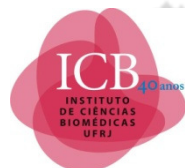




# Produtos Naturais em Química Medicinal



**Eliezer J. Barreiro**

Professor Titular



<http://evqfm.com.br/>

**Parte 3**

25/01/2017

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

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



Laboratório de Avaliação e Síntese de Substâncias Bioativas



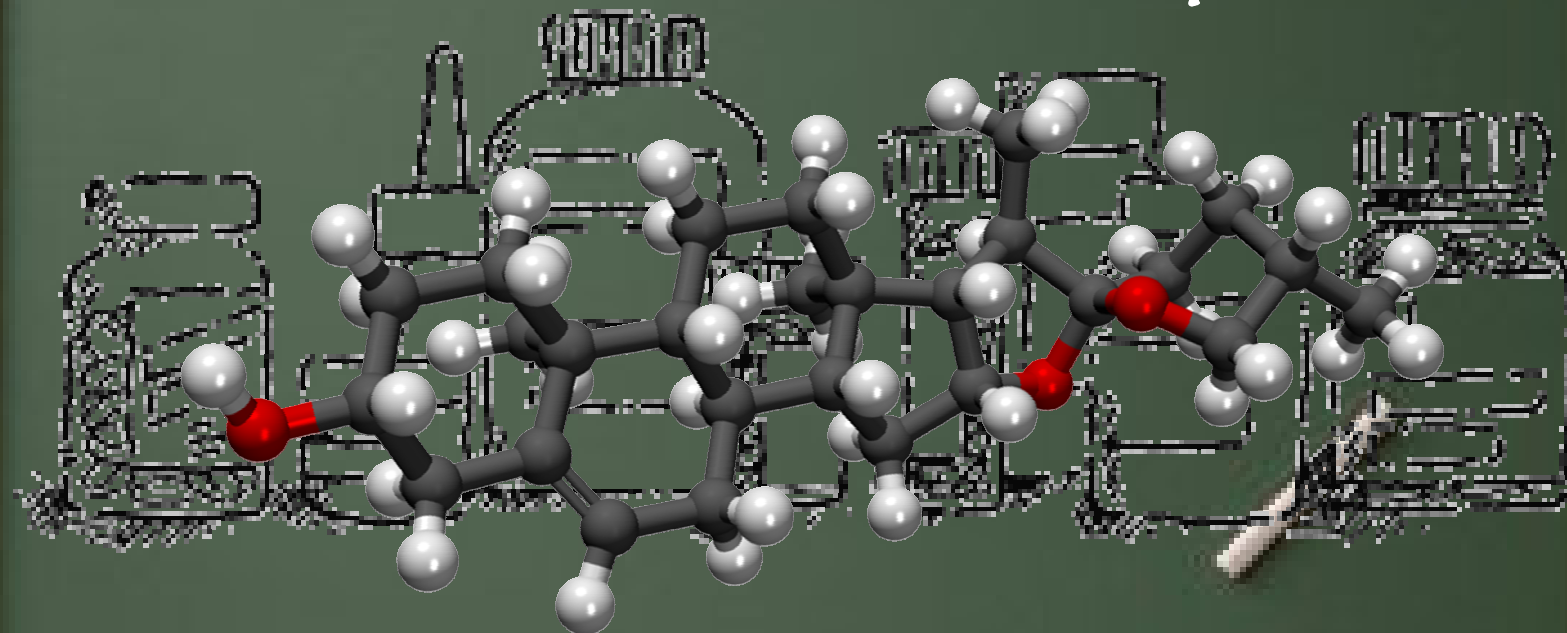
# Produtos Naturais em Química Medicinal

## Sumário;

Preâmbulo; Bibliografia; **O início:** os PRODUTOS NATURAIS e o Brasil; Patrimônio genético **BRASILEIRO**; o fármaco dos Índios: bloqueadores **glanglionares**; Daniel Bovet; **captopril**; A **ORIGEM** dos fármacos; As **classes** dos PN's; **QUIMIODIVERSIDADE**; *quimiotipo*; CONCEITO de *hit-natural*; **as moléculas pioneiras**; A **DIGOXINA**, o décimo dos **FÁRMACOS**; A **importância** da **CONFORMAÇÃO**; **ALCALOIDES**; **MORFINA**; **STREPTASE** molecular; **tramadol** & *tapentadol*; PN's & **quiralidade**; bent Samuelsson; Sune bergstron; John VANE = **AAS**; **icosanoides**; **mais alcaloides**; Prêmio **NOBEL** 2015; PN's & Agatha **Cristie**/**Patricia Highsmith**; PN's **PSICOATIVOS**, psicodélicos (**THC**, **LSD**); **Substâncias NATURAIS** afrodisíacas; **NATUREZA & funções químicas exóticas**; **Scaffolds** NATURAIS; **DIOSGENINA** & contraceptivos; **SIMILARIDADE MOLECULAR**; PN'S & câncer; **Vinca**; *taxanos*; **epotilonas**; **Wall & Wani**; **ECTENAISCIDINA**; **PN** marinhos; *os fungos*; **Fleming**; **Ernest Chain**; Howard **FLOREY** = **penicilina**; **antibióticos**; **mais BOLOR**; **ESTATINAS**; **PN's** de **animais**; **epibatidina**; PN's como "**bióforos naturais**"; **EXEMPLOS "DE casa"**; **LASSBio-294**; **EPÍLOGO**

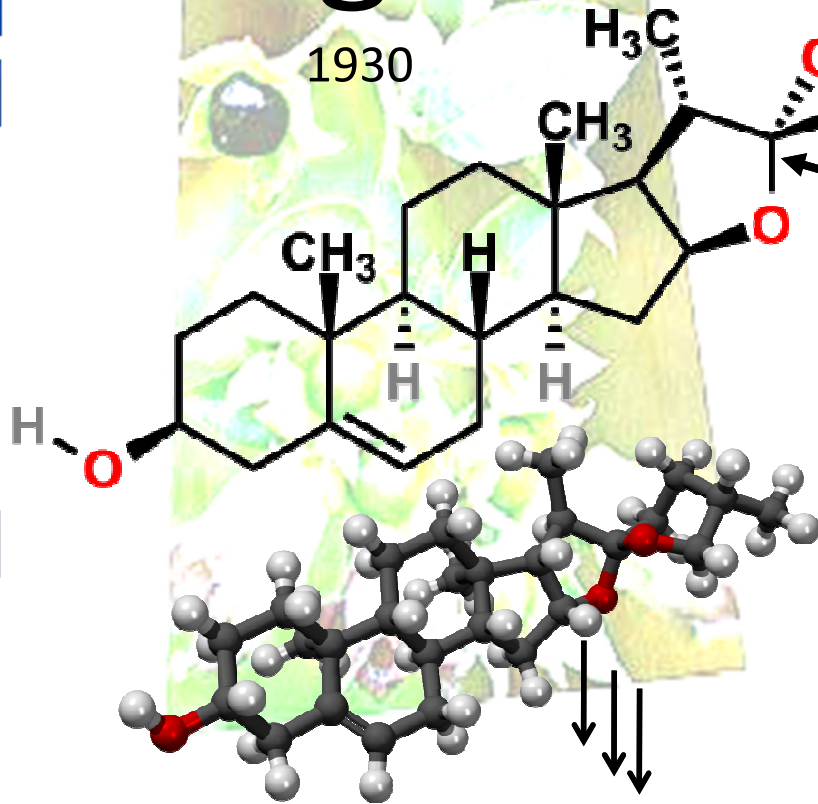


◇ Os PN'e & contraceptivos





# Diosgenina



Degradação de Marker

Laboratorios Syntex SA

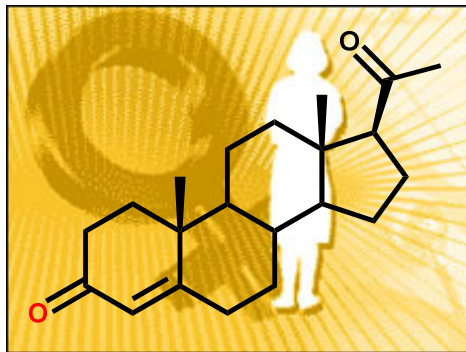


Russell Marker 1902-1995

*Dioscorea mexicana* Scheidw

**Russell E Marker**

RE Marker, Sterols. CXIII. Sapogenins. XLII. The conversion of the sapogenins to pregnenolones". *J. Am. Chem. Soc.*, **62** 3350-3352 (1940); P Lehmann, A Bolivar, R Quintero, Russell E. Marker - Pioneer of the Mexican steroid industry, *J. Chem. Ed.*, **50**, 195-9 (1973).



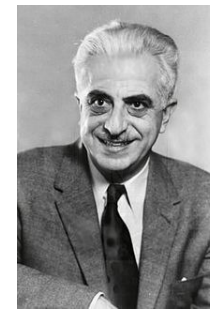
progesterona

1995

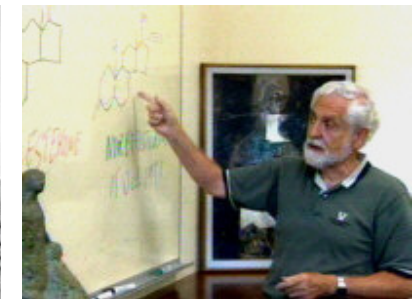


**Mario Molina**

Instituto de Química UNAM

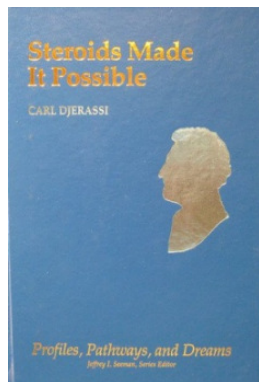


**Gregory Pinkus**

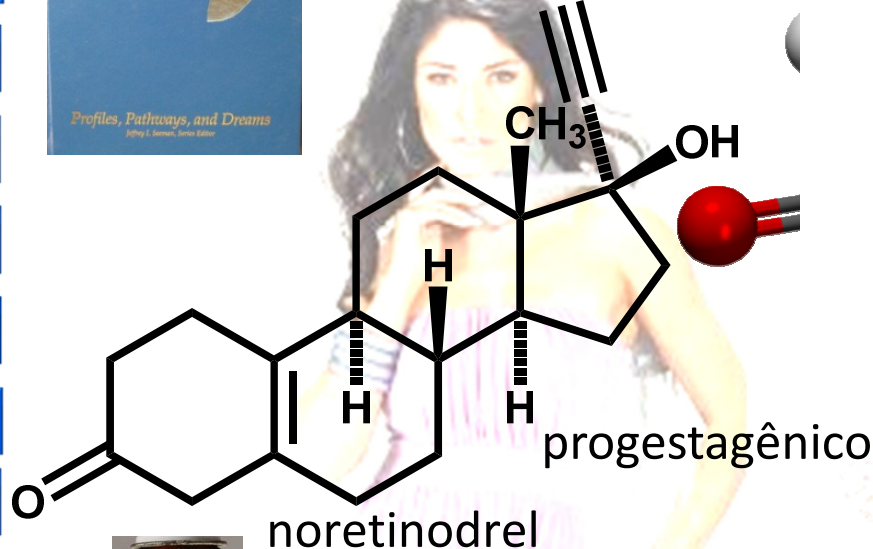
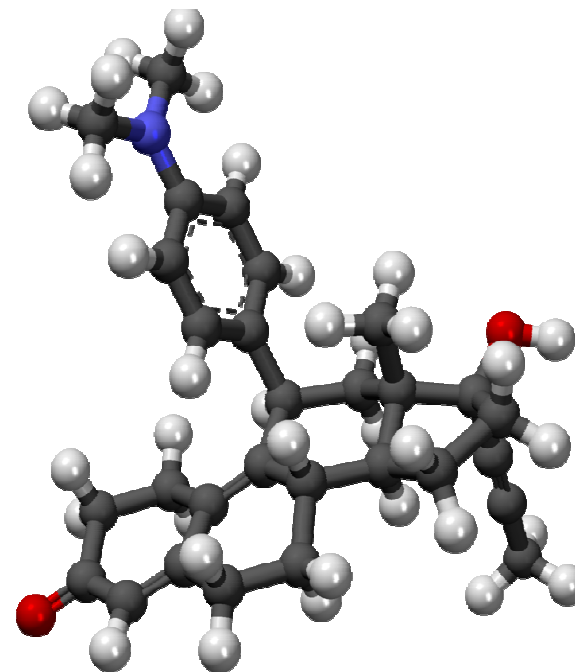


**Carl Djerassi**

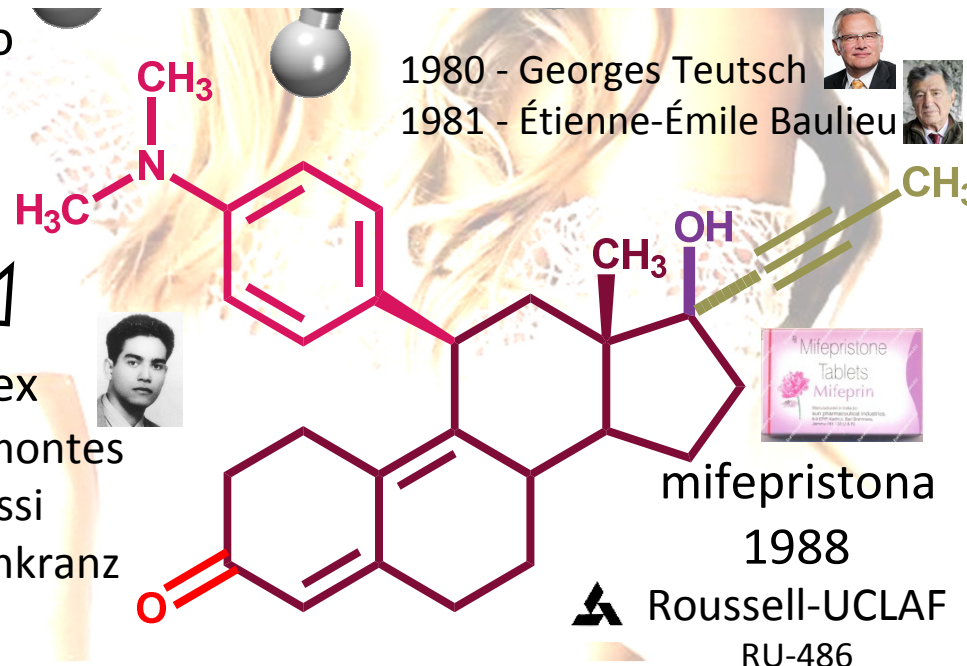
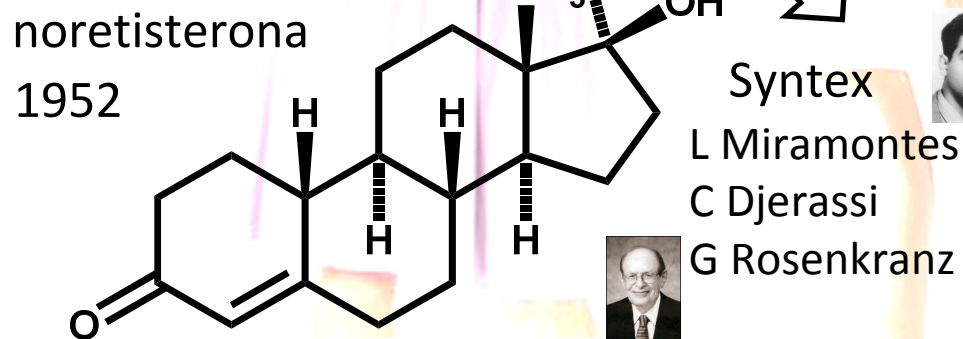
# Contraceptivos



# A pílula



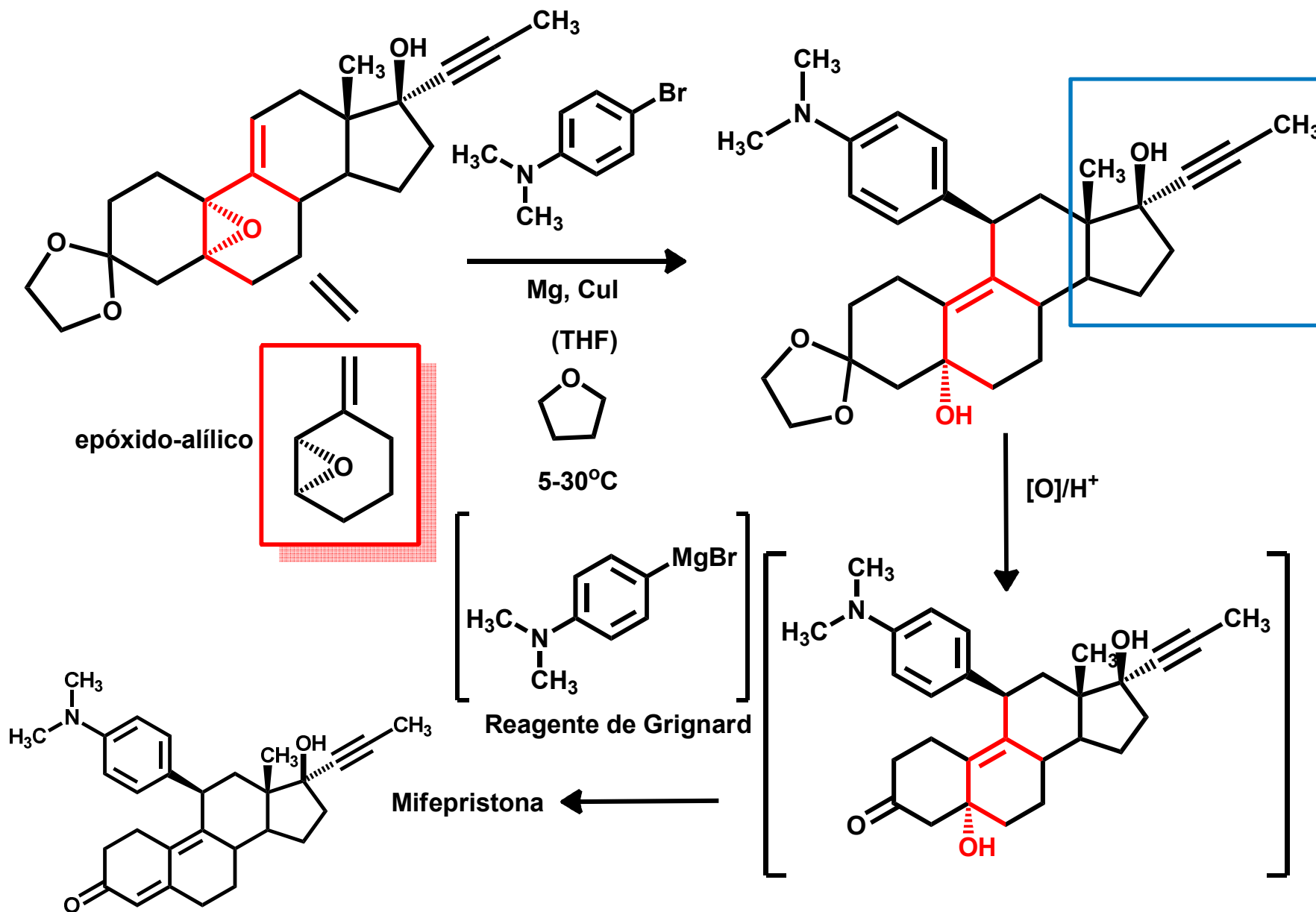
1951  
SEARLE



Mais de 147 milhões de mulheres utilizaram a pílula contraceptiva até ca. 2010



# Serendipidade na obtenção do RU-486

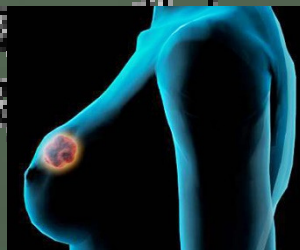




◊ PN's ea

Quimioterapia

do Câncer





# Quimioterapia do Câncer

## Produtos naturais vegetais

Quimiodiversidade;

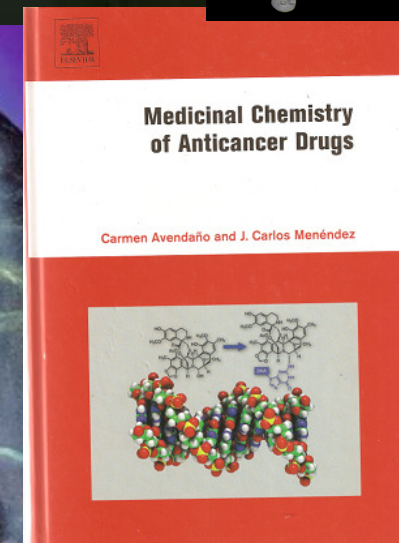
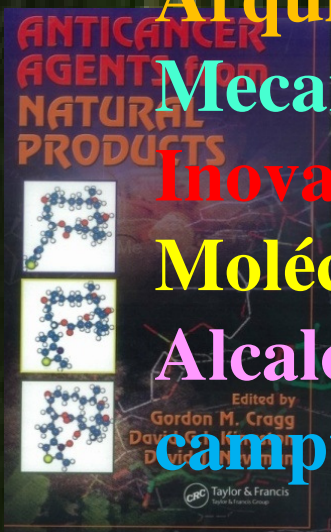
Arquiteturas moleculares originais;

Mecanismo de ação inovadores;

Inovações terapêuticas;

Moléculas otimizadas;

Alcalóides da **Vinca**, podofilotoxina, **camptotecina**, taxoides, **epotilona**, etc



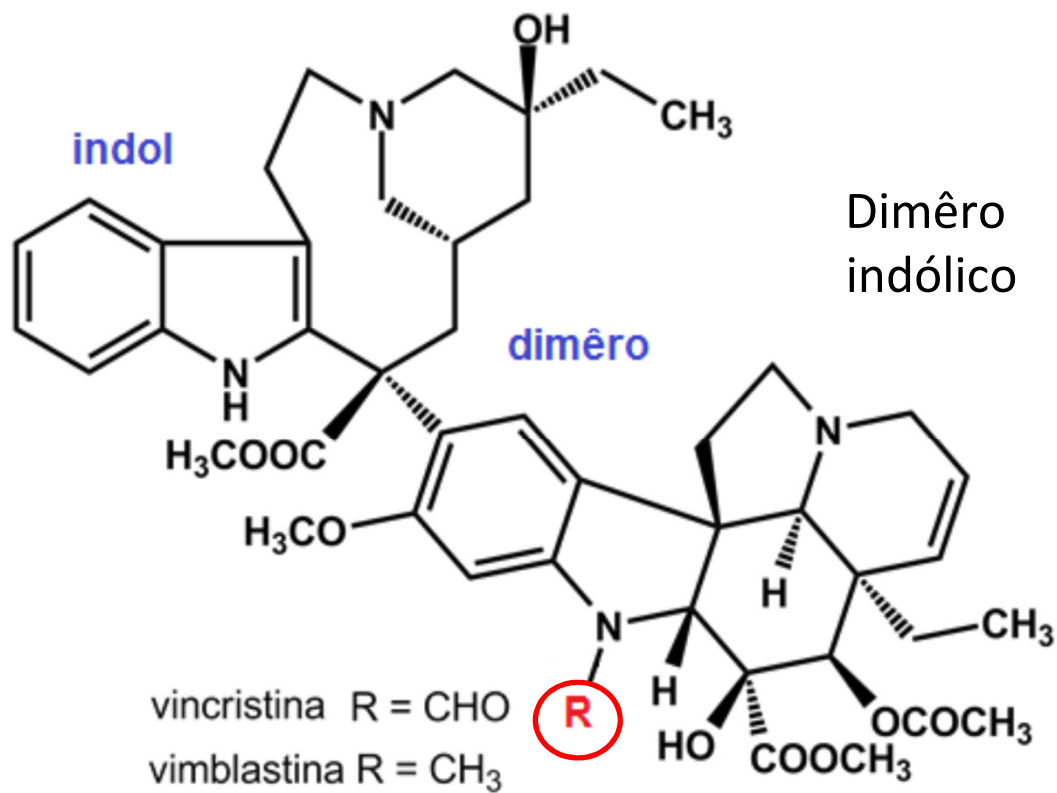
GM Crag, PG Grothaus, DJ Newman, Natural products in drug discovery: recent advances, em *Plants Bioactives & Drug Discovery*, V Cechinel Filho Ed., Wiley, 2012, p. 1- 42.

AL Demain, P Vaishnav, Natural products for cancer chemotherapy, *Microbial Biotechnology* 2011, 6, 687; D Shewach Introduction to cancer chemotherapy, *Chem. Rev.* 2009, 109, 2859 (*Special Issue*); AK Mukherjee et al., Advances in Cancer Therapy with Plant Based Natural Products, *Curr. Med. Chem.* 2001, 8, 1467

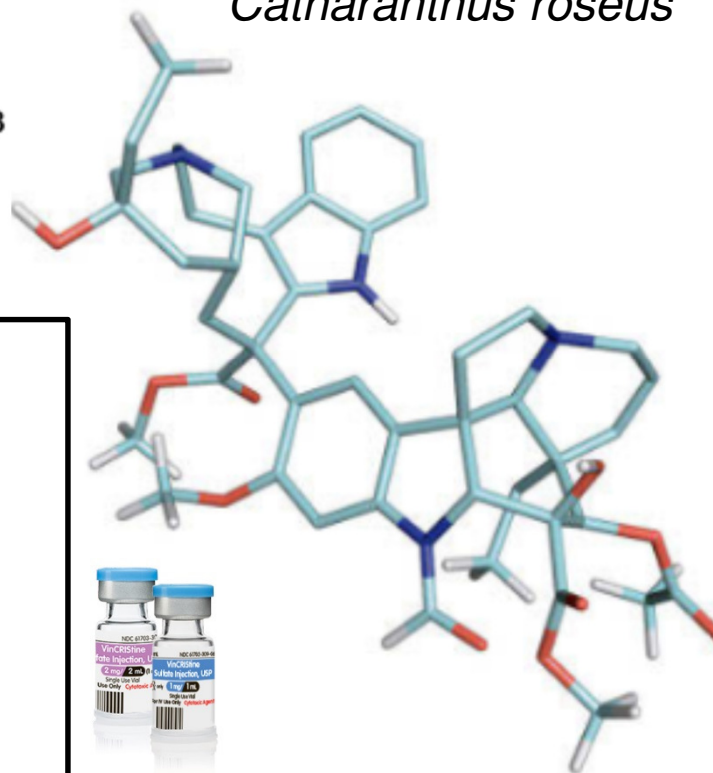




# Alcaloides da Vinca



*Catharanthus roseus*



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



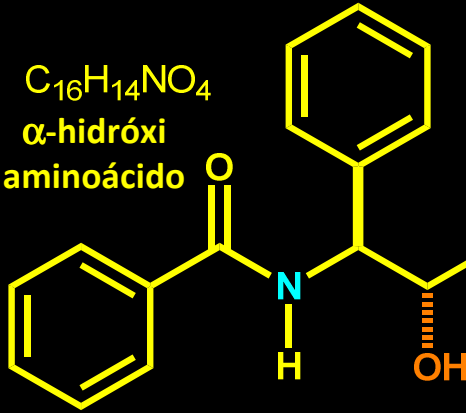
1958 – NY Academy of Sciences Congress  
Noble, describe vinblastine  
Gordon Svoboda, Eli Lilly vincristine

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



# Câncer

$C_{16}H_{14}NO_4$   
 $\alpha$ -hidróxi  
aminoácido

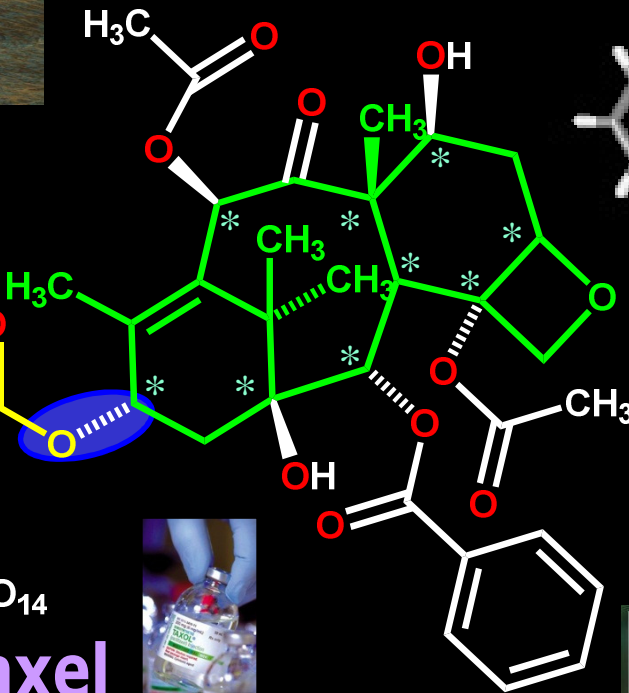


$C_{47}H_{51}NO_{14}$

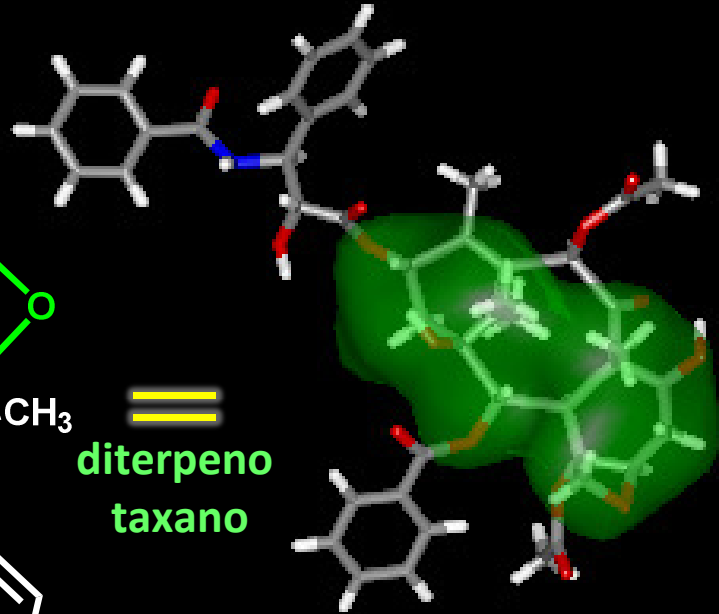
1965

Paclitaxel

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



diterpeno  
taxano

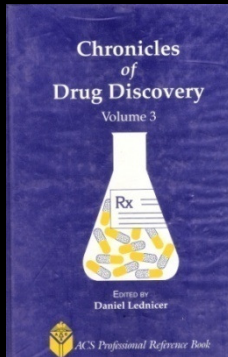


## Inibidores de tubulinas (MoA)

Res. Triangle Park, 1967



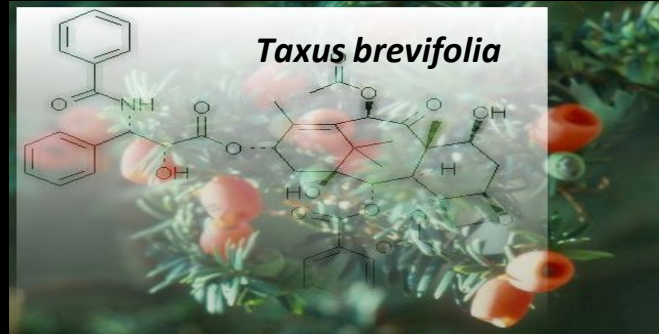
M. E. Wall & M. C. Wani  
1996 - National Cancer Institute  
Award of Recognition



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



blockbuster  
2010



*Taxus brevifolia*



\*P. Poitier &  
A.E. Greene

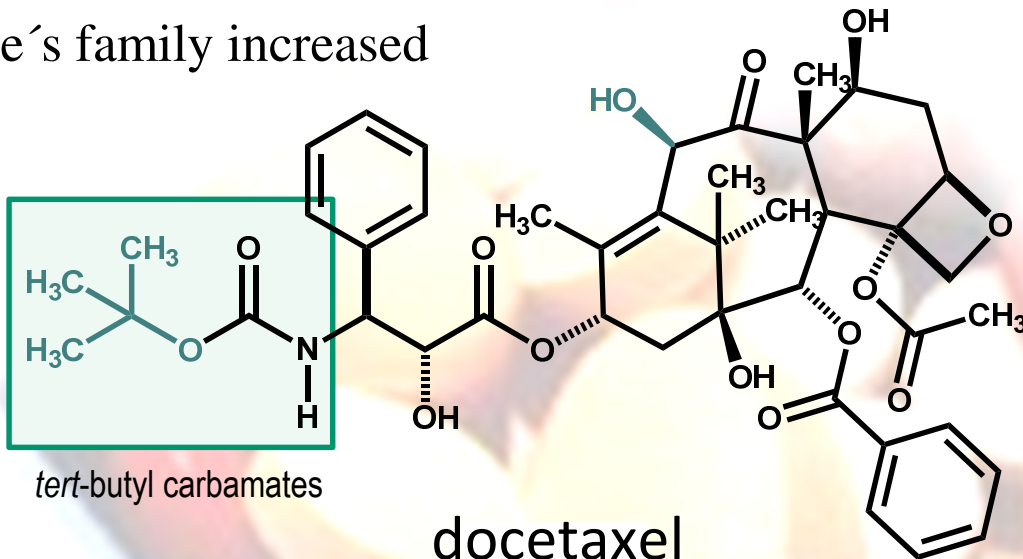
Docetaxel\*  
Cabazitaxel (Jevtana<sup>R</sup>)  
Ortataxel&





# A família dos taxanos cresceu...

The taxane's family increased



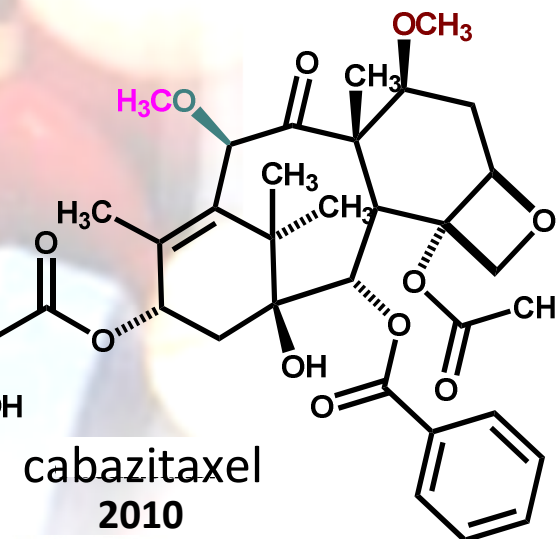
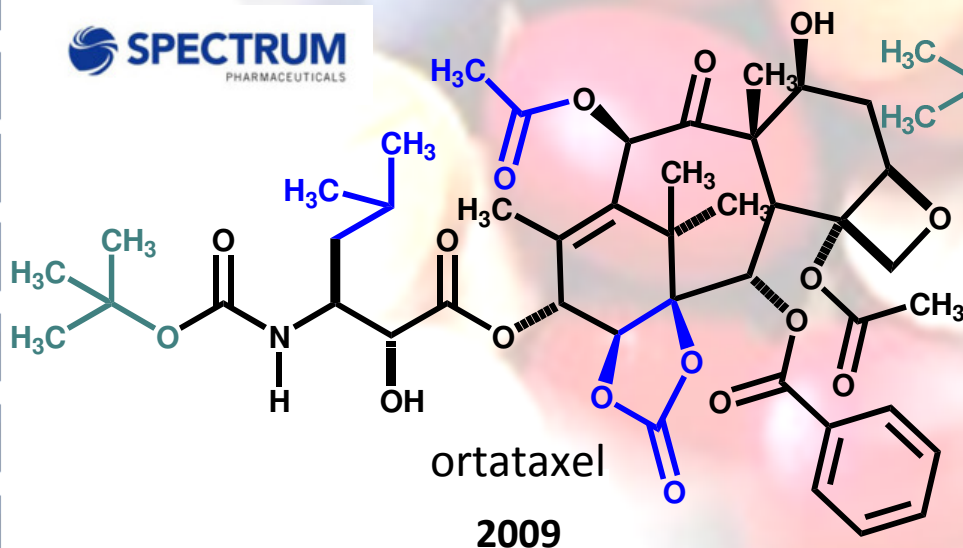
Pierre Potier  
(1934-2006)



Andy E Greene  
Un Grenoble



## Câncer



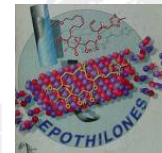
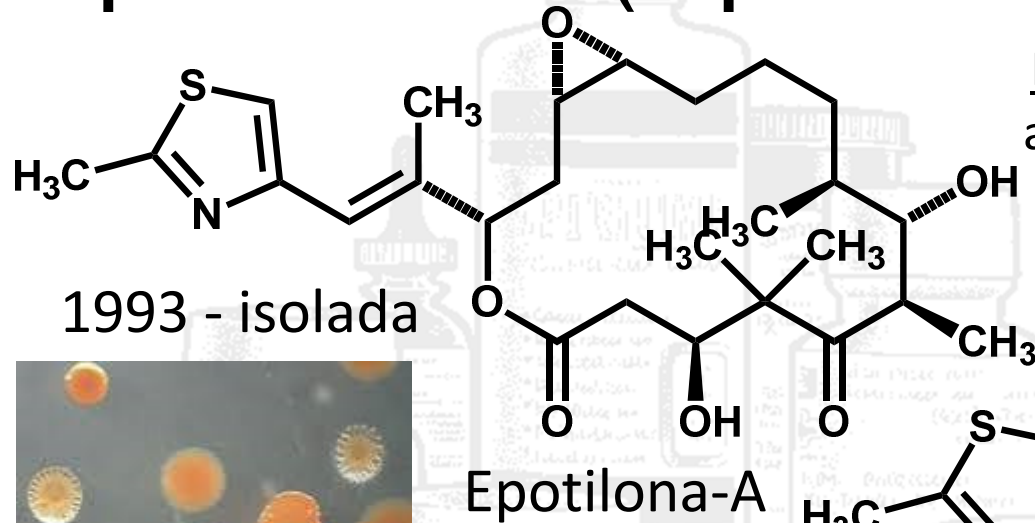
Y-F Wang et al., Natural taxanes: developments since 1928, *Chem. Rev.* **2011**, *111*, 7652



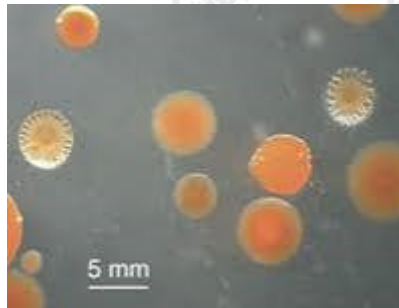
# Epotilonas (Epothilones)

## Câncer

Primeiro macrociclo de 16 membros  
aprovado para tratamento do câncer  
metástatico de mama



Inibidor de microtúbulo



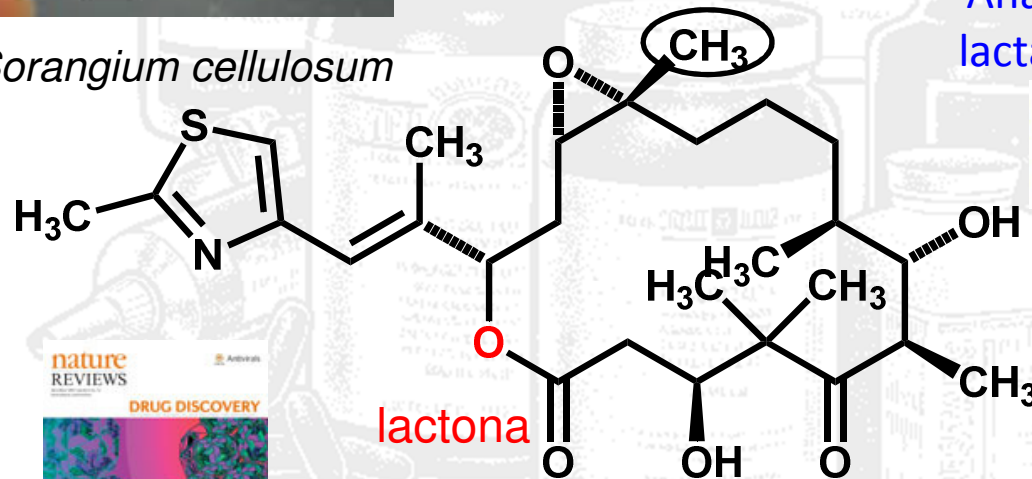
*Sorangium cellulosum*



Análogo  
lactâmico

HN

Química  
Medicinal



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 Hudis, S Kar, P. Kirkpatrick,  
*Nat. Rev. Drug Discov.* **2007**, 6, 953





# Análogos de Epothilonas

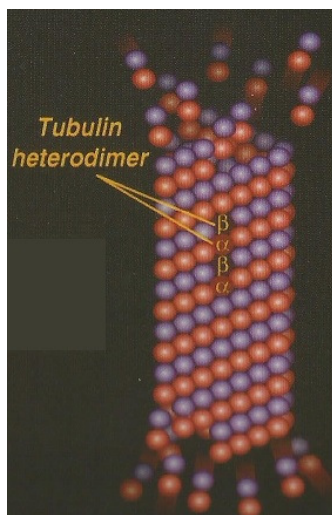
Analogues of Epothilones

X = NH, NCH<sub>3</sub>, O, S, CH=CH

homologue

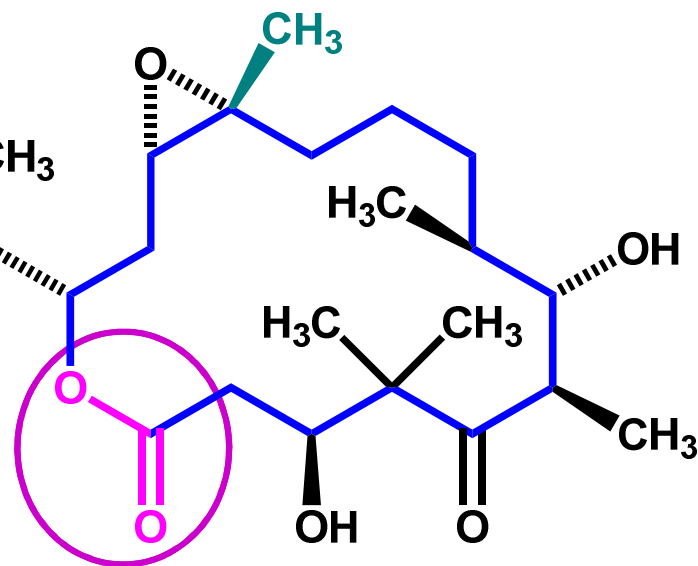
R = H, CH<sub>3</sub>

hetero-arila



Química Medicinal

Isosteres



lactona

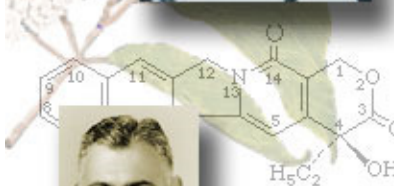


Professor Dieter Schinzer  
University of Magdeburg





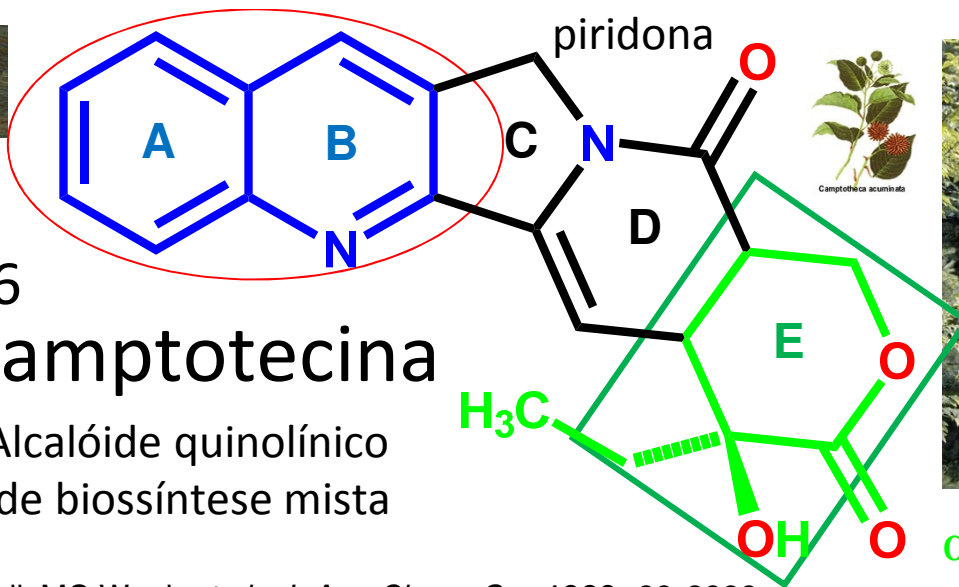
# Câncer



1966

## camptotecina

Alcalóide quinolínico  
de biossíntese mista

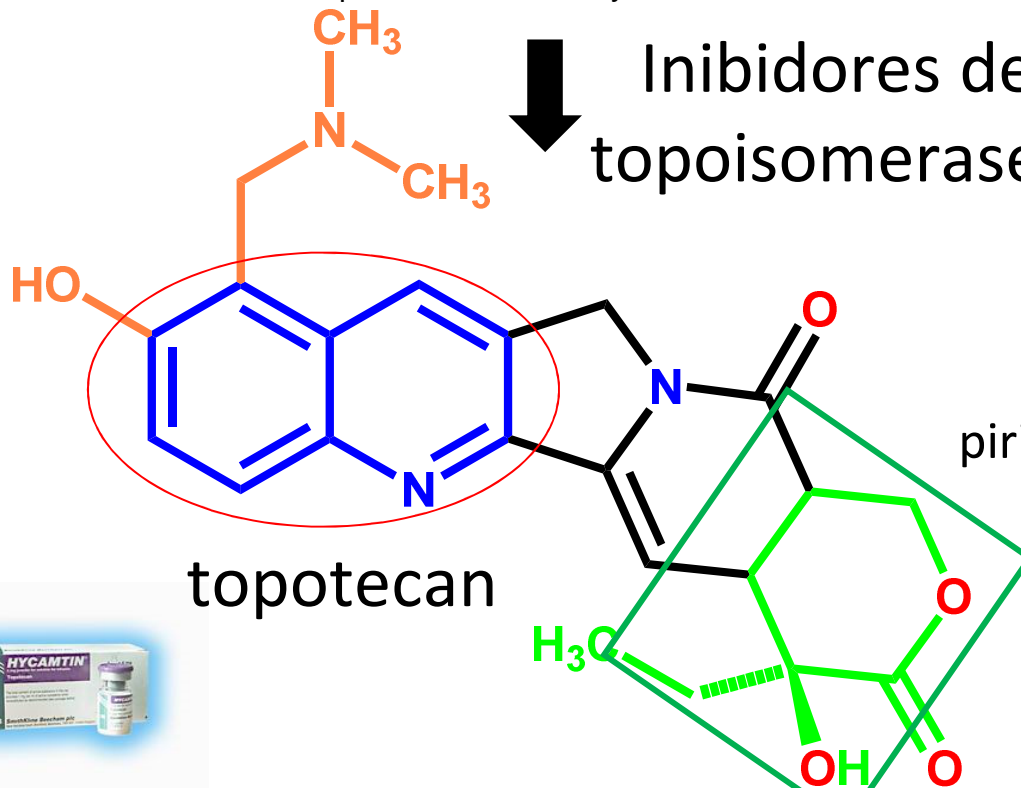


*Camptotheca acuminata*

ME Wall, MC Wani, *et al.*, *J. Am. Chem. Soc.* **1966**, *88*, 3888

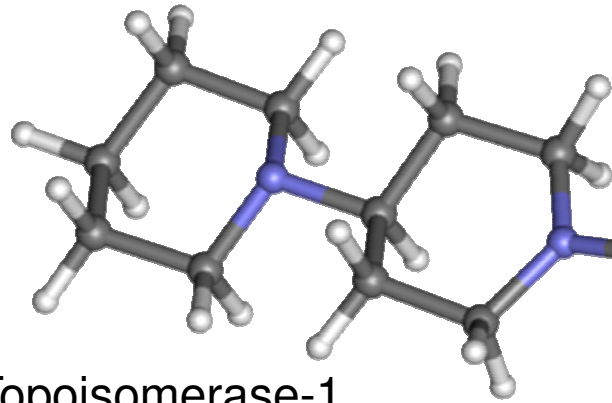
ME Wall, MC Wani, "Camptothecin: Discovery to Clinic" *Ann. NY Acad. Sci.* **1996**, *803*, 1

↓  
Inibidores de  
topoisomerase-1

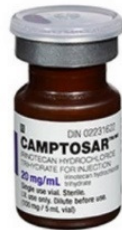


topotecan





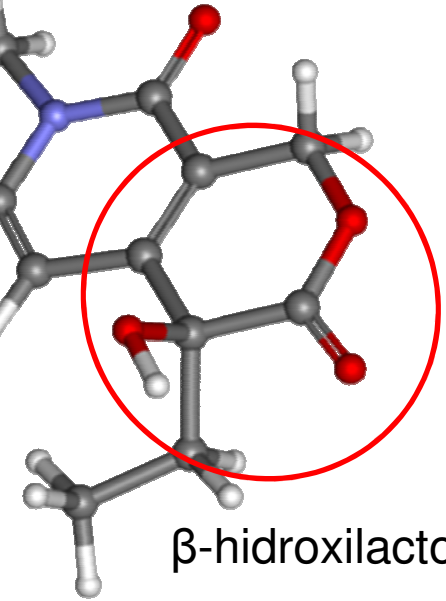
Topoisomerase-1  
1000 X CPT  
glioblastoma



1996  
**irinotecan**  
(Camptosar<sup>®</sup>)  
Pró-fármaco

**carboxilesterases**  
*In vivo*

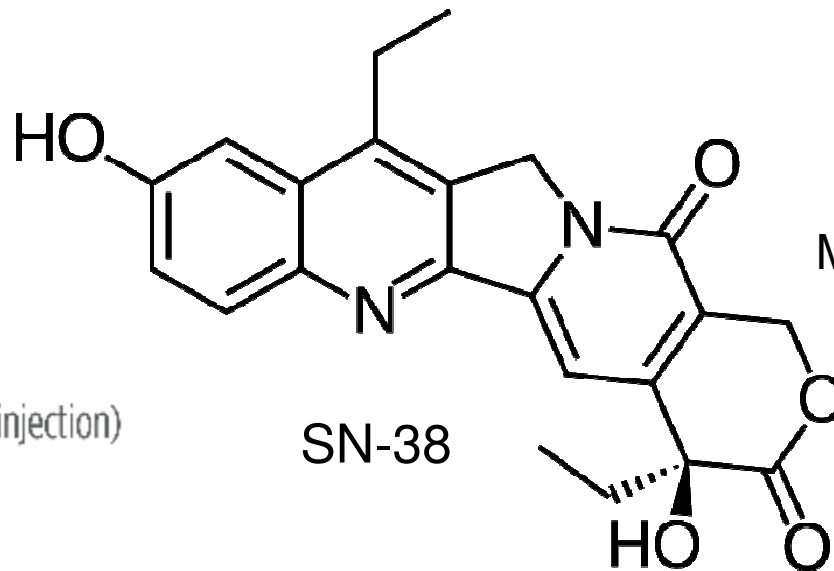
Molécula  
*domesticada*



$\beta$ -hidroxilactona

2015 - FDA

 **onivyde**<sup>™</sup>  
(irinotecan liposome injection)



SN-38

Metabólito ativo



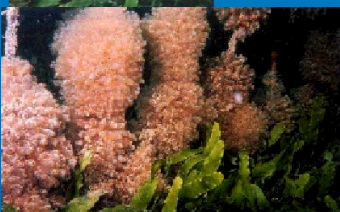
# Yondelis<sup>R</sup> (ET-743)

Alcalóide tetraidroisoquinolínico de origem marinha

# Ecteinascidina

Síntese Total

49 etapas



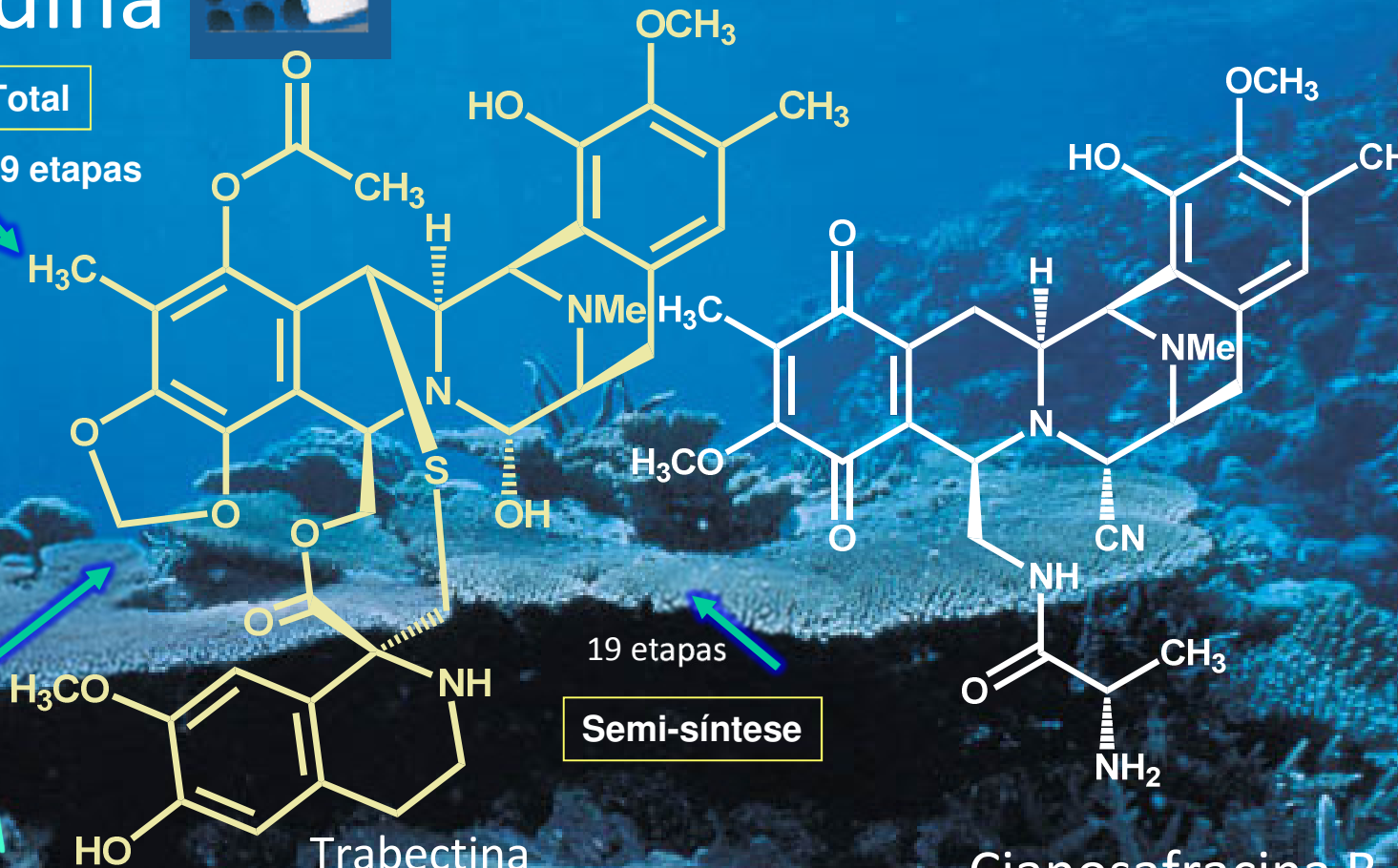
*Ecteinascidia turbinata*

Marinocultura

19 etapas

Semi-síntese

# Pharma-Mar SA



Trabectina

Cianosafracina B

Nobel 1990

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



1928 -

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

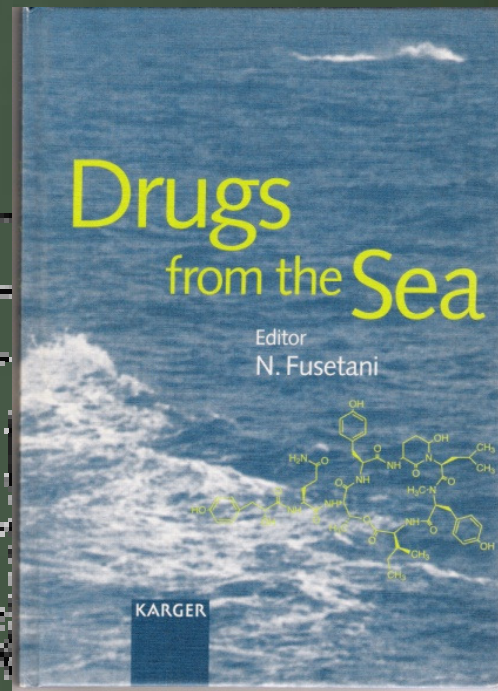
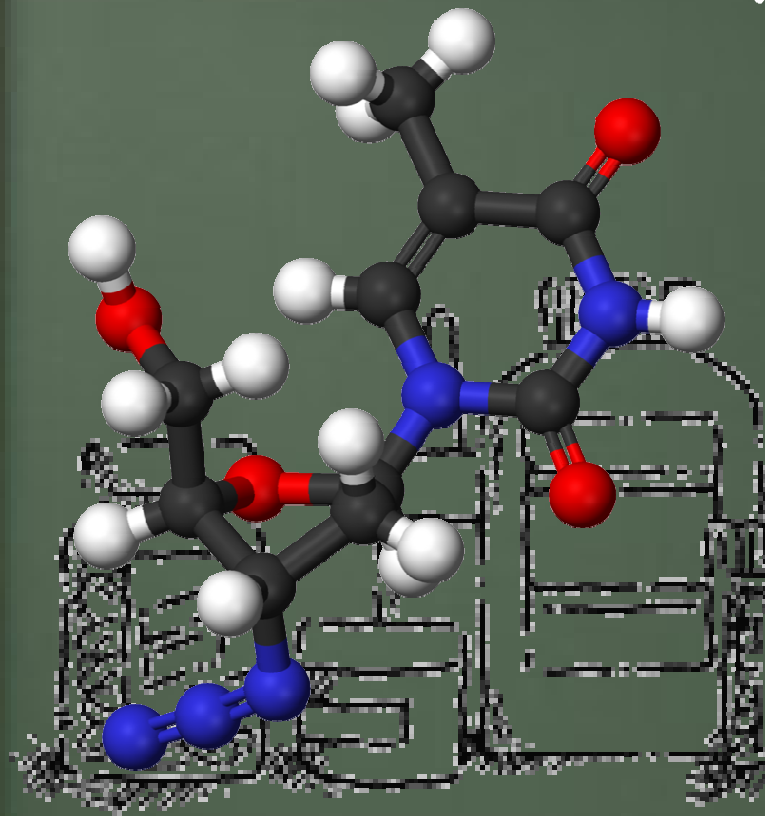


Fermentação  
*Pseudomonas fluorescens*





# ◇ PN's do mar.



L V Costa-Lotufo, D V Wilke, P C Jimenez, R A Epifanio, *Quím. Nova* 2009, 32, 703

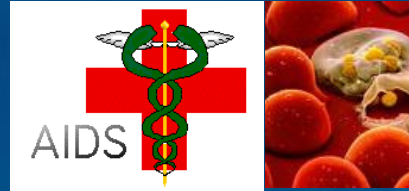
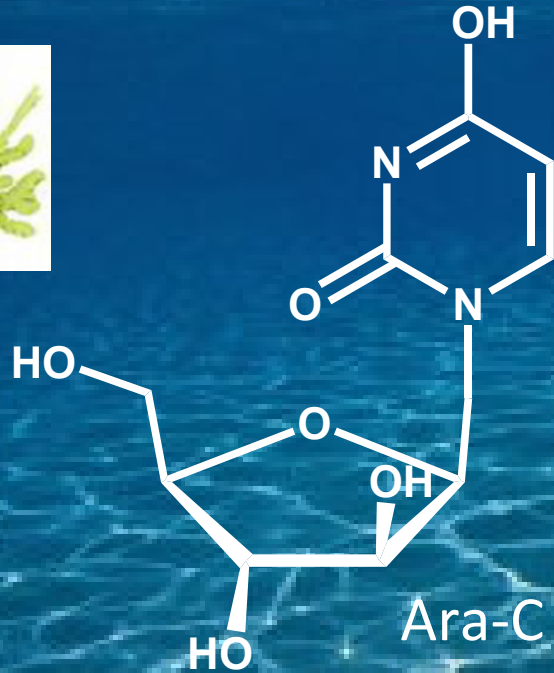
T F Molinsky *et al.*, *Nat. Rev. Drug Discov.* 2009, 8, 69



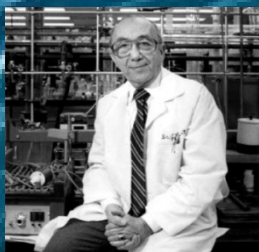
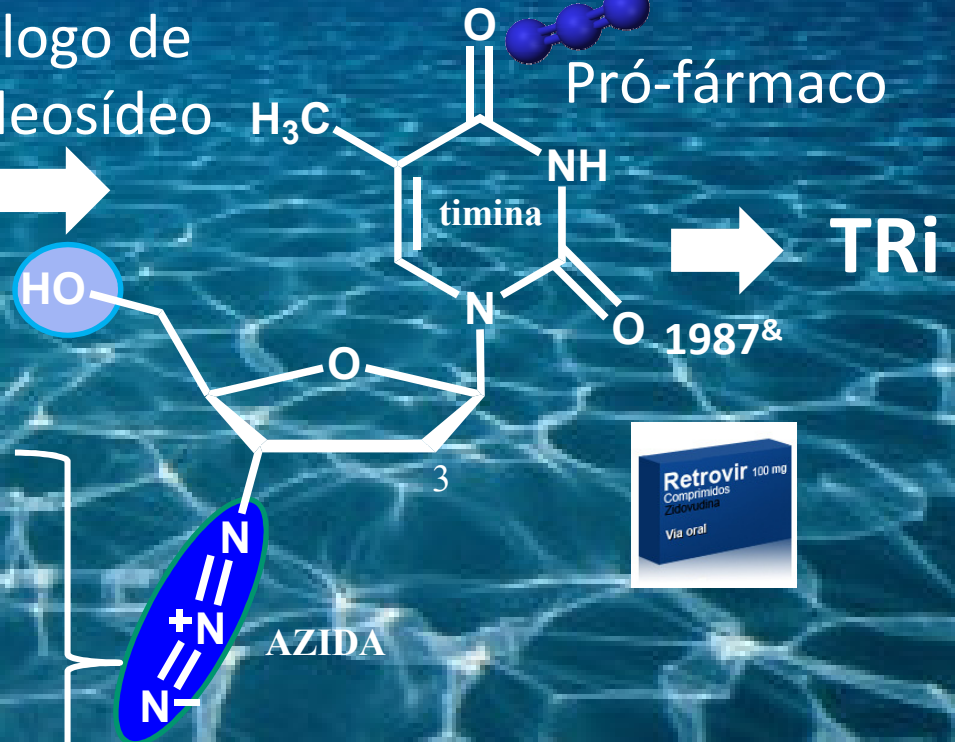
# Produtos Naturais do Mar



algas



Análogo de nucleosídeo



Jerome Horowitz

1964-sintetizada\*  
 1984- Burroughs Wellcome  
 1987- H Mitsuya & S Broder,  
*Nature* 1987, 325, 773&

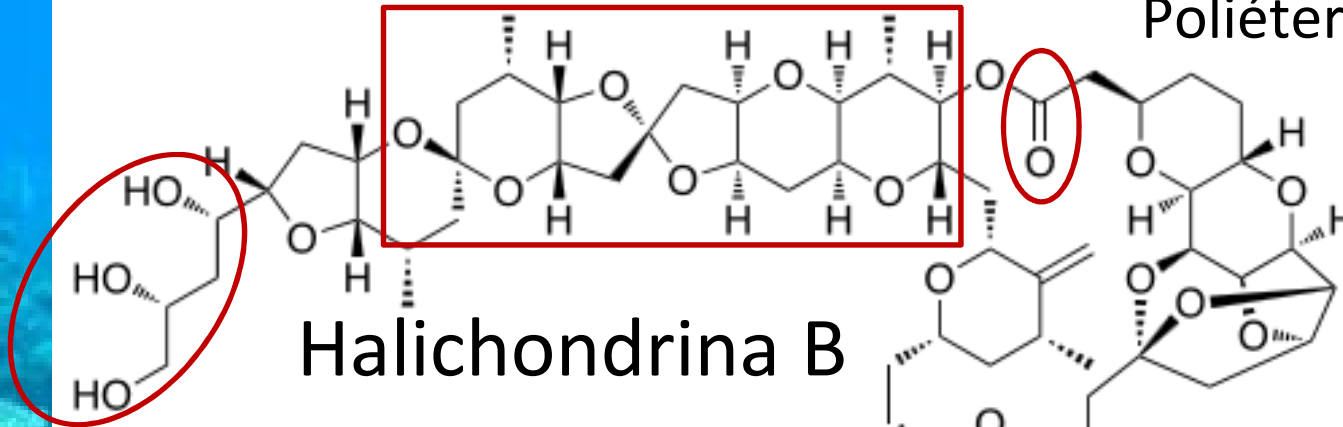
## Zidovudina (AZT)

\* J Horowitz et al., *J Org Chem* 1964, 29, 2076



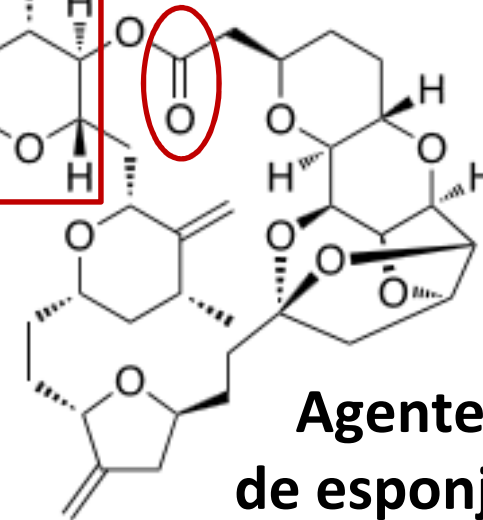
# Striptease molecular

Poliétermacrocíclico

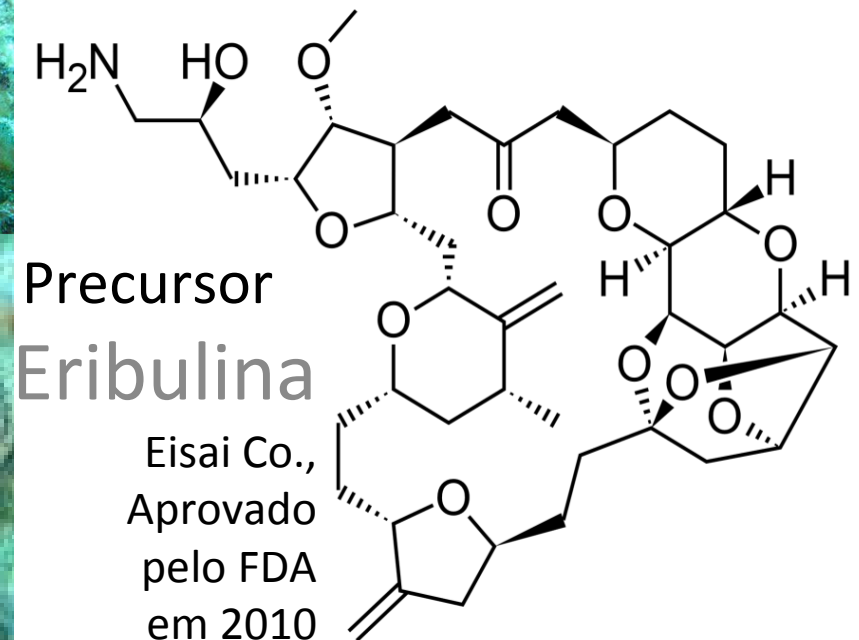


**Halichondrina B**

*Halichondria okadai*  
Hirata & Uemura, in 1986



**Agente oncolítico  
de esponja marinha**



Precursor  
**Eribulina**

Eisai Co.,  
Aprovado  
pelo FDA  
em 2010

1 ton. de esponja  
produz 300 mg



Síntese: Yoshito Kishi et al.  
Harvard University, 1992\*

**Câncer**

\* *J. Am. Chem. Soc.* 1992, 114, 3162–3164.



# Ziconotido



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

Uso intratecal



*Conus magus*

elan

1980 - Michael McIntosh & Baldomero Olivera



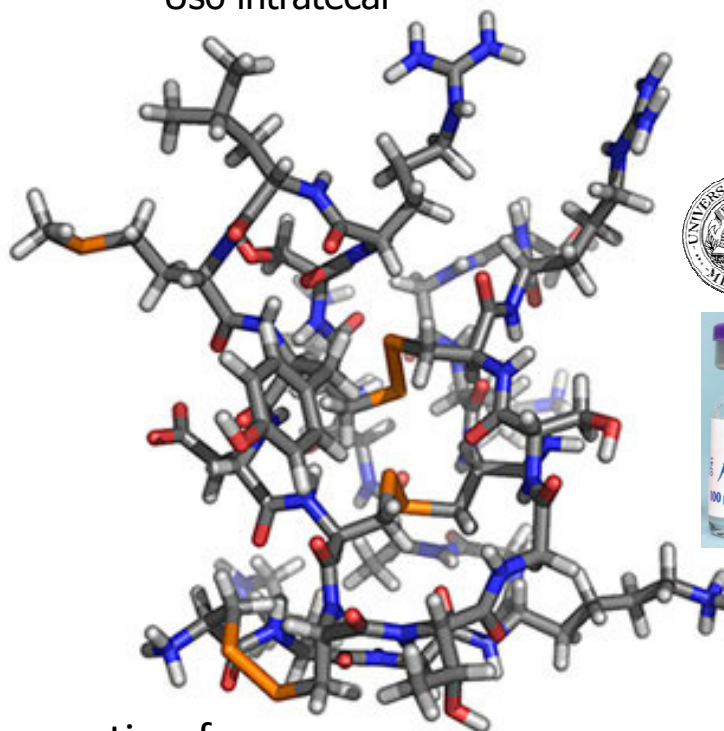
SNX-111

Neurex (Menlo Park, CA)



Elan Pharmaceuticals  
(Dublin, Ireland)

Análogo da  
 $\omega$ -conotoxina



E Prommer, Ziconotide: a new option for refractory pain, *Drugs Today* **2006**, 42, 369

H-Cys-Lys-Gly-Lys-Gly-Ala-Lys-Cys-Ser-Arg-Leu-Met-Tyr-Asp-Cys-Cys-Thr-Gly-Ser-Cys-Arg-Ser-Gly-Lys-Cys-NH<sub>2</sub>

Antagonista de canais Ca<sup>++</sup> voltagem dependentes tipo-N

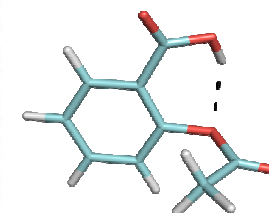
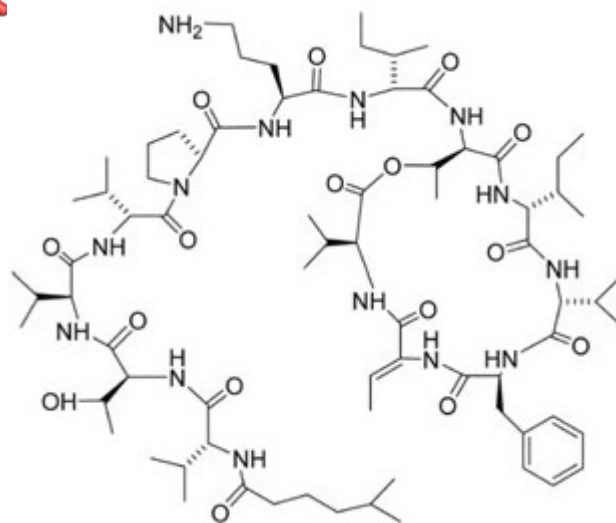
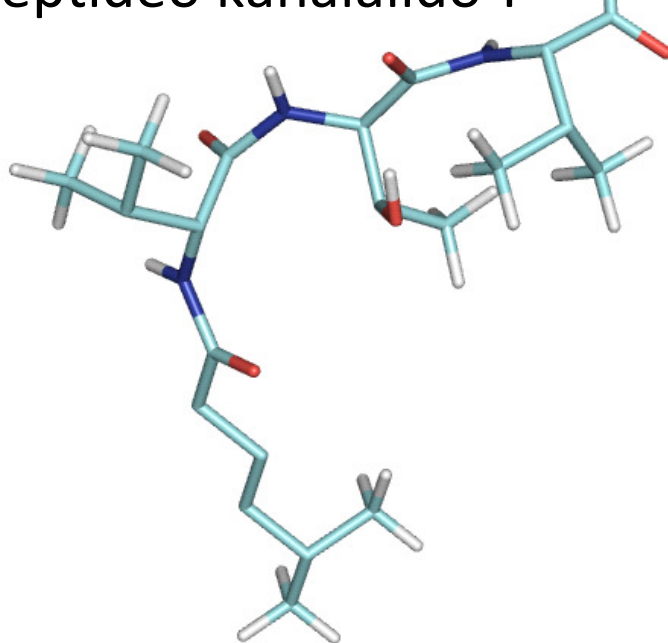
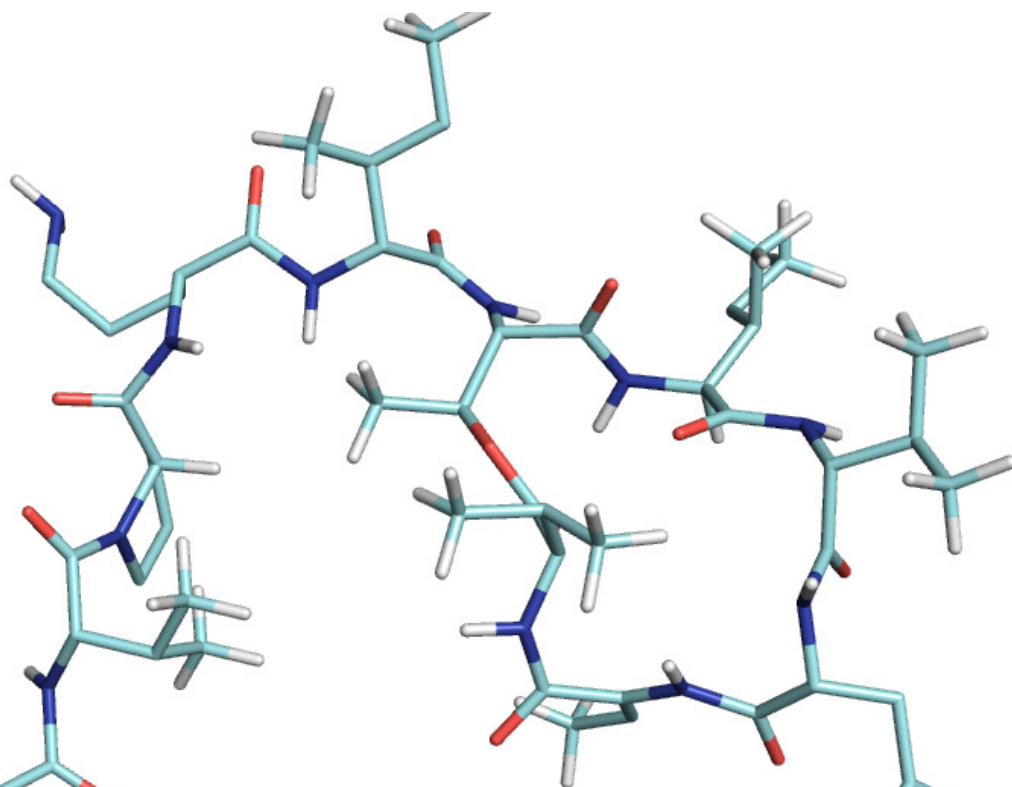




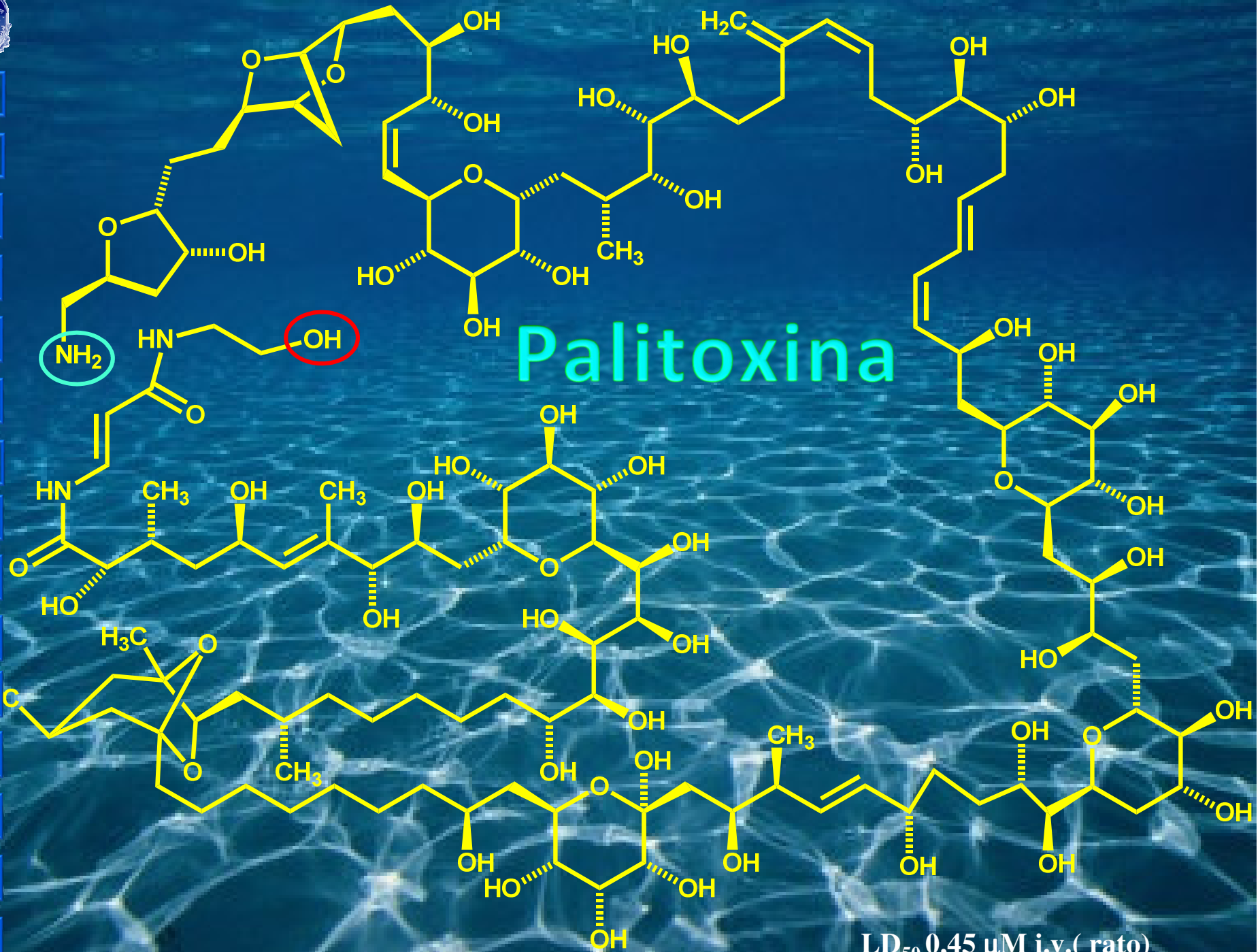
# Molusco



*Elysia rufescens*  
depsipeptídeo kahalalido-F



AAS

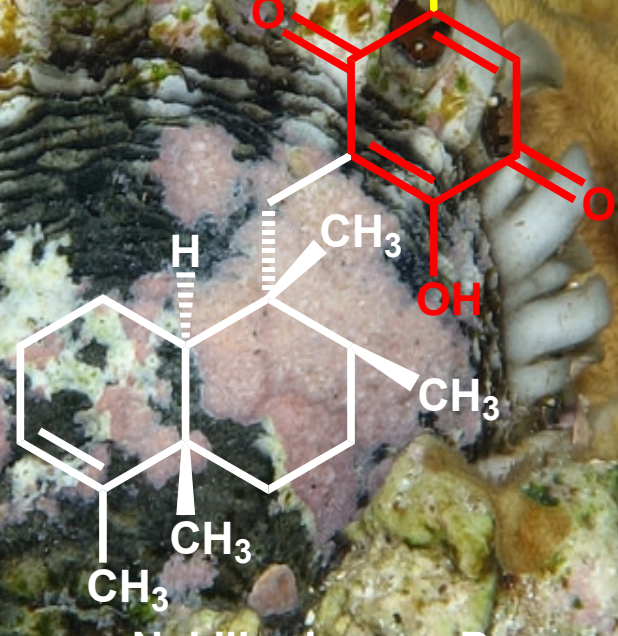
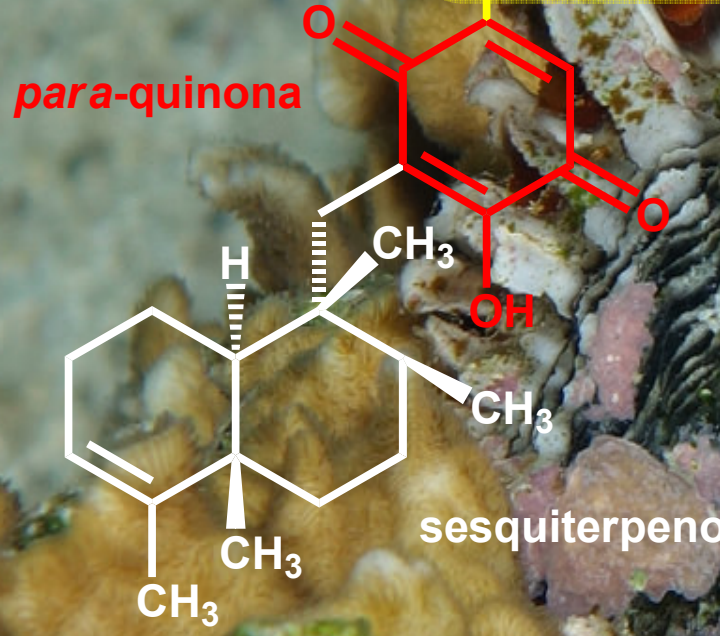
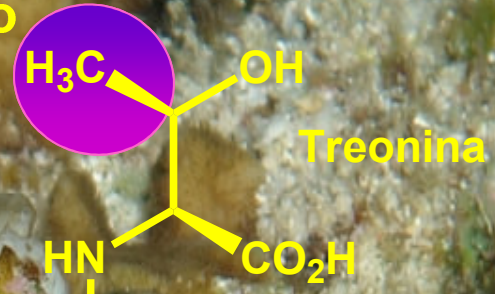
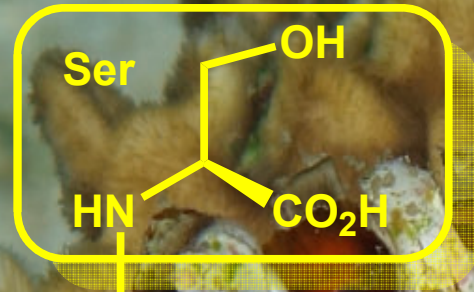


$LD_{50}$  0,45  $\mu$ M i.v.( rato)



# Spongiidae

hidróxi-amino-ácido



sesquiterpeno

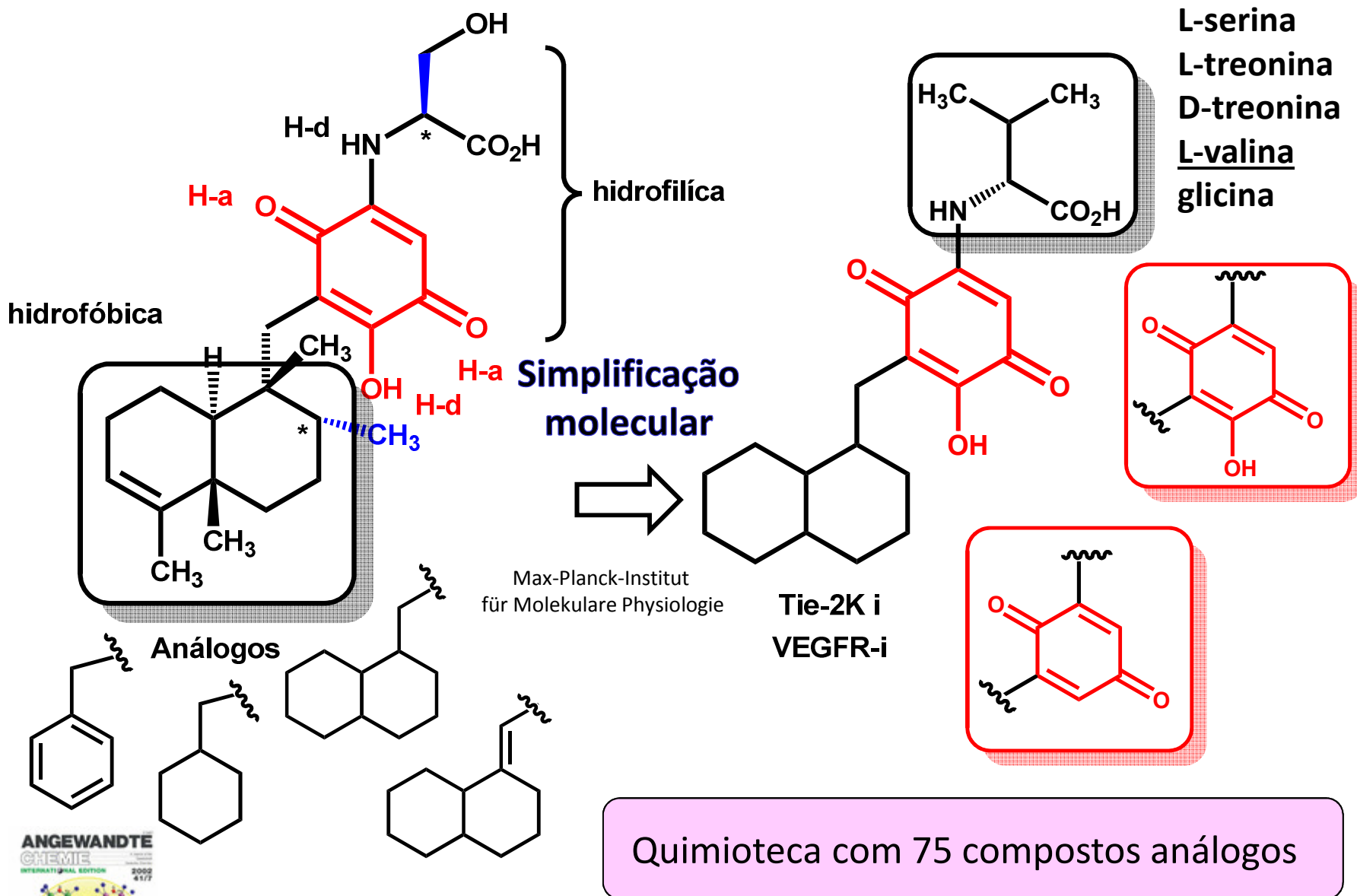
Nakijiquinones C

Nakijiquinones D

PKC+

PKC+

& c-erbB-2 Kinase



H Waldmann et al., *Angew Chem Internat Ed* **2002**, 41, 1174





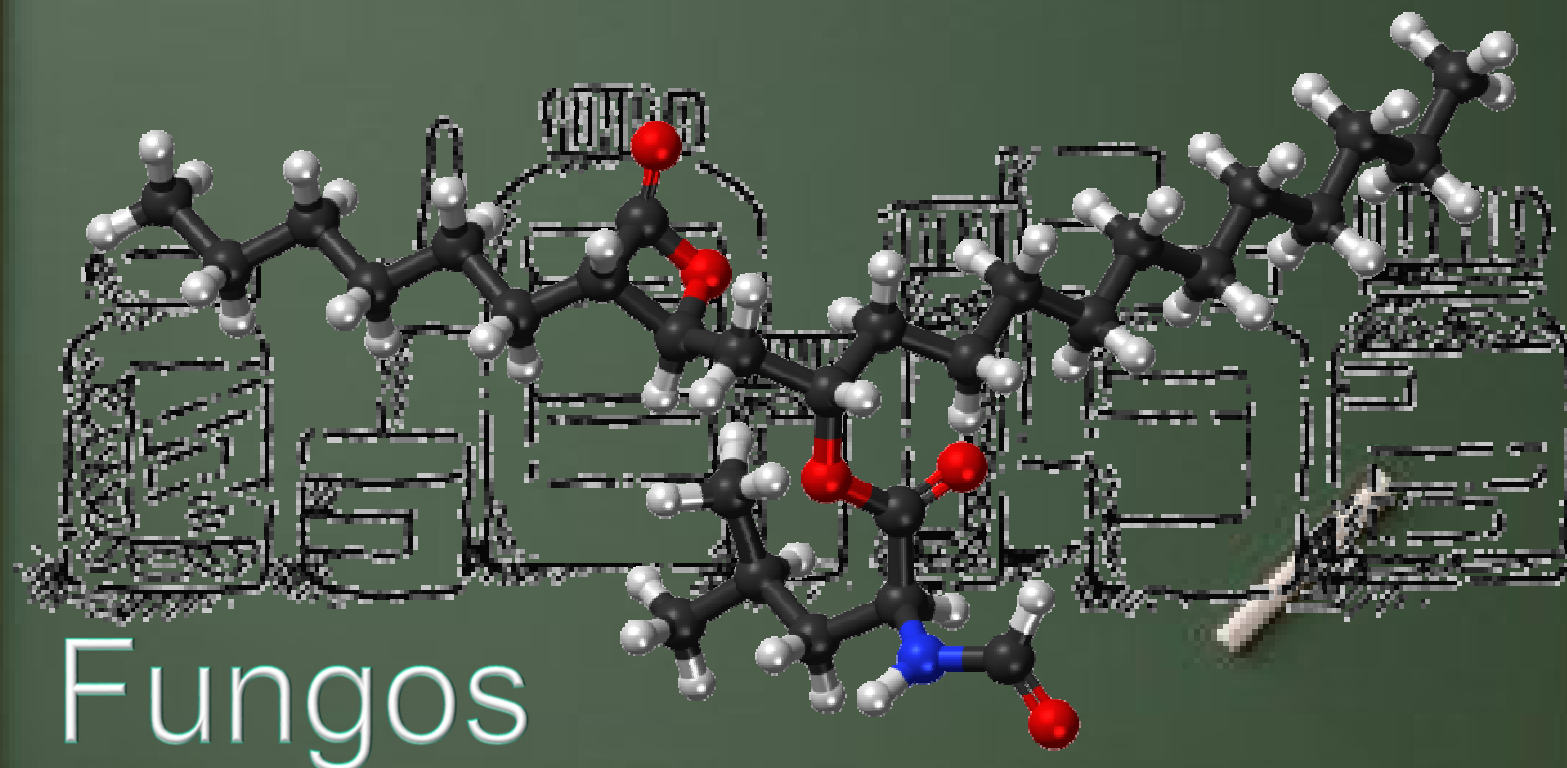
# Produtos Naturais em Química Medicinal

## Sumário;

Preâmbulo; Bibliografia; **O início:** os PRODUTOS NATURAIS e o Brasil; Patrimônio genético **BRASILEIRO**; o fármaco dos Índios: bloqueadores **glanglionares**; Daniel Bovet; **captopril**; A **ORIGEM** dos fármacos; As **classes** dos PN's; **QUIMIODIVERSIDADE**; *quimiotipo*; CONCEITO de *hit-natural*; **as moléculas pioneiras**; A **DIGOXINA**, o décimo dos **FÁRMACOS**; A **importância** da **CONFORMAÇÃO**; **ALCALOIDES**; **MORFINA**; **STREPTASE** molecular; **tramadol** & *tapentadol*; PN's & **quiralidade**; bent Samuelsson; Sune bergstron; John VANE = **AAS**; **icosanoides**; **mais alcaloides**; Prêmio **NOBEL** 2015; PN's & Agatha **Cristie**/**Patricia Highsmith**; PN's **PSICOATIVOS**, psicodélicos (**THC**, **LSD**); **Substâncias NATURAIS** afrodisíacas; **NATUREZA** & funções químicas **exóticas**; **Scaffolds** NATURAIS; **DIOSGENINA** & contraceptivos; **SIMILARIDADE MOLECULAR**; PN'S & **câncer**; **Vinca**; **taxanos**; **epotilonas**; **Wall & Wani**; **ECTENAISCIDINA**; **PN** marinhos; **os fungos**; **Fleming**; **Ernest Chain**; Howard **FLOREY** = **penicilina**; **antibióticos**; **mais** **BOLOR**; **ESTATINAS**; **PN's** de **animais**; **epibatidina**; PN's como "**bióforos naturais**"; **EXEMPLOS "DE casa"**; **LASSBio-294**; **EPÍLOGO**



## ◇ Outros PN's





# Do *bolor* às moléculas salva-vidas...



## antibioticoterapia

Fungos

Sir Alexander Fleming (64)

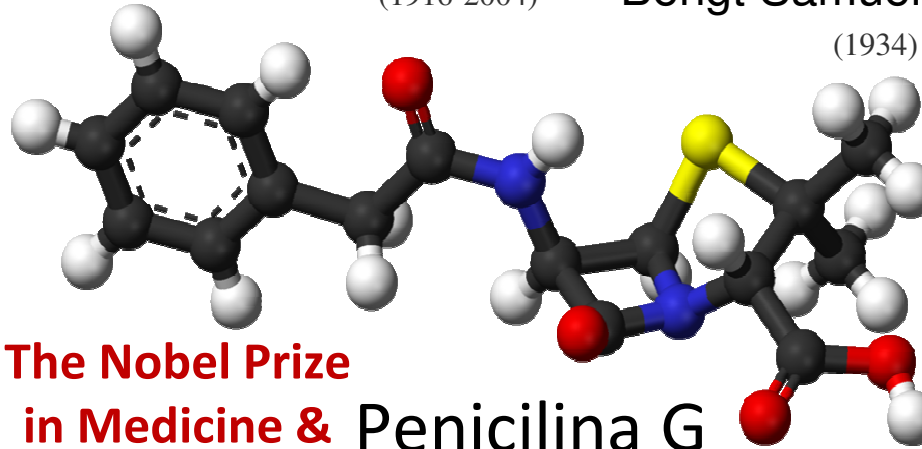
1929



1945



(1881-1955)



(1916-2004)

Bengt Samuelsson (48)

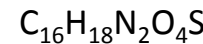
(1934)



1964

The Nobel Prize  
in Medicine &  
Physiology  
1945

Penicilina G



Dorothy C. Hodgkin (54)

(1910-1994)



The Nobel Prize  
in Chemistry  
1964



E. Boris Chain (39)

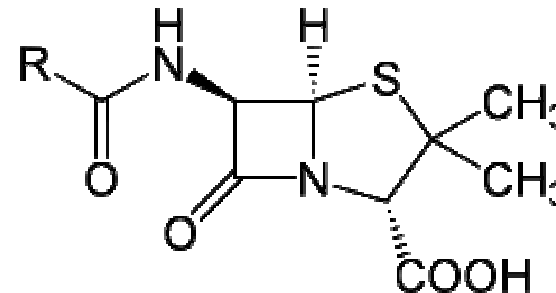
(1906-1979)

Howard W. Florey (47)

(1898-1968)

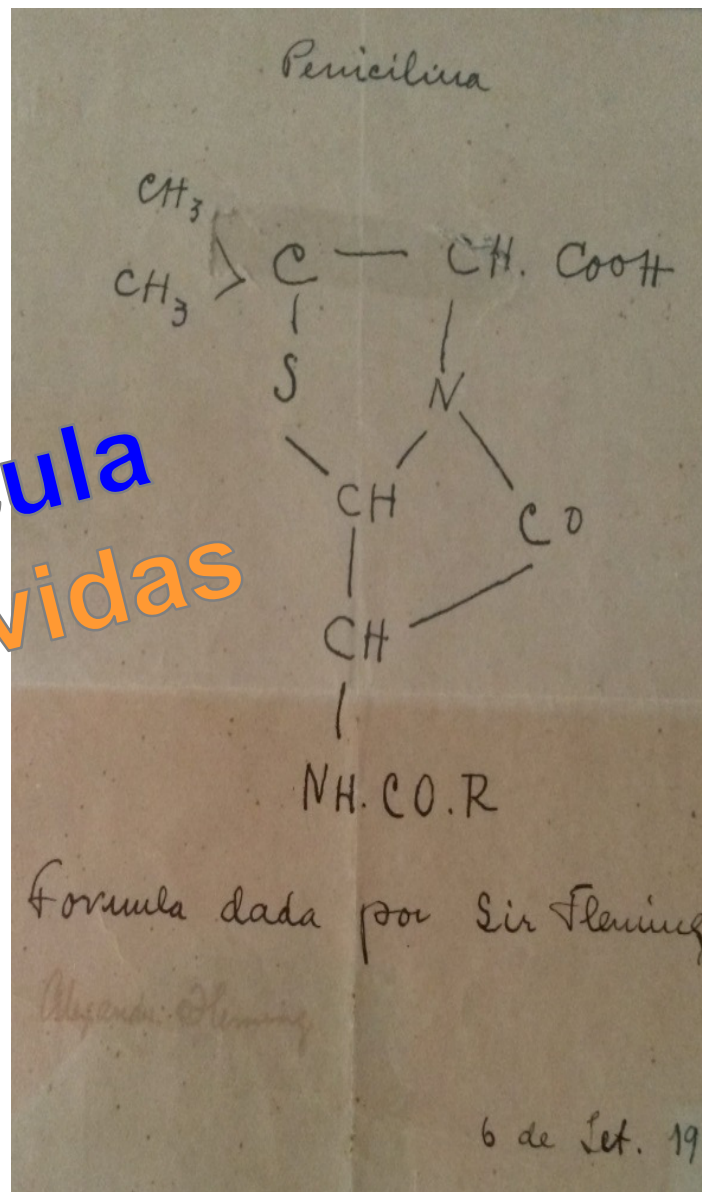
Antibióticos  
 $\beta$ -lactâmicos

Benzetacil





**Molécula**  
**Salva-vidas**

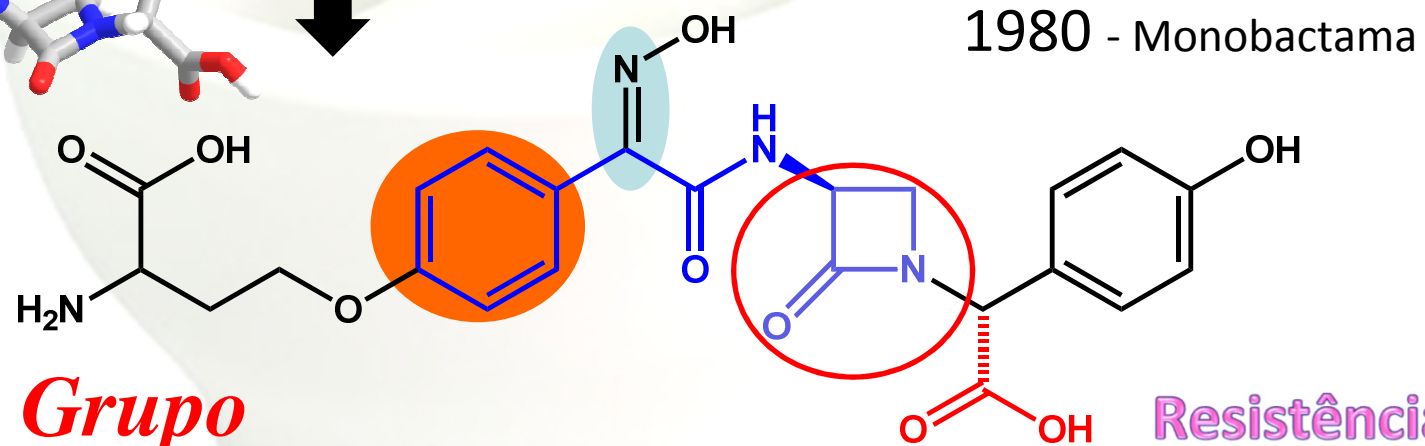
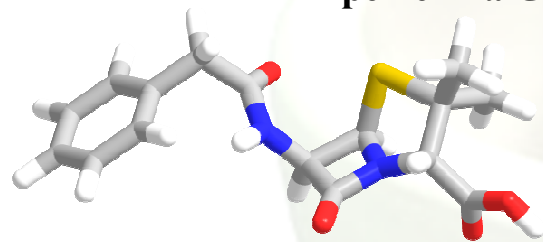
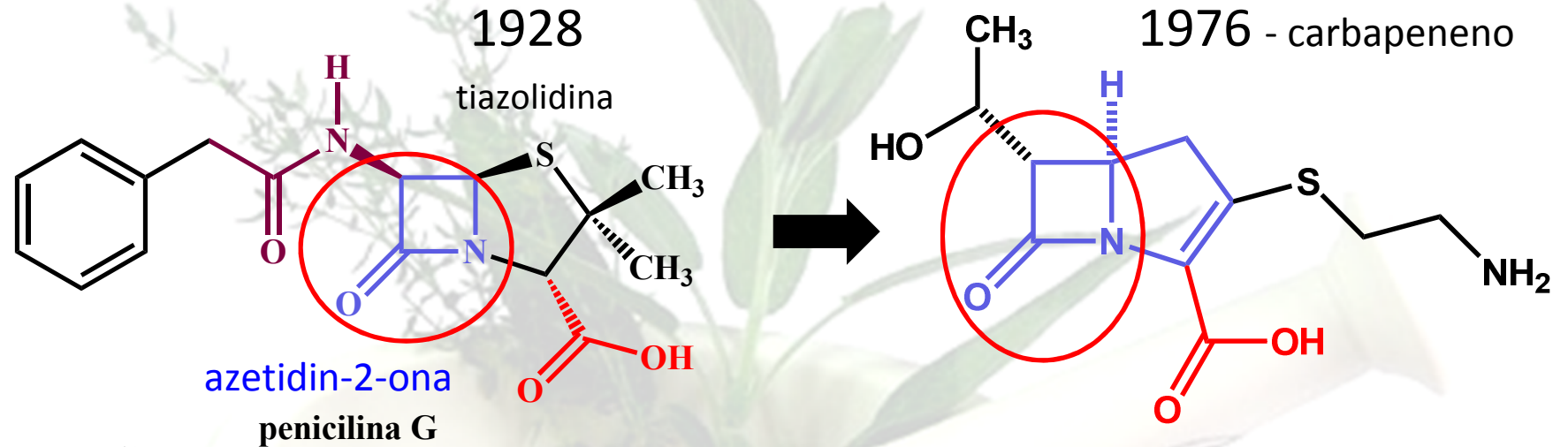


Quadro no escritório de trabalho do Professor E. J. Barreiro na UFRJ

Frame in the office of Professor Barreiro (at UFRJ)



# A evolução dos $\beta$ -lactâmicos...



*Grupo farmacofórico*

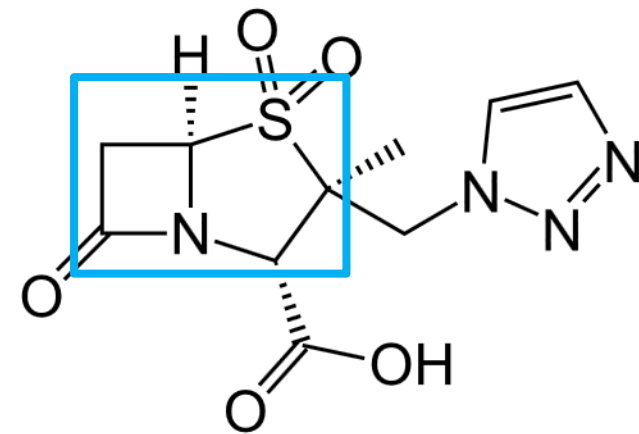
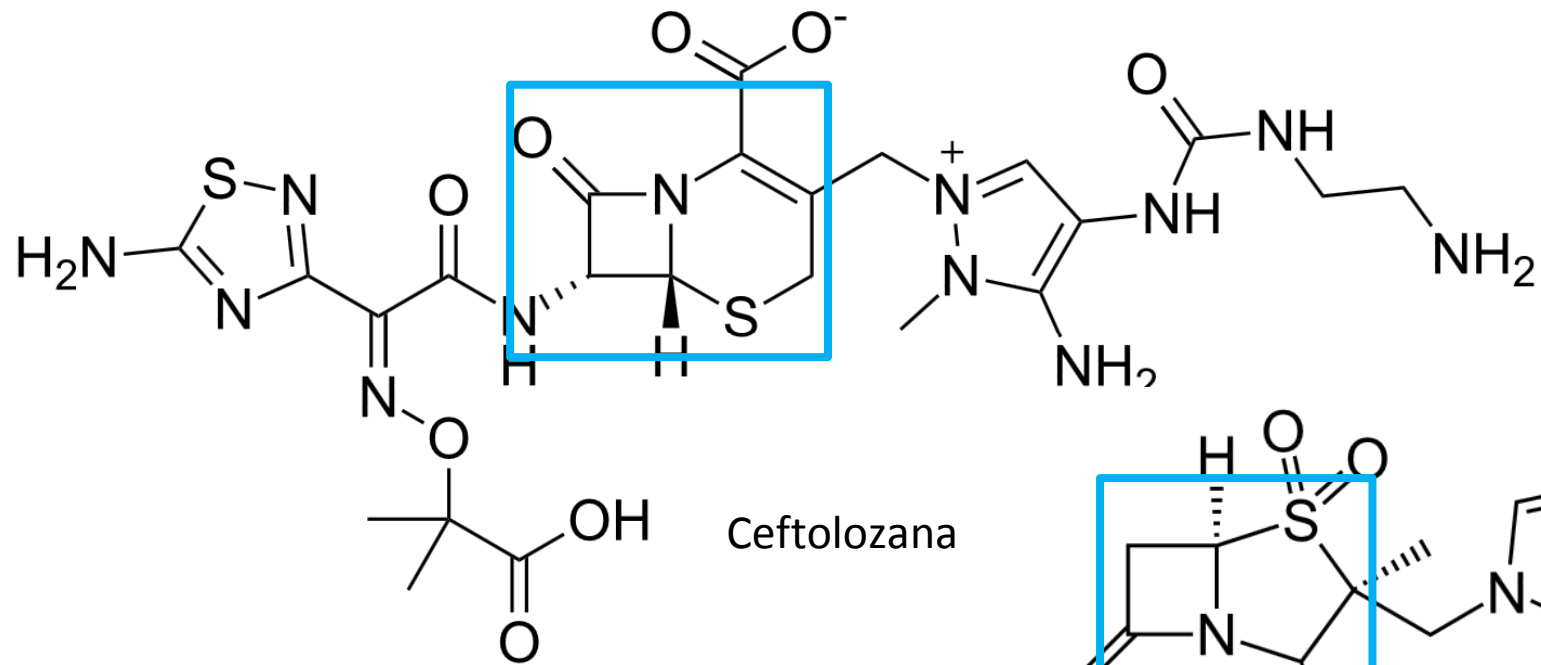
nocardicina  
*Nocardia uniformis*

Resistência  
( $\beta$ -lactamase)





# Antibióticos recientes

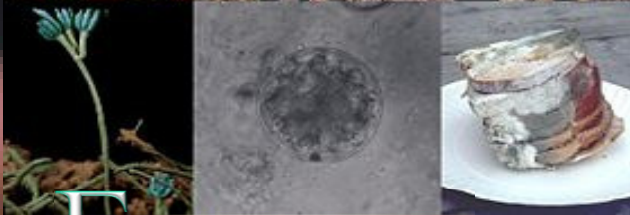
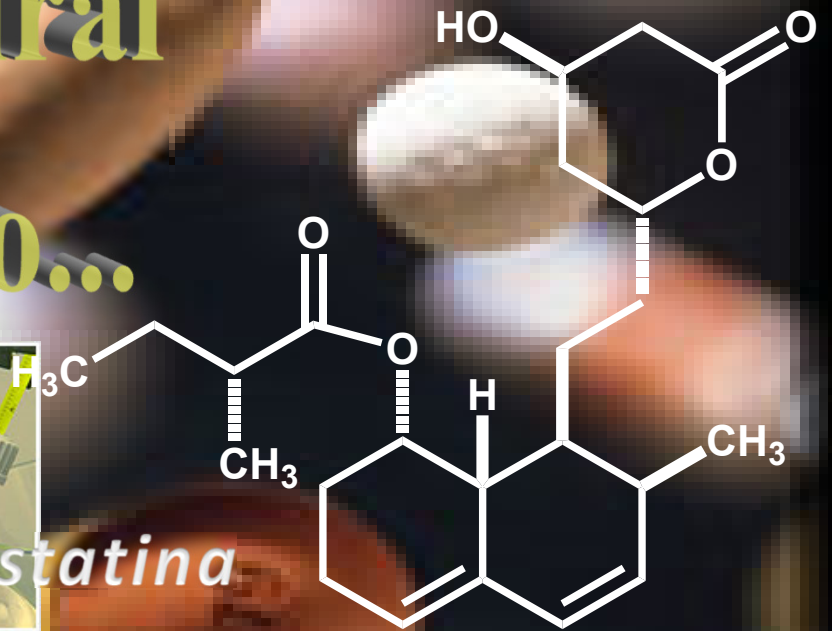


Cefalosporinas  
Penicilinas

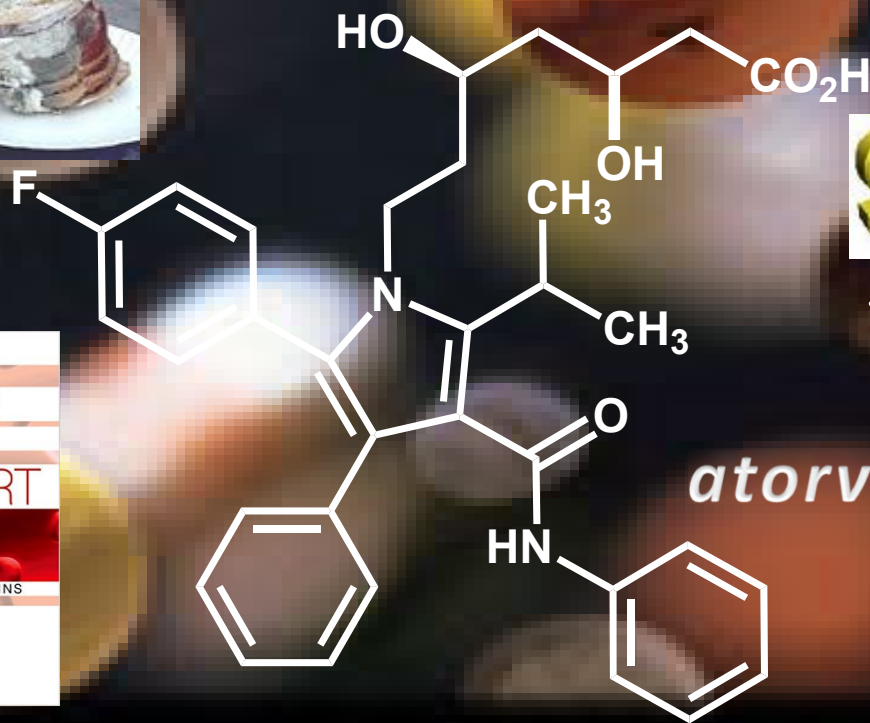




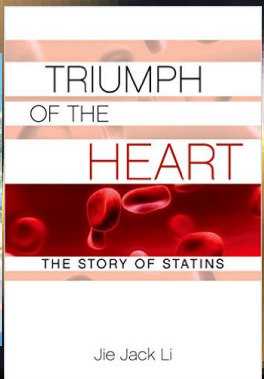
# Do protótipo natural ao Super-fármaco...



Fungos

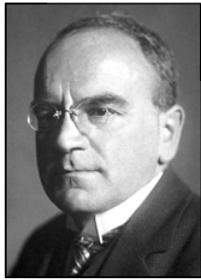


atorvastatina





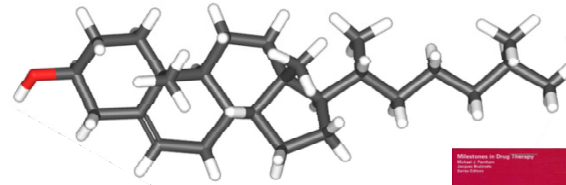
# Estatina\$, inovação bilionária



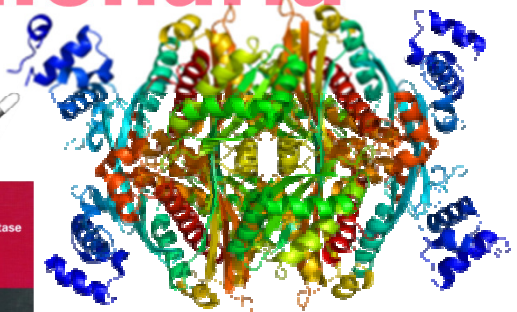
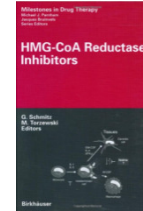
Heinrich Wieland (50)  
(1877-1957)



Adolf Windaus (52)  
(1876-1959)



colesterol



HMGCoAR

1927



1964



Konrad Bloch (53)  
(1912-2000)

1928



Feodor Lynen (54)  
(1911-1979)



John Cornforth (58)  
(1917-2013)

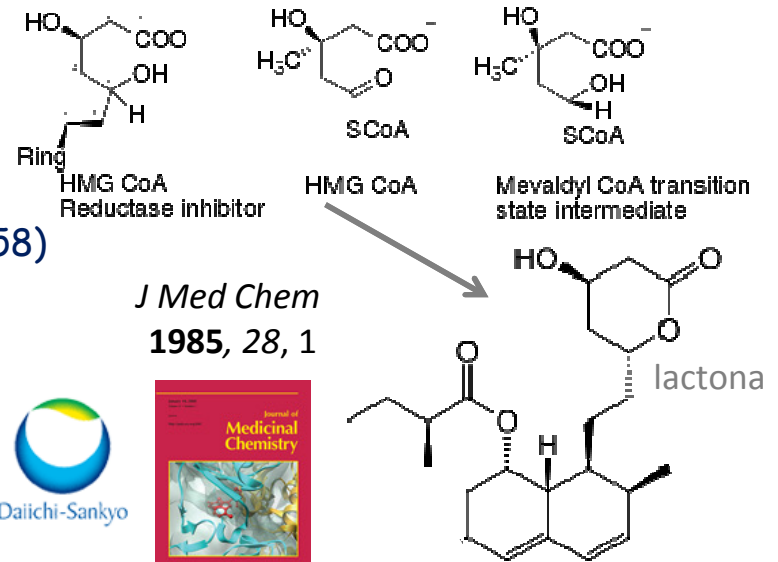
1975



Akira Endo  
(1933)



*J Med Chem*  
1985, 28, 1

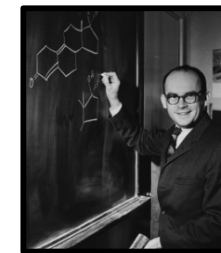


Mevilonina /compactina

1979 Simvastatina

Arthur A Patchet

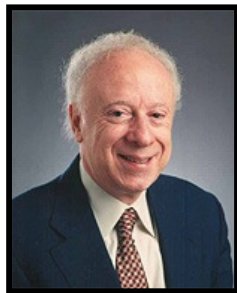
(1929)



New Lead Discovery Department  
Merck Co.

1985

LDL



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

(1940)

(1941)

University of Texas, Dallas



Albert Lasker Award  
for Clinical  
Medical Research, 2008







# Estatina\$, inovação bilionária

**Akira Endo, Sankyo Co**

Lasker Award 2008

1975 – Mevastatina (ML-263b)



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

## Prototipo natural

### Similaridade molecular



A.Endo, *J. Antibiot.*

**1976**, 29, 1346

*Penicillium citrinum*

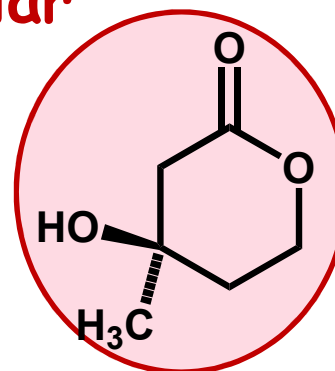
*Idem, Ibid*, **1979**, 32, 852

*Monascus ruber*

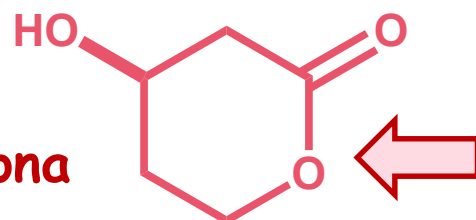
(compactina)

## Mevalolactona

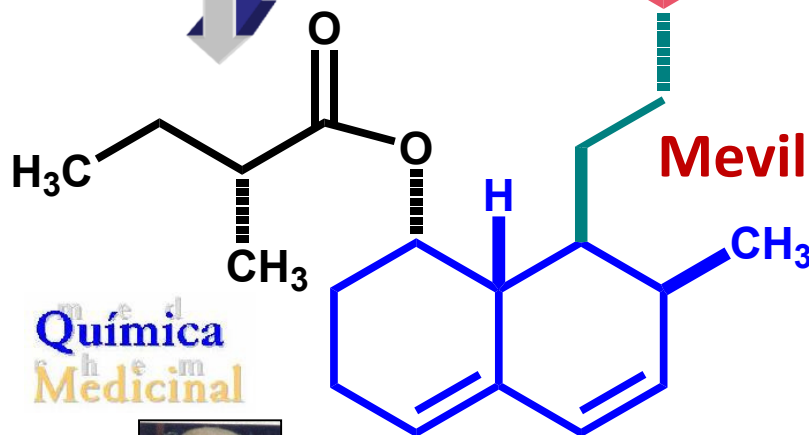
### HMG-CoA redutase



$\gamma$ -lactona



### Mevilonina



Química Medicinal

therapeutic innovation



## Lovastatina (MK-803)

1978 – Merck & Co.

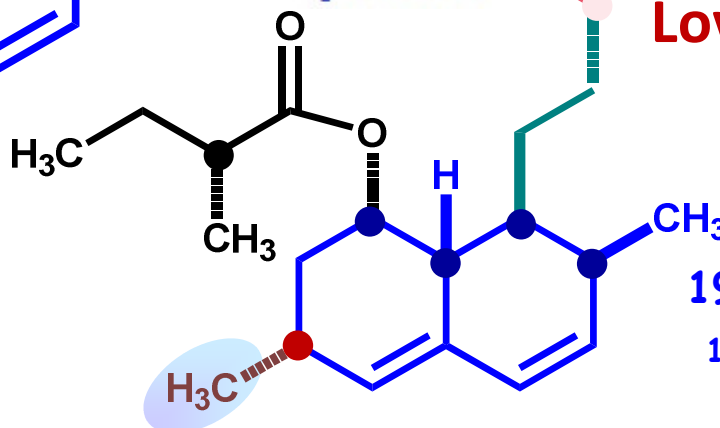
*Aspergillus terreus*



**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

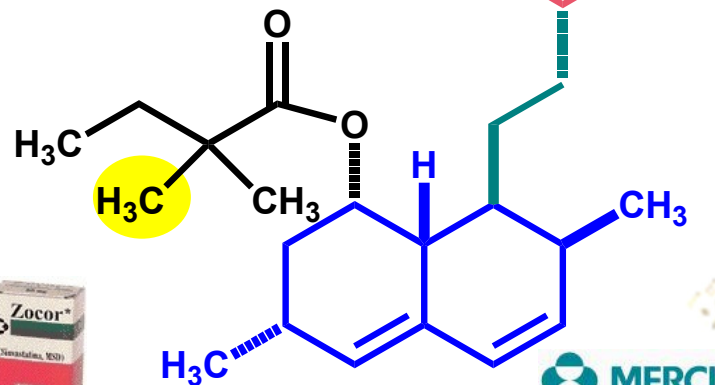
*J Med Chem* **2003**, *45*, 5609

# Estatina\$

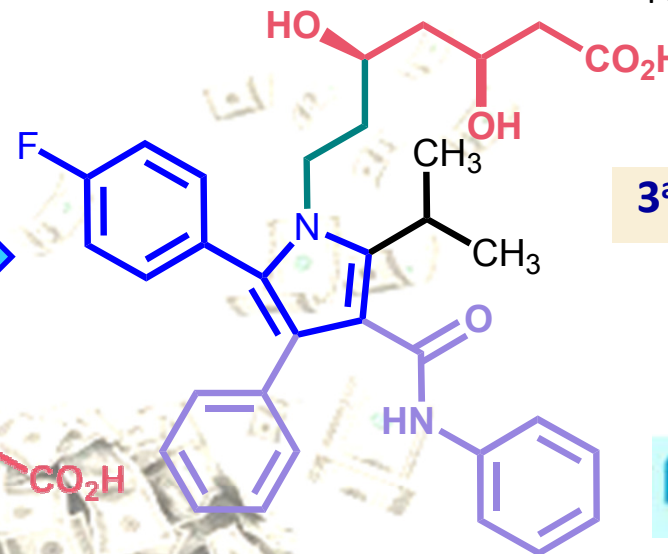
## 5-HMGC<sub>o</sub>ARI



Bruce Roth  
Parke-Davis Co



simvastatina  
1986



atorvastatina  
1991

3<sup>a</sup> geração



"patent cliff"



Química  
med  
Medicinal  
chem



AstraZeneca

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

US\$ 8,7 bi (2014) rosuvastatina  
2004

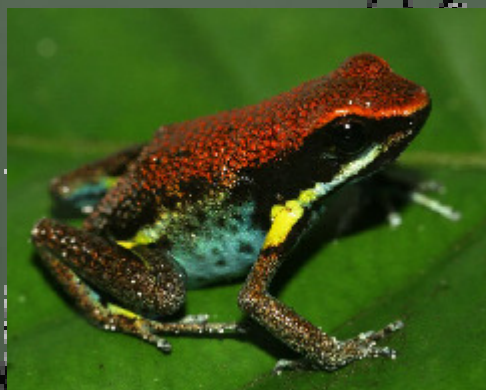


World Top  
selling drug

O mercado mundial de estatinas foi ca. **US\$ 31 bilhões** (2015)



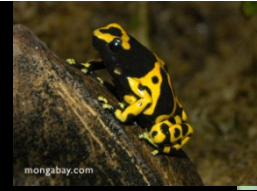
## ◇ Outros PN's



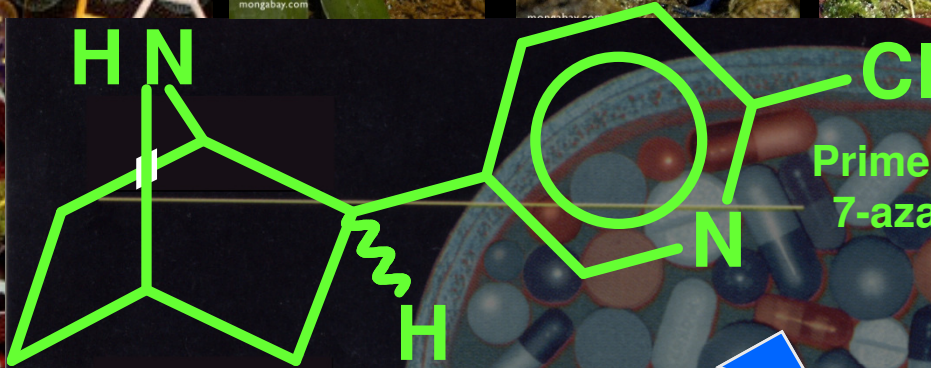
Sapos e outros bichos



protótipo natural



Un. Maryland, EUA



Primeiro quimiotipo natural:  
7-azabicyclo[2.2.1]heptano



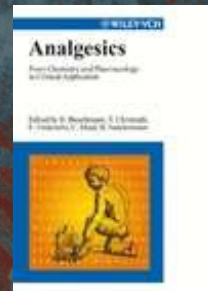
John W Daly

1933-2008

# Epibatidina

analgésico

200-400 vezes mais  
potente  
que a morfina



Editorial, *J Nat Prod* 2010, 73, 300

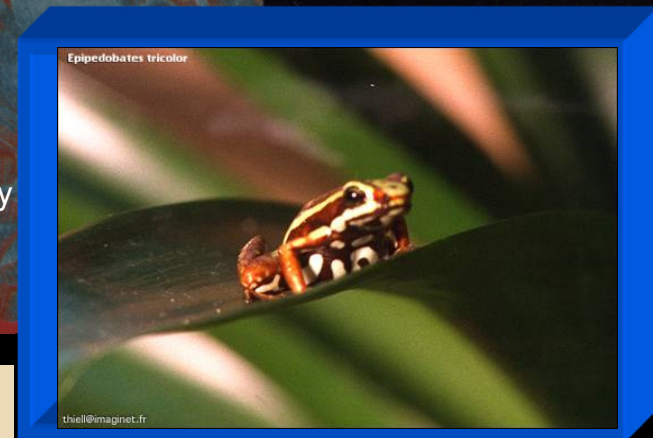
Primeiro alcalóide não-opióide,  
organo-clorado.



J W Daly, "Ernest Guenther Award in Chemistry of Natural Products. Amphibian Skin: A Remarkable Source of Biologically Active Arthropod Alkaloids", *J. Med. Chem.* 2003, 46, 445-452

1992

J W Daly, "Thirty Years of Discovering Arthropod Alkaloids in Amphibian Skin", *J. Nat. Prod.* 1998, 61, 162

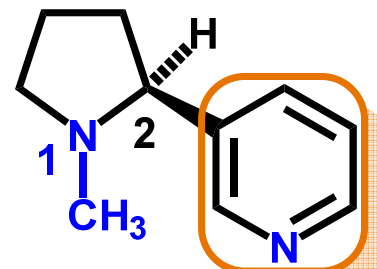
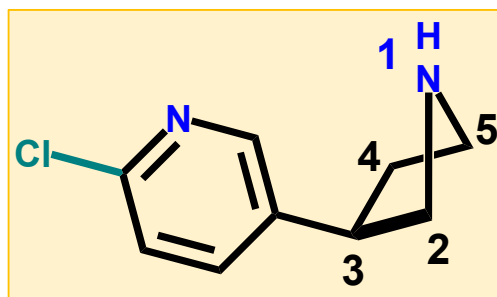
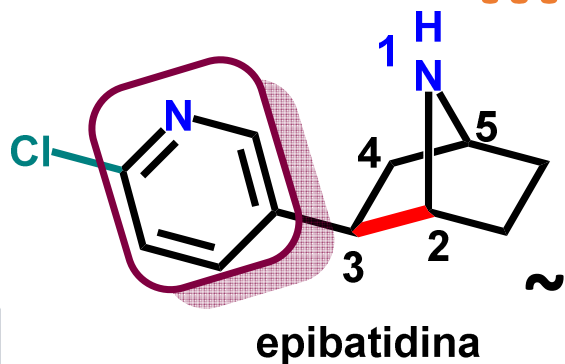


*Epipedobates tricolor*

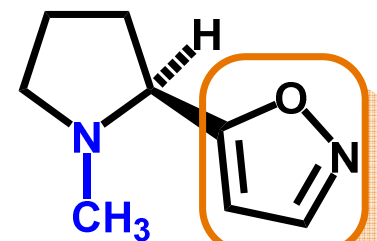
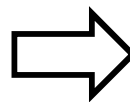


# Domesticando produtos naturais

## Similaridade Molecular

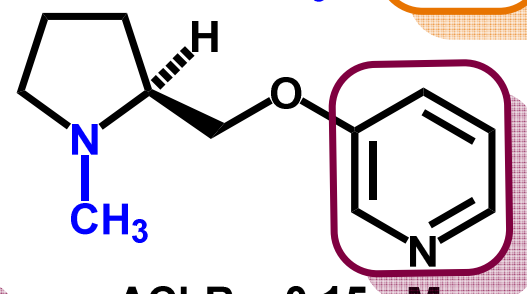
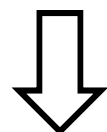


nicotina

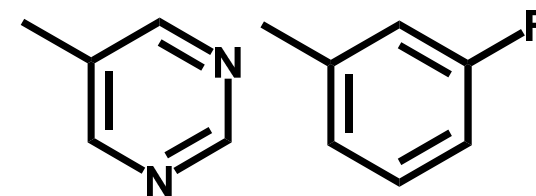
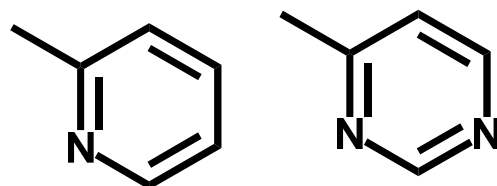
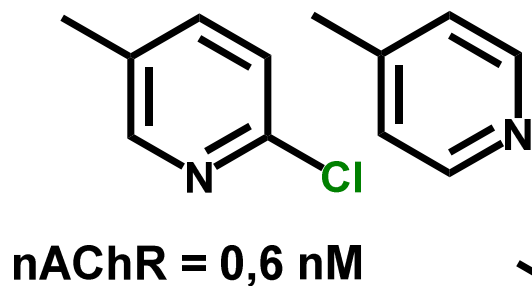


CH<sub>3</sub>

abbvie

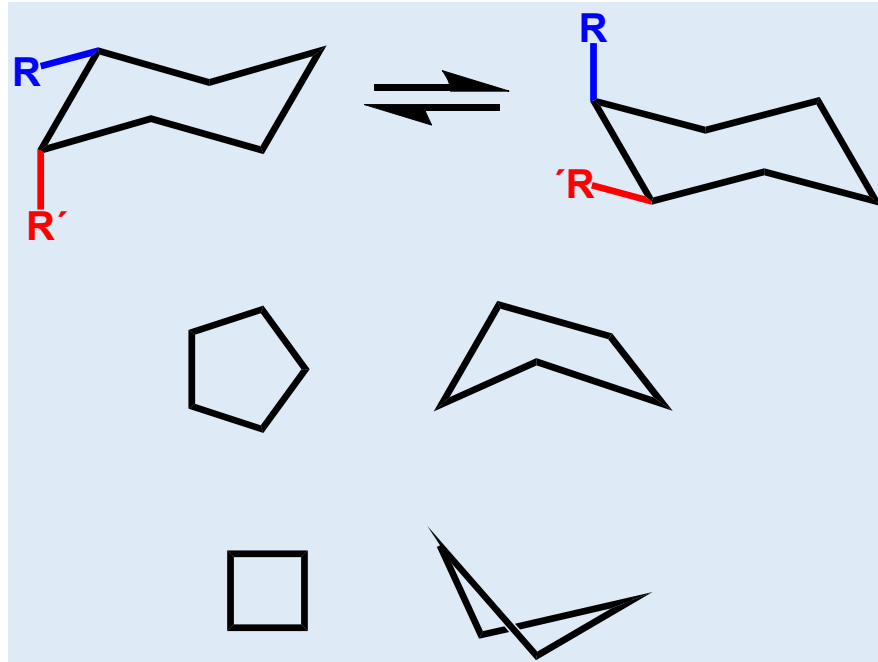


nAChR = 0,15 nM

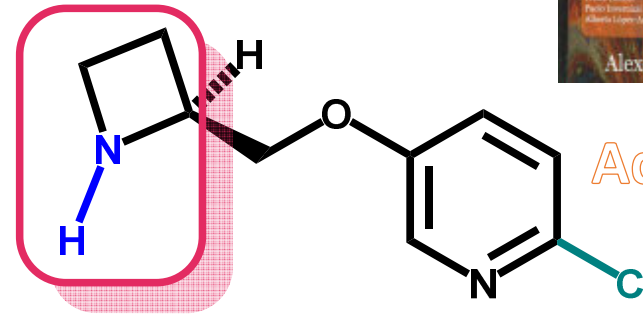




# Domesticando produtos naturais

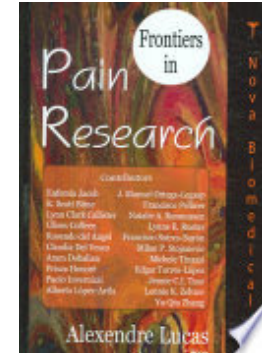


azetidina



Ebaniclina

Tebaniclina



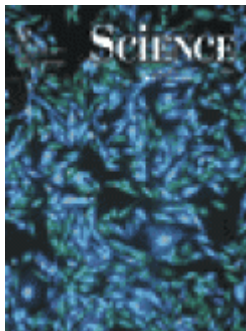
Addictive



nAChR = 0,04 nM

ABT-594

[α4β2 subtypes](#)



AW Bannon, MW Decker, MW Holladay, P Curzon, D Donnelly-Roberts, RD Porsolt, M Williams, SP Arneric, Broad-Spectrum, Non-Opioid Analgesic Activity by Selective Modulation of Neuronal Nicotinic Acetylcholine Receptors, *Science* **1998**, 279, 77.



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



F I M