Chemistry and Pharmacology of *Iboga* Alkaloids

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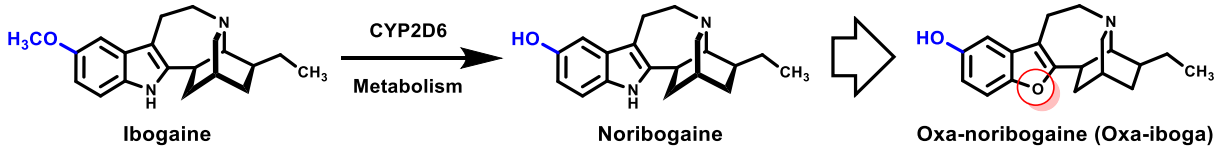

Ibogaine **Noribogaine** **Oxa-noribogaine (Oxa-iboga)**

Ibogaine is the major psychoactive alkaloid of *Tabernanthe iboga*, a shrub native to West Central Africa. Since the 1960's, ibogaine has been known for its ability to interrupt drug addiction. Considering the growing drug use and drug overdose epidemics in the U.S., there is an urgent need for new therapeutics to treat opioid use disorder (OUD) and other substance use disorders (SUDs) - and ibogaine represents an important prototype in this direction. Two recent observational clinical studies confirmed the earlier reports of ibogaine's effects that include a rapid and long-lasting relief of opioid withdrawal symptoms and cravings, and an increased rate and duration of abstinence in opioid-dependent subjects. The observed response size was comparable to that of methadone replacement therapy. These clinical observations have been replicated in preclinical rodent models of SUDs, including attenuation of self-administration of opioids, cocaine, alcohol and nicotine, mitigation of naloxone-precipitated withdrawal symptoms, and reversal of analgesic tolerance in opioid-dependent animals. The current mechanistic model for ibogaine invokes a role for several key molecular targets, including the α3β4 nicotinic receptor, kappa opioid receptor (KOR), and monoamine transporters. An active metabolite, noribogaine, also makes a significant contribution to the pharmacological effects of ibogaine.

We have developed new synthetic methods for *de novo* synthesis of the *iboga* alkaloid scaffold, which unlocks unlimited exploration of its pharmacology. We have found that substitution of the indole amine group with other heteroatoms enables accentuation of specific mechanisms of the noribogaine pharmacological profile. Specifically, our research focused on benzofuran analogs of noribogaine (*oxa*-noribogaine) that represent a new class of KOR modulators. Our preliminary results have shown that *oxa*-noribogaine induces a potent analgesia with no sedative/dissociative side effects in mice, and complete and long-lasting suppression of morphine self-administration in rats. Furthermore, we explored the *oxa-iboga* system in terms of opioid receptor pharmacology and signaling, off-target pharmacology, *in vivo* target validation, and efficacy examination in rat models of OUD.

Our central hypothesis is that the benzofuran *iboga* analogs represent an atypical class of KOR modulators that enables the favorable separation of analgesia and side effects, as well as the efficacy in OUD models.