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<th><strong>Title</strong></th>
<th>Discovery of antiviral small molecules against Hepatitis C virus</th>
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<td><strong>Author(s)</strong></td>
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<td><strong>Citation</strong></td>
<td>Li, E. (2014, March). Discovery of antiviral small molecules against Hepatitis C virus. Presented at Discover URECA @ NTU poster exhibition and competition, Nanyang Technological University, Singapore.</td>
</tr>
<tr>
<td><strong>Date</strong></td>
<td>2014</td>
</tr>
<tr>
<td><strong>URL</strong></td>
<td><a href="http://hdl.handle.net/10220/24257">http://hdl.handle.net/10220/24257</a></td>
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Introduction

Hepatitis C virus (HCV) NS5B protein is an RNA-dependent RNA polymerase. It has a structure that resembles the right hand with a thumb, palm and finger domain. There are at least four allosteric sites in NS5B RdRp for inhibitor binding (Figure 1).

Results

From a dataset of 310 compounds, 18 compounds, of diverse structures and activity levels, were identified as the training set molecules (Figure 2). These compounds were able to generate a pharmacophore model (Figure 3) that has strong correlation of 0.971 between the compounds’ experimental and estimated IC50 values.

The remaining 292 compounds in the dataset form the test set to validate the pharmacophore model. The strong correlation of 0.944 between the compounds’ estimated and experimental IC50 values validates that our model can predict the inhibitory activities with high degree of accuracy.

Objective

To find novel lead compounds that target HCV NS5B RdRp Thumb Site II using in silico methods.

Research Methods

- Collate all identified Thumb Site II inhibitors with known half maximal inhibitory concentration (IC50) values
- Identify training set that can help to construct pharmacophore model that predicts the experimental IC50 values with good correlation
- Validate pharmacophore model with test set
- Screen library and conduct docking studies for potential novel inhibitor for NS5B RdRp Thumb Site II

Figure 1. Site I (back of the protein) and site II are two allosteric binding sites located at the thumb domain while site III and site IV are located at the palm domain. The red, green and blue regions represent the thumb, palm and finger domain respectively.

Figure 2. Training set of chosen pharmacophore model, consisting of 18 molecules.

Figure 3. Pharmacophore model for HCV NS5B Thumb Site II inhibitors. A) Pharmacophore model with 5 features, 1 negative ionizable feature (in dark blue), 1 hydrogen bond acceptor (in green), 1 ring aromatic feature (in orange) and 2 hydrophobic aliphatic features (in light blue). The grey sphere represents the exclusion volume. The distances (in Å) between the features are also shown. B) All features in the pharmacophore model are mapped to the most active molecule (1, 0.002 μM).

Figure 4. Estimated pIC50 against experimental pIC50 for compounds in the training and test set. The close fit of the data points to the linear line (in red) shows strong correlation between the two variables.

Pharmacophore screening and molecular docking studies were then conducted on a library of compounds which has been filtered by pharmacokinetic properties. This yielded a novel lead compound with an estimated IC50 value of 0.00237 μM and a high PLP fitness score of 77.33 (Figure 5).

Figure 5. Novel compound as HCV NS5B RdRp Thumb Site II inhibitor. A) The compound maps closely to the features in the pharmacophore model, which makes it an active inhibitor of NS5B RdRp at Thumb Site II. B) Molecular docking of the compound into Thumb Site II shows 2 hydrogen bonding with backbone amide (N-H) and side chain hydroxyl (O-H) of Ser476.