



# Fármacos:

# O papel da Química Medicinal



XXII Semana Acadêmica de Química - UFF



Aula 4

**UFRJ**

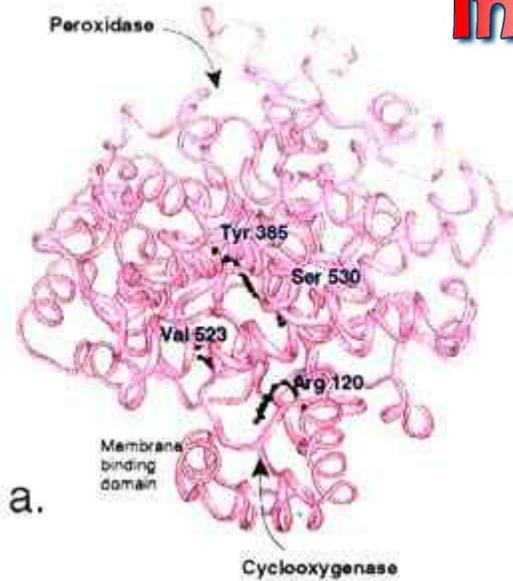
Eliezer j. Barreiro

Professor Titular

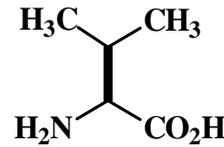




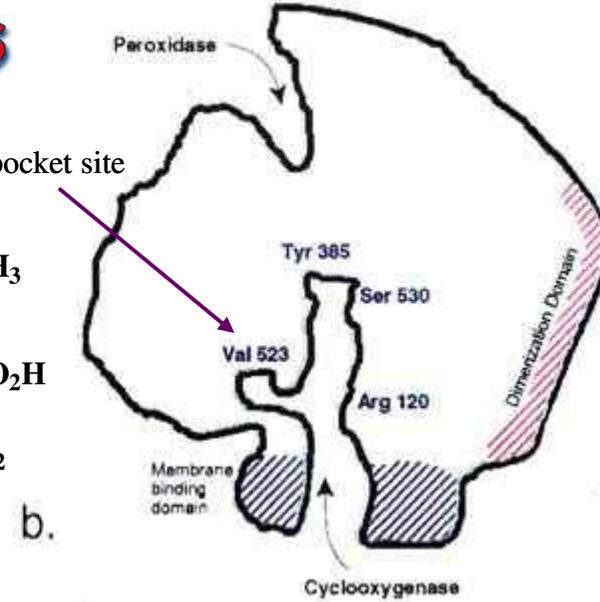
# COX-2 Inhibitors



Secondary pocket site



C<sub>5</sub>H<sub>11</sub>NO<sub>2</sub>  
Valina



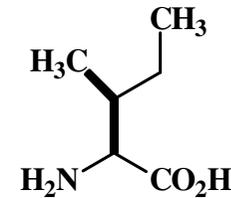
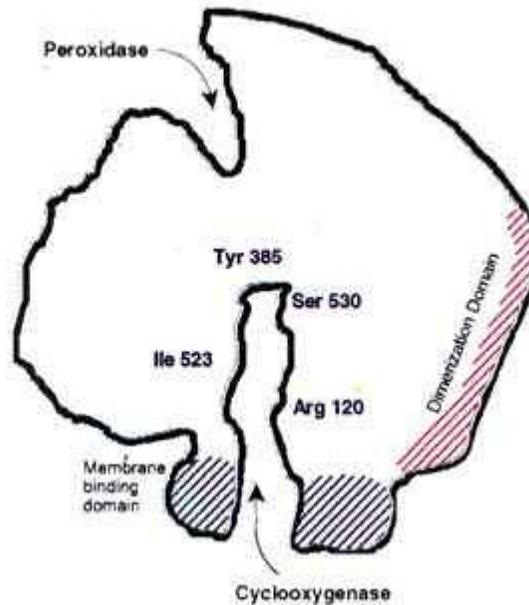
# COX-2

Inflamação,  
Câncer  
Endotélio vascular  
Rins  
Cérebro

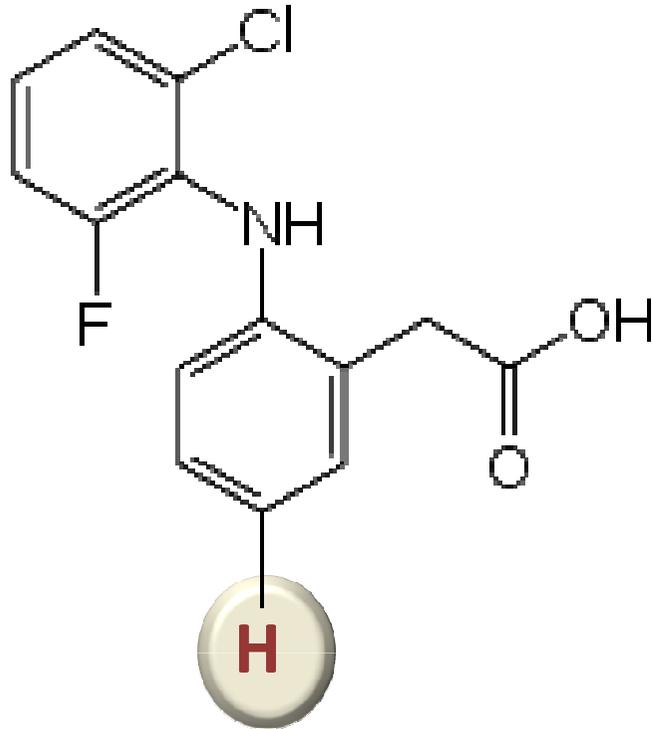
# COX-1

Plaquetas,  
Estômago,  
Rins

c.



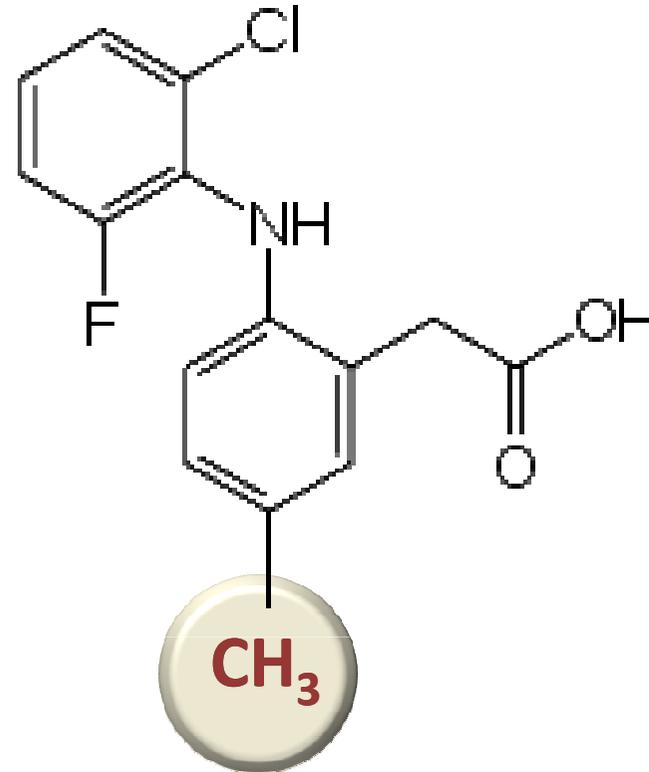
C<sub>6</sub>H<sub>13</sub>NO<sub>2</sub>  
Isoleucina



Diclofenaco



COX-1 >>>>> COX-2

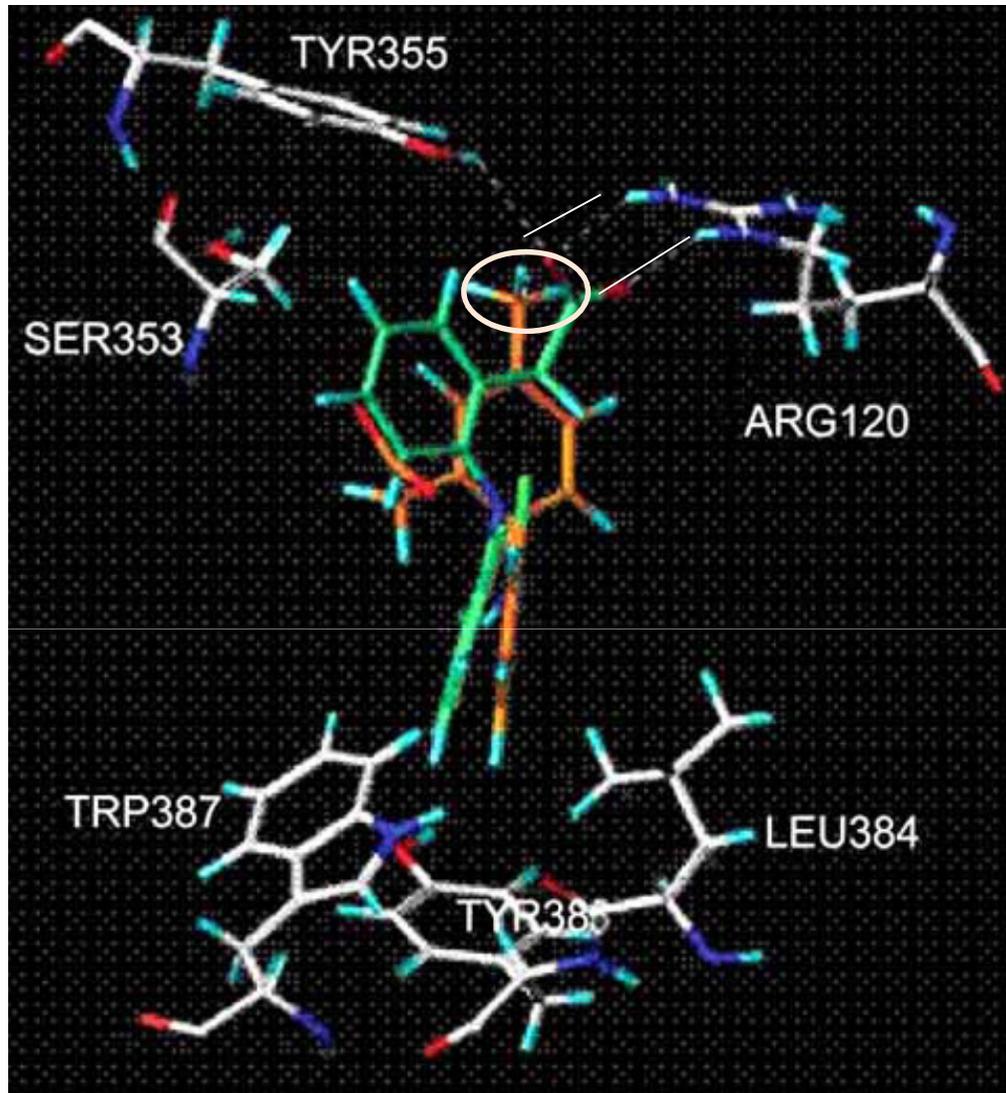
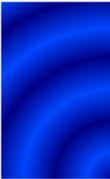
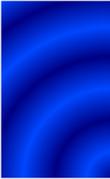


Lumiracoxibe

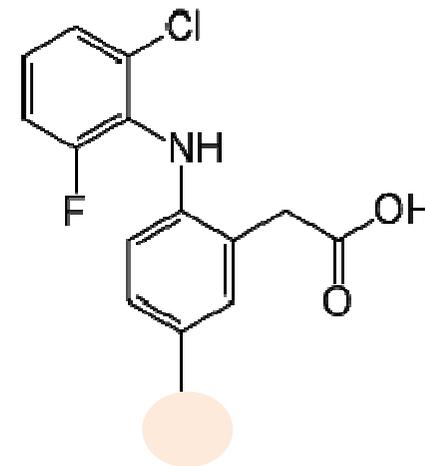
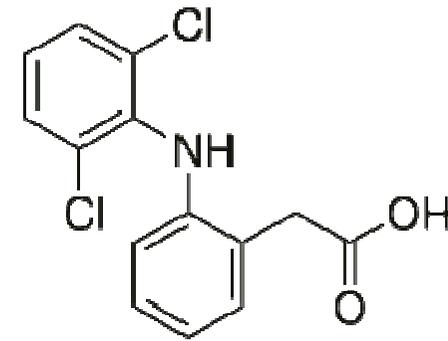


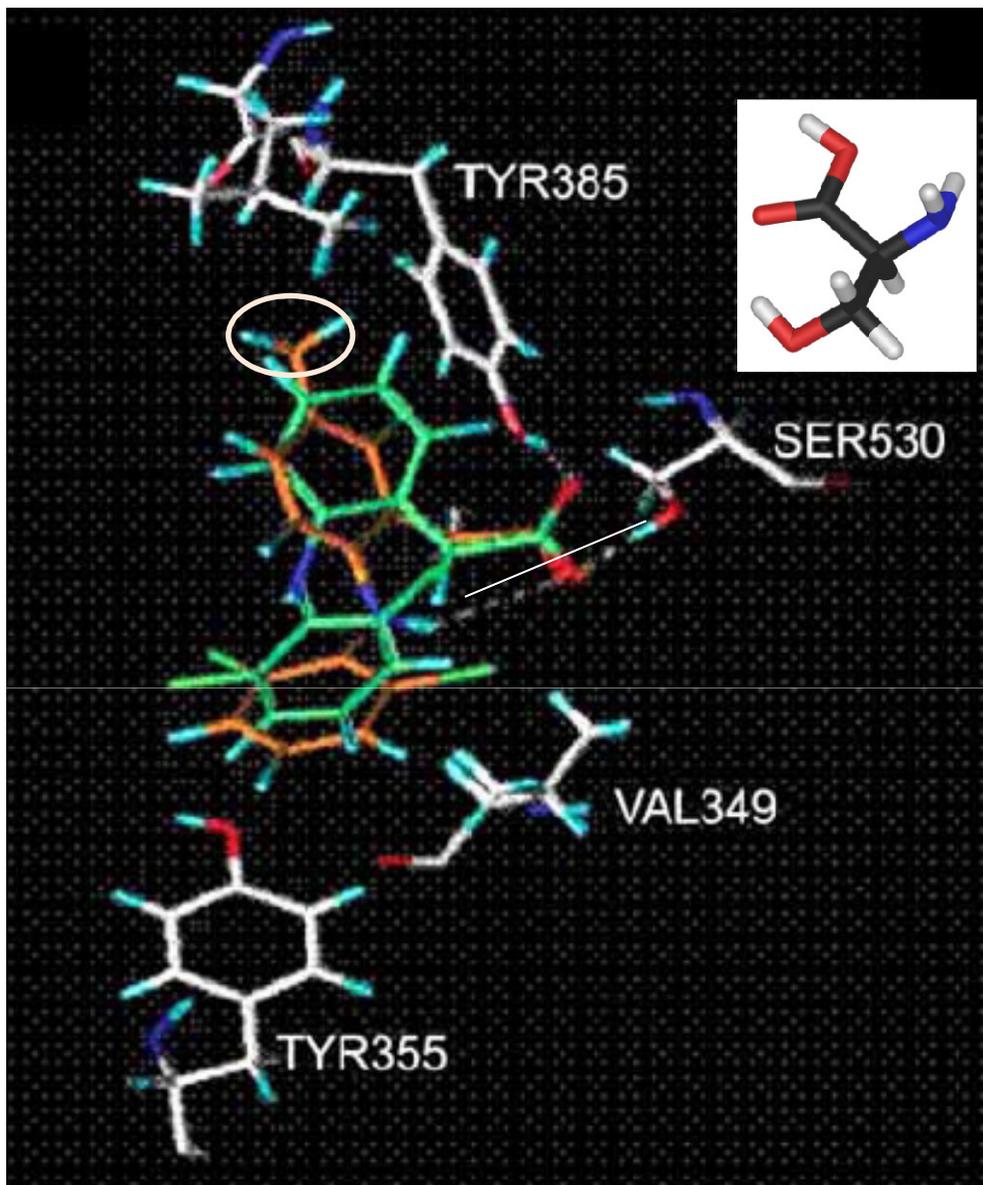
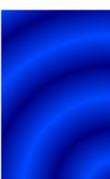
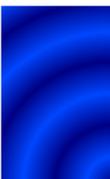
COX-2 > COX-1

O incrível efeito de um *inteligente* grupo metila !

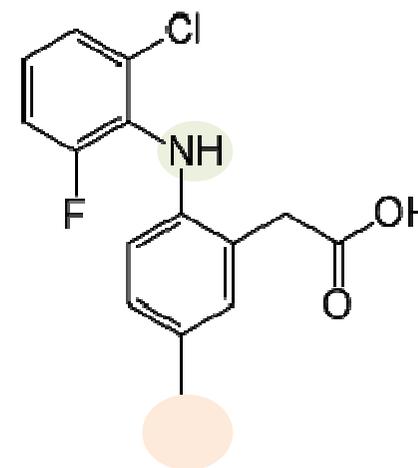
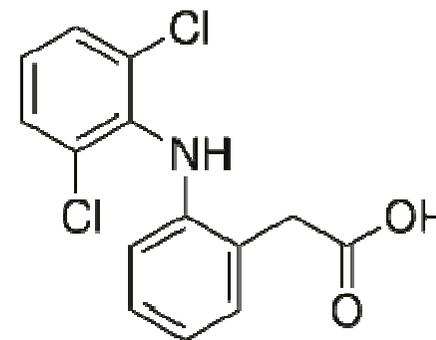


COX-1 active site with lumiracoxib  
and diclofenac (green)

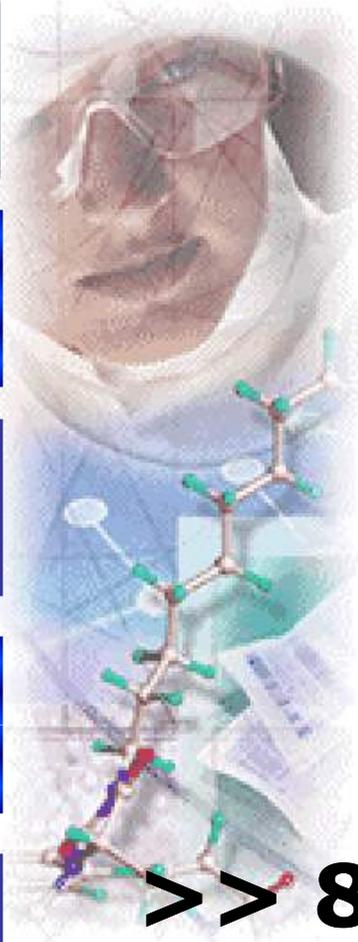




COX-2 active site with lumiracoxib  
and diclofenac (green)



C. M. Corrêa, A.F. de Paula, G. M.S. da Silva, C. M.R. Sant'Anna, C.A. M. Fraga, E.J. Barreiro, *Letters in Drug Design & Discovery*, **2007**, 4, 422



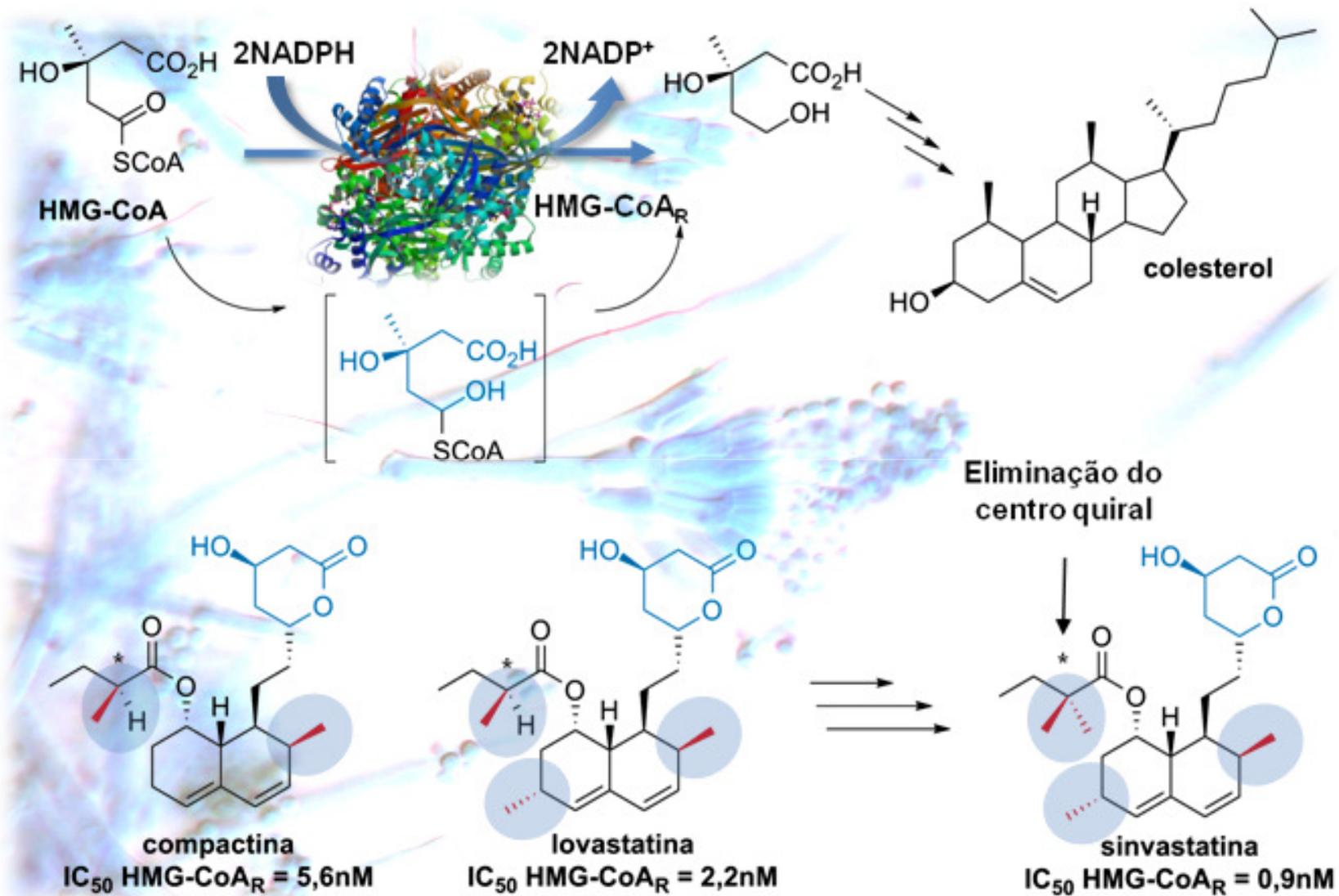
# *Os fármacos: sintéticos ...*

**>> 85% do arsenal terapêutico  
são de fármacos sintéticos**



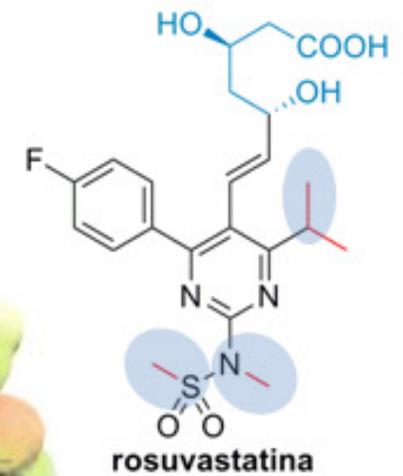
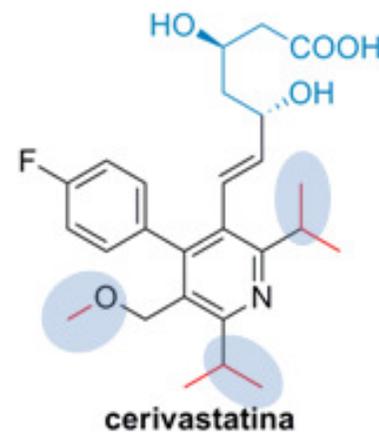
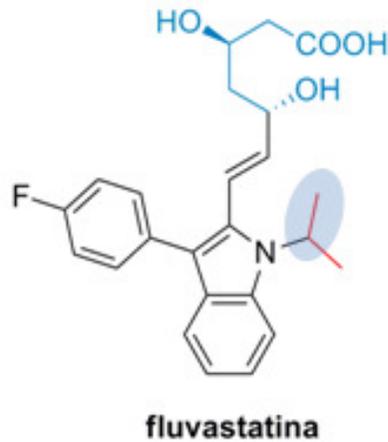
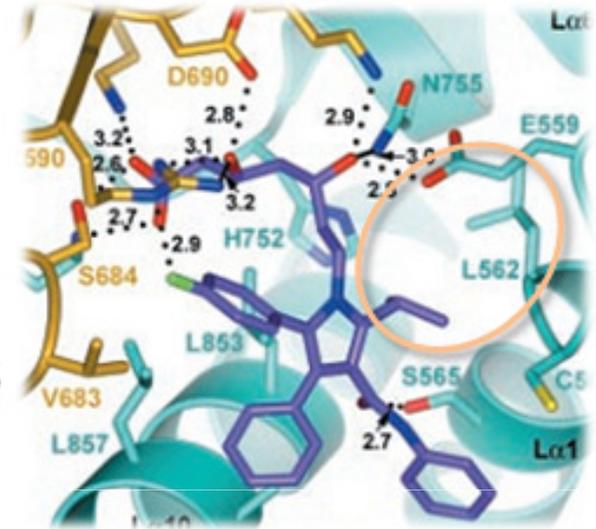
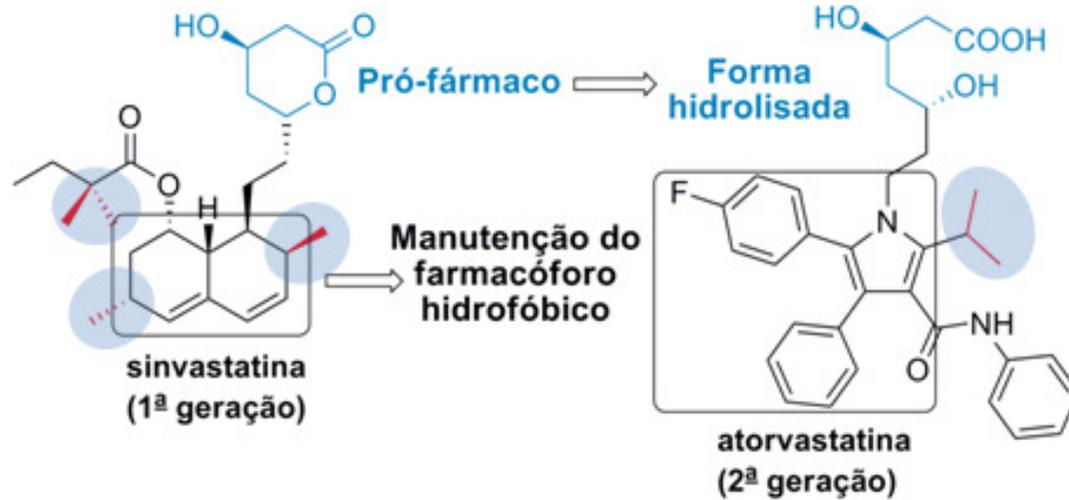


# Estatinas (1)



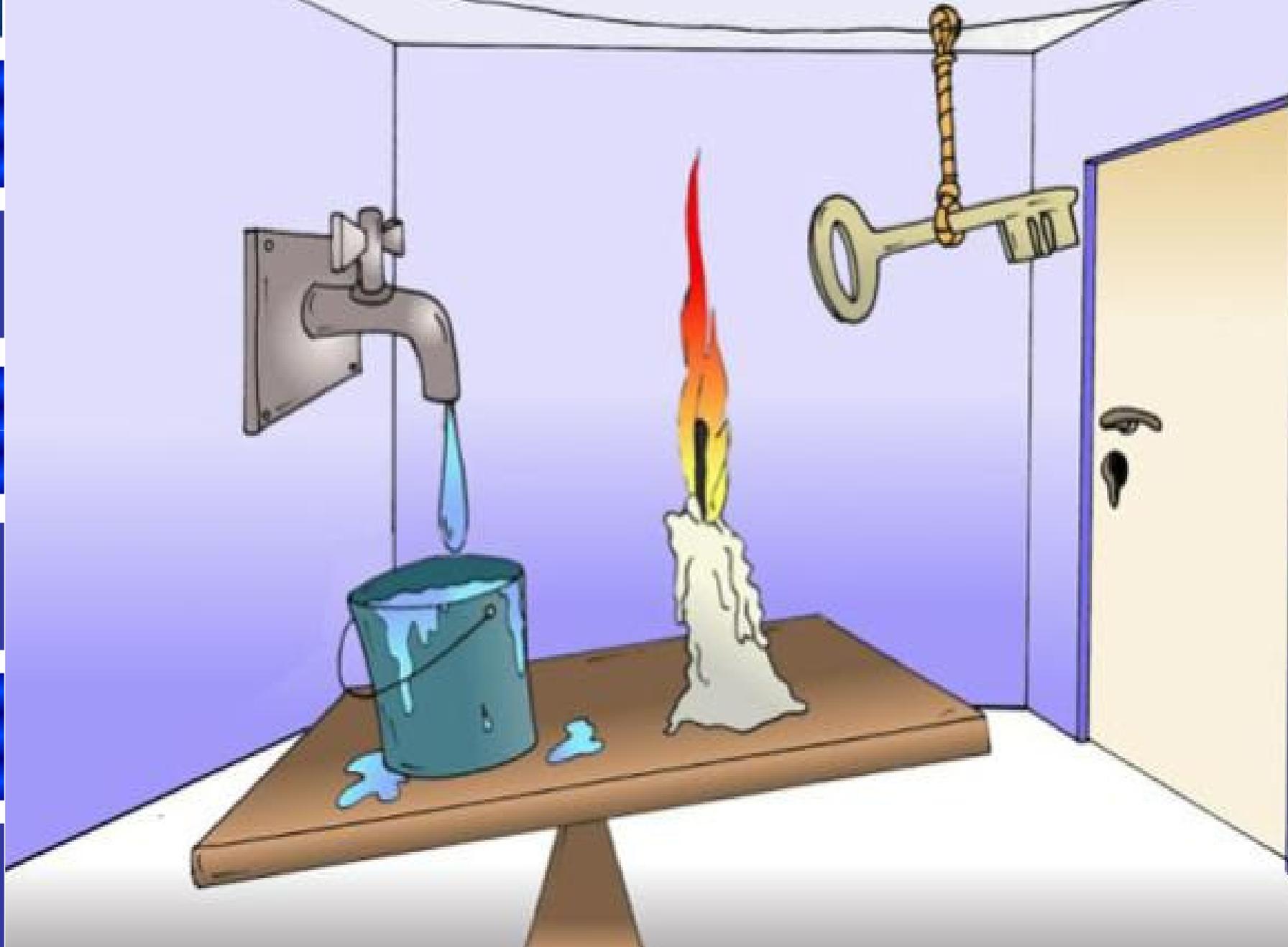


# Estatinas (2)





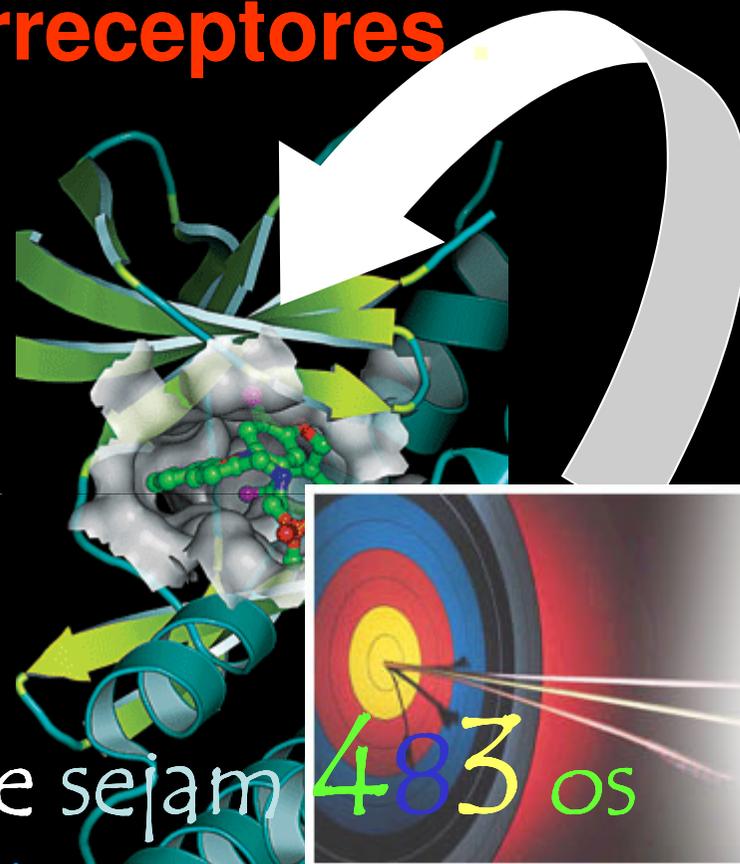
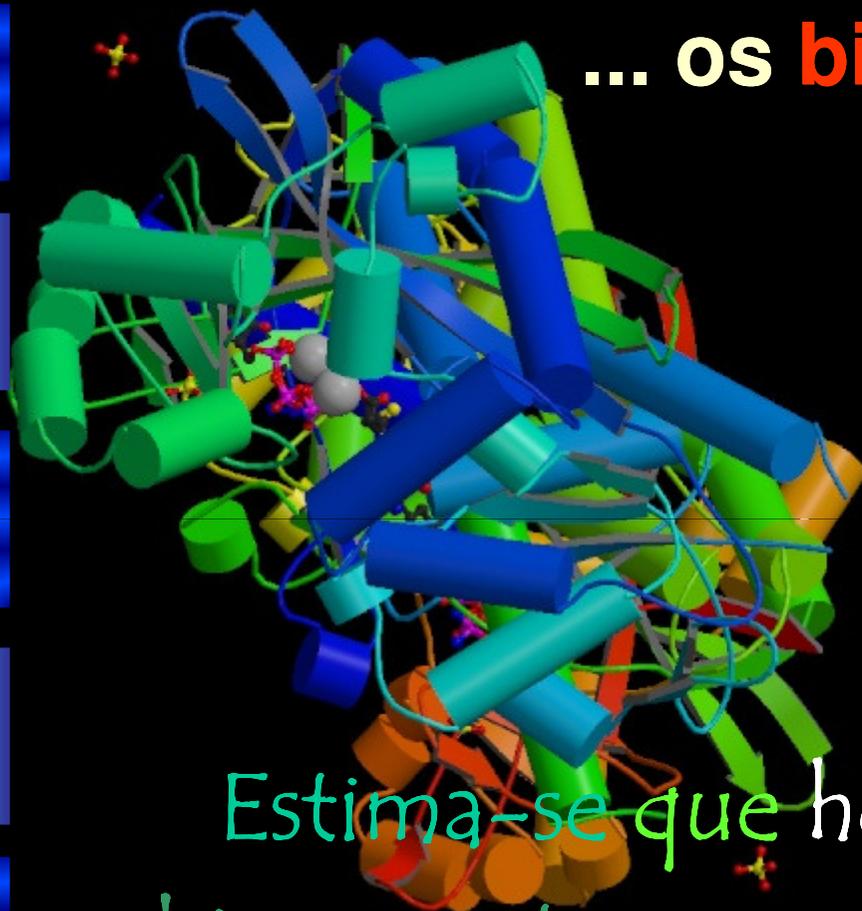
# O processo racional da descoberta de fármacos





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.



Biorreceptor

Estrutura 3D do alvo terapêutico

homologia

Sítio de reconhecimento molecular

*In silico*

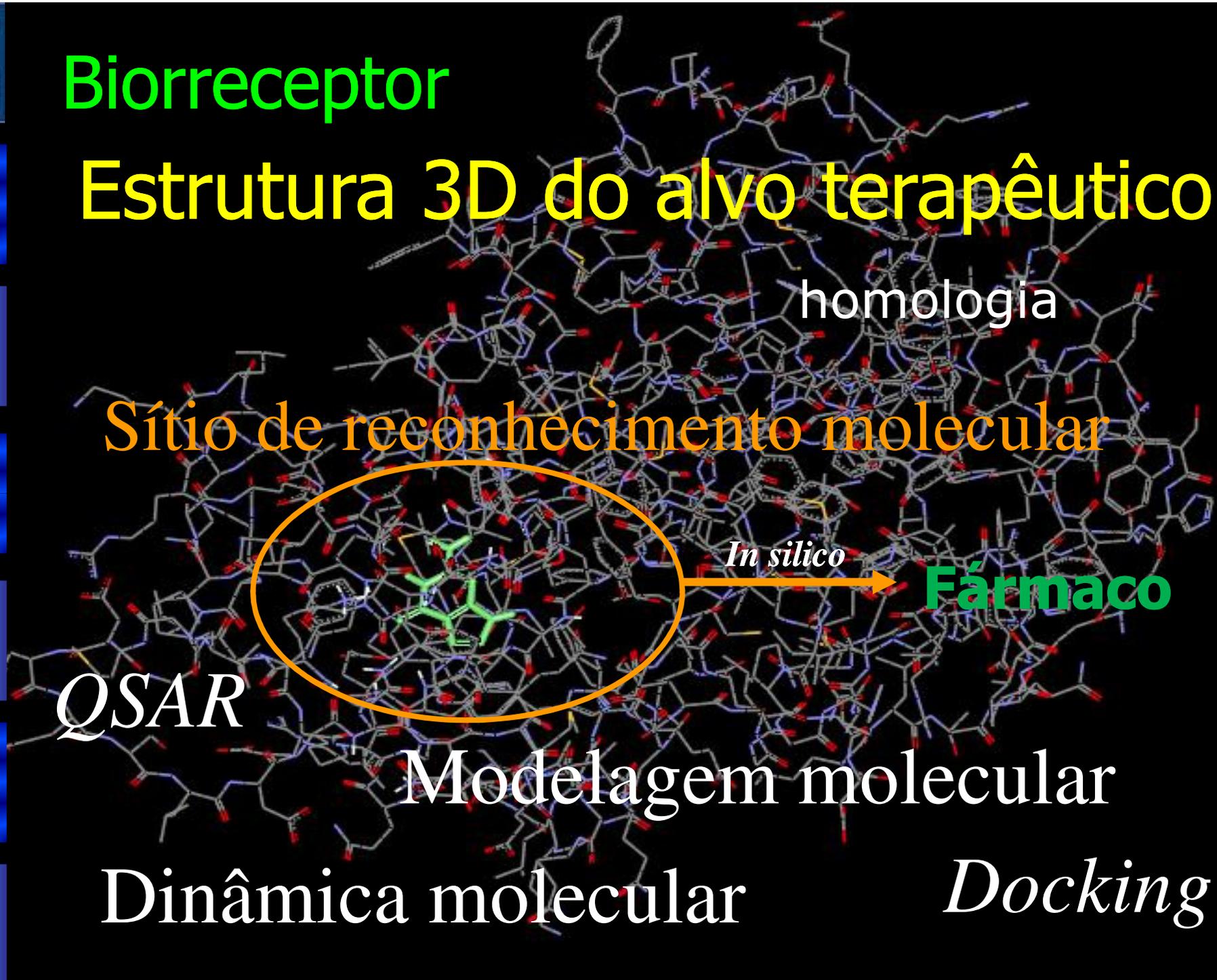
Fármaco

QSAR

Modelagem molecular

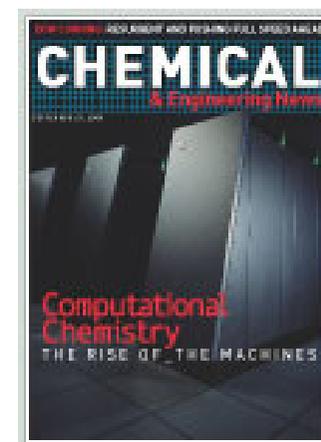
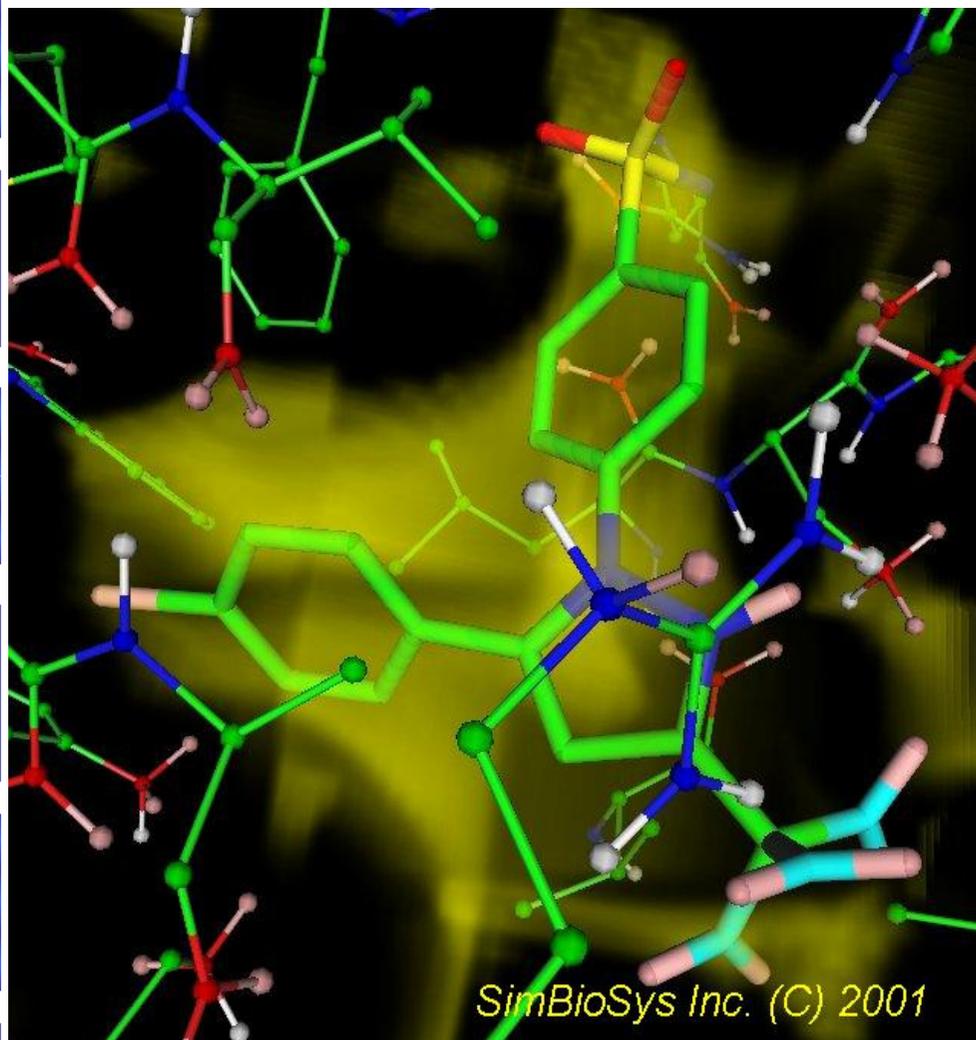
Dinâmica molecular

*Docking*





# Química Computacional





# Estruturas cristalográficas disponíveis no PDB

<http://www.wwpdb.org/>

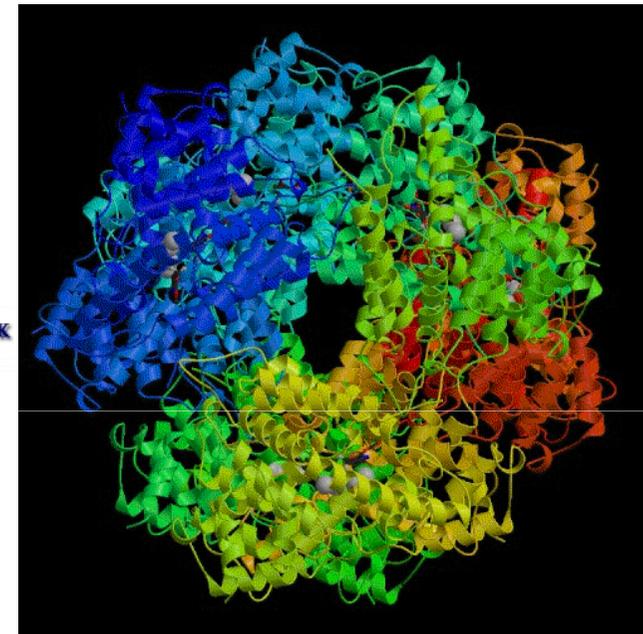


PDE4B - 1F0J

351 resíduos

*Metodo:* Difração de Raio-X

*Resolução:* 1.77 Å

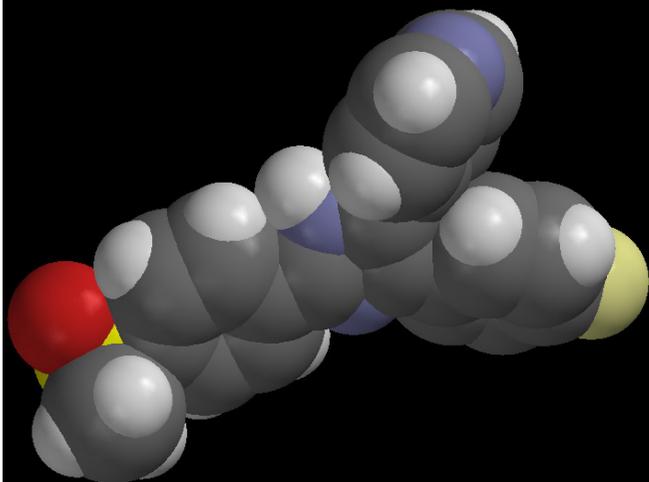


PDE4D - 1MKD

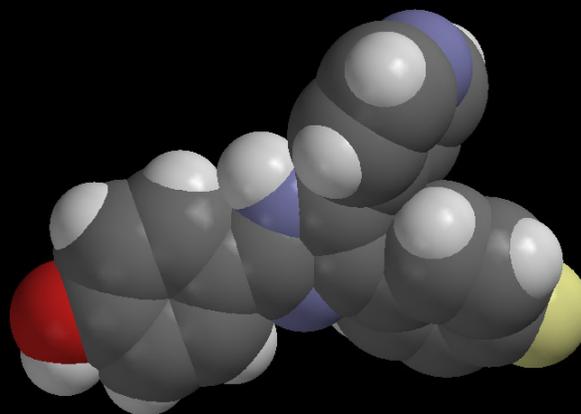
328 resíduos

*Metodo:* **Difração de Raio-X**

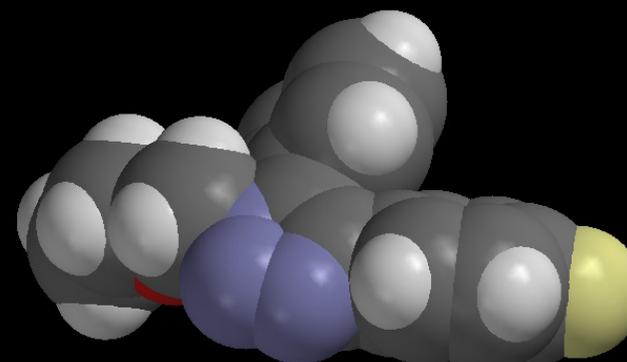
*Resolução:* 2.90 Å



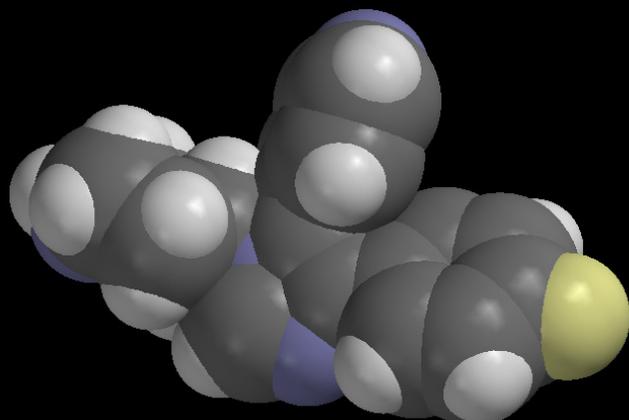
**SB203580**  
(volume: 368,59Å<sup>3</sup>)



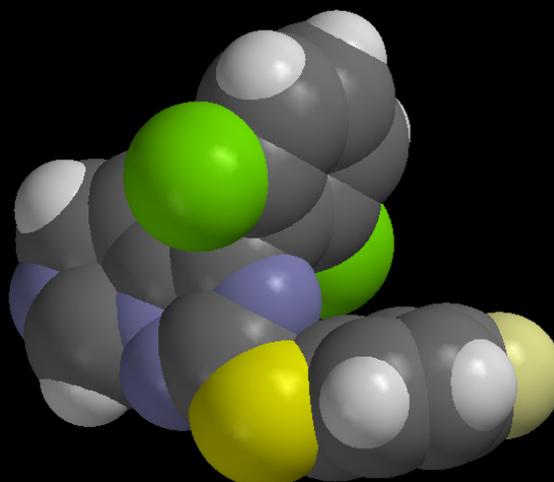
**SB202190**  
(volume: 330,40Å<sup>3</sup>)



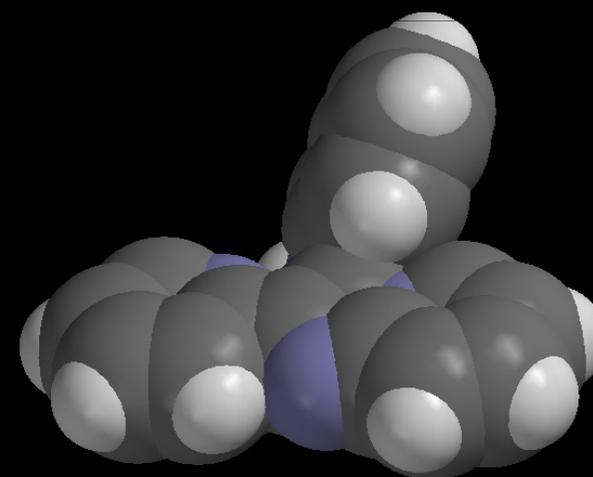
**J&J**  
(volume: 297,94Å<sup>3</sup>)



**SB235699**  
(volume: 331,66Å<sup>3</sup>)



**VX745**  
(volume: 354,05Å<sup>3</sup>)



**LASSBio-1135**  
(volume: 300,10Å<sup>3</sup>)



**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:**

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**Instructions to Journals**

**Documentation**

[Format](#)

[Annotation and Policies](#)

**Workshops and Task Forces**

[X-ray Validation](#)

[NMR Validation](#)

[wwPDBAC](#)

## Data Download Details

The wwPDB ftp site is quite large. As of September 21, 2008, it contains more than 443,000 files and requires over 94 GBbytes of storage. It will continue to grow with each weekly update. Fresh downloads will require substantial amount of time.

A number of download locations and options are provided. 

Access is available from: [the RCSB PDB \(USA\)](#) | [PDBe \(UK\)](#) | [PDBj \(Japan\)](#)

Please note: <ftp://ftp.rcsb.org> is no longer updated. Please access the PDB archive using one of the FTP sites listed in the left menu.

### RCSB PDB:

#### USING RSYNC PROTOCOL:

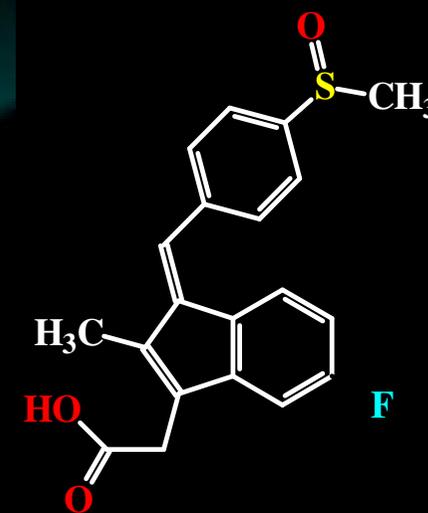
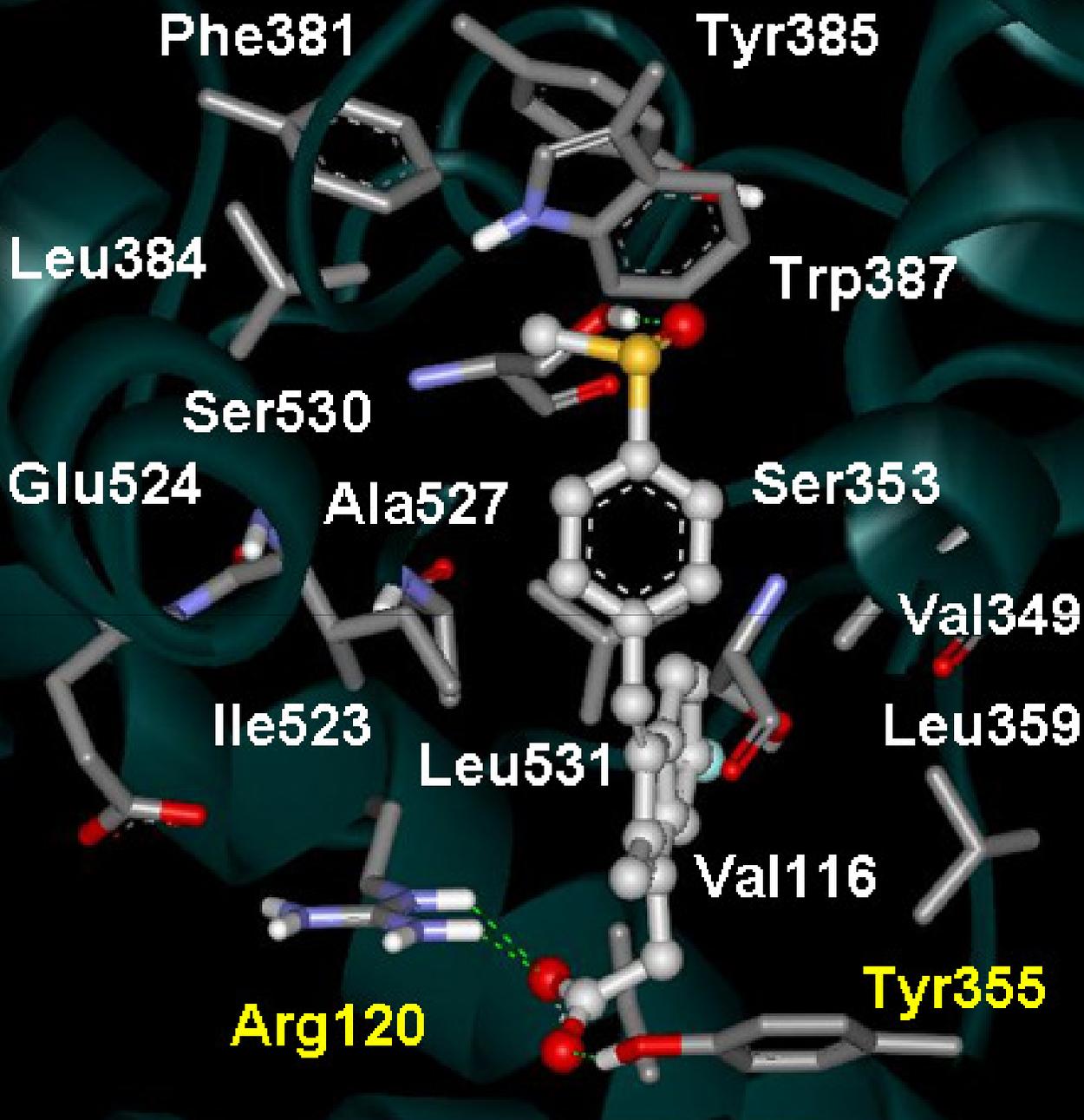
```
rsync --port=33444 ftp.wwpdb.org::
```

ftp	Top level of ftp tree approximately 66 GB ( /pub/pdb )
ftp_data	Data directory within ftp archive Aproximately 65.7 GB ( /pub/pdb/data )
ftp_derived	Derived data directory within ftp archive Aproximately 134 MB ( /pub/pdb/derived_data )
ftp_doc	Doc directory within ftp archive Aproximately 234 MB ( /pub/pdb/doc )

**Downloading coordinate files in PDB Exchange Format (mmCIF):** To download the entry files in PDB exchange format the following rsync command may be used:

```
rsync -rlpt -v -z --delete --port=33444 \
rsync.wwpdb.org::ftp_data/structures/divided/mmCIF/ ./mmCIF
```

**Downloading coordinate files in PDBML Format (xml):** To download the entry files in PDBML format the following rsync command may be used:



**Interações do sulindaco com COX-1**



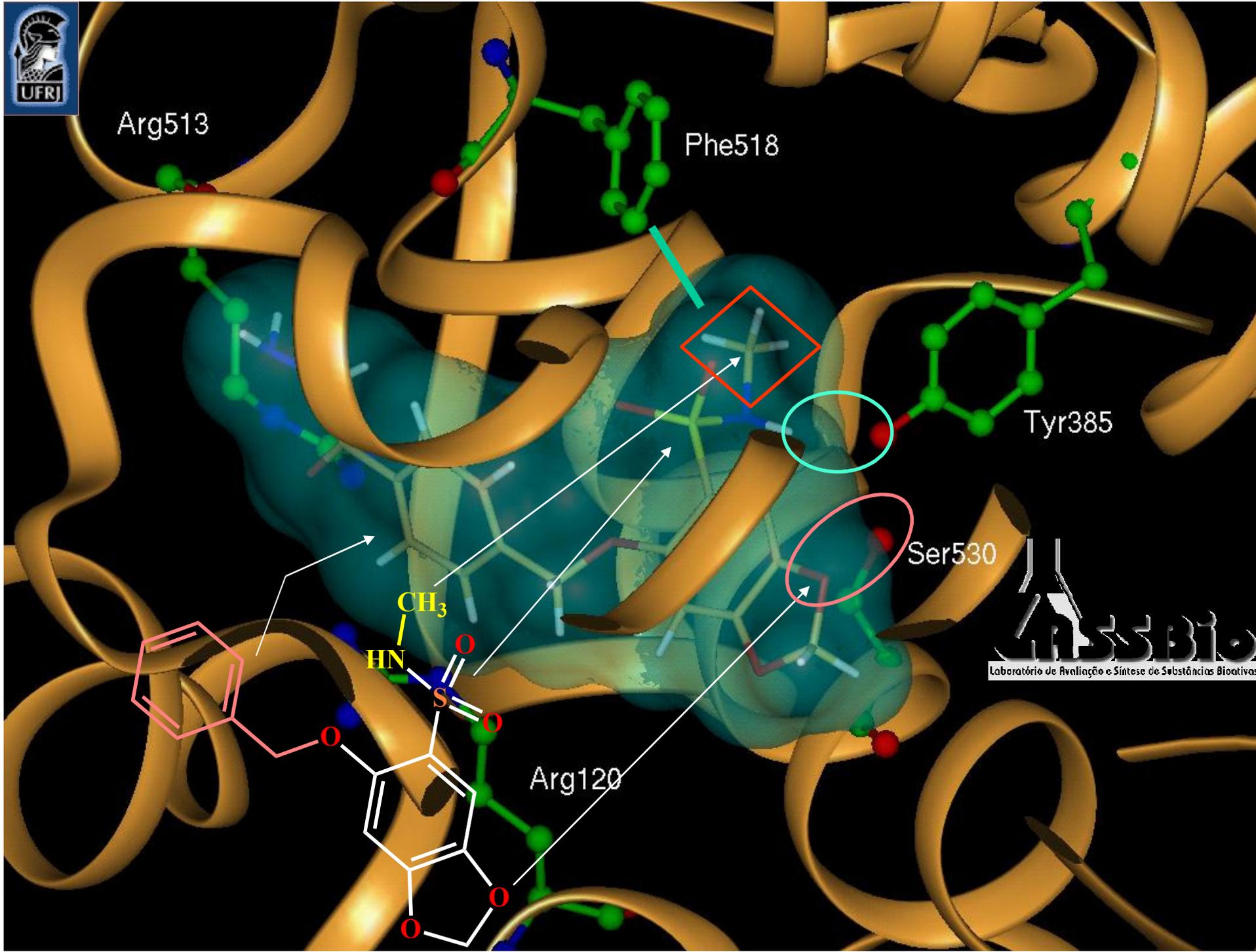
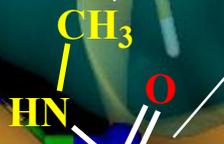
Arg513

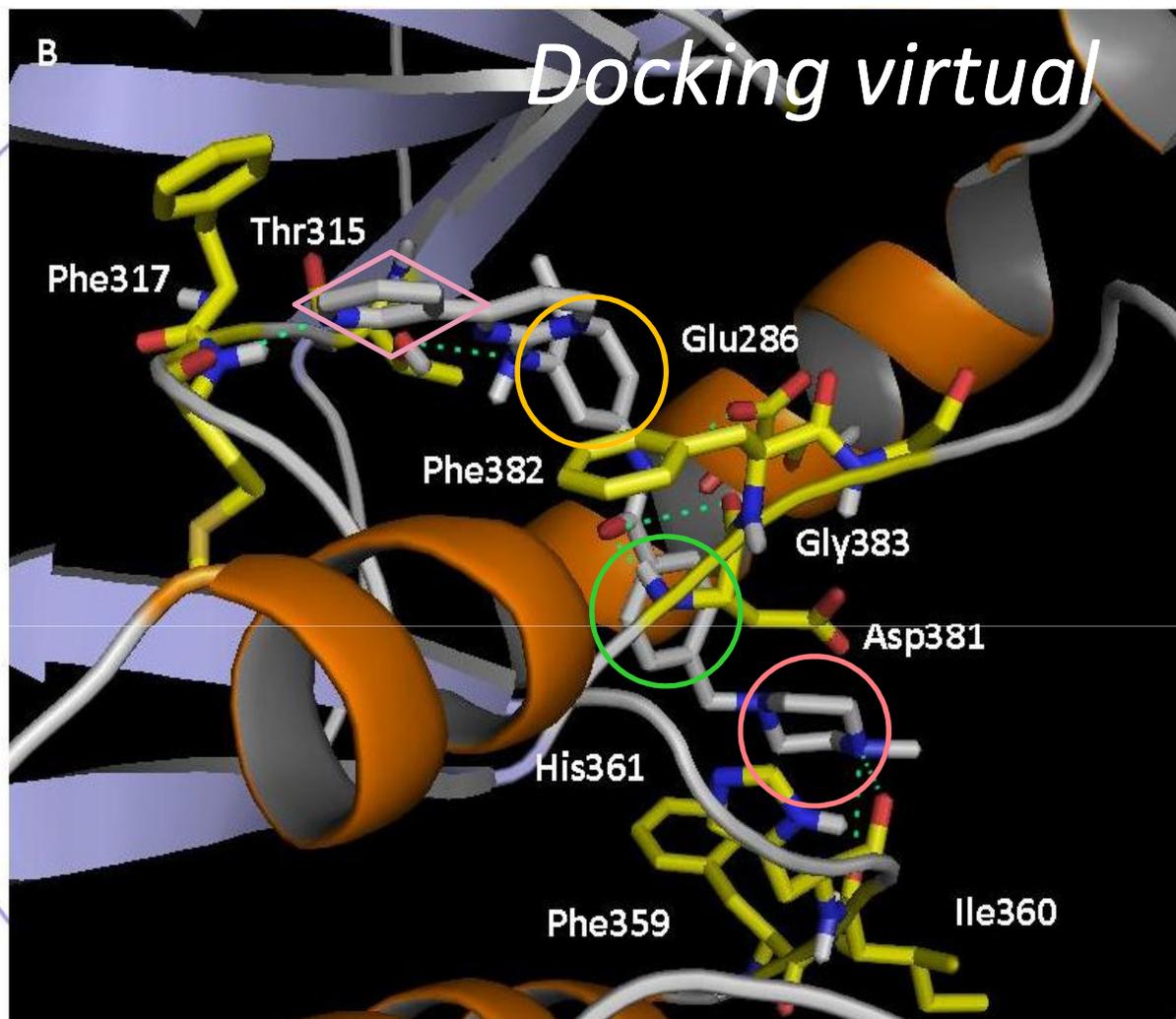
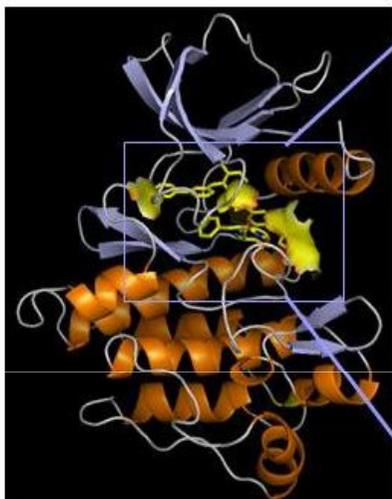
Phe518

Tyr385

Ser530

Arg120





Modos de ligação do imatinibe com a ABL. Os átomos de hidrogênio foram eliminados para facilitar a visualização. Ligações-H estão representadas por linhas pontilhadas verdes.

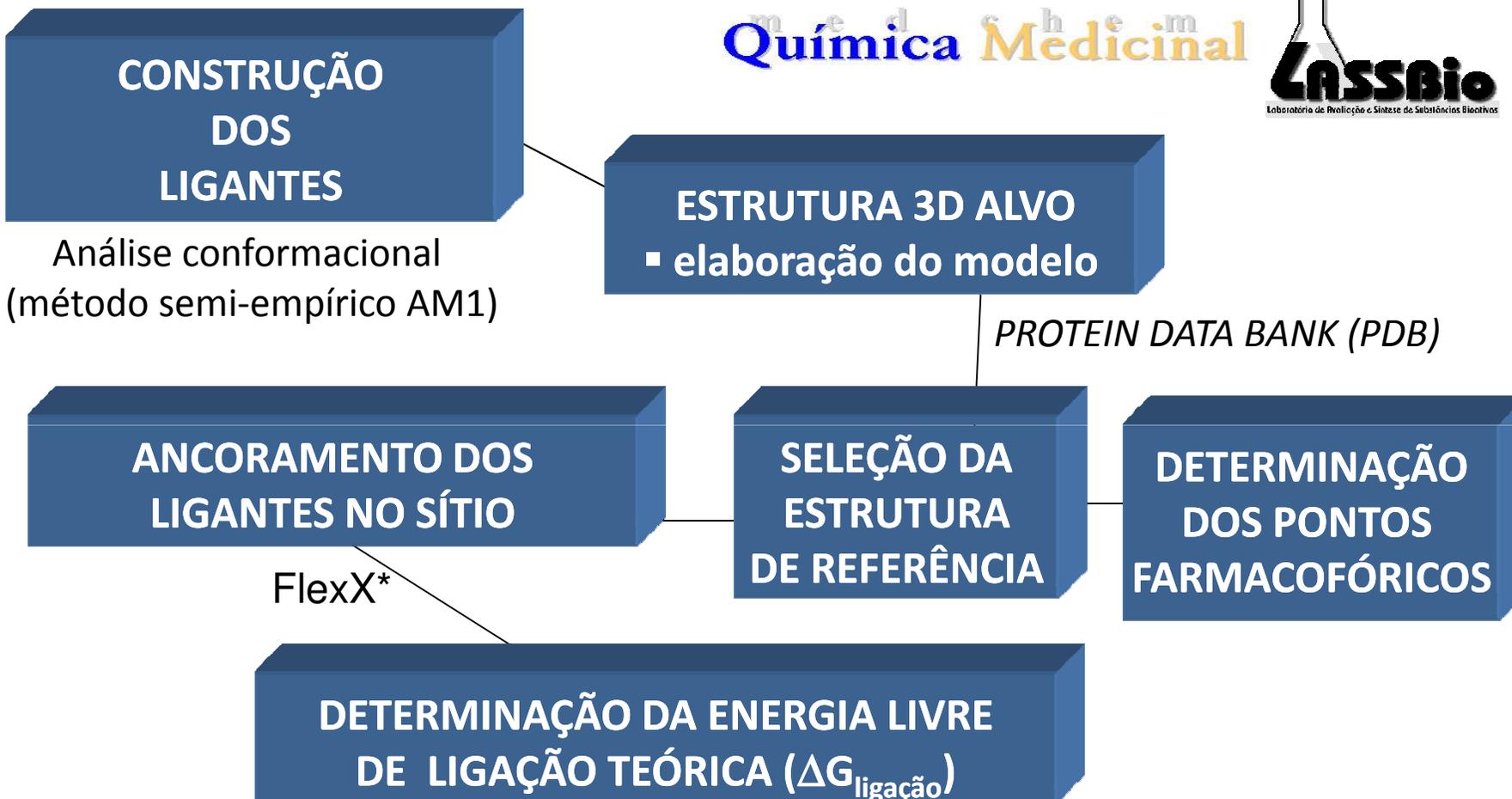
C.M. Avila, N. C. Romeiro, *Revista Virtual de Química* 2010, 2, 59

# Novos inibidores de tirosina quinase



# Metodologia: Estudos de *docking*

Química Medicinal



\* FlexX one of the most cited commercial docking software

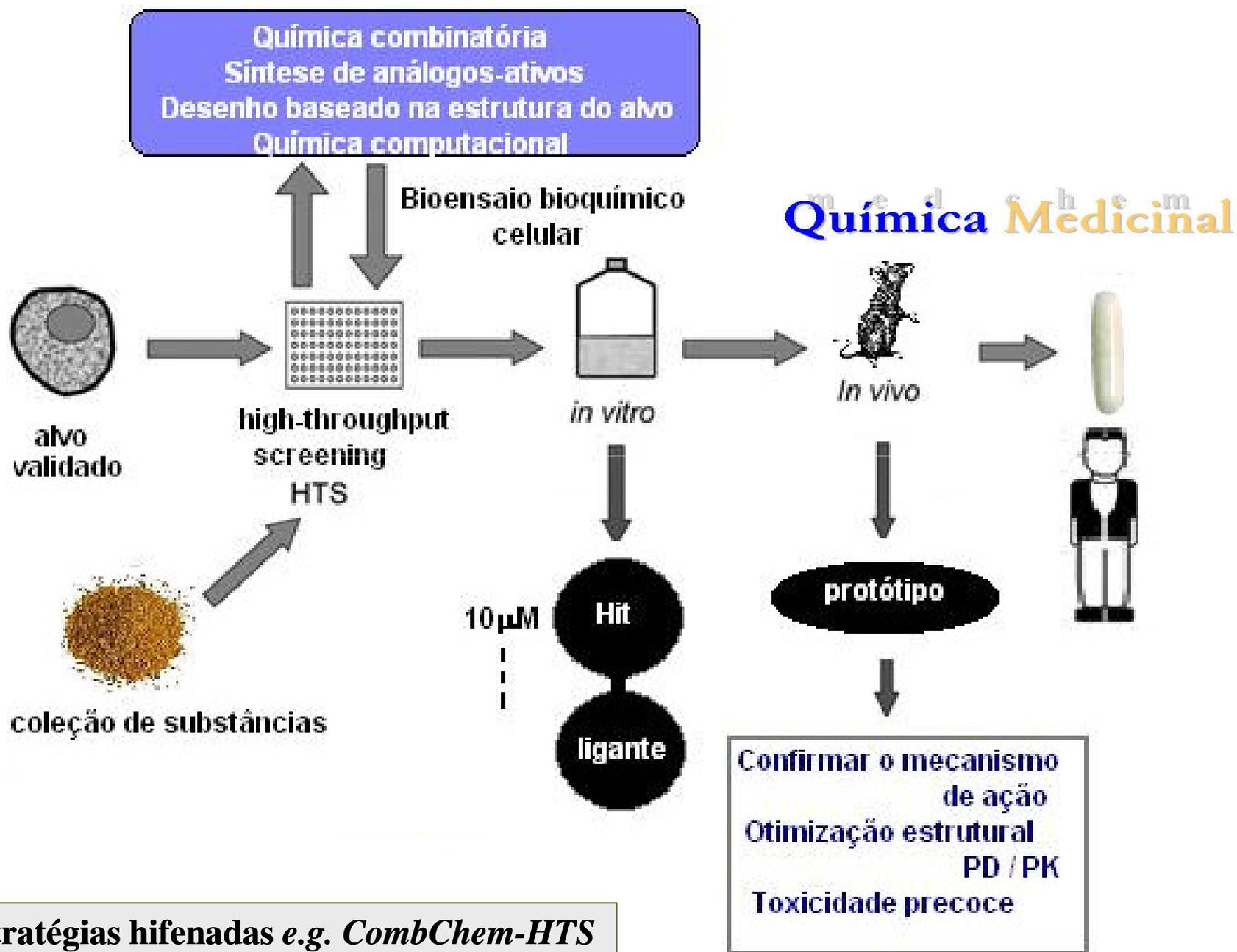
Sybyl, Version 8.0, Tripos Associates: St. Louis, MO, 2007 (Licença # 7512)

Spartan Pro; Wavefunction, Inc. 18401 Von Karman Avenue, Suite 370. Irvine, California 92612, USA (Licença # 1-001259 )

FlexiDock; GLIDE; Gold; AutoDock (GNU) General Public License;

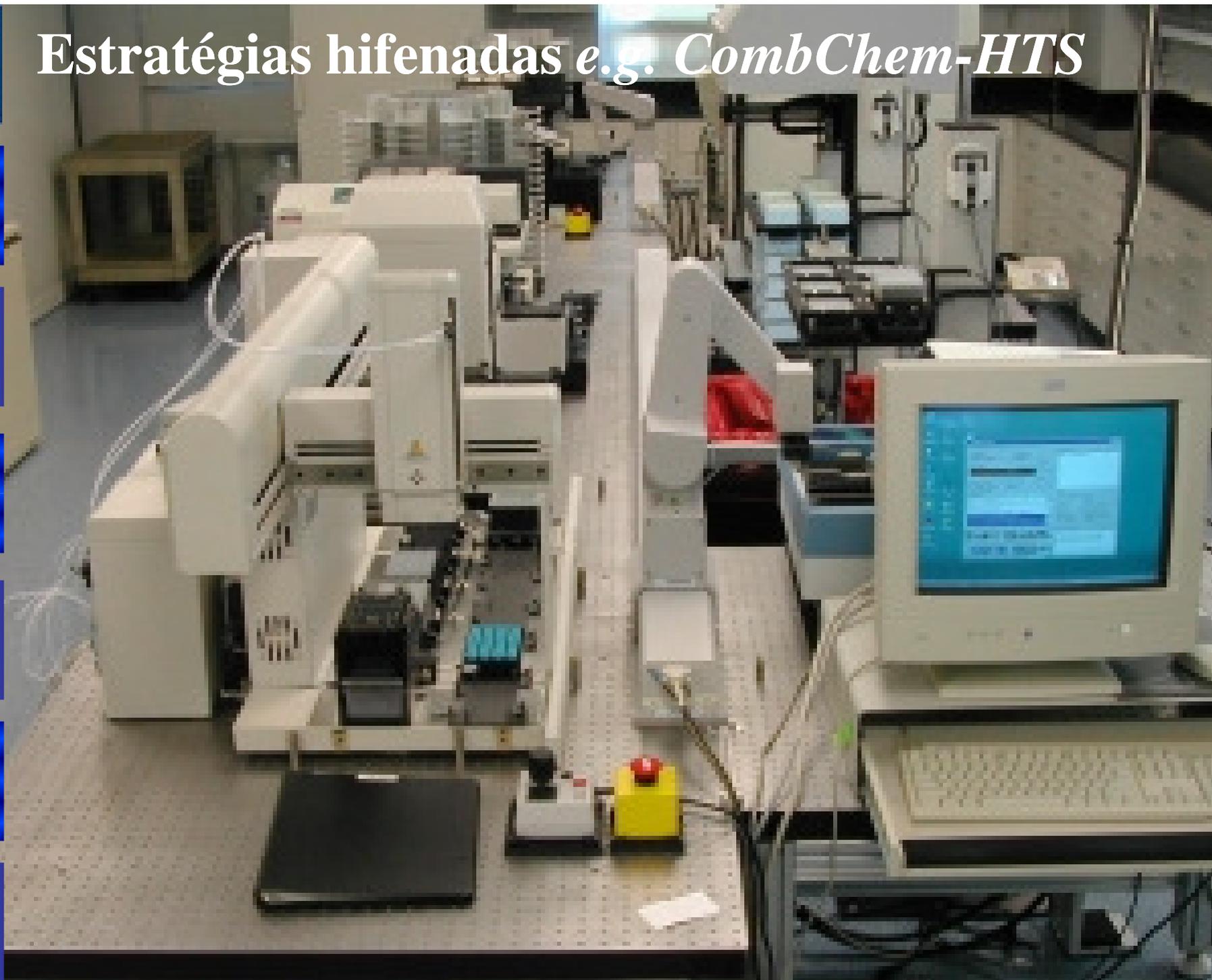


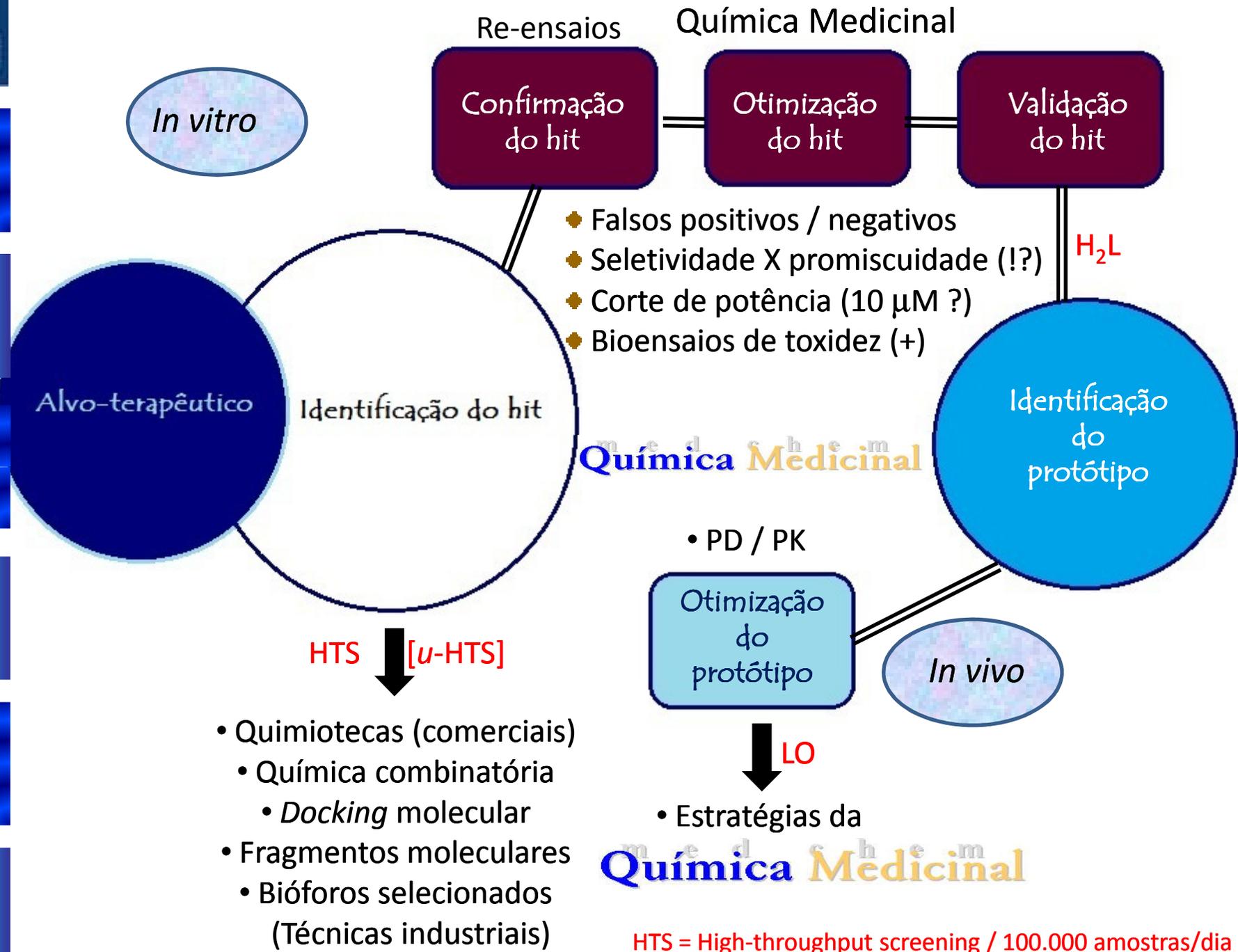
# Estratégias modernas industriais de descoberta de fármacos





# Estratégias hífenadas e.g. *CombChem-HTS*







## Fragmentos moleculares mais frequentes em fármacos \*

The most common substituents from World Drug Index							

\* P. Ertl, J Chem Inf Comput Sci 2003, 43, 374

