P-2.63

Revealing Psychedelic Mechanisms: A Molecular Dynamics Perspective on Membrane Interactions and Receptor Binding

Ali Asghar Hakami Zanjani [1]

[1] University of Southern Denmark, Odense, Denmark

The resurgence of psychedelics as potential treatments for psychiatric disorders demands a deeper understanding of their mechanisms of action. While receptor binding, particularly at the serotonin 5-HT2A receptor, is widely accepted, emerging evidence suggests an alternative membrane-mediated mechanism. Using cutting-edge molecular dynamics simulations and free energy calculations, we reveal how subtle chemical modifications in psilocin and related tryptamines influence both receptor interactions and membrane partitioning. Our results demonstrate that psilocin's tertiary amine enhances receptor binding but limits membrane disruption compared to serotonin. Moreover, we uncover a previously unidentified intermediate receptor conformation, offering new insights into ligand-induced activation. These findings bridge molecular pharmacology and membrane biophysics, providing a mechanistic framework for the rational design of next-generation antidepressants and neuropsychiatric therapeutics. These studies present a paradigm shift in understanding psychedelics, appealing to researchers in structural biology, drug discovery, and neuropharmacology.