**Trypsin-Labile Opioid Prodrugs for Extended-Release of Oxycodone and Hydromorphone**

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**Background/Introduction:** Every year in the United States prescription opioid abuse is responsible for tens of thousands of deaths and tens of billions of dollars in increased health care costs. Our goal was to develop trypsin-labile opioid prodrugs of oxycodone and hydromorphone that provided an extended-release profile following oral ingestion but were inactive following parenteral (IV) administration.

**Methods:** Signature Therapeutics’s prodrugs of oxycodone and hydromorphone were designed to release opioid via a two-step process including: 1) bioactivation by trypsin, followed by 2) a cyclization release reaction. Key molecular components include a chemically robust N-substituted carbamate functionality that covalently attaches the active opioid to a diamine linker, which is terminally substituted with a N-acylated L-arginine (amino acid) moiety. Upon oral dosing and exposure to trypsin, the amino acid moiety is cleaved by enzymatic hydrolysis, exposing a nucleophilic terminal amine. The otherwise stable carbamate linkage undergoes an intramolecular attack from the exposed nucleophilic terminal amine, resulting in liberation of the opioid at a controlled rate. This controlled cyclization rate allows for a non-formulation approach for delivering opioids in an extended-release manner. We measured the *in vitro* rate of appearance of opioid following exposure to trypsin, as well as the time-course of systemic opioid in rats and dogs following oral and intravenous administration. We also measured the ability of the opioid prodrug to cross into the central nervous system and the activity at the μ-opioid receptor.

**Results:** Following *in vitro* exposure to trypsin, cleavage of the amino acid component for both the oxycodone and hydromorphone prodrugs was rapid (t1/2 < 5min). However, the *in vitro* half-life for the subsequent intramolecular cyclization reaction, forming cyclic urea and releasing the opioid moiety was ~3 hours for both the oxycodone and hydromorphone prodrugs, under physiological conditions. Following oral administration of the opioids prodrug to rats, the oxycodone and hydromorphone concentrations peaked approximately 2 hours after administration. Following intravenous administration of the opioid prodrugs to rats, systemic conversion to parent opioid was extremely low (<0.01%). The oxycodone prodrug had 15% the potency of oxycodone at the μ-opioid receptor, and 1.2% the penetration across the blood brain barrier (rat), resulting in < 0.2% central activity of the opioid activity of intravenous oxycodone. The hydromorphone prodrug had < 0.1% of the potency of hydromorphone at the μ-opioid receptor, and < 2% of the penetration across the blood brain barrier (rat), resulting in potency << 0.01% of the opioid activity of intravenous hydromorphone.

**Conclusions:** We have created trypsin-labile, extended-release prodrugs of oxycodone and hydromorphone that release the parent opioid following oral administration. The extended-release profile is intrinsic to the molecular structure and thus cannot be overcome by physical methods (e.g., chewing). Minimal conversion of the prodrug to the active opioid occurs following parenteral (IV) administration, and the prodrugs have almost no ability to reach and activate the μ-opioid receptor within the central nervous system.

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