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MEETING ABSTRACT

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Comparative application of common virtual screening tools for the identification of novel μ opioid receptor agonists and antagonists

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Background: The μ opioid peptide (MOP) receptor, a G protein-coupled receptor (GPCR), is one of the oldest targeted opioid receptors for the treatment of pain and other human disorders including ileus, alcohol and drug addiction. Several opioid drugs, i.e. MOP agonists and antagonists, are available for clinical use or are valuable research probes. However, there is still limited information on the molecular mechanisms underlying the different biological effects of various ligands interacting with the MOP receptor. In 2012, the crystal structure of this receptor was elucidated in complex with the irreversible MOP antagonist β-funaltrexamine [1], and could provide first insights into potential binding modes. Within this study, commonly used virtual screening tools, including pharmacophore and shape-based modeling, and docking, were applied to identify novel MOP ligands, and to investigate whether these methods could discriminate between agonists and antagonists.

Methods: Multiple agonist and antagonist models were generated with the programs LigandScout 3.1 and ROCS 3.0.0. A docking workflow using GOLD 5.2 was established. The Maybridge database was screened with all methods and the resulting hits were ranked according to their respective Fit value. Top-ranked agonist and antagonist hits from all methods were tested in a radioligand binding assay at the human MOP receptor.

Results: The evaluation of the theoretical validation illustrated the differences in the suitability of the various *in silico* methods represented by pharmacophore and shape-based modeling, and docking. Particularly, docking appeared as an interesting approach since different interaction patterns of agonists and antagonists observed in this validation run suggested a possible mode of action. In the course of the prospective virtual screening, eighteen structurally novel and diverse molecules were selected for the biological evaluation and three of them showed a weak interaction with the human MOP receptor.

Discussion: The results obtained in this study suggest that some virtual screening tools might be better suitable than others. This may account for the investigation of the MOP receptor in particular, but might also apply for G protein-coupled receptors in general. Therefore, the method of choice for conducting GPCR-related projects should be carefully selected.

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