Supporting Information

Phosphonosulfonates Are Potent, Selective Inhibitors of Dehydrosqualene Synthase and Staphyloxanthin Biosynthesis in *Staphylococcus aureus*

By

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Table S1. Top ten "enzyme plus 2-descriptor" combinations with their coefficients and relative contributions for the *S. aureus* cell pIC_{50} predictions.

S. aureus (CrtM) pIC_{50} (cell) =	R^2	Relative Importance of pIC_{50}(enzyme)	Relative Importance of Descriptor B[a]	Relative Importance of Descriptor C[a]
1.07935 +1.07168 * crtm_new +0.01232 * PEOE_VSA-1 +0.38370 * E_stb	0.71715	1.000000	0.498511	0.929362
-0.51520 +0.93203 * crtm_new +0.01378 * vsa_hyd +0.27786 * E_stb	0.70532	1.000000	0.489720	0.773848
0.88476 +0.86354 * crtm_new -0.46499 * logS +0.24843 * E_stb	0.70334	1.000000	0.533638	0.746758
-1.83200 +0.93216 * crtm_new +0.01654 * PEOE_VSA_NEG +0.26955 * E_stb	0.70285	1.000000	0.486128	0.750599
1.32345 +0.89953 * crtm_new +0.52931 * logP(o/w) +0.24326 * E_stb	0.70124	1.000000	0.509204	0.701953
0.66970 +0.94974 * crtm_new +0.00704 * E_sol +0.01894 * PEOE_VSA_NEG	0.69410	1.000000	0.734455	0.546206
-2.44204 +0.91088 * crtm_new +0.02328 * PEOE_VSA_NEG -0.24100 * E_str	0.69302	1.000000	0.700314	0.762682
-2.28190 +0.90675 * crtm_new +0.00778 * ASA +0.25558 * E_stb	0.69268	1.000000	0.484585	0.731641
-0.53109 +0.90728 * crtm_new +0.01936 * vsa_hyd -0.24937 * E_str	0.69117	1.000000	0.706822	0.792306
-0.50061 +1.01675 * crtm_new +0.34050 * chi1_C +0.29099 * E_stb	0.68972	1.000000	0.429537	0.742886

[a] The cell activity data (pED_{50}) was fitted to the CrtM inhibition data using the following "enzyme plus 2-descriptor" equation:

$$pED_{50}\ (cell) = a \bullet pIC_{50}\ (CrtM) + b \bullet B + c \bullet C + d$$

where B, C are all non-Boolean (non-0 or non-1) descriptors computed in MOE. There were 117 such descriptors and all pairwise combinations were used to predict pED_{50} (cell). The 10 combinations having the highest R^2 value are shown in the Table. The highest training set R^2 value was $R^2 = 0.72$ which yielded a $R^2 = 0.62$ for a leave-2-out test set calculation. Using scrambled cell pIC50 data there was essentially no predictivity, $R^2 = 0.10$.

Table S2. Elemental analysis results of compounds.

compound	required C	required H	required N	found C	found H	found N
1	30.57	2.73		30.5	2.53	
(R)-**1**	22.63	1.9		22.49	2.16	
(S)-**1**	26.08	2.6		26.07	2.56	
3	38.35	3.6		38.357	3.55	
4	27.31	2.97		27.14	3.26	
5	35.22	3.33		35.45	3.39	
6	27.55	2.68		27.79	2.42	
7	34.28	3.05		34.28	3.21	
8	41.68	4.56		41.7	4.23	
9	24.57	2.06		24.8	1.98	
10	35.44	3.33		35.4	3.49	
11	22.31	1.98		22.07	1.92	
12	27.49	2.77		27.23	2.71	
13	38.07	4.2		38.2	4.14	
14	37.05	3.5		36.9	3.5	
15	36.71	3.28		36.96	3.52	
16	29.76	3.12	2.17	29.99	3.1	2.24
17	37.37	3.69		37.16	3.82	
18	38.39	3.22		38.12	3.56	
19	40.92	4.16	2.51	41.17	4.36	2.85
20	28.15	2.95		28.05	2.63	
21	34.09	3.58		34.2	3.36	
22	35.91	2.66		35.87	2.95	
24	37.2	3.64		37.281	3.669	
25	45.67	5.14		45.63	4.93	
26	45.38	3.97		45.55	4.06	
27	18.36	2.12		18.3	1.91	
28	38.9	3.41		38.82	3.38	
29	28.88	2.54		29.08	2.74	
30	33.77	3.67		33.96	3.71	
31	31.58	3.59		31.686	3.415	
32	37.49	3.5		37.5	3.27	
33	34.65	2.91		34.79	2.89	
34	29.45	2.74		29.85	2.91	
35	32.88	2.76		32.89	2.85	
36	32.29	3.35		32.38	3.51	

Figure S1. Representative dose-response curves of the staphyloxanthin inhibition in *S. aureus*.