Supplementary materials

Exploration of *N*-arylsulfonyl-indole-2-carboxamide derivatives as novel fructose-1,6-bisphosphatase inhibitors by molecular simulation

Yilan Zhao [a], Honghao Yang [a], Fengshou Wu [a], Xiaogang Luo [a, b, c], Qi Sun [a, c], Weiliang Feng [a] *, Xiulian Ju [a], Genyan Liu [a, c] *

[a] *Hubei Key Laboratory of Novel Reactor and Green Chemical Technology, Key Laboratory for Green Chemical Process of Ministry of Education, School of Chemical Engineering and Pharmacy, Wuhan Institute of Technology, Wuhan 430205, P. R. China*

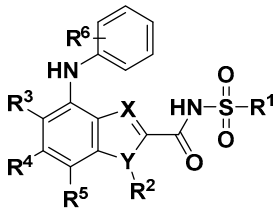
[b] *School of Materials Science and Engineering, Zhengzhou University, No. 100 Science Avenue, Zhengzhou City, 450001, Henan Province, P. R. China*

[c] *Key Laboratory of Novel Biomass-Based Environmental and Energy Materials in Petroleum and Chemical Industry, Wuhan Institute of Technology, Wuhan 430205, P. R. China*

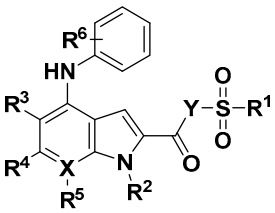
*Corresponding authors: Genyan Liu, Weiliang Feng

E-mail addresses: liugenyan@wit.edu.com (G. Liu); fengweiliangax@126.com

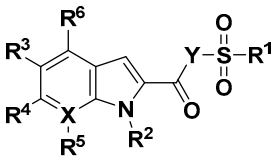
Table S1. Chemical structures and the experimental activity of the compounds as FBPIs.



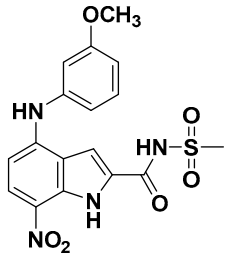
1-73



74-75



76-85



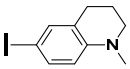
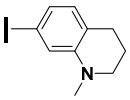
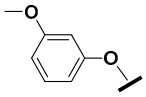
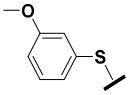
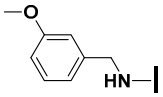
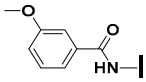
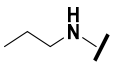
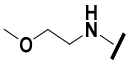
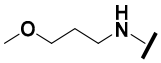
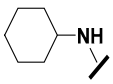
86

No.	X	Y	R^1	R^2	R^3	R^4	R^5	R^6	pIC_{50}	Predicted pIC_{50}
1	C	N	cPr	H	H	H	NO_2	2-OMe	5.538	5.637
2	C	N	Ph	H	H	H	NO_2	2-OMe	6.854	6.801
3	C	N	3-methoxyphenyl	H	H	H	NO_2	2-OMe	6.824	6.861
4#	C	N	4- methoxyphenyl	H	H	H	NO_2	2-OMe	6.721	6.618
5	C	N	2-fluorophenyl	H	H	H	NO_2	2-OMe	6.620	6.659
6	C	N	3-fluorophenyl	H	H	H	NO_2	2-OMe	6.854	6.827
7	C	N	4-fluorophenyl	H	H	H	NO_2	2-OMe	6.796	6.889
8	C	N	3-nitrophenyl	H	H	H	NO_2	2-OMe	7.000	6.962
9	C	N	4-nitrophenyl	H	H	H	NO_2	2-OMe	6.678	6.541
10	C	N	4-(trifluoromethoxy)phenyl	H	H	H	NO_2	2-OMe	6.659	6.642
11	C	N	thiophen-2-yl	H	H	H	NO_2	2-OMe	6.495	6.449
12#	C	N	naphthalen-2-yl	H	H	H	NO_2	2-OMe	6.553	6.300
13	C	N	Ph	H	H	H	NO_2	2-OMe	5.509	5.577
14	C	N	Ph	H	H	H	NO_2	4-OMe	6.000	5.963
15#	C	N	3-methoxyphenyl	H	H	H	NO_2	3-OEt	6.921	6.882
16#	C	N	3-methoxyphenyl	H	H	H	NO_2	3-OCF_2H	6.886	7.193
17	C	N	3-methoxyphenyl	H	H	H	NO_2	3-Me	6.824	6.649
18	C	N	3-methoxyphenyl	H	H	H	NO_2	3-Et	6.367	6.483
19	C	N	3-methoxyphenyl	H	H	H	NO_2	3-acetamido	6.796	6.826
20	C	N	3-methoxyphenyl	H	H	H	NO_2	3-F	5.996	6.121
21	C	N	3-methoxyphenyl	H	H	H	NO_2	4-F	5.821	5.879
22	C	N	3-methoxyphenyl	H	H	H	NO_2	3-CF_3	6.180	6.131
23	C	N	3-methoxyphenyl	H	H	H	NO_2	4-CF_3	6.041	6.000
24#	C	N	3-methoxyphenyl	H	H	H	NO_2	3-NO_2	6.854	7.100
25	C	N	3-methoxyphenyl	H	H	H	NO_2	4-NO_2	6.456	6.449
26	C	N	3-methoxyphenyl	H	H	H	NO_2	3-morpholino	6.509	6.557
27#	C	N	3-methoxyphenyl	H	H	H	NO_2	4- morpholino	5.963	6.007
28#	C	N	3-methoxyphenyl	H	H	H	NO_2	3,5-dimethoxy	6.854	6.857
29	C	N	3-methoxyphenyl	H	H	H	NO_2	2,3- dimethoxy	5.836	5.794
30	C	N	3-methoxyphenyl	H	H	H	NO_2	2,4- dimethoxy	5.893	5.962

Table S1. (Continued)

31[#]	C	N	3-methoxyphenyl	H	H	H	NO_2	4-Cl-3-OMe	6.921	6.915
32	C	N	3-methoxyphenyl	H	H	H	NO_2	4-F-3-OMe	6.398	6.333
33	C	N	3-methoxyphenyl	H	H	H	NO_2	3,4,5-triomethoxy	6.699	6.779
34	C	N	3-methoxyphenyl	H	F	H	NO_2	2-OMe	6.585	6.433
35	C	N	3-methoxyphenyl	H	Cl	H	NO_2	2-OMe	6.022	6.151
36	C	N	3-methoxyphenyl	H	Me	H	NO_2	2-OMe	6.022	5.896
37	C	N	3-methoxyphenyl	H	H	H	H	2-OMe	5.432	5.629
38[#]	C	N	3-methoxyphenyl	H	F	H	H	2-OMe	5.921	5.704
39	C	N	3-methoxyphenyl	H	Cl	H	NO_2	2-OMe	5.959	5.647
40	C	N	3-methoxyphenyl	H	Me	H	NO_2	2-OMe	5.444	5.512
41[#]	C	N	3-methoxyphenyl	H	H	F	NO_2	2-OMe	6.244	6.079
42[#]	C	N	3-methoxyphenyl	H	H	Cl	NO_2	2-OMe	6.796	7.102
43[#]	C	N	3-methoxyphenyl	H	H	CN	NO_2	2-OMe	6.444	6.538
44[#]	C	N	3-methoxyphenyl	H	H	CF_3	NO_2	2-OMe	6.292	6.137
45[#]	C	N	3-methoxyphenyl	Me	H	H	NO_2	3-OMe	7.398	7.181
46	C	N	3-methoxyphenyl	Et	H	H	NO_2	3-OMe	6.678	6.700
47	C	N	3-methoxyphenyl	iBu	H	H	NO_2	3-OMe	6.398	6.341
48	C	N	3-methoxyphenyl	Me	H	H	NO_2	3-Me	7.046	7.179
49[#]	C	N	3-methoxyphenyl	Me	H	H	NO_2	3-EtO	6.638	6.951
50	C	N	3-methoxyphenyl	Me	H	H	NO_2	3-acetamido	7.229	7.136
51[#]	C	N	3-methoxyphenyl	Me	H	H	NO_2	3,5-dimethoxy	7.200	7.373
52[#]	C	N	3-methoxyphenyl	Me	H	H	NO_2	3,4,5-trimethoxy	5.886	5.818
53	C	N	3-methoxyphenyl	Me	H	H	NO_2	4-Cl-3-OMe	7.200	7.125
54	C	N	4-methoxyphenyl	Me	H	H	NO_2	2-OMe	7.284	7.309
55	C	N	Ph	Me	H	H	Cl	2-OMe	6.745	6.810
56	C	N	3-methoxyphenyl	Me	H	H	Cl	2-OMe	6.824	6.817
57	C	N	2-fluorophenyl	Me	H	H	Cl	2-OMe	6.854	6.879
58[#]	C	N	3-fluorophenyl	Me	H	H	Cl	2-OMe	6.638	6.800
59[#]	C	N	4- fluorophenyl	Me	H	H	Cl	2-OMe	6.328	6.272
60	C	N	3-bromophenyl	Me	H	H	Cl	2-OMe	6.854	6.898
61	C	N	4-tolyl	Me	H	H	Cl	2-OMe	7.149	6.921
62	C	N	cyanophenyl	Me	H	H	Cl	2-OMe	7.252	7.324
63	C	N	3-isobutylphenyl	Me	H	H	Cl	2-OMe	6.027	6.119
64	C	N	pyridinyl	Me	H	H	Cl	2-OMe	6.658	6.683
65[#]	C	N	2-(trifluoromethoxy)phenyl	Me	H	H	Cl	2-OMe	6.114	6.062
66	C	N	3-(trifluoromethoxy)phenyl	Me	H	H	Cl	2-OMe	7.071	7.037
67	C	N	4-(trifluoromethoxy)phenyl	Me	H	H	Cl	2-OMe	7.155	7.047
68[#]	C	N	2-isobutylthiophene	Me	H	H	Cl	2-OMe	6.886	7.043
69	C	N	1-methylindoline	Me	H	H	Cl	2-OMe	6.229	6.325

Table S1. (Continued)

70	C	NH	3-methoxyphenyl	-	H	H	Cl	2-OMe	7.000	7.078
71	N	N	3-methoxyphenyl	Me	H	H	Cl	2-OMe	7.569	6.752
72	C	N		Me	H	H	Cl	2-OMe	6.268	6.235
73	C	N		Me	H	H	Cl	2-OMe	6.174	6.146
74	N	NH	3-methoxyphenyl	H	H	H	-	2-OMe	6.149	6.369
75	C	NH	3-methoxyphenyl	Me	H	H	Cl	2-OMe	7.538	7.594
76	C	NH	3-methoxyphenyl	H	H	H	NO_2		5.854	5.863
77	C	NH	3-methoxyphenyl	H	H	H	NO_2		6.155	6.136
78	C	NH	3-methoxyphenyl	H	H	H	NO_2		6.013	5.997
79	C	NH	3-methoxyphenyl	H	H	H	NO_2		6.060	6.070
80	C	NH	3-methoxyphenyl	H	H	H	NO_2		5.854	5.747
81	C	NH	3-methoxyphenyl	H	H	H	NO_2		5.770	5.754
82	C	NH	3-methoxyphenyl	H	H	H	NO_2		5.745	5.721
83	C	NH	3-methoxyphenyl	H	H	H	NO_2		5.699	5.575
84	C	NH	3-methoxyphenyl	H	H	H	NO_2		4.449	4.408
85	C	NH	Ph	H	H	H	NO_2	Cl	4.614	4.711
86	-	-	-	-	-	-	-	-	< 4.304	-

[#] The test set molecules used to validate the 3D-QSAR models.

Table S2. Chemical structures and docking scores of the twelve screened compounds.

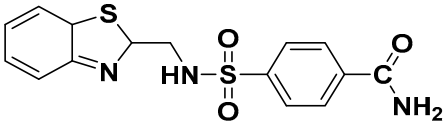
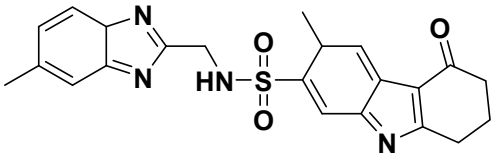
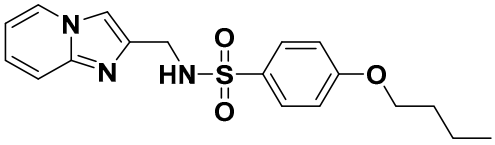
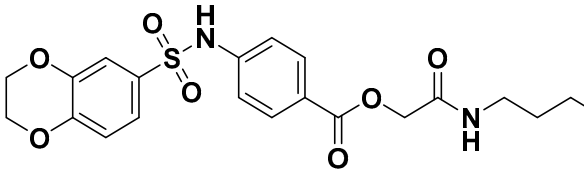
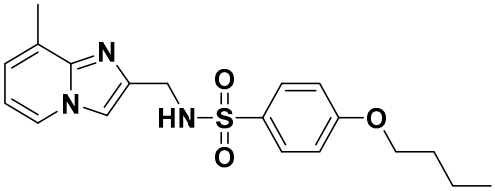
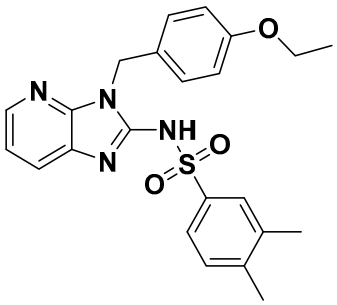
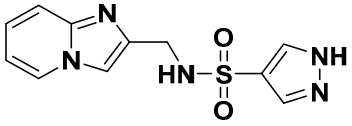
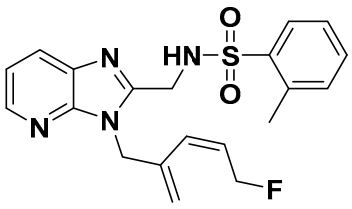
Hit compound	Structure	Total score
ZINC32837457		7.96
ZINC15733809 (VS01)		7.85
ZINC02961023 (VS02)		6.98
ZINC08670831		6.15
ZINC02961075 (VS03)		6.12
ZINC47146484		6.00
ZINC48903386		5.95
ZINC47147329		5.70

Table S2. (Continued)

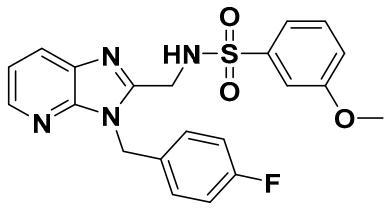
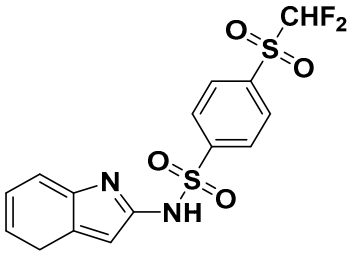
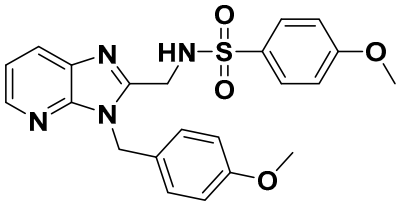
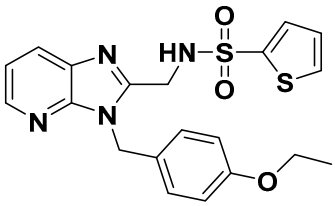
ZINC47147354		5.24
ZINC58356765		5.19
ZINC47146462		5.16
ZINC08600440		5.09

Table S3. Predicted ADME parameters and drug-like properties of compound **75** and the screened compounds.

Properties	Parameters	75	VS01	VS02	VS03
Physiochemical Properties	MW[a] (g/mol)	499.97	422.50	359.44	373.47
	Rotatable bonds	8	4	8	8
	H-bond acceptors	5	5	5	6
	H-bond donors	2	3	1	1
	TPSA[b] ($Å^2$)	107.04	116.09	81.08	81.08
Lipophilicity	iLOGP	3.44	1.73	3.20	3.28
	XLOGP3	4.85	2.97	3.48	3.84
	WLOGP	5.79	4.59	3.92	4.23
	MOLGP	2.35	1.51	1.35	1.58
	SILICOS-IT	3.02	4.50	1.98	2.51
	Consensus LogP	3.89	3.06	2.79	3.09
Water Solubility	ESOL Class	MS[c]	MS	MS	MS
	Ali Class	PS	MS	MS	MS
	SILICOS-IT Class	PS[d]	PS	PS	PS
Pharmacokinetics	GI[e] absorption	Low	High	High	High
	BBB[f] permeant	No	No	No	No
Drug-like Properties	Lipinski violations	0	0	0	0
	Ghose violations	3	0	0	0
	Verber violations	0	0	0	0
	Egan violations	0	0	0	0
	Muegge violations	0	0	0	0
	Bioavailability Score	0.55	0.55	0.55	0.55
Medicinal Chemistry	PAINS[g] alerts	0	0	0	0
	Brenk alerts	0	0	0	0
	Leadlikeness violations	3	1	2	3
	Synthetic accessibility	3.43	3.24	2.91	3.03

[a] Molecular weight. [b] Total polar surface area. [c] Moderately soluble. [d] Poorly soluble. [e] Gastrointestinal.

[f] Blood-brain barrier. [g] Pan assay interference compounds.

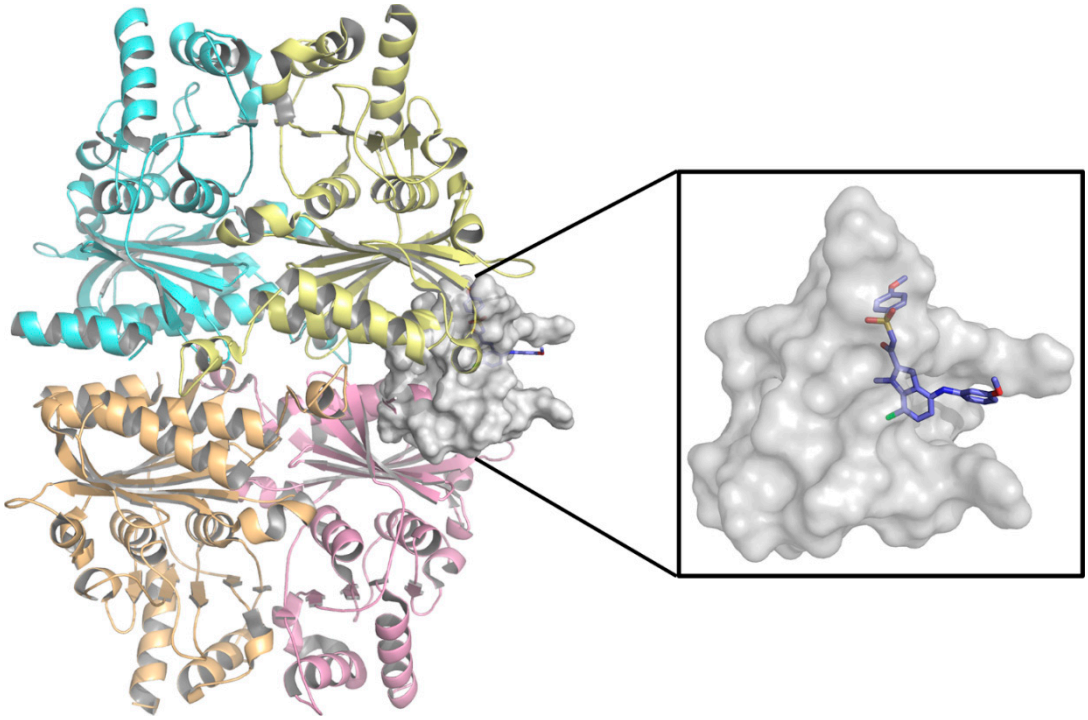


Figure S1. The 3D structure of FBPase in complex with compound **75** (PDB code: 6LW2). The AMP binding site is shown as a grey surface.

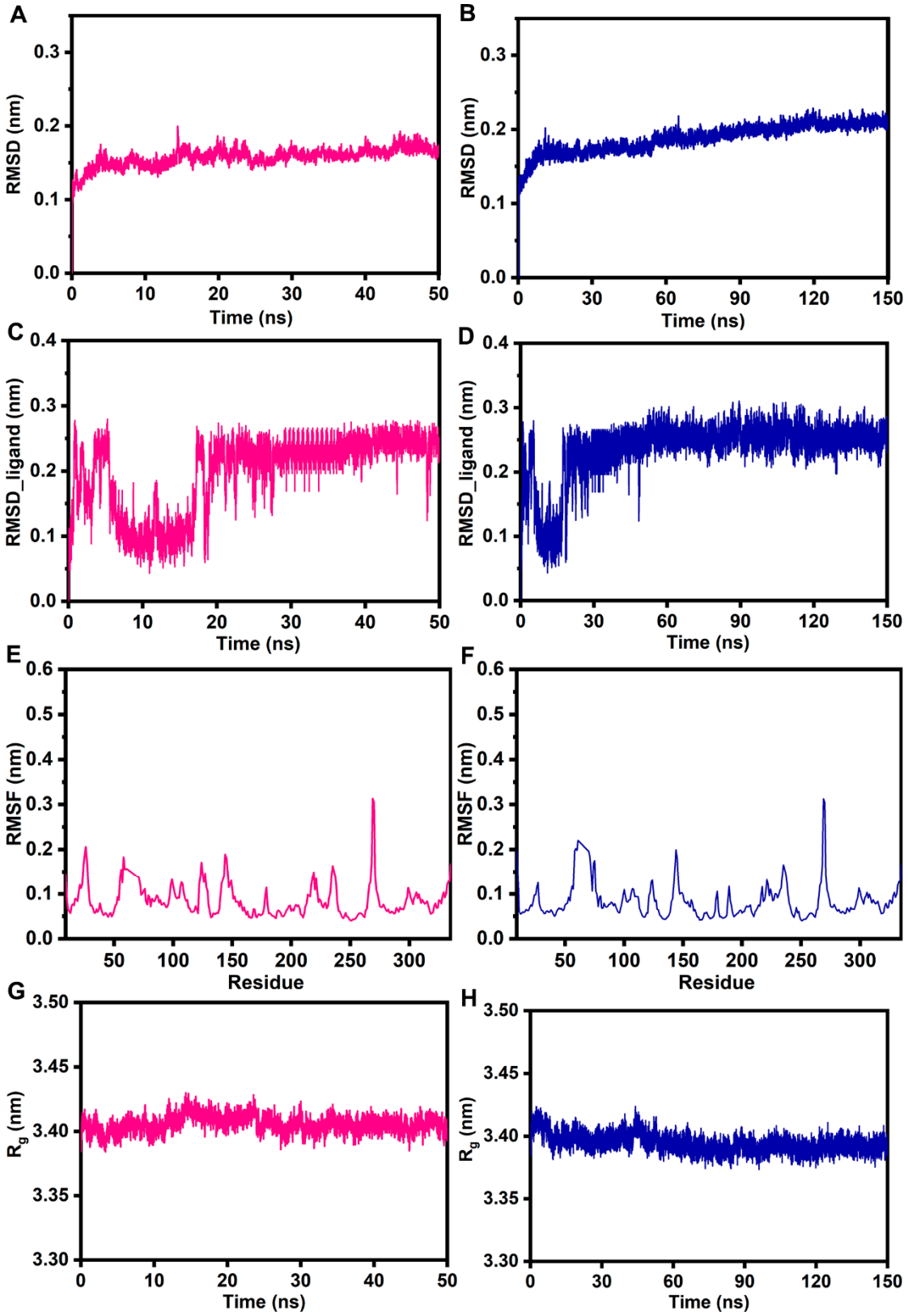


Figure S2. The MD results of the 50 ns (**A**, **C**, **E**, **G**) and 100 ns (**B**, **D**, **F**, **H**) simulations of FBPase-**75** complex: RMSD values of backbone atoms (**A**, **B**), RMSD values of ligand atoms (**C**, **D**), RMSF values of Chain A residues (**E**, **F**), and R_g values of the proteins (**G**, **H**).

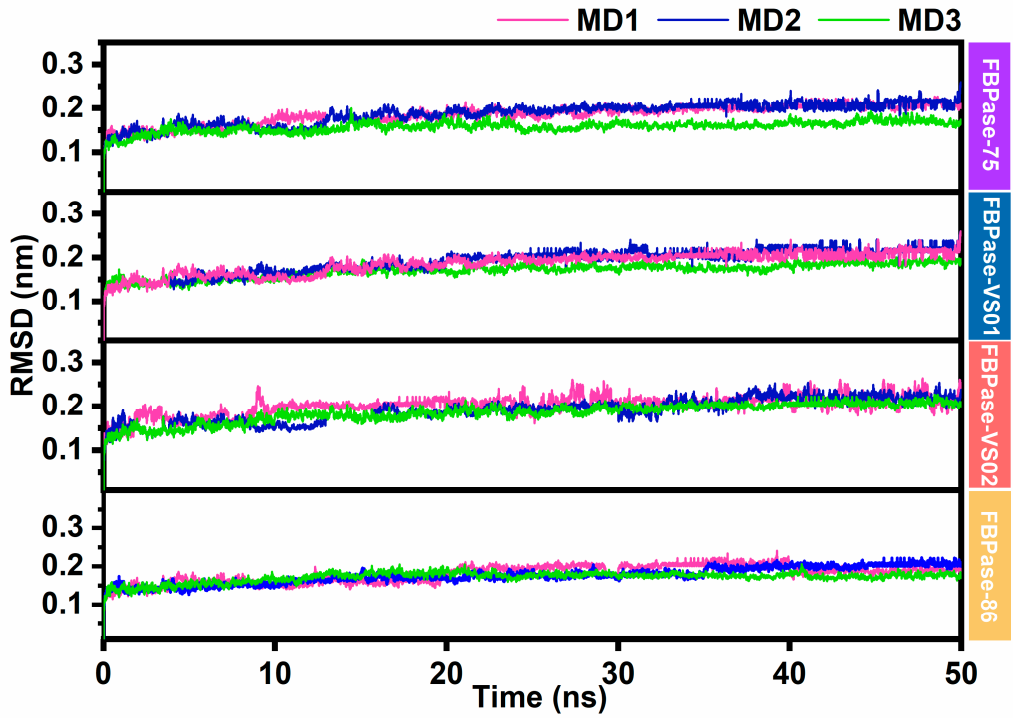


Figure S3. The RMSD plots of the protein backbones for the four complexes: FBPase-**75**, FBPase-**86**, FBPase-**VS01**, and FBPase-**VS02** derived from the triplicate MD simulations (MD1-MD3).

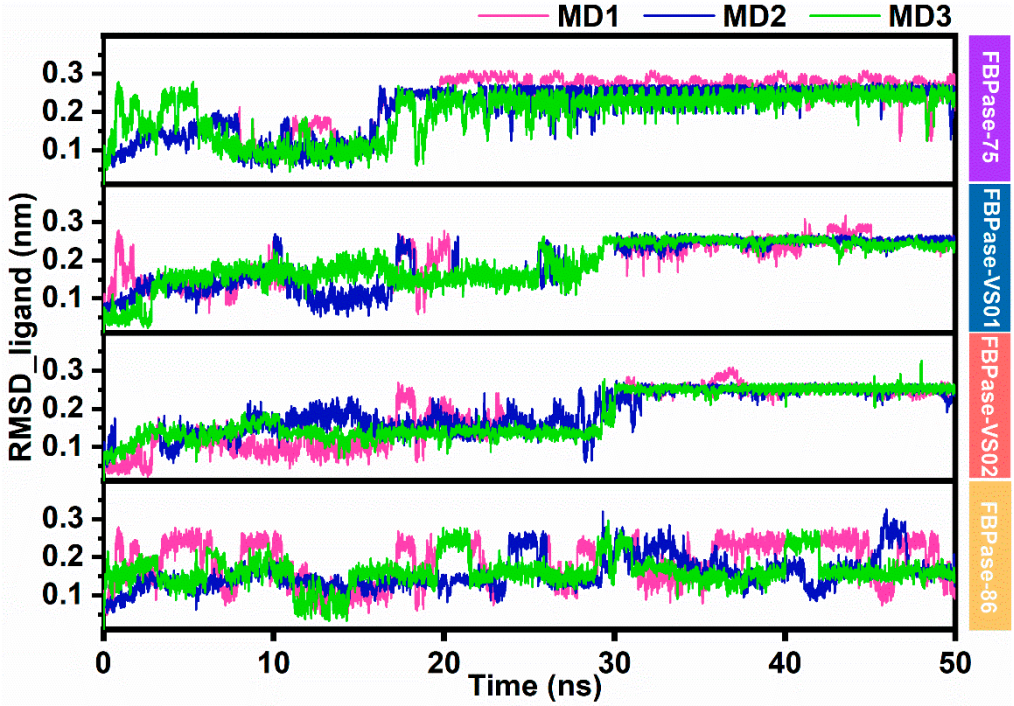


Figure S4. The RMSD plots of the ligands for the four complexes: FBPase-**75**, FBPase-**86**, FBPase-**VS01**, and FBPase-**VS02** derived from the triplicate MD simulations (MD1-MD3).

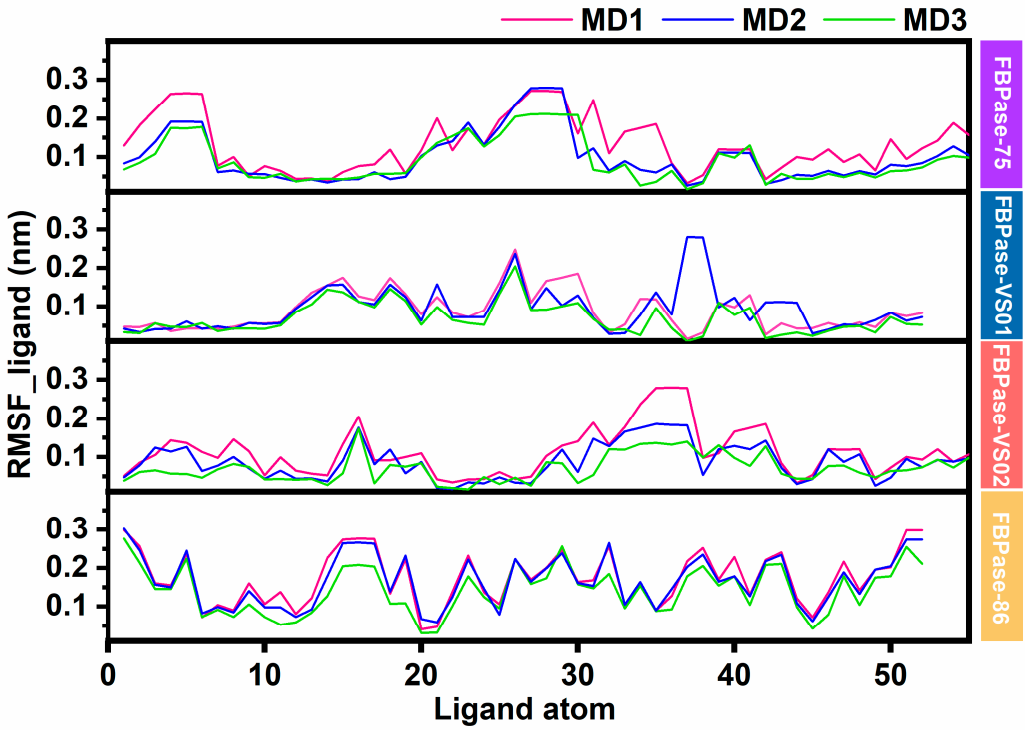


Figure S5. The RMSF plots of the ligands for the four complexes: FBPase-**75**, FBPase-**86**, FBPase-**VS01**, and FBPase-**VS02** derived from the triplicate MD simulations (MD1-MD3).

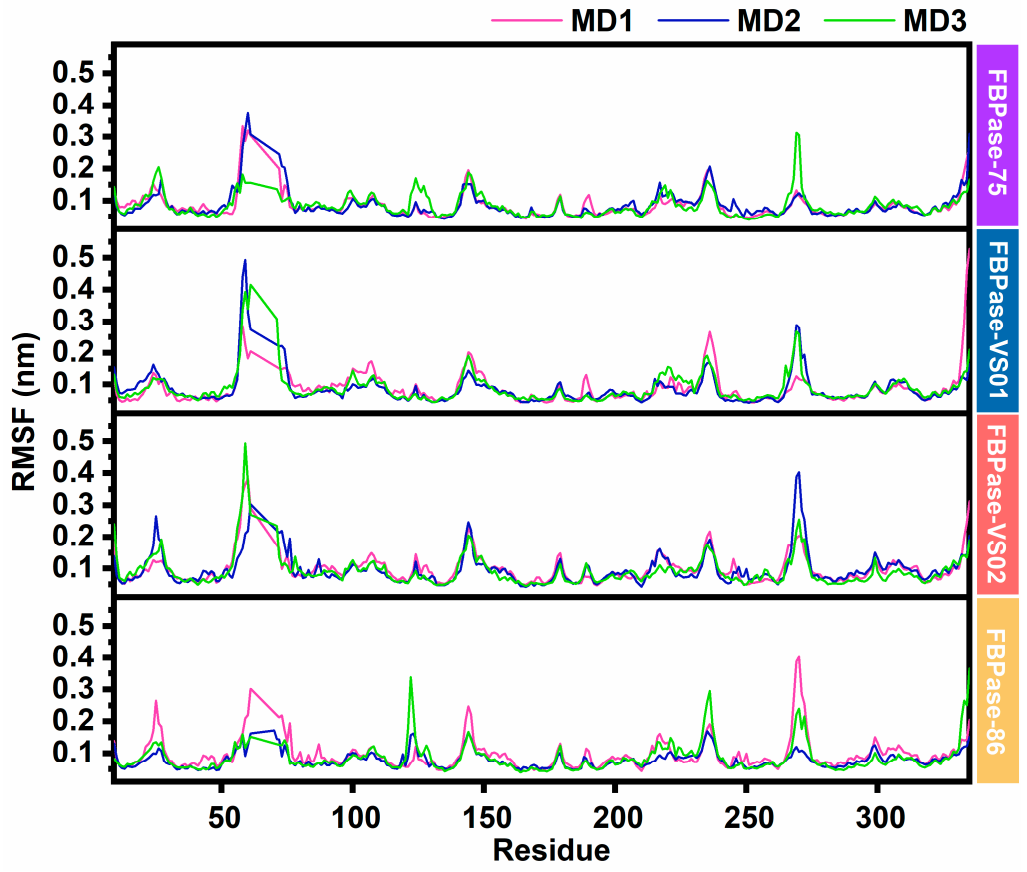


Figure S6. The RMSF plots of the Chain A residues for the four complexes: FBPase-**75**, FBPase-**86**, FBPase-**VS01**, and FBPase-**VS02** derived from the triplicate MD simulations (MD1-MD3).

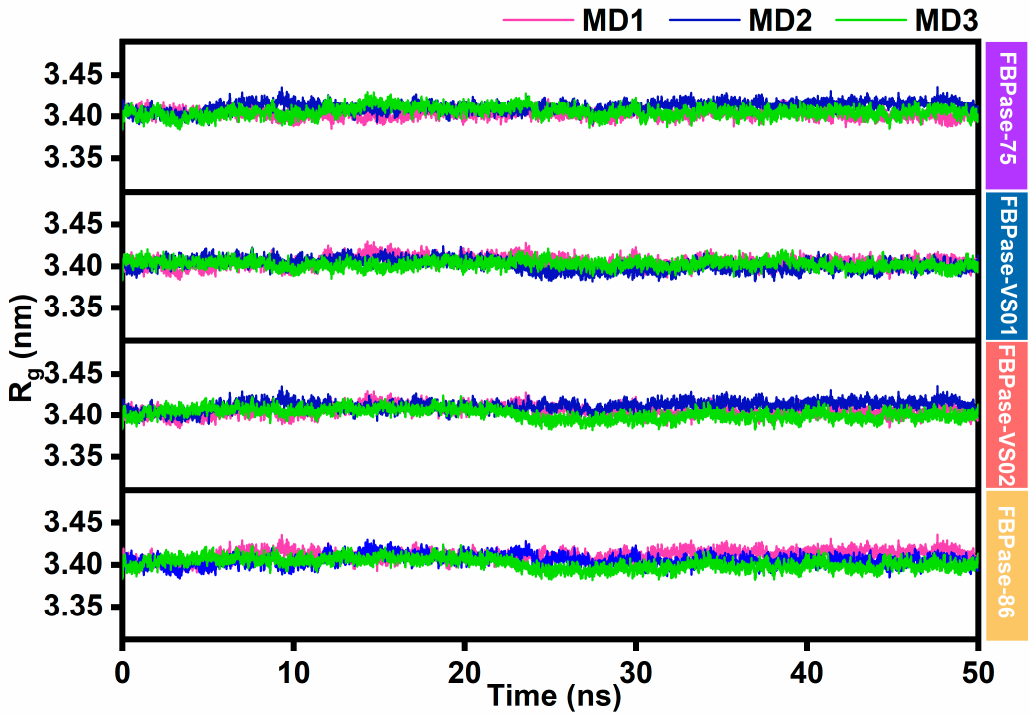


Figure S7. The R_g plots of the proteins for the four complexes: FBPase-**75**, FBPase-**86**, FBPase-**VS01**, and FBPase-**VS02** derived from the triplicate MD simulations (MD1-MD3).