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Treating Neurological Disorders Caused by Opioid Addiction – Targeting the μ Opioid Receptor

Inventors

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Patent status:
Patent pending and issued: U.S. and foreign rights are available.

License status:
This technology is available for licensing to industry for further development and commercialization.

Category:
Biomedical

VCU Tech #:
ZHA-09-004F, ZHA-13-106F, ZHA-16-064F, ZHA-16-065F, ZHA-18-094F

***In vitro* and *in vivo* data available**

Overview

Yan Zhang, PhD, Professor, Department of Medicinal Chemistry, Virginia Commonwealth University, a recognized expert in the study of drug design and development to treat various types of diseases, has developed novel compounds to treat neurological disorders related to opioid addiction.

Drug use disorder is a growing global epidemic. In 2018, over 72,000 people died in the US alone from opioid overdose. The two current methods for treating opioid addiction include detoxification and maintenance therapy using opioid receptor antagonists, such as naloxone and naltrexone. While effective, naloxone and naltrexone have the potential to cause hepatotoxicity, cardiovascular and pulmonary problems at higher doses.

The analgesic function and addiction/abuse liability of many clinically available opiates are due to their interaction with the μ opioid receptor (MOR). A number of MOR selective antagonists and partial agonists have been used for the treatment of opioid abuse and addiction.

Dr. Zhang has designed and synthesized a number of highly selective and potent opioid antagonists. The first compound identified as a peripherally selective MOR antagonist, NAP. Since NAP's discovery, generations of new compounds have been studied; NAQ, NAN, and NFP. ***In vitro* competition assays showed that NAQ, NAN, and NFP have superior selectivity for the MOR over existing compounds. *In vivo* withdrawal studies showed that NAQ, NAN, and NFP produced significantly less withdrawal symptoms compared to naloxone at similar doses. The findings suggest that these compounds may serve as a lead compound to develop novel dual selective ligands for treating opioid addiction and abuse.**

Key features

- Treatment of neurological disorders
  - Drug abuse
  - Drug addiction
  - Alcoholism
  - Neurological disorders related to opioid receptor functions
- Fewer withdrawal symptoms than current treatment
- Higher affinity and specificity for MOR

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Patent estate

Selective, non-peptide antagonists for the MOR and their methods of use are protected by an extensive international patent estate. Issued patents and patent applications ensure patent protection until 2030 at a minimum with the potential for additional protection. The novel compound, NFP, is the newest formulation with the potential for 20+ years of patent coverage.

The patent estate claims:

- Formulation of compounds and close analogs
- Methods of use for treating conditions related to addiction in which MOR is involved

Some of the patent family portfolio includes:

- 8,772,308
- 8,980,908
- 16/301,765
- 16/306,232

Additional information about the patent estate is available upon request.

Pharmacology Data Summary

Compound			**NAQ**	**NFP**	**NAN**
***In vitro* Pharmacology Studies**					
Binding Affinity Ki (nM) ± SEM	MOR		0.55 ± 0.15 nM	0.36 ± 0.02 nM	0.23 ± 0.02 nM
Function potency and efficacy ^{35}S-GTP[γS]-Binding	MOR	Potency EC_{50}, nM	4.36 ± 0.73 nM	1.20 ± 0.19 nM	3.9 ± 2.3 nM
		Efficacy (% max of DAMGO)	15.83 ± 2.53	34.97 ± 3.07	19.1 ± 3.3
***In vivo* Pharmacology Studies**					
Tail flick assay (mice, single dose)			No anti-nociceptive effect up to 100 mg/kg.	The percentage maximum possible effect (%MPE) of NFP was 6.2 ± 2.4% compared with 95.5 ± 4.5% of morphine (both at 10 mg/kg).	The percentage maximum possible effect (%MPE) of NAN (10 mg/kg) was 5.0 ± 2.5% compared to 94.9 ± 5.1% for morphine (10 mg/kg).

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Tail flick assay (mice, dose response)	The AD_{50} of NAQ was determined as 0.45 (0.27-0.78) mg/kg (95% CL)	Blockage effect to the antinociception of morphine at the doses of 4 mg/kg and shown more significant antinociception block effect at the doses of 8 mg/kg and 10 mg/kg. AD_{50} value of 2.82 (1.34-5.94) mg/kg with 95% CL.	The AD_{50} of NAN was determined as 2.39 (0.46-12.47) mg/kg (95% CL)
Withdraw study (morphine-pelleted mice)	No significant precipitation of withdraw syndromes up to 100 mg/kg. NAQ (10 mg/kg) also significantly decreased the hyper-locomotion induced by acute morphine without inducing any vertical jumps.	Cause no obvious wet dog shakes, jumping and paw tremors compared with well-known opioid antagonist, naloxone, even the dose up to 50 mg/kg. NFP did not develop tolerance at 10 mg/kg of morphine likely represents a combination of the direct antagonistic effects of NFP in combination with its ability to attenuate the development of tolerance.	NAN at a dose of 50 mg/kg produced significantly less wet-dog shakes and paw tremors than naltrexone at a dose of 1 mg/kg. NAN at a dose of 1 mg/kg produced significantly less escape jumps than naltrexone at 1 mg/kg.
PK			
Caco-2 bidirectional transport assay, PDR = $P_{app, B-A}/P_{app, A-B}$	1.2 Apparently not a Pgp substrate	8.85 As a moderate potency Pgp substrate	ND
GPCRs and ion channels screening	No significant binding to other receptors at 1 uM	No significant binding to other receptors at 1 uM	No significant binding to other receptors at 1 uM
Toxicology			
No obvious toxicity observed in any animal model studies to the highest doses tested.			

ND: not determined

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Selected Publications

- Guo Li, Lindsey C. Aschenbach, Jianyang Chen, Michael P. Cassidy, David L. Stevens, Bichoy H. Gabra, Dana E. Selley, William L. Dewey, Richard B. Westkaemper, Yan Zhang. Design, Synthesis and Biological Evaluation of 6α- and 6β-N-Heterocyclic Substituted Naltrexamine Derivatives as Mu Opioid Receptor Selective Antagonists. J. Med. Chem. 2009, 52, 1416-27. PMID: 19199782. PMCID: PMC2880636.

- Yunyun Yuan, Guo Li, Hengjun He, David L. Stevens, Patrick Kozak, Krista L. Scoggins, Pallabi Mitra, Phillip M. Gerk, Dana E. Selley, William L. Dewey, Yan Zhang. Identification of 6 □-and 6 □N-Heterocyclic Substituted Naltrexamine Derivatives as Novel Leads to Development of Mu Opioid Receptor Selective Antagonists. ACS Chem. Neurosci. 2011, 2 (7), 346–351. PMCID: PMC3369747.

- Yan Zhang, Amanda Braithwaite, Yunyun Yuan, John M. Streicher, Edward J. Bilsky. Behavioral and Cellular Pharmacology Characterization of 17-cyclopropylmethyl-3,14 β -dihydroxy-4,5 α -epoxy-6 α -(isoquinoline-3′ -carboxamido)morphinan (NAQ) as a Mu Opioid Receptor Selective Ligand. European J. Pharmacology, 2014, 736, 124-130. PMID: 24815322. PMCID: PMC4073486.

- Ahmad A. Altarifi, Yunyun Yuan, Yan Zhang, Dana E. Selley, S. Stevens Negus. Effects of the Novel, Selective and Low-Efficacy Mu Opioid Receptor Ligand NAQ on Intracranial Self-Stimulation in Rats. Psychopharmacology (Berl). 2015, 232, 815-24. PMID: 25178814. PMCID: PMC4310756.

- Justin N. Siemian, Samuel Obeng, Yan Zhang, Yanan Zhang, Jun-Xu Li. Antinociceptive interactions between the imidazoline I2 receptor agonist 2-BFI and opioids in rats: role of efficacy at the mu opioid receptor. J. Pharm. Expt. Ther. 2016 357(3):509-19. PMID: 27056847.

- Samuel Obeng, Yunyun Yuan, Abdulmajeed Jali, Dana E. Selley, Yan Zhang. In vitro and in vivo functional profile characterization of 17-cyclopropylmethyl-3,14β-dihydroxy-4,5α-epoxy-6α-(isoquinoline-3-carboxamido)morphinan (NAQ) as a low efficacy mu opioid receptor modulator. European Journal of Pharmacology. 2018, 827, 32-40. PMID: 29530590. PMCID: PMC5890425.

- Jeremy C. Cornelissen, Samuel Obeng, Kenner C. Rice, Yan Zhang, S. Stevens Negus, Matthew L. Banks. Application of Receptor Theory to the Design and Use of Fixed-Proportion Mu-Opioid Agonist and Antagonist Mixtures in Rhesus Monkeys. J. Pharmacol. Exp. Ther. 2018, 365(1), 37-47. PMID: 29330156. PMCID: PMC5830633.

- Samuel Obeng, Huiqun Wang, Abdulmajeed Jali, David L. Stevens, Hamid I. Akbarali, William L. Dewey, Dana E. Selley, Yan Zhang. Structure activity relationship studies of 6β- and 6α-indolylacetamidonaltrexamine derivatives as bitopic mu opioid receptor modulators and elaboration of 'message-address concept' to comprehend their functional conversion. ACS Chemical Neuroscience, Allostery special issue, 2018. doi: 10.1021/acschemneuro.8b00349. [Epub ahead of print]. PMID: 30156823.

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