A Química Medicinal e as Ciências Farmacêuticas

Eliezer J. Barreiro
Professor Titular

Universidade Federal do Rio de Janeiro

- As Ciências Farmacêuticas através dos tempos
- Os idos tempos da Farmacognosia...
- O *berço* da Química Medicinal
- Como *nascem* os fármacos?
- A inovação farmacêutica e o conhecimento científico
- Inovações farmacêuticas marcantes
- Uma inovação bilionária: as estatinas
- Os fármacos do século 21
- Um breve exemplo de "*casa*"
- Considerações finais

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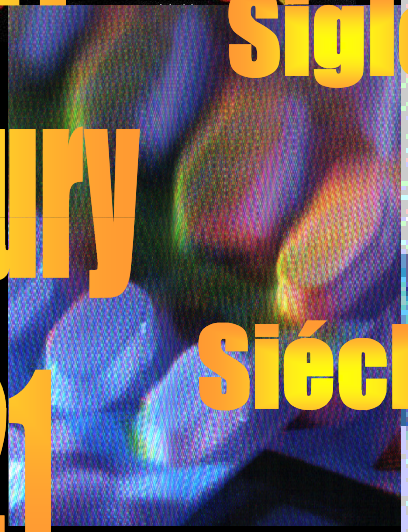
AS Ciências Farmacêuticas

Química Medicinal

Século 21

21th Century

Siécle 21



Siglo 21

21th Century

Século 21

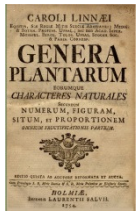
Interdisciplinaridade

Os idos tempos da *Farmacognosia*...

Antoine Laurent de Juisseau
1748-1832

Os vegetais e sua "*ordem admirável*"

1811



Farmacognosia

1789

François Magendie
1783-1855

Formulaire
1827

Fisiologia experimental

Farmacologia

alcalóides

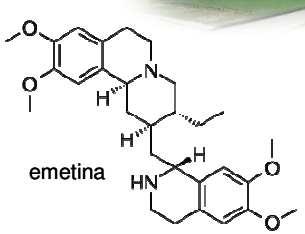
Pierre-Jean Robiquet
1780-1840

Joseph B Caventou
1795-1877

Pierre Joseph Pelletier
1788-1842

Substâncias puras

Fitoquímica



Química de PN

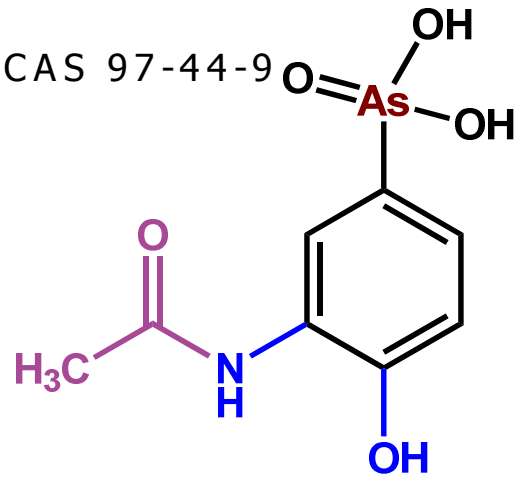
é uma ciência multidisciplinar que contempla o estudo das propriedades físicas, químicas, bioquímicas e biológicas dos fármacos ou dos fármacos potenciais de origem natural assim como busca novos fármacos a partir de fontes naturais (Soc. Bras. Farmacognosia)

O *berço* da Química Medicinal

Ernest Fourneau
1872-1949
Biografia de Fourneau

Stovarsol

CAS 97-44-9



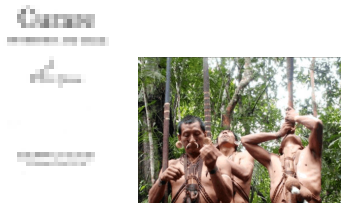
Institut Pasteur (1887)

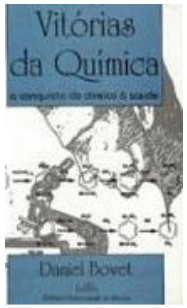
1911- Laboratoire de Chimie Thérapeutique

Institut Pasteur (Pierre Paul Emile Roux)

1º *paper* sobre *SAR*

Curare and Curare-like Agents.





Prêmio Nobel de Fisiologia/Medicina 1957

Daniel Bovet
1907-1992 *
Sulfonamidas, anti-histamínicos.

Química Medicinal chem

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

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Cronologia da Química Medicinal

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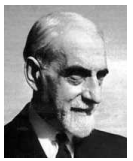
Fischer


Dale


penicilina


Fleming

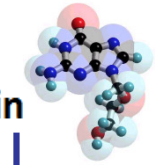

Vinca

indometacina


lovastatin

cimetidina

Valium^{R}

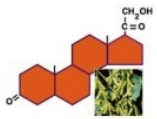

aciclovir


Black


imatinibe

1902 Fischer
1907 Salvarsan^{R}
1910 Dale
1911 Fourneau
1941 penicilina
1945 Fleming
1955 Vinca
1962 indometacina
1963 Valium^{R}
1975 cimetidina
1980 lovastatin
1981 aciclovir
1988 Black
2000 imatinibe

1889 AAS
1908 Ehrlich
1935 Domagk
1948 Ahlquist
1949 cortisona
1959 Kornberg
1960 talidomida / Librium^{R}
1964 propranolol
1977 captopril
1982 Vane
1999 celecoxibe



http://ejb-eliezer.blogspot.com

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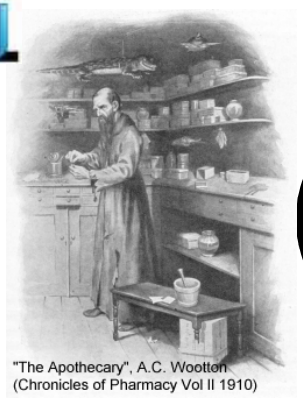
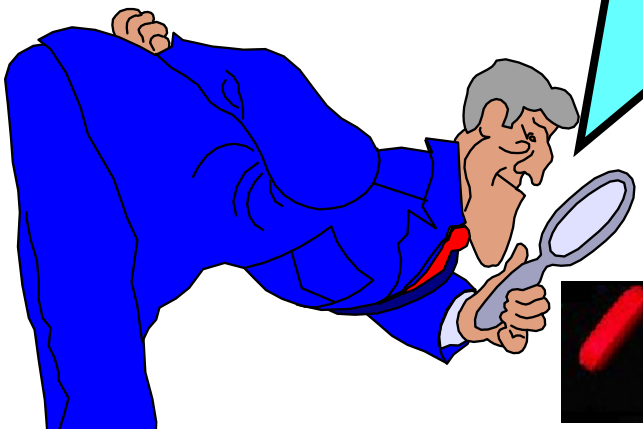
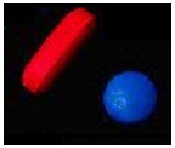
Química Medicinal

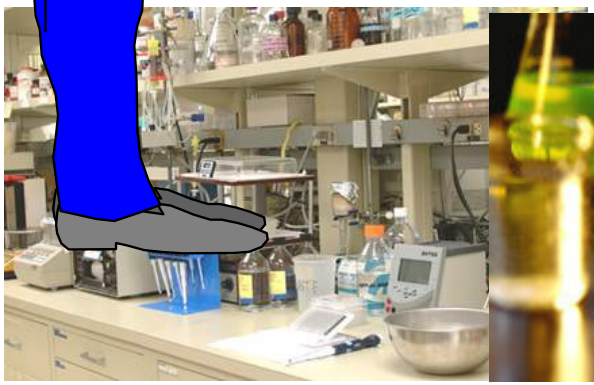


"The Apothecary", A.C. Wootton
(Chronicles of Pharmacy Vol II 1910)

Como nascem os fármacos?







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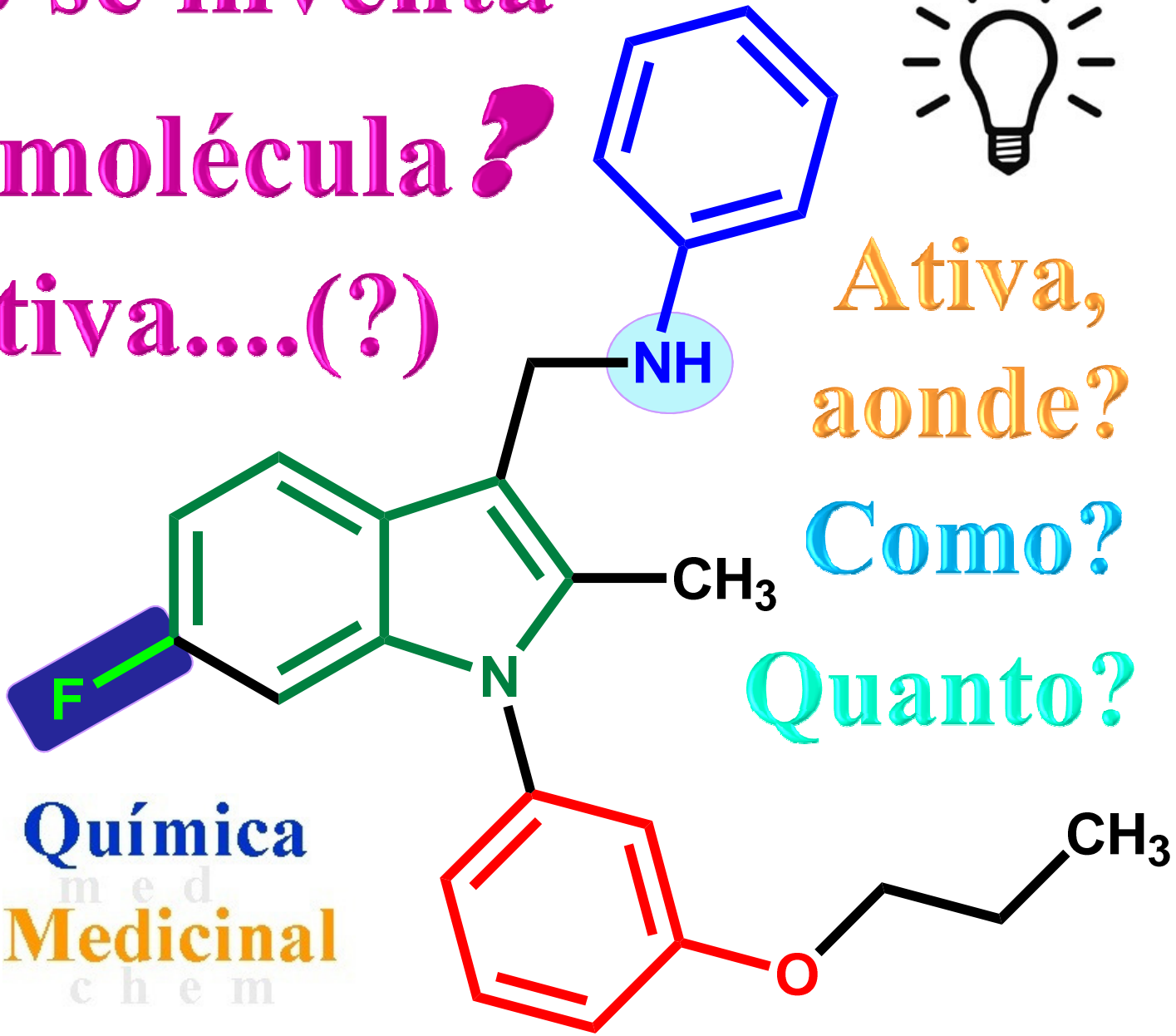
Como se inventa uma molécula Bioativa....(?)



Ativa, aonde?

Como?

Quanto?

S O

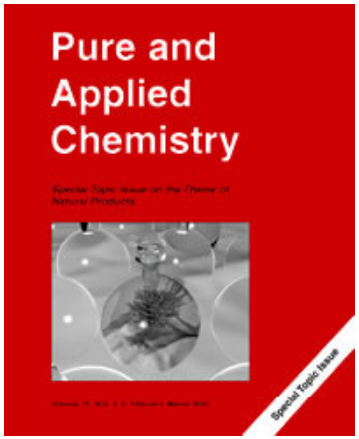
C N

X H

Química Medicinal

med chem

IUPAC - Subcommittee Medicinal Chemistry & Drug Development



Definição: Química 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 ou SAR).

Química Medicinal

IUPAC

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

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

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

Química Medicinal

Joseph G. Lombardino and John A. Lowe III‡*

Pfizer

2011- ACS Award in Industrial Chemistry (ziprazidone)

" ...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 & John A. Lowe, III

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

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

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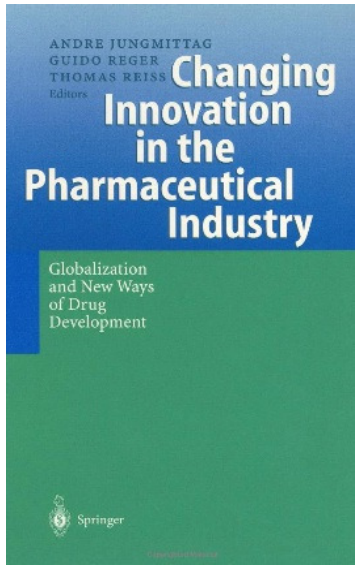
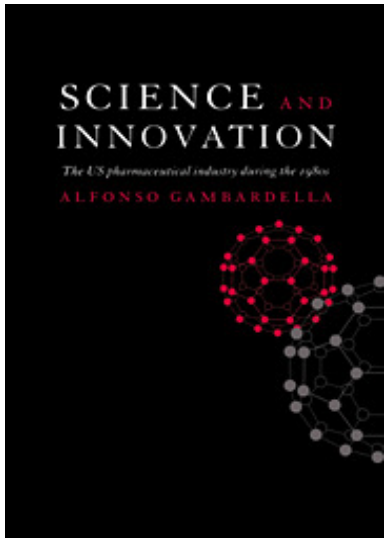
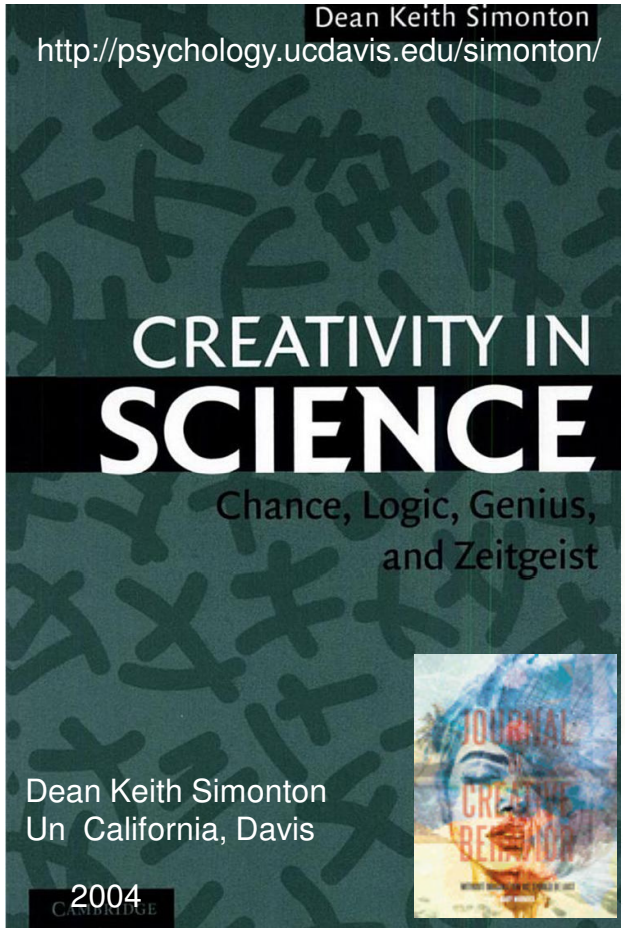


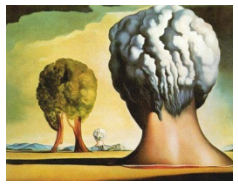


Cambridge University Press, Cambridge UK, 1995

A inovação tecnológica é um dos processos mais dinâmicos da atividade industrial que gera riqueza. ESTE dinamismo é acentuado na inovação farmacêutica que depende da efetiva interação entre **Ciência** & Tecnologia.

Invenção & Criatividade





"discoveries and inventions become virtually inevitable (1) as prerequisite kinds of knowledge accumulate in man's cultural store; (2) as the attention of a sufficient number of investigators is focused on a problem – by emerging social needs, or by developments internal to the particular science, or by both"

Robert K. Merton (1961)

The role of genius in scientific advance. New Scientist, 12, 306-308

"Ensaios de Sociologia da Ciência"

Era da economia do conhecimento!

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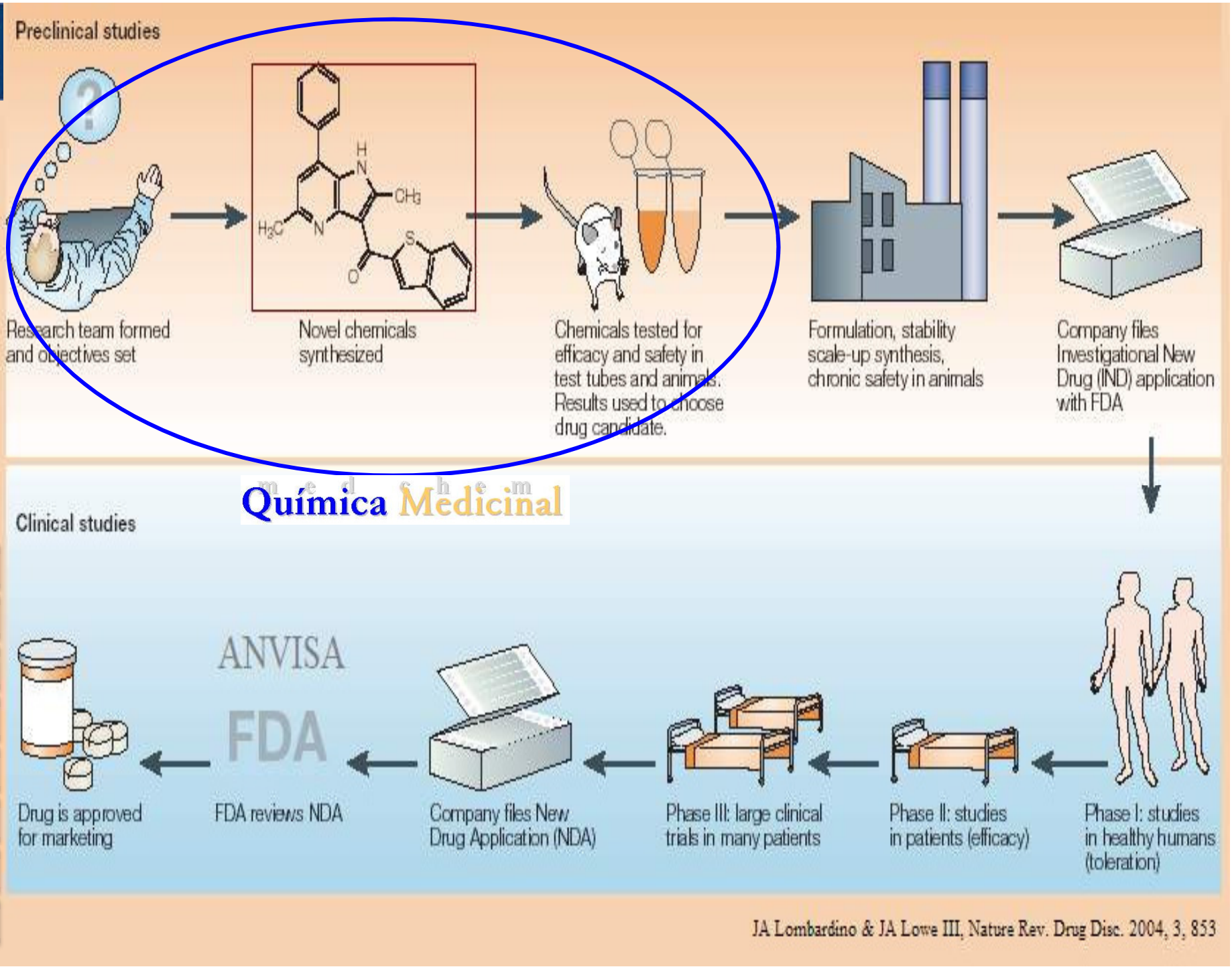
Química Medicinal



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

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"The search for new drugs … is an evolutionary process that is only likely to be successful if new methods merge with classical *medicinal chemistry* knowledge"

Hugo Kubinyi

www.kubinyi.de

Química Medicinal

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" Success isn't about finding the best idea.
It's about doing something with it. "

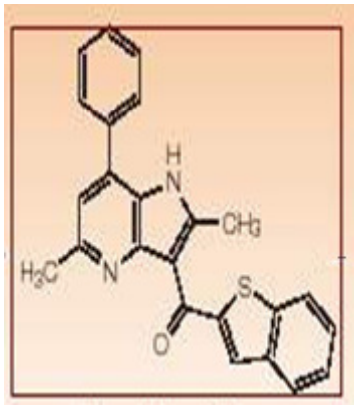
Idéia

Estado-da-arte

Inovadora

Criatividade

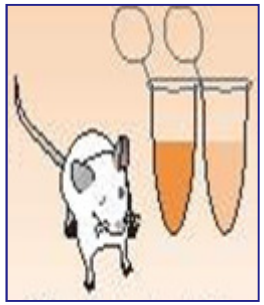
Originalidade



Estratégias

Química Medicinal

C H N O S Cl F



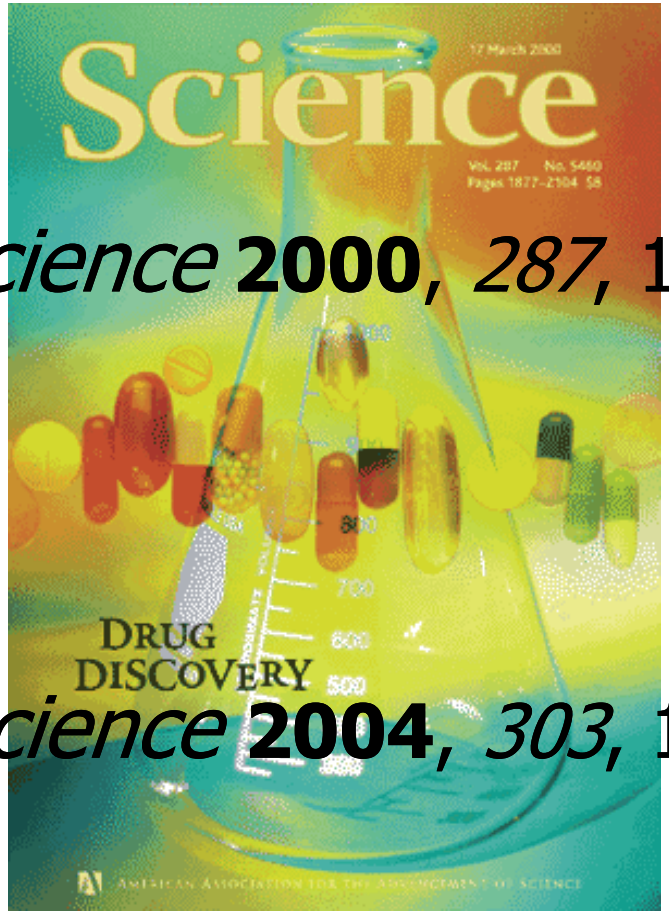
Método

Protótipo

A INOVAÇÃO FARMACÊUTICA

Universidade Federal do Rio de Janeiro

A inovação farmacêutica...



- *Science* **2000**, *287*, 1951 (J. Uppenbrink,J.Mervis)

- *Science* **2004**, *303*, 1713 (D. Kennedy)

...depende do conhecimento científico!

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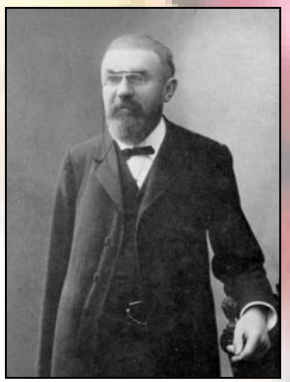
"Science is made of facts,

just as houses are made of stones;

but a mere collection of facts is

no more science

than a pile of stones a house"



Jules Henri Poincaré, 1902

Química Medicinal

med chem

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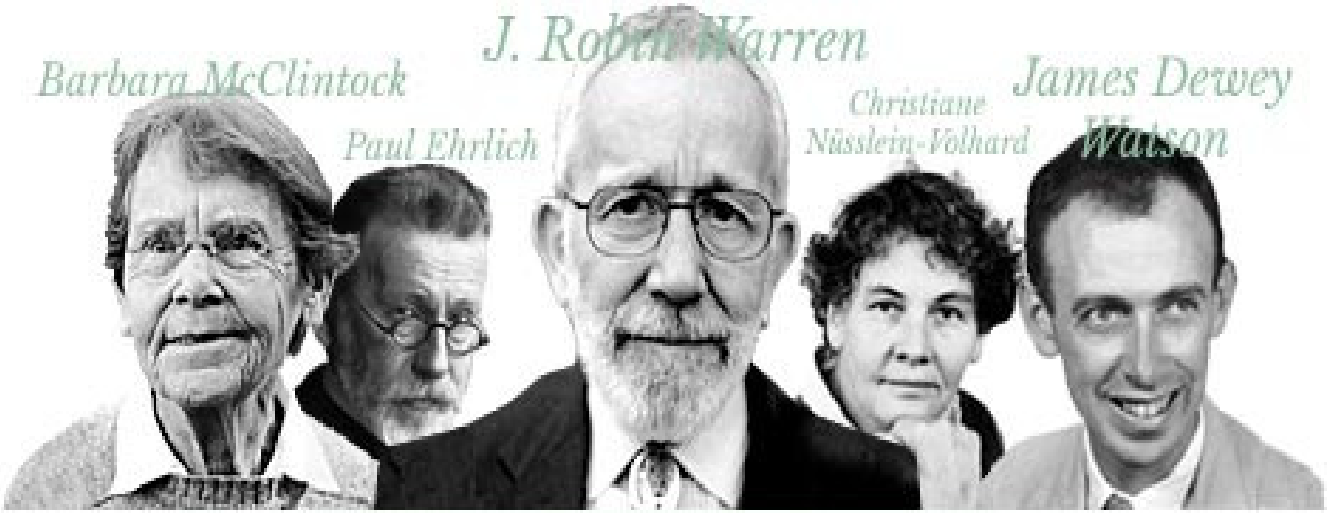
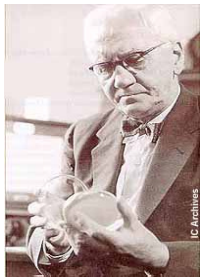
1902

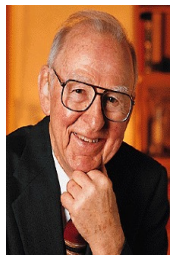


Alexander Fleming
Robert J. Lefkowitz

Emil Fischer
Sune K Bergström
George Hitchings
Ernest B Chain
Edwin G Krebs
Howard W. Florey

John R Vane





Dorothy C Hodgkin
Robert Robinson

Arieh Warshel
Brian K Kobilka
Gerhard Domagk

Martin Karplus
Gertrude B Elion
James W Black
Bengt I Samuelsson
Edmond H Fischer
Michael Levitt

2013

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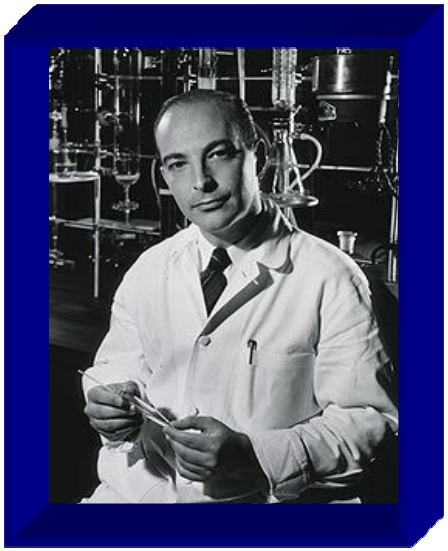


Prêmio Nobel, 1959

1987

The Two Cultures: Chemistry and Biology[1]

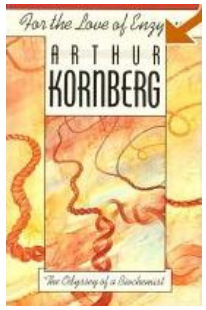
Arthur Kornberg

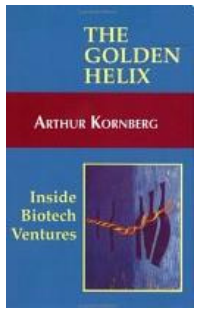
Department of Biochemistry, Stanford University, Stanford, California 94305

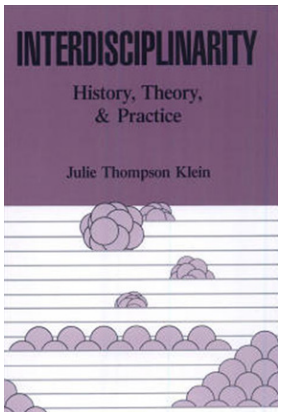
Received July 14, 1987

Arthur Kornberg
1918-2007

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







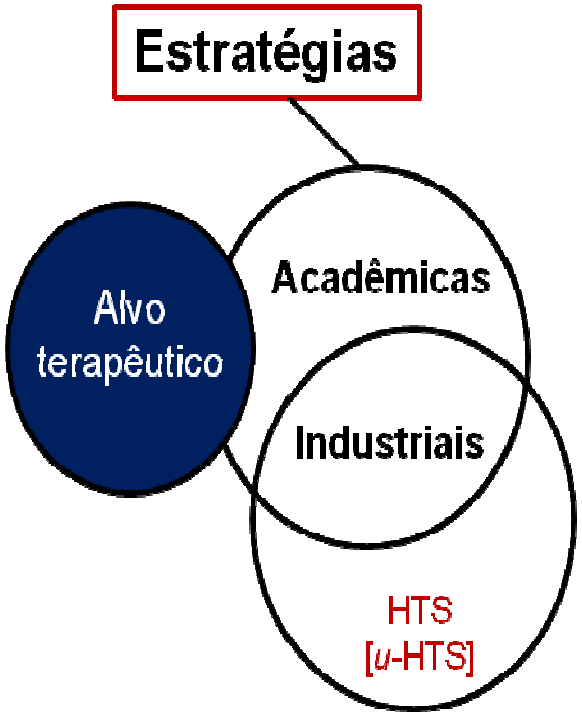
Química Medicinal

… was until recently the [illegible] of organic chemistry…

Interdisciplinaridade

[illegible] for [illegible]."

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



Química
med
Medicinal
chem

- Análogo ativo
- Planejamento racional
- Ancoramento molecular
- Bióforos selecionados
- Fragmentos moleculares

acadêmicas

In vivo

med chem
Química Medicinal

In vitro

industriais

- Quimiotecas (comerciais)
- Química combinatória
- Ancoramento molecular
- Fragmentos moleculares
- Técnicas hifenadas

Physiologic
A abordagem
approach
fisiológica

- PD / PK
- Toxidez

Composto protótipo

Ativo *in vivo*

Inovações farmacêuticas marcantes

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Século XX

1964

propranolol
cimetidina
captopril
omeprazola
imatinibe

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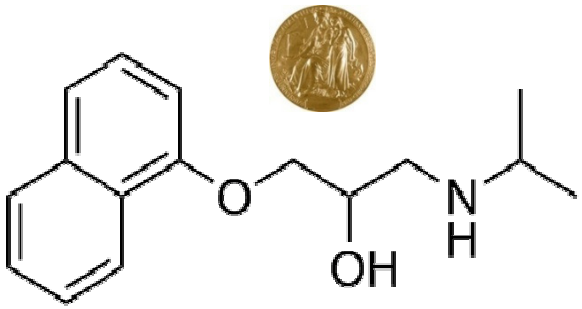
paclitaxel
lovastatina
penicilina

1942



Química
med
Medicinal
chem

Paradigma inicial

Mono-alvo

2011

século XX ⋮ século XXI

crizotinibe

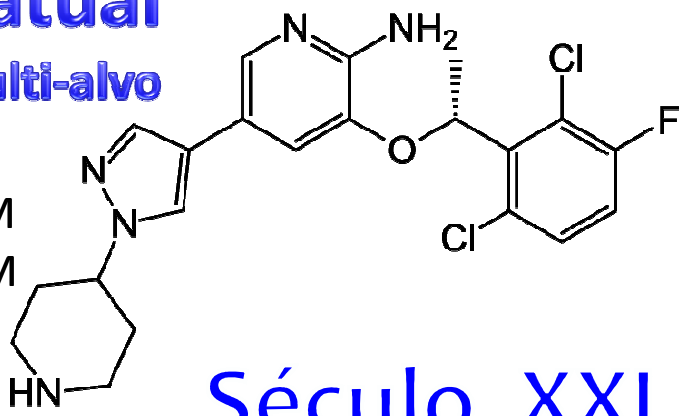
Paradigma atual

Multi-alvo

Inibidor duplo

c-MET TK IC_{50} = 8 nM

ALK IC_{50} = 20 nM



AT Shaw, U Yasothan, P Kirkpatrick, Crizotinib, *Nature Rev Drug Discov* **2011**, *10*, 897

Século XXI

EJ Barreiro, CAM Fraga, New Insigths for multifactorial disease therapy: the challenge of multifactorial drugs, *Curr Drug Therapy* **2008**, *3*, 1; JL Medina-Franco, MA Giulianotti, GS Welmaker, RA Houghten, Shifting from the single to the multitarget paradigm in drug discovery, *Drug Discov Today* **2013**, *18,* 495;

O Paradigma de Ehrlich-Fischer

Emil Fischer
1852 1919

The Nobel Prize in Chemistry 1902

LOCK & KEY CONCEPT

The Nobel Prize in Physiology or Medicine 1908

Paul Ehrlich
1854-1915

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

The Magic Bullet Theory

Química Medicinal

F Bosch, L Rosich, The Contributions of Paul Ehrlich to Pharmacology: A Tribute on the Occasion of the Centenary of His Nobel Prize, *Pharmacology*, **2008**, *82*, 171–179.

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Am J Physiol 1948, 153, 586

Raymond Ahlquist (1914

A STUDY OF THE ADRENOTROPIC RECEPTORS

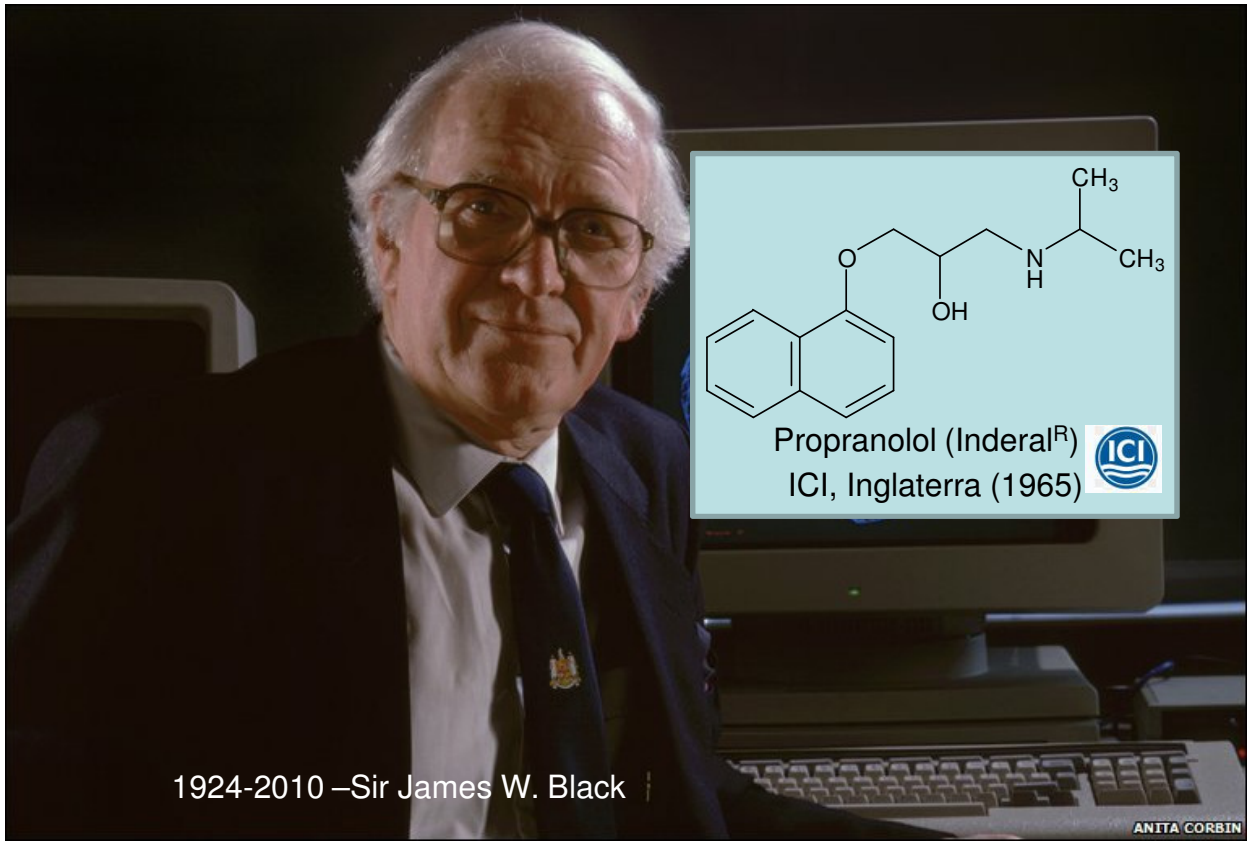
RAYMOND P. AHLQUIST

From the Department of Pharmacology, University of Georgia School of Medicine

AUGUSTA, GEORGIA

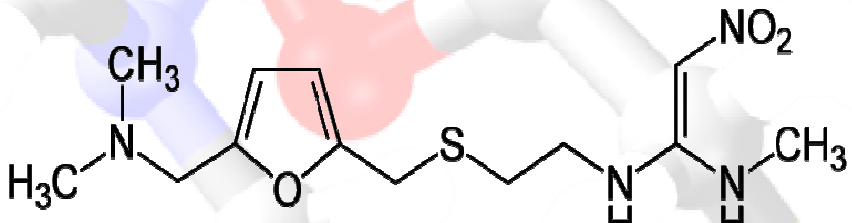
1905 – Henry Dale

Premio Nobel 1988



R Ganellin, W Duncan, Obituary James Black (1924-2010*), Nature* **2010**, *464*, 1292; CPPage, J Schaffhausen, NP Shankley, The scientific legacy of Sir James W. Black, *TiPS* **2011**, *32*, 181;

"... when it comes to drug discovery you're not trying to make complicated molecules, but make molecules that will be effective ... "



ranitidina

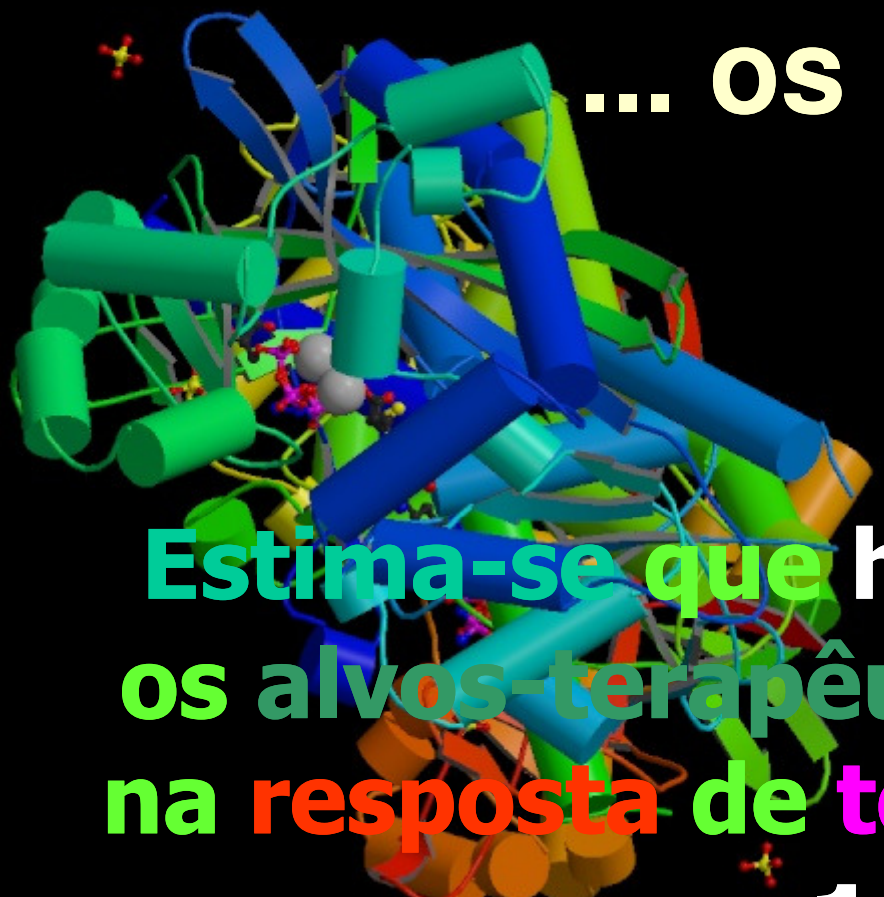
Barry J. Price

Research Director Glaxo (1967-1995)

Os fármacos atuam em alvos terapêuticos...

Química Medicinal

... os biorreceptores.



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

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

Universidade Federal do Rio de Janeiro

A maioria dos biorreceptores dos fármacos contemporâneos são enzimas …

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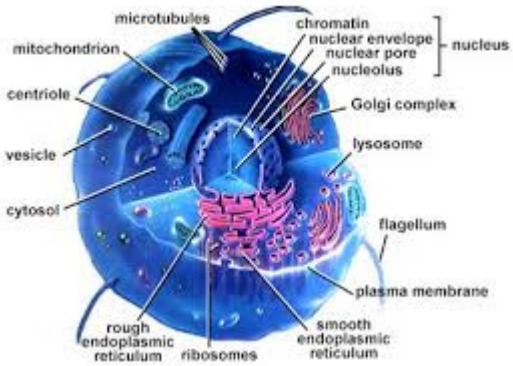
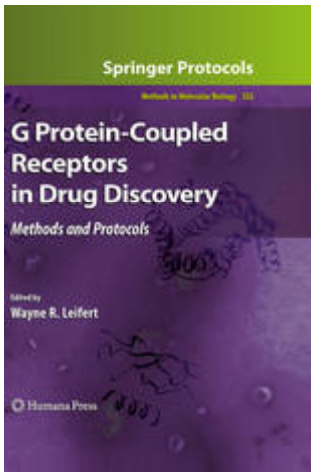
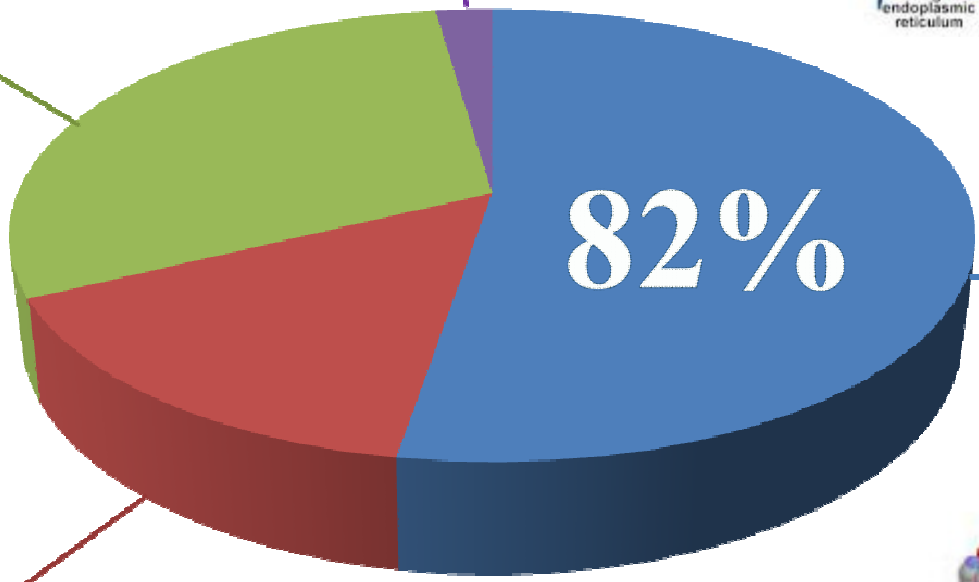


receptores nucleares
150

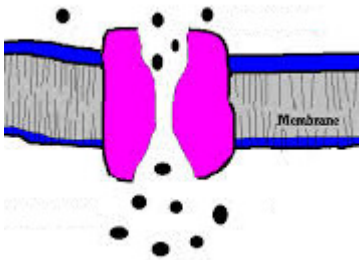
receptores acoplados a proteína G (GPCR)
2000

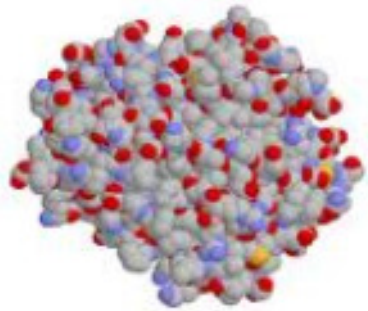




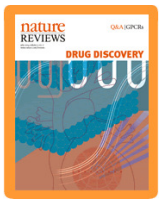
enzimas
3500

canais iônicos
1000



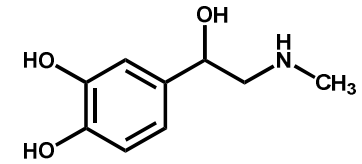


Química
Medicinal



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

O Prêmio Nobel de Química (2012)



Robert J. Lefkowitz

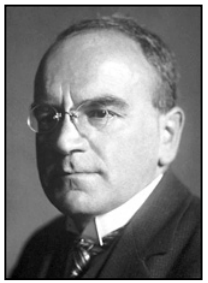
Brian K. Kobilka

a) Howard Hughes Medical Institute and Duke University Medical Center, EUA

b) Stanford University, School of Medicine, Stanford, EUA

"for studies of G-protein-coupled receptors"

Uma inovação bilionária: *as estatinas*



Heinrich Wieland
1877-1957

1927

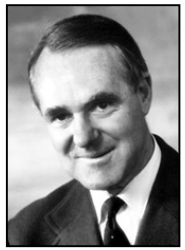
Konrad Bloch
1912-2000

Adolf OR Windaus
1876-1959

1928

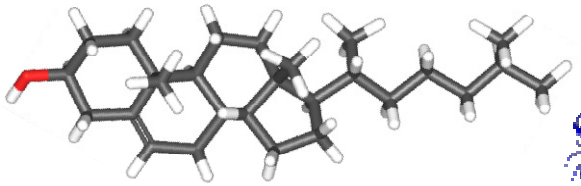
Feodor FK Lynen
1911-1979

1964

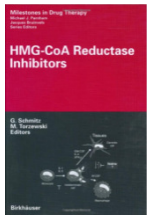


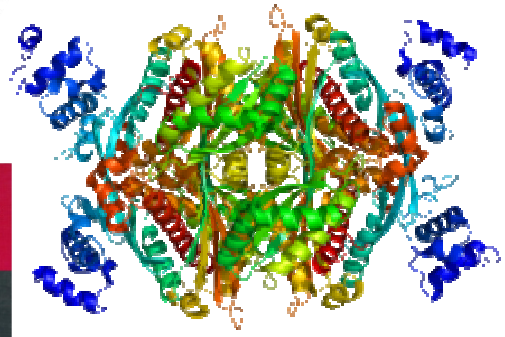
John Cornforth
1917-2013

1975

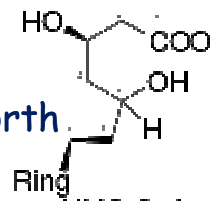


colesterol
1951

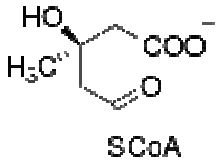




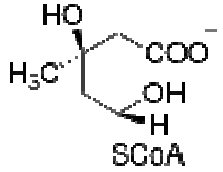
HMGCoAR



HMG CoA
Reductase inhibitor



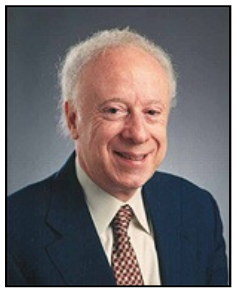
HMG CoA



Mevaldyl CoA transition
state intermediate

1985

LDL



Joseph L Goldstein

Michael S Brown

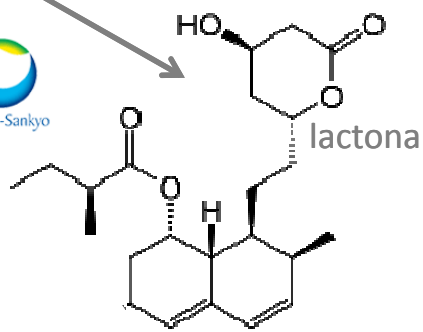
University of Texas, Dallas

J Med Chem
1985, *28*, 1

Akira Endo

Albert Lasker Award
for Clinical
Medical Research, 2008*

Daiichi-Sankyo

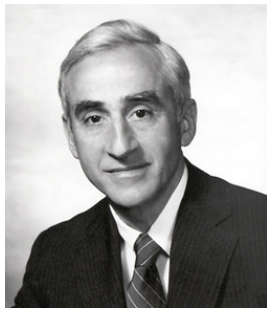


lactona

Mevilonina
/compactina

Química
Medicinal

* A Endo, A gift from nature: the birth of the statins, *Nature Medicine* **2008**, *14*, 26



Dr P. Roy Vagelos

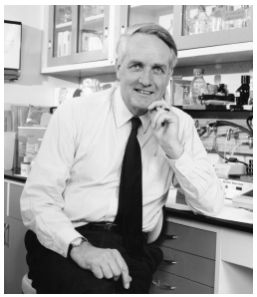
Vice-Presidente Pesquisa
Farmacêutica da Merck
(Presidente & CEO)

1976 - confidentiality agreement

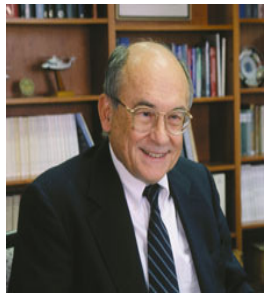
MERCK

Daiichi-Sankyo

Alfred W. Alberts

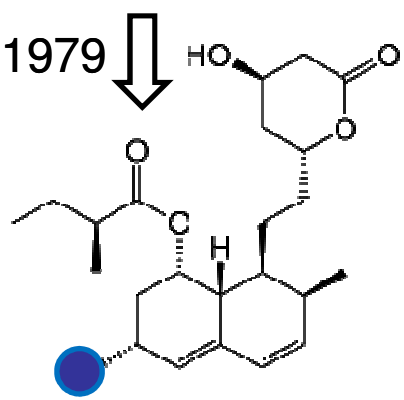


Georg Albers-Schönberg



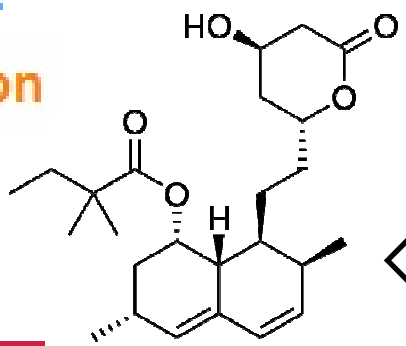
Arthur A. Patchett
Diretor do Departamento
New Lead Discovery
Alfred Burger Award 2002

1979



Aspergillus terreus

lovastatina



simvastatina
first-in-class

1982

ZOCOR (SIMVASTATIN)

therapeutic innovation

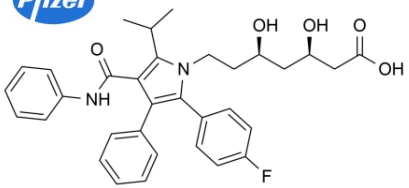
"blockbuster mentality"

J. Med. Chem. **1986,** *29,* 849

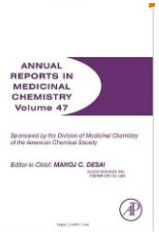
1991

atorvastatina
fifth-in-class

Pfizer



Química Medicinal



[A descoberta da lovastatina](#)
[Linha-do-tempo-da-quimica-medicinal](#)

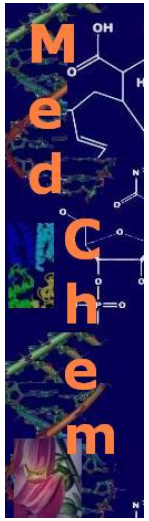
> 45 milhões de pessoas usaram estatinas (2005)

PS Anderson, Reflexions on medicinal chemistry at Merck, West Point, *Annu Rept Med Chem* **2012**, *47*, 3

Estatinas

Universidade Federal do Rio de Janeiro

Atorvastatina



1985 - Bruce Roth
Warner-Lambert
2013 SCI Perkin Medal

1991

Química Medicinal

1991 → 2011

ácido (*N*-pirrol)-3,5-di-hidróxi-heptanóico

Síntese: *ca.* 200 toneladas/ano

HMGCo-AR IC_{50} = 8,2 nM

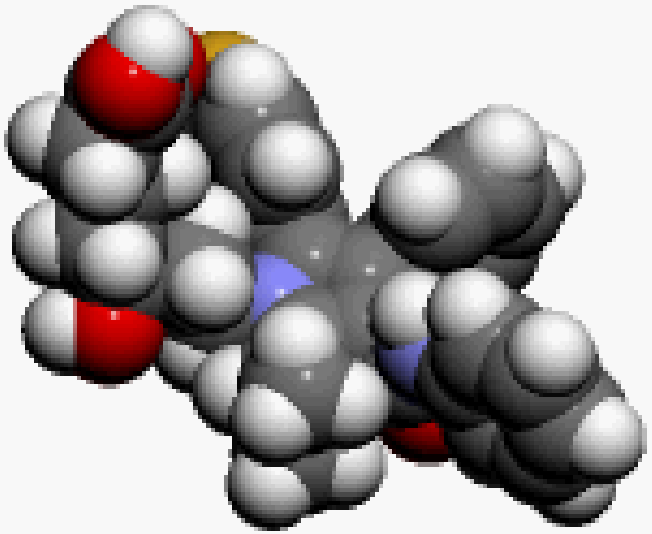
Fármaco recordista mundial em vendas: US$ 150 bilhões

B. D. Roth, *Progr. Med. Chem.* **2002**, *40*, 1-22
B. D. Roth, et al., *J. Med. Chem.* **1990**, *33*, 21-31

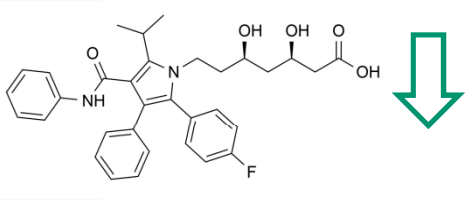
Atorvastatina

sintetizada em 1985, por Bruce D. Roth,
na Parke-Davis Warner-Lambert Co.
Patent US 5273995 Pfizer (1991)

19 etapas; 5% rendimento

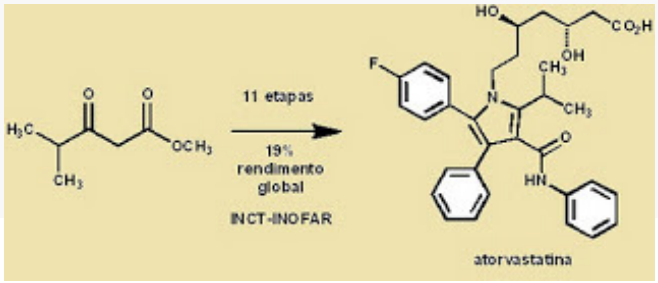


Estudo de rotas de síntese, a partir de intemediários primários de menor custo, de fármacos genéricos



Professor **Luiz Carlos Dias**
& Dr Adriano Siqueira Vieira
IQ, UNICAMP

11 etapas; 19% rendimento; 5g escala



- **INPI Patente 018110015039, 2011 (BR)**
  Nova rota de síntese da atorvastatina cálcica usando novos intermediários (25/04)

INCT-INOFAR: *www.inct-inofar.ccs.ufrj.br*

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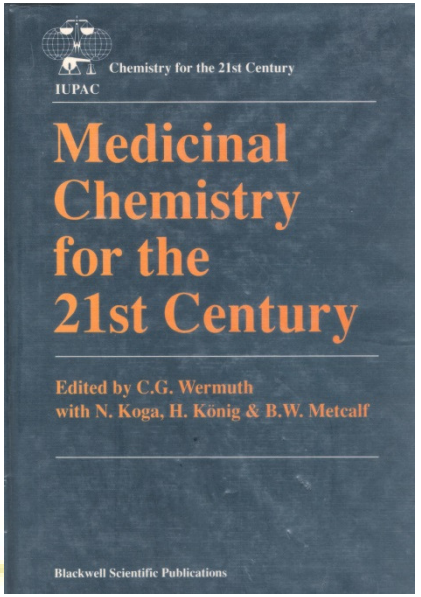
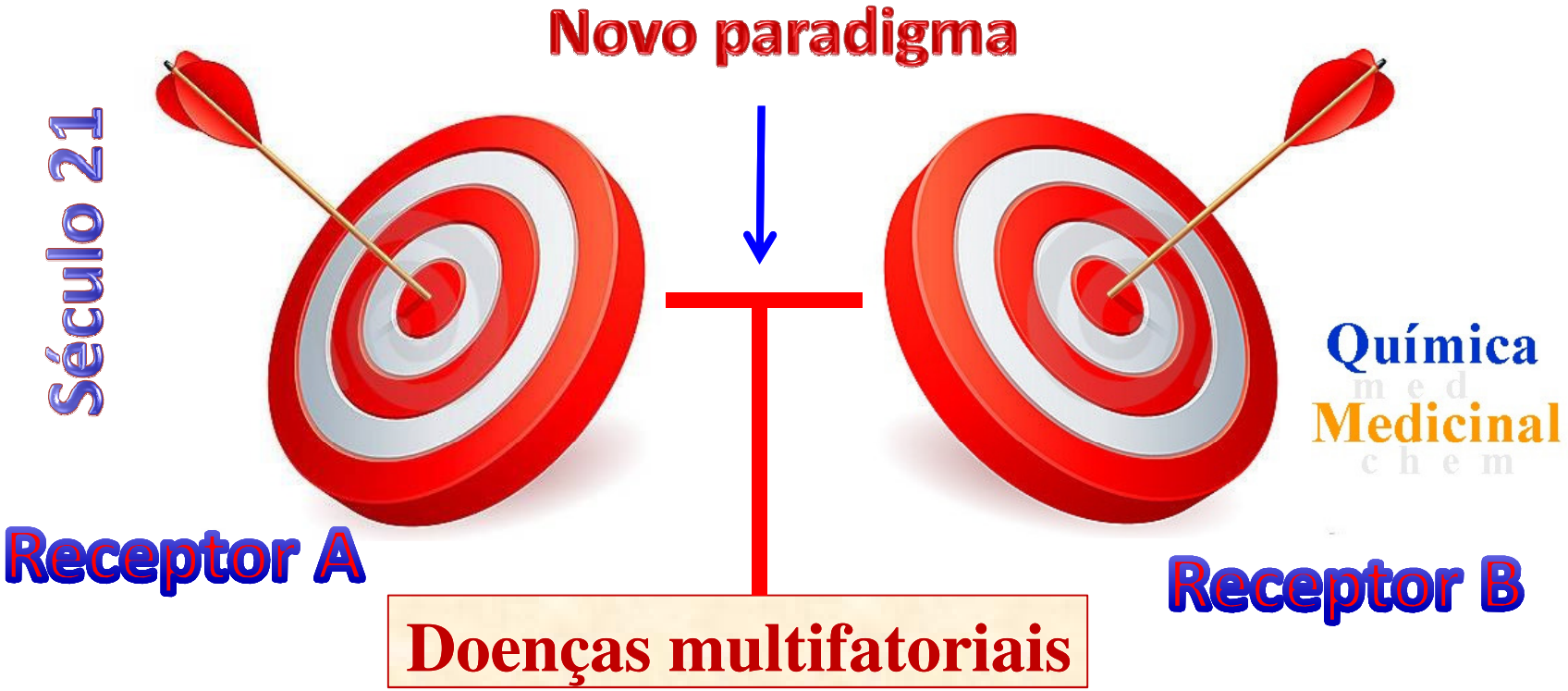
Fármacos do século 21



Química
m e d
Medicinal
c h e m

Fármacos do século 21



O desenho racional de fármacos multi-alvos depende da capacidade de combinarem-se padrões farmacofóricos múltiplos, capazes de terem reconhecimento molecular pelos receptores envolvidos na patologia multifatorial.

Y Bansal, O Silakari, **Multifunctional compounds**: Smart molecules for multifactorial diseases, *Eur. J. Med. Chem.* **2014**, *76*, 31; JL Medina-Franco et al. Shifting from the single to the **multitarget paradigm** in drug discovery, *Drug Discov. Today* **2013**, *18,* 495; C Hiller, J Kühhorn, P Gmeiner, Class A G-Protein-Coupled Receptor (GPCR) Dimers and Bivalent Ligands, *J. Med. Chem.* **2013**, *56*, 6542; G Phillips, M Salmon, Bifunctional compounds for the treatment of COPD, *Annu. Rev. Med. Chem*. **2012**, *47*, 209; S Reardon, A world of chronic disease, *Science* **2011**, *333*, 558.

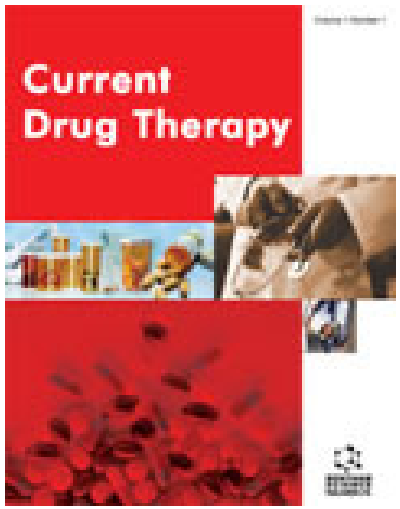
New Insights for Multifactorial Disease Therapy: The Challenge of the Symbiotic Drugs

Eliezer J. Barreiro and Carlos Alberto Manssour Fraga

Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, P.O. Box 68023, 21944-971, Rio de Janeiro, RJ, Brazil.

Abstract: Some physiopathological processes involved in the genesis of diseases could suggest the necessity of designing bioligands or prototypes that aggregate, in only one molecule, dual pharmacodynamical properties, becoming able to be recognized by two elected bioreceptors. This approach can have distinct aspects and, when a novel ligand or a prototype acts in two elected targets belonging to the same biochemical pathway, *e.g.* arachidonic acid cascade, it receives the denomination of dual or mix agent. On the other hand, if these two targets belong to distinct biochemical routes and both are related to the same disease, we can characterize the agents able to modulate it as symbiotic ligands or prototypes. In the present work, we provide some examples and applications of the molecular hybridization concept for the structural design of new symbiotic ligands and prototypes, especially those applied in the treatment of chronic-degenerative disorders.

Key Words: Symbiotic drugs; molecular hybridization; multifactorial diseases; therapeutic innovation; drug design; dual compounds.

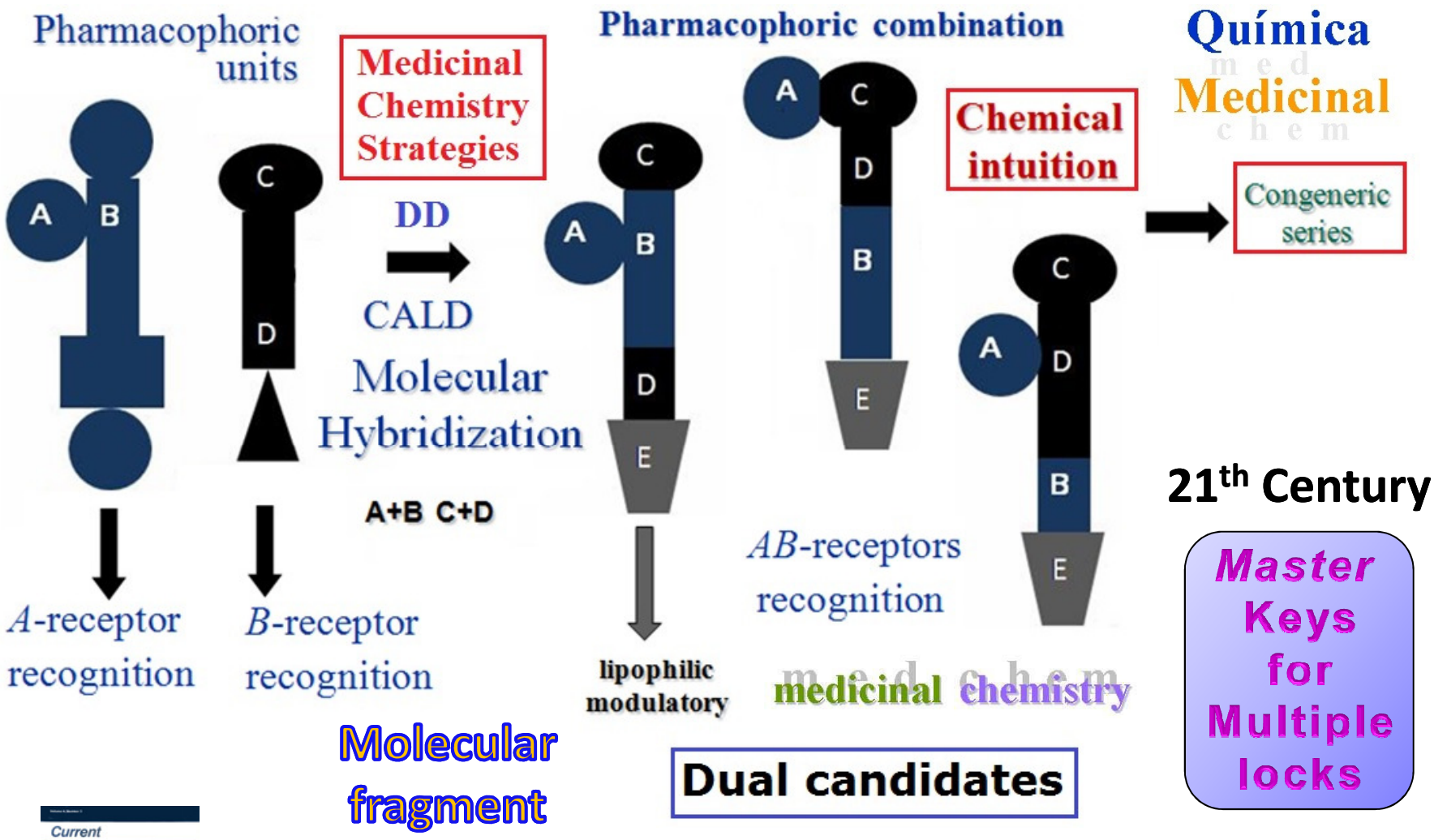


Fármacos simples, não curam doenças complexas!

Química
m e d
Medicinal
c h e m

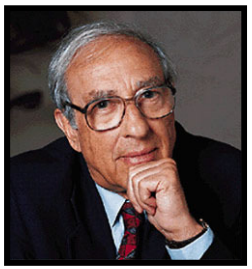
Universidade Federal do Rio de Janeiro

The rational-based design of multiple ligand



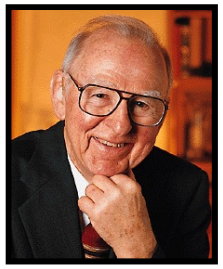
C Viegas-Jr, A Danuello, VS Bolzani, EJ Barreiro, CAM Fraga, Molecular Hybridization: A useful tool in the design of new drug prototypes, *Curr. Med. Chem.* **2007**, *14*, 1829

Inibidores de tirosina-quinases (TK)

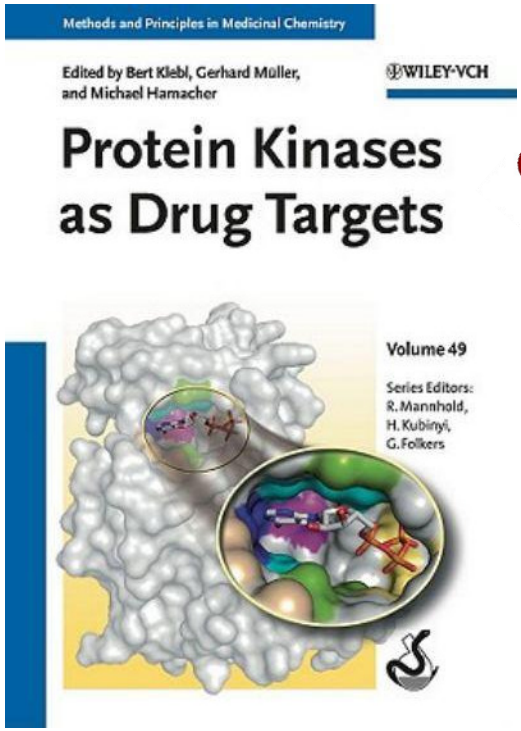


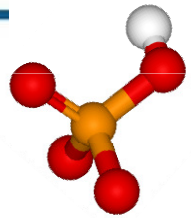
Edmond H Fischer

1992

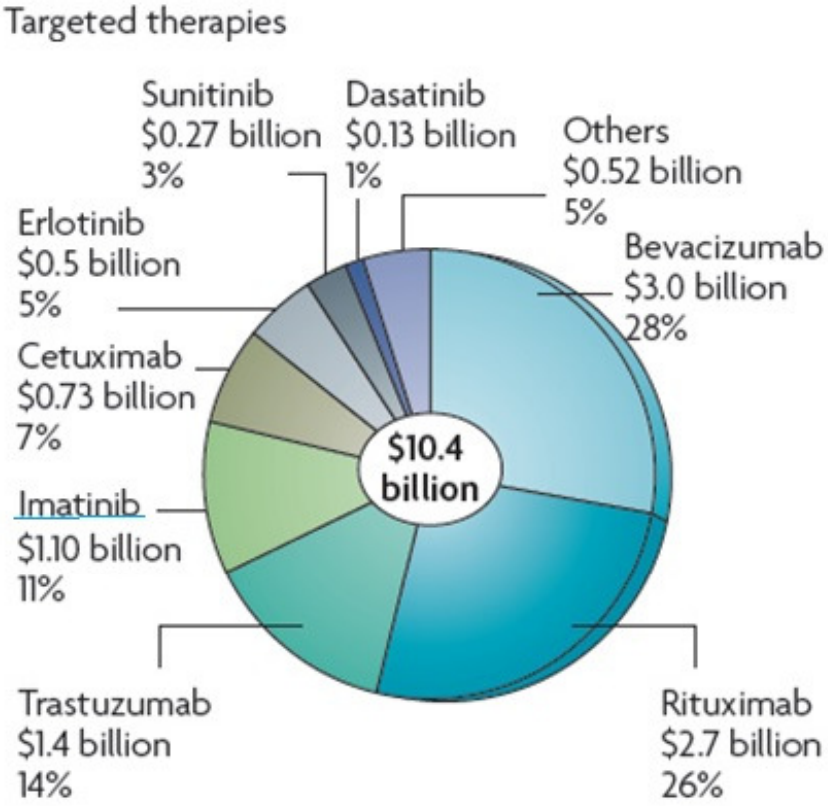


Edwin G Krebs
(1918 –2009)





quinoma



Market for targeted cancer therapies. US sales of targeted therapies share of the US market based on 2009 sales.

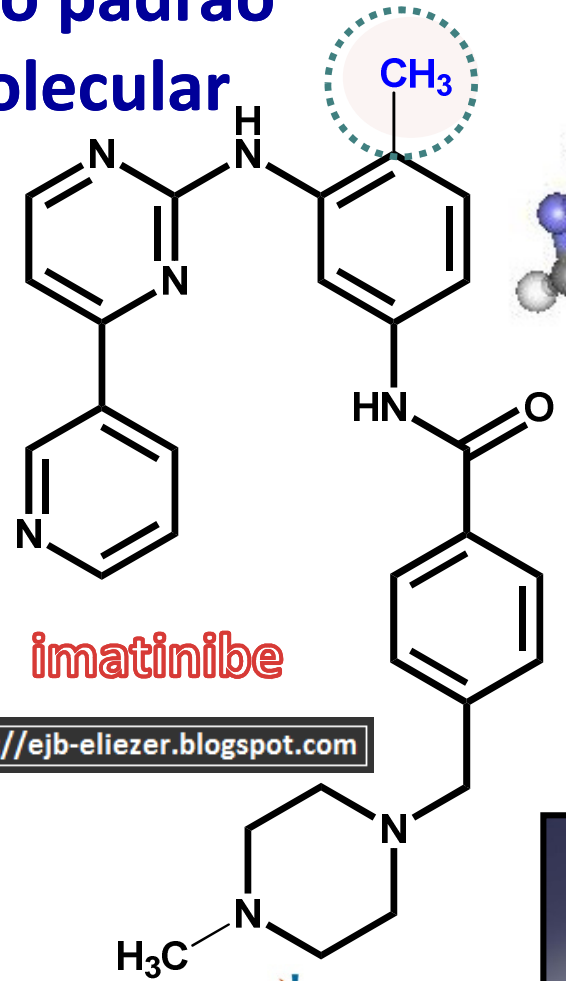
Sources: company reports

Vendas mundiais do imatinibe (2009): US$ 3,95 bi

S. Aggarwal, Targeted cancer therapies, *Nature Rev. Drug Discov.* **2010**, *9*, 427; P. Cohen, Timeline: **Protein kinases** — the major drug targets of the twenty-first century? *Nature Rev. Drug Discov.* **2002**, *1*, 309.

Universidade Federal do Rio de Janeiro

Novo padrão molecular



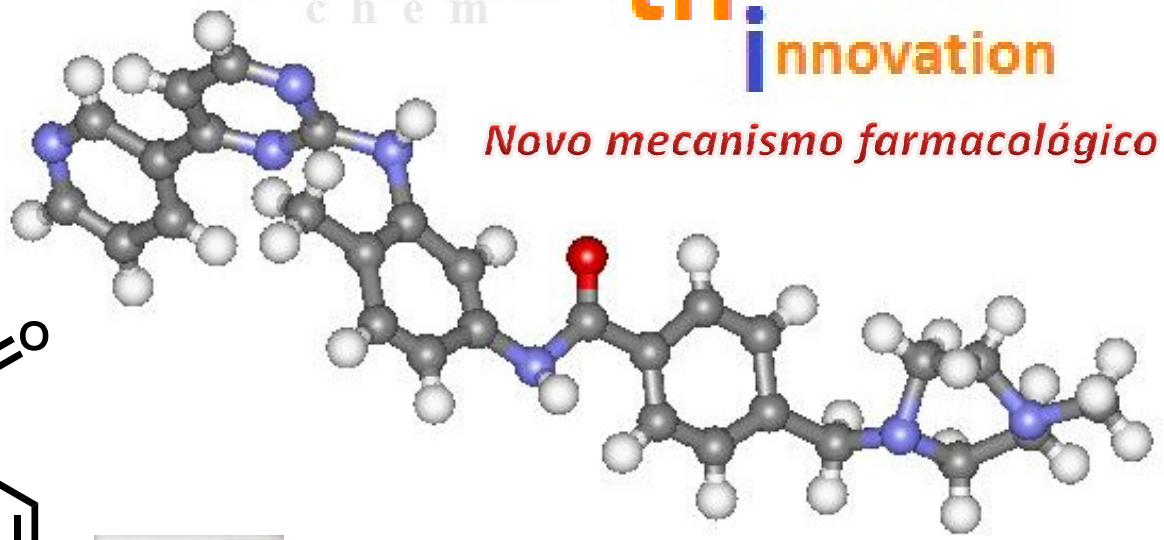
imatinibe

http://ejb-eliezer.blogspot.com

Química Medicinal

therapeutic innovation

Novo mecanismo farmacológico



1988 – Nicholas Lydon, Brian J. Druker & Charles L Sawyers &
1995 - Composto STI571 ++
2001 – Imatinibe (Gleevec^{R}, Novartis)[link]

Leucemia mielóide crônica (CML)

NOVARTIS

imatinibe

Nicholas B. Lydon
Blueprint Medicines Inc*

OREGON HEALTH & SCIENCE UNIVERSITY

Brian J. Druker*
Blueprint Medicines Inc

HHMI HOWARD HUGHES MEDICAL INSTITUTE

Charles L. Sawyers**
Blueprint Medicines Inc

& 2009 - Lasker Foundation Clinical Award (*J. Clin. Invest*. **2009**, *119*, 2863)

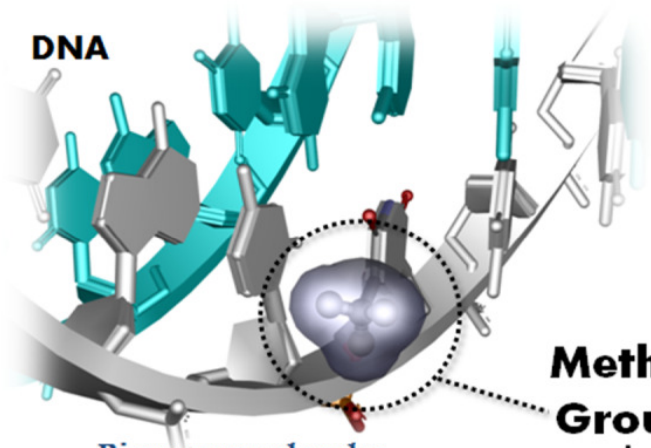
* B. J. Druker has been awarded with the 2012 Japan Prize in Healthcare and Medical Technology;

** C. L. Sawyers was named in 2011, Thomson Reuters Citation Laureate in Medicine;

UFRJ
Universidade Federal do Rio de Janeiro
CHEMICAL REVIEWS
Chem. Rev. 2011, *111*, 5215-5246
REVIEW
Índice de impacto: 41,28

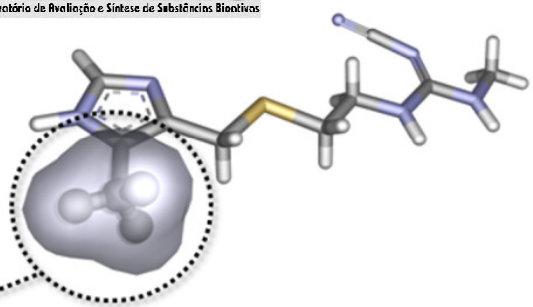
The Methylation Effect in Medicinal Chemistry

E. J. Barreiro, A. E. Kümmerle and C. A. M. Fraga



LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

Química Medicinal



Methyl Group

Biomacromolecules

CH/π interactions from the methyl group of timine. Conformational changes, wich could be involved on maintenance of life.

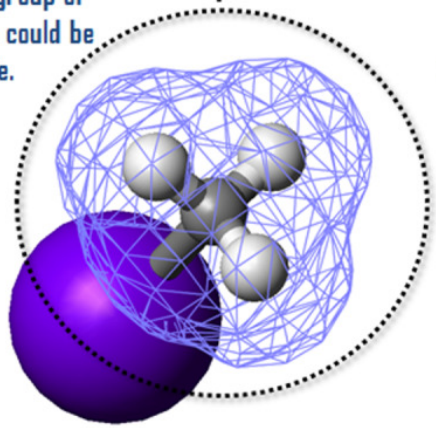
Micromolecules

The inductive eletronic effect of the methyl group is the responsible for the subtype receptors selectivity (H_2x H_1) on cimetidine

CH_3

15 Da

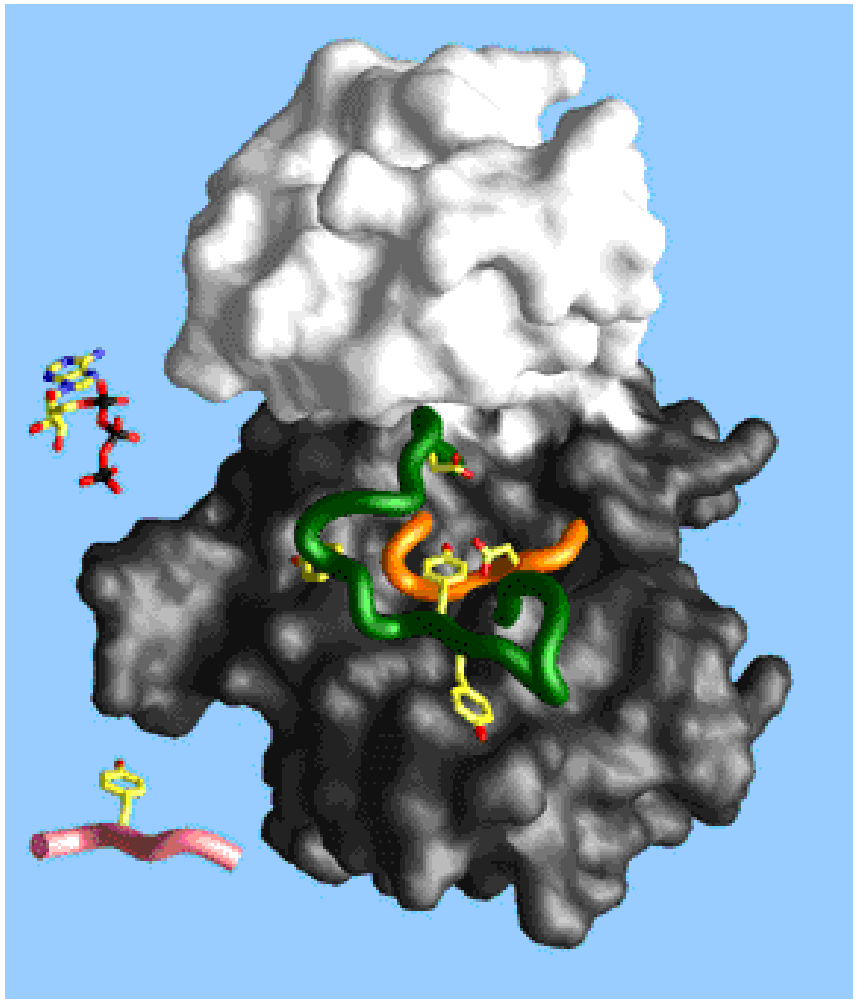
The stereoelectronic effects of the methyl group have great importance on biological events and are widely used by the Medicinal Chemistries in the development of new drugs.



Stereoelectronic Properties

MW = 15,03
MR = 5,65 cm³/mol
π hansch = 0,56
σ hammett = -0,17

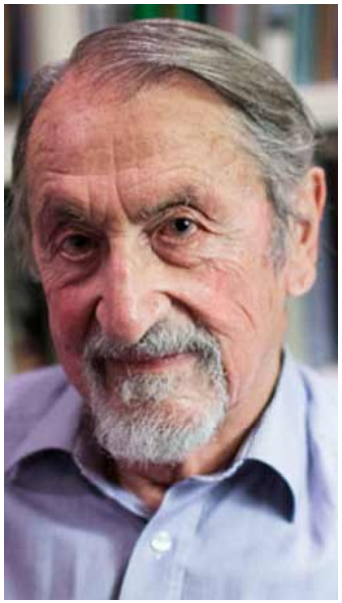
Estrutura 3D do receptor tirosina quinase (TKR)



Química Medicinal

N-terminal lobulo em branco & C-terminal em cinza escuro, sítio de ativação em verde contém:Y1158, Y1162 and Y1163; sítio catalítico em laranja comtém D1132; ATP e o substrato peptídico em rosa. (Hubbard, *EMBO J.* **1997**, *16*, 5572).

O Prêmio Nobel de Química (2013)



Michael Karplus [a]

Arieh Warshel [b]

Michael Levitt [c]

a) Université Strasbourg (FR) & Un Harvard (EUA)
b) University of South California (EUA)
c) University of Stanford (EUA)

" for developing computer models that predict complex chemical reactions"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LASSBio
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Cidade Universitária, ilha do Fundão,
Rio de Janeiro, RJ
Química Medicinal
Creado em 19/04/1994 Laboratório de Avaliação e Síntese de Substâncias Bioativas
A quimioteca do LASSBio tem 1895 moléculas bioativas.
eliezer © 2010

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Revista Virtual de Química

ISSN 1984-6835

Artigo

A história do LASSBio

As Longas Pernas do Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio®; http://www.farmacia.ufrj.br/lassbio): Histórico e Perspectivas

Barreiro, E. J.

Rev. Virtual Quim., **2013**, *5* (2), 266-282. Data de publicação na Web: 19 de janeiro de 2013

http://www.uff.br/rvq

LASSBio® 20 anos
Laboratório de Avaliação e Síntese de Substâncias Bioativas

Química Medicinal

Um exemplo de casa:Novo tinibe dual

Lidia M Lima, Maria L C Barbosa, Stefan Laufer (LASSBio-2013)

Universidade Federal do Rio de Janeiro

Química Medicinal

ureia

aceptor-H

5-methylisoxazole

donor-H

Tivozanib

mh/ms

3-bromoanilino

quinazoline

PD-153035

oral VEGF receptor tyrosine kinase inhibitor

inhibits tyrosine kinase activity of the EGFR

safrole

LASSBio

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classic ring bioisosterism

2-thiazole

aceptor-H

donor-H

classical functional groups isosterism

quinazoline

molecular simplification

VEGF & EGFR inhibitor

M L C Barbosa, L M Lima, R Tesch, C M R Sant'Anna, F Totzke, M HG Kubbutat, C Schächtele, S A Laufer, E J Barreiro, Novel 2-chloro-4-anilino-quinazoline derivatives as EGFR and VEGFR-2 dual inhibitors, *Eur J Med Chem* **2014**, *71*, 1-14.

Universidade Federal do Rio de Janeiro

Novel 2-chloro-4-anilino-quinazoline derivatives as EGFR and VEGFR-2 dual inhibitors

Maria Letícia de Castro Barbosa [a,b], Lídia Moreira Lima [a,b], Roberta Tesch [a], Carlos Mauricio R. Sant'Anna [c], Frank Totzke [d], Michael H.G. Kubbutat [d], Christoph Schächtele [d], Stefan A. Laufer [e], Eliezer J. Barreiro [a,b,*]

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[d] ProQinase GmbH, Freiburg, Germany
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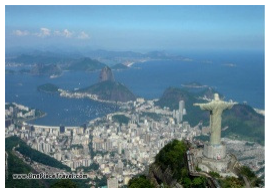
European Journal of Medicinal Chemistry 71 (2014) 1–14

Química Medicinal



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LASSBio-1630

Novel molecular pattern with EGFR/VEGFR dual activity!

Atividade dual

IC_{50} (EGFR) = 0,90 µM

IC_{50} (VEGFR) = 1,17 µM

Depósito de patente no INPI

MLC Barbosa, Novos derivados quinazolínicos funcionalizados inibidores duais das tirosina cinases receptoras EGFR & VEGFR-2, Tese de Doutorado, Instituto de Química, UFRJ, 2013.

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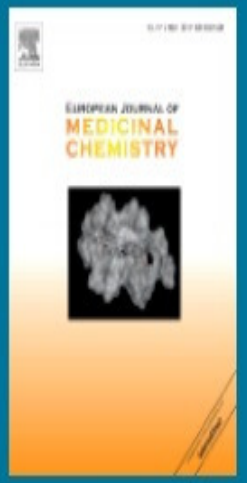

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Novel 2-chloro-4-anilino-quinazoline derivatives as EGFR and VEGFR-2 dual inhibitors

Maria Letícia de Castro Barbosa[a, b], Lídia Moreira Lima[a, b], Roberta Tesch[a], Carlos Mauricio R. Sant'Anna[c], Frank Totzke[d], Michael H.G. Kubbutat[d], Christoph Schächtele[d], Stefan A. Laufer[e], Eliezer J. Barreiro[a, b]

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3. Novel 2-chloro-4-anilino-quinazoline derivatives as EGFR and VEGFR-2 dual inhibitors

Maria Letícia de Castro Barbosa | Lídia Moreira Lima

Química med Medicinal chem

2014 - Prêmio melhor painel congresso Frontiers in Medicinal Chemistry,Tübingen,DE

"...discovery *consists* of seeing what everybody else **has seen** ***and*** **thinking what nobody else** has not thought..."

1937

Albert Szent-Györgiy **(1893-1986)**


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A Química
Medicinal
é simplesmente
fascinante!

Epílogo

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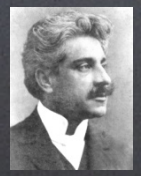
"Meditai se só as nações fortes podem fazer Ciência

ou se é a Ciência que as fazem fortes"



Oswaldo Cruz

1872-1917

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Rio2016
Muito obrigado, pela atenção.
Cristo Redentor, uma das sete maravilhas do mundo moderno