

Insights: Publications

[1,2,5]Oxadiazolo[3,4-b]pyrazine-5,6-diamine Derivatives as Mitochondrial Uncouplers for the Potential Treatment of Nonalcoholic Steatohepatitis

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Small molecule mitochondrial uncouplers are emerging as a new class of molecules for the treatment of nonalcoholic steatohepatitis. We utilized BAM15, a potent protonophore that uncouples the mitochondria without depolarizing the plasma membrane, as a lead compound for structure-activity profiling. Using oxygen consumption rate as an assay for determining uncoupling activity, changes on the 5- and 6-position of the oxadiazolopyrazine core were introduced. Our studies suggest that unsymmetrical aniline derivatives bearing electron withdrawing groups are preferred compared to the symmetrical counterparts. In addition, alkyl substituents are not tolerated, and the N-H proton of the aniline ring is responsible for the protonophore activity. In particular, compound 10b had an EC₅₀ value of 190 nM in L6 myoblast cells. In an in vivo model of NASH, 10b decreased liver triglyceride levels and showed improvement in fibrosis, inflammation, and plasma ALT. Taken together, our studies indicate that mitochondrial uncouplers have potential for the treatment of NASH.

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