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HS-1371, a novel kinase inhibitor of RIP3-mediated necroptosis

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Necroptosis is a type of programmed cell death that usually occurs under apoptotic-deficient conditions. Receptor-interacting protein kinase-3 (RIP3, or RIPK3) is a central player in necroptosis and its kinase activity is essential for downstream necroptotic signaling events. Since RIP3 kinase activity has been associated with various diseases, development of specific RIP3 inhibitors is an attractive strategy for clinical application. In this study, we identified a potent RIP3 inhibitor, HS-1371 using an extensive kinase cross-screening of our chemical libraries. The mechanism of action of this compound is via direct binding to RIP3 in an ATP-competitive and time-independent manner. HS-1371 inhibited TNF-induced necroptosis but did not inhibit TNF-induced apoptosis, indicating that this novel inhibitor has a specific inhibitory effect on RIP3-mediated necroptosis via suppression of RIP3 kinase activity. Our results suggest that HS-1371 could serve as a potential preventive or therapeutic agent for RIP3 hyperactivation-mediated diseases.

Biography

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