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Discovery of novel 1,3,4-thiadiazol-2-yl hydrazones of aromatic aldehydes as potent inhibitors of human platelet-aggregation with dual inhibitory activity

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Background and Aims: Based on the previous reports in the literature regarding the anti-platelet aggregation activity of hydrazone derivatives and in the search for novel anti-platelet compounds with the ultimate goal of offering new possibilities in anti-platelet therapy with better efficacy and safety profiles; in the present study a series of novel 1,3,4-thiadiazol-2-yl hydrazones have been prepared and evaluated for their anti-platelet aggregation activity.
Methods: The derivatives were prepared with a one-pot synthetic procedure by heating a mixture of thiocarbohydrazide, triethyl orthoformate and various aromatic aldehydes. The solids thus obtained were recrystallized from an appropriate solvent to afford the final compounds with acceptable analytical purity. Anti-platelet aggregation activity of the derivatives was measured by a previously reported turbidometric method using human blood samples. Compounds with the initial concentration of 100 µM were incubated in human platelet-rich-plasma (PRP) for 5 min and then platelet aggregation agonists (ADP or arachidonic acid) were added and the samples were monitored for 5 min. Indomethacin and aspirin were used as standard drugs and DMSO as negative control.
Results: The tested compounds were effective to inhibit the platelet aggregation induced by both ADP and arachidonic acid (AA). Among them, 3-pyridyl and 4-pyridyl derivatives inhibited the platelet aggregation induced by ADP with IC50 values of 18 µM and 3 µM respectively. On the other hand, 2-furyl and 2-thienyl derivatives inhibited the platelet aggregation induced by AA with IC50 values of 2 µM and 4 µM respectively, comparable to that of indomethacin (IC50 = 3 µM).
Conclusions: A series of novel 1,3,4-thiadiazol-2-yl hydrazones of aromatic aldehydes were prepared by a one-pot procedure and their anti-platelet activity was evaluated using ADP and AA as aggregation agonists. The derivatives effectively inhibited the platelet aggregation induced by both ADP and AA with IC50 values comparable to those of standard drugs.

Keywords: Anti-platelet aggregation; Arachidonic acid; 2-Thiadiazolyl hydrazones