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Extended Abstract

In silico analysis and molecular docking studies of coumarin-oxadiazole hybrids in search of anti-alzheimer's agents

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Abstract

Alzheimer's disease (AD) is an irreversible and a progressive neurodegenerative disease that causes brain atrophy (Lane et al., 2018). It is one of the leading causes of dementia in elderly population. AD starts slowly and dementia related symptoms gradually gets worsen over time. The currently available therapy offers only symptomatic relief and is ineffective in halting the progression of AD (Athar et al., 2021).

Coumarin, a bicyclic heterocyclic compounds, occurs naturally in several plant species. It is a versatile scaffold that exhibits a wide range of biological properties including anti-inflammatory, analgesic and antioxidant activities (Peng et al., 2013). Some synthetic coumarins have been reported to inhibit Acetylcholinesterase (AChE), β-secretase (BACE) and monoamine oxidase B (MAO-B) enzymes and thus it possesses pharmacophoric structural features that could be used to design and develop promising lead or drug candidates to fight against Alzheimer disease (AD) (Husain et al., 2021). Results of previously published studies have shown that coumarin conjugates with pyridinium salt, indole, tacrine, donepzil etc., (Hamulakova et al., 2014; Rehuman et al., 2021; Xie et al., 2016) inhibit AChE by binding at both catalytic active site (CAS) and peripheral anionic site (PAS) on the enzyme and also decreases amyloid beta (Aβ) aggregation.

This study aimed to identify potent coumarin based hybrid derivatives which are capable of acting as multiple target direct ligands (MTDL) *viz.,* AChE inhibitor, antioxidant and anti-inflammatory against AD by using computational studies. Two libraries comprising of 36 coumarin-1,3,4 oxadiazole hybrid compounds were designed by attaching various substituted 1,3,4 oxadiazole fragments at 3rd and 7th position on the coumarin moiety. The Simplified Molecular Input Line Entry System (SMILES) notations of the designed compounds were generated using Chemsketch (v12). *In silico* studies were performed to predict the bioactivity scores and physicochemical properties using the software Molinspiration (Khokar et al., 2021);

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the data on AChE inhibition, neuroprotection, antioxidants, and anti-inflammatory activities were generated from Prediction of Activity Spectra for Substances (PASS) online server (Khokar et al., 2021); The pharmacokinetic profile and toxicity were predicted using ADMETsar and OSIRIS software (Al-Dhahli et al., 2020) and Autodock Vina was used for the molecular docking of the hybrids on AChE (PDB ID: 5HQ3) and MAO-B (PDB ID: 3ZYX) and cyclooxygenase-2 (COX-2; PDB ID: 3KK6) enzymes. The 3D protein structures of enzymes were downloaded from the protein data bank. Galantamine and donepezil were used as reference compounds for comparison purpose.

Molecular weight of both series are comparable (360.37 - 436.42 vs 330.34 - 406.39) but miLogP values of compounds in series B (2.79 vs 4.15) are observed to be higher suggesting that they are slightly more lipophilic than series A compounds (2.18 - 3.48). It is expected that series B compounds will cross the blood brain barrier better than series A compounds and will reach the brain in higher concentration. None of the coumarin derivatives violated Lipinski's rule of five and Veber's rule indicating them to have good oral bioavailability (Lipinski, 2004). Further, designed compounds are predicted to be better enzyme inhibitors than ion channel modulators or GPCR ligands. Coumarin derivatives are predicted to possess strong biological activities and better pharmacokinetic profiles as AChE inhibitors after computational studies. PASS score of the compounds for antioxidant and anti-inflammatory activity was better than the two reference compounds. MAO-B inhibitory activity of series A compounds (Pa score=0.772 - 0.952) was much higher than the series B compounds (Pa score=0.229 - 0.464). Similarly, trend was noted for antioxidant and anti-inflammatory activity in particular for COX-2 inhibition. In general, compounds in series A appeared to be more potent than series B in exhibiting antioxidant, anti-inflammatory and MAO-B inhibitory activities. Based on PASS score, pharmacokinetic profile safety and toxicity results, twelve most potent compounds (six from each series) were selected for molecular docking studies. These compounds showed good binding energy score against MAO-B (-5.7 to -7.3), COX-2 (-5.7 to -7.0) and AChE (-5.1 to -6.2) kcal/mol. Interestingly, series B coumarin hybrids showed better binding energy on the three targets in comparison to series A compounds. Amongst all the designed coumarin derivatives, 3-[2-(5-(4-hydroxy-3-methoxy) benzylidine)-1,3,4-oxadiazolyl]-4-methyl coumarin was identified as the most potent neuroprotective compound. Based on the *in-silico* studies, it could be concluded that coumarin-oxadiazole hybrids are promising source of anti-AD drugs. However, further detailed *in vivo* studies are needed for the drug discovery process.

Keywords: Alzheimer's disease, Hybrids, Coumarin, Antioxidant, AChE

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Conflict of interests

The authors declare that there are no competing interests.

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