Supplementary Information

A View of the Inhibition Specificity of Aurintricarboxylic Acid Toward Protein Tyrosine Phosphatases: Implications for Structure-Based Phosphatase Inhibitor Design

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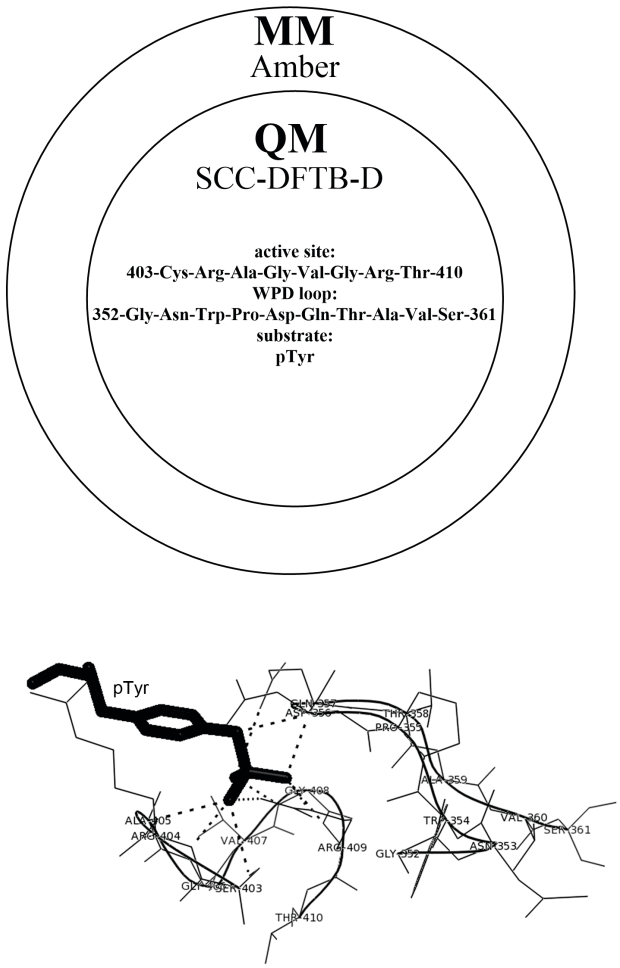

Figure S1. (Top) A two-layer QM/MM (SCC-DFTB-D/AMBER) model was used to investigate the higher affinity interaction between pTyr and wt YopH (PDB ID: 1YTN). (Bottom) Interactive conformation of pTyr relative to the substrate binding site with ten polar contacts (dashed line). The calculated values of thermodynamic quantities are: free energy - ΔG = -10.1 kcal mol^{-1}, enthalpy - ΔH = -23.7 kcal mol^{-1}, entropy - $T\Delta S$ = -13.6 kcal mol^{-1}, and entropic contribution, translational - $T\Delta S_{trans}$ = -8.1 kcal mol^{-1}, rotational - $T\Delta S_{rot}$ = -9.6 kcal mol^{-1}, vibrational - $T\Delta S_{vib}$ = 4.1 kcal mol^{-1}.

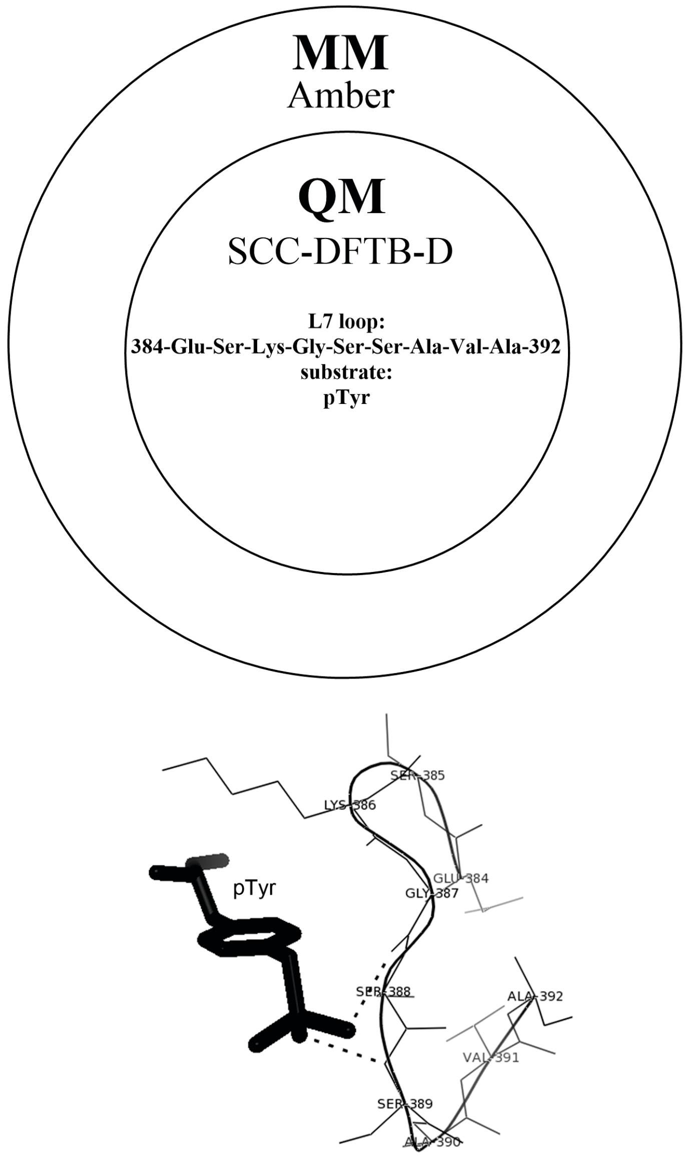

Figure S2. (Top) A two-layer QM/MM (SCC-DFTB-D/AMBER) model was used to investigate the lower affinity interaction between pTyr and wt YopH (PDB ID: 1YTN). (Bottom) Interactive conformation of pTyr relative to the substrate binding site with two polar contacts (dashed line). The calculated values of thermodynamic quantities are: free energy - ΔG = -4.9 kcal mol^{-1}, enthalpy - ΔH = -16.5 kcal mol^{-1}, entropy - $T\Delta S$ = -11.6 kcal mol^{-1}, and entropic contribution, translational - $T\Delta S_{trans}$ = -8.1 kcal mol^{-1}, rotational - $T\Delta S_{rot}$ = -9.6 kcal mol^{-1}, vibrational - $T\Delta S_{vib}$ = 6.1 kcal mol^{-1}.

Derivation of the Hill coefficient given by equation 44 in the main text

$$n_{\mathrm{H}} = \left. \frac{d \log\left(\frac{f}{1-f}\right)}{d \log[\mathrm{L}]} \right|_{\text{evaluated at } f=0.5}$$

Based on equation 43 from the main text:

$$n_{\mathrm{H}} = \frac{d \log\left(\frac{f}{1-f}\right)}{d \log[\mathrm{L}]} = \frac{d\,(\log\left(\frac{[\mathrm{L}]}{K_{\mathrm{D1}}} + 2\frac{[\mathrm{L}]}{K_{\mathrm{D1}}}\frac{[\mathrm{L}]}{K_{\mathrm{D2}}}\right) - \log\left(2 + \frac{[\mathrm{L}]}{K_{\mathrm{D1}}}\right))}{d \log[\mathrm{L}]} =$$

$$\frac{d \log\left(\frac{[\mathrm{L}]}{K_{\mathrm{D1}}} + 2\frac{[\mathrm{L}]}{K_{\mathrm{D1}}}\frac{[\mathrm{L}]}{K_{\mathrm{D2}}}\right)}{d \log[\mathrm{L}]} - \frac{d \log\left(2 + \frac{[\mathrm{L}]}{K_{\mathrm{D1}}}\right)}{d \log[\mathrm{L}]} =$$

$$\frac{d \log\left(\frac{[\mathrm{L}]}{K_{\mathrm{D1}}} + 2\frac{[\mathrm{L}]}{K_{\mathrm{D1}}}\frac{[\mathrm{L}]}{K_{\mathrm{D2}}}\right)}{\frac{1}{[\mathrm{L}]\ln 10} d[\mathrm{L}]} - \frac{d \log\left(2 + \frac{[\mathrm{L}]}{K_{\mathrm{D1}}}\right)}{\frac{1}{[\mathrm{L}]\ln 10} d[\mathrm{L}]} =$$

$$\frac{\frac{\left(\frac{[\mathrm{L}]}{K_{\mathrm{D1}}} + 2\frac{[\mathrm{L}]}{K_{\mathrm{D1}}}\frac{[\mathrm{L}]}{K_{\mathrm{D2}}}\right)'}{\left(\frac{[\mathrm{L}]}{K_{\mathrm{D1}}} + 2\frac{[\mathrm{L}]}{K_{\mathrm{D1}}}\frac{[\mathrm{L}]}{K_{\mathrm{D2}}}\right)\ln 10}}{\frac{1}{[\mathrm{L}]\ln 10}} - \frac{\frac{\left(2 + \frac{[\mathrm{L}]}{K_{\mathrm{D1}}}\right)'}{\left(2 + \frac{[\mathrm{L}]}{K_{\mathrm{D1}}}\right)\ln 10}}{\frac{1}{[\mathrm{L}]\ln 10}} =$$

$$\frac{\left(\frac{1}{K_{\mathrm{D1}}} + 4\frac{[\mathrm{L}]}{K_{\mathrm{D1}}K_{\mathrm{D2}}}\right)[\mathrm{L}]}{\left(\frac{[\mathrm{L}]}{K_{\mathrm{D1}}} + 2\frac{[\mathrm{L}]}{K_{\mathrm{D1}}}\frac{[\mathrm{L}]}{K_{\mathrm{D2}}}\right)} - \frac{\frac{[\mathrm{L}]}{K_{\mathrm{D1}}}}{\left(2 + \frac{[\mathrm{L}]}{K_{\mathrm{D1}}}\right)} =$$

$$\frac{\left(\frac{1}{K_{\mathrm{D1}}} + 4\frac{[\mathrm{L}]}{K_{\mathrm{D1}}K_{\mathrm{D2}}}\right)}{\left(\frac{1}{K_{\mathrm{D1}}} + 2\frac{[\mathrm{L}]}{K_{\mathrm{D1}}K_{\mathrm{D2}}}\right)} - \frac{\frac{[\mathrm{L}]}{K_{\mathrm{D1}}}}{\left(2 + \frac{[\mathrm{L}]}{K_{\mathrm{D1}}}\right)}$$

Based on equation 39 from the main text, $f = 0.5$ means that $\dfrac{\frac{[\mathrm{L}]}{K_{\mathrm{D1}}} + 2\frac{[\mathrm{L}]}{K_{\mathrm{D1}}}\frac{[\mathrm{L}]}{K_{\mathrm{D2}}}}{2 + 2\frac{[\mathrm{L}]}{K_{\mathrm{D1}}} + 2\frac{[\mathrm{L}]}{K_{\mathrm{D1}}}\frac{[\mathrm{L}]}{K_{\mathrm{D2}}}} = \frac{1}{2}$, i.e.

$$2\frac{[\mathrm{L}]}{K_{\mathrm{D1}}}+4\frac{[\mathrm{L}]}{K_{\mathrm{D1}}}\frac{[\mathrm{L}]}{K_{\mathrm{D2}}}=2+2\frac{[\mathrm{L}]}{K_{\mathrm{D1}}}+2\frac{[\mathrm{L}]}{K_{\mathrm{D1}}}\frac{[\mathrm{L}]}{K_{\mathrm{D2}}}$$, which gives $[\mathrm{L}]=\sqrt{K_{\mathrm{D1}}K_{\mathrm{D2}}}$.

For $[\mathrm{L}]=\sqrt{K_{\mathrm{D1}}K_{\mathrm{D2}}}$, the Hill coefficient becomes:

$$n_{\mathrm{H}}=\frac{\left(\frac{1}{K_{\mathrm{D1}}}+4\frac{\sqrt{K_{\mathrm{D1}}K_{\mathrm{D2}}}}{K_{\mathrm{D1}}K_{\mathrm{D2}}}\right)}{\left(\frac{1}{K_{\mathrm{D1}}}+2\frac{\sqrt{K_{\mathrm{D1}}K_{\mathrm{D2}}}}{K_{\mathrm{D1}}K_{\mathrm{D2}}}\right)}-\frac{\frac{\sqrt{K_{\mathrm{D1}}K_{\mathrm{D2}}}}{K_{\mathrm{D1}}}}{\left(2+\frac{\sqrt{K_{\mathrm{D1}}K_{\mathrm{D2}}}}{K_{\mathrm{D1}}}\right)}=$$

$$\frac{\left(\frac{1}{K_{\mathrm{D1}}}+\frac{4}{\sqrt{K_{\mathrm{D1}}K_{\mathrm{D2}}}}\right)}{\left(\frac{1}{K_{\mathrm{D1}}}+\frac{2}{\sqrt{K_{\mathrm{D1}}K_{\mathrm{D2}}}}\right)}-\frac{\sqrt{\frac{K_{\mathrm{D2}}}{K_{\mathrm{D1}}}}}{\left(2+\sqrt{\frac{K_{\mathrm{D2}}}{K_{\mathrm{D1}}}}\right)}=$$

$$\frac{\left(4+\sqrt{\frac{K_{\mathrm{D2}}}{K_{\mathrm{D1}}}}\right)}{\left(2+\sqrt{\frac{K_{\mathrm{D2}}}{K_{\mathrm{D1}}}}\right)}-\frac{\sqrt{\frac{K_{\mathrm{D2}}}{K_{\mathrm{D1}}}}}{\left(2+\sqrt{\frac{K_{\mathrm{D2}}}{K_{\mathrm{D1}}}}\right)}=$$

$$\frac{\left(4+\sqrt{\frac{K_{\mathrm{D2}}}{K_{\mathrm{D1}}}}-\sqrt{\frac{K_{\mathrm{D2}}}{K_{\mathrm{D1}}}}\right)}{\left(2+\sqrt{\frac{K_{\mathrm{D2}}}{K_{\mathrm{D1}}}}\right)}=\frac{4}{2+\sqrt{\frac{K_{\mathrm{D2}}}{K_{\mathrm{D1}}}}}=\frac{2}{1+\frac{1}{2}\sqrt{\frac{K_{\mathrm{D2}}}{K_{\mathrm{D1}}}}}$$