K4 A Study of an Active-State Cannabinoids 1 (CB1) Receptor Model and Synthetic Cannabinoid Interactions

Caroline Spencer, BS, 2000 Lexington Pointe Drive, Apt 4K, Oxford, MS 38655; Kelsey L. Pettus, BSc, University of Mississippi, 145 Martindale, University, MS 38677; Pankaj Pandey, PhD, University of Mississippi, 145 Martindale, University, MS 38677; Robert J. Doerksen, PhD, University of Mississippi, 145 Martindale, University, MS 38677; and Murrell Godfrey, PhD, University of Mississippi, Chemistry & Biochemistry, Coulter Hall, Rm 115, University, MS 38677*

After attending this presentation, attendees will better understand the interactions of select classes of synthetic cannabinoids and their metabolites with a CB1 receptor model.

This presentation will impact the forensic science community by contributing to the understanding of essential interactions between specific substituents of different classes of synthetic cannabinoids with specific CB1 receptor residues through molecular modeling.

Synthetic cannabinoids have emerged onto the drug scene as an alternative to marijuana.[1] Similar to Δ^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] Two cannabinoid receptor subtypes have been identified, CB1 and CB2. The binding of THC and synthetic cannabinoids to the CB1 receptor is believed to be the cause of the psychoactive effects due to the CB1 receptor's location in the brain.

In this study, an active-state CB1 receptor model proposed by the Doerksen lab was used to compare the ligand-receptor interactions between the CB1 receptor and the various families of synthetic cannabinoids and the THC compound. This study was done using Schrodinger's Maestro molecular modeling program. Synthetic cannabinoids from the different classes 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 prepped 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 were set to give the five best possible poses, or positions, for the ligand interacting with the receptor. Once the ligands were docked to the CB1 receptor model, the interactions were analyzed. The information collected from this study included the amino acid residue interaction with the ligands and the bond distances of these interactions, the docking score of each ligand and each pose, and ligand Ki values. This study was also able to show more specific information pertaining to these interactions such as the presence of Pi-Pi stacking, hydrophobic residue interactions, charged or polar residues, and solvent exposure.

Results from this study show the potential of revealing key residue interactions with the CB1 receptor and how the interactions vary by class and chemical structure within classes. Identifying the key interactions between the synthetic cannabinoids and the CB1 receptor has the potential for a better understanding of the effects of these drugs, including toxicity and potential for abuse. A computer program database could be developed to help predict new structures and different classes of synthetic cannabinoids that have not previously been identified. Future research will include studying more classes of synthetic cannabinoids and other synthetic drugs along with the metabolites of these substances.

Reference(s):

1. Liana F.; Walter F. Beyond THC: The New Generation of Cannabinoid Designer Drugs. *Frontiers in Behavioral Neuroscience*. 2011, 5.
2. Shim JY.; 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

Synthetic Cannabinoid, CB1 Receptor, Molecular Modeling