APPLICATION OF THE NOVEL PHARMACOPHORE MODELLING METHODOLOGY IN SEARCH FOR EBOLA VIRUS INHIBITORS

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The most important aspect of the Ebola virus lifecycle is 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].
Due to the increasing numbers of published NPC1 inhibitors (94 structures in May 2017) some standard *in silico* approaches, such as pharmacophore modelling, may be utilized for the discovery of new active compounds. In this study, all known NPC1 inhibitors were hierarchicaly clustered using Canvas [2] with manual refinements to ensure proper chemotypes classification. Multiple hypotheses were developed for each cluster, employing the previously utilized approach [3]. After aplication of DUD-like [4] test set, one model per cluster was selected (according to MCC statistics value) to form the linear combination of pharmacophore models, i.e. the first, general pharmacophore hypothesis of NPC1 inhibitors.
This combination will be applied as one of the steps in the virtual screening protocol reducing combinatorial library for selecting the most promising compounds for synthesis.
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References:
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