Antifibrotic effects of oxetanyl sulfoxides

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Technology description

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Currently, there are only two approved therapies for Idiopathic Pulmonary Fibrosis (IPF), pirfenidone and nintedanib, which are minimally effective at slowing the disease. These treatments are not effective at all in halting or reversing the progression of IPF. Therefore, there remains a great need for more effective therapies. Researchers at MUSC and Pittsburgh have found that a novel compound, MMS-350, can significantly reduce pro-fibrotic factors and ECM proteins both in vitro and in vivo.Figure 1demonstrates that in bleomycin treated mice oral doses of MMS-350 ameliorates fibrosis histologically (A), quantitatively reduces collagen α2I within 5 days of treatment (B), results in a large reduction of hydroxyproline levels (C), reduces weight loss and increases survival (87.5% vs 62.5%). MMS-350 is also useful in preventing, mitigating and/or treating injury caused by radiation exposure. Investigators also tested analogs of MMS-350 and identified analogs with enhanced potency that are effective at lower concentrations(Figure 2). The compounds identified reduced markers of fibrosis central to fibrosis in different organs such as Collagen, Fibronectin, IGFBP-3, CTGF, and αSMA in vitro in primary human fibroblasts(Figure 2), suggesting that the reduction of fibrosis is due to a multi-pronged effect. The compounds also reversed TGFbeta-induced fibrosis ex vivo in human skin in organ culture(Figure 3)with robust reduction in Collagen, Fibronectin and CTGF expression as examples of its anti-fibrotic effect in a human tissue. Testing of compounds in human skin makes the findings directly relevant to the human disease.

Overview

The pulmonary fibrosis market in the US and EU is projected to be worth more than $1.1B in 2017. A successful pulmonary fibrosis treatment could likely be applied to additional fibrosis diseases, including kidney and liver due to similar disease mechanisms. The hallmark of pulmonary fibrosis is thickening and scarring of the tissue caused by increased deposition of extracellular matrix (ECM) proteins such as collagen and fibronectin. Fibrosis is the final stage of many diseases such as IPF, liver cirrhosis, and certain autoimmune disorders. Scarring causes irreversible damage that usually leads to low quality of life, transplantation or death.

Key Words:Fibrosis, scleroderma, IPF, MMS-350, bis-oxetanyl sulfoxide, bleomycin, autoimmune

Application area

Treatment of idiopathic pulmonary fibrosis, treatment of fibroproliferative disorders and systemic sclerosis, treatment or prophylactic for radiation induced damage
Low toxicity, oral bioavailability, high solubility, treat and decrease fibrosis, radioprotector, radiomitigator

Institution

Medical University of South Carolina

Inventors

Peter Wipf
Distinguished Professor
Chemistry
Carol Feghali-Bostwick
Professor
Rheumatology

联系我们

叶先生

电 话：021-65679356

手 机：13414935137

邮 箱：yeyingsheng@zf-ym.com