

Presenter: Abigail Lenz, alenz@liberty.edu

Faculty mentor: Alan Fulp [abfulp@liberty.edu](mailto:abfulp@liberty.edu)

Department: Biology and Chemistry

Research area: Organic Chemistry (pharmaceutical focus)

## Design and Synthesis of Peripherally Selective CB1 Antagonist/CB2 Agonist to Hinder and Reverse Hepatic Fibrosis

Hepatic fibrosis, a precursor to cirrhosis, has recently increased incidence. The progression of fibrosis to cirrhosis is a dominant instigator of hepatic failure and liver cancer, thus making the inhibition of this progression a promising treatment option <sup>1</sup>.

There have been two cannabinoid receptors, CB1 and CB2, identified to date. Modulation of these gene protein coupled receptors is known to have psychoactive, inflammatory, and proliferative in humans <sup>2</sup>. These two receptors have been linked to liver fibrosis. The CB1 receptors in the liver enhance the progression of liver disease by promoting fibrinogenesis <sup>3</sup>. The CB2 receptors have been reported to inhibit or reverse fibrinogenesis <sup>4</sup>.

Therapies that target CB1 receptors in the central nervous system (CNS) have adverse mood-related side effects. However, peripherally selective CB1 antagonists provide an alternative strategy that avoids CNS side effects. This study aimed to synthesize peripherally selective CB1 antagonist/CB2 agonist that mitigates hepatic fibrosis and its secondary pathologies.

### References

1. Mahmoud, M. F.; Swefy, S. E.; Hasan, R. A.; Ibrahim, A., Role of cannabinoid receptors in hepatic fibrosis and apoptosis associated with bile duct ligation in rats. *European journal of pharmacology* **2014**, *742*, 118-24.
2. (a) Reichenbach, V.; Ros, J.; Fernandez-Varo, G.; Casals, G.; Melgar-Lesmes, P.; Campos, T.; Makriyannis, A.; Morales-Ruiz, M.; Jimenez, W., Prevention of fibrosis progression in CCl4-treated rats: role of the hepatic endocannabinoid and apelin systems. *The Journal of pharmacology and experimental therapeutics* **2012**, *340* (3), 629-37; (b) Tam, J.; Vemuri, V. K.; Liu, J.; Batkai, S.; Mukhopadhyay, B.; Godlewski, G.; Osei-Hyiaman, D.; Ohnuma, S.; Ambudkar, S. V.; Pickel, J.; Makriyannis, A.; Kunos, G., Peripheral CB1 cannabinoid receptor blockade improves cardiometabolic risk in mouse models of obesity. *The Journal of clinical investigation* **2010**, *120* (8), 2953-66.
3. Mallat, A.; Lotersztajn, S., Cannabinoid receptors as therapeutic targets in the management of liver diseases. *Drug news & perspectives* **2008**, *21* (7), 363-8.
4. Teixeira-Clerc, F.; Julien, B.; Grenard, P.; Tran Van Nhieu, J.; Deveaux, V.; Li, L.; Serriere-Lanneau, V.; Ledent, C.; Mallat, A.; Lotersztajn, S., CB1 cannabinoid receptor antagonism: a new strategy for the treatment of liver fibrosis. *Nature medicine* **2006**, *12* (6), 671-6.

