Supplementary Information

Spontaneous binding of potential COVID-19 drugs (Camostat and Nafamostat) to human serine protease TMPRSS2

Haixia Zhu[a, †], Wenhao Du[a, †], Menghua Song[a], Qing Liu[b], Andreas Herrmann[c] and Qiang Huang[a, d, *]

[a]*State Key Laboratory of Genetic Engineering, Shanghai Engineering Research Center of Industrial Microorganisms, MOE Engineering Research Center of Gene Technology, School of Life Sciences, Fudan University, Shanghai 200438, China*
[b]*State Key Laboratory of Quality Research in Chinese Medicines, School of Pharmacy, Macau University of Science and Technology, Macau, China*
[c]*Institute for Biology and IRI Lifesciences, Humboldt-Universität zu Berlin, 10115 Berlin, Germany*
[d]*Multiscale Research Institute of Complex Systems, Fudan University, Shanghai 201203, China*
†These first two authors contributed equally to this work.
*Corresponding authors. Email address: huangqiang@fudan.edu.cn (Q. Huang)

Table of Content

Figures

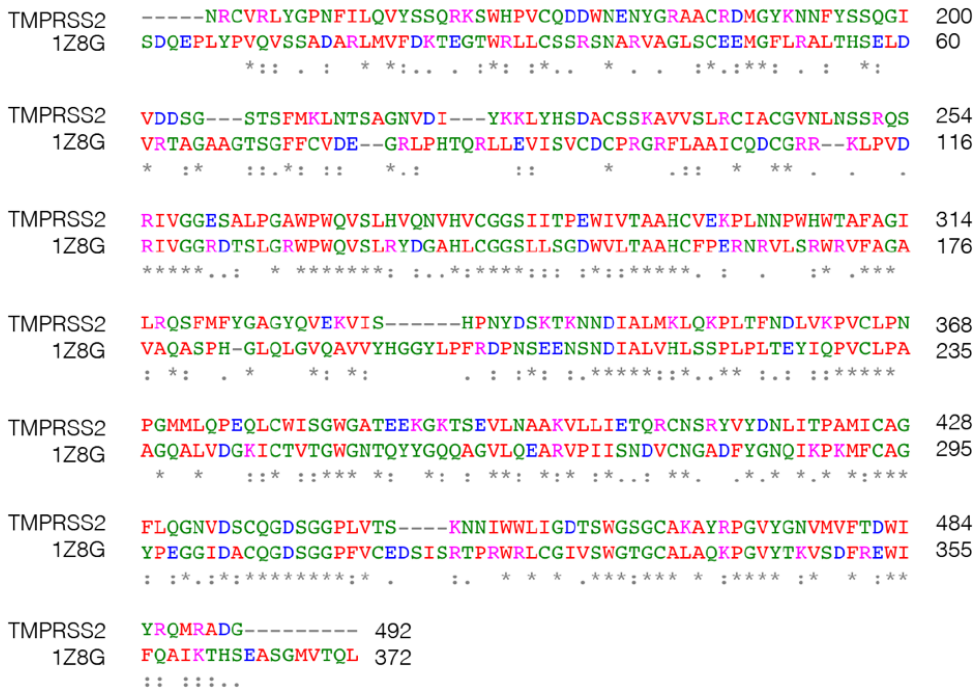

Fig. S1. Amino-acid sequence alignment of TMPRSS2-ECD and serine protease hepsin (sequence similarity: 33.8%). The sequence of the serine protease is taken from PDB ID: 1Z8G. Conserved residues are indicated by a (*), strongly similar residues by a (:) and weakly similar residues by a (.). The color codes of the residues are: basic, DE, red; acidic, KR, pink; polar, CGHNQSTY, green and hydrophobic, AFILMPVW, red.

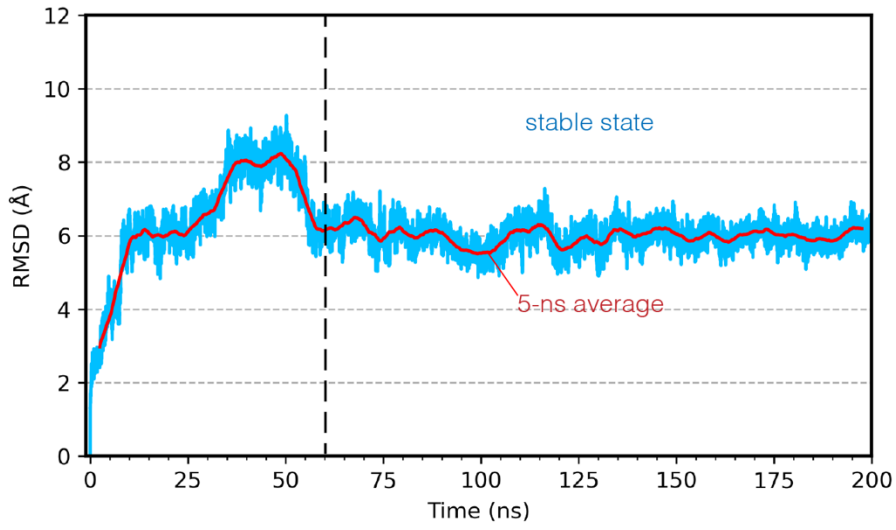

Fig. S2. Time-dependent RMSDs of the TMPRSS2-ECD model in the MD refinement. The initial structure of TMPRSS2-ECD is the reference structure for the RMSD calculations.

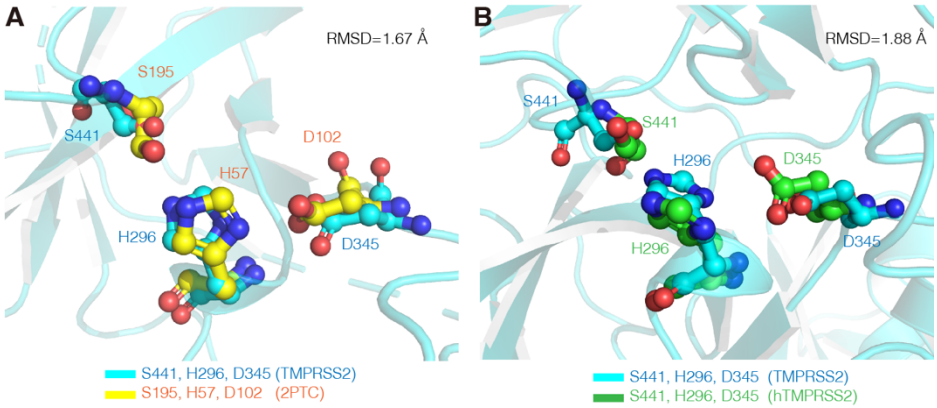

Fig. S3. Structural alignment of the catalytic amino acids of TMPRSS2 with trypsin and hTMPRSS2. (A) The RMSD of the catalytic triads of TMPRSS2 with trypsin (PDB ID: 2PTC) is 1.67 Å (where MPRSS2 in cyan, and trypsin in yellow). (B) The RMSD of the catalytic triads of TMPRSS2 with a recently published model (hTMPRSS2 on *Sci. Rep*. 2020, 10:15917) is 1.88 Å (where TMPRSS2 in cyan, and hTMPRSS2 in green).

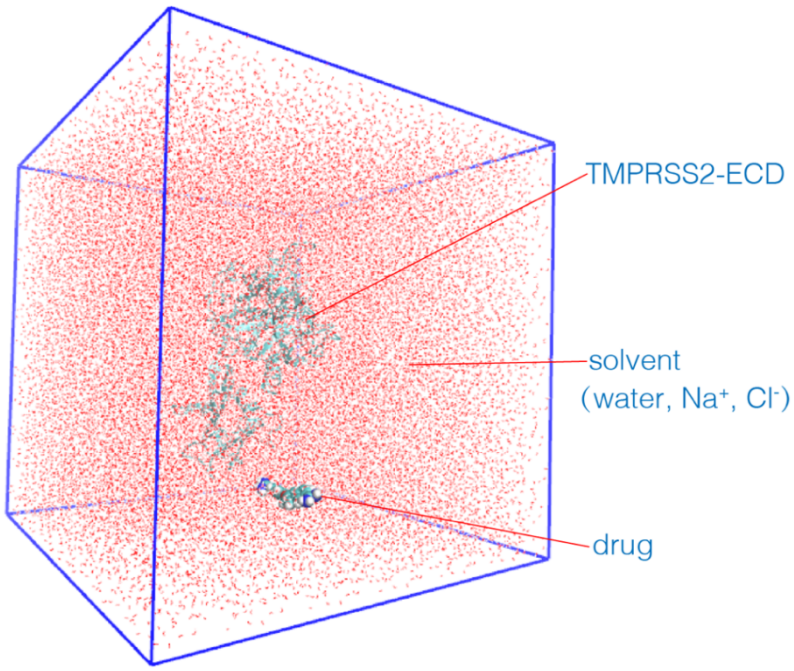

Fig. S4. A system for the spontaneous binding simulations. TMPRSS2-ECD is represented by the cartoon in cyan, the drug molecule (Camostat or Nafamostat) is represented by the spheres in cyan, and the solvent (water, Na^+ and Cl^-) are represented by the sticks in red.

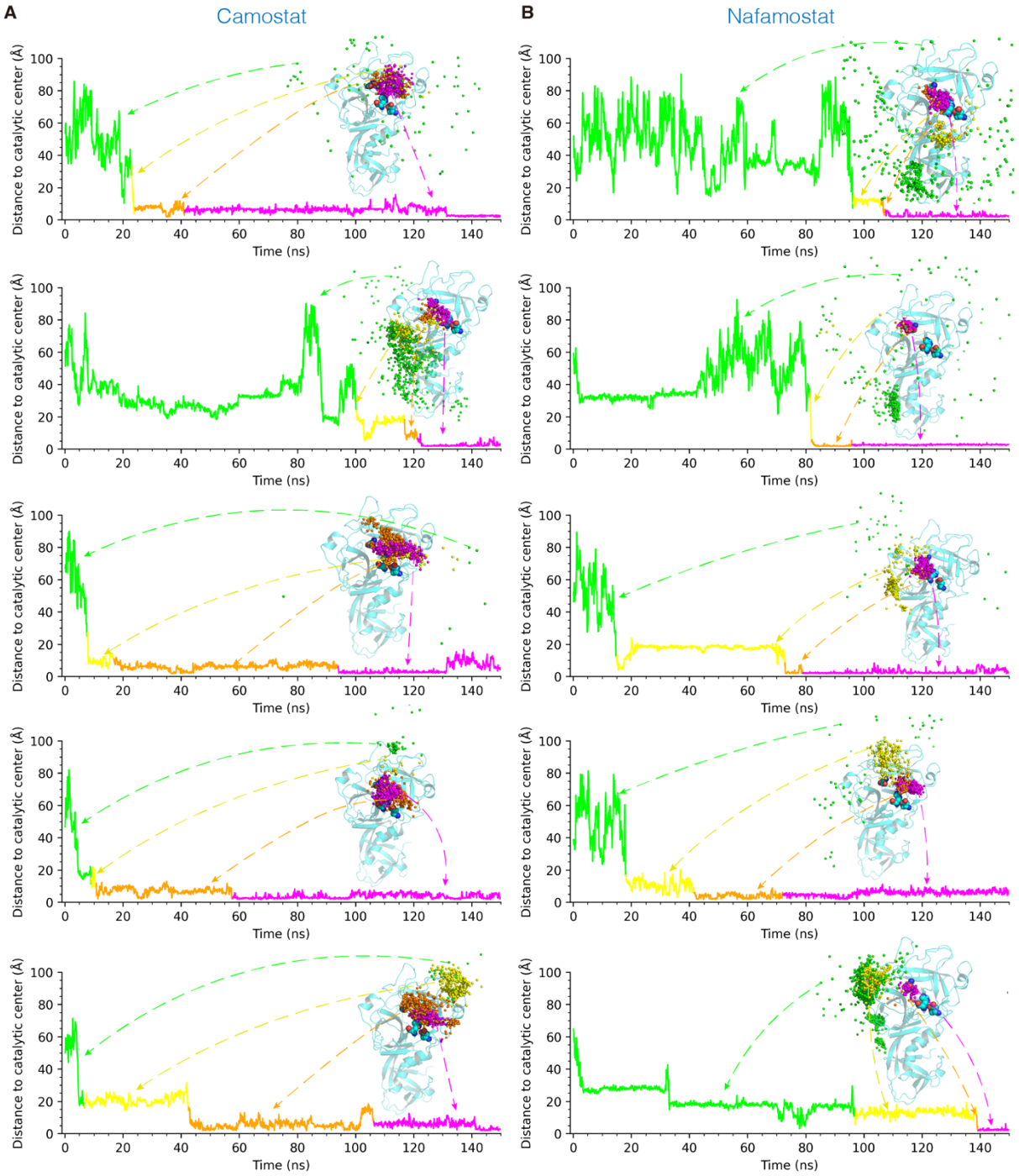

Fig. S5. Spontaneous binding processes to the catalytic center of TMPRSS2 in successful binding trajectories. (A) Time-dependent Camostat distance to the catalytic center (D_{cc}) in other 5 successful binding trajectories. (B) Time-dependent Nafamostat distance to the catalytic center (D_{cc}) in other 5 successful binding trajectories. TMPRSS2-ECD is represented by the cartoon in cyan, and corresponding drug positions represented by the drug atoms closest to the catalytic center (spheres in colors).

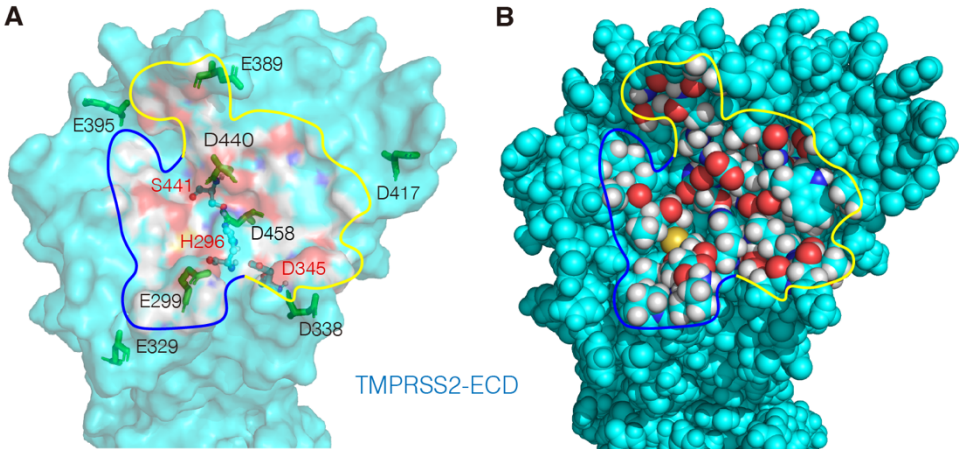

Fig. S6. 3D distributions of the Aps/Glu residues and oxygen atoms in/around the substrate-binding cavity of TMPRSS2. (A) The acidic amino acids (Asp/Glu) in/around the N-terminal and C-terminal binding regions are shown as sticks in green. (B) The oxygen atoms in the binding regions are shown as spheres in red.

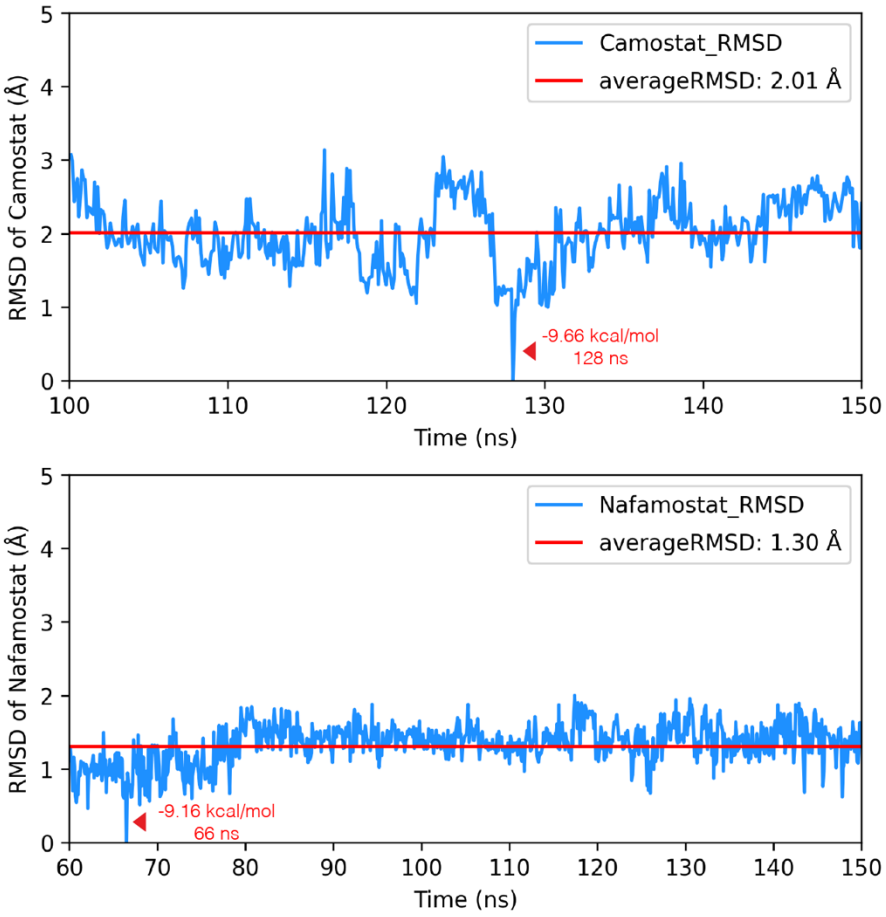

Fig. S7. The average RMSDs of drugs binding to the TMPRSS2 catalytic center. The average RMSDs of both drugs is less than 2.1 Å (Camostat:2.01 Å; Nafamostat:1.30 Å).The structure of drug with the lowest on-target binding free energy is the reference structure for the RMSD calculation.

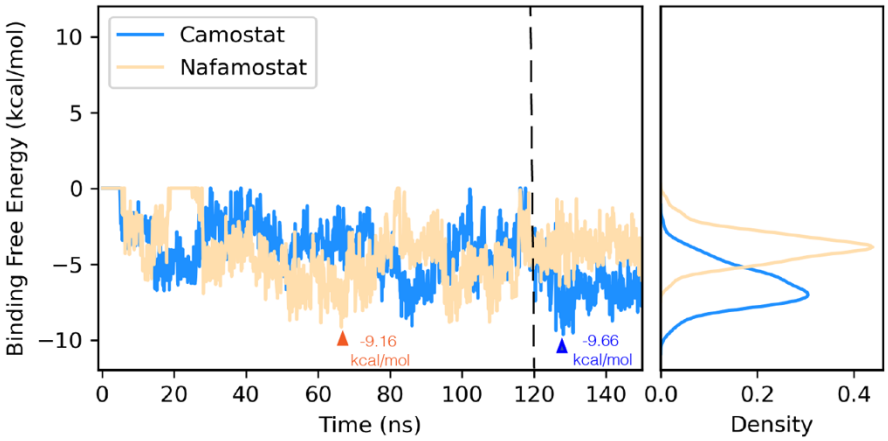

Fig. S8. Binding free energies of the drug-TMPRSS2 complexes formed in the spontaneous binding simulations in Fig. 3. The drug-TMPRSS2 complex conformations with the lowest binding free energy appear at ~128 ns (Camostat) and ~66 ns (Nafamostat), respectively. The free energy distributions of the drug-TMPRSS2 complexes in the last 30 ns (from 120 ns to 150 ns) trajectories are represented as the frequency densities in the right panel.

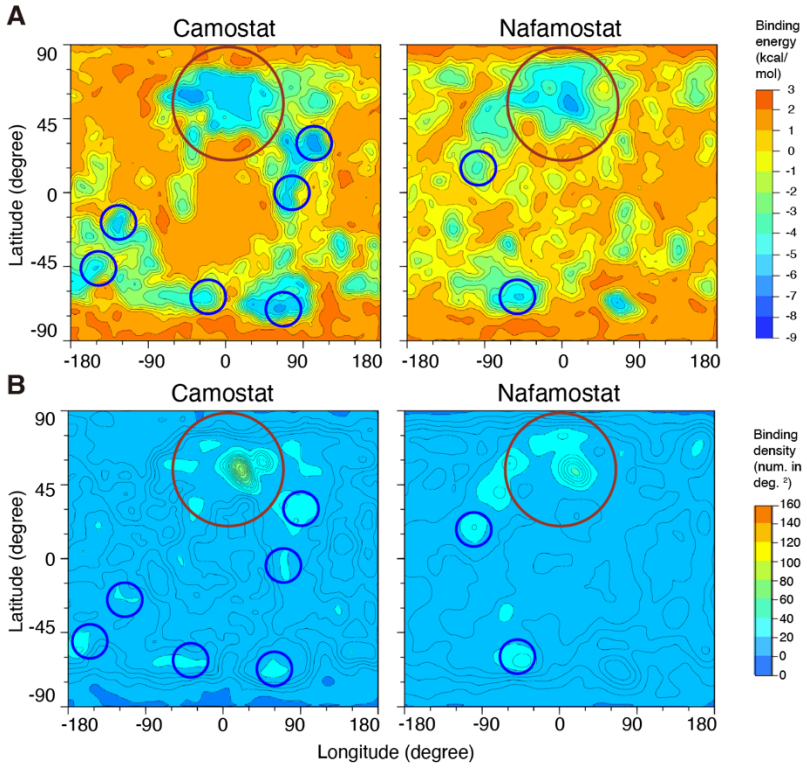

Fig. S9. The binding energy landscapes of all 30 spontaneous simulation trajectories. (A) The binding energy landscapes of the drug-TMPRSS2 complexes. (B) Corresponding binding probabilities of drugs. The on-target binding regions of drugs are indicated by red circles. The off-target binding hotspots with high binding probability are indicated by blue circles.

Movies

Movie S1. A typical spontaneous binding trajectory of Camostat to TMPRSS2. Please see the MPEG4 file: camo_binding.mp4. For the sake of clarity, solvent molecules and ions are removed.

Movie S2. A typical spontaneous binding trajectory of Nafamostat to TMPRSS2. Please see the MPEG4 file: nafa_binding.mp4. For the sake of clarity, solvent molecules and ions are removed.