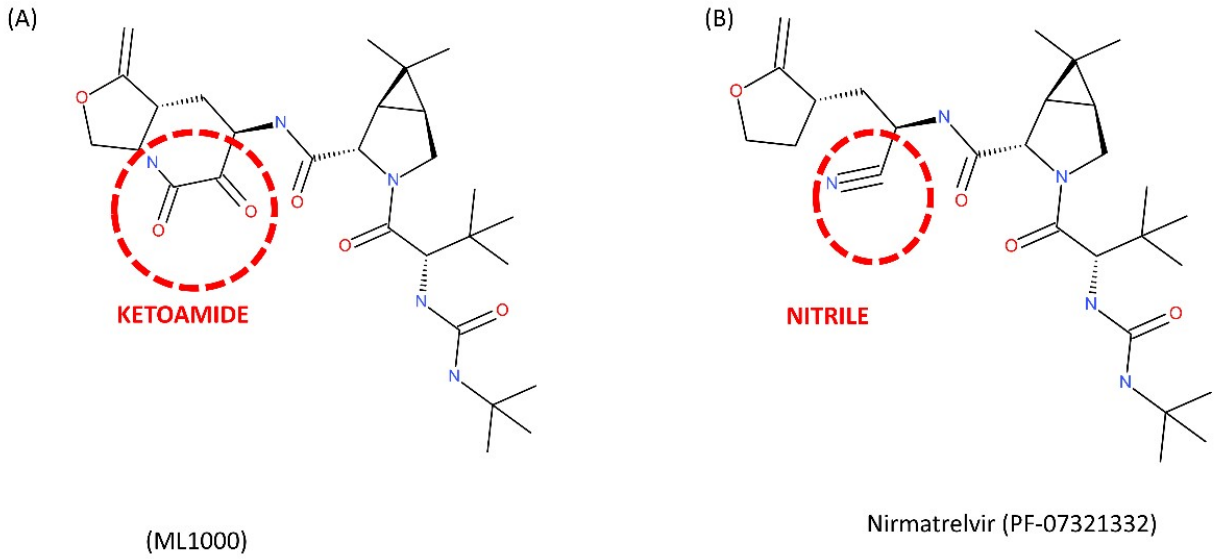

Figure S1. 3CLpro inhibitors (ML1000 and Nirmatrelvir). The two inhibitors have identical chemical skeletons. (A) ML1000 and (B) Nirmatrelvir (PF-07321332).

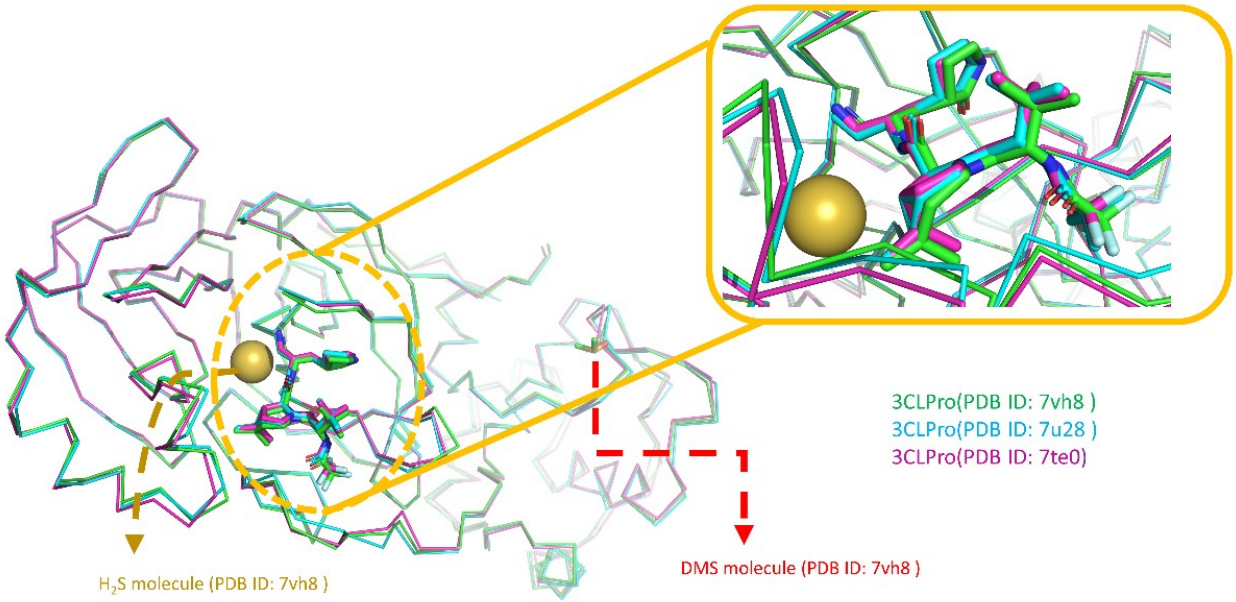

Figure S2. Three 3CLpro (PDB ID: 7vh8, 7TE0, and 7u28). The three 3CLpro (PDB ID: 7vh8, 7TE0, and 7u28) are colored in green, cyan, and magenta, respectively. The protein structural models are depicted by ribbons, and the ligands are depicted by sticks.

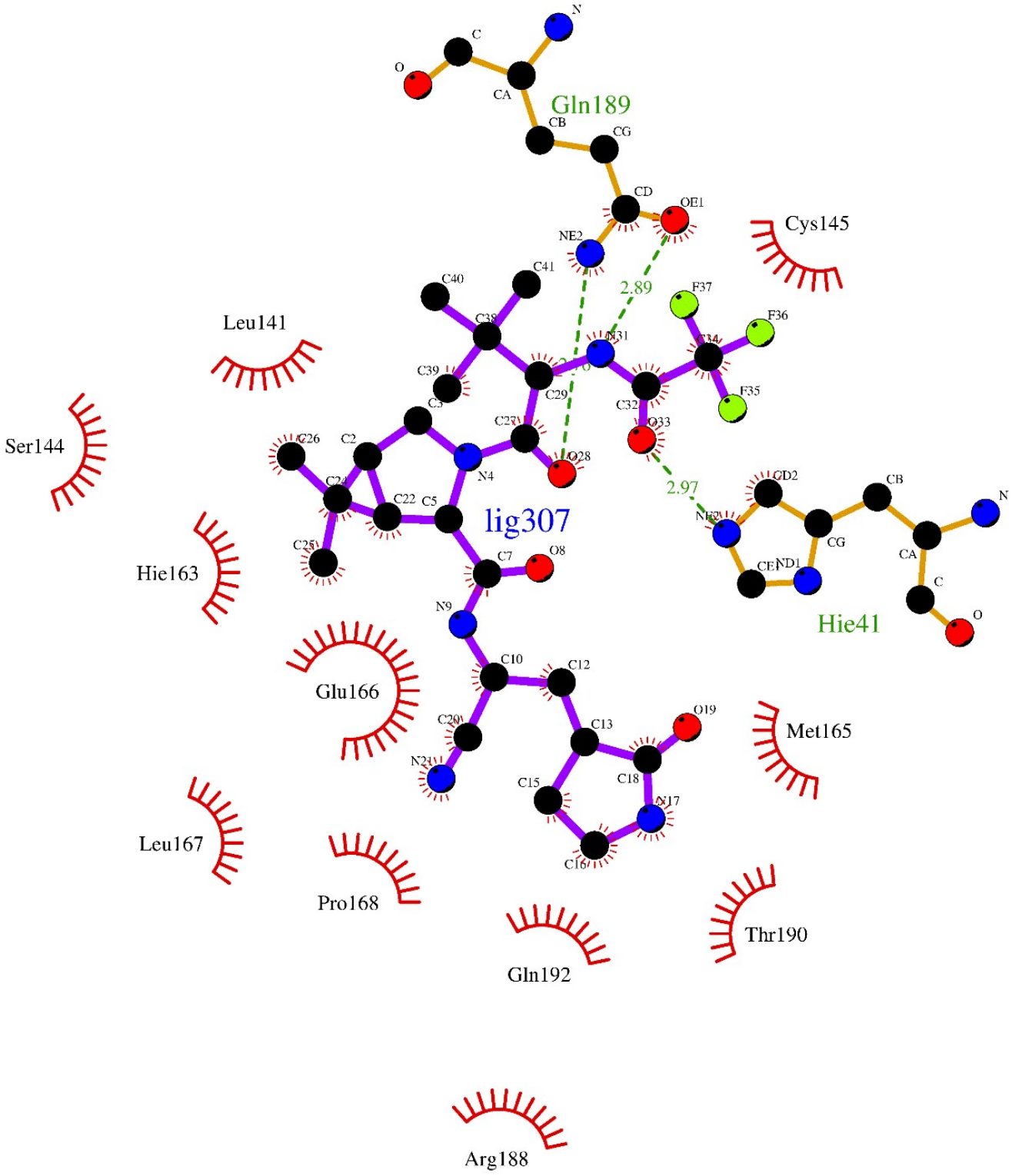

Figure S3. Binding mode of the bound state. Nirmatrelvir (lig307) is depicted by magenta sticks. Hydrogen bonds are indicated by green dotted lines. Nonbonding interactions are depicted by red eyelash structures.

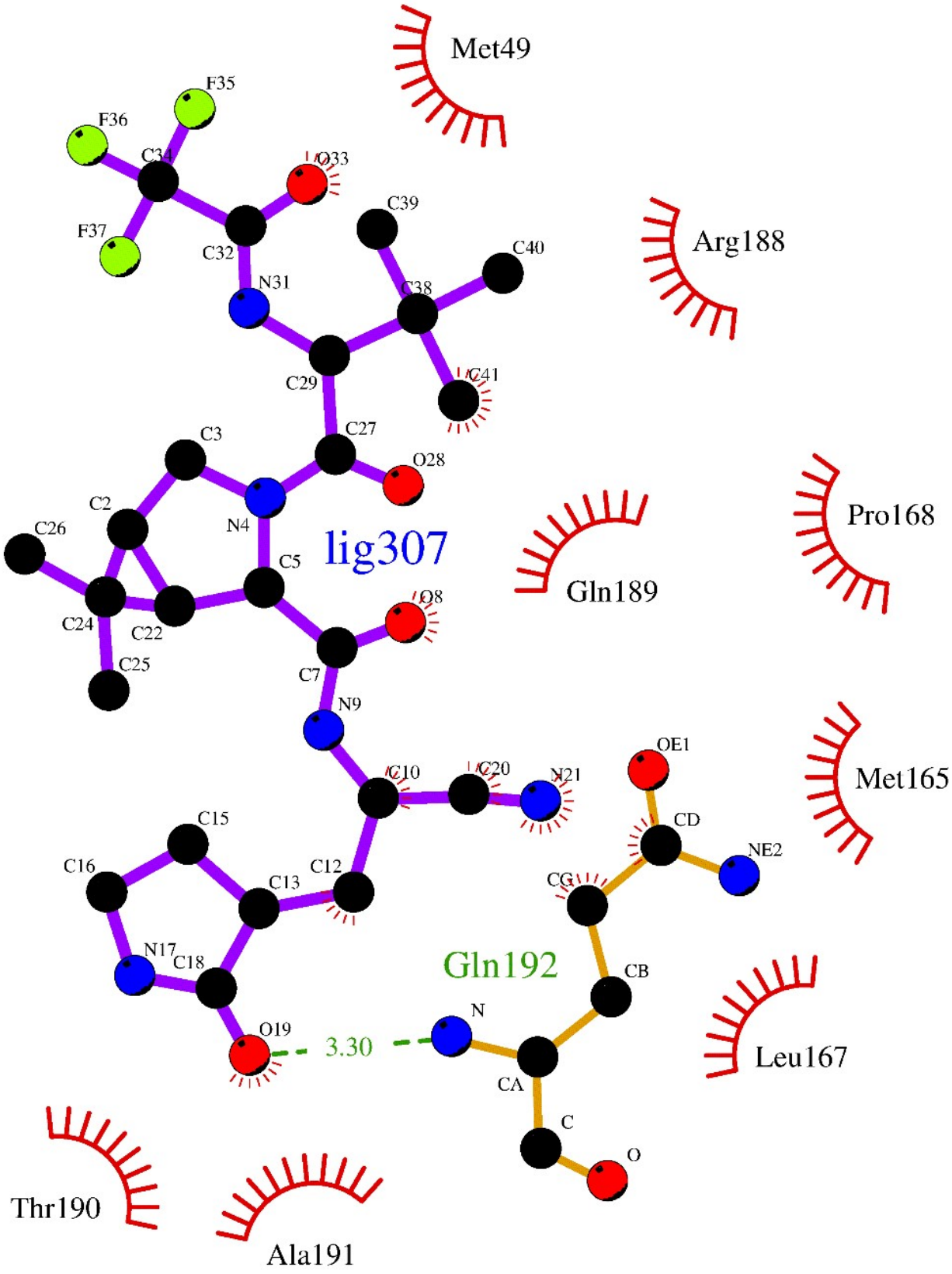

Figure S4. Binding mode of the intermediate I state. Nirmatrelvir (lig307) is indicated by magenta sticks. Hydrogen bonds are indicated by green dotted lines. Nonbonding interactions are depicted by red eyelash structures.

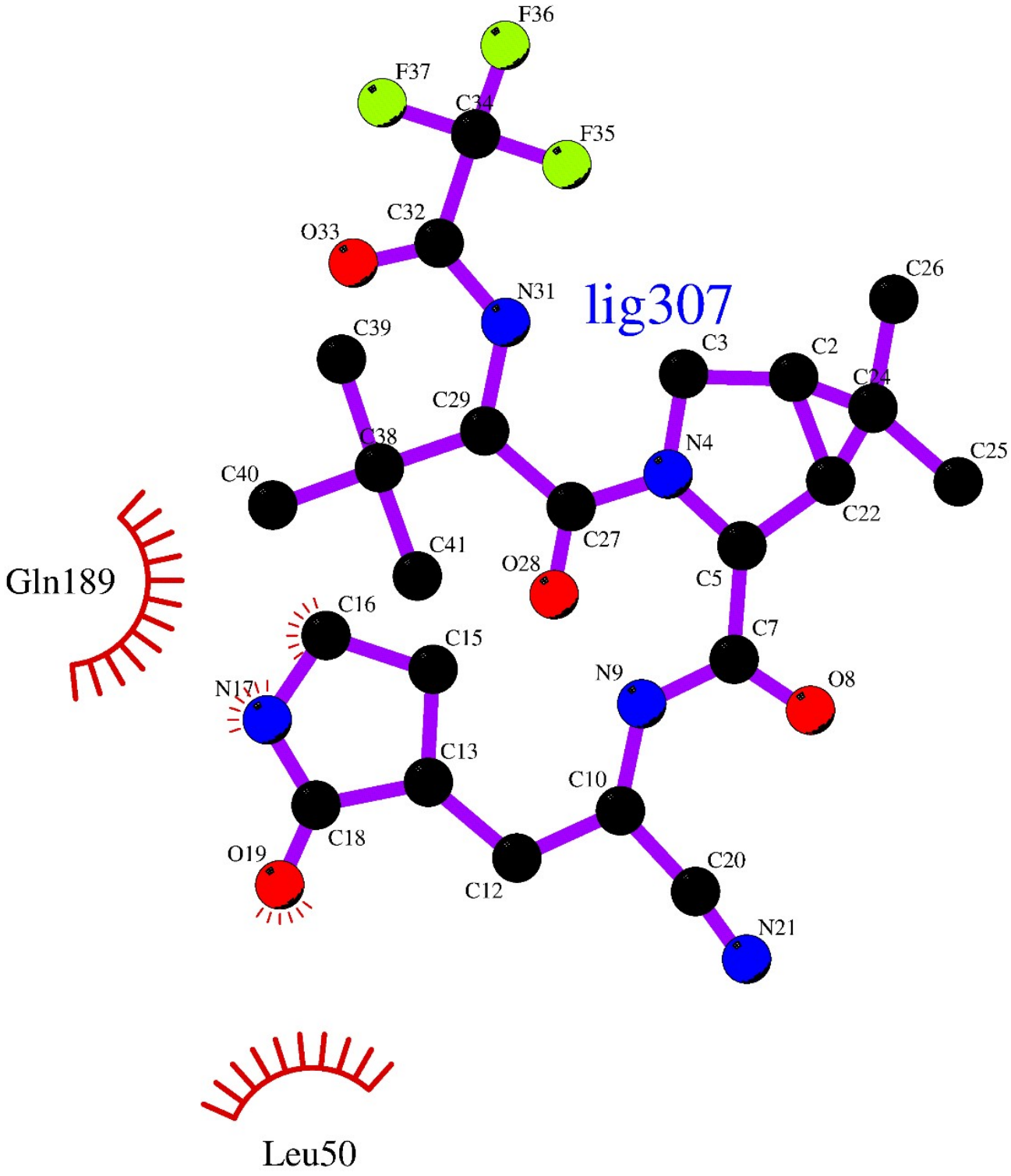

Figure S5. Binding mode of Intermediate II state. Nirmatrelvir (lig307) is depicted by magenta sticks. Hydrogen bonds are indicated by green dotted lines. Nonbonding interactions are depicted by red eyelash structures.

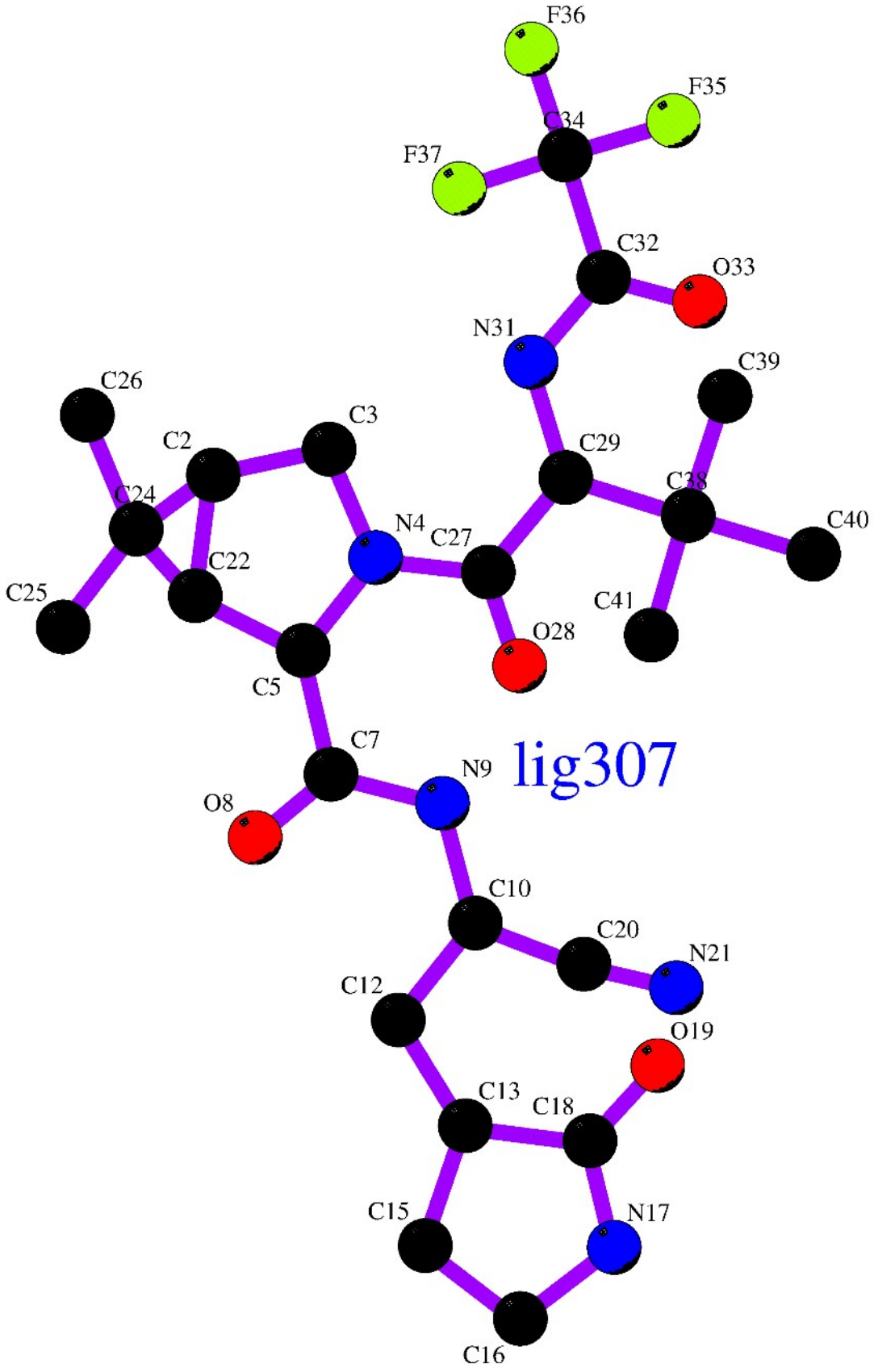

Figure S6. Binding mode of unbound state. Nirmatrelvir (lig307) is depicted by magenta sticks. Hydrogen bonds are indicated by green dotted lines. Nonbonding interactions are depicted by red eyelash structures.

Table S1. Comparisons of three 3CLpro structures (PDB ID: 7vh8, 7TE0 and 7u28)

PDB ID	7vh8	7te0	7u28
Resolution (X-RAY DIFFRACTION) (Å)	1.59	2.00	1.68
Ligands and solvent	Nirmatrelvir DMS H2S H2O	Nirmatrelvir H2O	Nirmatrelvir H2O