K54 The Use of Molecular Modeling to Investigate the Influence of Structural Characteristics on the Binding of Synthetic Cannabinoids to the CB1 Receptor

Caroline Spencer, BS, Oxford, MS 38655; Pankaj Pandey, PhD, University of Mississippi, University, MS 38677; Robert J. Doerksen, PhD, University of Mississippi, University, MS 38677; Murrell Godfrey, PhD, University of Mississippi, University, MS 38677*

Learning Overview: After attending this presentation, attendees will better understand the interactions between synthetic cannabinoids and the CB1 receptor and how structural changes of these compounds influence the interactions taking place within the binding pocket.

Impact on the Forensic Science Community: This presentation will impact the forensic science community by contributing to the understanding of essential interactions between specific substituents of synthetic cannabinoids with CB1 receptor residues through molecular modeling. The knowledge of these key interactions can help lead to a better understanding of the effects of these compounds and aid in the discovery of possible new synthetic cannabinoids.

Synthetic cannabinoids have emerged onto the drug scene as an alternative to illegal marijuana.[1] Like Δ-9 Tetrahydrocannabinol (Δ-9 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 located in the brain is believed to induce the psychoactive effects. Even though there are similarities between Δ-9 THC and synthetic cannabinoids, many synthetic cannabinoids have been determined to be full agonists for the CB1 receptor whereas Δ-9 THC is only a partial agonist.

In this study, an active-state CB1 receptor model, proposed by the Doerksen lab, was used to compare the ligand-receptor interactions between the JWH synthetic cannabinoids, developed by John W. Huffman, and the CB1 receptor.[3] This study focused on the napthoylindole group of JWH synthetic cannabinoids. This group includes JWH-007, 018, 073, 116, 122, 182, and 210.This study was accomplished using Schrödinger's Maestro molecular modeling software. JWH ligands were selected based on their affinity for binding to the CB1 receptor. The docking of the ligands to the receptor took place after both the ligands and CB1 receptor model were prepped for docking and a grid of the active site was generated. Parameters were set to give 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 the amino acid residues interaction with the ligands and the bond distances of these interactions, the docking score of each ligand and each pose, estimated binding affinities, and ligand Ki values. Once the known synthetic cannabinoids were analyzed, new structures were designed based on specific structural characteristics. The new structures were studied in the same way as the known synthetic cannabinoids to determine how these structural changes influence the binding and interactions of these compounds to the CB1 receptor.

The results of this study show the influence structural characteristics have on the docking score and relative binding affinity of the synthetic cannabinoids to the CB1 receptor. One structural characteristic examined in this study was the increasing alkyl chain length on the naphthalene group present in these ligands. The results were able to show a trend in docking score when increasing the alkyl chain length by one carbon on the naphthalene from no alkyl chain to a pentyl chain. The trend in docking scores was also shown to be dependent on the length of the alkyl chain (butyl or pentyl) that was on the nitrogen of the indole portion of the compound. However, when the structural characteristic of the carbonyl group was removed from the structures, the trend in docking scores was found to be reversed. A correlation was also seen with the docking score trend and the number of aromatic stacking interactions taking place in the binding pocket. Examining the JWH ligands docking revealed key interactions that were seen consistently in the active site. These interactions included Trp 279, Trp 356, Phe 177, and Phe 200. Identifying the key interactions between the synthetic cannabinoids and the CB1 receptor, and how their structural components influence the interactions, can lead to a better understanding of the effects of these drugs, including toxicity and potential for abuse. Future research will include the development of a database consisting of known synthetic cannabinoids, as well as newly designed synthetic cannabinoids, and pharmacological information of these compounds to aid in the rapid identification and understanding of synthetic cannabinoids as they appear in the drug market.

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