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Supplementary information:

RATIONAL DESIGN OF NOVEL SIRTUIN 1 ACTIVATORS VIA STRUCTURE-ACTIVITY INSIGHTS FROM APPLICATION OF QSAR MODELING

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Supplementary Table 1: Descriptors values of SIRT1 activators Scaffold A

Compound	HATS8u	Electronegativity	JGI7	Mor15p
A1	0.190	-0.122	0.011	1.148
A2	0.176	-0.127	0.010	1.107
A3	0.260	-0.139	0.010	1.170
A4	0.284	-0.128	0.009	1.126
A5	0.165	-0.136	0.010	1.052
A6	0.197	-0.114	0.010	0.973
A7	0.186	-0.122	0.010	0.786
A8	0.289	-0.114	0.009	0.289
A9	0.243	-0.130	0.009	0.652
A10	0.252	-0.116	0.009	0.710
A11	0.196	-0.114	0.010	1.058
A12	0.266	-0.112	0.010	0.970
A13	0.259	-0.115	0.010	0.520

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Supplementary Table 2: Descriptors values of SIRT1 activators Scaffold B

Compound	Mor22e	F10[C-O]	P1e
B1	0.197	2	0.565
B2	-0.191	4	0.618
B3	0.325	3	0.874
B4	0.269	6	0.529
B5	0.033	5	0.882
B6	-0.320	6	0.680
B7	-0.009	9	0.573
B8	0.224	6	0.689
B9	-0.057	11	0.665

Supplementary Table 3: Descriptors values of SIRT1 activators Scaffold C

Compound	RDF090m	BEHp2	R6m+	E2u
C1	8.004	3.822	0.014	0.413
C2	4.688	3.836	0.014	0.452
C3	8.575	3.816	0.016	0.406
C4	9.007	3.830	0.014	0.397
C5	6.355	3.818	0.011	0.436
C6	7.724	3.819	0.016	0.381
C7	6.447	3.819	0.014	0.461
C8	4.961	3.839	0.013	0.416

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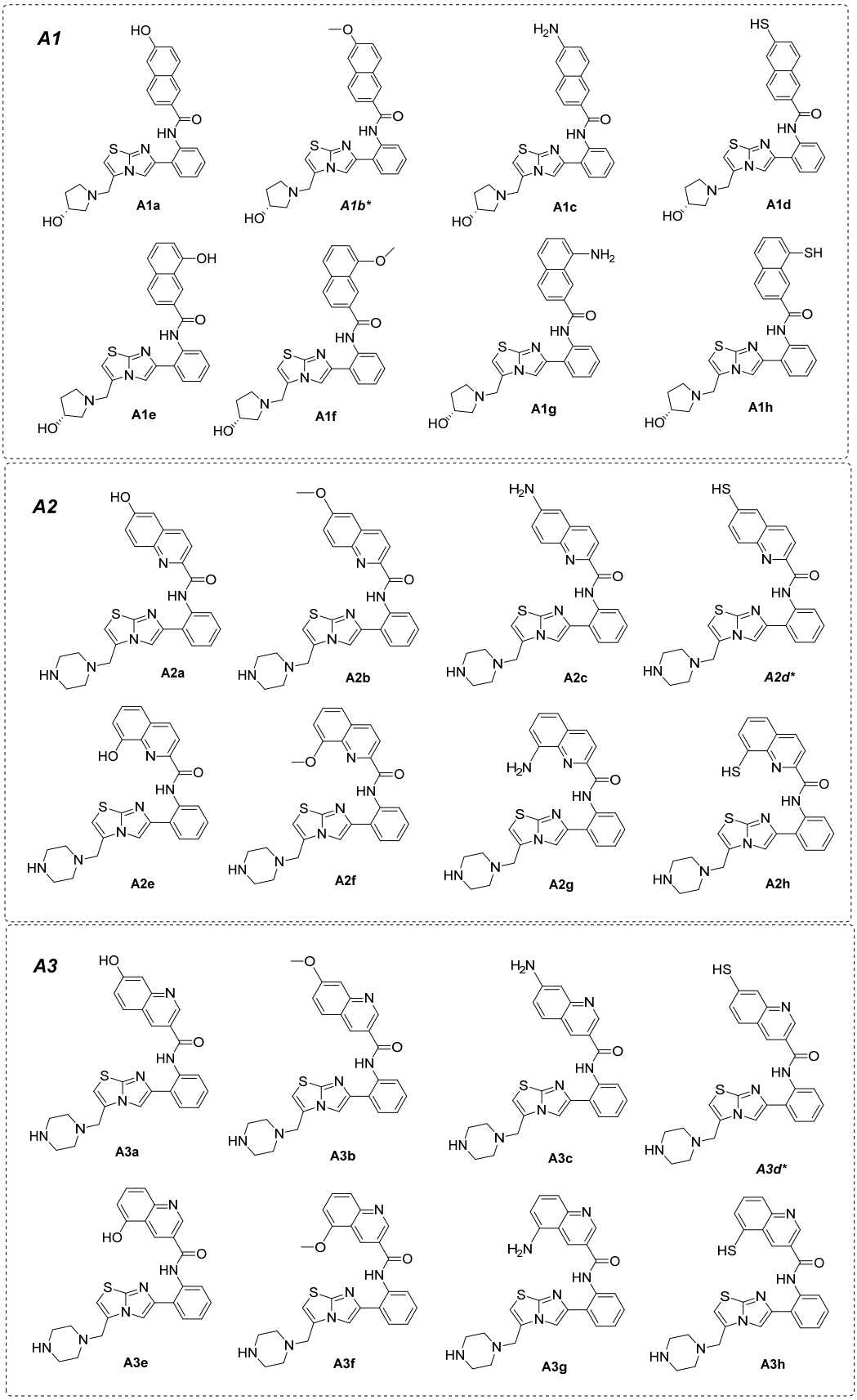
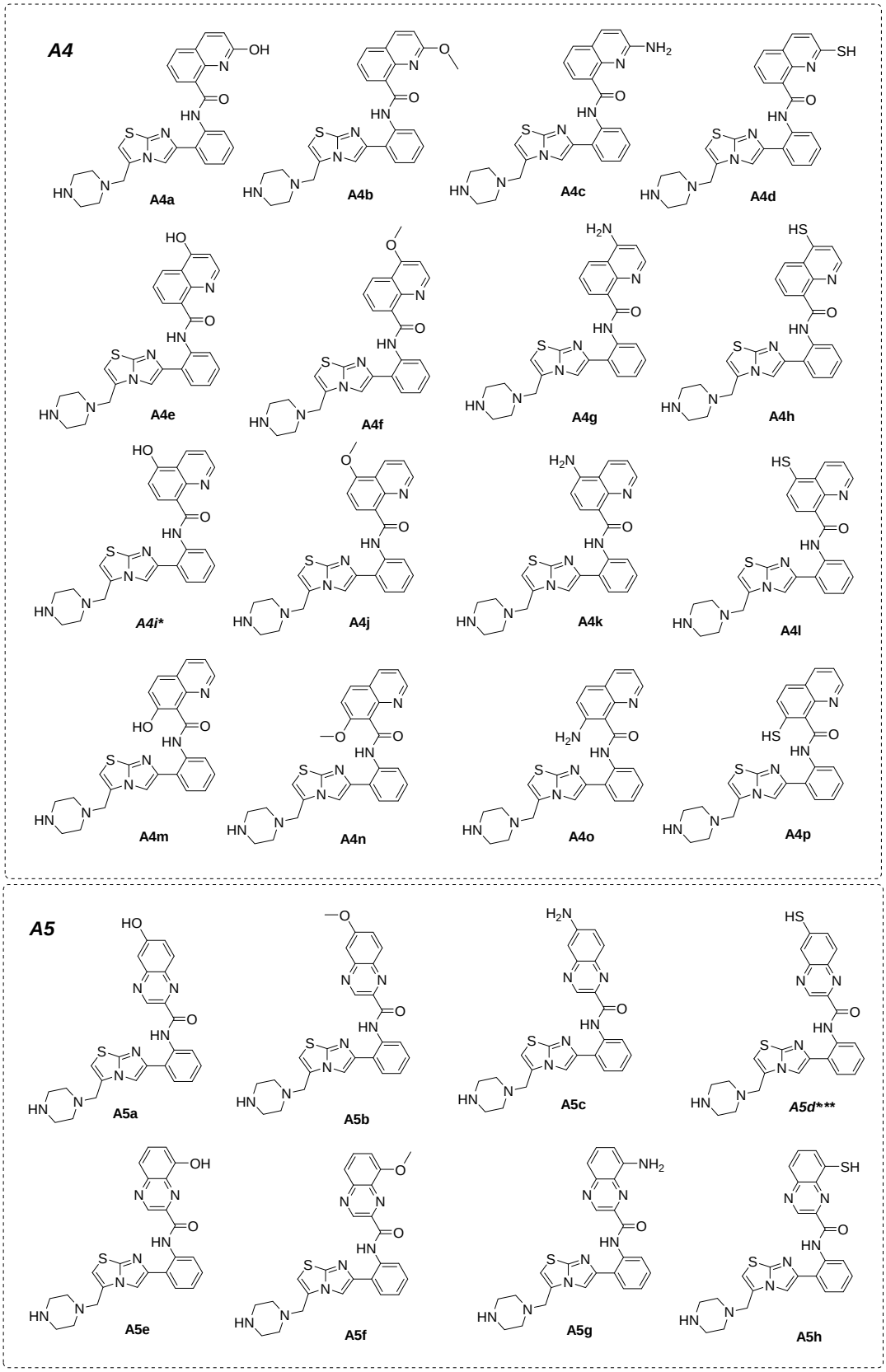
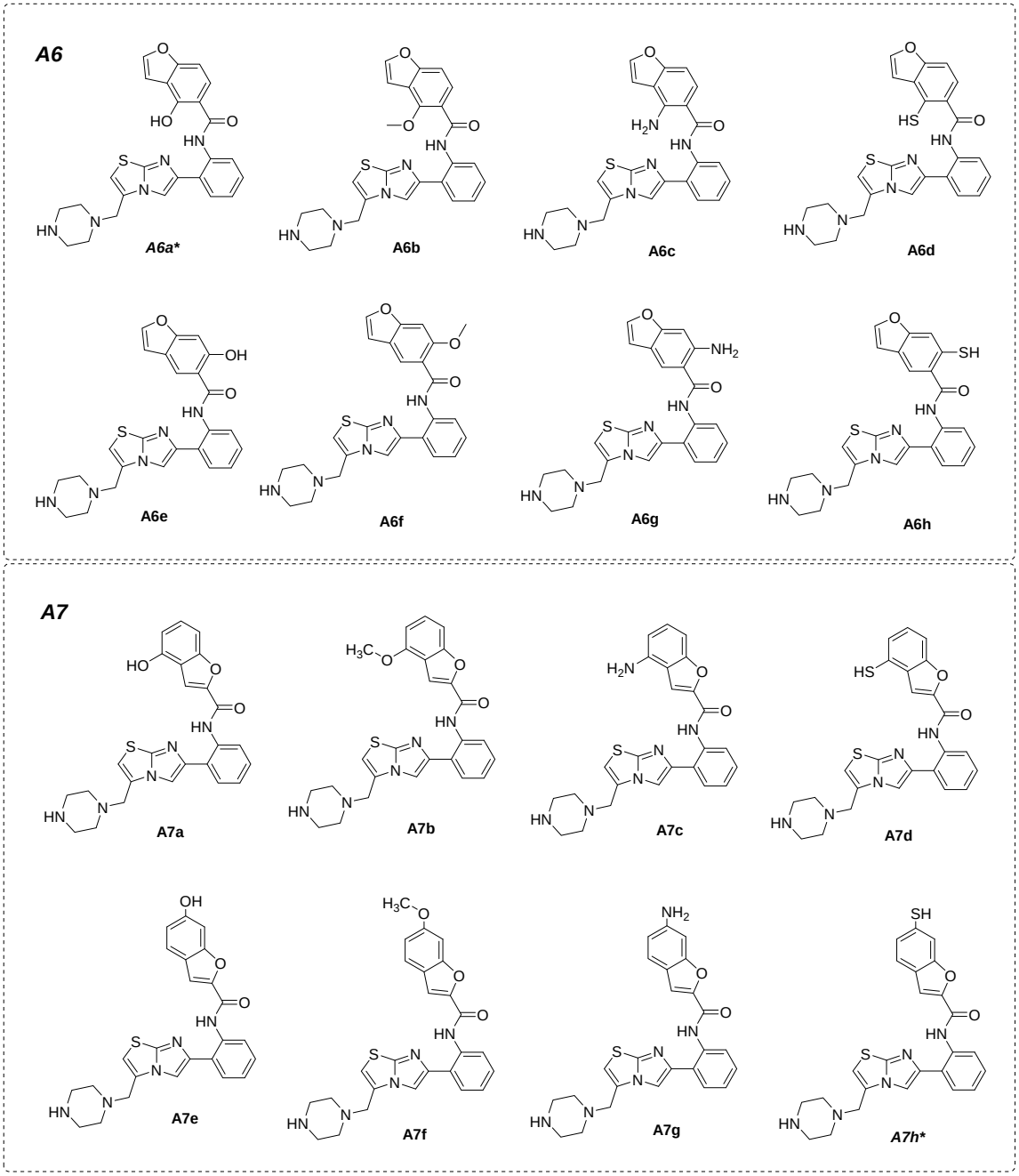


Supplementary Figure 1: Structurally modified compounds **A1-A3** (*The most potent compound in the modified subseries, ** The most potent compound of series A)



Supplementary Figure S1 (cont.): Structurally modified compounds **A4-A5** (*The most potent compound in the modified subseries, ** The most potent compound of series A)



Supplementary Figure 1 (cont.): Structurally modified compounds **A6-A7** (*The most potent compound in the modified subseries, ** The most potent compound of series A)

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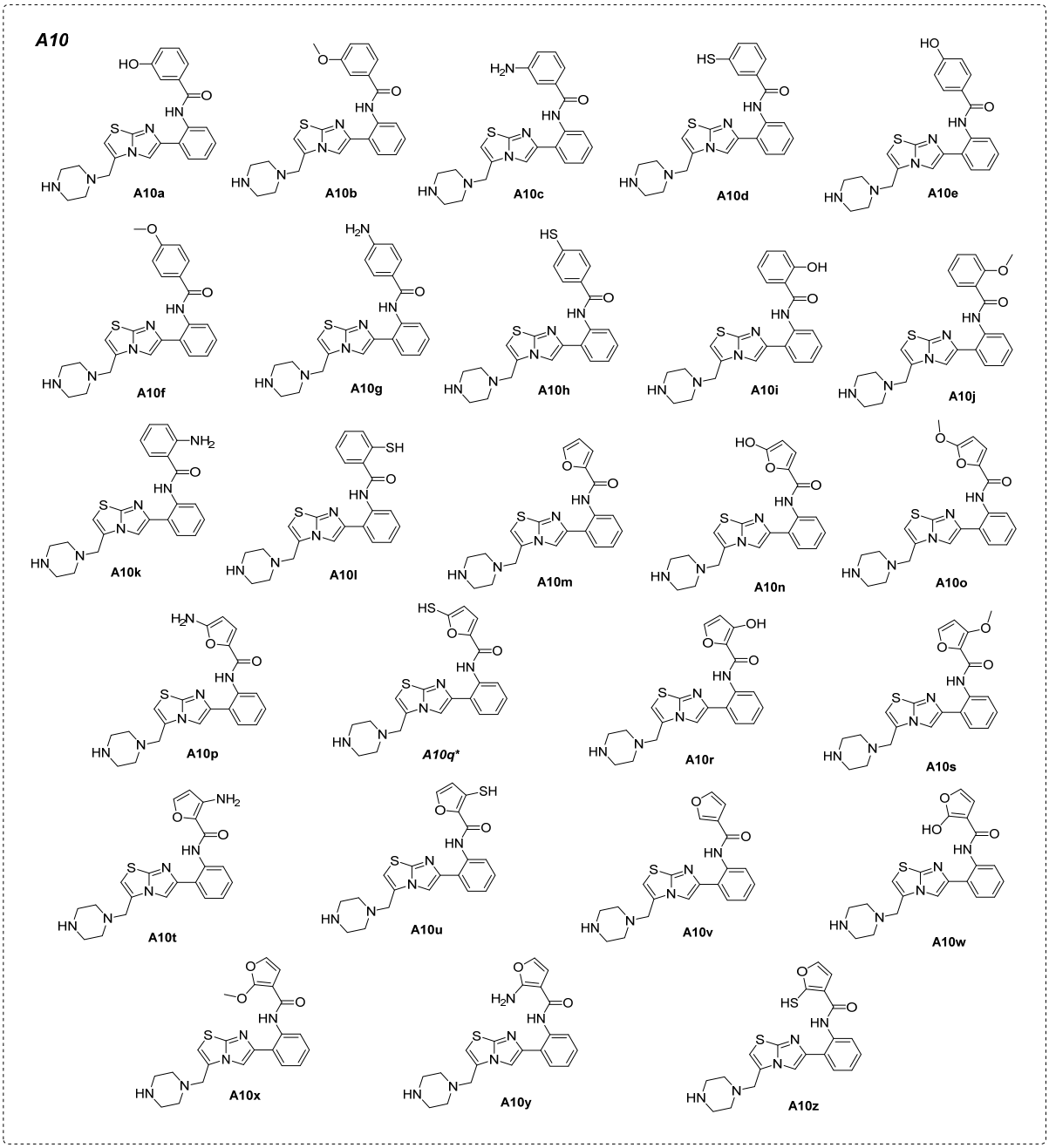

Supplementary Figure 1 (cont.): Structurally modified compounds **A10** (*The most potent compound in the modified subseries, ** The most potent compound of series A)

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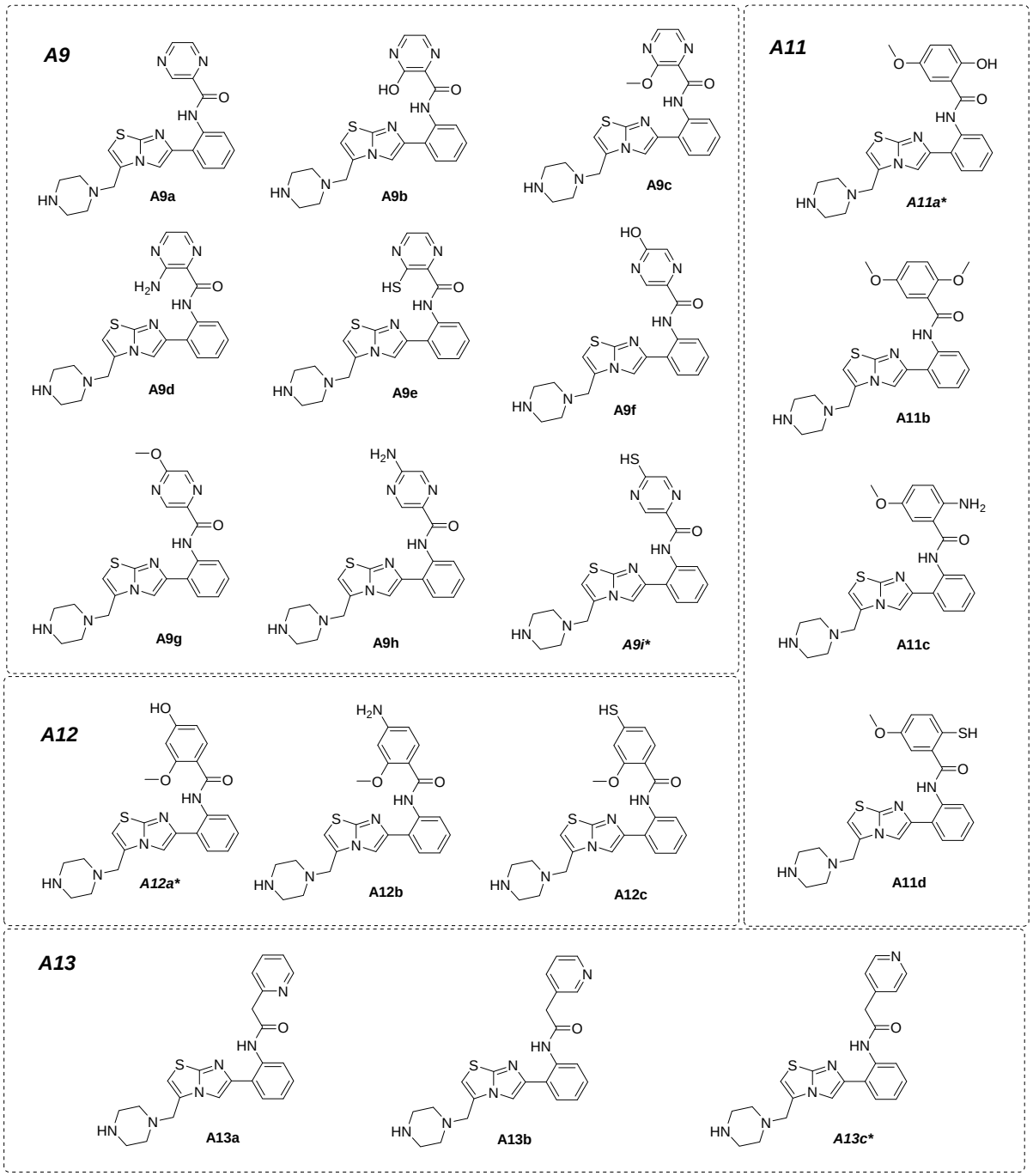

Supplementary Figure 1 (cont.): Structurally modified compounds **A9** and **A11-A13** (*The most potent compound in the modified subseries, ** The most potent compound of series A)

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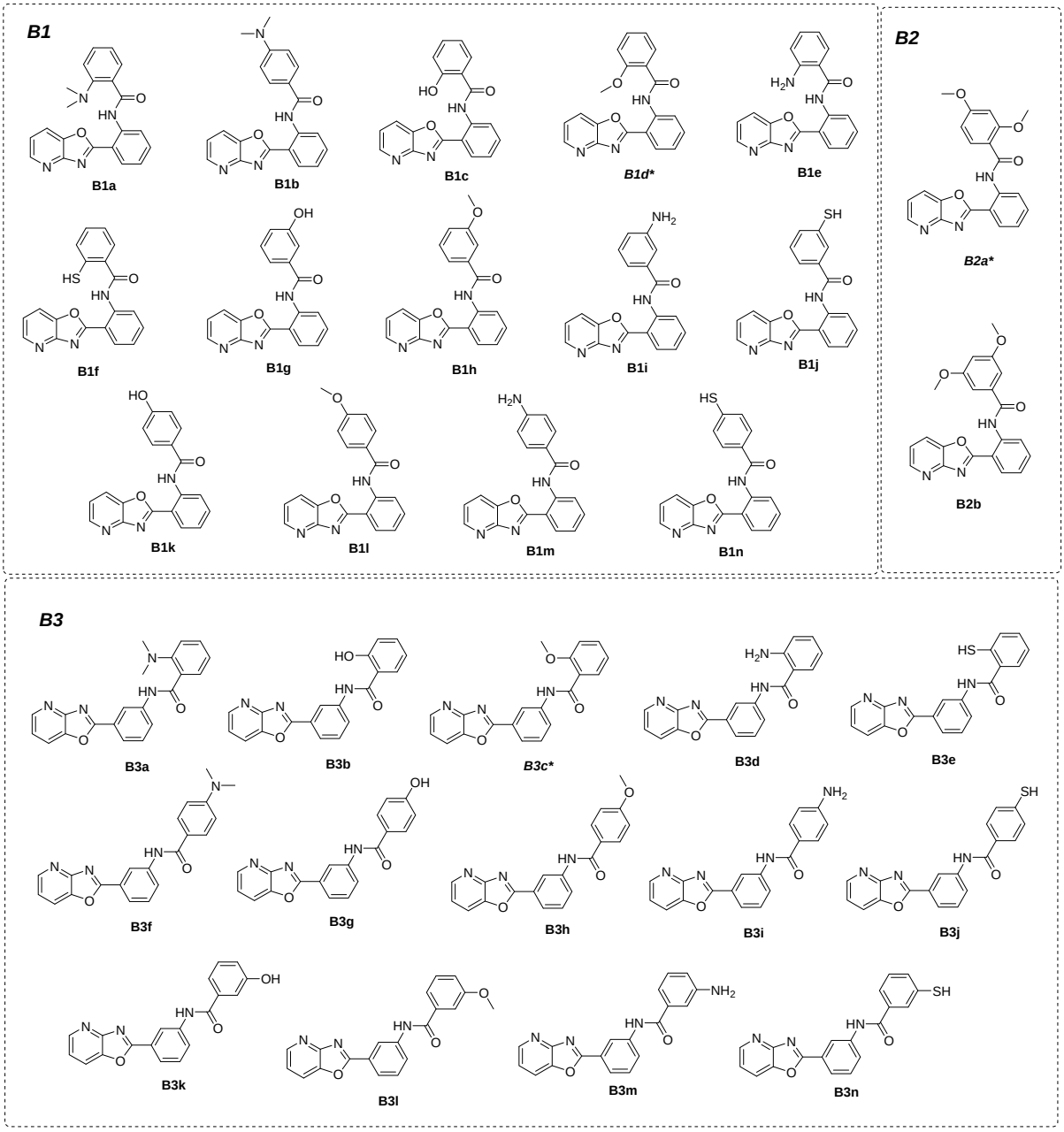
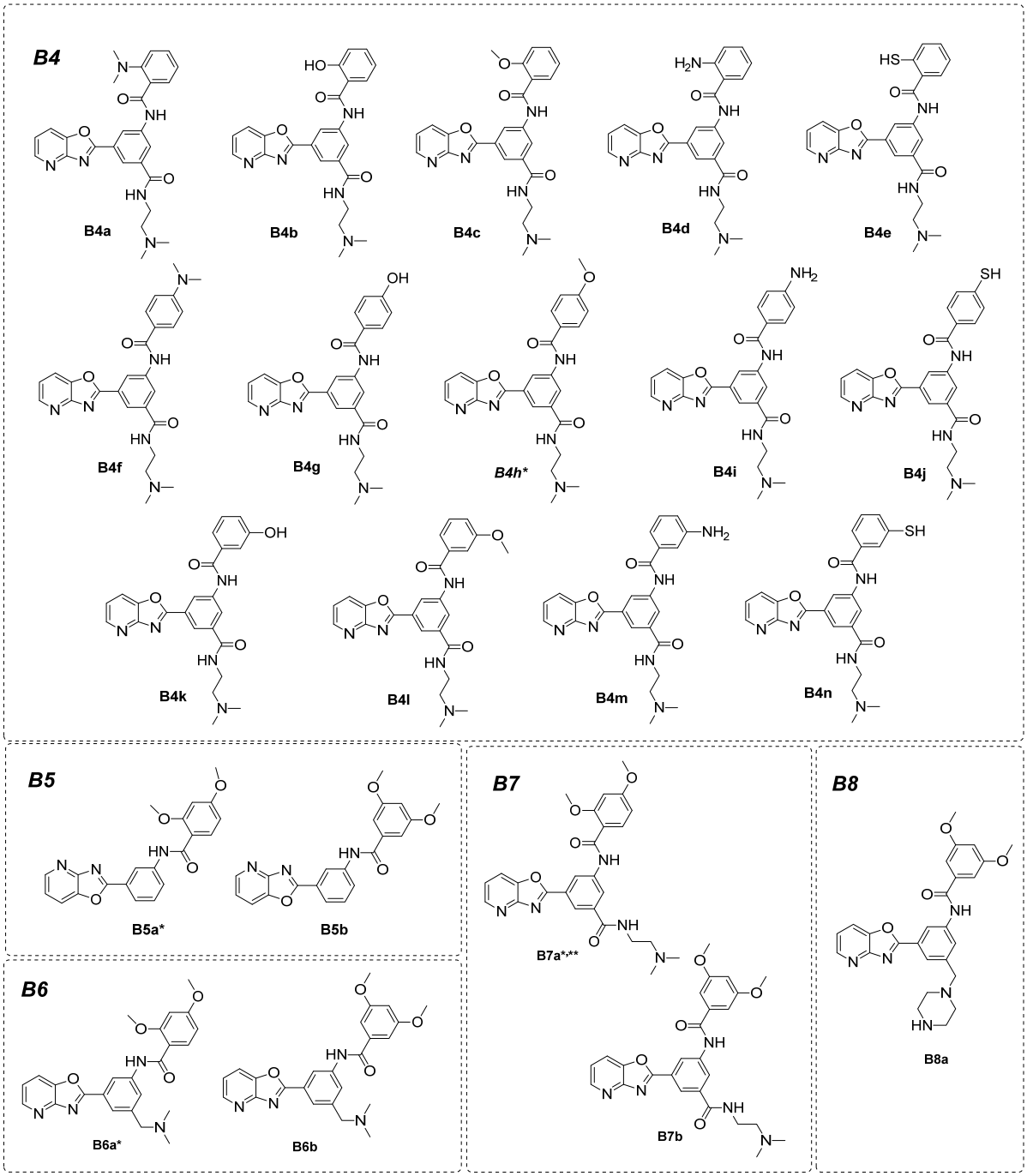


Supplementary Figure 2: Structurally modified compounds **B1-B3** (*The most potent compound in the modified subseries, ** The most potent compound of series B)



Supplementary Figure 2 (cont.): Structurally modified compounds **B4-B8** (*The most potent compound in the modified subseries, ** The most potent compound of series B)

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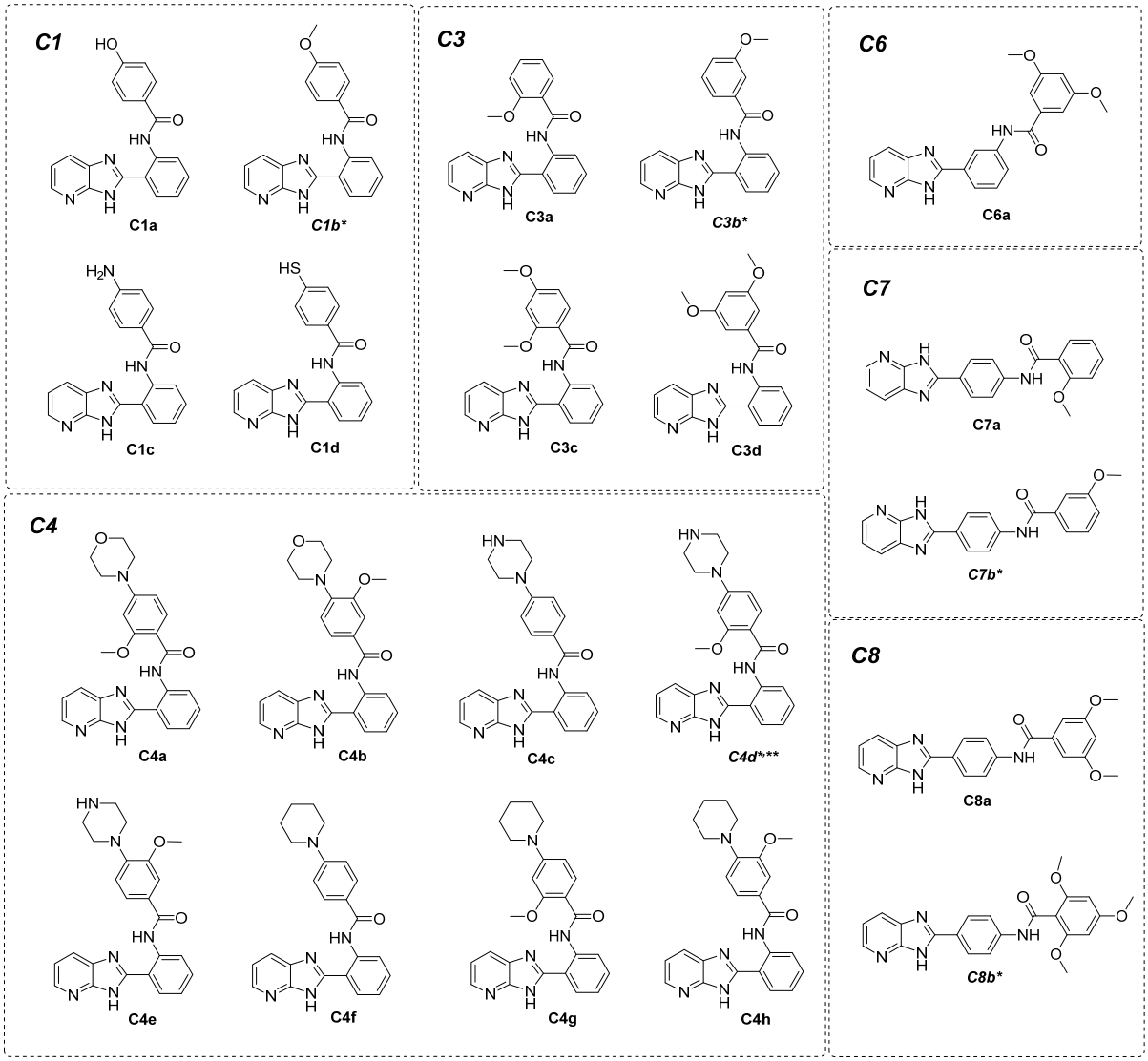

Supplementary Figure 3: Structurally modified compounds **C1-C8** (*The most potent compound in the modified subseries, ** The most potent compound of series C)

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Supplementary Table 4: Descriptors values and predicted $pEC_{1.5}$ of modified SIRT1 activators Scaffold A

Compound	HATS8u	Electronegativity	JGI7	Mor15p	Predicted $pEC_{1.5}$
A1a	0.181	-0.119	0.012	1.229	-2.170
A1b	0.182	-0.118	0.013	1.291	**-1.703***
A1c	0.176	-0.113	0.012	1.205	-2.487
A1d	0.170	-0.119	0.012	1.231	-2.087
A1e	0.183	-0.118	0.011	1.286	-2.891
A1f	0.176	-0.117	0.011	1.457	-2.985
A1g	0.177	-0.113	0.011	1.204	-3.091
A1h	0.169	-0.122	0.011	1.183	-2.447
A2a	0.167	-0.124	0.012	1.322	-1.740
A2b	0.166	-0.124	0.012	1.342	-1.780
A2c	0.171	-0.120	0.012	1.181	-1.994
A2d	0.171	-0.129	0.012	1.367	**-1.548***
A2e	0.181	-0.123	0.011	1.187	-2.507
A2f	0.176	-0.125	0.010	0.971	-2.753
A2g	0.170	-0.117	0.011	1.143	-2.694
A2h	0.171	-0.129	0.011	1.279	-2.082
A3a	0.180	-0.126	0.012	1.122	-1.647
A3b	0.167	-0.126	0.012	1.210	-1.595
A3c	0.174	-0.121	0.012	1.102	-1.896
A3d	0.178	-0.131	0.012	1.207	**-1.387***
A3e	0.165	-0.131	0.011	1.256	-1.850
A3f	0.220	-0.132	0.010	1.649	-3.195
A3g	0.163	-0.125	0.011	1.151	-2.146
A3h	0.157	-0.129	0.011	1.345	-1.936
A4a	0.322	-0.128	0.010	0.976	-4.176
A4b	0.295	-0.121	0.010	0.847	-4.255
A4c	0.310	-0.123	0.010	1.199	-4.511
A4d	0.245	-0.128	0.010	1.060	-3.391
A4e	0.278	-0.127	0.010	1.067	-3.831
A4f	0.261	-0.122	0.009	1.285	-4.687
A4g	0.274	-0.121	0.010	1.087	-4.138
A4h	0.251	-0.132	0.010	1.288	-3.359
A4i	0.280	-0.124	0.010	1.153	-4.087
A4j	0.251	-0.122	0.010	1.317	-3.984
A4k	0.269	-0.122	0.010	1.146	-4.095
A4l	0.308	-0.135	0.014	0.824	**-1.107***
A4m	0.275	-0.118	0.010	1.334	-4.479
A4n	0.323	-0.118	0.010	1.513	-5.154
A4o	0.290	-0.119	0.010	1.245	-4.541
A4p	0.232	-0.126	0.010	1.073	-3.381

***The most potent compounds in subseries, ** The most potent compound of series

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Supplementary Table 4 (cont.): Descriptors values and predicted $pEC_{1.5}$ of modified SIRT1 activators Scaffold A

Compound	HATS8u	Electronegativity	JGI7	Mor15p	Predicted $pEC_{1.5}$
A5a	0.156	-0.134	0.012	1.217	-0.965
A5b	0.152	-0.134	0.012	1.334	-1.009
A5c	0.150	-0.129	0.012	1.226	-1.231
A5d	0.155	-0.138	0.012	1.215	**-0.697*,****
A5e	0.160	-0.132	0.011	1.178	-1.675
A5f	0.159	-0.135	0.010	1.259	-2.111
A5g	0.156	-0.129	0.011	1.261	-1.879
A5h	0.160	-0.117	0.011	1.213	-2.654
A6a	0.203	-0.112	0.011	0.912	**-3.249***
A6b	0.225	-0.111	0.011	1.017	-3.604
A6c	0.241	-0.114	0.011	0.930	-3.533
A6d	0.255	-0.116	0.011	1.108	-3.692
A6e	0.206	-0.111	0.011	1.006	-3.429
A6f	0.279	-0.108	0.011	0.925	-4.338
A6g	0.232	-0.113	0.011	0.945	-3.507
A6h	0.235	-0.117	0.011	1.004	-3.311
A7a	0.176	-0.117	0.011	0.858	-2.635
A7b	0.148	-0.114	0.010	0.952	-3.120
A7c	0.194	-0.122	0.011	0.833	-2.458
A7d	0.170	-0.118	0.011	1.078	-2.622
A7e	0.184	-0.116	0.010	0.931	-3.368
A7f	0.176	-0.111	0.011	1.096	-3.126
A7g	0.182	-0.123	0.010	0.906	-2.910
A7h	0.148	-0.129	0.010	1.045	**-2.282***
A9a	0.219	-0.130	0.009	0.641	-3.325
A9b	0.226	-0.123	0.010	0.818	-3.342
A9c	0.253	-0.123	0.010	0.840	-3.670
A9d	0.277	-0.127	0.010	0.746	-3.579
A9e	0.285	-0.125	0.010	0.627	-3.754
A9f	0.219	-0.121	0.010	0.544	-3.236
A9g	0.241	-0.117	0.010	0.634	-3.761
A9h	0.209	-0.130	0.010	0.795	-2.713
A9i	0.193	-0.138	0.010	0.672	**-1.932***
A10a	0.243	-0.117	0.010	0.779	-3.891
A10b	0.220	-0.116	0.010	0.854	-3.770
A10c	0.236	-0.112	0.010	0.789	-4.108
A10d	0.244	-0.119	0.010	0.800	-3.747
A10e	0.231	-0.113	0.010	0.844	-4.036
A10f	0.205	-0.112	0.010	0.883	-3.829
A10g	0.195	-0.110	0.010	0.713	-3.746

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Supplementary Table 4 (cont.): Descriptors values and predicted $pEC_{1.5}$ of modified SIRT1 activators Scaffold A

Compound	HATS8u	Electronegativity	JGI7	Mor15p	Predicted $pEC_{1.5}$
A10h	0.188	-0.118	0.010	1.047	-3.363
A10i	0.236	-0.121	0.010	0.731	-3.532
A10j	0.269	-0.112	0.010	0.749	-4.479
A10k	0.276	-0.113	0.010	0.761	-4.448
A10l	0.295	-0.114	0.010	0.843	-4.649
A10m	0.355	-0.123	0.009	0.812	-5.309
A10n	0.249	-0.111	0.011	0.659	-3.625
A10o	0.221	-0.109	0.010	0.736	-4.109
A10p	0.240	-0.105	0.011	0.610	-3.893
A10q	0.249	-0.119	0.011	0.501	**-3.054***
A10r	0.267	-0.117	0.011	0.759	-3.506
A10s	0.248	-0.108	0.010	0.755	-4.454
A10t	0.277	-0.110	0.011	0.715	-4.044
A10u	0.293	-0.117	0.011	0.825	-3.835
A10v	0.228	-0.115	0.009	0.697	-4.413
A10w	0.284	-0.116	0.011	0.775	-3.817
A10x	0.276	-0.108	0.010	0.649	-4.728
A10y	0.293	-0.107	0.011	0.622	-4.325
A10z	0.300	-0.116	0.011	0.654	-3.877
A11a	0.195	-0.114	0.011	1.404	**-3.353***
A11b	0.266	-0.112	0.010	1.144	-4.694
A11c	0.263	-0.107	0.011	1.041	-4.290
A11d	0.247	-0.114	0.011	1.341	-3.890
A12a	0.236	-0.114	0.011	1.094	-3.582
A12b	0.222	-0.109	0.011	1.051	-3.702
A12c	0.234	-0.116	0.011	1.167	**-3.473***
A13a	0.259	-0.113	0.010	0.652	-4.200
A13b	0.220	-0.118	0.010	0.663	-3.491
A13c	0.223	-0.119	0.010	0.496	**-3.361***

***The most potent compounds in subseries, ** The most potent compound of series

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Supplementary Table 5: Descriptors values and predicted $pEC_{1.5}$ of modified SIRT1 activators Scaffold B

Compound	Mor22e	F10[C-O]	P1e	Predicted $pEC_{1.5}$
B1a	-0.043	0	0.700	-3.812
B1b	0.042	0	0.672	-3.831
B1c	-0.039	1	0.611	-3.533
B1d	-0.407	1	0.566	**-3.101***
B1e	-0.104	0	0.620	-3.588
B1f	0.130	0	0.600	-3.761
B1g	0.086	2	0.620	-3.571
B1h	-0.138	3	0.689	-3.415
B1i	0.089	0	0.558	-3.635
B1j	0.226	0	0.537	-3.716
B1k	0.165	1	0.574	-3.642
B1l	-0.138	1	0.683	-3.594
B1m	-0.027	0	0.605	-3.627
B1n	-0.052	0	0.594	-3.581
B2a	-0.640	2	0.591	**-2.845***
B2b	0.183	6	0.603	-3.242
B3a	0.193	5	0.807	-3.776
B3b	0.183	5	0.864	-3.886
B3c	0.055	6	0.822	**-3.585***
B3d	0.007	3	0.867	-3.923
B3e	0.139	3	0.821	-3.947
B3f	0.073	3	0.856	-3.960
B3g	0.205	5	0.852	-3.881
B3h	-0.064	5	0.875	-3.683
B3i	0.084	3	0.867	-3.993
B3j	0.184	3	0.861	-4.072
B3k	0.279	3	0.849	-4.134
B3l	-0.081	3	0.878	-3.865
B3m	0.188	3	0.872	-4.099
B3n	0.079	3	0.871	-3.997

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Supplementary Table 5 (cont.): Descriptors values and predicted $pEC_{1.5}$ of modified SIRT1 activators Scaffold B

Compound	Mor22e	F10[C-O]	P1e	Predicted $pEC_{1.5}$
B4a	-0.043	10	0.543	-2.526
B4b	-0.439	9	0.555	-2.284
B4c	-0.187	11	0.677	-2.581
B4d	-0.121	6	0.648	-3.058
B4e	-0.084	6	0.601	-2.993
B4f	-0.477	6	0.651	-2.738
B4g	-0.154	9	0.545	-2.524
B4h	-0.468	9	0.552	**-2.251***
B4i	-0.174	6	0.568	-2.841
B4j	-0.049	6	0.524	-2.863
B4k	-0.107	6	0.587	-2.943
B4l	-0.239	6	0.568	-2.782
B4m	0.172	6	0.708	-3.453
B4n	-0.268	6	0.591	-2.803
B5a	-0.579	8	0.863	**-2.899***
B5b	-0.162	3	0.831	-3.692
B6a	-0.624	11	0.698	**-2.224***
B6b	-0.579	3	0.709	-3.053
B7a	-0.786	14	0.603	**-1.589*,****
B7b	-0.869	6	0.523	-2.110
B8a	-0.275	11	0.572	-2.279

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Supplementary Table 6: Descriptors values and predicted $pEC_{1.5}$ of modified SIRT1 activators Scaffold C

Compound	RDF090u	BEHp2	R6m+	E2u	Predicted $pEC_{1.5}$
C1a	12.513	3.805	0.019	0.433	-2.410
C1b	13.246	3.808	0.032	0.424	**-2.167***
C1c	14.867	3.812	0.016	0.435	-2.465
C1d	11.672	3.830	0.038	0.431	-2.584
C3a	8.376	3.809	0.015	0.489	-3.085
C3b	17.390	3.809	0.016	0.440	**-2.305***
C3c	15.710	3.817	0.015	0.509	-2.944
C3d	17.005	3.816	0.019	0.501	-2.748
C4a	23.539	3.837	0.016	0.373	-2.086
C4b	20.759	3.837	0.015	0.378	-2.280
C4c	20.679	3.831	0.014	0.371	-2.154
C4d	28.043	3.838	0.013	0.380	**-1.948*,****
C4e	19.962	3.838	0.016	0.385	-2.364
C4f	18.278	3.834	0.014	0.347	-2.200
C4g	19.710	3.841	0.016	0.452	-2.812
C4h	29.155	3.841	0.014	0.454	-2.345
C6a	10.517	3.818	0.018	0.448	-2.848
C7a	12.476	3.813	0.012	0.500	-2.687
C7b	8.909	3.812	0.017	0.474	**-2.470***
C8a	8.474	3.819	0.024	0.414	-3.044
C8b	10.973	3.828	0.013	0.341	**-2.992***

***The most potent compounds in subseries, ** The most potent compound of series