Design and Synthesis of Opioid Peptidomimetics for Treatment of Addiction

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Medicinal Chemistry Student Seminar

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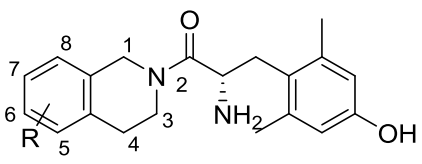
Drug misuse, abuse, and addiction are major health concerns. Drug overdose is the leading cause of accidental death in the U.S., and the negative societal and economic impacts of drug abuse are substantial. Cocaine is one of the most widely abused illegal drugs. Despite widespread understanding in the medical and research communities that addiction results in physiological changes in the brain, there is currently no FDA-approved pharmacological treatment for cocaine addiction, making this an important unmet medical need.

Opioids are capable of modulating pain, mood, and reward. The three major opioid receptor types - μ, δ, and κ opioid receptors (MOR, DOR, and KOR, respectively) - have each been shown to mediate a diverse assortment of molecular and cellular responses and to modulate a variety of pharmacological behaviors. The role of the opioid system in regulating the rewarding properties of drugs of abuse and the contribution of this system to the development of addiction are being extensively studied, and these reward-modulating properties demonstrate potential for opioids to be used in the treatment of addiction.

Traditional drug discovery favors the development of selective ligands. However, in the opioid field, there has been a move away from the development of selective ligands towards the development of multifunctional ligands as the potential utility of these agents has been demonstrated. Specifically, there is evidence to suggest that a MOR partial agonist/KOR agonist may be useful in the treatment of cocaine addiction. It has been demonstrated that KOR agonists have the potential to reduce cocaine self-administration in non-human primates. It has been suggested that weak MOR agonism may be able to mitigate dysphoria associated with KOR agonism, increasing the therapeutic potential of a KOR agonist. Thus, multifunctional MOR/KOR ligands offer potential advantages over selective KOR agonists.

The Dimethyltyrosine-Tetrahydroisoquinoline (DMT-Tiq) scaffold has been included in opioid ligands for decades. We are repurposing this classically DOR selective antagonist scaffold for development of novel multifunctional opioid ligands by taking advantage of the previously unexplored chemical space surrounding substitutions on the tetrahydroisoquinoline aromatic ring. Installation of a 7-benzyl pendant introduced strong KOR agonism. Preliminary results from a series of small modifications show promise towards the development of a MOR partial agonist/KOR agonist. Future efforts to improve this profile will be guided by computational models of compounds in this series docked to the orthosteric sites of MOR and KOR. We have begun to synthesize a number of structurally similar compounds with slightly different pharmacological profiles to test different balances between MOR and KOR agonism. Synthesis of additional analogues will continue, and the most promising compounds in this series will be screened in rats for their ability to block cocaine discrimination and in a stress-induced reinstatement assay for reduction of cocaine self-administration.

DMT-Tiq



Dimethyltyrosine - Tetrahydroisoquinoline (DMT-Tiq) scaffold with carbon numbering