



Universidade Federal do Rio de Janeiro

# *Estratégias de desenho molecular*

## *da Química Medicinal*

### *A abordagem fisiológica – Parte 2*

IX Semana de Química / DQ-UFSCar



***Eliezer J. Barreiro***

**Professor Titular**

**Universidade Federal do Rio de Janeiro**



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

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

**Instituto Nacional de Ciência e Tecnologia de Fármacos e Medicamentos  
(INCT-INOVAR)**



1. Definição & histórico da Química Medicinal: os pioneiros e as moléculas pioneiras;

---

2. Os fármacos e seus biorreceptores: o paradigma de Fischer-Ehrlich;

---

3. **A origem dos fármacos: *domesticando* e se inspirando nos produtos naturais;**

---

4. A fascinante criatividade da natureza & as moléculas “*impossíveis*” que viraram fármacos;

---

5. Do *bolor* às moléculas salva-vidas ou bilionárias;

---

6. A era dos fármacos sintéticos racionalmente planejados;

---

7. Considerações finais

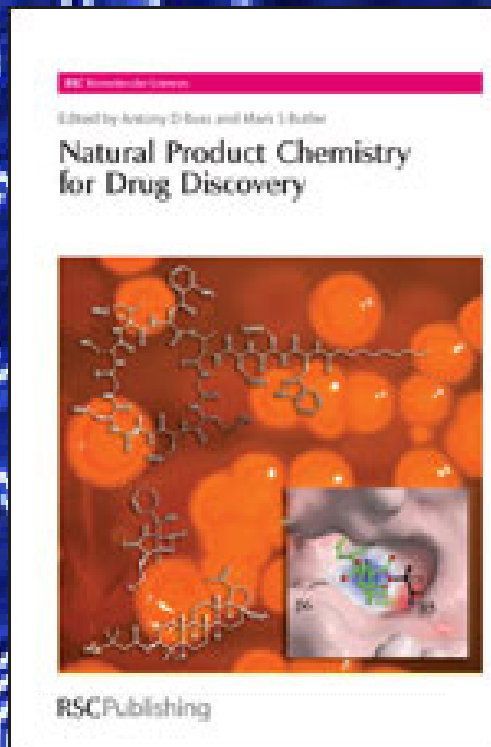


Universidade Federal do Rio de Janeiro

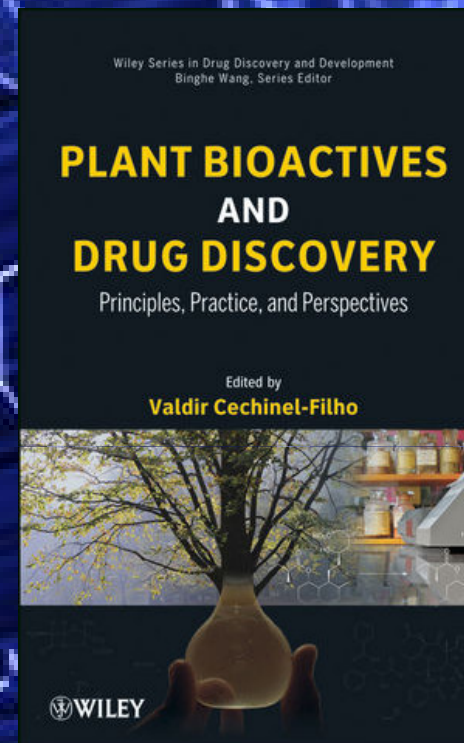
# Os produtos naturais e os fármacos

## *natural product-derived drugs*

**SK Wrigley, MA Hayes,  
R Thomas, EJT Chrystal  
& N Nicholson (Eds)**



**A D Buss & MS Butler  
(Eds)**

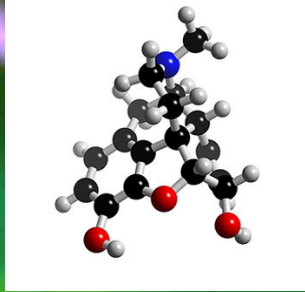


**V Cechinel-Filho (Editor)**

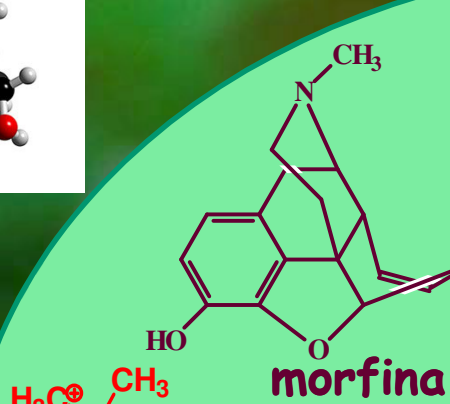


Universidade Federal do Rio de Janeiro

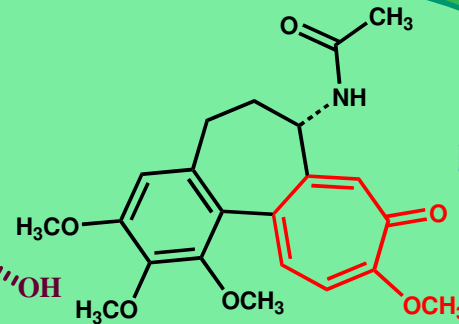
# Quimiodiversidade



Lantana - Lantana camara



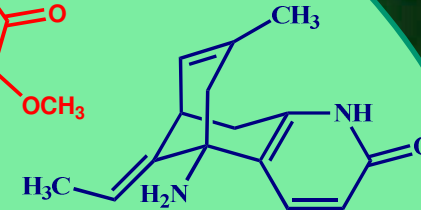
1806



1820

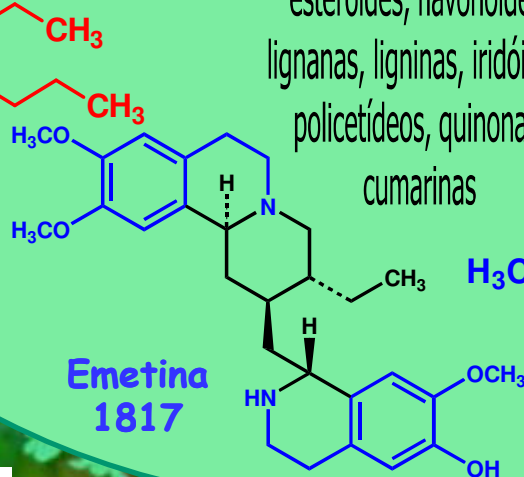
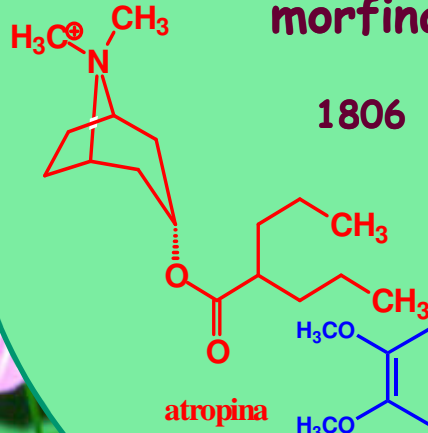
terpenos, alcalóides,  
esteróides, flavonóides,  
lignanas, ligninas, iridóides,  
policetídeos, quinonas,  
cumarinas

**huperzina-A**

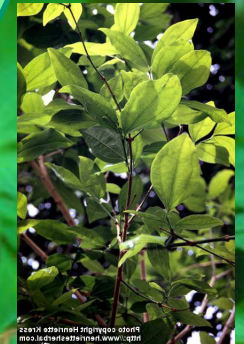
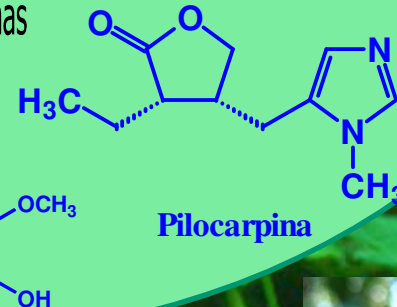


**Estriquinina**

1817



1817



22/01/2018 09:00:00 AM  
www.igmp.br





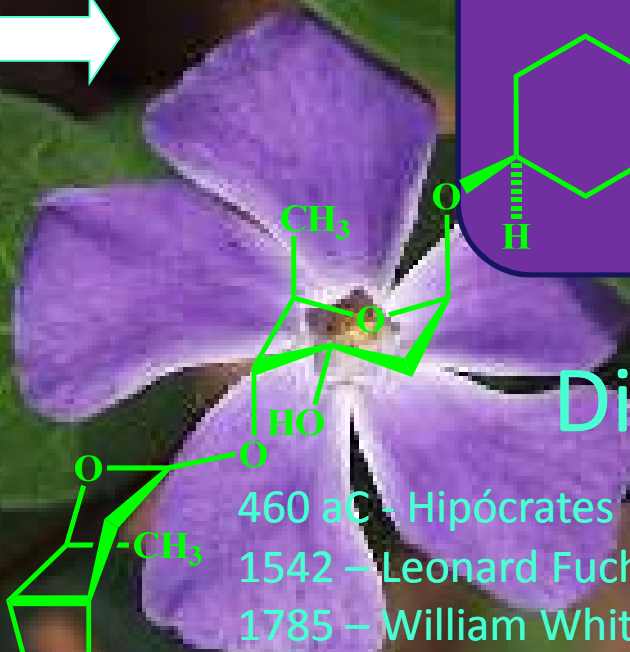
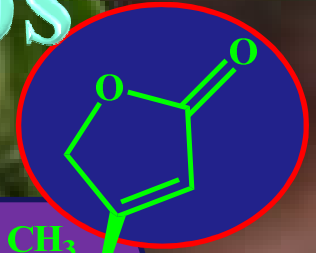
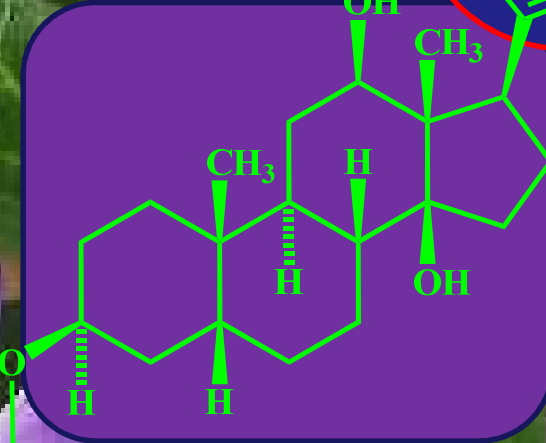
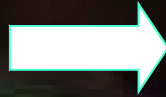
# Glicosídeos cardiotônicos

*Ebers Papyrus*

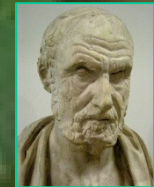
*bufanolidos cardenolidos*



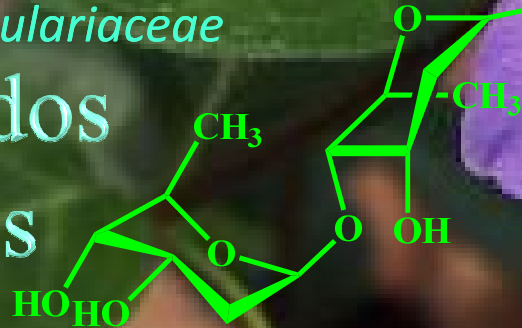
*Digitalis purpurea*  
*Digitalis lanata*  
Scrophulariaceae



## Digoxina



## O decano dos fármacos



- 460 aC - Hipócrates
- 1542 - Leonard Fuchs *Digitalis purpurea*
- 1785 - William Whitering, UK
- 1875 - Johann Schmiedeberg isola DGX
- 1928 - Sydney Smith, Burroughs Wellcome
- 1930 - Adolf Windaus, Un Göttingen (estrut)
- 1965 - JC Skou Na<sup>+</sup>/K<sup>+</sup>-ATPase
- 2008 - Zhang : inibe o fator de hipoxia
- 2011 - Huh descreve efeitos na IL-1

*Insuficiência cardíaca congestiva;*  
*Arritmias cardíacas;*



Universidade Federal do Rio de Janeiro

# Produtos Naturais Vegetais: Alcalóides

Alcalóides fenantrênicos e benzilisoquinolínicos (papaverina 0,2%)  
*Papaver somniferum*



1493-1541 - Marco Polo (Veneza) ⇒ Ópio

1805 (1820) ⇒ Friedrich W A Sertürner

farmacêutico alemão, isola a morfina

1853 – Henry How, Un Glasgow ⇒ sal 4<sup>ario</sup>

1874 – Wright obtém a heroína (UK)

1925 – Sir Robert Robinson



(1947)

1952 – M D Gates primeira síntese total

1954 - Beckett & Casey, Un. London

1972 – C Pert & S Snyder, Un John

Hopkins ⇒ receptores δ, κ, μ SNC

1975 - Kosterlitz & Hughes; endorfinas

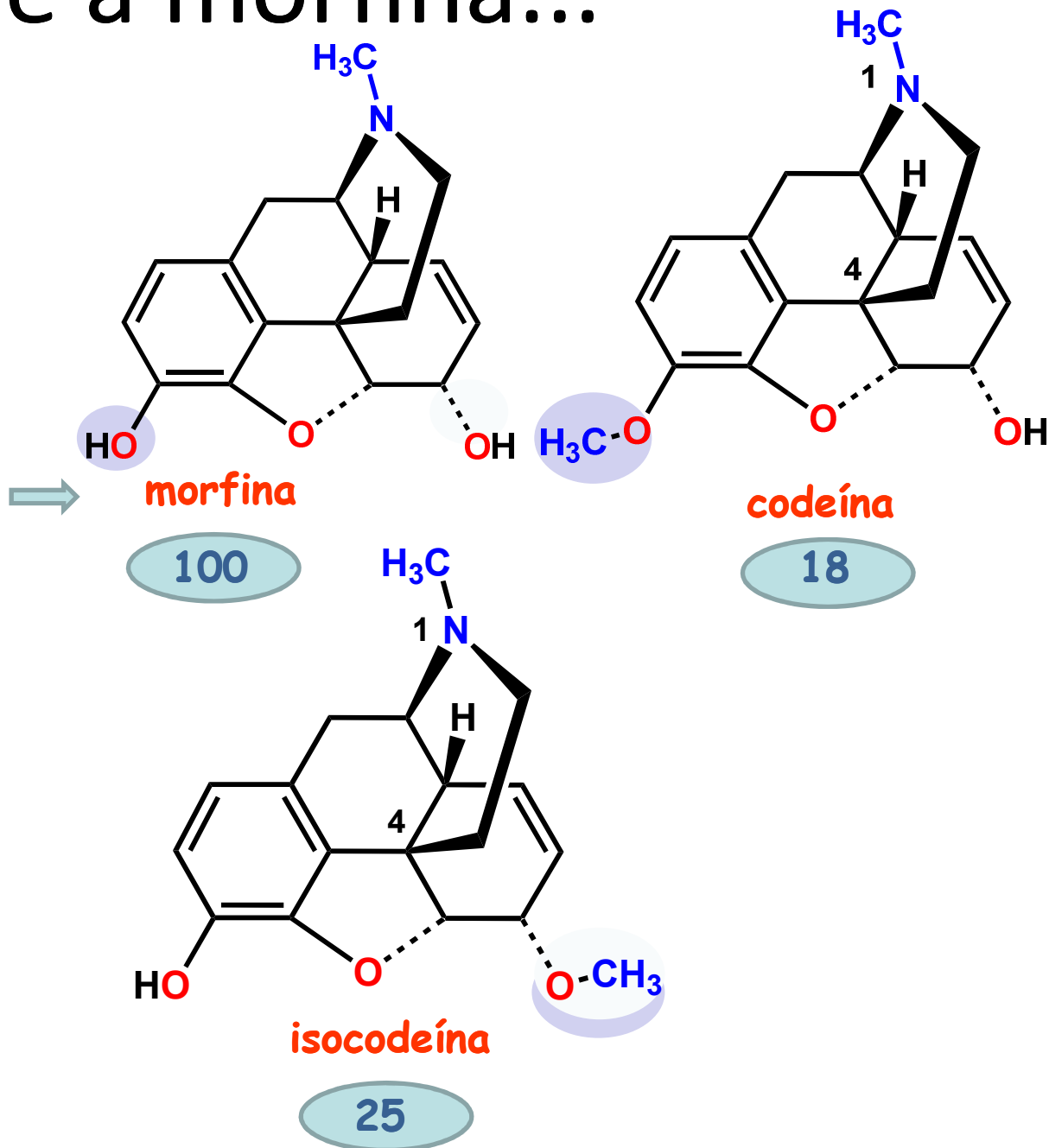


tolerância & dependência química;



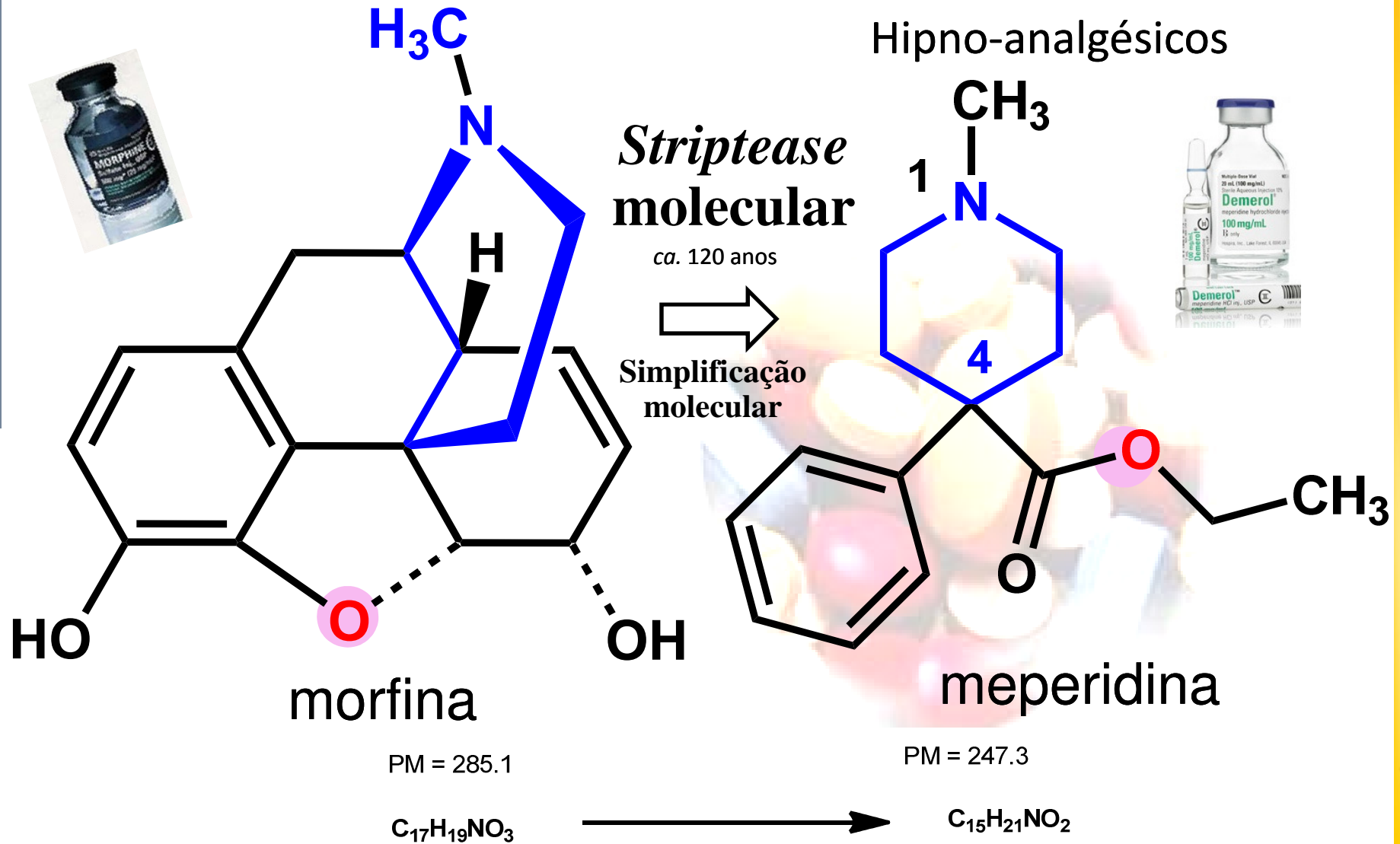
# A metila e a morfina...

Índice de atividade analgésica





# Derivados 4-fenilpiperidínicos



***Domesticando produtos naturais***





1. Definição & histórico da Química Medicinal: os pioneiros e as moléculas pioneiras;

---

2. Os fármacos e seus biorreceptores: o paradigma de Fischer-Ehrlich;

---

3. A origem dos fármacos: *domesticando* e se inspirando nos produtos naturais;

---

4. **A fascinante criatividade da natureza & as moléculas “*impossíveis*” que viraram fármacos;**

---

5. Do *bolor* às moléculas salva-vidas ou bilionárias;

---

6. A era dos fármacos sintéticos racionalmente planejados;

---

7. Considerações finais



Universidade Federal do Rio de Janeiro

# Mais sobre plantas & analgésicos...

1839 – *Spirea sp*

1853 – Charles Gerhardt AAS

1876 – salicina → AS

1897 – Arthur Eichengrün,

Heinrich Dreser,

Felix Hoffmann

1899 – AAS lançado Bayer

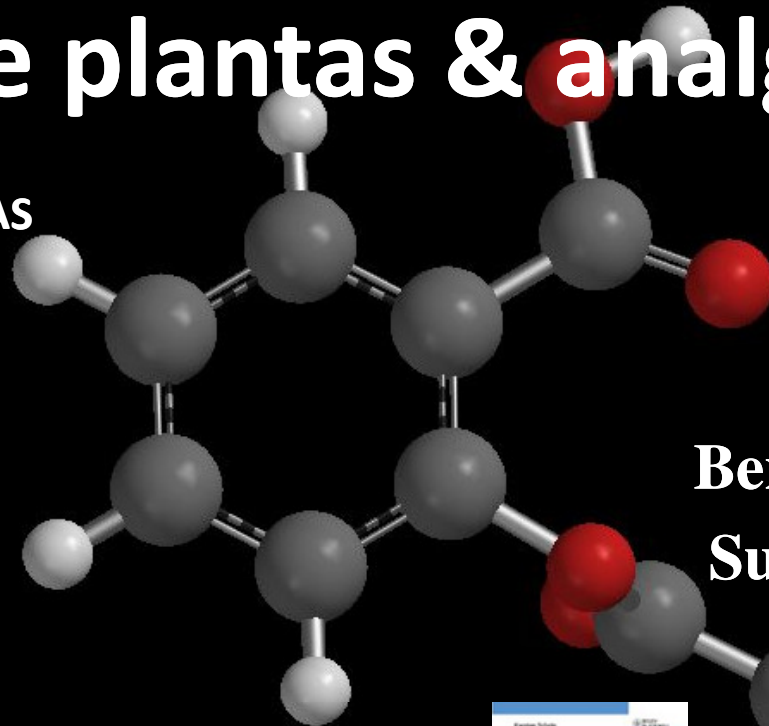
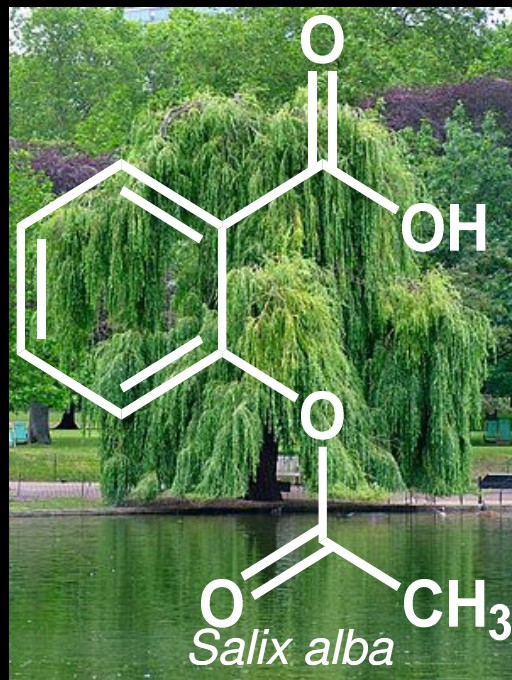


1982

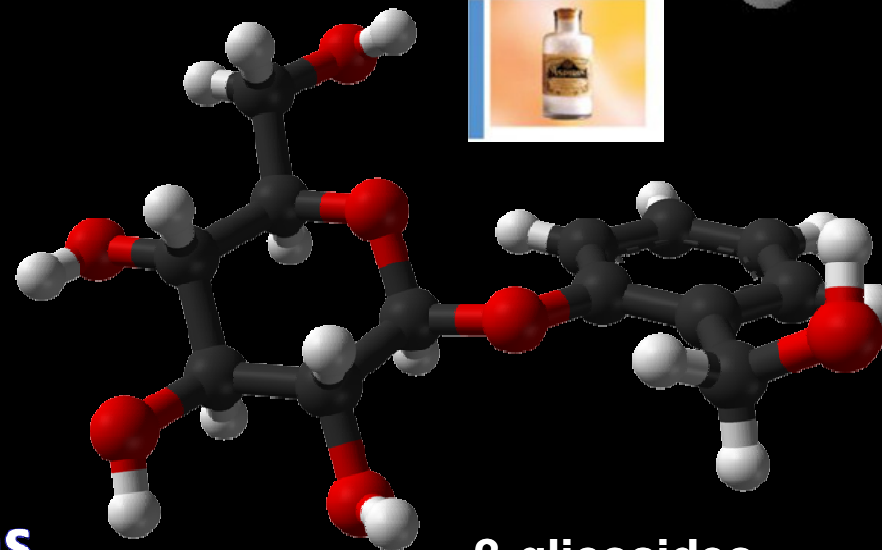
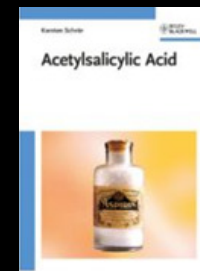
Bengt I. Samuelsson

Sune K. Bergström

John R. Vane



AAS



$\beta$ -glicosideo



Teoria das Assinaturas




1860 1880 1900 1920 1940 1960 1980 2000

Categories

 World headlines

 Aspirin's scientific contribution

 Facts about Aspirin

 Old Aspirin Print Ads  
[click here](#)

*Aspirin History*

**In 1897, Felix Hoffmann, a German chemist employed by Bayer and Company, was searching for a treatment for his father's arthritic pain and began to research acetylsalicylic acid, which worked well for arthritis pain.**

next 

[www.aspirin.com](http://www.aspirin.com)

 Visit your country site 



SEARCH ASPIRIN.COM



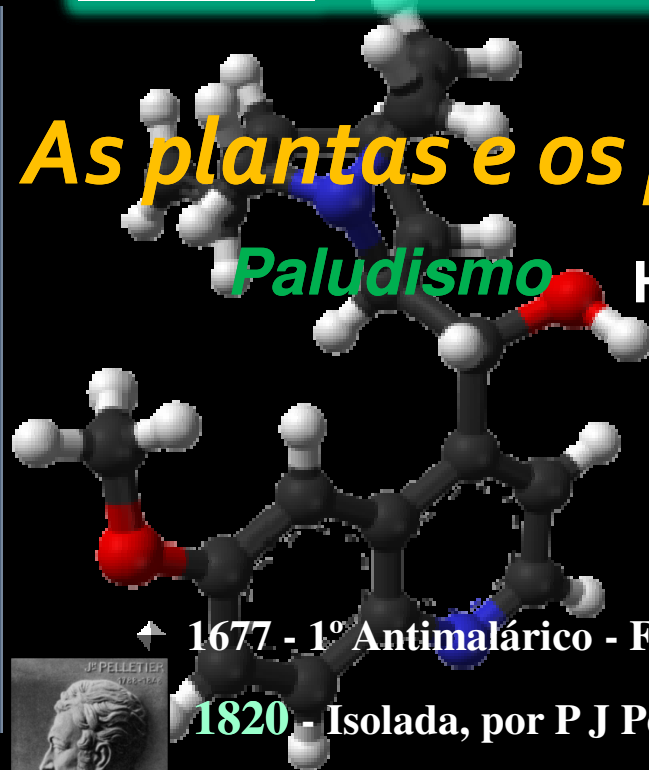


Universidade Federal do Rio de Janeiro

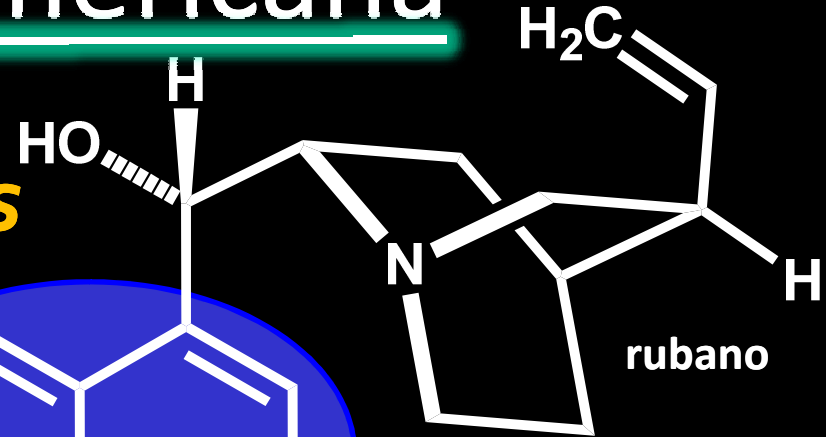
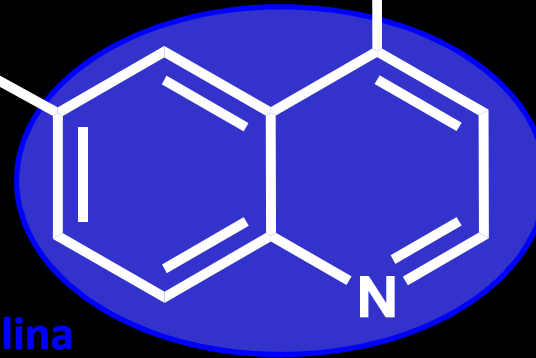
# Molécula latino-americana

## As plantas e os parasitas

### Paludismo



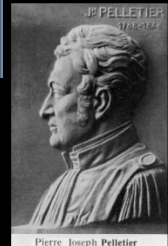
quinolina



rubano

## quinina

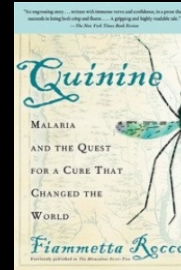
### Quinquina



1677 - 1º Antimalárico - Farmacopéia Britânica

1820 - Isolada, por P J Pelletier & J B Caventou

École de Pharmacie de Paris



1918 - Estrutura elucidada (P Rabe, AL)

1944 - síntese RB Woodward & WE Doering

RB Woodward & W Doering,  
*J Am Chem Soc* 1944, 66, 849

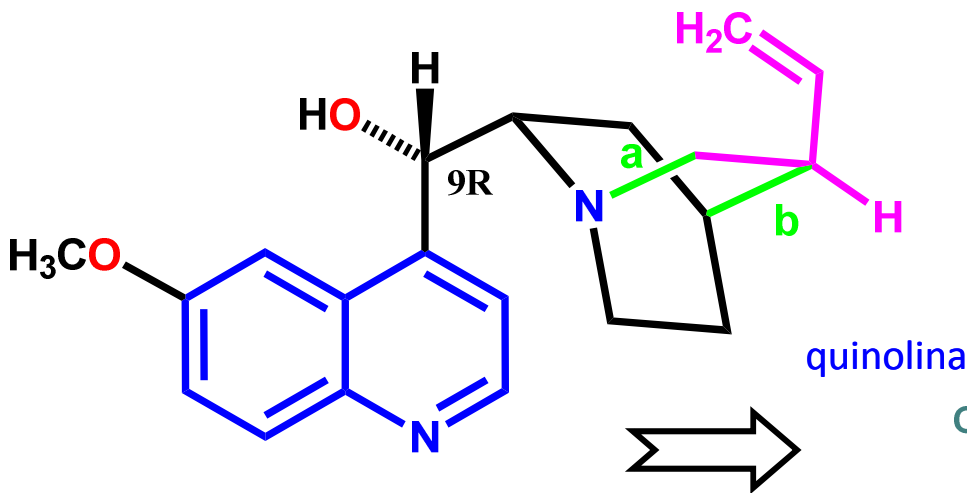


1944



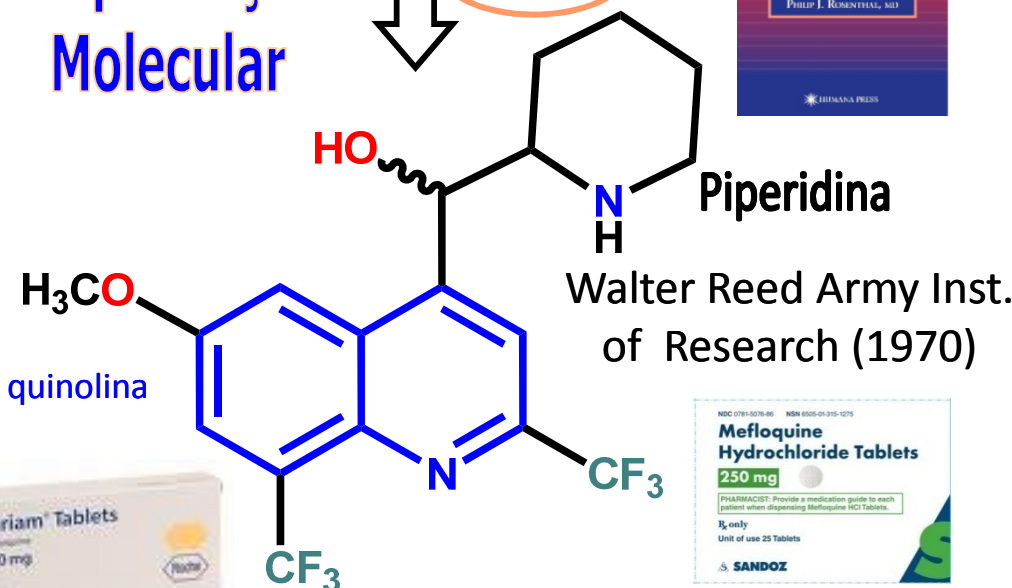
*Cinchona officinalis*

2001 - G Stork, síntese estereosseletiva



Quinina

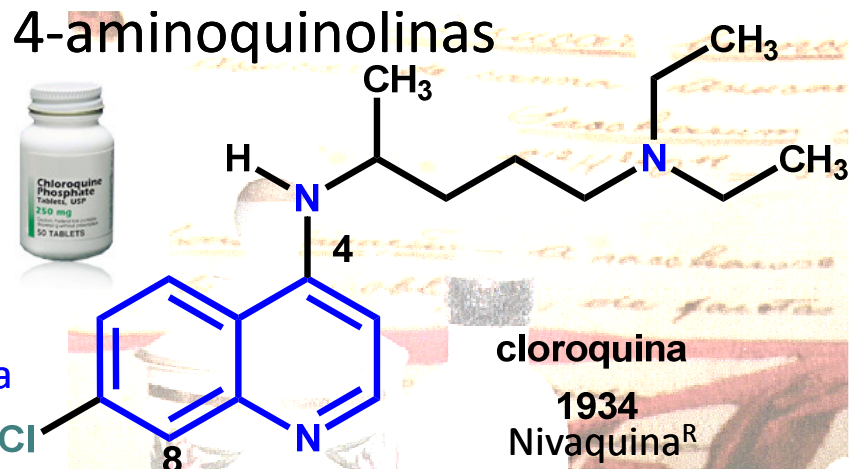
Simplificação Molecular



T<sub>1/2</sub> = 16d

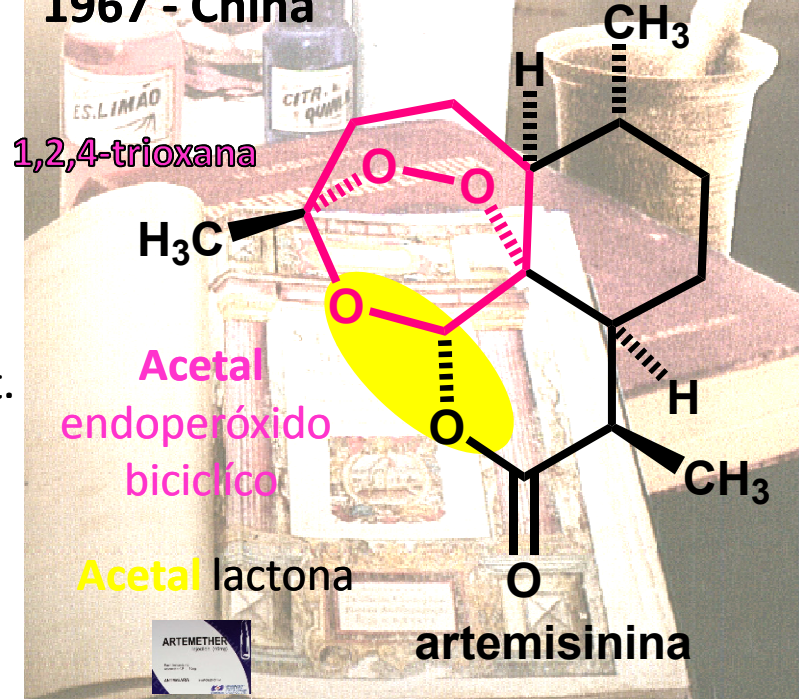
Mefloquina

1989 - FDA



De volta ao Oriente...

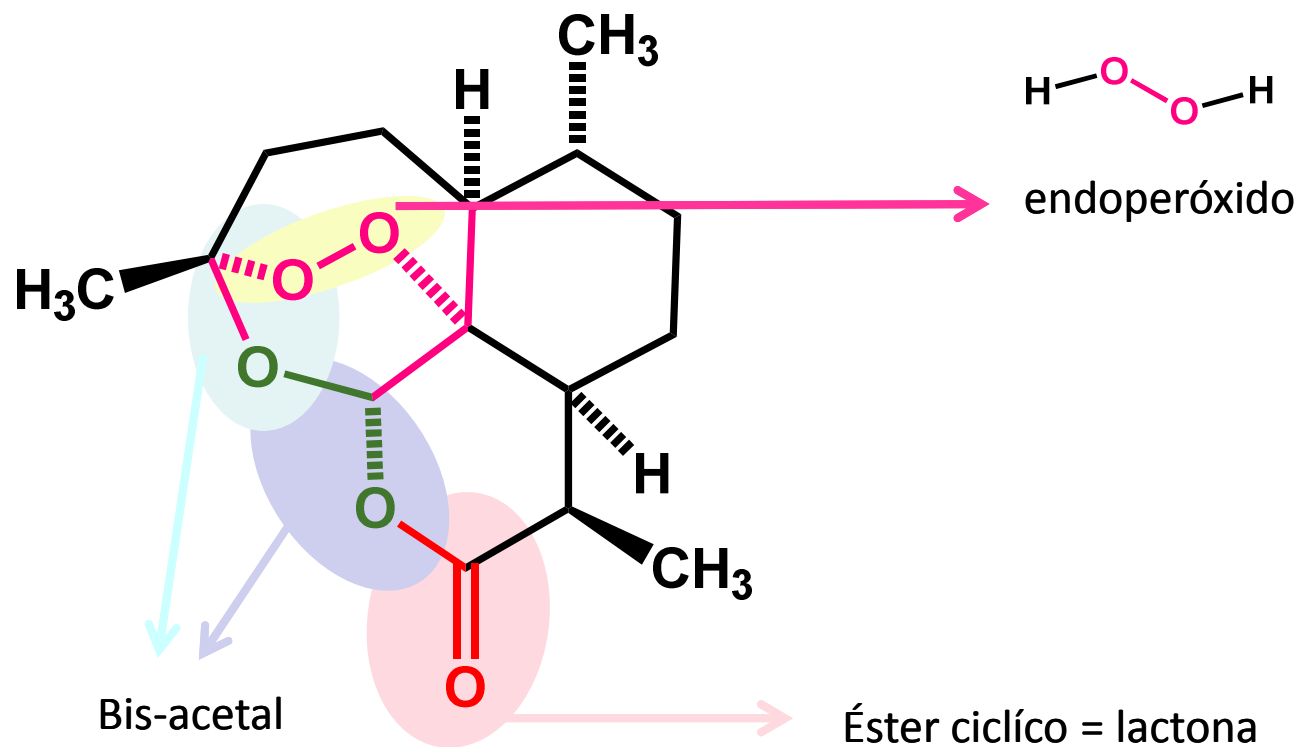
1967 - China



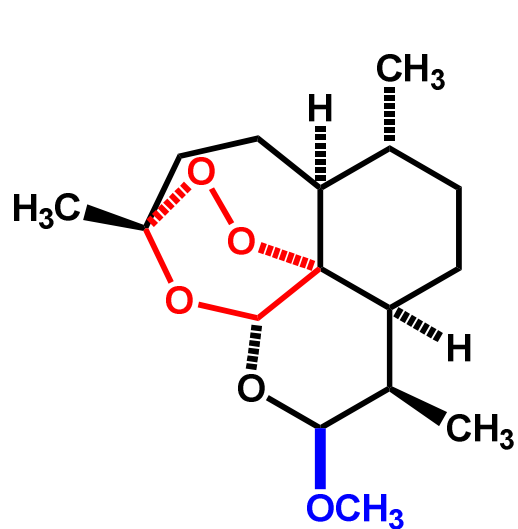
sesquiterpeno C<sub>15</sub>H<sub>22</sub>O<sub>5</sub>



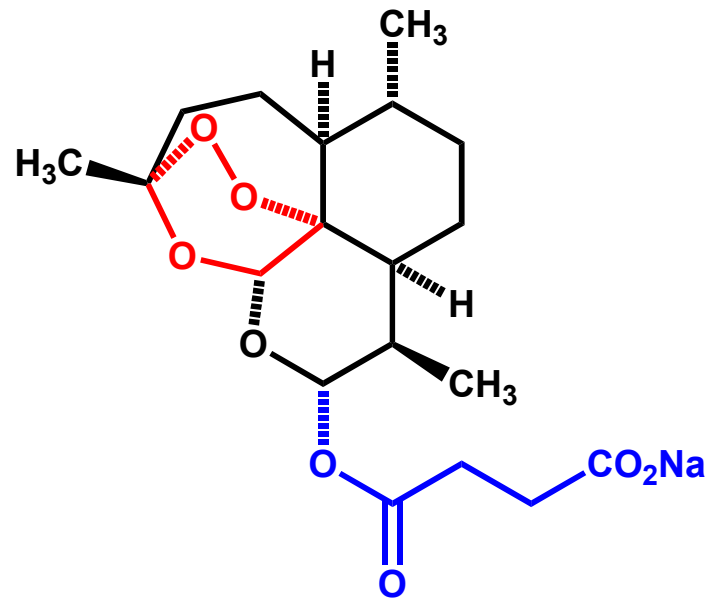
# A impressionante criatividade da mãe natureza



Sem o modelo da natureza o homem, certamente,  
nunca teria *inventado* tal padrão molecular!



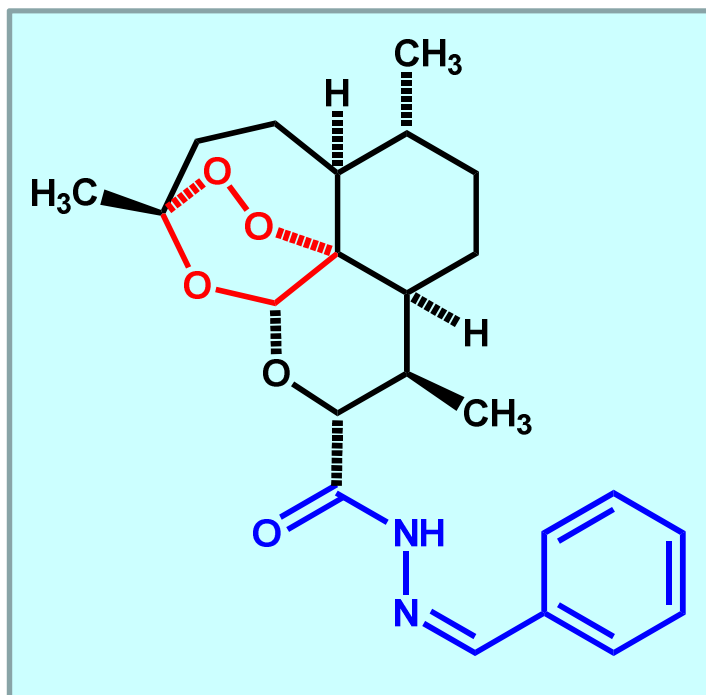
arteméter



artesanato de sódio



M A Avery, Olemiss

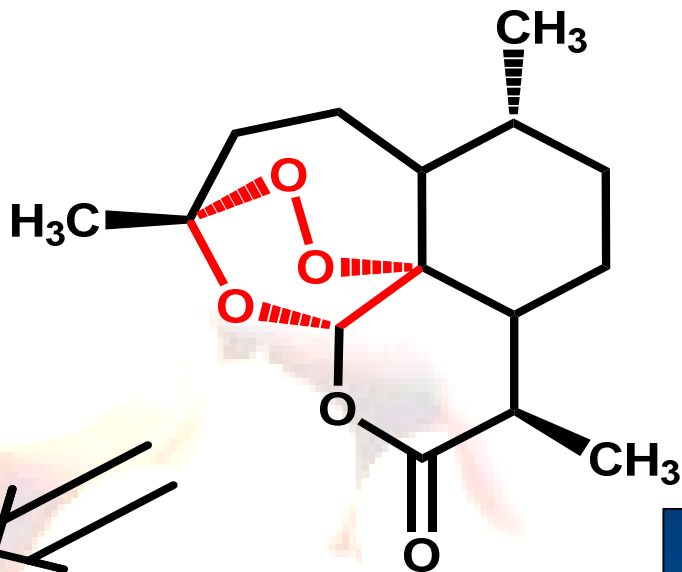


Mitchell A Avery, EJ Barreiro  
Maria Alvim-Gaston\*, 2001

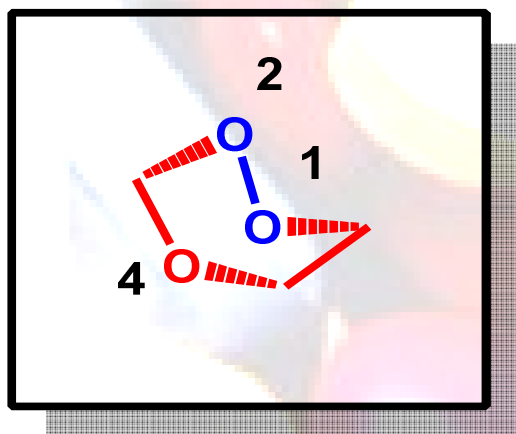
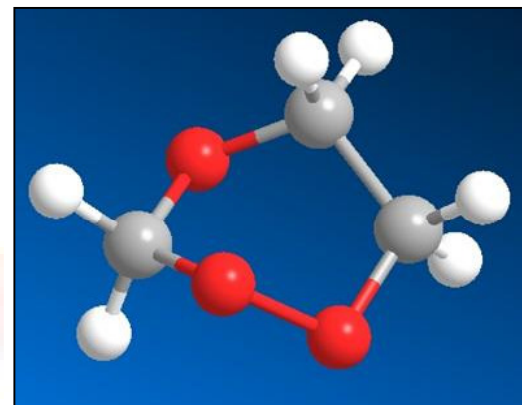
\* Atual Senior Research Scientist  
Eli Lilly Co., EUA



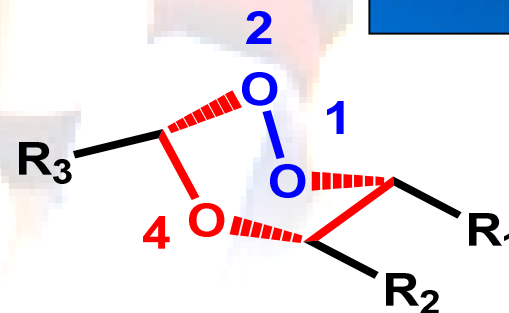
# Simplificação molecular



artemisina



1,2,4-trioxana



derivados 1,2,4-trioxana



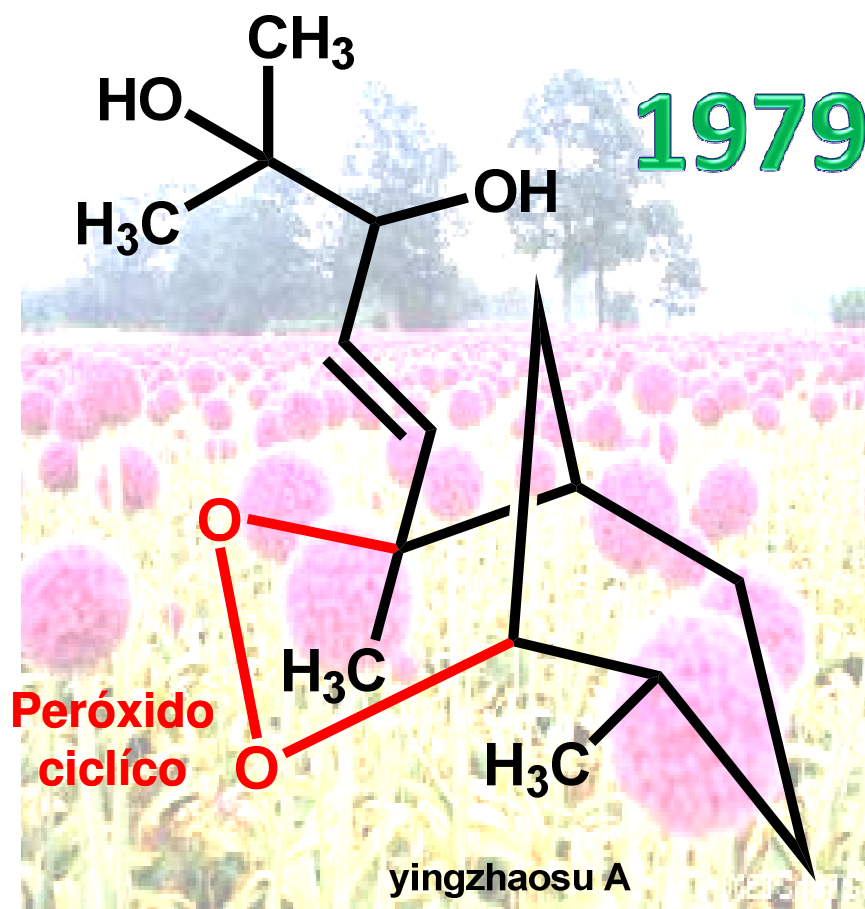
Gary H. Posner  
Un John Hopkins

RD Slack, AM Jacobine, GH Posner, "Antimalarial Peroxides: Advances in Drug Discovery and Design," *Med. Chem. Commun.*, **2012**, 3, 281-297

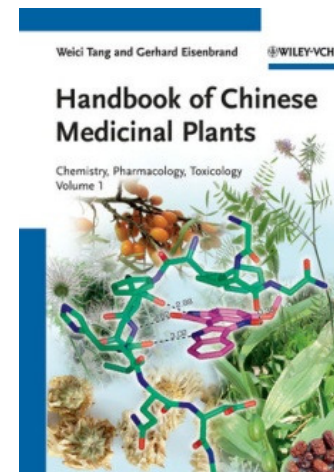




# Produtos naturais e malária



*Artabotrys unciatus* (L.) Meer.



XT Liang, DQ Yu, WL Wu, HC Deng, *Acta Chimica Sinica*, **1979**, 37, 215



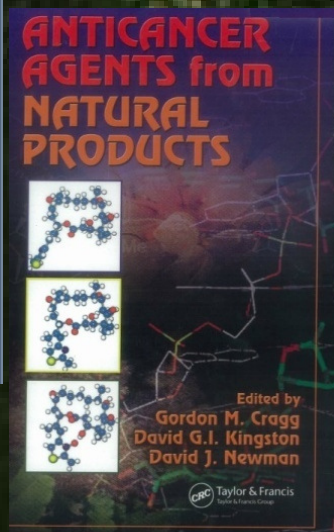
Universidade Federal do Rio de Janeiro



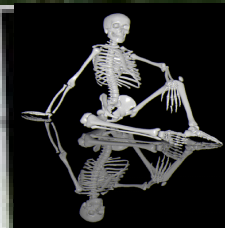
# Quimioterapia do Câncer



## Produtos naturais vegetais



Quimiodiversidade  
Estruturas originais  
Mecanismo de ação inovadores  
Inovações terapêuticas  
Moléculas otimizadas

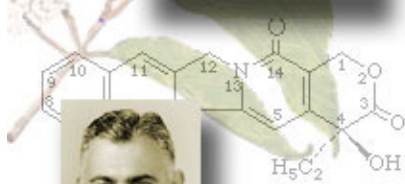


*Inter-alia:* Alcalóides da Vinca, podofilotoxina



# Câncer

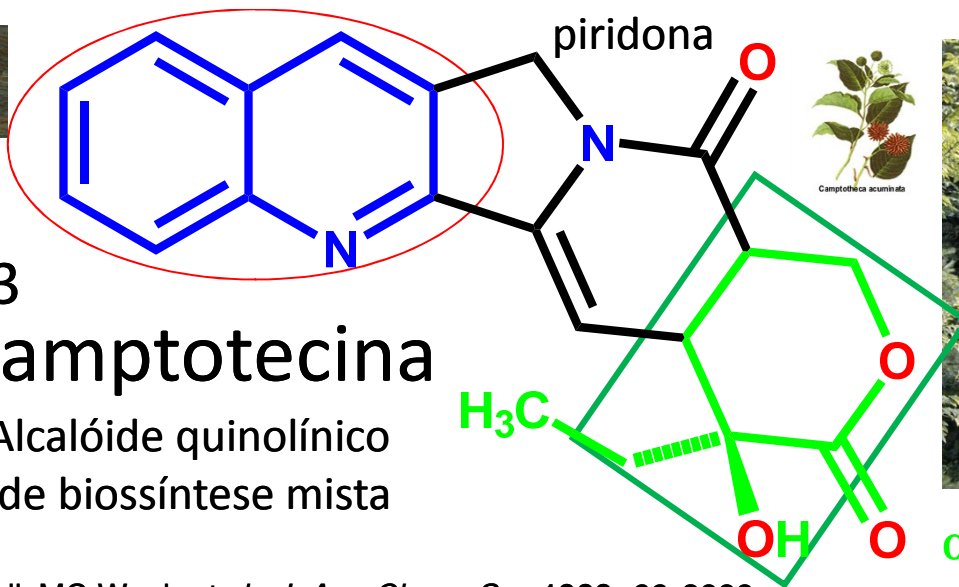
Universidade Federal do Rio de Janeiro



1963

## camptotecina

Alcalóide quinolínico de biossíntese mista

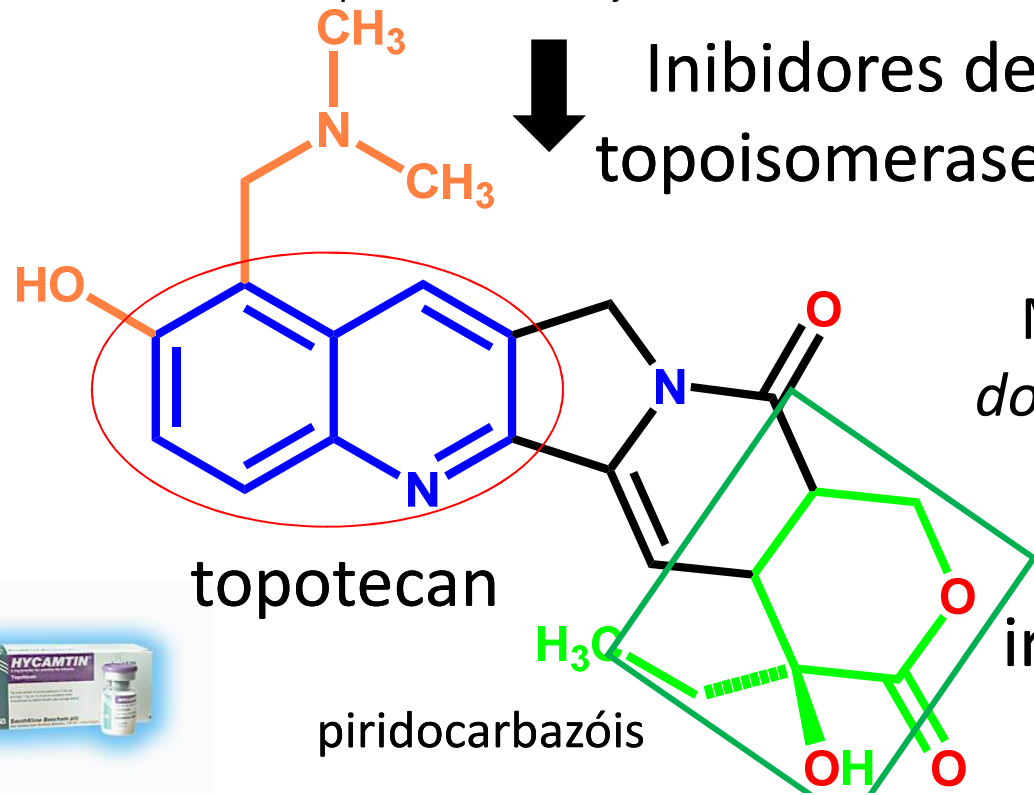


Camptotheca acuminata

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

Molécula domesticada



irinotecan

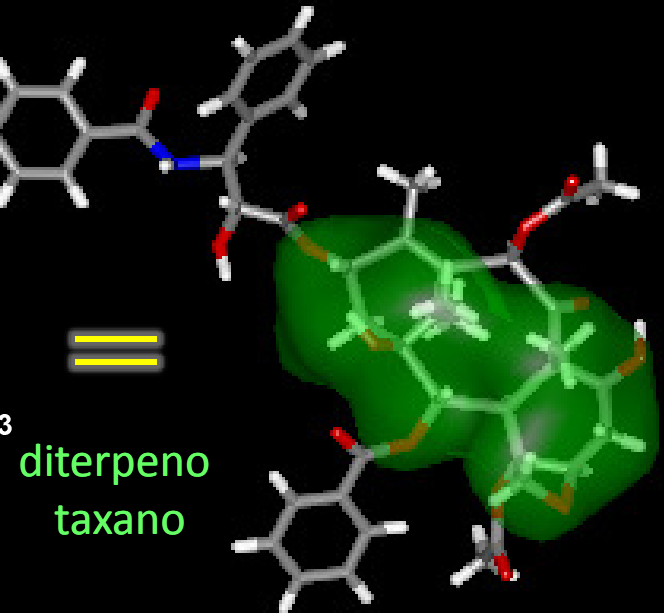
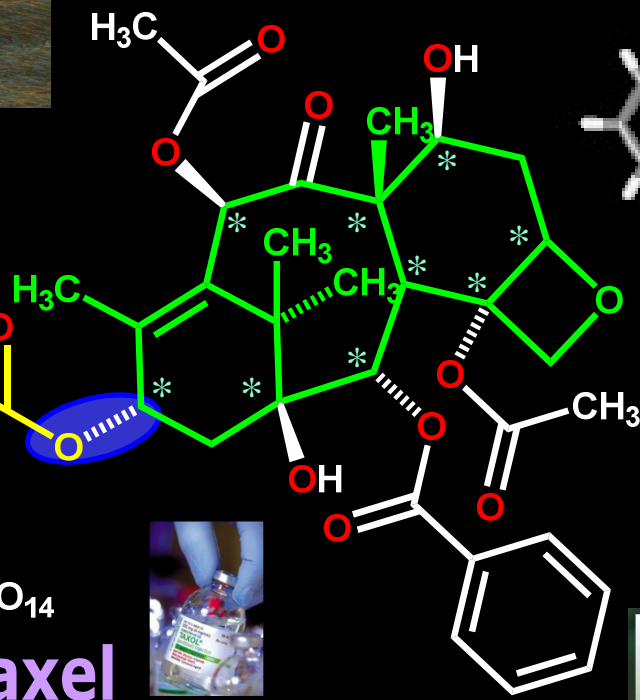
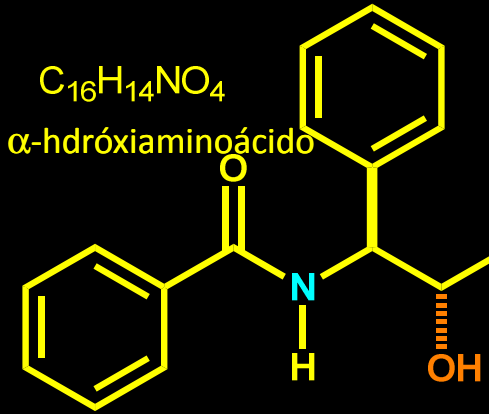
1996





Universidade Federal do Rio de Janeiro

# Câncer

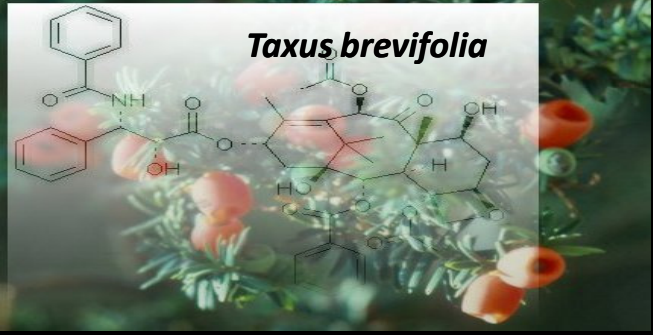


1965

## Paclitaxel

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

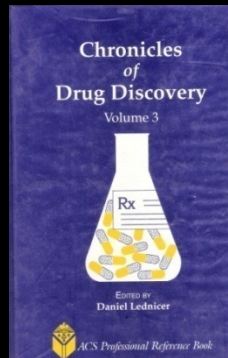
## Inibidores de tubulinas



Res. Triangle Park, 1967



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



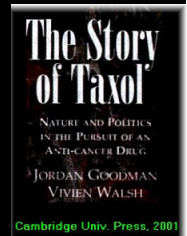
M. E. Wall,,  
 "Chronicles of Drug Discovery",  
 D. Lednicer, vol.3, ACS, 1993,  
 pp. 327-348



blockbuster  
2010



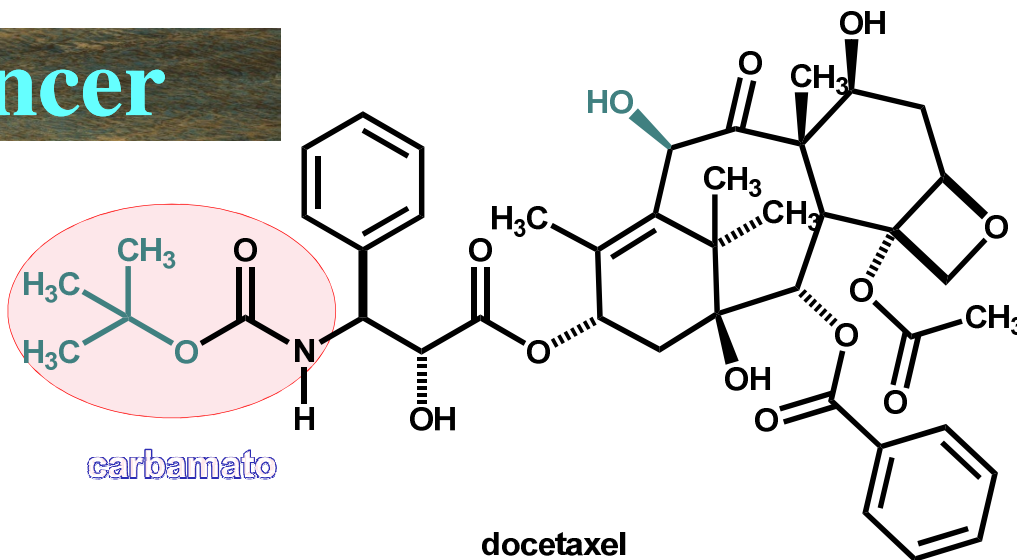
Docetaxel\*  
 Cabazitaxel (Jevtana<sup>R</sup>)  
 Ortataxel&





# A família dos taxanos cresceu...

## Câncer



docetaxel  
1996



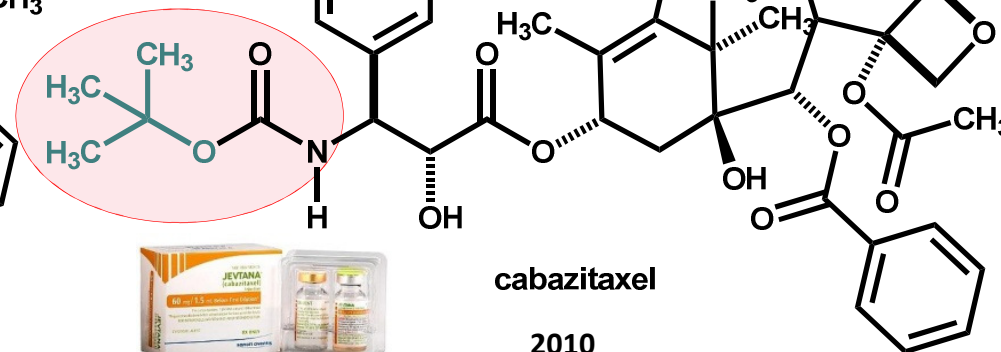
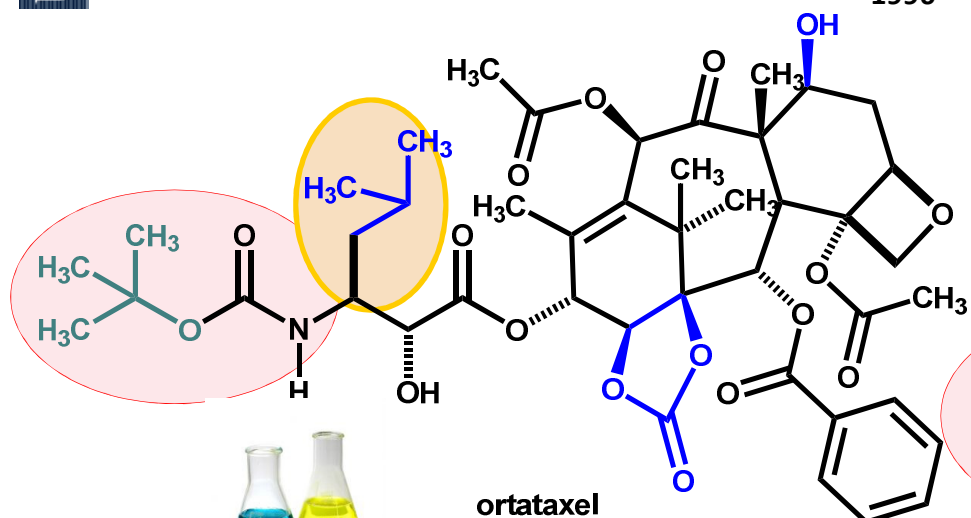
Pierre Potier  
1934-2006



Andy E Greene  
UJF-FR

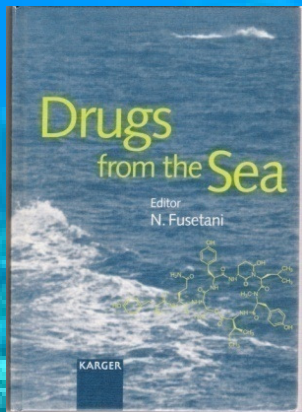


1339





Universidade Federal do Rio de Janeiro



N Fusetani



# Produtos naturais marinhos

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



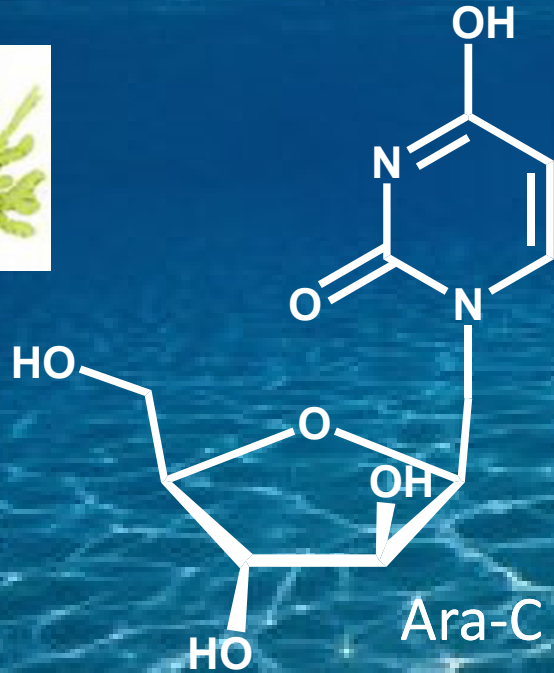


Universidade Federal do Rio de Janeiro

# Produtos Naturais do Mar



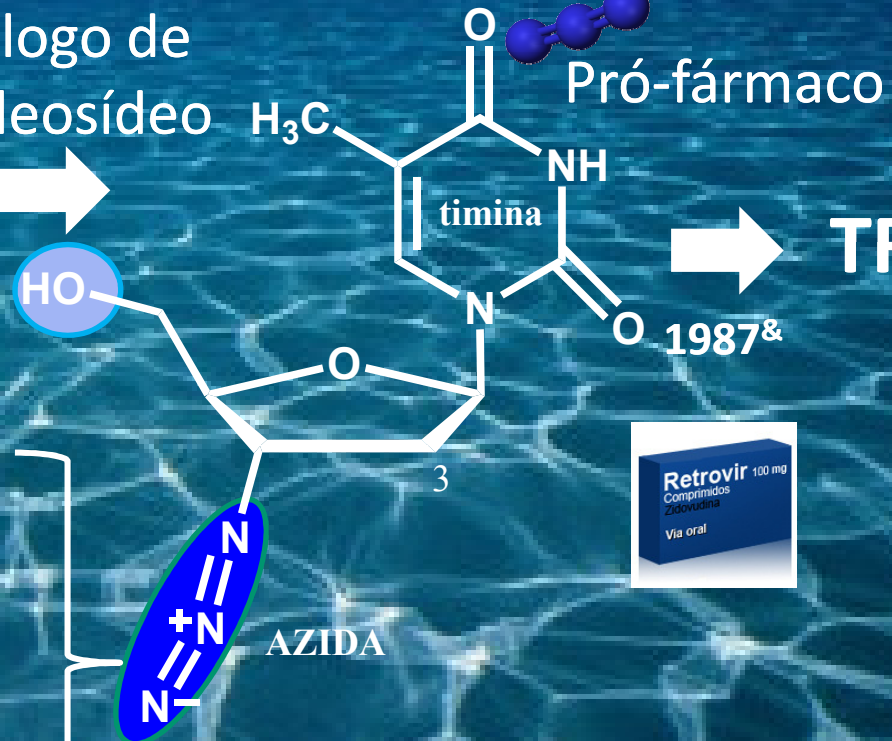
algas



Ara-C



Análogo de nucleosídeo



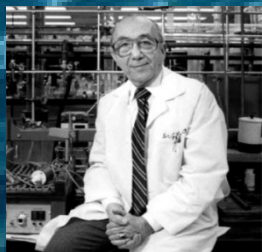
Pró-fármaco

TRI 1987&



Zidovudina (AZT)

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



Jerome Horwitz

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





1. Definição & histórico da Química Medicinal: os pioneiros e as moléculas pioneiras;

---

2. Os fármacos e seus biorreceptores: o paradigma de Fischer-Ehrlich;

---

3. A origem dos fármacos: *domesticando* e se inspirando nos produtos naturais;

---

4. A fascinante criatividade da natureza & as moléculas “*impossíveis*” que viraram fármacos;

---

5. **Do *bolor* às moléculas salva-vidas ou bilionárias;**

---

6. A era dos fármacos sintéticos racionalmente planejados;

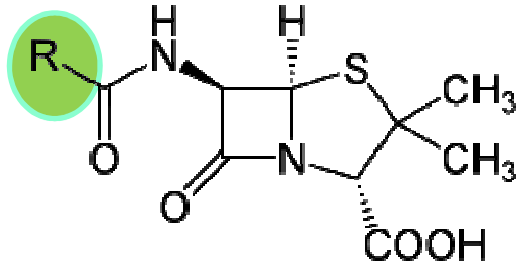
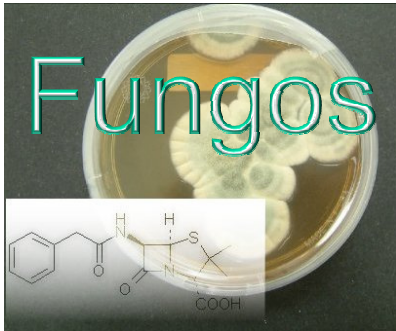
---

7. Considerações finais



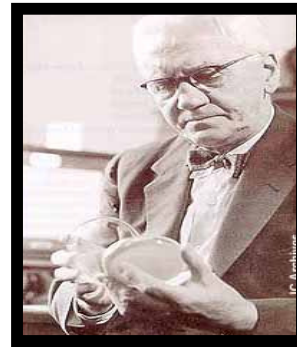
Universidade Federal do Rio de Janeiro

# Penicilina



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

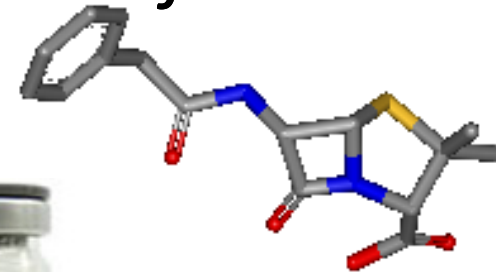
# antibioticoterapia



**Alexander Fleming**  
1881-1955

# Antibióticos $\beta$ -lactâmicos

*O acaso ajuda a sorte*



**Howard W. Florey**  
1898-1968



**1945**



**E. Boris Chain**  
1906-1979



**1965**  
**1947**



**Dorothy C. Hodgkin**  
1910-1994



**1964**

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



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





Universidade Federal do Rio de Janeiro

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

