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Microbiology Congress 2018: Identification of inhibitors of the anti-infective target DXS using ligand-based virtual screening - Adel Elmekes - Helmholtz Institute for Pharmaceutical Research Saarland (HIPS)

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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 precursor's isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP), while humans exclusively utilize an alternative pathway. The thiamine-diphosphate-dependent enzyme 1-deoxy-D-xylulose-5-phosphate synthase (DXS) catalyzes the first and rate-limiting step of the MEP pathway. To expand the structural diversity and obtain potent and selective inhibitors of DXS, we performed a ligand-based virtual screening (LBVS) campaign based on shape similarity to screen the ZINC database, starting from previously discovered DXS inhibitors as references. Biochemical evaluation of the top-scoring compounds against Mycobacterium tuberculosis DXS and further rounds of LBVS using the best hits as references afforded inhibitors in the single-digit micro molar range. In addition to the promising biochemical activity, the hits are active in cell based assays against Plasmodium falciparum and even drug-resistant strains of Mycobacterium tuberculosis. Further, assays demonstrated their selectivity over mammalian thiamine-diphosphate-dependent enzymes, their lack of cytotoxicity and validated DXS as the intracellular target.

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. 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 have 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.

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