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Structure based pharmacophore generation and its applications for identification of dipeptidyl peptidase –IV (DPP-IV) inhibitor

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In the long process of drug discovery program, virtual screening is a gestation period in which conceiving right hits is the bright future for developing drug candidate. A detailed understanding and critical analysis of all available structural information is indispensable for the development of virtual screening protocol. Various DPP-IV inhibitors have been approved in recent years for the management of type-2-diabetes. Structure based pharmacophores were generated using Discovery Studio 3.0. Crystal structure in protein data bank ID 1X70 bound to sitagliptin ligand was used for generation of structure based pharmacophore. Generated models were validated by receiver operating characteristic curve analysis and by pharmacophore-based screening of marketed DPP-IV inhibitors. Selected pharmacophore is having 5 pharmacophoric features AHPRR (A=HBA, H= Hydrophobe, P= Protonable basic group, R=Ring aromatic) and AUC value, sensitivity, specificity and selective score of was 0.921, 1, 0.7 and 9.1381 and identified marketed DPP-IV inhibitors as hits. Generated run against commercial compound libraries (Specs and ChemDiv). Prior to pharmacophore screening, database was prepared using filters for drug-likeness. The hits obtained from the Pharmacophore screening were docked in DPP-IV crystal structure (PDB id: 1X70) using FRED 2.5, OpenEye Inc. Docked poses of compounds were scored using Chemgauss3 and compounds were ranked and clustered. Top-ranked hits from virtual screening were identified. They are found to bind similarly to sitagliptin in DPP-IV active site, i.e., form salt bridge with Glu205 and/or Glu206 and make hydrophobic interactions with S1 and S2 subsite of DPP-IV. These compounds may serve hits for lead identification program for development of novel DPP-IV inhibitor.

Biography

Khushbu Patel is Postgraduate student in Pharmaceutical Science at Faculty of Pharmacy, Dharmsinh Desai University, Nadiad, Guajrat, India. She is doing her project work on Drug Dessiging using CADD.

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