World Academy of Science, Engineering and Technology
International Journal of Biomedical and Biological Engineering
Vol:13, No:10, 2019

Pharmacophore-Based Modeling of a Series of Human Glutaminyl Cyclase Inhibitors to Identify Lead Molecules by Virtual Screening, Molecular Docking and Molecular Dynamics Simulation Study

Authors : Ankur Chaudhuri, Sibani Sen Chakraborty

Abstract : In human, glutaminyl cyclase activity is highly abundant in neuronal and secretory tissues and is preferentially restricted to hypothalamus and pituitary. The N-terminal modification of β-amyloids (Aβs) peptides by the generation of a pyro-glutamyl (pGlu) modified Aβs (pE-Aβs) is an important process in the initiation of the formation of neurotoxic plaques in Alzheimer's disease (AD). This process is catalyzed by glutaminyl cyclase (QC). The expression of QC is characteristically up-regulated in the early stage of AD, and the hallmark of the inhibition of QC is the prevention of the formation of pE-Aβs and plaques. A computer-aided drug design (CADD) process was employed to give an idea for the designing of potentially active compounds to understand the inhibitory potency against human glutaminyl cyclase (QC). This work elaborates the ligand-based and structure-based pharmacophore exploration of glutaminyl cyclase (QC) by using the known inhibitors. Three dimensional (3D) quantitative structure-activity relationship (QSAR) methods were applied to 154 compounds with known IC50 values. All the inhibitors were divided into two sets, training-set, and test-sets. Generally, training-set was used to build the quantitative pharmacophore model based on the principle of structural diversity, whereas the test-set was employed to evaluate the predictive ability of the pharmacophore hypotheses. A chemical feature-based pharmacophore model was generated from the known 92 training-set compounds by HypoGen module implemented in Discovery Studio 2017 R2 software package. The best hypothesis was selected (Hypo1) based upon the highest correlation coefficient (0.8906), lowest total cost (463.72), and the lowest root mean square deviation (2.24Å) values. The highest correlation coefficient value indicates greater predictive activity of the hypothesis, whereas the lower root mean square deviation signifies a small deviation of experimental activity from the predicted one. The best pharmacophore model (Hypo1) of the candidate inhibitors predicted comprised four features: two hydrogen bond acceptor, one hydrogen bond donor, and one hydrophobic feature. The Hypo1 was validated by several parameters such as test set activity prediction, cost analysis, Fischer's randomization test, leave-one-out method, and heat map of ligand profiler. The predicted features were then used for virtual screening of potential compounds from NCI, ASINEX, Maybridge and Chembridge databases. More than seven million compounds were used for this purpose. The hit compounds were filtered by drug-likeness and pharmacokinetics properties. The selective hits were docked to the high-resolution three-dimensional structure of the target protein glutaminyl cyclase (PDB ID: 2AFU/2AFW) to filter these hits further. To validate the molecular docking results, the most active compound from the dataset was selected as a reference molecule. From the density functional theory (DFT) study, ten molecules were selected based on their highest HOMO (highest occupied molecular orbitals) energy and the lowest bandgap values. Molecular dynamics simulations with explicit solvation systems of the final ten hit compounds revealed that a large number of non-covalent interactions were formed with the binding site of the human glutaminyl cyclase. It was suggested that the hit compounds reported in this study could help in future designing of potent inhibitors as leads against human glutaminyl cyclase.

Keywords : glutaminyl cyclase, hit lead, pharmacophore model, simulation
Conference Title : ICCADD 2019 : International Conference on Computer-Aided Drug Design
Conference Location : Bali, Indonesia
Conference Dates : October 24-25, 2019