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Computational Approach to Identify Novel Chemotherapeutic Agents against Multiple Sclerosis

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Abstract : Multiple sclerosis (MS) is a chronic demyelinating autoimmune disorder, of the central nervous system (CNS). In the present scenario, the current therapies either do not halt the progression of the disease or have side effects which limit the usage of current Disease Modifying Therapies (DMTs) for a longer period of time. Therefore, keeping the current treatment failure schema, we are focusing on screening novel analogues of the available DMTs that specifically bind and inhibit the Sphingosine1-phosphate receptor1 (S1PR1) thereby hindering the lymphocyte propagation toward CNS. The novel drug-like analogs molecule will decrease the frequency of relapses (recurrence of the symptoms associated with MS) with higher efficacy and lower toxicity to human system. In this study, an integrated approach involving ligand-based virtual screening protocol (Ultrafast Shape Recognition with CREDO Atom Types (USRCAT)) to identify the non-toxic drug like analogs of the approved DMTs were employed. The potency of the drug-like analog molecules to cross the Blood Brain Barrier (BBB) was estimated. Besides, molecular docking and simulation using Auto Dock Vina 1.1.2 and GOLD 3.01 were performed using the X-ray crystal structure of Mtb LprG protein to calculate the affinity and specificity of the analogs with the given LprG protein. The docking results were further confirmed by DSX (DrugScore eXtented), a robust program to evaluate the binding energy of ligands bound to the ligand binding domain of the Mtb LprG lipoprotein. The ligand, which has a higher hypothetical affinity, also has greater negative value. Further, the non-specific ligands were screened out using the structural filter proposed by Baell and Holloway. Based on the USRCAT, Lipinski's values, toxicity and BBB analysis, the drug-like analogs of fingolimod and BG-12 showed that RTL and CHEMBL1771640, respectively are non-toxic and permeable to BBB. The successful docking and DSX analysis showed that RTL and CHEMBL1771640 could bind to the binding pocket of S1PR1 receptor protein of human with greater affinity than as compared to their parent compound (Fingolimod). In this study, we also found that all the drug-like analogs of the standard MS drugs passed the Bell and Holloway filter.

Keywords : antagonist, binding affinity, chemotherapeutics, drug-like, multiple sclerosis, S1PR1 receptor protein
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