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4-substituted coumarins as promising acetylcholinesterase inhibitors

Fatemeh Abolghasemi, Akram Mohammadi, Fariba Mousavipour

Faculty of Pharmacy, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

Abstract: A series of 4-hydroxycoumarin derivatives were designed and synthesized as new acetylcholinesterase (AChE) inhibitors, which could be considered for Alzheimer's disease therapeutics.
Among the 19 coumarin-derived compounds tested toward Electrophorus electricus acetylcholinesterase (eelAChE) and horse serum butyrylcholinesterase (eqBChE), N-(1-benzylpiperidin-4-yl)acetamide derivative 4m displayed highest AChE inhibitory activity (IC50 = 1.2 μM) and favorable selectivity (37 times). The docking study of the most potent compound 4m, indicated that Phe330 is responsible for ligand recognition and trafficking by forming p-cation interaction with benzylpiperidine moiety. Furthermore, the formation of an additional pi-pi interaction between coumarin moiety and Trp279 of peripheral anionic site could stabilize the ligand in the active site resulting in more potent inhibition of the enzyme.

Keyword: Alzheimer's disease, Acetylcholinesterase inhibitor, coumarin