

Princípios de Química Medicinal

MedChem

24ª Semana da Química do Instituto de Química da UFRJ
09-13 de maio de 2016



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Instituto de Ciências Biomédicas

Universidade Federal do Rio de Janeiro



Parte 3

Sumário

Introdução; O processo de inovação de fármacos; O paradigma de Ehrlich & Fischer; Os alfabetos bioquímicos; As fases da ação dos fármacos; Aspectos moleculares da ação dos fármacos; Breve noção sobre o papel dos produtos naturais na descoberta de fármacos; Aspectos da química computacional: modelagem molecular; Estratégias para o desenho de novos candidatos a fármacos; Exemplos selecionados: LASSBio-UFRJ.

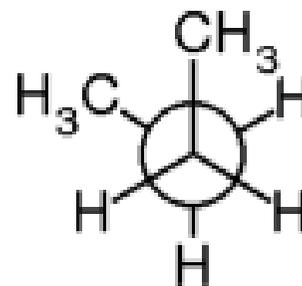
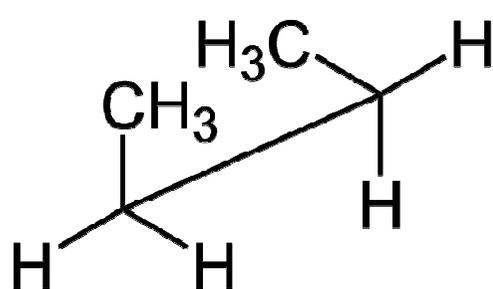


Software para editar estruturas químicas

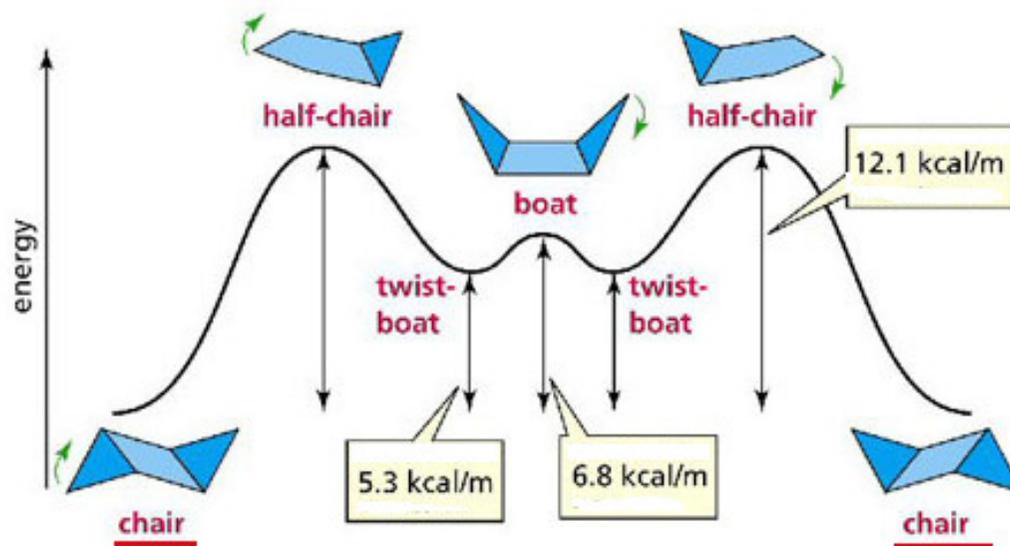
Elemental	Dotmatics	proprietary	Windows, iOS	freeware for PCs, iPhone, iPad
ICEDIT	InfoChem	proprietary	Windows	chemical structure and reaction editor (see ICEDIT)
ChemTool			Linux, Unix	2D editor for chemical structural formulas, written in C using GTK
ChemWindow	Bio-Rad	proprietary		available as part of the KnowItAll software environment; Freeware for academic research and teaching
ICM-Chemist	MolSoft	proprietary	available for Windows, Mac and Linux	Easy to use graphical user interface desktop chemistry editor
JChemPaint		LGPL	platform-independent	2D structural formula editor written in Java
KnowItAll	Bio-Rad	proprietary	Windows	Freeware for academic research and teaching
Ihdraw	Lennard Wasserthal	GPL	Linux	chemdraw cdx/cdxml compatible FOSS clone, search function
MarvinSketch/View	ChemAxon	proprietary	platform-independent	commercial and freeware versions (see terms). Chemical editor and viewer, desktop version (Java Beans)
MarvinSpace	ChemAxon	proprietary	platform-independent	commercial and freeware versions (see terms). 3D macromolecular visualization and ligand editing, desktop version (Java Beans)
MedChem Designer	Simulations Plus	proprietary	Windows	freeware - includes free S+logP, S+logD(7.4), TPSA, PEOE sigma charges, HBD, HBA, and Rule of 5 calculations.
molsKetch		GPL		multiplatform editor, based on Qt4
ODYSSEY	Wavefunction, Inc.	proprietary	Mac OS X, Windows	
SketchEl		GPL	platform-independent	multiplatform editor, Java , available on SourceForge



Fatores estruturais: conformação



43 KJ mol⁻¹



Sir Derek Barton

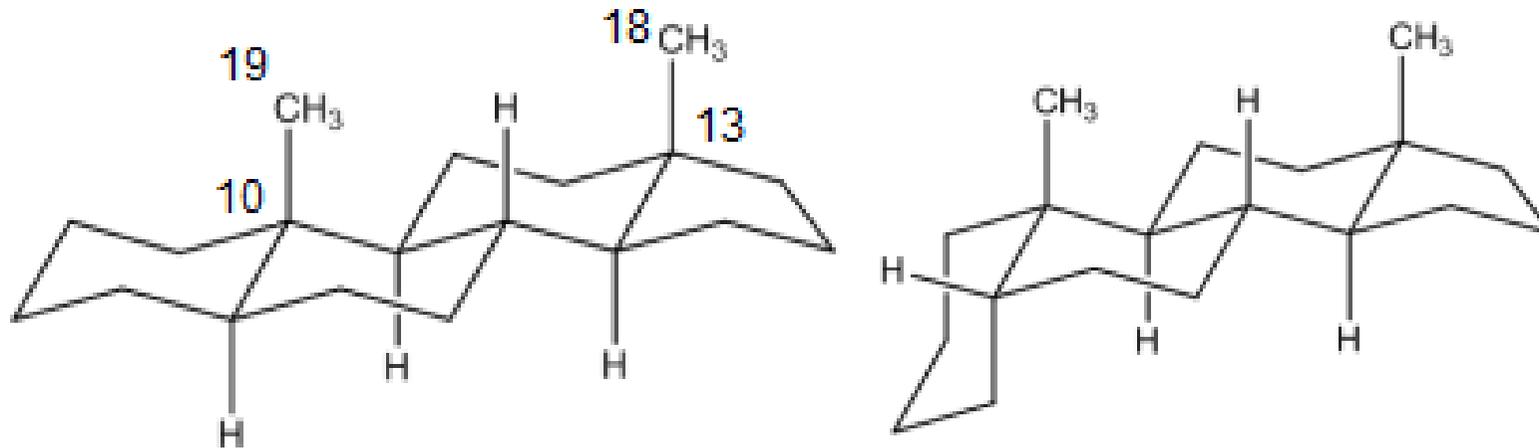
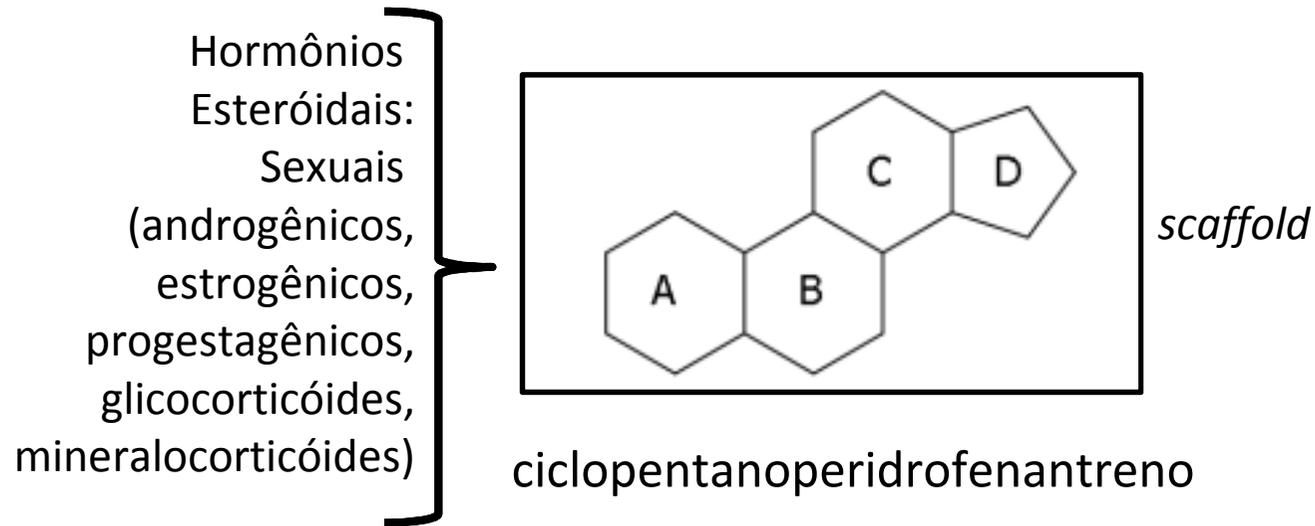
1918-1998



1969

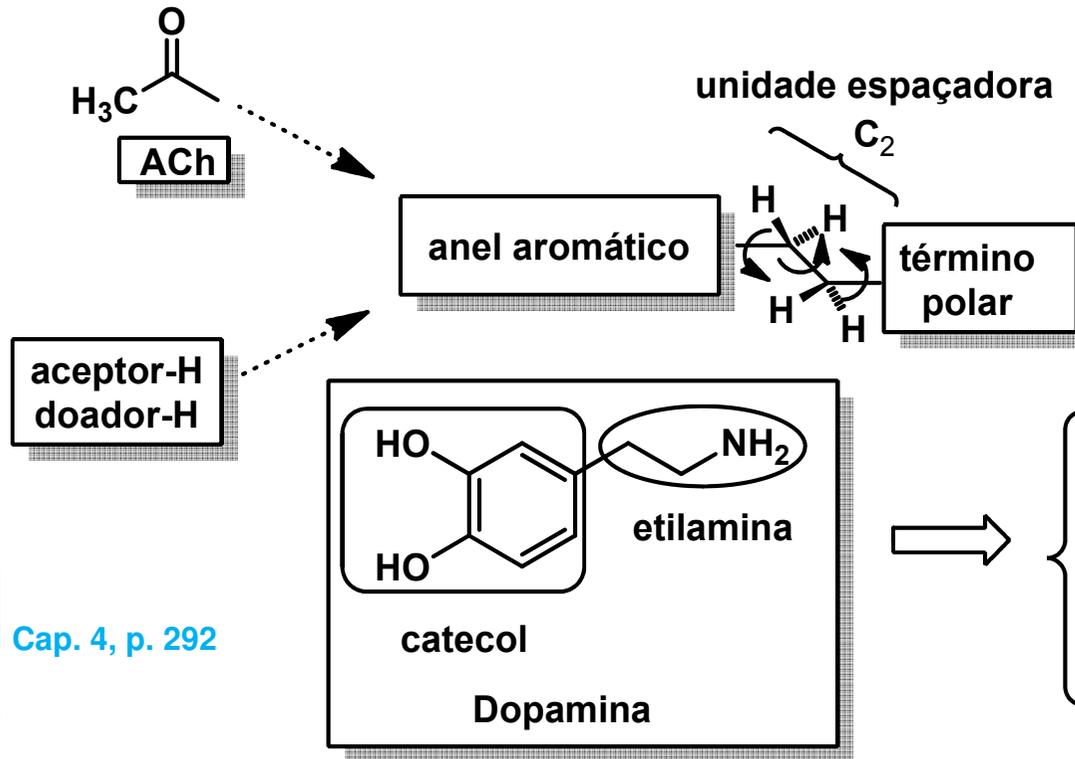
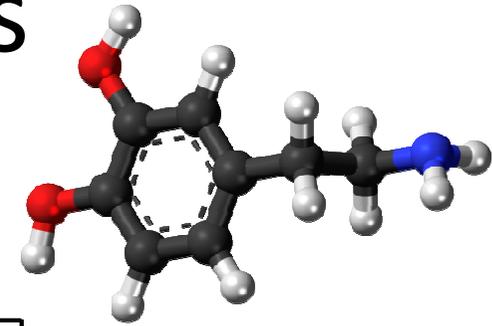


Fatores conformacionais

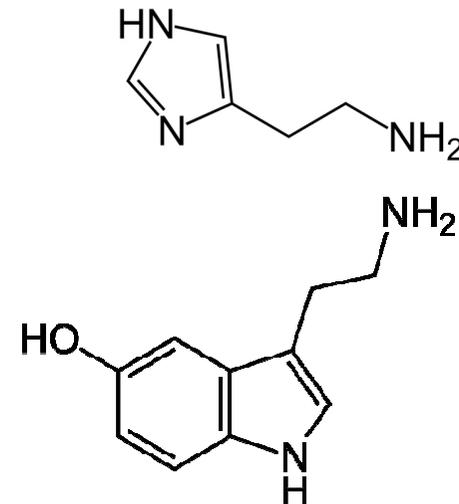
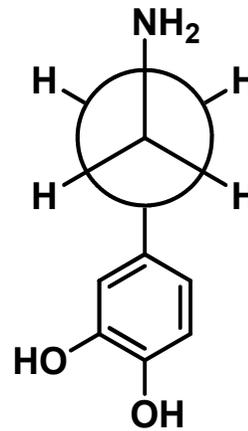
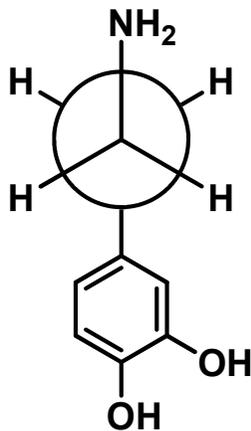
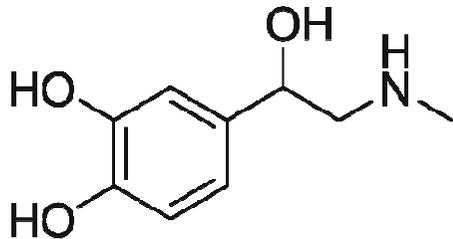
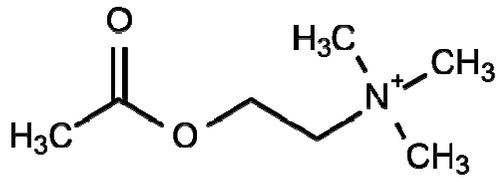




Aminas biogênicas

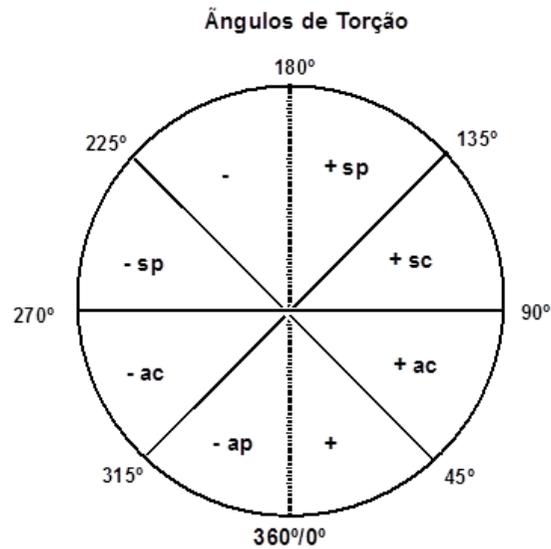


Cap. 4, p. 292

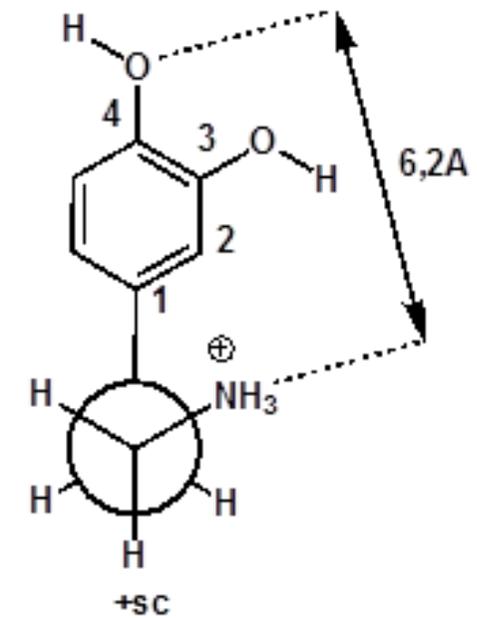
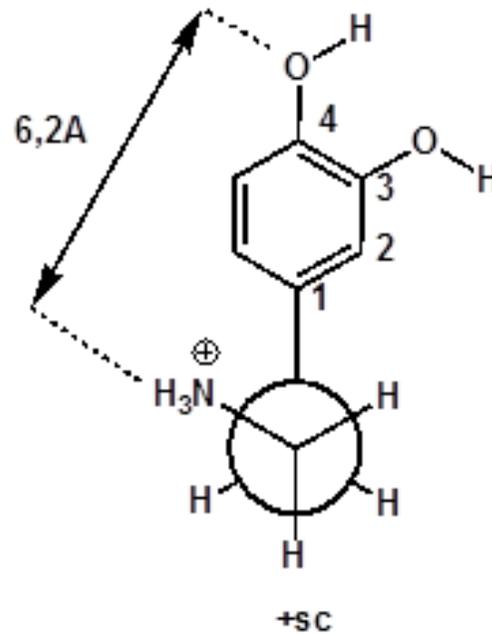
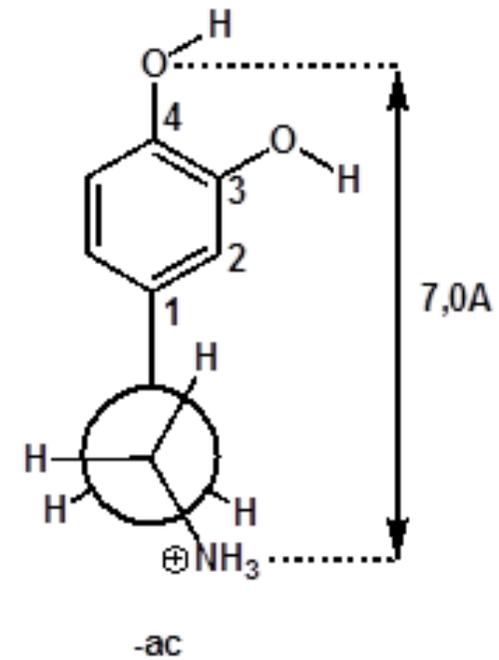
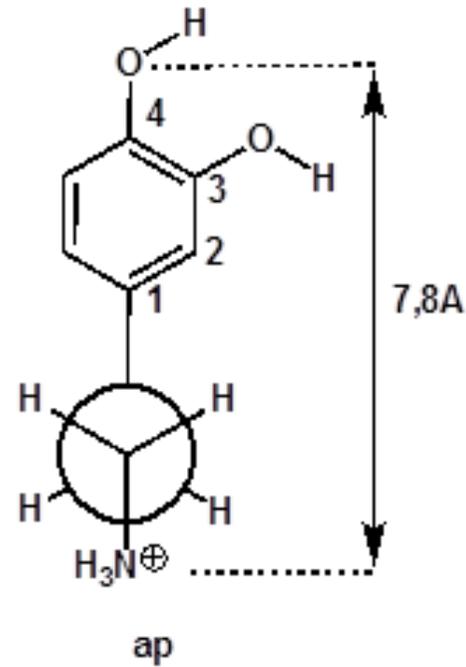
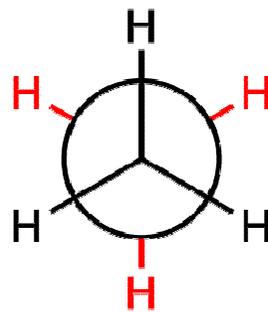


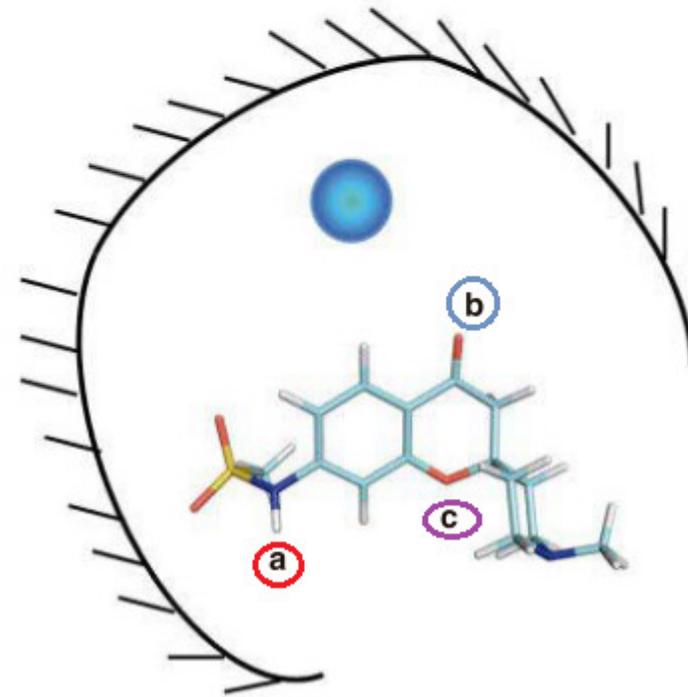
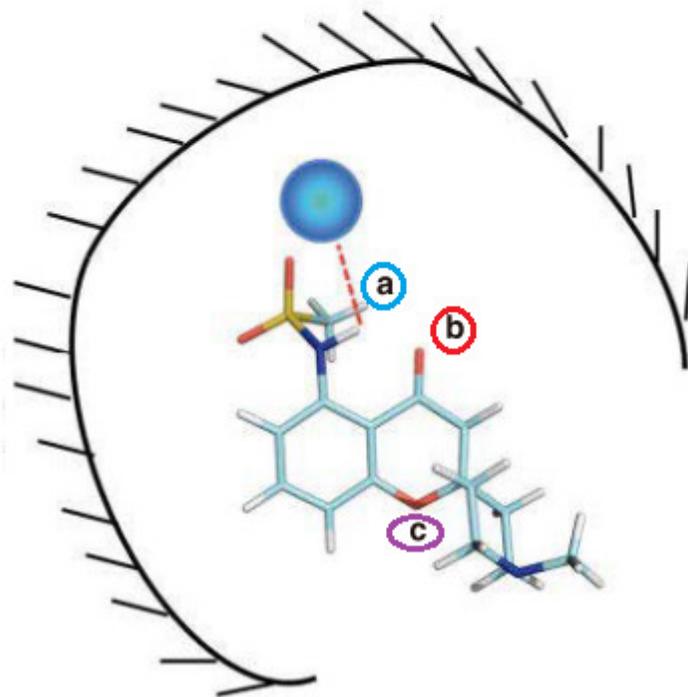
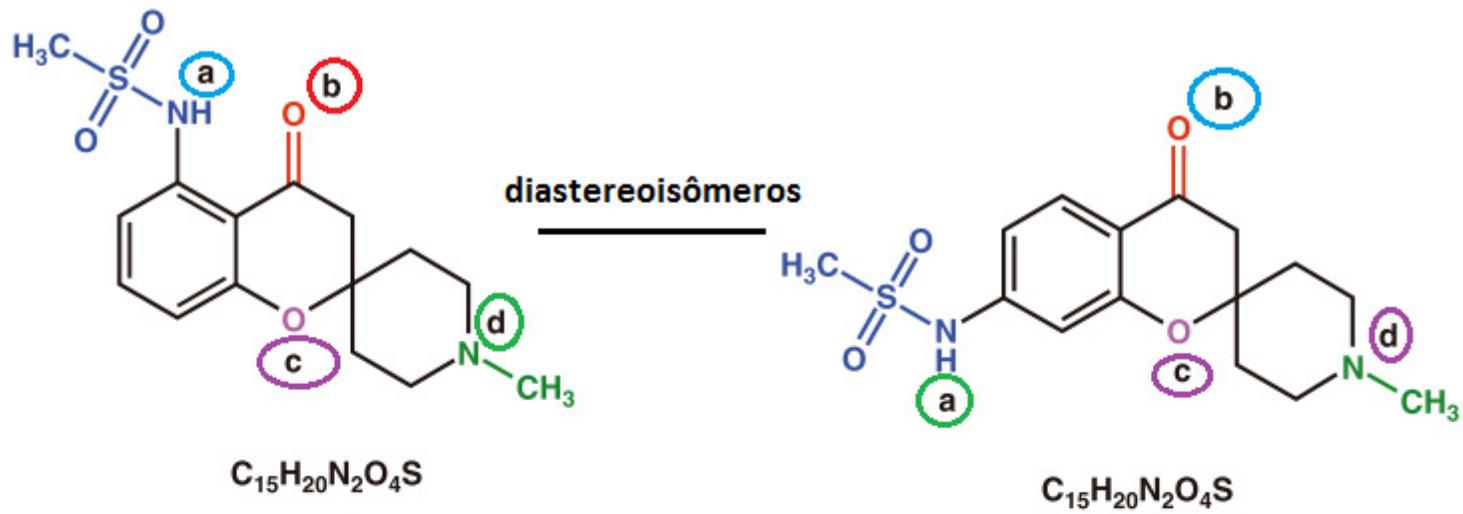


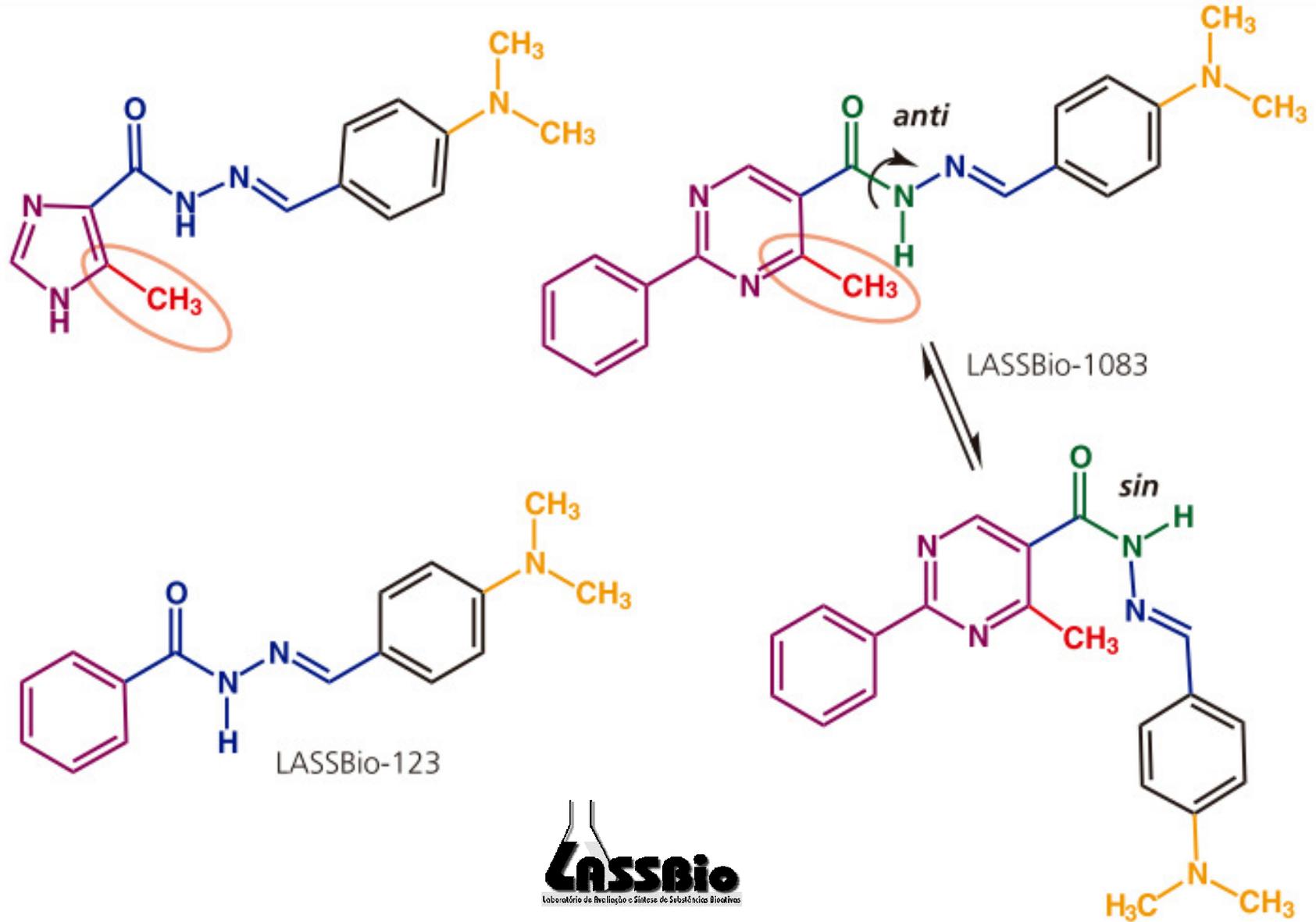
Confômeros



Projeção de
Newman

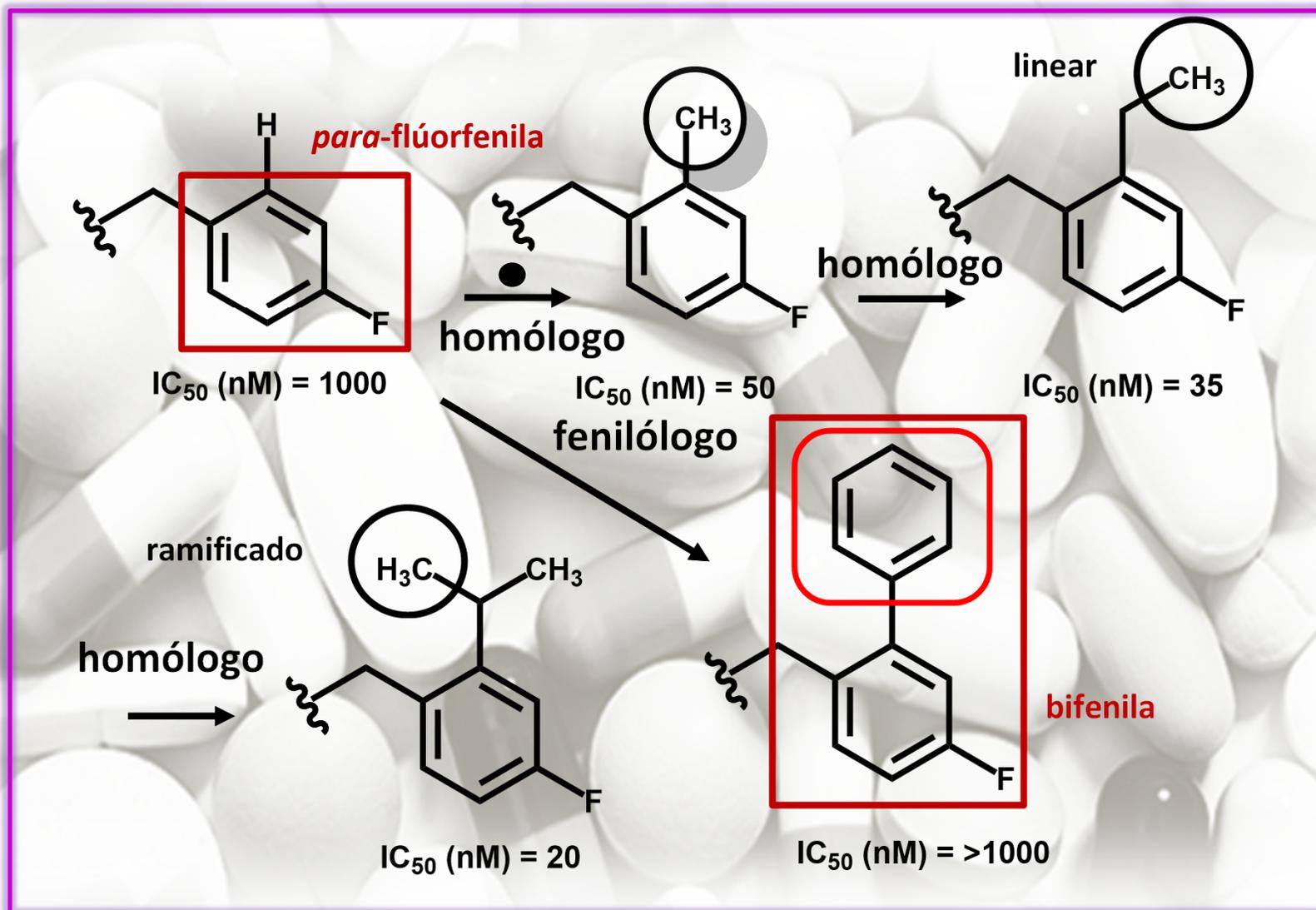








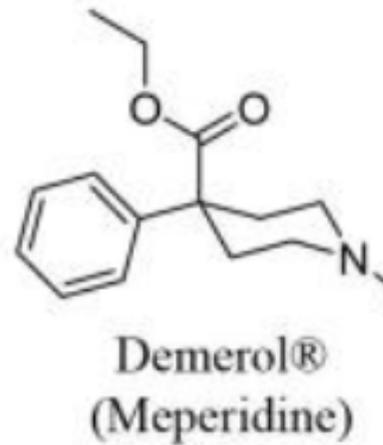
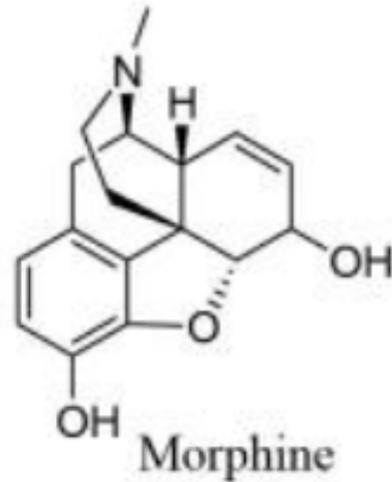
> Diversidade química: novo *molecular scaffold*



Conceito de *scaffold* (andaime): sistema cíclico; anel; núcleo; (core, framework, ring, nucleous)



Qual poderia ser uma explicação ?

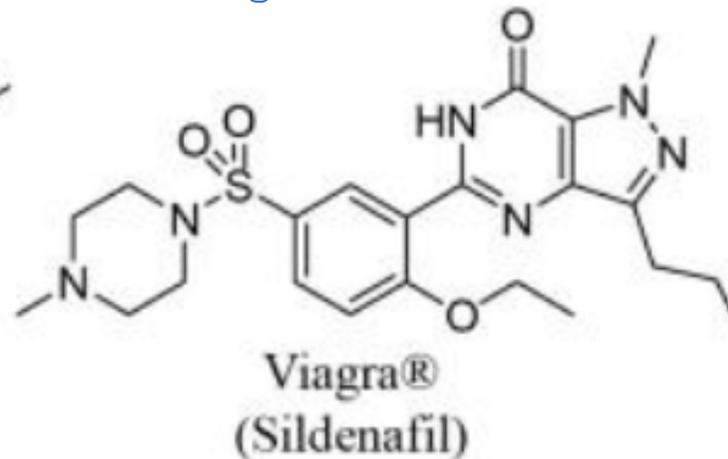


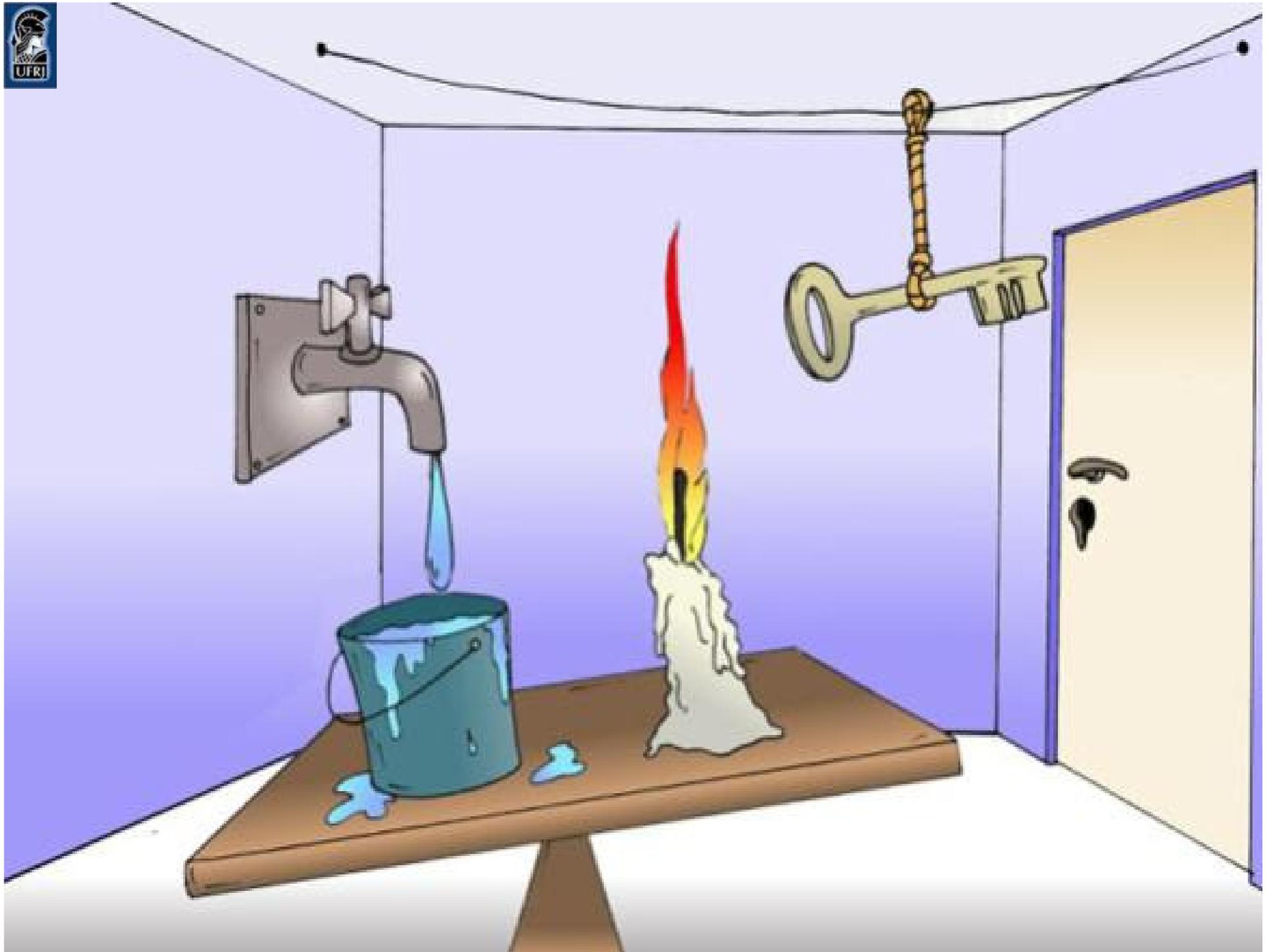
analgésicos



Mesmos efeitos!

anti-disfunção erétil







A Origem dos Fármacos

CAPÍTULO 3
A ORIGEM DOS FÁRMACOS 105

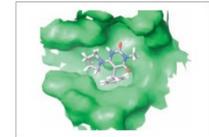


Produtos Naturais

Planejamento racional

Química medicinal

Sintéticos



vegetais



microorganismos
fungos
marinhos

Fármacos

Biofármacos

Processos biotecnológicos

sildenafil



Outros Fármacos

antibióticos

Acaso



metabolismo



sulfas
diuréticas

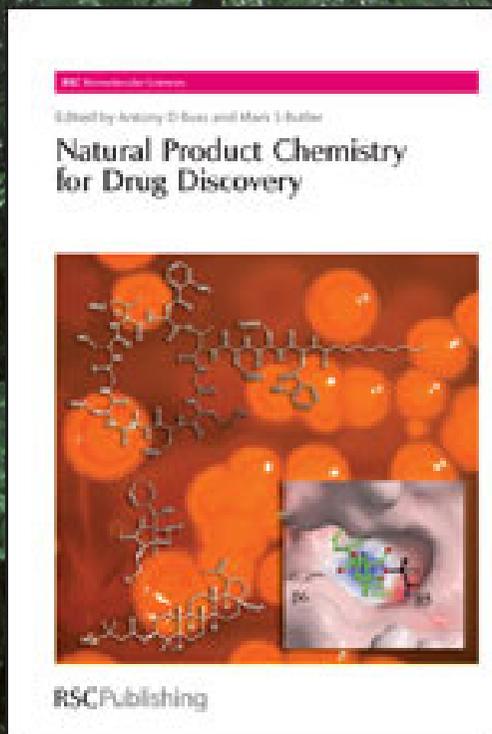
ansiolíticos



Os produtos naturais e os fármacos

natural product-derived drugs

SciELO- Cientific Electronic Library Online



2009

A D Buss & MS Butler
(Eds)



2012

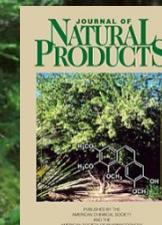
V Cechinel-Filho (Editor)

Inter-alia: 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; EJ Barreiro, VS Bolzani,

Quim. Nova 2009, 32, 679

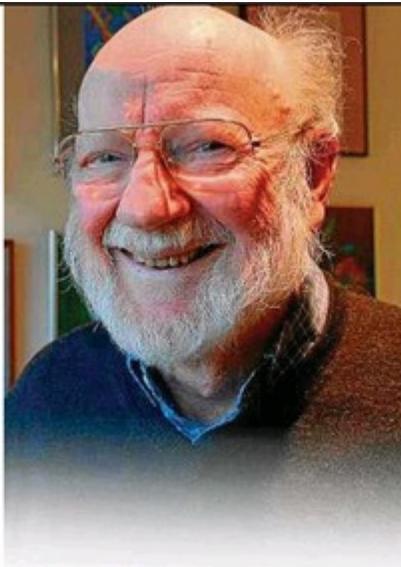




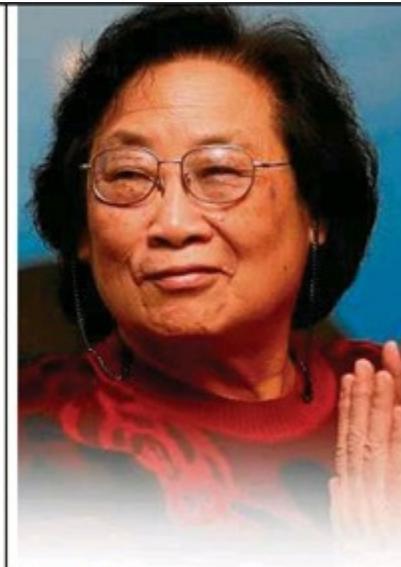
Prêmio Nobel de Medicina 2015



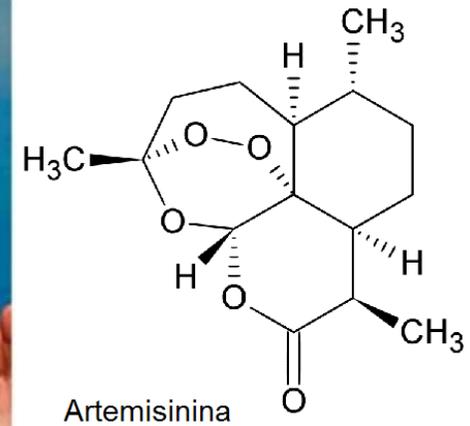
Satoshi Omura



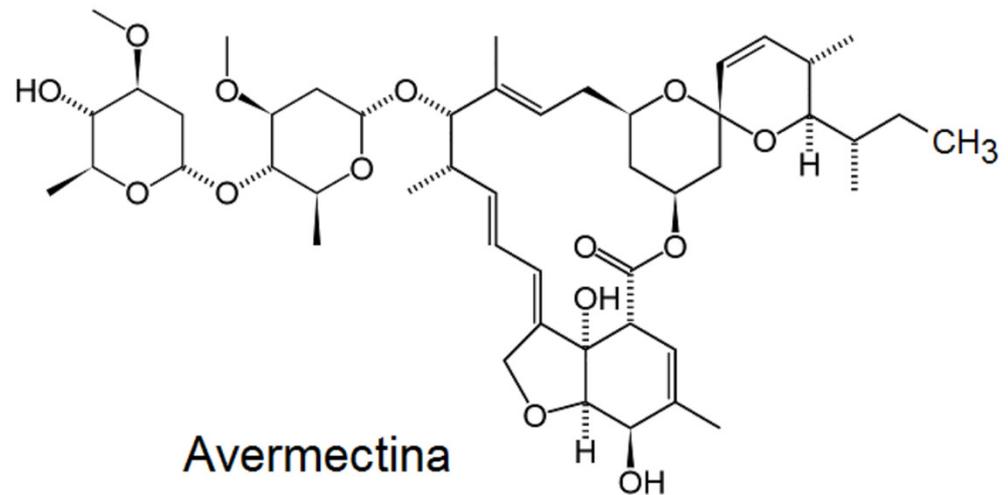
William Campbell



Youyou Tu



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





Glicosídeos cardiotônicos

Ebers Papyrus



Digitalis purpurea
Digitalis lanata
Dedaleira
Plantaginaceae

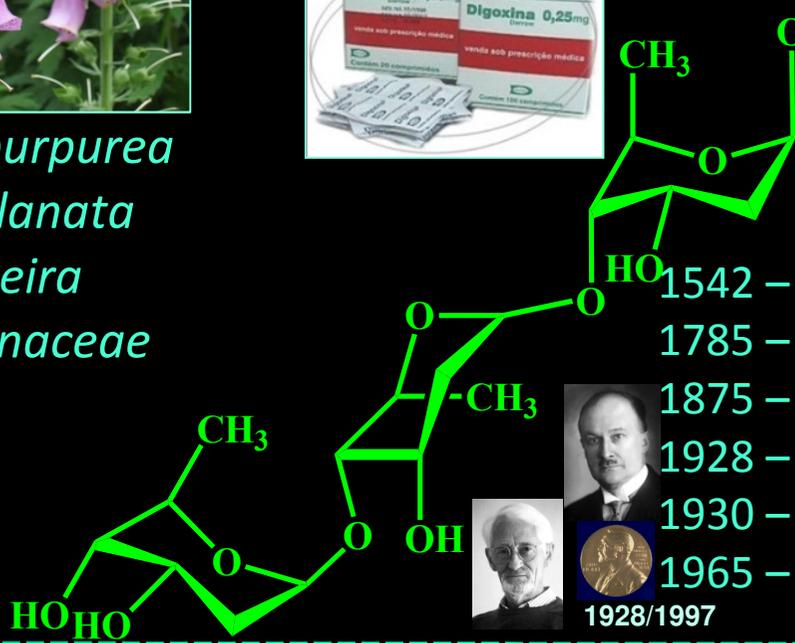
O decano dos fármacos



bufanolidos cardenolidos



Digoxina



1542 – Leonhard Fuchs *Digitalis purpurea*

1785 – William Withering, UK

1875 – Johann Schmiedeberg isola DGX

1928 – Sydney Smith, Burroughs Wellcome

1930 – Adolf OR Windaus, Un. Göttingen, AL

1965 – JC Skou* / O Hansen (Na⁺/K⁺-ATPase)



1928/1997



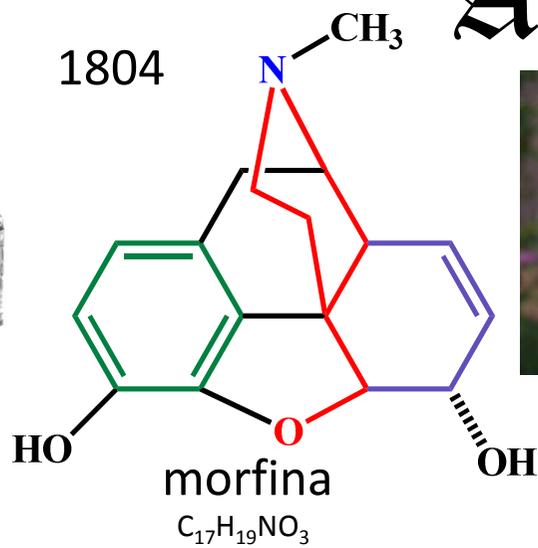
& H Zhang *et al.*, Digoxin and other cardiac glycosides inhibit hypoxia inducible factor-1 (HIF-1a) synthesis and block tumor growth, *PNAS* **2008**, *105*, 19579;

* JR Huh *et al*, Digoxin and its derivatives suppress T(H)17 cell differentiation ..., *Nature* **2011**, *472*, 486



As moléculas pioneiras...

1804



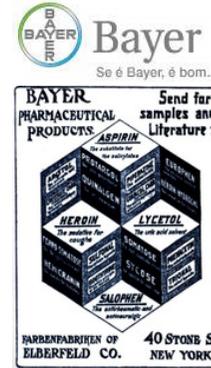
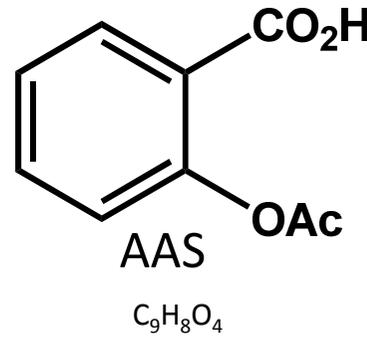
Friedrich W. A. Sertürner
1783- 1841



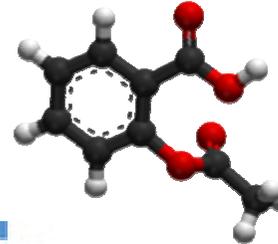
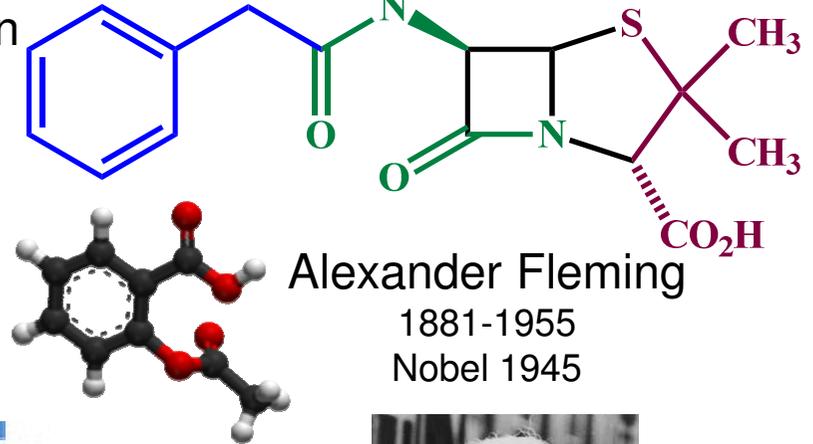
Sir Robert Robinson
1886-1975
Nobel 1947



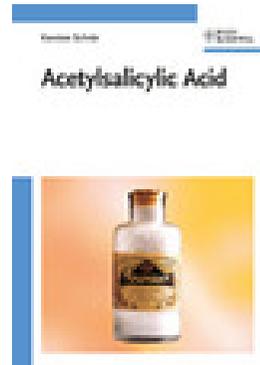
1897



Felix Hoffman
1868- 1946



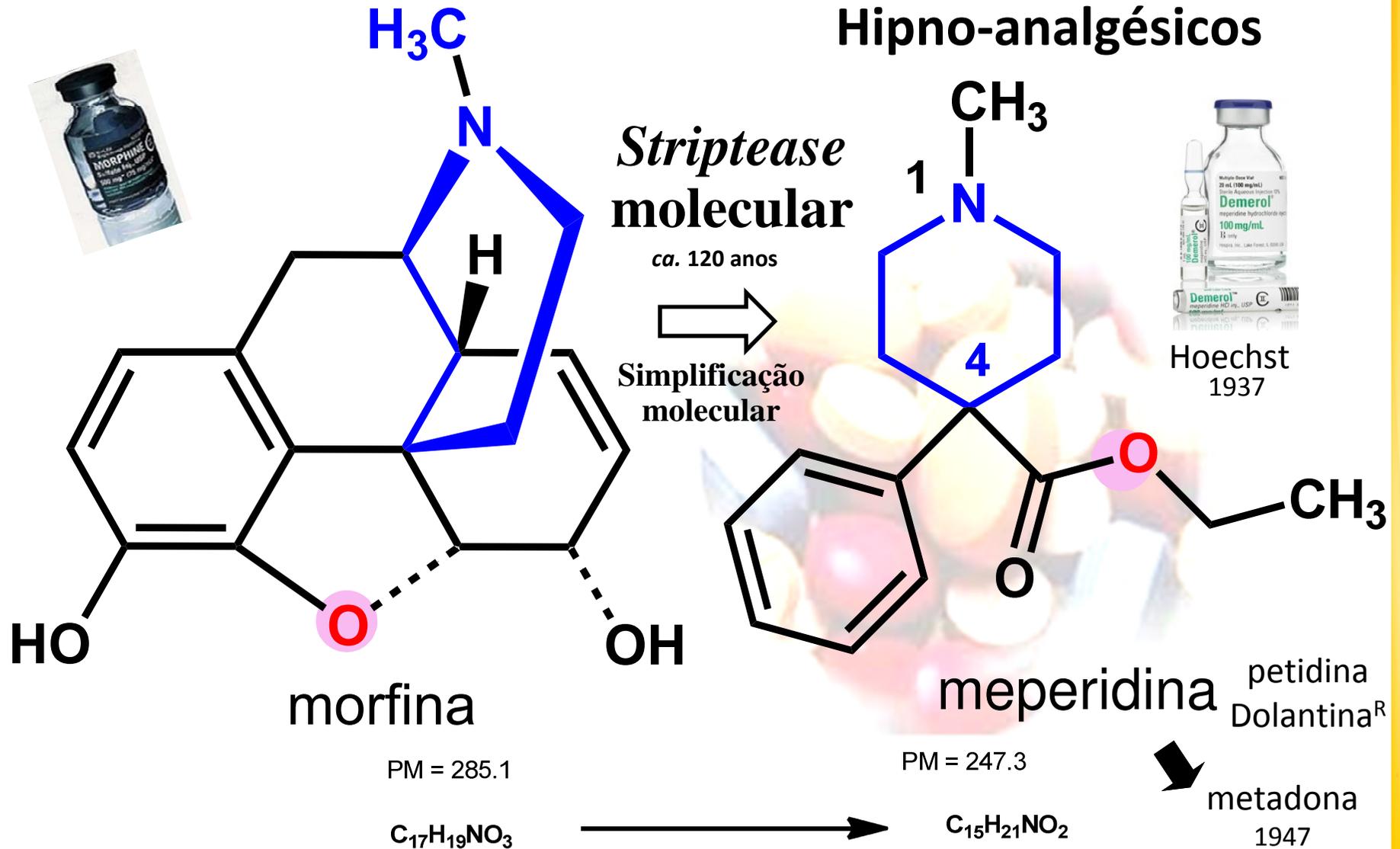
1929
penicilina
 $C_{16}H_{18}N_2O_4S$



Library of Congress



Derivados 4-fenilpiperidínicos



Domesticando produtos naturais

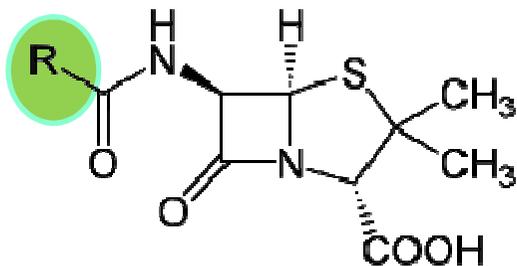


Molécula *salva-vidas*...

Antibióticos β -lactâmicos



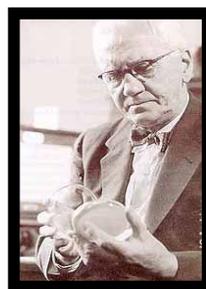
- 1877 – L. Pasteur
- 1897 - Ernst Duchesne, Lyon
- 1928 – A Fleming, Londres
- 1939 – Flory & Chain
- 1943 – RB Woodward, R Robinson
- 1945 - Dorothy C. Hodgkin
- 1948 – Patente do processo
- 1957 – John Sheehan, MIT



Penicilina



Dorothy C. Hodgkin
1910-1994
MD Vargas, *Rev Virtual Quim* **2012**, 4, 85



Alexander Fleming
1881-1955



Howard W. Florey
1898-1968



Dorothy C. Hodgkin
1910-1994

antibioticoterapia

O acaso ajuda a sorte



E. Boris Chain
1906-1979

1945



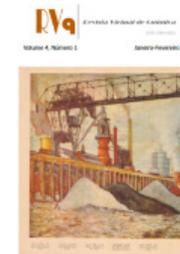
1964



Fungos

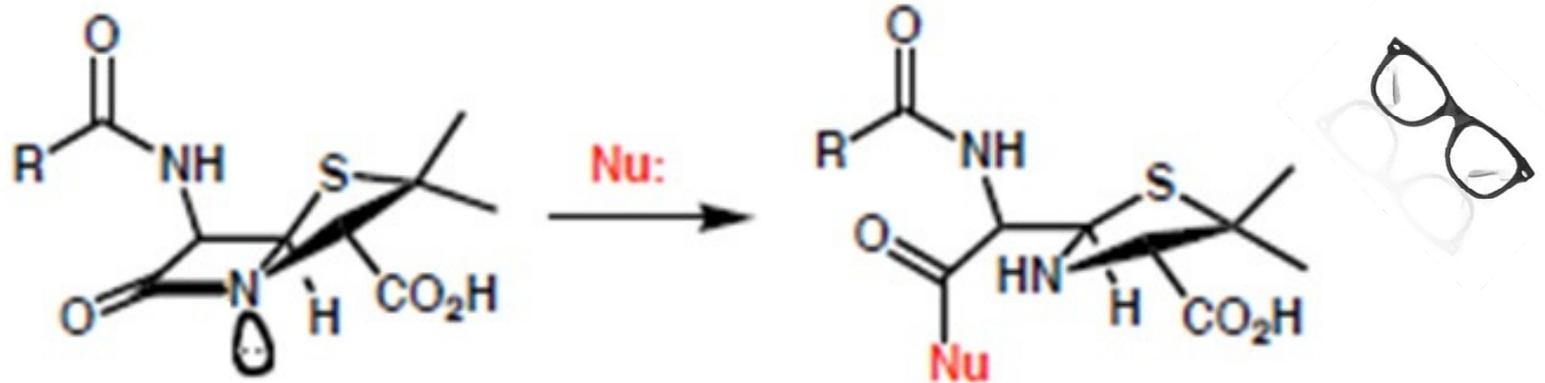


EB Chain *et al.*,
Lancet **1940**, 2, 226



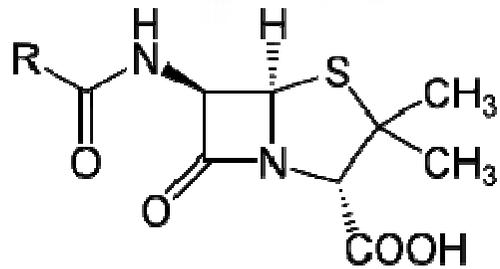


O sistema β -lactâmico

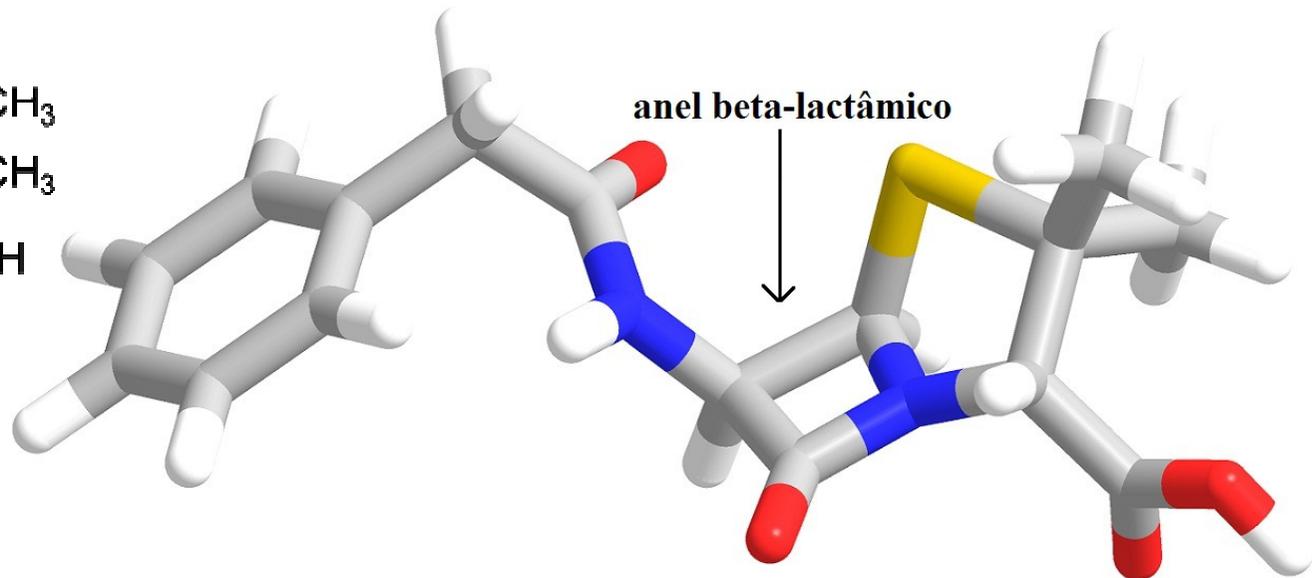


anel beta-lactâmico
de conformação
piramidal definida

Importância dos aspectos conformacionais

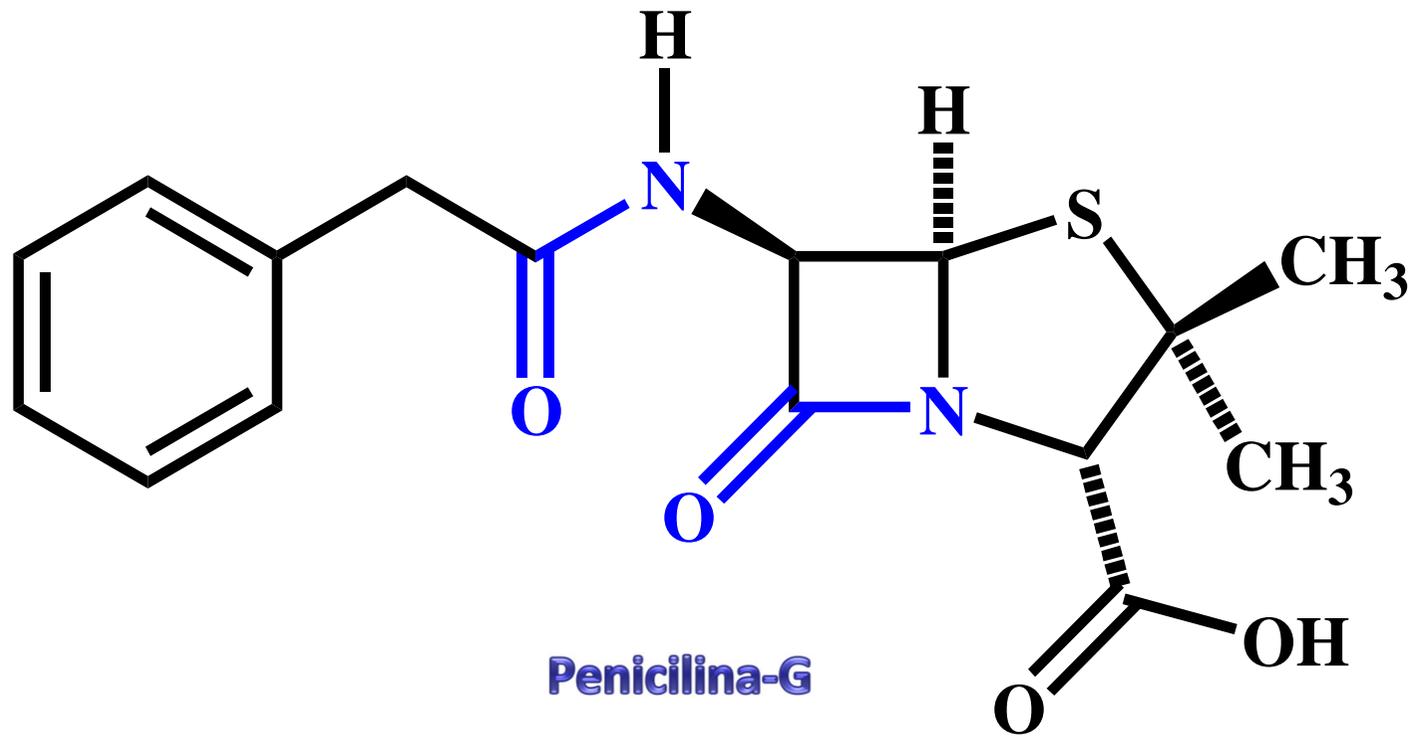


Química
med
Medicinal
chem





Quantos grupos funcionais?

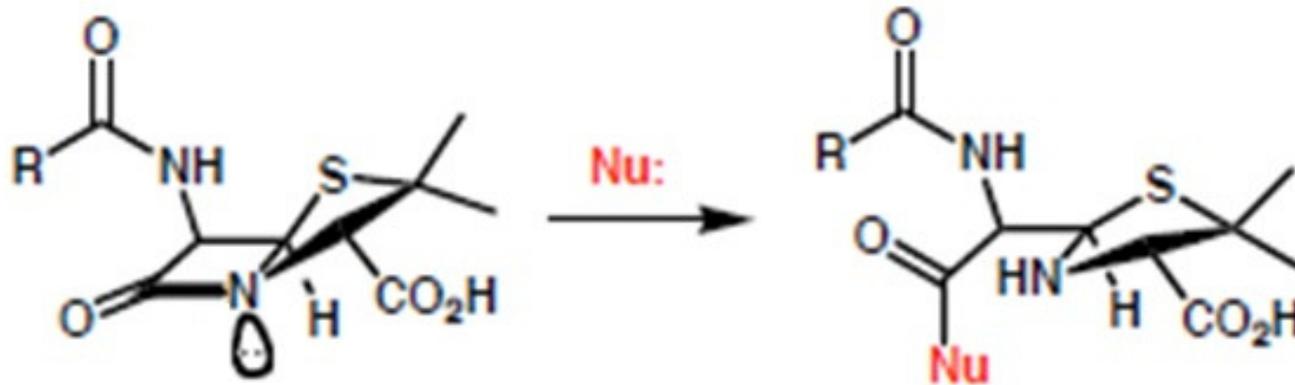


São todos "equivalentes"?

Quais são bio-equivalentes?

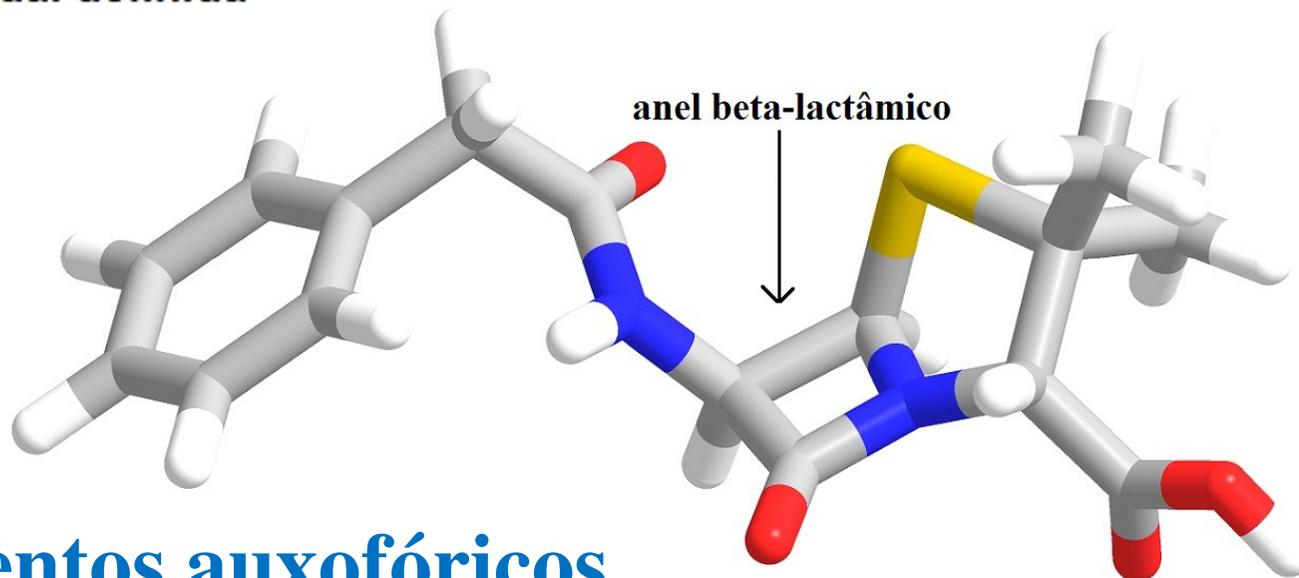


O sistema β -lactâmico



anel beta-lactâmico
de conformação
piramidal definida

Grupamento farmacofórico



Grupamentos auxofóricos



Câncer

Ecteinasclidina



Yondelis^R (ET-743)

Alcalóide tetraidroisoquinolínico de origem marinha
Sarcoma avançado de tecidos moles

Síntese Total

49 etapas



Ecteinascidia turbinata

Marinocultura



Semi-síntese

19 etapas

Cianosafracina B



Fermentação
Pseudomonas fluorescens

100 vezes mais ativo que Taxol^R

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

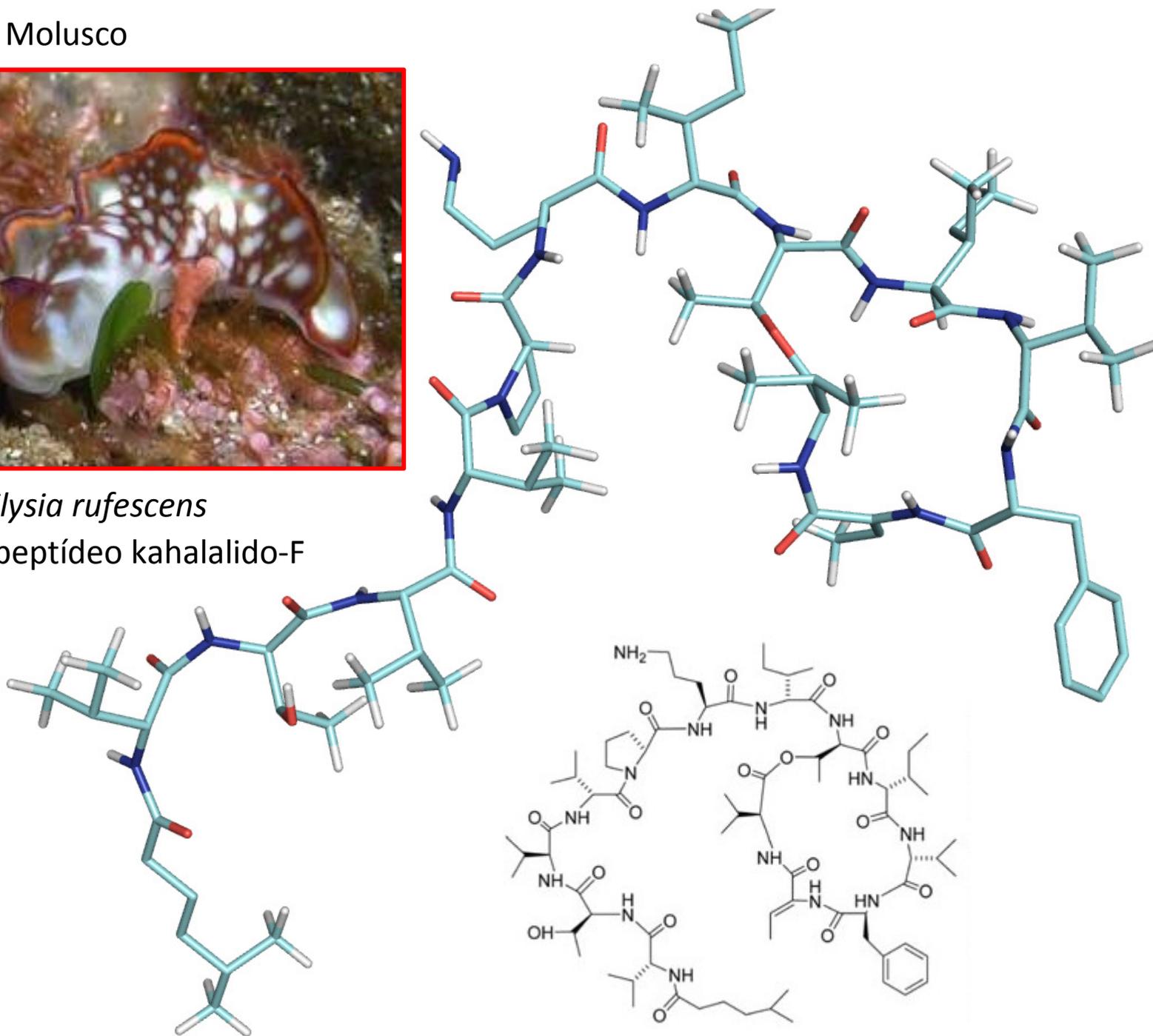
- ✓ **Natural:** KL Rinehart *et al*, *J. Nat. Prod.* **1990**, 53, 771
- ✓ **Síntese:** EJ Corey *et al*, *J. Am. Chem. Soc.* **1996**, 118, 9202
- ✓ **Hími-síntese:** I Manzanares *et al*, *Org Lett.* **2000**, 2, 2545



Molusco

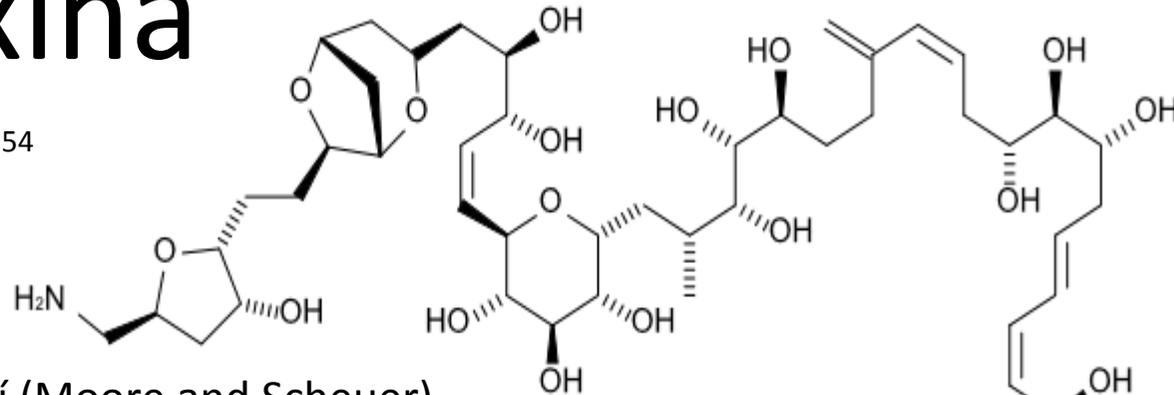


Elysia rufescens
depsipeptídeo kahalalido-F





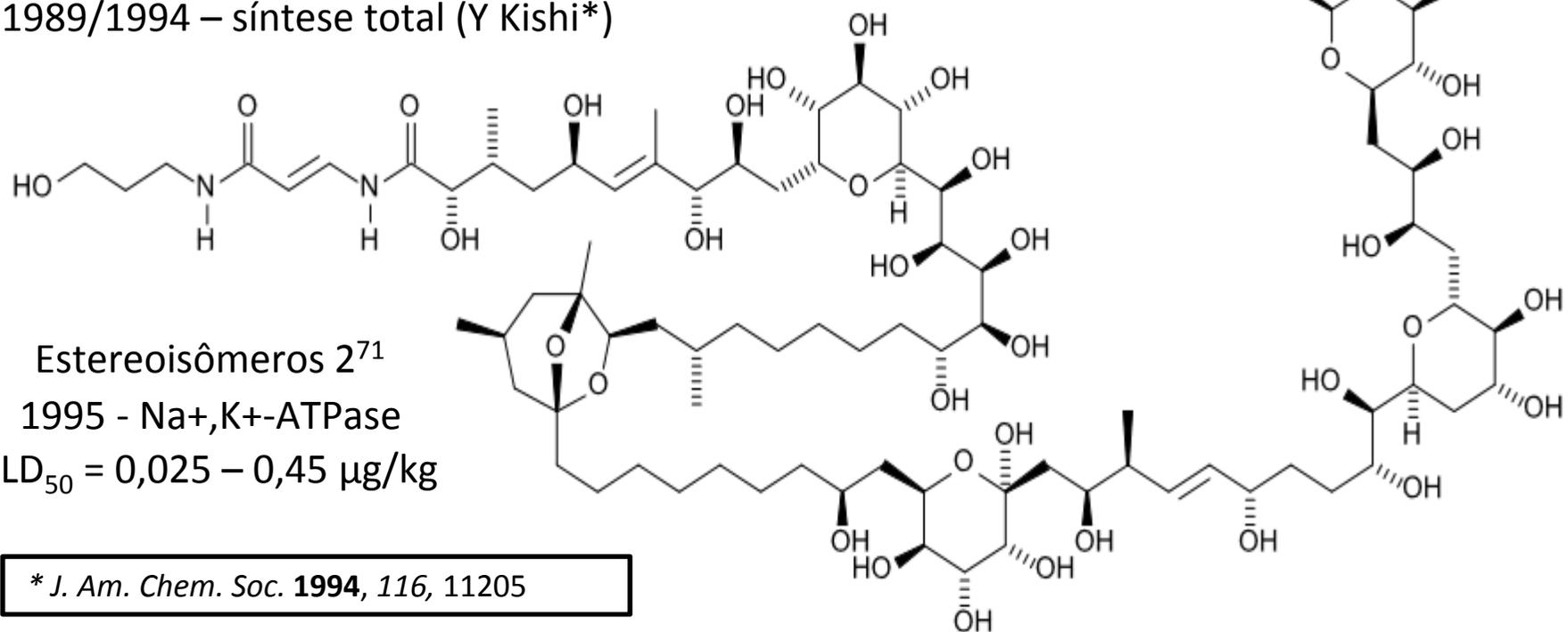
Palitoxina



1971 – isolada Havaí (Moore and Scheuer)

1982 – estrutura

1989/1994 – síntese total (Y Kishi*)



Estereoisômeros 2^{71}

1995 - Na⁺,K⁺-ATPase

LD₅₀ = 0,025 – 0,45 µg/kg

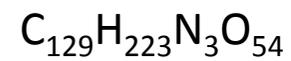
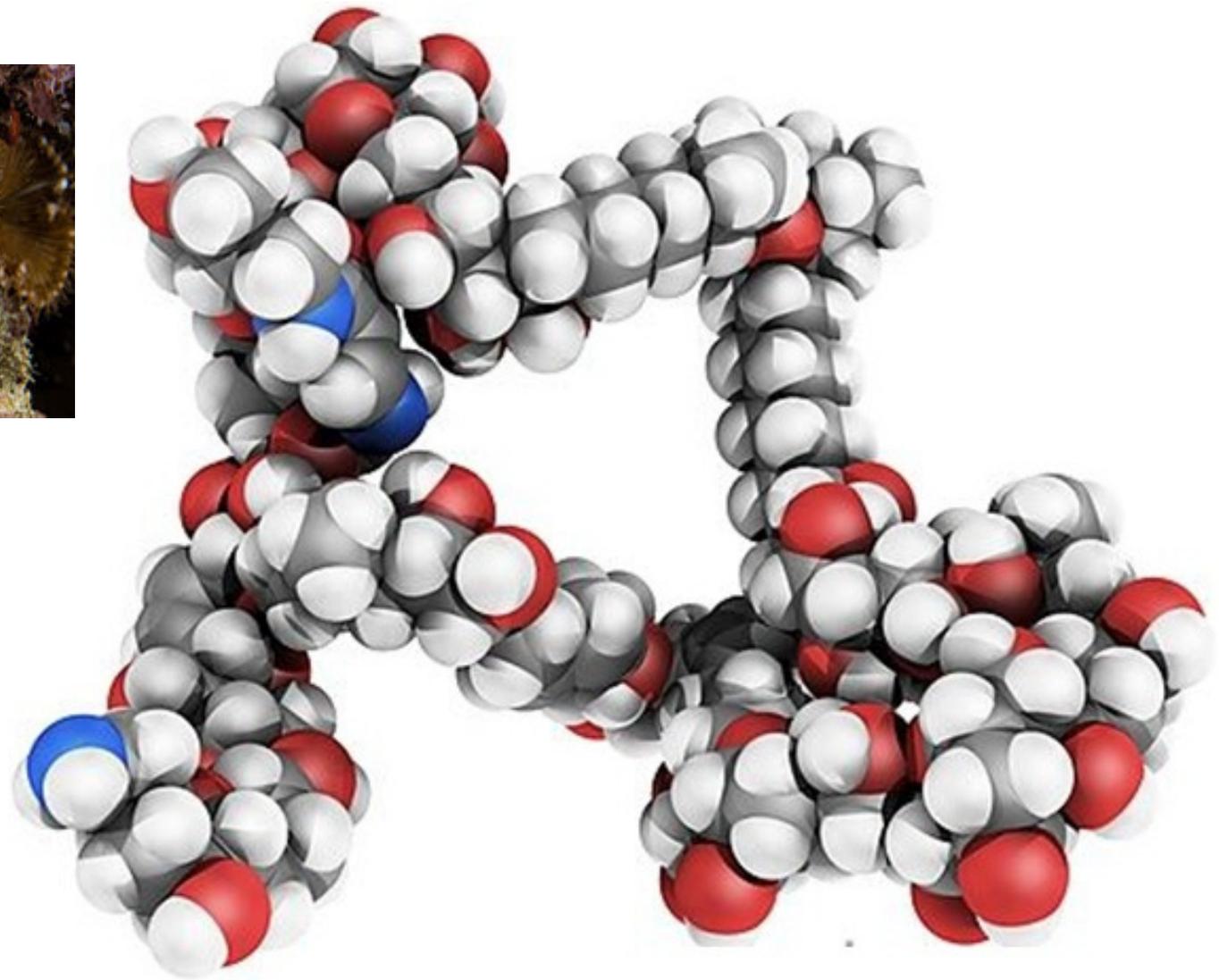
* *J. Am. Chem. Soc.* **1994**, *116*, 11205



Estrutura 3D da palitoxina

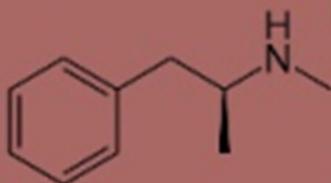


Palythoa sp





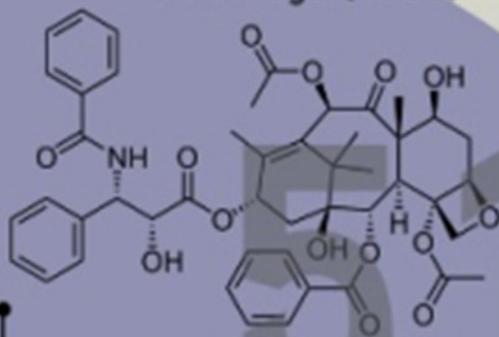
How many steps does it take?



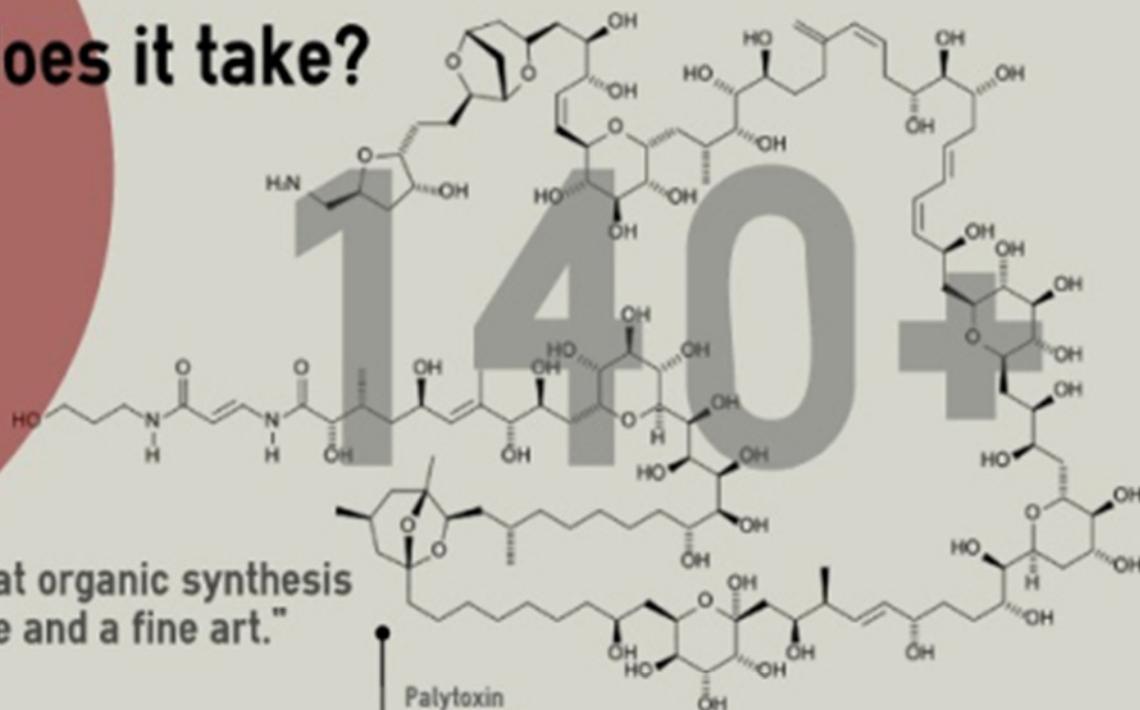
Methamphetamine
Illicit drug
Molecular weight: 149 g/mol
Stereocentres: 1
Possible stereoisomers: 2
Synthesised in 2 steps from pseudoephedrine

"It is sometimes said that organic synthesis is both an exact science and a fine art."

A. Fredga (1965)

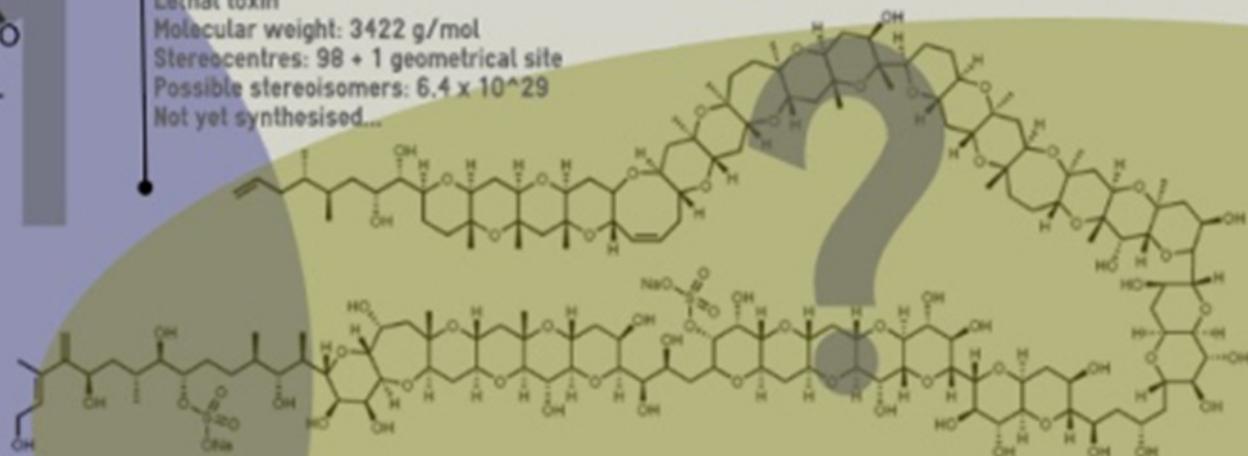


Paclitaxel (Taxol)
Anticancer drug
Molecular weight: 854 g/mol
Stereocentres: 11
Possible stereoisomers: 2048
Synthesised in 51 steps (Nicolaou)



Palytoxin
Lethal toxin
Molecular weight: 2680 g/mol
Stereocentres: 64 + 7 geometrical sites
Possible stereoisomers: 2.4×10^{21}
Synthesised in 39 steps from 7 precursors (140+ steps total) (Kishi)

Maitotoxin
Lethal toxin
Molecular weight: 3422 g/mol
Stereocentres: 98 + 1 geometrical site
Possible stereoisomers: 6.4×10^{29}
Not yet synthesised...





Patrimônio genético brasileiro





chave



fechadura

