K31 A Study of an Active-State CB1 Receptor Model and JWH Synthetic Cannabinoids

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After attending this presentation, attendees will better understand the interactions between synthetic cannabinoids from the JWH family with an active-state CB1 receptor model.

This presentation will impact the forensic science community by contributing to the understanding of essential interactions between specific substituents of JWH synthetic cannabinoids with specific CB1 receptor residues through molecular modeling. The knowledge of these key interactions can help forensic chemists predict the structure of new and undiscovered families of synthetic cannabinoids.

Synthetic cannabinoids have emerged onto the drug scene as an alternative to illegal marijuana.[1] Like delta-9-tetrahydrocannabinol (THC), the main psychoactive ingredient in marijuana, synthetic cannabinoids interact with G-coupled protein receptors found in the brain, immune system, and peripheral organs.[2] There have been two cannabinoid receptors identified: CB1 and CB2. The binding of THC and synthetic cannabinoids to the CB1 receptors that are prevalent in the brain, activating the receptors, is believed to be the cause of the drugs' psychoactive effects. In the 1990s, John W. Huffman et al. developed a large series of synthetic cannabinoids. (These compounds were all given the name JWH-XXX, after Huffman.) Many JWH compounds have been found to have similar effects as THC, functioning as CB1 receptor agonists.[3] These JWH compounds are seen in many synthetic cannabinoid or "Spice" drugs and have become an important area of research in the forensic science community.

In this study, an active-state CB1 receptor model, prepared by the Doerksen lab, was used to compare the ligand-receptor interactions between the CB1 receptor, the JWH synthetic cannabinoid family, and the THC compound. This study was conducted using Schrödinger's Maestro molecular modeling software. Synthetic cannabinoids from the JWH family were selected based on their affinity to bind to the CB1 receptor. The docking of the ligands to the receptor took place after both the synthetic cannabinoid ligands and CB1 receptor model were prepared for docking and a grid of the active site was generated. In order to increase understanding of the interactions between cannabinoids and the CB1 receptor, parameters can be set to provide the five best possible poses, or positions, for the ligands. Once the ligands were docked to the CB1 receptor model, the interactions were thoroughly analyzed. The information collected from this study includes: (1) the amino acid residue interactions with the ligands and the bond distances of these interactions; (2) the docking score of each ligand and each pose; and, (3) estimated binding affinities. This study revealed: the specifics of the interactions, such as the presence of π-π stacking; which interacting residues are hydrophobic, charged, or polar; and whether solvent exposure was important for parts of the molecules.

Results from this study reveal which residue interactions with the CB1 receptor are important for the JWH compounds and how these interactions vary between compounds within this family. Identifying the key interactions between the synthetic cannabinoids and the CB1 receptor is a step toward a better understanding of the effects of these drugs, including toxicity and potential for abuse. The long-term goal is to develop a database and computer program to help predict new structures and different classes of synthetic cannabinoids that have not previously been identified. Future research will include studying all classes of synthetic cannabinoids and other synthetic drugs in addition to the metabolites of these substances.

Reference(s):

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2. Shim J.Y., Bertalovitz A.C., Kendall D.A. Identification of Essential Cannabinoid-Binding Domains Structural Insights Into Early Dynamic Events In Receptor Activation. *J. Biol. Chem.* 2011, 286, 33422-33435.
3. Vardakou I. et al. Spice Drugs as a New Trend: Mode of Action, Identification and Legislation. *Toxicology Letters*. Vol. 197, no. 3, Jan. 2010, pp. 157–162., doi:10.1016/j.toxlet.2010.06.002.

Synthetic Cannabinoid, CB1 Receptor, Molecular Modeling