



Universidade Federal do Rio de Janeiro

# A interdisciplinaridade da Química Farmacêutica Medicinal

XI Encontro Nacional de Professores de Química Farmacêutica  
Universidade Federal de Pernambuco, Recife, PE  
30 de setembro de 2010



Eliezer J. Barreiro

Professor Titular  
UFRJ





m e d  
**Química**  
**Farmacêutica**  
chem  
**Medicinal**



## IUPAC - Subcommittee Medicinal Chemistry & Drug Development

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**Química Farmacêutica Medicinal** é a disciplina que estuda os aspectos relacionados à *descoberta* ou *invenção* dos 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).

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**IUPAC**

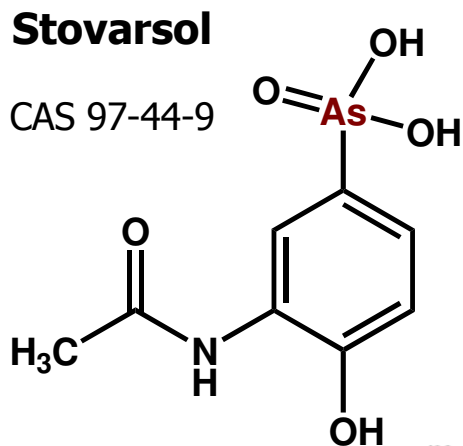
*Pure & Appl. Chem.*, Vol. 70, No. 5, pp. 1129–1143, 1998.  
Printed in Great Britain.  
© 1998 IUPAC



# O berço da Química Farmacêutica Medicinal



Ernest Fourneau  
1872-1949



Institut Pasteur (1887)

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1911- Laboratoire de Chimie Thérapeutique

Institut Pasteur (Emile Roux)

1911-1944 – J. Tréfouël, Th. Tréfouël,  
G. Benoit, D. Bovet, F. Nitti

Prontosil rubrum  
(sulfonamidas)

Curare: SAR

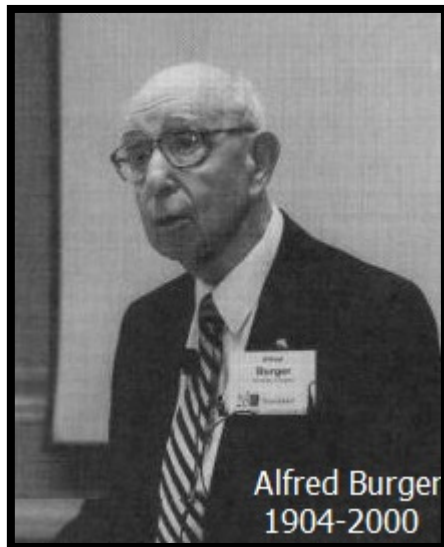


Daniel Bovet  
1907-1992

Prêmio Nobel de  
Fisiologia/Medicina

1957



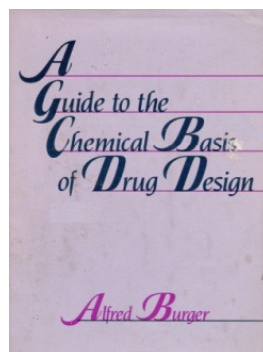
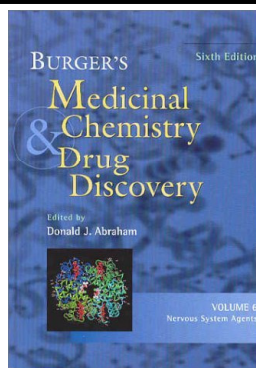


# Química Farmacêutica Medicinal

## Prof. Alfred Burger

(1904-2000)

University of Virginia  
EUA

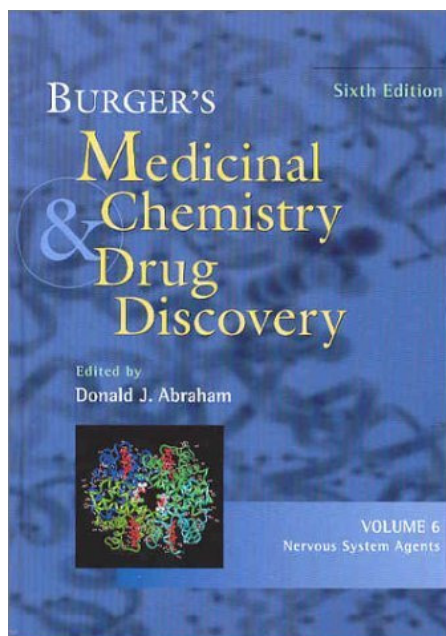


1958 – cria o Journal of the Medicinal and Pharmaceutical Chemistry → depois Journal of Medicinal Chemistry

“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

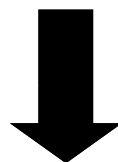




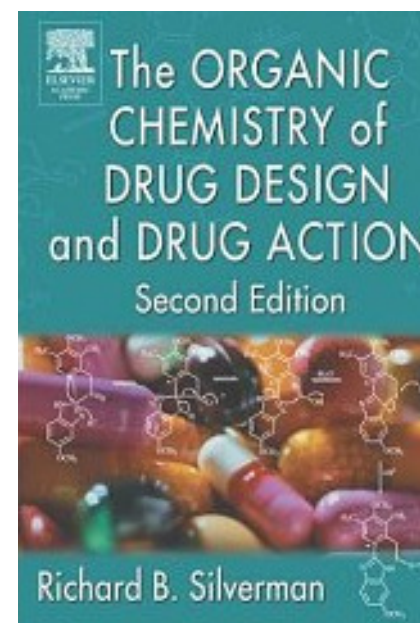
**“ Medicinal Chemistry tried to be based on the ever-increasing hope that biochemical rationales for drug discovery ”**



**Alfred Burger, 1980**

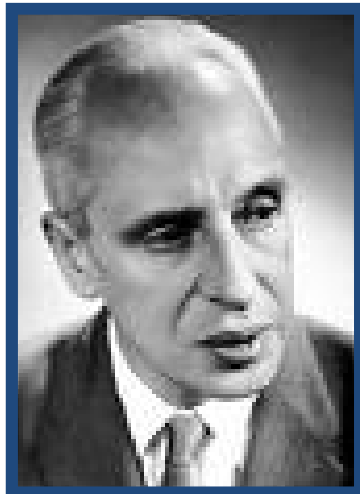


**“ Medicinal Chemistry is the *science* that deals with the discovery or design of new therapeutic chemicals and their development into useful medicines...”**

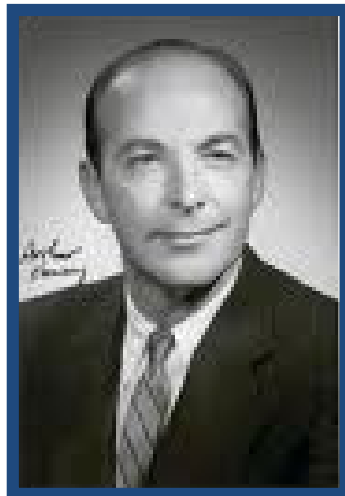


**Richard B. Silverman, 1992**





Severo Ochoa  
1905-1993



Arthur Kornberg  
1918-2007

# Prêmio Nobel de Fisiologia/Medicina 1959



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

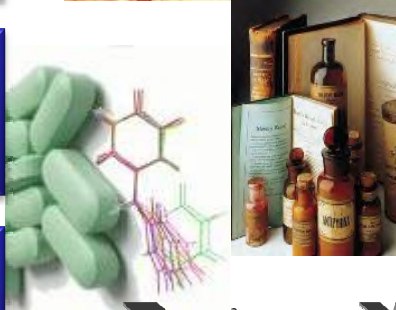
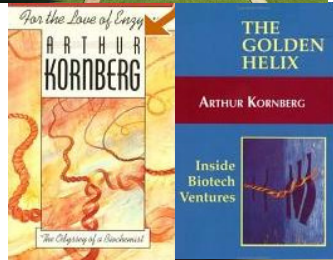
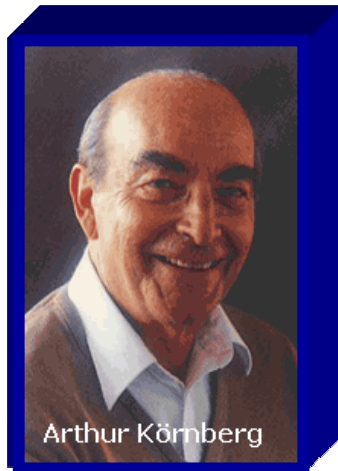


ARTHUR KORNBERG

The biologic synthesis of deoxyribonucleic acid

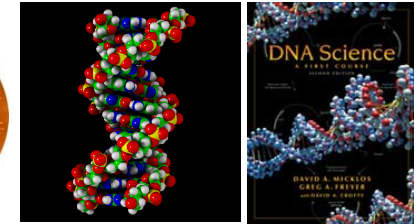
*Nobel Lecture, December 11, 1959*

## Interdisciplinaridade



# Nobel Prize, 1959

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



*“We have the paradox of the two cultures,*

**chemistry and biology,**

*growing further apart even as they*

*discover more common ground....*

**Pharmaceutical chemistry was until**

*recently the bastion of organic chemistry...*

*in the search for alternative or superior*

*drugs for the treatment of various diseases.”*

**Arthur Kornberg**

*Biochemistry* 1987, 26, 6888-6891

**Interdisciplinaridade**

## Slide 7

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### EJB2

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; 27/08/2010





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chem





## The American Chemical Society, Division of Medicinal Chemistry

### Vision Statement and Strategic Initiatives

1. Provide, support and advocate education in medicinal chemistry.
2. Be a strong advocate for interdisciplinary, cutting edge research as reflected in our programming, policy and global outreach.
  - \* Symposia that provide medicinal chemists with advances in the basic understanding of interdisciplinary core concepts in drug discovery.
  - Increase collaboration with international societies to become more global in outlook.
  - Enhance national meeting content to provide a forum for people who work in related areas to meet and interact.
  - Sponsor or organize a newly emerging therapeutic target conference.
  - Get involved with ACS Perspectives at the planning level (or develop our own workshops).
3. Increase opportunities for member participation and involvement in Division affairs.
4. Enhance communication by targeting:



**Desde os primeiros**

**fármacos...**

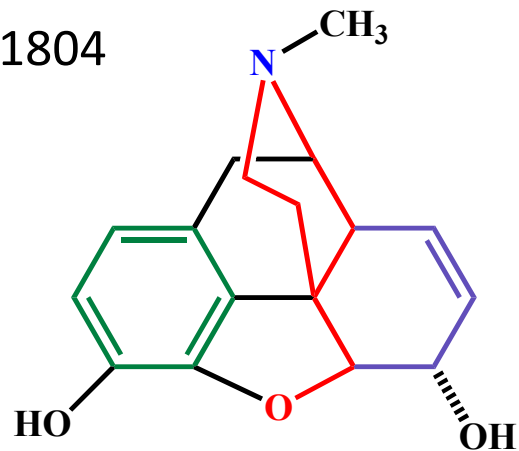
**...a contribuição.**

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**Farmacêutica**  
*chem*  
**Medicinal**



# Os primeiros fármacos...

1804



morfina

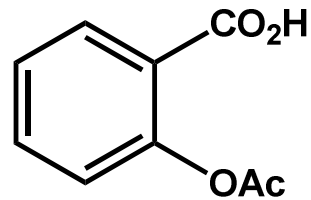
$C_{17}H_{19}NO_3$

Friedrich W. A. Sertürner

1783- 1841



1897



AAS

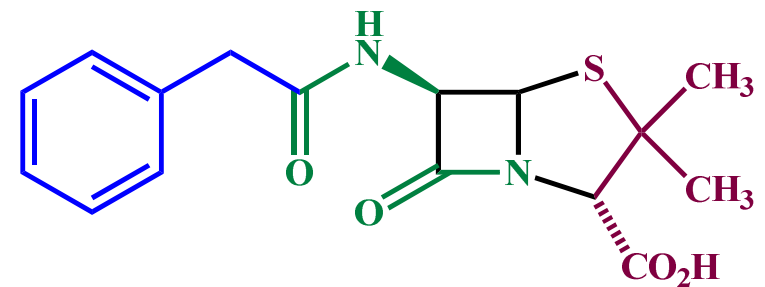
$C_9H_8O_4$

Felix Hoffman

1868- 1946



1929



penicilina

$C_{16}H_{18}N_2O_4S$

Alexander Fleming

1881-1955

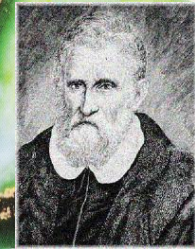
Nobel 1945



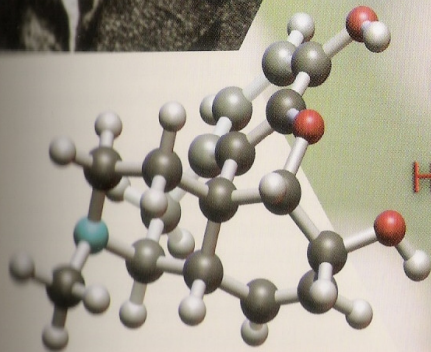




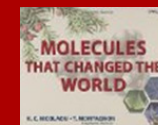
Marco Polo, praça de San Marco, Veneza, IT  
Ópio: *Papaver somniferum*  
morfina, codeína, heroína  
1804 -Friedrich W.A. Sertürner  
1952 – M. Gates, síntese  
Hipno-analgésicos sintéticos:  
4-fenilpiperidinas / meperidina  
Beckett & Casey, 1954  
Tolerância & Dependência química



P. W. Schiller, *Progr. Med. Chem.* 1991, 28, 301



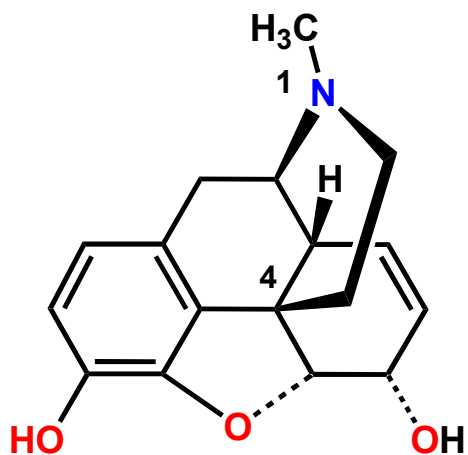
Adaptado de K. C. Nicolaou & T. Montagnon, "Molecules that change the world".



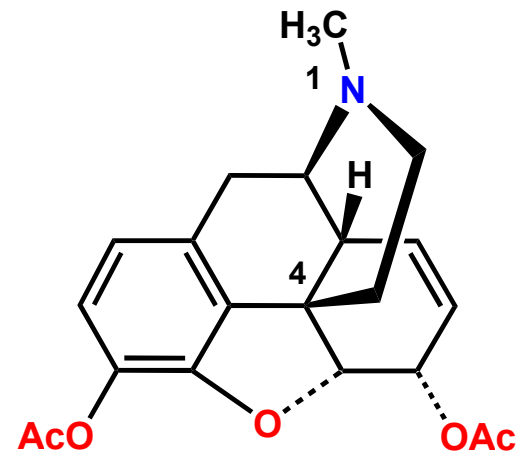




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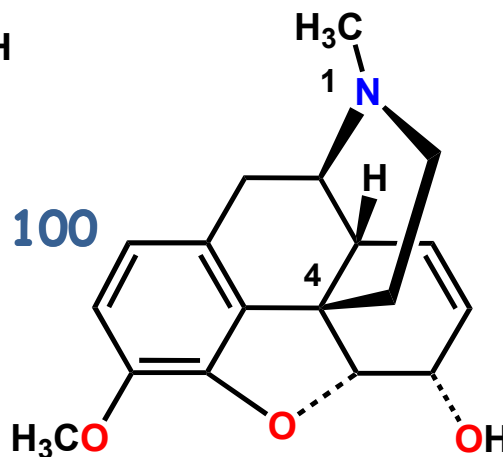


**morfina**



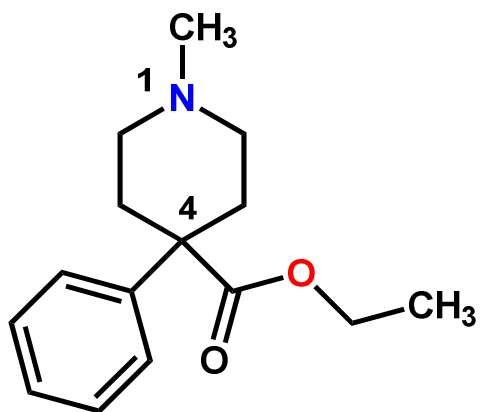
**heroína**

Índice de atividade = 100



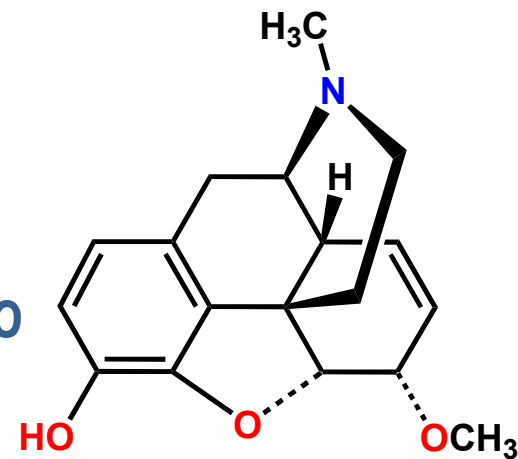
**codeína**

Índice de atividade = 20



**meperidina**

1947



**isocodeína**

Índice de atividade = 50



# Fármaco Centenário

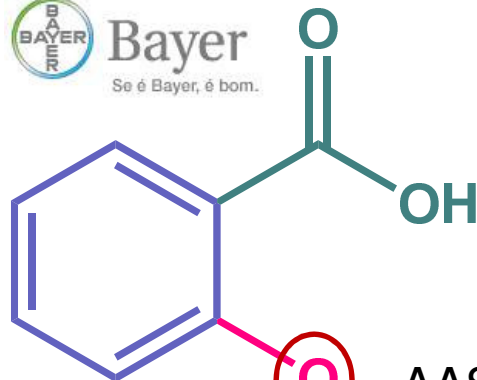
S. Jourdier, "From A Miracle Drug", Royal Society of Chemistry, UK

Acetylsalicylic Acid



**Bayer**

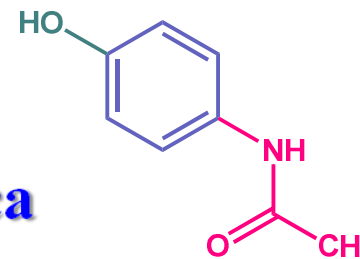
Se é Bayer, é bom.



Felix Hoffmann

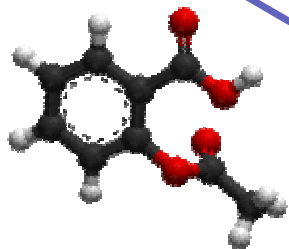
1868-1946

med  
**Química**  
Farmacêutica  
chem  
**Medicinal**



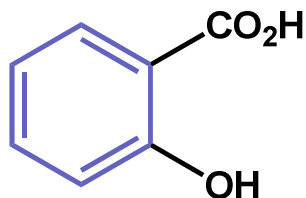
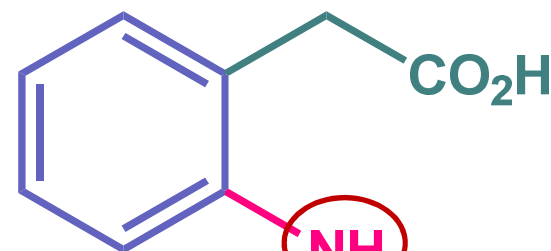
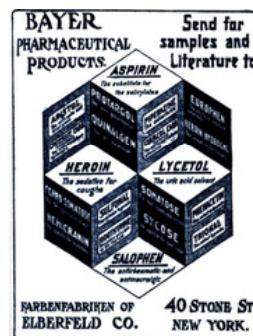
acetaminofeno

1956



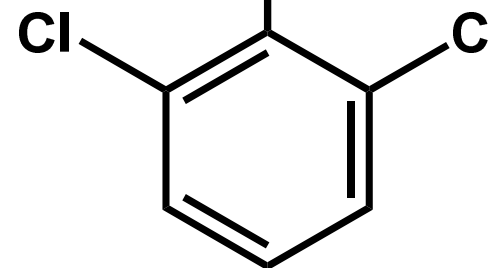
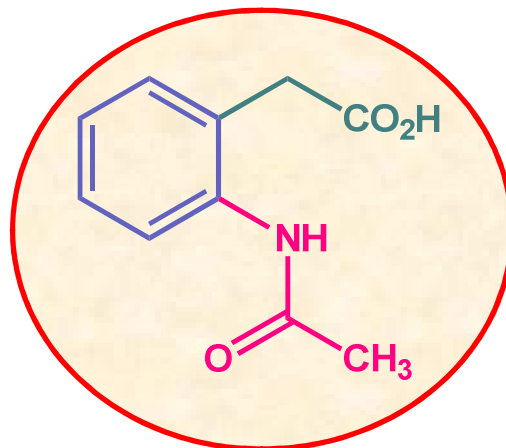
AAS

1899



Charles F. Gerhardt

1816-1856



diclofenaco

1980





# Antibioticoterapia



Alexander Fleming  
1881-1955

A. Fleming, *Br. J. Exp. Pathol.*, **10**, 226 (1929)

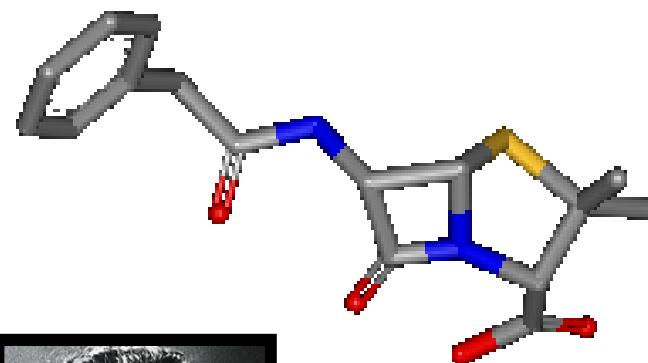
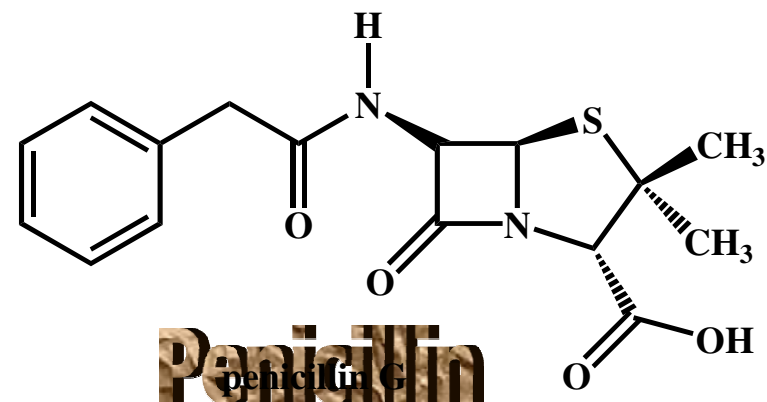
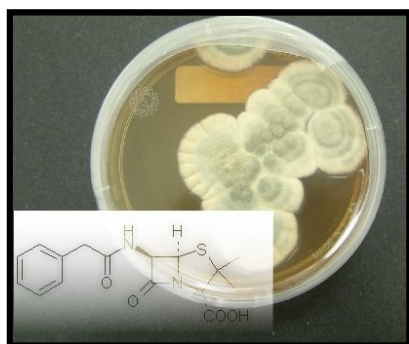


<http://nobelprize.org>

## 1929



Howard Walter Florey  
1898-1968



## 1941

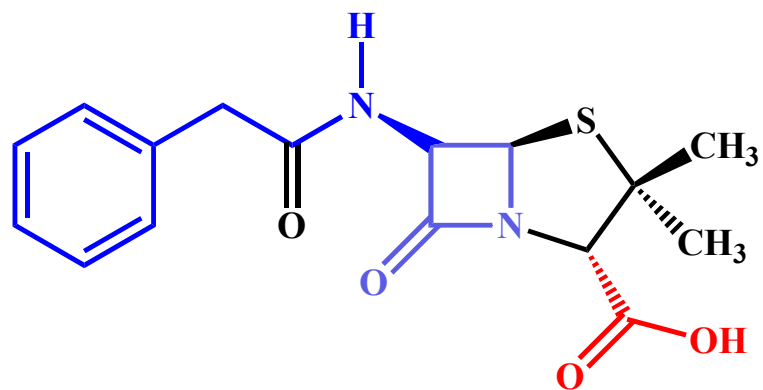


Ernst Boris Chain  
1906-1999

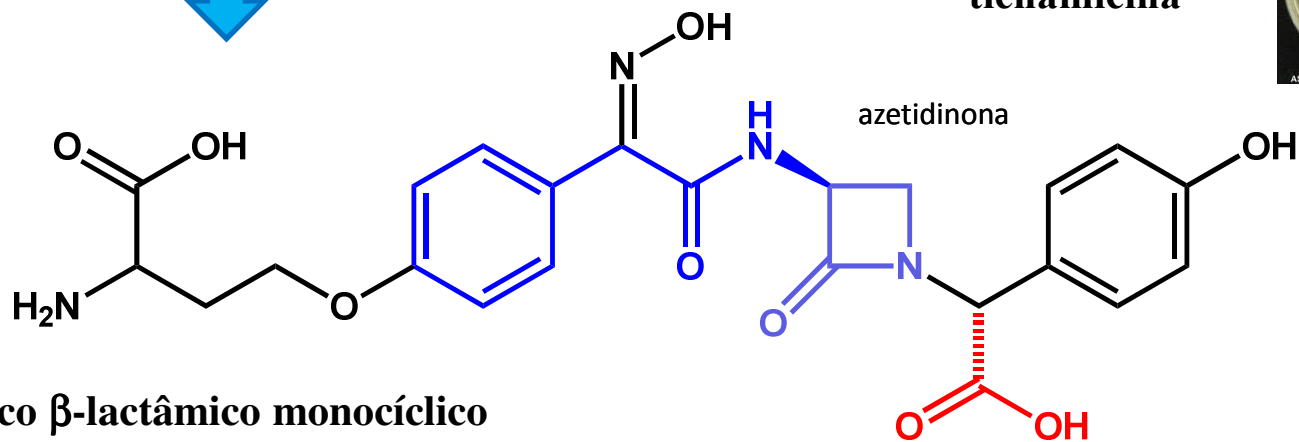


# Nobel Prize of Medicine 1945





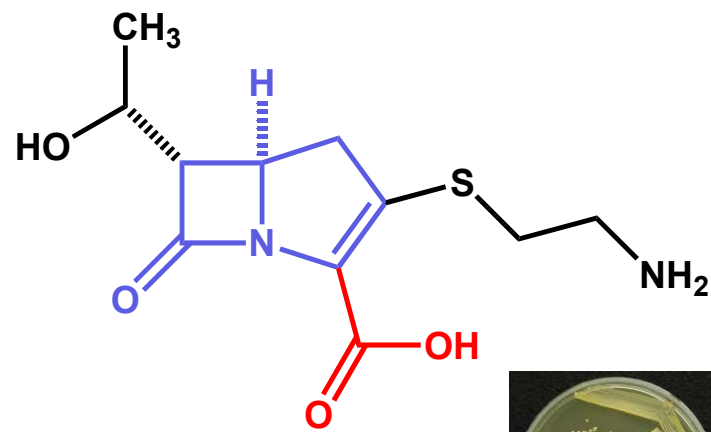
penicillin G



Antibiótico  $\beta$ -lactâmico monocíclico

*Nocardia uniformis*

Ativo *via oral*



tienamicina



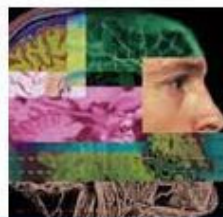
azetidinona

nocardicina



**Os fármacos  
contemporâneos**

*m e d*  
**Química**  
**Farmacêutica**  
*chem*  
**Medicinal**



# the **Pharmaceutical Century**

TEN DECADES OF DRUG DISCOVERY

ACS PUBLICATIONS  
HIGH QUALITY. HIGH IMPACT.

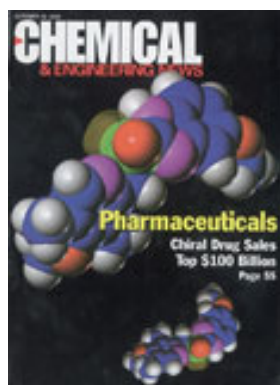
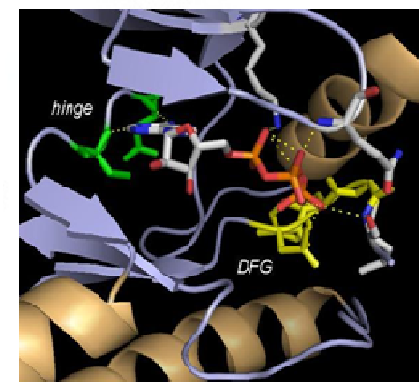


[Analytical Chemistry](#) | [Chemical & Engineering News](#) | [Modern Drug Discovery](#)  
[Today's Chemist at Work](#) | [E-Mail Us](#) | [Electronic Readers Service](#)

1800s to 1919

<http://pubs.acs.org/journals/pharmcent/Ch10.html>

Publicação da *American Chemical Society*, do fim de 2000 (250 páginas), abordando o desenvolvimento científico da ciência dos fármacos, década/década, ao longo do século 20 eleito como o "Século Farmacêutico".



Antivirais

Cardiovasculares **SNC**

Oncolíticos Antibióticos

Anti-inflamatórios

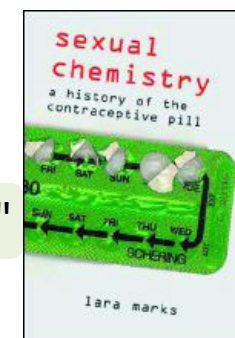
Analgésicos

Anti-hipertensivos

Contraceptivos

L. Marker, "Sexual Chemistry: A History of the Contraceptive Pill"

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**Farmacêutica**  
chem  
**Medicinal**





*Química*  
Farmacêutica  
*Medicinal*

*cimetidina*

*Química*  
*Medicinal*

*Química*  
Farmacêutica  
*Medicinal*

*propranolol*

*Química*  
Farmacêutica  
*Medicinal*

*captopril*

*Química*  
*Medicinal*

*celecoxibe*



*Química*  
*Medicinal*

*estatinas*

*losartana*

*Química*  
Farmacêutica  
*Medicinal*

*indinavir*



*Química*  
*Medicinal*

*imatinibe*

*sildenafil*

*Química*  
*Medicinal*

*Química*  
Farmacêutica  
*Medicinal*



*maraviroc*

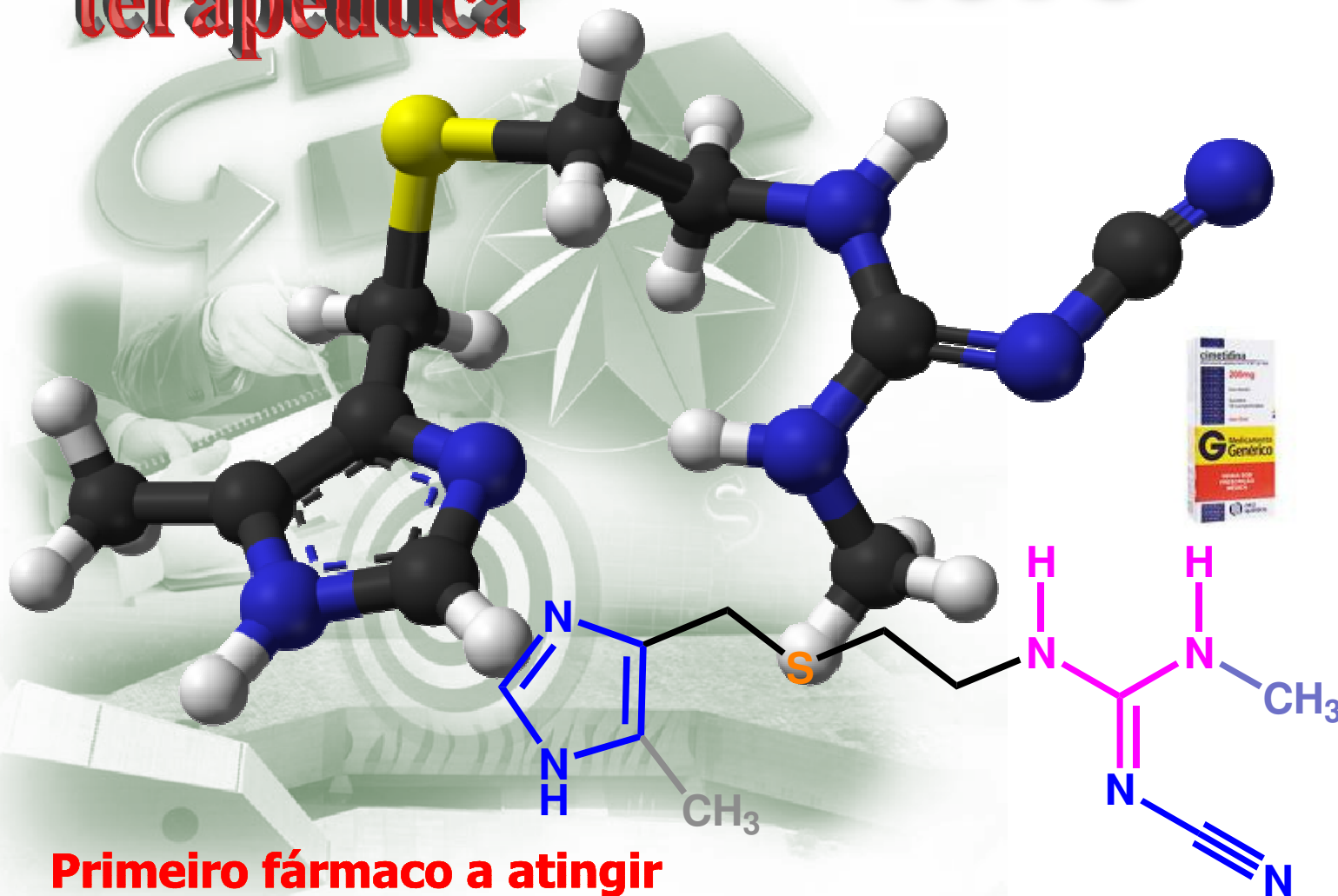




**Inovação  
terapêutica**

**1975**

**Cimetidina**

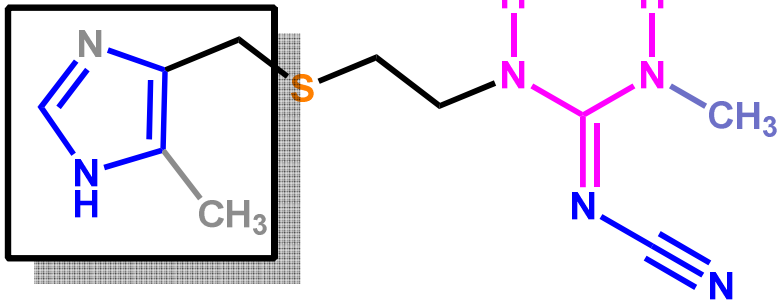


**Primeiro fármaco a atingir  
US\$ 1 bilhão em vendas,  
no ano do lançamento**





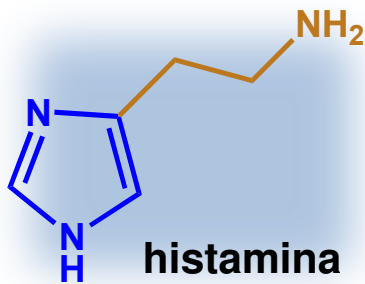
metil-imidazola



cimetidina  
1976

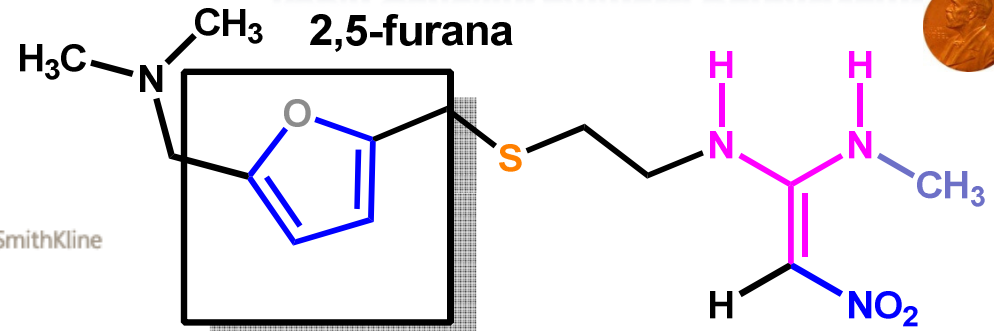


Robin Ganellin, Emmett, Durant, James Black



Mannich

2,5-furana



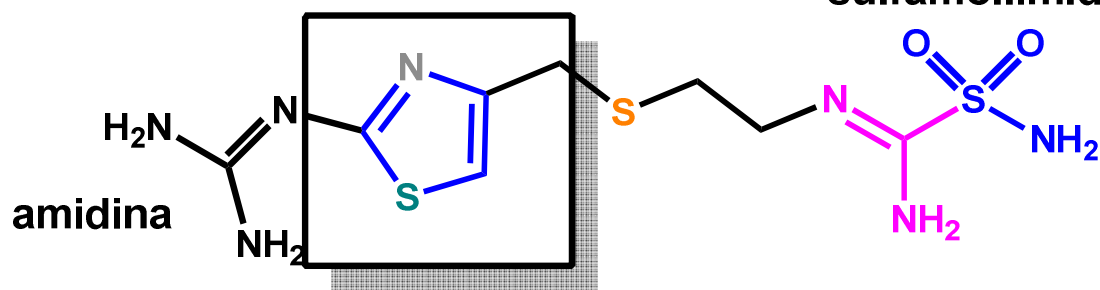
ranitidina  
1981

nitro

lamina



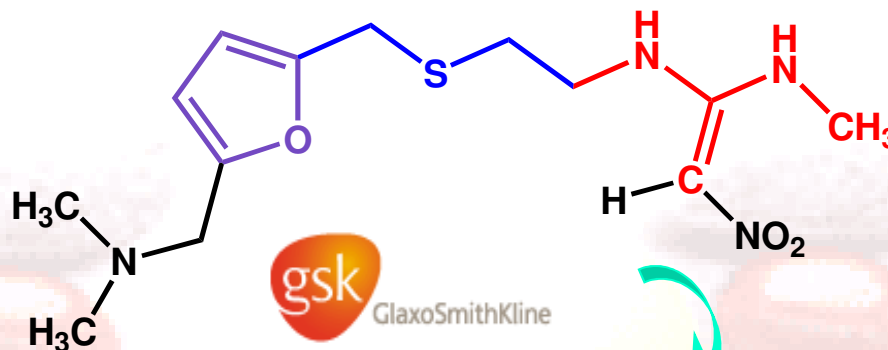
tiazola



famotidina  
1982

med  
**Química**  
**Farmacêutica**  
chem  
**Medicinal**





med  
**Química**  
**Farmacêutica**  
chem  
**Medicinal**

**2008 annual results: US\$ 36,5 bi**  
**( ~ > 10%/y)**

**ca. 21% do faturamento origina-se em NP's**

**Investimentos RD&I: > US\$ 2,04 bilhões**

**4 produtos com vendas > US\$ 1 bi**

**80 fábricas em 37 países com 100.000 empregos**

**(ca. 16.500 em RD&I)**

**Pipeline: 51 projetos em fase pré-clínica**

**158 projetos em desenvolvimento:**

**85 NCE's, 20 vacinas, 45 produtos**



## Top 15 Global corporations

	Empresa	Vendas (US\$mi)	Sede
1	Pfizer	43,363	US
2	GlaxoSmithKline	36,506	UK
3	Novartis	36,506	Switzerland
4	Sanofi-Aventis	35,642	France
5	AstraZeneca	32,516	UK/Sweden
6	Hoffmann-La Roche	30,336	Switzerland
7	Johnson & Johnson	29,425	US
8	Merck & Co.	26,191	US
9	Abbott	19,466	US
10	Eli Lilly and Company	19,140	US
11	Amgen	15,794	US
12	Wyeth	15,682	US
13	Teva	15,274	Israel
14	Bayer	15,660	Germany
15	Takeda	13,819	Japan



sanofi aventis



Amgen Inc.







# THE ROLE OF THE MEDICINAL CHEMIST IN DRUG DISCOVERY THEN AND NOW

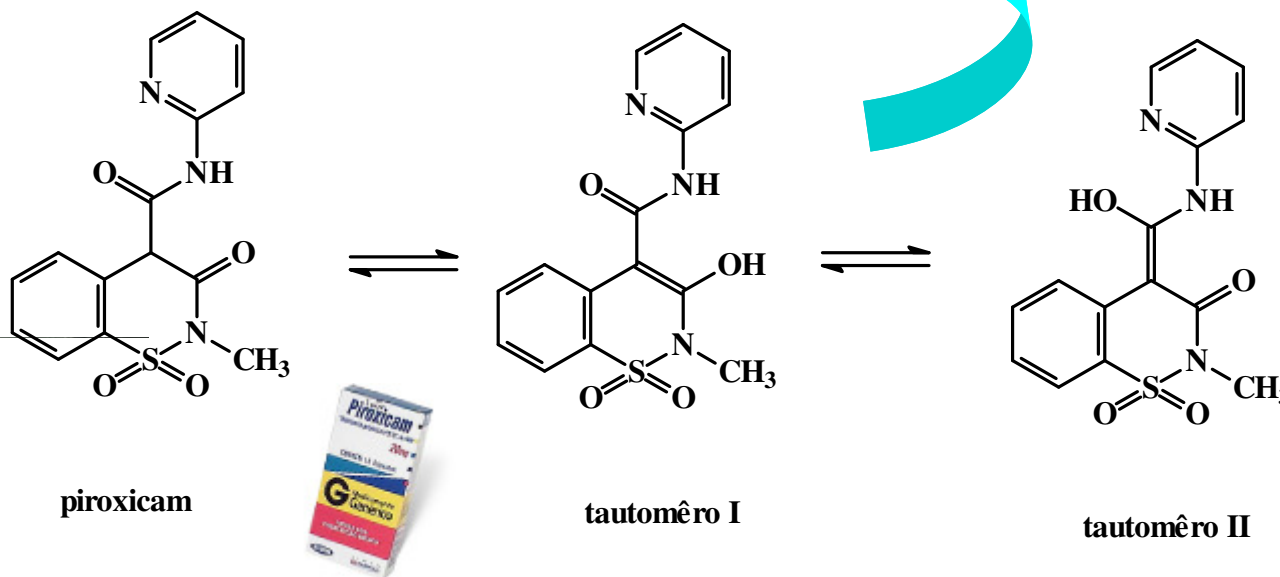
Joseph G. Lombardino\* and John A. Lowe III†

LEAD COMPOUND  
 STRUCTURE-ACTIVITY  
 RELATIONSHIP  
 COMBINATORIAL TECHNOLOGY  
 NEW MOLECULAR ENTITY  
 HIT  
 PHARMACOKINETICS



Elias J. Corey & Joseph Lombardino, Pfizer, 1950

## The role of the medicinal chemist



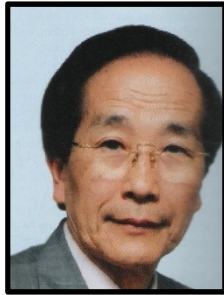
piroxicam  
ziprasidona

"... Making millions of new chemicals robotically does not, apparently, lead to more new drugs."

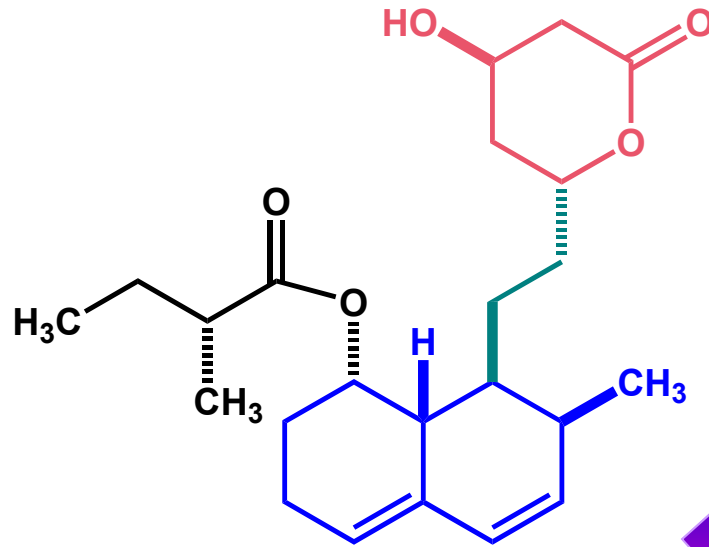


***Os fármacos***  
***bilionários***





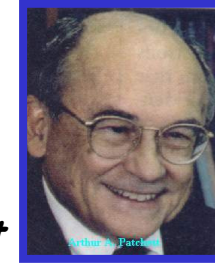
Akira Endo



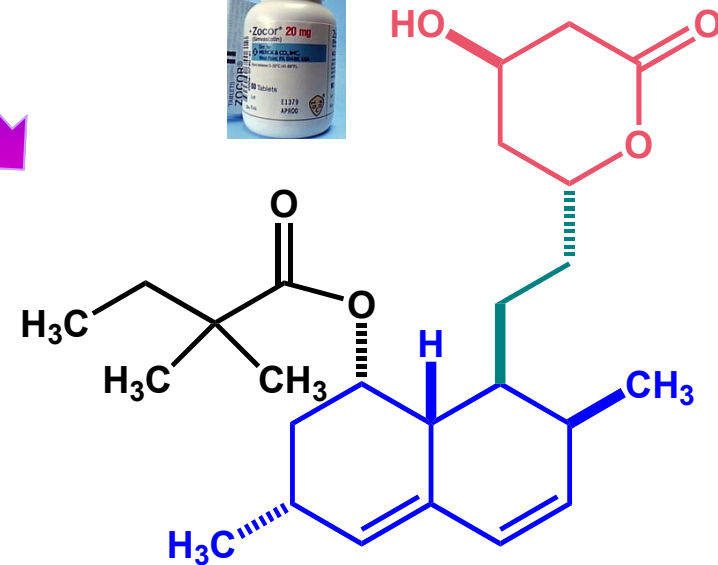
mevastatina  
1975

A.Endo, Compactin (ML-236B) and related compounds as potential cholesterol-lowering agents that inhibit HMG-CoA reductase, *J.Med.Chem.*1985,28,401

med  
**Química**  
Farmacêutica  
chem  
**Medicinal**

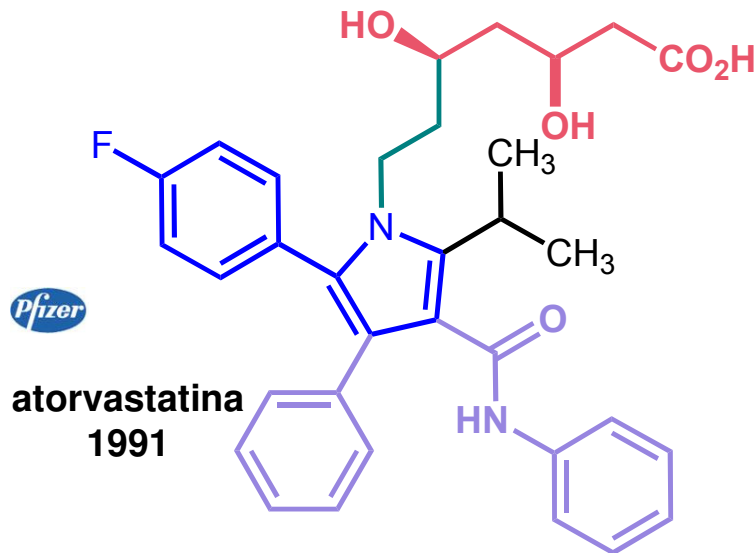


Arthur A. Patchett

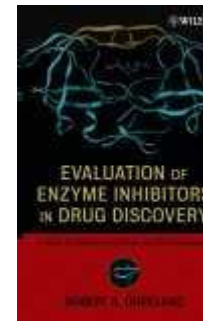


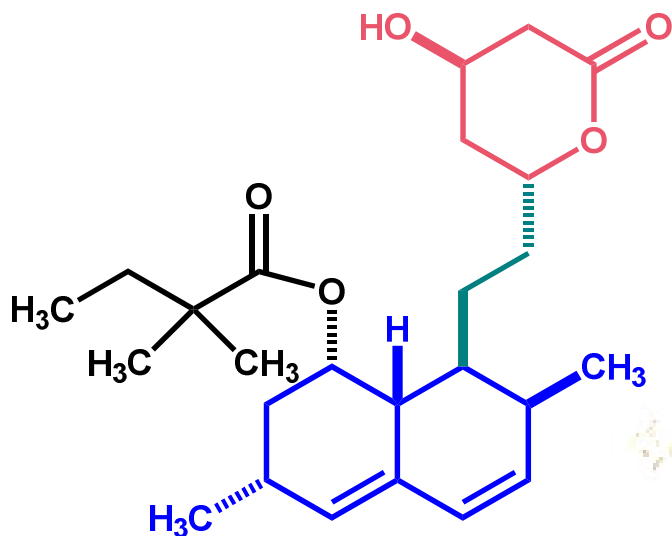
simvastatina  
1986

US\$ 5,5 bi  
(2007)



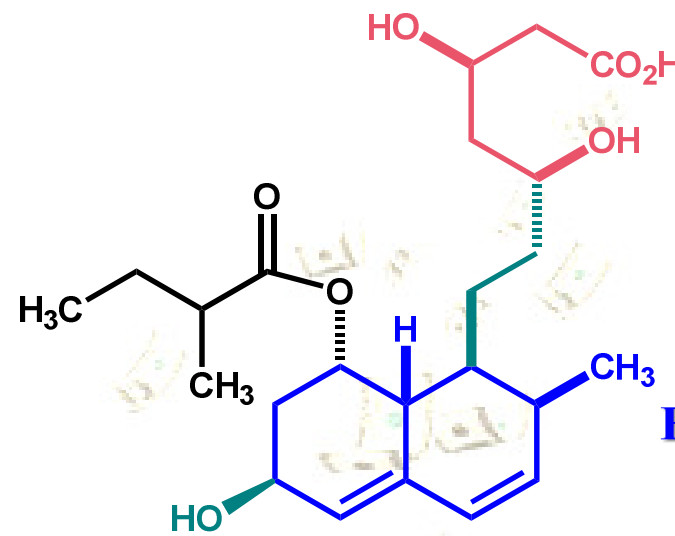
atorvastatina  
1991





simvastatina

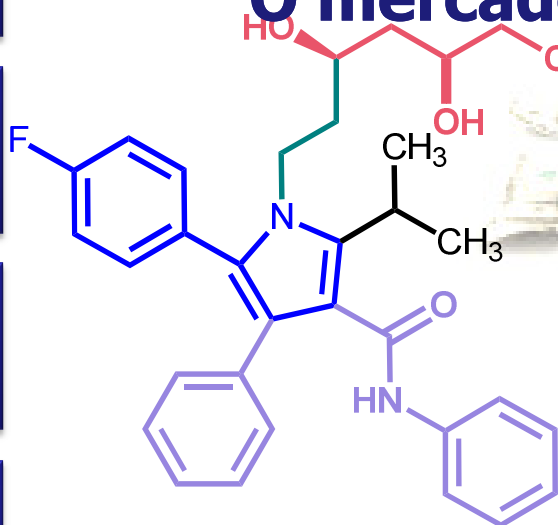
1986



pravastatina

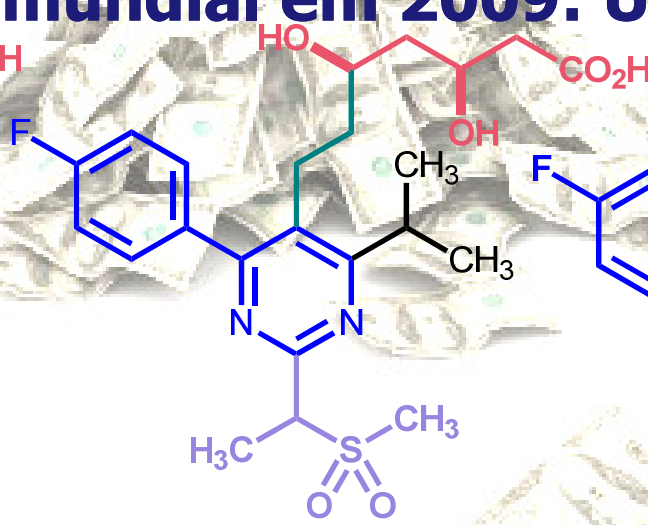
1988

## O mercado mundial em 2009: US\$ 26 bi



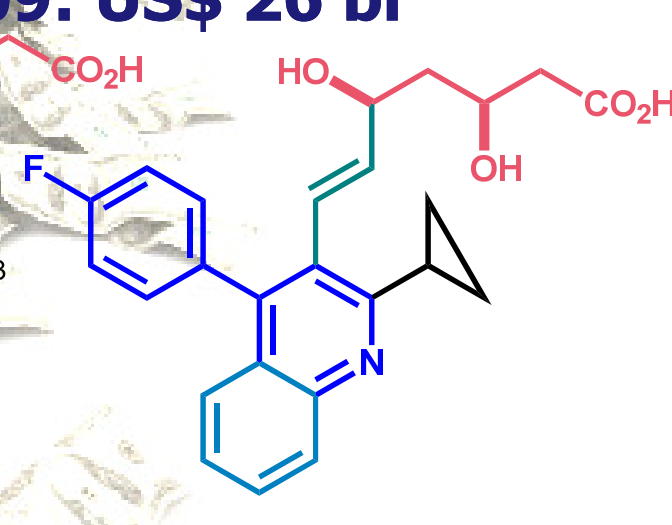
atorvastatina

1991



rosuvastatina

2004



pitavastatina

2009



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Farmacêutica  
chem  
**Medicinal**

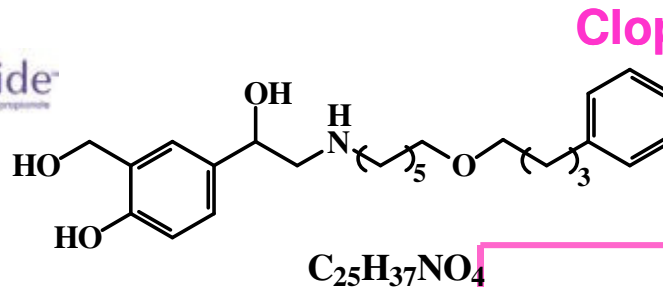
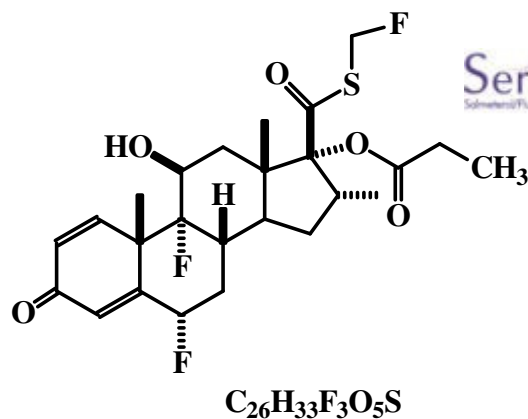


As estatinas movimentaram *ca.* R\$ 290 milhões por ano no Brasil em 2008





# Top-5 drugs in world market (2009)\*



**Etanercept**  
(Enbrel<sup>®</sup>, biofármaco)

**Olanzapine** ZYPREXA  
Intramuscular  
(Remicade<sup>®</sup>, biofármaco)

**Montelukast**  
(Singulair<sup>®</sup>, Merck)

**Rosuvastatine**  
(Crestor<sup>®</sup>, AZ)

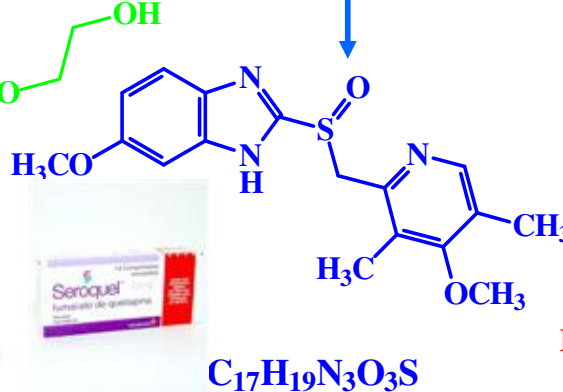
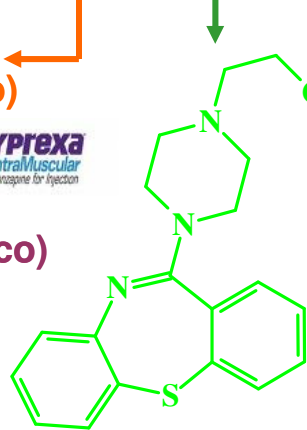
**68,1**  
(8,2%)



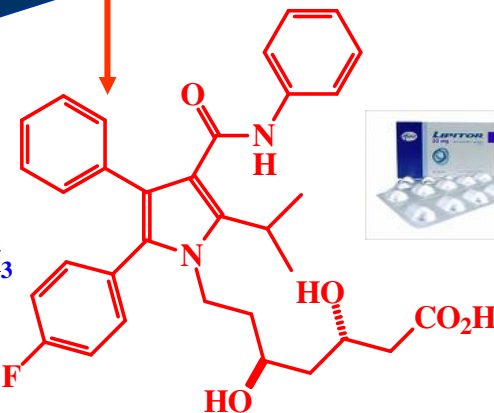
**Quetiapine (AZ, 2012)**

\* SJ Ainsworth, C&EN 2009 (07/12) 13-21

US\$ bi



**Esomeprazole (AZ)**



**Atorvastatin**  
(Pfizer; 06/2011)





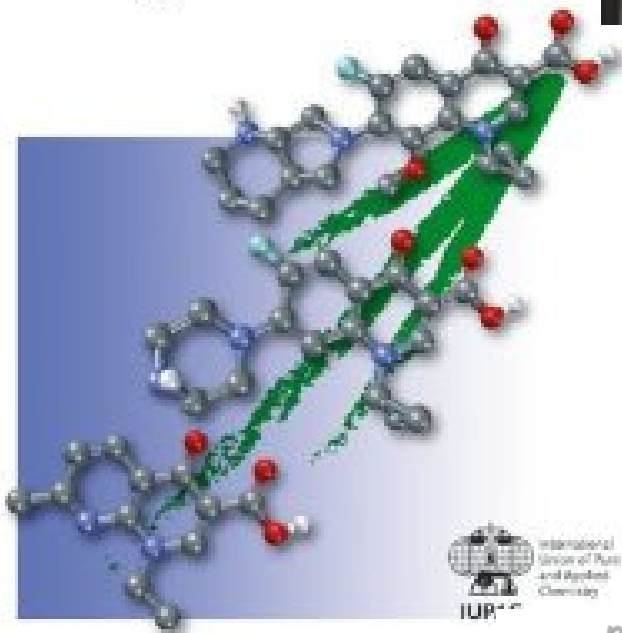
Janos Fischer is research laboratory head at Richter Ltd., Budapest, Hungary.

Robin Ganellin is Emeritus Professor of Medicinal Chemistry at University College London, UK.

Edited by  
János Fischer and C. Robin Ganellin

WILEY-VCH

# Analogue-based Drug Discovery



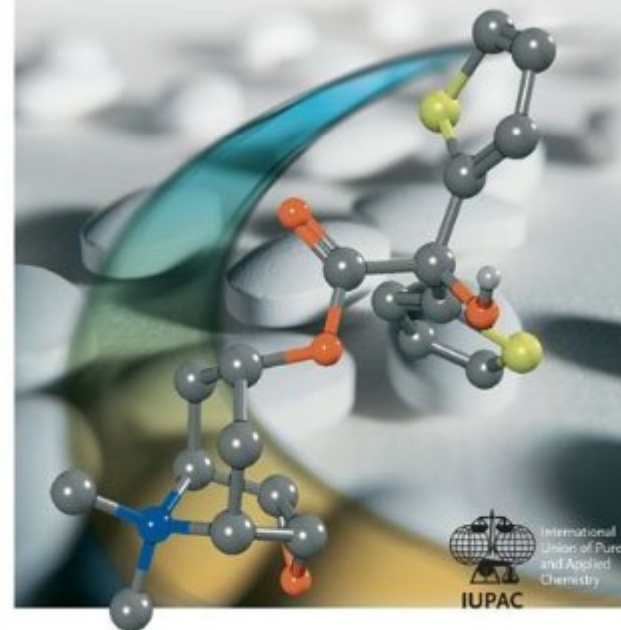
ISBN-10 3527325492  
Setembro de 2010

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**Farmacêutica**  
*chem*  
**Medicinal**

Edited by  
János Fischer and C. Robin Ganellin

WILEY-VCH

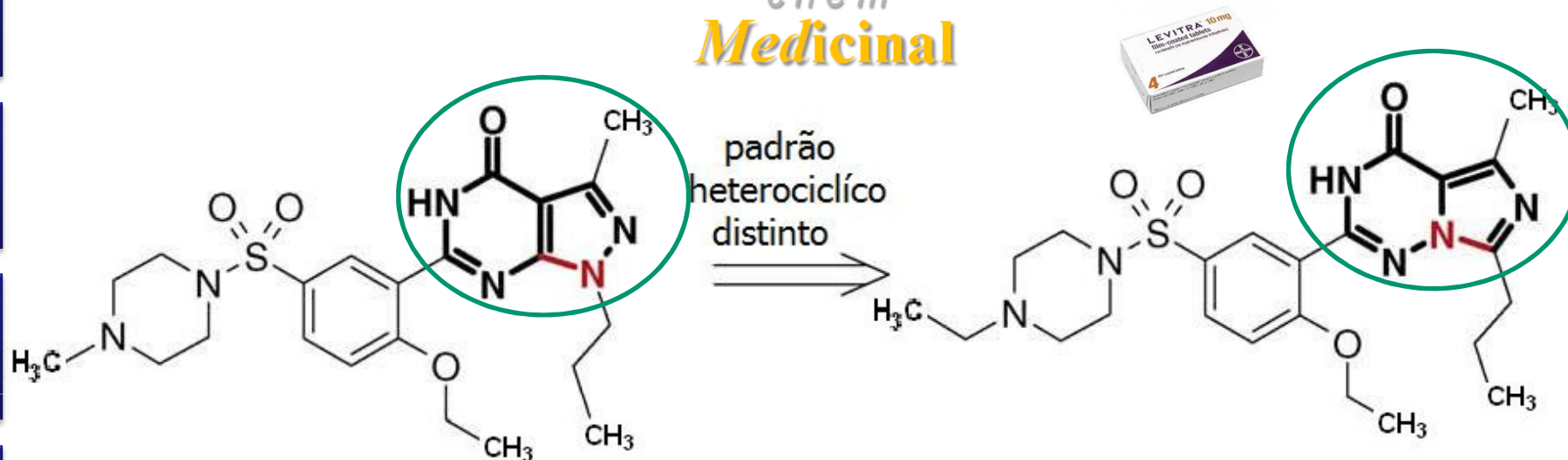
# Analogue-based Drug Discovery II



ISBN-10 3527325492  
Setembro de 2010



med  
**Química**  
Farmacêutica  
chem  
**Medicinal**



Sildenafil  
Viagra®  
Pfizer

março 1998

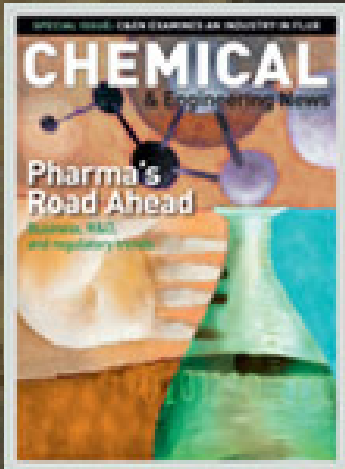
Bioisosterismo\*

Vardenafil  
Levitra®  
Bayer

agosto 2003



LM Lima & EJ Barreiro, Bioisosterism: A Useful Strategy for Molecular Modification and Drug Design, *Current Medicinal Chemistry*, 2005, **12**, 23-49



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chem  
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*“...history suggests  
drug discovery  
is **art** as well as **science**  
and relies heavily on the skill  
of experienced drug hunters...”*

(C&EN, June 19, 2006)

***Science & art in drug discovery...***





Síntese Orgânica

Interdisciplinaridade

Química Orgânica

Bioinformática

Farmacologia

Toxicologia



Universidade Federal do Rio de Janeiro

**PURDUE**  
UNIVERSITY

Dept. of Medicinal Chemistry  
and Molecular Pharmacology  
School of Pharmacy and Pharmaceutical Sciences



2

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0

8

Pharmacy School Rankings		
1	<b>University of California--San Francisco</b>   San Francisco, CA	4.7
2	<b>University of North Carolina--Chapel Hill</b>   Chapel Hill, NC	4.4
3	<b>University of Minnesota</b>   Minneapolis, MN	4.3
4	<b>University of Texas--Austin</b>   Austin, TX	4.2
5	<b>Purdue University</b>   West Lafayette, IN	4.1

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chem  
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Uma prova da interdisciplinaridade...!



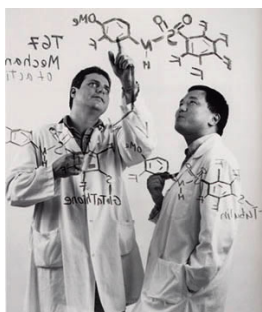
**Considerações**

***finais***



**"Science has contributed immensely to human progress and to the development of modern society.**

**The application of scientific knowledge continues to furnish powerful means for solving many of the challenges facing humanity...."**



**Kofi Annan**

**U.N. – Secretary-General**

**A Challenge to the World's Scientists**

**Science** 2003, 299, 1485





instituto nacional de Fármacos e Medicamentos  
de ciência e tecnologia

[www.inct-inofar.ccs.ufrj.br](http://www.inct-inofar.ccs.ufrj.br)

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Project CNPq 573.564/2008-6

**RV9**

Revista Virtual de Química

ISSN 1994-6835

Volume 2, Número 1

Janeiro-Março 2010



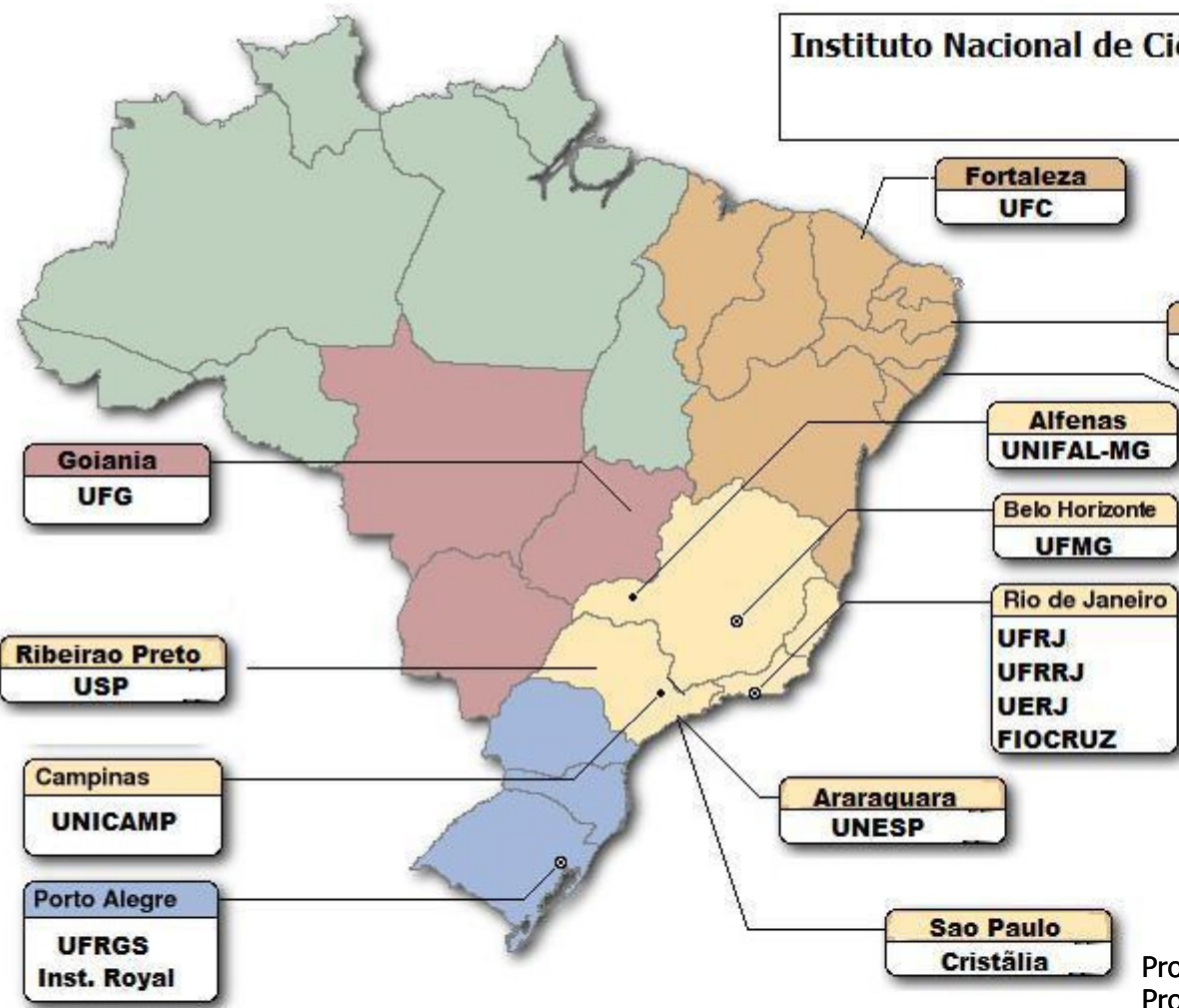
[www.ufrj.br/rv9](http://www.ufrj.br/rv9)

## A missão do INCT-INOVAR

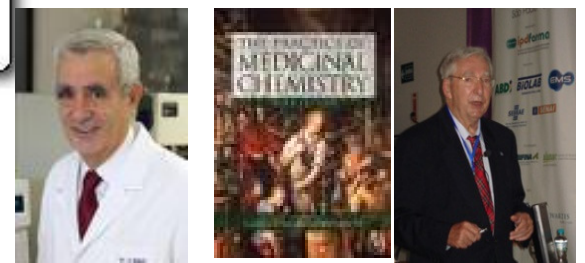
- Organizar as competências científicas nacionais em uma rede efetiva de pesquisa em fármacos;
- Apoiar projetos de pesquisa científica multi-institucionais voltados para novos fármacos;
- Contribuir para a inovação incremental e radical em novos fármacos e genéricos;
- Estudar e desenvolver a síntese total de genéricos, intermediários avançados e matérias-primas;
- Contribuir para a formação científica qualificada de pessoal em química medicinal & farmacologia;
- Promover a divulgação das ciências dos fármacos e dos medicamentos, assim como seu uso racional e seguro;

Instituto Nacional de Ciência e Tecnologia de Fármacos & Medicamentos  
**INCT - INOFAR**

CNPq 573.564/2008-6



Foreign scientific consultants



Prof. Antonio Monge, Universidad de Navarra, SP;  
Prof. Camille G. Wermuth, Prestwick Co., Ilkirch, FR

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**Slide 37**

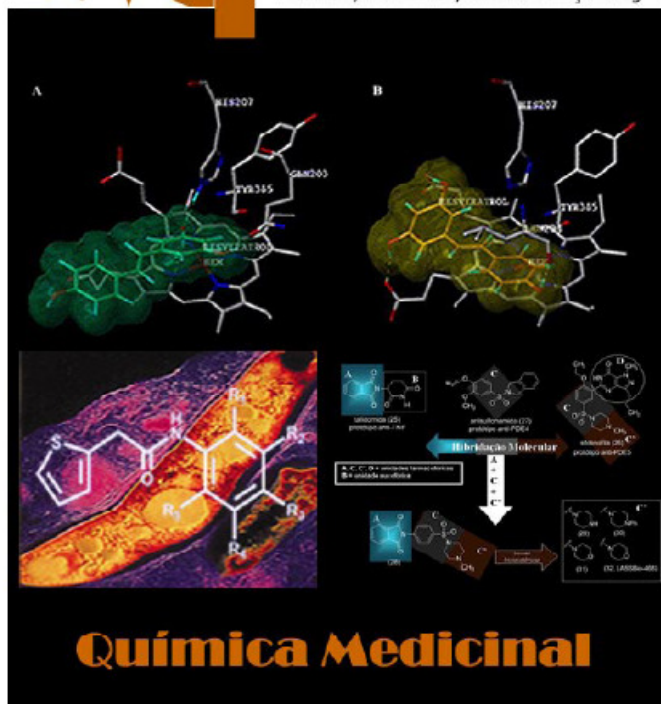
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**EJB4**

**INCT-INOVAR**

Eliezer J Barreiro; 02/05/2010





*O medicamento é instrumento essencial à preservação, manutenção e promoção da Saúde. O acesso ao medicamento representa um importante fator de inclusão social que depende da disponibilidade do fármaco – princípio ativo contido no medicamento e que em 85% dos casos é de origem sintética. Neste cenário, a importância do saber-fazer fármacos e medicamentos passa a representar um componente estratégico para o pleno exercício da soberania de nosso País. A universalização do acesso ao medicamento, para o cumprimento do preceito de nossa Carta Magna de 1988, quanto ao direito de todos os brasileiros e brasileiras à Saúde, depende, mais do que possa parecer, deste componente.*

1. A inovação em fármacos: O processo de planejamento racional
2. O principal paradigma da química medicinal moderna: A descoberta do composto-protótipo
3. Novos compostos-protótipos descobertos no *Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio®)*

Artigo de Divulgação



**A Química Medicinal e o paradigma do composto-protótipo**

**Barreiro, E. J.\***

Rev. Virtual Quim., 2009, 1 (1), 18-26. Data de publicação na Web: 30 de Janeiro de 2009

<http://www.uff.br/rvq>







# Química Farmacêutica Medicinal



Sistemas sociais otimizam tratamento de curto prazo; novas empresas surgem; fármacos como complementos para tratamento; diagnósticos através biomarcadores; biocomputação;

C i ê n c i a

E m p r e s a r i a l

Universidade: E&P qualificação pessoal, empreendedorismo, PPP, ciência básica

Assegurar o caráter científico do ensino farmacêutico

Universidade-indústria

N O V O S t r a t a m e n t o s

Tratamento não-farmacológico

Tratamento Farmacológico

Novos fármacos surgirão sem participação IF?

Atrofia da atividade inovadora no setor privado;

IF crise de criatividade & do fármaco *blockbuster*

V o c a c i o n a l

C i ê n c i a

Doenças crônicas em população idosa maior; custos operacionais menores na IF; doenças cardiovasculares & diabetes;

Superar o clássico paradigma de Ehrlich-Fischer





# Convite



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*chem*  
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**24 a 28 de janeiro de 2011.**

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Universidade Federal do Rio de Janeiro



Lidia M. Lima



Ana Luisa  
P. Miranda



Carlos A M Fraga

# Agradecimentos



"Meditai se só as nações fortes podem fazer Ciência, ou se é a Ciência que as fazem fortes"



Epilogo





# Muito obrigado !



**Corcovado mountain with the statue of Cristo Redentor  
one of the new seven wonders of the world.**

