Biological activity of a small molecule indole analog, 1-[(1H-indol-3-yl)methylene]-2-phenylhydrazine (HMPH), in chronic inflammation


A synthetic small molecule, 1-[(1H-indol-3-yl)methylene]-2-phenylhydrazine (HMPH) was conveniently synthesised by a one-step reaction, purified and characterised by chromatographic and spectroscopic methods. HMPH scavenged free radicals and inhibited lipopolysaccharide (LPS)-induced ROS generation and NO release in RAW-264.7 cells without signs of any detectable cytotoxicity. HMPH inhibited lipid peroxidation (LPO) with IC50 of 135 ± 9 as against 58 ± 8 μM for α-tocopherol. Further, HMPH (>50 μM) significantly reduced the LPS-induced TNF-α release in mouse peritoneal macrophages and in human peripheral blood mononuclear cells (PBMCs). HMPH did not show any visible signs of toxicity in rats up to 400 mg/kg/intraperitoneal and 2000 mg/kg/oral. HMPH at 25 and 50 mg/kg attenuated neutrophil infiltration in air-pouch lavage and bronchoalveolar lavage (BAL) in rat models. HMPH also reduced myeloperoxidase (MPO), nitrite and TNF-α in air-pouch lavage in addition to MPO in plasma. HMPH reduced acute paw-inflammation in carrageenan-induced paw-edema. HMPH consistently decreased both ipsilateral and contralateral paw inflammation, minimised the clinical scores of arthritis, prevented body weight (B.wt.) loss, attenuated serum C-reactive protein (C-RP) and rheumatoid factors (RF) in rat model of adjuvant-induced arthritis. Histopathology and radio-graphical reports show that HMPH reduced bone erosion in both ipsilateral and contralateral paw joints. Failure to inhibit COX suggests that effectiveness of HMPH in both acute and chronic inflammation is mediated by a multimodal mechanism involving modulation of immunity, attenuating TNF-α, protecting bone attrition and reducing oxidative stress.

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1. Introduction

Inflammatory responses address a wide variety of noxious stimuli such as infections, antigens and physical/chemical injuries. NSAIDs are among the most prominent class of anti-inflammatory drugs, chiefly acting via COX inhibition with antipyretic, analgesic...