Comparison of benzil and trifluoromethyl ketone (TFK)-mediated carboxylesterase inhibition using classical and 3-D quantitative structure activity relationship analysis

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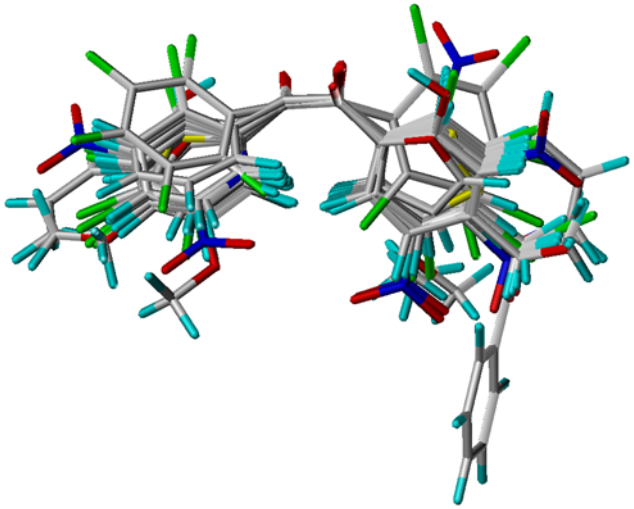

Figure S1. Superposition of all 32 benzil-analogs used to generate the CoMFA models.

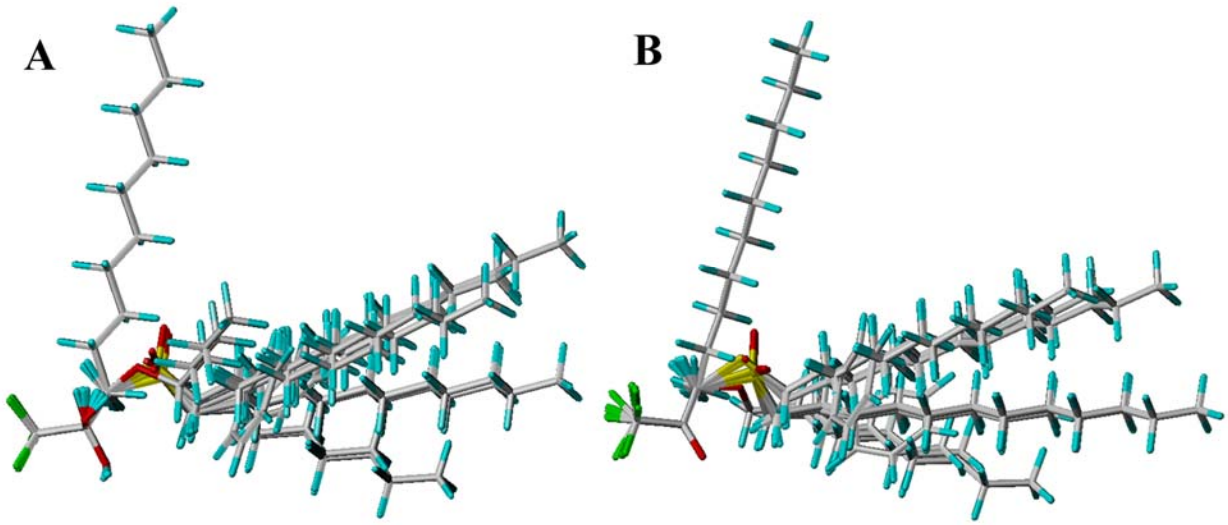

Figure S2. Superposition of TFKs in *gem*-diol (A) and ketone (B) geometries with all 17 TFK compounds.

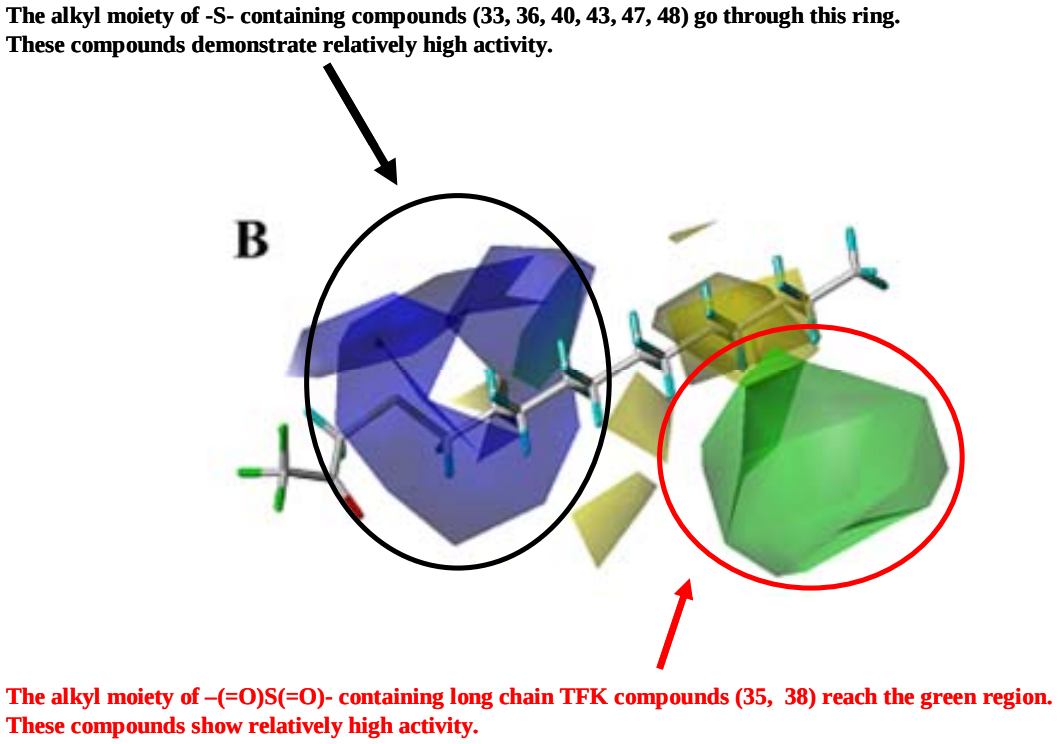

Figure S3. CoMFA map for the hiCE model with the TFK inhibitor in the ketone form. Specific areas of enhanced activity are described on the map.

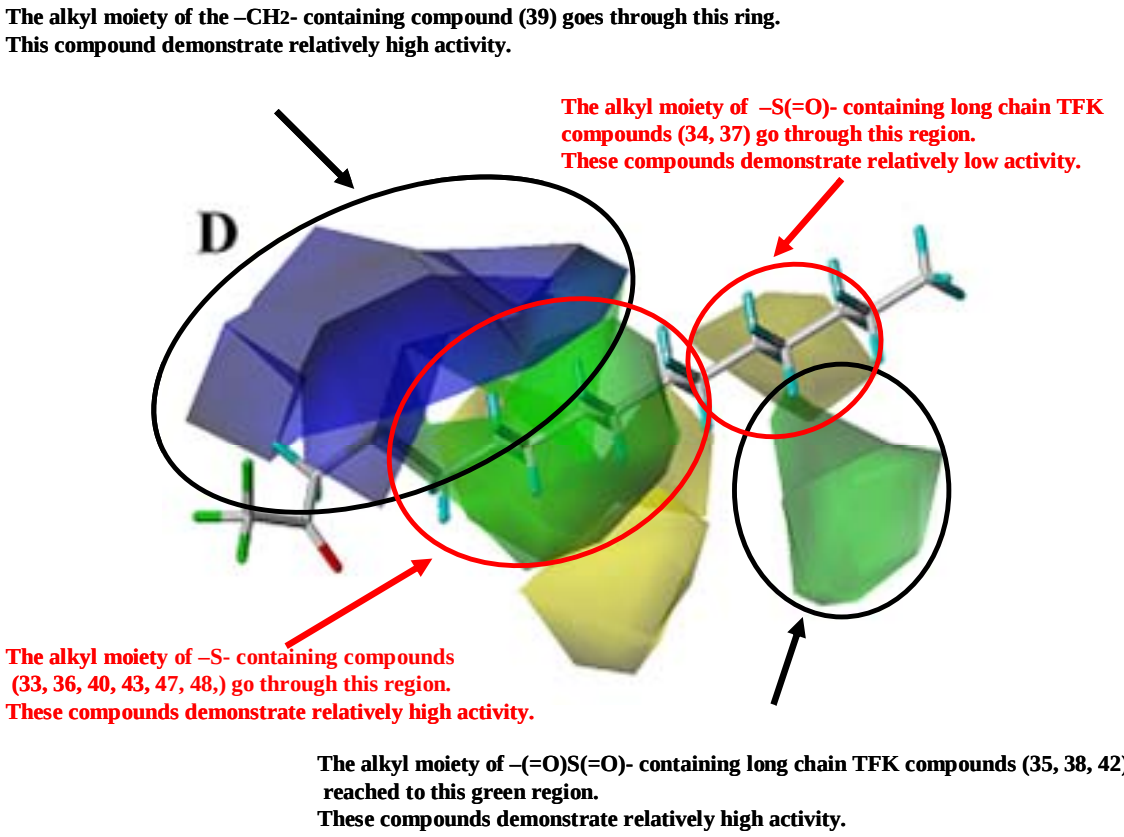

Figure S4. CoMFA map for the hCE1 model with the TFK inhibitor in the ketone form. Specific areas of enhanced activity are described on the map.

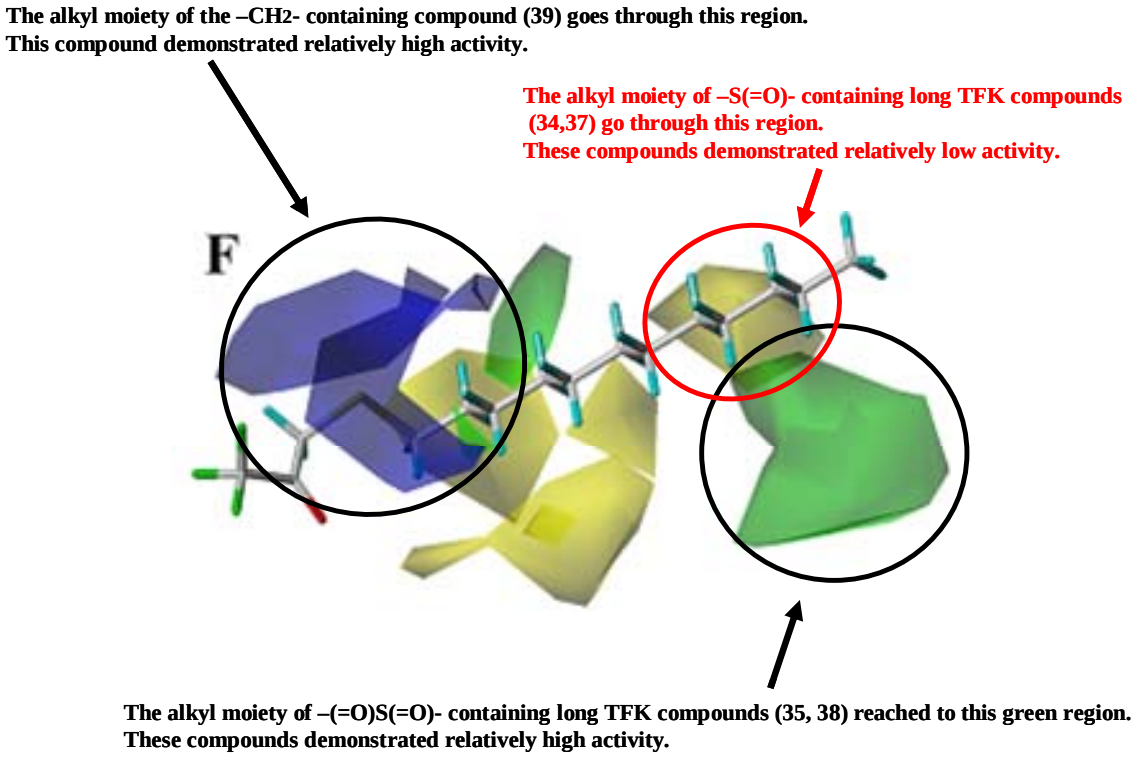

Figure S5. CoMFA map for the rCE model with the TFK inhibitor in the ketone form. Specific areas of enhanced activity are described on the map.

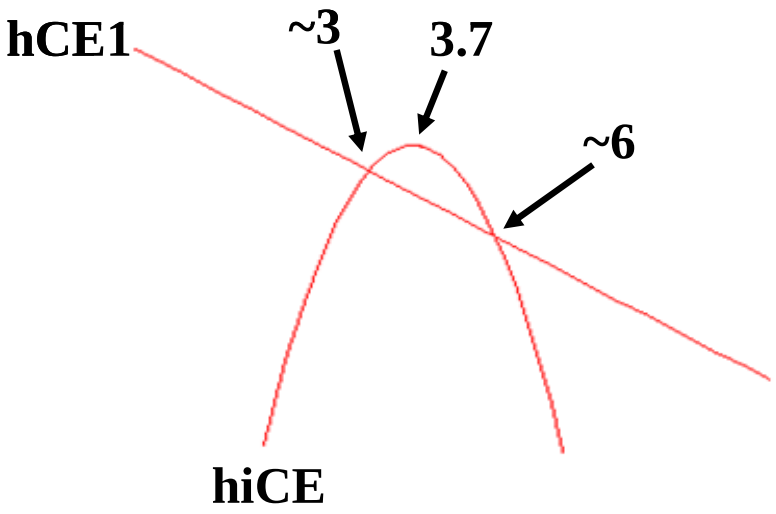

Figure S6. Graphs of the classical QSAR equations for the benzil-analogs displaying the volume dependence of hCE1 and hiCE (Eq. 1 and Eq. 2). To make the graphs, a distinct assumption was made that the log P term is constant (however, it ranges from -3.2 to 7.2). Accordingly, each equation was changed to the corresponding quadric equation using this hypothesis and graphed using GCalcPlus (ver. 2.03), with the resulting equations shown below:

$pK_i = -1.79\ vol^2 + 13.2\ vol + 17.0$ **(Eq. 1')**

$pK_i = -0.883\ vol + c$ (**Eq. 2'**)

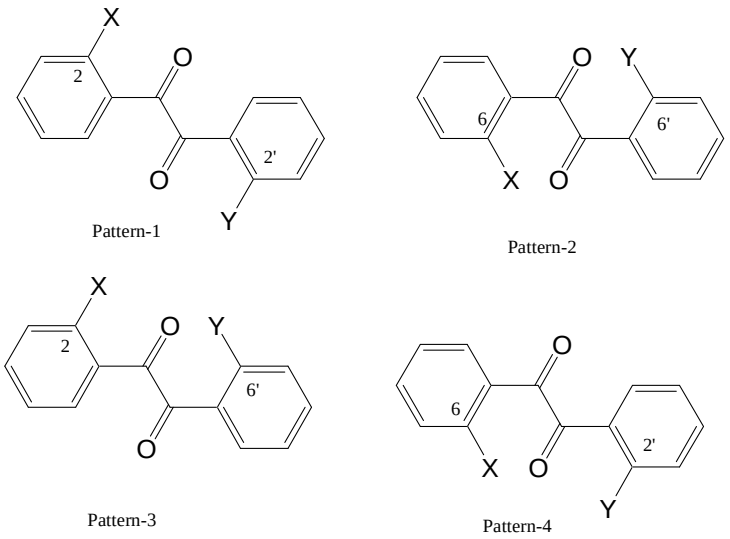

Figure S7. The four conformer patterns tested to determine the most stable conformation for construction of the superposition for the CoMFA model. Pattern 1 was selected as the template for model construction, even though the difference between Pattern 1 and 3 was only 4 kcal/mol with respect to the enthalpy of formation (ΔH).

Table S1. Experimental and predicted pK_i values and associated physicochemical parameters for all compounds based upon the mixed benzil-analog and TFK inhibitor CoMFA analysis.

Nº	Observed			log P	log P^2	vol	vol^2	Predicted		
	hiCE	hCE1	rCE					hiCE	hCE1	rCE
1	7.83	7.35	6.99	3.38	11.42	3.33	11.07	7.02	6.72	6.52
2	6.78	6.64	6.40	3.76	14.14	3.49	12.15	6.94	6.66	7.02
3	6.97	6.74	8.02	4.90	24.01	3.69	13.61	7.33	6.93	8.02
4	6.45	5.78	6.66	4.90	24.01	3.61	13.01	6.58	6.09	6.33
5	7.63	7.13	7.76	4.06	16.48	3.63	13.18	6.95	6.49	7.62
6	6.59	6.43	7.32	4.07	16.56	3.77	14.22	6.79	6.38	7.83
7	7.15	6.28	7.19	3.39	11.49	3.26	10.64	7.18	6.83	7.43
8	7.74	7.32	7.62	4.17	17.39	3.33	11.07	7.58	7.04	7.25
9	7.64	6.80	7.79	4.67	21.81	3.72	13.83	7.60	6.61	7.25
10	7.48	6.90	6.92	3.88	15.05	3.32	11.05	7.66	6.81	6.89
11	7.22	6.27	7.30	4.38	19.18	3.79	14.33	7.51	6.54	7.24
12	8.39	7.00	6.97	4.33	18.75	3.32	11.01	8.07	6.95	7.21
13	7.99	6.76	6.70	3.60	12.96	3.34	11.15	7.79	6.60	6.84
14	7.15	5.47	6.24	3.61	13.03	4.08	16.63	7.34	5.89	7.00
15	6.86	5.81	7.14	3.61	13.03	4.05	16.41	7.22	5.60	6.90
16	8.05	5.48	7.44	4.04	16.32	3.71	13.75	8.27	6.25	7.50
17	7.67	7.11	7.82	4.16	17.31	3.30	10.92	7.57	7.09	7.78
18	-	-	8.06	-1.38	1.90	4.39	19.28	7.96	4.96	8.19
19	8.10	6.53	7.92	0.59	0.35	3.32	11.02	8.31	6.33	7.85
20	7.51	6.67	7.66	0.09	0.01	3.31	10.99	7.32	6.77	7.71
21	6.68	-	6.28	-3.20	10.24	3.28	10.77	6.67	5.72	6.42
22	6.40	4.74	6.57	-3.20	10.24	4.00	15.99	6.33	4.59	6.05
23	7.14	-	7.27	4.68	21.90	4.02	16.19	7.32	6.32	7.31
24	6.42	5.77	6.08	7.20	51.84	3.96	15.71	5.92	5.86	6.84
25	8.25	8.10	8.21	4.89	23.91	3.29	10.80	8.07	8.26	8.62
26	5.98	6.67	6.06	2.84	8.07	2.92	8.55	6.28	7.03	6.98
27	5.18	6.44	5.62	2.84	8.07	2.86	8.19	5.60	6.83	5.60
28	7.24	7.52	8.66	4.61	21.25	3.47	12.04	6.75	7.18	7.97
29	6.63	6.68	8.15	4.61	21.25	3.45	11.91	6.72	7.10	7.62
30	5.10	5.93	5.07	1.24	1.54	2.66	7.09	5.55	6.28	5.32
31	6.82	6.90	6.32	0.90	0.81	3.17	10.04	6.90	6.25	5.95
32	7.07	6.59	8.98	5.73	32.83	4.59	21.11	7.05	6.23	8.75
33	7.82	7.15	6.80	6.63	43.96	2.02	4.07	7.57	7.18	6.98
34	7.27	5.72	5.96	5.12	26.21	2.01	4.05	6.88	5.42	5.69

35	7.49	6.13	6.82	5.04	25.40	2.02	4.07	7.67	6.07	6.62
36	6.82	6.89	6.80	5.57	31.02	2.02	4.06	7.01	6.92	6.80
37	5.72	5.28	5.60	4.06	16.48	2.02	4.06	6.13	5.26	5.54
38	7.10	6.10	6.66	3.98	15.84	2.01	4.05	6.97	5.82	6.26
39	7.66	6.82	6.85	5.11	26.11	2.01	4.03	8.02	6.98	6.70
40	6.66	6.72	6.82	4.51	20.34	2.02	4.07	6.60	6.69	6.63
41	5.62	4.83	5.31	3.00	9.00	2.01	4.03	5.21	4.84	5.15
42	5.33	5.82	5.32	2.92	8.53	2.01	4.05	5.65	5.52	5.70
43	6.25	6.48	6.60	3.46	11.97	2.02	4.06	6.14	6.42	6.39
44	4.17	4.10	4.64	1.95	3.80	2.01	4.03	4.50	4.61	4.86
45	4.56	5.01	4.82	1.87	3.50	2.01	4.03	4.75	5.26	5.32
46	5.04	5.48	5.57	2.76	7.62	2.02	4.07	4.71	5.46	5.39
47	5.77	6.10	6.38	2.40	5.76	2.02	4.07	5.79	6.12	6.10
48	6.12	6.92	6.39	2.91	8.47	2.02	4.07	5.91	6.39	6.32
49	4.29	4.86	4.87	1.32	1.74	2.01	4.04	4.14	5.09	5.17