

Supplementary Information

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Abstract: 5-HT₆ receptor has been implicated in a series of diseases including anxiety, depression, schizophrenia and cognitive dysfunctions. 5-HT₆ ligands have been reported to play a significant role in the treatment for central nervous system (CNS) diseases. Presently, a large series of 223 5-HT₆ ligands were studied using a combinational method by 3D-QSAR, molecular docking and molecular dynamics calculations for further improvement of potency. The optimal 3D models exhibit satisfying statistical results with r^2_{ncv} , q^2 values of 0.85 and 0.50 for CoMFA, 0.81 and 0.53 for CoMSIA, respectively. Their predictive powers were validated by external test set, showing r^2_{pred} of 0.71 and 0.76. The contour maps also provide a visual representation of contributions of steric, electrostatic, hydrophobic and hydrogen bond fields as well as the prospective binding models. In addition, the agreement between 3D-QSAR, molecular docking and molecular dynamics simulation proves the rationality of the developed models. These results, we hope, may be helpful in designing novel and potential 5-HT₆ ligands.

Keywords: 5-HT₆; 3D-QSAR; CoMFA; CoMSIA; molecular dynamics

Table S1. The observed and predicted pK_i values of the 3D-QSAR models.

No.	Observed	Ligand-based Models	
		CoMFA	CoMSIA
1	7.70	7.61	7.86
2	7.64	7.69	7.78
3	8.70	8.62	8.60
4*	8.57	8.62	8.61
5	8.07	8.34	8.43
6	8.82	8.71	8.68
7	8.26	8.41	8.52
8*	8.89	8.76	8.62
9	8.37	8.54	8.61
10	8.89	8.86	8.62
11	8.60	8.24	8.26
12*	8.25	8.67	8.54
13	8.85	8.75	8.58
14	8.30	8.26	8.40
15	8.66	8.71	8.59
16*	8.82	8.58	8.67
17	8.38	8.37	8.35
18	9.05	8.76	8.74
19	7.96	8.08	8.13
20*	8.08	8.46	8.45
21	8.48	8.49	8.49
22	9.00	8.85	8.77
23	8.24	8.40	8.74
24*	9.00	9.16	9.04
25	9.10	9.14	9.14
26	8.85	8.71	8.92
27	8.31	8.10	8.26
28*	8.44	7.76	7.98
29	8.43	8.49	8.55
30	8.89	8.49	8.54
31	8.12	8.23	8.42
32*	7.94	7.86	8.18
33	7.47	7.79	8.06
34	7.95	7.76	7.94
35	8.34	8.62	8.50
36	7.92	7.75	8.20
37	8.68	8.72	8.38
38	8.42	8.75	8.61
39	8.70	8.66	8.52

Table S1. Cont.

No.	Observed	Ligand-based Models	
		CoMFA	CoMSIA
40*	8.62	8.68	8.56
41	8.33	8.49	8.43
42	8.36	8.41	8.31
43	8.47	8.49	8.32
44	8.03	8.50	8.53
45	8.21	8.46	8.44
46	8.41	8.27	8.30
47	7.87	8.19	8.21
48	8.92	8.79	8.68
49	8.72	8.61	8.52
50	8.49	8.46	8.46
51	9.15	9.03	9.26
52	8.70	8.65	8.72
53	9.15	9.04	9.18
54	8.77	9.00	9.18
55	6.71	6.92	6.92
56*	7.48	7.36	7.22
57	7.64	7.34	7.29
58	7.72	7.50	7.18
59	7.39	7.32	7.22
60*	7.74	7.44	7.33
61	7.17	7.32	7.36
62	7.54	7.57	7.43
63	7.05	6.96	7.11
64*	7.34	7.37	7.35
65	7.62	7.74	7.47
66	7.72	7.76	7.57
67	7.48	7.59	7.55
68	7.92	7.57	7.16
69	7.72	7.73	7.63
70	7.30	7.36	7.42
71	6.91	6.85	6.99
72*	7.07	6.75	6.90
73	6.50	7.14	7.00
74	6.30	6.27	6.15
75	6.49	6.62	6.69
76*	6.60	6.42	6.54
77	7.92	7.68	7.69
78	8.10	7.76	8.14
79	7.30	7.23	7.36

Table S1. Cont.

No.	Observed	Ligand-based Models	
		CoMFA	CoMSIA
80	9.30	8.86	8.77
81	8.92	8.89	8.84
82	8.74	8.73	8.76
83	8.68	8.70	8.73
84*	7.82	8.36	8.53
85	8.64	8.86	8.57
86	8.89	9.01	8.81
87	7.74	7.59	7.54
88*	7.26	7.02	7.22
89	7.03	7.31	7.70
90	7.72	7.32	7.56
91	7.30	7.55	7.65
92	7.18	7.20	7.33
93	7.34	7.00	7.33
94	7.85	7.60	7.53
95	7.32	7.28	7.23
96*	6.91	6.91	6.89
97	8.42	8.07	8.00
98	8.02	7.79	7.77
99	7.39	7.49	7.39
100*	7.27	7.58	7.56
101	7.19	7.36	7.40
102	7.51	7.62	7.47
103	7.66	7.87	7.92
104*	7.66	7.65	7.32
105	7.48	7.18	7.18
106	7.60	7.96	7.98
107	7.89	7.97	7.81
108	8.51	8.09	7.95
109	7.28	6.92	7.17
110	6.71	6.93	7.07
111	8.15	7.99	8.03
112*	8.01	7.90	7.82
113	7.92	7.73	7.64
114	7.44	7.46	7.50
115	7.89	7.59	7.47
116	7.06	7.35	7.38
117	6.75	6.94	7.00
118	6.90	6.91	6.89
119	7.14	7.31	7.23

Table S1. Cont.

No.	Observed	Ligand-based Models	
		CoMFA	CoMSIA
120*	7.10	7.38	7.21
121	7.70	7.66	7.83
122	7.60	7.70	7.96
123	7.64	7.74	7.81
124*	8.26	8.27	8.24
125	8.38	8.67	8.29
126	8.33	8.27	7.87
127	8.32	8.15	8.17
128	9.00	8.50	8.48
129	8.33	8.76	8.72
130	7.06	7.45	7.59
131	8.64	8.14	8.21
132	9.52	8.65	8.59
133	8.70	8.86	8.75
134	7.35	7.56	7.75
135	7.35	7.75	7.86
136*	7.66	8.44	8.38
137	8.68	8.65	8.75
138	8.68	8.89	8.67
139	8.37	7.98	8.19
140*	8.54	8.67	8.70
141	7.93	7.88	8.13
142	8.05	7.96	8.09
143	9.00	8.87	8.91
144*	8.80	7.96	8.27
145	7.82	8.06	8.02
146	8.48	8.15	8.16
147	9.05	8.85	8.78
148*	9.05	9.52	9.29
149	7.31	7.10	7.61
150	7.04	7.08	7.46
151	6.91	7.23	7.30
152*	7.89	8.00	7.76
153	8.14	7.64	7.46
154	8.22	8.01	7.94
155	7.97	7.94	8.07
156	7.17	7.82	7.93
157	7.80	7.45	7.51
158	8.40	7.99	7.91
159	7.68	8.23	8.25

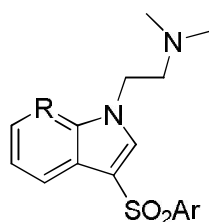
Table S1. *Cont.*

No.	Observed	Ligand-based Models	
		CoMFA	CoMSIA
160	8.15	8.18	8.21
161	8.25	8.45	8.33
162	6.95	6.86	6.77
163	8.30	8.18	8.04
164*	8.33	8.28	8.21
165	8.46	8.26	8.25
166	7.74	7.65	7.70
167	8.02	8.14	8.19
168*	8.30	8.25	8.23
169	7.74	7.70	7.73
170	7.82	8.41	8.37
171	7.14	7.98	7.94
172*	8.49	8.42	8.34
173	8.89	8.55	8.36
174	8.34	8.15	7.87
175	7.63	8.10	8.23
176*	8.22	8.18	8.21
177	8.82	8.93	8.93
178	8.55	9.04	8.97
179	8.55	8.57	8.64
180*	8.38	8.83	8.79
181	8.02	8.05	7.95
182	8.17	8.17	8.24
183	8.85	9.12	9.07
184*	8.37	8.29	8.32
185	9.15	8.63	8.77
186	8.77	8.32	8.45
187	8.46	8.54	8.38
188*	7.77	7.84	7.89
189	7.28	7.17	7.10
190	7.24	7.24	7.17
191	7.36	7.49	7.63
192*	7.77	7.88	7.79
193	7.52	7.57	7.75
194	7.18	7.55	7.61
195	7.77	7.64	7.65
196*	7.92	8.64	8.59
197	7.85	8.16	7.94
198	9.62	9.07	9.11
199	8.82	8.85	8.96

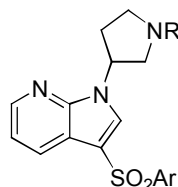
Table S1. Cont.

No.	Observed	Ligand-based Models	
		CoMFA	CoMSIA
200	8.96	8.85	8.99
201	7.62	7.95	7.74
202	7.36	7.20	7.11
203	7.19	7.12	6.87
204	7.92	7.79	7.54
205	7.51	7.58	7.56
206	8.47	8.49	8.50
207	8.32	8.32	8.07
208*	7.57	7.83	7.65
209	7.62	7.84	7.80
210	7.55	7.90	7.78
211	8.01	8.00	7.92
212	8.54	8.33	8.16
213	6.97	6.81	7.12
214	8.51	8.26	8.29
215	8.17	8.44	8.44
216*	9.00	8.65	8.57
217	9.10	8.89	8.77
218	8.20	8.42	8.36
219	8.64	8.55	8.46
220*	9.00	8.43	8.47
221	8.82	8.77	8.39
222	8.01	8.56	8.44
223	9.22	9.26	9.33

*, test set.

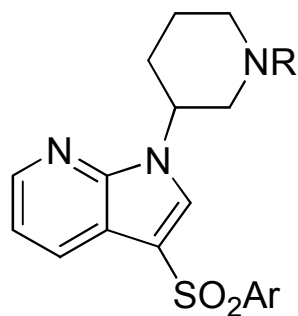
Table S2. The structures of molecules with skeleton type A in the dataset.

No.	Ar	R	CIC2	BEHv2	p <i>K</i> _i	Ref ^a
1	Ph	C	1.62	3.80	7.70	[14]
2	Ph	N	1.28	3.79	7.64	[14]



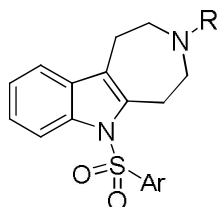
No.	Ar	R	CIC2	BEHv2	p <i>K</i> _i	Refa
3	2-FPh	H	0.74	3.79	8.70	[14]
4*	3-FPh	H	0.69	3.79	8.57	[14]
5	4-FPh	H	0.79	3.79	8.07	[14]
6	3-ClPh	H	0.69	3.80	8.82	[14]
7	4-ClPh	H	0.79	3.80	8.26	[14]
8*	3-BrPh	H	0.69	3.81	8.89	[14]
9	4-BrPh	H	0.79	3.81	8.37	[14]
10	3-CF ₃ Ph	H	0.75	3.82	8.89	[14]
11	Ph	Me	1.00	3.79	8.60	[14]
12*	2-FPh	Me	0.80	3.80	8.25	[14]
13	3-FPh	Me	0.75	3.80	8.85	[14]
14	4-FPh	Me	0.84	3.80	8.30	[14]
15	2-ClPh	Me	0.80	3.80	8.66	[14]
16*	3-ClPh	Me	0.75	3.80	8.82	[14]
17	4-ClPh	Me	0.84	3.80	8.38	[14]
18	3-BrPh	Me	0.75	3.81	9.05	[14]
19	Ph	Et	1.10	3.79	7.96	[14]
20*	3-FPh	Et	0.87	3.80	8.08	[14]
21	3-ClPh	Et	0.87	3.80	8.48	[14]
22	5-Cl-thien-2-yl	H	0.54	3.78	9.00	[14]
23	8-Quinolyl	H	0.94	3.93	8.24	[14]
24*	6-Cl-imidazo[2,1- <i>b</i>]thiazol-5-yl	H	0.40	3.90	9.00	[14]
25	6-Cl-imidazo[2,1- <i>b</i>]thiazol-5-yl	Me	0.48	3.90	9.10	[14]
26	6-Cl-imidazo[2,1- <i>b</i>]thiazol-5-yl	Et	0.61	3.90	8.85	[14]

Table S2. Cont.

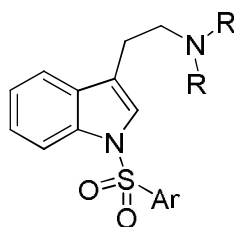


No.	Ar	R	CIC2	BEHv2	p <i>K</i> _i	Ref ^a
27	Ph	H	1.03	3.79	8.31	[14]
28*	Ph	Et	1.16	3.79	8.44	[14]
29	2-ClPh	H	0.83	3.80	8.43	[14]
30	3-ClPh	H	0.78	3.80	8.89	[14]
31	4-ClPh	H	0.87	3.80	8.12	[14]
32*	4-ClPh	Me	0.92	3.80	7.94	[14]
33	4-ClPh	Et	1.02	3.80	7.47	[14]
34	4-ClPh	<i>i</i> -Pr	1.10	3.80	7.95	[14]
35	3-CF ₃ Ph	H	0.83	3.82	8.34	[14]
36	4-CF ₃ Ph	H	0.92	3.82	7.92	[14]
37	3-CF ₃ Ph	Me	0.88	3.82	8.68	[14]
38	3-BrPh	H	0.78	3.81	8.42	[14]
39	2-FPh	H	0.83	3.79	8.70	[14]
40*	3-FPh	H	0.78	3.79	8.62	[14]
41	3-FPh	Me	0.83	3.79	8.33	[14]
42	3-FPh	Et	0.93	3.79	8.36	[14]
43	3-FPh	<i>i</i> -Pr	1.02	3.79	8.47	[14]
44	3-BrPh	<i>i</i> -Pr	1.02	3.81	8.03	[14]
45	3,5-diClPh	H	0.83	3.81	8.21	[14]
46	3,5-diClPh	Me	0.88	3.81	8.41	[14]
47	3,5-diClPh	Et	0.98	3.81	7.87	[14]
48	5-Cl-thien-2-yl	H	0.65	3.78	8.92	[14]
49	5-Cl-thien-2-yl	Me	0.72	3.78	8.72	[14]
50	5-Cl-thien-2-yl	Et	0.83	3.78	8.49	[14]
51	6-Cl-imidazo[2,1- <i>b</i>]thiazol-5-yl	H	0.51	3.90	9.15	[14]
52	6-Cl-imidazo[2,1- <i>b</i>]thiazol-5-yl	Me	0.58	3.90	8.70	[14]
53	6-Cl-imidazo[2,1- <i>b</i>]thiazol-5-yl	Et	0.70	3.90	9.15	[14]
54	6-Cl-imidazo[2,1- <i>b</i>]thiazol-5-yl	<i>i</i> -Pr	0.80	3.90	8.77	[14]

Table S2. Cont.

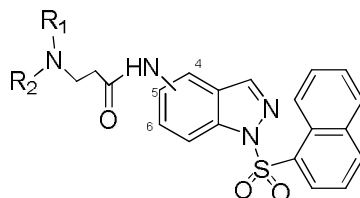


No.	Ar	R	CIC2	BEHv2	p <i>K</i> _i	Ref ^a
55	Ph	H	1.52	3.81	6.71	[15]
56*	3-F-Ph	H	1.19	3.81	7.48	[15]
57	4-F-Ph	H	1.22	3.81	7.64	[15]
58	2-Cl-Ph	H	1.27	3.82	7.72	[15]
59	3-Cl-Ph	H	1.19	3.82	7.39	[15]
60*	4-Cl-Ph	H	1.22	3.82	7.74	[15]
61	3-Me-Ph	H	1.22	3.84	7.17	[15]
62	4-Me-Ph	H	1.24	3.84	7.54	[15]
63	3-CF ₃ -Ph	H	1.22	3.84	7.05	[15]
64*	4-CF ₃ -Ph	H	1.24	3.84	7.34	[15]
65	5-Cl-Naph	H	1.40	3.98	7.62	[15]
66	2-MeO-Ph	H	1.26	3.82	7.72	[15]
67	4-MeO-Ph	H	1.22	3.82	7.48	[15]
68	3-MeO-Ph	H	1.19	3.82	7.92	[15]
69	3-MeO-Ph	Me	1.21	3.82	7.72	[15]
70	3-MeO-Ph	Et	1.29	3.82	7.30	[15]
71	3-MeO-Ph	<i>n</i> -Pr	1.26	3.82	6.91	[15]
72*	3-MeO-Ph	<i>i</i> -Pr	1.32	3.82	7.07	[15]
73	3-MeO-Ph	Bn	1.59	3.82	6.50	[15]
74	3-MeO-Ph	PhCH ₂ CH ₂	1.81	3.82	6.30	[15]
75	3-MeO-Ph	<i>c</i> -Pentyl	1.41	3.82	6.49	[15]
76*	3-MeO-Ph	<i>c</i> -Hexyl	1.53	3.82	6.60	[15]

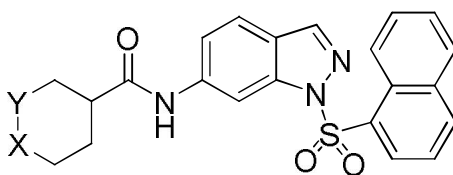


No.	Ar	R	CIC2	BEHv2	p <i>K</i> _i	Ref ^a
77	Ph	Et	1.61	3.81	7.92	[15]

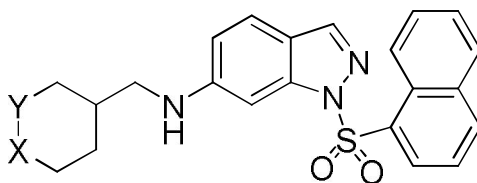
Table S2. Cont.



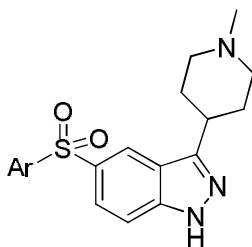
No	Position	R ₁	R ₂	CIC2	BEHv2	p <i>K</i> _i	Ref ^a
78	4	H	H	1.17	3.95	8.10	[16]
79	5	H	H	1.10	3.94	7.30	[16]
80	6	H	H	1.17	3.94	9.30	[16]
81	6	CH ₃	H	1.16	3.94	8.92	[16]
82	6	CH ₃	CH ₃	1.34	3.94	8.74	[16]
83	6	CH ₃ CH ₂	CH ₃ CH ₂	1.47	3.94	8.68	[16]
84 [*]	6	-CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ -		1.44	3.94	7.82	[16]



No.	X	Y	CIC2	BEHv2	p <i>K</i> _i	Ref ^a
85	NH	CH ₂	1.28	3.94	8.64	[16]
86	CH ₂	NH	1.21	3.94	8.89	[16]

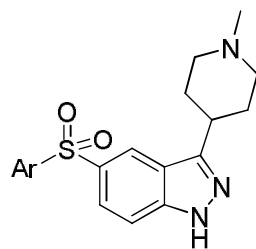


No.	X	Y	CIC2	BEHv2	p <i>K</i> _i	Ref ^a
87	NH	CH ₂	1.40	3.94	7.74	[16]

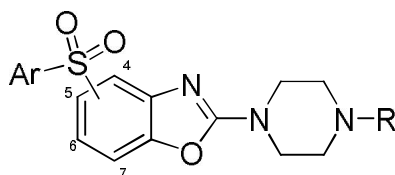


No.	Ar	CIC2	BEHv2	p <i>K</i> _i	Ref ^a
88 [*]	Ph	1.35	3.82	7.26	[17]
89	3-F-Ph	1.34	3.94	7.03	[17]
90	3-Cl-Ph	1.10	3.83	7.72	[17]
91	3-Me-Ph	1.13	3.85	7.30	[17]

Table S2. Cont.

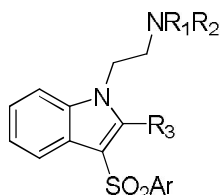


No.	Ar	CIC2	BEHv2	p <i>K</i> _i	Ref ^a
92	4-F-Ph	1.20	3.83	7.18	[17]
93	4-CF ₃ -Ph	1.22	3.84	7.34	[17]
94	4- <i>i</i> Pr-Ph	1.36	3.86	7.85	[17]
95	4-CF ₃ O-Ph	1.20	3.83	7.32	[17]
96*	4-MeO-Ph	1.20	3.83	6.91	[17]
97	1-Naph	1.38	3.96	8.42	[17]
98	2-Naph	1.44	3.96	8.02	[17]

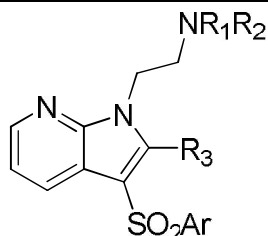


No.	Position	Ar	R	CIC2	BEHv2	p <i>K</i> _i	Ref ^a
99	4	Ph	H	1.63	3.78	7.39	[18]
100*	4	3-F-Ph	H	1.31	3.78	7.27	[18]
101	4	4-F-Ph	H	1.38	3.78	7.19	[18]
102	4	3-Cl-Ph	H	1.31	3.78	7.51	[18]
103	4	4- <i>i</i> Pr-Ph	H	1.48	3.82	7.66	[18]
104*	4	3-CF ₃ -Ph	H	1.33	3.80	7.66	[18]
105	4	4-CF ₃ -Ph	H	1.39	3.80	7.48	[18]
106	4	3-MeO-Ph	H	1.30	3.79	7.60	[18]
107	4	2,5-diCl-Ph	H	1.21	3.79	7.89	[18]
108	4	1-Naph	H	1.66	3.92	8.51	[18]
109	5	1-Naph	H	1.59	3.91	7.28	[18]
110	6	1-Naph	H	1.59	3.91	6.71	[18]
111	7	1-Naph	H	1.66	3.92	8.15	[18]
112*	4	1-Naph	Me	1.66	3.92	8.01	[18]
113	4	1-Naph	Et	1.74	3.92	7.92	[18]
114	4	1-Naph	<i>n</i> -Pr	1.68	3.92	7.44	[18]
115	4	1-Naph	<i>i</i> -Pr	1.71	3.92	7.89	[18]
116	4	1-Naph	<i>n</i> -Bu	1.69	3.92	7.06	[18]
117	4	1-Naph	<i>i</i> -Bu	1.78	3.92	6.75	[18]
118	4	1-Naph	Ph(CH ₂) ₃	1.97	3.92	6.90	[18]
119	4	1-Naph	<i>c</i> -Bu	1.68	3.92	7.14	[18]
120*	4	1-Naph	<i>c</i> -Pen	1.77	3.92	7.10	[18]

Table S2. Cont.

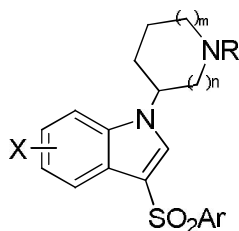


No.	Ar	R ₁	R ₂	R ₃	CIC2	BEHv2	p <i>K_i</i>	Ref ^a
121	Ph	Me	Me	H	1.62	3.80	7.70	[19]
122	Ph	H	H	H	1.46	3.80	7.60	[19]



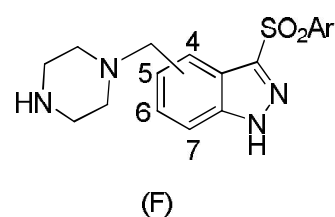
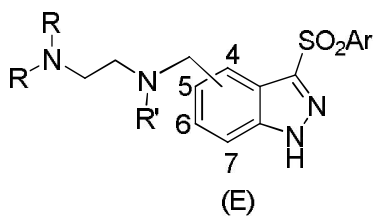
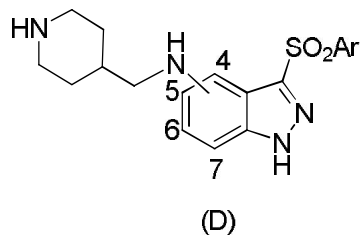
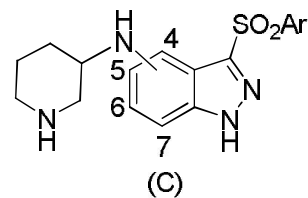
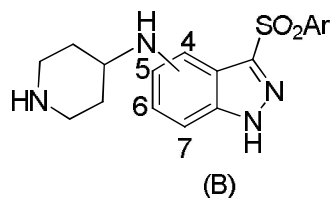
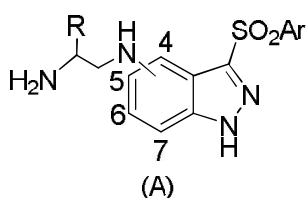
No.	Ar	R ₁	R ₂	R ₃	CIC2	BEHv2	p <i>K_i</i>	Ref ^a
123	Ph	Me	Me	H	1.28	3.79	7.64	[19]
124*	Ph	H	H	H	1.07	3.79	8.26	[19]
125	Ph	H	H	Me	1.11	3.79	8.38	[19]
126	Ph	Me	Me	Me	1.30	3.79	8.33	[19]
127	3-FPh	Me	Me	H	1.02	3.79	8.32	[19]
128	3-FPh	Me	H	H	0.78	3.79	9.00	[19]
129	3-FPh	H	H	H	0.76	3.79	8.33	[19]
130	3-FPh	-(CH ₂) ₄ -	H	H	1.16	3.79	7.06	[19]
131	3-ClPh	Me	Me	H	1.02	3.80	8.64	[19]
132	3-ClPh	Me	H	H	0.78	3.80	9.52	[19]
133	3-ClPh	H	H	H	0.76	3.80	8.70	[19]
134	3-ClPh	-(CH ₂) ₄ -	H	H	1.16	3.80	7.35	[19]
135	4-FPh	Me	Me	H	1.12	3.79	7.35	[19]
136*	4-FPh	H	H	H	0.88	3.79	7.66	[19]
137	2-CF ₃ Ph	H	H	H	0.88	3.82	8.68	[19]
138	3-CF ₃ Ph	H	H	H	0.83	3.81	8.68	[19]
139	3,5-DiClPh	Me	Me	H	1.07	3.80	8.37	[19]
140*	3,5-DiClPh	H	H	H	0.82	3.80	8.54	[19]
141	2,5-DiClPh	Me	Me	H	1.03	3.80	7.93	[19]
142	2,6-DiClPh	Me	Me	H	1.07	3.80	8.05	[19]
143	1-Naphthyl	Me	Me	H	1.43	3.94	9.00	[19]
144*	1-Naphthyl	H	H	H	1.27	3.94	8.80	[19]
145	2-Thienyl	Me	Me	H	0.91	3.77	7.82	[19]
146	5-Cl-thien-2-yl	Me	Me	H	0.91	3.78	8.48	[19]
147	6-Cl-imidazo[2,1- <i>b</i>][1,3]thiazo-5-yl	Me	Me	H	0.75	3.89	9.05	[19]
148*	6-Cl-imidazo[2,1- <i>b</i>][1,3]thiazo-5-yl	Me	H	H	0.48	3.89	9.05	[19]

Table S2. Cont.



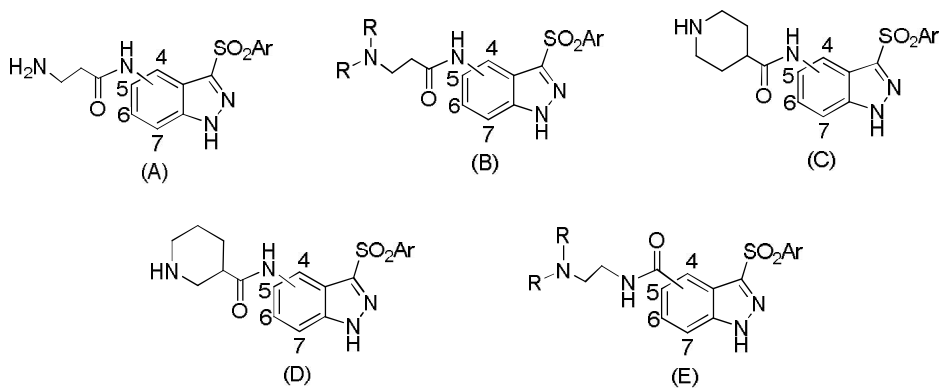
No.	Azacycle	Ar	X	R	CIC2	BEHv2	p <i>K</i> _i	Ref ^a
149	4-Piperidinyl	Ph	H	CH ₂ Ph	1.85	3.81	7.31	[20]
150	4-Piperidinyl	Ph	H	H	1.46	3.81	7.04	[20]
151	3-Piperidinyl	Ph	H	CH ₂ Ph	1.78	3.81	6.91	[20]
152*	3-Piperidinyl	Ph	H	H	1.37	3.81	7.89	[20]
153	3-Piperidinyl	Ph	H	Et	1.45	3.81	8.14	[20]
154	3-Piperidinyl	3-FPh	H	H	1.06	3.81	8.22	[20]
155	3-Piperidinyl	3-FPh	5-OMe	H	0.88	3.81	7.97	[20]
156	3-Piperidinyl	3-FPh	5-OMe	Me	0.93	3.81	7.17	[20]
157	3-Piperidinyl	3-FPh	5-OMe	Et	1.01	3.81	7.80	[20]
158	3-Piperidinyl	3-FPh	5-F	H	0.99	3.81	8.40	[20]
159	3-Piperidinyl	1-Naphthyl	H	H	1.51	3.97	7.68	[20]
160	3-Piperidinyl	1-Naphthyl	H	Me	1.52	3.97	8.15	[20]
161	3-Piperidinyl	8-Quinoliny	H	H	1.17	3.94	8.25	[20]
162	3-Pyrrolidinyl	Ph	H	CH ₂ Ph	1.77	3.81	6.95	[20]
163	3-Pyrrolidinyl	Ph	H	H	1.32	3.81	8.30	[20]
164*	3-Pyrrolidinyl	3-FPh	H	H	0.99	3.81	8.33	[20]
165	3-Pyrrolidinyl	3-FPh	H	Me	1.03	3.81	8.46	[20]
166	3-Pyrrolidinyl	3-FPh	4-F	H	0.92	3.81	7.74	[20]
167	3-Pyrrolidinyl	3-FPh	5-F	H	0.92	3.81	8.02	[20]
168*	3-Pyrrolidinyl	3-FPh	5-F	Me	0.96	3.81	8.30	[20]
169	3-Pyrrolidinyl	3-FPh	6-F	H	0.92	3.81	7.74	[20]
170	3-Pyrrolidinyl	3-FPh	5-Cl	H	0.77	3.81	7.82	[20]
171	3-Pyrrolidinyl	3-FPh	6-Cl	H	0.77	3.81	7.14	[20]
172*	3-Pyrrolidinyl	3-ClPh	H	H	0.99	3.81	8.49	[20]
173	3-Pyrrolidinyl	3-ClPh	H	Me	1.03	3.81	8.89	[20]
174	3-Pyrrolidinyl	3-ClPh	6-OMe	H	0.81	3.82	8.34	[20]
175	3-Pyrrolidinyl	1-Naphthyl	H	H	1.48	3.97	7.63	[20]
176*	3-Pyrrolidinyl	1-Naphthyl	H	Me	1.49	3.97	8.22	[20]
177	3-Pyrrolidinyl	8-Quinoliny	H	H	1.09	3.94	8.82	[20]
178	3-Pyrrolidinyl	8-Quinoliny	H	Me	1.12	3.94	8.55	[20]

Table S2. Cont.

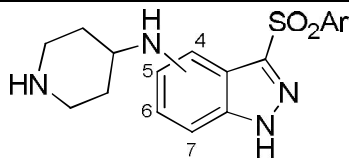


No.	Class	Position	R	R'	Ar	CIC2	BEHv2	p <i>K</i> _i	Ref ^a
179	B	4	-	-	1-Naph	1.33	3.95	8.55	[21]
180*	C	4	-	-	1-Naph	1.25	3.95	8.38	[21]
181	D	4	-	-	1-Naph	1.40	3.95	8.02	[21]
182	A	5	H	-	1-Naph	1.24	3.94	8.17	[21]
183	A	5	Me	-	1-Naph	1.14	3.94	8.85	[21]
184*	A	5	(<i>R</i>)- <i>i</i> Pr	-	1-Naph	1.25	3.94	8.37	[21]
185	B	5	-	-	1-Naph	1.27	3.94	9.15	[21]
186	C	5	-	-	1-Naph	1.19	3.94	8.77	[21]
187	D	5	-	-	1-Naph	1.34	3.94	8.46	[21]
188*	A	6	H	-	1-Naph	1.32	3.94	7.77	[21]
189	B	6	-	-	1-Naph	1.33	3.94	7.28	[21]
190	C	6	-	-	1-Naph	1.25	3.94	7.24	[21]
191	D	6	-	-	1-Naph	1.40	3.94	7.36	[21]
192*	A	7	H	-	1-Naph	1.39	3.94	7.77	[21]
193	B	7	-	-	1-Naph	1.40	3.95	7.52	[21]
194	C	7	-	-	1-Naph	1.32	3.95	7.18	[21]
195	D	7	-	-	1-Naph	1.46	3.95	7.77	[21]
196*	E	5	H	H	1-Naph	1.21	3.95	7.92	[21]
197	E	5	CH ₃	CH ₃	1-Naph	1.61	3.95	7.85	[21]
198	F	5	-	-	1-Naph	1.47	3.95	9.62	[21]

Table S2. Cont.



No	Class	Position	R	Ar	CIC2	BEHv2	p <i>K</i> _i	Ref ^a
199	A	5	-	1-Naph	1.10	3.94	8.82	[21]
200	C	5	-	1-Naph	1.22	3.94	8.96	[21]
201	A	6	-	1-Naph	1.17	3.94	7.62	[21]
202	B	6	CH ₃	1-Naph	1.34	3.94	7.36	[21]
203	B	6	CH ₃ CH ₂	1-Naph	1.47	3.94	7.19	[21]
204	B	6	-(CH ₂) ₅ -	1-Naph	1.44	3.94	7.92	[21]
205	C	6	-	1-Naph	1.28	3.94	7.51	[21]
206	A	7	-	1-Naph	1.24	3.95	8.47	[21]
207	B	7	CH ₃ CH ₂	1-Naph	1.40	3.95	8.32	[21]
208*	B	7	CH ₃ CH ₂	1-Naph	1.52	3.95	7.57	[21]
209	B	7	-(CH ₂) ₅ -	1-Naph	1.50	3.95	7.62	[21]
210	C	7	-	1-Naph	1.34	3.95	7.55	[21]
211	D	7	-	1-Naph	1.27	3.95	8.01	[21]
212	E	5	CH ₃	1-Naph	1.35	3.95	8.54	[21]
213	E	5	-(CH ₂) ₅ -	1-Naph	1.50	3.95	6.97	[21]



No.	Position	Ar	CIC2	BEHv2	p <i>K</i> _i	Ref ^a
214	5	Ph	1.17	3.80	8.51	[21]
215	5	3-F-Ph	0.93	3.80	8.17	[21]
216*	5	3-Cl-Ph	0.93	3.81	9.00	[21]
217	5	3-Me-Ph	0.97	3.83	9.10	[21]
218	5	4-F-Ph	1.01	3.80	8.20	[21]
219	5	4-Cl-Ph	1.01	3.81	8.64	[21]
220*	5	4- <i>i</i> Pr-Ph	1.17	3.84	9.00	[21]
221	5	4-CF ₃ -Ph	1.05	3.83	8.82	[21]
222	5	4-MeO-Ph	1.03	3.81	8.01	[21]
223	5	2-Naph	1.25	3.95	9.22	[21]

*, test set; ^a, from the corresponding reference.