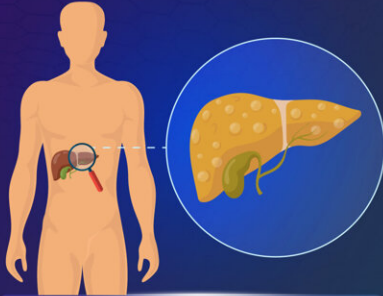


Researchers discover novel drug candidate to combat fatty liver disease

April 3 2024


A Novel Peripheral 5HT_{2A} Antagonist for Treating Metabolic Liver Diseases


Metabolic dysfunction-associated steatohepatitis (MASH), an advanced form of metabolic dysfunction-associated steatotic liver disease (MASLD), can lead to severe liver conditions




There is an urgent need for innovative therapeutic strategies to treat MASLD and MASH


Development of compound 11c for treating MASLD and MASH


 5HT_{2A} antagonists identified via drug library screening

 Molecular docking for compound optimization


In vivo efficacy of 11c


 Evaluation of compounds for 5HT_{2A} inhibitory potency


 60% bioavailability observed in rat and dog models


 **Effective in reducing fatty liver, inflammation, and fibrosis in:**


- diet-induced obesity male mice model
- choline-deficient, L-amino acid-defined, high-fat diet male mice model

 Conductation of chirality assessment to select the racemic compound

 Good pharmacokinetic profiles with reasonable half-life and oral bioavailability


 Low cytotoxicity and Low CYP inhibition

 Tissue distribution study using [¹⁴C]-labeled 11c

 [¹⁴C]-labeled compound 11c as a peripheral 5HT_{2A} antagonist

11c shows promise as a therapeutic agent for the treatment of MASLD and MASH with its anti-inflammatory and anti-fibrotic effects

Discovery of a peripheral 5HT_{2A} antagonist as a clinical candidate for metabolic dysfunction-associated steatohepatitis
 Pagire et al. (2024)
 Nature Communications | 10.1038/s41467-024-44874-3



Gwangju Institute of Science and Technology

Researchers discovered a compound 11c, a peripheral 5HT_{2A} antagonist, exhibits promising efficacy against metabolic dysfunction-associated steatohepatitis (MASH) and associated liver diseases, offering hope for improved treatment outcomes. Credit: Jin Hee Ahn from GIST, Korea.

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a burgeoning global health concern, posing a significant threat to public health and escalating the burden on health care resources. Characterized

by the accumulation of fat in the liver, MASLD increases the risk of progressing to more severe conditions such as metabolic dysfunction-associated steatohepatitis (MASH), which is marked by inflammation, ballooning, and potential fibrosis.

In response to the pressing need for effective treatments for these metabolic disorders, researchers led by Prof. Jin Hee Ahn from Gwangju Institute of Science and Technology (GIST) developed compound 11c, a novel peripheral 5HT_{2A} antagonist.

This research was made available online on January 20, 2024, and was [published](#) in *Nature Communications*, highlighting a significant therapeutic breakthrough. The compound showcased a promising profile and demonstrated efficacy in preclinical models, positioning it at the forefront of groundbreaking advancements in the field.

11c exhibits promising attributes, including robust biological activity and a favorable safety profile. Dr. Haushabhau Shivaji Pagire, first author and senior researcher at the Medicinal Chemistry Laboratory at GIST, says, "Our meticulous analyses have revealed a significant reduction in inflammatory and fibrosis markers, attesting to the potent anti-inflammatory and fibrotic effect of the compound. This action, targeting both inflammation and fibrosis, is a promising step forward in treating MASH."

The journey for discovering the compound from drug library screening to its refined form involved the identification of Desloratadine, a peripheral agent, which showed promising inhibitory effects. Molecular docking techniques played a pivotal role in transforming Desloratadine into the potent compound 11c.

"Based on in vitro, in vivo efficacy, tissue distribution data, DMPK and tox profiles, compound 11c shows promise as a therapeutic agent for the

treatment of MASLD and MASH," says Prof. Ahn.

Beyond its therapeutic potential, compound 11c displays an excellent safety profile, exhibiting hepatocyte and plasma stability, minimal cytotoxicity, and low cytochrome P450 inhibition. Noteworthy pharmacokinetic attributes, including over 60% oral bioavailability, position 11c as a compelling candidate for advancing MASH treatment.

Obesity-associated MASH currently ranks as the third leading cause of liver transplantation and is poised to surpass hepatitis C in this critical medical intervention. Compound 11c, identified as a promising oral treatment for MASH, holds [profound implications](#) for the future landscape of liver disease management. The researchers anticipate a transformative impact, signifying a pivotal advancement in the field.

Completing a successful preclinical study, compound 11c now stands on the brink of a crucial milestone—the Phase I clinical trial. This phase holds the promise to reveal the compound's performance in humans, offering insights that could potentially reshape the treatment landscape for metabolic disorders. The successful outcome of these trials could potentially usher in a paradigm shift in the treatment of [metabolic disorders](#).

More information: Haushabhau S. Pagire et al, Discovery of a peripheral 5HT2A antagonist as a clinical candidate for metabolic dysfunction-associated steatohepatitis, *Nature Communications* (2024). [DOI: 10.1038/s41467-024-44874-3](https://doi.org/10.1038/s41467-024-44874-3)

Provided by Gwangju Institute of Science and Technology

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