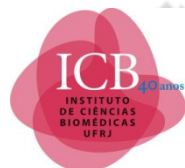




Produtos Naturais em Química Medicinal



Eliezer J. Barreiro

Professor Titular



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

Parte 2

24/01/2017

Laboratório de Avaliação e Síntese de Substâncias Bioativas

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



Laboratório de Avaliação e Síntese de Substâncias Bioativas



Sumário; *Produtos Naturais em Química Medicinal*

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 décano 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



Carbohydrate moiety



1785

William Withering
(1741-1799)

Digitalis lanata



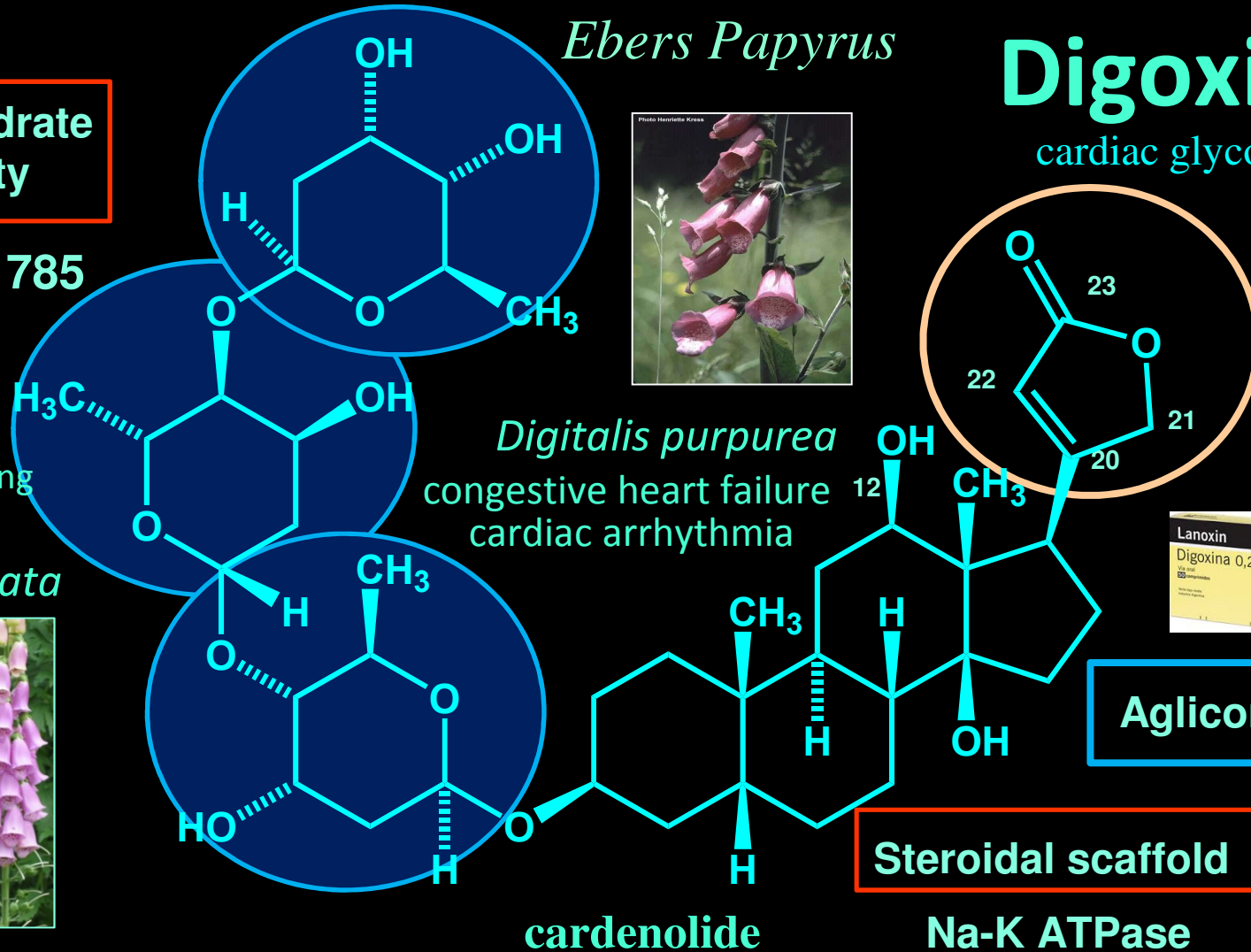
Ebers Papyrus



Digitalis purpurea
congestive heart failure
cardiac arrhythmia

Digoxina

cardiac glycoside



Old molecule, new receptors...

α -subunit of the Na⁺/K⁺ ATPase pump in the membranes of heart cells

Digoxin inhibit the hypoxia-inducible factor 1 (HIF-1) in 88% at 0.4 μ M &

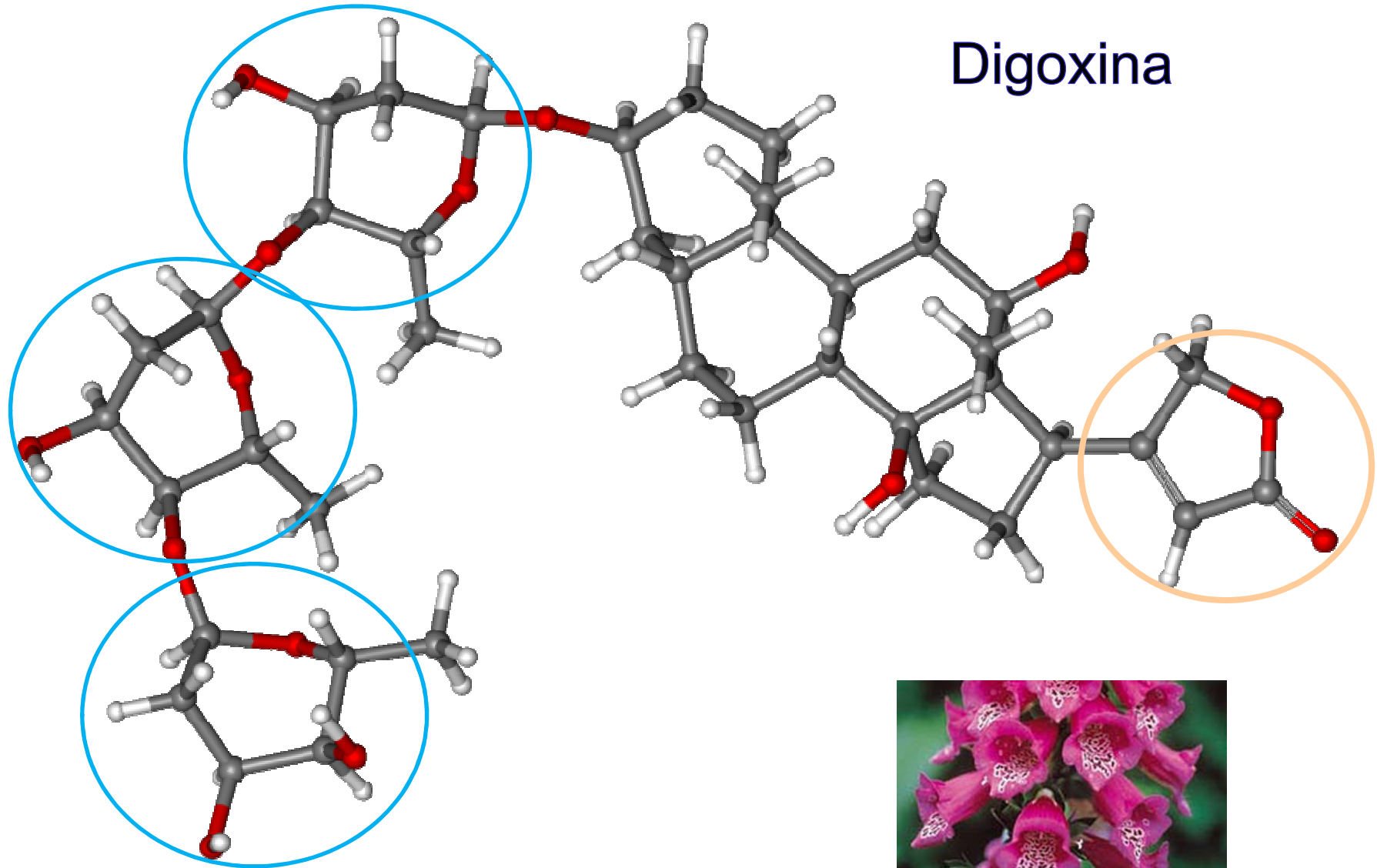
Digoxin inhibit interleukin-17 *

& H Zhang *et al.*, Digoxin and other cardiac glycosides inhibit HIF-1 α synthesis and block tumor growth, *PNAS* **2008**, *115*, 19579

* JR Huh *et al*, Digoxin and its derivatives suppress TH17 cell differentiation by antagonizing ROR γ t activity, *Nature* **2011**, *472*, 486

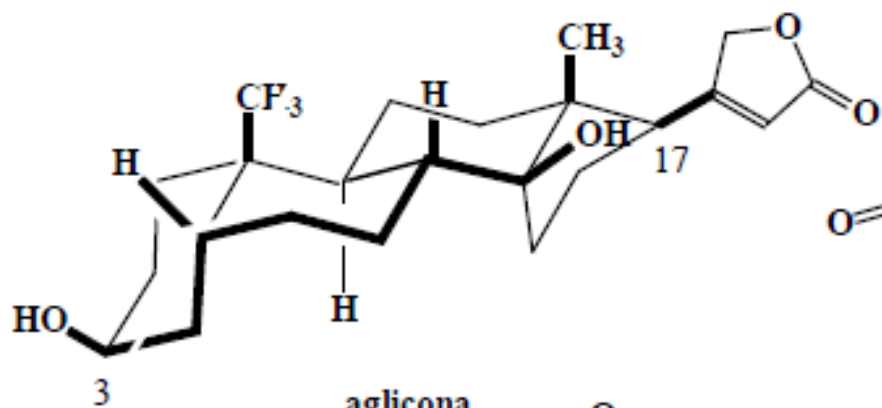


Aspectos conformacionais

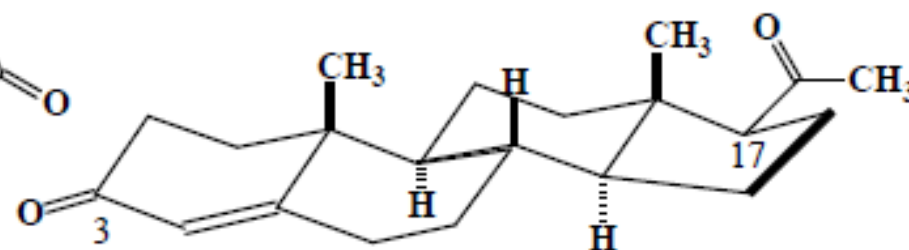
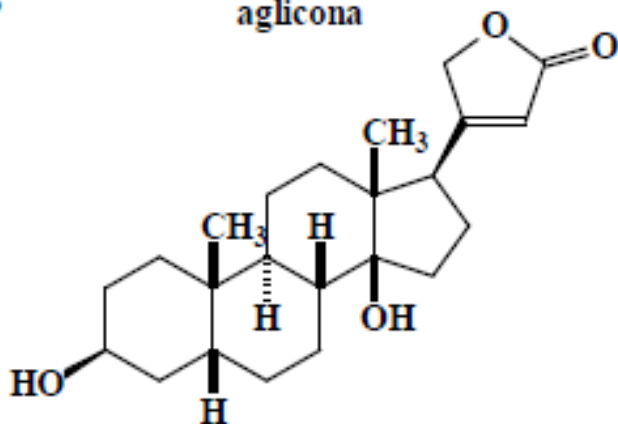




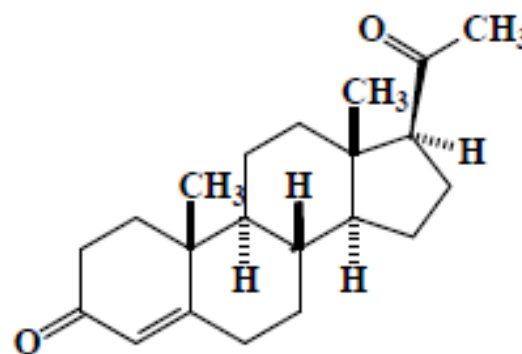
A importância da conformação



aglicona

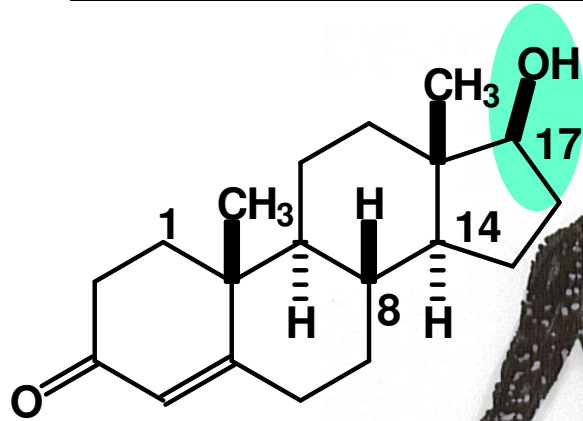


progesterona



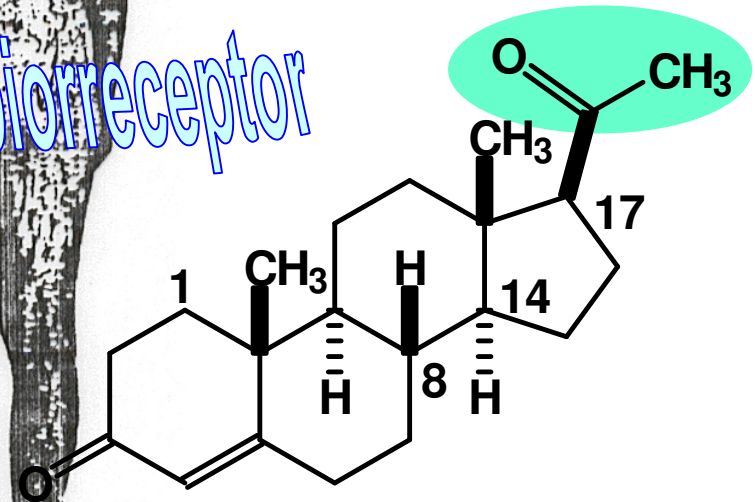


Similaridade Molecular



testosterona

no reconhecimento molecular pelo biorreceptor

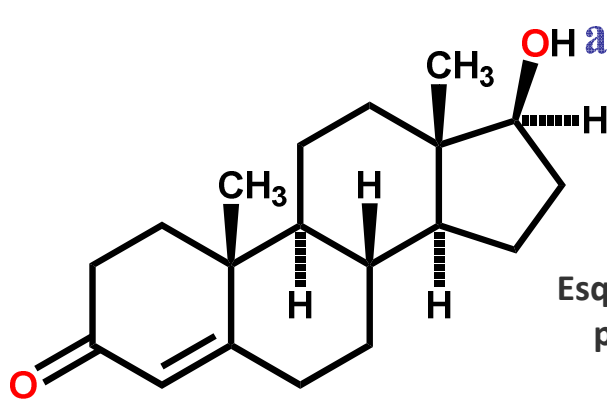


progesterona





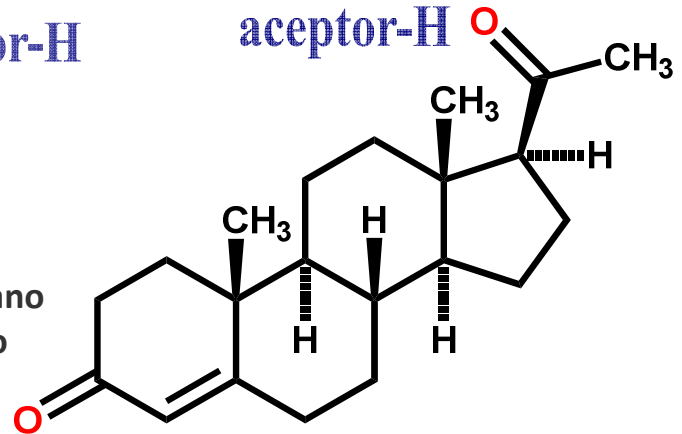
Similaridade Molecular



Testosterona

C₁₉

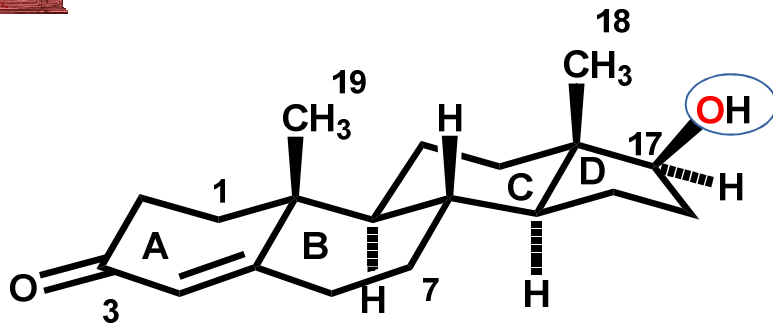
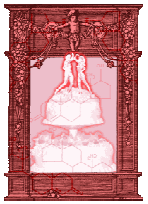
Esqueleto ciclopentano peridrofenantreno



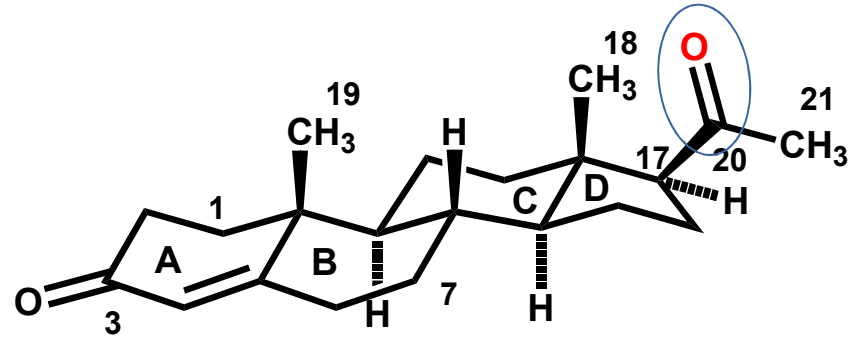
Progesterona

C₂₁

similaridade molecular



B/C C/D trans



B/C C/D trans



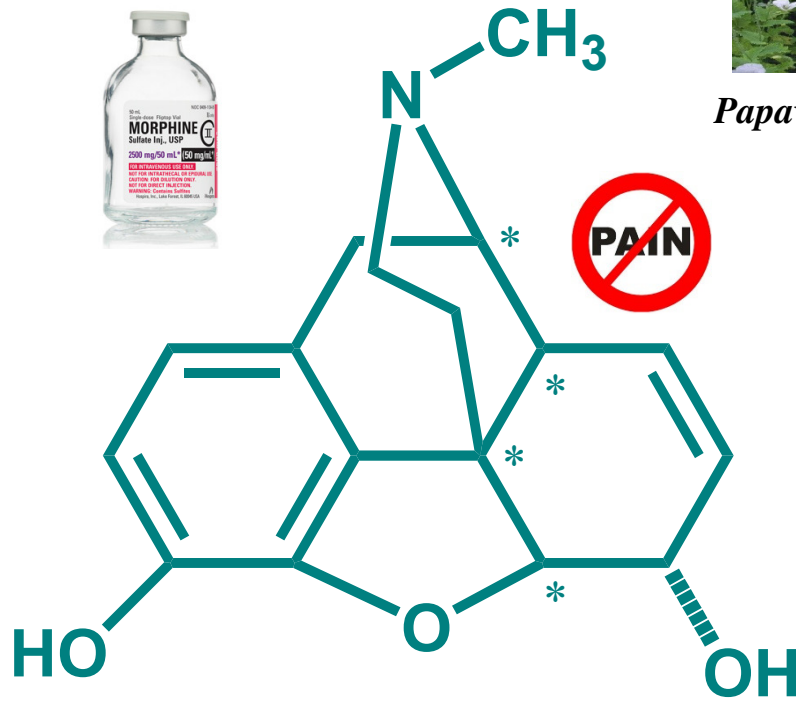
Moléculas pioneiras...

Alcaloides

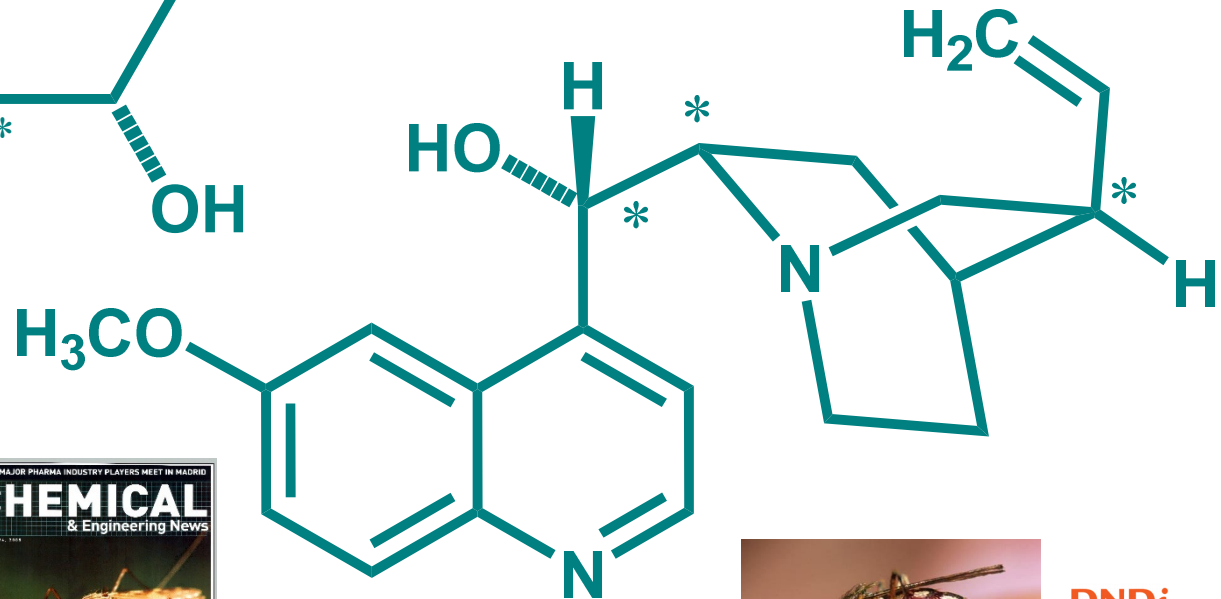
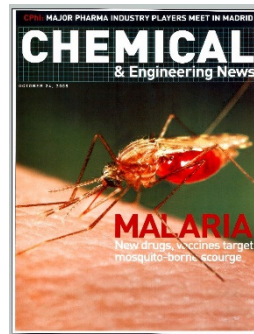




Papaver somniferum



Alcalóides = alcalinos = bases nitrogenadas naturais



MMV Medicines for Malaria Venture



DNDi



Moléculas pioneiras...

*Papaver
somniferum*

CH₃ Alcaloides

Emetina (1817)
Codeína (1932)
Papaverina (1848)

Friedrich Sertürner



1804

(1783-1841)

Sir Robert Robinson



1947



1886-1975

Marshall D. Gates, Jr.



1915-2003

University of Rochester

HO

morfina

C₁₇H₁₉NO₃

OH

1952*

* 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

From morphine to 4-phenylpiperidines

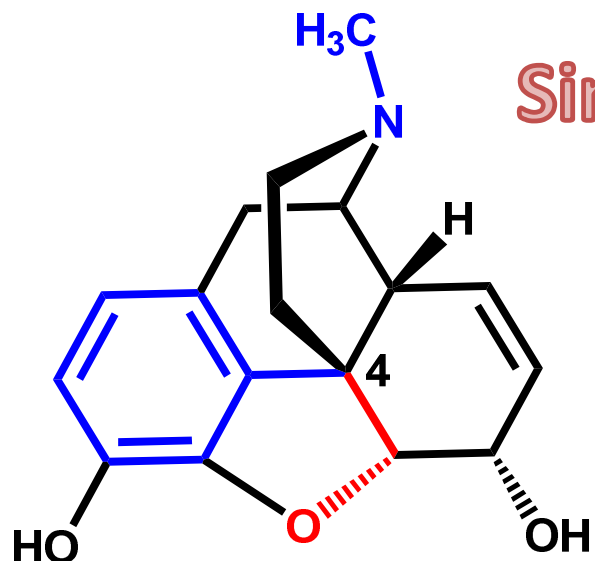
Química Medicinal

Simplificação molecular

Hipnoanalgésicos sintéticos

Metabolic-Soft moiety

Striptease molecular

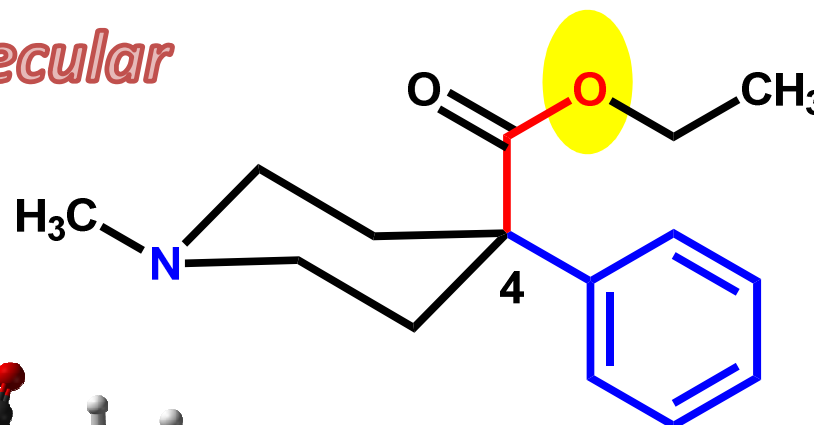
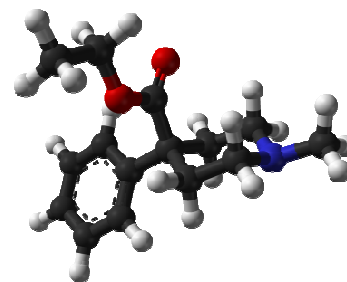


morfina

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

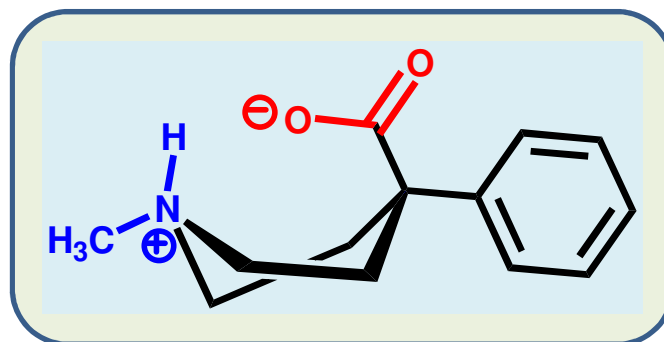


SM
⇒



meperidina
1939

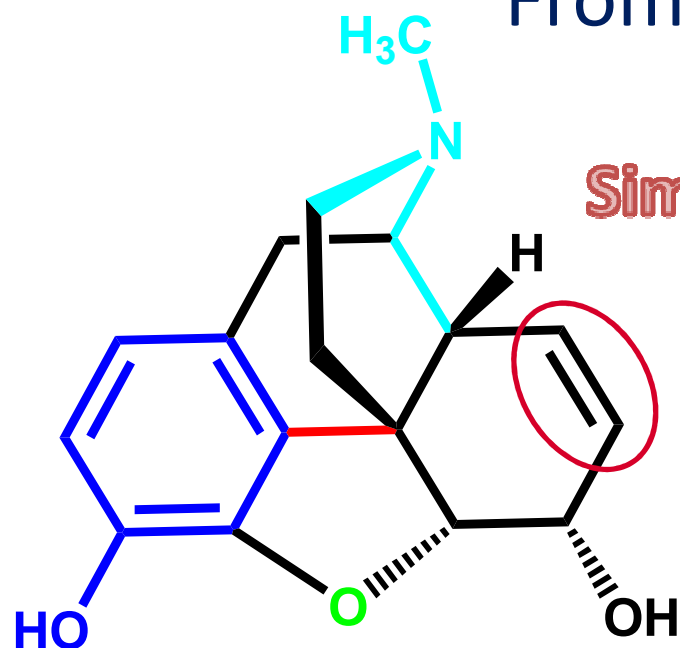
$C_{15}H_{21}NO_2$
PM = 247,2
 μ -opioid agonist





Da morfina ao tramadol

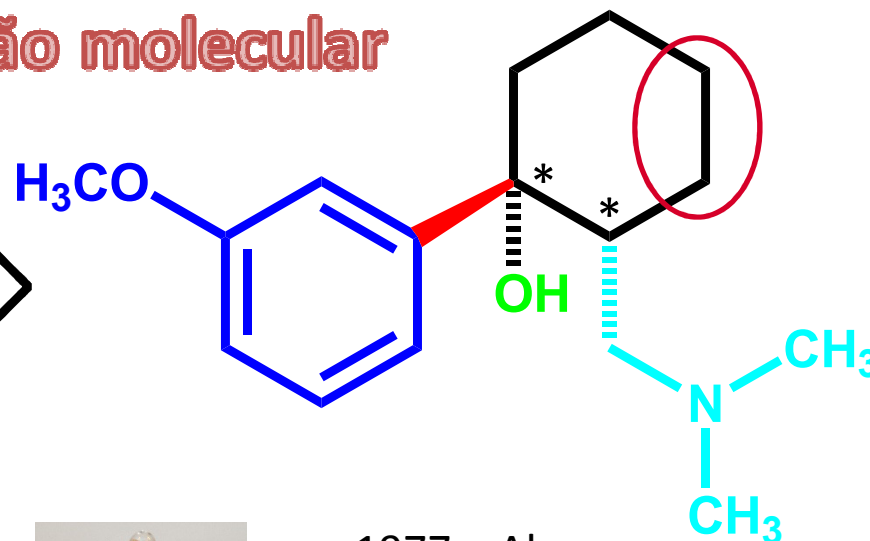
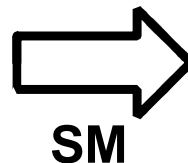
From morphine to tramadol



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

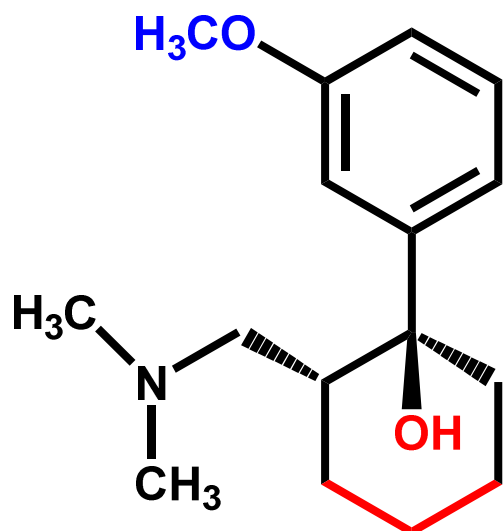
μ -opioid agonist



Da morfina ao tapentadol

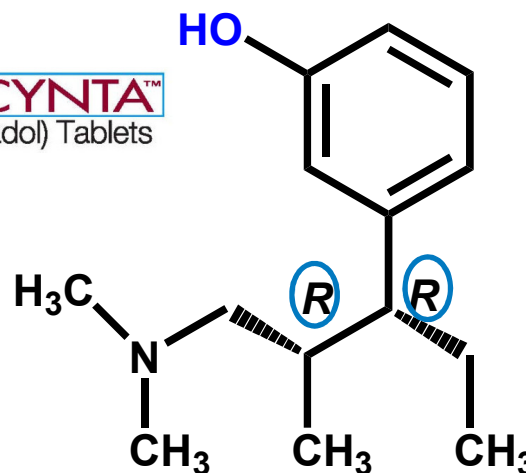


1980 - Helmut Buschmann



tramadol

NUCYNTA™
(tapentadol) Tablets

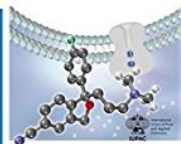


tapentadol

Química Medicinal

DUAL MECHANISM OF ACTION:
NOREPINEPHRINE REUPTAKE INHIBITOR
AND μ-OPIOID RECEPTOR AGONIST

Edited by Janos Fischer,
C. Robin Ganellin and David P. Rotella
WILEY-VCH
Analogue-based
Drug Discovery III

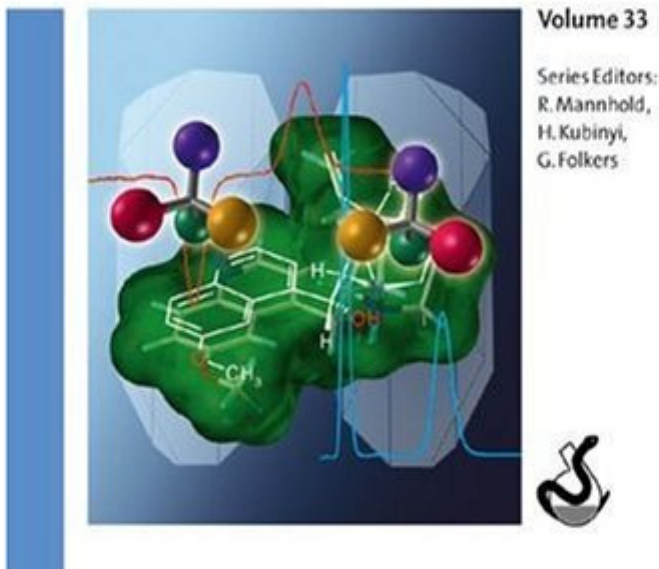


50mg dose of tapentadol (p.o.) = 30mg of morphine (p.o.) / 3mg of morphine (i.v.)

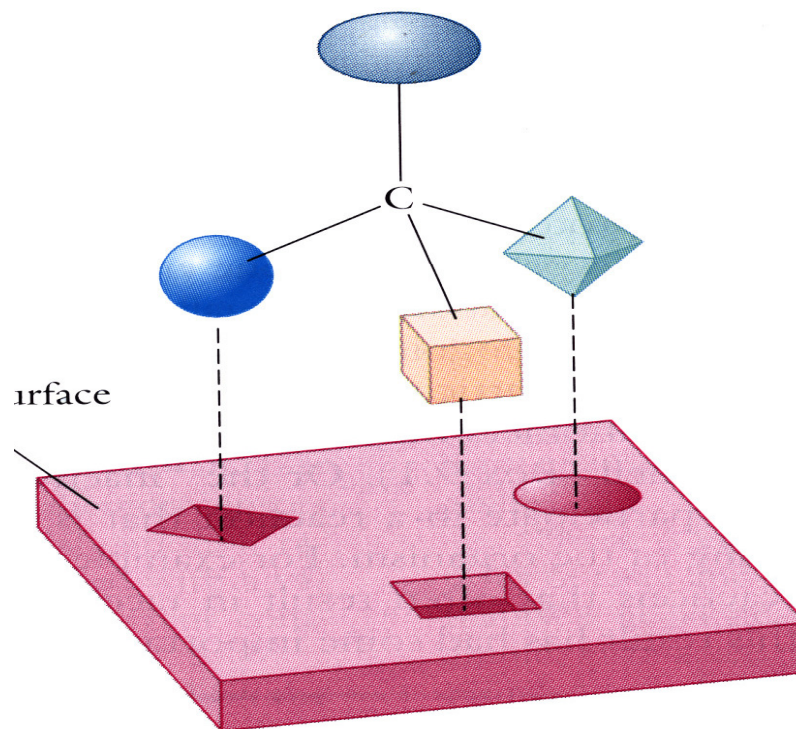
Helmut Buschmann. Tapentadol – From Morphine and Tramadol to the Discovery of Tapentadol. in Analogue-based Drug Discovery III, Edited by Janos Fischer, C. Robin Ganellin, and David P. Rotella. Wiley, 2013.



A quiralidade dos produtos naturais



Reconhecimento molecular



Other enantiomer does not fit enzyme active site

Modelo dos três pontos

Modelo de Easson-Stedman



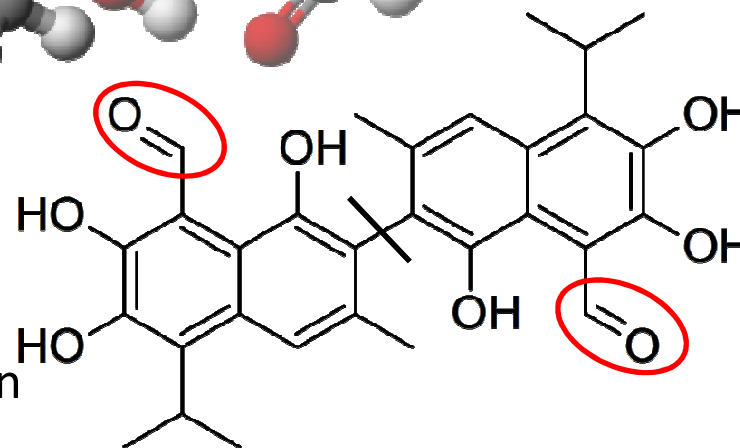
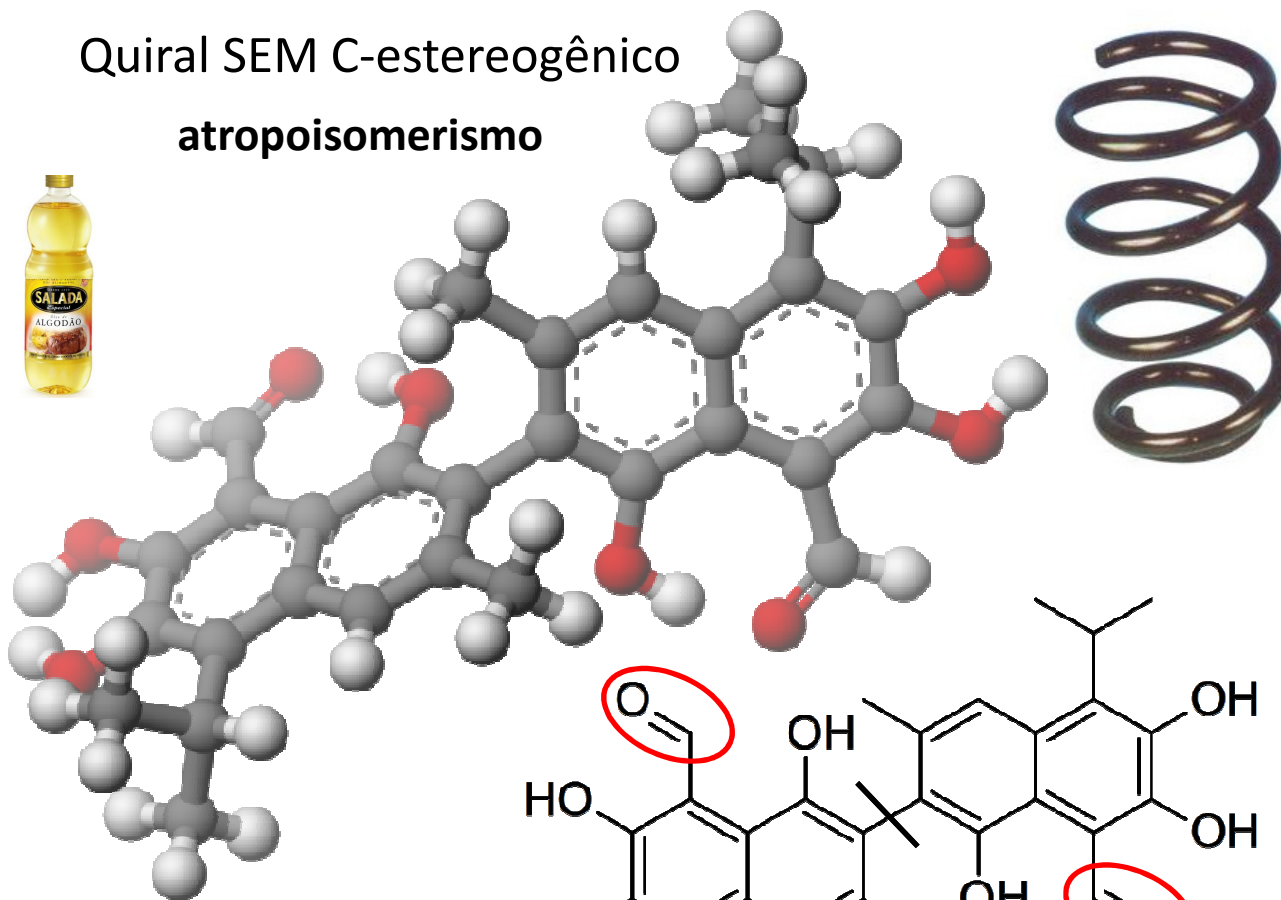
Gossipol

Gossypium hirsutum



Quiral SEM C-estereogênico

atropoisomerismo



AR Santos, AC Pinheiro, ACR Sodero, AS Cunha, MC Padilha, PM Sousa, SP Fontes, MP Veloso, CAM Fraga, Atropoisomerismo: o efeito da quiralidade axial em substâncias bioativas, *Quim Nova* **2007**, *30*, 125.

Stephen A. Matlin

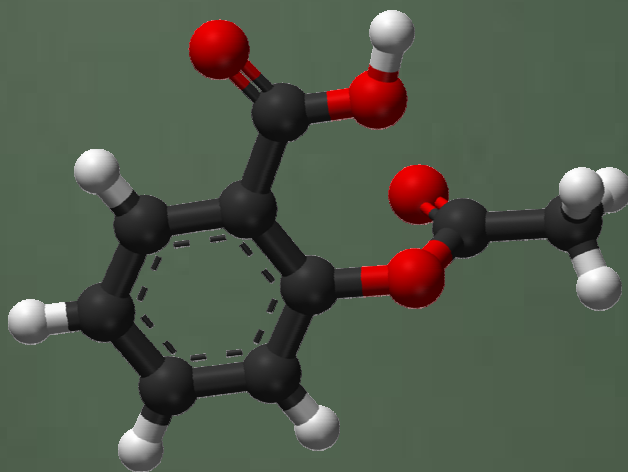


Institute of Global Health Innovation,
Imperial College London, UK;
Head of Strategic Development for the
International Organization for Chemical
Sciences in Development.

[Imperial College London](http://www.imperial.ac.uk)



Moléculas pioneiras (2)



AAS



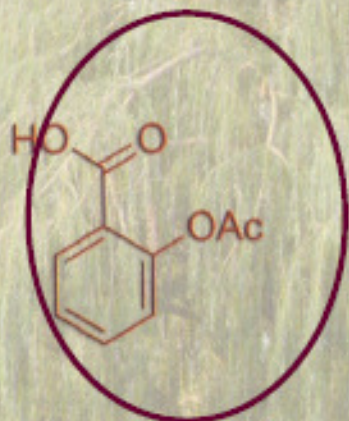


Mais de plantas & analgésicos...

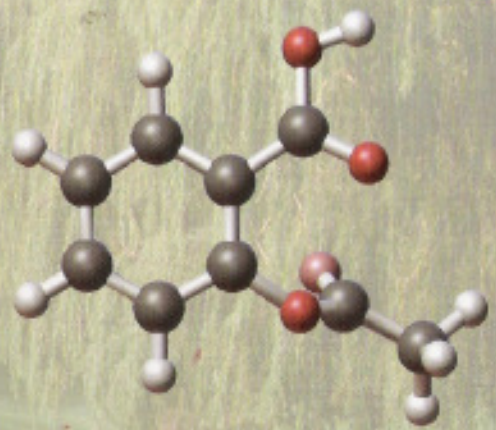
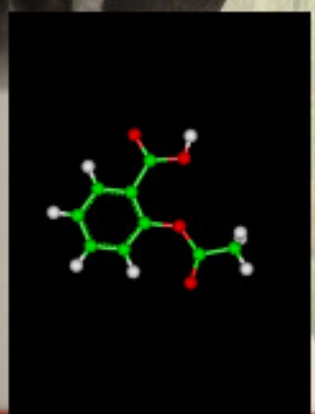


ácido acetilsalicílico

1899



- 1876 – TJ McLogan extrai a salicina
- 1853 – AAS sintetizado por CF Gerhardt
- 1897 – Felix Hoffmann & Heinrich Dreser
- 1899 – Aspirina[®]
- 1980 – mecanismo de ação
- 1982 – Prêmio Nobel
- 1990 – D Simmons & WL Xie
- 1999 – Coxibes
- 2002 – COX-2i & câncer



Aspirin[®]



Spirea sp



1839 – *Spirea sp*

1853 – Charles Gerhardt AAS

1876 – salicina → AS

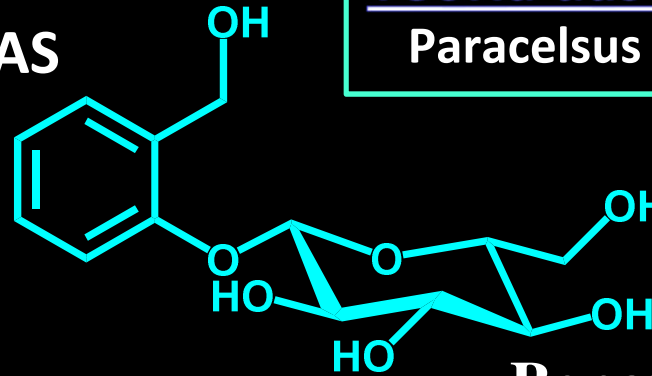
1897 – Arthur Eichengrün,
Heinrich Dreser,
Felix Hoffmann



1899 – AAS lançado Bayer

Teoria das Assinaturas

Paracelsus (1493-1541)

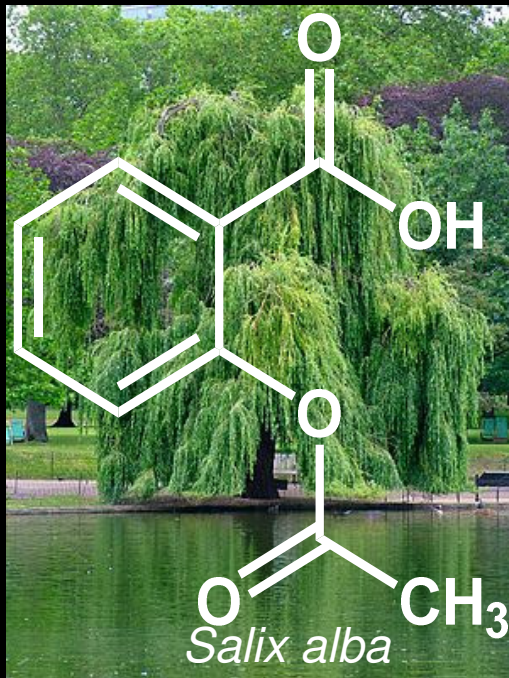
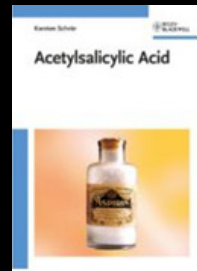


1982

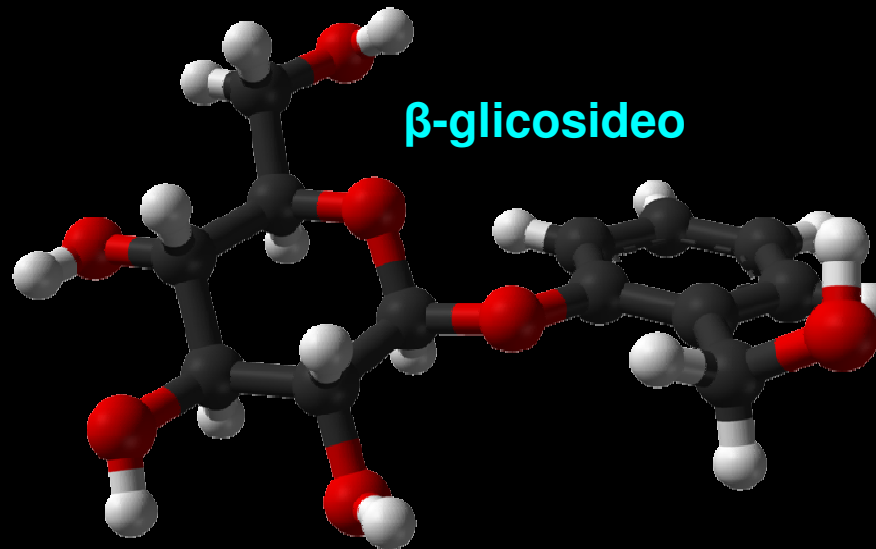
Bengt I. Samuelsson

Sune K. Bergström

John R. Vane



Acetatos famosos



β -glicosideo





Molécula pioneira

Ácido acetilsalicílico

AAS



Sune K. Bergström

(1916-2004)

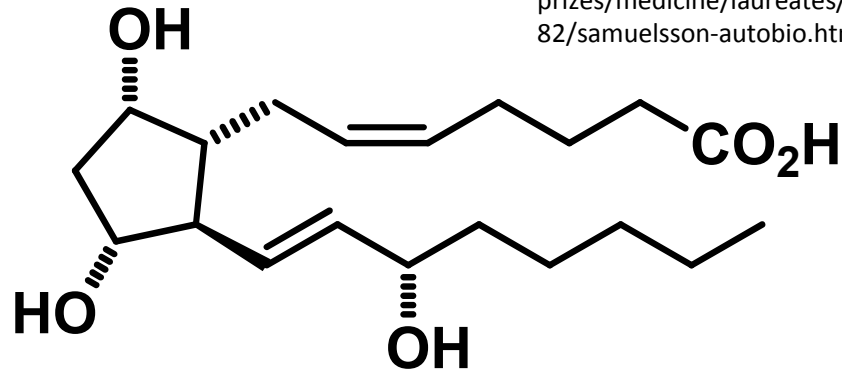
http://nobelprize.org/nobel_prizes/medicine/laureates/1982/bergstrom-autobio.html



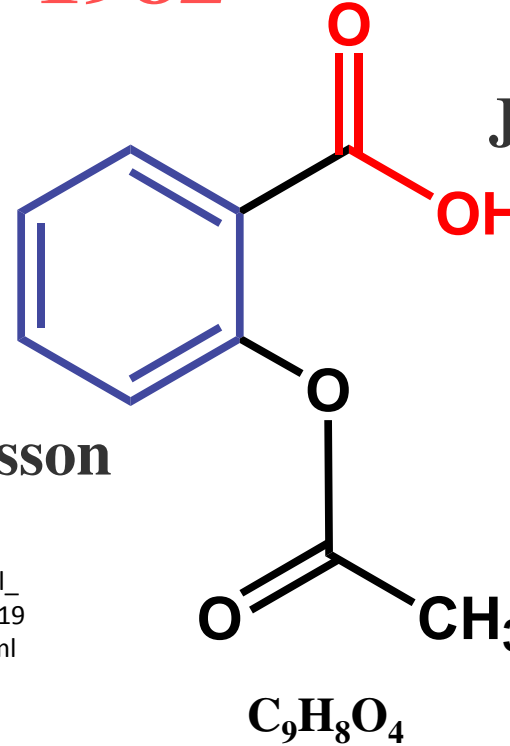
Bengt I. Samuelsson

(1934-)

http://nobelprize.org/nobel_prizes/medicine/laureates/1982/samuelsson-autobio.html



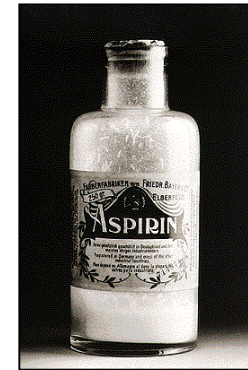
1982



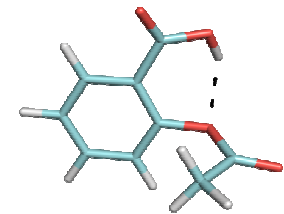
John R. Vane

(1927-2004)

http://nobelprize.org/nobel_prizes/medicine/laureates/1982/vane-autobio.html



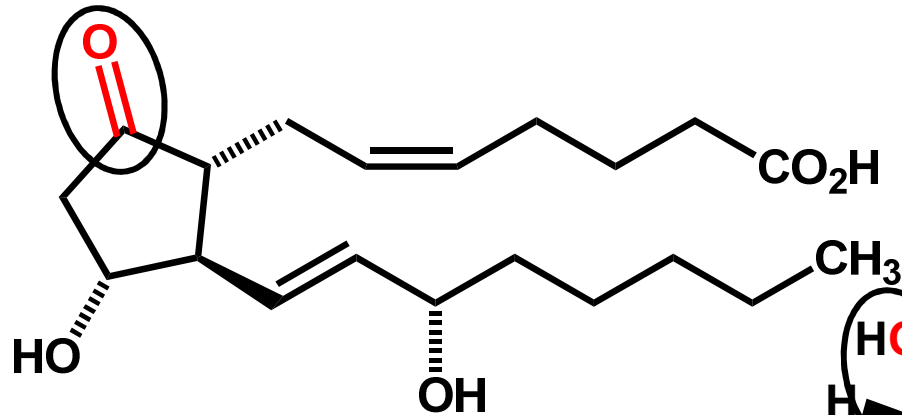
1889 ➡ 1982



AAS

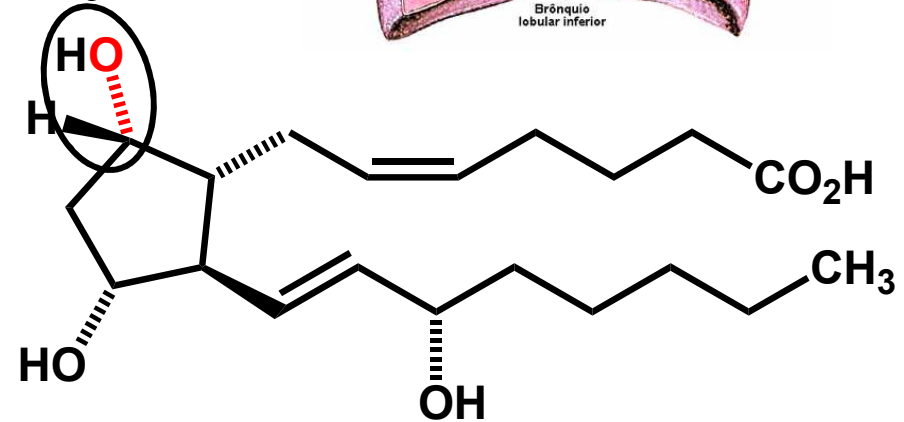
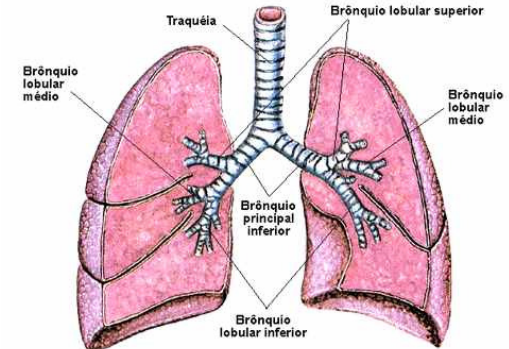


Icosanoides



PGE₂

PGF_{2α} em cães provoca intensa broncodilatação



PGF_{2α}

PGF_{2α} em cães provoca severa broncoconstrição

Similaridade X Dissimilaridade





Produtos Naturais em Química Medicinal

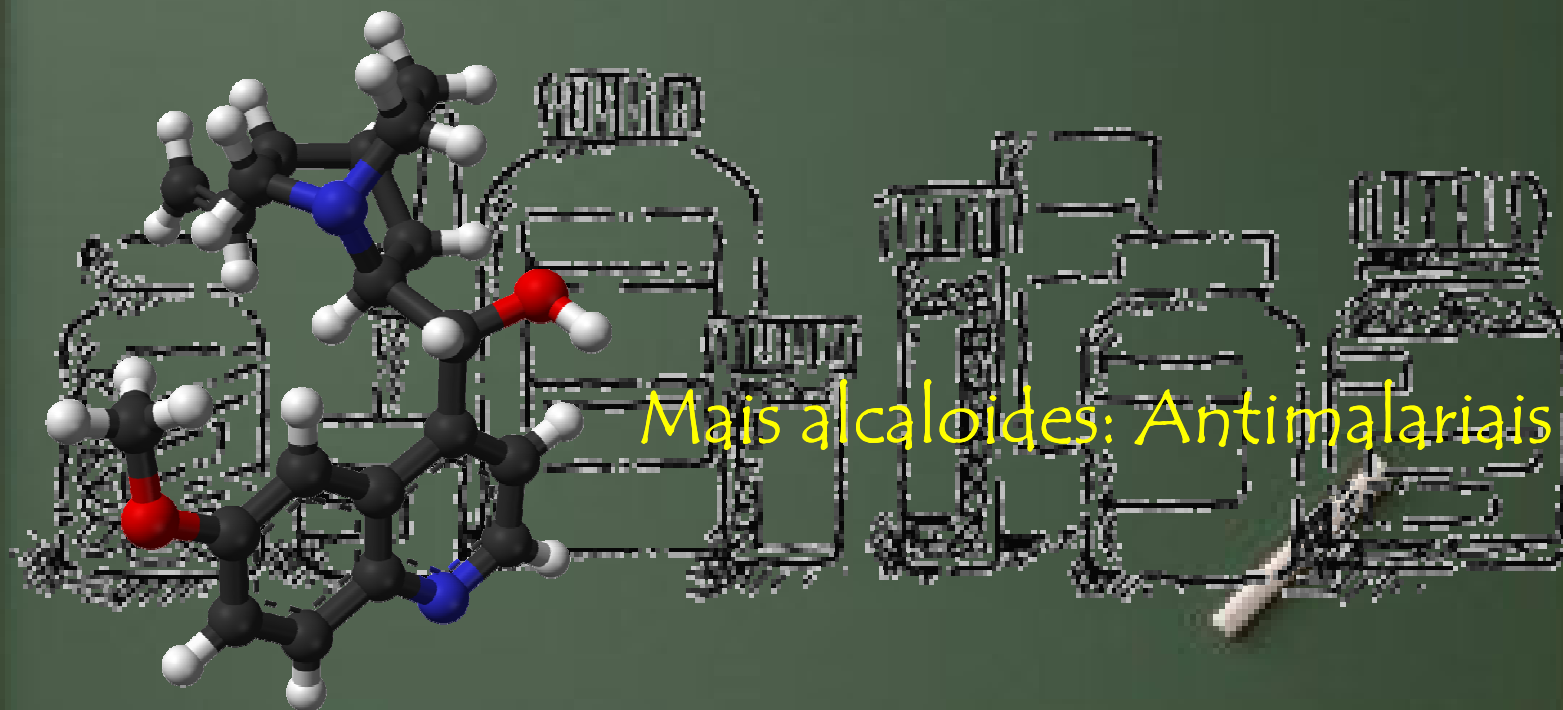
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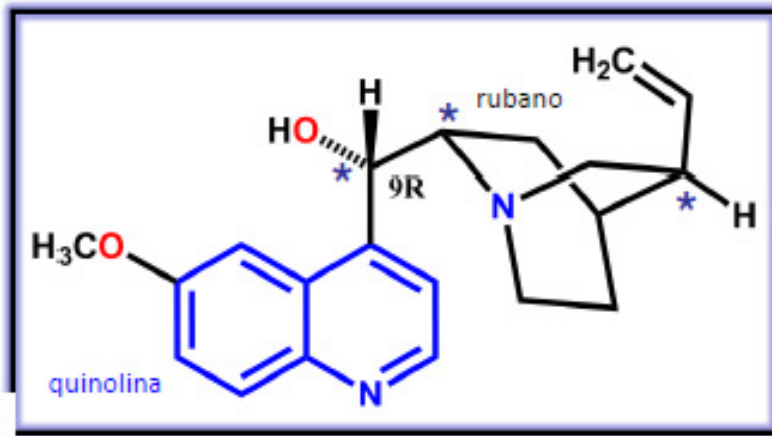
Moléculas pioneiras...

◊ Uma molécula das Américas.





As plantas e os parasitas



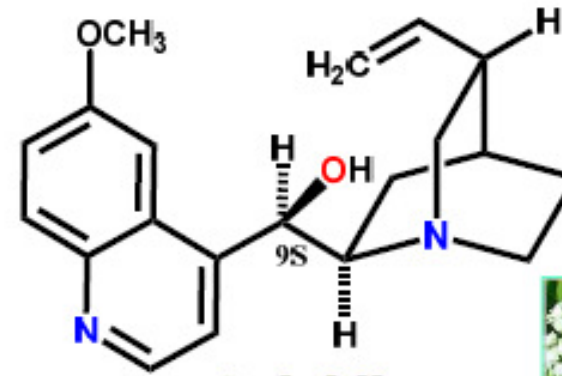
Quinina



1º Antimalárico (Farmacopéia Britânica, 1677);
 Isolada em 1820 por P.J. Pelletier & J. B. Caventou
 École de Pharmacie de Paris



Leia: M. Delepine, *J. Chem. Ed.* 1954, 28, 454

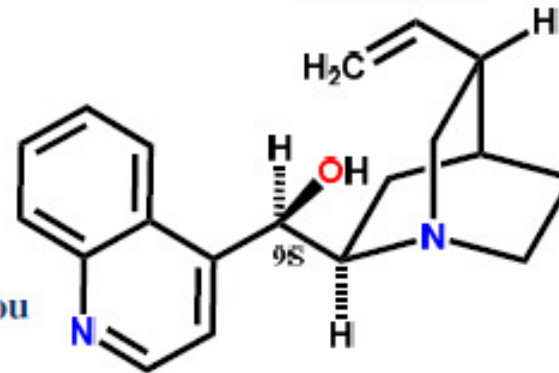


Quinidina

anti-arritmico



Cinchona officinalis



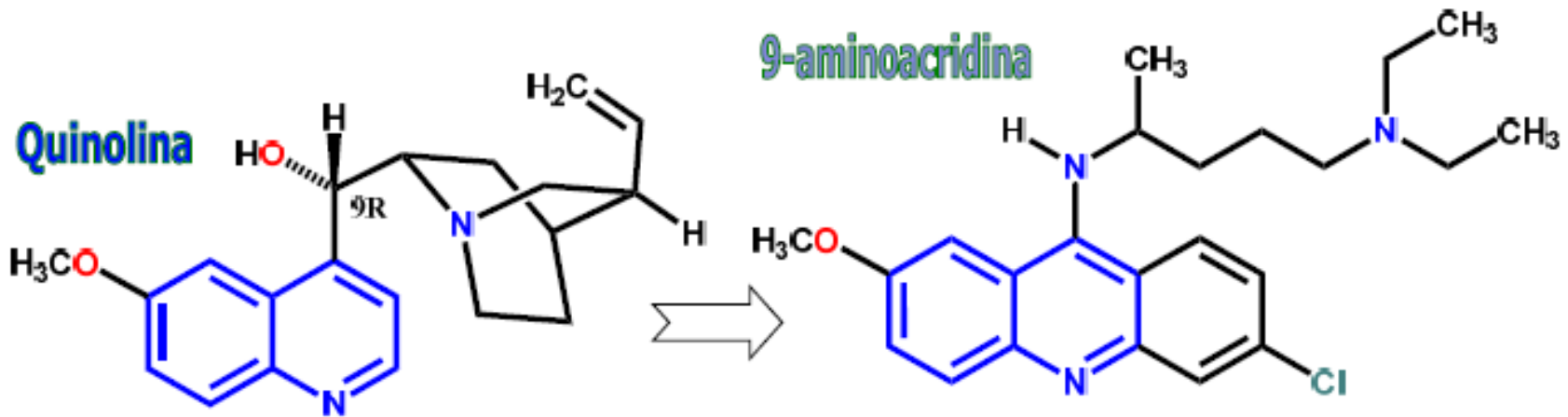
Cinchonina



Cinchonidina



Medicamentos antimaláricos



Quinina

1931

Mepacrina

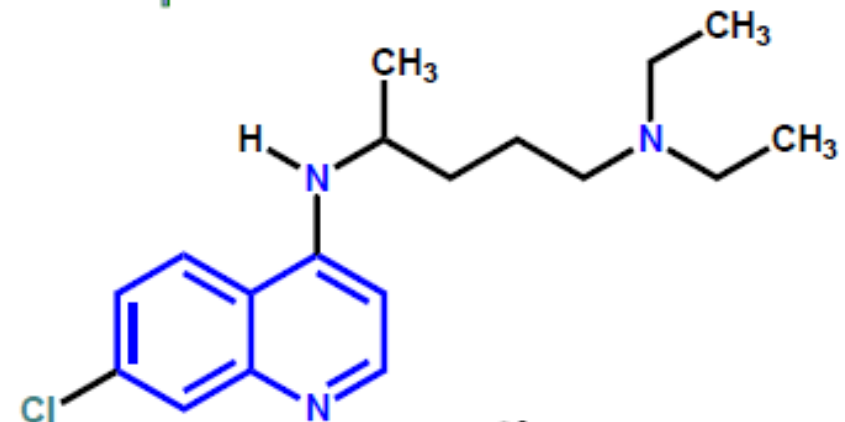
8-aminoquinolina

4-aminoquinolina



Primaquina

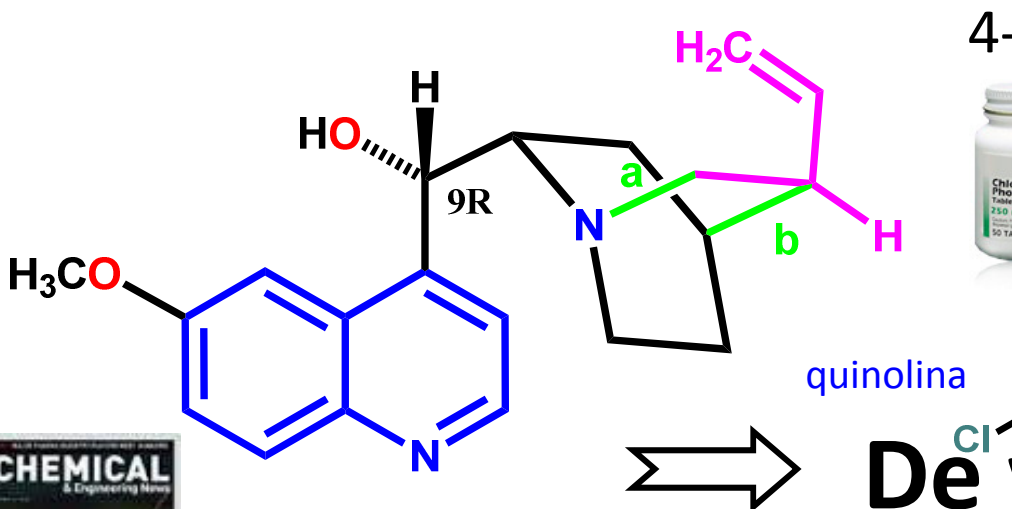
1946



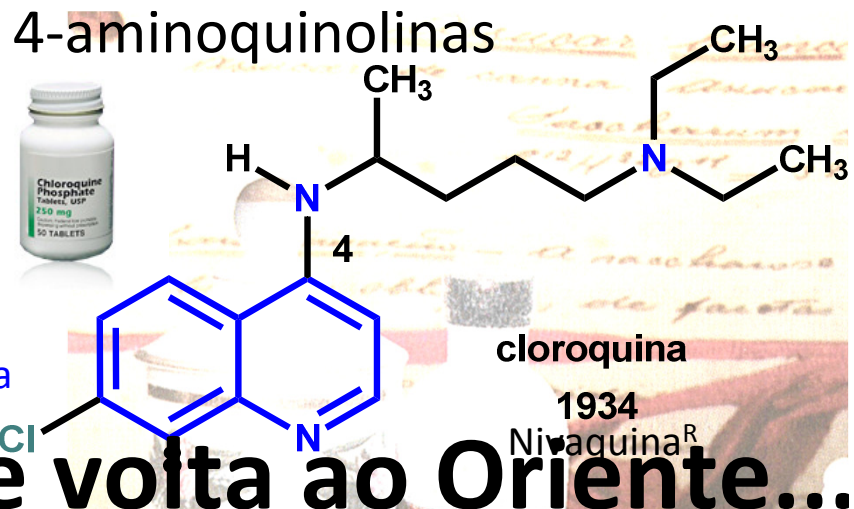
1934

Cloroquina

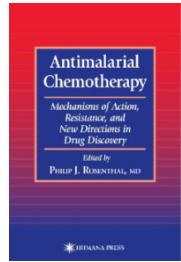




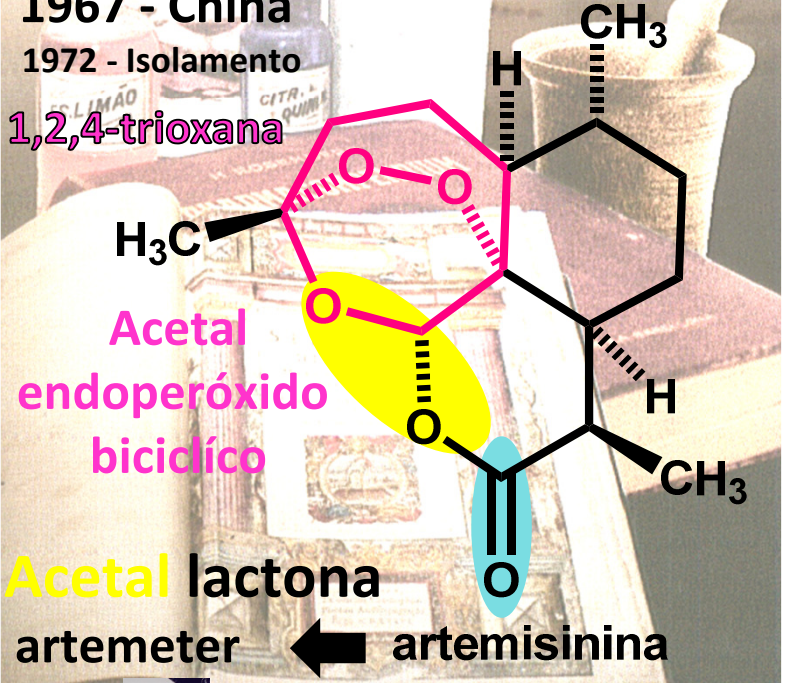
Quinina *Química Medicinal*



De volta ao Oriente...



1967 - China
1972 - Isolamento
1,2,4-trioxana



1985 - introd
1989 - FDA **sesquiterpeno**

$C_{15}H_{22}O_5$
GH Posner, Un J-H

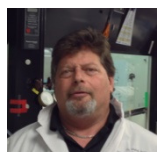
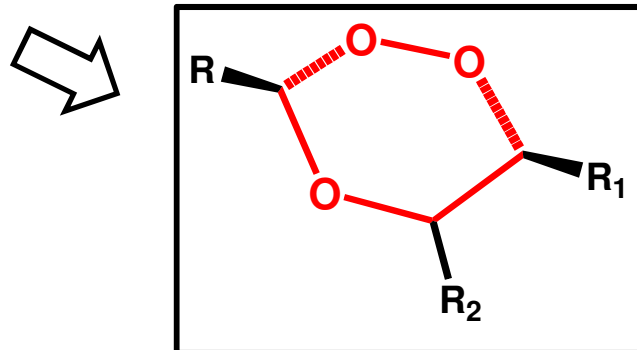
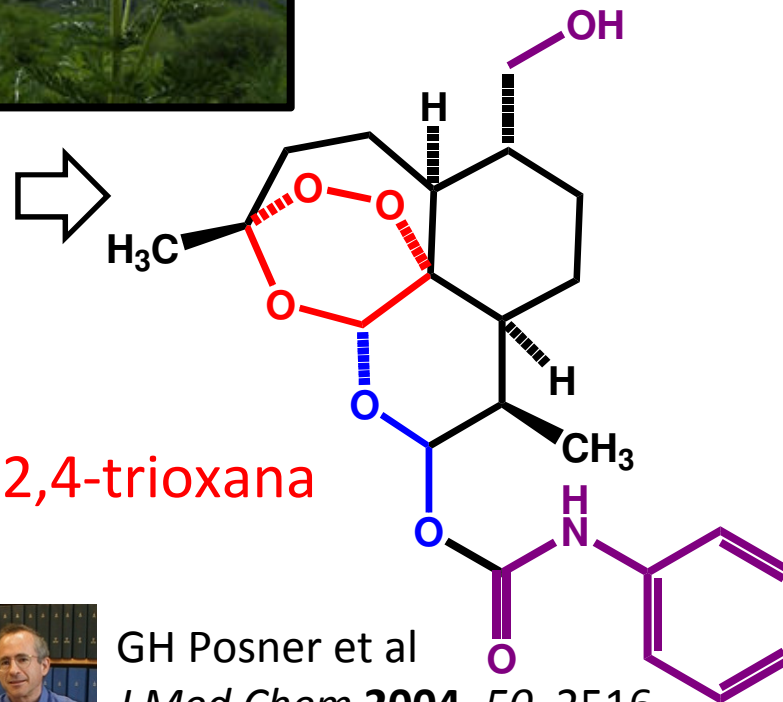
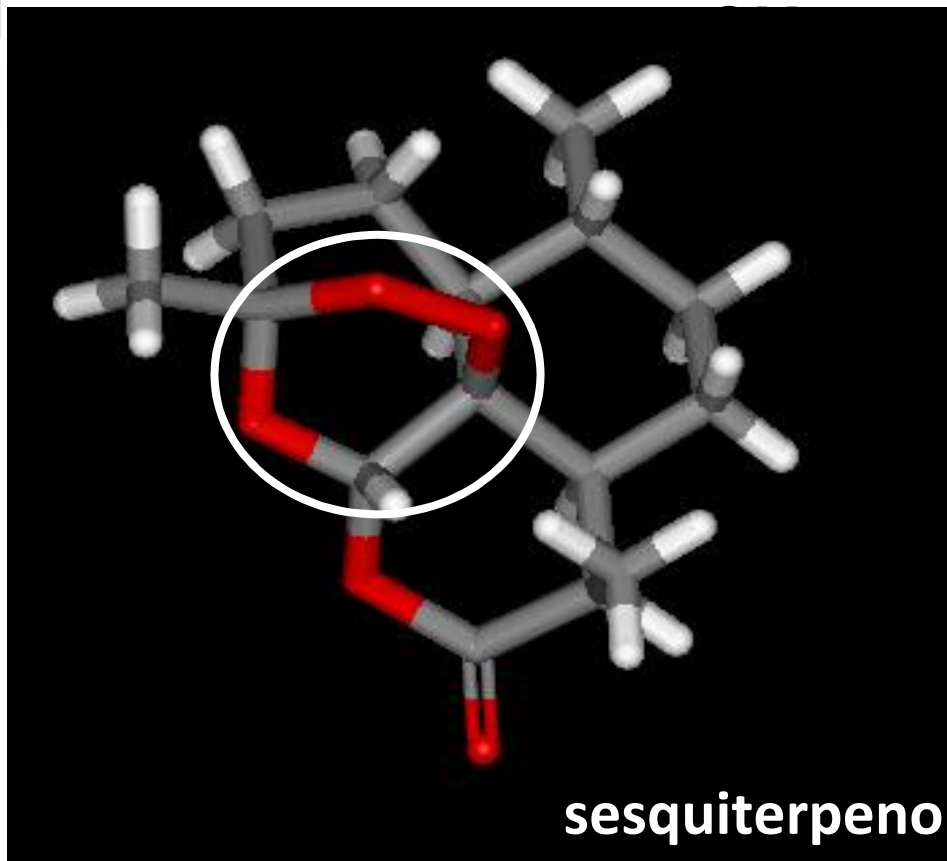


Artemisinina

Qinghaosu



Artemisia annua



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

MA Avery, M Alvim-Gaston, EJ Barreiro, FE Cohen, *J Med Chem* **2002**, 45, 292

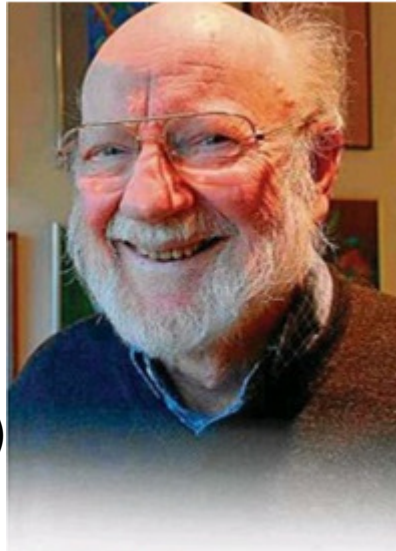




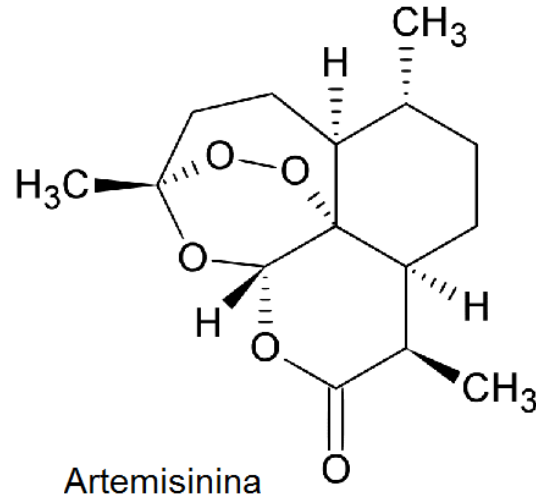
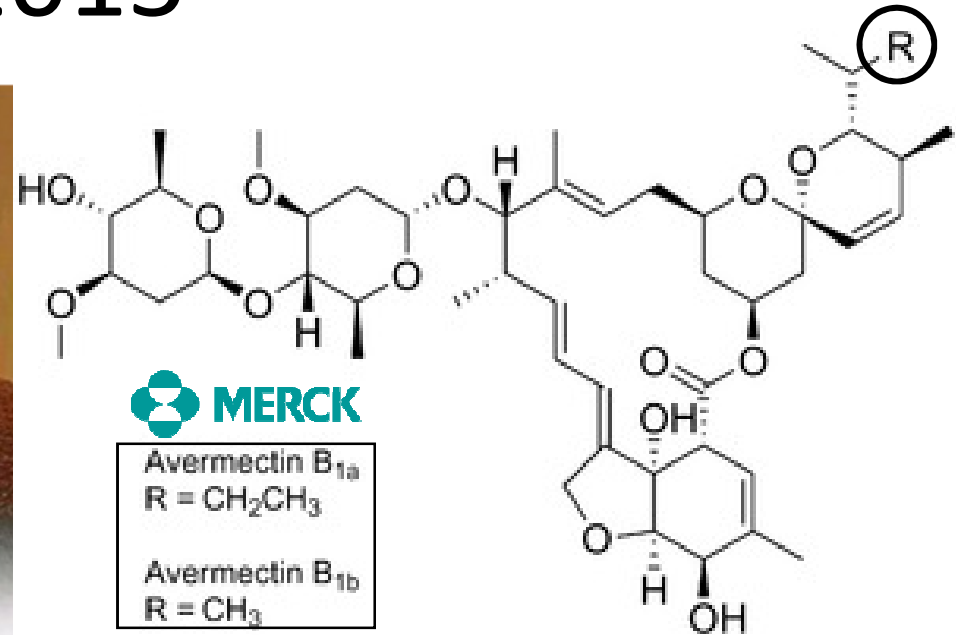
Prêmio Nobel de Medicina 2015



Satoshi Omura (Japão)



William C. Campbell (Irlanda)



Tu Youyou
(1930-)





Produtos Naturais em Química Medicinal

Sumário;

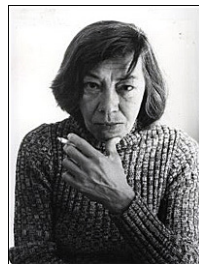
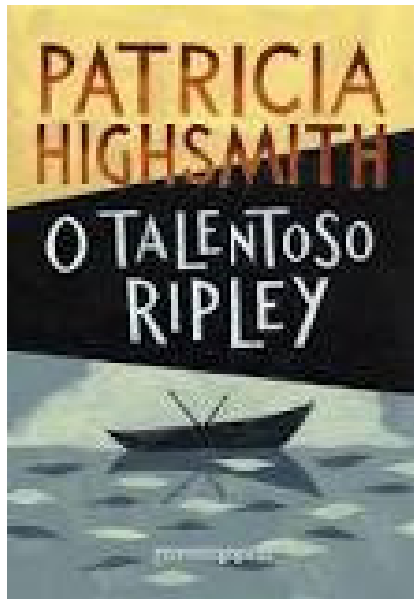
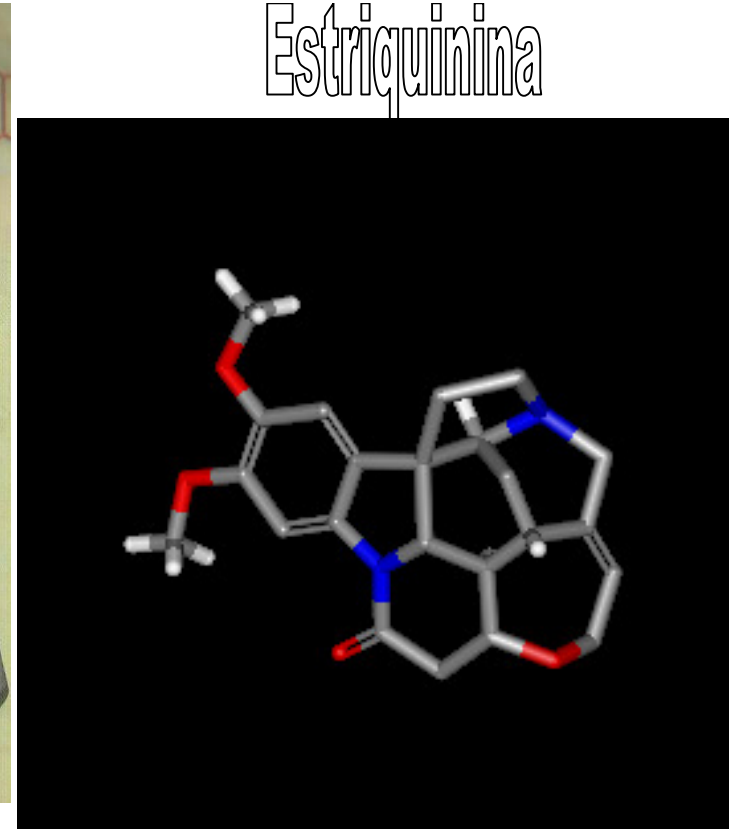
Preâmbulo; Bibliografia; **O início**: os PRODUTOS NATURAIS e o Brasil; Patrimônio genético **BRASILEIRO**; o fármaco dos Índios: bloqueadores **glanglionares**; Daniel Bovet; **captopril**; A **ORIGEM** dos fármacos; As **classes** dos PN's; **QUIMIODIVERSIDADE**; *quimiotipo*; CONCEITO de *hit-natural*; 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**; 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**; EPILOGO



Alcaloides



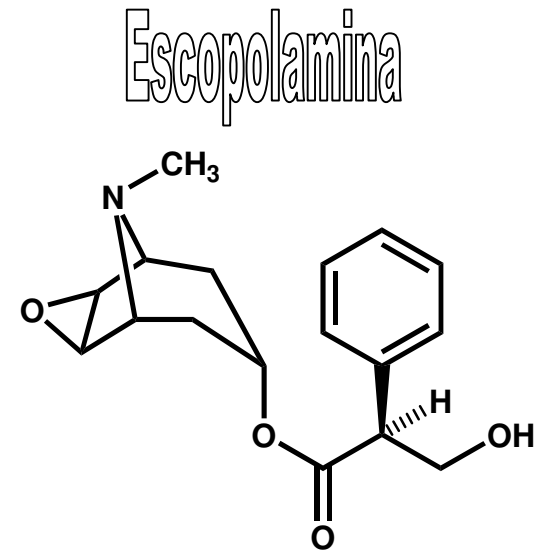
Strychnos nux vomica



(1921-1955)

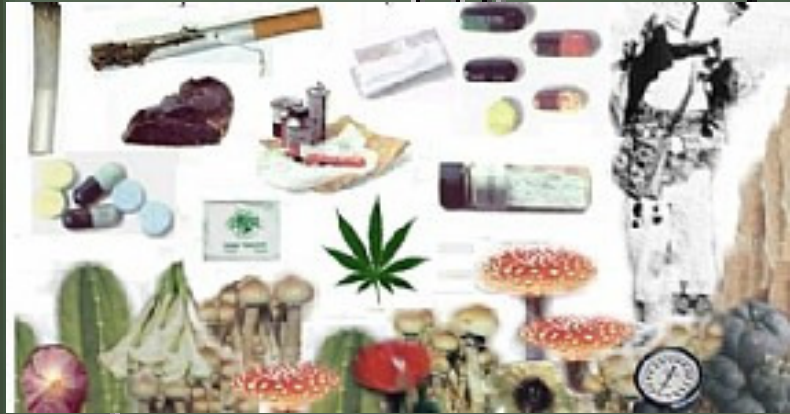


(1890-1976)





◆ Os PN's neuroativos
& afrodisíacos





Substâncias ativas no SNC

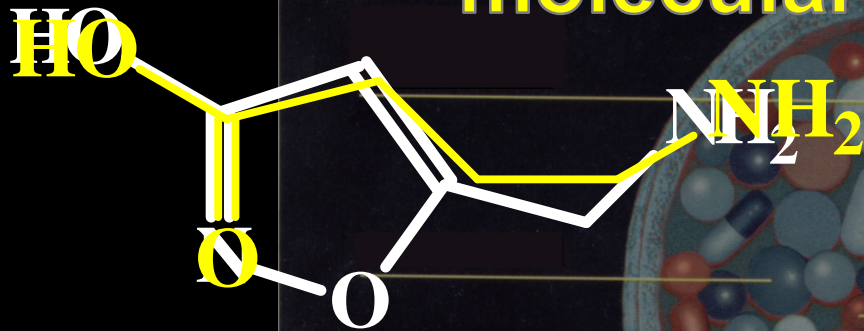
alucinogêno

Zé Ramalho



Amanita muscaria

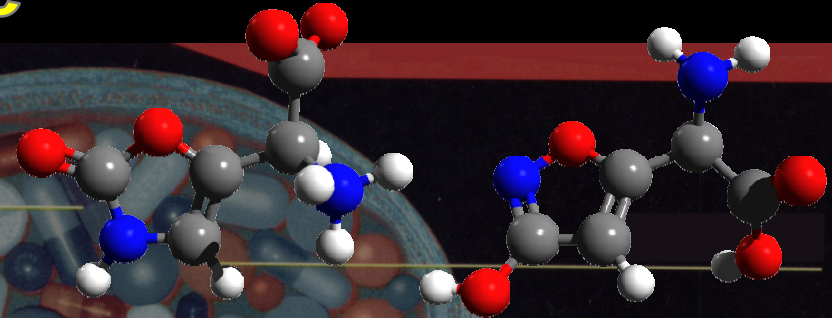
Similaridade molecular



ALCALOIDE

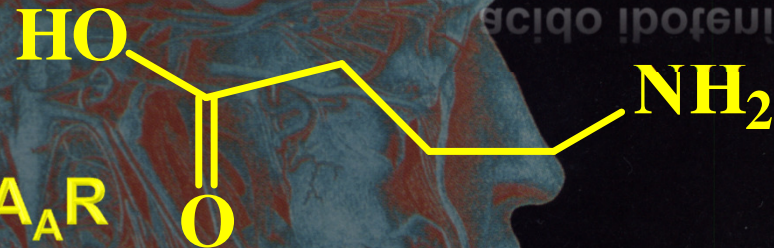
Muscimol

PSICOATIVA



muscazone

ácido ibotênico



GABA_AR

Ácido γ-aminobutírico

X. Chen, M. Decker, Multi-Target Compounds Acting in the Central Nervous System Designed From Natural Products, *Curr Med Chem* 2013, 20, 1673.

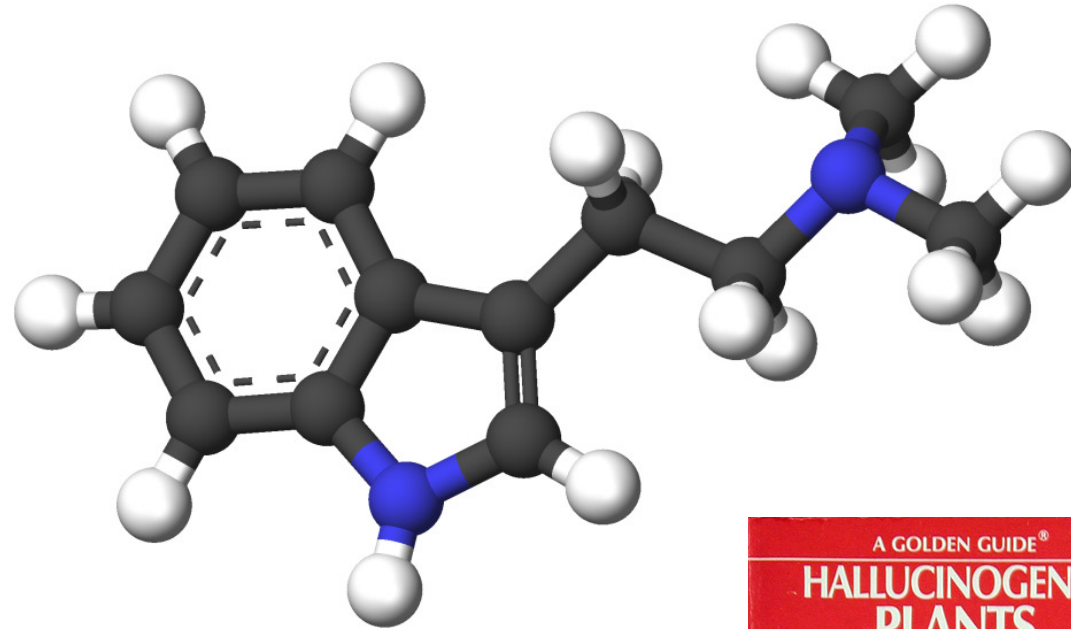


Alcaloides psicoativos

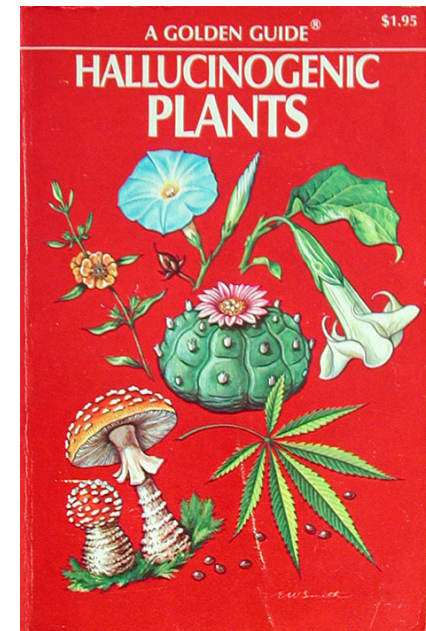
Triptaminas



Virola surinamensis



Acanthaceae, Aceraceae,
Apocynaceae, Fabaceae
(Leguminosae), Caesalpinioideae
subfamily, Malpighiaceae,
Myristicaceae (*Virola* spp),
Ochnaceae, Poaceae (Gramineae),
Polygonaceae, Punicaceae,
Rubiaceae, Rutaceae, Urticaceae

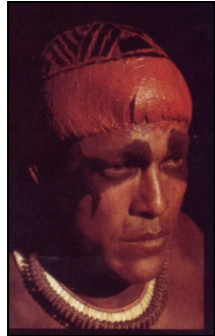




Alcaloides psicoativos

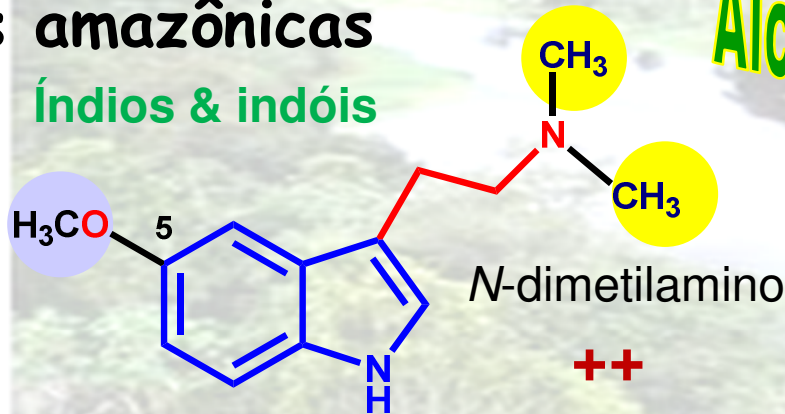
Virolas amazônicas

Índios & indóis



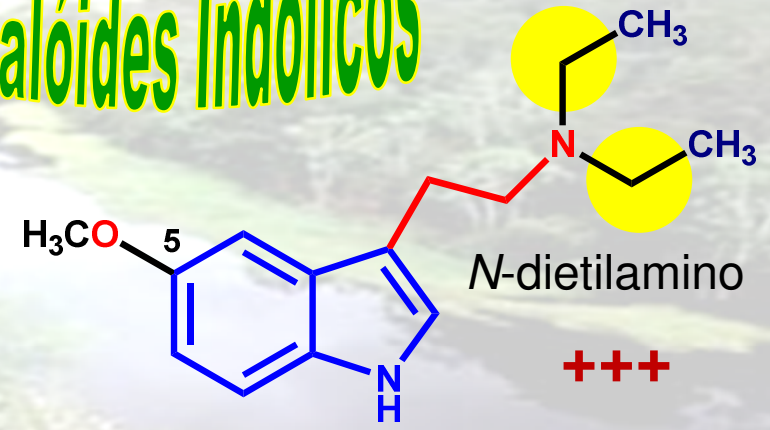
3 metilas

Alcalóides Indólicos



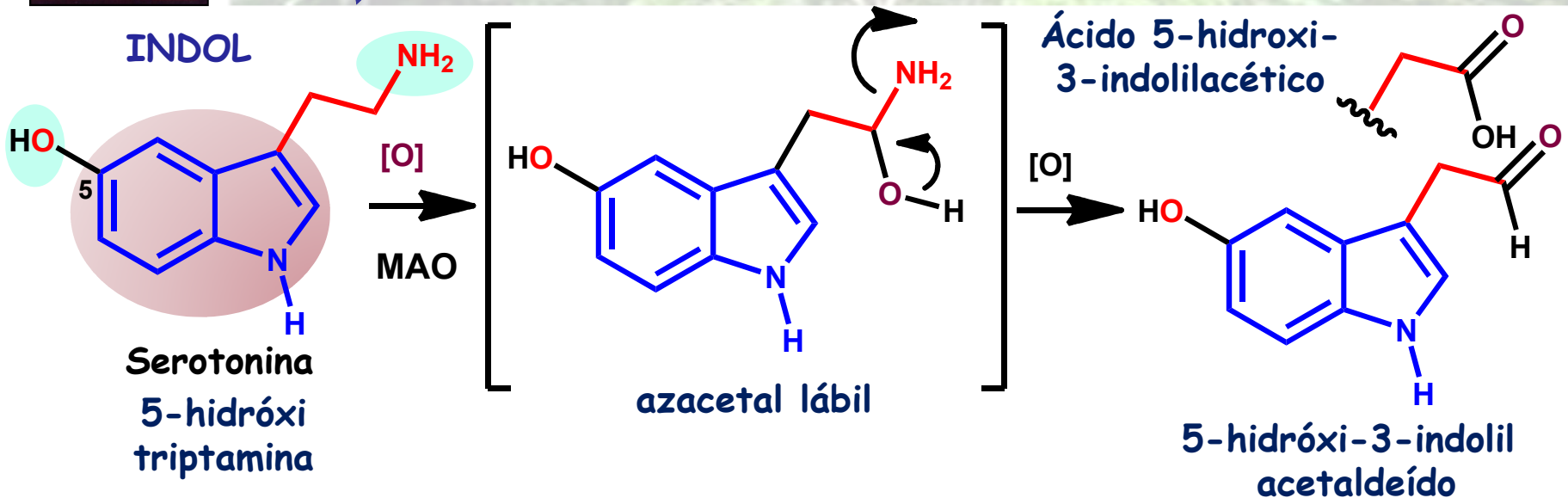
3-indolil-etilaminas

efeitos alucinogênicos



N-dimetilomólogo

Similaridade molecular

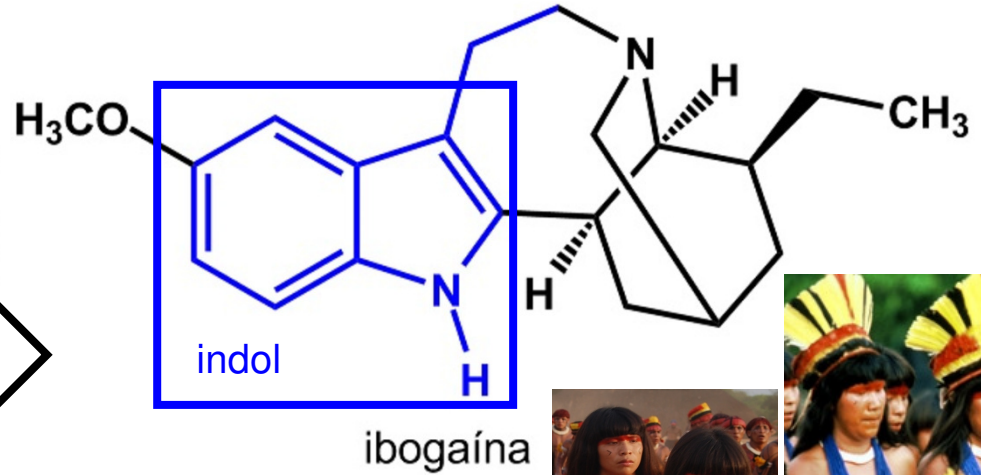
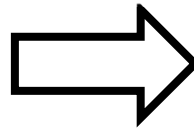




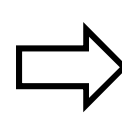
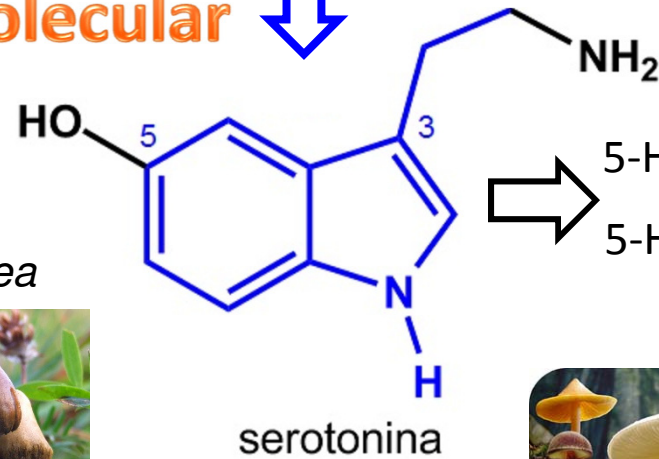
Alcaloides psicoativos



Tabernanthe iboga
Apocinácea



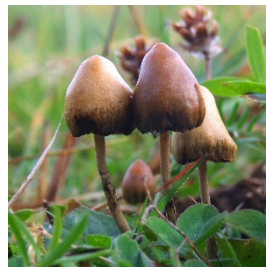
Similaridade Molecular



5-HT_{1A}
5-HT_{2A} } GPCR

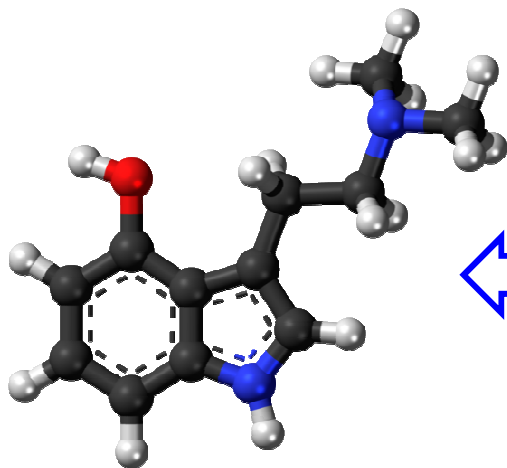


Amanita muscaria



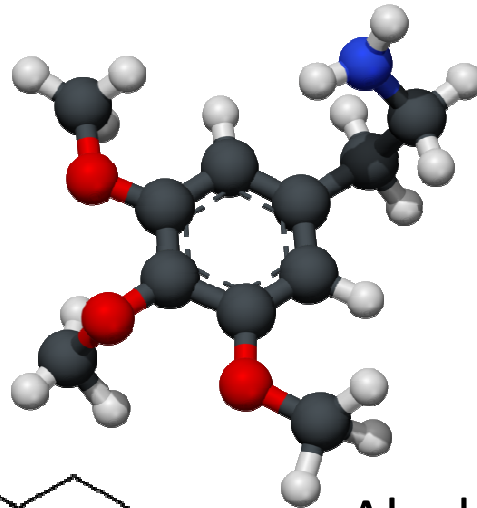
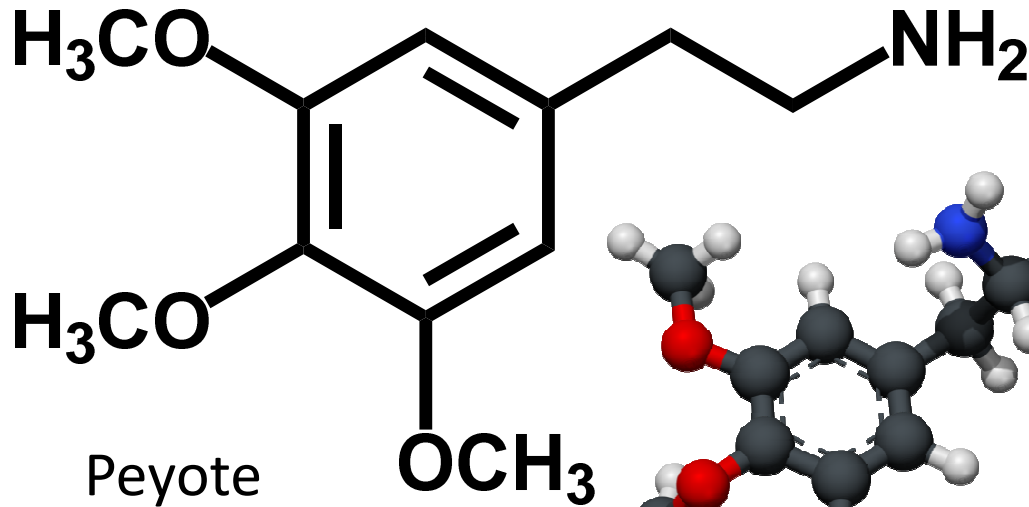
Psilocybe semilanceata

Cogumelos psicodélicos





Mescalina



Lophophora williamsii v Cardona

(*Lophophora williamsii*)



San Pedro Cactus

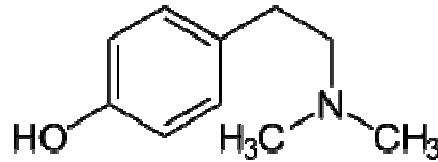


1897 - Arthur Heffter

1919 - Ernst Späth



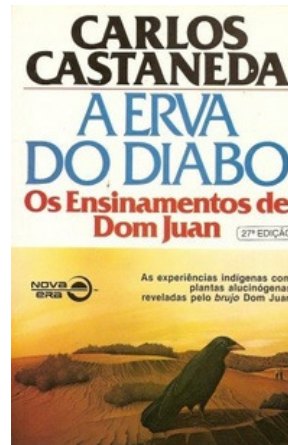
Mazatecas



Alcaloide
psicodélico



Aldous
Huxley
(1894-1963)



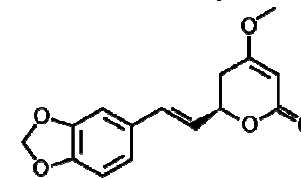
Carlos Castaneda
(1925-1998)



Kava-kava

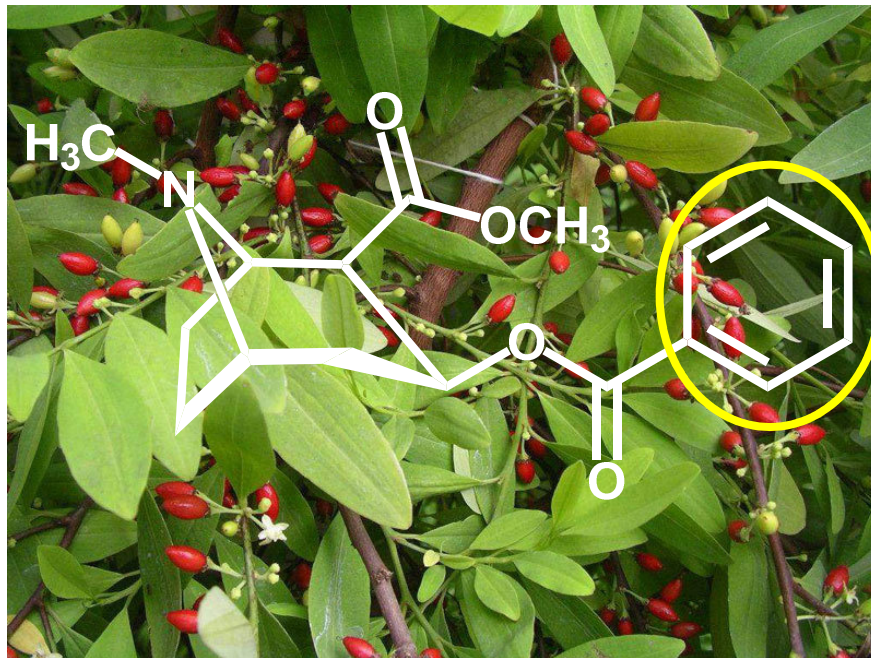


Echinopsis pachanoi





Cocaína

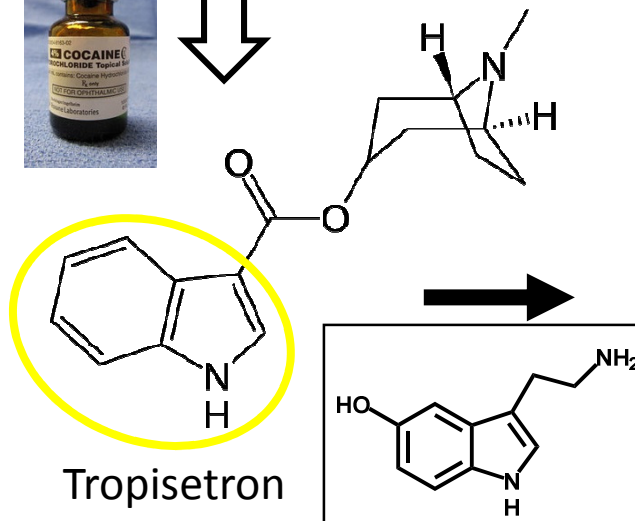
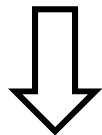


Alcaloide tropânico

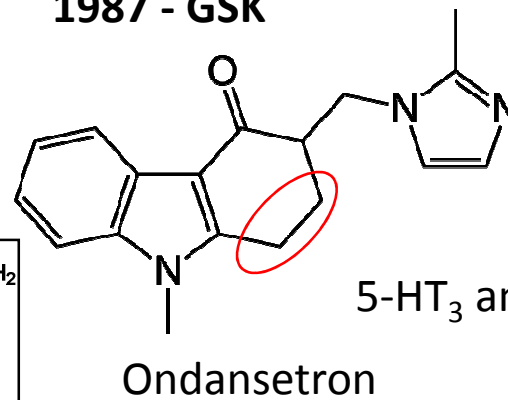
5-HT₃ >>> 5-HT₂



Alosetron, bemesetron, cilansetron, dolasetron, granisetron, lurosetron, palonosetron, ramosetron, ricasetron, tropisetron, zatsetron.



1987 - GSK

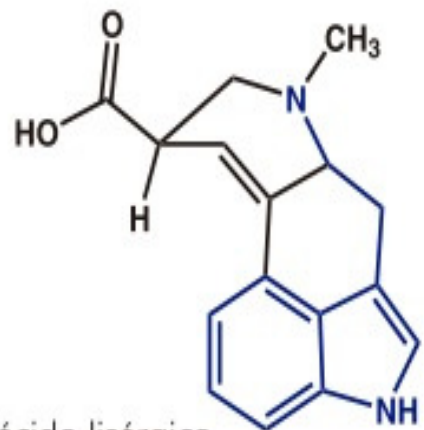


5-HT₃ antagonista

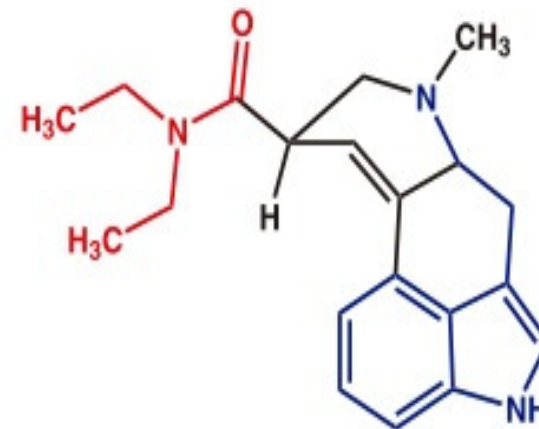




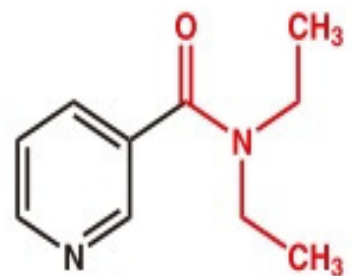
Dietilamida do ácido lisérgico (LSD)



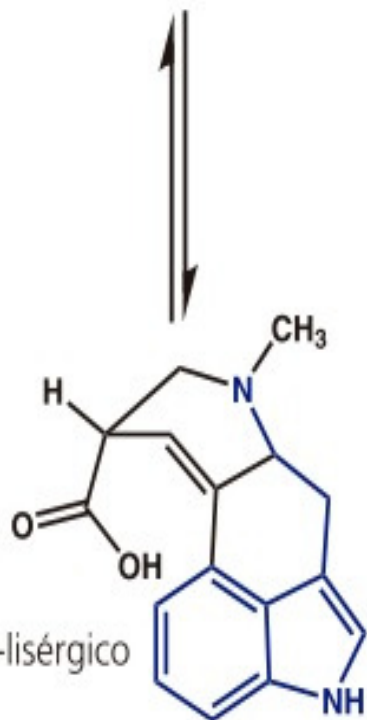
ácido lisérgico



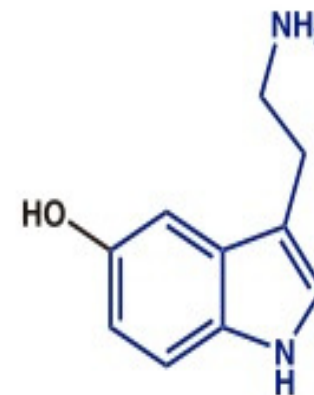
dietilamida do ácido lisérgico (LSD)



niquetamida



ácido iso-lisérgico

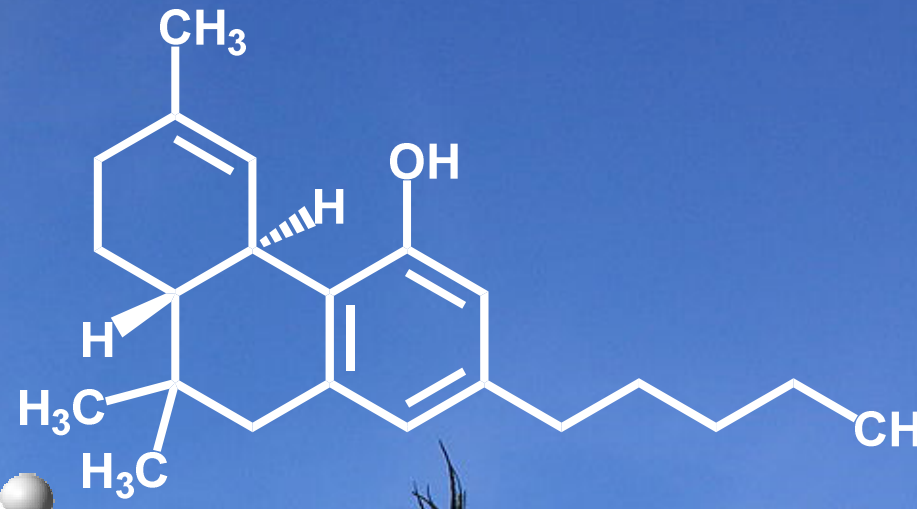
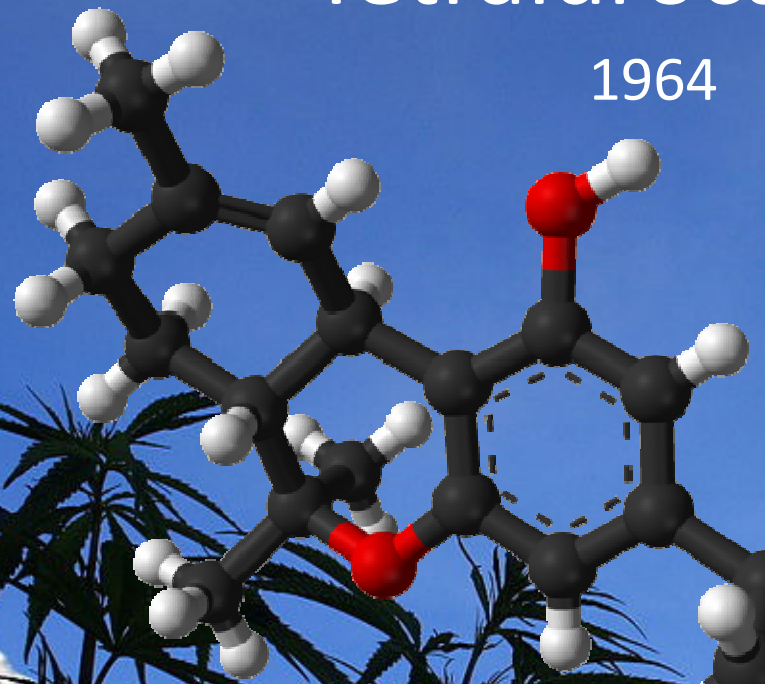


serotonina



Tetrahydrocannabinol

1964

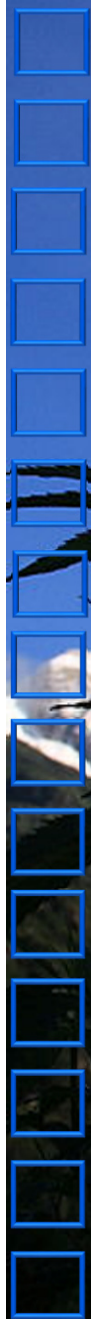


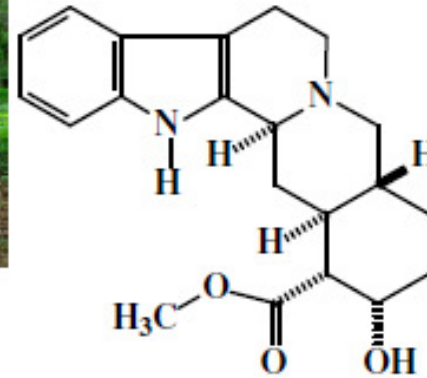
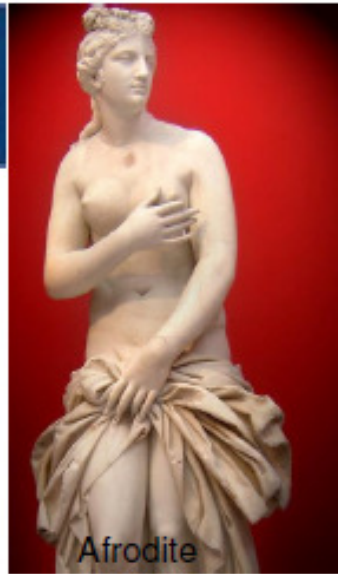
dronabinol

Cannabis sativa

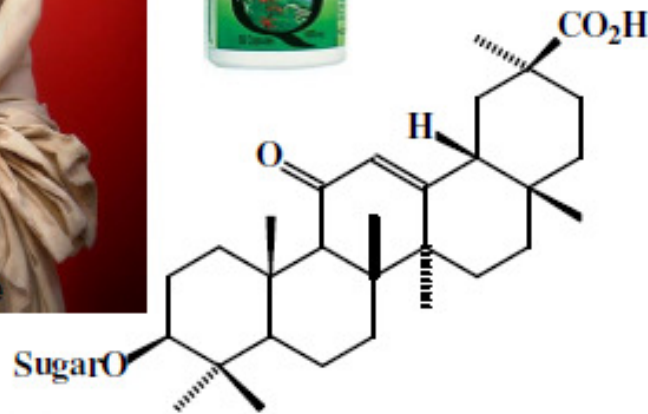


Raphael Mechoulam, Yechiel Gaoni e
Habib Edery no Instituto Weizmann





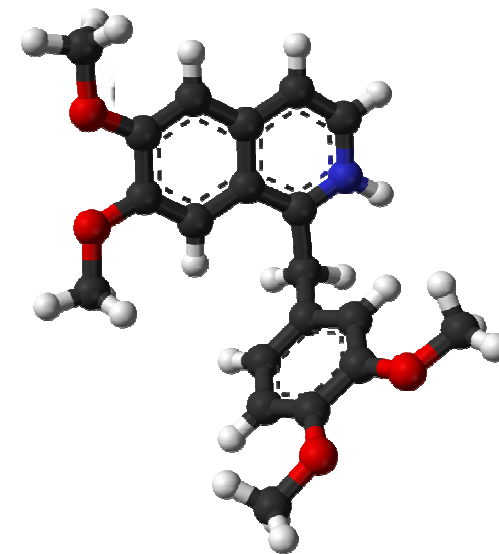
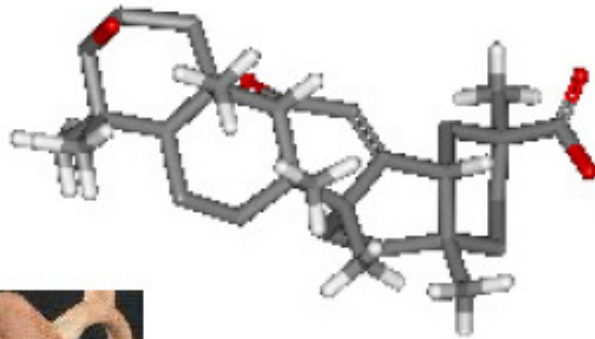
ioimbina



SugarO



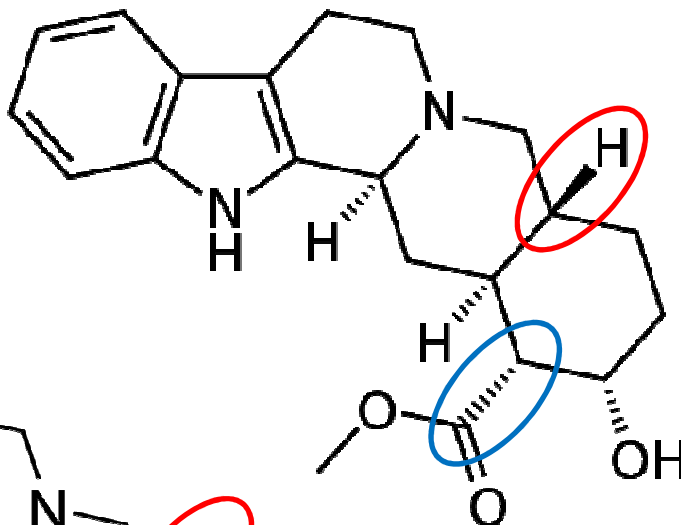
Yohimbe bark (Rubiaceae)
Aspidosperma sp., Apocynaceae



Produtos Naturais Afrodisíacos

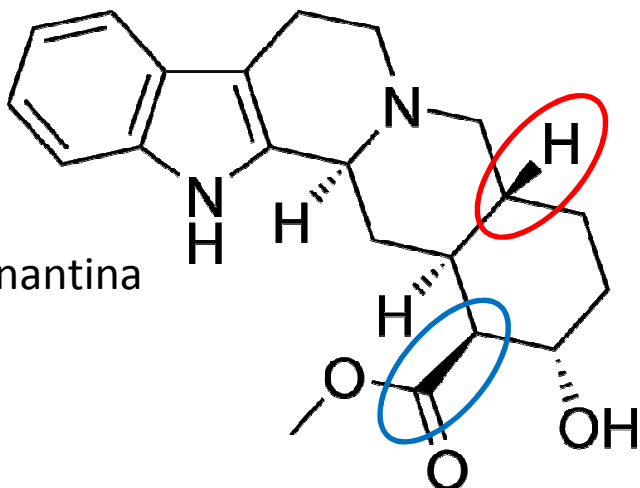


Ioimbina
 α_2 receptors



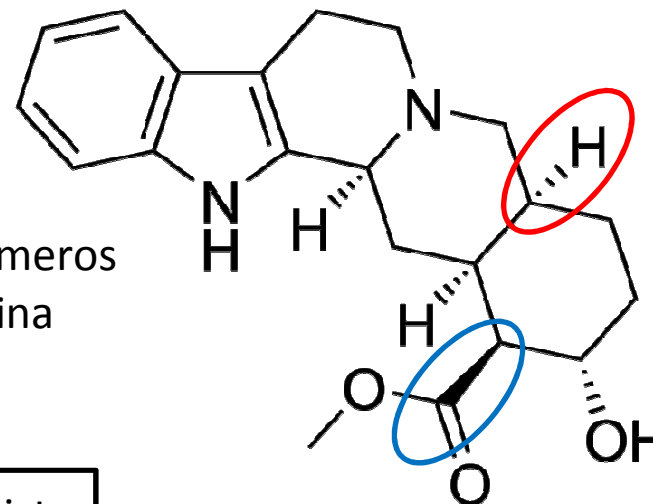
Pausinystalia yohimbe

Corinantina



30-vezes > α_2 que α_1

Diastereoisômeros
da ioimbina



Rauwolfscina ou raubasina,
isoioimbina, α -ioimbina
ou corinantidina

<p>α_2-adrenergico antagonista. >> 5-HT_{1A} parcial agonista & 5-HT_{2A} & 5-HT_{2B} antagonista</p>

