**Pharmacological Characterization of the Novel Phenylethylmorphan ACH.1.132: A Putative Opioid Mu Agonist/Delta Antagonist**

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**Introduction:** Current opioid therapy for the treatment of moderate to severe pain is associated with significant side effects that limit their clinical utility. These side effects include the development of tolerance, physical dependence and addiction liability. It has been proposed that inhibition of d opioid receptor function during µ agonist stimulation may attenuate the development of these adverse effects while maintaining desired analgesic effects. The focus of our research has been to synthesize a single chemical entity that has both mu agonist and delta antagonist properties (e.g., ACH.1.132). Our hypothesis was that compounds that simultaneously stimulate mu receptors and antagonize d receptors would produce antinociception with less side effects compared to morphine.

**Methods:** Male ICR mice (25-35 g) were used to test the antinociceptive effects of ACH.1.132 and morphine in the 55°C tail flick test and the acetic acid abdominal constriction assay. In vivo receptor selectivity was determined by pre-treating mice with µ (b-FNA), d (naltrindole), and k (nor-BNI) selective antagonists. Mice were also evaluated for acute and chronic physical dependence using naloxone to precipitate withdrawal. Lastly, the development of tolerance was examined using repeated injections of the respective agonists for three days and determining potencies of the agonists in the tail-flick assay.

**Results:** ACH.1.132 was found to be approximately 50 times more potent than morphine in the 55°C tail flick test and ten times more potent in the abdominal constriction test. The primary site of action for these effects was µ opioid receptors in the CNS. Similar levels of acute and chronic dependence were found between ACH.1.132 and morphine, however ACH.1.132 produced significantly less tolerance.

**Conclusion:** ACH.1.132 produced dose-related antinociceptive effects, being more potent than morphine with similar efficacy. ACH.1.132 produced equivalent levels of physical dependence compared to morphine and less tolerance. The results are discussed in the context of developing an ideal ratio of µ agonist/d antagonist activity and the dissociation of opioid tolerance from physical dependence.