Strategies and Tactics for Lead Optimization of Melanin Concentrating Hormone Receptor Antagonists for the Treatment of Obesity

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The discovery of small molecule melanin concentrating hormone receptor (MCHr1) antagonists as novel therapeutic agents for the treatment of obesity has been actively pursued across the pharmaceutical industry. While multiple chemotypes of small molecule MCHr1 antagonists have been identified and shown to deliver weight loss in animal models of obesity, many of these lead compounds have been found to cross-react with the hERG channel and/or demonstrate deleterious effects on cardiovascular hemodynamic parameters. Unfortunately, all initial lead compounds negatively effected hemodynamics in a pentobarbital-anesthetized dog cardiovascular model at low multiples of their corresponding plasma concentrations. Consequently, an inactin-anesthetized rat cardiovascular model was used for rapid screening of more than 130 compounds from 15 unique chemical series. Subsequent optimization afforded advanced compounds that combined rat and dog cardiovascular safety with oral activity in a diet-induced-obese mouse efficacy model. Our lead optimization process for a diverse set of MCHr1 antagonists, focusing on optimization of selectivity profile, brain penetration, cardiovascular safety, efficacy, and *in vivo* therapeutic index will be presented.

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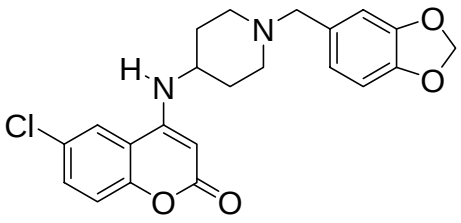

IC_{50} 2 nM
Ca^{2+} flux IC_{50} 28 nM
DIO mouse (10 mpk):
Br AUC 4166 ng*hr/g
Brain $t_{1/2}$ 12.7 h