IN SILICO ANALYSIS AND IDENTIFICATION OF POTENT INHIBITORS FOR HUMAN SERINE/THREONINE PROTEIN KINASE PIM-3 INVOLVED IN HEPATIC CANCER

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Abstract

PIM3 belongs to a family of proto oncogenes that encode serine/threonine protein kinases in human. Pim-3 is involved in cell cycle progression, suppression of apoptosis and proliferation of human hepatoma cell lines. During normal cell cycle progression, Bcl-2 associated death promoter (BAD protein) inactivates Bcl-2 and Bcl-xL there by promoting apoptosis. However, phosphorylation of BAD protein by Pim-3 leaves Bcl-2 free to inhibit Bax-triggered apoptosis. Thus, designing inhibitors against Pim-3 would stop BAD phosphorylation, hence would be highly useful for development of novel means of cancer therapeutics. Computer aided drug designing approach was followed here to explore lead molecules targeting human Pim-3. For this, proteomic nature and phylogeny of human Pim-3 was studied. A homology model of human Pim-3 was generated based on crystal structure of human Pim-1 (PDB ID: 1XWS) using Modeller9v7. Pim-1 inhibitor 'BI1' was incorporated into the 3D model and further energy minimized by applying OPLS force field in Maestro

v9.0. The stereochemistry assessment of the model had revealed a highly reliable model with 94.8% of residues in the most favored region and no residues in disallowed region of Ramachandran plot. The human Pim-3 3D model inhibitor (BI1) complex was analyzed to locate active site residues such as Leu44, Gly45, Phe49, Val52, Ala65, Lys67, Glu89, Ile104, Leu120, Glu121, Arg122, Pro123, Glu171, Leu174, Ile185 and Asp186. These active site residues were further confirmed using SiteMap. BI1 and two published Pim family inhibitors (Imidazo[1,2-b]pyridazine, SGI-1776) structural analogs were searched from more than one million entries of Ligand.Info Metadatabase and an in house library of 1171 compounds was prepared. Maestro 9.0 virtual screening protocol was used to check binding affinity of 1171 compounds into Pim-3 active site through sequential application of flexible Glide HTVS (Virtual High Throughput Screening), SP and XP method respectively. Fifteen lead molecules identified in the present study were proposed as potential drug molecules against human Pim-3. Lead'**1**' was observed to have higher binding affinity towards human Pim-3 with lowest XP Gscore (-11.90 kcal/mol). The docking complex was observed to be highly stabilized through formation of hydrogen bond with Glu124 and Van der Waal interactions with active site residues. From the present study, it can be concluded that the generated model of human Pim-3 can be used for further studies and lead '1' structure would be highly useful for designing novel inhibitors against hepatic cancer.

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