POLYFLUOROALKYL-2-HYDROXYIMINO-1,3-DIKETONES AS NEW SELECTIVE CARBOXYLESTERASE INHIBITORS

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Carboxylesterases (CES, EC 3.1.1.1) are important enzymes of hydrolytic metabolism for major therapeutic agents and other xenobiotics containing an ester group, as well as endogenous esters and thioesters, including lipids. We have shown that the polyfluoroalkyl-2-imino-1,3-dione scaffold is promising for the design of specific CES inhibitors. In this work, a number of polyfluoroalkyl-2-hydroxyimino-1,3-diketones (DKs) of the general formula was obtained:

Analysis of the esterase profile demonstrated that DKs effectively and selectively inhibit CES with a very weak inhibition of structurally related cholinesterases. Quantum-mechanical calculations of the DK structure agree with the results of X-ray diffraction analysis. The ¹⁹F NMR and QM calculations showed the ease of hydration of CF₃-substituted DKs in polar media, which explains the close anti-CES activity of the ketone and hydrated forms. The mechanism of CES inhibition by diketones and their hydrates was consistent with the results of enzymatic kinetics, molecular docking and QM/MM calculations. All compounds possess high antiradical activity and have favorable ADMET profiles. They are of interest as potential candidates for CES inhibition in biomedical applications.

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