

**Aula 3 – 10/06**

# **Tópicos Especiais em Química Medicinal**

**Tópicos Especiais  
em Química Medicinal**  
Código: **BMF-777**  
Carga Horária: 45 horas  
Créditos: 3 créditos

Edição 2005

# Biorreceptores



# O paradigma de Fischer



**Emil Fischer**

1852-1919

**1902**

E. Fischer, *Ber. Dtsch. Chem. Ges.* **1890**, 23, 799



**LOCK & KEY**  
CONCEPT

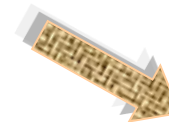


**Biorreceptor**

macrobiomolécula  
baseado no sítio de  
reconhecimento



**Novos  
Fármacos  
Século XX**



**Ligante**

micromolécula

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**Estratégias da  
Química Medicinal**

**Desenho  
baseado no ligante  
/ análogo-ativo**

chave

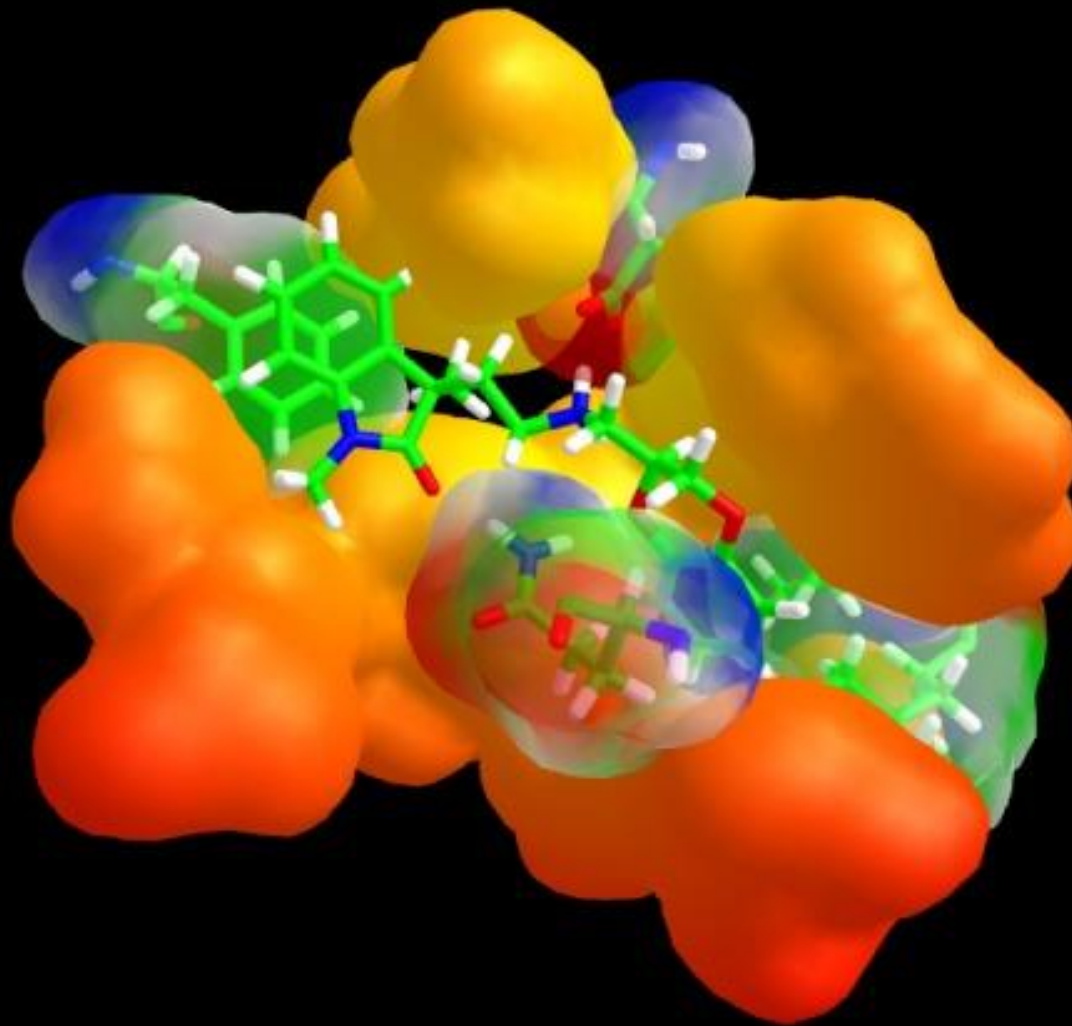


*fechadura*

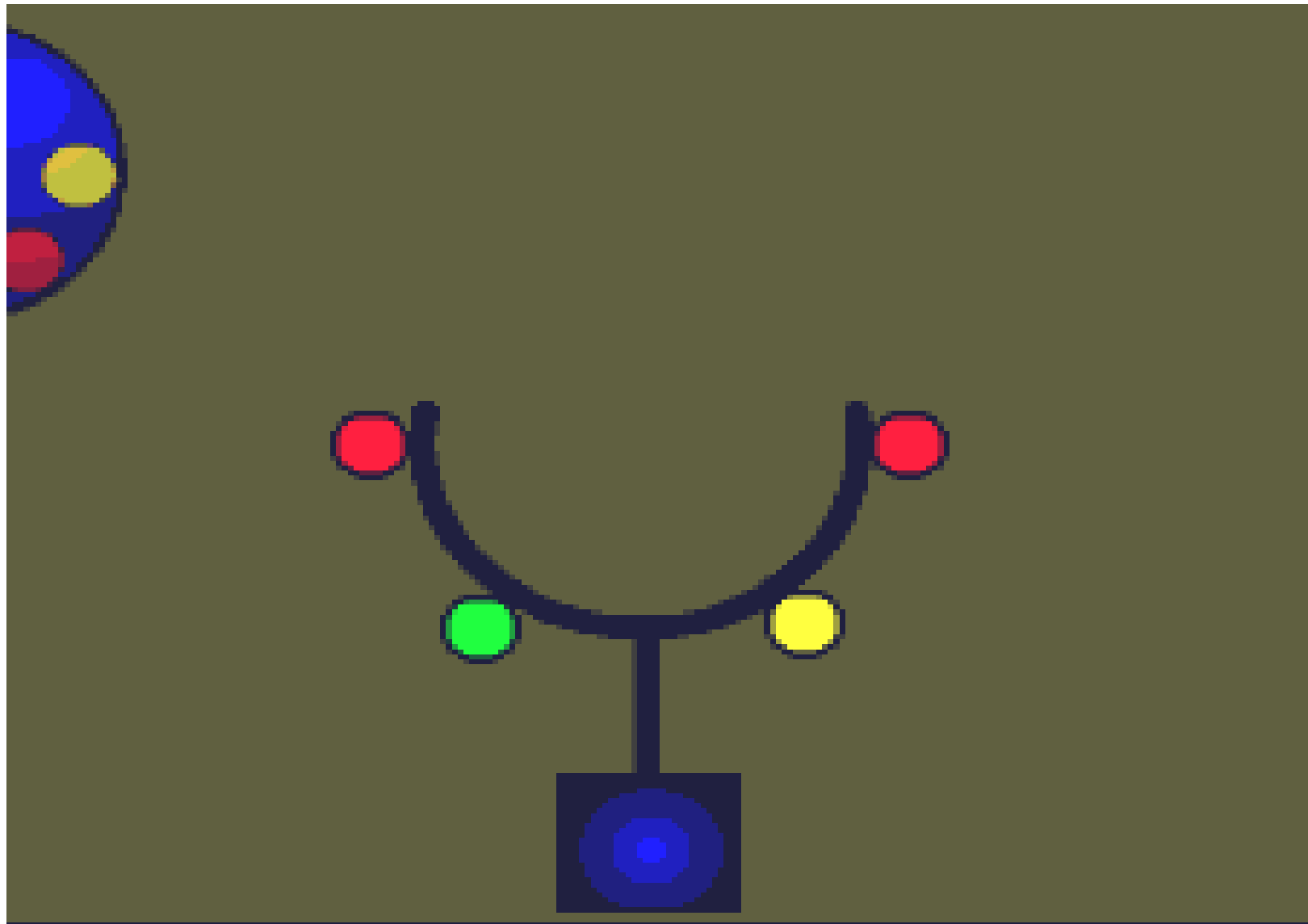




# As interações moleculares



**Fármaco - Biorreceptor**



**Potência & eficácia**



Os fármacos atuam em alvos terapêuticos...

... os **bioreceptores**.

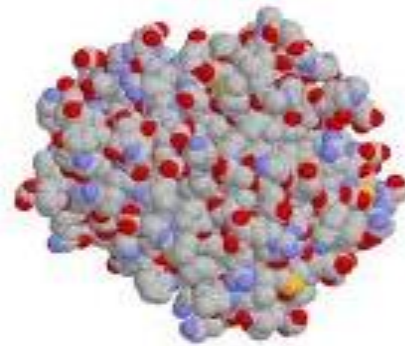
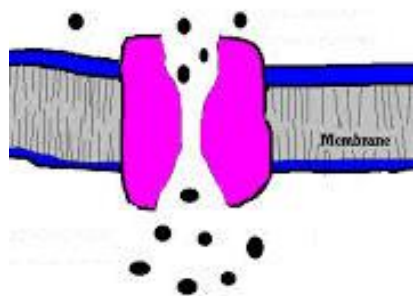
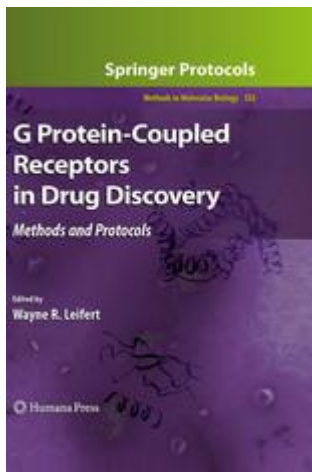
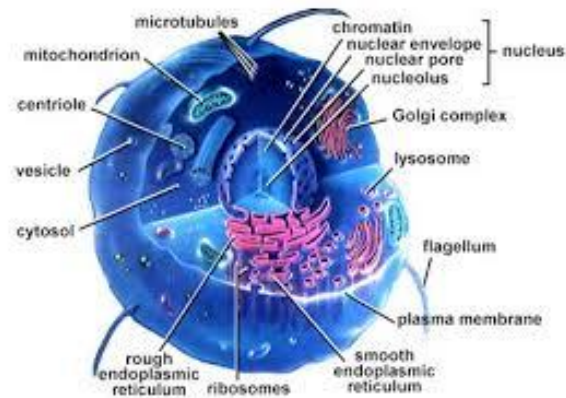
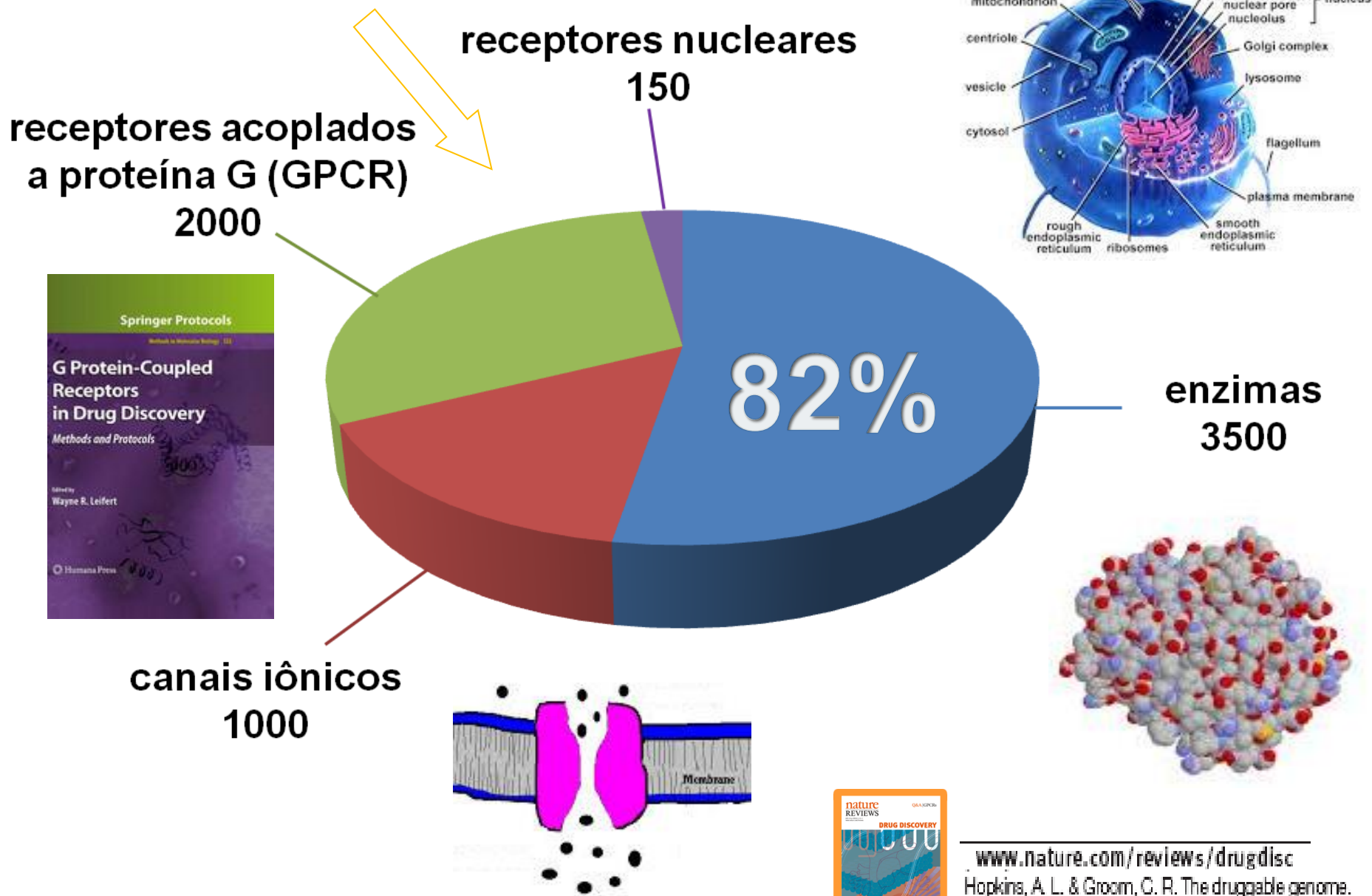


São 4 os tipos de alvos-  
terapêuticos envolvidos na

resposta de todos os fármacos:

GPCR; **Quinases**; **RH**; **Nucleares**

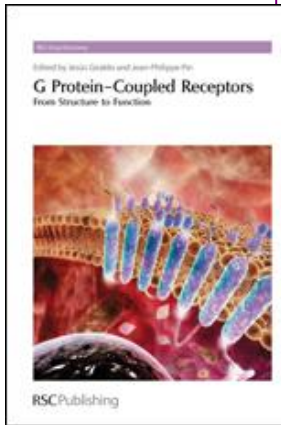
# A maioria dos biorreceptores dos fármacos contemporâneos são enzimas ...



[www.nature.com/reviews/drugdisc](http://www.nature.com/reviews/drugdisc)  
Hopkins, A. L. & Groom, C. R. The druggable genome. *Nature Rev. Drug Discov.* 1, 727-30 (2002).



# Receptores acoplados a proteína-G



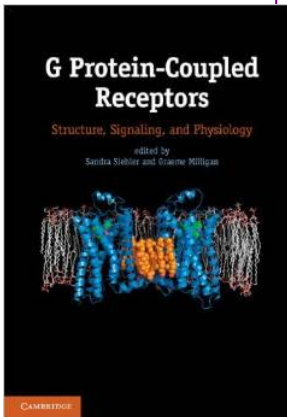
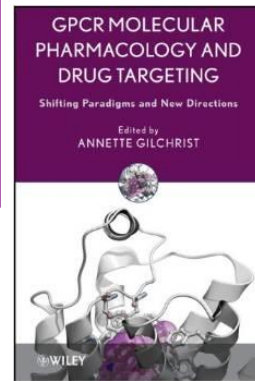
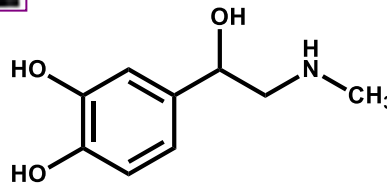
**Robert J. Lefkowitz**  
Duke University



**2012**

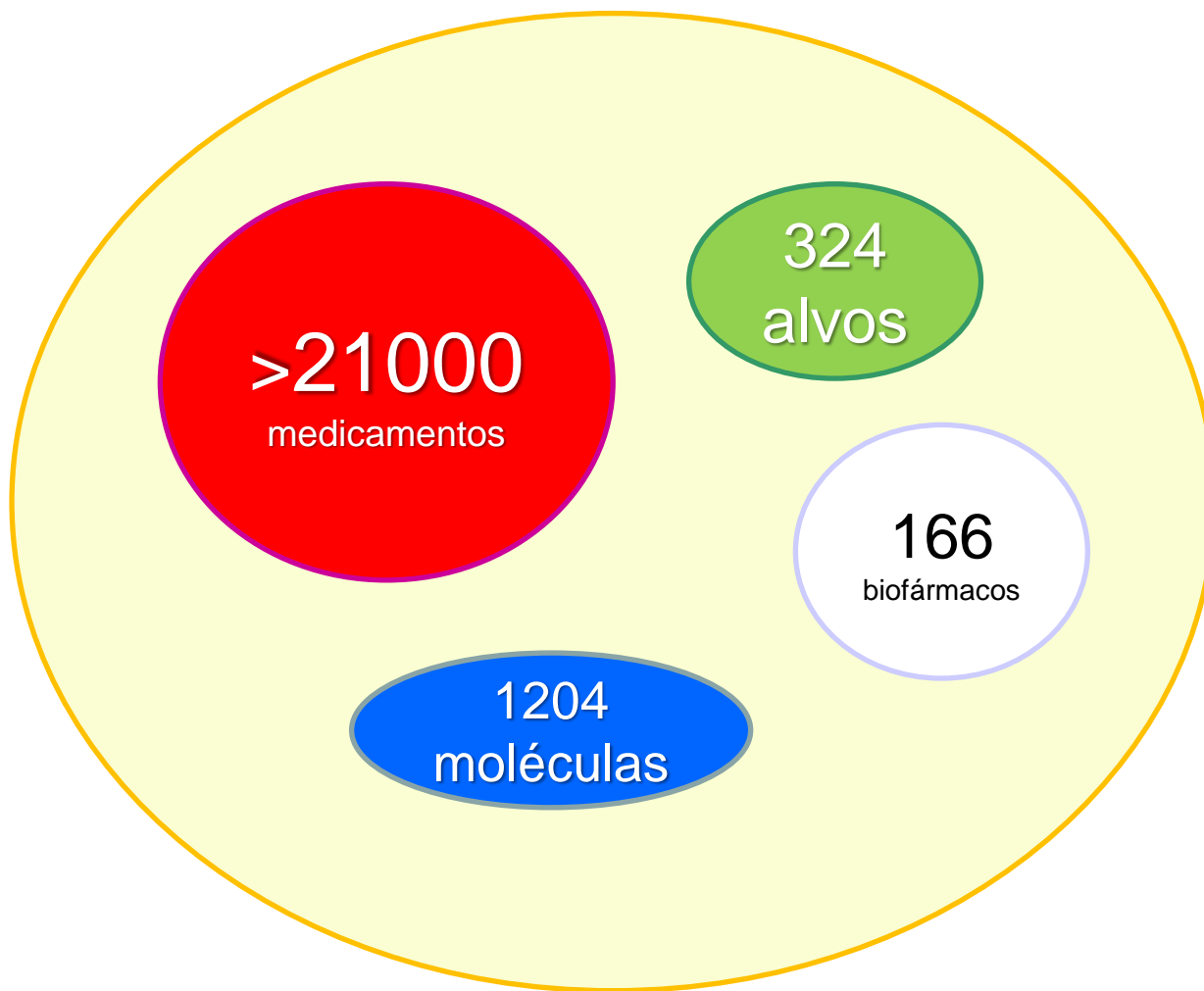


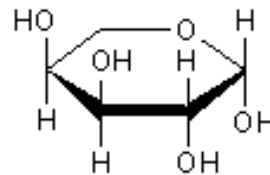
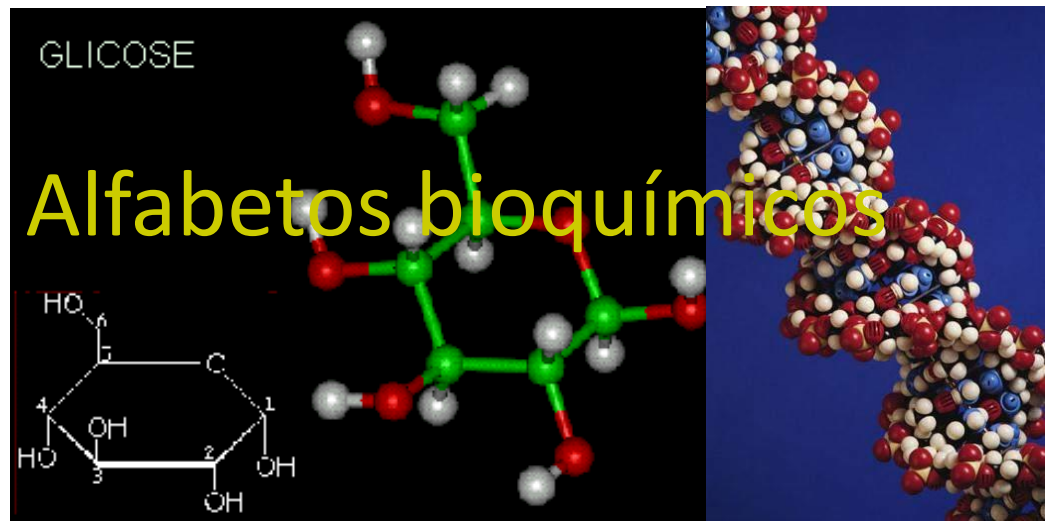
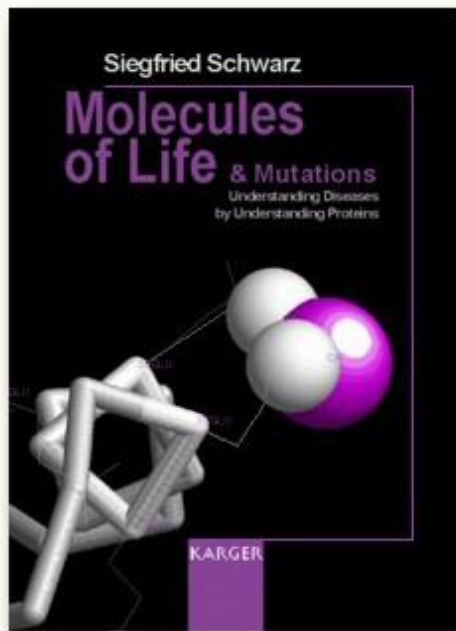
**Brian K. Kobilka**  
Duke University



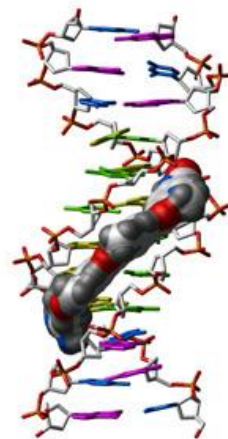
- a) Howard Hughes Medical Institute & Duke University Medical Center, Durham, NC, USA
- b) Stanford University School of Medicine, Stanford, CA, USA

***GPCR's***





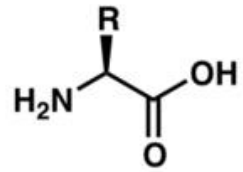
$\beta$ -L-Arabinose



Model Compound Bound to the Minor Groove of a DNA Molecule

*Carboídratos*  
*Lipídeos*  
*ácidos nucleícos*  
*proteínas*

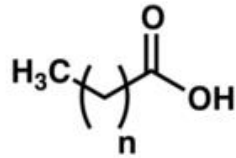
# Alfabetos bioquímicos



amino ácidos



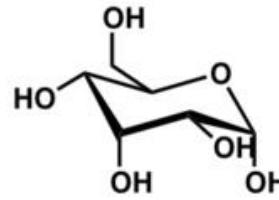
proteínas



ácidos graxos



fosfolípidos



carboidratos



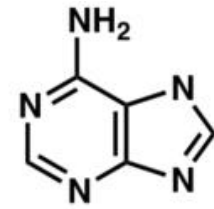
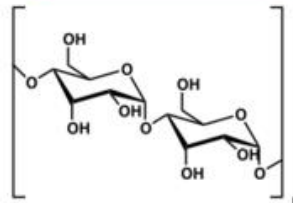
glicerol



mono  
sacarídeos



poli-  
sacarídeos



bases nucleícas



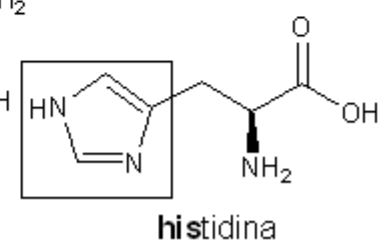
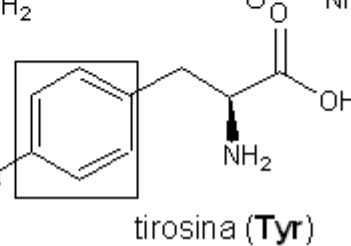
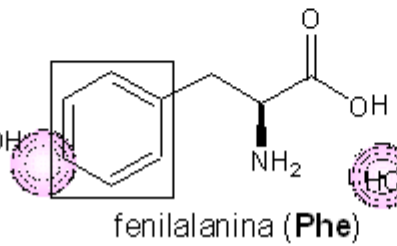
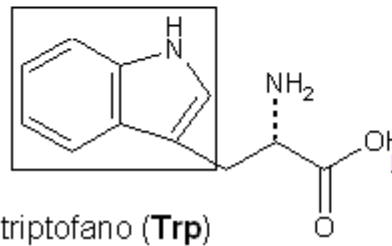
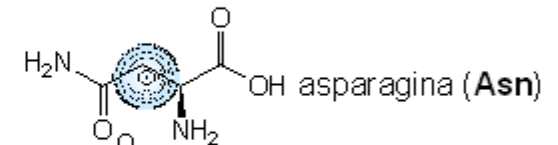
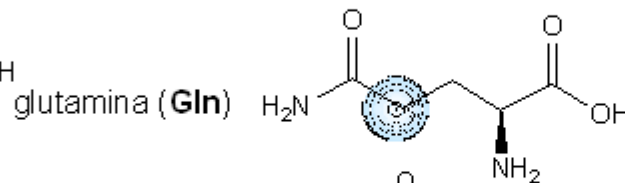
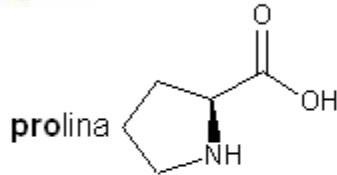
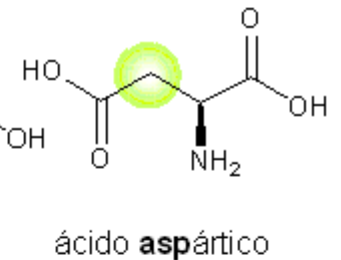
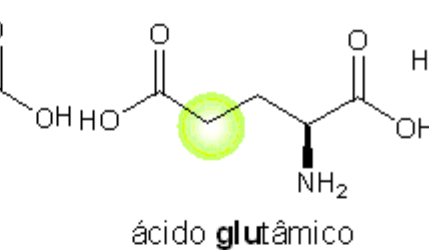
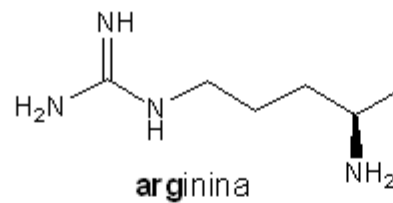
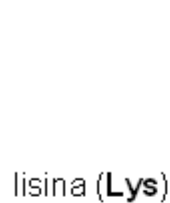
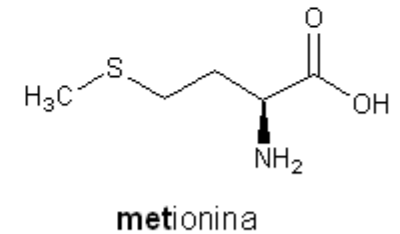
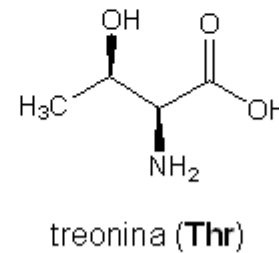
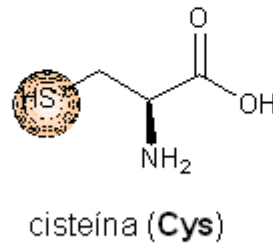
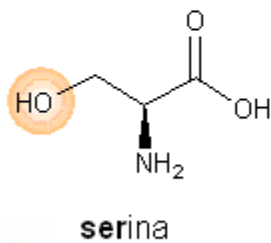
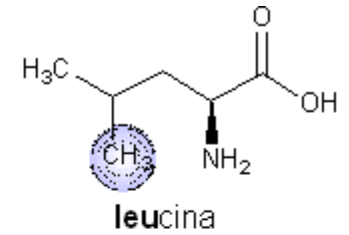
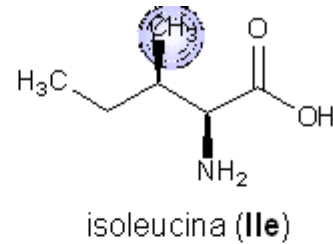
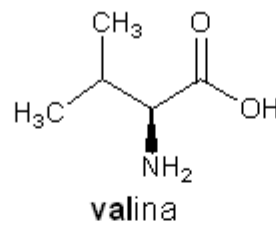
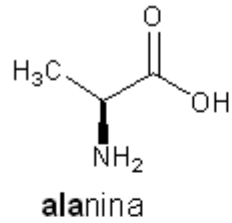
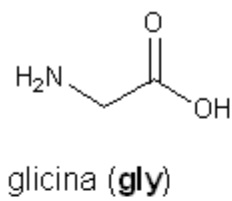
nucleotídeos



DNA/RNA



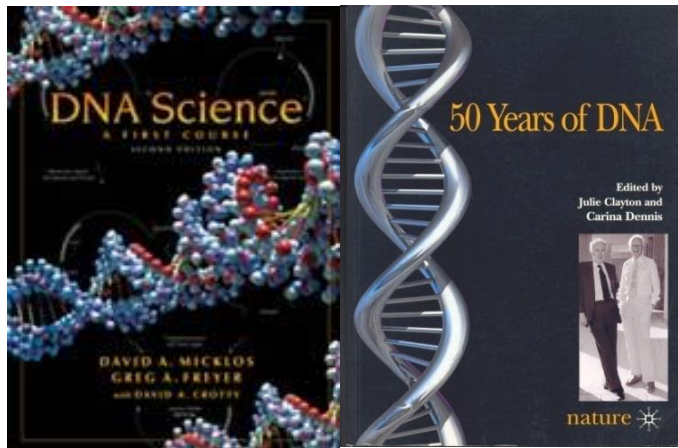
# O "alfabeto" protéico ...



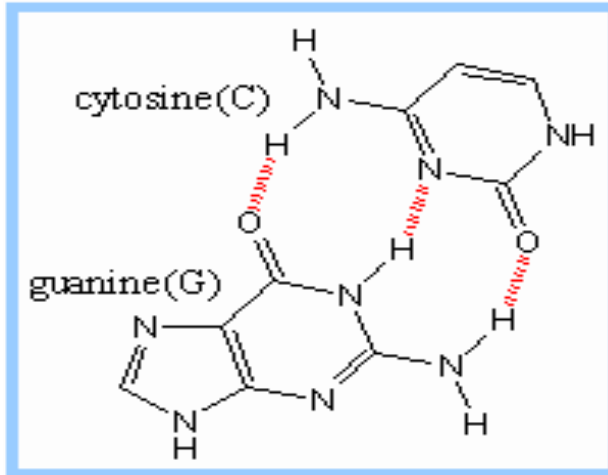


“for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material”  
 Prêmio Nobel de Medicina e Fisiologia 1962

65 anos  
 65 anos



J. Clayton & C. Dennis, Eds., “50 Years of DNA”, Nature Pub. 2003.



Ligações de Hidrogênio entre Guanina (G) / Citosina (C) e Adenina (A) / Timidina (T)

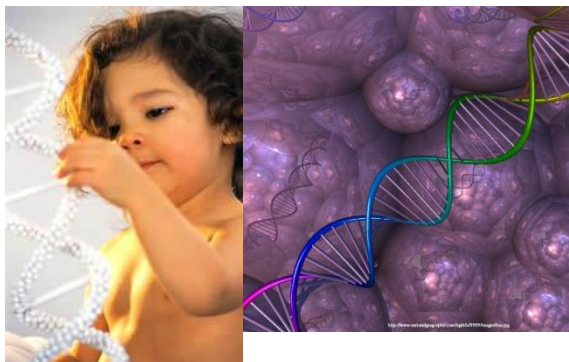


J. D. Watson & F. H. C. Crick, M. Wilkins

65 anos

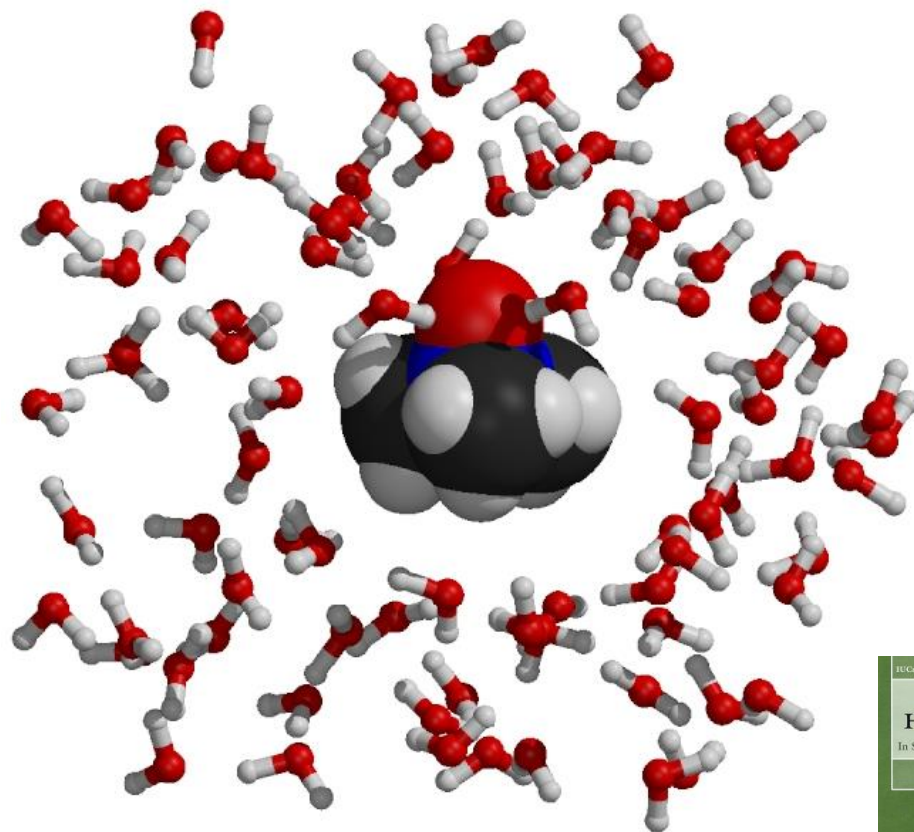
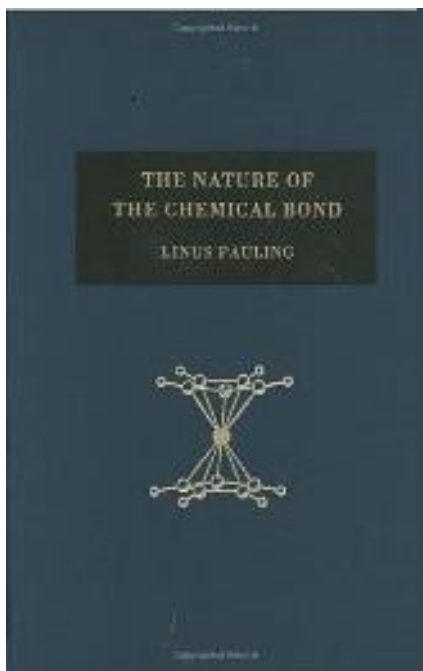
DNA

1953-2018



Moléculas da vida...

# A importância das “ligações” frágeis...



**Linus C. Pauling**

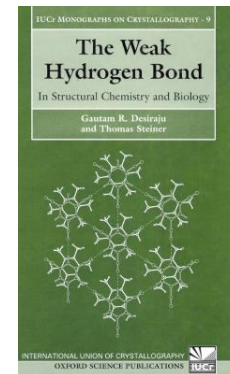
1901-1994

**1954, 1962**



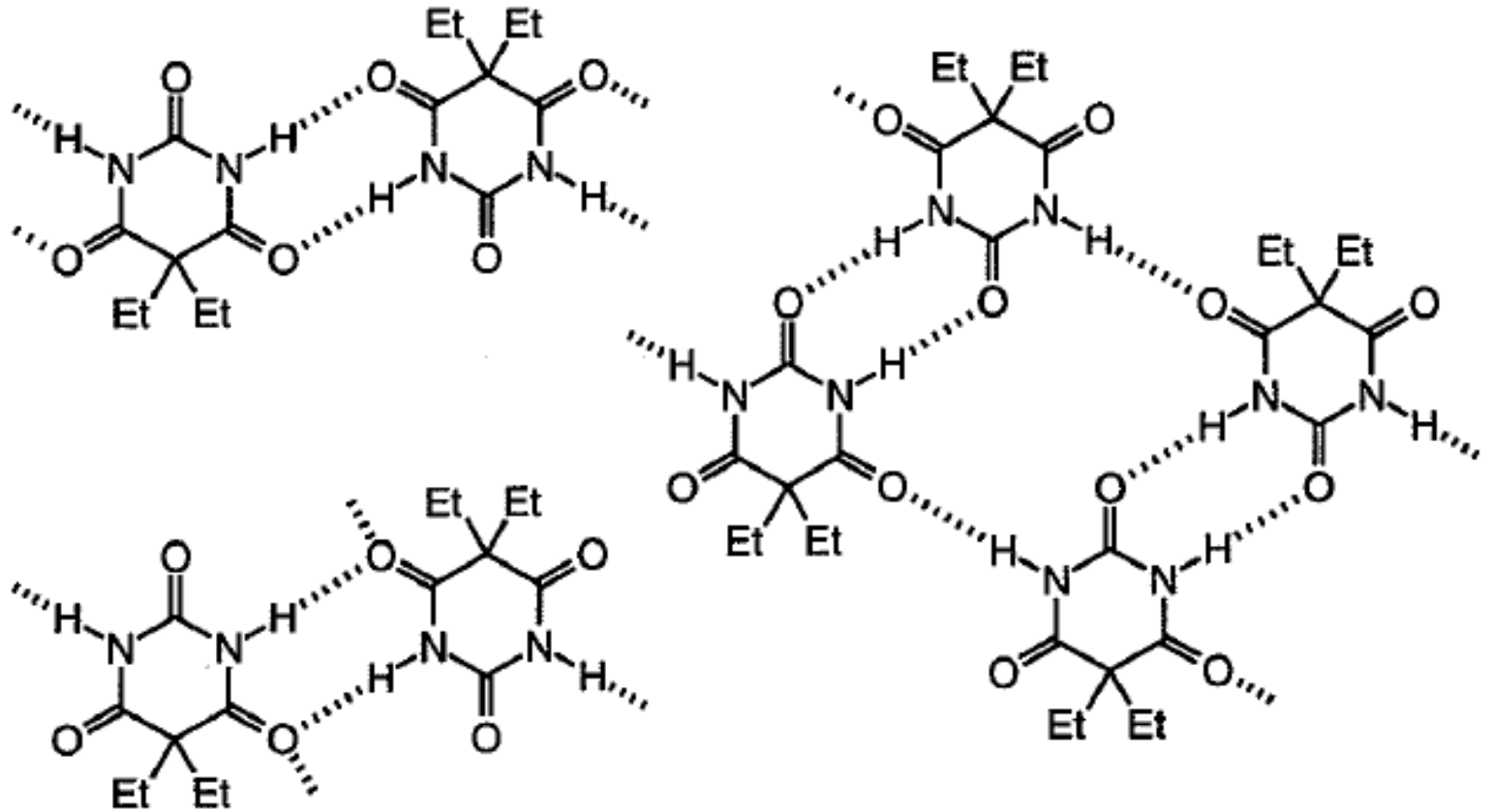
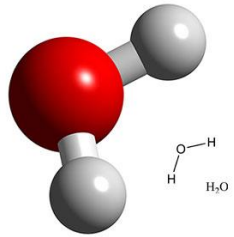
“ligações”  
de hidrogênio ...

*ligação-H*





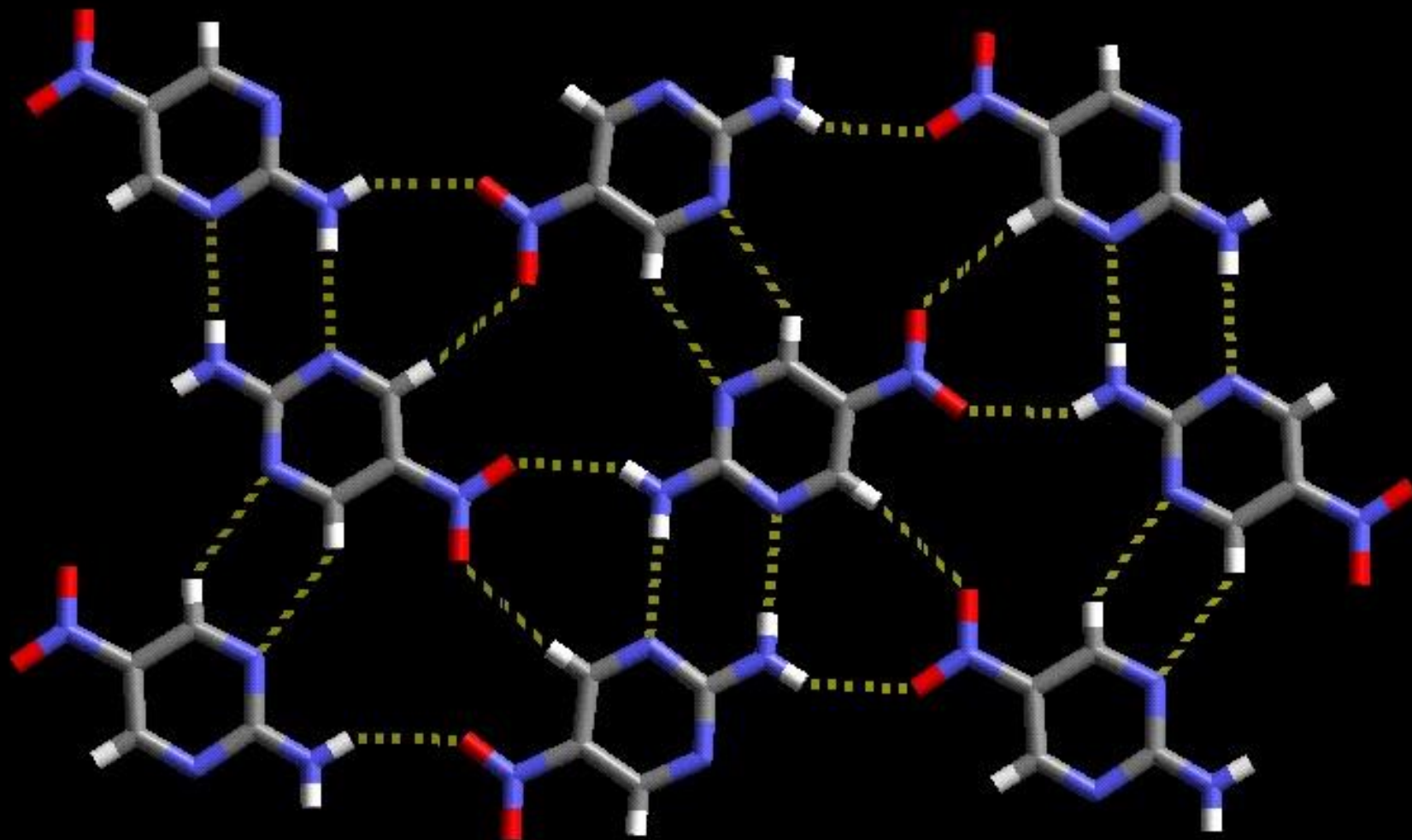
# Consequências interação-H



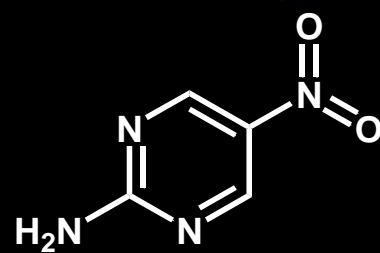
polymorphs of 5,5-diethylbarbituric acid.

*ligação-H*



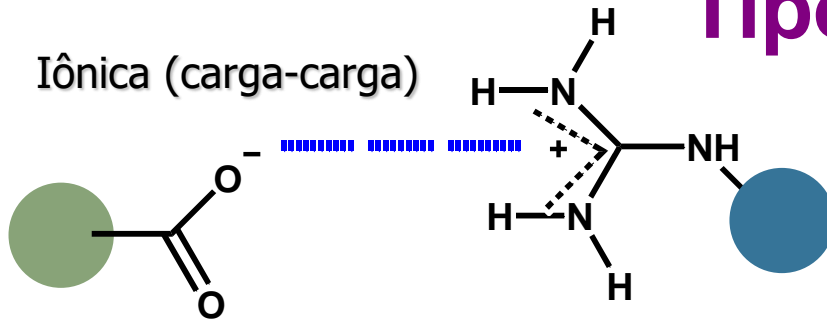


5-nitro-2-aminopirimidina



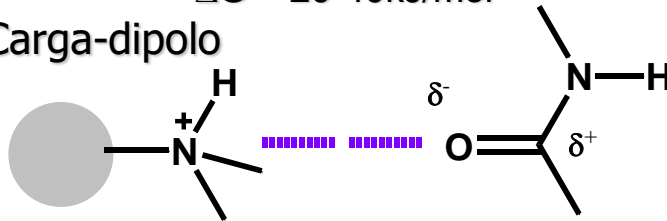
# Tipos de interações F-R

Iônica (carga-carga)



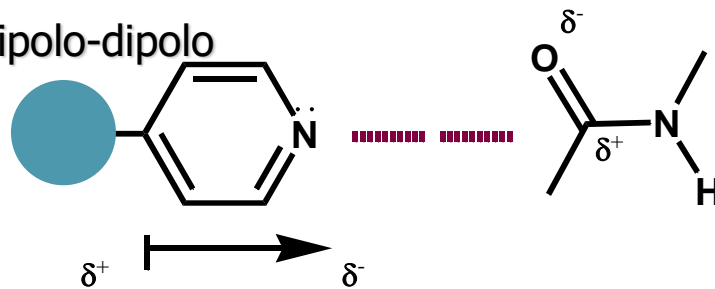
$$\Delta G = 20-40 \text{ kJ/mol}$$

Carga-dipolo



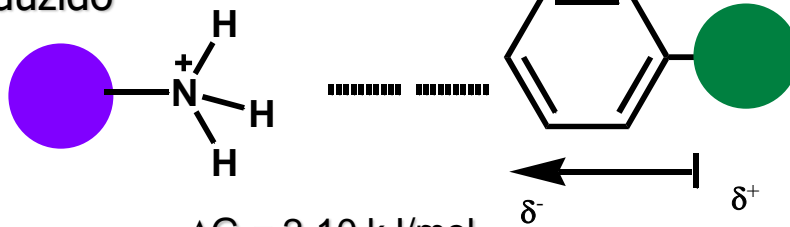
$$\Delta G = 12-20 \text{ kJ/mol}$$

Dipolo-dipolo



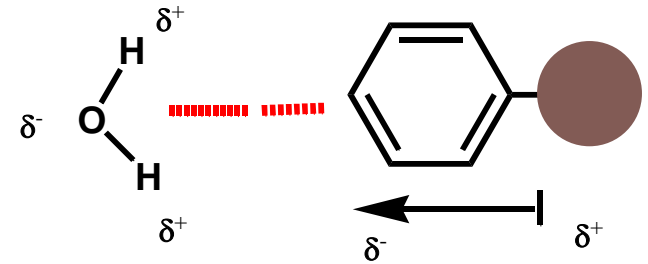
$$\Delta G = 4-12 \text{ kJ/mol}$$

Carga-dipolo induzido



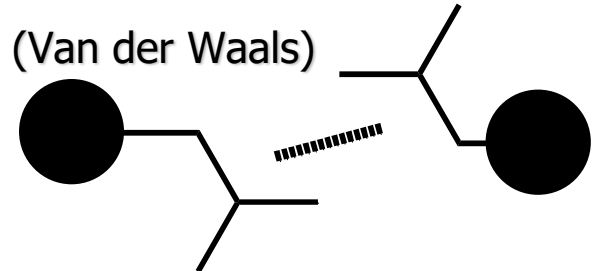
$$\Delta G = 2-10 \text{ kJ/mol}$$

Dipolo induzido-dipolo



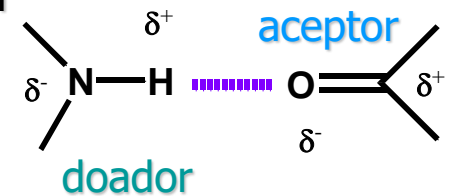
$$\Delta G = 2 \text{ kJ/mol}$$

Dispersão (Van der Waals)



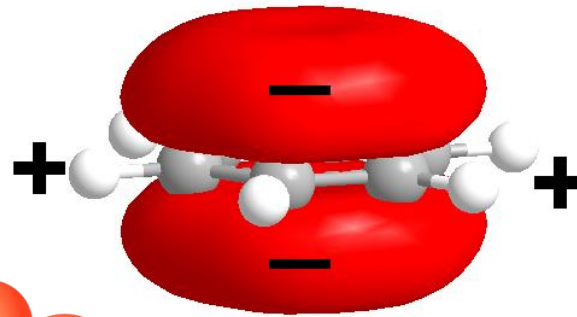
$$\Delta G = 2-4 \text{ kJ/mol}$$

Ligação-H



$$\Delta G = 4-30 \text{ kJ/mol}$$

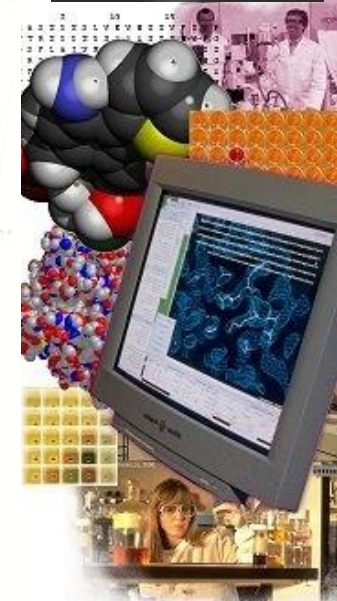
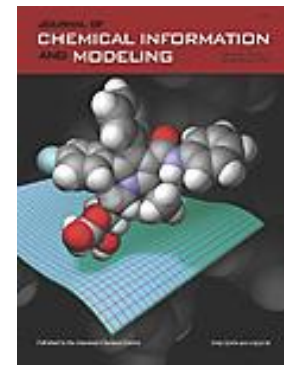
# Interações $\pi$



<b>cation-<math>\pi</math></b>		cation: Lys, Arg  $\pi$ donor: Phe, Trp, Tyr	0.2–2.5
<b><math>\pi</math>-<math>\pi</math></b>	<p>sandwich      T-shaped      parallel displaced</p>	Phe, Tyr, Trp, His	0.5–1.0
<b>van der Waals</b>	<p>side chains drug</p>	Ala, Val, Leu, Ile	0.5–1.0



# Química Computacional



**Modelagem molecular**



# Química Computacional



2013



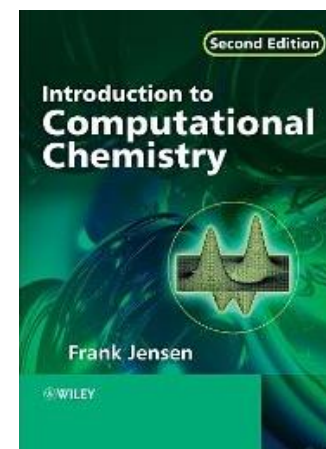
Ariel Warshel  
(1940 - )



Michael Levitt  
(1947 - )



Martin Karplus  
(1930 - )



*Modelagem & dinâmica molecular*

*“for the development of multiscale models for complex chemical systems”*



**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](#)

**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.


september; setembro
[Desativar](#)

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:



# Docking Molecular

**SELEÇÃO DOS LIGANTES**

Quimioteca (FBDD)

[Quimioteca da LASSBio](#)

**ANÁLISE CONFORMACIONAL**  
(método semi-empírico AM1)

CAPÍTULO 5

UMA INTRODUÇÃO À MODELAGEM MOLECULAR APLICADA À QUÍMICA MEDICINAL 231



**ESTRUTURA do BIORRECEPTOR**

▪ PDB\*

▪ Construção do modelo

*FlexX / Gold*

*\*PROTEIN DATA BANK*

**ANCORAMENTO DOS LIGANTES (hit)**



Dr Laurent Dardenne  
<https://dockthor.lncc.br>

Virtual Screening

**SELEÇÃO DA ESTRUTURA DE REFERÊNCIA**

**IDENTIFICAÇÃO DO SÍTIO DE RECONHECIMENTO**

Mapa farmacofórico 3D/SAR

**DETERMINAÇÃO DA ENERGIA LIVRE DE INTERAÇÃO ( $\Delta G_{\text{interação}}$ )**

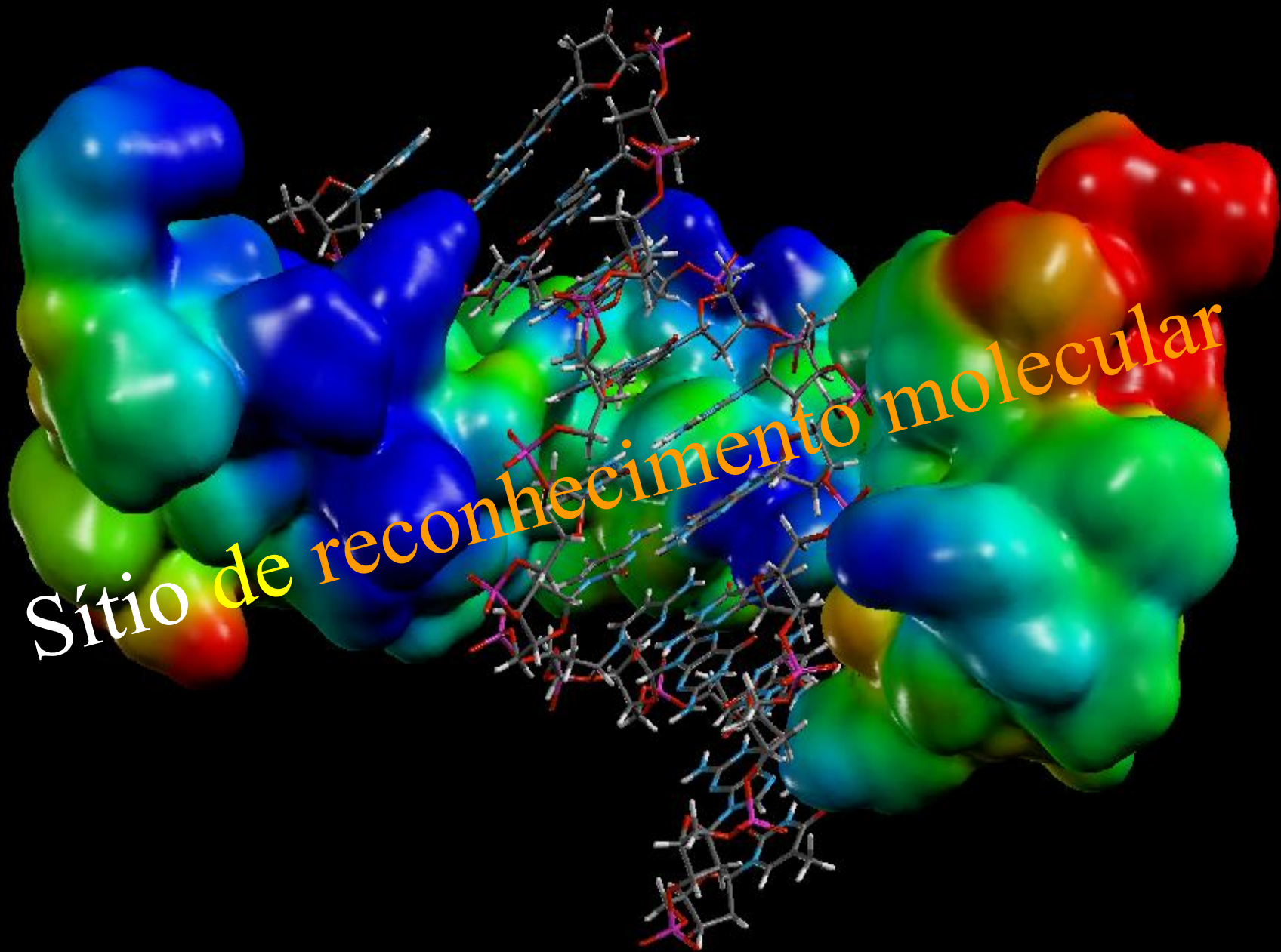
Sybyl, Version 8.0, Tripos Associates  
Spartan Pro 14.0, Wavefunction, Inc.

KNIME; Biovia Discovery

GOLD (Jones et al. 1997; Portal da CAPES); Glide (Schr)

**Hit**  
**(10  $\mu$ M; >30  $\mu$ M)**

**Validação**  
**(h<sub>2</sub>l)**

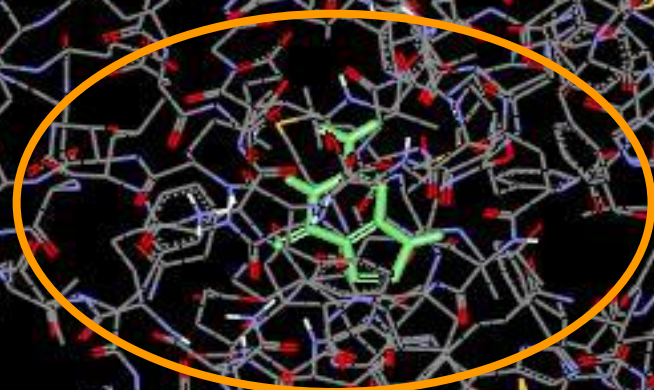






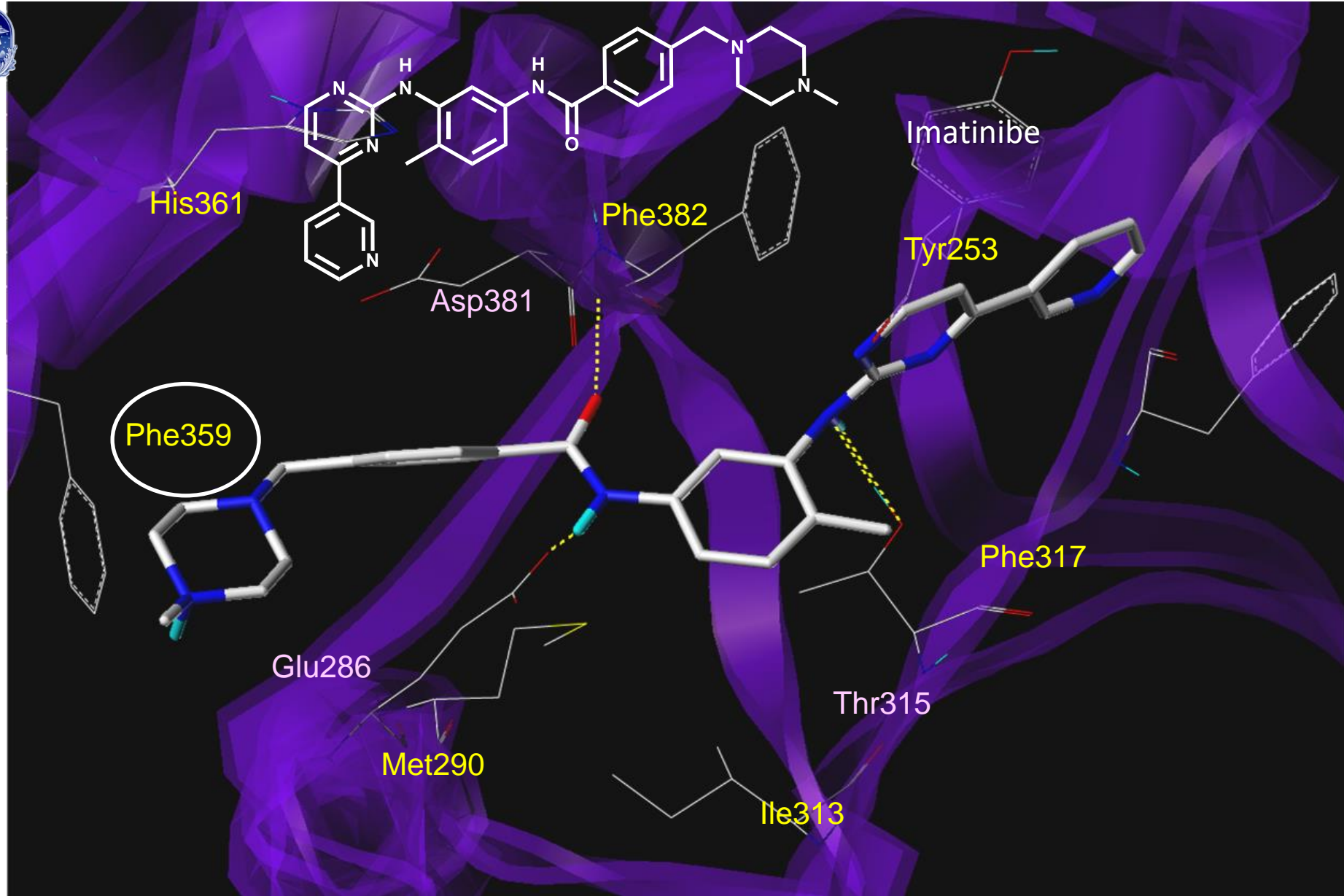
Biorreceptor

Estrutura 3D do alvo terapêutico



Fármaco

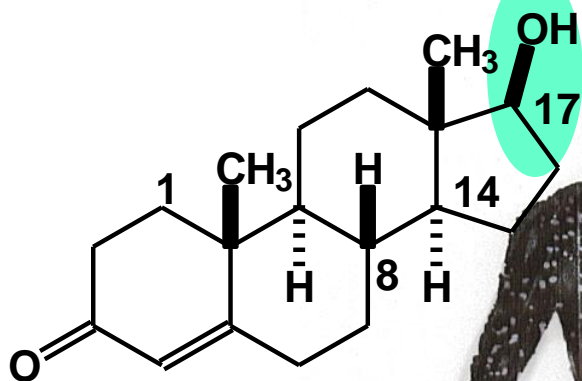
Sítio de reconhecimento molecular



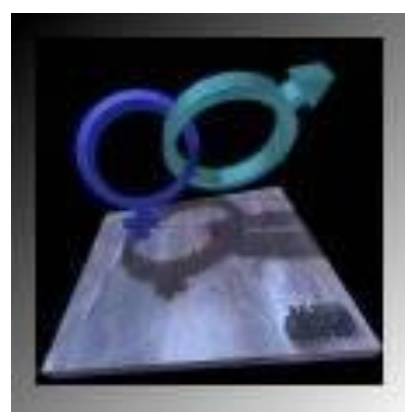
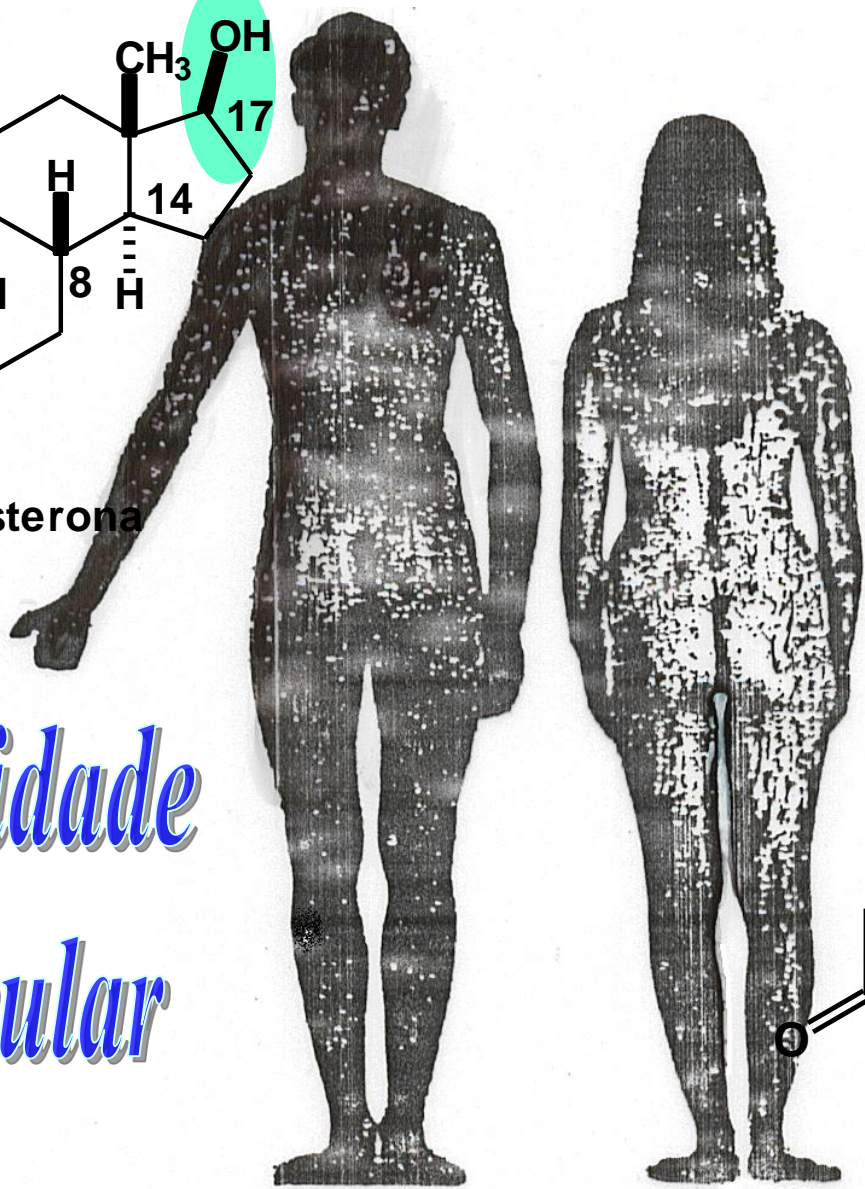
Estrutura do imatinibe complexado no domínio da *h*-ABL-K (código no PDB: 2HYY; Resolução= 2,4 Å) obtida por ancoramento molecular com o programa FlexX (licença # 7512).. Valor de energia livre de ligação teórica ( $\Delta G_{lig}$ ) de -35,751 kJ/mol.



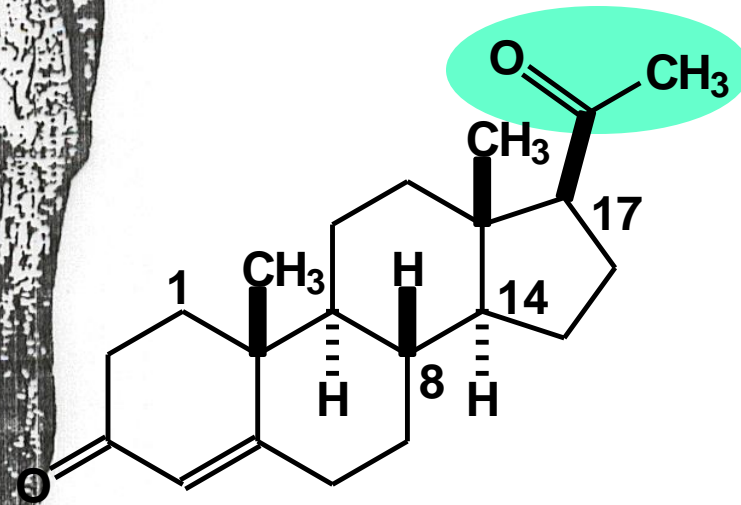
# Reconhecimento Molecular-II



testosterona



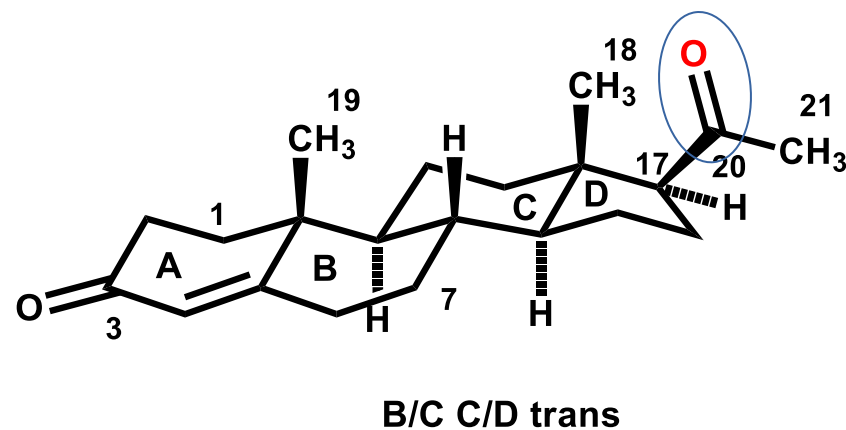
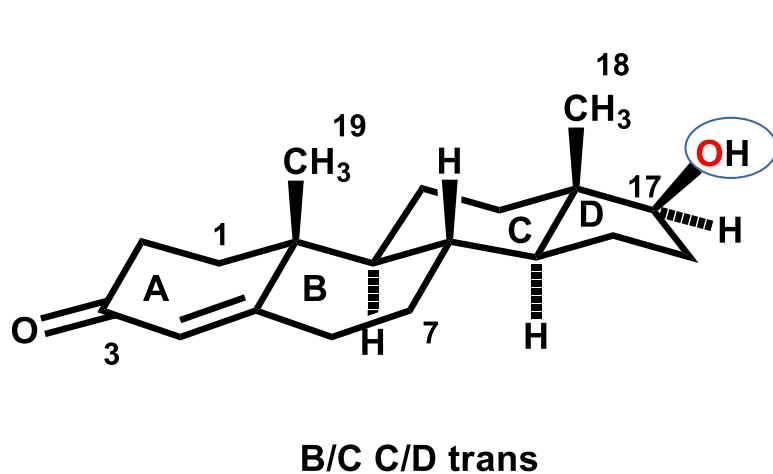
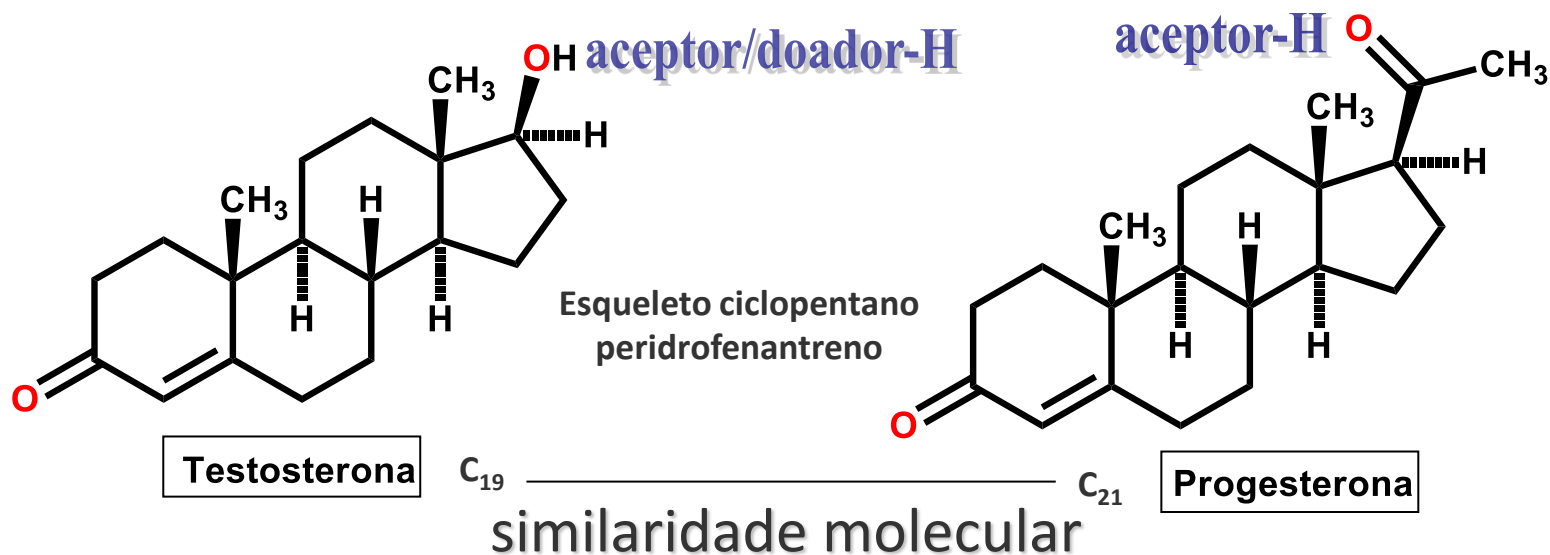
*Similaridade*  
*Molecular*

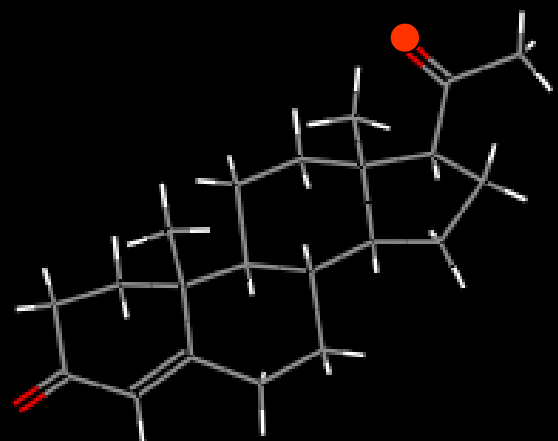


progesterona

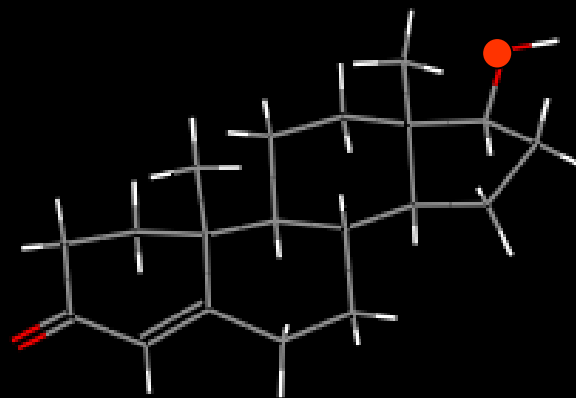
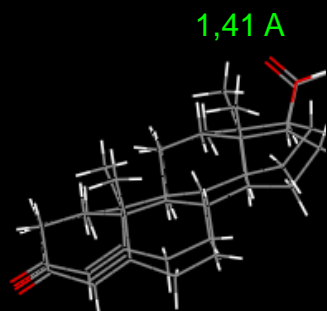


# Reconhecimento Molecular

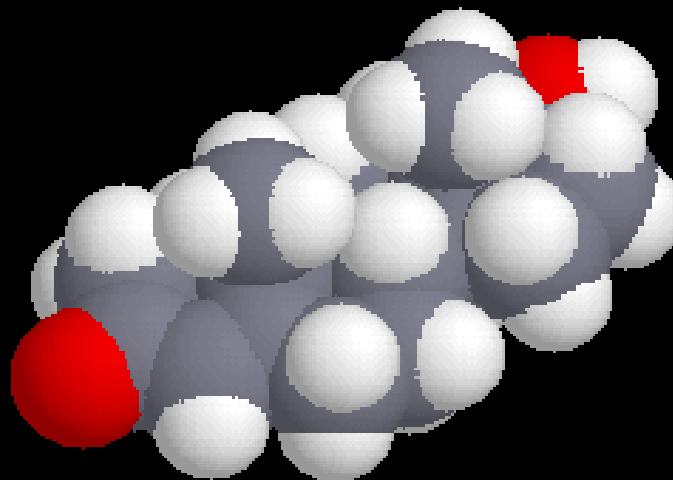
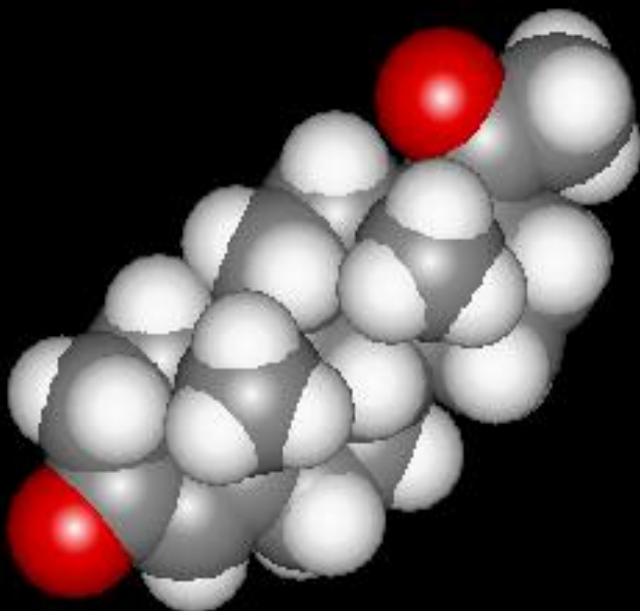




progesterona



testosterona

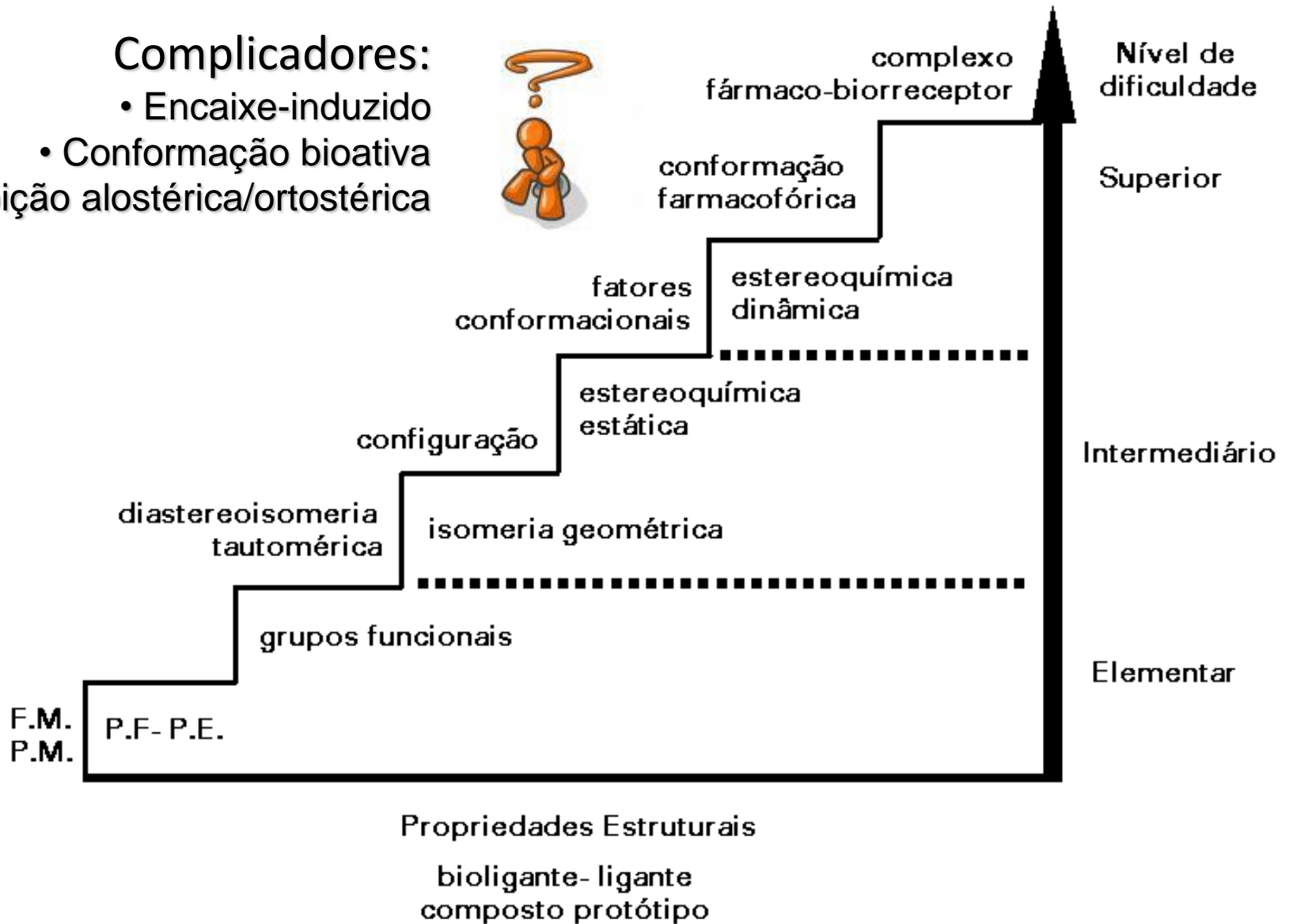




# Nível hierárquico da descrição da complementaridade F-R

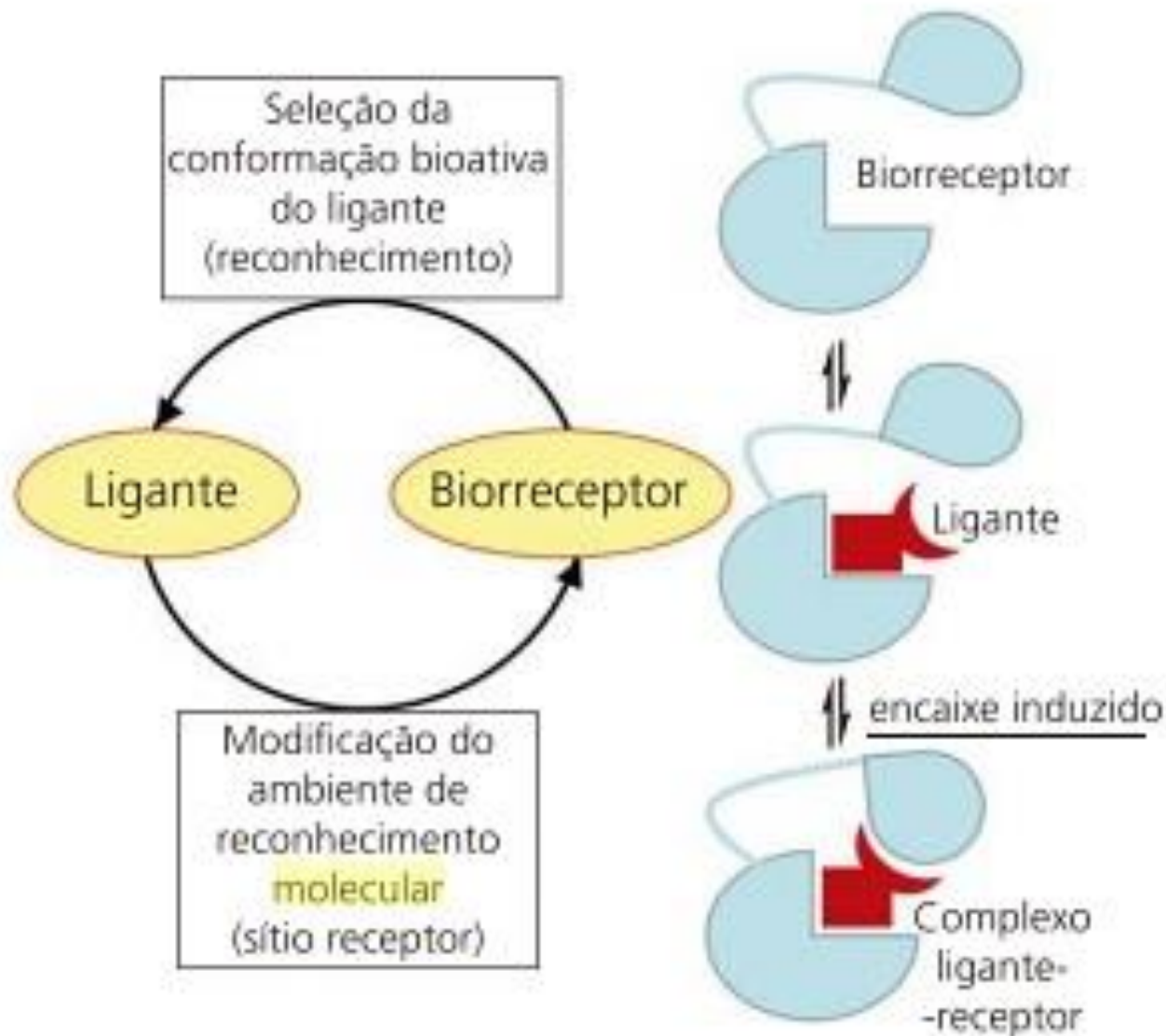
Complicadores:

- Encaixe-induzido
- Conformação bioativa
- Inibição alostérica/ortostérica





# O encaixe induzido F-R



**Altera a energia livre do sistema**