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).

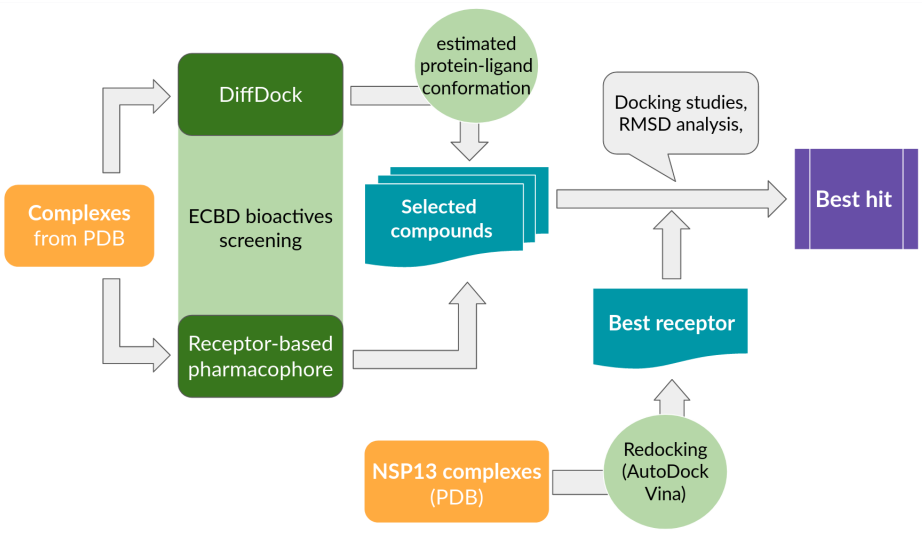

Figure 1: Workflow figure

ML-based approach:

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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.

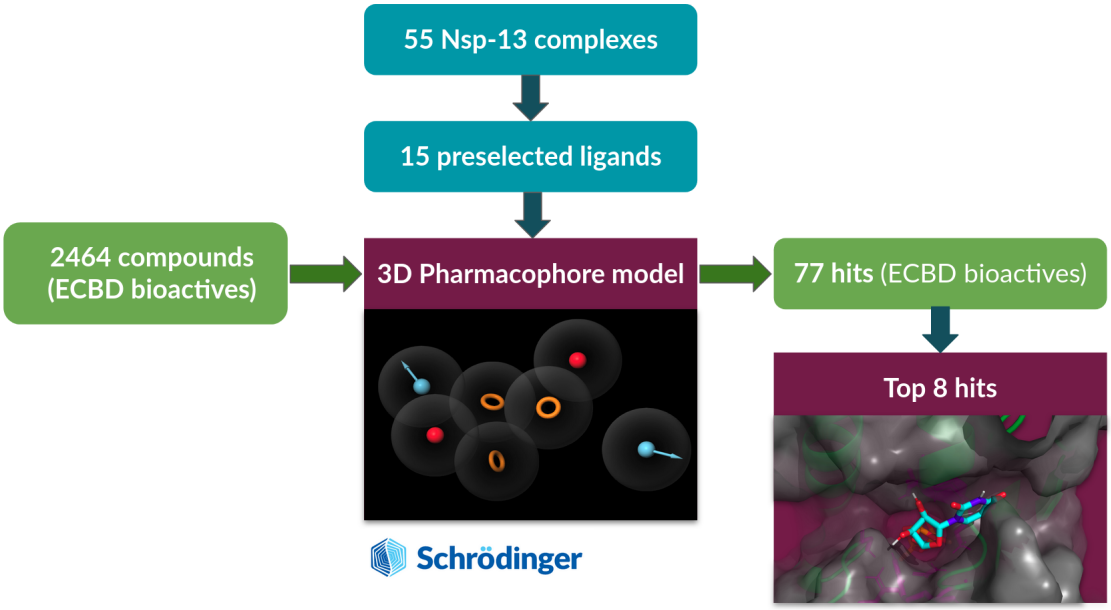

Figure 2: Result figure for pharmacophore-based approach

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