Comparison of pharmacophore-based and ML approach to finding inhibitors of Sars-Cov-2 Nsp-13

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1 Materials & Methods

In our pipeline, we have explored two different approaches to identify potential inhibitors of Sars-Cov-2 Nsp-13 helicase: pharmacophore-based and ML-based.

Pharmacophore-based approach:

- preselection of 55 Nsp-13 complexes with ligands (other than simple ions or ADP) from PDB database,
- superposition of reference (7KRN - in complex with ADP) and query structures, to identify ligands located near the ADP binding site (result: 15 complexes of Sars-Cov-2 Nsp-13 with ligands near the ADP binding site),
- redocking (MGLTools, Autodock Vina) of the chosen complexes and selection of 7NN0 receptor as the reference structure based on binding affinity score (-10.7 kcal/mol) and similarities of the location of the native and redocked ligand,
- construction of receptor-based pharmacophore hypothesis in Schrödinger Maestro Phase,
- virtual screening of ECBD bioactives database (76 hits) and validation using DUDE databases of active molecules and decoys (12 out of 139 hits were active compounds),
- docking of 76 hits obtained from virtual screening and visual analysis of the results,
- best results (with binding affinity ≤ -9 kcal/mol).

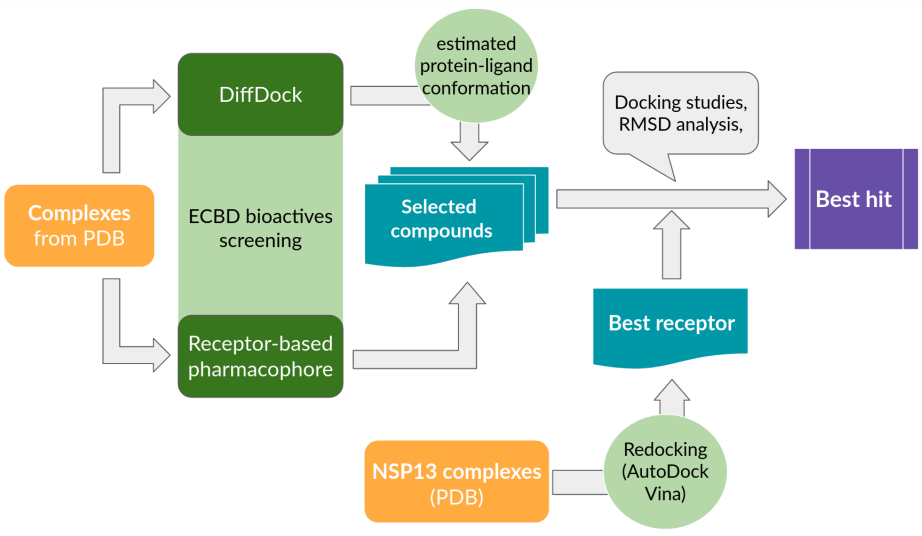

Figure 1: Workflow figure

ML-based approach:

- selection of 2 Nsp-13 structures from PDB database - 6ZSL and 7NN0, limited from 8 structures due to limited computational resources
- alignment and preparation with OpenBabel, pdbtools and reduce
- virtual screening of ECBD bioactives database - whole protein docking with DiffDock
- selection of best pose for each ligand-structure pair - DiffDock confidence score
- minimization and scoring with GNINA - a fork of VINA with added CNN pose scoring
- best results based on VINA score and CNN score
- comparison with results of EOS300008 in vitro assay

2 Results

The receptor-based pharmacophore model consisted of three types of features: 2 donors, 3 aromatic rings, and 2 negative charges. After virtual screening and docking simulations, we got 8 ligands with binding affinity ≤ -9 kcal/mol, 4 of which were ATP, UTP, GTP, and ADP.

Among the 8 hits, we found 4 molecules (ECBD codes EOS101850, EOS101674, EOS102024, and EOS101092). Two of them have their trade names defined in the ChEMBL database: Folotyn and Tomudex. Especially Folotyn is a promising result since it has been previously identified as a potential Covid-19 remedy. Visual summary of pharmacophore-based approach is presented on Fig. 2.

The ML-based approach correctly identified EOS101383 - Idarubicin as a potential inhibitor, in accordance with the EOS300008 assay. Further validation is needed to determine discrimination performance.

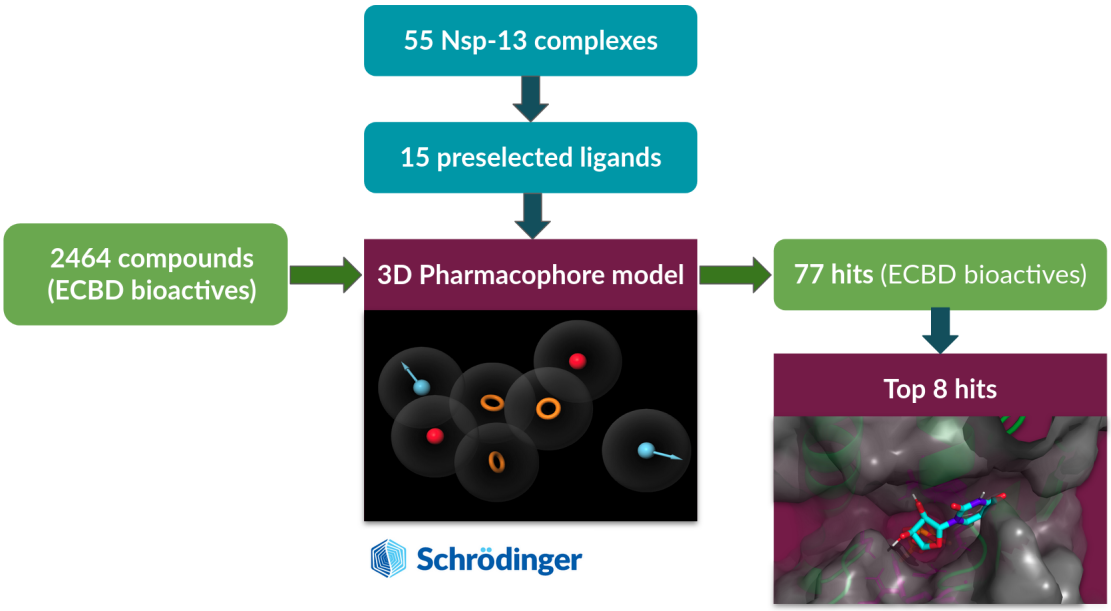

Figure 2: Result figure for pharmacophore-based approach

For references, see the full version of the final report.