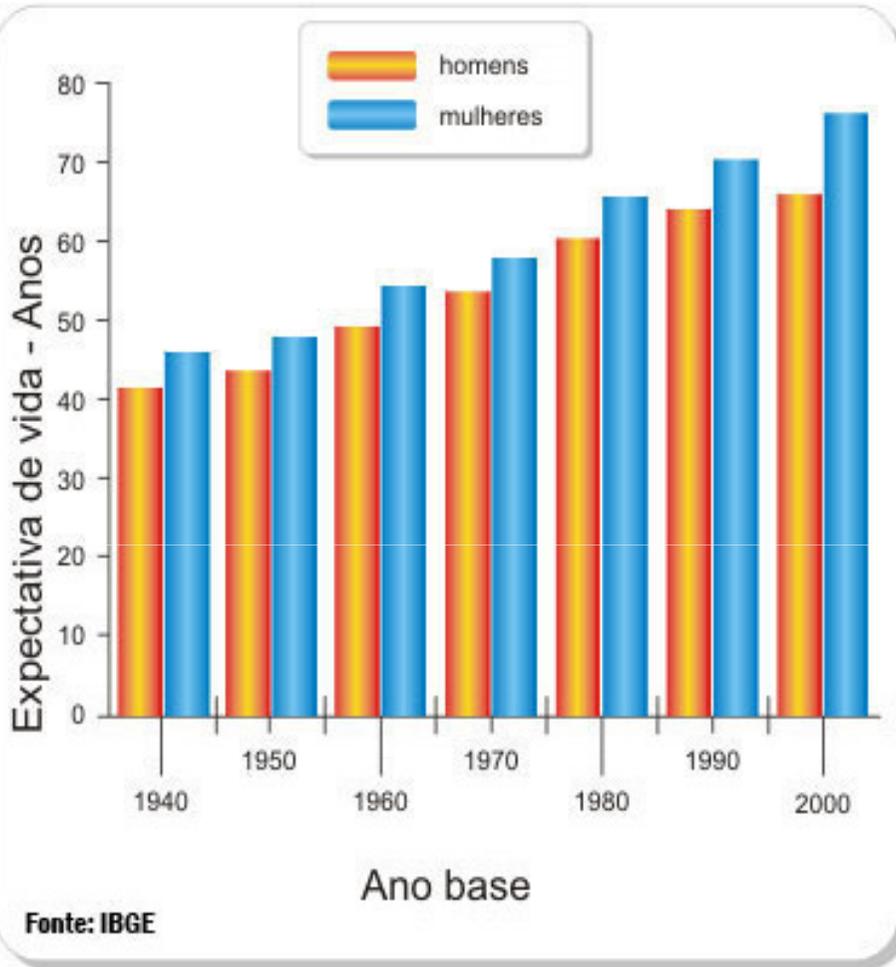
Fármacos:

o que são?

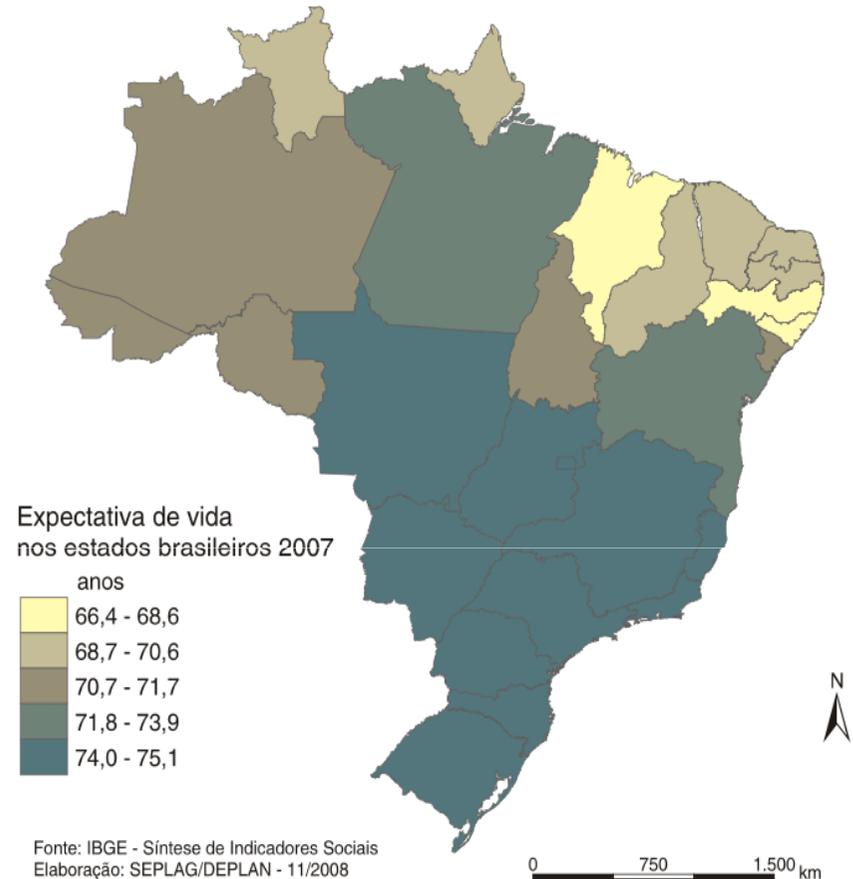




Expectativa de vida do brasileiro



(<http://ibge.gov.br/>)



www.scp.rs.gov.br/uploads/Expect_Brasil_07p.gif



Os fármacos... salvam vidas !



Fármacos e medicamentos...



... são essenciais à atenção farmacêutica da população por corrigirem, recuperarem, manterem e promoveram a Saúde, sendo, portanto, agentes de inclusão social imprescindíveis à soberania da Nação.



Fármaco / Medicamento

Lei 5991 de 17/12/1973

Medicamento é um *produto farmacêutico, tecnicamente* obtido ou elaborado com finalidade profilática, curativa, paliativa ou para fins de diagnóstico.



RESOLUÇÃO N° 338, DE 06 DE MAIO DE 2004

É instrumento de recuperação, manutenção, preservação, *promoção da Saúde.*



Declaração da Cúpula do Milênio da Nações Unidas

Nova Iorque, 6 a 8 de setembro de 2000



O Projeto do Milênio

Secretaria-Geral das Nações Unidas em 2002



2015



“...Países em desenvolvimento **provavelmente** **continuarão** imersos na pobreza, **a menos que** possam **fazer o que** países **desenvolvidos**

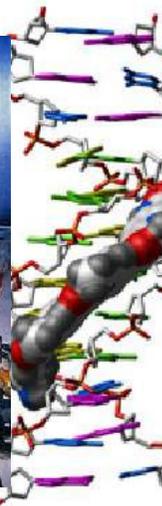
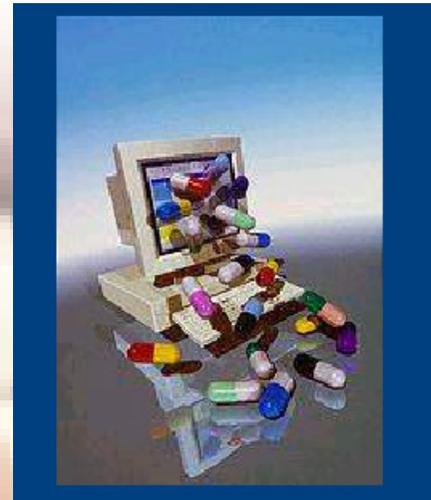
fizeram **para** atingir o **crescimento sustentável**: ***incorporar ciência***.

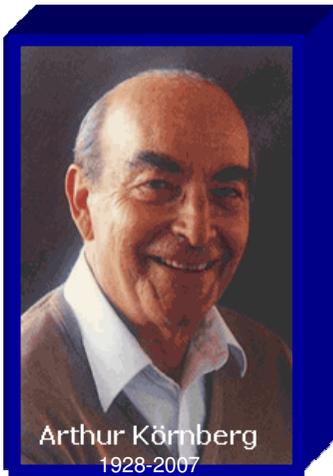
tecnologia e inovação em **suas estratégias** econômicas ... ”

<http://www.unmillenniumproject.org>



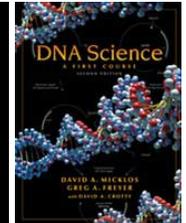
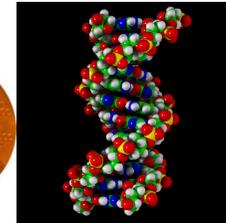
Como são descobertos os fármacos ?





Nobel Prize, 1959

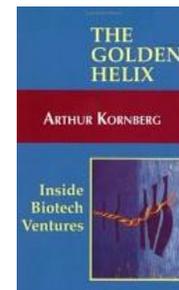
“for their discovery of the mechanisms in the biological synthesis of RNA and DNA”



We have the paradox of the two cultures, chemistry and biology, growing further apart even as they discover more common ground. For the chemists, the chemistry of biological systems is either too mundane or too complex...”



Farmácia



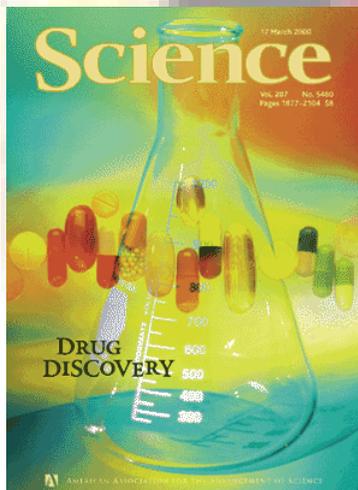
Arthur Kornberg
Annual Meeting of AAAS, 1987



Fármacos

“...Change is in the air for drug discovery... the excitement of this interdisciplinary field at a time of transition ...”

J. Uppenbrink & J. Mervis (Eds.),
Science 287, 1951 (2000)
(*Special Issue*)



Drug Discovery



Processo de Descoberta de Fármacos



Química Medicinal

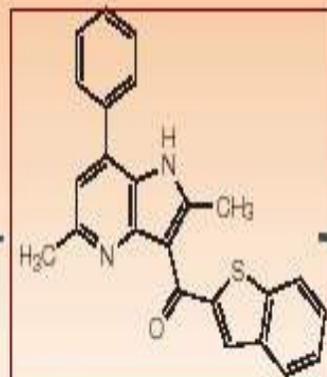
>> 85% do arsenal terapêutico são fármacos sintéticos!



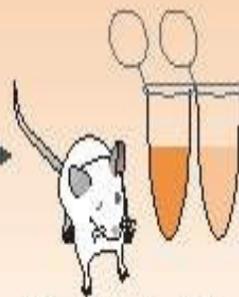
Preclinical studies



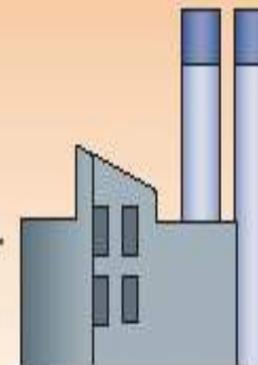
Research team formed and objectives set



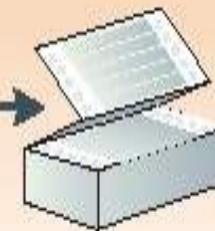
Novel chemicals synthesized



Chemicals tested for efficacy and safety in test tubes and animals. Results used to choose drug candidate.



Formulation, stability scale-up synthesis, chronic safety in animals



Company files Investigational New Drug (IND) application with FDA

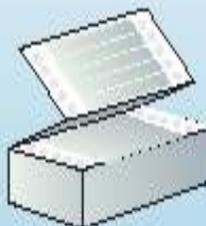
Clinical studies



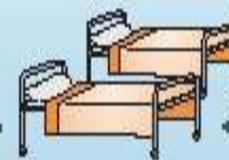
Drug is approved for marketing

ANVISA
FDA

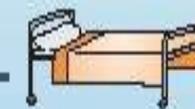
FDA reviews NDA



Company files New Drug Application (NDA)



Phase III: large clinical trials in many patients



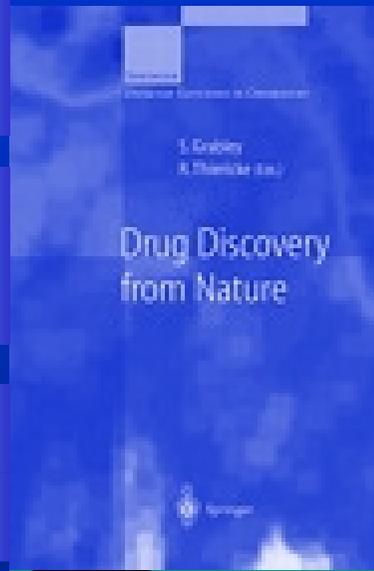
Phase II: studies in patients (efficacy)



Phase I: studies in healthy humans (toleration)



Patrimônio genético brasileiro

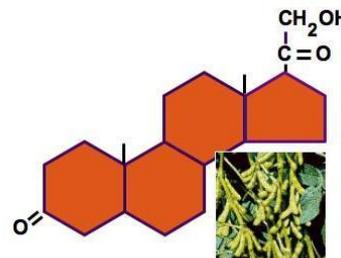




Produtos Naturais na Descoberta de Fármacos

{ **vegetais** > microrganismos, fungos > mar }

- **Fármacos anti-câncer, antibióticos, antifúngicos:** ausência de resistência cruzada
- **Diversas classes terapêuticas (bioinspiração)**
- **Índice terapêutico (IT)**
- **Nova entidade química (NCEs = *New chemical entity*)**
- **Inovação terapêutica: mecanismo de ação inovador**
- **Acessibilidade sustentável**
- **Abundância natural adequada: ensaios pré-clínicos & clínicos**
- **Bióforos naturais**
- **Moléculas *domesticáveis***



• AL Harvey, Natural products in drug discovery, *Drug Discovery Today* **2008**, 13, 894

• C Viegas Jr, VS Bolzani, EJ Barreiro, CAM Fraga, New anti-Alzheimer drugs from biodiversity: the role of the natural acetylcholinesterase inhibitors, *Mini-Rev. Med. Chem.* **2005**, 5, 915

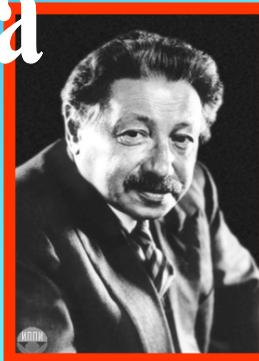


Antibioticoterapia

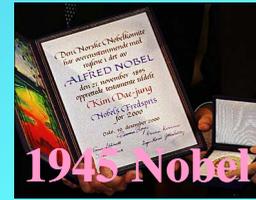
Moléculas Salva-vidas...



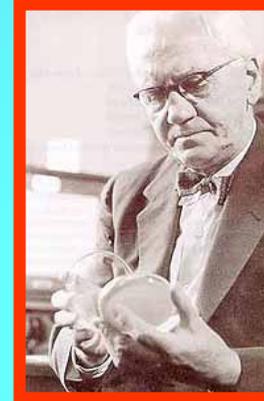
Antibióticos β-lactâmicos



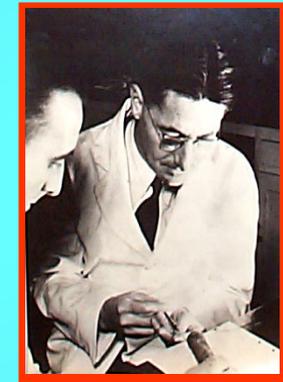
E. B. Chain
1906-1979



1945 Nobel



Sir A. Fleming
1881-1955



Sir H. W. Florey
1898-1968



a nel β-lactâmico





Vinblastina

Câncer



Vinca rosea Linn., Apocynaceae



Velban^R (Lilly)

R. L. Noble *et al.*, *Ann. N.Y. Acad. Sci.* 76, 882-894 (1958)

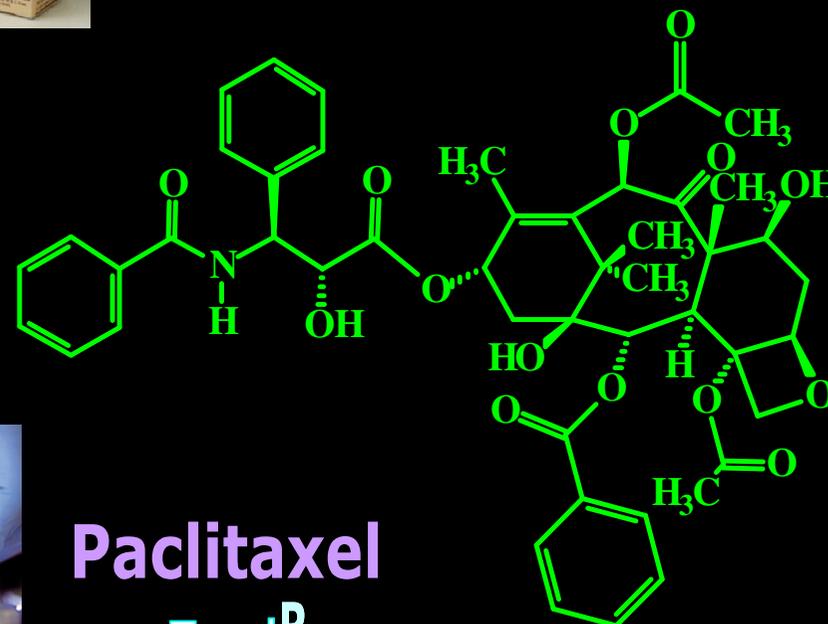
Res. Triangle Park, 1967



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



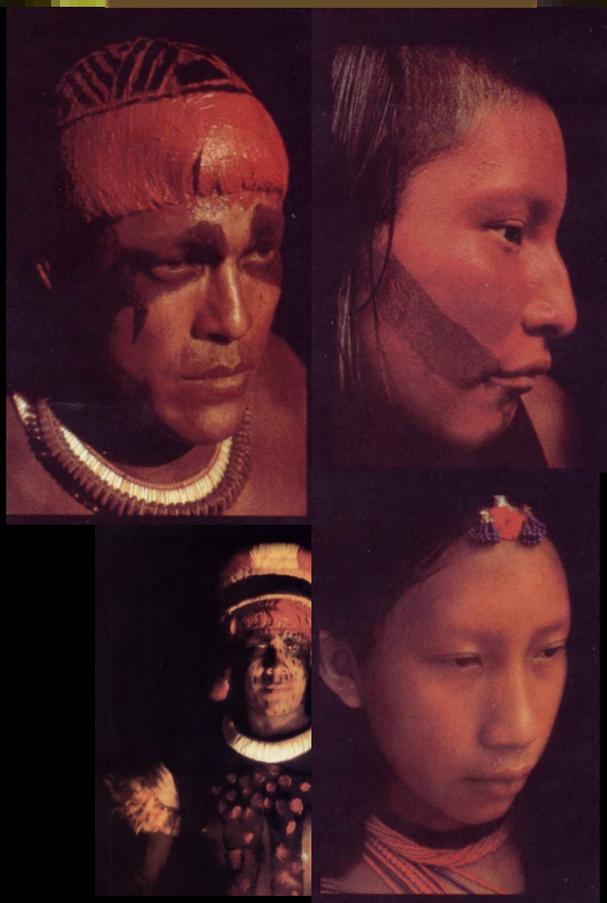
Paclitaxel
Taxol^R



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

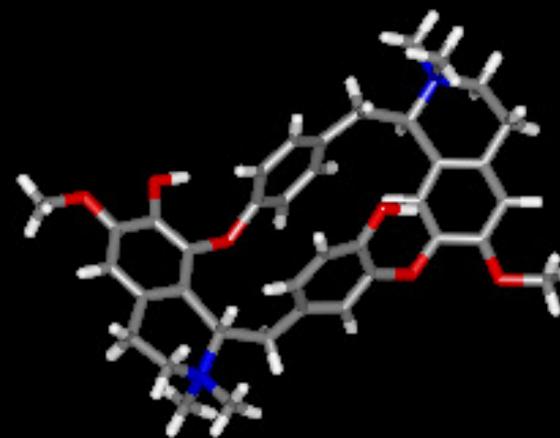


Curare



Bloqueadores
ganglionares

Fármaco dos Índios



d-tubocurarina



“Específico Pessoa”, criado pelo farmacêutico José Torquato Pessoa na cidade de Camocim, no Ceará, como preparado antiofídico (Francisco José de Abreu Matos)

Produtos Naturais

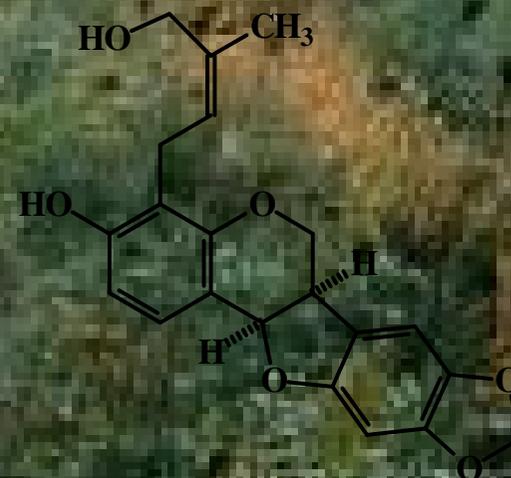
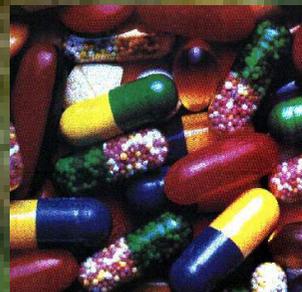


www.iq.ufrj.br/gigantes/otto/angelo.pdf

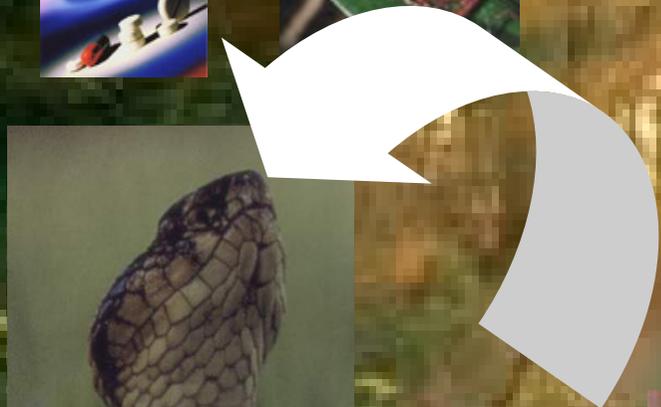
Un. Columbia EUA

K. Nakanishi, ACS, 1991

“A Wandering Natural Products Scientist”
Cabenequine-A



Tetrahedron Lett. 1982, 23, 3855



C O S
N H

