Supplementary Information (SI) for Physical Chemistry Chemical Physics.
This journal is © the Owner Societies 2026

Comparative binding mechanisms of SND1 with MTDH and small-molecule inhibitors: Insights from molecular dynamics simulation and free energy calculation

Xi Zhu[1], Jiarui Chang[1], Min Fang[1], Xinyu Wu[1], Zhixiang Yin[1], John Z. H. Zhang[2,3], Fenghua Qi[4*], Tong Zhu[3,5*], and Ya Gao[1*]

[1]School of Mathematics, Physics and Statistics, Shanghai University of Engineering Science, Shanghai 201620, China
[2] Faculty of Synthetic Biology, Shenzhen University of Advanced Technology, Shenzhen 518107, China
[3]NYU-ECNU Center for Computational Chemistry at NYU Shanghai, Shanghai 200062, China
[4] School of Electronic Engineering, Nanjing Xiaozhuang University, Nanjing 211171, China
[5]Shanghai Engineering Research Center of Molecular Therapeutics & New Drug Development, School of Chemistry and Molecular Engineering, East China Normal University, Shanghai 200062, China

*Corresponding author e-mail:
qifenghua@njxzc.edu.cn; tzhu@lps.ecnu.edu.cn; gaoya@sues.edu.cn

Table S1. Binding free energy for MTDH-SND1 complex in three replicas. Errors are expressed as the standard error of the mean, and all values are in kcal/mol.

replica	ΔE_{vdw}	ΔE_{ele}	ΔG_{gb}	ΔG_{np}	ΔH	$-T\Delta S$	ΔG_{cal}
1	-110.27±0.37	-695.3±2.73	719.1±2.35	-10.49±0.02	-96.94±0.66	86.40±0.00	-10.54±0.66
2	-89.44±0.39	-580.0±2.00	599.6±1.91	-8.0±0.03	-78.49±0.39	67.25±0.00	-11.24±0.39
3	-105.54±0.40	-653.1±1.84	679.1±1.71	-9.90±0.02	-89.38±0.43	71.48±0.00	-17.90±0.43

Table S2. Energy contributions of mutant residues in SND1 binding with MTDH and other 9 small molecule inhibitors obtained by the ASIE method. All values are in kcal/mol.

Systems	**Residues**	$\Delta\Delta E_{vdw}$	$\Delta\Delta E_{ele}$	$\Delta\Delta G_{gb}$	$\Delta\Delta G_{np}$	$\Delta\Delta H$	$-T\Delta\Delta S$	$\Delta\Delta G_{bind}$
MTDH	Arg20	-0.07	12.37	-10.23	0.19	2.26	-2.86	-0.60
	Gln22	0.29	0.39	-0.52	0.02	0.18	-0.81	-0.63
	Pro23	1.05	0.34	-0.55	0.08	0.91	-0.56	0.35
	Pro27	1.12	-0.22	0.11	-0.01	1.01	-0.53	0.48
	Pro28	0.90	0.35	-0.37	0.02	0.90	-0.21	0.69
	Arg71	0.97	8.02	-6.84	0.02	2.16	-0.48	1.68
	Lys72	0.47	7.41	-6.52	0.02	1.38	-0.93	0.45
	Lys73	0.04	6.07	-5.32	0.00	0.78	-0.15	0.63
	Ile75	1.28	0.07	-0.06	0.03	1.31	-0.50	0.81
	Lys77	0.34	9.12	-8.04	0.02	1.44	-0.75	0.69
	Phe228	0.92	1.12	-1.83	0.11	0.32	-0.85	-0.53
	Glu231	2.92	-5.28	4.45	0.23	2.32	-1.23	1.09
	Phe234	4.49	0.31	-1.38	0.34	3.76	-1.08	2.68
	Phe235	1.98	-0.54	0.35	0.08	1.87	-0.60	1.27
	Ser238	0.74	-0.31	0.42	0.03	0.88	-0.23	0.65
	Arg239	6.07	11.11	-9.16	0.48	8.50	-2.76	5.74
	Leu240	1.31	-0.43	0.28	0.06	1.22	-0.43	0.79
	Gln242	0.05	-0.74	0.70	0.00	0.01	-0.03	-0.02
	Arg243	2.09	14.92	-12.18	0.34	5.18	-3.00	2.18
	Asp244	0.86	-8.84	7.81	0.05	-0.12	-0.33	-0.65
	Hie263	3.65	3.30	-3.13	0.26	4.09	-1.77	2.32
	Asn265	1.98	0.91	-0.95	0.13	2.07	-1.99	0.08
	Asn267	0.03	-0.35	0.34	0.00	0.03	-0.05	-0.02
	Ile268	0.79	0.13	-0.14	0.04	0.81	-0.11	0.70
	Leu271	0.64	0.30	-0.52	0.06	0.48	-0.17	0.31
	Glu275	0.52	-6.01	5.20	0.07	-0.22	-0.45	-0.67
	Phe277	2.25	0.24	-1.14	0.14	1.49	-0.57	0.91
	Arg308	2.01	8.09	-6.83	0.39	3.66	-3.46	0.20
	Total	**39.70**	**61.84**	**-56.04**	**3.20**	**48.68**	**-26.89**	**21.79**
	Arg20	0.03	0.09	-0.09	0.00	0.03	-0.01	0.02
	Arg71	0.03	0.04	-0.03	0.00	0.04	-0.01	0.03
	Ile75	0.06	0.01	0.00	0.00	0.07	0.00	0.07

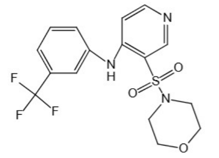
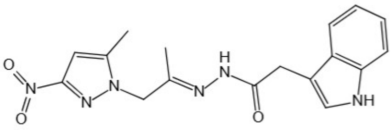
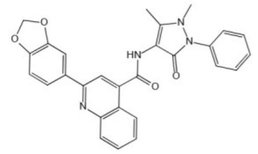
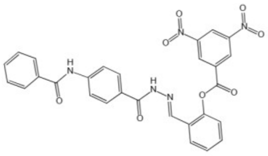
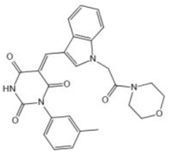
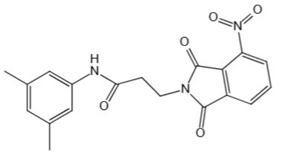
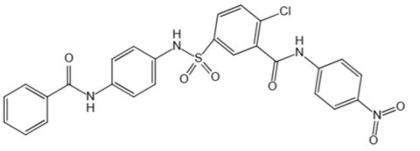
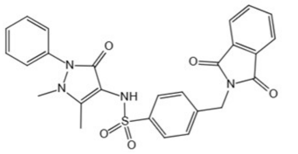
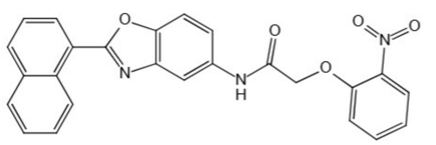
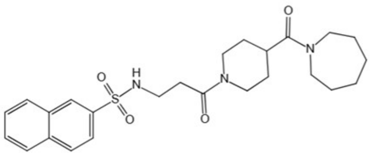
L3	Ser238	0.02	-0.05	0.04	0.00	0.01	0.00	0.01
	Arg239	1.81	0.30	-0.32	0.14	1.93	-0.74	1.19
	Leu240	1.58	0.13	-0.34	0.13	1.50	-0.60	0.90
	Gln242	0.01	0.02	-0.02	0.00	0.01	-0.00	0.01
	Arg243	3.44	0.07	-0.18	0.28	3.61	-1.27	2.34
	Asp244	0.05	-0.02	0.01	0.00	0.04	-0.04	0.00
	Hie263	4.94	0.78	-1.22	0.25	4.75.	-3.01	1.74
	Pro264	0.54	-0.04	0.05	0.02	0.57	-0.21	0.36
	Asn265	0.30	-0.04	-0.06	0.01	0.21	-0.13	0.08
	Ile268	1.69	0.12	-0.14	0.06	1.73	-0.71	1.02
	Leu271	1.01	-0.03	-0.11	0.12	0.99.	-0.27	0.72
	Total	**15.54**	**1.29**	**-2.34**	**1.01**	**15.49**	**-7.03**	**8.46**
L4	Ile75	0.08	0.02	-0.00	0.00	0.10	-0.02	0.08
	Lys77	0.03	0.08	-0.08	0.00	0.04	-0.05	-0.01
	Phe235	1.22	-0.66	0.43	0.06	1.06	-0.11	0.95
	Arg239	2.78	3.71	-2.78	0.34	4.06	-3.06	1.00
	Leu240	0.79	-0.06	-0.02	0.06	0.77	-0.14	0.63
	Arg243	4.16	0.71	-0.74	0.40	4.52	-2.01	2.52
	Val245	0.12	-0.01	0.02	0.00	0.13	-0.00	0.13
	Ile261	0.14	-0.01	0.01	0.01	0.15	-0.00	0.15
	Hie263	3.000	0.44	-0.83	0.13	2.75	-0.34	2.41
	Asn265	1.95	1.31	-1.23	0.14	2.17	-1.97	-0.20
	Asn267	0.05	-0.03	0.03	0.00	0.06	-0.01	0.05
	Ile268	0.93	0.06	-0.13	0.03	0.89	-0.12	0.77
	Leu271	3.57	0.04	-0.63	0.29	3.27	-0.64	2.63
	Lys274	0.22	-0.34	0.28	0.01	0.17	-0.03	0.14
	Glu275	1.13	-0.07	-0.06	0.23	1.23	-0.51	0.72
	Total	**20.16**	**5.20**	**-5.71**	**1.70**	**21.35**	**-9.01**	**12.34**
L5	Ile7	0.25	0.01	-0.01	0.00	0.25	-0.01	0.24
	Arg20	3.56	0.30	-0.41	0.40	3.85	-1.61	2.24
	Gln22	0.05	-0.03	0.01	0.00	0.03	-0.01	0.02
	Ile75	0.36	-0.01	-0.08	0.03	0.30	-0.12	0.18
	Lys77	0.10	-0.03	0.01	0.00	0.08	-0.00	0.08
	Glu78	0.02	-0.04	0.03	0.00	0.01	-0.00	0.01
	Phe235	1.31	-0.53	0.25	0.05	1.08	-0.23	0.85
	Ser238	0.70	-0.10	0.02	0.01	0.62	1.36	1.98
	Arg239	4.05	2.24	-1.58	0.40	5.11	-3.85	1.26
	Leu240	0.09	-0.08	0.13	0.00	0.14	-0.00	0.14
	Arg243	3.51	1.95	-1.48	0.45	4.43	-1.85	2.58
	Hie263	1.27	1.32	-1.15	0.04	1.48	-0.46	1.02
	Asn265	2.09	-1.08	0.71	0.14	1.86	-0.46	1.40
	Ile268	0.23	0.04	-0.02	0.00	0.25	-0.01	0.24
	Leu271	2.20	0.16	-0.59	0.25	2.02	-0.56	1.46

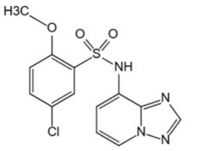
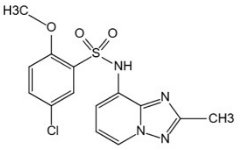
	Lys274	0.54	-0.45	0.36	0.07	0.52	-0.11	0.42
	Glu275	0.82	0.20	-0.27	0.17	0.92	-0.39	0.54
	Total	**21.15**	**3.86**	**-4.07**	**2.02**	**22.95**	**-8.30**	**14.65**
L6	Arg71	1.36	0.05	0.03	0.04	1.48	-0.25	1.22
	Lys72	0.67	-0.17	0.13	0.02	0.65	0.23	0.88
	Lys73	0.05	-0.10	0.08	0.00	0.03	-0.01	0.02
	Ile75	1.01	0.02	0.03	0.01	1.07	-0.21	0.86
	Lys77	0.19	-0.10	0.08	0.01	0.18	-0.06	0.12
	Ser238	0.01	0.01.	-0.01	0.00	0.01	0.00	0.01
	Arg239	2.08	1.64	-1.12	0.28	2.88	-1.24	1.64
	Leu240	1.14	0.02	0.01	0.06	1.23	-0.16	1.07
	Gln242	0.05	0.02	-0.01	0.00	0.06	-0.02	0.04
	Arg243	3.09	0.92	-0.64	0.22	3.59	-1.10	2.49
	Asp244	1.06	-0.18	0.10	0.06	1.04	-0.16	0.88
	Hie263	4.24	0.23	-0.57	0.21	4.11	-1.11	3.00
	Asn265	0.65	1.87	-1.17	0.10	1.44	-1.54	-0.1
	Asn267	0.02	-0.02	0.04	0.00	0.04	0.00	0.04
	Ile268	0.73	0.03	-0.02	0.06	0.80	-0.32	0.48
	Leu271	1.29	0.02	-0.13	0.16	1.34	-0.58	0.76
	Total	**17.64**	**4.24**	**-3.17**	**1.23**	**19.94**	**-6.53**	**13.41**
L8	Phe235	0.32	-0.03	-0.02	0.00	0.27	-0.04	0.23
	Ser238	0.01	0.03	-0.03	0.00	0.01	0.00	0.01
	Arg239	1.79	-0.10	0.06	0.15	1.89	-1.52	0.37
	Leu240	1.63	0.03	-0.23	0.09	1.52	-0.18	1.34
	Arg243	0.62	0.12	-0.10	0.02	0.66	-0.15	0.51
	Hie263	3.00	0.06	-0.50	0.09	2.66	-0.99	1.67
	Pro264	0.09	0.01	0.03	0.00	0.13	-0.01	0.12
	Asn265	1.44	2.23	-1.93	0.13	1.88	-1.17	0.71
	Asn267	0.24	-0.08	0.12	0.00	0.28	-0.08	0.20
	Ile268	1.52	0.04	-0.16	0.06	1.46	-0.14	1.32
	Glu270	0.93	1.22	-1.03	0.17	1.29	-0.19	1.10
	Leu271	2.95	0.07	-0.68	0.26	2.60	-0.64	1.96
	Lys274	1.90	1.48	-1.27	0.31	2.43	-1.42	1.01
	Glu275	0.14	0.04	-0.05	0.00	0.12	-0.46	-0.34
	Lys294	0.70	-0.43	0.37	0.06	0.70	-0.05	0.65
	Leu295	0.06	0.05	-0.02	0.00	0.09	0.00	0.09
	Total	**17.34**	**4.75**	**-5.44**	**1.34**	**17.98**	**-7.07**	**10.91**
	Ile7	1.22	0.15	-0.33	0.14	1.18	-0.61	0.57
	Arg20	1.02	2.96	-2.04	0.24	2.18	-3.66	-1.48
	Gln22	0.32	-0.06	0.01	0.02	0.29	-0.53	-0.24
	Lys77	0.08	0.13	-0.12	0.00	0.09	-0.01	0.08
	Glu78	0.22	-0.02	-0.01	0.02	0.21	-0.15	0.06
	Phe234	1.37	-0.01	-0.58	0.12	0.90	-0.43	0.47

L9	Ser238	1.01	0.10	-0.23	0.00	0.88	-0.62	0.26
	Arg239	6.59	0.84	-0.76	0.34	7.01	-1.62	5.39
	Leu240	0.78	-0.16	0.10	0.04	0.77	-0.08	0.69
	Arg243	0.99	0.78	-0.69	0.06	1.14	-0.63	0.51
	Val245	0.04	-0.02	0.04	0.00	0.06	0.00	0.06
	Ile261	0.05	-0.01	0.02	0.00	0.06	0.00	0.06
	Hie263	1.61	0.86	-0.92	0.05	1.60	-0.65	0.95
	Asn265	1.77	0.08	-0.42	0.09	1.52	-0.50	1.02
	Asn267	0.04	0.03	-0.03	0.00	0.04	-0.01	0.03
	Ile268	0.68	0.00	-0.03	0.03	0.68	-0.09	0.59
	Leu271	0.67	0.01	-0.09	0.06	0.65	-0.13	0.52
	Total	**18.43**	**5.66**	**-6.08**	**1.23**	**19.25**	**-8.47**	**10.78**
L10	Phe235	0.92	-0.22	0.13	0.06	0.89	-0.38	0.51
	Arg239	5.22	0.83	-0.85	0.40	5.60	-2.86	2.73
	Leu240	0.70	-0.11	0.00	0.07	0.66	-0.71	-0.05
	Arg243	4.76	0.42	-0.45	0.30	5.03	-0.88	4.15
	Hie263	2.09	-0.23	-0.04	0.08	1.91	-0.40	1.51
	Asn265	1.75	1.00	-0.81	0.09	2.03	-0.57	1.46
	Asn267	0.09	-0.20	0.17	0.00	0.06	-0.01	0.05
	Ile268	0.54	-0.01	0.00	0.02	0.55	-0.10	0.45
	Leu271	0.24	0.03	-0.08	0.01	0.20	-0.09	0.12
	Glu275	0.08	0.08	-0.09	0.00	0.09	-0.04	0.05
	Phe301	0.00	-0.01	0.01	0.00	0.01	0.00	0.01
	Arg308	0.03	-0.04	0.04	0.00	0.03	-0.02	0.01
	Total	**16.45**	**1.51**	**-1.93**	**1.03**	**17.06**	**-6.05**	**11.01**
A2	Phe234	0.01	-0.03	0.04	0.00	0.02	0.00	0.02
	Arg239	3.06	1.53	-0.91	0.33	4.01	-1.41	2.60
	Leu240	1.39	0.16	-0.31	0.09	1.33	-0.56	0.77
	Arg243	0.89	-0.47	0.39	0.07	0.88	-0.14	0.74
	Val245	0.25	0.01	0.01	0.03	0.30	-0.07	0.23
	Hie263	4.35	-0.54	-0.03	0.15	3.94	-1.57	2.37
	Asn265	1.41	0.49	-0.56	0.07	1.41	-0.74	0.67
	Asn267	0.10	-0.05	0.07	0.00	0.12	0.00	0.12
	Ile268	1.33	0.12	-0.10	0.05	1.40	-0.16	1.24
	Leu271	2.45	0.10	-0.36	0.20	2.39	-1.02	1.37
	Total	**15.28**	**1.24**	**-1.71**	**0.97**	**15.78**	**-5.67**	**10.11**
A6	Ile7	0.01	0.01	-0.01	0.00	0.01	0.00	0.01
	Arg20	0.02	0.16	-0.15	0.00	0.04	0.00	0.04
	Ile75	0.10	0.04	-0.01	0.00	0.13	0.00	0.13
	Lys77	0.08	0.21	-0.20	0.00	0.09	0.00	0.09
	Phe234	0.01	0.00	0.02	0.00	0.03	0.00	0.03
	Phe235	0.16	-0.14	0.11	0.00	0.13	-0.02	0.11
	Ser238	0.02	-0.04	0.03	0.00	0.01	0.00	0.01

Arg239	1.94	-0.08	0.04	0.12	2.02	-2.14	-0.12
Leu240	1.05	-0.16	0.14	0.06	1.09	-0.85	0.24
Arg243	5.30	1.34	-1.27	0.43	5.80	-1.26	4.54
Hie263	4.66	0.92	-1.10	0.11	4.59	-1.22	3.37
Asn265	1.95	0.90	-0.58	0.13	2.40	-0.95	1.45
Ile268	0.96	0.10	-0.01	0.02	1.08	-0.36	0.72
Leu271	0.92	-0.09	-0.04	0.11	0.90	-0.68	0.22
Total	**17.19**	**3.18**	**-3.04**	**0.98**	**18.32**	**-7.47**	**10.84**

Table S3. Structures and dissociation constants of 12 small molecule inhibitors.

Compounds	Chemical structure	K_D (μM)
L1		467±87.1
L3		194±37.4
L4		11.3±2.10
L5		2.64±0.36
L6		5.53±0.30
L7		4.36±1.38
L8		0.214±0.002
L9		29.8±19.6
L10		3.04±0.10
L12		13.6±4.24

A2		87.4±4.42
A6		89.7±33.0

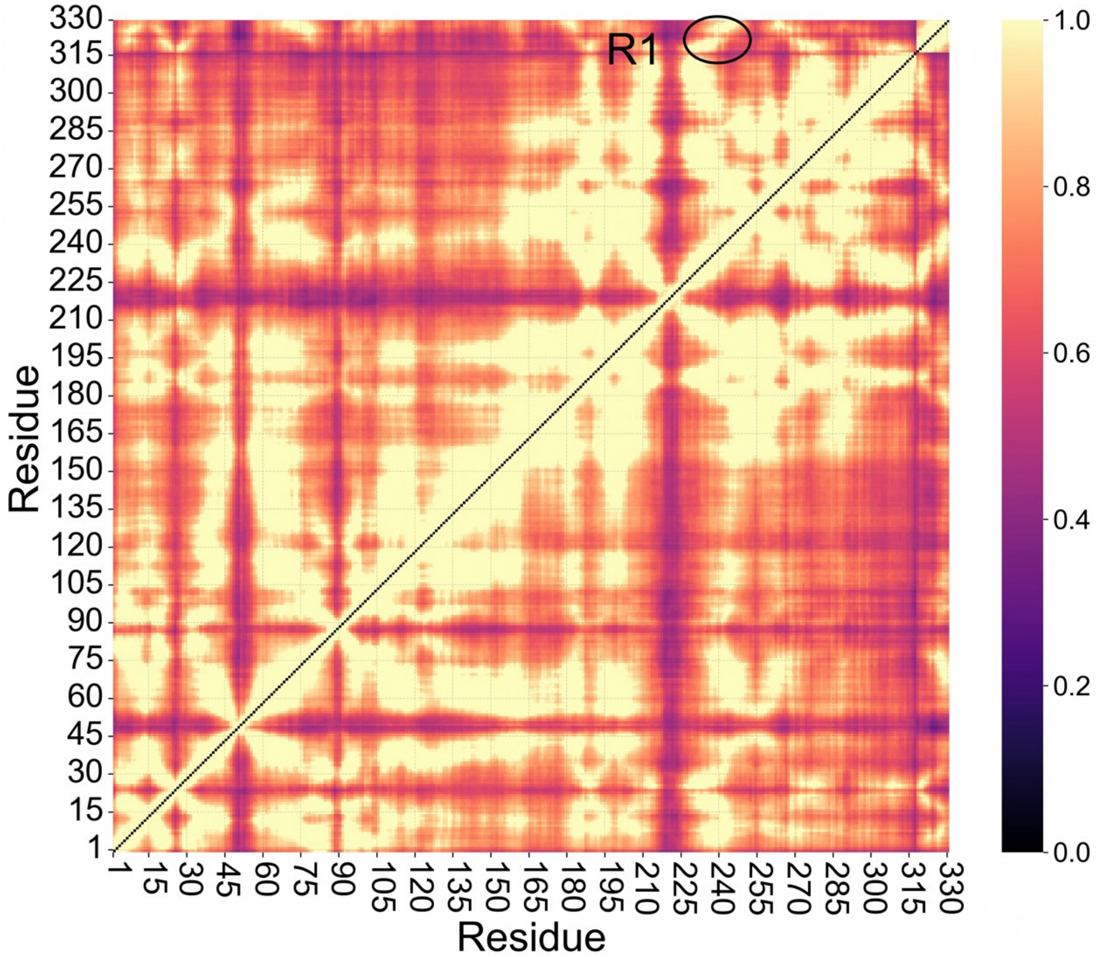


Figure S1. Mutual information (MI) matrix of the MTDH-SND1 complex. The black box indicates the R1 region with significant information coupling.

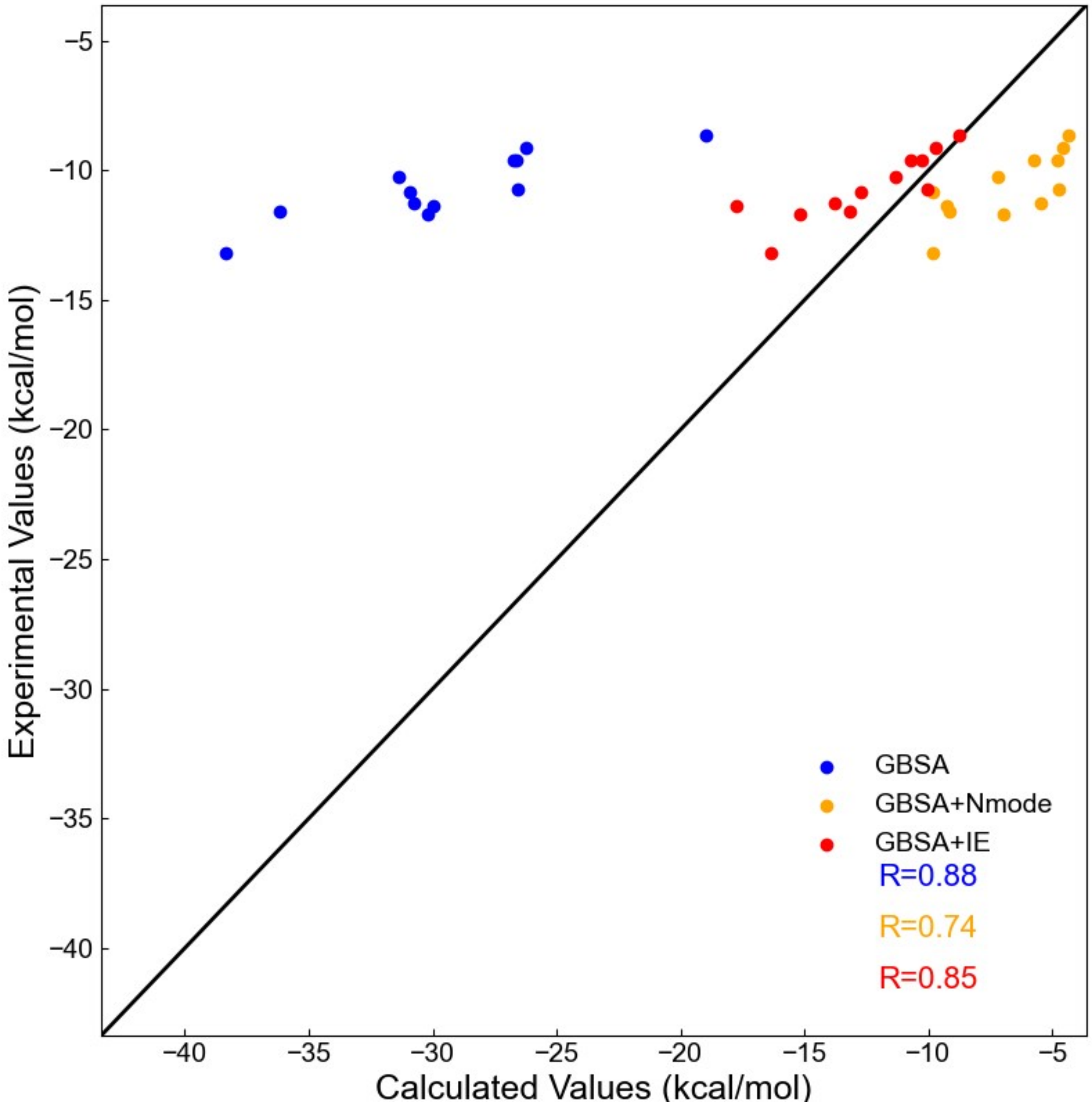


Figure S2. Correlation coefficients between theoretically calculated free energies obtained by GBSA, GBSA+Nmode, GBSA+IE methods and experimental values.