Development of Potent Adenosine Monophosphate

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Abstract

Previously, we reported the identification of a thiazolidinedione-based adenosine monophosphate activated protein kinase (AMPK) activator, compound 1 (N-[4-({3-[(1-methylcyclohexyl) methyl]-2,4-dioxothiazolidin-5-ylidene}methyl)phenyl]-4-nitro-3-(trifluoromethyl)benzenesulfonamide), which provided a proof of concept to delineate the intricate role of AMPK in regulating oncogenic signaling pathways associated with cell proliferation and epithelial–mesenchymal transition (EMT) in cancer cells. In this study, we used 1 as a scaffold to conduct lead optimization, which generated a series of derivatives. Analysis of the antiproliferative and AMPK-activating activities of individual derivatives revealed a distinct structure–activity relationship and identified 59 (N-(3-nitrophenyl)-N'-{4-[(3-{[3,5-bis(trifluoromethyl)phenyl]methyl}-2,4-dioxothiazolidin-5-ylidene) methyl]phenyl}urea) as the optimal agent. Relative to 1, compound 59 exhibits multifold higher potency in upregulating AMPK phosphorylation in various cell lines irrespective of their liver kinase B1 (LKB1) functional status, accompanied by parallel changes in the phosphorylation/expression levels of p70S6K, Akt, Foxo3a, and EMT-associated markers. Consistent with its predicted activity against tumors with activated Akt status, orally administered 59 was efficacious in suppressing the growth of phosphatase and tensin homologue (PTEN)-null PC-3 xenograft tumors in nude mice. Together, these findings suggest that 59 has clinical value in therapeutic strategies for PTEN-negative cancer and warrants continued investigation in this regard.

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