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Binding mechanism of inhibitors to SARS-CoV-2 main protease deciphered by multiple replica molecular dynamics simulations

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Table S1. Results of computational alanine-scanning mutagenesis on inhibitors-M^{pro} binding.

complexes[a]	Residue	$\Delta\Delta E_{ele}$	$\Delta\Delta E_{vdW}$	$\Delta\Delta G_{nonpol}$	$\Delta\Delta G_{gb}$	$\Delta\Delta G_{ele+gb}$	$\Delta\Delta G$[b]
Masitinib-M^{pro}	M49	0.10	1.49	0.11	-0.51	-0.41	1.19
	E140	-0.14	0.27	-0.02	0.04	-0.1	0.15
	L141	-0.04	0.13	0	0.09	0.05	0.18
	N142	-0.02	1.12	0.1	-0.91	-0.93	0.29
	H163	0.7	0.72	0.02	-0.79	-0.09	0.65
	H164	0.11	0.23	0.01	-0.27	-0.16	0.08
	M165	0.33	1.23	0.05	-0.31	0.02	1.31
	E166	0.79	1.46	0.09	-1.4	-0.51	0.94
	Q189	2.65	1.9	0.18	-2.62	0.03	2.11
O6K-M^{pro}	M49	0.19	1.80	0.18	-0.61	-0.42	1.41
	E140	0.69	0.66	0.04	-0.66	0.03	0.73
	L141	1.10	0.87	0.05	-0.74	0.36	1.28
	N142	1.35	1.59	0.16	-1.97	-0.62	1.13
	H163	8.19	0.47	0.01	-4.64	3.55	4.03
	H164	0.23	0.37	0.01	-0.33	-0.1	0.25
	M165	0.34	1.31	0.06	-0.48	-0.14	1.23
	E166	-0.41	2.71	0.19	-0.72	-1.13	1.77
	Q189	1.04	1.73	0.15	-1.69	-0.65	1.23
FJC-M^{pro}	M49	0.17	1.81	0.16	-0.22	-0.05	1.92
	E140	-0.47	0.46	-0.02	0.32	-0.15	0.28
	L141	-0.01	0.18	0	0.15	0.14	0.30
	N142	1.96	0.94	0.08	-2.24	-0.28	0.74
	H163	9.38	0.41	0	-5.16	4.22	4.63
	H164	0.27	0.25	0	-0.26	0.01	0.26
	M165	0.41	2.23	0.13	-0.37	0.04	2.40
	E166	8.99	2.05	0.1	-7.68	1.31	3.45
	Q189	0.29	1.16	0.15	-1.18	-0.89	0.42
GQU-M^{pro}	M49	-0.64	0.46	0.01	0.69	0.05	0.52
	E140	-0.35	0.47	-0.02	0.21	-0.14	0.31
	L141	-0.04	0.14	0	0.13	0.09	0.23
	N142	1.32	1.85	0.16	-2.26	0.94	1.07
	H163	8.82	0.41	-0.01	-5.03	3.79	4.19
	H164	0.21	0.62	0.02	-0.32	-0.11	0.53
	M165	0.35	1.86	0.08	-0.34	0.01	1.95
	E166	1.59	1.90	0.11	-0.7	0.89	2.90
	Q189	0.94	1.33	0.13	-1.78	-0.84	0.62

[a]All values are given in kcal/mol.

[b]$\Delta\Delta G = \Delta G_{mut} - \Delta G_{WT}$

Table S2. Energetic contributions of clusters to bindings of inhibitors to the M^{pro}

complexes[a]	cluster 1 (C1)	cluster 2 (C2)	cluster 3 (C3)	cluster 4 (C4)
Masitinib-M^{pro}	-5.09	-2.94	-4.61	-3.63
O6K-M^{pro}	-3.37	-8.12	-9.79	-2.29
FJC-M^{pro}	-2.77	-7.18	-12.44	-1.82
GQU-M^{pro}	-1.84	-6.64	-12.43	-1.67

[a]All values are given in kcal/mol.

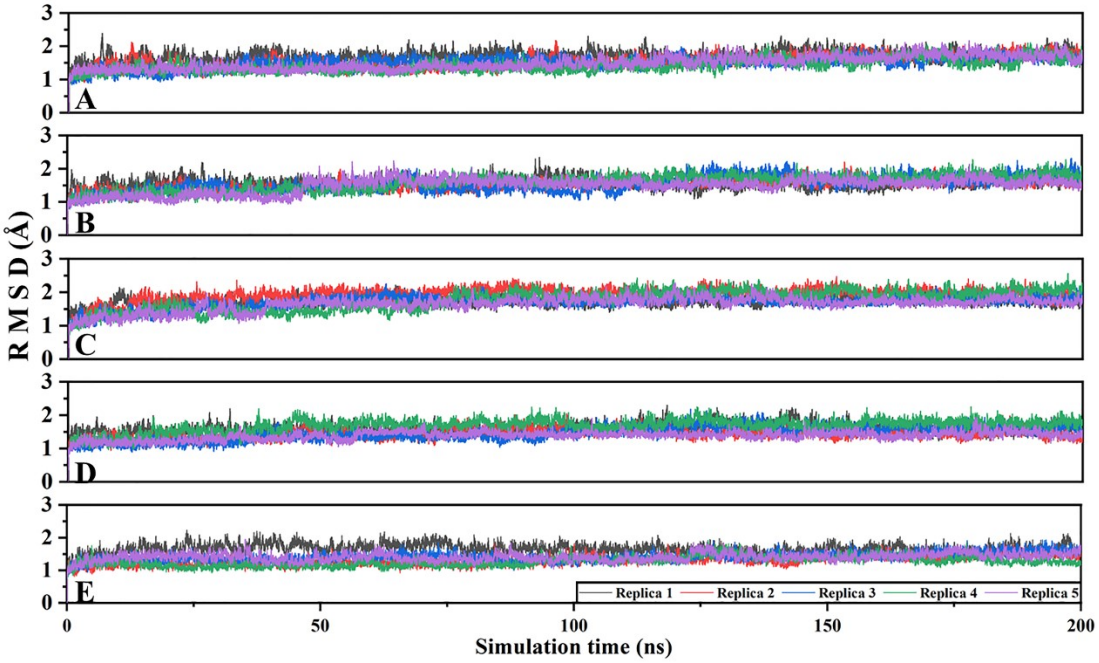

Fig. S1 Root-mean-square deviations (RMSDs) of backbone atoms in the M^{pro}: (A) the *apo* M^{pro}, (B) the masitinib-bound M^{pro}, (C) the O6K-bound M^{pro}, (D) the FJC-bound M^{pro}, (D) the GQU-bound M^{pro}.

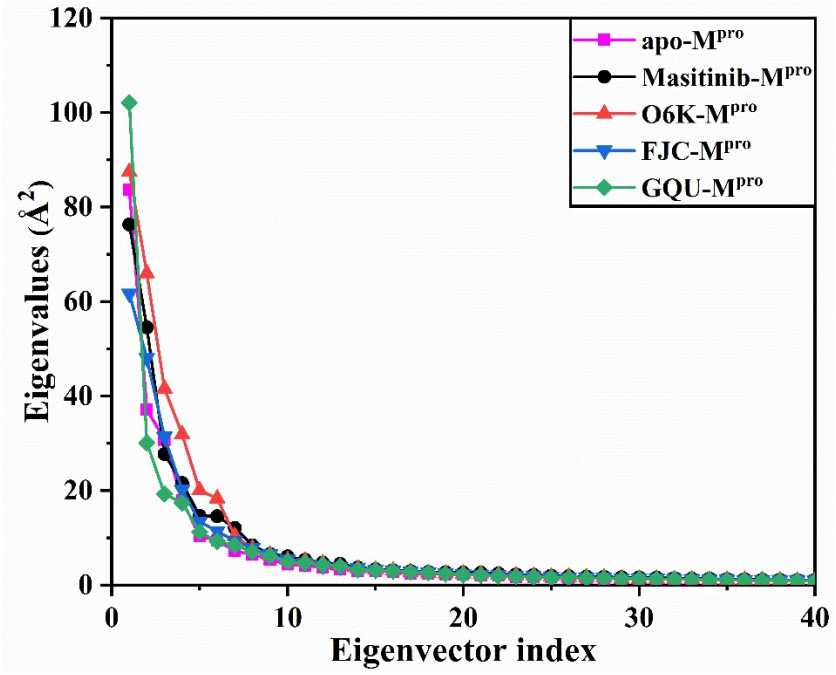

Fig. S2 The function of the eigenvalues VS the eigenvector indices obtained from principal component analysis performed on the single joined MRMD trajectory.

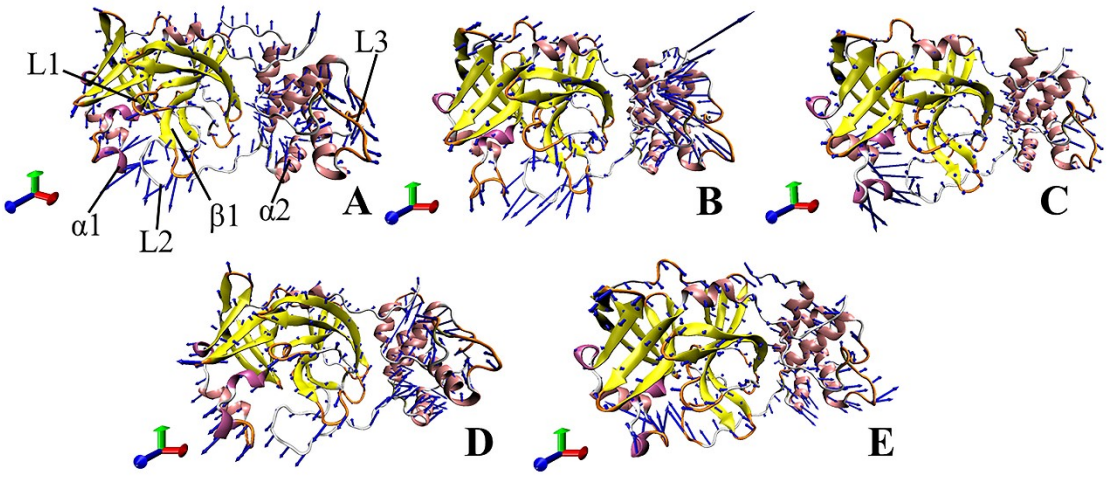

Fig. S3 Collective motions corresponding to the first eigenvector obtained from principal component analysis performed on the single joined MRMD trajectory: (A) the *apo* M^{pro}, (B) the masitinib-bound M^{pro}, (C) the O6K-bound M^{pro}, (D) the FJC-bound M^{pro} and (E) the GQU-bound M^{pro}.

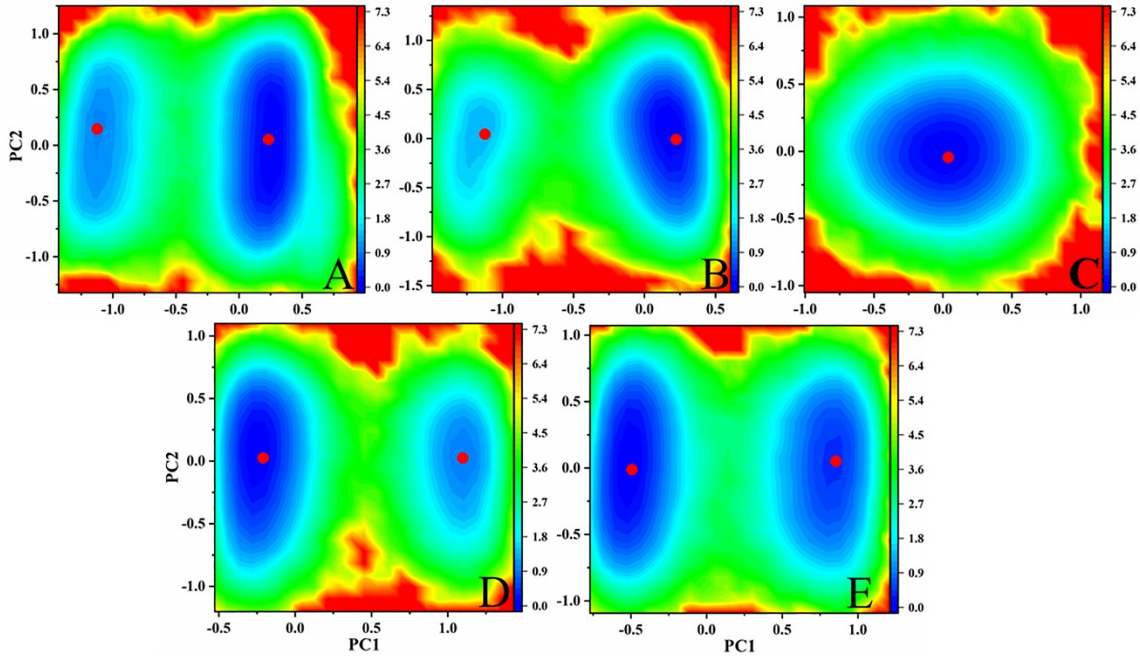

Fig. S4. Free energy landscapes of loop L1 in the M^{pro} projected on the first two eigenvectors: (A) the *apo* M^{pro}, (B) the masitinib-bound M^{pro}, (C) the O6K-bound M^{pro}, (D) the FJC-bound M^{pro} and (E) the GQU-bound M^{pro}.

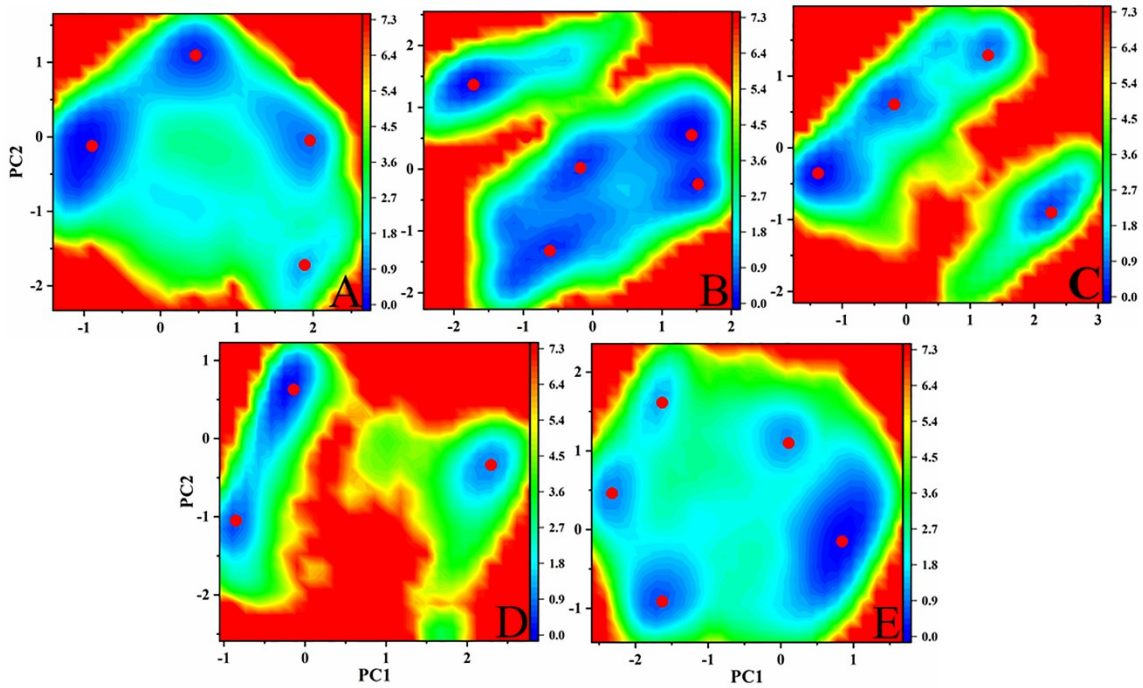

Fig. S5. Free energy landscapes of loop L2 in the M^{pro} projected on the first two eigenvectors: (A) the *apo* M^{pro}, (B) the masitinib-bound M^{pro}, (C) the O6K-bound M^{pro}, (D) the FJC-bound M^{pro} and (E) the GQU-bound M^{pro}.

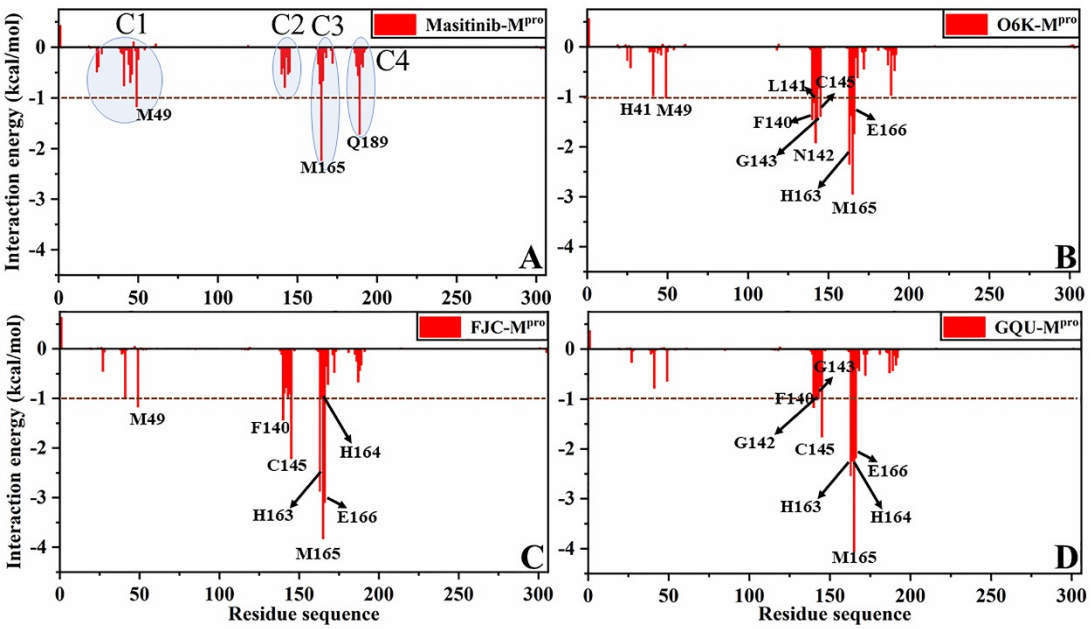

Fig. S6 Interactions of inhibitors with separate residues in the M^{pro}: (A) the masitinib-M^{pro} compound, (B) the O6K-M^{pro} compound, (C) the FJC-M^{pro} compound and (D) the GQU-M^{pro} compound.

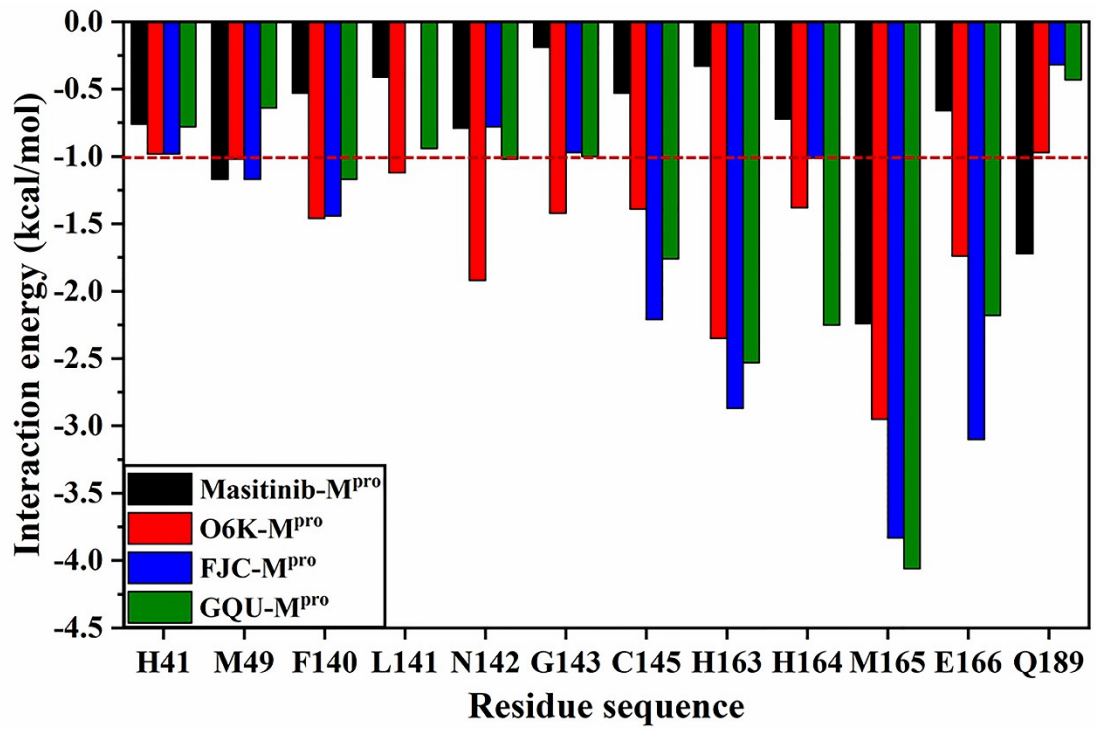

Fig. S7 Interactions of inhibitors with significant residues in the M^{pro}.