Supporting materials

Discovery of Novel Antifungal Resorcylate Aminopyrazole Hsp90 Inhibitors Based on Structural Optimization by Molecular Simulation

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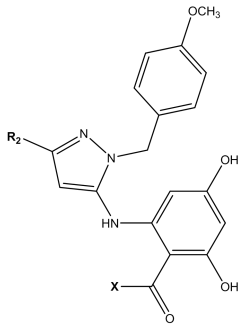
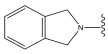
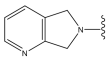
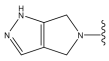
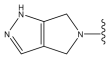
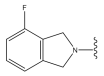
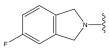
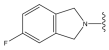
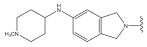
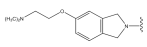
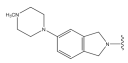
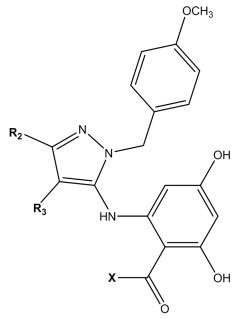
Table S1 Experimental and predicted activity values of compounds

No.	Structure				pEC_{50}	CoMFA		CoMSIA	
	X	R_1	R_2	R_3	Obs.	Pred.	Err%.	Pred.	Err%.



1		Ph	6.292	6.516	3.560	6.510	3.465
2		CH_3	6.735	6.537	2.940	6.651	1.247
3		CH_3	6.804	7.009	3.013	6.962	2.322
4		Ph	7.201	6.856	4.791	6.842	4.985
5*		CH_3	6.932	6.694	3.433	7.185	3.650
6		CH_3	7.268	7.141	1.747	7.094	2.394
7		Ph	5.982	6.389	6.804	6.374	6.553
8		Ph	7.638	7.695	0.746	7.928	3.797
9		Ph	7.854	7.864	0.127	7.835	0.242
10		CH_3	6.845	6.890	0.657	6.858	0.190
11		Ph	6.550	6.551	0.015	6.450	1.527



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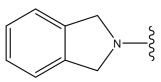

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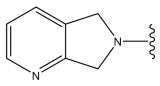

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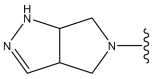
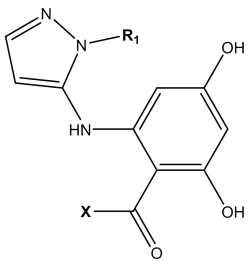


C

12	A	H	H	7.387	7.144	3.290	7.092	3.994
13*	A	H	CH_3	7.658	7.447	2.755	6.900	9.898
14	A	H	^{i}Pr	6.833	6.817	0.234	6.797	0.527
15*	A	H	Bn	6.333	7.233	14.211	6.916	9.206
16*	B	Et	H	7.854	8.020	2.114	8.115	3.323
17	C	Et	H	7.921	7.971	0.631	8.031	1.389
18	B	^{i}Pr	H	7.886	7.877	0.114	7.778	1.370
19*	C	^{i}Pr	H	8.046	8.077	0.385	8.063	0.211
20	B		H	7.854	8.042	2.394	8.186	4.227
21	C		H	7.854	8.002	1.884	8.134	3.565
22	B		H	8.222	8.027	2.372	7.758	5.643



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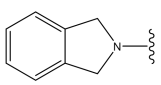

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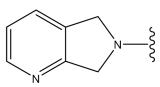

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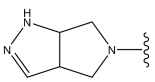

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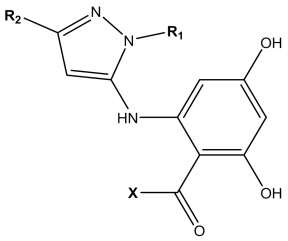
23	A	CH_3	6.955	6.768	2.689	6.913	0.604
24	B	CH_3	6.205	6.460	4.110	6.554	5.624
25	C	CH_3	6.424	6.468	0.685	6.536	1.743
26	A	^{i}Pr	7.119	7.079	0.562	7.120	0.014
27	A	^{i}Bu	7.456	7.426	0.402	7.513	0.764
28	B	^{i}Bu	6.932	7.129	2.842	7.182	3.606
29	A		8.046	7.831	2.672	7.895	1.877
30	B		7.824	7.936	1.431	8.053	2.927
31	C		8.097	8.093	0.049	8.086	0.136
32	A	Ph	7.854	7.934	1.019	7.629	2.865
33	B	Ph	7.678	7.627	0.664	7.498	2.344
34	C	Ph	7.824	7.740	0.818	7.532	3.732
35	A	Cy	7.886	7.876	0.127	7.610	3.500
36*	B	Cy	7.796	7.876	1.026	7.673	1.578
37*	C	Cy	7.854	8.173	4.062	7.878	0.306
38	A	Bn	7.824	7.654	2.173	7.692	1.687
39	B	Bn	7.745	7.761	0.207	7.850	1.356
40	A		7.387	7.428	0.555	7.606	2.965
41	B		6.845	6.809	0.526	6.822	0.336

42	A			7.481	7.522	0.548	7.532	0.655
43	B			7.097	7.133	0.507	6.941	2.198
44*	C			7.387	7.780	5.320	7.721	4.521
45	B			7.921	8.008	1.098	7.716	2.588
46*	C			7.921	7.957	0.454	7.707	2.702
47	B			7.602	7.599	0.039	7.456	1.921
48	C			7.678	7.826	1.928	7.772	1.224



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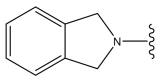

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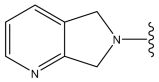

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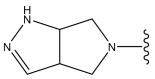
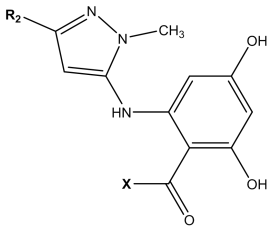


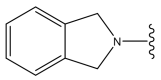
C

49	A		CH_3	6.917	6.910	0.101	6.754	2.357
50	A		CH_3	6.936	6.943	0.101	7.221	4.109
51	A		CH_3	6.873	6.839	0.495	7.017	2.095
52	A	CH_3	Ph	6.484	6.260	3.455	6.500	0.247
53	B	CH_3	Ph	6.403	6.303	1.562	6.415	0.203

54*	C	CH_3	Ph	6.672	6.502	2.548	6.695	0.345
55*	B	^{t}Bu	Ph	6.421	6.650	3.566	6.560	2.165
56	C	^{t}Bu	Ph	6.740	6.687	0.786	6.931	2.834
57*	C		Ph	7.469	7.354	1.540	7.281	2.517
58	C	^{i}Bu	Ph	7.155	7.019	1.901	6.910	3.424



Amide substitution("X"):



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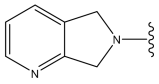

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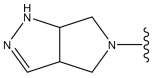

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59*	B		^{i}Pr	6.807	6.846	0.573	6.579	3.349
60	C		^{i}Pr	7.027	7.014	0.185	7.049	0.313
61*	C		Cy	7.018	7.087	0.983	7.091	1.040
62*	A			6.223	6.337	1.832	6.378	2.491
63	B			6.100	6.043	0.934	6.046	0.885
64	C			6.400	6.498	1.531	6.357	0.672
65	A			6.242	6.214	0.449	6.367	2.003
66	B			5.987	5.925	1.036	6.035	0.802
67	C			6.402	6.298	1.624	6.151	3.921

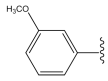
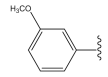
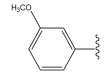
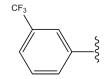
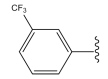
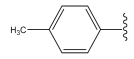
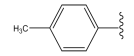
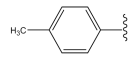
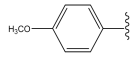
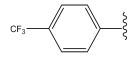
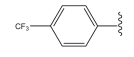
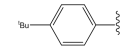
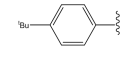
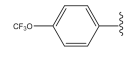
68	A		5.785	5.591	3.354	5.442	5.929
69	B		5.301	5.612	5.867	5.594	5.527
70	C		5.726	5.796	1.222	5.869	2.497
71	B		6.226	6.195	0.498	6.259	0.530
72	C		6.532	6.649	1.791	6.571	0.597
73	A		5.972	5.995	0.385	6.223	4.203
74*	B		5.750	5.710	0.696	5.892	2.470
75	C		6.197	6.244	0.758	6.395	3.195
76	B		5.943	5.927	0.269	5.833	1.851
77	B		6.496	6.615	1.832	6.536	0.616
78	C		6.987	6.842	2.075	6.820	2.390
79	B		6.625	6.525	1.509	6.428	2.974
80*	C		7.149	6.733	5.511	6.735	5.791
81*	A		6.873	6.373	7.275	6.525	5.063

Table S2 Free energy decomposition for key residues of Hsp90

Residue	Van de Waals	Electrostatic	Polar Solvation	Non-Polar Solvation	Total
Compound 22 / Hsp90 system					
Asn40	-3.9560	-0.1595	-0.6469	-2.4176	-7.1799
Asp82	1.4692	-9.4740	2.4240	-0.4720	-6.0528
Thr174	-1.2878	-3.9953	1.4200	-1.0946	-4.9578
Met87	-1.9696	-1.2399	0.3208	-1.4408	-4.3295
Leu37	-1.4122	-2.3770	1.1146	-1.1474	-3.8219
Asn95	-1.9529	0.7833	-1.0485	-1.4774	-3.6956
ALA44	-1.9280	0.0169	-0.5313	-1.2228	-3.6651
Phe127	-1.4753	-0.1606	0.1572	-1.1036	-2.5824
Compound M7 / Hsp90 system					
Asn40	-3.8908	-0.6977	-1.4185	-2.4626	-8.4696
Asp82	1.2224	-9.4003	3.0566	-0.4364	-5.5576
Asn95	-2.8965	0.3715	-0.9114	-1.9558	-5.3922
Leu37	-2.1847	-2.2116	0.5889	-1.4828	-5.2901
Met87	-2.1537	-0.5374	0.0833	-1.3804	-3.9882
Thr174	-1.2714	-2.2123	1.1989	-0.9126	-3.1974
ALA44	-1.5719	0.1412	-0.5469	-1.2075	-3.1850
Phe127	-1.7174	-0.4970	0.3757	-0.9723	-2.8109
Compound M9 / Hsp90 system					

Asn40	-3.6768	-0.7024	-1.2136	-2.2457	-7.8386
Asp82	1.5722	-11.8732	4.0488	-0.4450	-6.6973
Asn95	-2.9049	-0.0104	-0.8979	-2.0077	-5.8209
Met87	-2.4175	-0.6757	0.0919	-1.4747	-4.4760
Leu37	-2.1709	-1.4959	0.6314	-1.3486	-4.3839
Phe127	-2.2039	-0.6987	0.4821	-1.3260	-3.7465
Thr174	-1.2658	-2.4604	1.2470	-0.9764	-3.4556
ALA44	-1.5837	0.1504	-0.6350	-1.1832	-3.2516

Table S3 SMILES format for the designed molecules

No.	SMILES format
M1	CC(C)CC1=CC=C(CN2C(NC3=CC(O)=CC(O)=C3C(N4CC5=NC=CC=C5C4)=O)=CC=N2)C=C1
M2	CC(C)CC1=CC=C(CN2C(NC3=CC(O)=CC(O)=C3C(N4CC(C=NNC5)=C5C4)=O)=CC=N2)C=C1
M3	CC(C)CC1=CC=C(CN2C(NC3=CC(O)=CC(O)=C3C(N4CC5=C(C4)NN=C5)=O)=CC=N2)C=C1
M4	COC1=CC=C(CN2C(NC3=CC(O)=CC(O)=C3C(N4CC5=C(C=C(C=N5)O)C4)=O)=CC(C6CCCC6)=N2)C=C1
M5	COC1=CC=C(CN2C(NC3=CC(O)=CC(O)=C3C(N4CC5=C(C=C(C=N5)C(O)=O)C4)=O)=CC(C6CCCC6)=N2)C=C1
M6	COC1=CC=C(CN2C(NC3=CC(O)=CC(O)=C3C(N4CC5=C(C=C(C=N5)OC)C4)=O)=CC(C6CCCC6)=N2)C=C1
M7	COC1=CC=C(CN2C(NC3=CC(O)=CC(O)=C3C(N4C[C@@H]5[C@@H](C4)NN=C5O)=O)=CC(C6CCCC6)=N2)C=C1
M8	COC1=CC=C(CN2C(NC3=CC(O)=CC(O)=C3C(N4C[C@@H]5[C@@H](C4)NN=C5C(O)=O)=O)=O)=CC(C6CCCC6) =N2)C=C1

M9	COC1=CC=C(CN2C(NC3=CC(O)=CC(O)=C3C(N4C[C@@H]5[C@@H](C4)NN=C5OC)=O)=CC(C6CCCC6)=N2)C=C1
M10	COC1=CC(C2CCCC2)=C(CN3C(NC4=CC(O)=CC(O)=C4C(N5CC6=C(C5)C=NN6)=O)=CC=N3)C=C1