



Universidade Federal do Rio de Janeiro



A Importância da Interdisciplinaridade na Descoberta de Fármacos

I Workshop Multidisciplinar de Fármacos e Medicamentos



20-21 de julho de 2016

Petrolina, PE

WorkFar

Eliezer J. Barreiro



Professor Titular - UFRJ



Laboratório de Avaliação e Síntese de Substâncias Bioativas

Laboratório de Avaliação e Síntese de Substâncias Bioativas

<http://www.lassbio.icb.ufrj.br/>





Instituto Nacional de
Ciência e Tecnologia

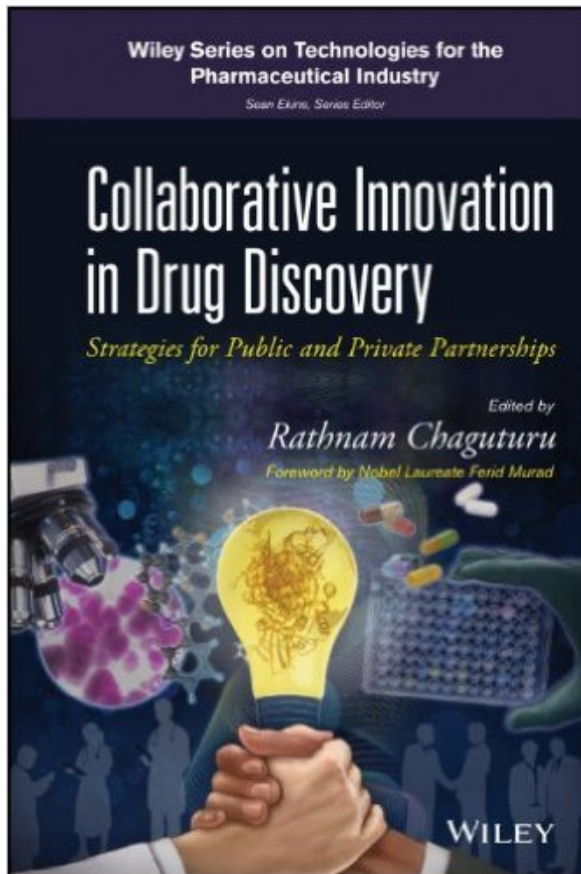
de Fármacos e Medicamentos

www.inct-inofar.ccs.ufrj.br

Sumário

- ❖ A inovação tecnológica & farmacêutica;
- ❖ O processo da descoberta de fármacos & a interdisciplinaridade; 
- ❖ Os fármacos e o prêmio Nobel;
- ❖ Importantes inovações farmacêuticas;
- ❖ A experiência do  - ICB/UFRJ;
Laboratório de Avaliação e Síntese de Substâncias Bioativas
- ❖ Finalização & Convites.

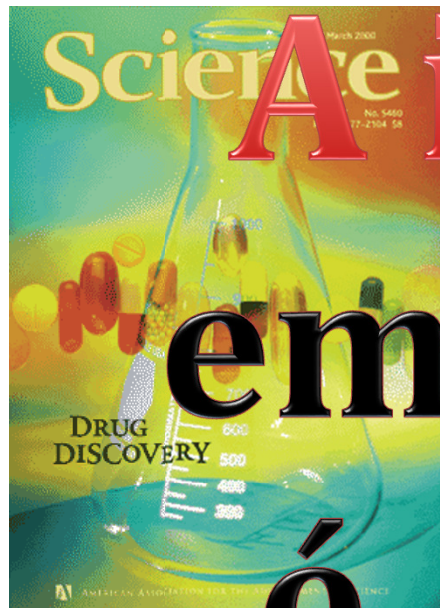
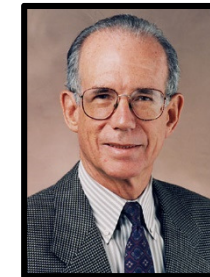
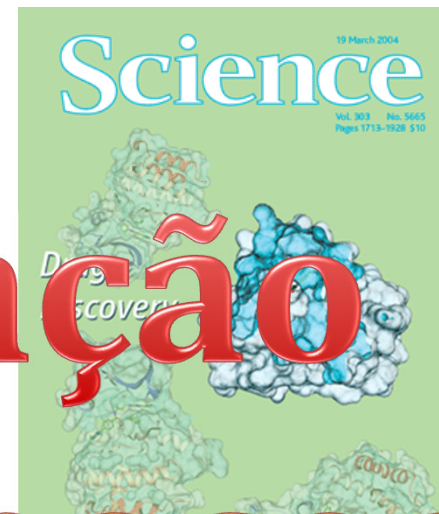
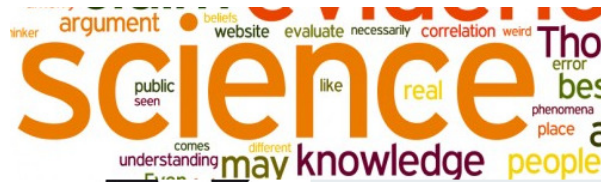
A inovação tecnológica



CEO of iDDPartners, US

[XXII Escola de Verão em Química Farmacêutica Medicinal](#)
(LASSBio/ICB-UFRJ, 2016)

é o processo **mais** dinâmico da atividade industrial. Este **dinamismo** é **acentuado na** inovação farmacêutica que, **mais do que** qualquer outra, depende da **efetiva interação entre** **Ciência & Tecnologia.**



A inovação

em fármacos

[OnLine](#)

• *Science* **2004**, 303, 1713

(Donald Kennedy)

é baseada

• *Science* **2000**, 287, 1951

(Julia Uppenbrink, J. Mervis)

em Ciência!

• *Science* **2005**, 309, 728

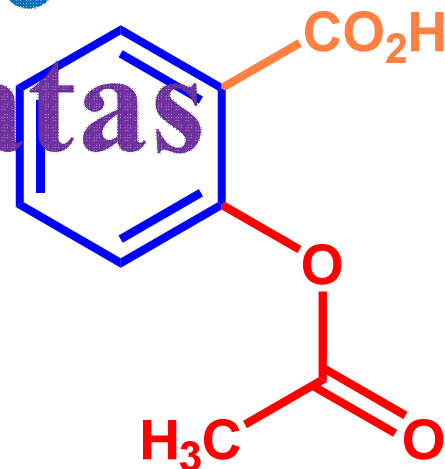
(Jeffrey Mervis)



Ciências da Saúde

Química

Ciências Exatas



1889

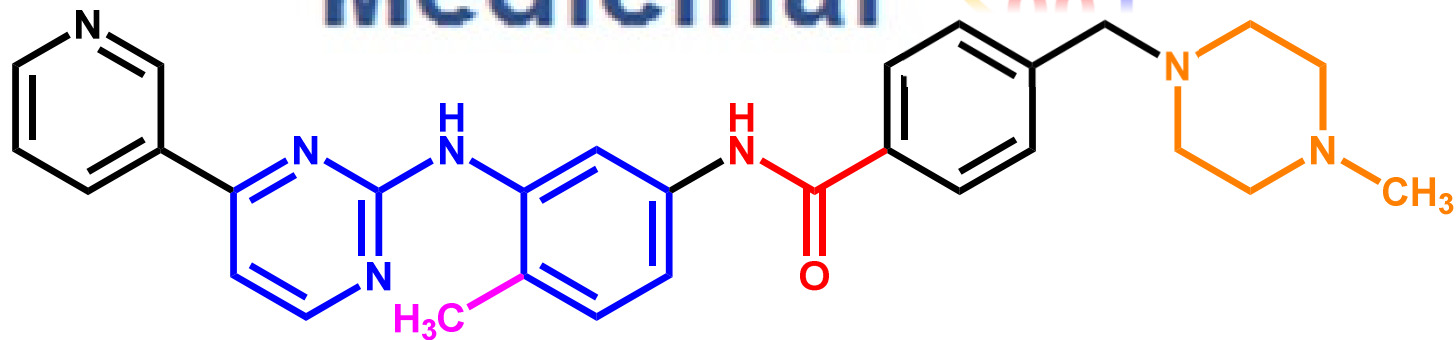


112y

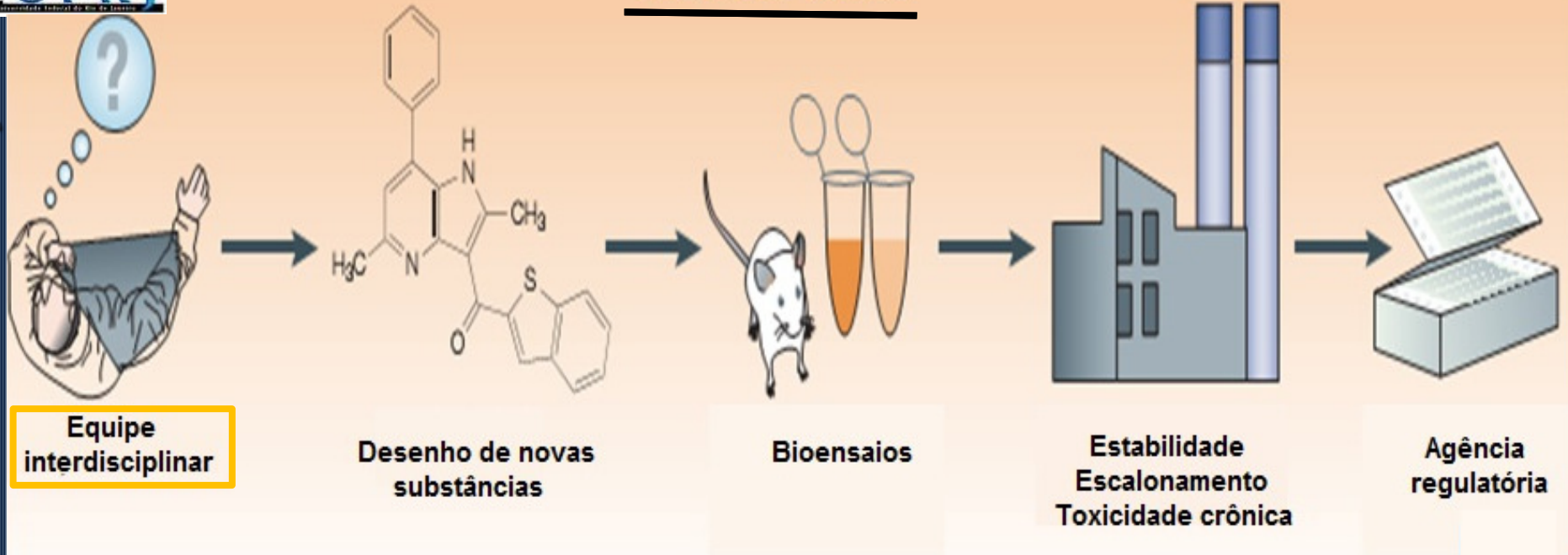
Ciências Biológicas

Medicinal

2001



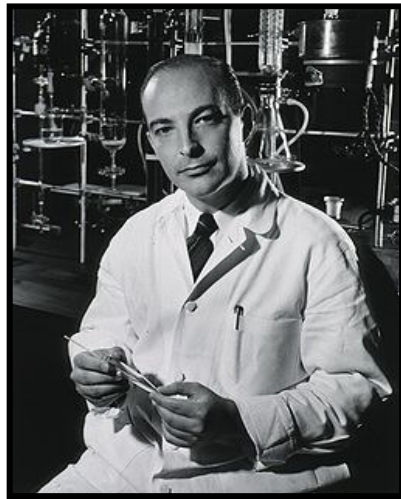
Fase pré-clínica



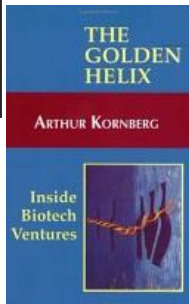
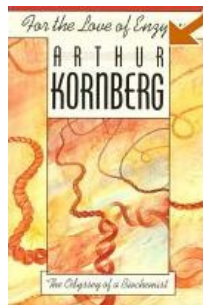
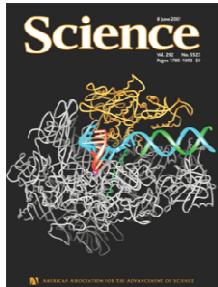
Fase clínica

O processo *D2* é complexo & interdisciplinar...





Arthur Kornberg (41)
1918-2007

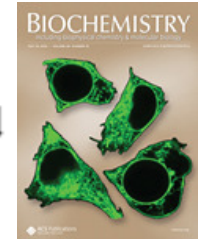


Prêmio Nobel, 1959



Nobel

The Two Cultures: Chemistry and Biology¹



Arthur Kornberg

Department of Biochemistry, Stanford University, Stanford, California 94305

Received July 14, 1987

“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...”


Biochemistry 1987, 26, 6888-6891



162 laureados em *Química*



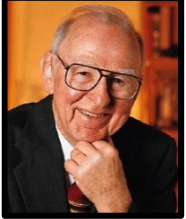
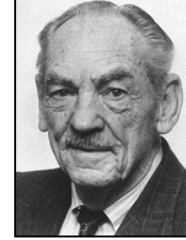
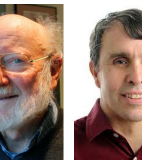
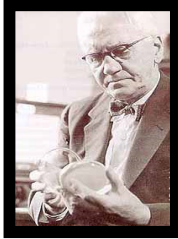
210 laureados em *Medicina*



1901-2015

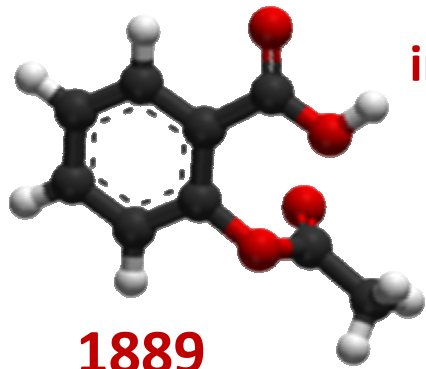
O prêmio Nobel & os fármacos

1901



2015

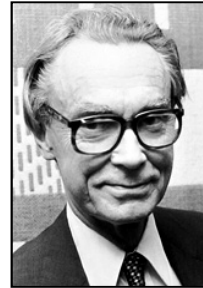
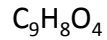




1889

**The Nobel Prize
in Medicine & Physiology
1982**

AAS



Sune Bergström (66)

(1916-2004) 

John Vane (55)
(1927-2004)



Bengt Samuelsson (48)

(1934) 

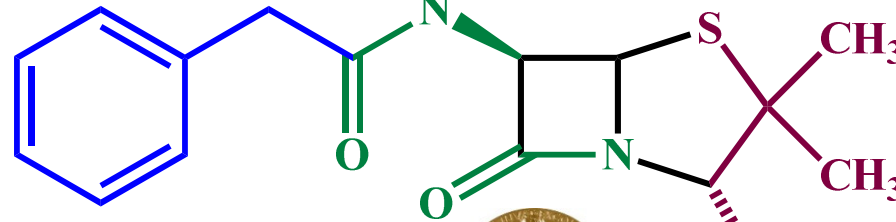


Sir Alexander Fleming (64)

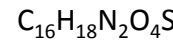
(1881-1955)



1929



penicilina



E. Boris Chain (39)

 (1906-1979)

Howard W. Florey (47)

(1898-1968)



Dorothy C. Hodgkin (54)

(1910-1994) 

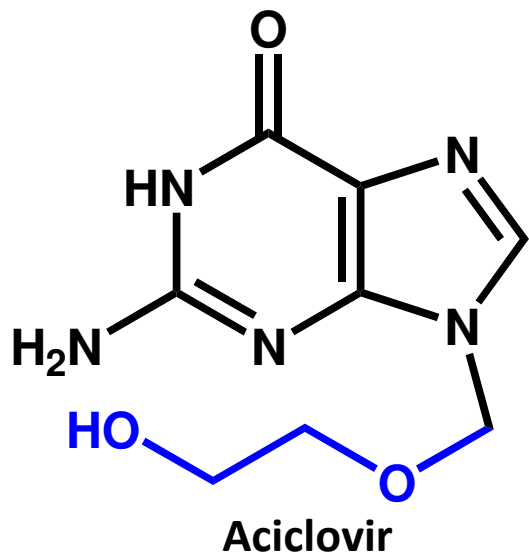


**The Nobel Prize
in Medicine & Physiology
1945**

**The Nobel Prize
in Chemistry
1964**



Burroughs Wellcome
(atual GSK)



1936



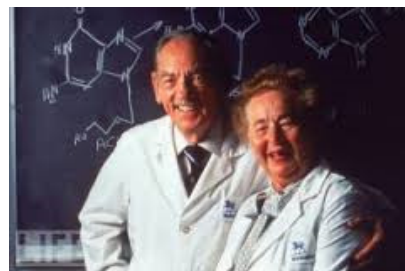
Otto Loewi (63)
(1873-1961)



Henry H. Dale (61)
(1875-1968)



Raymond Ahlquist (1914-1983)



George Hitchings (83)
(1905-1998)



6-mercaptopurina,
azatioprina,
alopurinol, trimetoprim,
nelarabina

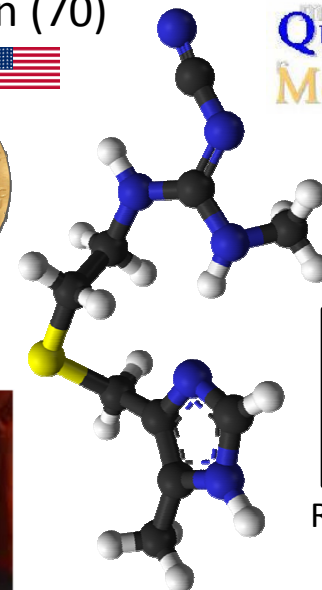
Gertrude B Elion (70)
(1918-1999)



1988



James W. Black (64)
(1924 - 2010)



Química
e
Medicinal



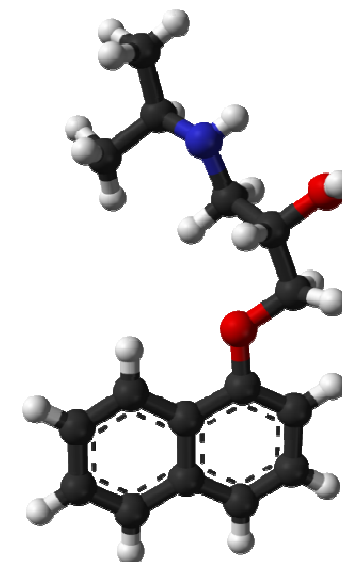
R Ganellin



Cimetidina (SK&F)

ICI

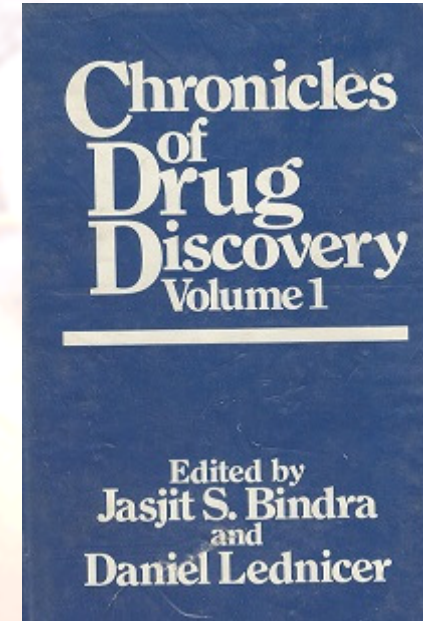
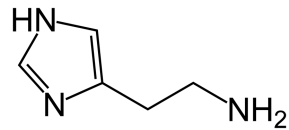
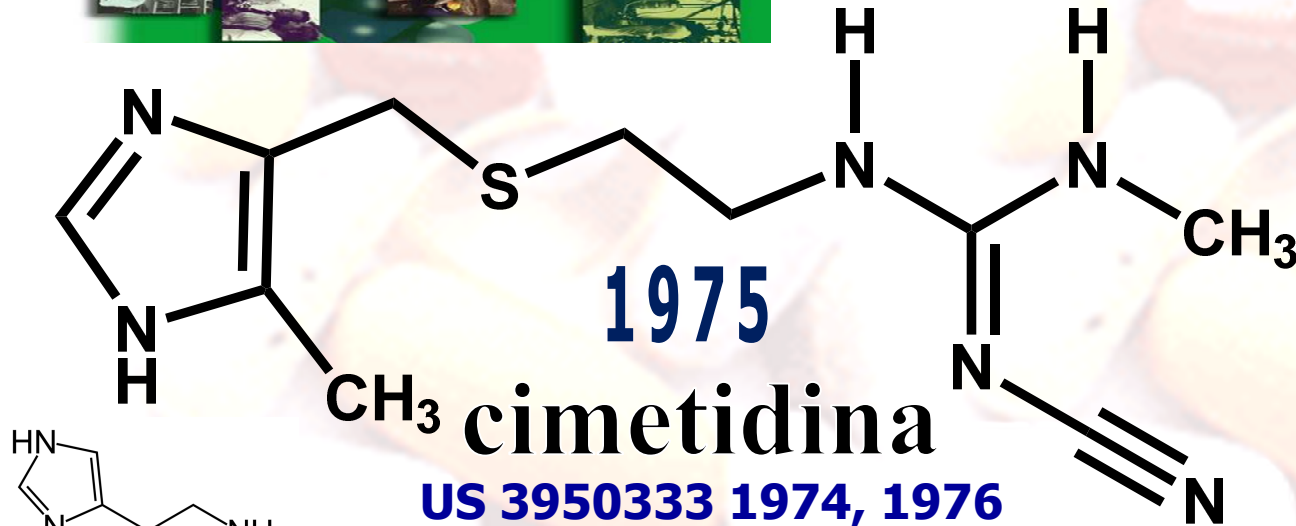
Propranolol



M Colvin, Gertrude Belle Elion (1918-1999), *Science* **1999**, 1480; JL Marx,
The 1988 Nobel Prize for Physiology or Medicine, *Science* **1988**, 242, 516.

1

Primeiro fármaco a atingir US\$
1 bilhão em vendas ao ano
(1979)



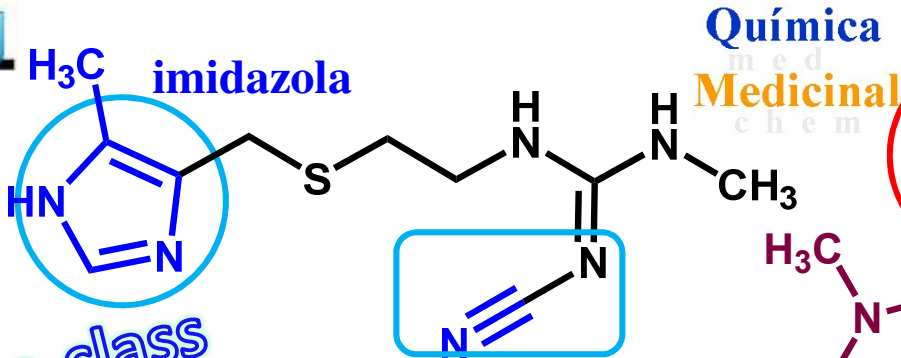
= importante **inovação** terapêutica !

Química
Medicinal

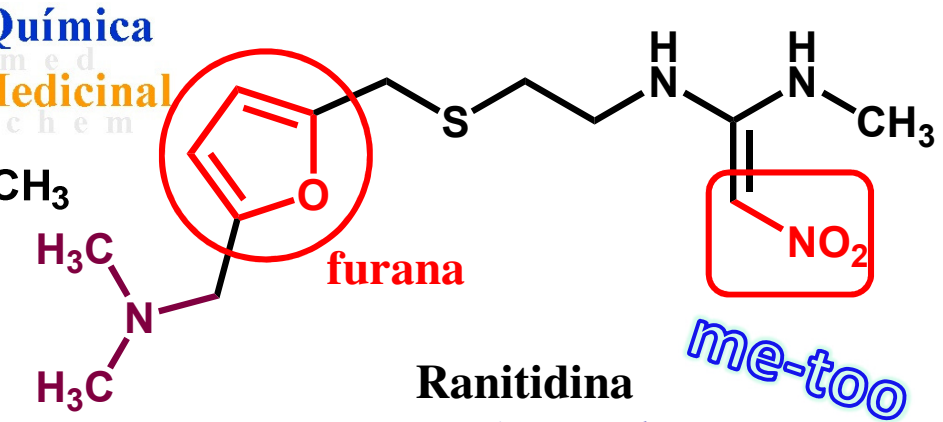
Farmacologia

1975 - SK&F
(Black, Ganellin,
Emmet & Durant)

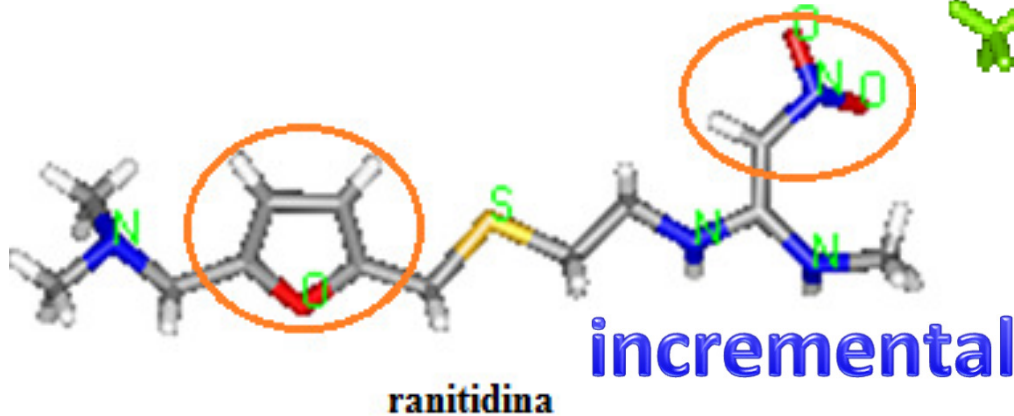
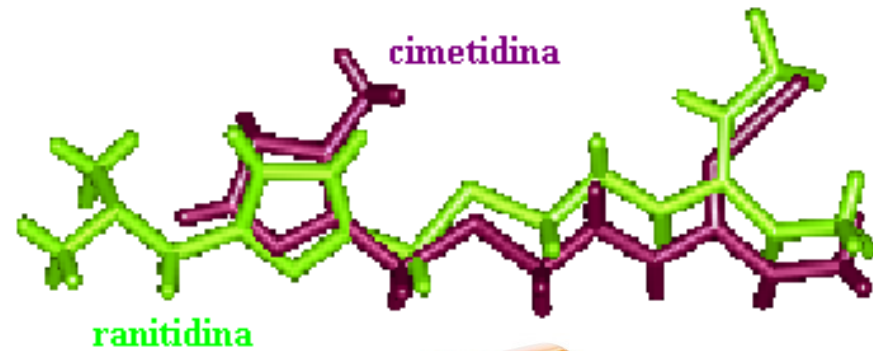
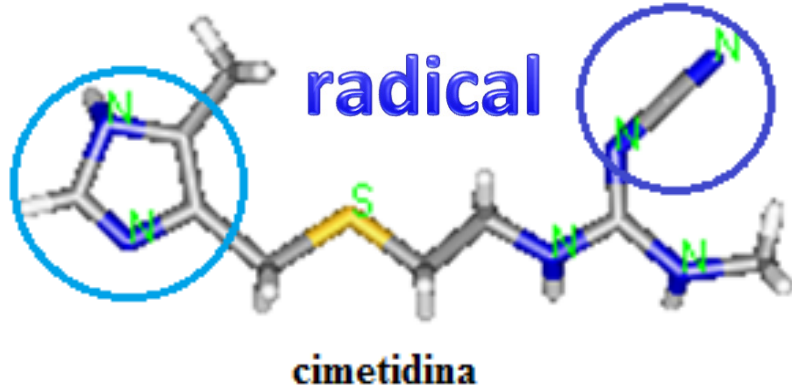




Robin Ganellin *et al.*, 1974
 US 3950333 1974, 1976 - SK&F
Brit. J. Pharmacol. **53**, 435 (1975)



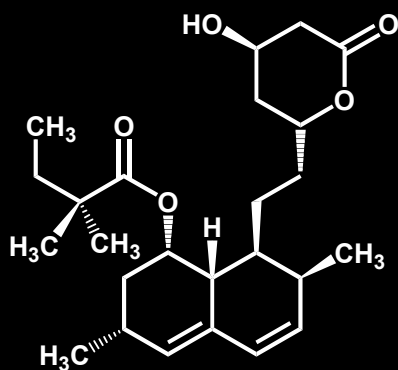
Barry J. Price *et al.*, 1978
 US 4128658 1978 - Allen & Hanburys
Brit. J. Pharmacol. **66**, 464 (1979)



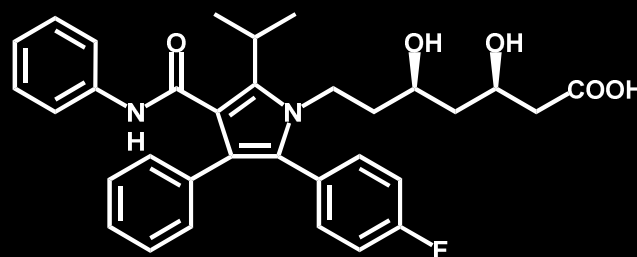
Molécula\$ inteligente\$ & valio\$a\$



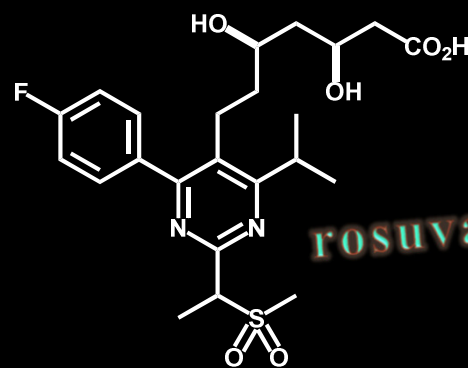
E\$tatina\$



simvastatina

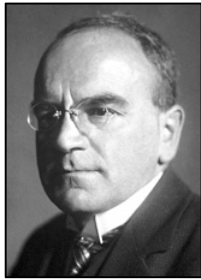


atorvastatina



rosuvastatina

As estatinas: inovação bilionária



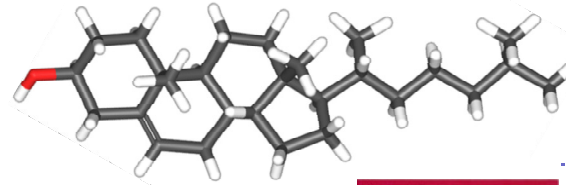
Heinrich O Wieland (50)
(1877-1957)

1927



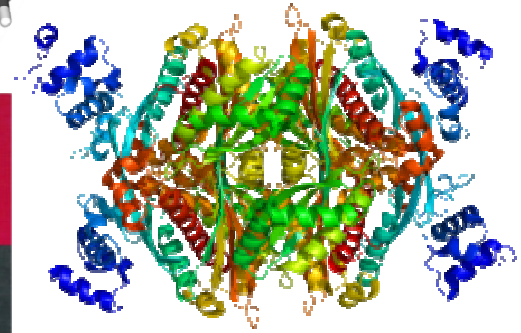
Adolf Windaus (52)
(1876-1959)

1928

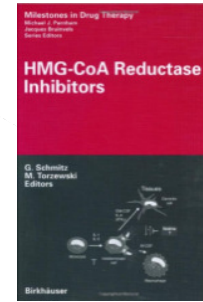


colesterol

best-selling
pharmaceuticals



HMGCoAR



1964



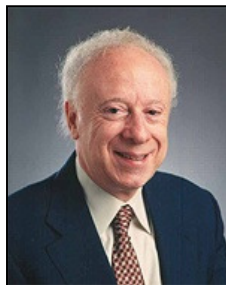
Konrad Bloch (53)
(1912-2000)



Feodor Lynen (54)
(1911-1979)

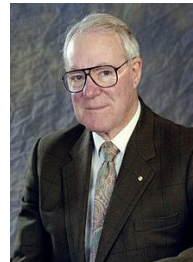
1985

LDL



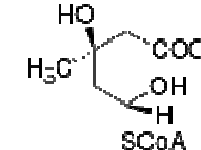
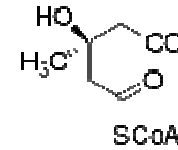
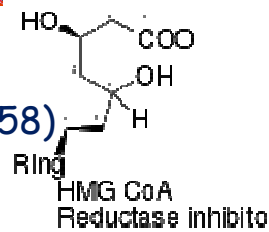
Joseph L Goldstein (45) Michael S Brown (44)
(1940) (1941)

University of Texas, Dallas



John Cornforth (58)
(1917-2013)

1975



HMG CoA Reductase inhibitor HMG CoA Mevaldyl CoA transition state intermediate



Akira Endo
(1933)

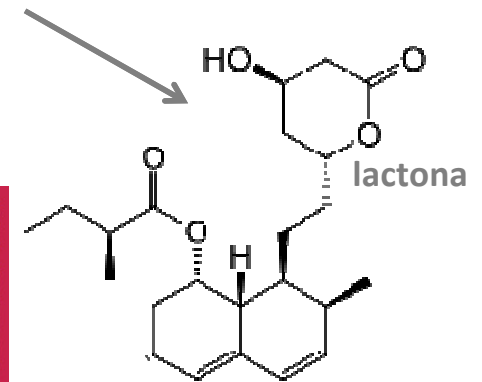
1976



Daiichi-Sankyo



J Med Chem
1985, 28, 1



Mevinolina/
Ccompactina

Albert Lasker Award
for Clinical
Medical Research, 2008



Akira Endo, Sankyo Co

1975 – Mevastatina (ML-263b)

A.Endo, *J. Med. Chem.* **1985**, 28, 1;
idem, *Proc Jpn Acad SerB* **2010**, 86, 484



Daiichi-Sankyo

Metabólito de Fungo

Estatinas



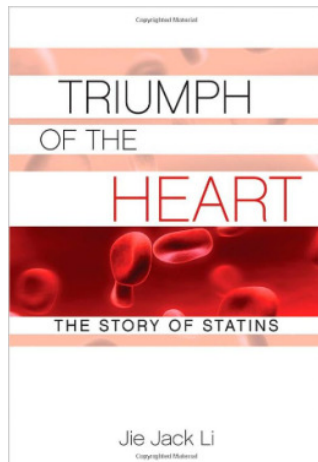
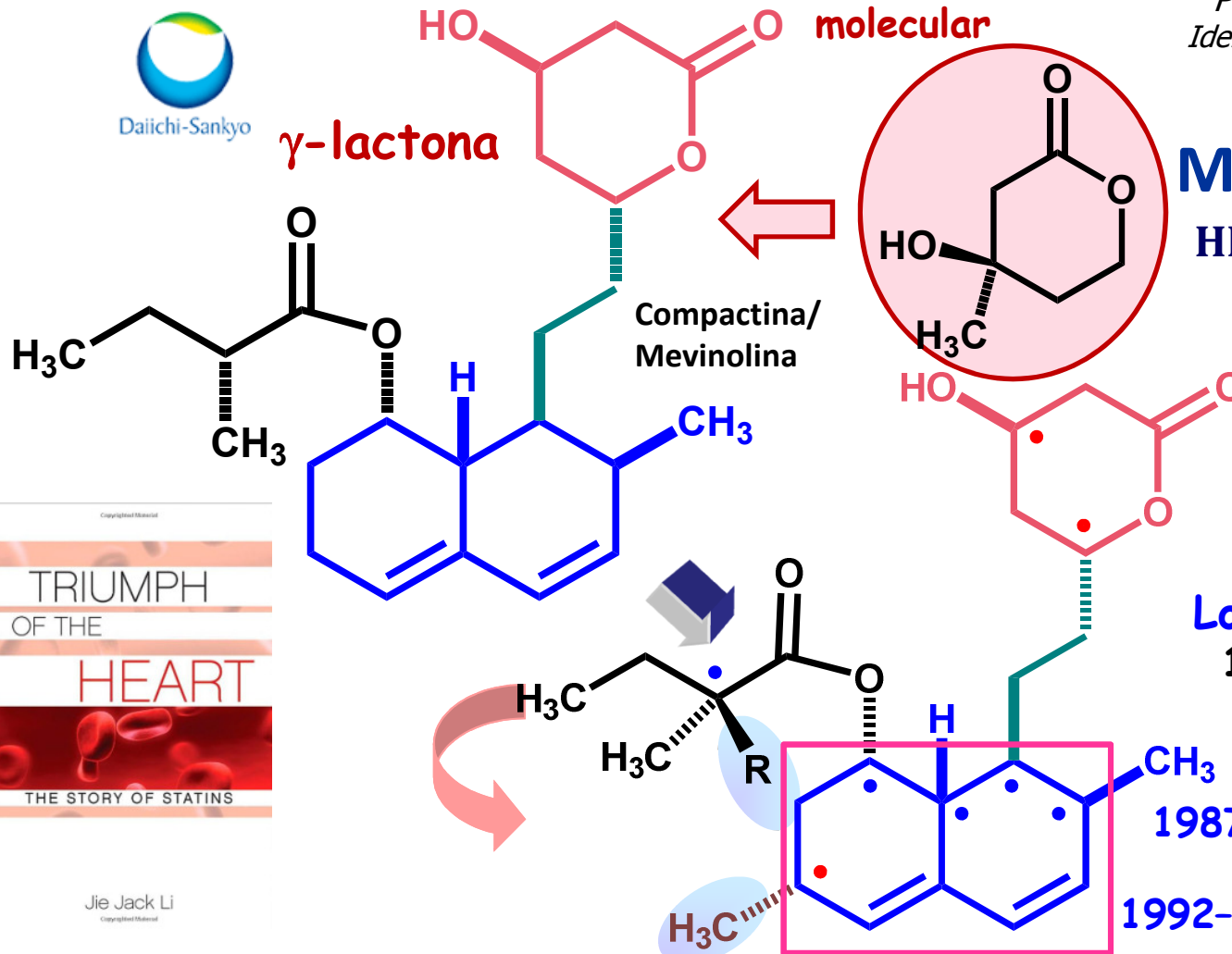
A.Endo, *J. Antibiot.* **1976**, 29, 1346

Penicillium citrinum
Idem, *Ibid*, **1979**, 32, 852
Monascus ruber
(compactina)

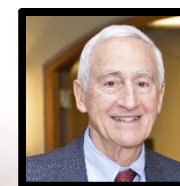
Protótipo

natural Similaridade molecular

γ -lactona



A descoberta das estatinas



Roy Vagelos



Clayton H. Heathcock
1982 - Total synthesis
of compactin
(mevastatin)

Universidade da
California-Berkeley



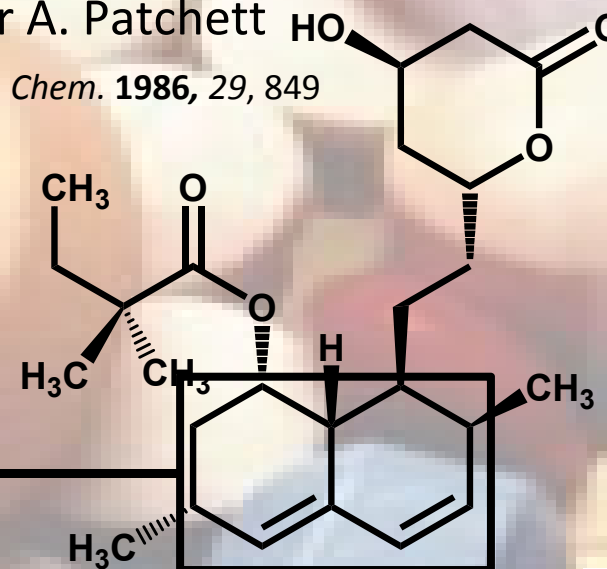
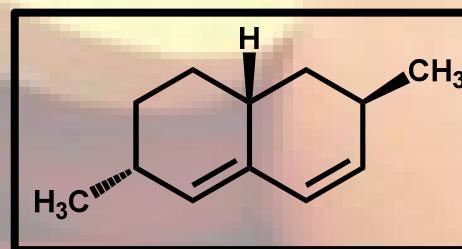
medicinal chemistry



HMGC_oAR 1976 - Arthur A. Patchett

SANKYO

J. Med. Chem. 1986, 29, 849



1987 - simvastatina
2008 - Vitoryn^R



“...In 2009, statins were used to treat 30 million people.”

B M Silber, *Science Transl Med* 2010, 2, 1

Estatinas

Atorvastatina

Maior *bestseller* da história dos fármacos

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

1991 → 1997



Química
medicinal
chem
Warner-Lambert
Pfizer



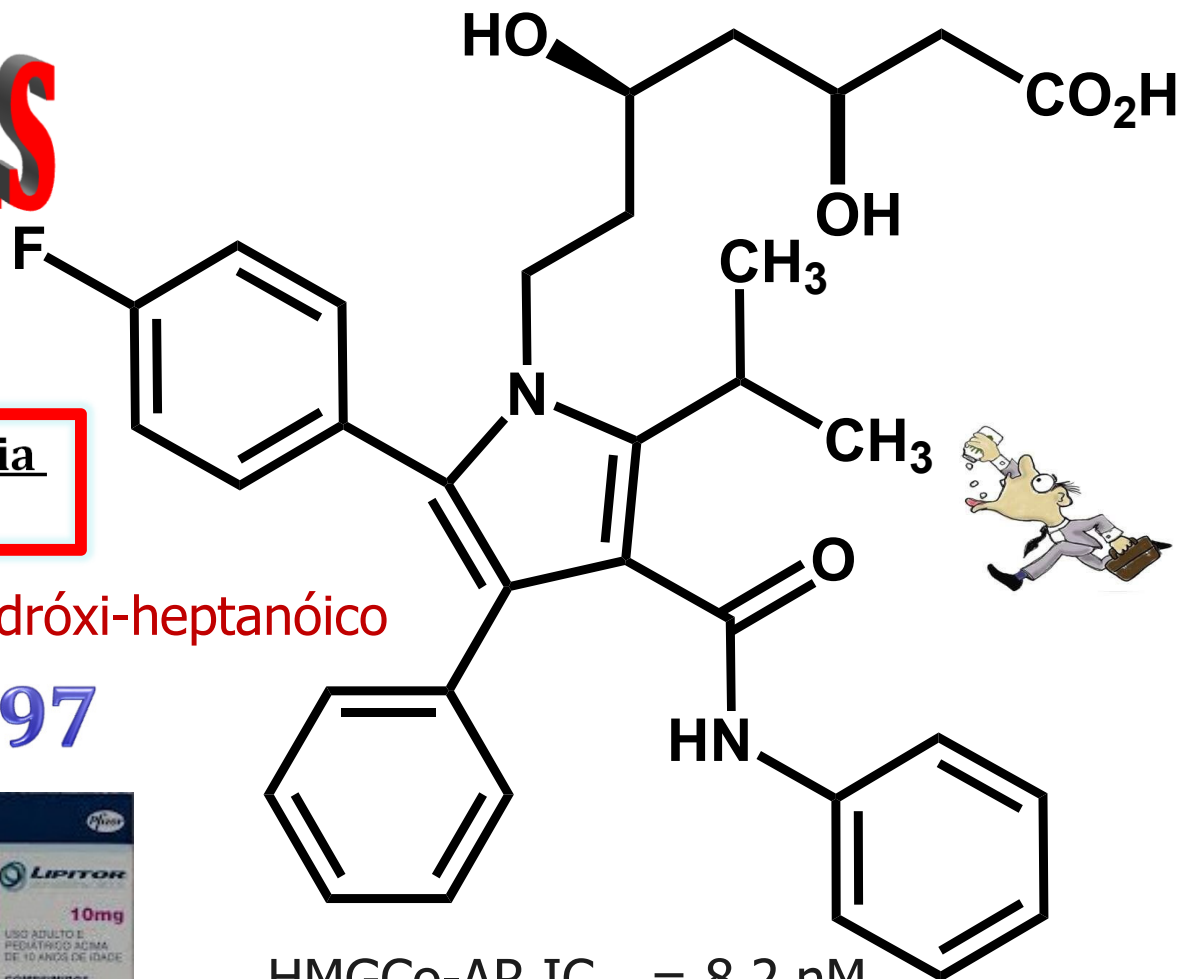
Dr Bruce D. Roth

2013 SCI Perkin Medal



B. D. Roth, *Progr. Med. Chem.* **2002**, *40*, 1-22

B. D. Roth, et al., *J. Med. Chem.* **1990**, *33*, 21-31



HMGC_o-AR IC₅₀ = 8,2 nM

Biodisponibilidade = **12%**

2005 – US\$ 13 bi; 2011 – US\$ 13,3 bi;

Síntese: *ca.* 220 toneladas/ano
ca. >> 30 milhões de pessoas (2005)

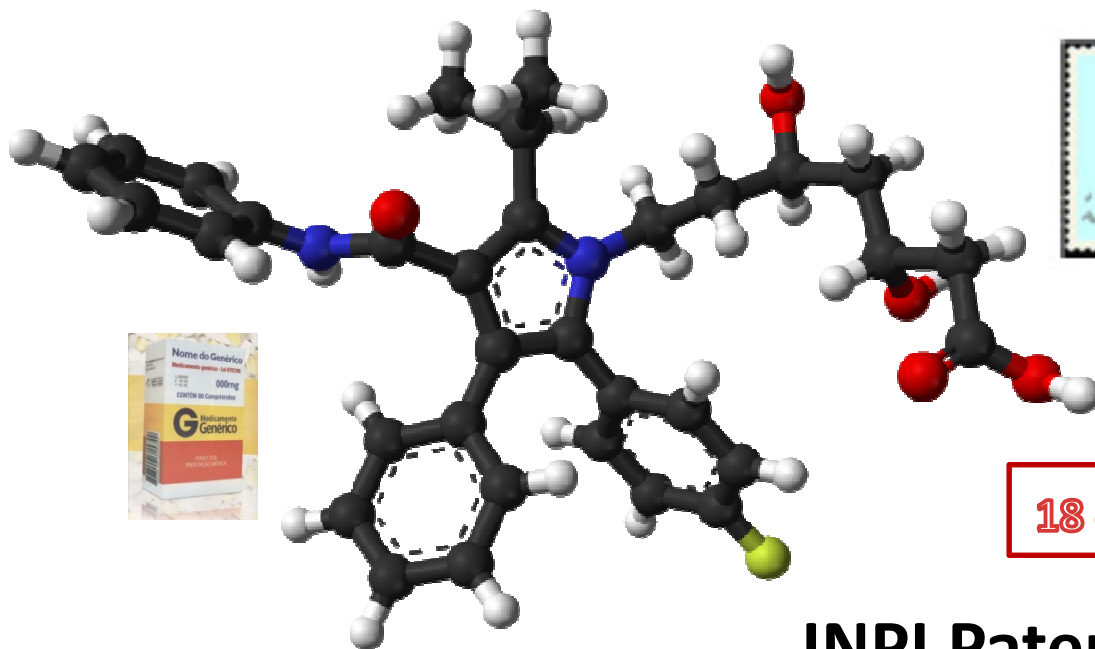


Total de Vendas => US\$ 150 bilhões (1991-2011)

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 intermediários
primários de menor custo,
de fármacos genéricos:



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

18 etapas; 19% rendimento; 5g escala

• **INPI Patente 018110015039, 2011**

**Nova rota de síntese da atorvastatina
cálcica usando novos intermediários.**

UNICAMP / UFRJ

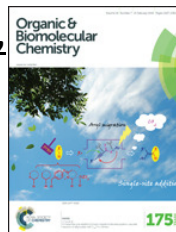


Luiz C. Dias, Adriano S. Vieira, Eliezer J. Barreiro

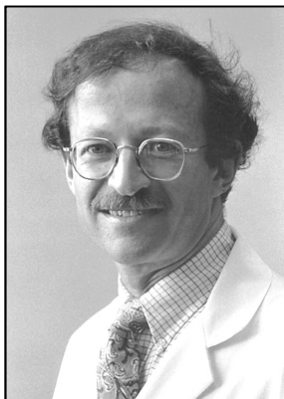
The total synthesis of calcium atorvastatin,

Org. Biomol. Chem. **2016**, *14*, 2291

DOI: 10.1039/C5OB02546J



Uma inovação extraordinária:



os tinibes

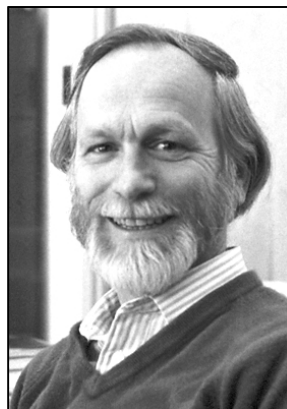
Harold E. Varmus (50)



(1939)



1989

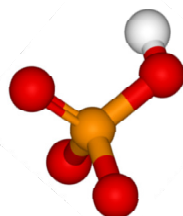
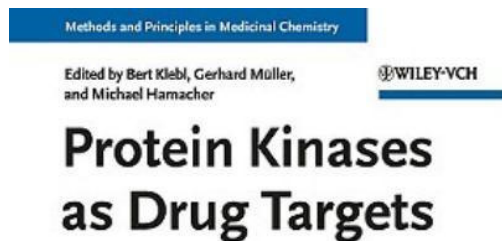


“for their discovery of the cellular origin of retroviral oncogenes”

J. Michael Bishop (53)



(1936)



kinoma



Edwin G. Krebs (72)



(1918–2009)



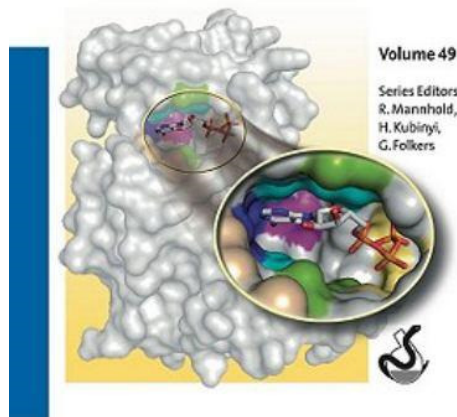
1992



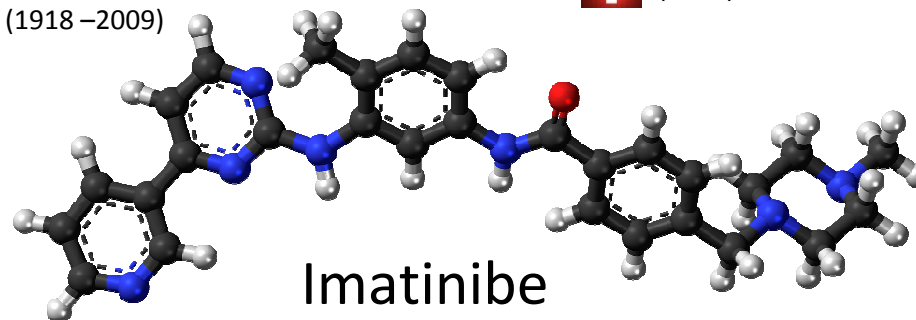
Edmond H. Fischer (72)



(1920)



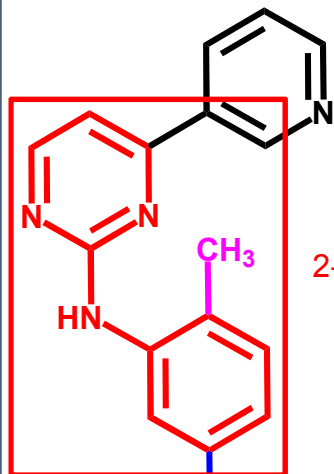
2001



Imatinibe

Nature Reviews Drug Discovery 2002, 1, 493-502

New molecular pattern



high-throughput screening

2-phenylaminopyrimidine

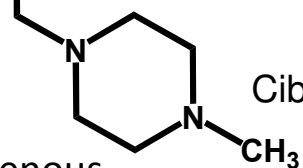


benzamide

imatinib
(STI571)

April 1992

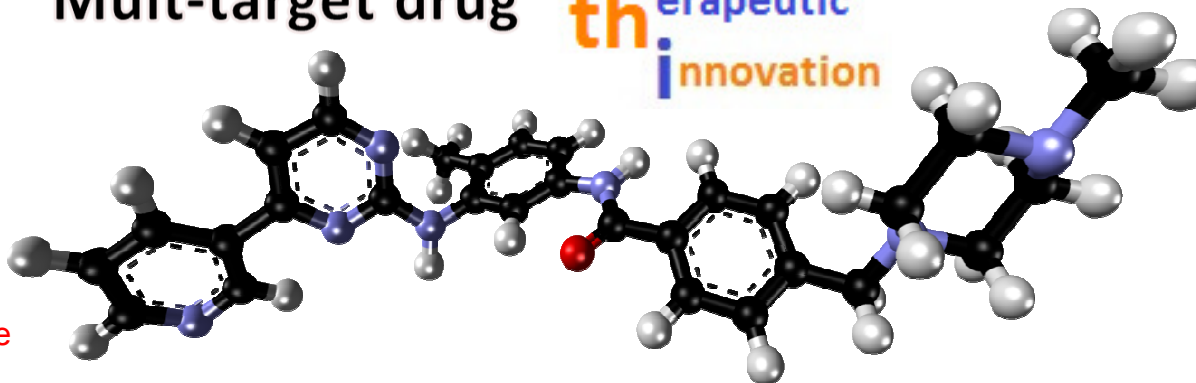
chronic myelogenous leukemia (CML)



Ciba-Geigy

Mult-target drug

therapeutic innovation



NOVARTIS

tyrosine-kinase inhibitor

2001



1988 – Nicholas Lydon, Brian J. Druker & Charles L Sawyers &

1995 - Compound STI571 ++

2001 – Imatinib (Gleevec[®], [Novartis](#))[\[link\]](#)

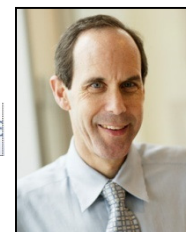
[*Nature Rev Drug Discov* 2002, 1, 493]

WW: US\$ ca. 5.1 bi (2014)

medicinal chemistry



Nicholas B. Lydon
(Blueprint Medicines Inc)



Brian J. Druker*
Blueprint Medicines Inc



Charles L. Sawyers**
Blueprint Medicines Inc

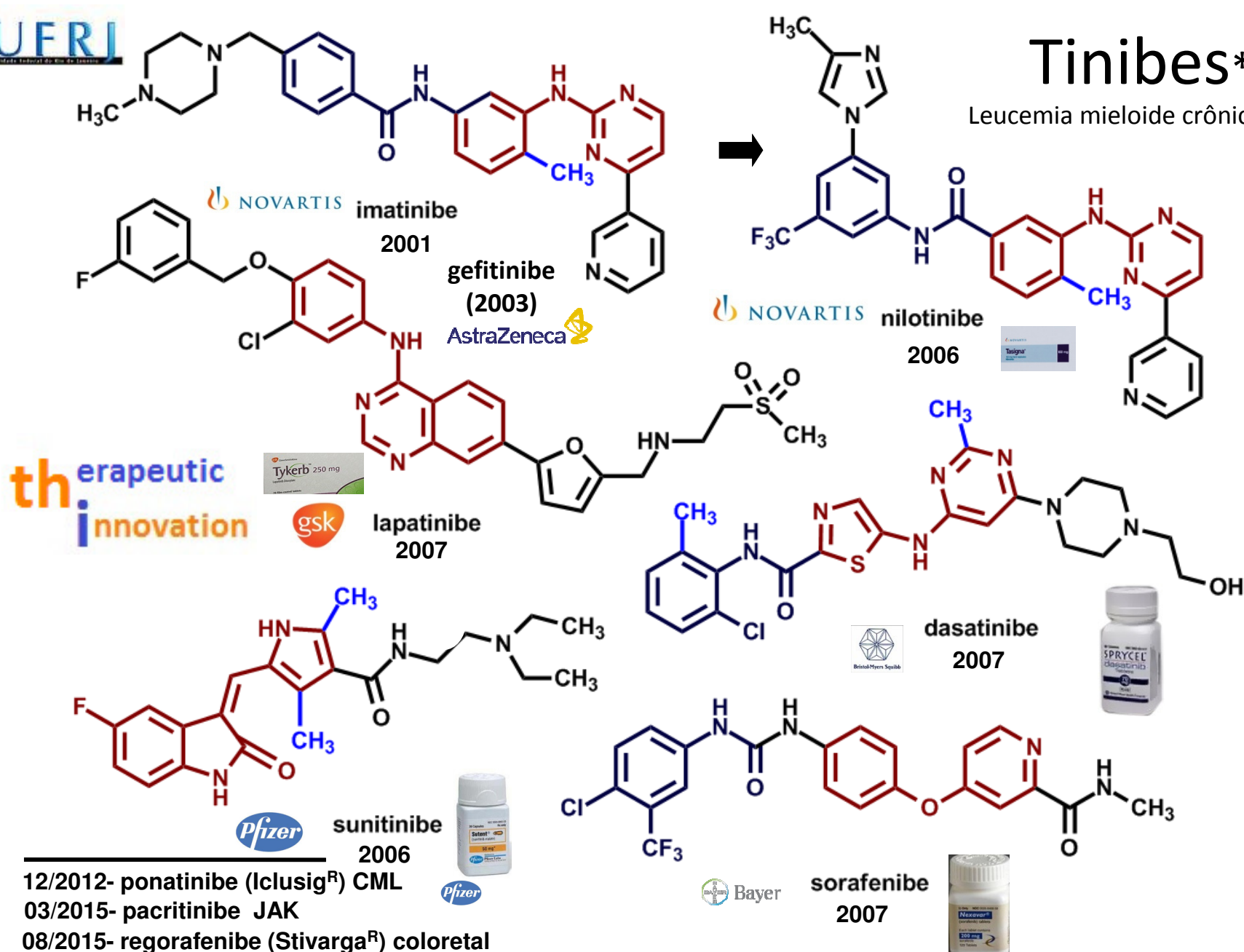
& 2009 - Lasker Foundation Clinical Award (*J. Clin. Invest.* 2009, 119, 2863)

* Has been awarded with the 2012 Japan Prize in Healthcare and Medical Technology;

** Was named in 2011, Thomson Reuters Citation Laureate in Medicine;

Tinibes*

Leucemia mieloide crônica (CML)



12/2012- ponatinibe (Iclusig[®]) CML
 03/2015- pacritinibe JAK
 08/2015- regorafenibe (Stivarga[®]) coloretal
 02/2016 – imatinibe genérico (US2/pill)

• Mercado mundial em 2014: US\$ 20,2 bi*

* C. W. Lindsley, *ACS Med. Chem. Lett.* **2014**, 5, 1066



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20 anos do LASSBio

MEMÓRIA FOTOGRÁFICA DO WORKSHOP 20 ANOS LASSBio

[Album de Fotos](#)



Prof. Helio M. Neves, Prof. Paulo B. R. Costa & Prof. Clezer J. Barreto

É assim começou o primeiro dia do evento de comemoração do LASSBio e seus 20 anos.



Prof. Clezer J. Barreto & Prof. Petronio Carlos C. Neto

Bom Vindos!

Últimas Notícias

Vem aí mais uma edição!



Escola de Verão
em Química Farmacêutica e Medicinal

23 a 27
janeiro
2017



CCS, UFRJ, junho 2016

Cio

Criado

ICB

INSTITUTO DE CIÊNCIAS BIOMÉDICAS UFRJ

INCT



inofar

Fármacos do século 21

“Multi-target paradigm for innovative ligand identification”

Novo paradigma

Química
med
Medicinal
chem



**Fármacos simples,
não curam doenças**

Receptor A

complexas

Receptor B

Doenças multifatoriais

O desenho racional de fármacos *multi-alvos* depende da capacidade de se combinarem fragmentos moleculares farmacofóricos, capazes de assegurar o reconhecimento molecular pelos receptores envolvidos.

M L Bognesi, A Cavalli, Multitarget Drug Discovery and Polypharmacology, *ChemMedChem* **2016**, *11*, 1190; A Anighoro et al., **Polypharmacology**: challenges and opportunities in drug discovery, *J. Med. Chem.* **2014**, *57*, 7874; 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; JR Morphy, CJ Harris, Eds., Designing multi-target drugs, RSC Publishing, 2012; E J Barreiro, C A M Fraga, New insights for multifactorial diseases therapy..., *Curr Drug Therapy* **2008**, *3*, 1; K Strebhardt, A Ullrich, Paul Ehrlich's magic bullet concept: 100 years of progress. *Nat Rev Cancer* **2008**, *8*, 473.

Novo inibidor dual de cinases

VEGFR / EGFR

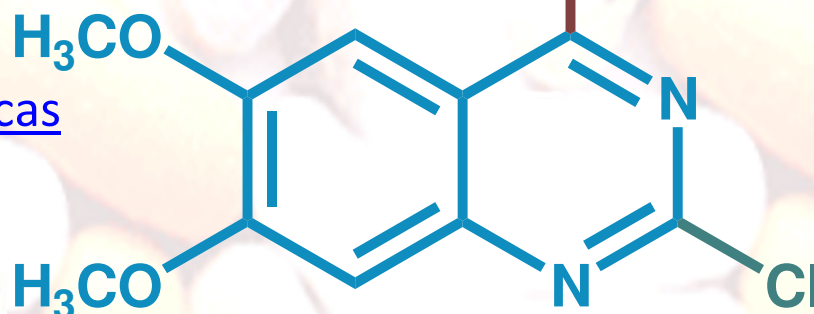
medicinal chemistry

LASSBio-1819



Etapas hierárquicas

Dual
Inhibitors
Dual

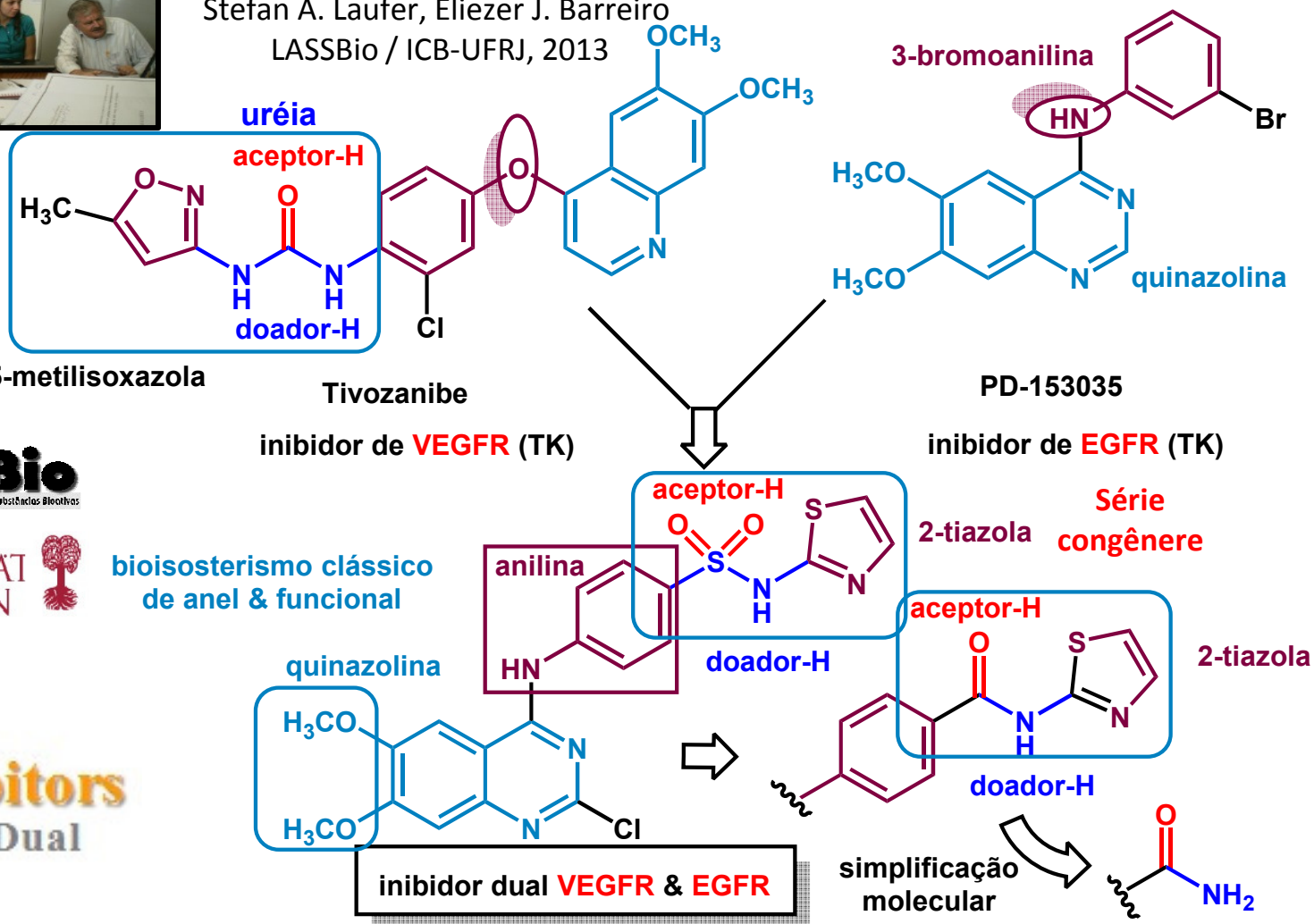


LASSBio
Laboratório de Avaliação e Síntese de Substâncias Bioativas

1. Mapa farmacofórico computacional (CAMD) para cada alvo: EGFR+VEGFR;
2. Desenho molecular de estruturas originais com melhor pontuação de encaixe virtual (molecular docking);
3. Síntese de nova série congênere com diversidade molecular adequada;
4. Ensaio de binding numa plataforma de cinases;
5. Seleção do melhor ligante;
6. **Patente;**
7. Publicações / teses;
8. Otimização do ligante identificado;

Novo inibidor dual de quinases

Lidia M. Lima, Maria Leticia C. Barbosa,
Stefan A. Laufer, Eliezer J. Barreiro
LASSBio / ICB-UFRJ, 2013



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; C Viegas Jr et al., *Molecular Hybridization: an useful tool in the design of new drugs prototypes*, *Curr. Med. Chem.* **2007**, 14, 103;

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

Maria Leticia 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,*}

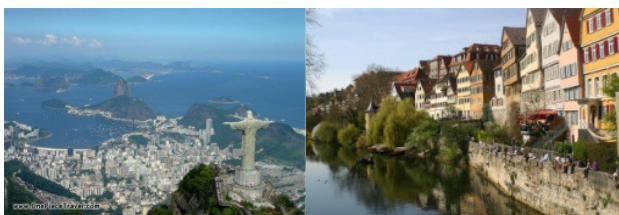
^a Laboratory of Evaluation and Synthesis of Bioactive Substances (LASSBio), Federal University of Rio de Janeiro, P.O. Box 68024, 21944-971 Rio de Janeiro, RJ, Brazil[†]

^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

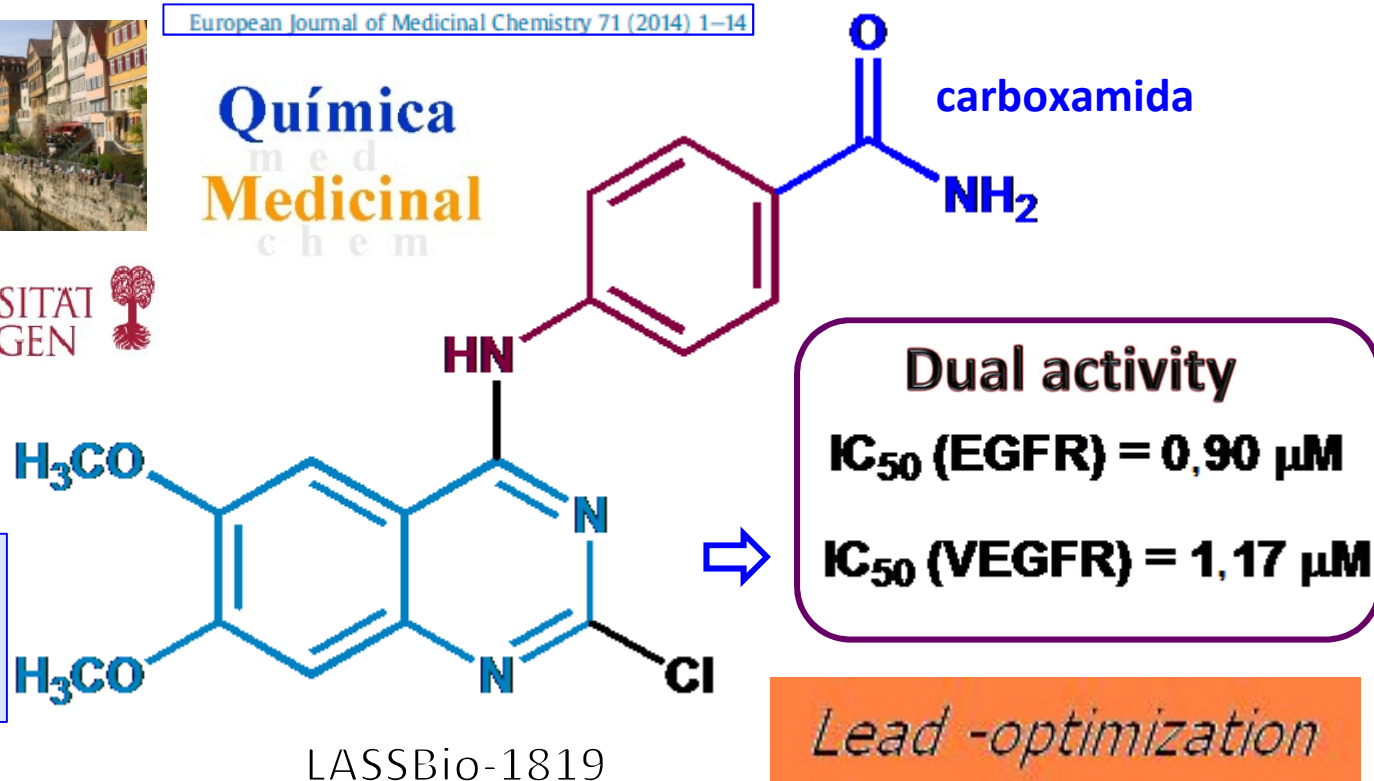
^d ProQinase GmbH, Freiburg, Germany

^e Department of Pharmaceutical/Medicinal Chemistry, Institute of Pharmacy, Eberhard-Karls-University Tübingen, Tübingen, Germany



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

Química
med
Medicinal
chem



Novel molecular pattern
with EGFR/VEGFR
dual activity !

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.

Patente

(12) PEDIDO INTERNACIONAL PUBLICADO SOB O TRATADO DE COOPERAÇÃO EM MATÉRIA DE PATENTES (PCT)

(19) Organização Mundial da Propriedade Intelectual
Secretaria Internacional



(10) Número de Publicação Internacional
WO 2014/113859 A1

(43) Data de Publicação Internacional
31 de Julho de 2014 (31.07.2014)

WIPO | PCT

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24 de Janeiro de 2013 (24.01.2013) BR
- (71) Requerente : UNIVERSIDADE FEDERAL DO RIO DE JANEIRO [BR/BR]; Av. Pedro Calmon, 550 - Prédio Reitoria - 2º andar, Ilha do Fundão, CEP-21941-901 Rio de Janeiro - RJ (BR).
- (72) Inventores : DE LACERDA BARREIRO, Eliezer Jesus; Rua Haddock Lobo, 35/603, Estácio, CEP-20296-130 Rio de Janeiro - RJ (BR). DE CASTRO BARBOSA, Maria Letícia; Rua Bulhões de Carvalho, 271/502, Ipanema, CEP-22081-000 Rio de Janeiro - RJ (BR). MOREIRA LIMA, Lidia; Rua Ambaítinga, 160/301, Praia da Bandeira (Ilha do Governador), CEP-21.921-520 Rio de Janeiro - RJ (BR). LAUFER, Stefan, Andreas; Otto-Erbe-Weg, 86, 72070 Tübingen/bw (DE). RABELLO DE SANT'ANNA, Carlos Maurício; Rua Juraci Camargo, 25/301, Ilha do Governador, Rio de Janeiro (BR). TESCH, Roberta; Rua Rio Preto, 100, Vila da Penha, CEP-21211-100 Rio de Janeiro - RJ (BR).
- (74) Mandatários : PEREIRA, Ricardo et al.; Agência UFRJ de Inovação, Rua Hélio de Almeida s/n, Incubadora de Empresas, Prédio2, Cid Universitária, CEP-21941-972 Rio de Janeiro-RJ (BR).
- (81) Estados Designados (sem indicação contrária, para todos os tipos de proteção nacional existentes) : AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW,

BR 10 2013 001809 0
Jan 2013



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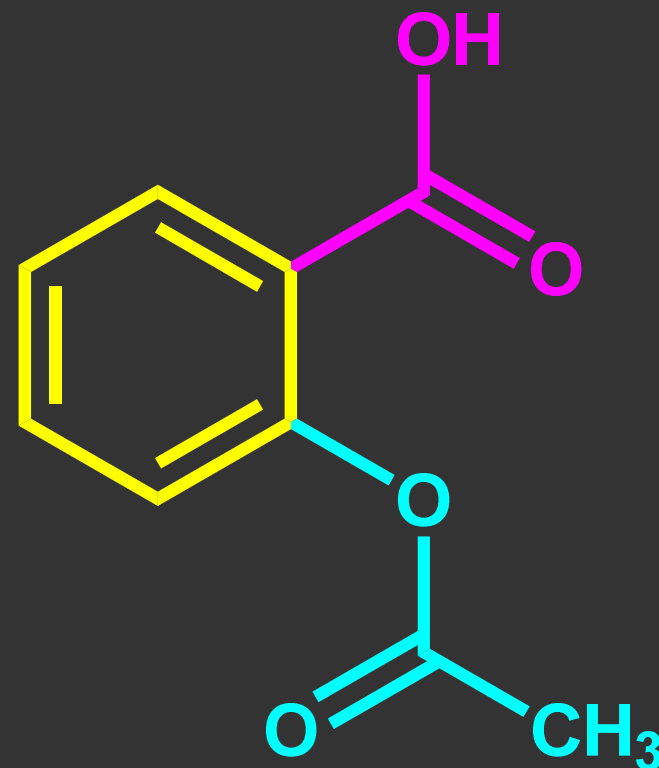
Os medicamentos
foram **uma das**
maiores **invenções**
do século 20 !

São moléculas que mudam o mundo!

CONVITE

De fármacos e suas descobertas

Pretende-se tratar de temas, opiniões, comentários sobre a Ciência dos Fármacos, seu uso seguro e benefícios. Aspectos da formação qualificada de universitários e pós-graduandos nas Ciências dos Fármacos também são de interesse.



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Muito Obrigado !