Development of δ-Opioid Receptor (DOR) Positive Allosteric Modulators (PAMs) for the Treatment of Depression

Sherrice Zhang
Advisor: Dr. Andy White
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Currently, more than 7% (17.3 million) of the adults in the U.S. have experienced at least one episode of major or persistent depression. Common treatment for depression includes selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). However, less than 50% of treated patients report full remission after 3 years of treatment. Recent studies show that activation of DORs with an agonist has great potential for treating depression. Since activated DORs have been shown to be effective for treating depression, research has been done on developing DOR agonists. However, serious on-target side effects such as convulsions have been observed with DOR agonists. It has been found that these antidepressant effects to the opiate agonists are induced by the coupling of G-proteins.

To address these problems, we attenuate the level of different signaling pathways by changing the conformations, which is known as biased agonism, through allosteric modulation. First, in order to achieve biased agonism, the biomolecular interaction between the ligands and the δ-opioid receptors must favor a particular receptor conformation that will in turn favor the binding to either G-proteins or β-arrestins. Ligands that are G-proteins-biased can enhance the desired therapeutic properties with reduced side effects. Second, allosteric modulation of the receptors are thought to be a safer therapeutic strategy. The positive allosteric modulation can increase not only the affinity but also the efficacy of the orthosteric ligands. PAMs can induce the biased agonism by modulating the activated signaling pathways of the unbiased ligands to the desired pathway through changing the conformations of the receptor. We are optimizing the lead compound, BMS986187, which is a known DOR selective PAM, to gain not only potency and efficacy, but also brain penetrant properties and selectivity over μ-opioid receptors.