Modeling and characterization of selective ligands for β-adrenoceptors

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G-protein coupled receptors covering one fourth of human genome is subjected to extensive interest of pharmaceutical industry. 30 to 40 percent of marketed drugs is targeted to GPCR family. [1] Yet, intrinsic flexibility of transmembrane proteins in signaling cascade makes GPCR proteins an area that needs more detail. β-adrenoceptors as a sub-class of GPCRs, is expressed in smooth muscle in lungs, heart and kidney.[2] Conformational flexibility of β-adrenoceptors and shared common motifs in signal transduction leads to adverse effects by activation/stabilization of non-targeted β-adrenoceptors. Thus, understanding of agonist/antagonist binding mechanism triggering functional activity is the utmost important topic in the area. Pursuant to the topic, in this study we have parametrized a human β2-adrenoceptor (hβ2-Ar) antagonist given as the Compound 4 of Reference [3]. The selectivity of this antagonist for hβ2-Ar compared to hβ1-Ar and hβ3-Ar is experimentally reported [3] which we have compared with our docking and steered molecular dynamics simulation results. [4]

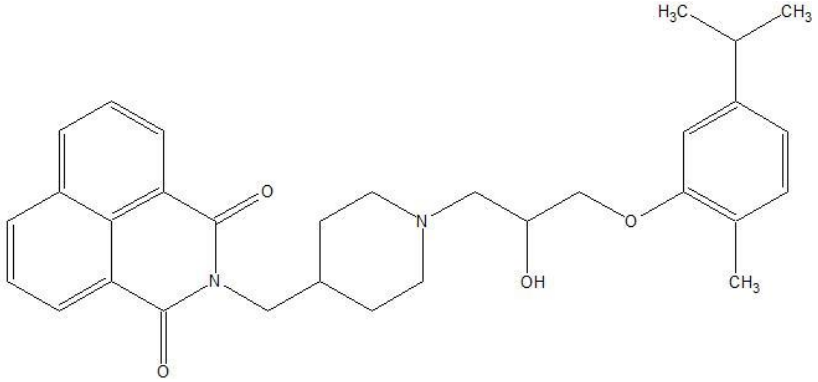

Figure 1. (*3-[(1-{2-hydroxy-3-[5-methyl-2-(propan-2-yl)phenoxy]butyl}pyrrolidin-3-yl)methyl]-3-azatricyclo[7.3.1.0^{5},^{13}]trideca-1(13),5,7,9,11-pentaene-2,4-dione*)

In order to predict the physiochemical properties of selective ligands for the β proteins, we performed a high affinity compound search of FDA Approved ZINC database for β-adrenoceptors through pharmacophore-based high-throughput virtual screening and docking, consisting of 3355 molecules using Molegro [5]. Docking results were complemented with steered molecular dynamics simulations. Compounds that are high affinity binders for hβ2-Ar, hβ1-Ar and hβ3-Ar are classified according to their ligand binding pocket interactions and compared with the experimentally known β2-selective compound.

Compound is formed in Chimera and initial minimization of generated file performed in Scrödinger Package. Initial mol2 and force field files is produced in Ante-chamber module with AM1-BCC charge model. Further parametrization of compound performed in Red [6]. Red program generates parameter files using RESP/ESP charges and Gaussian, Firefly and Gamess orientation algorithms. Gaussian orientation algorithm and RESP charge derivation is used in charge fitting. Atom charge values are fitted to reproduce the MEP (Molecular Electrostatic Potential) in a two stage fit. ESP charge derivation used in fitting to the reproduce the MEP to enable usage of acquired mol2 files in CHARMM, OPLS and AMBER force field simulations.

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