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ORIGINAL ARTICLE

Noval 1-substituted-3,5-dimethyl-4-[(substituted phenyl) diazenyl] pyrazole derivatives: Synthesis and pharmacological activity

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KEYWORDS

Pyrazoles;
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Hepatotoxic effect

Abstract Several-1-carbothioamide-3,5-dimethyl-4-[(substituted phenyl) diazenyl] pyrazoles **2a–d**, 1-(pyridine-4-ylcarbonyl)-3,5-dimethyl-4-[(substituted phenyl) diazenyl] pyrazoles **3a–d**, 1-(5-chloro-6-fluoro-1,3-benzothiazole-2-yl)thiocarbamoyl-3,5-dimethyl-4-[(substituted phenyl) diazenyl] pyrazoles **4a–d** and 1-[(1,2,4-triazole-4-yl) carbothioamide]-3,5-dimethyl-4-[(substituted phenyl) diazenyl] pyrazoles **5a–d** were synthesized. The structures of the newly synthesized compounds were supported by IR, ^{1}H NMR and mass spectral data. These compounds were investigated for their, anti-inflammatory, analgesic, ulcerogenic, lipid peroxidation, antibacterial and antifungal activities. Some of the synthesized compounds showed potent anti-inflammatory activity along with minimal ulcerogenic effect and lipid peroxidation, compared to ibuprofen and flurbiprofen. Some of the tested compounds also showed moderate antimicrobial activity against tested bacterial and fungal strains.

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1. Introduction

Currently, available non-steroidal anti-inflammatory drugs (NSAIDs) like, ibuprofen, flurbiprofen, fenbufen and naproxen exhibit gastric toxicity. Long-term use of these drugs has been associated with gastro-intestinal (GI) ulceration, bleeding and nephrotoxicity (Kimmey, 1992). The GI damage from NSAIDs is generally attributed to two factors, i.e. local irritation by the carboxylic acid moiety, common to most NSAIDs (topical effect) and decreased tissue prostaglandin production, which undermines the physiological role of cytoprotective prostaglandins in maintaining GI health and homeostasis (Smith et al., 1998; Hawkey et al., 2000). The pharmacological activity of NSAIDs is related to the suppression of prostaglandin biosynthesis from arachidonic acid by inhibiting cyclooxygenases (COXs) (Smith et al., 1998; Warner et al., 1999). The chronic use of NSAIDs including ibuprofen may elicit appreciable GI toxicity (Lanza, 1998). Therefore synthetic approaches based upon NSAIDs chemical modification has been taken with the aim of improving NSAID safety profile. In view of the potential biological activities (Ahuwalia and Mittal, 1989; Werbal and

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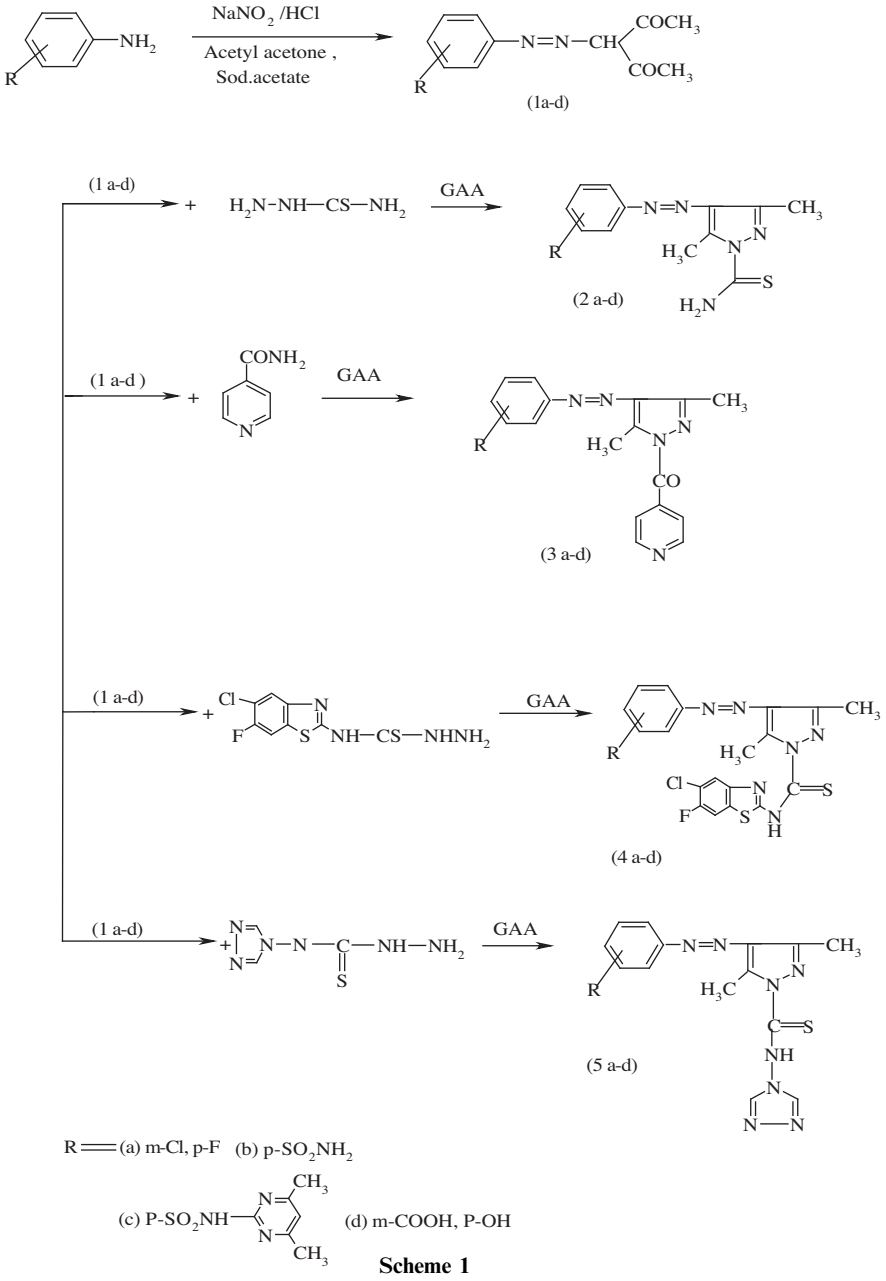
Elslager, 1968; Garg and Prakash, 1971; Kabra et al., 1977) of arylazo pyrazoles we report herein the synthesis of some new-1-(substituted)-3,5-dimethyl-4-[(substituted phenyl) diazenyl] pyrazoles. The synthesis involves treatment of acetyl acetone with different diazonium salt in the presence of sodium acetate when 3-[(substituted phenyl) diazenyl] pentane-2, 4-dione **1a–d** are obtained. The later on treatment with carbothioamide, pyridine-4-ylcarbonyl, 5-chloro-6-fluoro-1,3-benzothiazole-2-yl-thiocarbamoyl and 1,2,4-triazole-4-yl carbothioamide furnished 1-(substituted)-3,5-dimethyl-4-[(substituted phenyl) diazenyl] pyrazoles (Scheme 1). In view of the reported antimicrobial activity of pyrazole, these compounds were also tested for their antibacterial and antifungal activities against some selected microbes. Two selected compounds were also studied for their hepatotoxic effects on rat liver. The structures of the various compounds were assigned on the basis of IR, ^{1}H NMR and mass spectral data.

2. Chemistry

Carbothioamide-3,5-dimethyl-4-[(substituted phenyl) diazenyl] pyrazoles (**2a–d**), 1-(pyridine-4-ylcarbonyl)-3,5-dimethyl-4-[(substituted phenyl) diazenyl] pyrazoles (**3a–d**), 1-(5-chloro-6-fluoro-1,3-benzothiazole-2-yl) thiocarbamoyl-3,5-dimethyl-4-[(substituted phenyl) diazenyl] pyrazoles (**4a–d**) and 1-[(1,2,4-triazole-4-yl) carbothioamide]-3,5-dimethyl-4-[(substituted phenyl) diazenyl] pyrazoles (**5a–d**) were obtained by cyclization of intermediates **1a–d** with thiosemicarbazide, isonicotinic acid hydrazide, 5-chloro-6-fluoro-1,3-benzothiazole-2-yl-thiosemicarbazide and N-4H-1,2,4-triazol-4-ylhydrazine. The interme-



Scheme 1

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