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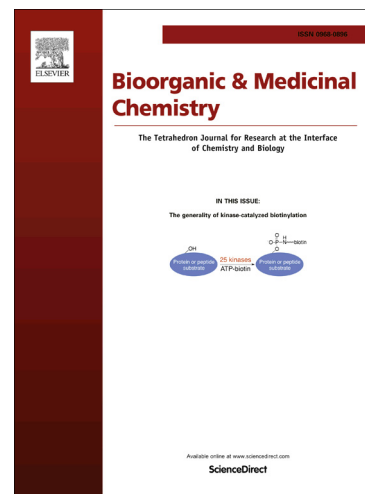
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1 **Design, synthesis, biological evaluation, and molecular modeling studies of**
2 **chalcone-rivastigmine hybrids as cholinesterase inhibitors**

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18 **Abstract**

19 A series of novel chalcone-rivastigmine hybrids were designed, synthesized, and
20 tested in vitro for their ability to inhibit human acetylcholinesterase and
21 butyrylcholinesterase. Most of the target compounds showed hBChE selective activity
22 in the micro- and submicromolar ranges. The most potent compound **3** exhibited
23 comparable IC₅₀ to the commercially available drug (rivastigmine). To better
24 understand their structure activity relationships (SAR) and mechanisms of
25 enzyme-inhibitor interactions, kinetic and molecular modeling studies including
26 molecular docking and molecular dynamics (MD) simulations were carried out.
27 Furthermore, compound **3** blocks the formation of reactive oxygen species (ROS) in
28 SH-SY5Y cells and shows the required druggability and low cytotoxicity, suggesting
29 this hybrid is a promising multifunctional drug candidate for Alzheimer's disease
30 (AD) treatment.

31 **Keywords**

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