Molecular Modelling of Potential anti-Alzheimer Agents Using Chemoinformatics Tools

Abstract

Alzheimer's disease (AD) is a progressive neuropathological disorder, found in the most common form of dementia, which causes severe brain deterioration and cognitive function loss. The root cause of AD is still uncertain, which is one of the main reasons for being incurable. At present only symptomatic treatment is available, which is based on several hypotheses that were found to be associated with AD. In the present thesis work, numerous in silico techniques was employed to study the potential leads against AD. The main objective was to use different in silico approaches to find and improve potential anti-Alzheimer's leads against several crucial targets involved in AD. Along with the single-target drug designing approach, we have also focused on identifying or designing dual-binding site AChE inhibitors, as well as multi-target inhibitors. Further, we have explored the selectivity issue of inhibitors against AChE over BuChE, which is a commonly observed issue while designing molecules against enzymes. Although we used a variety of in silico methods, such as QSAR, QSAAR, molecular docking, pharmacophore modeling, virtual screening, and so on, the majority of our work is focused on developing predictive and statistically robust QSAR models. The QSAR approach is used extensively in the lead optimization step of any drug development effort to reduce time, money, and, most importantly, animal sacrifice. A QSAR model is used to identify the structural features responsible for the activity as well as to achieve selectivity. Additionally, we have also developed the quantitative structure activity-activity relationship (QSAAR) and selectivity-based models to explore the most important features contributing to the dual inhibition against the respective targets. Furthermore, the model provides significant information for designing new compounds with improved activity, and it is used to predict the activity of a query or newly designed compound.

Keywords: Alzheimer's disease, dementia, QSAR, in silico, AChE, BuChE