Supporting Information

Computational Mutation Scanning and Drug Resistance

Mechanisms of HIV-1 Protease Inhibitors

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Supporting Information Available

Figure S1 for the RMSD and some key internuclear distances *versus* the simulation time for wild-type HIV-1 protease binding with inhibitors; Figure S2 for comparison between the X-ray structures of the WT and mutated HIV-1 protease; Figure S3 for the RMSD and some key internuclear distances *versus* the simulation time for SQV binding with the I54M mutant, APV binding with the V82F mutant, and IDV binding with the R8Q mutant; Tables S1 to S9 for the detailed energetic results in comparison with the corresponding experimental data. Tables S10 for the comparison between the X-ray structures of the WT and mutated HIV-1 protease in the RMSD of the backbone and ligand atoms. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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(A) SQV binding with HIV-1 protease
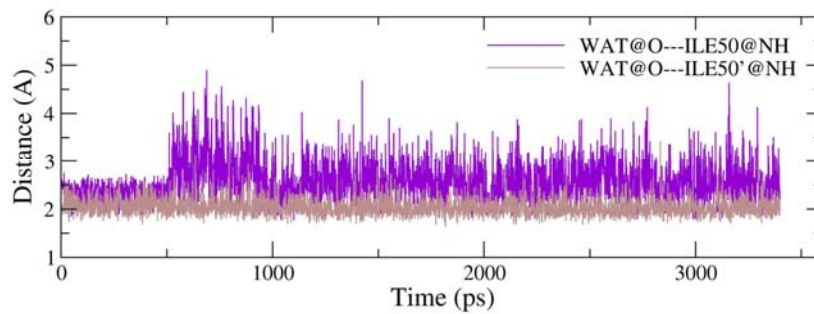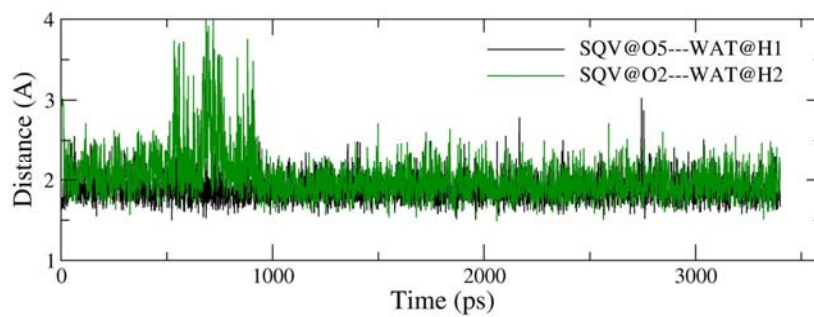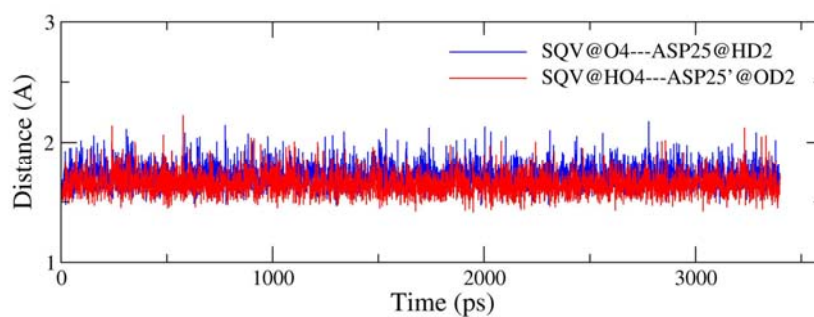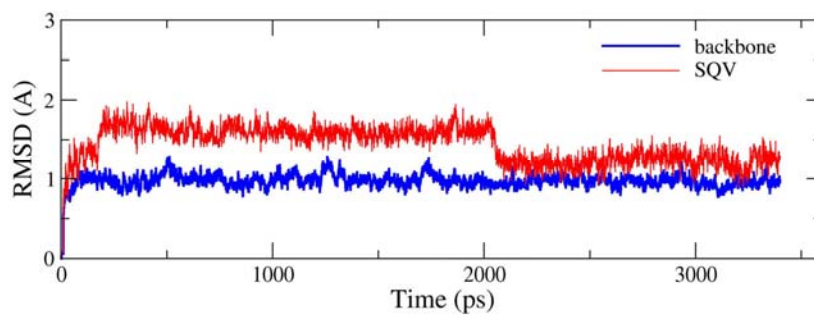
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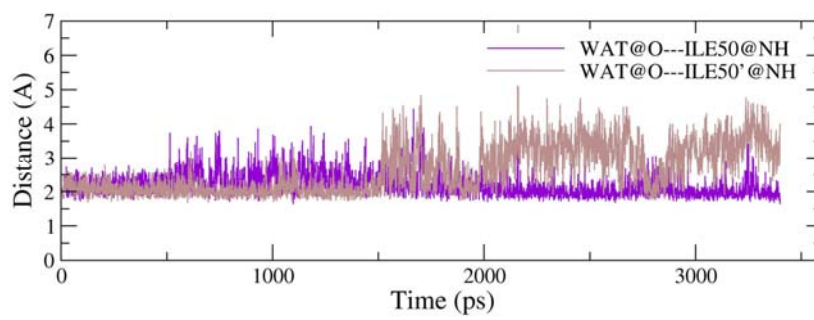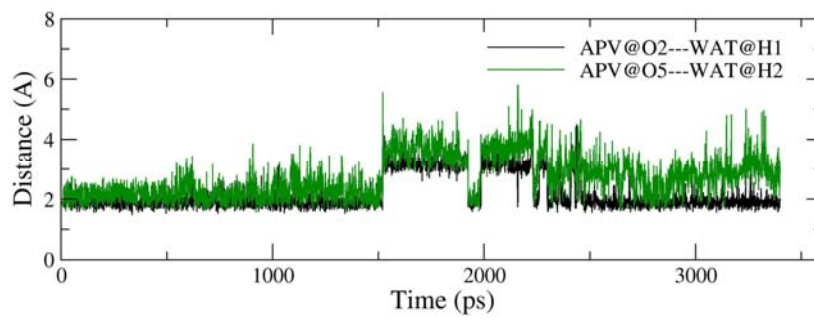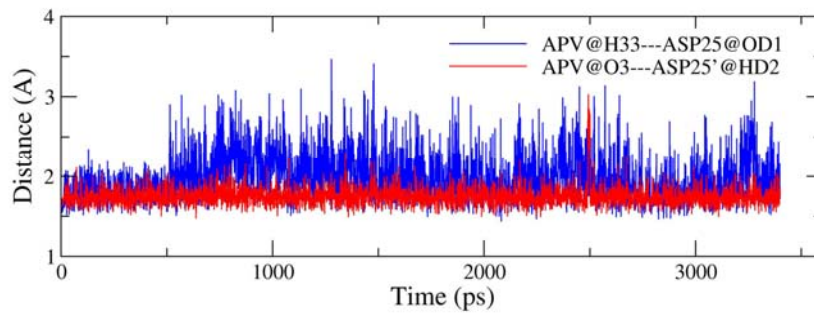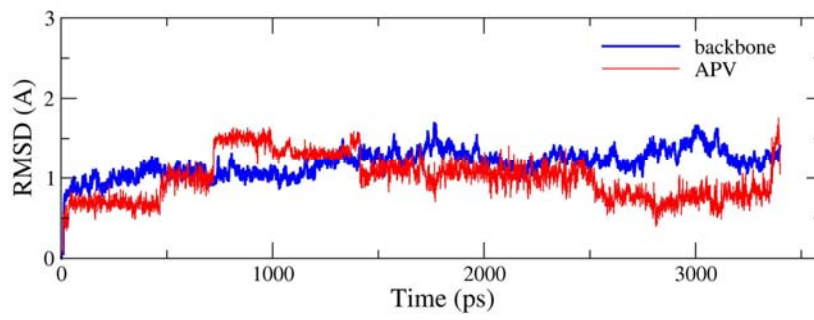
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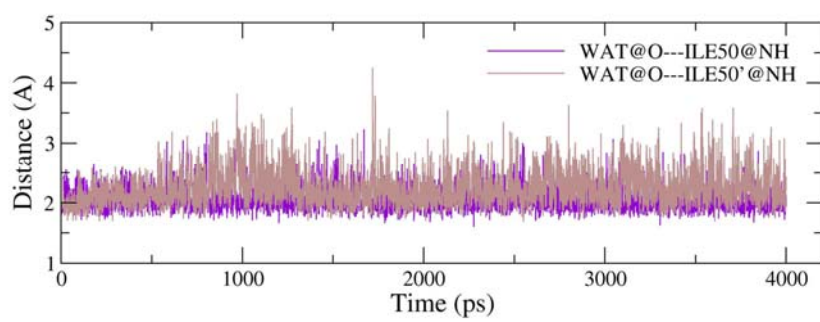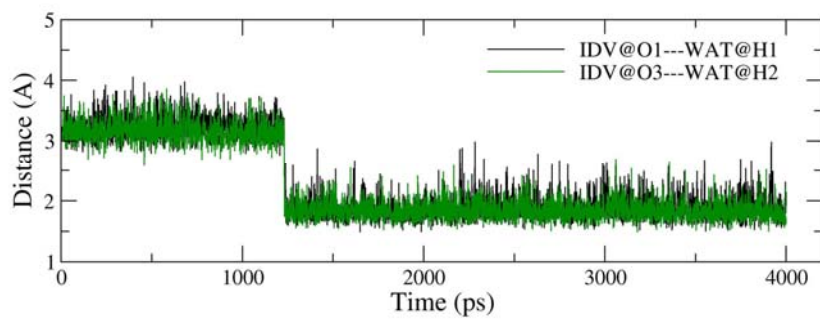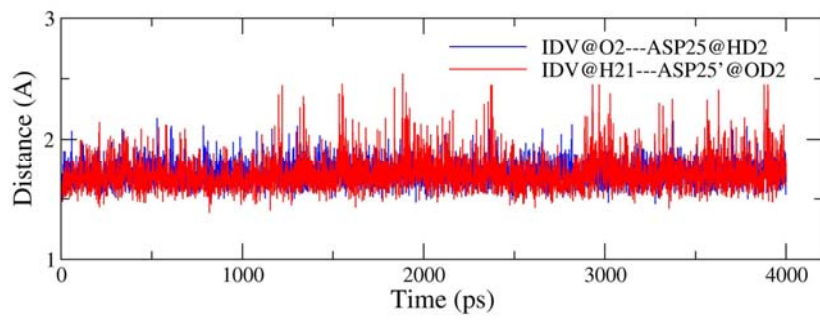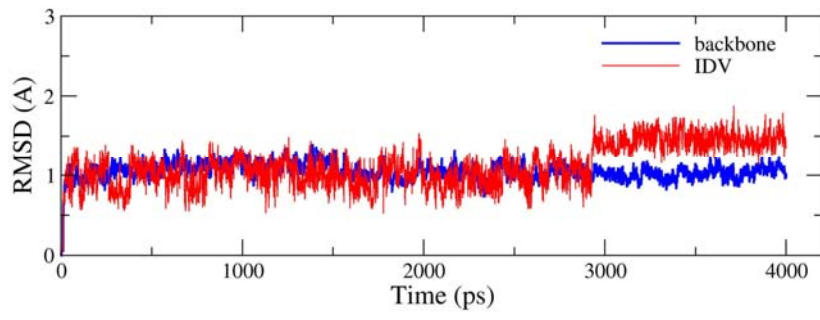
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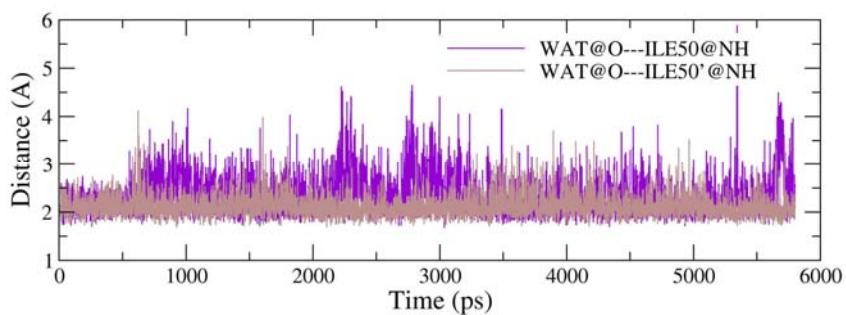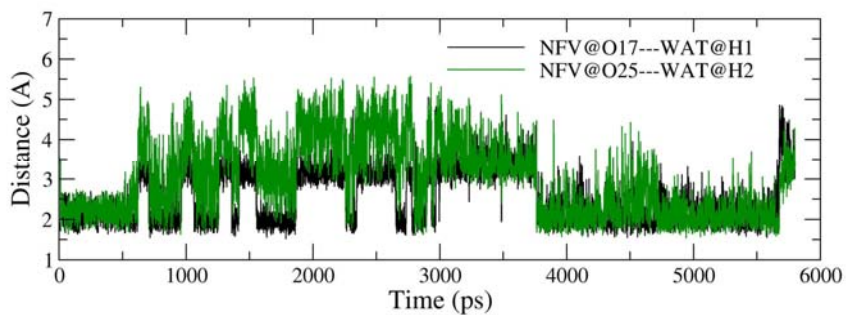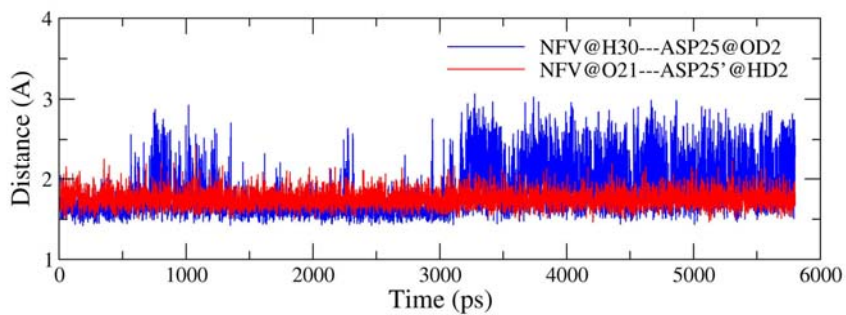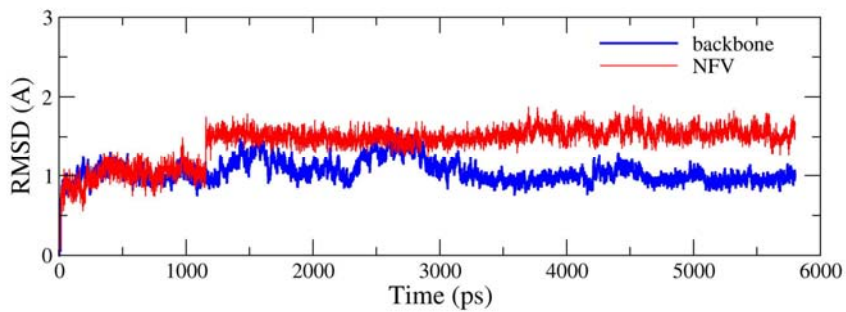
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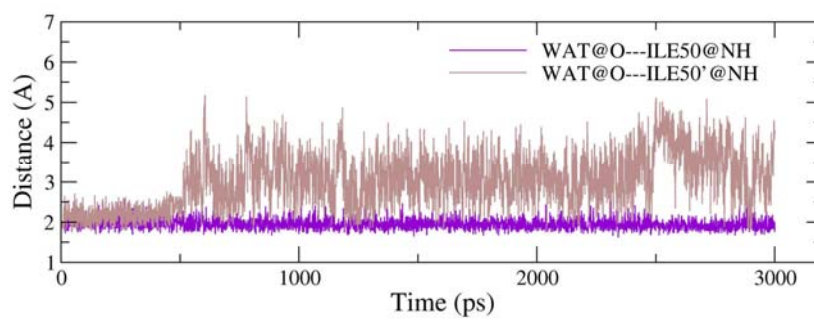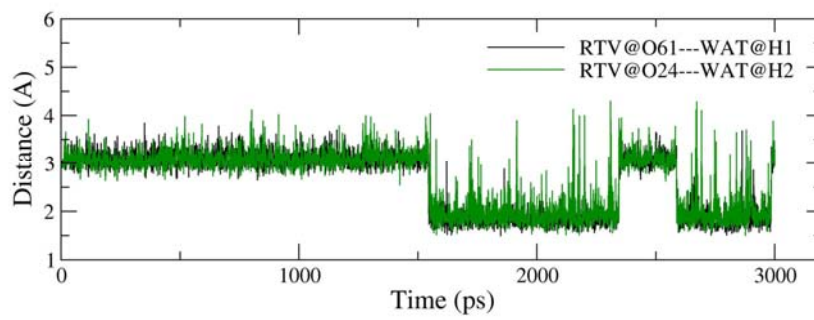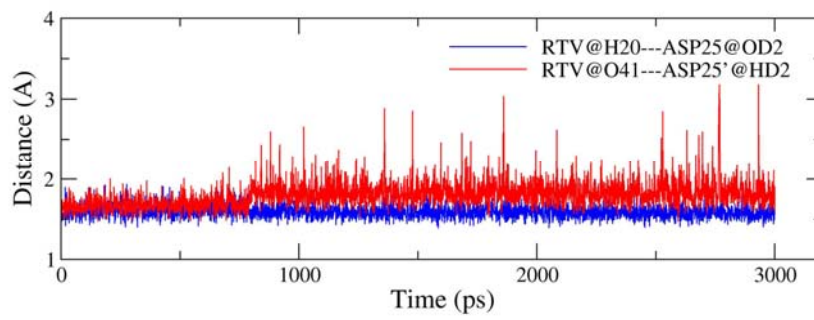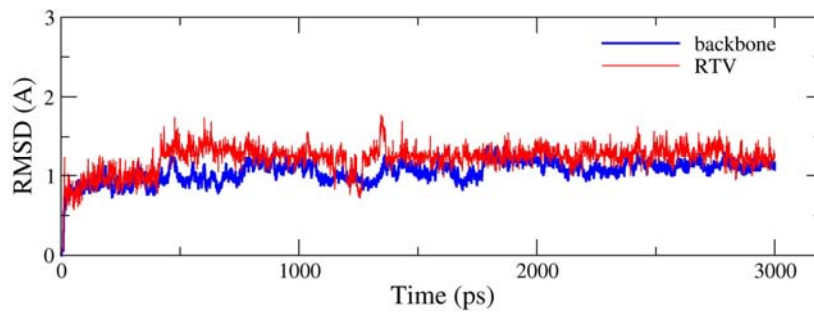
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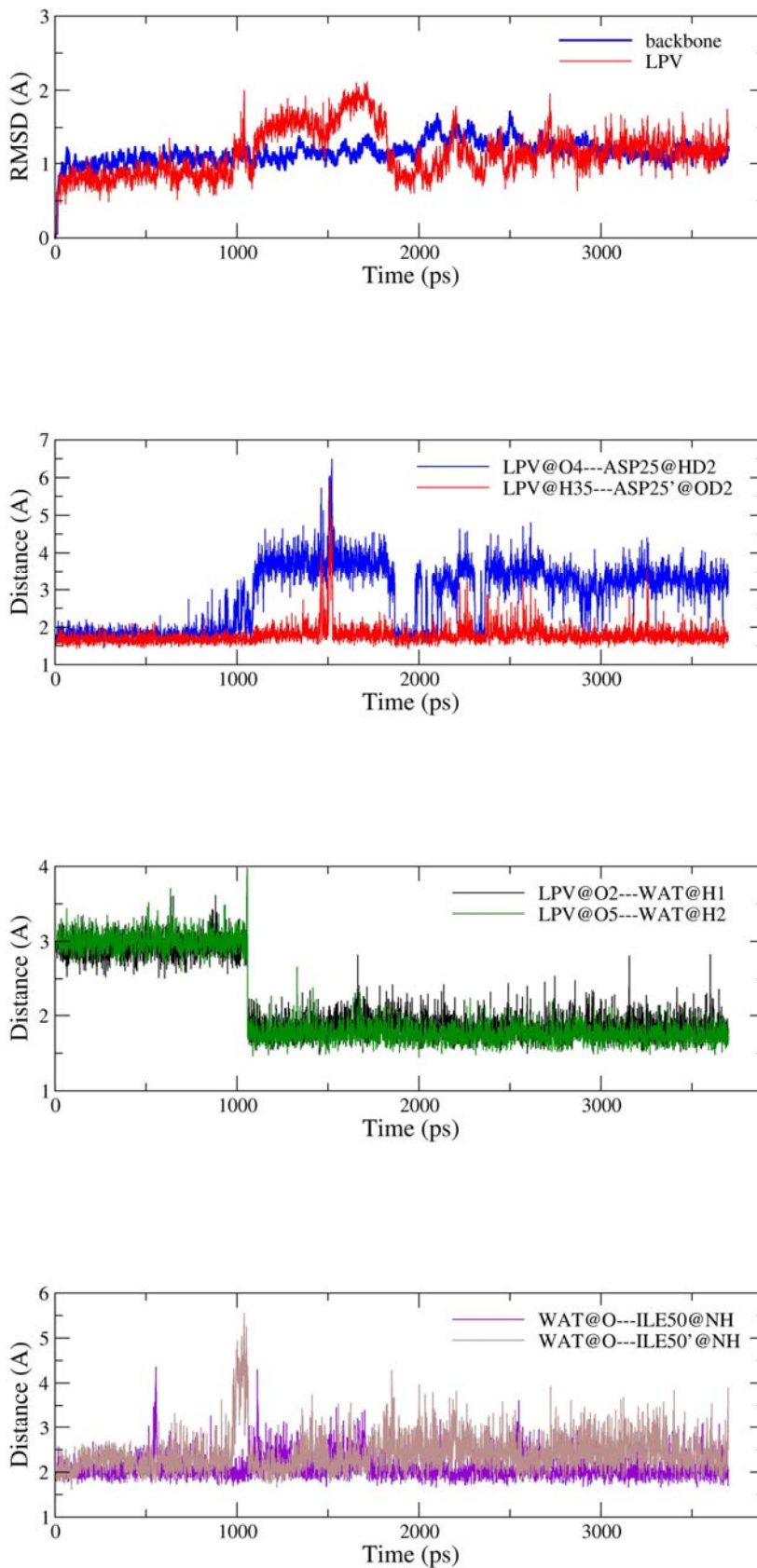
Figure S1. MD trajectories for HIV-1 protease binding with inhibitors: RMSD representing the root-mean-square deviation of the simulated positions of the protein backbone atoms and

inhibitor atoms from those in the initial structure; plots of the key internuclear distances *vs* the simulation time for the inhibitors binding with the HIV-1 protease. The distances shown in the figure are associated with the hydrogen bonds between the inhibitor and Asp25 (25'), between the inhibitor and water molecule (WAT), and between the inhibitor and Ile50 (50').

A

B

C

D

E

F

S9
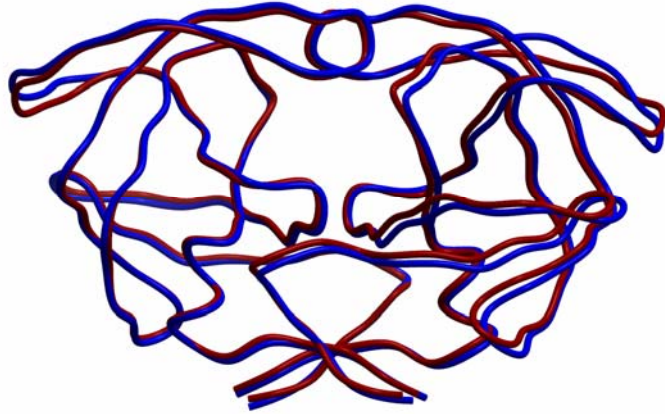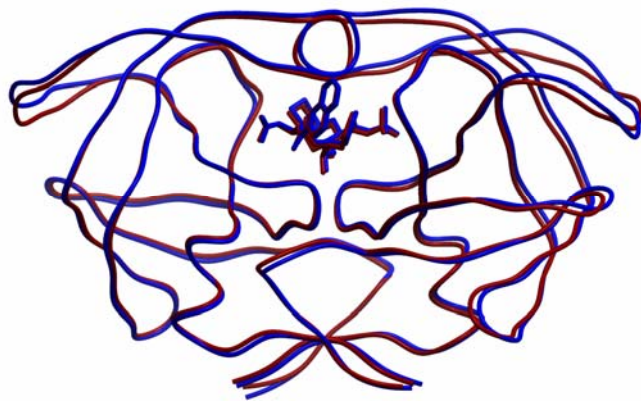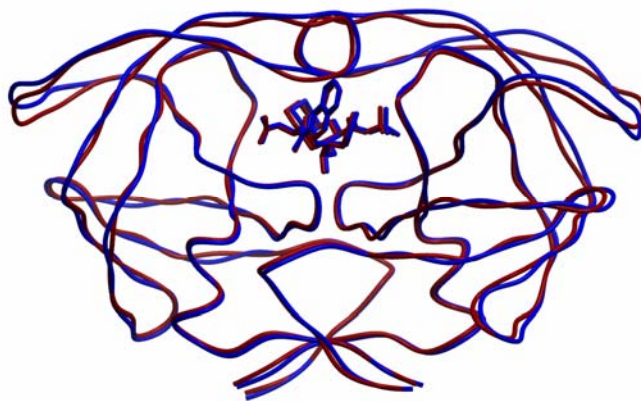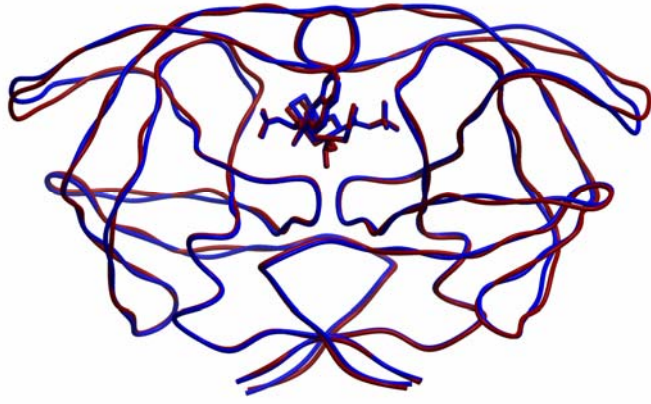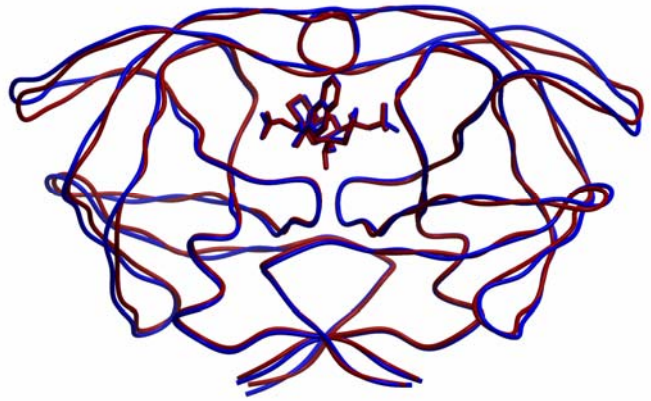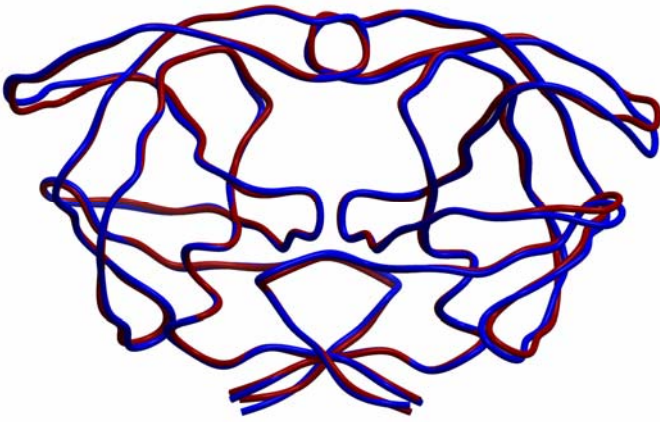
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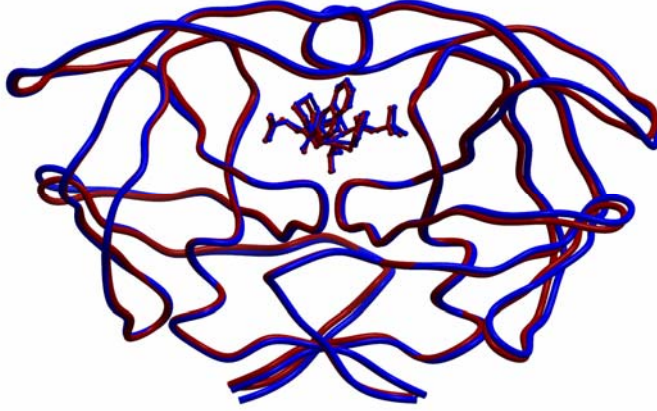
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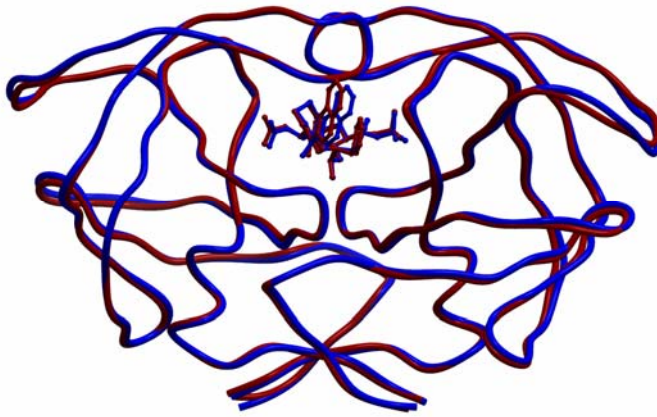
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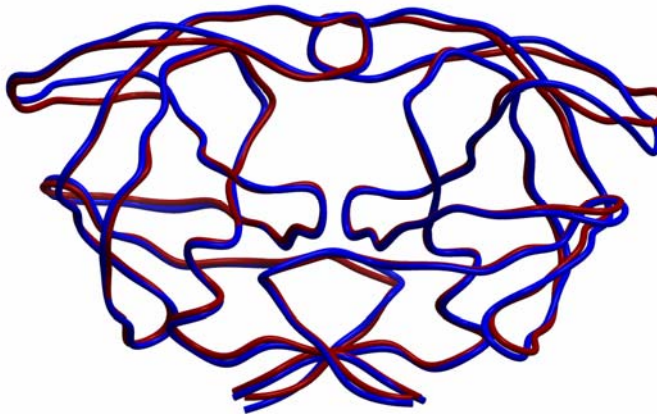
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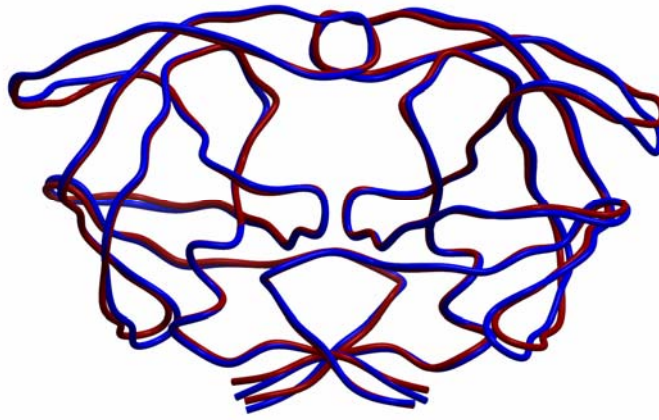
K

Figure S2. Comparison between the X-ray structures of the WT and mutated HIV-1 protease (WT in blue and mutant in red): (A) G48V mutant with the WT; (B) I50V mutant with the WT; (C) I54M mutant with the WT; (D) V82A mutant with the WT; (E) I84V mutant with the WT; (F) A71T/V82A mutant with the WT; (G) Q7K/I64V/T80N mutant with the WT; (H) Q7K/I64V/T80S mutant with the WT; (I) Q7K/D25N/L63P/V82A mutant with the WT; (J) T31D/V32I/L33V/E34A/E35G/M36I/S37E/I47V/V82I mutant with the WT; (K) L10F/I13V/G16A/K20M/V32I/K43T/M46V/I47V/I54M/I64V/A71T/V82A mutant with the WT.

(A) The I54M mutant binding with SQV
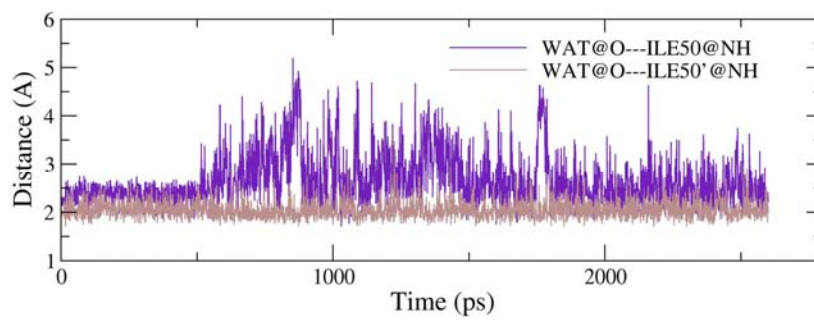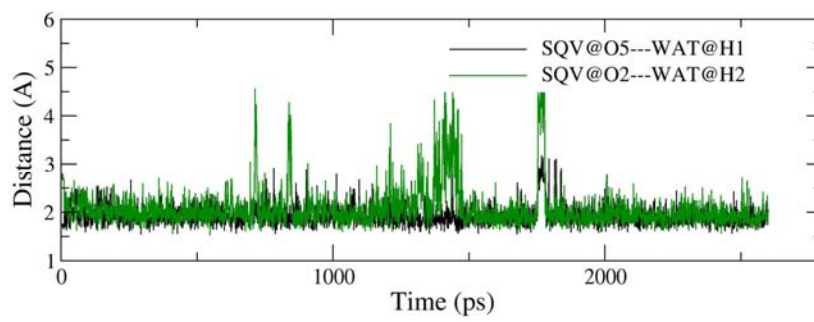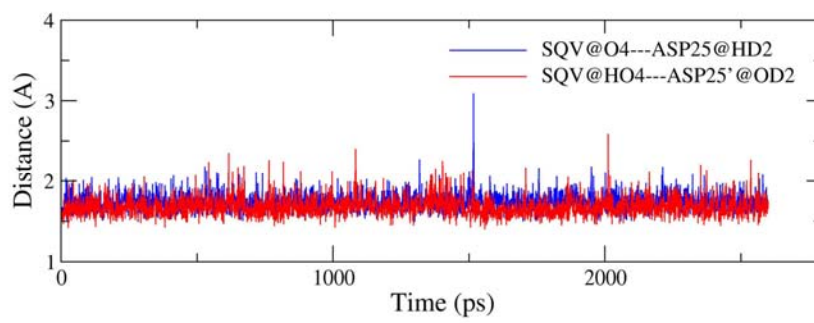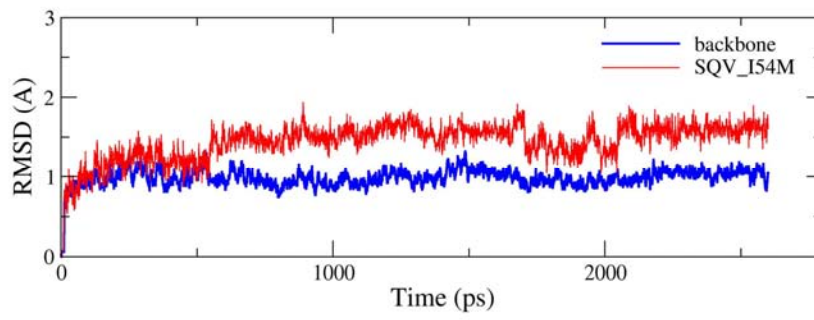
(B) V82F mutant binding with APV
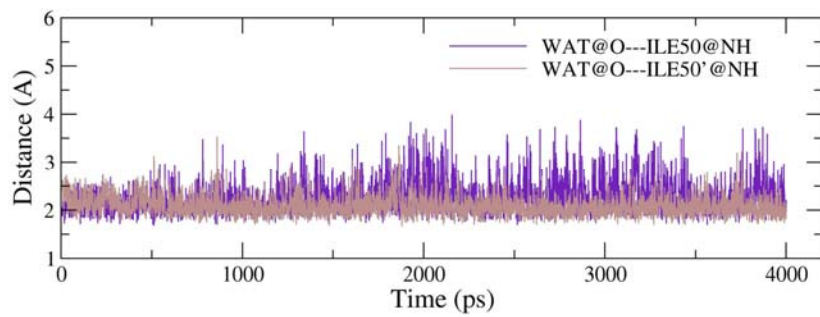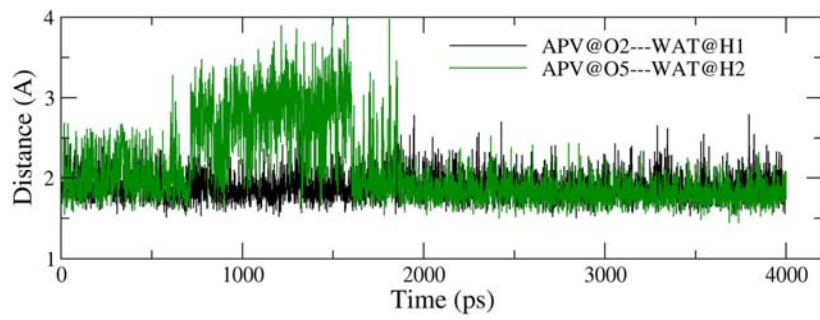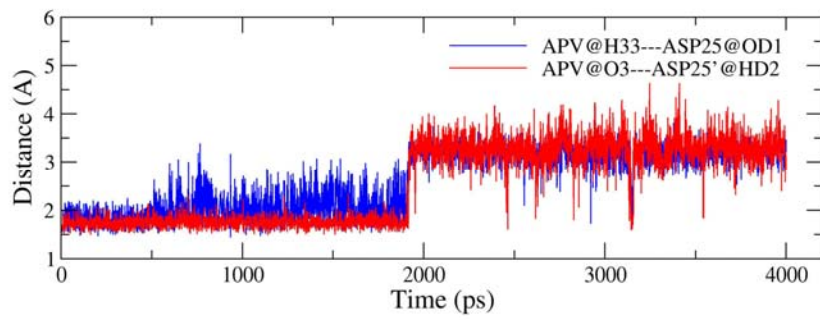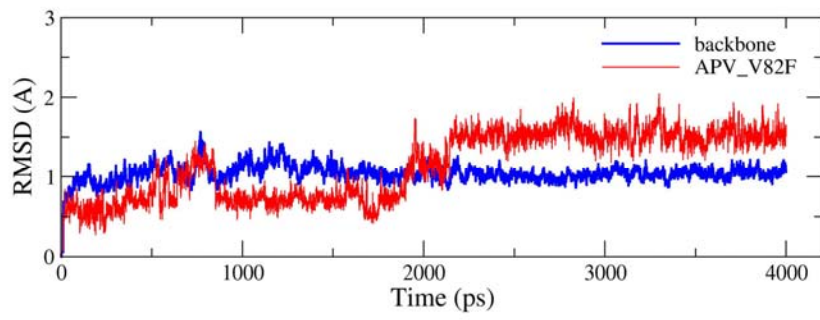
(C) The R8Q mutant binding with IDV
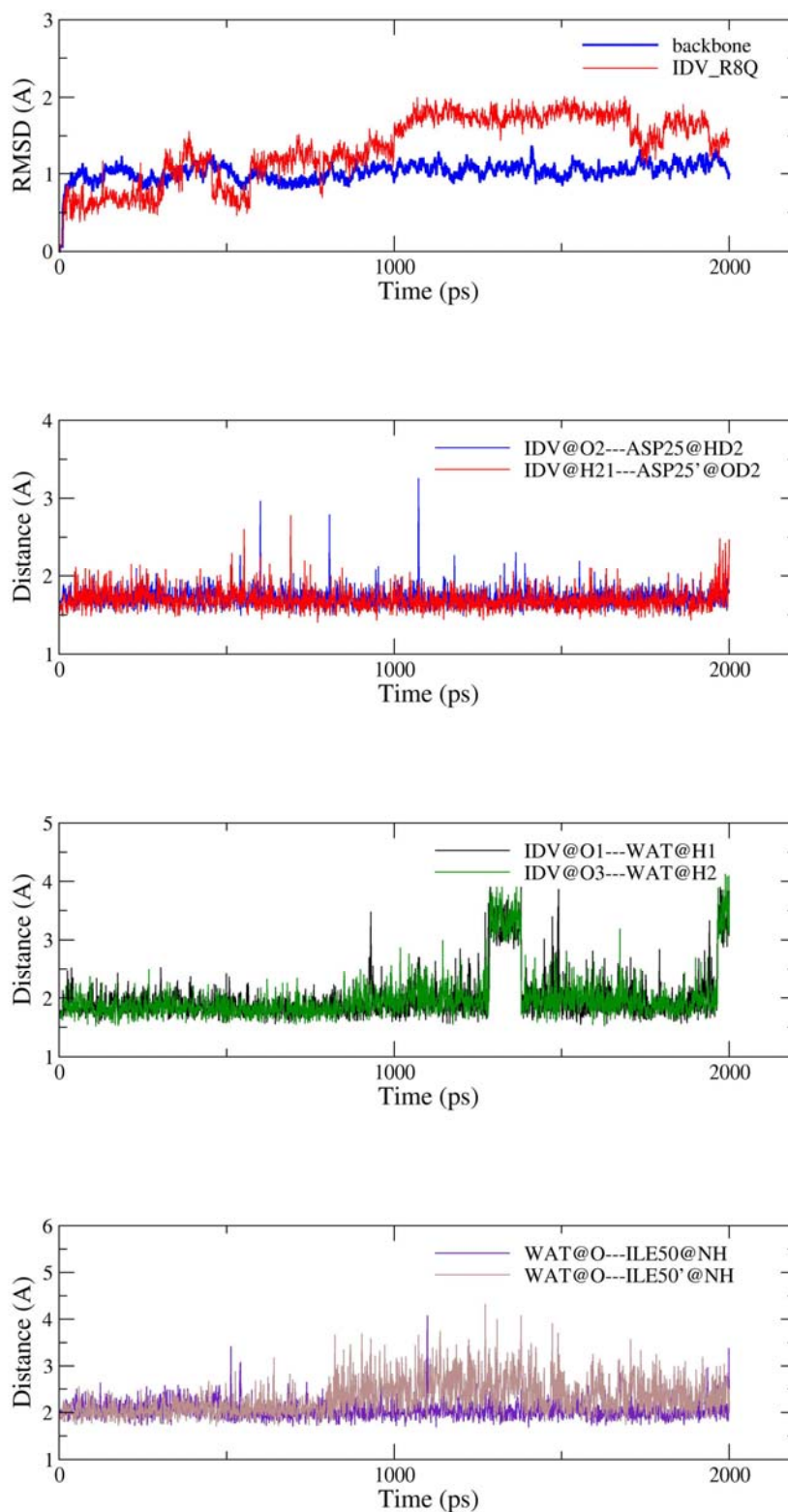
Figure S3. MD trajectories for the I54M mutant binding with SQV (A), the V82F mutant binding with APV (B), and the R8Q mutant binding with IDV (C): RMSD representing the root-mean-square deviation of the simulated positions of the protein backbone atoms and inhibitor atoms from those in the initial structure; plots of the key internuclear distances *vs* the

simulation time. The distances shown in the figure are associated with the hydrogen bonds between the inhibitor and Asp25 (25'), between the inhibitor and water molecule (WAT), and between the inhibitor and Ile50 (50').

Table S1. Binding free energies calculated for the WT HIV-1 protease with six drugs in clinical use (kcal/mol)

Inhibitor	ΔE_{ele}	ΔE_{vdW}	ΔE_{MM}	ΔG_{PB}	ΔG_{np}	ΔE_{bind}	$-T\Delta S_{conf}$	$-T\Delta S_{solv}$	$-T\Delta S$	ΔG_{bind}	ΔG_{exp}
SQV	-93.04	-70.90	-163.94	99.55	-6.98	-71.37	60.98	-23.49	37.49	-33.88	-14.32 [ref. 55]
RTV	-78.37	-74.96	-153.32	84.19	-6.98	-76.11	61.44	-25.56	35.88	-40.23	-14.92 [ref. 55]
IDV	-85.75	-74.89	-160.65	102.04	-6.97	-65.58	64.37	-25.04	39.33	-26.26	-13.14 [ref. 55]
NFV	-59.69	-71.17	-130.86	84.82	-6.30	-52.34	57.74	-23.70	34.04	-18.30	-12.24 [ref. 56]
APV	-74.29	-62.85	-137.15	86.00	-5.68	-56.83	54.86	-20.58	34.28	-22.55	-12.60 [ref. 56]
LPV	-63.82	-66.34	-130.16	78.19	-6.56	-58.53	56.22	-24.17	32.05	-26.48	-14.30 [ref. 57]

Table S2. Experimental and calculated binding free energy changes (kcal/mol) of SQV in complex with the wild-type and mutant HIV-1 protease

SQV	RL	$\Delta\Delta E_{ele}$	$\Delta\Delta E_{vdw}$	$\Delta\Delta E_{MM}$	$\Delta\Delta G_{pb}$	$\Delta\Delta G_{np}$	$\Delta\Delta E_{cal}$	$-T\Delta\Delta S_{conf}$	$-T\Delta\Delta S_{solv}$	$-T\Delta\Delta S$	$\Delta\Delta G_{cal}$	$\Delta\Delta G_{exp}$
WT	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
A71T/V82A	1.53 [ref. 68]	0.05	1.97	2.03	-0.28	-0.03	1.72	-1.92	0.57	-1.35	0.37	0.25
G48V	160.00 [ref. 55]	-0.92	7.43	6.52	-0.28	0.02	6.26	1.05	-0.22	0.83	7.09	3.01
G48V/L90M	1767.50 [ref. 59]	-1.00	7.55	6.54	-0.24	0.03	6.34	0.99	-0.15	0.84	7.18	4.44
I47V	0.50 [ref. 56]	0.08	0.49	0.57	-0.24	-0.01	0.31	-2.00	0.07	-1.93	-1.62	-0.41
I50V	24.00 [ref. 57]	-0.25	1.76	1.52	2.00	-0.07	3.45	-2.09	0.82	-1.27	2.18	1.89
I54M	5.00 [ref. 57]	-0.09	-0.05	-0.14	0.16	0.09	0.01	0.30	0.00	0.30	0.31	0.95
I54V	15.00 [ref. 57]	-0.05	0.09	0.04	0.12	0.00	0.16	-0.07	0.02	-0.05	0.11	1.61
I84V	17.00 [ref. 60]	0.05	2.85	2.90	1.26	-0.12	4.04	-2.09	0.69	-1.40	2.64	1.68
L10F	1.75 [ref. 70]	-0.10	-0.02	-0.12	0.09	-0.02	-0.06	0.10	0.01	0.11	0.05	0.33
L10F/I50V	33.70 [ref. 56]	-0.40	1.72	1.31	1.99	-0.07	3.24	-2.00	0.84	-1.16	2.08	2.09
L10F/I84V	21.00 [ref. 70]	-0.08	2.75	2.66	1.05	-0.10	3.62	-2.05	0.68	-1.37	2.25	1.81
L90M	2.70 [ref. 60]	-0.24	0.06	-0.17	0.08	-0.01	-0.10	-0.03	0.05	0.02	-0.08	0.59
M46I	1.00 [ref. 70]	-0.03	-0.01	-0.05	0.14	-0.01	0.08	0.14	-0.07	0.07	0.15	0.00
M46I/I84V	4.50 [ref. 69]	-0.02	2.83	2.81	1.20	-0.11	3.89	-2.01	0.62	-1.39	2.50	0.89
V32I	1.60 [ref. 69]	-0.22	0.43	0.22	-0.44	0.02	-0.21	1.26	-0.31	0.95	0.74	0.28
V32I/I84V	14.20 [ref. 69]	-0.16	3.16	3.00	0.57	-0.08	3.49	-0.90	0.39	-0.51	2.98	1.57

| V82A | 1.67 [*ref.* 62] | 0.13 | 1.96 | 2.10 | -0.14 | -0.05 | 1.90 | -2.02 | 0.60 | -1.42 | 0.48 | 0.30 |
| V82I | 7.30 [*ref.* 62] | 0.19 | -0.01 | 0.19 | -0.59 | -0.01 | -0.41 | 1.94 | -0.08 | 1.86 | 1.45 | 1.18 |

Table S3. Comparison between the CMS and MD results.

			RL	ΔE_{ele}	ΔE_{vdW}	ΔE_{MM}	ΔG_{PB}	ΔG_{np}	ΔE_{bind}	$-T\Delta S_{conf}$	$-T\Delta S_{solv}$	$-T\Delta S$	ΔG_{bind}
SQV	CMS	I54M	5	-93.13	-70.95	-164.08	99.71	-6.98	-71.36	61.28	-23.49	37.79	-33.57
	MD		[*ref.* 67]	-100.88	-70.72	-171.6	106.22	-7.06	-72.45	61.46	-23.27	38.19	-34.26

Table S4. Experimental and calculated binding free energy changes (kcal/mol) of RTV in complex with the wild-type and mutant HIV-1 protease

RTV	RL	$\Delta\Delta E_{ele}$	$\Delta\Delta E_{vdw}$	$\Delta\Delta E_{MM}$	$\Delta\Delta G_{pb}$	$\Delta\Delta G_{np}$	$\Delta\Delta E_{cal}$	$-T\Delta\Delta S_{conf}$	$-T\Delta\Delta S_{solv}$	$-T\Delta\Delta S$	$\Delta\Delta G_{cal}$	$\Delta\Delta G_{exp}$
WT	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
G48V	70.00 [*ref.* 55]	2.82	-0.68	2.13	-0.25	-0.09	1.79	1.92	-0.57	1.35	3.14	2.52
G48V/L90M	90.00 [*ref.* 55]	2.81	-0.68	2.12	-0.25	-0.09	1.79	1.97	-0.49	1.48	3.27	2.67
I84V	33.70 [*ref.* 64]	0.27	3.07	3.33	0.66	-0.13	3.86	-2.08	0.43	-1.65	2.21	2.09
L90M	5.00 [*ref.* 60]	-0.13	0.06	-0.07	-0.02	0.01	-0.09	-0.05	0.08	0.03	-0.06	0.95
M46I	1.90 [*ref.* 69]	-0.06	0.01	-0.06	0.01	-0.01	-0.06	-0.05	-0.04	-0.09	-0.15	0.38
M46I/I84V	9.40 [*ref.* 69]	0.21	3.05	3.25	0.62	-0.13	3.74	-2.09	0.39	-1.70	2.04	1.33
R8Q	23.10 [*ref.* 69]	-0.39	2.92	2.52	0.65	0.15	3.33	-1.11	0.53	-0.58	2.75	1.86
V32I	3.40 [*ref.* 69]	0.06	0.65	0.69	-1.01	0.03	-0.28	1.57	0.25	1.82	1.54	0.73
V32I/I84V	63.50 [*ref.* 69]	0.28	3.69	3.95	-0.15	-0.08	3.72	-0.50	0.66	0.16	3.88	2.46
V82A	11.20 [*ref.* 62]	-0.11	2.92	2.80	0.03	0.02	2.85	-1.56	1.07	-0.49	2.36	1.43
V82F	90.00 [*ref.* 60]	-0.76	1.77	1.00	0.91	-0.08	1.83	1.44	-0.08	1.36	3.19	2.67
V82F/I84V	700.00 [*ref.* 62]	-0.46	4.74	4.27	1.65	-0.20	5.71	-0.64	0.43	-0.21	5.50	3.89
V82I	14.70 [*ref.* 62]	-0.15	0.75	0.59	0.18	0.00	0.77	2.04	-0.14	1.90	2.67	1.59

Table S5. Experimental and calculated binding free energy changes (kcal/mol) of IDV in complex with the wild-type and mutant HIV-1 protease

IDV	RL	$\Delta\Delta E_{ele}$	$\Delta\Delta E_{vdw}$	$\Delta\Delta E_{MM}$	$\Delta\Delta G_{pb}$	$\Delta\Delta G_{np}$	$\Delta\Delta E_{cal}$	$-T\Delta\Delta S_{conf}$	$-T\Delta\Delta S_{solv}$	$-T\Delta\Delta S$	$\Delta\Delta G_{cal}$	$\Delta\Delta G_{exp}$
WT	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

	RL	$\Delta\Delta E_{ele}$	$\Delta\Delta E_{vdw}$	$\Delta\Delta E_{MM}$	$\Delta\Delta G_{pb}$	$\Delta\Delta G_{np}$	$\Delta\Delta E_{cal}$	$-T\Delta\Delta S_{conf}$	$-T\Delta\Delta S_{solv}$	$-T\Delta\Delta S$	$\Delta\Delta G_{cal}$	$\Delta\Delta G_{exp}$
A71T/V82A	3.50 [ref. 68]	-0.51	1.98	1.48	0.37	-0.03	1.82	-1.48	0.22	-1.26	0.56	0.74
G48V	5.00 [ref. 60]	0.30	0.52	0.83	-1.53	-0.05	-0.75	2.01	-0.74	1.27	0.52	0.95
G48V/L90M	7.37 [ref. 68]	0.52	0.47	1.00	-1.74	-0.03	-0.77	2.04	-0.70	1.34	0.57	1.18
I47V	3.00 [ref. 70]	-0.46	1.24	0.79	0.28	-0.02	1.05	-2.06	0.19	-1.87	-0.82	0.65
I50V	10.00 [ref. 70]	-3.64	3.15	-0.48	3.33	-0.03	2.82	-1.93	0.24	-1.69	1.13	1.37
I84V	8.10 [ref. 64]	-0.34	2.28	1.94	1.29	-0.09	3.14	-1.98	-0.04	-2.02	1.12	1.24
L10F	4.00 [ref. 70]	0.13	-0.20	-0.06	0.14	0.00	0.09	-0.04	-0.05	-0.09	0.00	0.82
L10F/I84V	24.00 [ref. 70]	-0.42	2.16	1.74	1.40	-0.10	3.04	-1.91	-0.07	-1.98	1.06	1.89
L90M	1.40 [ref. 60]	0.23	-0.08	0.16	-0.51	-0.01	-0.36	0.06	0.01	0.07	-0.29	0.20
M46I	4.00 [ref. 70]	0.05	-0.05	0.01	-0.15	0.00	-0.14	0.01	-0.08	-0.07	-0.21	0.82
M46I/I84V	21.50 [ref. 69]	-0.46	2.25	1.81	1.21	-0.10	2.92	-2.00	-0.14	-2.14	0.78	1.82
R8Q	8.20 [ref. 69]	5.66	1.97	7.64	-2.12	0.21	5.73	-2.79	0.97	-1.82	3.91	1.25
V32I	8.00 [ref. 69]	-0.14	0.59	0.46	-0.40	0.02	0.08	1.76	0.10	1.86	1.94	1.23
V32I/I84V	80.30 [ref. 69]	-0.54	2.85	2.32	1.12	-0.08	3.36	-0.25	0.01	-0.24	3.12	2.60
V82A	2.70 [ref. 68]	-0.57	1.93	1.36	0.76	-0.05	2.07	-1.50	0.17	-1.33	0.74	0.59
V82F	84.70 [ref. 69]	0.81	1.73	2.54	-0.47	0.02	2.09	1.27	-0.24	1.03	3.12	2.63
V82F/I84V	128.00 [ref. 57]	0.20	3.61	3.83	0.99	-0.06	4.76	-0.61	-0.07	-0.68	4.08	2.88
V82I	6.90 [ref. 69]	-0.61	-0.39	-0.99	0.83	0.00	-0.16	2.35	-0.17	2.18	2.02	1.15

Table S6. Experimental and calculated binding free energy changes (kcal/mol) of NFV in complex with the wild-type and mutant HIV-1 protease

NFV	RL	$\Delta\Delta E_{ele}$	$\Delta\Delta E_{vdw}$	$\Delta\Delta E_{MM}$	$\Delta\Delta G_{pb}$	$\Delta\Delta G_{np}$	$\Delta\Delta E_{cal}$	$-T\Delta\Delta S_{conf}$	$-T\Delta\Delta S_{solv}$	$-T\Delta\Delta S$	$\Delta\Delta G_{cal}$	$\Delta\Delta G_{exp}$
WT	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
G48V	3.00 [ref. 60]	-0.11	-0.51	-0.62	0.49	-0.03	-0.16	2.00	-0.21	1.79	1.63	0.65
G48V/L90M	4.00 [ref. 55]	-0.03	-0.48	-0.51	0.41	-0.03	-0.13	1.97	-0.17	1.80	1.67	0.82
I84V	7.50 [ref. 64]	-0.47	2.28	1.81	1.75	-0.12	3.44	-1.99	0.41	-1.58	1.86	1.20
L90M	2.00 [ref. 55]	0.15	0.04	0.19	-0.18	0.01	0.02	-0.08	0.03	-0.05	-0.03	0.41
V82A	4.29 [ref. 62]	0.90	1.76	2.66	0.02	-0.04	2.64	-1.57	0.29	-1.28	1.36	0.86
V82F	15.00 [ref. 60]	0.32	2.39	2.71	0.39	-0.02	3.07	0.72	-0.02	0.70	3.77	1.61

	RL	$\Delta\Delta E_{ele}$	$\Delta\Delta E_{vdw}$	$\Delta\Delta E_{MM}$	$\Delta\Delta G_{pb}$	$\Delta\Delta G_{np}$	$\Delta\Delta E_{cal}$	$-T\Delta\Delta S_{conf}$	$-T\Delta\Delta S_{solv}$	$-T\Delta\Delta S$	$\Delta\Delta G_{cal}$	$\Delta\Delta G_{exp}$
V82F/I84V	86.00 [ref. 62]	-0.09	4.33	4.24	1.98	-0.13	6.08	-1.35	0.47	-0.88	5.20	2.64
V82I	17.50 [ref. 62]	1.08	-0.08	0.99	-0.01	-0.01	0.98	2.18	-0.22	1.96	2.94	1.70

Table S7. Experimental and calculated binding free energy changes (kcal/mol) of APV in complex with the wild-type and mutant HIV-1 protease

APV	RL	$\Delta\Delta E_{ele}$	$\Delta\Delta E_{vdw}$	$\Delta\Delta E_{MM}$	$\Delta\Delta G_{pb}$	$\Delta\Delta G_{np}$	$\Delta\Delta E_{cal}$	$-T\Delta\Delta S_{conf}$	$-T\Delta\Delta S_{solv}$	$-T\Delta\Delta S$	$\Delta\Delta G_{cal}$	$\Delta\Delta G_{exp}$
WT	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
G48V	4.00 [ref. 55]	0.85	-0.12	0.75	-0.87	-0.03	-0.15	1.87	-0.13	1.74	1.59	0.82
G48V/L90M	11.00 [ref. 55]	1.12	-0.26	0.87	-1.00	-0.03	-0.17	1.77	-0.04	1.73	1.56	1.42
I47V	0.67 [ref. 66]	-0.61	1.12	0.52	0.50	-0.02	1.00	-1.98	0.28	-1.70	-0.70	-0.24
I50V	65.00 [ref. 57]	-3.40	3.45	0.07	3.31	-0.02	3.36	-1.70	0.29	-1.41	1.95	2.48
I84V	23.00 [ref. 70]	-0.30	2.54	2.26	1.44	-0.09	3.61	-1.98	0.01	-1.97	1.64	1.86
L10F	0.83 [ref. 69]	-0.12	-0.06	-0.17	0.04	0.00	-0.13	0.16	-0.01	0.15	0.02	-0.11
L10F/I50V	60.00 [ref. 69]	-3.44	3.31	-0.11	3.28	-0.03	3.15	-1.70	0.30	-1.40	1.75	2.43
L10F/I84V	20.00 [ref. 70]	-0.23	2.45	2.23	1.33	-0.08	3.48	-1.75	-0.04	-1.79	1.69	1.78
L90M	3.00 [ref. 55]	0.18	-0.07	0.12	-0.04	0.00	0.07	-0.06	0.04	-0.02	0.05	0.65
M46I	0.50 [ref. 66]	0.14	0.00	0.16	-0.11	0.00	0.05	-0.09	-0.03	-0.12	-0.07	-0.41
V82A	1.73 [ref. 62]	0.14	1.50	1.65	-0.03	-0.03	1.59	-1.64	0.45	-1.19	0.40	0.33
V82F	0.35 [ref. 62]	0.33	0.62	0.96	0.21	-0.01	1.16	1.53	-0.19	1.34	2.50	-0.62
V82F/I84V	100.00 [ref. 62]	0.23	3.01	3.25	1.57	-0.07	4.74	-0.24	-0.10	-0.34	4.40	2.73
V82I	3.30 [ref. 62]	0.21	-0.05	0.17	0.00	0.01	0.18	1.93	-0.06	1.87	2.05	0.71

Table S8. Experimental and calculated binding free energy changes (kcal/mol) of LPV in complex with the wild-type and mutant HIV-1 protease

LPV	RL	$\Delta\Delta E_{ele}$	$\Delta\Delta E_{vdw}$	$\Delta\Delta E_{MM}$	$\Delta\Delta G_{pb}$	$\Delta\Delta G_{np}$	$\Delta\Delta E_{cal}$	$-T\Delta\Delta S_{conf}$	$-T\Delta\Delta S_{solv}$	$-T\Delta\Delta S$	$\Delta\Delta G_{cal}$	$\Delta\Delta G_{exp}$
WT	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
L10I/L90M	1.40 [ref. 65]	-0.05	0.02	-0.03	-0.09	0.01	-0.12	-0.12	0.05	-0.07	-0.19	0.20
M46I/I54V	1.50 [ref. 65]	0.18	0.07	0.25	-0.02	0.00	0.23	-0.09	-0.06	-0.15	0.08	0.24
V82A	3.77 [ref. 58]	-0.13	1.15	1.03	0.12	-0.03	1.12	-0.78	0.43	-0.35	0.77	0.79
V82A/I84V	7.60 [ref. 65]	-0.27	3.46	3.19	1.16	-0.09	4.26	-2.74	1.50	-1.24	3.02	1.20

	RL	ΔE_{ele}	ΔE_{vdW}	ΔE_{MM}	ΔG_{PB}	ΔG_{np}	ΔE_{bind}	$-T\Delta S_{conf}$	$-T\Delta S_{solv}$	$-T\Delta S$	ΔG_{bind}	$\Delta\Delta G_{bind}$
V82F	2.85 [ref. 58]	-0.03	1.17	1.14	0.55	-0.04	1.65	0.20	0.01	0.21	1.86	0.62
V82T	2.77 [ref. 58]	-0.06	0.46	0.40	0.92	-0.01	1.30	-0.04	0.15	0.11	1.41	0.60

Table S9. Comparison of the CMS with MD results calculated for the mutations that induce binding mode changes.

			RL	ΔE_{ele}	ΔE_{vdW}	ΔE_{MM}	ΔG_{PB}	ΔG_{np}	ΔE_{bind}	$-T\Delta S_{conf}$	$-T\Delta S_{solv}$	$-T\Delta S$	ΔG_{bind}	$\Delta\Delta G_{bind}$
IDV	CMS	R8Q	8.20	-80.09	-72.92	-153.01	99.92	-6.76	-59.85	61.58	-24.07	37.51	-22.34	3.92
	MD		[ref. 69]	-69.58	-71.17	-140.75	82.74	-6.72	-64.73	61.80	-23.42	38.38	-26.35	-0.09
APV	CMS	V82F	0.35	-73.96	-62.23	-136.19	86.21	-5.69	-55.67	56.39	-20.77	35.62	-20.05	2.50
	MD		[ref. 62]	-62.14	-61.14	-123.29	73.97	-5.40	-54.72	51.11	-19.17	31.94	-22.78	-0.23

Table S10. Comparison between the overall X-ray crystal structures of wild-type HIV-1 protease and its mutants. All of the crystal structures have a ligand (SQV) bound in the binding pocket, unless indicated otherwise (N.A.: Not Applicable, with an inhibitor other than SQV).

Mutation type of HIV-1 protease (pdb entry)	RMSD of backbone atoms	RMSD of ligand atoms
G48V (3CYW)	0.60	N.A.
I50V (3CYX)	0.55	0.21
I54M (3D1X)	0.47	0.10
V82A (2NMY)	0.59	0.17
I84V (2NNK)	0.64	0.19
A71T/V82A (1ODX)	0.43	N.A.
Q7K/I64V/T80N (2FGV)	0.55	0.55
Q7K/I64V/T80S (2FGU)	0.53	0.57
Q7K/D25N/L63P/V82A (1MTB)	0.37	0.62
T31S/V32I/L33V/E34A/E35G/ M36I/S37E/I47V/V82I (1BDQ)	0.69	N.A.
L10F/I13V/G16A/K20M/V32I/K43T/M46V/ I47V/I54M/I64V/A71V/V82A (2RKF)	0.48	N.A.