Structure-based screening in search of SARS-CoV-2 Nsp13 helicase inhibitors

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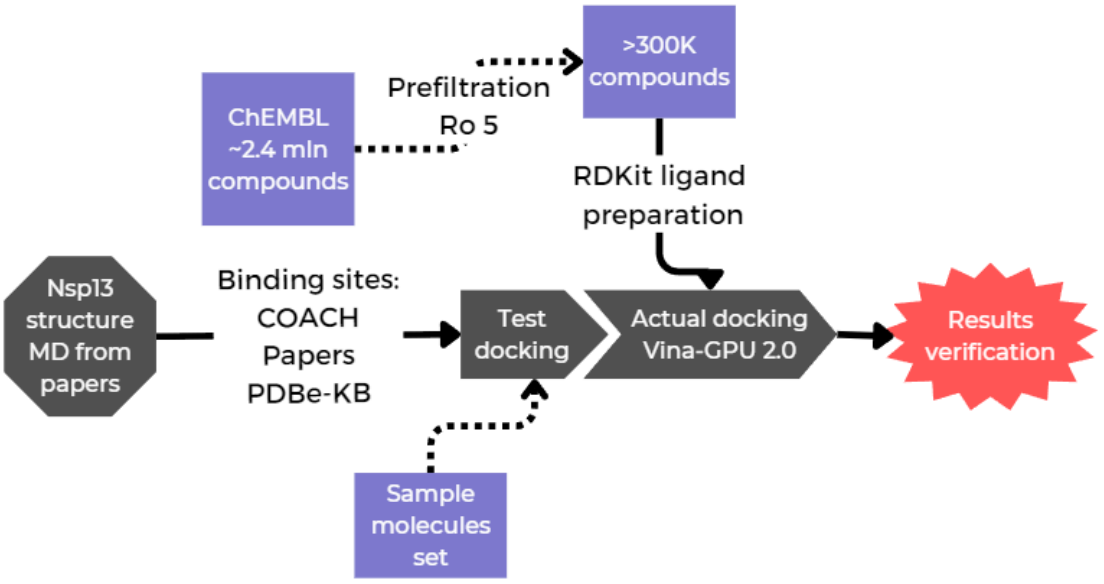
Summary

The main goal of the project was to identify candidate SARS-CoV-2 Nsp13 inhibitors using a set of resolved protein structures. The approach we used was Structure-based High-Throughput Virtual Screening (HTVS).



A binding pocket for the docking was selected by rationally integrating binding residues data from the COACH tool for the site prediction, PDBe-KB database and residues identified in previous studies. All residues that are present in the final docking box are the part of the Nsp13 ATP binding site.

Compounds from the ChEMBL, a database of bioactive molecules with drug-like properties, with an initial amount around 2,4 mln were prefiltered in terms of Lipinski's rule of five. 346,885 candidate ligands obtained from the prefiltration were used in a virtual screening.

Prefiltrated ligands and protein structures were preprocessed using the RDKit tool and a screening test was then performed using a set of Nsp13 inhibitors known from previous studies. After testing, virtual screening and rigid docking was performed on a representative protein structure using Vina-GPU 2.0 and the process was accelerated by CUDA Toolkit 11.5.

From the obtained results, 203 ligands with the free energy of binding above -10 kcal/mol were filtered out, and the remaining compounds were subjected to a more detailed analysis. These compounds underwent toxicity and synthetic accessibility predictions using the eToxPred tool, and the 5 best candidate inhibitors were selected from among the 50 least potentially toxic compounds based on their previous appearance in biological assays documented in the PubChem database.

According to our initial plan we have made several attempts to perform molecular dynamic simulation using two tools - GROMACS and CHARMM-GUI, but unfortunately due to technical obstacles encountered and lack of time, we were unable to complete the simulations.

As the next verification steps we may suggest performing molecular dynamics simulations and flexible docking for the best candidates, and analyze more deeply their potential interactions with the host enzymes.