Multifunctional iminochromene-2H-carboxamide derivatives containing different aminomethylene triazole with BACE1 inhibitory, neuroprotective and metal chelating properties targeting Alzheimer's disease

Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder known for the presence of amyloid beta plaques resulting from the sequential action of β-secretase and γ-secretase on amyloid precursor protein. We developed and synthesized, through click reactions, a new family of iminochromene carboxamides containing different aminomethylene triazole. The BACE1 inhibition, neuroprotective capacity and metal chelation of these derivatives make them ideal candidates against AD. Most of the synthesized compounds were shown to have potent BACE1 inhibitory activity in a FRET assay, with an IC50 value of 2.2 μM for the most potent compound. Moreover, molecular modeling evaluation of these BACE1 inhibitors demonstrates the vital role of the amine and amide linkers through hydrogen bond interactions with key amino acids in the BACE1 active site. Our in vitro neuroprotective evaluations in PC12 neuronal cells of Aβ-induced neuroprotection demonstrated promising activity for most of the compounds as neuroprotective agents. Based on our findings, we propose that introduction of a phthalimide substitute on the triazole ring shown to be interesting multifunctional lead compound worthy of further study. © 2017 Elsevier Masson SAS.