Probing the binding mechanism of novel dual NF-κB/ AP-1 inhibitors by 3D-QSAR, docking and molecular dynamics simulations

Shaojie Ma,[a,d] Shepei Tan,[a] Danqing Fang,[b*] Rong Zhang,[a] Shengfu Zhou,[a] Wenjuan Wu,[a*] and Kangcheng Zheng[c]

[a]: Department of Physical Chemistry,College of Pharmacy, Guangdong Pharmaceutical University, Guangzhou 510006, China. E-mail: wuwenjuan83@126.com; Tel: +86 2039352119

[b]: Department of Cardiothoracic Surgery, Affiliated Second Hospital of Guangzhou Medical University, Guangzhou 510260, China

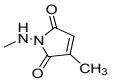
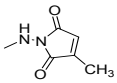
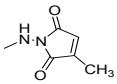
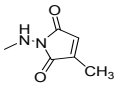
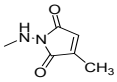
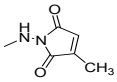
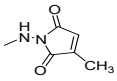
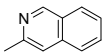
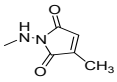
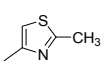
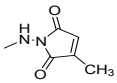
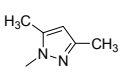
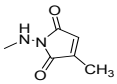
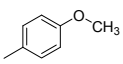
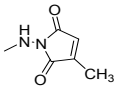
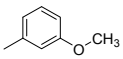
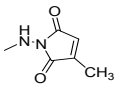
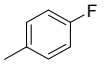
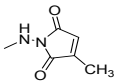
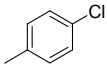
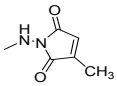
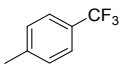
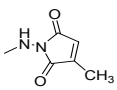
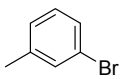
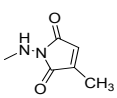
[c]: School of Chemistry and Chemical Engineering, Sun Yat-Sen University, Guangzhou 510275, China

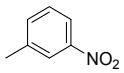
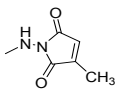
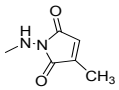
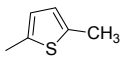
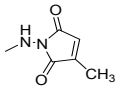
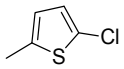
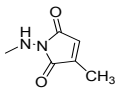
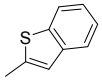
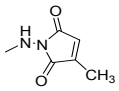
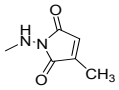
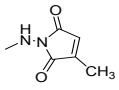
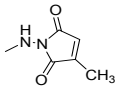
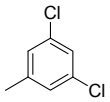
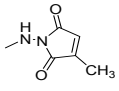
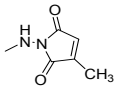
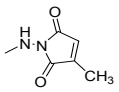
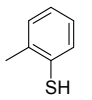
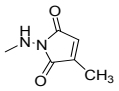
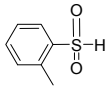
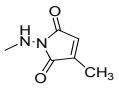
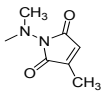
[d]: Department of Pharmacy, Kangda College of Nanjing Medical University, Lianyungang 222000, China

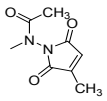
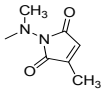
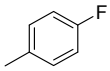
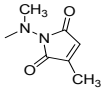
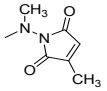
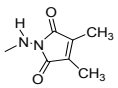
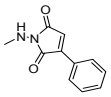
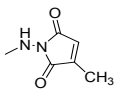
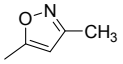
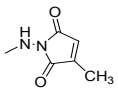
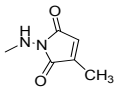
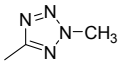
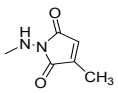
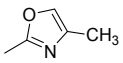
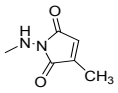
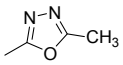
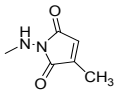
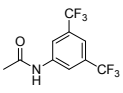
Electronic Supplementary Information

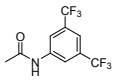
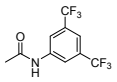
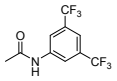
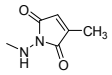
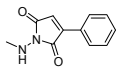
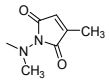
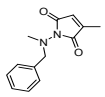
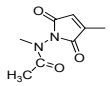
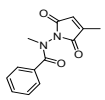
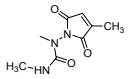
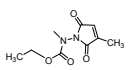
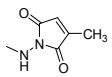
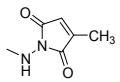
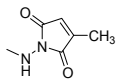
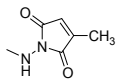
Table of Contents

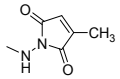
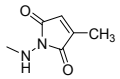
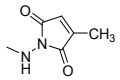
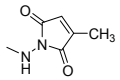
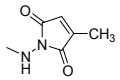
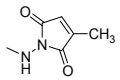
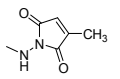
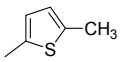
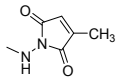
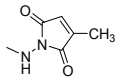
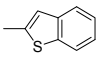
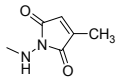
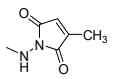
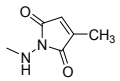
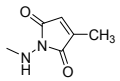
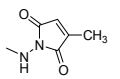
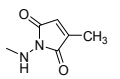
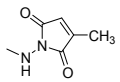
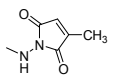
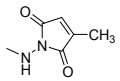
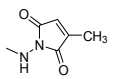
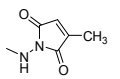
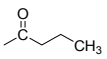
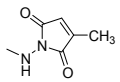
Table S1 Structures, Biological Activities and CoMFA Results of the Studied Compounds.

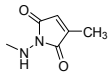
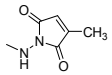
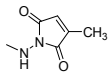
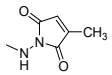
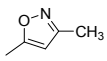
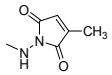
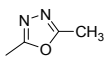
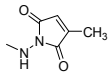
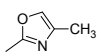
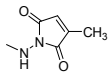
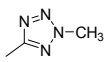
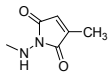
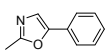
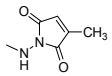
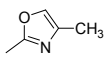
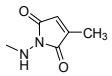
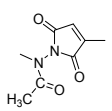
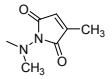
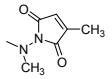
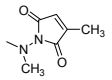
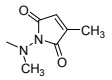
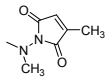
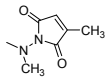
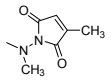
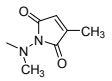
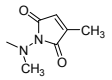
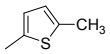
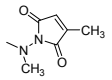
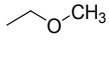
No.	R_1	R_2	R_3	R_4	R_5	pIC_{50} (expt.)	CoMFA Pred. pIC_{50}	CoMFA Res.
1	CF_3		CO_2Et	H		6.00	5.35	0.66
2*	Me		CO_2Et	H		4.80	5.19	-0.39
3*	Et		CO_2Et	H		5.00	5.15	-0.15
4*	t-Bu		CO_2Et	H		6.00	6.24	-0.24
5*	SMe		CO_2Et	H		6.70	6.27	0.43
6	4-Pyridyl		CO_2Et	H		5.22	5.27	-0.05
7			CO_2Et	H		5.70	5.29	0.41
8*			CO_2Et	H		5.22	4.96	0.27
9			CO_2Et	H		5.10	5.25	-0.16
10			CO_2Et	H		5.00	5.15	-0.15
11			CO_2Et	H		6.05	5.91	0.14
12			CO_2Et	H		5.30	5.51	-0.21
13*			CO_2Et	H		6.16	5.86	0.29
14			CO_2Et	H		6.52	6.46	0.07
15			CO_2Et	H		6.40	6.59	-0.19
16*			CO_2Et	H		6.16	6.57	-0.41

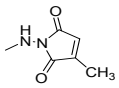
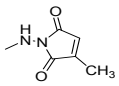
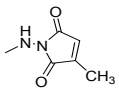
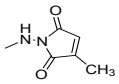
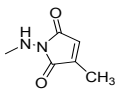
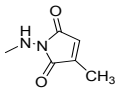
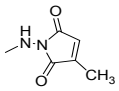
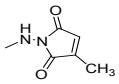
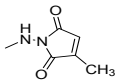
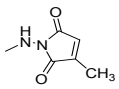
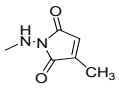
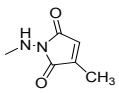
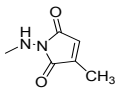
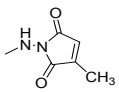
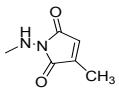
17			CO_2Et	H	5.16	5.20	-0.04
18	3-Thienyl		CO_2Et	H	7.00	6.59	0.42
19*			CO_2Et	H	6.69	6.76	-0.06
20*			CO_2Et	H	6.52	6.62	-0.10
21			CO_2Et	H	5.40	5.34	0.06
22			CO_2Et	H	6.70	6.73	-0.03
23			CO_2Et	H	6.00	5.76	0.24
24*			CO_2Et	H	5.70	5.56	0.14
25			CO_2Et	H	6.52	6.63	-0.10
26	Benzyl		CO_2Et	H	5.16	5.29	-0.13
27	Phenoxy		CO_2Et	H	4.82	4.84	-0.02
28			CO_2Et	H	6.00	6.61	-0.61
29			CO_2Et	H	5.00	4.81	0.19
30*	Phenyl		CO_2Et	H	5.70	5.71	-0.01

31	Phenyl		CO_2Et	H	5.40	5.37	0.02
32*	2-Thienyl		CO_2Et	H	6.00	5.75	0.25
33			CO_2Et	H	5.23	5.73	-0.20
34*	Et		CO_2Et	H	5.00	5.54	-0.54
35	CF_3		CO_2Et	H	5.00	5.11	-0.11
36	CF_3		CO_2Et	H	4.70	4.91	-0.21
37	CF_3		CO_2Et	H	5.00	5.25	-0.25
38*	2-Thienyl			H	6.52	6.22	0.30
39	2-Thienyl		CN	H	5.30	5.56	-0.26
40*	2-Thienyl			H	6.70	6.63	0.07
41	2-Thienyl			H	6.70	6.59	0.11
42	2-Thienyl			H	6.52	6.10	0.42
43	2-Thienyl			H	6.70	6.65	0.05
44	Cl	H		CF_3	7.30	6.71	0.59

45	Cl	H		H	6.52	6.69	-0.17
46*	Cl	H		i-Pro	6.30	6.55	-0.25
47	Cl	H		Phenyl	6.40	6.61	-0.21
48		CF_3	CO_2Et	H	5.70	5.51	0.19
49*		CF_3	CO_2Et	H	5.80	5.30	0.50
50	NH_2	CF_3	CO_2Et	H	4.52	5.26	-0.74
51		CF_3	CO_2Et	H	5.43	5.28	0.16
52		CF_3	CO_2Et	H	5.41	5.74	-0.33
53		CF_3	CO_2Et	H	6.52	6.44	0.08
54		CF_3	CO_2Et	H	6.35	6.70	-0.35
55*		CF_3	CO_2Et	H	6.39	6.78	-0.39
56		CF_3	CO_2Et	H	6.08	6.44	-0.36
57		CF_3	CO_2Et	H	6.23	6.34	-0.11
58*		CF_3	CO_2Et	H	6.42	6.27	0.15
59		H	CO_2Et	H	4.89	4.93	-0.05
60		Me	CO_2Et	H	5.72	6.35	-0.63
61*		Et	CO_2Et	H	6.40	5.82	0.58
62		CF_2CF_3	CO_2Et	H	6.70	5.96	0.74

63		Phenyl	CO_2Et	H	5.92	5.75	0.18
64*		Benzyl	CO_2Et	H	5.42	5.74	-0.32
65		CH_2OMe	CO_2Et	H	5.22	5.21	0.02
66			CO_2Et	H	6.00	6.05	-0.05
67		2-Thienyl	CO_2Et	H	6.85	7.01	-0.15
68*		3-Thienyl	CO_2Et	H	6.70	6.64	0.06
69			CO_2Et	H	7.35	7.19	0.15
70*			CO_2Et	H	6.28	6.12	0.17
71			CO_2Et	H	6.10	6.30	-0.20
72			CO_2Et	H	5.66	5.59	0.06
73*			CO_2Et	H	5.82	6.23	-0.41
74		CF_3	$COCMe_3$	H	6.68	6.35	0.33
75		CF_3	COOH	H	4.52	4.65	-0.13
76		CF_3	$CONH_2$	H	4.52	4.67	-0.15
77		CF_3	$CONMe_2$	H	4.52	4.36	0.17
78*		CF_3	Acetyl	H	5.36	5.93	-0.58
79		CF_3	Phenoxy	H	7.01	6.82	0.19
80		CF_3		H	5.19	5.10	0.10
81*		Et	Phenoxy	H	6.19	5.92	0.27
82		Et		H	6.35	6.35	-0.00
83		Et		H	6.92	6.98	-0.06

84*		Et	CH_2OH	H	5.31	5.66	-0.35
85		Et	CN	H	5.96	5.46	0.50
86		Me	Acetyl	H	5.11	4.86	0.25
87		Et		H	5.00	5.15	-0.15
88		Et		H	5.00	5.05	-0.05
89*		Et		H	6.08	6.30	-0.22
90		Et		H	5.00	5.17	-0.17
91		Et		H	5.55	5.43	0.12
92*		2-Thienyl		H	6.12	5.88	0.24
93		2-Thienyl	CO-t-Bu	H	7.30	7.27	0.03
94*		i-Pro	CO_2Et	H	6.37	6.45	-0.09
95		CF_2CF_3	CO_2Et	H	6.35	6.30	0.07
96		Et	CO_2Et	H	7.46	6.78	0.68
97*			CO_2Et	H	6.89	6.34	0.55
98			CO_2Et	H	5.77	5.73	0.04
99		Et	CO_2Et	H	6.39	6.49	-0.10
100		CF_2CF_3	CO_2Et	H	6.46	6.46	-0.00
101		2-Thienyl	CO_2Et	H	7.03	7.11	-0.08
102		3-Thienyl	CO_2Et	H	6.92	7.07	-0.15
103*			CO_2Et	H	6.46	6.09	0.36
104*		Et		H	6.20	6.64	-0.44

105	2-Thienyl			7.22	7.24	-0.02
106	Phenyl			7.00	7.13	-0.13
107*	CF_3			7.00	7.06	-0.06
108	2-Thienyl		7-OMe	8.10	7.99	0.11
109	2-Thienyl		8-OMe	8.52	7.76	0.77
110	2-Thienyl		9-OMe	7.70	8.09	-0.40
111*	2-Thienyl		10-OMe	7.30	7.33	-0.03
112	2-Thienyl		8,9-Di-OMe	7.30	7.39	-0.09
113	2-Thienyl		8,9,10-Tri-OMe	7.40	7.36	0.04
114*	2-Thienyl		7-F	7.30	7.16	0.14
115	2-Thienyl		8-Cl	7.70	7.68	0.02
116	2-Thienyl		7-Me	7.70	7.55	0.15
117	2-Thienyl		9-(N-morpholy)	6.70	6.90	-0.20
118	2-Thienyl		9-(NMe_2)	7.40	7.35	0.05
119	CF_3		7-OMe	8.00	7.91	0.09

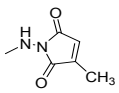
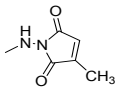
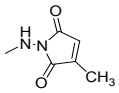
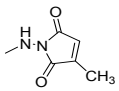
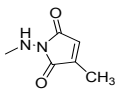
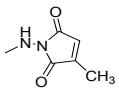
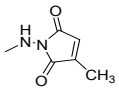
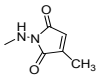
120	CF_3		8-OMe	7.52	7.67	-0.15
121	CF_3		7-Me	6.40	6.64	-0.24
122[*]	CF_3		8-SMe	7.10	7.52	-0.42
123[*]	CF_3		8-SO_2Me	6.00	6.51	-0.51
124	CF_3		8-SO_2Me	5.05	5.04	0.01
125[*]	CF_3		8-OH	7.00	7.59	-0.59
126	CF_3		9-(1-Piperidyl)	6.70	6.82	-0.12
127	CF_3		9-(NMe_2)	7.70	7.87	-0.18

Table S2 The energy scores of different binding sites (1-7) and the experimental values.

No.	site 1	site 2	site 3	site 4	site 5	site 6	site 7	pIC_{50}
1	-59.4	-38.4	-42.9	-62.6	-14.6	-11.0	-20.8	6.00
2	-57.7	-36.2	-45.2	-54.4	-13.4	-11.4	-18.9	4.80
3	-59.2	-39.9	-40.8	-59.0	-13.4	-10.6	-19.1	5.00
4	-60.4	-35.1	-42.7	-60.4	-13.4	-11.6	-20.6	6.00
5	-62.9	-39.3	-48.4	-64.1	-14.1	-14.1	-20.0	6.70
6	-64.5	-39.1	-37.8	-63.9	-12.6	-12.1	-20.4	5.22
7	-57.2	-34.0	-47.3	-58.1	-13.0	-14.9	-21.2	5.70
8	-68.3	-30.1	-2.1	-64.7	-13.5	-13.2	-23.3	5.22
9	-63.1	-43.2	-40.7	-64.5	-12.2	-12.3	-22.6	5.10
10	-60.2	-40.6	-43.8	-58.6	-13.7	-12.8	-21.7	5.00
11	-52.7	-28.9	-24.4	-62.3	-12.5	-13.4	-21.1	6.05
12	-60.0	-28.0	-46.3	-59.5	-12.5	-12.8	-20.7	5.30
13	-59.0	-39.8	-42.0	-59.9	-12.7	-12.5	-20.7	6.16
14	-60.6	-36.6	-41.2	-60.1	-15.2	-14.6	-21.1	6.52
15	-61.8	-26.7	-44.5	-59.5	-12.4	-14.2	-21.7	6.40
16	-57.0	-30.4	-39.9	-58.5	-14.1	-14.6	-20.8	6.16
17	-65.8	-42.8	-56.3	-63.1	-13.1	-14.4	-23.3	5.16
18	-60.9	-39.5	-52.4	-62.2	-14.1	-12.3	-21.0	7.00
19	-61.9	-41.7	-41.1	-64.7	-13.8	-14.0	-22.4	6.69
20	-61.4	-33.6	-42.3	-64.4	-12.3	-13.5	-21.3	6.52
21	-59.4	-28.4	-36.4	-64.1	-13.2	-15.6	-24.8	5.40
22	-65.3	-43.0	-49.8	-63.5	-15.1	-12.4	-21.3	6.70
23	-60.8	-35.7	-50.8	-62.1	-13.1	-13.6	-22.1	6.00
24	-63.3	-39.8	-44.1	-58.8	-13.3	-13.1	-21.7	5.70
25	-55.5	-39.4	-46.0	-58.5	-13.4	-11.9	-21.0	6.52
26	-57.8	-40.6	-44.9	-58.8	-12.0	-12.6	-21.9	5.16
27	-62.7	-41.3	-44.4	-63.3	-15.1	-12.7	-21.6	4.82
28	-64.1	-34.3	-53.5	-60.6	-12.5	-12.0	-20.9	6.00
29	-72.1	-36.6	-43.1	-63.8	-19.8	-16.1	-27.4	5.00
30	-66.9	-37.8	-54.8	-56.5	-15.4	-16.2	-22.4	5.70
31	-60.5	-45.4	-48.9	-55.2	-13.9	-16.8	-23.3	5.40
32	-68.2	-39.4	-52.3	-59.4	-16.0	-17.3	-23.1	6.00
33	-63.3	-36.6	-53.0	-56.5	-14.5	-16.4	-22.4	5.23
34	-63.4	-38.4	-46.1	-53.3	-14.1	-14.9	-20.2	5.00
35	-61.9	-40.1	-42.7	-57.8	-14.0	-11.4	-21.1	5.00
36	-58.7	-24.1	-50.2	-57.3	-12.2	-15.3	-22.5	4.70
37	-58.5	-35.7	-45.6	-58.0	-14.6	-10.9	-19.7	5.00
38	-62.9	-25.8	-53.0	-66.5	-12.5	-15.7	-21.9	6.52
39	-53.8	-38.3	-53.1	-59.6	-12.9	-13.2	-17.3	5.30
40	-63.3	-32.7	-48.1	-67.3	-14.8	-14.2	-21.2	6.70
41	-66.4	-26.1	-49.1	-69.4	-12.7	-13.8	-20.1	6.70

42	-65.0	-27.2	-55.8	-68.8	-13.2	-16.5	-21.9	6.52
43	-67.1	-40.7	-49.4	-65.2	-12.4	-14.3	-19.6	6.70
44	-58.9	-36.2	-47.7	-56.4	-14.1	-12.8	-20.3	7.30
45	-56.0	-32.2	-54.8	-56.0	-13.6	-14.2	-19.3	6.52
46	-59.1	-34.9	-45.7	-58.1	-13.4	-13.5	-21.1	6.30
47	-66.8	-35.7	-49.3	-55.9	-14.9	-14.0	-21.6	6.40
48	-57.1	-41.1	-47.4	-57.4	-15.9	-14.5	-21.7	5.70
49	-57.1	-39.5	-47.0	-55.7	-15.8	-15.5	-21.8	5.80
50	-43.6	-35.0	-40.2	-45.1	-12.2	-11.4	-15.2	4.52
51	-63.4	-38.5	-42.7	-55.9	-16.2	-15.5	-24.8	5.43
52	-58.6	-38.2	-47.0	-53.1	-16.4	-16.2	-22.7	5.41
53	-62.4	-35.6	-45.4	-49.3	-14.5	-16.3	-19.5	6.52
54	-65.8	-36.7	6.0	-55.0	-12.6	-12.9	-22.1	6.35
55	-74.6	-38.4	-43.9	-60.9	-15.3	-13.1	-27.4	6.39
56	-63.0	-39.0	-34.8	-54.6	-12.6	-12.9	-23.6	6.08
57	-68.9	-37.1	-44.8	-55.9	-13.8	-13.3	-24.6	6.23
58	-72.8	-36.7	-52.5	-57.7	-13.6	-14.6	-23.9	6.42
59	-55.2	-37.1	-43.7	-52.6	-14.1	-14.6	-20.6	4.89
60	-57.3	-42.7	-51.0	-54.7	-14.3	-15.2	-21.4	5.72
61	-58.7	-36.4	-47.7	-57.2	-15.8	-16.1	-22.7	6.40
62	-58.9	-33.1	-50.0	-60.1	-15.3	-15.4	-19.9	6.70
63	-67.4	-38.0	-39.5	-62.5	-14.7	-14.5	-22.6	5.92
64	-64.2	-33.1	-55.6	-55.3	-16.5	-17.7	-22.1	5.42
65	-62.3	-39.7	-51.9	-61.1	-15.8	-17.1	-22.9	5.22
66	-60.1	-39.6	-50.7	-55.2	-15.5	-17.2	-24.5	6.00
67	-65.0	-42.7	-52.6	-62.6	-15.1	-15.5	-24.1	6.85
68	-68.3	-36.0	-51.0	-68.4	-18.0	-14.2	-22.9	6.70
69	-64.4	-38.2	-52.2	-57.1	-15.9	-14.9	-25.6	7.35
70	-63.3	-36.0	-50.5	-57.9	-16.5	-17.7	-23.5	6.28
71	-63.7	-41.8	-52.3	-61.4	-16.6	-16.2	-23.9	6.10
72	-62.8	-39.4	-56.2	-58.1	-15.4	-17.0	-23.1	5.66
73	-61.8	-36.3	-50.5	-58.9	-15.4	-15.7	-22.4	5.82
74	-61.3	-37.0	-46.1	-58.8	-14.4	-15.3	-21.2	6.68
75	-54.1	-39.8	-50.4	-56.7	-15.1	-14.4	-21.9	4.52
76	-52.8	-40.9	-47.9	-54.8	-15.1	-14.7	-21.2	4.52
77	-58.9	-38.8	-47.9	-56.4	-15.3	-14.4	-22.0	4.52
78	-53.8	-40.4	-48.2	-54.1	-14.3	-14.7	-20.8	5.36
79	-63.0	-37.6	-44.3	-55.1	-14.9	-16.7	-22.5	7.01
80	-55.2	-40.4	-49.2	-54.8	-13.9	-14.9	-20.3	5.19
81	-63.5	-42.9	-46.3	-59.0	-15.7	-17.3	-23.2	6.19
82	-58.5	-41.5	-49.5	-58.3	-14.3	-16.1	-20.8	6.35
83	-60.7	-39.1	-49.6	-62.8	-17.5	-14.3	-21.9	6.92
84	-54.8	-39.9	-43.0	-59.9	-15.0	-13.7	-20.6	5.31

85	-54.8	-39.4	-43.6	-60.1	-15.3	-13.9	-21.3	5.96
86	-54.9	-41.5	-48.4	-58.7	-14.6	-13.6	-20.3	5.11
87	-56.0	-41.0	-48.9	-54.4	-13.4	-13.3	-20.4	5.00
88	-60.5	-42.8	-50.9	-57.0	-13.9	-16.2	-20.8	5.00
89	-56.9	-39.0	-50.5	-54.1	-14.0	-15.4	-20.9	6.08
90	-62.1	-40.9	-48.0	-57.2	-14.8	-15.3	-21.4	5.00
91	-63.5	-27.0	-55.0	-63.1	-12.3	-14.7	-22.0	5.55
92	-64.4	-42.0	-47.8	-58.5	-14.2	-15.6	-22.4	6.12
93	-61.9	-37.9	-52.5	-62.9	-14.2	-14.7	-24.4	7.30
94	-71.7	-34.7	-44.2	-67.5	-17.9	-13.9	-25.2	6.37
95	-63.1	-37.1	-40.7	-50.0	-15.9	-15.0	-20.9	6.35
96	-61.1	-37.2	-45.5	-51.7	-15.0	-14.6	-21.0	7.46
97	-66.2	-43.7	-58.8	-60.7	-16.8	-16.4	-23.6	6.89
98	-65.3	-34.8	-48.4	-59.0	-16.6	-18.1	-23.7	5.77
99	-66.9	-39.9	-33.7	-53.4	-16.2	-16.9	-22.4	6.39
100	-64.1	-38.6	-39.0	-50.7	-14.7	-15.5	-20.9	6.46
101	-68.2	-33.4	-45.3	-53.3	-15.7	-15.8	-23.2	7.03
102	-67.6	-37.2	-47.7	-51.8	-15.9	-17.6	-21.4	6.92
103	-58.6	-40.0	-51.2	-58.3	-13.6	-16.4	-22.4	6.46
104	-58.2	-38.5	-52.0	-50.8	-13.8	-13.9	-20.0	6.20
105	-59.6	-42.0	-51.2	-61.7	-14.0	-15.1	-20.1	7.22
106	-60.5	-39.9	-47.0	-60.2	-12.8	-16.1	-20.1	7.00
107	-57.3	-36.1	-41.4	-52.6	-15.9	-14.4	-19.6	7.00
108	-63.8	-29.0	-49.2	-61.8	-12.8	-15.1	-21.5	8.10
109	-64.2	-32.3	-51.5	-69.5	-12.4	-15.4	-22.3	8.52
110	-64.1	-33.4	-49.7	-58.8	-15.5	-15.9	-21.6	7.70
111	-63.4	-39.8	-55.2	-62.4	-12.4	-15.4	-21.8	7.30
112	-68.1	-28.6	-47.3	-63.3	-14.6	-17.2	-23.2	7.30
113	-72.0	-30.2	-43.3	-64.1	-12.9	-17.6	-25.4	7.40
114	-59.3	-37.8	-52.1	-60.2	-12.8	-15.1	-20.2	7.30
115	-60.9	-37.3	-52.3	-66.8	-13.7	-15.4	-20.9	7.70
116	-59.8	-38.9	-43.3	-55.2	-13.3	-14.9	-20.1	7.70
117	-56.7	-31.2	25.1	-69.9	-13.6	-16.9	-24.1	6.70
118	-66.2	-35.5	-40.1	-62.6	-12.8	-15.3	-22.7	7.40
119	-59.5	-36.3	-43.9	-52.3	-15.4	-12.6	-20.1	8.00
120	-61.1	-38.2	-45.2	-63.8	-16.5	-14.9	-21.0	7.52
121	-60.8	-37.1	-42.0	-48.1	-14.0	-14.5	-18.6	6.40
122	-63.8	-40.3	-43.5	-67.2	-16.0	-14.9	-19.3	7.10
123	-56.9	-32.7	-48.2	-64.3	-14.3	-13.4	-20.8	6.00
124	-69.5	-31.8	-42.0	-71.7	-16.9	-16.6	-27.3	5.05
125	-60.1	-35.0	-43.7	-59.7	-16.8	-14.5	-21.7	7.00
126	-60.6	-39.7	-16.7	-59.5	-16.3	-15.9	-23.0	6.70
127	-64.3	-34.8	-37.1	-56.7	-16.2	-15.6	-22.2	7.70

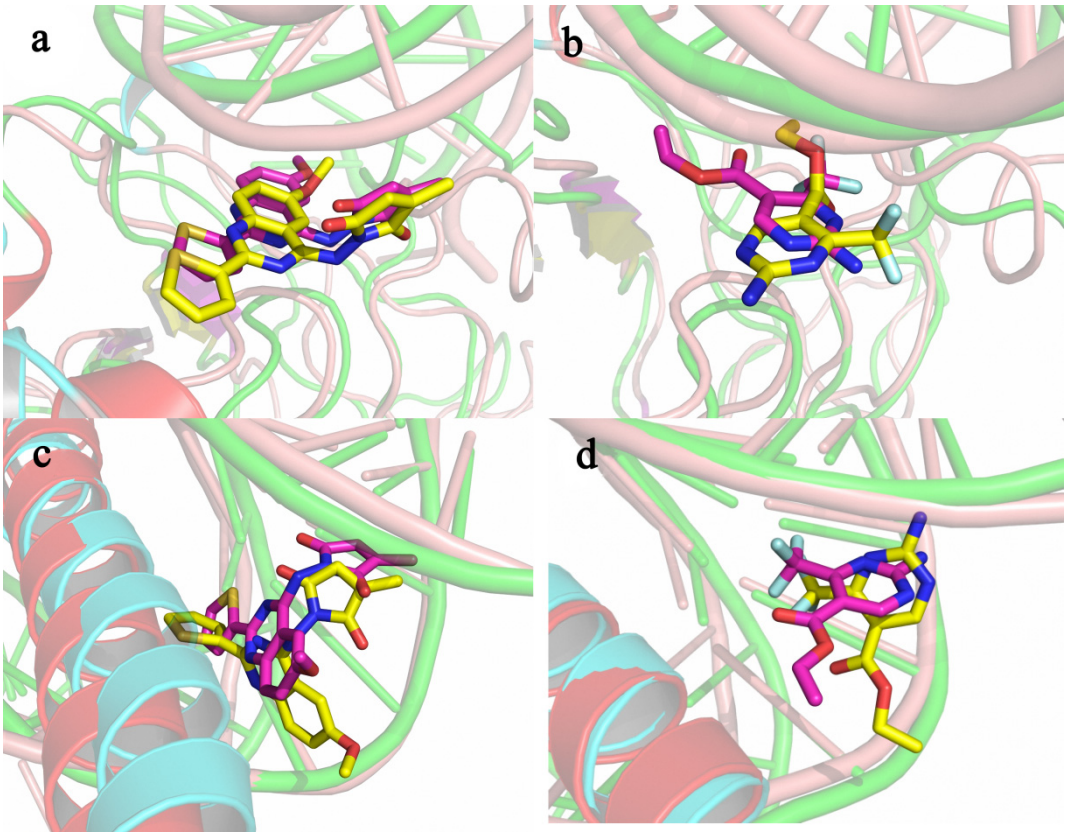


Fig.S1 Superimposition of the average structure from the last 2 ns of the MD simulation (magenta) and the initial structure (yellow). (a) Compound **109**-1NFK complex, (b) Compound **50**-1NFK complex, (c) Compound **109**-2H7H complex, (d) Compound **50**-2H7H complex.