



Planejamento Racional de Fármacos

Parte 1

I Jornada Ciências Farmacêuticas
da Universidade Federal de Alagoas

Maceio, 19 de agosto de 2010



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



Planejamento = ato ou efeito de planejar;



Racional = que procede da razão; que tem por objeto a razão, em que há coerência, lógica, inteligente;



Planejamento Racional de fármacos



O fármaco...





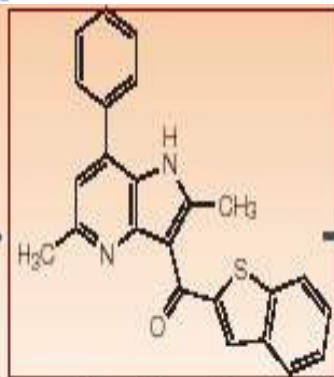
Preclinical studies

Química Medicinal

Mini-curso: Planejamento racional de fármacos - UFPA (19/08/2010)

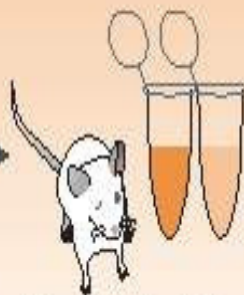


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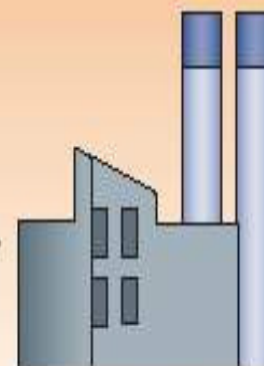


Novel chemicals synthesized

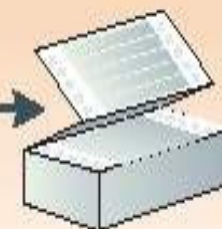
Lead compound
Composto-protótipo



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

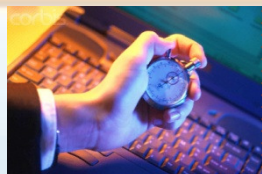


Formulation, stability scale-up synthesis, chronic safety in animals



Company files Investigational New Drug (IND) application with FDA

Clinical studies



O processo de descoberta/invenção de novos fármacos é complexo...



Drug is approved for marketing

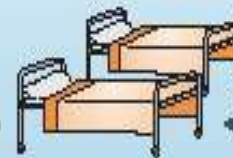
ANVISA

FDA

FDA reviews NDA



Company files New Drug Application (NDA)



Phase III: large clinical trials in many patients



Phase II: studies in patients (efficacy)



Phase I: studies in healthy humans (toleration)

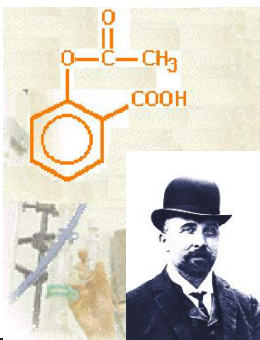


JA Lombardino & JA Lowe III, Nature Rev. Drug Disc. 2004, 3, 853

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Cronologia da descoberta de fármacos

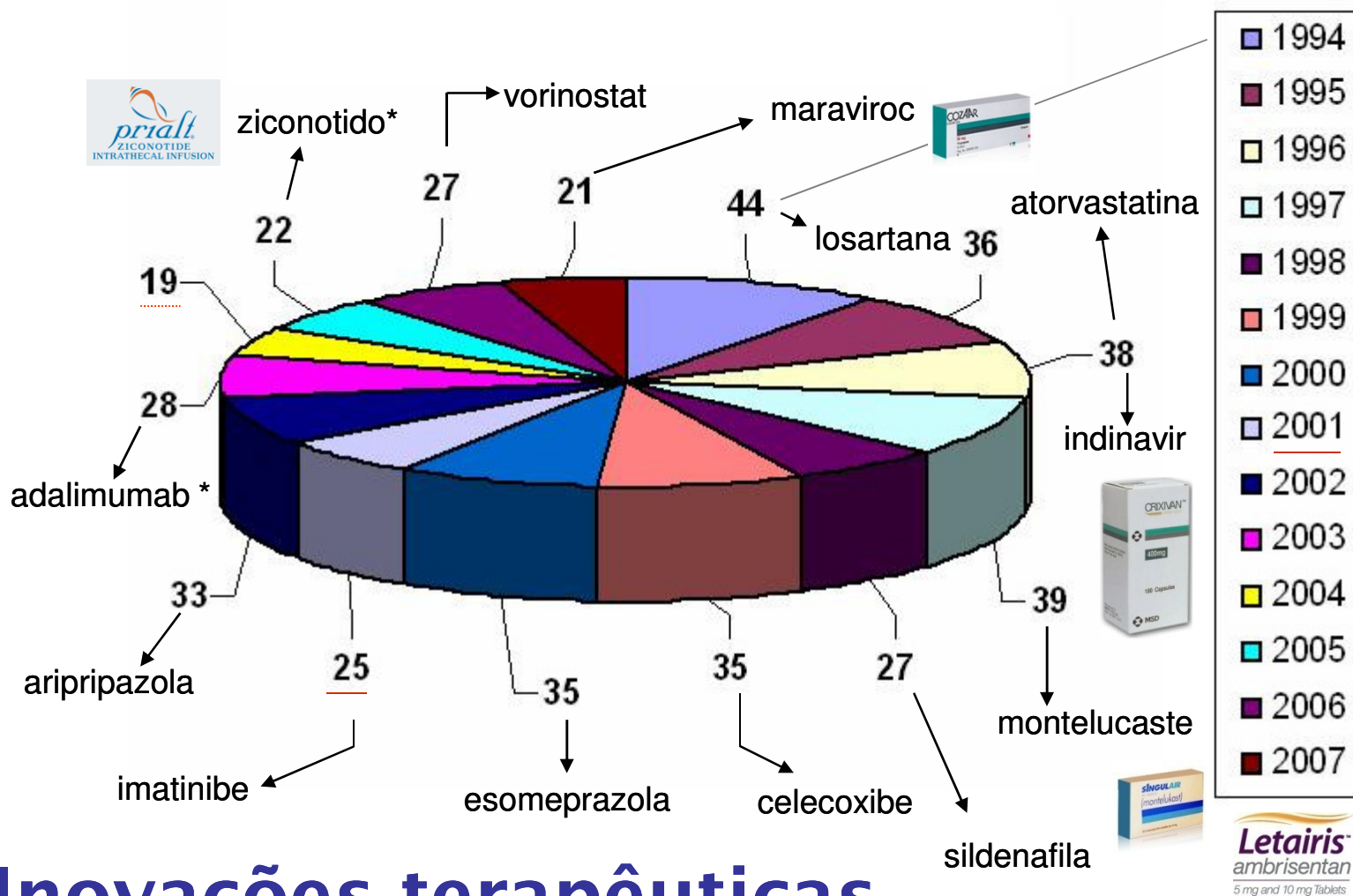


AAS *	1889	1986	ciprofloxacina fluoxetina
barbitúricos	1923	1987	zidovudina lovastatina
cloroquina	1934	1988	cetirizina, enalapril
sulfonamidas	1935	1989	ozagrel mifepristona
penicilina	1942	1990	salmeterol, amlodipina
nitrofurano	1952	1991	alpidem, paroxetina
progesterona	1953	1992	paclitaxel
talidomida	1954	1993	tacrina, fanciclovir
haloperidol	1958	1994	irinotecan, pimobendano
verapamil	1962	1995	indinavir, losartano
indometacina	1963	1996	docetaxel, atorvastatina
propranolol	1964	1997	zafirlukast, montelukast
salbutamol	1968	1998	infiximabe sildenafil efavirenz
<i>prostaglandinas</i>	1970	1999	celecoxibe orlistate oseltamivir
oxamniquina	1970	2000	galantamina rofecoxibe
cimetidina nifedipina	1975	2001	imatinibe <i>rosiglitazona</i>
atenolol	1976	2002	voriconazola, etoricoxibe
captopril	1977	2003	gefitinibide, aripiprazola
tamoxifeno	1978	2004	rosuvastatina, rofecoxibe
praziquantel	1979	2005	pregabalina, Caduet ^R
oxicams	1980	2006	risperidona, erlotinibe
ranitidina aciclovir	1981	2007	maraviroc*, ambrisentan
mefloquina misoprostol	1985	2008	etravirina
		2009	pitavastatina





Novos fármacos lançados por ano / 1994 - 2007

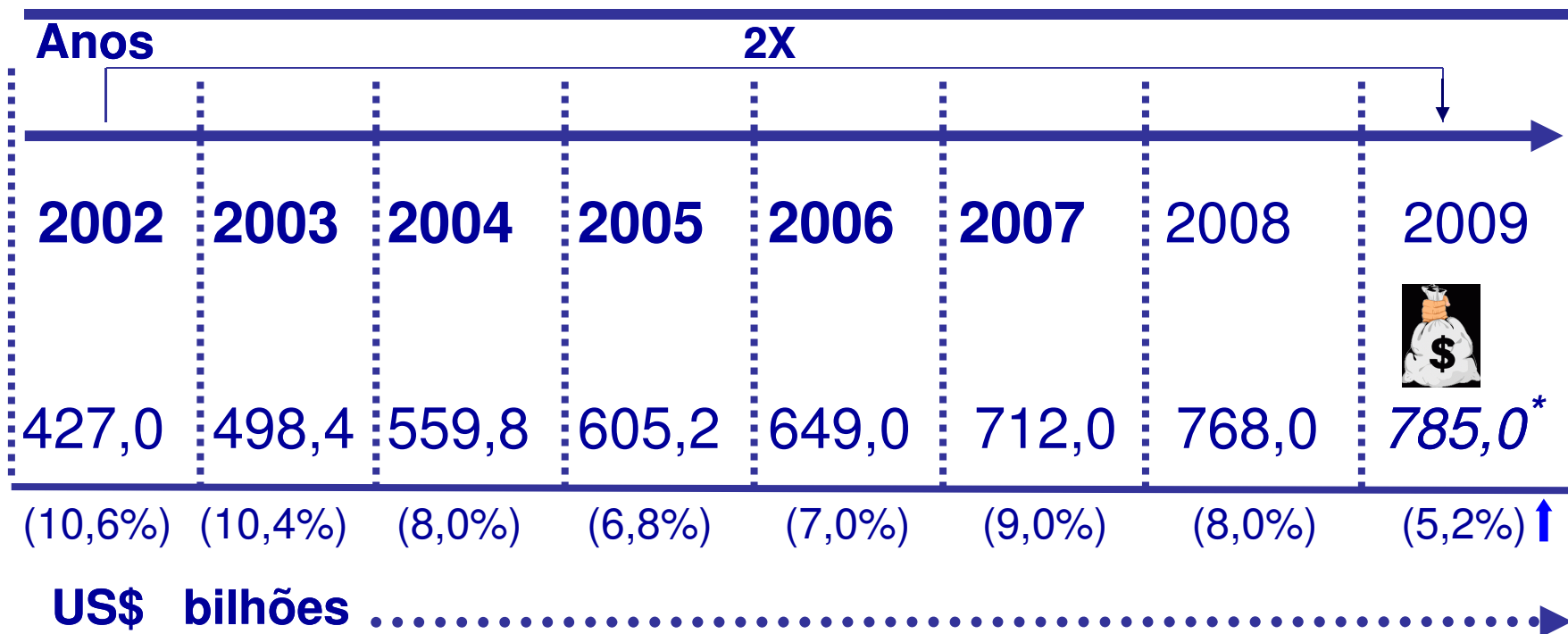


Inovações terapêuticas

ca. 30 novos fármacos lançados / ano



Mercado Farmacêutico Mundial



América Latina:

Brasil: 1,6% (10º lugar) = US\$ 11,6 bilhões

Top-10: US\$ 561,9 bilhões (USA: US\$ 300 bilhões = 40%; Jp, Fr, Al.)




*Fonte: SJ Ainsworth C&EN, Dec. 07, p.13, 2009

Principais classes terapêuticas:

oncológicos (6,9%)

& anti-lipêmicos (4,7%)

2010-2013: osteoporose, DRC



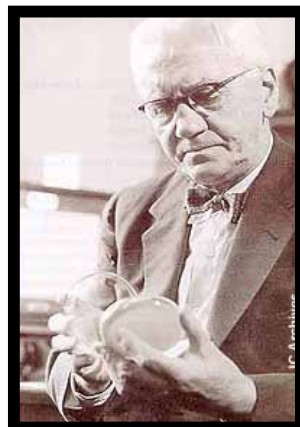
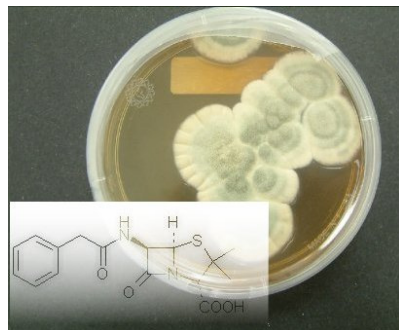
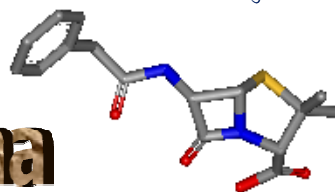
Os Fármacos e o Prêmio Nobel



Os fármacos e o Nobel !

Mini-curso: Planejamento racional de fármacos - UFPA (19/08/2010)

Penicilina



1945 - Alexander Fleming



1945 - Ernest B. Chain



1945- Howard W. Florey



<http://nobelprize.org>

■ 195 pesquisadores ganharam o Prêmio Nobel de Medicina desde 1901

“for their discoveries of important principles for drug treatment”



1988 - J.W. Black



1988 -G.B. Elion



1988 -G.H. Hitchings

Inter-alia:
Propranolol
Cimetidina
Aciclovir



Os fármacos e o Nobel !

Mini-curso: Planejamento racional de fármacos - UFAL (19/08/2010)



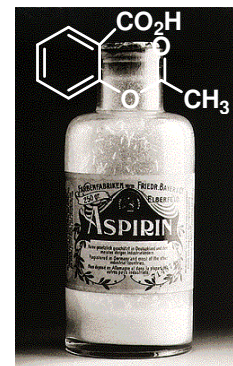
1982 –S.B.Bergstöm



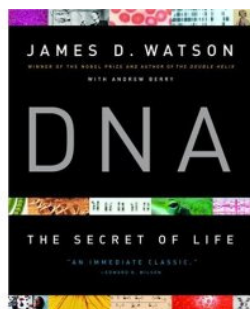
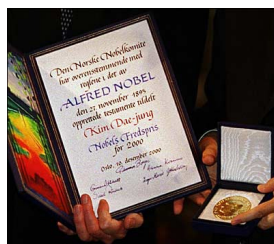
1982 –B.I.Samuelsson



1982 –J.R. Vane



1982 – AAS



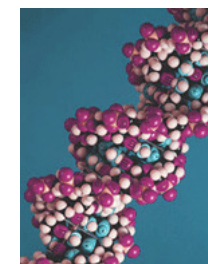
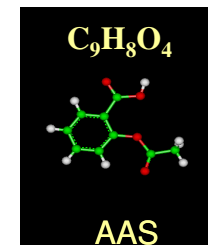
• 157 pesquisadores ganharam o Prêmio Nobel de Química desde 1901

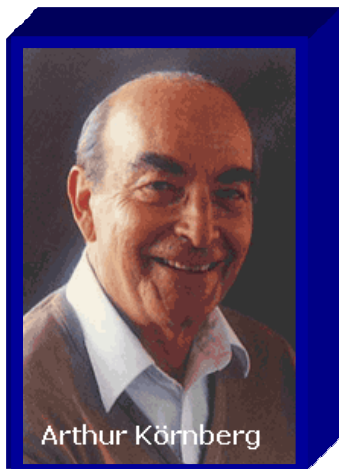


1937 -Albert Szent-Györgi



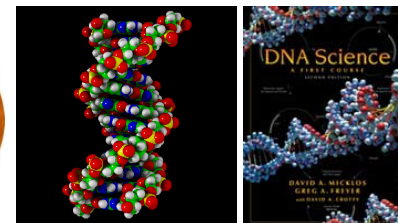
1959- Arthur Kornberg





Nobel Prize, 1959

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



“We have the paradox of the two cultures,

chemistry and biology,

growing further apart even as they

discover more common ground....

Pharmaceutical chemistry was until

recently the bastion of organic chemistry...

in the search for alternative or superior

drugs for the treatment of various diseases.”

Arthur Kornberg

Biochemistry 1987, 26, 6888-6891

Interdisciplinaridade

Diapositivo 11

EJB2

Kornberg definiu as bases da interdisciplinaridade das ciências dos fármacos quando antecipou a necessidade de aproximar-se a Química e a Biologia.

Eliezer J. Barreiro; 04/03/2010



Interdisciplinaridade



O Paradigma
de Ehrlich &
Fischer



O paradigma de Ehrlich & Fischer



Emil Fischer

1852-1919

1902



Paul Ehrlich

1854-1915

1908



LOCK & KEY
CONCEPT



Planejamento racional

Biorreceptor

macrobiomolécula
baseado no sítio de reconhecimento

BSRM
BL-AA

Fármaco

micromolécula

baseado no ligante / análogo-ativo



THE LANCET

"In patients with locally advanced or high-risk local prostate cancer, addition of local radiotherapy to endocrine treatment halved 10-year prostate-cancer-specific mortality."

Physiologic
A abordagem
approach
fisiológica

P. Ehrlich, *Chemotherapeutics: scientific principles, methods and results.* Lancet 1913, 2, 445





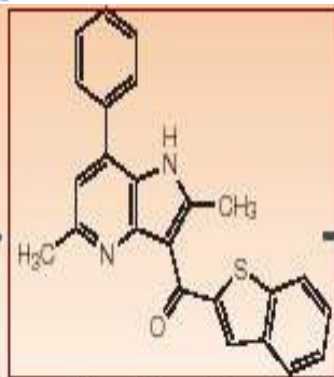
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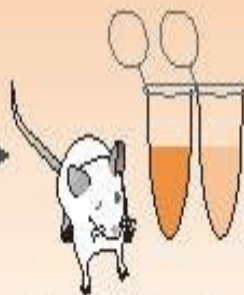


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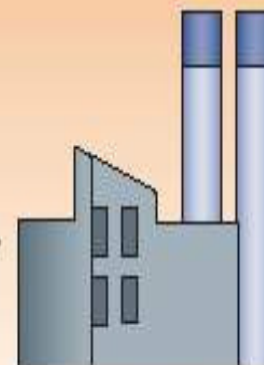


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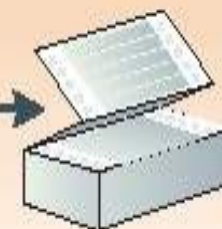
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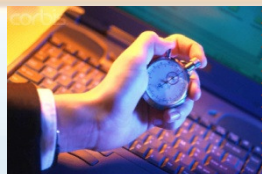


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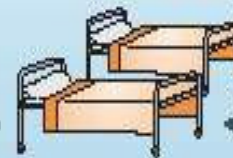
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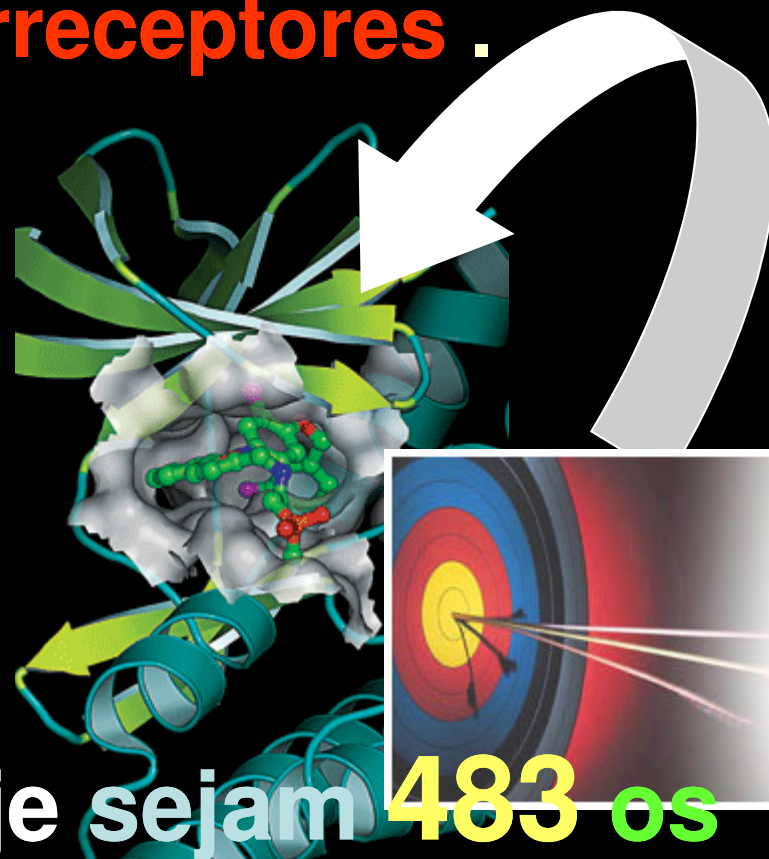
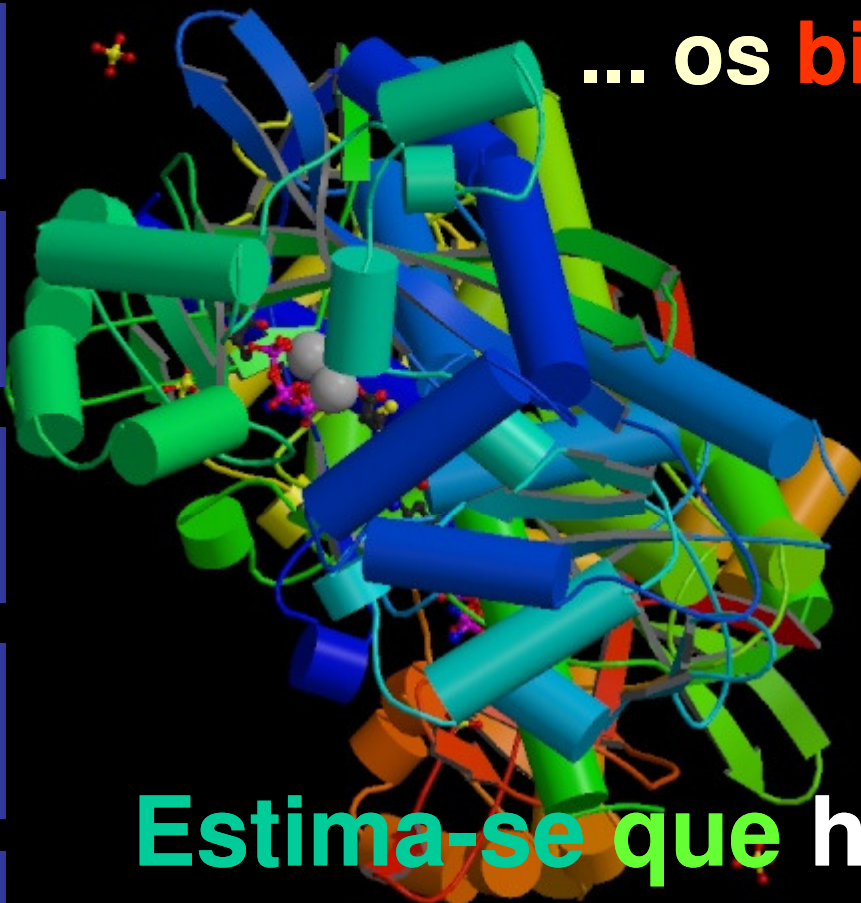


Os biorreceptores



Os fármacos atuam em alvos terapêuticos...

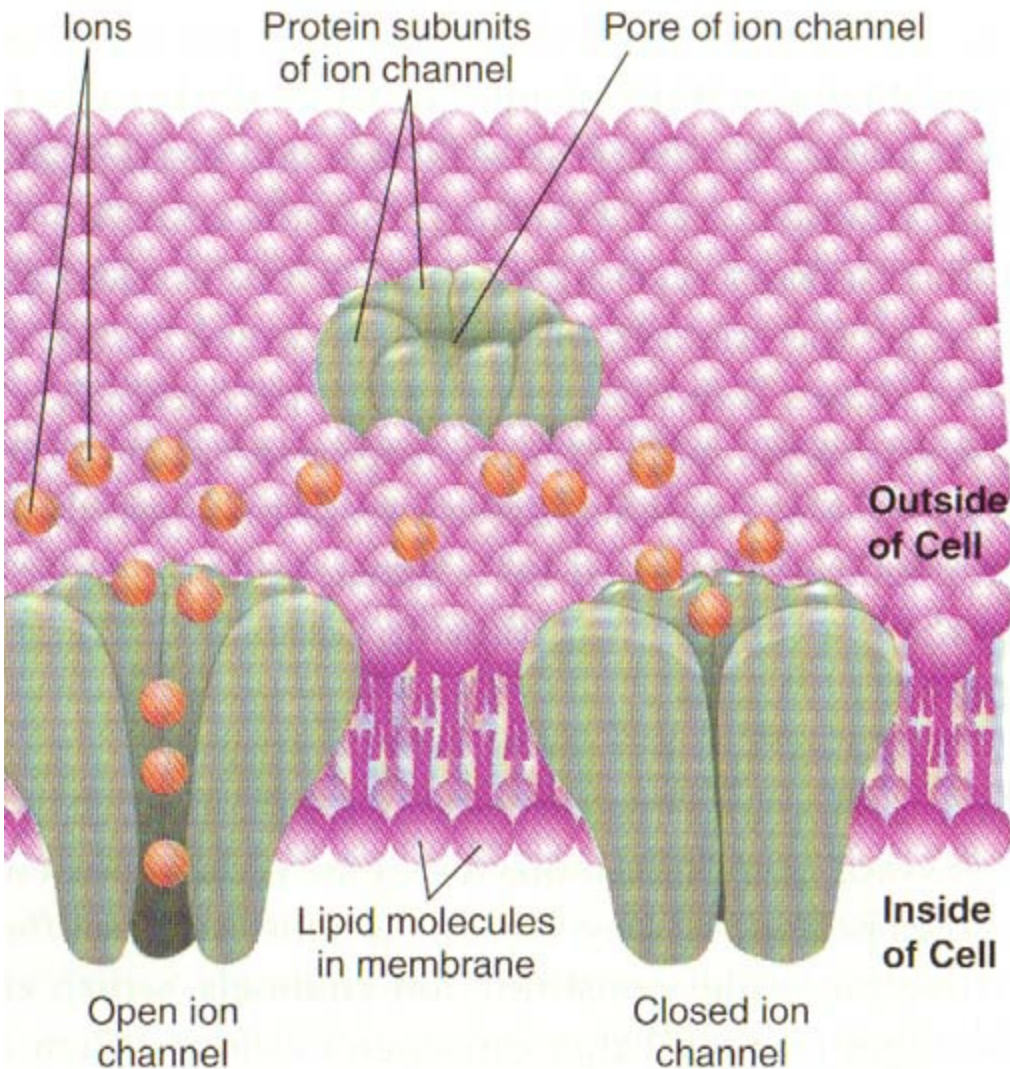
... os **bioreceptores**.



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

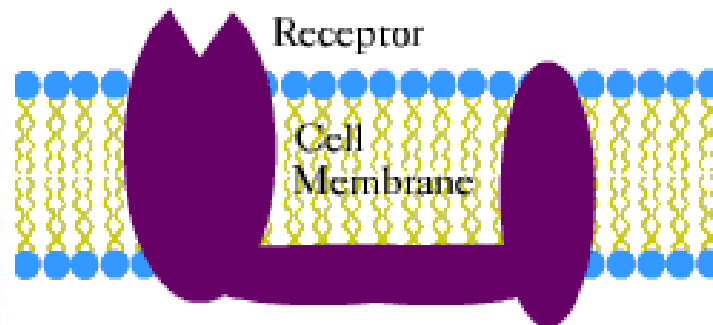


Biorreceptores



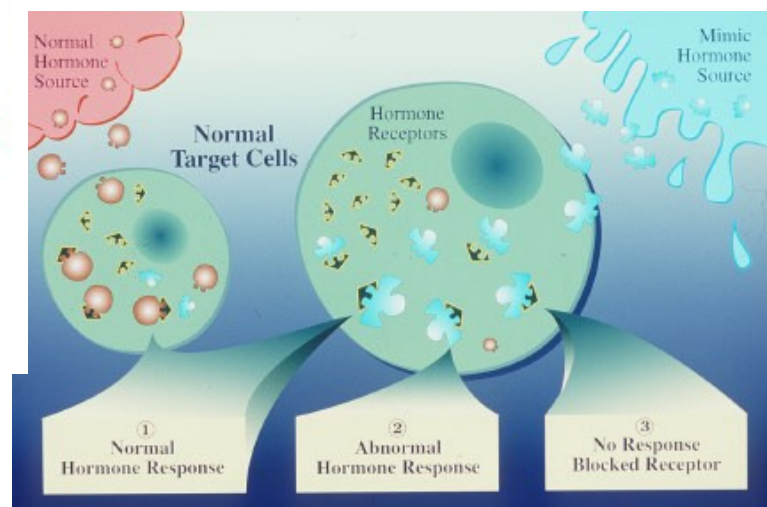
Canais iônicos

Transmembrânicos



Membrânicos

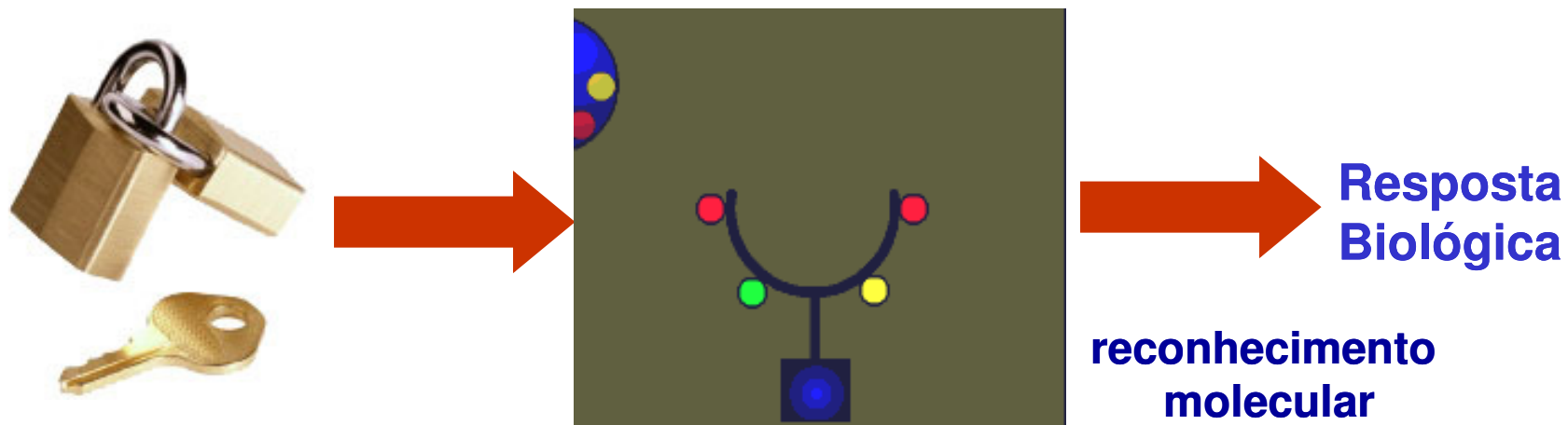
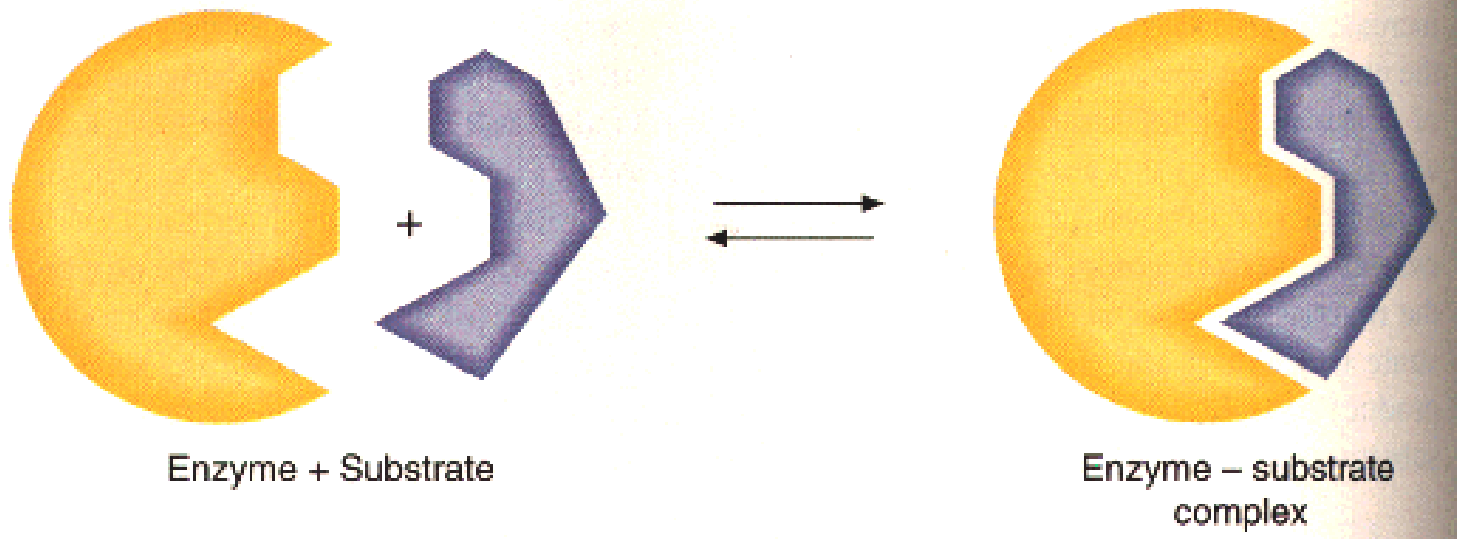
Intracelulares





Modelo Chave-Fechadura

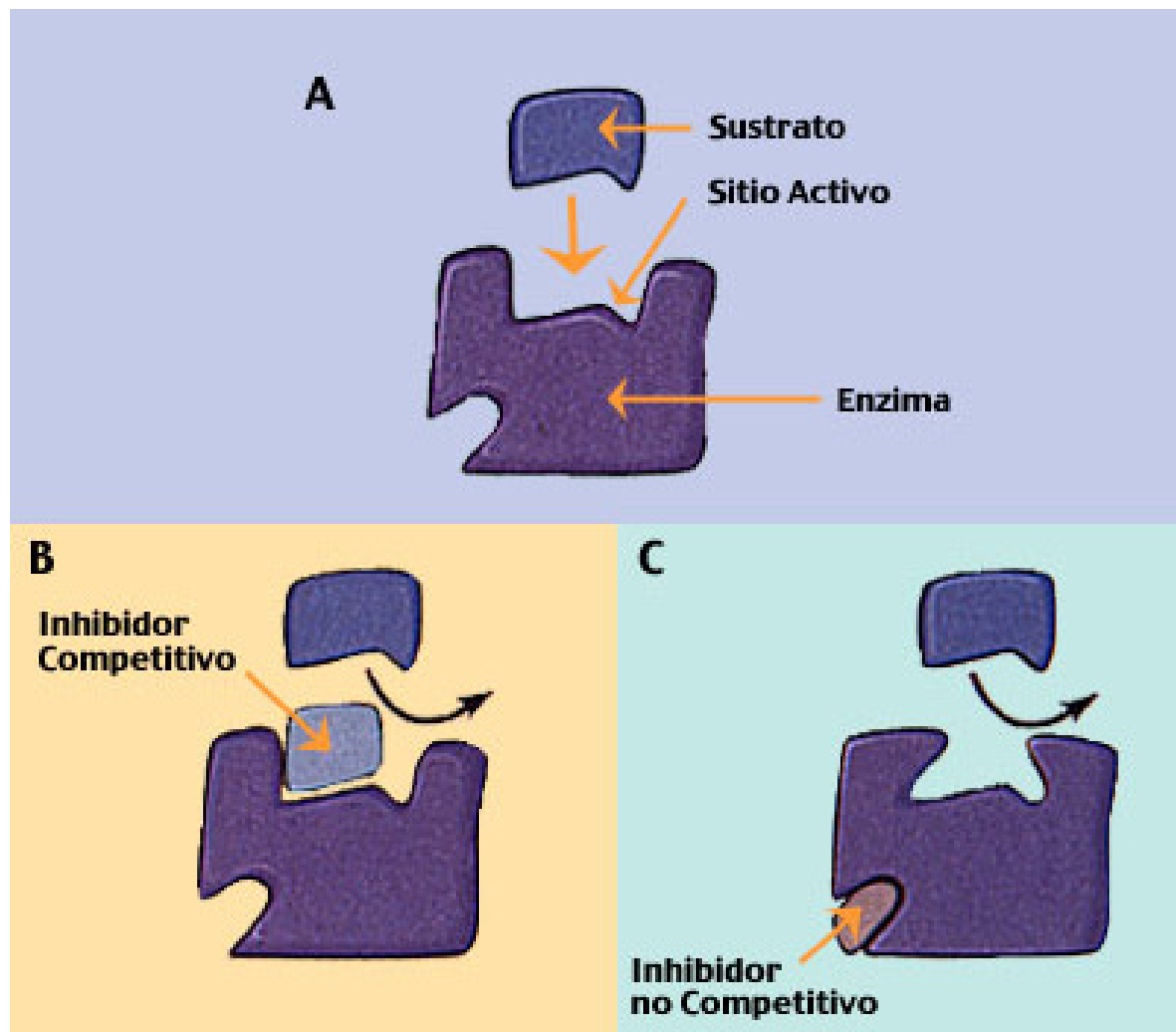
Enzyme Catalysis





Interação Fármaco-Receptor

Inibição Competitiva e Não-competitiva





A maioria dos biorreceptores dos fármacos contemporâneos são enzimas ...

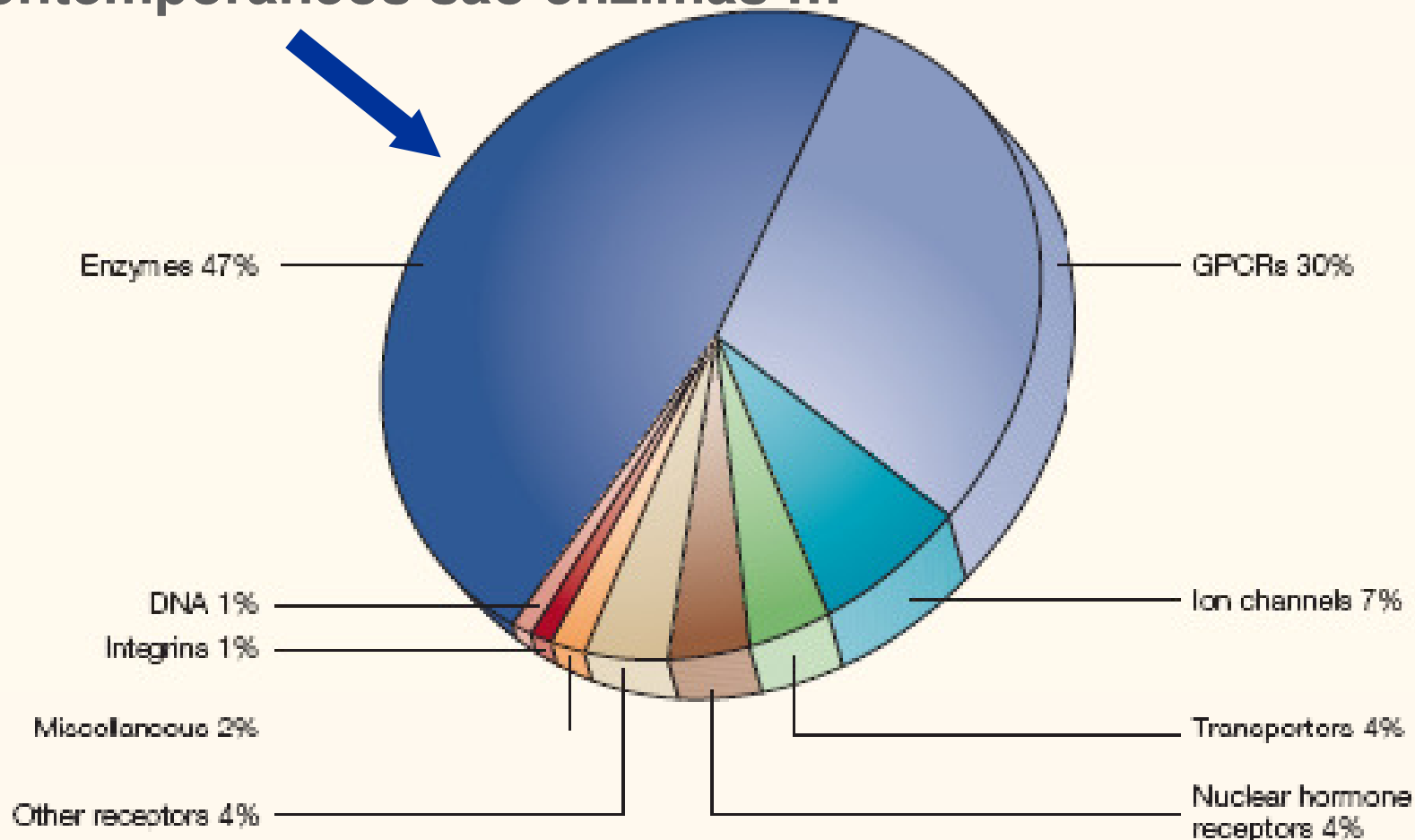
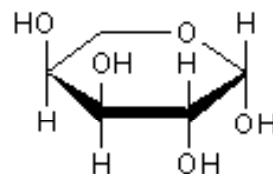
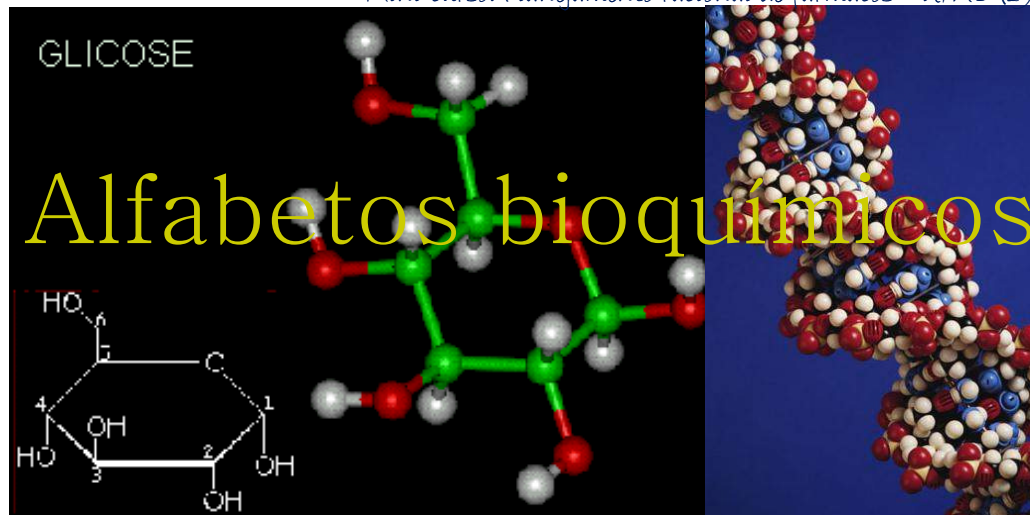
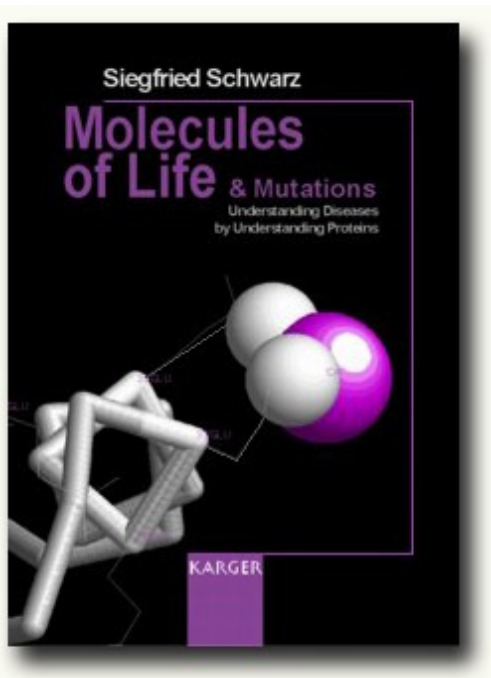


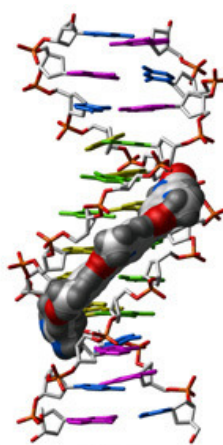
Figure 4 | Marketed small-molecule drug targets by biochemical class. GPCR, G-protein-coupled receptor.

...de apenas 130 famílias distintas de proteínas !





β -L-Arabinose



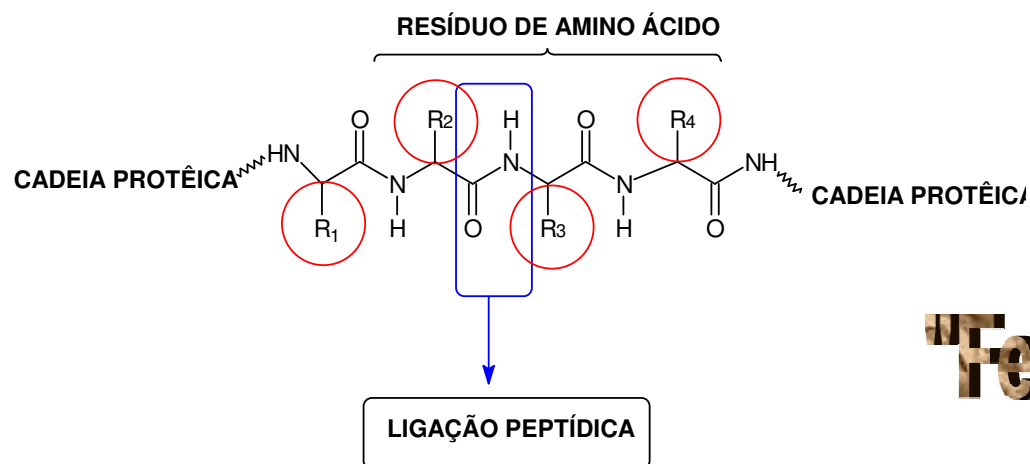
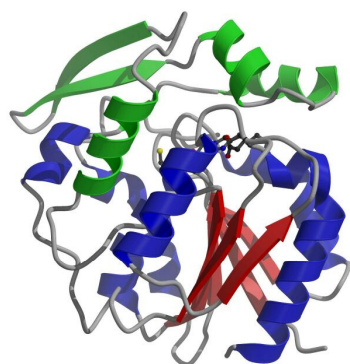
Model Compound Bound to the Minor Groove of a DNA Molecule

Carboídratos
Lípídeos
ácidos nucleícos
proteínas





Estrutura Primária das Proteínas



"Fechadura"

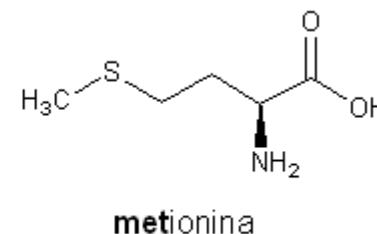
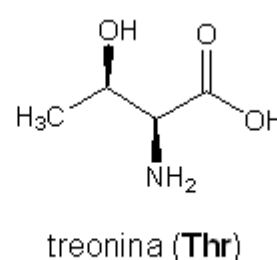
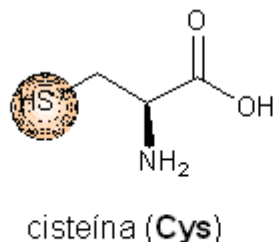
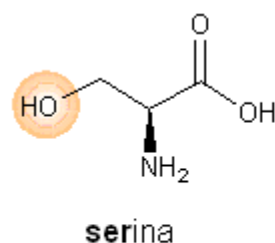
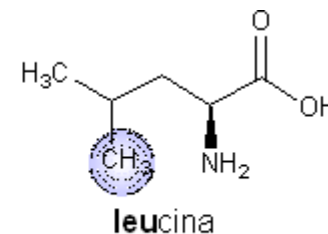
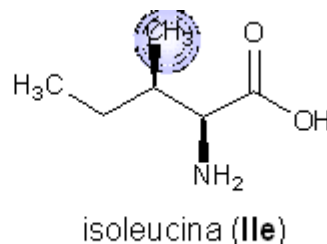
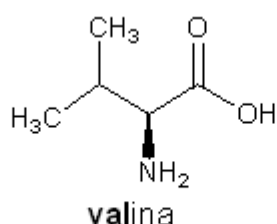
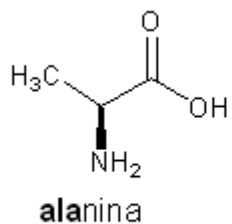
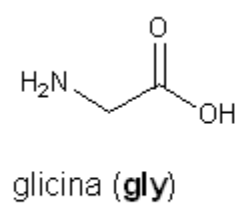
AMINO ÁCIDOS: {
Essenciais: His, Ile, Leu, Lys, Met, Phe, Thr, Trp, Val
Não-essenciais: Ala, Arg, Asn, Asp, Cys, Glu, Gln, Gly, Pro, Ser, Tyr



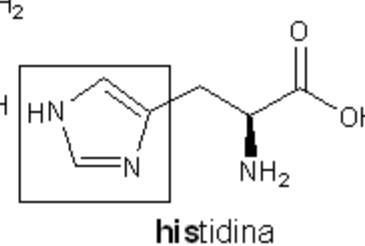
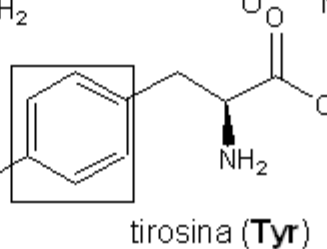
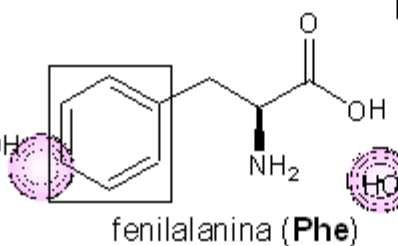
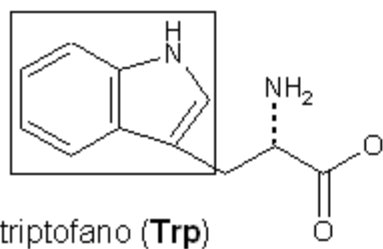
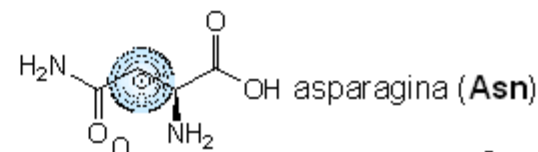
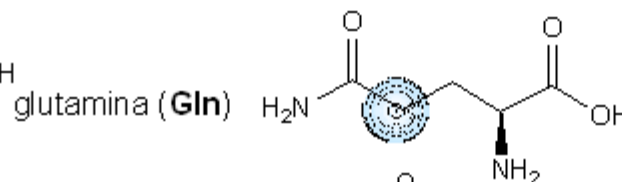
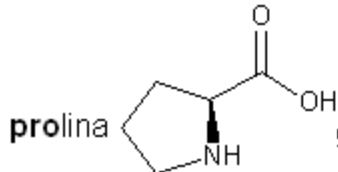
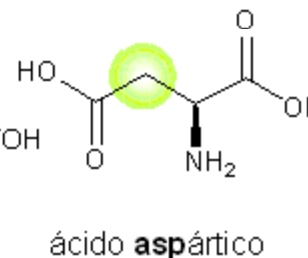
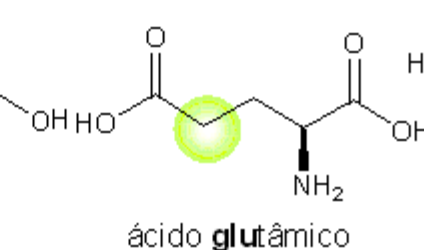
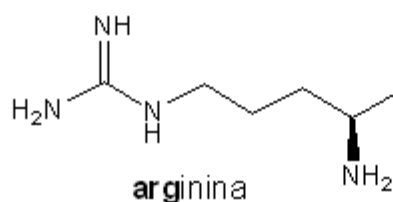
...a maioria dos biorreceptores de fármacos são proteínas !



O "alfabeto" protéico ...



lisina (**Lys**)





A quimiodiversidade na natureza...

20 amino-ácidos essenciais

400 dipeptídeos

8.000 tripeptídeos...

64.000.000 hexa peptídeos

10^{400} proteínas com PM ~ 30 kD



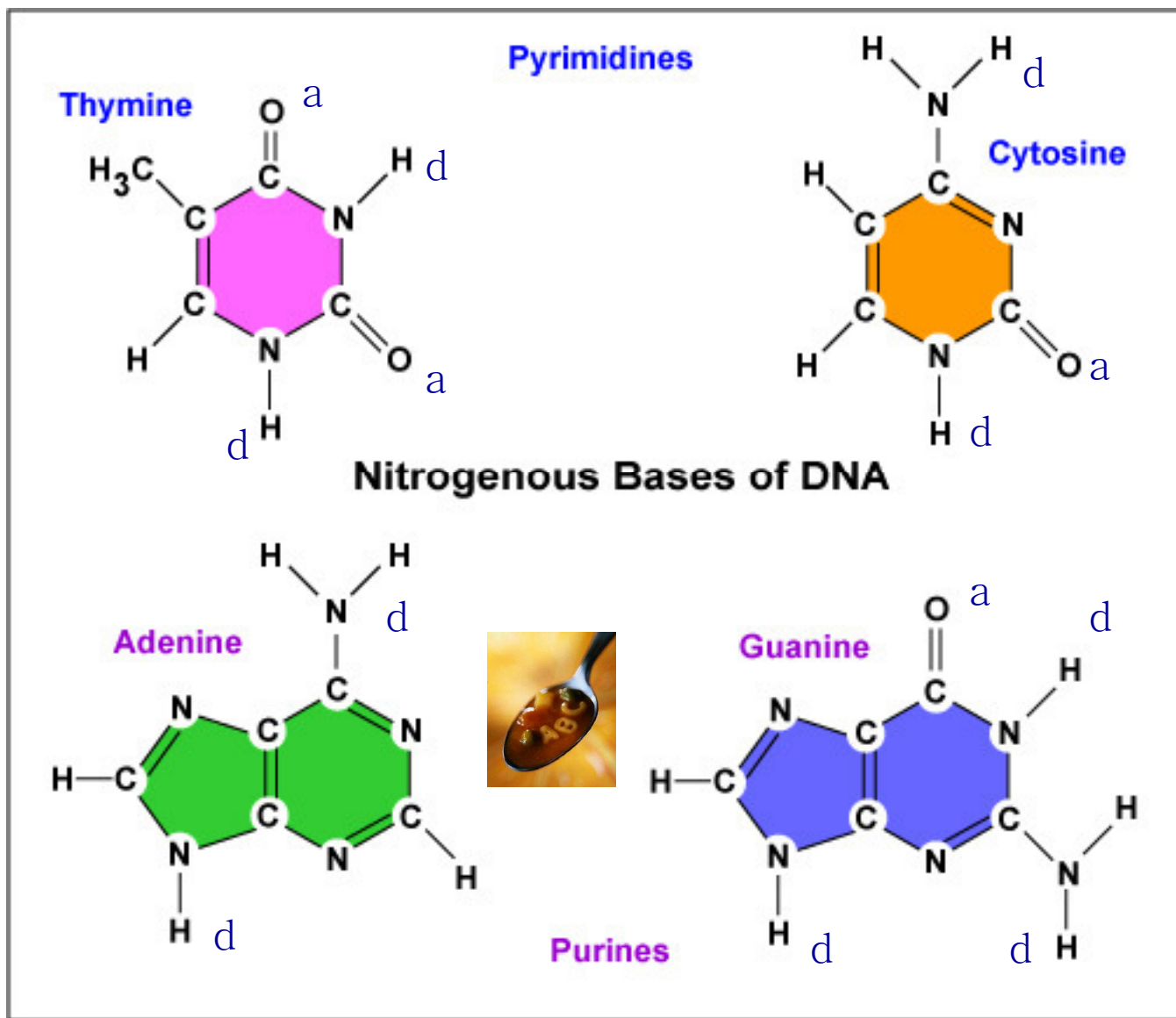
100 amino-ácidos modificados

ca. 1.000.000.000.000 hexapeptídeos...

... e apenas 4 bases nucleicas codificam todos os organismos !

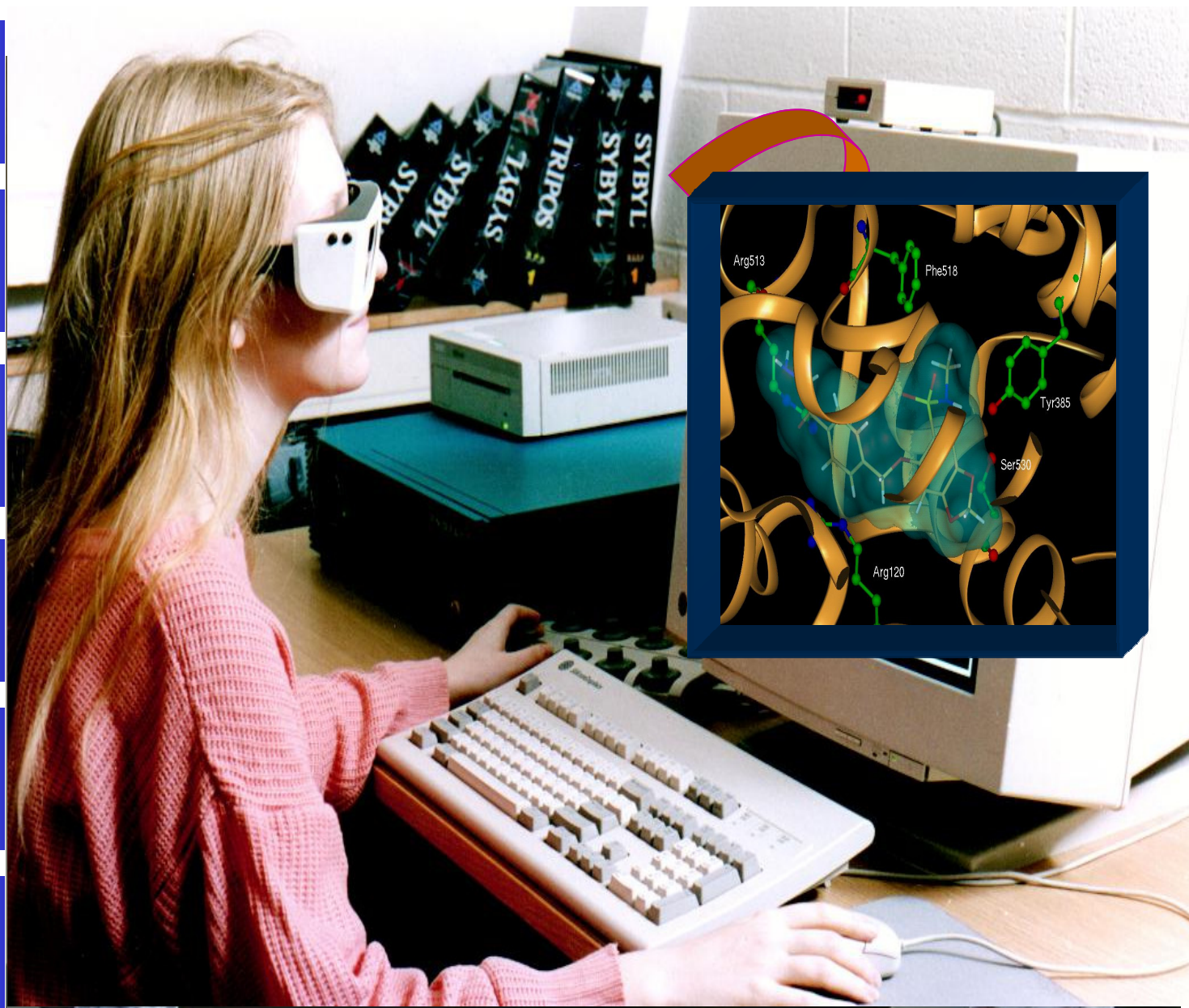
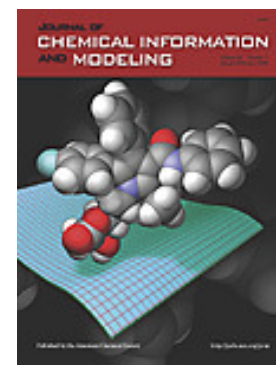


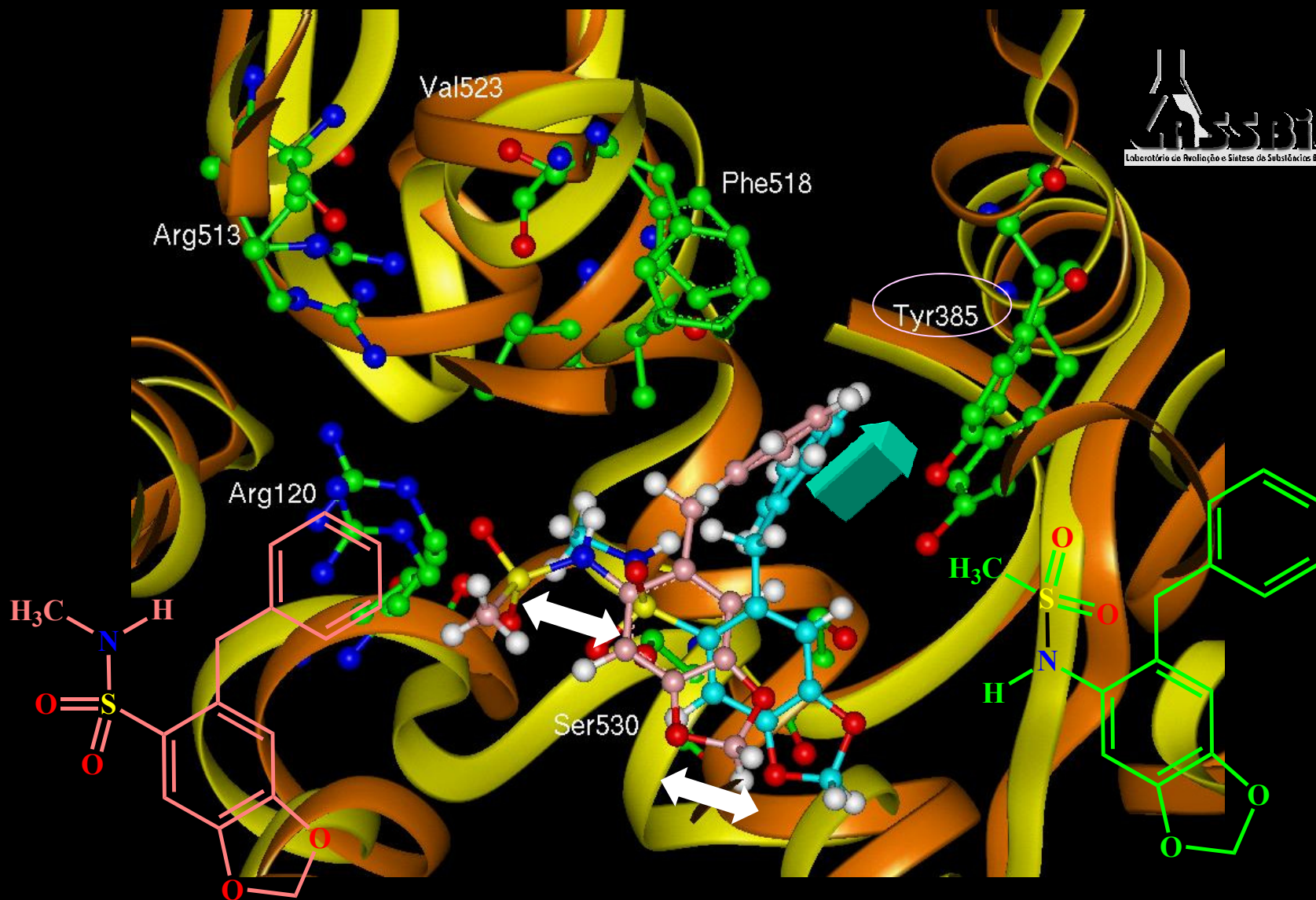
“ligações” de hidrogênio ...



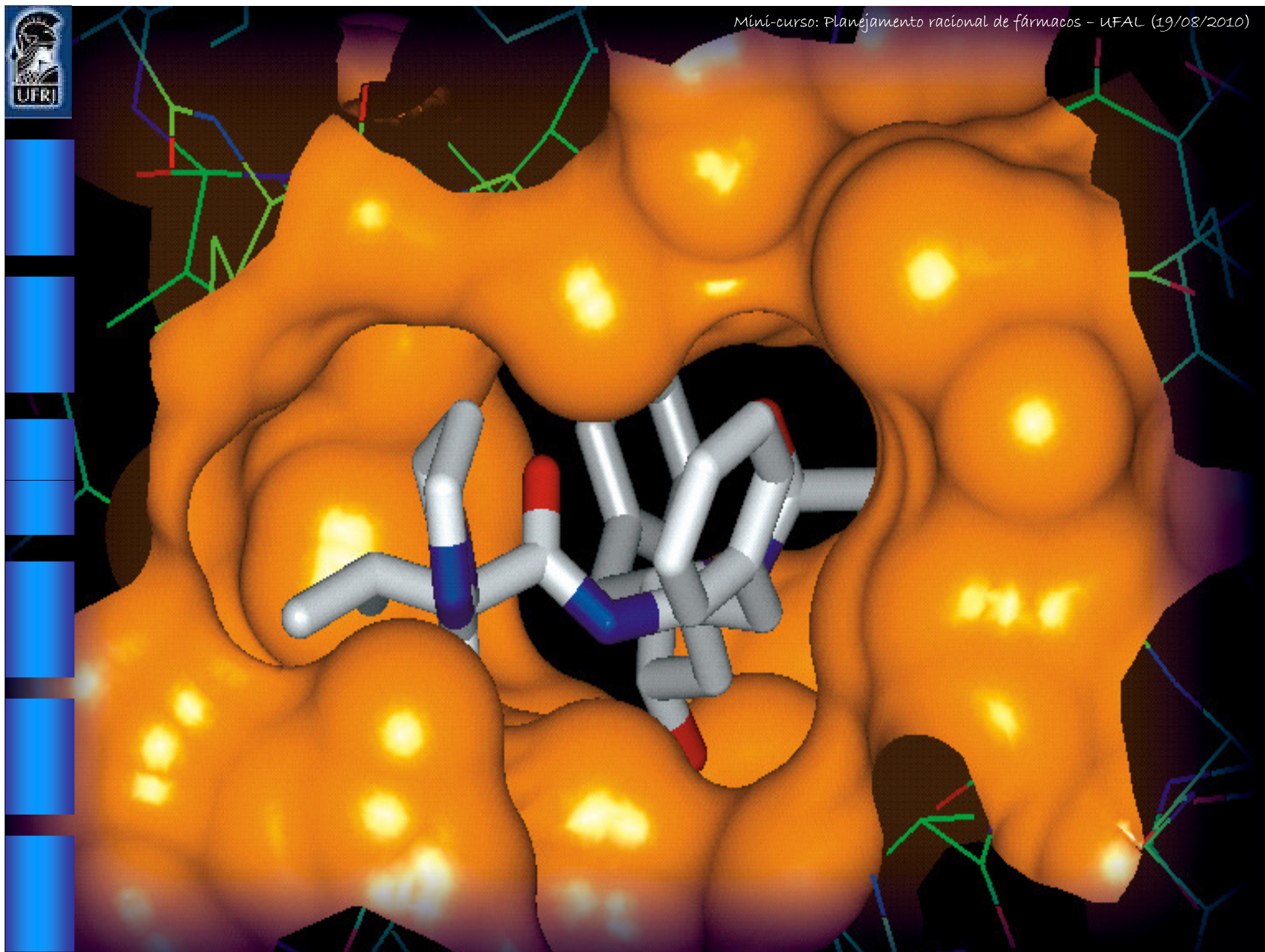


Bioformática





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



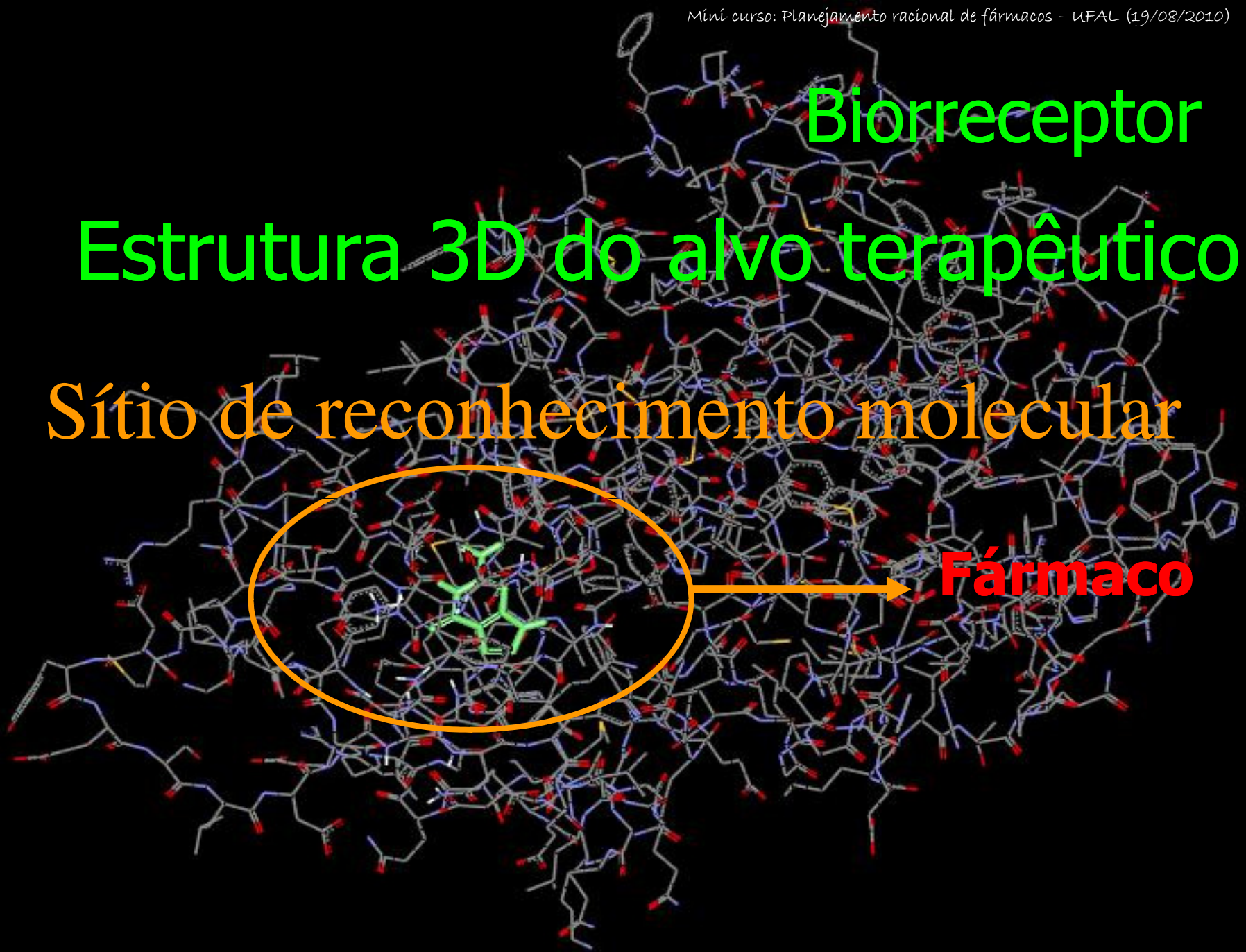


Biorreceptor

Estrutura 3D do alvo terapêutico

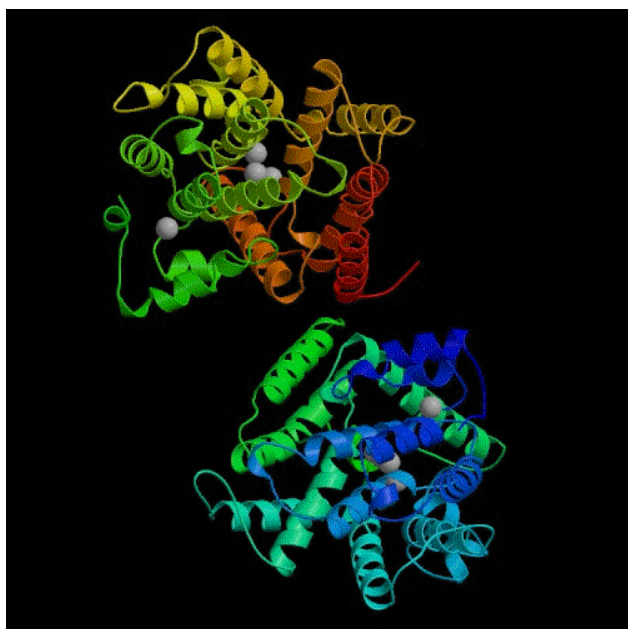
Sítio de reconhecimento molecular

Fármaco





Estruturas cristalográficas disponíveis no PDB

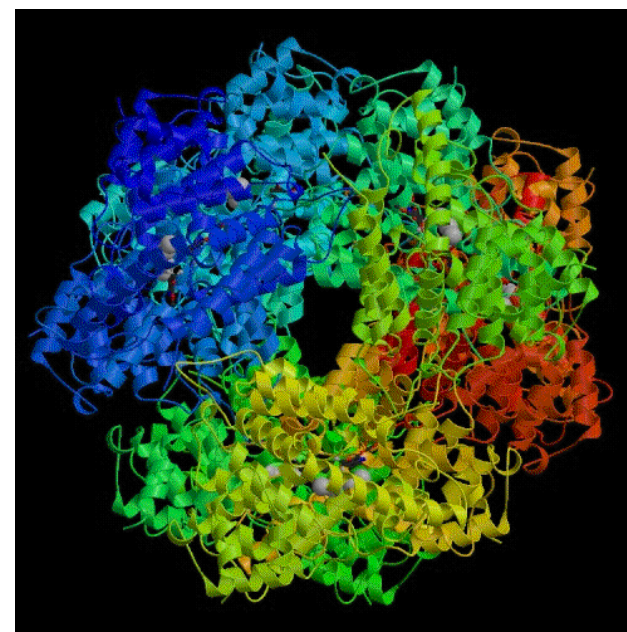


PDE4B - 1F0J

351 resíduos

Metodo: Difração de Raio-X

Resolução: **1.77 Å**

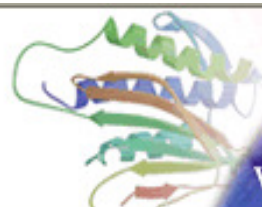


PDE4D - 1MKD

328 resíduos

Metodo: **Difração de Raio-X**

Resolução: **2.90 Å**



Access the PDB FTP:

[RCSB PDB](#) | [PDBe](#) | [PDBj](#)

[Archive Download](#)

[Chemical Component Dictionary](#)

Deposit Data to the PDB:

[RCSB PDB](#) | [PDBe](#)

[PDBj](#) | [BMRB](#)

Search for Structures:

[RCSB PDB](#) | [PDBe](#)

[PDBj](#) | [BMRB](#)

PDB Archive Snapshots:

[RCSB PDB](#) | [PDBj](#)

Instructions to Journals

Documentation

[Format](#)

[Annotation and Policies](#)

The Worldwide Protein Data Bank (wwPDB) consists of organizations that act as deposition, data processing and distribution centers for PDB data. The founding members are **RCSB PDB** (USA), **PDBe** (Europe) and **PDBj** (Japan)¹. The **BMRB** (USA) group joined the wwPDB in 2006. The mission of the wwPDB is to maintain a single Protein Data Bank Archive of macromolecular structural data that is freely and publicly available to the global community.

This site provides information about services provided by the individual member organizations and about projects undertaken by the wwPDB.

wwPDB Statement on Retraction of UAB PDB Entries

16-December-2009

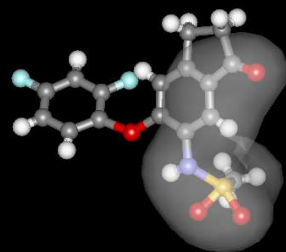
Coordinated wwPDB Release of Data

The PDB archive can be accessed at FTP sites at the RCSB PDB, PDBe, and PDBj. The update schedules for these sites have been coordinated to be simultaneous. All updates now occur at the target time of Wednesday 00:00 UTC (**Coordinated Universal Time**).

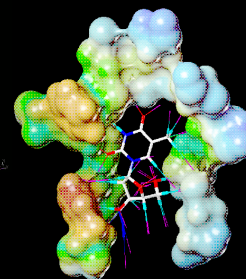
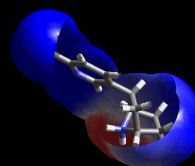
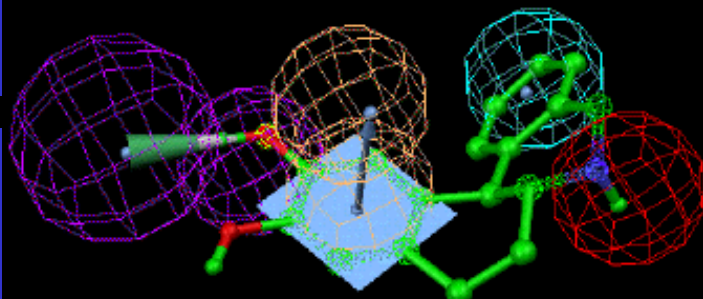
There is no change to the timeline for structure release requests. Any author correspondence required to release a PDB entry should be sent to the appropriate wwPDB member site by 12 noon local time on Thursdays in order for the entry to be prepared for release. This correspondence (which can include citation information, responses to outstanding issues, etc.) should be sent to:



Química Medicinal



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





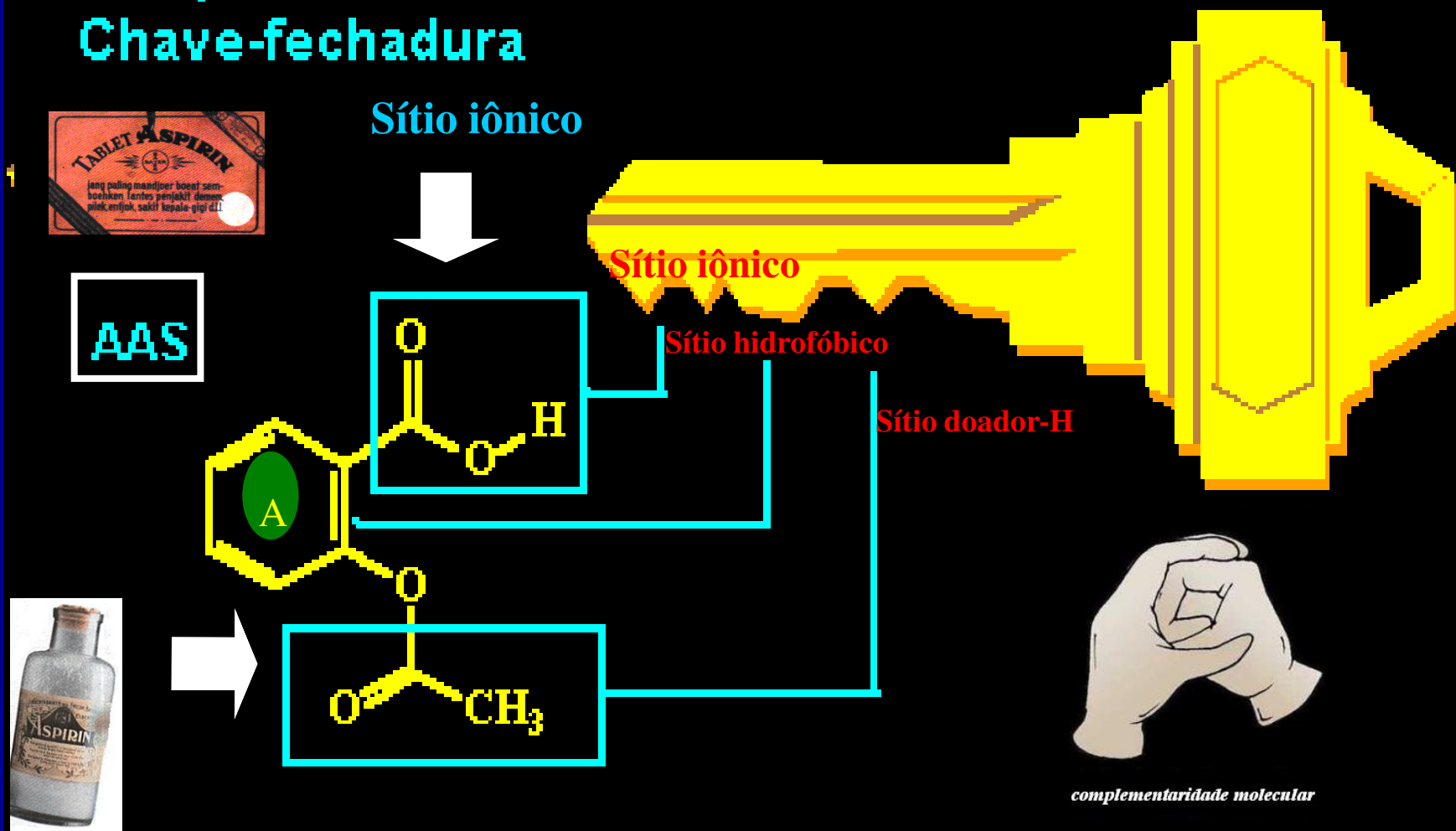
O modelo
Chave-fechadura
As chaves...





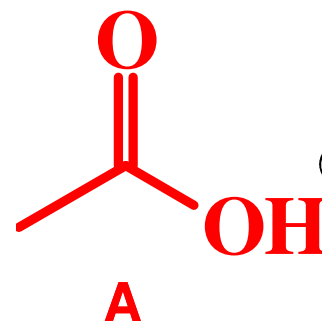
O Centenário Modelo "Chave-Fechadura"

Complementaridade do modelo Chave-fechadura

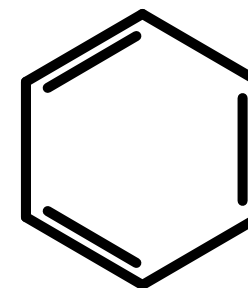
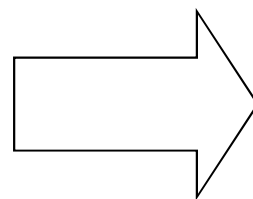
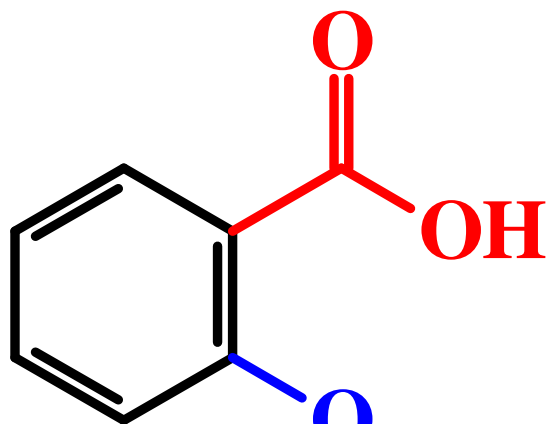




Dissecação Molecular



ácido carboxílico

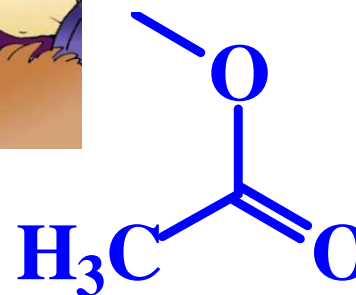
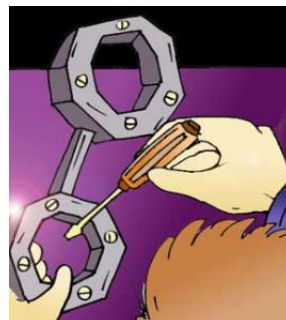


B

fenila



Ácido acetilsalicílico

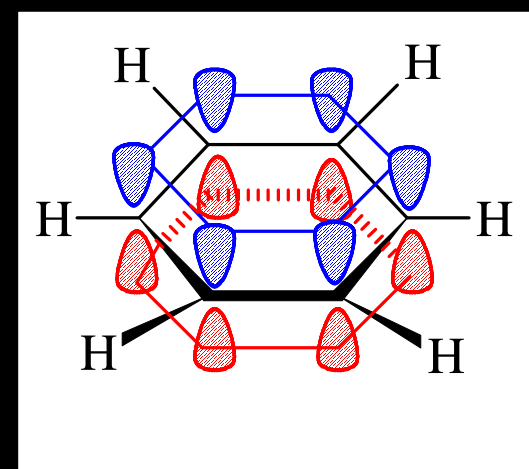
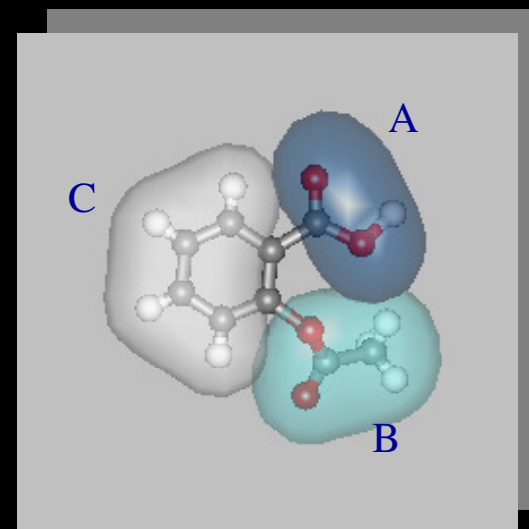
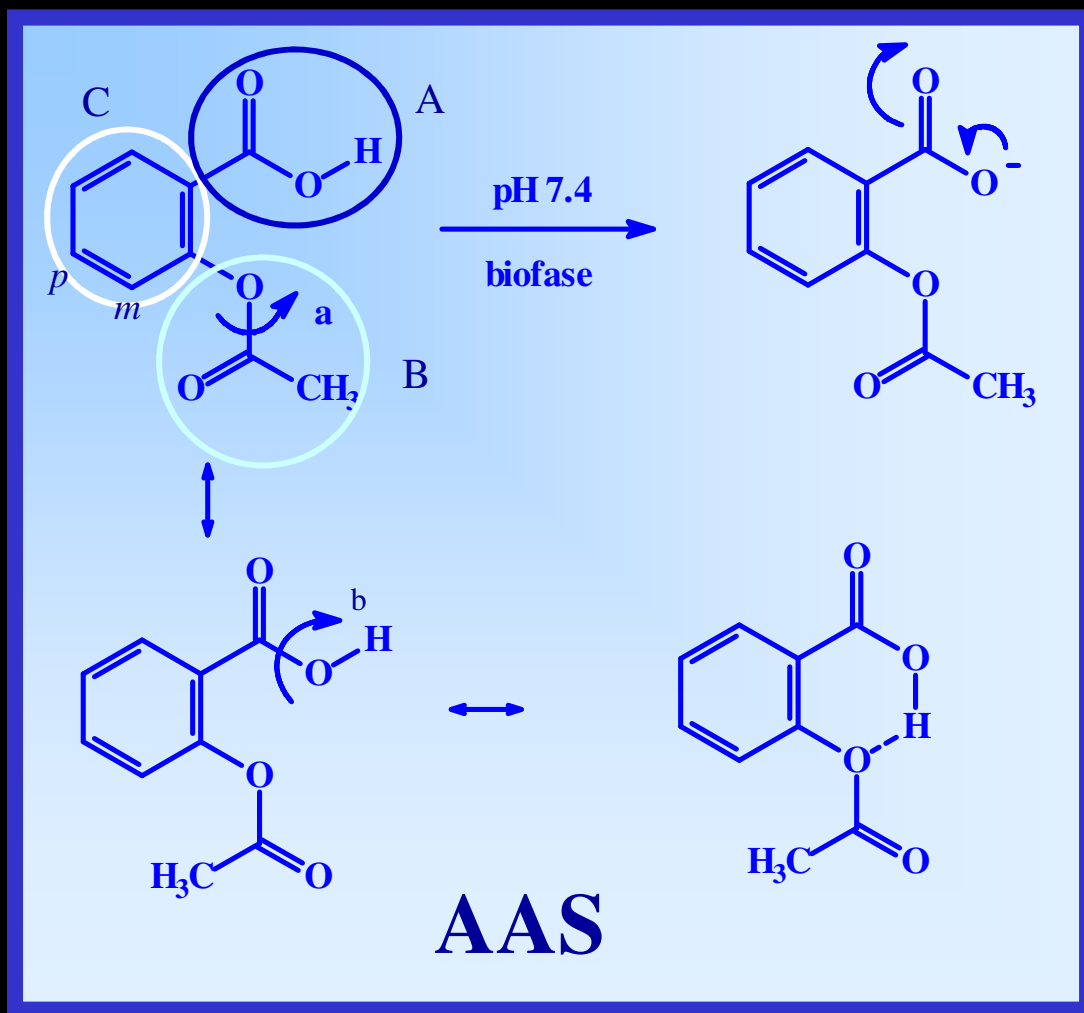


éster

C

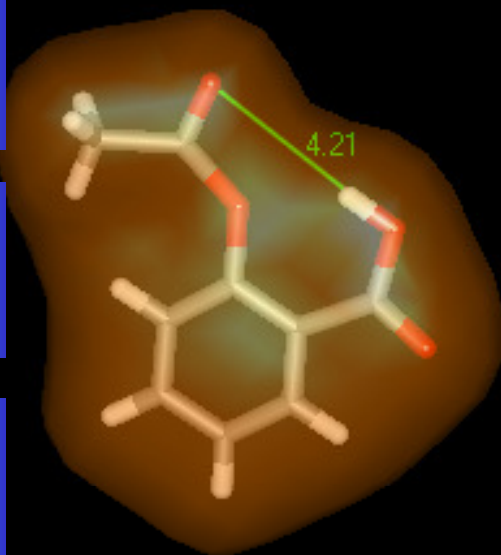


A hierarquia dos grupos funcionais

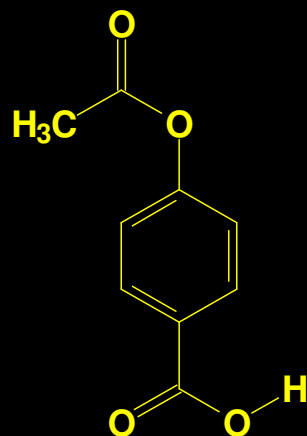
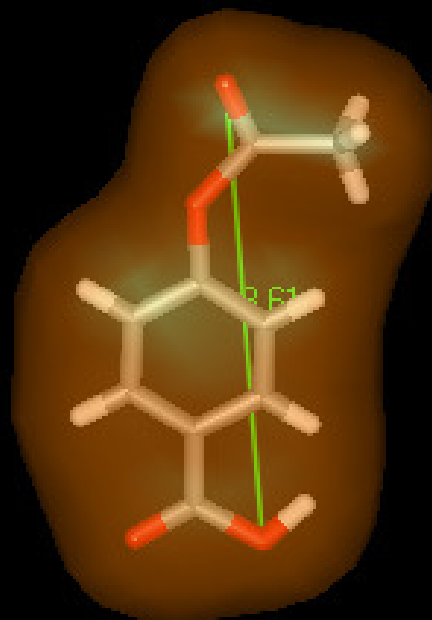




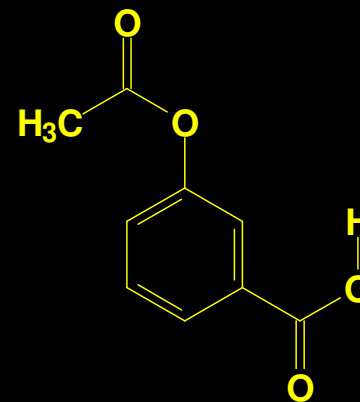
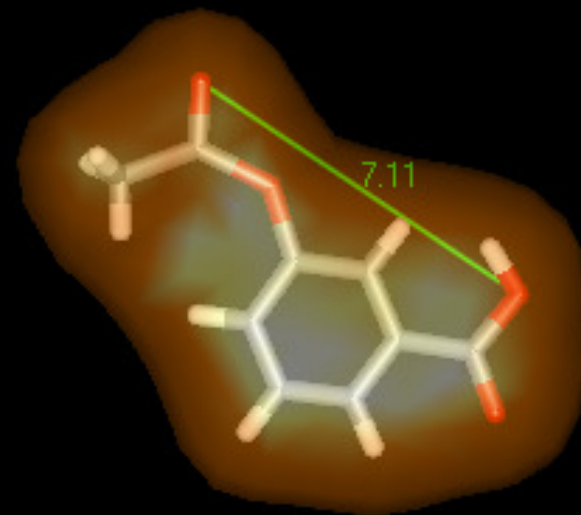
Regioisomêros do ácido acetil salicílico (AAS)



orto



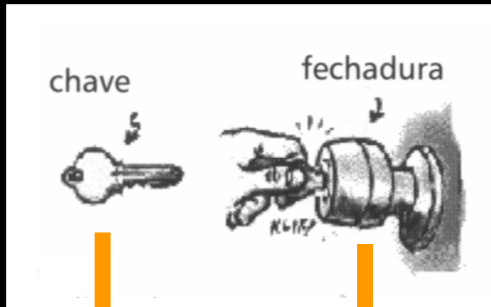
para



meta

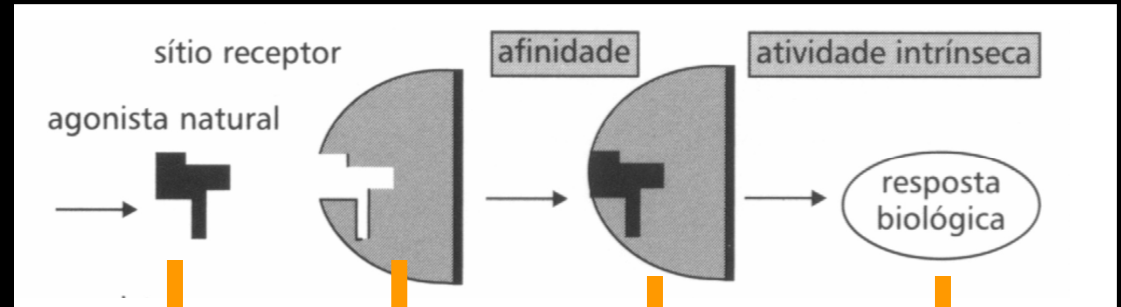


O Centenário Modelo "Chave-Fechadura"



Fármaco
Substrato
natural

Enzima
= Alvo
terapêutico

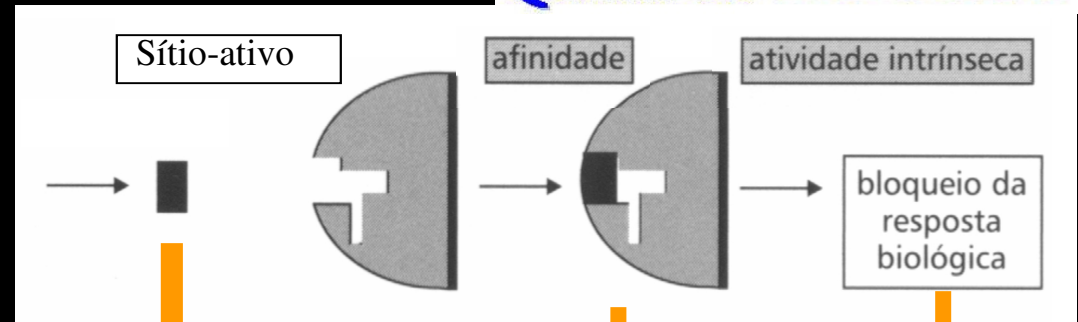


Ácido
araquidônico

PGHS-1
PGHS-2
icosanóide

PGE₂
inflamação

Química Medicinal



Inibidor: AAS

PGHS-2
PGHS-1

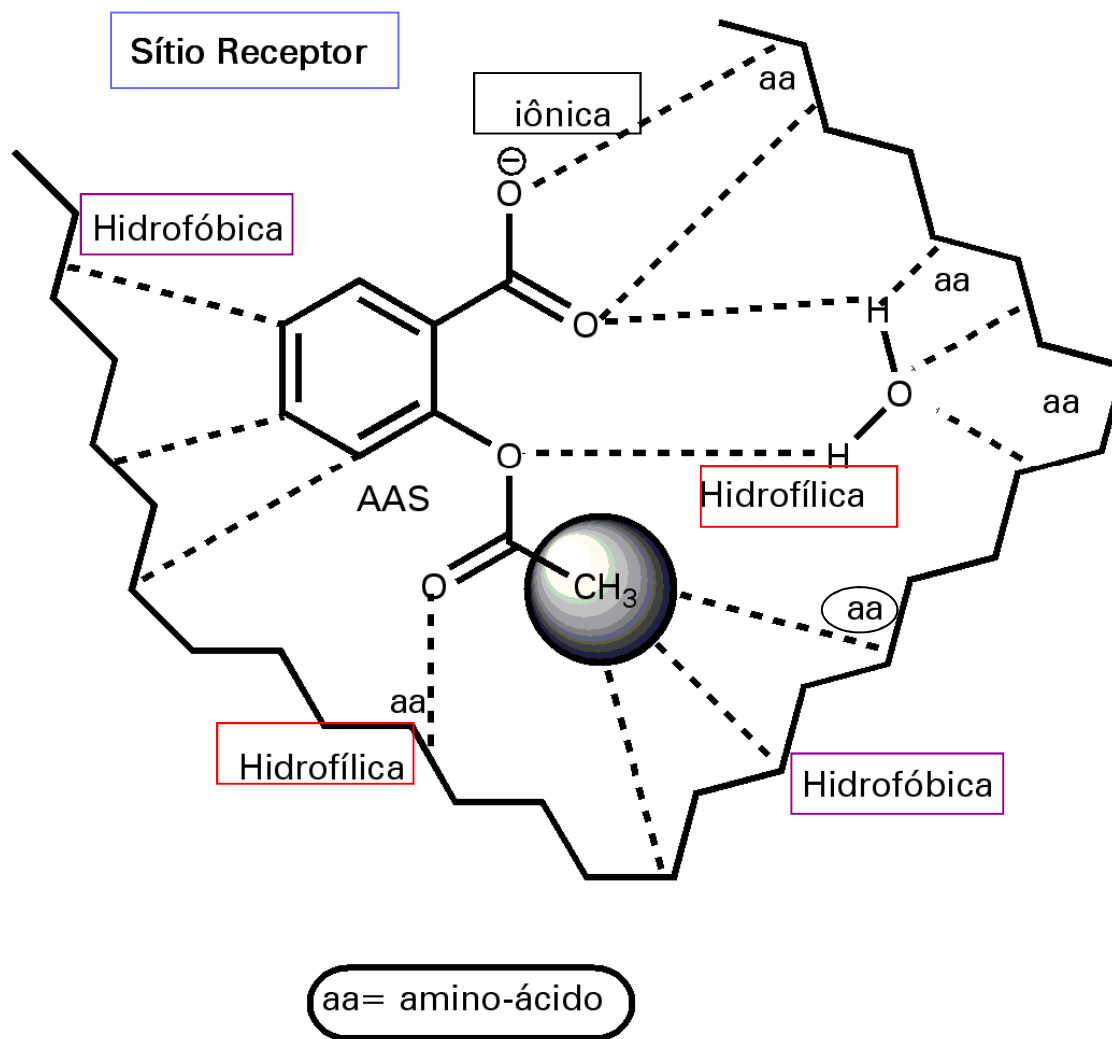
NSAI

NSAI = antiinflamatórios não-esteróides





Modêlo topográfico das interações AAS-R





Interação Fármaco-Receptor

Modelo "Chave-Fechadura"

"Fechadura"




?

"Chaves"



Reconhecimento
Molecular

Complementaridade
Molecular



A biofase...
(PK)



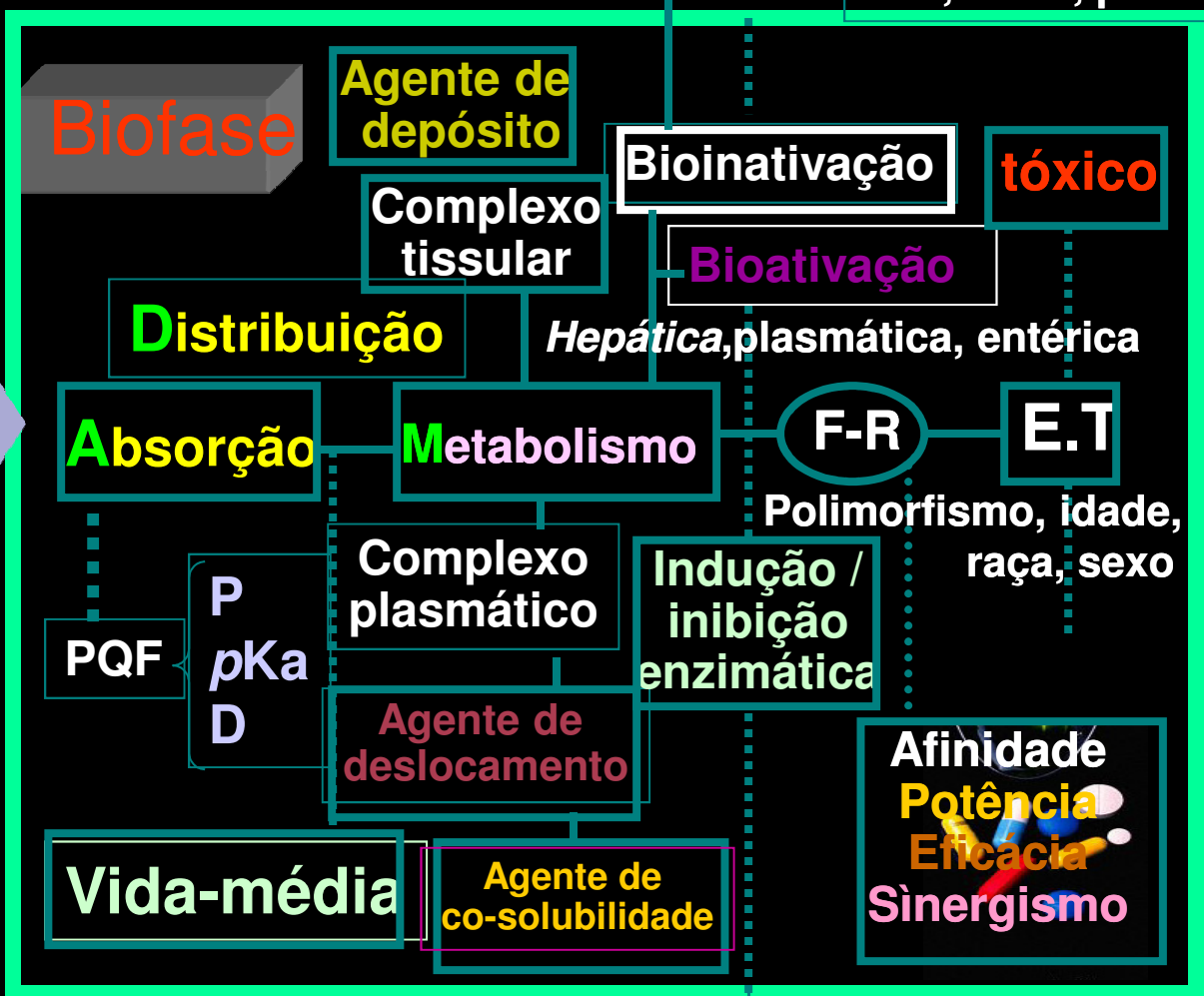
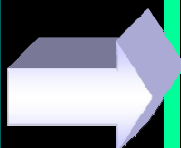
Medicamento

Química Medicinal

F
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Fase farmacêutica

F
O
R
M
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A
Ç
ÃO



Fármaco

Fase farmacocinética (ADME)

Fase farmacodinâmica



Laboratório de Avaliação e Síntese de Substâncias Bioativas

Obrigado!

Corcovado, uma das sete maravilhas do mundo contemporâneo