SynAPPse: A Novel QSAR Modeling App for the Rapid Identification of AChE Inhibitors for Alzheimer's Disease

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Alzheimer's Disease (AD) is a leading cause of death, affecting over 55 million worldwide. Despite its prevalence, there is no effective treatment or cure for AD. The acetylcholinesterase (AChE) protein is a promising target for AD treatment because inhibiting AChE can boost acetylcholine levels, crucial for cognition. However, existing AChE inhibitors, like donepezil, have success rates as low as 40%. Moreover, the speed and cost of standard screening techniques impede the search for novel inhibitors. Thus, this study aimed to develop a machine learning-based Quantitative Structure-Activity Relationship (QSAR) model to rapidly identify novel AChE inhibitors based only on their structural characteristics. First, an exploratory analysis of 119 molecules from the ChEMBL database compared Lipinski descriptor levels between biologically active and inactive molecules for AChE. U-tests revealed that molecular weight, number of hydrogen bond donors, and number of hydrogen bond acceptors levels were significantly lower in active molecules, while hydrophobicity levels were similar across active and inactive molecules. Next, 38 models were trained to predict AChE bioactivity using data containing 4695 molecules' structures. The decision tree model was shown to have the best accuracy (R-squared = 0.86), uniformity (RMSE = 0.57), and efficiency (0.16 seconds/molecule). The decision tree then screened 100,000 orally bioavailable molecules from ChEMBL with unknown bioactivities against AChE, yielding 221 novel molecule candidates. Given its speed and accuracy in identifying molecule candidates, this innovative machine learning-based QSAR modeling approach can advance therapeutic development for Alzheimer's Disease and also a broad spectrum of other diseases.

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