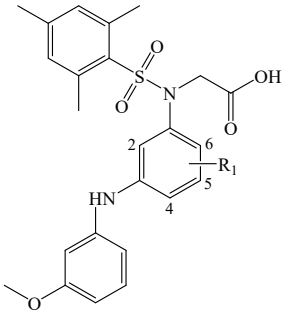
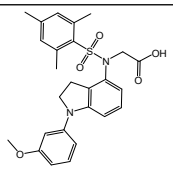
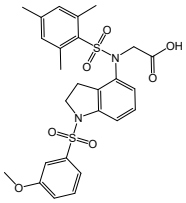
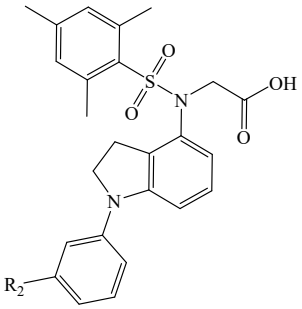
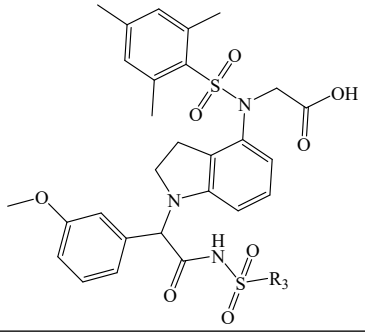
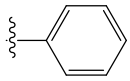
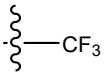
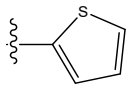
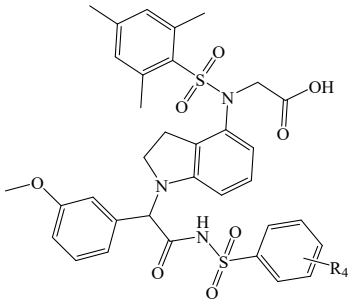
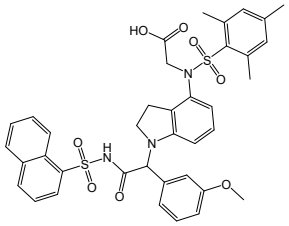
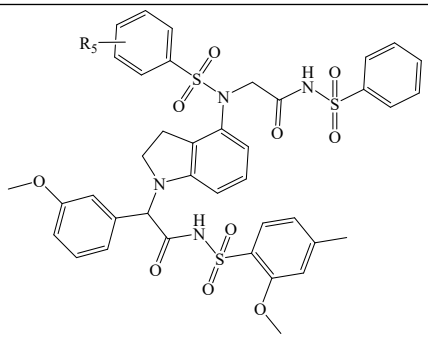
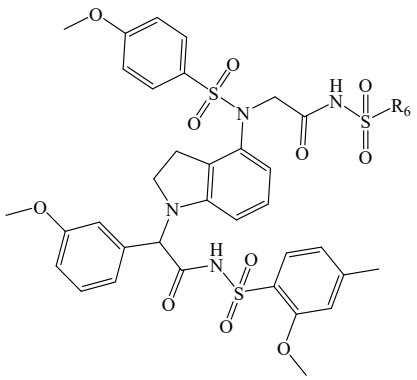
Supplementary Materials

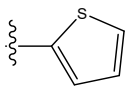
Table S1 Experimental and predicted activity values of compounds.

No.	R_1	Obs.	CoMFA	Err(%)	CoMSIA	Err%
						
1*	5-CH_3	4.03	4.106	1.883	4.007	0.568
2	4-CH_3	4.019	4.042	0.580	3.979	1.000
3	2-CH_3	4.522	4.503	0.425	4.511	0.245
4	H	3.993	4.017	0.596	3.96	0.816
5	2-F	4.097	4.102	0.117	4.066	0.759
6	2-OCH_3	4.257	4.248	0.207	4.268	0.249
No.	Structure	Obs.	CoMFA	Err(%)	CoMSIA	Err%
7		4.84	4.88	0.816	4.774	1.372
8		4.812	4.883	1.467	4.856	0.906
No.	R_2	Obs.	CoMFA	Err(%)	CoMSIA	Err%
						
9	4-OCH_3	4.009	4.029	0.499	4.072	1.584

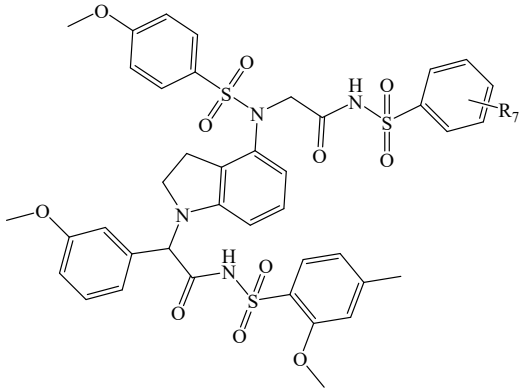
10	H	4.376	4.163	4.872	4.226	3.430
11	3-CN	4.605	4.632	0.582	4.629	0.515
12	3-NO_2	4.564	4.572	0.164	4.577	0.289
13	2,3-CH_3	4.008	4.074	1.657	4.094	2.158
No.	R_3	Obs.	CoMFA	Err(%)	CoMSIA	Err%
						
14*		5.74	5.604	2.362	5.59	2.620
15		5.243	5.255	0.231	5.436	3.685
16		5.311	5.383	1.359	5.278	0.619
17*		5.287	5.518	4.377	5.503	4.078
No.	R_4	Obs.	CoMFA	Err(%)	CoMSIA	Err%
						
18*	4-OCH_3	5.47	5.677	3.790	5.71	4.382
19	4-CH_3	5.857	5.725	2.257	5.682	2.991
20*	4-F	5.544	5.558	0.258	5.579	0.637
21	4-Cl	5.535	5.581	0.840	5.62	1.543
22*	4-Br	5.53	5.608	1.405	5.633	1.855
23*	2-OCH_3	5.879	5.711	2.849	5.641	4.045
24	2-CH_3	5.747	5.772	0.433	5.829	1.425

25	2-OCH_2CH_3	5.592	5.574	0.315	5.646	0.964
26	2-CH_2CH_3	5.446	5.498	0.946	5.513	1.239
27	2-Cl	5.559	5.535	0.425	5.592	0.594
28	2-Br	5.631	5.586	0.794	5.586	0.803
29*	2-OCF_3	5.014	5.31	5.903	5.448	8.650
30*	2,4-CH_3	5.577	5.905	5.883	5.921	6.175
31*	2,4-OCH_3	6.194	5.83	5.872	6.058	2.199
No.	Structure	Obs.	CoMFA	Err(%)	CoMSIA	Err%
32		5.742	5.698	0.759	5.714	0.484
No.	R_5	Obs.	CoMFA	Err(%)	CoMSIA	Err%
						
33	2,4,6-CH_3	7.237	7.258	0.283	7.046	2.643
34	4-OCH_3	7.194	7.1	1.312	7.106	1.223
35	4-CH_3	6.959	6.946	0.187	6.974	0.210
36	3-OCH_3	6.824	6.826	0.035	6.853	0.426
37	H	6.62	6.619	0.018	6.703	1.252
No.	R_6	Obs.	CoMFA	Err(%)	CoMSIA	Err%



38		5.759	5.762	0.059	5.614	2.513
39		5.287	5.272	0.291	5.337	0.951

No.	R_7	Obs.	CoMFA	Err(%)	CoMSIA	Err%



40	4-CH_3	6.921	6.905	0.231	6.917	0.052
41	4-F	6.886	7.024	2.011	7.074	2.723
42	4-CF_3	6.398	6.411	0.209	6.364	0.533
43	4-OCH_2CH_3	7.319	7.294	0.342	7.273	0.633

Table S2 SMILES format for the designed molecules.

No.	SMILES format
N1	O=[S](=O)(N(C=1C2=C(C([H])=C([H])C=1[H])N(C([H])([H])C2([H])[H])[C@@]([H])(C(=O)N([H])[S](=O)(=O)C=3C([H])=C([H])C(=C([H])C=3OC([H])([H])[H])C([H])([H])[H])C=4C([H])=C([H])C([H])=C(OC([H])([H])[H])C=4[H])C([H])([H])C(=O)N([H])[S](=O)(=O)c6c(c5C([H])=C(N([H])c5c([H])c6[H])C([H])([H])[H])C([H])([H])[H])C=7C([H])=C([H])C(OC([H])([H])[H])=C([H])C=7[H]

N2 O=[S](=O)(N(c1c2c(c([H])c([H])c1[H])N(C([H])([H])C2([H])[H])[C@@]([H])(C(=O)N([H])[S](=O)(=O)c3c([H])c([H])c(c([H])c3OC([H])([H])[H])C([H])([H])[H])c4c([H])c([H])c([H])c(OC([H])([H])[H])c4[H])C([H])([H])C(=O)N([H])[S](=O)(=O)c6c(c5c([H])c(n([H])c5c([H])c6[H])C([H])([H])[H])C([H])([H])C([H])([H])[H])c7c([H])c([H])c(OC([H])([H])[H])c([H])c7[H]

N3 O=[S](=O)(N(C=1C2=C(C([H])=C([H])C=1[H])N(C([H])([H])C2([H])[H])[C@@]([H])(C(=O)N([H])[S](=O)(=O)C=3C([H])=C([H])C(=C([H])C=3OC([H])([H])[H])C([H])([H])[H])C=4C([H])=C([H])C([H])=C(OC([H])([H])[H])C=4[H])C([H])([H])C(=O)N([H])[S](=O)(=O)c6c(c5C([H])=C(N([H])c5c([H])c6[H])C([H])([H])[H])C([H])([H])C([H])([H])C([H])([H])C([H])([H])[H])C=7C([H])=C([H])C(OC([H])([H])[H])=C([H])C=7[H]

N4 O=[S](=O)(N(C=1C2=C(C([H])=C([H])C=1[H])N(C([H])([H])C2([H])[H])[C@@]([H])(C(=O)N([H])[S](=O)(=O)C=3C([H])=C([H])C(=C([H])C=3OC([H])([H])[H])C([H])([H])[H])C=4C([H])=C([H])C([H])=C(OC([H])([H])[H])C=4[H])C([H])([H])C(=O)N([H])[S](=O)(=O)c6c(c5C([H])=C(N([H])c5c([H])c6[H])C([H])([H])[H])[C@]([H])(C([H])([H])C([H])([H])[H])C([H])([H])[H])C=7C([H])=C([H])C(OC([H])([H])[H])=C([H])C=7[H]

N5 O=[S](=O)(N(c1c2c(c([H])c([H])c1[H])N(C([H])([H])C2([H])[H])[C@@]([H])(C(=O)N([H])[S](=O)(=O)c3c([H])c([H])c(c([H])c3OC([H])([H])[H])C([H])([H])[H])c4c([H])c([H])c([H])c(OC([H])([H])[H])c4[H])C([H])([H])C(=O)N([H])[S](=O)(=O)c6c(c5c([H])c(n([H])c5c([H])c6[H])C([H])([H])[H])C([H])([H])C([H])([H])C([H])([H])C([H])([H])C([H])([H])[H])c7c([H])c([H])c(OC([H])([H])[H])c([H])c7[H]

N6 O=[S](=O)(N(c1c2c(c([H])c([H])c1[H])N(C([H])([H])C2([H])[H])[C@@]([H])(C(=O)N([H])[S](=O)(=O)c3c([H])c([H])c(c([H])c3OC([H])([H])[H])C([H])([H])[H])c4c([H])c([H])c([H])c(OC([H])([H])[H])c4[H])C([H])([H])C(=O)N([H])[S](=O)(=O)c6c(c5c([H])c(n([H])c5c([H])c6[H])C([H])([H])[H])C([H])([H])C([H])([H])C([H])([H])C([H])([H])C([H])([H])C([H])([H])[H])c7c([H])c([H])c(OC([H])([H])[H])c([H])c7[H]

N7 O=[S](=O)(N(c1c2c(c([H])c([H])c1[H])N(C([H])([H])C2([H])[H])[C@@]([H])(C(=O)N([H])[S](=O)(=O)c3c([H])c([H])c(c([H])c3OC([H])([H])[H])C([H])([H])[H])c4c([H])c([H])c([H])c(OC([H])([H])[H])c4[H])C([H])([H])C(=O)N([H])[S](=O)(=O)c6c(c5c([H])c(n([H])c5c([H])c6[H])C([H])([H])[H])C([H])([H])C([H])([H])C([H])([H])C([H])([H])C([H])([H])C([H])([H])C([H])([H])[H])c7c([H])c([H])c(OC([H])([H])[H])c([H])c7[H]

N8 O=[S](=O)(N(C=1C2=C(C([H])=C([H])C=1[H])N(C([H])([H])C2([H])[H])[C@@]([H])(C(=O)N([H])[S](=O)(=O)C=3C([H])=C([H])C(=C([H])C=3OC([H])([H])[H])C([H])([H])[H])C=4C([H])=C([H])C([H])=C(OC([H])([H])[H])C=4[H])C([H])([H])C(=O)N([H])[S](=O)(=O)c6c(c5C([H])=C(N([H])c5c([H])c6[H])C([H])([H])[H])C([H])([H])C([H])([H])C([H])([H])C([H])([H])[H])C([H])([H])C([H])([H])C([H])([H])C([H])([H])C([H])([H])C([H])([H])[H])C=7C([H])=C([H])C(OC([H])([H])[H])=C([H])C=7[H]

N9	O=[S](=O)(N(c1c2c(c([H])c([H])c1[H])N(C([H])([H])C2([H])[H])[C@@]([H])(C(=O)N([H])[S](=O)(=O)c3c([H])c([H])c(c([H])c3OC([H])([H])[H])C([H])([H])[H])c4c([H])c([H])c([H])c(OC([H])([H])[H])c4[H])C([H])([H])C(=O)N([H])[S](=O)(=O)c6c(c5c([H])c(n([H])c5c([H])c6[H])C([H])([H])[H])C([H])([H])C([H])([H])C([H])([H])C([H])([H])C([H])([H])C([H])([H])C([H])([H])C([H])([H])[H])c7c([H])c([H])c(OC([H])([H])[H])c([H])c7[H]
N10	O=[S](=O)(N(C=1C2=C(C([H])=C([H])C=1[H])N(C([H])([H])C2([H])[H])[C@@]([H])(C(=O)N([H])[S](=O)(=O)C=3C([H])=C([H])C(=C([H])C=3OC([H])([H])[H])C([H])([H])[H])C=4C([H])=C([H])C([H])=C(OC([H])([H])[H])C=4[H])C([H])([H])C(=O)N([H])[S](=O)(=O)c6c(c5C([H])=C(N([H])c5c([H])c6[H])C([H])([H])[H])C([H])([H])C([H])([H])C([H])([H])C([H])([H])C([H])([H])C([H])([H])C([H])([H])C([H])([H])C([H])([H])C([H])([H])[H])C=7C([H])=C([H])C(OC([H])([H])[H])=C([H])C=7[H]

Table S3 Free energy decomposition for key residues of Keap1.

Residue	Van de Waals	Electrostatic	Polar Solvation	Non-Polar Solvation	Total
Compound43 / Keap1 system					
Tyr334	-3.408	-0.391	0.610	-2.069	-5.259
Ser363	-1.108	-2.291	-0.067	-0.863	-4.328
Gly364	-0.420	-0.113	-0.241	-0.243	-1.018
Arg380	-1.117	-4.617	2.026	-0.603	-4.311
Asn414	-0.343	-0.776	-0.017	-0.125	-1.262
Arg415	-3.774	-4.025	-2.697	-2.788	-13.284
Gln530	-0.863	-2.714	-0.415	-0.591	-4.583
Ser555	-0.759	-3.707	0.939	-0.549	-4.076
Ala556	-1.823	0.680	-0.535	-1.310	-2.989
Ser602	-1.152	-3.057	0.157	-0.627	-4.679
Compound N1 / Keap1 system					
Tyr334	-2.329	-0.465	0.858	-1.648	-3.584

Ser363	-1.116	-3.761	-0.148	-0.925	-5.950
Gly364	-2.371	-0.452	-0.794	-1.375	-4.992
Arg380	-2.366	-3.461	0.725	-1.303	-6.404
Asn414	-1.218	-1.937	-1.419	-0.554	-5.127
Arg415	-3.918	-6.610	-0.342	-2.716	-13.586
Gln530	-0.882	-4.646	-0.138	-0.707	-6.374
Ser555	-0.615	-5.753	1.133	-0.632	-5.867
Ala556	-2.186	-0.861	0.965	-1.622	-3.703
Ser602	-0.877	-0.775	0.735	-0.511	-1.428
Compound N3 / Keap1 system					
Tyr334	-4.647	-0.718	0.862	-2.863	-7.366
Ser363	-1.838	-0.972	-0.096	-1.158	-4.065
Gly364	-1.944	-0.627	-0.405	-1.132	-4.108
Arg380	-1.303	0.875	-1.853	-1.082	-3.362
Asn414	-0.677	-0.097	-0.893	-0.301	-1.968
Arg415	-3.220	-4.856	1.355	-2.035	-8.757
Gln530	-0.113	-0.258	-0.230	-0.026	-0.627
Ser555	-0.416	-0.504	0.117	-0.090	-0.893
Ala556	-2.164	-1.207	0.015	-1.577	-4.933
Ser602	-0.867	-4.560	0.041	-0.709	-6.094
Compound N4 / Keap1 system					
Tyr334	-1.793	-0.249	0.312	-1.469	-3.198

Ser363	-0.291	-4.677	-0.172	-0.680	-5.820
Gly364	-1.994	1.842	-1.274	-1.225	-2.651
Arg380	-2.521	-2.383	-0.104	-1.457	-6.464
Asn414	-1.121	-2.758	-0.823	-0.665	-5.367
Arg415	-4.935	-1.970	-1.721	-3.337	-11.962
Gln530	-0.742	-5.546	0.197	-0.728	-6.819
Ser555	-0.753	-5.870	1.240	-0.662	-6.045
Ala556	-2.300	-0.564	0.175	-1.703	-4.392
Ser602	-0.811	-0.612	0.793	-0.481	-1.110
Compound N5 / Keap1 system					
Tyr334	-2.668	-0.619	1.054	-1.984	-4.217
Ser363	-1.274	-1.896	-0.112	-0.820	-4.101
Gly364	-2.047	-0.190	-0.960	-1.279	-4.476
Arg380	-2.175	-2.327	-0.610	-1.262	-6.374
Asn414	-1.038	-2.707	-1.577	-0.533	-5.855
Arg415	-4.138	-4.126	-1.109	-2.728	-12.101
Gln530	-0.379	-2.842	0.495	-0.312	-3.038
Ser555	-0.650	-3.276	1.221	-0.462	-3.166
Ala556	-2.405	-1.335	0.602	-1.613	-4.751
Ser602	-0.797	-1.017	1.061	-0.455	-1.207
Compound N8 / Keap1 system					
Tyr334	-1.543	0.027	0.416	-0.851	-1.951

Ser363	-1.264	-1.073	0.235	-0.727	-2.828
Gly364	-2.503	-0.306	-1.446	-1.452	-5.707
Arg380	-2.791	-4.505	1.441	-1.622	-7.477
Asn414	-0.805	-3.195	-1.423	-0.630	-6.052
Arg415	-4.455	-4.210	-1.899	-2.951	-13.515
Gln530	-0.430	-0.709	0.050	-0.289	-1.378
Ser555	-0.976	0.197	-0.390	-0.577	-1.746
Ala556	-2.173	-0.994	0.271	-1.654	-4.551
Ser602	-0.861	-3.277	1.230	-0.689	-3.598