

Química Medicinal



Mini-curso 17

62ª Reunião Anual SBPC - UFRN



27-30 julho de 2010



LASSBio

UFRJ

Eliezer j. Barreiro

Professor Titular

Parte 2





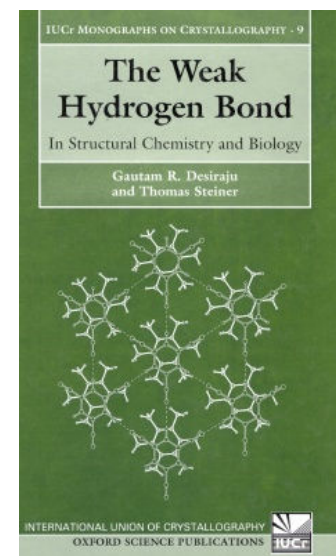
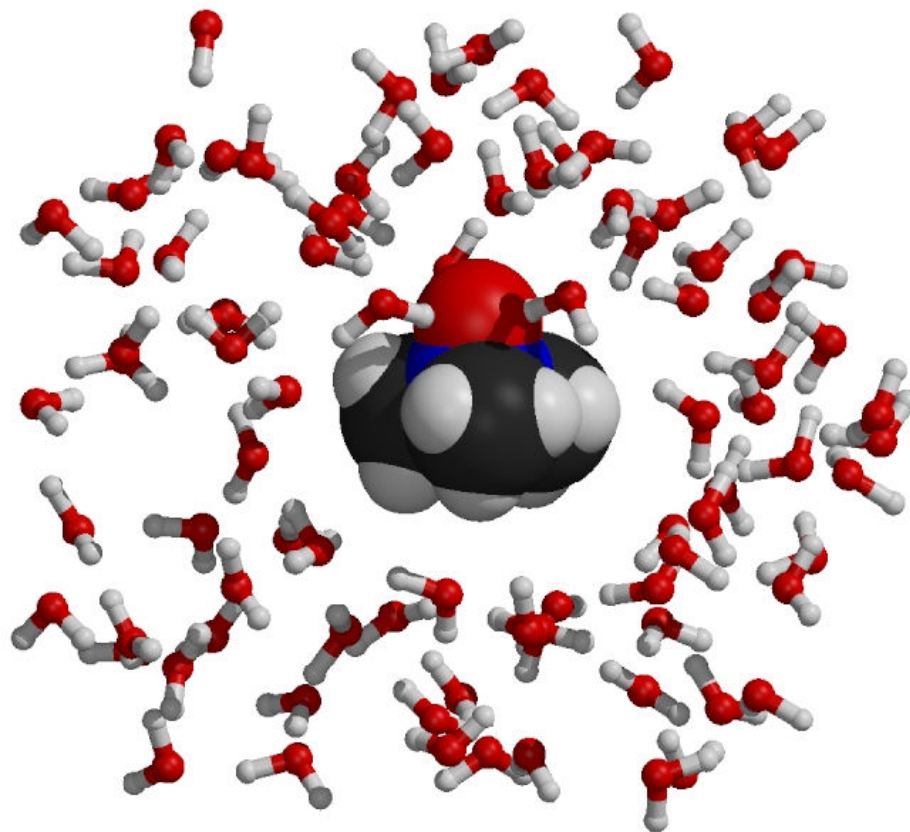
***A importância das
interações frágeis***



**Química
Medicinal**



A importância das “*ligações*” frágeis...



“*ligações*”
de hidrogênio ...

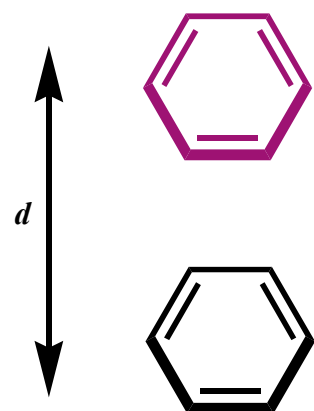


Linus Pauling, 1939

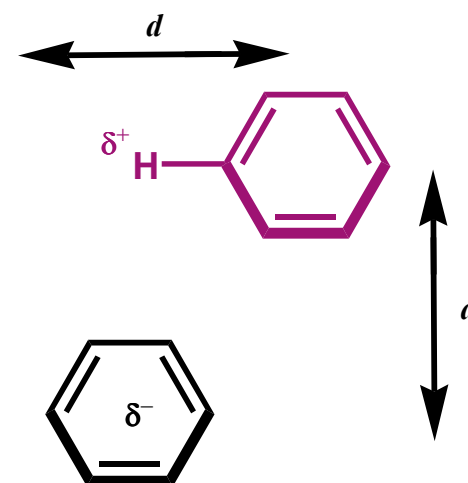




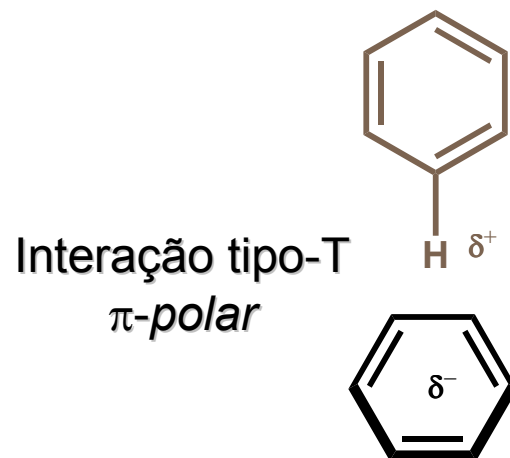
Interações π - π



Interação sanduíche
 π -stacking



Interação paralela

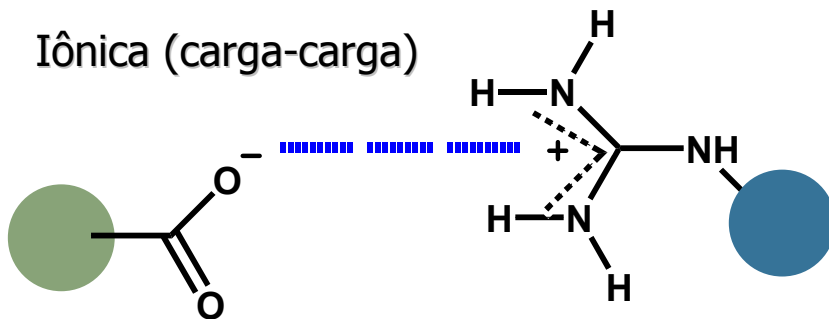


Interação tipo-T
 π -polar



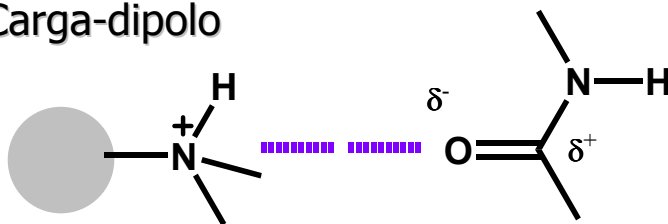
Tipos de interações

Iônica (carga-carga)



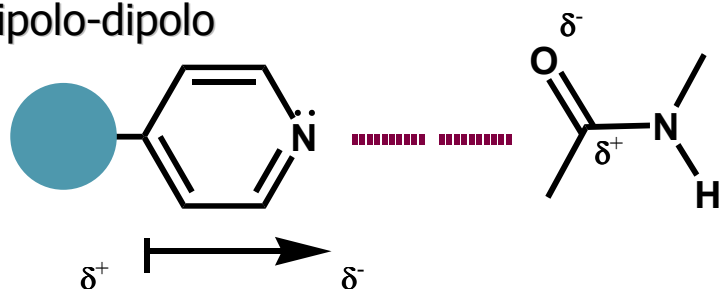
$$\Delta G = 20-40 \text{ kJ/mol}$$

Carga-dipolo



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

Dipolo-dipolo



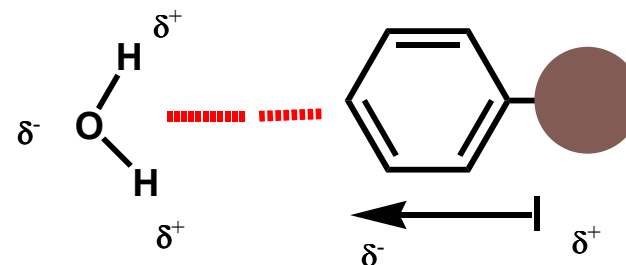
$$\Delta G = 4-12 \text{ kJ/mol}$$

Carga-dipolo induzido



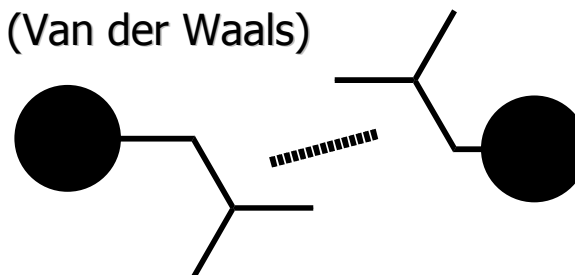
$$\Delta G = 2-10 \text{ kJ/mol}$$

Dipolo induzido-dipolo



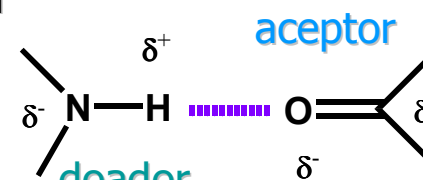
$$\Delta G = 2 \text{ kJ/mol}$$

Dispersão (Van der Waals)



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

Ligação-H



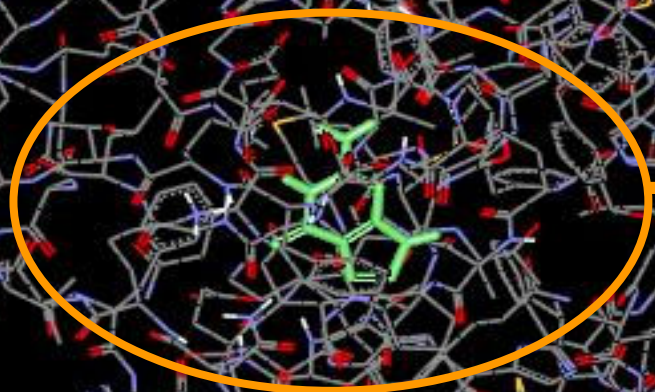
$$\Delta G = 4-30 \text{ kJ/mol}$$



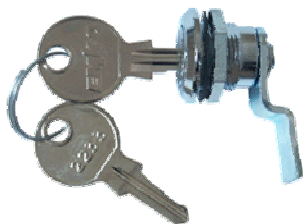
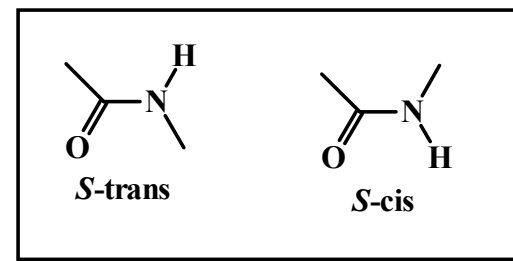
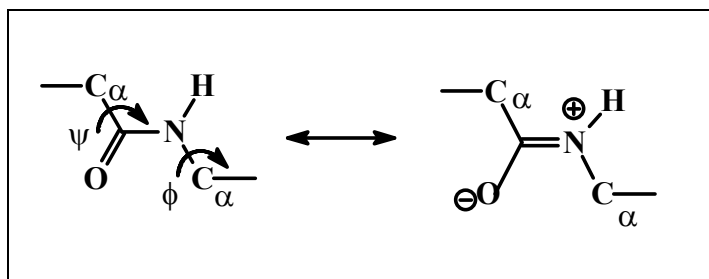
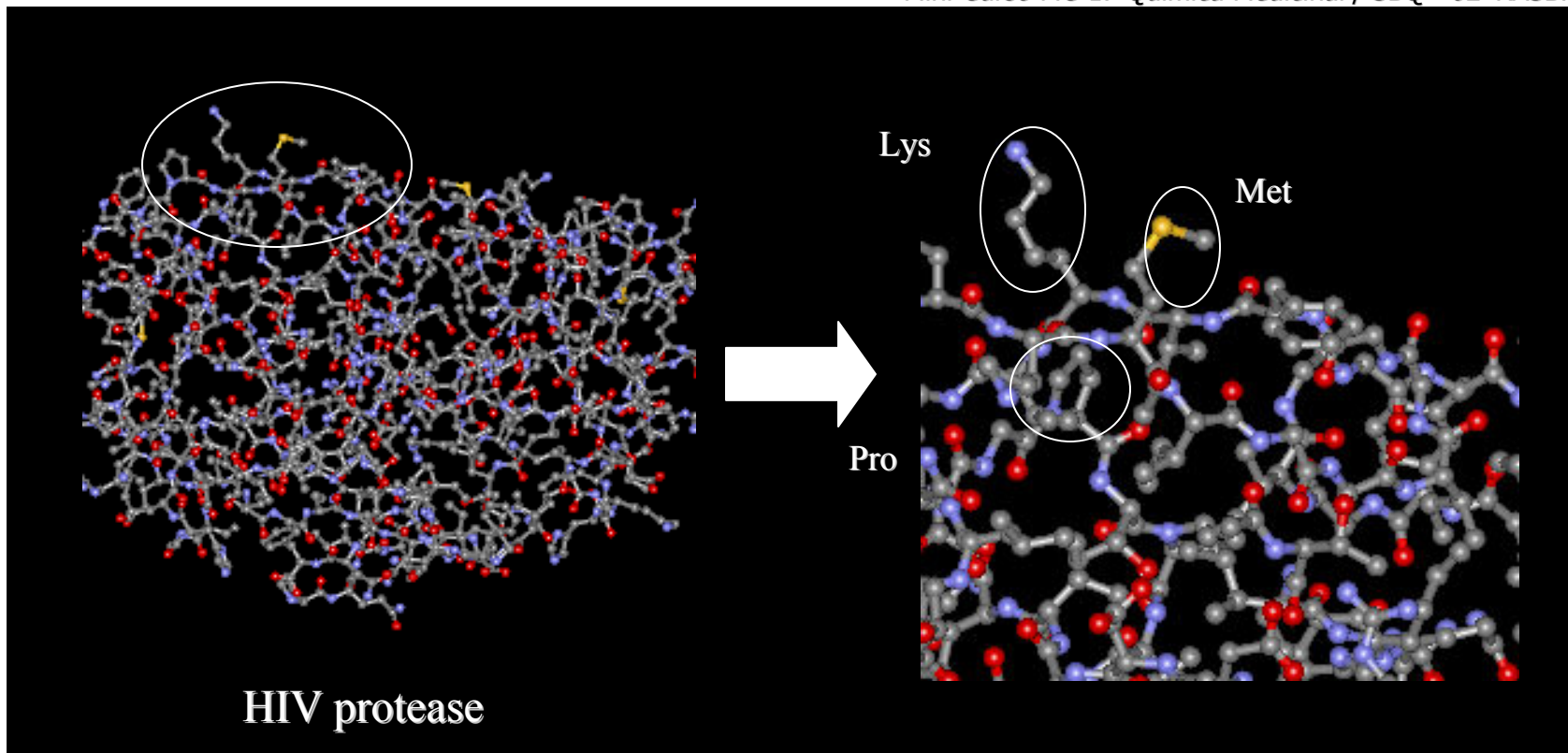
Biorreceptor

Estrutura 3D do alvo terapêutico

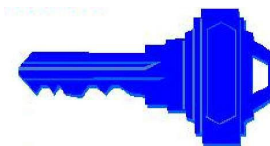
Sítio de reconhecimento molecular



Fármaco

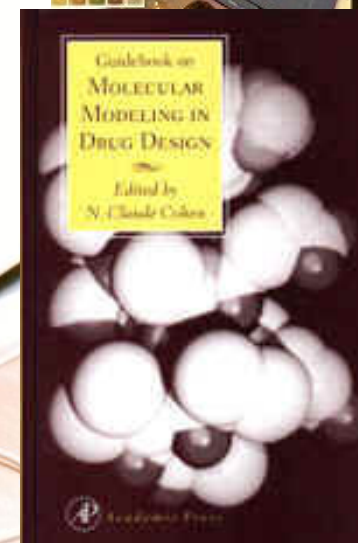
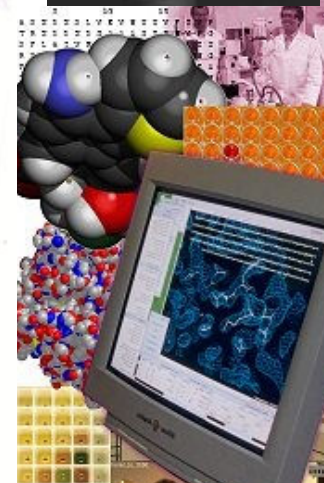
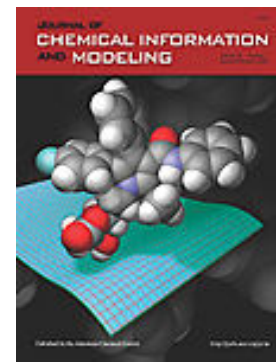


proteínas
enzimas
biorreceptores





Modelagem Molecular





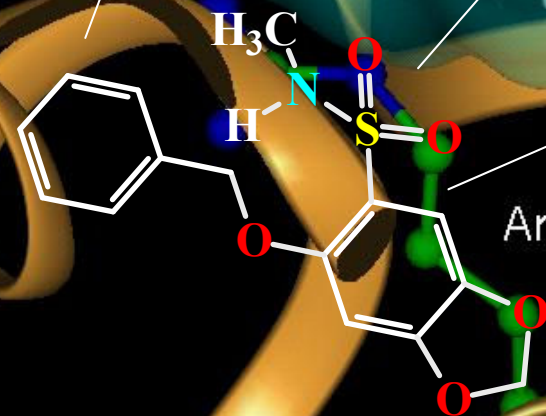
Arg513

Phe518

Tyr385

Ser530

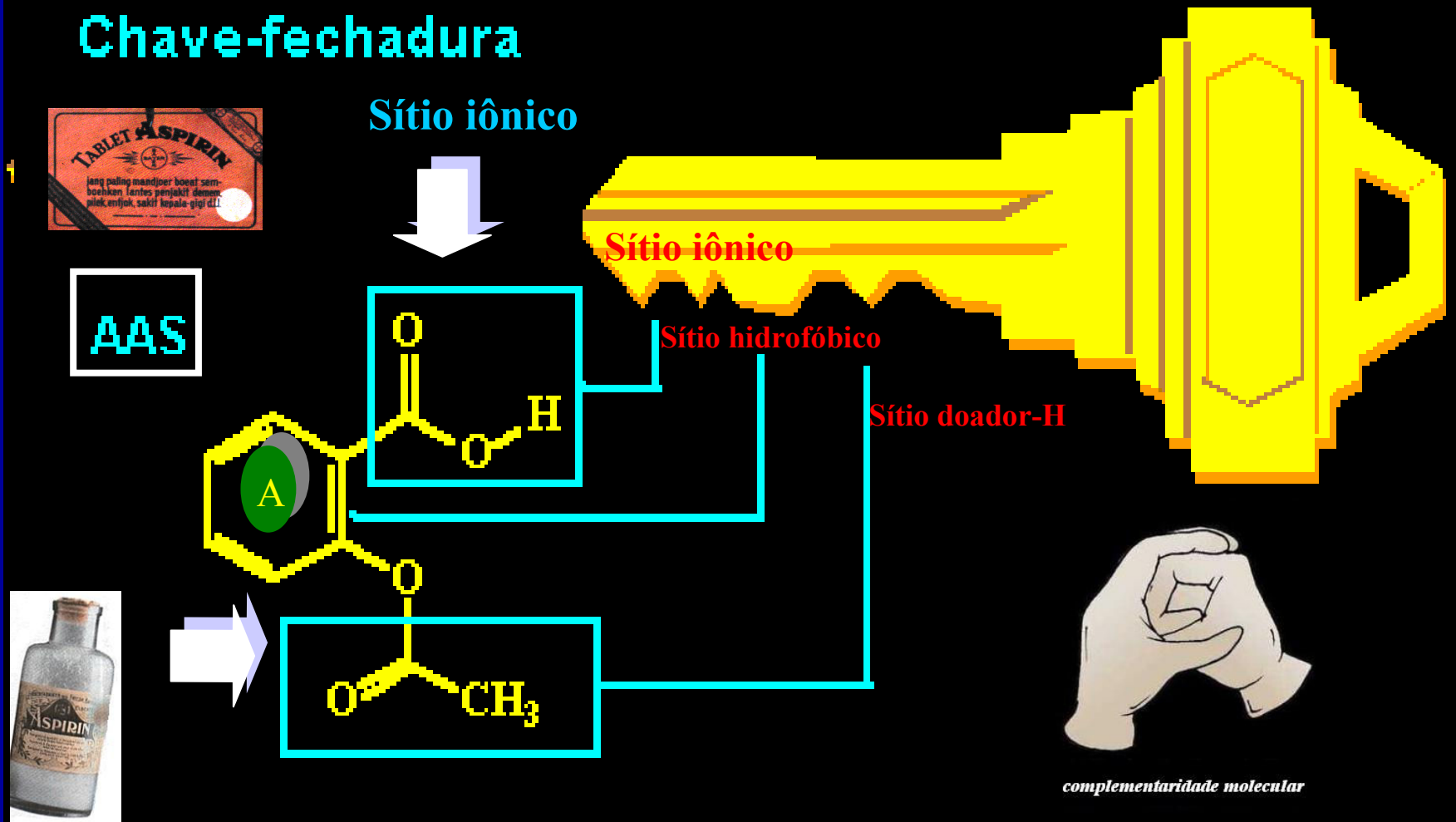
Arg120





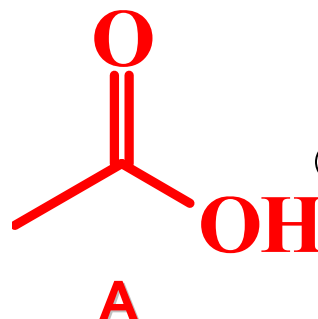
O Centenário Modelo "Chave-Fechadura"

Complementaridade do modelo Chave-fechadura

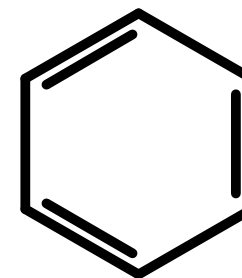
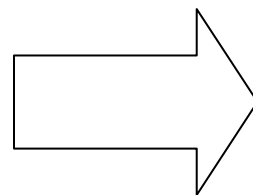
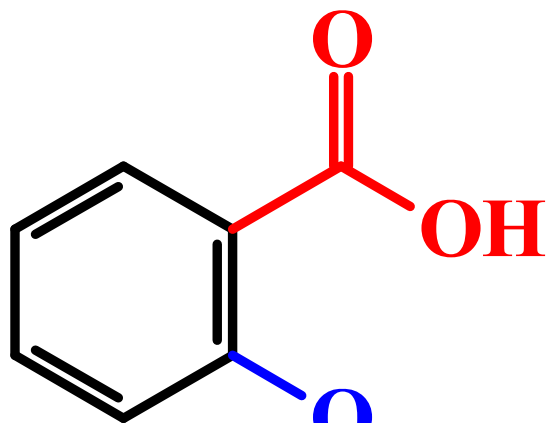




Dissecação Molecular



ácido carboxílico

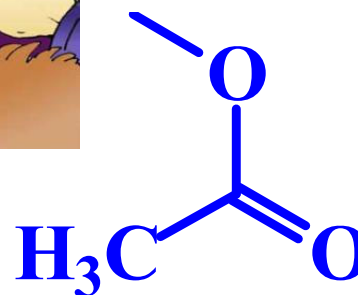
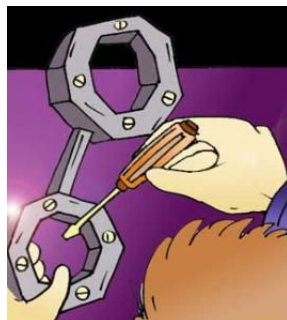


B

fenila



Ácido acetilsalicílico

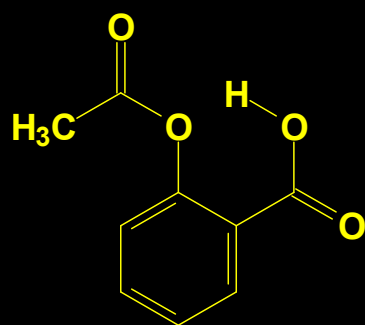
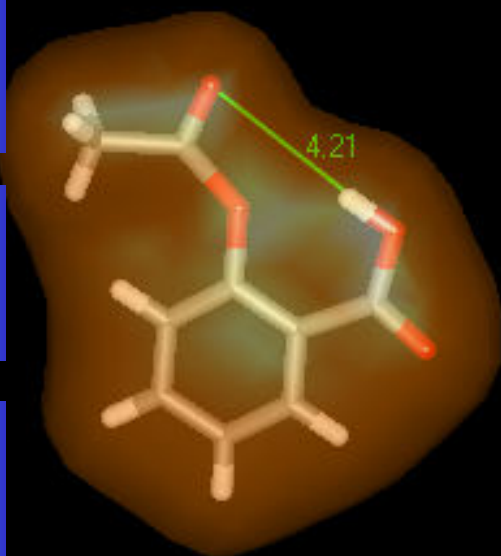


éster

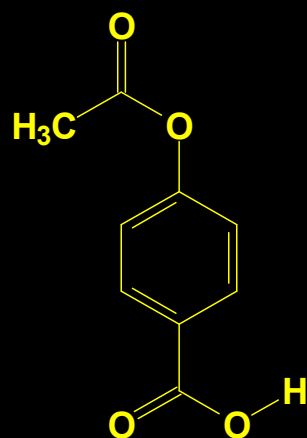
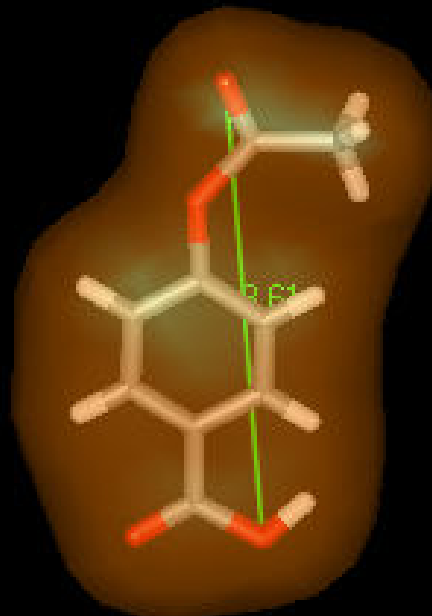
C



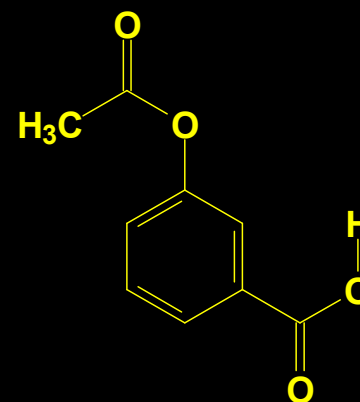
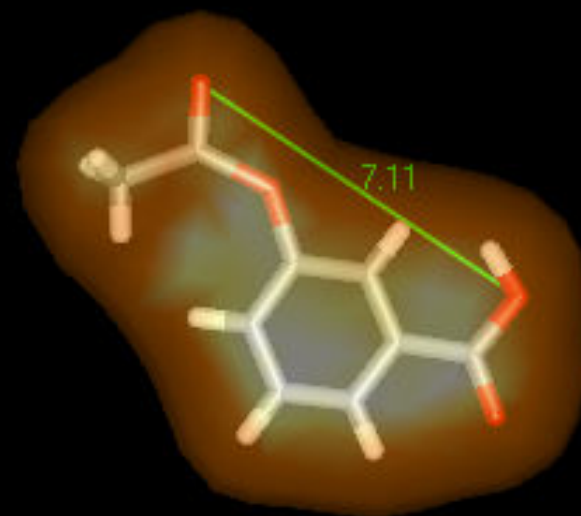
Regioisomêros do ácido acetil salicílico (AAS)



orto



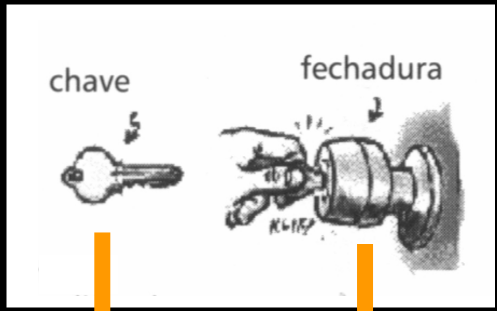
para



meta

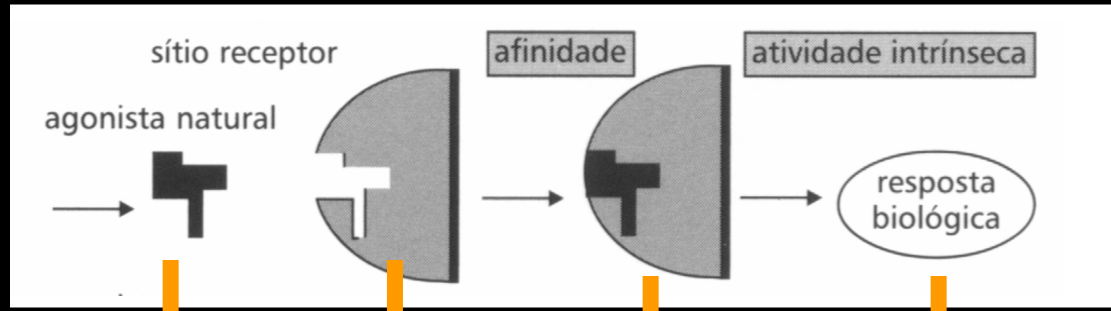


O Centenário Modelo "Chave-Fechadura"



Fármaco
Substrato natural

Enzima
= Alvo terapêutico

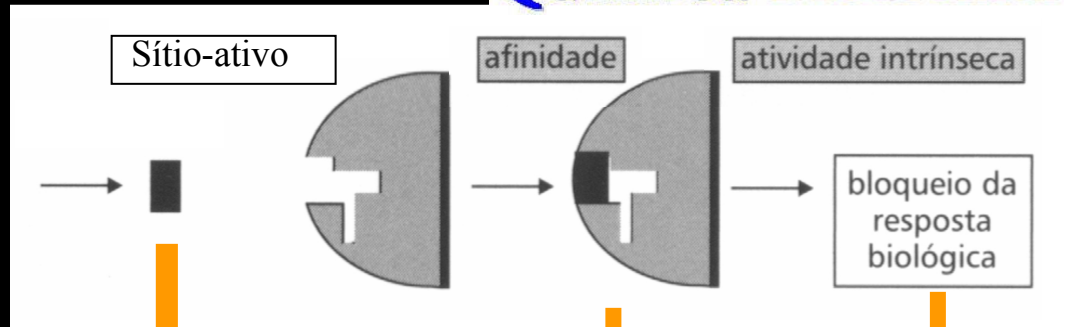


Ácido araquidônico

PGHS-1
PGHS-2
PGE₂ icosanóide

inflamação

Química Medicinal

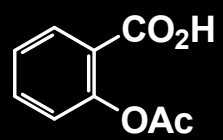


Inibidor: AAS

PGHS-2
PGHS-1

NSAI

NSAI = antiinflamatórios não-esteróides





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

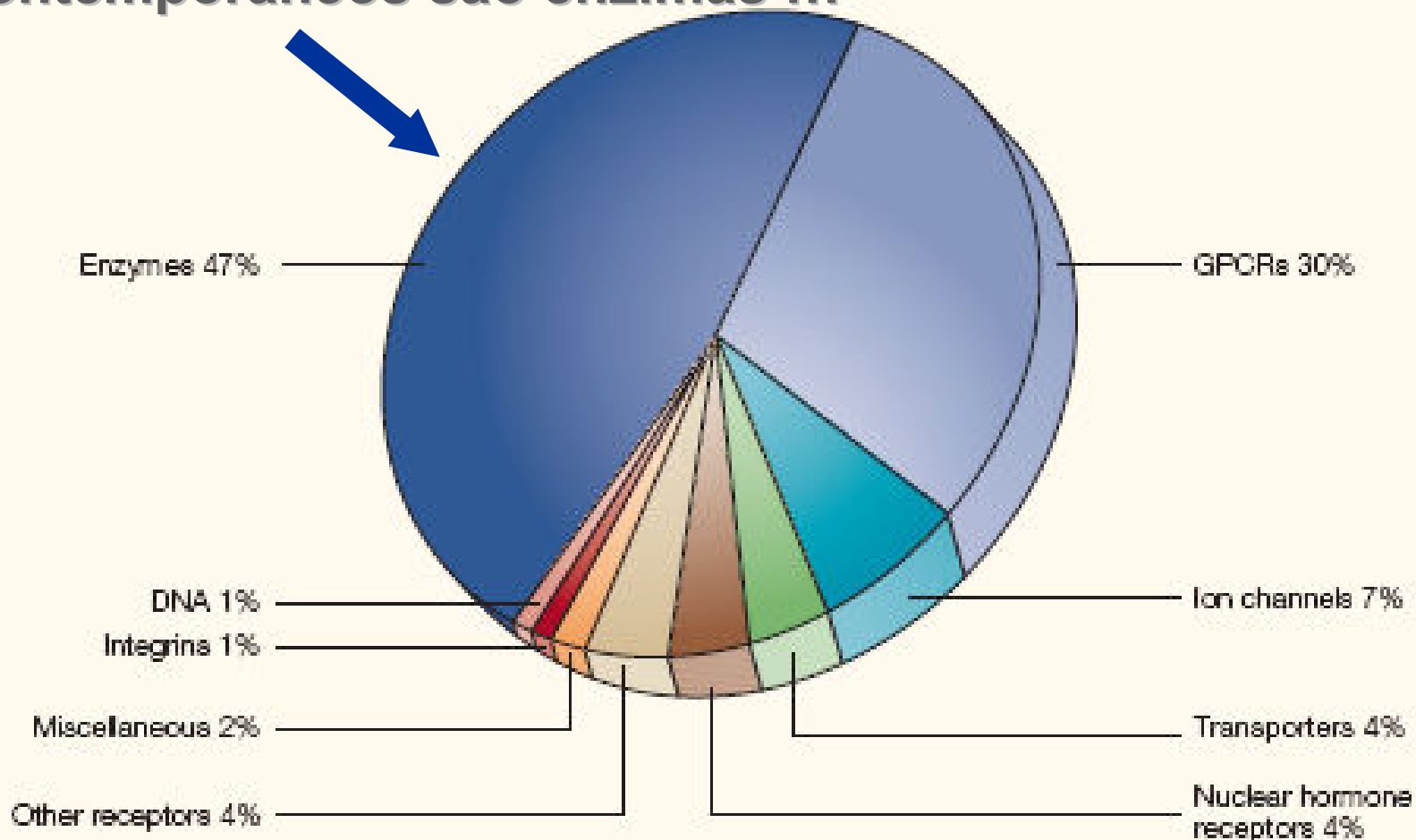
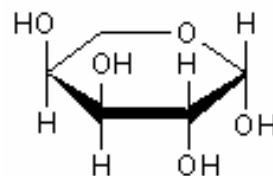
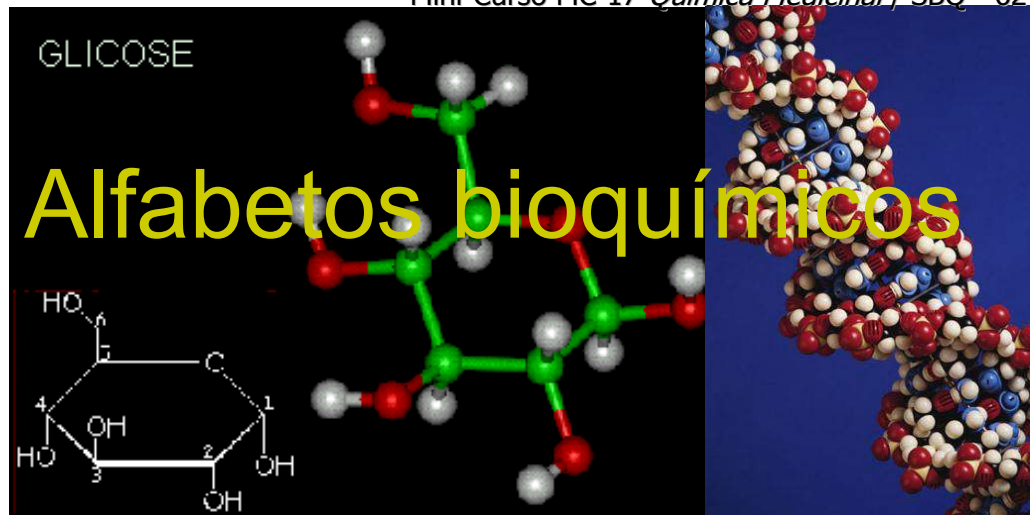
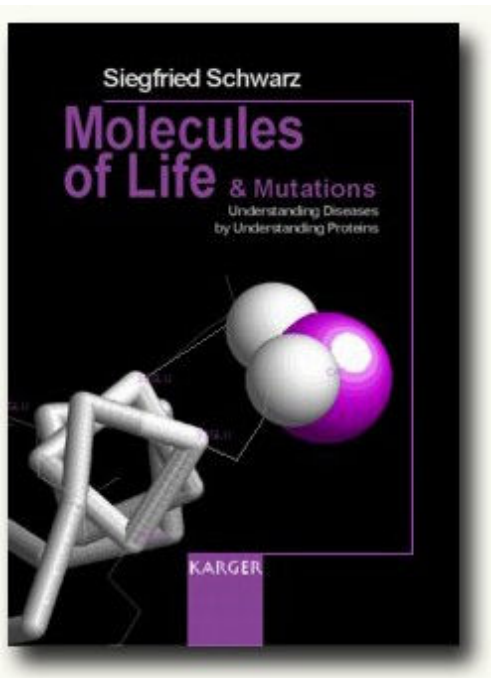


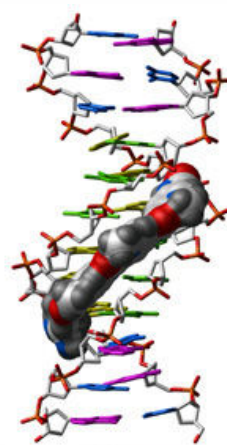
Figure 4 | Marketed small-molecule drug targets by biochemical class. GPCR, G-protein-coupled receptor.

...de apenas 130 famílias distintas de proteínas !





β -L-Arabinose



Model Compound Bound to the Minor Groove of a DNA Molecule

Carboídratos

Lipídeos

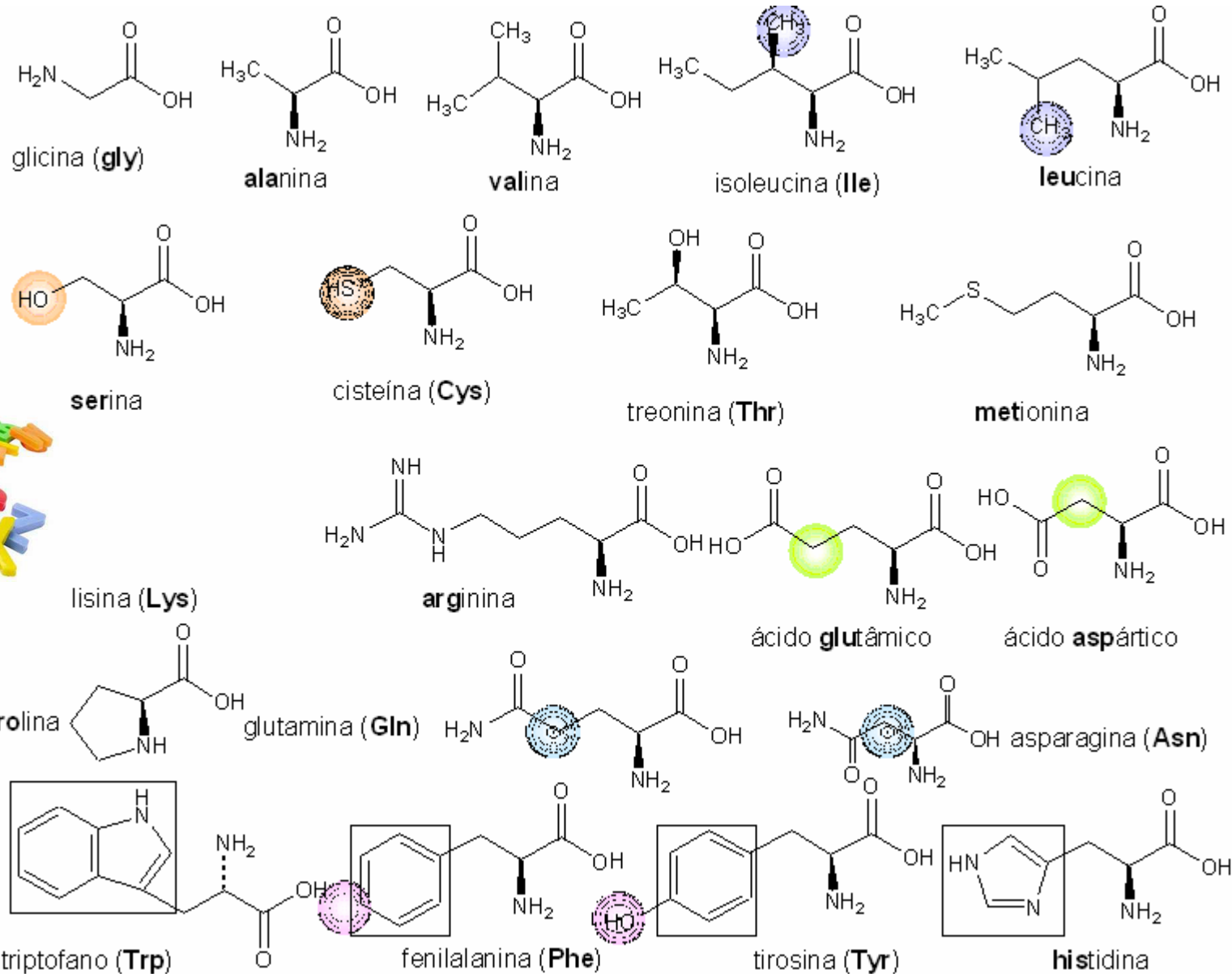
ácidos nucleícos

proteínas



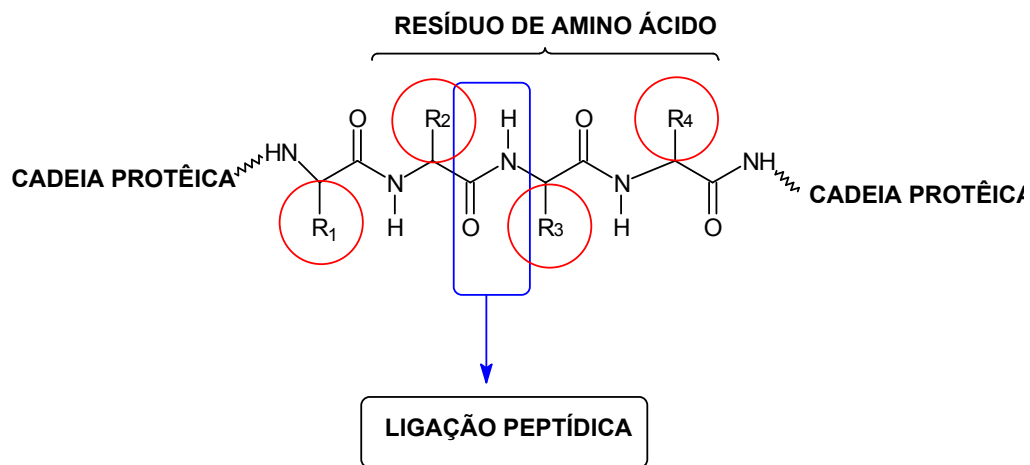
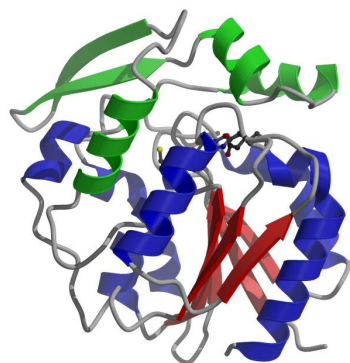
“ligações” de hidrogênio ...

Mini-Curso MC-17 *Química Medicinal* / SBQ - 62ª RASBPC





Estrutura Primária das Proteínas



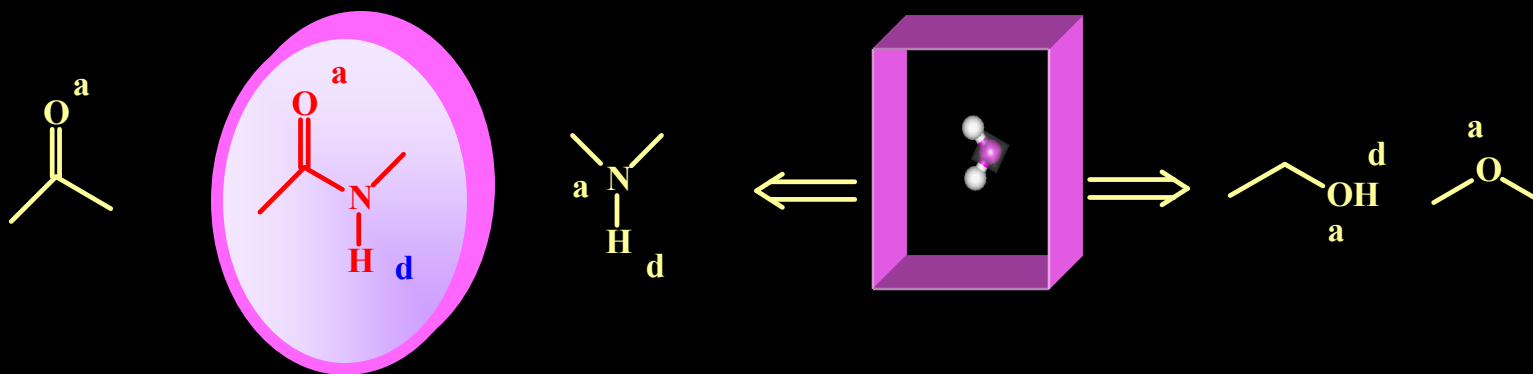
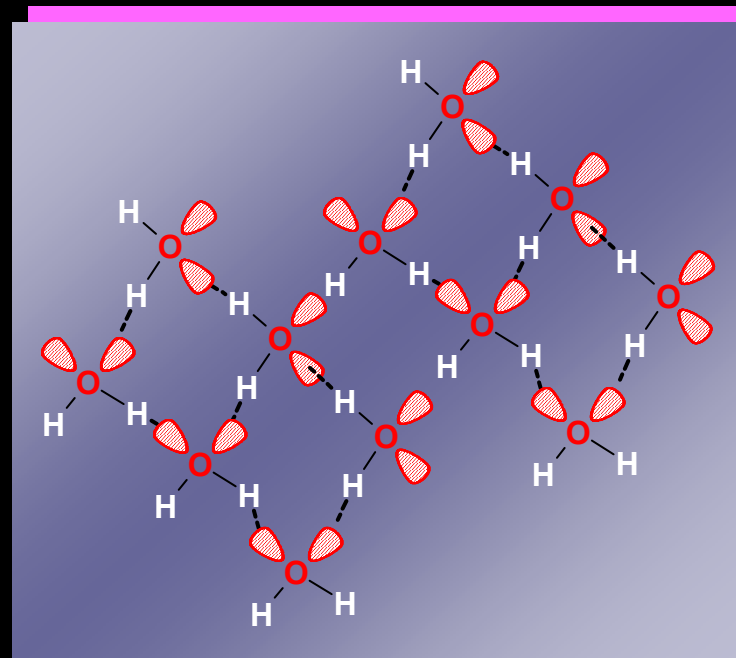
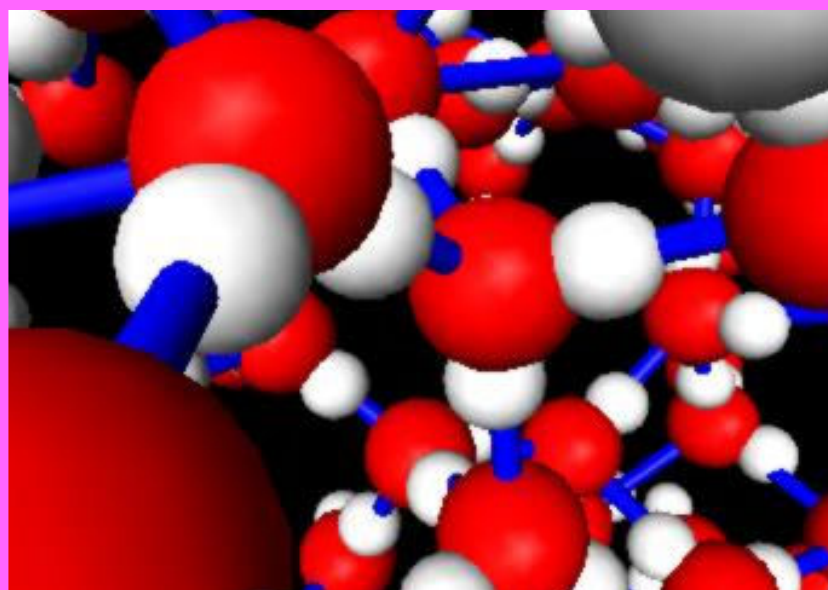
- AMINO ÁCIDOS: {
- Essenciais: His, Ile, Leu, Lys, Met, Phe, Thr, Trp, Val
 - Não-essenciais: Ala, Arg, Asn, Asp, Cys, Glu, Gln, Gly, Pro, Ser, Tyr

"Fechadura"



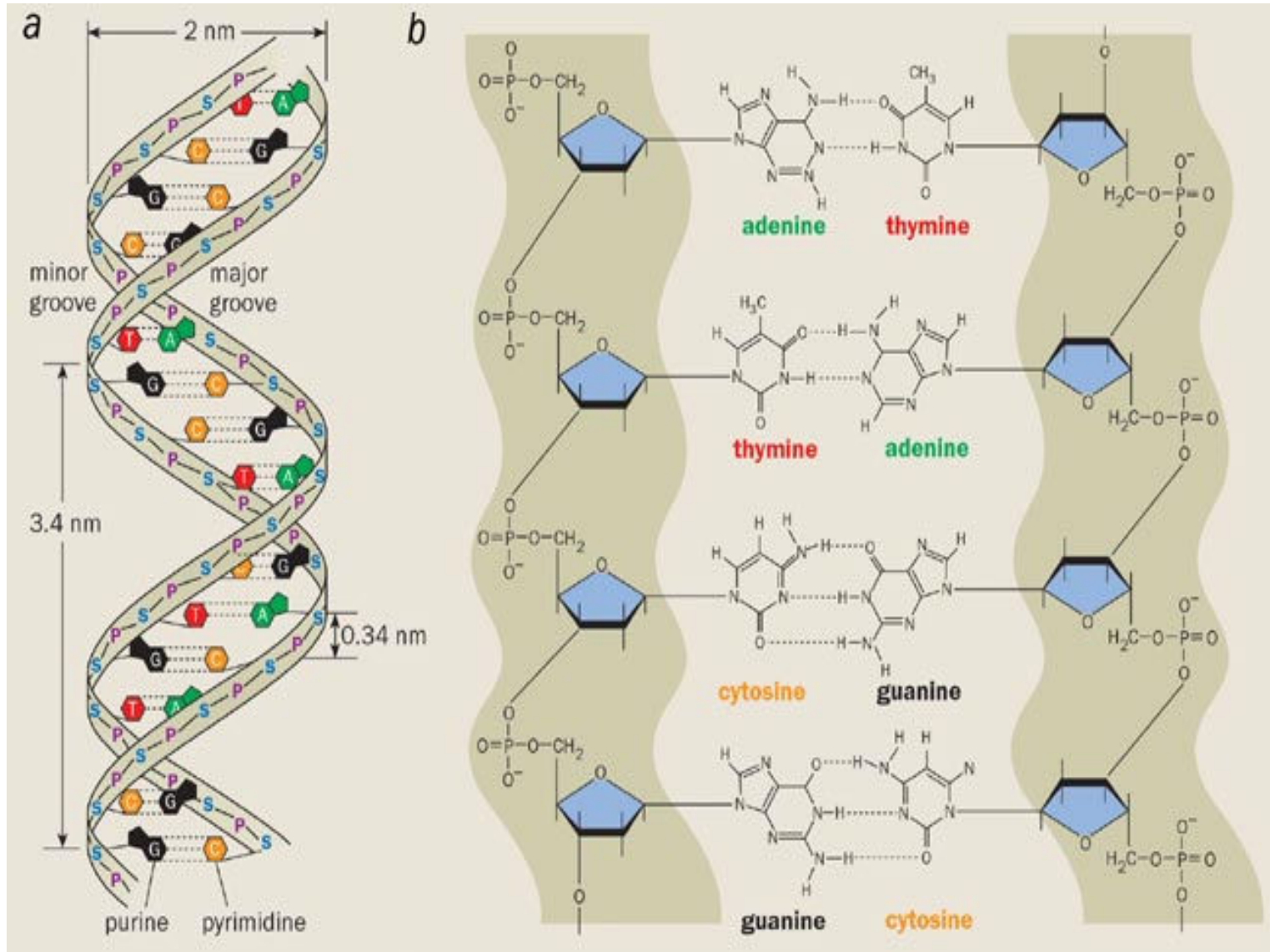


A ligação de hidrogênio





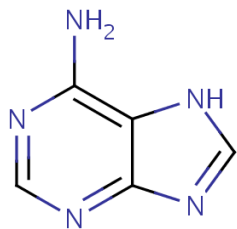
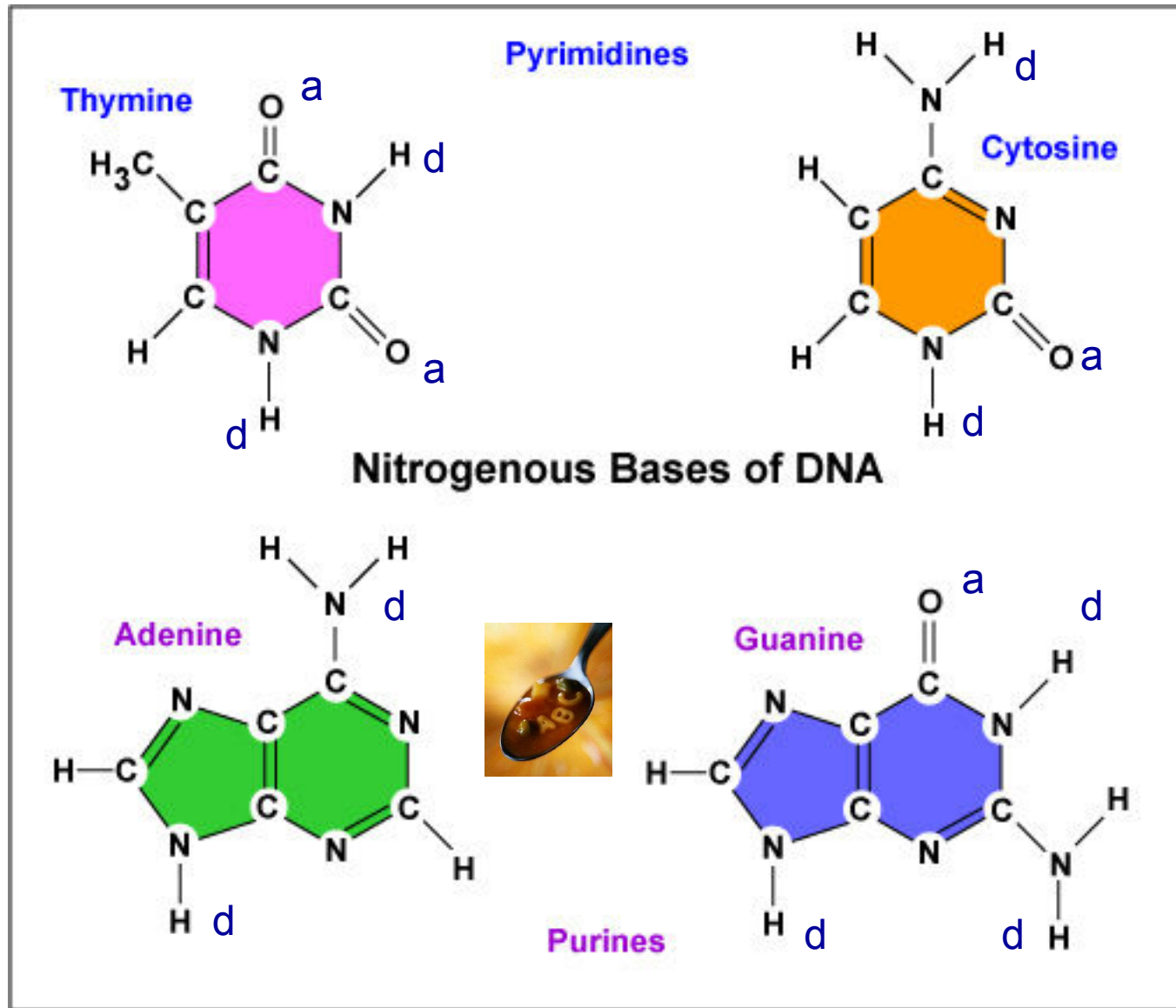
A Importância da Ligação de Hidrogênio



...alfabeto de 4 letras apenas... para 20 AA essenciais

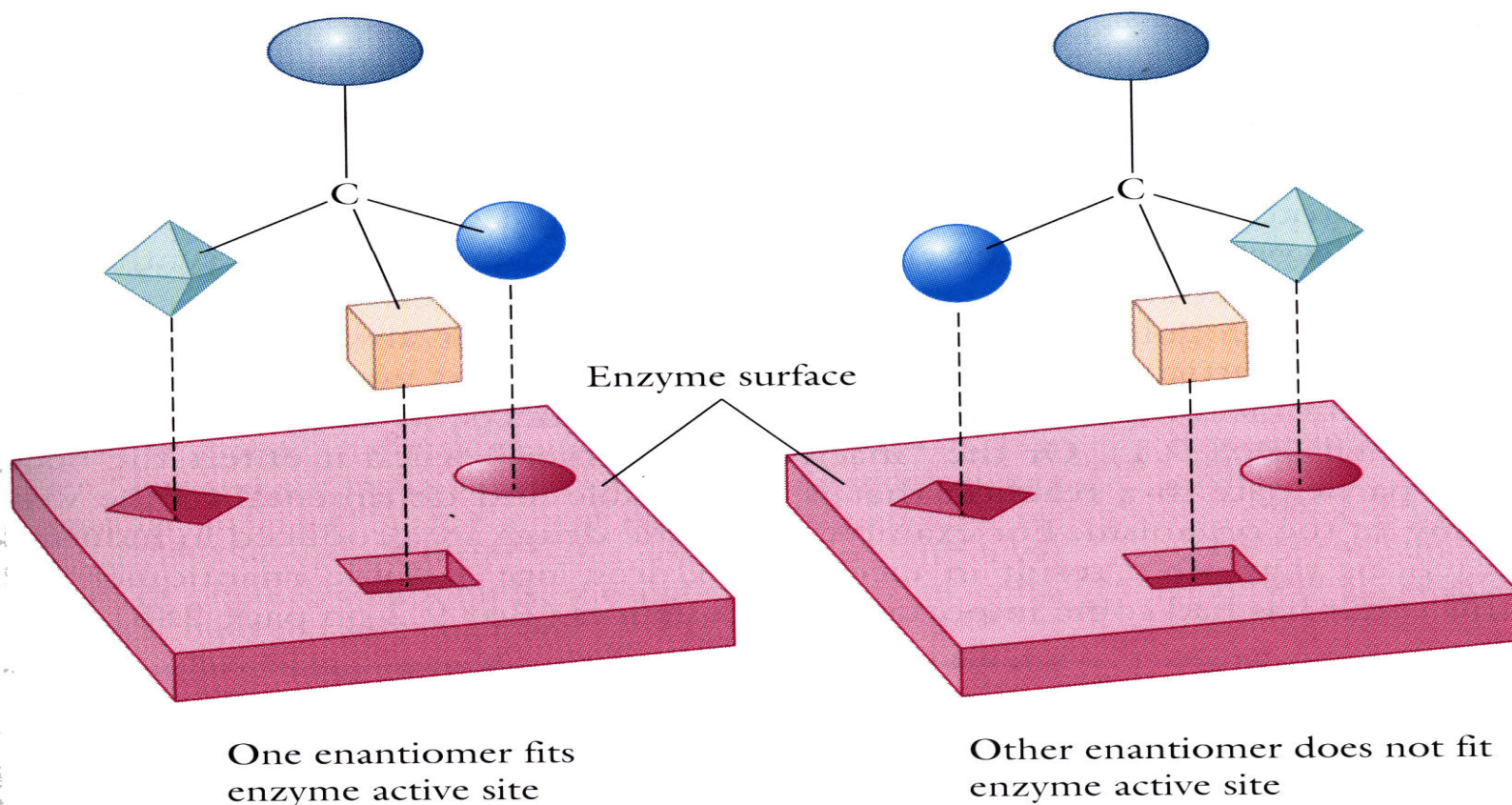


“ligações” de hidrogênio ...



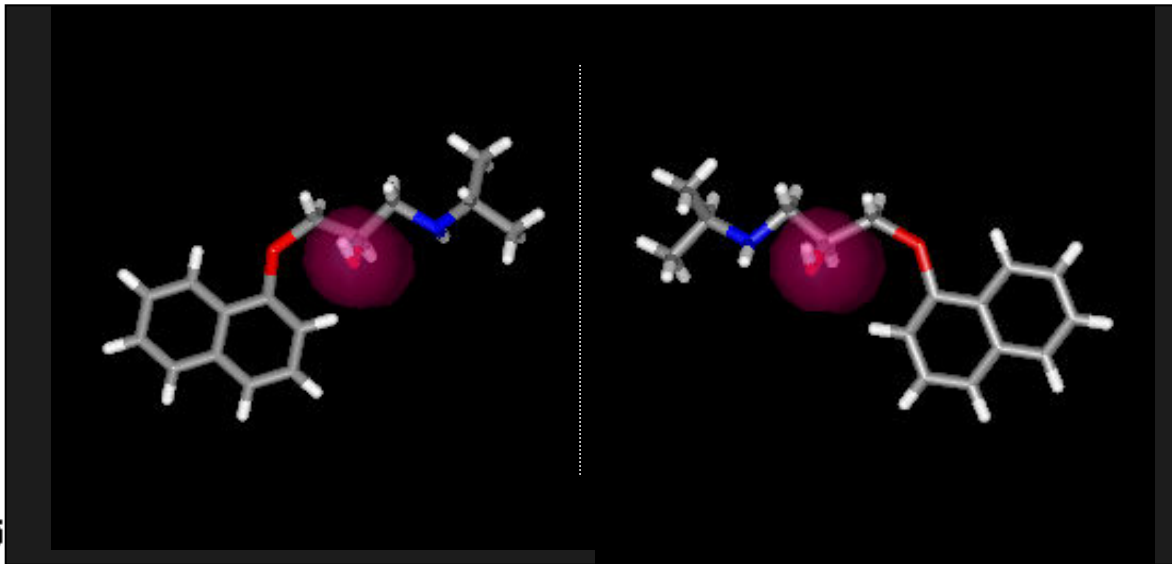


A quiralidade da vida...



Modelo dos três pontos

Modelo de Easson-Stedman



Eutômero
Distômero

Interação hidrofóbicas

