Inhibition mechanism and hot-spot prediction of nine potential drugs for SARS-CoV-2 M^{pro} by large-scale molecular dynamic simulations combined with the accurate binding free energy calculations

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Figure S1. Superposition structures of different M^{pro} obtained between 6LU7 (green) with (A) 5RHA, (B) 6WQF, (C) 7AKU, (D) 7K3T, (E) 7K6E and (F) 7KPH from PDB database. The values are RMSDs with 6LU7. (All in Å)

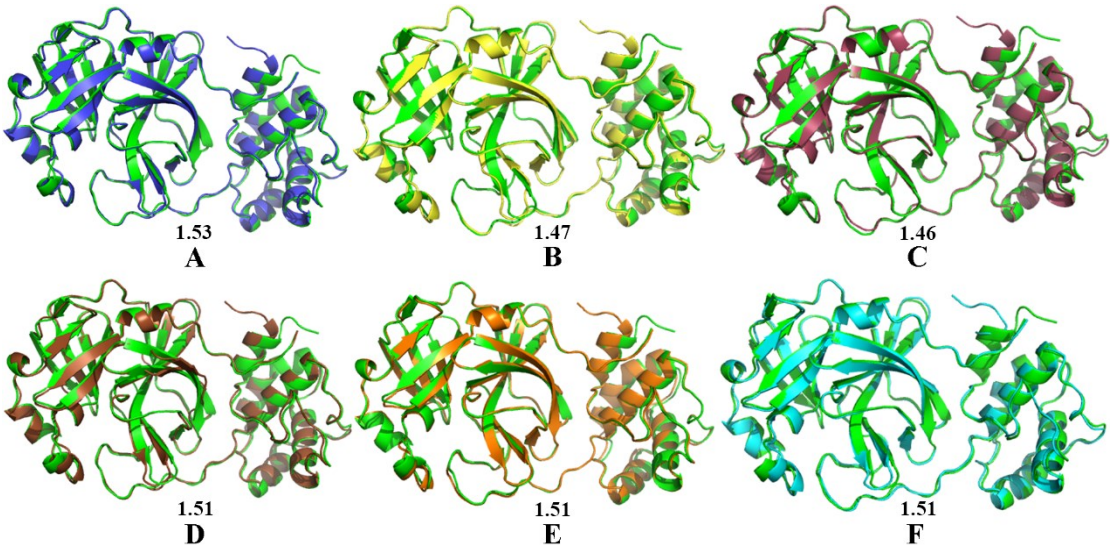

Figure S2. The time evolution of the distance between nine drugs and binding pocket residues for three docking structures in (A) Favipiravir, (B) Ritonavir, (C) Arbidol, (D) Chloroquine, (E) Saquinavir, (F) Darunavir, (G) Indinavir, (H) Carfilzomib and (I) H-chloroquine with M^{pro} (monomer) systems, respectively.

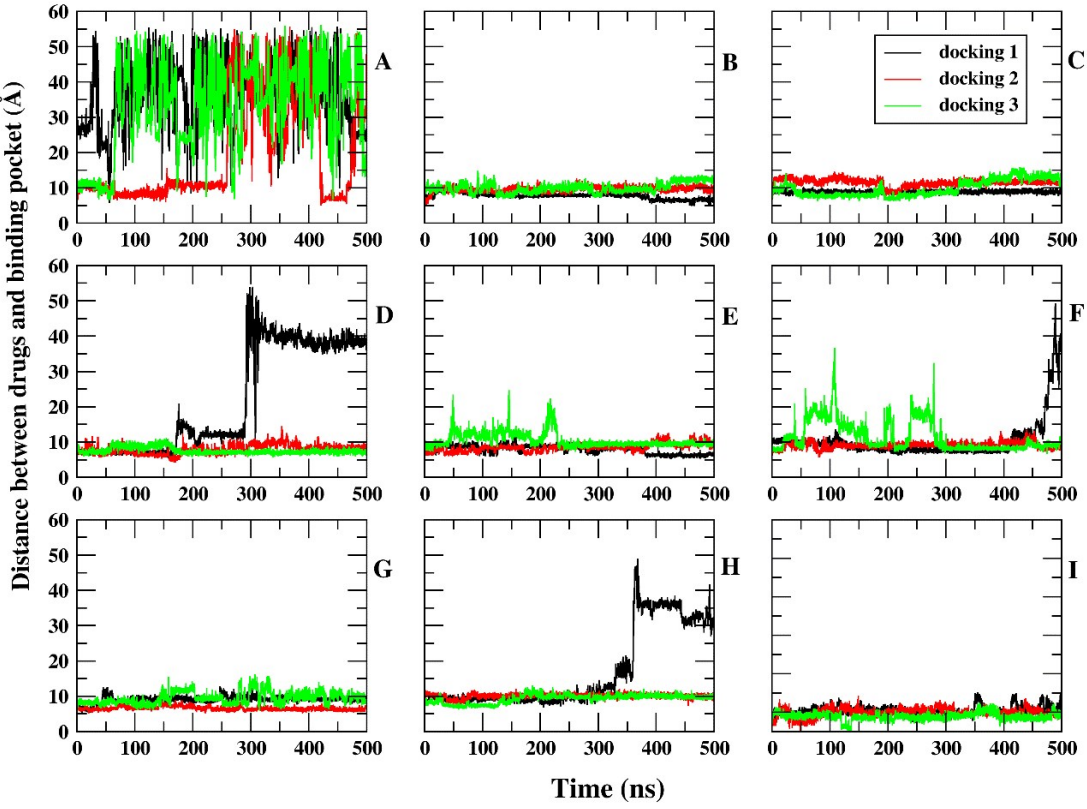

Figure S3. The 2D-RMSD (Å) of Cα atom of binding pocket residues during the entire 500 ns MD simulation in (A) Ritonavir, (B) Arbidol, (C) Chloroquine, (D) Saquinavir, (E) Darunavir, (F) Indinavir, (G) Carfilzomib and (H) H-chloroquine with monomeric M^{pro} system.

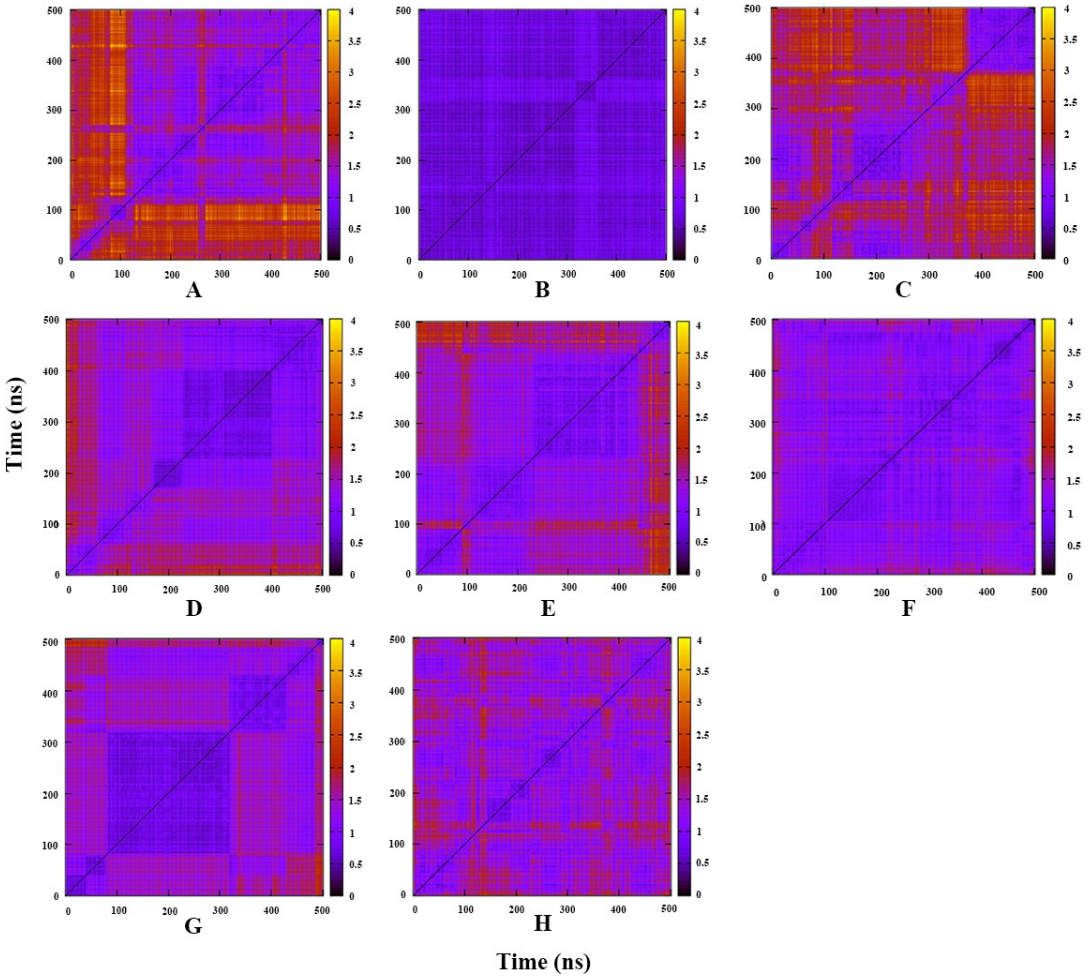

Figure S4 Dynamic cross-correlation maps reflecting relative motions between C_α atoms of M^{pro} (dimer with Cys145/Hid41) with (A) the apo state, (B) Ritonavir, (C) Arbidol and (D) Saquinavir.

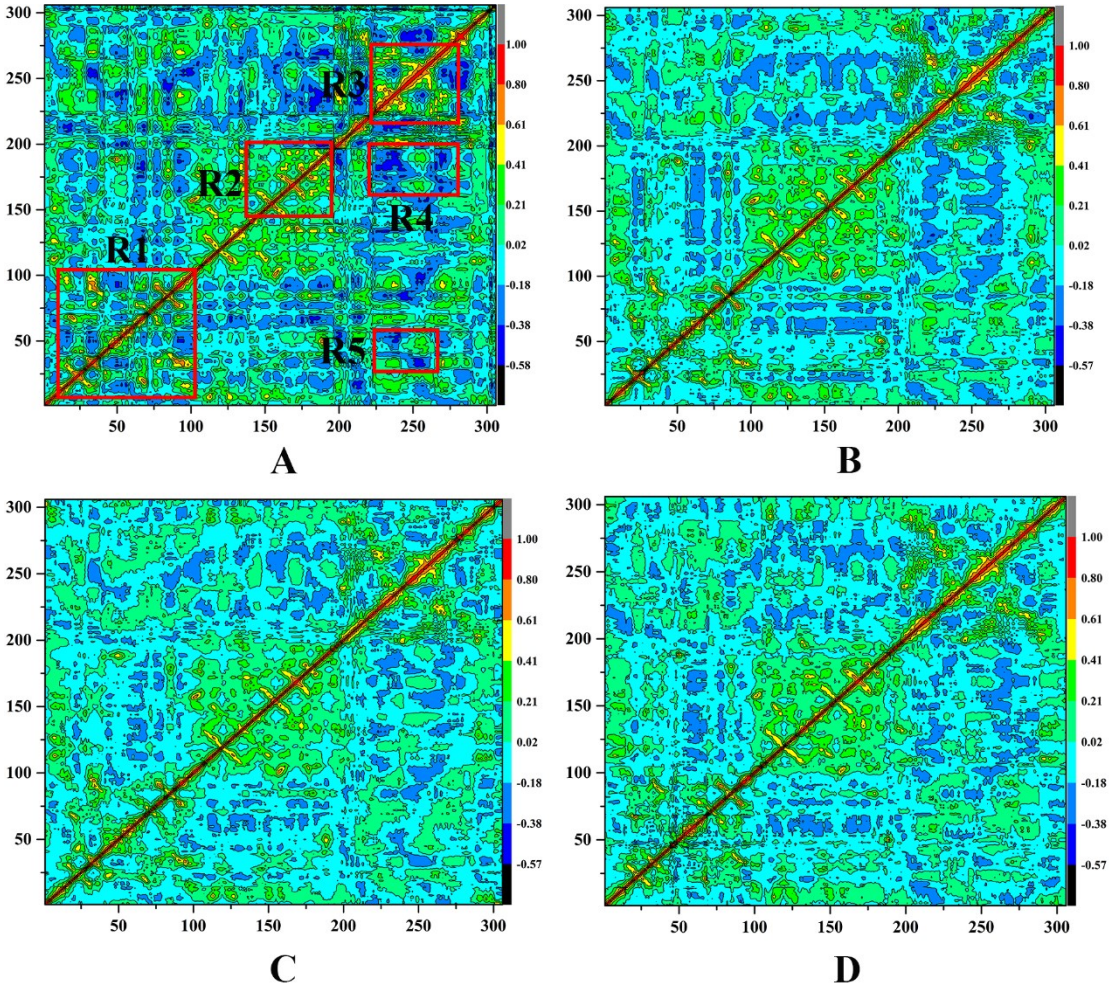

Figure S5. 2D structures of Ritonavir, Saquinavir and Arbidol. The common structures are highlighted in green.

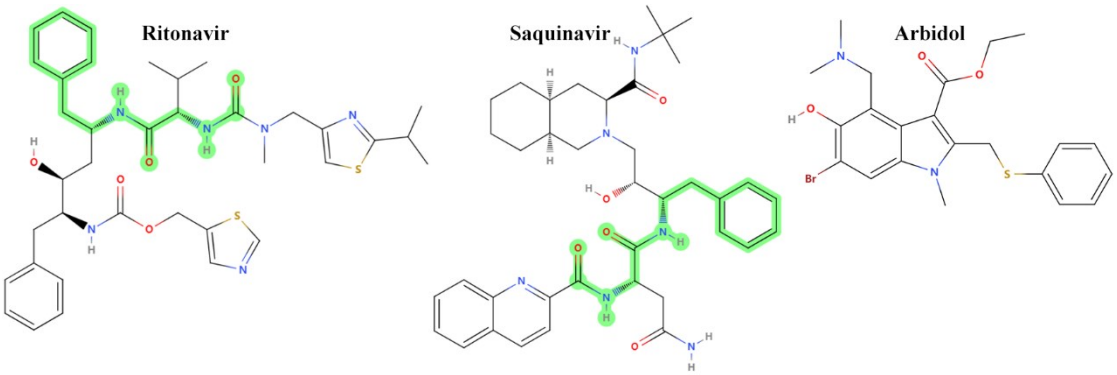

Table S1. The energy terms for eight drugs to monomeric M^{pro} of each docking structure. $\Delta G_{*/HCT}$, $\Delta G_{*/OBC1}$, $\Delta G_{*/OBC2}$, and $\Delta G_{*/PB}$ represent calculated by GB^{HCT}, GB^{OBC1}, GB^{OBC2}, and PBSA method, respectively. The * represent nonpolar solvation energy or polar solvation energy. (All values are in kcal/mol)

Drug	Structure	ΔE_{ele}	ΔE_{vdW}	$\Delta G_{np/HCT}$	$\Delta G_{gb/HCT}$	$\Delta G_{np/OBC1}$	$\Delta G_{gb/OBC1}$	$\Delta G_{np/OBC2}$	$\Delta G_{gb/OBC2}$	$\Delta G_{np/PB}$	$\Delta G_{pb/PB}$
Ritonavir	docking1	-39.66±0.6	-50.30±0.4	-7.34±0.0	48.91±0.4	-5.09±0.0	52.98±0.4	-5.09±0.0	40.23±0.6	-6.44±0.0	60.52±0.5
	docking2	-29.93±0.5	-57.29±0.4	-7.49±0.0	42.53±0.4	-5.20±0.0	48.40±0.4	-5.20±0.0	30.78±0.7	-6.55±0.0	52.75±0.5
	docking3	-9.24±0.6	-59.47±0.6	-8.43±0.0	28.37±0.5	-5.85±0.0	34.82±0.5	-5.85±0.0	27.48±0.6	-7.26±0.0	37.09±0.7
Arbidol	docking1	-18.16±0.4	-48.11±0.3	-6.08±0.0	30.95±0.4	-4.22±0.0	33.57±0.4	-4.22±0.0	3.36±0.7	-5.49±0.0	38.64±0.5
	docking2	-18.66±0.4	-47.71±0.3	-6.05±0.0	30.93±0.4	-4.20±0.0	32.05±0.3	-4.20±0.0	-2.09±0.6	-5.48±0.0	40.81±0.5
	docking3	-8.67±0.3	-43.80±0.3	-5.64±0.0	20.65±0.3	-3.92±0.0	24.23±0.3	-3.92±0.0	5.15±0.5	-5.17±0.0	31.12±0.4
Chloroquine	docking2	-6.61±0.3	-37.57±0.4	-5.18±0.0	16.99±0.3	-3.60±0.0	20.88±0.3	-3.60±0.0	-9.56±0.6	-4.82±0.0	27.00±0.4
	docking3	-9.69±0.4	-40.49±0.3	-4.92±0.0	17.47±0.2	-3.42±0.0	20.18±0.2	-3.42±0.0	-15.28±0.6	-4.63±0.0	26.17±0.3
Saquinavir	docking1	-147.42±0.9	-42.17±0.4	-7.03±0.0	153.86±0.8	-4.88±0.0	156.11±0.9	-4.88±0.0	144.72±1.1	-6.21±0.0	160.32±0.8
	docking2	-151.50±1.9	-37.23±0.6	-6.49±0.0	158.63±1.5	-4.51±0.0	160.09±1.4	-4.51±0.0	140.86±1.5	-5.80±0.0	165.50±1.5
	docking3	-170.00±1.0	-37.81±0.4	-6.43±0.0	173.38±0.9	-4.46±0.0	171.74±0.9	-4.46±0.0	150.91±0.9	-5.76±0.0	184.09±1.0
Darunavir	docking1	-11.70±0.7	-31.39±1.2	-4.74±0.2	23.00±0.9	-3.29±0.1	27.27±1.0	-3.29±0.1	-14.42±1.2	-4.49±0.1	29.78±1.4
	docking2	-31.81±0.5	-40.30±0.4	-5.68±0.0	37.23±0.3	-3.84±0.0	41.84±04	-3.94±0.0	-12.93±0.8	-5.19±0.0	45.35±0.4
	docking3	-12.42±1.0	-33.84±0.5	-4.96±0.1	21.43±0.9	-3.45±0.0	25.45±0.9	-3.45±0.0	-4.56±0.8	-4.66±0.0	27.17±1.0
Indinavir	docking1	-187.88±1.5	-48.47±0.3	-6.93±0.0	198.75±1.4	-4.81±0.0	205.28±1.5	-4.81±0.0	196.65±1.7	-6.13±0.0	206.28±1.4
	docking2	-262.86±1.7	-38.34±0.4	-6.36±0.0	266.06±1.6	-4.41±0.0	274.29±1.6	-4.41±0.0	263.30±1.7	-5.70±0.0	273.76±1.6
	docking3	-222.85±2.2	-40.78±0.6	-6.09±0.0	234.71±2.1	-4.23±0.0	240.48±2.0	-4.23±0.0	221.04±2.3	-5.51±0.1	247.38±2.5
Carfilzomib	docking1	-20.99±1.2	-26.81±0.8	-3.98±0.1	28.52±1.1	-2.76±0.1	32.82±1.2	-2.76±0.1	36.68±1.4	-3.92±0.1	33.98±1.5
	docking2	-23.49±0.6	-54.25±0.3	-7.79±0.0	35.45±0.4	-5.41±0.0	40.17±0.5	-5.41±0.0	25.51±0.8	-6.78±0.0	45.47±0.6
	docking3	-17.03±0.6	-51.42±0.4	-7.63±0.0	35.32±0.6	-5.30±0.0	40.05±0.6	-5.30±0.0	33.99±1.0	-6.66±0.0	53.51±0.7
H-chloroquine	docking1	-8.90±0.4	-38.66±0.7	-5.34±0.1	19.81±0.4	-3.71±0.0	22.75±0.4	-3.71±0.0	-4.59±0.9	-4.94±0.0	27.47±0.6
	docking2	-7.19±0.3	-34.36±0.4	-4.90±0.0	16.10±0.3	-3.41±0.2	18.96±0.3	-3.41±0.0	-17.14±0.8	-4.61±0.0	21.93±0.5
	docking3	-9.11±0.4	-38.80±0.4	-5.53±0.0	20.15±0.3	-3.84±0.0	23.62±0.3	-3.84±0.0	-2.80±0.7	-5.08±0.0	33.48±0.5

Table S2. Binding free energy for eight drugs to monomeric M^{pro} of each docking structure. Enthalpic contribution is obtained from Table S1 and the entropic contribution is calculated using interaction entropy (IE) and Normal mode methods, respectively. (All values are in kcal/mol)

Drug	Structure	IE	Nmode	GB^{HCT}_IE	GB^{OBC1}_IE	GB^{OBC2}_IE	PBSA_IE	GB^{HCT}_Nmode	GB^{OBC1}_Nmode	GB^{OBC2}_Nmode	PBSA_Nmode
Ritonavir	docking1	18.41±0.0	23.00±3.2	-29.97±0.4	-23.66±0.4	-36.41±0.7	-17.46±0.5	-25.38±3.2	-19.07±3.2	-31.82±3.3	-12.88±3.2
	docking2	14.12±0.0	31.55±2.9	-38.04±0.5	-29.89±0.5	-47.51±0.9	-26.89±0.5	-20.61±2.9	-12.46±2.9	-30.08±3.0	-9.47±2.9
	docking3	19.66±0.0	29.48±2.8	-29.11±0.5	-20.09±0.5	-27.42±0.8	-19.22±0.5	-19.29±2.8	-10.27±2.8	-17.60±2.9	-9.41±2.8
Arbidol	docking1	13.46±0.0	18.53±2.3	-27.93±0.3	-23.45±0.3	-53.66±0.7	-19.66±0.3	-22.86±2.3	-18.38±2.3	-48.59±2.4	-14.59±2.3
	docking2	11.12±0.0	22.64±1.6	-30.37±0.3	-27.40±0.3	-61.55±0.6	-19.92±0.3	-18.85±1.6	-15.88±1.6	-50.03±1.7	-8.40±1.6
	docking3	11.89±0.0	17.78±2.1	-25.57±0.4	-20.27±0.4	-39.35±0.7	-14.62±0.4	-19.68±2.1	-14.38±2.1	-33.46±2.2	-8.73±2.1
Chloroquine	docking2	13.78±0.0	14.72±2.0	-18.50±0.4	-13.12±0.4	-43.56±0.7	-8.22±0.4	-17.56±2.0	-12.18±2.0	-42.62±2.1	-7.28±2.0
	docking3	10.14±0.0	18.44±2.4	-27.48±0.3	-23.27±0.3	-58.73±0.7	-18.48±0.4	-19.18±2.4	-14.97±2.4	-50.43±2.5	-10.18±2.4
Saquinavir	docking1	25.94±0.0	27.68±1.8	-21.82±0.5	-12.42±0.5	-23.81±0.9	-9.54±0.6	-20.08±1.9	-10.68±1.9	-22.07±2.0	-7.80±1.9
	docking2	30.23±0.0	28.87±2.0	-6.37±0.6	-2.92±0.6	-22.15±1.1	1.19±0.6	-7.73±2.1	-4.28±2.1	-23.51±2.3	-0.17±2.1
	docking3	23.24±0.0	24.52±3.2	-17.61±0.3	-17.29±0.3	-38.12±0.8	-6.23±0.5	-16.33±3.2	-16.01±3.2	-36.84±3.3	-4.95±3.2
Darunavir	docking1	20.64±0.0	19.00±0.6	-4.20±1.0	1.52±0.9	-40.17±2.6	2.83±0.7	-5.84±1.2	-0.11±1.1	-41.81±2.7	1.20±0.9
	docking2	15.11±0.0	23.01±1.2	-25.45±0.4	-19.10±0.4	-73.87±0.9	-16.85±0.4	-17.55±1.3	-11.20±1.3	-65.97±1.5	-8.95±1.3
	docking3	22.54±0.0	22.52±1.5	-7.26±0.6	-1.72±0.5	-31.73±1.1	-1.21±0.5	-7.28±1.6	-1.74±1.6	-31.75±1.9	-1.23±1.6
Indinavir	docking1	30.87±0.0	24.24±1.5	-13.67±0.3	-5.03±0.3	-13.65±0.9	-5.35±0.4	-20.30±1.5	-11.66±1.5	-20.28±1.7	-11.98±1.6
	docking2	32.02±0.0	26.13±1.9	-9.49±0.4	0.68±0.4	-10.31±0.7	-1.14±0.4	-15.38±1.9	-5.21±1.9	-16.20±2.0	-7.03±1.9
	docking3	30.00±0.0	21.50±2.0	-5.02±0.7	2.61±0.6	-16.83±1.0	8.23±0.7	-13.52±2.1	-5.89±2.1	-25.33±2.2	-0.27±2.1
Carfilzomib	docking1	16.49±0.0	19.00±1.4	-6.78±0.8	-1.26±0.7	2.60±1.1	-1.25±0.6	-4.27±1.6	1.25±1.6	5.11±1.8	1.26±1.5
	docking2	19.27±0.0	28.00±1.0	-30.81±0.4	-23.70±0.4	-38.37±0.8	-19.79±0.4	-22.08±1.1	-14.97±1.1	-29.64±1.3	-11.06±1.1
	docking3	19.32±0.0	23.15±2.0	-21.43±0.4	-14.38±0.4	-20.43±0.8	-2.28±0.6	-17.60±2.0	-10.55±2.0	-16.60±2.2	1.55±2.1
H-chloroquine	docking1	18.23±0.0	22.73±2.7	-14.86±0.6	-10.29±0.6	-37.63±0.9	-6.80±0.6	-10.36±2.8	-5.79±2.8	-33.13±2.8	-2.30±2.8
	docking2	11.30±0.0	21.18±1.7	-19.06±0.3	-14.70±0.3	-50.79±1.0	-12.93±0.3	-9.18±1.7	-4.82±1.7	-40.91±2.0	-3.05±1.7
	docking3	13.32±0.0	21.19±1.2	-19.97±0.5	-14.80±0.4	-41.23±1.0	-6.19±0.4	-12.10±1.3	-6.93±1.3	-33.36±1.6	1.68±1.3

Table S3. The average decomposed energy values of each hot-spot residues in Ritonavir−M^{pro} (monomeric). (All values are in kcal/mol)

Residue	ΔE_{vdW}	ΔE_{ele}	ΔG_{gb}	ΔG_{np}	ΔH
Gln189	-6.32	-8.11	8.32	-1.11	-7.21
Met165	-5.60	-1.60	1.70	-0.65	-6.17
Met49	-3.37	-0.24	1.16	-0.53	-2.95
Glu166	-3.07	-4.36	5.01	-0.51	-2.87
Leu167	-2.21	-0.77	0.88	-0.19	-2.29
Pro168	-1.97	-0.32	0.66	-0.38	-2.02
Hie41	-2.37	-0.49	1.13	-0.27	-2.00

Table S4. The average decomposed energy values of each hot-spot residues in Arbidol−M^{pro} (monomeric). (All values are in kcal/mol)

Residue	ΔE_{vdW}	ΔE_{ele}	ΔG_{gb}	ΔG_{np}	ΔH
Met49	-4.63	-0.42	1.13	-0.53	-4.45
Met165	-3.97	-0.91	1.10	-0.47	-4.26
Hie41	-4.49	-1.86	3.27	-0.39	-3.45
Asn142	-2.92	-0.37	1.22	-0.47	-2.53
Asp187	-2.05	-3.04	3.01	-0.13	-2.21
Gln189	-3.29	-0.43	2.12	-0.54	-2.14
Arg188	-2.42	0.35	0.17	-0.13	-2.03

Table S5. The average decomposed energy values of each hot-spot residues in Chloroquine−M^{pro} (monomeric). (All values are in kcal/mol)

Residue	ΔE_{vdW}	ΔE_{ele}	ΔG_{gb}	ΔG_{np}	ΔH
Met165	-5.08	-0.17	0.28	-0.47	-5.44
Gln189	-5.58	-1.83	3.09	-0.86	-5.18
Asp187	-1.77	0.22	-1.25	-0.07	-2.86
Hie41	-3.66	-1.08	2.48	-0.33	-2.57
Arg188	-2.31	-3.02	3.44	-0.09	-1.98

Table S6. The energy terms for eight drugs to dimeric M^{pro} (Cys145/Hie41) of each docking structure. $\Delta G_{*/HCT}$, $\Delta G_{*/OBC1}$, $\Delta G_{*/OBC2}$, and $\Delta G_{*/PB}$ represent calculated by GB^{HCT}, GB^{OBC1}, GB^{OBC2}, and PBSA method, respectively. The * represent nonpolar solvation energy or polar solvation energy. (All values are in kcal/mol)

Drug	Structure	ΔE_{ele}	ΔE_{vdW}	$\Delta G_{np/HCT}$	$\Delta G_{gb/HCT}$	$\Delta G_{np/OBC1}$	$\Delta G_{gb/OBC1}$	$\Delta G_{np/OBC2}$	$\Delta G_{gb/OBC2}$	$\Delta G_{np/PB}$	$\Delta G_{pb/PB}$
Ritonavir	docking1	-22.06±0.4	-60.62±0.3	-7.86±0.0	38.22±0.3	-5.46±0.0	45.11±0.3	-5.46±0.0	37.64±0.5	-6.38±0.0	54.55±0.4
	docking2	-24.62±0.4	-55.57±0.3	-7.60±0.0	38.87±0.3	-5.28±0.0	45.74±0.4	-7.60±0.0	41.09±0.7	-6.02±0.0	50.48±0.4
	docking3	-13.77±0.5	-52.68±0.3	-7.66±0.0	31.62±0.4	-5.32±0.0	38.55±0.4	-5.32±0.0	36.32±0.7	-6.23±0.0	47.25±0.4
Arbidol	docking1	-12.89±0.3	-43.23±0.2	-5.93±0.0	24.36±0.2	-4.12±0.0	25.37±0.3	-4.12±0.0	-5.72±0.6	-4.92±0.0	34.72±0.4
	docking2	-9.44±0.2	-43.01±0.3	-5.60±0.0	21.03±0.2	-3.89±0.0	24.28±0.2	-3.89±0.0	9.48±0.5	-4.68±0.0	31.07±0.3
	docking3	-10.760±0.3	-43.70±0.2	-6.14±0.0	21.64±0.2	-4.26±0.0	25.18±0.2	-4.26±0.0	10.33±0.4	-5.08±0.0	31.43±0.3
Chloroquine	docking1	-6.59±0.2	-34.75±0.5	-4.81±0.0	14.99±0.1	-3.34±0.0	18.44±0.2	-3.34±0.0	-1.79±0.5	-4.08±0.0	22.12±0.2
	docking2	-5.14±0.3	-30.19±0.3	-4.38±0.0	13.52±0.2	-3.05±0.0	17.06±0.2	-3.05±0.0	3.46±0.4	-3.76±0.0	19.18±0.2
	docking3	-9.36±0.2	-40.12±0.2	-5.20±0.0	18.86±0.1	-3.61±0.0	22.40±0.1	-3.61±0.0	-19.71±0.5	-4.37±0.0	28.94±0.2
Saquinavir	docking2	-19.17±0.5	-48.14±0.3	-6.76±0.0	34.29±0.4	-4.66±0.0	39.42±0.4	-4.66±0.0	20.18±0.8	-5.52±0.0	44.31±0.4
	docking3	-15.96±0.4	-48.06±0.4	-7.33±0.0	30.12±0.2	-5.09±0.0	35.22±0.3	-5.09±0.0	0.51±0.7	-5.97±0.0	41.97±0.4
Darunavir	docking1	-24.10±0.6	-47.47±0.3	-6.44±0.0	36.23±0.4	-4.47±0.0	42.59±0.4	-4.47±0.0	-37.89±0.8	-5.30±0.0	46.46±0.6
	docking2	-21.38±0.5	-35.12±0.3	-5.07±0.0	31.72±0.4	-3.52±0.0	37.08±0.4	-3.52±0.0	-23.12±0.7	-4.28±0.0	39.84±0.4
	docking3	-32.93±0.5	-49.64±0.3	-6.77±0.0	44.83±0.4	-4.70±0.0	51.57±0.4	-4.70±0.0	-17.94±0.9	-5.55±0.0	57.43±0.4
Indinavir	docking1	-263.79±1.8	-45.44±0.3	-6.60±0.0	271.16±1.7	-4.58±0.0	278.61±1.8	-4.58±0.0	273.57±1.9	-5.43±0.0	278.67±1.7
	docking2	-270.46±1.2	-43.63±0.3	-7.55±0.0	281.18±1.1	-5.23±0.0	289.35±1.2	-5.25±0.0	298.11±1.3	-6.15±0.0	293.48±1.2
	docking3	-291.29±2.2	-60.05±0.3	-8.10±0.0	299.76±2.1	-5.63±0.0	309.05±2.2	-5.63±0.0	339.92±2.5	-6.56±0.0	320.47±2.3
Carfilzomib	docking2	-16.76±0.4	-56.53±0.3	-7.99±0.0	36.28±0.4	-5.55±0.0	42.34±4.0	-5.55±0.0	5.74±0.8	-6.48±0.0	51.41±0.4
	docking3	-12.05±0.4	-46.56±0.3	-7.06±0.0	29.72±0.3	-4.90±0.0	35.41±0.3	-4.90±0.0	22.29±0.9	-5.78±0.0	39.69±0.4
H-chloroquine	docking1	-8.87±0.2	-37.83±0.3	-5.37±0.0	19.46±0.2	-3.73±0.0	23.01±0.2	-3.73±0.0	-8.21±0.9	-4.51±0.0	29.19±0.3
	docking2	-11.11±0.3	-40.05±0.3	-5.43±0.0	20.90±0.3	-3.77±0.0	23.87±0.3	-3.77±0.0	-17.85±0.7	-4.55±0.0	30.93±0.4
	docking3	-7.88±0.3	-26.73±0.3	-3.86±0.0	14.40±0.3	-2.68±0.0	16.75±0.2	-2.68±0.0	-0.01±0.6	-3.37±0.0	19.22±0.3

Table S7. Binding free energy for eight drugs to dimeric M^{pro} (Cys145/Hie41) of each docking structure. Enthalpic contribution is obtained from Table S6 and the entropic contribution is calculated using interaction entropy (IE) and Normal mode methods, respectively. (All values are in kcal/mol)

Drug	Structure	IE	Nmode	GB^{HCT}_IE	GB^{OBC1}_IE	GB^{OBC2}_IE	PBSA_IE	GB^{HCT}_Nmode	GB^{OBC1}_Nmode	GB^{OBC2}_Nmode	PBSA_Nmode
Ritonavir	docking1	10.48±0.0	28.03±2.6	-41.85±0.2	-32.55±0.2	-40.02±0.6	-24.03±0.2	-24.30±2.6	-15.01±2.6	-22.47±2.7	-6.49±2.6
	docking2	12.22±0.0	27.25±1.8	-36.69±0.3	-27.49±0.3	-34.46±0.7	-23.66±0.3	-21.66±1.8	-12.47±1.8	-19.44±1.9	-8.63±1.8
	docking3	14.47±0.0	29.51±2.5	-28.02±0.3	-18.75±0.3	-20.98±0.6	-10.96±0.4	-12.98±2.5	-3.71±2.5	-5.94±2.6	4.08±0.5
Arbidol	docking1	9.84±0.0	19.30±1.6	-27.85±0.3	-25.02±0.2	-56.11±0.7	-16.48±0.2	-18.39±1.6	-15.57±1.6	-46.65±1.7	-7.03±1.6
	docking2	9.39±0.0	21.54±2.3	-27.63±0.3	-22.67±0.3	-37.47±0.6	-16.67±0.2	-15.48±2.3	-10.53±2.3	-25.33±2.4	-4.52±2.3
	docking3	7.74±0.0	19.58±1.9	-31.22±0.2	-25.80±0.2	-40.65±0.4	-20.37±0.2	-19.38±1.9	-13.96±1.9	-28.81±1.9	-8.53±1.9
Chloroquine	docking1	6.63±0.0	20.09±2.2	-24.53±0.2	-19.61±0.2	-39.83±0.5	-16.67±0.2	-11.08±2.2	-6.15±2.2	-26.38±2.3	-3.21±2.2
	docking2	9.68±0.0	20.47±2.5	-16.52±0.3	-11.64±0.3	-25.23±0.6	-10.23±0.3	-5.73±2.5	-0.85±2.5	-14.45±2.6	0.56±2.5
	docking3	7.03±0.0	19.17±1.2	-28.78±0.2	-23.65±0.2	-65.75±0.6	-17.88±0.3	-16.65±1.2	-11.52±1.2	-53.62±1.3	-5.75±1.2
Saquinavir	docking2	16.19±0.0	22.36±2.0	-23.53±0.3	-16.35±0.3	-35.60±0.7	-12.32±0.3	-17.37±2.0	-10.19±2.0	-29.44±2.1	-6.16±2.0
	docking3	10.23±0.0	24.34±1.7	-30.99±0.3	-23.65±0.3	-58.36±0.8	-17.79±0.4	-16.88±1.7	-9.55±1.7	-44.26±1.9	-3.69±1.7
Darunavir	docking1	18.56±0.0	24.31±1.8	-23.20±0.4	-14.88±0.4	-95.35±1.2	-11.85±0.3	-17.46±1.8	-9.14±1.8	-89.61±2.2	-6.11±1.8
	docking2	16.53±0.0	20.79±1.1	-13.31±0.4	-6.40±0.4	-66.59±0.8	-4.40±0.3	-9.06±1.2	-2.15±1.2	-62.34±1.4	-0.14±1.1
	docking3	15.33±0.0	24.23±1.5	-29.17±0.3	-20.36±0.3	-89.87±1.0	-15.36±0.4	-20.28±1.5	-11.47±1.5	-80.98±1.8	-6.47±1.6
Indinavir	docking1	34.82±0.0	25.48±1.9	-9.84±0.3	-0.37±0.3	-5.41±0.7	-1.16±0.4	-19.18±1.9	-9.72±1.9	-14.76±2.0	-10.50 ±1.9
	docking2	28.15±0.0	25.63±1.6	-12.31±0.3	-1.83±0.3	6.93±0.7	1.40±0.4	-14.84±1.6	-4.35±1.6	4.41±1.7	-1.12±1.6
	docking3	31.56±0.0	28.41±2.1	-28.11±0.3	-16.35±0.3	14.53±1.4	-5.86±0.4	-31.26±2.1	-19.50±2.1	11.38±2.5	-9.01±2.1
Carfilzomib	docking2	12.63±0.0	28.51±2.2	-32.38±0.3	-23.87±0.3	-60.47±0.7	-15.73±0.3	-16.50±2.2	-7.99±2.2	-44.60±2.3	0.15±2.2
	docking3	13.61±0.0	29.19±2.3	-22.34±0.3	-14.49±0.3	-27.60±0.7	-11.08±0.3	-6.77±2.3	1.08±2.3	-12.03±2.4	4.50±2.3
H-chloroquine	docking1	7.38±0.0	17.96±2.0	-25.24±0.3	-20.04±0.2	-51.25±0.9	-14.64±0.3	-14.67±2.0	-9.46±2.0	-40.67±2.2	-4.06±0.3
	docking2	10.08±0.0	21.48±1.6	-25.60±0.3	-20.97±0.3	-62.69±0.8	-14.69±0.3	-14.21±1.6	-9.58±1.6	-51.30±1.8	-3.30±1.6
	docking3	9.58±0.0	19.00±2.7	-14.49±0.3	-10.96±0.3	-27.72±0.7	-9.18±0.3	-5.08±2.7	-1.55±2.7	-18.30±2.8	0.24±2.7

Table S8. Binding free energy for eight drugs to dimeric M^{pro} (Cys145/Hie41) using 12 calculation methods. (All values are in kcal/mol)

Method	Ritonavir	Arbidol	Chloroquine	Indinavir	Saquinavir	Darunavir	Carfilzomib	H-chloroquine
GB^{HCT}	-47.91±0.3	-37.89±0.3	-31.06±0.2	-48.26±0.3	-40.47±0.3	-38.70±0.4	-40.48±0.3	-30.79±0.3
GB^{OBC1}	-38.65±0.3	-33.49±0.2	-26.08±0.2	-37.69±0.3	-33.22±0.3	-30.69±0.4	-32.30±0.3	-26.34±0.3
GB^{OBC2}	-44.21±0.6	-53.73±0.6	-51.39±0.6	-26.16±0.9	-60.20±0.8	-100.75±1.0	-57.16±0.7	-56.23±0.8
PBSA	-31.94±0.3	-26.83±0.2	-22.71±0.3	-33.38±0.4	-28.27±0.4	-27.34±0.3	-26.52±0.3	-21.85±0.3
GB^{HCT}_IE	-35.52±0.3	-28.90±0.3	-23.28±0.2	-16.75±0.3	-27.26±0.3	-21.90±0.4	-27.36±0.3	-21.78±0.3
GB^{OBC1}_IE	-26.26±0.3	-24.50±0.2	-18.30±0.2	-6.18±0.3	-20.00±0.3	-13.88±0.4	-19.18±0.3	-17.33±0.3
GB^{OBC2}_IE	-31.82±0.6	-44.74±0.6	-43.61±0.6	5.35±0.9	-46.98±0.8	-83.94±1.0	-44.04±0.7	-47.22±0.8
PBSA _IE	-19.55±0.3	-17.84±0.2	-14.93±0.3	-1.87±0.4	-15.06±0.4	-10.53±0.3	-13.40±0.3	-12.84±0.3
GB^{HCT}_Nmode	-19.65±2.3	-17.75±1.9	-11.15±2.0	-21.76±1.9	-17.13±1.9	-15.60±1.5	-11.63±2.3	-11.31±2.1
GB^{OBC1}_Nmode	-10.39±2.3	-13.35±1.9	-6.17±2.0	-11.19±1.9	-9.87±1.9	-7.59±1.5	-3.46±2.3	-6.86±2.1
GB^{OBC2}_Nmode	-15.95±2.4	-33.60±2.0	-31.48±2.0	0.34±2.2	-36.85±2.0	-77.64±1.8	-28.31±2.4	-36.76±2.3
PBSA_Nmode	-3.68±1.6	-6.69±1.9	-2.80±2.0	-6.88±1.9	-4.92±1.9	-4.24±1.5	2.32±2.3	-2.37±1.5

Table S9. The average decomposed energy values of each hot-spot residues in Ritonavir−M^{pro} (dimer Cys145/Hie41). (All values are in kcal/mol)

Residue	ΔE_{vdW}	ΔE_{ele}	ΔG_{gb}	ΔG_{np}	ΔH
Gln189	-6.21	-5.05	5.99	-1.02	-6.30
Met165	-4.65	-1.36	1.04	-0.37	-5.33
Glu166	-4.14	-2.86	2.66	-0.65	-4.99
Met49	-3.35	-0.61	1.03	-0.45	-3.37
His163	-0.54	-3.79	1.87	-0.04	-2.50
Asp187	-2.77	-1.99	2.47	-0.21	-2.50
Gln192	-2.48	-0.48	0.81	-0.22	-2.36
Pro168	-2.33	0.07	0.44	-0.47	-2.30

Table S10. The average decomposed energy values of each hot-spot residues in Arbidol−M^{pro} (dimer Cys145/Hie41). (All values are in kcal/mol)

Residue	ΔE_{vdW}	ΔE_{ele}	ΔG_{gb}	ΔG_{np}	ΔH
Met49	-3.87	-0.69	1.15	-0.52	-3.94
Met165	-3.63	-0.66	1.10	-0.45	-3.65
Asn142	-3.07	-1.23	1.87	-0.51	-2.93
Gln189	-4.29	-1.01	2.96	-0.57	-2.91
Gly143	-1.41	-1.99	1.22	-0.21	-2.39
Cys145	-2.10	-0.51	0.42	-0.21	-2.39
Hie41	-2.81	-0.59	1.52	-0.30	-2.19

Table S11. The average decomposed energy values of each hot-spot residues in Saquinavir−M^{pro} (dimer Cys145/Hie41). (All values are in kcal/mol)

Residue	ΔE_{vdW}	ΔE_{ele}	ΔG_{gb}	ΔG_{np}	ΔH
Gln189	-7.97	-10.87	12.08	-1.33	-8.08
Met165	-3.75	-0.33	0.44	-0.47	-4.12
Met49	-2.96	-0.37	0.85	-0.43	-2.91
Ala191	-2.10	-0.59	0.78	-0.42	-2.34
Hie41	-2.92	-0.99	2.14	-0.44	-2.22

Table S12. The energy terms for eight drugs to dimeric M^{pro} (Cys145/Hid41) of each docking structure. $\Delta G_{*/HCT}$, $\Delta G_{*/OBC1}$, $\Delta G_{*/OBC2}$, and $\Delta G_{*/PB}$ represent calculated by GB^{HCT}, GB^{OBC1}, GB^{OBC2}, and PBSA method, respectively. The * represent nonpolar solvation energy and polar solvation energy, respectively. (All values are in kcal/mol)

Drug	Structure	ΔE_{ele}	ΔE_{vdW}	$\Delta G_{np/HCT}$	$\Delta G_{gb/HCT}$	$\Delta G_{np/OBC1}$	$\Delta G_{gb/OBC1}$	$\Delta G_{np/OBC2}$	$\Delta G_{gb/OBC2}$	$\Delta G_{np/PB}$	$\Delta G_{pb/PB}$
Ritonavir	docking1	-10.00±0.4	-51.48±0.3	-7.17±0.0	27.34±0.3	-4.98±0.0	33.03±0.3	-4.98±0.0	28.72±0.7	-5.86±0.0	36.19±0.4
	docking2	-17.48±0.5	-54.12±0.3	-7.36±0.0	34.47±0.3	-5.11±0.0	40.80±0.3	-5.11±0.0	41.38±0.6	-6.00±0.0	45.72±0.4
	docking3	-22.00±0.4	-61.38±0.3	-8.51±0.0	39.87±0.3	-5.91±0.0	48.88±0.3	-5.91±0.0	41.28±0.6	-6.86±0.0	54.69±0.4
Arbidol	docking1	-15.61±0.3	-48.92±0.2	-5.97±0.0	28.64±0.2	-4.14±0.0	30.31±0.3	-4.14±0.0	-12.23±0.7	-4.95±0.0	39.78±0.3
	docking2	-5.48±0.2	-40.22±0.4	-5.25±0.0	14.95±0.2	-3.65±0.0	17.73±0.2	-3.65±0.0	9.91±0.4	-4.41±0.0	22.47±0.3
	docking3	-10.03±0.3	-39.81±0.2	-5.42±0.0	21.51±0.2	-3.77±0.0	24.90±0.2	-3.77±0.0	11.94±0.4	-4.54±0.0	30.47±0.3
Chloroquine	docking1	-15.75±0.5	-37.34±0.3	-5.15±0.0	21.58±0.3	-3.58±0.0	24.70±0.3	-3.58±0.0	-11.26±0.7	-4.34±0.0	31.92±0.5
	docking2	-2.24±0.2	-28.22±0.3	-4.30±0.0	11.34±0.2	-2.99±0.0	14.51±0.2	-2.99±0.0	1.18±0.3	-3.70±0.0	16.84±0.3
	docking3	-3.93±0.1	-29.66±0.2	-4.53±0.0	14.36±0.2	-3.15±0.0	16.93±0.2	-3.15±0.0	-11.45±0.4	-3.87±0.0	21.31±0.2
Saquinavir	docking1	-27.48±0.4	-54.76±0.2	-7.78±0.0	45.40±0.3	-5.41±0.0	52.84±0.3	-5.41±0.0	32.33±0.6	-6.32±0.0	61.48±0.3
	docking2	-20.02±0.3	-48.31±0.3	-7.34±0.0	33.04±0.3	-5.10±0.0	38.16±0.3	-5.10±0.0	4.52±0.5	-5.99±0.0	41.17±0.4
	docking3	-11.67±0.4	-50.29±0.2	-6.95±0.0	25.78±0.3	-4.82±0.0	30.55±0.3	-4.82±0.0	4.74±0.7	-5.69±0.0	38.25±0.4
Darunavir	docking1	-17.53±0.8	-45.09±0.2	-6.65±0.0	36.01±0.6	-4.62±0.0	42.56±0.6	-4.62±0.0	-25.83±1.1	-5.47±0.0	47.38±0.7
	docking2	-22.42±0.5	-41.21±0.4	-5.59±0.0	33.57±0.3	-3.88±0.0	39.77±0.4	-3.88±0.0	-25.84±1.2	-4.67±0.0	42.51±0.4
	docking3	-23.40±0.4	-47.80±0.3	-6.19±0.0	36.30±0.3	-4.30±0.0	41.11±0.3	-4.30±0.0	-35.85±0.8	-5.12±0.0	45.87±0.3
Indinavir	docking1	-247.04±1.2	-59.01±0.2	-7.92±0.0	261.55±1.2	-5.50±0.0	270.79±1.2	-5.50±0.0	274.91±1.5	-6.43±0.0	278.27±1.2
	docking2	-308.15±1.8	-53.36±0.3	-8.16±0.0	314.79±1.7	-5.67±0.0	321.89±1.7	-5.50±0.0	330.29±1.9	-6.61±0.0	330.20±1.7
	docking3	-259.53±0.9	-40.34±0.3	-6.56±0.0	272.14±1.0	-4.56±0.0	278.73±1.0	-4.56±0.0	283.64±1.1	-5.40±0.0	283.66±1.0
Carfilzomib	docking2	-20.82±0.4	-44.06±0.3	-7.20±0.0	36.91±0.3	-5.00±0.0	43.34±0.3	-5.00±0.0	40.88±0.8	-5.88±0.0	48.88±0.4
	docking3	-17.47±0.3	-45.21±0.6	-6.66±0.0	30.82±0.3	-4.62±0.0	36.97±0.4	-4.62±0.0	15.74±0.7	-5.47±0.0	37.51±0.5
H-chloroquine	docking1	-7.17±0.2	-37.57±0.3	-5.38±0.0	18.30±0.2	-3.73±0.0	21.72±0.2	-3.73±0.0	-6.03±0.9	-4.51±0.0	28.34±0.4
	docking2	-21.20±0.4	-42.86±0.2	-5.46±0.0	29.33±0.2	-3.79±0.0	31.78±0.2	-3.79±0.0	-24.06±0.8	-5.46±0.0	29.33±0.3

Table S13. Binding free energy for eight drugs to dimeric M^{pro} (Cys145/Hid41) of each docking structure. Enthalpic contribution is obtained from Table S12 and the entropic contribution is calculated using interaction entropy (IE) or Normal mode methods, respectively. (All values are in kcal/mol)

Drug	Structure	IE	Nmode	GB^{HCT}_IE	GB^{OBC1}_IE	GB^{OBC2}_IE	PBSA_IE	GB^{HCT}_Nmode	GB^{OBC1}_Nmode	GB^{OBC2}_Nmode	PBSA_Nmode
Ritonavir	docking1	12.70±0.0	21.97±2.2	-28.63±0.3	-20.75±0.3	-25.06±0.7	-18.47±0.3	-19.34±2.2	-11.46±2.2	-15.78±2.3	-9.18±2.2
	docking2	13.64±0.0	22.33±2.2	-30.85±0.3	-22.27±0.3	-21.69±1.0	-18.24±0.4	-22.16±2.2	-13.58±2.2	-13.00±2.4	-9.55±2.2
	docking3	14.34±0.0	27.77±2.4	-37.68±0.3	-26.57±0.3	-33.66±0.7	-21.21±0.4	-24.25±2.4	-13.14±2.4	-20.24±2.5	-7.79±2.4
Arbidol	docking1	8.07±0.0	21.48±1.6	-33.79±0.2	-30.29±0.2	-72.82±0.7	-21.63±0.2	-20.39±1.6	-16.89±1.6	-59.42±1.7	-8.23±1.6
	docking2	11.69±0.0	22.77±1.7	-24.30±0.3	-19.92±0.3	-27.74±0.6	-15.95±0.3	-13.22±1.7	-8.85±1.7	-16.66±1.8	-4.87±1.7
	docking3	8.16±0.0	21.44±2.2	-25.59±0.2	-20.55±0.2	-33.50±0.5	-15.74±0.2	-12.31±2.2	-7.27±2.2	-20.22±2.3	-2.46±2.2
Chloroquine	docking1	15.01±0.0	19.49±2.2	-21.64±0.4	-16.95±0.5	-52.91±1.3	-10.49±0.3	-17.17±2.2	-12.48±2.3	-48.43±2.6	-6.02±2.2
	docking2	6.92±0.0	17.59±1.1	-16.49±0.2	-12.00±0.2	-25.33±0.5	-10.39±0.2	-5.83±1.1	-1.34±1.1	-14.67±1.2	0.28±1.1
	docking3	7.06±0.0	20.58±2.4	-16.70±0.2	-12.74±0.2	-41.12±0.5	-9.09±0.2	-3.18±2.4	0.78±2.4	-27.60±2.5	4.43±2.4
Saquinavir	docking1	13.28±0.0	25.00±2.3	-31.34±0.2	-21.52±0.2	-42.03±0.6	-13.80±0.4	-19.63±2.3	-9.81±2.3	-30.32±2.4	-2.09±2.3
	docking2	15.43±0.0	24.29±2.7	-27.19±0.3	-19.84±0.3	-53.52±0.5	-17.71±0.3	-18.34±2.7	-10.98±2.7	-44.67±2.7	-8.85±2.7
	docking3	14.53±0.0	24.82±1.3	-28.59±0.3	-21.69±0.2	-47.51±0.7	-14.86±0.3	-18.30±1.3	-11.4±1.3	-37.22±1.5	-4.57±1.3
Darunavir	docking1	20.59±0.0	21.95±2.3	-12.67±0.3	-4.10±0.3	-72.48±1.2	-0.13±0.3	-11.31±2.3	-2.74±2.3	-71.12±2.6	1.24±2.3
	docking2	20.04±0.0	23.34±1.4	-15.60±0.5	-7.70±0.4	-73.30±1.6	-5.74±0.4	-12.31±1.5	-4.40±1.5	-70.00±2.1	-2.44±1.5
	docking3	14.61±0.0	25.25±2.6	-26.49±0.2	-19.79±0.2	-96.74±0.9	-15.84±0.3	-15.85±2.6	-9.15±2.6	-86.10±2.8	-5.20±2.6
Indinavir	docking1	23.32±0.0	25.16±3.0	-29.11±0.3	-17.44±0.3	-13.32±1.0	-10.88±0.3	-27.26±3.0	-15.59±3.0	-11.48±3.2	-9.04±3.0
	docking2	37.66±0.0	26.20±2.6	-17.20±0.3	-7.60±0.3	0.80±0.9	-0.24±0.4	-28.67±2.6	-19.07±2.6	-10.67±2.8	-11.71±2.6
	docking3	27.77±0.0	30.47±2.1	-6.51±0.3	2.09±0.3	6.99±0.6	6.17±0.3	-3.82±2.1	4.79±2.1	9.69±2.2	8.87±2.1
Carfilzomib	docking2	12.95±0.0	27.28±2.3	-22.17±0.3	-13.54±0.3	-16.01±0.8	-8.88±0.3	-7.85±2.3	0.79±2.3	-1.68±2.4	5.45±2.3
	docking3	12.68±0.0	28.25±2.8	-25.83±0.5	-17.65±0.4	-38.88±0.5	-17.96±0.3	-10.26±2.8	-2.08±2.8	-23.31±2.8	-2.39±2.8
Hydroxychloroquine	docking1	10.40±0.0	21.62±2.6	-21.41±0.3	-16.34±0.3	-44.09±0.9	-10.50±0.3	-10.20±2.6	-5.13±2.6	-32.88±2.8	0.72±2.6
	docking2	9.32±0.0	23.97±2.2	-30.87±0.2	-26.76±0.3	-82.59±0.9	-15.54±0.3	-16.22±2.2	-12.11±2.2	-67.94±2.4	-0.89±2.2

Table S14. Binding free energy for eight drugs to dimeric M^{pro} (Cys145/Hid41) using 12 calculation methods. (All values are in kcal/mol)

Method	Ritonavir	Arbidol	Chloroquine	Indinavir	Saquinavir	Darunavir	Carfilzomib	H-chloroquine
GB^{HCT}	-45.94±0.3	-37.20±0.2	-27.94±0.3	-47.19±0.3	-43.45±0.3	-36.66±0.3	-36.82±0.4	-36.00±0.2
GB^{OBC1}	-36.75±0.3	-32.90±0.2	-23.56±0.3	-37.23±0.3	-35.43±0.2	-28.94±0.3	-28.41±0.3	-31.41±0.3
GB^{OBC2}	-40.36±0.8	-54.00±0.6	-49.45±0.8	-31.43±0.8	-62.10±0.6	-99.25±1.2	-40.26±0.6	-73.20±0.9
PBSA	-32.86±0.4	-27.08±0.2	-19.66±0.2	-31.23±0.3	-29.89±0.3	-25.65±0.3	-26.24±0.3	-22.88±0.3
GB^{HCT}_IE	-32.38±0.3	-27.89±0.2	-18.28±0.3	-17.61±0.3	-29.04±0.3	-18.25±0.3	-24.00±0.4	-26.14±0.2
GB^{OBC1}_IE	-23.19±0.3	-23.59±0.2	-13.90±0.3	-7.65±0.3	-21.02±0.2	-10.53±0.3	-15.60±0.3	-21.55±0.3
GB^{OBC2}_IE	-26.80±0.8	-44.69±0.6	-39.79±0.8	-1.84±0.8	-47.69±0.6	-80.84±1.2	-27.45±0.6	-63.34±0.9
PBSA _IE	-19.30±0.4	-17.77±0.2	-9.99±0.2	-1.65±0.3	-15.46±0.3	-7.23±0.3	-13.42±0.3	-13.02±0.3
GB^{HCT}_Nmode	-21.92±2.3	-15.31±1.8	-8.72±1.9	-19.92±2.6	-18.75±2.1	-13.15±2.1	-9.05±2.6	-13.21±2.4
GB^{OBC1}_Nmode	-12.73±2.3	-11.00±1.8	-4.35±1.9	-9.96±2.6	-10.73±2.1	-5.43±2.1	-0.65±2.6	-8.62±2.4
GB^{OBC2}_Nmode	-16.34±2.4	-32.10±1.9	-30.23±2.1	-4.15±2.7	-37.40±2.2	-75.74±2.5	-12.50±2.6	-50.41±2.6
PBSA_Nmode	-8.84±2.3	-5.19±1.8	-0.44±1.9	-3.96±2.6	-5.17±2.1	-2.14±2.1	1.53±2.6	-0.09±2.4

Table S15. The average decomposed energy values of each hot-spot residues in Ritonavir−M^{pro} (dimer Cys145/Hid41). (All values are in kcal/mol)

Residue	ΔE_{vdW}	ΔE_{ele}	ΔG_{gb}	ΔG_{np}	ΔH
Met165	-5.79	-3.11	1.88	-0.48	-7.51
Gln189	-5.48	-4.37	6.18	-0.86	-4.53
Glu166	-6.21	2.78	1.07	-0.88	-3.25
Met49	-3.21	-0.27	0.89	-0.44	-3.03
Asn142	-4.15	-1.78	4.13	-0.79	-2.59

Table S16. The average decomposed energy values of each hot-spot residues in Arbidol−M^{pro} (dimer Cys145/Hid41). (All values are in kcal/mol)

Residue	ΔE_{vdW}	ΔE_{ele}	ΔG_{gb}	ΔG_{np}	ΔH
Gln189	-6.30	-1.96	3.97	-0.88	-5.17
Met49	-3.23	-0.55	0.85	-0.43	-3.36
Met165	-3.12	0.23	0.26	-0.37	-3.00
Arg188	-2.86	-0.93	1.51	-0.15	-2.44

Table S17. The average decomposed energy values of each hot-spot residues in Saquinavir−M^{pro} (dimer Cys145/Hid41). (All values are in kcal/mol)

Residue	ΔE_{vdW}	ΔE_{ele}	ΔG_{gb}	ΔG_{np}	ΔH
Gln189	-7.32	-10.22	10.35	-1.30	-8.49
Met165	-4.31	-2.29	1.05	-0.48	-6.03
Glu166	-4.01	-0.12	2.11	-0.63	-2.65
Met49	-2.79	-0.17	1.03	-0.47	-2.41
Cys145	-1.64	-1.41	1.03	-0.18	-2.21
Thr190	-2.59	-1.80	2.39	-0.20	-2.20
Gln192	-1.99	-2.07	2.21	-0.23	-2.07
His163	-0.81	-3.29	2.14	-0.06	-2.01