Electronic Supplementary Material (ESI) for RSC Advances.

Supplementary Information

Identifying MurI Uncompetitive Inhibitors by Correlating Decomposed Binding Energies with Bioactivities

Xiu Le, Qiong Gu* and Jun Xu*

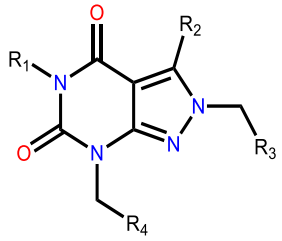
Research Center for Drug Discovery, School of Pharmaceutical Sciences, Sun Yat-Sen University, Guangzhou 510006, P.R.China

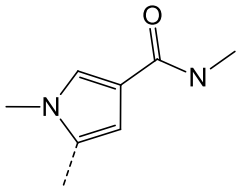
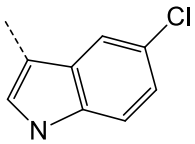
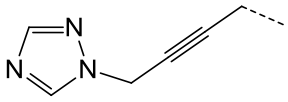
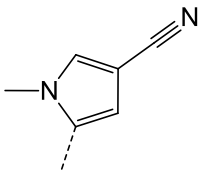
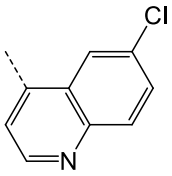
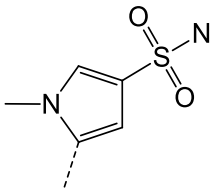
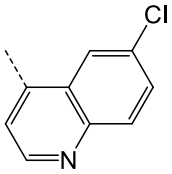
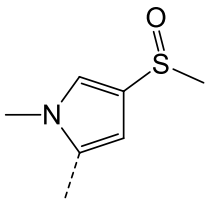
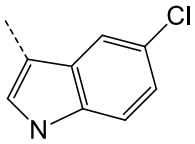
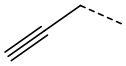
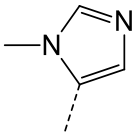
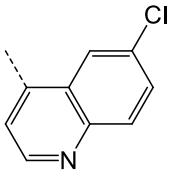
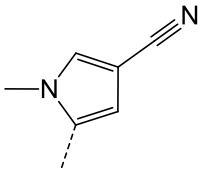
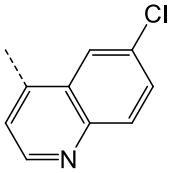
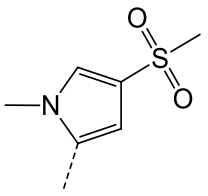
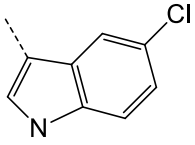
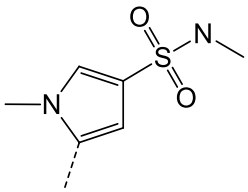
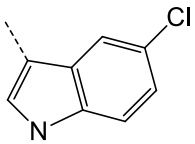
*To whom correspondence should be addressed.

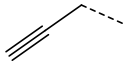
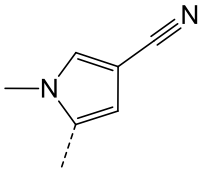
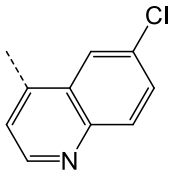
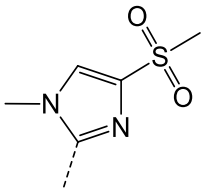
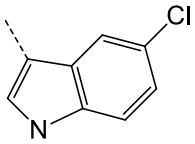
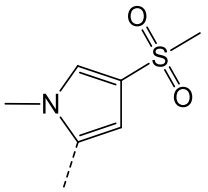
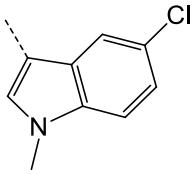
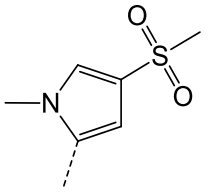
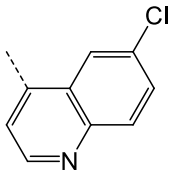
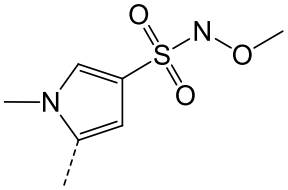
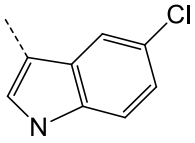
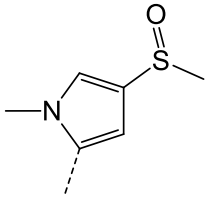
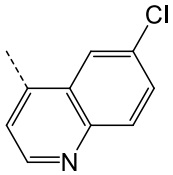
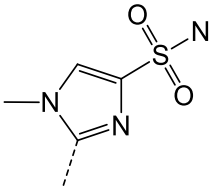
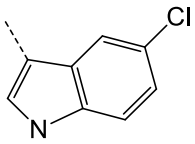
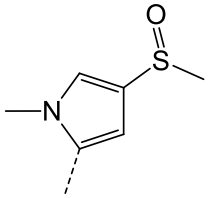
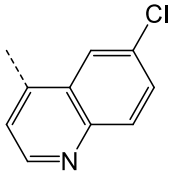
(QG) E-mail: guqiong@mail.sysu.edu.cn

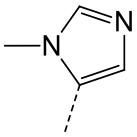
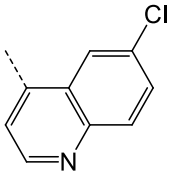
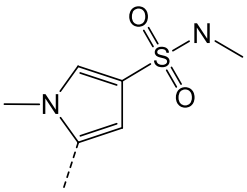
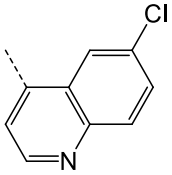
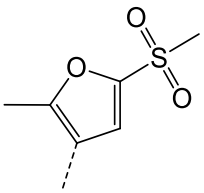
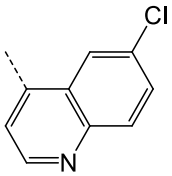
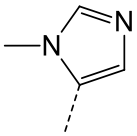
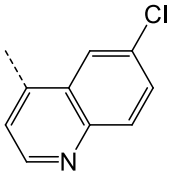
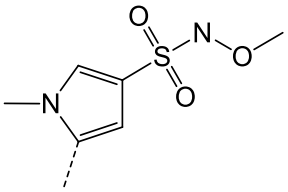
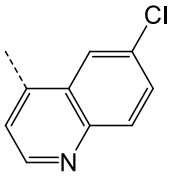
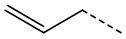
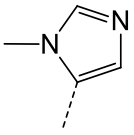
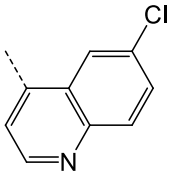
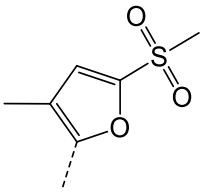
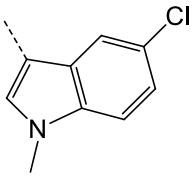
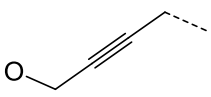
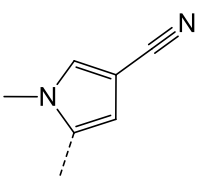
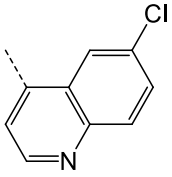
(JX) E-mail: junxu@biochemomes.com

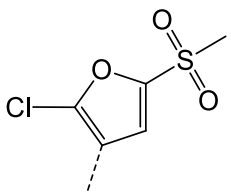
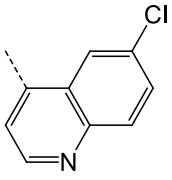
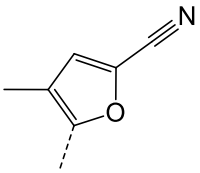
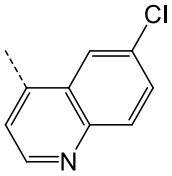
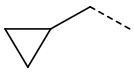
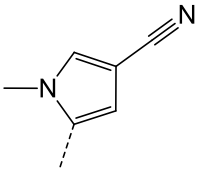
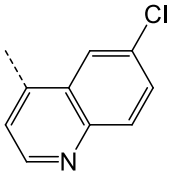
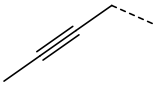
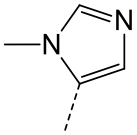
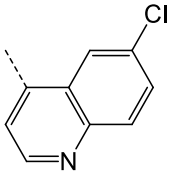
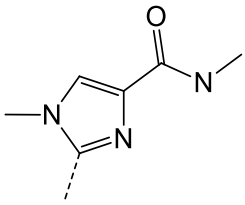
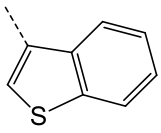
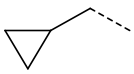
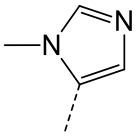
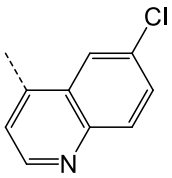
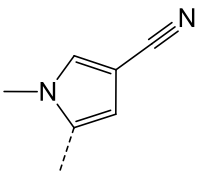
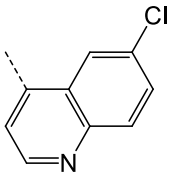
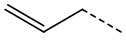
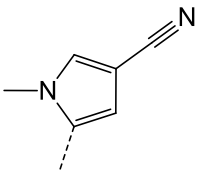
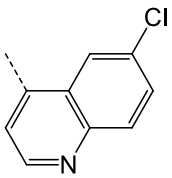
Table S1. Chemical structures and pIC_{50} values of the 69 compounds used in development of the 3D-QSAR models.

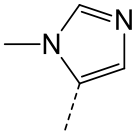
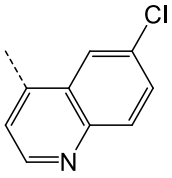
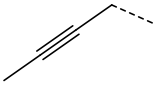
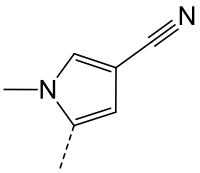
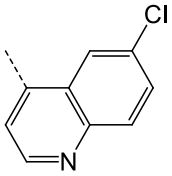
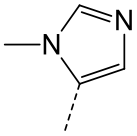
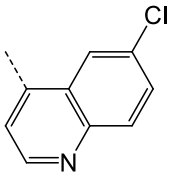
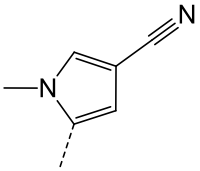
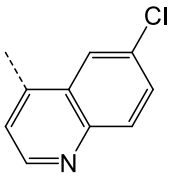
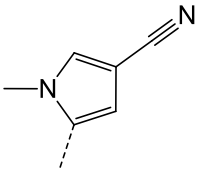
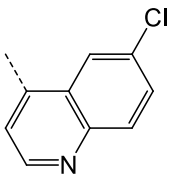
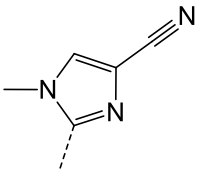
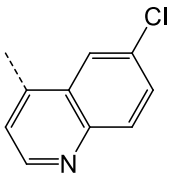
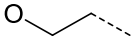
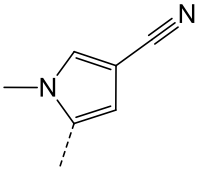
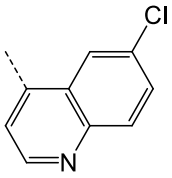


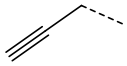
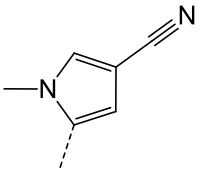
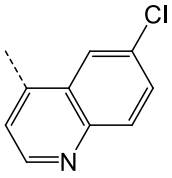
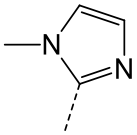
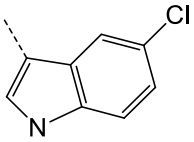
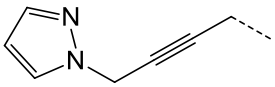
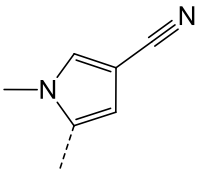
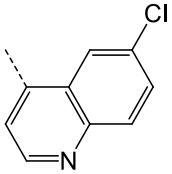
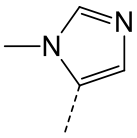
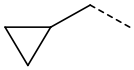
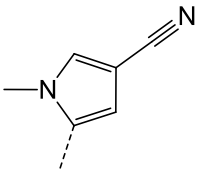
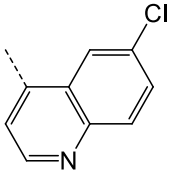
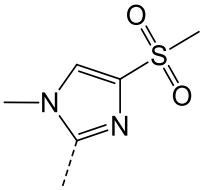
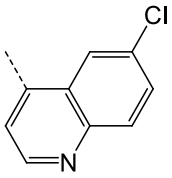
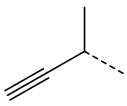
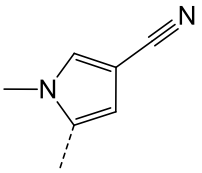
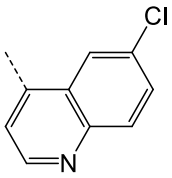
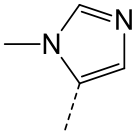
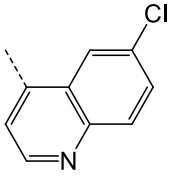
ID	IC_{50} (nM)	R1	R2	R3	R4
1	6	Me			*i*-Pro
2	13				*c*-Pro
3	16	Me			*c*-Pro
4[a]	23	Me			*c*-Pro
5	24				*c*-Pro
6	25	Me			*c*-Pro
7[a]	26	Me			*c*-Pro
8[b]	27	Me			*c*-Pro

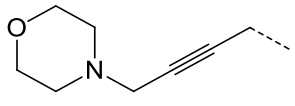
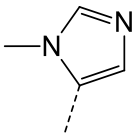
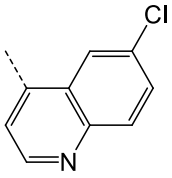
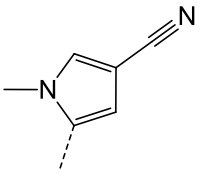
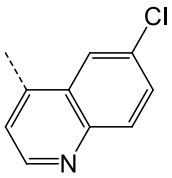
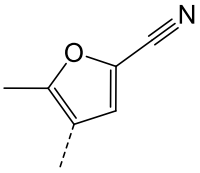
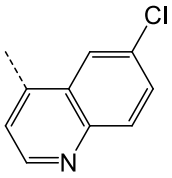
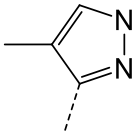
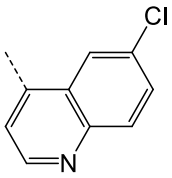
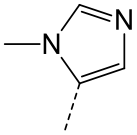
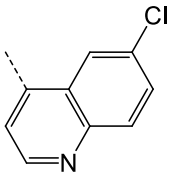
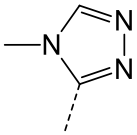
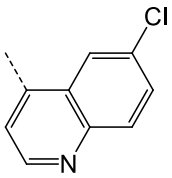
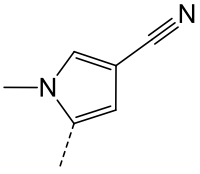
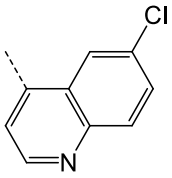
9	28				*c*-Pro
10	31	Me			*c*-Pro
11	33	Me			*c*-Pro
12	34	Me			*c*-Pro
13[a]	36	Me			*c*-Pro
14	37	Me			*c*-Pro
15[a]	38	Me			*c*-Pro
16	39	Me			*c*-Pro

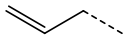
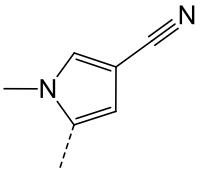
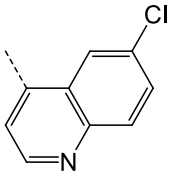
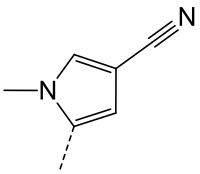
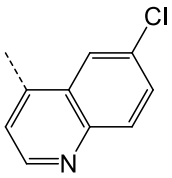
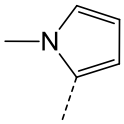
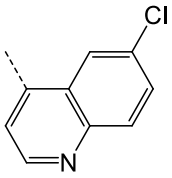
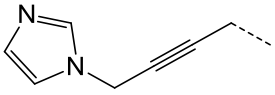
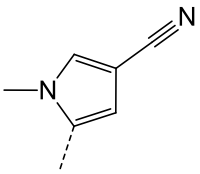
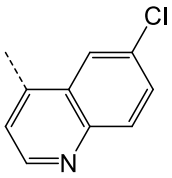
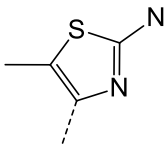
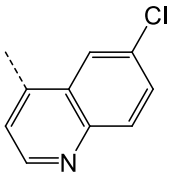
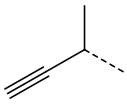
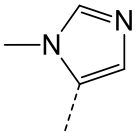
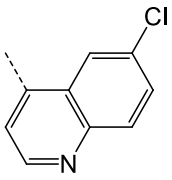
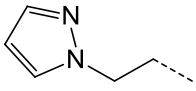
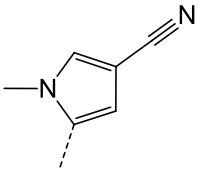
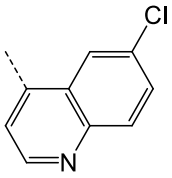
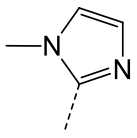
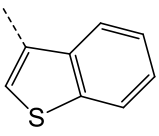
17[b]	41	Me			*c*-Pro
18[a]	44	Me			*c*-Pro
19	51	Me			*c*-Pro
20	54				*c*-Pro
21	55	Me			*c*-Pro
22[a]	56				*c*-Pro
23[a]	57	Me			*c*-Pro
24	57				*c*-Pro

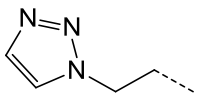
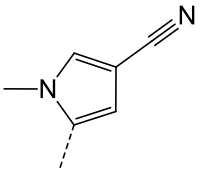
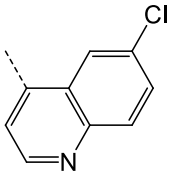
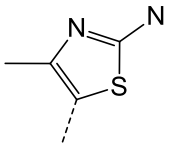
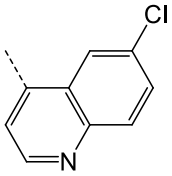
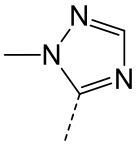
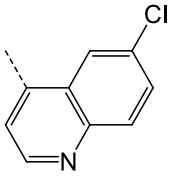
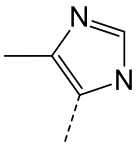
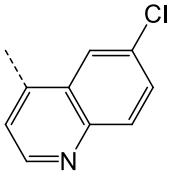
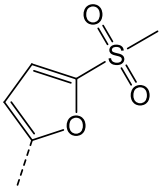
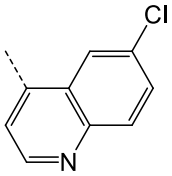
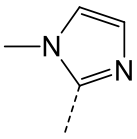
25	59	Me			*c*-Pro
26[a]	60	Me			*c*-Pro
27	62				*c*-Pro
28	63				*c*-Pro
29	67	Me			*i*-Pro
30	69				*c*-Pro
31	70	Et			*c*-Pro
32[ab]	70				*c*-Pro

33[b]	72	Et			*c*-Pro
34[a]	74				*c*-Pro
35	79	*c*-Pro			*c*-Pro
36[b]	80	*c*-Pro			*c*-Pro
37	86	Me			*i*-Pro
38[a]	87	Me			*c*-Pro
39	88				*c*-Pro

40[b]	89				*c*-Pro
41	103	Me			*i*-Pro
42	120				*c*-Pro
43[b]	120	Me		1-naphthyl	*i*-Pro
44	150				*c*-Pro
45	160	Me			*c*-Pro
46	160				*c*-Pro
47[ab]	170	Me			*i*-Pro

48[a]	170				*c*-Pro
49[b]	180	Et			*c*-Pro
50	220	Me			*c*-Pro
51[a]	220	Me			*c*-Pro
52	220	*i*-Pro			*c*-Pro
53[a]	230	Me			*c*-Pro
54	240	*i*-Pro			*c*-Pro

55	250				*c*-Pro
56	250	*c*-Pro			*c*-Pro
57[ab]	260	Me			*i*-Pro
58	260				*c*-Pro
59	280	Me			*c*-Pro
60[b]	460				*c*-Pro
61	470				*c*-Pro
62	503	Me			*i*-Pro

63	670				*c*-Pro
64[ab]	740	Me			*c*-Pro
65[a]	810	Me			*c*-Pro
66	900	Me			*c*-Pro
67[a]	1,400	Me	4-Pyridyl	1-naphthyl	*i*-Pro
68[b]	1,500	Me			*c*-Pro
69	2,200	Me		3-indolyl	*i*-Pro

[a] Test set for the MM/GBSA-PLSR model.

[b] Test set for CoMFA and CoMSIA models.

Table S2. Y-randomization test for the MM/GBSA-PLSR model.

Trial	R^2	Q^2	Trial	R^2	Q^2	Trial	R^2	Q^2
Original	0.962	0.822	Rand-34	0.630	-2.717	Rand-68	0.481	-1.256
Rand-1	0.546	-1.056	Rand-35	0.544	-1.995	Rand-69	0.516	-3.507
Rand-2	0.692	-0.587	Rand-36	0.662	-1.727	Rand-70	0.620	-1.004
Rand-3	0.660	-0.801	Rand-37	0.742	-0.883	Rand-71	0.613	-4.545
Rand-4	0.511	-2.381	Rand-38	0.628	-3.167	Rand-72	0.618	-1.754
Rand-5	0.565	-2.072	Rand-39	0.694	-0.801	Rand-73	0.557	-2.575
Rand-6	0.670	-1.349	Rand-40	0.639	-2.351	Rand-74	0.629	-3.382
Rand-7	0.537	-1.359	Rand-41	0.653	-1.126	Rand-75	0.581	-1.649
Rand-8	0.617	-3.438	Rand-42	0.501	-3.348	Rand-76	0.506	-3.440
Rand-9	0.535	-2.480	Rand-43	0.652	-1.065	Rand-77	0.633	-1.704
Rand-10	0.662	-1.173	Rand-44	0.552	-3.459	Rand-78	0.773	-0.020
Rand-11	0.530	-1.995	Rand-45	0.674	-1.256	Rand-79	0.649	-3.435
Rand-12	0.627	-4.192	Rand-46	0.598	-1.357	Rand-80	0.623	-2.103
Rand-13	0.536	-3.562	Rand-47	0.645	-0.755	Rand-81	0.754	-1.407
Rand-14	0.580	-1.615	Rand-48	0.759	-1.302	Rand-82	0.660	-2.167
Rand-15	0.794	-0.737	Rand-49	0.677	-0.868	Rand-83	0.613	-2.093
Rand-16	0.589	-2.858	Rand-50	0.658	-0.131	Rand-84	0.523	-2.172
Rand-17	0.601	-2.291	Rand-51	0.632	-0.351	Rand-85	0.555	-1.783
Rand-18	0.638	-4.257	Rand-52	0.785	-2.043	Rand-86	0.604	-1.491
Rand-19	0.628	-3.655	Rand-53	0.515	-1.791	Rand-87	0.510	-6.792
Rand-20	0.540	-1.028	Rand-54	0.483	-3.609	Rand-88	0.545	-3.318
Rand-21	0.666	-1.758	Rand-55	0.705	-0.539	Rand-89	0.494	-3.270
Rand-22	0.698	-3.081	Rand-56	0.467	-4.075	Rand-90	0.546	-1.948
Rand-23	0.654	-3.009	Rand-57	0.529	-5.085	Rand-91	0.625	-2.149
Rand-24	0.573	-2.081	Rand-58	0.698	-1.041	Rand-92	0.761	-1.941
Rand-25	0.659	-1.256	Rand-59	0.491	-3.054	Rand-93	0.648	-3.284
Rand-26	0.693	-1.039	Rand-60	0.563	-1.250	Rand-94	0.625	-1.983
Rand-27	0.600	-1.443	Rand-61	0.673	-0.951	Rand-95	0.623	-4.281
Rand-28	0.610	-2.861	Rand-62	0.595	-1.409	Rand-96	0.738	-1.619
Rand-29	0.754	-0.170	Rand-63	0.612	-1.225	Rand-97	0.475	-2.339
Rand-30	0.578	-1.112	Rand-64	0.496	-1.587	Rand-98	0.597	-1.462
Rand-31	0.581	-1.777	Rand-65	0.585	-2.631	Rand-99	0.495	-2.662
Rand-32	0.467	-1.384	Rand-66	0.600	-1.958	Rand-100	0.494	-1.905
Rand-33	0.573	-1.041	Rand-67	0.584	-2.938			

Table S3. Predicted pIC_{50} values and respective residuals generated from the ligand-based and structure-based 3D-QSAR models.

ID	IC_{50} (nM)	pIC50	Ligand-based		Structure-based	Residual		
			CoMFA	CoMSIA	(MM/GBSA-PLSR)	CoMFA	CoMSIA	MM/GBSA-PLSR
1	6	-0.778	-0.706	-0.798	-0.782	-0.072	0.020	0.004
2	13	-1.114	-1.171	-1.103	-0.977	0.057	-0.011	-0.137
3	16	-1.204	-1.337	-1.191	-1.072	0.133	-0.013	-0.132
4	23	-1.362	-1.140	-1.380	-1.712	-0.222	0.018	0.350
5	24	-1.380	-1.592	-1.567	-1.513	0.212	0.187	0.133
6	25	-1.398	-1.733	-1.813	-1.374	0.335	0.415	-0.024
7	26	-1.415	-1.429	-1.268	-1.554	0.014	-0.147	0.139
8	27	-1.431	-1.284	-1.142	-1.263	-0.147	-0.289	-0.169
9	28	-1.447	-1.393	-1.502	-1.590	-0.054	0.055	0.143
10	31	-1.491	-1.706	-1.719	-1.575	0.215	0.228	0.083
11	33	-1.519	-1.556	-1.488	-1.578	0.037	-0.031	0.059
12	34	-1.531	-1.538	-1.504	-1.510	0.007	-0.027	-0.021
13	36	-1.556	-1.533	-1.548	-2.016	-0.023	-0.008	0.459
14	37	-1.568	-1.541	-1.511	-1.660	-0.027	-0.057	0.092
15	38	-1.580	-1.558	-1.537	-1.543	-0.022	-0.043	-0.037
16	39	-1.591	-1.487	-1.636	-1.524	-0.104	0.045	-0.067
17	41	-1.613	-1.960	-1.945	-1.731	0.347	0.332	0.118
18	44	-1.643	-1.628	-1.614	-1.811	-0.015	-0.029	0.168
19	51	-1.708	-1.687	-1.722	-1.915	-0.021	0.014	0.208
20	54	-1.732	-1.565	-1.729	-1.741	-0.167	-0.003	0.008
21	55	-1.740	-1.772	-1.718	-1.760	0.032	-0.022	0.020
22	56	-1.748	-1.961	-1.853	-2.048	0.213	0.105	0.300
23	57	-1.756	-1.822	-1.788	-2.079	0.066	0.032	0.323
24	57	-1.756	-1.784	-1.797	-1.819	0.028	0.041	0.063
25	59	-1.771	-1.775	-1.787	-1.761	0.004	0.016	-0.010
26	60	-1.778	-1.822	-1.615	-2.007	0.044	-0.163	0.229
27	62	-1.792	-1.887	-1.873	-1.811	0.095	0.081	0.019
28	63	-1.799	-1.911	-1.792	-1.908	0.112	-0.007	0.109
29	67	-1.826	-1.736	-1.794	-1.924	-0.090	-0.032	0.098
30	69	-1.839	-2.059	-1.911	-1.940	0.220	0.072	0.101
31	70	-1.845	-1.883	-1.904	-1.770	0.038	0.059	-0.075
32	70	-1.845	-1.777	-1.823	-2.336	-0.068	-0.022	0.491
33	72	-1.857	-2.127	-2.028	-1.974	0.270	0.171	0.117
34	74	-1.869	-1.717	-1.782	-2.047	-0.152	-0.087	0.178
35	79	-1.898	-2.118	-1.884	-1.922	0.220	-0.014	0.024
36	80	-1.903	-1.883	-1.801	-1.941	-0.020	-0.102	0.037
37	86	-1.934	-1.741	-1.834	-2.151	-0.193	-0.100	0.217
38	87	-1.940	-2.081	-2.187	-1.880	0.141	0.247	-0.060

39	88	-1.944	-1.925	-1.971	-1.849	-0.019	0.027	-0.095
40	89	-1.949	-1.715	-1.814	-1.953	-0.234	-0.135	0.003
41	103	-2.013	-2.074	-1.942	-2.086	0.061	-0.071	0.073
42	120	-2.079	-2.128	-2.055	-2.036	0.049	-0.024	-0.043
43	120	-2.079	-2.508	-2.473	-2.028	0.429	0.394	-0.051
44	150	-2.176	-2.190	-2.202	-2.051	0.014	0.026	-0.125
45	160	-2.204	-2.051	-2.169	-2.238	-0.153	-0.035	0.033
46	160	-2.204	-2.243	-2.396	-2.046	0.039	0.192	-0.158
47	170	-2.230	-1.967	-1.964	-2.010	-0.263	-0.266	-0.220
48	170	-2.230	-2.205	-2.224	-2.253	-0.025	-0.006	0.022
49	180	-2.255	-2.206	-2.233	-2.192	-0.049	-0.022	-0.064
50	220	-2.342	-2.188	-2.229	-2.283	-0.154	-0.113	-0.059
51	220	-2.342	-2.140	-2.368	-2.489	-0.202	0.026	0.146
52	220	-2.342	-2.353	-2.113	-2.325	0.011	-0.229	-0.017
53	230	-2.362	-2.306	-2.298	-2.196	-0.056	-0.064	-0.166
54	240	-2.380	-2.191	-2.114	-2.256	-0.189	-0.266	-0.124
55	250	-2.398	-2.152	-2.252	-2.394	-0.246	-0.146	-0.004
56	250	-2.398	-2.303	-2.261	-2.235	-0.095	-0.137	-0.162
57	260	-2.415	-2.184	-2.130	-2.141	-0.231	-0.285	-0.274
58	260	-2.415	-2.420	-2.317	-2.488	0.005	-0.098	0.073
59	280	-2.447	-2.486	-2.377	-2.377	0.039	-0.070	-0.070
60	460	-2.663	-2.192	-2.161	-2.397	-0.471	-0.502	-0.265
61	470	-2.672	-2.661	-2.696	-2.802	-0.011	0.024	0.130
62	503	-2.702	-2.686	-2.750	-2.710	-0.016	0.048	0.008
63	670	-2.826	-2.767	-2.844	-2.802	-0.059	0.018	-0.024
64	740	-2.869	-2.551	-2.638	-3.250	-0.318	-0.231	0.381
65	810	-2.908	-3.025	-2.922	-3.347	0.117	0.014	0.438
66	900	-2.954	-2.835	-2.963	-2.893	-0.119	0.009	-0.062
67	1400	-3.146	-3.361	-3.187	-3.254	0.215	0.041	0.108
68	1500	-3.176	-1.281	-3.164	-3.213	-1.895	-0.012	0.037
69	2200	-3.342	-3.069	-3.333	-3.292	-0.273	-0.009	-0.050

Table S4. Coefficients (Coeff) and standard-deviation-weighted coefficients (StDev*Coeff) of the MM/GBSA-PLSR model.

Interaction	Residue	Position	Coeff	StDev*Coeff
Van der Waals	Val10	Sidechain	-0.0049	-0.0015
	Phe13	Sidechain	-0.0135	-0.0050
	Ser14	Sidechain	0.0207	0.0025
	Ile149	Sidechain	0.0958	0.0198
	Glu150	Sidechain	0.0091	0.0017
	Ser152	Sidechain	0.0943	0.0261
	Leu154	Sidechain	0.1372	0.0328
	Leu186	Sidechain	0.0583	0.0392
	Trp244	Sidechain	-0.1603	-0.0516
	Gln248	Sidechain	-0.0942	-0.0331
	Trp252	Sidechain	-0.0058	-0.0056
	Glu150	Backbone	0.0221	0.0050
	Leu186	Backbone	0.1622	0.0420
	Trp252	Backbone	-0.0253	-0.0028
Electrostatic	Phe13	Sidechain	-0.0542	-0.0040
	Lys17	Sidechain	-0.0416	-0.0330
	Lys21	Sidechain	0.0995	0.0311
	Glu150	Sidechain	0.0436	0.0543
	Ser152	Sidechain	0.0949	0.0536
	Glu155	Sidechain	-0.0322	-0.0135
	Trp244	Sidechain	0.1010	0.0460
	Arg247	Sidechain	-0.0243	-0.0140
	Gln248	Sidechain	-0.0241	-0.0332
	Lys250	Sidechain	0.0350	0.0097
	Glu251	Sidechain	0.0184	0.0124
	Trp252	Sidechain	0.1184	0.1000
	Lys254	Sidechain	-0.0566	-0.0118
	Val10	Backbone	0.0627	0.0104
	Gly11	Backbone	0.0333	0.0053
	Ile149	Backbone	-0.0035	-0.0017
	Glu150	Backbone	-0.0267	-0.0263
	Ser152	Backbone	-0.0012	-0.0002
	Pro185	Backbone	-0.0766	-0.0239
	Leu186	Backbone	0.0155	0.0150
	Gln189	Backbone	-0.0987	-0.0309
	Trp252	Backbone	0.1086	0.0126
Polar solvation	Lys17	Sidechain	0.0347	0.0274
	Lys21	Sidechain	-0.1023	-0.0333
	Ser152	Sidechain	-0.1150	-0.0446

Glu155	Sidechain	0.0477	0.0195
Trp244	Sidechain	0.0170	0.0069
Arg247	Sidechain	0.0221	0.0129
Gln248	Sidechain	0.1013	0.1128
Lys250	Sidechain	-0.0332	-0.0094
Glu251	Sidechain	-0.0175	-0.0115
Trp252	Sidechain	-0.0446	-0.0289
Lys254	Sidechain	0.0654	0.0137
Gly11	Backbone	-0.0428	-0.0056
Ile149	Backbone	0.0260	0.0104
Glu150	Backbone	0.0378	0.0343
Ser152	Backbone	-0.0488	-0.0076
Pro185	Backbone	0.0848	0.0243
Leu186	Backbone	-0.1076	-0.0540
Trp252	Backbone	-0.0433	-0.0046

Discussion on the outlier compound 68 occurring in the CoMFA model

The reason that compound **68** occurs as an outlier in the CoMFA model is present here. The CoMFA model overestimates the affinity of compound **68** due to the "favorable" steric interaction between methylsulfonyl group near residues Trp244, Gln248, and Trp252 (Figure S1A). For such a polar group, hydrogen-bonding acceptor contribution may be more suitable to depict its interaction, as suggested by the CoMSIA model. Two cyan polyhedra near Trp244 and Trp252 indicate that hydrogen-bonding acceptor groups are not recommended in these regions (Figure S1B). To some extent, the MM/GBSA-PLSR model supports this argument. Adverse electrostatic interactions with Trp244 and Trp252 (magenta colored moieties in Figure S1B) impedes compound **68**'s binding, although van der Waals interactions with them as well as Gln248 are beneficial (marine colored moieties in Figure S1A). To sum up, hydrogen bonding to Trp252 reduces the affinity of compound **68** to a much lower level than the CoMFA model expects.

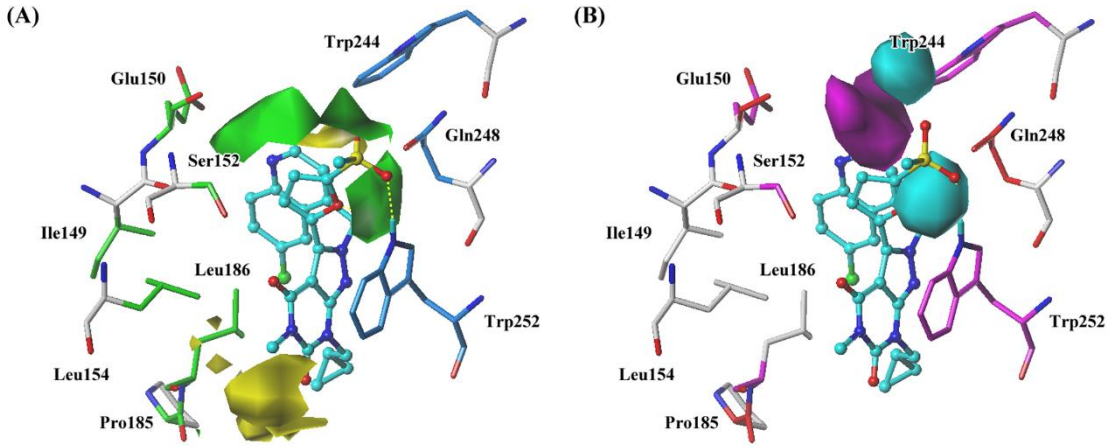


Figure S1. Conformation of compound **68** covered by the CoMFA steric maps and the CoMSIA hydrogen-bonding acceptor maps within the MurI pocket colored by MM/GBSA-PLSR steric and electrostatic components. Polyhedra contour maps represent regions where: (A) more steric bulky (green) or less steric bulky (yellow) groups, (B) groups having H-bond acceptor (magenta) or not (cyan) are preferred to enhance activity. Colored atoms indicate regions where: (A) van der Waals (marine or green) and (B) electrostatic (red or magenta) interactions are favorable or unfavorable.