

Samidorphan: Discovery of a Medication to Treat Central Nervous System Disorders

At Rensselaer Polytechnic Institute, the main goal of Professor Mark Wentland's research group is to design, synthesize and characterize oral, long-acting modulators of opioid G protein-coupled receptors (GPCRs) as medications to treat cocaine abuse and other central nervous system disorders in humans.

A common structural feature of a large number of opioids is a phenolic-OH group (see prototypic opioid pharmacophore below) that plays a crucial role in molecular recognition via H-bonding to a histidine residue of a mu opioid GPCR. For many opioids, however, this OH group is responsible for poor oral bioavailability and/or short half-life via O-glucuronidation.

In 2001, we published the first report that a carboxamide group (CONH₂) was an effective replacement for this prototypic phenolic-OH group of many opioids. In addition to high affinity binding to opioid GPCRs, certain carboxamido-substituted opioids have much improved pharmacokinetic properties (relative to their phenolic-OH counterparts) as a consequence of high metabolic stability. Since 2001 our research group has focused on capitalizing on this discovery to achieve our main goal. Our first-generation opioid modulator in this series was 8-carboxamidocyclazocine (8-CAC). Subsequent optimization of 8-CAC provided the highly potent mu-antagonist, samidorphan. Samidorphan first appeared in the scientific literature in 2005. Our publications describing these discoveries as well as a wealth of structure-activity relationship data are cataloged in PubMed.

In 2006, Rensselaer signed a license agreement granting Alkermes Inc, exclusive rights to a library of opioid compounds discovered by our team. Alkermes has subsequently sponsored multiple Phase 1, 2 and 3 clinical trials involving the use of samidorphan to treat CNS disorders. Two combination medications containing samidorphan are currently in late-stage development - ALKS 5461 (samidorphan in combination with buprenorphine) and ALKS 3831 (samidorphan in combination with olanzapine) have potential for treating patients with major depressive disorder and schizophrenia, respectively. The following press releases from Alkermes provide additional information:

Alkermes Announces U.S. Food and Drug Administration Acceptance of ALKS 3831 New Drug Application for Treatment of Schizophrenia and Bipolar I Disorder

Alkermes Receives Complete Response Letter From U.S. Food and Drug Administration for ALKS 5461 New Drug Application

![Prototypic opioid pharmacophore](image1.png)

![8-CAC](image2.png)

![Samidorphan](image3.png)

Prototypic opioid pharmacophore

8-CAC

Samidorphan

$K_i$(mu) = 0.31 nM

$K_i$(mu) = 0.052 nM
In addition to samidorphan, other compounds from Rensselaer's patent estate that have entered clinical trials are ALKS 37, ALKS 7106 and ALKS 7119.

Collaborators for this opioid GPCR modulator research program are:
   - Dr. Jean Bidlack and coworkers at the University of Rochester
   - Discovery and development personnel at Alkermes, Inc.

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