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Virtual screening platform on structure based pharmacophore hypothesis to design potential human LDH-A inhibitors against cancer

Vibhu Jha
University of Pisa, Italy

Human Lactate dehydrogenase A (LDH-A) has been identified as a potential therapeutic target in cancer cell metabolism as it catalyzes conversion of pyruvate to lactate in presence of cofactor NADH. Based on latest medicinal chemistry research on LDH-A inhibitors, we have developed a pharmacophore model using consisting of four pharmacophore features: two H-bond acceptors and two hydrophobic aromatic rings (keeping one H-bond acceptor mandatory for activity). The presence of co factors such as Zn^{2+} and NADH on crystal structure of LDH-A was also taken into consideration. The pharmacophore model was subjected to Phase Virtual Screening on 1,500,000 commercially available compounds of Enamine database. Selected compounds were filtered out from structure-based pharmacophore search method. Crystal structure of LDH-A (PDB ID: 5W8K) with cofactor NADH was taken for further docking studies. In order to find the most accurate docking pose, self docking analysis on selected protein with 13 docking programs was performed, followed by the selection of 10 docking programs for further post-docking studies that showed docking pose within an average RMSD of 1.5 Å. The successful docked compounds were subjected to consensus docking platfrom in order to search the common docking pose amongst all docking procedures and compounds were selected from consensus level 6, 7 and 8 which showed similar binding mode as of co-crystallized ligand. Ligand-protein complexes of filtered compounds were then analyzed through a final post-docking filter Molecular Dynamics (MD) Simulations with AMBER 16 software in order to confirm the stability of the predicted binding modes. The final compounds from overall study are currently under biochemical studies for LDH-A inhibitory activity.

e: vibhu.jha@farm.unipi.it

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