Prediction of potential inhibitors of the Sars-CoV-2 Helicase (NSP13) by virtual screening and MD simulations

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Methods

We conducted a structure-based virtual screening campaign for identification of possible NSP13 inhibitors among molecules present in European Chemical Biology Database (ECBD) [1]. Two structures of NSP13 were used, representing the apoenzyme (7NIO) and the ATP-analogon bound protein (7NN0). An overview of the complete workflow can be seen in Figure 1. We used a common docking software, AutoDock Vina [2]. As docking is computationally intensive, the database was pre-filtered to only include compounds with drug-like properties and low toxicity scores predicted by the webtool ADMETlab 2.0 [3]. In order to increase docking accuracy, NSP13 binding pockets were predicted by combining output from Fpocket and P2Rank tools [4,5]. Molecular dynamics (MD) simulation was used to analyse molecular interactions between the NSP13 protein and the proposed inhibitors. Finally, possible influence of known mutations in the sequence of NSP13 on binding of the proposed inhibitors was assessed to determine the applicability of results to SARS-CoV-2 variants.

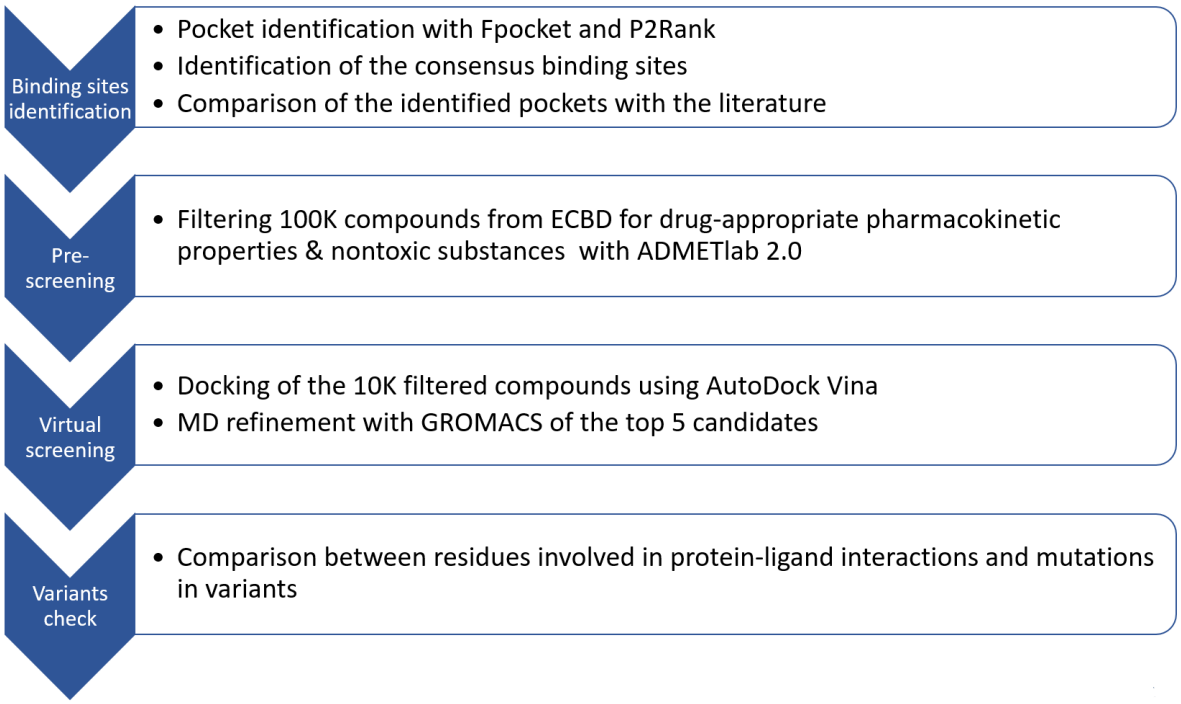

Figure 1. The workflow was performed for both 7NIO and 7NN0 NSP13 structures.

Results

By merging Fpocket and P2Rank predictions we obtained five consensus pockets for 7NIO and three for 7NN0. We later on used only the top-ranked pocket for each protein, which has the greatest overlap with the previously described ATP-binding pocket. Molecular docking identified several molecules with docking scores below -13 kcal/mol. Identical molecules were identified as the five best-ranked potential inhibitors for both analysed structures. Two substructures contributing to low (better) docking scores were identified (Figure 2). MD simulations of the five best-ranked compounds enabled calculation of the root-mean-square deviation (RMSD) of the ligand. As reported previously, ranking based on RMSD was not in agreement with the docking scores [6]. MD simulation enabled identification of residues involved in hydrogen bonds between the ligand and the protein. Known SARS-CoV-2 mutations do not affect these residues. The comparison of results with the Prague Team 2 did not yield any meaningful results, due to great difference in both the data and the methodology.

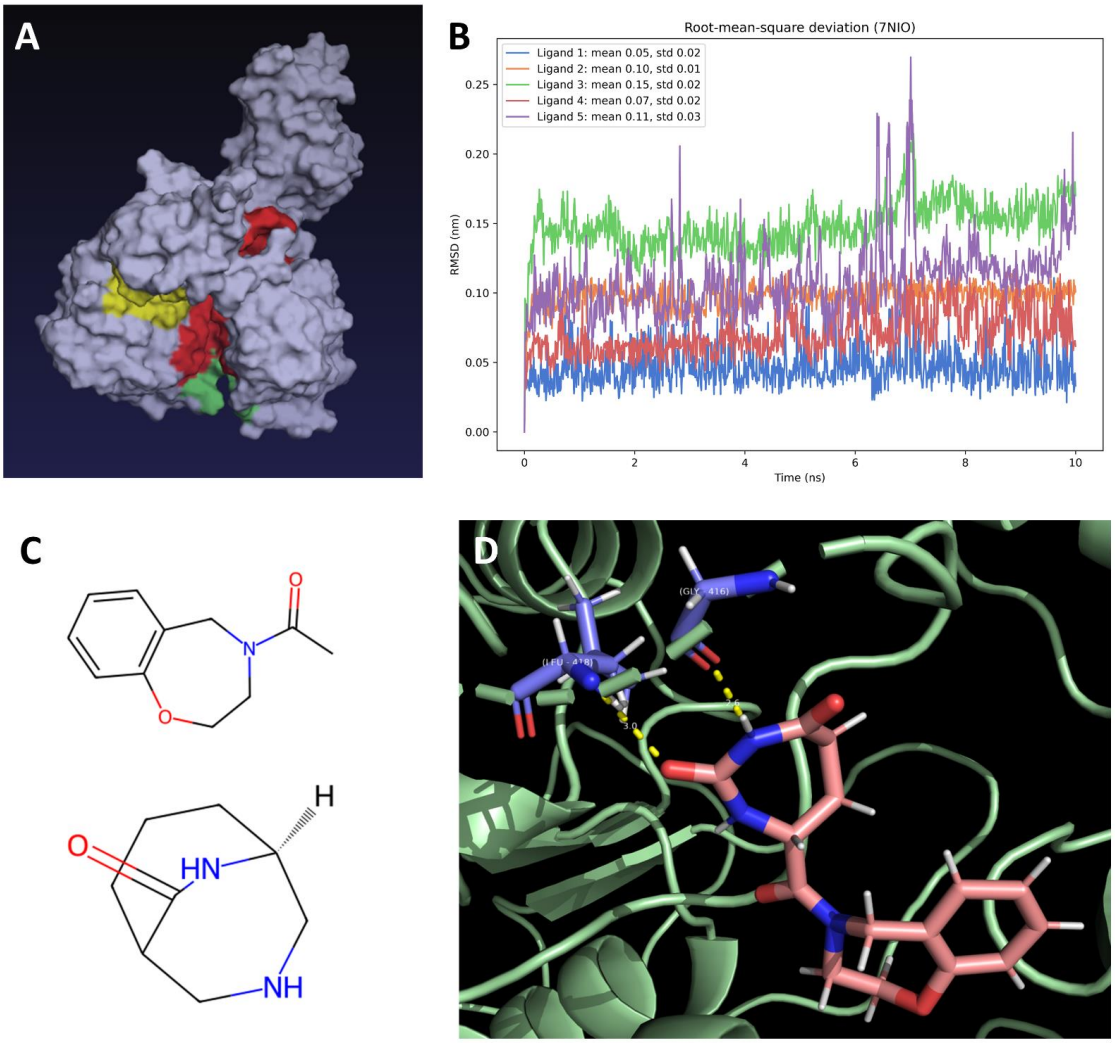

Figure 2. Result figure showing A. the visualization of binding sites, B. RMSDs from MD simulations, C. identified substructures and D. the best scored compound with H-bonds.

References

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