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Abstract

Synthesis of New Purine Nucleosides as potential Metal Chelators and Anticholinesterase Agents †

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Abstract: Alzheimer's disease (AD) is a neurodegenerative disease characterized by multiple factors, such as the progressive decline in the levels of the neurotransmitter acetylcholine, and the deregulation of the homeostasis of bio-metals, such as copper, zinc and iron. Acetylcholine is hydrolyzed by acetylcholinesterase and butyrylcholinesterase and the current therapeutic strategies are based on the treatment of AD patients with these enzymes' inhibitors. Although these strategies are focused on symptomatic relief of the disease, recent studies have shown that the long-term use of these drugs may lead to disease-modifying benefits. The deregulation of the bio-metals' homeostasis has been related to oxidative stress and to the induction of Ab aggregation and tau hyperphosphorylation and aggregation. Since AD is a multifactorial disease, discovering a multi-target drug could be an interesting challenge, leading to a disease-modifying therapy. In this context, mannosylpurines synthesized by our group have already shown potent butyrylcholinesterase (BChE) inhibition. Aiming at the discovery of multitarget drug candidates, we have synthesized a new series of mannosyl and rhamnosylpurines and evaluated copper chelation and cholinesterase inhibition. The results obtained will be presented and discussed.

Keywords: nucleosides; synthesis; cholinesterase inhibitors; metal chelation; Alzheimer's disease

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Author Contributions: Methodology (synthetic approaches, metal chelation and anticholinesterase activity) was conceived by A.R. and N.C. Synthesis and structure characterization of the new nucleosides was carried out by C.M., supervised by A.R. and N.X., and by J.B., I.S., M.C., and M.J.F. supervised by A.R., while chelation studies were evaluated by C.M., J.B., and I.S. supervised by N.C. and A.R. The anticholinesterase activity was evaluated by M.d.C. Computational studies were carried out by K.S., A.F., and J.N.C.L. The original draft was written by C.M., reviewed and edited by A.R. All authors have read and agreed to the published version of the manuscript.

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