

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

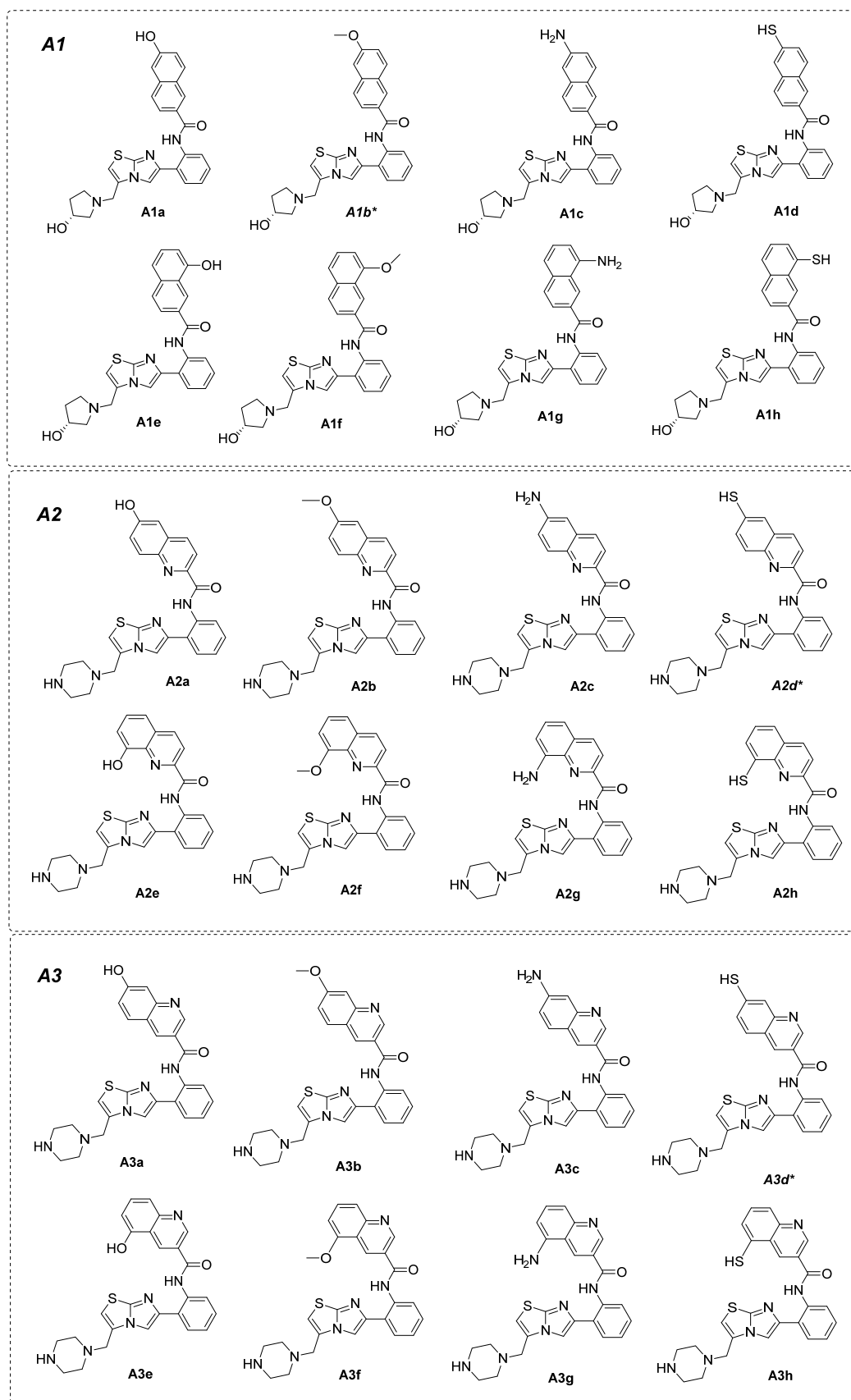
| Compound | HATS8u | Electronegativity | JGI7 | Mor15p |
|----------|--------|-------------------|-------|--------|
| A1 | 0.190 | -0.122 | 0.011 | 1.148 |
| A2 | 0.176 | -0.127 | 0.010 | 1.107 |
| A3 | 0.260 | -0.139 | 0.010 | 1.170 |
| A4 | 0.284 | -0.128 | 0.009 | 1.126 |
| A5 | 0.165 | -0.136 | 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 |

Supplementary Table 2: Descriptors values of SIRT1 activators Scaffold B

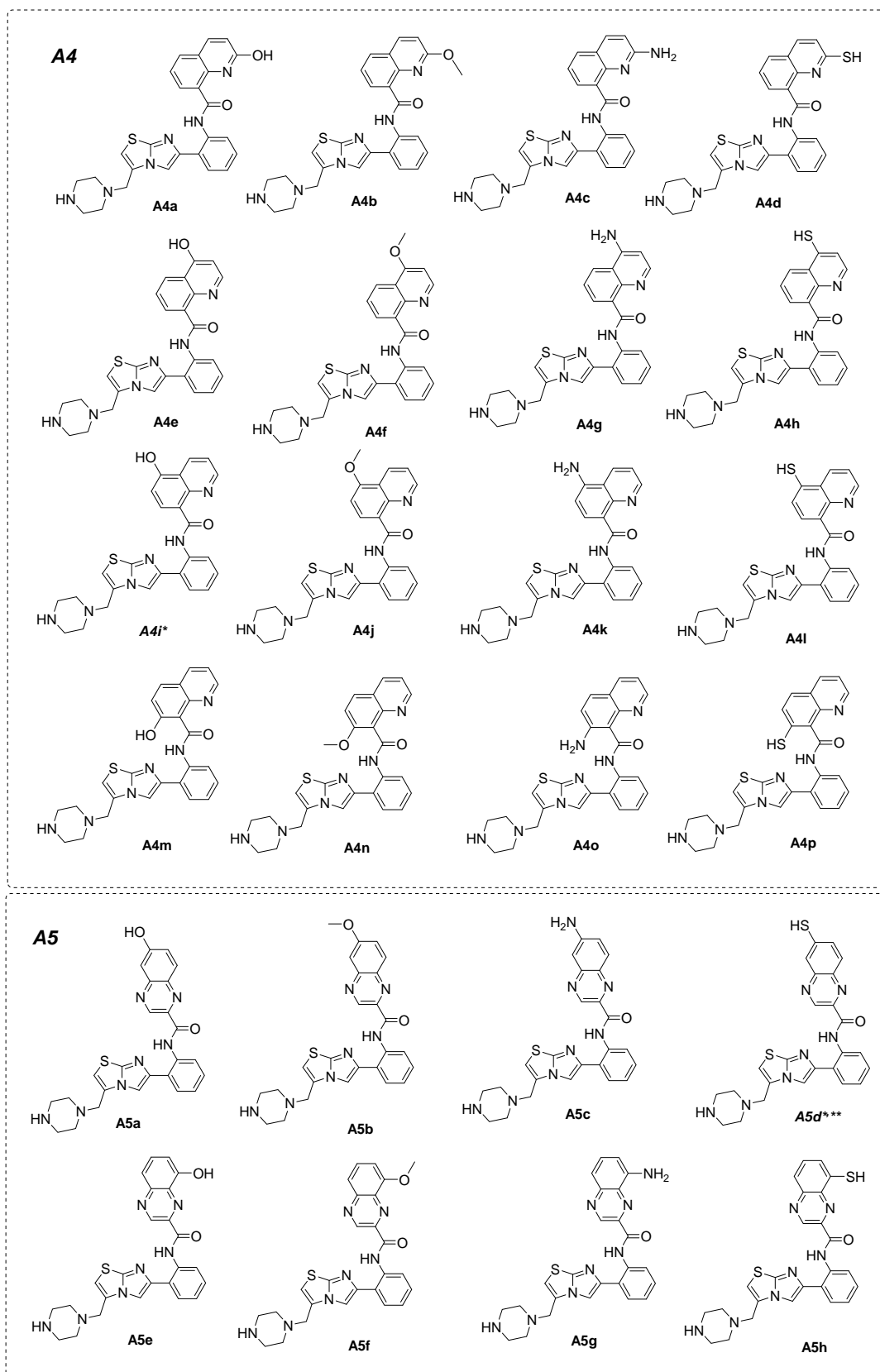
| Compound | Mor22e | F10[C-O] | P1e |
|----------|--------|----------|-------|
| B1 | 0.197 | 2 | 0.565 |
| B2 | -0.191 | 4 | 0.618 |
| B3 | 0.325 | 3 | 0.874 |
| B4 | 0.269 | 6 | 0.529 |
| B5 | 0.033 | 5 | 0.882 |
| B6 | -0.320 | 6 | 0.680 |
| B7 | -0.009 | 9 | 0.573 |
| B8 | 0.224 | 6 | 0.689 |
|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

Supplementary Table 3: Descriptors values of SIRT1 activators Scaffold C

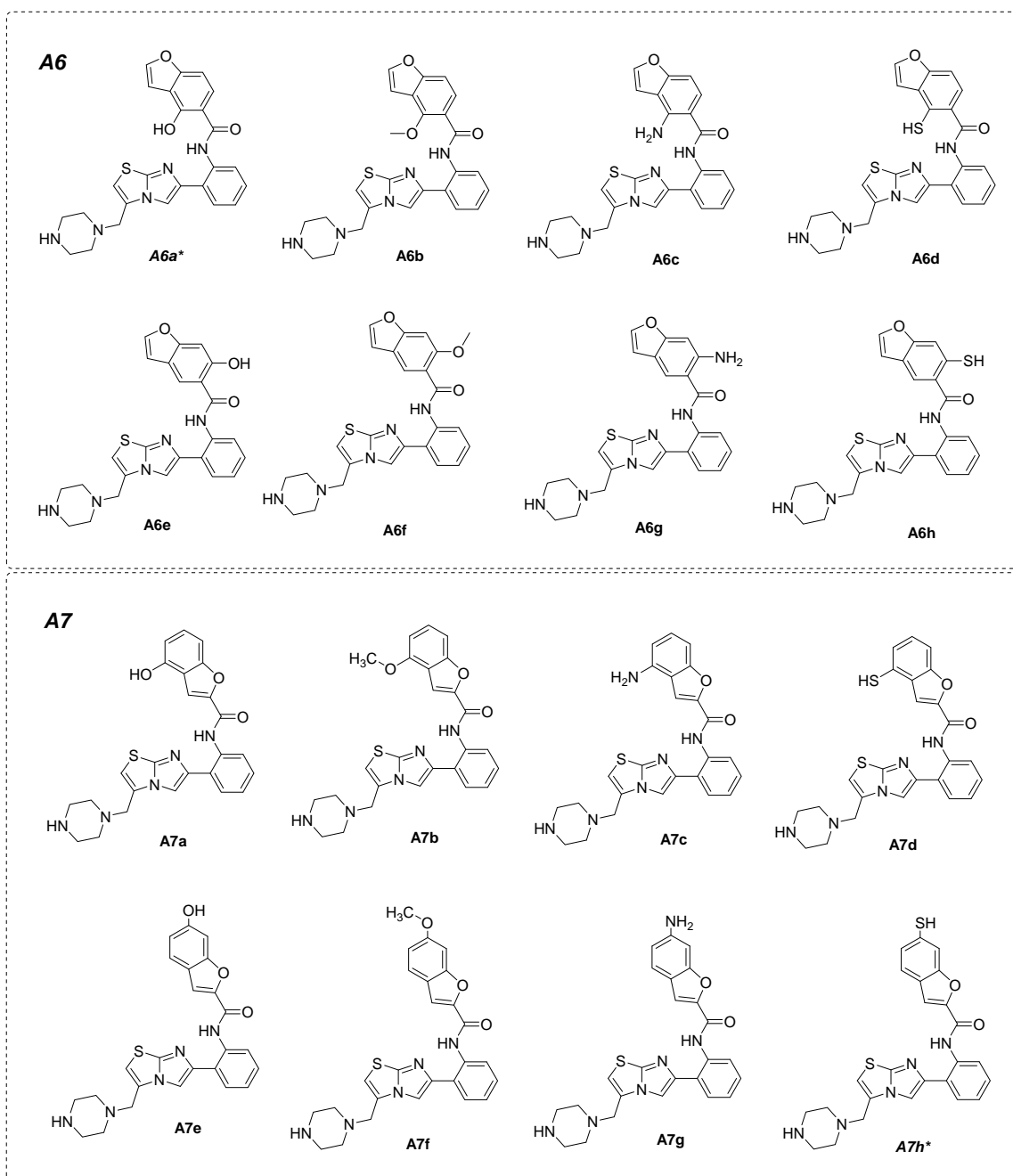
| Compound | RDF090m | BEHp2 | R6m+ | E2u |
|----------|---------|-------|-------|-------|
| C1 | 8.004 | 3.822 | 0.014 | 0.413 |
| C2 | 4.688 | 3.836 | 0.014 | 0.452 |
| C3 | 8.575 | 3.816 | 0.016 | 0.406 |
| C4 | 9.007 | 3.830 | 0.014 | 0.397 |
| C5 | 6.355 | 3.818 | 0.011 | 0.436 |
| C6 | 7.724 |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



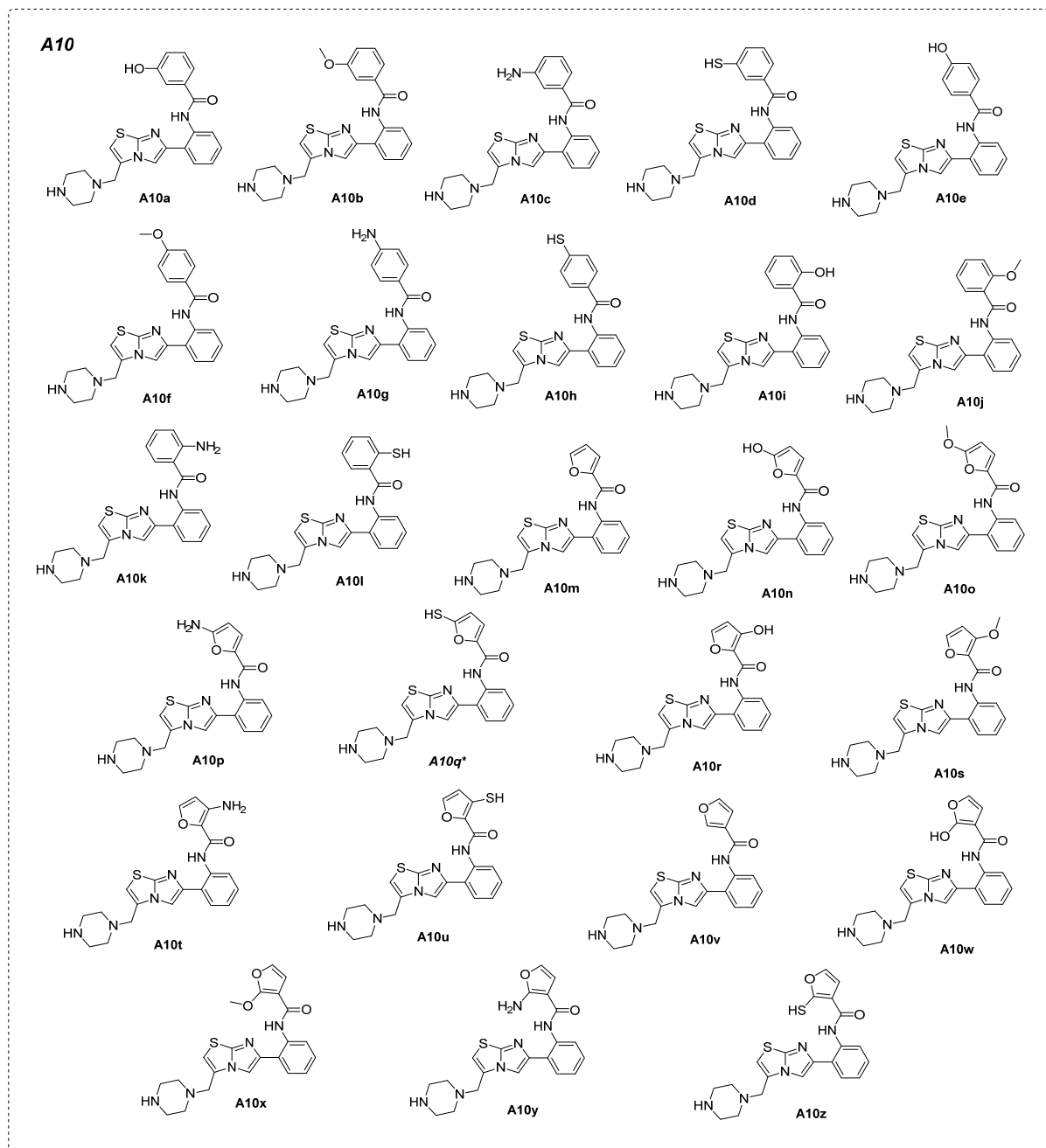
Supplementary Figure 1: Structurally modified compounds **A1-A3** (*The most potent compound in the modified subseries, ** The most potent compound of series A)



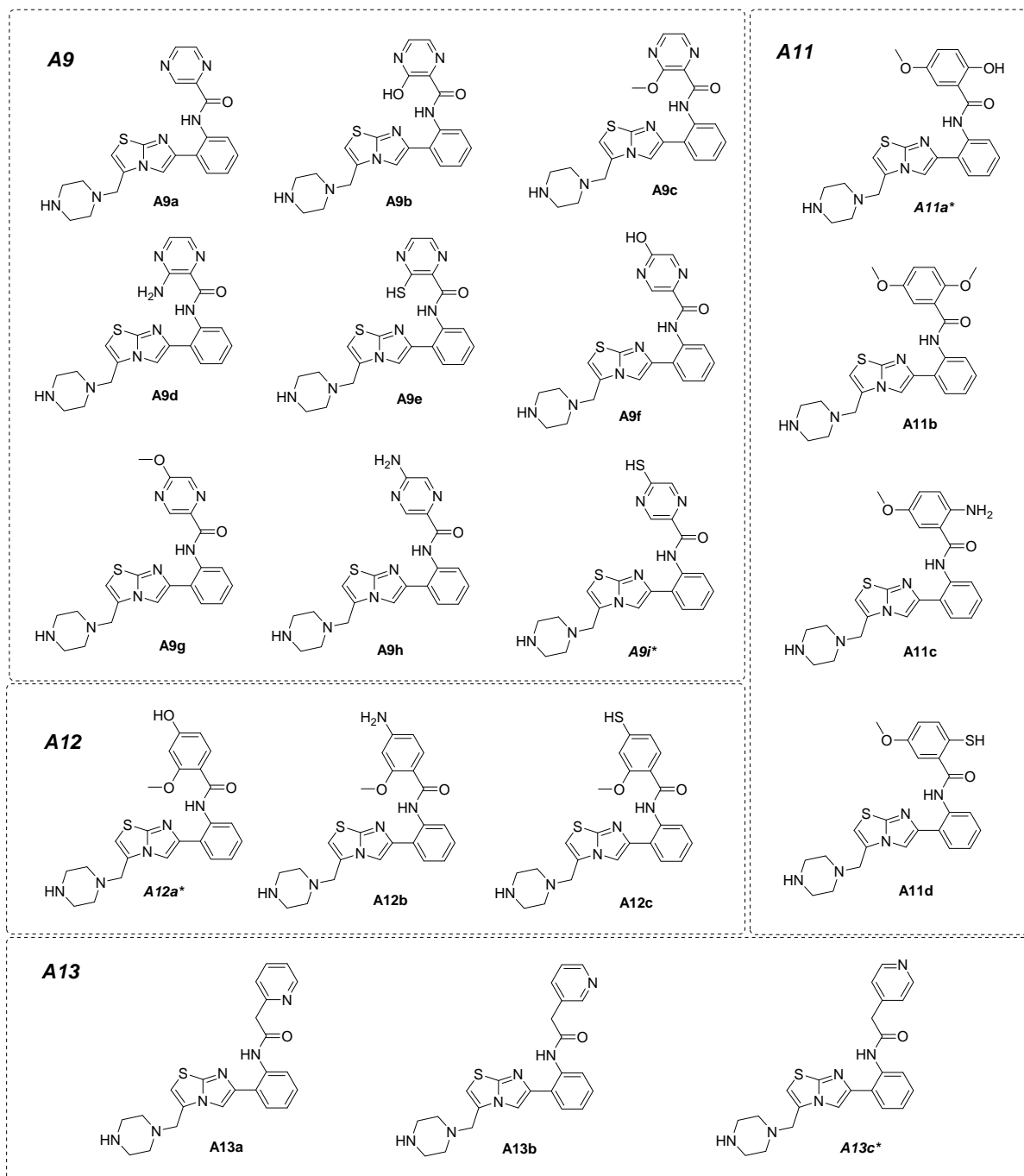
Supplementary Figure S1 (cont.): Structurally modified compounds **A4-A5** (*The most potent compound in the modified subseries, ** The most potent compound of series A)



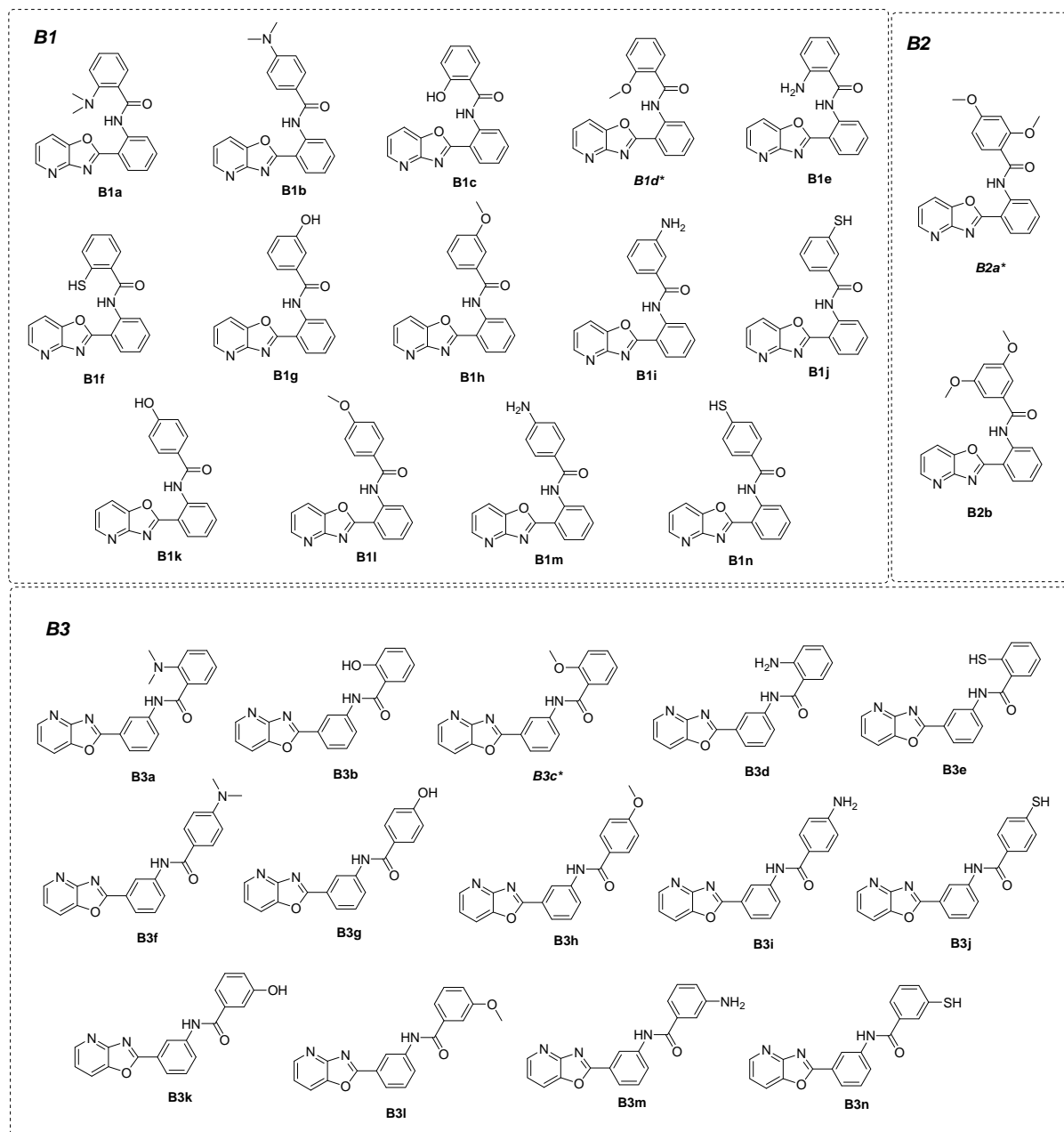
Supplementary Figure 1 (cont.): Structurally modified compounds **A6-A7** (*The most potent compound in the modified subseries, ** The most potent compound of series A)



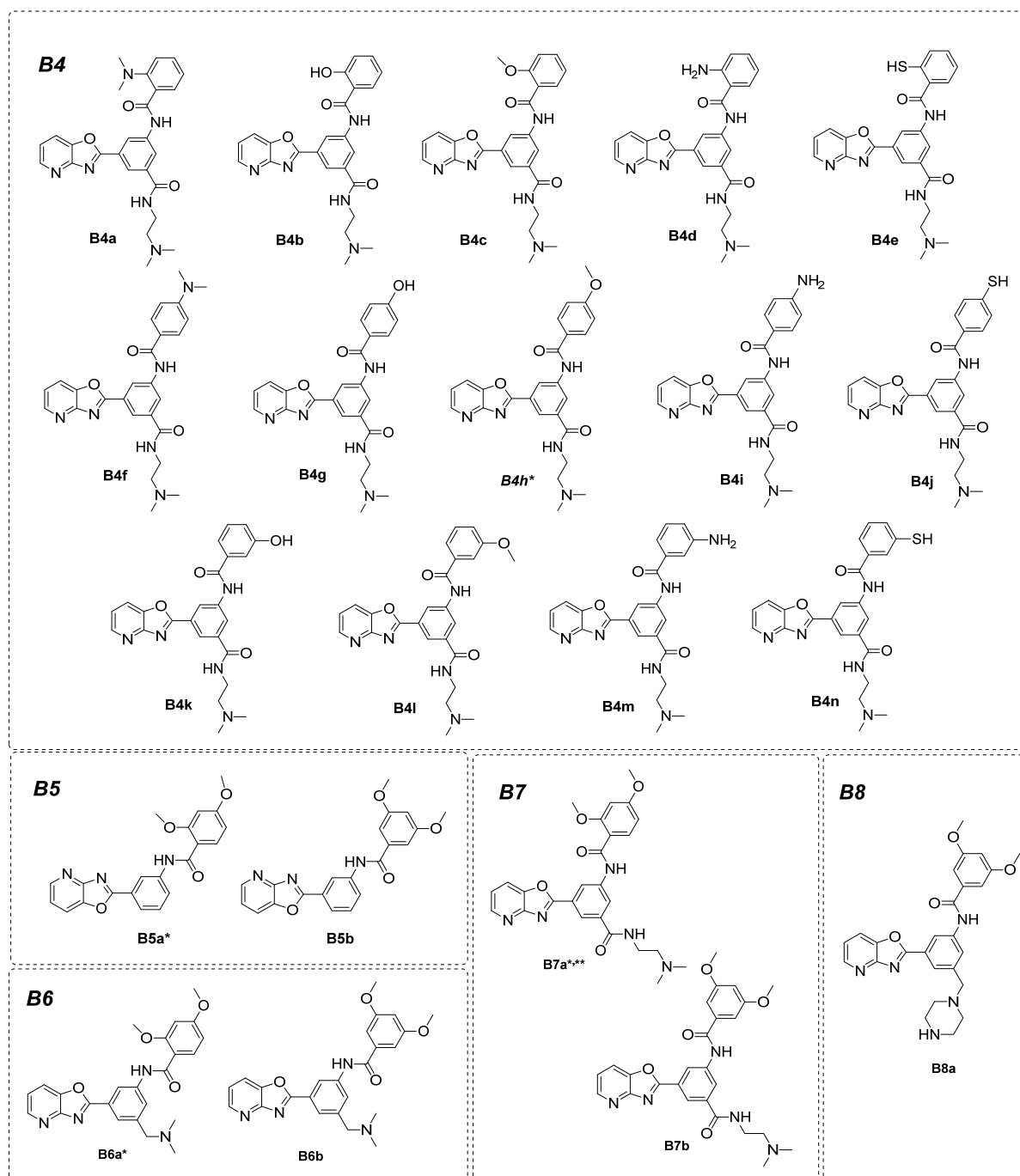
Supplementary Figure 1 (cont.): Structurally modified compounds **A10** (*The most potent compound in the modified subseries, ** The most potent compound of series A)



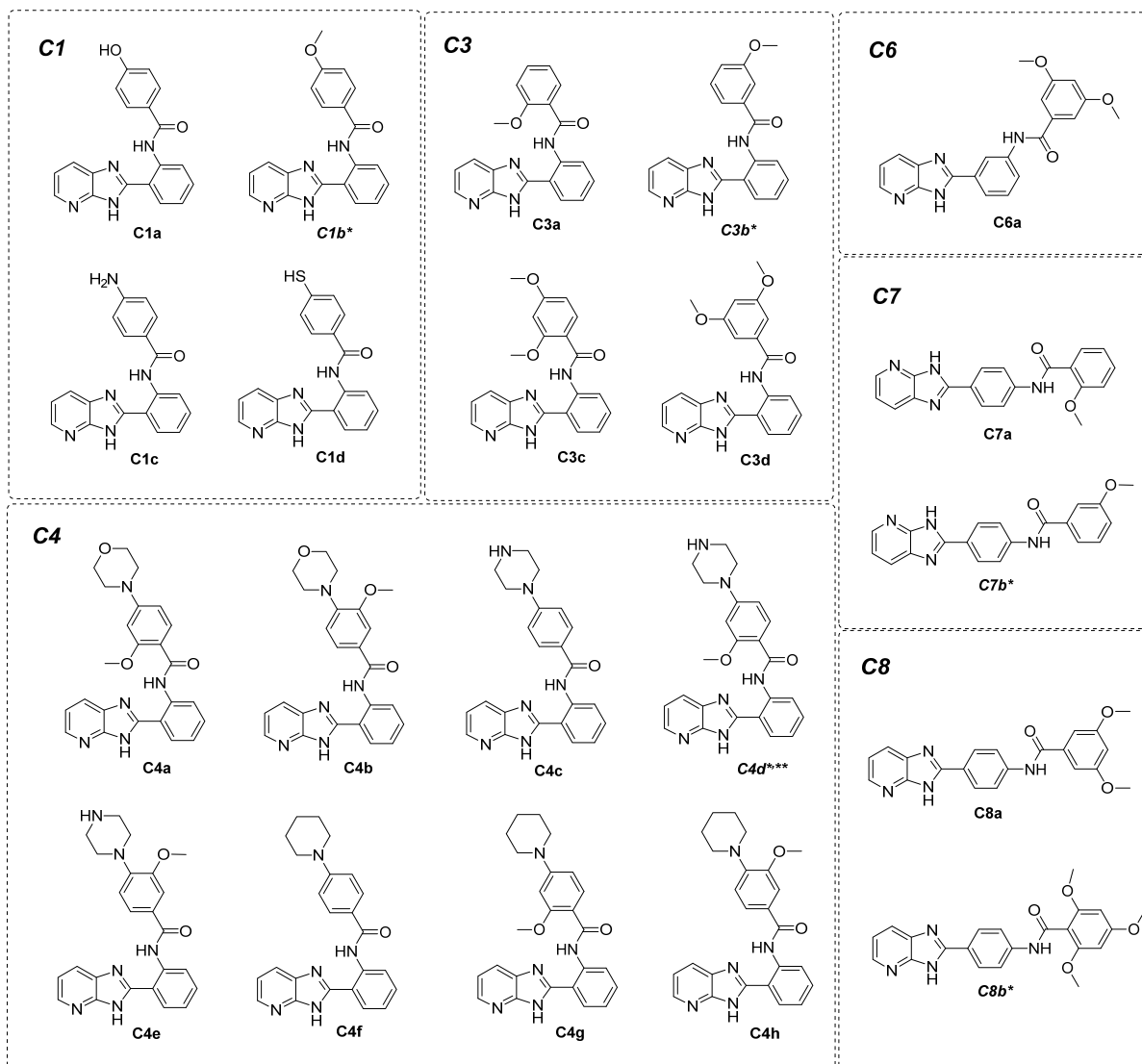
Supplementary Figure 1 (cont.): Structurally modified compounds **A9** and **A11-A13** (*The most potent compound in the modified subseries, ** The most potent compound of series A)



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)



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

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

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 |

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

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

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 |

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

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 |

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

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