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SIFT-GUIDED AGONIST/ANTAGONIST DIFFERENTIATION FOR BETA2-AR LIGANDS

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The results of ligand docking often fail to provide proper distinction between active and inactive compounds and between agonists and antagonists in particular, especially when only docking scores are considered. In order to predict the functional activity of a tested compound *in silico*, a docking protocol with Structural Interaction Fingerprint (SIFt, [1])-based automatically applied constraints, enabling evaluation of the functionality of ligands was developed. In the presented case of beta2-AR, annotated ligands were extracted from ChEMBL database (version 17) [2]. The initial docking was performed for 2 agonist- and 8 antagonist-bound crystal structures of beta2-AR. Calculation of SIFt profiles (as in previous research [3]) for those results enabled the distinction of agonist and antagonist binding modes, as well as highlighting the conformational differences in crystal structures of beta2-AR. The constraints were developed from the differences in those binding modes, and as shown by extensive cross-docking experiments (using Schrodinger's Glide [4]), expressed promising enhancement of docking performance for agonist-antagonist differentiation. A proper implementation of SIFt-based functional constraints may greatly improve virtual screening cascades by adding a highly desirable information about the potential functional activity of tested molecules.

Acknowledgments

The study was partially supported by the Polish-Norwegian Research Programme operated by the National Centre for Research and Development under the Norwegian Financial Mechanism 2009-2014 in the frame of Project PLATFORMex (Pol-Nor/198887/73/2013).

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