Virtual Screening and In Vitro Assays for Acetylcholinesterase Inhibitors with Quaternary Ammonium Using the ZINC Database


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Alzheimer's disease (AD) is a neurodegenerative disorder associated with loss of brain neurons and affects a large number of people. The use of acetylcholinesterase (AChE) inhibitors has been considered one of the strategies to treat AD since they increase the concentration of acetylcholine in the brain. We aimed to search for new AChE inhibitors by in silico virtual screening methods using ZINC database followed by in vitro enzymatic method. The presence of a quaternary ammonium moiety and the Lipinski Rules of Five were used as the first criterion of selection of hits. After that, the resulting compounds were submitted to molecular docking (AutoDock Vina 1.1 program), using Torpedo californica AChE (PDB ID: 1EA5) as macromolecule. The hits with lowest binding free energy ($\Delta G_{\text{bind}}$) were chosen to evaluate their in vitro inhibitory activity using purified AChE from Electrophorus electricus, according to Ellman's method (Biochem Pharm 7:88, 1961). From ZINC, 382 hit candidates were first selected. After molecular docking, 15 hits were pointed with lowest $\Delta G_{\text{bind}}$ ranging from -13.0 to -10.0 kcal/mol. Two hits (ZINC codes 2417539 and 4311794) were chosen to evaluate their in vitro AChE inhibition. The hit 2417539 was able to significantly inhibit AChE at concentrations ranging from 1.95 to 125 $\mu$mol/L ($IC_{50} = 5.10 \pm 0.14$ $\mu$mol/L). However, the hit 4311794 was able to significantly ($P > 0.05$) inhibit AChE only at 125 $\mu$mol/L ($IC_{50} > 125$ $\mu$mol/L). More studies should be conducted in order to evaluate the use of compound 2417539 for the treatment of AD.

Keywords: virtual screening, acetylcholinesterase, Alzheimer's disease, medicinal biochemistry
Supported by: CNPq and FAPERGS.