Virtual screening approach for identifying the potent antidote against botulinum neurotoxin serotypes A, B, E, and F using two softwares

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Abstract

Botulinum neurotoxins are the most poisonous substances reported and listed in category ‘A’ of biowarfare agent. These neurotoxins cause flaccid paralysis of muscles by inhibiting acetylcholine release at the neuromuscular junction, and leads to death. The light chain (catalytic domain) is responsible for cleavage of SNAREs and inhibition of its activity stops the progress of neuroparalysis. Serotype identification is a time-consuming process; hence development of inhibitor against human botulism causing serotypes will be advantageous. Computer assisted screening approaches have been proved a proficient *in silico* method in the drug discovery and development. In present study, ligand-based *in silico* method was applied to identify the “hits” against human intoxicating BoNTs based on their binding affinities and ADMET analysis. A computational approach for docking 35 designed ligands to the catalytic domain of serotype BoNT/A; B; E and F, using Molegro Virtual Docker (MVD) and AutoDock suite was performed. The screening of the best ‘hits’ among the docked complexes was done on the basis of least docking score and common ligands, in both the programs. Analysis of molecular docking of the complexes shows a high binding affinity for the target with Moldock score between -139.85 and -88.24 kcal mol⁻¹. Total five SMNPIs i.e., A9, A14, A15, A18 and A36 provided better binding affinities with the target protein BoNT/A (-109.17, -107.95, -103.12, -108.29, and -112.38 kcal mol⁻¹), whereas for BoNT/B ligands A6, A10, and A31 has showed score of -112.56, -123.93 and -115.13 kcal mol⁻¹. Ligands A6, A12, A18, and A24 exhibited the docking score ranged from -117.20 to -132.19 kcal mol⁻¹ for BoNT/E, and for BoNT/F, only two ligands namely, A4 and A32 appeared to be potential inhibitors with the score of (-115.41, and -117.99 kcal mol⁻¹). The designed ligands were expected to be less toxic considering the Lipinski, Ghose, Veber and Egan rules with a bioavailability score of 0.56. Therefore, in this study we identified ‘hits’ that could be further progressed for experimental studies leading to develop drug against botulism.

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