MeetEU Project - Team Heidelberg - Team 1 – Identification and Enhancement of novel Sars-CoV-2 NSP13 Helicase Inhibitors

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1 Abstract

Even though the development of vaccines against Sars-CoV-2 was successful during the recent pandemic, the amount of FDA approved drugs for the therapy of Covid-19 is still limited to Paxlovid and Veklury, Olumiant and Actemra (**FDACOVID**). One possibility to accelerate the development of new therapies for Covid19 is to screen already approved drugs for effects against the viral reproduction. In this years MeetEU project, we investigated the NSP13 helicase of Sars-CoV-2 and tried to find compounds that could be repurposed for this therapy, as well as novel compounds that could lead to an effective treatment of Covid19. Using our *in-silico* pipeline enables us to evaluate possible drug candidates, suggest novel structures based on already approved drugs and investigate their toxicity, while being cheaper and less labor intensive than projects limited to wet-lab work.

Abbreviations

COVID-19	coronavirus disease 2019
FDA	food and drug administration
MD	molecular dynamics
MM-PBSA	molecular mechanics energies combined with the Poisson-Boltzmann and surface area continuum solvation
NSP13	non-structural protein 13
RMSD	root mean square deviation
RMSF	root mean square fluctuation
RTC	replication transcription complex
SARS-CoV-2	severe acute respiratory syndrome coronavirus type 2
SAscore	synthetic accessibility score
ssRNA	single-stranded RNA
Vina	AutoDock Vina 1.1.2
ZBD	zinc-binding domain

1.1 Moecular Docking

The molecular docking was done twice. For the initial screening of the ligands AutoDock Vina 1.1.2 (Vina) was utilized (Trott and Olson 2010). As the receptor the monomer of 6ZSL was used which includes only chain A. Especially for Vina the zinc ions were also removed and the resulting structure was converted into the pdbqt format through AutoDockTools 1.5.7 (Goodsell et al. 2021). The consensus pocket was introduced as the grid box with lengths of 30 Å. The exhaustiveness was set to 30 and the maximum number of binding modes to 9. Taking advantage of multithreading, Vina uses the 28 CPUs accessible on the multi-core server (Che et al. 2023). A filter was applied on the set of ligands assuring only 3D structures smaller than the specified grid box were screened against the receptor (1428 from the ZINC database and 3592 from the ECBD database). The filter was implemented in Python 3.11.6 and executed together with the Vina command in Bash script. The resulting 9 different conformations for each ligand were ranked by their affinity scores and only the best value was considered in further steps. A number of ligands were later found to have multiple docking results due to an overlap between the two datasets and in accordance with previous steps only the best score was kept. The remaining 4863 ligands were ranked by their affinity score and the top one hundred were selected for next steps.
A second molecular docking was performed with those top scorers from the screening as well as ADP and ATP. The docking software Glide provided by Schrödinger Inc (Friesner et al. 2004). was accessed through Maestro 2022.3 (Schrödinger Release 2022-3). The included tools Protein Preparation Wizard and LigPrep (Madhavi Sastry et al. 2013) were utilized to prepare the monomer helicase and ligands for the docking process with the OPLS4 force field (Lu et al. 2021). The pH value was set to 7.0. The ligand preparation generates depending on the initial structure a varying amount of conformations. In the analysis of the results only the best performing conformation was included. The Receptor Grid Generation panel was used to generate the receptor grid with the same binding pocket as in Vina. The docking with Glide was performed at standard precision (SP) mode and with flexibility of the ligands enabled (Halgren et al. 2004). The criteria for the selection of the best performing ligands was chosen to be the docking score. The interactions between the top scoring ligands and the receptor were noted down.

2 Results

3 Discussion and Outlook

4 Supplementary Material

References

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