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Synthesis and neuroprotective activity of novel 5,6-diaryl-1,2,4-triazine derivatives with ethyl acetate moiety against H_2O_2 and Aβ-induced neurotoxicity

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Alzheimer's disease (AD) is a neuropathological 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 Aβ aggregation, anti-inflammatory agents, cholinesterase, and β- and γ-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 H_2O_2 and β-amyloid induced toxicity in PC-12 and SH-SY5Y cells and the extent of cell viability and apoptosis were assessed. The synthesis of compounds (3a-f) was started by 1,2-diketones, in which triazine ring closure was performed by thiosemicarbazide and alkylation by ethyl chloroacetate to afford compounds 3a-f. Synthetic route for compounds 8a-e was started by an acylation reaction of anisole with phenyl acetic acid derivatives. The oximation in the alpha position of carbonyl group was performed by use of sodium methoxide and butylnitrite. The next two steps were performed similarly to afford final compounds 8a-e. All compounds showed significant neuroprotective activity with EC_{50} values ranging from 14-30 μM. 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 EC_{50} of 14 μM 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. Morphologic evaluation of cells by DAPI staining and TUNEL assay showed the effectiveness of this compound to improve neurite outgrowth in neuronal cells.

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Anticancer activity of some [1,2,4]triazepino[2,3-a] quinazoline derivatives: Monolayer and multicellular spheroids *in vitro* models

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In this study, five derivatives of triazepino[2,3-a] quinazoline-2,7(1H)-dione were synthesized and their anticancer activities were investigated both in two-dimensional-monolayer and three-dimensional-multicellular spheroids cancer models. All the five compounds showed very high anticancer activities against the 11 cancer cell types that have been investigated in the monolayer model. Comparing the results of both monolayer and multicellular spheroids models of the anticancer activity of these five compounds, we can conclude that the meta-methyl derivative induced its anticancer activity through apoptosis to give the best results in the monolayer model. However, in the multicellular spheroids model its apoptotic activity induced moderate anticancer activity (64% cytotoxicity). On the other hand, both two nitro-derivatives either in meta-position or para-position, did not show potent pro-apoptotic activities toward the monolayer model but showed very high cytotoxic activity toward the multicellular spheroids model (100%). These results reveal that the cell death mechanism induced by both nitro-compounds is exerted via other path than the apoptosis. Interestingly, all the tested compounds were generally safe to normal cells spheroids when tested at the same concentration.

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