



Mini Curso - 004

Planejamento de candidatos a novos fármacos

Parte 1

Eliezer J. Barreiro

Professor Titular - UFRJ



64ª Reunião Anual da SBPC

22 a 27 de Julho de 2012 | UFMA | São Luís, MA

CIÊNCIA, CULTURA E SABERES TRADICIONAIS PARA ENFRENTAR A POBREZA.

SB
PC

Ementa

Breve introdução histórica da Química Medicinal; O papel dos pioneiros; Os fármacos e os produtos naturais; Estratégias de desenho molecular de novos candidatos a fármacos; Considerações finais.



Universidade Federal do Rio de Janeiro



Cidade Universitária, ilha do Fundão

Química Medicinal

De onde venho...



Laboratório de Avaliação e Síntese de Substâncias Bioativas

19/04/1994 Laboratório de Avaliação e Síntese de Substâncias Bioativas



Molecular Modelagem
Modeling Molecular



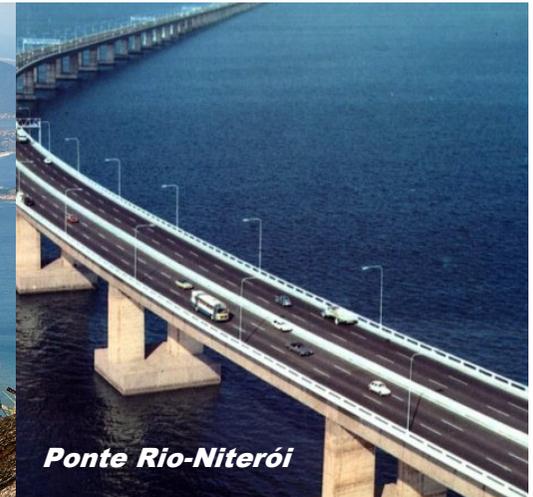
Pharmacology
Farmacologia



Morro do Corcovado



Pão de Açúcar



Ponte Rio-Niterói



Copacabana



Vista de Copacabana do Pão de Açúcar



Ipanema



Antigo estádio do Maracanã



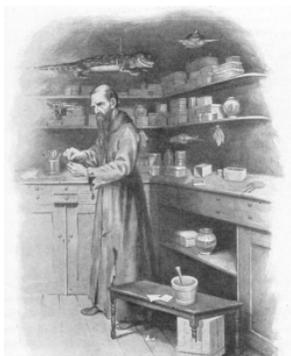
Barra da Tijuca



Jardim Botânico



Universidade Federal do Rio de Janeiro



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

Como **n**a **S**Ce m
OS fármacos?

Química Medicinal



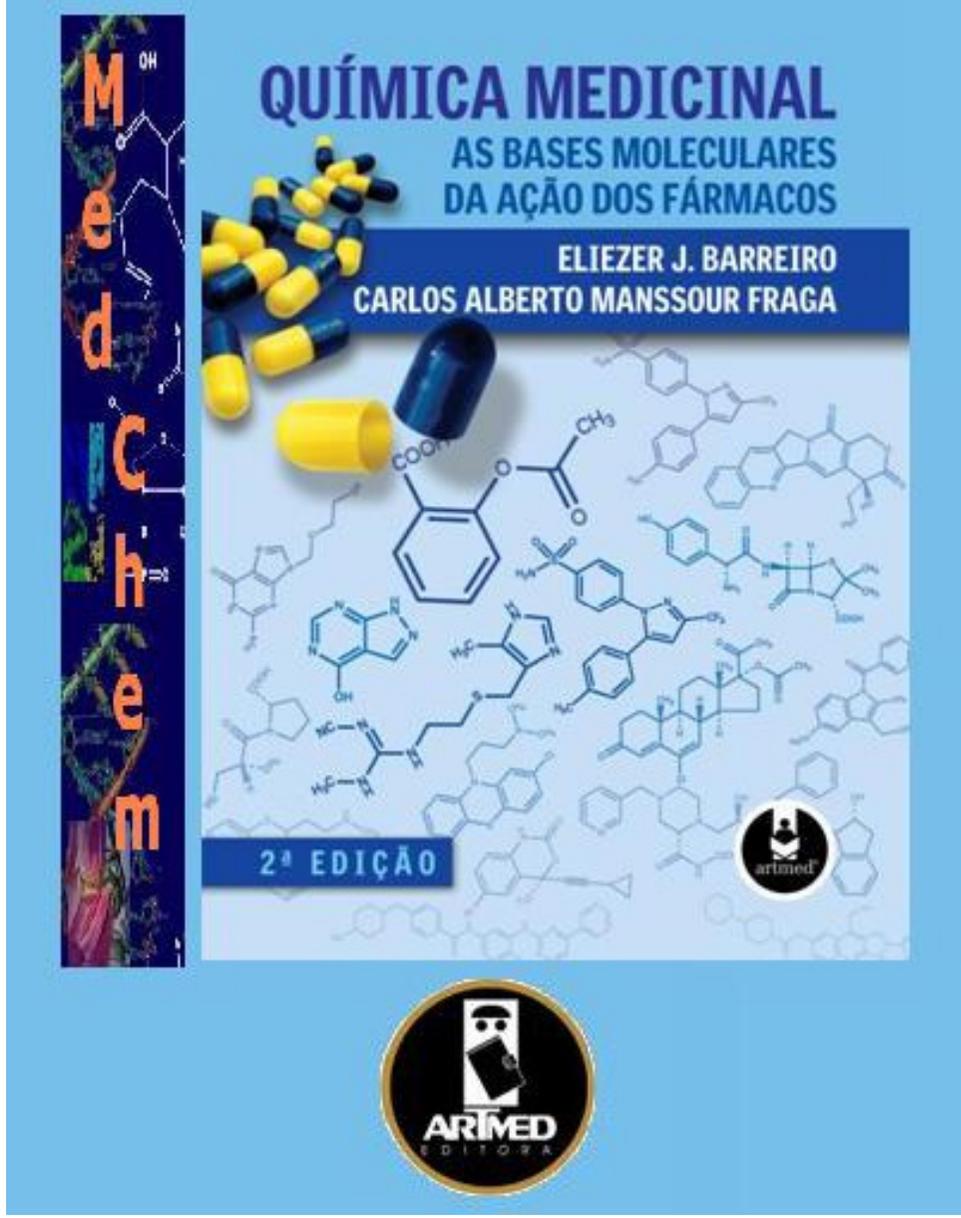
Química Medicinal





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Bibliografia



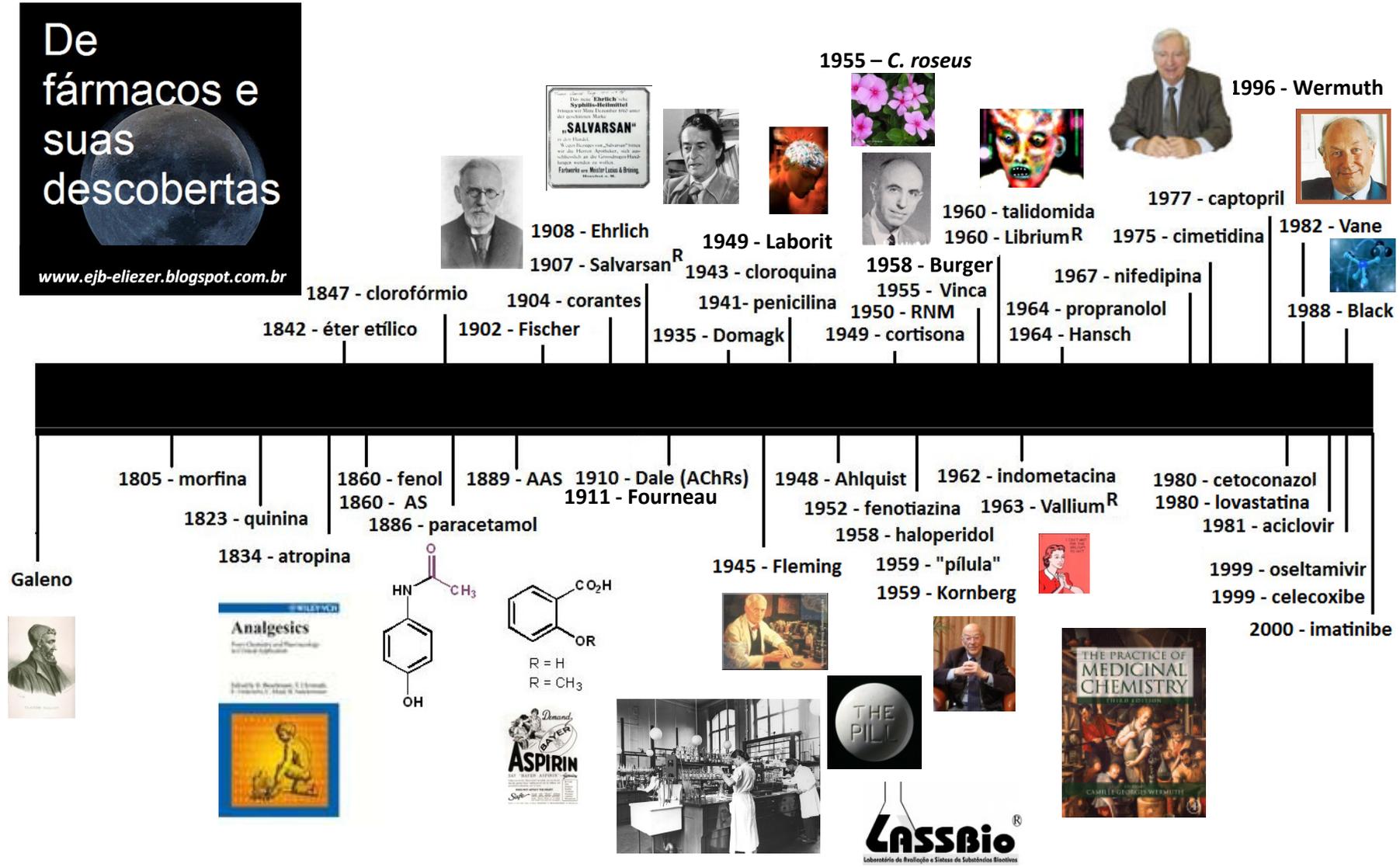


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Cronologia histórica da **Química Medicinal**

De fármacos e suas descobertas

www.ejb-eliezer.blogspot.com.br





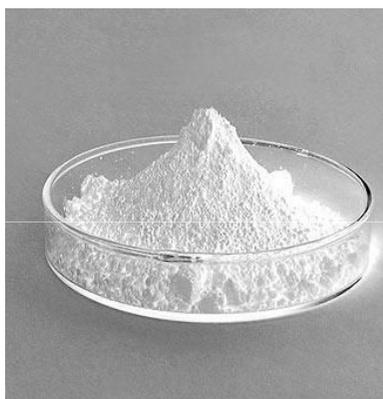
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Fármaco...

Formas Farmacêuticas 

Farmoquímico

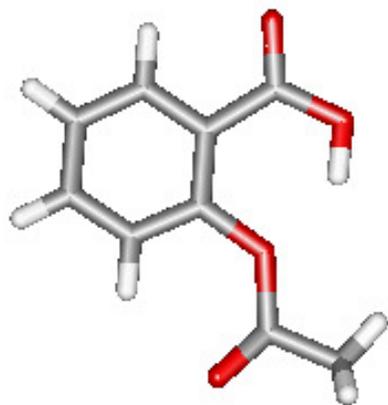


Pureza farmacopêica



Tecnologia Farmacêutica

Princípio ativo



IFA

ácido acetilsalicílico

.... & medicamento





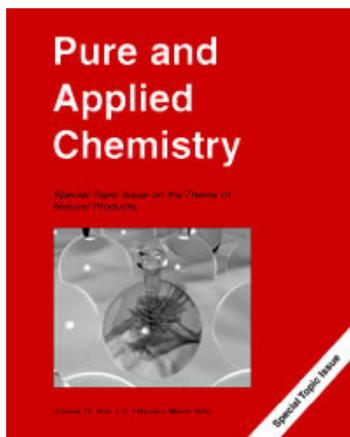
O que é um fármaco ?

• **Fármaco...**

- É uma substância orgânica (pureza > 98%) com propriedades farmacoterapêuticas para uso médico, capaz de recuperar, promover, manter ou preservar a Saúde;
- tem elevada eficácia para o(s) alvo(s) terapêutico(s) (PD);
- poucas propriedades tóxicas;
- potente e eficaz com biodisponibilidade adequada, ativo em doses baixas, por via oral, se possível em uma única dose ao dia;
- tem boa absorção sendo estável metabolicamente (PK):
 - Propriedades físico-químicas críticas para a atividade do fármaco por via oral: solubilidade, partição passiva membrana/água, peso molecular, ligações-H;
- acessível por rota sintética em escala, a custos aceitáveis;
- protegido por patente para determinada(s) indicação(ões) terapêutica(s);

• ... as propriedades moleculares dos fármacos são objeto do estudo da

Química Medicinal



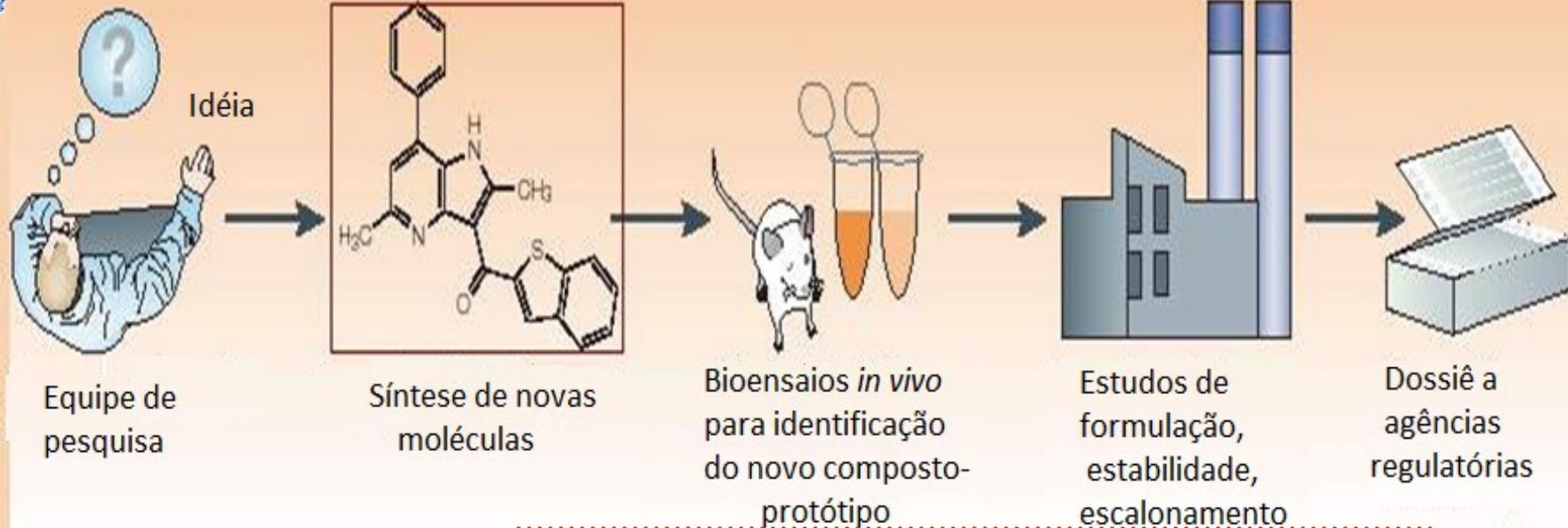
IUPAC - Subcommittee Medicinal Chemistry & Drug Development

Química Medicinal é a disciplina que estuda os aspectos relacionados à *descoberta* ou *invenção* de **fármacos**, os aspectos moleculares envolvidos em seu mecanismo de ação e aqueles que governam a *absorção*, *distribuição*, *metabolismo*, *eliminação* e *toxicidade* (ADMET), incluindo a compreensão da relação entre a estrutura química e a atividade terapêutica (REA).



Fase pré-clínica

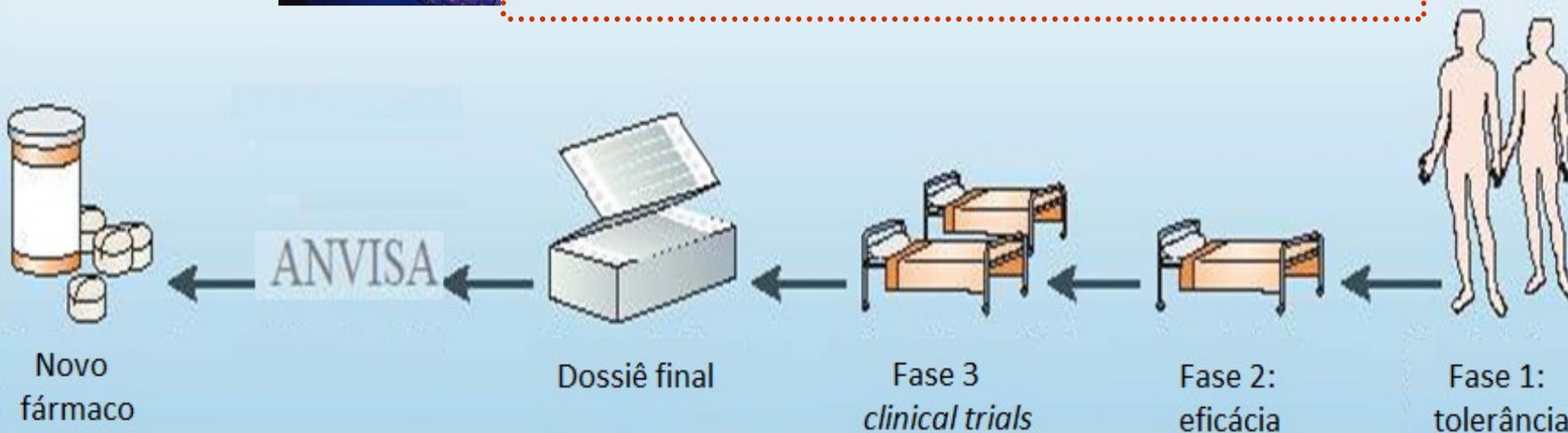
Química Medicinal



Estudos clínicos



O processo de planejamento de novos fármacos é complexo !





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Os Pioneiros...

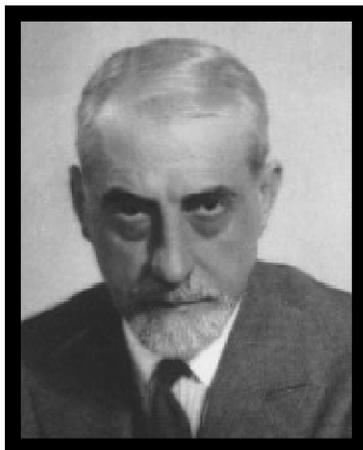


^{m e d}
Química
^{e h e m}
Medicinal



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O berço da Química Medicinal

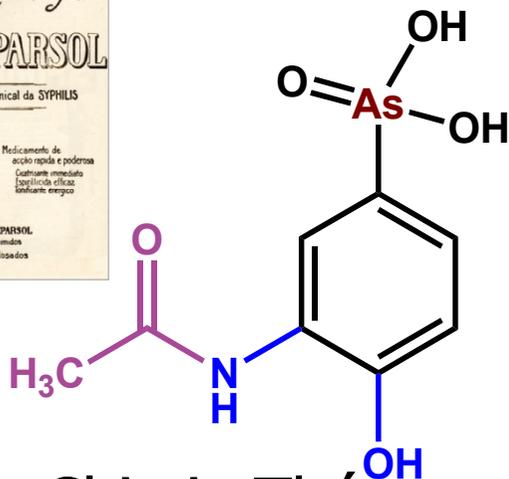


Ernest Fourneau
1872-1949



Stovarsol

CAS 97-44-9



Institute Pasteur (1887)

1911- Laboratoire de Chimie Thérapeutique

Institut Pasteur (Emile Roux)

1911-1944 – Jacques Tréfouël (1897-1977)

Thérese Tréfouël (1892-1978)

Germaine Benoit (1901-1983)

Federico Nitti (1903-1947)



Daniel Bovet
1907-1992 *

* Farmacêutico suíço
Doutor *h.c.* UFRJ

Prêmio
Nobel
1957



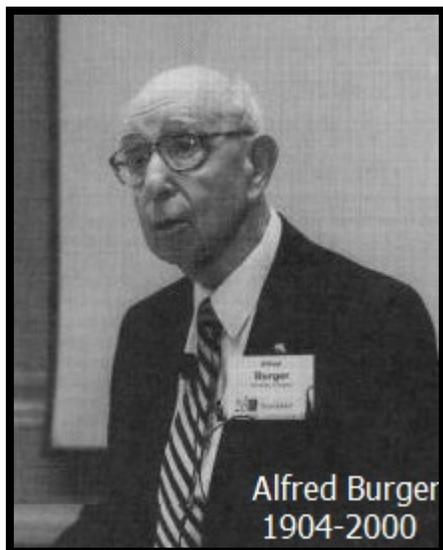
Sulfonamidas,
anti-histamínicos.
Curare: SAR



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



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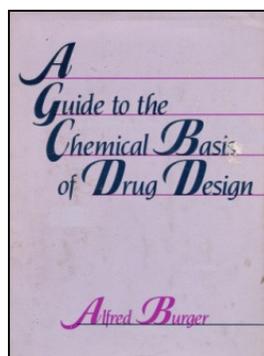
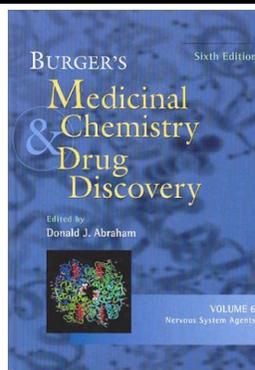
Química Medicinal

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



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Química Medicinal

“...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



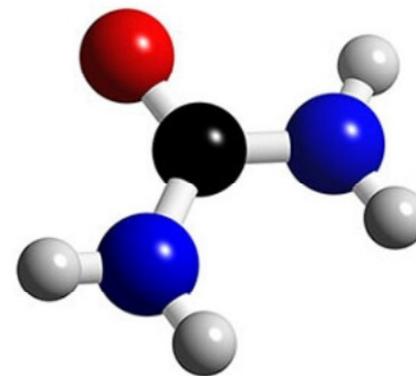
The Role of the Medicinal Chemist in Drug Discovery – Then and Now,

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



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As moléculas
pioneiras...



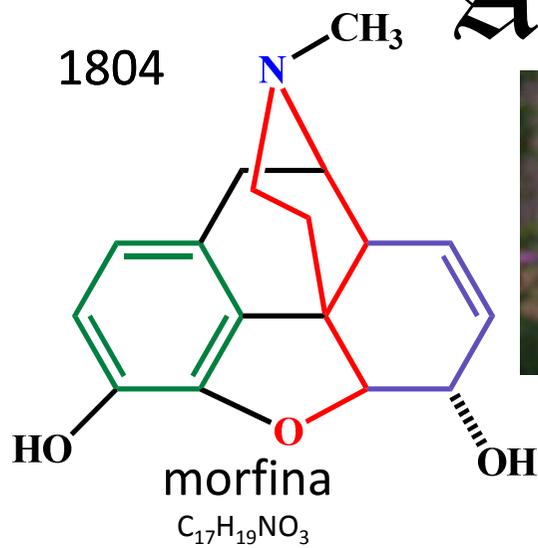
Química
Medicinal



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As moléculas pioneiras...

1804



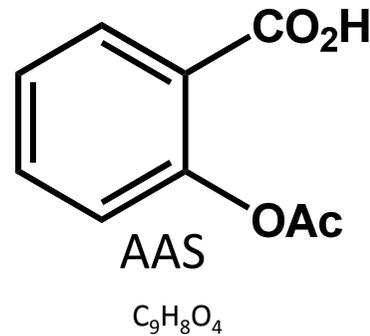
Friedrich W. A. Sertürner
1783- 1841



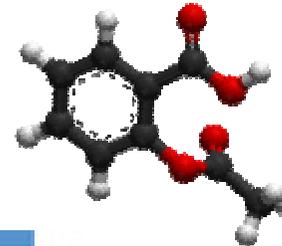
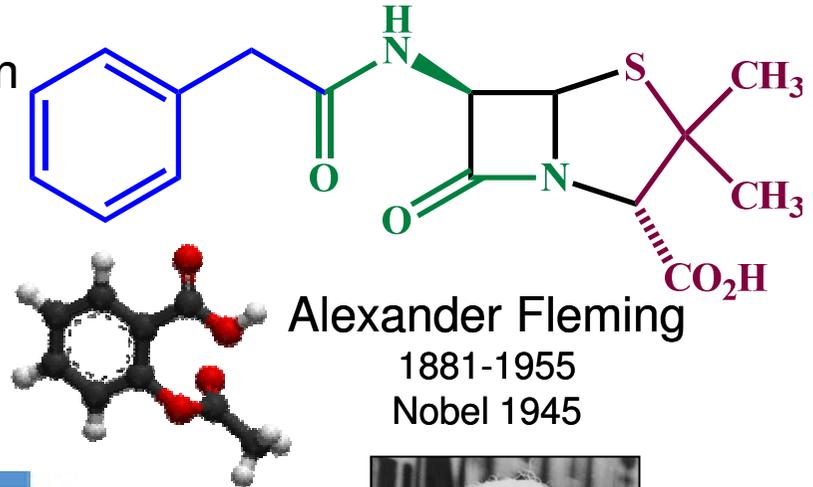
Sir Robert Robinson
1886-1975
Nobel 1947



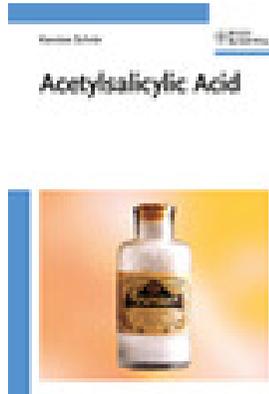
1897



Felix Hoffman
1868- 1946



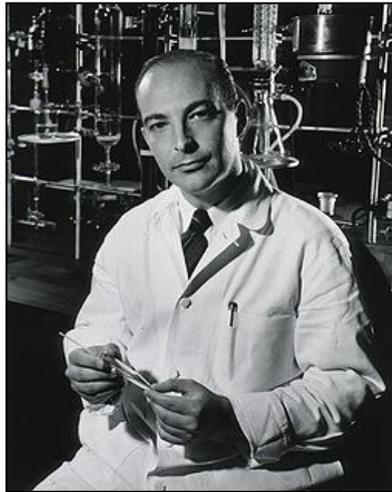
1929
penicilina
 $C_{16}H_{18}N_2O_4S$





Os fármacos e o prêmio Nobel





Prêmio Nobel, 1959



FORUM

The Two Cultures: Chemistry and Biology¹

Arthur Kornberg

Department of Biochemistry, Stanford University, Stanford, California 94305

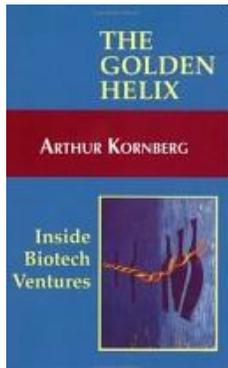
Received July 14, 1987

Arthur Kornberg *“Much of life can be understood in rational terms if expressed in the language of chemistry... the*

1918-2007

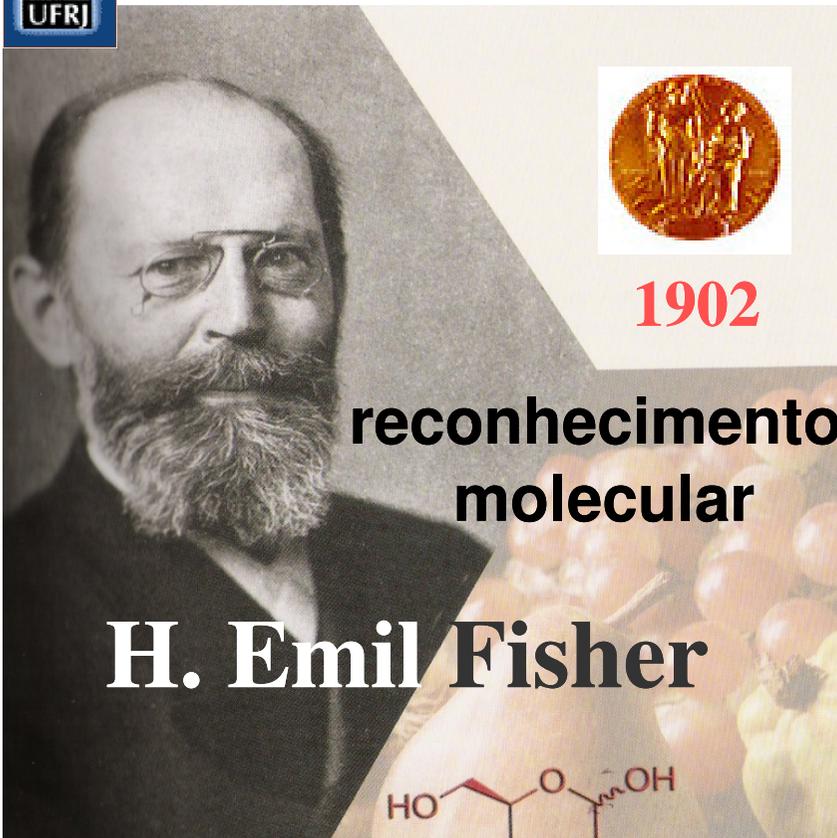
historical roots of chemistry and biology are intertwined in many places...

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





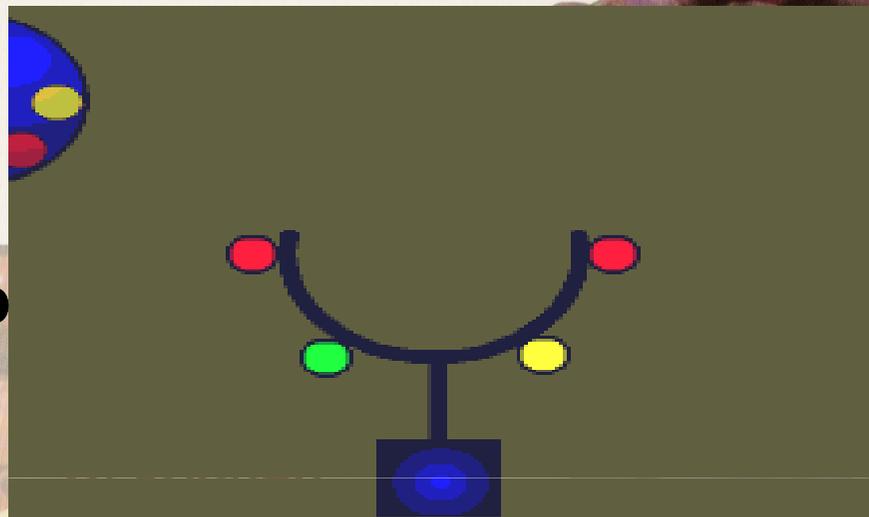
Modelo centenário Chave-fechadura



1902

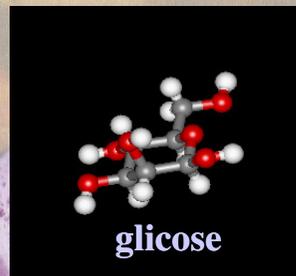
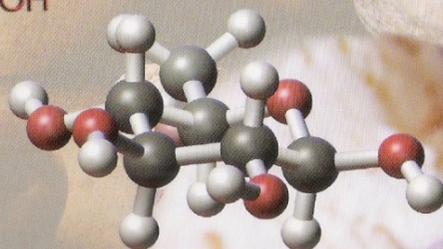
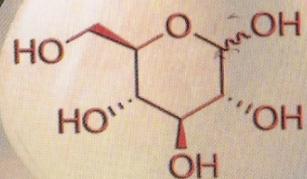
reconhecimento
molecular

H. Emil Fisher



LOCK & KEY

CONCEPT



glucose





Os fármacos atuam em alvos terapêuticos...

Química Medicinal

... os biorreceptores.



* 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.



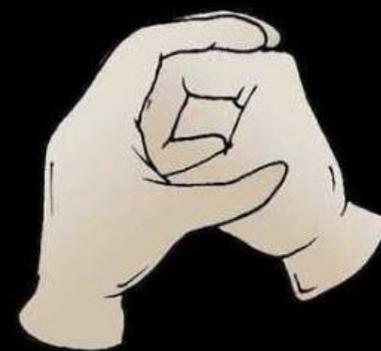
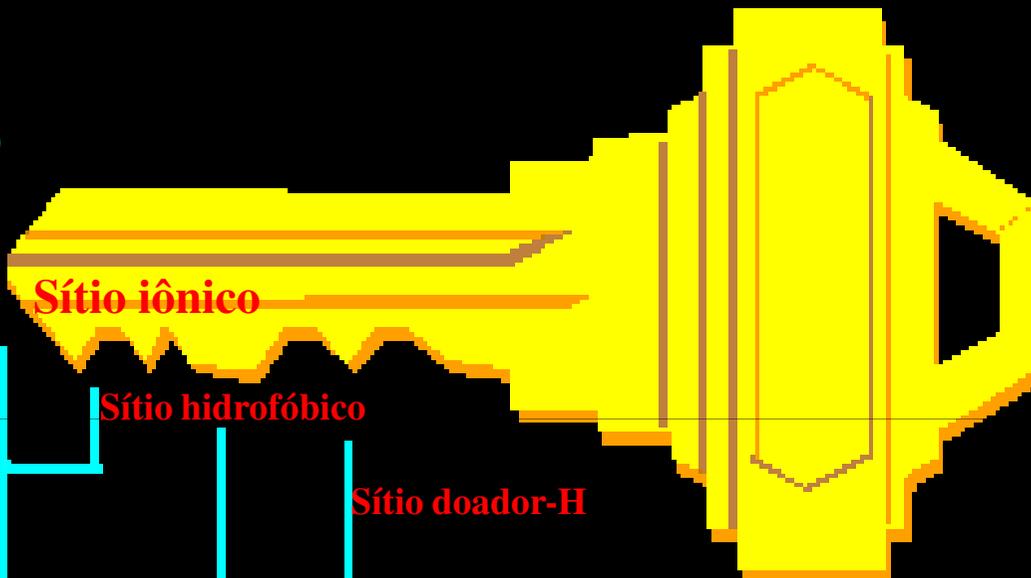
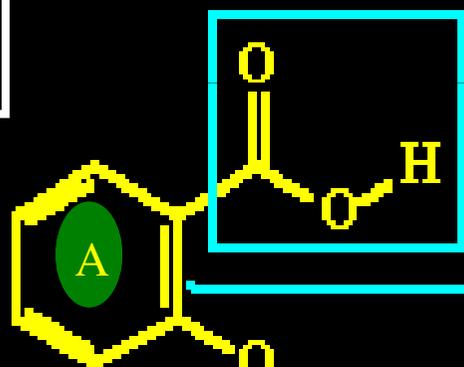
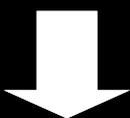
O Centenário Modelo "Chave-Fechadura"

Complementaridade do modelo Chave-fechadura



AAS

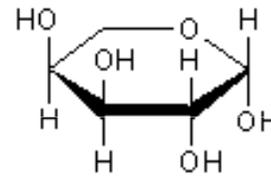
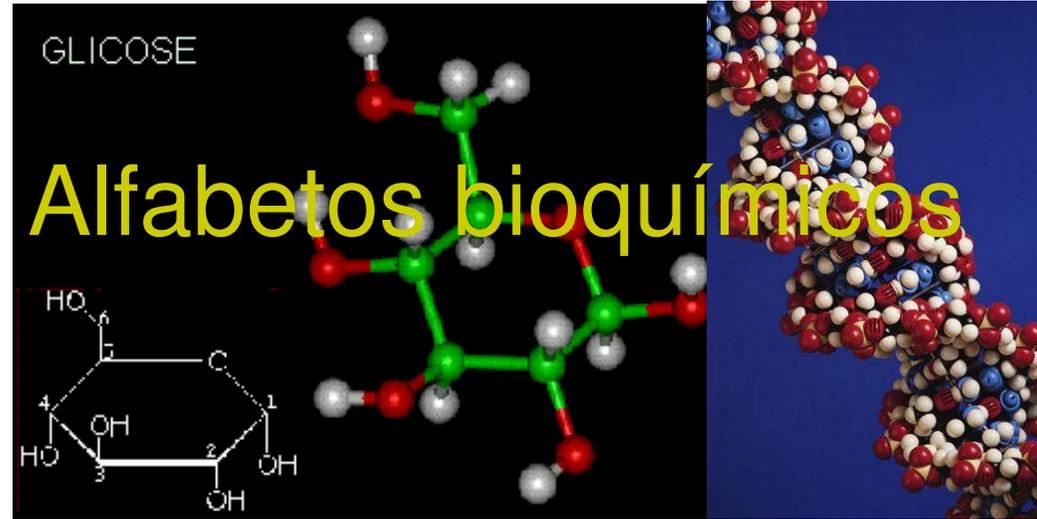
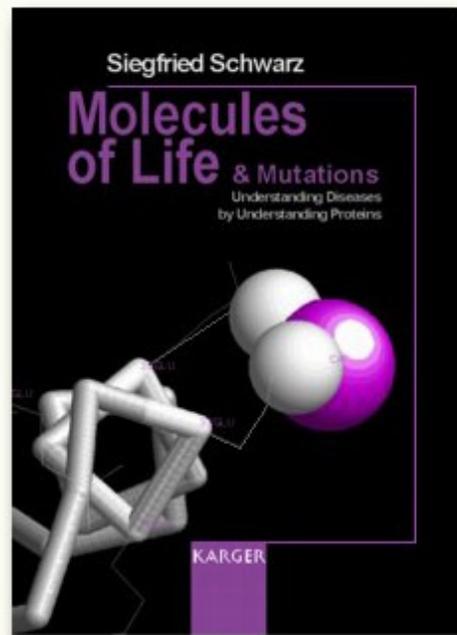
Sítio iônico



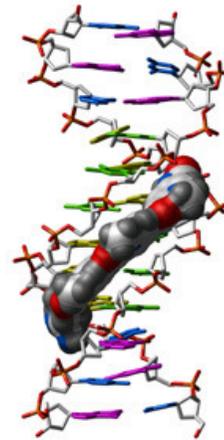
complementaridade molecular



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β -L-Arabinose



Model Compound Bound to the Minor Groove of a DNA Molecule

Carboídratos

Lipídeos

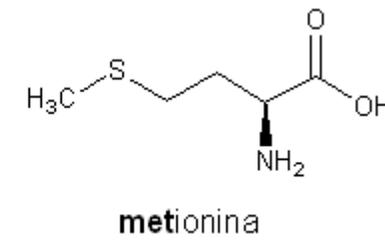
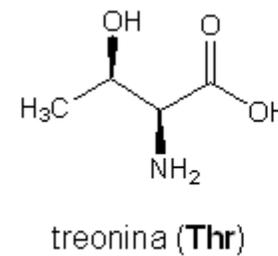
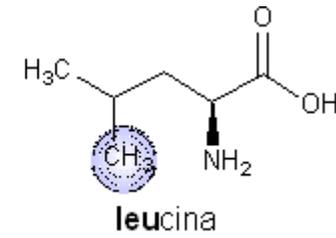
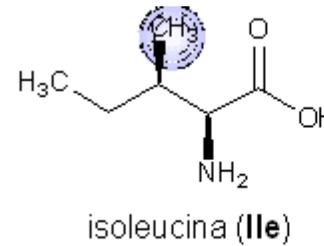
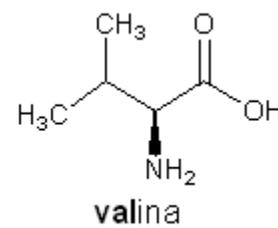
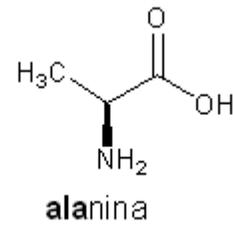
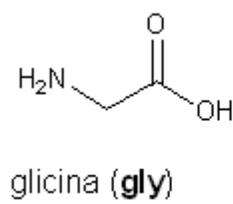
ácidos nucleícos

proteínas

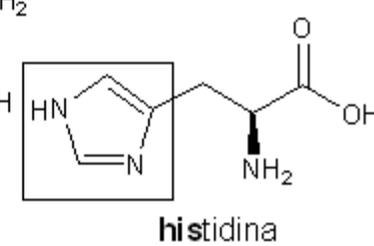
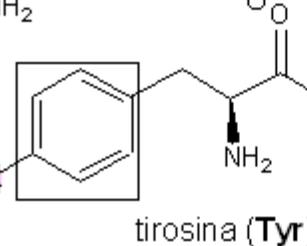
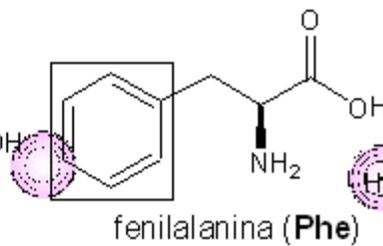
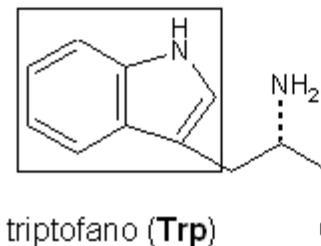
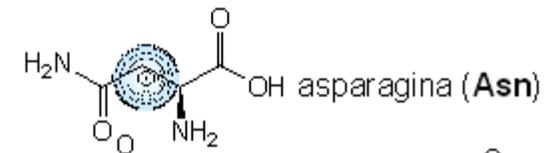
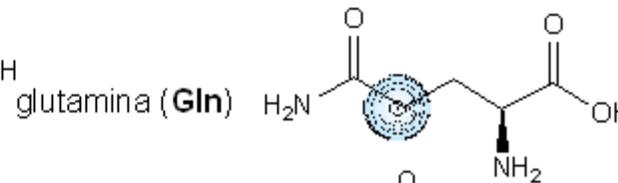
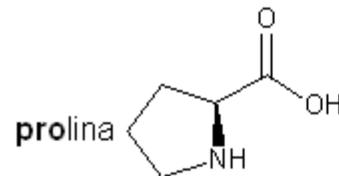
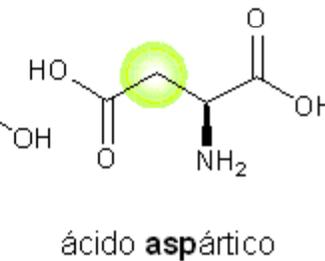
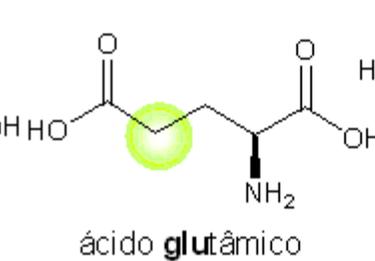
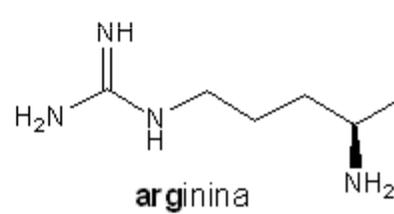




O "alfabeto" do proteoma ...

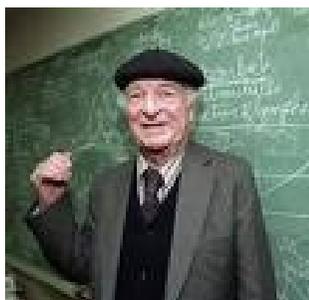
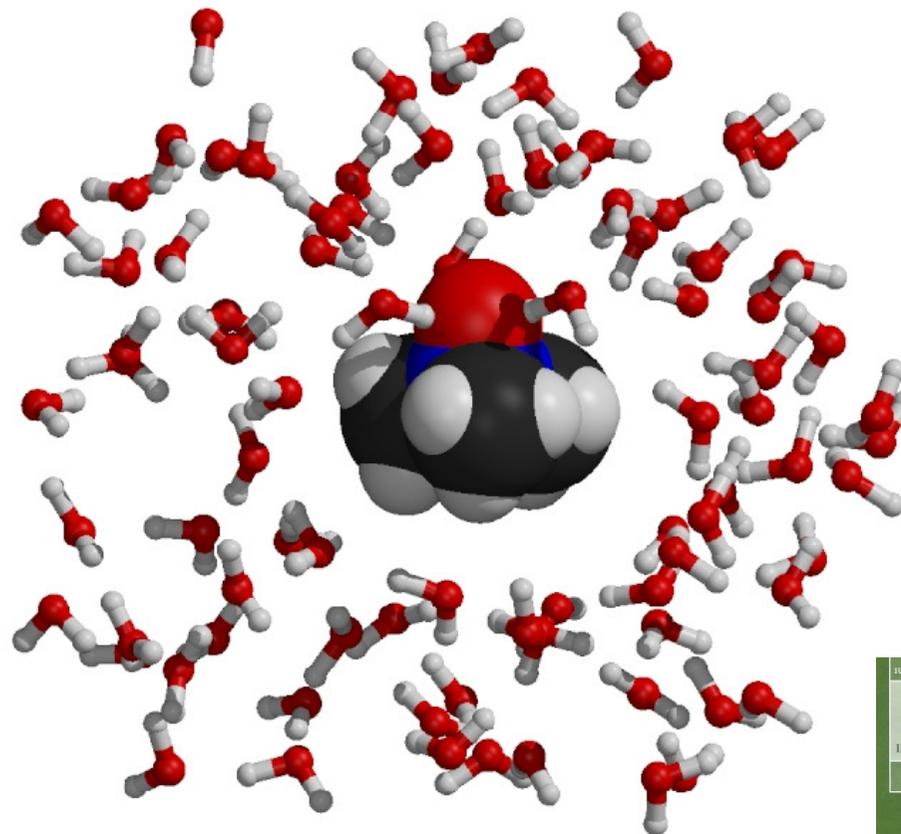
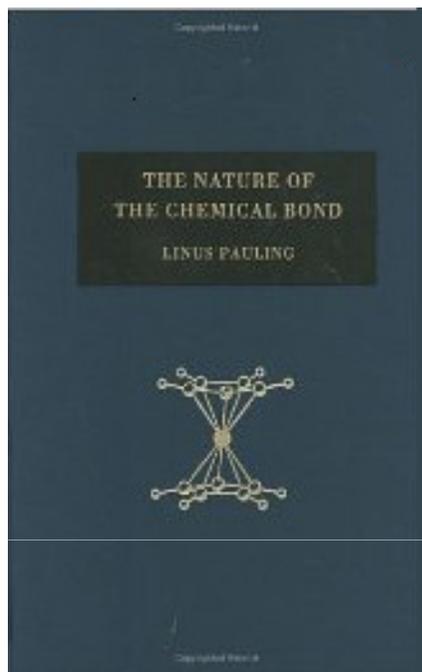


lisina (**Lys**)





A importância das “ligações” frágeis...

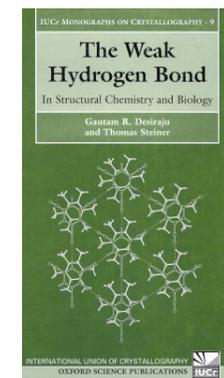


Linus C. Pauling
1901-1994

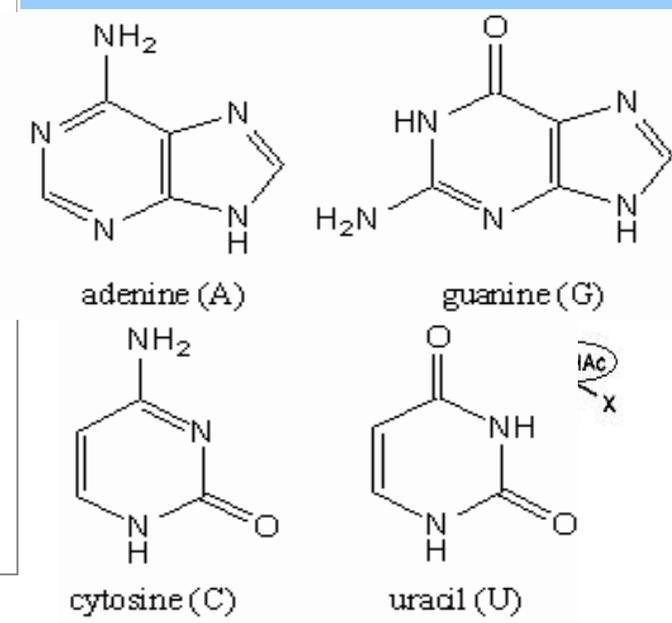
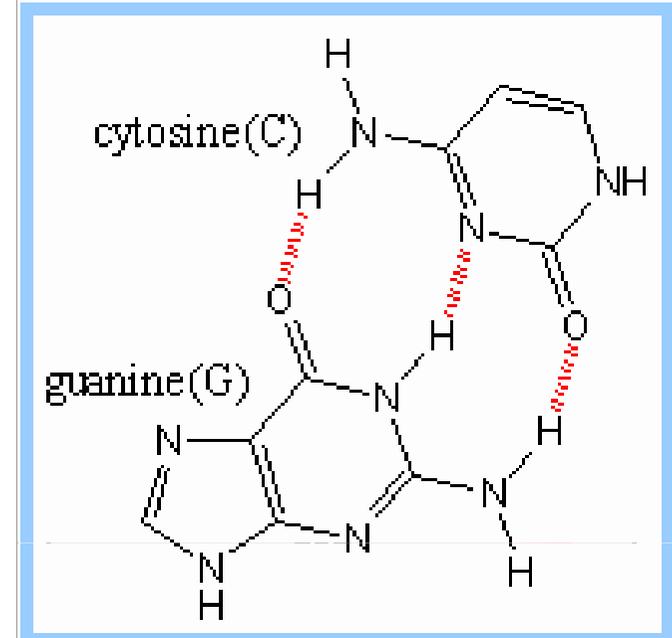
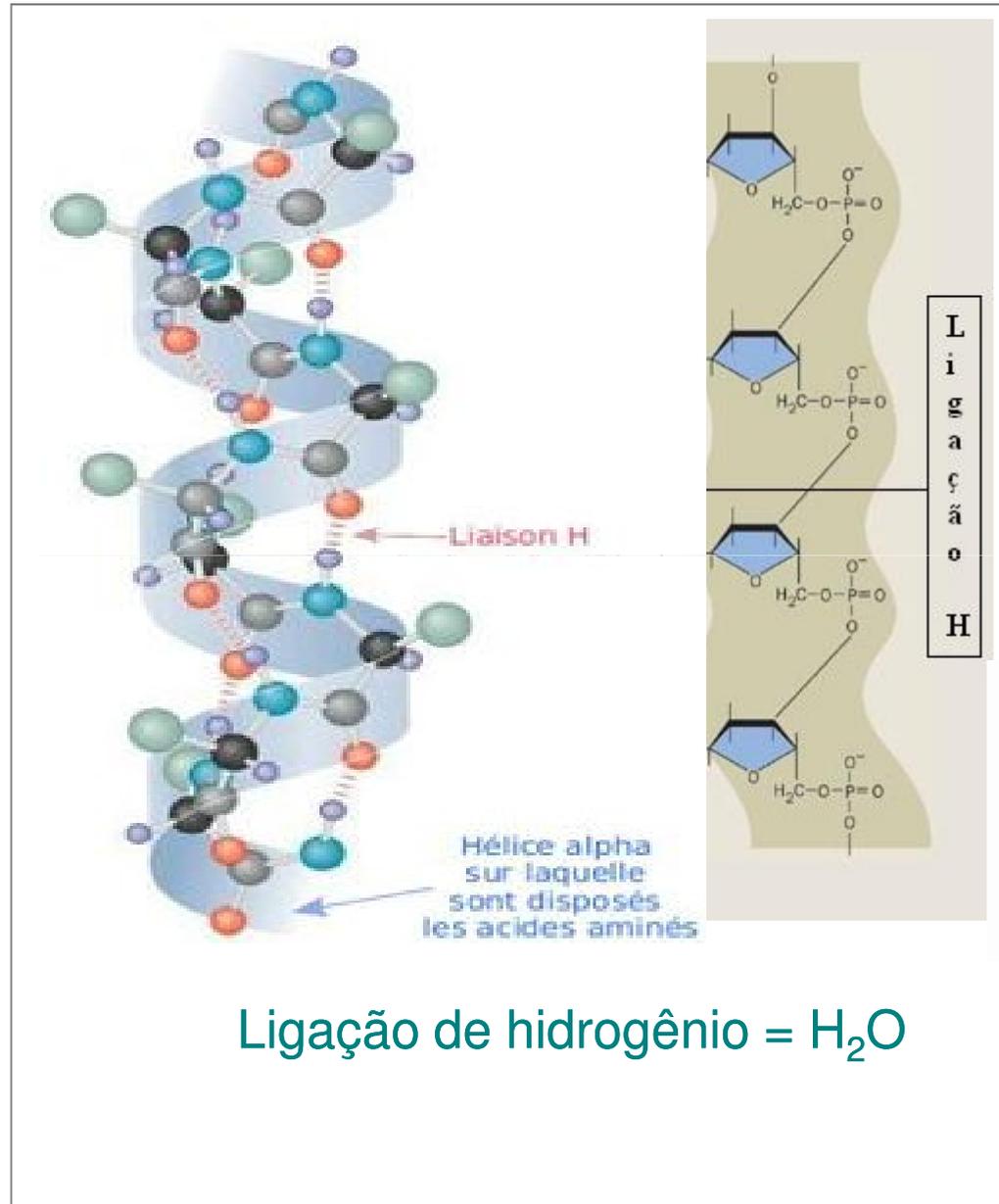
1954, 1962



“ligações”
de hidrogênio ...

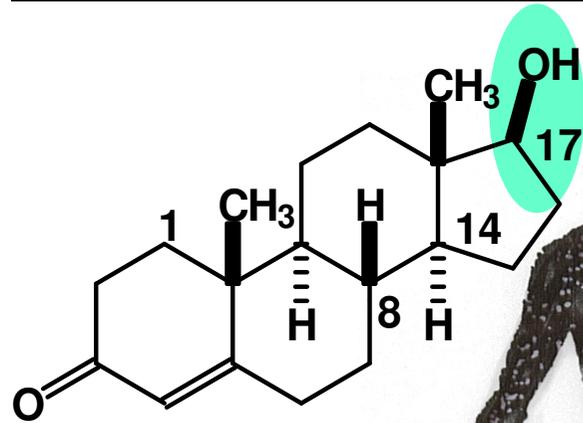


Proteínas, carboidratos, DNA, lipídeos, canais iônicos





Similaridade & Dissimilaridade Molecular



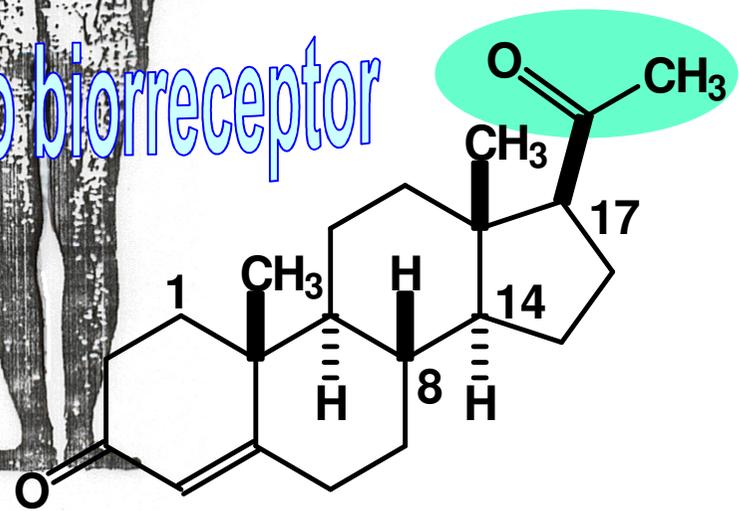
testosterona



no reconhecimento molecular do biorreceptor

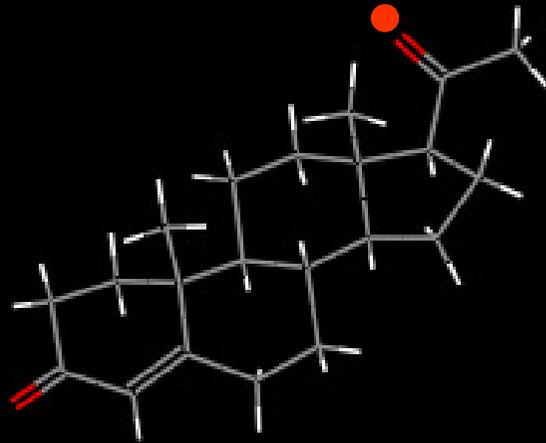


similaridade molecular

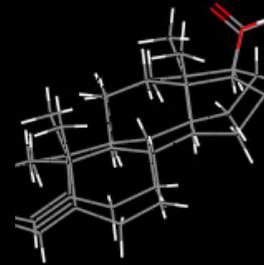


progesterona

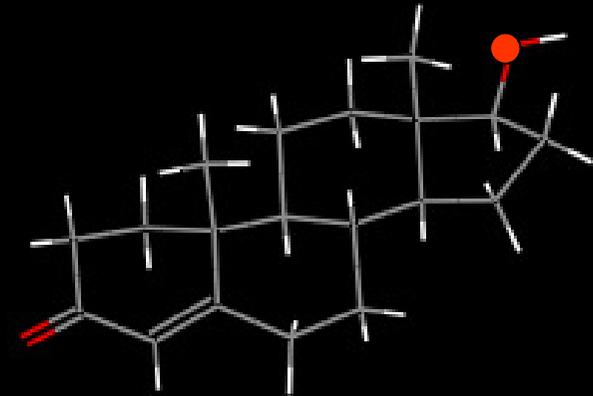
Similaridade & reconhecimento molecular



progesterona



1,41 A



testosterona

