Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

Molecular Investigation of the Dual Inhibition Mechanism for Targeted P53 Regulator MDM2 / MDMX Inhibitors

*Xiaoyu Zhao, Danyang Xiong, Song Luo, Lili Duan**

School of Physics and Electronics, Shandong Normal University, Jinan, 250014, China

Corresponding author (duanll@sdnu.edu.cn)

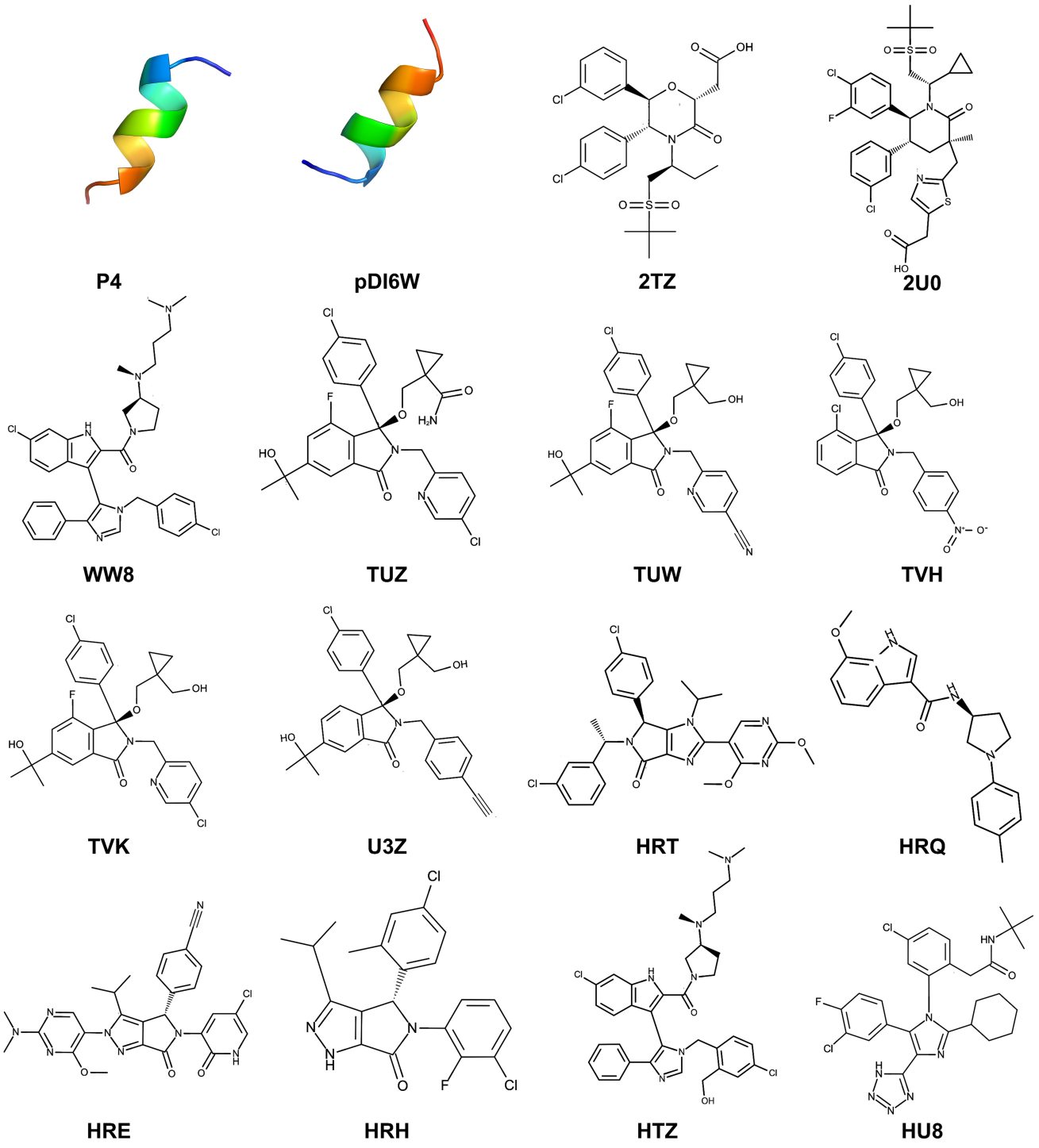

Figure S1. The structure of 16 potential inhibitors, including two short peptides and 14 non-peptides inhibitors.

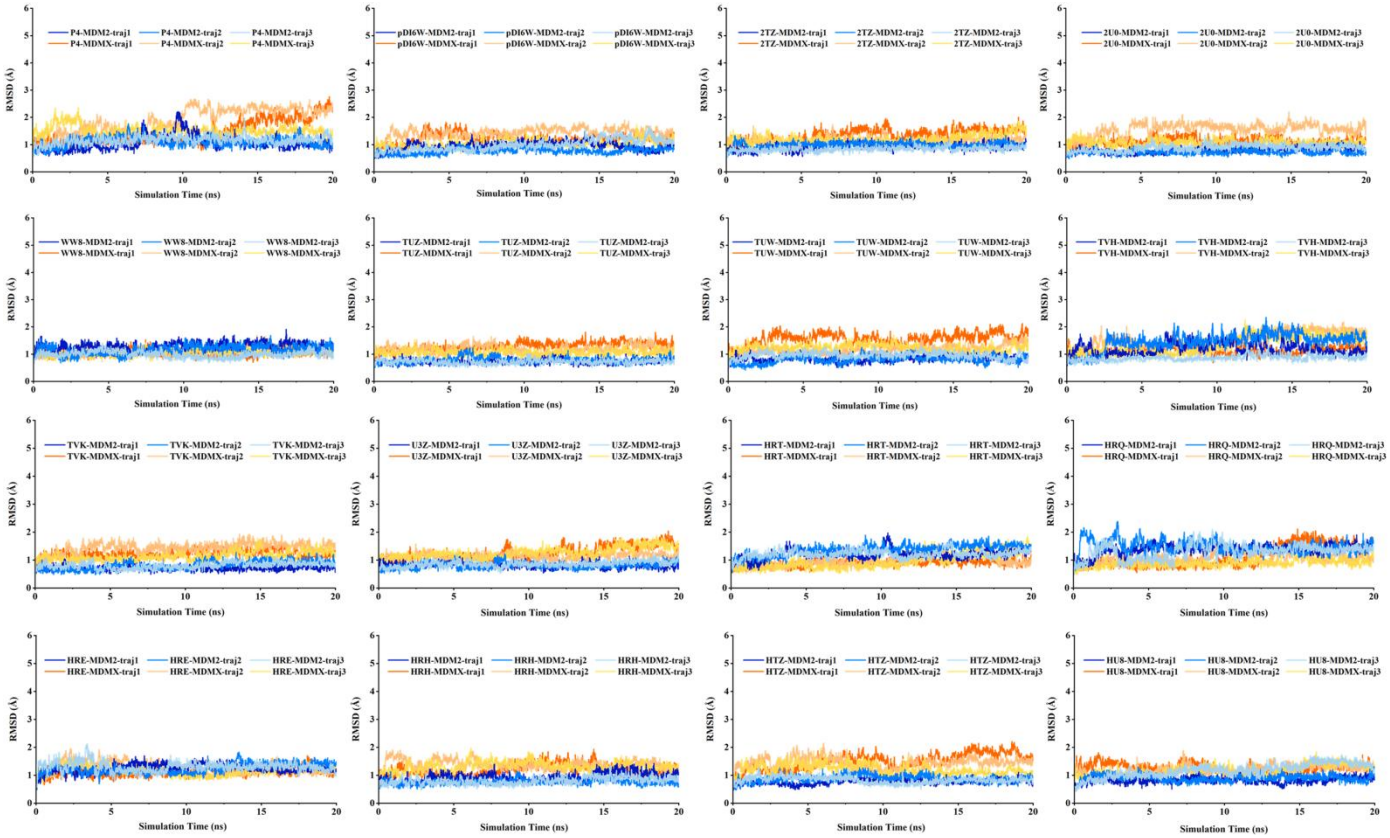

Figure S2. The root mean square deviation (RMSD) of the protein backbone atoms relative to the corresponding initial conformation for the 16-pair systems, and three MD trajectories are shown for each system, respectively.

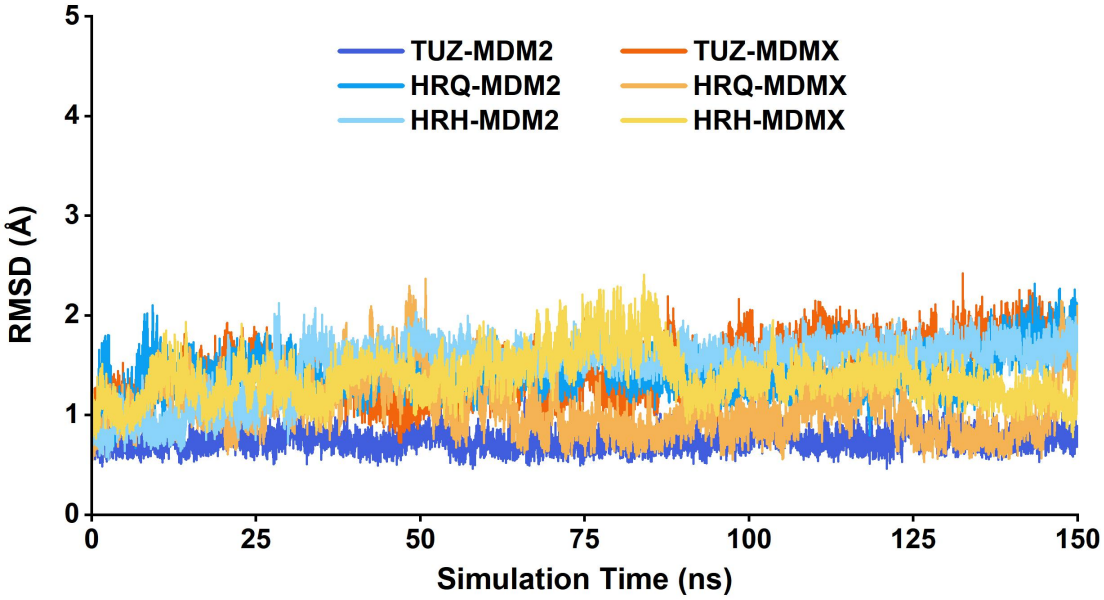

Figure S3. The root mean square deviation (RMSD) of the protein backbone atoms relative to the corresponding initial conformation for TUZ, HRQ, and HRH extended to 150 ns MD simulation, respectively.

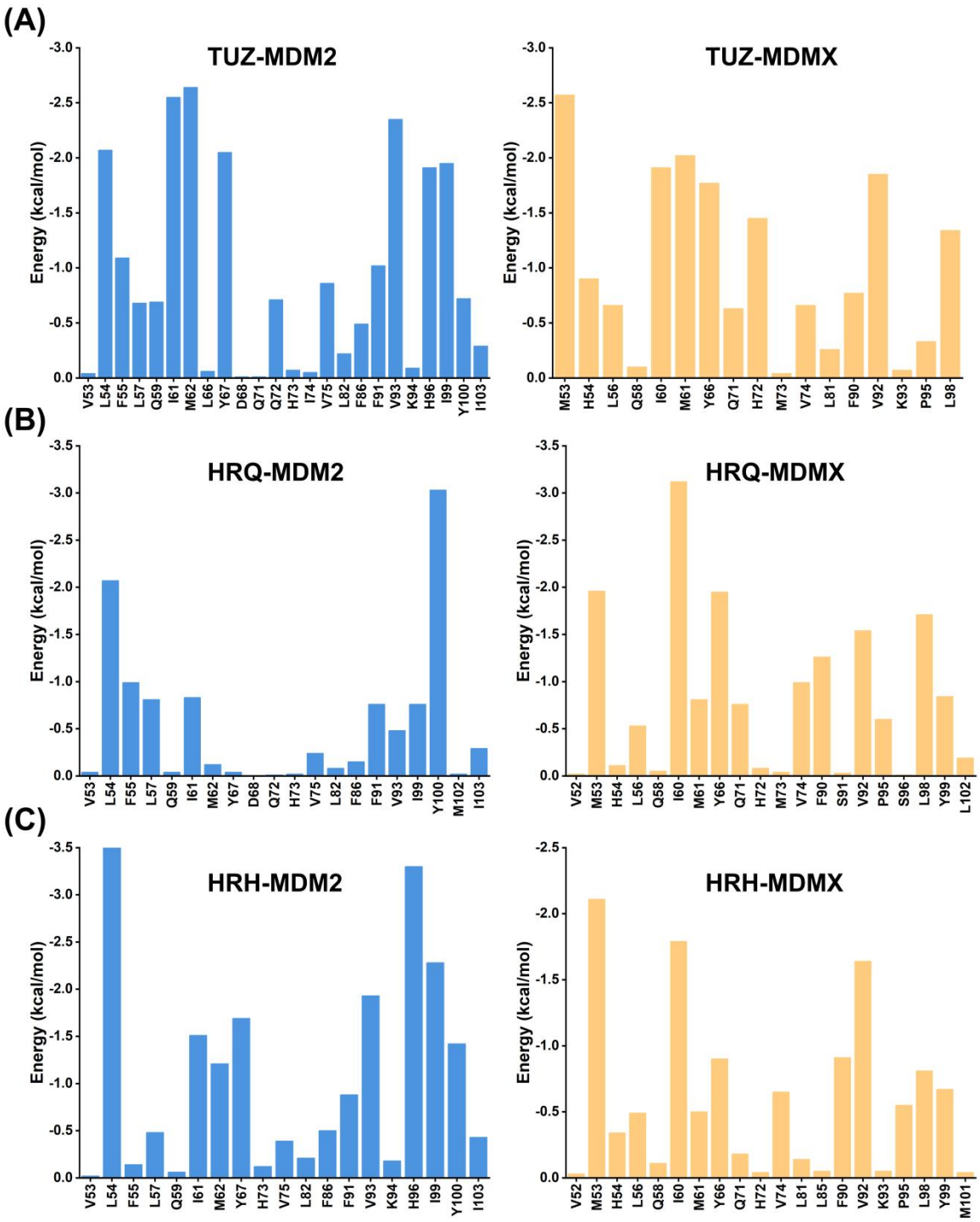

Figure S4. The van der Waals energy contributed by individual residues when (A) TUZ, (B) HRQ, and (C) HRH bind to MDM2 and MDMX, respectively.

Table S1. The binding free energy for each docking structure of inhibitors lacks a suitable crystal structure against MDM2/MDMX.

Complex	Structure	ΔE_{vdW}	ΔE_{ele}	ΔG_{gb}	ΔG_{np}	ΔH	$-T\Delta S$	ΔG_{bind}
2TZ—MDMX	Docking 1	-10.48	-0.93	1.86	-1.17	-10.71	2.98	-7.73
	Docking 2	-11.56	0.07	1.75	-1.48	-11.21	2.99	-8.22
	Docking 3	-11.18	-1.24	3.16	-1.35	-10.60	3.12	-7.49
2U0—MDMX	Docking 1	-18.06	-0.59	2.81	-2.12	-17.95	4.26	-13.70
	Docking 2	-12.87	-0.68	2.24	-1.63	-12.95	2.99	-9.95
	Docking 3	-10.73	-0.78	2.30	-1.31	-10.52	2.21	-8.31
WW8—MDM2	Docking 1	-21.33	-0.84	4.20	-2.55	-20.52	4.39	-16.13
	Docking 2	-18.87	-0.84	3.98	-2.34	-18.07	3.67	-14.40
	Docking 3	-18.26	-0.37	3.10	-1.96	-17.49	3.00	-14.49
TUZ—MDMX	Docking 1	-13.28	-0.22	1.68	-1.36	-13.18	2.62	-10.57
	Docking 2	-13.88	-1.20	3.25	-1.31	-13.14	2.79	-10.35
	Docking 3	-17.81	-1.49	3.61	-2.16	-17.86	3.85	-14.01
TUW—MDMX	Docking 1	-12.89	-4.47	5.54	-1.80	-13.63	4.42	-9.21
	Docking 2	-13.77	-1.70	3.59	-1.53	-13.41	3.29	-10.12
	Docking 3	-15.65	-0.98	3.43	-1.68	-14.88	3.26	-11.62
TVH—MDM2	Docking 1	-20.02	-0.75	3.05	-2.14	-19.86	4.27	-15.60
	Docking 2	-15.97	0.76	1.27	-1.64	-15.57	3.50	-12.06
	Docking 3	-18.66	-0.88	2.88	-2.08	-18.74	3.74	-15.00
TVH—MDMX	Docking 1	-12.55	-0.48	1.89	-1.40	-12.54	2.86	-9.68
	Docking 2	-12.68	0.23	0.74	-1.22	-12.92	2.94	-9.98
	Docking 3	-10.50	-2.14	2.69	-1.35	-11.30	2.98	-8.32
TVK—MDMX	Docking 2	-14.19	-0.65	3.10	-1.33	-13.06	2.60	-10.46
	Docking 3	-13.31	-1.46	3.34	-1.64	-13.08	3.63	-9.44
	Docking 3	-13.20	-1.18	3.60	-1.48	-12.26	3.15	-9.11
U3Z—MDMX	Docking 1	-14.23	-1.42	3.66	-1.63	-13.61	3.41	-10.20
	Docking 2	-13.40	-1.63	3.53	-1.41	-12.90	3.40	-9.49
	Docking 3	-13.59	-1.74	3.81	-1.59	-13.10	3.46	-9.63
HRT—MDM2	Docking 1	-22.48	-3.97	5.22	-2.34	-23.57	4.71	-18.86
	Docking 2	-20.30	-2.04	3.80	-2.22	-20.76	4.25	-16.50
	Docking 3	-20.82	-2.64	4.46	-2.30	-21.29	4.29	-17.00
HRQ—MDM2	Docking 1	-10.98	-3.12	3.95	-1.53	-11.69	3.98	-7.71
	Docking 2	-13.24	-0.97	3.08	-1.14	-12.28	2.28	-10.00
	Docking 3	-10.53	-1.17	2.39	-1.18	-10.49	2.37	-8.12
HRH—MDMX	Docking 1	-14.17	-0.53	2.09	-1.69	-14.30	2.74	-11.56
	Docking 2	-8.66	-0.48	1.25	-1.02	-8.89	1.77	-7.12
	Docking 3	-15.21	-0.38	2.00	-1.84	-15.43	3.57	-11.86
HTZ—MDMX	Docking 1	-18.36	-4.15	5.12	-2.12	-19.50	4.37	-15.12
	Docking 2	-11.25	-1.66	3.65	-1.26	-10.52	2.76	-7.76
	Docking 3	-14.46	-0.75	2.27	-1.52	-14.46	2.93	-11.53
HU8—MDMX	Docking 1	-11.49	-2.76	3.02	-1.58	-12.82	3.16	-9.65
	Docking 2	-12.08	0.21	1.57	-1.38	-11.68	2.51	-9.17
	Docking 3	-17.09	-1.64	2.79	-1.96	-17.90	4.29	-13.61

Table S2. Each energy terms of binding free energy of residues within 5 Å from the binding interface of P4−MDM2/MDMX obtained by the ASIE method (all values are in kcal/mol). The average results of the three trajectories are displayed.

Systems	Residues	$\Delta\Delta E_{vdW}$	$\Delta\Delta E_{ele}$	$\Delta\Delta G_{gb}$	$\Delta\Delta G_{np}$	$\Delta\Delta H$	$-T\Delta\Delta S$	$\Delta\Delta G_{bind}$
MDM2	K51	-0.83	-19.55	17.90	-0.50	-2.97	3.21	0.24
	V53	-0.05	0.07	-0.07	0.00	-0.05	0.00	-0.04
	L54	-3.06	-0.45	1.04	-0.39	-2.86	0.37	-2.49
	F55	-0.33	-0.14	0.34	-0.01	-0.13	0.09	-0.04
	L57	-0.78	0.04	0.08	-0.04	-0.70	0.14	-0.55
	Q59	-0.14	-0.27	0.32	0.00	-0.09	0.11	0.01
	I61	-2.07	-0.07	0.38	-0.22	-1.97	0.72	-1.26
	M62	-2.15	-0.21	1.11	-0.37	-1.61	1.28	-0.33
	Y67	-3.18	-0.23	0.46	-0.21	-3.17	0.43	-2.74
	Q71	-0.07	-0.04	0.06	0.00	-0.04	0.02	-0.02
	Q72	-2.54	-2.22	1.54	-0.34	-3.56	0.83	-2.73
	H73	-0.93	-0.62	0.75	0.00	-0.8	-0.05	-0.85
	V75	-0.69	-0.09	0.17	-0.06	-0.68	0.08	-0.59
	F86	-0.29	-0.09	0.26	-0.01	-0.13	0.01	-0.12
	F91	-0.69	-0.10	0.44	-0.06	-0.41	0.06	-0.35
	V93	-3.32	-0.08	0.45	-0.43	-3.40	0.61	-2.78
	K94	-1.02	-2.16	2.13	-0.14	-1.19	0.36	-0.83
	E95	-0.05	3.97	-3.70	0.00	0.22	0.05	0.28
	H96	-2.49	-0.64	0.93	-0.24	-2.45	0.56	-1.88
	I99	-1.48	-0.08	0.20	-0.20	-1.56	0.39	-1.17
	Y100	-1.30	-0.51	0.64	-0.15	-1.32	0.52	-0.80
	I103	-0.64	-0.11	0.19	-0.06	-0.63	0.04	-0.59
MDMX	V49	-0.09	-0.04	0.08	0.00	-0.05	0.02	-0.03
	K50	-0.98	-24.61	22.38	-0.64	-3.86	3.32	-0.54
	V52	-0.05	0.06	-0.06	0.00	-0.05	0.00	-0.04
	M53	-3.05	-2.03	2.71	-0.35	-2.72	0.95	-1.77
	H54	-0.72	0.26	-0.07	-0.05	-0.58	0.16	-0.42
	L56	-0.63	0.03	0.06	-0.02	-0.57	0.05	-0.52
	Q58	-0.16	0.17	-0.09	0.00	-0.09	0.06	-0.03
	I60	-1.93	-0.07	0.37	-0.21	-1.84	0.64	-1.21
	M61	-2.42	-0.43	1.35	-0.39	-1.89	1.28	-0.62
	Y66	-2.99	-0.15	0.36	-0.16	-2.95	0.41	-2.53
	E70	-0.02	-1.71	1.56	-0.08	-0.24	0.60	0.35
	Q71	-2.59	-2.09	1.53	-0.33	-3.49	0.81	-2.67
	H72	-0.96	-0.10	0.22	0.00	-0.84	0.03	-0.81
	V74	-0.72	-0.10	0.19	-0.08	-0.71	0.10	-0.61
	F90	-0.88	-0.20	0.59	-0.10	-0.59	0.11	-0.47
	V92	-3.41	-0.10	0.55	-0.47	-3.44	0.73	-2.71
	K93	-1.20	-1.49	1.50	-0.16	-1.34	0.41	-0.93
	P95	-0.65	-0.28	0.27	-0.08	-0.75	0.25	-0.50
	L98	-1.35	-0.16	0.45	-0.23	-1.29	0.33	-0.96
	Y99	-1.35	-0.11	0.39	-0.19	-1.26	0.24	-1.01
	L102	-0.14	-0.17	0.21	0.00	-0.10	0.01	-0.10

Table S3. Each energy terms of binding free energy of residues within 5 Å from the binding interface of pDI6W−MDM2/MDMX obtained by the ASIE method (all values are in kcal/mol). The average results of the three trajectories are displayed.

Systems	Residues	$\Delta\Delta E_{vdW}$	$\Delta\Delta E_{ele}$	$\Delta\Delta G_{gb}$	$\Delta\Delta G_{np}$	$\Delta\Delta H$	$-T\Delta\Delta S$	$\Delta\Delta G_{bind}$
	K51	-0.88	-13.27	12.24	-0.23	-2.14	1.71	-0.43
	V53	-0.04	0.06	-0.06	0.00	-0.05	0.00	-0.05
	L54	-2.93	-0.50	0.84	-0.32	-2.91	0.41	-2.50
	F55	-0.22	-0.10	0.24	0.00	-0.08	0.04	-0.03
	L57	-0.76	0.05	0.06	-0.04	-0.68	0.10	-0.57
	Q59	-0.15	-0.31	0.35	-0.02	-0.13	0.18	0.05
	I61	-1.96	-0.07	0.39	-0.21	-1.85	0.73	-1.12
	M62	-2.37	-0.85	1.67	-0.39	-1.93	1.35	-0.58
	Y67	-3.11	-0.07	0.26	-0.17	-3.08	0.32	-2.76
	Q72	-2.57	-1.85	1.48	-0.31	-3.26	0.91	-2.35
MDM2	H73	-1.04	-0.80	0.90	0.03	-0.90	-0.05	-0.95
	V75	-0.74	-0.10	0.17	-0.06	-0.73	0.08	-0.65
	F86	-0.26	-0.07	0.23	-0.01	-0.11	0.01	-0.10
	F91	-0.69	-0.12	0.46	-0.06	-0.41	0.05	-0.36
	V93	-3.41	-0.12	0.49	-0.44	-3.47	0.77	-2.71
	K94	-2.08	-2.78	2.69	-0.35	-2.53	0.57	-1.97
	E95	-0.05	4.00	-3.72	0.00	0.23	0.03	0.26
	H96	-2.47	-0.03	0.31	-0.23	-2.42	0.49	-1.93
	I99	-1.85	-0.21	0.35	-0.27	-2.00	0.35	-1.63
	Y100	-1.34	-3.07	2.47	-0.25	-2.18	1.05	-1.14
	I103	-0.36	-0.10	0.15	-0.02	-0.33	0.01	-0.32
	V49	-0.36	-0.12	0.29	-0.04	-0.22	0.11	-0.12
	K50	-0.90	-16.71	15.47	-0.33	-2.47	2.40	-0.07
	V52	-0.05	0.04	-0.05	0.00	-0.05	0.00	-0.05
	M53	-3.69	-2.25	3.16	-0.47	-3.24	1.09	-2.16
	H54	-0.28	0.51	-0.39	-0.01	-0.16	0.05	-0.11
	L56	-0.63	-0.01	0.11	-0.02	-0.55	0.06	-0.49
	Q58	-0.09	0.37	-0.31	0.00	-0.03	0.04	0.01
	I60	-1.87	-0.08	0.38	-0.22	-1.79	0.57	-1.22
	M61	-1.39	-0.12	0.69	-0.22	-1.05	0.63	-0.42
	Y66	-2.91	-0.22	0.46	-0.24	-2.91	0.43	-2.48
MDMX	Q71	-2.46	-2.81	2.27	-0.34	-3.33	1.10	-2.23
	H72	-1.03	-0.22	0.30	0.03	-0.92	0.03	-0.89
	M73	-0.08	0.21	-0.20	0.00	-0.07	0.02	-0.05
	V74	-0.69	-0.10	0.19	-0.08	-0.67	0.12	-0.56
	F90	-0.93	-0.23	0.61	-0.09	-0.64	0.13	-0.51
	V92	-3.44	-0.10	0.53	-0.46	-3.48	0.88	-2.60
	K93	-1.86	-1.91	1.86	-0.30	-2.20	0.58	-1.62
	P95	-0.56	-0.35	0.32	-0.06	-0.65	0.25	-0.41
	L98	-1.53	-0.17	0.50	-0.25	-1.44	0.32	-1.13
	Y99	-2.26	-0.48	0.68	-0.37	-2.44	0.60	-1.84
	L102	-0.19	-0.21	0.29	0.00	-0.11	0.02	-0.09

Table S4. Each energy terms of binding free energy of residues within 5 Å from the binding interface of 2TZ−MDM2/MDMX obtained by the ASIE method (all values are in kcal/mol). The average results of the three trajectories are displayed.

Systems	Residues	$\Delta\Delta E_{vdW}$	$\Delta\Delta E_{ele}$	$\Delta\Delta G_{gb}$	$\Delta\Delta G_{np}$	$\Delta\Delta H$	$-T\Delta\Delta S$	$\Delta\Delta G_{bind}$
	V53	-0.04	-0.01	0.00	0.00	-0.05	0.00	-0.05
	L54	-2.21	-0.06	0.35	-0.35	-2.28	0.54	-1.74
	F55	-1.02	-0.05	0.25	-0.15	-0.98	0.30	-0.68
	L57	-0.61	-0.07	0.10	-0.02	-0.61	0.03	-0.57
	Q59	-0.61	-0.24	0.36	-0.06	-0.56	0.17	-0.40
	I61	-1.64	0.00	0.08	-0.21	-1.76	0.54	-1.22
	M62	-1.70	-0.29	0.47	-0.27	-1.8	0.48	-1.33
	Y67	-1.19	-0.02	0.15	-0.13	-1.19	0.18	-1.01
	H73	-0.19	-0.01	0.06	-0.01	-0.15	0.04	-0.11
MDM2	V75	-0.37	0.00	0.02	-0.02	-0.36	0.01	-0.35
	L82	-0.23	-0.02	0.05	-0.01	-0.20	0.00	-0.20
	F86	-0.54	-0.11	0.20	-0.04	-0.49	0.04	-0.45
	F91	-0.90	0.19	0.12	-0.08	-0.67	0.10	-0.56
	V93	-1.60	-0.01	0.33	-0.12	-1.40	0.19	-1.21
	K94	-0.63	-0.89	0.85	-0.11	-0.79	0.44	-0.34
	H96	-3.46	-1.02	0.92	-0.38	-3.94	1.06	-2.88
	I99	-2.38	-0.07	0.16	-0.27	-2.55	0.53	-2.03
	Y100	-0.17	0.00	0.01	0.00	-0.16	0.01	-0.14
	I103	-0.55	-0.01	0.03	-0.04	-0.57	0.03	-0.54
	M53	-1.97	0.01	0.19	-0.20	-1.97	0.42	-1.55
	H54	-1.25	-0.54	0.72	-0.14	-1.22	0.4	-0.82
	Y55	-0.02	0.00	0.00	0.00	-0.01	0.00	-0.01
	L56	-0.43	0.00	0.01	-0.01	-0.43	0.06	-0.37
	Q58	-0.36	0.04	0.04	-0.04	-0.33	0.12	-0.21
	Y59	-0.01	0.00	0.00	0.00	-0.01	0.00	-0.01
	I60	-1.13	0.02	0.09	-0.15	-1.17	0.42	-0.75
	M61	-0.78	-0.2	0.44	-0.13	-0.67	0.34	-0.33
	Y66	-0.70	-0.07	0.19	-0.09	-0.67	0.18	-0.49
MDMX	Q71	-0.14	-0.02	0.06	-0.01	-0.12	0.03	-0.09
	H72	-0.03	-0.04	0.04	0.00	-0.03	0.00	-0.02
	M73	-0.02	0.00	0.00	0.00	-0.02	0.00	-0.02
	V74	-0.43	0.00	0.05	-0.05	-0.43	0.09	-0.34
	L81	-0.06	0.01	0.00	0.00	-0.05	0.00	-0.05
	F90	-0.69	-0.01	0.18	-0.08	-0.61	0.14	-0.47
	V92	-1.51	0.01	0.20	-0.24	-1.55	0.39	-1.16
	K93	-0.06	0.09	-0.07	0.00	-0.05	0.03	-0.01
	P95	-0.51	0.01	0.01	-0.05	-0.54	0.10	-0.44
	L98	-0.96	0.00	0.12	-0.14	-0.97	0.29	-0.68

Table S5. Each energy terms of binding free energy of residues within 5 Å from the binding interface of 2U0−MDM2/MDMX obtained by the ASIE method (all values are in kcal/mol). The average results of the three trajectories are displayed.

Systems	Residues	$\Delta\Delta E_{vdW}$	$\Delta\Delta E_{ele}$	$\Delta\Delta G_{gb}$	$\Delta\Delta G_{np}$	$\Delta\Delta H$	$-T\Delta\Delta S$	$\Delta\Delta G_{bind}$
MDM2	V53	-0.03	-0.01	0.00	0.00	-0.05	0.00	-0.05
	L54	-1.88	-0.10	0.27	-0.25	-1.95	0.43	-1.52
	F55	-1.30	-0.14	0.22	-0.15	-1.36	0.32	-1.04
	L57	-0.65	-0.08	0.09	-0.04	-0.68	0.15	-0.53
	Q59	-0.82	-0.12	0.25	-0.08	-0.77	0.21	-0.56
	I61	-1.85	0.00	0.05	-0.20	-2.01	0.51	-1.49
	M62	-1.91	-0.59	0.64	-0.30	-2.16	0.59	-1.57
	Y67	-2.36	-0.10	0.33	-0.26	-2.40	0.33	-2.06
	K70	-0.21	0.05	-0.02	0.00	-0.19	0.03	-0.16
	H73	-0.86	0.07	0.07	-0.10	-0.82	0.21	-0.61
	V75	-0.51	-0.03	0.04	-0.04	-0.55	0.02	-0.52
	F86	-0.49	-0.13	0.21	-0.03	-0.44	0.03	-0.42
	F91	-0.66	-0.31	0.39	-0.11	-0.69	0.27	-0.42
	V93	-1.97	-0.11	0.14	-0.08	-2.02	0.11	-1.91
	K94	-1.24	-0.48	0.52	-0.16	-1.36	0.67	-0.68
	H96	-4.20	-1.20	0.61	-0.20	-5.00	0.99	-4.01
	I99	-2.48	-0.06	0.07	-0.28	-2.75	0.53	-2.23
	Y100	-0.34	0.00	0.04	-0.02	-0.33	0.08	-0.25
	I103	-0.48	-0.01	0.03	-0.03	-0.50	0.02	-0.48
MDMX	V52	-0.02	-0.01	0.00	0.00	-0.02	0.00	-0.02
	M53	-1.39	0.11	0.15	-0.17	-1.30	0.29	-1.01
	H54	-1.05	-0.09	0.28	-0.10	-0.97	0.18	-0.79
	L56	-0.34	-0.02	0.02	-0.01	-0.34	0.02	-0.32
	Q58	-0.38	-0.05	0.10	-0.03	-0.36	0.11	-0.25
	I60	-1.38	0.05	0.05	-0.15	-1.44	0.34	-1.10
	M61	-1.21	-0.12	0.39	-0.18	-1.12	0.36	-0.76
	L65	-0.03	-0.02	0.02	0.00	-0.04	0.00	-0.04
	Y66	-2.54	-0.14	0.38	-0.28	-2.57	0.53	-2.04
	Q71	-0.83	0.01	0.14	-0.13	-0.81	0.26	-0.56
	H72	-0.05	-0.04	0.05	0.00	-0.05	0.00	-0.04
	M73	-0.02	0.02	-0.03	0.00	-0.03	0.00	-0.03
	V74	-0.58	0.01	0.01	-0.06	-0.61	0.06	-0.56
	L81	-0.09	0.00	0.01	0.00	-0.08	0.00	-0.08
	L85	-0.04	0.00	0.01	0.00	-0.03	0.00	-0.03
	F90	-0.77	-0.09	0.25	-0.08	-0.69	0.10	-0.60
	S91	0.00	-0.01	0.01	0.00	-0.01	0.00	-0.01
	K93	-0.08	0.11	-0.09	0.00	-0.07	0.04	-0.03
	P95	-0.26	-0.02	0.00	-0.03	-0.31	0.05	-0.26
	L98	-0.96	-0.02	0.15	-0.16	-0.98	0.31	-0.67

Table S6. Each energy terms of binding free energy of residues within 5 Å from the binding interface of WW8−MDM2/MDMX obtained by the ASIE method (all values are in kcal/mol). The average results of the three trajectories are displayed.

Systems	Residues	$\Delta\Delta E_{vdW}$	$\Delta\Delta E_{ele}$	$\Delta\Delta G_{gb}$	$\Delta\Delta G_{np}$	$\Delta\Delta H$	$-T\Delta\Delta S$	$\Delta\Delta G_{bind}$
MDM2	V53	-0.02	-0.01	0.00	0.00	-0.03	0.00	-0.03
	L54	-2.68	-0.13	0.55	-0.31	-2.57	0.48	-2.09
	F55	-0.95	-0.10	0.30	-0.11	-0.87	0.31	-0.56
	L57	-0.76	-0.06	0.11	-0.04	-0.74	0.05	-0.69
	Q59	-0.22	-0.02	0.08	-0.01	-0.17	0.03	-0.14
	I61	-1.87	-0.01	0.24	-0.23	-1.87	0.52	-1.35
	M62	-1.76	-0.07	0.48	-0.29	-1.64	0.36	-1.27
	L66	-0.03	-0.02	0.01	0.00	-0.04	0.00	-0.04
	Y67	-1.83	-0.10	0.28	-0.26	-1.91	0.27	-1.64
	E69	-0.05	-0.05	0.07	0.00	-0.03	0.01	-0.03
	Q72	-0.39	0.10	0.01	-0.06	-0.34	0.07	-0.27
	H73	-0.10	0.00	0.03	0.00	-0.07	0.01	-0.06
	I74	-0.03	0.00	-0.01	0.00	-0.04	0.00	-0.04
	V75	-0.63	-0.01	0.10	-0.06	-0.60	0.07	-0.53
	L82	-0.10	-0.01	0.03	-0.01	-0.09	0.00	-0.09
	F86	-0.56	-0.12	0.25	-0.05	-0.48	0.08	-0.40
	F91	-0.95	0.04	0.30	-0.10	-0.71	0.21	-0.49
	S92	-0.01	0.00	0.00	0.00	-0.01	0.00	-0.01
	V93	-1.74	0.01	0.25	-0.21	-1.69	0.33	-1.37
	K94	-0.06	-0.06	0.07	0.00	-0.05	0.01	-0.05
	H96	-0.93	0.08	0.04	-0.08	-0.88	0.13	-0.75
	I99	-2.04	-0.08	0.26	-0.25	-2.12	0.50	-1.62
	Y100	-1.24	-0.04	0.25	-0.18	-1.21	0.21	-1.00
	M102	-0.02	-0.03	0.04	0.00	-0.02	0.00	-0.02
	I103	-0.50	-0.01	0.05	-0.03	-0.50	0.03	-0.47
MDMX	V52	-0.04	0.00	-0.01	0.00	-0.05	0.00	-0.05
	M53	-2.15	-0.42	0.75	-0.27	-2.08	0.44	-1.65
	H54	-0.90	-0.08	0.21	-0.09	-0.87	0.22	-0.65
	L56	-0.84	-0.02	0.09	-0.05	-0.82	0.04	-0.78
	Q58	-0.24	-0.09	0.14	-0.01	-0.19	0.02	-0.16
	I60	-2.09	-0.05	0.31	-0.25	-2.08	0.66	-1.41
	M61	-1.76	-0.04	0.40	-0.30	-1.70	0.35	-1.34
	Y66	-1.89	-0.05	0.29	-0.29	-1.94	0.35	-1.59
	Q71	-0.59	-0.02	0.13	-0.08	-0.57	0.12	-0.45
	H72	-0.38	-0.07	0.12	-0.02	-0.35	0.07	-0.28
	V74	-1.15	0.04	0.19	-0.14	-1.06	0.18	-0.88
	L81	-0.40	-0.05	0.09	-0.04	-0.39	0.02	-0.38
	F90	-1.37	0.09	0.35	-0.17	-1.09	0.26	-0.83
	V92	-2.92	-0.09	0.52	-0.31	-2.80	0.66	-2.14
	P95	-0.34	-0.05	0.01	-0.03	-0.41	0.10	-0.31
	L98	-1.81	-0.06	0.30	-0.27	-1.85	0.49	-1.35
	Y99	-0.75	0.04	0.09	-0.10	-0.72	0.14	-0.58

Table S7. Each energy terms of binding free energy of residues within 5 Å from the binding interface of TUZ−MDM2/MDMX obtained by the ASIE method (all values are in kcal/mol). The average results of the three trajectories are displayed.

Systems	Residues	$\Delta\Delta E_{vdW}$	$\Delta\Delta E_{ele}$	$\Delta\Delta G_{gb}$	$\Delta\Delta G_{np}$	$\Delta\Delta H$	$-T\Delta\Delta S$	$\Delta\Delta G_{bind}$
MDM2	V53	-0.04	-0.02	0.01	0.00	-0.05	0.00	-0.04
	L54	-2.03	-0.15	0.45	-0.20	-1.94	0.61	-1.33
	F55	-1.35	-0.53	0.81	-0.15	-1.21	0.55	-0.66
	L57	-0.77	-0.04	0.08	-0.04	-0.77	0.11	-0.66
	Q59	-0.63	-0.12	0.22	-0.06	-0.59	0.15	-0.45
	I61	-2.45	0.07	0.05	-0.22	-2.55	0.28	-2.27
	M62	-2.58	-0.55	0.83	-0.38	-2.68	0.56	-2.12
	L66	-0.05	-0.06	0.05	0.00	-0.06	0.00	-0.06
	Y67	-1.93	-0.27	0.33	-0.23	-2.10	0.40	-1.70
	D68	-0.01	-0.51	0.48	0.00	-0.03	0.01	-0.03
	Q71	-0.01	0.01	-0.01	0.00	-0.01	0.00	-0.01
	Q72	-0.76	-0.13	0.20	-0.10	-0.80	0.15	-0.65
	H73	-0.07	-0.10	0.09	0.00	-0.07	0.01	-0.06
	I74	-0.04	-0.07	0.06	0.00	-0.05	0.00	-0.04
	V75	-0.70	0.01	0.05	-0.05	-0.70	0.05	-0.65
	L82	-0.25	0.00	0.04	-0.01	-0.22	0.00	-0.21
	F86	-0.53	-0.08	0.16	-0.03	-0.48	0.02	-0.45
	F91	-1.02	0.08	0.21	-0.09	-0.81	0.12	-0.69
	V93	-2.24	0.00	0.35	-0.24	-2.12	0.39	-1.73
	K94	-0.10	-0.13	0.14	0.00	-0.09	0.04	-0.06
	H96	-1.86	-0.04	0.22	-0.20	-1.89	0.39	-1.50
	I99	-1.96	-0.04	0.11	-0.22	-2.11	0.45	-1.66
	Y100	-0.77	-0.01	0.08	-0.05	-0.75	0.18	-0.56
	I103	-0.38	-0.01	0.02	-0.02	-0.38	0.01	-0.36
MDMX	M53	-1.20	-0.25	0.43	-0.17	-1.19	0.32	-0.87
	H54	-0.90	-0.29	0.36	-0.09	-0.92	0.23	-0.69
	Y55	-0.02	0.00	0.00	0.00	-0.02	0.00	-0.02
	L56	-0.35	0.00	0.01	-0.01	-0.35	0.05	-0.30
	Q58	-0.58	-0.10	0.17	-0.05	-0.57	0.16	-0.41
	I60	-1.70	0.03	0.20	-0.14	-1.61	0.31	-1.30
	M61	-2.21	-0.17	0.64	-0.32	-2.06	0.58	-1.48
	Y66	-2.42	-0.09	0.27	-0.23	-2.48	0.34	-2.14
	Q71	-0.37	-0.09	0.14	-0.05	-0.37	0.14	-0.23
	H72	-0.25	-0.05	0.06	-0.01	-0.25	0.05	-0.20
	M73	-0.05	-0.03	0.02	0.00	-0.06	0.00	-0.06
	V74	-0.68	-0.02	0.07	-0.05	-0.68	0.10	-0.58
	L81	-0.01	0.00	0.00	0.00	-0.01	0.00	-0.01
	F90	-0.53	0.02	0.12	-0.04	-0.43	0.05	-0.38
	S91	0.00	0.01	-0.01	0.00	-0.01	0.00	-0.01
	V92	-2.25	0.00	0.27	-0.23	-2.21	0.41	-1.80
	K93	-0.17	0.07	-0.05	-0.02	-0.17	0.03	-0.14
	P95	-0.29	-0.02	0.02	-0.03	-0.33	0.06	-0.26
	L98	-0.84	0.01	0.10	-0.13	-0.85	0.23	-0.62

Y99	-0.15	0.00	0.02	-0.02	-0.14	0.01	-0.13
L102	-0.03	0.00	0.00	0.00	-0.03	0.00	-0.03

Table S8. Each energy terms of binding free energy of residues within 5 Å from the binding interface of TUW−MDM2/MDMX obtained by the ASIE method (all values are in kcal/mol). The average results of the three trajectories are displayed.

Systems	Residues	$\Delta\Delta E_{vdW}$	$\Delta\Delta E_{ele}$	$\Delta\Delta G_{gb}$	$\Delta\Delta G_{np}$	$\Delta\Delta H$	$-T\Delta\Delta S$	$\Delta\Delta G_{bind}$
MDM2	V53	-0.04	-0.01	0.01	0.00	-0.05	0.00	-0.05
	L54	-2.26	0.04	0.45	-0.28	-2.06	0.46	-1.59
	F55	-1.01	-0.16	0.38	-0.13	-0.91	0.40	-0.51
	Y56	-0.06	0.00	0.01	0.00	-0.05	0.00	-0.05
	L57	-0.73	-0.03	0.07	-0.04	-0.72	0.09	-0.63
	Q59	-0.84	-0.05	0.18	-0.09	-0.80	0.17	-0.63
	I61	-2.52	0.06	0.07	-0.22	-2.61	0.31	-2.30
	M62	-2.32	-0.52	0.85	-0.35	-2.33	0.62	-1.71
	L66	-0.06	-0.06	0.05	0.00	-0.07	0.00	-0.06
	Y67	-1.67	-0.13	0.25	-0.22	-1.76	0.31	-1.46
	D68	-0.01	-0.49	0.47	0.00	-0.04	0.01	-0.03
	Q71	-0.01	0.00	0.01	0.00	-0.01	0.00	-0.01
	Q72	-0.35	-0.01	0.05	-0.04	-0.34	0.06	-0.28
	H73	-0.08	-0.11	0.10	0.00	-0.08	0.02	-0.07
	I74	-0.06	-0.07	0.04	0.00	-0.09	0.01	-0.07
	V75	-1.01	0.01	0.07	-0.09	-1.01	0.10	-0.92
	L82	-0.21	-0.01	0.04	0.00	-0.18	0.00	-0.18
	F86	-0.52	-0.07	0.16	-0.04	-0.47	0.02	-0.46
	F91	-1.05	0.08	0.26	-0.11	-0.83	0.19	-0.64
	V93	-2.38	0.00	0.41	-0.23	-2.19	0.37	-1.83
	K94	-0.11	-0.13	0.14	0.00	-0.10	0.03	-0.07
	H96	-2.04	0.01	0.09	-0.21	-2.15	0.36	-1.79
	I99	-2.35	-0.03	0.22	-0.26	-2.42	0.40	-2.02
	Y100	-0.68	-0.26	0.30	-0.07	-0.72	0.18	-0.55
	I103	-0.32	-0.02	0.04	-0.01	-0.32	0.01	-0.31
MDMX	M53	-0.78	-0.27	0.42	-0.13	-0.76	0.26	-0.50
	H54	-1.41	-0.31	0.58	-0.20	-1.33	0.30	-1.03
	Y55	-0.03	-0.01	0.01	0.00	-0.02	0.00	-0.02
	L56	-0.19	-0.02	0.02	0.00	-0.19	0.02	-0.18
	Q58	-0.49	-0.68	0.66	-0.08	-0.59	0.33	-0.27
	I60	-1.47	-0.05	0.36	-0.11	-1.27	0.29	-0.98
	M61	-2.02	-0.11	0.53	-0.25	-1.85	0.54	-1.31
	Y66	-2.77	-1.16	1.08	-0.30	-3.15	0.93	-2.22
	Q71	-0.87	0.04	0.07	-0.13	-0.88	0.23	-0.65
	H72	-0.13	0.05	-0.03	0.00	-0.12	0.01	-0.11
	M73	-0.03	-0.05	0.04	0.00	-0.03	0.00	-0.03
	V74	-0.34	0.00	0.05	-0.02	-0.31	0.02	-0.29
	F90	-0.36	0.04	0.07	-0.03	-0.29	0.04	-0.24
	S91	-0.01	-0.01	0.01	0.00	-0.01	0.00	-0.01
	V92	-1.91	0.04	0.26	-0.23	-1.84	0.34	-1.50
	K93	-0.09	0.04	-0.03	0.00	-0.08	0.02	-0.06
	P95	-0.41	-0.01	0.01	-0.06	-0.47	0.10	-0.37
	L98	-0.71	0.01	0.10	-0.12	-0.72	0.22	-0.50

Y99	-0.05	0.00	0.01	0.00	-0.04	0.00	-0.03
L102	-0.01	0.01	-0.01	0.00	-0.01	0.00	-0.01

Table S9. Each energy terms of binding free energy of residues within 5 Å from the binding interface of TVH−MDM2/MDMX obtained by the ASIE method (all values are in kcal/mol). The average results of the three trajectories are displayed.

Systems	Residues	$\Delta\Delta E_{vdW}$	$\Delta\Delta E_{ele}$	$\Delta\Delta G_{gb}$	$\Delta\Delta G_{np}$	$\Delta\Delta H$	$-T\Delta\Delta S$	$\Delta\Delta G_{bind}$
MDM2	L54	-2.13	-0.09	0.39	-0.26	-2.09	0.51	-1.57
	F55	-0.82	-0.07	0.27	-0.09	-0.71	0.30	-0.41
	L57	-0.79	-0.01	0.08	-0.05	-0.78	0.10	-0.68
	Q59	-0.75	-0.09	0.18	-0.08	-0.75	0.18	-0.57
	I61	-2.23	0.03	0.10	-0.20	-2.30	0.43	-1.87
	M62	-1.42	-0.08	0.25	-0.21	-1.46	0.38	-1.08
	Y67	-1.86	-0.14	0.27	-0.19	-1.93	0.32	-1.61
	D68	-0.01	0.10	-0.09	0.00	0.00	0.00	0.01
	Q72	-0.35	-0.04	0.08	-0.04	-0.35	0.09	-0.26
	H73	-0.09	-0.05	0.06	0.00	-0.08	0.01	-0.07
	I74	-0.02	0.00	0.00	0.00	-0.02	0.00	-0.02
	V75	-0.59	0.00	0.05	-0.05	-0.59	0.04	-0.55
	F86	-0.49	-0.05	0.15	-0.04	-0.43	0.03	-0.40
	F91	-0.94	0.06	0.22	-0.09	-0.76	0.12	-0.65
	S92	-0.01	-0.01	0.01	0.00	-0.01	0.00	-0.01
	V93	-1.74	0.02	0.19	-0.24	-1.76	0.53	-1.22
	K94	-0.08	-0.10	0.11	0.00	-0.07	0.02	-0.05
	H96	-0.96	-0.03	0.10	-0.08	-0.96	0.20	-0.77
	I99	-1.80	-0.05	0.16	-0.21	-1.90	0.32	-1.58
	Y100	-0.73	-0.04	0.14	-0.10	-0.73	0.19	-0.54
	I103	-0.38	-0.01	0.03	-0.03	-0.38	0.03	-0.35
MDMX	V52	-0.02	-0.01	0.00	0.00	-0.03	0.00	-0.03
	M53	-1.33	-0.09	0.20	-0.13	-1.34	0.32	-1.02
	H54	-0.73	0.03	0.08	-0.06	-0.67	0.06	-0.61
	L56	-0.25	-0.03	0.03	0.00	-0.24	-0.01	-0.25
	Q58	-0.07	0.01	0.01	0.00	-0.05	0.01	-0.05
	Y59	-0.02	-0.01	0.00	0.00	-0.02	0.00	-0.02
	I60	-1.73	-0.03	0.16	-0.19	-1.78	0.41	-1.38
	M61	-1.36	-0.11	0.26	-0.18	-1.40	0.43	-0.96
	L65	-0.01	0.00	-0.01	0.00	-0.02	0.00	-0.02
	Y66	-1.50	-0.35	0.45	-0.24	-1.64	0.58	-1.06
	Q71	-0.10	-0.02	0.04	-0.01	-0.08	0.01	-0.07
	H72	-0.06	-0.02	0.02	0.00	-0.06	0.00	-0.07
	M73	-0.01	0.01	-0.01	0.00	-0.01	0.00	-0.01
	V74	-0.50	-0.02	0.07	-0.04	-0.49	0.07	-0.42
	L81	-0.08	-0.01	0.02	0.00	-0.07	0.00	-0.07
	L85	-0.05	-0.01	0.02	0.00	-0.04	0.00	-0.04
	F90	-0.53	-0.16	0.25	-0.06	-0.50	0.10	-0.40
	V92	-1.11	-0.04	0.09	-0.14	-1.20	0.20	-1.00
	K93	-0.06	0.05	-0.04	0.00	-0.05	0.01	-0.04
	P95	-1.14	0.01	-0.04	-0.10	-1.27	0.26	-1.01
	L98	-0.87	-0.07	0.17	-0.14	-0.91	0.42	-0.48
	Y99	-0.34	-0.01	0.06	-0.04	-0.33	0.05	-0.28

M101	-0.03	-0.04	0.04	0.00	-0.03	0.00	-0.03
L102	-0.03	0.00	0.00	0.00	-0.02	0.00	-0.02

Table S10. Each energy terms of binding free energy of residues within 5 Å from the binding interface of TVK−MDM2/MDMX obtained by the ASIE method (all values are in kcal/mol). The average results of the three trajectories are displayed.

Systems	Residues	$\Delta\Delta E_{vdW}$	$\Delta\Delta E_{ele}$	$\Delta\Delta G_{gb}$	$\Delta\Delta G_{np}$	$\Delta\Delta H$	$-T\Delta\Delta S$	$\Delta\Delta G_{bind}$
MDM2	V53	-0.04	-0.01	-0.01	0.00	-0.05	0.00	-0.05
	L54	-2.11	-0.11	0.43	-0.21	-1.99	0.63	-1.37
	F55	-1.01	-0.21	0.47	-0.14	-0.90	0.40	-0.50
	Y56	-0.06	0.00	0.01	0.00	-0.05	0.00	-0.05
	L57	-0.70	-0.03	0.07	-0.03	-0.69	0.05	-0.64
	Q59	-0.68	-0.11	0.21	-0.07	-0.65	0.13	-0.52
	I61	-2.48	0.06	0.06	-0.21	-2.57	0.27	-2.30
	M62	-2.60	-0.54	0.81	-0.38	-2.72	0.55	-2.16
	L66	-0.06	-0.06	0.05	0.00	-0.07	0.00	-0.07
	Y67	-1.90	-0.18	0.27	-0.23	-2.03	0.33	-1.70
	D68	-0.01	-0.46	0.44	0.00	-0.03	0.01	-0.02
	Q71	-0.01	0.01	-0.01	0.00	-0.01	0.00	-0.01
	Q72	-0.72	-0.15	0.20	-0.10	-0.78	0.20	-0.58
	H73	-0.07	-0.09	0.09	0.00	-0.07	0.01	-0.06
	I74	-0.05	-0.07	0.05	0.00	-0.06	0.01	-0.06
	V75	-0.85	0.00	0.06	-0.08	-0.86	0.08	-0.78
	L82	-0.24	-0.02	0.05	-0.01	-0.21	0.00	-0.21
	F86	-0.55	-0.11	0.20	-0.03	-0.50	0.03	-0.47
	F91	-1.04	0.04	0.28	-0.10	-0.82	0.16	-0.66
	V93	-2.39	0.03	0.36	-0.26	-2.25	0.39	-1.87
	K94	-0.10	-0.11	0.12	0.00	-0.09	0.03	-0.06
	H96	-1.65	-0.07	0.21	-0.18	-1.69	0.37	-1.32
	I99	-2.06	-0.05	0.15	-0.24	-2.20	0.39	-1.81
	Y100	-0.75	-0.05	0.11	-0.05	-0.74	0.12	-0.63
	I103	-0.34	-0.01	0.03	-0.02	-0.34	0.01	-0.33
MDMX	M53	-0.47	-0.09	0.16	-0.07	-0.46	0.13	-0.33
	H54	-1.10	-0.28	0.52	-0.17	-1.03	0.33	-0.70
	Y55	-0.02	-0.01	0.01	0.00	-0.01	0.00	-0.01
	L56	-0.12	-0.01	0.02	0.00	-0.12	0.01	-0.11
	Q58	-0.52	-0.50	0.57	-0.08	-0.53	0.25	-0.27
	I60	-1.44	-0.03	0.38	-0.11	-1.20	0.32	-0.88
	M61	-2.89	-0.09	0.72	-0.37	-2.62	0.72	-1.90
	Y66	-2.10	-0.01	0.18	-0.18	-2.12	0.28	-1.83
	Q71	-0.57	0.03	0.05	-0.07	-0.55	0.14	-0.41
	H72	-0.27	-0.03	0.06	-0.01	-0.26	0.05	-0.20
	M73	-0.06	-0.04	0.02	0.00	-0.08	0.00	-0.08
	V74	-0.62	-0.03	0.10	-0.04	-0.59	0.18	-0.41
	L81	-0.02	0.00	0.01	0.00	-0.02	0.00	-0.02
	F90	-0.28	0.00	0.10	-0.01	-0.19	0.02	-0.17
	S91	-0.01	-0.01	0.01	0.00	-0.01	0.00	-0.01
	V92	-2.20	0.00	0.36	-0.27	-2.12	0.49	-1.64
	K93	-0.10	0.01	0.00	0.00	-0.09	0.03	-0.06
	P95	-0.27	0.00	0.01	-0.04	-0.30	0.06	-0.24

L98	-0.45	0.00	0.07	-0.07	-0.45	0.11	-0.34
Y99	-0.05	0.00	0.02	0.00	-0.04	0.00	-0.04

Table S11. Each energy terms of binding free energy of residues within 5 Å from the binding interface of U3Z−MDM2/MDMX obtained by the ASIE method (all values are in kcal/mol). The average results of the three trajectories are displayed.

Systems	Residues	$\Delta\Delta E_{vdW}$	$\Delta\Delta E_{ele}$	$\Delta\Delta G_{gb}$	$\Delta\Delta G_{np}$	$\Delta\Delta H$	$-T\Delta\Delta S$	$\Delta\Delta G_{bind}$
MDM2	V53	-0.04	-0.02	0.00	0.00	-0.06	0.00	-0.06
	L54	-2.47	-0.13	0.50	-0.26	-2.37	0.57	-1.79
	F55	-0.97	-0.14	0.38	-0.12	-0.85	0.37	-0.49
	Y56	-0.06	-0.01	0.02	0.00	-0.05	0.00	-0.05
	L57	-0.70	-0.08	0.13	-0.03	-0.68	0.05	-0.63
	Q59	-0.77	-0.10	0.22	-0.09	-0.73	0.16	-0.56
	I61	-2.44	0.03	0.16	-0.22	-2.47	0.30	-2.18
	M62	-2.53	-0.45	0.91	-0.39	-2.46	0.67	-1.79
	L66	-0.05	-0.05	0.04	0.00	-0.07	0.00	-0.06
	Y67	-1.42	-0.08	0.18	-0.16	-1.47	0.27	-1.20
	D68	-0.01	-0.39	0.37	0.00	-0.03	0.01	-0.02
	Q71	-0.02	0.01	-0.01	0.00	-0.01	0.00	-0.01
	Q72	-0.53	-0.07	0.13	-0.07	-0.55	0.06	-0.48
	H73	-0.15	-0.01	0.04	0.00	-0.12	0.02	-0.10
	I74	-0.06	-0.05	0.03	0.00	-0.10	0.01	-0.09
	V75	-1.05	0.01	0.10	-0.09	-1.03	0.11	-0.91
	L82	-0.20	-0.01	0.05	0.00	-0.17	0.00	-0.16
	F86	-0.50	-0.13	0.23	-0.03	-0.43	0.03	-0.40
	F91	-1.09	-0.05	0.38	-0.11	-0.86	0.18	-0.69
	V93	-2.26	-0.06	0.35	-0.22	-2.19	0.36	-1.83
	K94	-0.10	-0.44	0.43	0.00	-0.11	0.03	-0.08
	E95	-0.03	0.23	-0.20	0.00	0.00	0.00	0.00
	H96	-1.74	-0.28	0.41	-0.15	-1.76	0.19	-1.57
	R97	-0.04	-0.16	0.15	0.00	-0.06	0.00	-0.05
	I99	-2.40	-0.10	0.26	-0.24	-2.49	0.37	-2.12
	Y100	-0.65	-0.05	0.17	-0.07	-0.60	0.52	-0.08
	I103	-0.37	-0.01	0.04	-0.02	-0.35	0.01	-0.33
MDMX	M53	-0.44	0.01	0.10	-0.06	-0.39	0.13	-0.25
	H54	-0.98	-0.43	0.62	-0.15	-0.94	0.32	-0.63
	Y55	-0.06	-0.01	0.02	0.00	-0.04	0.00	-0.04
	L56	-0.07	0.01	0.00	0.00	-0.06	0.00	-0.06
	Q58	-0.50	-0.40	0.44	-0.07	-0.53	0.29	-0.24
	Y59	-0.01	-0.01	0.01	0.00	-0.02	0.00	-0.02
	I60	-1.68	-0.08	0.35	-0.13	-1.54	0.35	-1.19
	M61	-2.47	-0.31	0.77	-0.34	-2.35	0.67	-1.69
	Y66	-2.55	-0.08	0.29	-0.26	-2.59	0.48	-2.11
	Q71	-0.52	0.02	0.02	-0.04	-0.52	0.07	-0.44
	H72	-0.20	-0.01	0.03	-0.01	-0.19	0.04	-0.15
	M73	-0.02	0.01	-0.01	0.00	-0.02	0.00	-0.03
	V74	-0.68	-0.06	0.18	-0.06	-0.61	0.28	-0.33
	F90	-0.32	-0.08	0.22	-0.01	-0.20	0.03	-0.17
	S91	-0.02	0.00	-0.01	0.00	-0.02	0.00	-0.02
	V92	-2.19	-0.08	0.37	-0.27	-2.17	0.56	-1.61

K93	-0.06	-0.04	0.04	0.00	-0.05	0.01	-0.04
P95	-0.40	0.02	0.01	-0.05	-0.43	0.11	-0.32
L98	-0.32	-0.03	0.12	-0.04	-0.27	0.04	-0.23
Y99	-0.25	-0.04	0.09	-0.03	-0.23	0.04	-0.19
L102	-0.01	0.00	0.00	0.00	-0.01	0.00	-0.01

Table S12. Each energy terms of binding free energy of residues within 5 Å from the binding interface of HRT−MDM2/MDMX obtained by the ASIE method (all values are in kcal/mol). The average results of the three trajectories are displayed.

Systems	Residues	$\Delta\Delta E_{vdW}$	$\Delta\Delta E_{ele}$	$\Delta\Delta G_{gb}$	$\Delta\Delta G_{np}$	$\Delta\Delta H$	$-T\Delta\Delta S$	$\Delta\Delta G_{bind}$
	K51	-0.24	0.05	-0.03	-0.03	-0.25	0.05	-0.20
	V53	-0.03	-0.02	0.00	0.00	-0.04	0.00	-0.04
	L54	-2.51	-0.08	0.32	-0.34	-2.62	0.55	-2.07
	F55	-0.32	-0.07	0.11	-0.01	-0.30	0.03	-0.27
	L57	-0.64	-0.11	0.13	-0.04	-0.65	0.08	-0.58
	Q59	-0.10	-0.06	0.08	0.00	-0.08	0.01	-0.07
	I61	-2.01	0.05	0.00	-0.21	-2.17	0.32	-1.86
	M62	-2.71	-0.33	0.59	-0.36	-2.80	0.70	-2.10
	Y67	-2.87	-0.19	0.28	-0.29	-3.08	0.65	-2.44
	Q72	-0.98	-0.39	0.36	-0.16	-1.17	0.41	-0.76
MDM2	H73	-0.11	-0.02	0.03	0.00	-0.10	0.01	-0.09
	V75	-0.50	0.01	0.01	-0.04	-0.51	0.02	-0.49
	L82	-0.28	-0.01	0.04	-0.02	-0.26	0.01	-0.25
	F86	-0.51	-0.06	0.15	-0.03	-0.45	0.03	-0.42
	F91	-0.89	0.10	0.17	-0.09	-0.70	0.11	-0.59
	V93	-2.25	0.02	0.41	-0.21	-2.04	0.41	-1.62
	K94	-0.24	-1.08	1.02	-0.02	-0.31	0.19	-0.13
	H96	-1.42	-0.68	0.64	-0.17	-1.63	0.43	-1.20
	I99	-1.63	-0.03	0.12	-0.20	-1.74	0.34	-1.39
	Y100	-0.38	0.00	0.05	-0.03	-0.36	0.03	-0.33
	I103	-0.57	0.00	0.02	-0.06	-0.61	0.04	-0.56
	M53	-2.41	-0.22	0.57	-0.35	-2.42	0.73	-1.69
	H54	-0.13	-0.17	0.20	0.00	-0.11	0.01	-0.09
	L56	-0.57	-0.10	0.11	-0.03	-0.59	0.11	-0.48
	Q58	-0.11	-0.08	0.10	0.00	-0.09	0.01	-0.08
	I60	-2.08	0.04	0.05	-0.23	-2.22	0.38	-1.83
	M61	-3.02	-0.62	0.83	-0.39	-3.21	0.75	-2.46
	Y66	-2.07	-0.12	0.18	-0.19	-2.20	0.40	-1.80
	D67	-0.04	-0.11	0.11	0.00	-0.04	0.03	0.00
	Q68	-0.25	-0.15	0.20	-0.04	-0.25	0.08	-0.17
	E70	-0.04	0.27	-0.24	0.00	-0.01	0.02	0.01
MDMX	Q71	-1.24	-0.02	0.18	-0.13	-1.21	0.33	-0.89
	H72	-0.22	-0.09	0.10	0.00	-0.22	0.05	-0.17
	M73	-0.04	0.01	-0.02	0.00	-0.06	0.00	-0.06
	V74	-0.65	0.00	0.02	-0.07	-0.69	0.15	-0.54
	L81	-0.19	0.00	0.03	-0.01	-0.18	0.00	-0.17
	F90	-1.05	-0.05	0.26	-0.10	-0.93	0.16	-0.77
	S91	-0.02	0.08	-0.09	0.00	-0.03	0.00	-0.04
	V92	-2.72	-0.15	0.55	-0.31	-2.63	0.61	-2.02
	P95	-0.43	0.00	0.00	-0.05	-0.48	0.13	-0.34
	L98	-1.17	-0.03	0.21	-0.19	-1.18	0.50	-0.69
	Y99	-0.85	0.03	0.11	-0.11	-0.82	0.12	-0.69

Table S13. Each energy terms of binding free energy of residues within 5 Å from the binding interface of HRQ−MDM2/MDMX obtained by the ASIE method (all values are in kcal/mol). The average results of the three trajectories are displayed.

Systems	Residues	$\Delta\Delta E_{vdW}$	$\Delta\Delta E_{ele}$	$\Delta\Delta G_{gb}$	$\Delta\Delta G_{np}$	$\Delta\Delta H$	$-T\Delta\Delta S$	$\Delta\Delta G_{bind}$
MDM2	V53	-0.02	0.00	-0.01	0.00	-0.03	0.00	-0.03
	L54	-1.14	-0.04	0.20	-0.08	-1.06	0.25	-0.82
	F55	-0.58	-0.10	0.24	-0.07	-0.51	0.19	-0.31
	L57	-0.75	-0.05	0.10	-0.07	-0.77	0.14	-0.63
	Q59	-0.33	-0.25	0.20	-0.06	-0.44	0.20	-0.23
	I61	-1.49	-0.03	0.21	-0.15	-1.46	0.31	-1.15
	M62	-1.10	-0.23	0.32	-0.14	-1.14	0.35	-0.79
	Y67	-1.93	-0.60	0.70	-0.19	-2.02	0.51	-1.51
	Q72	-0.09	-0.06	0.07	0.00	-0.08	0.00	-0.07
	H73	-0.04	-0.03	0.03	0.00	-0.04	0.00	-0.04
	I74	-0.01	0.00	-0.01	0.00	-0.01	0.00	-0.01
	V75	-0.49	-0.04	0.20	-0.05	-0.38	0.08	-0.30
	L82	-0.07	-0.01	0.04	0.00	-0.04	0.00	-0.04
	F86	-0.09	-0.01	0.06	0.00	-0.04	0.00	-0.04
	F91	-0.40	0.00	0.17	-0.03	-0.27	0.05	-0.22
	V93	-0.86	-0.01	0.12	-0.10	-0.85	0.19	-0.67
	I99	-0.85	-0.02	0.12	-0.15	-0.90	0.27	-0.63
	M102	-0.02	-0.02	0.02	0.00	-0.01	0.00	-0.01
	I103	-0.10	0.00	0.01	0.00	-0.10	0.00	-0.09
MDMX	V52	-0.02	-0.01	0.00	0.00	-0.03	0.00	-0.03
	M53	-1.73	-0.69	0.81	-0.21	-1.82	0.56	-1.26
	H54	-0.11	-0.02	0.05	0.00	-0.08	0.01	-0.07
	L56	-0.47	-0.04	0.09	-0.01	-0.43	0.05	-0.38
	Q58	-0.07	-0.03	0.05	0.00	-0.05	0.00	-0.04
	I60	-3.02	-0.11	0.42	-0.16	-2.87	0.46	-2.41
	M61	-0.84	-0.25	0.35	-0.14	-0.88	0.39	-0.49
	Y66	-1.90	-0.13	0.26	-0.14	-1.92	0.47	-1.45
	Q71	-0.52	-0.12	0.19	-0.06	-0.52	0.04	-0.48
	H72	-0.09	-0.09	0.09	0.00	-0.08	0.00	-0.08
	M73	-0.05	0.03	-0.05	0.00	-0.07	0.01	-0.06
	V74	-1.02	-0.04	0.34	-0.03	-0.75	0.34	-0.41
	F90	-1.30	-0.67	1.15	-0.13	-0.96	0.32	-0.64
	S91	-0.03	0.08	-0.08	0.00	-0.03	0.00	-0.03
	V92	-1.31	-0.05	0.18	-0.15	-1.32	0.26	-1.07
	P95	-0.72	-0.08	0.05	-0.09	-0.84	0.26	-0.57
	S96	-0.01	-0.03	0.03	0.00	0.00	0.00	0.00
	L98	-1.48	-0.08	0.35	-0.19	-1.40	0.35	-1.05
	Y99	-0.87	-0.04	0.22	-0.15	-0.85	0.19	-0.67
	L102	-0.06	0.00	0.02	0.00	-0.04	0.00	-0.04

Table S14. Each energy terms of binding free energy of residues within 5 Å from the binding interface of HRE−MDM2/MDMX obtained by the ASIE method (all values are in kcal/mol). The average results of the three trajectories are displayed.

Systems	Residues	$\Delta\Delta E_{vdW}$	$\Delta\Delta E_{ele}$	$\Delta\Delta G_{gb}$	$\Delta\Delta G_{np}$	$\Delta\Delta H$	$-T\Delta\Delta S$	$\Delta\Delta G_{bind}$
MDM2	V53	-0.03	-0.03	0.03	0.00	-0.03	0.00	-0.03
	L54	-2.55	0.05	0.27	-0.35	-2.57	0.60	-1.98
	F55	-0.11	-0.04	0.07	0.00	-0.08	0.01	-0.07
	L57	-0.72	-0.29	0.36	-0.05	-0.70	0.08	-0.62
	Q59	-0.09	-0.03	0.06	0.00	-0.07	0.01	-0.06
	I61	-2.59	0.02	0.13	-0.29	-2.73	0.37	-2.36
	M62	-3.75	-0.21	0.85	-0.48	-3.59	0.74	-2.85
	Y67	-2.22	-0.17	0.25	-0.25	-2.38	0.30	-2.08
	Q72	-0.85	-0.15	0.27	-0.11	-0.83	0.21	-0.61
	H73	-0.11	-0.07	0.07	0.00	-0.11	0.01	-0.10
	I74	-0.06	-0.03	0.00	0.00	-0.09	0.00	-0.09
	V75	-0.73	0.00	0.06	-0.07	-0.73	0.07	-0.66
	L82	-0.48	-0.09	0.20	-0.05	-0.42	0.03	-0.39
	F86	-0.66	-0.35	0.57	-0.09	-0.53	0.15	-0.38
	F91	-1.06	0.02	0.34	-0.11	-0.81	0.15	-0.66
	V93	-2.49	-0.23	0.51	-0.16	-2.37	0.40	-1.97
	K94	-0.24	-1.33	1.27	-0.01	-0.30	0.17	-0.13
	H96	-3.26	-2.52	2.20	-0.28	-3.86	1.18	-2.68
	I99	-2.64	-0.02	0.19	-0.27	-2.73	0.37	-2.36
	Y100	-1.03	-0.01	0.11	-0.11	-1.04	0.17	-0.86
	I103	-0.61	-0.01	0.09	-0.07	-0.59	0.04	-0.55
MDMX	V52	-0.03	-0.02	0.02	0.00	-0.03	0.00	-0.03
	M53	-2.26	0.06	0.48	-0.30	-2.02	0.53	-1.49
	H54	-0.16	0.01	0.03	0.00	-0.12	0.01	-0.10
	L56	-0.80	-0.20	0.29	-0.06	-0.77	0.01	-0.76
	Q58	-0.08	-0.06	0.09	0.00	-0.05	0.00	-0.05
	I60	-2.03	0.02	0.17	-0.25	-2.09	0.67	-1.42
	M61	-2.58	-0.20	0.60	-0.36	-2.53	0.59	-1.94
	Y66	-2.54	-0.13	0.29	-0.27	-2.64	0.51	-2.13
	Q68	-0.15	-0.11	0.13	-0.01	-0.14	0.04	-0.10
	Q71	-1.05	0.11	0.05	-0.12	-1.01	0.34	-0.67
	H72	-0.14	-0.08	0.05	0.00	-0.17	0.02	-0.15
	M73	-0.06	0.01	-0.02	0.00	-0.09	0.00	-0.08
	V74	-0.97	-0.03	0.14	-0.11	-0.98	0.19	-0.79
	L81	-0.44	-0.13	0.21	-0.06	-0.42	0.03	-0.39
	L85	-0.31	-0.11	0.16	-0.04	-0.30	0.03	-0.27
	F90	-1.19	-0.23	0.49	-0.14	-1.06	0.20	-0.86
	V92	-2.42	-0.10	0.60	-0.25	-2.18	0.59	-1.59
	K93	-0.08	-0.56	0.53	0.00	-0.10	0.04	-0.07
	P95	-0.40	-0.05	0.03	-0.05	-0.47	0.17	-0.30
	L98	-1.84	-0.01	0.39	-0.31	-1.77	0.70	-1.07
	Y99	-0.85	0.02	0.12	-0.12	-0.84	0.13	-0.71
	M101	-0.16	-0.36	0.35	-0.01	-0.18	0.04	-0.15

Table S15. Each energy terms of binding free energy of residues within 5 Å from the binding interface of HRH−MDM2/MDMX obtained by the ASIE method (all values are in kcal/mol). The average results of the three trajectories are displayed.

Systems	Residues	$\Delta\Delta E_{vdW}$	$\Delta\Delta E_{ele}$	$\Delta\Delta G_{gb}$	$\Delta\Delta G_{np}$	$\Delta\Delta H$	$-T\Delta\Delta S$	$\Delta\Delta G_{bind}$
MDM2	V53	-0.03	-0.02	0.01	0.00	-0.04	0.00	-0.04
	L54	-2.97	-0.04	0.27	-0.39	-3.15	0.60	-2.55
	F55	-0.12	0.02	0.00	0.00	-0.10	0.01	-0.09
	L57	-0.59	-0.09	0.10	-0.03	-0.61	0.02	-0.59
	Q59	-0.04	-0.06	0.07	0.00	-0.03	0.00	-0.03
	I61	-1.68	0.00	0.08	-0.21	-1.81	0.46	-1.34
	M62	-1.15	0.07	0.09	-0.20	-1.19	0.28	-0.91
	Y67	-1.72	0.02	0.23	-0.18	-1.65	0.27	-1.38
	H73	-0.11	-0.01	0.05	0.00	-0.08	0.01	-0.08
	V75	-0.39	0.00	0.04	-0.02	-0.38	0.01	-0.37
	L82	-0.23	-0.02	0.05	-0.01	-0.20	0.01	-0.20
	F86	-0.56	-0.09	0.19	-0.04	-0.51	0.04	-0.47
	F91	-0.88	0.14	0.18	-0.09	-0.64	0.14	-0.50
	V93	-1.93	0.00	0.43	-0.09	-1.58	0.19	-1.39
	K94	-0.16	-0.30	0.31	-0.01	-0.16	0.02	-0.13
	H96	-3.20	-2.00	1.64	-0.32	-3.88	1.23	-2.64
	I99	-2.36	-0.10	0.21	-0.27	-2.52	0.35	-2.18
	Y100	-1.09	0.05	0.05	-0.11	-1.09	0.23	-0.86
	I103	-0.50	-0.01	0.02	-0.03	-0.52	0.02	-0.50
MDMX	V52	-0.01	0.00	0.00	0.00	-0.01	0.00	-0.01
	M53	-1.59	-0.07	0.36	-0.22	-1.52	0.28	-1.23
	H54	-0.67	-0.05	0.15	-0.07	-0.64	0.16	-0.47
	L56	-0.66	0.01	0.04	-0.04	-0.65	0.07	-0.58
	Q58	-0.24	-0.14	0.15	-0.02	-0.25	0.05	-0.20
	I60	-1.76	0.00	0.10	-0.20	-1.85	0.46	-1.40
	M61	-0.62	-0.13	0.19	-0.09	-0.66	0.20	-0.46
	Y66	-0.52	-0.01	0.06	-0.04	-0.52	0.07	-0.45
	Q71	-0.05	0.01	0.01	0.00	-0.04	0.01	-0.03
	H72	-0.04	-0.01	0.01	0.00	-0.04	0.00	-0.04
	V74	-0.89	-0.01	0.06	-0.11	-0.94	0.21	-0.73
	L81	-0.32	-0.02	0.05	-0.03	-0.33	0.02	-0.31
	L85	-0.22	-0.01	0.03	-0.02	-0.22	0.02	-0.19
	F90	-1.07	0.00	0.21	-0.12	-0.99	0.24	-0.75
	S91	-0.01	-0.02	0.01	0.00	-0.01	0.00	-0.01
	V92	-1.39	0.00	0.11	-0.21	-1.48	0.36	-1.11
	K93	-0.04	0.01	-0.01	0.00	-0.03	0.00	-0.03
	P95	-0.31	0.01	-0.03	-0.04	-0.36	0.05	-0.32
	L98	-1.68	0.02	0.14	-0.24	-1.75	0.42	-1.33
	Y99	-0.51	-0.01	0.10	-0.07	-0.49	0.06	-0.43
	M101	-0.08	-0.03	0.03	0.00	-0.08	0.00	-0.08

Table S16. Each energy terms of binding free energy of residues within 5 Å from the binding interface of HTZ−MDM2/MDMX obtained by the ASIE method (all values are in kcal/mol). The average results of the three trajectories are displayed.

Systems	Residues	$\Delta\Delta E_{vdW}$	$\Delta\Delta E_{ele}$	$\Delta\Delta G_{gb}$	$\Delta\Delta G_{np}$	$\Delta\Delta H$	$-T\Delta\Delta S$	$\Delta\Delta G_{bind}$
MDM2	K51	-0.04	-0.07	0.07	0.00	-0.04	0.01	-0.03
	V53	-0.04	-0.01	-0.01	0.00	-0.05	0.00	-0.05
	L54	-2.26	-0.24	0.49	-0.20	-2.22	0.52	-1.70
	F55	-1.03	-0.15	0.33	-0.12	-0.98	0.37	-0.61
	Y56	-0.06	0.00	0.01	0.00	-0.05	0.00	-0.05
	L57	-0.82	-0.05	0.12	-0.03	-0.79	0.10	-0.69
	Q59	-0.46	-0.10	0.20	-0.04	-0.39	0.09	-0.31
	I61	-1.85	0.00	0.30	-0.21	-1.77	0.70	-1.07
	M62	-2.21	-0.02	0.51	-0.35	-2.07	0.42	-1.65
	L66	-0.06	-0.03	0.02	0.00	-0.06	0.00	-0.06
	Y67	-2.45	-0.14	0.38	-0.35	-2.56	0.37	-2.19
	Q72	-0.77	0.02	0.15	-0.12	-0.72	0.14	-0.58
	H73	-0.16	0.00	0.04	0.00	-0.12	0.01	-0.11
	V75	-0.59	0.00	0.09	-0.05	-0.55	0.03	-0.51
	L82	-0.27	-0.03	0.08	-0.01	-0.22	0.01	-0.21
	F86	-0.58	-0.12	0.24	-0.04	-0.50	0.04	-0.46
	F91	-1.04	0.02	0.31	-0.09	-0.81	0.16	-0.64
	V93	-1.71	-0.02	0.28	-0.18	-1.63	0.45	-1.19
	K94	-0.13	-0.10	0.12	0.00	-0.12	0.01	-0.10
	E95	-0.03	0.21	-0.18	0.00	0.00	0.00	0.00
	H96	-2.60	0.21	0.09	-0.25	-2.55	0.44	-2.12
	I99	-2.00	-0.07	0.16	-0.22	-2.13	0.39	-1.74
	Y100	-0.93	-0.08	0.19	-0.06	-0.87	0.09	-0.77
	I103	-0.40	-0.01	0.05	-0.02	-0.38	0.01	-0.37
MDMX	V49	-0.10	-0.01	0.01	-0.01	-0.11	0.02	-0.09
	K50	-0.46	-0.31	0.33	-0.05	-0.49	0.11	-0.39
	E51	0.00	0.10	-0.09	0.00	0.01	0.00	0.01
	V52	-0.02	0.00	-0.01	0.00	-0.03	0.00	-0.03
	M53	-2.35	-0.97	1.03	-0.23	-2.51	0.54	-1.97
	H54	-1.16	-0.34	0.34	-0.11	-1.27	0.36	-0.91
	Y55	-0.03	0.00	0.00	0.00	-0.02	0.00	-0.02
	L56	-0.33	-0.02	0.05	-0.01	-0.31	0.04	-0.27
	Q58	-0.06	-0.03	0.05	0.00	-0.04	0.01	-0.03
	Y59	-0.02	0.00	0.00	0.00	-0.02	0.00	-0.02
	I60	-1.71	0.01	0.15	-0.21	-1.76	0.34	-1.42
	M61	-0.97	-0.29	0.39	-0.14	-1.02	0.23	-0.78
	L65	-0.02	-0.01	0.00	0.00	-0.02	0.00	-0.02
	Y66	-0.80	-0.03	0.13	-0.12	-0.81	0.23	-0.59
	D67	-0.01	-0.07	0.06	0.00	-0.01	0.00	-0.01
	Q71	-0.23	0.00	0.05	-0.04	-0.22	0.06	-0.17
	H72	-0.08	-0.03	0.04	0.00	-0.08	0.01	-0.07
	M73	-0.01	0.01	-0.01	0.00	-0.02	0.00	-0.02
	V74	-0.66	-0.01	0.06	-0.06	-0.67	0.09	-0.58

L81	-0.07	0.00	0.02	0.00	-0.05	0.00	-0.05
L85	-0.04	0.00	0.01	0.00	-0.03	0.00	-0.03
F 90	-0.79	-0.01	0.30	-0.09	-0.59	0.21	-0.38
S91	-0.01	0.00	-0.01	0.00	-0.02	0.00	-0.02
V92	-1.99	-0.02	0.24	-0.24	-2.01	0.45	-1.55
K93	-0.04	-0.09	0.09	0.00	-0.04	0.01	-0.03
P95	-0.68	0.00	0.02	-0.05	-0.72	0.18	-0.53
P97	-0.01	0.00	-0.01	0.00	-0.01	0.00	-0.01
L98	-1.04	-0.03	0.23	-0.16	-0.99	0.31	-0.69
Y99	-0.92	-0.07	0.19	-0.11	-0.90	0.15	-0.74
M101	-0.03	0.01	-0.01	0.00	-0.03	0.00	-0.02
L102	-0.06	0.01	0.00	0.00	-0.05	0.00	-0.05

Table S17. Each energy terms of binding free energy of residues within 5 Å from the binding interface of HU8−MDM2/MDMX obtained by the ASIE method (all values are in kcal/mol). The average results of the three trajectories are displayed.

Systems	Residues	$\Delta\Delta E_{vdW}$	$\Delta\Delta E_{ele}$	$\Delta\Delta G_{gb}$	$\Delta\Delta G_{np}$	$\Delta\Delta H$	$-T\Delta\Delta S$	$\Delta\Delta G_{bind}$
MDM2	L54	-3.09	-0.07	0.33	-0.45	-3.28	0.67	-2.61
	F55	-1.28	-0.28	0.42	-0.17	-1.31	0.50	-0.81
	L57	-0.58	0.00	0.04	-0.02	-0.57	0.10	-0.47
	Q59	-0.69	-0.15	0.26	-0.07	-0.65	0.14	-0.51
	I61	-1.74	0.02	0.01	-0.19	-1.91	0.54	-1.36
	M62	-1.48	-0.02	0.21	-0.24	-1.53	0.33	-1.20
	Y67	-1.29	-0.02	0.12	-0.17	-1.35	0.17	-1.18
	Q72	-0.17	-0.01	0.06	-0.01	-0.14	0.02	-0.12
	H73	-0.16	-0.02	0.05	-0.01	-0.14	0.03	-0.11
	V75	-0.54	-0.01	0.02	-0.04	-0.57	0.03	-0.54
	L82	-0.15	-0.01	0.02	0.00	-0.14	0.00	-0.14
	F86	-0.33	-0.04	0.09	-0.02	-0.30	0.01	-0.29
	F91	-0.75	-0.02	0.13	-0.06	-0.70	0.09	-0.62
	V93	-2.32	-0.03	0.42	-0.14	-2.07	0.56	-1.52
	K94	-0.77	0.26	-0.13	-0.07	-0.71	0.10	-0.61
	H96	-3.33	-1.74	1.19	-0.31	-4.19	0.99	-3.19
	I99	-2.00	-0.03	0.04	-0.20	-2.19	0.34	-1.86
	Y100	-0.60	-0.12	0.14	-0.05	-0.62	0.05	-0.57
	I103	-0.27	-0.01	0.01	-0.01	-0.28	0.01	-0.27
MDMX	V49	-0.03	0.00	0.00	0.00	-0.03	0.01	-0.02
	K50	-0.71	-0.10	0.13	-0.13	-0.81	0.17	-0.64
	E51	-0.02	-0.06	0.06	0.00	-0.01	0.00	-0.01
	V52	-0.01	0.00	-0.01	0.00	-0.02	0.00	-0.02
	M53	-2.23	-0.51	0.72	-0.30	-2.33	0.62	-1.71
	H54	-1.35	-0.79	0.67	-0.13	-1.60	0.50	-1.11
	Y55	-0.03	0.00	0.00	0.00	-0.03	0.00	-0.03
	L56	-0.27	0.05	-0.06	-0.01	-0.29	0.04	-0.25
	Q58	-0.49	-0.15	0.19	-0.04	-0.49	0.13	-0.36
	I60	-1.27	-0.01	0.05	-0.15	-1.39	0.22	-1.17
	M61	-0.80	-0.05	0.19	-0.11	-0.77	0.28	-0.49
	Y66	-0.39	-0.07	0.12	-0.07	-0.40	0.07	-0.33
	Q71	-0.07	0.00	0.01	-0.01	-0.06	0.01	-0.05
	H72	-0.27	0.01	0.03	-0.03	-0.27	0.07	-0.20
	V74	-0.65	0.01	0.13	-0.07	-0.58	0.17	-0.41
	L81	-0.04	0.01	-0.01	0.00	-0.04	0.00	-0.04
	L85	-0.03	0.01	-0.01	0.00	-0.03	0.00	-0.03
	F90	-0.91	0.13	0.07	-0.10	-0.82	0.12	-0.70
	S91	0.00	0.01	-0.01	0.00	-0.01	0.00	-0.01
	V92	-2.04	0.00	0.14	-0.24	-2.14	0.46	-1.68
	K93	-0.06	0.12	-0.10	0.00	-0.05	0.01	-0.04
	P95	-0.43	0.01	0.00	-0.05	-0.46	0.08	-0.38
	P97	-0.01	0.00	0.00	0.00	-0.01	0.00	-0.01
	L98	-0.86	0.01	0.04	-0.14	-0.95	0.29	-0.67

Y99	-0.51	-0.02	0.11	-0.06	-0.48	0.08	-0.40
M101	-0.01	0.02	-0.02	0.00	-0.01	0.00	-0.01
L102	-0.05	0.00	0.00	0.00	-0.05	0.00	-0.05