



Universidade Federal do Rio de Janeiro



# Os produtos naturais e a descoberta de fármacos inovadores

Natural products and innovative drug discovery



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### Laboratório de Avaliação e Síntese de Substâncias Bioativas

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

### Instituto Nacional de Ciência e Tecnologia de Fármacos e Medicamentos

### INCT-INO FAR

<http://www.inct-inofar.ccs.ufrj.br>





A narrativa:

- Introdução: PN & fármacos
- Moléculas pioneiras
- Quimioterapia do câncer
- Mais fármacos inovadores
- LASSBio & os bióforos naturais
- Considerações Finais



WILEY-VCH

Os fármacos são...

**MOLECULES  
THAT CHANGED THE  
WORLD**

...uma das maiores invenções do século XX

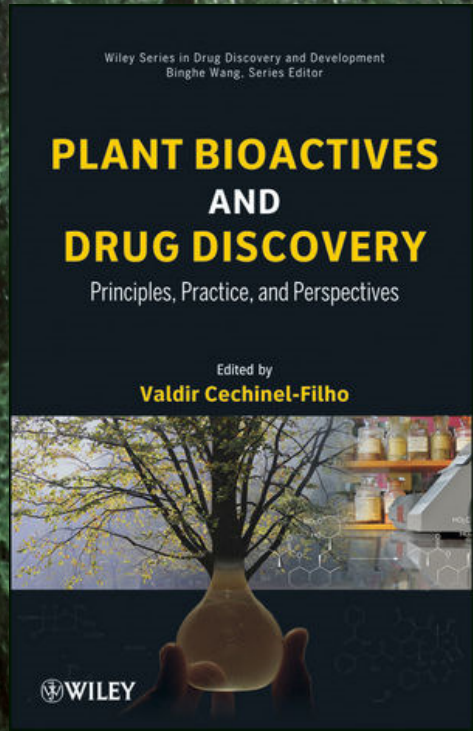
K. C. NICOLAOU • T. MONTAGNON



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# Os produtos naturais e os fármacos

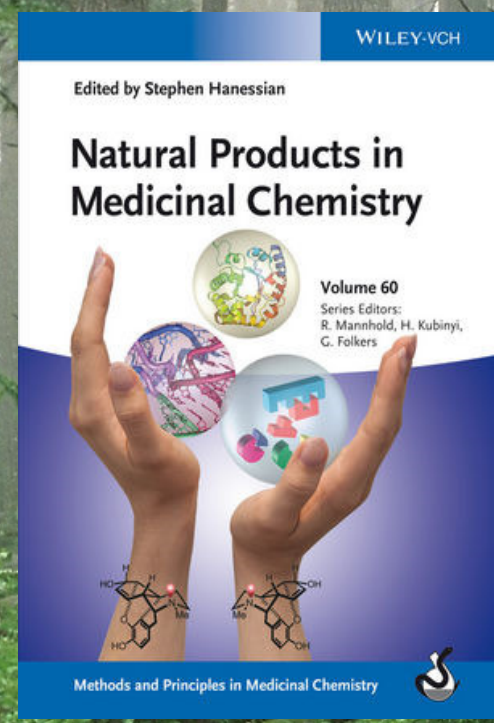
## natural product-derived drugs



2012



V. Cechinel-Filho (Editor)



2014



S. Hanessian (Editor)

*Inter-alia:* AL Harvey et al, *Nat. Rev. Drug Discov.* 2015, 14, 111; GA Cordell, MD Colvard, *J. Nat. Prod.* 2012, 75, 514; D Newman, GM Cragg, *J. Nat. Prod.* 2012, 75, 311; DGI Kingston, *J. Nat. Prod.* 2011, 74, 496; *Natural Product Chemistry for Drug Discovery*, AD Buss, MS Butler Eds., RSC Publishing, 2012; EJ Barreiro, VS Bolzani, *Quim. Nova* 2009, 32, 679

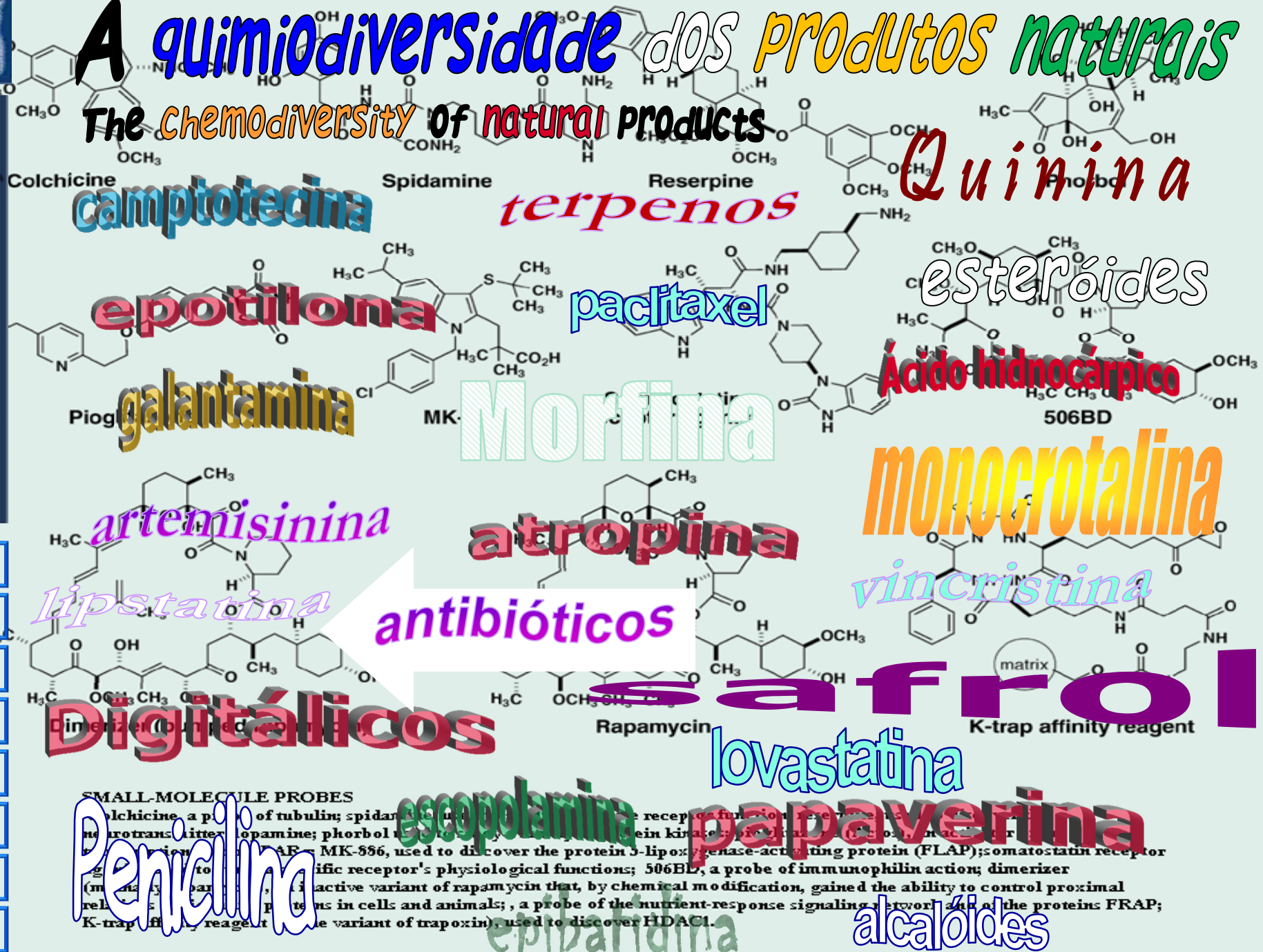




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# A quimiodiversidade dos produtos naturais

## The chemodiversity of natural products



### SMALL-MOLECULE PROBES

Colchicine, a probe of tubulin; spidamine, used to discover the receptor function of tyrosine kinases; reserpine, a probe of neurotransmitter reuptake; ropamine; phorbol, a probe of protein kinase C; vincristine, a probe of microtubule function; epotilona, a probe of the protein 5-lipoxygenase-activating protein (FLAP); somatostatin receptor agonist, a probe of specific receptor's physiological functions; 506BL, a probe of immunophilin action; dimerizer (mimicking the active variant of rapamycin that, by chemical modification, gained the ability to control proximal signaling pathways in cells and animals); , a probe of the nutrient-response signaling network and of the proteins FRAP; K-trap affinity reagent (the variant of trapoxin), used to discover HDAC1.



*Moléculas pioneiras...*

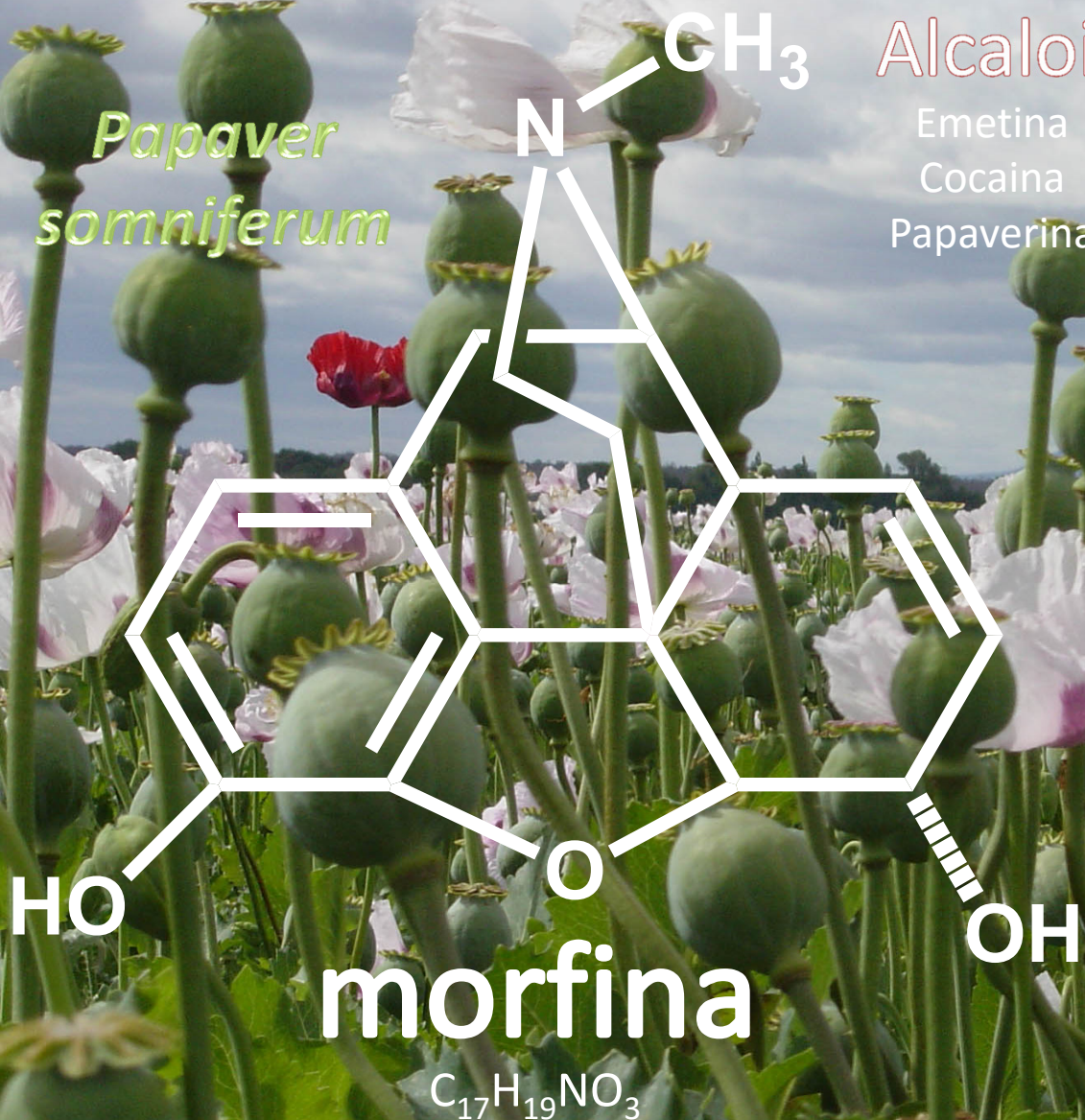
*Pioneering molecules ...*





# Moléculas pioneiras...

*Papaver  
somniferum*



Alcaloides

Emetina  
Cocaina  
Papaverina

1804

Friedrich Sertürner



(1783-1841)

Sir Robert Robinson



1947



1886-1975

Marshall D. Gates, Jr.



1915-2003

University of Rochester

\* Evans 1982; Fuchs 1988; Parker;1992; Overman 1993;  
Mulzer-Trauner 1996; White 1999; Taber 2002; Trost 2002;  
Fukuyama 2006; Guillou 2008; Magnus 2009; Stork 2009.



# Da morfina às 4-fenilpiperidinas

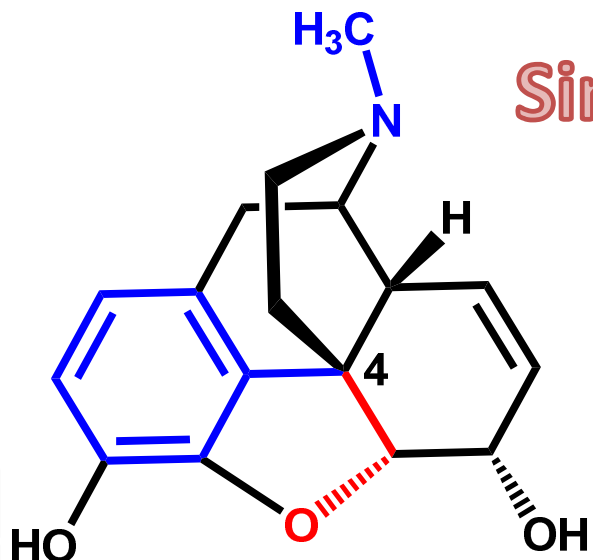
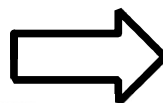
## Morphine to 4-phenylpiperidines

Química Medicinal

### Simplificação molecular

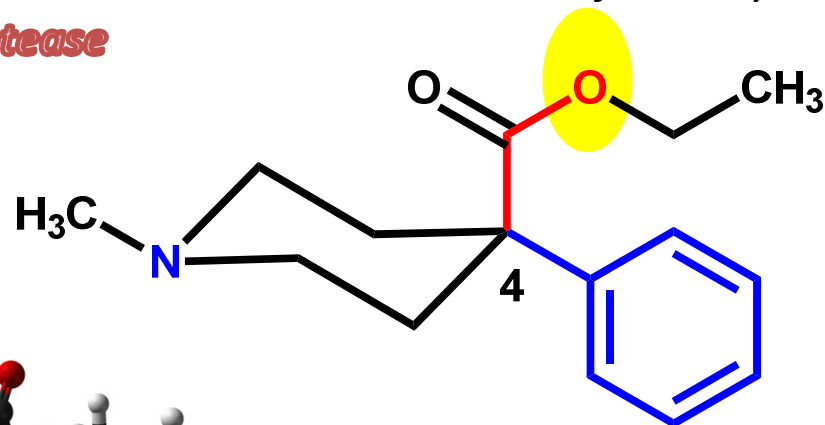
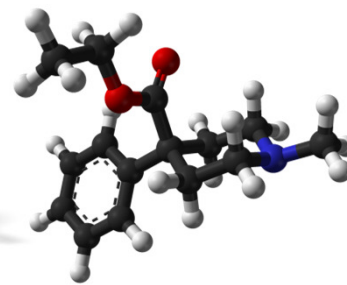
*Molecular striptease*

SM



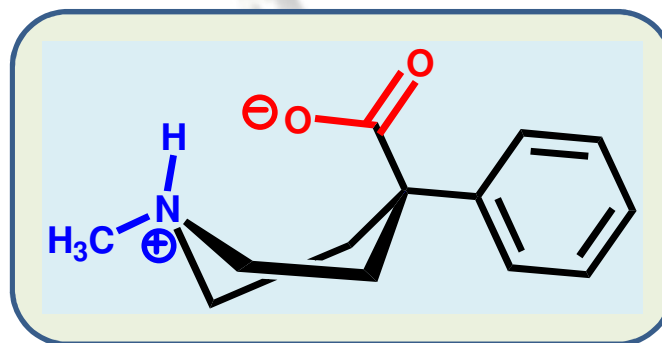
morfina

$C_{17}H_{19}NO_3$   
PM = 285,3



meperidina  
1939

$C_{15}H_{21}NO_2$   
PM = 247,2  
 $\mu$ -opioid agonist



Hipnoanalgésicos  
sintéticos

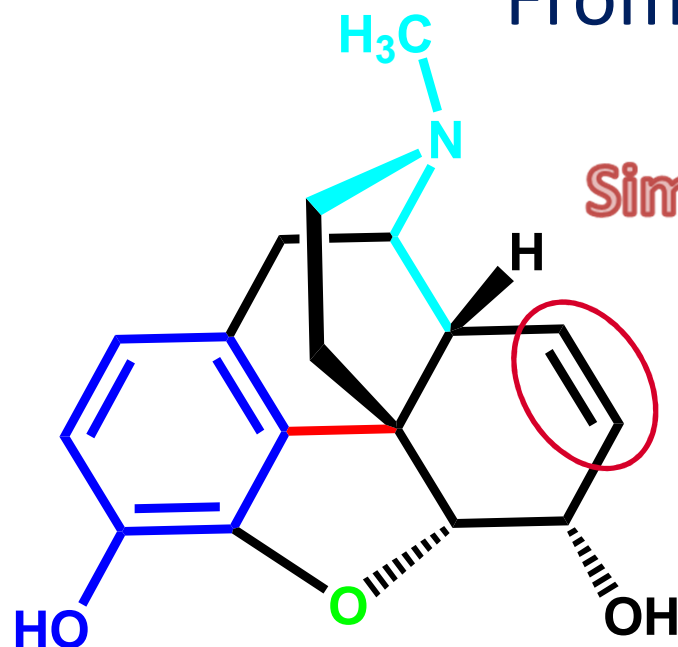
Metabolic-Soft moiety





# Da morfina ao tramadol

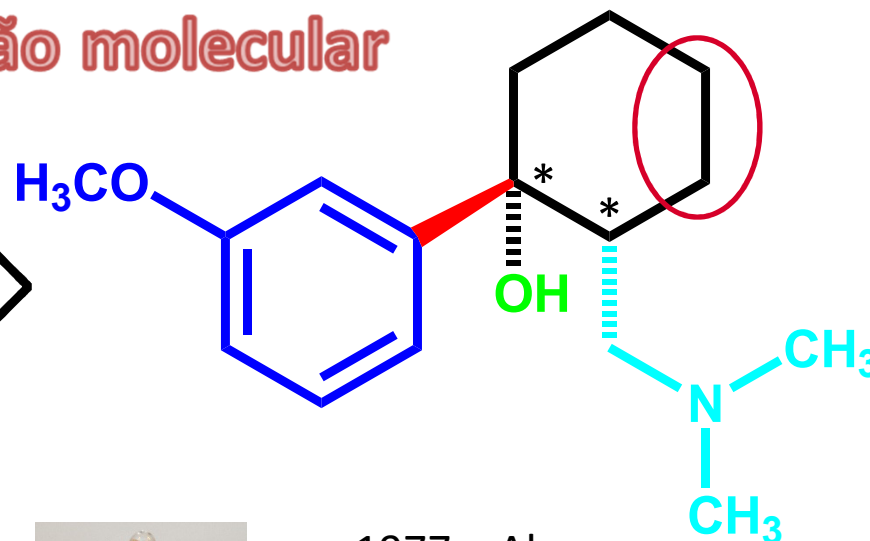
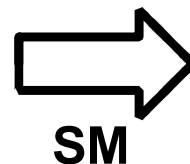
## From morphine to tramadol



morfina

$C_{17}H_{19}NO_3$   
PM = 285,3

Simplificação molecular



1977 – Alem.

tramadol

$C_{16}H_{25}NO_2$   
PM = 263,2

Química Medicinal

(+)-(1R,2R) / (-)-(1S,2S)-enantiomers

1/10 M

$\mu$ -opioid agonist



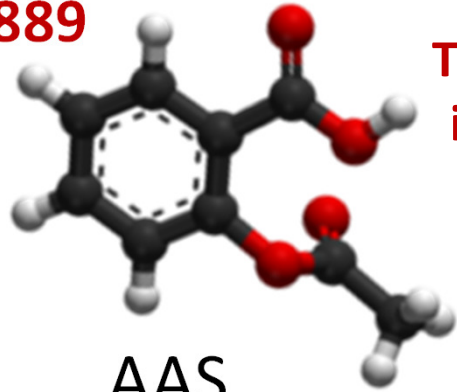


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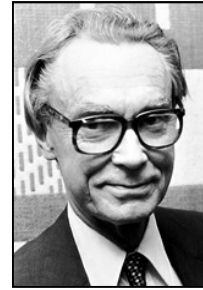
# Moléculas pioneiras...

1889



AAS  
 $C_9H_8O_4$

The Nobel Prize  
in Medicine &  
Physiology  
1982



1982

John Vane (55)  
(1927-2004)



1929

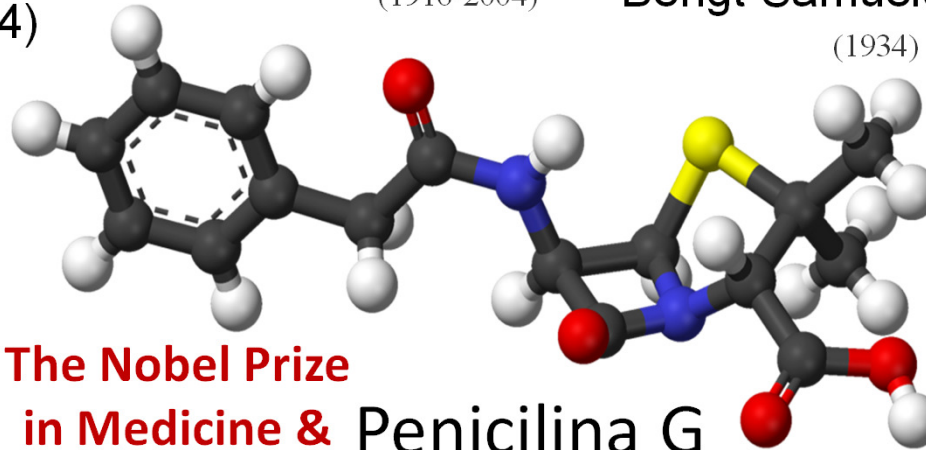
Sune Bergström (66)  
(1916-2004)

Bengt Samuelsson (48)  
(1934)

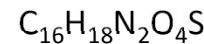
Sir Alexander Fleming (64)



(1881-1955)



The Nobel Prize  
in Medicine & Physiology  
1945



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

1964



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



The Nobel Prize  
in Chemistry  
1964

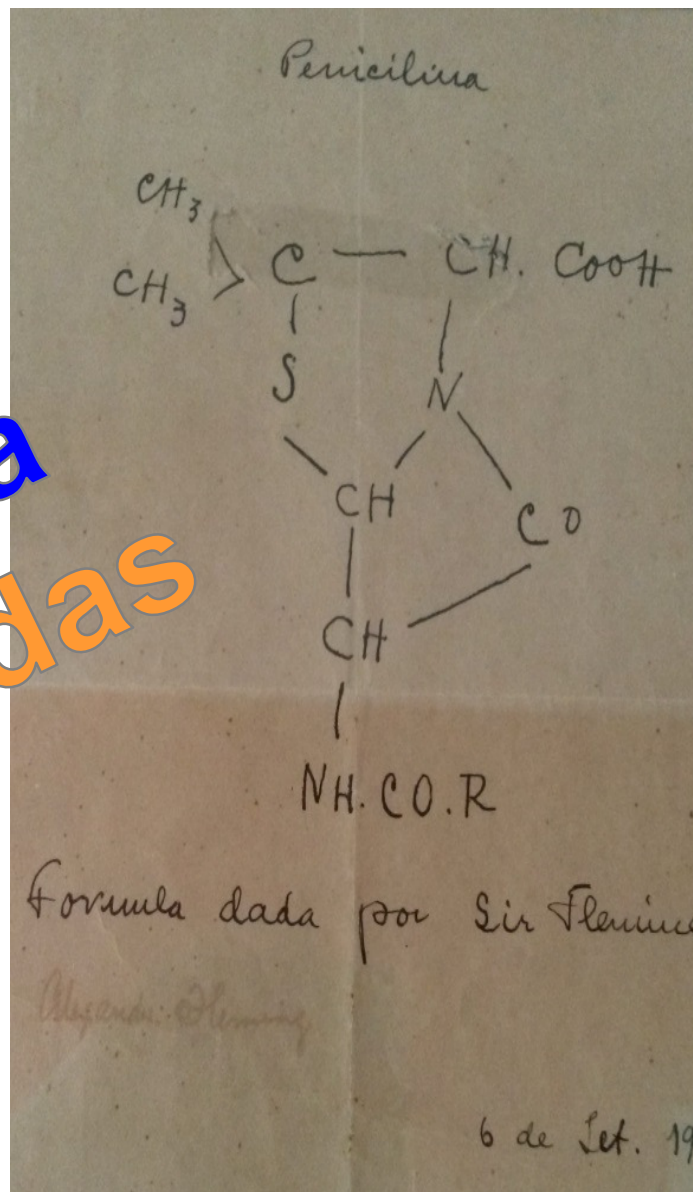


Howard W. Florey (47)  
(1898-1968)

*Do bolor ao fármaco inovador...*



# Molécula Salva-vidas



Quadro no escritório de trabalho do Professor E. J. Barreiro na UFRJ

Frame in the work office of Professor Barreiro at UFRJ



# Quimioterapia do Câncer

## Produtos naturais



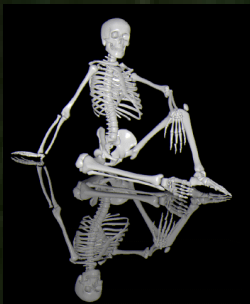
Quimiodiversidade

Estruturas originais

Mecanismo de ação inovadores

Inovações terapêuticas

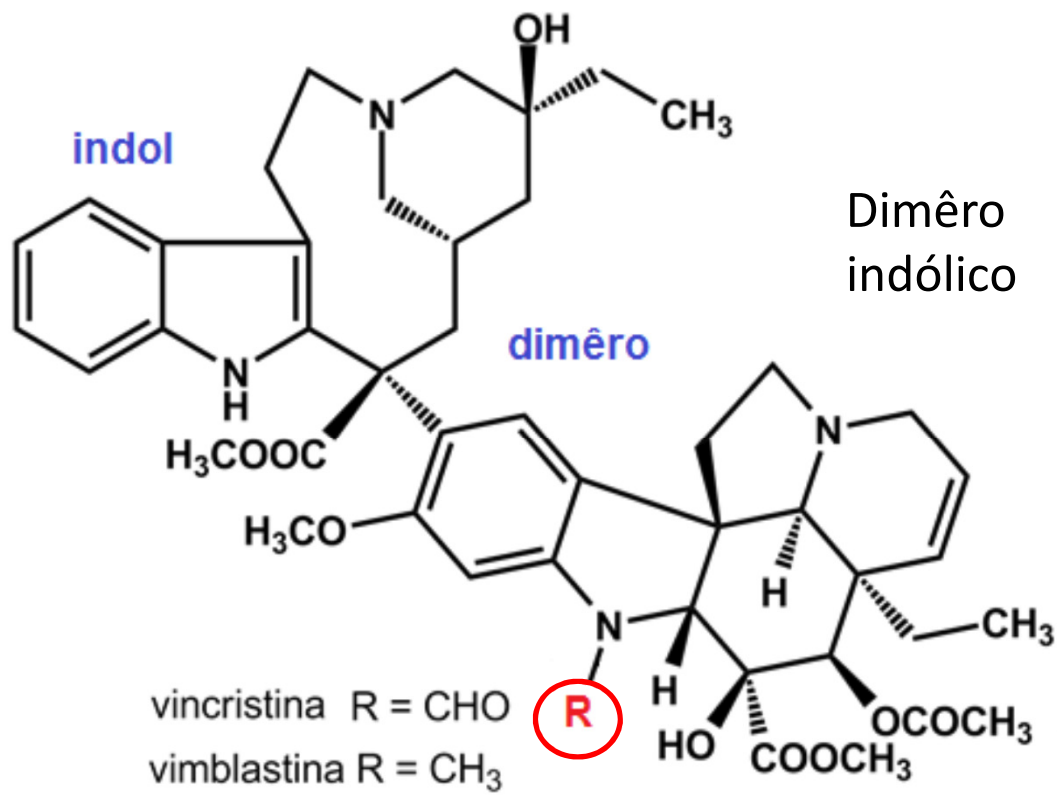
Moléculas *domesticadas*



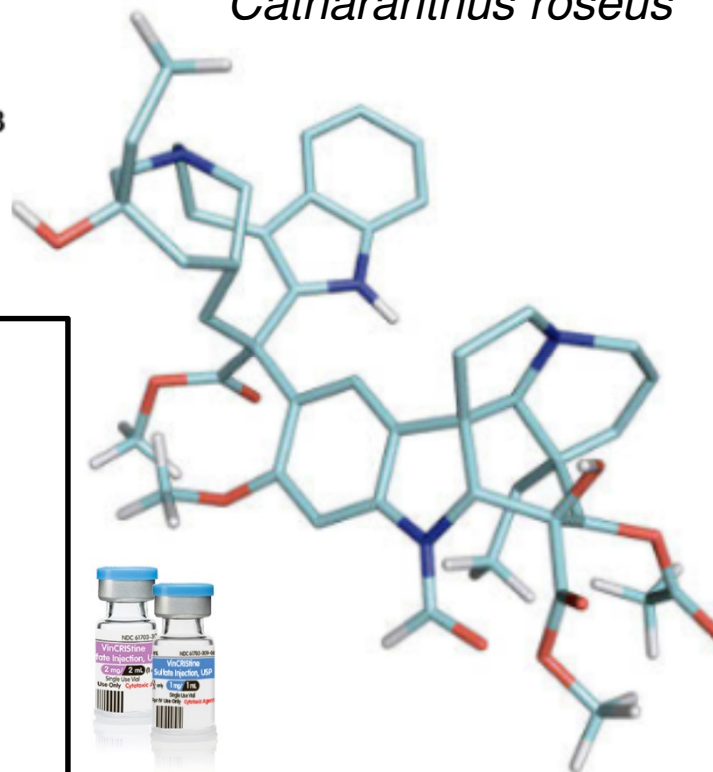
*Inter-alia*: Alcalóides da Vinca, podofilotoxina



# Alcaloides da *Vinca*



*Catharanthus roseus*



1950 - Robert L. Noble & Charles T. Beer (isol.)  
University of Western Ontario,  
Canada



1958 – NY Academy of Sciences Congress  
Noble, describe vinblastine  
Gordon Svoboda, Eli Lilly vincristine

1963 – Eli Lilly (Oncovin<sup>®</sup>)[FDA]

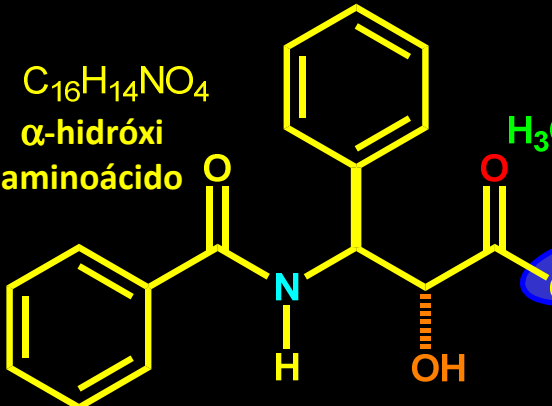




# Câncer

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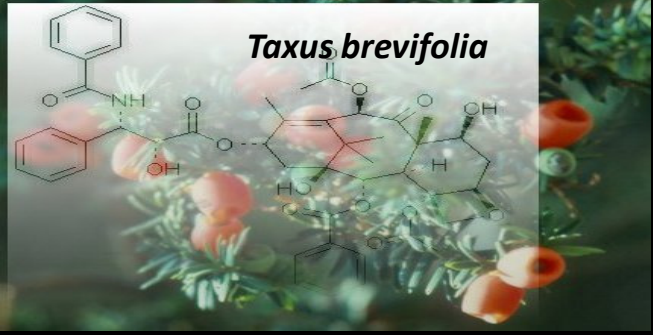
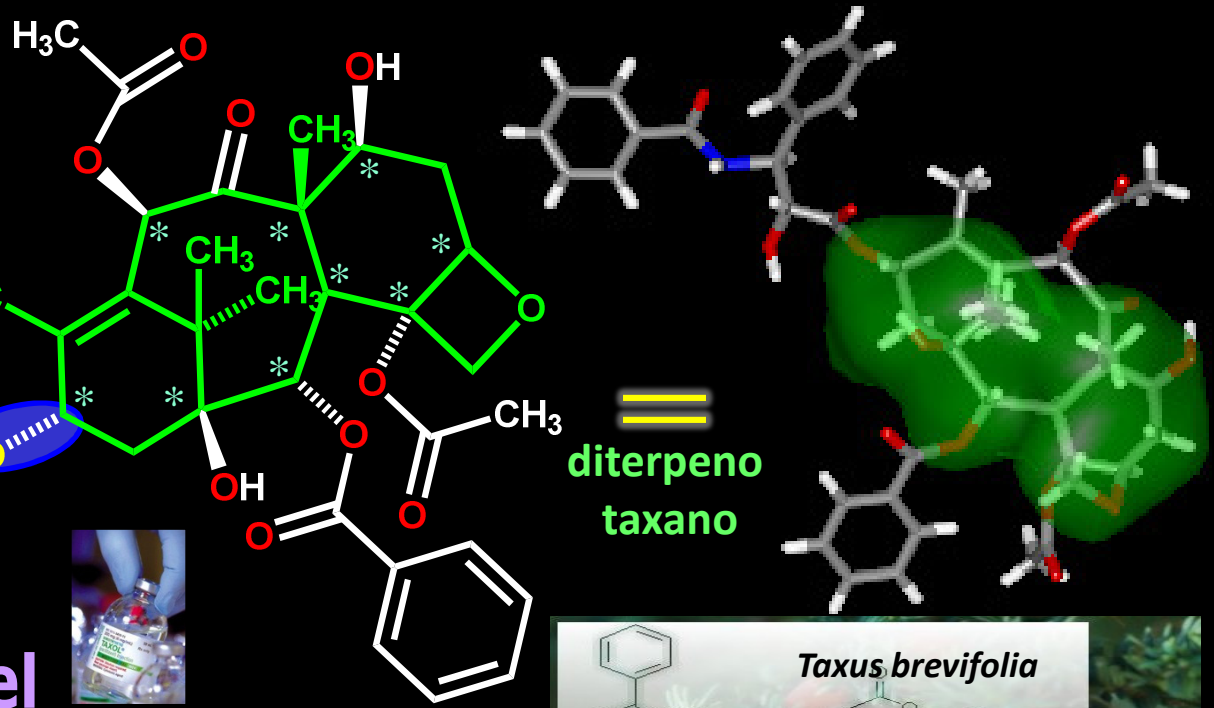
C<sub>16</sub>H<sub>14</sub>NO<sub>4</sub>  
α-hidróxi  
aminoácido



C<sub>47</sub>H<sub>51</sub>NO<sub>14</sub>

## 1965 Paclitaxel

M. C. Wani et al., J. Am. Chem. Soc. 1971, 93, 2325

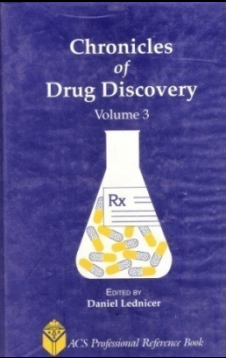


## Inibidores de tubulinas (MoA)

Res. Triangle Park, 1967



M. E. Wall & M. C. Wani  
1996 - National Cancer Institute  
Award of Recognition



M. E. Wall,,  
"Chronicles of Drug Discovery",  
D. Lednicher, vol.3, ACS, 1993,  
pp. 327-348



blockbuster  
2010

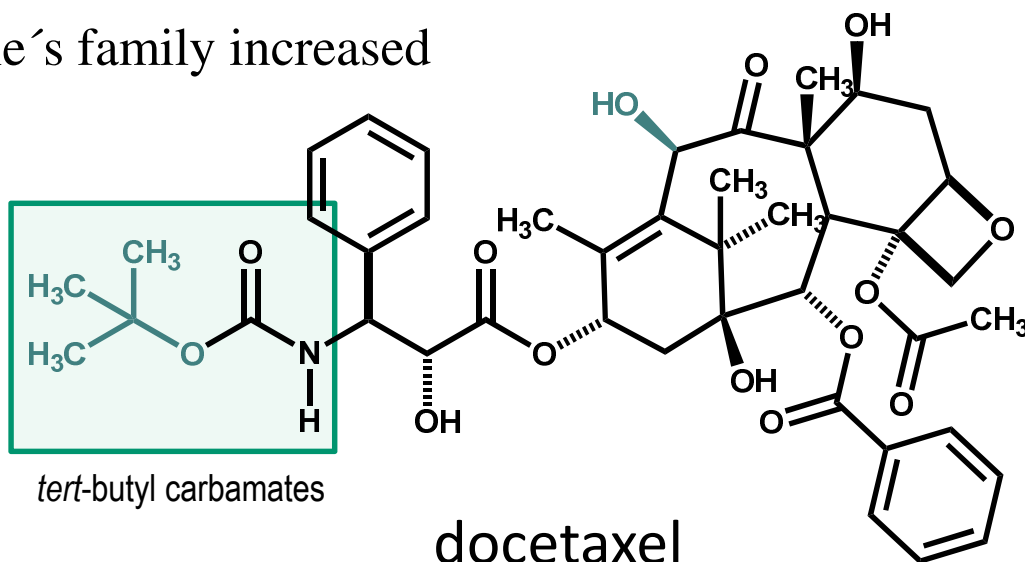
\*P. Poitier &  
A.E. Greene  
Docetaxel\*  
Cabazitaxel (Jevtana<sup>R</sup>)  
Ortataxel&





# A família dos taxanos cresceu...

The taxane's family increased



docetaxel

1996

US\$ 3,1 bi (2010)



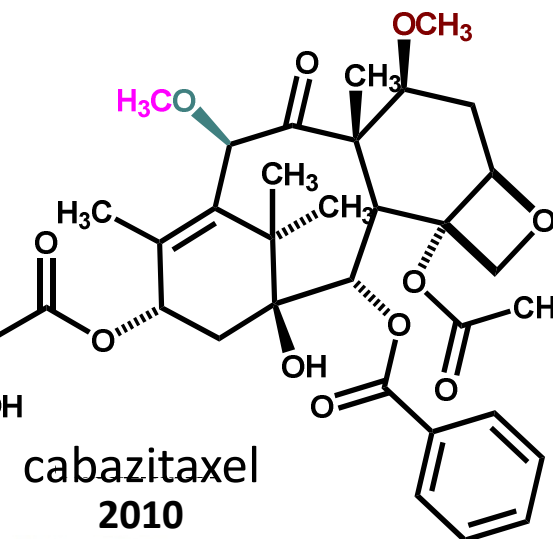
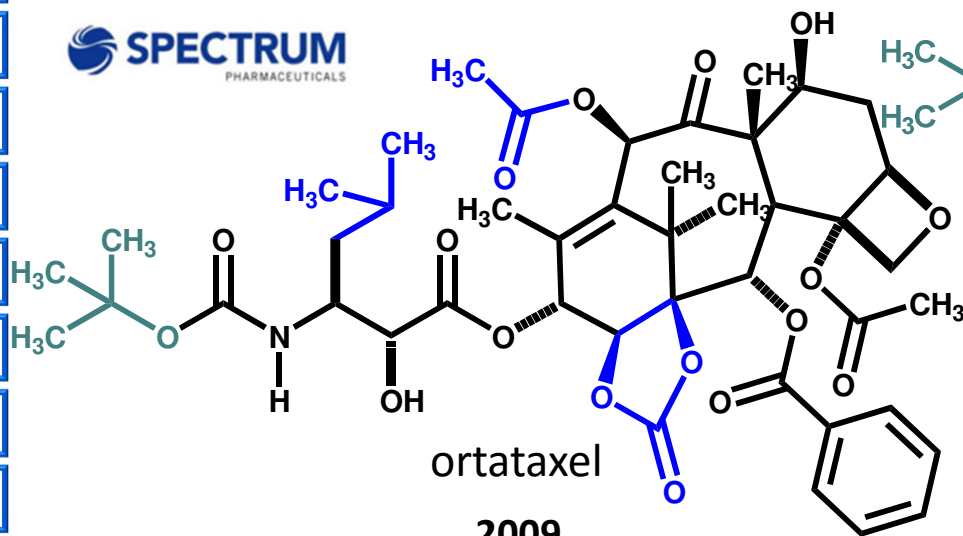
Pierre Potier  
(1934-2006)



Andy E Greene  
Un Grenoble



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Y-F Wang et al., Natural taxanes: developments since 1928, *Chem. Rev.* **2011**, *111*, 7652

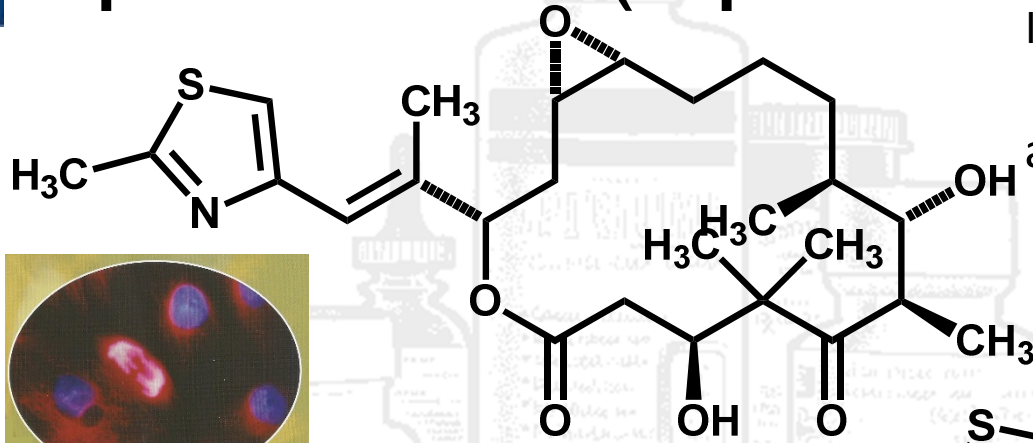


# Epotilonas (Epothilones)

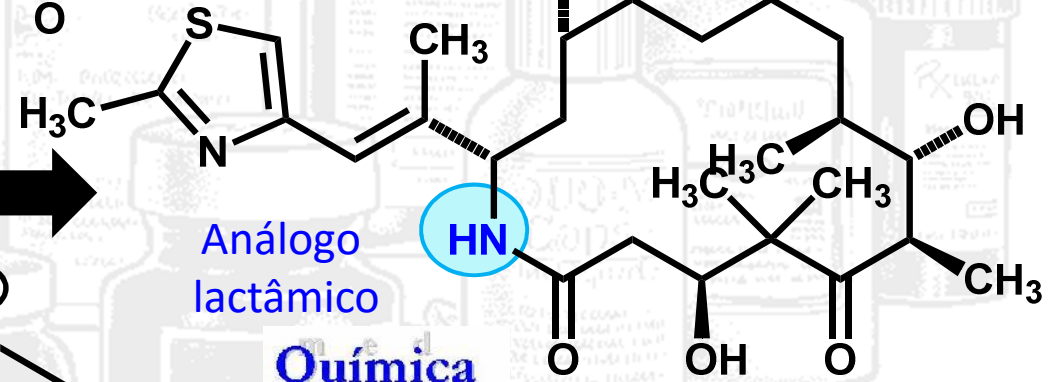
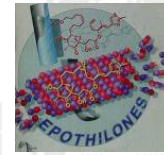
## Câncer

Isoladas de *Sorangium cellulosum* (1993)  
Primeiro macrociclo de 16 membros  
aprovado para tratamento do câncer  
metástatico de mama

Inibidor de microtúbulo

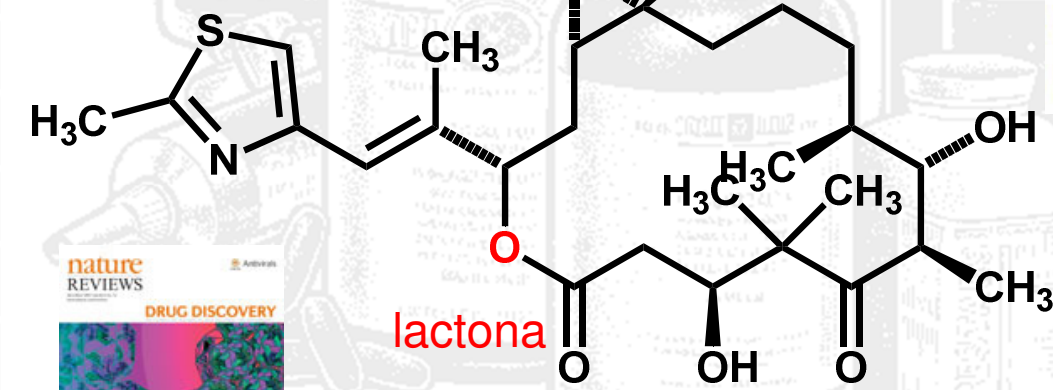
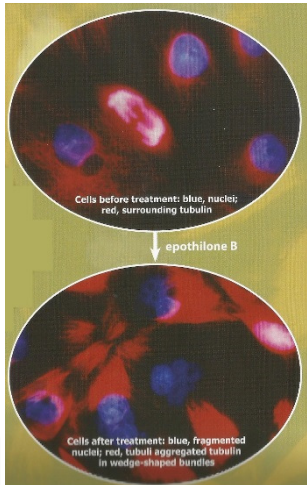


Epotilona-A



Análogo  
lactâmico

Química  
Medicinal



lactona

Epotilona-B (patupilona)



Ixabepilona

Ixempra<sup>R</sup>

BMS, 2007

Via fermentativa bacteriana,  
ativo em células taxano-R

US\$ 18.000-23.000 / trat.

A Conlin, M Fournier, C Hudniss, S Kar, P. Kirkpatrick, *Nat. Rev. Drug Discov.* **2007**, *6*, 953







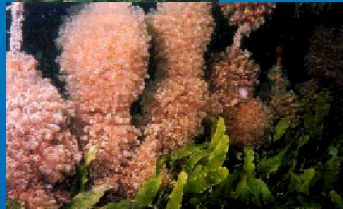
# Yondelis<sup>R</sup> (ET-743)

Alcalóide tetraidroisoquinolínico de origem marinha

# Ecteinascidina

Síntese Total

49 etapas



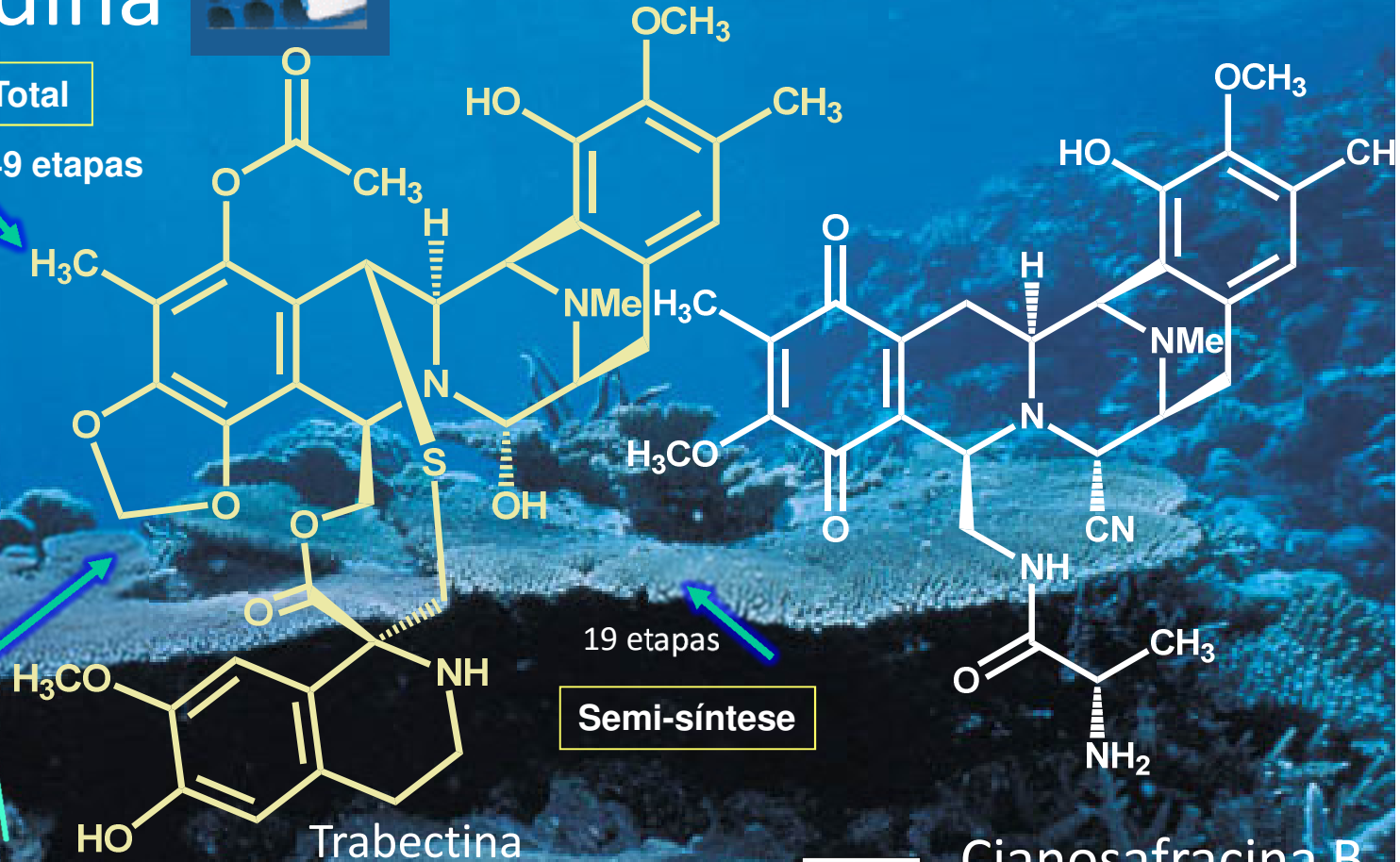
*Ecteinascidia turbinata*

Marinocultura

19 etapas

Semi-síntese

# Pharma-Mar SA



Trabectina

Cianosafracina B

Nobel 1990



1928 -

## 100 vezes mais ativo que Taxol<sup>R</sup>

C Cuevas, A Franchesch, *Nat. Prod. Rep.* **2009**, 26, 322

- ✓ **Natural:** KL Rinehart *et al*, *J. Nat. Prod.* **1990**, 53, 771
- ✓ **Síntese:** EJ Corey *et al*, *J. Am. Chem. Soc.* **1996**, 118, 9202
- ✓ **Hemi-síntese:** I Manzanares *et al*, *Org Lett.* **2000**, 2, 2545



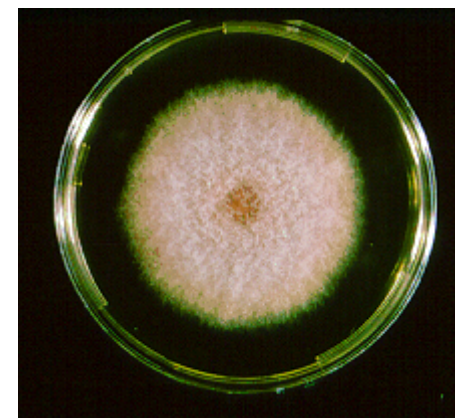
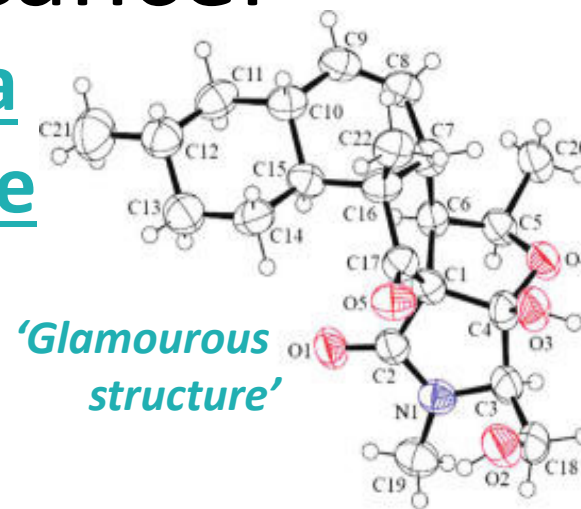
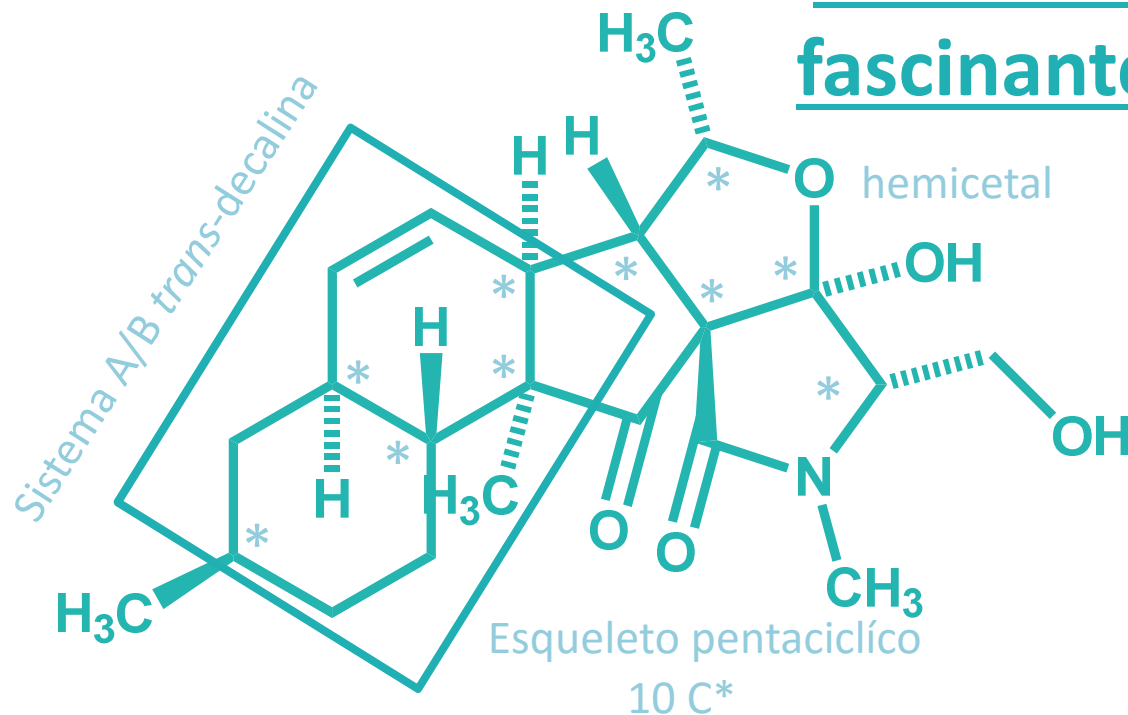
Fermentação  
***Pseudomonas fluorescens***



# Produtos naturais & câncer

Natural products & cancer

Estrutura fascinante



*Fusarium sp*

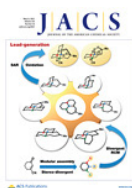
**KRIBB**  
Korea Research Institute of  
Bioscience & Biotechnology

**(+)-fusarisetina\***

Inibe a migração e metastase  
de células cancerosas

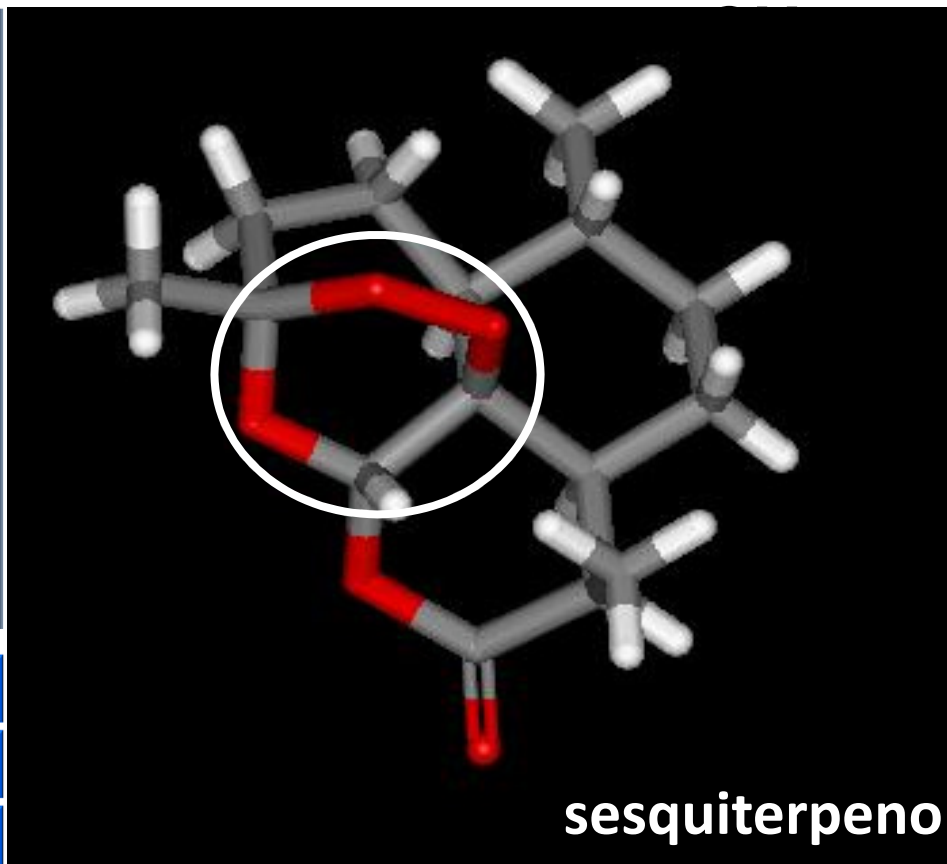
\* Isolamento: J-H Jang, Y Asami, J-P Jang, S-O Kim, DO Moon, K-S Shin, D Hashizume, M Muroi, T Saito, H Oh, BY Kim, H Osada, JS Ahn, *J. Am. Chem. Soc.* **2011**, *133*, 6865.

\* Síntese: J Xu, EJE Caro-Diaz, L Trzoss, EA Theodorakis, *J. Am. Chem. Soc.* **2012**, *134*, 5072; J Deng, B Zhu, Z-Y Lu, H-X Yu, A Li, *J. Am. Chem. Soc.* **2012**, *134*, 920.

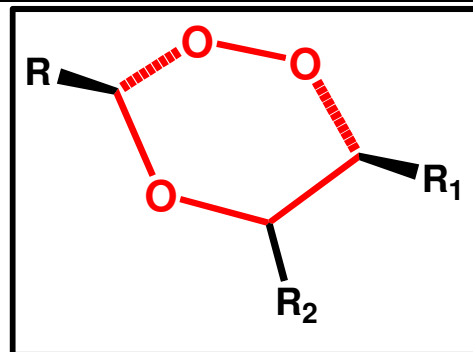




# Artemisinina



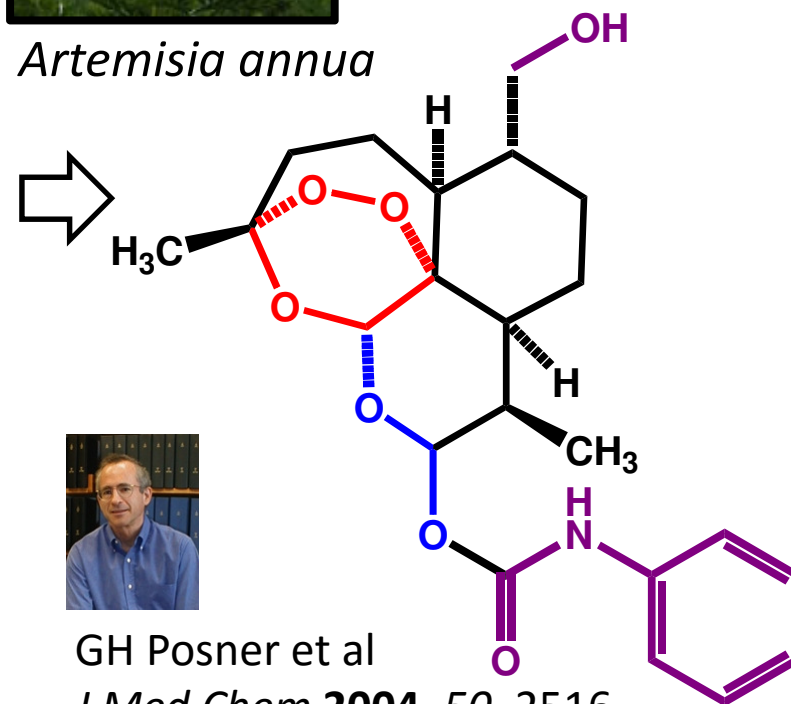
1,2,4-trioxana



Qinghaosu



*Artemisia annua*



GH Posner et al  
*J Med Chem* **2004**, *50*, 2516  
Johns Hopkins University



**Novos padrões moleculares,**

**Novos mecanismos de ação.**

New molecular patterns,  
New mechanisms of action





*Mais Fármacos*

*Inovadores...*

*More Innovative Drugs...*



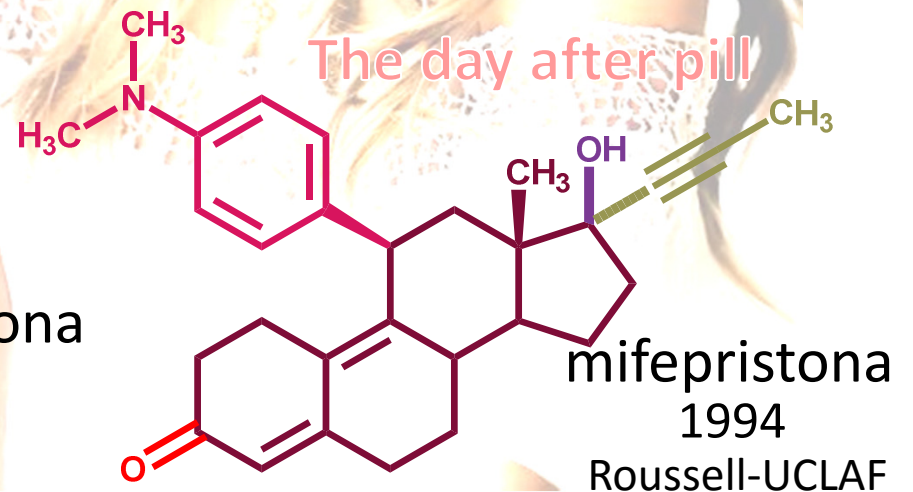
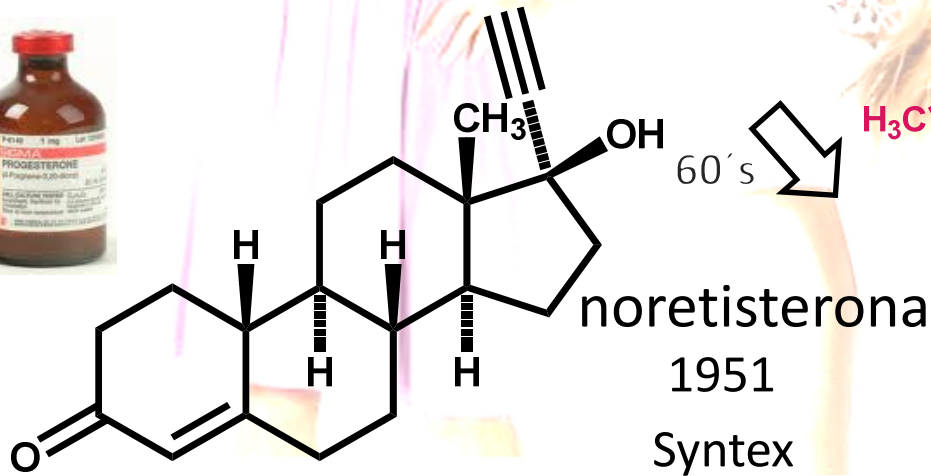
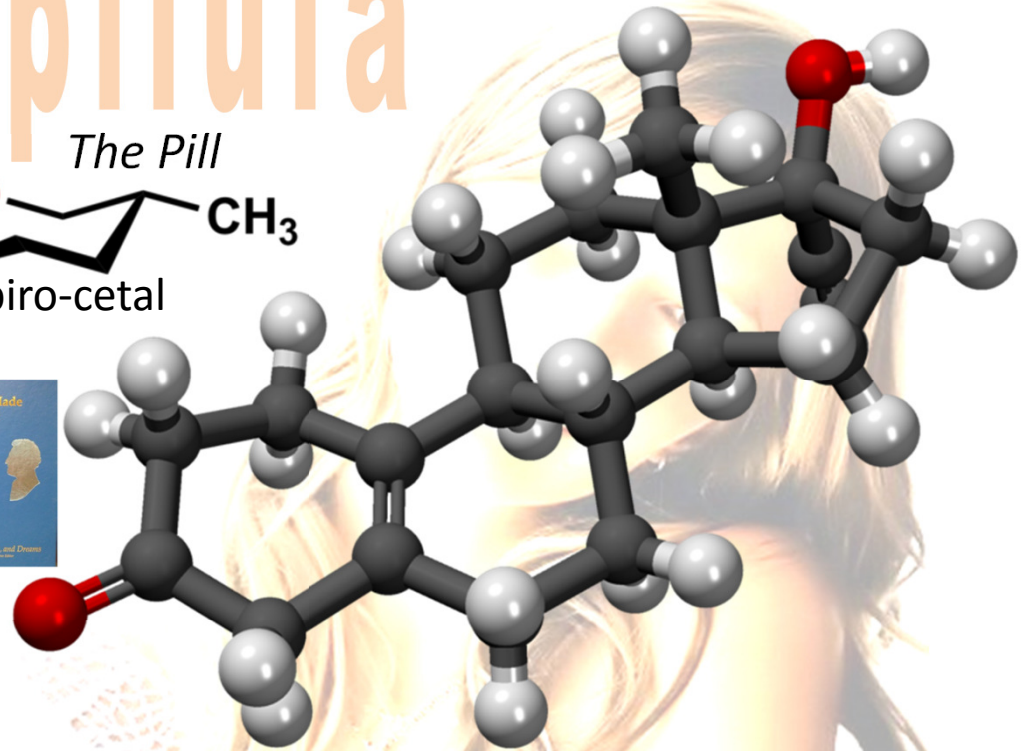
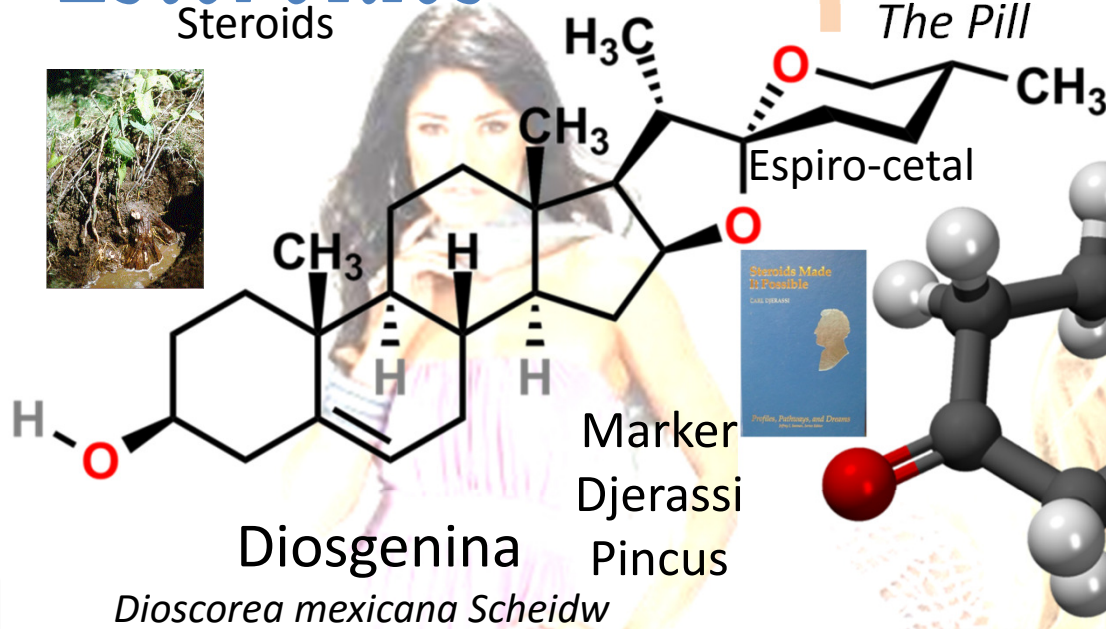


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# Esteróides

Steroids

# A pílula



Mais de 125 milhões de mulheres utilizaram a pílula contraceptiva (2010)





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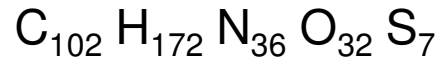
# Ziconotido

1980 - Michael McIntosh & Baldomero Olivera



*Conus magus*

Neurex (Menlo Park, CA)



FDA em 28/12/2004; Eur Comm. em 22/02/2005

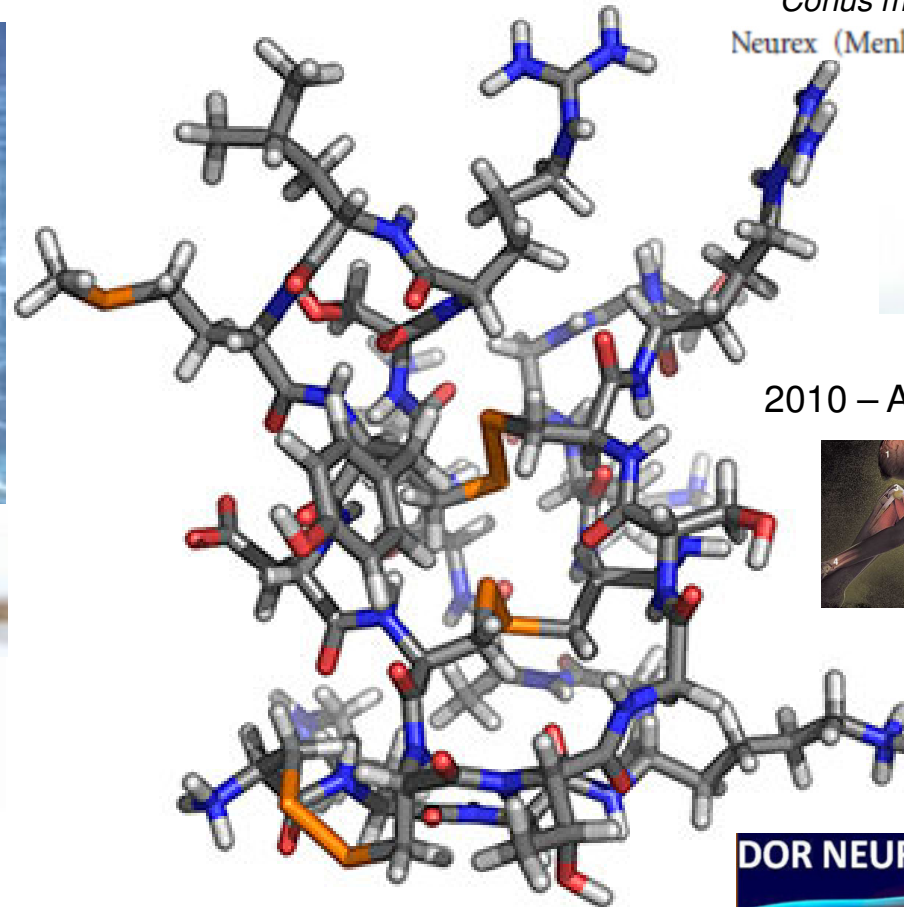
Uso intratecal

synthetic  $\omega$ -conotoxin peptide mar

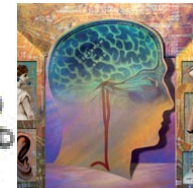
Ziconotido

DRUGS FOR PAIN

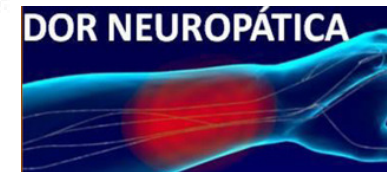
Howard S. Smith, MD



2010 – Azur Pharma



25 AA's



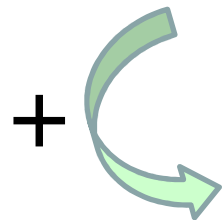
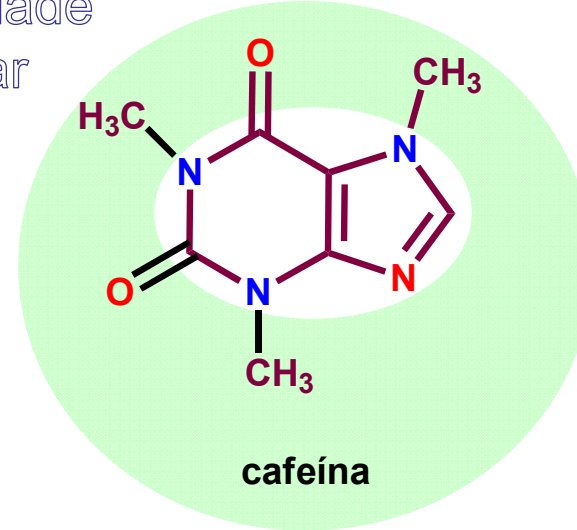
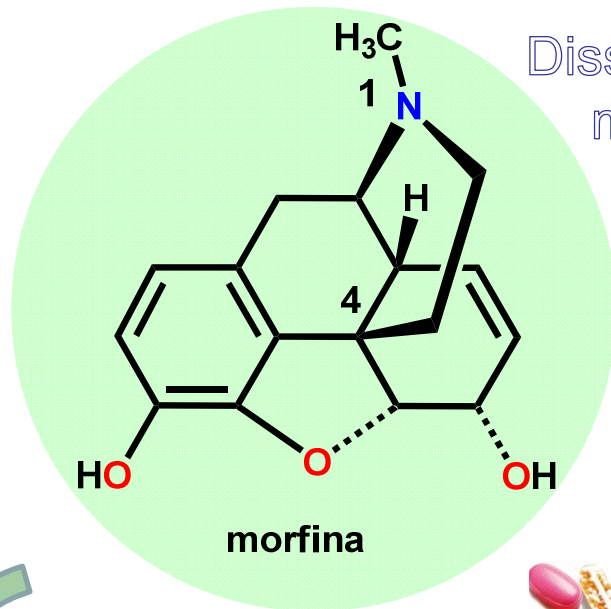
Antagonista de canais  $Ca^{++}$  voltagem dependentes tipo-*N*



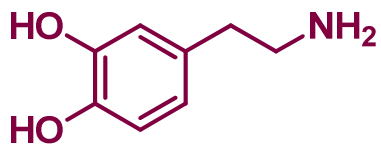
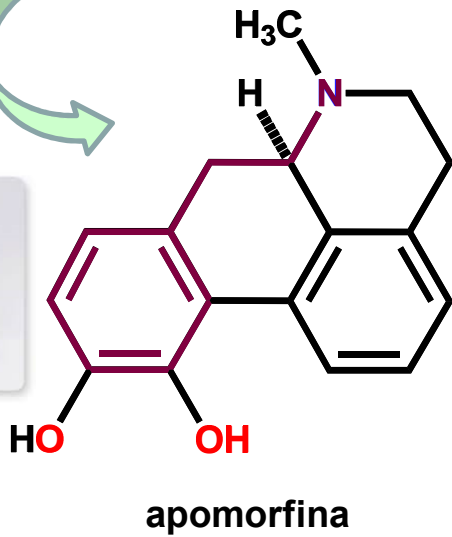
# Diferentes, mas semelhantes!

Different, but similar

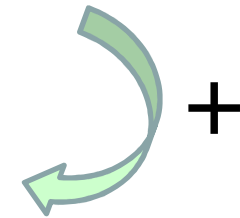
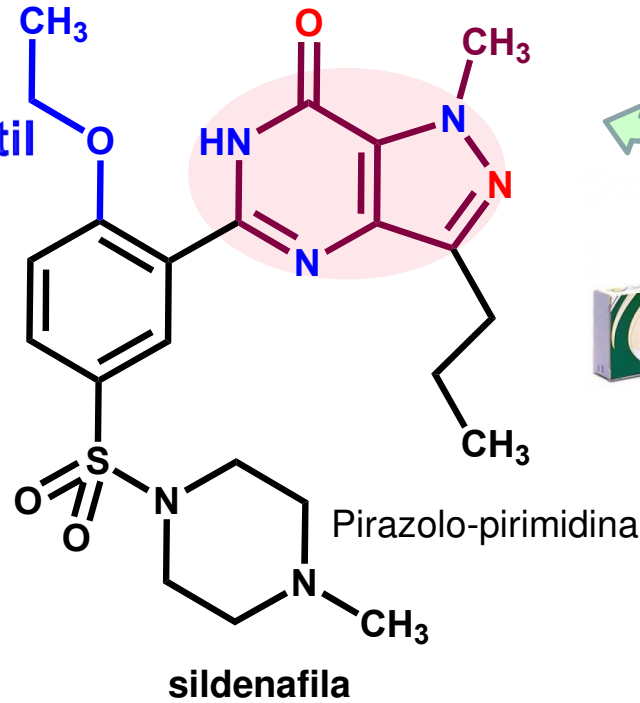
Dissimilaridade molecular



Uprima



Disfunção erétil



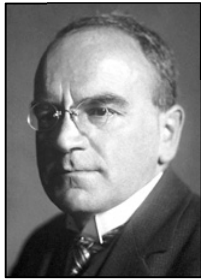
PDE-5i





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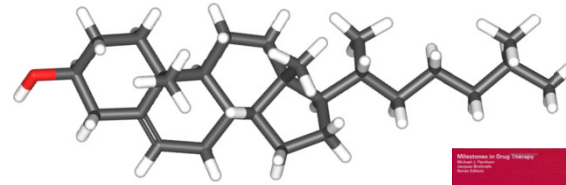
# Estatina\$, inovação bilionária



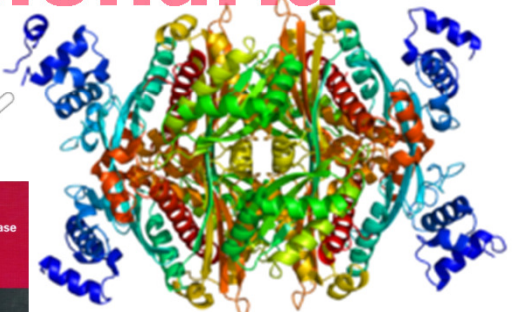
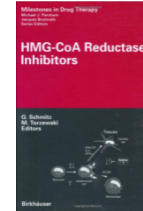
Heinrich Wieland (50)  
(1877-1957)



Adolf Windaus (52)  
(1876-1959)



colesterol



HMGCoAR

1927



1928



Konrad Bloch (53)  
(1912-2000)

1964

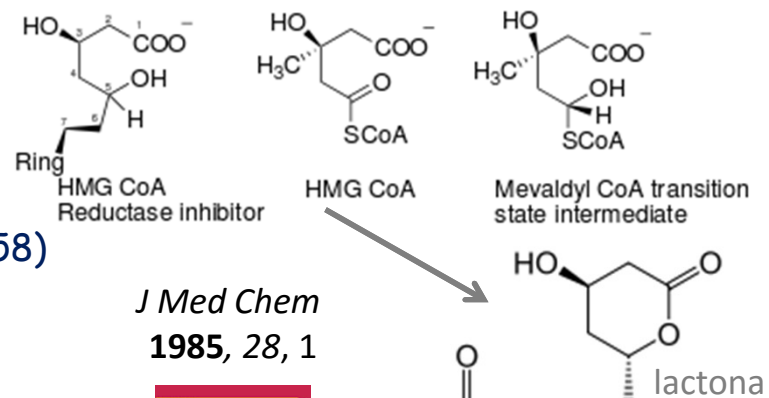


Feodor Lynen (54)  
(1911-1979)

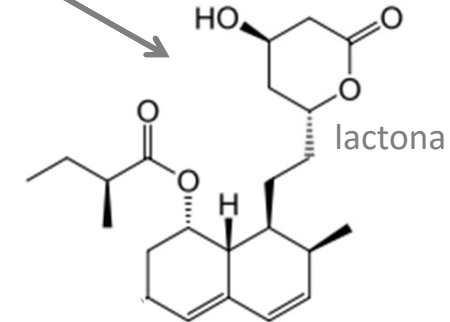


John Cornforth (58)  
(1917-2013)

1975



J Med Chem  
1985, 28, 1

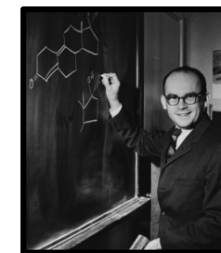


Mevilonina /compactina

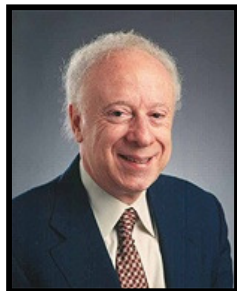
1979 Simvastatina

Arthur A Patchet

(1929)



New Lead Discovery Department  
Merck Co.



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

(1940)

(1941)

University of Texas, Dallas

1985

LDL



Akira Endo  
(1933)

Albert Lasker Award  
for Clinical  
Medical Research, 2008





Universidade Federal do Rio de Janeiro



**Akira Endo, Sankyo Co**

Lasker Award 2008

1975 – Mevastatina (ML-263b)



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

# Estatina\$, inovação bilionária

## Prototipo natural

### Similaridade molecular



A.Endo, *J. Antibiot.*

**1976**, 29, 1346

*Penicillium citrinum*

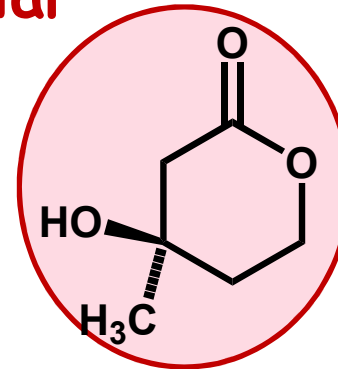
*Idem, Ibid*, **1979**, 32, 852

*Monascus ruber*

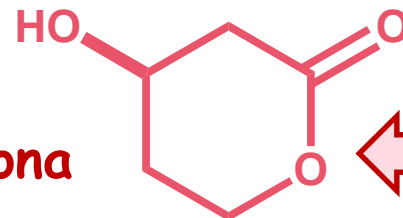
(compactina)

## Mevalolactona

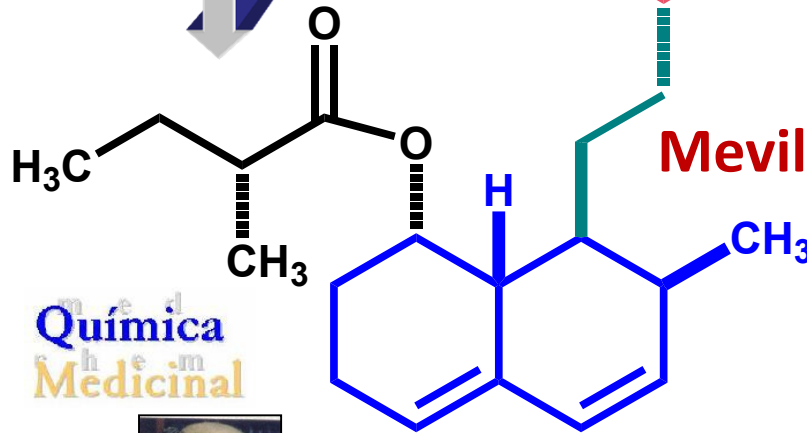
HMG-CoA redutase



$\gamma$ -lactona



## Mevilonina



Química Medicinal

therapeutic innovation



## Lovastatina (MK-803)

1978 – Merck & Co.

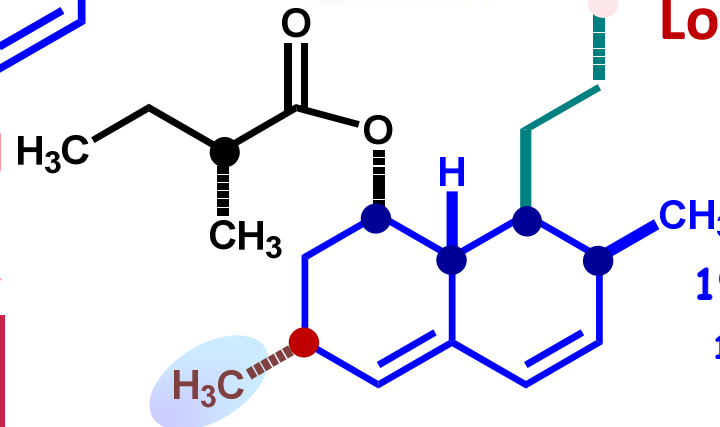
*Aspergillus terreus*



**Arthur A Patchett**

Alfred Burger Award 2002

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



1987 – MS&D (Mevacor<sup>R</sup>)

1988 – Mevacor<sup>R</sup> US\$ 260mi



Arthur A Patchett

*J Med Chem* **2003**, 45, 5609

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Química  
med  
Medicinal  
chem

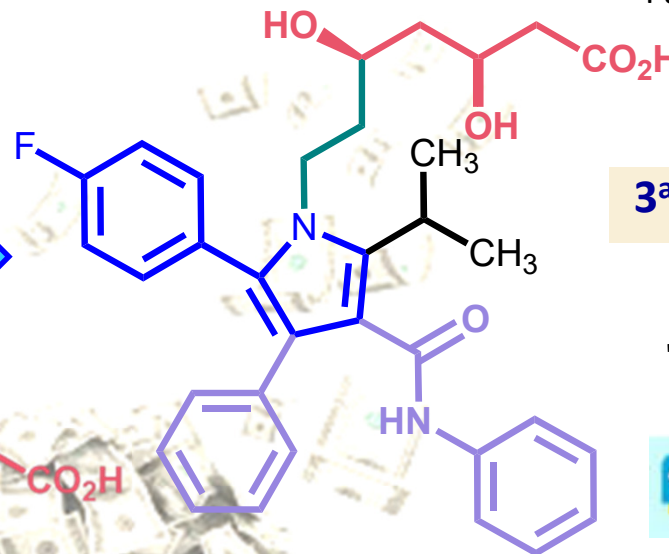
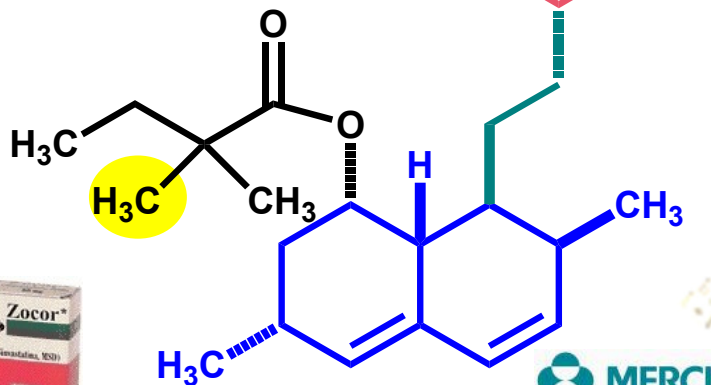


AstraZeneca

IC<sub>50</sub> HMG-CoAR = 5 nM

**US\$ 8,7 bi (2014)**

rosuvastatina  
2004



atorvastatina  
1991

World Top  
selling drug



5-HMGC<sub>o</sub>ARi

# Estatina\$



Bruce Roth  
Parke-Davis Co

3<sup>a</sup> geração



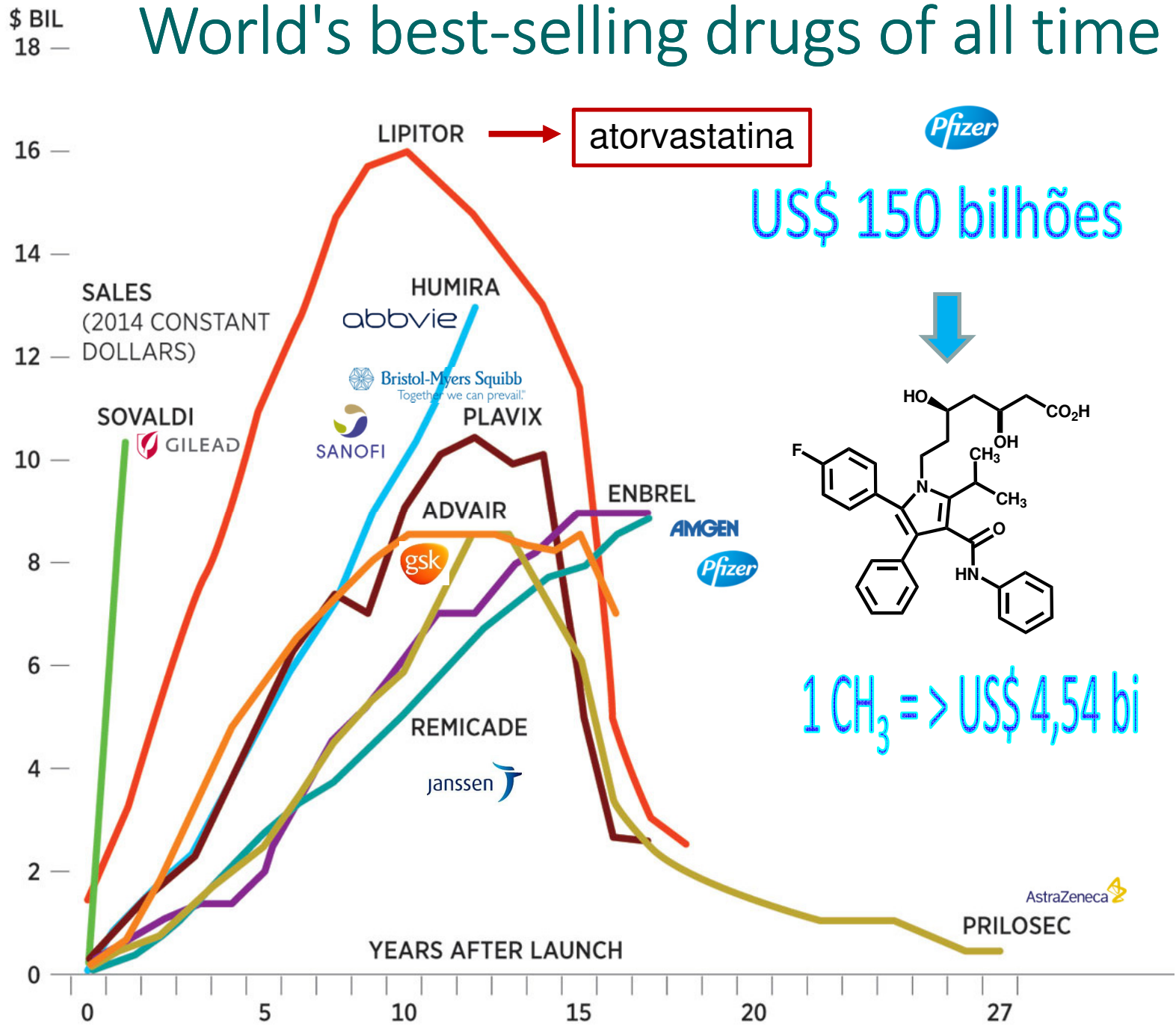
"patent cliff"



O mercado mundial de estatinas foi de ca. US\$ 26 bilhões (2013)



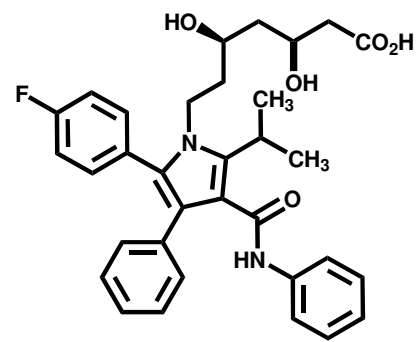
# World's best-selling drugs of all time



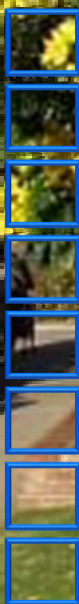
atorvastatina



US\$ 150 bilhões



1 CH<sub>3</sub> => US\$ 4,54 bi



# O uso de produtos naturais abundantes como bióforos



Laboratório de Avaliação e Síntese de Substâncias Bioativas



Universidade Federal do Rio de Janeiro



Química Medicinal

# LASSBio

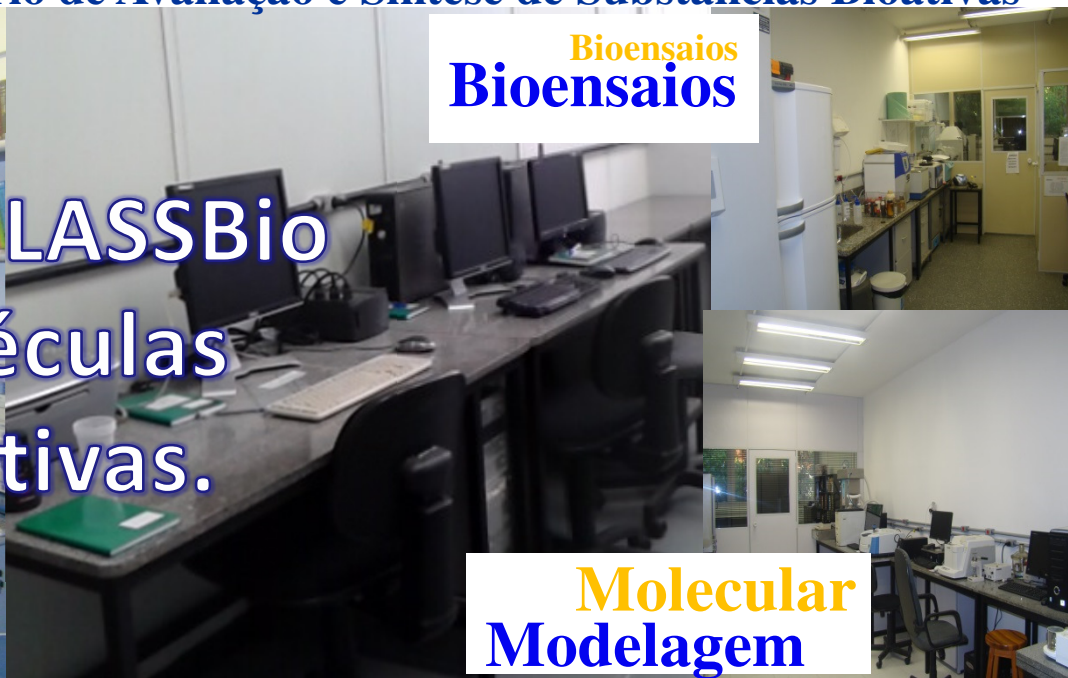
Laboratório de Avaliação e Síntese de Substâncias Bioativas

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

Criado em 19/04/1994 Laboratório de Avaliação e Síntese de Substâncias Bioativas



A quimioteca do LASSBio  
tem 1950 moléculas  
originais bioativas.



Bioensaios  
Bioensaios

Molecular  
Modelagem



**RVQ**

*Revista Virtual de Química*

ISSN 1984-6835

**A história do LASSBio**

Artigo

**As Longas Pernas do Laboratório de Avaliação e Síntese de  
Substâncias Bioativas (LASSBio®;  
<http://www.farmacia.uff.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

**RVQ** | *Revista Virtual de Química*  
ISSN 1984-6835  
Volume 5, Número 2 | Março-Abril 2013



[www.uff.br/rvq](http://www.uff.br/rvq)

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

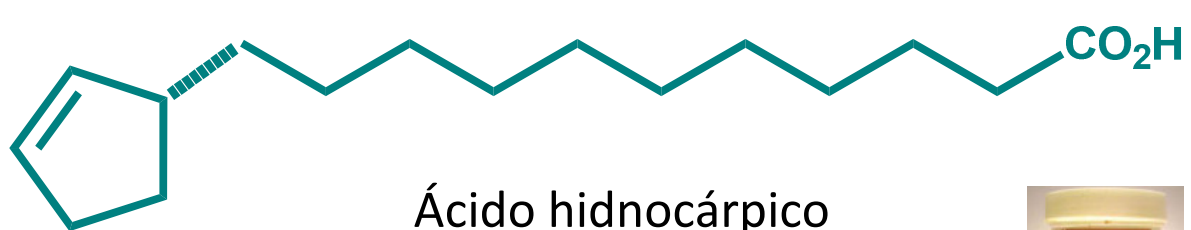
**LASSBio**  
Laboratório de Avaliação e Síntese de Substâncias Bioativas

**Química**  
m e d  
**Medicinal**  
c h e m



# Produtos naturais como blocos moleculares

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Óleo de Sapucainha  
Cole & Cardoso, 1938



1982

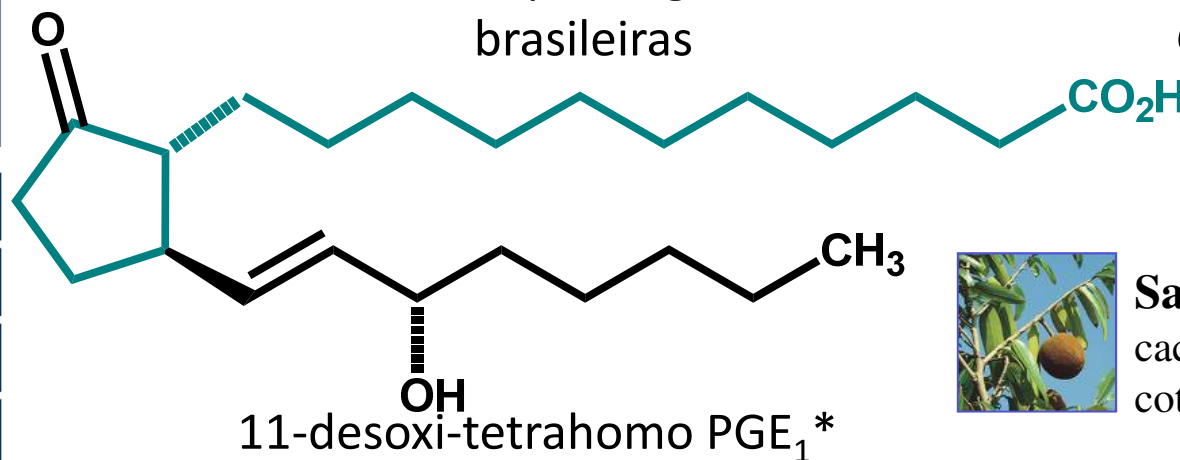


Similaridade molecular

Primeiras prostaglandinas brasileiras



*Carpotroche brasiliensis*, Endl  
Flacourtiácea



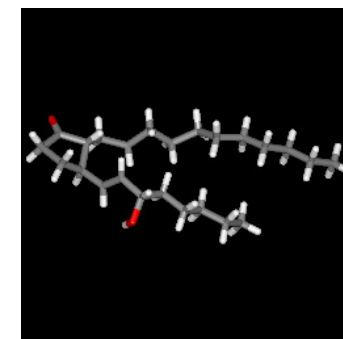
AS Oliveira, JA Lima, CM Rezende,  
AC Pinto, *Quim. Nova* **2009**, 32, 139



Sapucainha, Papo de anjo, Pau de cachimbo, Canudo de pito, Fruta de cotia, Fruta de macaco.

EJ Barreiro, LNLFGomes, Prostaglandin Analogues. Synthesis of Tetrahomoprostaglandin Derivatives From Natural Hydnocarpic Acid Isolated From Sapucainha Oil, *J. Chem. Res.* **1983**, 2701;

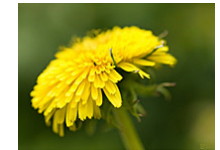
\*EJ Barreiro, LNLFGomes, Novo Método de Síntese de Prostaglandinas Modificadas da Série 11-desoxi PG E1". INPI, PI 38201866, 02/04/1982; *Chem. Abstr.*, **100**, 17452lu (1984).







# Protótipo natural



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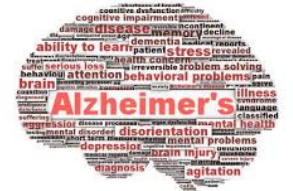
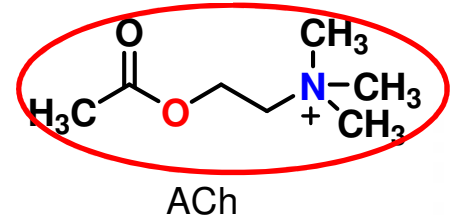


**Bióforo etanol-amina incluso**

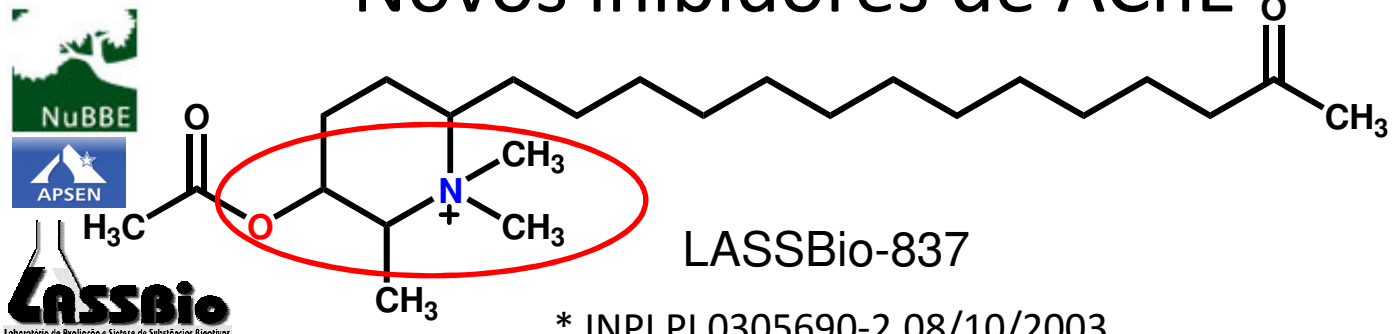


fragmento biofórico

**Similaridade molecular**



## Novos inibidores de AChE\*



\* INPI PI 0305690-2 08/10/2003  
 \* Patent NZ554392 (15/10/2004)



*Cassia leptophylla*  
Leguminosa

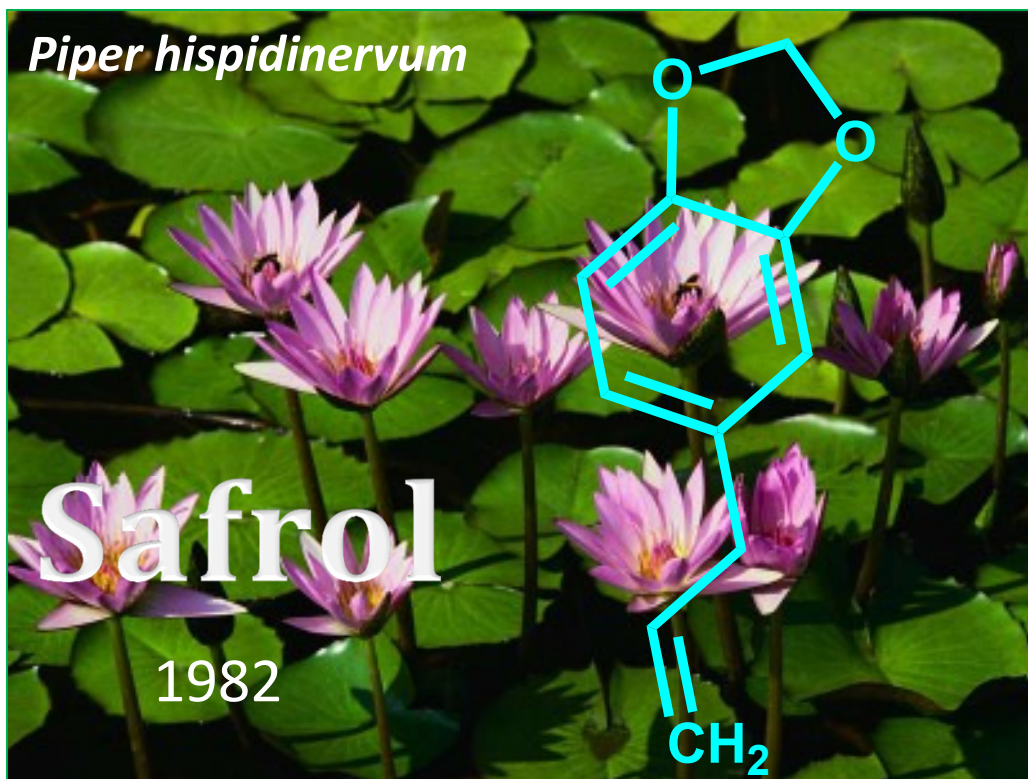


MS Alexandre-Moreira, C Viegas Jr; AP Miranda,  
 VS Bolzani, EJ Barreiro, *Planta Med.* **2003**, 69, 795





*Piper hispidinervum*



Safrol

1982

CH<sub>2</sub>

D Riva *et al.*, *Acta Amazonica* **2011**, 41, 297

Oléo de Sassafrás *Ocotea pretiosa*

E. J. Barreiro, P. R. R. Costa, P. R. V. R. Barros e W. M. Queiroz, "An Improved Synthesis of Indole Derivatives Related to Indomethacin from Natural Safrole", *Journal of Chemical Research (S)*, 102-103; (M) 1142-1165, (1982)

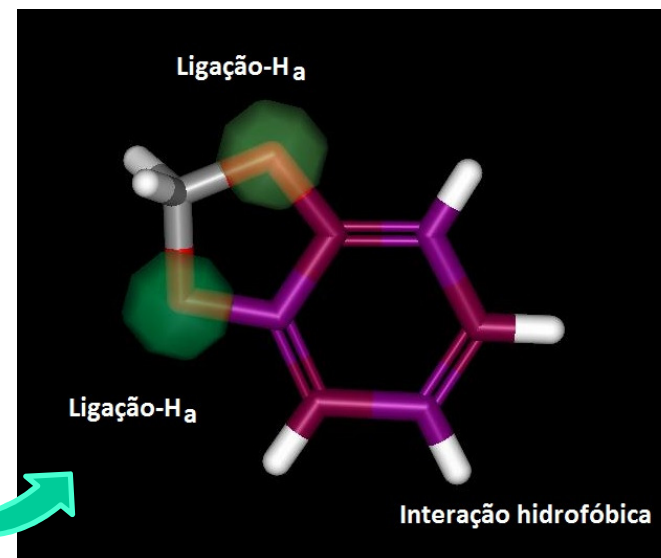
E. J. Barreiro & C. A. M. Fraga, "A Utilização do Safrol, Principal Componente Químico do Óleo de Sassafrás, na Síntese de Substâncias Bioativas na Cascata do Ácido Araquidônico: Anti-inflamatórios, Analgésicos e Anti-trombóticos", *Química Nova*, **22**, 744-759 (1999)

82% safrol

Química  
med  
Medicinal  
chem

LASSBio

Laboratório de Avaliação e Síntese de Substâncias Bioativas



Benzodioxola

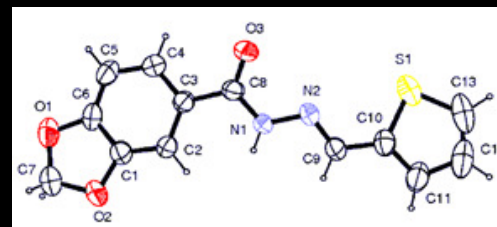
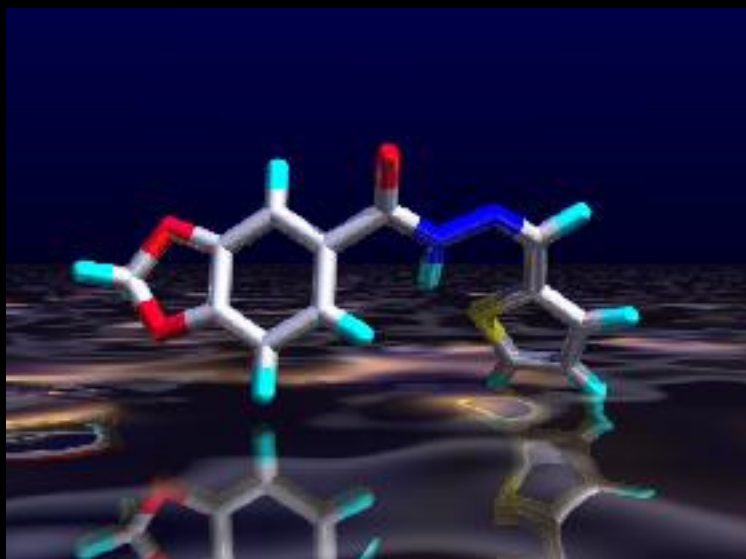
Bióforo natural privilegiado



# LASSBio-294

## Novo protótipo de fármaco cardioativo com novo MoA

Universidade Federal do Rio de Janeiro



Patente

*Thienylhydrazone with digitalis-like properties (positive inotropic effects)*



**C<sub>13</sub>H<sub>10</sub>N<sub>2</sub>O<sub>3</sub>S**

PM 274

CAS # 314021-07-3

**License agreement**

**\* US Patent US7091238 15/08/2006**

**\* European Patent EP1532140; WO-0078754**

**Estudos de fase pré-clínica concluídos**

JR Azevedo, J-J Letourneau, F Espitalier, MI Ré, Solubility of a New Cardioactive Prototype Drug in Ionic Liquids, *J. Chem. Eng. Data* **2014**, 59, 1766; CM Leal, SL Pereira, AE Kümmerle, DM Leal, R Tesch, CMR Sant'Anna, CAM Fraga, EJ Barreiro, RT Sudo, G Zapata-Sudo, Antihypertensive profile of 2-thienyl-3,4-methylenedioxybenzoyl hydrazone is mediated by activation of the A<sub>2A</sub> adenosine receptor, *Eur. J. Med. Chem.* **2012**, 55; A G M Fraga, L L Silva, CAM Fraga, EJ Barreiro, CYP1A2-mediated biotransformation of cardioactive 2-thienylidene-3,4-methylene dioxymethylhydrazone (LASSBio-294) by rat liver microsomes and human recombinant CYP enzymes, *Eur. J. Med. Chem.* **2011**, 46 349; EJ Barreiro, Strategy of molecular simplification in rational drug design: The discovery of a new cardioactive agent, *Quim. Nova* **2001**, 25, 1172.



*Considerações*

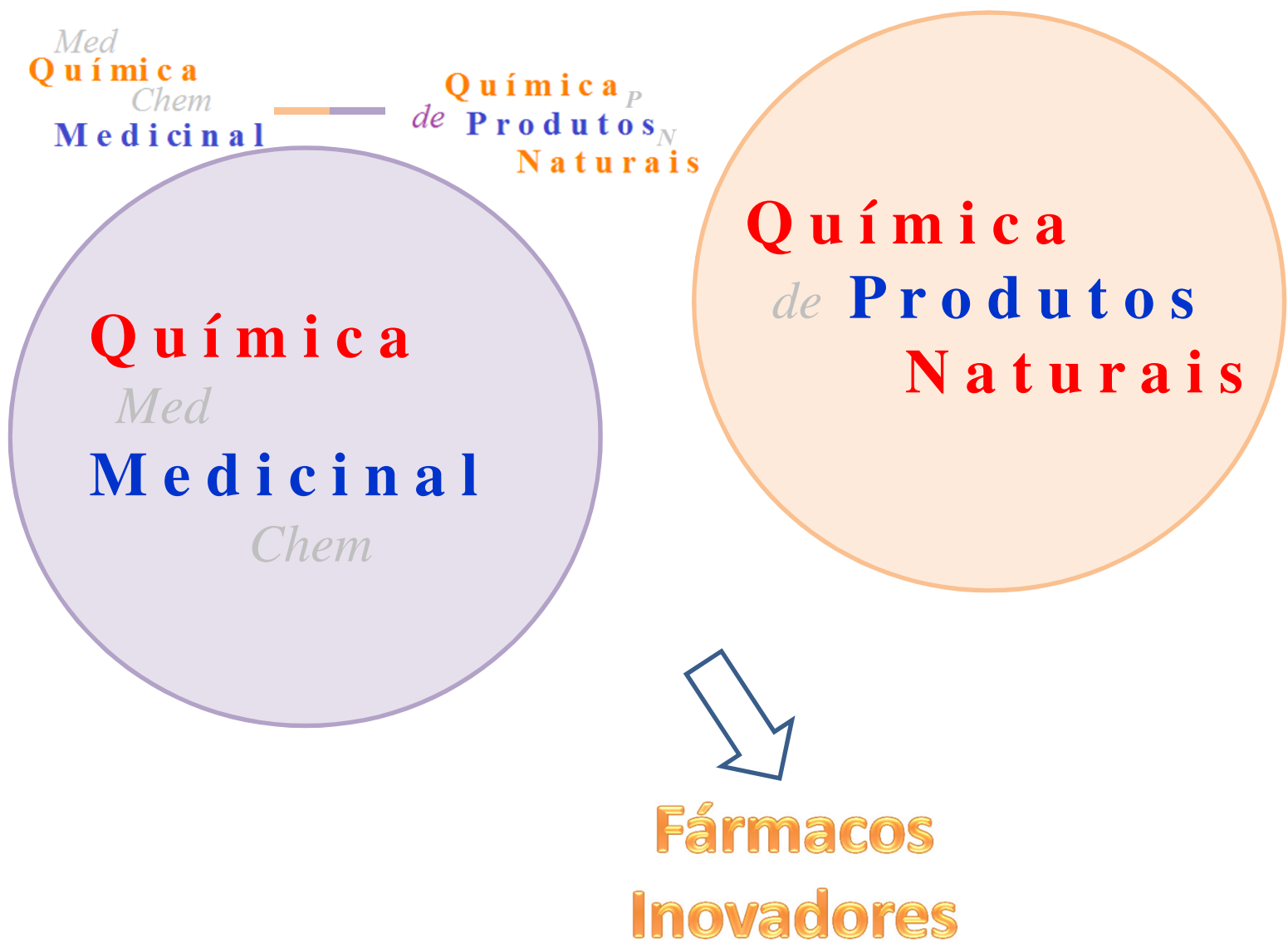
*Finais...*

*Concluding remarks...*





# Considerações Finais





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40  
5 RIO  
450

# Muito Obrigado pela presença e pela atenção!

[ejbarreiro@ccsdecania.ufrj.br](mailto:ejbarreiro@ccsdecania.ufrj.br)

Praia do Boqueirão, Saquarema, RJ