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ORIGINAL PAPER

Virtual screening of imidazole analogs as potential hepatitis C virus NS5B polymerase inhibitors

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Hepatitis C virus (HCV) infection is a global health threat and current therapies warrant the need for novel HCV therapies. Several synthetic analogs targeting HCV serine protease and RNA-dependent RNA polymerase have entered clinical development. To investigate the novel HCV NS5B RdRp polymerase inhibitor, screening of a designed data set consisting of benzimidazole analogs by the FlexX docking approach was performed. Binding interactions at the active sites (PDB ID: 2DXS) were evaluated leading to the rationalization of further synthesis and evaluation procedures.

Keywords: virtual screening, anti-HCV, NS5B polymerase, FlexX docking

Introduction

In modern drug discovery, virtual screening of compound libraries has become a standard procedure. Availability of a suitable structure of the target molecule for molecular docking helps to discriminate between putative binders and non-binders in large databases of chemicals and also to reduce the number of compounds to be subjected to experimental testing substantially. The contribution of molecular docking to replacing experimental studies of protein ligand complexes by modeling their structures and binding affinities in silico has made it a key computational chemistry technique. It is routinely applied in drug discovery.

Molecular docking algorithms are regularly used to virtually screen large numbers of compounds to identify potential leads for a particular protein target. Virtual screening of compound databases using detailed structure of the drug target can greatly enhance the success in the lead discovery process (Rester, 2008; Lyne et al., 2004; Doman et al., 2002; Guido et al., 2000). In the virtual screening process, a large database is docked into the protein and a single position for each molecule is selected and scored by the same scoring functions used to calculate the binding mode prediction. At the end of the screening process, a specific number of compounds is selected for testing in experimental assays. Thus, docking is a virtual screening tool and the compounds with poor shape and complementarity to the protein-binding site score poorly and they are at the bottom of the list of scored compounds. A part of the best-scoring compounds is expected to be enriched with a large number of active compounds.

Nonstructural protein of the hepatitis C virus (HCV) NS5B (66 kDa), RNA-dependent RNA polymerase is an important therapeutic target as it is a prime in replicating the HCV RNA genome and the host lacks its functional equivalent (Behrens et al., 1996; Moradpour et al., 2007; Wang & Heinz,

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