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Supplementary Information

Binding kinetics study of SARS-CoV-2 main protease and potential inhibitors via molecular dynamics simulations

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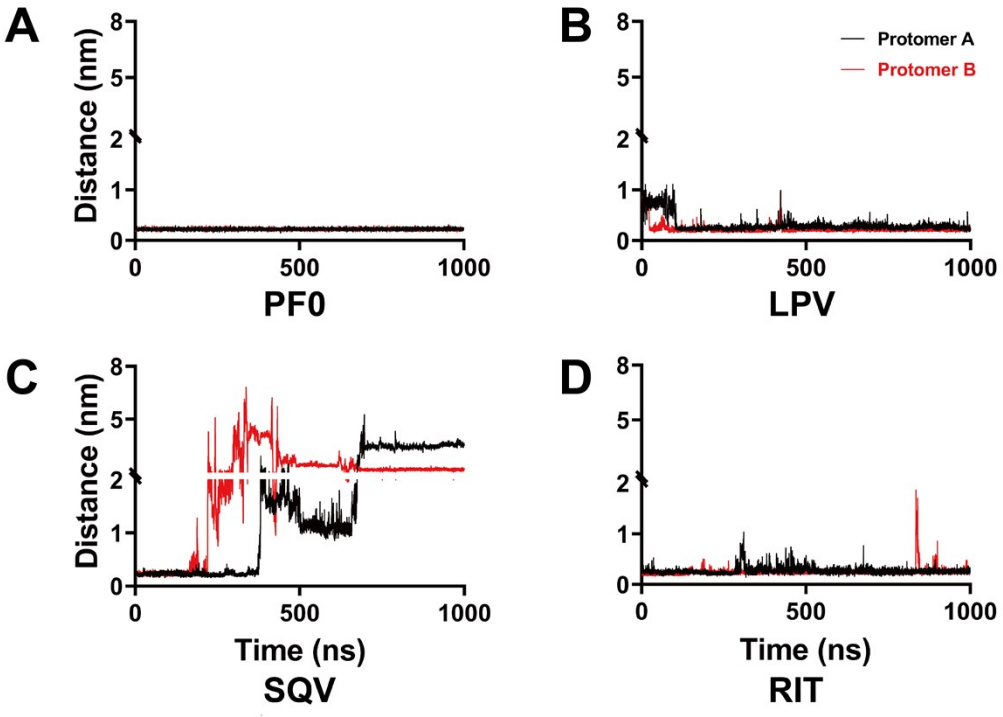
S1 Table. The initial bound fractions of inhibitors in REMD simulations

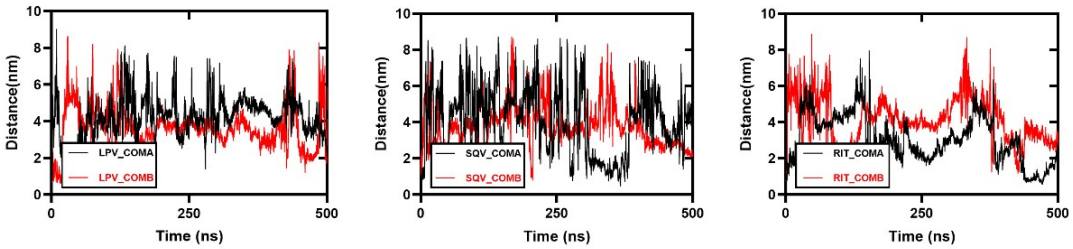
	PF0	LPV	SQV	RIT
REMD for dimer	140/140	139/140	140/140	136/140
ratio	1	0.993	1	0.971

S2 Table. Predicted kinetic parameters and the affinities at 310 K

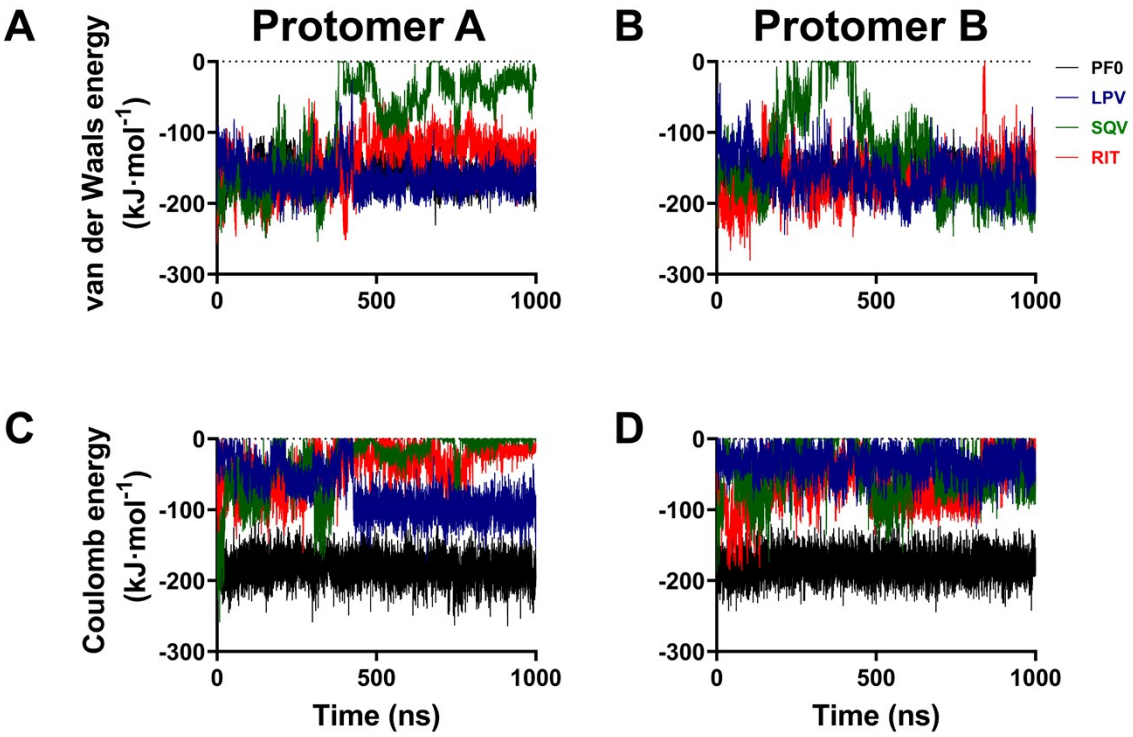
	LPV	SQV	RIT	PF0
k_{off} (s^{-1})	3.61e6	1.84e6	2.01e6	Exceeded Range
k_{on} ($M^{-1}\cdot s^{-1}$)	1.38e8	2.92e8	2.85e8	Exceeded Range.
affinity (μM)	2.61e4	6.29e3	7.08e3	Exceeded Range



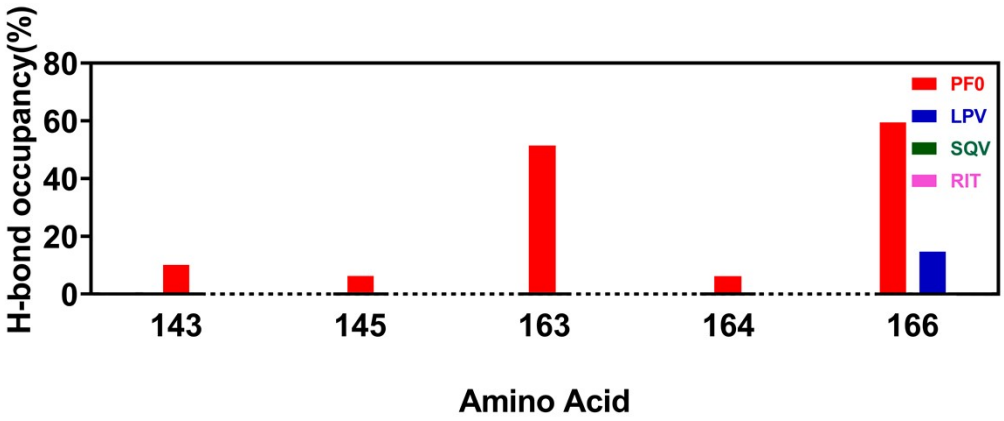
S1 Fig. The minimal distance between the inhibitors and the catalytic dyad of M^{pro}. The red and black lines represent the two protomers, respectively.



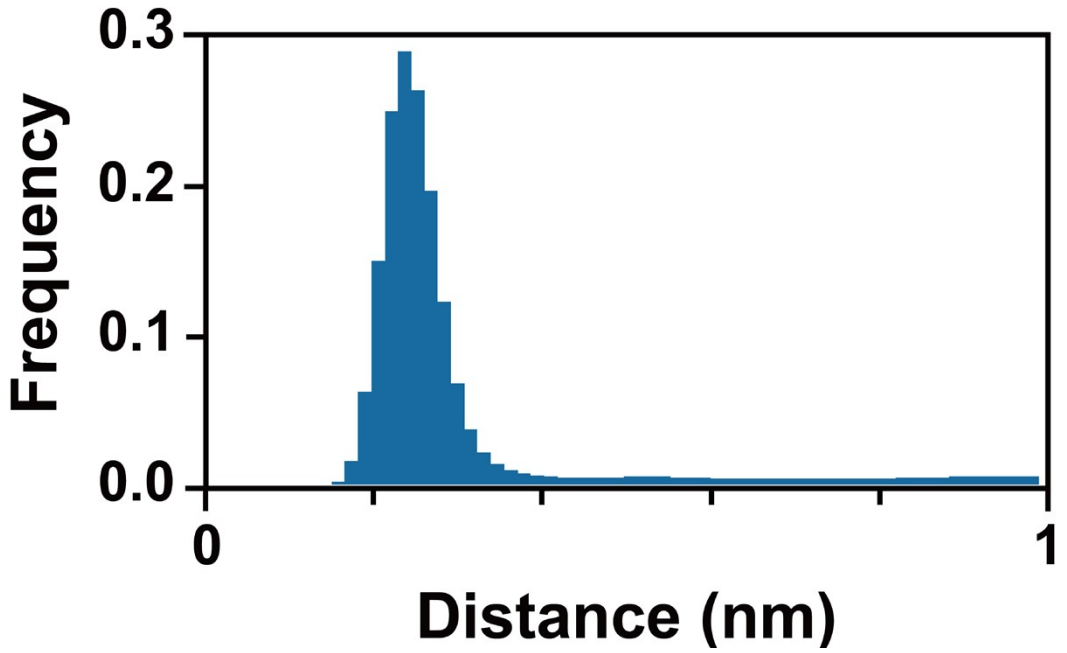
S2 Fig. The distances of COMs between the catalytic dyad of M^{pro} and inhibitors of the M^{pro}–HIV-1 PR complex with the second highest docking score.



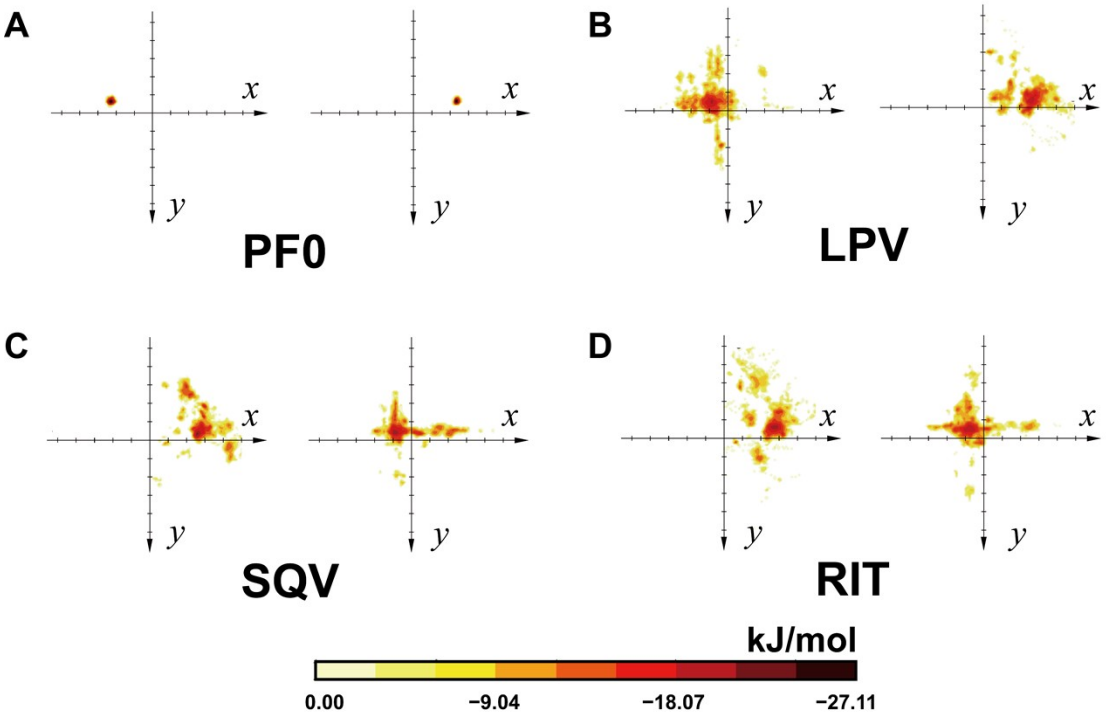
S3 Fig. The non-bonded interaction energy between the inhibitors and the protomers. A and B. The van der Waals energy between the four inhibitors and the two protomers, respectively. C and D. The coulomb energy between the four inhibitors and the two protomers, respectively.



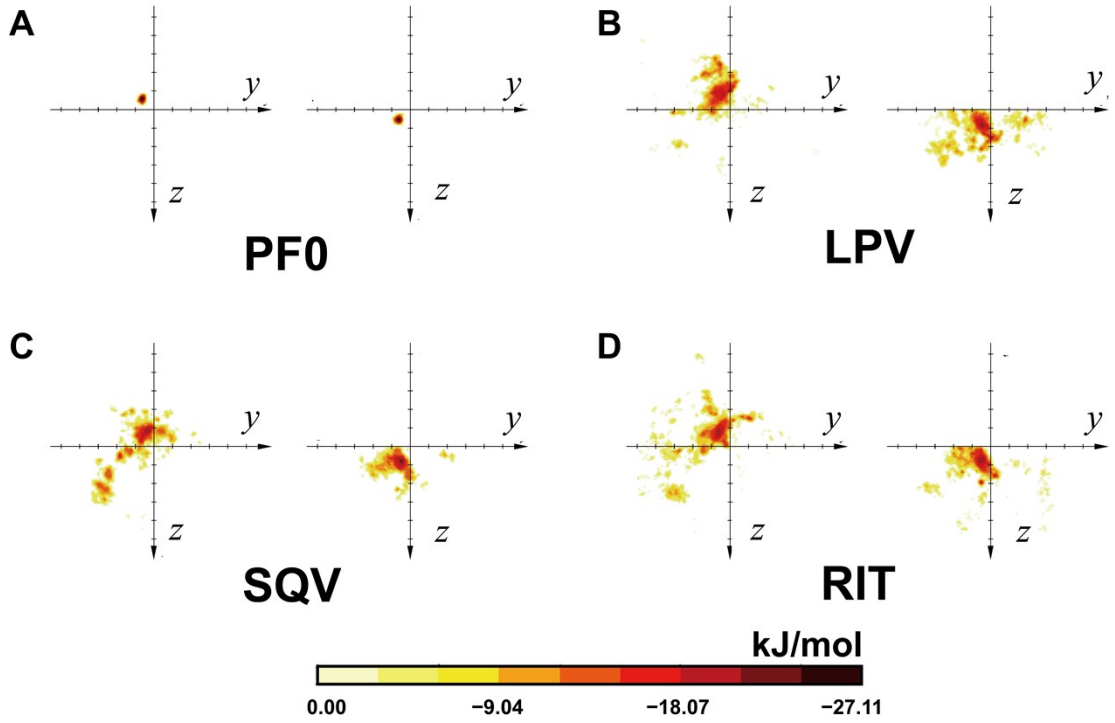
S4 Fig. The H-bond occupancy of the binding pocket of protomer B. Only the residues formed H-bonds with occupancies >5% are shown.



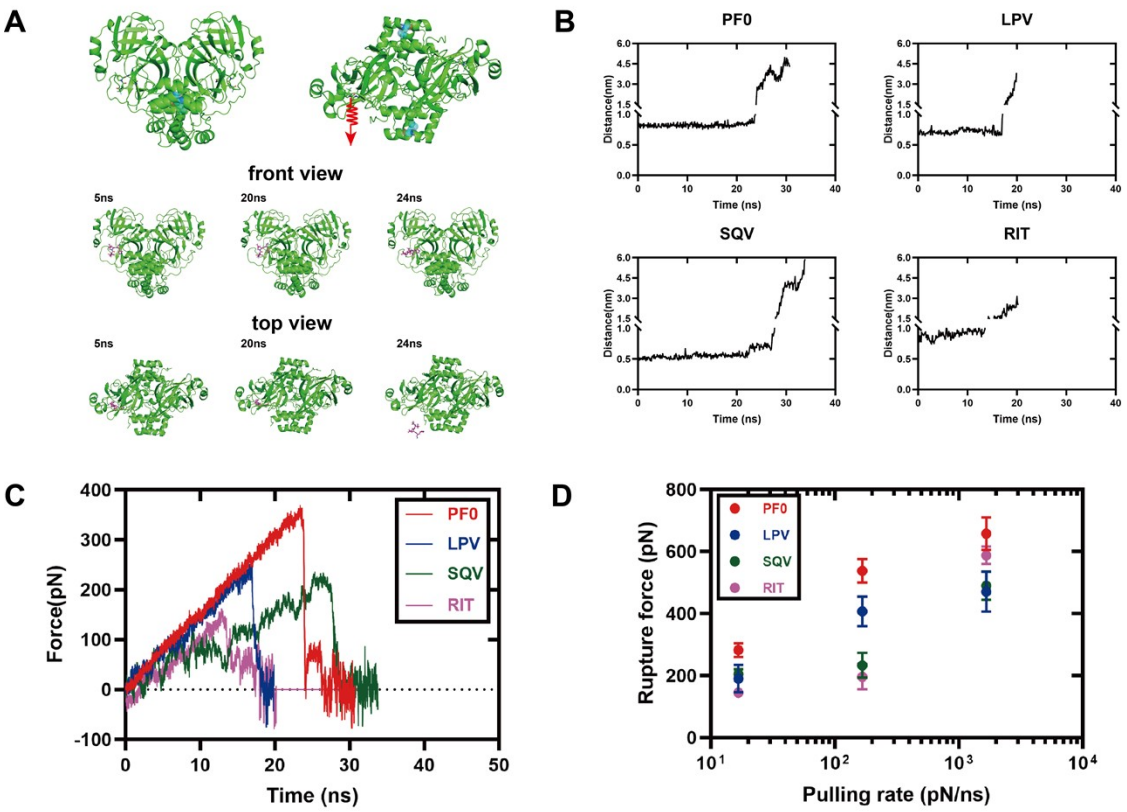
S5 Fig. The distribution of the minimal distance between inhibitors and the catalytic dyad.



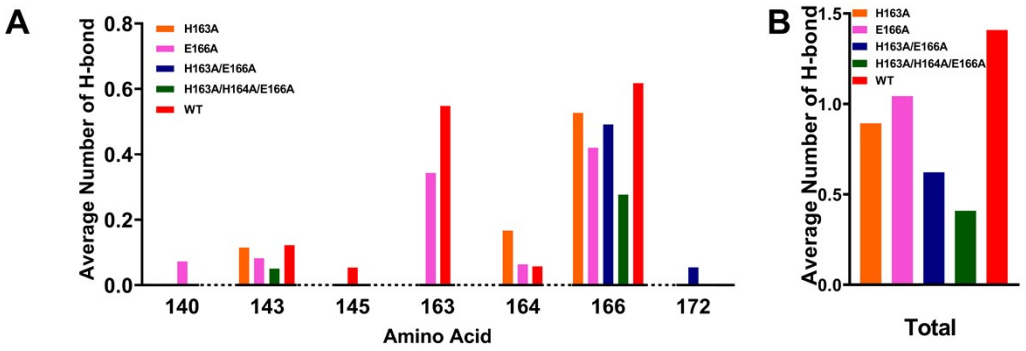
S6 Fig. The inhibitors binding free energy landscape in the XY-plane.



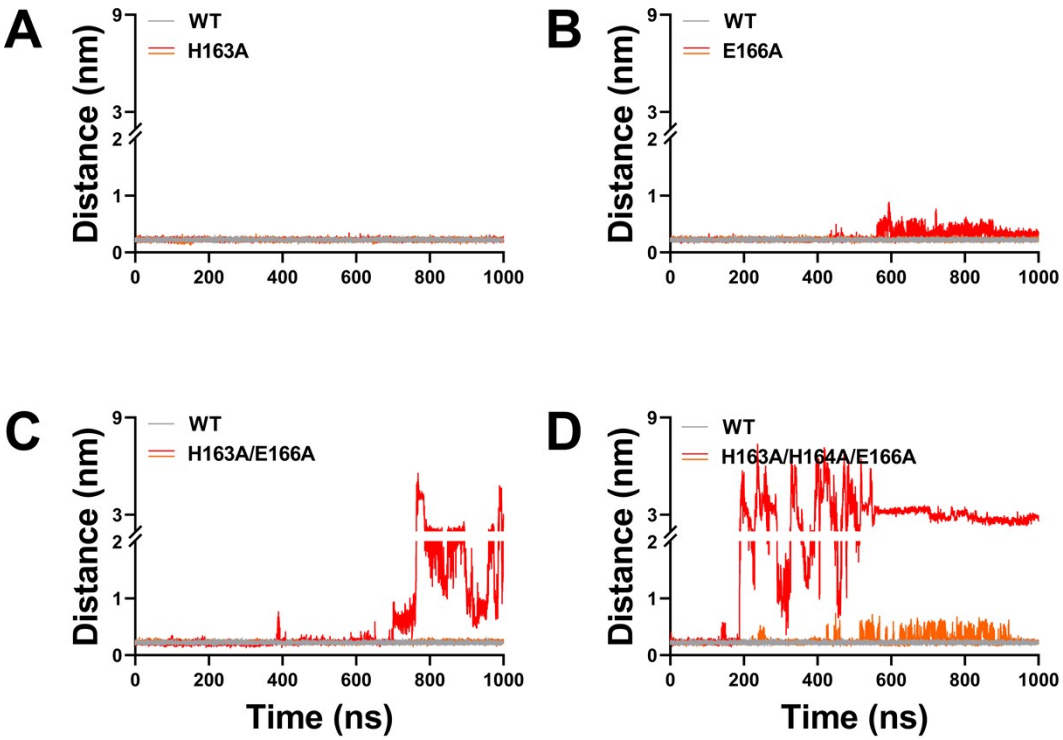
S7 Fig. The inhibitors binding free energy landscape in the YZ-plane



S8 Fig. SMD results of PF0 and HIV-1 PR inhibitors dissociated from the M^{pro} by pulling forces. A. The front and top views of M^{pro}–PF0 complex in the SMD simulations. **B.** The COM distances between the inhibitors and M^{pro}. **C.** The pulling force varied with simulation time in SMD simulations. **D.** The mean rupture forces of all inhibitors bound complexes calculated by the SMD simulations in terms of pulling rates. The mean rupture forces at a certain loading rate were averaged over three repeats.



S9 Fig. The average number of H-bond between inhibitors and the binding pocket of M^{pro} variants in the cMD simulations. A. The average number of H-bonds between the inhibitors and each residue in the binding pocket of M^{pro} variants to PF0 in cMD, and only the residues form an average number of H-bond >0.05 are shown. B. The average number of H-bonds between the binding pocket of M^{pro} variants and PF0 in cMD.



S10 Fig. Minimal distance between PF0 and the catalytic dyad of the M^{pro} variants. The colored lines indicate the minimal distance of the catalytic dyad of two protomers to the inhibitors, PF0 (A), LPV (B), SQV (C), and RIT (D). The red and orange, respectively, indicate two protomers of M^{pro} variants. The gray lines indicate the distance of PF0 to the catalytic dyad of one WT protomer.