Novel Potent Inhibitors for CIP2A with Mutational Classification Method

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The human cancerous inhibitor of PP2A (CIP2A) is regarded as a novel target for cancer therapy as it’s overexpression in 65% to 90% of tissues in almost all studied human cancers correlates with cancer progression, disease aggressivity in lung cancer besides poor survival and resistance to chemotherapy in breast cancer. Here, I combined homology modelling with quality estimation for a reliable model of CIP2A. Solvent mapping and Molecular dynamics (MD) simulations were implemented for Identification of ligand hot spots. Virtual screening using ligand ZINC database resulted in 996 Lipinski compliant hits that were filtered according to their physicochemical and pharmacophore properties then docked and scored using docking methods of AutoDock and Vina by calculating binding free energies of docking interactions exhibited with identified Cavities to identify novel ligands for CIP2A. Ten newly synthesized complexes were Docked against CIP2A and examined in vitro for their anti-tumor activities against HepG-2, MCF-7 and HCT-116 human carcinoma cell lines using MTT assay. Five complexes showed anticancer activities and potential inhibitory action against CIP2A significantly higher than these of Doxorubicin while Two Complexes showed the best IC50 values. Bioinformatics methods were used to evaluate structural and functional impact of CIP2A SNPs, SIFT predicted 3 nsSNPs as intolerable, PolyPhen assessed 5 nsSNPs as damaging and I-Mutant showed large stability decrease for these nsSNPs. Resulted model was evaluated by Machine learning Algorithms and achieved best performance by ANN multilayer perceptron classifier with 93.75% accuracy, 0.909 sensitivity and 0.833 precision. This research provides significant results for cancer Drug discovery and genome-wide association studies.

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