Design and Synthesis of Bifunctional Opioid Receptor Peptidomimetics

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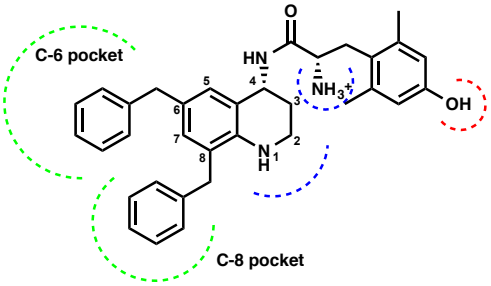
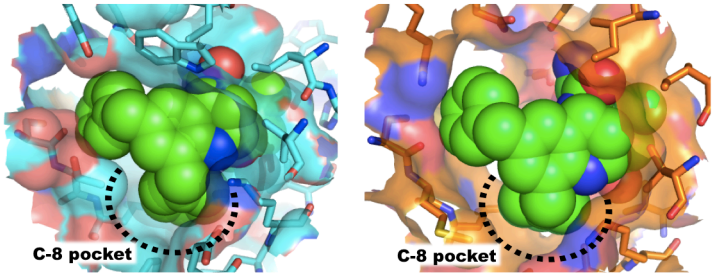
Currently, opioid analgesics are the most efficacious drugs for the treatment of moderate to severe pain. Although opioids such as morphine are effective, their prolonged use can result in the development of tolerance and dependence. However, several studies in mouse models have demonstrated that stimulation of the μ opioid receptor (MOR), with concomitant blockade of the δ opioid receptor (DOR), can produce antinociception while *decreasing the risk of tolerance and dependence*. For pharmacokinetic simplicity, we are developing agents that elicit both MOR agonism (ag) and DOR antagonism (antag) with a single ligand. Toward this goal, we have developed a series of peptidomimetics based on a novel tetrahydroquinoline (THQ) scaffold that show high affinity for both MOR and DOR, with significantly less affinity for the κ opioid receptor (KOR). Importantly, these ligands exhibit the desired MOR(ag)/DOR(antag) *in vitro* profile and represent a promising lead in the development of opioid analgesics with reduced side effects.



Our previously reported THQ-based peptidomimetics show *in vivo* activity as analgesics following peripheral administration, as measured by the warm water tail withdrawal (WWTW) assay in mice. However, many of our reported ligands showed a higher binding affinity for MOR over DOR, which could diminish the effects of DOR antagonism, a key component in the reduction of side effects. Guided by computational models, X-ray structures, and pharmacological data, we probe new chemical space near the C-8 position of the THQ scaffold. Initial substitutions suggest that occupancy of the pocket near the C-8 position elicits a significantly improved balance in binding (K_i = 1 nM) at MOR and DOR. Supported by our models and binding data, deep, lipophilic pendants at the C-8 position may generate important non-polar contacts within the DOR binding pocket that facilitate improved binding. Incorporation of polar moieties at the same position may cause a change in ligand conformation, mitigating the positive effects of C-8 binding pocket occupancy. In the effort of developing drug-like peptidomimetics with *in vivo* analgesic activity, a variety of C-8 substitutions have been synthesized and assayed. Mouse studies on this novel series of C-8 substituted ligands show efficacy in the WWTW assay.



We hypothesize that further optimization at the C-8 position will yield opioid ligands that elicit both activation of MOR and blockade of DOR. As such, continued development of these balanced MOR/DOR ligands may yield potent analgesics with reduced tolerance and dependence liabilities commonly associated with clinically used opioids.

We additionally seek to develop a series of potent MOR/KOR ligands, with the potential to aid in cocaine abuse therapy. Emerging pre-clinical and clinical studies have shown positive results of mixed-efficacy MOR/KOR opioids regarding their ability to reduce cocaine self-administration and prevent relapse once drug abstinence has been established in cocaine or polydrug dependent patients. Using preliminary THQ-based MOR/KOR-selective leads, we plan to continue developing bifunctional opioid peptidomimetics as investigational agents in the treatment of drug dependence.