

Title: Unlocking the Therapeutic Potential of DMT's: Molecular Modelling Insights into Mechanisms and Clinical Prospects

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Abstract: Depression is a critical mental ailment as it impacts about 5% of the global population, prompting scientists to create more efficacious antidepressants. The monoamine-deficiency hypothesis suggests that depression is caused by the depletion of certain neurotransmitters like serotonin, norepinephrine, and dopamine in the brain, where serotonin plays the most critical role among all and has been extensively studied in the context of depression. Serotonin 5-hydroxytryptamine 2A receptors (5-HT_{2A}Rs) are abundant in the brain, particularly in memory and thought-related regions of the central nervous system. Numerous hallucinogens, antipsychotics, and antidepressants target 5-HT_{2A}Rs together with endogenous 5-HT to exert their effects. Research indicates that 5-MeO-DMT increases serotonin levels across nerve cells, leading to enhanced life satisfaction, convergent thinking, mindfulness, and reduced levels of despair and anxiety. A comparative study is conducted to analyze the binding affinity and stability of 5-MeO-DMT, a hallucinogenic psychedelic, in comparison to its non-hallucinogenic analog 6-MeO-DMT through in silico studies. To assess whether 6-MeO-DMT is a viable option for treating depression. 5-MeO-DMT and 6-MeO-DMT were drawn using Marvin software, and molecular docking was conducted using Schrodinger's Suite 2020-1 to analyze the binding affinity and interaction of the sketched molecules in the active binding pocket of 5-HT_{2A}R. The XP docking data showed the gscores of 5-MeO-DMT (-8.01 kcal/mol) and 6-MeO-DMT (-7.43 kcal/mol). Additionally, MM-GBSA revealed binding free energies (ΔBind) of -39.20 and 52.41 kcal/mol for 5-MeO-DMT and 6-MeO-DMT, respectively, where 6-MeO-DMT exhibited superior scores. Computational analysis were also conducted for other molecular properties, including radius of gyration, molecular surface area, solvent-accessible surface area, and polar surface area.

Keywords: 5-MeO-DMT; 6-MeO-DMT; antidepressant; HT_{2A}R.

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