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Structure-Guided Optimization of Sulphonamide as Gamma–Secretase Inhibitors for the Treatment of Alzheimer's Disease

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Abstract : In older people, Alzheimer's disease (AD) is turning out to be a lethal disease. According to the amyloid hypothesis, aggregation of the amyloid β–protein (Aβ), particularly its 42-residue variant (Aβ42), plays direct role in the pathogenesis of AD. Aβ is generated through sequential cleavage of amyloid precursor protein (APP) by β–secretase (BACE) and γ–secretase (GS). Thus in the treatment of AD, γ-secretase modulators (GSMs) are potential disease-modifying as they selectively lower pathogenic Aβ42 levels by shifting the enzyme cleavage sites without inhibiting γ–secretase activity. This possibly avoids known adverse effects observed with complete inhibition of the enzyme complex. Virtual screening, via drug-like ADMET filter, QSAR and molecular docking analyses, has been utilized to identify novel γ–secretase modulators with sulphonamide nucleus. Based on QSAR analyses and docking score, some novel analogs have been synthesized. The results obtained by in silico studies have been validated by performing in vivo analysis. In the first step, behavioral assessment has been carried out using Scopolamine induced amnesia methodology. Later the same series has been evaluated for neuroprotective potential against the oxidative stress induced by Scopolamine. Biochemical estimation was performed to evaluate the changes in biochemical markers of Alzheimer's disease such as lipid peroxidation (LPO), Glutathione reductase (GSH), and Catalase. The Scopolamine induced amnesia model has shown increased Acetylcholinesterase (AChE) levels and the inhibitory effect of test compounds in the brain AChE levels have been evaluated. In all the studies Donapezil (Dose: 50µg/kg) has been used as reference drug. The reduced AChE activity is shown by compounds 3f, 3c, and 3e. In the later stage, the most potent compounds have been evaluated for Aβ42 inhibitory profile. It can be hypothesized that this series of alkyl-aryl sulphonamides exhibit anti-AD activity by inhibition of Acetylcholinesterase (AChE) enzyme as well as inhibition of plaque formation on prolong dosage along with neuroprotection from oxidative stress.

Keywords : gamma-secretase inhibitors, Alzzheimer's disease, sulphonamides, QSAR
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