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Structure-Based Virtual Screening to Identify CLDN4 Inhibitors

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Abstract : Claudins are the important components of the tight junctions that play a key role in paracellular permeability. Among various members of Claudin family, Claudin 4 (CLDN4) is found to be overexpressed in ovarian, pancreatic carcinomas and other epithelial malignancies. Therefore, in this study, an attempt has been made to identify potent inhibitors for CLDN4 from the ZINC database using virtual screening, molecular docking and molecular dynamics simulations. A well refined molecular model of CLDN4 was built using Prime of Schrodinger v10.2(Template- PDB ID: 4P79). Approximately, 6 million compounds from ZINC database are subjected to high-throughput virtual screening (HTVS) against the active site of CLDN4. Molecular docking using GLIDE predicted ARG31, ASN142, ASP146 and ARG158 as critically important residues. Furthermore, three compounds from ZINC database (ZINC96331839, ZINC36533519 and ZINC75819394) showed highly promising ADME properties and binding affinity with stable conformation. The therapeutic efficiency of these lead compounds is evaluated and confirmed by in-vitro and in-vivo studies which leads to the development of novel anti-cancer drugs.

Keywords : ADME property, inhibitors, molecular docking, virtual screening
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