**Supplemental Figure 7. Alchemical free energy calculations show a wide range of protein and ligand conformations are adopted.**

**(A)** ΔGbind MBAR estimates (*y-*axis) for Ro 08-2750 (*left*) RoOH (*center*) and Ro A6 (*right*) at different harmonic restraint cutoffs (*x-axis*). The error bars correspond to ± the statistical uncertainty calculated for each cutoff. This reweighting step is important to remove the bias introduced by the harmonic restraint. The inset ΔGbind was calculated at the 20Å cutoff. **(B)** A conformational change is induced when Nusashi is in complex (green) with Ro 08-2750 (*right*) or RoOH (*center*), when compared to apo Musashi (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 Clustering with an 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 3 most populated clusters for Ro 08-2750. The protein structure and solid ligand pose corresponds to the cluster center, while the ligand poses shown transparently are from 10 randomly sampled frames assigned to that cluster. Sidechains within 4Å of any of the ligands are shown in lines.  **(E)** The top 4 most populated clusters for RoOH. The protein structure and solid ligand pose corresponds to the cluster center, while the ligand poses shown transparently are from 10 randomly sampled frames assigned to that cluster. Sidechains within 4Å of any of the ligands are shown in lines.