Macrocyclic MEK1/2 inhibitor with efficacy in a mouse model of cardiomyopathy caused by lamin A/C gene mutation.


Abstract

Signaling mediated by extracellular signal-regulated kinases 1 and 2 (ERK1/2) is involved in numerous cellular processes. Mitogen-activated protein kinase kinases (MEK1/2) catalyze the phosphorylation of ERK1/2, converting it into an active kinase that regulates the expression of numerous genes and cellular processes. Inhibitors of MEK1/2 have demonstrated preclinical and clinical efficacy in certain cancers and types of cardiomyopathy. We report the synthesis of a novel, allosteric, macrocyclic MEK1/2 inhibitor that potently inhibits ERK1/2 activity in cultured cells and tissues of mice after systemic administration. Mice with dilated cardiomyopathy caused by a lamin A/C gene mutation have abnormally increased cardiac ERK1/2 activity. In these mice, this novel MEK1/2 inhibitor is well tolerated, improves left ventricular systolic function, decreases left ventricular fibrosis, has beneficial effects on skeletal muscle structure and pathology and prolongs survival. The novel MEK1/2 inhibitor described herein may therefore find clinical utility in the treatment of this rare cardiomyopathy, other types of cardiomyopathy and cancers in humans.

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KEYWORDS: Cardiomyopathy; Emery-Dreifuss muscular dystrophy; Extracellular signal-regulated kinase; Lamin; MEK inhibitor; Mitogen-activated protein kinase

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