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Novel inhibitors of HINT1 to treat neuropathic pain and addiction

Small-molecule inhibitors of hHint1 (and their synthesis) for use in basic CNS research and treatment of neuropathic pain and addiction.

IP Status: Issued US Patent; **Issued Patent No.** 10,513,520

Applications

- Hint1 basic research
- Neuropathic pain therapeutic
- Addiction treatment (opioid or nicotine)
- Mitigate opioid dependence formation

Key Benefits & Differentiators

- **Potent inhibitor of hHint1:** Binds hHint1 with up to 16 times greater affinity than the currently known inhibitor.
- **Ready for optimization at the molecular level:** Detailed structural information of inhibitor binding via high-resolution crystallography combined with kinetic studies available to guide development for use in research or patients.
- **Optimized for a variety of formulation and applications:** Increased solubility of the compounds facilitate their use in a wide variety of formulations (both internal and topical) and research applications.

Human Hint1 is a potential new drug target

Traditional opiate-based pain therapeutics are linked to opioid use disorders, thus necessitating the development of novel, non-additive alternatives. One potential target for such new compounds is the human Histidine Triad Nucleotide Binding Protein 1 (hHint1). hHint1 is involved in the regulation of a broad range of CNS functions including opioid signaling, tolerance, neuropathic pain, and nicotine dependence. These roles, along with its widespread expression in the brain, have led hHint1 to be of high interest for research and therapeutic targeting. Given hHINT1's role in modulating tolerance to opioids, it is a viable non-opioid receptor target for the next generation of pain medications. Researchers at the University of Minnesota rationally designed and synthesized hHint inhibitors that bind the protein with submicromolar affinities. These unique small-molecules could be used to further determine the role of Hint1 in the CNS or developed into therapeutics for indications for which there are limited options.

Potent and soluble Hint1 inhibitors

Previous work using the hHint inhibitor Tryptamine Guanosine carbamate (TrpGc) has shown that hHint1 inhibition is a successful strategy to enhance the pain relieving effects of morphine while preventing tolerance. However, TrpGc exhibits low solubility which limits the applications

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Category
Life Sciences/Human Health
Life Sciences/Neuroscience
Life Sciences/Pharmaceuticals
Agriculture & Veterinary/Veterinary Medicine

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it can be used in. The newly developed inhibitors are nucleoside analogs containing acyl-sulfamate or acyl-sulfimide that show increased solubility as well as binding to hHint1, up to 16 times higher affinity than TrpGc. These favorable properties facilitate the use of these compounds in a variety of applications and formulations as well as in the treatment of indications ranging from neuropathic pain and drug dependence.

Phase of Development

Target indication validated in vivo with tool compound TrpGc. In vitro binding of inhibitors confirmed using ITC and high-resolution x-ray crystallography. In vivo studies with lead compounds pending.

Researchers

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Publications

Design, synthesis, and characterization of Sulfamide and Sulfamate Nucleotidomimetic inhibitors of hHint1
ACS Medicinal Chemistry Letters, 2016, 7, 780−784
A new therapeutic target to enhance opioid antinociception and block mechanical allodynia
Neuropharmacology, 89 (2015) 412e423

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