

Analgesic activity of novel anti-platelet indole-based hydrazones; data reveals new clues to the mechanism of action of the studied analogues

P. Aghaei^{1,*}, V. Mashayekhi², K. Haj Mohammad Ebrahim Tehrani², F. Kobarfard³, M. Faizi¹

¹*Department of Pharmacology and Toxicology, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

²*Department of Medicinal Chemistry, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

³*Department of Medicinal Chemistry, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran; Phytochemistry Research Centre, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

Background and Aims: Our previous studies led to the discovery of hydrazone derivatives of indole as potent inhibitors of platelet aggregation induced by arachidonic acid. Arachidonic acid, a platelet aggregation agonist, transforms to its active metabolite thromboxane A₂ through several steps. Since the initial steps of arachidonic acid metabolism is common to the bioformation of pain and inflammation mediators; assessment of analgesic and anti-inflammatory activities of the described anti-platelet analogues is favorable to both deciphering their action mechanism and introducing new analgesic/anti-inflammatory leads. Based on this philosophy, this study was conducted to evaluate the analgesic activity of novel indole-based analogues by acetic acid induced writhing test.

Methods: Male NMRI mice (10 in each group) were injected intraperitoneally by the solutions of test compounds (100 mg/kg), Celecoxib as standard drug (10 mg/kg) and vehicle. After 30 min, 0.7% acetic acid solution (10 ml/kg) was injected intraperitoneally. The number of writhes induced in each mouse was observed for 20 minutes period starting 5 minutes after injection of acetic acid. The analgesic activity was expressed in terms of percentage inhibition of writhes. Statistical analysis of the data was performed on GraphPad Prism 5.0 (2007) software package and p value < 0.05 was considered significant.

Results: The tested analogues effectively reduced the number of writhes compared to vehicle. Indole-2-carboxaldehyde phenylhydrazone and 5-bromoindole-3-carboxaldehyde 1,3,4-thiadiazol-2-ylhydrazone were among the most active derivatives which inhibited the reflexes by 66.4% and 67% respectively.

Conclusions: A series of novel anti-platelet analogues were evaluated for their analgesic activity using writhing test. The analogues effectively reduced the writhing reflexes. Data suggest that these analogues may exert their anti-platelet effects, at least partly by intervening in the pathways common to those leading to production of pain mediators namely leukotrienes and prostaglandins.

Keywords: Analgesic; Anti-platelet; Writhing test; Leukotriene; Prostaglandin