

Title – Cannabinoid Receptor Modulators for the Treatment of Liver Fibrosis

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Abstract

This research intends to address the issue of non-alcoholic fatty liver disease. This disease is an accumulation of fat in the liver that can result in inflammation of the liver, cirrhosis, steatohepatitis (NASH) and potentially even liver failure. This disease is affecting more and more people, and the number keeps growing due to the increasing amount of obese Americans. One reported method to mitigate alcoholic and non-alcoholic liver fibrosis is the modulation of cannabinoid receptors (CB1 and CB2). While CB1 receptors can facilitate liver fibrosis, the antagonists can be anti-fibrotic. Not only are the CB1 antagonists anti-fibrotic, but the CB2 receptor agonists are also anti-fibrotic. Because of this property, it is hypothesized that compounds that obtain both CB1 antagonist activity and CB2 agonist activity would be highly effective in attenuating liver fibrosis. However, because CB1 antagonists have established adverse effects on the central nervous system – the brain and spinal cord – these compounds should not be able to penetrate the CNS. This research focuses on tethering a peripherally selective CB1 antagonist with one of four different compounds with known CB2 agonist activity.

One of these four different compounds, when tethered, may help the compound to affect both CB1 and CB2 receptors, thus making the compound more effective. The compound AZ11713908 has been noted as a peripherally selective CB1/CB2 agonist, while the other three compounds are CB2 agonists selective against CB1. Once synthesized, these compounds will be tested to determine their effect on both the cannabinoid receptors and on liver fibrosis. This research should serve as the basis of cannabinoid receptor modulator development and potential NASH treatment and potentially develop interest in the liver fibrosis field.

Christian worldview integration

Our research is informed by a Christian worldview in several important ways. First, our research is driven by a desire to serve those living with obesity and liver failure. We want to do this, specifically, by increasing the body of scientific and experimental knowledge about key receptors in the liver. We are motivated to explore ways to improve liver function because we believe that every person is created in the image of God. The Christian worldview affirms, and we embrace, that every human life is valuable and deserves our care and protection. Additionally, our research may help those working in the pharmaceutical industry to create more effective and reasonably priced drugs. These drugs in turn can help improve the quality of life of those who live with common illnesses including obesity and fatty liver disease.

Another way that a Christian worldview influences our research is that it enhances our appreciation of the body's systems. According to the theory of evolution, many of the organs and functions of the body may be remnants from our ancestral past, vestigial from the apes that preceded us. However, the Christian worldview affirms that our bodies are wonderfully designed by God and that the organs, systems, and pathways are specifically designed to the human race. This means that many aspects of the human body can be understood and even

influenced in ways that benefit our health. Thus the Christian worldview inherently promotes scientific research, like that which we are performing, in its teachings about the value of human life and the creative work of God.