



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.



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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*

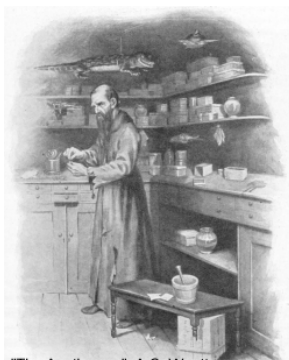


*Jardim Botânico*





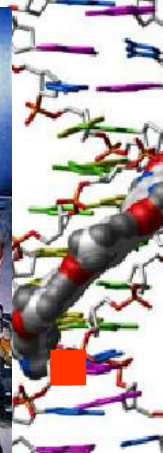
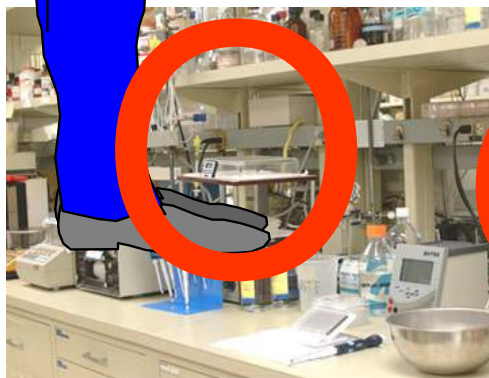
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"The Apothecary", A.C. Woolton. (Chronicles of Pharmacy Vol II 1910)

Como **n**a **S**Ce m  
OS fármacos?

Química Medicinal



Química Medicinal

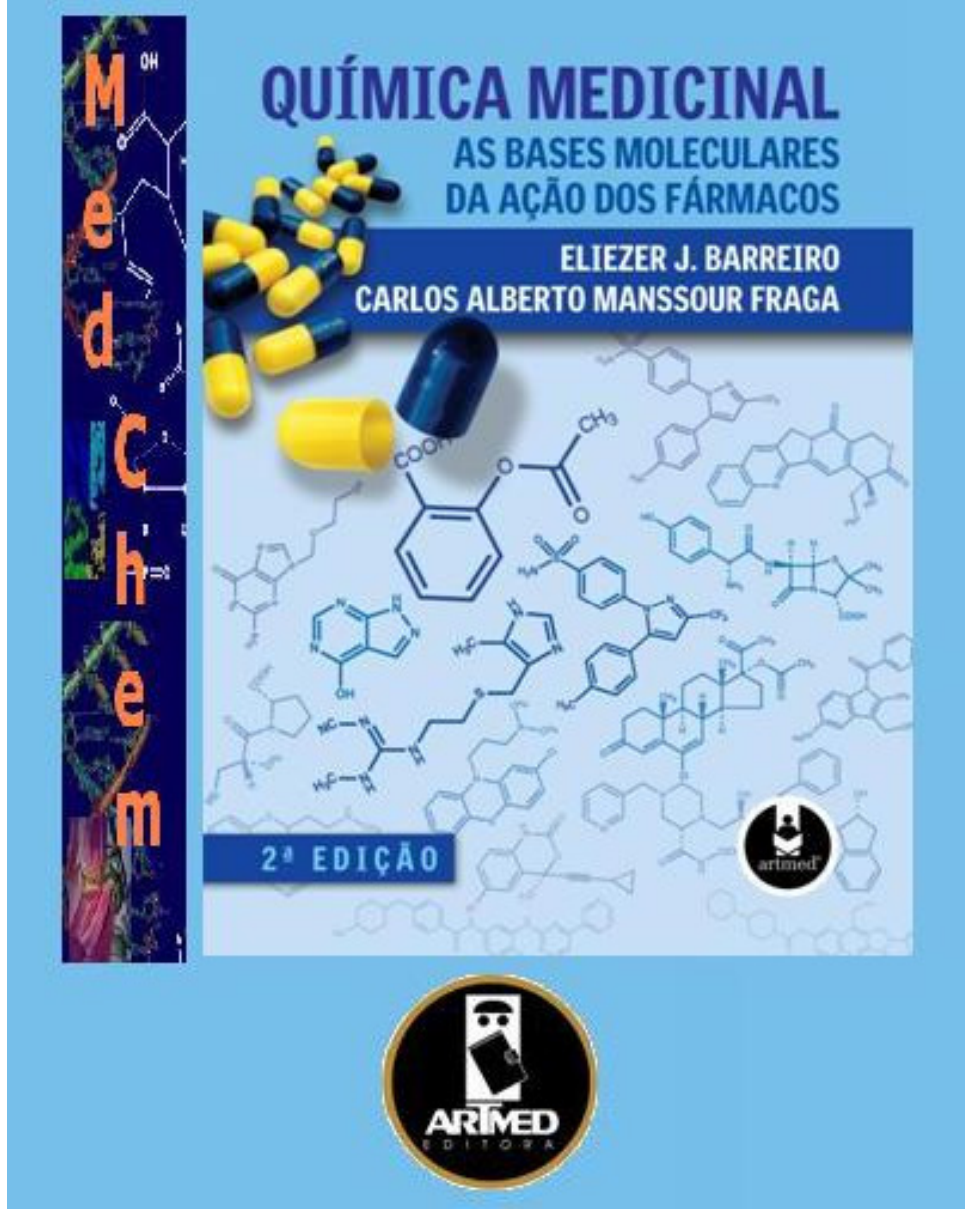






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# Bibliografia





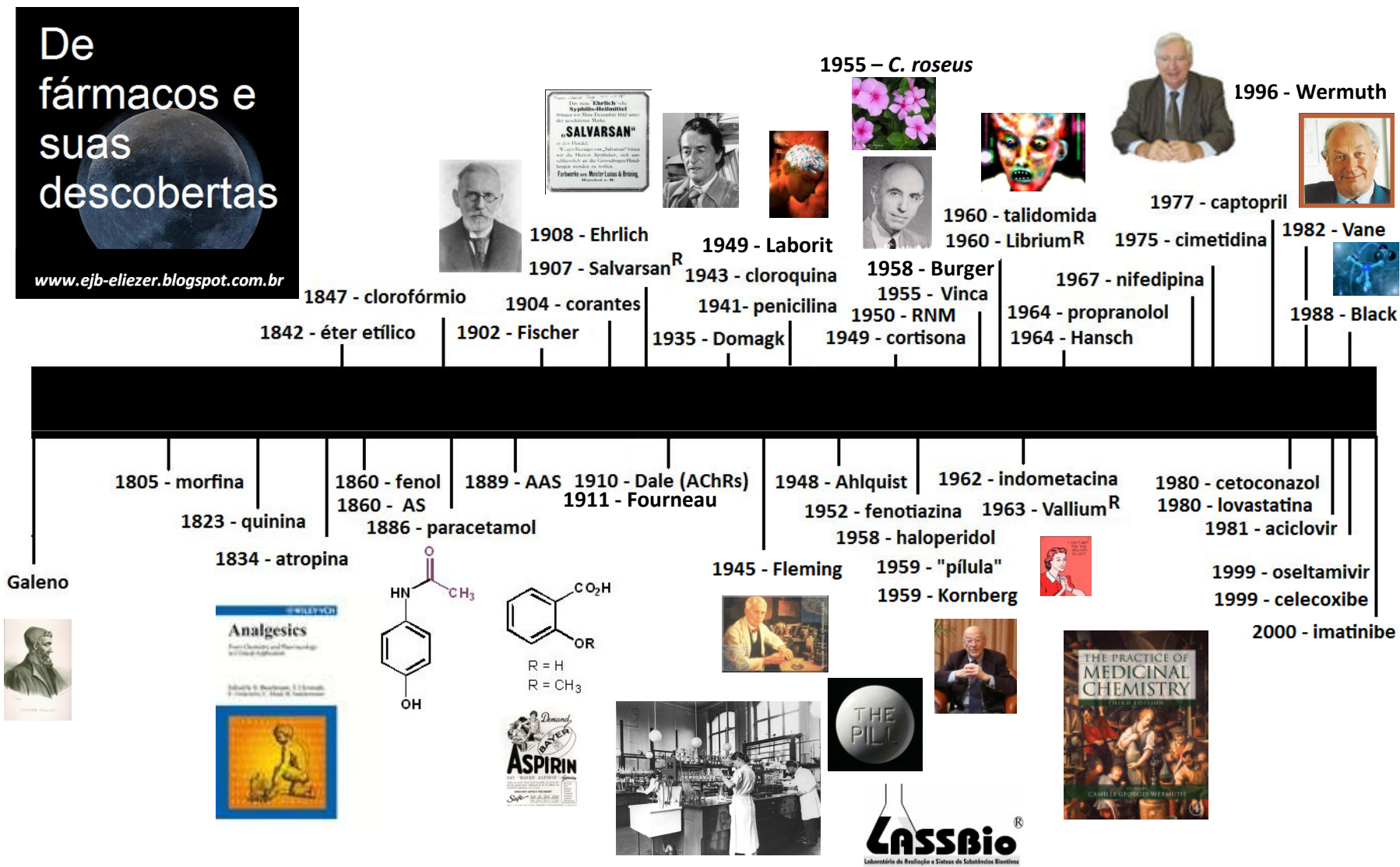


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# Cronologia histórica da **Química Medicinal**

## De fármacos e suas descobertas

[www.ejb-eliezer.blogspot.com.br](http://www.ejb-eliezer.blogspot.com.br)



[www.ejb-eliezer.blogspot.com.br](http://www.ejb-eliezer.blogspot.com.br)





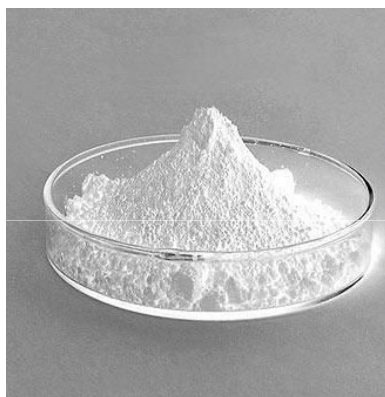
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# Fármaco...

Formas Farmacêuticas 

Farmoquímico

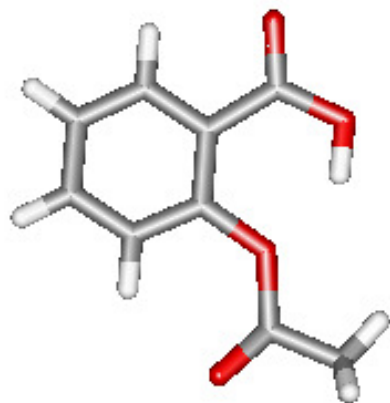


Pureza farmacopêica



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

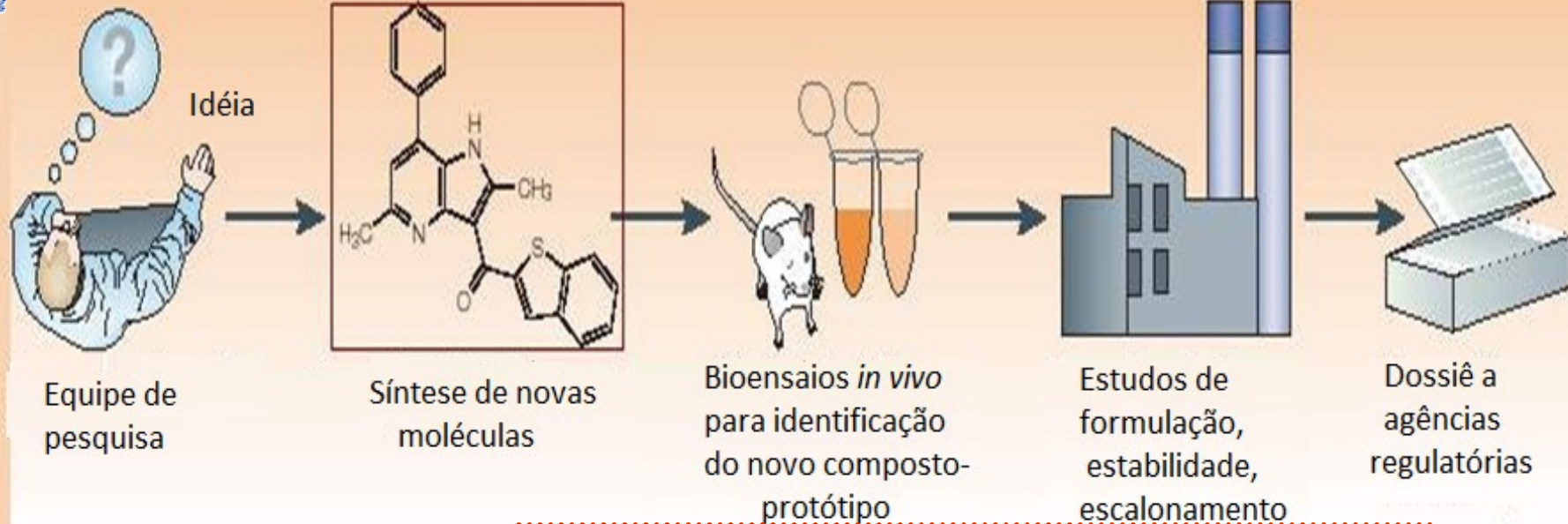
**Química Medicinal** é a disciplina que estuda os aspectos relacionados à descoberta ou invenção de **fármacos**, os aspectos moleculares envolvidos em seu mecanismo de ação e aqueles que governam a *absorção*, *distribuição*, *metabolismo*, *eliminação* e *toxicidade* (ADMET), incluindo a compreensão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



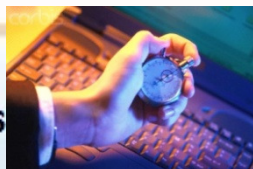


### Fase pré-clínica

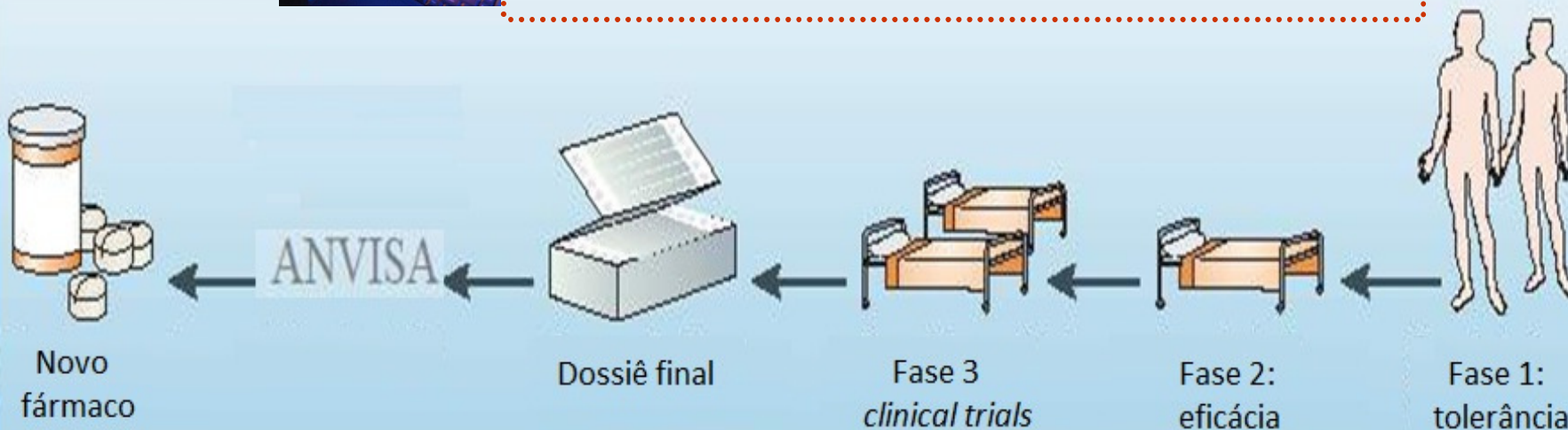
### Química Medicinal



### Estudos clínicos



O processo de planejamento de novos fármacos é complexo !





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Os Pioneiros...



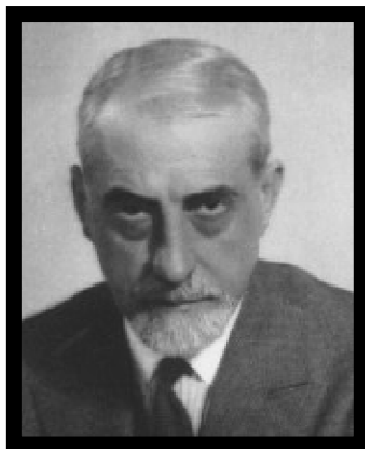
<sup>m e d</sup>  
**Química**  
<sup>e h e m</sup>  
**Medicinal**





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# O berço da Química Medicinal

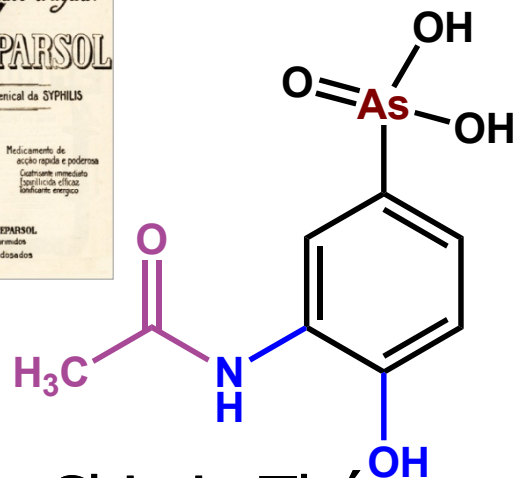


Ernest Fourneau  
1872-1949



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



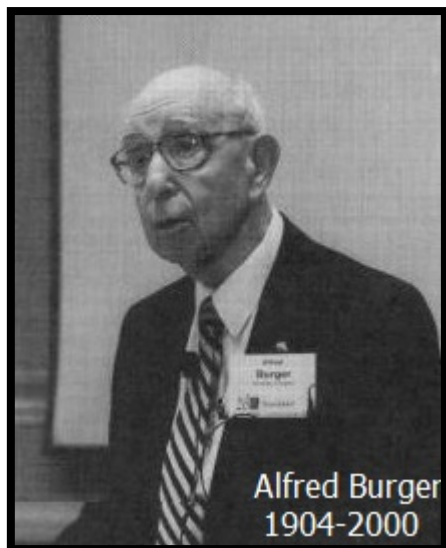
Sulfonamidas,  
anti-histamínicos.  
Curare: SAR



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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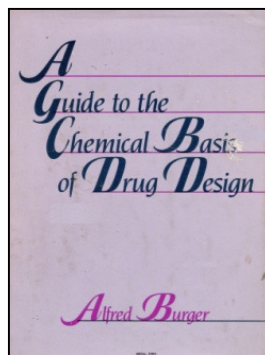
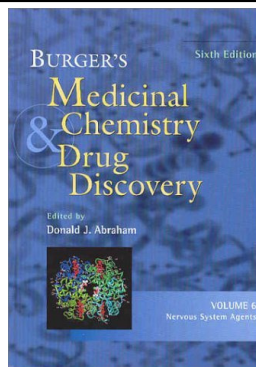
med chem  
Química Medicinal

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**



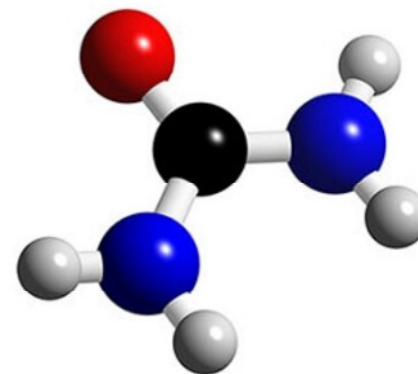
*The Role of the Medicinal Chemist in Drug Discovery – Then and Now,*

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



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As moléculas  
pioneiras...



Química  
Medicinal

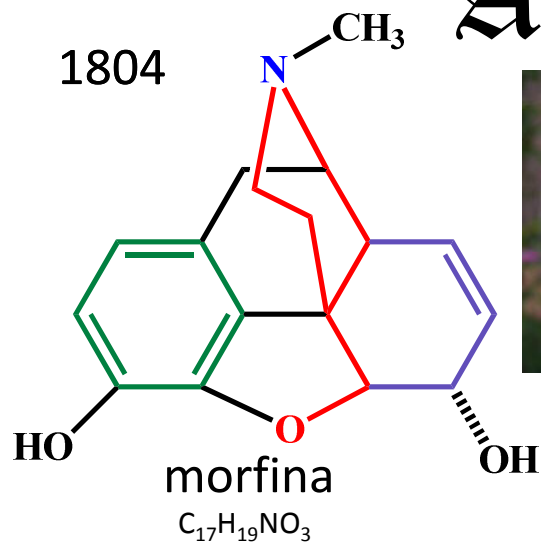




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# As moléculas pioneiras...

1804



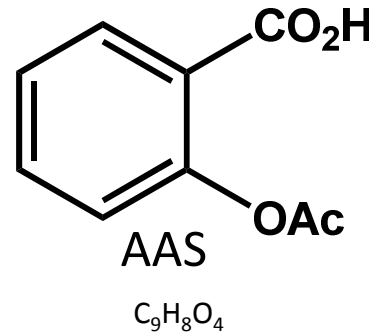
Friedrich W. A. Sertürner  
1783- 1841



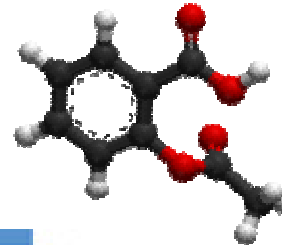
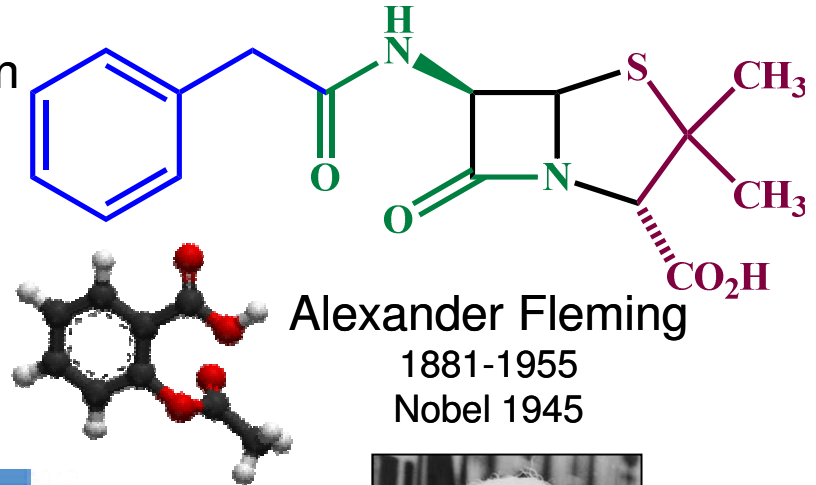
Sir Robert Robinson  
1886-1975  
Nobel 1947



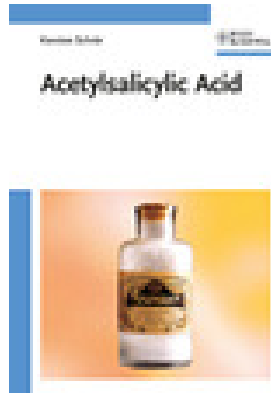
1897



Felix Hoffman  
1868- 1946



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

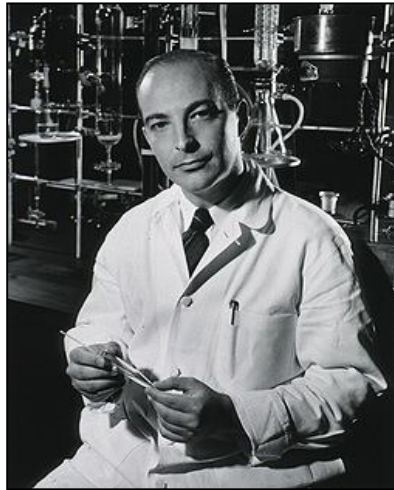




# Os fármacos e o prêmio Nobel







# Prêmio Nobel, 1959



FORUM

## The Two Cultures: Chemistry and Biology<sup>1</sup>

Arthur Kornberg

Department of Biochemistry, Stanford University, Stanford, California 94305

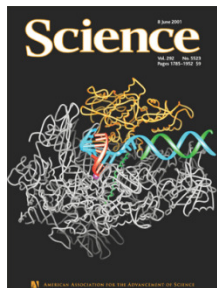
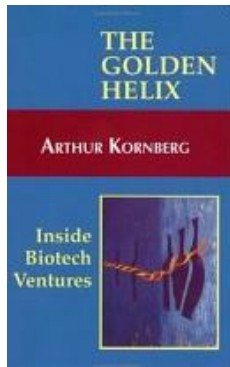
Received July 14, 1987

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...*

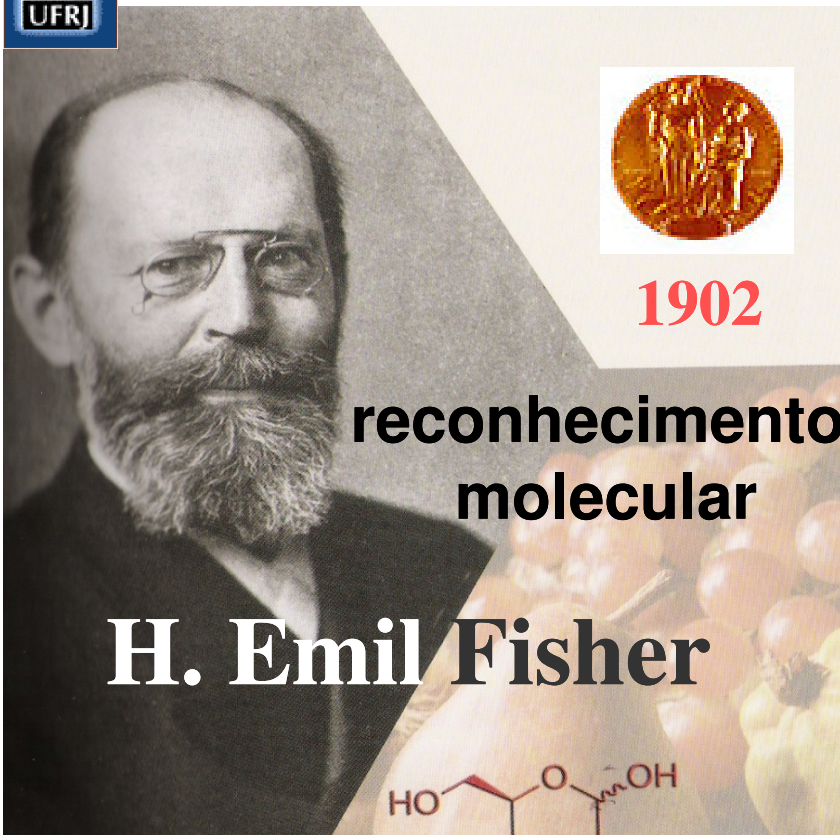
*Pharmaceutical chemistry was until recently the bastion of organic chemistry... in the search for alternative or superior drugs for the treatment of various diseases...”*







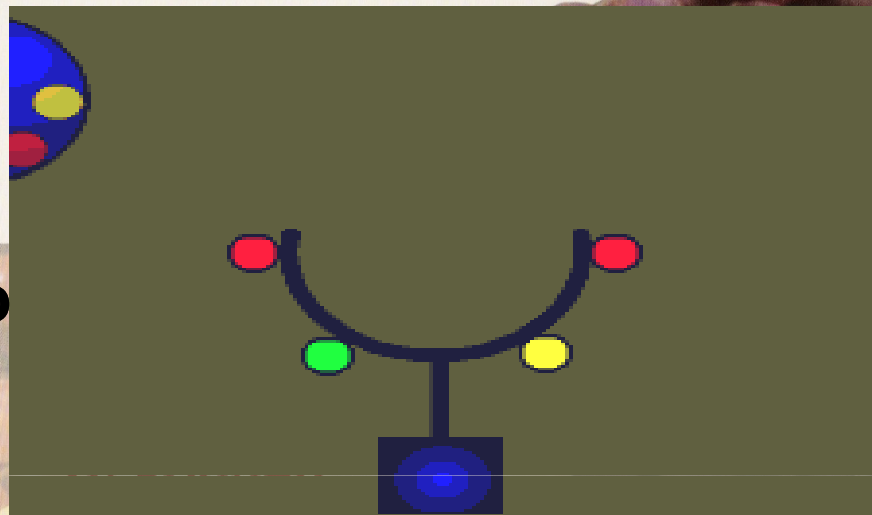
# Modelo centenário Chave-fechadura



1902

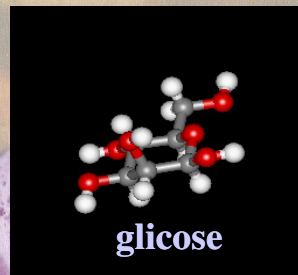
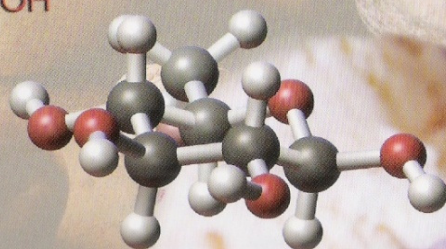
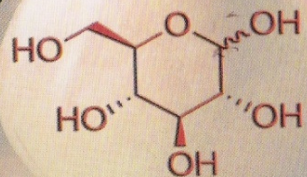
reconhecimento  
molecular

H. Emil Fisher



**LOCK & KEY**

**CONCEPT**







# Os fármacos atuam em alvos terapêuticos...

Química Medicinal

## ... os biorreceptores.



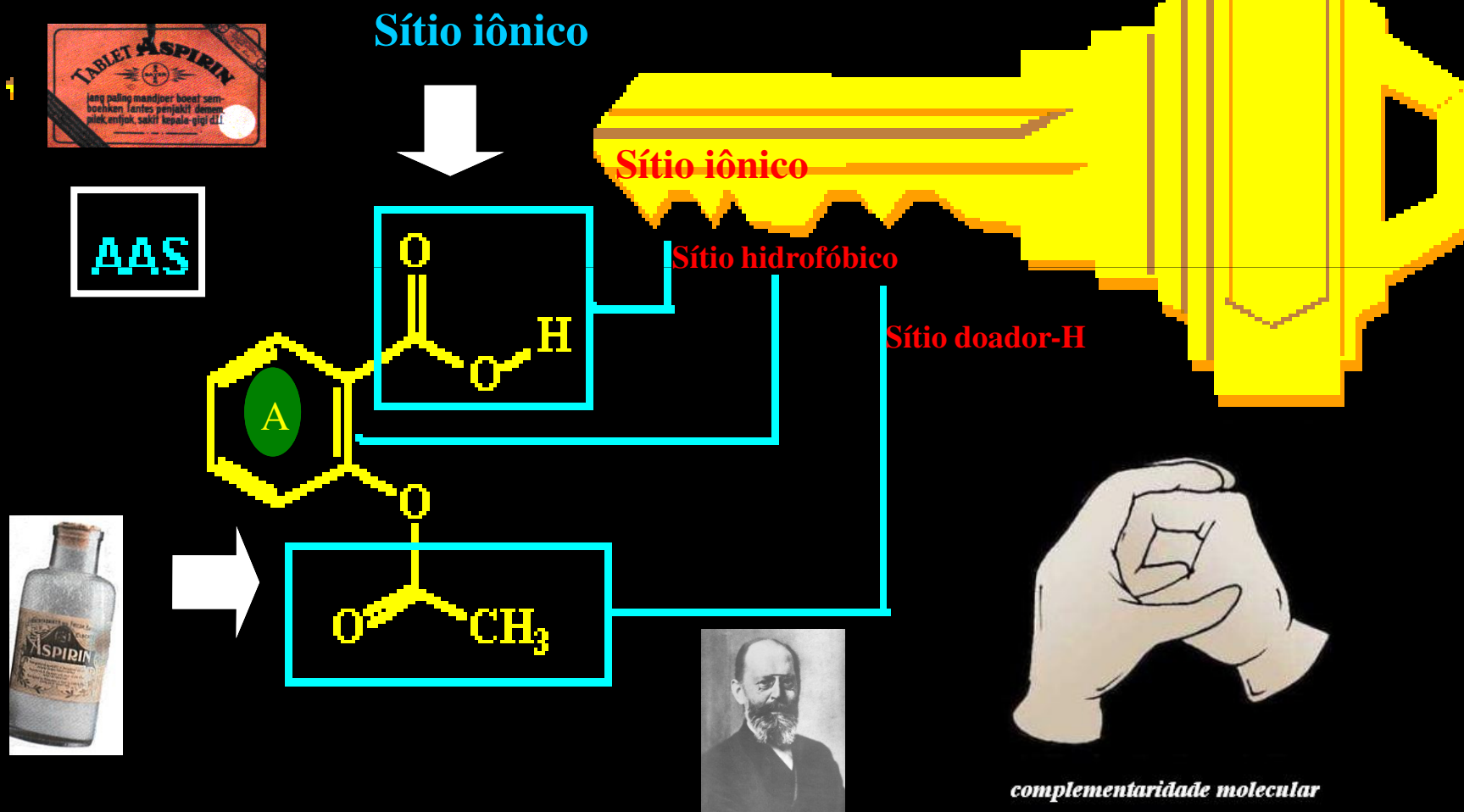
\* J. Drews, "Editorial: What's in a number?", *Nature Rev. Drug Discov.* **2006**, *5*, 975;  
J. Drews & S. Ryser, Classic drug targets, *Nature Biotechnol.* **1997**, *15*, 1318;  
& J.P. Overington, A-L Bissan & A.L. Hopkins, *Nature Rev. Drug Discov.* **2006**, *5*, 993;  
Estes autores estimam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





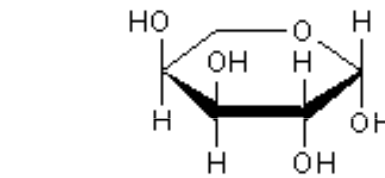
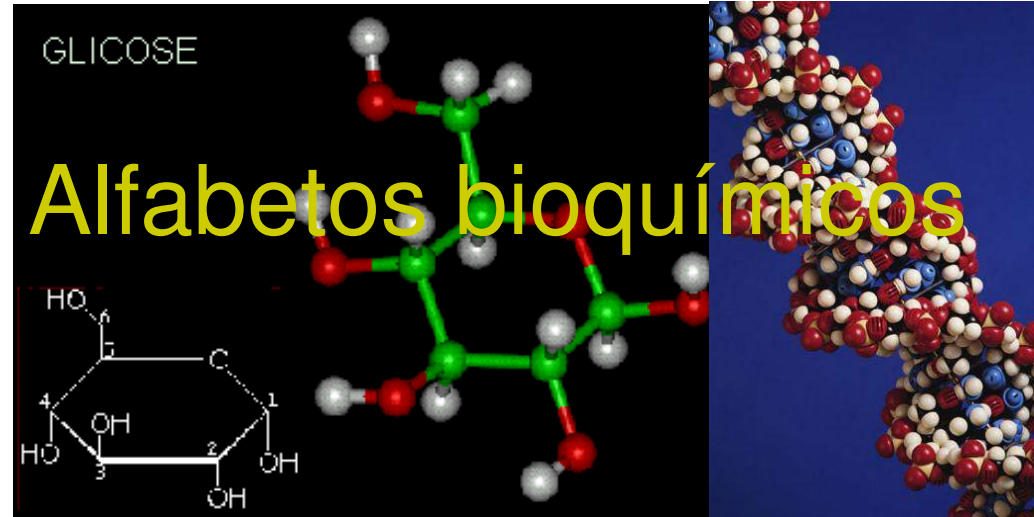
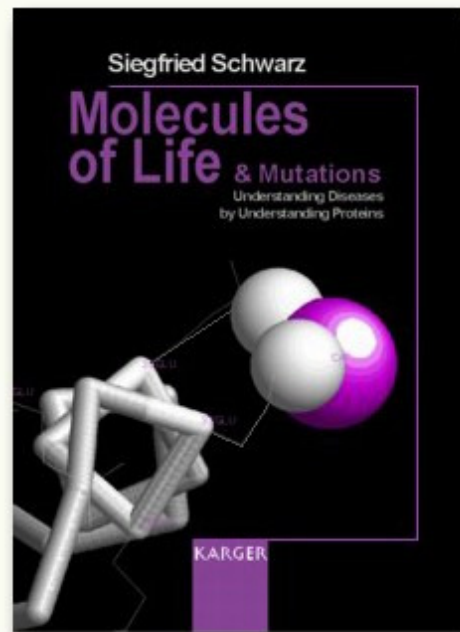
# O Centenário Modelo "Chave-Fechadura"

## Complementaridade do modelo Chave-fechadura

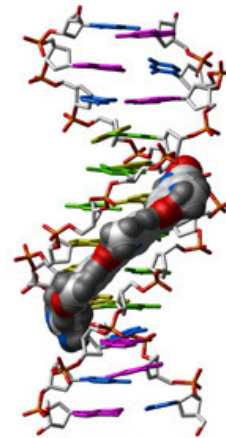




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$\beta$ -L-Arabinose



Model Compound Bound to the Minor Groove of a DNA Molecule

*Carboídratos*

*Lipídeos*

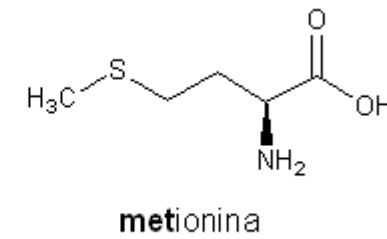
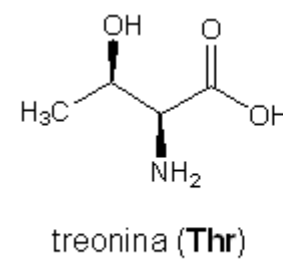
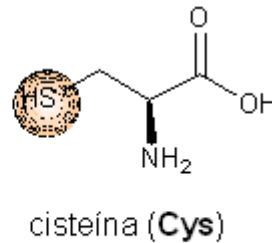
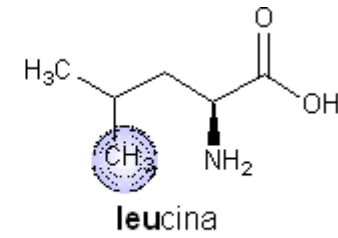
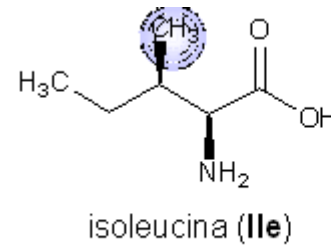
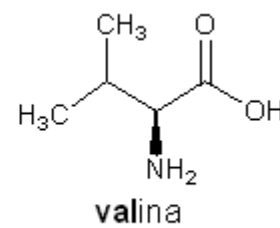
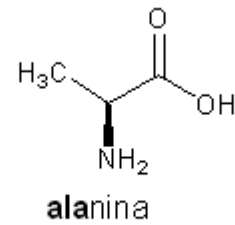
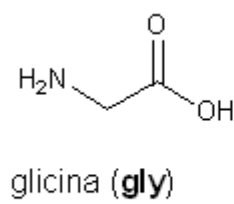
*ácidos nucleícos*

*proteínas*

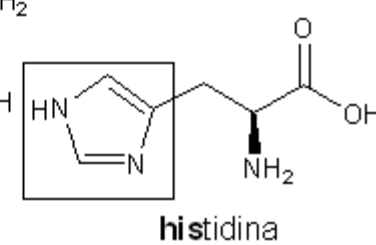
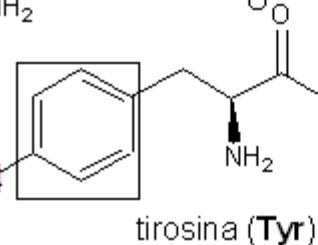
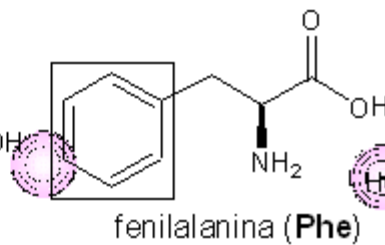
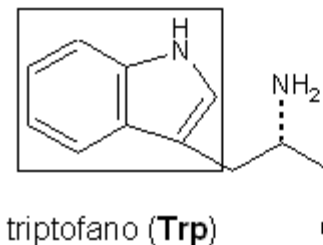
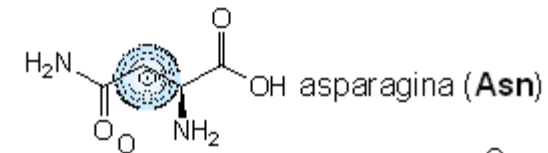
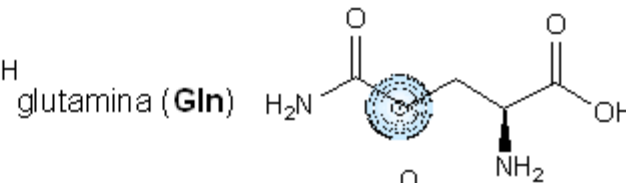
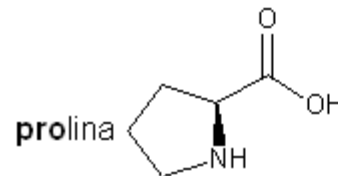
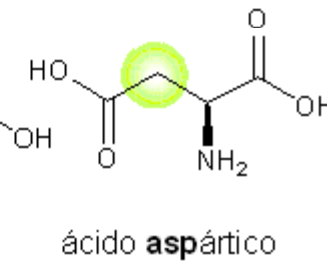
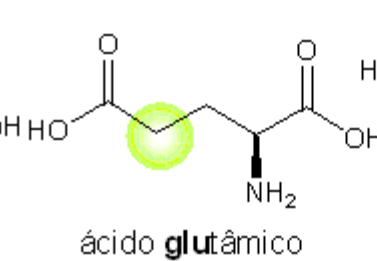
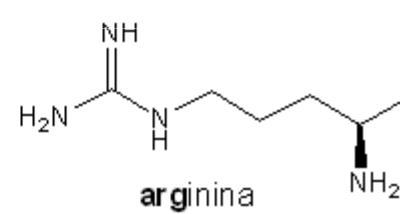




# O "alfabeto" do proteoma ...



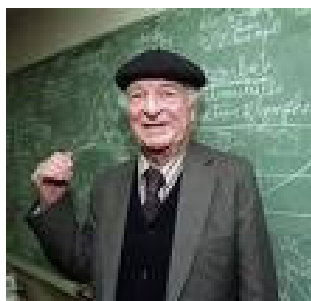
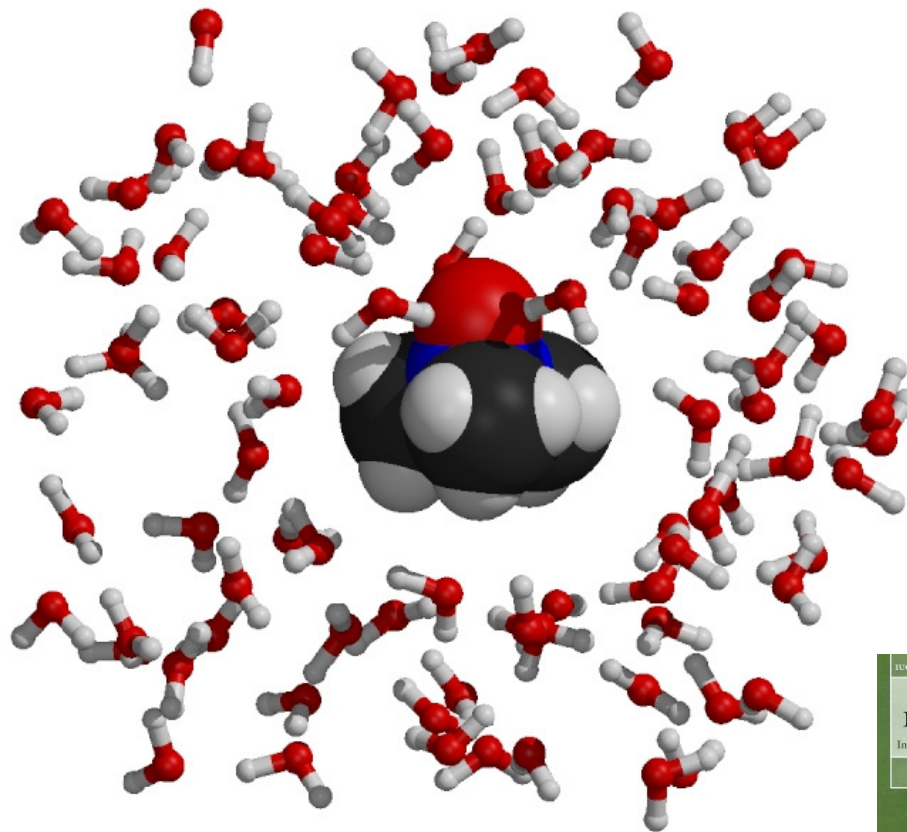
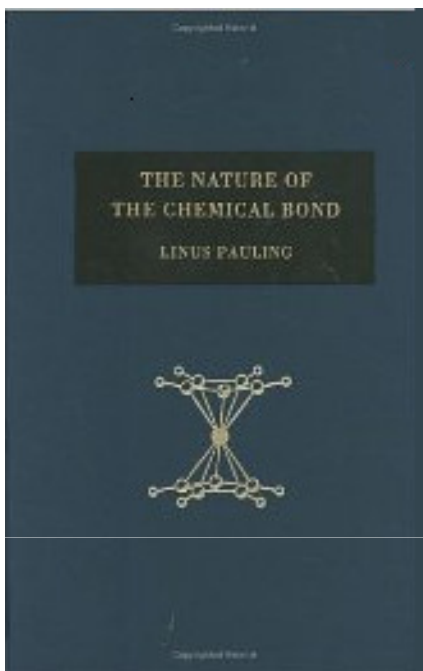
lisina (**Lys**)







# A importância das “ligações” frágeis...

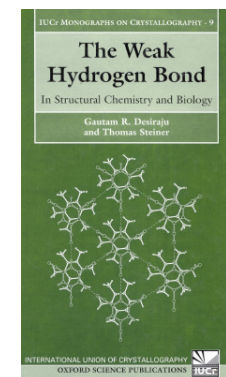


**Linus C. Pauling**  
1901-1994

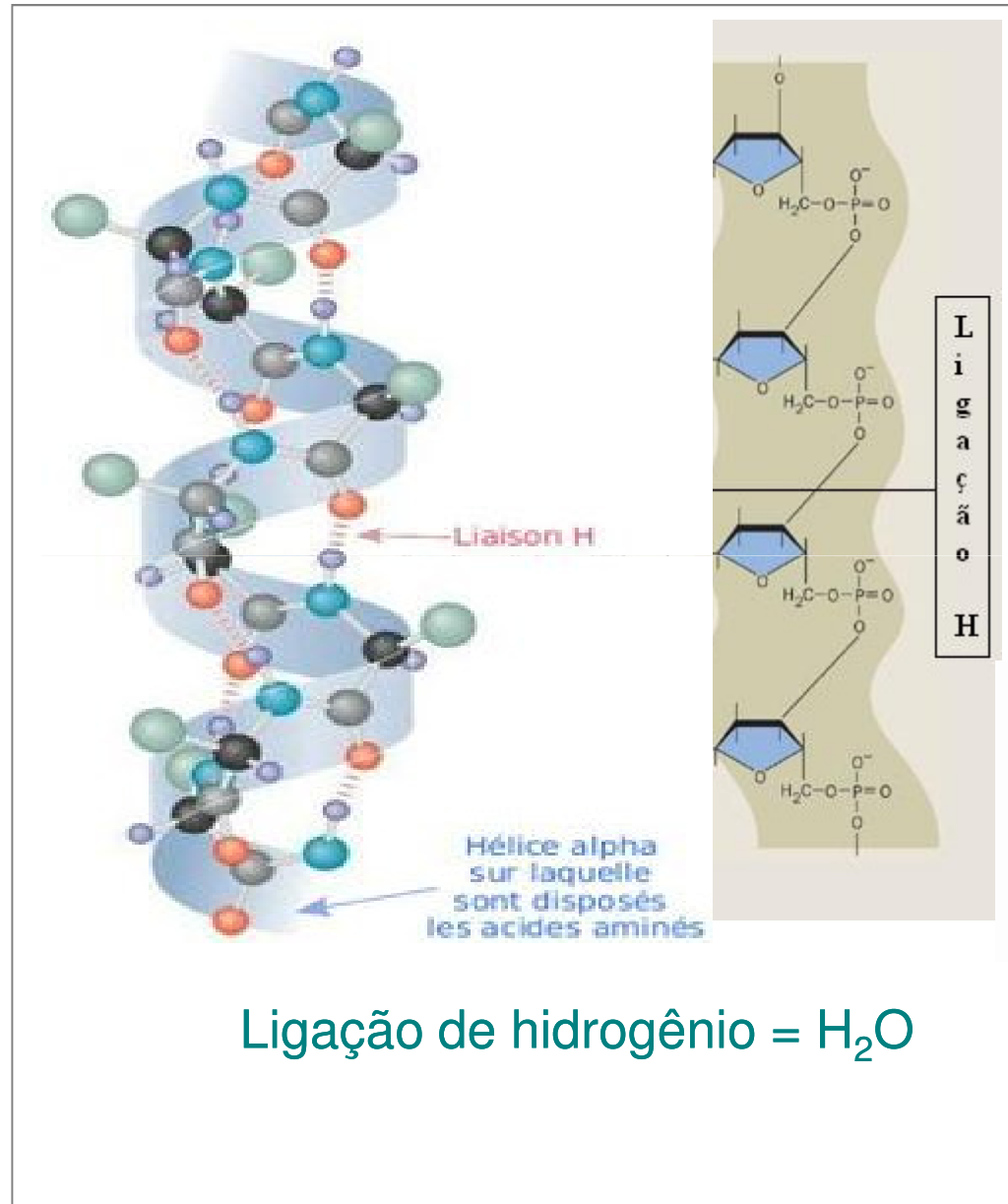
1954, 1962



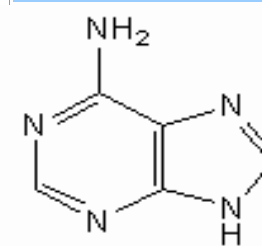
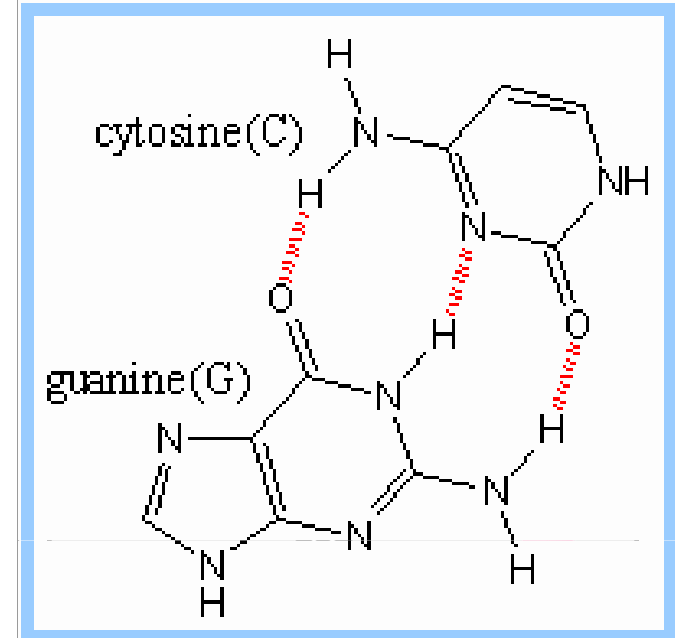
“ligações”  
de hidrogênio ...



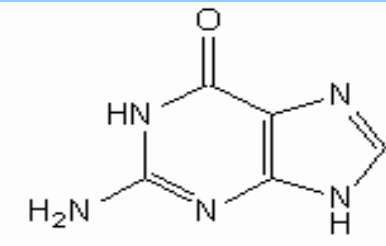
# Proteínas, carboidratos, DNA, lipídeos, canais iônicos



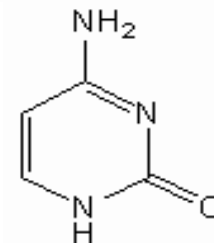
Ligação de hidrogênio = H<sub>2</sub>O



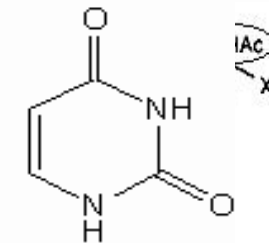
adenine (A)



guanine (G)



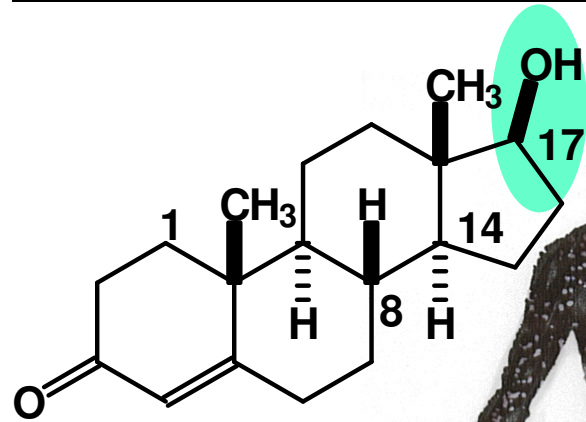
cytosine (C)



uracil (U)



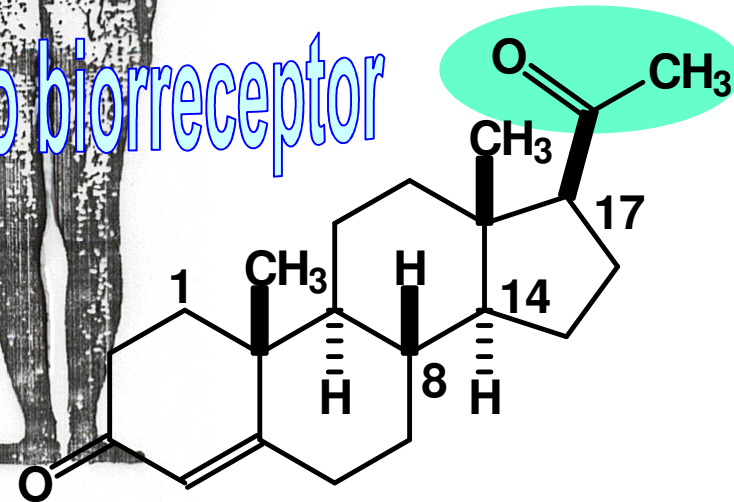
# Similaridade & Dissimilaridade Molecular



testosterona



no reconhecimento molecular do biorreceptor

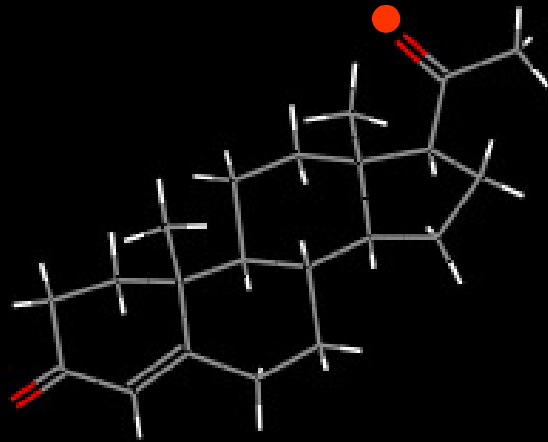


progesterona

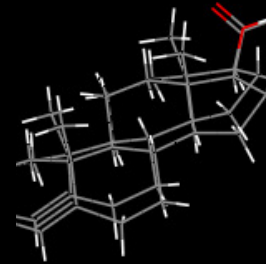




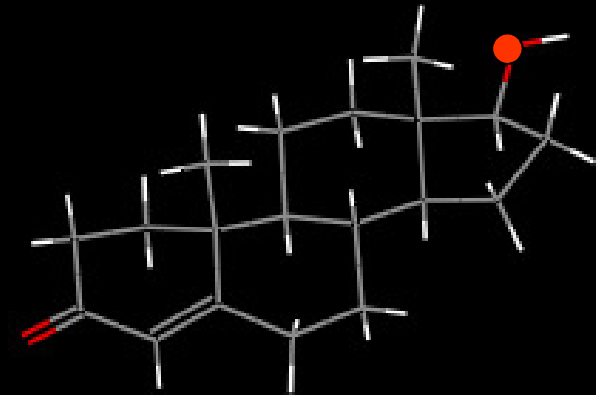
Similaridade & reconhecimento molecular



progesterona



1,41 A



testosterona

