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

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February 2024

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 FDA 2023. 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. HIER KOMMT EINE ABBILDUNG HIN

2 Introduction

2.1 Lead Drug Enhancement

In order to enhance the binding affinity of our drug candidates and thus their performance, we used AutoGrow4 (Version 4.0.3) Spiegel and Durrant 2020 to generate novel compounds. Starting with the best binding compounds of our initial docking simulation with AutoDock Vina as generation zero, multiple new structures are generated by combining sub-structures of the first generation or by passing them through a set of possible chemical reactions after converting them into their respective SMILES codes. All of the generated compounds are ranked by their binding affinity. After passing several filters the best performing compounds are used as the seed for the next generation. Using this algorithm, compounds are found, which show higher binding affinities than the first generation. As AutoGrow4 labels all new structures by the path by which they were obtained, we can also evaluate the synthesizability.

2.2 Molecular Dynamics Simulation

As the last step of our pipeline, a MD simulation is conducted using the best scoring compounds as a ligand in the binding pocket of the NSP13 protein. Using GROMACS (Version 2023.3) Abraham et al. 2015, this enables us to interpret the stability of the protein-ligand interaction, as well as to identify important residues for the interaction. Using a given force-field, a set of equations describing different forces between the atoms and residues in the protein and ligand, the movement of all atoms in the system can be simulated and analysed. However, this is only possible in a very limited timeframe with a small time step size. As this process is rather resource heavy, it has to be conducted on a cluster with access to a GPU.

2.3 Estimation of Toxicity and Synthetic Accessibility

After identifying the lead compounds that exhibit optimal binding affinity within the consensus pocket, an evaluation of the general toxicity and synthetic accessibility of these compounds was performed using *e*ToxPred (Pu et al. 2019). This additional step helps estimate the suitability of the compounds as real-life pharmaceuticals against COVID-19. The Tox-score allows for a general assessment of the predicted risk vs. benefit ratio. Moreober, *e*ToxPred allows for an insight into the ease of synthesis, reflected by the synthetic accessibility score (SAscore), of the compounds in a laboratory setting.

3   Material and Methods

3.1   Toxicity and Synthetic Accessibility Prediction using *e*ToxPred

Following lead optimisation, the toxicity of the given compounds was estimated using *e*ToxPred (Pu et al. 2019). In accordance to the paper, a Tox-score threshold of 0.58 was selected to differentiate between toxic and non-toxic compounds, where all compounds with a Tox-score below 0.58 are deemed non-toxic.

4   Results

5   Discussion and Outlook

6   Supplementary Material

References

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