Universidade Federal do Rio de Janeiro

O processo de planejamento racional de novos fármacos

MC Noturno

Parte 2

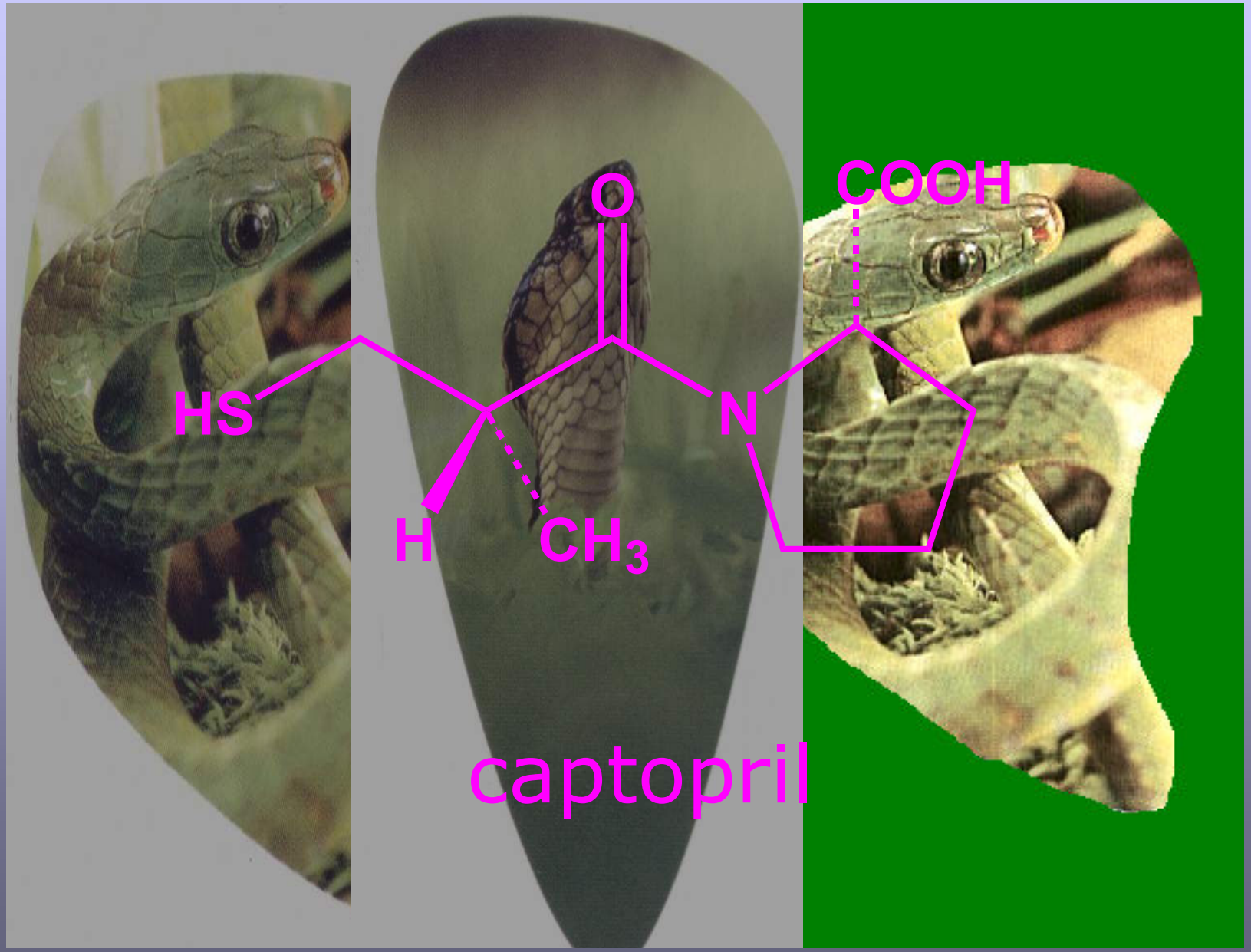
Reunião Regional da SBPC em Boa Vista, RR
19 - 22 de outubro de 2010

Eliezer J. Barreiro

Professor Titular

UFRJ

Produtos naturais não-vegetais

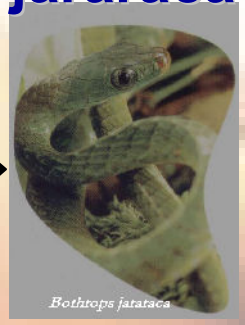


Da serpente à inovação terapêutica...

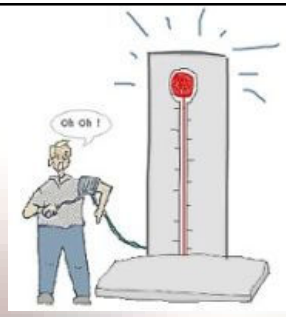
Inovação terapêutica

M. O. Rocha e Silva
1910-1983

jararacá

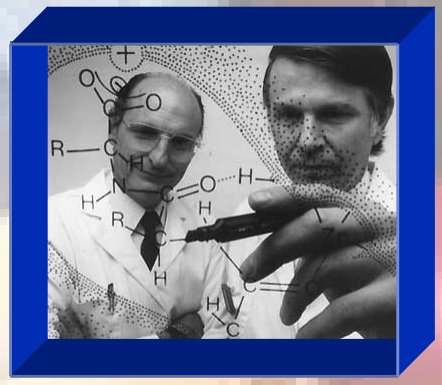


S. H. Ferreira
1934-

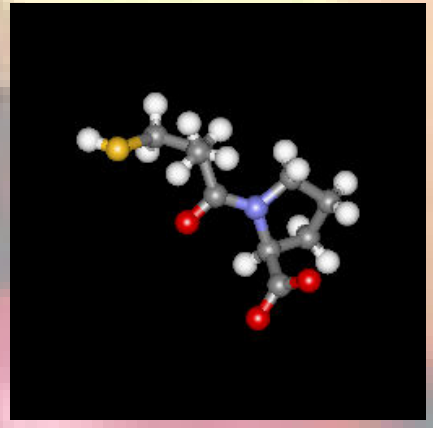


Bradicinina

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



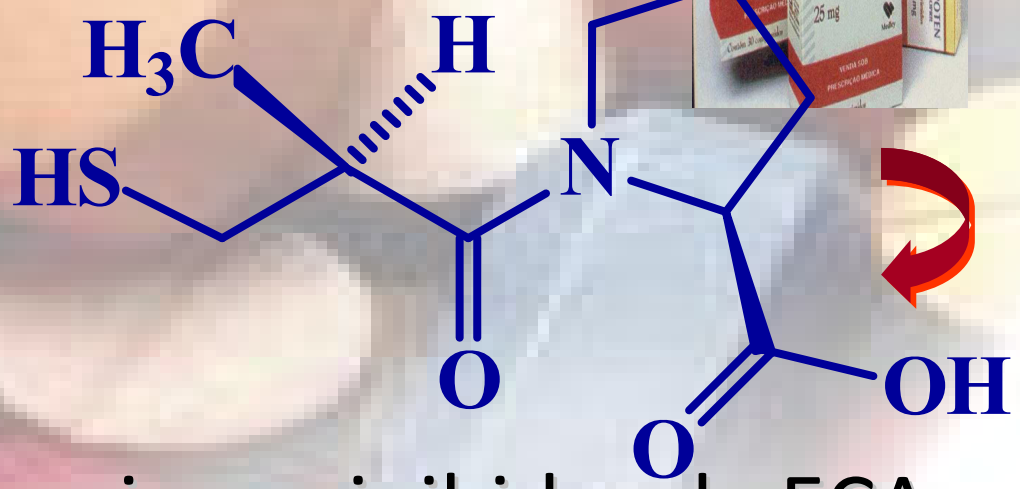
D. W. Cushman & M. A. Ondetti



SQUIBB

Bristol-Myers Squibb

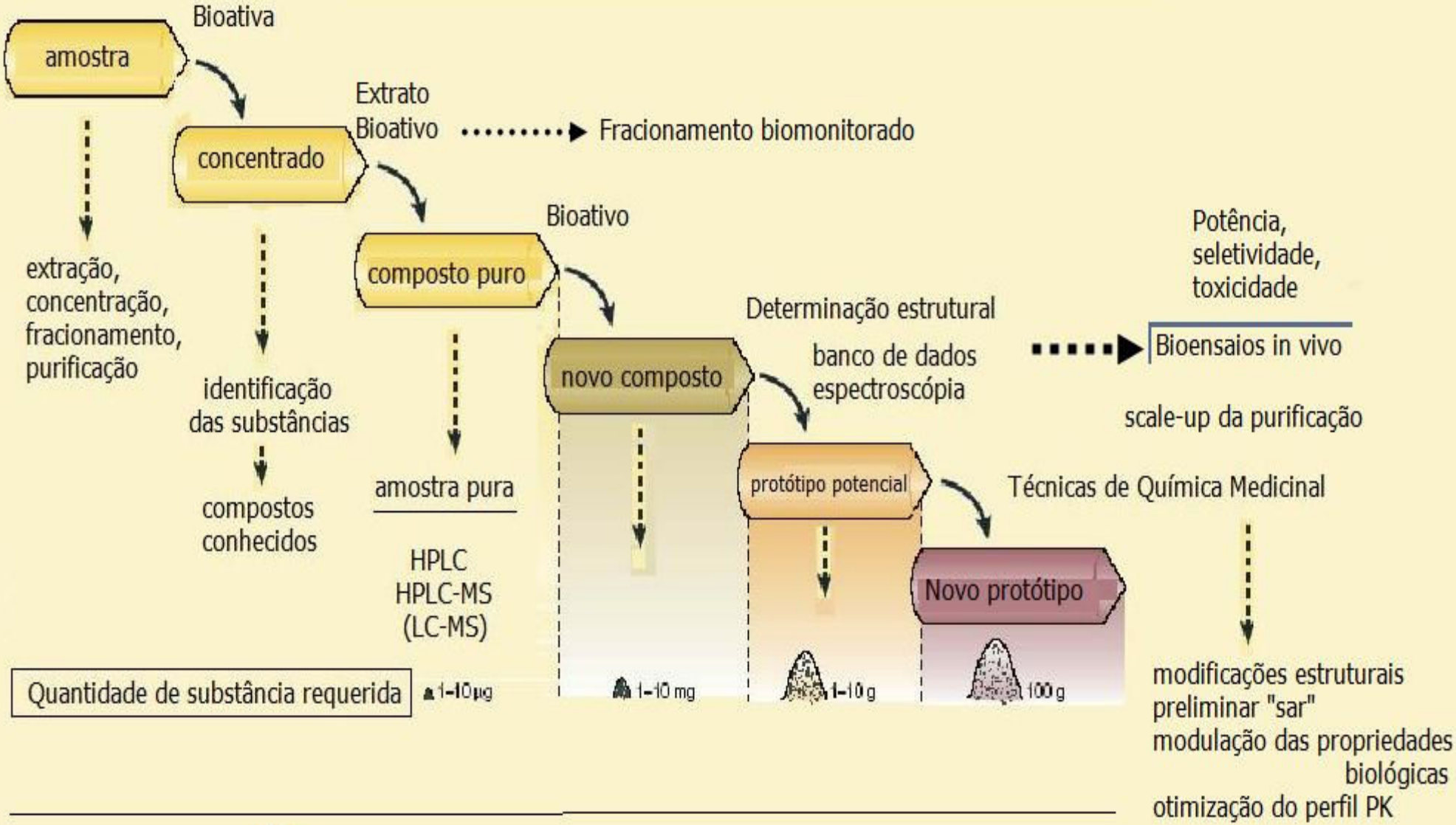
Captopril



Novo mecanismo: inibidor da ECA

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

Processo de descoberta de novos hits-naturais



Adaptado de

F. E. Koehn & G. T. Carter, The evolving role of natural products in drug discovery, Nature Review Drug Discovery, 2005, 4, 206-220

química nova

www.scielo.br

Quim. Nova, Vol. 32, No. 3, 679-688, 2009

BIODIVERSIDADE: FONTE POTENCIAL PARA A DESCOBERTA DE FÁRMACOS

Eliezer J. Barreiro*

Departamento de Fármacos, Faculdade de Farmácia, Centro de Ciências da Saúde, Universidade Federal do Rio de Janeiro, CP 68006, 21944-910 Rio de Janeiro - RJ, Brasil

Vanderlan da Silva Bolzani***

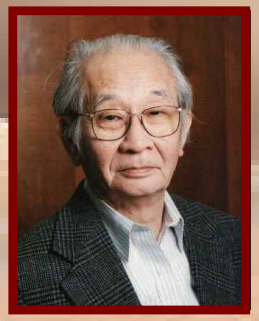
Instituto de Química, Universidade Estadual Paulista, Rua Francisco Degni, s/n, 14800-900, Araraquara - SP, Brasil

Recebido em 16/1/09; aceito em 6/4/09; publicado na web em 9/4/09

BIODIVERSITY: POTENTIAL SOURCE FOR DRUG DISCOVERY. In economic terms, biodiversity transcends the boundaries usually given to conventional industries because it is a valuable source of biological and chemical data of great use to drug discovery. Certainly, the use of natural products has been the single most successful strategy in the discovery of novel medicines, and most of the medical breakthroughs are based on natural products. Half of the top 20 best-selling drugs are natural products, and their total sales amounted to US$ 16 billions shows the importance of natural products, which is evidenced by the new chemical entities (NCE) approved by regulatory authorities around the world in the past decade. Recently, the approval of the alkaloid galanthamine as a medicine to treat Alzheimer's disease shows that natural compounds from plants will continue to reach the market. The huge biological diversity of the Brazilian biomes, by its ability to generate new knowledge and technological innovation can be a fantastic alternative as raw material for drug discovery.

"*Específico Pessoa*", criado pelo farmacêutico José Torquato Pessoa, de Camocim, Ceará, como preparado antiofídico.

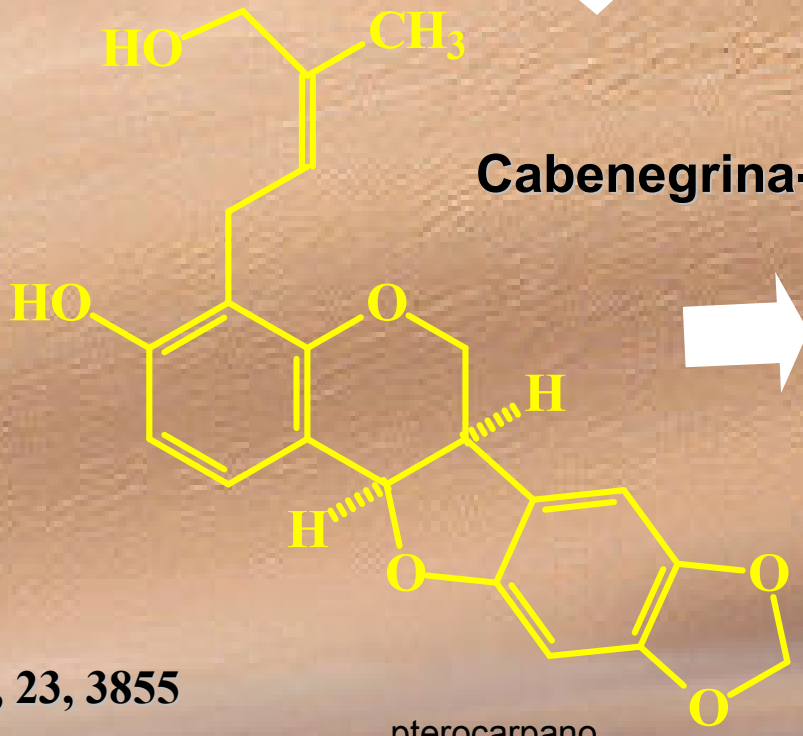
(Francisco José de Abreu Matos)



Koji Nakanishi

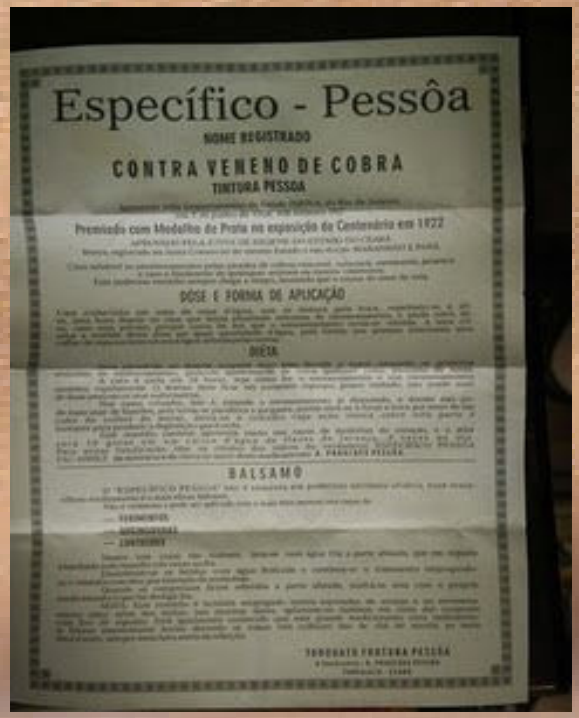
ACS, 1991
University of Columbia, EUA
"A Wandering Natural Products Scientist "

Tetrahedron Lett. 1982, 23, 3855



Cabenegrina-A

pterocarpano



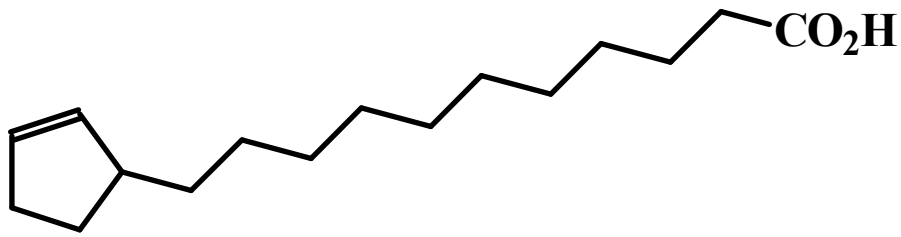
www.farmacia.ufrj.br/lassbio

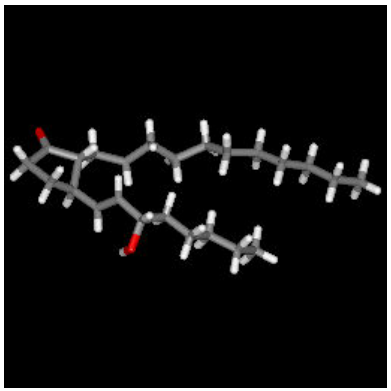
O uso de produtos naturais abundantes

LASSBio

Laboratório de Avaliação e Síntese de Substâncias Bioativas

Produtos naturais como blocos moleculares



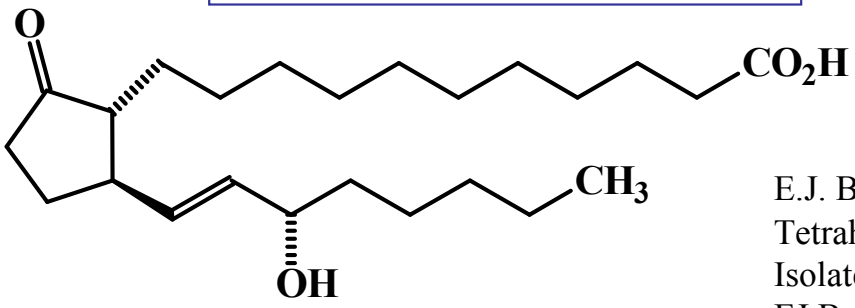


ácido hidnocárpico

C. brasiliensis

Carpotroche brasiliensis, Endl
Flacourtiácea

Primeiras prostaglandinas brasileiras



11-desoxi-tetrahomoPGE$_1$

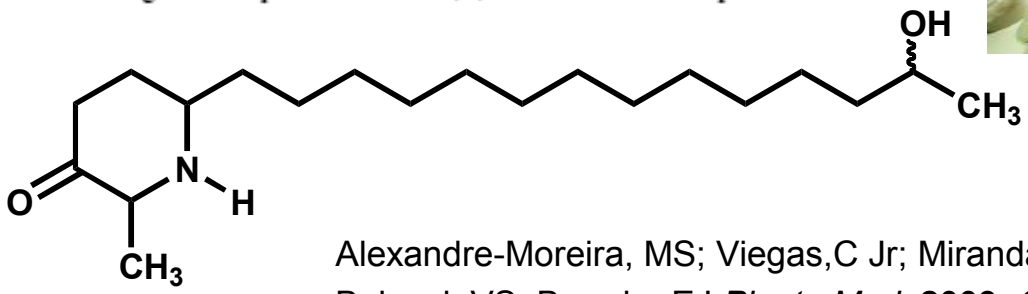
Sapucainha, Papo de anjo, Pau de cachimbo, Canudo de pito, Fruta de cotia, Fruta de Macaco, Beribá do mato; Fruta da lepra, Pau de lepra, Ruchuchú

Ocorrência: Rio de Janeiro, Minas Gerais, Espírito Santo, Bahia

E.J. Barreiro, L N LF Gomes, Prostaglandin Analogues. Synthesis of Tetrahomoprostaglandin Derivatives From Natural Hydnocarpic Acid Isolated From Sapucainha Oil..*J. Chem. Res*. **1983**, 2701
EJ Barreiro, LNLF Gomes, Novo Método de Síntese de Prostaglandinas Modificadas da Série 11-desoxi PG E1". **INPI, PI 38201866**, 02/04/1982
Chem. Abstr., 100, 17452lu (1984)].

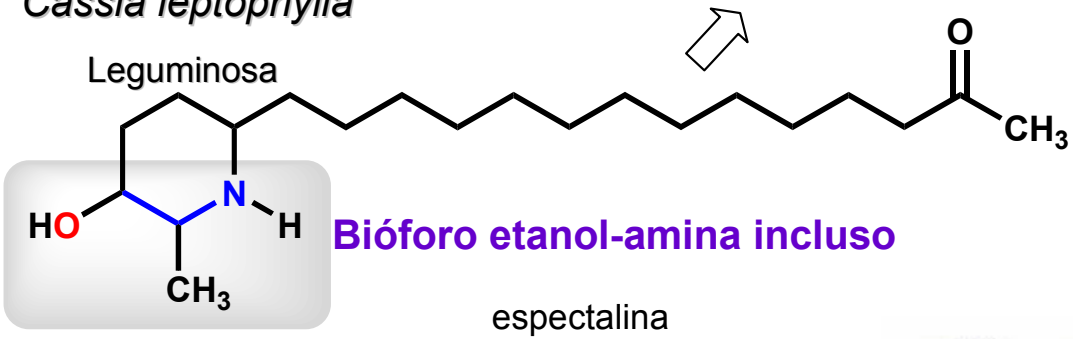
Cassia leptophylla

Design Concept of the New 2,3,6-Trisubstituted Piperidine Derivatives



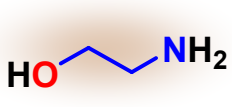
Alexandre-Moreira, MS; Viegas,C Jr; Miranda, ALP; Bolzani, VS; Barreiro,EJ *Planta Med*. **2003**, *69*, 795-9

Leguminosa

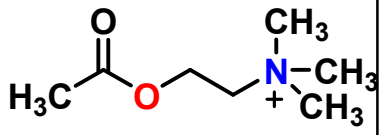


Bióforo etanol-amina incluso

espectalina



etanol-amina



ACh

Protótipo natural

Química Medicinal

Instituto Nacional de Ciência e Tecnologia de Fármacos e Medicamentos

www.inct-inofar.ccs.ufrj.br

NuBBE

LASSBio®

APSEN

LASSBio

Laboratório de Avaliação e Síntese de Substâncias Bioativas

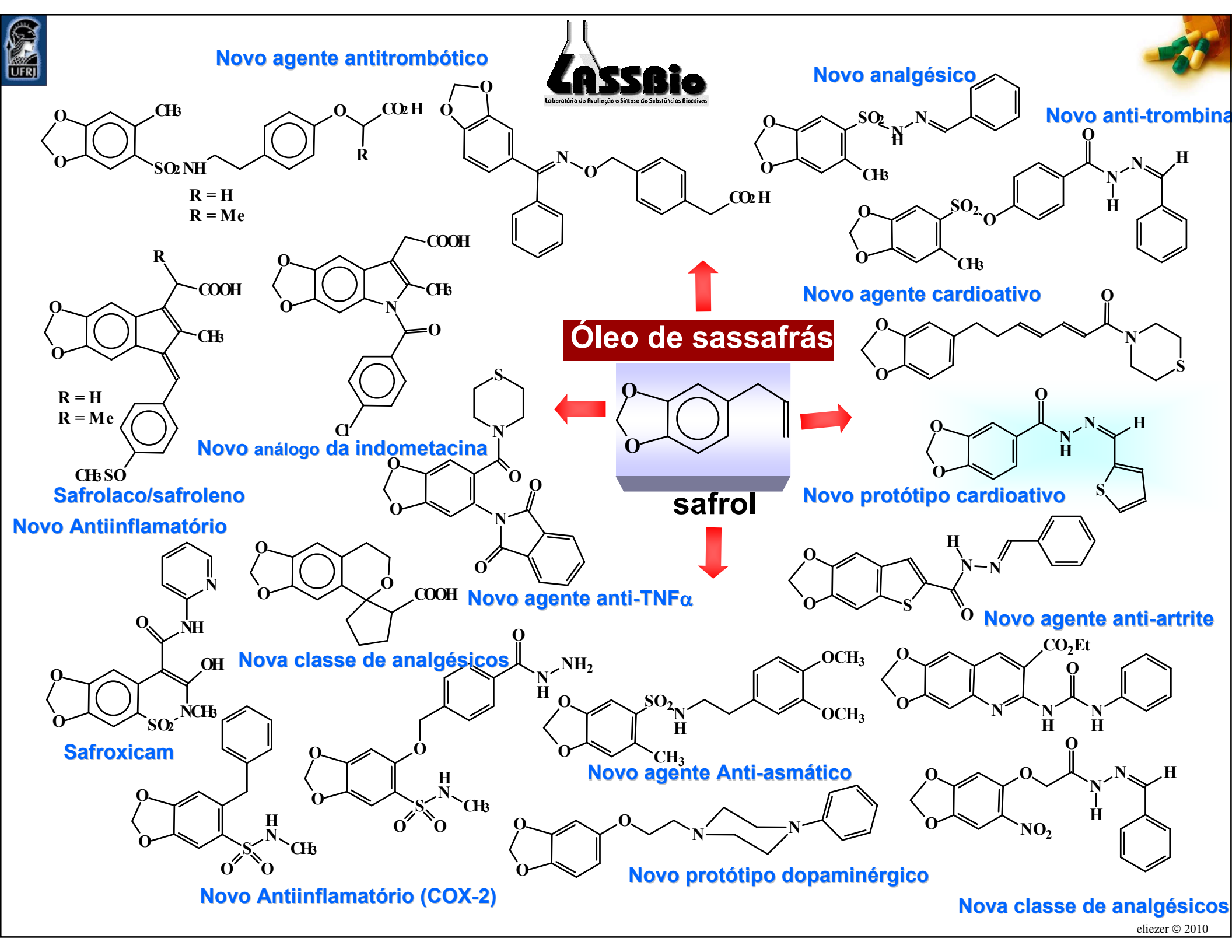
O Uso do Safrol

1982...

$C_{10}H_9O_2$

E. J. Barreiro & C. A. M. Fraga, "*A Utilização do Safrol, Principal Componente Químico do Óleo de Sassafrás, na Síntese de Substancias Bioativas na Cascata do Ácido Araquidônico: Anti-inflamatórios, Analgésicos e Anti-trombóticos*", *Química Nova*, *22*, 744 (1999).

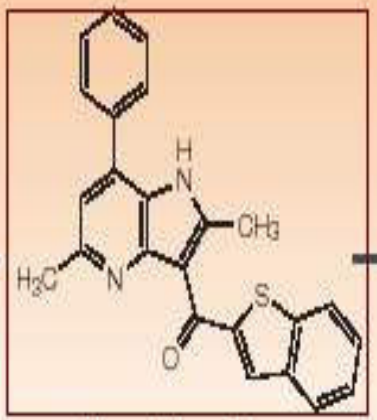
http://www.scielo .br



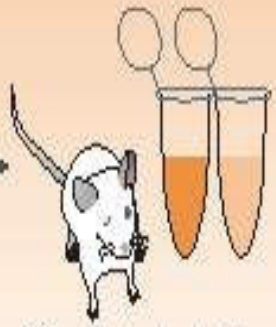
Como nascem os fármacos

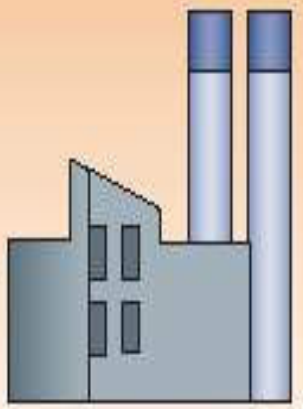
A cadeia da descoberta de fármacos

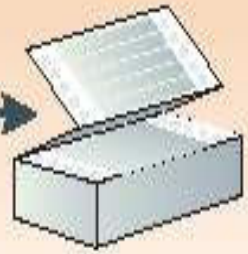

Research team formed and objectives set



Novel chemicals synthesized

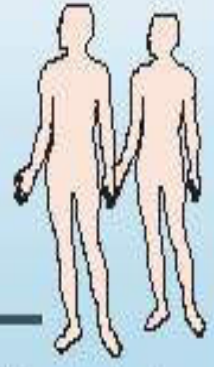

Chemicals tested for efficacy and safety in test tubes and animals. Results used to choose drug candidate.

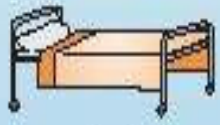

Formulation, stability scale-up synthesis, chronic safety in animals

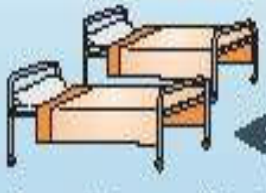

Company files Investigational New Drug (IND) application with FDA

O processo da descoberta de fármacos é complexo...

Clinical studies


Phase I: studies in healthy humans (toleration)


Phase II: studies in patients (efficacy)


Phase III: large clinical trials in many patients


Company files New Drug Application (NDA)

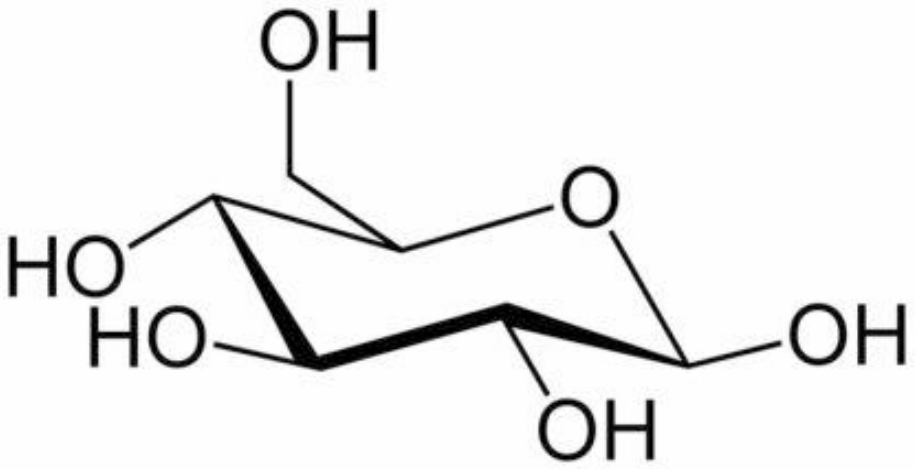
ANVISA

FDA

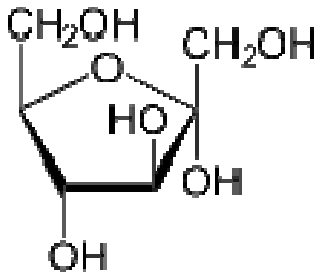
FDA reviews NDA


Drug is approved for marketing

JA Lombardino & JA Lowe III, Nature Rev. Drug Disc. 2004, 3, 853



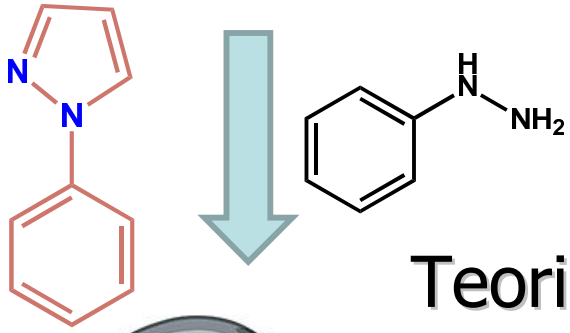
Glicose



frutose

The Nobel Prize in Chemistry 1902
Emil Fischer

Emil Fischer
1852-1919



Teoria da chave-fechadura

Complementaridade molecular

Reconhecimento molecular

Interação fármaco-receptor

O paradigma de Fischer

Emil Fischer

1852-1919

1902

LOCK & KEY CONCEPT

Biorreceptor

macrobiomolécula

baseado no sítio de reconhecimento

Planejamento racional

Fármaco

micromolécula

baseado no ligante / análogo-ativo

Robin Ganellin gives his views on medicinal chemistry and drug discovery

Interview by Stephen L. Carney

C. Robin Ganellin, FRS, Smith Kline & French Professor Medicinal Chemistry, University College London

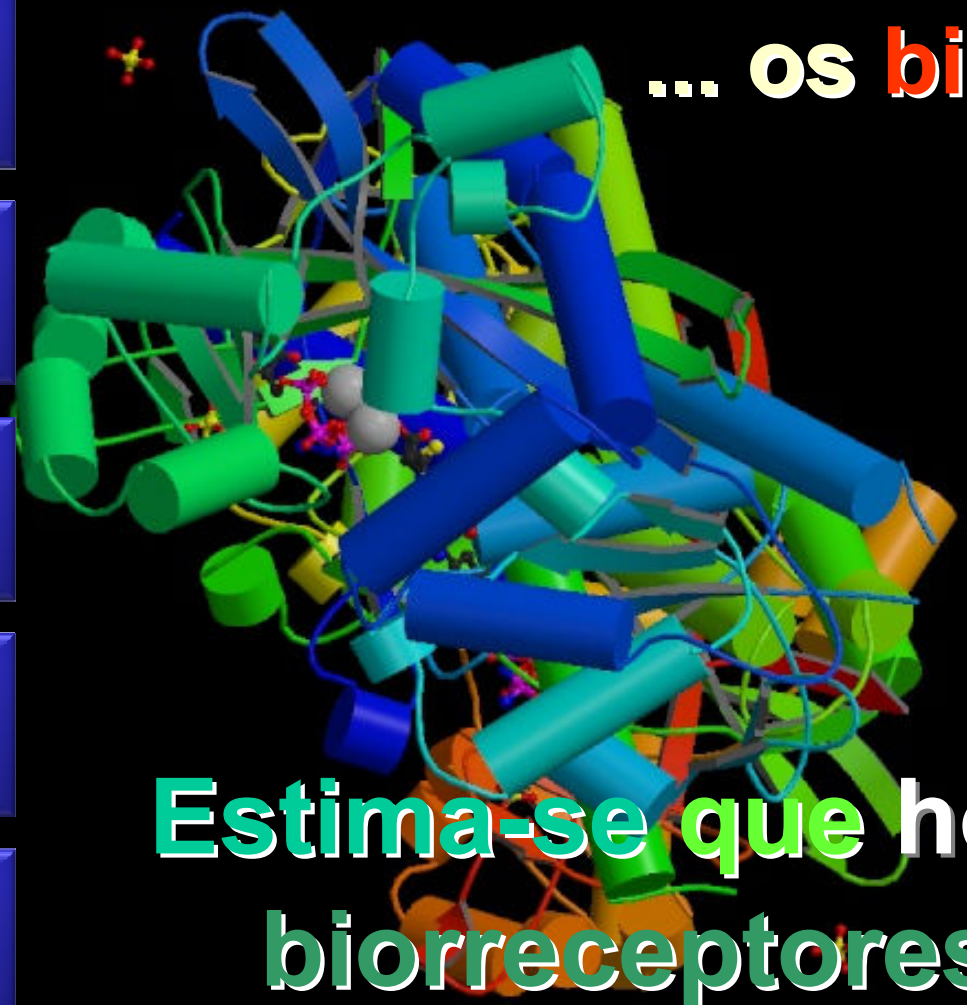
Physiologic approach

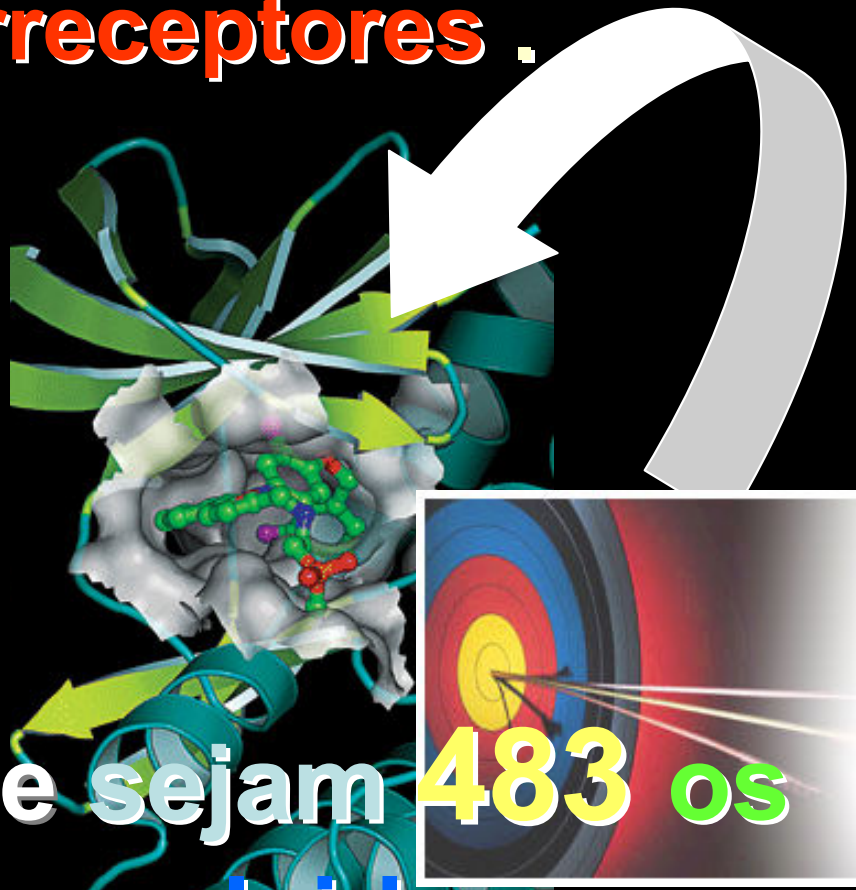
A abordagem fisiológica

C. Robin Ganellin, *Drug Discovery Today* **2004**, *9*, 158

Os fármacos atuam em alvos terapêuticos...

... os biorreceptores .

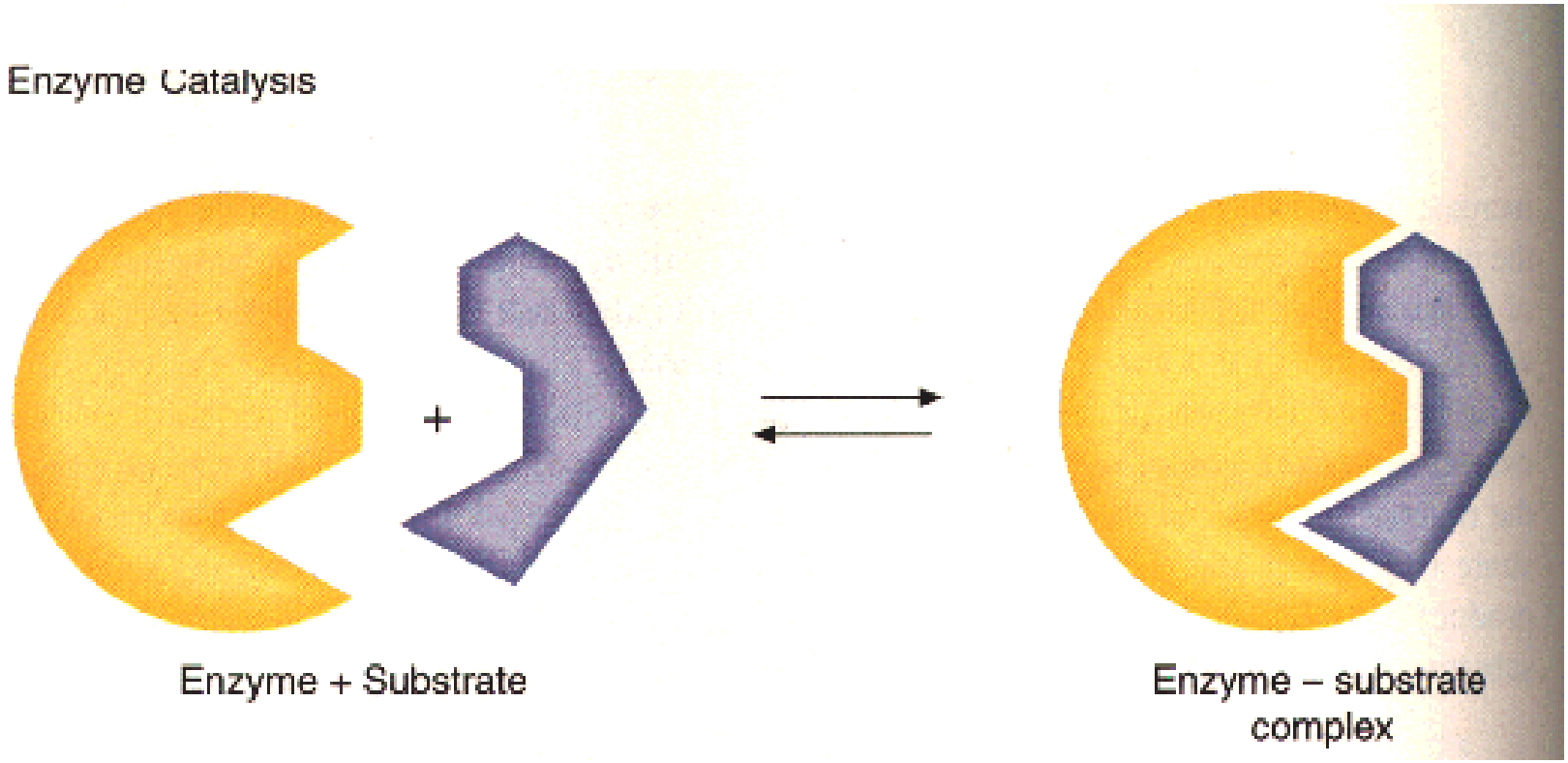


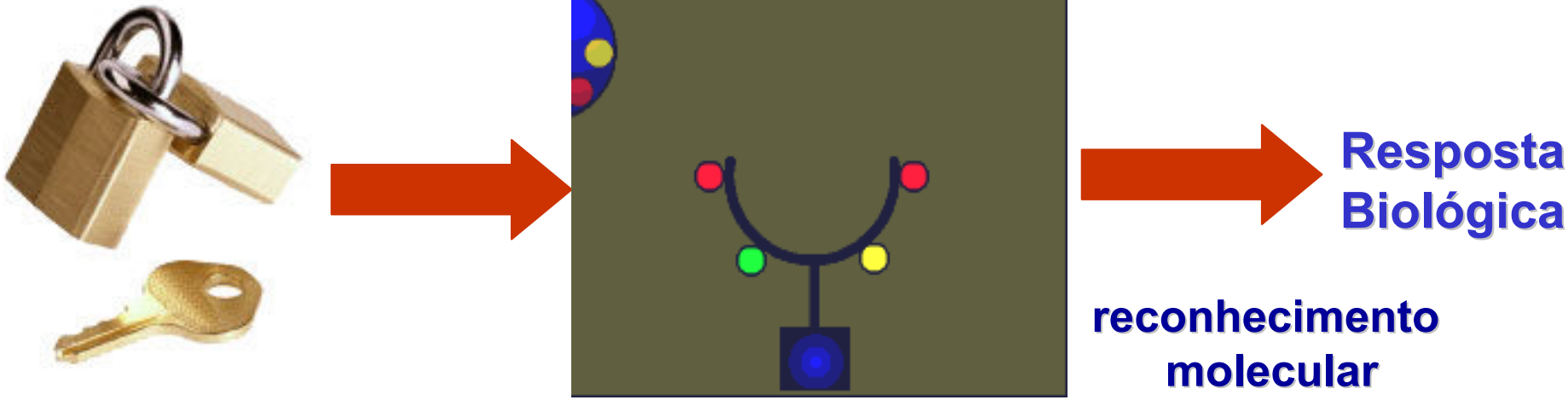


Estima-se que hoje sejam 483 os biorreceptores envolvidos na resposta terapêutica de todos os fármacos contemporâneos.

J. Drews, S. Ryser, **Classic drug targets**. *Nature Biotechnol. 1997,* 15, 1318

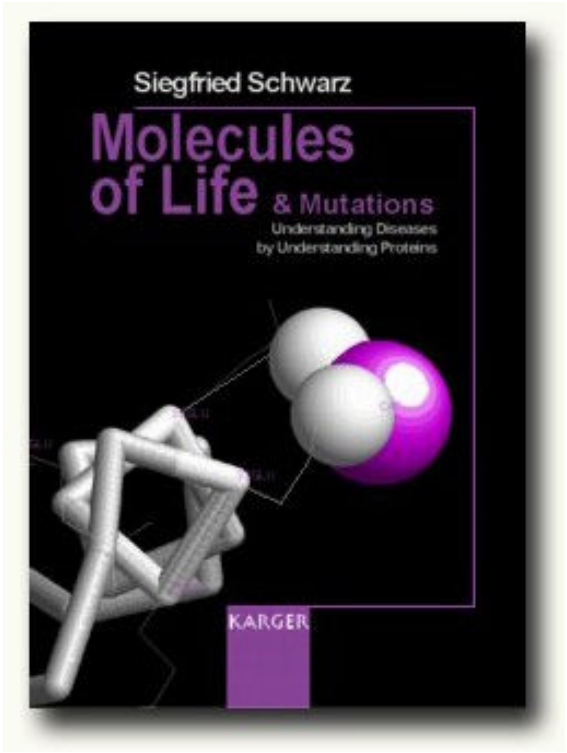
Modelo Chave-Fechadura

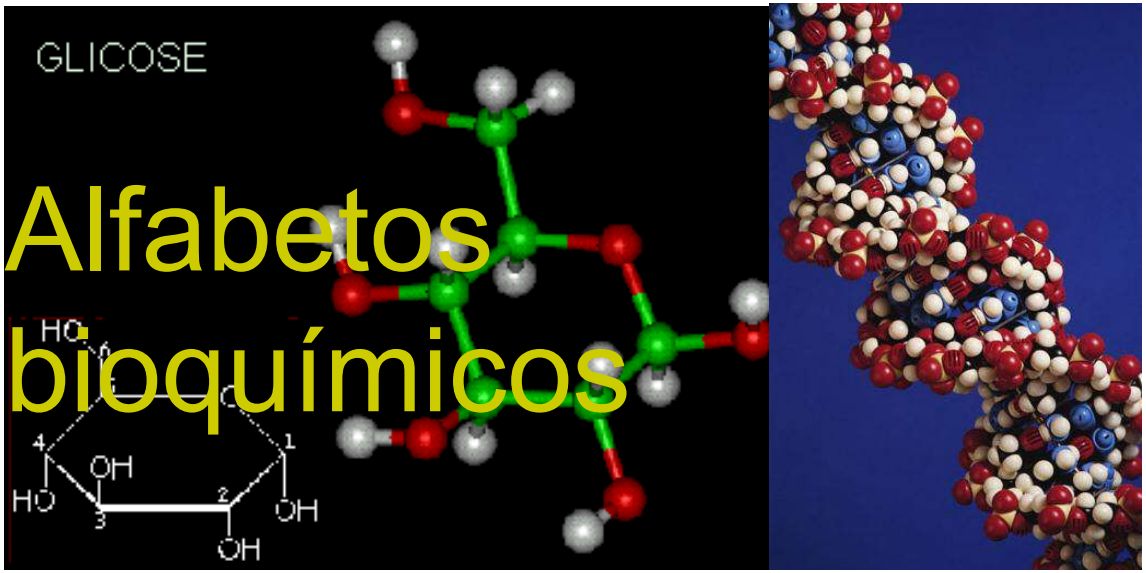




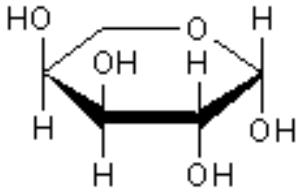
Resposta Biológica

reconhecimento molecular

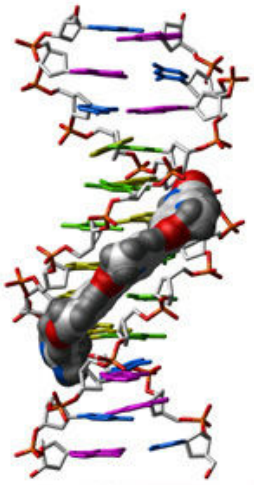




Alfabetos bioquímicos



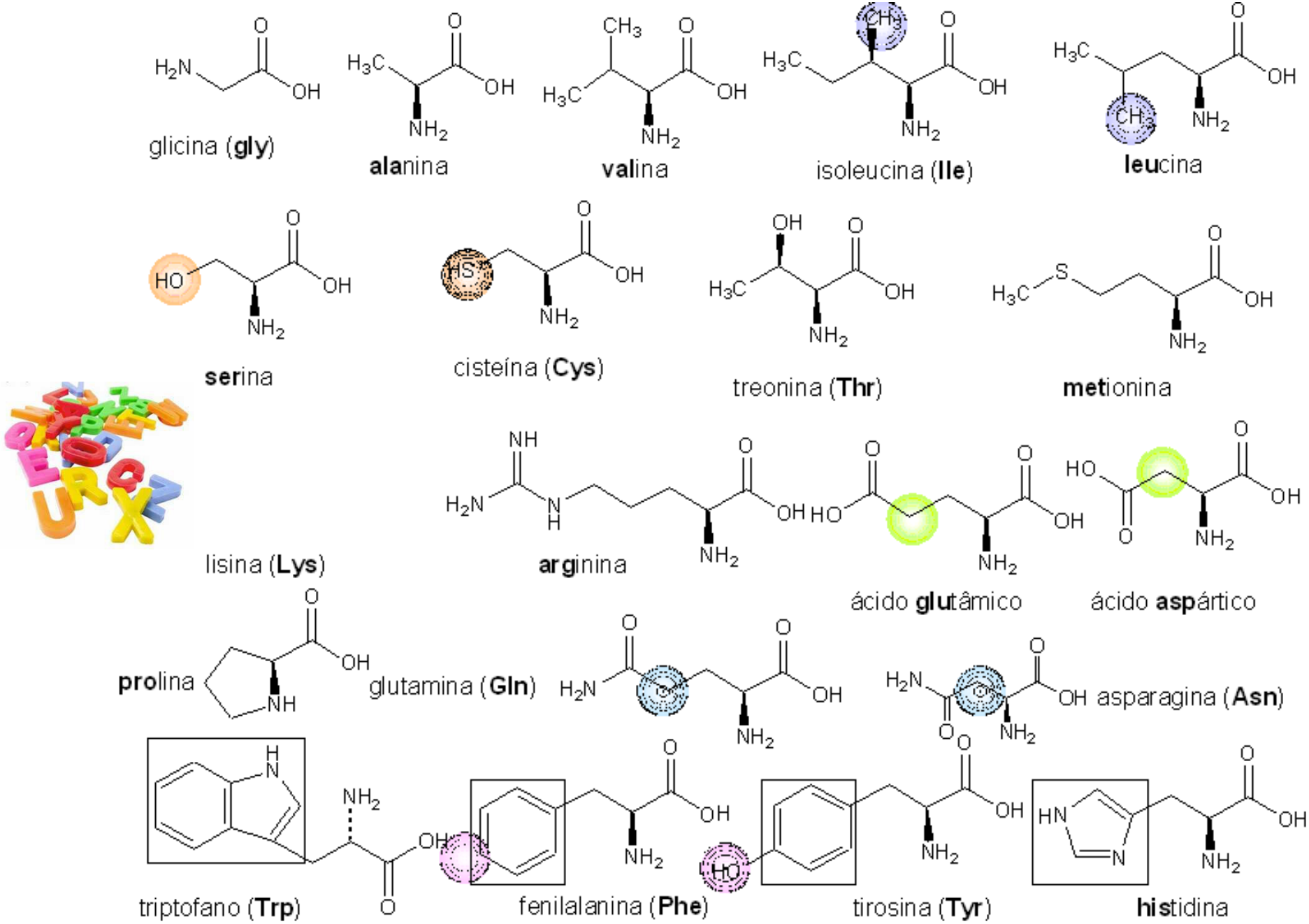
β-L-Arabinose



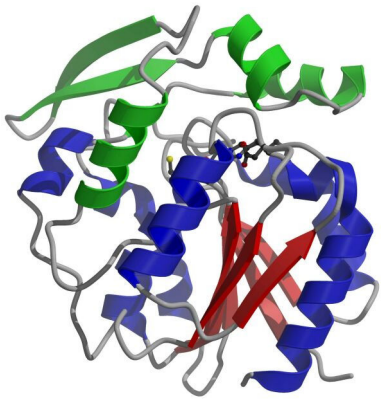
Model Compound Bound to the Minor Groove of a DNA Molecule

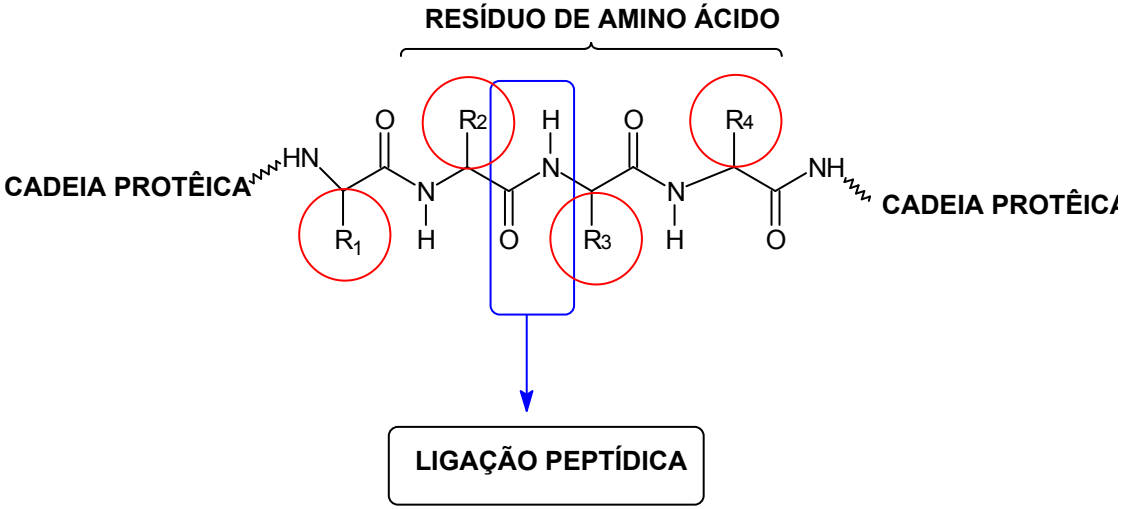
Carboidratos
Lipídeos
ácidos nuclêicos
proteínas

Amino-ácidos essenciais



Estrutura Primária das Proteínas





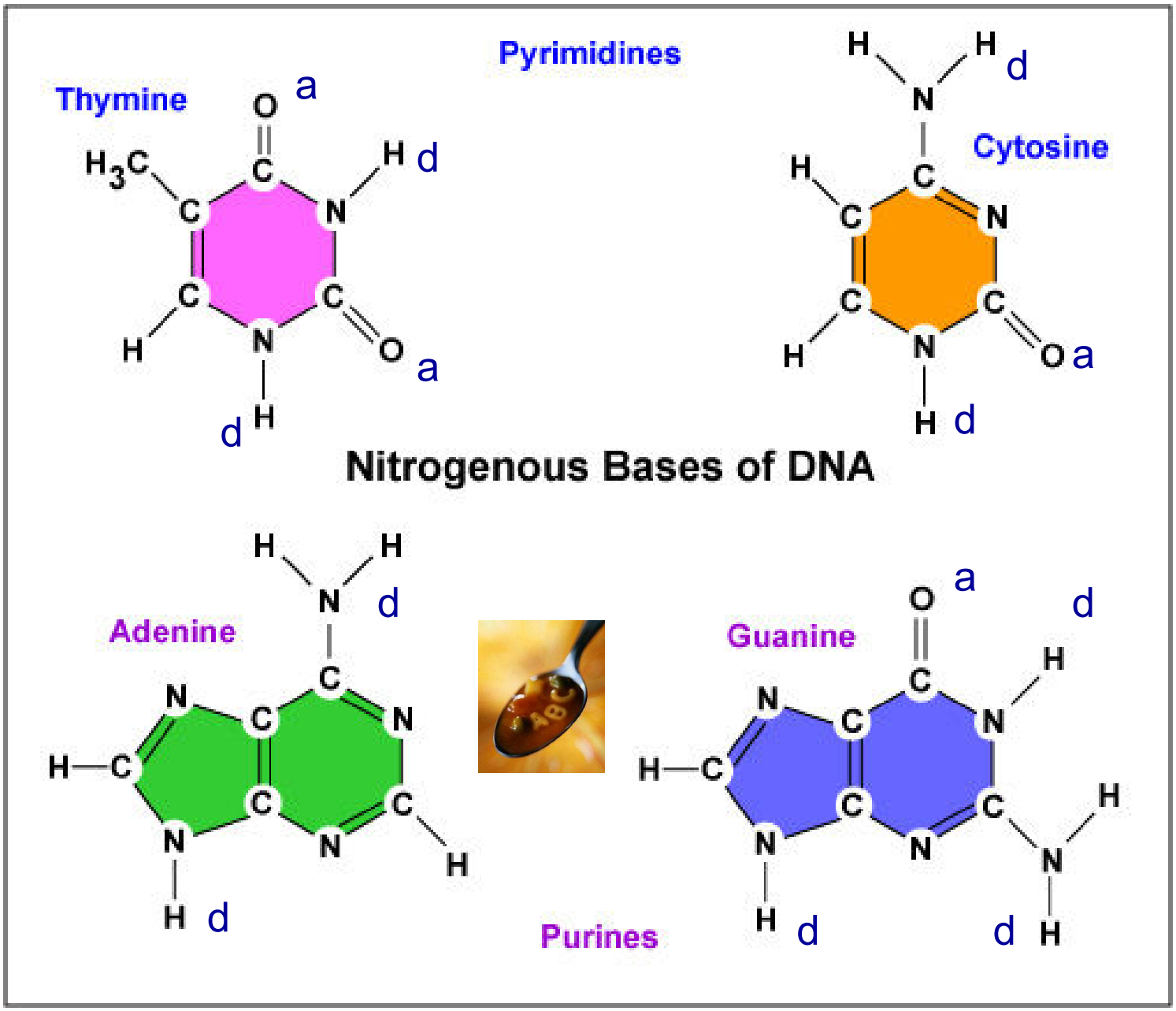
AMINO ÁCIDOS:

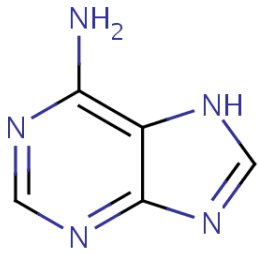
Essenciais: His, Ile, Leu, Lys, Met, Phe, Thr, Trp, Val

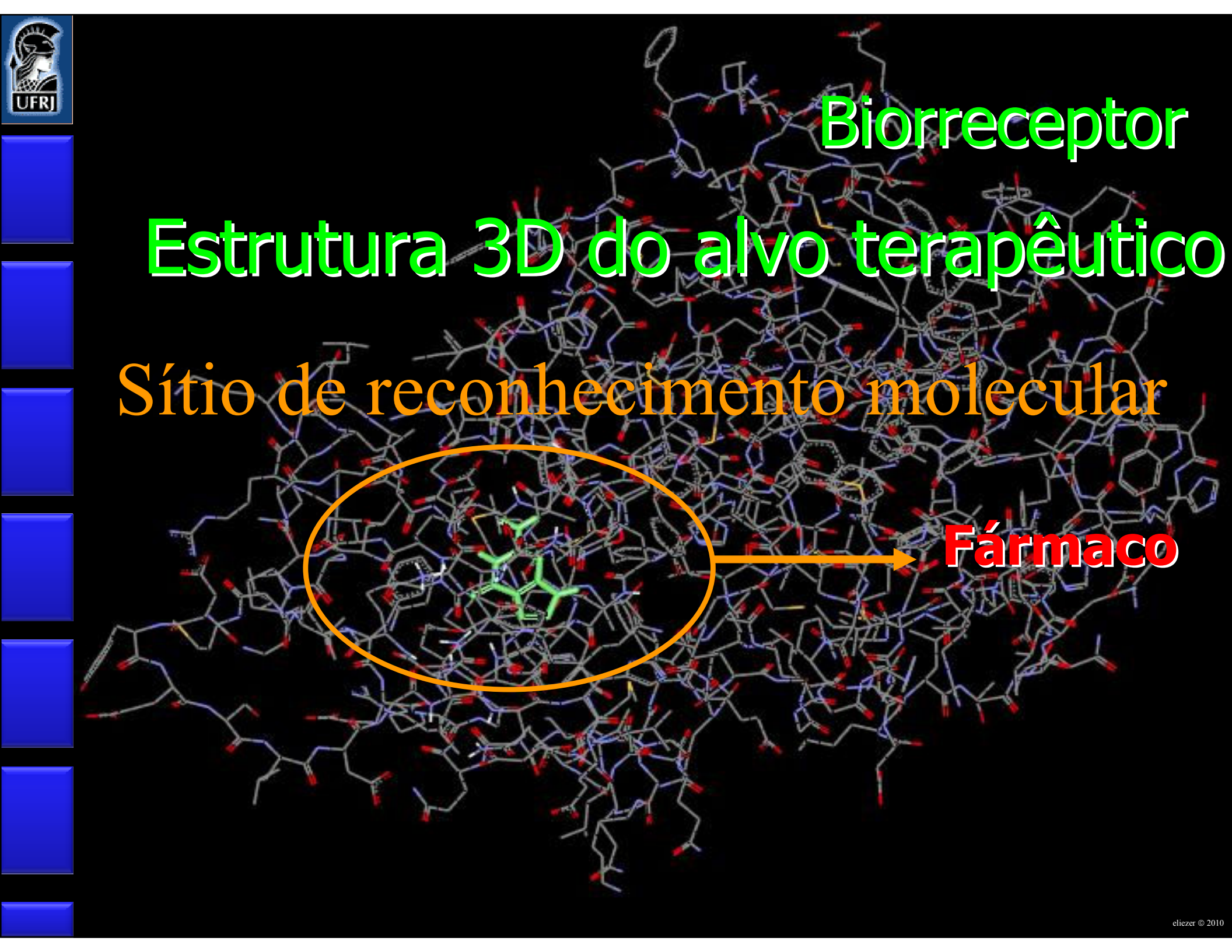
Não-essenciais: Ala, Arg, Asn, Asp, Cys, Glu, Gln, Gly, Pro, Ser, Tyr

"Fechadura"

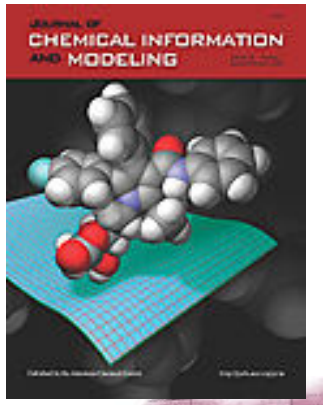
"ácidos nuclêicos...

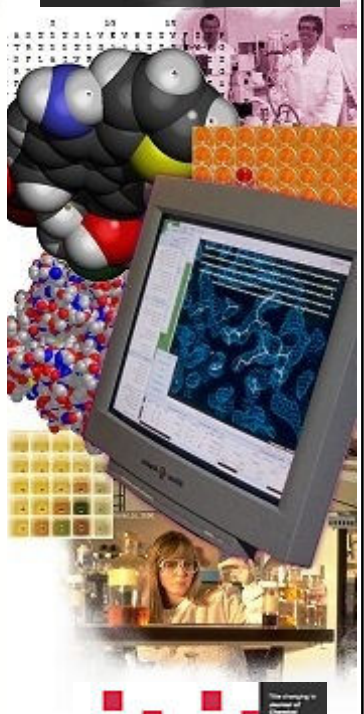


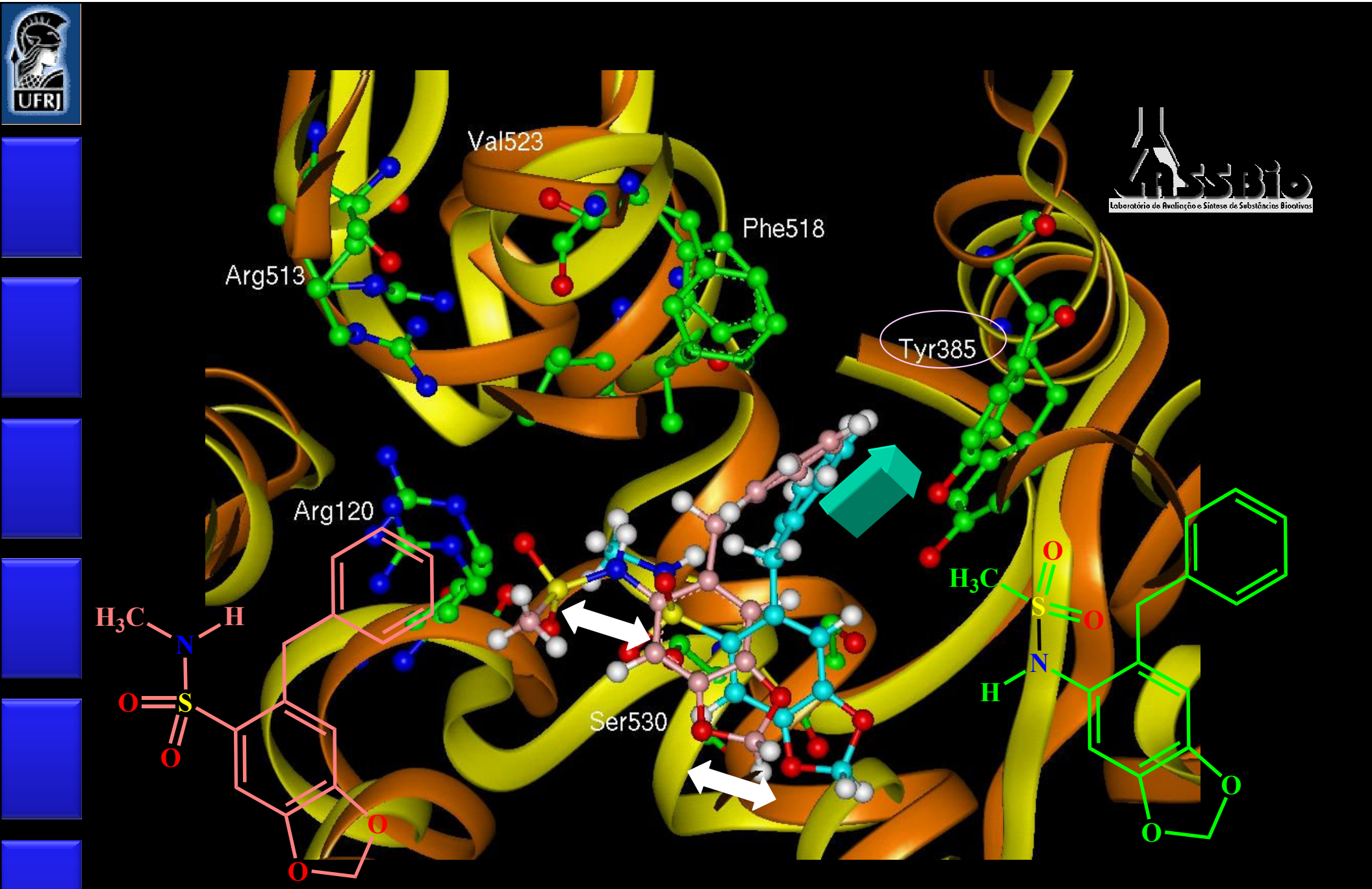




Bioformática

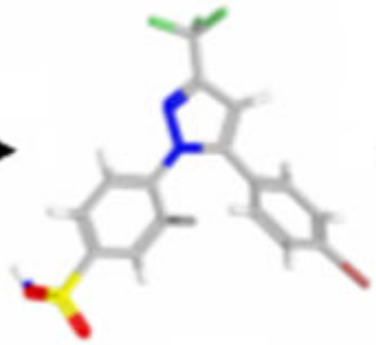




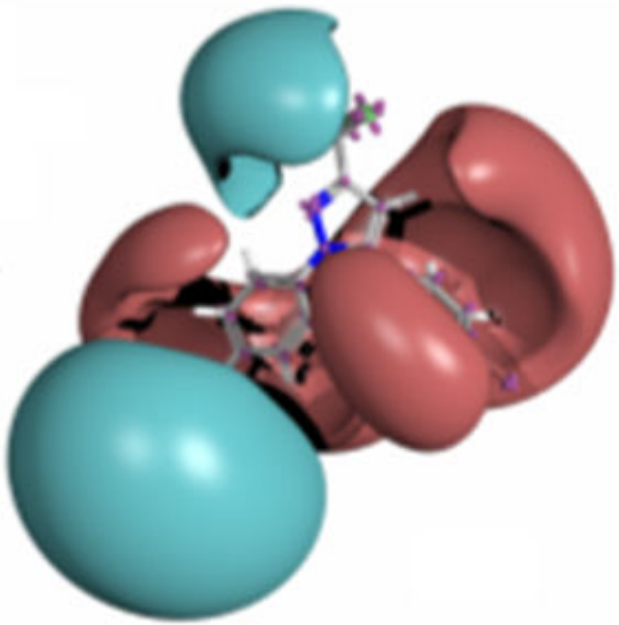


Complexo formado entre LASSBio-257 (verde) e o LASSBio-258 (rosa) com o sítio de reconhecimento molecular da PGHS-2.

2D

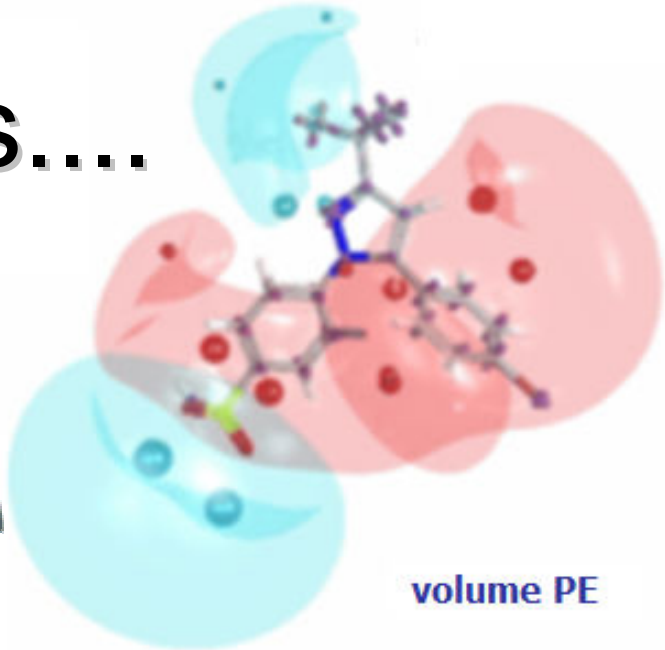


3D

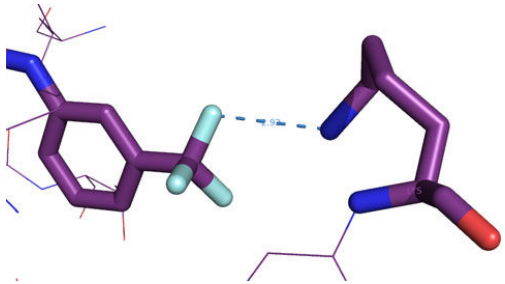


MPE

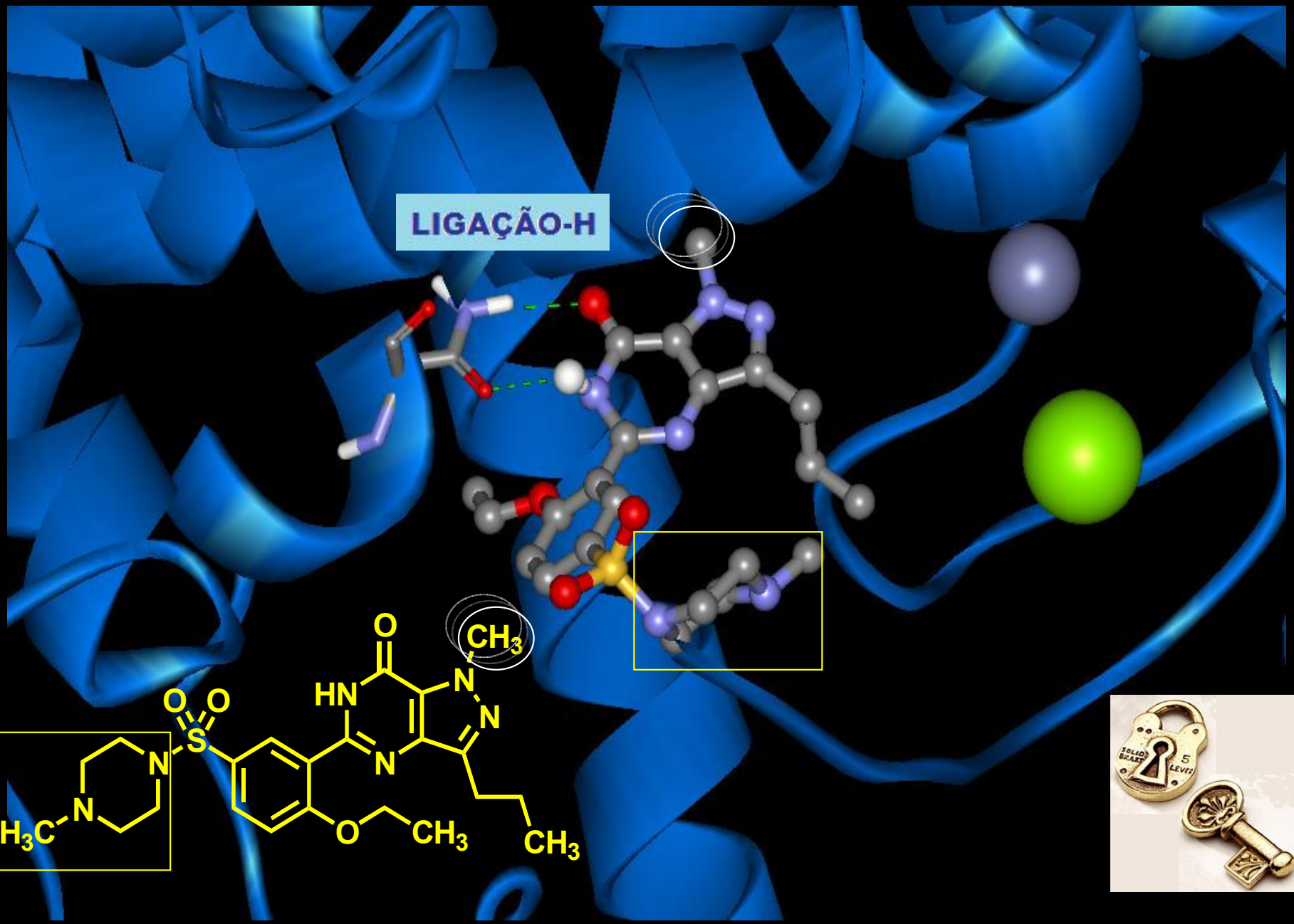
As chaves....



volume PE

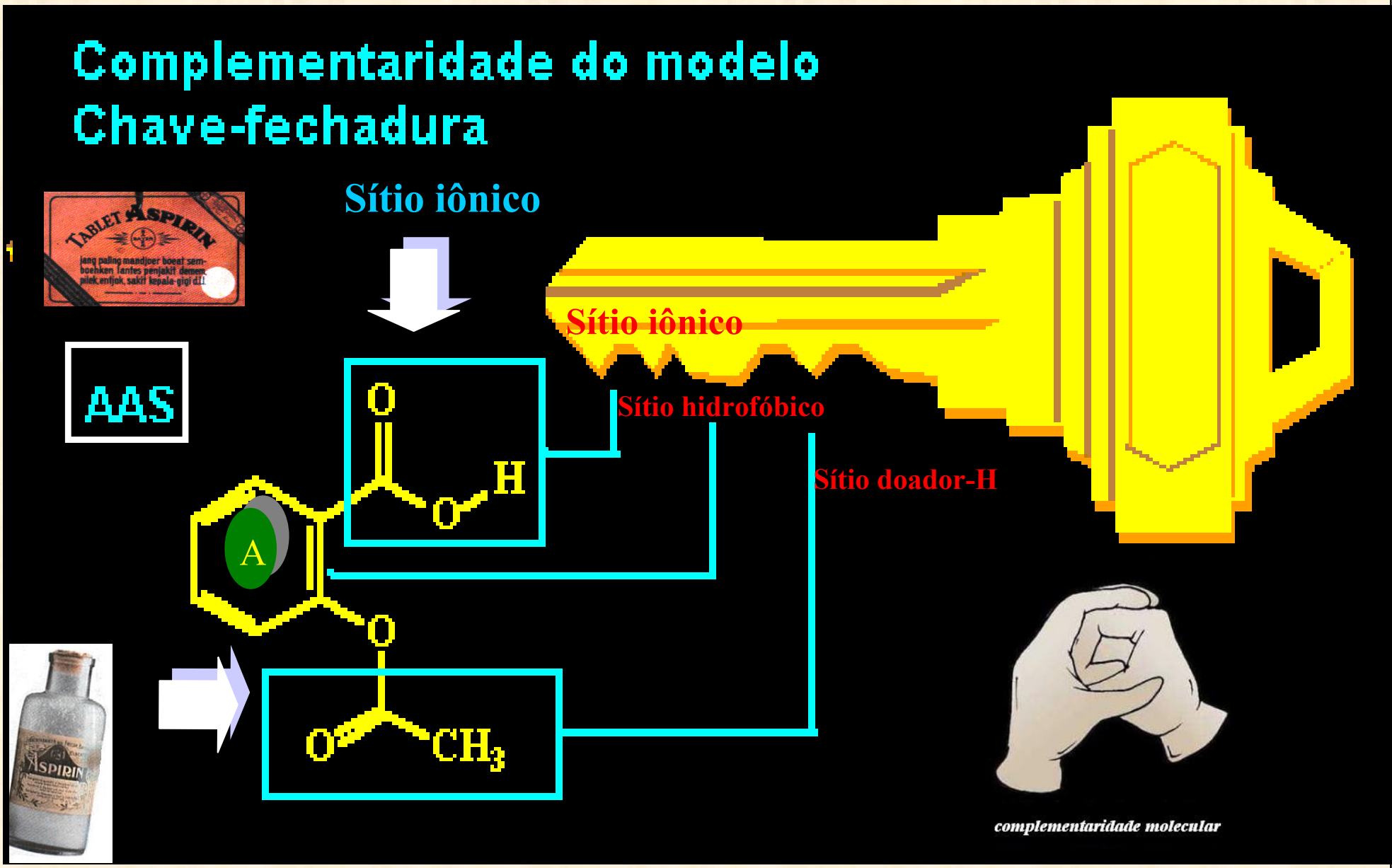


A estrutura 3D dos biorreceptores

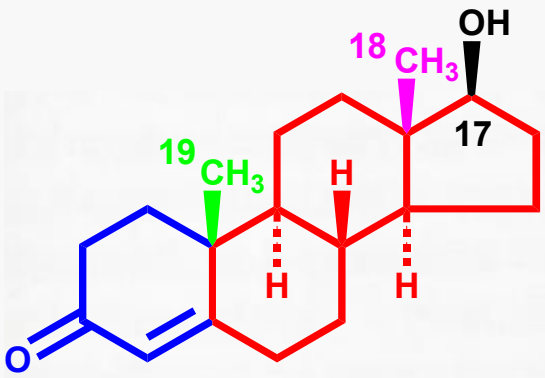


Interações do sildenafila (Viagra^{R}) com seu alvo-terapêutico (fosfodiesterase V)

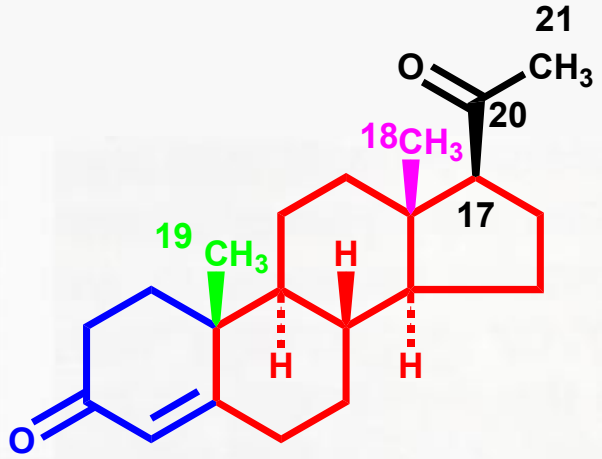
O Centenário Modelo *"Chave-Fechadura"*



A similaridade e a dissimilaridade molecular

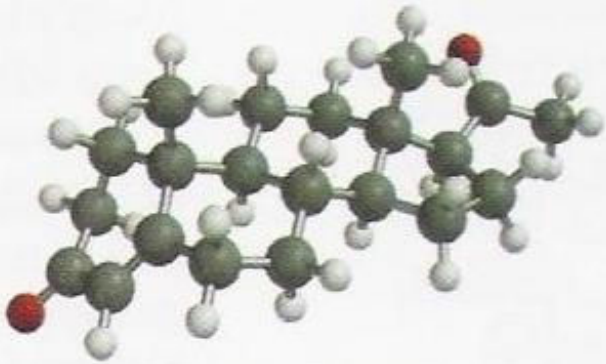


Testeosterone
$C_{19}H_{28}O_2$



Progesterone
$C_{21}H_{30}O_2$

Testosterone



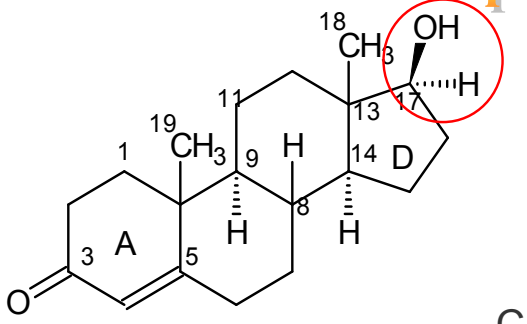
Progesterone

...no processo de reconhecimento molecular pelo biorreceptor

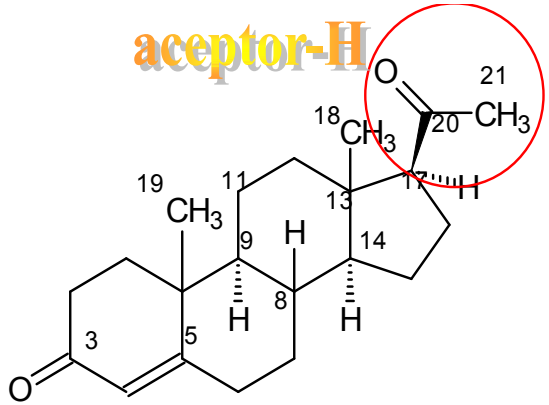
Similaridade & Dissimilaridade Molecular

Biorreceptor

aceptor/doador-H

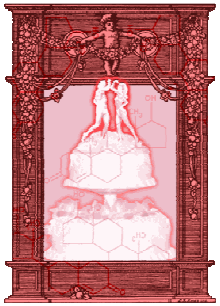


aceptor-H

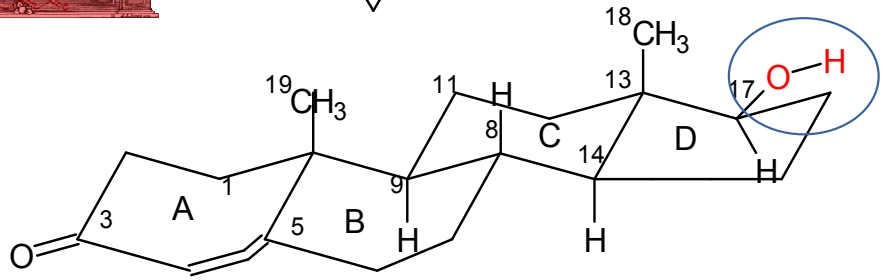


Esqueleto ciclopentano peridrofenantreno

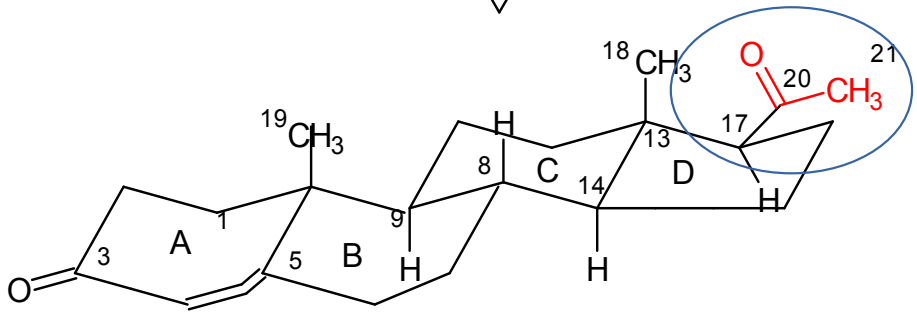
C_{19} C_{21}



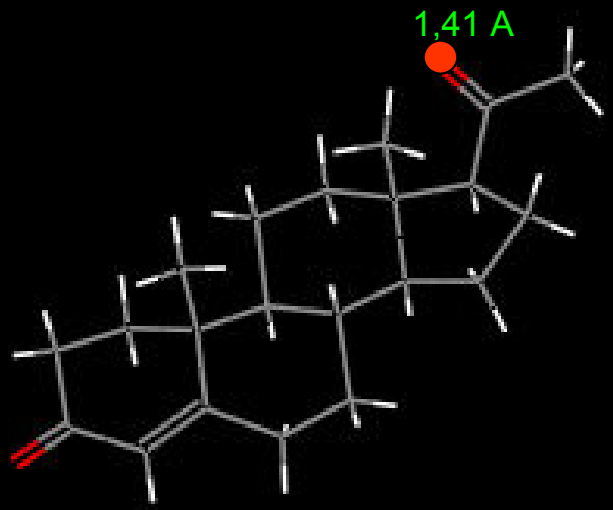
Testosterona — similaridade molecular — Progesterona

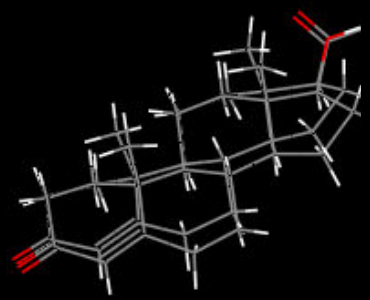


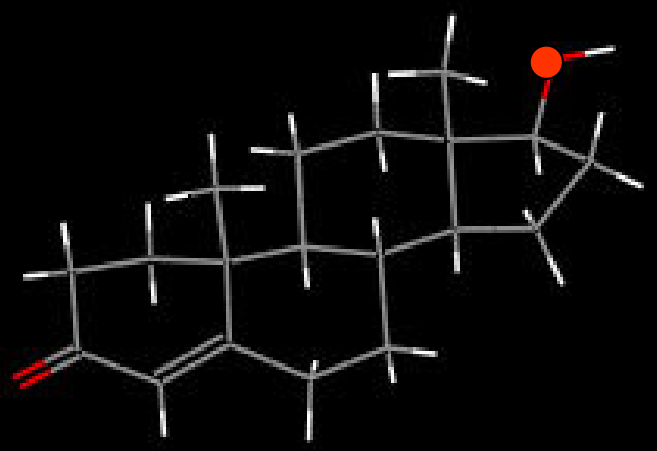
B/C C/D trans



B/C C/D trans







progesterona

testosterona