Abstract

Alzheimer's disease (AD) is a progressive, age-related neurodegenerative disorder characterized by memory loss, cognitive decline, and behavioral disturbances. Despite the availability of acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine) and the NMDA receptor antagonist memantine, current therapies only provide symptomatic relief without halting disease progression. Recent research highlights the importance of multi-target-directed ligands (MTDLs) that can modulate multiple pathological factors of AD, including cholinergic dysfunction, oxidative stress, amyloid-beta (Aβ) aggregation, and monoamine oxidase-B (MAO-B) activity. In the present study, a series of **8-hydroxyquinoline-pyrazolone** and **8-hydroxyquinoline-pyrimidinone** derivatives were designed, synthesized, and characterized by IR, MS, and ^{1}H NMR spectroscopy. The synthesized compounds were evaluated for their anti-AD potential through acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) inhibition, MAO-B inhibition, radical scavenging, metal chelation, and cell viability assays. Among the tested derivatives, compounds **106, 107, 118, and 138** exhibited the most potent activity, with IC_{50} values of 26.23 ± 10.56 nM, 16.02 ± 4.48 nM, 15.11 ± 8.41 nM, and 19.14 ± 11.21 nM, respectively. These findings suggest that 8-hydroxyquinoline–pyrimidinone and 8-hydroxyquinoline–pyrazolone scaffolds represent promising lead structures that may be further developed into multifunctional small molecules for the treatment of Alzheimer's disease.