A Química Medicinal & A Descoberta de Fármacos

2ª Semana de Química
Universidade Federal de Uberlândia
21 de julho de 2014

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Professor Titular

U F R J

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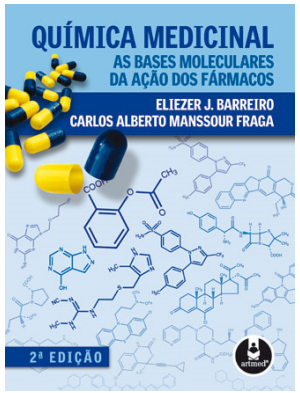
Instituto Nacional de Ciência e Tecnologia
de Fármacos e Medicamentos
INCT-INOFAR

Química Medicinal

Universidade Federal do Rio de Janeiro

Definição

estuda os fatores moleculares relacionados ao modo de ação dos fármacos, incluindo a compreensão da relação entre a estrutura química e a atividade (SAR), além das propriedades que governam sua absorção, distribuição, metabolismo, eliminação (ADME) e toxicidade.



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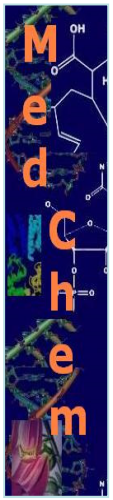
THE ROLE OF THE MEDICINAL CHEMIST IN DRUG DISCOVERY — THEN AND NOW

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,

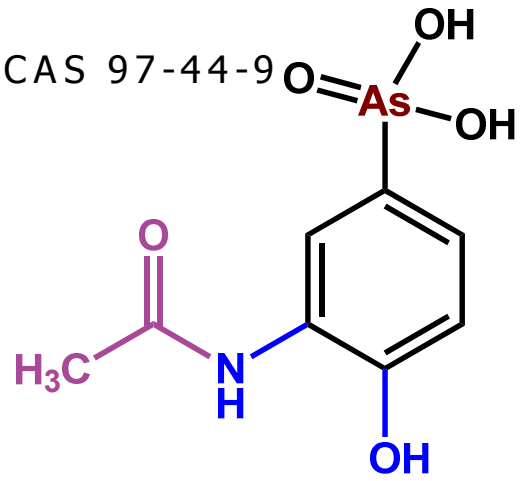
Nature Rev. Drug Disc. **2004**, *3*, 853.

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)

1ª *publicação* sobre *SAR(REA)*

Curare and Curare-like Agents.

Prêmio Nobel de Fisiologia/Medicina 1957

Daniel Bovet
1907-1992

Sulfonamidas, anti-histamínicos.

J-P Fourneau, Ernest Fourneau foundateur de la Chimie Pharmaceutique française, *Revue de l´Histoire de la Pharmacie*, t.XXXIV, nº 275, 335-355; A Oliverio, Daniel Bovet. 23 March 1907-8 April 1992, *Biographical Memoirs of Fellows of the Royal Society*, 39, 60–66 (1994).

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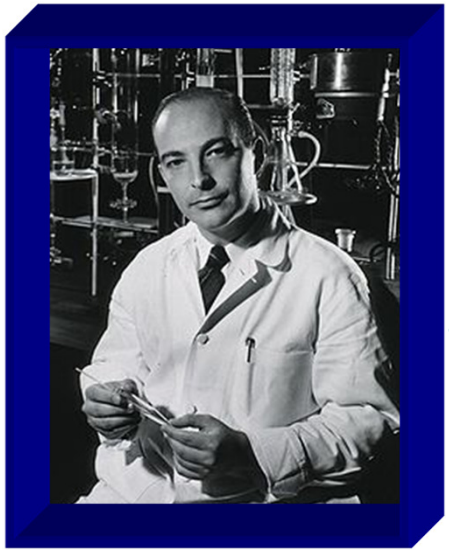


Prêmio Nobel, 1959

1987

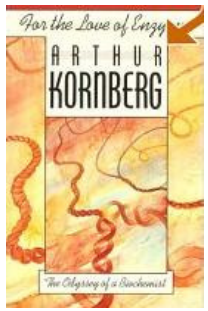
The Two Cultures: Chemistry and Biology[1]

Arthur Kornberg

Department of Biochemistry, Stanford University, Stanford, California 94305

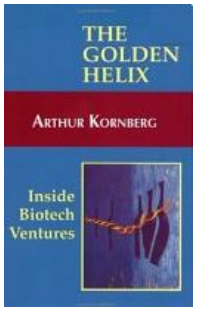
Received July 14, 1987

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…***

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



Química Medicinal

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

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UFRJ

med Química Medicinal chem

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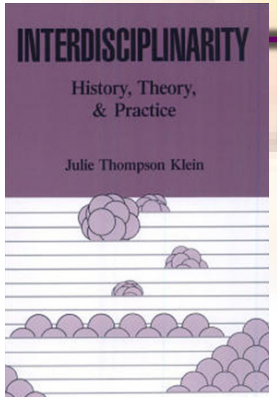
A **interdisciplinaridade**

exige novos arranjos temporais & institucionais, para plena capacitação profissional !

⇩

A cadeia de inovação em fármacos é complexa e interdisciplinar!



"...is far more than a relatively recent addition to educational jargon. It´s a mode of thought..."

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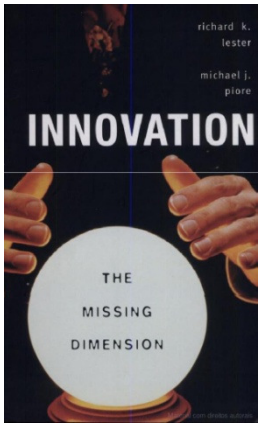
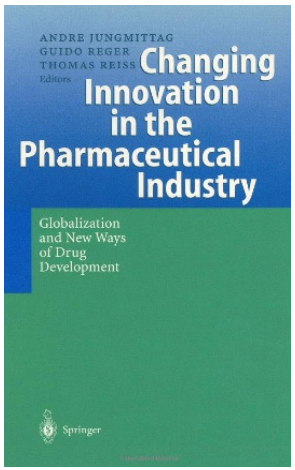
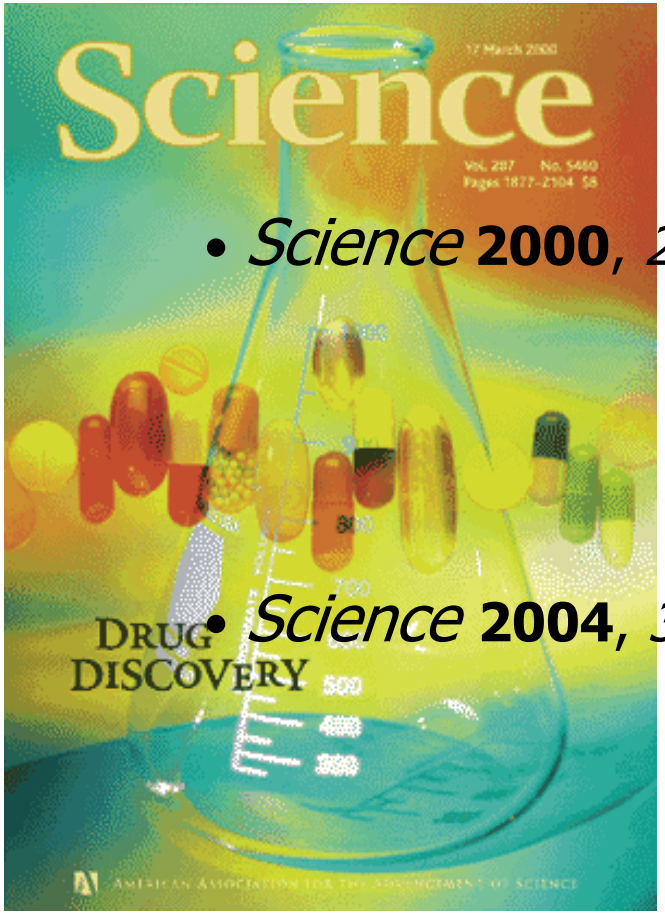




A inovação tecnológica é um dos processos mais dinâmicos da atividade industrial que gera riqueza. ESTE dinamismo é acentuado na inovação farmacêutica que depende da *efetiva* interação entre **Ciência** & Tecnologia.

A inovação farmacêutica...



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

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

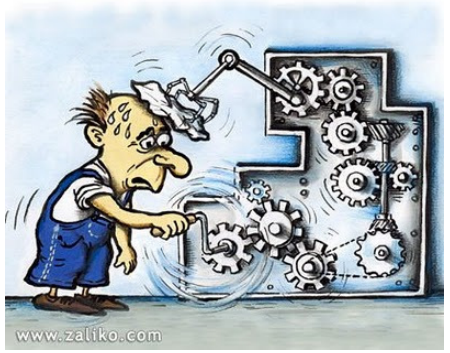
...depende do conhecimento científico!

A inovação farmacêutica...

Descoberta

(Descobrir)

ato ou efeito de descobrir (algo), retirando-lhe a proteção, a cobertura, a capa ou invólucro que cobre, esconde; descobrimento; descobridores;



(Inventar)

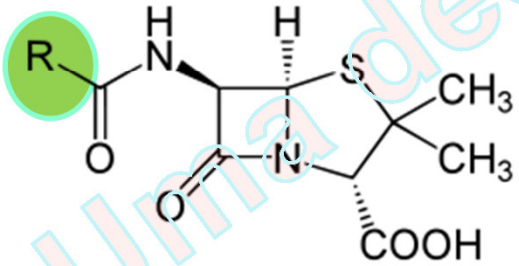
criação de algo através do conhecimento científico, técnico; coisa inventada; invento; inventores;

Invenção

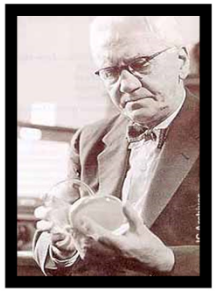
Molécula salva-vidas...

Antibióticos β-lactâmicos

1877 – L. Pasteur
1897 - Ernest Duchesne, Lyon
1928 – A Fleming, Londres
1939 – Florey & Chain
1943 – RB Woodward, R Robinson
1945 - Dorothy C. Hodgkin
1948 – Patente de processo
1957 –John Sheehan, MIT



Penicilina



Alexander Fleming
1881-1955

Howard W. Florey
1898-1968

Dorothy C. Hodgkin
1910-1994

antibioticoterapia

O acaso ajuda a sorte

E. Boris Chain
1906-1979

1945

EB Chain *et al.*, *Lancet* **1940**, *2*, 226

1964

MD Vargas, *Rev Virtual Quim* **2012**, *4*, 85

Fungos

Uma descoberta fantástica!

Am J Physiol 1948, 153, 586

Raymond Ahlquist (1914

A STUDY OF THE ADRENOTROPIC RECEPTORS

RAYMOND P. AHLQUIST

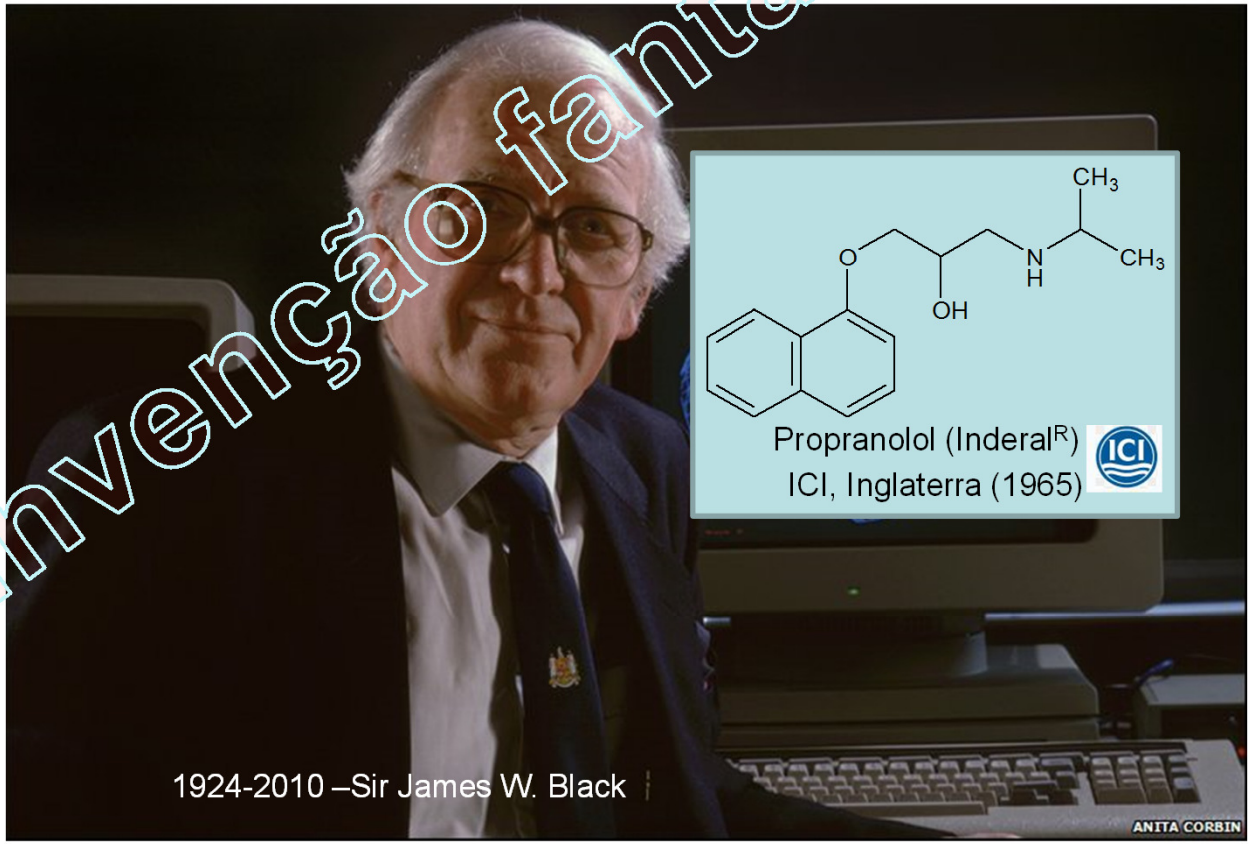
From the Department of Pharmacology, University of Georgia School of Medicine

AUGUSTA, GEORGIA

Henry Dale

1936

Premio Nobel 1988



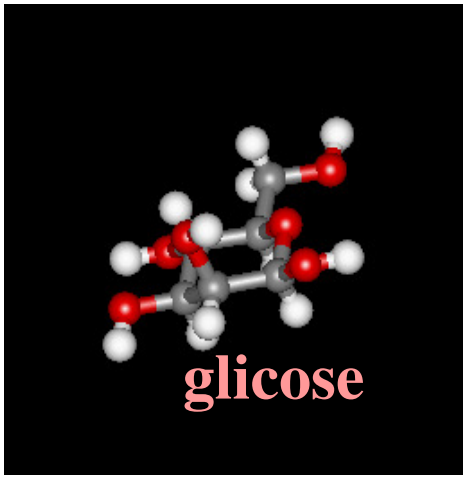
R Ganellin, W Duncan, Obituary James Black (1924-2010), *Nature* **2010**, *464*, 1292; CPPage, J Schaffhausen, NP Shankley, The scientific legacy of Sir James W. Black, *TiPS* **2011**, *32*, 181;

O Modelo Chave-Fechadura

medicinal chemistry

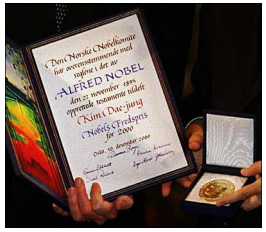
LOCK & KEY CONCEPT

(Emil Fischer, 1894)



carboidratos

1902

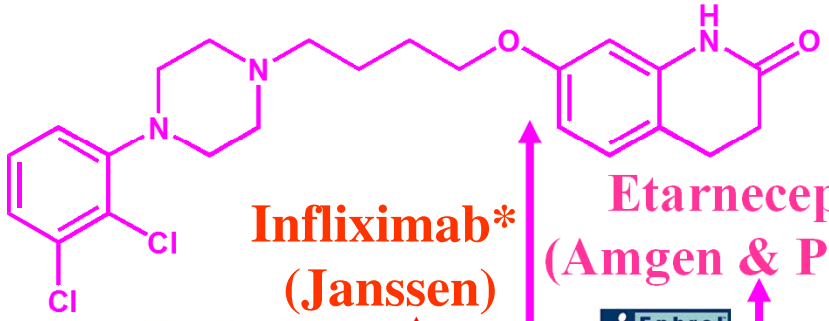


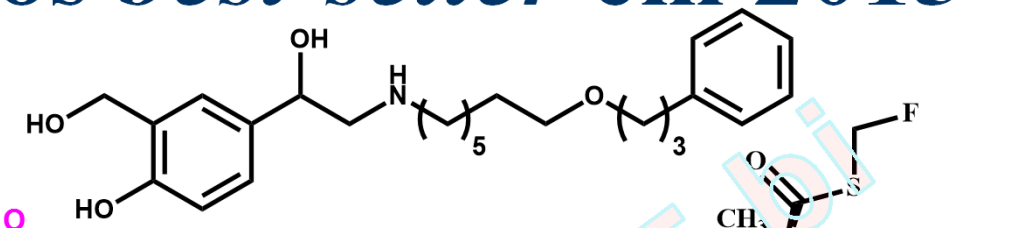
"Em termos figurados, eu gostaria de dizer que enzima e glicosído tem que encaixar como uma chave-fechadura, de maneira a interagir quimicamente uma com a outra".

Este modelo influenciou decisivamente o processo de descoberta de novos fármacos ao longo do século XX.

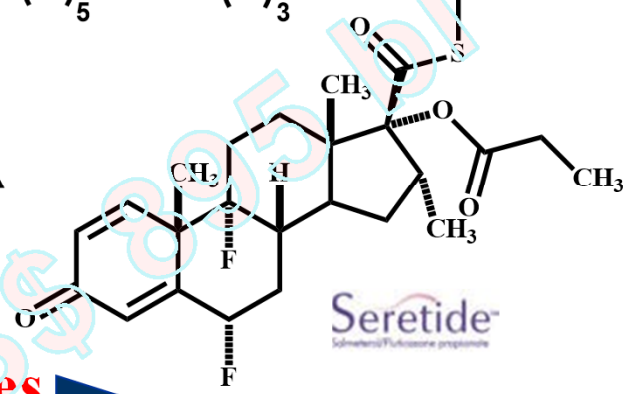
Os medicamentos *best-seller* em 2013

Aripiprazola (BMS)





fluticazona
salmeterol
(GSK)



Infliximab*
(Janssen)

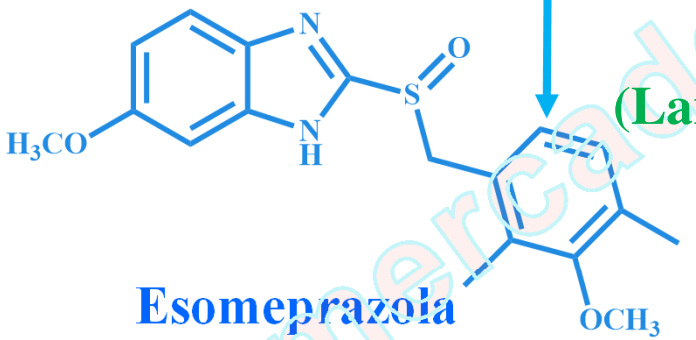
Remicade
INFLIXIMAB

Etarnecept*
(Amgen & Pfizer)

Enbrel
etanercept

em US$ bilhões

1	2,0	7,7	7,8	7,8	7,9	7,9	8,2	9,2	9,8	66,3



Esomeprazola
(AZ)

Insulina
(Lantus, Sanofi)

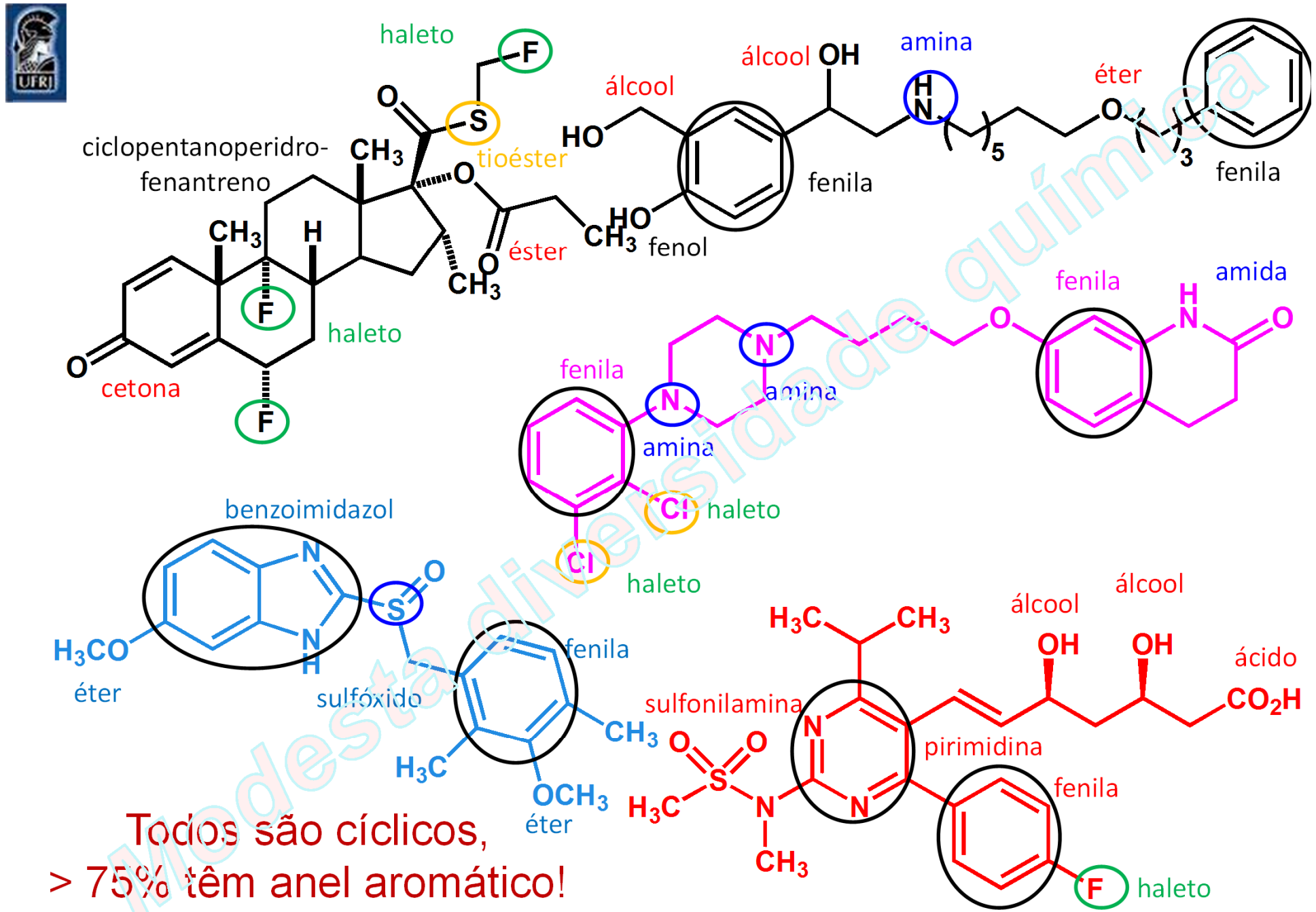
Rosuvastatina (AZ)

Adalimumab*
(Abbott)

HUMIRA

* Biofármacos:
anti-TNFα

Fonte:http://www.statista.com/statistics



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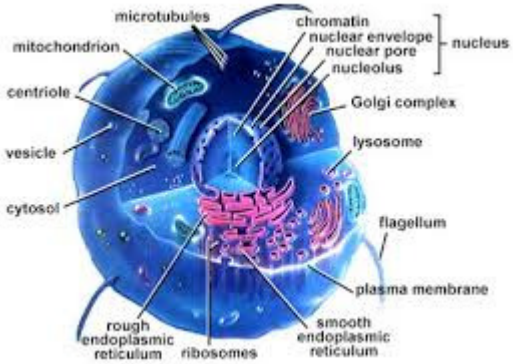
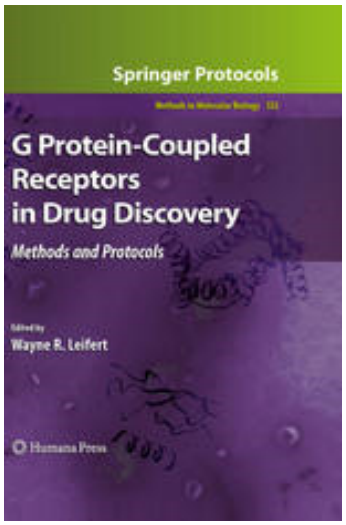
Os *medicamentos* foram uma das principais invenções do século XX !

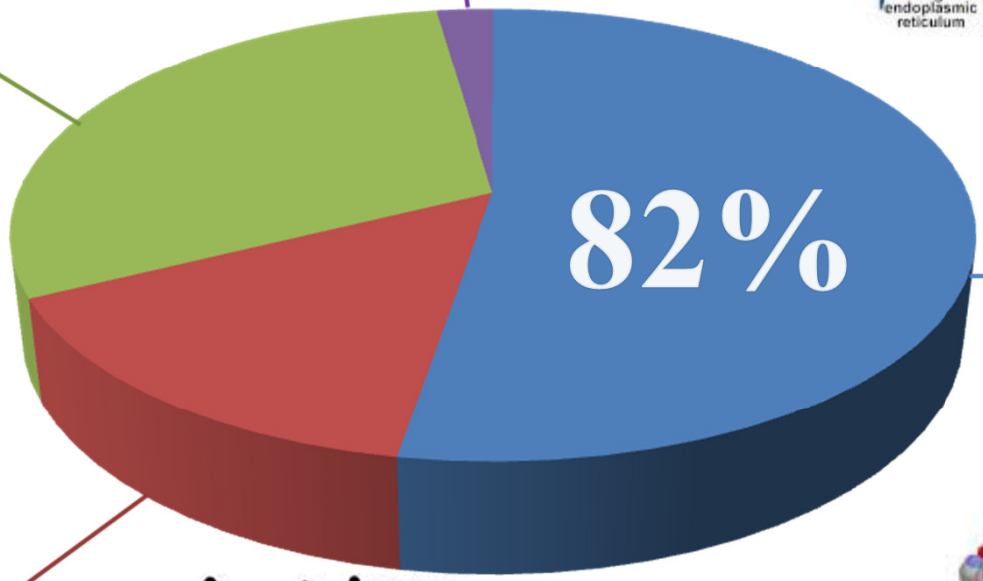
A maioria dos biorreceptores dos fármacos contemporâneos são enzimas …



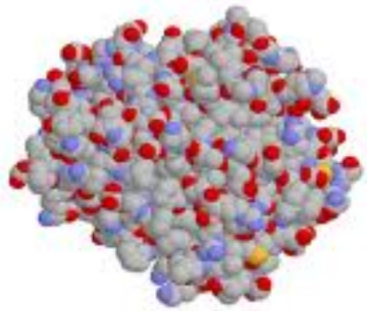
receptores nucleares
150

receptores acoplados a proteína G (GPCR)
2000

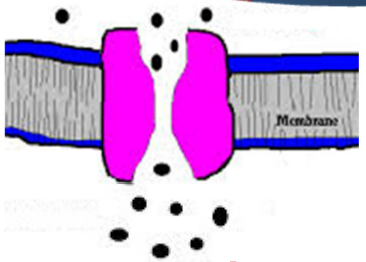




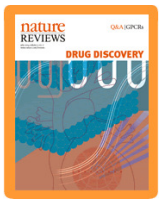
enzimas
3500



canais iônicos
1000



O total dos biorreceptores dos fármacos são 543!



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

The Nobel Prize in Chemistry 2012

Photo: U. Montan

Robert J. Lefkowitz

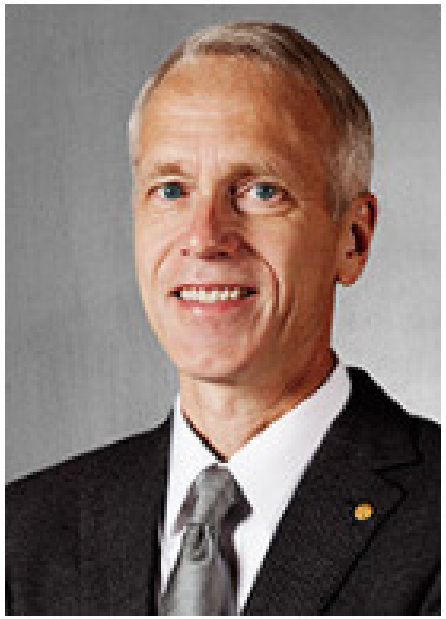
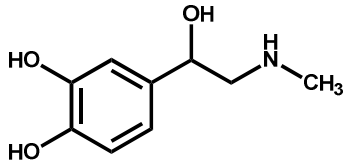


Photo: U. Montan

Brian K. Kobilka



[a] Howard Hughes Medical Institute and Duke University Medical Center, Durham, NC, USA

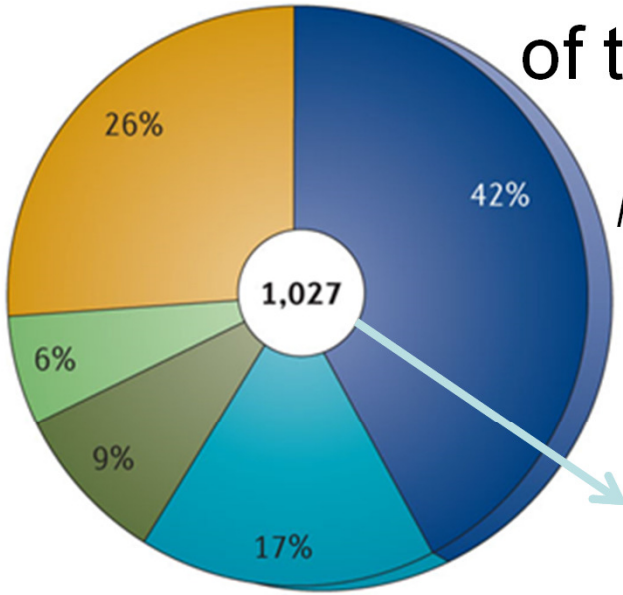
[b] Stanford University School of Medicine, Stanford, CA, USA

"for studies of G-protein-coupled receptors"

Novelty in the target landscape of the pharmaceutical industry*

P. Agarwal, P. Sanseau, L. R. Cardon

Nature Rev. Drug Discov. **2013**, *12*, 575--576



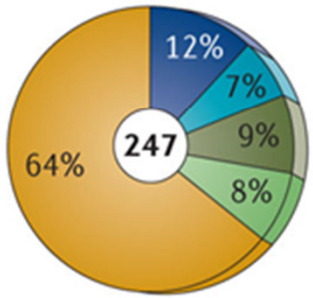
A percentagem dos alvos foi tabulada pelo número de empresas que estão estudando-os (apenas *h*-alvos foram tabulados)

Número total de alvos estudados em programas de pesquisa nas empresas farmacêuticas

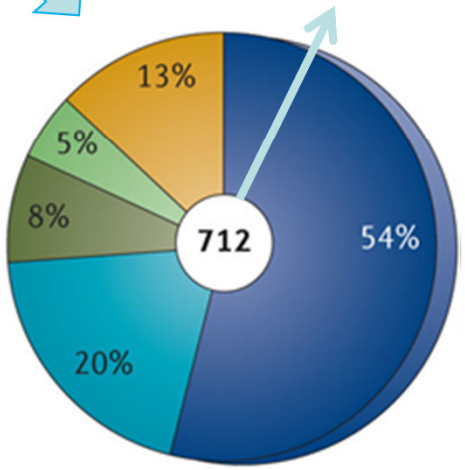
Alvos estudados por muitas organizações

β-sítio da APP-clivagem enzima 1 (BACE1), α7-nAChR, GPR119, mGluR5, H_3R, Microtúbulo associado a PTN tau (MAPT)

Alvos estudados por 5 ou mais organizações



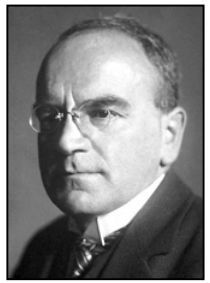
247 são alvos "comprovados" (que tem fármaco no mercado)



712 são alvos "novos" (sem fármacos no mercado)

* *Inter-alia:* Pfizer, J& J, Novartis, Bayer, Roche, Merck, Sanofi, GSK, Abbott, AZ

Uma inovação terapêutica bilionária: *as estatinas*

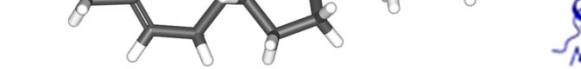


Heinrich Wieland
1877-1957

1927

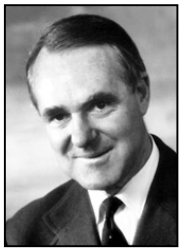
Adolf OR Windaus
1876-1959

1928

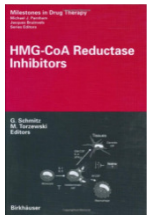


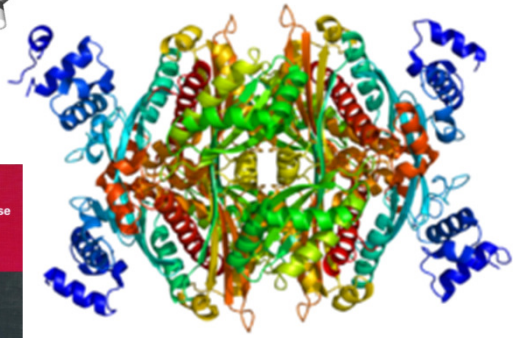
colesterol
1951

1975

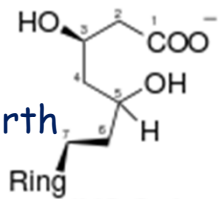


John Cornforth
1917-2013

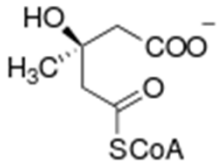




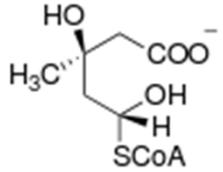
HMGCoAR



HMG CoA
Reductase inhibitor



HMG CoA



Mevaldyl CoA transition state intermediate

Konrad Bloch
1912-2000

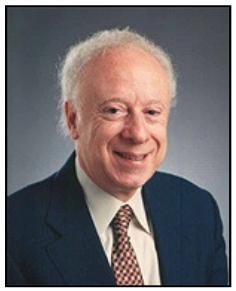
Feodor FK Lynen
1911-1979

1964

1985

LDL

J Med Chem
1985, *28*, 1



Joseph L Goldstein

Michael S Brown

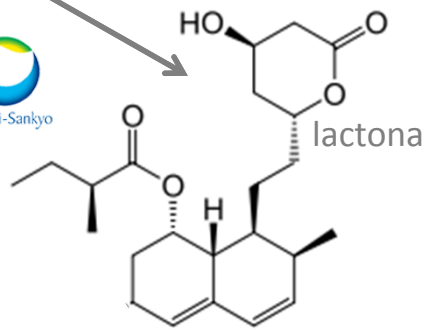
University of Texas, Dallas

Fungos

Akira Endo

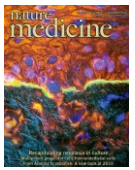
Albert Lasker Award
for Clinical
Medical Research, 2008*

Daiichi-Sankyo



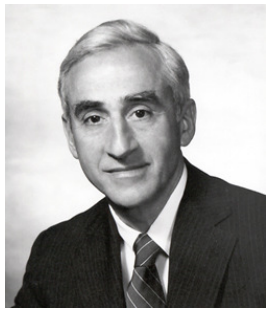
lactona

Mevilonina
/compactina



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

Universidade Federal do Rio de Janeiro



Dr P. Roy Vagelos

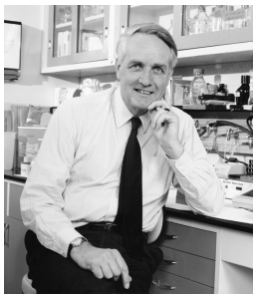
Vice-Presidente Pesquisa Farmacêutica da Merck (Presidente & CEO)

1976 - confidentiality agreement

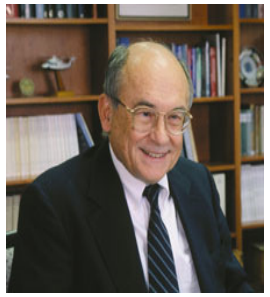
MERCK

Daiichi-Sankyo

Alfred W. Alberts



Georg Albers-Schönberg



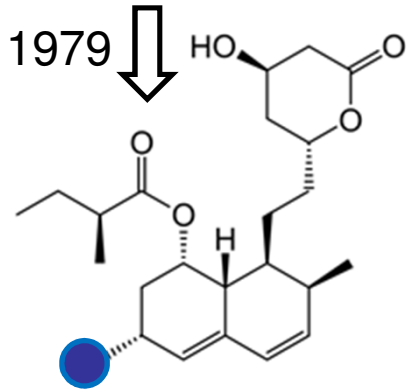
Arthur A. Patchett

Diretor do Departamento New Lead Discovery

Alfred Burger Award 2002

therapeutic innovation

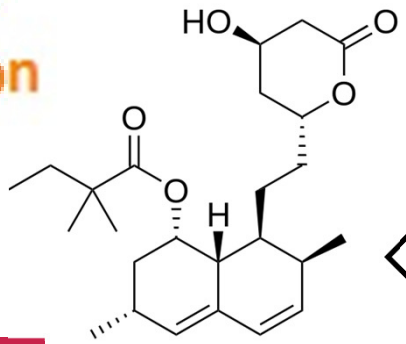
1979



Aspergillus terreus

lovastatina

A descoberta da lovastatina



simvastatina

first-in-class

1982

ZOCOR (SIMVASTATIN)

1991

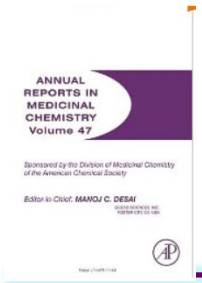
Pfizer atorvastatina

fifth-in-class

"blockbuster mentality"

Química Medicinal

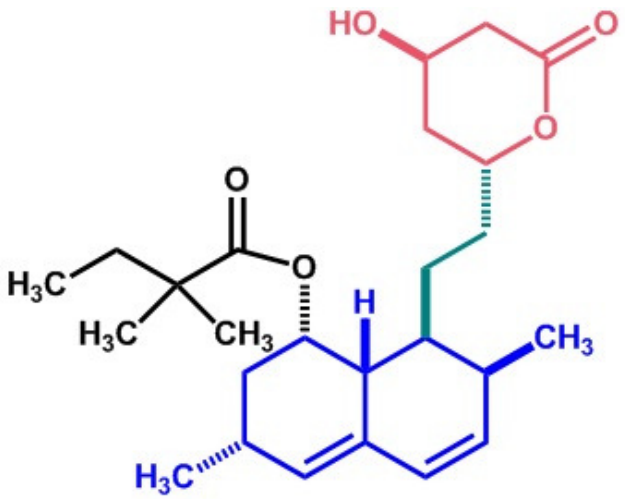
J. Med. Chem. **1986,** *29*, 849



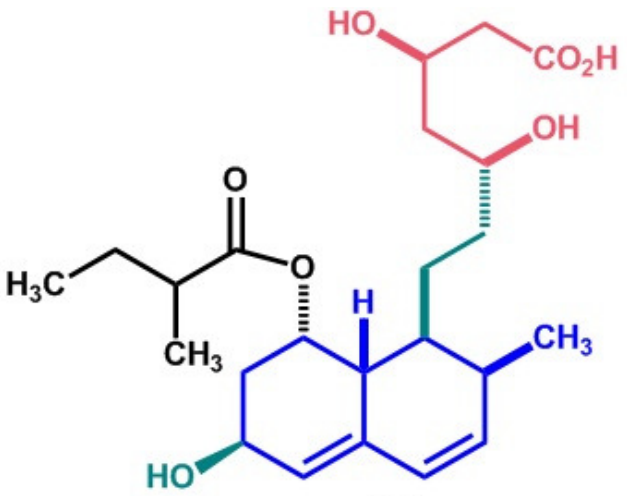
> 45 milhões de pessoas usaram estatinas (2005)

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

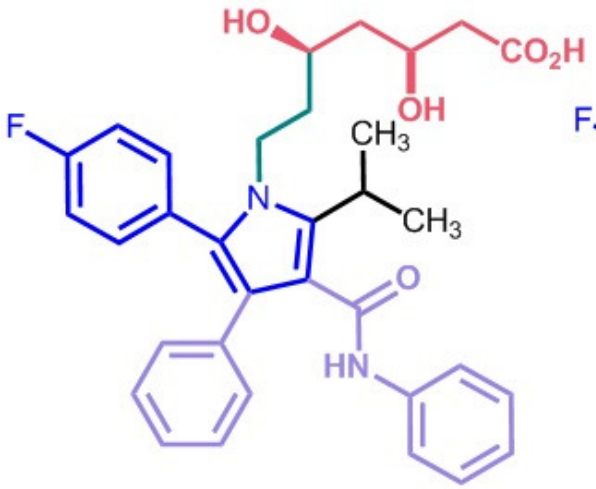
Estatinas



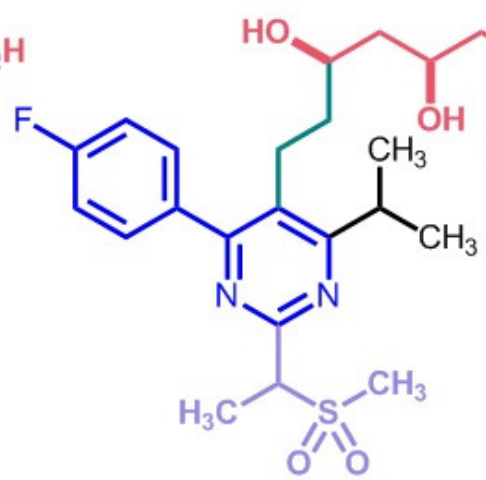
simvastatina
1986



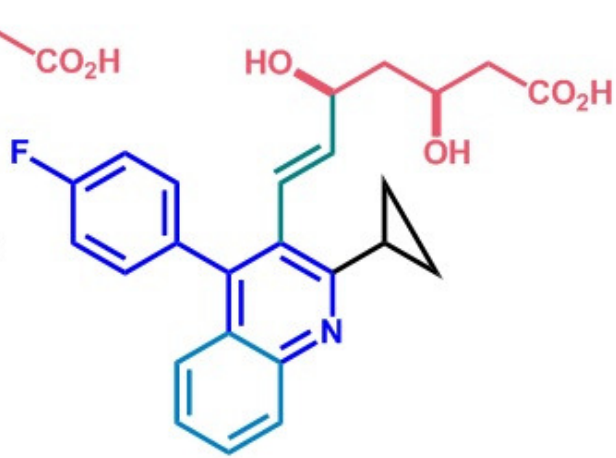
pravastatina
1988



atorvastatina
1991



rosuvastatina
2004



pitavastatina
2009

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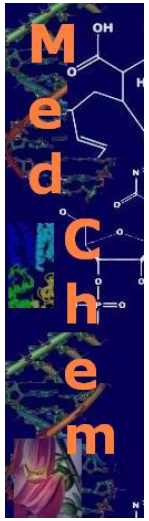
Atorvastatina

Estatinas

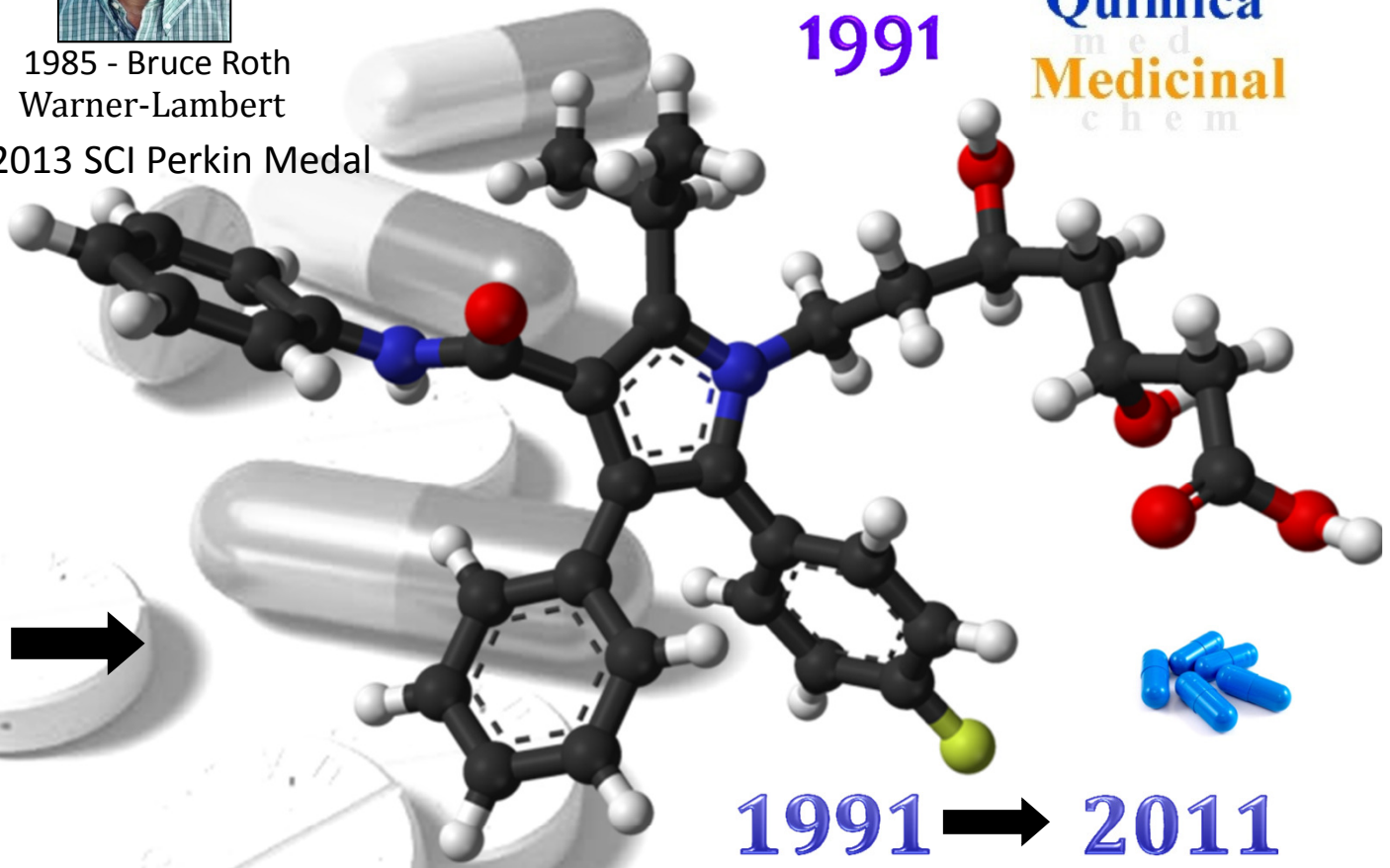
1985 - Bruce Roth
Warner-Lambert
2013 SCI Perkin Medal

1991

Química Medicinal



Pfizer



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

A Química Medicinal

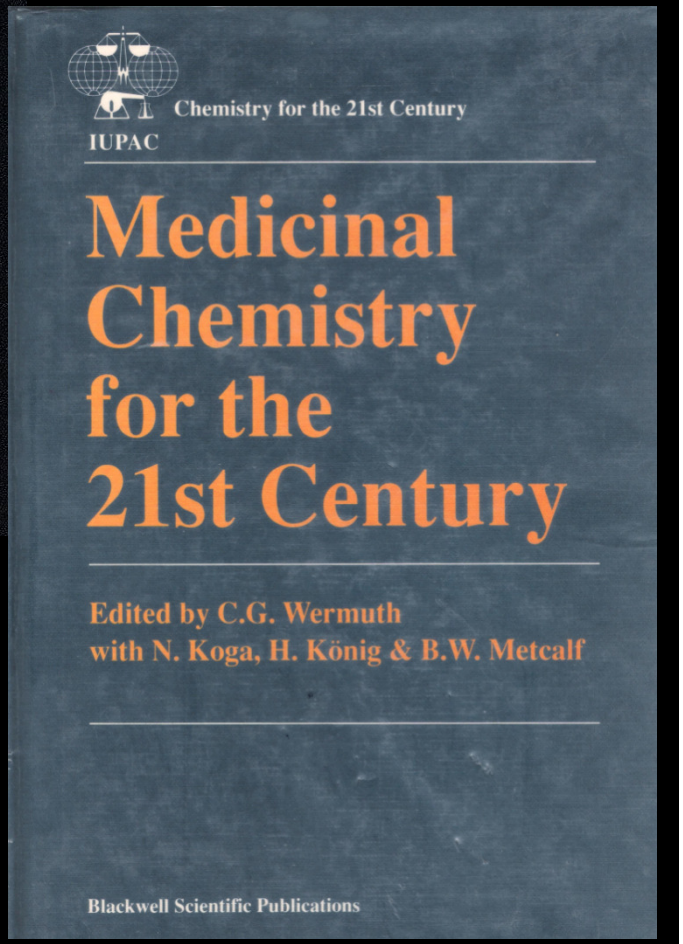
Universidade Federal do Rio de Janeiro

UFRJ

Século 21

Siglo 21

21st Century



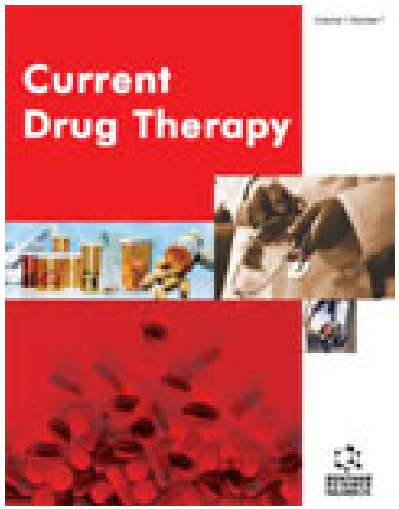
New Insights for Multifactorial Disease Therapy: The Challenge of the Symbiotic Drugs

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.

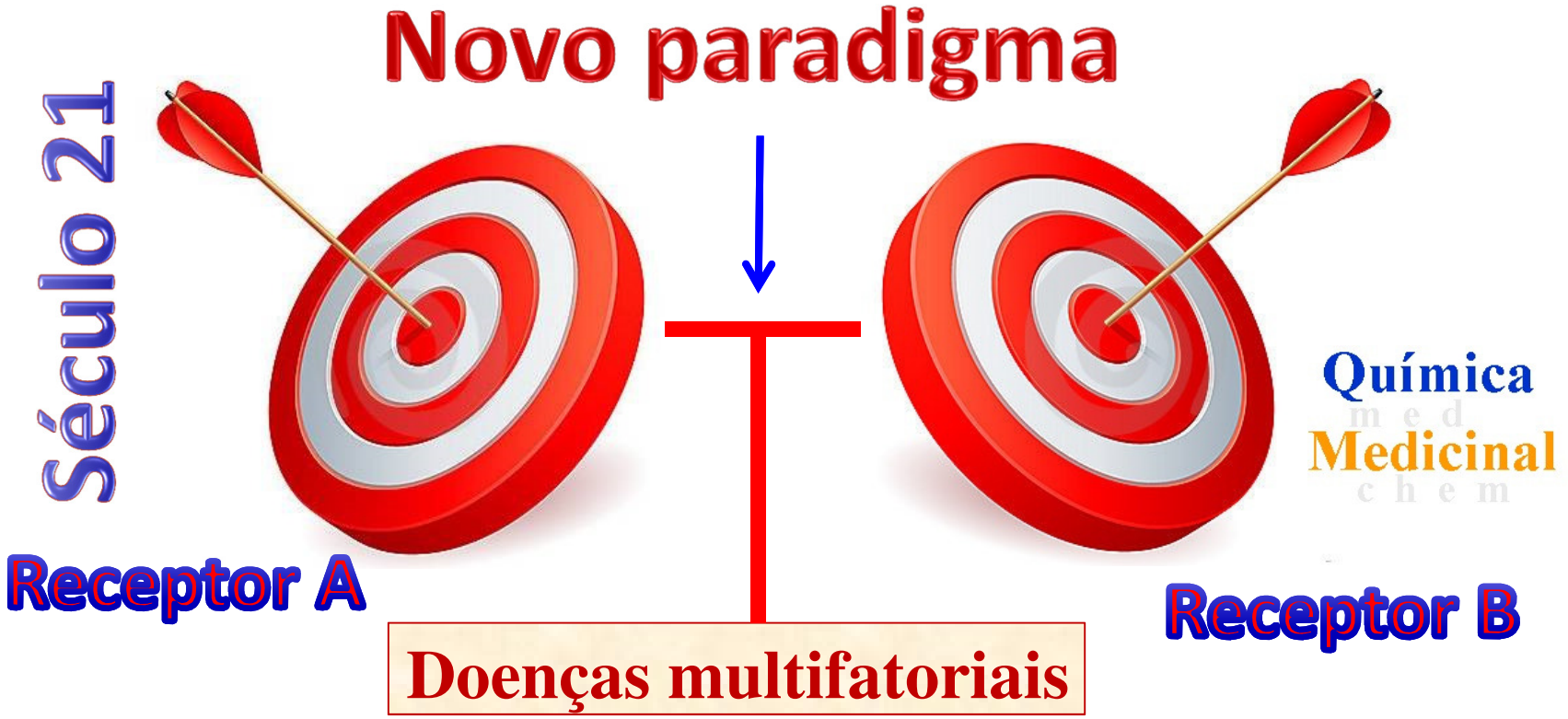
Abstract: Some physiopathological processes involved in the genesis of diseases could suggest the necessity of designing bioligands or prototypes that aggregate, in only one molecule, dual pharmacodynamical properties, becoming able to be recognized by two elected bioreceptors. This approach can have 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!

Fármacos do século 21

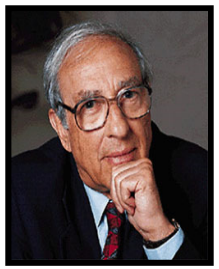


Química Medicinal

O desenho racional de fármacos *multi-alvos* depende da capacidade de se combinarem fragmentos moleculares farmacofóricos, capazes de assegurarem reconhecimento molecular pelos receptores envolvidos na patologia multifatorial

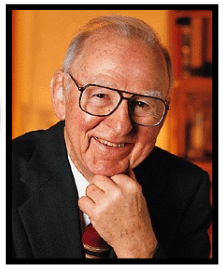
JL Medina-Franco et al. Shifting from the single to the **multitarget paradigm** in drug discovery, *Drug Discov. Today* **2013**, *18,* 495; C Hiller, J Kühhorn, P Gmeiner, Class A G-Protein-Coupled Receptor (GPCR) Dimers and Bivalent Ligands, *J. Med. Chem.* **2013**, *56*, 6542; G Phillips, M Salmon, **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.

Inibidores de tirosina-cinases (TK)

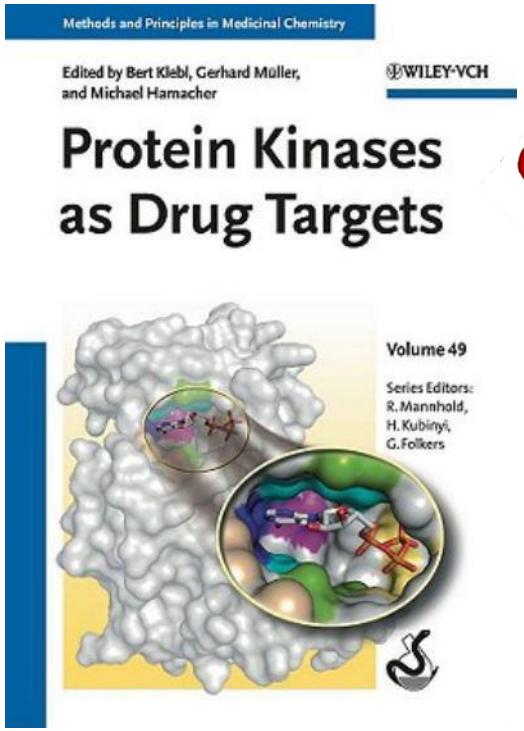


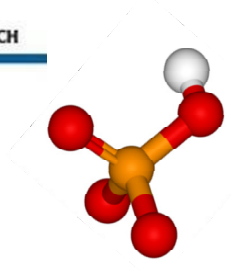
Edmond H. Fischer
(1920 -)

1992

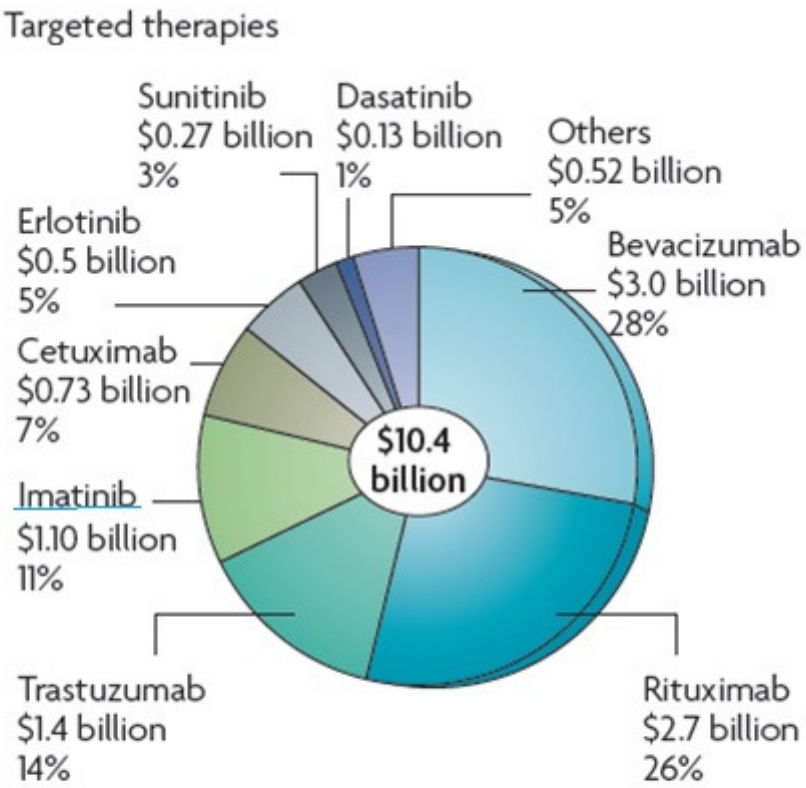


Edwin G. Krebs
(1918 –2009)





cinoma



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

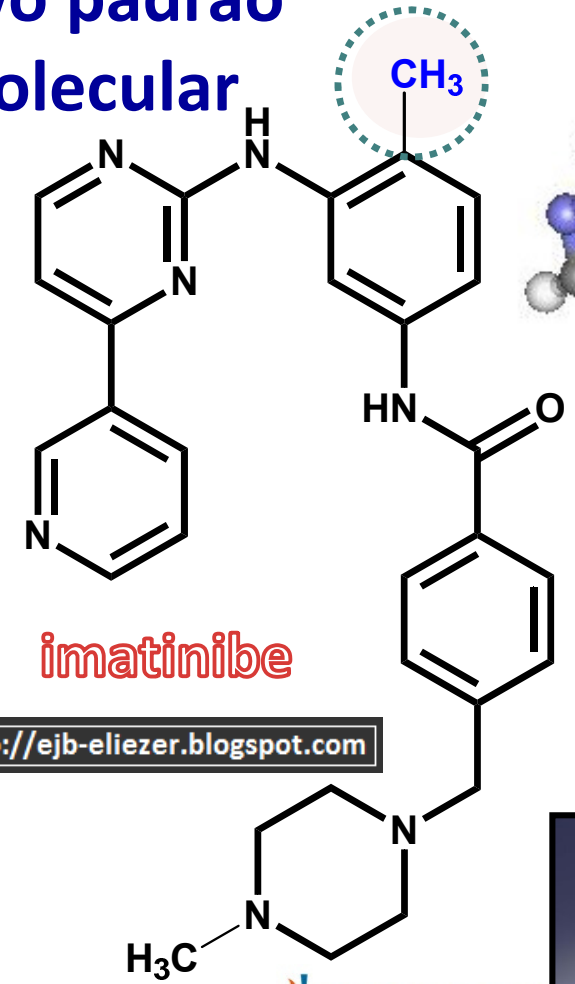
Sources: company reports

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

Leucemia mielóide crônica (CML)

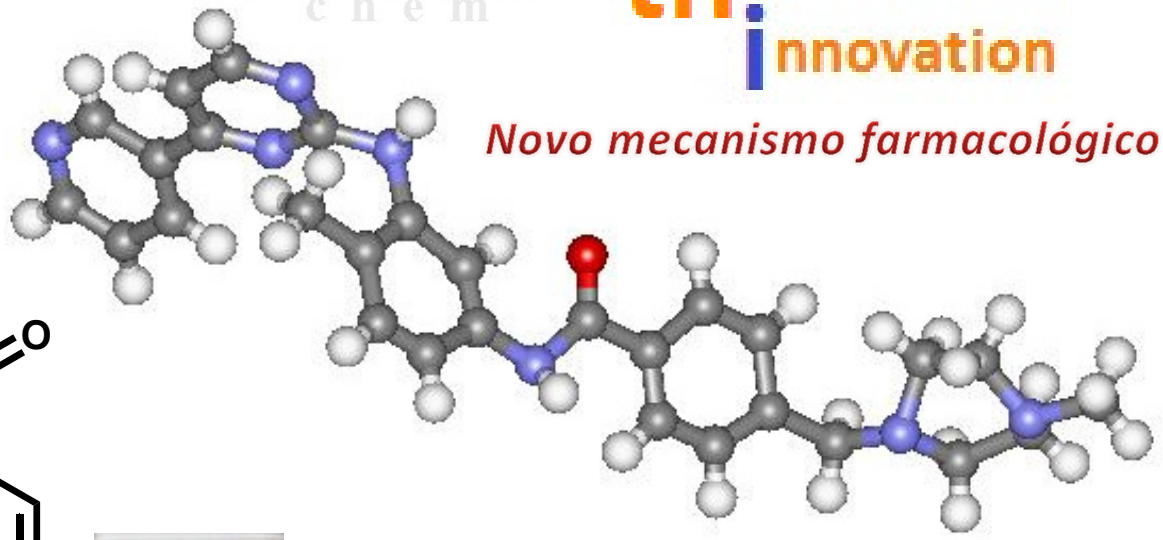
NOVARTIS

imatinibe

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]

Nicholas B. Lydon
Blueprint Medicines Inc*

Brian J. Druker*
Blueprint Medicines Inc

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;

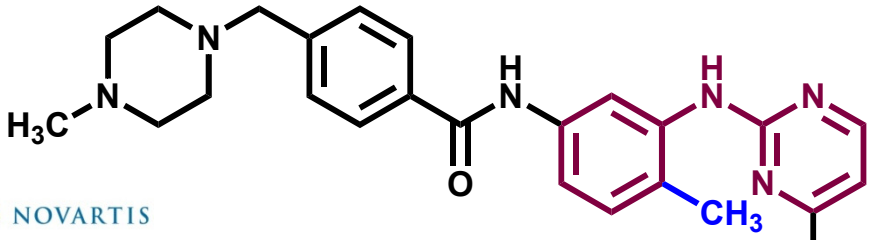
** C. L. Sawyers was named in 2011, Thomson Reuters Citation Laureate in Medicine;

Universidade Federal do Rio de Janeiro

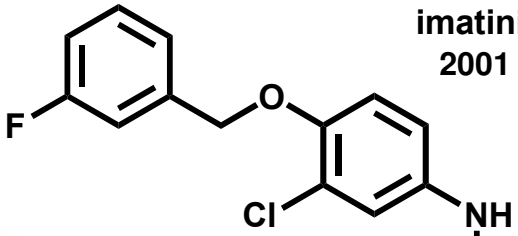
Tinibes*

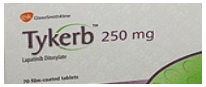
Leucemia mielóide crônica (CML) &

NOVARTIS



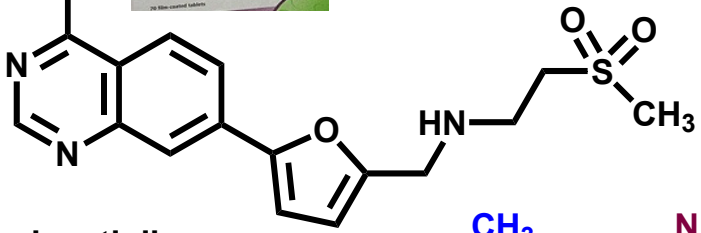
imatinib
2001



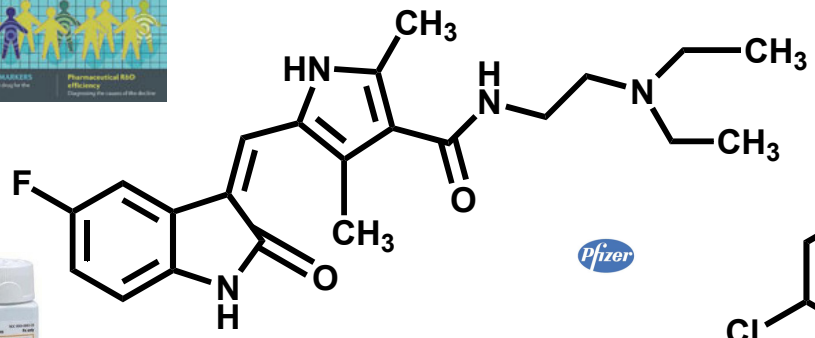


e

therapeutic innovation

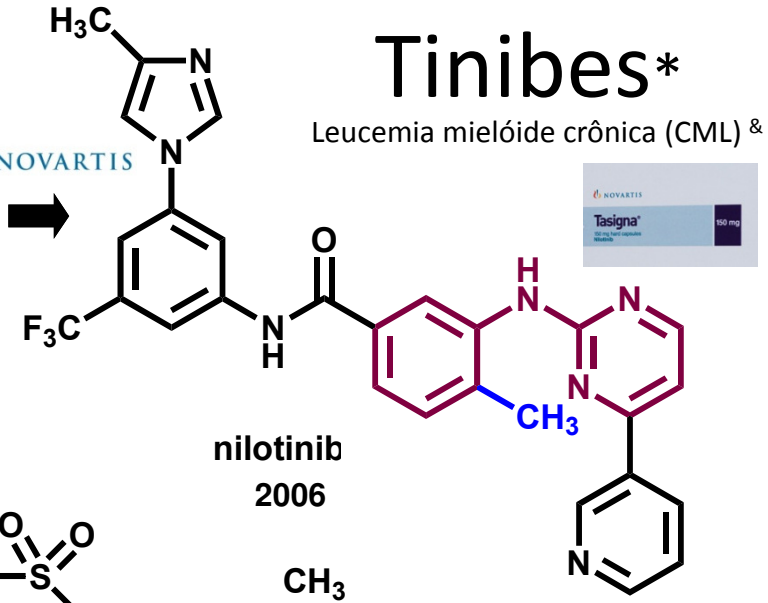


lapatinib
2007

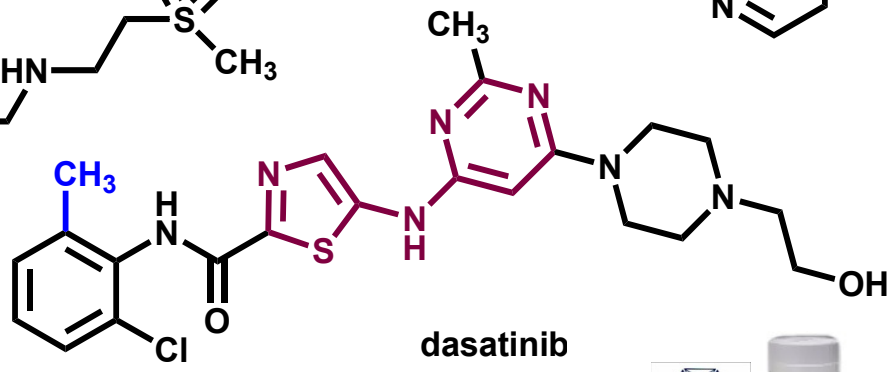


sunitinib
2006

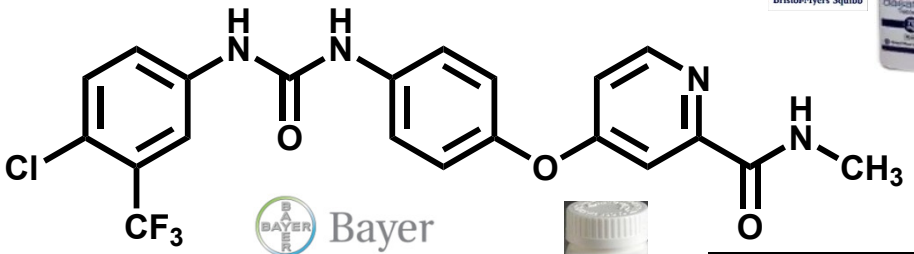
NOVARTIS



nilotinib
2006



dasatinib
2007



Bayer

sorafenib
2007

2011- crizotinibe
2012- bosutinibe

Pfizer

- **Mercado EUA (2009): US$ 18,5 bi ***

http://ejb-eliezer.blogspot.com

- S Aggarwal, *Nature Rev Drug Discov* **2010**, *9*, 427

& R Ren, *Nature Rev Cancer* **2005**, *5*, 172

CHEMICAL REVIEWS

Chem. Rev. 2011, 111, 5215–5246

REVIEW

Fator de Impacto = 40,19

pubs.acs.org/CR

The Methylation Effect in Medicinal Chemistry

Eliezer J. Barreiro,*[,†,‡,§] Arthur E. Kümmerle,[||,†,§] and Carlos A. M. Fraga[†,‡,§]

[†]Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, CCS, Cidade Universitária, CP 68.006, 21941-902 Rio de Janeiro, RJ, Brazil

[‡]Programa de Pós-Graduação em Farmacologia e Química Medicinal, Instituto de Ciências Biomédicas, Universidade Federal do Rio de Janeiro, Cidade Universitária, Ilha do Fundão, Rio de Janeiro, RJ, Brazil

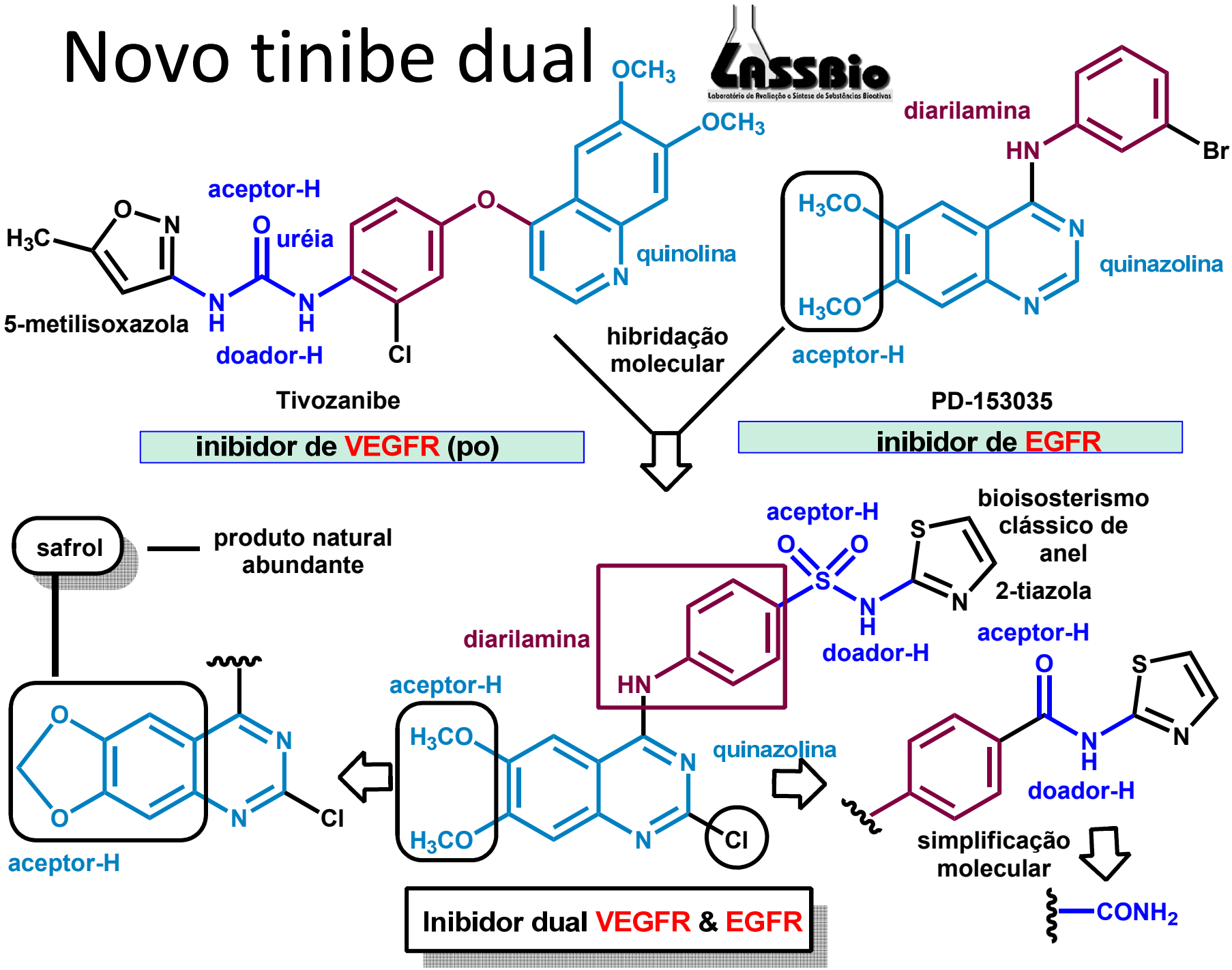
[§]Programa de Pós-Graduação em Química, Instituto de Química, Universidade Federal do Rio de Janeiro, Cidade Universitária, Ilha do Fundão, Rio de Janeiro, RJ, Brazil

dx.doi.org/10.1021/cr200060g

www.uff.br/**RVQ**

AS de Miranda, *Rev. Virtual Quim*. **2011**, *3*, 228

Novo tinibe dual



Universidade Federal do Rio de Janeiro

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

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,*]

[a] Laboratory of Evaluation and Synthesis of Bioactive Substances (LASSBio), Federal University of Rio de Janeiro, P.O. Box 68024, 21944-971 Rio de Janeiro, RJ, Brazil
[b] Graduate Program of Chemistry (PGQu), Chemistry Institute, Federal University of Rio de Janeiro, Rio de Janeiro, RJ, Brazil
[c] Department of Chemistry, Federal Rural University of Rio de Janeiro (UFRRJ), Seropédica, RJ, Brazil
[d] ProQinase GmbH, Freiburg, Germany
[e] Department of Pharmaceutical/Medicinal Chemistry, Institute of Pharmacy, Eberhard-Karls-University Tübingen, Tübingen, Germany

European Journal of Medicinal Chemistry 71 (2014) 1–14

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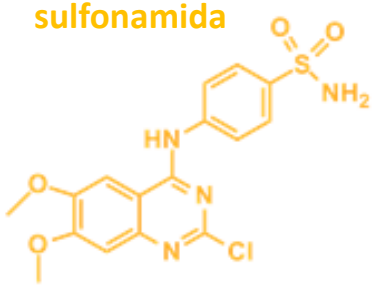
Atividade dual

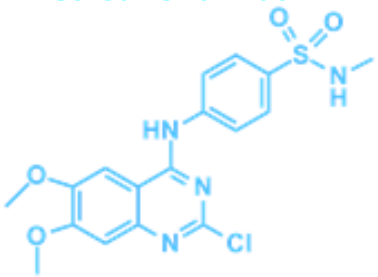
Novo padrão molecular com atividade dual sobre EGFR/VEGFR

sulfonamida



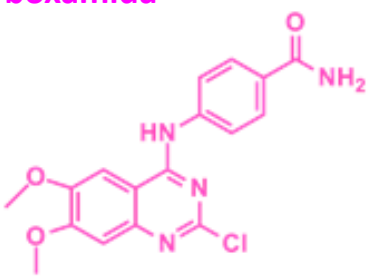
LASSBio-1814
EGFR: IC_{50} = 2,37 µM
VEGFR-2: IC_{50} = 1,02 µM

metilsulfonamida



LASSBio-1816
EGFR: IC_{50} = 1,63 µM
VEGFR-2: IC_{50} = 0,85 µM

carboxamida



LASSBio-1819
EGFR: IC_{50} = 0,90 µM
VEGFR-2: IC_{50} = 1,17 µM

Depósito de patente no INPI, BR 102013 0018090 24/01/2013

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


Universidade Federal do Rio de Janeiro
UFRJ
A Química
MedicInal
é simplesmente
fAscInante!
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ISSN 1984-6835

A história do LASSBio

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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

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Química Medicinal chem


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CARLOS ALBERTO MANSSOUR FRAGA
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AS BASES MOLECULARES DA AÇÃO DOS FÁRMACOS
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