Pharmacophore base and 3d-qsar studies in discovery and identification of natural product inhibitors that target mitochondrial complex i

Samad Nejad-Ebrahimi
Shahid Beheshti University, Iran

Abstract

Respiratory complex I (NADH-ubiquinone Oxidoreductase) is the largest protein complex of the respiratory chains that catalyzes the transfer of electrons from NADH to coenzyme Q10 (CoQ10). Dysfunction of this protein complex can cause many hereditary and degenerative diseases. Notwithstanding many types of research, the mechanism of action of this complex is not entirely understood. Hence, increasing number of inhibitors of mammalian Complex I may bring about clues to the enzyme mechanism. In this study, a virtual screening method combined with pharmacophore. The strategy used for the virtual screening of natural compounds modeling was utilized to search and identify new potential for discovering lead compounds. Natural compounds acting on inhibition of mitochondrial complex I. To this aim, a 3D QSAR model was made and validated to be utilized in virtual screening in-order to identify a new scaffold. Then the lead compounds were subsequently subjected to molecular docking studies for their binding to the X-ray structure of the biological target. Two different types of crystal structure of the target-structure of membrane arm and structure of membrane and peripheral arm-were selected to investigate the Interface between peripheral and membrane arm as well as ubiquinone access. For all molecular modeling, the small-Molecular Drug Discovery Suite 2015-2(Schrodinger, LLC, New York, NY, 2016) was used. DQA, 2-decyl-4-quinazolinylamine, was included as a positive control in this study. As result, several compounds showed good binding affinity to the targets and finally 10 compounds with the highest binding affinities, much more than DQA, were selected as potent compounds. Based on computed docking score these compounds, with the docking score range of -7.9 – -10.85 KJ/mol, have a high tendency to inhibit complex I. Also, all Inhibitors acted on the ubiquinone reduction site of this complex. It is hoped these compounds can be good candidates in the focus of biomedical researches, and their backbone structural scaffold can present as building blocks in designing drug-like molecules for respiratory complex I. Chemical features based 3D pharmacophore models were developed for HSP90 based on the known inhibitors using Discovery Studio V2.1. An optimal pharmacophore model was brought forth and validated using a decoy set, external test set and Fischer's randomization method. The best five features pharmacophore model, Hypo1, includes two hydrogen bond acceptors, three hydrophobic features, which has the highest correlation coefficient (0.93), cost difference (73.88), low RMS (1.24), as well as it shows a high goodness of fit and enrichment factor. Hypo1 was used as a 3D query for virtual screening to retrieve potential inhibitors from Maybridge and Scaffold databases. The hit compounds were subsequently subjected to molecular docking studies and finally, 36 compounds were obtained based on consensus scoring function. Human chymase is a very important target for the treatment of cardiovascular diseases. Using a series of theoretical methods like pharmacophore modeling, database screening, molecular docking and Density Functional Theory (DFT) calculations, an investigation for identification of novel chymase inhibitors, and to specify the key factors crucial for the binding and interaction between chymase and inhibitors is performed. A highly correlating (r = 0.942) pharmacophore model (Hypo1) with two hydrogen bond acceptors, and three hydrophobic aromatic features is generated. After successfully validating "Hypo1", it is further applied in database screening. Hit compounds are subjected to various drug-like filtrations and molecular docking studies. Finally, three structurally diverse compounds with high GOLD fitness scores and interactions with key active site amino acids are identified as potent chymase hits. Moreover, DFT study is performed which confirms very clear trends between electronic properties and inhibitory activity (IC50) data thus successfully validating "Hypo1" by DFT method. Therefore, this research exertion can be helpful in the development of new potent hits for chymase. In addition, the combinational use of docking, orbital energies and molecular electrostatic potential analysis is also demonstrated as a good endeavor to gain an insight into the interaction between chymase and inhibitors. Cyclophilin D (CypD) is a peptidyl prolyl isomerase F that resides in the mitochondrial matrix and associates with the inner mitochondrial membrane during the mitochondrial membrane permeability transition. CypD plays a central role in opening the mitochondrial membrane permeability transition pore (mPTP) leading to cell death and has been linked to Alzheimer's disease (AD). Because CypD interacts with amyloid beta (Aβ) to exacerbate mitochondrial and neuronal stress, it is a potential target for drugs to treat AD. Since appropriately designed small organic molecules might bind to CypD and block its interaction with Aβ, 20 trial compounds were designed using known procedures that started with fundamental pyrimidine and sulfonamide scaffolds know to have useful therapeutic effects. Two-dimensional (2D) quantitative structure–activity relationship (QSAR) methods were applied to 40 compounds with known IC50 values. These formed a training set and were followed

by a trial set of 20 designed compounds. A correlation analysis was carried out comparing the statistics of the measured IC50 with predicted values for both sets. Selectivity-determining descriptors were interpreted graphically in terms of principle component analyses. These descriptors can be very useful for predicting activity enhancement for lead compounds. A 3D pharmacophore model was also created. Molecular dynamics simulations were carried out for the 20 trial compounds with known IC50 values, and molecular descriptors were determined by 2D QSAR studies using the Lipinski rule-of-five. Fifteen of the 20 molecules satisfied all 5 Lipinski rules, and the remaining 5 satisfied 4 of the 5 Lipinski criteria and nearly satisfied the fifth. Our previous use of 2D QSAR, 3D pharmacophore models, and molecular docking experiments to successfully predict activity indicates that this can be a very powerful technique for screening large numbers of new compounds as active drug candidates. These studies will hopefully provide a basis for efficiently designing and screening large numbers of more potent and selective inhibitors for CypD treatment of AD.

Biography:

Samira Norouzi is a M.Sc. student of medicinal chemistry in the Medicinal Plants and Drugs Research Institute at Shahid Beheshti University under the supervision of Dr. Samad N. Ebrahimi. She is passionate about the evaluation as well as investigation in computational drug design, and she has built this model based on long-time studies, researches, and evaluation on scaffold of respiratory protein complex I inhibitors. This approach can shed light on discovering new drugs and help biomedical researchers to find out the exact mechanism of action of this large protein.