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MEETING ABSTRACT

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Diphenethylamine derivatives, a novel class of κ opioid receptor ligands: molecular modeling, synthesis and pharmacological activities

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Background: In recent years, the κ opioid peptide (KOP) receptor has received great attention as a prominent drug discovery target toward treatment of pain, depression, and drug addiction. There is considerable evidence that selective KOP agonists produce antinociception in animal models, while they do not cause physical dependence or respiratory depression, therefore being greatly attractive as potential analgesics. On the other hand, KOP antagonists and partial agonists have prospective value as antidepressants, anxiolytics and anti-addiction drugs [1]. The breakthrough in the opioid field made in 2012 in resolving the 3D structure of the human KOP receptor is nowadays providing significant details of the ligand binding pathways into this receptor at the molecular level, and ultimately gives essential insights for the design of ligands with new pharmacological properties targeting the KOP receptor. Recently, we have described the discovery of a new molecular scaffold for KOP ligands within the class of diphenethylamines [2]. The *N*-cyclopropylmethyl-substituted analogue was a selective KOP partial agonist, while the *N*-cyclobutylmethyl-substituted derivative (HS665) was identified as a novel highly selective KOP agonist with potent antinociceptive activity. With the currently available crystal structure of the human KOP receptor, the present study was undertaken to investigate the structural features that promote binding of these diphenethylamines to the KOP receptor via docking and molecular dynamics simulations.

Methods: The structural features that promote binding of the diphenethylamines to the human KOP receptor was investigated using docking calculations and molecular dynamics simulations. Radioligand and functional binding assays were performed with newly designed ligands in Chinese hamster ovary (CHO) cells expressing the human opioid receptors.

Results: *In silico* investigations revealed that the hydrogen bond formed by the phenolic hydroxyl group of HS665 with His291 is essential for KOP affinity and agonist activity. The hydrophobic pocket formed by the residues Val108, Ile316, and Tyr320 appears to be important for hosting the *N*-substituent, indicating that a chain of six carbon atoms is the critical length for agonist interaction. Biological studies with the radiolabeled form of HS665 confirmed its high affinity and KOP receptor specificity, making this molecule a valuable tool in probing KOP receptor pharmacology.

Discussion: The combination of molecular modeling and Pharmacological outcomes aided in the design of novel interesting KOP ligands from the series of diphenethylamines that was supported by structure–activity relationship studies. The current investigations provide further understanding of the binding mode of diphenethylamine derivatives as a novel class of KOP ligands, and may be instrumental to the development of new KOP receptor therapeutics.

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