Electronic Supplementary Material (ESI) for RSC Advances.

Supporting Information

Adequate Prediction for Inhibitor Affinity of 12Aβ$_{40}$ Photofibril Using Linear Interaction Energy Method

Son Tung Ngo,[a,b,*] Binh Khanh Mai,[c,†,*] Philippe Derreumaux[def] and Van V. Vu[g]

[a]Laboratory of Theoretical and Computational Biophysics, Ton Duc Thang University, Ho Chi Minh City, Vietnam

[b]Faculty of Applied Sciences, Ton Duc Thang University, Ho Chi Minh City, Vietnam

[c]Institute for Computational Science and Technology (ICST), Quang Trung Software City, Ho Chi Minh City, Vietnam

[d]Laboratoire de Biochimie Theorique, UPR 9080 CNRS, IBPC, Universite Paris 7, 13 rue Pierre et Marie Curie, 75005, Paris, France

[e]Laboratory of Theoretical Chemistry, Ton Duc Thang University, Ho Chi Minh City, Vietnam

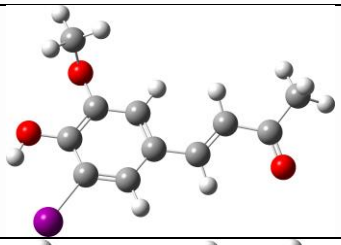
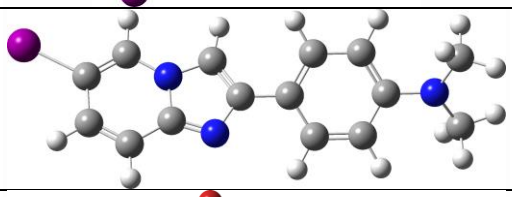
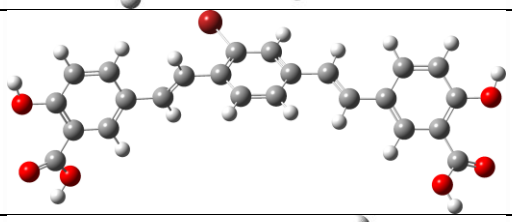
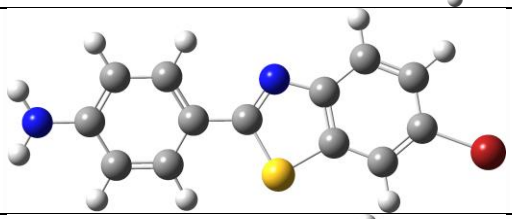
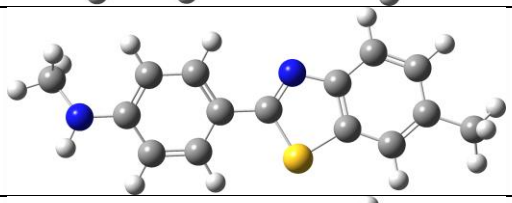
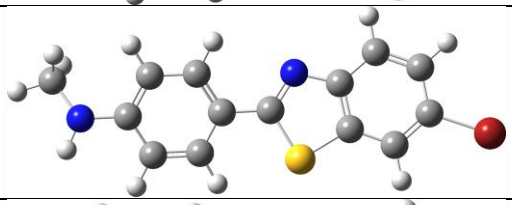
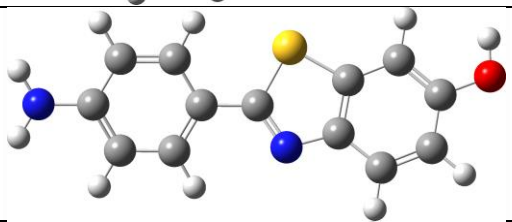
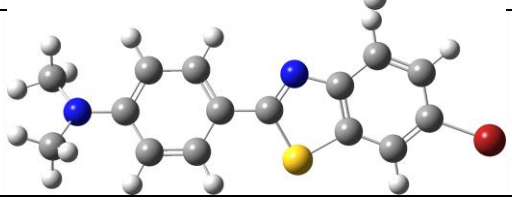
[f]Faculty of Pharmacy, Ton Duc Thang University, Ho Chi Minh City, Vietnam

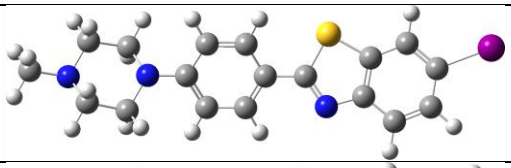
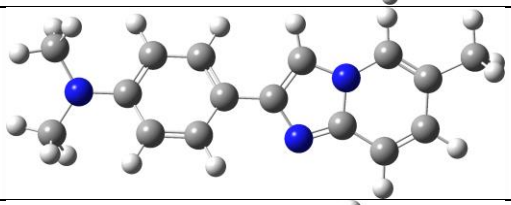
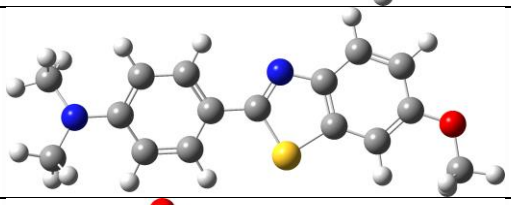
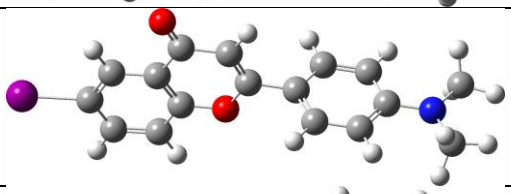
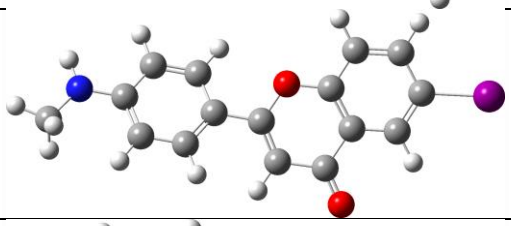
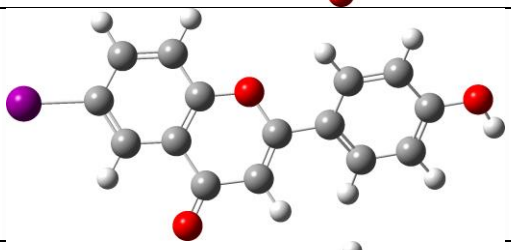
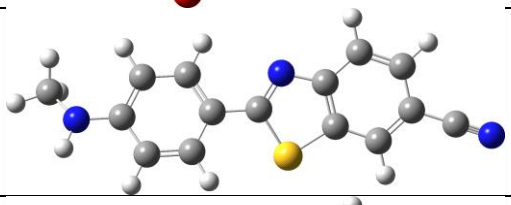
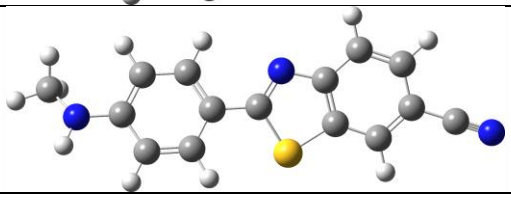
[g]NTT Hi-Tech Institute, Nguyen Tat Thanh University, Ho Chi Minh City, Vietnam

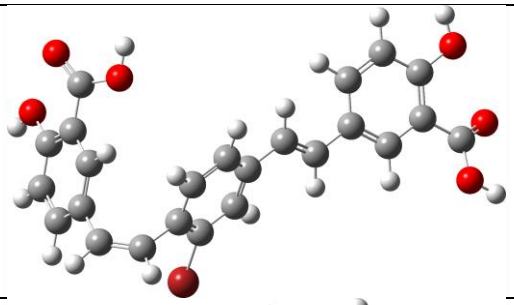
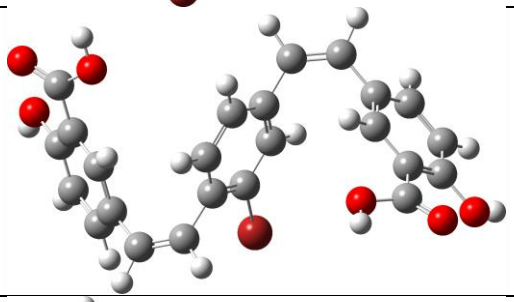
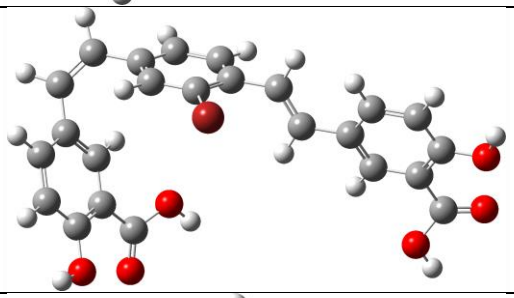
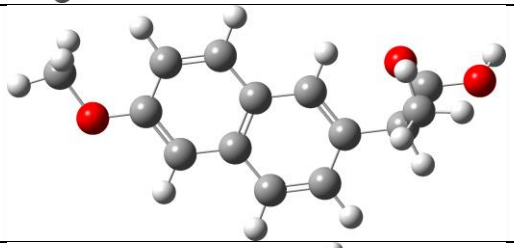
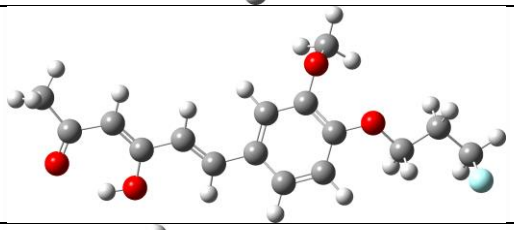
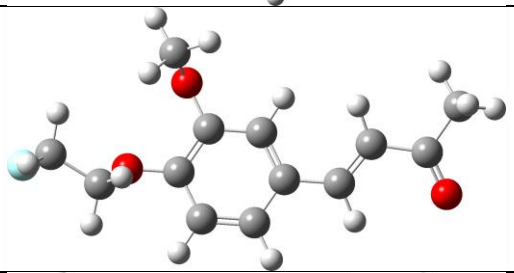
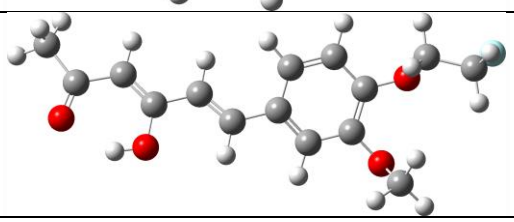
[†]Present address: Department of Organic Chemistry, Stockholm University, SE-106 91 Stockholm, Sweden.

*Emails: ngosontung@tdtu.edu.vn and binh.khanh.mai@su.se

Table S1. List of amyloid inhibitors with PubChem ID and experimental K_i values.

N⁰	Compound	Pubchem ID	Structure	K_i (nM)
1	CHEMBL81260[1]	10064445		19.97
2	CHEMBL78012[2]	10133297		15.00
3	CHEMBL74704[3]	10184360		0.11
4	CHEMBL92852[4]	10335228		7.20
5	CHEMBL330529[4]	10422457		10.00
6	CHEMBL328660[4]	10426074		1.70
7	CHEMBL93884[4]	10444413		46.00
8	CHEMBL55401[5]	10496851		1.90

9	CHEMBL58092[5]	10844298		5.40
10	CHEMBL78621[3]	11054105		242.00
11	CHEMBL328430[4]	11129817		1.90
12	CHEMBL375934[6]	11574659		13.20
13	CHEMBL224643[6]	11632242		22.60
14	CHEMBL388844[6]	11703303		72.50
15	CHEMBL92802[4]	11821524		8.60
16	CHEMBL1908959[7]	1358096		10.09

17	CHEMBL305634[2]	15521136		0.19
18	CHEMBL76112[2]	15521135		0.13
19	CHEMBL74348[2]	15521137		0.27
20	NAPROXEN[8]	156391		
21	(3Z,5E)-6-[4-(3-fluoropropoxy)-3-methoxyphenyl]-4-hydroxyhexa-3,5-dien-2-one[1]	16087292		316.30
22	CHEMBL387276[1]	16087303		232.70
23	(3Z,5E)-6-[4-(2-fluoroethoxy)-3-methoxyphenyl]-4-hydroxyhexa-3,5-dien-2-one[1]	16087304		958.10

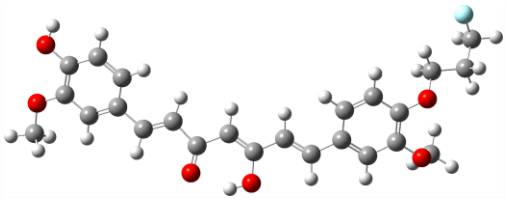
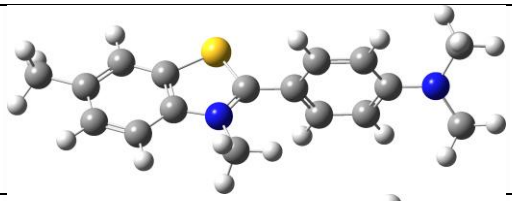
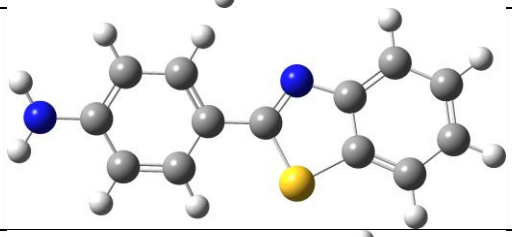
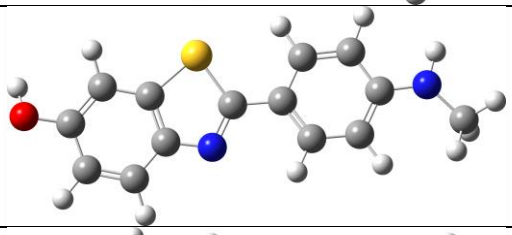
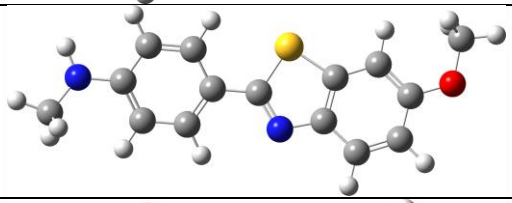
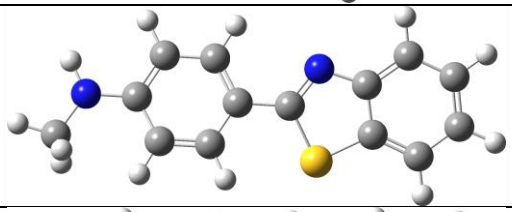
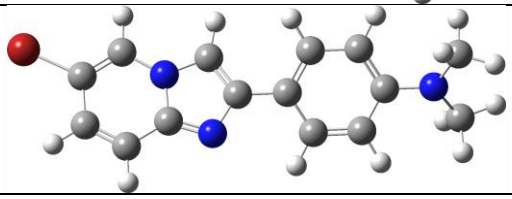
24	(1E,4Z,6E)-7-[4-(3-fluoropropoxy)-3-methoxyphenyl]-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)hepta-1,4,6-trien-3-one[1]	16087306		0.07
25	Thioflavin T[5]	16954		116.00
26	4-(1,3-benzothiazol-2-yl)aniline[4]	234475		37.00
27	Pittsburgh Compound-B[9]	N/A		4.3
28	CHEMBL94230[4]	9835167		4.90
29	CHEMBL93334[4]	9837643		11.00
30	CHEMBL81260[3]	9839907		10.30

Table S2. Average interaction energies (kcal/mol) of each ligand with their surroundings at the bound and free states along their calculated LIE and experimental binding free energies.

Pubchem ID	$\langle V_{l-s}^{vdW} \rangle_b$	$\langle V_{l-s}^{vdW} \rangle_f$	$\langle V_{l-s}^{elec} \rangle_b$	$\langle V_{l-s}^{elec} \rangle_f$	ΔG_{exp}
10064445	-34.0	-17.4	-16.2	-23.7	-10.6
10133297	-42.6	-23.4	-11.1	-15.4	-10.7
10184360	-42.2	-19.6	-114.1	-144.9	-13.7
10335228	-34.5	-18.8	-10.3	-23.3	-11.2
10422457	-37.0	-22.1	-5.9	-10.3	-11.0
10426074	-39.9	-22.8	-6.2	-10.5	-12.0
10444413	-28.1	-15.8	-27.8	-30.7	-10.1
10496851	-42.0	-24.8	-4.2	-9.2	-12.0
10844298	-48.3	-29.7	-6.7	-12.5	-11.3
11054105	-37.0	-23.0	-7.5	-14.5	-9.1
11129817	-43.2	-24.0	-4.8	-12.1	-12.0
11574659	-41.1	-25.5	-14.3	-16.3	-10.8
11632242	-39.7	-23.4	-14.6	-21.2	-10.5
11703303	-32.4	-20.0	-21.3	-27.1	-9.8
11821524	-37.9	-23.4	-11.4	-16.9	-11.1
1358096	-43.7	-26.5	-6.0	-12.1	-11.0
15521136	-38.3	-18.0	-124.4	-146.1	-13.3
15521135	-37.0	-17.9	-121.0	-139.2	-13.6
15521137	-37.2	-18.0	-121.6	-138.4	-13.1
156391 (Naproxen)	-24.2	-10.9	-70.8	-87.8	-11.3
16087292	-37.7	-24.4	-12.8	-22.2	-8.9
16087303	-30.3	-19.1	-14.1	-22.1	-9.1
16087304	-38.7	-22.2	-9.7	-20.9	-8.3
16087306	-49.9	-33.1	-11.4	-34.1	-13.9
16954 (Thioflavin T)	-37.7	-25.5	-10.1	-7.2	-9.5
234475	-27.9	-15.9	-21.9	-24.5	-10.2
Pittsburgh Compound-B	-38.4	-19.6	-18.0	-21.7	-11.5
9835167	-39.8	-22.7	-9.6	-14.6	-11.4
9837643	-34.0	-20.5	-6.4	-11.5	-10.9
9839907	-40.0	-23.6	-6.6	-13.8	-11.0

Table S3. Binding free energies of each ligand with 12Aβ_{11-40} oligomer by using MM/PBSA and FEP methods.

Pubchem ID	ΔE_{vdW}	ΔE_{Elec}	ΔG_{sur}	ΔG_{PB}	$-T\Delta S$	$\Delta G_{MM/PBSA}$	ΔG_{FEP}
10064445	1.55	-38.67	-4.58	18.51	26.95	3.76	-8.16
10133297	-4.54	-37.20	-4.88	12.83	27.13	-6.65	-20.65
10184360	312.96	-45.13	-7.58	-283.12	29.04	6.18	-33.85
10335228	-3.00	-37.59	-4.80	21.95	26.23	2.79	-16.99
10422457	-2.42	-37.71	-5.14	20.49	26.51	1.72	-17.54
10426074	-7.37	-43.16	-4.95	22.49	26.94	-6.05	-24.34
10444413	-11.90	-33.58	-4.39	24.71	26.92	1.77	-5.75
10496851	-3.80	-44.44	-5.27	20.97	26.97	-5.57	-24.71
10844298	-4.29	-52.35	-6.34	16.81	27.98	-18.18	-26.50
11054105	-4.62	-41.57	-5.44	20.81	27.25	-3.56	-19.63
11129817	-4.56	-42.93	-5.46	20.97	27.22	-4.76	-24.24
11574659	-3.81	-43.55	-5.69	27.06	27.55	1.57	-23.04
11632242	-2.77	-40.57	-5.33	21.15	27.05	-0.47	-11.30
11703303	-9.25	-31.67	-5.16	21.53	26.49	1.94	-8.02
11821524	-3.57	-40.56	-5.31	22.24	26.91	-0.29	-27.77
1358096	-3.80	-45.01	-5.51	15.31	27.13	-11.87	-28.56
15521136	286.71	-37.26	-5.82	-281.41	28.70	-9.08	-30.28
15521135	334.64	-36.85	-6.22	-322.03	28.54	-1.92	-26.71
15521137	289.18	-36.43	-6.79	-278.45	28.17	-4.33	-35.85
156391 (Naproxen)	130.35	-35.23	-4.54	-126.29	27.50	-8.21	-17.73
16087292	-6.52	-40.37	-6.20	22.22	28.05	-2.84	-26.27
16087303	-13.53	-36.35	-5.22	31.31	27.23	3.45	-14.23
16087304	-4.31	-40.20	-5.74	21.72	28.58	0.05	-5.75
16087306	-20.55	-57.46	-7.96	49.47	30.65	-5.85	-29.05
16954 (Thioflavin T)	-216.02	-31.36	-4.71	229.23	27.24	4.38	-11.41
234475	-15.03	-29.18	-4.41	27.54	25.73	4.65	-16.37
Pittsburgh Compound-B	-9.85	-40.89	-4.72	26.48	26.81	-2.18	-24.69
9835167	-11.15	-37.99	-5.04	30.55	26.85	3.22	-18.35
9837643	-6.67	-34.73	-4.51	17.17	26.45	-2.29	-19.43
9839907	-5.46	-44.66	-5.26	26.10	27.16	-2.11	-24.21

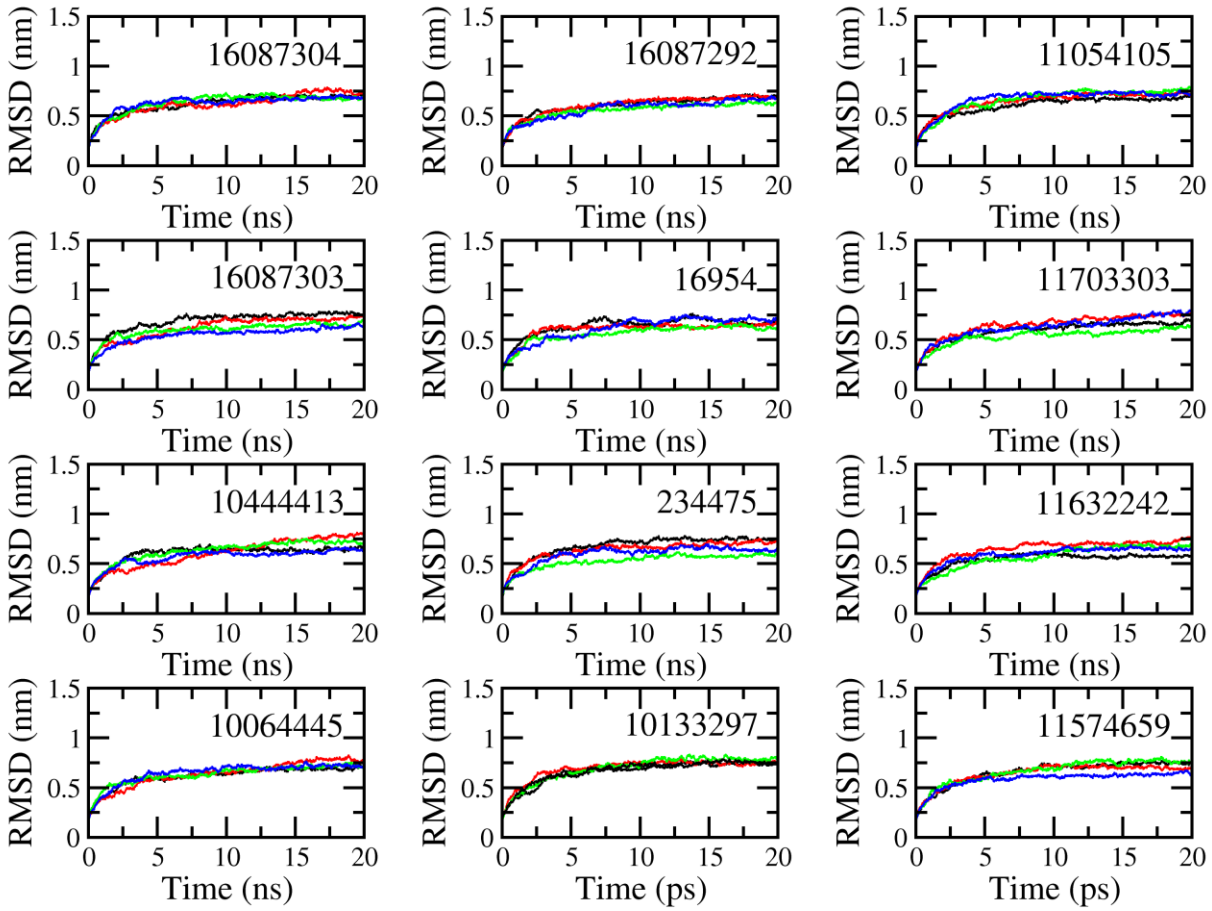
Table S4. The binding free energies was estimated using LIE and experimental approaches of training set comprising of 20 complexes. In particular, the parameter α, β, and γ were assigned as shown as equation (2) of the main text. The unit is of kcal/mol.

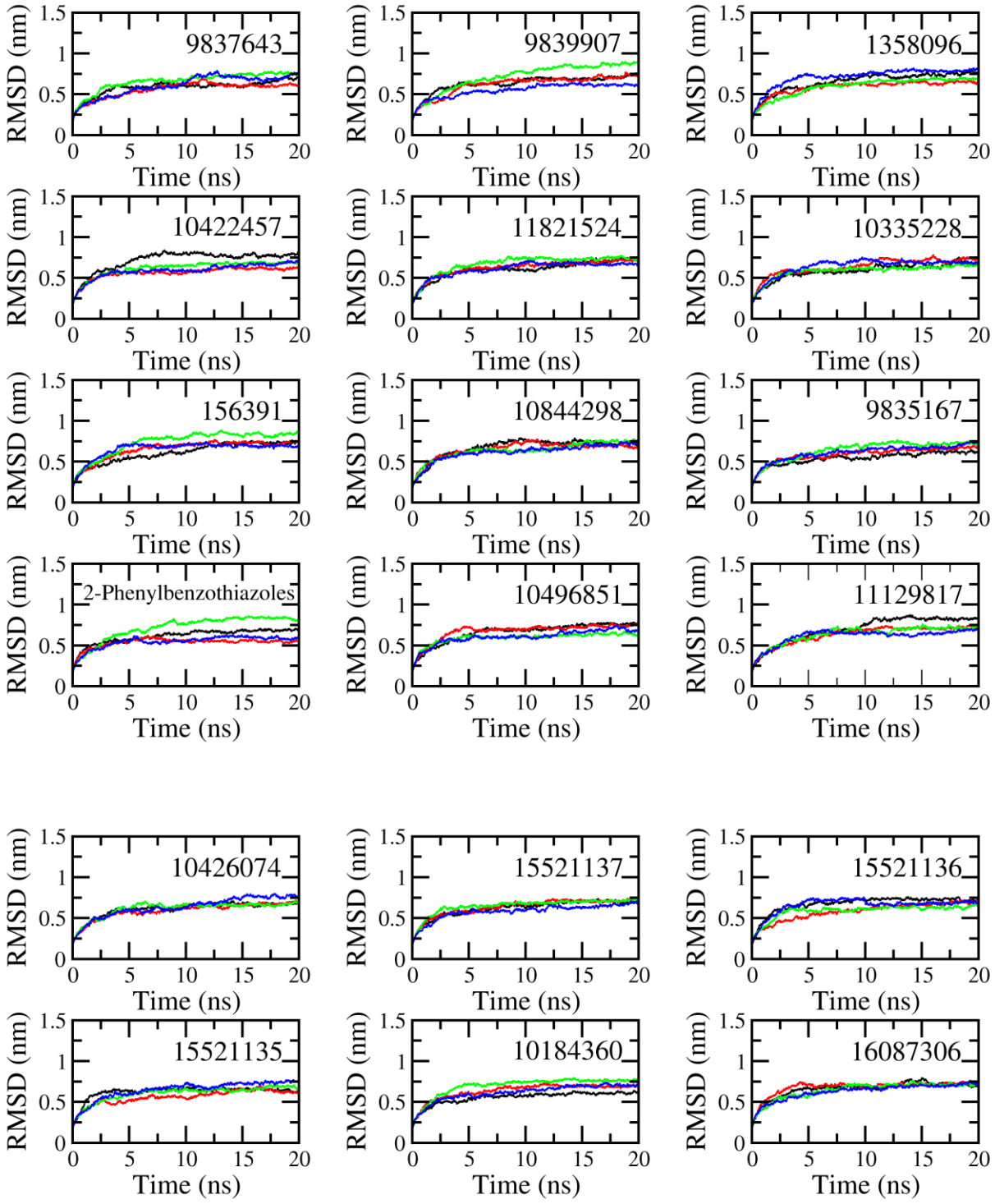
Pubchem ID	ΔG_{LIE}	ΔG_{exp}
10064445	-11.05	-10.57
10184360	-13.91	-13.67
10335228	-11.04	-11.18
10426074	-11.01	-12.04
10444413	-9.57	-10.07
10844298	-11.52	-11.35
11054105	-10.26	-9.08
11574659	-10.49	-10.82
11632242	-10.92	-10.49
11703303	-9.75	-9.80
1358096	-11.14	-10.98
15521136	-12.80	-13.34
15521135	-12.28	-13.57
156391	-10.54	-11.32
16087303	-9.51	-9.10
16087304	-11.17	-8.26
16954	-9.25	-9.52
234475	-9.49	-10.20
9835167	-11.06	-11.41
9839907	-10.95	-10.96

Table S5. The binding free energies was estimated using LIE and experimental approaches of testing set comprising of 10 complexes. In particular, the parameter α, β, and γ were assigned as shown as equation (2) of the main texts. The unit is of kcal/mol.

Pubchem ID	ΔG_{LIE}	ΔG_{exp}
10133297	-11.64	-10.74
10496851	-11.09	-11.97
11821524	-10.35	-11.07
15521137	-12.24	-13.13
16087306	-11.84	-13.94
2-phenylbenzothiazoles	-11.47	-11.48
10422457	-10.40	-10.98
16087292	-10.19	-8.92
9837643	-10.01	-10.92
11129817	-11.80	-11.97

Figure S1. RMSD values during MD simulations.

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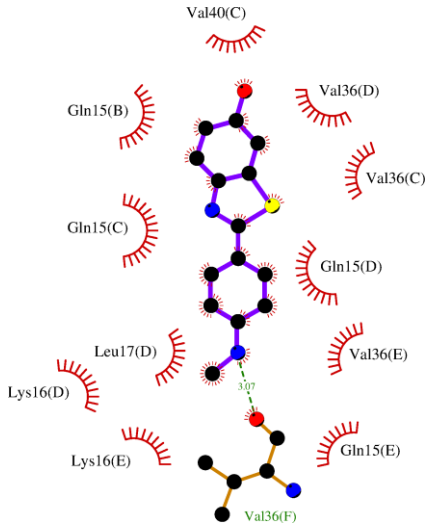
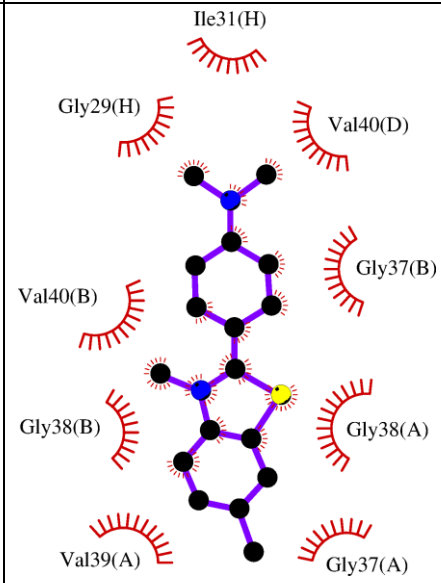
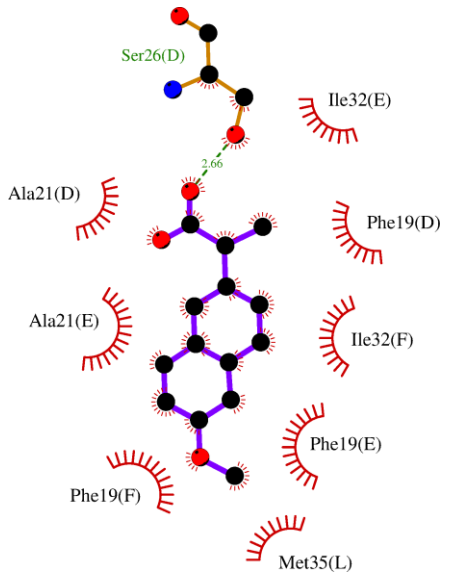
9839907
1358096
10422457
11821524
10335228
156391
10844298
9835167
2-Phenylbenzothiazoles
10496851
11129817
10426074
15521137
15521136
15521135
10184360
16087306
RMSD (nm)
Time (ns)
0
0.5
1
1.5
0
5
10
15
20

Figure S2. 2-D protein-ligand interaction diagrams

Pittsburgh Compound-B	***16954***	***156391***
		
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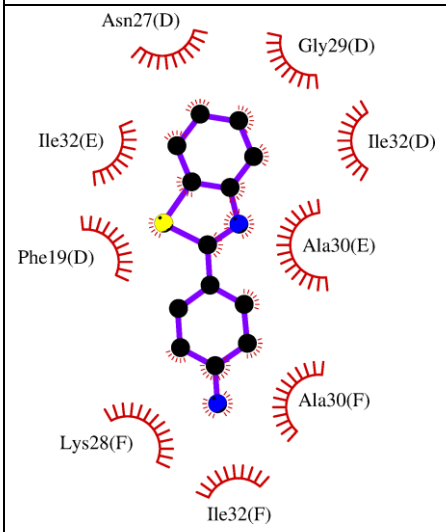	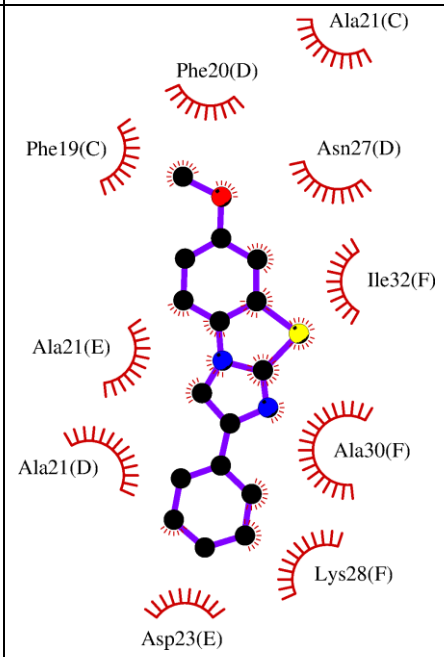	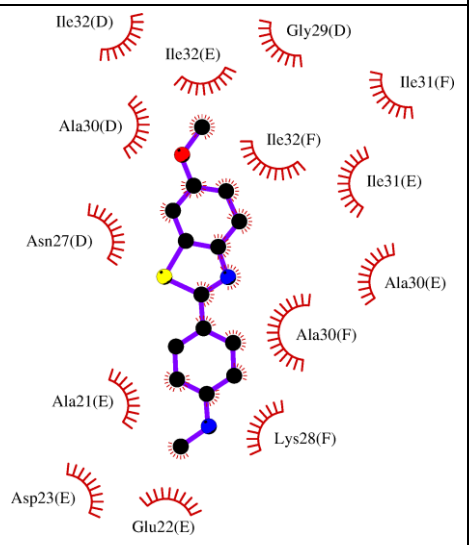

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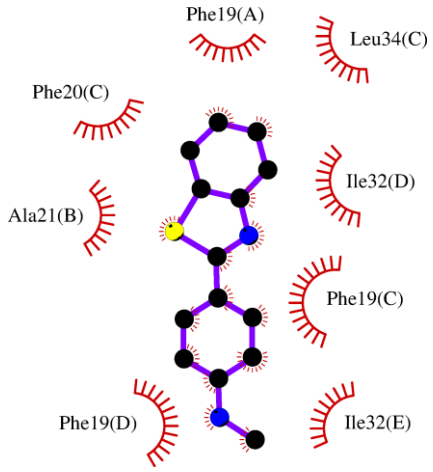	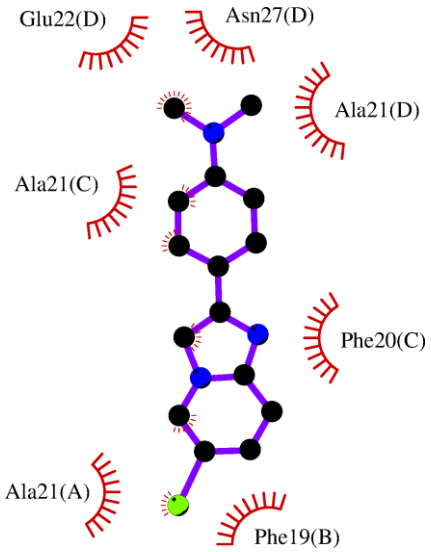	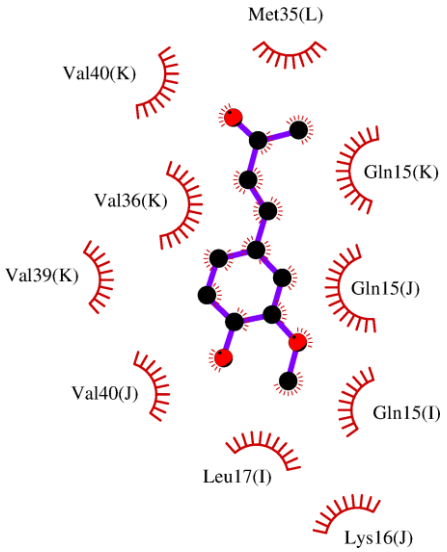
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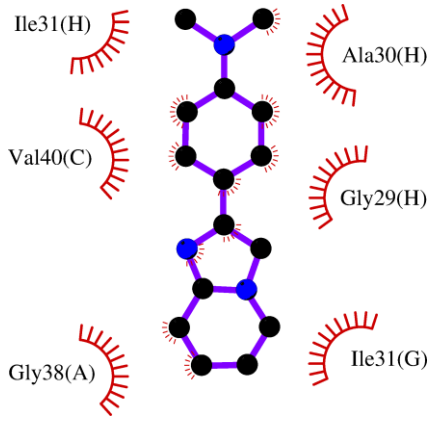	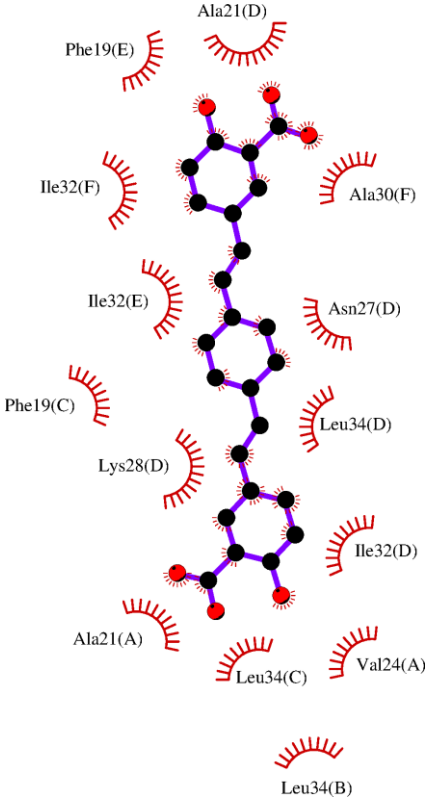	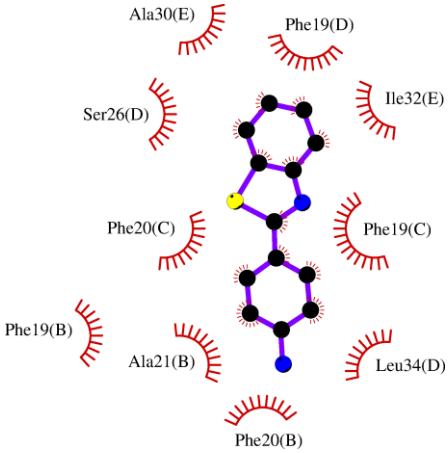
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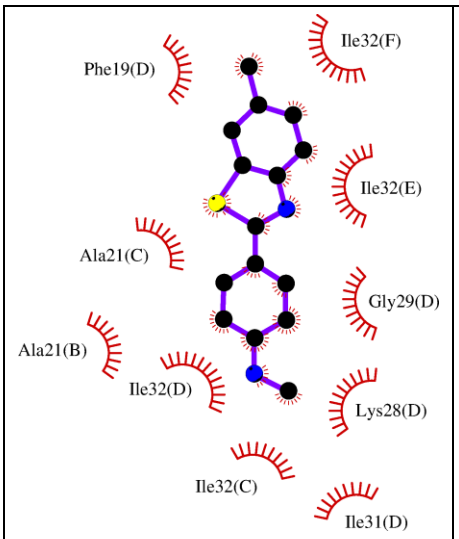

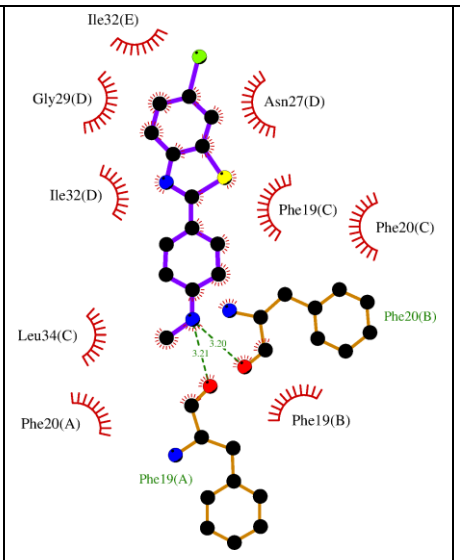

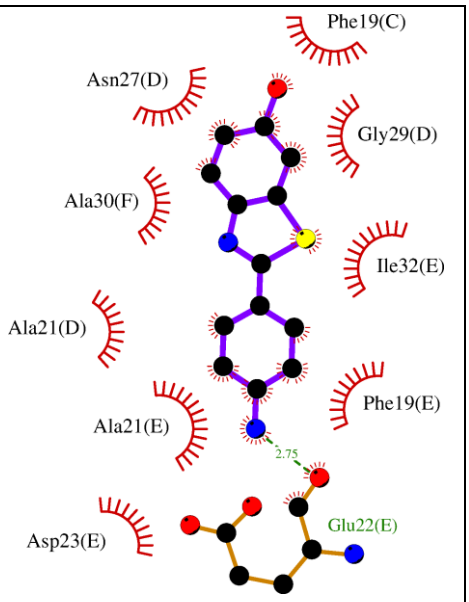

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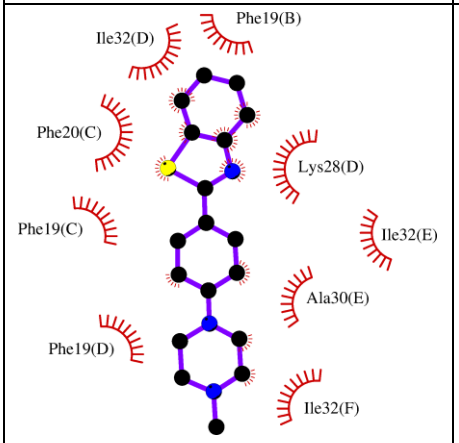

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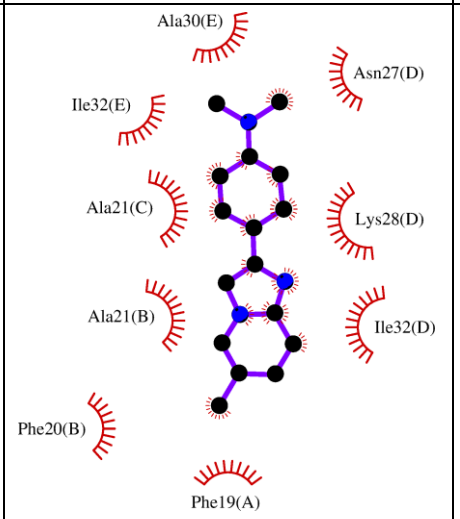

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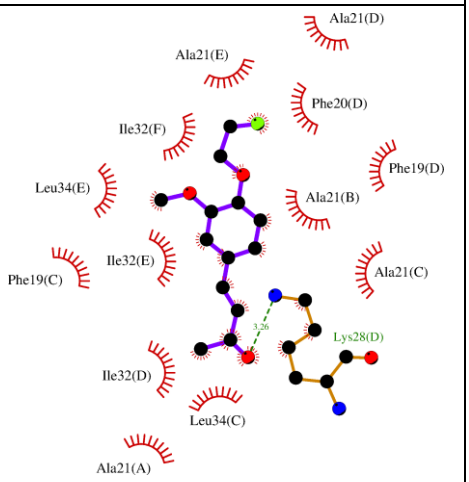
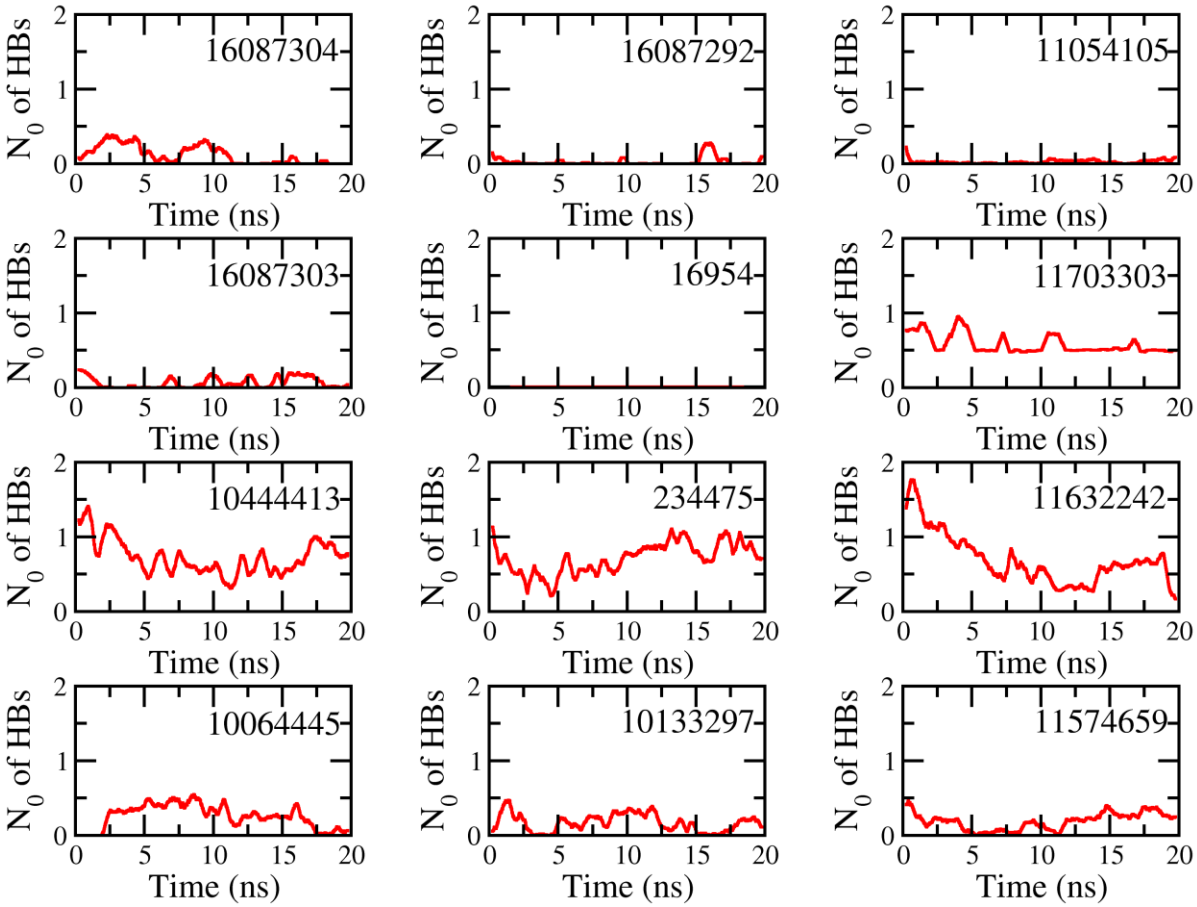
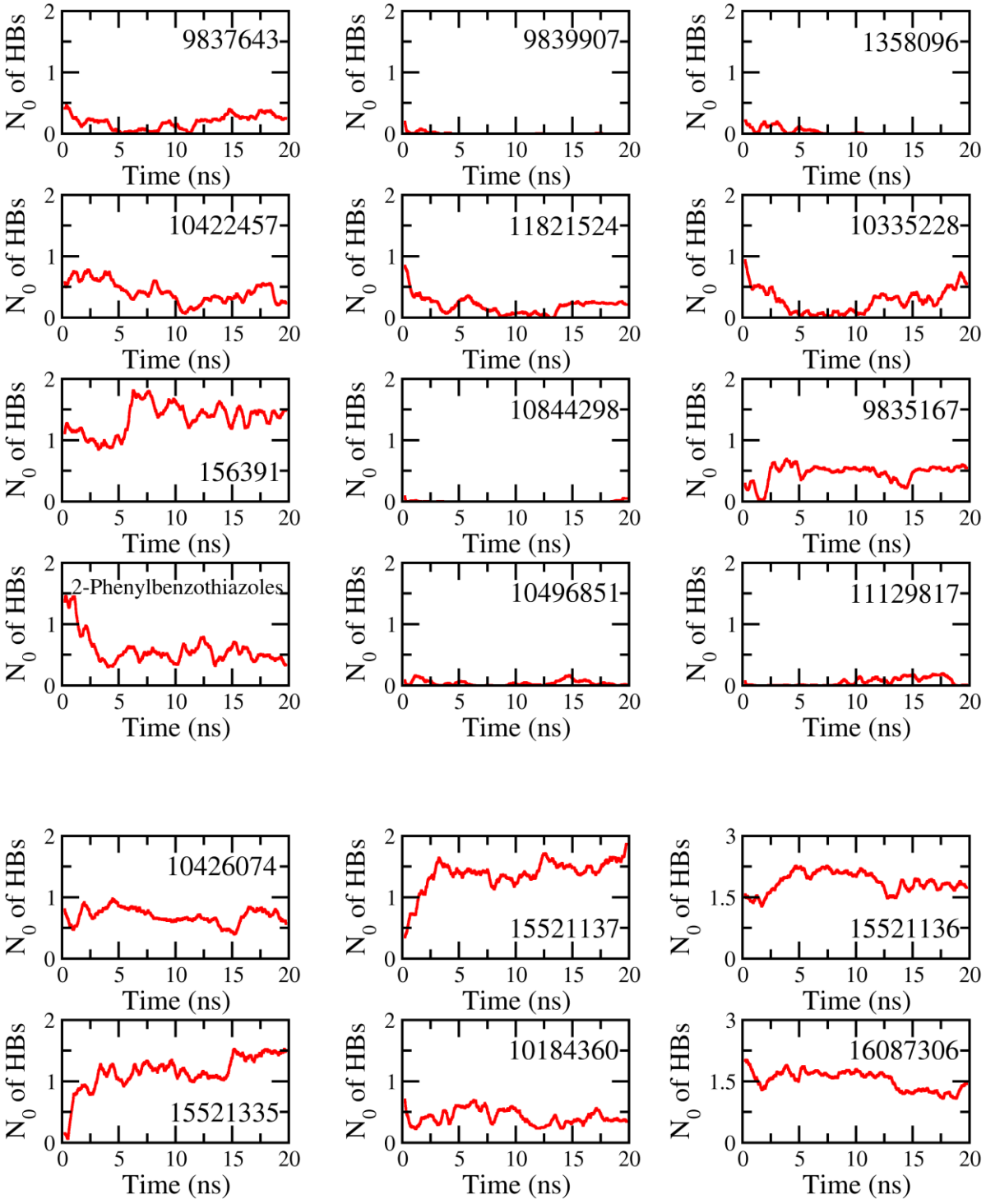


Figure S3. Number of HBs during MD simulations.

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9835167
2-Phenylbenzothiazoles
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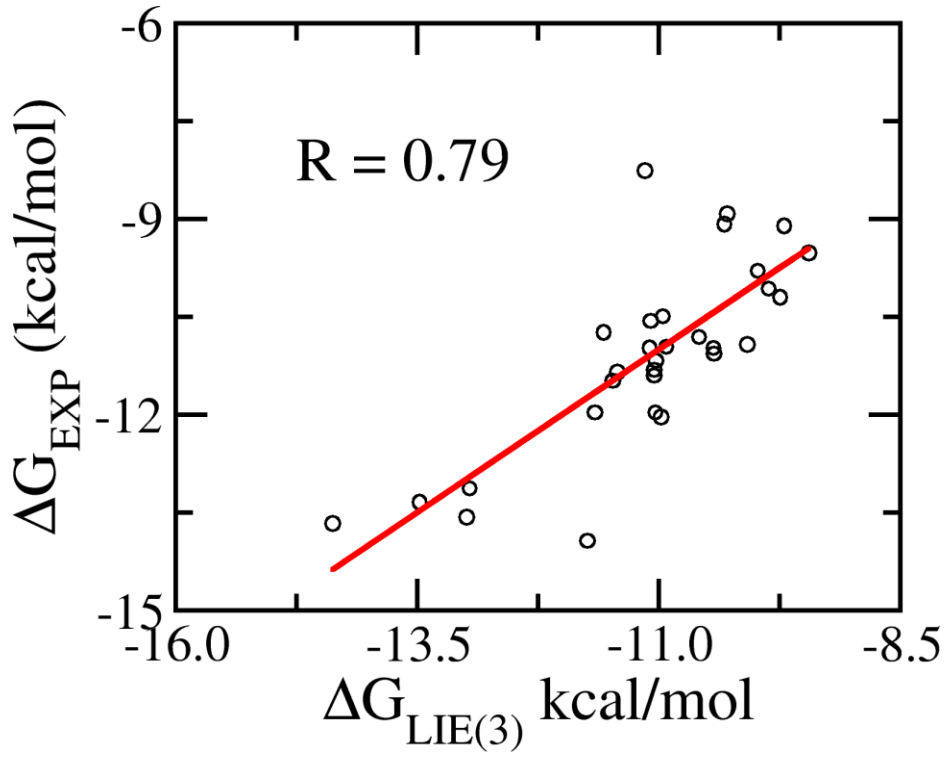
11129817
10426074
15521137
15521136
15521335
10184360
16087306
N0 of HBs
Time (ns)

Figure S4. Correlation between experimental binding free energies and that calculated using LIE model with the separation of *β* value (eq. 3)



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