

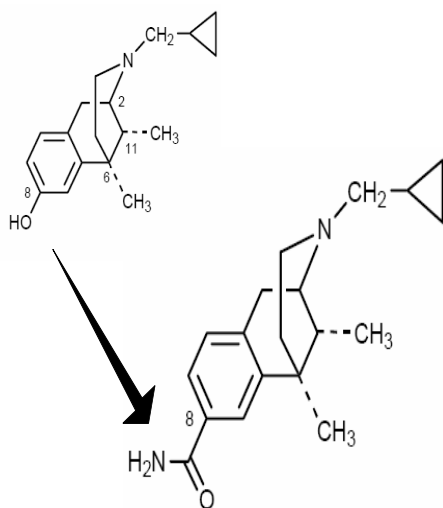


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New Opiate Technology to treat addiction and manage pain

Many opioid receptor-interactive compounds, including those used for analgesia and for treating drug addiction, have limited utility due to poor oral bioavailability and/or very rapid clearance from the body. As part of a NIH/NIDA-sponsored effort to identify orally available and long-lasting agents to treat cocaine and heroin addiction in humans, researchers at Rensselaer have discovered that a carboxamide group (CONH_2) can replace the phenolic OH groups of many opiates without any loss in binding affinity. Among the hundreds of potentially useful compounds that can be derived by this method, Rensselaer scientists have made and evaluated over twenty carboxamide derivatives of known phenolic OH-containing opiates. At least six of the highly active (in vitro) compounds have been made in large enough scale for evaluation in mice or monkeys for analgesic or anticocaine properties. Patents covering the compounds and methods are under evaluation by U.S. and foreign patent offices.

This process can be used to produce a portfolio of opiate compounds with enhanced oral bioavailability .



Compounds produced by the Rensselaer method have the potential to treat the following addictive disorders through long-lasting oral administration

- Nicotine
- Cocaine
- Alcohol
- Heroin

Compounds may also have applications for treatment of severe pain, particularly in patients who cannot metabolize codeine.

For additional information

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Opiate Technology intellectual property protection

PATENT

COVERAGE

**U.S. 6,784,187
Issued**

- A structurally defined genus of morphinans in which the phenol is replaced by any of our entire catalog of isosteres, including formamide and nitrogen-linked isosteres
- Analogs of naloxone, naltrexone, oxymorphone, nalorphine, nalbuphine and similar compounds

**U.S 10/409,803
Allowed**

- Methods for treating pain, pruritis, diarrhea, irritable bowel syndrome, gastrointestinal motility disorder, obesity, respiratory depression, convulsions, coughing, hyperalgesia and drug addiction with these compounds.
- Methanobenzazocines (cyclazocine, ketocyclazocine, pentazocine and the like)
- Four-ring morphinans (butorphanol, dextromethorphan ring system), six-ring morphinans (buprenorphine, etorphine, diprenorphine ring system), miscellaneous fused multi-ring systems

**Europe 01992702.9
Allowed**

- Structures (methanobenzazocines through four-, five, and six-ring morphinans) in which the phenol is converted to a carbon-linked substituent, e.g. a carboxamide, thioamide, hydroxyamidine, methanol, methylthiol or methylamine.

Europe 03013544.6

- Above claims, as well as structures in which the phenol is converted into an ester, ketone or a formamide
- Other derivatives in which the phenol is replaced by a nitrogen-attached residue
- Processes for converting benzomorphan (or morphinan) phenol to a carboxamide, a hydroxamide or a thiocarboxamide.

Japan P2002-539332

- Composition claims to all significant modifications (carboxamide, thioamide, hydroxamide, formamide, etc.) and all of the ring systems (methanobenzazocines, four-, five-, and six-ring morphinans).

Japan P2003-422779

- Methods / use of above

Canada 2,426,942

- Examination not yet requested

Australia 045 AAU

- Examination not yet requested

O-glucuronidation of the phenolic OH in the liver, brain, and other organs is the major cause of poor in vivo performance of opiate derivatives.

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The phenolic hydroxyl (OH) group of 4,5 α -epoxymorphinans (morphine, codeine, buprenorphine, naltrexone, etc.) and 2,6-methano-3-benzazocines (pentazocine, cyclazocine, etc.) is what allows efficient binding to opioid receptors. This same hydroxyl group, however, is often the cause of poor oral bioavailability and rapid clearance rates of the drug from the body.

Researchers have developed methods such as the prodrug approach and alternate drug delivery systems to avoid these opiate pharmacokinetic and metabolism problems. For example, the prodrug codeine is administered as a pill to be absorbed through the intestinal wall, then transformed during the first pass through the liver into its biologically active form, morphine. In another example, sublingual delivery is used to mitigate the poor oral bioavailability of Buprenorphine (Suboxone®), an opiate approved in 2002 to treat heroin addiction. The pill is placed under the tongue for direct absorption because O-glucuronidation occurring during the first pass through the liver inactivates the drug when it is administered orally.

Unfortunately, prodrug and alternate delivery systems are not desirable in all circumstances. Liver polymorphisms prevent many individuals from processing prodrugs, and alternate delivery systems cannot replicate the convenience of oral administration. An ideal solution is to substitute the problematic phenolic hydroxyl group with better-performing functional groups. Attempts at making such a substitution in the past, however, generally resulted in the complete or near-complete loss of receptor binding.

Researchers at Rensselaer have a solution to the opiate phenolic hydroxyl substitution problem. As part of an effort to identify orally available and long-lasting agents to treat cocaine and heroin addiction in humans, Rensselaer scientists discovered that a carboxamide group (CONH₂) can replace the phenolic hydroxyl groups of many opiates without any loss in binding affinity.

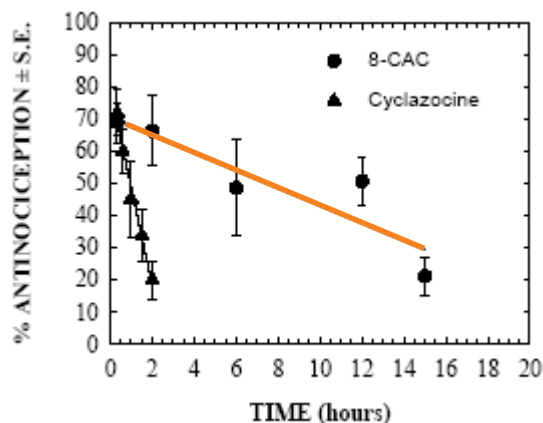
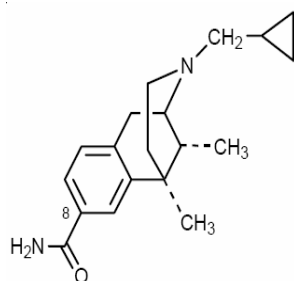
Core structures in which the phenolic hydroxyl / CONH₂ replacement has been successfully demonstrated include morphine, naltrexone, naltrindole, cyclazocine and enantiomers, EKC and enantiomers, ketocyclazocine, Mr2034, buprenorphine, and others. This method is not limited to OH replacement by carboxamides - formamide, thiocarboxamide, and hydroxamic acid may replace the phenolic hydroxyl group as well.

Opioid binding affinity

Researchers have produced and evaluated over twenty carboxamide derivatives of known phenolic hydroxide-containing opiates. In twelve of these cases, binding affinity to opioid receptors was comparable to the original compound, and in three cases, superior activity was observed. When this substitution was performed on cyclazocine, the lead compound for the cocaine addiction research, the resulting novel carboxamide, 8-CAC, had very similar receptor binding affinity to cyclazocine in vitro. Additionally, when evaluated in mice 8-CAC showed a fifteen hour duration of antinociception (the human equivalent of analgesia) compared to a two hour duration for cyclazocine.

In several new compounds, opioid binding affinity actually increased after substituting the OH.

Modification of cyclazocine by the Rensselaer method produced 8-CAC, a compound with similar binding affinity and increased duration in vivo.



Six highly active (in vitro) compounds have been made in large enough scale for evaluation in mice or monkeys for analgesic or anticocaine properties.

Applications

Rensselaer's new opiate technology has great potential to treat certain addictive disorders by ameliorating the pharmacokinetic problems associated with phenolic hydroxyl-containing opiates currently used to treat these afflictions. For example, the carboxamide analogue to buprenorphine has very similar in vitro potency and pharmacology profile to buprenorphine. Buprenorphine

(Suboxone®) must be administered sublingually, causing greater inconvenience to the patient compared to the oral administration of the Rensselaer compound.

Rensselaer scientists synthesized a carboxamide analogue of naltrexone (Revia®), which is used for the treatment of alcohol dependence, and found it to be highly active. Naltrexone has low oral bioavailability (5 to 40%) due to high first-pass metabolism. In an attempt to increase oral activity and duration of action, researchers outside of Rensselaer are developing alternate delivery systems for the drug, such as skin patches and extended release formulations. Rensselaer's approach to evaluate the carboxamide analogue of naltrexone is much simpler than elaborate formulation strategies, and more convenient for the end-user than patches.

This technology is applicable to the treatment of severe pain as well. For example, *CYP2D6* mediated O-demethylation of codeine to morphine is central to its analgesic effects. However, *CYP2D6* is one of several P450 metabolizing enzymes that is polymorphically distributed in humans. Defective splicing, gene deletion, and natural mutations of *CYP2D6* result in a "poor metabolizer" profile in these subsets of patients and low efficacy of orally delivered codeine. By eliminating the prodrug approach, orally administered carboxamido-derivatives of codeine, hydrocodone (e.g., active ingredient of Lortab®), and oxycodone (e.g., active ingredients of OxyContin® and Percodan®) have the potential to treat severe pain without the problems associated with dependence on *CYP2D6* activation.

Up to 20% of individuals of certain ethnicities are very poor metabolizers of orally delivered codeine.

Current and future studies

- ▶ The large-scale synthesis of the carboxamide derivatives of buprenorphine, nalbuphine and butorphanol are nearly complete. In vivo evaluation of these derivatives will commence soon thereafter.
- ▶ The design and synthesis of analogues containing structural variant of the CONH₂ group is actively underway. This will help define the pharmacophore and further understanding of the elements important to molecular recognition to opioid receptors.

Selected publications

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