Pharmacophore-based Virtual Screening to Identify New β_3-Adrenergic Receptor Agonists

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β_3-Adrenergic receptors (β_3-ARs), as well as β_1-ARs and β_2-ARs, belong to the G-protein coupled receptors (GPCRs). Activation of these receptors leads to thermogenesis and lipolysis in adipose tissues [1]. Only a few β_3-AR agonists are available for clinical treatment such as mirabegron indicated for overactive bladder (OAB) [2]. Drug design and discovery using pharmacophore-based virtual screening has been applied to discover new candidate compounds [3]. Pharmacophore modeling on β_3-ARs was conducted yet with no experimentally confirmation [4]. This study was aimed to generate ligand-based pharmacophore models to identify new compounds as β_3-ARs agonists and validate those hits also experimentally.

Various β_3-ARs agonists were collected as a dataset to build the pharmacophore model. The models were established using LigandScout v3.12 (Inte:Ligand GmbH, Vienna). The selected model was used for virtual screening against 3 commercial compound databases. To select the candidate compounds, the screening results were filtered by the physicochemical parameters derived from highly active β_3-ARs agonists and a docking evaluation. The physicochemical properties were calculated with Datawarrior v4.7.2. The docking was done with GOLD v5.7.0 employing a homology model of β_3-AR. To confirm the activity of the candidate compounds, the in vitro assay was performed.

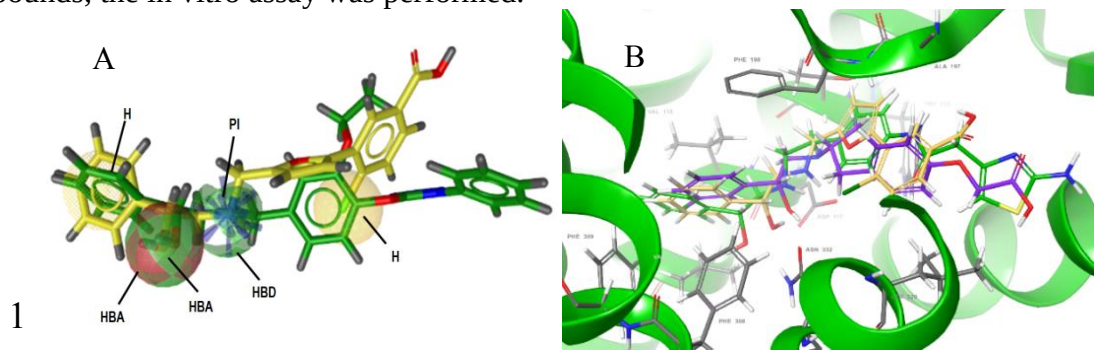

Figure 1. A: Ligand-based pharmacophore model for β_3-AR consisting of both H (Hydrophobic interaction) on the hydroxy end and amine end; HBD (Hydrogen Bond Donor), HBA (Hydrogen Bond Acceptor), and PI (Positive Ionizable Area) on the center. B: Docking pose of Nav16 (yellow), BRL37344 (purple,) and mirabegron (green).

Two out of 20 tested compounds, Nav16 and Nav19 were found to be active both in CHO cell lines expressing human and mouse β_3-ARs. Both compounds increased the cAMP level with EC_{50}s of 12.6 µM and 21.7 µM in CHO-hβ_3AR cells and 3.43 µM and 2.14 µM in CHO-mβ_3AR cells, respectively. Figure 1A depicts both compounds fitted perfectly to the pharmacophore features. Figure 1B shows the similarity of Nav16 docking pose with BRL37344 (selective β_3AR agonist) and mirabegron bound to the receptor.

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