Title: **Predicting the Conformational Change of the 5-HT-2C Receptor in Response to CTW0415: Applications in Treating Substance Use Disorder**

Substance use disorder is an increasingly relevant issue that has yet to be fully explored in terms of pharmacological treatments. The serotonin type 2C (5-HT-2C) receptor has been targeted as a potential treatment for obesity and multiple psychiatric disorders including depression, anxiety, and substance use disorders. Serotonin is a major modulator of dopamine activity in the brain, in which the 5-HT-2C receptor has a major influence on dopamine inhibition and is involved in influencing the effects of antipsychotics. CTW0415 is a newly discovered positive allosteric modulator (PAM) for the 5-HT-2C receptor with implications in the development of treatments involving the 5-HT-2C receptor through the potentiation of agonist-induced effects. In this project, we modeled the theoretical conformational change to the 5-HT-2C receptor's structure that results in increased agonist efficacy in response to the binding of CTW0415. We predict that the increased agonist efficacy from CTW0415 comes from a less sterically-hindered Gαq in response to the disrupted π-cation stabilization of 5-HT-2C bound to Gαq and stabilization of the active conformation of the receptor. The show this proposed mechanism we developed using 3D printing, a simplified model to illustrate the change as a consumer level. Our model of the proposed conformational change of the 5-HT-2C receptor in response to CTW0415 has implications in the development of drugs that target the 5-HT-2C receptor in pharmacological treatments.