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Abstract

The search for new and potent cholinesterase inhibitors is an ongoing quest mobilizing many organic chemistry groups around the world as these molecules have been shown to treat the late symptoms of Alzheimer's disease as well as to act as neuroprotecting agents. In this work, we disclose the synthesis of novel 2-acetamidopurine nucleosides and, for the first time, regioselective N 7-glycosylation with 2-acetamido-6-chloropurine, promoted by trimethylsilyl triflate, was accomplished by tuning the reaction conditions (acetonitrile as solvent, 65 oC, 5h) starting from 1-acetoxy bicyclic glycosyl donors, or by direct coupling of a methyl glucopyranoside with the nucleobase to obtain only N 7 nucleosides in reasonable yield (55-60%). The nucleosides as well as their sugar precursors were screened for acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibition. While none of the compounds tested inhibited AChE, remarkably, some of the N 7 nucleosides and sugar bicyclic derivatives showed potent inhibition towards BChE. Nanomolar inhibition was obtained for one compound competing well with rivastigmine, a drug currently in use for the treatment of Alzheimer's disease. Experimental results showed that the presence of benzyl groups on the carbohydrate scaffold and the N 7-linked purine nucleobase were necessary for strong BChE inactivation.
A preliminary evaluation of the acute cytotoxicity of the elongated bicyclic sugar precursors and nucleosides was performed indicating low values, in the same order of magnitude as those of rivastigmine.

Keywords: Purine nucleosides; Regioselective N 7-glycosylation; BChE inhibition ; Alzheimer disease