

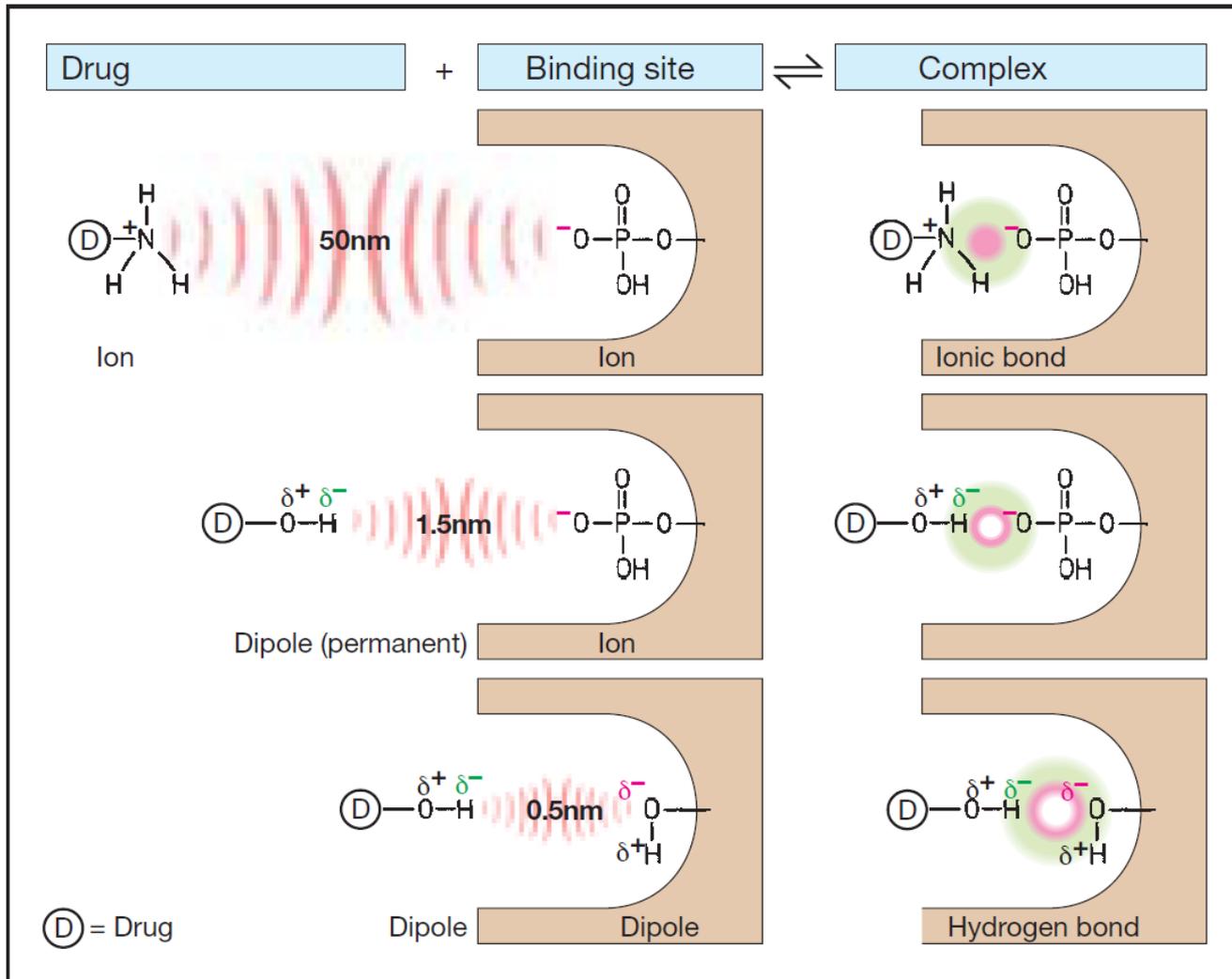
# **Disciplina**

# **Química Medicinal**

**Prof. Dr. Andrei Leitão**

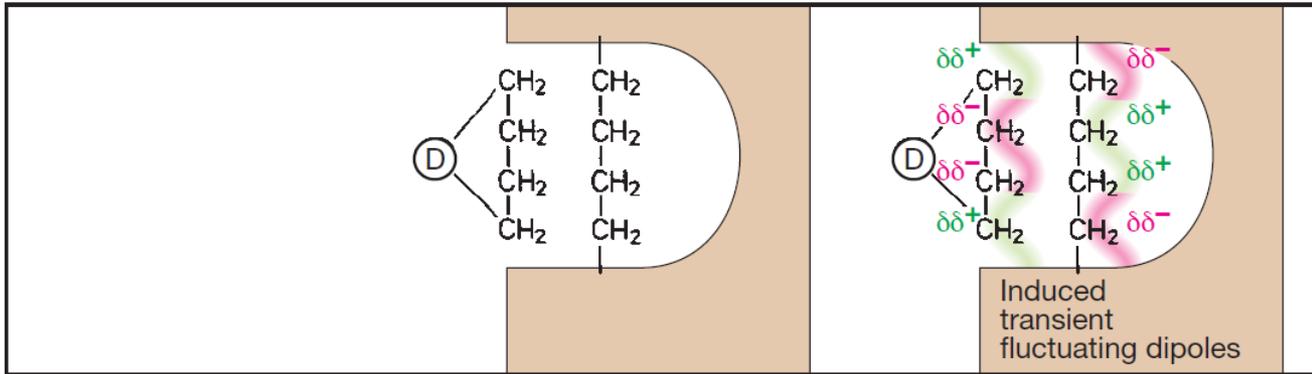
# **Planejamento baseado na estrutura do alvo (SBDD ou TBDD)**

# Interações intermoleculares

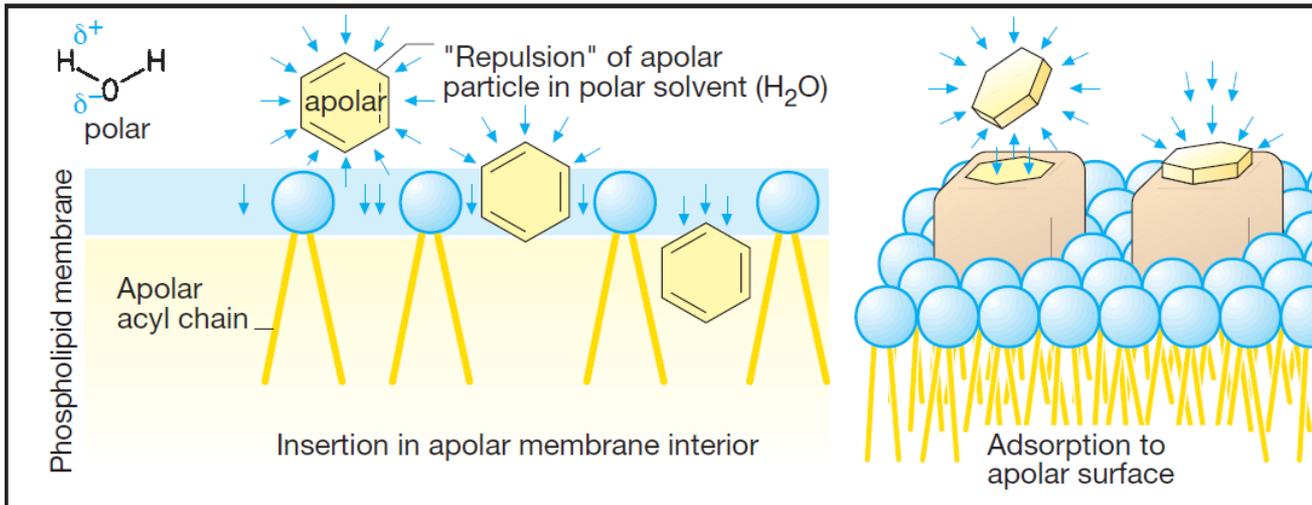


A. Electrostatic attraction

# Interações intermoleculares



## B. van der Waals' bond

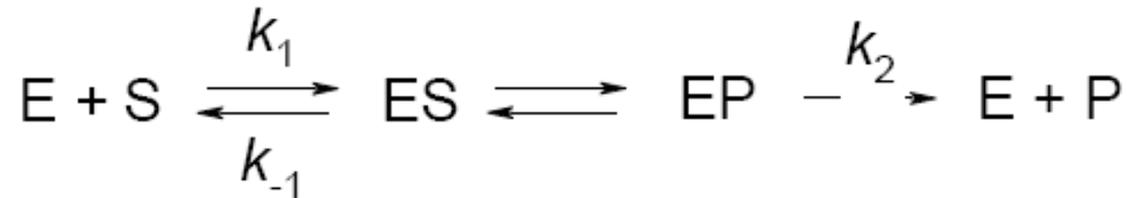


## C. Hydrophobic interaction

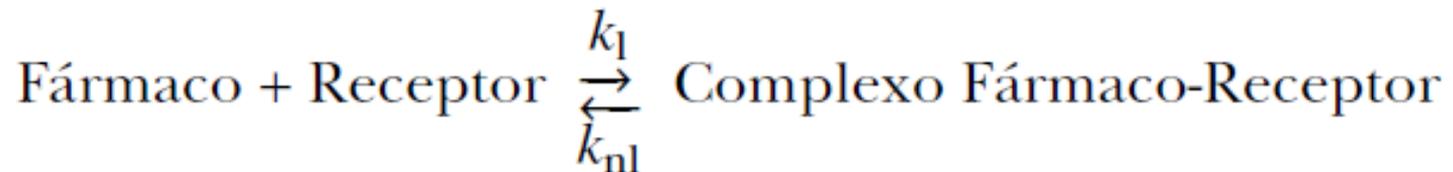
# Interação entre ligante e macromolécula

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- Cinética enzimática:



- Interação entre um ligante e um alvo macromolecular:



# Interação entre ligante e macromolécula

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Constante de associação entre o fármaco e o receptor biológico:

$$K_A = \frac{[\text{Complexo Fármaco-Receptor}]}{[\text{Fármaco}] [\text{Receptor}]} = \frac{k_1}{k_{nl}}$$

Constante de dissociação entre o fármaco e o receptor biológico:

$$K_D = \frac{[\text{Fármaco}] [\text{Receptor}]}{[\text{Complexo Fármaco-Receptor}]} = \frac{k_{nl}}{k_1}$$

Relação entre  $K_A$  e  $K_D$ :

$$K_A = \frac{1}{K_D}$$

# Relação com a termodinâmica

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Relação entre energia livre e a constante de equilíbrio

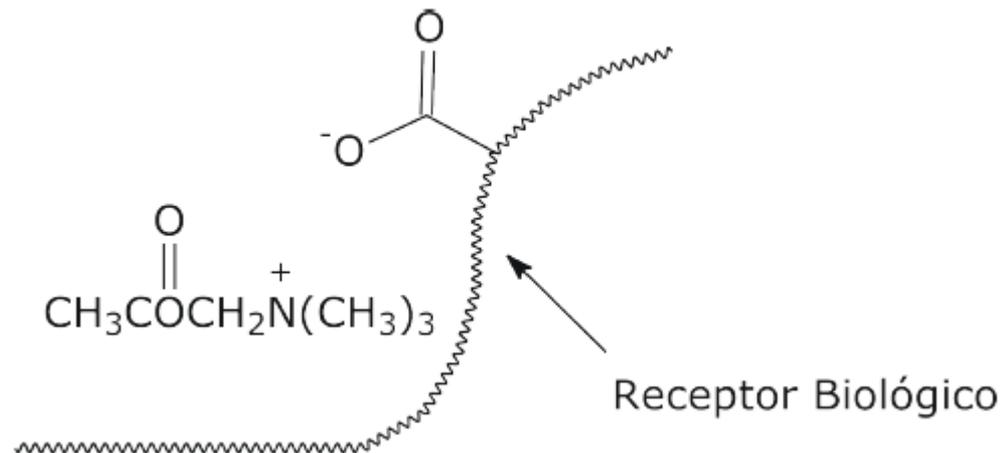
$$\Delta G^0 = -RT \ln K$$

Variações na energia livre de  $-2$  a  $-3$  kcal mol<sup>-1</sup> ( $-8,4$  a  $-12,6$  kJ mol<sup>-1</sup>) podem causar um grande efeito no cocomplexo estudado.

# Relação com a termodinâmica

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- Interação eletrostática
- Podem alterar  $G$  em  $-5 \text{ kcal mol}^{-1}$  ( $-21 \text{ kJ mol}^{-1}$ )
- Exemplo: acetilcolina



# Relação com a termodinâmica

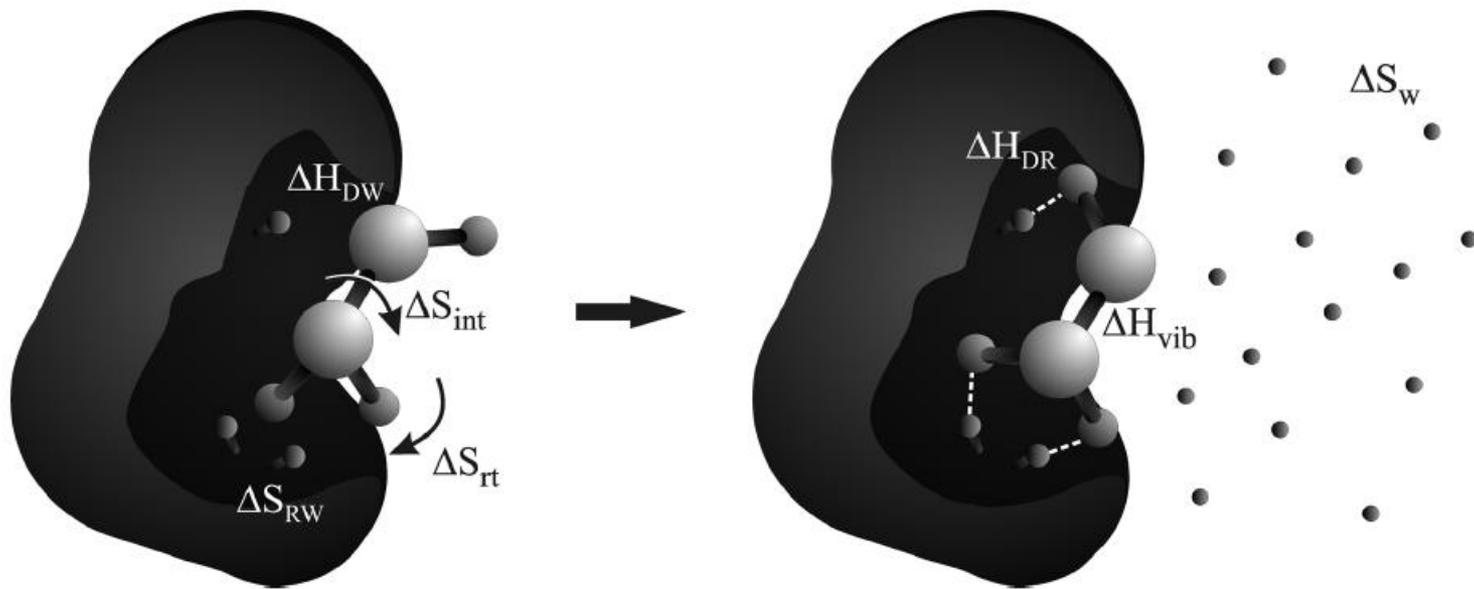
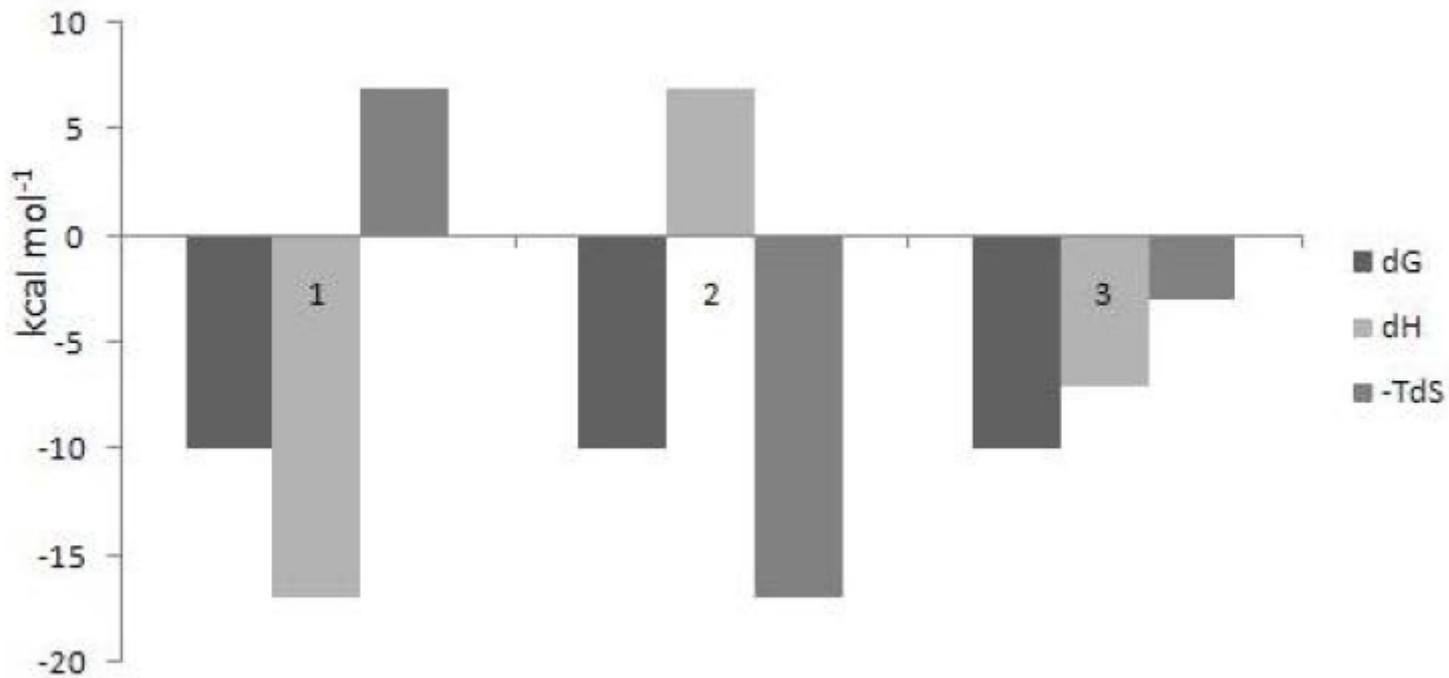


Figura 10.4 Representação esquemática da interação fármaco-receptor

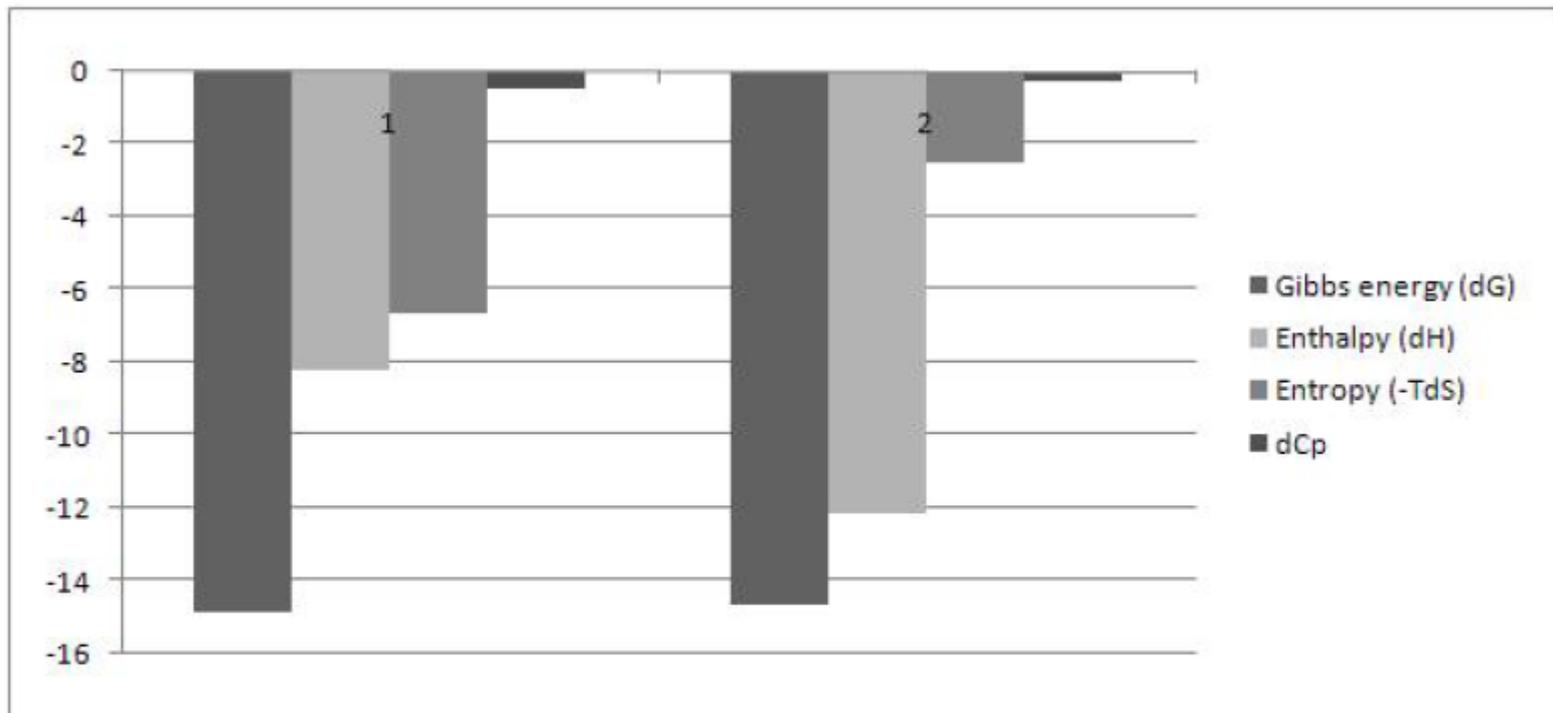
$S_{rt}$  = entropia de rotação,  $S_{int}$  = entropia interna do fármaco,  $S_{RW}$  = entropia solvente-receptor,  $S_w$  = entropia do solvente,  $H_{vib}$  = entalpia vibracional,  $H_{DW}$  = entalpia da interação fármaco-solvente,  $H_{DR}$  = entalpia da interação fármaco-receptor

# Relação com a termodinâmica

- Três possíveis perfis de inibidores enzimáticos

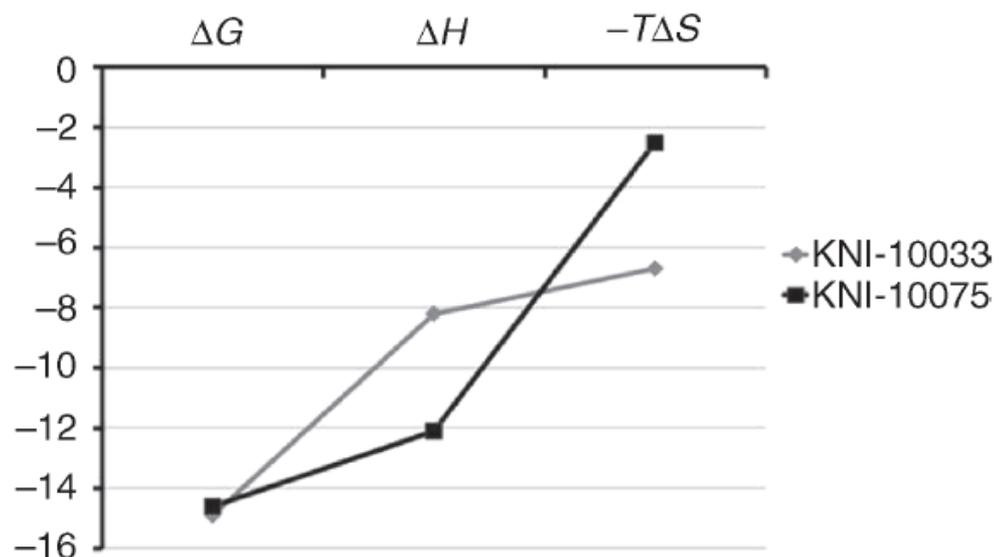
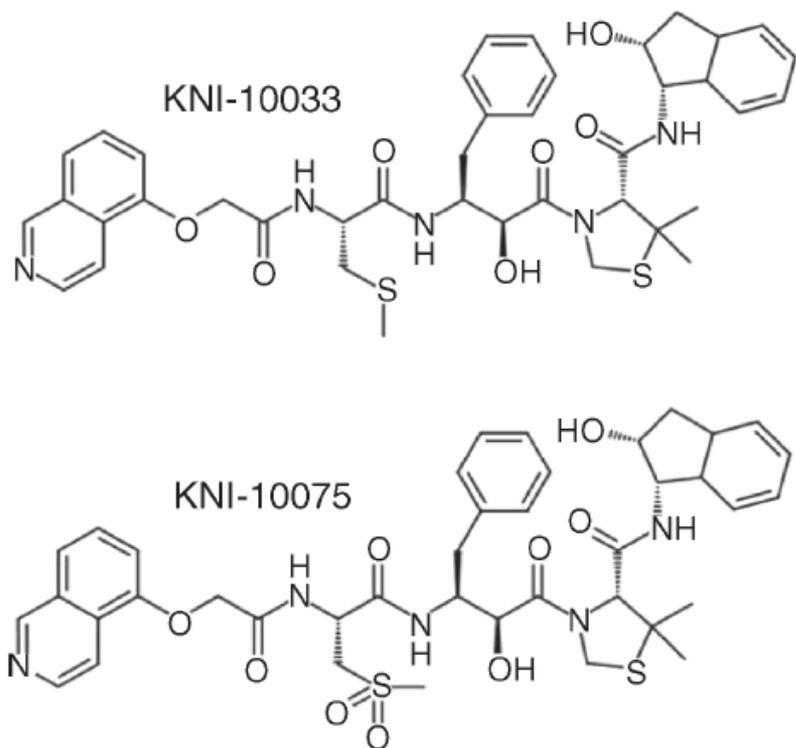


# Relação com a termodinâmica

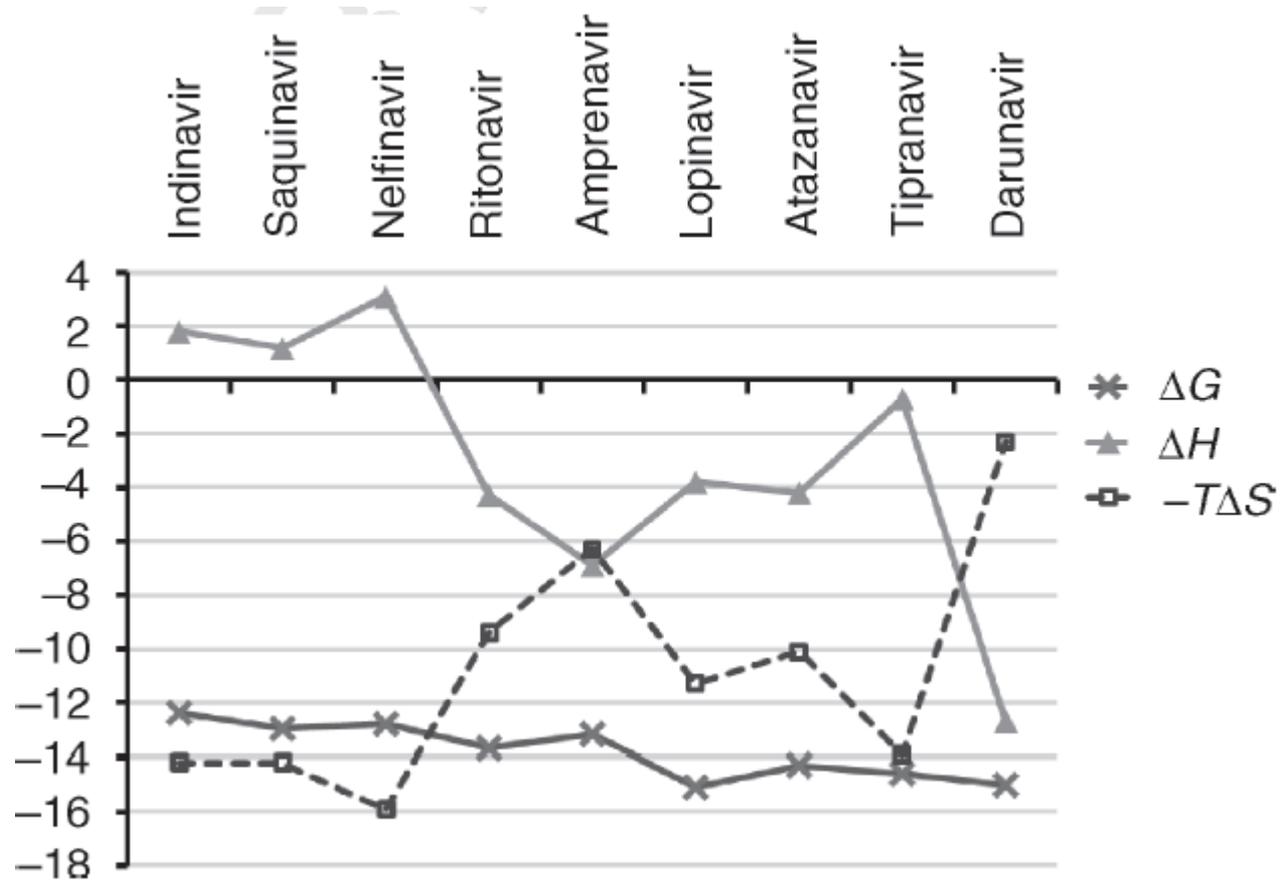


**Figure 14.** ITC thermodynamic signature of two inhibitors (1, KNI-10033 and 2, KNI-10075) bound to wild type HIV protease. In order to  $\Delta G$  to be kept almost unchanged by improving binding through  $\Delta H$ ,  $\Delta S$  has to compensate the enthalpy change<sup>67</sup>.

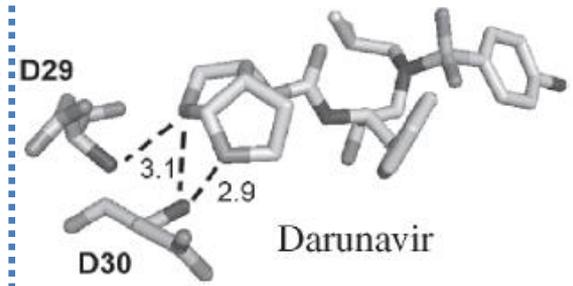
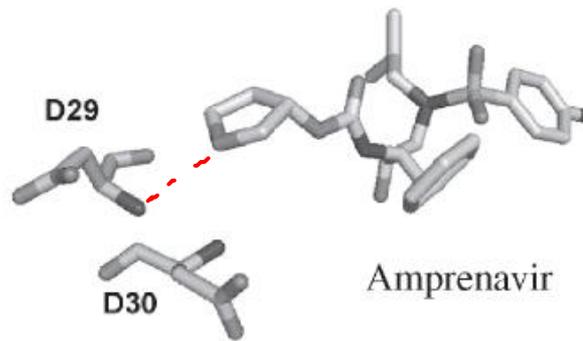
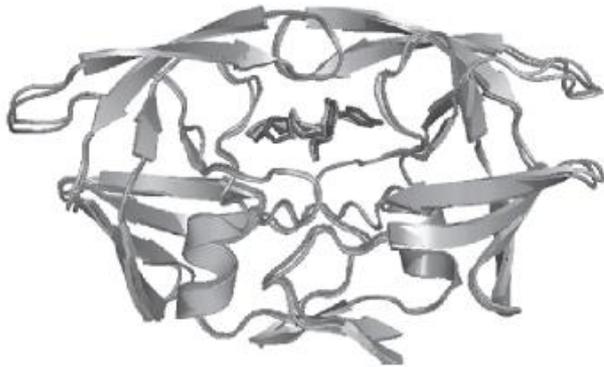
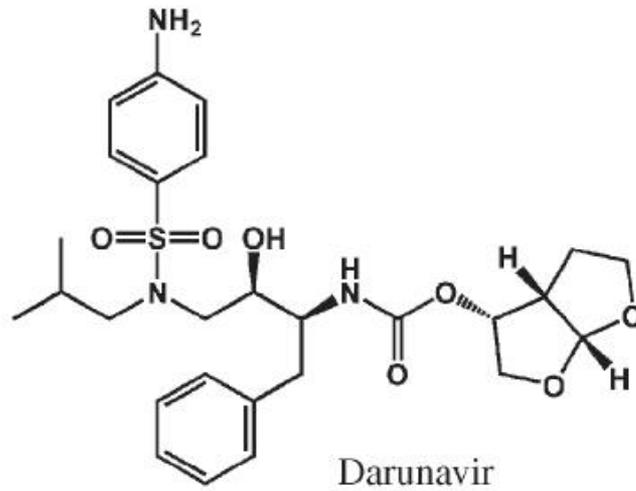
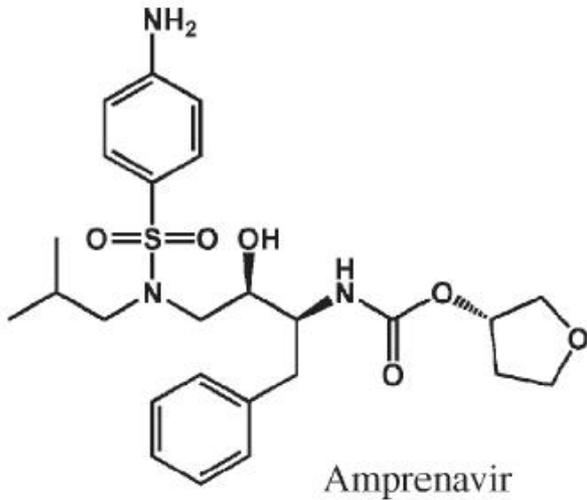
# Assinatura termodinâmica



# Assinatura termodinâmica (2)

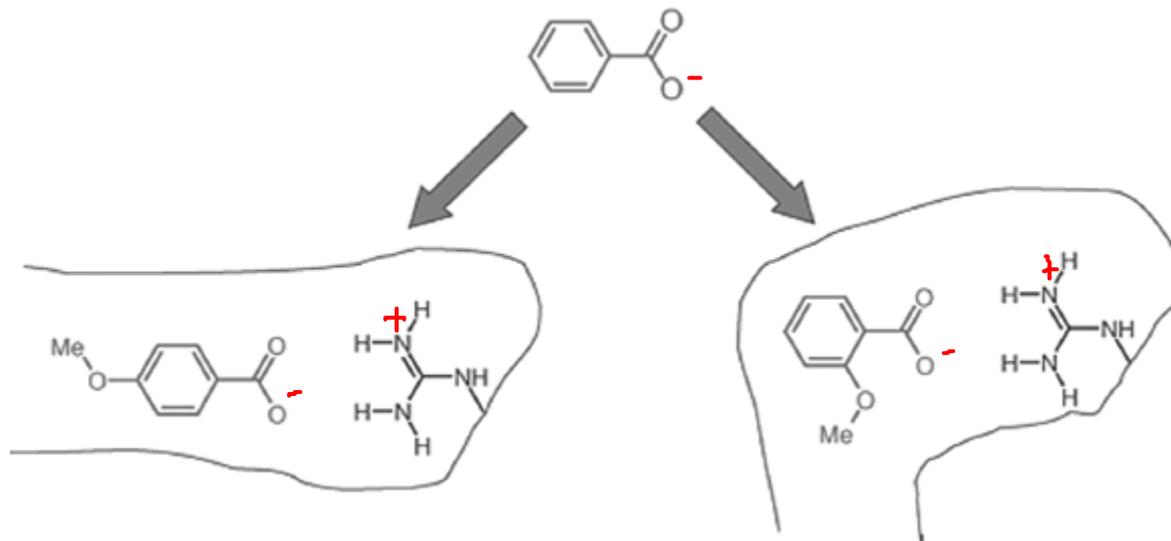


# Complementaridade

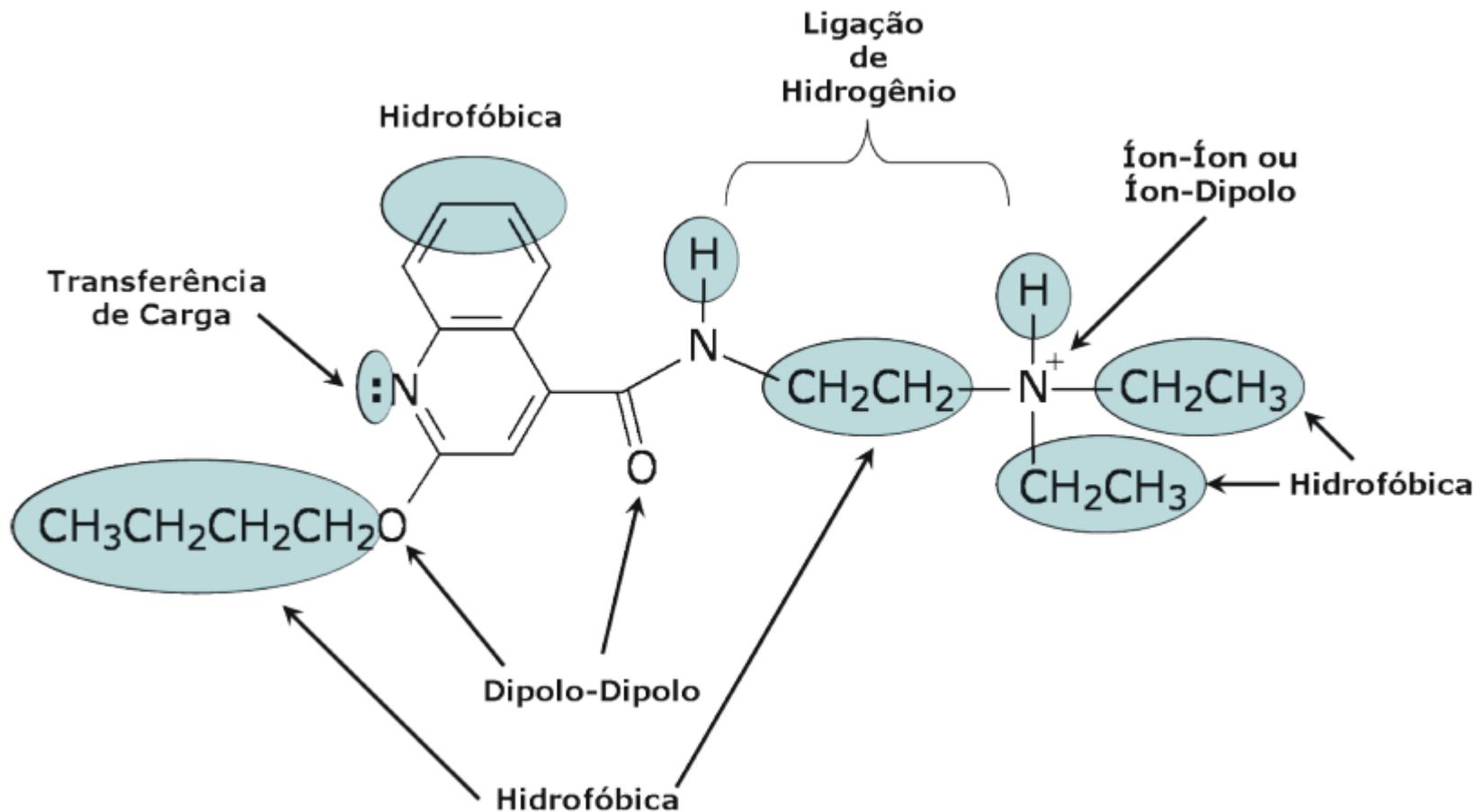


# Complementaridade (2)

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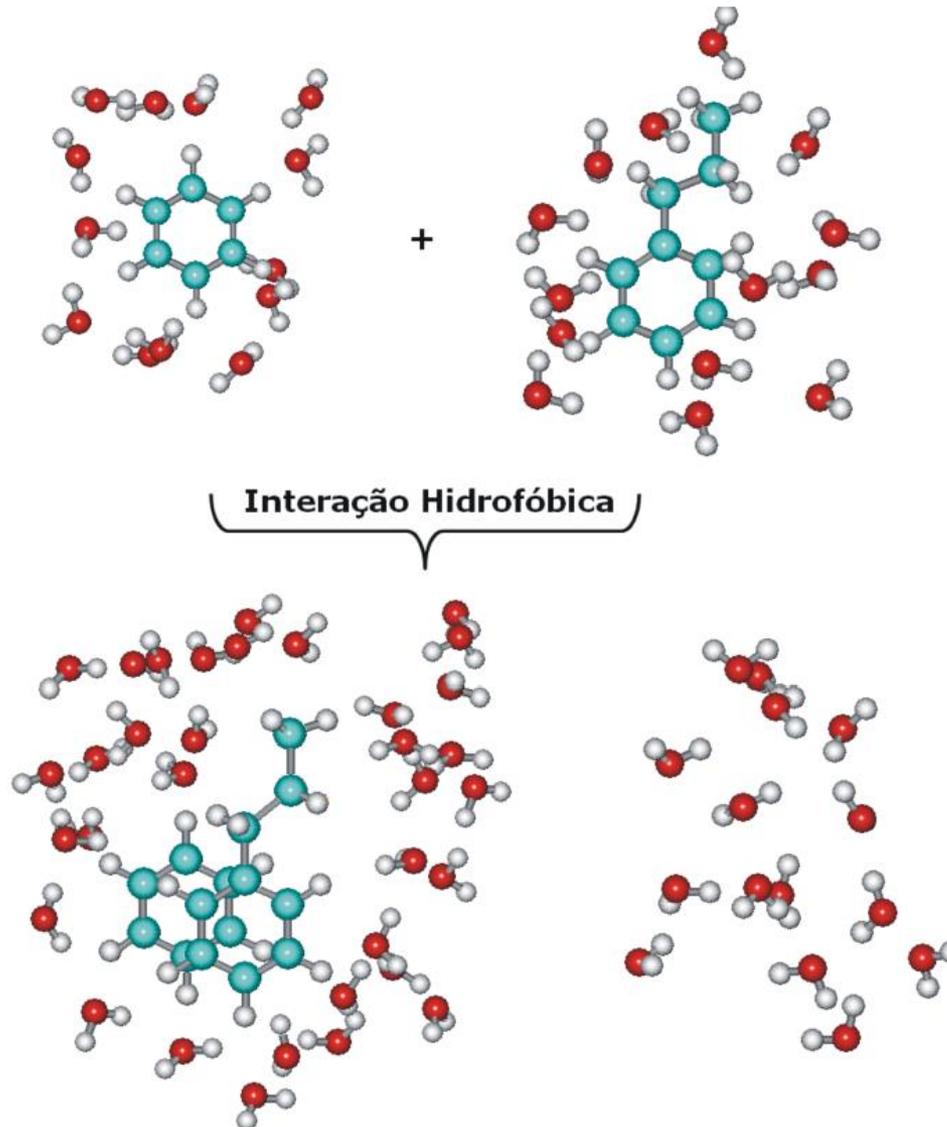


# Interações intermoleculares e grupos funcionais

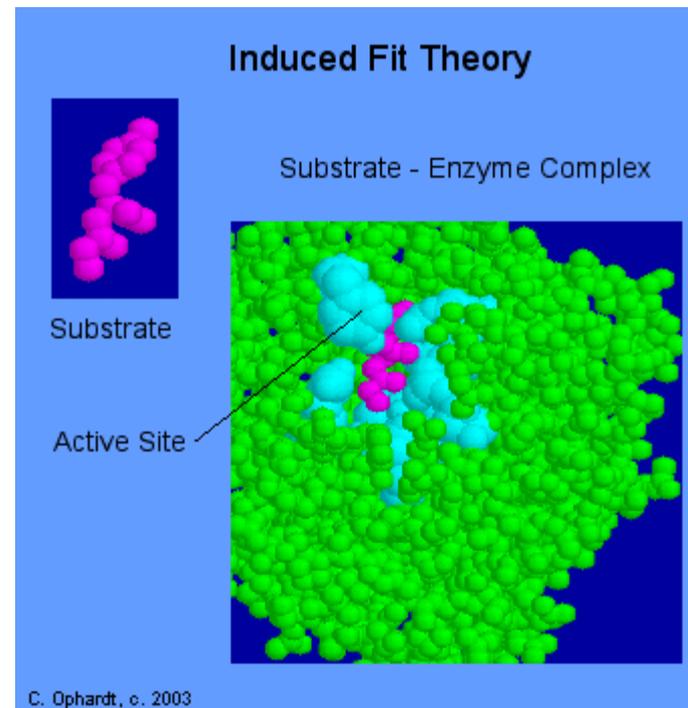
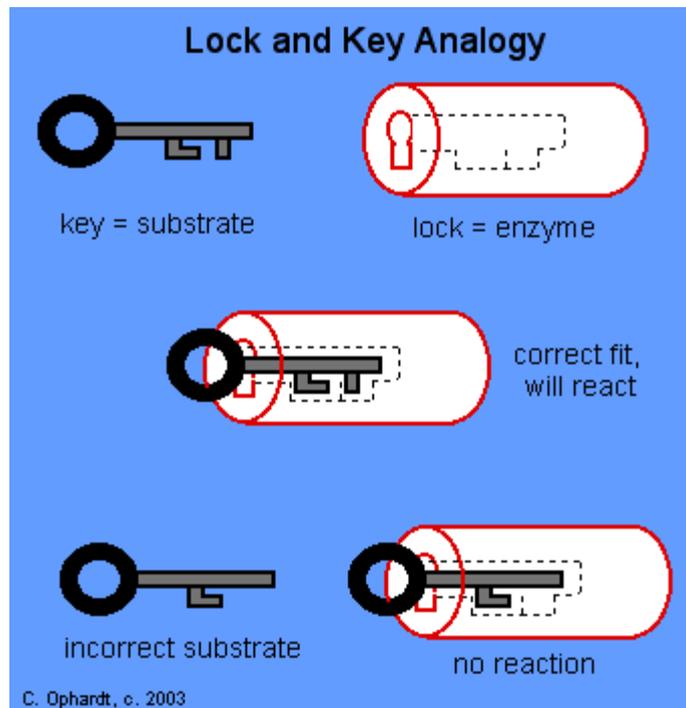


# Interação hidrofóbica

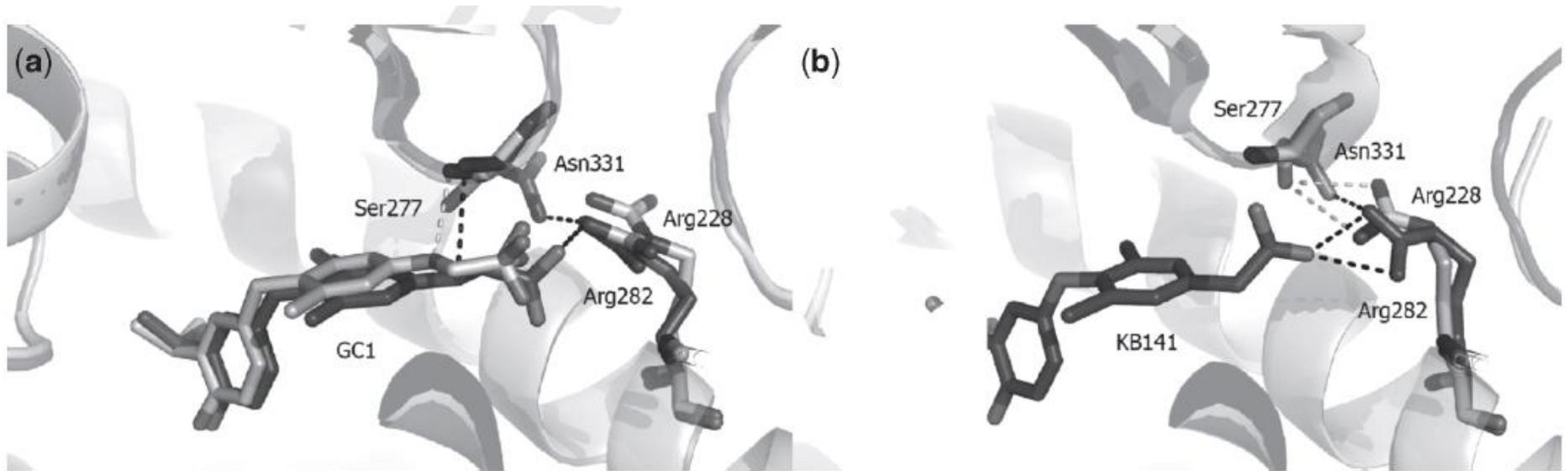
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# Rigidez vs. flexibilidade

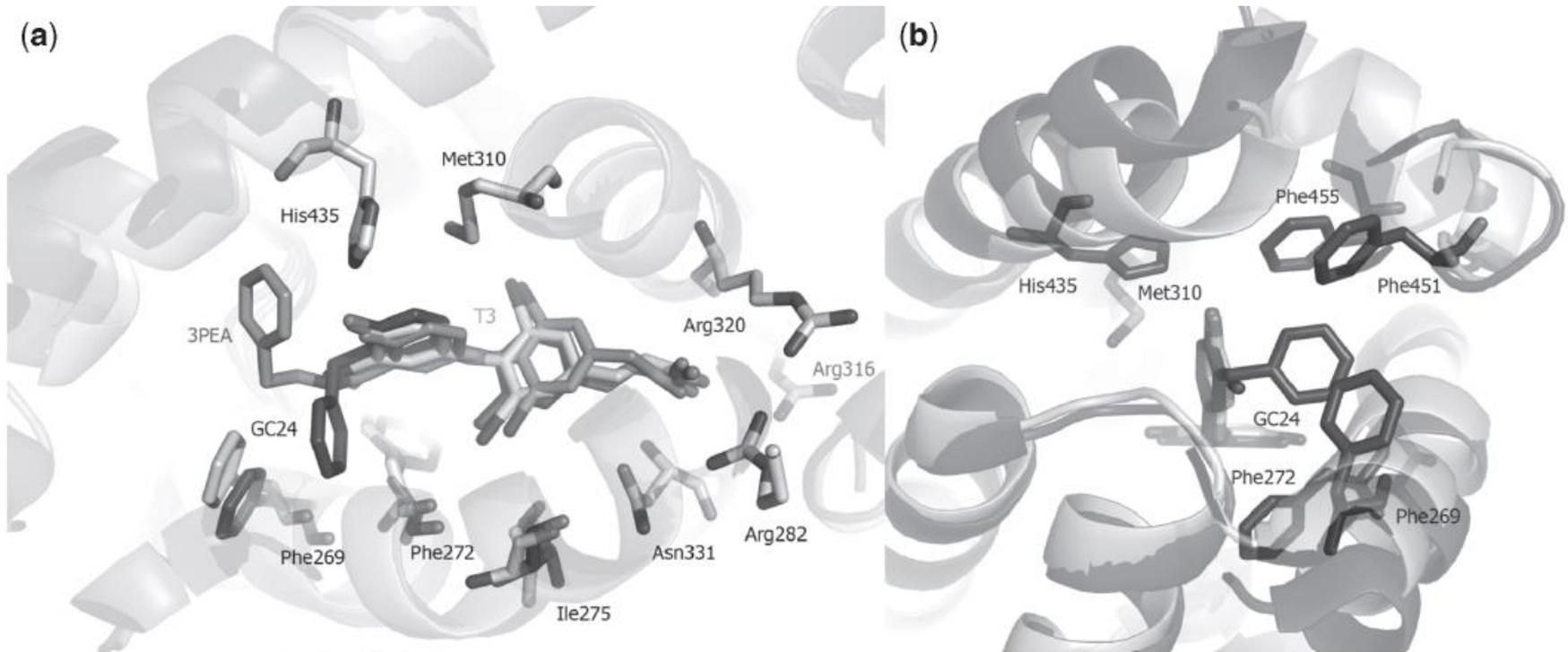


# Ajuste induzido



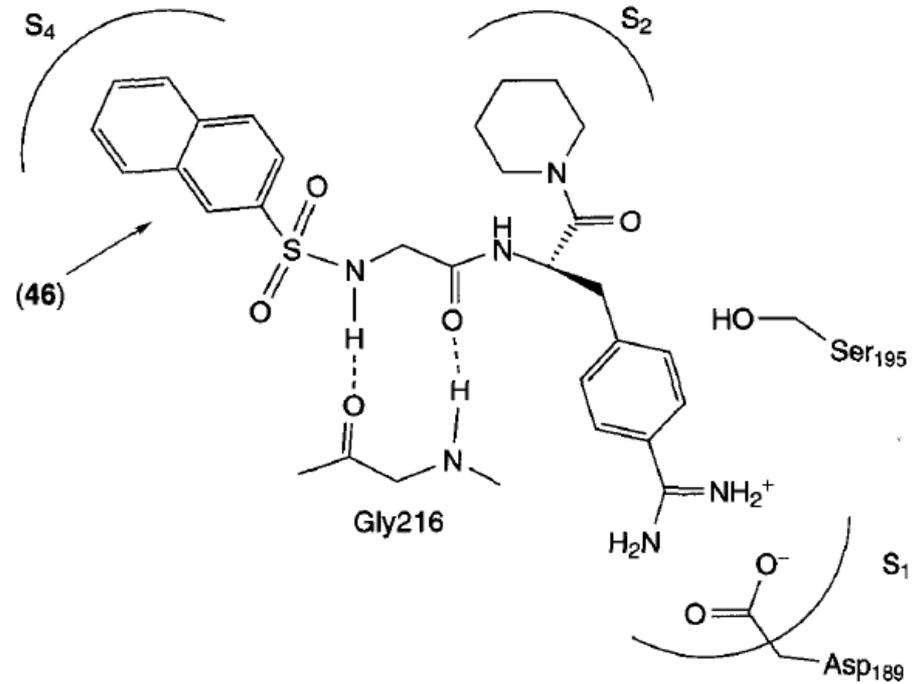
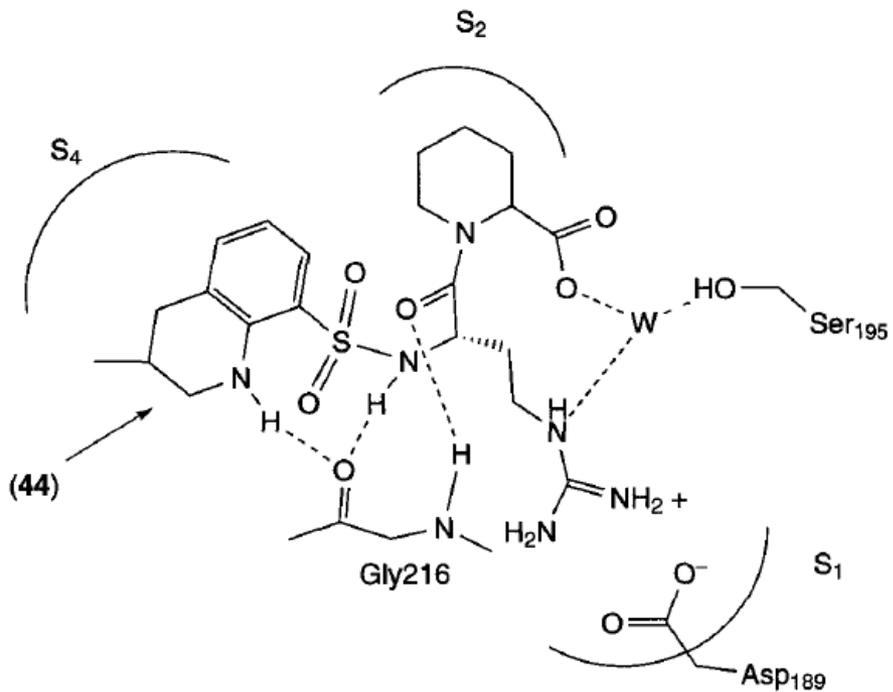
**Figure 6.** The side chains of (a) GC1 and (b) KB141 (PDB IDs: 1NAV (TR $\alpha$ ) and 1NAX (TR $\beta$ )) influence TR $\beta$  selectivity by establishing different hydrogen-bond network patterns, which is dependent on the presence of Asn331 in TR $\beta$ . TR $\alpha$  structures are shown in light gray, whereas the TR $\beta$  structures are shown in black.

# Ajuste induzido



**Figure 7.** Thyroid hormone receptor isoforms are challenged to accommodate compounds with a bulky 3'-substitution. (a) Comparison of GC24 (PDB ID: 1Q4X in black), 3'-PEA (PDB ID: 1R6G in dark gray), and T3 (PDB ID: 2H6W in light gray) binding TRβ. (b) The outer cavity expansion and the hydrophobic cluster formation provoked by GC24 when binding TRβ. The TRβ crystal structure in complex with T3 is shown in light gray cartoon, whereas the complex with GC24 is shown in black. The amino acid residues that composed the so-called hydrophobic cluster with GC24 are shown as sticks and named. Figures were generated with the Pymol software (De Lano Scientific). Nitrogen and iodine atoms are colored in black, oxygen and sulfur in dark gray.

# Estudo comparativo entre ligantes



# Representação gráfica da interação ligante-macromolécula

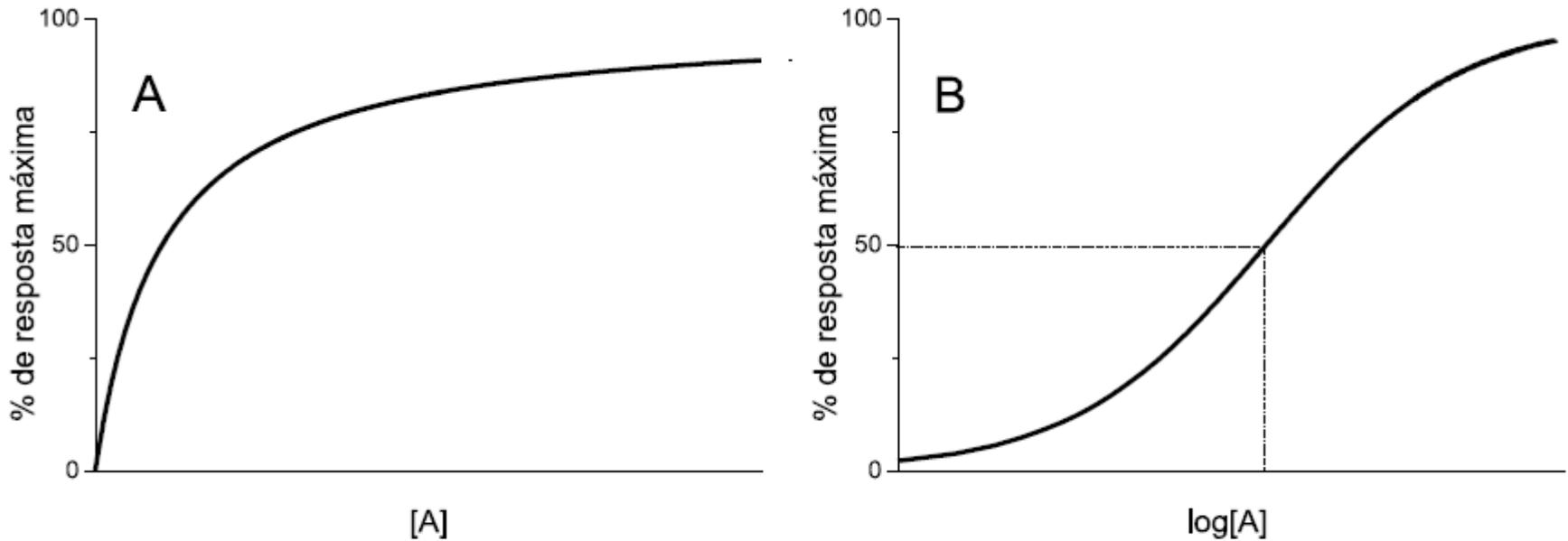


Figura 1.34 Representações gráficas teóricas das relações entre as respostas farmacológicas e as doses em escala de concentração linear (A) e em escala logarítmica (B)