RWJ-58259: A Selective Antagonist of Protease Activated Receptor-1

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ABSTRACT

Protease activated receptor-1 (PAR-1) is a key mediator of the cellular actions of α-thrombin. Thus, antagonism of this unique G-protein coupled receptor with a small molecule represents a means of selectively inhibiting thrombin’s cellular actions without inhibiting its proteolytic activity. RWJ-58259 ((αS)-N-[(1S)-3-amino-1-[[[(phenylmethyl)-amino]carbonyl]propyl]-α-[[[[1-(2,6-dichlorophenyl)methyl]-3-(1-pyrrolidinylmethyl)-1H-indazol-6-yl]amino]carbonyl]amino]-3,4-difluorobenzenepropanamide) is a potent and selective inhibitor of PAR-1 identified as part of a synthetic chemistry program based upon a de novo design approach. RWJ-58259 inhibited thrombin-induced platelet aggregation in human platelets with an IC₅₀ of 0.37 µM without inhibiting thrombin’s proteolytic activity or aggregation induced by other agonists. RWJ-58259 was not effective in guinea pig models of thrombosis. This reflected the presence of a second thrombin-sensitive receptor system in guinea pigs (PAR-3/c47) and the selectivity of RWJ-58259 for PAR-1. However, RWJ-58259 was effective in a non-human primate model of thrombosis. Because human platelets have a PAR expression profile similar to the non-human primate, PAR-1 antagonism has the potential to be antithrombotic in humans. RWJ-58259 also inhibited thrombin-induced intracellular calcium signaling and proliferation in rat vascular smooth muscle cells. Perivascular application of RWJ-58259 in vivo significantly inhibited arterial injury-induced stenosis in a rat model of balloon angioplasty. These preclinical results suggest a potential clinical utility of RWJ-58259 for treatment of thrombotic disorders and vascular injury associated with acute coronary interventions and atherosclerosis. Given the potential role of PAR-1 in thrombin’s actions in other cell types and disease states, RWJ-58259 provides a means for assessing additional clinical effects.
utilities of PAR-1 antagonism in disease conditions such as inflammation, cancer and neurodegeneration.