FUNCTIONAL CHARACTERIZATION OF PSYCHEDELIC NEW PSYCHOACTIVE SUBSTANCES USING DIFFERENT 5- HT2AR BIOASSAYS

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The serotonin 2A receptor (5-HT2AR), besides being involved in a variety of physiological processes, is the main pharmacological target of serotonergic psychedelics, amongst which the prototypical substance LSD and psychedelic new psychoactive substances (NPS). This latter group is designed to mimic the effects of the prototypical substances, while being structurally divergent from them and from each other. Due to the rapid pace at which these substances emerge on the drug market, they are –and often remain– poorly characterized in terms of potency and efficacy. Furthermore, the structure-activity relationship of these compounds and their mechanisms on a molecular level remain to be elucidated further, leading to our aim of contributing to their characterization. To this end, two highly similar assays were set up, employing NanoBiT® functional complementation technology, to monitor recruitment of either β-arrestin 2 or an engineered miniGαq protein to the activated 5-HT2AR. As a first application we tested a panel of thirty structurally diverse compounds in the β-arrestin 2 bioassay, allowing for the establishment of a structure-activity relationship between substances belonging to the so-called groups of 2C-X, DOx and NBOMe substances. The results obtained additionally correlated with reported common dose estimates for the psychedelic substances. In a second application, the two bioassays were employed simultaneously, allowing the estimation of ligand bias, which can be defined as the preference of a certain ligand towards one assay. Here, several statistically significantly biased substances were identified. In conclusion, we successfully set up two 5-HT2AR bioassays that yield more insight into the molecular mechanism of existing and emerging psychedelic substances.