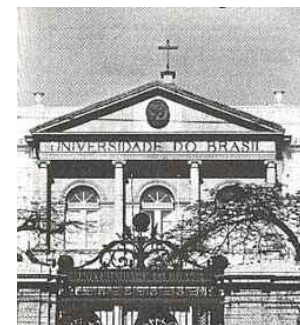




Introdução à Química Farmacêutica Medicinal Parte 1



Eliezer J. Barreiro

Universidade Federal do Rio de Janeiro



Introdução à Química Farmacêutica Medicinal

1. Introdução

Definição e evolução da Química Medicinal

Como nascem os fármacos?

Fármacos e Medicamentos

2. A Origem dos Fármacos I

Papel dos produtos naturais

O Decano dos Fármacos

Domesticando moléculas selvagens: morfina, quinina

Anti-câncer: Vinca, Taxol[®] *et al.*;

Diosgenina e a esteróideterapia

Índios & indóis

O episódio do *Específico Pessoa*

... de cobras e outros bichos, aos inibidores da ECA

Introdução à Química Farmacêutica Medicinal

3. A Origem dos Fármacos II

Produtos naturais de origem marinha

O acaso na descoberta de fármacos: *serendipity*

Fármacos sintéticos: AAS

4. As razões moleculares da ação dos fármacos

O centenário modelo “*chave-fechadura*” de Emil Fisher

A bioinformática e a Química Medicinal

Construção de mapas topográficos de biorreceptores

O conceito de grupamento farmacofórico

Fatores estruturais e atividade: similaridade e dissimilaridade

Introdução à Química Farmacêutica Medicinal

5. Planejamento racional de fármacos

O processo da descoberta de fármacos

A estratégia da abordagem fisiológica: mecanismo de ação

O paradigma do composto-protótipo

Estratégias modernas para a descoberta de fármacos

A importância do metabolismo: ADME

Fármacos inteligentes

Estratégias de desenho estrutural:

- A importância do bioisosterismo: análogos & *me-too*
- O processo de hibridação molecular
- O processo de simplificação molecular

6. Considerações finais

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Química Medicinal

*é uma disciplina que estuda os aspectos relacionados
à descoberta, invenção e preparação de
substâncias bioativas,
de interesse terapêutico, i.e. fármacos.*

Monge et al., Eur. J. Med. Chem. 2000, 35, 1121

C. R. Ganellin et al., Eur. J. Med. Chem. 2000, 35, 163

C. G. Wermuth et al., Pure Appl. Chem. 1998, 70, 1129

Ann. Rep. Med. Chem. 1998, 33, 385.

Eur. J. Med. Chem. 1996, 31, 747.

*Estuda os fatores moleculares do modo de ação dos fármacos,
incluindo a compreensão*

IUPAC

<http://www.iupac.org>

*da relação entre a estrutura química e a atividade terapêutica,
absorção, distribuição, metabolismo, eliminação e toxicidade.*



IUPAC

Chemistry and Human Health Division (VII)
Subcommittee on Medicinal Chemistry
and Drug Development.



Pure Applied Chem. 1998, **70**, 1129–1143

IUPAC

INTERNATIONAL UNION OF PURE AND APPLIED CHEMISTRY

CHEMISTRY AND HUMAN HEALTH DIVISION
MEDICINAL CHEMISTRY SECTION

GLOSSARY OF TERMS USED IN MEDICINAL CHEMISTRY

(IUPAC Recommendations 1998)

Prepared for publication by

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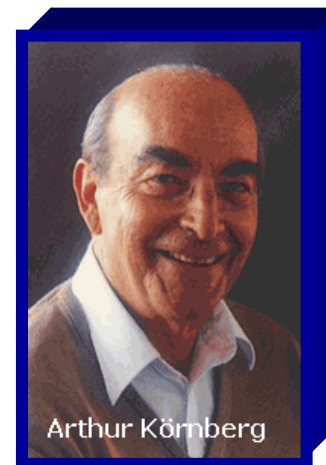
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<http://www.iupac.org/publications/pac/1998/7005/index.html>

<http://www.chemdiv.com/en/Information/glossary/>

Nobel Prize, 1959

“for their discovery of the mechanisms in the biological synthesis of RNA and DNA”



Arthur Kornberg

“We have the paradox of the two cultures, chemistry and biology, growing further apart even as they discover more common ground. For the chemists, the chemistry of biological systems is either too mundane or too complex...”

Arthur Kornberg

Annual Meeting of AAAS, 1987



Prêmio Nobel de Química
2006

Roger Kornberg, 2006

medicinal chemistry



Science

Drug Design

“...Change is in the air for drug discovery... the excitement of this

interdisciplinary field at a time

Drug Discovery

of transition ...”

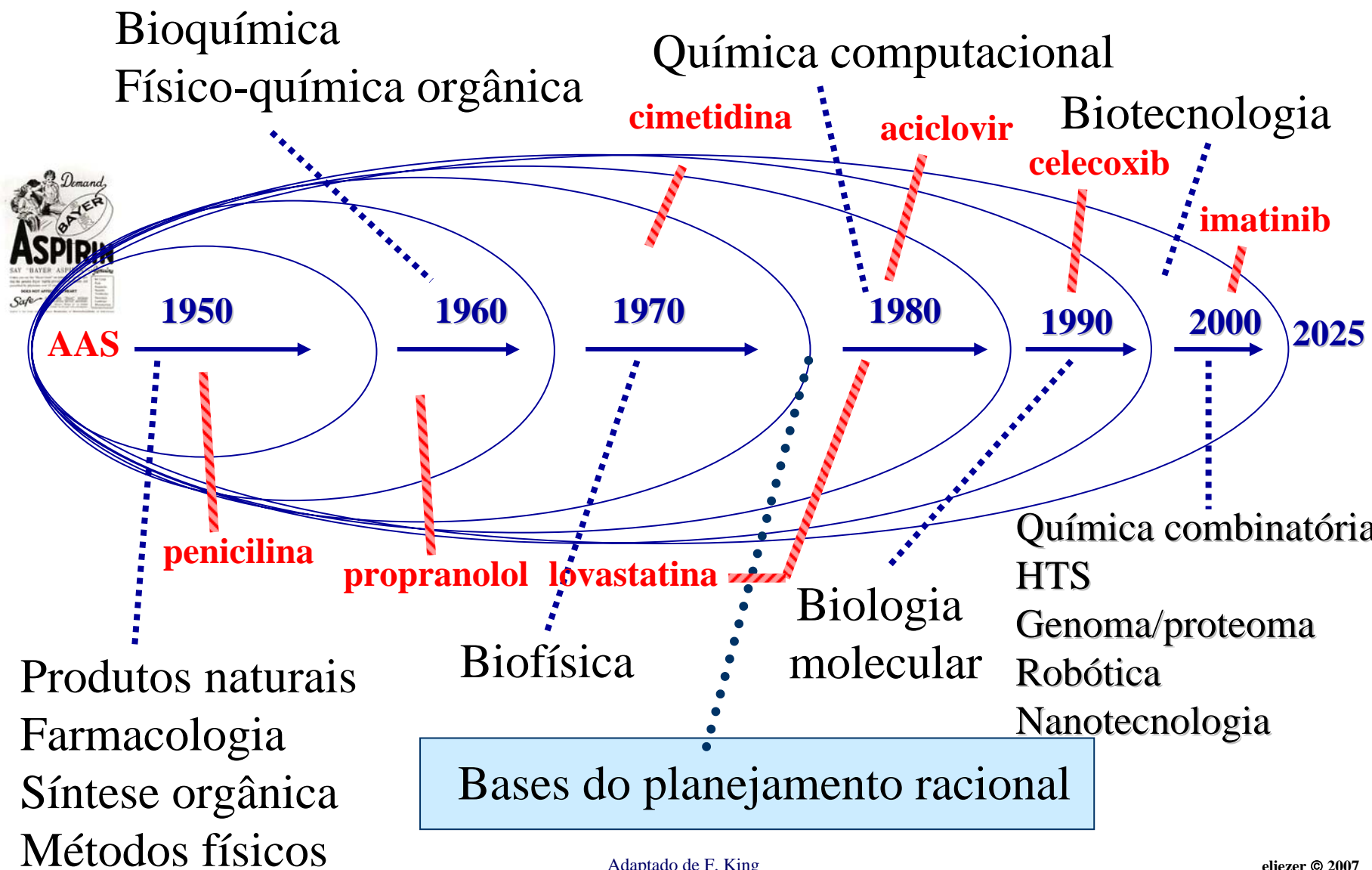


Uppenbrink & J. Mervis (Eds.),

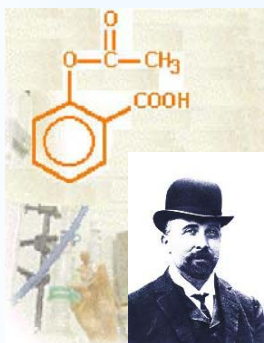
Science 287, 1951 (2000)

(Special Issue)

A evolução da Química Medicinal



Cronologia da Descoberta de Fármacos



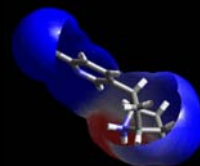
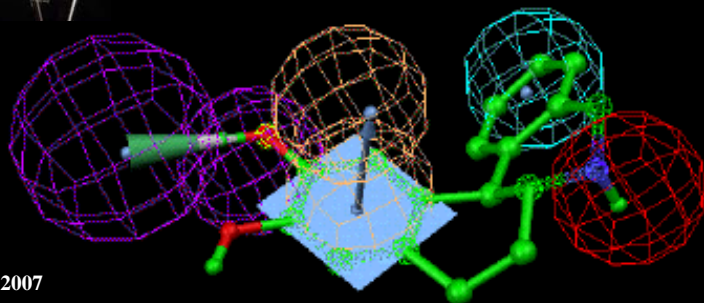
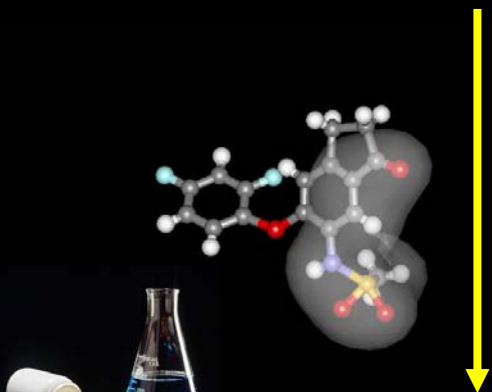
AAS *	1889	1981	ranitidina
barbitúricos	1923	1985	misoprostol
cloroquina	1934	1985	mefloquina
sulfonamidas	1935	1987	azidovudina
penicilina	1942	1987	lovastatina
nitrofurano	1952	1989	ozagrel
progesterona	1953	1989	mifepristona
talidomida	1954	1989	fluoxetina
haloperidol	1958	1990	salmeterol, amlodipina
verapamil	1962	1993	tacrina, fanciclovir
indometacina	1963	1995	indinavir, saquinavir
propranolol	1964	1996	docetaxel, atorvastatina
salbutamol	1968	1996	zileuton, efavirenz, olanzapina
prostaglandinas	1970	1997	zafirlukast, montelukast
oxamniquina	1970	1998	infliximab
nifedipina	1975	1999	celecoxib orlistat sildenafil
cimetidina	1976	2000	galantamina rofecoxib
atenolol	1976	2001	imatinib
captopril	1977	2002	apomorfina, etoricoxib
oxicams	1980	2003	varденаfil, gefitinibid, aripiprazola
praziquantel	1980	2004	rosuvastatina, rofecoxib
aciclovir	1981	2005	pregabalin, Caduet ^R
		2006	risperidona, vorinostat (Zolynza ^R)

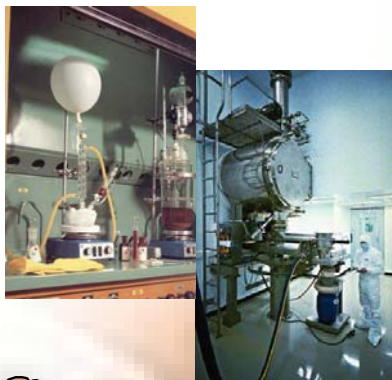




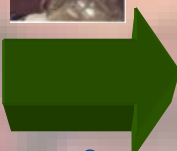
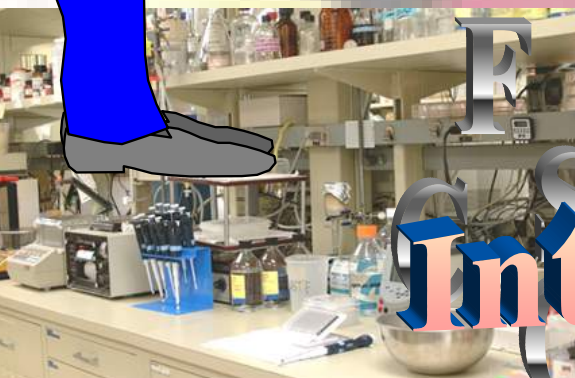
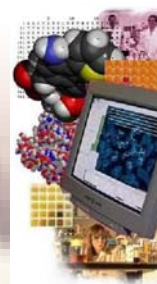
Química Medicinal

Atualmente, os novos fármacos, capazes de atuarem em **qualquer alvo-terapêutico**, são *descobertos* por planejamento **racional**.



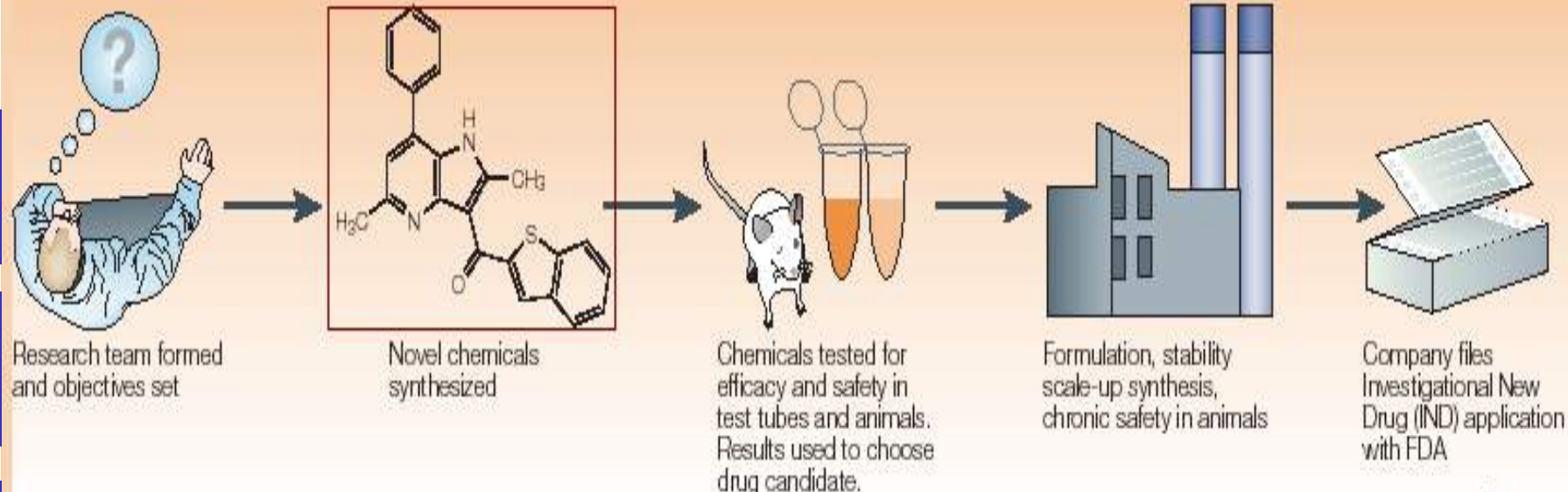


Como nascem os
fármacos ?

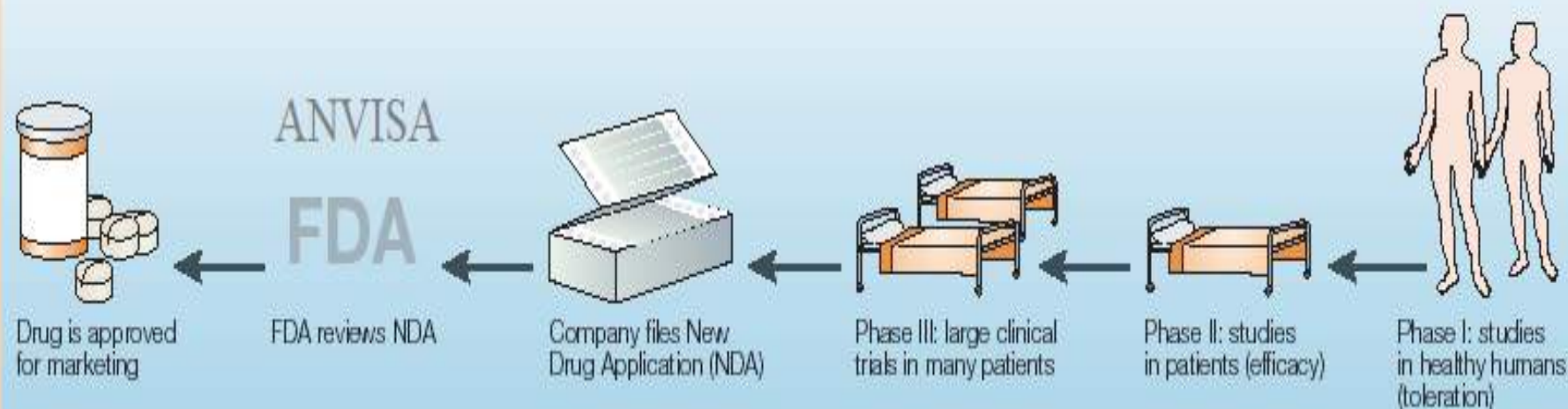


Interdisciplinaridade

Preclinical studies



Clinical studies



Fármaco / Medicamento



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Origem dos Fármacos

85%

Produtos Naturais

propranolol
cimetidina
atorvastatina
robótica

Sintéticos

Fármacos

Novos

marinhos
AZT, ET-743

microorganismos,
fungos
antibióticos

vegetais
taxol^R
galantamina



Estudo do
metabolismo

penicilinas



hicantona
oxifenilbutazona

CADD

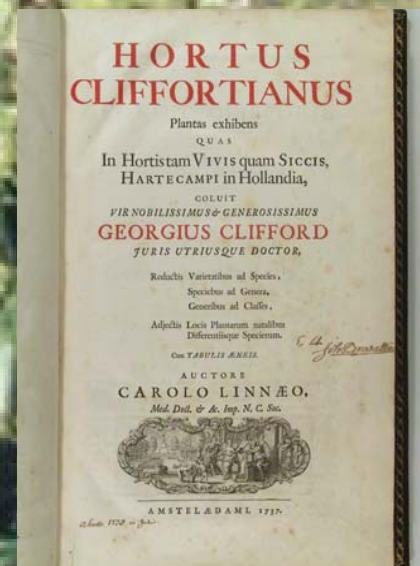
sulfas
diuréticas



Acaso

benzodiazepínicos

Produtos Naturais e os Fármacos



C Viegas Jr, V S Bolzani, EJ Barreiro, *Quim Nova* 2006, 29, 326-337

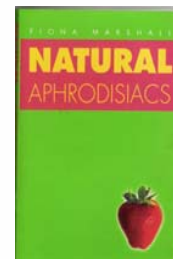
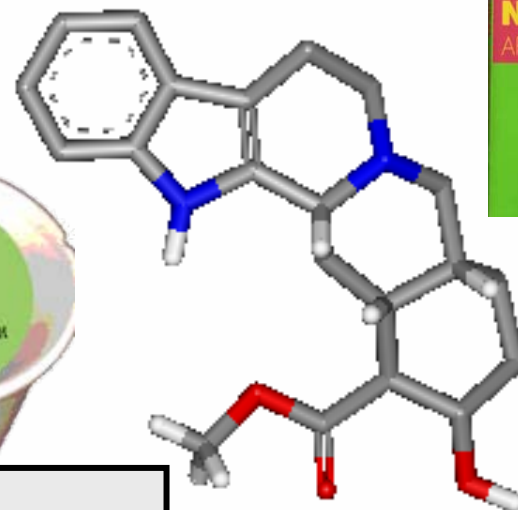
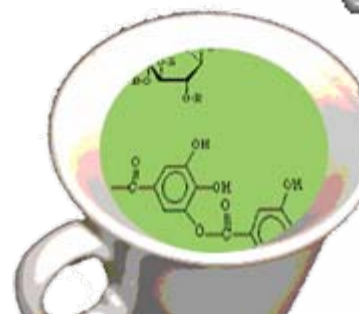
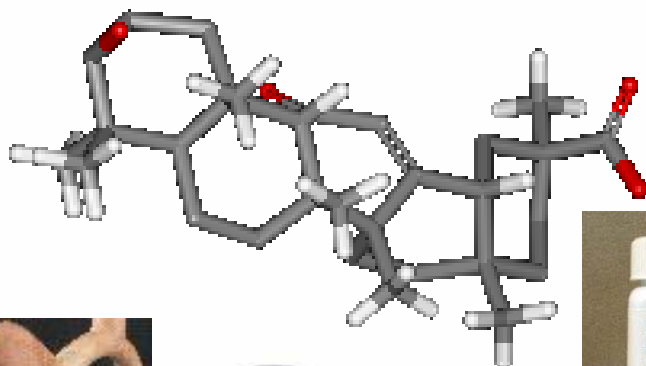
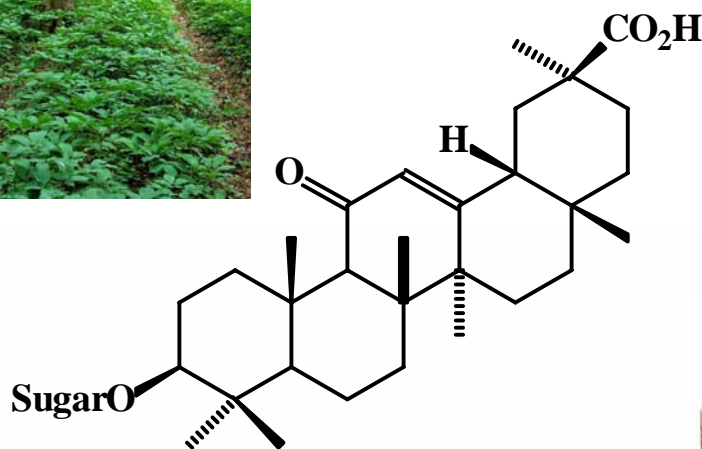
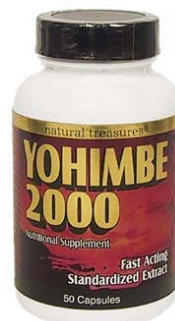
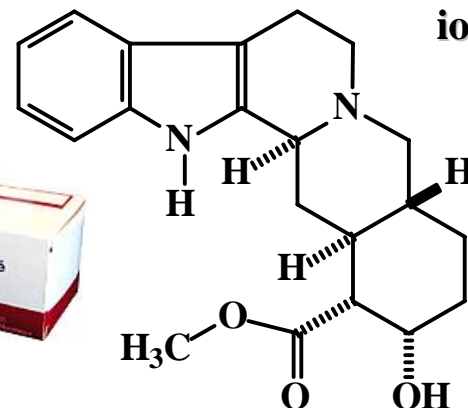


Produtos Naturais

Afrodisíacos

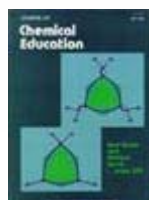
Aphrodisiacs are substances that stimulate/increase sexual desire and performance.

ioimbina



Adaikan PG; Ratnam SS. Pharmacology of penile erection in humans. *Cardiovasc Intervent Radiol.* 1988, 11, 191-4.

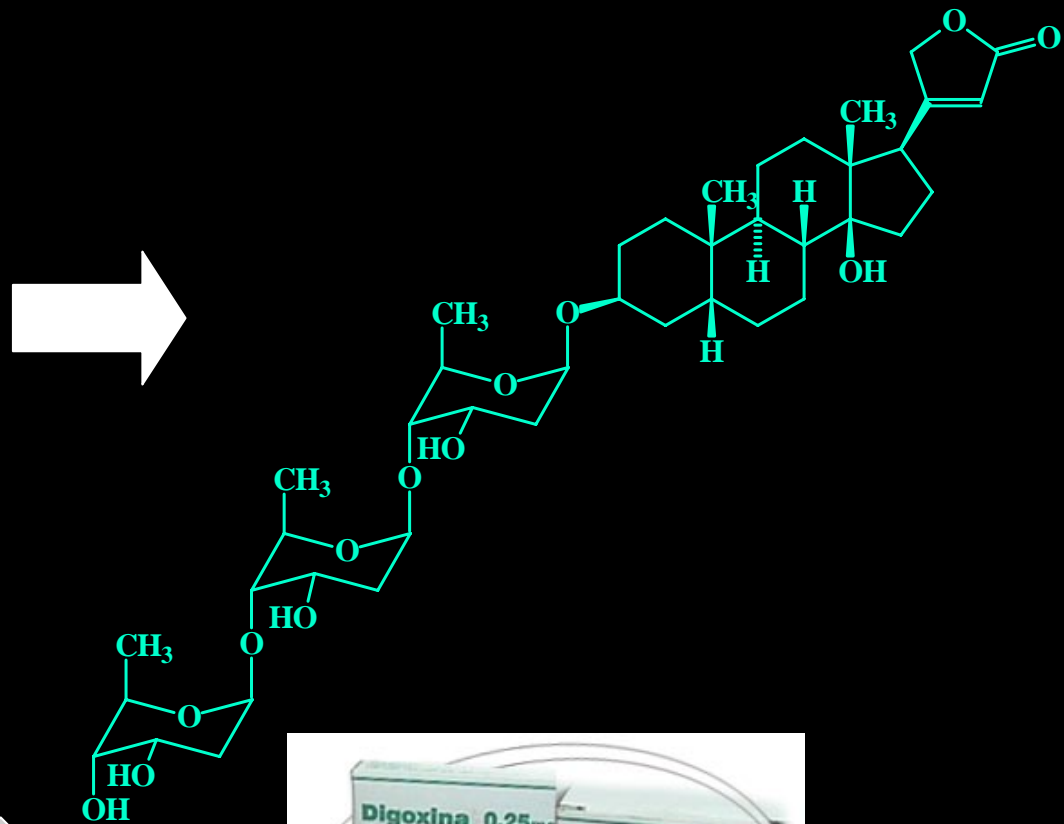
Yohimbe bark (Rubiaceae)
***Aspidosperma* sp., (Apocynaceae)**



T. G. Waddell, H. Jones & A.L. Keith
***J. Chem. Ed.* 1980, 57, 341-342**

Waddell TG, Ibach D Modern chemical aphrodisiac, *Indian J Pharm Sci.*, 1989, 51, 79-82.

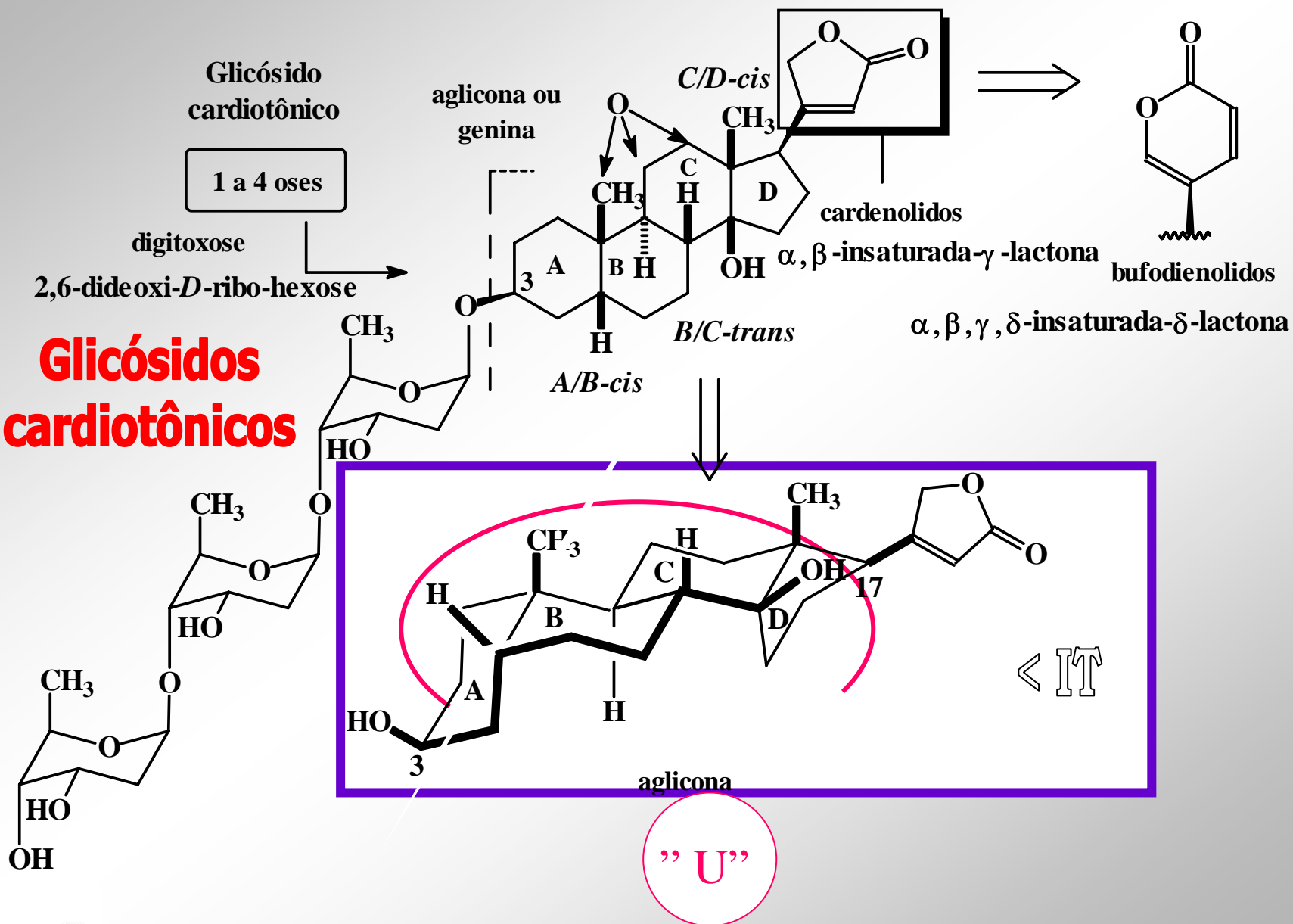
Glicosídeos Cardiotônicos

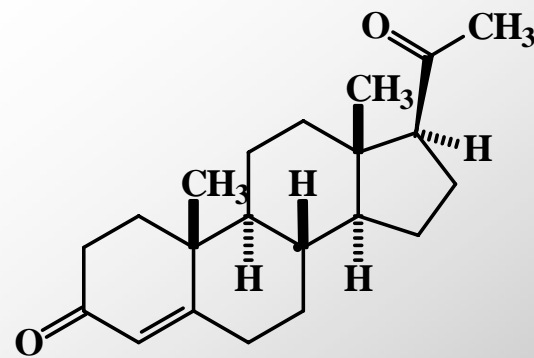
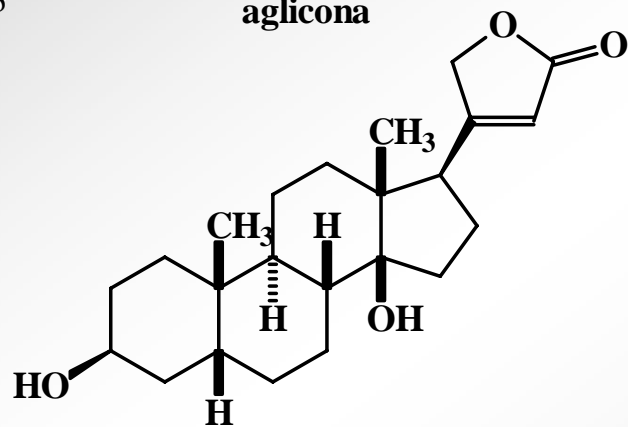
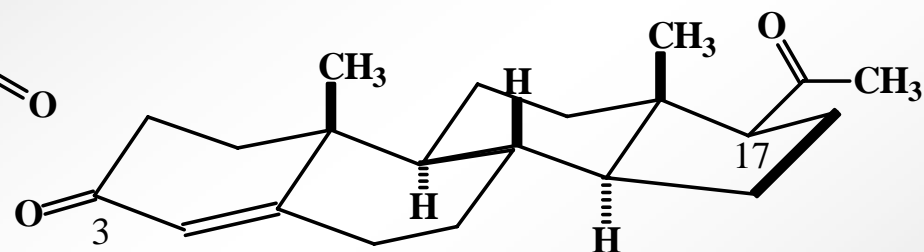
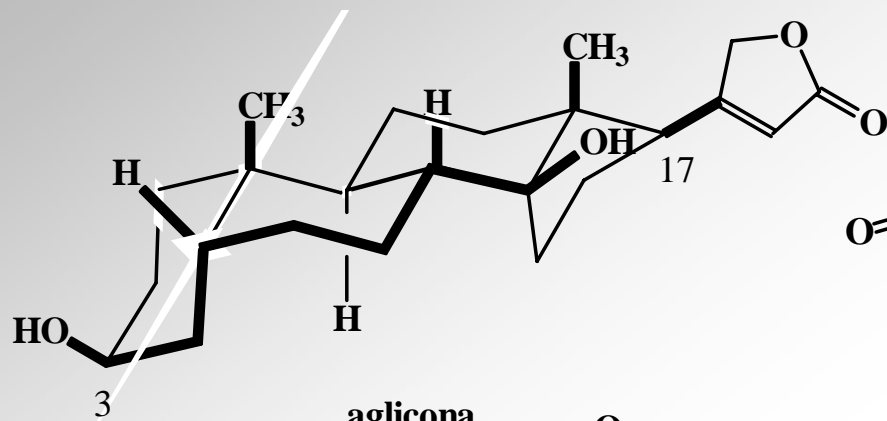


Decano dos Fármacos

1,000 kg of das folhas secas produzem 1 kg de digoxina

Glicósidos cardiotônicos





A Importância da Conformação

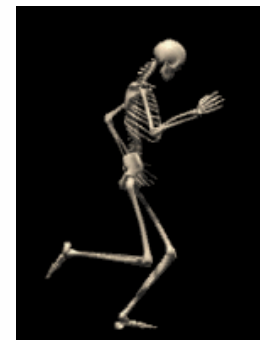
Índice Terapêutico

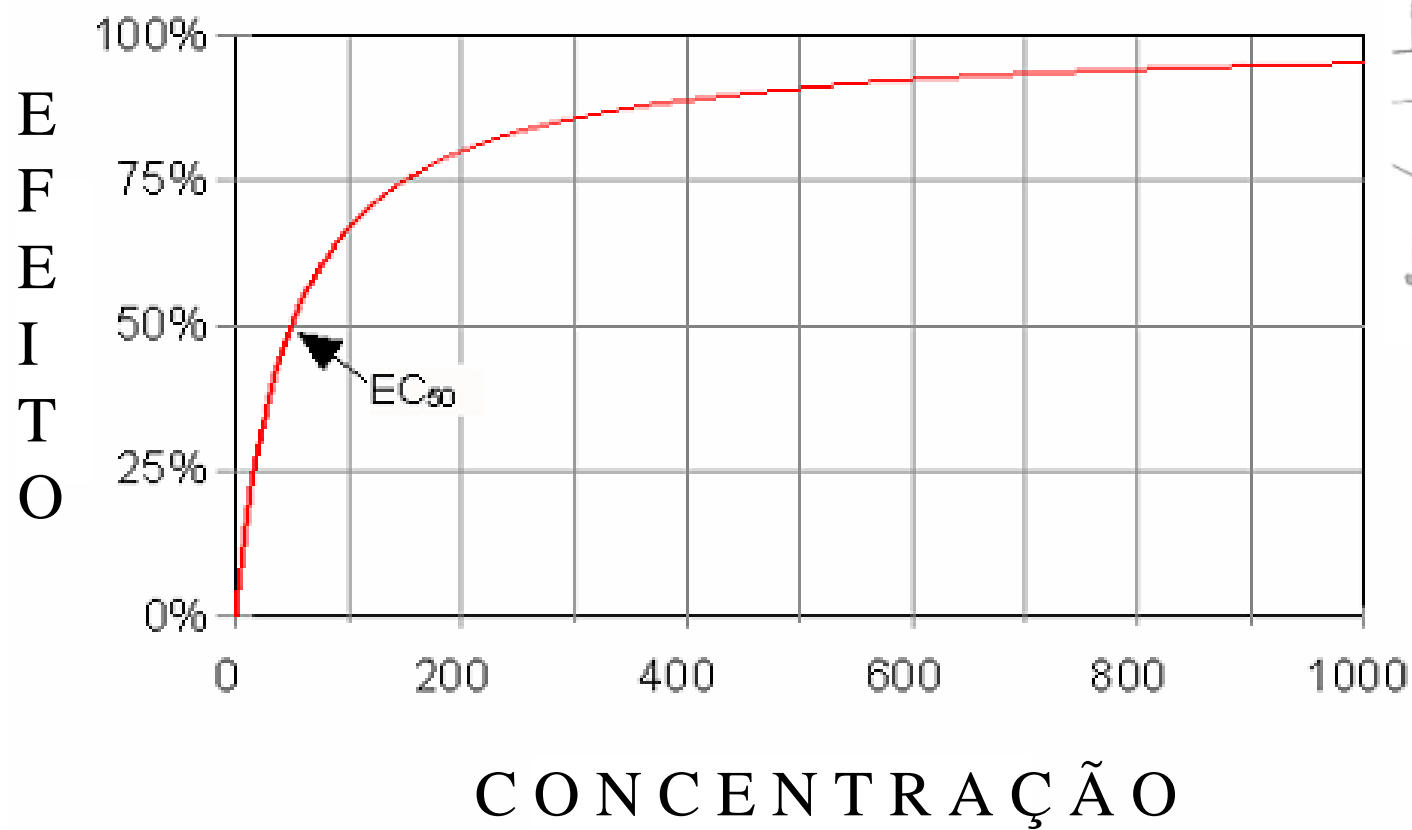
Compreende a relação entre a dose letal cinquenta e a dose efetiva cinquenta.

$$IT = \frac{LD_{50}}{ED_{50}}$$

OMS

$IT > 10$





in vivo



$EC_{50} = ED_{50}$ Dose efetiva em 50%

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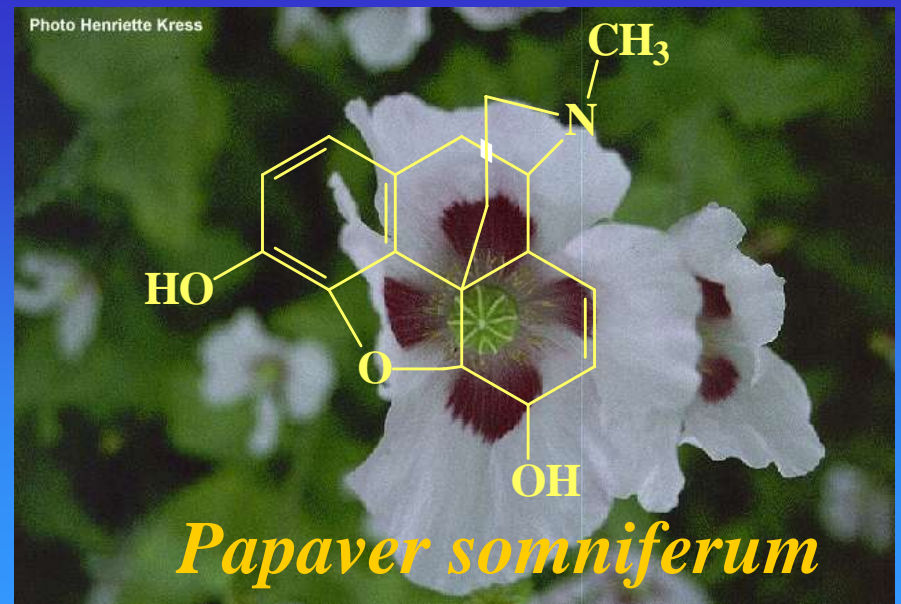
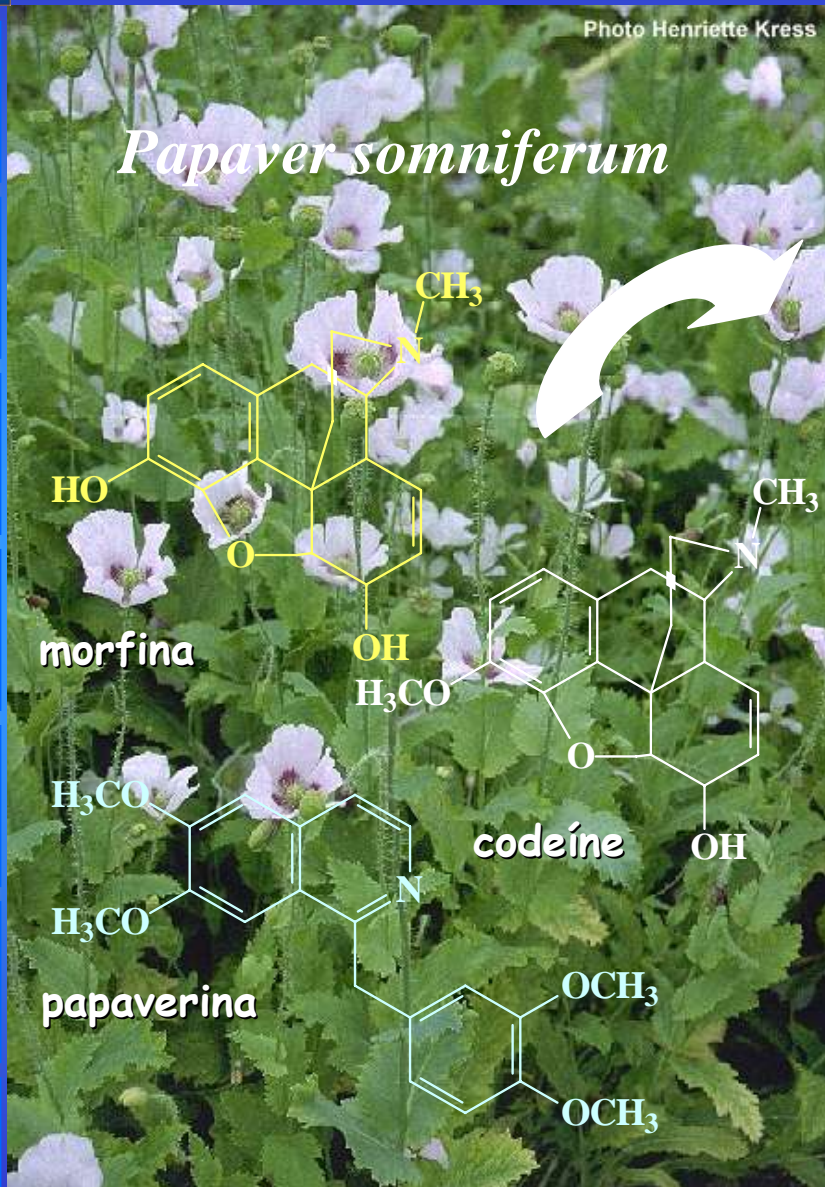
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1493-1541 Marco Polo (Veneza) ⇒ Ópio

1806 ⇒ Friedrich Sertürner isola a morfina ("Morpheus") ⇒ hipno-analgesia

P. W. Schiller, *Progr. Med. Chem.* 1991, 28, 301

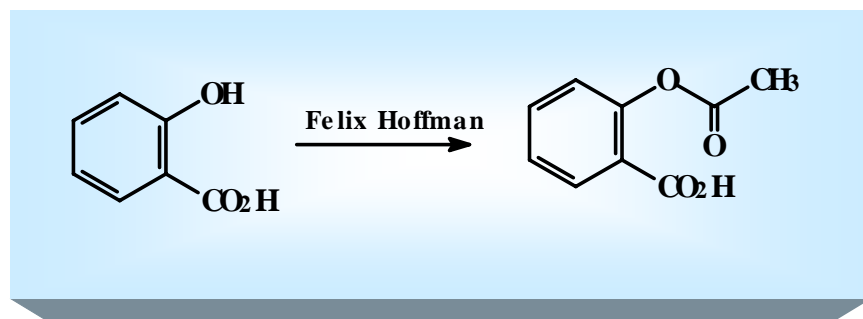
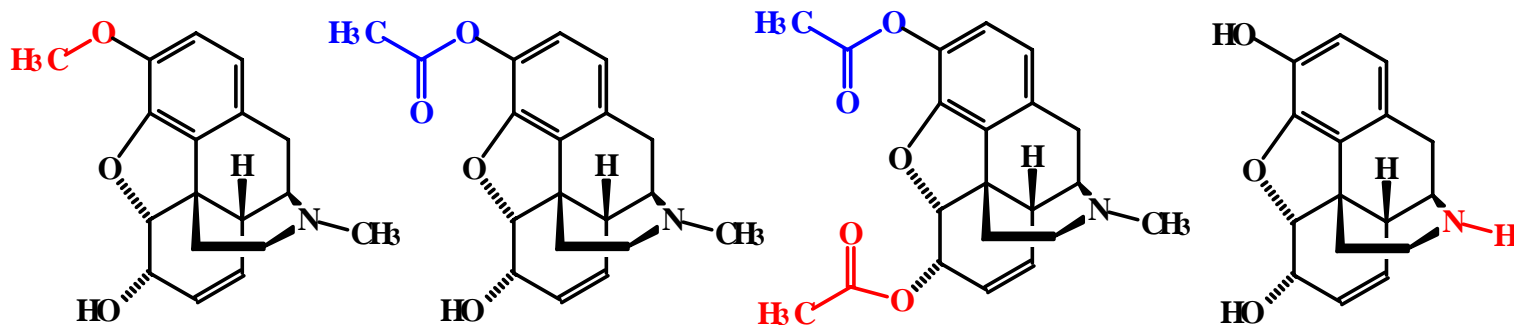
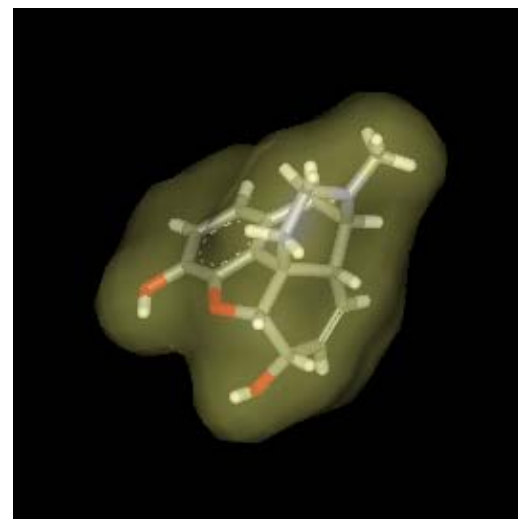
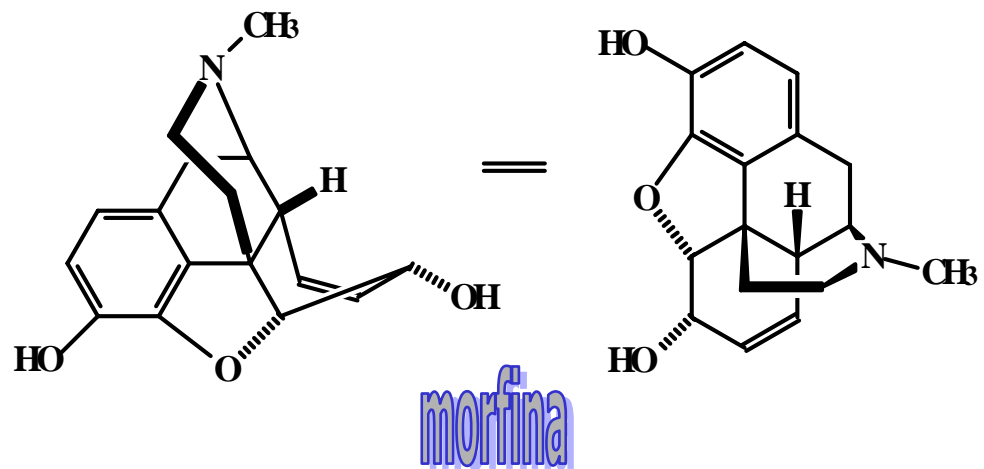
Sub-tipos de receptores centrais: δ , κ , μ

Alcalóides fenantrênicos e

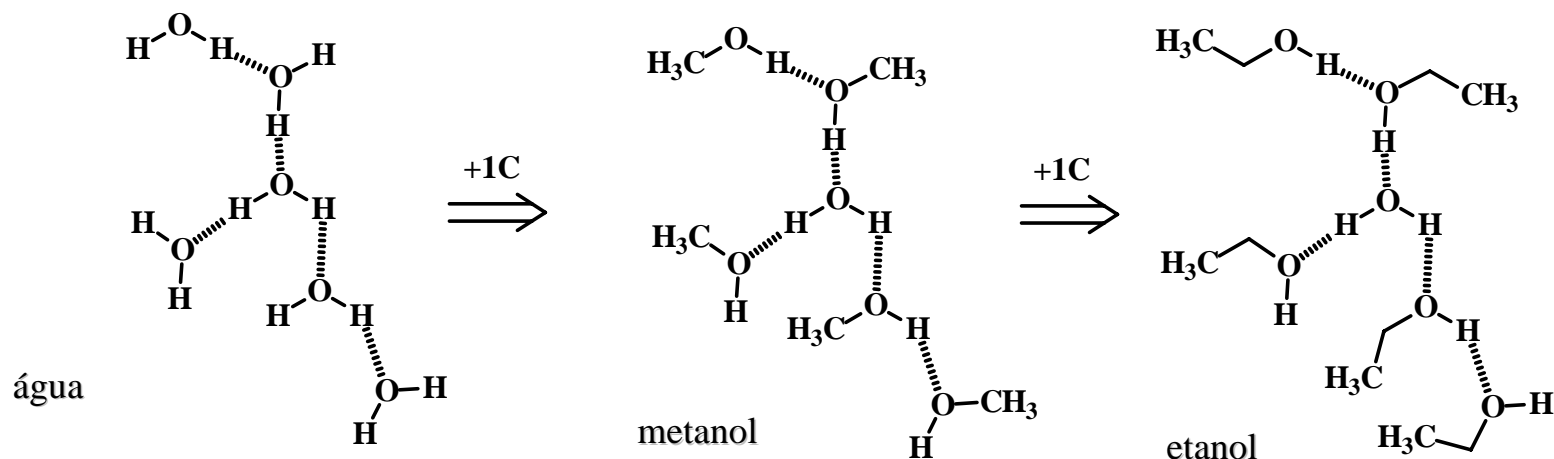
benzilisquinolínicos

(papaverina 0,2%)

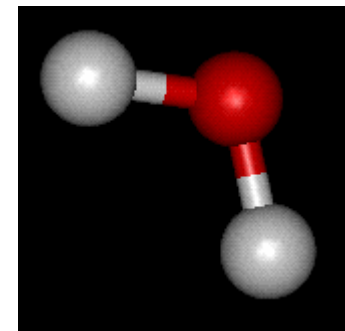
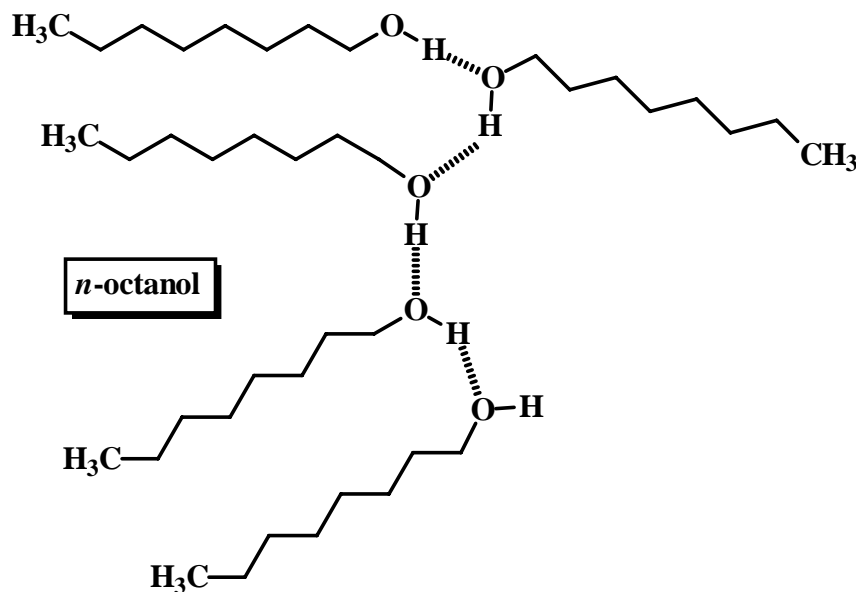
analgesia central; tolerância; dependência química;
síndrome de abstinência



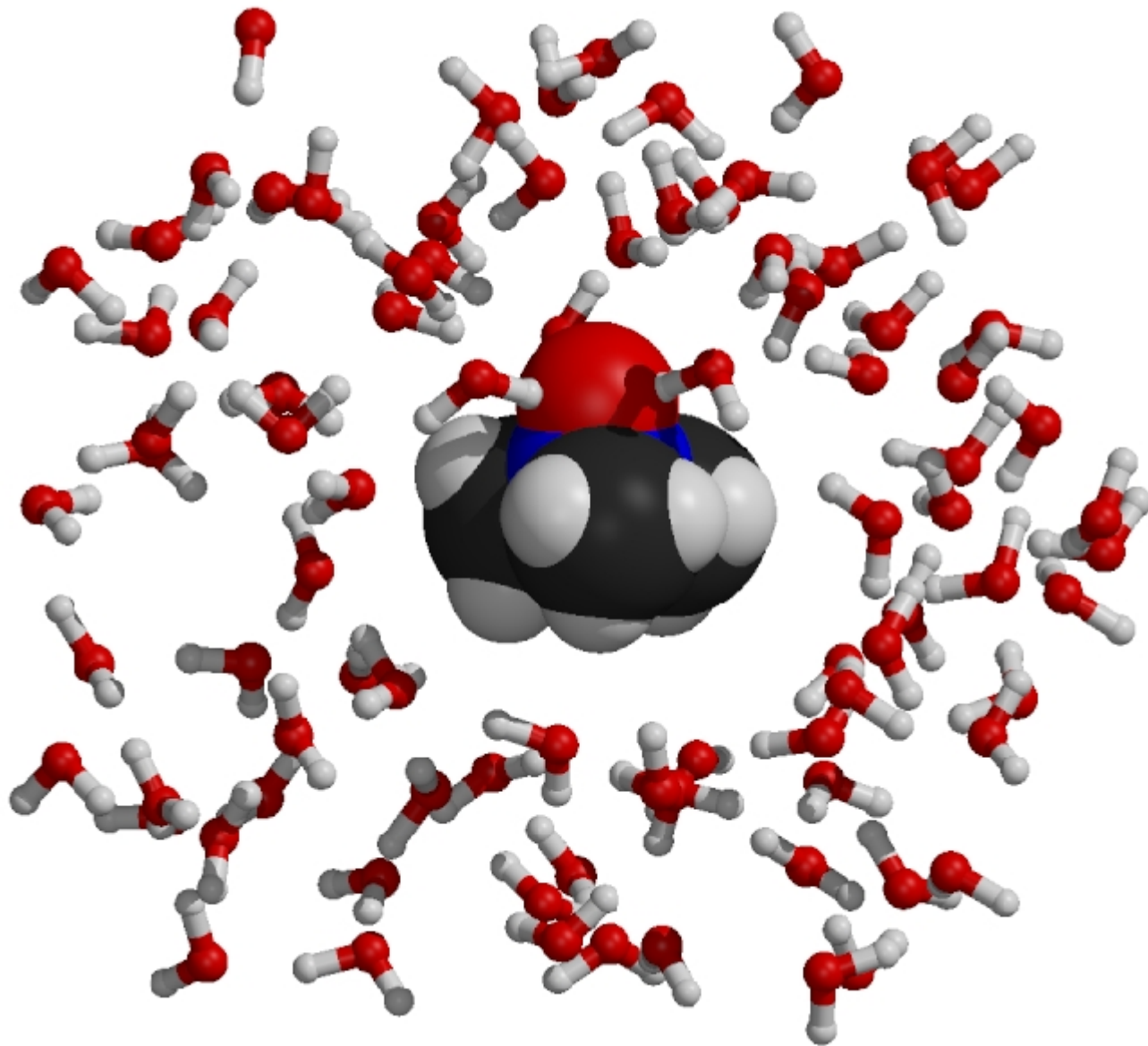
Visão dos Grupos Funcionais



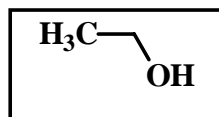
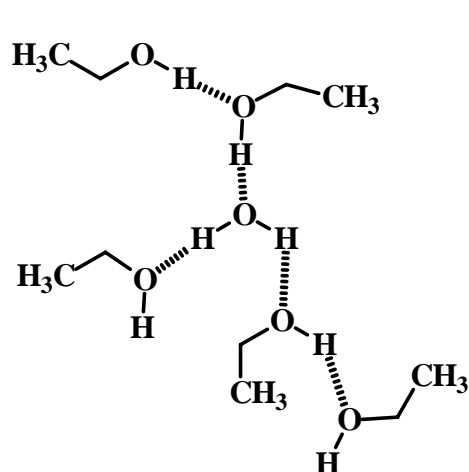
Ligação-H



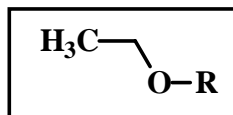
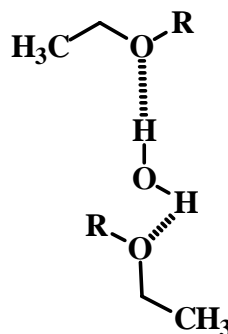
Visão dos Grupos Funcionais



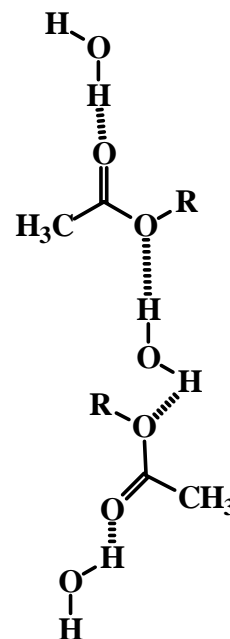
Visão dos Grupos Funcionais



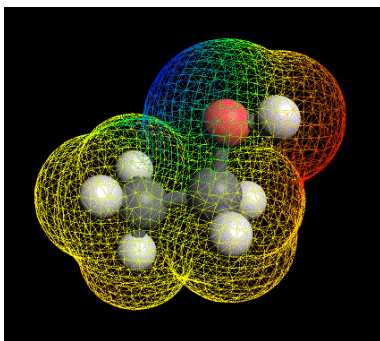
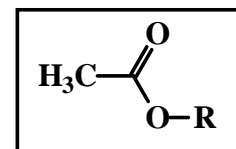
álcool



éter

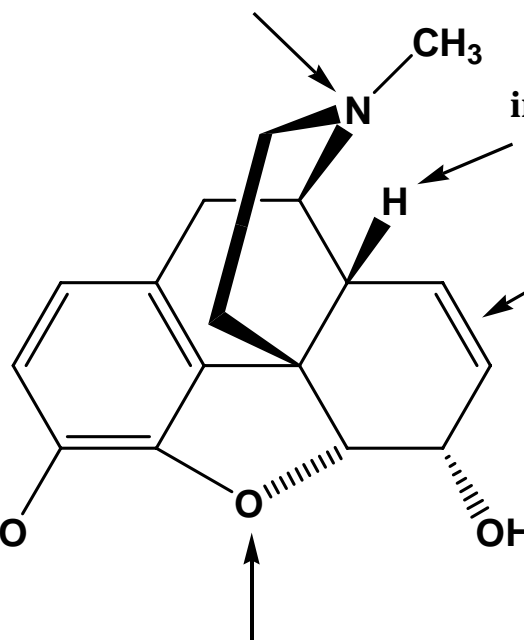


éster



N-CH₂-CH₂Ph aumenta a atividade
N-CH₂-CH=CH₂ produz antagonismo

- * remoção da hidróxila reduz a atividade;
- * troca bioisostérica reduz a atividade;
- * metilação reduz a atividade;
- * acetilação reduz a atividade;



introdução de hidróxila
aumenta a atividade

redução da insaturação
aumenta a atividade

- * redução da hidróxila aumenta a atividade;
- * oxidação a carbonila reduz a atividade;
- * acetilação aumenta a atividade;

remoção aumenta a atividade



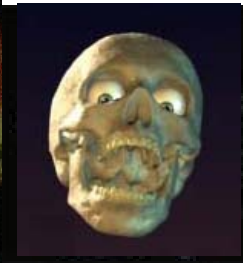
Papaver somniferum



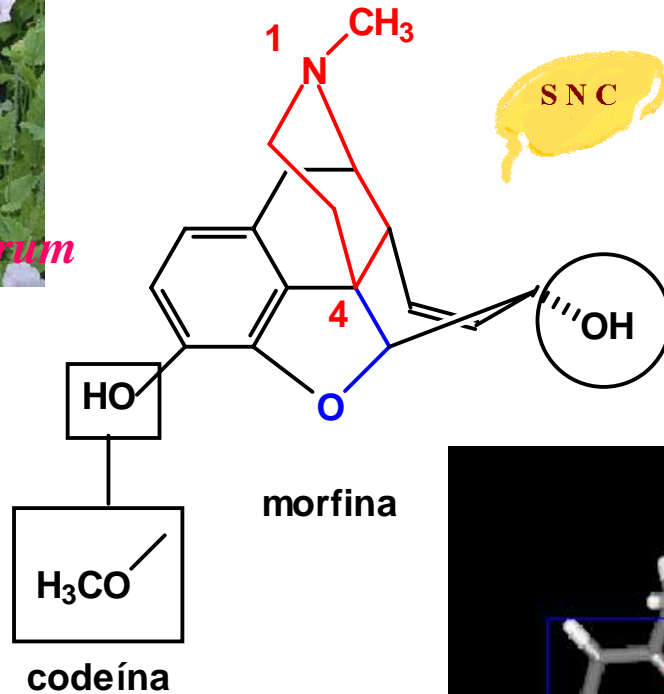
Papaver somniferum
Opium Poppy



DOR

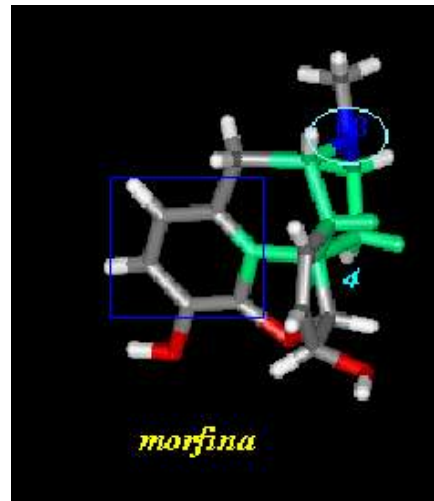


Gênese dos Analgésicos Centrais

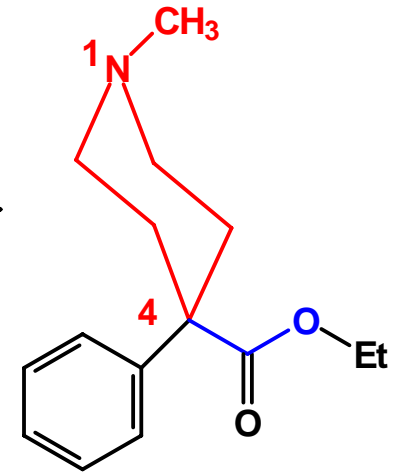


morfina

codeína



"strip-tease"
molecular
simplificação
molecular



4-fenilpiperidinas

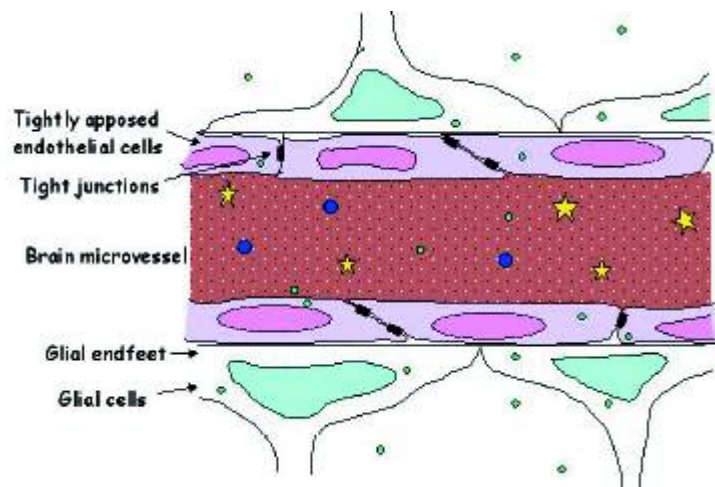
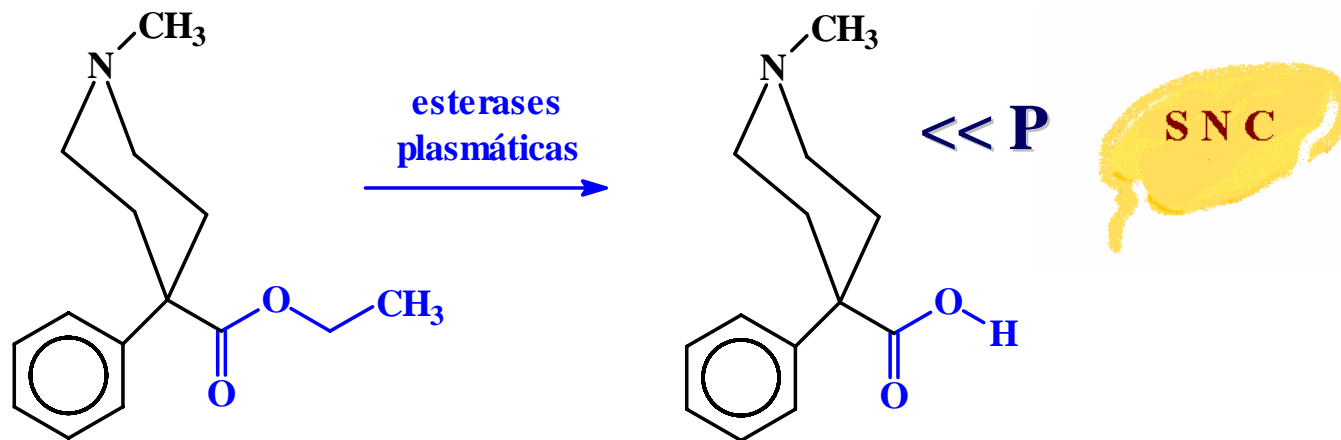
meperidina
Dolantina^R



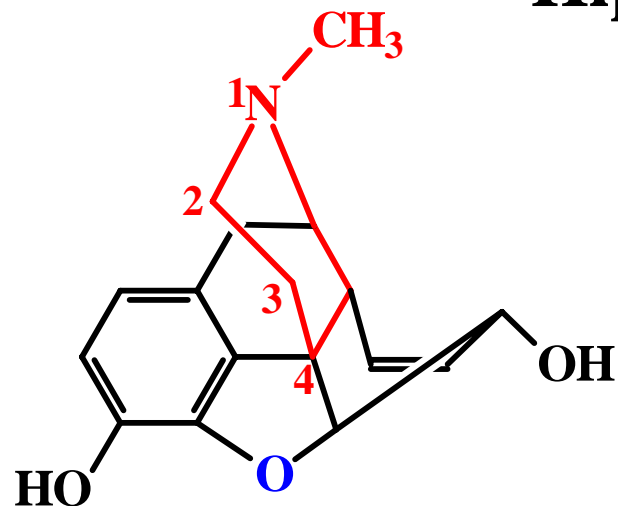
metadona
Fenadona^R

Schultz et al., 1947

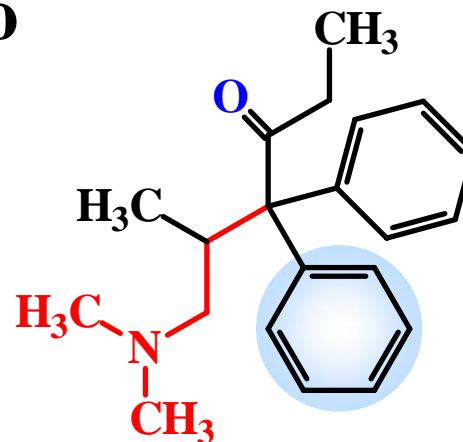




Hipno-analgésico sintético



morfina



metadona



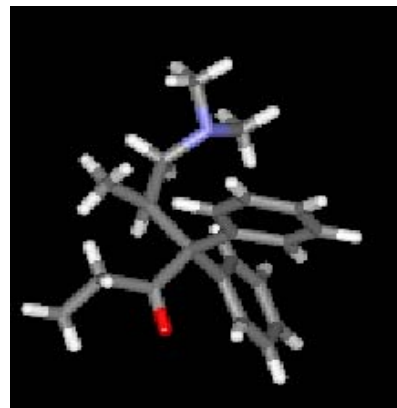
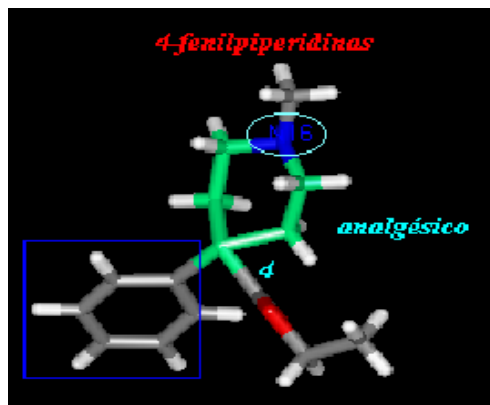
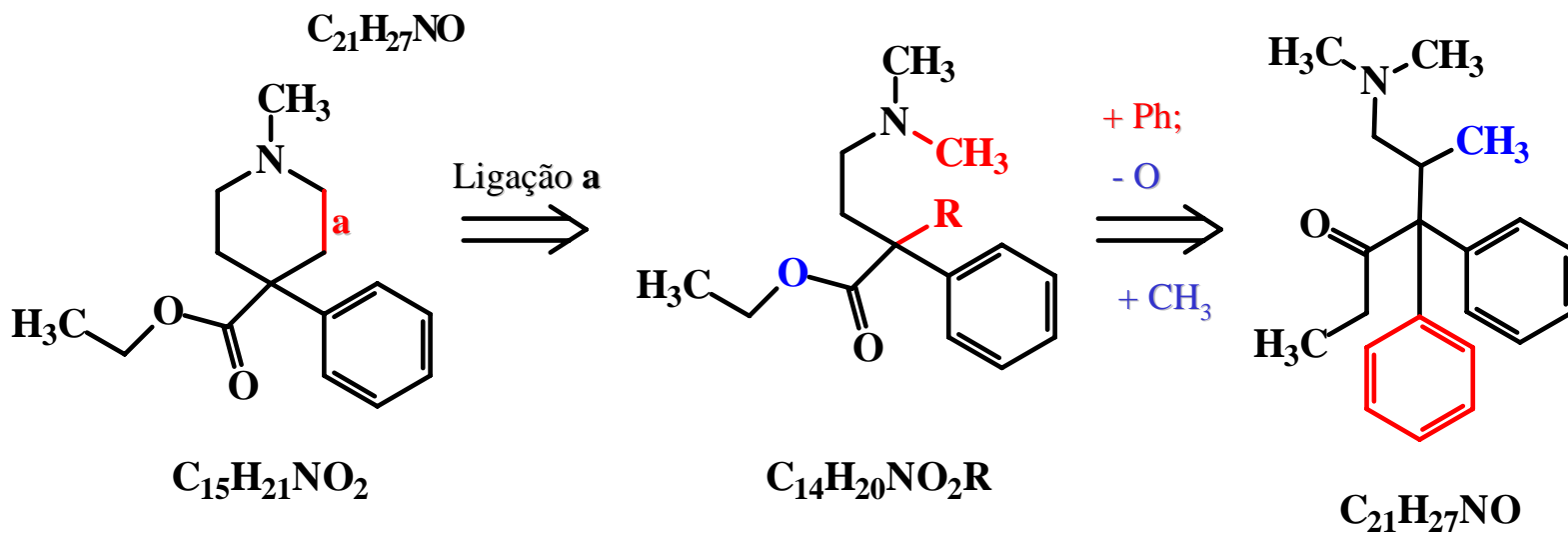
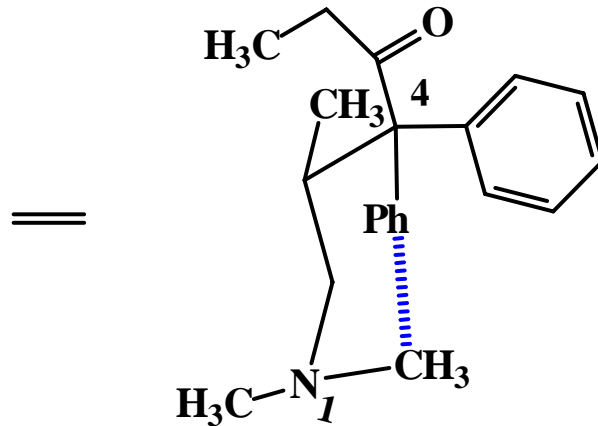
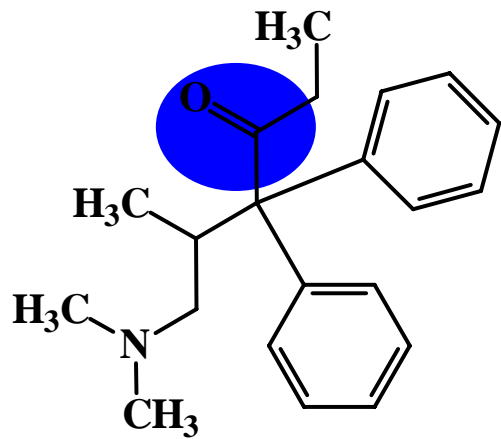
1947

6-Dimetilamino-4,4-difenil-3-heptanona

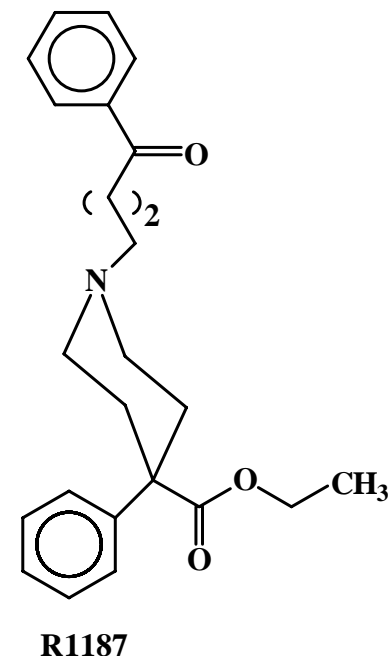
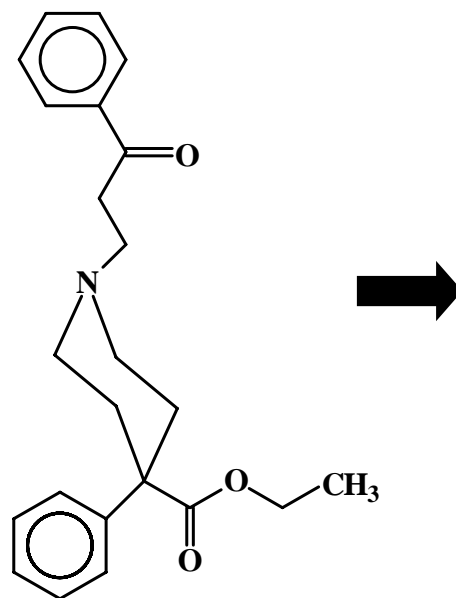
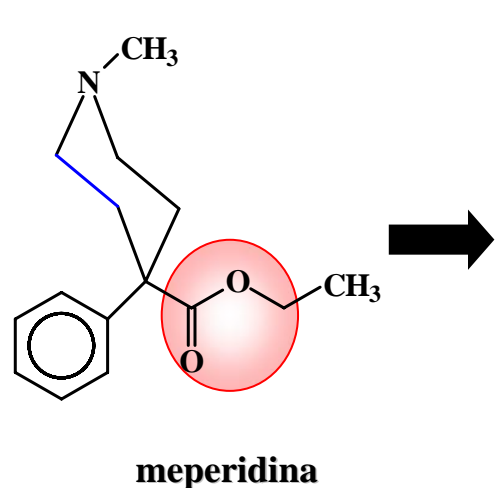
$C_{21}H_{27}NO$

Depridol





... da morfina às butirofenonas...!



Paul Janssen
1926-2003

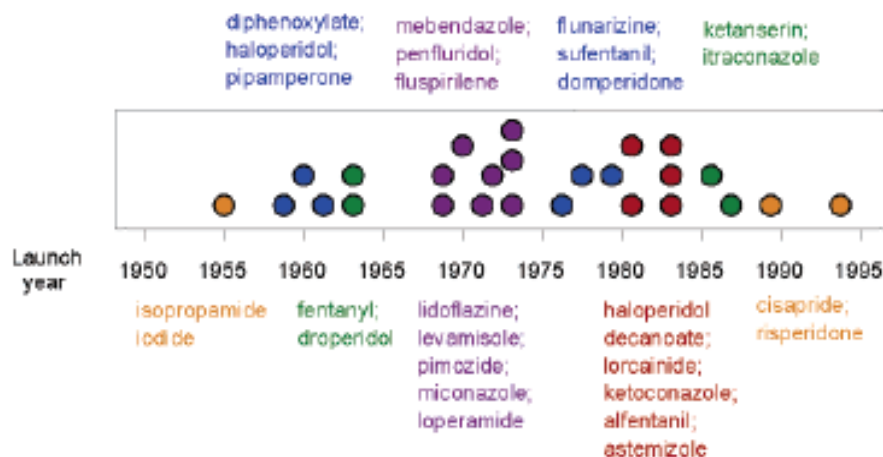
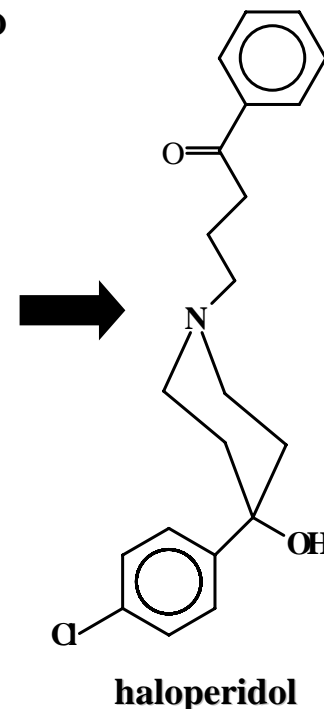
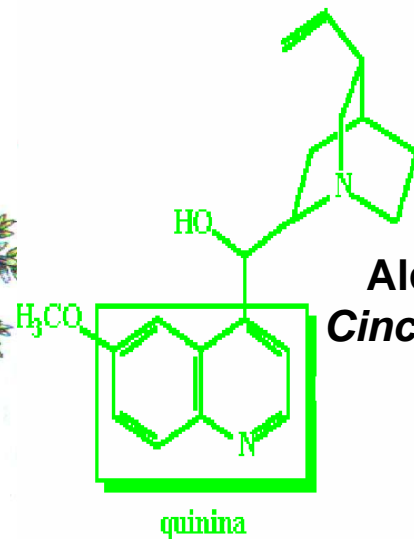
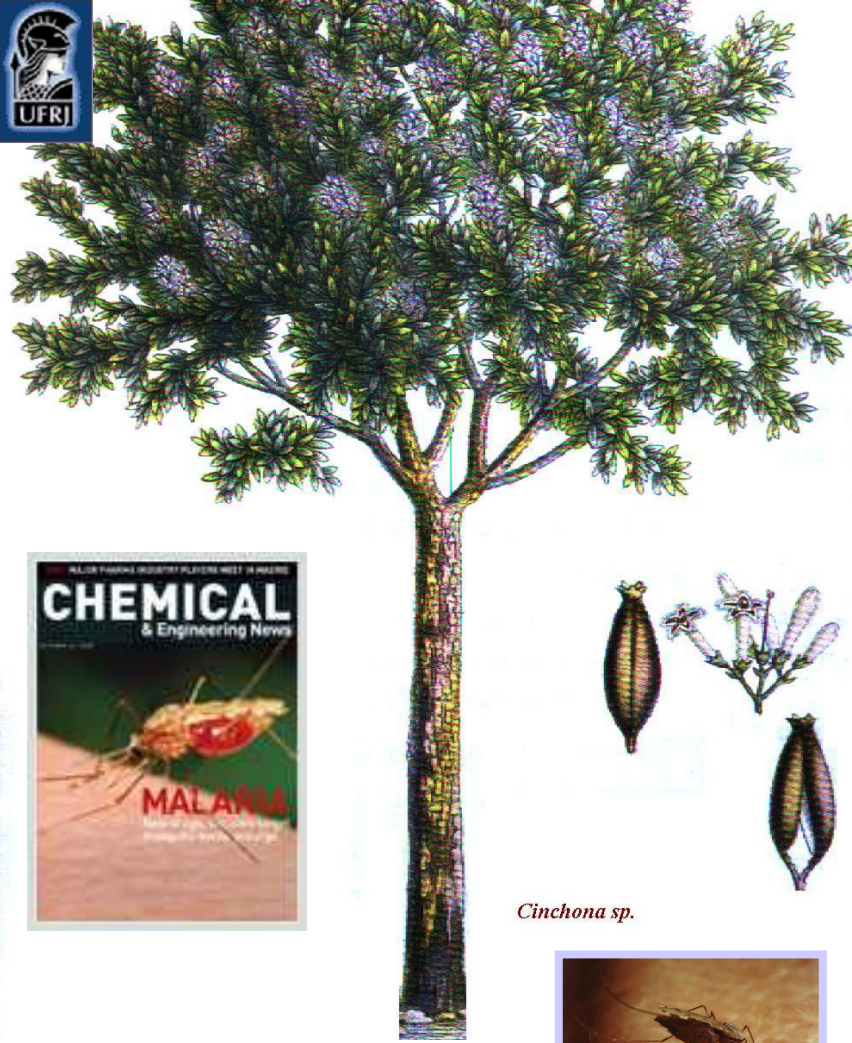


Figure 1. Some major pharmaceuticals introduced under Dr. Paul Janssen's leadership.



R.A. Galembo, Jr., F. E. Janssens, P. J. Lewi, B. E. Maryanoff, "In Memoriam: Dr Paul A. J. Janssen (1926-2003)", *J. Med. Chem.* 2005, **48**, 1668.

Quinina

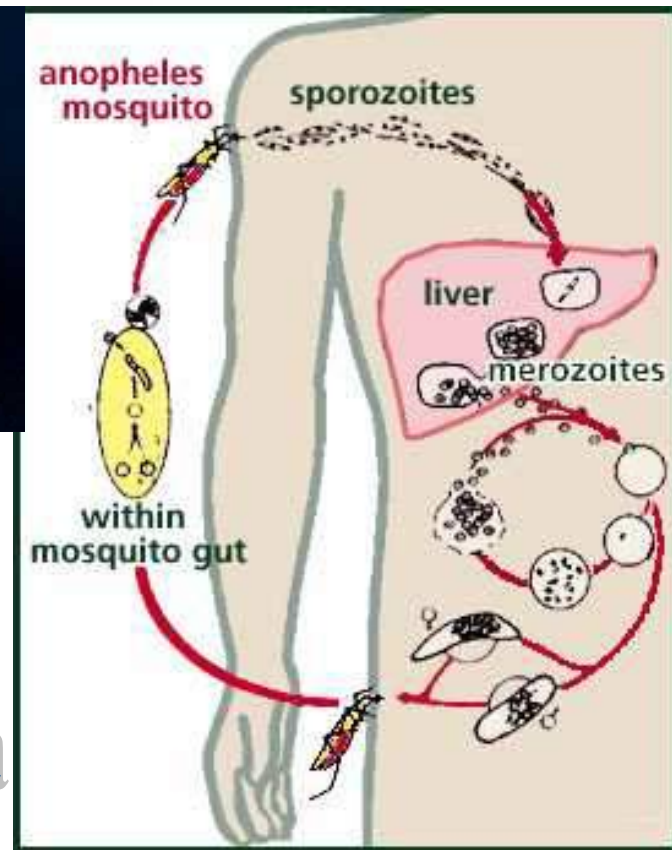


Alcalóide quinolínico isolado de *Cinchona officinalis* que originou os fármacos anti-maláricos quinolínicos.

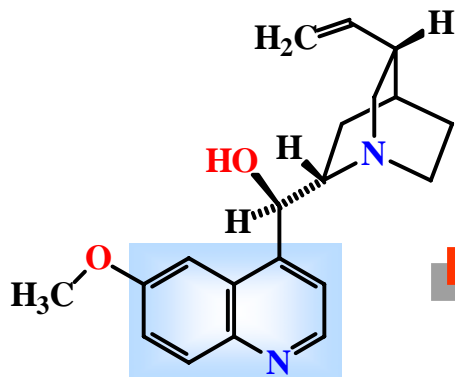


Condessa del Cinchon
Francisca Henriquez de Rivera
(1576-1639)

A Quinina e a Malária

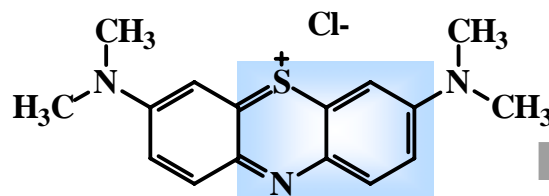


A gênese dos antimalaríais: quinina, protótipo natural



Bernardino Gomes, 1811
Pelletier & Caventou, 1820
R. Woodward & W. E. Doering
J. Am. Chem. Soc. 1944, 66, 849.

Quinina

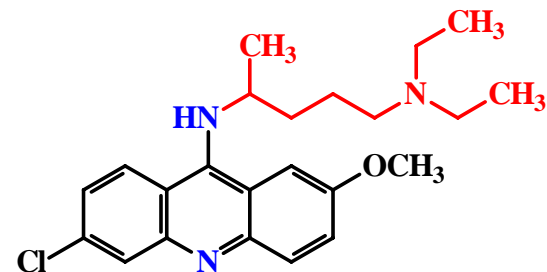


Azul de metileno
(Heinrich Caro, 1876;
Paul Ehrlich, 1881)

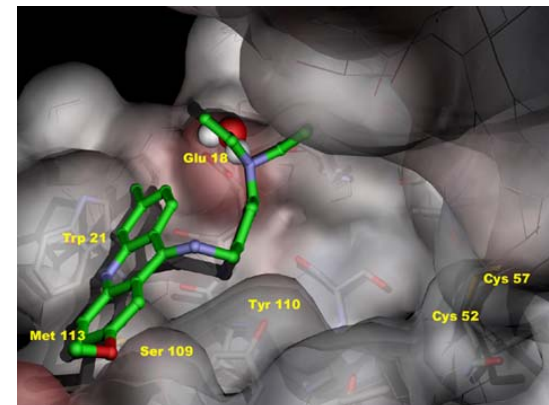


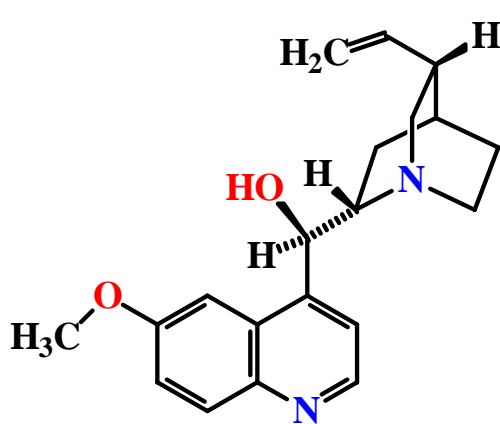
Azul de metileno como antimalarial:
JL Vennerstrom *et al.*, *Antimicrob.*
Agents Chemother. 1995, 39, 2671.

9-aminoacridina

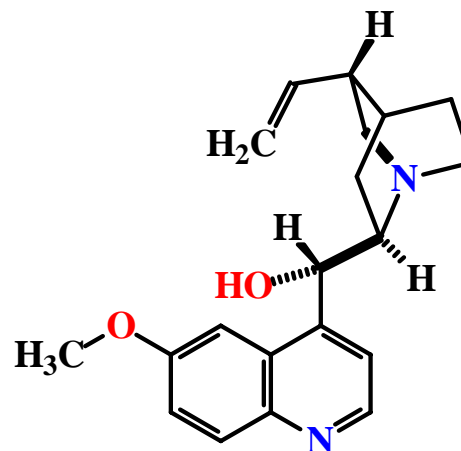


Mepacrina (1932)





quinina



quinidina

1833 – (D)-isômero ótico (0.25-3.0%)

Isolado por L. Henry & A. Delondre

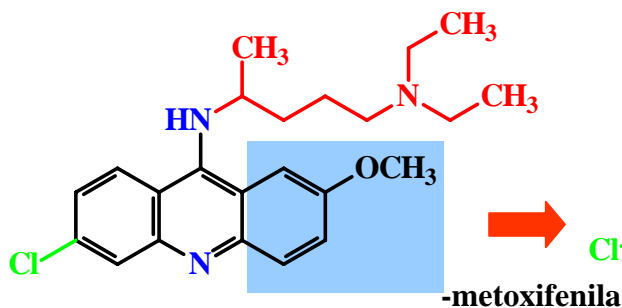
Configuração: Prelog, Zalán,

Helv. Chim. Acta 27, 535 (1944)

1912 –efeito cardioativo reconhecido
antiarrítmico

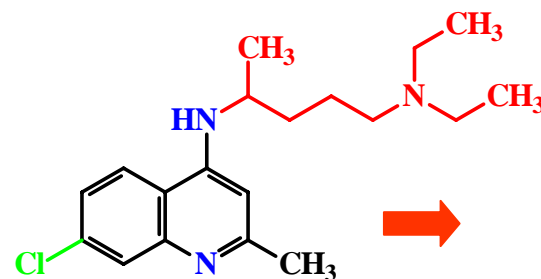


9-aminoacridina



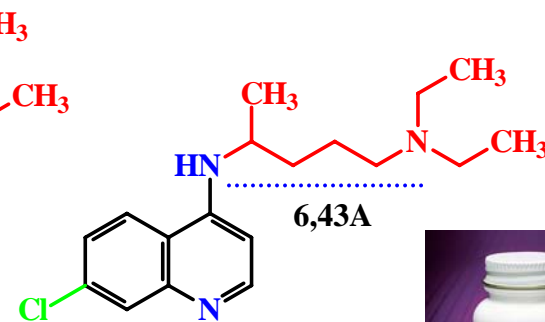
mepacrina

4-aminoquinolina



santoquina

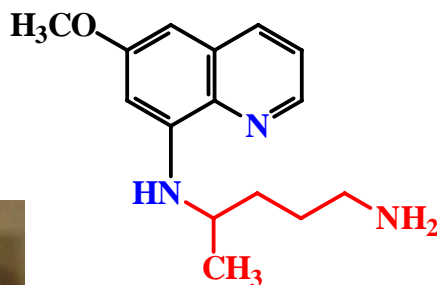
4-aminoquinolina



Cloroquina
(1934)
fotossensibilizante

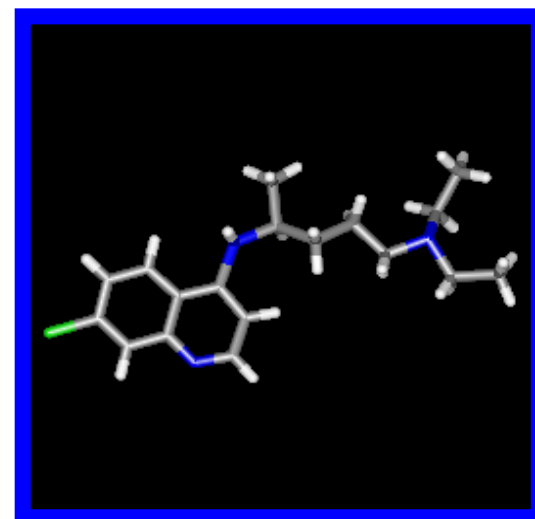


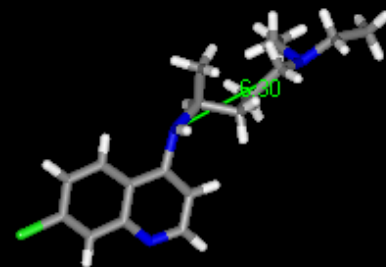
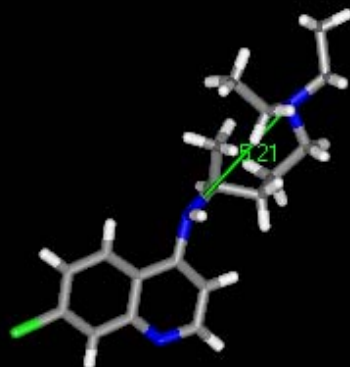
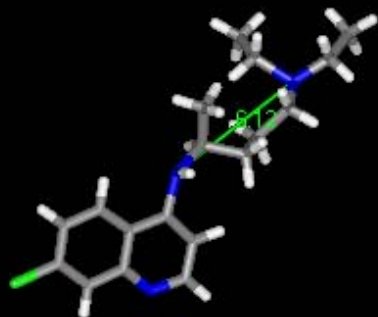
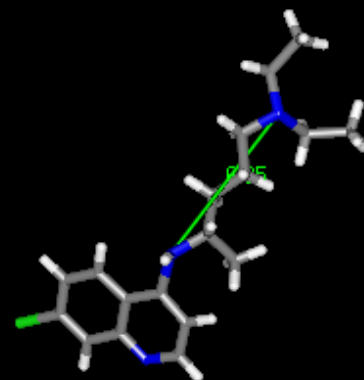
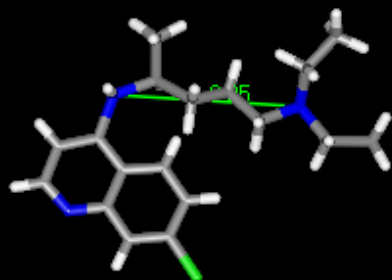
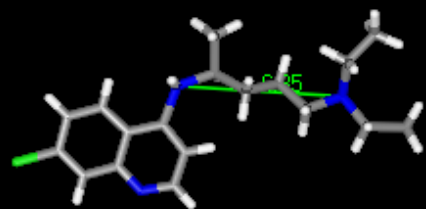
8-aminoquinolina

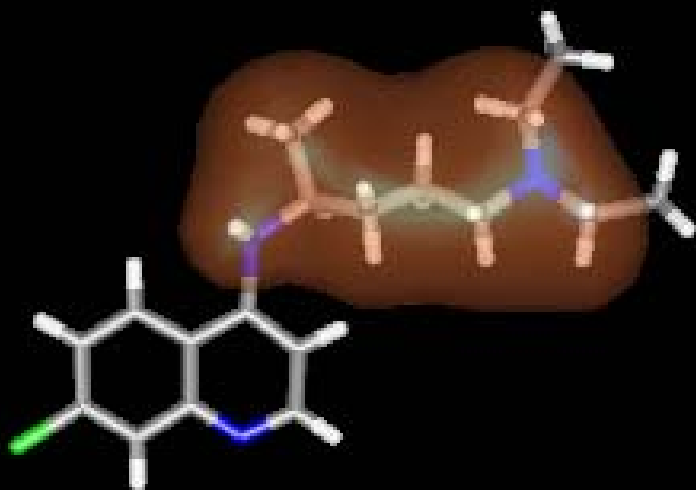


Primaquina
1944 –Un. Columbia

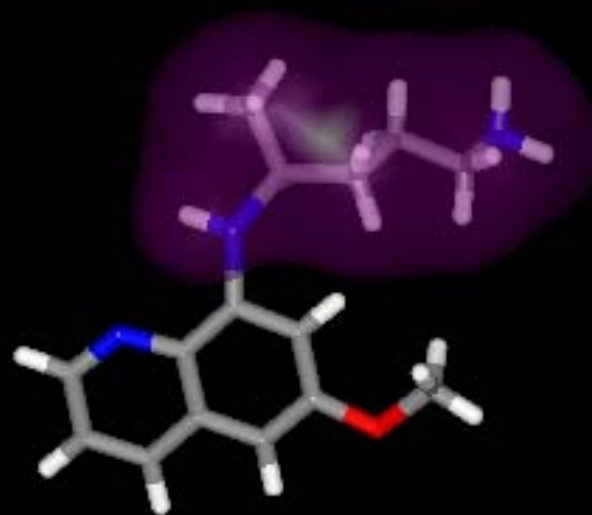
hemolítico



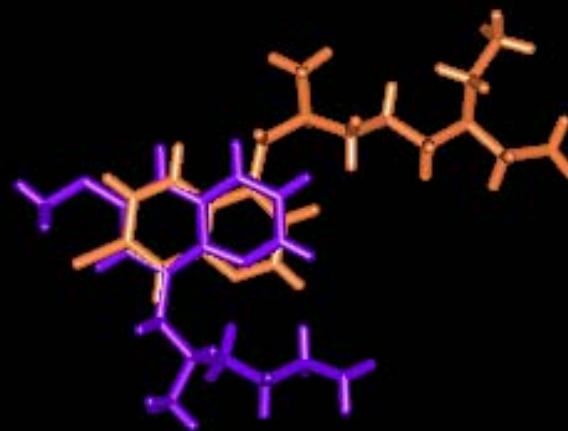
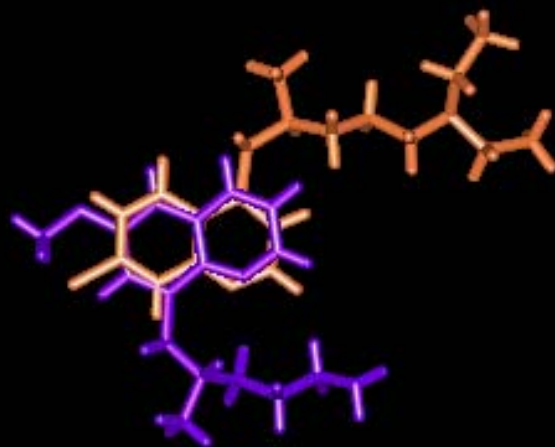




cloroquina



primaquina

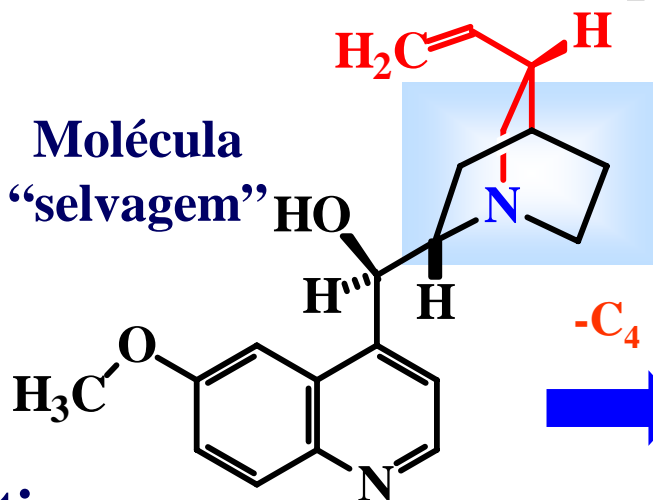


Cloroquina-primaquina

Evolução dos Antimalaríais: O produto natural como protótipo



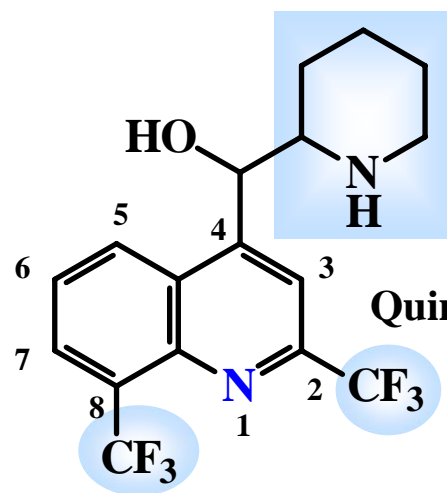
Molécula
“selvagem”



Protótipo
natural

quinina

quinuclidinil



mefloquina

piperidinil

Molécula
“domesticada”

Quinolina-metanol

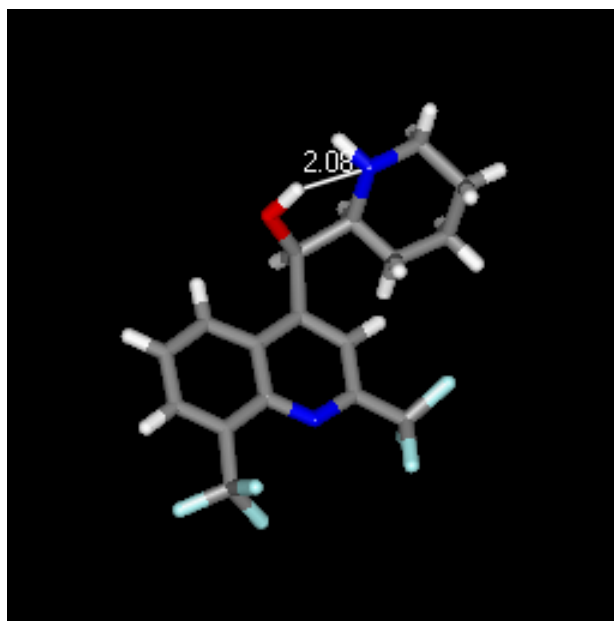
Larian^R

C. J. Ohnmacht *et al.*, J. Med. Chem. 14, 926 (1971)



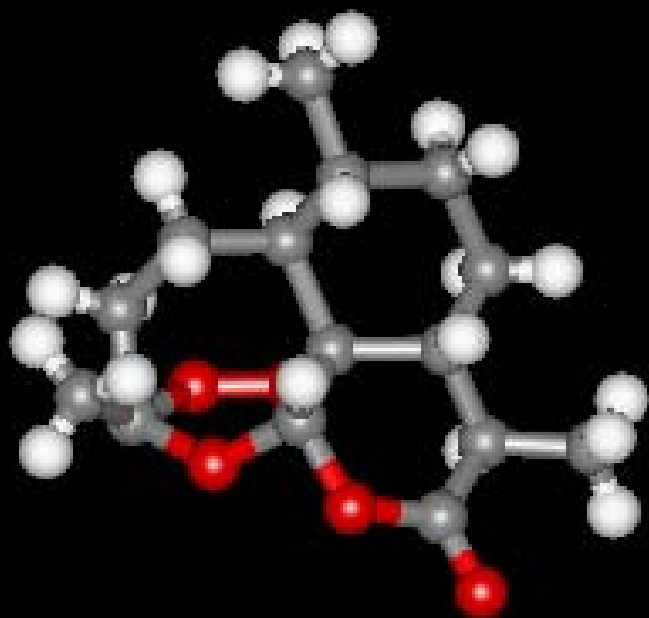
Walter Reed Institute
US Army

Uma única dose ao dia p.o.





Artemisinina



Malária

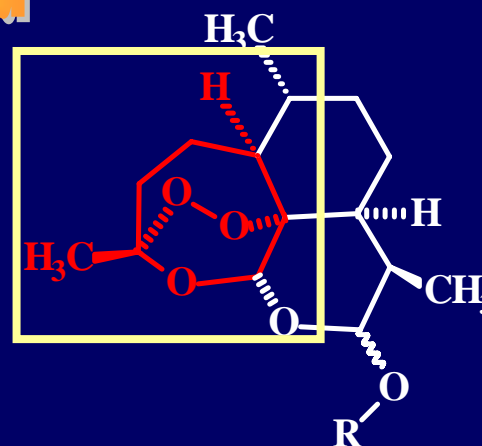
ADME

Qinghao

trioxana



Simplificação
molecular



Gary H. Posner

farmacóforo
natural



Artemisia annua (Composita)

Trond Steen

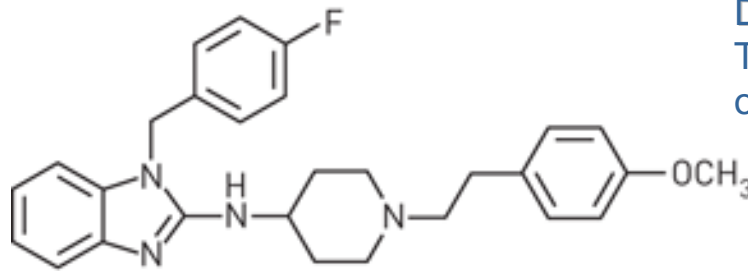
G. H. Posner *et al.*, J. Am. Chem. Soc. 117, 5885 (1995)

Borstnik, K.; Paik, I.-H.; Posner, G. H. **Malaria: New Chemo-therapeutic Peroxide Drugs.** *Mini-Rev. Med. Chem.* 2002, 2, 573.

Avery, M. A.; Alvim-Gaston, M.; Woolfrey, J. R. Synthesis and Structure-Activity Relationships of Peroxidic Antimalarials

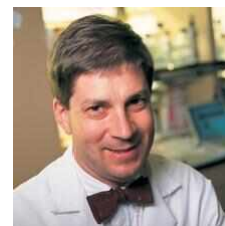
Based on Artemisinin. *Adv. Med. Chem.* 1999, 4, 125.

Screening a library of more than 2687 existing drugs, Sullivan and co-workers have identified an antihistamine that shows activity against malaria.



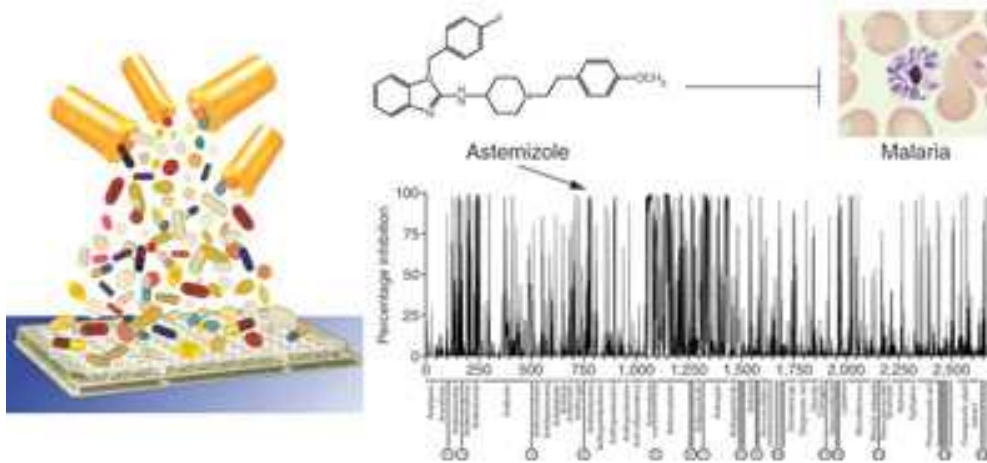
Astemizole

David J. Sullivan Jr.
The Johns Hopkins University School
of Medicine, Baltimore, Maryland



Chong CR, Chen X, Shi L, Liu JO, Sullivan DJ Jr. A clinical drug library screen identifies astemizole as an antimalarial agent. Nat. Chem. Biol. 2006, 2, 415-416.

The antihistamine astemizole and its principal human metabolite are promising new inhibitors of chloroquine-sensitive and multidrug-resistant parasites, and they show efficacy in two mouse models of malaria.





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Saturday, May 22, 12:42

MSF is an independent humanitarian medical aid agency committed to two objectives: providing medical aid whenever needed, regardless of race, religion, politics or sex and raising awareness of the plight of the people we help.



**Sudanese
refugee
crisis**



**A weapon of
mass destruction**
no one is
talking about



Burundi

Deprived of access
to healthcare

Current crisis - future catastrophe in Darfur, Sudan, unless immediate action is taken

"The international community has known the extent of the crisis in Darfur for many months," said Ton Koene, MSF Emergency Coordinator. "But people are still facing attacks. People are still terrified. Although some food has been distributed, much more is needed in the coming weeks - if not, more children and their parents will die".

[Go](#) [here](#) for more...

May 11: [Catastrophic conditions for Sudanese refugees in Chad](#)
Feb 17, 2004: [Massive aid urgently needed in Darfur, Sudan](#)
Feb 24, 2004: [Measles and malnutrition increasing in Sudan's Darfur region](#)

ALSO: [Sudanese refugee crisis in Chad](#)

MSF calls for the Israeli forces to stop firing on civilians in Gaza and to cease the massive destruction of homes

MSF demands unhindered access to provide relief. On the ground, our teams - though officially authorised to travel - are having guns pointed at them and their path blocked by tanks. The risks being run by our own volunteers, as well as other humanitarian agencies, are very significant.

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OTHER HEADLINES

MSF concerns about ongoing deportation of diamond miners confirmed by joint assessment

► To date, the Angolan authorities claim to have deported about 53,000 Congolese nationals, illegal diamond miners, through this region and have announced that a further 50,000 to 100,000 people will be deported through this region in the near future. [Go](#)

In the Shadow of Just Wars

► Challenges to humanitarian action. [Go](#)

Khayelitsha 2001-2004
Celebrating 1,000 people on antiretrovirals

► [Go](#)

**1000
people on
ARVs
Khayelitsha
2004**

Move with the threat

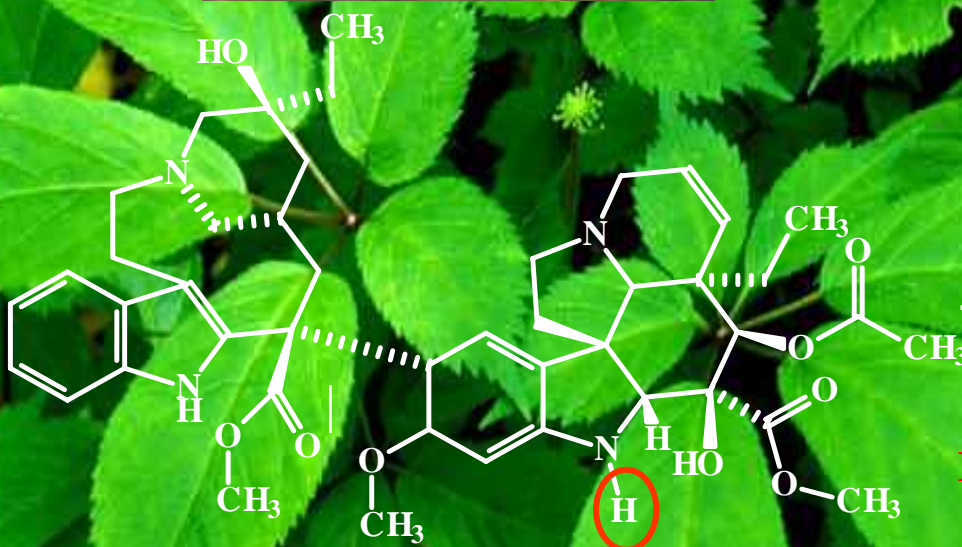
[Press Releases](#)

Agentes Anti-câncer de Origem Vegetal



Câncer

Catharanthus roseus
(*Vinca rosea*, Apocynaceae)



Alcalóides

E. Wenkert, 1955

Inibidor mitótico (metafase)

Alcalóides bis-indólicos

vincristina R = H
vinblastina R = CHO

Paclitaxel

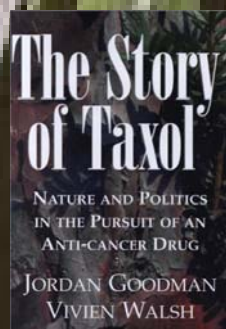


M. E. Wall & M. C. Wani
Res. Triangle Park, 1967

**1996 - National Cancer
Institute Award of Recognition**

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

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

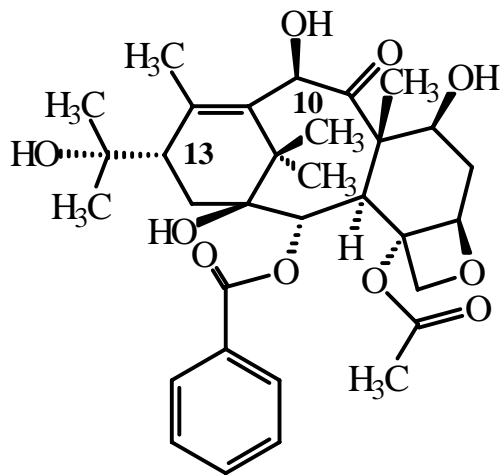


Terpenos

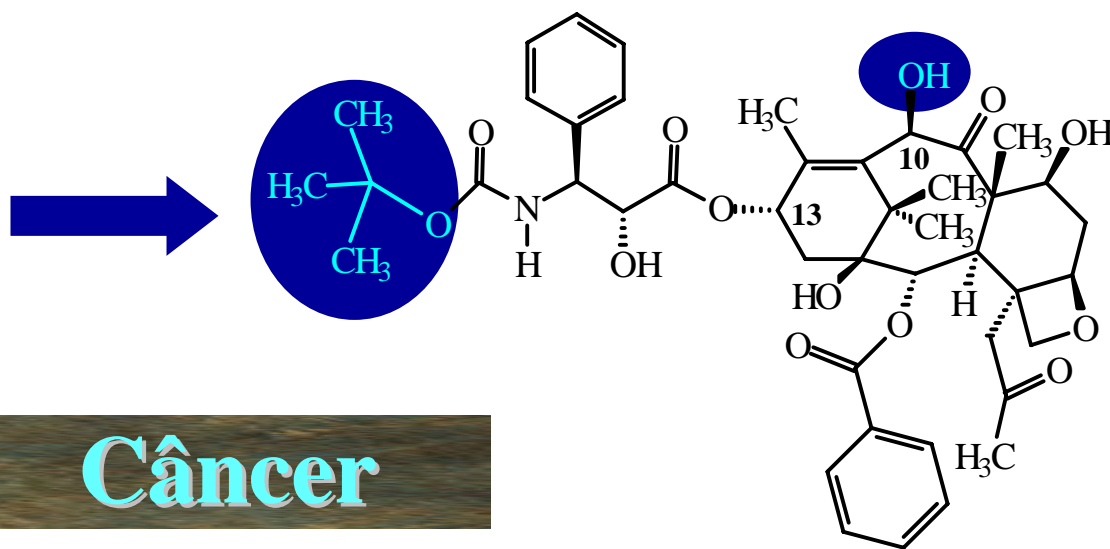
M. C. Wani *et al.*, J. Am. Chem. Soc. 93, 2325 (1971)



Hemisíntese do Taxotere^R



acetylbaconin-III

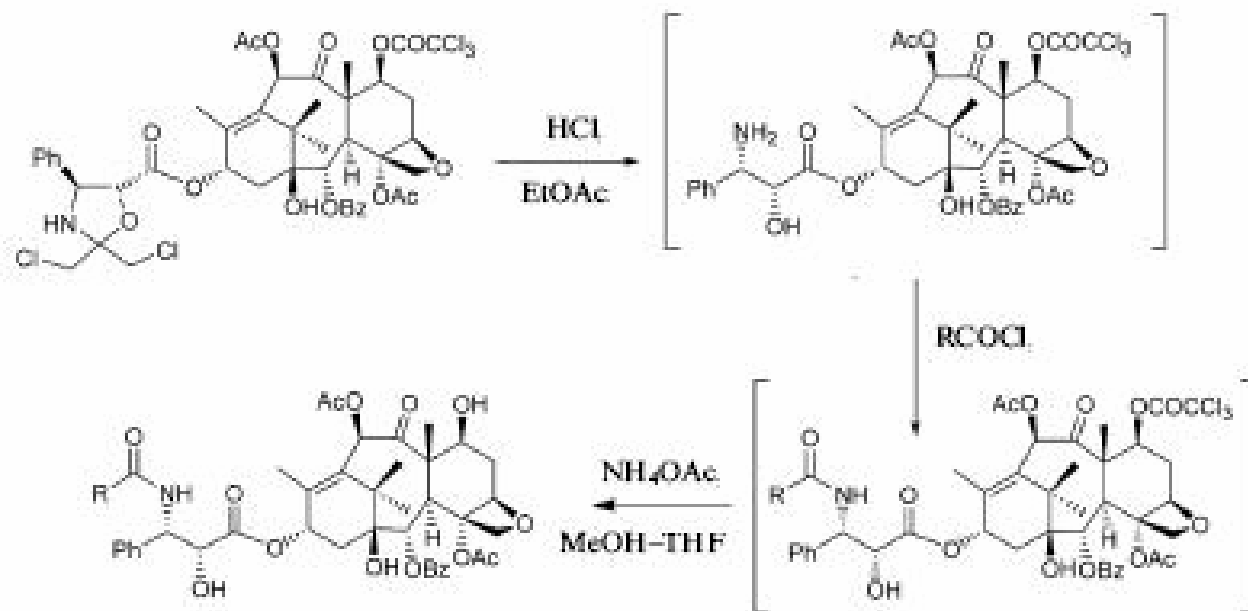
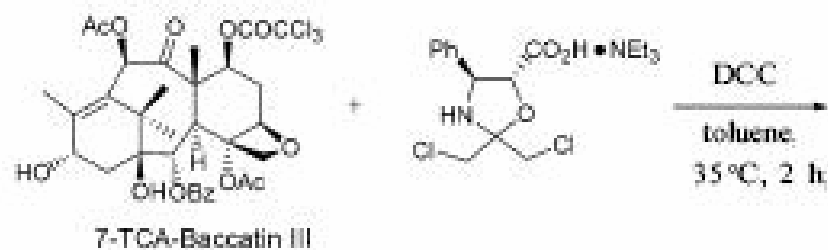


taxotere

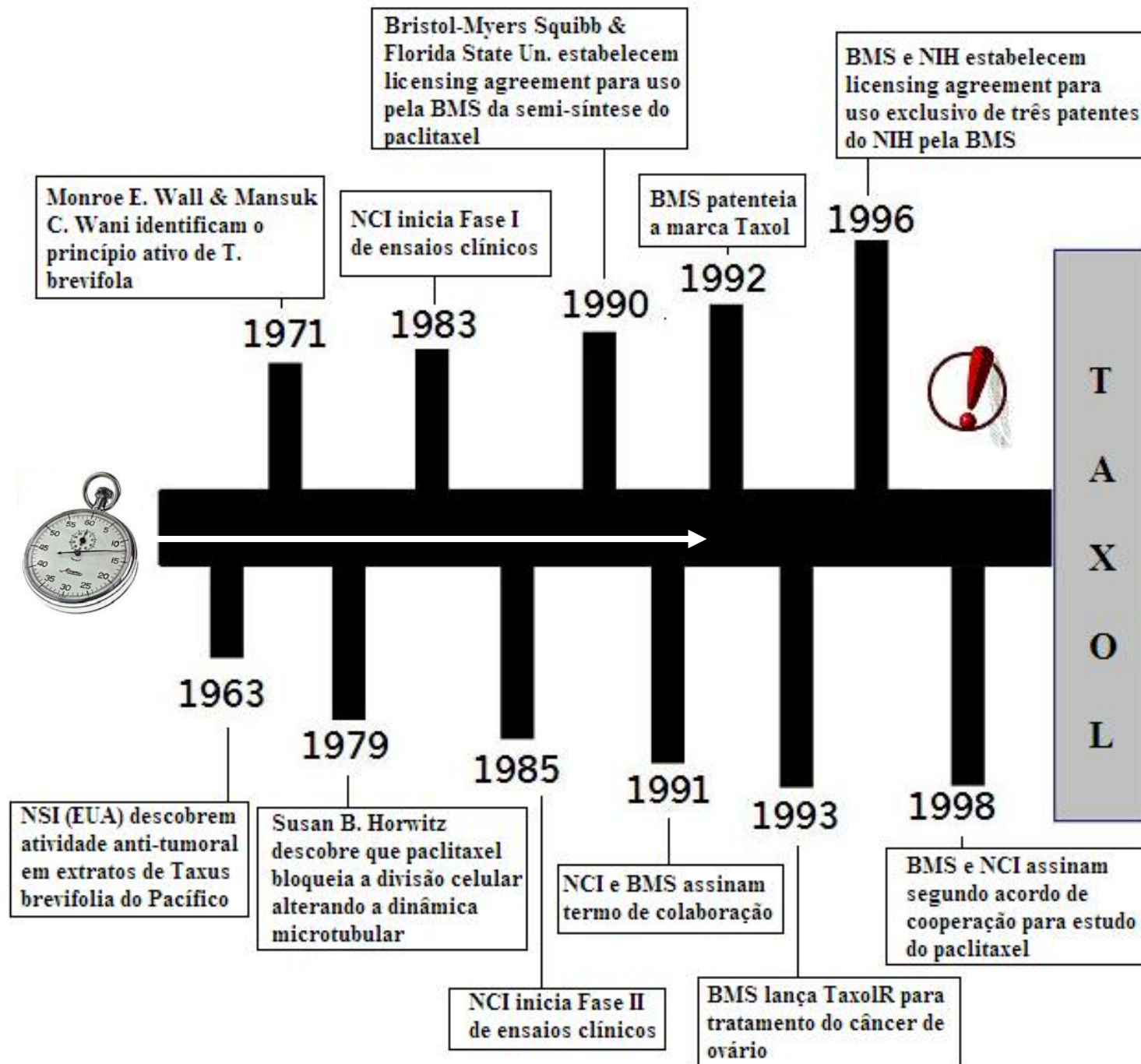
Greene *et al.*, *J. Org. Chem.* 1991, 56, 6939

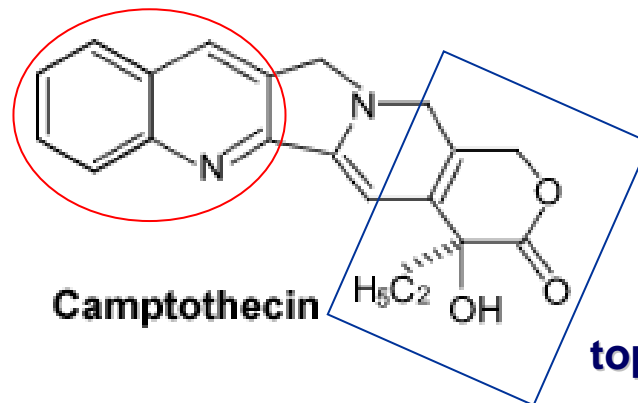
D.GUÉNARD, F. GUERITTE-VOEGELEIN, P. POTIER,
"Taxol and Taxotere: Discovery, Chemistry, and
Structure-Activity Relationships", *Acc. Chem.
Res.* 1993, 26, 160-167.

E. J. Roh *et al.*, *Bioorganic & Medicinal Chemistry* 2002, 10, 3145.



EJ Roh, Bioorganic Medicinal Chemistry 2002, 10, 3145.





Camptothecin

Inibidor de topoisomerase-1

alcalóide
quinolínico de biossíntese mista

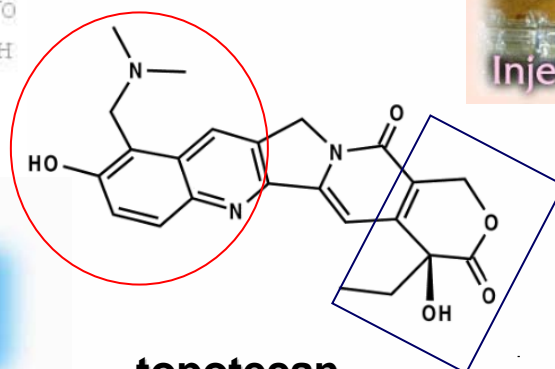


Camptotheca acuminata

Wall, ME & Wani, MC **“Camptothecin: Discovery to Clinic”**
Annals of the New York Academy of Sciences 1996, 803, 1

Wall, ME, MC Wani, CE Cook, KH Palmer, AT McPhail, GA Sim, “Plant antitumor agents. 1. The isolation and structure of camptothecin, a novel alkaloidal leukemia and tumor inhibitor from *Camptotheca acuminata*” *J. Am. Chem. Soc.* 1966, 88, 3888.

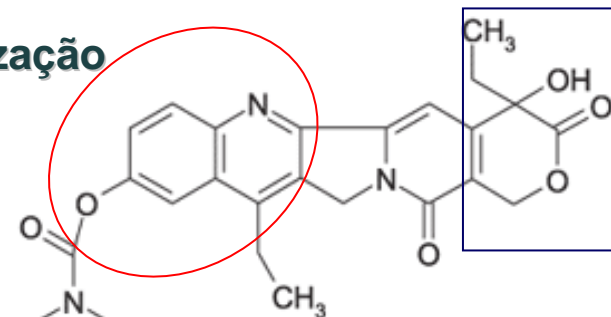
Molécula
“domesticada”



topotecan
SK&B



Otimização



.HCl .3H₂O

Irinotecan
Upjohn



1. Introdução

Definição e evolução da Química Medicinal

Como nascem os fármacos?

Fármacos e Medicamentos

2. A Origem dos Fármacos I

Papel dos produtos naturais

O Decano dos Fármacos

Domesticando moléculas selvagens: morfina, quinina

Anti-câncer: Vinca, Taxol[®] *et al.*;

Diosgenina e a esteróideterapia

Índios & indóis

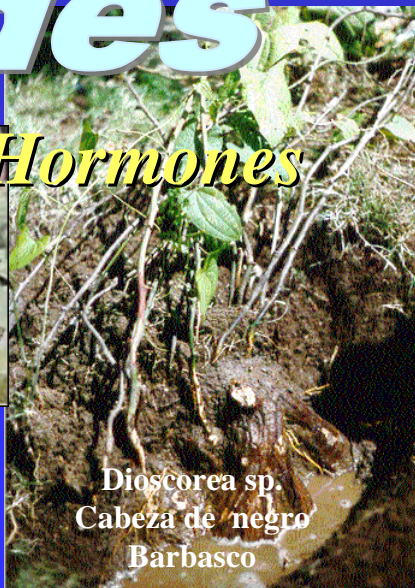
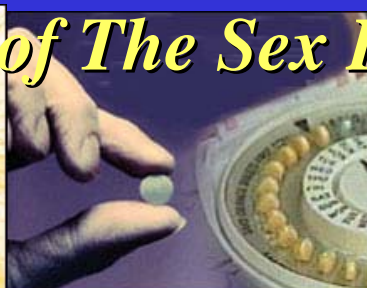
O episódio do *Específico Pessoa*

... de cobras e outros bichos, aos inibidores da ECA



esteróides

The decade of The Sex Hormones



Russell E. Marker (1902-1995)

& Gregory Pincus

(J. Chem. Educ. 1973, 50, 195).

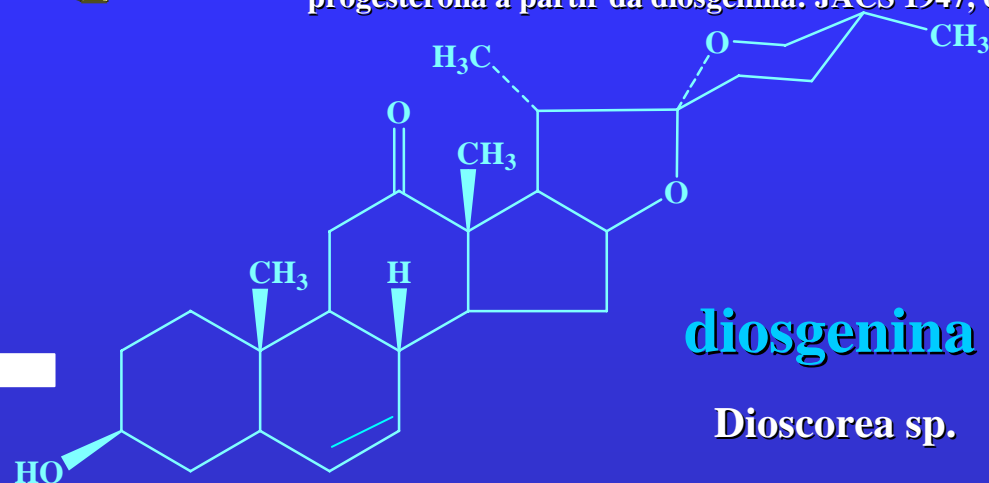
Em 1937 no “Pond Laboratory” da Universidade da Pensilvania, EUA, Marker concluiu a primeira síntese da progesterona a partir da diosgenina: JACS 1947, 69, 2167

A Pílula Contraceptiva



<http://www.djerassi.com/>

progesterona



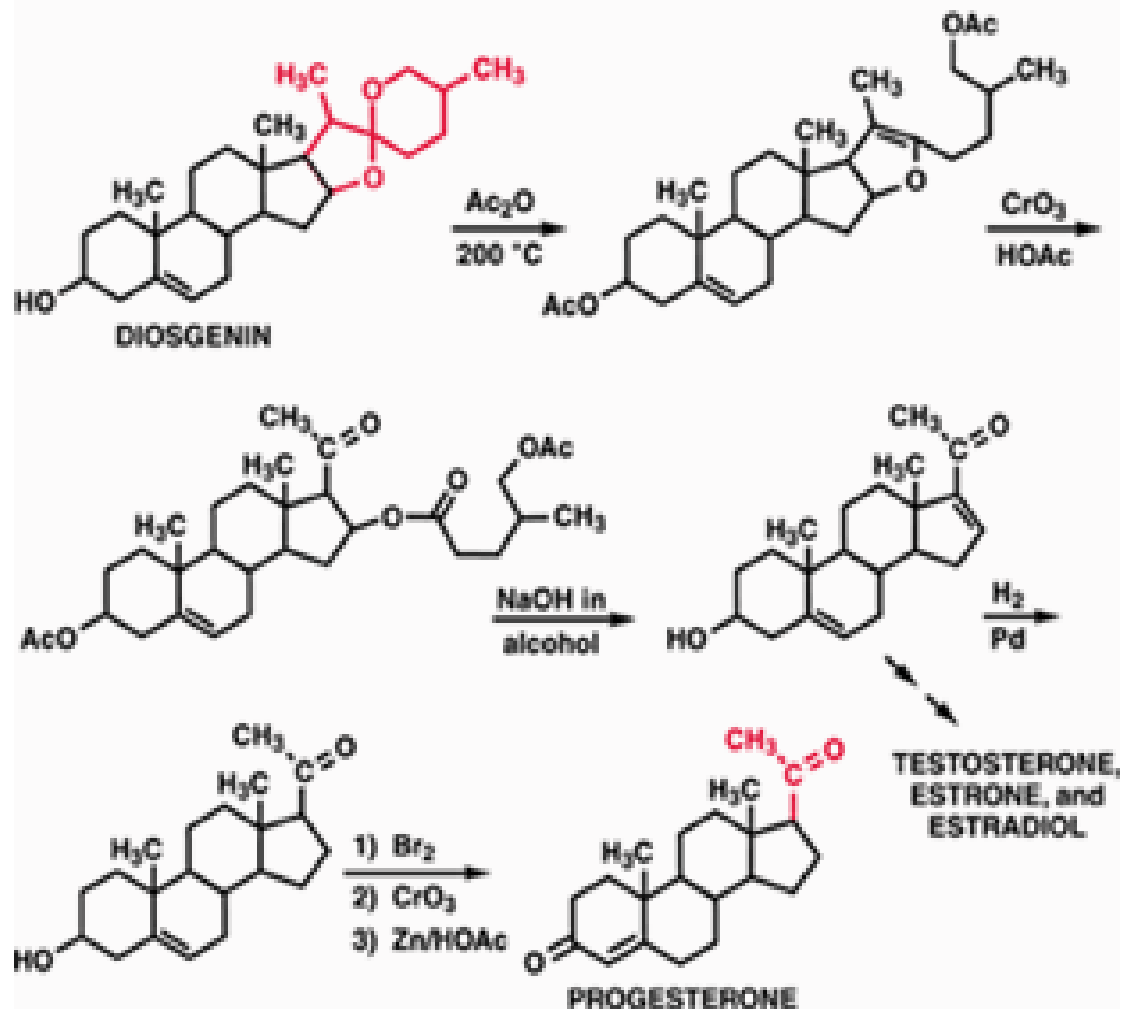
diosgenina

Dioscorea sp.

P. A. Lehman et al, *J. Chem. Ed.* **1973**, 50, 195.

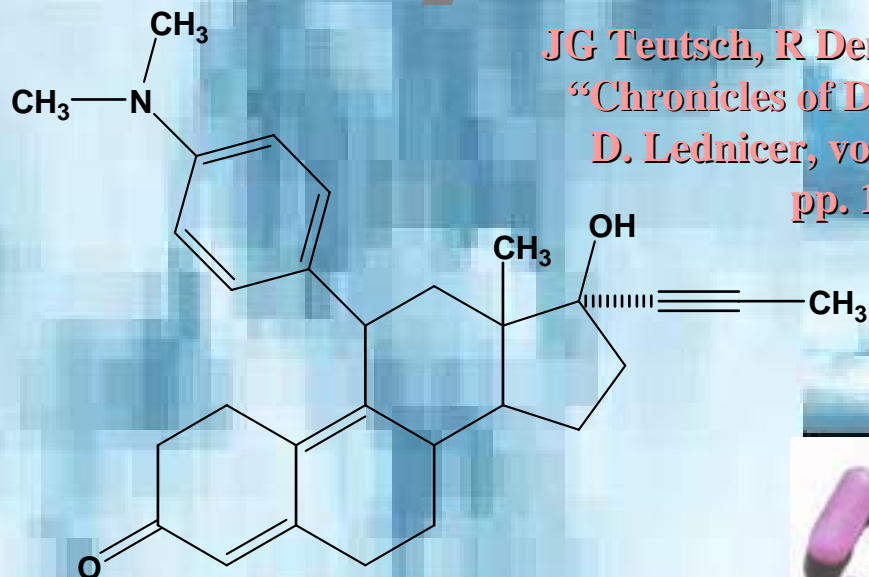


THE "MARKER DEGRADATION"



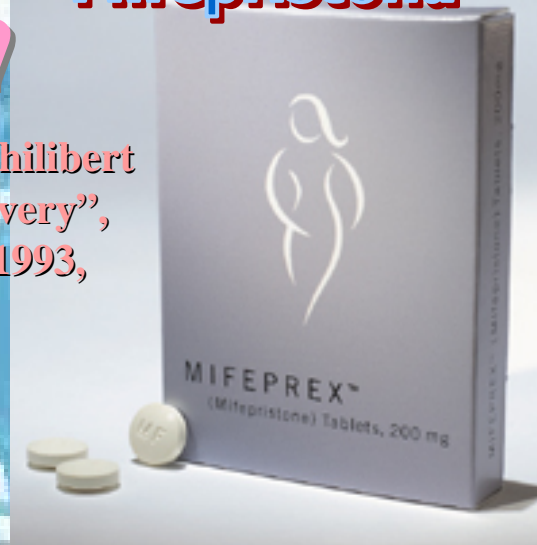


mifepristona



JG Teutsch, R Deraedt, D Philibert
"Chronicles of Drug Discovery",
D. Lednicer, vol.3, ACS, 1993,
pp. 1-43

Mifepristona



RU 486

1982

Inovações terapêuticas



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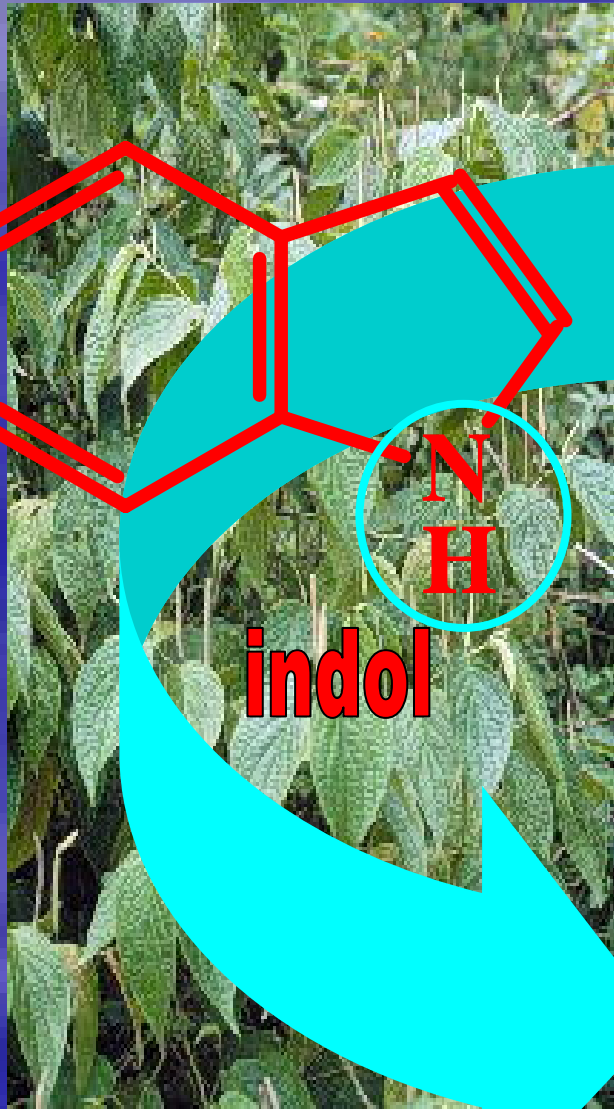
O episódio do *Específico Pessoa*

... de cobras e outros bichos, aos inibidores da ECA

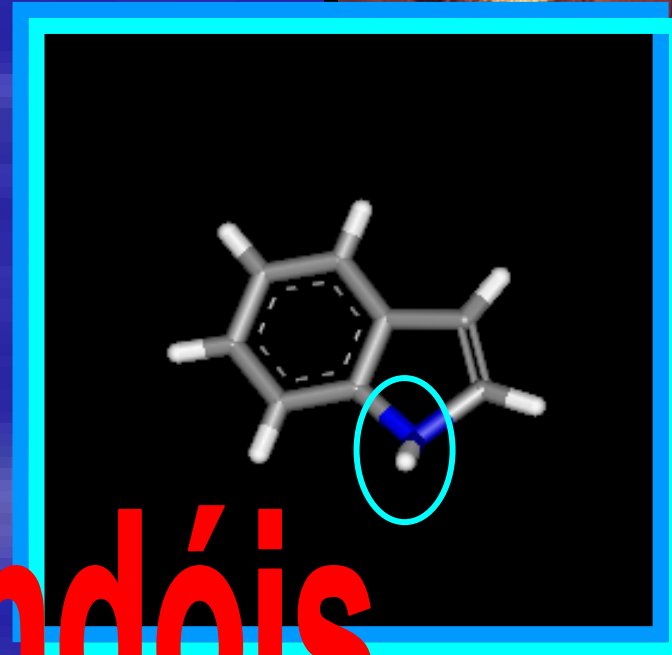


Patrimônio genético brasileiro





índios

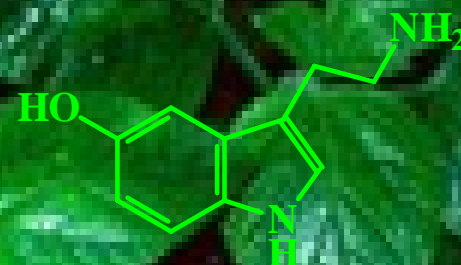
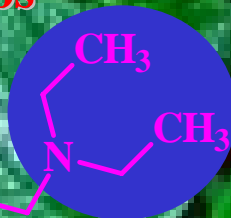
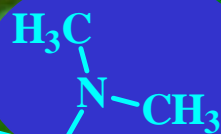


indóis

Alcalóides indólicos

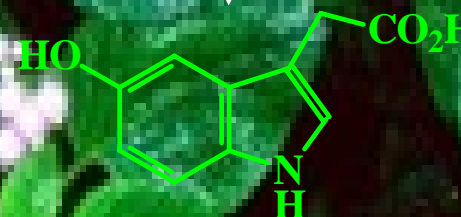
Virola sp

H₃CO



serotonina

MAO



Substâncias naturais alucinogênicas

Produtos Naturais

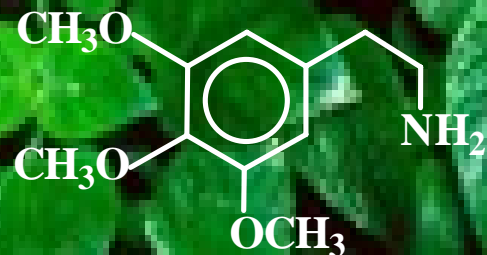


SNC



Aril-etil aminas:
mescalina

Peyot



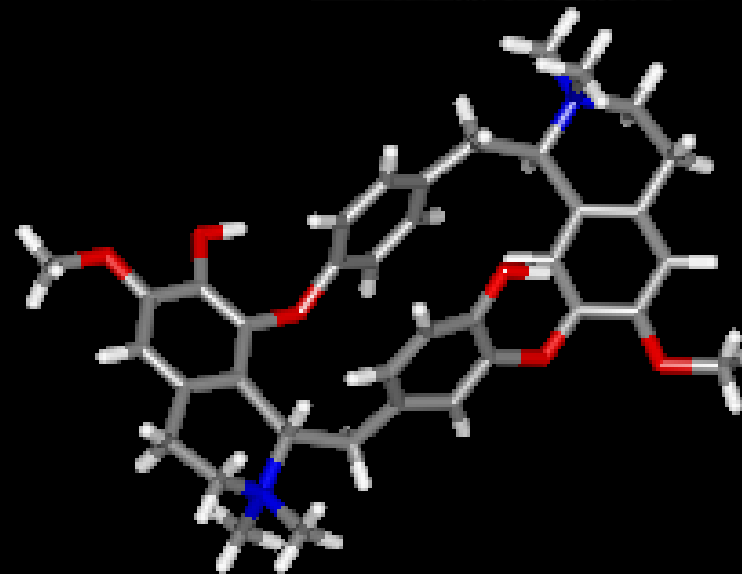
Cactus: *Lophephora sp.*

Castañeda: Segredos de D. Juan

Fármaco dos Índios



Bloqueadores ganglionares



d-tubocurarina

Chondrodendron_tomentosum



“Específico Pessoa”, criado pelo farmacêutico José Torquato Pessoa na cidade de Camocim, no Ceará, como preparado antiofídico (Francisco José de Abreu Matos)



www.iq.ufrj.br/gigantes/otto/angelo.pdf

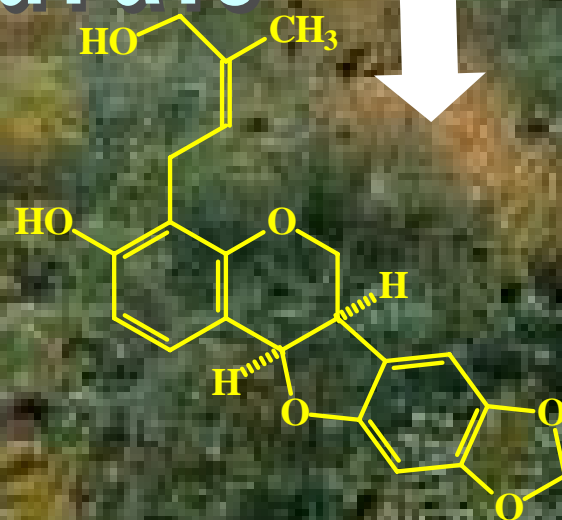
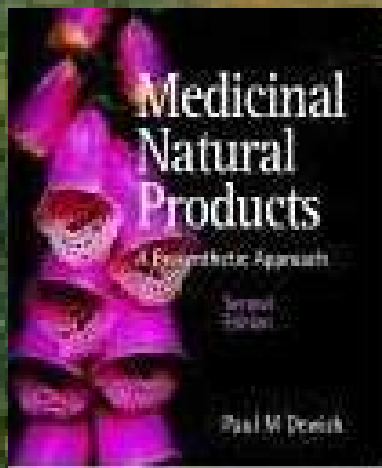
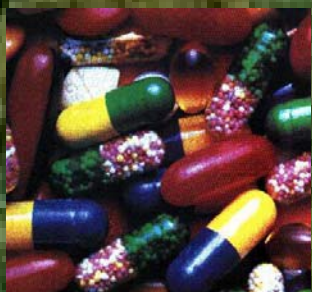
Un. Columbia EUA

K. Nakanishi, ACS, 1991

“A Wandering Natural Products Scientist “

Cabenegrine-A Tetrahedron Lett. 1982, 23, 3855

Produtos Naturais



1. Introdução

Definição e evolução da Química Medicinal

Como nascem os fármacos?

Fármacos e Medicamentos

2. A Origem dos Fármacos I

Papel dos produtos naturais

O Decano dos Fármacos

Domesticando moléculas selvagens: morfina, quinina

Anti-câncer: Vinca, Taxol[®] *et al.*;

Diosgenina e a esteróideterapia

Índios & indóis

O episódio do *Específico Pessoa*

... de cobras e outros bichos, aos inibidores da ECA





Inovações terapêuticas



M. O. Rocha e Silva
1910-1983



S. H. Ferreira
1934-

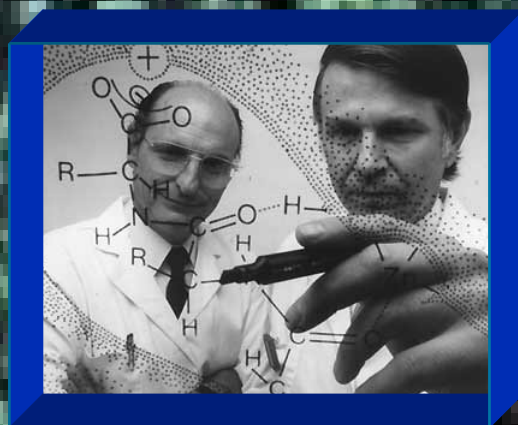
S.H. Ferreira, A Bradykinin-potentiating factor (BFP) present in the venom of *Bothrops jararaca*, *Brit. J. Pharmacol.* 1965, 24, 163.



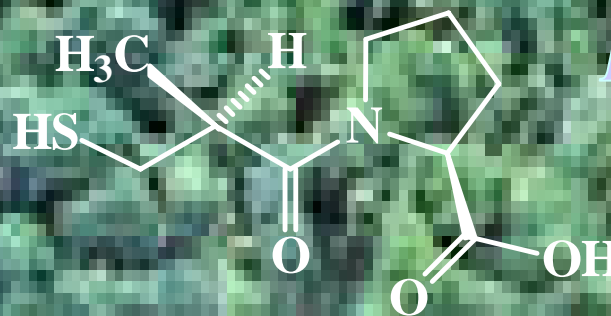
Descoberta do sistema
renina-angiotensina
(RAS)



Inibidor
ECA



D. W. Cushman & M. A. Ondetti

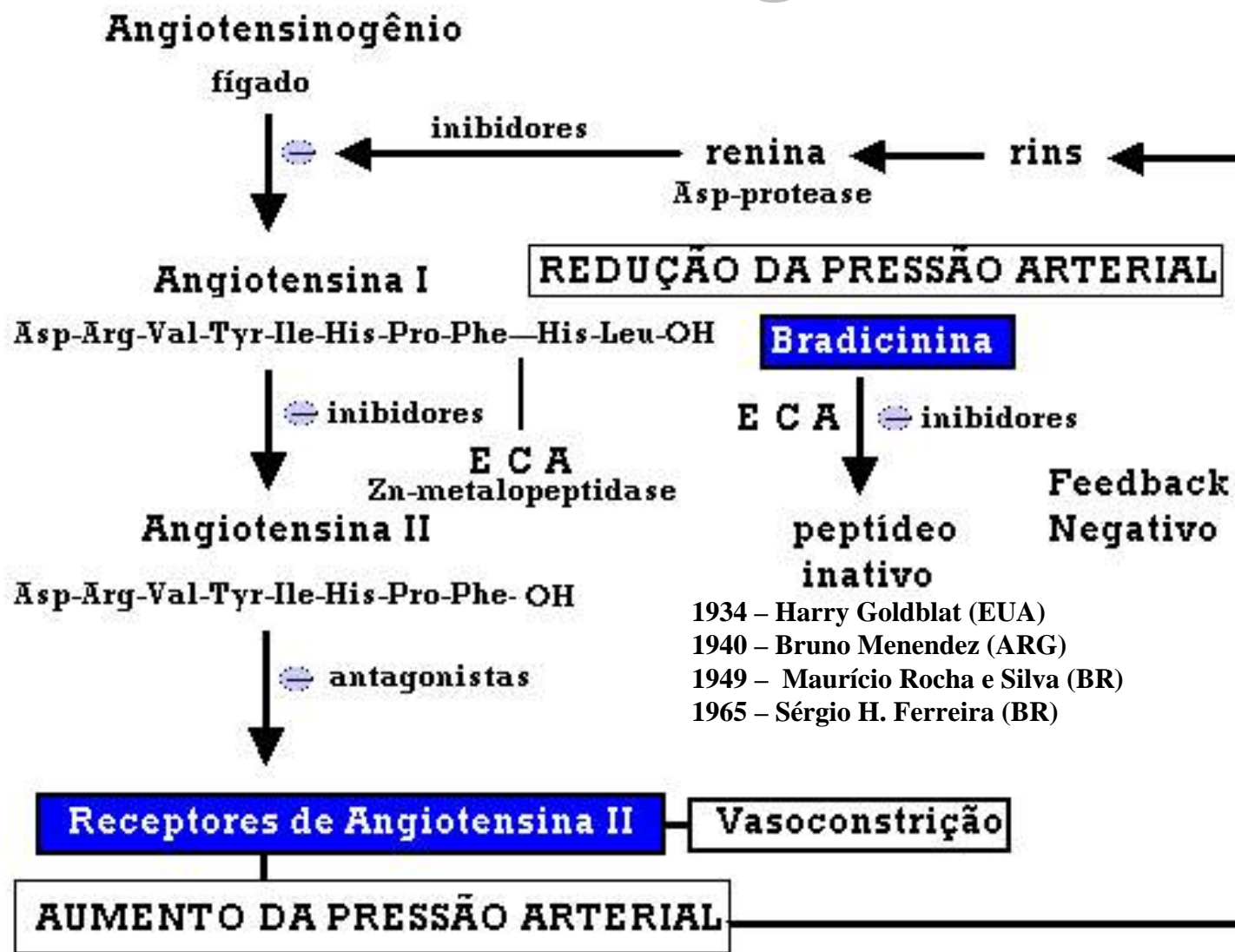


Captopril
(Capoten[®])

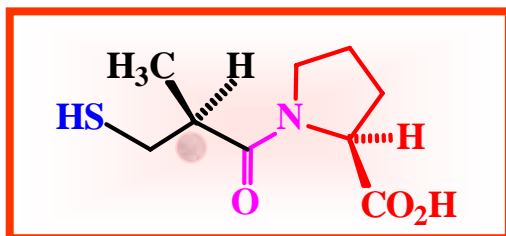


M. A. Ondetti, D. W. Cushman & B. Rubin, *Chronicles of Drug Discovery*, vol. 2,
J.S. Bindra & D. Lednicer, Eds., Wiley, Nova Iorque, 1983, p. 1-32

Sistema Renina-Angiotensina



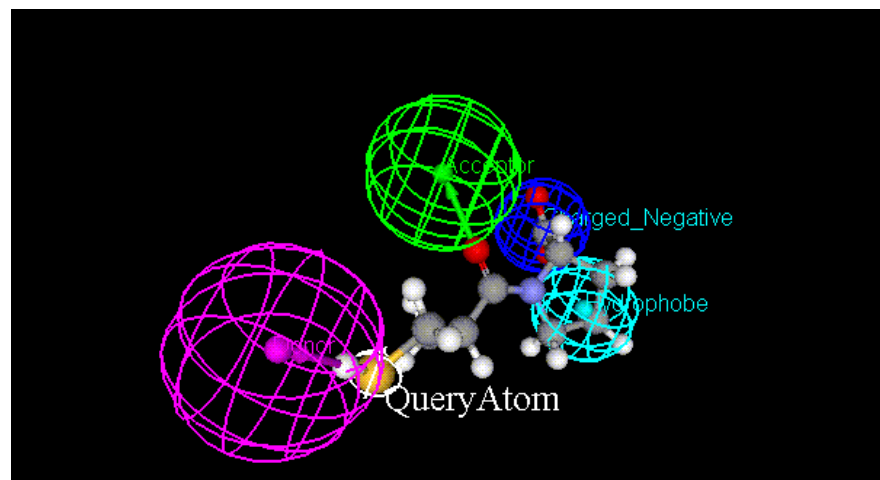
Agentes Anti-hipertensivos: inibidores da ECA



Captopril

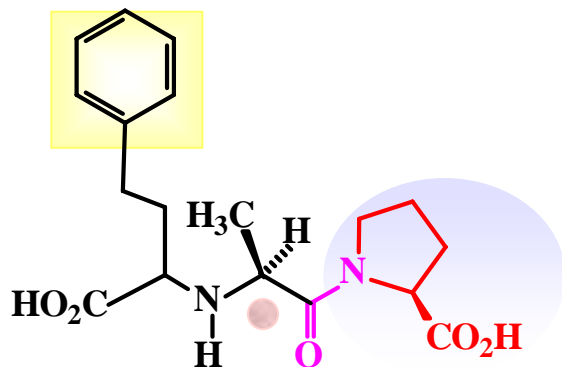
ACEi = 10

Ondetti, 1997
Squibb [SQ14,225)
IC₅₀ = 23nM

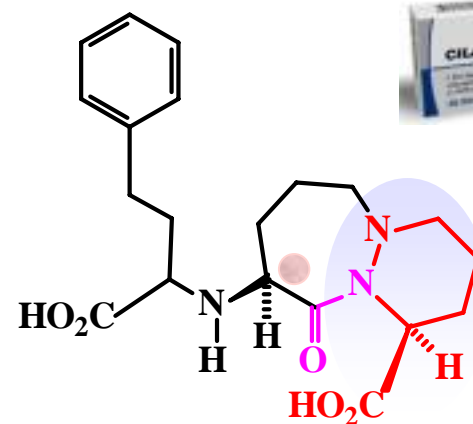


> interação

anelação: > conformação bioativa



Enalapril
Merck, 1980



Cilazapril
1986



Anti-hipertensivos inibidores da enzima conversora

Compound	Company	Target	Protease class
Captopril	Bristol-Myers Squibb	ACE	Metallo
Enalapril	Merck		
Lisinopril	AstraZeneca		
Trandolapril	Abbott		
Zofenopril	Menarini group		
Ramipril	Aventis		
Moexipril	Boehringer Mannheim		
Imidapril	Trinity Pharmaceuticals		
Perindopril	Daiichi Pharmaceutical, Servier/Solvay		
Qinapril	Pfizer		
Fosinopril	Bristol-Myers Squibb		
Benazepril	Novartis		
Cilazapril	Roche		

3. A Origem dos Fármacos II

Produtos naturais de origem marinha

O acaso na descoberta de fármacos: *serendipity*

Fármacos sintéticos: AAS

4. As razões moleculares da ação dos fármacos

O centenário modelo “*chave-fechadura*” de Emil Fisher

A bioinformática e a Química Medicinal

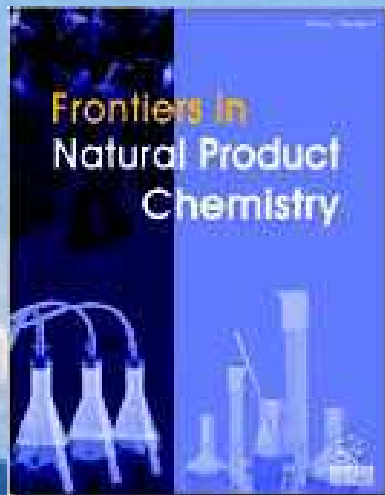
Construção de mapas topográficos de biorreceptores

O conceito de grupamento farmacofórico

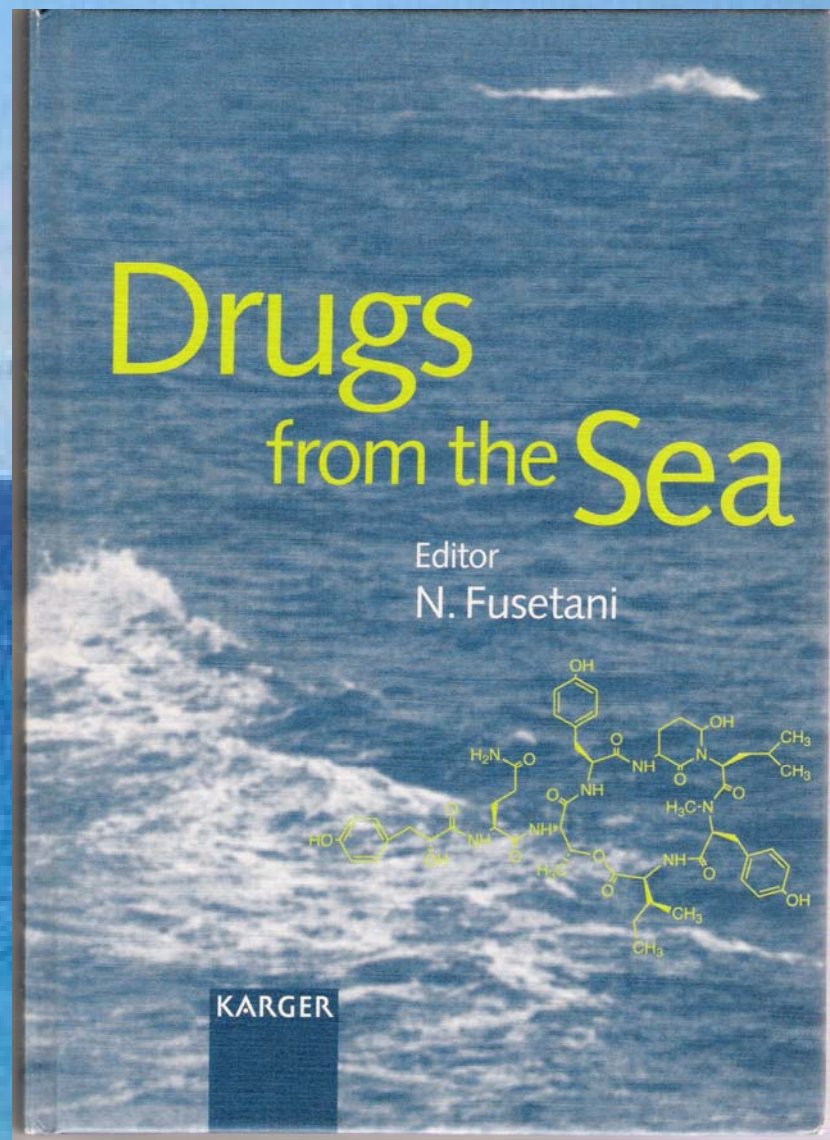
Fatores estruturais e atividade: similaridade e dissimilaridade



Produtos Naturais do Mar



N. Fusetani

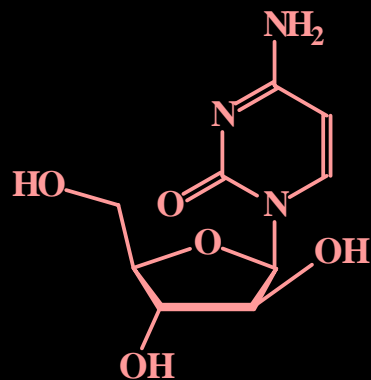


Marine organisms – a source of bioactive substances

Esponjas



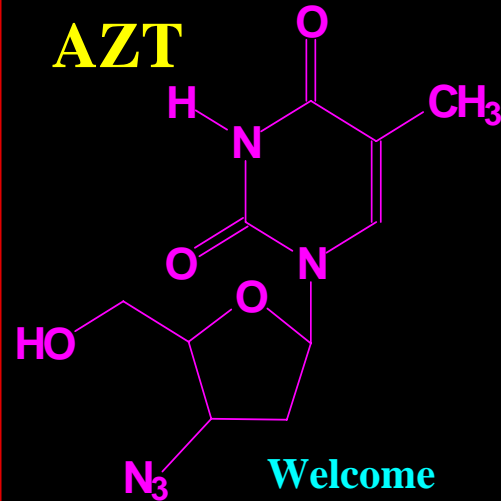
β -Citosina-arabinosido



citarabina (Ara-C)

1959

AZT



Welcome

H. Mitsuya *et al.*, 1985



R. Gallo, 1980

Corals



JP Horwitz *et al.*, *J. Org. Chem.* 1964, 29, 2076

Retrovir

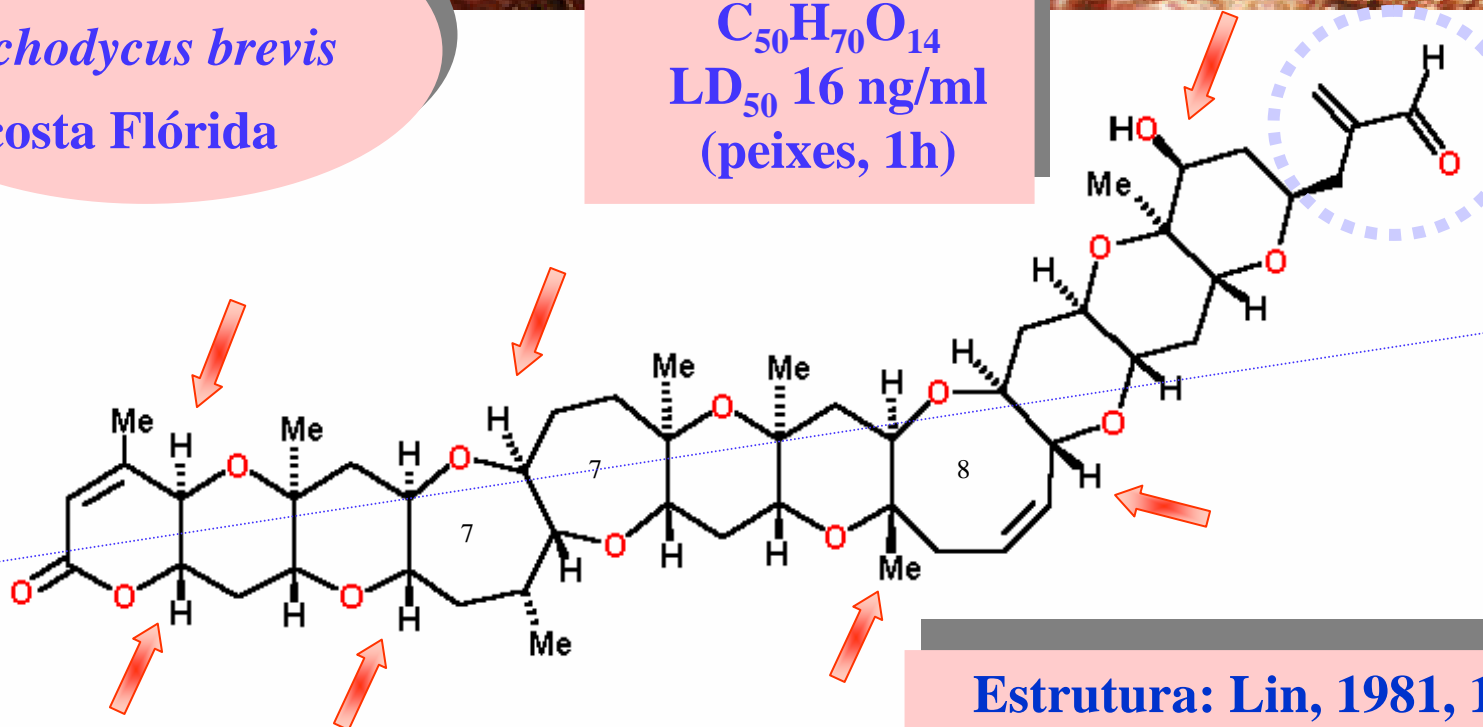


zidovudina (AZT)

Brevitoxina B

Alga vermelha
Ptychodiscus brevis
costa Flórida

$C_{50}H_{70}O_{14}$
 LD_{50} 16 ng/ml
(peixes, 1h)

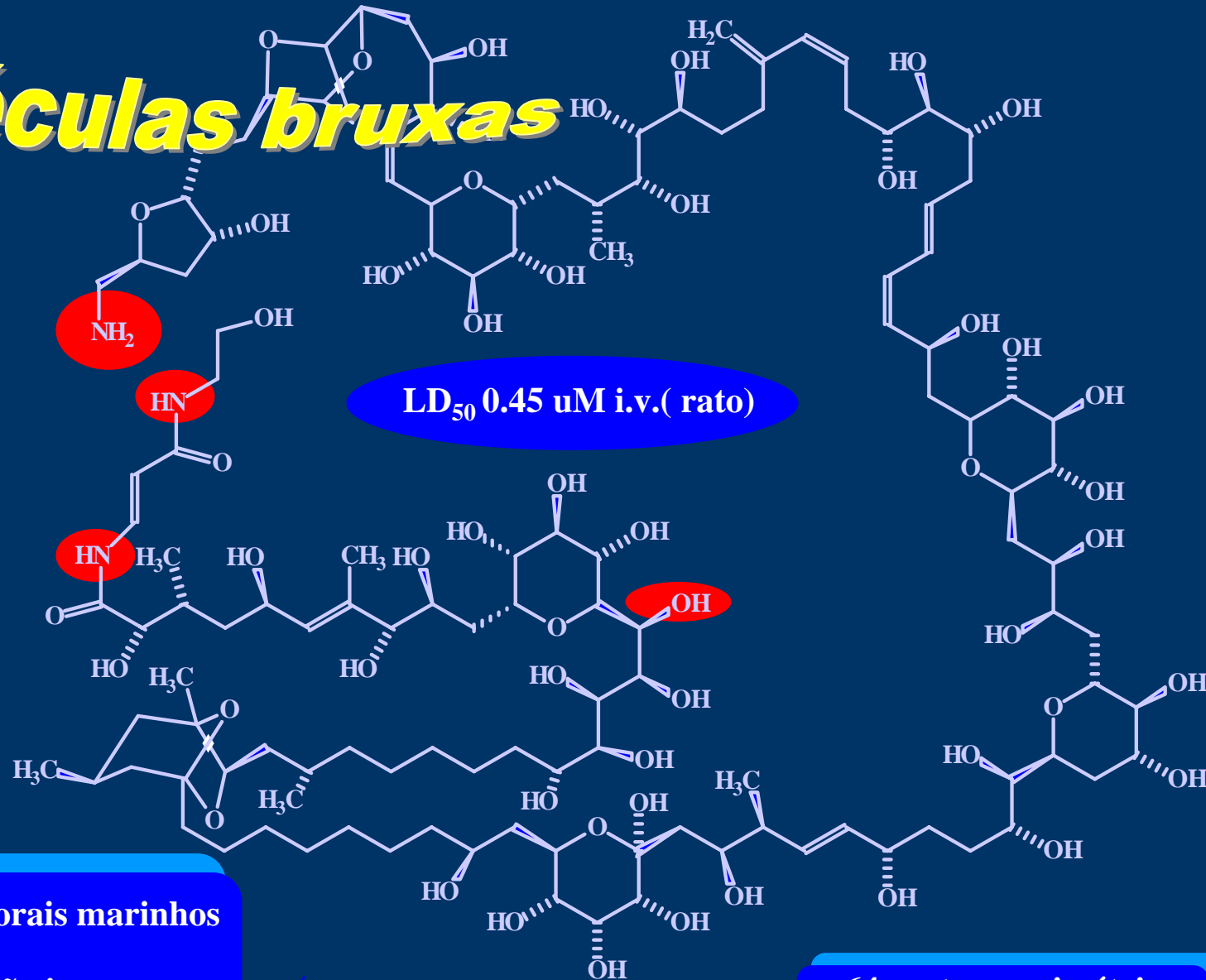
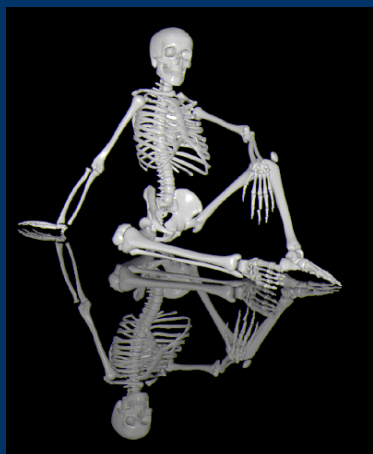


Síntese: Nicolaou, 1995
23 centros estereogênicos
11 ciclos *trans*

Estrutura: Lin, 1981, 1987
Atividade: canais de sódio
("Probe" farmacológico)

J Am. Chem. Soc., **117**, 117 & 1173 (1995)].

Moléculas bruxas



LD₅₀ 0.45 uM i.v.(rato)

1971 - Isolada de corais marinhos do gen. *Palythoa*

1982 - vasoconstrição intensa

1983 -estrutura elucidada

1989 -síntese total estereosseletiva

Palitoxina

C₁₂₉H₂₂₇N₃O₅₄
PM 2684.20

64 centros assimétricos
8 ligações duplas
42 grupos hidroxilas

2⁶⁴ isômeros

Y. Kishi *et al.*, 1989

Pharma
Mar



Yondelis™ (ET-743, trabectedina)



Síntese Total

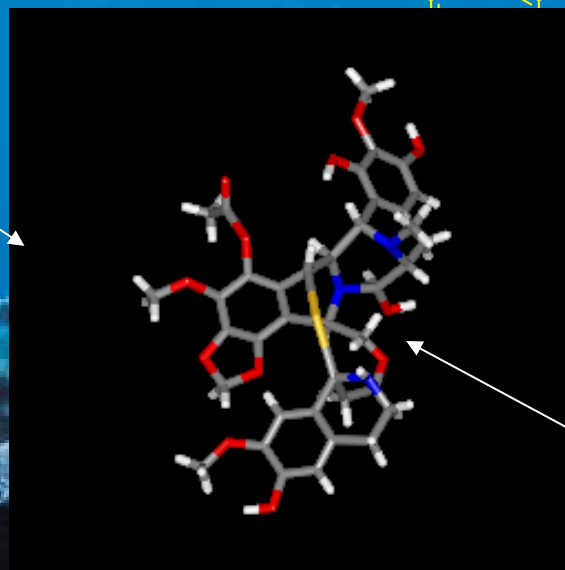


Ecteinascidia turbinata

Marinocultura

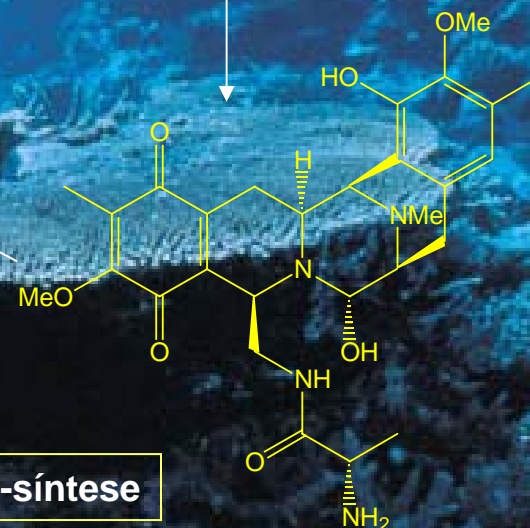
Bio-Mar

49 etapas



ET 743

Fermentação
Pseudomonas fluorescens



Safracina B

Semi-síntese

Derivado tetraidroquinolínico
100 vezes mais ativo que taxol

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

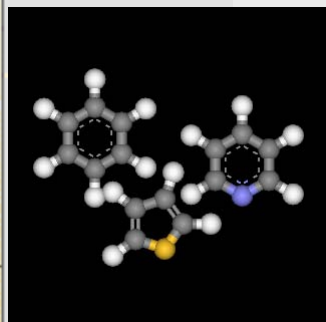
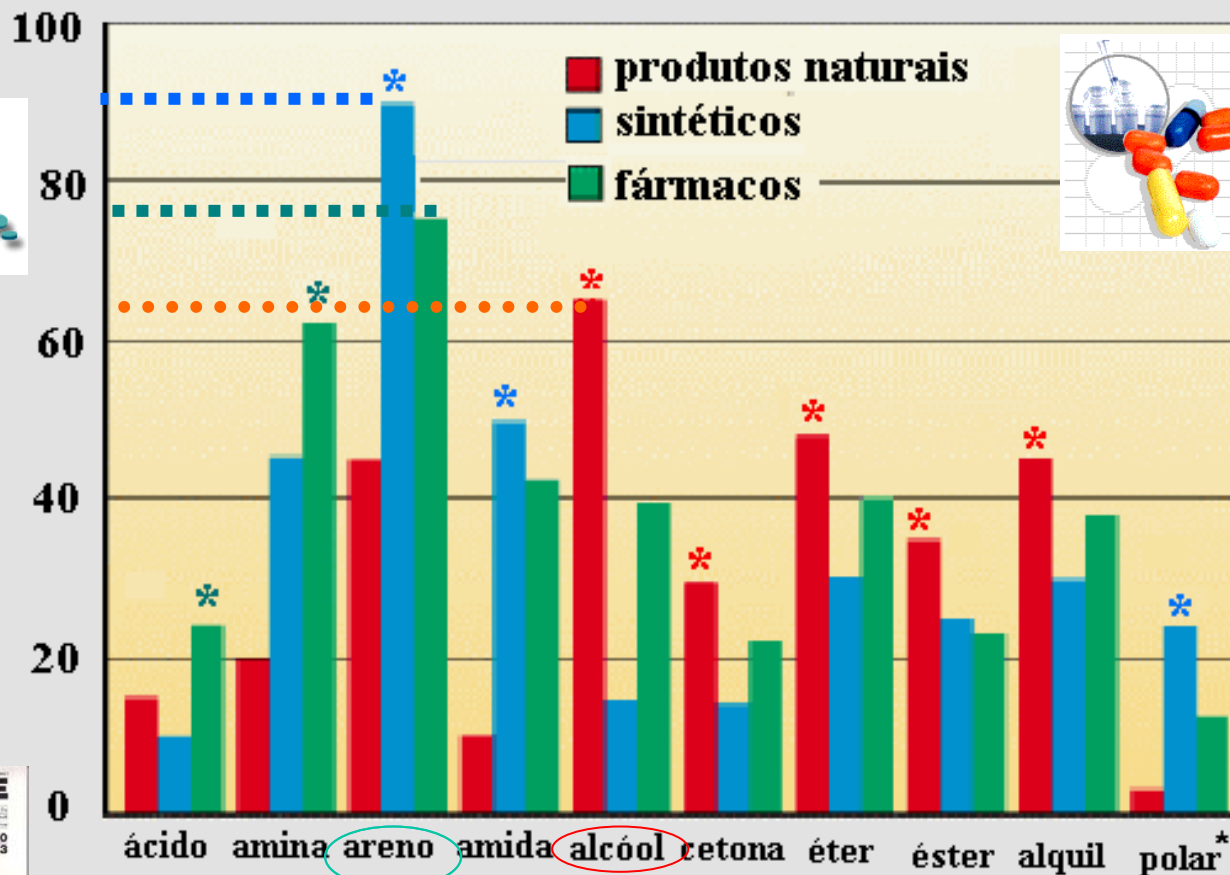
Chemical Review, 1995

Nobel 1990



1928 -

Frequência dos Grupos Funcionais Clássicos em Diferentes Compostos



Fonte: *Angewandte Chemie*

3. A Origem dos Fármacos II

Produtos naturais de origem marinha

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O acaso ...

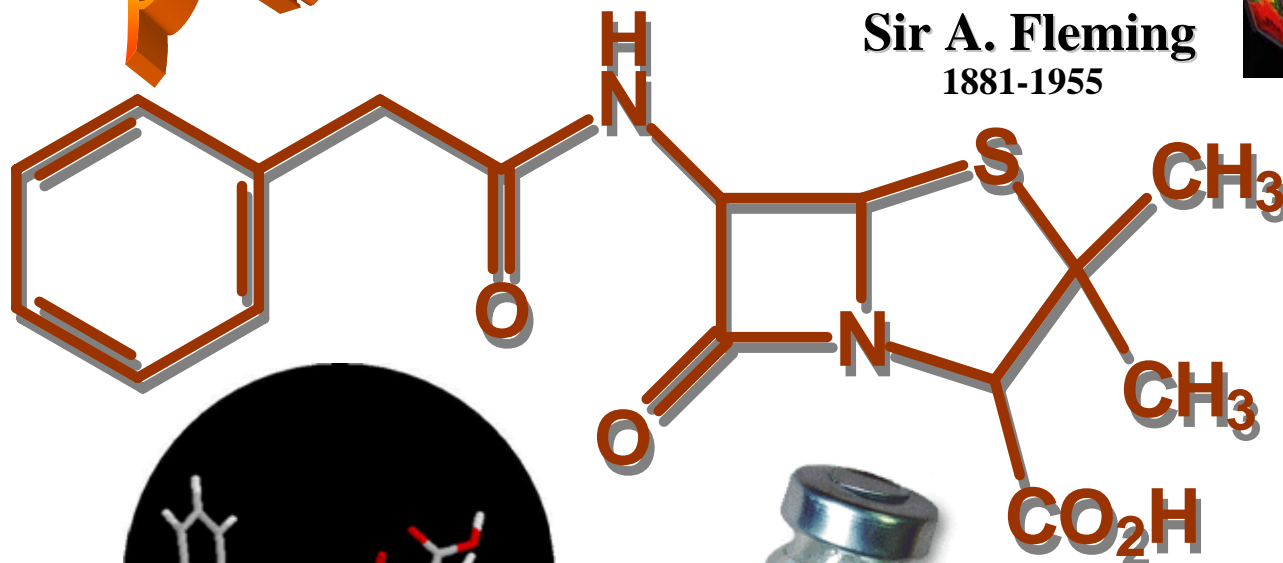


Antibioticoterapia

Penicilinas

Moléculas Salva-vidas

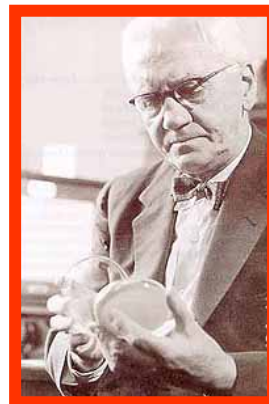
β -lactâmicos



serendipity



Sir H. W. Florey
1898-1968



Sir A. Fleming
1881-1955



1945



E. B. Chain
1906-1979



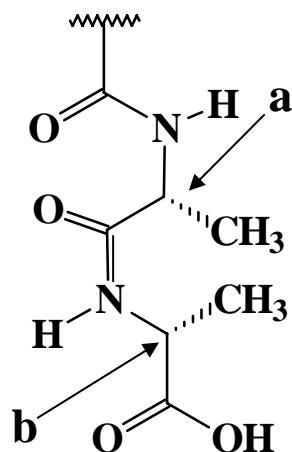
Penicillium notatum



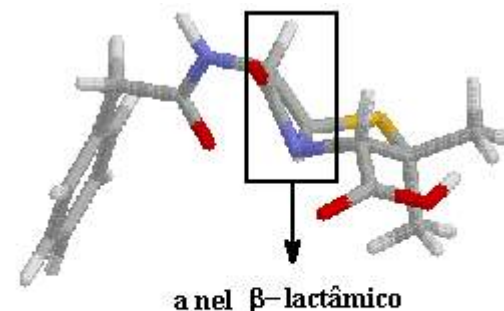
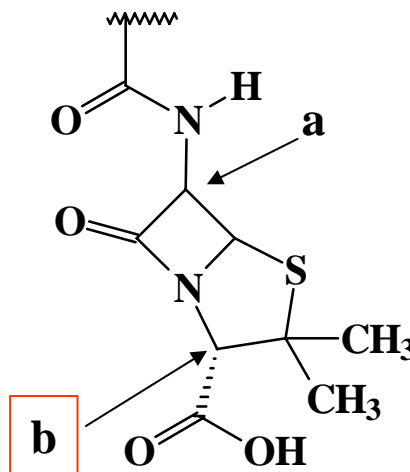
Mecanismo Molecular de Ação dos Antibióticos beta-lactâmicos

PM Blumberg & JL Stroming, Interaction of penicillin with bacterial Cell – Penicillin-binding proteins and penicillin-sensitive enzymes, *Bacterial Reviews* 1974, 38, 291-335.

cadeia peptídica



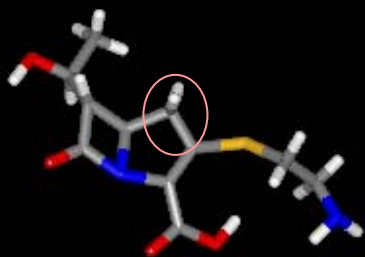
Penicilina G



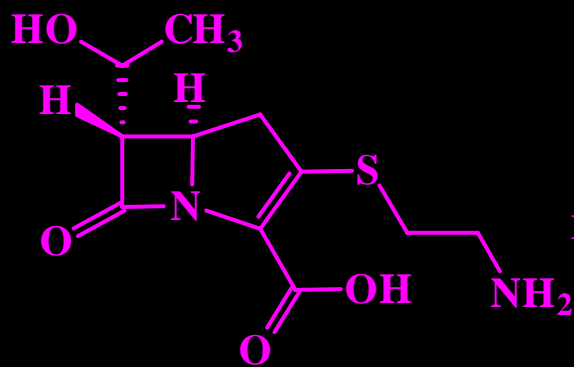
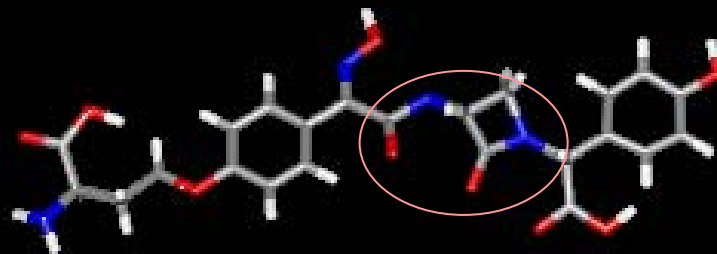
Inibição da *D*-alaninacarboxipeptidase do microorganismo, prevenindo a inserção da unidade dipeptídica acil-*D*-alanil-*D*-alanina, etapa final da construção da membrana celular externa.

Novas Gerações de Antibióticos

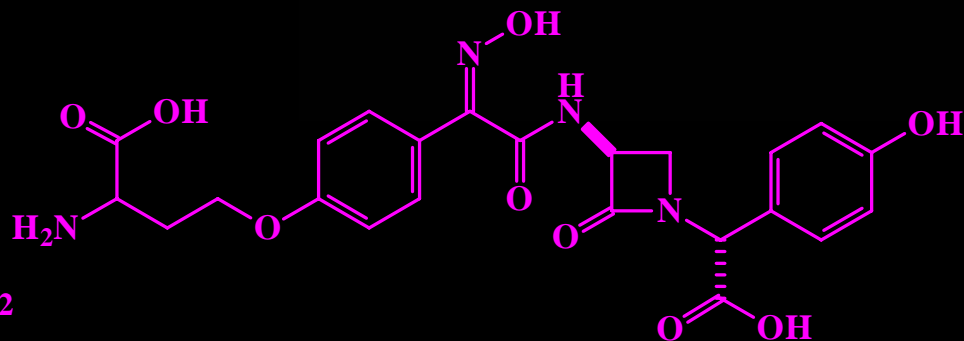
Antibiótico β -lactâmico
do Grupo dos Carbapenenos
Resistente à β -lactamases



Antibiótico β -lactâmico monocíclico
Nocardia uniformis
Ativo via Oral
azetidinones
(Sintético)



tienamicina



nocardicina



Os Fármacos.

sintéticos ...



Características dos Fármacos



Heterocíclicos
62%



N 95%

S 28%

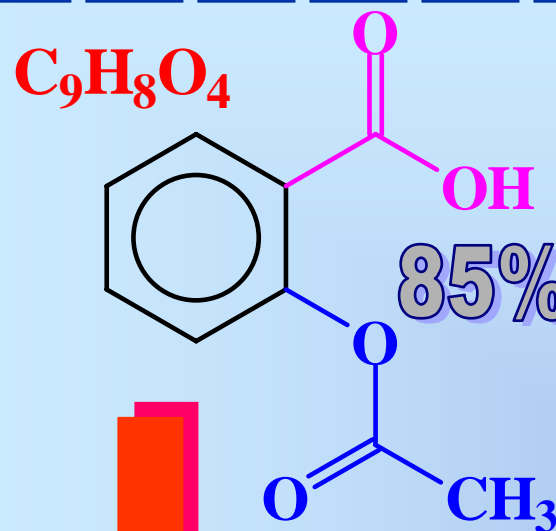
O 18%



Não-heterocíclicos
38%



HJ Roth et al., 1988



ácido acetil salicílico

85% dos fármacos modernos
são sintéticos



3. A Origem dos Fármacos II

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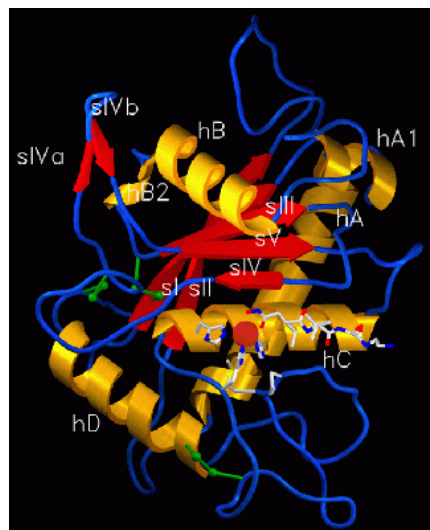
A bioinformática e a Química Medicinal

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Modelo Chave-Fechadura



Receptor



LOCK & KEY
CONCEPT



Fármaco

A importância dos fatores estruturais

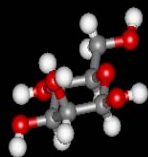
LOCK & KEY CONCEPT



1902



Hermann Emil Fischer
1852-1919

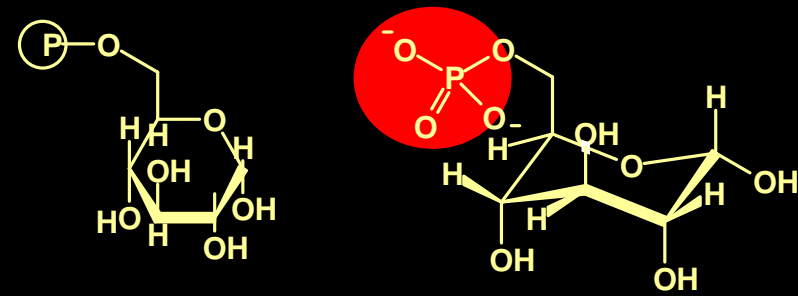
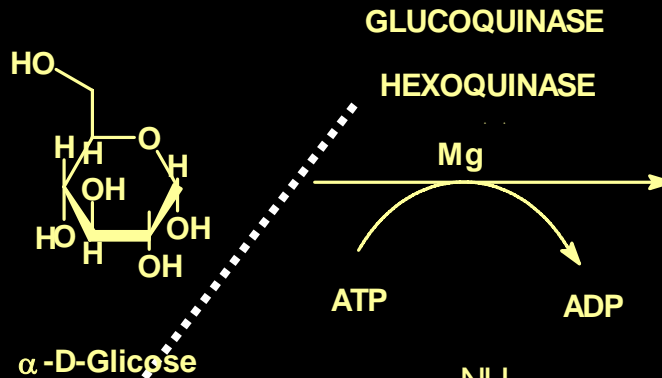
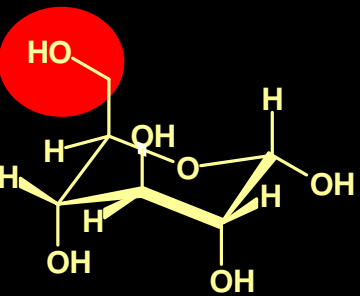


glicose

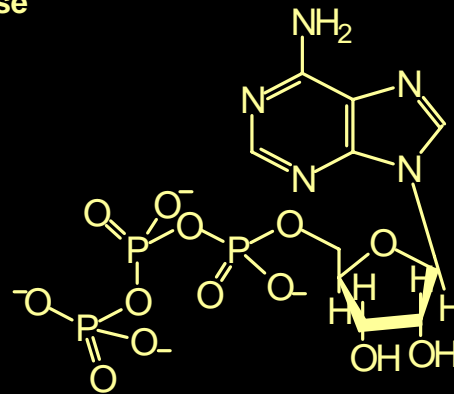


Química Medicinal

Reação enzimática: modelo micro-macromolecular



$\alpha\text{-D-Glucose-6-fosfato}$

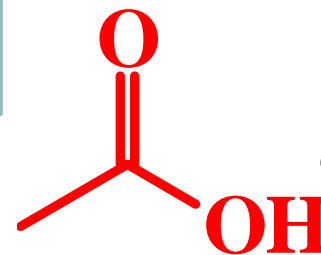


adenosina-trifosfato

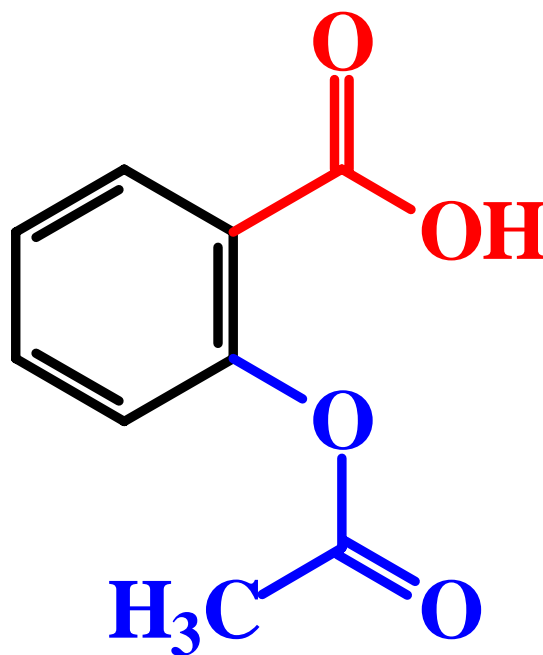


Biocatálise enzimática: monomolecular, bimolecular; co-fatores, co-enzimas

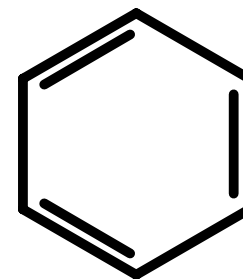
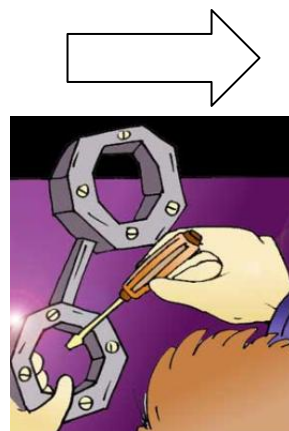
Dissecação Molecular



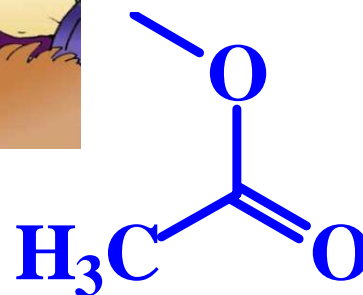
ácido carboxílico



Ácido acetilsalicílico



fenila

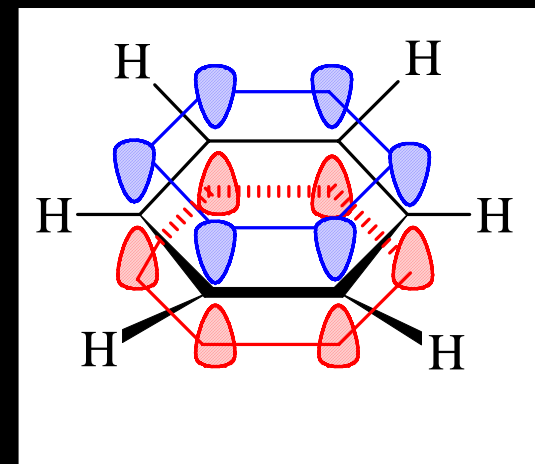
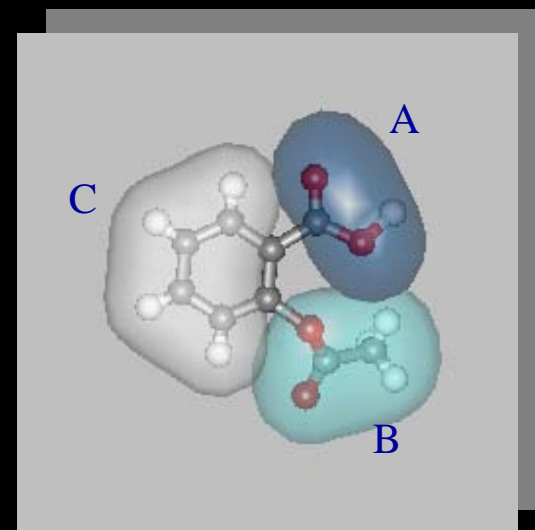
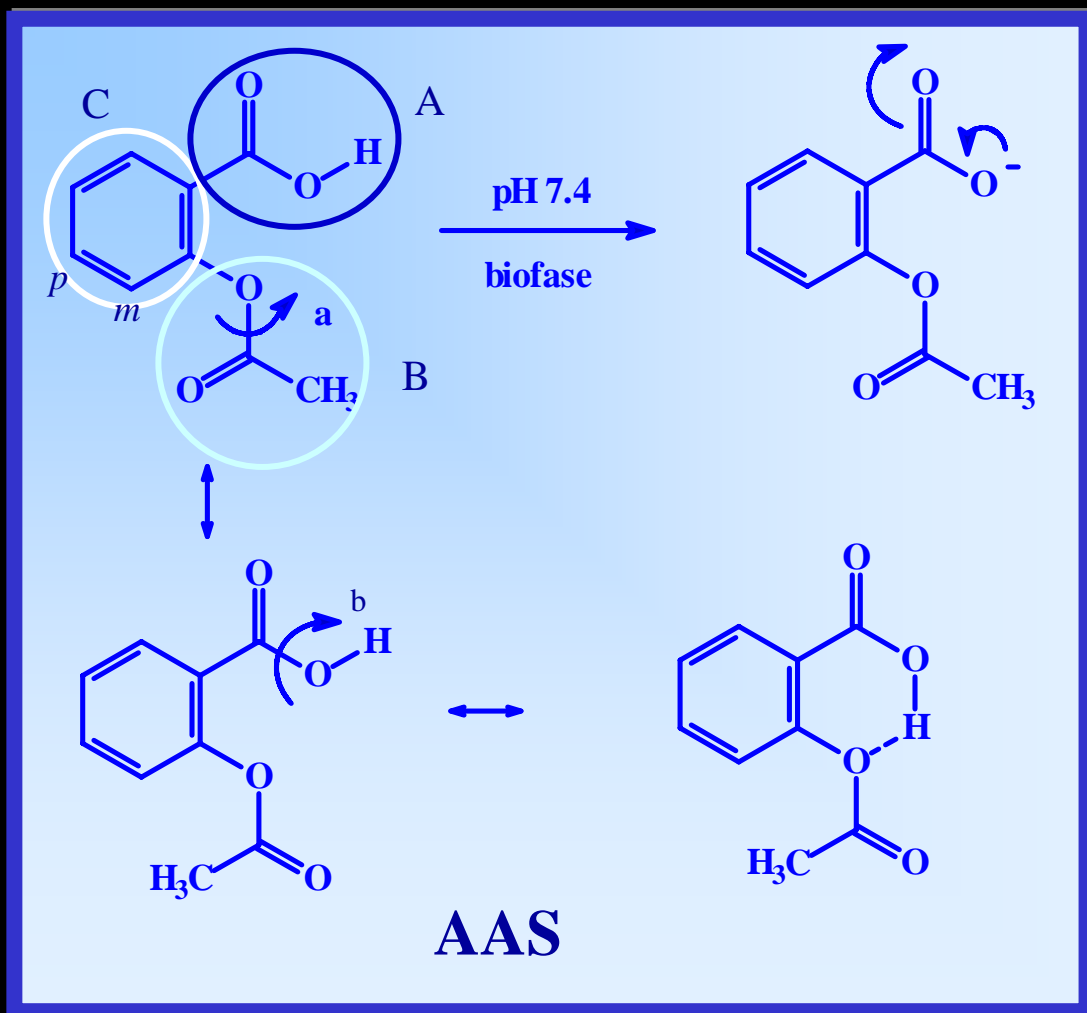


éster

Pontos farmacofóricos

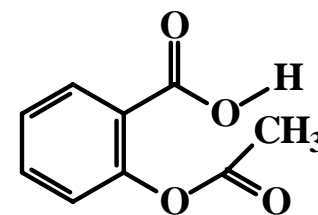
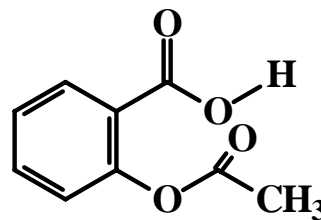
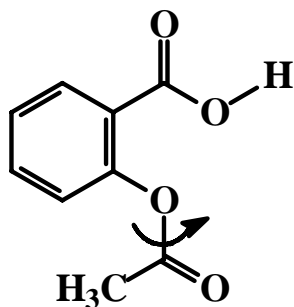
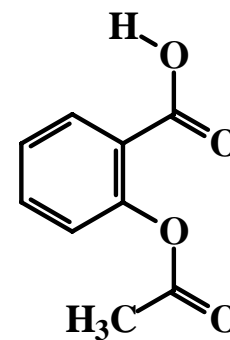
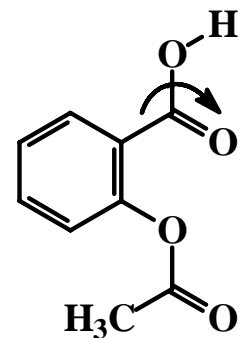
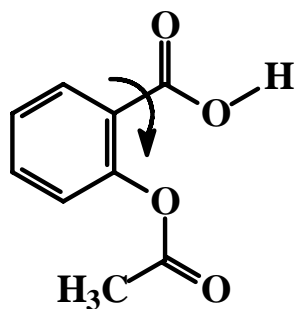
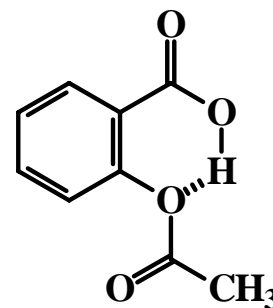
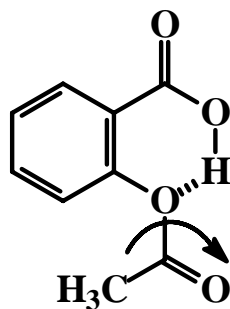
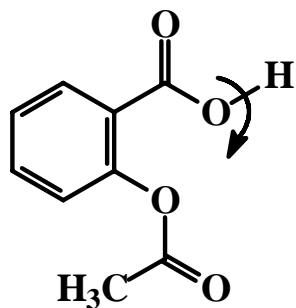
Grupos farmacofóricos

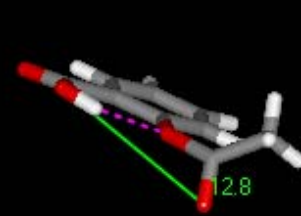
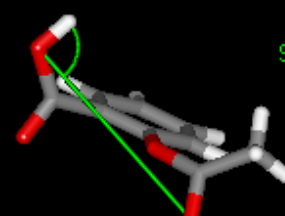
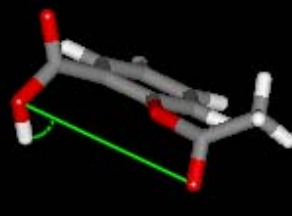
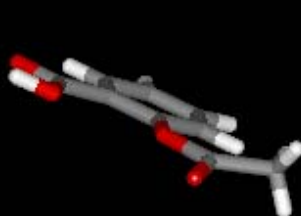
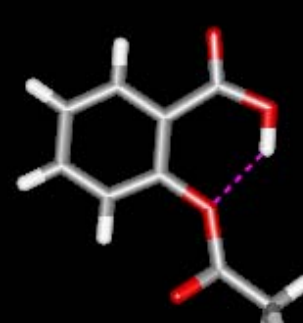
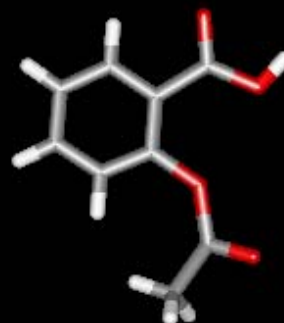
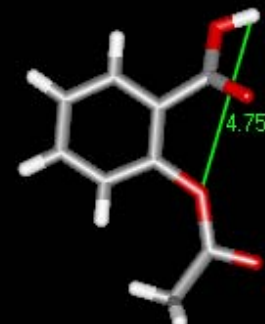
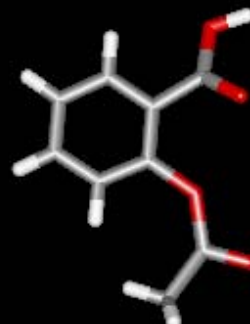
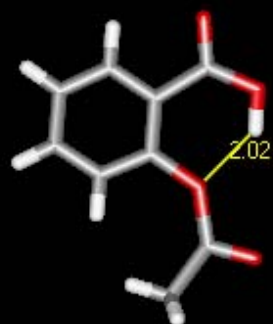
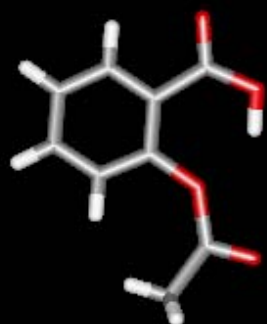
Visão dos Grupos Funcionais



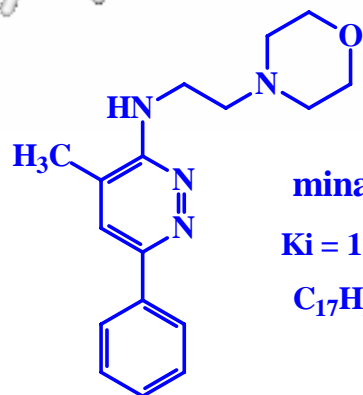
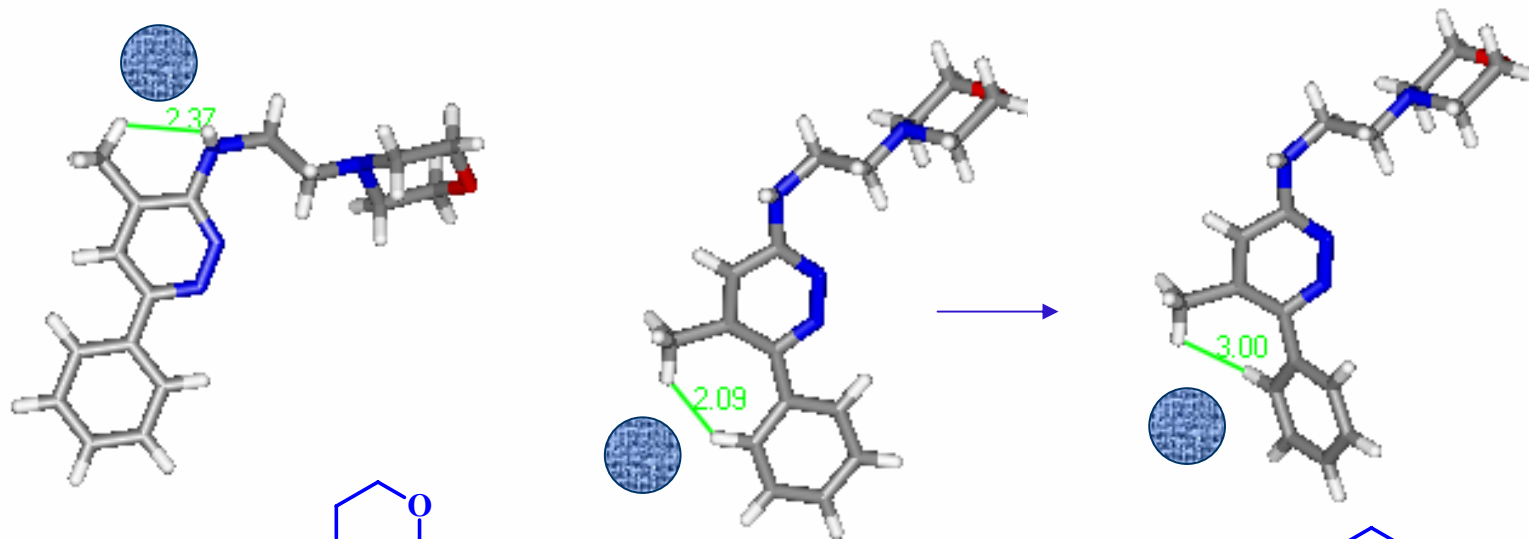
Visão dos Grupos Funcionais

Confôrmeros do ácido acetilsalicílico

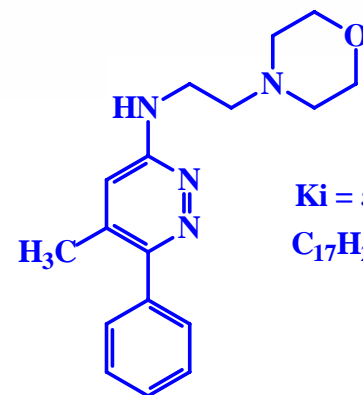
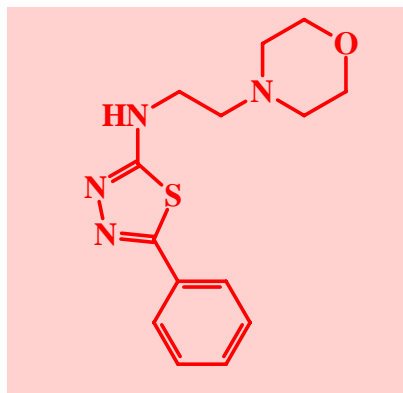




O conhecimento da estrutura química da “chave”: *efeitos conformacionais orto-*



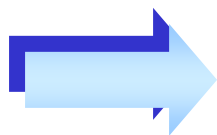
minaprina
K_i = 1700 nM
C₁₇H₂₂N₄O



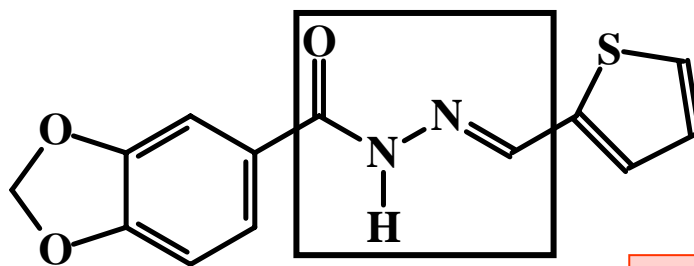
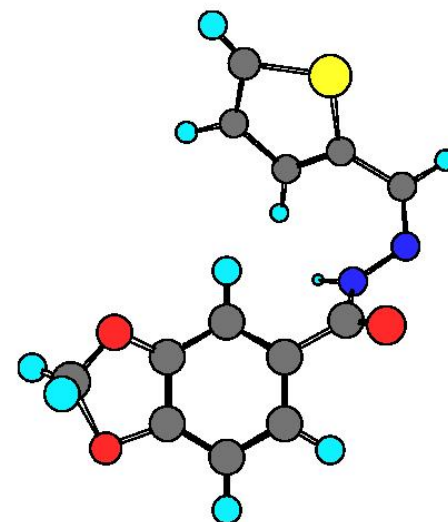
K_i = 55 nM
C₁₇H₂₂N₄O

Visão dos Grupos Funcionais:NAH

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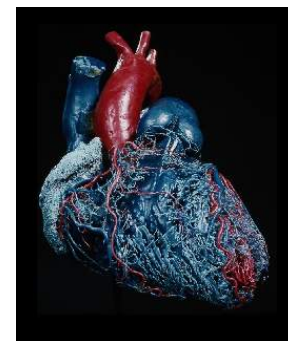
Química Medicinal



LASSBio-294

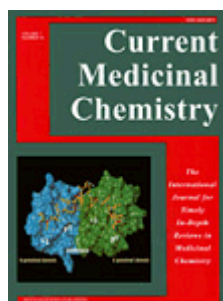
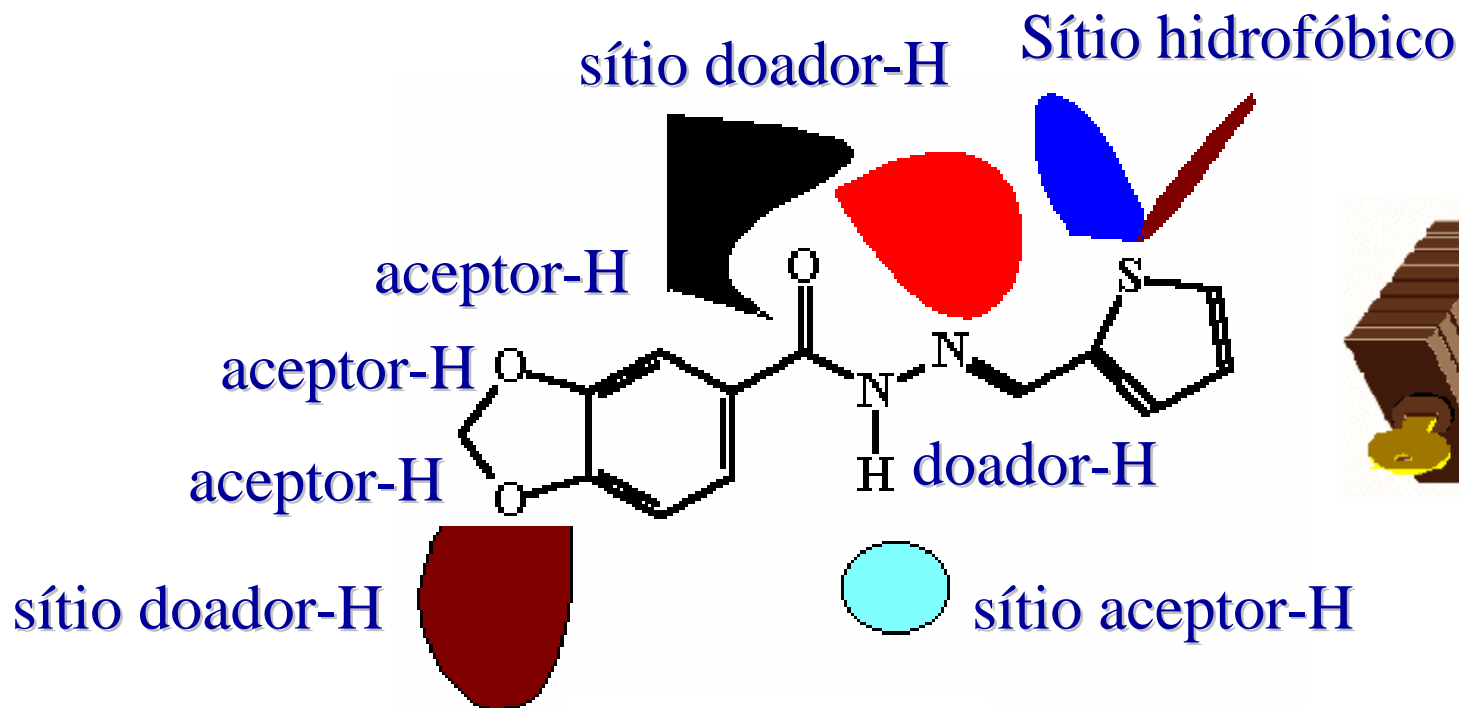
$C_{13}H_{10}N_2O_3S$
PM 274

cardioativo

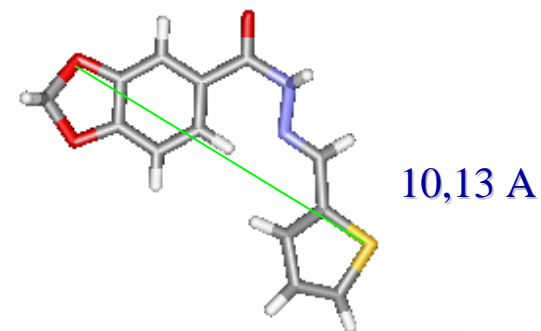
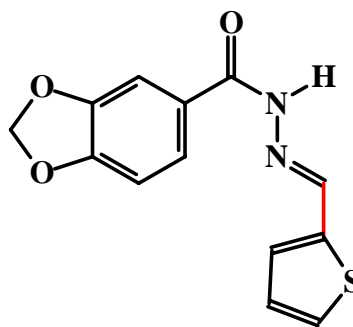
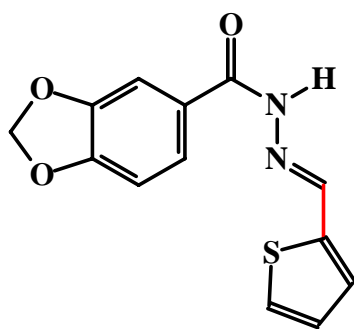
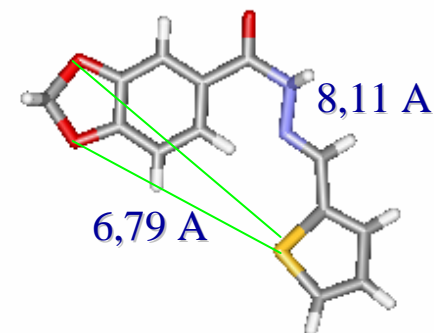
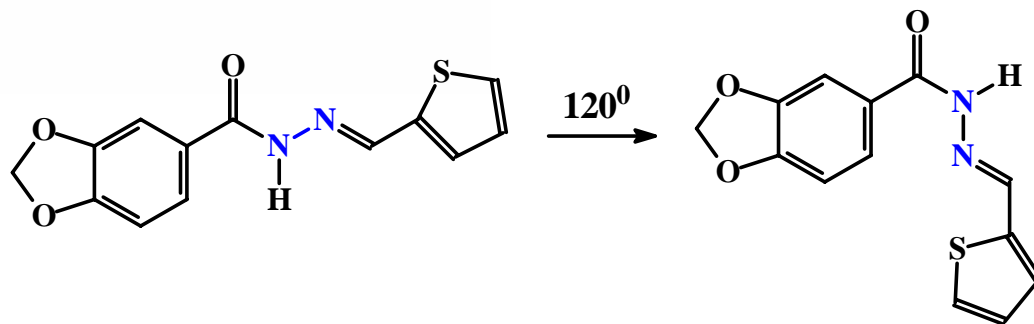
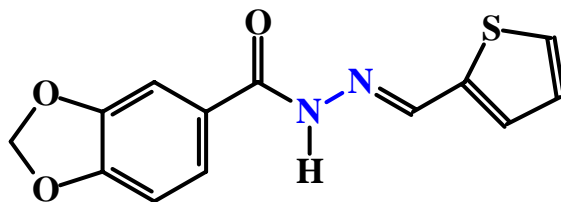
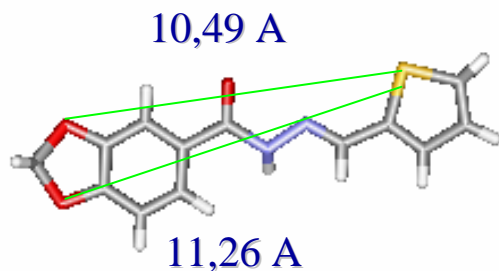


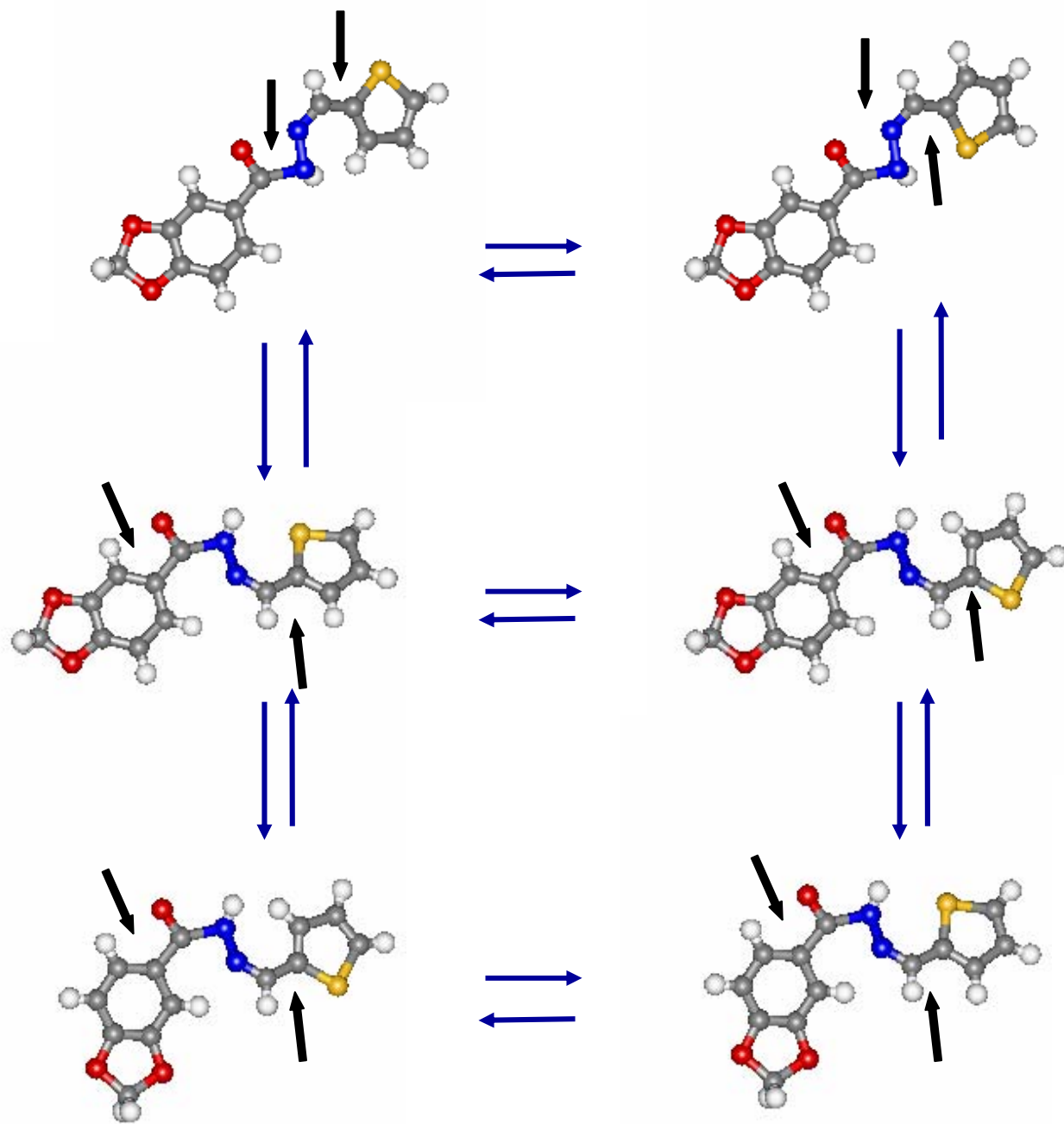
Visão dos Grupos Funcionais

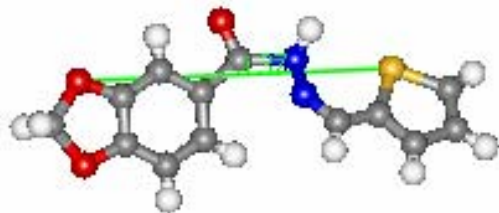
Provável modelo topográfico de interação: NAH



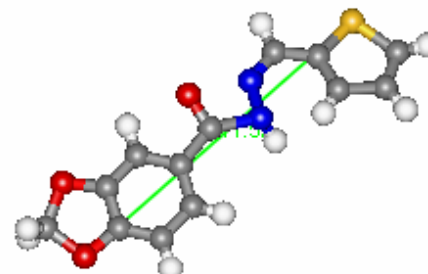
O conhecimento da estrutura química da “chave”: *efeitos conformacionais*



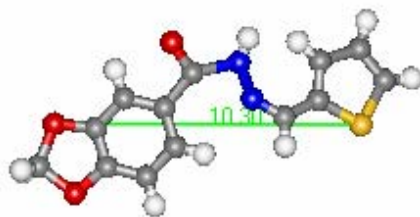




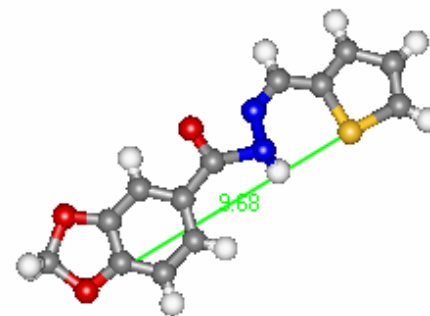
9,37 A



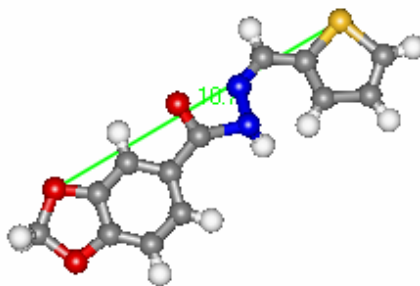
11,52 A



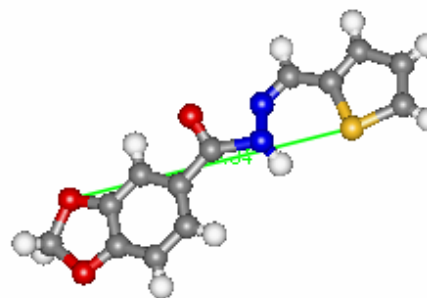
10,30 A



9,68 A

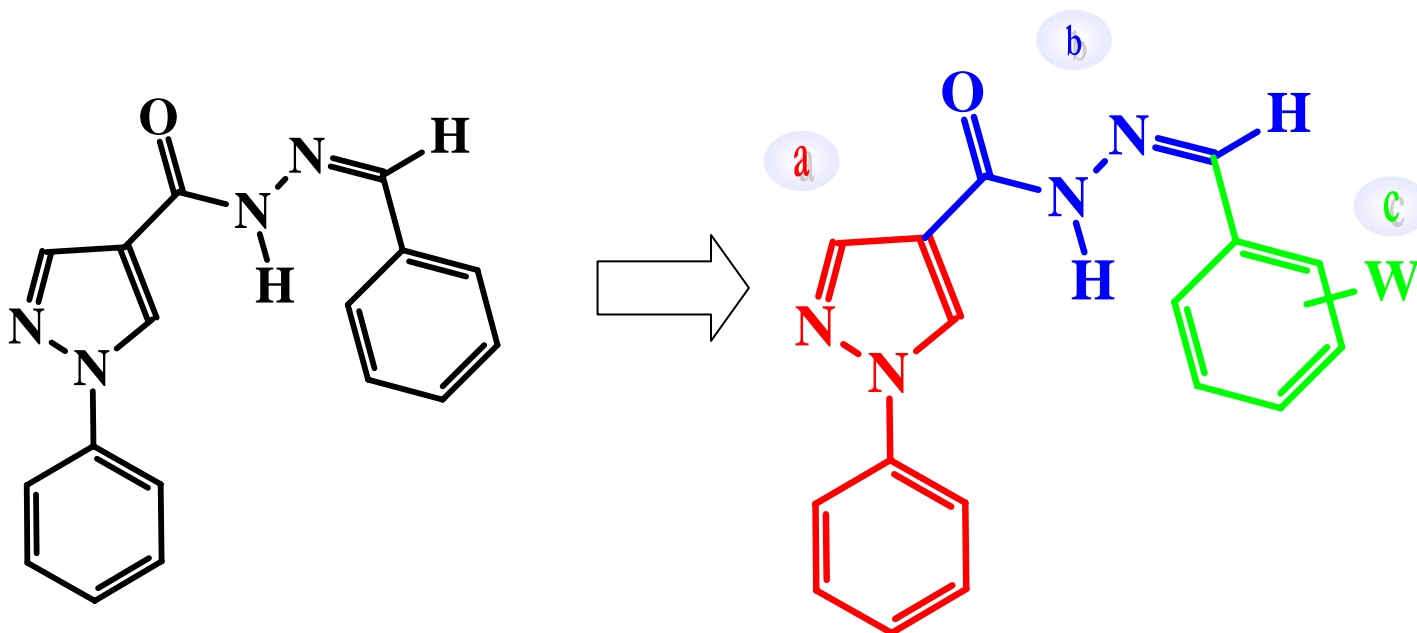


10,71 A



9,34 A

Visão dos Grupos Funcionais

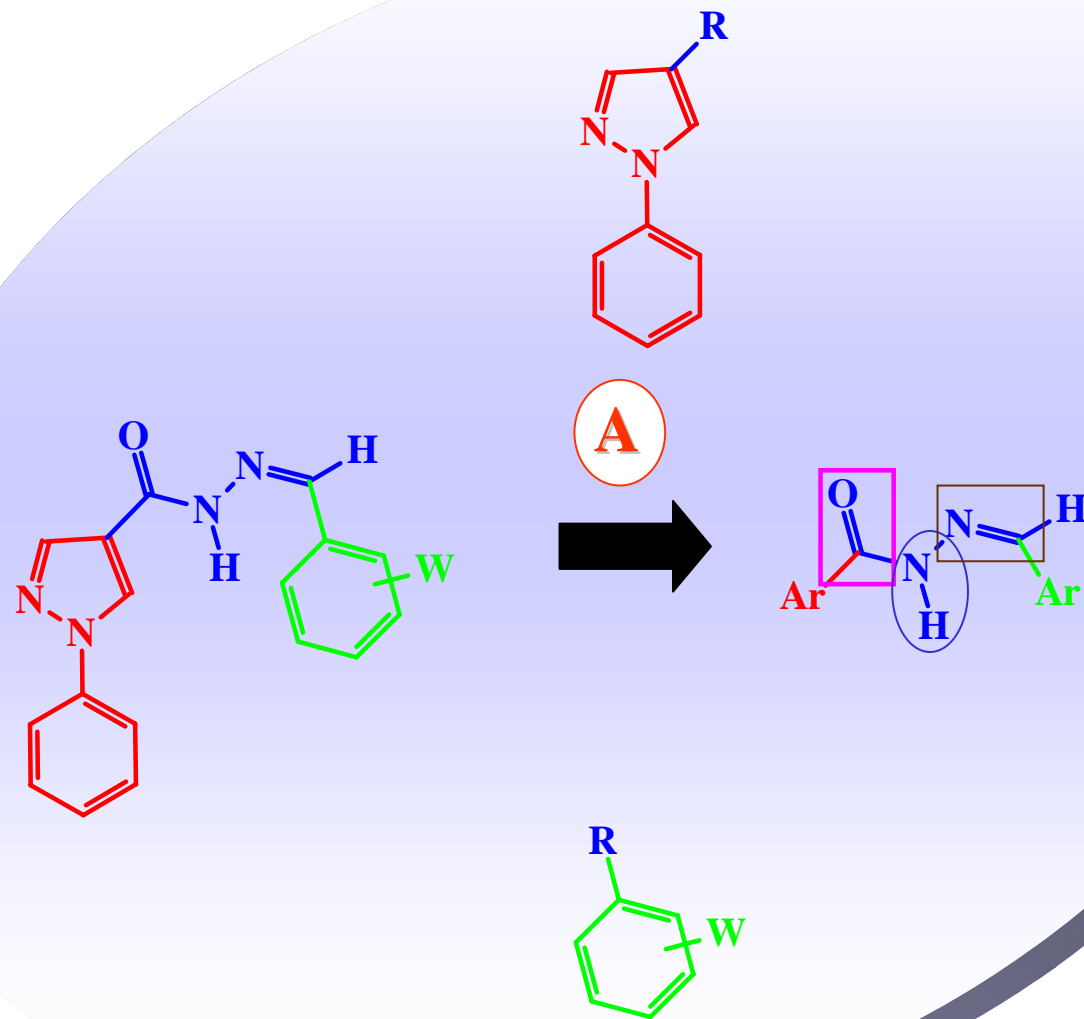


N-acilidrazona

- Qual sub-unidade **a-c** é farmacofórica ?
- Como construir uma série congênere?
- Como otimizar o composto-protótipo?



Construção da Diversidade Estrutural de NAH

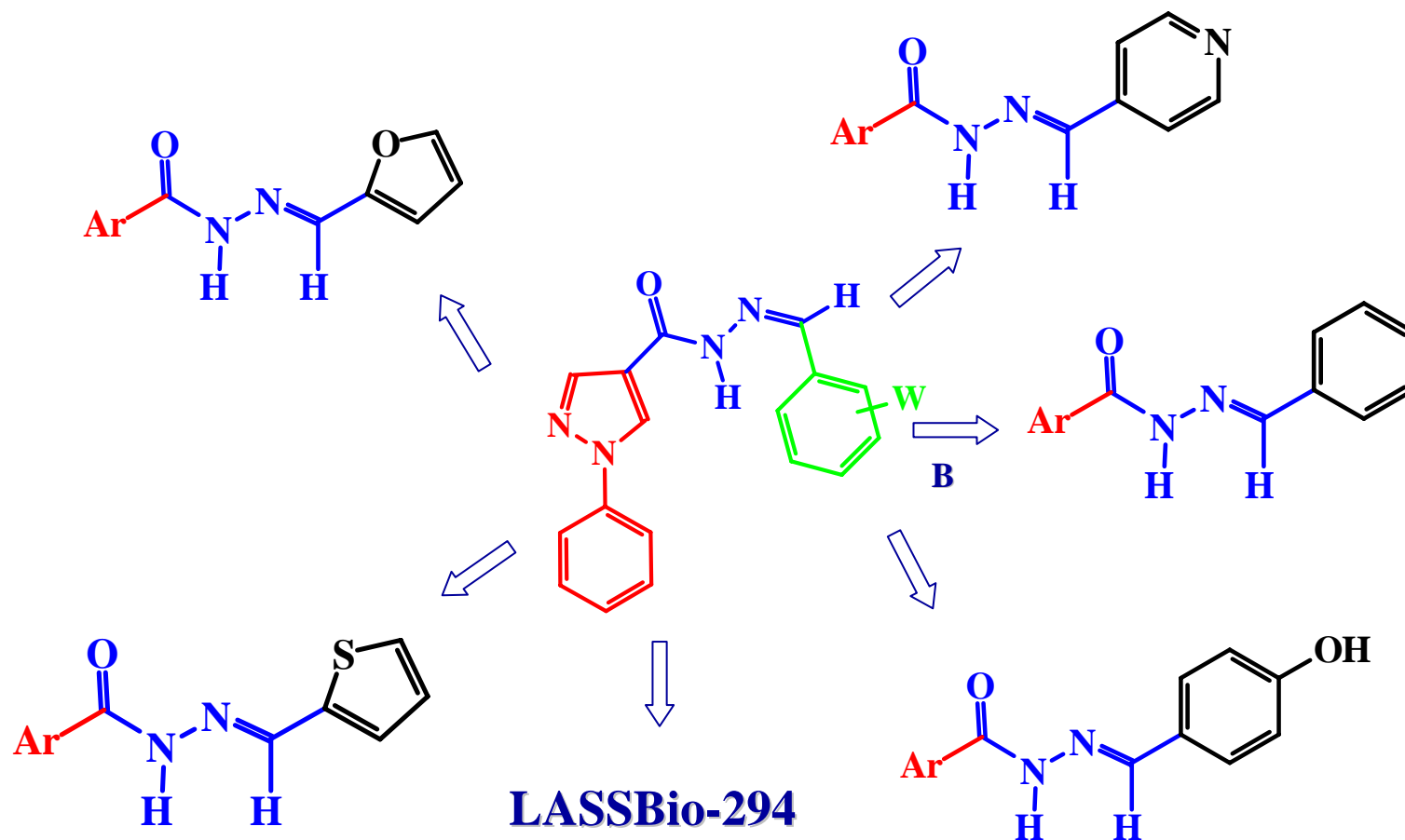


> espaço molecular

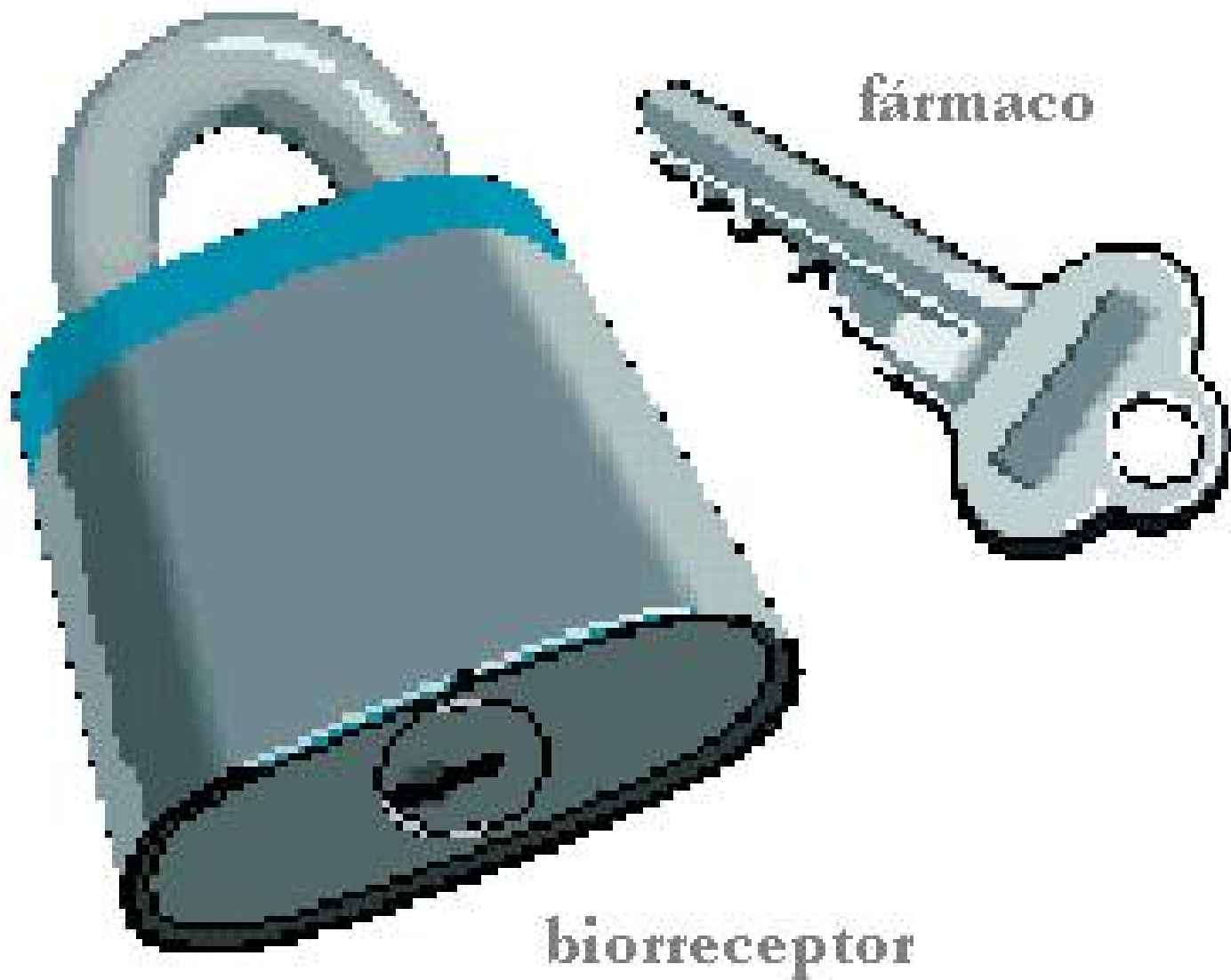




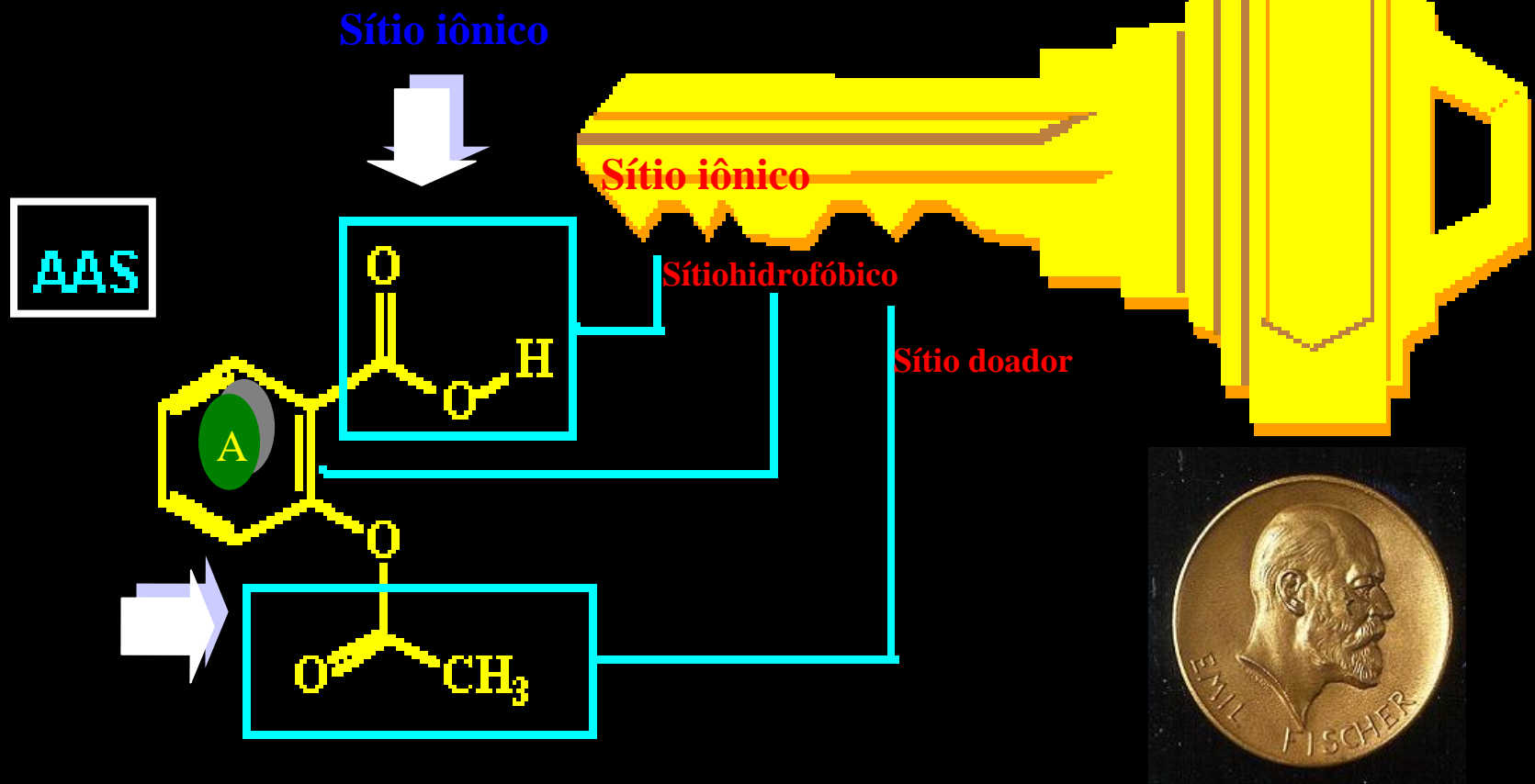
A diversidade molecular



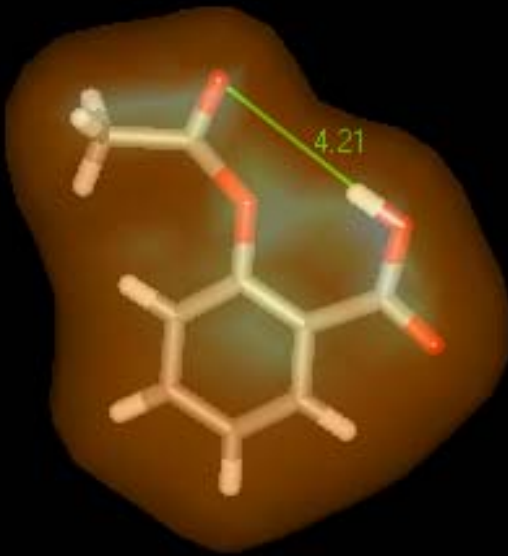
Modelo Chave-fechadura



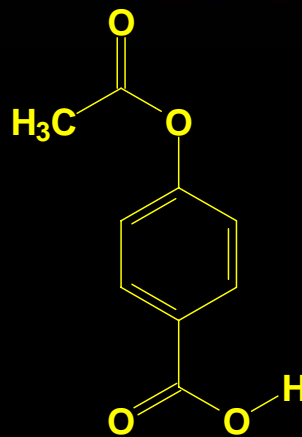
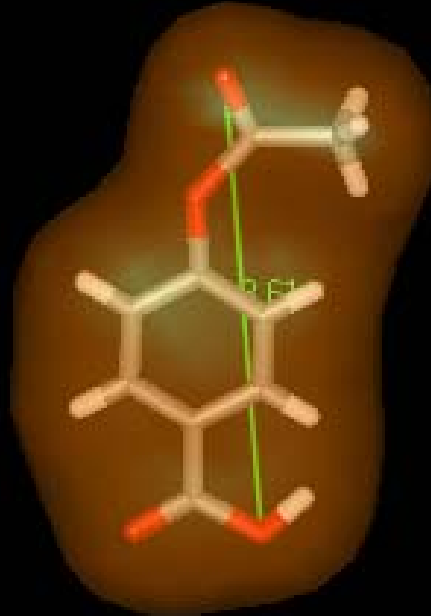
Complementaridade do modelo Chave-fechadura



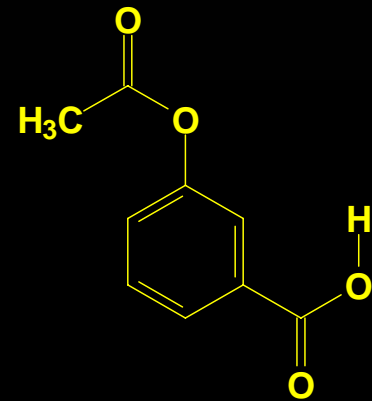
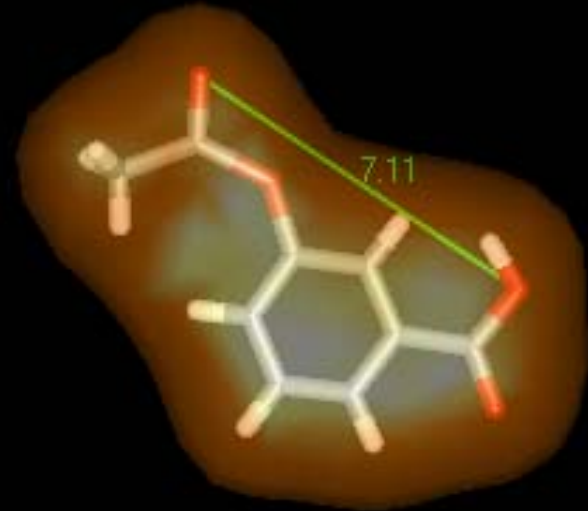
Isomêros do Ácido Acetil Salicílico (AAS)



orto

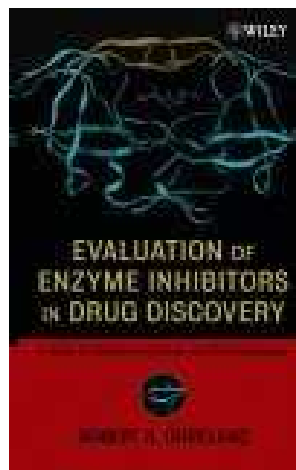
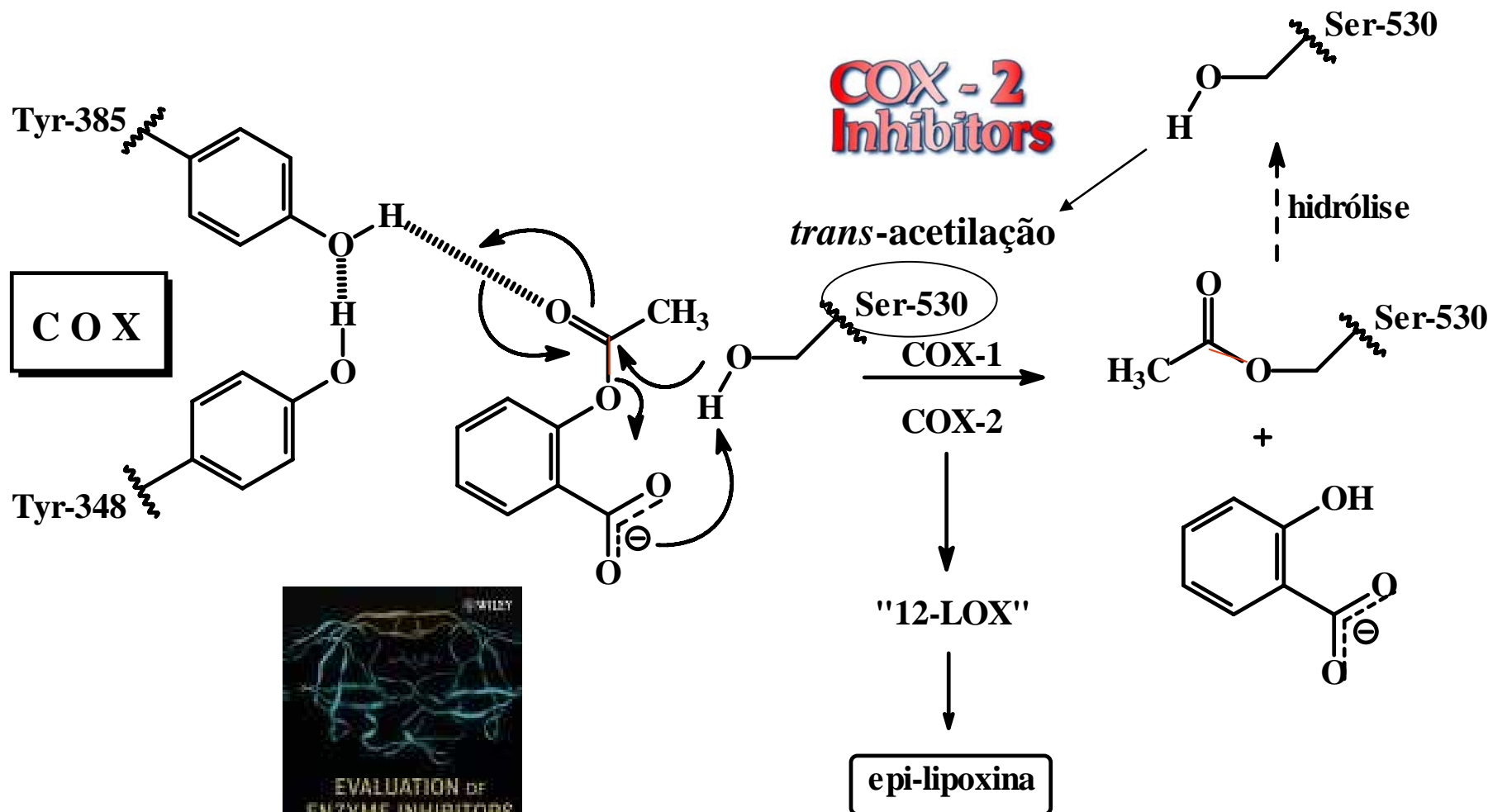


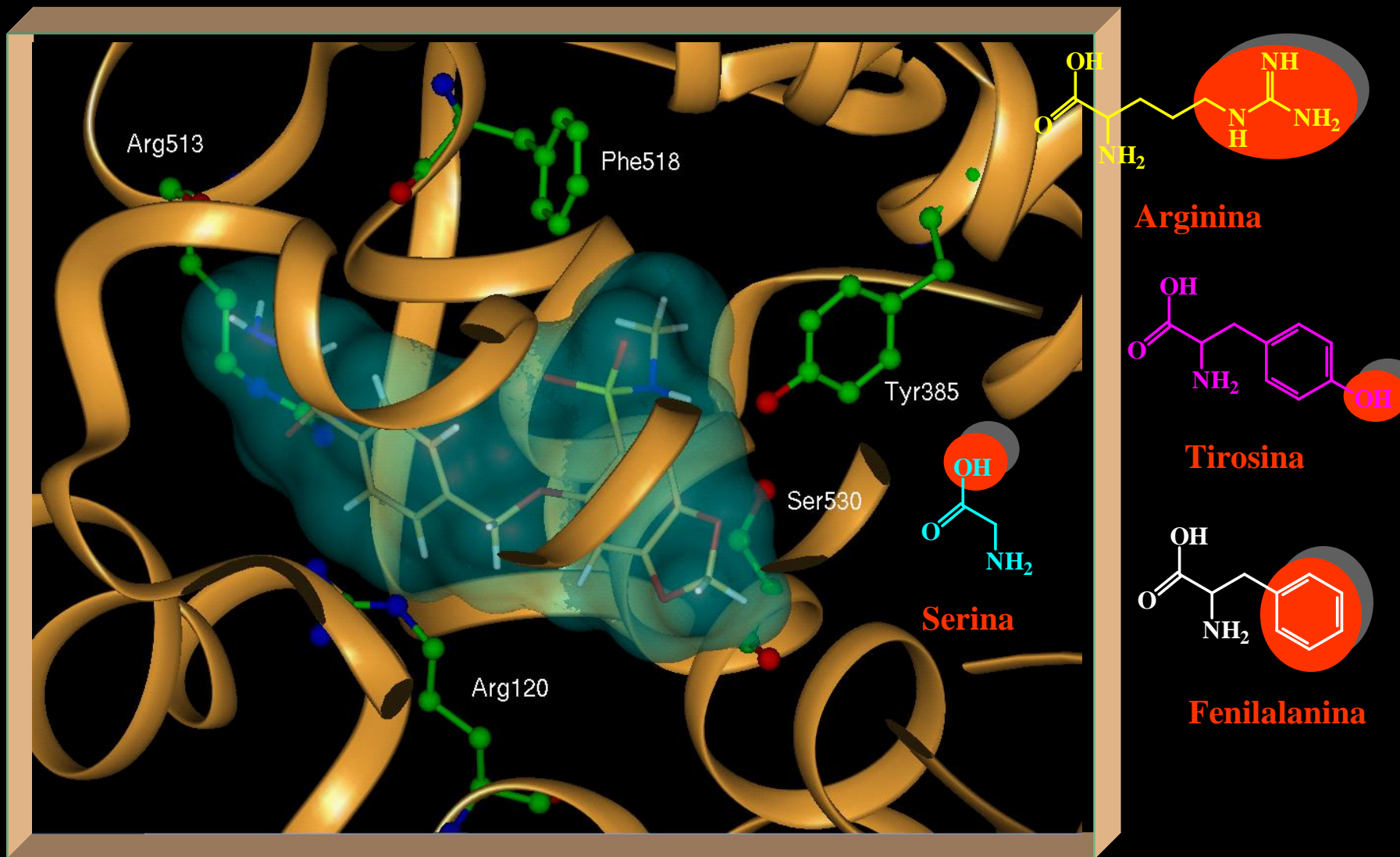
para



meta

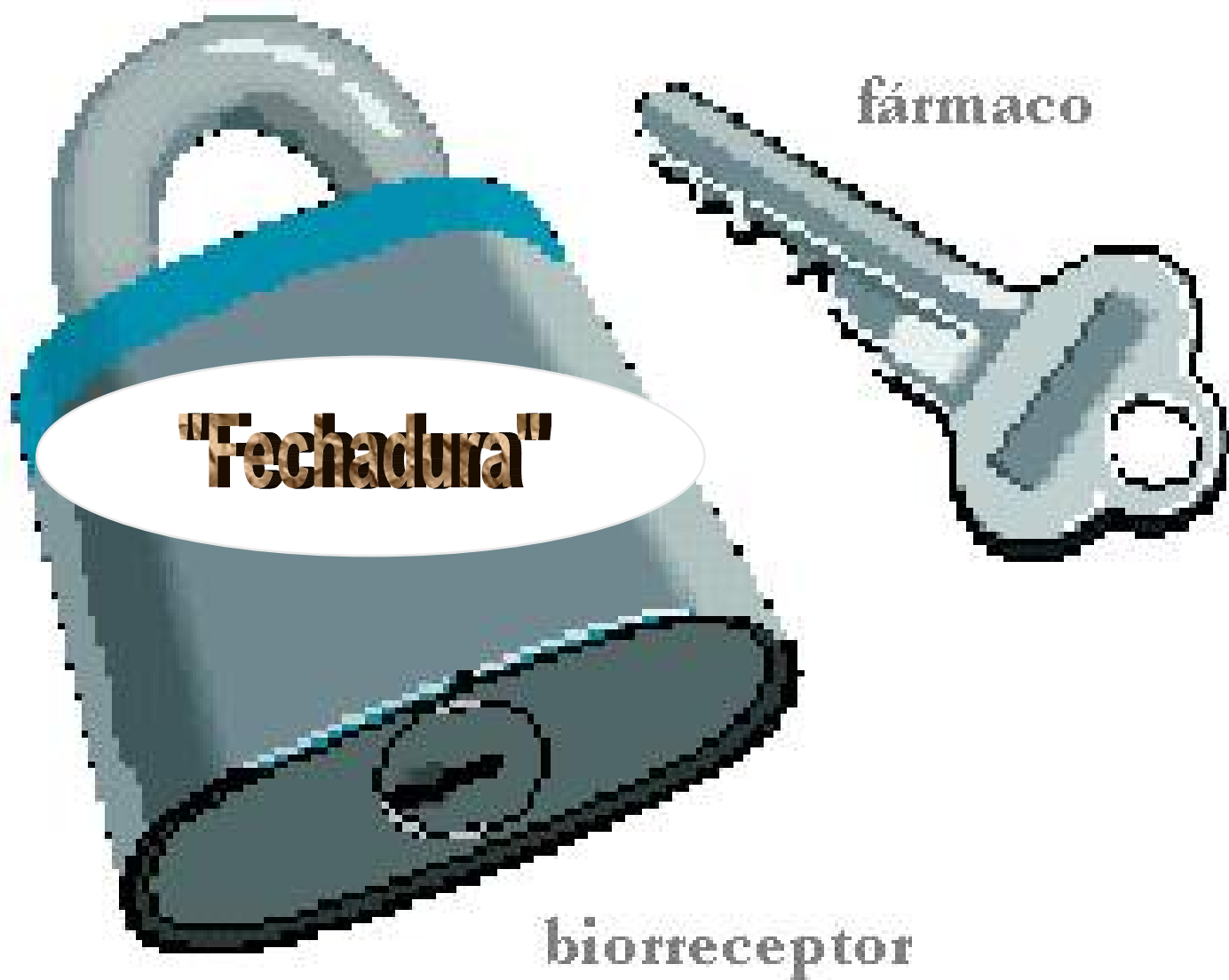
Mecanismo molecular de ação do AAS



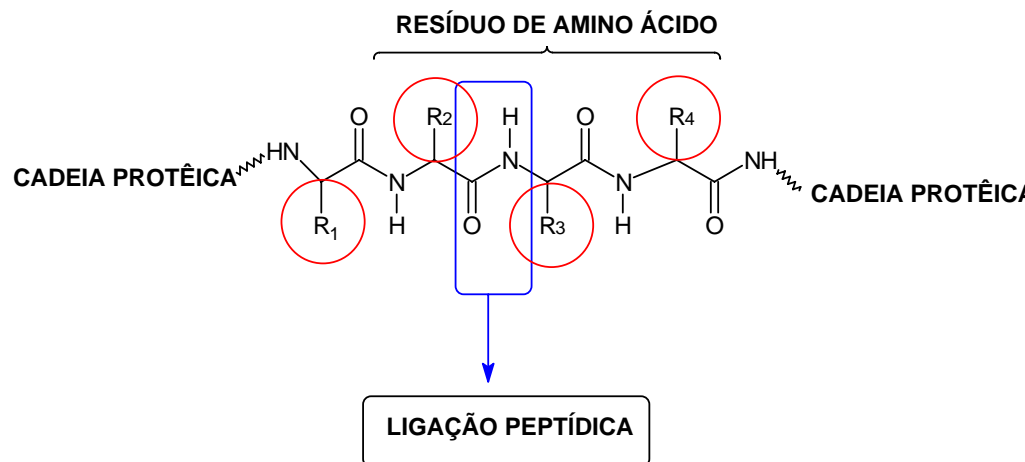


E. J. Barreiro et al., Selective PGHS-2 Inhibitors: A Rational Approach for Treatment of the Inflammation, *Current Medicinal Chemistry*, 9, 849-867 (2002).

Modelo Chave-fechadura



Estrutura Primária das Proteínas



AMINO ÁCIDOS: {

- Essenciais: His, Ile, Leu, Lys, Met, Phe, Thr, Trp, Val
- Não-essenciais: Ala, Arg, Asn, Asp, Cys, Glu, Gln, Gly, Pro, Ser, Tyr

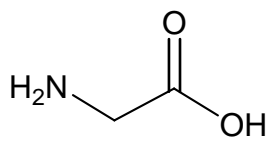
Força das Ligações Droga-Bioreceptor:

{

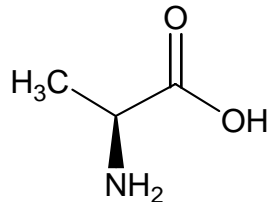
- Covalente: >200kJ/mol
- Iônica: 20kJ/mol
- Hidrogênio: 7-40kJ/mol
- Van der Waals: 1.9kJ/mol

"Fechadura"

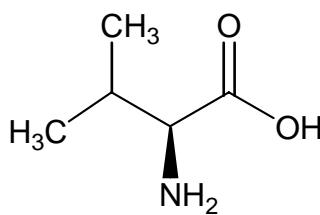




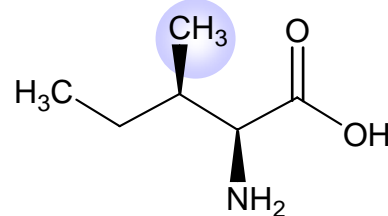
glicina (**gly**)



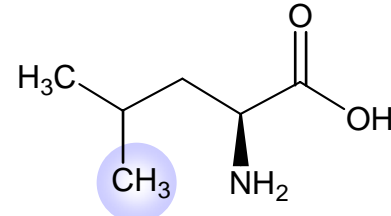
alanina



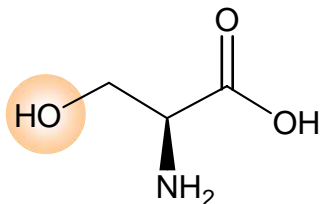
valina



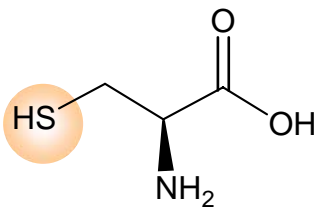
isoleucina (**Ile**)



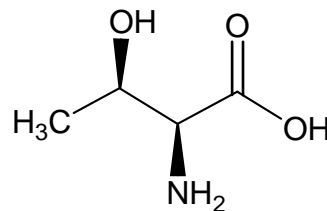
leucina



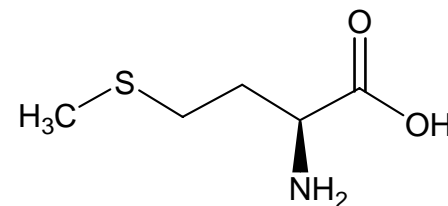
serina



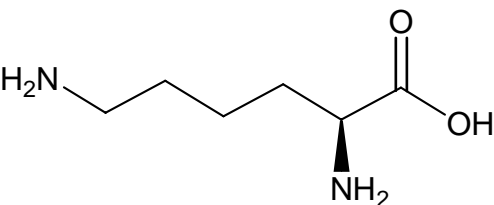
cisteína (**Cys**)



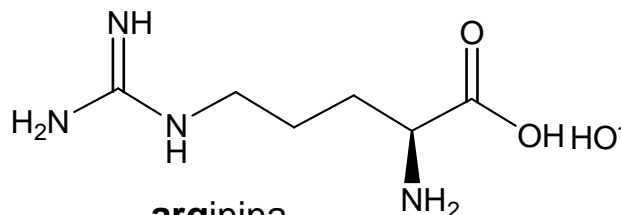
treonina (**Thr**)



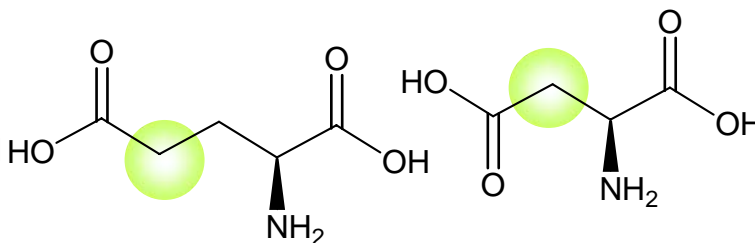
metionina



lisina (**Lys**)

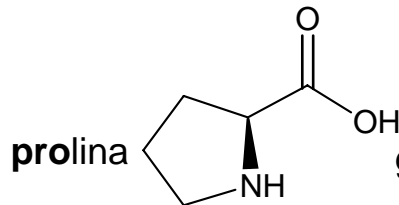


arginina

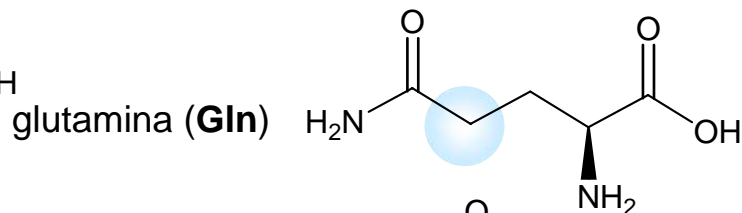


ácido glutâmico

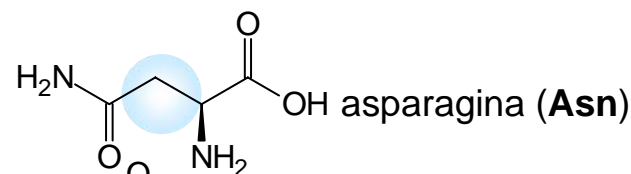
ácido aspártico



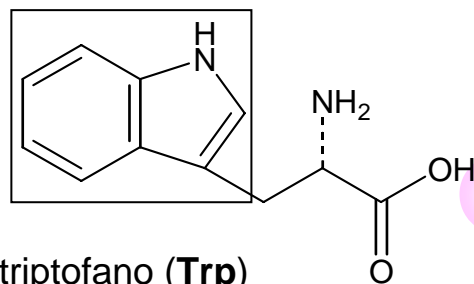
prolina



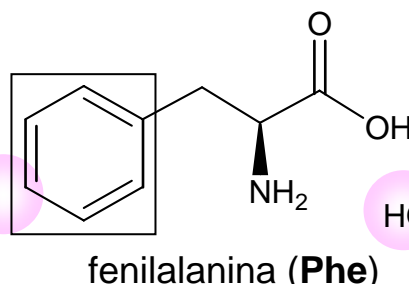
glutamina (**Gln**)



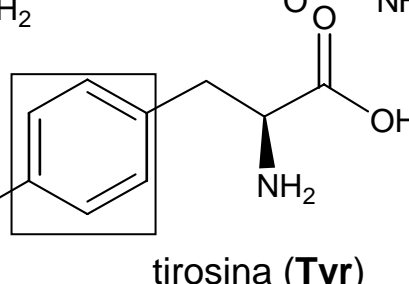
asparagina (**Asn**)



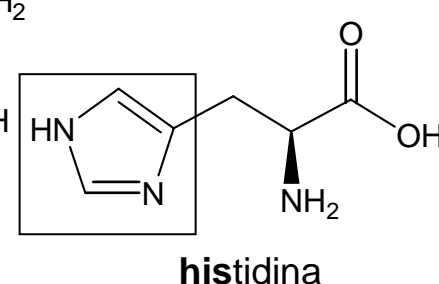
triptofano (**Trp**)



fenilalanina (**Phe**)



tirosina (**Tyr**)



histidina



A B C D
E F G H I
J K L M
N O P Q
R S T U Y Z
V W X



PROTEÍNAS
P R O T E Í N A S

Diversidade Molecular

C

+C

C-C

+C

C-C-C

+C

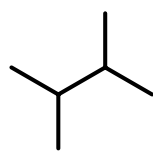
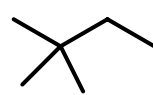
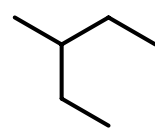
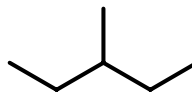
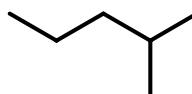
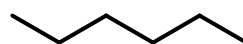
+C

C-C-C-C

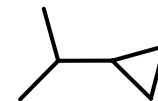
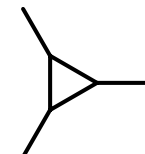
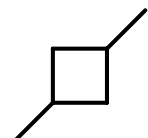
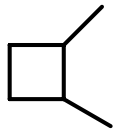
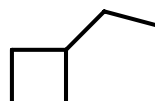
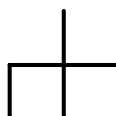
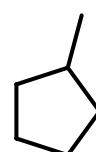
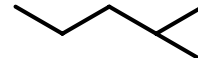
+C

C-C-C-C-C

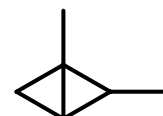
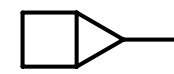
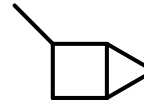
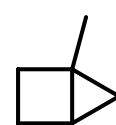
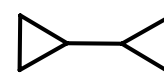
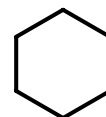
C₆H₁₄



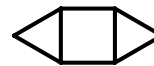
C₆H₁₂



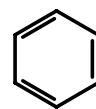
C₆H₁₀



C₆H₈



C₆H₆



24 compostos