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Pharmacological Properties of JDTic: A Novel Kappa-Opioid Receptor Antagonist


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Antagonists selective for the kappa-opioid receptor have shown activity in animal models representing several central nervous system disorders including stress, depression, schizophrenia, and relapse to substance abuse. Suitable kappa-opioid receptor antagonists could therefore offer relief from such maladies. At the outset of our work, however, there were no orally active kappa-opioid receptor antagonists. Overcoming this hurdle presented a significant challenge.

Existing potent and selective compounds were all derived from the oxymorphone molecular scaffold, an opiate similar to morphine, and were believed to have common modes of receptor selective binding. To surmount the shortcomings associated with existing antagonists, we began our work starting from an unrelated phenylpiperidine scaffold. These efforts culminated in the discovery of JDTic, the prototype of a novel class of kappa-opioid receptor antagonist. In vitro studies revealed picomolar antagonist potency for the kappa-opioid receptor coupled with high selectivity as compared to the remaining opioid receptors, mu and delta. More importantly, JDTic exhibited activity in animal studies following oral administration.

In three different animal models and three different species, JDTic dose-dependently reversed the actions of kappa-opioid receptor selective agonists while simultaneously sparing the activity of morphine-like compounds. The latter finding was important since it suggested that JDTic would not interfere with the activity of morphine-like medications used for relief of severe pain and would not precipitate withdrawal in opiate addicts. Together these findings revealed that JDTic is an orally active, long-acting, potent, and selective kappa-opioid receptor antagonist suitable for further development.

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