Supporting Information for: Crystal-Structures-Guided Design of Fragment-Based Drugs for Inhibiting the Main Protease of SARS-CoV-2

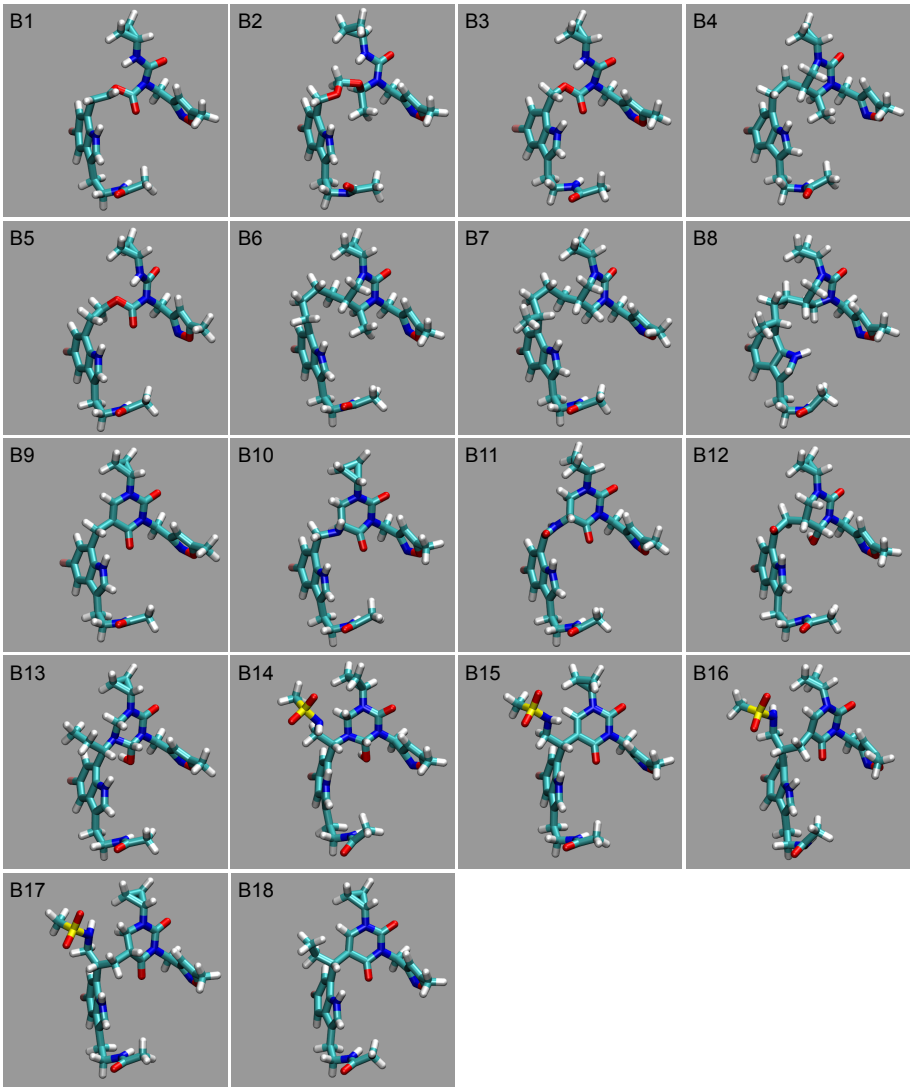

Figure S1: Th unsuccessful designs of other 18 fragment-based drug ligands, from B1 to B18. The ligands from B14 to B17 were merged from all three fragments as listed in the main text. The rest were merged from U0P and HWH only. Various linker molecules were tested for ligand stability. For each drug, at least two MD simulations were carried out. These ligands are not as stable as B19 inside the active site of Mpro.

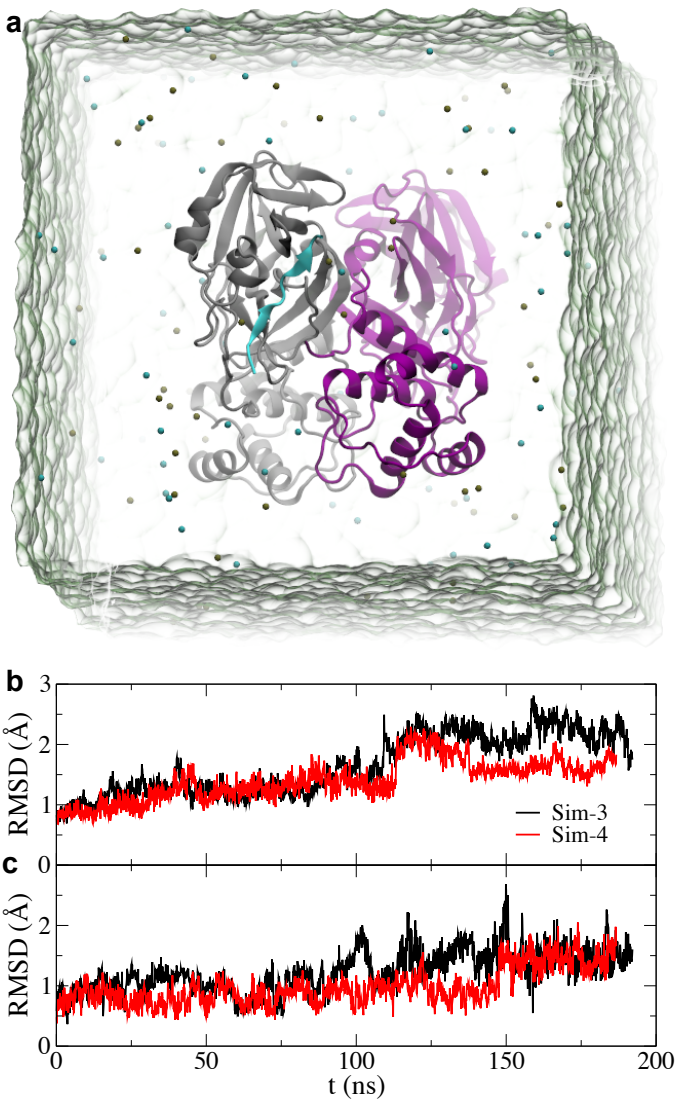

Figure S2: MD simulation of Mpro bound with the native ligand. a) Simulation system. The native ligand is colored in cyan and is in the cartoon representation. Others are illustrated same as those in Fig. 2 in the main text. b) RMSDs of backbone atoms in the host protein, *i.e.* the momoner in gray in (a). c) RMSDs of heavy atoms in the native ligand.

Synthesis steps for B19 without the methanesulfonamide group (report from RXN software)