Spiro-isoxazolonechromans-3 alleviates LPS-induced acute lung injury in mice via inhibiting inflammation through modulating JAK1/STAT pathway

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Abstract

Acute lung injury (ALI) is a serious clinical disease with a mortality rate of 30-40%. We designed and synthesized a structurally novel compound, Spiro-isoxazolonechromans-3 (SI-3), to seek a new approach for treating excessive inflammation in ALI. In the present study, we induced RAW 264.7 cells with LPS and injected LPS intraperitoneally in BALB/c mice to establish an ALI model. Molecular docking results showed SI-3 located in the hydrophobic pocket of Janus Kinase 1 (JAK1) and interacted with JAK1 through amino acid residue Leu959. SI-3 selectively inhibited the JAK1 enzyme activity with an IC50 of 9 nM and is non-toxic. In vitro, LPS-induced macrophage proliferation, activation, and secretion of inflammatory cytokines were inhibited by SI-3, which promoted macrophage apoptosis. In vivo, SI-3 improved the survival rate of ALI mice by reducing pathological lung injury and inflammatory response. Both in vivo and in vitro, we discovered that SI-3 exerted a downregulatory impact on the JAK1-STAT pathway according to the results of western-blot studies and showed the same effect in JAK1-overexpressing macrophages. Overall, SI-3 could reduce LPS-induced inflammatory response and promote macrophage apoptosis by inhibiting JAK1 kinase and affecting JAK1/JAK3-STAT pathway, resulting in significant anti-inflammatory effects, which alleviated the LPS-induced ALI in mice.

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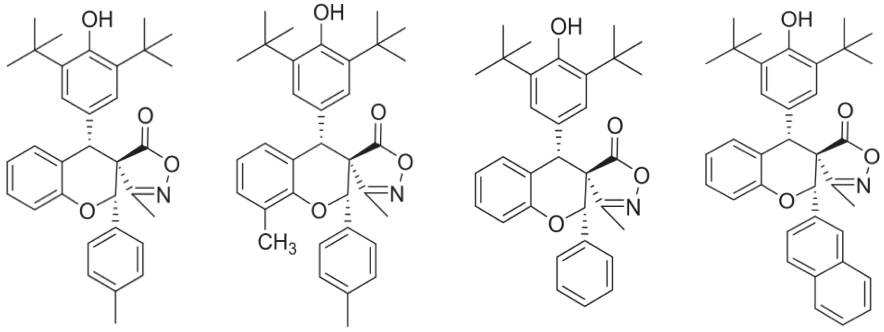

SI-1 SI-2 SI-3 SI-4