Computational Prediction of Nonabine as a Novel Cannabinoid Receptor Subtype 2 Selective Agonist

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Cannabinoid receptor subtype 2 (CB2), a G protein-coupled receptor within the endocannabinoid system (ECS), has shown promise as a therapeutic target in cancer and inflammatory diseases due to its immunomodulatory properties and peripheral localization. This receptor is distinguished from the CB1 receptor, which is associated with psychoactive effects due to its central nervous system localization, making CB2 an appealing target for therapies that minimize psychoactive side effects. Nonabine, a synthetic analog of ?9-tetrahydrocannabinol (THC), synthesized in the 1970s, has demonstrated antiemetic effects but remains unexplored as a potential CB2 agonist. In this study, we applied computational molecular docking and structural analysis techniques to assess nonabines' affinity and binding interactions with CB2. Compared with established CB2 agonist CP55940, nonabine demonstrated a binding conformation and stability within the CB2 orthosteric pocket. Comparative analysis revealed a slightly stronger binding affinity to CB2 than CB1, indicating potential selectivity for CB2 with reduced psychoactive effects. Key interactions, particularly with residues SER285, PHE94, and ILE110, indicate nonabine's potential to act selectively on CB2, as it aligns with the binding patterns of other selective CB2 agonists. Our work contributes to the understanding of CB2-targeted therapeutics, highlighting nonabines' potential in addressing immune-related diseases and cancers. As a candidate for selective CB2 engagement, nonabine holds promise for novel therapeutic applications in oncology and inflammatory diseases, emphasizing the growing need for CB2-specific drugs that provide therapeutic efficacy while minimizing adverse psychoactive outcomes.

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