Design, Synthesis, and Biological Evaluation of Sirtinol Analogues as Class III Histone/Protein Deacetylase (Sirtuin) Inhibitors

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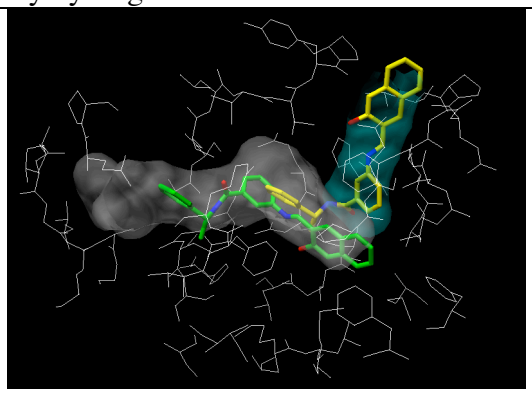
Supporting Information

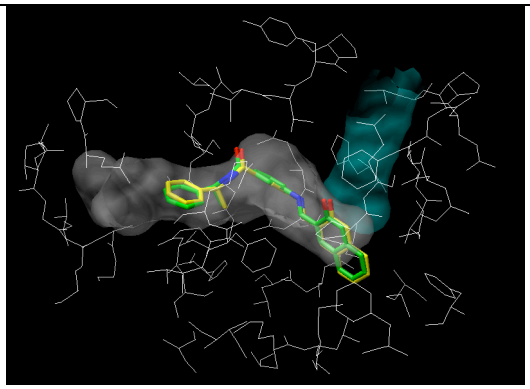
Binding Mode Analysis of 7 and 8

Previous docking studies[53] revealed that (*R*)- and (*S*)-sirtinol (**9** and **10**), while mimicking the backbone of the p53, could act as Ac-K binding site competitors by blocking the entrance channel of the acetylated lysine. Differently, in the present paper *meta*- and *para*-sirtinol (**7** and **8**) are showed to bind the Sir2-Af2 enzyme in a more efficient fashion, by fully occupying either the Ac-K or the NAD^+ substrate binding sites (Figure A).

Figure A. (*R*)-7 (1), (*S*)-7 (2), (*R*)-8 (3), and (*S*)-8 (4) docked conformations. In yellow colored carbon atoms it is displayed the inhibitor binding mode obtained in the absence of both the NAD^+ and Ac-K substrates. In green colored carbon atoms is reported the inhibitor docked conformation in the presence of only the p53 substrate. For interpretation purposes the NAD^+ and Ac-K volumes are displayed in white and cyan, respectively. 5 Å core of the Sir2-Af2 (white wire) is also displayed. For the sake of clarity hydrogen atoms are omitted

1





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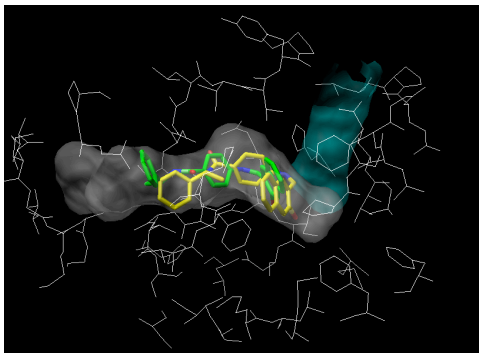

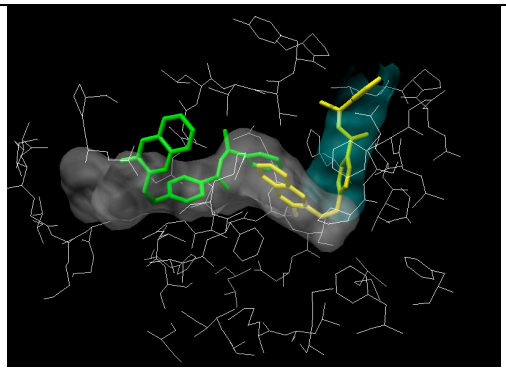

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Analyses

compd	MW	calculated, %			found, %		
		C	H	N	C	H	N
1	394.47	79.17	5.62	7.10	79.29	5.68	6.85
2	378.47	82.51	5.86	7.40	82.19	5.81	7.72
3	319.36	75.22	5.37	4.39	75.44	5.41	4.18
4	291.31	74.22	4.50	4.81	73.95	4.46	5.08
5	290.32	74.47	4.86	9.65	74.61	4.90	9.52
6	272.31	79.40	4.44	10.29	79.22	4.38	10.47
7	394.47	79.17	5.62	7.10	79.32	5.70	6.88
8	394.47	79.17	5.62	7.10	78.85	5.52	7.44
9	394.47	79.17	5.62	7.10	79.36	5.64	6.91
10	394.47	79.17	5.62	7.10	78.95	5.54	7.28