

# A Química Medicinal

(Planejamento Racional de Novos Fármacos)

XXXVI Semana da Química “Ciência, tecnologia e sociedade: em busca do conhecimento”

**unesp** Instituto de Química, UNESP – Araraquara, 25-29 de setembro de 2006

**Eliezer J. Barreiro**

**UFRJ**

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



**Universidade Federal do Rio de Janeiro**

## 1. A Química (Farmacêutica) Medicinal: definição

## 2. Como se descobrem os fármacos?

## 3. A origem dos fármacos

3.1. O Papel dos produtos naturais na descoberta de fármacos

3.2 O Acaso e a descoberta de fármacos

3.3 Os fármacos sintéticos

## 4. O processo da descoberta

4.1. A abordagem fisiológica e a diversidade molecular

4.2 O paradigma do composto-protótipo: interações fármaco-biorreceptor

4.3 A importância dos fatores estruturais/conformacionais: grupos farmacofóricos/toxicofóricos

## 5. O planejamento racional

5.1 Fármacos inteligentes: Cimetidina; atovarstatina; celecoxib; me-too; imatinib

5.2 A diversidade molecular dos fármacos sintéticos

5.3 A diversidade molecular de novos protótipos descobertos no LASSBio, UFRJ

## 6. As estratégias de desenho estrutural da Química (Farmacêutica) Medicinal

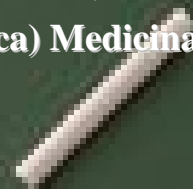
6.1 Bioisosterismo: LASSBio-346, LASSBio-501

6.3 Hibridação molecular: LASSBio-756

6.4 Simplificação molecular: LASSBio-294

6.5 Desenho de protótipos simbióticos: LASSBio-468

## 7. Conclusões

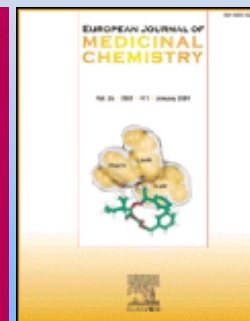
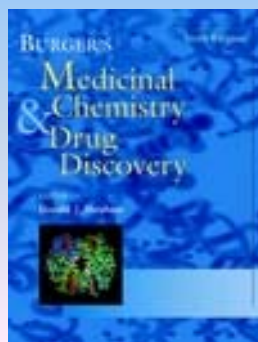
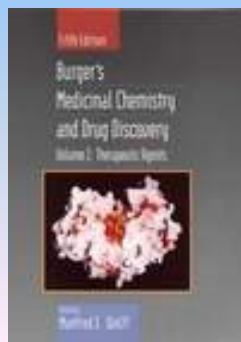




# Química Medicinal

“Tries to be based on the ever increasing hope that biochemical rationales for **drug discovery** may be found”

*J. Med. Chem.* (ACS) vol. 34, 1991



**Prof. Alfred Burger**

(1904-2000)

University of Virginia

EUA



*Eur. J. Med. Chem.*, 31, 747 (1996)

## Química Medicinal

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

*Estuda os fatores moleculares do seu modo de ação,  
incluindo a compreensão  
da relação entre a estrutura química e a atividade (SAR),  
a absorção, distribuição, metabolismo, eliminação e toxicidade.*







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

**IUPAC**

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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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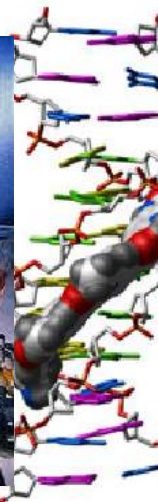
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Como se descobrem  
os fármacos?



# Origem dos Fármacos

85%

**Produtos Naturais**

atorvastatina

propranolol

cimetidina

**Sintéticos**

**Fármacos**

robótica  
**Novos**

marinhos  
AZT, ET-743

microorganismos,  
fungos  
antibióticos

CADD

sulfas  
diuréticas



penicilinas

hicantona  
oxifenilbutazona

**Acaso**

benzodiazepínicos

**Estudo do  
metabolismo**

paclitaxel  
camptotecina

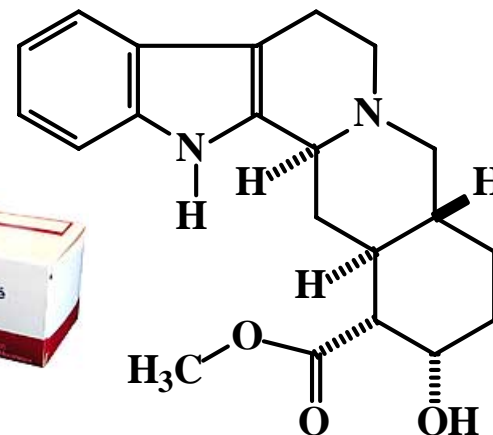
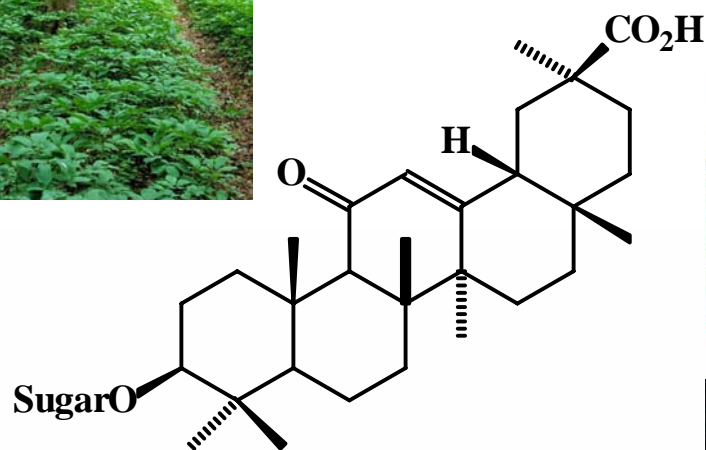




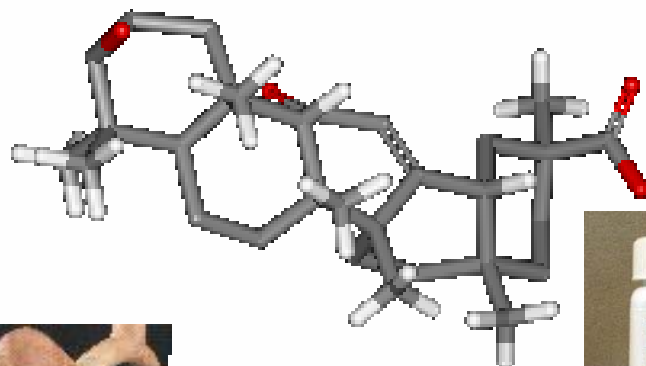


# Produtos Naturais

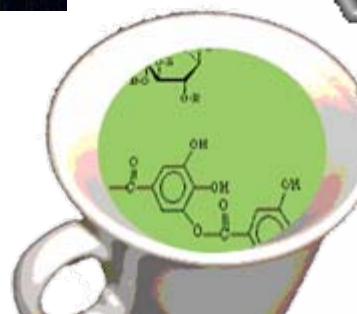
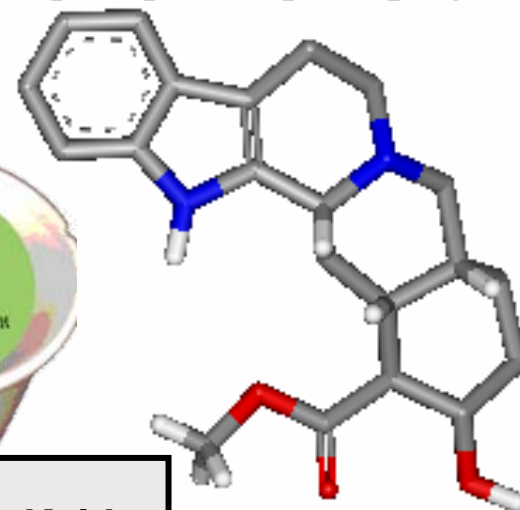
## Afrodisíacos



ioimbina



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

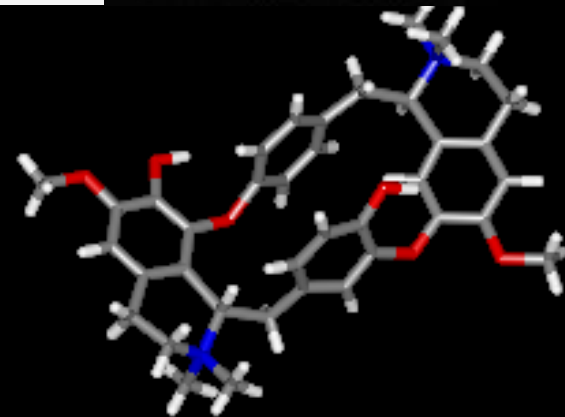


T. G. Waddell, H. Jones & A.L. Keith  
*J. Chem. Ed.* 1980, 57, 341

# Curare

## Fármaco dos Índios

### Bloqueadores ganglionares



### d-tubocurarina

*Chondrodendron tomentosum*

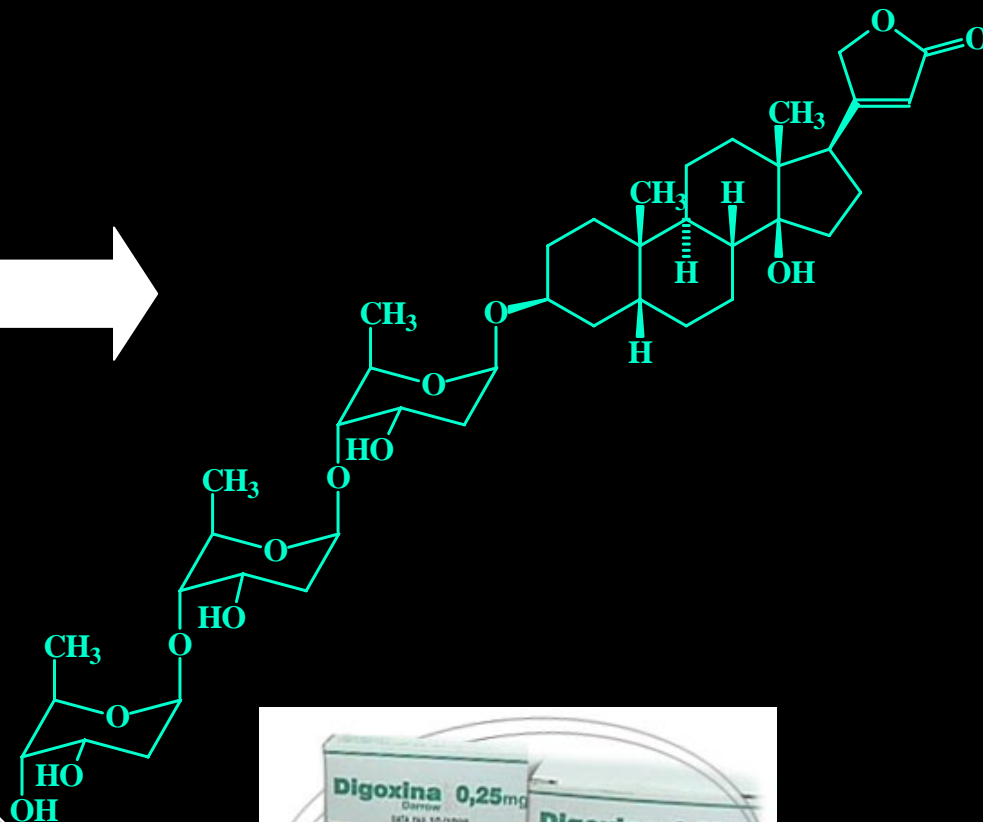
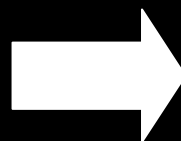


Photo Henriette Kress



*Digitalis purpurea*

# Glicosídeos Cardiotônicos

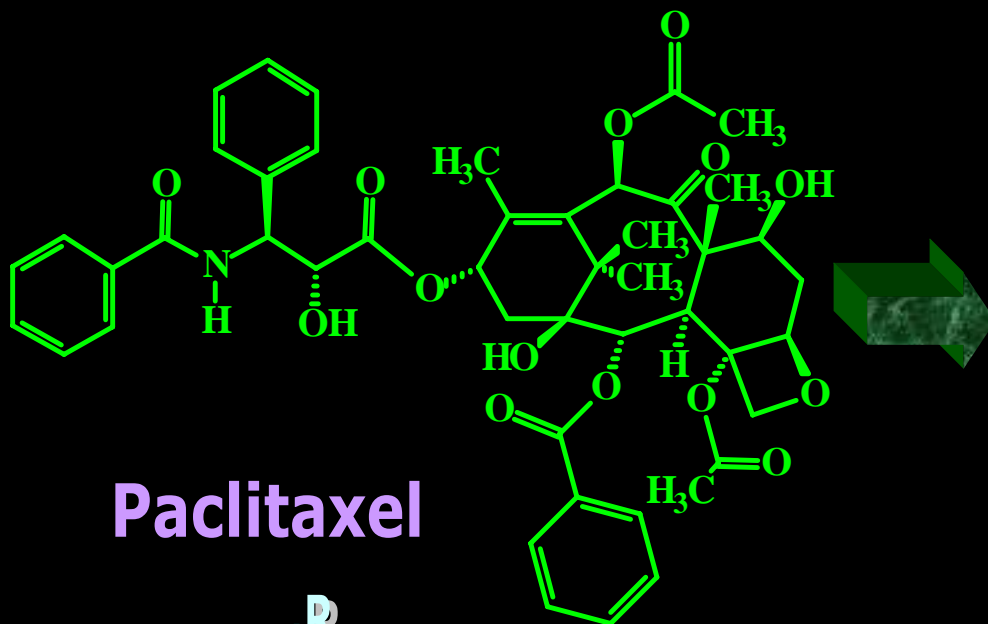


## Decano dos Fármacos



*1,000 kg of dried foxglove leaves to make 1 kg of pure digoxin*





**Paclitaxel**

**Taxol<sup>®</sup>**

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



**M. E. Wall & M. C. Wani**

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



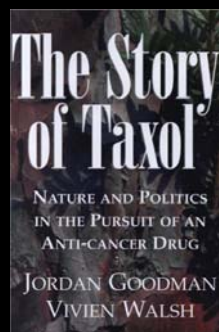
*Taxus bacatta*



**Res. Triangle Park, 1967**



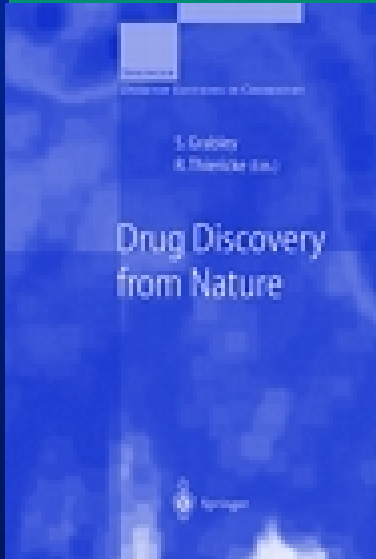
*Taxus bacatta*



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



# Patrimônio genético brasileiro

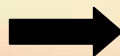




# Inovação terapêutica



M. O. Rocha e Silva  
1910-1983



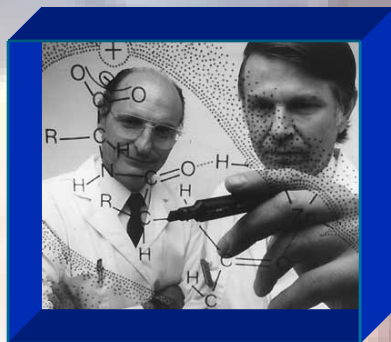
Bradicinina  
(W. Beraldo, 1949)



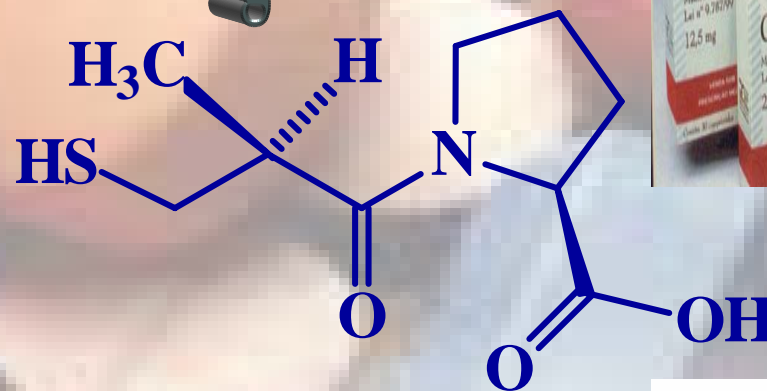
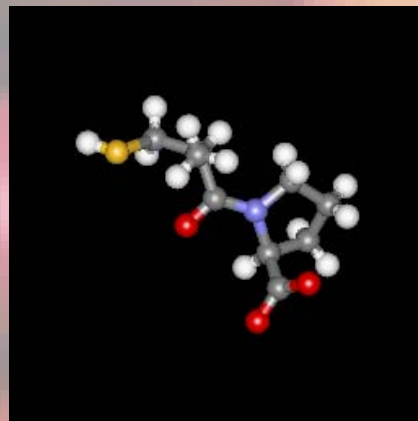
S. H. Ferreira  
1934-

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

## Inibidores da Enzima Conversora de Angiotensina



D. W. Cushman & M. A. Ondetti



Captopril

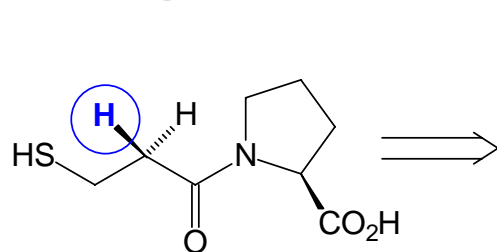


M. A. Ondetti, D. W. Cushman & B. Rubin, *Chronicles of Drug Discovery*, vol. 2, J.S. Bindra & D. Lednicer, Eds., Wiley, Nova Iorque, 1983, p. 1-32

## Anti-hipertensivos inibidores da enzima conversora

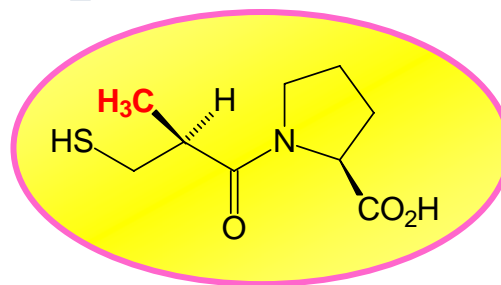
Compound	Company	Target	Protease class
Captopril	Bristol-Myers Squibb	ACE	Metallo
Enalapril	Merck		
Lisinopril	AstraZeneca		
Trandolapril	Abbott		
Zofenopril	Menarini group		
Ramipril	Aventis		
Moexipril	Boehringer Mannheim		
Imidapril	Trinity Pharmaceuticals		
Perindopril	Daiichi Pharmaceutical, Servier/Solvay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

# Agentes Anti-hipertensivos: inibidores da ACE



ACEi = 1

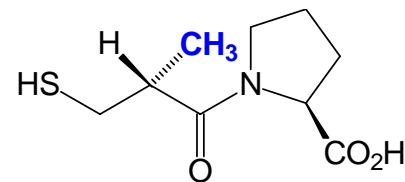
**Eutômero**



Captopril

ACEi = 10

Ondetti, 1997  
Squibb [ SQ14,225)  
IC<sub>50</sub> 23nM

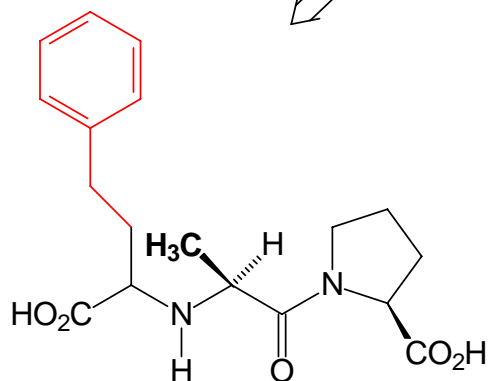


ACEi = 0.1

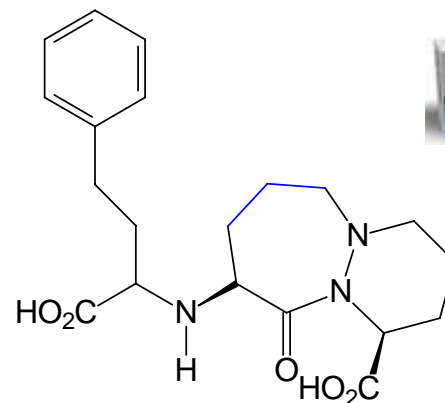
**Distômero**

> interação

anelação: > conformação bioativa



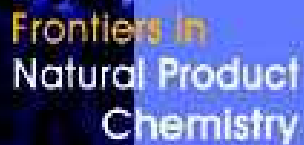
**enalapril**



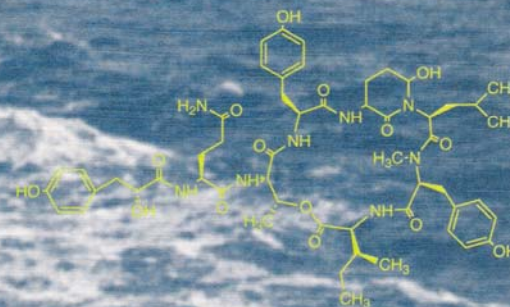
**cilazapril**







Editor  
N. Fusetani



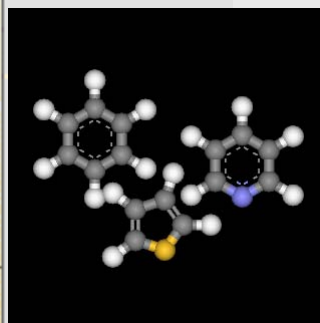
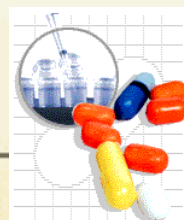
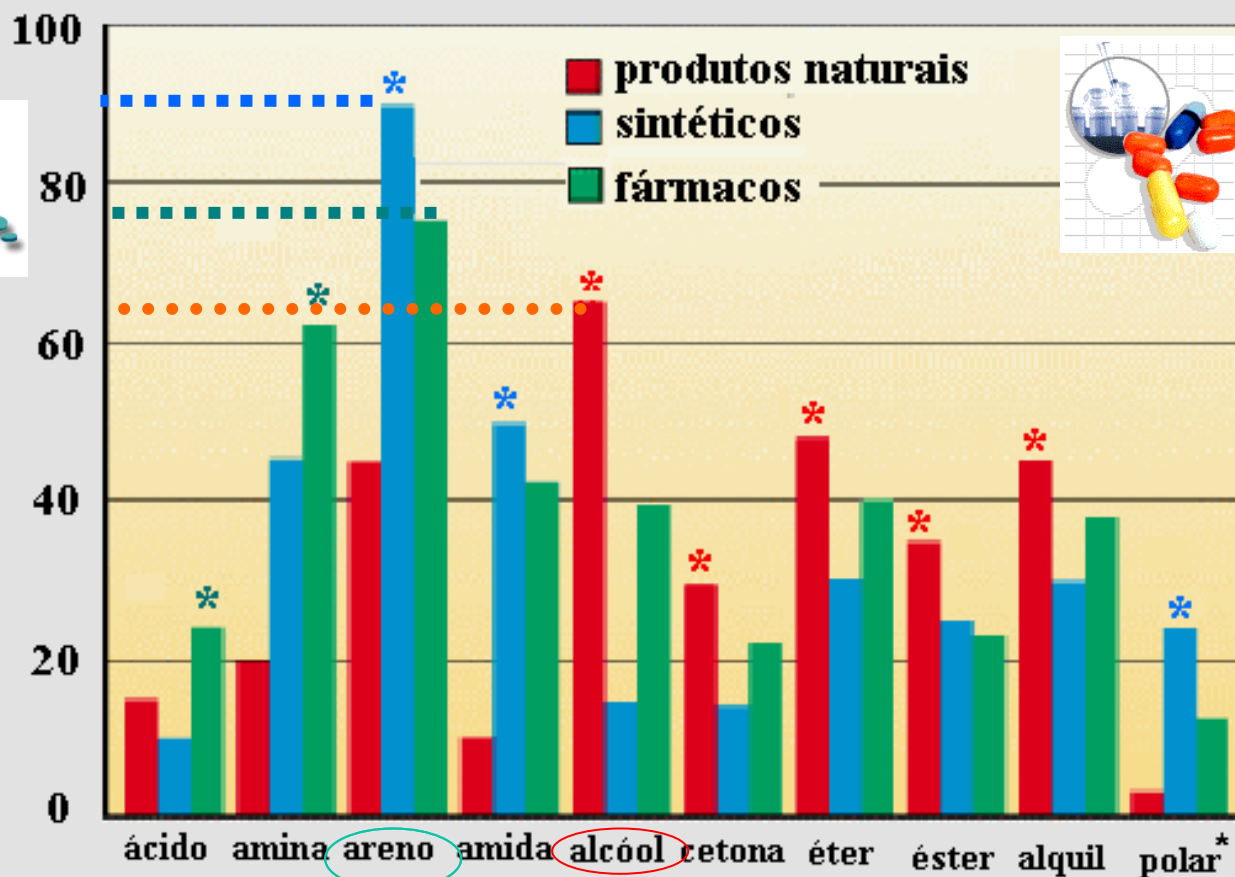
KARGER

# Produtos Naturais Marinhos em Ensaios Clínicos

Composto	Organismo	Fase	Doença
KRN7000	Porifera	I	câncer
IPL-567	Porifera	I	inflamação
methopetrosin	Celenterata	I	inflamação
GST-21	nemertea	I	Alzheimer
Dolastatina 10	molusco	II	câncer
LU-103793	molusco	I	câncer
Ziconitido	molusco	III	dôr
Briostatina	Briozoa	II	câncer
Didemnina B	Urocordarta	II	câncer
Ecteinascidina 743	Urocordata	II	câncer
Esqualamina	Cordata	I	câncer

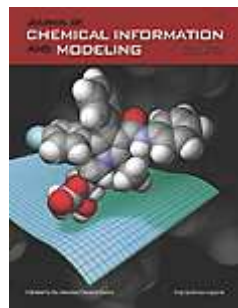


# *Frequência dos Grupos Funcionais Clássicos em Diferentes Compostos*

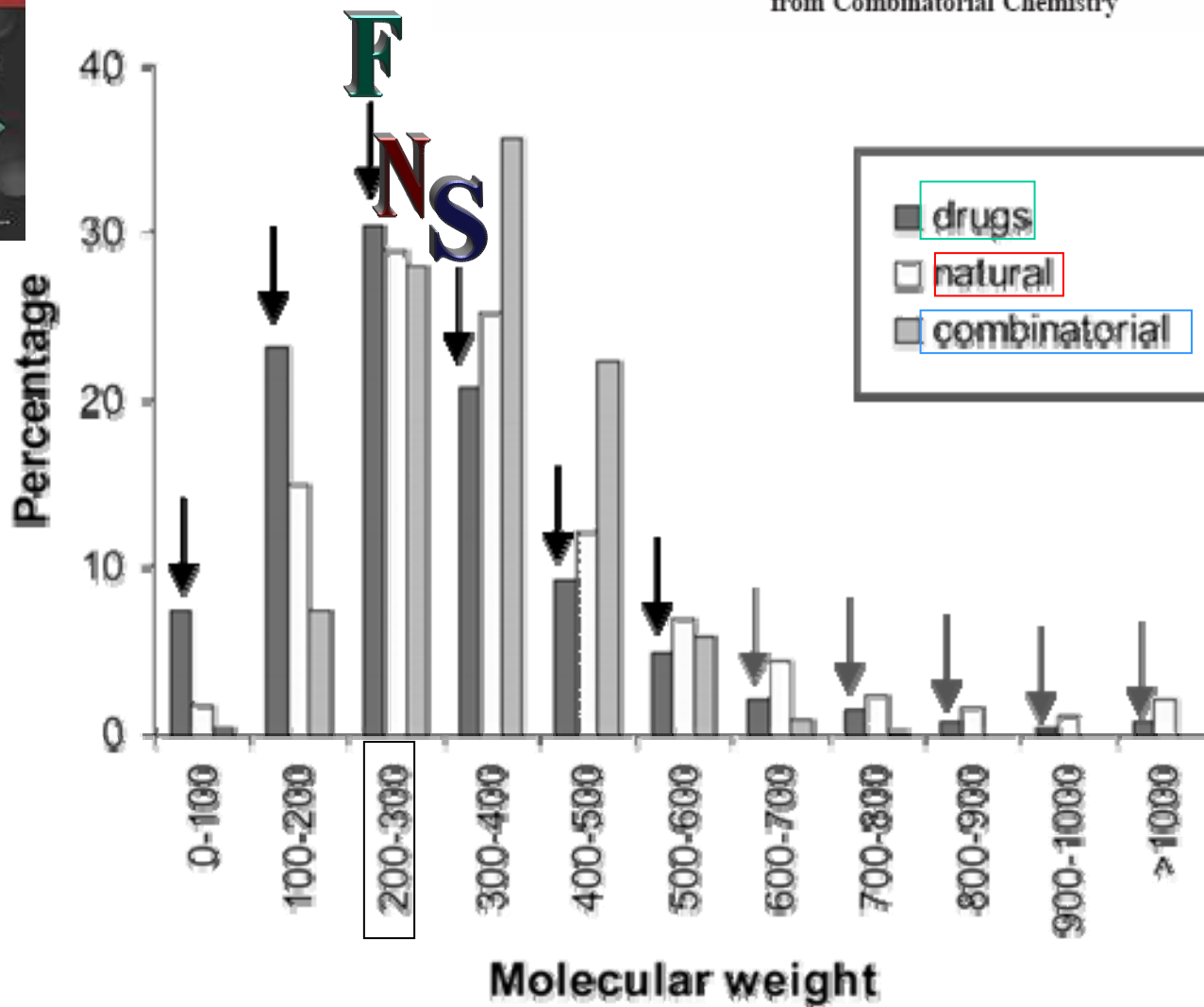
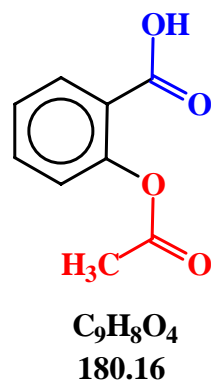


\* grupos polares: F, CN, NO<sub>2</sub>

Fonte: *Angewandte Chemie*



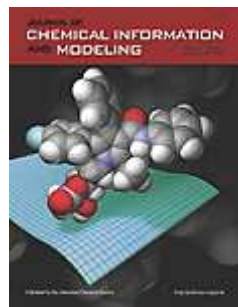
# Property Distributions: Differences between Drugs, Natural Products, and Molecules from Combinatorial Chemistry



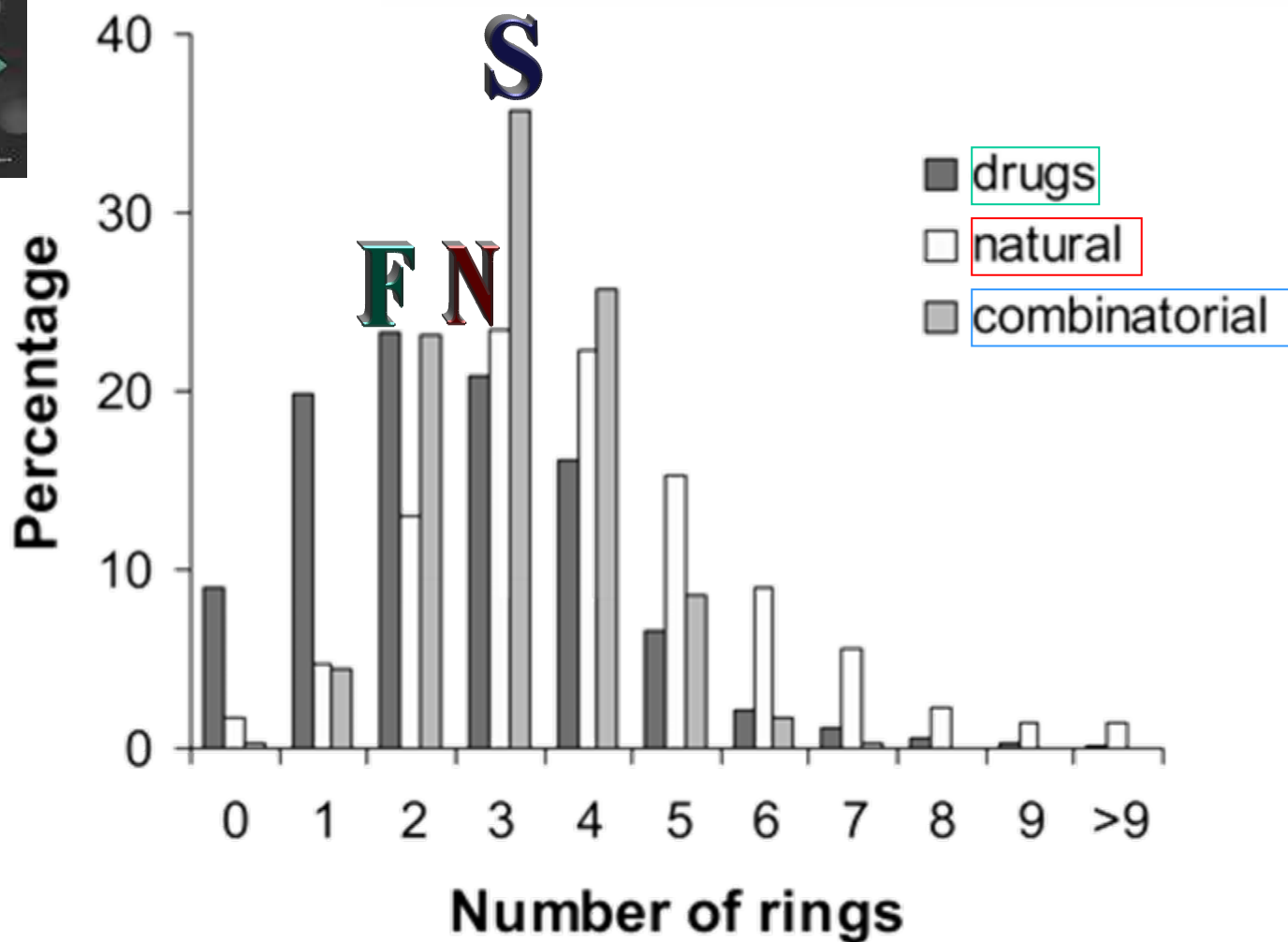
The molecular weight distribution among drug molecules, natural products, and compounds from combinatorial synthesis.

(M. Pekar & JM Schmidt, J. Chem. Inf. Comput. Sci., 43 (1), 218-227, 2003).

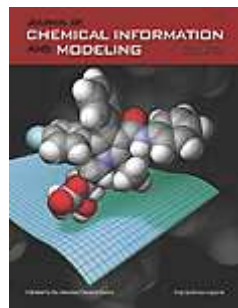




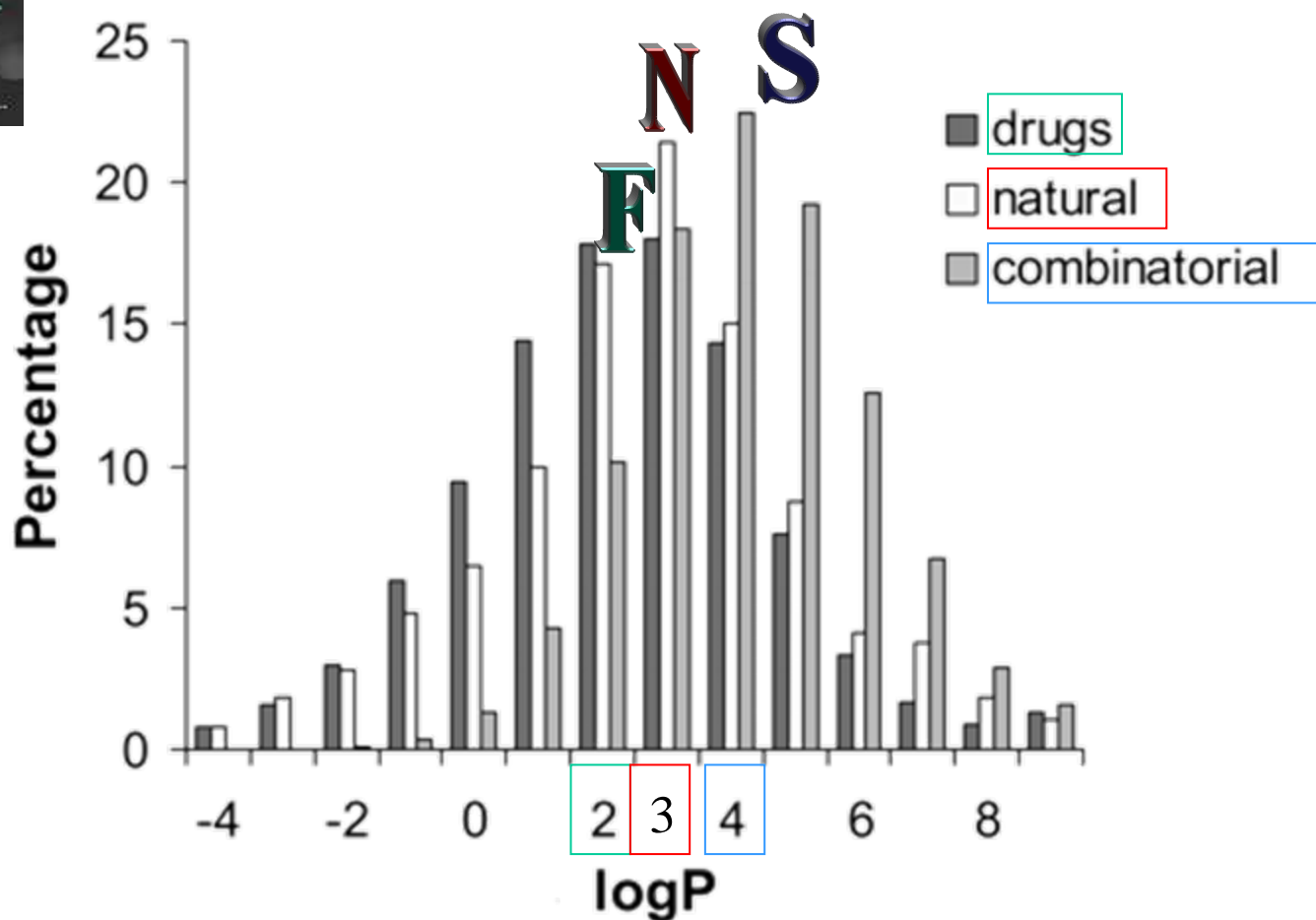
# Property Distributions: Differences between Drugs, Natural Products, and Molecules from Combinatorial Chemistry



(M. Feher & JM Schmidt, J. Chem. Inf. Comput. Sci., 43 (1), 218 -227, 2003).



# Property Distributions: Differences between Drugs, Natural Products, and Molecules from Combinatorial Chemistry



(M. Feher & JM Schmidt, *J. Chem. Inf. Comput. Sci.*, 43 (1), 218 -227, 2003).

# The the process of discovering natural-product hits

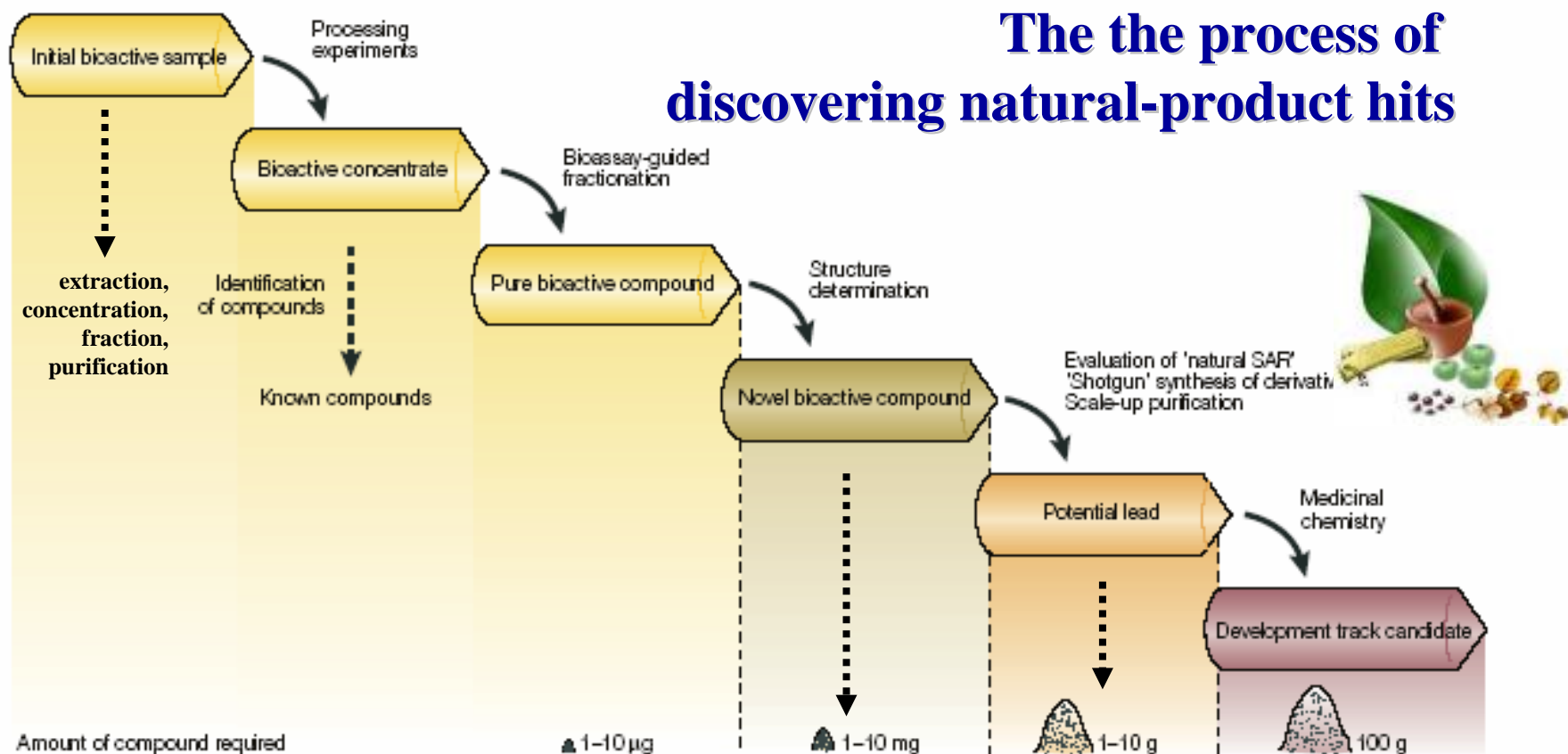


Figure 5 | Chemical process for natural product discovery. The natural product is extracted from the source, concentrated, fractionated and purified yielding essentially a single biologically active compound. Identification of known compounds, thereby avoiding replication of previous efforts, has been greatly aided by directly coupled HPLC-mass spectrometer (LC-MS) systems and natural-product databases<sup>57</sup>. *De novo* structure determination of compounds that are novel has been revolutionized by advances in spectroscopic techniques, particularly in high-resolution nuclear magnetic resonance technologies. Although the determination of complex structures is technically challenging, it is no longer a major impasse in the drug discovery process. In those cases in which the biological activity profile meets criteria for potency and selectivity, preliminary structure-activity relationship (SAR) studies are conducted and the purification process is scaled up. Once the feasibility of modulating biological response through synthetic modification is established, the hit is declared a lead and proceeds onward for additional optimization by traditional medicinal chemistry.



F.E. Koehn, G.T. Carter,  
The evolving role of natural products in drug discovery

*Nature Rev. Drug Disc.* .2005, **4**, 206 - 220

# esteróides



Russell Marker

Gregory Pincus (1903-1987)

Russell E. Marker & Gregory Pincus

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

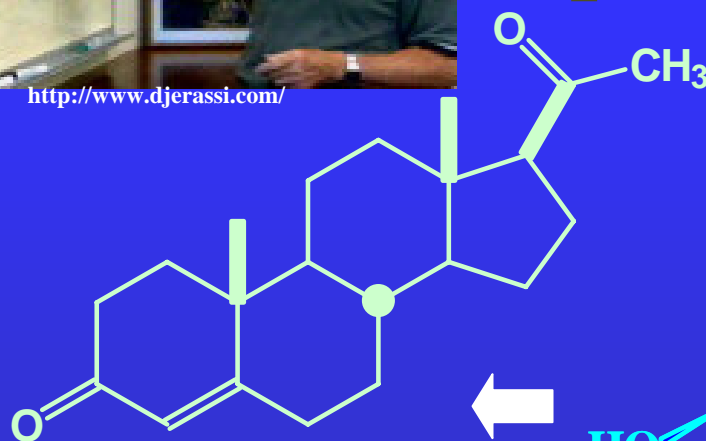
Em 1937 no “Pond Laboratory” da Universidade da Pensilvânia, EUA, Marker concluiu a primeira síntese da progesterona a partir da diosgenina

## A Pílula Contraceptiva

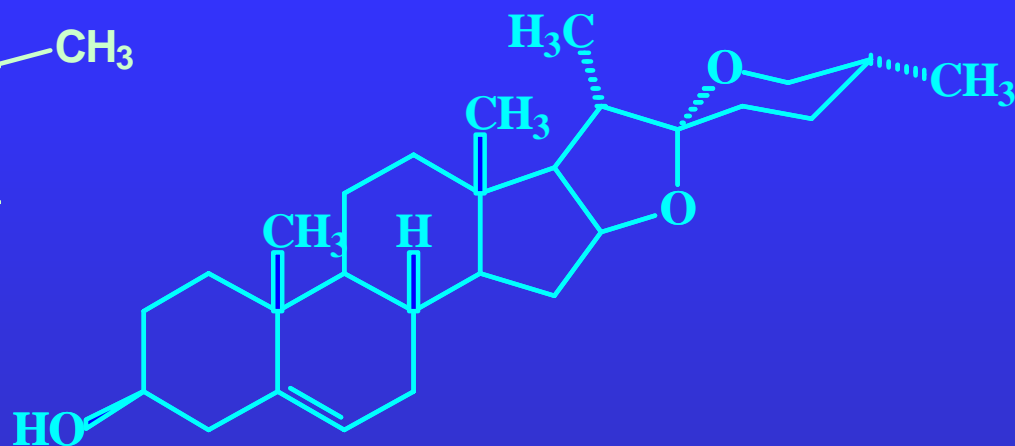


Carl Djerassi

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



progesterona

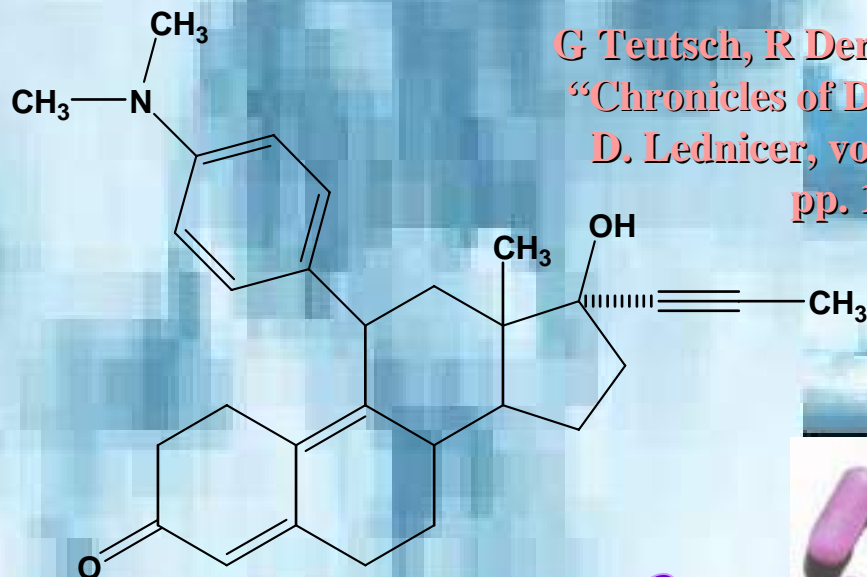


diosgenina

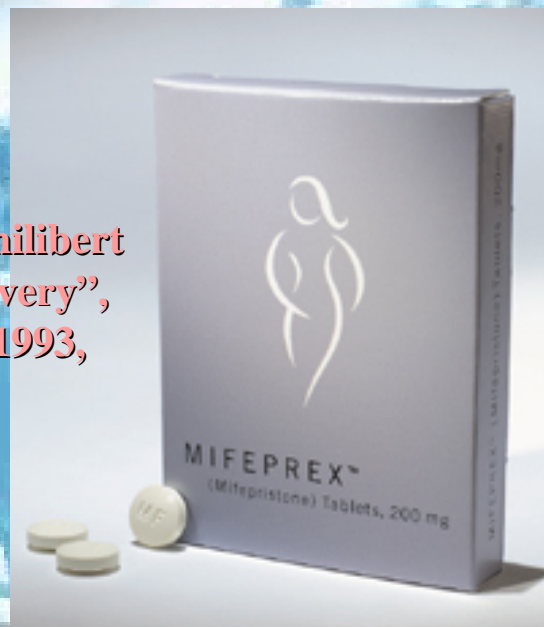




# Mifepristona



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



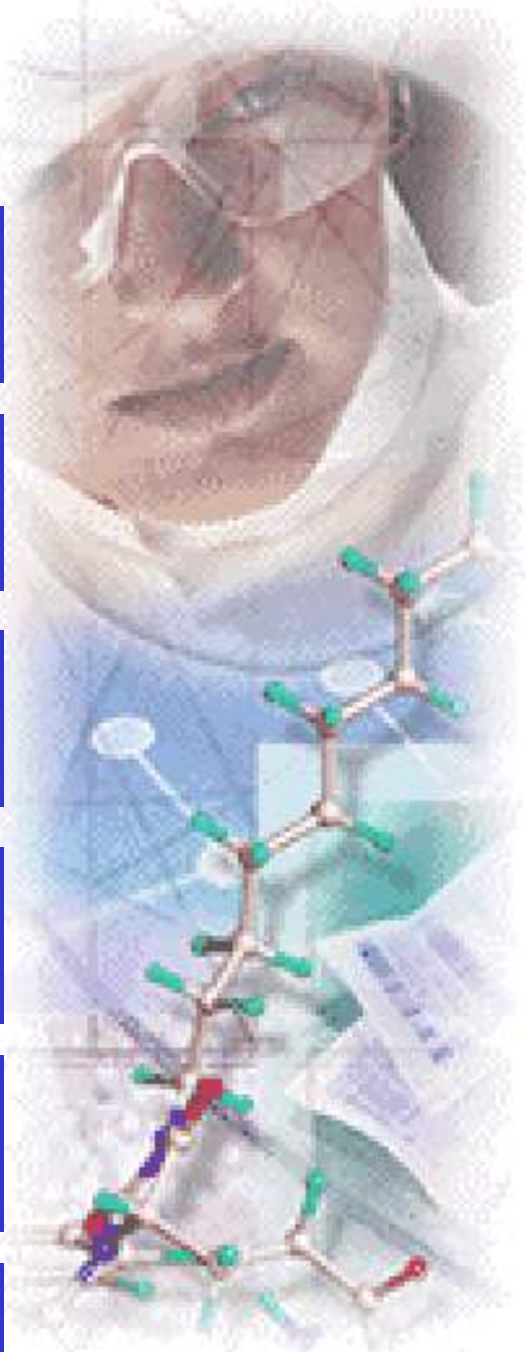
RU 486



<http://pubs.acs.org/cen/coverstory/83/8325/8325RU-486.html>

*mifepristona*





*O acaso ...*



# Antibioticoterapia

## Moléculas Salva-vidas...

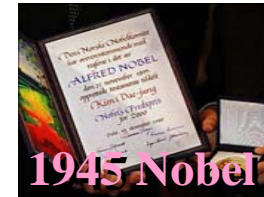
### Antibióticos $\beta$ -lactâmicos

# penicilinas

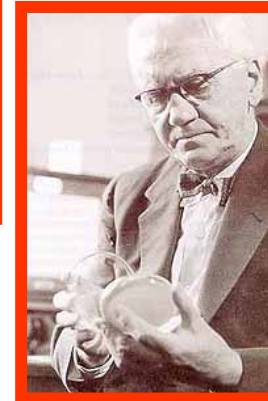
# cefalosporinas



E. B. Chain  
1906-1979



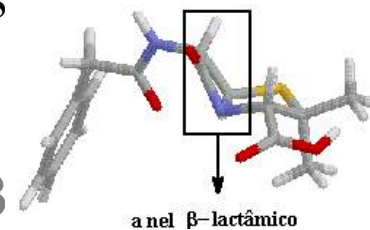
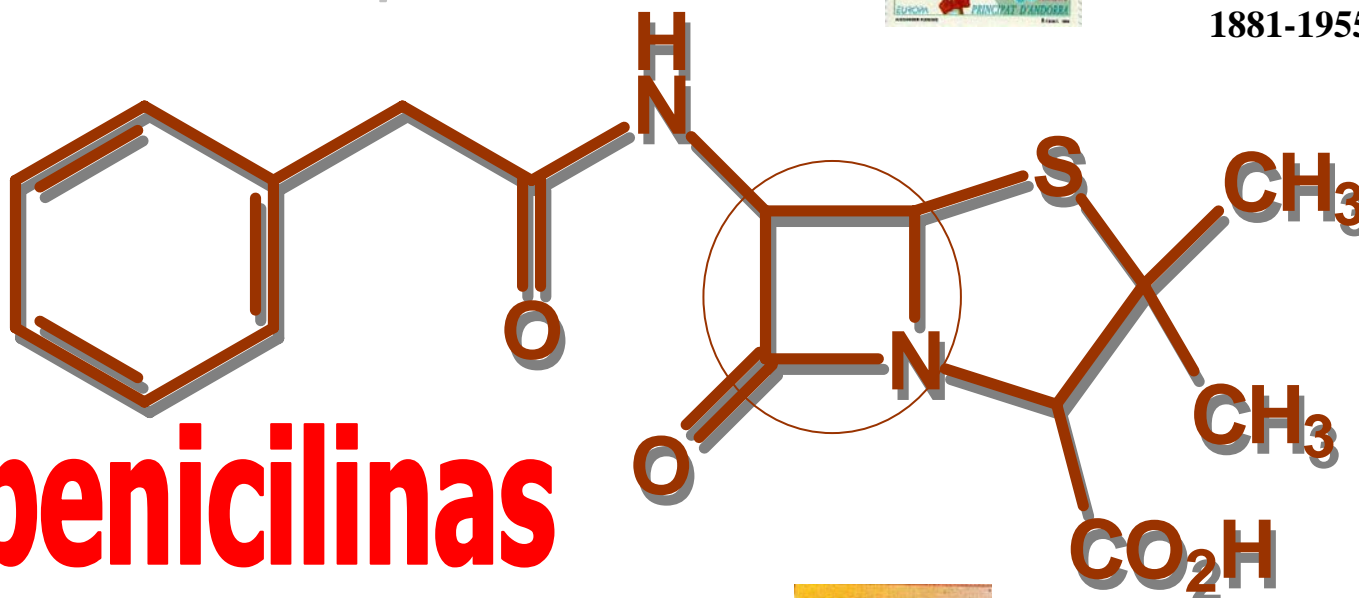
1945 Nobel



Sir H. W. Florey  
1898-1968



Sir A. Fleming  
1881-1955



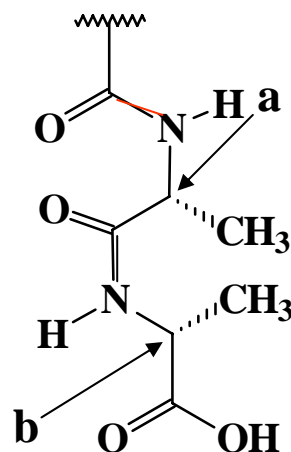




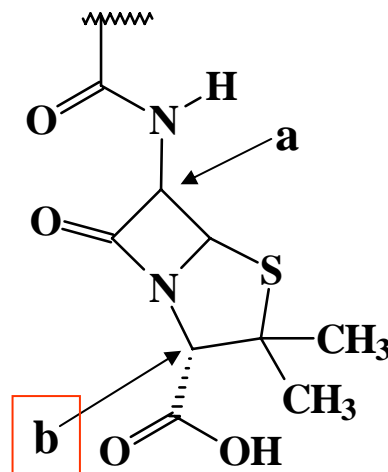
# Mecanismo Molecular de Ação dos Antibióticos beta-lactâmicos

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*

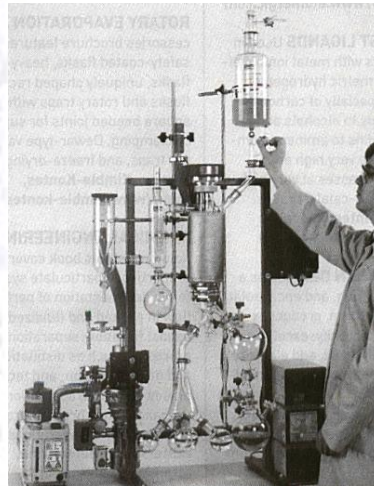
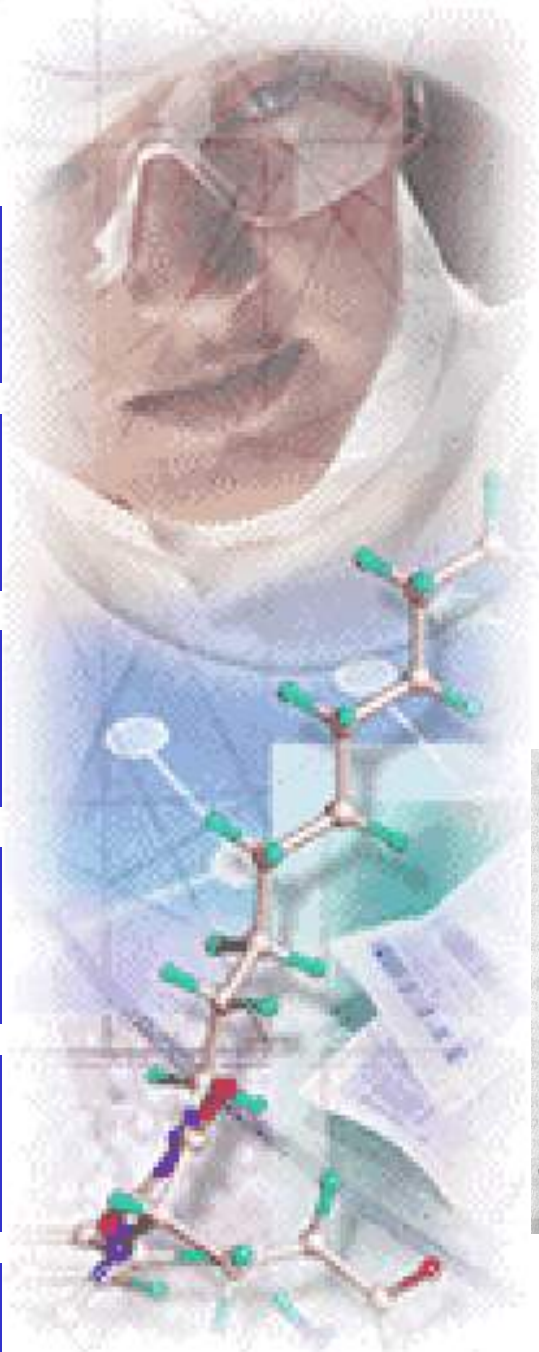


*Penicilina G*

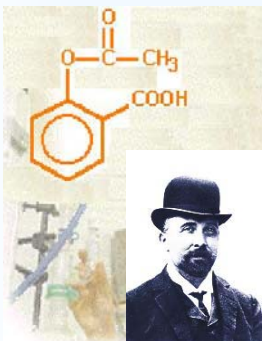


Inibição da *D*-alaninacarboxipeptidase do microorganismo, prevenindo a inserção da unidade dipeptídica acil-*D*-alanil-*D*-alanina, etapa final da construção da membrana celular externa.

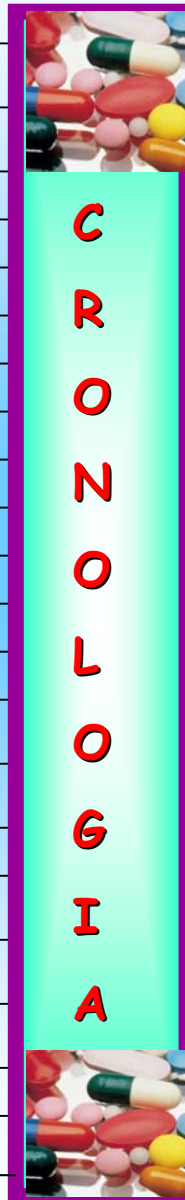
# *Os fármacos: sintéticos ...*



# Cronologia da Descoberta de Fármacos



AAS *	1889
barbitúricos	1923
cloroquina	1934
sulfonamidas	1935
penicilina	1942
nitrofurano	1952
progesterona	1953
talidomida	1954
haloperidol	1958
verapamil	1962
indometacina	1963
propranolol	1964
salbutamol	1968
prostaglandinas	1970
oxamniquina	1970
nifedipina	1975
cimetidina	1976
atenolol	1976
captopril	1977
oxicams	1980
praziquantel	1980
aciclovir	1981



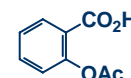
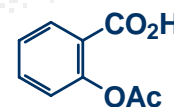
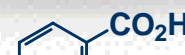
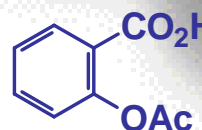
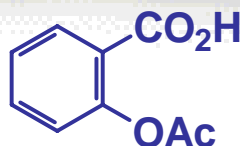
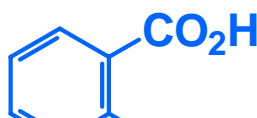
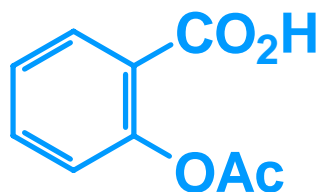
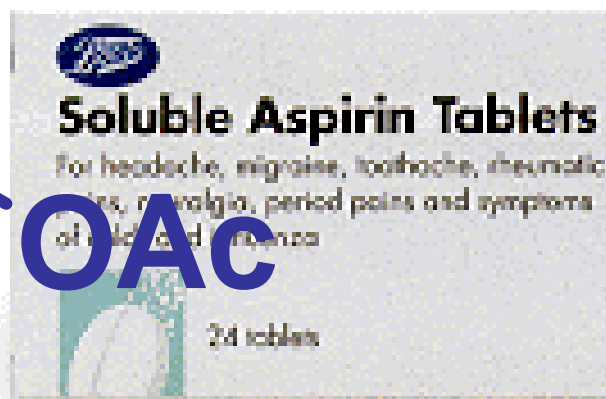
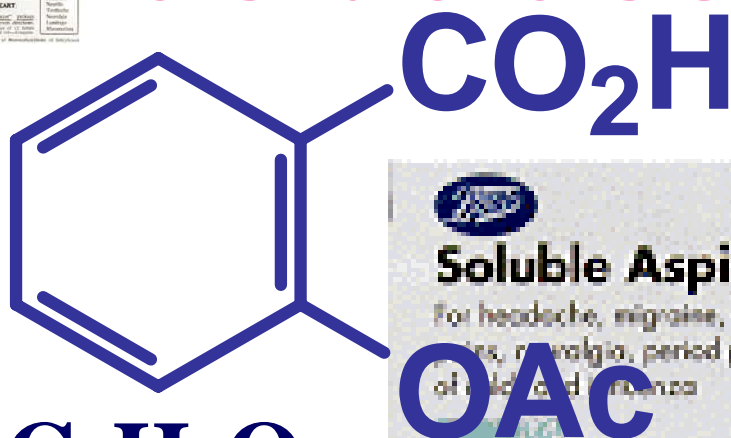
1981	ranitidina
1985	misoprostol
1985	mefloquina
1987	azidovudina
1987	lovastatina
1989	ozagrel
1989	mifepristona
1989	fluoxetina
1990	salmeterol, amlodipina
1993	tacrina, fanciclovir
1995	indinavir, saquinavir
1996	docetaxel, atorvastatina
1996	zileuton, efavirenz, olanzapina
1997	zafirlukast, montelukast
1998	infliximab
1999	celecoxib orlistat sildenafil
2000	galantamina rofecoxib
2001	imatinib
2002	apomorfina, etoricoxib
2003	varденаfil, gefitinibid, aripiprazola
2004	rosuvastatina, rofecoxib, zileuton
2005	pregabalin, Caduet <sup>R</sup>







# ácido acetil salicílico



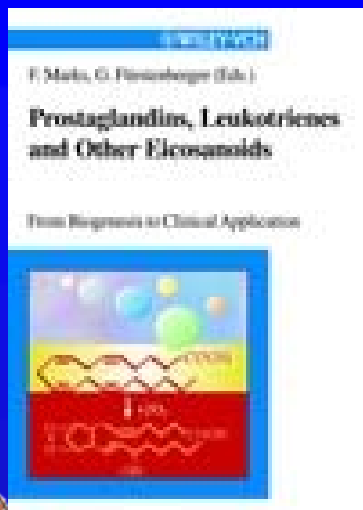
85% dos fármacos modernos

são sintéticos

medicamentos



# Teoria das Assinaturas



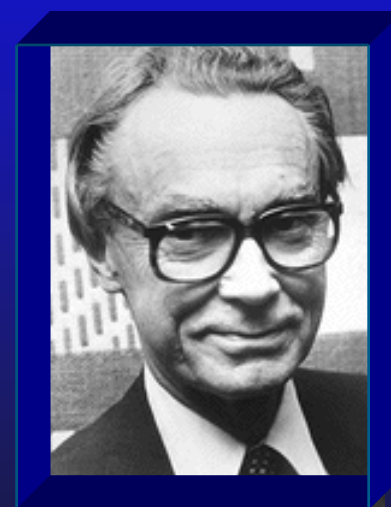
ML Tainter, AJ Ferris  
**ASPIRIN in the  
Modern Therapy  
A Review**  
Bayer Corp, NY,  
1969



**Bengt I. Samuelsson**  
1934-



**Sir John Robert Vane**  
1927-2004



**Sune Karl Bergström**  
1916-2004



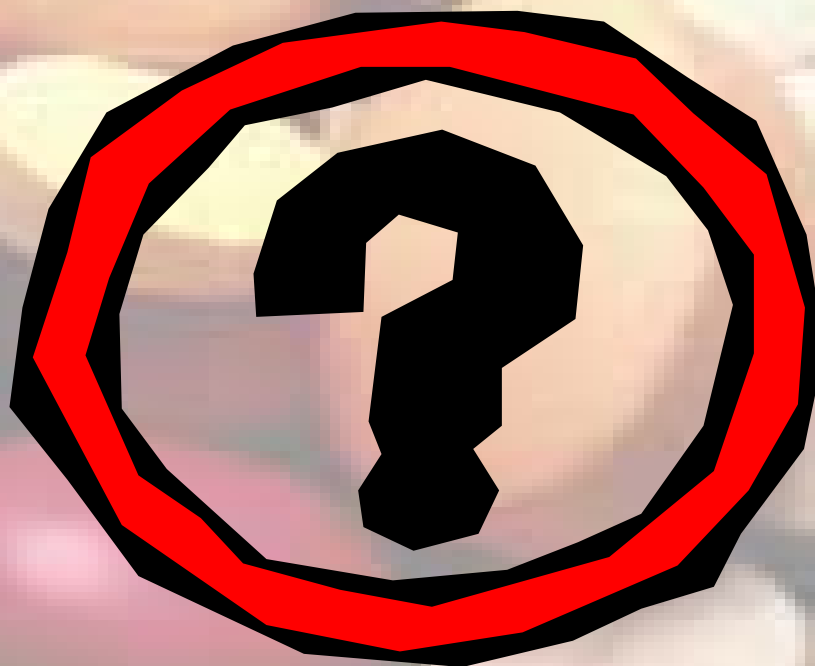
1982



## Molécula Centenária



# Perguntas

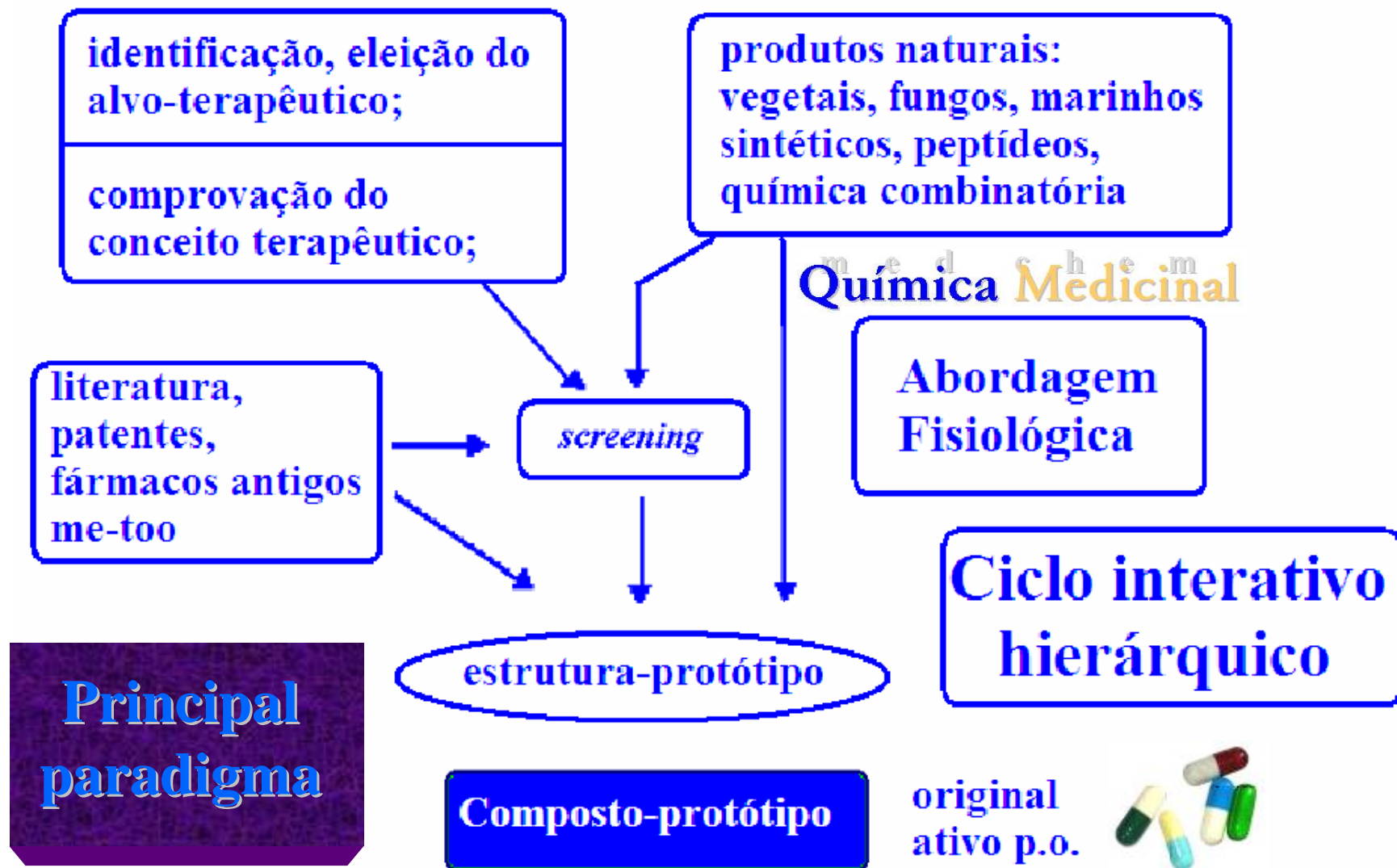


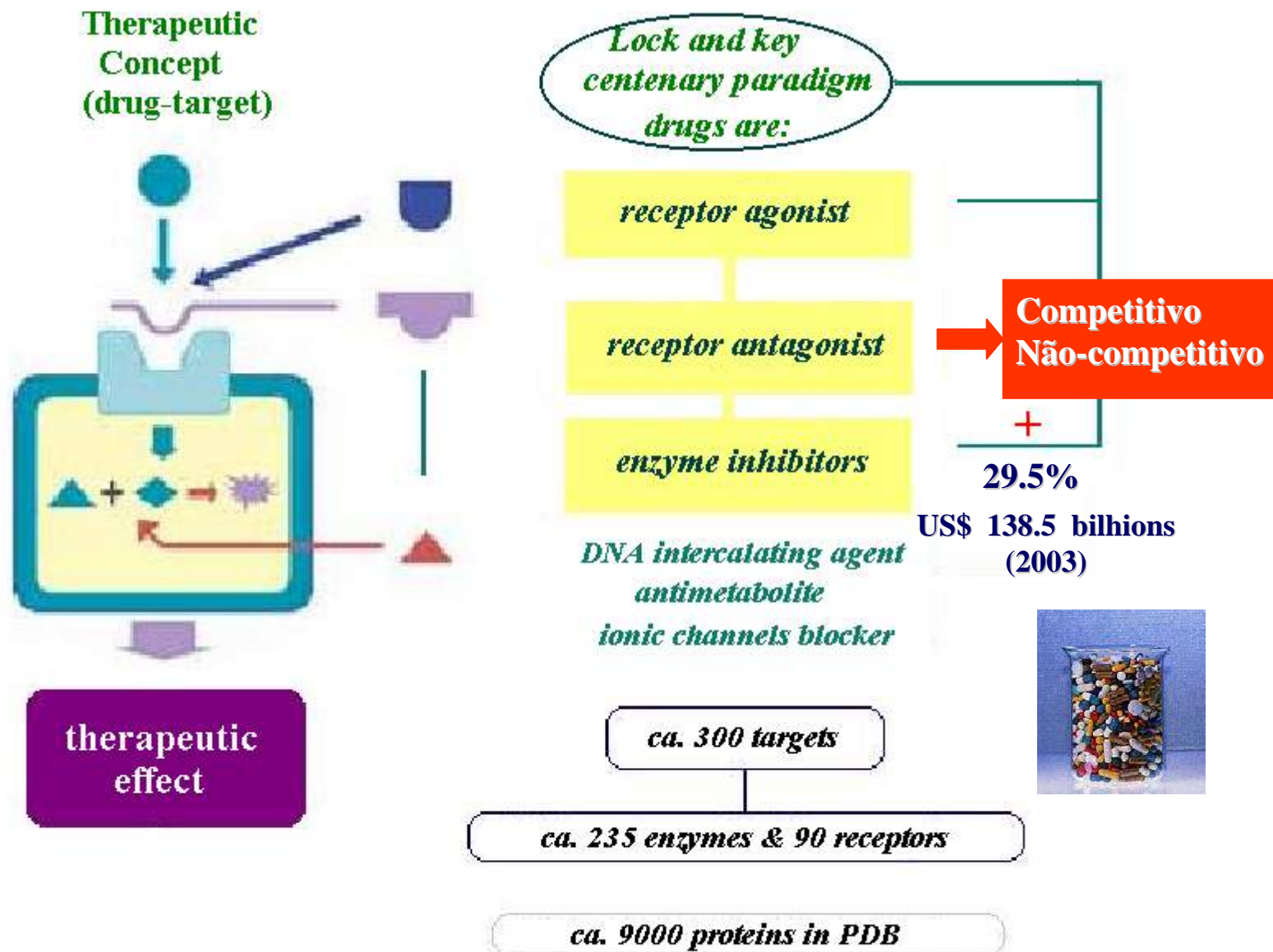


# *O processo de descoberta...*



# A Estratégia da Abordagem Fisiológica





**C**

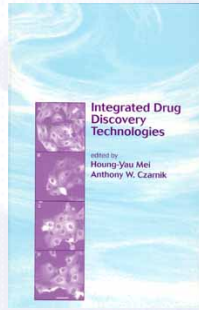
**H**

**O**

**N**

**S**

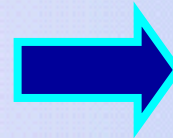
**Padrão molecular  
original**



**Anthony W. Czarnik  
1995**

# *A Diversidade Molecular*

**10<sup>180</sup>**  
**COMPOSTOS**



*Candidato  
a  
Fármaco*

**Processá-los**



**1 composto/segundo**

**estável em água  
sem ligação tripla**

**CLogP ~3-5**

**10<sup>172</sup>  
anos**

**100-300.000  
compostos/semana  
podem ser bioensaiados**

*in vitro*



lead compound

# Química Medicinal

## Composto-Protótipo

Um composto que exibe propriedades farmacológicas que comprovam seu valor como ponto de partida para desenvolvimento de um fármaco.



*in vivo*

*Lead Optimization*



## Otimização

Processo de modificação molecular planejada do composto-protótipo, visando maximizar suas propriedades farmacológicas.

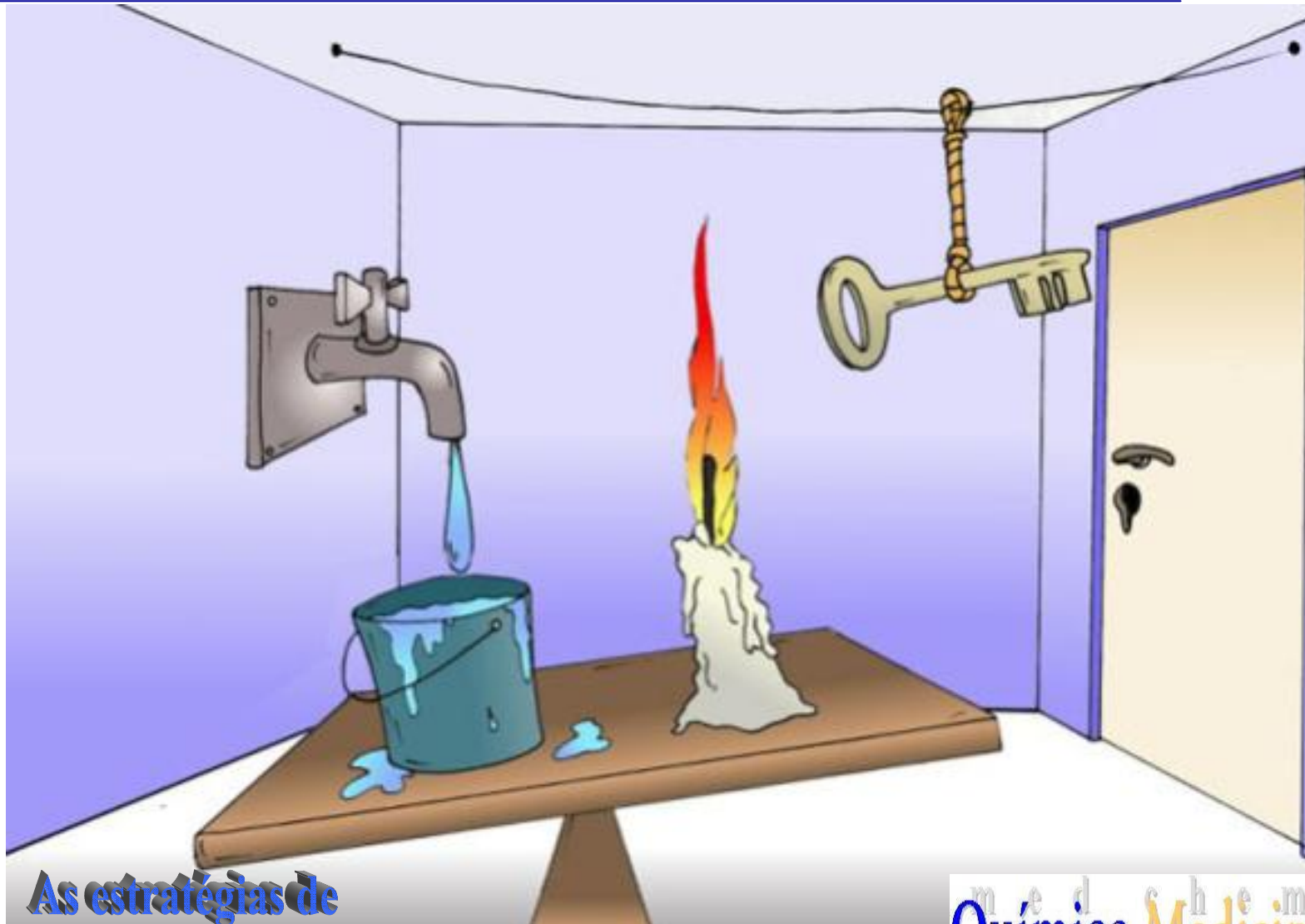
# Composto-protótipo

*“ O composto-protótipo é o primeiro derivado puro, identificado em uma série congênere de novas substâncias, bioensaiadas em modelos animais padronizados relacionados à patologia a ser tratada”*



## *Otimização do Composto-protótipo*





As estratégias de  
desenho estrutural...



Fármaco

medicamento  
Química Medicinal



# A importância dos fatores estruturais

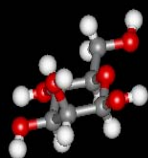
## LOCK & KEY CONCEPT



1902



Hermann Emil Fischer  
1852-1919



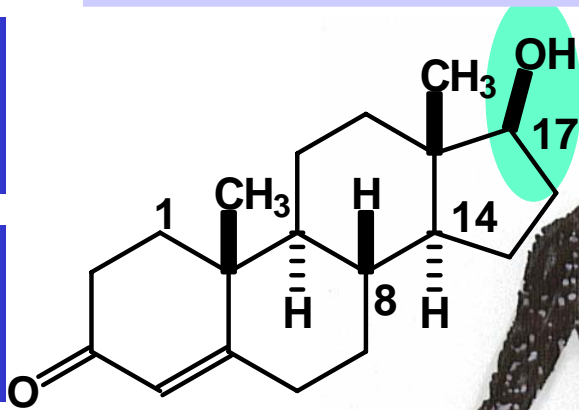
glicose



Química Medicinal



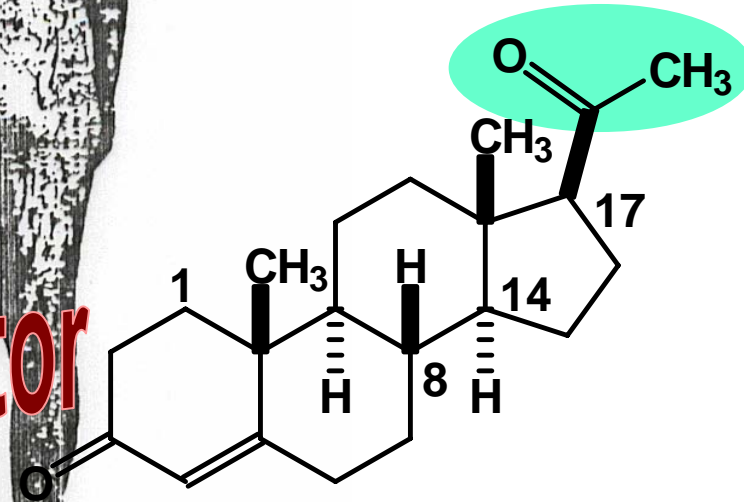
# Similaridade & Dissimilaridade Molecular



testosterona



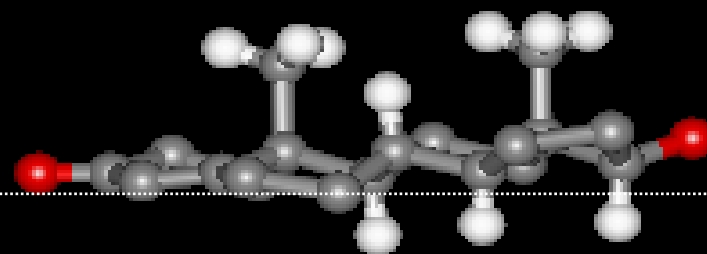
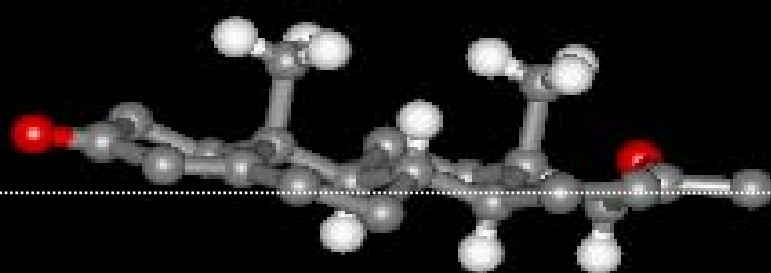
Seletividade do Biorreceptor



progesterona

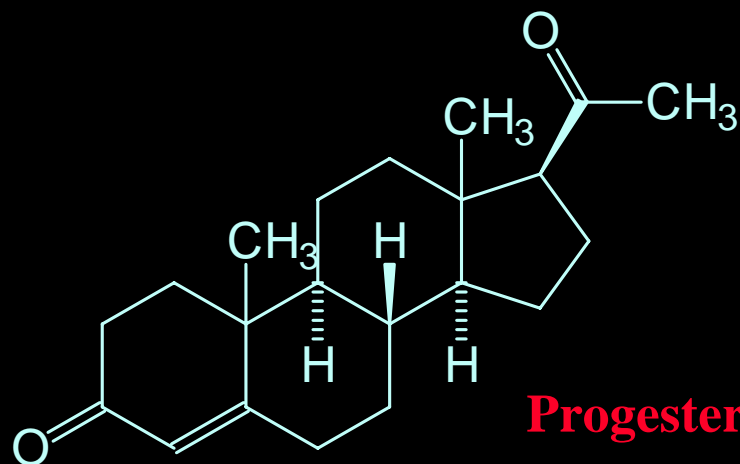


# Similaridade & Dissimilaridade Molecular



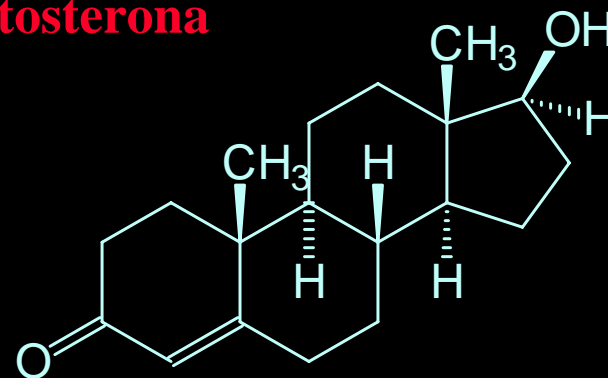
C-17

C-17

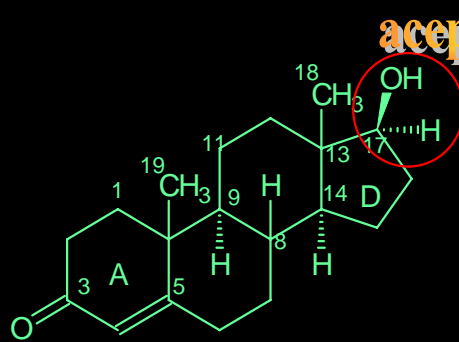


**Progesterona**

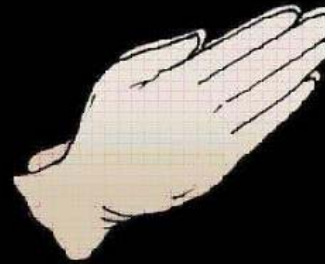
**Testosterona**



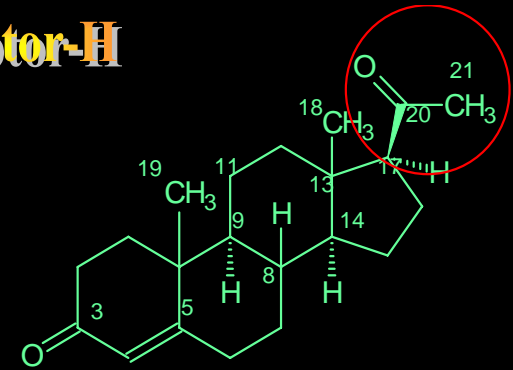
# Similaridade & Dissimilaridade Molecular



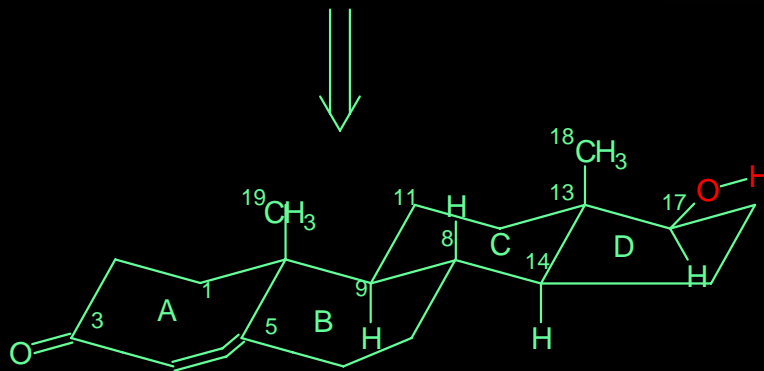
Testosterona



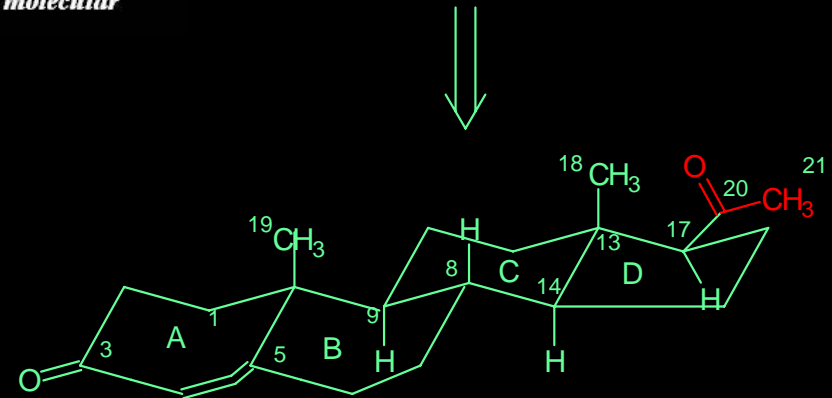
*similaridade molecular*



Progesterona

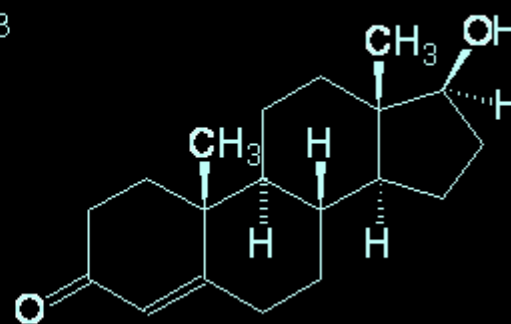
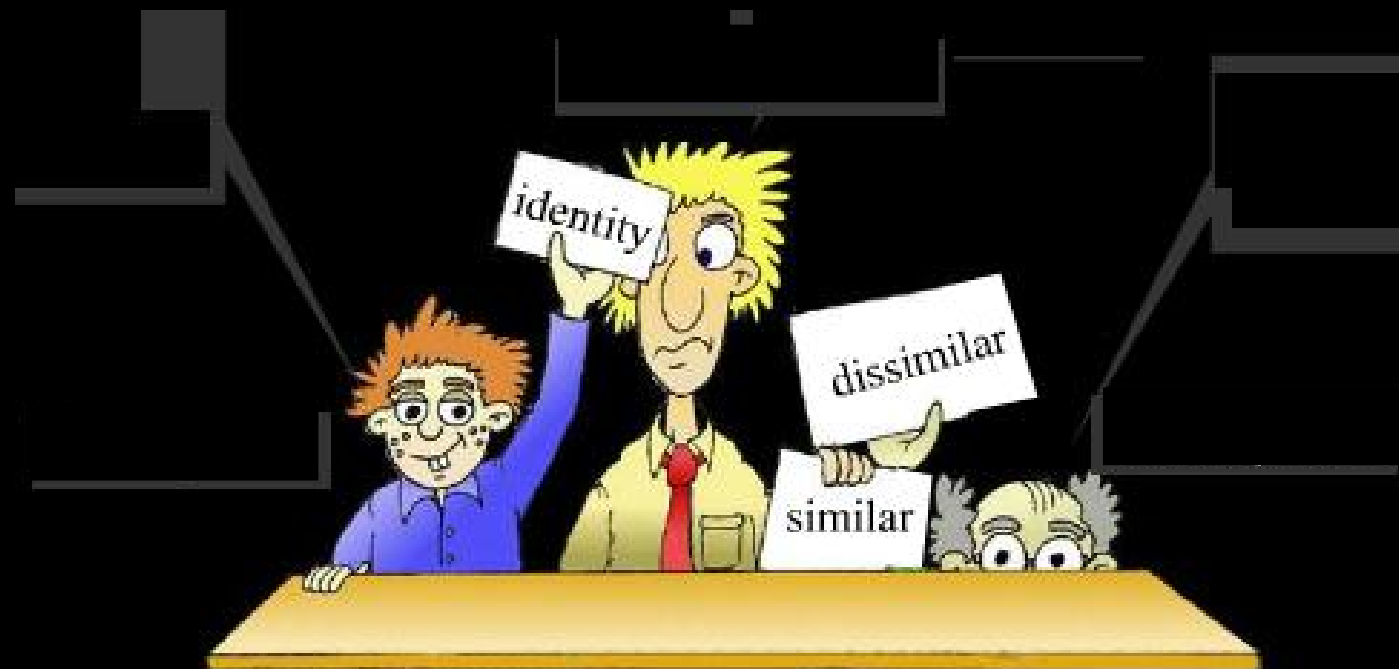


B/C C/D trans

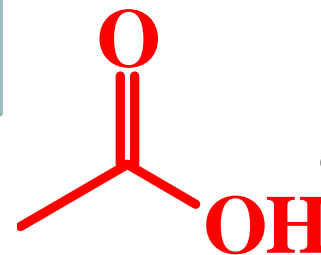


B/C C/D trans

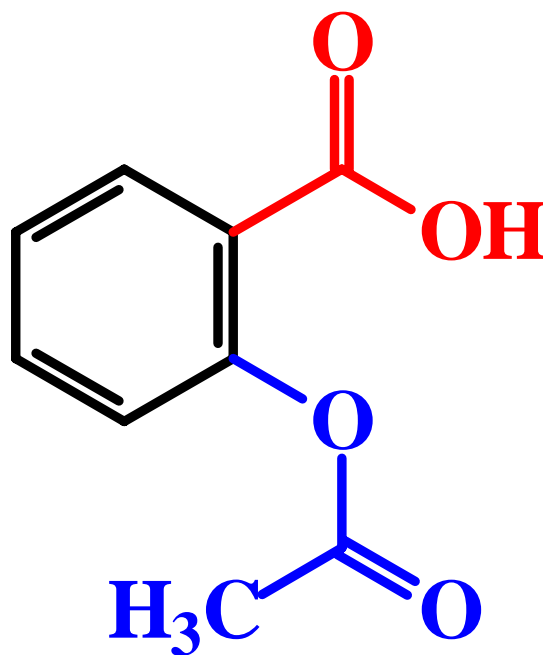




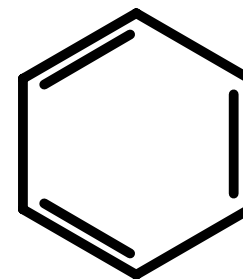
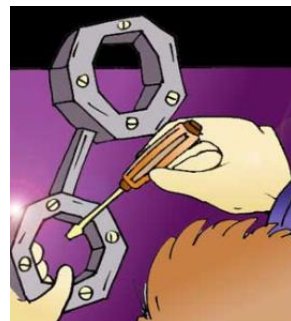
# Dissecação Molecular



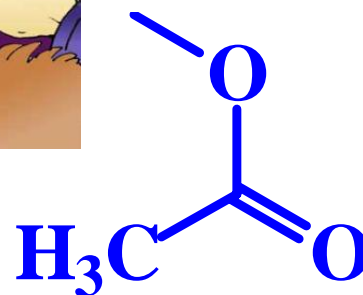
ácido carboxílico



Ácido acetilsalicílico



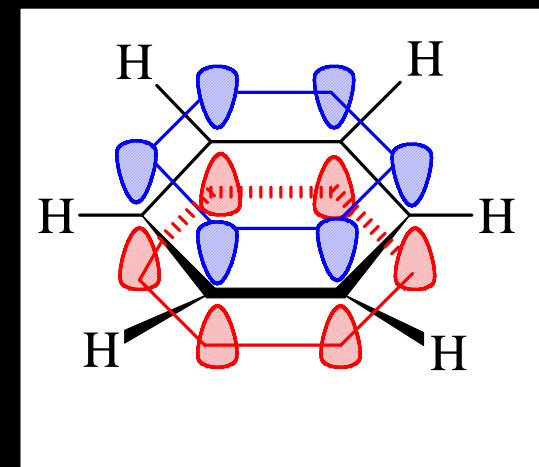
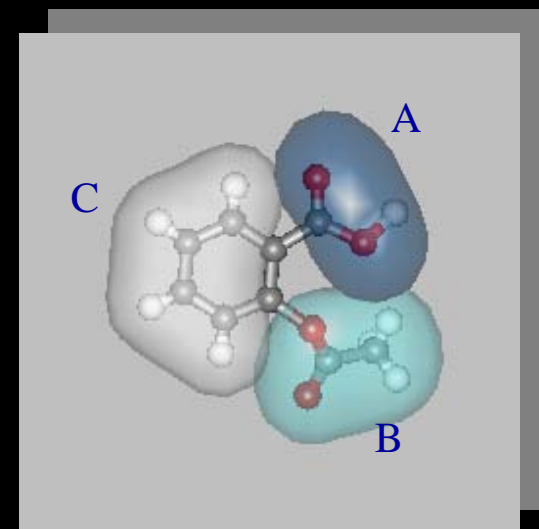
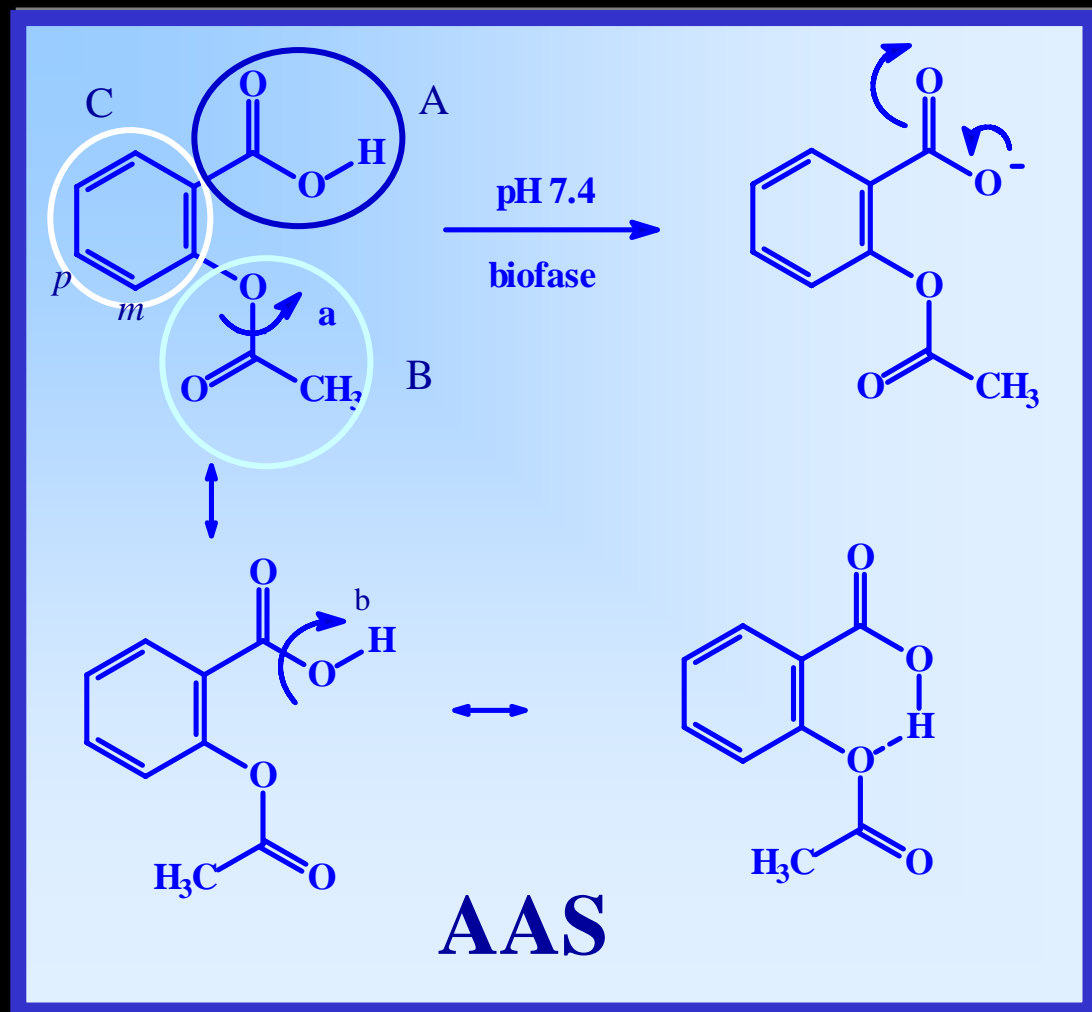
fenila



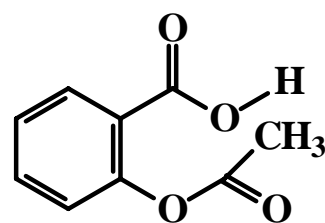
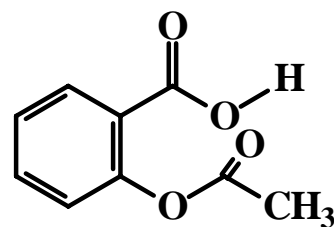
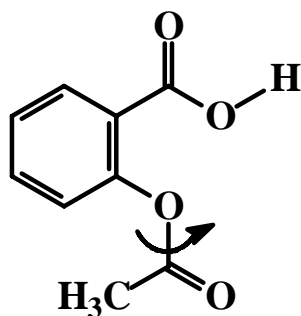
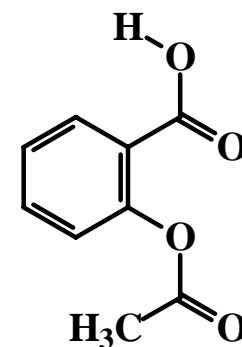
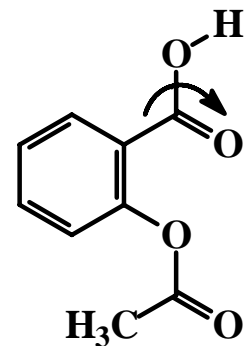
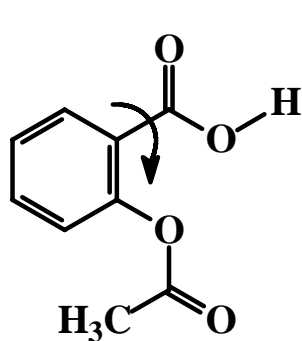
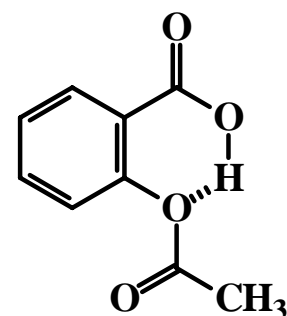
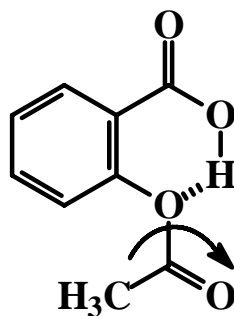
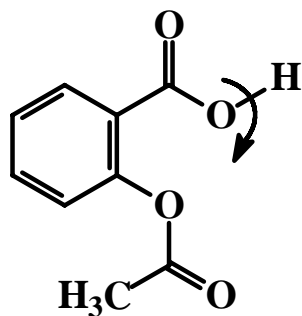
éster

Pontos farmacofóricos  
Grupos farmacofóricos

# A hierarquia dos grupos funcionais

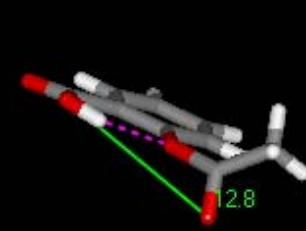
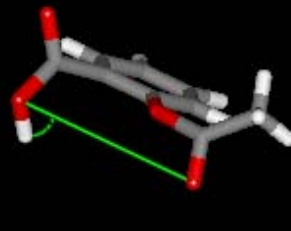
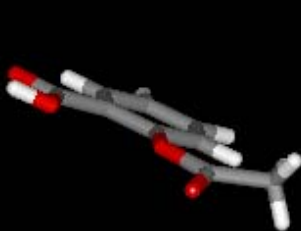
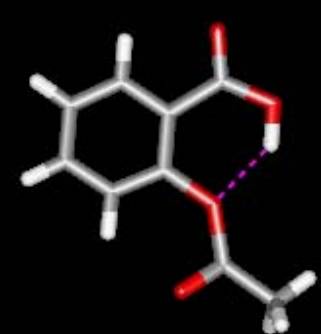
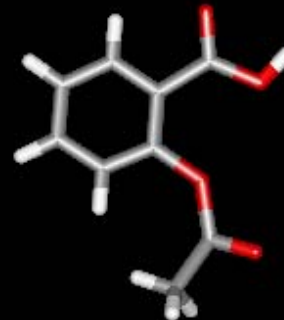
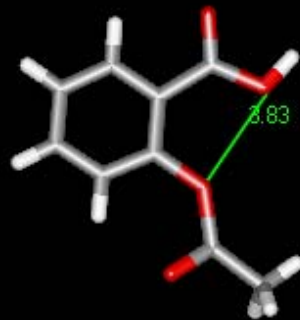
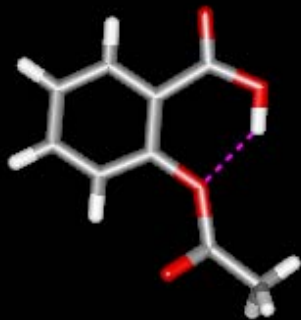
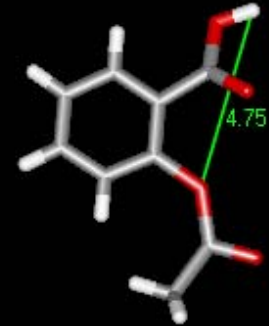
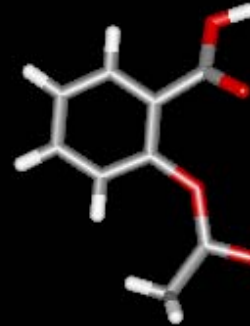
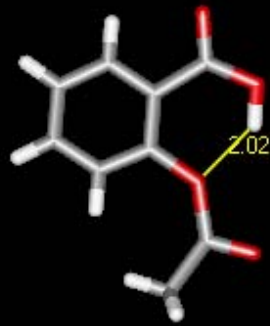
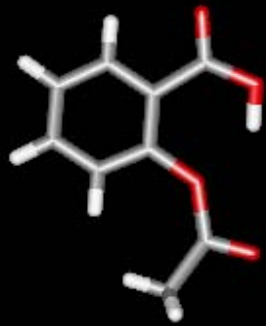


# Rotâmeros do ácido acetilsalicílico





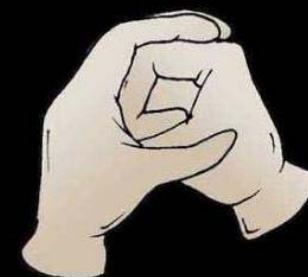
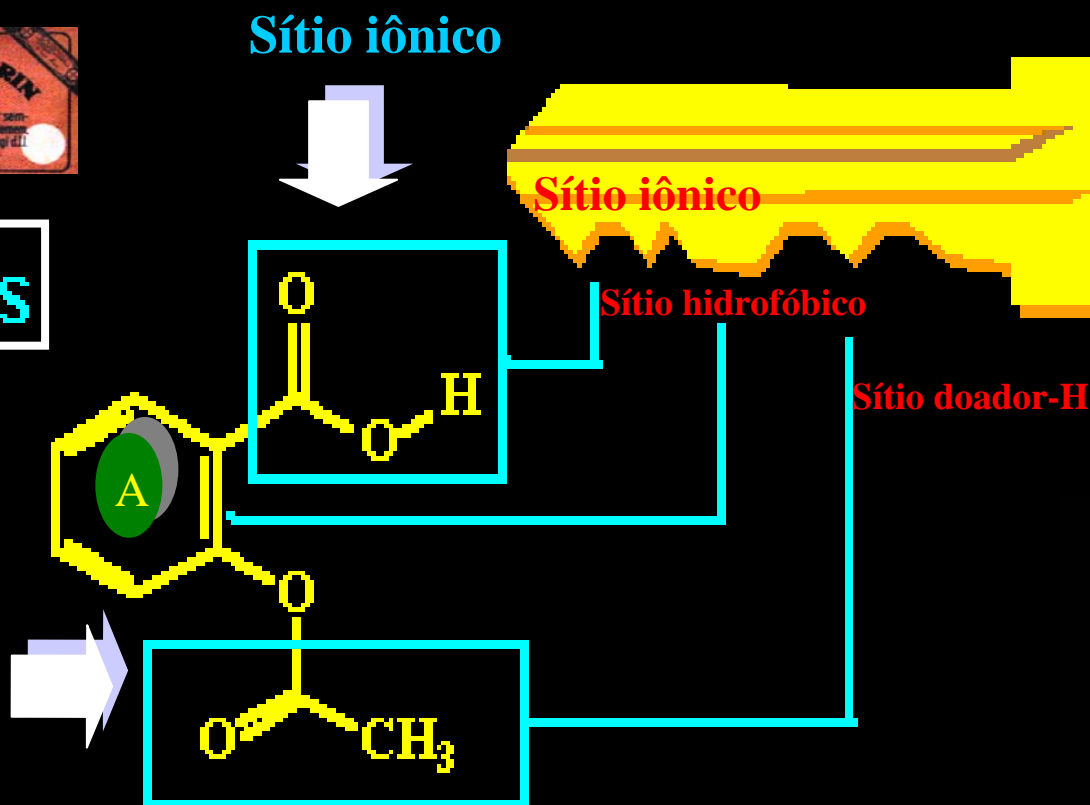
# Confôrmers do ácido acetilsalicílico



# Complementaridade do modelo Chave-fechadura

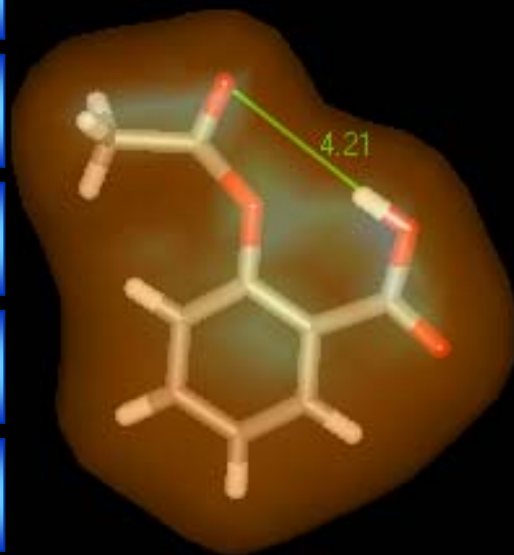


AAS

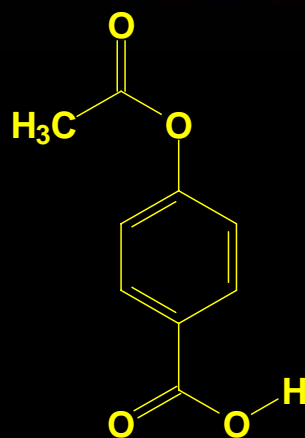
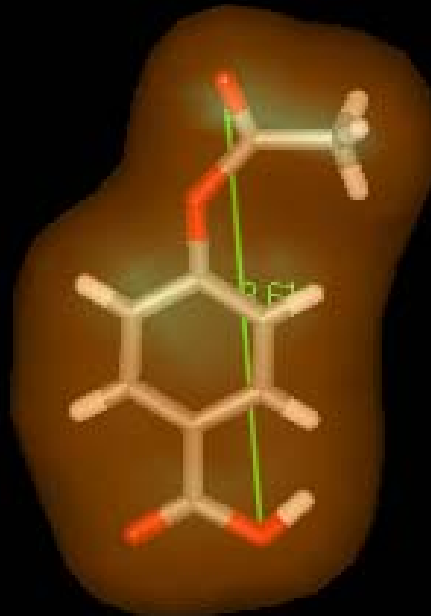


complementaridade molecular

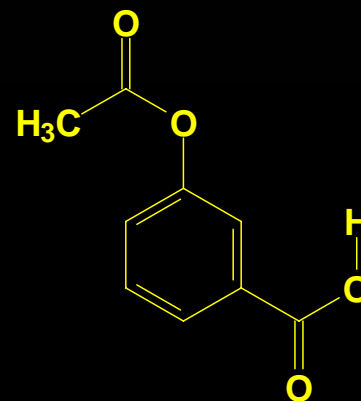
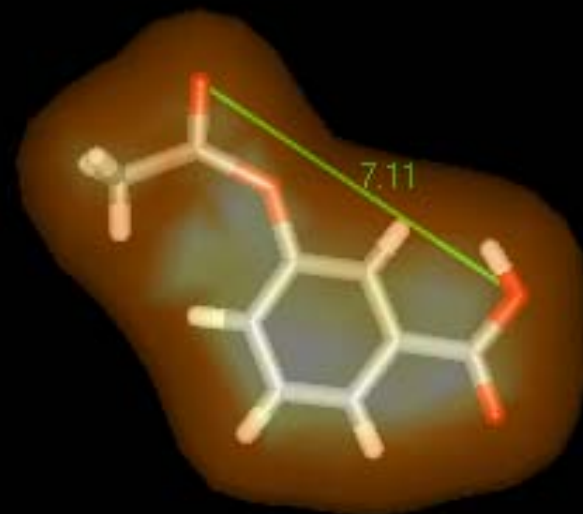
# Isomêros do Ácido Acetil Salicílico (AAS)



*orto*

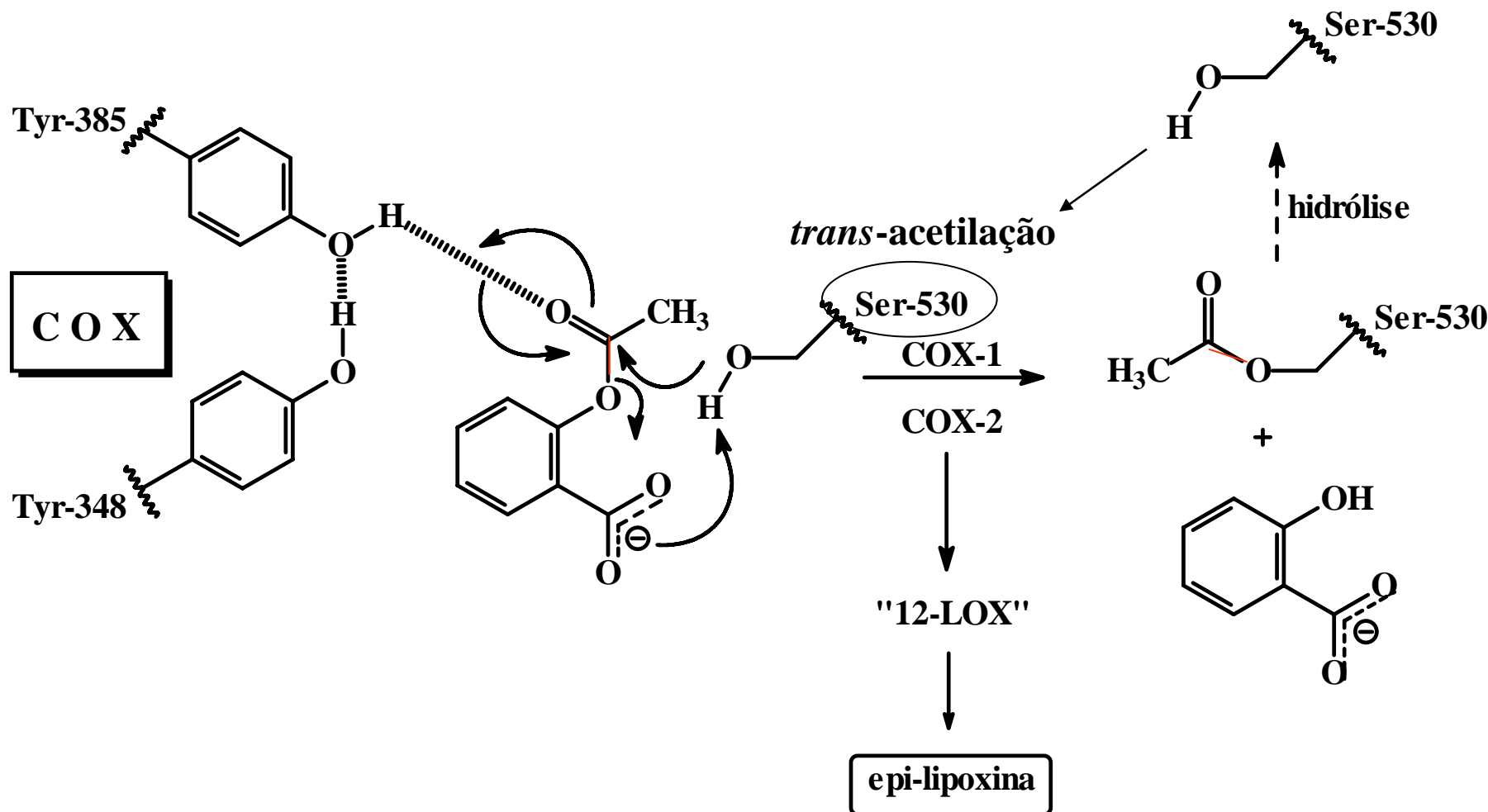


*para*

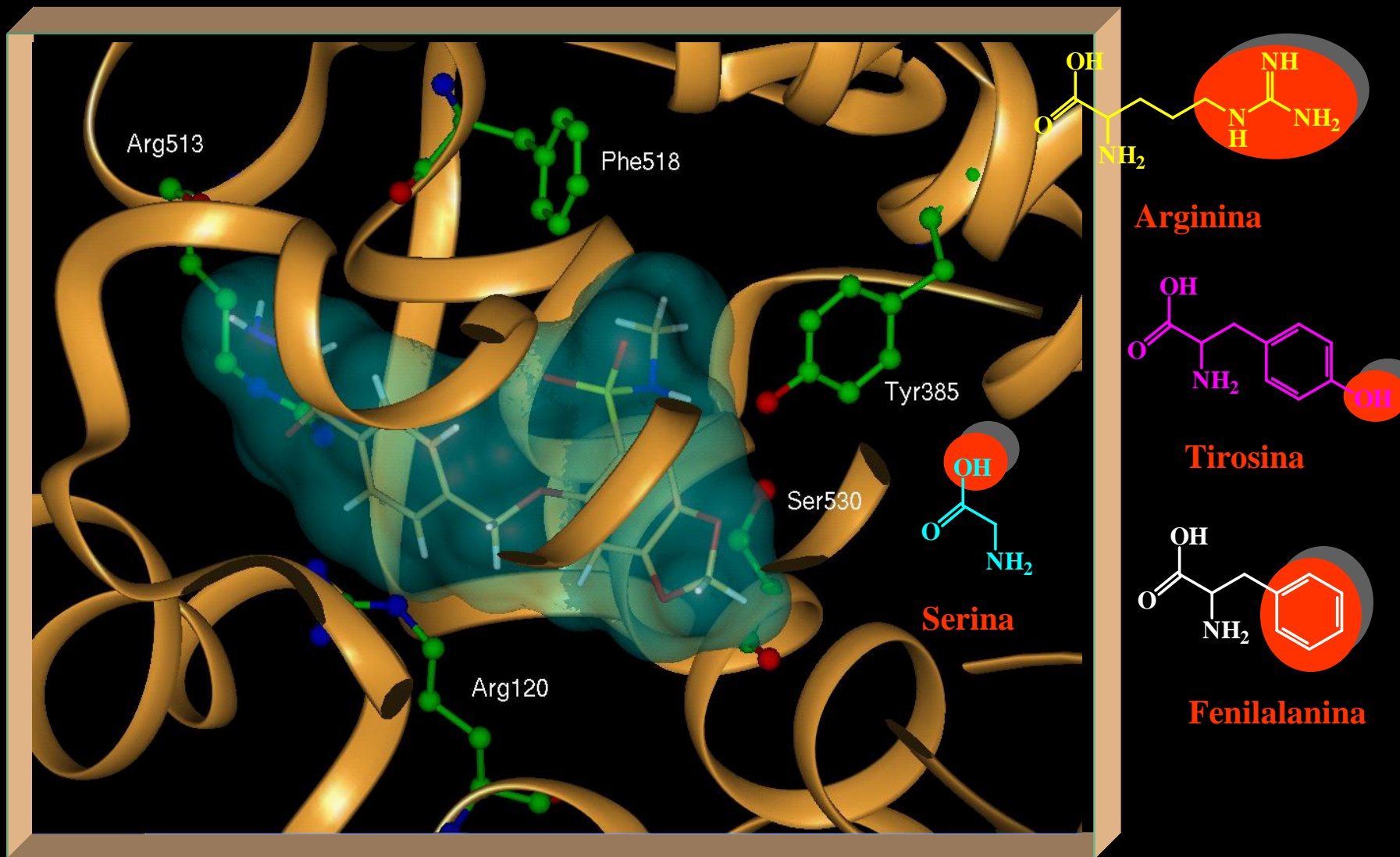


*meta*

# 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).**