

1 Rational design of promiscuous binding  
2 modulators of p53 inducing E3(Ub)-ligases  
3 (Mdm2 and Pirh2) as anticancer agents: An *in*  
4 *silico* approach<sup>†</sup>

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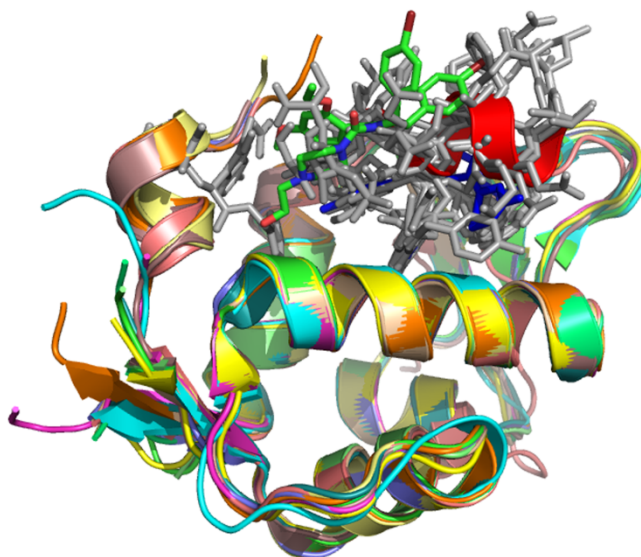
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16 <sup>†</sup>Electronic Supplementary Information (ESI)

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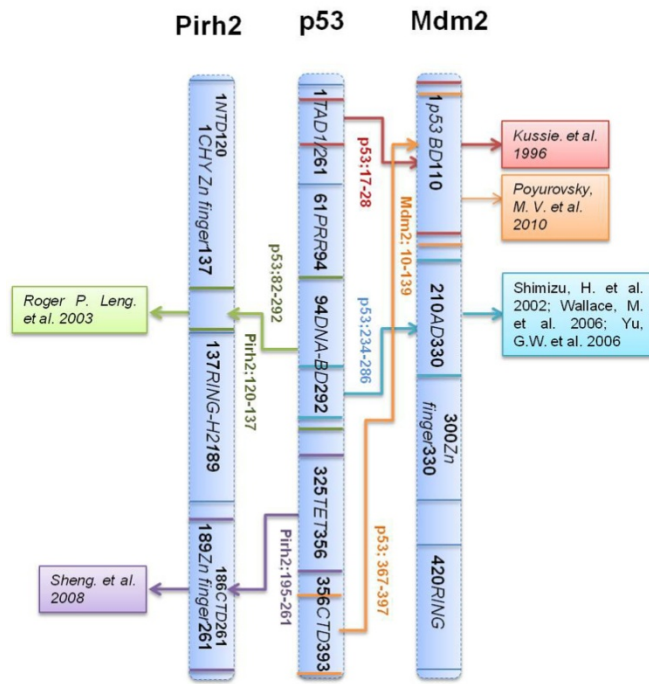
## 1 Supplementary Figures



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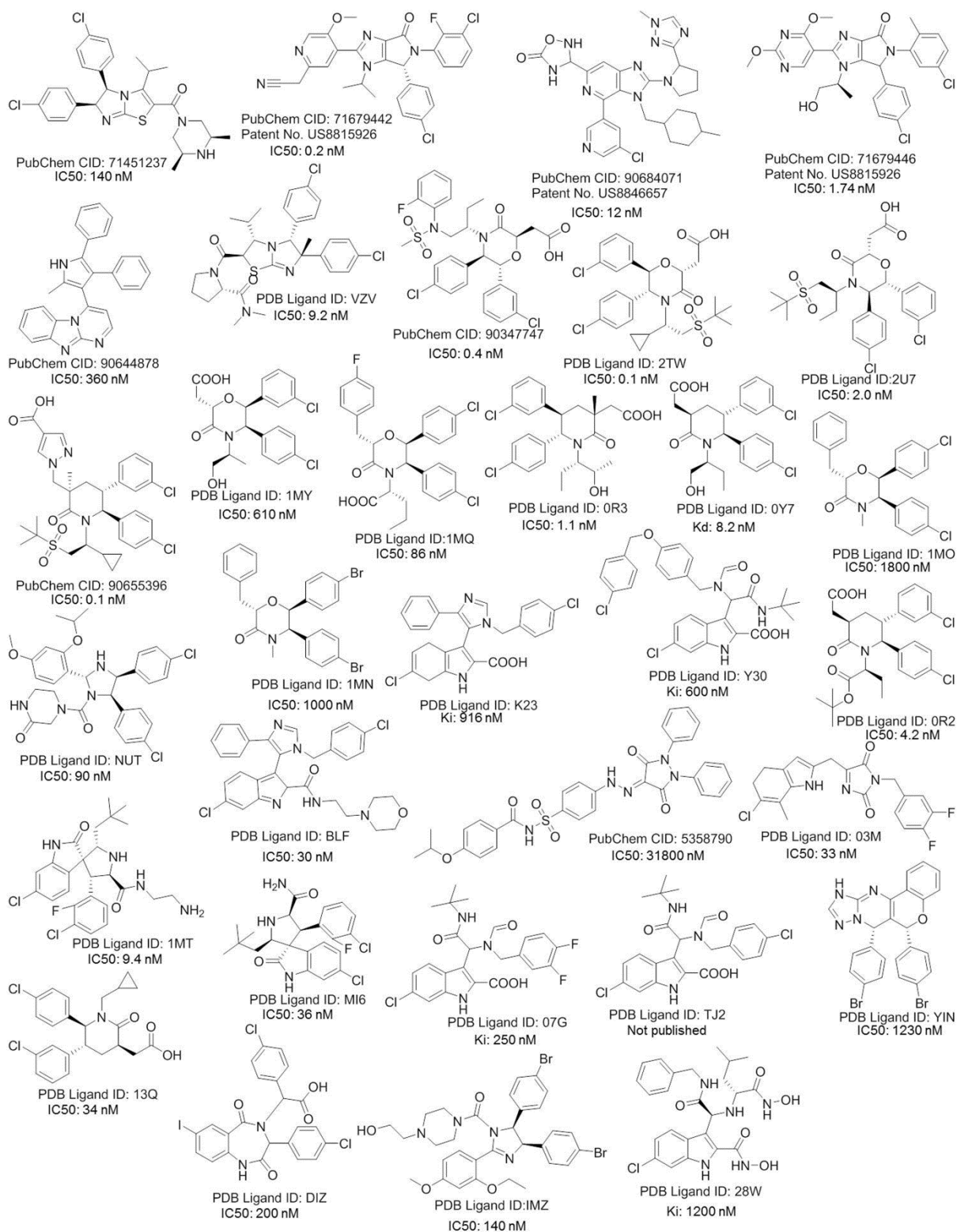
3 **Supplementary Fig. S1.** Molecular overlay of the co-crystal structures of Mdm2 (p53 binding domain) and p53  
4 inhibitors deposited in the RCSB PDB database (PDB IDs: 1RV1, 1T4F, 2GV2, 3EQS, 3JZK, 3JZR, 3JZS, 3LBK,  
5 4HG7, 4JV9, 4JVE). The p53 peptide is shown in red cartoon, Nutlin 3a is shown as blue carbon sticks, MI-291  
6 is shown as green carbon sticks showing similar mode of binding as Nutlins, while all other inhibitors are shown  
7 as grey sticks.

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**Supplementary Fig. S2.** An overview of the regions involved Mdm2, Pirh2 and p53 interaction network.



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2 **Supplementary Fig. S3.** 2D structures of 32 small molecule Mdm2 inhibitors used as reference set for screening  
 3 using 2D fingerprints based approach.

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## 1 Supplementary Tables

### 2 Supplementary Table S1. 3D pharmacophore shape similarity scores, 2D fingerprint similarity scores and GoldScores of the twelve Mdm2 and Pirh2 promiscuous binding ligands

Sl. No.	Mdm2 and Pirh2 promiscuous binding ligands MMsINC code	3D pharmacophore based similarity scores with respect to Mdm2 binding p53 TAD residues	2D similarity scores with respect to reference Mdm2 ligands	GoldScore_Fitness	3D pharmacophore based similarity scores with respect to Pirh2 binding p53 TET or2 residues	2D similarity scores with respect to reference Mdm2 ligands	GoldScore_Fitness
1	MMs01995558	0.87 <sup>£</sup>	0.31 <sup>α</sup>	68.21	-	-	77.94
2	MMs03095003	0.83 <sup>£</sup>	0.40 <sup>β</sup>	63.95	-	-	63.94
3	MMs02480859	0.84 <sup>£</sup>	0.35 <sup>β</sup>	62.06	-	-	53.10
4	MMs01995562	0.85 <sup>£</sup>	0.33 <sup>β</sup>	59.91	-	-	69.14
5	MMs03738126	0.83 <sup>£</sup>	0.35 <sup>δ</sup>	59.64	-	-	75.84
6	MMs01437581	0.81 <sup>#</sup>	0.33 <sup>γ</sup>	67.16	-	-	75.08
7	MMs03598193	0.83 <sup>£</sup>	0.34 <sup>γ</sup>	57.92	-	-	70.85
8	MMs00889221	0.48 <sup>§</sup>	0.35 <sup>δ</sup>	56.01	-	-	73.84
9	MMs02943764	-	-	63.62	0.76 <sup>#</sup>	0.31 <sup>δ</sup>	68.38
10	MMs01100743	-	-	61.63	0.76 <sup>#</sup>	0.30 <sup>δ</sup>	70.55
11	MMs02948293	-	-	57.30	0.82 <sup>£</sup>	0.31 <sup>δ</sup>	66.58
12	MMs02995593	-	-	58.08	0.83 <sup>£</sup>	0.31 <sup>δ</sup>	72.51

3 <sup>#</sup>Fingerprint-based filtering of shape similarity score <sup>£</sup>Based only on shape similarity score <sup>§</sup>Shape based filtering of pharmacophoric similarity score <sup>α</sup>Tanimoto score <sup>β</sup>Dice score <sup>γ</sup>Cosine score

4 <sup>δ</sup>Target score

1 **Supplementary Table S2.** Compounds with experimental IC<sub>50</sub> values available in the literature for Mdm2 pBD  
 2 binding and their GoldScore\_Fitness

Serial No.	PubChem Compound ID	IC <sub>50</sub> (nM)	GoldScore_Fitness	Log IC <sub>50</sub>
<b>Actives</b>				
1	90655385	0.1	65.3065	-1
2	90655387	0.1	64.2162	-1
3	90655399	0.1	64.1835	-1
4	73386675	0.1	64.0023	-1
5	90655406	0.1	63.744	-1
6	73386677	0.1	63.2019	-1
7	90655404	0.1	62.7767	-1
8	86766856	0.07	62.344	-1.15490196
9	90655393	0.1	62.1738	-1
10	76329003	0.1	62.0535	-1
11	73386678	0.1	61.3939	-1
12	90655401	0.1	60.9333	-1
13	90655381	0.1	60.4699	-1
14	90655396	0.1	60.2144	-1
15	86767015	0.13	59.9125	-0.88605665
16	90655398	0.1	59.5414	-1
17	71678437	0.135	59.0366	-0.86966623
18	86766984	0.09	58.9185	-1.04575749
19	86767047	0.152	58.2602	-0.81815641
20	71678433	0.12	58.2427	-0.92081875
21	67999919	0.1	58.0257	-1
22	86766900	0.14	57.9297	-0.85387196
23	89715239	0.14	57.8459	-0.85387196
24	71679764	0.1	57.6349	-1
25	68001087	0.1	56.9562	-1
26	71680278	0.15	56.7504	-0.82390874
27	71679934	0.13	56.6751	-0.88605665
28	86766976	0.11	56.5817	-0.95860731
29	71680281	0.08	56.3639	-1.09691001
30	68000692	0.1	56.2395	-1
31	71678097	0.16	56.1983	-0.79588002
32	86707772	0.09	55.9575	-1.04575749
33	86766862	0.15	55.936	-0.82390874
34	90655372	0.1	55.7956	-1

35	86766854	0.14	55.7165	-0.85387196
36	86766885	0.16	55.6369	-0.79588002
37	86767041	0.081	55.546	-1.09151498
38	71678434	0.16	55.4751	-0.79588002
39	71680109	0.15	55.4713	-0.82390874
40	71679763	0.08	55.4011	-1.09691001
41	71678772	0.13	55.3134	-0.88605665
42	90655394	0.1	55.2536	-1
43	86766998	0.08	55.0057	-1.09691001
44	86766882	0.16	54.9976	-0.79588002
45	86767021	0.15	54.9688	-0.82390874
46	86766878	0.11	54.533	-0.95860731
47	71678602	0.16	54.4482	-0.79588002
48	58573858	0.1	54.3965	-1
49	71678265	0.107	54.2917	-0.97061622
50	86767012	0.15	54.1925	-0.82390874
51	86766932	0.09	54.1126	-1.04575749
52	71678606	0.059	54.0505	-1.22914799
53	86766875	0.17	53.8746	-0.76955108
54	86766961	0.11	53.8526	-0.95860731
55	76332677	0.1	53.7453	-1
56	86766990	0.05	53.6231	-1.30103
57	68000593	0.1	53.6084	-1
58	86766873	0.13	53.4666	-0.88605665
59	71655944	0.04	53.4633	-1.39794001
60	71678258	0.089	53.4077	-1.05060999
61	73,386,676	0.1	53.397	-1
62	71680112	0.11	53.3635	-0.95860731
63	86767011	0.12	52.6863	-0.92081875
64	86766962	0.16	52.6291	-0.79588002
65	76328992	0.1	52.544	-1
66	71678432	0.17	52.394	-0.76955108
67	90655407	0.1	51.9748	-1
68	90655377	0.1	51.9373	-1
69	86766863	0.13	51.8388	-0.88605665
70	89715231	0.1	51.5259	-1
71	86767013	0.08	51.0025	-1.09691001
72	86766877	0.15	50.7103	-0.82390874
73	71678103	0.124	50.6071	-0.90657831
74	86707771	0.07	50.4432	-1.15490196
75	71678945	0.07	50.3151	-1.15490196

76	71678259	0.1015	50.2866	-0.99353396
77	86766964	0.11	50.1134	-0.95860731
78	71679762	0.11	49.9591	-0.95860731
79	86766851	0.17	49.0998	-0.76955108
80	90655392	0.1	48.9465	-1
81	86767046	0.117	48.7183	-0.93181414
82	76321813	0.1	48.7023	-1
83	71679280	0.11	48.4153	-0.95860731
84	90655374	0.1	47.9445	-1
85	59249286	74	45.6998	1.86923172
86	56591348	76	43.0392	1.88081359
87	11433190	100	48.5231	2
88	53318520	230	53.8106	2.36172784
89	90684107	250	51.5344	2.39794001
90	58433781	510	40.4301	2.70757018
91	90644884	550	46.6135	2.74036269
92	9917797	700	48.1945	2.84509804
93	90644880	810	45.606	2.90848502
94	51350512	900	51.2305	2.95424251
95	77461139	1,000	34.2813	3
<b>Inactives</b>				
96	51350513	1,400	50.6571	3.14612804
97	71305070	2,000	47.397	3.30103
98	51350784	2,300	50.3016	3.36172784
99	90654511	4,000	36.5992	3.60205999
100	71663864	5,000	46.1967	3.69897
101	51349701	6,000	41.6084	3.77815125
102	71717127	8,100	44.1269	3.90848502
103	44176193	10,200	55.5125	4.00860017
104	44472961	13,000	66.0306	4.11394335
105	71717128	14,100	40.8173	4.14921911
106	73355683	15,000	37.8133	4.17609126
107	51351127	17,000	57.4678	4.23044892



108	44472953	18,000	65.625	4.25527251
109	44176179	19,000	48.3084	4.2787536
110	44472958	24,000	68.5635	4.38021124
111	44176178	25,000	49.3913	4.39794001
112	44176189	27,000	54.5592	4.43136376
113	51351130	29,000	51.0196	4.462398
114	44390659	30,000	47.5585	4.47712125
115	44472959	41,000	66.9988	4.61278386
116	44472951	63,000	69.4564	4.79934055
117	44472949	>100,000 <sup>δ</sup>	69.4647	5.00004343
118	44472979	>100,000 <sup>δ</sup>	68.7535	5.00004343
119	16090445	243,000	66.7637	5.38560627
120	16090445	243,000	65.4939	5.38560627
121	17783233	>250,000 <sup>δ</sup>	62.5627	5.39795738
122	16090454	70,100	61.7862	4.84571802
123	16090403	88,000	61.7342	4.94448267
124	16090444	96,000	61.2575	4.98227123
125	44176164	311,000	60.6453	5.49276039
126	16090450	275,000	60.558	5.43933269
127	16090455	69,700	60.0687	4.84323278
128	52943865	209,000	59.8484	5.32014629
129	44176162	85,000	58.0368	4.92941893
130	16090434	92,000	57.4713	4.96378783
131	16090444	96,000	56.061	4.98227123
132	51351128	>100,000 <sup>δ</sup>	55.7345	5.00004343
133	16090397	191,000	55.7304	5.28103337
134	16090456	64,300	55.585	4.80821097
135	44176170	>250,000 <sup>δ</sup>	55.3392	5.39795738
136	44176163	70,000	55.3067	4.84509804
137	16090408	290,000	54.6841	5.462398

138	44176168	103,000	54.4984	5.01283722
139	16090443	214,000	54.4335	5.33041377
140	44176165	326,000	54.3508	5.5132176
141	44176167	103,000	53.9604	5.01283722
142	16090396	116,000	53.6411	5.06445799
143	44176170	>250,000 <sup>δ</sup>	53.6018	5.39795738
144	44176166	181,000	53.3422	5.25767857
145	16090443	214,000	53.0858	5.33041377
146	16090388	439,000	52.6788	5.64246452
147	51351004	175,000	52.4232	5.24303805
148	16090436	66,000	52.1586	4.81954394
149	16090438	78,000	51.5976	4.8920946
150	16090409	70,200	49.5501	4.84633711
151	44176169	>250,000 <sup>δ</sup>	49.9471	5.39795738
152	16090456	64,300	49.9328	4.80821097
153	16090384	90,000	49.9269	4.95424251
154	16090404	380,000	49.9122	5.5797836
155	16090410	74,300	49.9054	4.87098881
156	16090394	221,000	49.8066	5.34439227
157	51351129	252,000	49.8272	5.40140054
158	51351258	>200,000 <sup>δ</sup>	49.8281	5.30105171
159	16090441	315,000	49.7317	5.49831055
160	12871998	>250,000 <sup>δ</sup>	49.7338	5.39795738
161	16090440	281,000	49.6737	5.44870632
162	7067864	117,000	49.3603	5.06818586
163	16090453	70,000	49.3498	4.84509804
164	16090437	393,000	49.327	5.59439255
165	14126638	250,000	49.1409	5.39794001
166	16090387	284,000	49.0969	5.45331834
167	16090441	315,000	49.0173	5.49831055

168	25147779	58,600	48.7449	4.76789762
169	23690457	345,000	48.4412	5.5378191
170	51351257	>200,000 <sup>δ</sup>	48.2225	5.30105171
171	16090449	413,000	48.2133	5.61595005
172	51349974	>100,000 <sup>δ</sup>	48.1146	5.00004343
173	5988917	206,000	47.6004	5.31386722
174	44588491	101,300	47.5711	5.00560945
175	51349972	>100,000 <sup>δ</sup>	47.2705	5.00004343
176	44588491	101,300	47.2031	5.00560945
177	16090439	79,000	47.0528	4.89762709
178	179269	>295,000 <sup>δ</sup>	46.8344	5.46983674
179	51349973	>100,000 <sup>δ</sup>	46.3891	5.00004343
180	16090401	490,000	46.2622	5.69019608
181	51349975	>100,000 <sup>δ</sup>	46.0543	5.00004343
182	51350252	>200,000 <sup>δ</sup>	45.5151	5.30105171
183	16090448	>500,000 <sup>δ</sup>	45.2447	5.69897869
184	16090442	206,000	45.2354	5.31386722
185	16090395	97,000	45.1074	4.98677173
186	16090446	232,000	44.7713	5.36548798
187	3608080	74,000	44.538	4.86923172
188	51351003	214,000	44.2716	5.33041377
189	51350118	>200,000 <sup>δ</sup>	44.175	5.30105171
190	51350115	88,000	44.1372	4.94448267
191	51349702	87,000	44.0129	4.93951925
192	51350119	>200,000 <sup>δ</sup>	44.0065	5.30105171
193	44588490	120,800	43.9058	5.08206693
194	51349835	54,000	43.8841	4.73239376
195	16090393	58,000	43.6429	4.76342799
196	51350114	>100,000 <sup>δ</sup>	43.1686	5.00004343
197	51350120	>200,000 <sup>δ</sup>	43.1391	5.30105171

198	51350253	>200,000 <sup>δ</sup>	42.2392	5.30105171
199	51349702	87,000	42.195	4.93951925
200	51349839	96,000	42.0731	4.98227123
201	1114145	>75,000 <sup>δ</sup>	41.9181	4.87511917
202	72697858	>100,000 <sup>δ</sup>	41.3138	5.00004343
203	72697857	>100,000 <sup>δ</sup>	41.1872	5.00004343
204	44421760	>100,000 <sup>δ</sup>	40.7492	5.00004343
205	72697859	>100,000 <sup>δ</sup>	40.7269	5.00004343
206	51349840	>100,000 <sup>δ</sup>	40.7128	5.00004343
207	259166	>250,000 <sup>δ</sup>	40.6425	5.39795738
208	71818716	>100,000 <sup>δ</sup>	40.0732	5.00004343
209	51349561	69,000	39.9586	4.83884909
210	44588489	58,600	39.5688	4.76789762
211	16090405	>500,000 <sup>δ</sup>	39.4625	5.69897869
212	72697716	>100,000 <sup>δ</sup>	39.0453	5.00004343
213	72697714	>100,000 <sup>δ</sup>	38.8709	5.00004343

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2 <sup>δ</sup>In these cases, a penalty of 10 was added to the IC<sub>50</sub> values in order to obtain a quantitative measure and con-  
3 verted into LogIC<sub>50</sub> values.

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