**Supplemental Figure 7. Alchemical free energy calculations show that both protein and ligands adopt a conformationally heterogeneous ensemble of binding poses.**

**(A)** Computed binding free energy (ΔGbind) estimates from alchemical free energy calculations (*y-*axis) for Ro 08-2750 , RoOH , and Ro A6 for different definitions of the “bound” complex as a function of distance cutoff (*x-axis*). Reported statistical errors and error bars correspond one standard error. The inset ΔGbind was calculated for a cutoff of 20Å. **(B)** In the alchemical Hamiltonian replica exchange simulations, a conformational change is induced when Musashi is bound (“Complex”; green) to Ro 08-2750 (*right*) or RoOH (*center*), as compared to apo Musashi (“Apo”; gray). Ro A6 (*left*) does not induce the same conformational change. **(C)** The cluster centers for Ro 08-2750 (*left*) RoOH (*center*) and Ro A6 (*right*), derived using regular spatial custering with a ligand RMSD cutoff of 1Å. Ro A6 (*right*) produced a much larger number of clusters than Ro 08-2750 (*left*) or RoOH (*center*). **(D)** The top three most populous clusters for Ro 08-2750. The protein structure and solid-color ligand pose depict cluster centers, while transparent ligand poses depict 10 randomly sampled frames assigned to that cluster. Sidechains within 4Å of any of the ligands are shown as lines.  **(E)** The top four most populous clusters for RoOH, using the same depiction scheme as (D).