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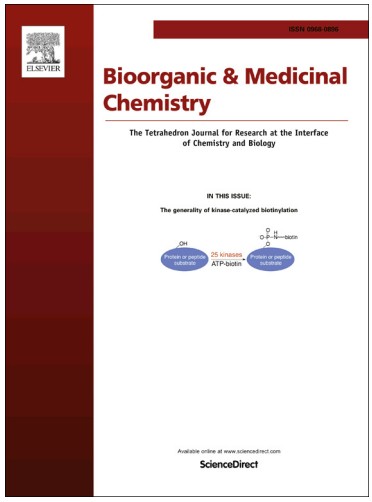

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Design, synthesis, biological evaluation, and molecular modeling studies of chalcone-rivastigmine hybrids as cholinesterase inhibitors

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Abstract

A series of novel chalcone-rivastigmine hybrids were designed, synthesized, and tested in vitro for their ability to inhibit human acetylcholinesterase and butyrylcholinesterase. Most of the target compounds showed hBChE selective activity in the micro- and submicromolar ranges. The most potent compound **3** exhibited comparable IC_{50} to the commercially available drug (rivastigmine). To better understand their structure activity relationships (SAR) and mechanisms of enzyme-inhibitor interactions, kinetic and molecular modeling studies including molecular docking and molecular dynamics (MD) simulations were carried out. Furthermore, compound **3** blocks the formation of reactive oxygen species (ROS) in SH-SY5Y cells and shows the required druggability and low cytotoxicity, suggesting this hybrid is a promising multifunctional drug candidate for Alzheimer's disease (AD) treatment.

Keywords