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In silico identification of novel PKC βII inhibitors: ligand and receptor based pharmacophore modeling, virtual screening, and molecular dynamics study

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The Protein Kinase C βII (PKCβII) belongs to conventional class of Protein kinase C enzyme and is preferentially activated during diabetic cardiomyopathy [1]. An effective inhibition of PKCβII is the potential option to directly treat the diabetic cardiomyopathy. Till date only one selective PKCβII inhibitor, ruboxistaurin reached phase III clinical trial for diabetic complications. Thus, there is an urgent need for exploring available chemical space for new PKCβII inhibitors. The sequential virtual screening workflow based on ligand and receptor based query was followed to identify novel PKCβII inhibitors. Three different strategies were followed for developing the ligand based model by HipHop module implemented in Catalyst, using: (I) three active and six moderately active compounds; (II) 17 active compounds; (III) docked poses of the compounds used in strategy (II). Receptor based query was developed based on the cocrystallised crystal structure of PKCβII with 2-methylbisindolylmaleimide (2mBIM) using the Unity module of Sybyl7.1. The best hypotheses from both methods consist of six features *viz.* one hydrogen bond donor (D), two hydrogen bond acceptor (A), two hydrophobic-aromatic (HYD) and one ring aromatic (R). Virtual screening scheme based on these 3D hypotheses identified a few molecules with higher docking score than the existing inhibitors. In addition, comparative molecular dynamics (MD) simulation studies of uncomplexed PKCβII and its complexes with 2mBIM, ruboxistaurin and newly identified compounds were performed to analyze the binding mode of the molecules. This study showed that complexed form of PKCβII was more stable than uncomplexed one during simulation period, and showed the stable H-bond formation with Glu421, Val423. This reveals the favorable interactions of identified compounds with PKCβII.

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Reference

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