Synthesis and biological evaluation of quinazolinone-based hydrazones with potential use in Alzheimer's disease


abstract

Discovering multifunctional agents for the treatment of Alzheimer's disease (AD) is an attractive therapeutic approach. BACE1 (β-site amyloid precursor protein cleaving enzyme 1) inhibitors may play a pivotal role in treating AD. Therefore, the discovery of novel non-peptide BACE1 inhibitors with desirable blood brain barrier permeability is a favorable approach for treatment. Moreover, the antioxidant potential of a drug could serve as an added value for designing dual-acting therapeutic agents. Here, we report the design, synthesis and biological evaluation of quinazolinone-hydrazone derivatives as new multi-target candidates for the treatment of AD. The compounds were investigated for their in vitro BACE1 inhibitory potential using a FRET-based enzymatic assay and also screened for antioxidant activity using DPPH. Among them, compound 4h bearing a 2,3-dichlorophenyl moiety showed the highest activity with an IC50 value of 3.7 μM against BACE1. In addition, compound 4i with a 2,4-dihydroxyphenyl scaffold demonstrated moderate BACE1 inhibitory activity (IC50 = 27.6 μM) with a significant antioxidant effect (IC50 = 8.4 μM). Furthermore, docking studies revealed strong interaction between compound 4h and the key residues of BACE1 active site. These results demonstrate that quinazolinone-hydrazone derivatives represent a valuable scaffold for the discovery of novel non-peptidic BACE1 inhibitors. © 2017 Elsevier Inc.