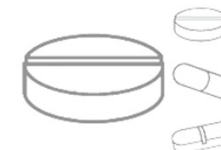




31 de janeiro de 2017

Interface entre Química e Farmacologia!



Eliezer J. Barreiro

ejbarreiro@ccsdecania.ufrj.br

Professor Titular

Laboratório de Avaliação e Síntese de Substâncias Bioativas
Instituto de Ciências Biomédicas



Universidade Federal do Rio de Janeiro

Instituto Nacional de Ciência e Tecnologia
de Fármacos e Medicamentos



www.inct-inofar.ccs.ufrj.br





UFRJ

Cidade Universitária, ilha do Fundão,
Rio de Janeiro, RJ

Laboratório de Avaliação e Síntese de Substâncias Bioativas



De onde venho...



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P e r g u n t a s ?

P e r g u n t a s ?

P e r g u n t a ?

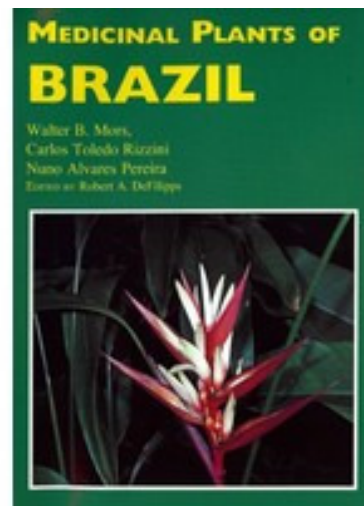
Interface entre Química e Farmacologia !

Índice

Interface Química & Farmacologia

Inter-alia:

- Alaíde Braga de Oliveira
- Angelo C. Pinto
- Ben Gilbert
- Domingos José Freire Júnior
- Ezequiel Correia dos Santos
- Francisco Mattos
- Maria Auxiliadora C. Kaplan
- Mario Saraiva
- Mauro Taveira Magalhães
- Massayoshi Yoshida
- Nídia F. Roque
- Otto Richard Gottlieb
- Raimundo Bráz F^o
- Theodoro Peckolt
- Walter Baptiste Mors





Interface Farmacologia & Química

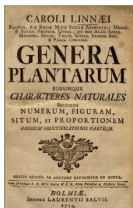


O início ...



Antoine Laurent de Jussieu
1748-1832

Os vegetais e sua
"ordem admirável"

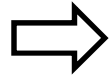


1811

Farmacognosia



1789



François Magendie
1783-1855



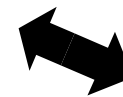
Formulaire
1827
Fisiologia
experimental

1849

Farmacologia



Pierre-Jean Robiquet
1780-1840



Pierre Joseph Pelletier
1788-1842

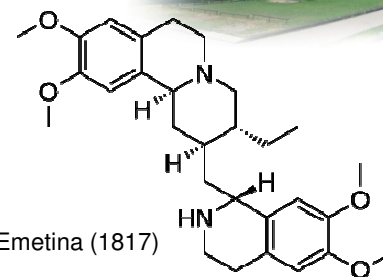
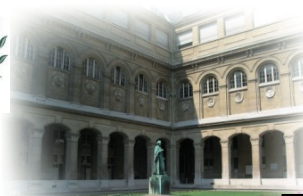


Substâncias puras

Fitoquímica



Química de PN



Emetina (1817)
Ipecacuanha

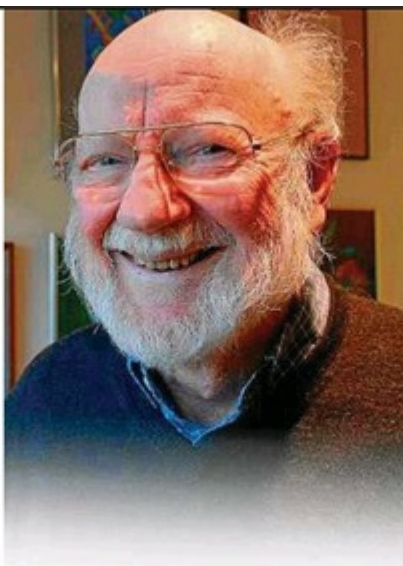


alcalóides

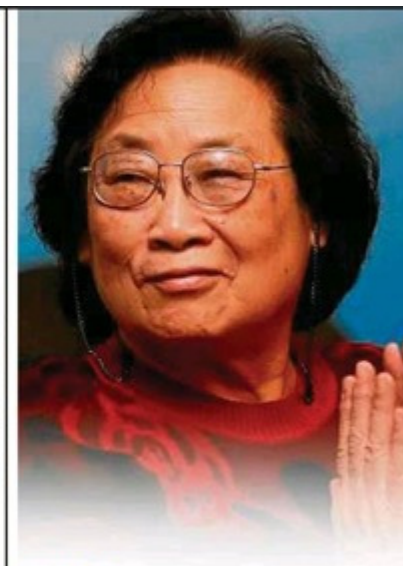
Prêmio Nobel de Medicina 2015



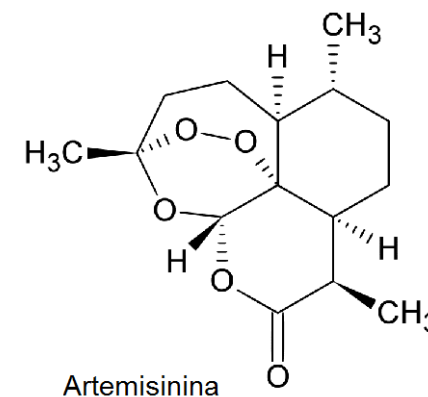
Satoshi Omura



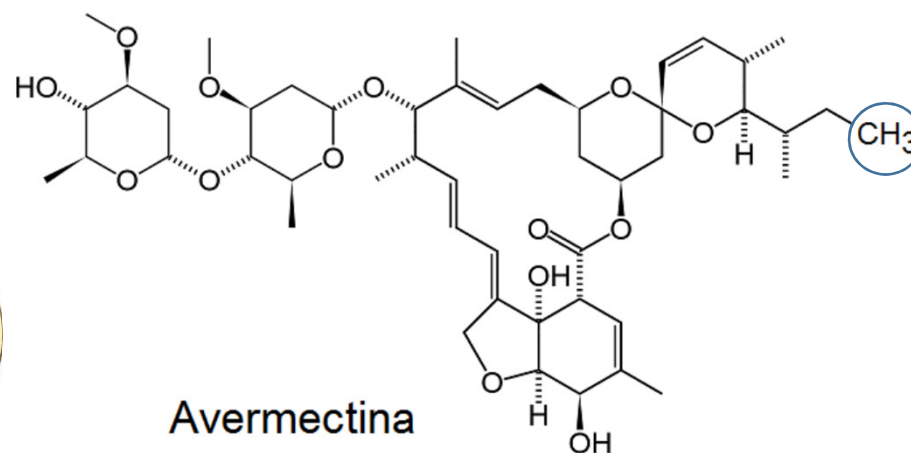
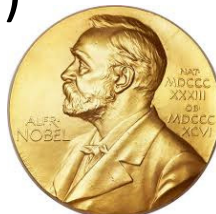
William Campbell



Youyou Tu



William C. Campbell (Irlanda)
 Satoshi Omura (Japão)
 Youyou Tu (China)



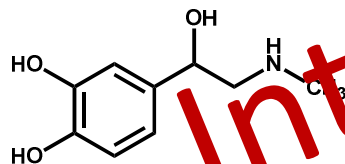
The Nobel Prize in Chemistry 2012



Photo: U. Montan
Robert J. Lefkowitz



Photo: U. Montan
Brian K. Kobilka



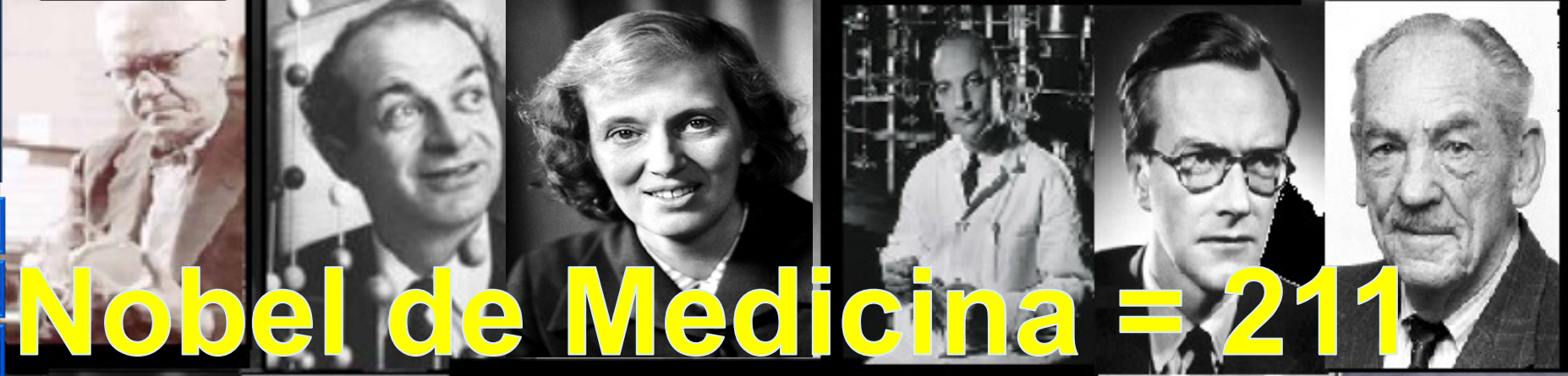
Interdisciplinaridade

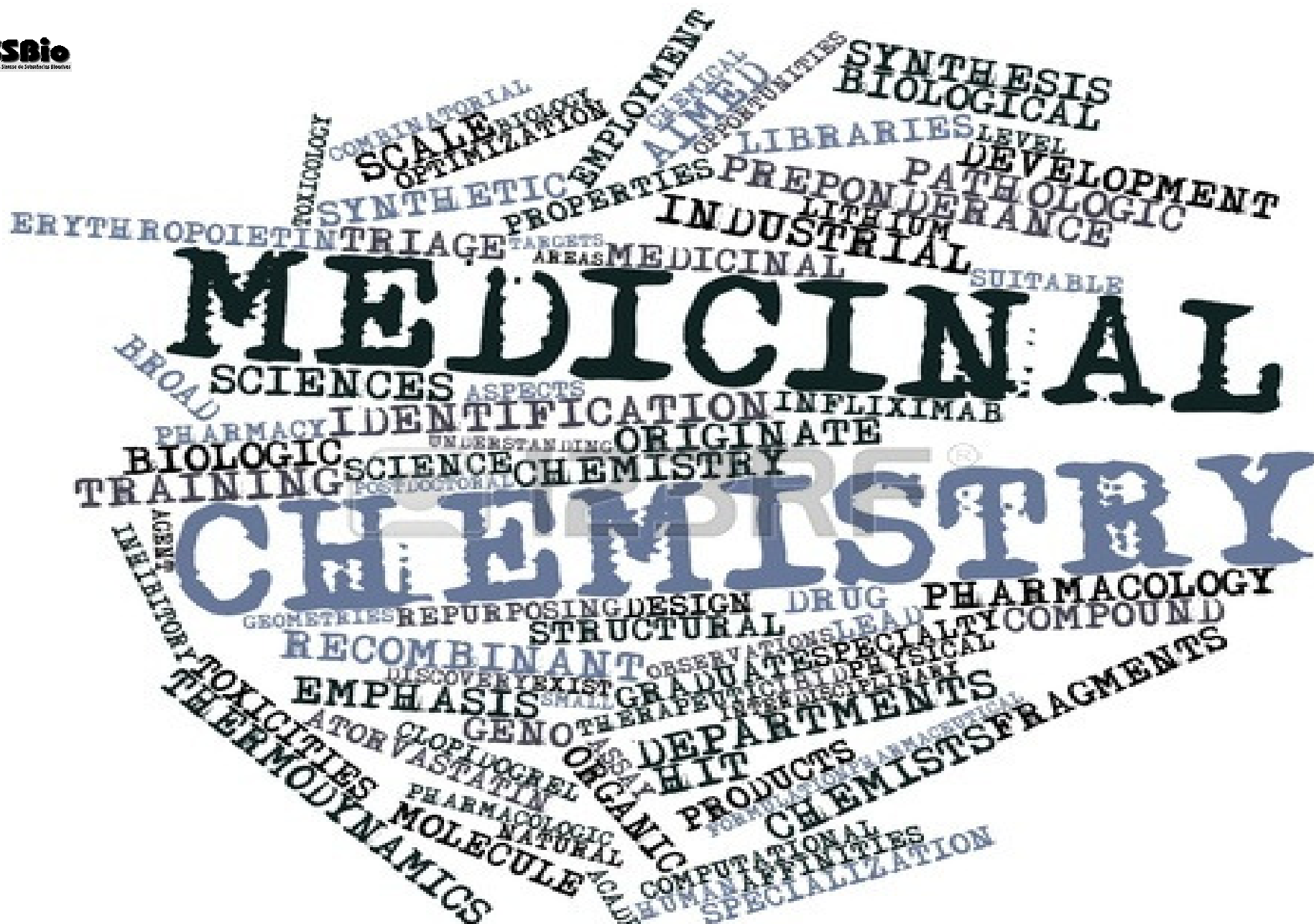
- a) Howard Hughes Medical Institute and Duke University Medical Center, Durham, NC, USA
- b) Stanford University School of Medicine, Stanford, CA, USA

“for studies of G-protein-coupled receptors”

Nobelistas 1901-2016

Universidade Federal do Rio de Janeiro





Interdisciplinar

Interdisciplinaridade: a integração de conhecimentos de diferentes áreas para a solução de problemas complexos.

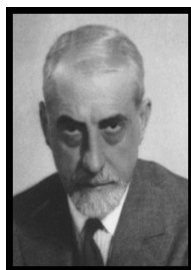


Emil Fischer (50)



1852-1919

The Nobel Prize in
Chemistry
1902



Ernest Fourneau (39)

1872-1949

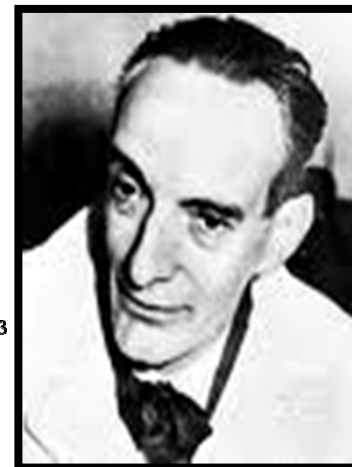


Paul Ehrlich (54)



1854-1915

The Nobel Prize in
Physiology or Medicine
1908

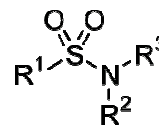


Daniel Bovet (45)

1907-1992



The Nobel Prize in
Physiology or Medicine
1952



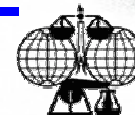
Química
med
Medicinal
chem

Interface

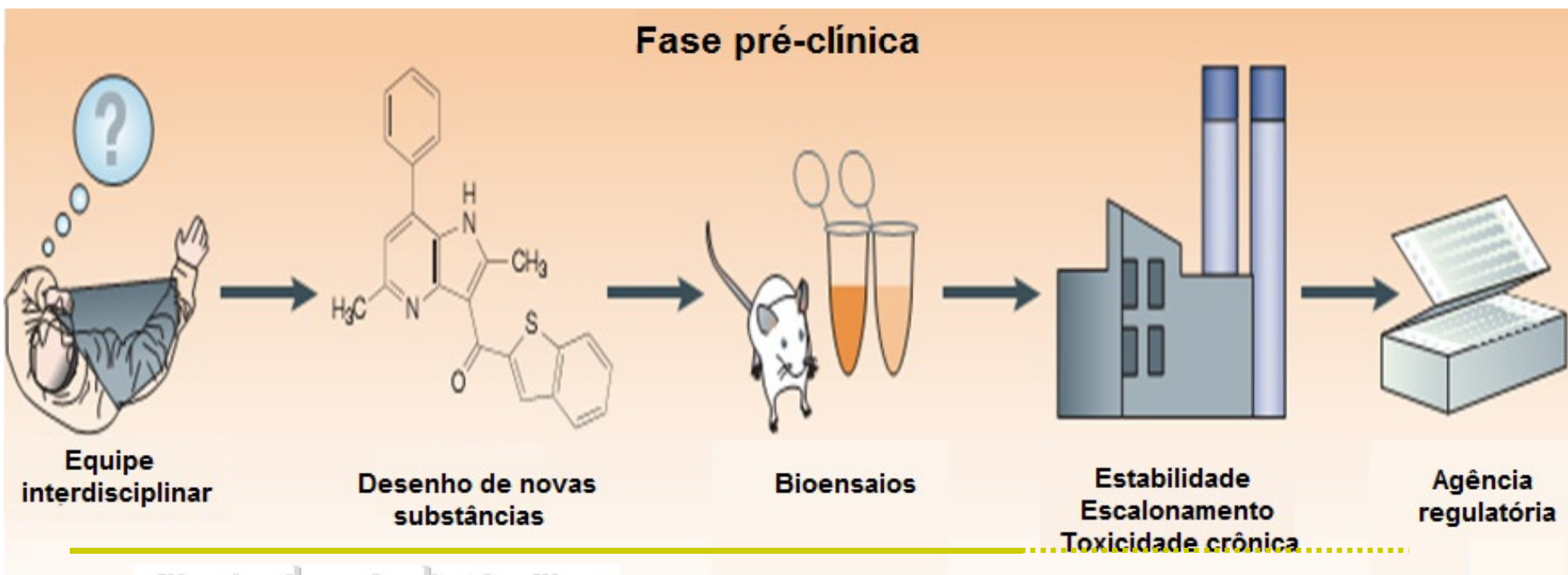
Química Medicinal

É uma disciplina baseada em Química, que combina sua expertise com a Farmacologia, para descobrir novas entidades químicas, originais, de aplicação terapêutica. Inclui os estudos de todos aspectos moleculares da estrutura, responsáveis pelas propriedades terapêuticas.

É uma disciplina translacional na inovação em fármacos.



O processo da descoberta de novo fármaco



Química Medicinal

Fase clínica

É um desafio complexo...





Desafios complexos necessitam de abordagens **interdisciplinares**, que exigem arranjos temporais & **institucionais** próprios!



A **interface** entre **Química** e **a Farmacologia** é o **fármaco**!



Professor Peter Weingart,
Diretor do Center for Interdisciplinary Research,
Universidade de Bielefeld, Alemanha.

([conferência no IEA \(USP\) em 28 de julho de 2015](#)).

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

NATURE REVIEWS | DRUG DISCOVERY VOLUME 3 | OCTOBER 2004 | 853

Joseph G. Lombardino* and John A. Lowe III[†]

“As a scientist involved at the very earliest stages of drug discovery, the medicinal chemist.....”



INTERDISCIPLINARY TEAMS

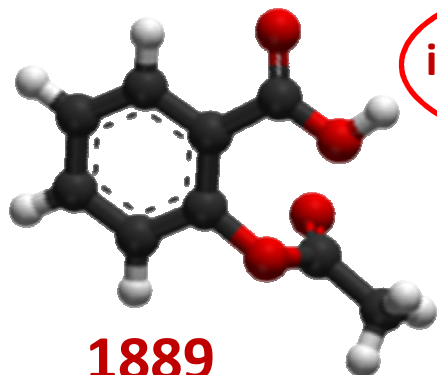
The role of pharmacology in drug discovery

NATURE REVIEWS | DRUG DISCOVERY VOLUME 1 | MARCH 2002 | 237

Bertil B. Fredholm, William W. Fleming, Paul M. Vanhoutte and Théophile Godfraind

“It is obvious that pharmacology is one of the most important scientific disciplines that underpin research in drug discovery.”





1889

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

AAS
C₉H₈O₄



John Vane (55)
(1927-2004)



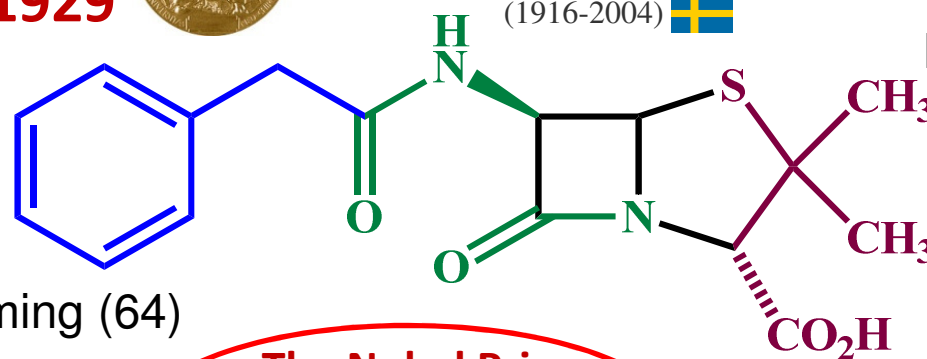
Sune Bergström (66)
(1916-2004)



1929



Sir Alexander Fleming (64)
(1881-1955)



Bengt Samuelsson (48)
(1934)



E. Boris Chain (39)
(1906-1979)



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

penicilina

C₁₆H₁₈N₂O₄S



Howard W. Florey (47)
(1898-1968)



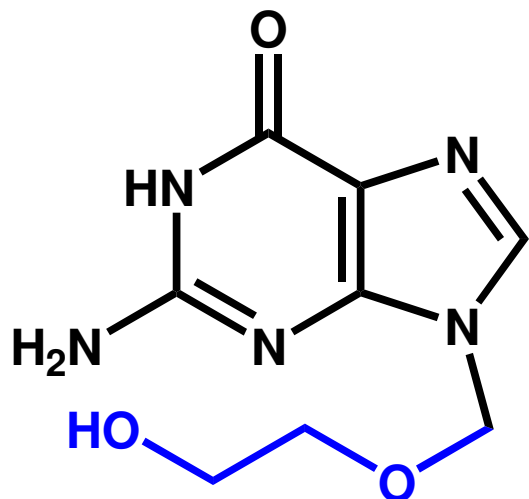
**The Nobel Prize
in Chemistry
1964**



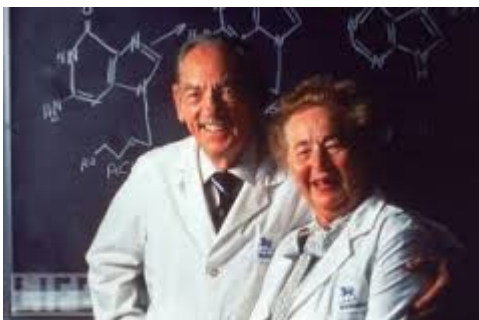
Dorothy C. Hodgkin (54)
(1910-1994)



Burroughs Wellcome
(atual GSK)



1977 - aciclovir



George Hitchings (83)
(1905-1998)

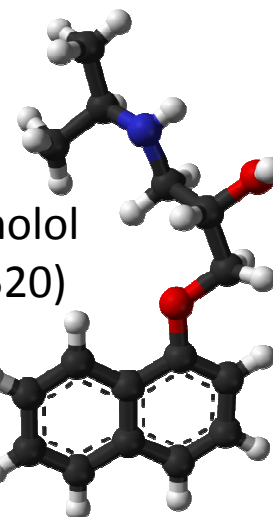


6-mercaptopurina,
azatioprina,
alopurinol, trimetoprim,
nelarabina

Gertrude B Elion (70)
(1918-1999)



1988



Propranolol
(ICI-45520)



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



1958 - 
1960 - [ICI-38174](#)

Dr John Stephenson

[História do propranolol](#)



1936



Otto Loewi (63)
(1873-1961)



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



Raymond Ahlquist
(1914-1983)



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

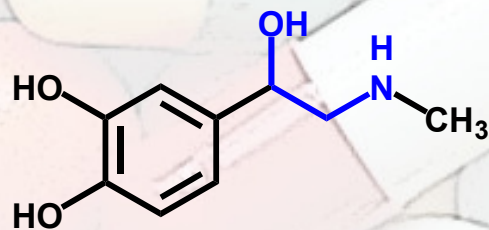
Química
med
Medicinal
chem

Pharmacology
Farmacologia

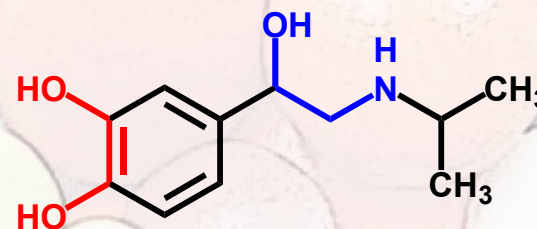
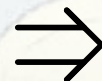
JW Black & JS Stephenson

As bases racionais da gênese do propranolol

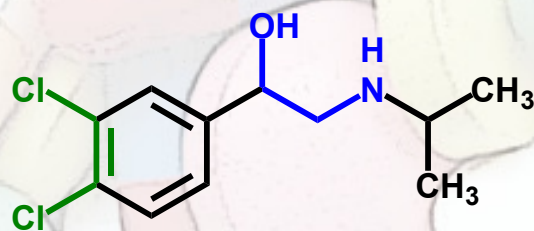
EJB- Blog Propranolol



adrenalina



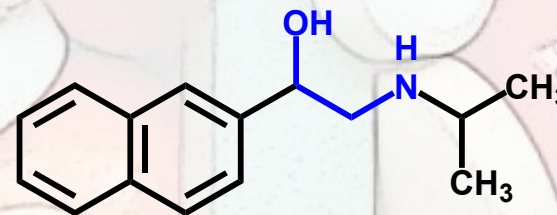
análogo isopropílico



1957 - DCI
β-bloqueador

Irwin H Slater & C. E. Powell

Lilly

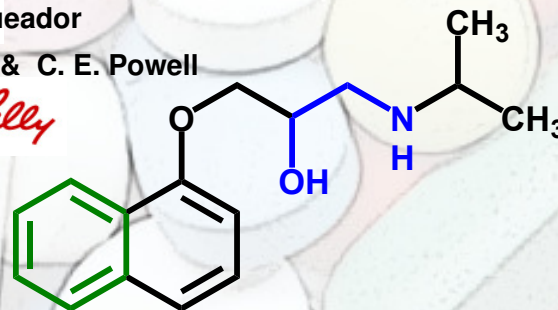


pronetalol

J. Black et al., *Br. J. Pharmacol. Chemother.* **1965**, 25, 577



1964



propranolol



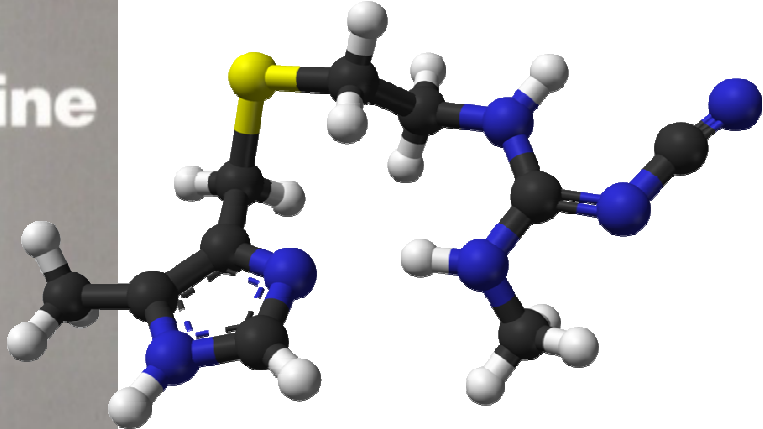
Melanie Patricia Stapleton* is the 1997 winner of the Texas Heart Institute Award for Undergraduate Writing in the History of Cardiovascular Medicine and Surgery. This is her winning paper.

* M P Stapleton, Sir James Black and propranolol. The role of the basic sciences in the history of cardiovascular pharmacology, *Tex Heart Inst J.* **1997**, 24, 336

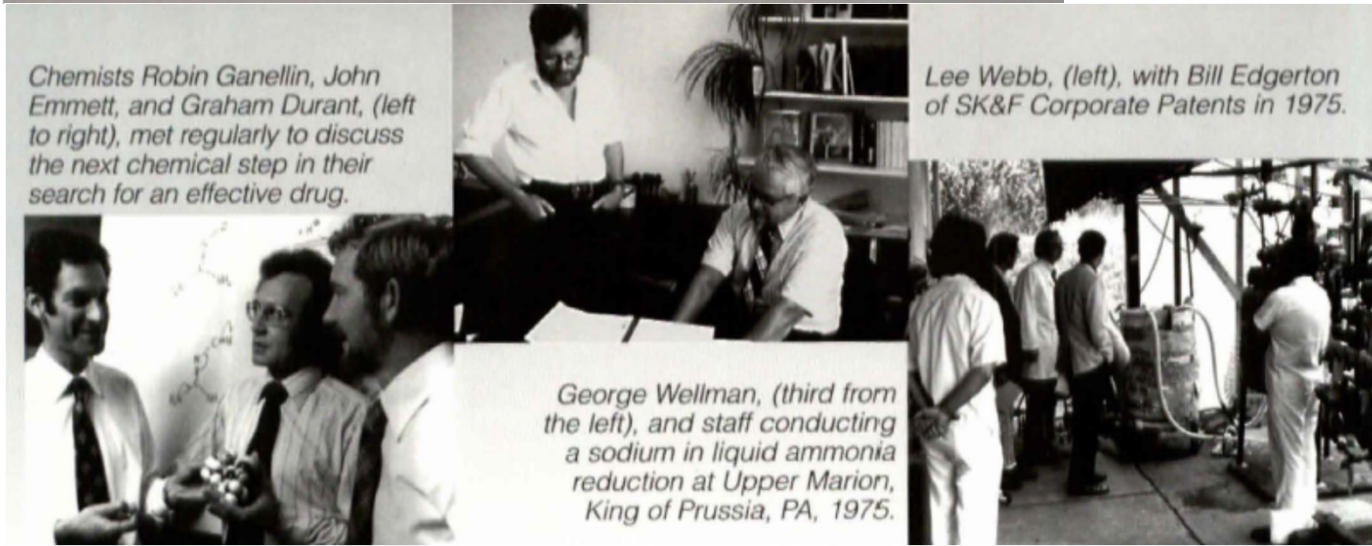


An International Historic
 Chemical Landmark
[ACS Historic Landmarks](#)
**The discovery of histamine
 H₂-receptor antagonists**
 1998

Cimetidina



1976



Chemists Robin Ganellin, John Emmett, and Graham Durant, (left to right), met regularly to discuss the next chemical step in their search for an effective drug.

Lee Webb, (left), with Bill Edgerton of SK&F Corporate Patents in 1975.

George Wellman, (third from the left), and staff conducting a sodium in liquid ammonia reduction at Upper Marion, King of Prussia, PA, 1975.

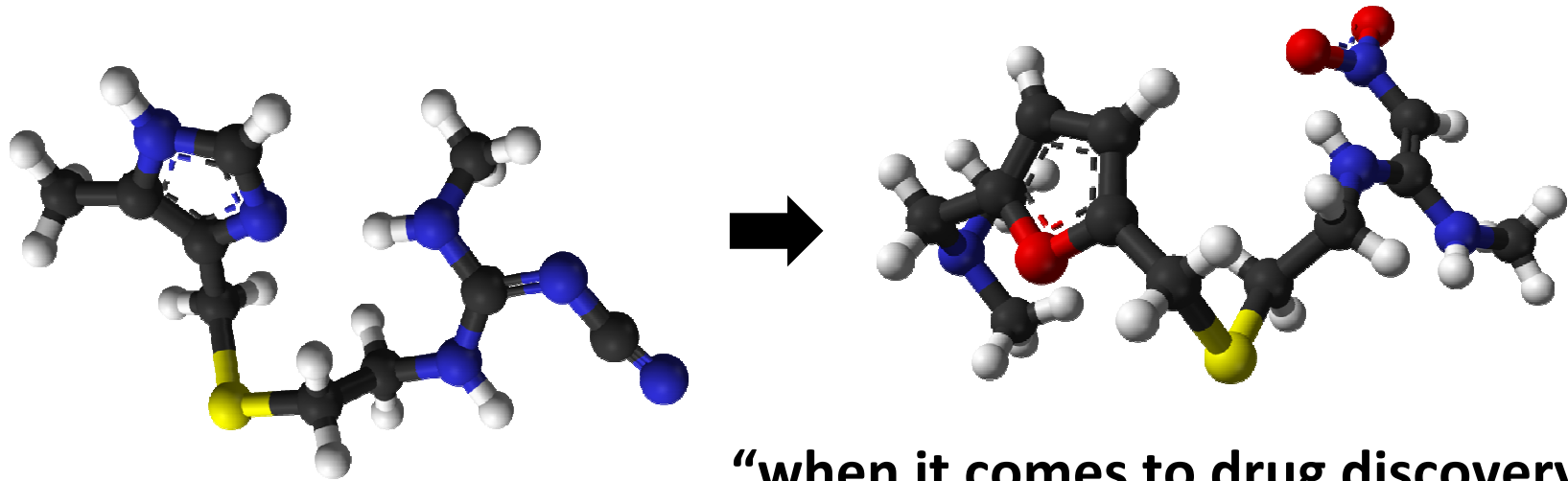


R Ganellin

Química
 Medicinal

"The innovator's skill, is in 'seeing what everybody has seen, and thinking what nobody has thought", Claude Bernard.

Cimetidina & Ranetidina



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

1715 - Allen & Hanburys Ltd



1958 - Glaxo



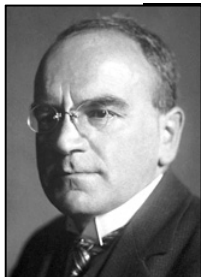
Barry John Price

(1943-)



Do *bolor* até uma inovação bilionária...

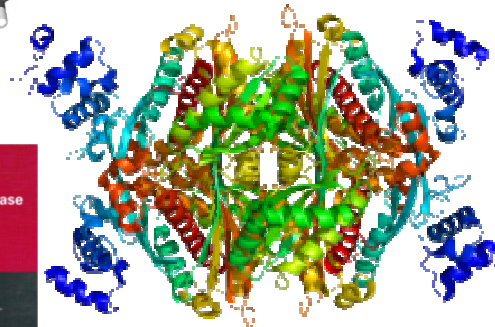
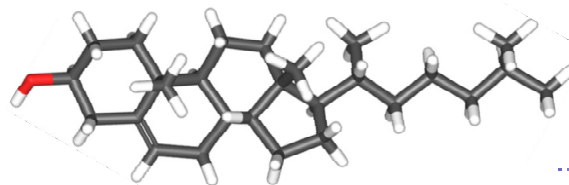
Universidade Federal do Rio de Janeiro



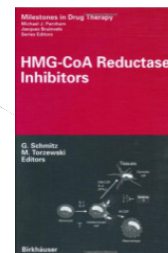
Heinrich O Wieland (50)
 (1877-1957)
1927



Adolf Windaus (52)
 (1876-1959)
1928



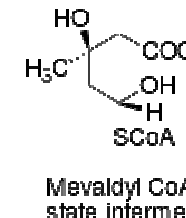
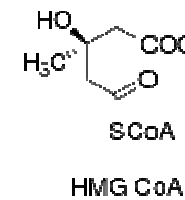
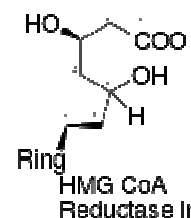
HMGCoAR



1975



John Cornforth (58)
 (1917-2013)



1964



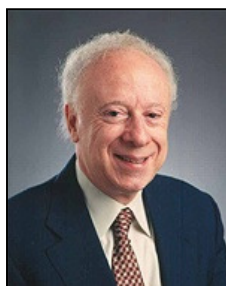
Konrad Bloch (53)
 (1912-2000)



Feodor Lynen (54)
 (1911-1979)

1985

LDL



Joseph L Goldstein (45)
 (1940)



Michael S Brown (44)
 (1941)



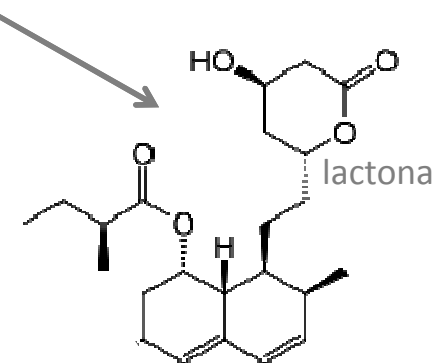
Akira Endo
 (1933)



1976



J Med Chem
1985, 28, 1



Mevinolina /compactina



Akira Endo, Sankyo Co

Lasker Award 2008

1975 – Mevastatina (ML-263b)



A.Endo, *J. Med. Chem.* **1985**, 28, 1

E\$tatina\$, a inovação bilionária

Prototipo natural

Similaridade molecular



A.Endo, *J. Antibiot.*

1976, 29, 1346

Penicillium citrinum

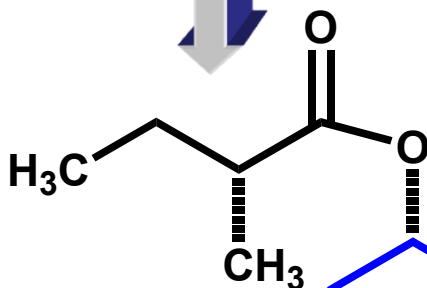
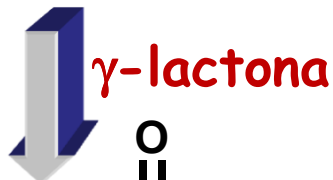
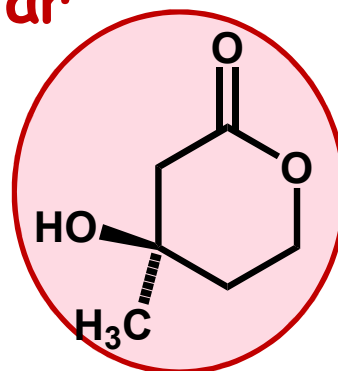
Idem, Ibid, **1979**, 32, 852

Monascus ruber

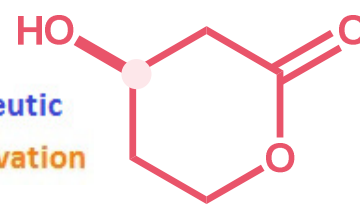
(compactina)

Mevalolactona

HMG-CoA redutase



Mevilonina



Roy Vagelos

CEO MSD

NAS Award for Chemistry

in Service to Society

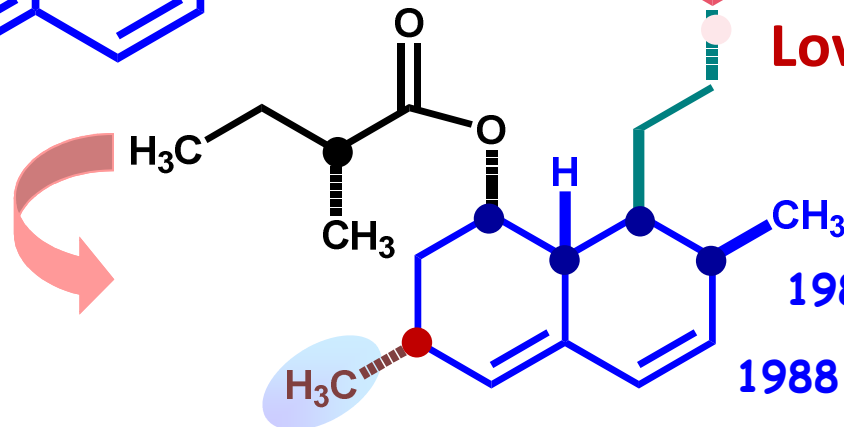
Química
 Medicinal



Arthur A Patchett

Alfred Burger Award 2002

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



Lovastatina (MK-803)

1978 – Merck & Co.

Aspergillus terreus

1987- **MERCK (Mevacor^R)**

1988 – Mevacor^R US\$ 260mi





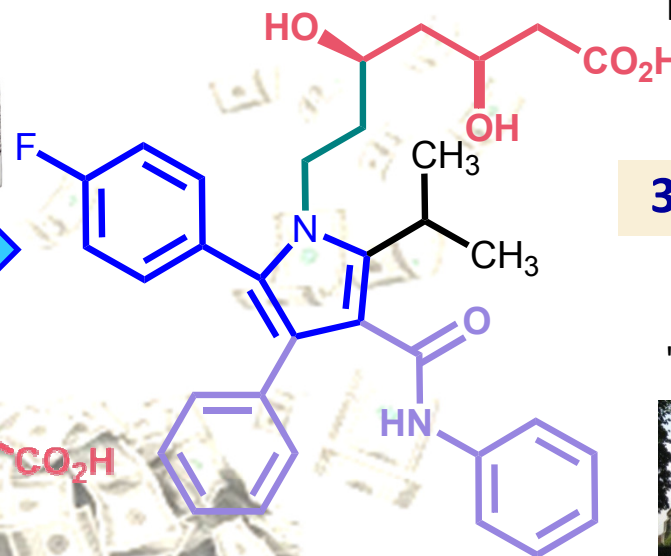
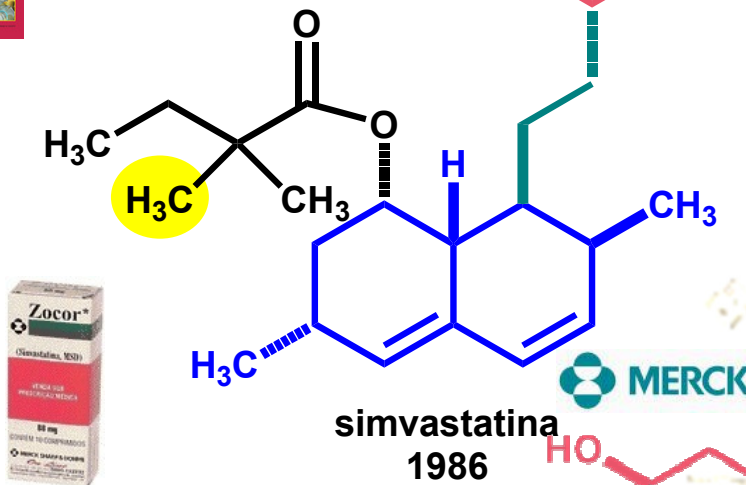
Arthur A Patchett
J Med Chem 2003, 45, 5609

Estatina\$

5-HMGCoARI



Bruce Roth
Parke-Davis Co



3^a geração



"patent cliff"



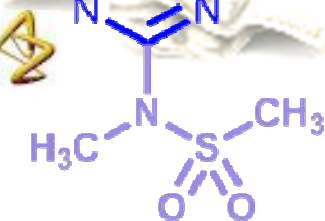
US\$ 150 bi

Química
med
Medicinal
chem



AstraZeneca

"super-statin"



IC₅₀ HMG-CoAR = 5 nM

rosuvastatina
2004

CAS 147098-20-2



World Top
selling drug

US\$ 5,07 bi (2015)



www.inct-inofar.ccs.ufrj.br





“... With the advent of *in vitro* test systems about 30 years ago, ... drug discovery shifted from animal studies to target-oriented research. This strategy works well in cases in which a certain disease is related to a unique target that can be modulated by a small molecule.”



Professor Hugo Kubinyi

Universität Heidelberg
&
BASF Ludwigshafen

medicinal chemistry



Indometacina



Wistar



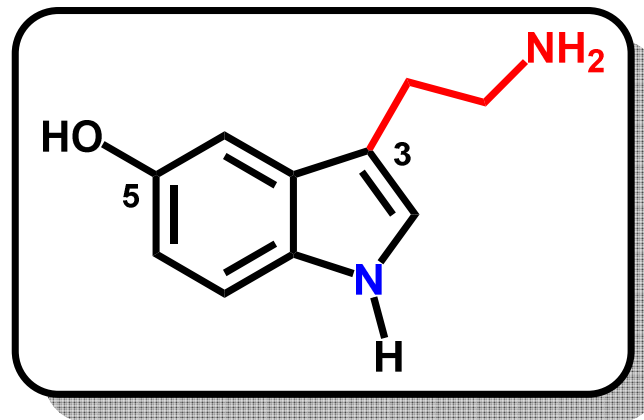
Charles A Winter
(1903-1999)



Tsung-Ying Shen
(1924-)

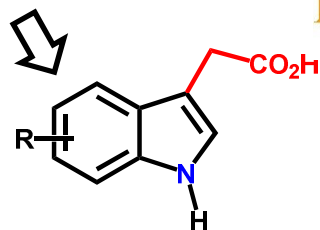


The first winner of the
Alfred Burger Award (1980)



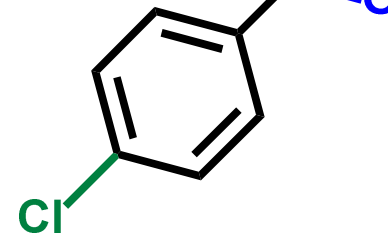
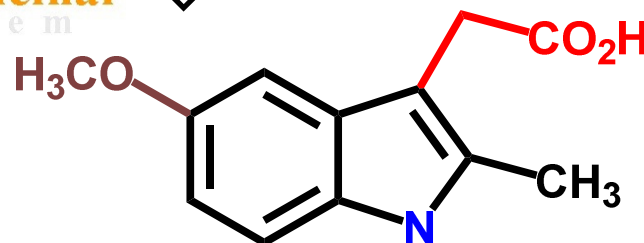
Química
med
Medicinal
chem

300 compostos



Merck Institute for
Therapeutic Research

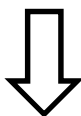
TY Shen, 1963



indometacina



C. Gordan Van Arman
Wyeth lab., Radnor
Pennsylvania



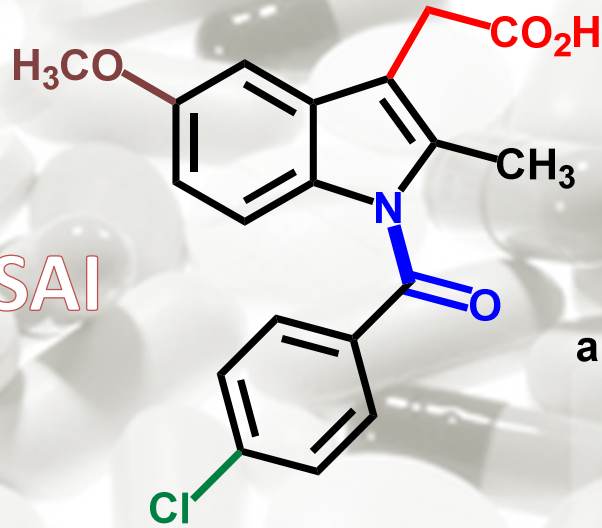
Cg-i PE model
Carrageenan-induced paw oedema

Pharmacology
Farmacologia

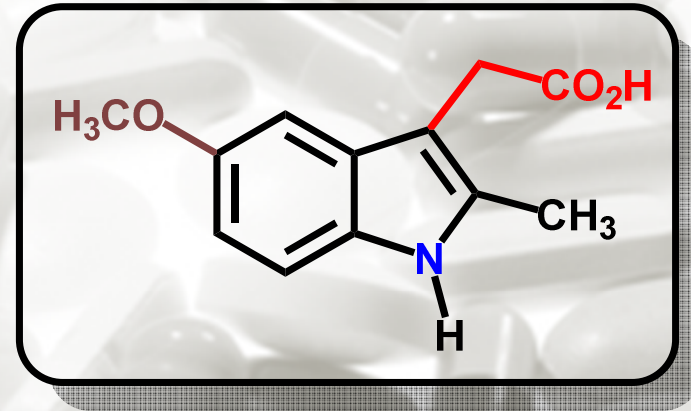


Indometacina

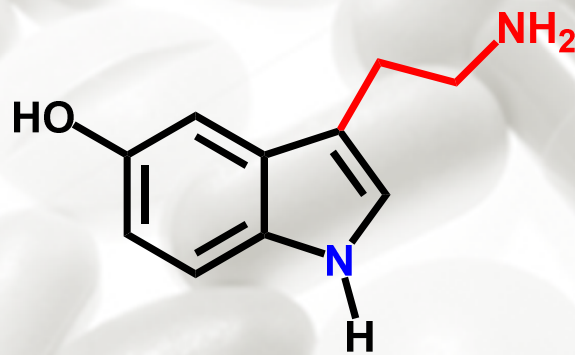
NSAI



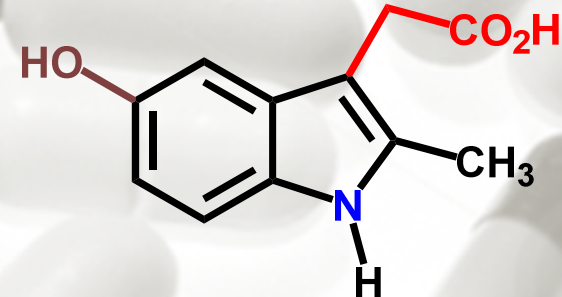
indometacina



ácido 3-indolilacético



serotonina

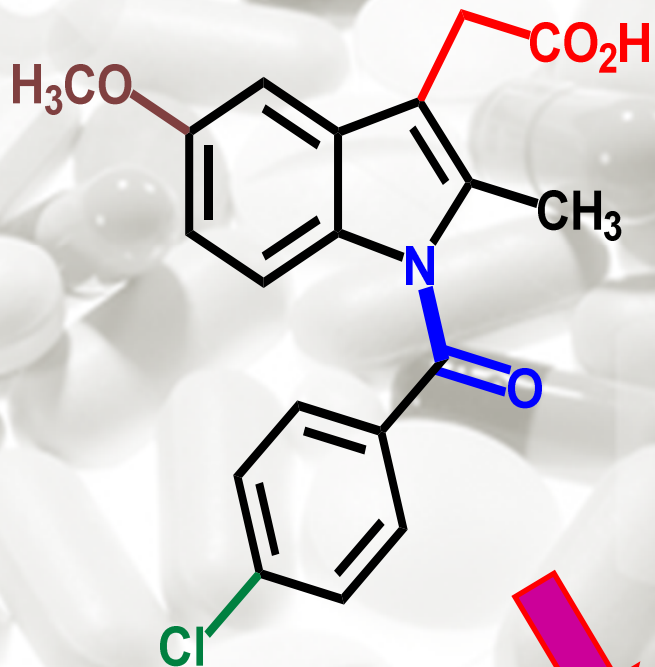




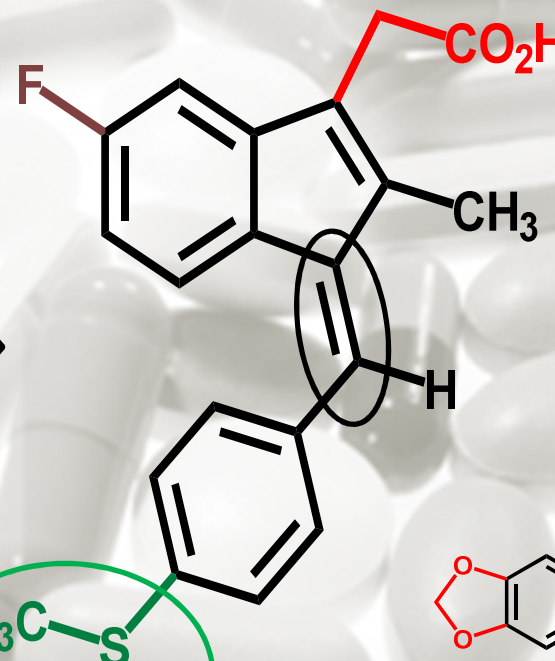
Indometacina \Rightarrow Sulindaco



1972 - T.Y. Shen



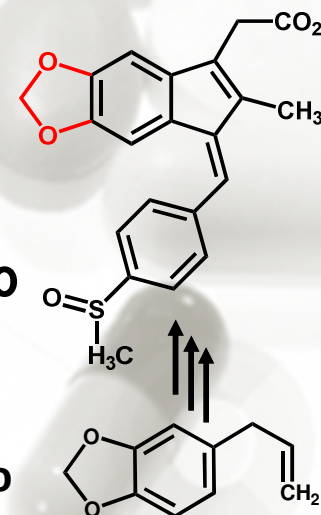
indometacina



sulindaco

NSAI

Pró-fármaco



EJ Barreiro, MEF Lima, The synthesis and anti-inflammatory properties of a new sulindac analogue synthesized from natural safrole, *Journal of Pharmaceutical Sciences* **1992**, *81*, 1219-1222



Nextdoor

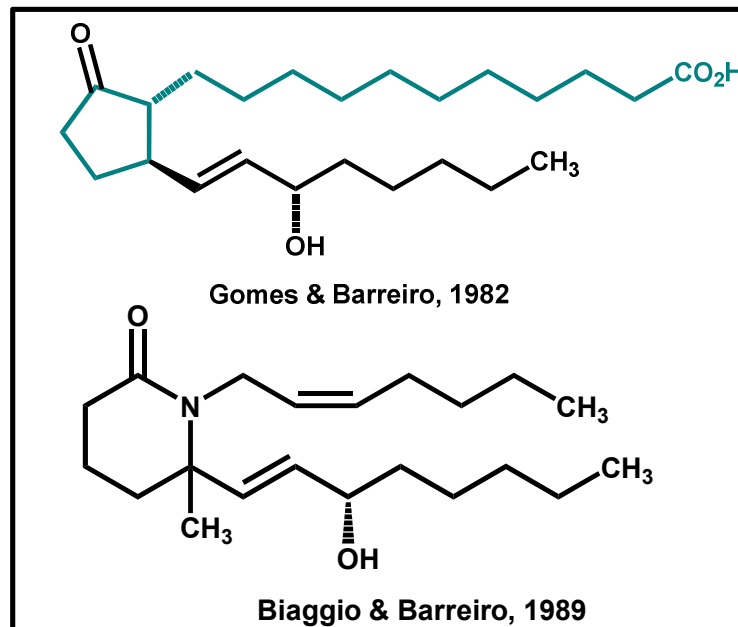


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Química
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Antonio José Lapa (EPM)
João Batista Calixto (UFSC)
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LASSBio-1425, an analog of thalidomide, decreases triglyceride levels and increases HDL cholesterol levels by inhibition of TNF- α production

Milla Machado Fumian^a, Nadia Alice Vieira da Motta^a, Rodolfo Maia^b, Carlos Eliezer Jesus Barreiro^b, Fernanda Carla Ferreira de Brito^{a,*}

RESEARCH ARTICLE

PLOS ONE
PLOS ONE 2016, 11(5):e0156271.
doi:10.1371/journal.pone.0156271

Paper

Non-competitive Inhibitor of Nucleoside Hydrolyase Identified by Fragment-based Drug Discovery

Marina Amaral Alves, Charlotte Nirma, Mayara M. Moreira, Rosemberg O. Soares, Pedro G. Pascutti, F. Noel, Paulo Costa, Carlos Sant'Anna, Eliezer J. Barreiro, Lídia Moreira Lima and Luzineide Tinoco

RSC Adv., 2016, Accepted Manuscript

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Laboratório de Avaliação e Síntese de Substâncias Bioativas



Cell Physiol Biochem 2016;38:821-835
(DOI:10.1159/000443037)

Respiratory and Systemic Effects of LASSBio596 Plus Surfactant in Experimental Acute Respiratory Distress Syndrome

Silva J.D.^a · de Oliveira G.P.^a · Samary C.S.^a · Araujo C.C.^a · Padilha G.A.^a · e Silva Filho F.C.^b · da Silva R.T.^c · Einicker-Lamas M.^c · Morales M.M.^d · Capelozzi V.L.^e · da Silva V.M.^e · Lima L.M.^f · Barreiro E.J.^f · Diaz B.L.^g · Garcia C.S.N.B.^{a,i} · Rocco P.R.M.^a

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Synthesis, Cytotoxic Activity and Docking Studies of LASSBio-1586 Isosteres

Teiliane Rodrigues Carneiro^{1,2}, Daniel Nascimento do Amaral¹, Maria Luisa Gomez Porras¹, Augusto César Aragão Oliveira², Bruno Coêlho Cavalcanti², Cláudia Pessoa^{2,3}, Eliezer J. Barreiro¹, Lídia Moreira Lima^{1,*}

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Journal of Medicinal Chemistry

J. Med. Chem. 2016, 59, 655–670

Article
pubs.acs.org/jmc

Design, Synthesis, and Pharmacological Evaluation of Novel N-Acylhydrazone Derivatives as Potent Histone Deacetylase 6/8 Dual Inhibitors

The total synthesis of calcium atorvastatin†

Luiz C. Dias,^{*,a} Adriano S. Vianna

A practical and convergent asymmetric synthesis of calcium atorvastatin (1) was performed via a mediated aldol reaction of β -keto ester. Calcium atorvastatin was obtained from aldehyde

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2017

Rev. Virtual Quim., 2015, 7 (2), 495-538. Data



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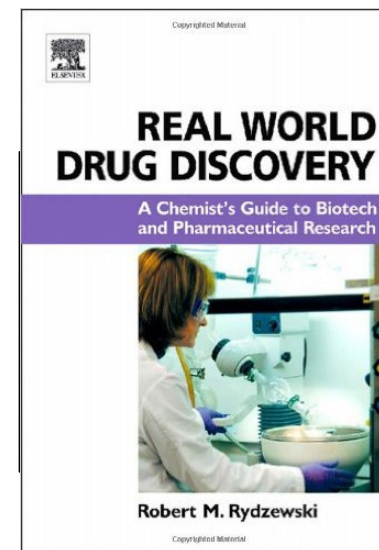
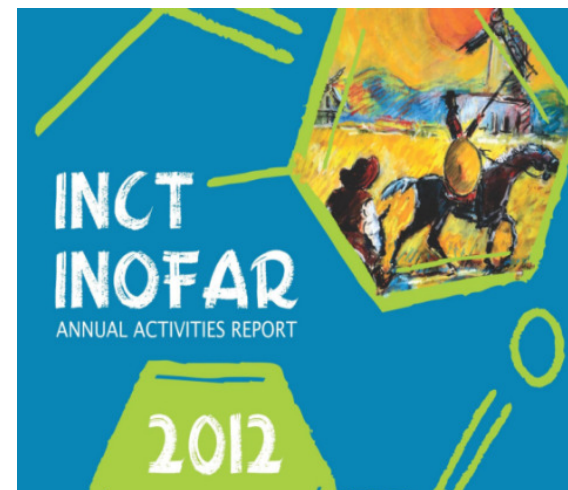
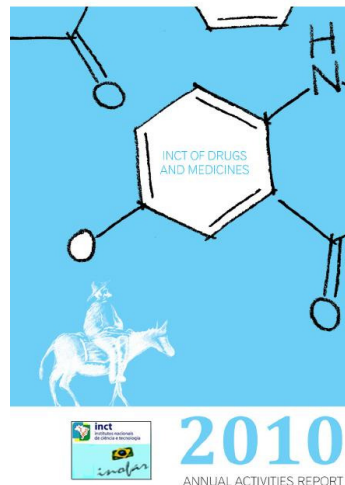
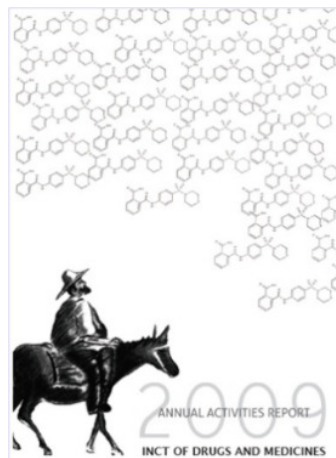
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Annual Activities Report



www.inct-inofar.ccs.ufrj.br/download/aar/2016.pdf

“..the **problem** will not be
our ability to do things.
The **terrible problem** is,
what will we choose
to do next?”

Sir James W. Black
(1924-2010)



