Supporting Information

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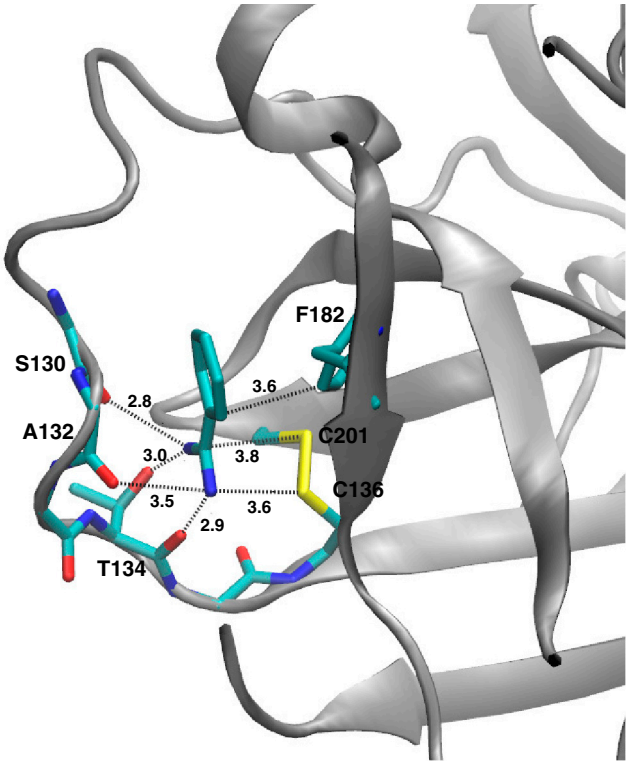

Fig. S1. The structure of the most stable pose found on the back of the protein. The distances reported in the figure are in angstrom and are averages over a 60 ns molecular dynamics simulation.

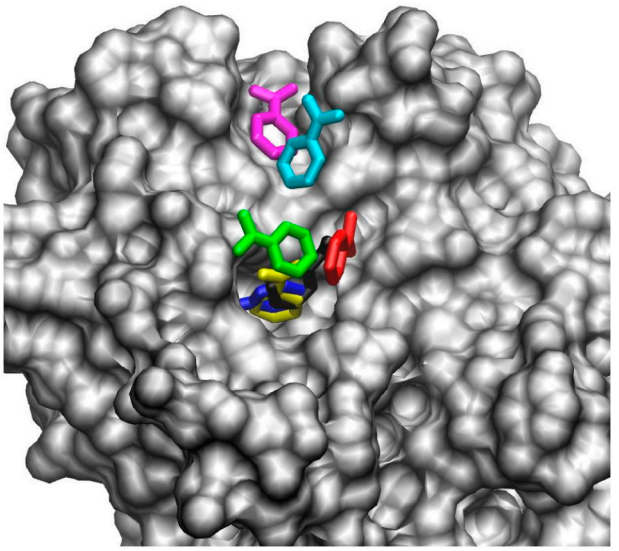

Fig. S2. An overview of the protein surface around the binding site showing the location of the poses described in Fig. 4*B*. Each ligand molecule is colored, using the scheme from Fig. 4*B*, to indicate which pose is being shown.

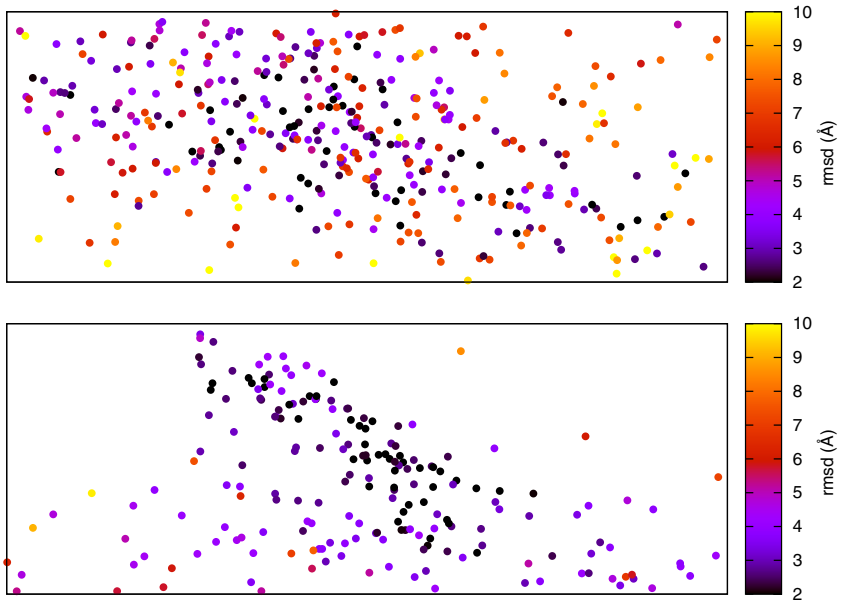

Fig. S3. Comparison of how well two different sketch-map representations separate conformations close to the binding pose from other conformations. Only the part of the map where the binding pose is located is shown and the points are colored according to the rmsd from the experimental binding pose. (*Upper*) All points were used in the construction of the map. (*Lower*) Only points within 15 Å rmsd were used and σ in the switching function was reduced to 8. The map in the *Lower* panel has fewer yellow points among the black ones, which indicates that this projection better separates the various poses.

Table S1. List of reference poses obtained from EADock

Pose	Energy	rmsd (Å)	Interactions	Stability (ns)	Remarks
1	−19.2	1.4	189, 219	>1	crystallographic pose
2	−7.8	3.7	219	>1	—
3	−10.4	3.6	213, 219	0.1	goes to crystallographic pose
4	2.5	27.4	47, 239, 242	—	—
5	1.5	25.9	61	—	—
6	−2.4	18.1	(153)	—	—
7	5.3	27.7	47, 239, 242	—	—
8	1.1	20.7	202	—	—
9	1.5	26.4	63, 86	0.3	—
10	−0.9	21.2	92, 94	—	—
11	0.5	20.8	135, 137, 202	0.1	—
12	−1.7	5.2	191, 214	>1	—
13	-0.2	18.7	152, 153	>1	—
14	4.5	20.9	97	—	—
15	6.4	18.4	(94)	—	—
16	4.2	24.8	204, 210	—	—
17	2.3	28.3	47, 239, 242	—	—
18	3.9	20.2	(94)	—	—
19	5.5	31.8	(119)	—	—
20	−4.8	3.5	195, 216, 219	—	goes to crystallographic pose
21	0.8	27.6	47, 239, 242	—	—
22	3.9	21.5	(90)	—	—
23	3.9	31.0	(82)	—	—
24	3.5	18.1	188	—	—
25	7.2	7.8	(219)	—	—
26	1.6	19.9	129, 165	0.5	—
27	3.3	23.5	134, 204, 210	—	—

For each pose, the EADock energy, the ligand rmsd from the crystal structure, the interacting residues (all residues within 2.2 Å of the ligand, or, if there is no such residue, the closest residue in brackets) and the approximate stability time is reported. The stability time is computed from a single molecular dynamics simulation starting from each pose and is defined as the time during which the running average (over 10 ps windows) of the ligand rmsd from the starting structure stays below 2.5 Å; no value means less than 0.1 ns.

Table S2. Criteria for selecting the poses shown in Fig. 4 *B* and *C*, based on the description of these states in ref. 1

State	Necessary interactions (with some atom–atom distance below 3 Å)
S2	benzamidine ring interacts with Y39 side chain and Y151 side chain
S3	benzamidine tail interacts with (T98 main chain or L99 main chain) and (Q175 main chain or T177 main chain)
TS1	benzamidine tail interacts with N97 main chain oxygen
TS2	benzamidine tail interacts with H57 side chain and S214 side chain
TS3	benzamidine tail interacts with S217 main chain oxygen

Note that some of the residues are mislabeled in ref. 1 (G. De Fabritiis, private communication). In each case, we first selected all frames from our reconnaissance metadynamics method trajectories satisfying the interactions. Then, the frames in each group were clustered using the GROMACS `g_cluster` utility with a cutoff of 1.5 Å, and the cluster most resembling the corresponding figure in ref. 1 was selected. Finally, for the coloring of points in Fig. 4*B* we calculated the ligand rmsd between each snapshot and these representative poses, and classified a snapshot as belonging to a particular state if the rmsd was less than 2.5 Å

1. Buch I, Giorgino T, De Fabritiis G (2011) Complete reconstruction of an enzyme-inhibitor binding process by molecular dynamics simulations. *Proc Natl Acad Sci USA* 108:10184–10189.