Supporting Information

Design, Synthesis, Biological Evaluation and Structure-Activity Relationships of Substituted Phenyl 4-(2-Oxoimidazolidin-1-yl)benzenesulfonates as New Tubulin Inhibitors Mimicking Combretastatin A-4

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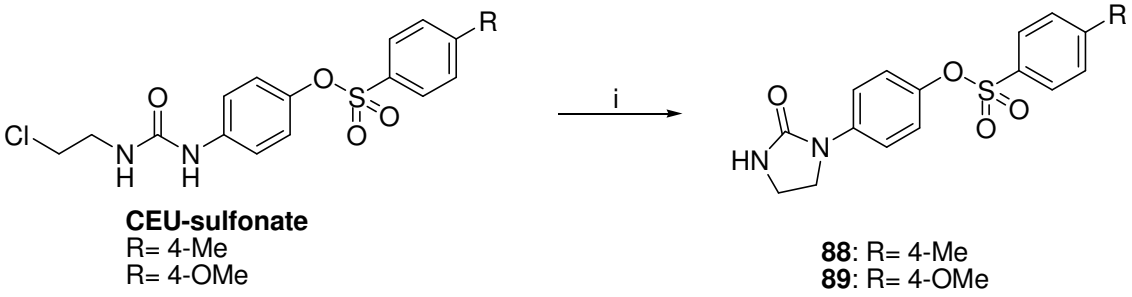

Scheme 1. Synthesis of compound **88** and **89**. Reagents: (i) Al_2O_3·KF, CH_3CN.

General preparation of compounds 88 and 89. To a stirred solution of the appropriate *N*-phenyl-*N'*-(2-chloroethyl)urea derivative (0.4 mmol) in acetonitrile (10 mL) a mixture of aluminum oxide and potassium fluoride (6:4) (4.0 mmol) was added. The suspension was refluxed overnight. After cooling, the mixture was filtered, and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel.

4-(2-oxoimidazolidin-1-yl)phenyl 4-methylbenzenesulfonate (88). Flash chromatography (methylene chloride to methylene chloride/methanol (90:10)) and washed with acetone. Yield: 20%; White solid; m.p.: 149-150°C; IR: 2877, 1683 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.75-7.72 (m, 2H, Ar), 7.55-7.47 (m, 4H, Ar), 7.07 (s, 1H, NH), 6.96-6.93 (m, 2H, Ar), 3.84-3.79 (m, 2H, CH_2), 3.42-3.36 (m, 2H, CH_2), 2.44 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ 158.8, 145.7, 143.0, 139.8, 131.5, 130.2, 128.3, 122.2, 117.7, 44.4, 36.4, 21.2; HRMS (ES+) *m/z* found 333.0108; $C_{16}H_{16}N_2O_4S$ (M^+ + H) requires 333.0909.

4-(2-oxoimidazolidin-1-yl)phenyl 4-methoxybenzenesulfonate (89). Flash chromatography (methylene chloride to methylene chloride / ethyl acetate (70:30)). Yield: 33%; White solid; m.p.: 126-127°C; IR: 3236, 1688 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.64-7.61 (m, 2H, Ar), 7.36-7.33 (m, 2H, Ar), 6.90-6.81 (m, 4H, Ar), 3.82-3.76 (m, 5H, CH_2 and CH_3), 3.48-3.43 (m, 2H, CH_2), 3.36 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 164.2, 159.9, 144.4, 138.9, 130.7, 126.3, 122.6, 118.4, 114.4, 55.7, 45.2, 37.2; HRMS (ES+) *m/z* found 348.9856; $C_{16}H_{16}N_2O_5S$ (M^+ + H) requires 349.0858.

Table 1. Evaluation of the antiproliferative activity of compounds **88** and **89** on HT-29, M21, and MCF-7 cell lines

Compd	IC_{50} (nM)[a]		
	HT-29	**M21**	**MCF-7**
88	462	282	579
89	882	509	996

[a]IC_{50}: Expressed as the concentration of drug inhibiting cell growth by 50%.

Table 2. CoMSIA Models Predicted Activities of Models A, B, and C

Compd[a]	Model A HT-29		Model B M21		Model C MCF7	
	Calcd	**Res**	**Calcd**	**Res**	**Calcd**	**Res**
9	7.005	0.477	7.09	0.495	6.934	0.588
10	7.439	-0.32	7.488	-0.22	7.36	-0.116
11	7.055	-0.242	7.135	-0.21	6.976	-0.16
12	6.78	0.099	6.899	-0.019	6.738	0.069
13	6.464	-0.101	6.554	-0.097	6.371	-0.071
14	5.328	-0.238	5.542	-0.235	5.327	-0.365
15	6.801	-1.27	6.914	-1.066	6.752	-1.23
16	7.302	-0.087	7.357	-0.073	7.207	-0.146
17	7.494	-0.375	7.524	-0.309	7.381	-0.219
18	6.791	-0.044	6.976	-0.076	6.776	-0.119
19	6.992	0.402	7.099	0.528	6.912	0.167
20	7.084	0.097	7.244	0.103	7.029	0.109
21	7.084	0.21	7.188	0.278	7.008	0.204
22	7.39	-0.133	7.458	-0.057	7.254	-0.107
23	7.223	-0.501	7.432	-0.608	7.157	-0.588
24	7.296	0.213	7.342	0.425	7.203	0.098
25	7.269	0.023	7.314	0.095	7.176	0.125
26	7.561	0.431	7.587	0.484	7.463	0.378
27	7.475	-0.093	7.491	-0.104	7.367	-0.188
28	7.35	0.173	7.428	0.08	7.211	0.312
29	7.085	-0.126	7.198	-0.27	6.962	-0.203
30	7.082	0.304	7.144	0.318	6.976	0.284
31	7.17	0.372	7.269	0.544	7.08	0.42
32	7.594	-1.13	7.63	-0.979	7.43	-0.939
33	7.523	-0.051	7.523	0.047	7.398	-0.107
34	7.067	0.47	7.107	0.431	6.975	0.494
35	7.18	0.562	7.264	0.478	7.109	0.613
36	7.44	0.399	7.491	0.348	7.327	0.559
37	7.297	0.08	7.381	-0.004	7.205	0.062
38	8.142	-0.184	8.149	-0.191	7.966	-0.223
39	6.93	0.066	6.969	0.027	6.804	0.417
40	5.94	0.035	6.321	0.459	6.04	0.526
41	7.526	-0.033	7.558	-0.064	7.428	-0.101
42	7.63	-0.162	7.645	-0.176	7.513	-0.202
43	7.415	-0.242	7.51	-0.336	7.335	-0.279
44	8.002	0.096	8.145	-0.047	7.906	0.113
45	8.175	0.223	8.289	0.109	8.063	0.238
46	7.484	0.53	7.511	0.503	7.321	0.429
47	7.323	-0.199	7.373	-0.249	7.203	-0.212
48	7.467	-0.022	7.539	-0.094	7.355	-0.025
49	7.371	-0.231	7.413	-0.274	7.24	-0.199
50	6.859	0.004	6.901	-0.038	6.71	0.04
51	6.086	0.088	6.448	-0.008	6.159	0.062

52	7.012	0.102	7.054	-0.241	6.908	-0.191
53	6.69	0.424	6.719	0.395	6.563	0.384
54	6.132	-0.022	6.149	-0.039	6.003	0.033
55	6.989	0.37	7.069	0.29	6.907	0.342
56	6.944	0.023	7.021	-0.003	6.849	-0.007
57	6.578	-0.312	6.619	-0.353	6.467	-0.417
58	4.796	0.204	4.86	0.14	4.68	0.32
59	6.932	0.128	7.074	0.163	6.877	0.178
60	6.845	0.062	6.91	0.141	6.751	0.029
61	6.874	-0.053	6.928	0.046	6.735	-0.049
62	5.815	0.185	5.88	0.366	5.721	0.279
63	5.887	-0.024	6.269	-0.231	5.987	-0.169
64	6.938	-0.198	7.027	-0.134	6.863	-0.376
65	7.211	-0.056	7.35	-0.09	7.085	-0.085
66	6.221	0.1	6.417	0.118	6.217	-0.102
67	5.298	-0.599	5.458	-0.759	5.3	-0.601
68	5.481	0.048	5.634	-0.092	5.434	-0.113
69	5.188	0.113	5.23	0.071	5.172	0.129
70	5.278	0.023	5.294	0.007	5.246	0.055
71	5.669	-0.368	5.642	-0.341	5.606	-0.305
72	5.507	-0.206	5.518	-0.217	5.471	-0.17
73	5.825	-0.277	5.867	-0.123	5.737	-0.37
74	5.389	-0.088	5.455	0.048	5.312	-0.011
75	5.677	-0.376	5.688	-0.387	5.655	-0.354
76	5.365	-0.064	5.369	-0.068	5.332	-0.031
77	5.612	-0.311	5.657	-0.356	5.573	-0.272
78	5.691	0.622	5.808	0.804	5.638	0.497
79	5.332	0.81	5.368	0.564	5.308	0.675
80	5.294	0.007	5.386	-0.085	5.29	0.011
81	5.193	0.108	5.217	0.084	5.158	0.143
88	6.204	0.132	6.305	0.245	6.145	0.093
89	6.127	-0.073	6.203	0.09	6.055	-0.053

[a]Compounds **88** and **89** were included in the models but were not described in this study. Synthesis, chemical characterization and antiproliferative activity are described in the supplemental data section.

Table 3. CoMFA Models Predicted Activities of Models G, H, and I

Compd[a]	Model G HT-29		Model H M21		Model I MCF7	
	Calcd	**Res**	**Calcd**	**Res**	**Calcd**	**Res**
9	6.975	0.507	7.053	0.532	6.904	0.619
10	7.305	-0.186	7.37	-0.103	7.232	0.012
11	7.083	-0.27	7.19	-0.265	7.014	-0.198
12	7.057	-0.178	7.142	-0.263	6.979	-0.172
13	6.766	-0.404	6.855	-0.398	6.676	-0.376
14	5.436	-0.346	5.638	-0.33	5.435	-0.473
15	6.757	-1.227	6.891	-1.043	6.718	-1.196
16	7.099	0.116	7.115	0.169	7.002	0.059
17	7.421	-0.302	7.455	-0.24	7.307	-0.146
18	6.968	-0.22	7.072	-0.173	6.89	-0.233
19	7.408	-0.013	7.528	0.099	7.304	-0.226
20	7.201	-0.02	7.412	-0.066	7.131	0.007
21	7.069	0.225	7.215	0.251	7.007	0.205
22	7.587	-0.33	7.632	-0.231	7.416	-0.269
23	6.707	0.015	6.797	0.027	6.614	-0.045
24	7.099	0.409	7.152	0.615	7.017	0.284
25	7.094	0.199	7.134	0.274	7.008	0.293
26	7.577	0.415	7.605	0.467	7.473	0.369
27	7.595	-0.213	7.636	-0.249	7.482	-0.303
28	7.282	0.241	7.419	0.09	7.149	0.374
29	6.955	0.003	7.162	-0.234	6.849	-0.089
30	6.865	0.521	6.958	0.505	6.794	0.466
31	7.376	0.166	7.512	0.3	7.287	0.213
32	7.146	-0.681	7.109	-0.457	6.998	-0.507
33	7.366	0.105	7.4	0.17	7.262	0.029
34	7.023	0.515	7.104	0.434	6.957	0.511
35	7.454	0.288	7.529	0.214	7.352	0.37
36	7.276	0.562	7.375	0.464	7.189	0.697
37	7.071	0.306	7.14	0.237	6.991	0.276
38	7.874	0.084	7.847	0.112	7.687	0.055
39	6.992	0.004	7.014	-0.018	6.889	0.333
40	5.728	0.247	5.989	0.79	5.735	0.831
41	7.811	-0.317	7.832	-0.339	7.689	-0.362
42	7.972	-0.504	7.986	-0.517	7.832	-0.52
43	7.701	-0.527	7.746	-0.573	7.577	-0.522
44	8.255	-0.157	8.413	-0.315	8.12	-0.102
45	8.357	0.041	8.372	0.026	8.18	0.121
46	7.394	0.62	7.466	0.548	7.261	0.488
47	6.921	0.203	6.93	0.194	6.826	0.165
48	7.191	0.253	7.222	0.223	7.086	0.244
49	6.99	0.149	6.978	0.161	6.877	0.164
50	6.619	0.244	6.573	0.29	6.495	0.254
51	6.305	-0.131	6.53	-0.09	6.259	-0.039

52	6.885	0.229	6.957	-0.144	6.808	-0.092
53	6.652	0.462	6.762	0.352	6.576	0.37
54	5.947	0.163	6.033	0.077	5.884	0.153
55	7.305	0.053	7.412	-0.053	7.212	0.037
56	6.852	0.114	6.907	0.111	6.754	0.088
57	6.632	-0.366	6.7	-0.434	6.536	-0.486
58	5.225	-0.225	5.317	-0.317	5.129	-0.129
59	6.84	0.221	6.96	0.276	6.764	0.291
60	6.783	0.123	6.886	0.164	6.724	0.056
61	6.862	-0.041	6.854	0.121	6.704	-0.018
62	5.768	0.232	5.847	0.398	5.725	0.275
63	5.66	0.204	5.933	0.105	5.672	0.146
64	7.297	-0.557	7.418	-0.525	7.194	-0.708
65	6.545	0.61	6.752	0.508	6.49	0.51
66	6.505	-0.185	6.678	-0.143	6.475	-0.359
67	5.485	-0.786	5.615	-0.916	5.491	-0.792
68	5.456	0.072	5.553	-0.011	5.409	-0.088
69	5.292	0.009	5.355	-0.054	5.285	0.016
70	5.148	0.153	5.191	0.11	5.138	0.163
71	5.359	-0.058	5.324	-0.023	5.318	-0.017
72	5.315	-0.014	5.29	0.011	5.282	0.019
73	5.786	-0.237	5.877	-0.132	5.7	-0.334
74	5.48	-0.179	5.639	-0.135	5.418	-0.117
75	5.75	-0.449	5.772	-0.471	5.727	-0.426
76	5.474	-0.173	5.507	-0.206	5.457	-0.156
77	5.649	-0.348	5.67	-0.369	5.611	-0.31
78	5.659	0.654	5.793	0.819	5.607	0.528
79	5.55	0.593	5.598	0.333	5.527	0.456
80	5.294	0.007	5.384	-0.083	5.276	0.025
81	5.121	0.18	5.153	0.148	5.114	0.187
88	6.745	-0.409	6.969	-0.419	6.709	-0.472
89	6.522	-0.467	6.679	-0.385	6.48	-0.478

[a]Compounds **88** and **89** were included in the models but were not described in this study. Synthesis, chemical characterization and antiproliferative activity are described in the supplemental data.