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Serotonin 2A Receptor (5-HT2AR) Activation by 25H-NBOMe Positional Isomers: In Vitro Functional Evaluation and Molecular Docking

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Abstract

Serotonergic psychedelics are defined as compounds having serotonin 2A receptor (5-HT2AR) activation as an important pharmacological mechanism. These compounds include the phenylalkylamine class, containing substances with e.g. 2C-X structures (phenethylamines) or their N-methoxybenzyl analogues (NBOMes). Besides their abuse potential, psychedelics are increasingly recognized for having therapeutic benefits. However, many psychedelics remain incompletely characterized, even concerning their structure-activity relationships. Here, five positional isomers of 25H-NBOMe, with two methoxy groups on the different positions of the phenyl ring of the phenethylamine moiety, were subjected to split-nanoluciferase assays assessing the in vitro recruitment of cytosolic proteins to the 5-HT2AR. Furthermore, molecular docking at the 5-HT2AR allowed estimation of which residues interact with the specific isomers' methoxy groups. Although the optimal substitution pattern of N-unsubstituted phenylalkylamines has been extensively studied, this is the first comparative evaluation of the functional effects of the positioning of the methoxy groups in the phenethylamine moiety of NBOMes.

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Keywords

bioassay, molecular docking, new psychoactive substances, psychedelic, serotonin receptor, structure-activity relationship

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