Targeting SARS-CoV-2 M3CLpro by HCV NS3/4a Inhibitors: *In Silico* Modeling and *In Vitro* Screening.

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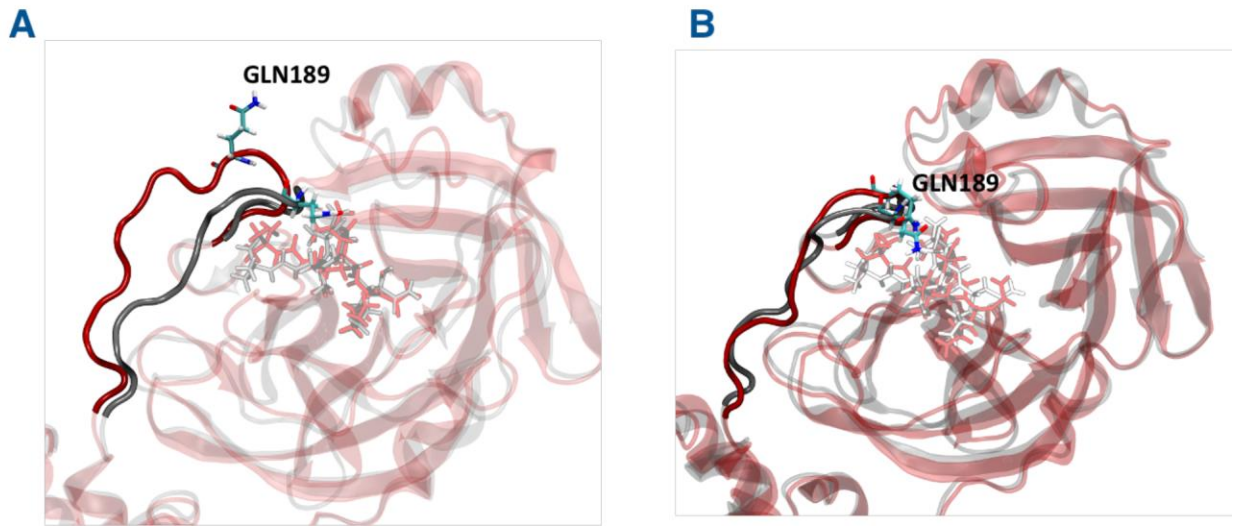

Figure S1. Loop composed of residues 186 to 198 shifts away from the (A) covalently bound Boceprevir compared to (B) non covalently bound Boceprevir. Here initial and final states of the M3CLpro chain A (secondary structure representation) and Boceprevir (licorice representation) is shown in grey and red colors respectively.

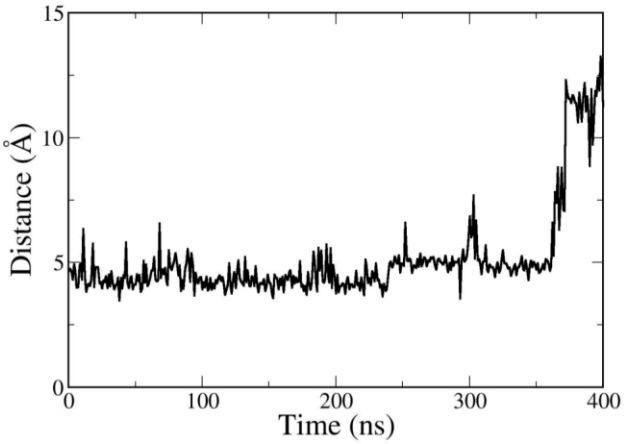

Figure S2. Distance between COMs of Gln^{189} and Boceprevir covalently bound to M3CLpro during 400ns MD simulation.

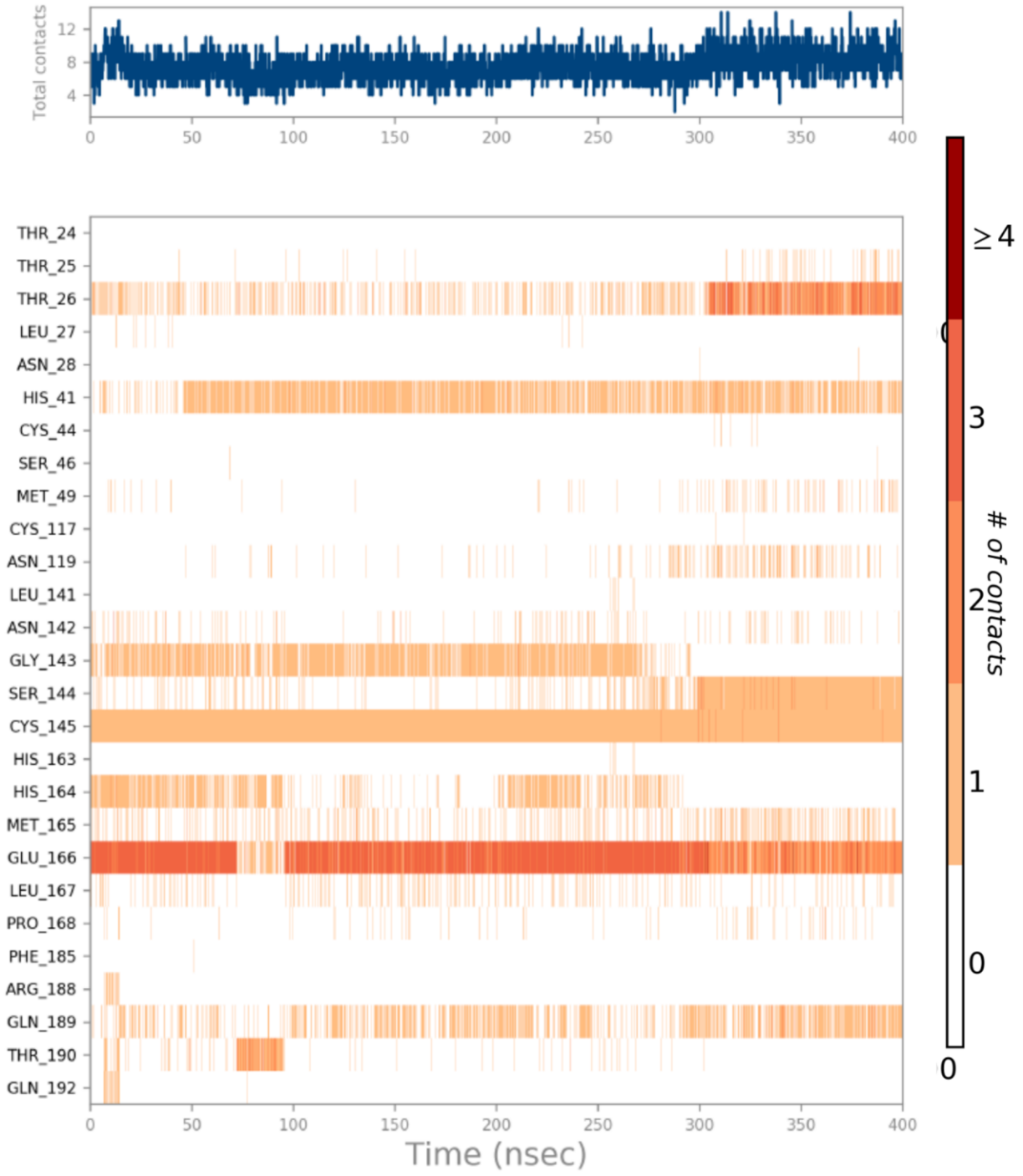

Figure S3. A timeline representation of total contacts M3CLpro makes with the covalently bound Boceprevir (top panel) and specific residues interacting with M3CLpro in each trajectory frame (lower panel).

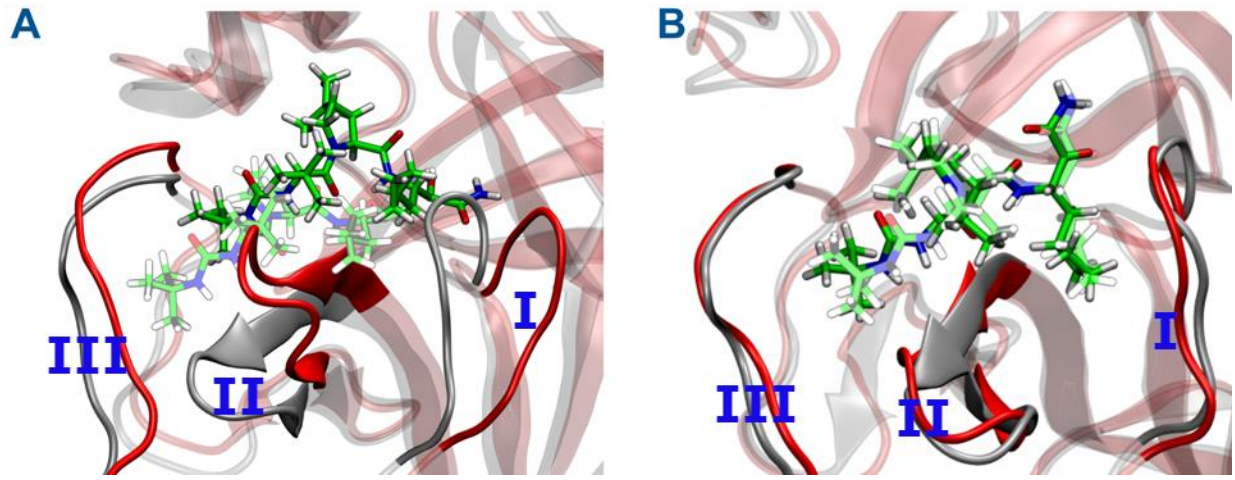

Figure S4. Comparison of the last frame of the first 1ns (gray color) and last frame of the 400ns (red color). **A.** The system of the covalently bound boceprevir **B.** The system in which boceprevir is non-covalently complexed with M3CLpro. Boceprevir is represented as licorice with dark shade for the last frame of the 1ns and with light shade for the last frame of the 400ns. Loops I (residues: 139 to 144), II (residues: 165 to 173), and III (residues: 189 to 195) shifted in A.

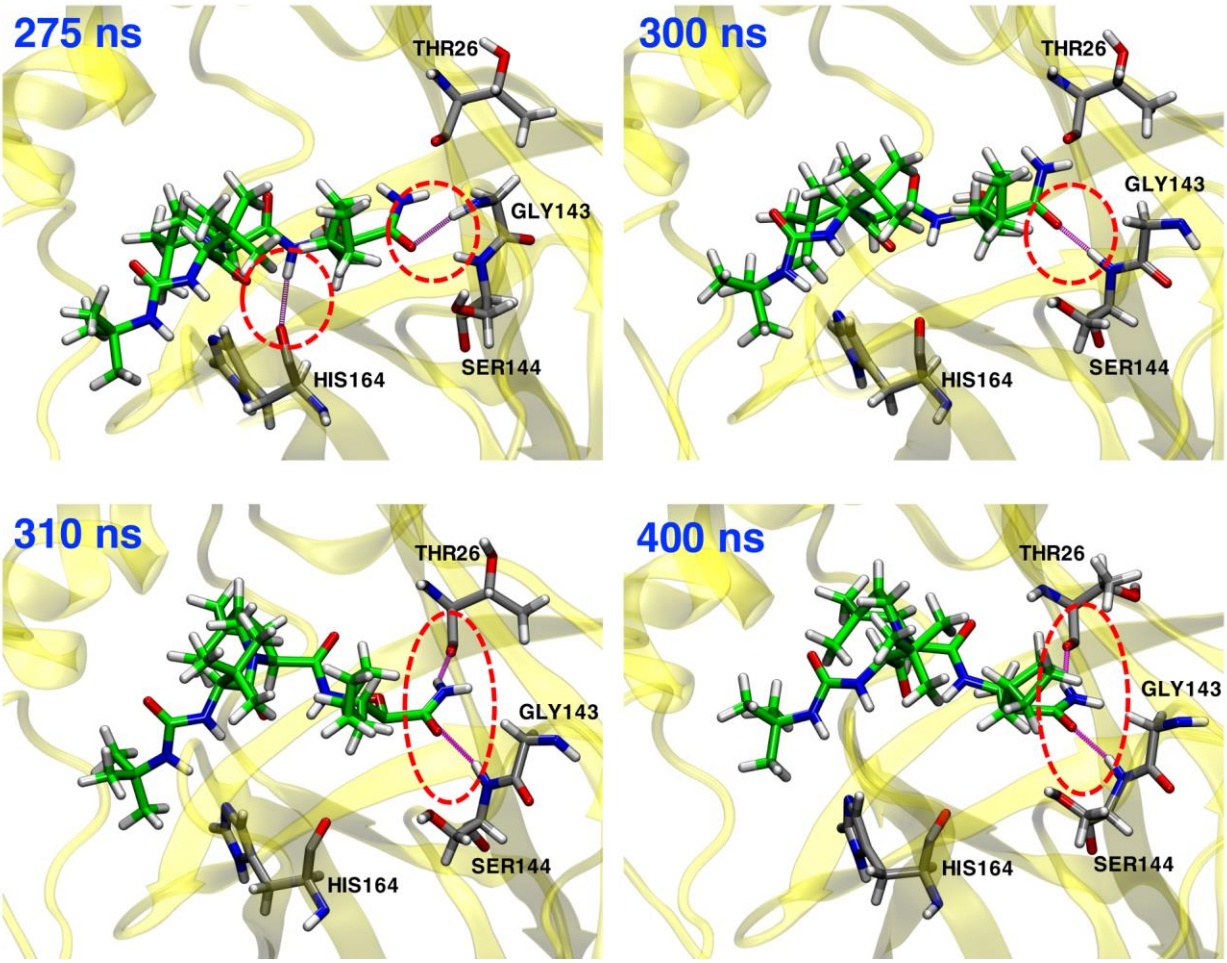

Figure S5. Hydrogen bonds (magenta) between boceprevir and Thr^{26}, Gly^{143}, Ser^{144}, and His^{164} at ~275ns, ~300ns, ~310ns, and ~400ns.

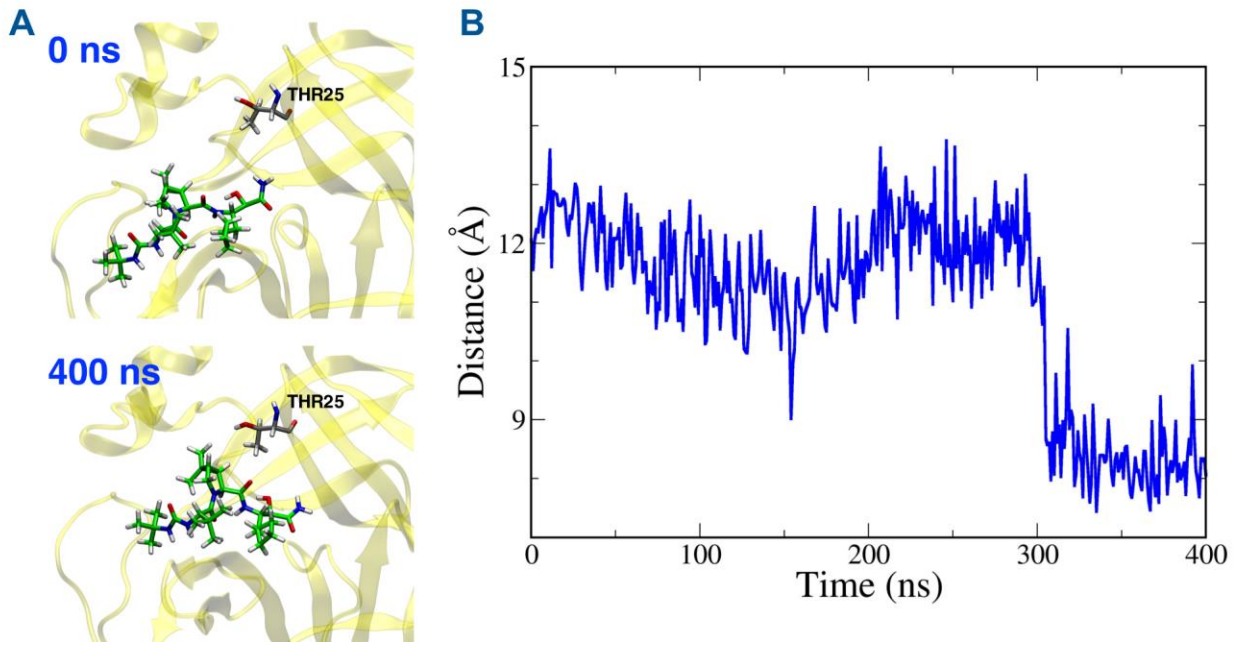

Figure S6. (A) Boceprevir and Thr^{25} at the beginning and end of 400ns simulation of system 1. (B) The distance between the C_α of Thr^{25} and the amine of the azabicyclo ring of boceprevir.

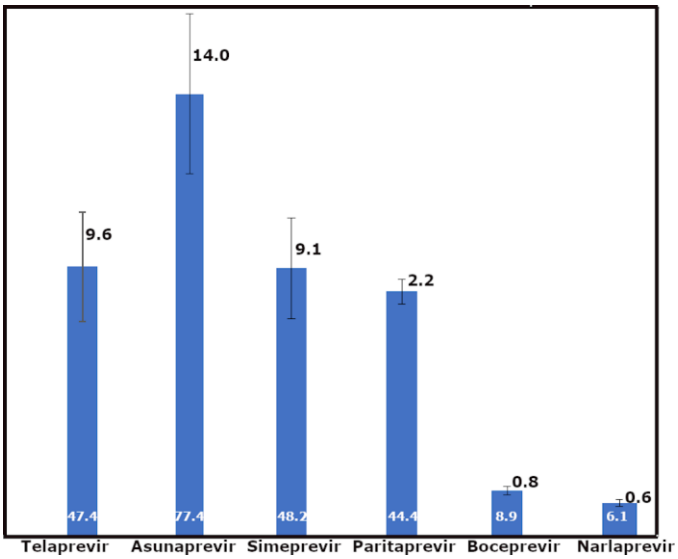

Figure S7. IC50 results of selected HCV NS3/4a protease inhibitors against M3CLpro (SARS-CoV-2). IC50 values are shown in white font and the errors in black.

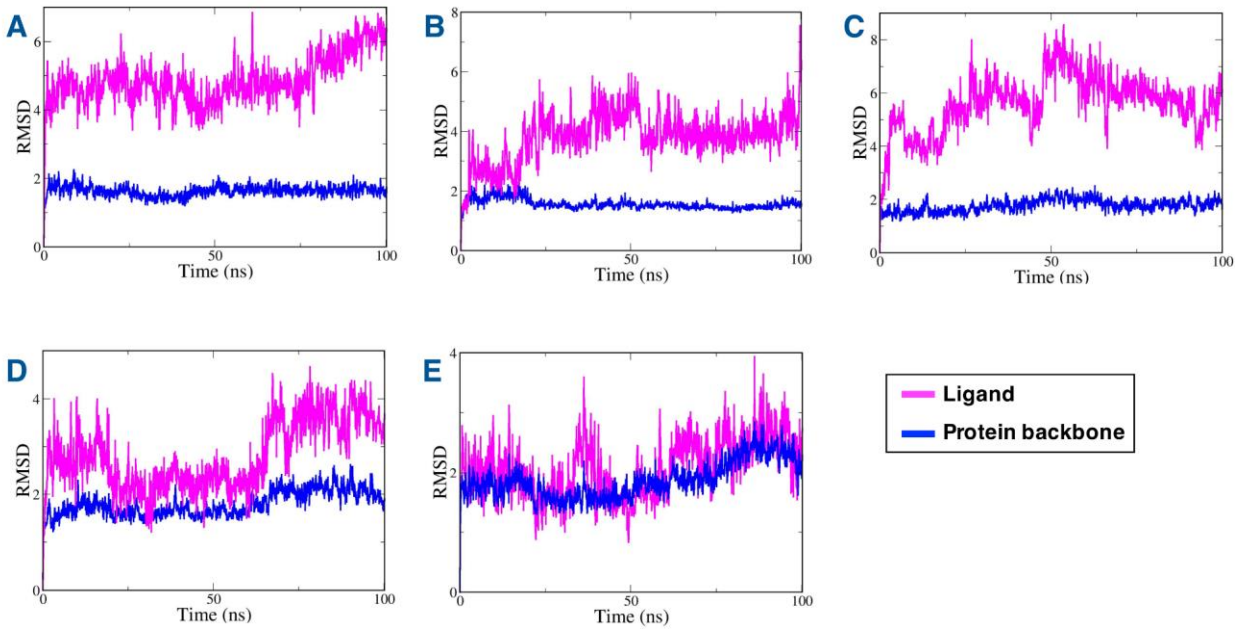

Figure S8. RMSDs of HCV inhibitors (magenta) and M3CLpro (blue) during 100ns simulations of (A) simeprevir (B) paritaprevir (C) asunaprevir (D) narlaprevir (E) telaprevir with M3CLpro.

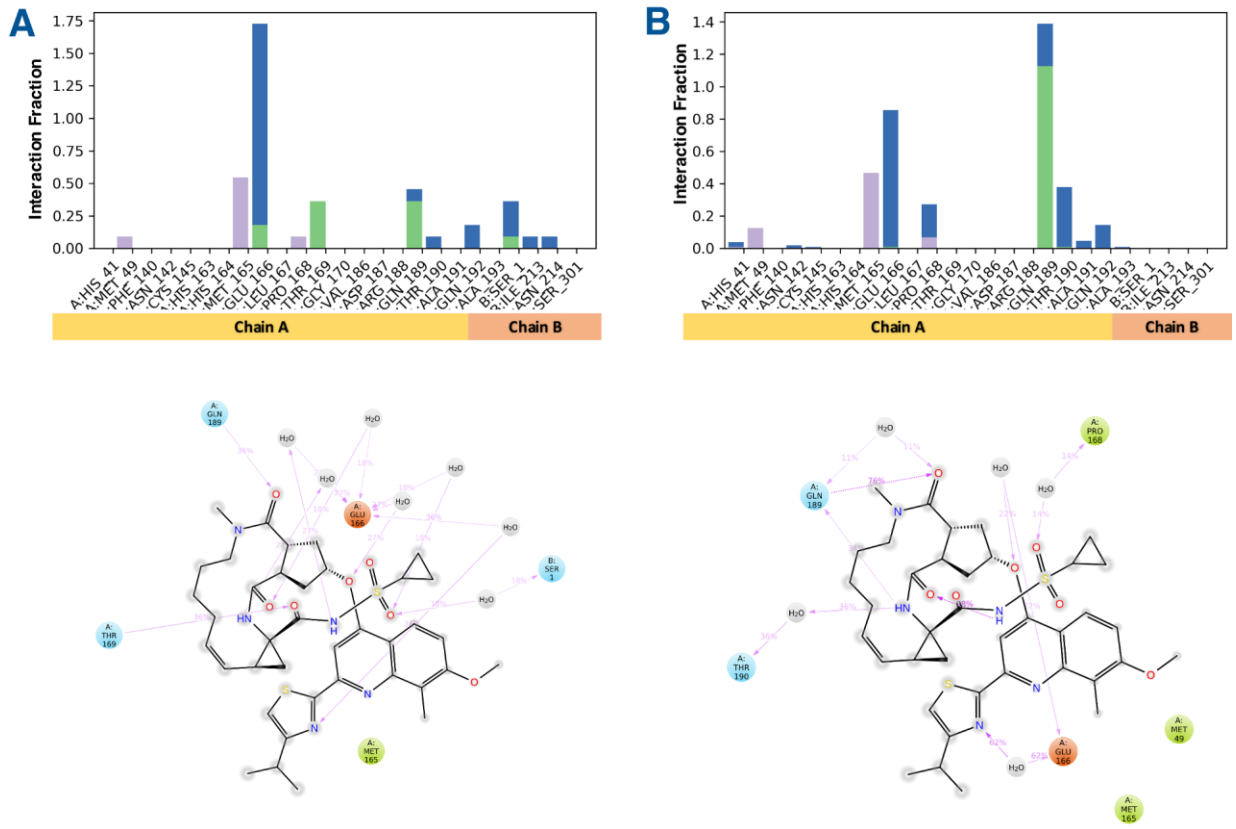

Figure S9. Interaction fraction (top panel) and 2D interaction diagram (lower panel) of simeprevir bound with M3CLpro during (A) initial 1ns and (B) last 10ns.

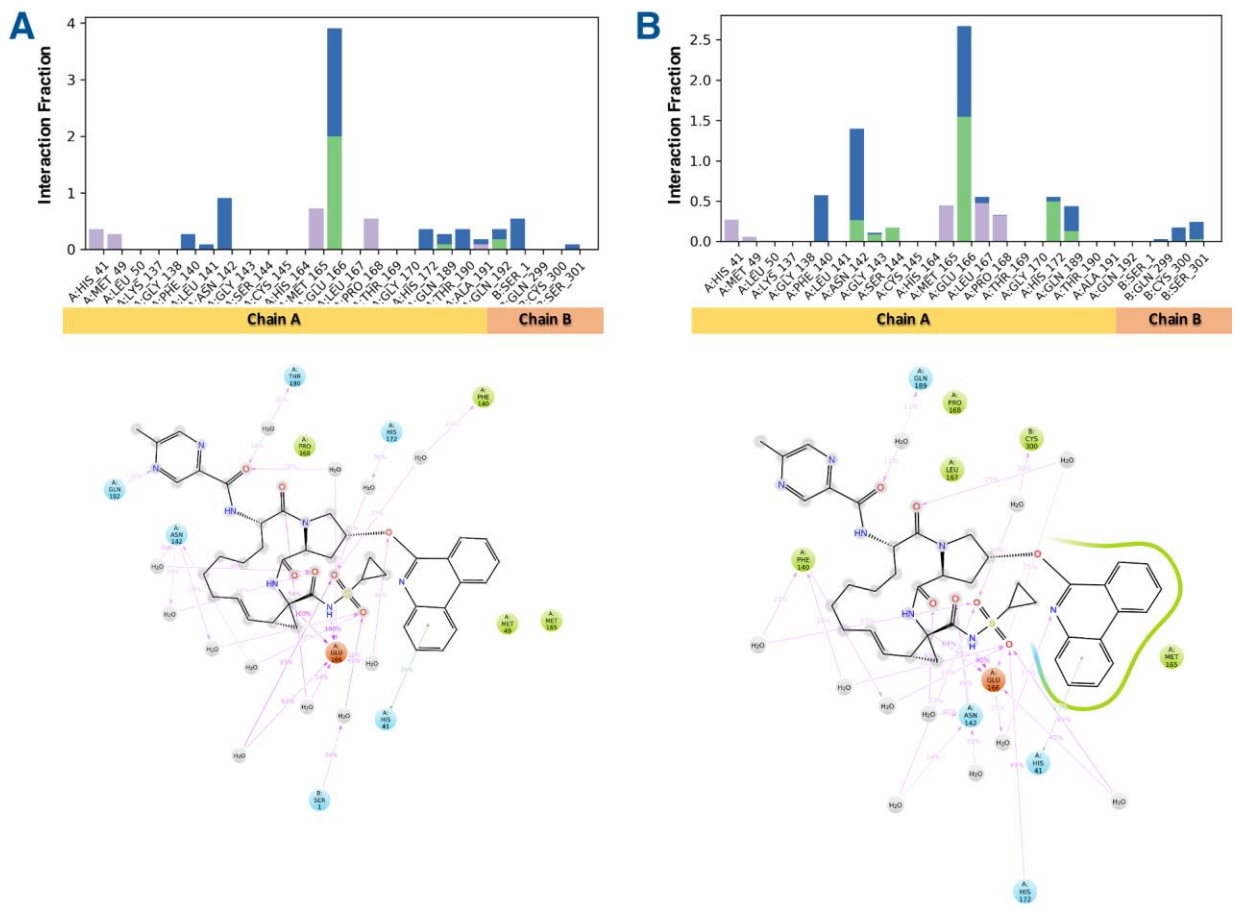

Figure S10. Interaction fraction (top panel) and 2D interaction diagram (lower panel) of paritaprevir bound with M3CLpro during (A) initial 1ns and (B) last 10ns.

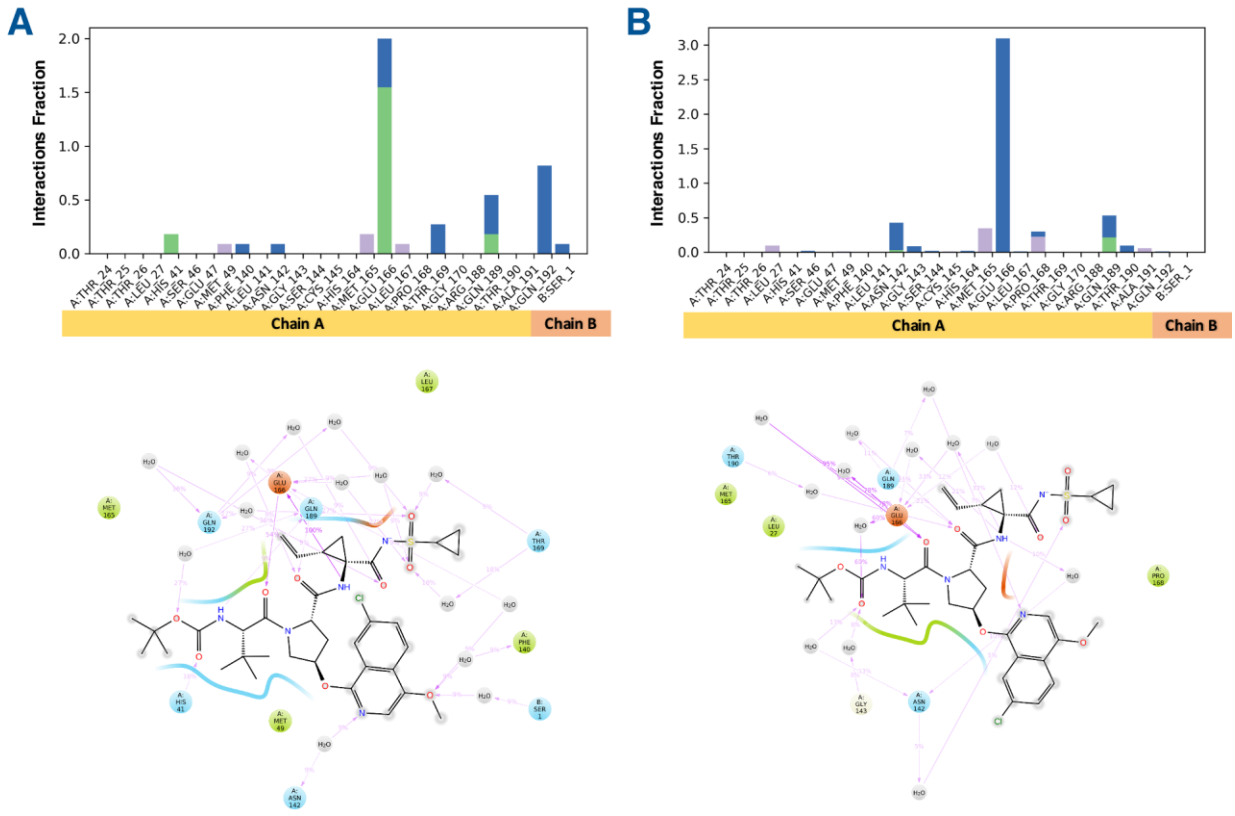

Figure S11. Interaction fraction (top panel) and 2D interaction diagram (lower panel) of asunaprevir bound with M3CLpro during (A) initial 1ns and (B) last 10ns.

SMILES of reported compounds

>Boceprevir:

CC1(C2C1C(N(C2)C(=O)C(C(C)(C)C)NC(=O)NC(C)(C)C)C(=O)NC(CC3CCC3)C(=O)C(=O)N)C

>Teleprevir

CCCC(C(=O)C(=O)NC1CC1)NC(=O)C2C3CCCC3CN2C(=O)C(C(C)(C)C)NC(=O)C(C4CCCCC4)NC(=O)C5=NC=CN=C5

>Narlaprevir

CCCCC(C(=O)C(=O)NC1CC1)NC(=O)C2C3C(C3(C)C)CN2C(=O)C(C(C)(C)C)NC(=O)NC4(CCCCC4)CS(=O)(=O)C(C)(C)C

>Asunaprevir

CC(C)(C)C(C(=O)N1CC(CC1C(=O)NC2(CC2C=C)C(=O)NS(=O)(=O)C3CC3)OC4=NC=C(C5=C4C=C(C=C5)Cl)OC)NC(=O)OC(C)(C)C

>Simeprevir

CC1=C(C=CC2=C1N=C(C=C2OC3CC4C(C3)C(=O)N(CCCCC=CC5CC5(NC4=O)C(=O)NS(=O)(=O)C6CC6)C)C7=NC(=CS7)C(C)C)OC

>Paritaprevir

CC1=CN=C(C=N1)C(=O)NC2CCCCCC=CC3CC3(NC(=O)C4CC(CN4C2=O)OC5=NC6=CC=CC=C6C7=CC=CC=C75)C(=O)NS(=O)(=O)C8CC8