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Novel synthesis of 2-(4-((alkyl (aryl) amino) methyl) phenyl)-4h-chromen-4-one derivatives: a dual function lead for Alzheimer's disease therapy

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Background and Aims: The investigation of acetylcholinesterase (AChE) inhibitors has gained further interest recently, because the involvement of the peripheral site of the enzyme in the β-amyloid (Aβ) aggregation process has been disclosed. We present here, for the first time, a direct evidence of the Aβ antiaggregating action of an AChE inhibitor purposely designed to bind at both the catalytic and the peripheral sites of the human enzyme. We design, synthesis, and in vitro biological properties of a compound that represents a novel class of AChE inhibitors endowed with the ability to partially block the action of AChE on Aβ.
Methods: In this work, we have synthesized a series of novel compounds. We first designed new inhibitors following a computational approach based on docking simulations carried out on the structure of human AChE. Then, we selected and synthesized 2-(4-((alkyl (aryl) amino) methyl) phenyl)-4H-chromen-4-one through a fast convenient method. Finally, we tested on the isolated enzyme the ability to inhibit both the catalytic and the Aβ proaggregating actions of AChE.
Results: Target compounds were characterized by 1H, 13C-NMR and Mass spectra. Evaluation of synthesized compound for their anti-Alzheimer activity showed good to excellent activity for these compounds.
Conclusions: Despite their far from optimal pharmacological profile, AChE inhibitors are the only drugs available for the clinical treatment of AD now. Therefore, besides the exploration of alternative approaches targeting early events in the neurotoxic cascade, it still seems worthwhile to try to improve this class of drugs, for which a vast amount of pharmacological evidence and expertise exists.

Keywords: Flavone; Alzheimer; Chromenone