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Homology modeling of MCH1 receptor and validation by docking/scoring and protein-aligned CoMFA

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ABSTRACT

Homology modeling is becoming a valid method for obtaining three-dimensional coordinates for proteins. However, it is hard to judge the qualities of the resulting models warranting robust subsequent validations. In an attempt to evaluate the quality of Melanin-concentrating hormone 1 receptor (MCH1R) homology models, a number of homology structures were scanned for potential binding cavities. Subsequently, a group of 35 benzylpiperidines' MCH1R inhibitors were docked into each of the proposed binding sites via four different scoring functions. The docked structures were utilized to construct corresponding protein-aligned comparative molecular field analysis (CoMFA) models by employing probe-based (H^+, OH, CH_3) energy grids and genetic partial least squares (G/PLS) statistical analysis. The docking-based alignment succeeded in accessing self-consistent CoMFA models upon employing JAIN scoring function in one of the proposed binding pockets in a particular homology model. Furthermore, a ligand-based pharmacophore model was developed for the same set of inhibitors and was found to agree with the successful docking configuration. Therefore, we proved that the overall procedure of docking, scoring, and CoMFA evaluation can be a useful tool to validate homology models, which can be of value for structure-based design, *in-silico* screening, and in understanding the structural basis of ligand binding to MCH1R.