Supporting Information

Reactivity versus Steric Effects in Fluorinated Ketones as Esterase Inhibitors: A Quantum Mechanical and Molecular Dynamics Study

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Chemical characterization of compound 4 and its trifluoromethyl carbinol precursor

Trifluoromethyl carbinol. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 4.11 (m), 3.70-3.42 (m, 4H), 3.17 (b, 1H), 1.58 (t, $J = 6.8$ Hz), 1.4-1.2 (m, 10H), 0.87 (t, $J = 7.2$ Hz) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 124.18 (q$_{CF}$, $J = 280$ Hz), 69.27 (q$_{CCF}$, $J = 30.6$ Hz), 67.94, 31.77, 29.35, 29.32, 29.2, 25.91, 22.62, 14.04 ppm. $^{19}$F NMR (376.4 MHz, CDCl$_3$): $\delta$ -78.35 (d, $J = 6.3$ Hz) ppm. Elemental analysis: calculated for C$_{11}$H$_{21}$F$_3$O$_2$: C, 54.53; H, 8.74; F, 23.52; found: C, 54.35; H, 8.8; F, 23.71.

Compound 4. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 3.60 (t, $J = 7$ Hz, 2H), 3.62 (s, 2H), 3.52 (t, $J = 6.5$ Hz, 2H), 1.61 (m, 2H), 1.27 (b, 12H), 0.87 (t, $J = 7$ Hz, 3H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 188.70 (q, $J = 34.4$ Hz, CO) 122.47 (q$_{CF}$, $J = 284$ Hz), 115.28 (q$_{CF}$, $J = 290.6$), 92.33 (q$_{CCF}$, $J = 32.3$ Hz), 72.80, 69.62, 31.77, 29.40, 29.31, 29.18, 25.86, 22.63, 14.07 ppm. $^{19}$F NMR (282 MHz, CDCl$_3$): $\delta$ -78.48 (s, COCF$_3$), -85.88 (s, C(OH)$_2$CF$_3$) ppm. HRMS: calculated for C$_{11}$H$_{19}$F$_3$O$_2$ (M$^+$): 239.1252; found: 239.1259.
Figure S1. Time evolution of the (top) potential energy (kcal/mol) and (bottom) the positional root-mean square deviation (Å) of the backbone atoms along the 10 ns trajectories sampled for the hCE1 complexes with inhibitors 14 (black), 15 (green) and 16 (red).