Recently a great deal of attention has been given to butyrylcholinesterase (BChE) as a rediscovered target in Alzheimer’s disease (AD). Based on this, present study has focused on: i) generating homogeneous *in vitro* data on a panel of butyrylcholinesterase inhibitors using a robust experimental platform and ii) deriving a structural-activity relationship among butyrylcholinesterase inhibitors using 3D QSAR.

In a previous screening study intended to search for acetylcholinesterase (AChE) inhibitors using a library of more than 56,000 commercially available compounds, 350 positive hits were identified. Their potencies (measured through mean inhibitory concentrations, IC$_{50}$ values) were studied and 284 compounds were found to display IC$_{50}$ values lower than 10 µM. Current investigations was focused on screening those 284 AChE inhibitors for possible inhibition of BChE. To conduct the primary screening study, an assay for BChE inhibitory activity, which is based on photometric detection of Ellman reaction’s products, was optimized. As a general criteria, potencies of positive hits displaying more than 50% inhibition on the initial screening, were further determined.
3D conformations of all positive hits were generated and protonation states were adjusted. Conformers were created. An X-ray structure of human BChE was retrieved from PDB database. All inhibitors were docked into the BChE active sites in order to align the inhibitors into the most probable binding mode. CoMFA (Comparative molecular field analysis) and CoMSIA (Comparative molecular similarity indices analysis) analysis was performed using Sybyl 8.0. CoMFA and CoMSIA yielded $r^2$ values of 0.75 and 0.91 respectively. Model was validated with an external set of compounds. CoMFA and CoMSIA model can make prediction with a moderate statistical accuracy even though there is certain amount of ambiguity in the prediction.

Keywords: Butyrylcholinesterase (BChE), Alzheimer’s disease (AD), quantitative structure-activity relationship (QSAR), 3D-QSAR, CoMFA (Comparative molecular field analysis), CoMSIA (Comparative molecular similarity indices analysis).