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Discovery of HIV-I protease inhibitors: Pharmacophore mapping, Virtual Screening, Docking, and *In Silico* Pharmacokinetic and Toxicities Prediction

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Abstract : HIV-I protease is one of three critical enzymes for survival of virus which is responsible for Acquired Immunodeficiency Syndrome. The currently available protease inhibitors have demerits viz. drug resistance, severe side effects and poor pharmacokinetic profile. In course of our current research to discover novel HIV-I protease inhibitors, combination of ligand and structure based drug design approaches were used. A ligand based pharmacophore hypotheses were generated from clinically used FDA approved using DISCOtech and was refined using GASP. A structure based pharmacophore hypothesis was generated using phase. The features obtained fromfour different pharmacophore were hydrogen bond donor, hydrogen bond acceptor and hydrophobic region with distance geometry. These features were used to obtain substructures from databases like ZINC and NCI. A total 148 substructures having Q_{fit} value more than 99 were studied to design 25 potent triazine derivatives which were docked to find 10 hits. *In silico* pharmacokinetic and toxicities properties were calculated usingSWISSADME and pkCSM. The outcome obtained was satisfactory and all compounds had better pharmacokinetic profiles and they were free from toxicities. The present study will help to discover novel and bioactive leads for protease inhibitory activity.

Key words : HIV protease; Pharmacophore hypothesis; Molecular docking; Molecular dynamics; Virtual screening.

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