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Friday, August 13, 2021 11:43 AM

The linear interaction energy (LIE) method was developed by Johan Åqvist's group and is a popular tool for lead optimization [1, 2]. The binding free energy is estimated based on the difference in the energetics of the interactions between ligand and receptor in the "bound" versus "unbound" states (i.e. the endpoints).

$$\Delta G_{bind} = \beta\left(\langle V^{elec}_{bound}\rangle - \langle V^{elec}_{unbound}\rangle\right) + \alpha\left(\langle V^{vdw}_{bound}\rangle - \langle V^{vdw}_{unbound}\rangle\right) + \gamma \quad (1)$$

The various parameters α, β and γ are dependent upon the force field, polarity of the small molecule, and the hydrophobicity of the binding pocket. Useful relations to keep in mind are ...

$K_i = \frac{[E][I]}{[E-I^*]}$ $K_i = 0.018\,nM = 1.8e-11$ (2)

$\Delta G_{bind} = -RT\ln\left(1/K_i\right) = RT\ln K_i = \Delta H - T\Delta S$ (3)

$V^{elec}_{unbound} = -105.99 \approx -106.0$ kcal/mol

$V^{vdw}_{unbound} = 44.0562 \approx 44.06$ kcal/mol

$V^{vdw}_{bound} = -374.58$ kcal/mol

$V^{elec}_{Bound} = -6499.65$

$\Delta G_{Bind} = -RT\ln\left(\frac{1}{K_i}\right)$ $R = 1.98e-3$, $T = 298$, $K_i = 1.8e-11$

$= -(1.98e-3)(298)\cdot\ln\left(\frac{1}{1.8e-11}\right)$

$= -14.6$

$-14.6 = \beta\left[(-6499.65) - (-106)\right] + \alpha\left[(-374.58) - (44.06)\right]$