Fig. S1

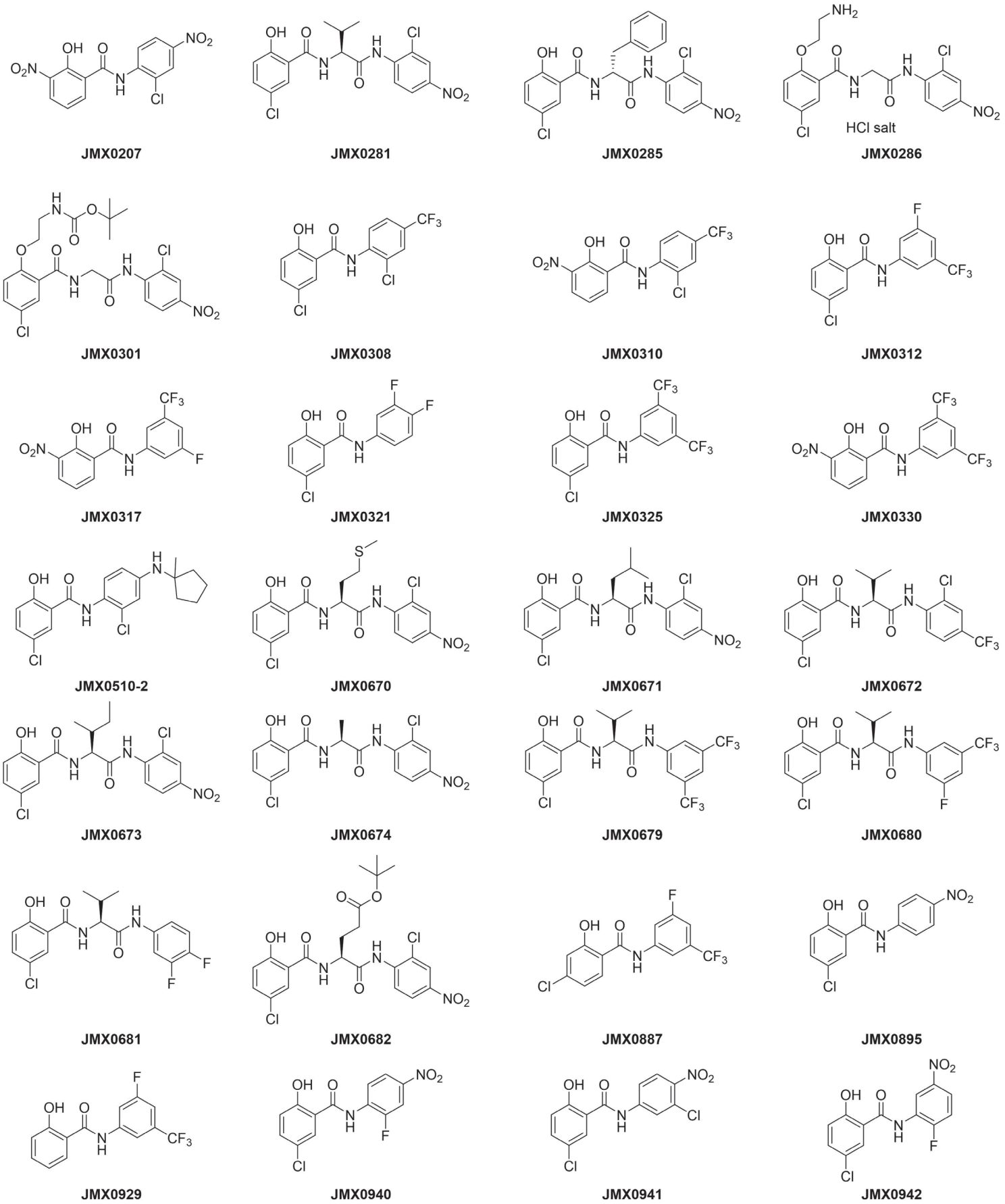

Fig. S1. The structures of active niclosamide derivatives against SARS-CoV-2

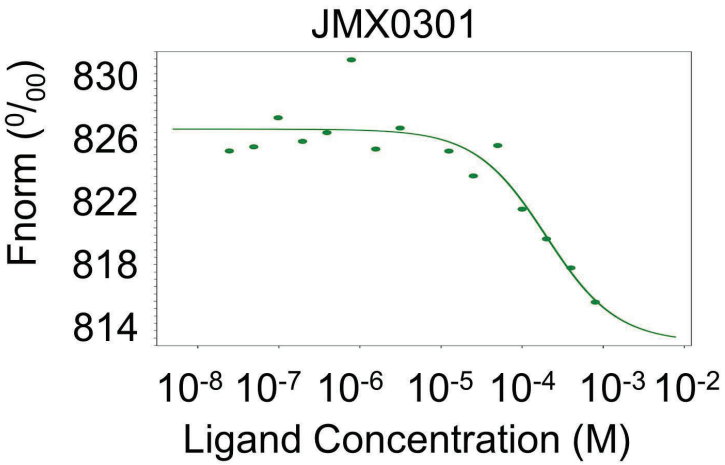

Fig. S2. Analysis of JMX0301 binding to recombinant SARS-CoV-2 3CLpro: Dose response curve upon titrating 600 μM to 9 μM for JMX0301 against 10 nM of 3CLpro using Microscale Thermophoresis technique (MST). The K_D obtained was 34 μM.

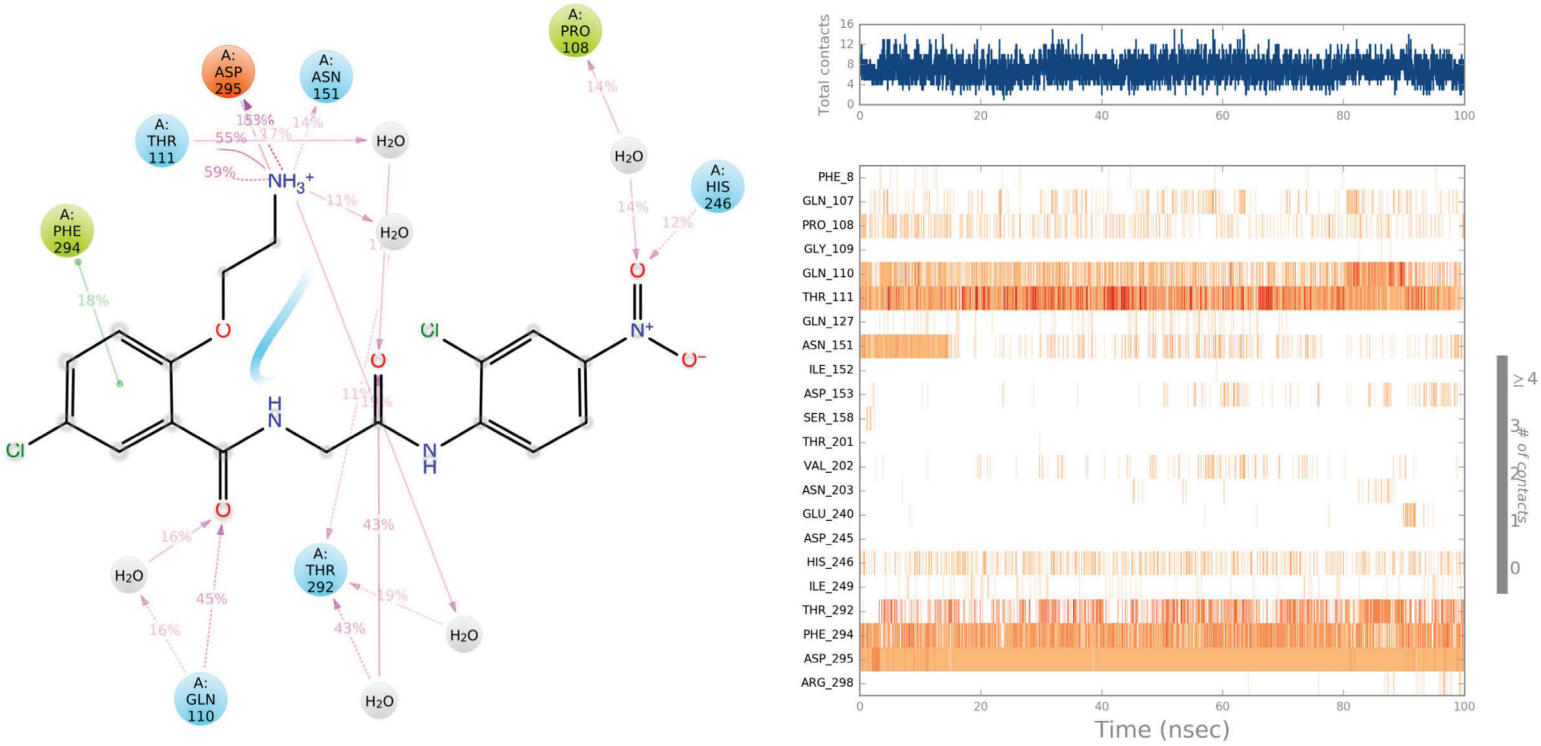

Fig. S3. Contacts established between 3CLpro and JMX0286 over 100 ns simulation in the allosteric site. Left panel. Schematic view of predominant ligand atom interactions that occur with amino acid residues during the simulation time. Some residues may engage in multiple interactions of a single type (e.g., H-bond, etc.) with the same ligand atom. Hence, is it possible to cumulate >100% frequency of interaction. Right panel. (Top) Total number of contacts over the course of the trajectory. (Bottom) Analysis of residues interacting with the ligand, detailed by trajectory frame. Darker shade of orange indicates multiple protein/ligand contacts by amino acid residue.

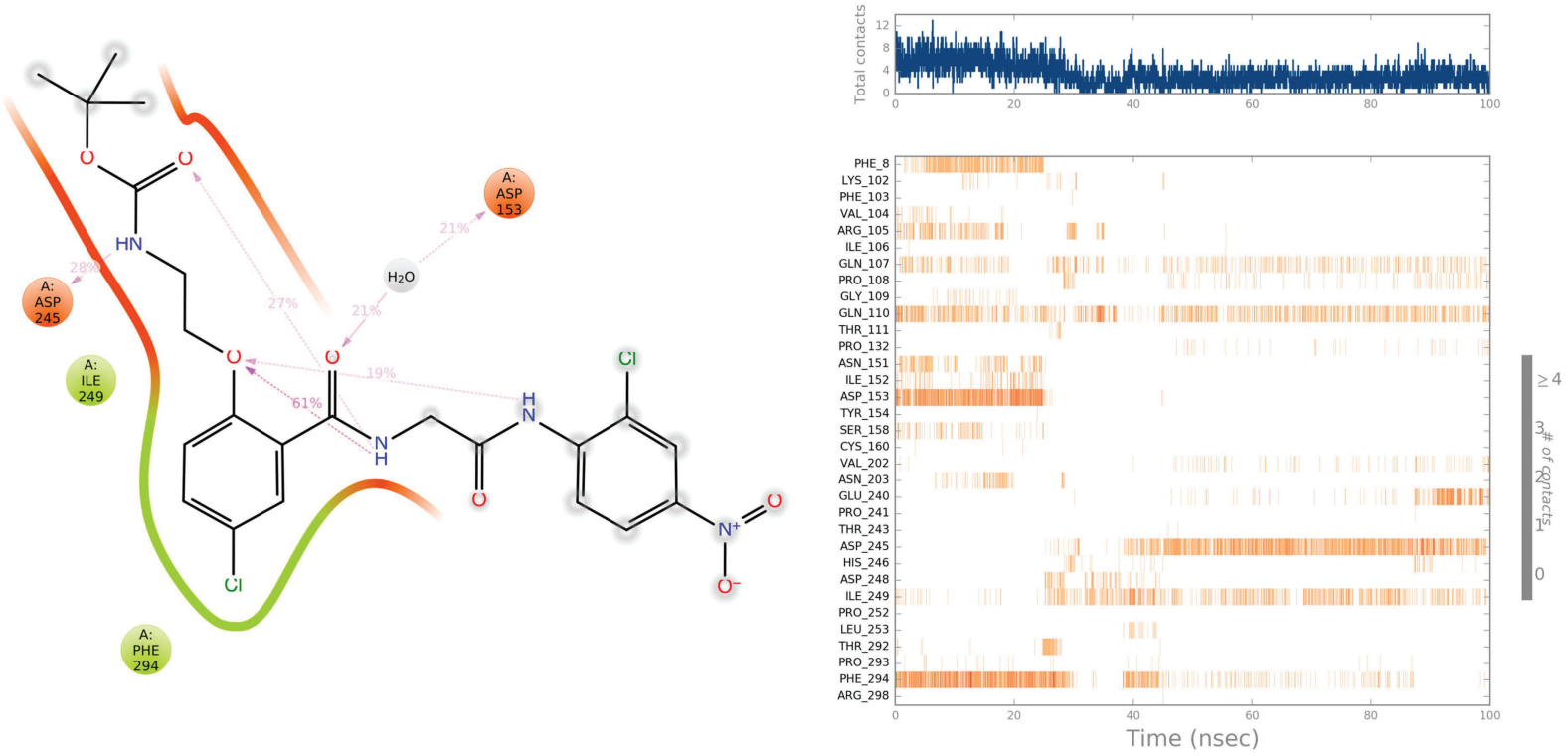

Fig. S4. Contacts established between 3CLpro and JMX0301 over 100 ns simulation in the allosteric site. Schematic view of predominant ligand atom interactions that occur with amino acid residues during the simulation time. Some residues may engage in multiple interactions of a single type (e.g., H-bond, etc.) with the same ligand atom. Hence, is it possible to cumulate >100% frequency of interaction. Right panel. (Top) Total number of contacts over the course of the trajectory. (Bottom) Analysis of residues interacting with the ligand, detailed by trajectory frame. Darker shade of orange indicates multiple protein/ligand contacts by amino acid residue.

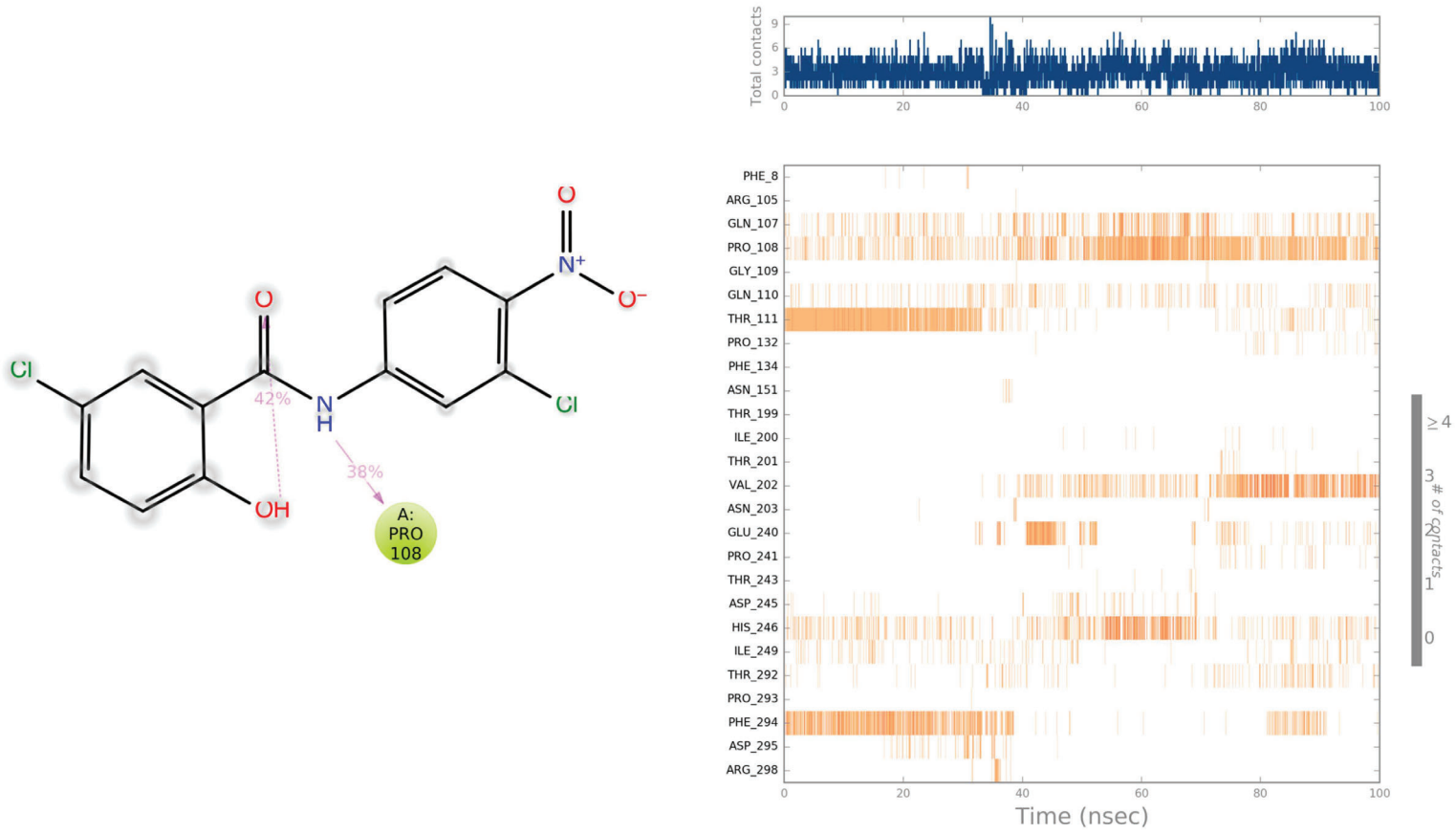

Fig. S5. Contacts established between 3CLpro and JMX0941 over 100 ns simulation in the allosteric site. Schematic view of predominant ligand atom interactions that occur with amino acid residues during the simulation time. Some residues may engage in multiple interactions of a single type (e.g., H-bond, etc.) with the same ligand atom. Hence, is it possible to cumulate >100% frequency of interaction. Right panel. (Top) Total number of contacts over the course of the trajectory. (Bottom) Analysis of residues interacting with the ligand, detailed by trajectory frame. Darker shade of orange indicates multiple protein/ligand contacts by amino acid residue.

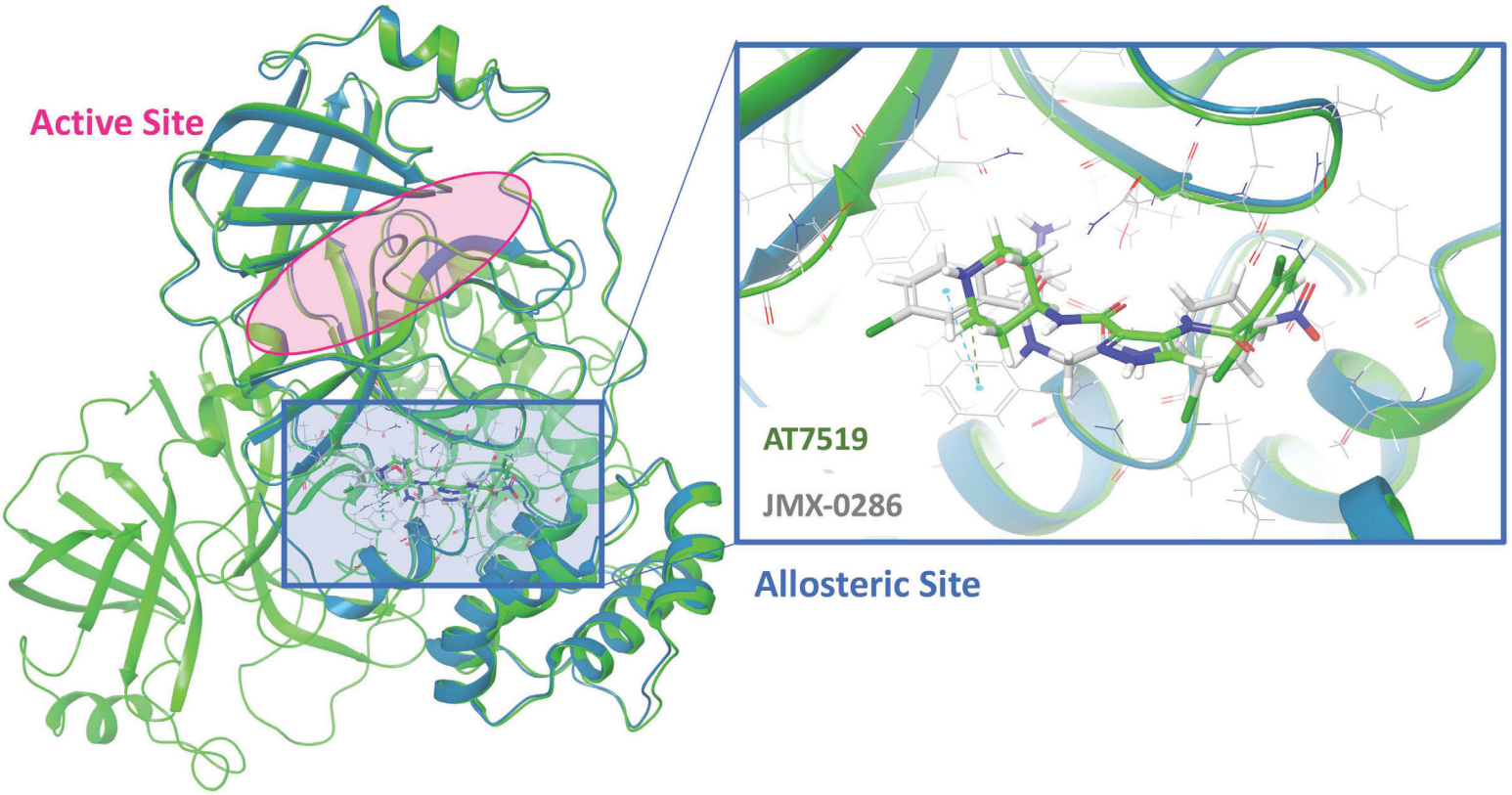

Figure S6. Comparison of binding modes of allosteric ligands. Structural superimposition between the experimental structure of 3CLpro in complex with the allosteric AT7519 ligand (PDB-ID 7AGA) and the docking model of 3CLpro in complex with JMX0286. The protein and ligand atoms are shown in new-cartoon and licorice representation, respectively. In the 3CLpro/AT7519 complex, the protein is colored in blue and the ligand in green. In the 3CLpro/JMX0286 complex, the protein is colored in green and the ligand in gray. (Right panel) The location of the active and the allosteric sites are highlighted in a red and blue shapes, respectively. (Left panel) Zoom-in view of the allosteric site showing superposition between the allosteric ligands.