New purine nucleosides as copper chelators and cholinesterase inhibitors for Alzheimer's disease

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Alzheimer's disease (AD), despite being the most common form of dementia, is a multifactorial neurodegenerative disease that has no efficient treatment yet. Metal dyshomeostasis, especially copper dyshomeostasis, and the progressive decline of the level of the neurotransmitter acetylcholine (ACh) are two factors that contribute to the pathology, the first being related to several AD features such as the oxidative stress, the Aβ aggregation and the τ-protein hyperphosphorylation. ACh may be hydrolyzed by two enzymes: acetyl- and butyrylcholinesterase (AChE and BChE, respectively) that, in addition to this role, may form toxic complexes with Aβ and/or contribute to its aggregation and accumulation.

Nucleosides have been widely known for their therapeutic properties and the mannosylpurine nucleosides previously synthesized in our group showed a potent BChE inhibition. In this context, we now present the synthesis of new rhamnosyl- and mannosylpurine nucleosides by two different methods for the coupling of N^6-benzoyladenine with glycosyl donors. Catalysis by trimethylsilyl triflate under microwave irradiation or by iodine under conventional heating gave the target molecules with exclusive formation of the N^9 isomers with the latter methodology. Compounds' structure was confirmed by computational studies. Moreover, their metal chelation ability was evaluated, the chelation site disclosed, and the cholinesterase inhibition determined. To conclude, in this work it was possible to obtain the first nucleoside-based molecules with potential to become dual-target drugs against AD.

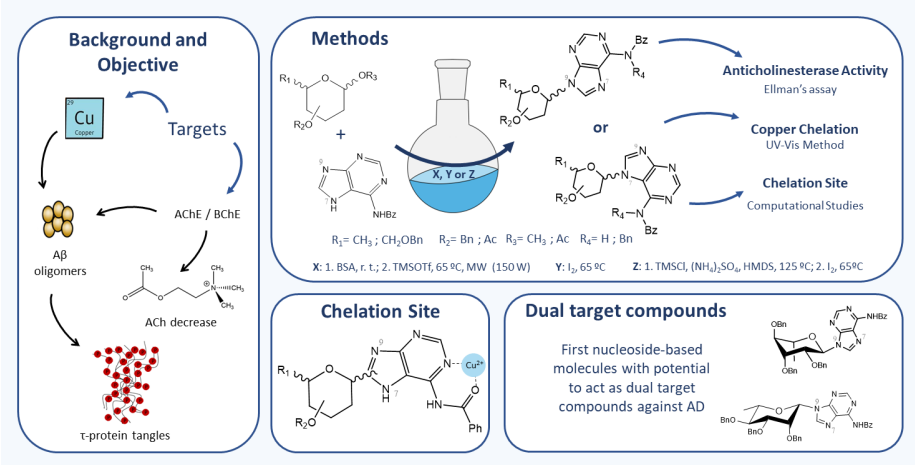

Illustration of this work's objectives, methods and results

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