MEET-EU Project

Identification of new SARS-CoV-2 NSP13 helicase inhibitors

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1 Introduction

SARS-CoV-2 is the RNA virus responsible for the global COVID-19 pandemic. The main goal of this project is to create end-to-end pipeline that will help to identify potential inhibitors for NSP13 helicase. The input of the final pipeline will be the one of the resolved conformation of NSP13 helicase and the library of ligands. Our pipeline will use different existed tools for identifying and characterisation of possible binding pockets of the protein, preparation of the ligands and virtual screening.

2 Materials and Methods

2.1 Pipeline description

After testing various packages for consecutive steps of Structure-Based Drug Design, we have chosen more classical tools as P2rank, RDkit, Open Babel and AutoDock Vina for our final pipeline. We selected 6ZSL resolved crystal structure of the SARS-CoV-2 NSP13 helicase for future identification of binding sites and performing the molecular docking simulations.

2.2 Database of compounds

The possible inhibitor's molecules were downloaded from the ZINK20 database, a free chemical database of commercially-available compounds for virtual screening. [1] As a result, we have 3416 molecules that were represented in sdf format. All of these molecules also presented in Pilot Library that was provided for Meet-EU.

2.3 Pipeline Testing

To validate the efficacy of the implemented pipeline, we conducted preliminary testing using a set of 100 ligands sourced from the ZINK20 database. The output of the pipeline provided a comprehensive list of ligands along with their respective scores, indicative of their potential possibility of binding with pocket. As another validation step, we tried our pipeline with 4 know inhibitors that also gave us a positive scores of docking.

2.4 High-Performance Computing Deployment

Following the preliminary testing phase, our pipeline was deployed on the High-Performance Computing (HPC) cluster hosted by the Bioinformatics Institute of France. This strategic utilization of the HPC cluster facilitated the access to computational power needed for the execution of molecular docking and scoring procedures across the entirety of the prepared molecules sourced from the ZINK20 database.

3 Results

3.1 Top 10 best-scored ligands

The obtained result, after completing the execution of our pipeline on HPC clusters, was the list of ligands along with their molecular docking scores related to our detected binding pocket in the NSP13 helicase. Subsequently, we sorted this output to identify the top 10 highest-ranked molecules, which now stand as the final results from our pipeline. The top 10 highest-ranked ligands are presented in Table 1

3.2 Comparative Analysis of Helicase Inhibitor Search Approaches

This project was a part of the Meet-EU consortium. Our team collaborated with two other teams from Warsaw and Milan Universities, testing different approaches to search for

ZINC_NAME	EOS_NAME	Score
ZINC000008815796	EOS606	8.9
ZINC000008589409	EOS102429	8.7
ZINC000006580945	EOS101914	8.5
ZINC000065232480	EOS1323	8.4
ZINC000043203317	EOS100581	8.2
ZINC000096115282	EOS94	8.2
ZINC000009504660	EOS1047	8.0
ZINC000001547088	EOS100840	8.0
ZINC000011859368	EOS2149	7.9
ZINC000004100613	EOS102423	7.9

Table 1: Table of the the top 10 highest-ranked ligands

NSP13 helicase inhibitors. We compared the obtained best-scored ligands by our pipeline and Milan University team's approach and found that we had no matches in these sets of molecules.

References

[1] John J Irwin, Khanh G Tang, Jennifer Young, Chinzorig Dandarchuluun, Benjamin R Wong, Munkhzul Khurelbaatar, Yurii S Moroz, John Mayfield, and Roger A Sayle. Zinc20—a free ultralarge-scale chemical database for ligand discovery. *Journal of chemical information and modeling*, 60(12):6065–6073, 2020.