

9th International Conference on

ALZHEIMER'S DISEASE & DEMENTIA

October 16-18, 2017 | Rome, Italy

Neuroprotective activity of novel 1,2,4-triazine derivatives against H₂O₂ and A β -induced neurotoxicity, new leads for Alzheimer's

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Alzheimer's disease (AD) is a neuropathologic disorder characterized by intracellular neurofibrillary tangles and amyloid aggregates in the CNS. In recent years numerous approaches have been used to combat AD like small molecule inhibitors of A β aggregation, anti-inflammatory agents, cholinesterase, α - and β -secretase. Herein, we report synthesis of some 5,6-diaryl-1,2,4-triazines 3a-f and 8a-e as potential agents for treatment of AD. We evaluated them against both H₂O₂ and β -amyloid induced toxicity in PC-12 and SH-SY5Y cells and the extent of cell viability and apoptosis were assessed during 24 and 48 h of treatment. All compounds showed significant neuroprotective activity with EC₅₀ values ranging from 14-30 μ M. Most compounds could increase cell viability compared to amyloid treated group. Surprisingly, 3-thioxo-1,2,4-triazin-2(3H)-yl) acetate derivative 8e was the most potent compound in both tests with EC₅₀ of 14 μ M in H₂O₂ induced apoptosis and could increase 40% of cell viability revealed by cytometric analysis with Annexin V/PI staining. It was also shown that 8e has more neuroprotective activity than Quercetin in beta-amyloid induced toxicity. Moreover, compound 8e attenuated late-apoptosis from 42% to 6% ($P < 0.005$) and 7% to 1% at 24 and 48 hour respectively compared to amyloid treated cells. Similarly, apoptosis was reduced from 12% to 4% at 24 hours. LDH release was not changed at any time points, pointing anti-apoptotic effect of compound 8e. Morphologic evaluation of cells by DAPI staining and TUNEL assay showed the effectiveness of this compound to improve neurite outgrowth and to prevent apoptosis and DNA fragmentation in neuronal cells.

Biography

Hamid Irannejad has completed his Pharm.D at Kerman University of Medical Sciences and PhD at Tehran University of Medical Sciences, IRAN. Postdoctoral studies was accomplished at University of Siena, Italy, under the supervision of Prof. Maurizio Botta. Currently, he is serving as an assistant professor at Mazandaran University of Medical Sciences. He has published nearly 20 papers in reputed journals in the field of medicinal chemistry.

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