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Extended Abstract

Synthesis, In Vitro Profiling, and In Vivo Efficacy Studies of a New Family of Multitarget Anti-Alzheimer Compounds †

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Simultaneous modulation of several targets or pathological events with a key pathogenic role is a promising strategy to tackle thus far difficult-to-cure or incurable multifactorial diseases, such as Alzheimer's disease (AD). In this scenario, multitarget compounds, i.e., single molecules that hit several targets, are superior to other multitarget strategies that are based on the use of more than one drug (drug cocktails, fixed-dose combinations), in terms of simpler drug development and better patient compliance, efficiency, and safety.

In the frame of our research line devoted to the development of novel anti-AD drug candidates, we have recently prepared a new class of multitarget compounds, which were designed by combining pharmacophoric moieties of a known antioxidant agent (7-methoxy-2,2-dimethylchroman-6-ol (CR-6)) and an acetylcholinesterase (AChE) inhibitor (6-chlorotacrine), to primarily address two important pathological events of AD, namely oxidative stress and cholinergic deficit. Here, we present the synthesis of three short series of CR-6–chlorotacrine hybrids, featuring different linker functionalities (amide, inverse amide, or amine) and lengths, and their in vitro biological activities against AChE, butyrylcholinesterase, BACE-1, and β-amyloid and tau protein aggregation, their antioxidant activity, and BBB permeability. We will also show the results of the in vivo efficacy studies of two selected compounds in double transgenic APP/PS1 mice, a well-established mouse model of AD (behavioral studies, effects on amyloid pathology and oxidative stress).

References

1. Sanvicens, N.; Gomez-Vicente, V.; Messeguer, A.; Cotter, T.G. The radical scavenger CR-6 protects SH-SY5Y neuroblastoma cells from oxidative stress-induced apoptosis: effect on survival pathways. *J. Neurochem.* **2006**, *98*, 735–747.
2. Vázquez-Jiménez, L.; Garrido, M.; Miceli, M.; Prats, E.; Ferrer-Montiel, A.; Teixidó, M.; Jimeno, C.; Messeguer, A. Synthesis and in vitro, ex-vivo and in vivo activity of hybrid compounds linking a potent ROS and RNS scavenger activity with diverse substrates addressed to pass across the blood-brain barrier. *Eur. J. Med. Chem.* **2016**, *123*, 788–802.