

Insights: Publications

6-Amino[1,2,5]oxadiazolo[3,4-b]pyrazin-5-ol Derivatives as Efficacious Mitochondrial Uncouplers in STAM Mouse Model of Nonalcoholic Steatohepatitis

J. Med. Chem. 2020, 63, 6203–6224

May 11, 2020

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Small molecule mitochondrial uncouplers have recently garnered great interest for their potential in treating nonalcoholic steatohepatitis (NASH). In this study, we report the structure–activity relationship profiling of a 6-amino[1,2,5]oxadiazolo[3,4-b]pyrazin-5-ol core, which utilizes the hydroxy moiety as the proton transporter across the mitochondrial inner membrane. We demonstrate that a wide array of substituents is tolerated with this novel scaffold that increased cellular metabolic rates in vitro using changes in oxygen consumption rate as a readout. In particular, compound SHS4121705 (12i) displayed an EC₅₀ of 4.3 μ M in L6 myoblast cells and excellent oral bioavailability and liver exposure in mice. In the STAM mouse model of NASH, administration of 12i at 25 mg kg^{−1} day^{−1} lowered liver triglyceride levels and improved liver markers such as alanine aminotransferase, NAFLD activity score, and fibrosis. Importantly, no changes in body temperature or food intake were observed. As potential treatment of NASH, mitochondrial uncouplers show promise for future development.

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