Receptor Chemoprint Based Pharmacophore Modeling and Virtual Screening Approach to Obtain the Novel Hits in Search of Dopamine Receptor Subtype Selective and Potent Agonists

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The ligand-based method has been very popular for a long time, however, the quality of the pharmacophore model generated by ligand-based method affected significantly by conformation generation method and the selection of training set molecules. The receptor chemoprint approach could be efficiently employed to predict more accurate pharmacophore. Diverse chemical moieties for D2R-agonists with wide range of activity have been reported. Although, dopamine receptors (DRs) are broadly classified into D1-type (D_1R and D_5R) and D_2-type (D_2R, D_3R and D_4R), D_2R and D_3R are only pharmacologically important target for Parkinson's disease (PD). L-dopa remains the gold standard for the medication of PD, in spite of having poor selectivity with DRs. In the present study active site residues of D2R were mapped and pharmacophore model were generated with Ligandscout 3.02. Refined pharmacophore having three hydrophobic region, two hydrogen bond donor, and one hydrogen bond acceptor was subjected with ZINC database to obtain the novel hits as plausible selective and potent D2R-agonists. Following the Lipinski's rule of five, finally 40 hits were obtained and validated using docking simulation analysis with D2R. Docking simulation results, demonstrated 20 compounds having binding free energy

(ΔG) between 10-16 Kcal/mol with significant inhibition constant (Ki) 0.19 nM to 11.7 nM. From the best of our knowledge the structure based pharmacophore modeling strategy has been used first time for generation of pharmacophore models for the rational design of D2R agonists. This investigation provides the new ideas about the structure based pharmacophore model for DRs that can be used in advance 3D database screening to discover novel and potential lead compounds.