Development of the virtual screening cascade in search for inhibitors of Niemann-Pick C1 protein as a anti Ebola agents

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The most important aspect of the Ebola virus lifecycle is an entry into the host cell. In the crucial step virus' glycoprotein binds to Niemann-Pick C1 protein (NPC1) and releases the viral core into the cytoplasm. Therefore, inhibition of NPC1 can effectively block spreading of the virus at an early stage of infection [1].

Last years, a number of published NPC1 inhibitors significantly increased (94 structures in May 2017) which allowed for application of computational approaches routinely used in computer-aided drug design. In this study, we developed a virtual screening (VS) protocol oriented at the identification of the new NPC1 inhibitors. The VS cascade consists of pharmacophore filter, docking protocol and post-docking ADME filter.

Pharmacophore filter, using previously utilized approach [2], led to the linear combination of pharmacophore models which are the first general pharmacophore hypothesis of NPC1 inhibitors. Docking protocol was oriented on the application of Induced Fit Docking (IFD) technique [3] for the development of efficient screening models. Recently, the crystal structure of NPC was released (PDB:5I31) but preliminary results showed that its performance in screening experiments was highly unsatisfactory. This issue was solved by the application of IFD along with data fusion method.

All VS stages were optimized to maximize the screening parameters in the retrospective experiments. The whole VS cascade will be used for screening the combinatorial library for searching the most promising compounds for the synthesis.

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References:

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