Molecular Docking, Pharmacophore Modeling, and Virtual Screening for the Discovery of New Reverse Transcriptase Inhibitors

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Abstract

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) have gained a definitive place in the antiretroviral combination therapies used to treat HIV. In this study the chemical feature based pharmacophore models of different classes of NNRT inhibitors of HIV-1 have been developed. The best HypoRefine pharmacophore model, Hypo 1, which has the best correlation coefficient (0.95) and the lowest RMS (0.97), contains two hydrogen bond acceptors, one hydrophobic and one ring aromatic feature, as well as four excluded volumes. Hypo1 was further validated by test set and Fischer validation method and was then utilized as a 3D search query to perform a virtual screening to retrieve potential inhibitors. Moreover the hit compounds were subsequently subjected to filtering by Lipinski's rule of five, and docking studies. Finally ADME studies was successfully performed on 7 top ranked compounds.

Introduction

The human immunodeficiency virus (HIV) is a retrovirus that cause acquired immunodeficiency syndrome (AIDS), which is known to the loss of helper T-lymphocytes and heavy damage to the lymphatic tissues [1].

Pharmacophore approaches have become one of the main tools in drug discovery. According to the definition by IUPAC, a pharmacophore model is 'an ensemble of steric and electronic features that is necessary to ensure the optimal supra molecular interactions with a specific biological target and to trigger (or block) its biological response'. Moreover virtual screening is a valuable computational method alongside traditional high throughput screening technique for discovery of new active compounds in the pharmaceutical industry [2], and success of a virtual screening is defined as finding interesting new scaffolds from many hits [3].

In the present study, we firstly collected structurally diverse sets of the NNRT inhibitors from different references that a total of 219 compounds were obtained. Based on these collected NNRTIs, we developed quantitative pharmacophore models to identify the critical pharmacophore features necessary for potent NNRT inhibitors, clarify the quantitative structure–activity relationship for the known NNRTIs, as well as to perform a pharmacophore-based search in the ZINC 3D database. Finally in silico ADME studies was performed on resulting compounds to compare the computed ADME descriptor values with the accepted ranges.

Materials & methods

A set of 219 non-nucleoside reverse transcriptase inhibitors was collected from literature. The biological activity value for the inhibitors is concentration required to reduce HIV-induced cytopathic effect by 50%, EC_{50} (μM), ranging from 0.001 to 154.62, and were measured using the MTT method in MT-4 cells for their biological activity against wild-type HIV-1 strain III_B. For carrying out pharmacophore modeling, the total compounds were divided into training (23) and test (196) sets, also the most and the least active compounds in the set, were included in the training set. All computational works were done using Accelrys Discovery Studio package version 2.5.

Results

The best pharmacophore model, Hypo1, maped with one of the most active compounds is shown in Figure 1, is characterized by the lowest total cost value (110.67), the highest cost difference (66.94), the lowest RMSD (0.97), and the best correlation coefficient (0.95), and contains four features, including two hydrogen bond acceptors, one hydrophobic and one ring aromatic features
. For validation of pharmacophore model (Hypo 1), a diverse test set containing 196 molecules was used, with a correlation coefficient of 0.61 that is significant at the confidence level of 95%. Moreover, to estimate the statistical relevance of Hypo1, the cross-validation using the Cat-Scramble based on Fischer's randomization test in confidence level of 95% was performed. The original hypotheses are far more superior to those of the 19 random hypotheses generated. Docking computations employed to find the probable binding conformations of all NNRTIs and achieve closer conformations to bioactive ones for pharmacophore model generation. To validate the docking reliability, root-mean-square distance (RMSD) value was calculated between co-crystal and the re-docked ligand using Gold algorithm and Gold score as the scoring function, which is 0.6 Å. 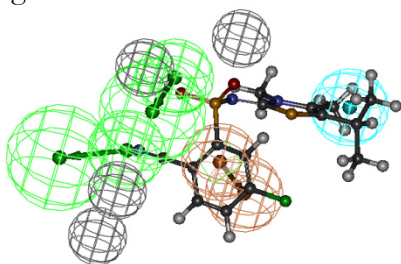Hypo1, was used as a 3D virtual screening query for retrieving novel and potent candidates from ZINC chemical database, which comprised a collection of 56441 compounds. To further refine the retrieved molecules, the selected hits were docked into the allosteric site of RT (pdb code of 3DLG) as a structure based screening using a fast screening method, LibDock, within Discovery Studio 2.5 program package. The predicted binding modes in the NNIBP were ranked based on the LibDock score, and the top one third of ranked molecules were docked into the NNIBP using the powerful docking method of Gold using Gold score as scoring function. 7 out of retrieved hits that scored a high Gold fitness score were selected for further evaluation. To investigate the pharmacokinetic parameters of retrieved compounds, skin-permeability coefficient ($logK_p$), apparent Caco-2 and MDCK permeability that the higher the value of MDCK cell, higher the cell permeability, log BB, aqueous solubility (log S), maximum of transdermal transport rate (J_m), human oral absorption in the gastrointestinal tract (GI), $logK_{hsa}$ for serum protein binding were computed. Nearly all the structures presented acceptable values for the properties analyzed for 95% of known drugs.

Fig. 1; Mapping of Hypo1 with one of the most active

Conclusion

In this study, molecular docking, 3D-QSAR pharmacophore, virtual screening and ADME studies were performed on a divers set of non-nucleoside reverse transcriptase derivatives in order to predict the potential biological activity of compounds and finding the probable lead compounds from virtual screening. LibDock was used as a fast and Gold method as the final docking based screening methods. These methods allowed us to select 7 molecules with high binding affinity towards NNIBP from the ZINC database. Finally in silico ADME studies was successfully conducted on resulting compounds to compare the computed values of ADME descriptors with the accepted ranges. Nearly all the structures presented acceptable values for the properties analyzed for 95% of known drugs.

References

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