



Mini Curso - 004

Planejamento de candidatos a novos fármacos

Parte 2

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Professor Titular - UFRJ



Ementa

Breve introdução histórica da Química Medicinal; O papel dos pioneiros; Os fármacos e os produtos naturais; Estratégias de desenho molecular de novos candidatos a fármacos; Considerações finais.

64ª Reunião Anual da SBPC

22 a 27 de Julho de 2012 | UFMA | São Luís, MA

CIÊNCIA, CULTURA E SABERES TRADICIONAIS PARA ENFRENTAR A POBREZA.

SB
PC



Como as chaves
acham as
fechaduras ?

Como os fármacos
chegam aos
alvos terapêuticos ?



Medicamento

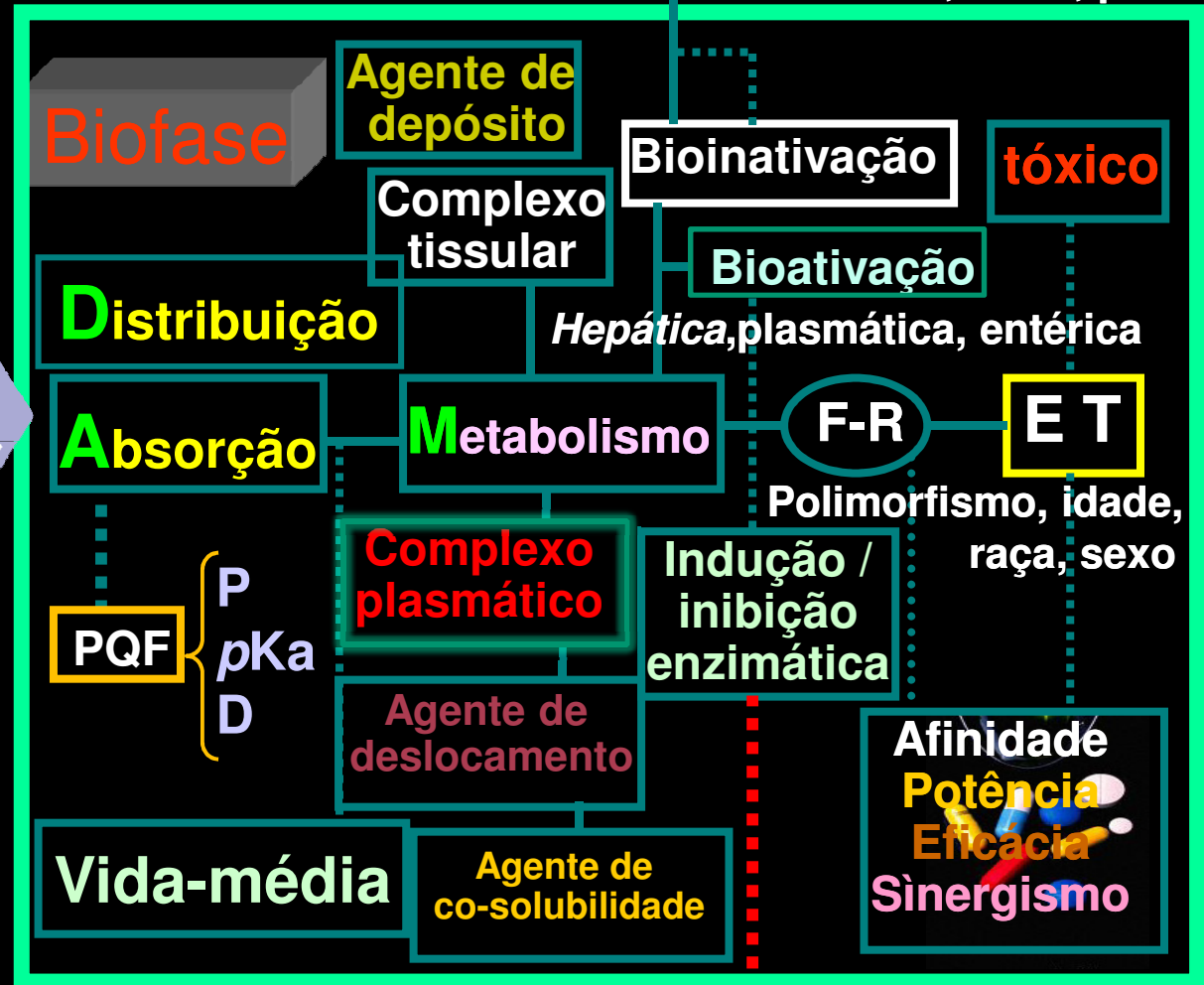
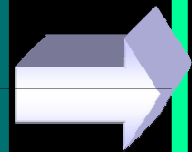
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Fármaco

Fase farmacêutica



Fase farmacocinética

(ADME)

Fase farmacodinâmica



Fase Farmacocinética (PK)

Biofase

pH Absorção

Concentração

Meia-vida

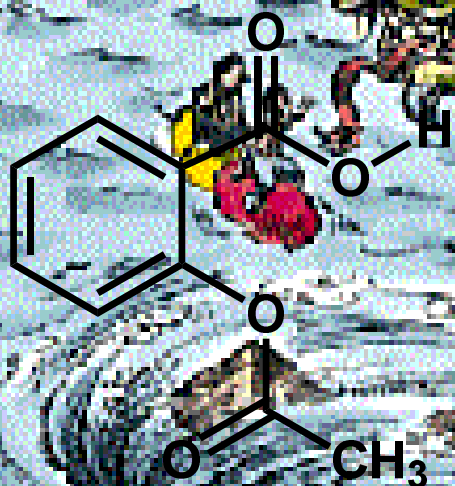
Posologia

Complexação plasmática

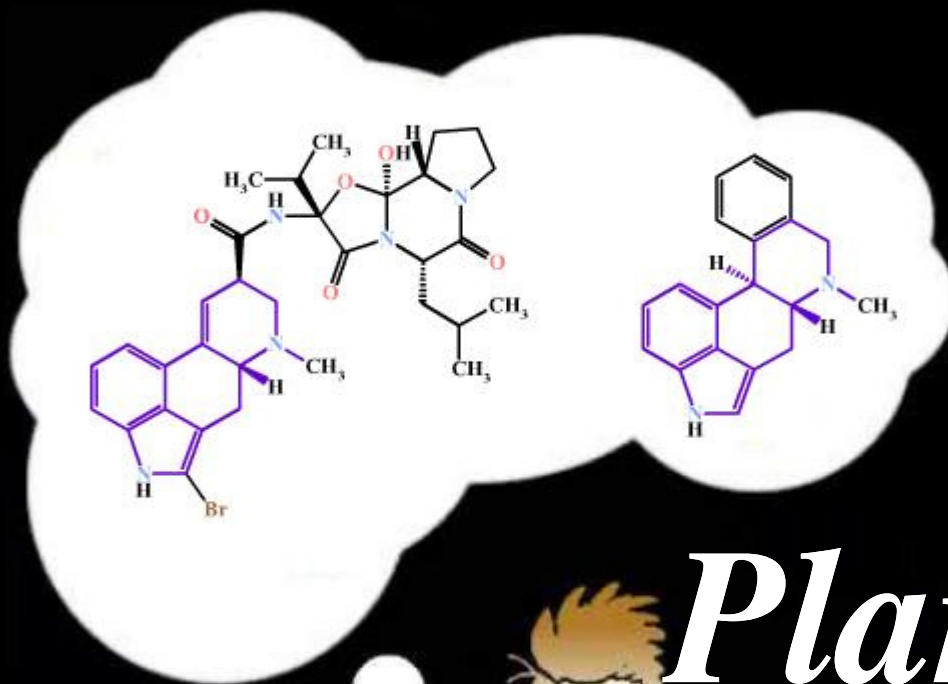
Deposito tissular

Metabolismo

Eliminação



Fármacos Inteligentes

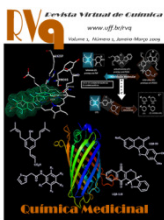
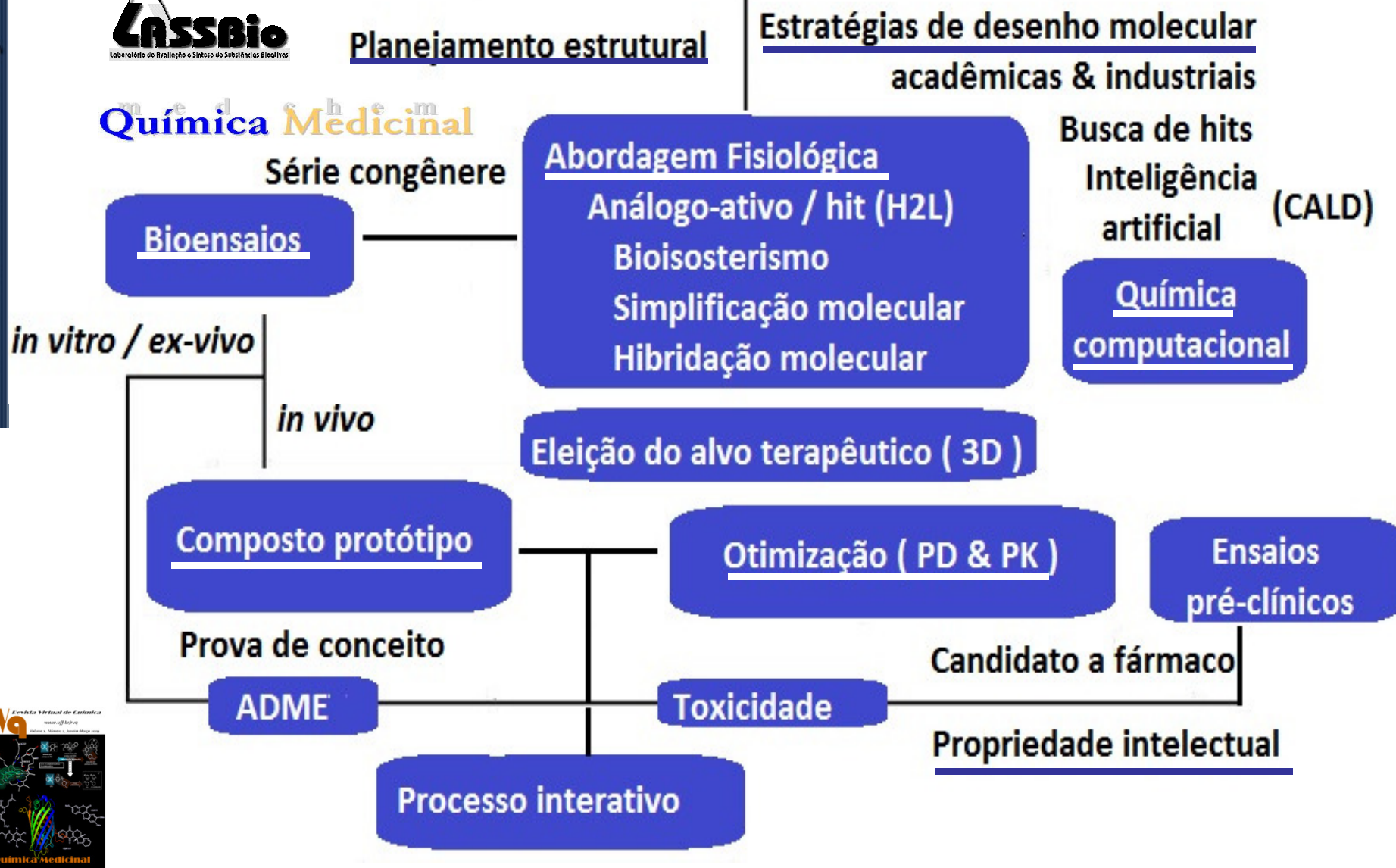


*Planejamento
racional*



Química Medicinal

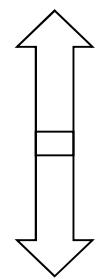
Químico Medicinal



Descoberta

(Descobrir)

ato ou efeito de descobrir (algo), retirando-lhe a proteção, a cobertura, a capa ou invólucro que cobre, esconde; descobrimento;



(Inventar)

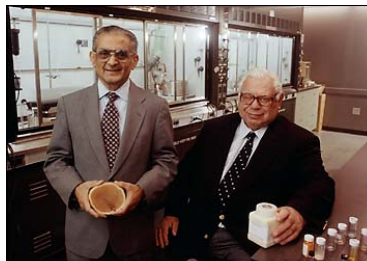
criação de algo através do conhecimento científico, técnico; coisa inventada; invento;

Invenção

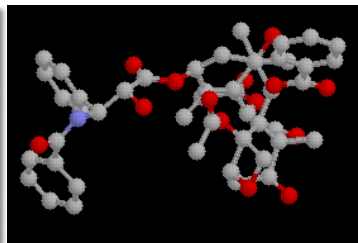


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Uma descoberta



M. E. Wall & M. C. Wani



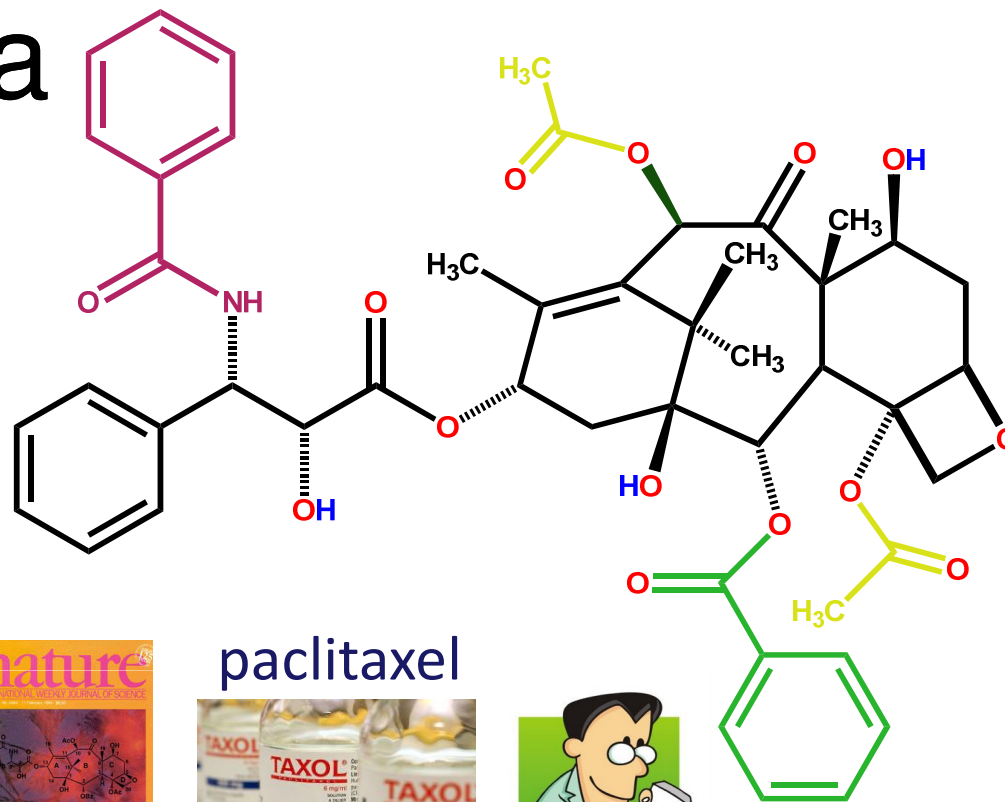
Miguel Ondetti
Bristol-Myers Squibb
Pharmaceutical Research
Institute



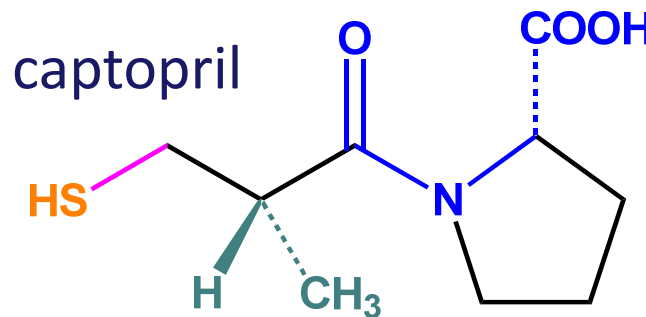
David Cushman
Bristol-Myers Squibb
Pharmaceutical Research
Institute



paclitaxel



Química Medicinal



...e uma invenção



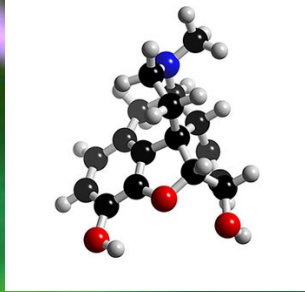
Origem dos Fármacos



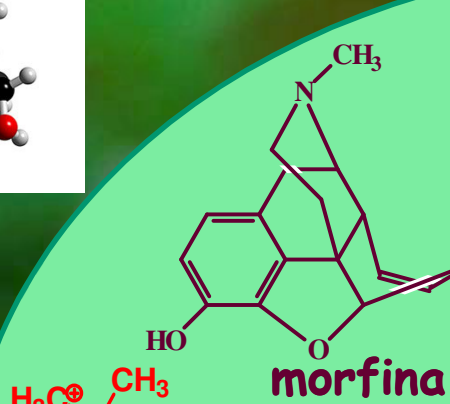


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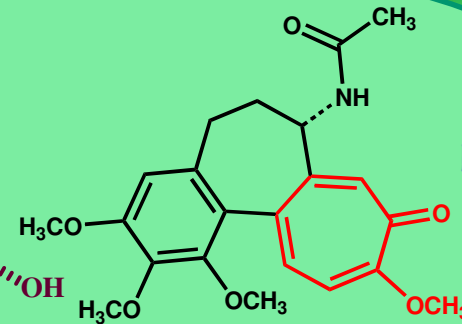
Quimiodiversidade



Lantana - Lantana camara



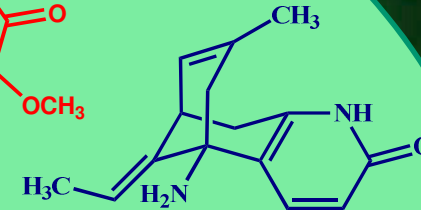
1806



1820

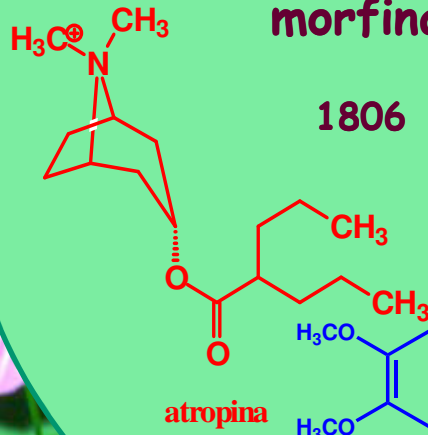
terpenos, alcalóides,
esteróides, flavonóides,
lignanas, ligninas, iridóides,
policetídeos, quinonas,
cumarinas

huperzina-A

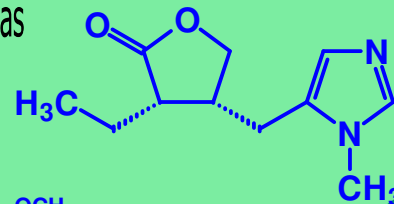
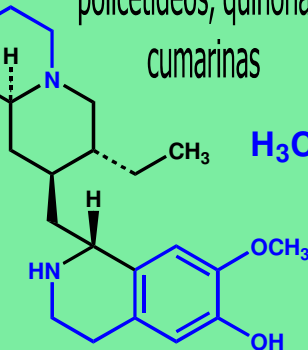


Estriquinina

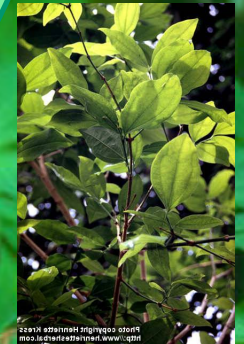
1817



Emetina
1817



Pilocarpina



22/01/2016 09:00:00 AM
www.igmp.org.br





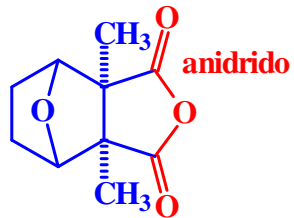
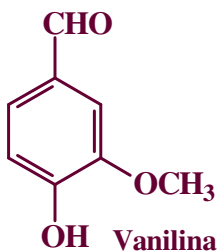
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Produtos Naturais Afrodisíacos

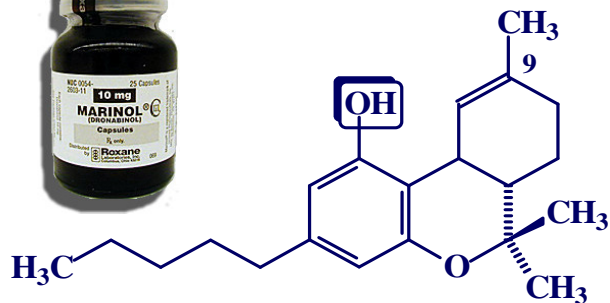
J. Chem. Ed. 1980, 57, 341

T. G. Waddell, H. Jones & A.L. Keith

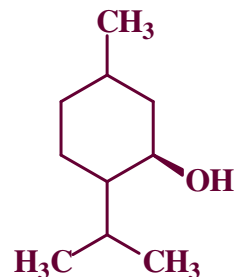
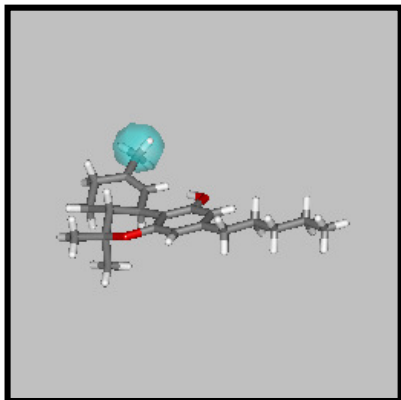
“... the well known flavoring substances which has unquestionable aphrodisiac qualities...”. In: Herbal Aphrodisiacs”, Cal., USA, 1971



Cantaridina
Cantharis vesicatoria

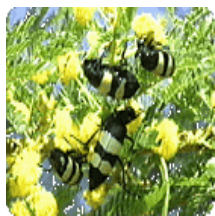


THC
Canabis sativa



Mentol

Volátil

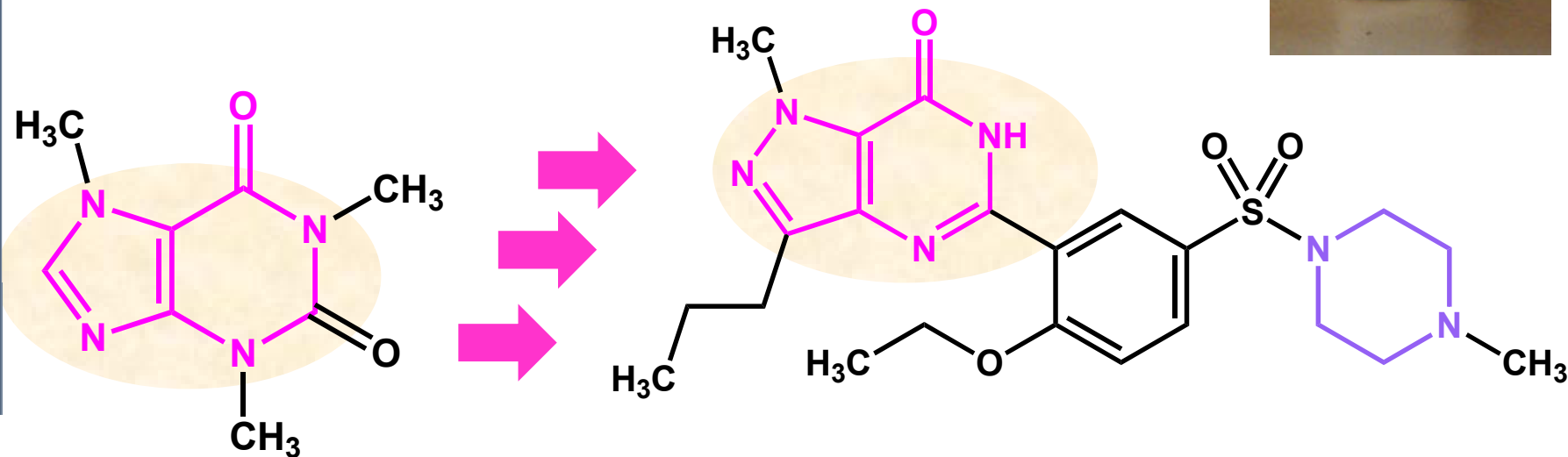


cafeína

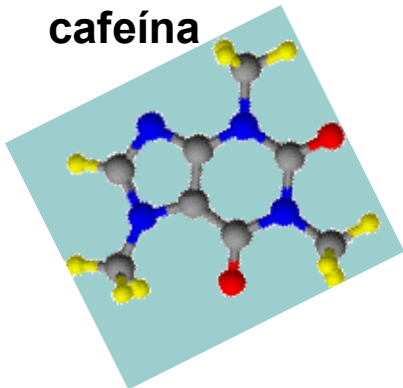
AFRODISIACOS



Da cafeína à sildenafil...



cafeína

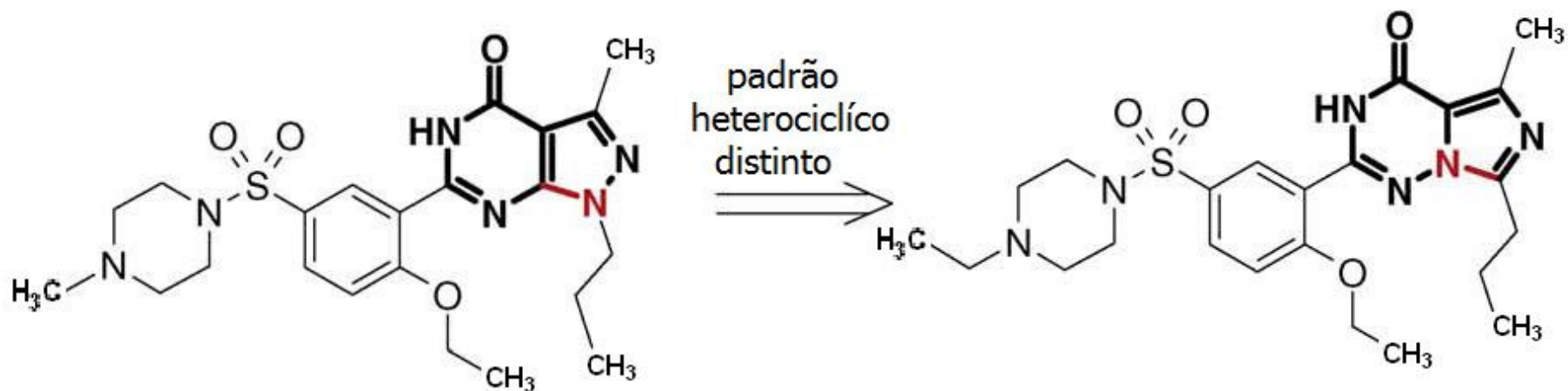


sildenafil

Patente expirou em 2010, no BR

US\$ > 3,5 bi (2009)

Simon Campbell, XII, EVQFM, UFRJ, 2006



Sildenafil
Viagra®
Pfizer



março 1998

Vardenafil
Levitra®
Bayer



agosto 2003



medchem
Química Medicinal



Glicosídeos cardiotônicos

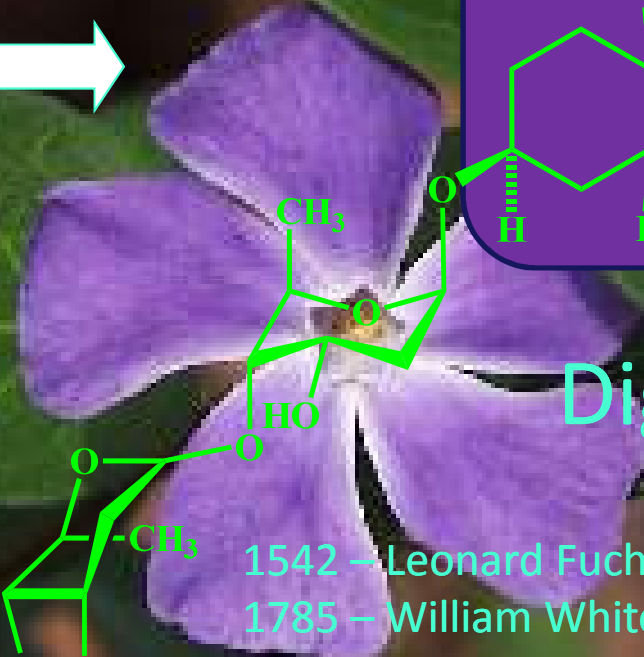
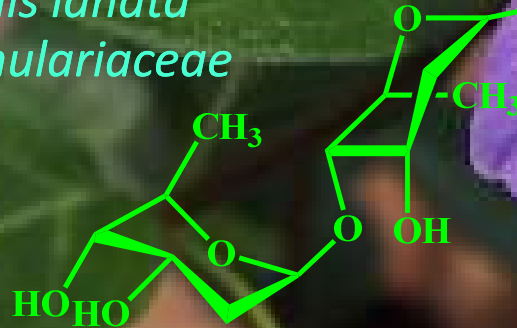
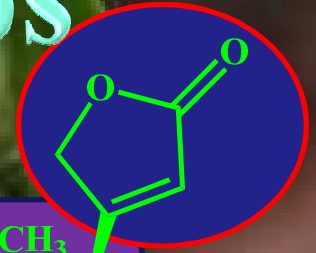
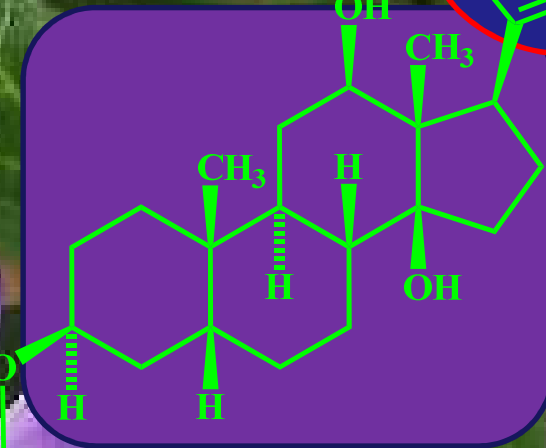
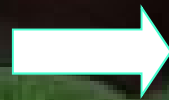
Ebers Papyrus



Digitalis purpurea
Digitalis lanata
Scrophulariaceae

bufanolidos cardenolidos

O decano dos fármacos



Digoxina



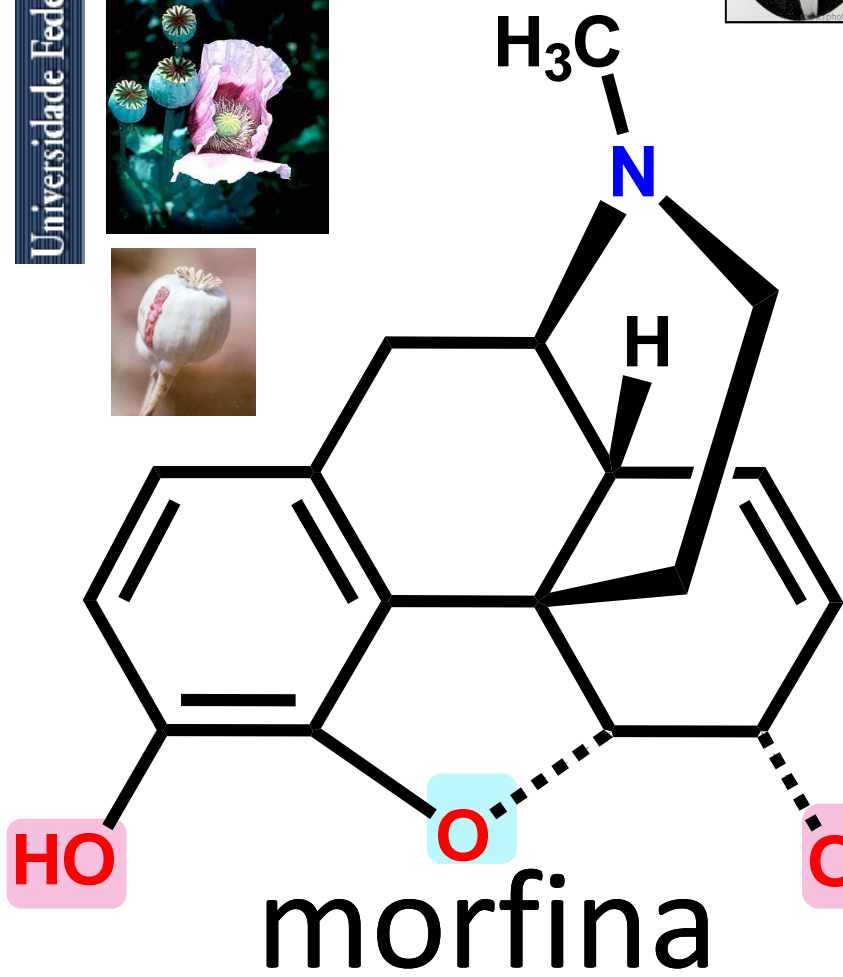
- 1542 – Leonard Fuchs *Digitalis purpurea*
- 1785 – William Whitering, UK
- 1875 – Johann Schmiedeberg isola DGX
- 1928 – Sydney Smith, Burroughs Wellcome
- 1930 - Adolf Windaus, Un Göttingen (estrut)
- 1965 – JC Skou Na⁺/K⁺-ATPase
- 2008 – Zhang : inibe o fator de hipoxia
- 2011 – Huh descreve efeitos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



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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^{ario}

1874 – Wright obtém a heroína (UK)

1925 – Sir Robert Robinson  (7)

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

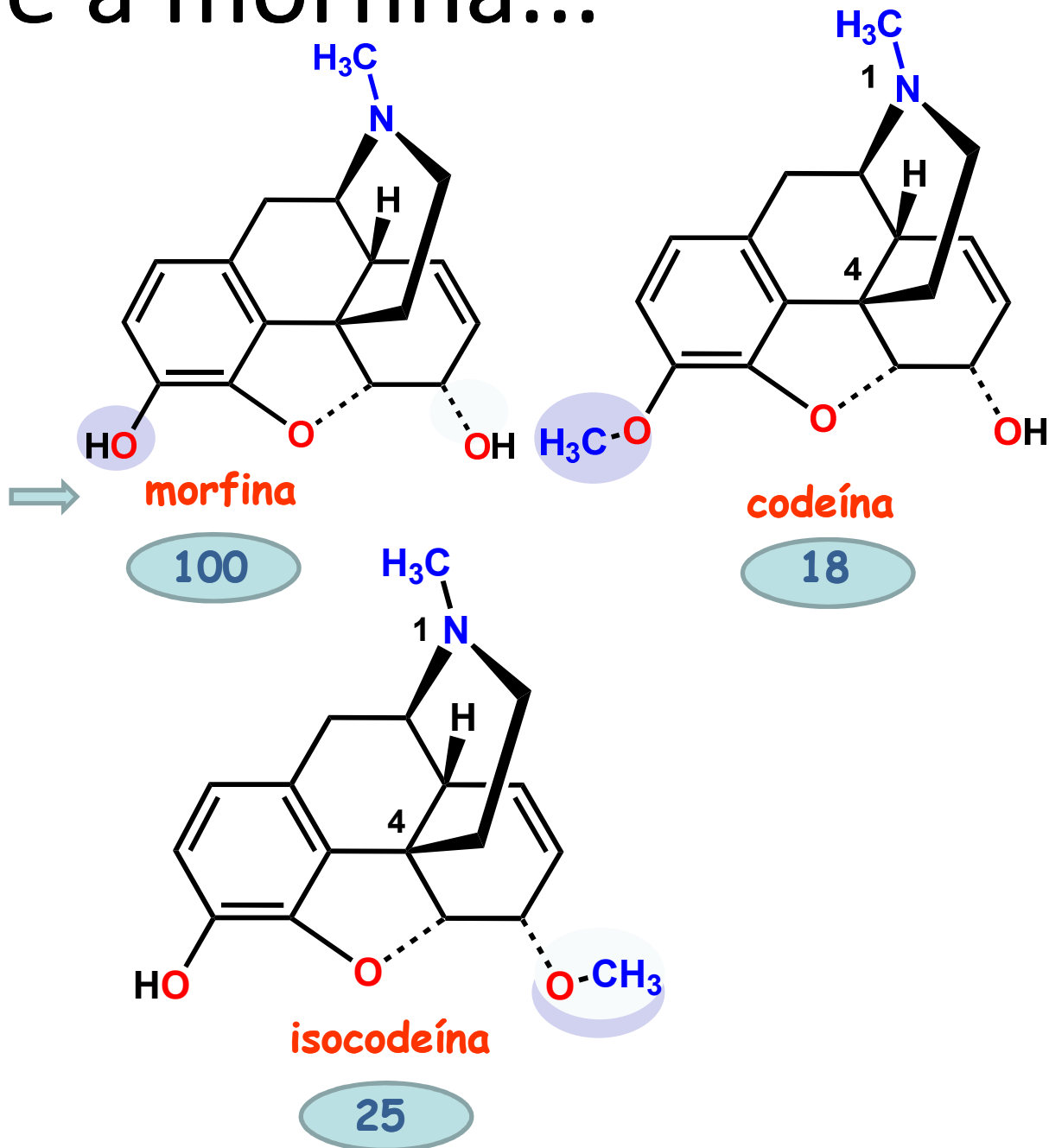
tolerância & dependência química;

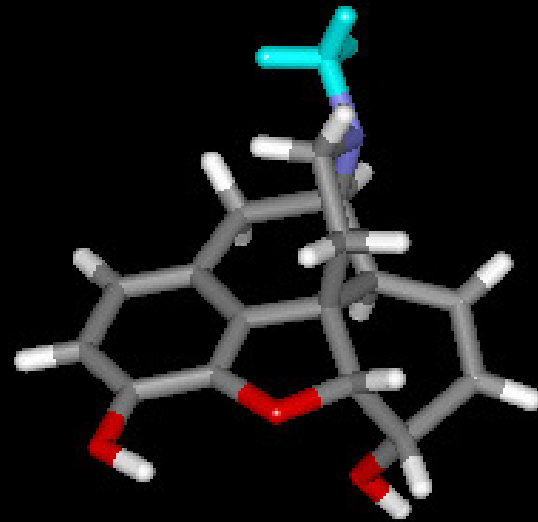




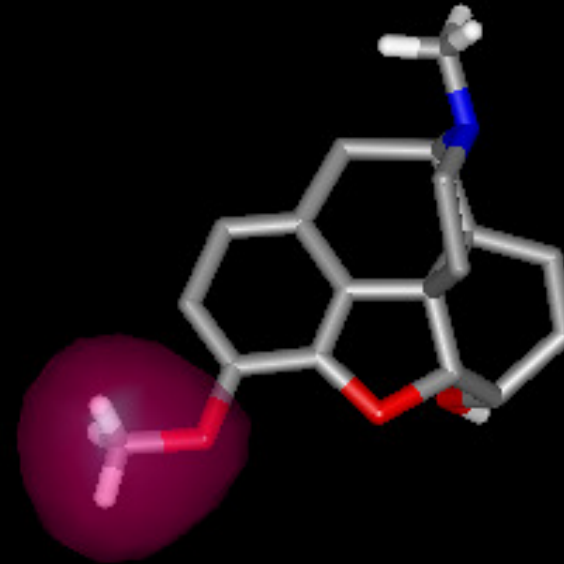
A metila e a morfina...

Índice de atividade analgésica

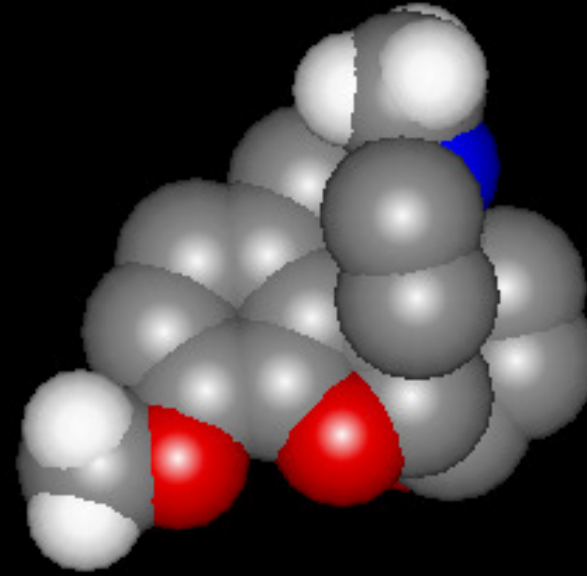
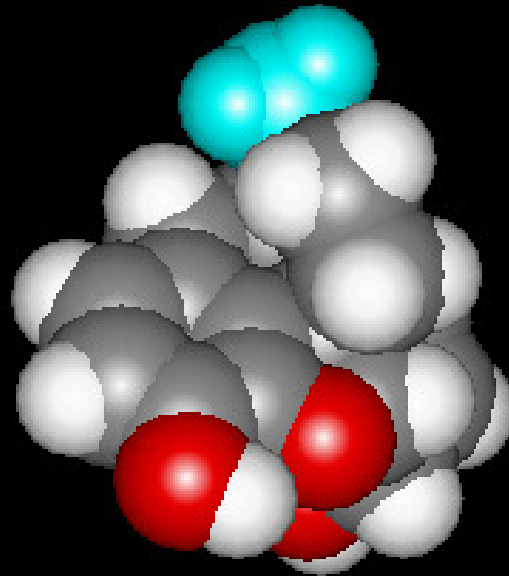




morfina

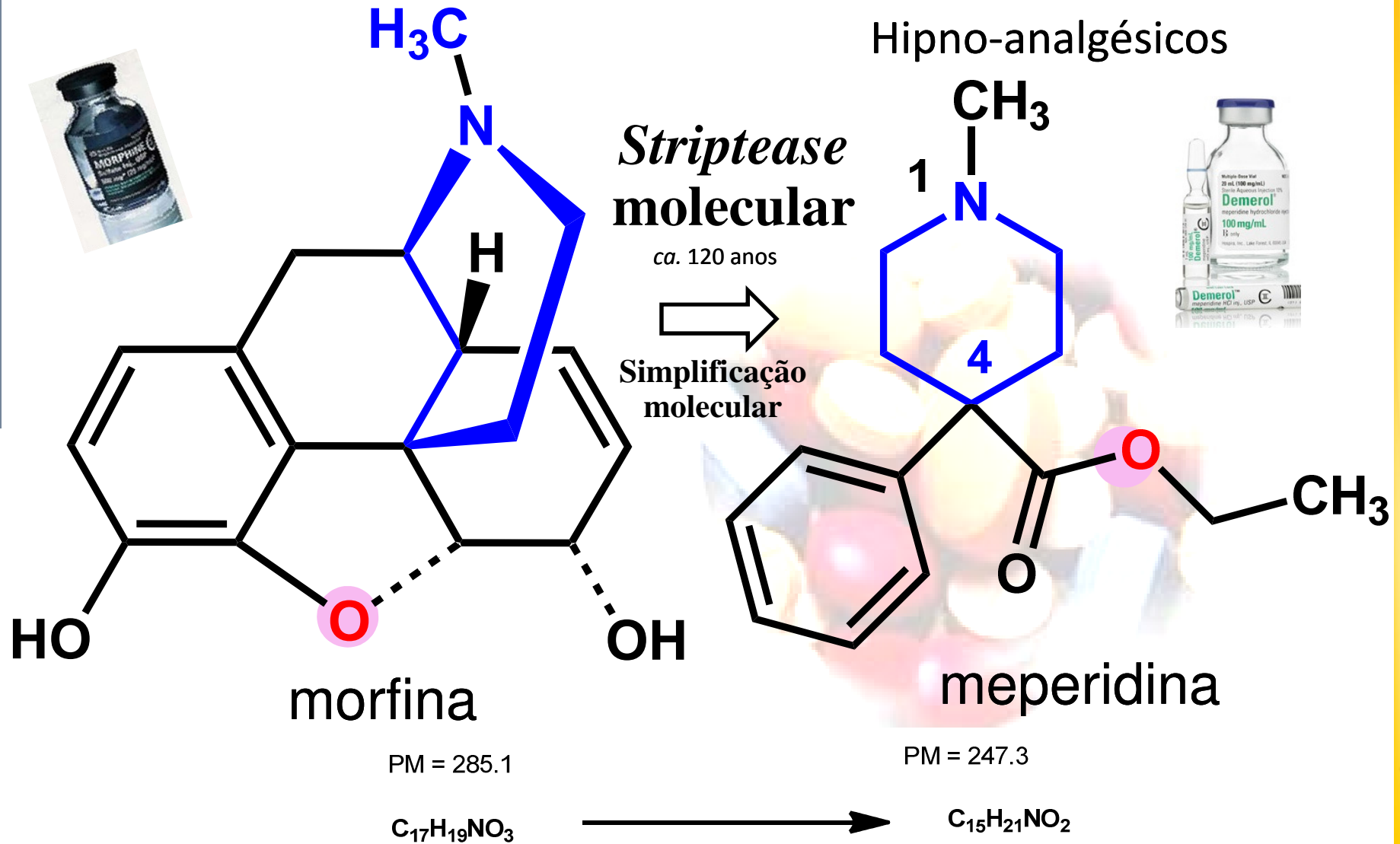


codeína





Derivados 4-fenilpiperidínicos



Domesticando produtos naturais



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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

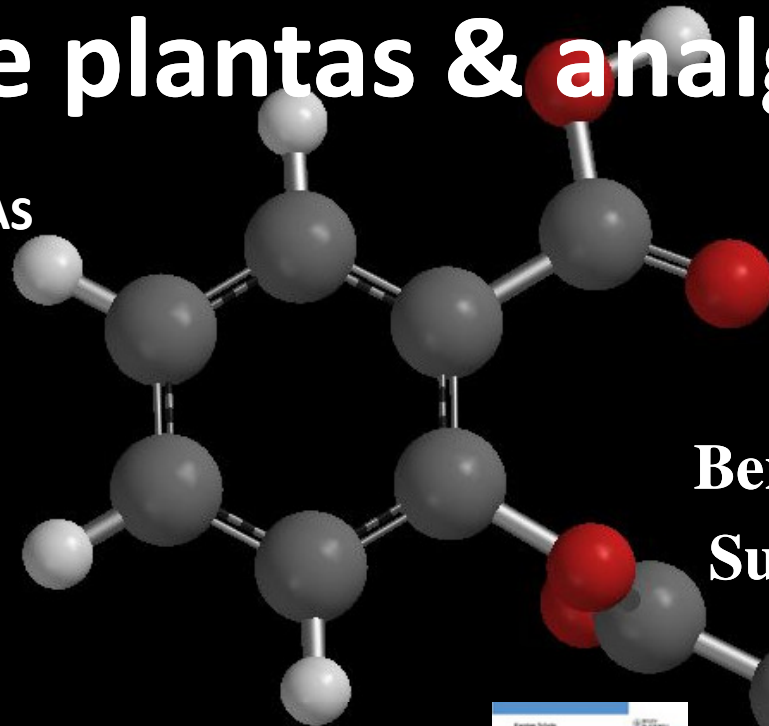
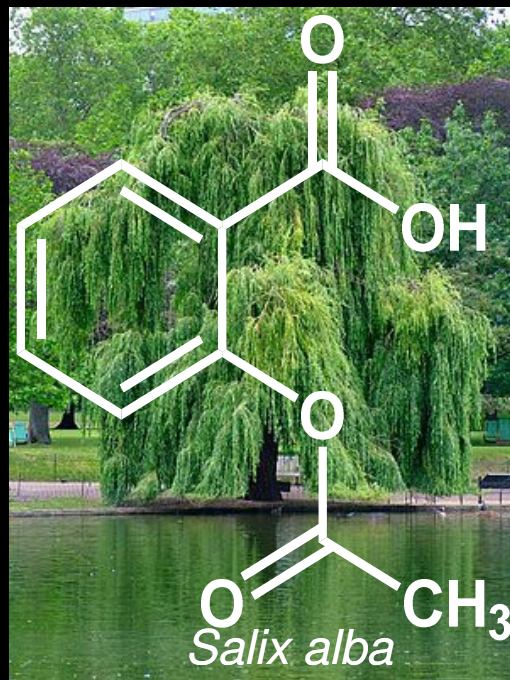


1982

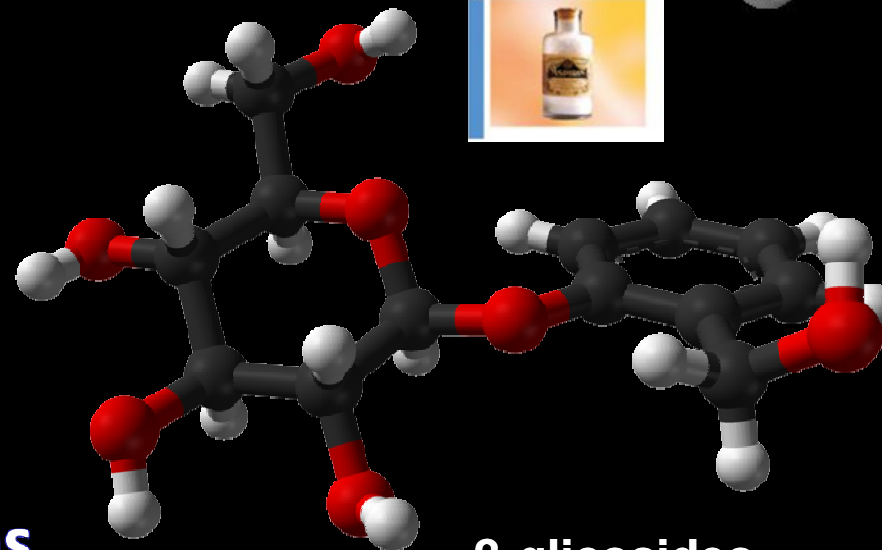
Bengt I. Samuelsson

Sune K. Bergström

John R. Vane



AAS



β -glicosideo



Teoria das Assinaturas

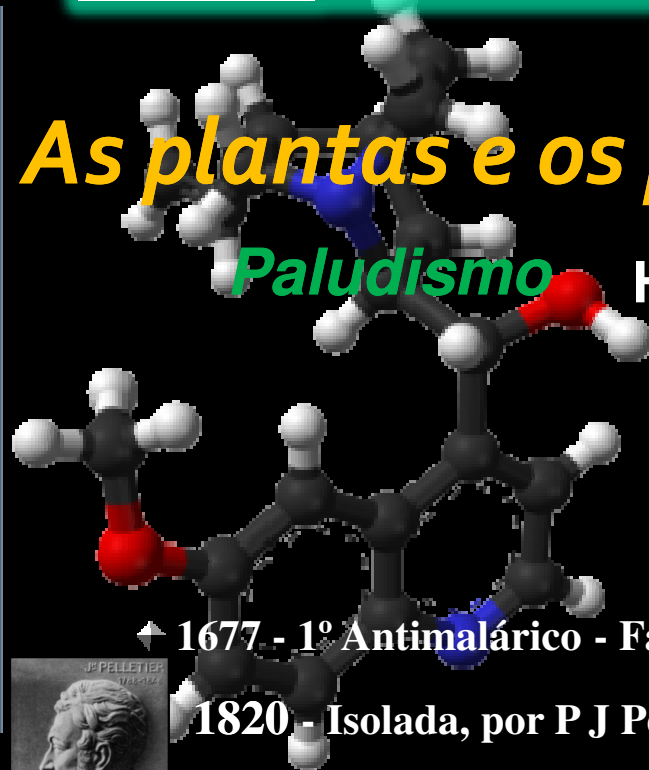


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Molécula latino-americana

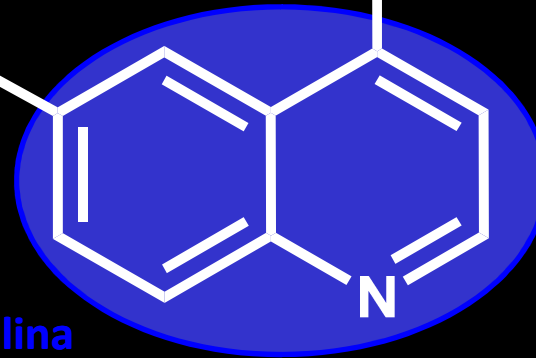
As plantas e os parasitas

Paludismo



H₃CO

quinolina



rubano

quinina

Quinquina

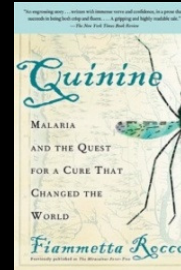
1677 - 1º Antimalárico - Farmacopéia Britânica



Pierre Joseph Pelletier

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

École de Pharmacie de Paris



Cinchona officinalis

1918 – Estrutura elucidada (P Rabe, AL)

1944 – síntese RB Woodward & WE Doering

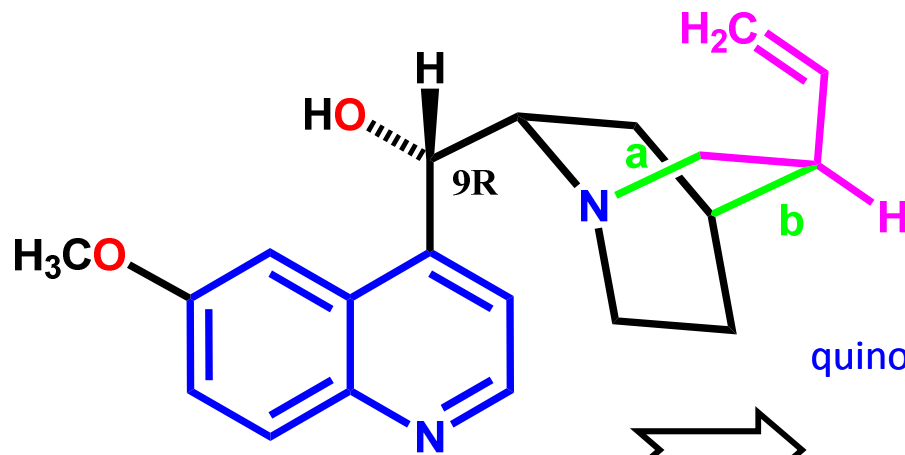
RB Woodward & W Doering,
J Am Chem Soc 1944, 66, 849



1944

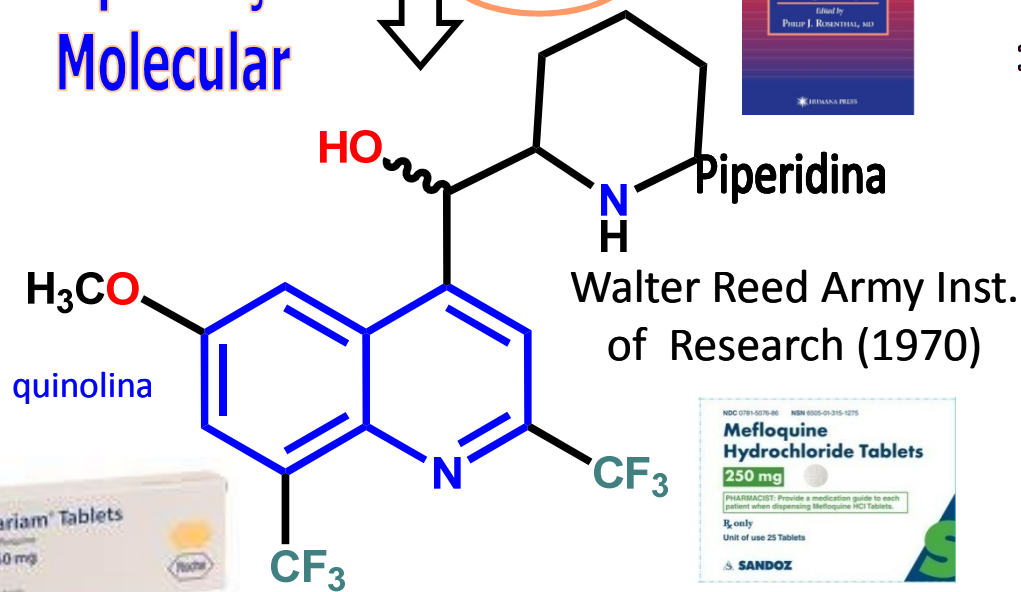
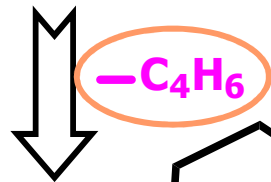


2001 – G Stork, síntese estereosseletiva



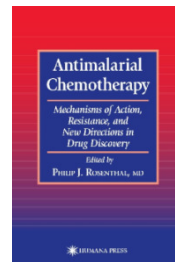
Quinina

Simplificação Molecular



Mefloquina

T_{1/2} = 16d

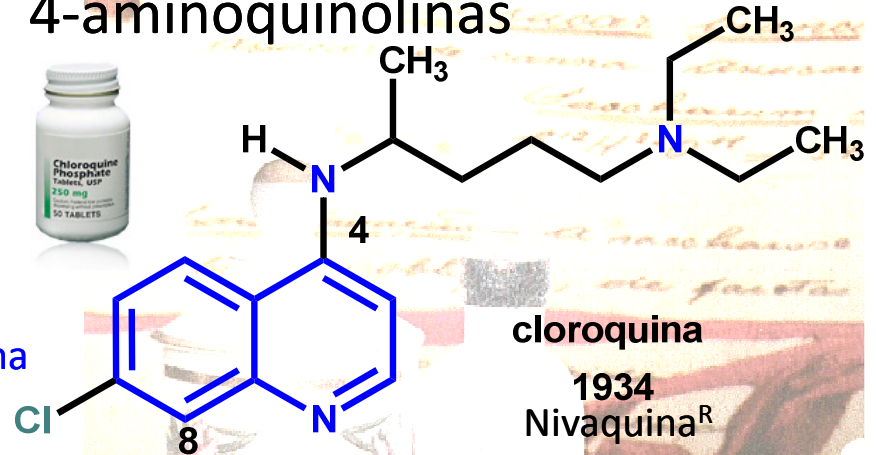


Walter Reed Army Inst. of Research (1970)



1989 - FDA

4-aminoquinolinas



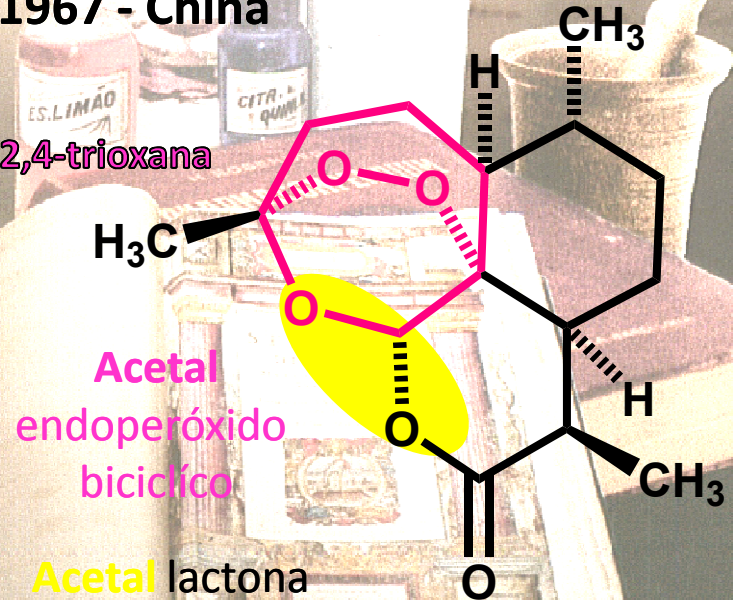
cloroquina

1934 Nivaquina^R

De volta ao Oriente...

1967 - China

1,2,4-trioxana



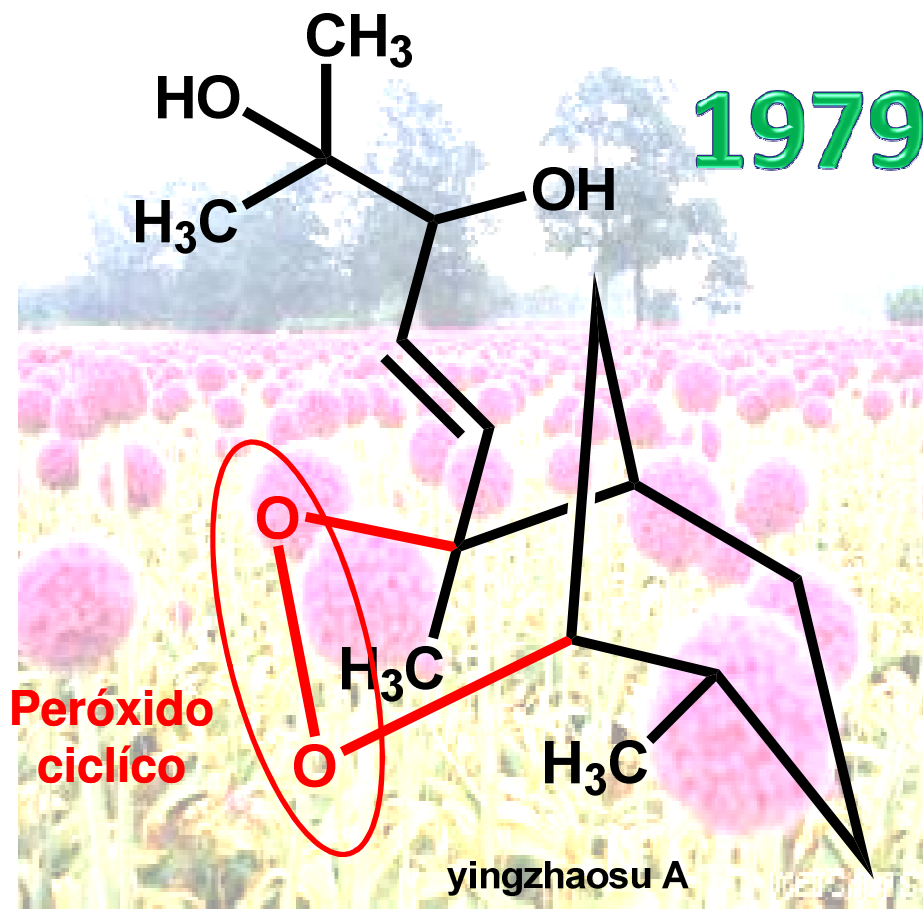
artemisinina

sesquiterpeno C₁₅H₂₂O₅

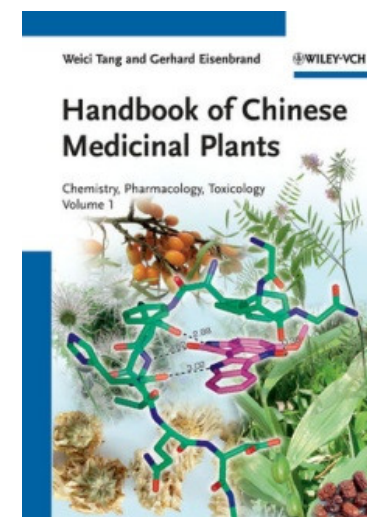




Produtos naturais e malária



Artabotrys unciatus (L.) Meer.



Similaridade Molecular