

Figure S1 3D-structures of morphine, IBNtxA, and their complexes with 7TM, and G1 hMOR-1 receptors obtained from Glide XP docking. TM1 is colored in purple.

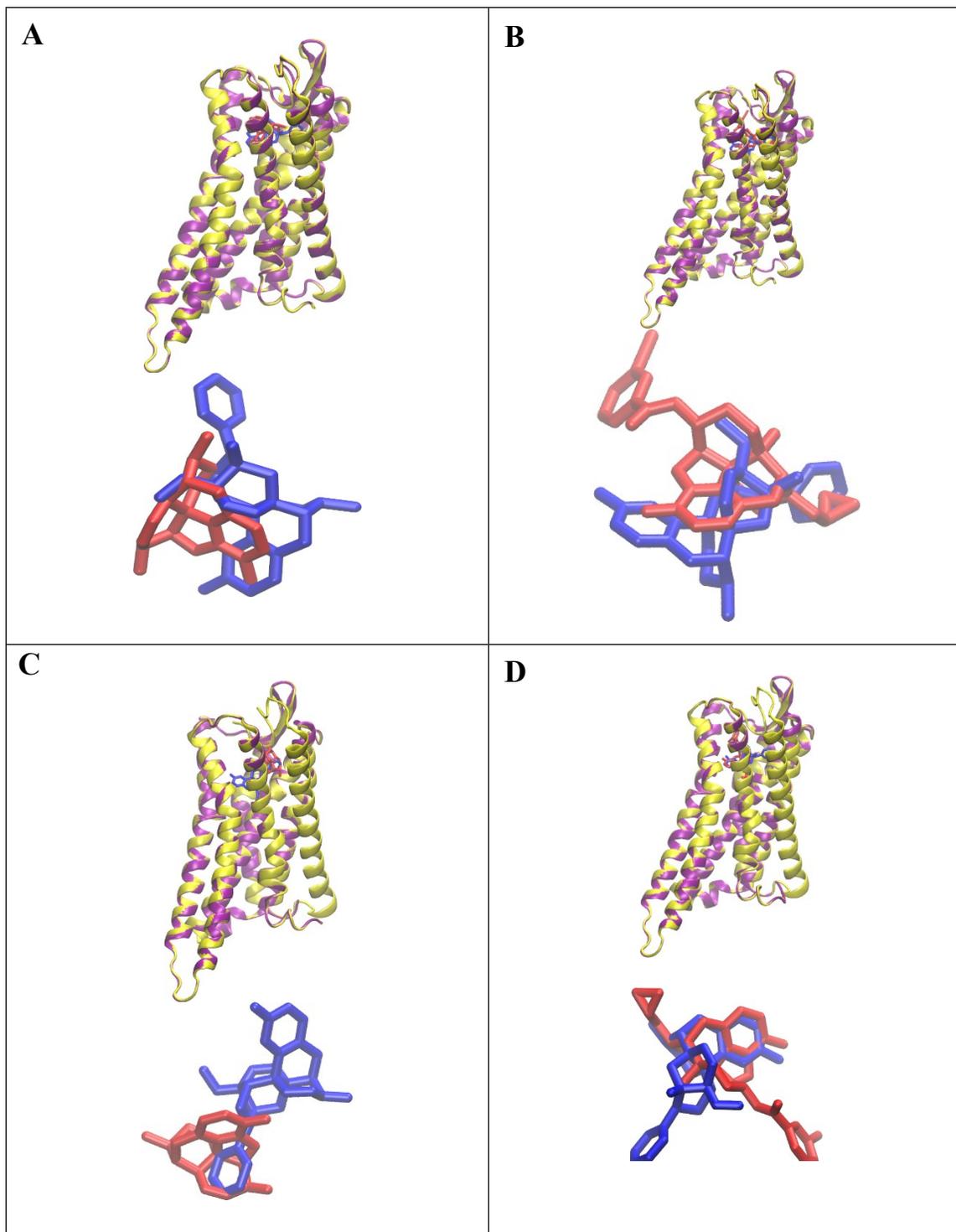


Figure S2 Comparison between the docked complexes to the active crystal complex (crystal 7TM receptor/yellow-BU72/blue). **A:** docked 7TM/purple-Morphine/red. **B:**

docked 7TM/purple-IBNtxA/red). **C:** docked G1/purple-Morphine/red. **D:** docked G1/purple-IBNtxA/red.

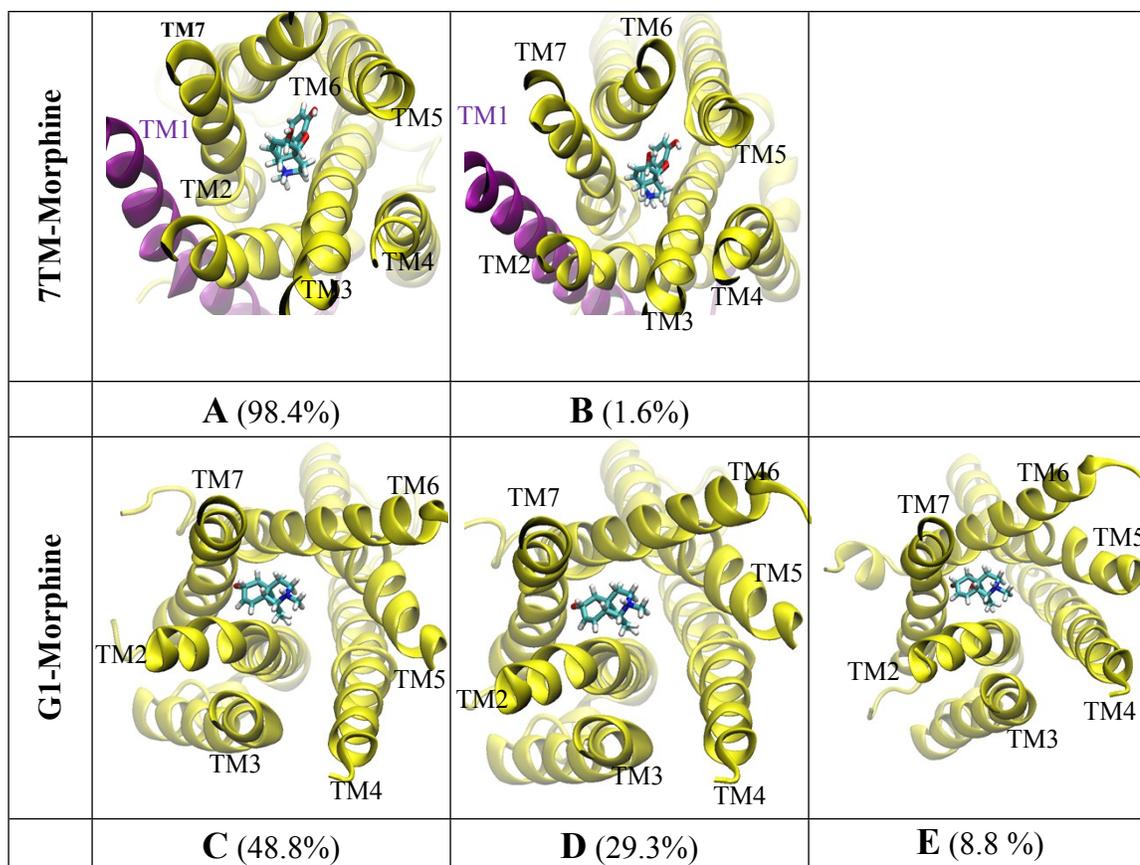


Figure S3 Representative receptor-morphine structures of top structural families from the clustering analysis. Abundance is annotated. The extracellular and intracellular loops were truncated for clarity.

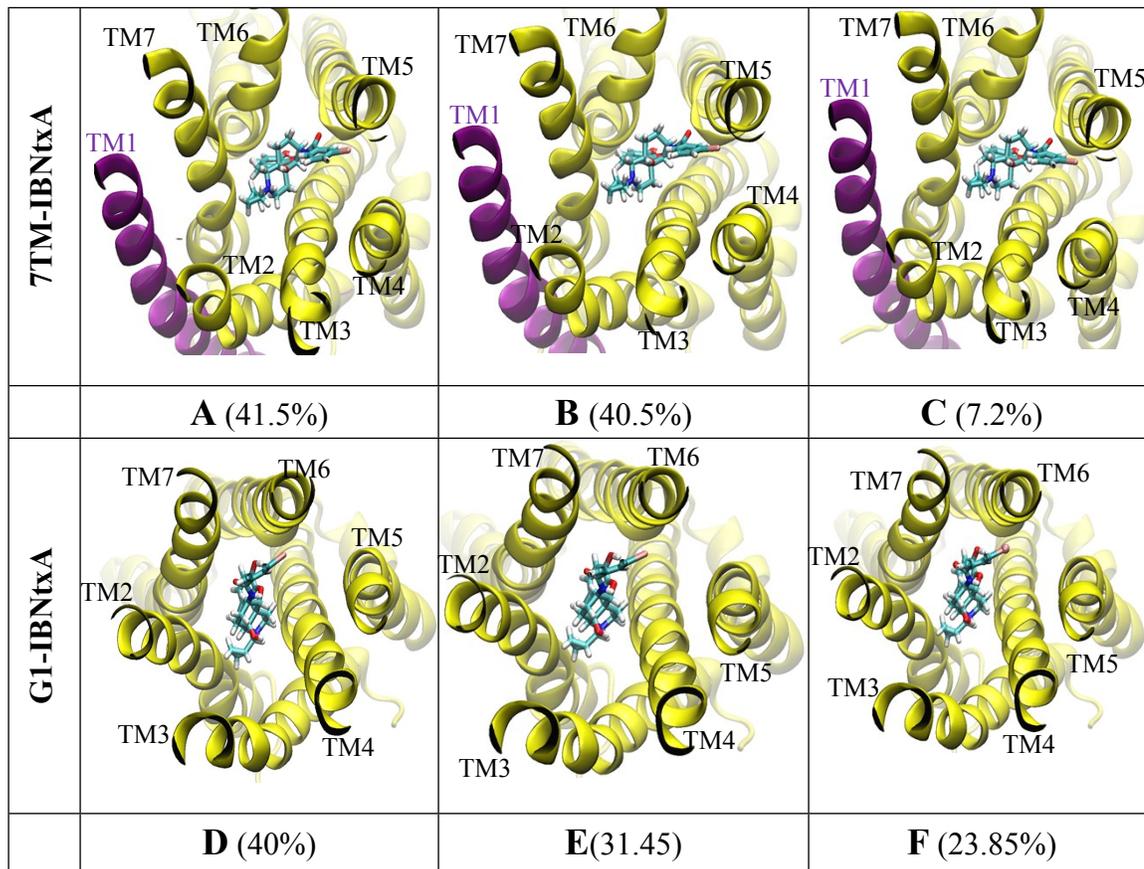


Figure S4 Representative receptor-IBNtxA structures of top complexes structural families from the clustering analysis. Abundance is annotated. The extracellular and intracellular loops were truncated for clarity.

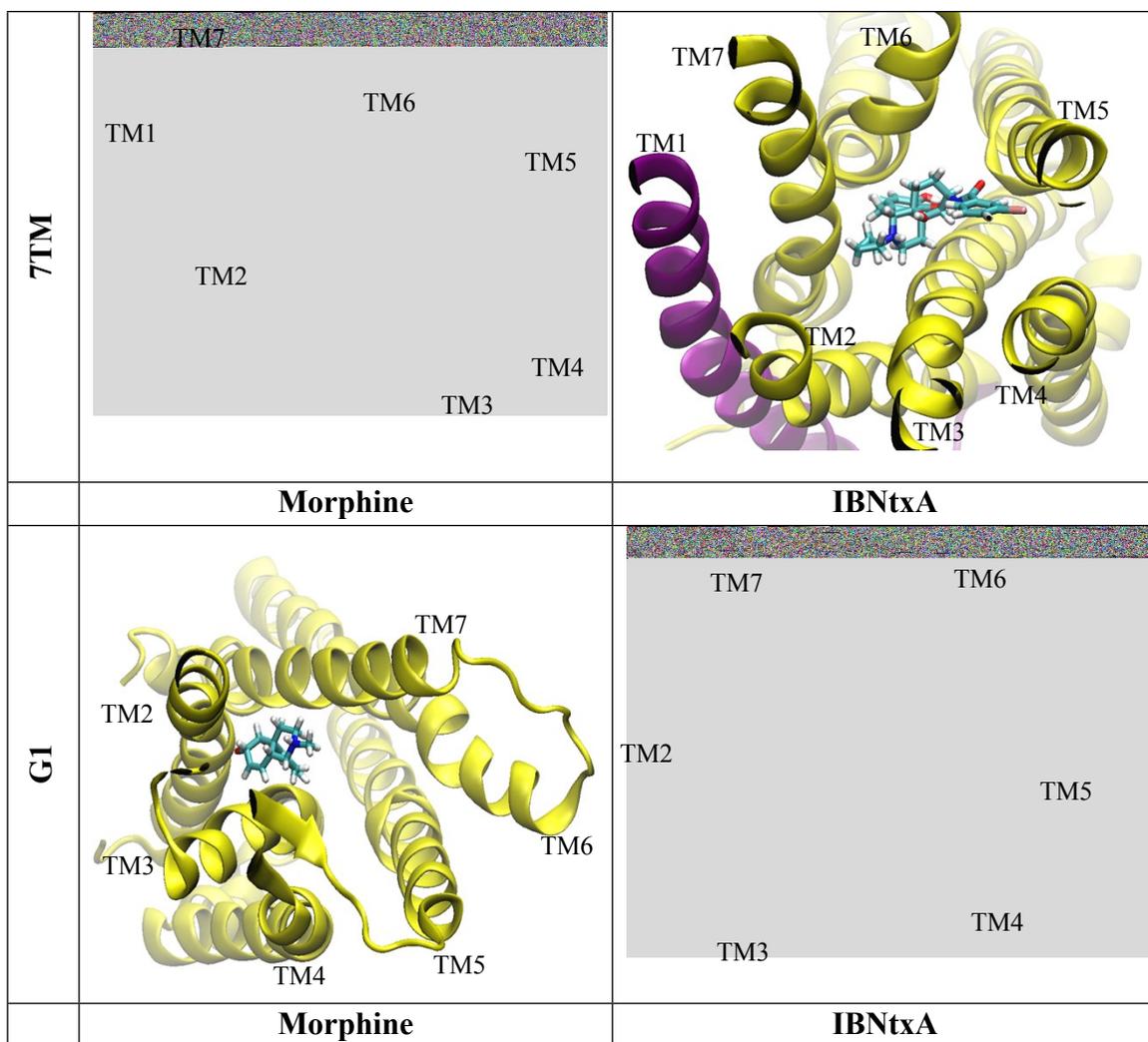


Figure S5 Comparisons of the most abundant structure of Morphine and IBNtxA in complex with both 7TM and G1 from the simulations. The extracellular and intracellular loops were truncated for clarity.

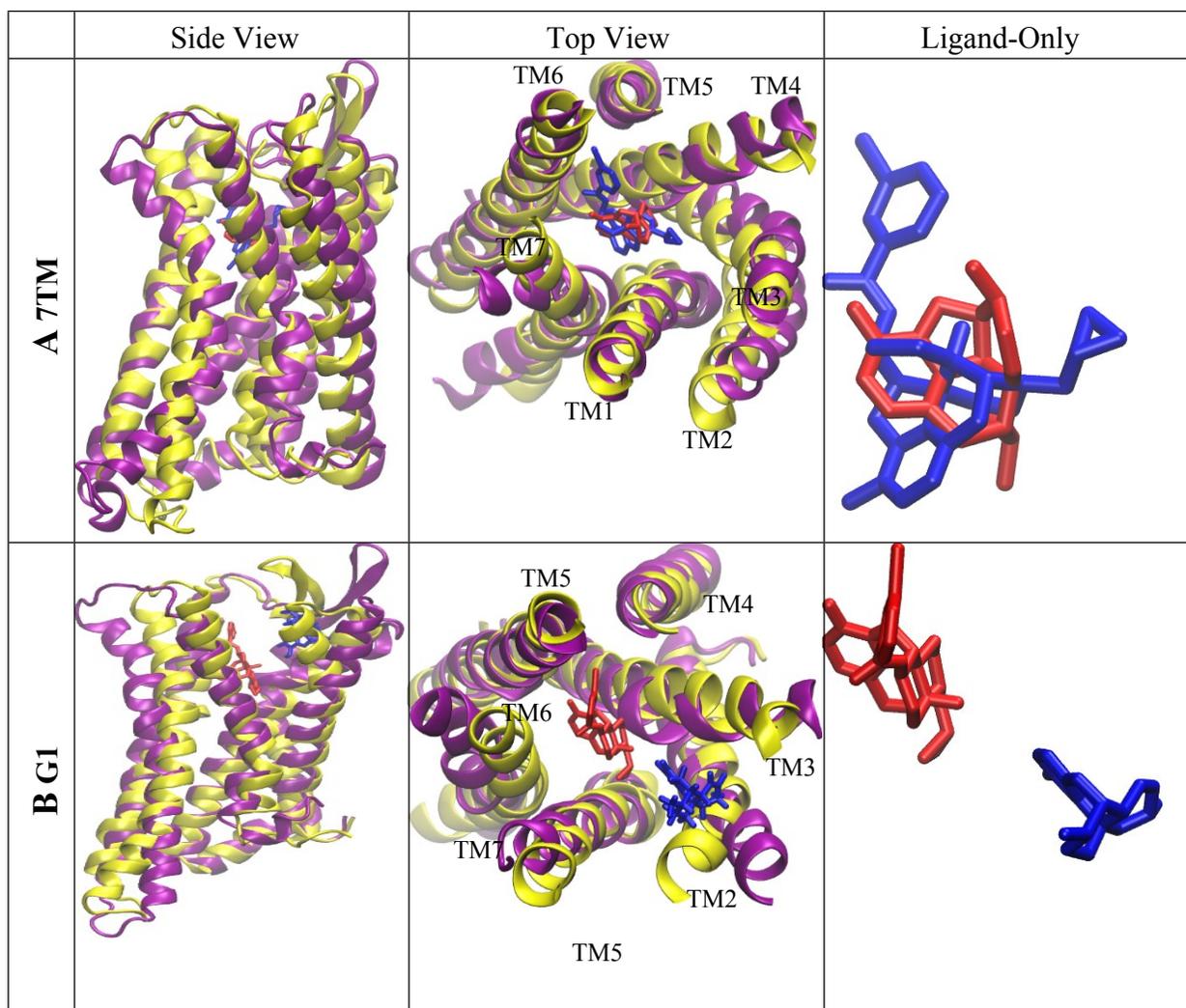


Figure S6 Structural superposition of the most abundant complexes from the MD simulations. **A** (MD 7TM/yellow-Morphine/red VS. MD 7TM/purple-IBNtxA/blue) **B** (MD G1/yellow-IBNtxA/red VS. MD G1/purple-Morphine/blue).

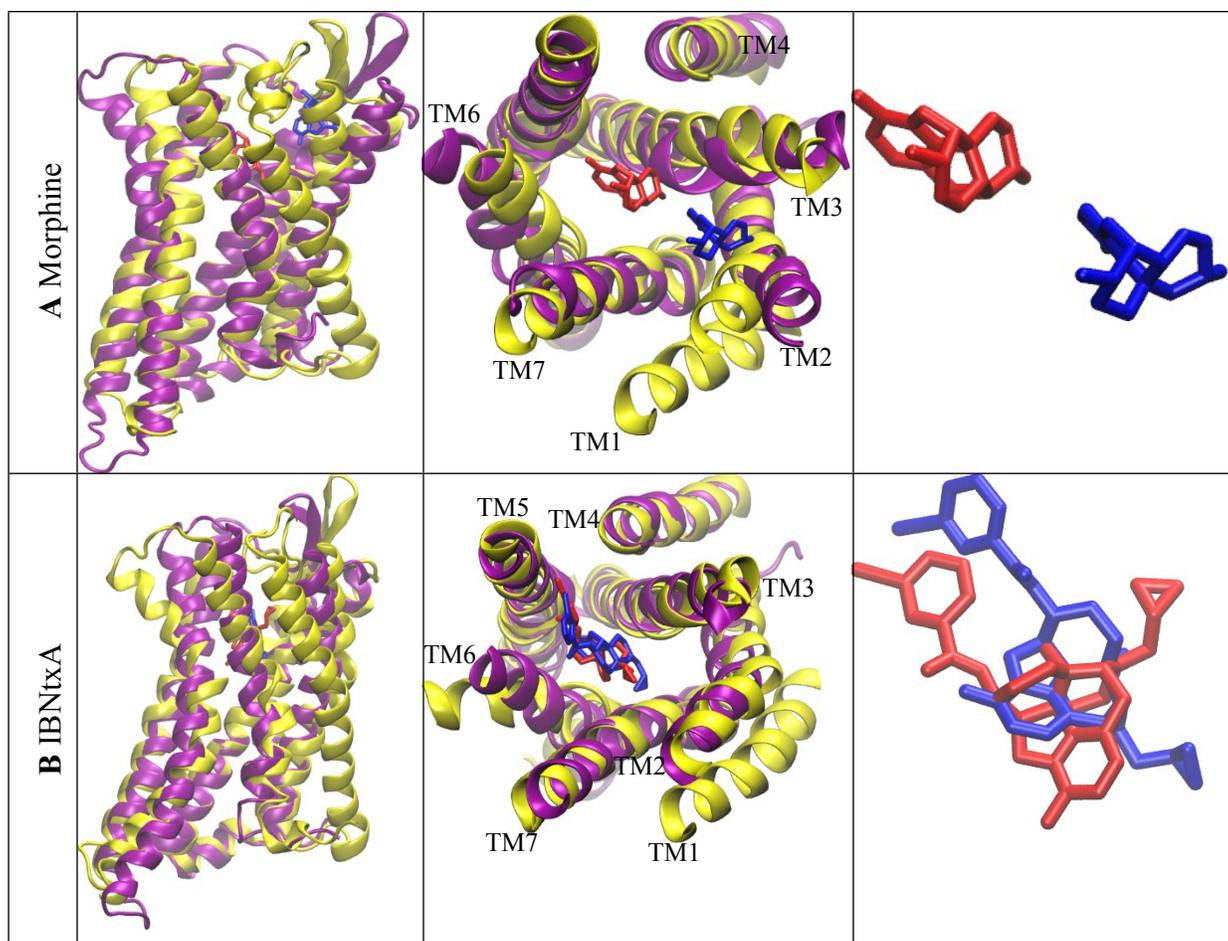


Figure S7 Structural Superposition of the most abundant complexes from the MD simulations. **A** (MD 7TM/yellow-Morphine/red VS. MD G1/purple-Morphine/blue). **B** (MD 7TM/yellow-IBNtxA/red VS. MD G1/purple-Morphine/blue).

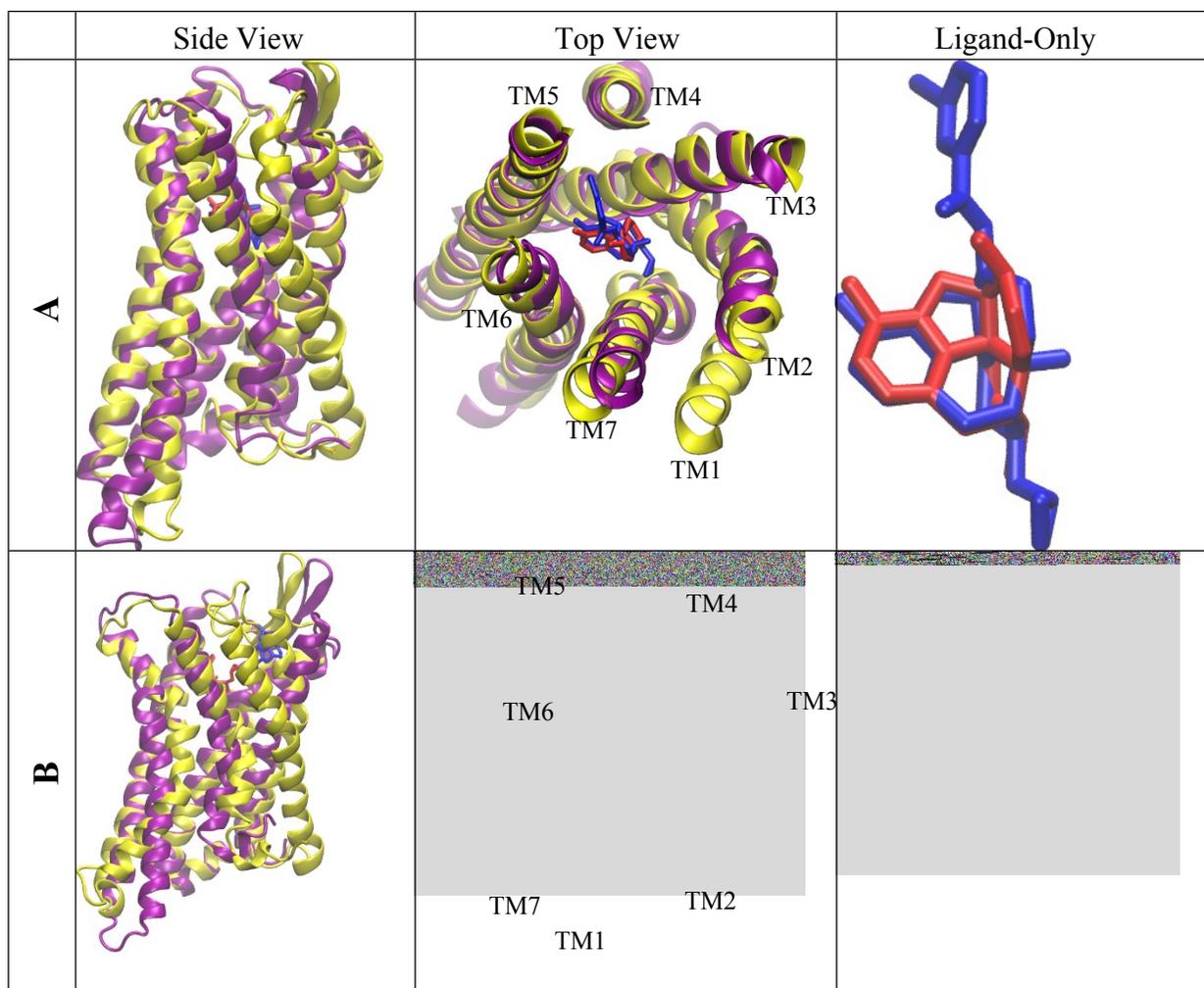


Figure S8 Structural superimposition of the most abundant complexes from the MD simulations. **A** (7TM/yellow-Morphine/red VS G1/purple-IBNtxA/blue). **B** (7TM/yellow-IBNtxA/red VS G1/purple-Morphine/blue).

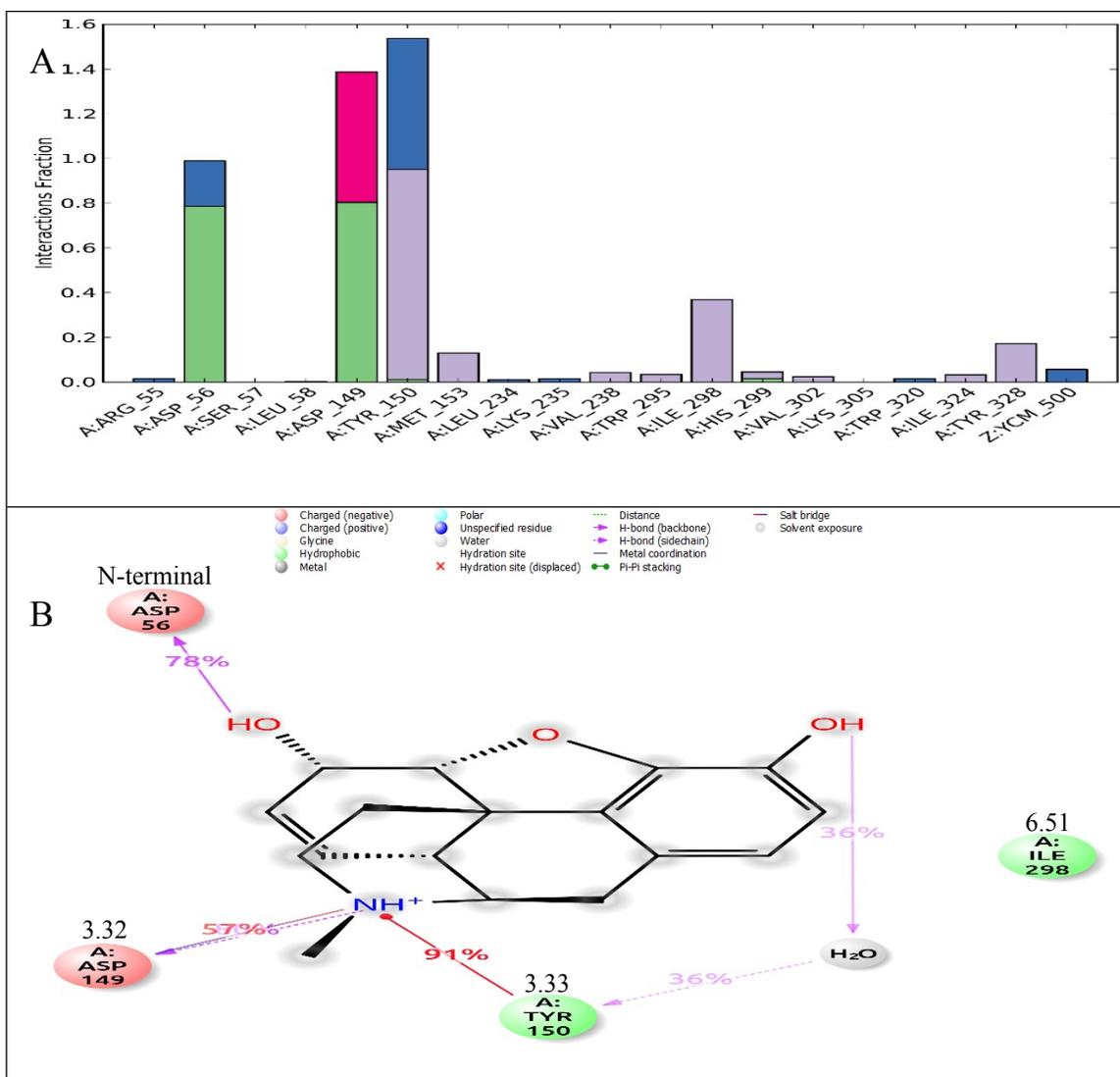


Figure S9 Contacts of Morphine to 7TM. The genetic numbering is annotated for each interacting residue. **A:** Interaction fraction over the MD trajectory. **B:** Ligand-residue interactions persisting more than 30% of simulation time.

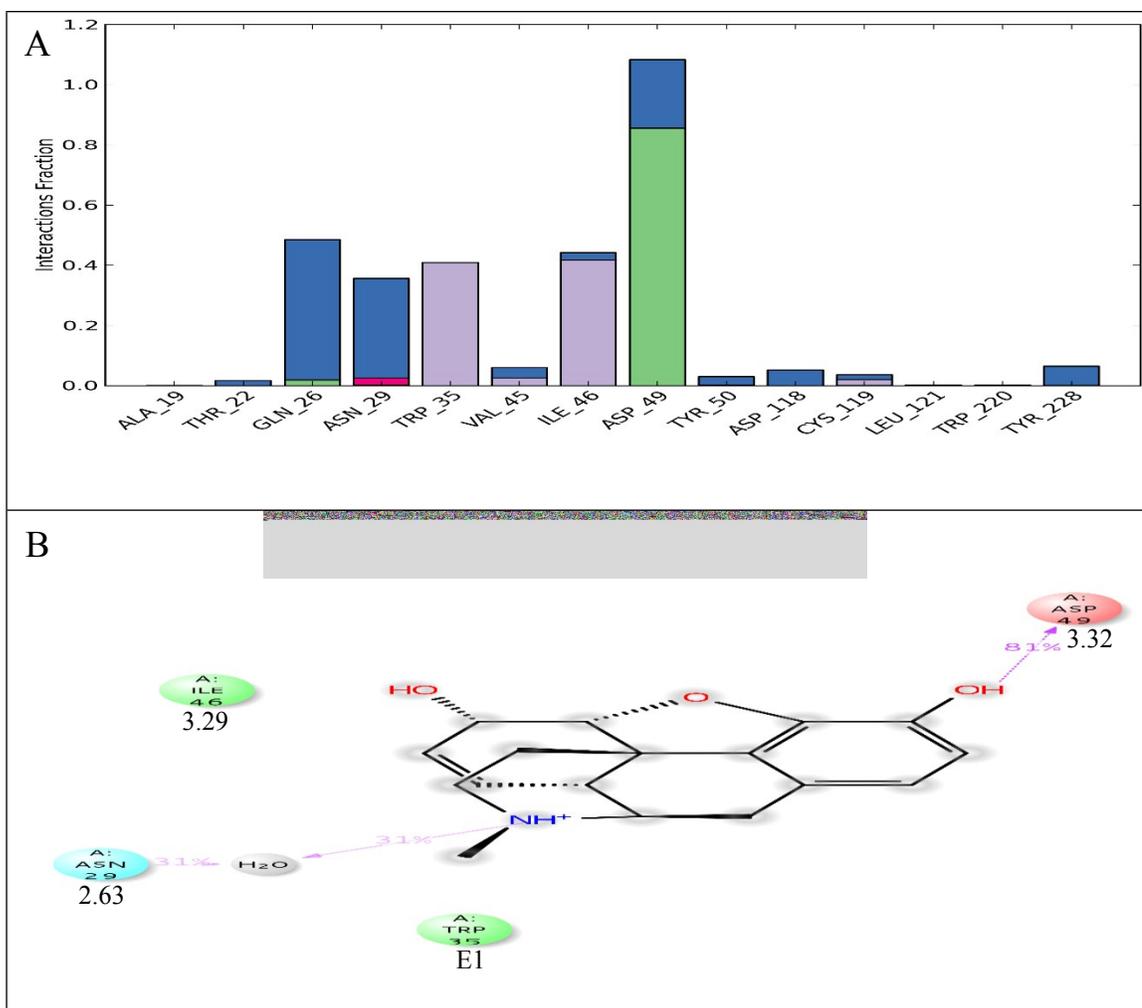


Figure S10 Contacts of Morphine to G1. The genetic numbering is annotated for each interacting residue. **A:** Interactions fraction over the MD trajectory. **B:** Illustrates interactions persist more than 30% of simulation time.

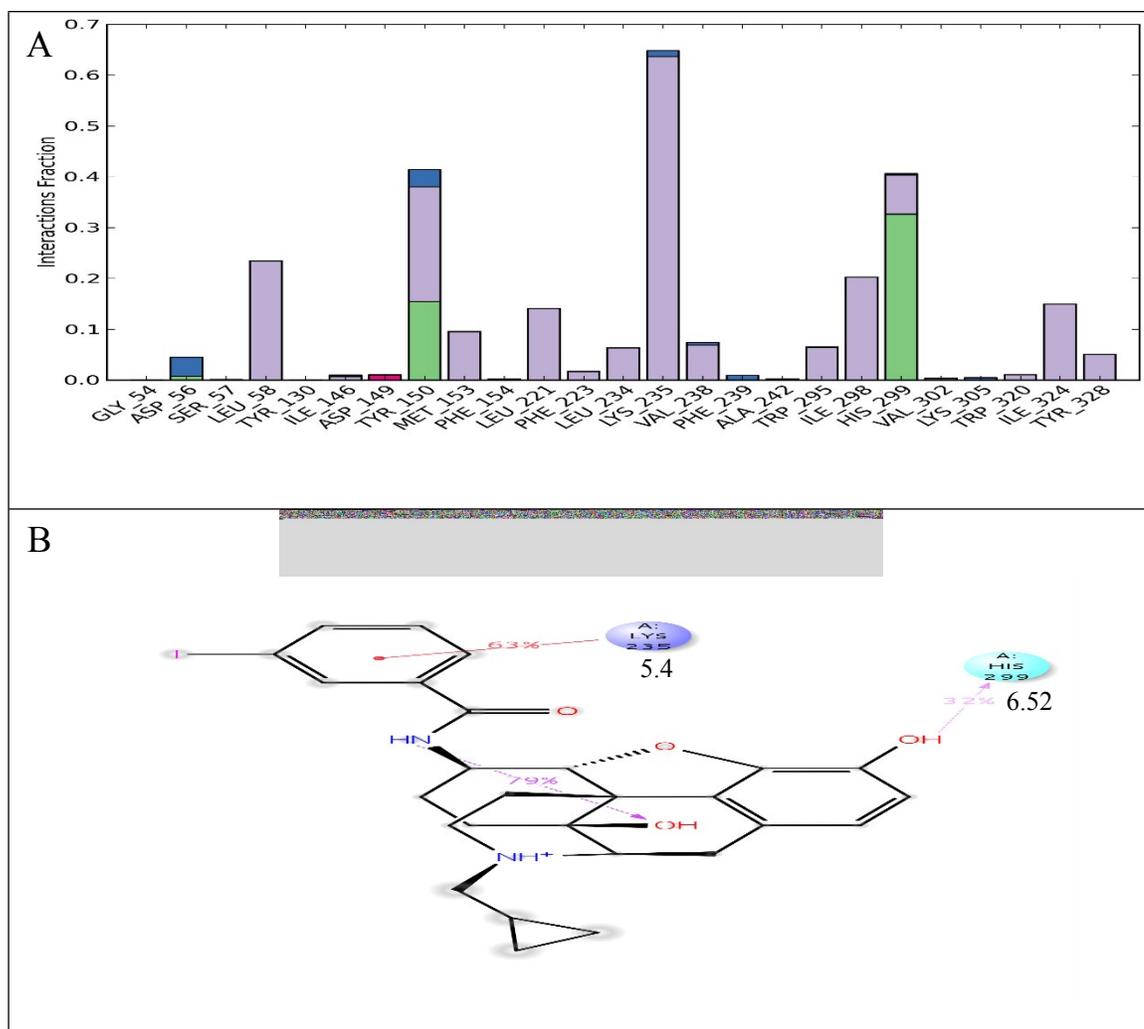


Figure S11 Contacts of IBNtxA to 7TM. The genetic numbering is annotated for each interacting residue. **A:** Interactions fraction over the MD trajectory. **B:** Illustrates interactions persist more than 30% of simulation time. **C:** The ligand protein contacts over the MD trajectory.

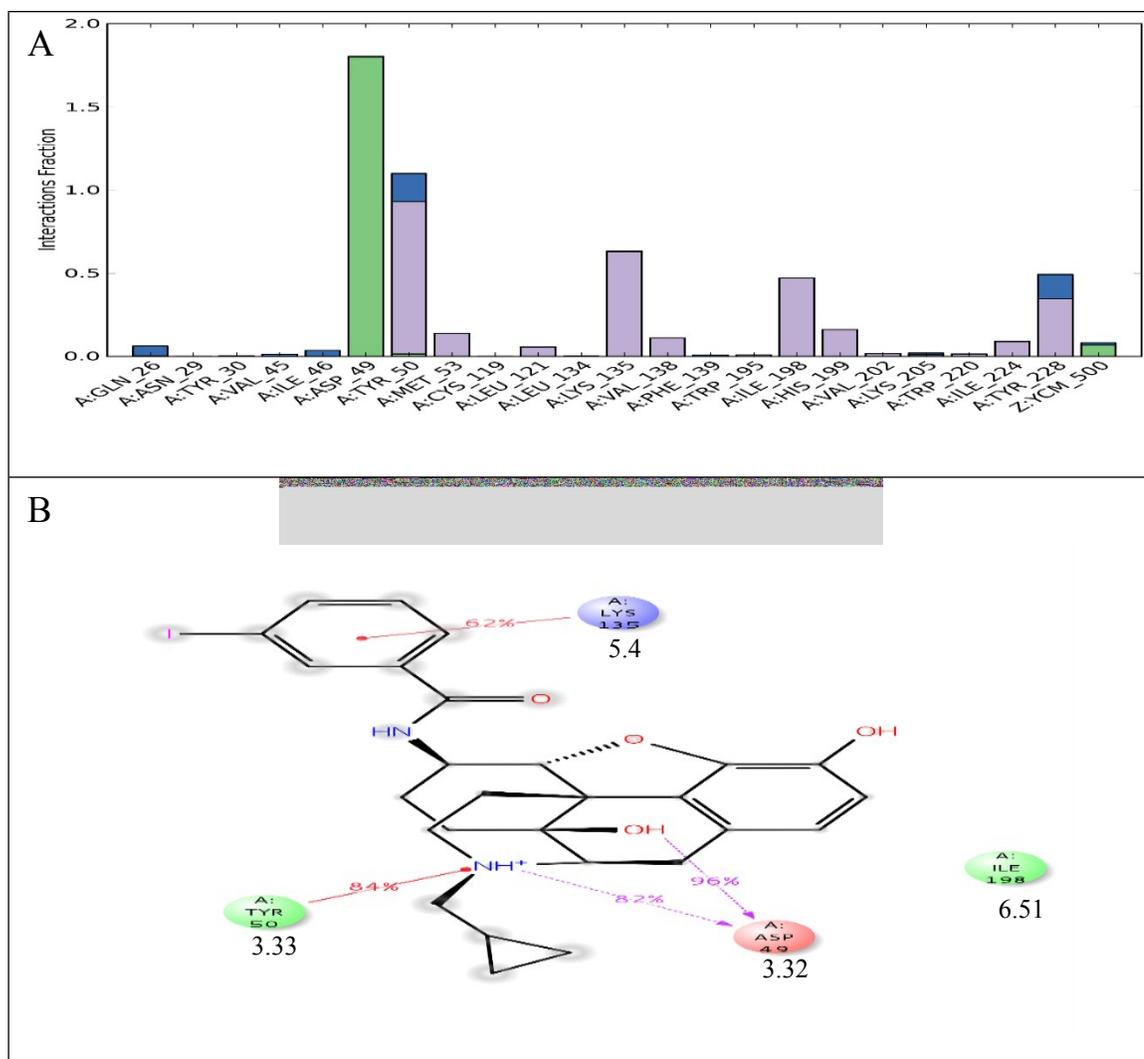


Figure S12 Contacts of IBNtxA to G1. The genetic numbering is annotated for each interacting residue. **A:** Interactions fraction over the MD trajectory. **B:** Illustrates interactions persist more than 30% of simulation time.

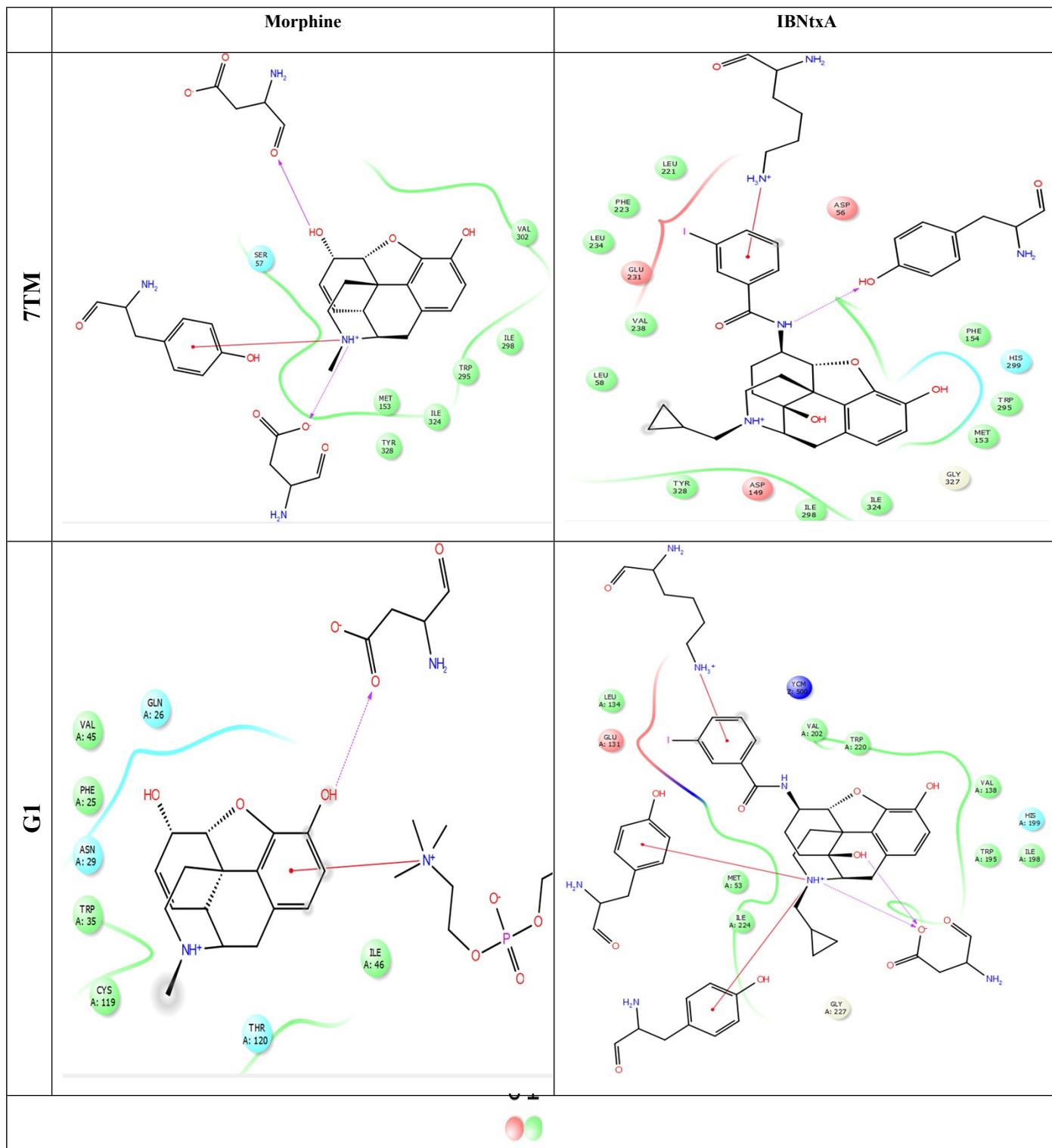


Figure S13 detailed protein-ligand interactions persisting more than 30% of the simulation time.

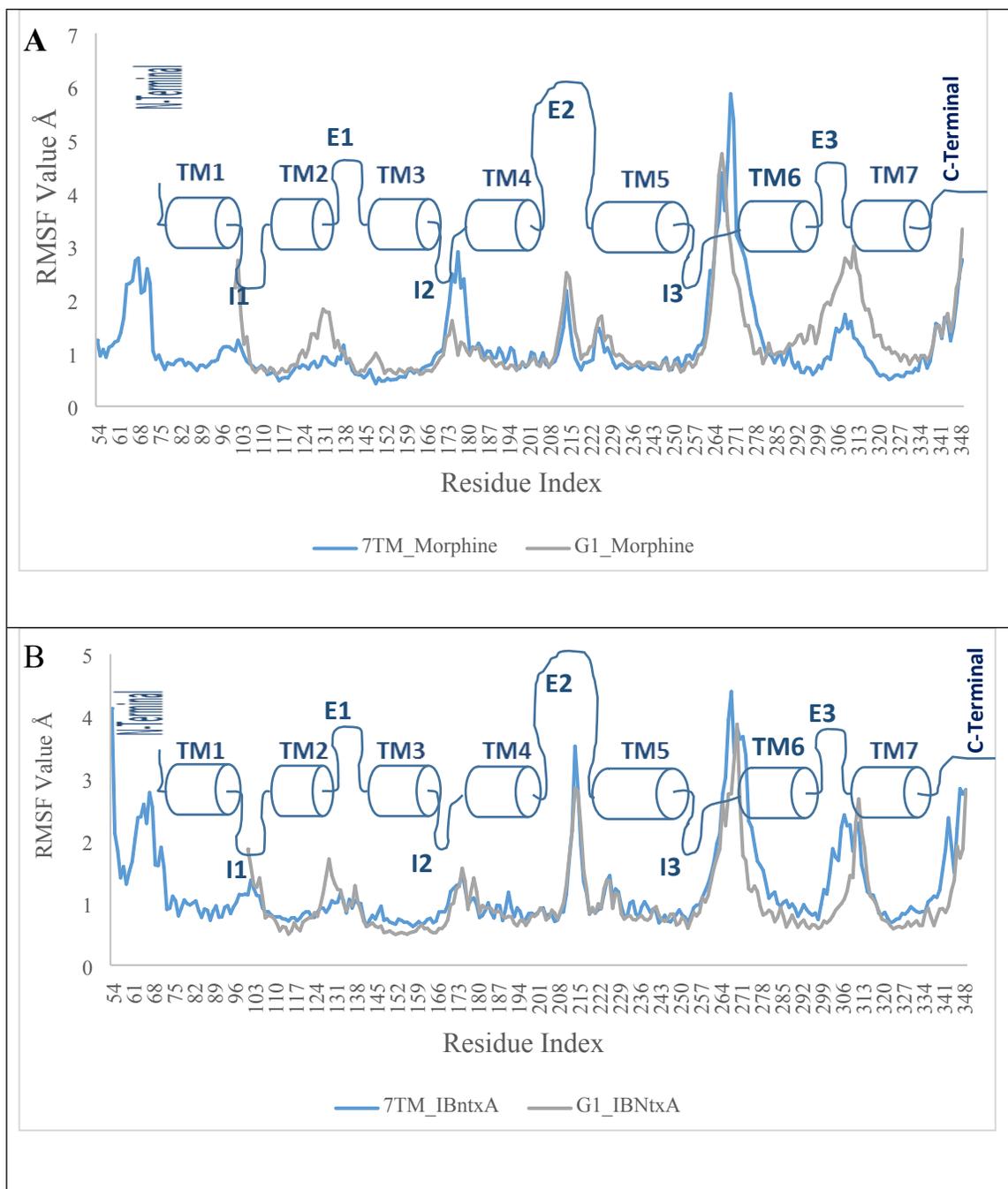


Figure S14 C α RMSF diagrams of the complexes. **A:** 7TM-Morphine VS G1-Morphine. **B:** 7TM-IBNtxA and G1-IBNtxA. The residue index is shown for the full length 7TM receptor. In G1 receptor, the RMSF diagram starts at the TM2 skipping TM1 as a result of truncation.

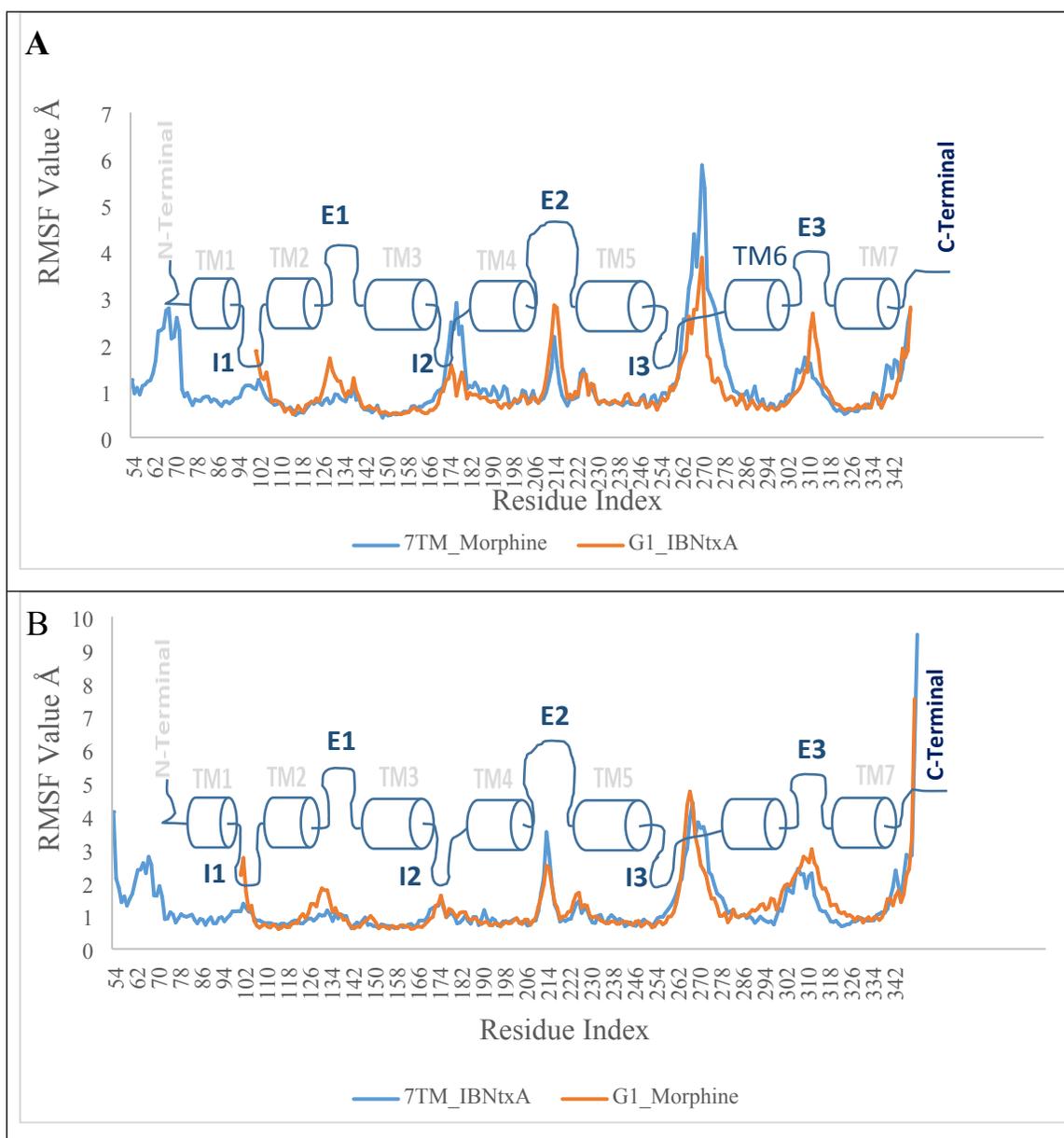


Figure S15 α RMSF diagrams of the complexes. **A:** Active complexes (7TM-Morphine and G1-IBNtxA). **B:** Inactive complexes (7TM-IBNtxA and G1-Morphine). Residue index is shown for the full length 7TM receptor. In G1 receptor, the RMSF diagram starts at the TM2 skipping TM1 as a result of truncation.

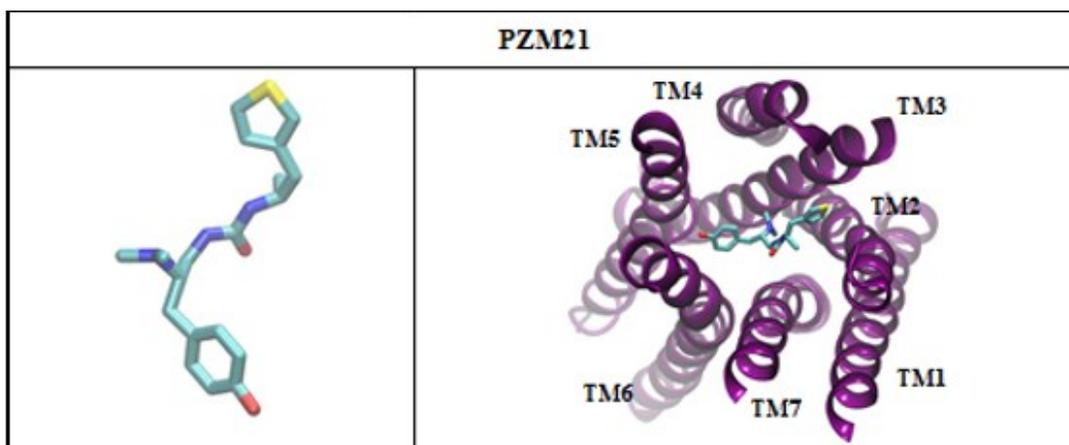


Figure S16 3D-structures of a G-protein biased MOR agonist, PZM21, and its complexes with 7TM receptor obtained from Glide XP docking.

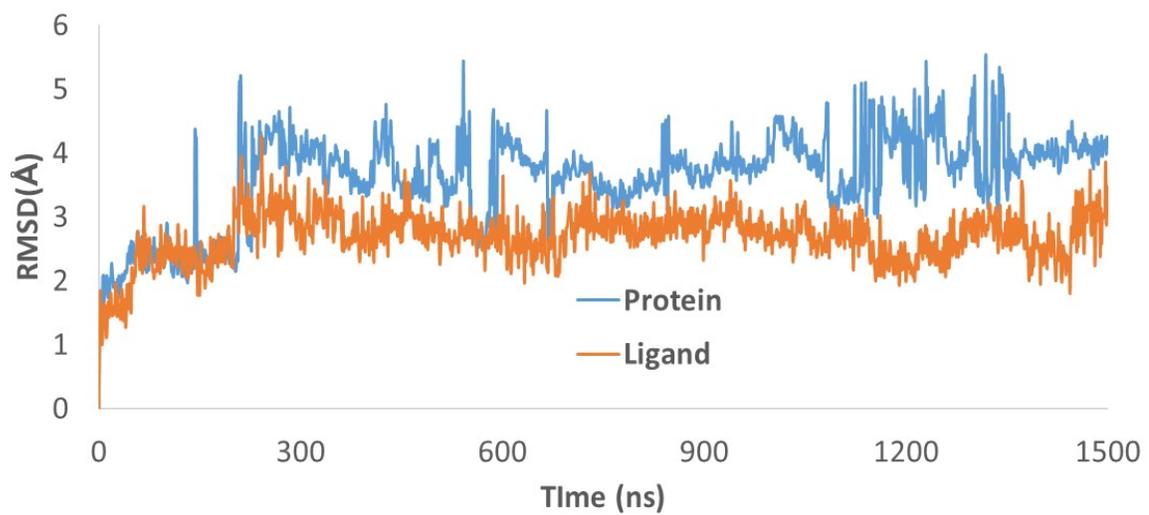


Figure S17 RMSDs of 7TM-PZM21.

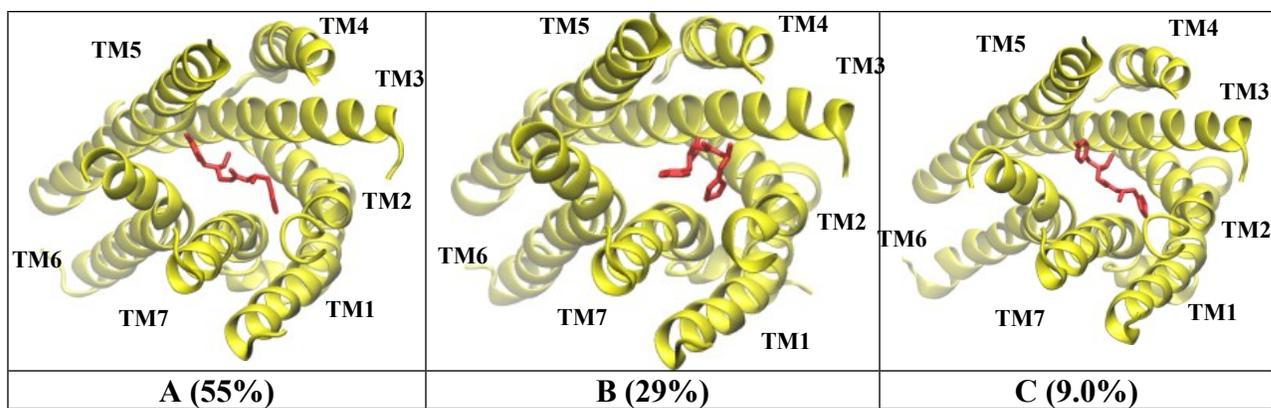


Figure S18 Representative structures of top clusters from the MD simulation of 7TM-PZM21.

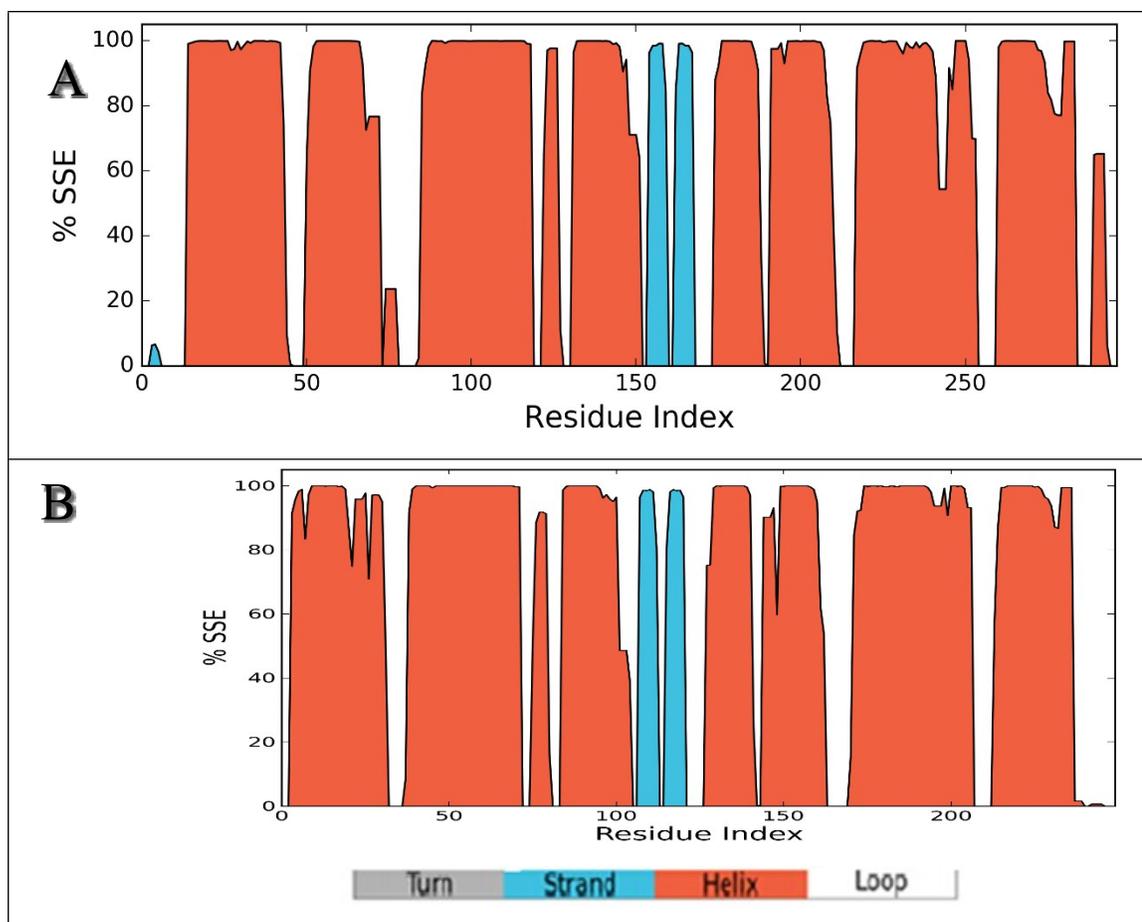


Figure S19 Comparison of secondary structure element (SSE) between 7TM-PZM21(A) and G1-IBNtxA (B).

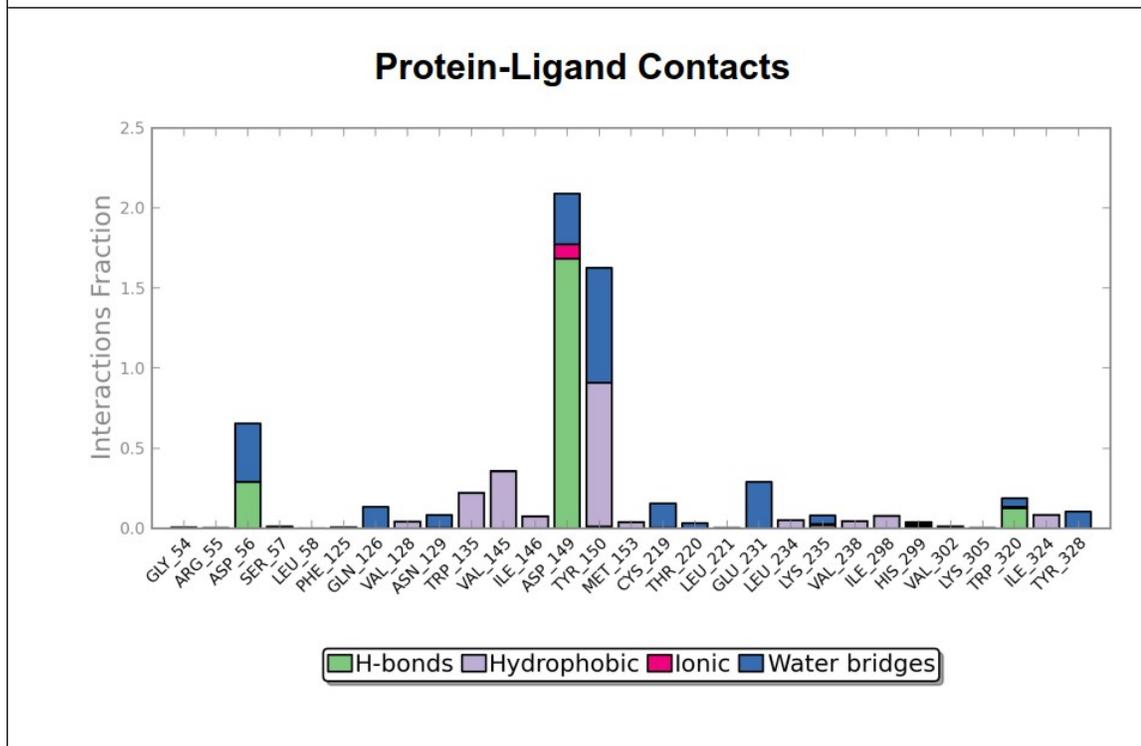
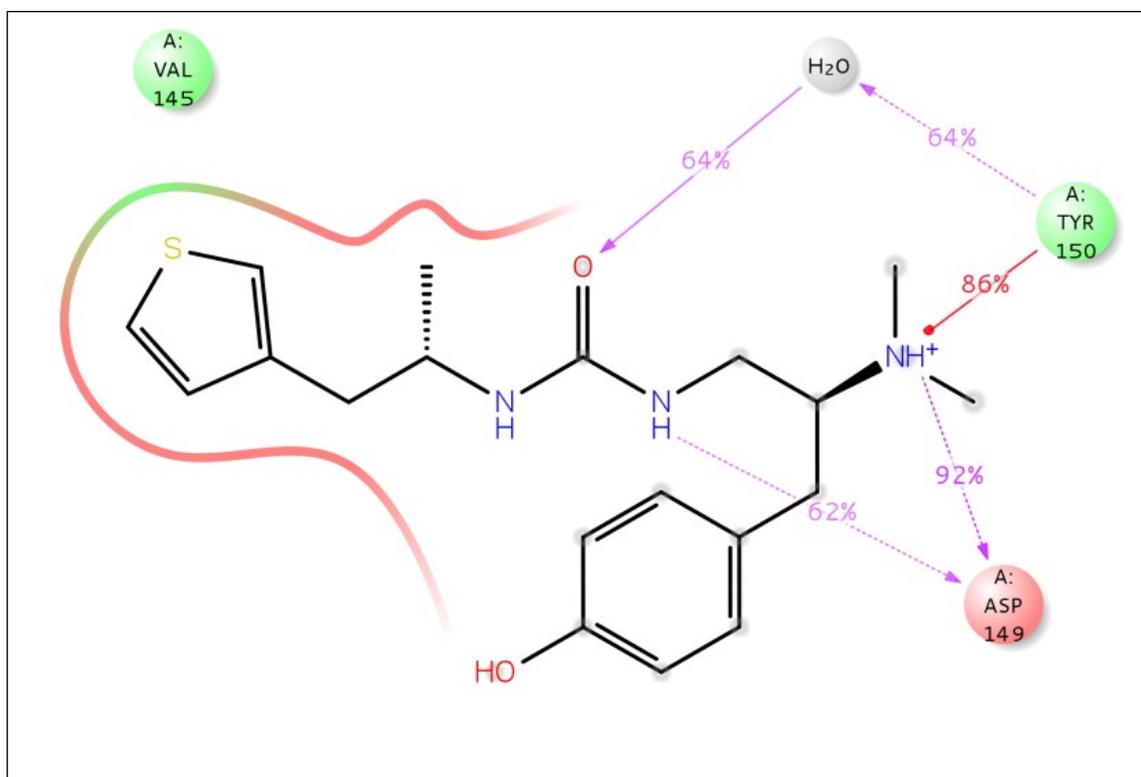


Figure S20 Protein-Ligand Contacts for 7TM-PZM21.