


# Discovery of a potent and orally active dual GPBAR1/CysLT1R modulator for the treatment of metabolic fatty liver disease

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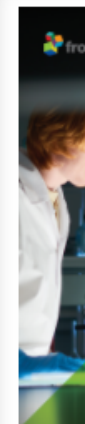
The final version of the article will be published here soon pending final quality checks

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Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are two highly prevalent human diseases caused by excessive fat deposition in the liver. While multiple approaches have been suggested, NAFLD/NASH remains an unmet clinical need. Here we report the discovery of a novel class of hybrid molecules designed to function as cysteinyl leukotriene receptor 1 (CysLT1R) antagonists and G protein bile acid receptor 1 (GPBAR1/TGR5) agonists for the treatment of NAFLD/NASH. The most potent of these compounds generated by harnessing the scaffold of previously described CysLT1R antagonists showed efficacy in reversing liver histopathology features in a preclinical model of NASH, reshaping the liver transcriptome and the lipid and energy metabolism in the liver and adipose tissues. In summary, the present study described a novel orally active dual CysLT1R antagonist/GPBAR1 agonist that effectively protects against the development of NAFLD/NASH, showing promise for further development.



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