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ORIGINAL ARTICLE

Synthesis and anti-inflammatory activity of some new 1,3,4-thiadiazoles containing pyrazole and pyrrole nucleus

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Anti-inflammatory activity

Abstract A new series of 1,3,4-thiadiazole with pyrazole-3-carboxamides (**3a–f**) and pyrrole-3-carboxamide (**4a–f**) moiety are prepared using intermediate compounds 1,3,4-thiadiazolacrylamides (**2a–f**). The structures of newly synthesized compounds were confirmed on the basis of their ^{1}H NMR, ^{13}C NMR, LCMS mass, FT-IR and elemental analysis data results. Among all the compounds (12), seven compounds were found to exhibit significant anti-inflammatory activity with 77.27, 75.89, 76.24, 68.55, 63.72, 57.41, 53.05% and 81.00, 80.55, 78.62, 71.45, 68.95, 61.89, 56.32% inhibition in paw edema at 3 h and 5 h respectively, compared to the standard drug indomethacin (74.82 and 80.32% at 3 h and 5 h). Compounds **3c, 3d** and **4c** exhibited potent activity than standard drug.

1. Introduction

Inflammation is a complex defensive mechanism of the body to any noxious stimulus; this process may vary from a localized to a generalized response characterized by the accumulation of fluids and leukocytes leading to edema and pain (Cunha et al., 2008). This inflammatory response seems to be mediated by different physiological and immunological mediators that play a role in acute and chronic inflammation (Kanaka Padmanabham and Giles, 2011). Acute inflammation occurs as the initial response to tissue injury, being mediated by the release of autacoids, for example, serotonin, thromboxanes, histamine and leukotrienes (Sherwood and Toliver-Kinsky, 2004). On the other hand, the chronic inflammatory process involves the release of diverse mediators, as interleukins, interferon and tumor necrosis factor α (TNF–α), and a cytokine that plays a major role in this kind of inflammatory process

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and whose production is associated with some inflammatory diseases such as rheumatoid arthritis (Spirchez et al., 2012; Mangge et al., 1995).

Non-steroidal anti-inflammatory drugs are commonly used for the treatment of pain and inflammation associated with different diseases particularly rheumatoid arthritis (Patrinani et al., 2011), however their chronic use may cause GIT ulceration, bleeding and renal injury (Wolfe et al., 1999). Therefore, although there are a number of anti-inflammatory drugs available in the market, there is a need to develop novel drugs with better safety profile. 1,3,4-thiadiazoles are an important class of heterocyclic compounds that exhibit a broad spectrum of biological activities such as anti cancer (Badr and Barwa, 2011; Miyahara et al., 1982; Al-Soud et al., 2008), antiviral (Chen et al., 2010; Al-Masoudi et al., 2004; Invidiata et al., 1996), antibacterial (Maddila and Jonnalagadda, 2012; Maddila et al., 2012), antioxidant (Khan et al., 2010; Shih and Ke, 2004), anxiolytic (Invidiata et al., 1991), anti-tubercular (Andanappa et al., 2004), anticonvulsant (Stillings et al., 1986; Gupta et al., 2009) and anti-inflammatory activities (Rostom et al., 2009; Schenone et al., 2006) etc.

In the pursuit and design of new drugs, the development of hybrid molecules through the combination of different pharmacophores in one frame may lead to compounds with interesting biological profiles. Prompted by these observations, in the present study, the synthesis and anti-inflammatory screening of new 1,3,4-thiadiazole derivatives incorporating with different pyrazole-3-carboxamide and pyrrole-3-carboxamide moiety pharmacophores as hybrid molecules possessing anti-inflammatory activity are aimed.

2. Results and discussion

2.1. Chemistry

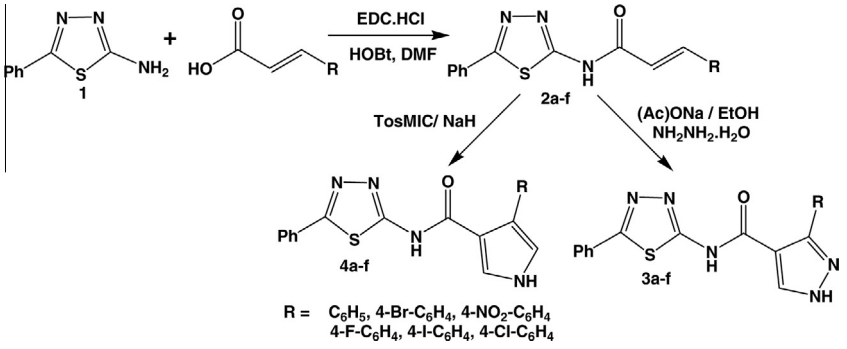
The compound (*E*)-3-(4-substitutedphenyl)-*N*-(5-phenyl-1,3,4-thiadiazol-2-yl) acrylamide (**2a–f**) was synthesized via the single step process of 5-phenyl-1,3,4-thiadiazol-2-amine with substituted cinnamic acid in the presence of EDC·HCl, HOBt condition. It was then converted into 4-(4-substitutedphenyl)-*N*-(5-phenyl-1,3,4-thiadiazol-2-yl)-1*H*-pyrazole-3-carboxamides (**3a–f**) by cyclization with hydrazines under microwave irradiation in the presence of sodium acetate as a catalyst to a good yield. Reacting 1,3,4-acrylamides (**2a–f**) with TosMIC (Tosylmethyl isocyanide) and NaH at room temperature resulted in the formation of the corresponding 4-(4-substitutedphenyl)-*N*-(5-phenyl-1,3,4-thiadiazol-2-yl)-1*H*-pyrrole-3-carboxamide (**4a–f**). (Scheme 1.). The structures of the newly synthesized compounds were confirmed on the basis of IR, ^{1}H-NMR, ^{13}C-NMR, MS spectrometry and elemental analysis.

All the synthesized compounds gave satisfactory analyses for the proposed structures, which were confirmed on the basis of their spectral data. The IR spectra of compounds **2a–f** exhibited characteristic absorption bands at 3315–3334 cm^{-1}, 1630–1658 cm^{-1} and 1562–1580 cm^{-1} for NH, CONH and C═N functional groups, while ^{1}H NMR spectrum showed a broad singlet region of NH at δ 10.42–10.51, multiplet of aromatic rings at δ 7.06–8.21 and two doublets of single protons of ═CH at range of δ 7.06–8.21 and 6.85–7.09 ppm which proved the synthetic nucleus **2a–f**.

The IR spectra of compounds **3a–f** exhibited characteristic absorption bands at 3320–3342 cm^{-1}, 1665–1687 cm^{-1}, 1564–1580 cm^{-1}, and 1263–1296 & 1175–1222 cm^{-1} corresponding to the NH, CONH, C═N and C–S–C stretching respectively. Similarly the ^{1}H NMR spectra displayed peaks in the range of δ 13.70–13.76 ppm for NH, δ 8.62–8.88 ppm for CONH and δ 7.84–7.96 ppm for pyrazole–CH. The IR spectra of compounds **4a–f** revealed characteristic absorption bands at 3286–3297 cm^{-1} for NH, 1681–1695 cm^{-1} for CONH and 1573–1581 cm^{-1} corresponding to C═N stretching vibrations. The ^{1}H NMR spectra displayed peaks in the range of δ 10.64–10.73 ppm for NH, δ 8.08–8.35 ppm for CONH and δ 6.76–6.83 & 6.70–6.77 ppm for pyrrole CH respectively. The ^{13}C NMR and Mass spectral data of compounds **3a–f** and **4a–f** are given in the experimental section.

3. Biological assay

All the synthesized compounds were evaluated for their anti-inflammatory activity against carrageenan-induced acute paw edema in Wistar albino rats weighing 150–200 g, using Plethysmometer following the method of Winter (Winter et al., 1962). The animals were weighed and divided into control, standard, test groups each group contained six rats. The first group of rats was treated with 0.1 mL of 0.5% gum acacia suspension orally (control), second group was administered with a dose of 10 mg/kg of the suspension of indomethacin (standard) and the test group was treated with equimolar dose of the suspension of test compounds relative to standard drug. After 30 min, the animals were injected with 0.1 mL of 1% carrageenan in normal saline, subcutaneously to the sub-



Scheme 1 Synthetic route employed for the synthesis of target molecules.