Design and Synthesis of the Novel Coumarin-Quinoline Hybrids as Multitarget Inhibitors of the Acetylcholinesterase, Butyrylcholinesterase and Monoamine oxidase-B

Mahboubeh Mansourian
Faculty of Medicine, University of Medical Sciences of Yasuj-Yasuj

Abstract: Designing hybrid compounds as selective multitarget chemical object is a challenge, opportunity, and new idea to better performance against specific multiple targets. Inhibition of acetylcholinesterase (AChE), butyrylcholinesterase (BuChE) and Monoamine oxidase-B (MAO-B) are considered an important therapeutic strategies for the treatment of Alzheimer's disease (AD). A series of novel hybrids with the coumarin-quinoline scaffold as anti-AD potential compounds have been designed and synthesized by ugi-reaction. To understand the enzymes–inhibitors interactions and the selectivity of the best compound towards AChE, BuChE and MAO-B, molecular modeling studies were performed. Docking studies confirm that these compounds block both catalytic and peripheral sites of AChE and BuChE and MAO-B as well as. The careful analysis of this investigation revealed that the compounds L1, L4 and L8 for AChE and L6 and L14 for BuChE and L4 for MAO-B as the most promising compounds based on the docking score energies and hydrogen bonds distances. The results of this investigation provide valuable information on the design of coumarin-quinoline derivatives as multitarget inhibitors of the AChE, BuChE and MAO-B.

Keywords: Acetylcholinesterase (AChE); Butyrylcholinesterase (BuChE); Monoamine oxidase-B (MAO-B); Coumarin-Quinoline Hybrids; Synthesis; Molecular docking

References:

[1] Alipour, M.; Khoobi, M.; Foroumadi, A.; Nadri, H.; Moradi, A.; Sakhteman, A.; Grandi, M.; Shafiee, A. Novel coumarin derivatives bearing N-benzyl pyridinium moiety: potent and dual binding site acetylcholinesterase inhibitors. Bioorg. Med. Chem. 2012, 20, 7214−7222.
[2] Abdolmalekia A and Ghasemi J.B. Dual-acting of Hybrid Compounds - A New Dawn in the Discovery of Multi-target Drugs: Lead Generation Approaches. Current Topics in Medicinal Chemistry, 2017, 17, 1-19.
[3] Daoud I, Bouarab S and Ghalem S. Docking, dynamic simulation and quantum mechanics studies of pyrazinamide derivatives as novel inhibitors of Acetylcholinesterase and Butyrylcholinesterase. Der Pharma Chemica, 2015, 7(9):307-321.
[4] Fernández-Bachiller, M. I.; Pérez, C.; González-Muñoz, G. C.; Conde, S.; López, M. G.; Villaroya, M.; García, A. G.; Rodríguez-Franco, M. I. Novel tacrine-8-hydroxyquinoline hybrids as multifunctional agents for the treatment of Alzheimer's disease, with neuroprotective, cholinergic, antioxidant, and copper-complexing properties. J. Med. Chem. 2010, 53, 4927−4937.
[5] Hamulakova S, Janovec L, Hrabinova M, Spilovska K, Korabecny J, Kristian P, Kuca K, and Imrich J. Synthesis and Biological Evaluation of Novel Tacrine Derivatives and Tacrine−Coumarin Hybrids as Cholinesterase Inhibitors. *J. Med. Chem.*, 2014, 57 (16), pp 7073–7084.
[6] Kumar, A.; Singh, A. A review on Alzheimer's disease pathophysiology and its management: An update. Pharmacol. Rep. 2015, 67, 195–203.
[7] Mantoani S. P, Chierrito T. P. C, Vilela A. F. L, Cardoso C. L, Martínez A, and Carvalho I. Novel Triazole-Quinoline Derivatives as Selective Dual Binding Site Acetylcholinesterase Inhibitors. Molecules 2016, 21, 193.