



Fármacos:

O papel da Química Medicinal



XXII Semana Acadêmica de Química - UFF

Aula 1



UFRJ

Eliezer j. Barreiro

Professor Titular

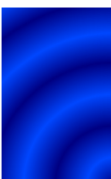
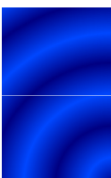
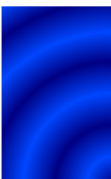




OBRIGADO PELA PRESENÇA

ejbarreiro@ccsdecania.ufrj.br

<http://ejb-eliezer.blogspot.com/>



QUÍMICA MEDICINAL

AS BASES MOLECULARES DA AÇÃO DOS FÁRMACOS

ELIEZER J. BARREIRO
CARLOS ALBERTO MANSSOUR FRAGA

2ª EDIÇÃO





DEFINIÇÃO; HISTÓRICO; os Pioneiros; Ernest forneau; Alfred Burger; a EVOLUÇÃO da QUÍMICA Medicinal; *a linha do TeMPO* da Química Medicinal; moléculas *pioneiras*; os FÁRMACOS e o **Nobel**; Emil Fischer; Paul Ehrlich; Robert KOCH; Alexander Fleming; **Ernest** Chain; Howard FLOREY; bent *Samuelsson*; SUNE bergstron; John VANE; George Hitchings; Gertrude Belle ELION; Arthur Kornberg; a INTERDISCIPLINARIDADE; os FÁRMACOS e os medicamentos; características estrutrais dos FÁRMACOS; o processo de *descoberta*; o mercado farmacêutico mundial & do BRASIL; novos fármacos; as *fases DA ação* dos FÁRMACOS; as razões moleculares DA ação dos fármacos; o PARADIGMA de *Ehrlich & Fischer*; BIORRECEPTORES; modelo chave-fechadura; AS ligações frágeis; TIPOS de interações FÁRMACOS-biorreceptores; reconhecimento MOLECULAR; Topografia 3D dos BIORRECEPTORES; bioinformática & QUÍMICA COMPUTACIONAL; dissecação molecular; QUEM são OS BIORRECEPTORES; a quiralidade; SIMILARIDADE e dissimilaridade MOLECULAR; FASE farmacocinética; *metabolismo* dos fármacos; CYP450; RATO transgênico; *origem* dos FÁRMACOS; os produtos NATURAIS; os índios e os indóis; **curare**; BLOQUEADORES ganglionares; decano dos fÁRMACOS; teoria das assinaturas; *domesticando* moléculas; STREPTASE molecular; MORFINA; analgésicos SINTÉTICOS; quinina; *anti-maláricos*; alcalóides da VINCA; Taxol[®]; camptotecina; FÁRMACOS anti-câncer; o MAR como *fonte* de fármacos; HIV; FÁRMACOS *e serpentes*; sistema RENINA-ANGIOTENSINA; MOLÉCULAS e comportamento; fármacos sintéticos; CONCEITO de composto-PROTÓTIPO; grupamentos farmacofóricos, *auxofóricos* e toxicofóricos; MOLÉCULAS inteligentes; Planejamento RACIONAL; antagonistas de biorreceptores; inibidores enzimáticos; bióforos *naturais*; PRODUTOS NATURAIS como PROTÓTIPOS; abordagem fisiológica; LASSBio; considerações finais; SCIELO; *bibliografia*; EPÍLOGO; agradecimentos.



Definição:

Química Medicinal

Chemistry and Human Health Division (VII)
Subcommittee on Medicinal Chemistry and Drug Development.



é a disciplina que estuda os aspectos relacionados à descoberta, invenção e preparação dos fármacos, princípio-ativo dos medicamentos.

Estuda os fatores moleculares do seu modo de ação, incluindo a compreensão da relação entre a estrutura química e atividade (SAR/QSAR), absorção, distribuição, metabolismo, eliminação e toxicidade.

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



A **Química Medicinal** é a disciplina chave, de vital importância para a indústria farmacêutica. Os **Químicos Medicinais** participam do processo da descoberta de novos fármacos e solucionam problemas relacionados à otimização das propriedades farmacológicas das moléculas.

<http://www.iupac.org>

C. R. Ganellin *et al.*, *Eur. J. Med. Chem.* 2000, **35**, 163
Monge *et al.*, *Eur. J. Med. Chem.* 2000, **35**, 1121



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.

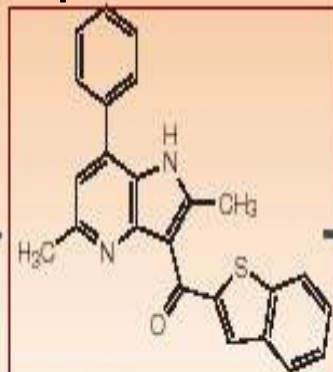


Preclinical studies

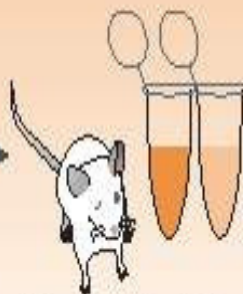
O processo da descoberta de novos fármacos é complexo...



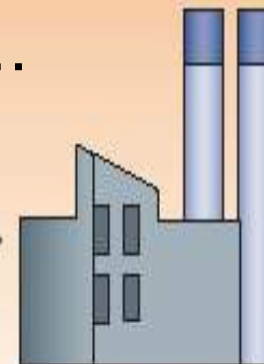
Research team formed and objectives set



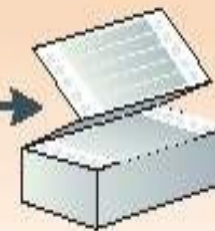
Novel chemicals synthesized



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

Química Medicinal



Drug is approved for marketing

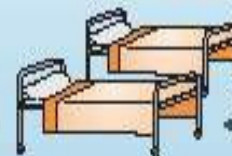
ANVISA

FDA

FDA reviews NDA



Company files New Drug Application (NDA)



Phase III: large clinical trials in many patients



Phase II: studies in patients (efficacy)



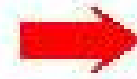
Phase I: studies in healthy humans (toleration)





O fármaco...

Princípio ativo



Forma farmacêutica



cristalização

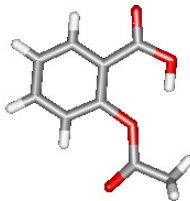


cristalização

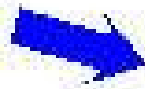


Medicamento

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 físico-químicas críticas para a atividade do fármaco por via oral: solubilidade, boa partição passiva membrana/água, peso 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

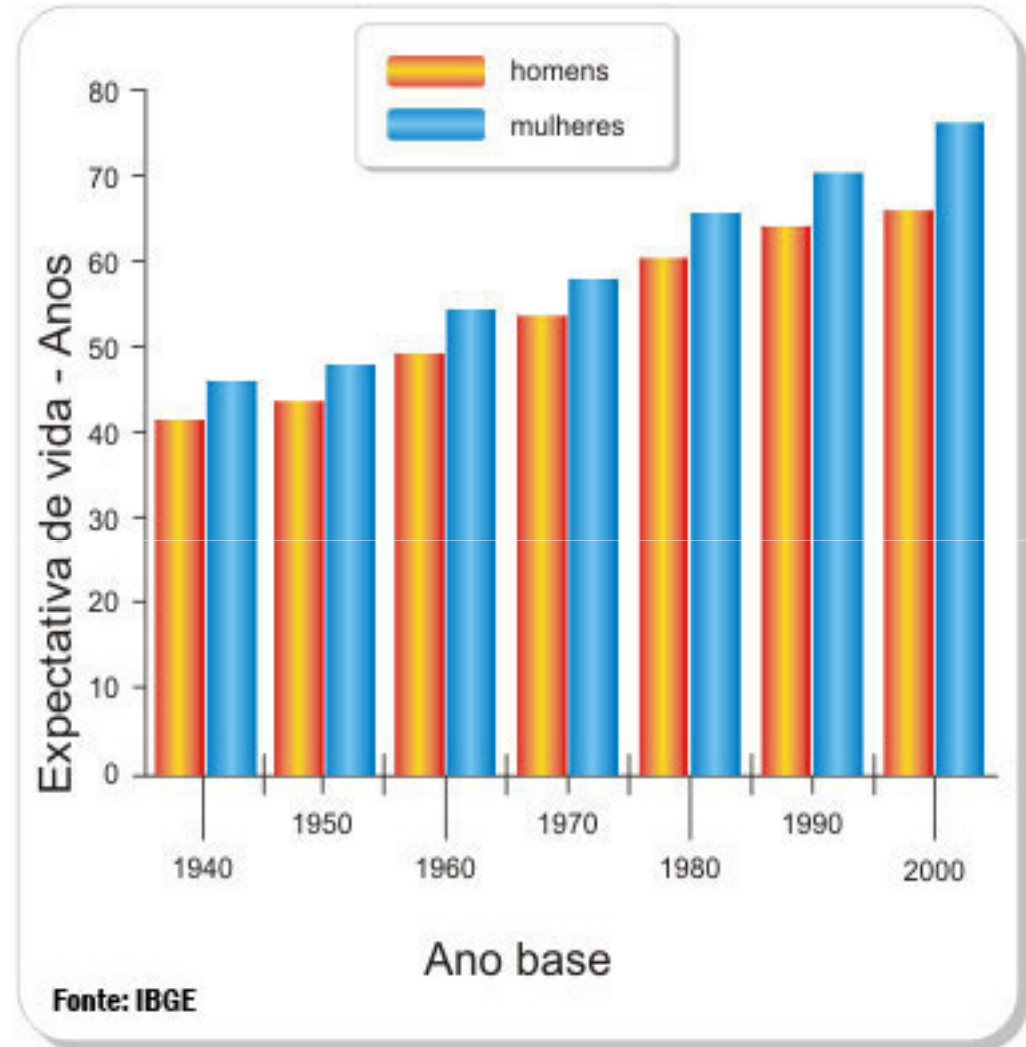
Química Medicinal



Aumento na expectativa de vida...



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



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



Declaração da Cúpula do Milênio da Nações Unidas

Nova Iorque, 6 a 8 de setembro de 2000



O Projeto do Milênio

Secretaria-Geral das Nações Unidas em 2002



2015



“...Países em desenvolvimento **provavelmente** **continuarão** imersos na pobreza, a **menos que** possam fazer o que países desenvolvidos fizeram **para** atingir o **crescimento sustentável**: **incorporar ciência**, **tecnologia e inovação** em **suas estratégias** econômicas ...”

<http://www.unmillenniumproject.org>



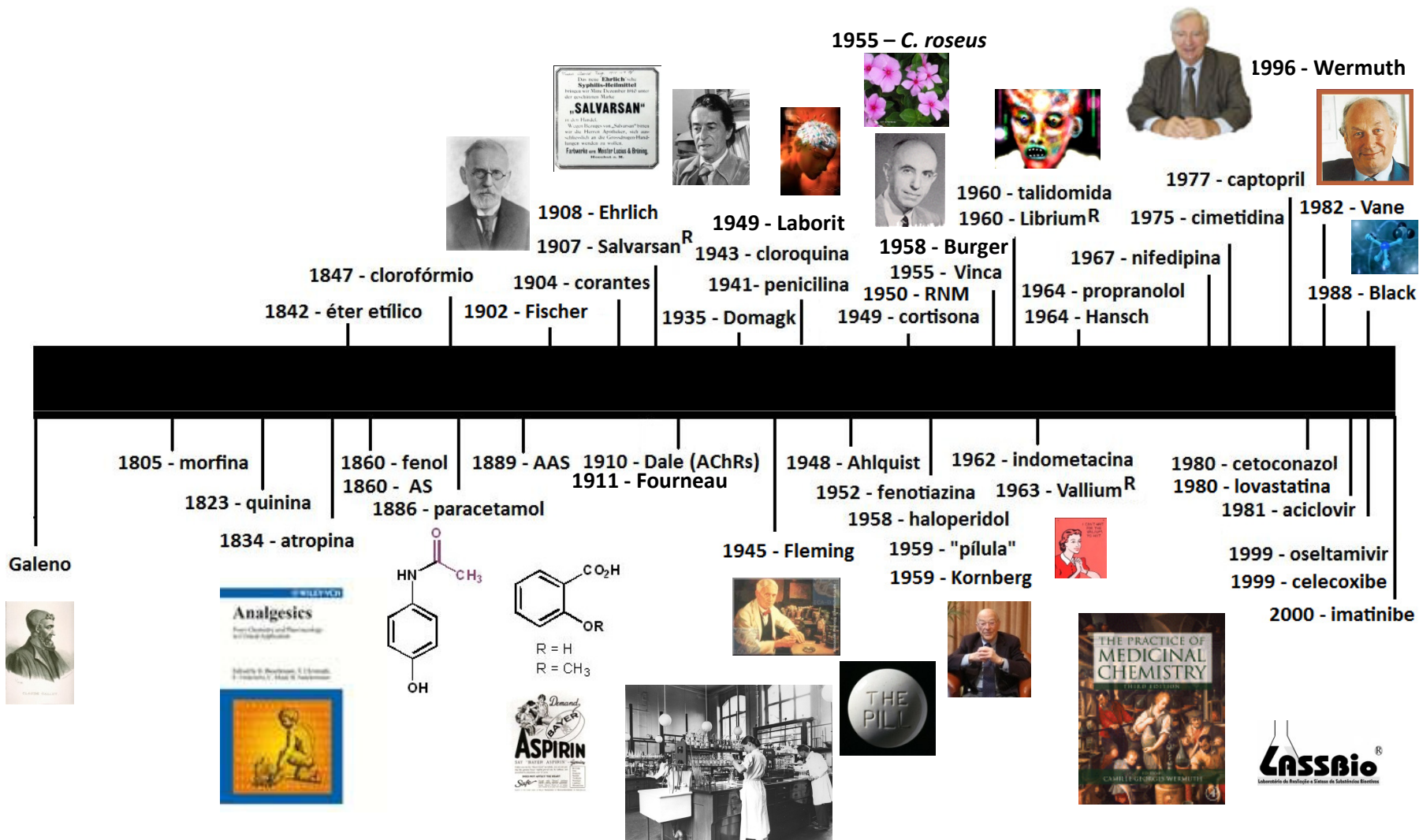
**Histórico do planejamento
racional de fármacos e a
Química Medicinal:
*Os pioneiros***

Química
Medicinal

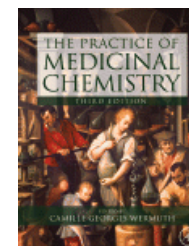
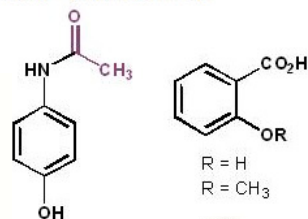




Cronologia histórica da Química Medicinal

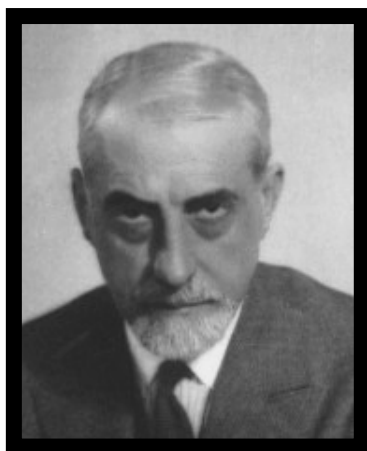


Galeno





O berço da Química Medicinal

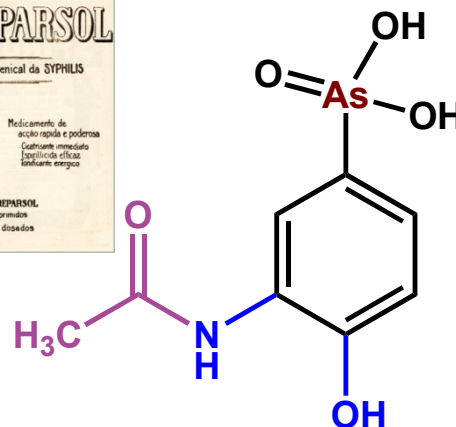


Ernest Fourneau
1872-1949



Stovarsol

CAS 97-44-9



Institut Pasteur (1887)

1911- Laboratoire de Chimie Thérapeutique

Institut Pasteur (Emile Roux)

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



Daniel Bovet
1907-1992 *

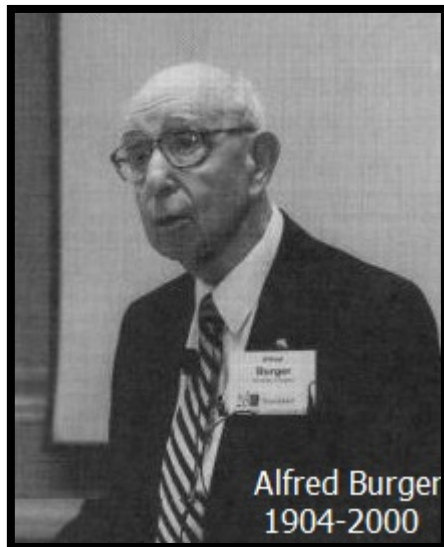
* Farmacêutico suíço
Doutor *h.c.* UFRJ

Prêmio Nobel de
Fisiologia/Medicina
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

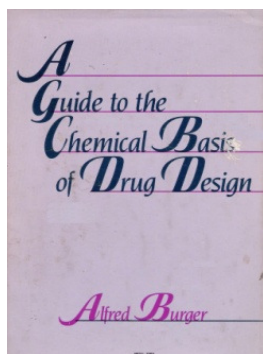
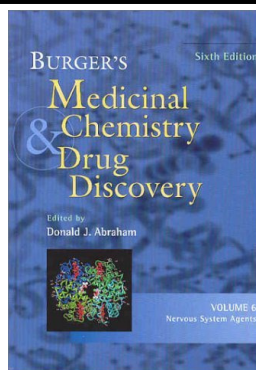


Química Medicinal

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



“...The unprecedented increase in human life expectancy, which has almost doubled in a hundred years, is mainly due to drugs and to those who discovered them.”

Alfred Burger em “The practice of medicinal chemistry”, Wiley, 1970, 4–9.

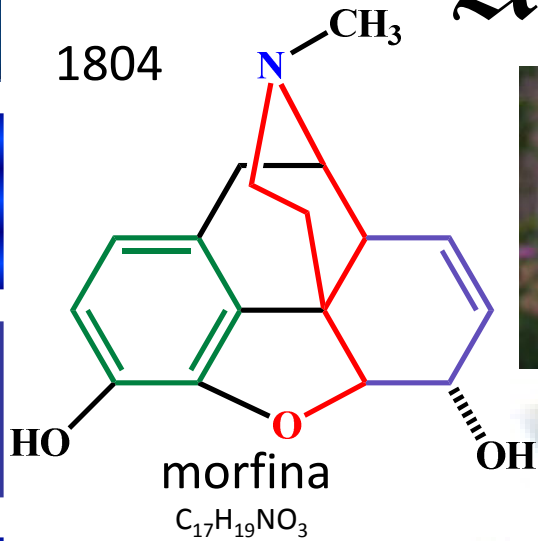


Química
Medicinal



As moléculas pioneiras...

1804

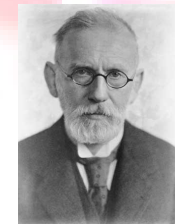
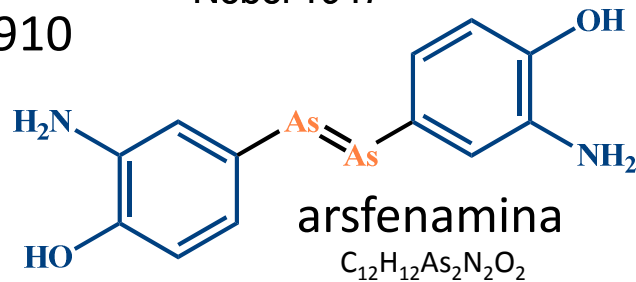


Friedrich W. A. Sertürner
1783- 1841



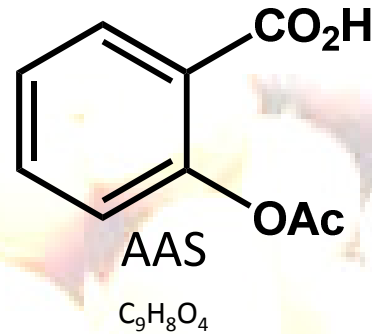
Sir Robert Robinson
1886-1975
Nobel 1947

1910



Paul Ehrlich
1854-1915
Nobel 1908

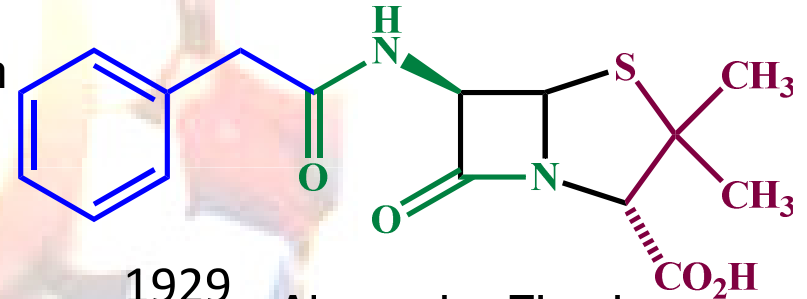
1897



Felix Hoffman
1868- 1946



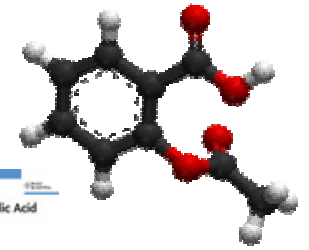
1929

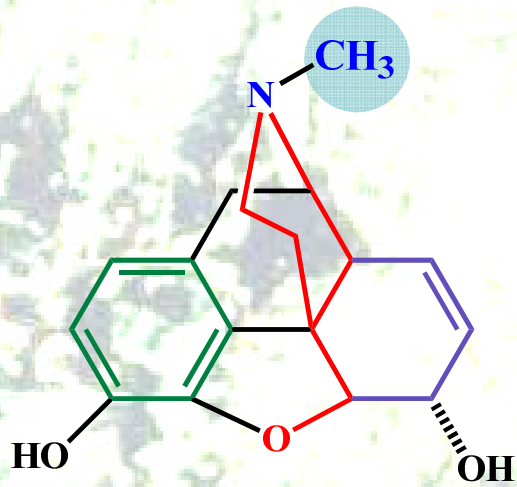


Alexander Fleming
1881-1955
Nobel 1945



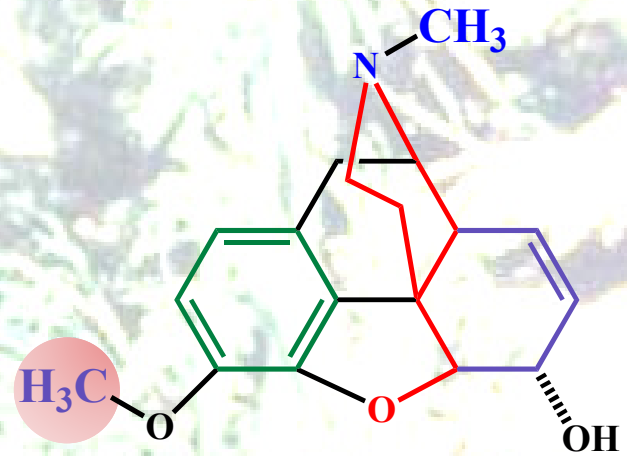
Library of Congress





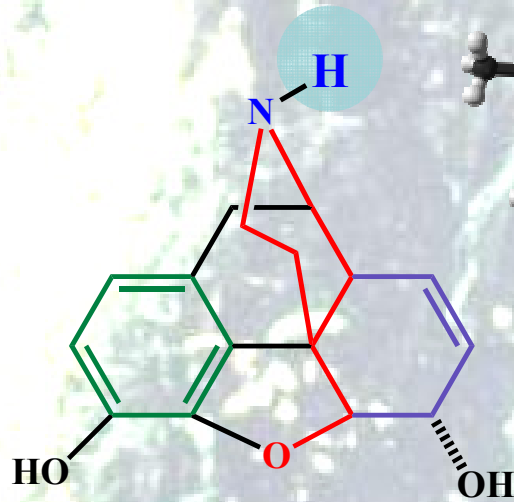
morfina

1853 - Henry How
Un Glasgow
1º derivado sal 4^{ario}

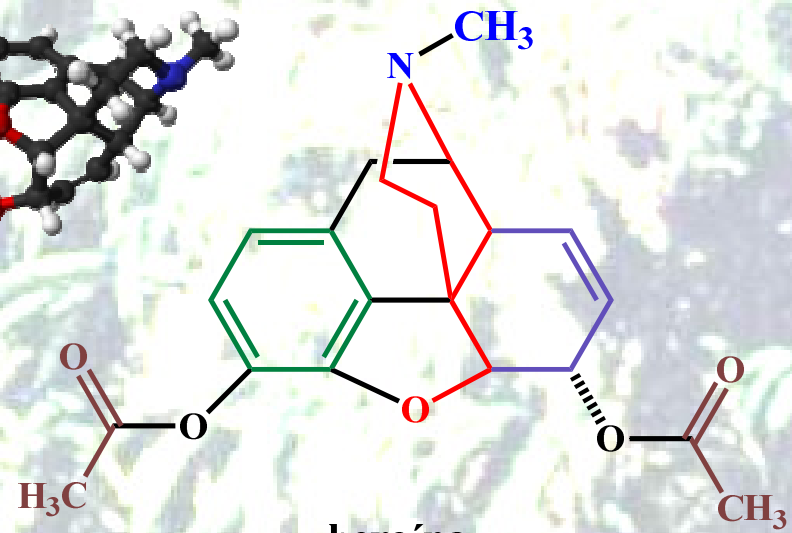
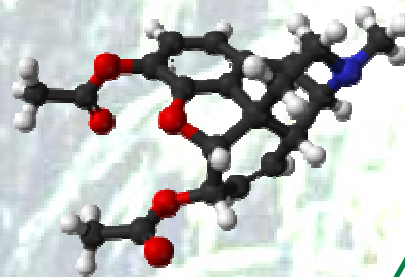


codeína

O-metil morfina

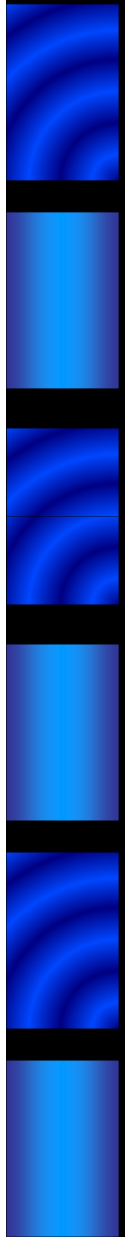
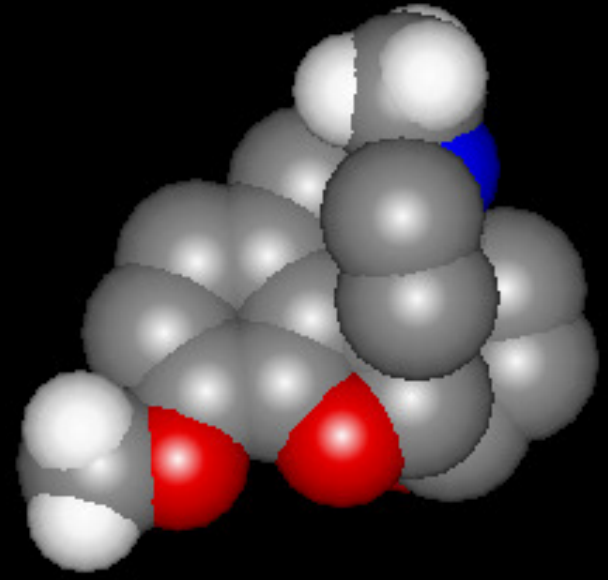
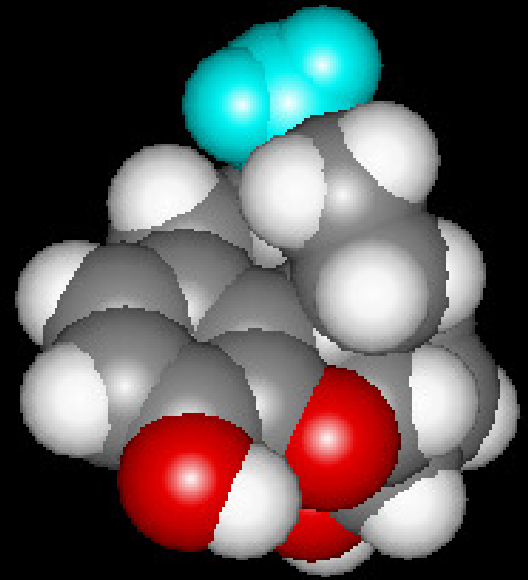
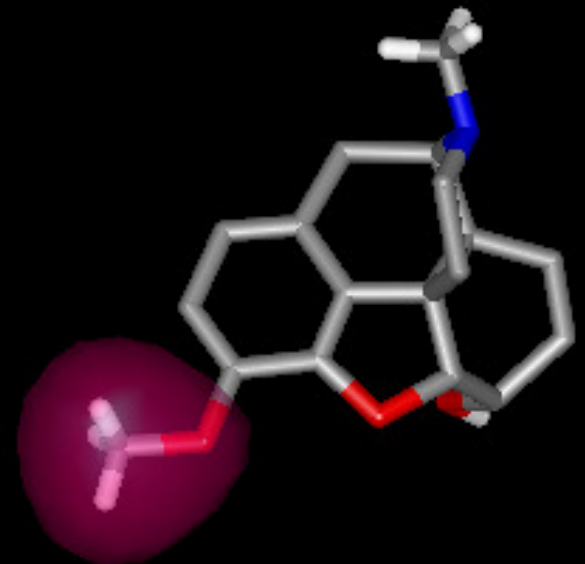
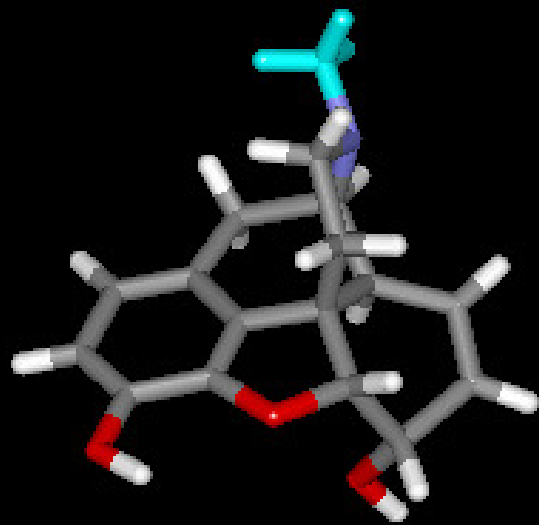


nor-morfina



heroína

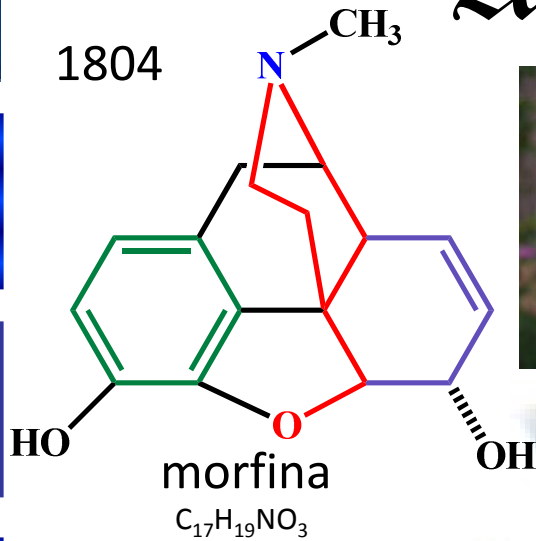
Diacetil-morfina





As moléculas pioneiras...

1804

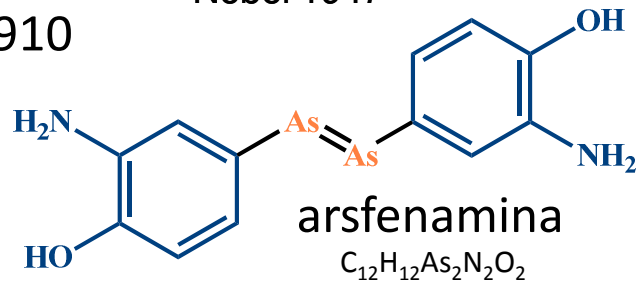


Friedrich W. A. Sertürner
1783- 1841

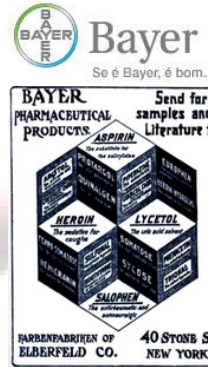
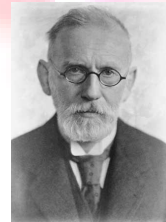


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1886-1975
Nobel 1947

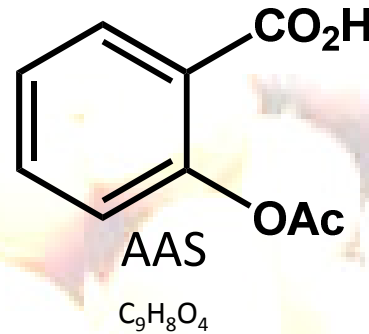
1910



Paul Ehrlich
1854-1915
Nobel 1908



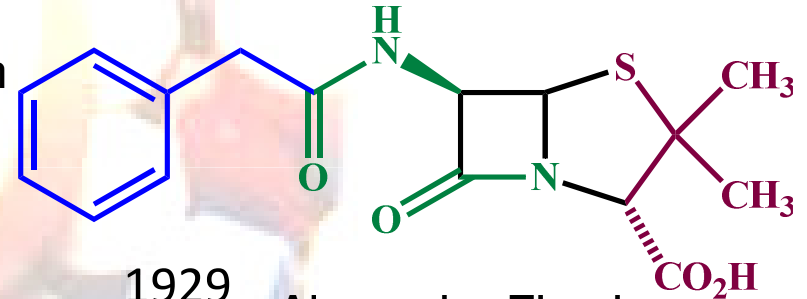
1897



Felix Hoffman
1868- 1946



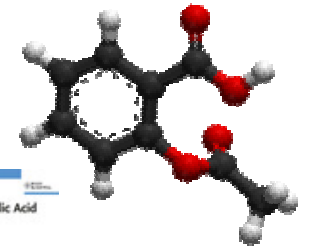
1929



Alexander Fleming
1881-1955
Nobel 1945

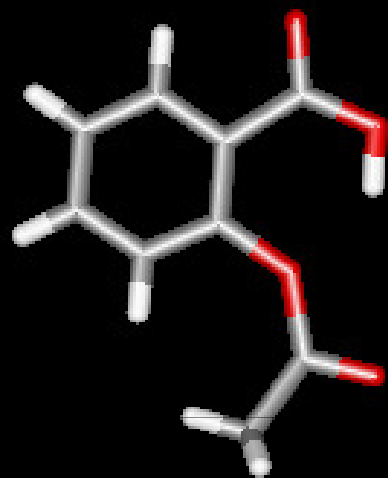


Library of Congress

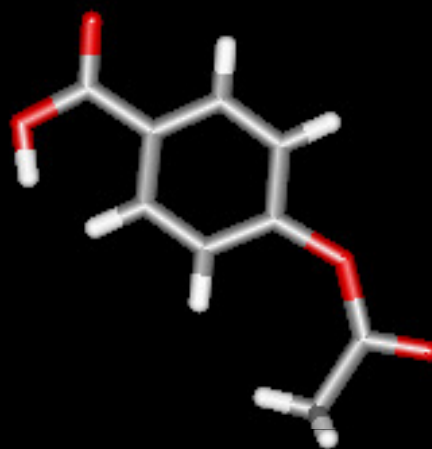




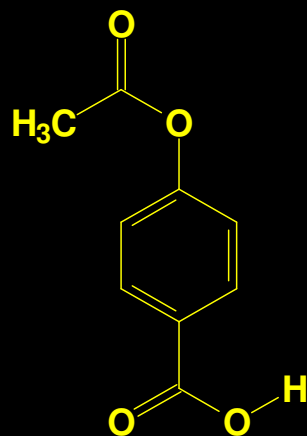
Isomêros do ácido acetil salicílico (AAS)



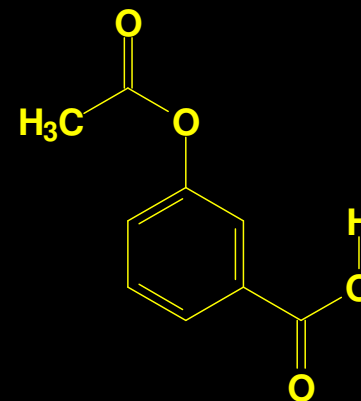
orto



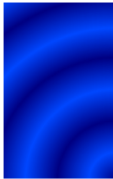
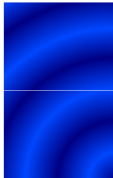
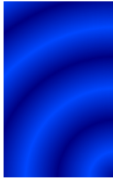
para



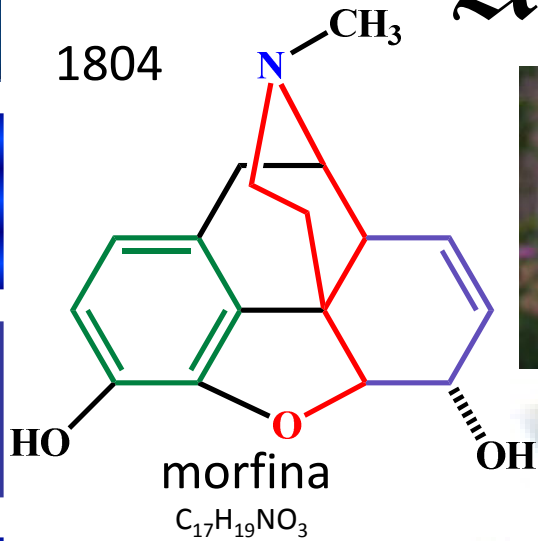
meta



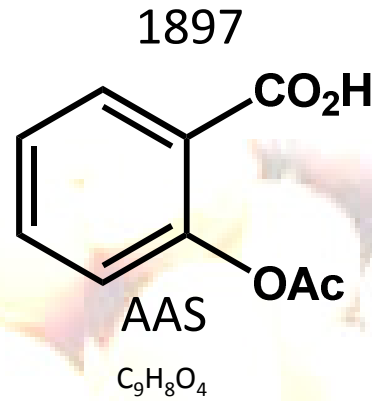
As moléculas pioneiras...



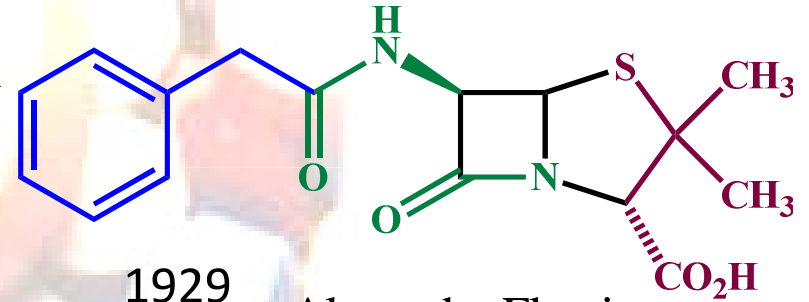
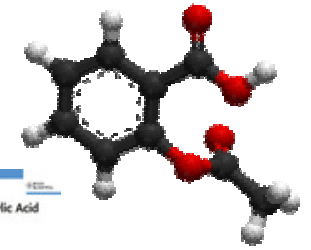
1804



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1783- 1841

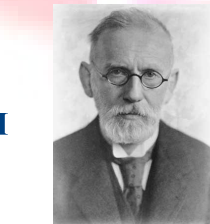


Felix Hoffman
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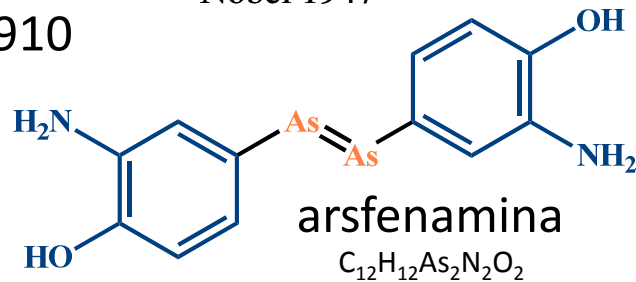
1929 Alexander Fleming
1881-1955
Nobel 1945

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



Paul Ehrlich
1854-1915
Nobel 1908

1910



Library of Congress



Med
Chem



Paul Ehrlich

1854-1915

Nobel 1908

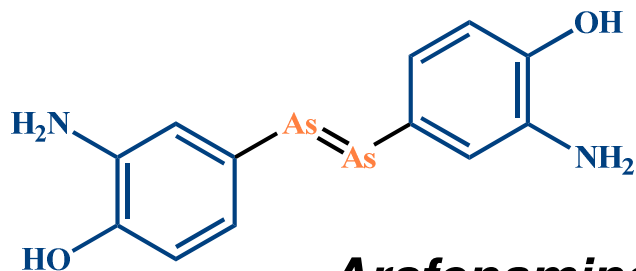


Patente 10 de junho de 1909;
Farbwerk Hoeschst 1910

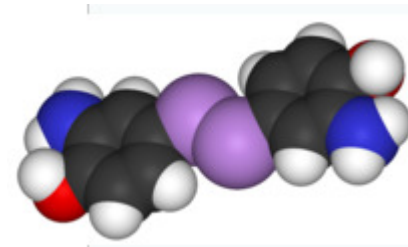
Ber. 1912, 45, 756

Berichte der
Deutschen
Chemischen
Gesellschaft

Deutsche
Chemische
Gesellschaft, ...

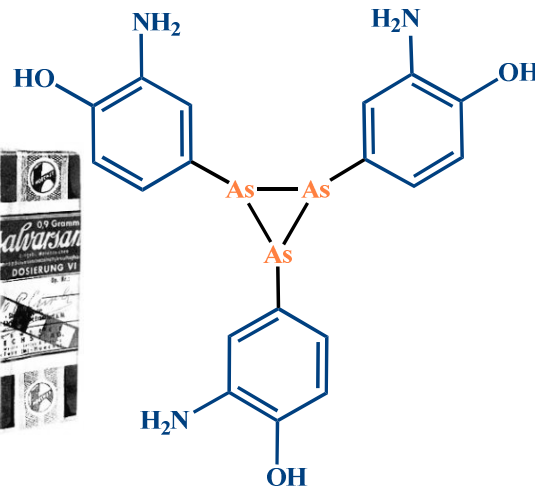


Arsfenamina

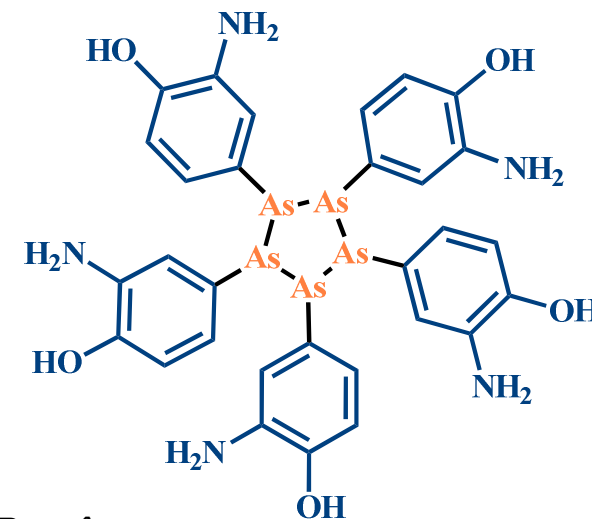
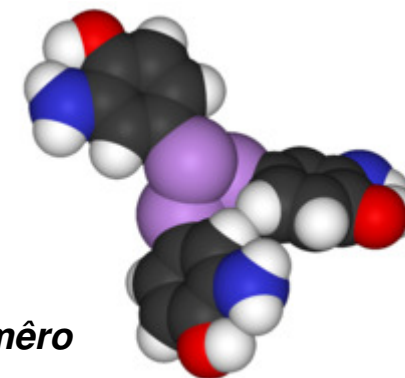


Salvarsan^R

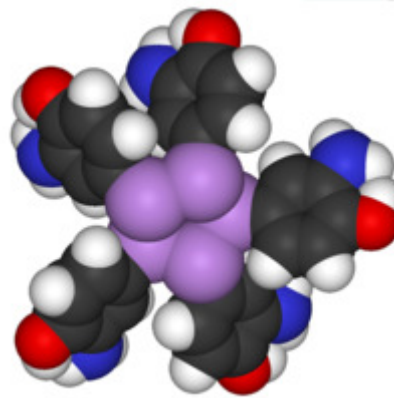
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Trimêro



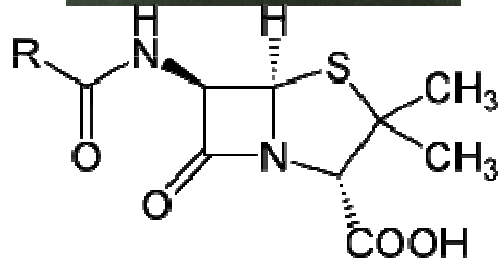
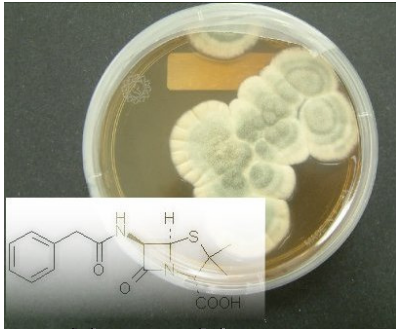
Pentâmero



NC Lloyd, HW Morgan, BK Nicholson, RS Ronimus "The composition of Ehrlich's salvarsan: resolution of a century-old debate". *Angew. Chem. Int. Ed. Engl.* 2005, 44, 941.



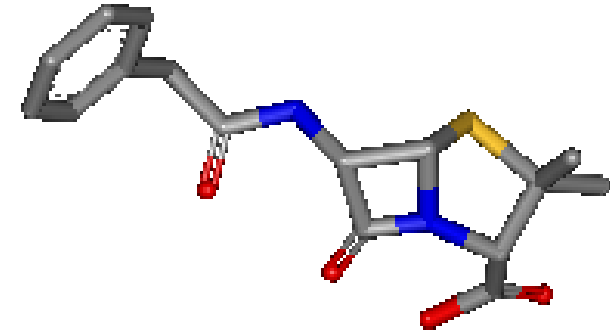
Fármaco Salva-vidas



- 1896 - Robert Duchesne
- 1928 – A Fleming
- 1939 – Florey & Chain
- 1943 - Andrew J Moyer
- 1945 - Dorothy C. Hodgkin
- 1948 - Patente
- 1957 –John Sheehan



Alexander Fleming
1881-1955



Penicilina



Howard W. Florey
1898-1968



<http://nobelprize.org>

1945



Ernest B. Chain
1906-1979