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Design, synthesis and biological evaluation of new anti-IPF agents

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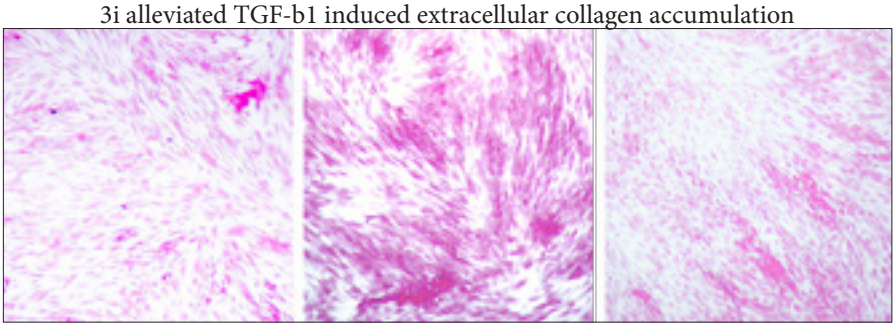
Statement of the Problem: Idiopathic pulmonary fibrosis (IPF) is a severe life-threatening disease with very poor prognosis. IPF patients die within 3 to 5 years after diagnosis mostly due to respiratory failure. To date only 2 small molecule drug (Pirfenidone and Nintedanib) were approved by FDA for IPF treatment, yet they treatment outcome were far from promising. There is an urgent need for novel anti-IPF agents. Methodology & Theoretical Orientation: Matrine and cinnamic acid was rationally hybrid by amidation reactions. An in vitro anti-fibrotic agent screening model was established based on TGF-ß1 induced human fetal lung fibroblast (MRC-5) myofibroblast transformation. Extracellular total collagen accumulation was quantified by Picro-Sirius Red staining. Transient fibroblast and myofibroblast markers (ACTA2, COL1a1, FSP-1, FAP and P-4-H) expression was determined by immunocytochemistry (ICC) methods. Findings: 46 novel matrine-cinnamic acid hybrid compounds were synthesized and evaluated for their anti-fibrotic activity. 10 ng/mL TGF-ß1 significantly induces myogenetic phenotype formation with elevated extracellular total collagen accumulation and myofibroblast markers expression. Pretreatment of matrine-cinnamic acid hybrid alleviated TGF-ß1 induced myogenic transformation. Conclusion & Significance: Compound 3i exhibited an inhibitory effect against TGF-ß1 induced total collagen accumulation in MRC-5 fibroblast with the IC50 value of 1.2ßM, which was about 2000 times more potent then Pirfenidone.

3i alleviated TGF-b1 induced extracellular collagen accumulation



TGFß1 0ng/mL TGFß1 10ng/mL TGFß1 10ng/mL + 3i

Biography

Lingyu Li is a PhD candidate dedicated in structural modification of bioactive natural products. In searching for novel and promising anti-IPF agents, he has achieved a IPF agent library of more than 100 compounds by semisynthetic methods and established a novel rapid IPF agent screening model.

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