	Bound ensamble	Unbound ensamble
Asp39.A		**52.11**
Lys43.A	41.80	64.89
Ser98.A		**71.78**
Gly99.A		**60.90**
Lys101.A	77.62	71.38
Gln118.A	48.66	44.11
Phe119.A	**40.45**	
Gly120.A	**41.02**	
Arg346.A	54.64	59.47
Arg347.A		**40.07**
Arg380.A	64.67	70.72
Lys137.B	75.81	67.31
Gln154.B	**48.28**	
Phe155.B	**44.34**	
Gly156.B	**46.54**	
A346.B	52.23	70.16
Arg380.B	85.79	92.11

Table S1. NTD-ATP hydrogen bonds plotted in the bound and unbound ensembles. The bonds found for at least 40% of the samples collection in either one of the two ensembles are reported in the table. The interactions that are present uniquely in one sample are underlined.

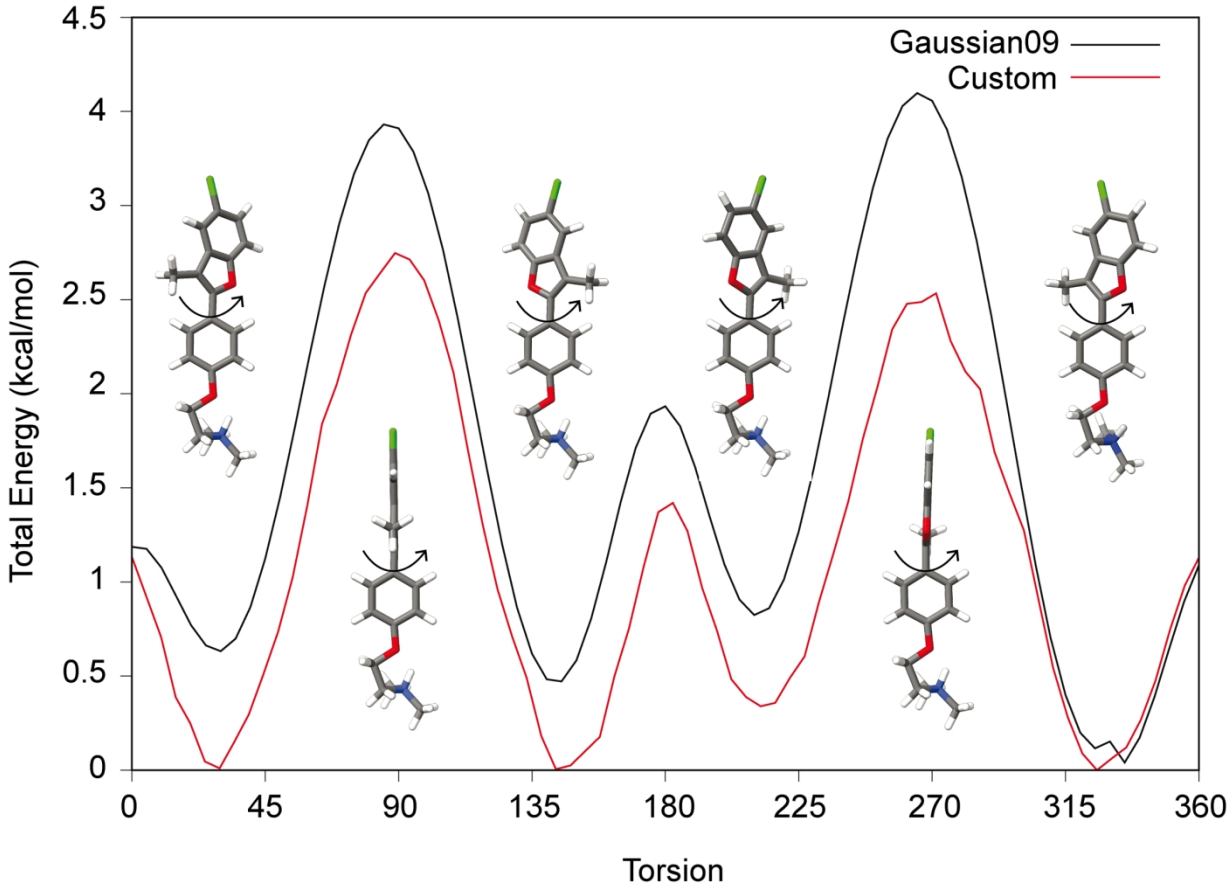


Figure S1. Scan of the torsional angle located at the bond connecting benzene and benzofuran in compound 18. The Gaussian profile (black line) is confronted with the result of the custom potential reconstructed as described in the Methods section (red line).

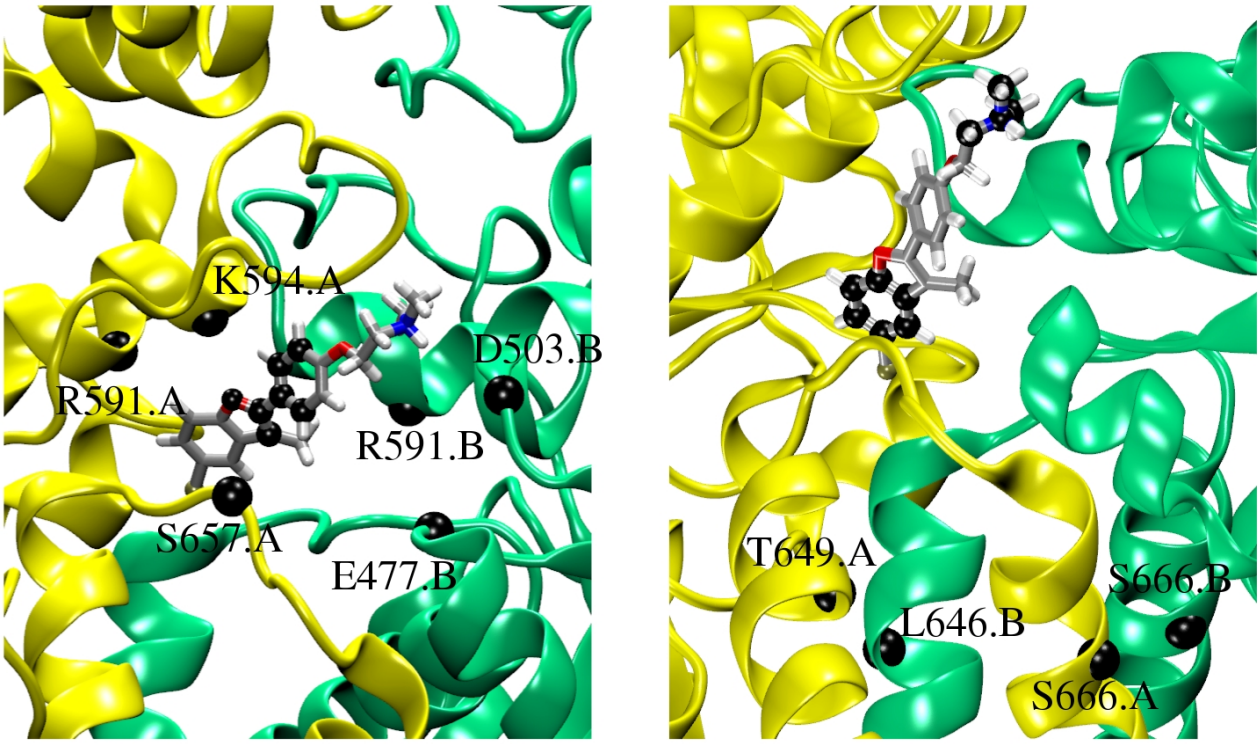


Figure S2. Depiction of the protein's and ligand's atoms (black spheres) exploited to build the points the two selected CVs, i.e. distance between the ligand and the allosteric site (left panel) and torsion of the ligand into the channel (right panel).

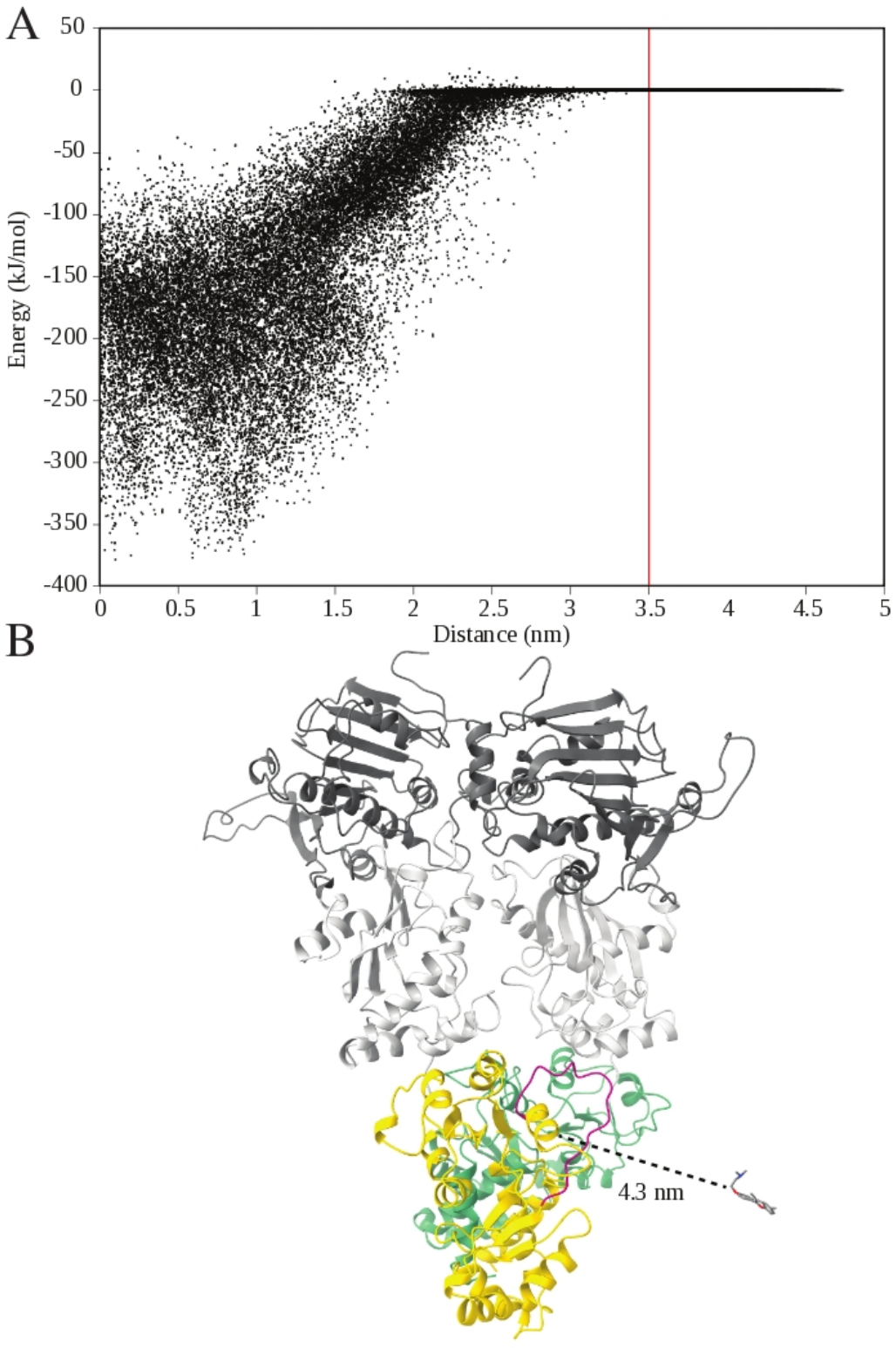


Figure S3. (A) Plot of the sum of the non-bonded interactions energy calculated between the ligand and the protein. (B) Representative snapshot extracted by the FM trajectory showing the ligand in the fully unbound state at a distance of 4.3 nm form the center of mass of the allosteric site. Hsp90 NTDs are reported in grey, MDs in light grey and the MDs:CTDs forming the site are shown in yello and green for protomers A and B, respectively.

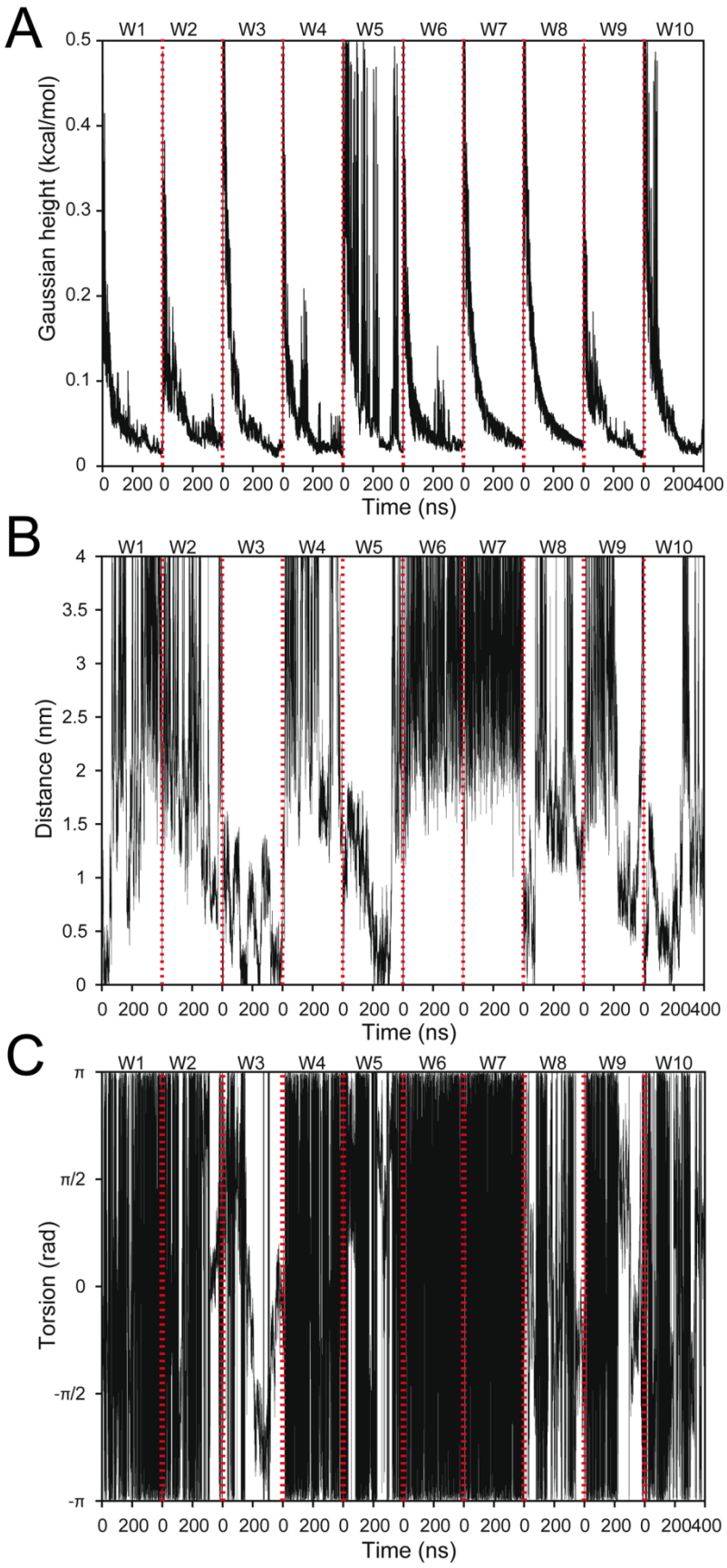


Figure S4. Evolution along the 10 multiple walkers of the Gaussian height (A), distance (B) and torsion (C).

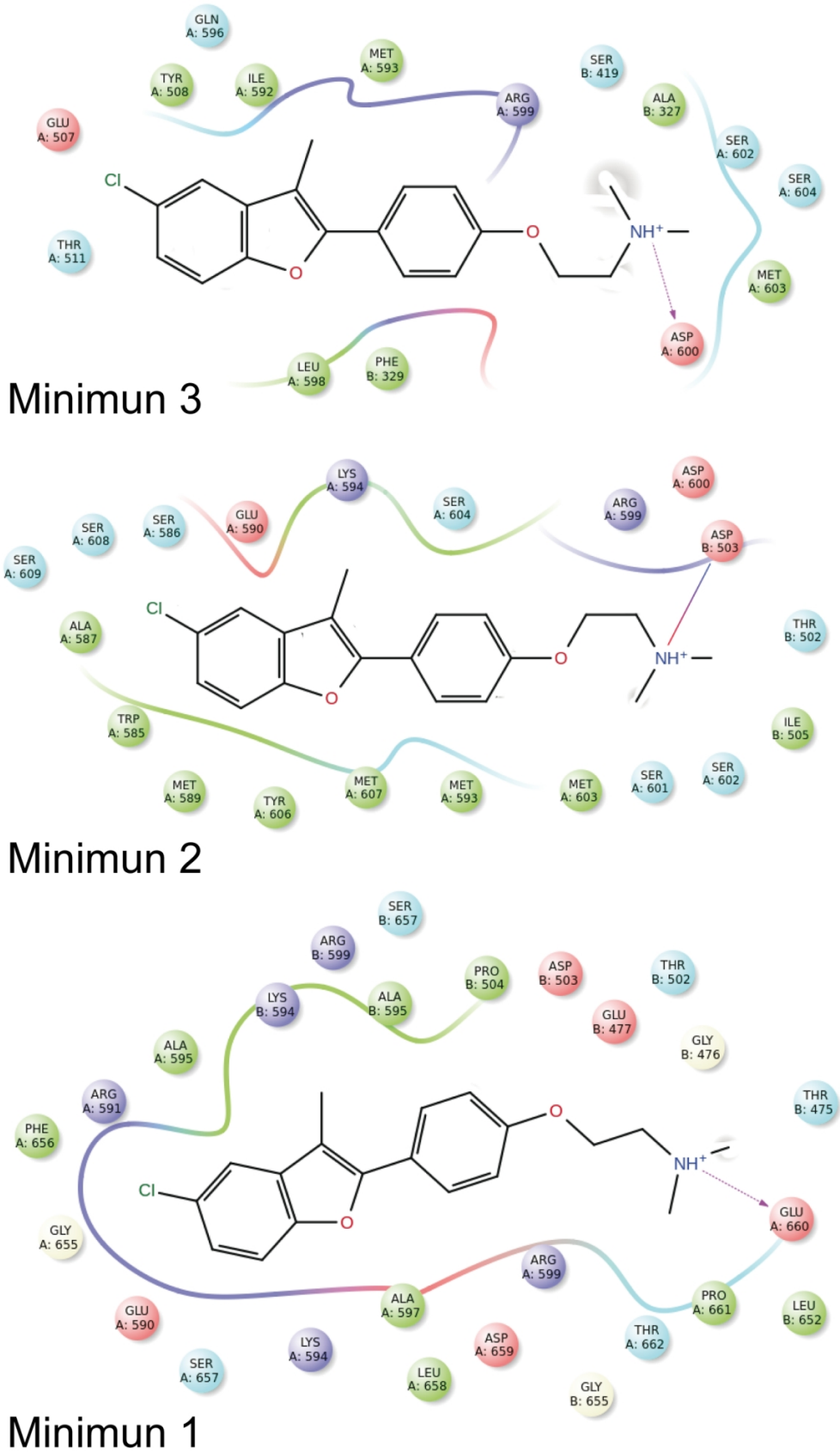
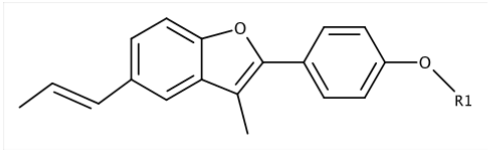
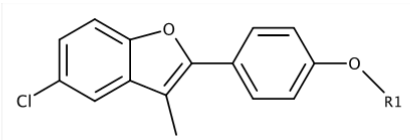


Figure S5. Scheme of the contacts occurring between **18** and the allosteric site calculated for the centroids of the main representative family of structures of each of the three minima.



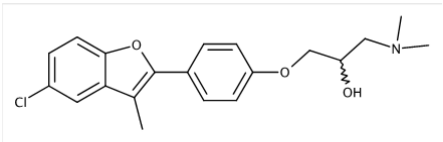
1 R1 = a-L-Rha ref 35 of the main text



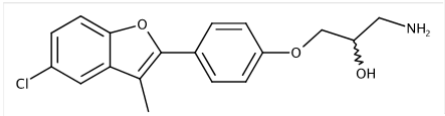
4 R1 = a-L-Rha ref 35 of the main text

10 R1 = a-D-Man ref 35 of the main text

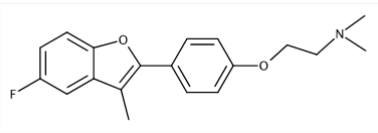
12 R1 = b-D-Gal ref 35 of the main text



24 see ref 38 of the main text



25 see ref 38 of the main text



26 see ref 38 of the main text

Figure S6. The figure depicts the structures of the compounds that were docked into the 3 minima found by FM simulations. The numbers of the compounds are the same as those that can be found in the original references, described in the main text.

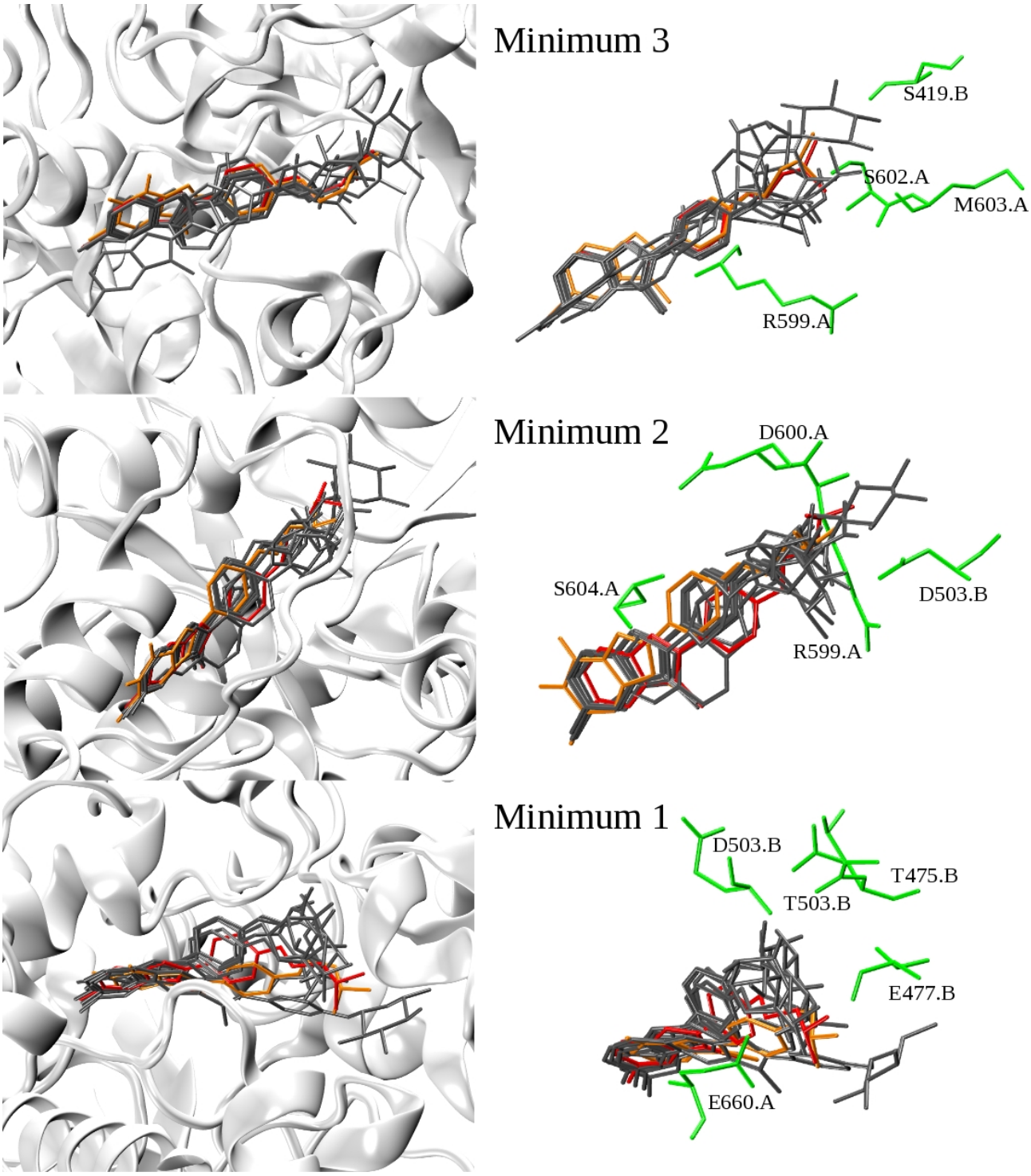


Figure S7. Superposition of the best pose of each compound as reported in Figure S6 and of compound **18** docked against the three minima obtained by FM. The configuration of 18 found by FM is shown in red while its docked pose is shown in orange. All the other compound are reported in grey. The right panel shown for each minimum the most recurring interacting residues.

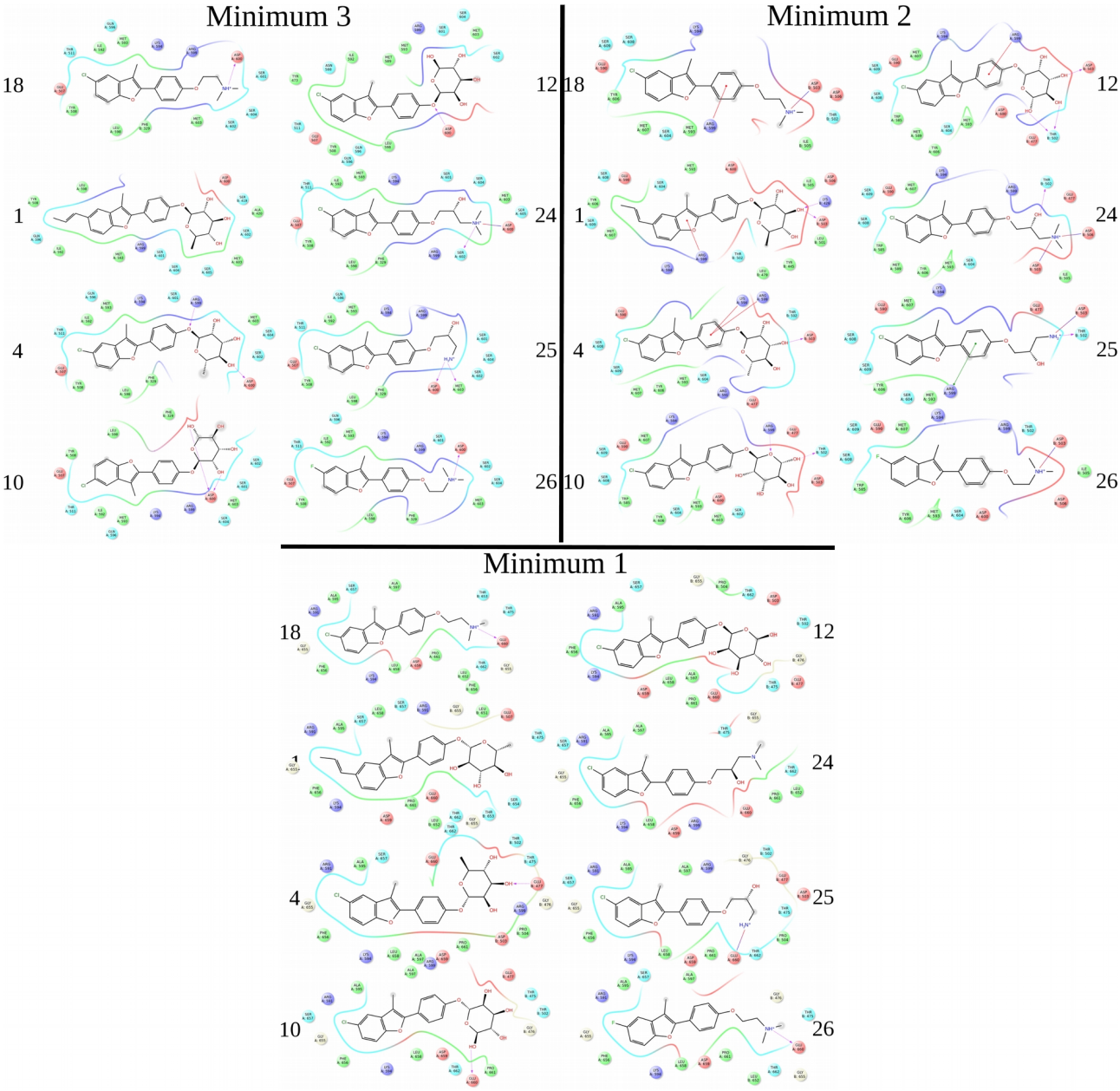


Figure S8. Scheme of the contacts occurring upon docking of **18** and the compounds reported in Figure S6 with the allosteric site calculated for the centroids of the main representative family of structures of each of the three minima.

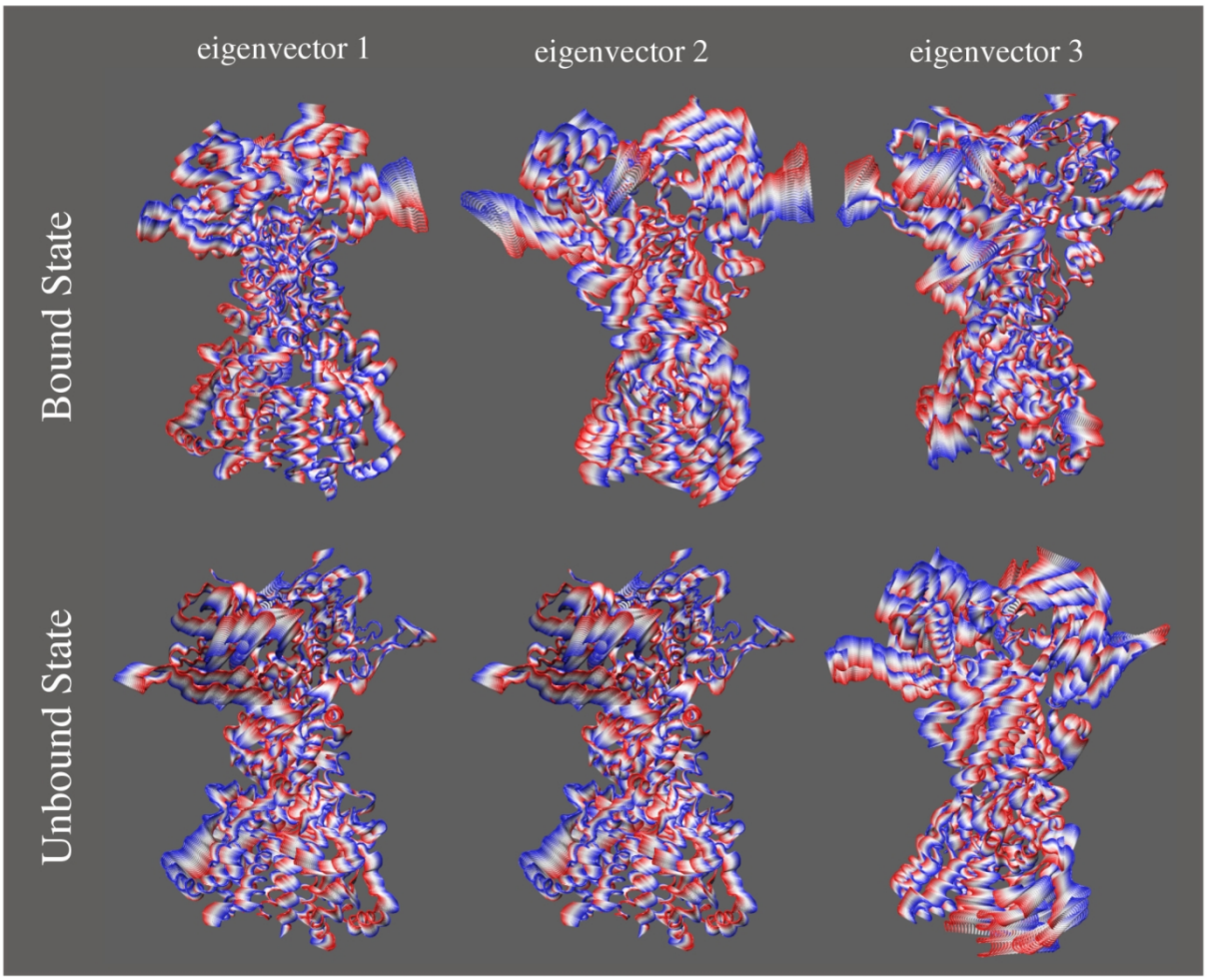


Figure S9. Structural projection of the motion described by the first three eigenvectors in the bound (upper panel) and unbound (lower panel) ensembles.

Movie S1. Protein-Ligand interaction path. The movie shows the trajectory extracted from FM simulations, filtered to show only the bound ensemble. Here we describe the route of entrance of the ligand into the binding pocket, from minimum 3 to minimum 2 and finally to minimum 1 where it is finally fully buried into the site.