
Universidade Federal do Rio de Janeiro

# Planejamento de Fármacos

XIV Semana de Química *Professor Edson Rodrigues*:
Ano Internacional da Química

Instituto de Química de São Carlos – USP

*Parte 1*


## Eliezer J. Barreiro

**Professor Titular**

**Universidade Federal do Rio de Janeiro**

Laboratório de Avaliação e Síntese de Substâncias Bioativas

**http://www.farmacia.ufrj.br/lassbio**

Instituto Nacional de Ciência e Tecnologia em Fármacos e Medicamentos – INCT–INOFAR

**Programa de Desenvolvimento de Fármacos – ICB-UFRJ**

# O fármaco…


ácido acetilsalicílico

É o fármaco formulado galenicamente…

# O que é um fármaco ?

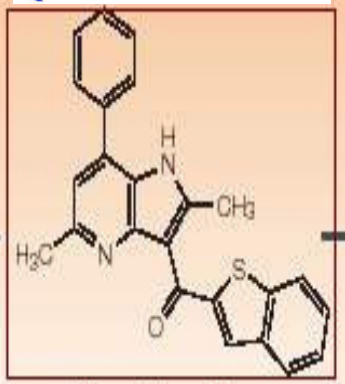
- **Fármaco…**
  - É uma substância orgânica (> 99%) com propriedades farmacoterapêuticas para uso médico, capaz de recuperar, promover, manter ou preservar o estado de Saúde;
  - Tem elevada eficácia para o alvo terapêutico (PD);
  - Não tóxico;
  - Potente *in vivo* com boa biodisponibilidade: ativo em doses baixas, usado por oral em dose-única ao dia;
  - Bem absorvido e estável metabolicamente (PK):
    - Propriedades fisíco-químicas críticas para a atividade do fármaco por via oral: solubilidade, boa partição passiva membrana/água, pêso molecular, ligações-H;
  - Proteção intelectual (*i.e.* patenteável = conteúdo inventivo);
  - Acessível sinteticamente em custos aceitáveis (*scale-up*);
  - Tem aplicação médica segura & inovadora (?);

- **… as propriedades moleculares dos fármacos são objeto do estudo da** Química Medicinal

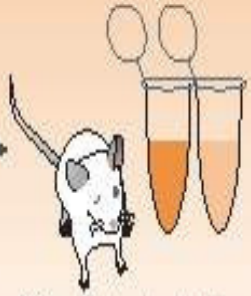
Química Medicinal

Preclinical studies

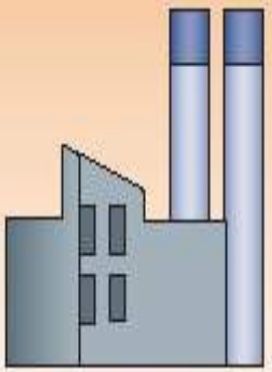
Research team formed and objectives set



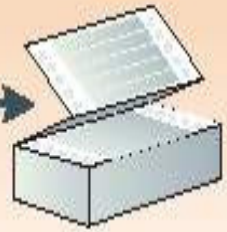

Novel chemicals synthesized



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

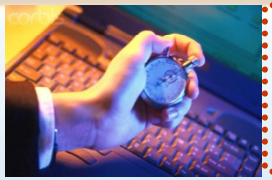


Formulation, stability scale-up synthesis, chronic safety in animals

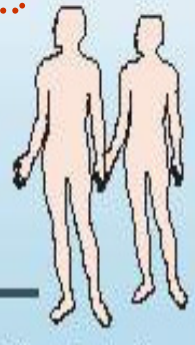


Company files Investigational New Drug (IND) application with FDA

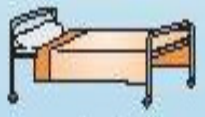
Clinical studies



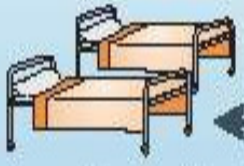
O processo do desenvolvimento de novos fármacos é complexo…



Phase I: studies in healthy humans (toleration)



Phase II: studies in patients (efficacy)



Phase III: large clinical trials in many patients

Company files New Drug Application (NDA)

ANVISA

FDA

FDA reviews NDA

Drug is approved for marketing

JA Lombardino & JA Lowe III, Nature Rev. Drug Disc. 2004, 3, 853

**“ ...medicinal chemists today live in exciting times... their work can have a beneficial effect on millions of suffering patients – surely an important motivating factor for any scientist...”**



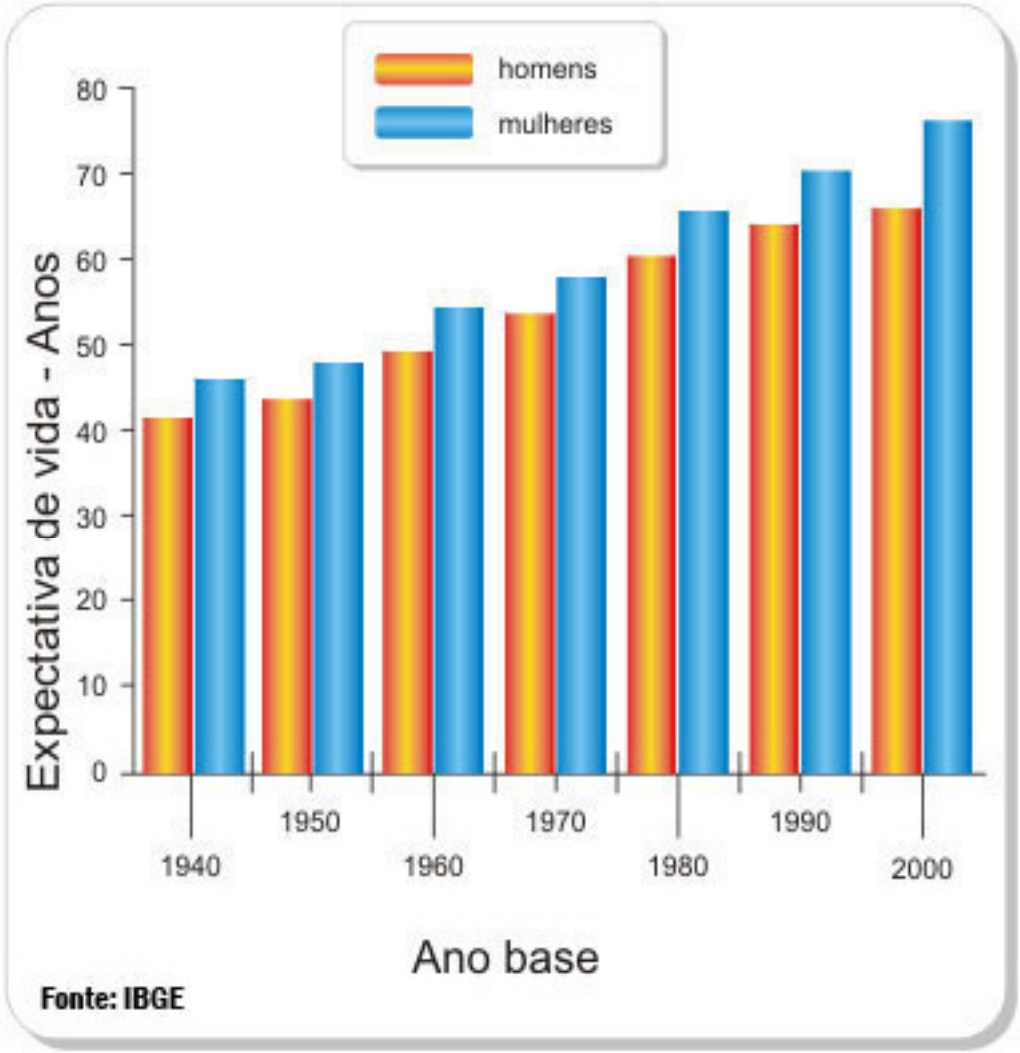
Joseph G. Lombardino

*The Role of the Medicinal Chemist in Drug Discovery – Then and Now*,

***Nature Rev. Drug Disc.*** 2004, **3**, 853.

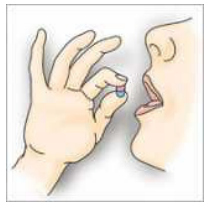
# Aumento na expectativa de vida...

http://clubeficaz.com.br/clubes/vivasaude/files/2008/12/idosos-291x300.jpg

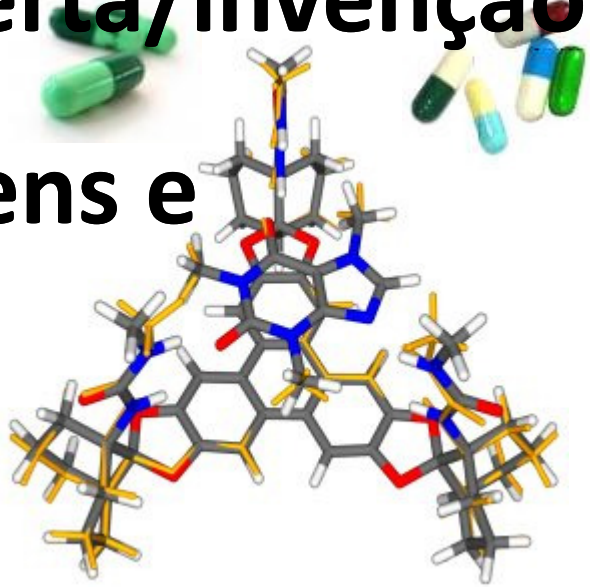



...os fármacos tem muito a ver com isso!

# Química Medicinal



**A Química Medicinal estuda as razões moleculares da ação dos fármacos, sua descoberta/invenção empregando abordagens e estratégias interativas multidisciplinares.**



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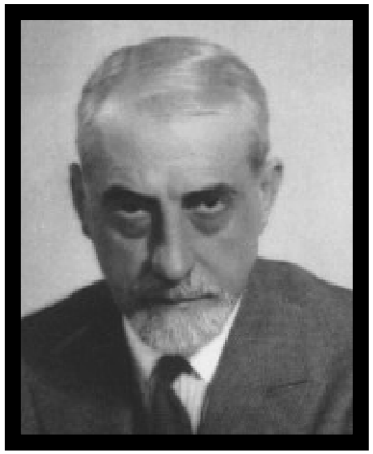
# Os pioneiros

Química Medicinal

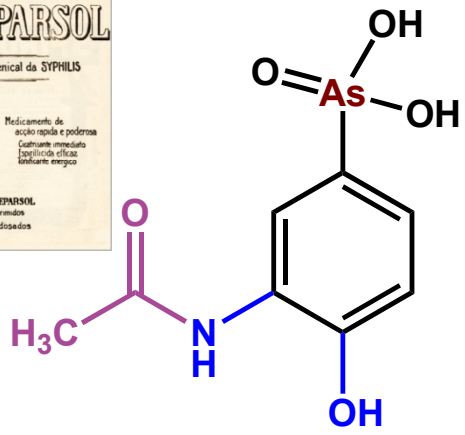
# O berço da Química Medicinal



Ernest Fourneau
1872-1949


**Stovarsol**

CAS 97-44-9




Institut Pasteur (1887)

## 1911- Laboratoire de Chimie Thérapeutique

Institut Pasteur (Emile Roux)

1911-1944 – Jacques Tréfouël (1897-1977)
Théreze Tréfouël (1892-1978)
Germaine Benoit (1901-1983)
Federico Nitti (1903-1947)

Daniel Bovet
1907-1992 *

*Farmacêutico suiço
Doutor *h.c.* UFRJ

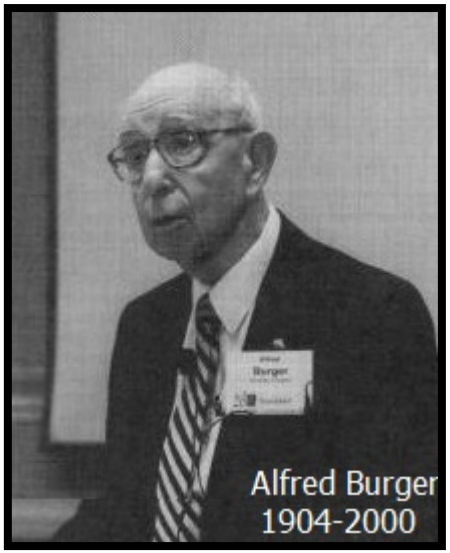
Prêmio Nobel de Fisiologia/Medicina 1957

Sulfonamidas, anti-histamínicos.
Curare: SAR

J-P Fourneau, « Ernest Fourneau foundateur de la Chimie Pharmaceutique française », *Revue de l´Histoire de la Pharmacie*, t.XXXIV, nº 275, 335-355

# Química Medicinal

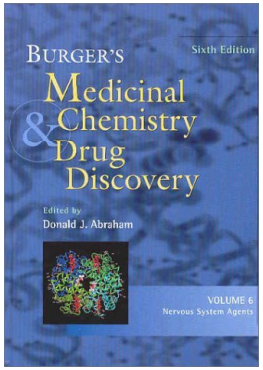
# Prof. Alfred Burger

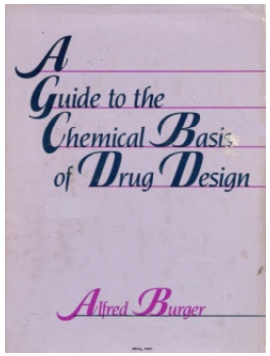



**(1904-2000)**

**University of Virginia**

**EUA**





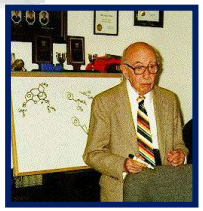

II = 5,207

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 (1962)

"...The unprecedented increase in human life expectancy, which has almost doubled in a hundred years, is mainly due to drugs and to <u>those who discovered them</u>."



Alfred Burger

em "The practice of medicinal chemistry", Wiley, 1970, p. 4.

# Cronologia histórica da Química Medicinal

Galeno

1805 - morfina

1823 - quinina

1834 - atropina

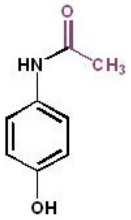

1847 - clorofórmio

1842 - éter etílico

1860 - fenol

1860 - AS

1886 - paracetamol



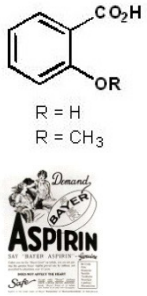

1889 - AAS

1904 - corantes

1902 - Fischer


1908 - Ehrlich

1907 - Salvarsan R







1910 - Dale (AChRs)

1911 - Fourneau

1935 - Domagk

1941- penicilina

1943 - cloroquina

1949 - Laborit

1945 - Fleming

1948 - Ahlquist

1949 - cortisona

1950 - RNM

1955 - Vinca

1958 - Burger

1952 - fenotiazina

1958 - haloperidol

1959 - "pílula"

1959 - Kornberg


1955 – *C. roseus*

1960 - talidomida

1960 - Librium R

1962 - indometacina

1963 - Vallium R

1964 - propranolol

1964 - Hansen

1967 - nifedipina

1975 - cimetidina

1977 - captopril

1980 - cetoconazol

1980 - lovastatina

1981 - aciclovir

1982 - Vane

1988 - Black

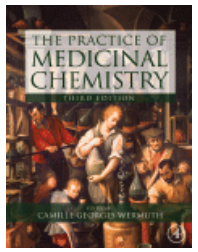
1996 - Wermuth



1999 - oseltamivir

1999 - celecoxibe

2000 - imatinibe

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# Os fármacos e o Prêmio Nobel

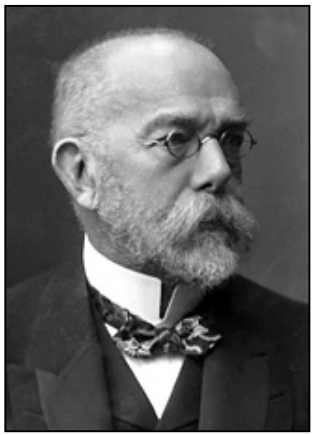
Química Medicinal

# Os fármacos e o Nobel !

**Emil Fischer**

1852-1919

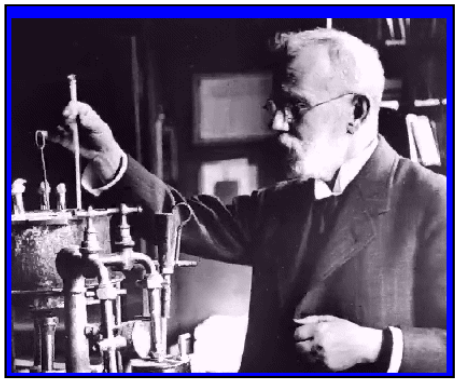
**1902**

**Robert Koch**

1843-1910

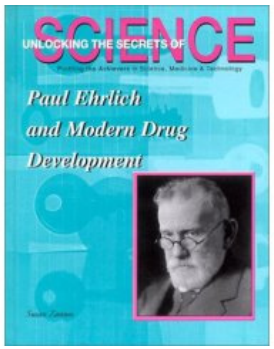
**1905**



**Paul Ehrlich**

1854-1915

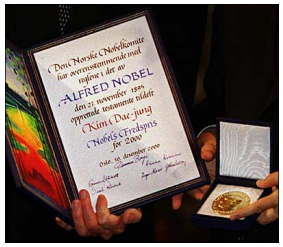
**1908**


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

# Os fármacos e o Nobel !

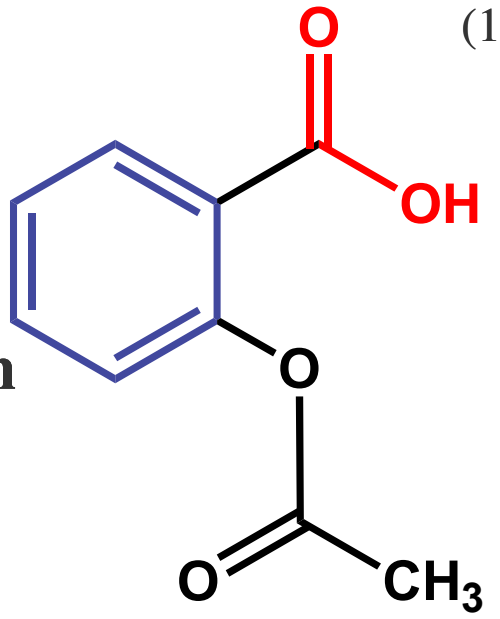
1982



**John R. Vane**
(1927-2004)

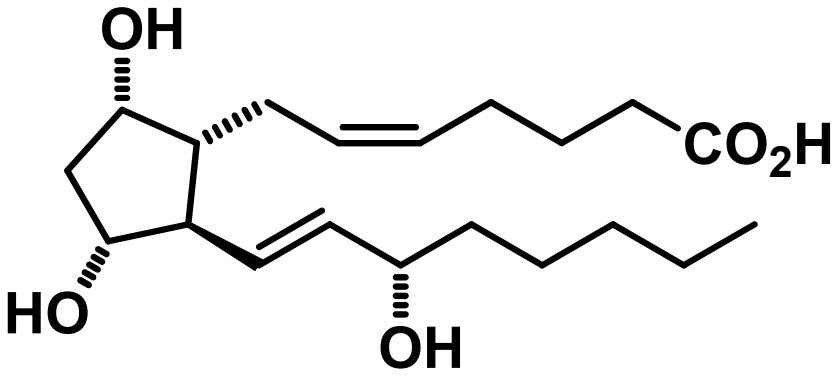
**Sune K. Bergström**
(1916-2004)

**Bengt I. Samuelsson**
(1934-



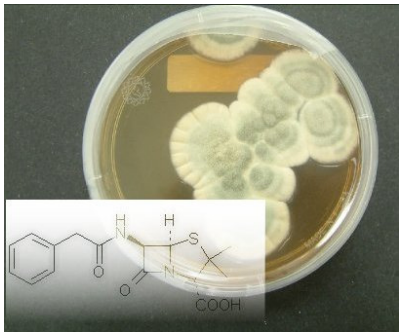

$C_9H_8O_4$


1982 – AAS

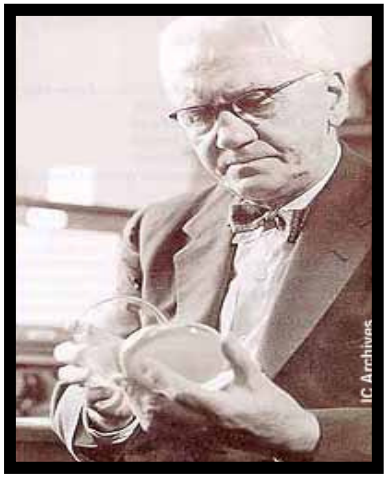



Prostaglandina $F_{2\alpha}$

# Os fármacos e o Nobel !

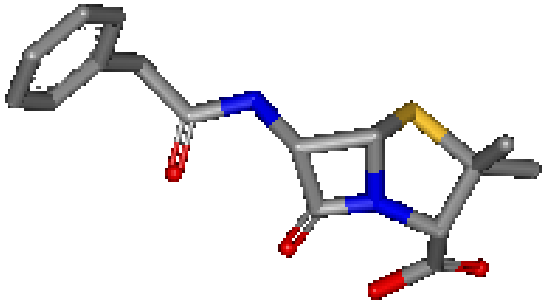


- **196 pesquisadores ganharam o Prêmio Nobel de Medicina (1901-2010)**



**Alexander Fleming**

1881-1955



**Penicilina**

**Howard W. Florey**

1898-1968

http://nobelprize.org

**1945**

**Ernest B. Chain**

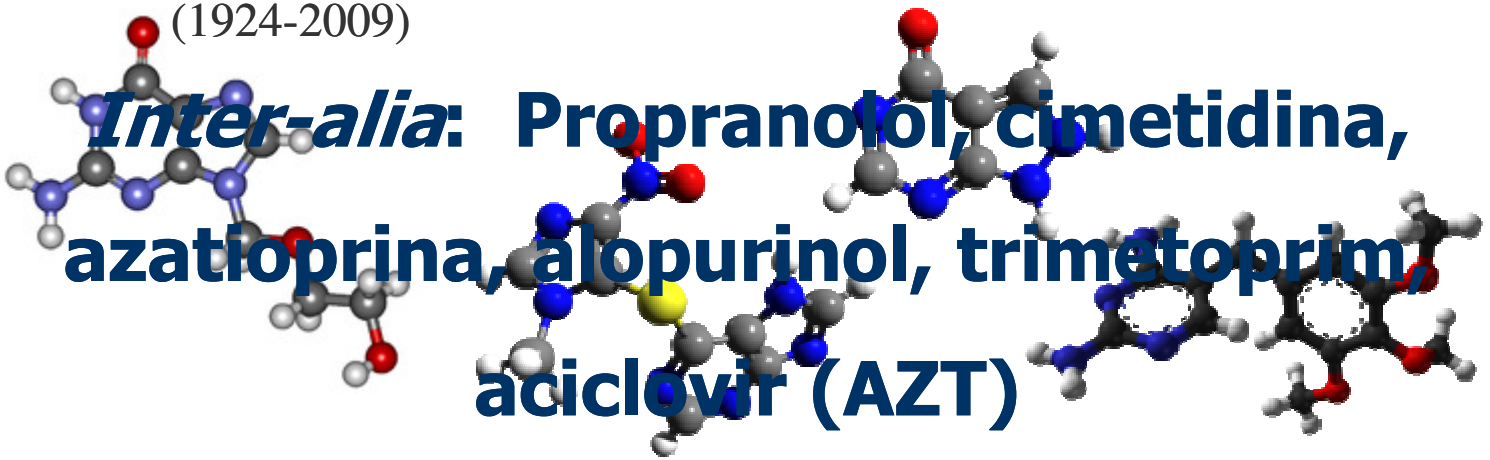
1906-1979

# “for their discoveries of important principles for drug treatment"

James W. Black
(1924-2009)

George Hitchings (1905-1998)

Gertrude B. Elion (1918-1999)



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

1988

EJB3

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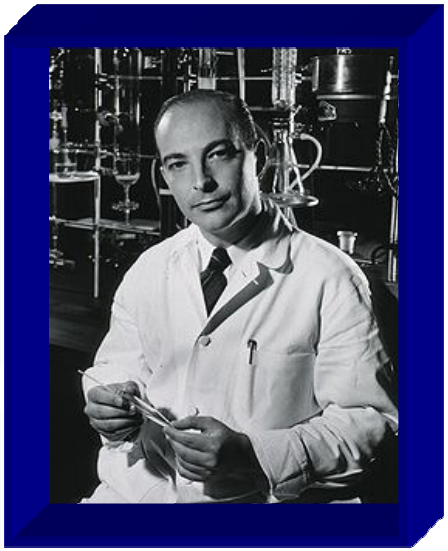


Arthur Kornberg
1918-2007

# Prêmio Nobel, 1959

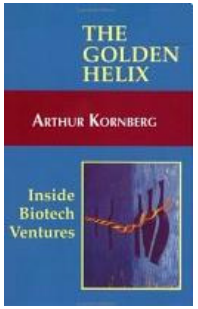
1987

## The Two Cultures: Chemistry and Biology[1]

Arthur Kornberg

*Department of Biochemistry, Stanford University, Stanford, California 94305*

*Received July 14, 1987*




*"Much of life can be understood in rational terms if expressed in the language of chemistry... the historical roots of* **chemistry** *and* **biology** *are intertwined in many places…*

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

University of Stanford

Química Medicinal


*Biochemistry* **1987,** *26,* 6888-6891

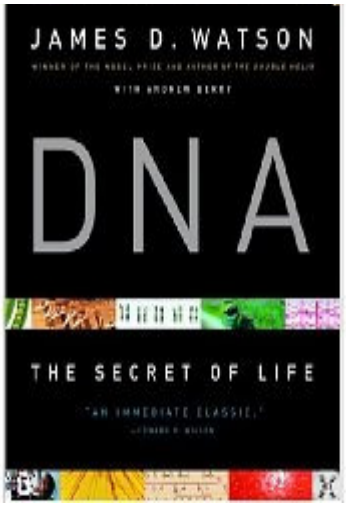
**Slide 18**

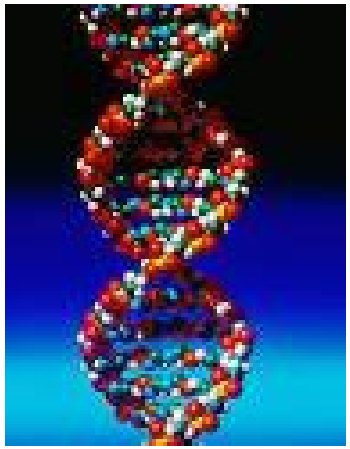
**EJB3**

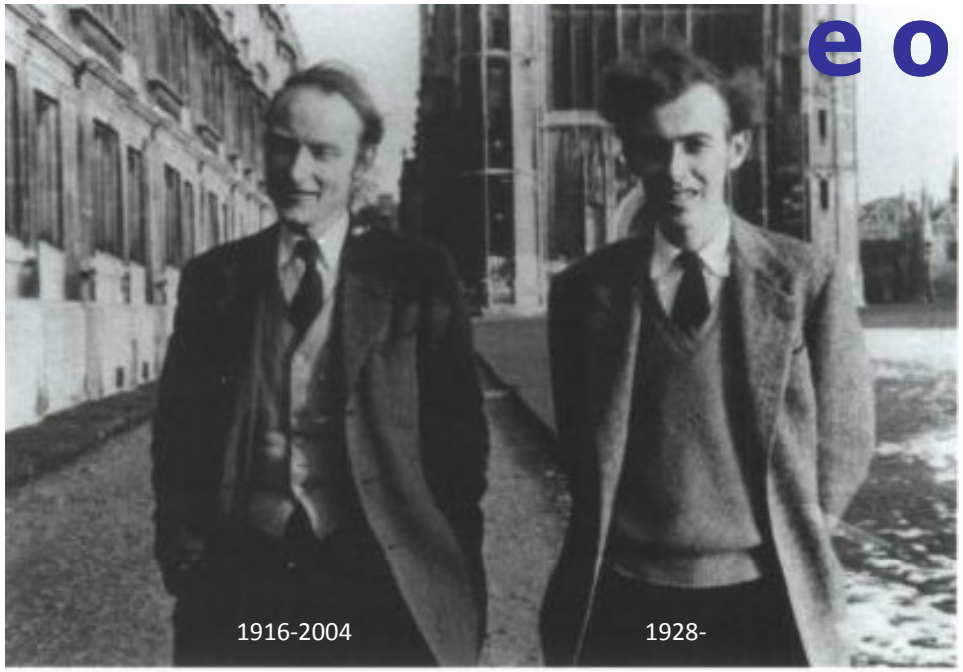
Kornberg definiu as bases da interdisciplinaridade das ciências dos fármacos quando antecipou a necessidade de aproximar-se a Química e a Biologia.

Eliezer J. Barreiro; 04/03/2010

# Os fármacos e o Nobel !






Francis Crick and James Watson in Cambridge, England, 1953
(Courtesy of the James D. Watson Special Collection. Cold Spring Harbor Laboratory Archives. From Watson J.D. 1968, *The Double Helix*. Atheneum Press, New York.)

*1962*


Maurice H. F. Wilkins

## *O físico Crick & biólogo Watson*

J. D. Watson & F. H. C. Crick, Nature *1953,* **171**, 737–738

## Interdisciplinaridade

**Slide 19**

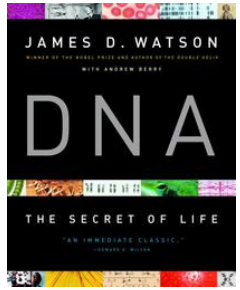
**EJB4**

Exemplos de extraordinárias conquistas do conhecimento humano deveram-se às associações de capacidades e competências complementares, essenciais à sua consecução: e.g. DNA em publicação de apenas 2 páginas em prestigioso periódico científico que resultou, décadas depois, na era ômica.

JD Watson & FHC Crick, Nature, 1953, 171, 737-738

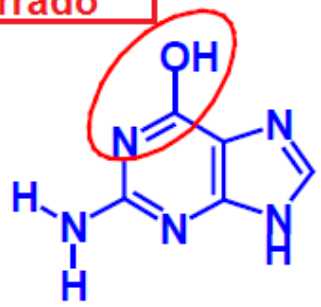
Eliezer J. Barreiro; 04/03/2010

# The Discovery of the DNA Double Helix

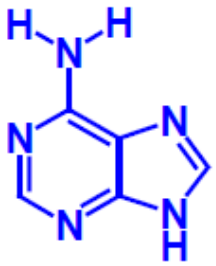



**Summer 1952:** Erwin Chargaff critisizes that Francis Crick and James Watson are ignorant about the structures of the bases

tautômero errado

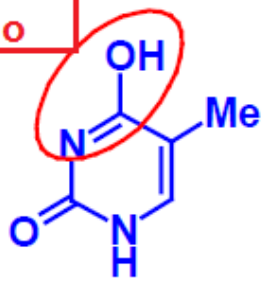


guanine

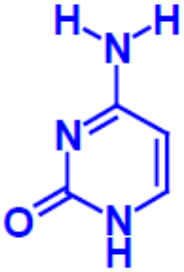


adenine

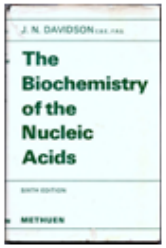
tautômero errado



thymine



cytosine




J. N. Davidson, The Biochemistry of Nucleic Acids, London, 1950

---

early 1953: Pauling publishes a DNA model with a phosphate core

February 27, 1953: Jerry Donohue corrects the formulas of the bases

February 28, 1953: Watson and Crick derive the correct DNA model

April 02, 1953: Manuscript sent to Nature; published April 25, 1953

cited from: J. Watson and A. Berry, DNA. The Secret of Life, 2003

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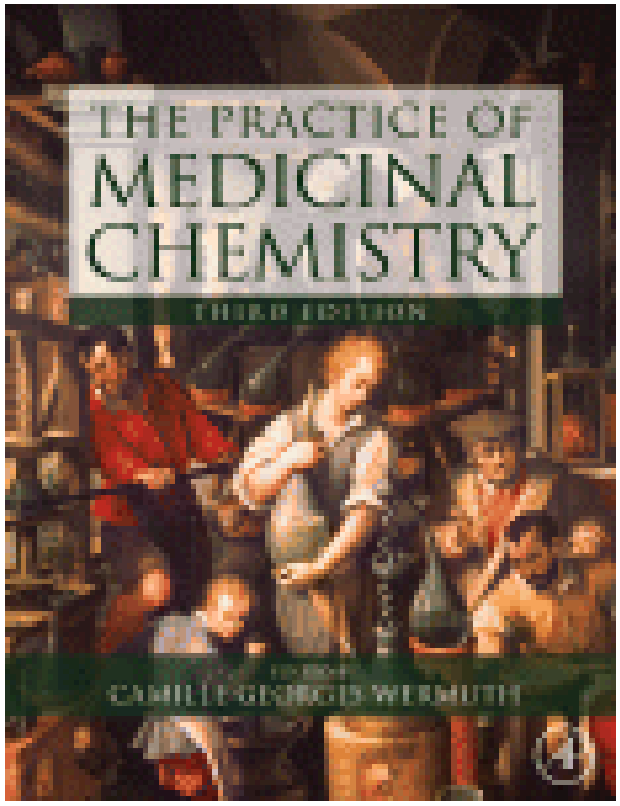
Vide: H. Kubinyi , Drug research: myths, hype and reality, Nature Rev Drug Discov 2003, 2, 665

m e d

# Química Farmacêutica Medicinal

c h e m




Parte 1

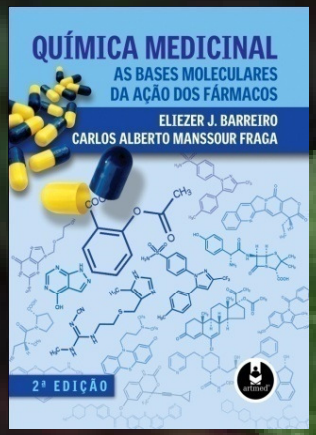
H. Kubinyi Ed. Section

Capítulo 1

François Chast

A history of drug discovery

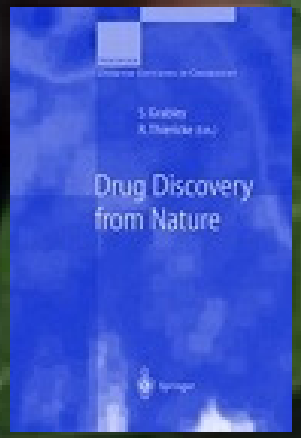
# A origem dos fármacos:
# O Papel dos Produtos Naturais

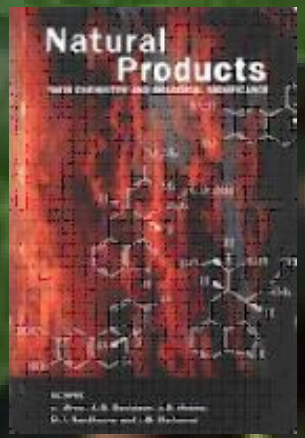



Capítulo 2

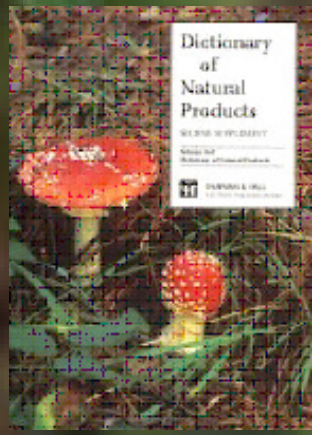
## diversidade de quimiotipos

**monoterpenos, diterpenos, triterpenos, sesquiterpenos, alcalóides, esteróides, flavonóides, lignanas, neolignanas, iridoides,**

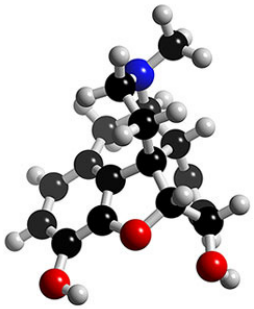


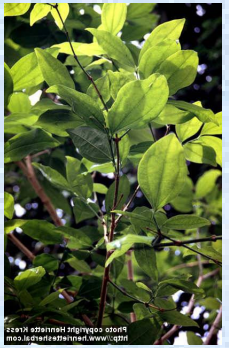




## Quimiodiversidade



# Quimiodiversidade





morfina
1806

Colcichina
1820

huperzina-A

atropina

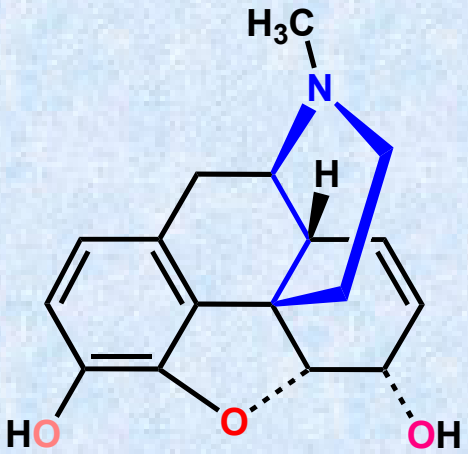
Estriquinina
1817

Emetina
1817

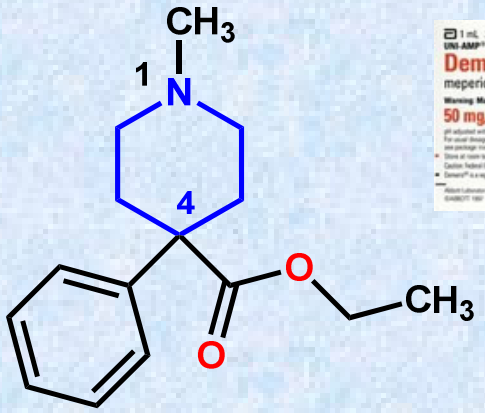
picrotoxina

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

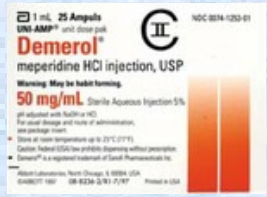
# Da morfina aos hipno-analgésicos sintéticos

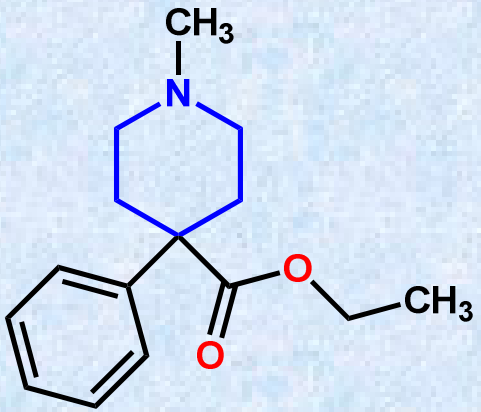



morfina

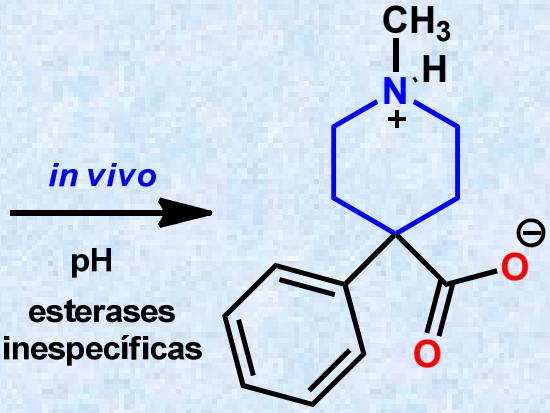



4-fenilpiperidinas



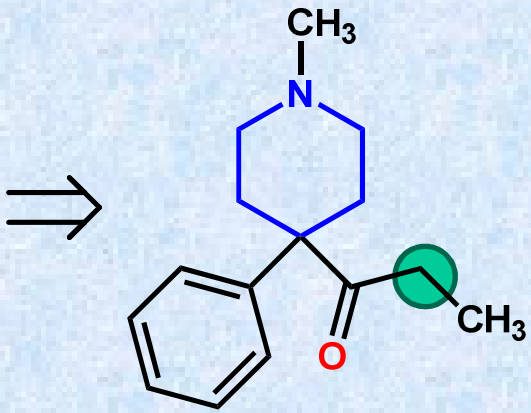




4-fenilpiperidinas




<< ClogP = 2,03 (calc.)

*"zwiterium"*




2ª geração

emetina

Dissecação molecular

Fragmento molecular A

Fragmento molecular B

Similaridade molecular

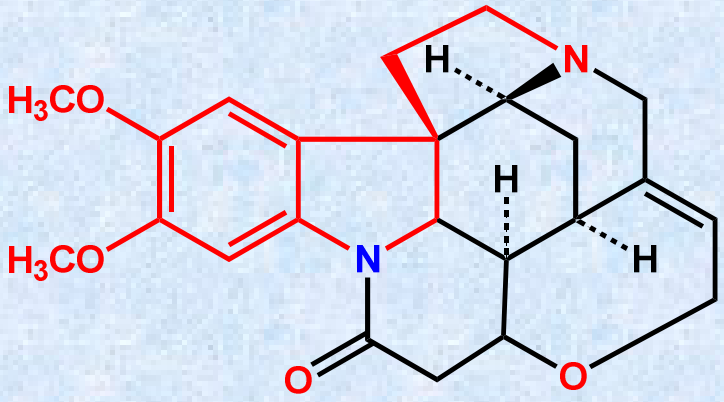
sub-unidade

etilamina

catecol

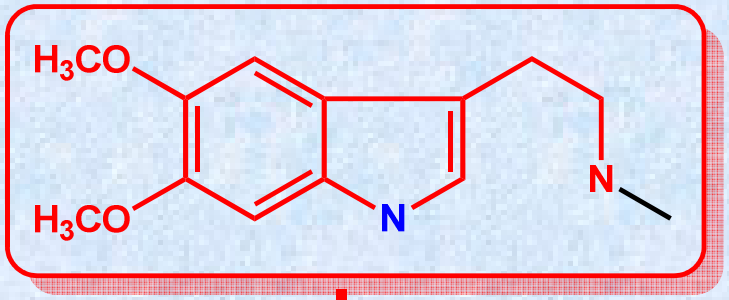
sub-unidade

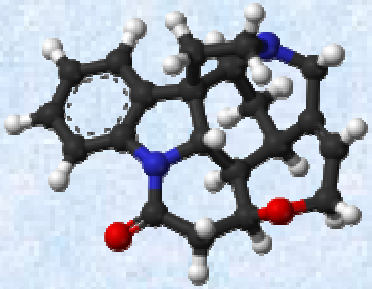
Biorreceptores adrenérgicos



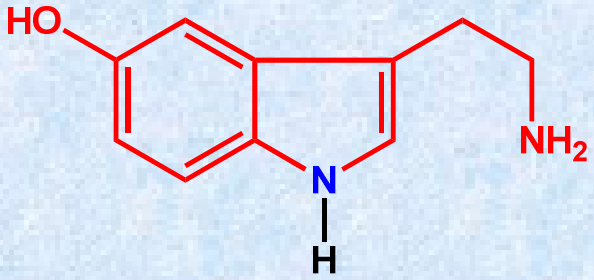

estriquinina

Dissecação molecular



Similaridade molecular




Serotonina

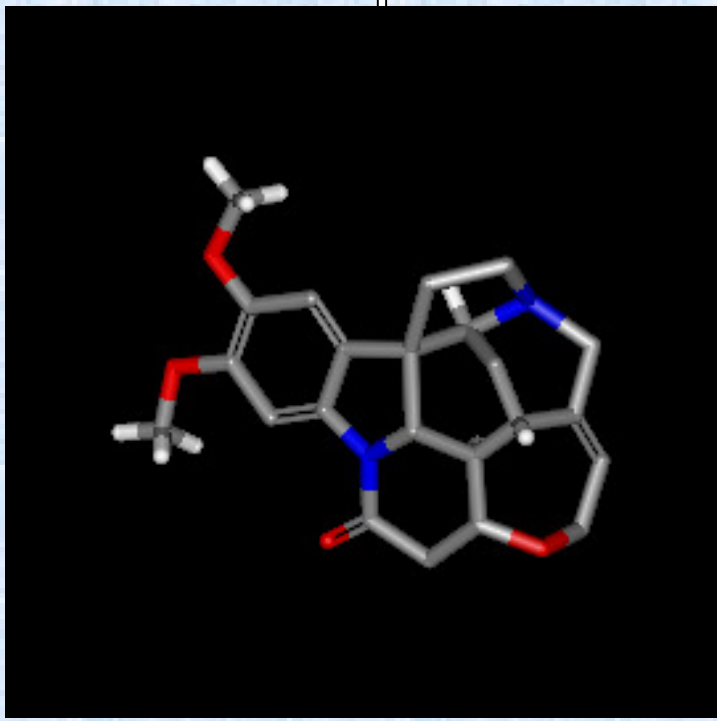
Biorreceptores serotoninérgicos

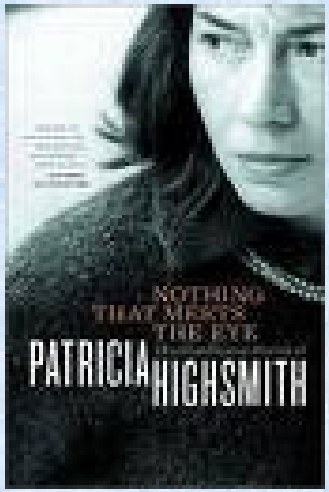
Biorreceptores acetilcolina

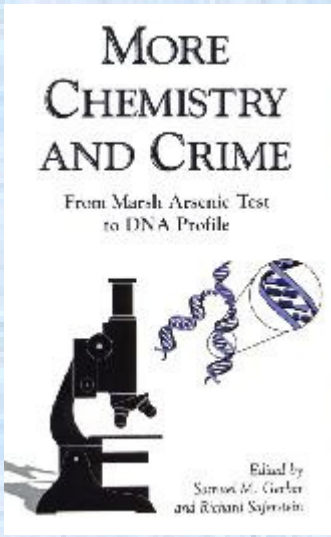
# Moléculas mortais

*Strychnos nux vomica*

## Estriquinina

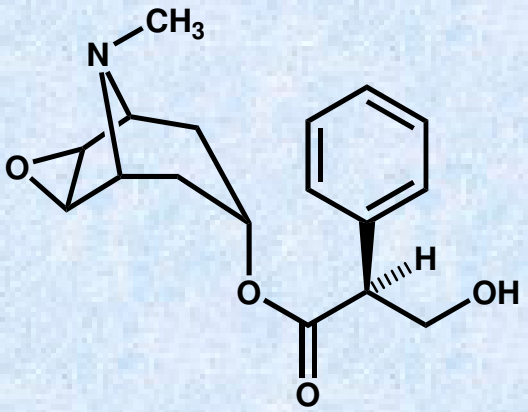


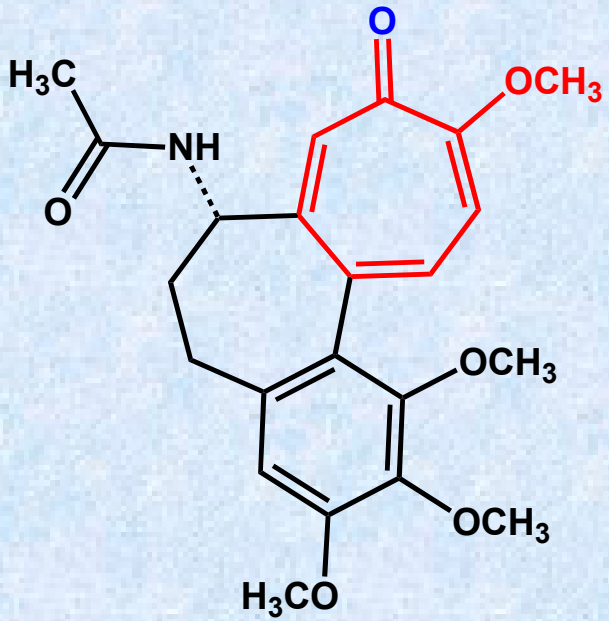




## Escopolamina

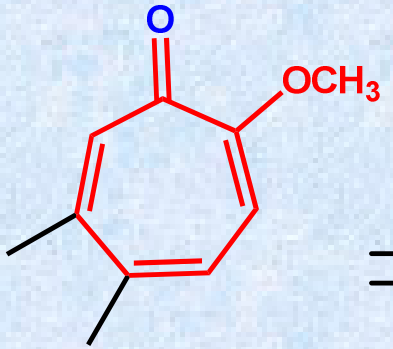




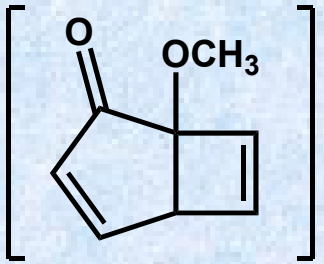

colcichina

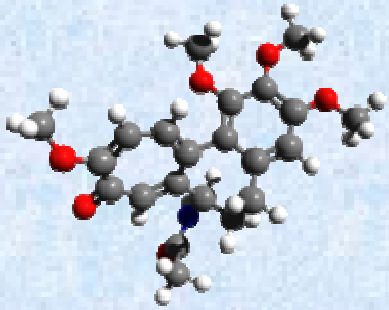
Inibidor de tubulina

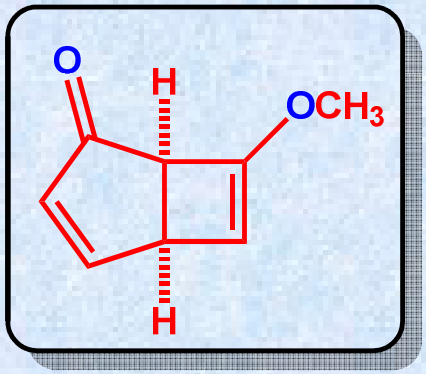
Dissecação molecular




2-metoxitropolona



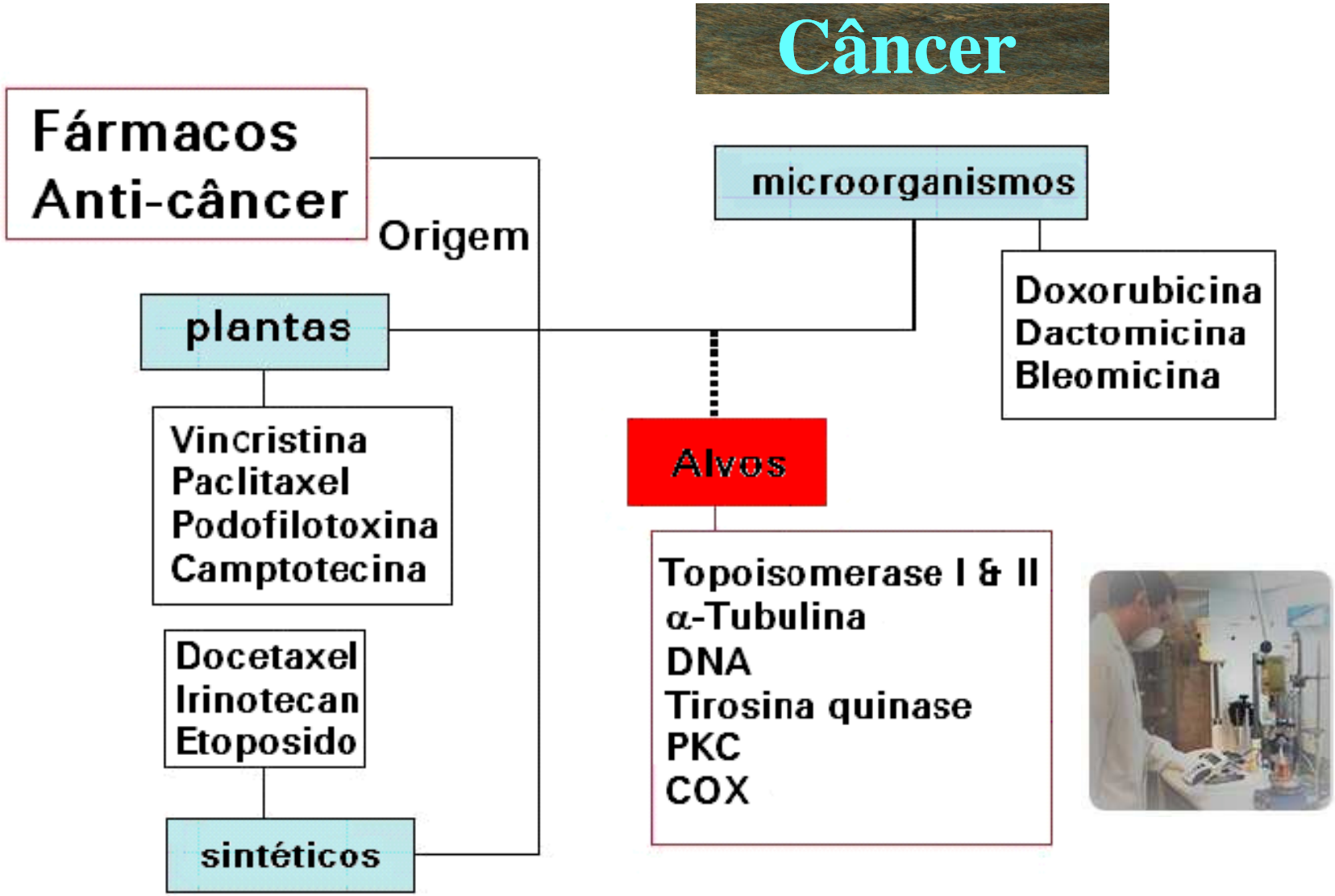



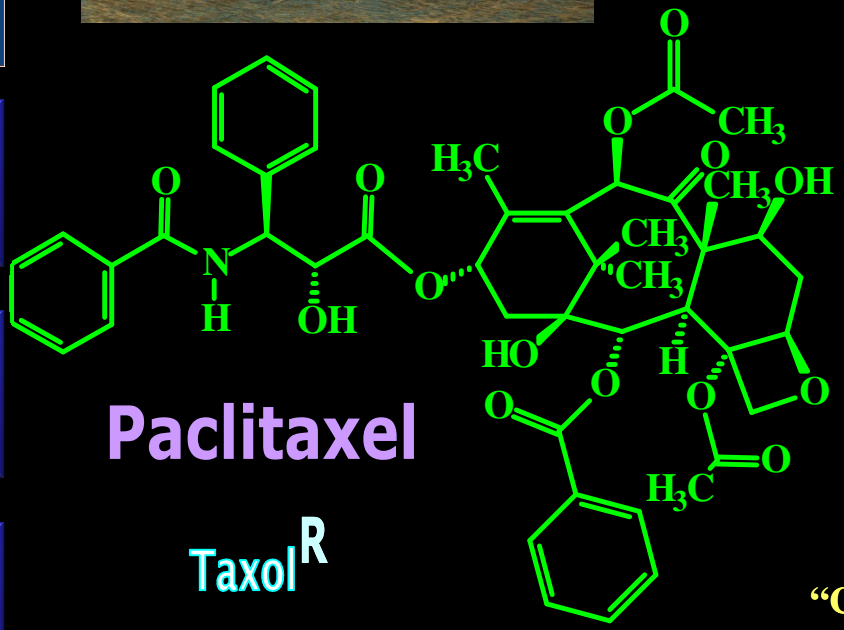

biciclo[3.2.2]heptano

fotossensibilizante

# Produtos naturais com propriedades anti-câncer



# Câncer



**Paclitaxel**

**Taxol**[R]

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

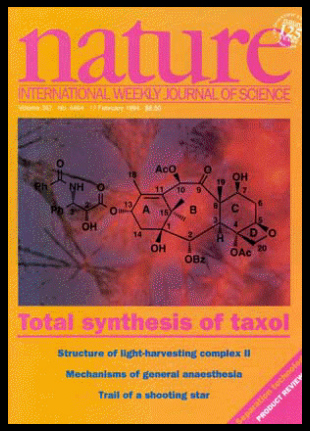
Res. Triangle Park, 1967

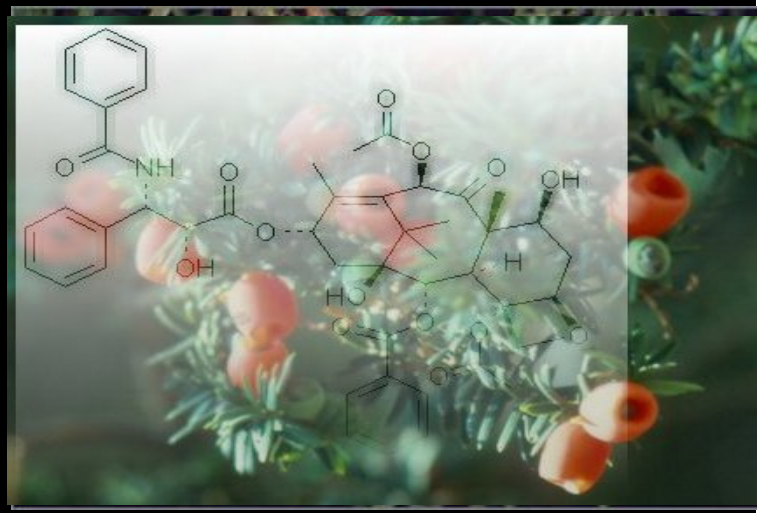
**M. E. Wall & M. C. Wani**

**1996 - National Cancer Institute Award of Recognition**

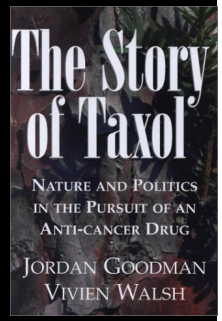


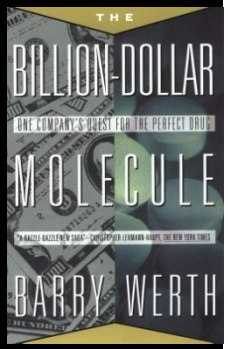
**M. E. Wall,,**
**"Chronicles of Drug Discovery",**
**D. Lednicer, vol.3, ACS, 1993,**
**pp. 327-348**



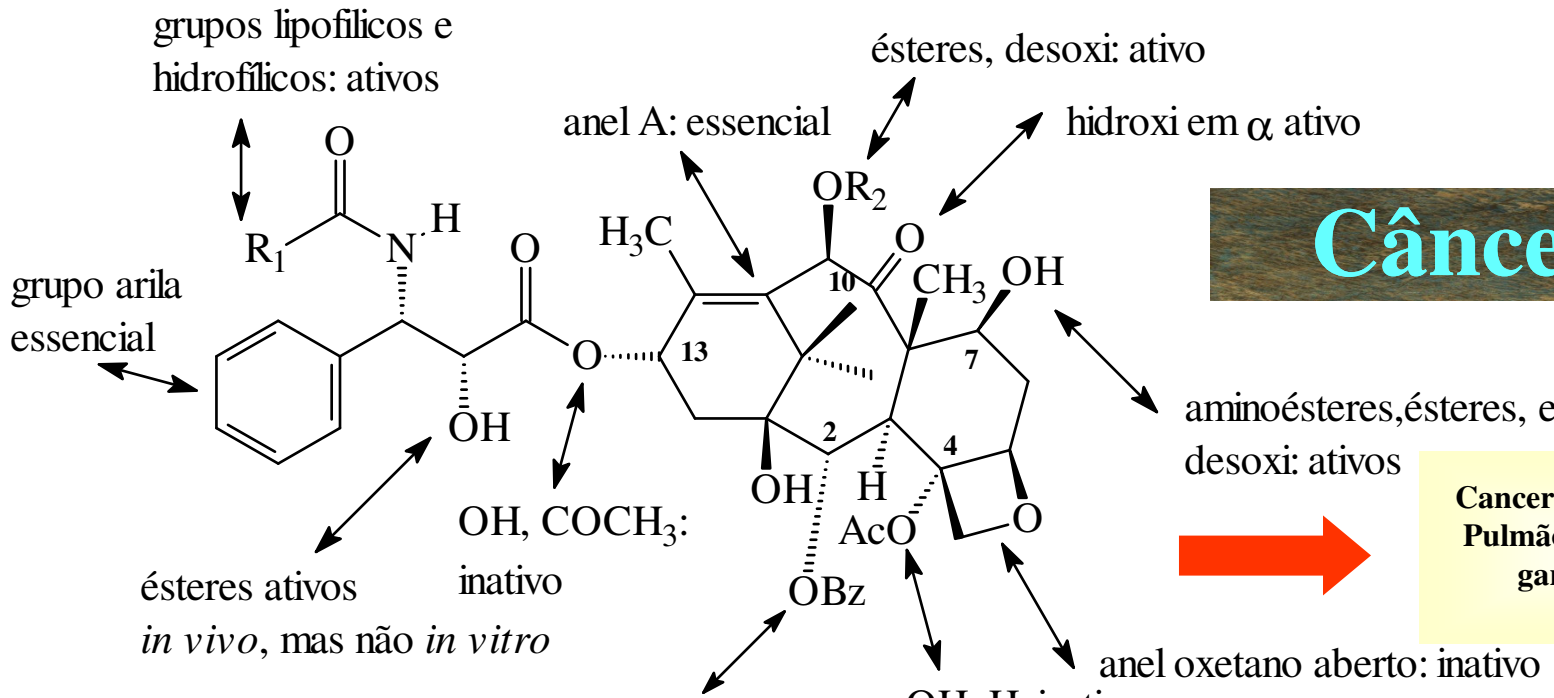



*Taxus bacatta*



# SAR dos taxóides




**Câncer**

**Cancer de mama, Pulmão ,cérebro, garganta**

**Taxol** (*taxus brevifolia*)

**(Paclitaxel; Bristol-Myers Squibb, 1992)**

(uso: parenteral)

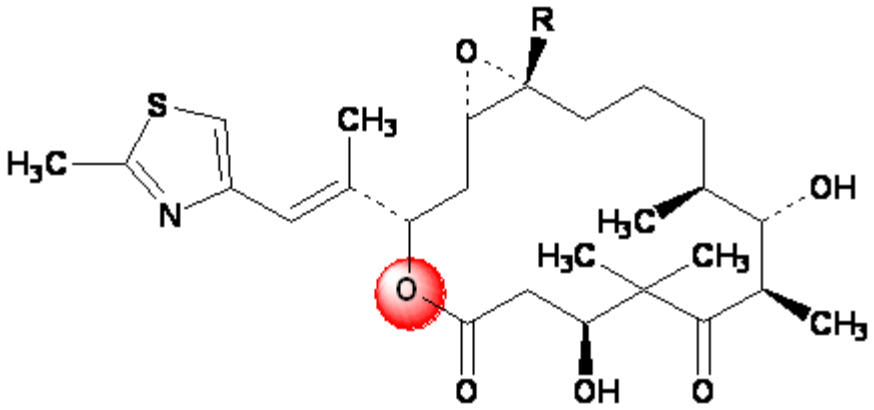
**Taxotere ($R_2$= H, $R_1$= OBu)**
**Análogo sintético do taxol**
**($R_1$= Ph, $R_2$= Ac)**

**Baixa biodisponibilidade**

**Toxicidade: Medula óssea**
**Neutropenia**

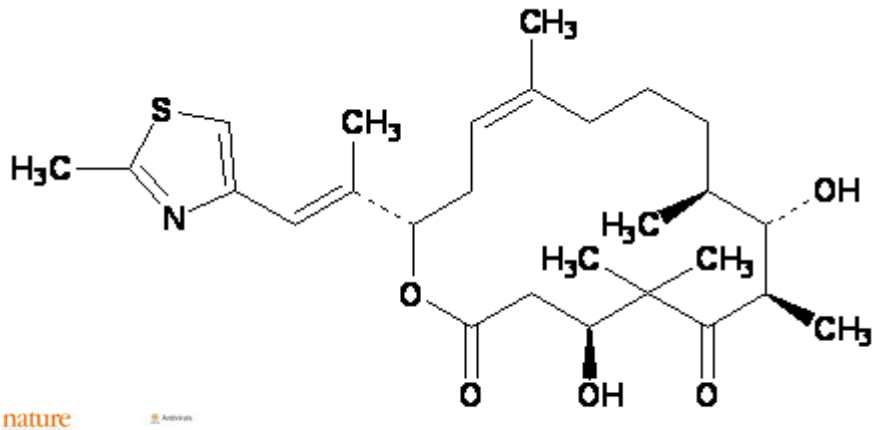
**"Natural Compounds in Cancer Therapy: Promising Nontoxic Antitumor Agents from Plants and Other Natural Sources", J. Boik, Medical Press, Princeton, 2001.**

*Isolada de Sorangium cellulosum em 1993*



Epotilona A R = H

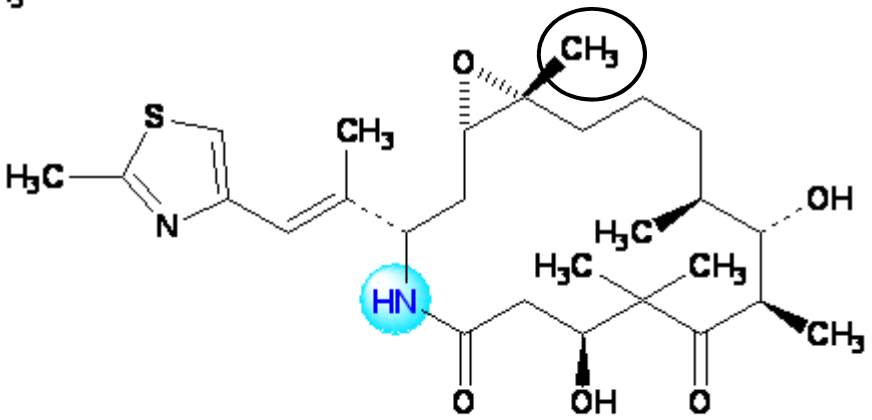
Epotilona B R = $CH_3$



Epotilona D

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

**Análogo semi-sintético**



Ixabepilona

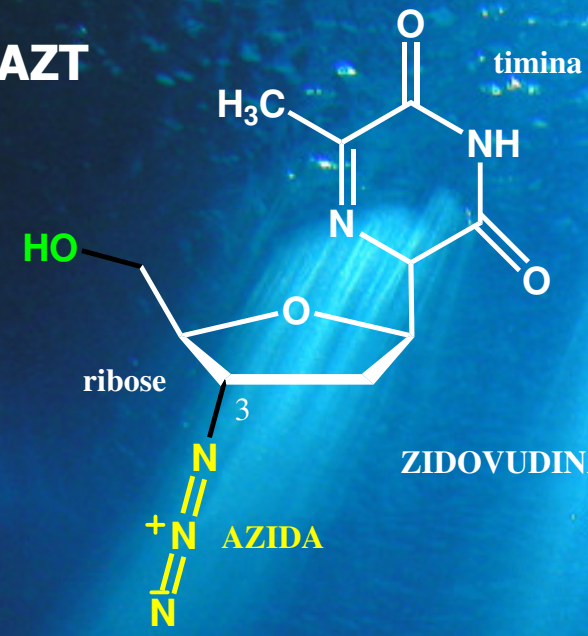
Ixempra$^{R}$

BMS, Out. 2007

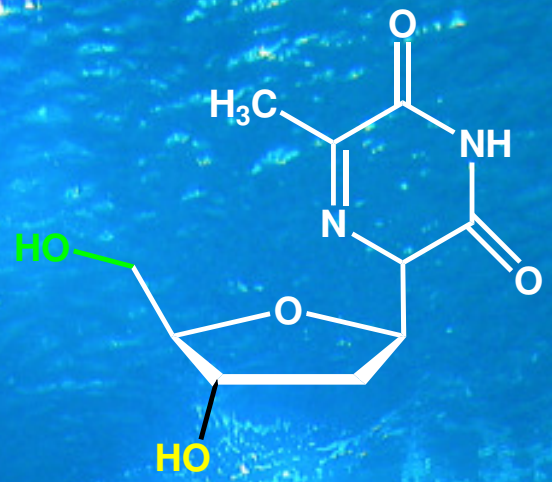
**Via fermentativa bacteriana, ativo em células taxano-R**


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

**AZT**




ZIDOVUDINA




TIMIDINA

**Primeiro anti-HIV inibidor da transcriptase-reversa**





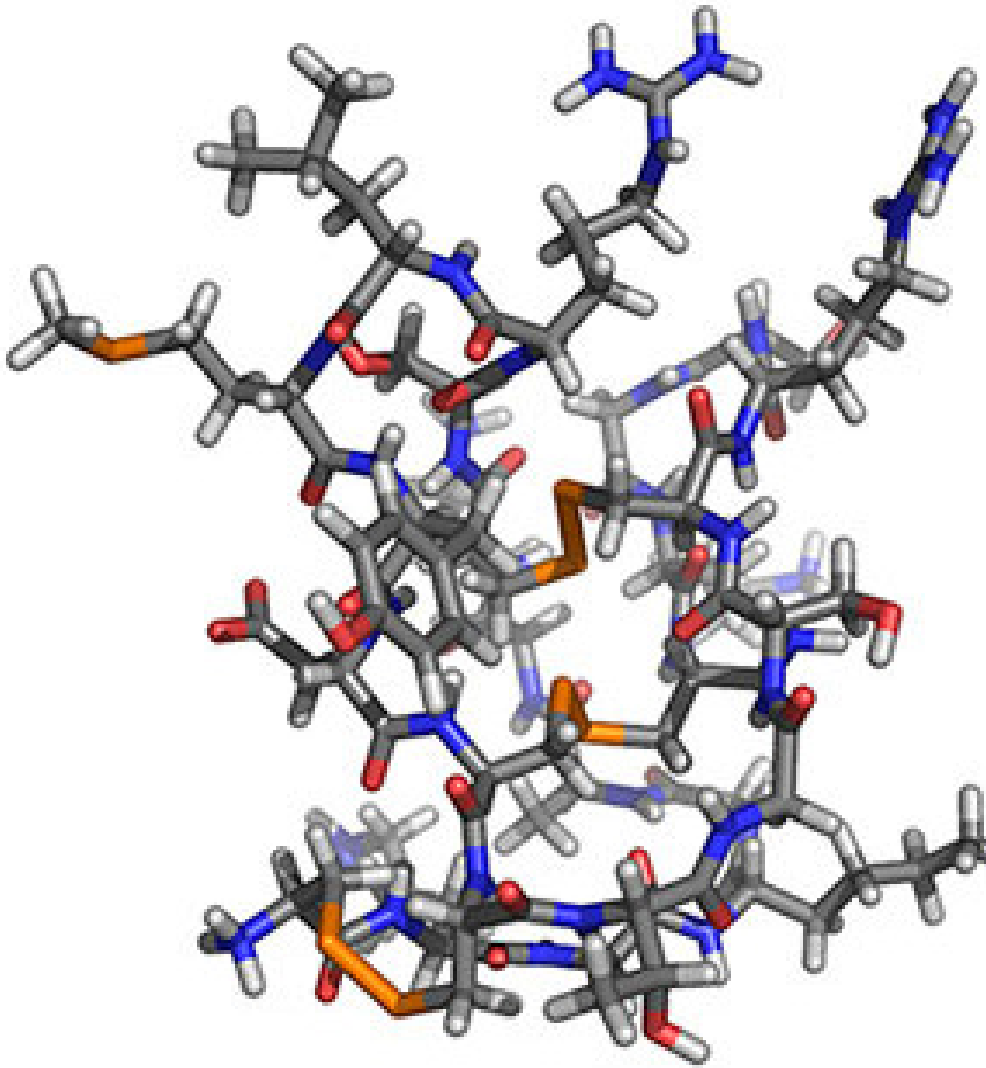
1980 - Michael McIntosh & Baldomero Olivera

# Ziconotido

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

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

Uso intratecal



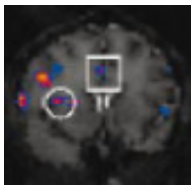
*Conus magus*

SNX-111

Neurex (Menlo Park, CA)

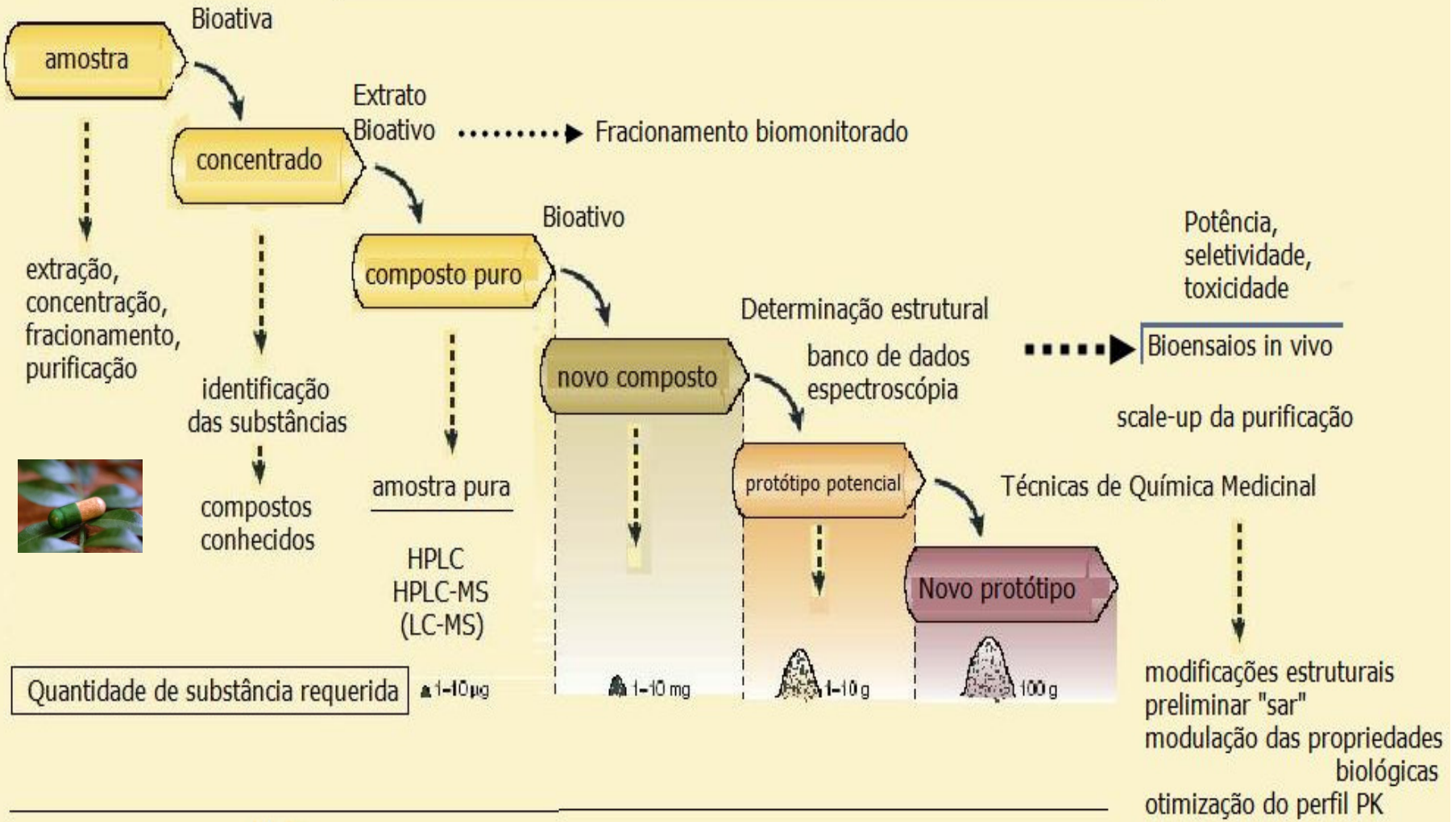

Elan Pharmaceuticals

(Dublin, Ireland



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

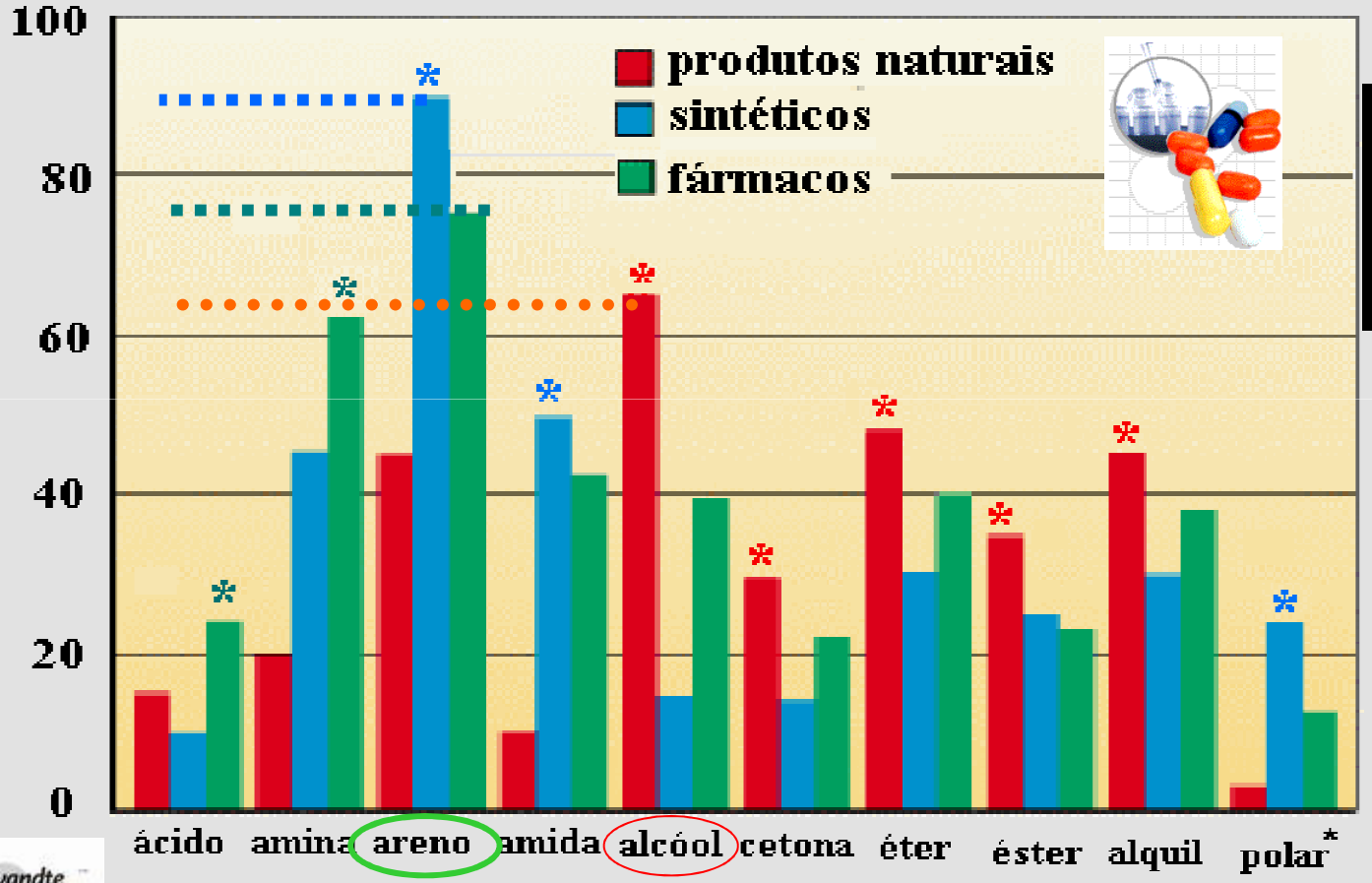
# Processo de descoberta de novos hits-naturais



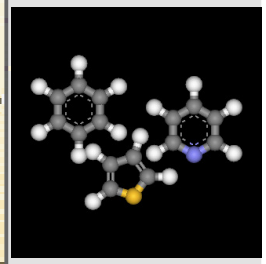

Adaptado de

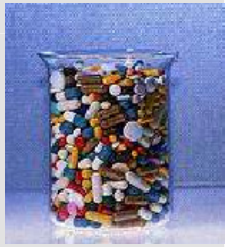

F. E. Koehn & G. T. Carter, The evolving role of natural products in drug discovery, Nature Review Drug Discovery, 2005, 4, 206-220

# *Freqüência dos Grupos Funcionais Clássicos em Diferentes Compostos*







* **grupos polares: F, CN, $NO_2$**


Fonte: *Angewandte Chemie*

química nova

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

# BIODIVERSIDADE: FONTE POTENCIAL PARA A DESCOBERTA DE FÁRMACOS

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

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

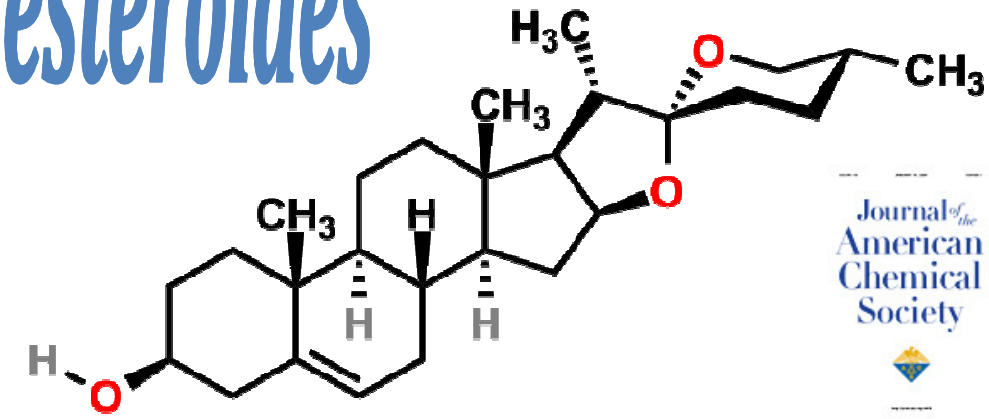
Universidade Federal do Rio de Janeiro

# Os fármacos e os PN´s

2011 SBQ ANO INTERNACIONAL DA QUÍMICA


Química Medicinal

# esteróides



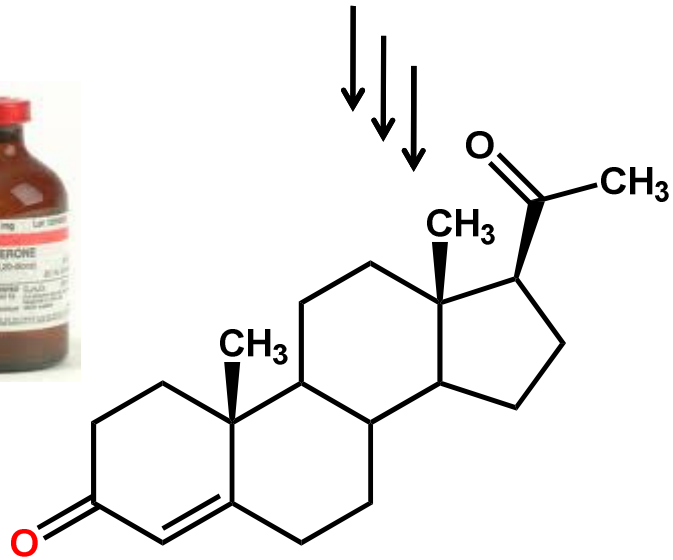

diosgenina

Journal of the American Chemical Society

## Laboratorios Syntex SA

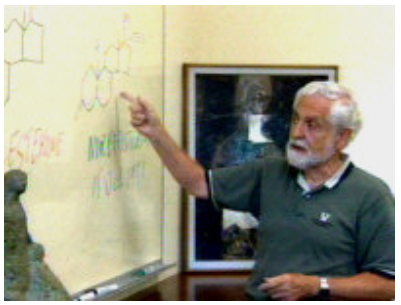

*Dioscorea mexicana Scheidw*

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

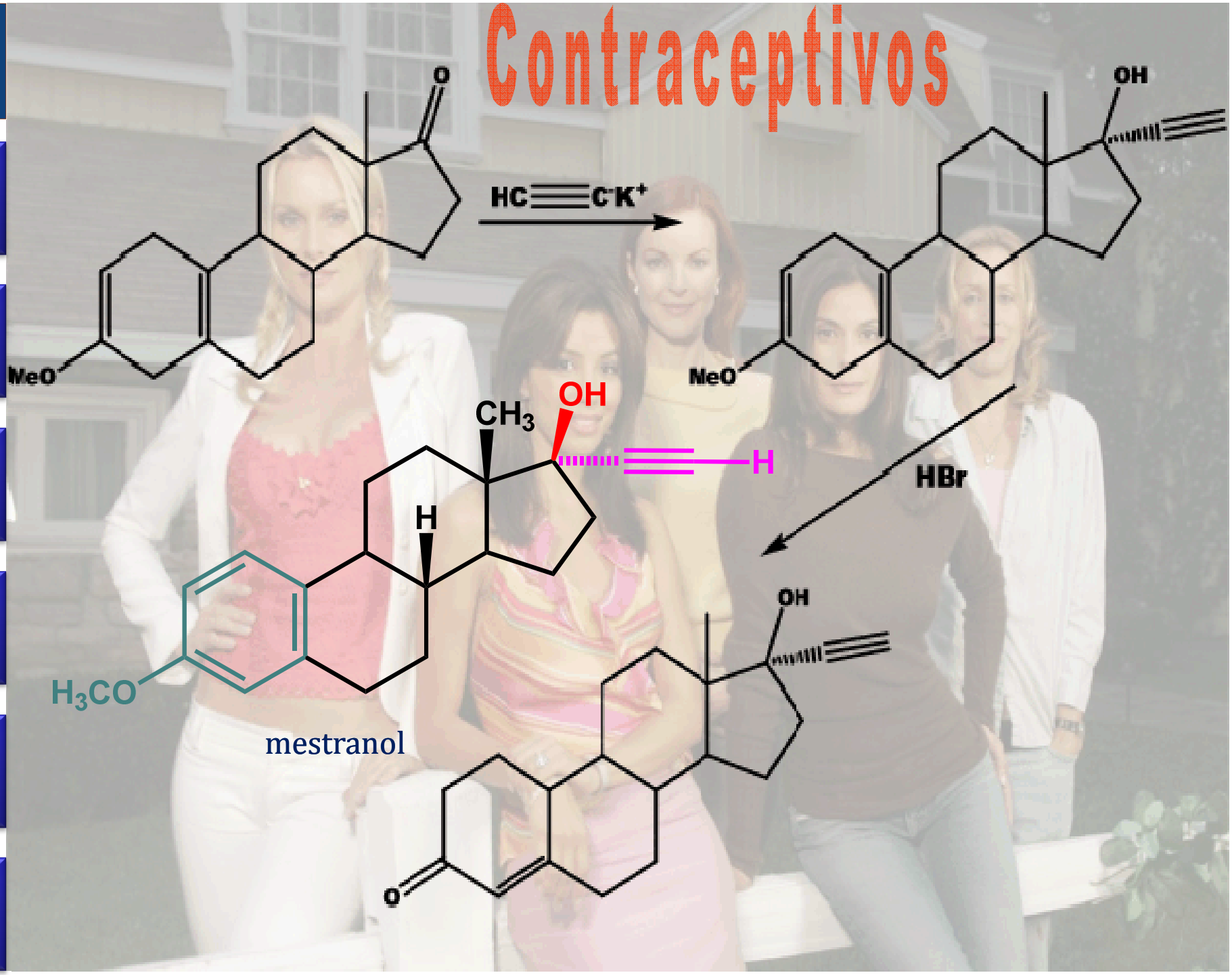
# A Pílula Contraceptiva



**Carl Djerassi**

eliezer © 2010

# Contraceptivos

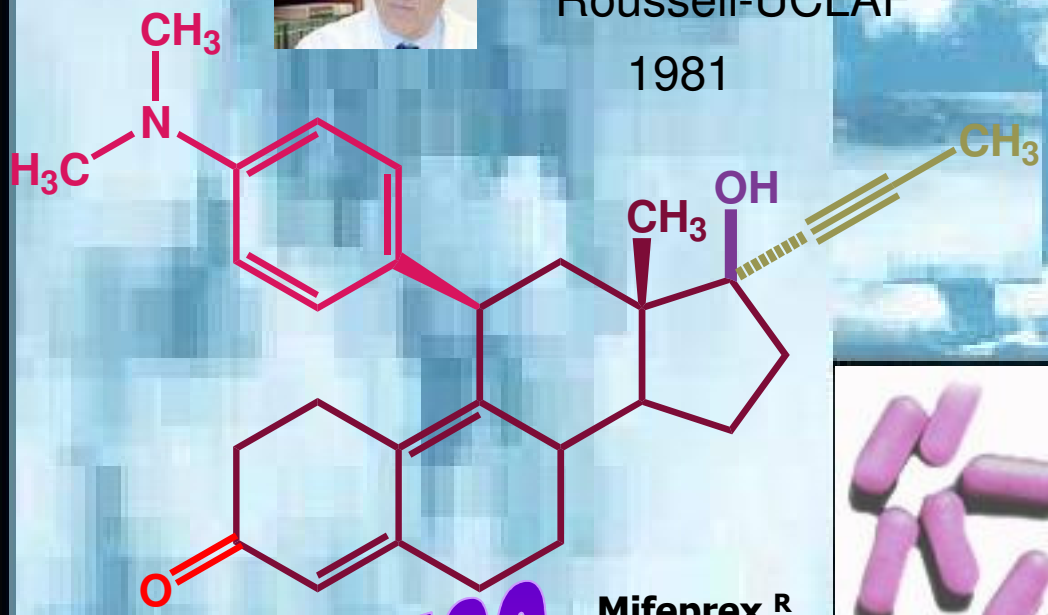



mestranol

# mifepristona

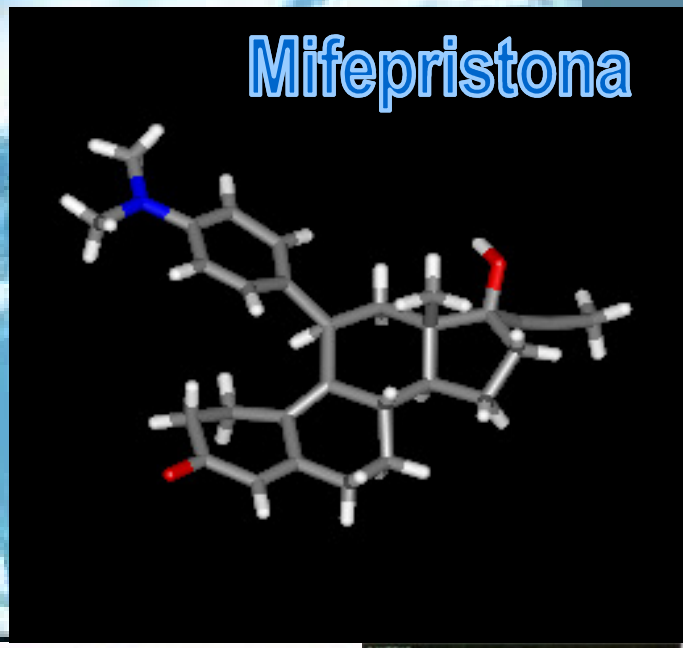
Etienne-Emile Beaulieu
Roussell-UCLAF

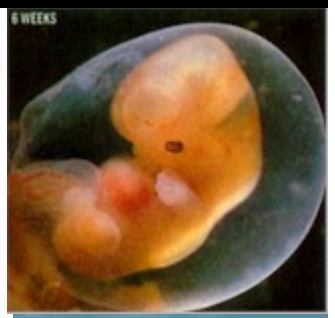
1981

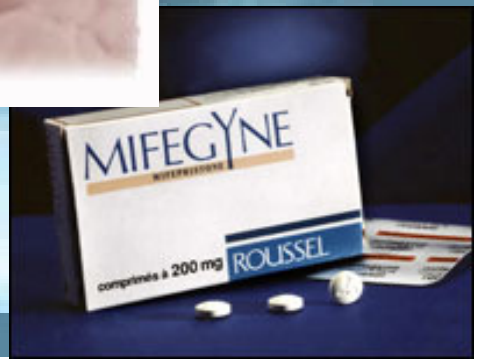



RU 486

Mifeprex R



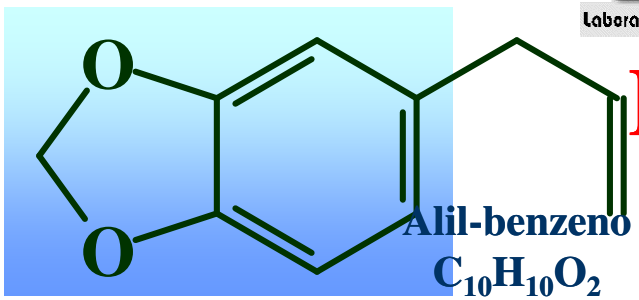

Pílula do dia seguinte

# Oléo de Sassafrás

*Ocotea pretiosa Mezz.*
*Canela Sassafrás*

## Produto natural brasileiro abundante

LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

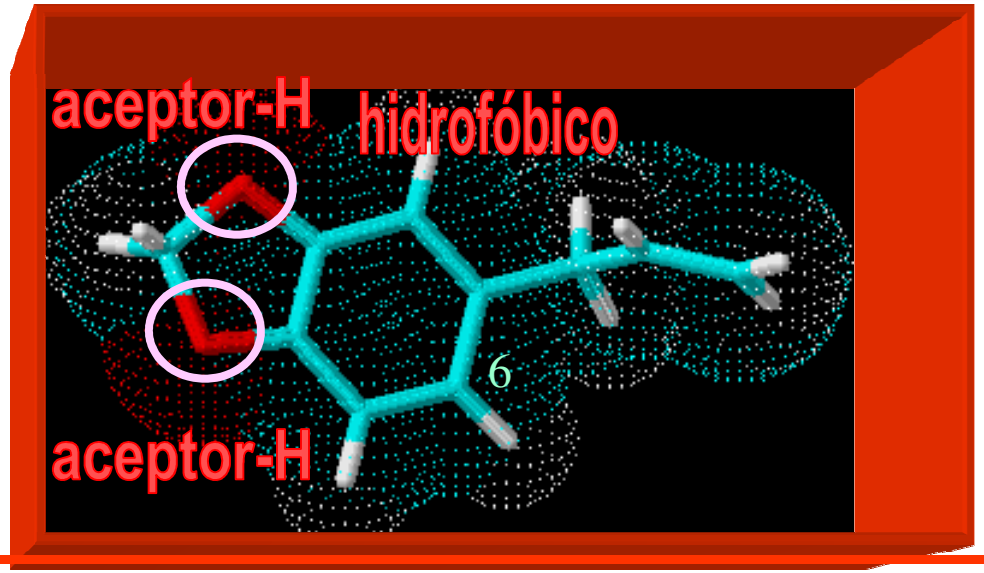



Alil-benzeno
$C_{10}H_{10}O_2$

## Pimenta longa



## Safrol



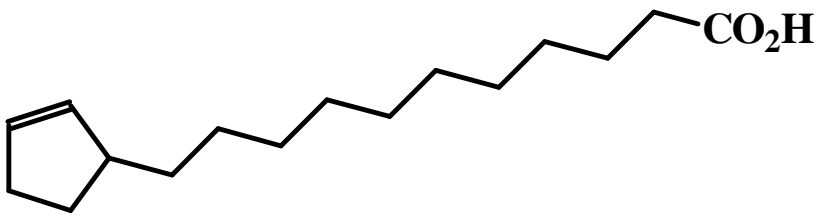

## Bióforo Natural

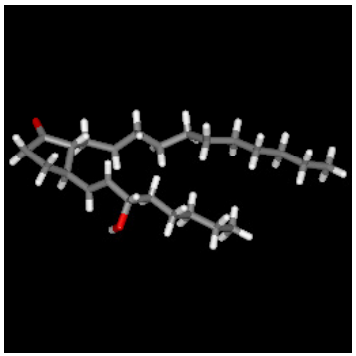
www.scielo.br

Embrapa Acre
32 hectares
90% de safrol
(Ro)

E. J. Barreiro & C. A. M. Fraga, "A Utilização do Safrol, Principal Componente Químico do Óleo de Sassafrás, na Síntese de Substâncias Bioativas na Cascata do Ácido Araquidônico: Anti-inflamatórios, Analgésicos e Anti-trombóticos", *Química Nova*, 22, 744 (1999).

# Produtos naturais como blocos moleculares



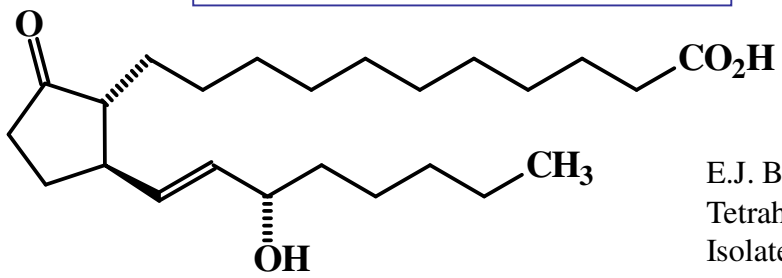



**ácido hidnocárpico**

***C. brasiliensis***

*Carpotroche brasiliensis, Endl*
*Flacourtiácea*

Primeiras prostaglandinas brasileiras




**11-desoxi-tetrahomoPGE$_1$**

**Sapucainha**, Papo de anjo, Pau de cachimbo, Canudo de pito, Fruta de cotia, Fruta de Macaco, Beribá do mato; Fruta da lepra, Pau de lepra, Ruchuchú

Ocorrência: Rio de Janeiro, Minas Gerais, Espírito Santo, Bahia


E.J. Barreiro, L N LF Gomes, Prostaglandin Analogues. Synthesis of Tetrahomoprostaglandin Derivatives From Natural Hydnocarpic Acid Isolated From Sapucainha Oil..*J. Chem. Res*. **1983**, 2701
EJ Barreiro, LNLF Gomes, Novo Método de Síntese de Prostaglandinas Modificadas da Série 11-desoxi PG E1". **INPI, PI 38201866**, 02/04/1982
*Chem. Abstr*., 100, 17452lu (1984)].

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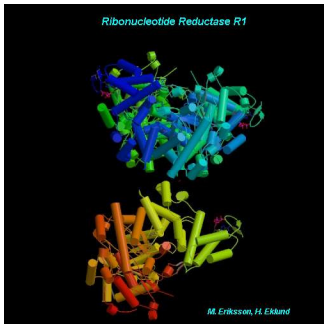
UFRJ

2011 ANO INTERNACIONAL DA QUÍMICA

SBQ

# Os fármacos e os biorreceptores




Química Medicinal

# Os fármacos atuam em alvos terapêuticos...

Química Medicinal

## ... os biorreceptores.

**Estima-se que hoje sejam 483* os alvos-terapêuticos envolvidos na resposta de todos os fármacos que totalizam 1204 moléculas.&**


* J. Drews, "Editorial: What's in a number?", *Nature Rev. Drug Discov.* **2006**, *5*, 975;
J. Drews & S. Ryser, Classic drug targets, *Nature Biotechnol.* **1997**, *15*, 1318;
& J.P. Overington, A-L Bissan & A.L. Hopkins, *Nature Rev. Drug Discov.* **2006**, *5*, 993;
Estes autores estimam em 324 os biorreceptores de todos os fármacos contemporâneos.

# A maioria dos biorreceptores dos fármacos contemporâneos são enzimas …

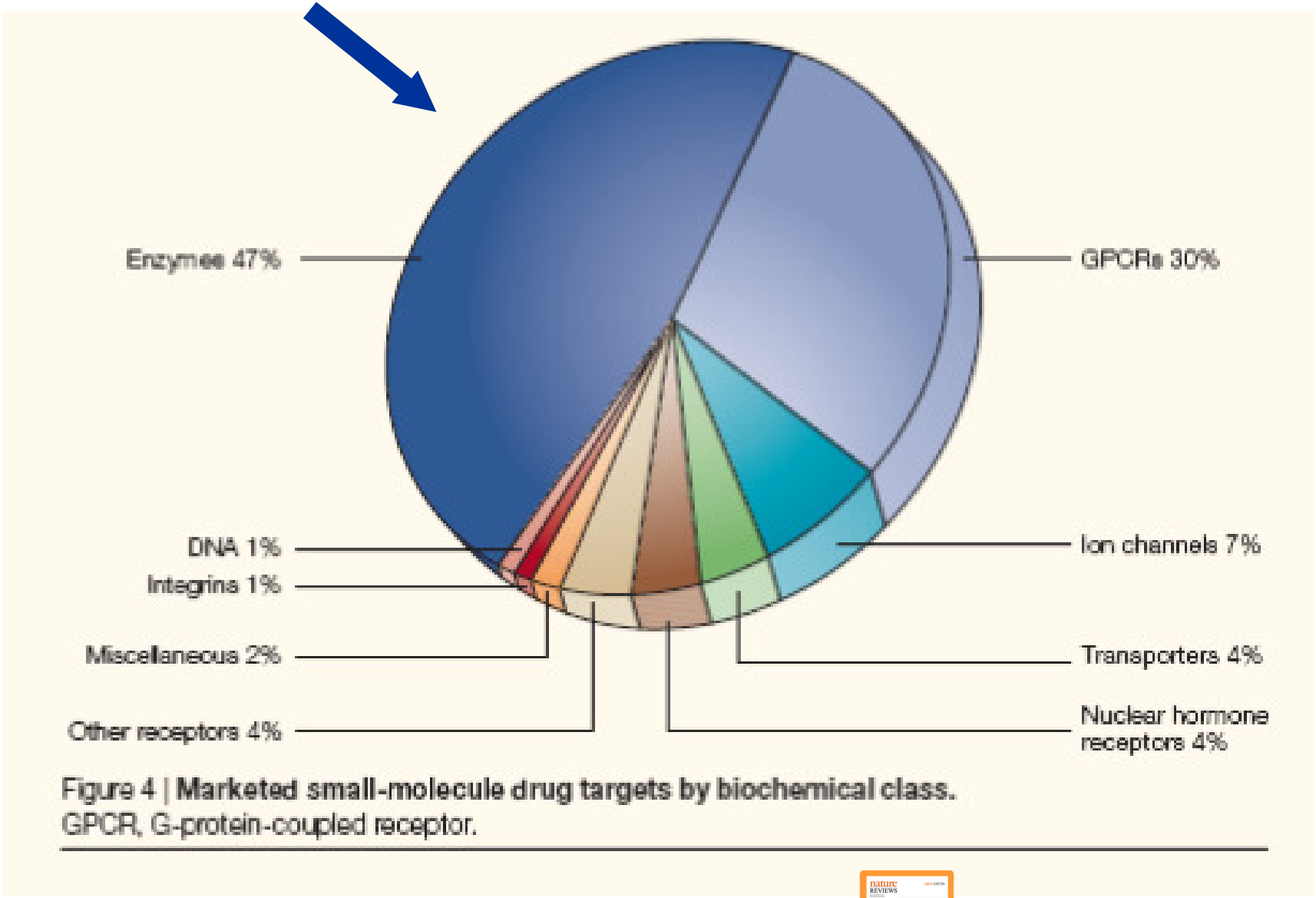



Figure 4 | **Marketed small-molecule drug targets by biochemical class.** GPCR, G-protein-coupled receptor.


www.nature.com/reviews/drugdisc

Hopkins, A. L. & Groom, C. R. The druggable genome. *Nature Rev. Drug Discov.* 1, 727–30 (2002).

# O "alfabeto" protêico ...

glicina (**gly**)

**ala**nina

**val**ina

isoleucina (**Ile**)

**leu**cina

**ser**ina

cisteína (**Cys**)

treonina (**Thr**)

**met**ionina

lisina (**Lys**)

**arg**inina

ácido **glu**tâmico

ácido **asp**ártico

**pro**lina

glutamina (**Gln**)

asparagina (**Asn**)

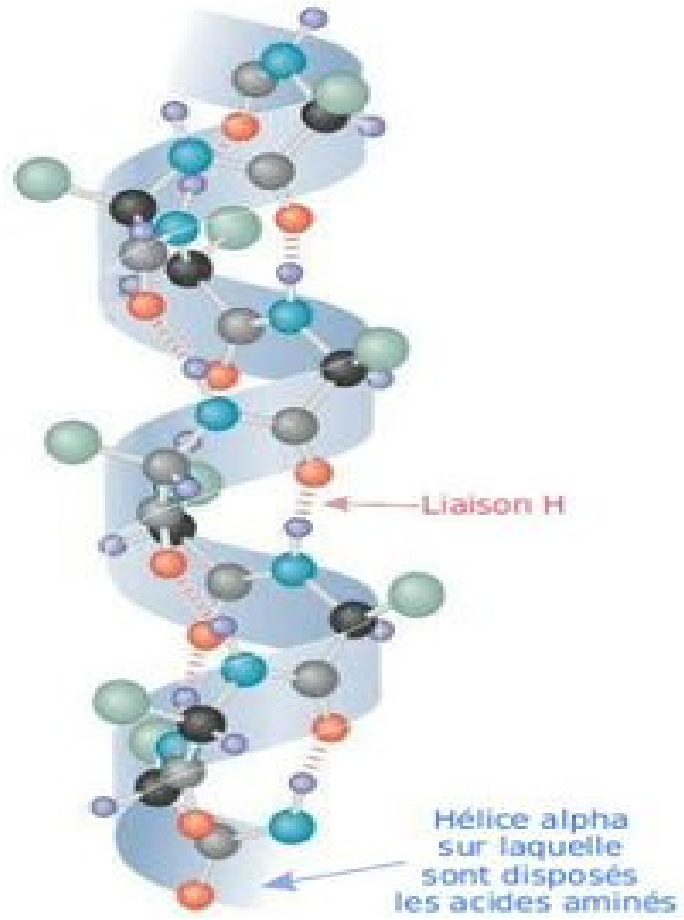
triptofano (**Trp**)

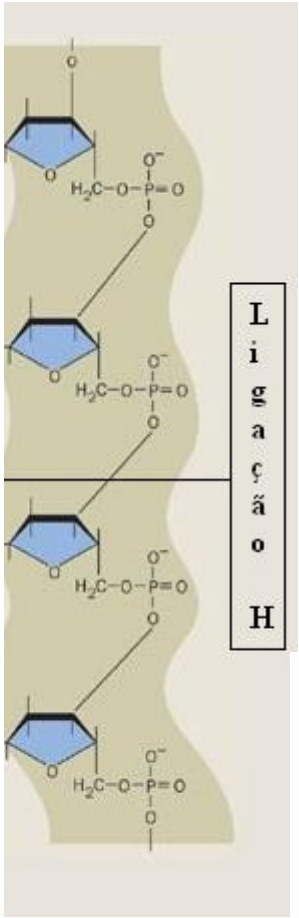
fenilalanina (**Phe**)

tirosina (**Tyr**)

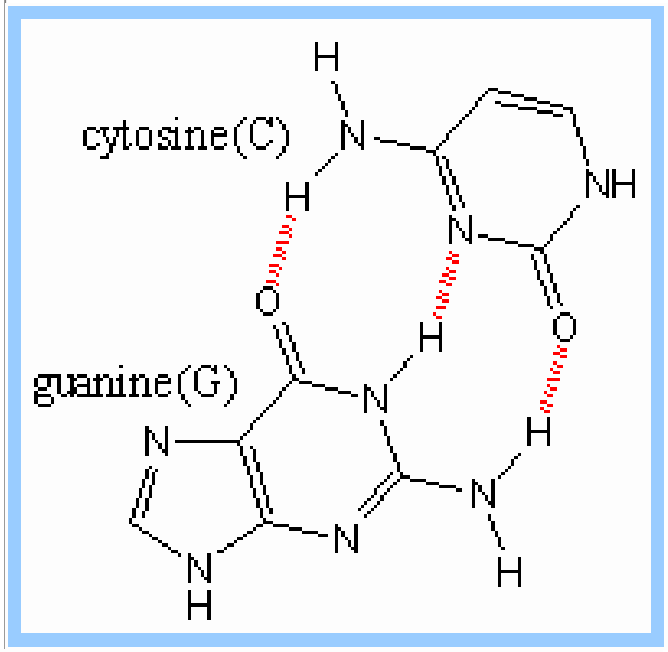
**his**tidina

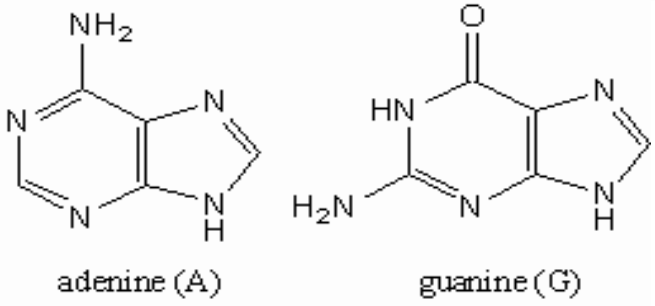
# Proteínas, carboidratos, DNA, lipídeos, canais iônicos

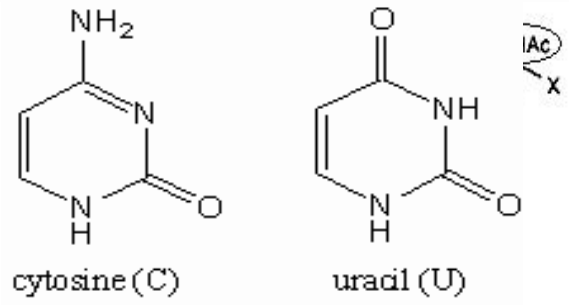



Ligação de hidrogênio = $H_2O$



# A quimiodiversidade na natureza...

**20 amino-ácidos essenciais**

↓

**400 dipeptídeos**

**8.000 tripeptídeos...**

**64.000.000 hexa peptídeos**

**$10^{400}$ proteínas com PM ~ 30 kD**

↓

São conhecidos *ca.* 19 milhões de compostos orgânicos (300-500 Da)

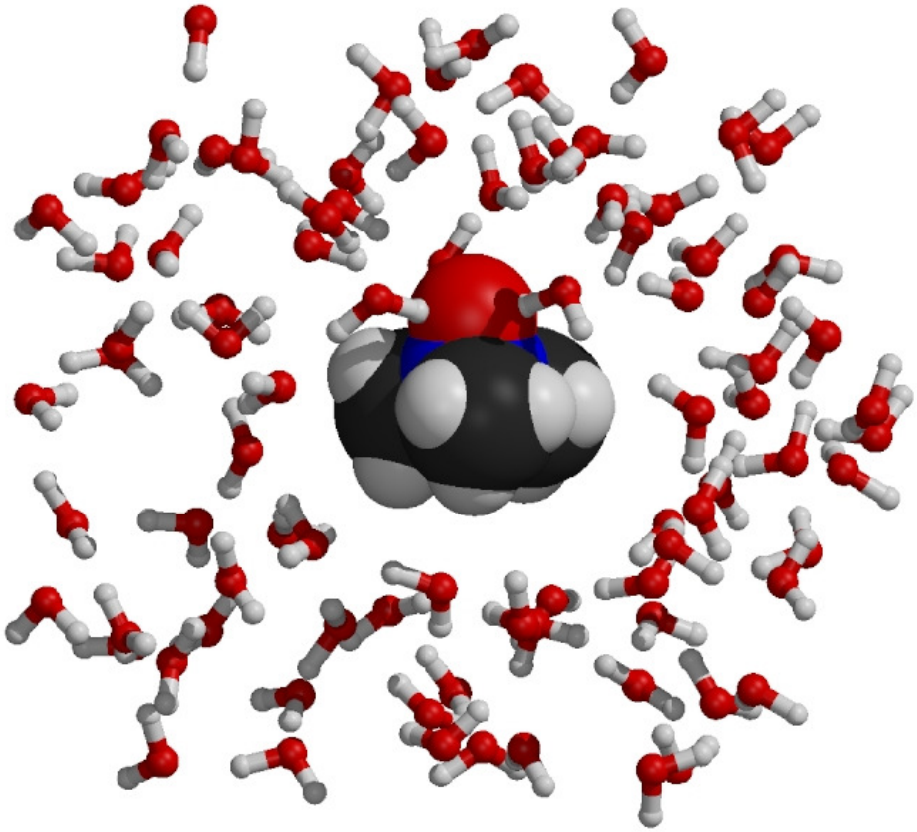
**100 amino-ácidos modificados**

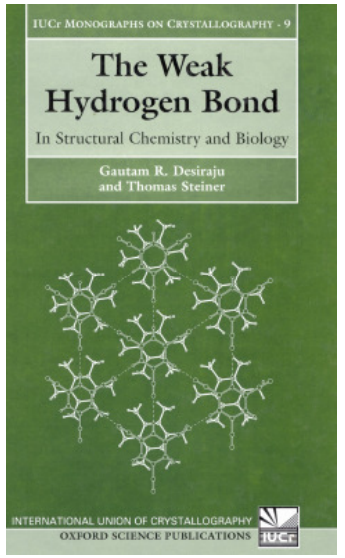
↓

**ca. 1.000.000.000.000 hexapeptídeos...**

**... e apenas 4 bases nuclêicas codificam todos os organismos !**

# A importância das "*ligações*" frágeis...






## "*ligações*" de hidrogênio ...

D—H.....A

**Linus Pauling, 1939**

# O Paradigma de Ehrlich & Fischer

Química Medicinal

# O paradigma de Ehrlich & Fischer

**Emil Fischer**

1852-1919

**1902**

E. Fischer, Ber. Dtsch. Chem. Ges. 1890, 23, 799

**Paul Ehrlich**

1854-1915

**1908**


**Planejamento racional**

**Biorreceptor**

**macrobiomolécula**

**baseado no sítio de reconhecimento**

**BSRM**

**BL-AA**

**Fármaco**

**micromolécula**

**baseado no ligante / análogo-ativo**

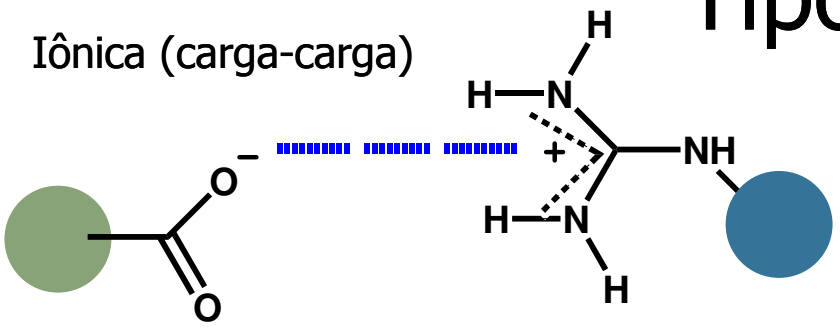

Physiologic approach

**A abordagem fisiológica**


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

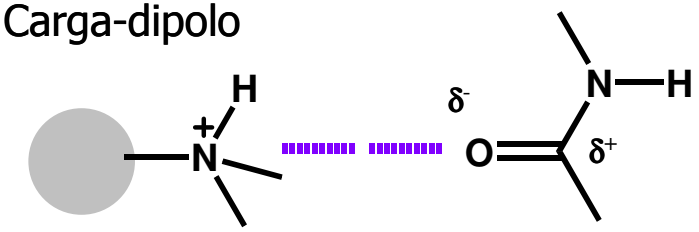
# Tipos de interações F-R

Iônica (carga-carga)



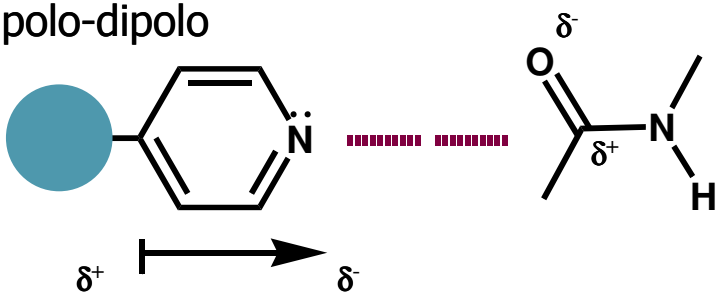
ΔG = 20-40kJ/mol

Carga-dipolo



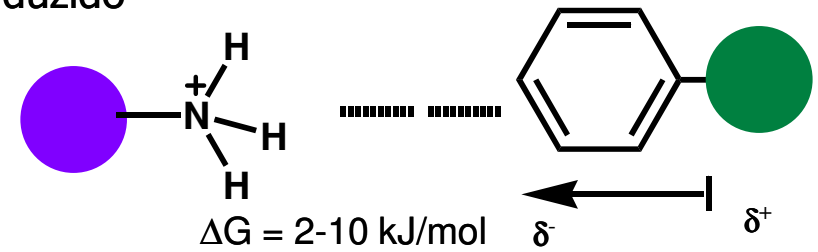
ΔG = 12-20kJ/mol

Dipolo-dipolo



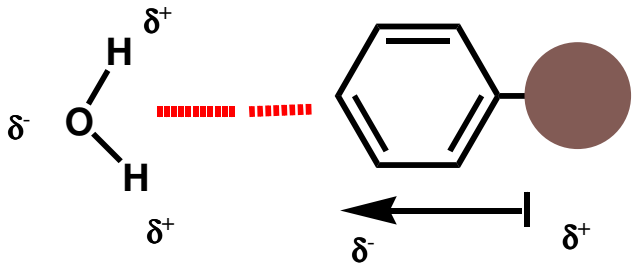
ΔG = 4-12 kJ/mol

Carga-dipolo induzido



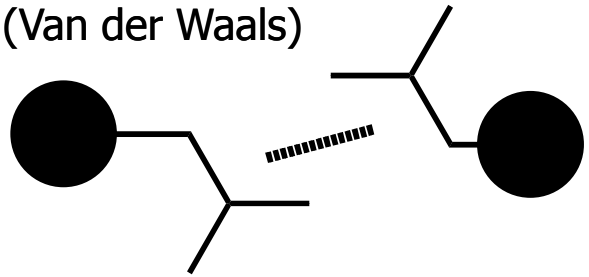
ΔG = 2-10 kJ/mol

Dipolo induzido-dipolo



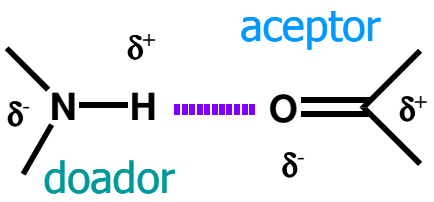
ΔG = 2 kJ/mol

Dispersão (Van der Waals)



ΔG = 2-4 kJ/mol

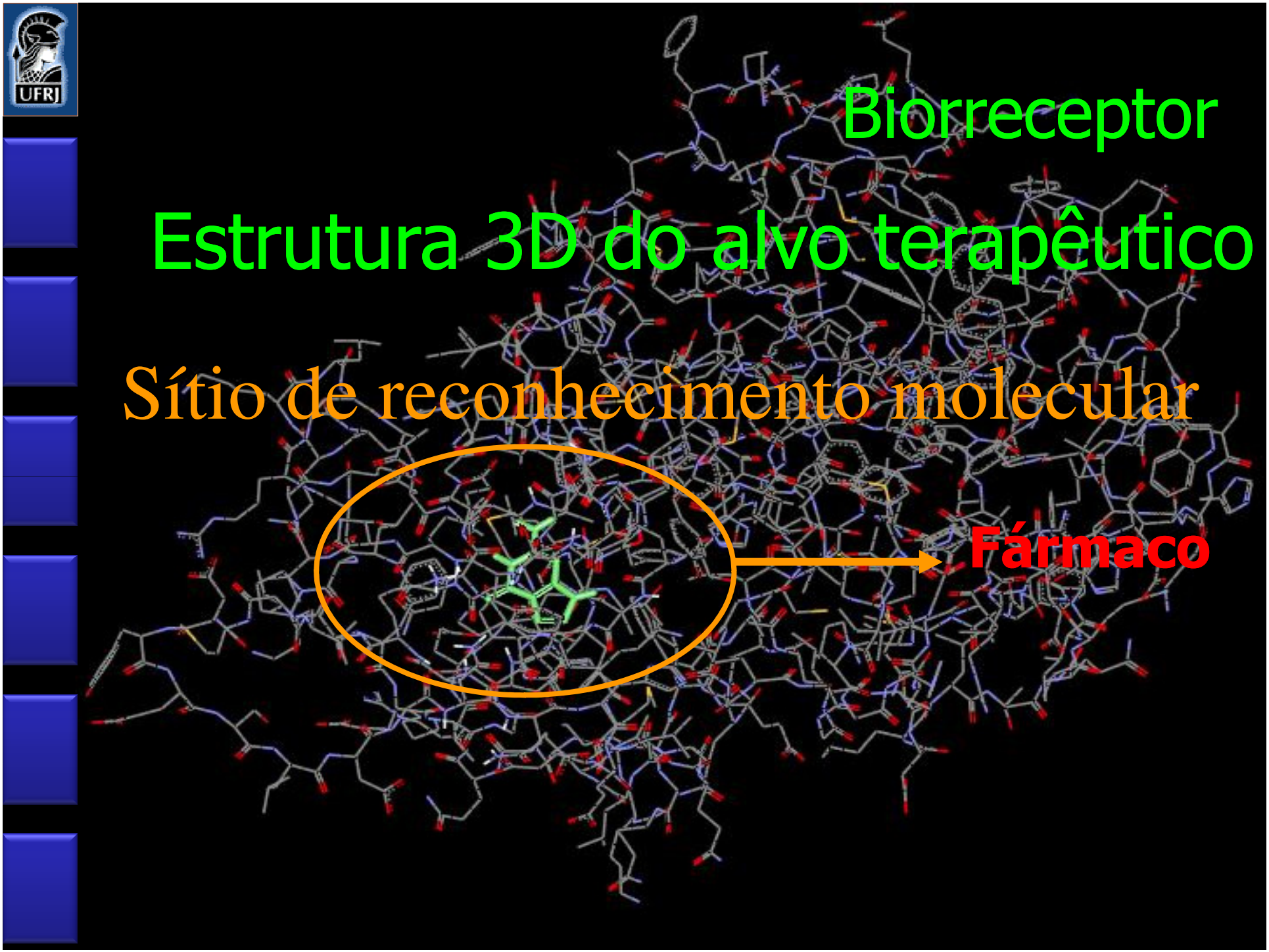
Ligação-H



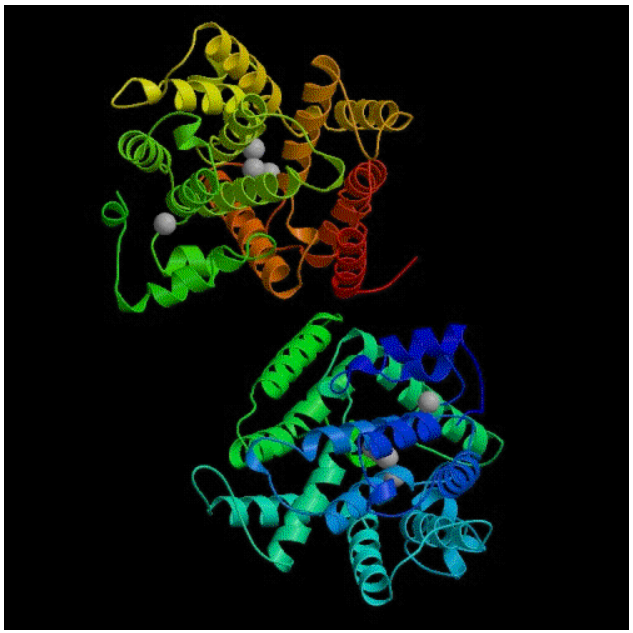

ΔG = 4-30 kJ/mol

# Nível hierárquico da descrição da complementaridade F-R

Complicadores:
- Encaixe-induzido
- Conformação bioativa
- Inibição alostérica/ortostérica


Biorreceptor
Estrutura 3D do alvo terapêutico
Sítio de reconhecimento molecular
Fármaco

# Estruturas cristalográficas disponíveis no PDB

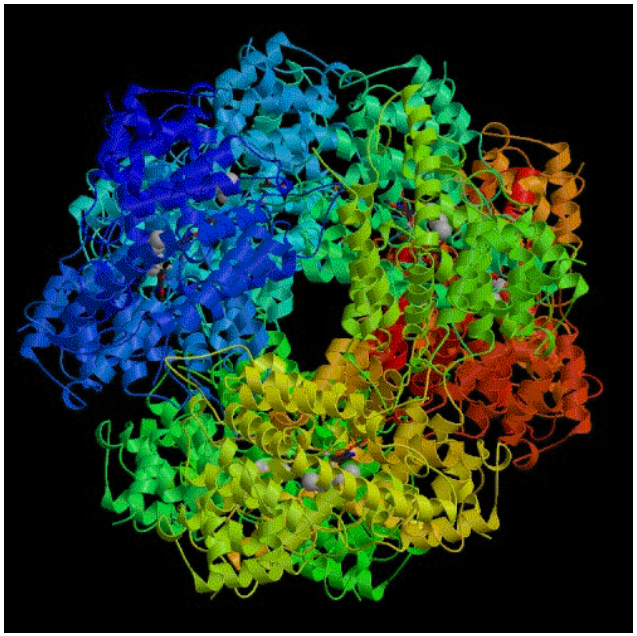


PDE4B - 1F0J

351 resíduos

*Metodo:* Difração de Raio-X

*Resolução:* **1.77 Å**

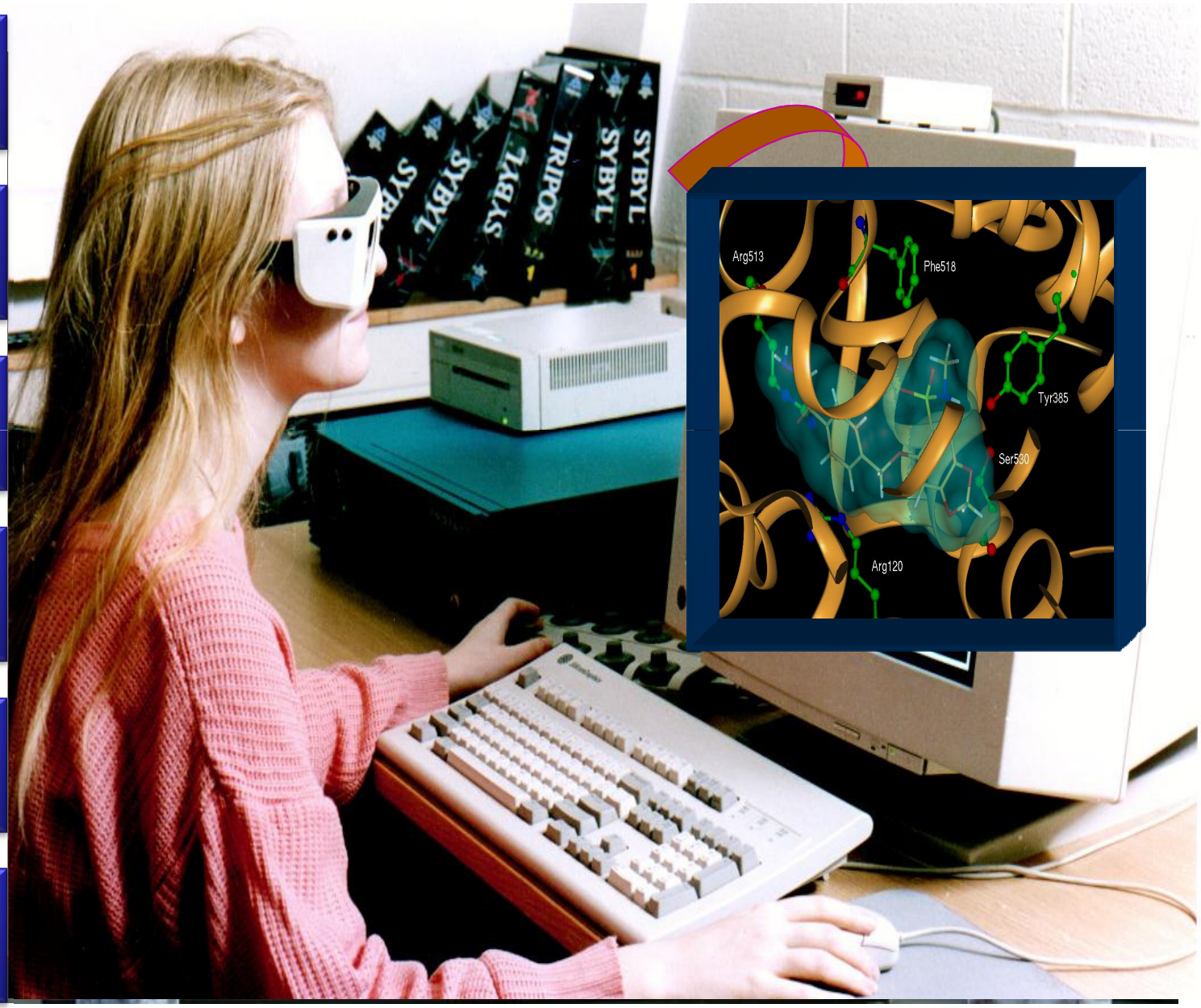


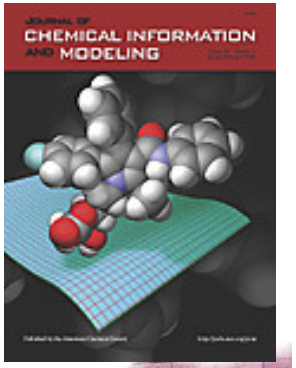
PDE4D - 1MKD

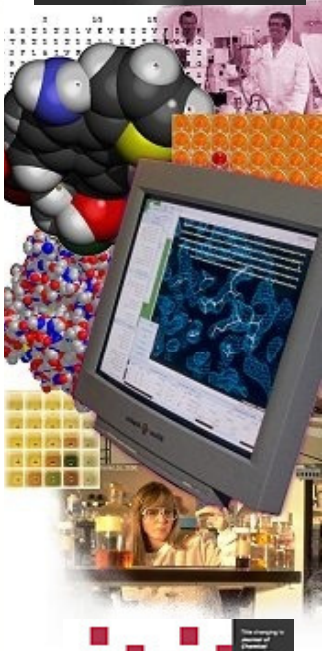
328 resíduos

*Metodo:* **Difraçao de Raio-X**

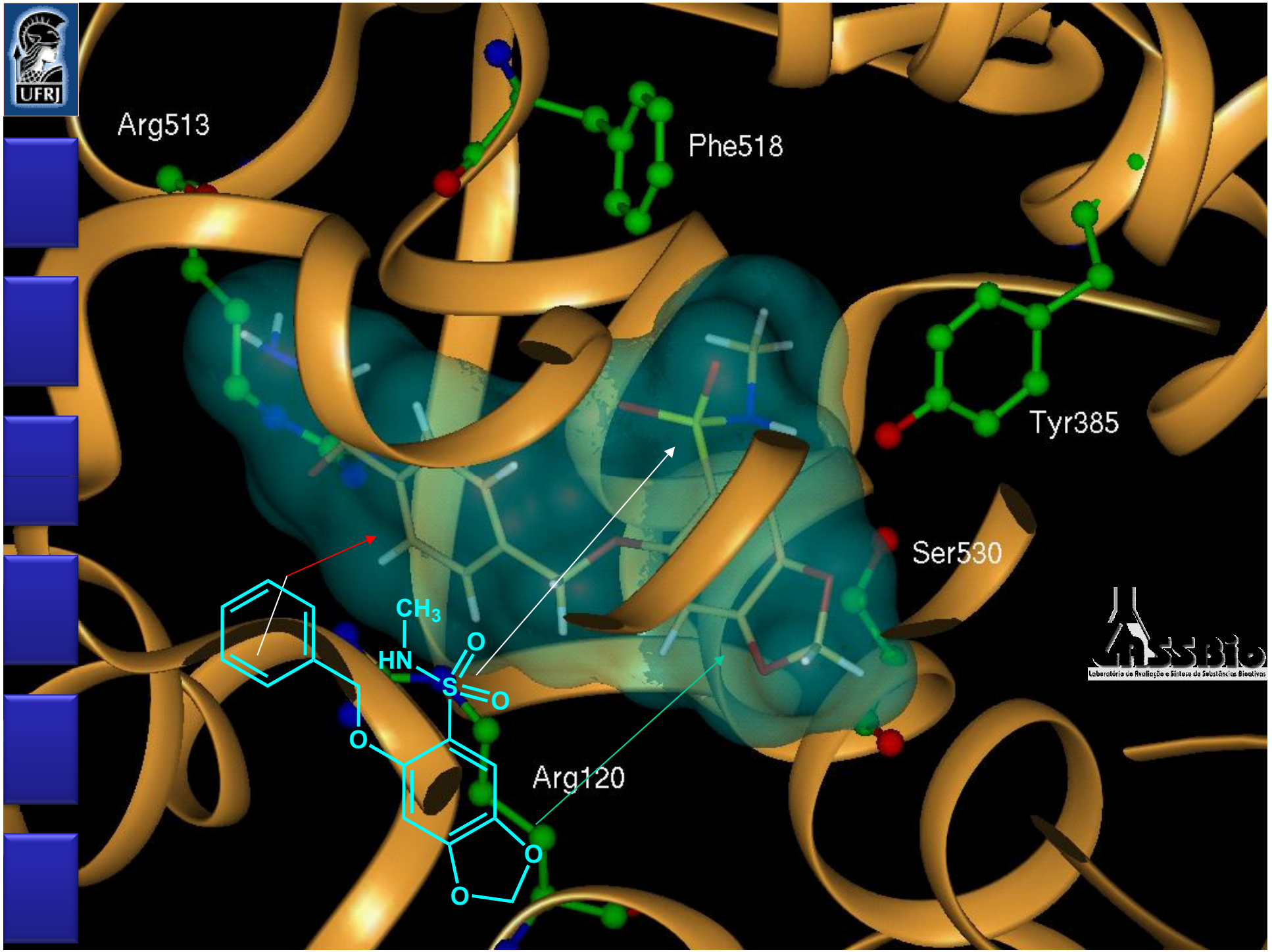
*Resolução:* **2.90 Å**

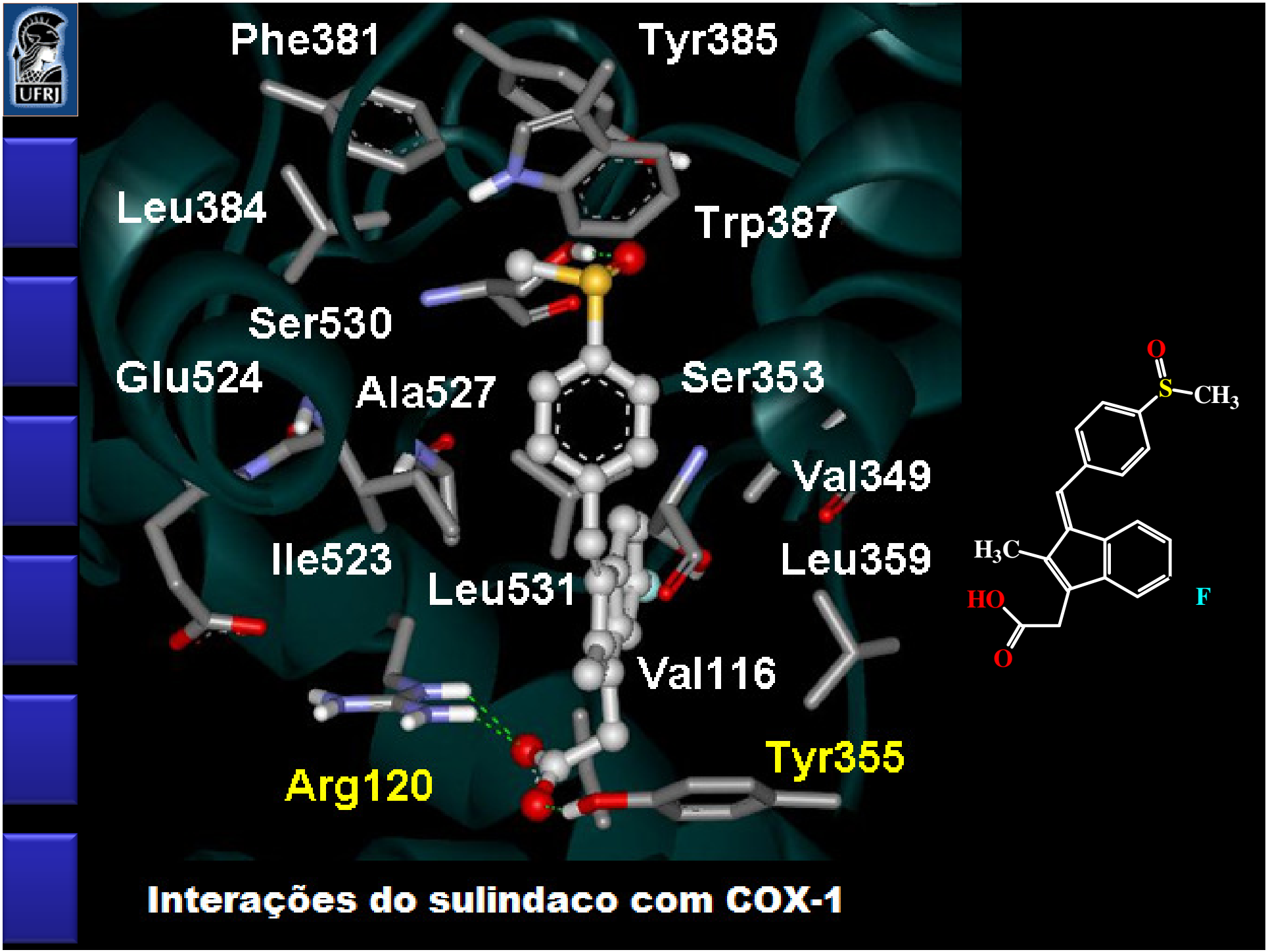

SYBYL
TRIPOS
SYBYL
SYBYL
SYBYL
Arg513
Phe518
Tyr385
Ser530
Arg120


JOURNAL OF
CHEMICAL INFORMATION
AND MODELING



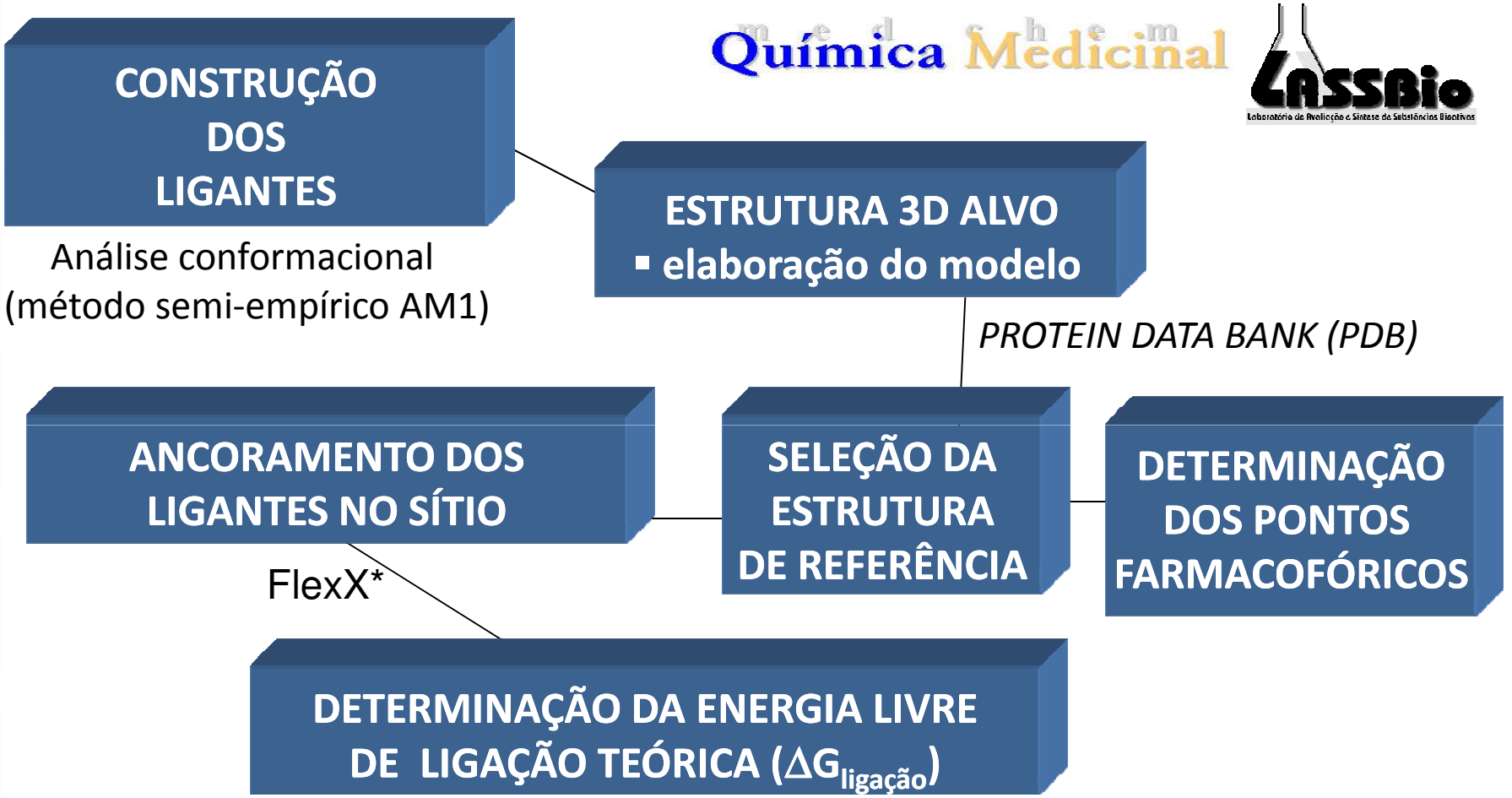

Chemical
Information and
Computer Sciences


Arg513
Phe518
Tyr385
Ser530
Arg120
CH3
HN
S
O
O
O
O
O
O
UFRJ
LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas




Interações do sulindaco com COX-1

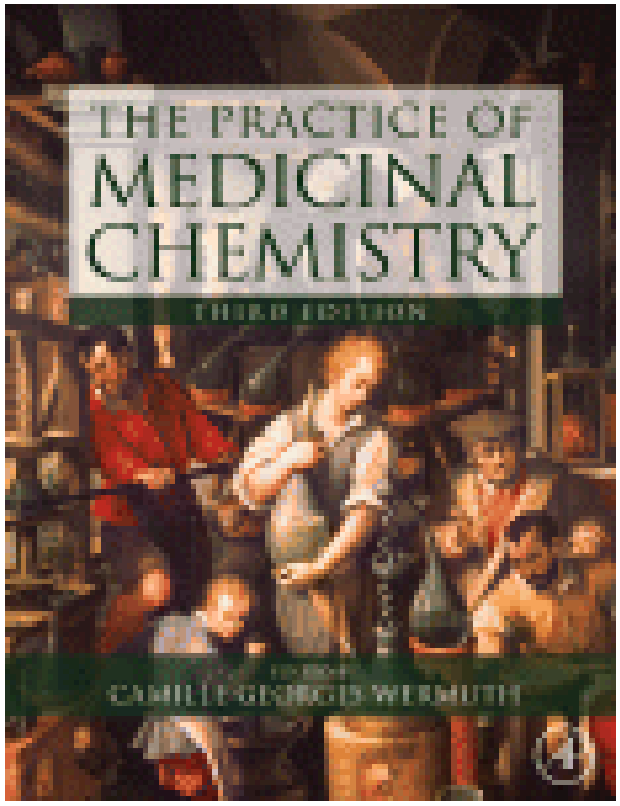
# Metodologia: Estudos de *docking*




* FlexX one of the most cited commercial docking software

---

Sybyl, Version 8.0, Tripos Associates: St. Louis, MO, 2007 (**Licença # 7512**)
Spartan Pro; Wavefunction, Inc. 18401 Von Karman Avenue, Suite 370. Irvine, California 92612, USA (**Licença # 1-001259** )
FlexiDock; GLIDE; Gold; AutoDock (GNU) General Public License;




Parte 2
J. Proudfoot Ed.
Section

Capítulo 10

T Langer & S D Bryant

*In Silico* screening: hit finding from database mining