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

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1 Abstract

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 [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 oerforming 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 [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.

3 Material and Methods

4 Results

5 Discussion and Outlook

6 Supplementary Material

References

[Abraham et al., 2015] Abraham, M. J., Murtola, T., Schulz, R., Páll, S., Smith, J. C., Hess, B., and Lindahl, E. (2015). GROMACS: High performance molecular simulations through multi-level parallelism from laptops to supercomputers. *SoftwareX*, 1:19–25.

[Spiegel and Durrant, 2020] Spiegel, J. O. and Durrant, J. D. (2020). AutoGrow4: an open-source genetic algorithm for de novo drug design and lead optimization. *Journal of Cheminformatics*, 12(1):25.