Identification of Inhibitors of the Anti-Infective Target DXS Using Ligand-Based Virtual Screening

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Abstract:

The enzymes of the methylerythritol phosphate (MEP) pathway are important drug targets given that pathogens such as Mycobacterium tuberculosis and Plasmodium falciparum use this pathway for the biosynthesis of the essential isoprenoid precursors isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP), while humans exclusively utilize an alternate pathway. The thiamine-diphosphate-dependent enzyme 1-deoxy-D-xylulose-5-phosphate synthase (DXS) catalyzes the primary and rate-limiting step of the MEP pathway. To expand the structural diversity and acquire potent and selective inhibitors of DXS, we performed a ligand-based virtual screening (LBVS) campaign supported shape similarity to screen the ZINC database, ranging from previously discovered DXS inhibitors as references. Biochemical evaluation of the top-scoring compounds against tubercle bacillus DXS and further rounds of LBVS using the simplest hits as references afforded inhibitors within the single-digit micromolar range. In addition to the promising biochemical activity, the hits are active in cellbased assays against Plasmodium falciparum and even drug-resistant strains of tubercle bacillus . Further, assays demonstrated their selectivity over mammalian thiamine-diphosphate-dependent enzymes, their lack of cytotoxicity and validated DXS because the intracellular target.

Introduction:

HIV infection is initiated by fusion of the virus with the target cell through binding of the viral gp120 protein with the CD4 cell surface receptor protein and the CXCR4 or CCR5 co-receptors. There is currently considerable interest in developing novel ligands which will modulate the conformations of those co-receptors and, hence, ultimately block virus-cell fusion. This article define a detailed comparison of the performance of receptor-based and ligand-based virtual screening approaches to find CXCR4 and CCR5 antagonists that could potentially serve as HIV entry inhibitors. Because no crystal structures for these proteins are available, homology models of CXCR4 and CCR5 have been built, using bovine rhodopsin as the template. For ligand-based virtual screening, several shape-based and property-based molecular comparison approaches are compared, using high-affinity ligands as query molecules. These methods were compared by virtually screening a library assembled by us, consisting of 602 known CCR5 and CXCR4 inhibitors and a few 4700 similar presumed inactive molecules. For each receptor, the library was queried using known binders, and therefore the enrichment factors and variety of the resulting virtual hit lists were analyzed. Overall, ligand-based shape-matching searches yielded higher enrichments than receptor-based docking, exclusively for CXCR4. The results obtained for CCR5 suggest the likelihood that different active scaffolds bind in several ways within the CCR5 pocket.

Methods:

Ligand based virtual screening (LBSV)

Ligand based virtual screening approaches utilize structure-activity data from a set of known actives molecules in order to identify likelihood drug candidates for experimental confirmation.52 Quantitative structure-activity relationships (QSAR), pharmacophore modeling, similarity or substructure searching and three-dimensional shape matching are a number of the strategies that are utilized in LBSV method. Quantitative Structure Activity Relationship (QSAR) is one among the frequently used approach in ligand based virtual screening. Generally, QSAR is employed to review the structural or physiochemical relationship of active molecules with their biological targets.53–55 top quality data, diverse set compounds, appropriate descriptors, suitable mathematical algorithm and proper validation sets are required for the development of any effective and successful QSAR model. There are certain reports that showed the influence of these features on any model development.56–58 However, despite these challenges, these models are still prefer as they reduced the time, cost and false hit rates for any designed biological assay. Machine learning algorithms are among the most popular tools used to perform a robust and quantitative structure activity relationship modeling. These techniques applied to QSAR modeling are not only useful for virtual screening but also play an important role in predicting the parameters of pharmacological and pharmaceutical relevance. Different machine learning methods have been proposed with its own advantages and disadvantages. Some of these methods named as, Neural Network,59 Support Vector Machines,60 PLS61 and Decision Tree Classification.62 The use of these techniques in the chemistry field has increased in the last decades.63–66 they're applied for the calculation of the optimal distance between the descriptors of active and inactive compounds. The models developed by these algorithms have potential to discriminate the biologically active compounds from the inactive compounds for their likelihood of interacting with the target. These techniques are helpful in developing the effective prediction models and to discover the optimal decision for your problem. The output may depend on the size of the dataset which is known to be the major drawback of these methods. Adequate amount of data size is necessary to get the optimal output. Another, major drawback of ligand based virtual screening is its addiction on existing ligands information as templates which limits the scaffold diversity as comparison to structure based virtual screening.

Results:

Nan Li et al.,74 screened the SPECS compound library by using structural based virtual screening to spot the potential inhibitors of the histidine kinase (HK) VicK protein from S. pneumonia. Based on molecular diversity, shape complementarities, and therefore the potential to make hydrogen bonds and hydrophobic interactions within the binding pocket, they identified a series of 105 compounds. Six of them were then validated in vitro and were found to inhibit the growth of S. pneumonia. These compounds were found potential in decreasing the mortality of the mice infected by S. pneumonia. Finally, the authors reported that these compounds were the primary inhibitors of HK with antibacterial activity in vitro and in vivo, and were novel causes be drugs that can helpful to combat pneumococcal infection.

Conclusion

Despite the advancement that drawn the positive impact on structure or ligand based virtual screening approaches, challenges related to these methods remained unsolved. We are still lacking a cutting edge technology that can helpful in predicting the accurate binding pose of the compounds. However, careful database preparation, judicious methods choices with optimized parameters, use of proper positive controls can increases probability of any virtual screening experiments success. In this article, we have discussed some of the recent developments in virtual screening methods that can be against the multidrug resistance strains.

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