

Insights: Publications

Oxadiazolopyridine Derivatives as Efficacious Mitochondrial Uncouplers in the Prevention of Diet-Induced Obesity

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Small-molecule mitochondrial uncouplers are gaining recognition as potential therapeutics for metabolic diseases such as obesity, diabetes, and nonalcoholic steatohepatitis (NASH). Specifically, heterocycles derived from BAM15, a potent and mitochondria-selective uncoupler, have yielded promising preclinical candidates that are efficacious in animal models of obesity and NASH. In this study, we report the structure–activity relationship studies of 6-amino-[1,2,5]oxadiazolo[3,4-b]pyridin-5-ol derivatives. Using oxygen consumption rate as a readout of mitochondrial uncoupling, we established 5-hydroxyoxadiazolopyridines as mild uncouplers. In particular, SHM115, which contains a pentafluoro aniline, had an EC₅₀ value of 17 μ M and exhibited 75% oral bioavailability. SHM115 treatment increased the energy expenditure and lowered the body fat mass in two diet-induced obesity mouse models, including an obesity prevention model and an obesity reversal model. Taken together, our findings demonstrate the therapeutic potential of mild mitochondrial uncouplers for the prevention of diet-induced obesity.

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