Supporting Information

Table 1: Average range of motion of selected sets of atoms at 300 K measured from two 400 ps simulations, one with C_α harmonic restraints and the other without harmonic restraints. The values reported are four times the root mean squared displacement averaged over the given sets of atoms. The observed range of motion of C_α atoms and sidechain and ligand atoms are approximately the same regardless of the application of weak harmonic restraints. Furthermore the observed range of motion for the C_α atoms without restraints is smaller than allowed by the applied restraints. The force constant of 0.3 kcal/mol/Å^2 applied on the C_α atoms allows a 4 Å range of motion.

	With Restraints	Without Restraints
C_α atoms[a]	1.0 Å	1.0 Å
Ligand [b]	2.4 Å	2.0 Å
Side Chains [c]	3.0 Å	3.8 Å

[a] The C_α atoms that are restrained in the replica exchange simulation.

[b] C_{18} terminal atom of the ligand.

[c] $C_{\delta 1}$ of Leu75 and C_ζ of Phe87.