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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

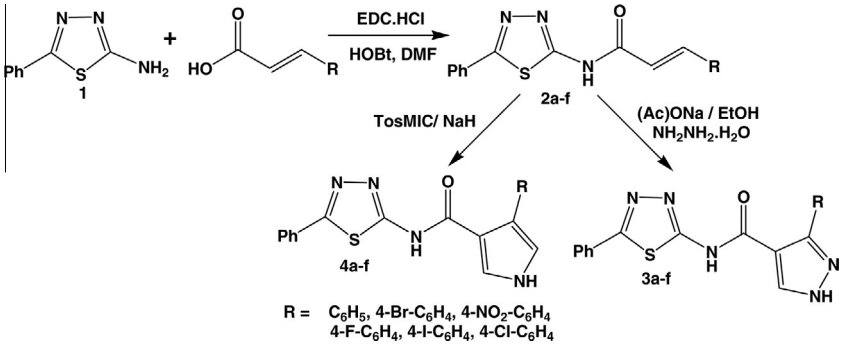
The compound (*E*)-3-(4-substitutedphenyl)-*N*-(5-phenyl-1,3,4-thiadiazol-2-yl) acrylamide (**2a–f**) was synthesized via the single step process of 5-phenyl-1,3,4-thiadiazol-2-amine with substituted cinnamic acid in the presence of EDC·HCl, HOBt condition. It was then converted into 4-(4-substitutedphenyl)-*N*-(5-phenyl-1,3,4-thiadiazol-2-yl)-1*H*-pyrazole-3-carboxamides (**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.

Table 1 Results of anti-inflammatory activity of 1,3,4-thiadiazoles derivatives against carrageenan induced rat paw edema model.

Compounds	3 h		5 h	
	Swel ± SE	% inhibition	Swel ± SE	% inhibition
Edema induced by carrageenan (% edema inhibition relative to control)				
3a	0.534 ± 0.042[a]	38.70	0.515 ± 0.033[b]	41.42
3b	0.371 ± 0.065[c]	57.41	0.335 ± 0.090[c]	61.89
3c	0.198 ± 0.049[c]	77.27	0.167 ± 0.084[c]	81.00
3d	0.210 ± 0.043[c]	75.89	0.171 ± 0.076[c]	80.55
3e	0.409 ± 0.040[c]	53.05	0.384 ± 0.088[b]	56.32
3f	0.274 ± 0.061[c]	68.55	0.201 ± 0.57[c]	71.45
4a	0.657 ± 0.051[d]	24.57	0.631 ± 0.042[a]	28.22
4b	0.510 ± 0.057[d]	41.45	0.486 ± 0.114[b]	44.71
4c	0.207 ± 0.021[c]	76.24	0.188 ± 0.066[c]	78.62
4d	0.316 ± 0.058[c]	63.72	0.273 ± 0.089[c]	68.95
4e	0.575 ± 0.091[b]	33.99	0.551 ± 0.074[b]	37.32
4f	0.463 ± 0.091[a]	46.85	0.398 ± 0.074[c]	54.73
Indomethacin	0.218 ± 0.029[c]	74.82	0.173 ± 0.045[c]	80.32
Control	0.871 ± 0.040	—	0.879 ± 0.078	—

Swel, mean difference in rat paw volume between right and left paw ± S.E; % inhibition, $(1-Vt/Vc)\times 100$; Vt, mean increase in paw volume of test; Vc, mean increase in paw volume of control group of rats.

[a] $p < 0.05$;

[b] $p < 0.01$;

[c] $p < 0.001$ significantly different from standard;

[d] ns, not significant.

plantar region of the right hind paw. The paw volume was measured at 0 h, 1 h, 3 h and 5 h, using plethysmometer. The amount of edema in the drug-treated groups was compared in relation to the control group with the corresponding time intervals. Results are calculated as mean ± SEM, and different groups were compared using one way analysis of variance ANOVA followed by dunnet's-*t*-test and results are tabulated in Table 1.

3.1. Biological results

The results of anti-inflammatory activity are summarized in Table 1. The tested compounds, **3c, 3d, 4c, 3f, 4d, 3b** and **3e** were found to be active and have significant activity (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) when compared to the standard drug indomethacin (74.82 and 80.32% at 3 h and 5 h). Compounds **3c, 3d** and **4c** were more active than the standard drug indomethacin. From the biological activity data, the structural activity relationship (SAR) can be drawn as follows. Compounds having electron withdrawing group on the pyrazole-3-carboxamide and pyrrole-3-carboxamide in 1,3,4-thiadiazole ring. The 1,3,4-thiadiazole linked pyrazole-3-carboxamide compounds **3a–f** are responsible for better activity compared to 1,3,4-thiadiazole linked pyrrole-3-carboxamide for compounds **4a–f**. Substitution of weak electron withdrawing groups and no substituted groups on pyrazole and pyrrole attached thiadiazole ring decreases the activity but is comparable with the standard. Compounds having substitution like $-NO_2$, F group on the pyrazoles and pyrrole ring are showing potential activity (March, 2005). Whereas the remaining compounds having weak electron withdrawing groups attached on the pyrazole and pyrrole with thiadiazoles significantly diminish the activity. These data suggest that functionality of the pyrazole and pyrrole group is playing an important role in the enzymatic interactions responsible for anti-inflammatory activity.

4. Experimental

All reagents and solvents were purchased and used without further purification. Melting points determined on a Fisher–Johns melting point apparatus were uncorrected. Crude products were purified by column chromatography on silica gel of 60–120 mesh. The IR spectra (KBr pellets) were recorded on a Vertex 70 Bruker spectrometer. The NMR spectra were recorded on a varian 300 MHz spectrometer for ^{1}H NMR. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Bruker 100 MHz spectrometer. The chemical shifts were reported as ppm down field using TMS as an internal standard. The mass spectra of the new compounds were recorded on a triple quadrupole mass spectrometer Varian 1200 L/MS/MS with electrospray interface (ESI), coupled with a high performance liquid chromatography with Varian Prostar 240 SDM ternar pump. The instrument was operated in positive ion mode.

*4.1. General procedure for the synthesis of (E)-3-(4-substitutedphenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)acrylamide derivatives (**2a–f**)*

A stirred solution of compound 5-phenyl-1,3,4-thiadiazol-2-amine (1 mmol) in CH_2Cl_2 (50 mL) was treated with the appropriate substituted cinnamic acid, EDC·HCl (0.15 mmol), HOBt (0.05 mmol) and refluxed overnight. Then purification with recrystallization afforded the corresponding compound as white powder.

*4.2. N-(5-phenyl-1,3,4-thiadiazol-2-yl)cinnamamide (**2a**)*

Yield: 88 %; mp 196–198 °C; IR (υ cm^{-1}, KBr): 3315 (NH), 1658 (CONH), 1628 (C=C), 1574 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.86 (d, J = 15.6 Hz, 1H), 7.25–7.58 (m, 10H, ArH), 7.64 (d, J = 15.7 Hz, 1H), 10.46 (bs, 1H, NH); (ESI−MS) m/z: 308 $[M+H]^+$. *Anal.* Calcd. for $C_{17}H_{13}N_3OS$: C, 66.43; H, 4.26; N, 13.67. Found: C, 66.39; H, 4.29; N, 13.63.

*4.3. (E)-3-(4-bromophenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)acrylamide (**2b**)*

Yield: 91 %; mp 175–176 °C; IR (υ cm^{-1}, KBr): 3327 (NH), 1630 (CONH), 1621 (C=C), 1575 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.89 (d, J = 15.6 Hz, 1H), 7.18–7.50 (m, 9H, ArH), 7.66 (d, J = 15.6 Hz, 1H), 10.42 (bs, 1H, NH); (ESI−MS) m/z: 386 $[M+2H]^+$. *Anal.* Calcd. for $C_{17}H_{12}BrN_3OS$: C, 52.86; H, 3.13; N, 10.88. Found: C, 52.91; H, 3.08; N, 10.83.

*4.4. (E)-3-(4-nitrophenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)acrylamide (**2c**)*

Yield: 90 %; mp 203–205 °C; IR (υ cm^{-1}, KBr): 3324 (NH), 1645 (CONH), 1630 (C=C), 1562 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.09 (d, J = 16.2 Hz, 1H), 7.27–8.21 (m, 9H, ArH), 7.73 (d, J = 16.2 Hz, 1H), 10.51 (bs, 1H, NH); (ESI−MS) m/z: 353 $[M+H]^+$. *Anal.* Calcd. for $C_{17}H_{12}N_4O_3S$: C, 57.95; H, 3.43; N, 15.90. Found: C, 57.99; H, 3.47; N, 15.92.

*4.5. (E)-3-(4-fluorophenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)acrylamide (**2d**)*

Yield: 88 %; mp 169–170 °C; IR (υ cm^{-1}, KBr): 3322 (NH), 1641 (CONH), 1626 (C=C), 1578 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.85 (d, J = 15.6 Hz, 1H), 7.06–7.48 (m, 9H, ArH), 7.68 (d, J = 15.6 Hz, 1H), 10.47 (bs, 1H, NH); (ESI−MS) m/z: 326 $[M+H]^+$. *Anal.* Calcd. for $C_{17}H_{12}FN_3OS$: C, 62.76; H, 3.72; N, 12.91. Found: C, 62.81; H, 3.68; N, 12.95.

*4.6. (E)-3-(4-iodophenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)acrylamide (**2e**)*

Yield: 89 %; mp 216–218 °C; IR (υ cm^{-1}, KBr): 3330 (NH), 1648 (CONH), 1633 (C=C), 1580 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.88 (d, J = 15.6 Hz, 1H), 7.14–7.60 (m, 9H, ArH), 7.69 (d, J = 15.6 Hz, 1H), 10.48 (bs, 1H, NH); (ESI−MS) m/z: 433 $[M+H]^+$. *Anal.* Calcd. for $C_{17}H_{12}IN_3OS$: C, 47.13; H, 2.79; N, 9.70. Found: C, 47.07; H, 2.73; N, 9.77.

*4.7. (E)-3-(4-chlorophenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)acrylamide (**2f**)*

Yield: 90 %; mp 171–173 °C; IR (υ cm^{-1}, KBr): 3334 (NH), 1635 (CONH), 1627 (C=C), 1571 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.92 (d, J = 15.6 Hz, 1H), 7.24–7.49 (m, 9H, ArH), 7.67 (d, J = 15.6 Hz, 1H), 10.46 (bs, 1H, NH); (ESI−MS) m/z: 342 $[M+H]^+$. *Anal.* Calcd. for $C_{17}H_{12}ClN_3OS$: C, 59.73; H, 3.54; N, 12.29. Found: C, 59.77; H, 3.57; N, 12.33.

*4.8. General procedure for the synthesis of 4-(4-substitutedphenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-1H-pyrazole-3-carboxamide derivatives (**3a–f**)*

Equimolar amounts (1 mmol) of compound **2** and different hydrazines were mixed in ethanolic sodium acetate (10 ml) and refluxed under microwave irradiation (140–210 W) for about 30–35 min using a synthetic microwave oven. The reactions were monitored by TLC. The mixture was concentrated in a water bath and poured into ice-cold water. The precipitate obtained was filtered, washed, dried and purified by recrystallization from ethanol.

*4.9. 4-Phenyl-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-1H-pyrazole-3-carboxamide (**3a**)*

Yield: 93 %; mp 253–254 °C; IR (υ cm^{-1}, KBr): 3324 (NH), 1665 (CONH), 1565 (C=N), 1283, 1195 (C–S–C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.28–7.77 (m, 10H, ArH), 7.96 (s, 1H, pyrazole-CH), 8.62 (bs, 1H, CONH), 13.76 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 123.27, 127.78, 128.69, 130.08, 132.34, 133.47, 134.30, 137.17, 151.33, 165.48, 176.52; (ESI−MS) m/z: 348 $[M+H]^+$. *Anal.* Calcd. for $C_{18}H_{13}N_5OS$: C, 62.23; H, 3.77; N, 20.16. Found: C, 62.25; H, 3.73; N, 20.19.

*4.10. 4-(4-Bromophenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-1H-pyrazole-3-carboxamide (**3b**)*

Yield: 90 %; mp 214–215 °C; IR (υ cm^{-1}, KBr): 3328 (NH), 1673 (CONH), 1580 (C=N), 1263, 1205 (C–S–C), 630 (C–Br); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.30–7.65 (m, 9H, ArH), 7.89 (s, 1H, pyrazole-CH), 8.67 (bs, 1H, CONH), 13.73 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 123.31, 125.07, 127.83, 128.91, 130.24, 130.51, 132.36, 133.29, 133.53, 134.41, 136.96, 151.34, 165.50, 176.73; (ESI−MS) m/z: 426 $[M+H]^+$. *Anal.* Calcd. For $C_{18}H_{12}BrN_5OS$: C, 50.71; H, 2.84; N, 16.43. Found: C, 50.69; H, 2.87; N, 16.40.

*4.11. 4-(4-Nitrophenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-1H-pyrazole-3-carboxamide (**3c**)*

Yield: 87 %; mp 230–232 °C; IR (υ cm^{-1}, KBr): 3342 (NH), 1687 (CONH), 1576 (C=N), 1273, 1175 (C–S–C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.31–8.32 (m, 10H, ArH & pyrazole-CH), 8.83 (bs, 1H, CONH), 13.70 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 120.07, 123.43, 127.84, 128.98, 129.65, 130.26, 132.33, 133.41, 133.54, 144.61, 149.23, 151.42, 165.51, 176.76; (ESI−MS) m/z: 393 $[M+H]^+$. *Anal.* Calcd. for $C_{18}H_{12}N_6O_3S$: C, 55.10; H, 3.08; N, 21.42. Found: C, 55.12; H, 3.11; N, 21.47.

*4.12. 4-(4-Fluorophenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-1H-pyrazole-3-carboxamide (**3d**)*

Yield: 91 %; mp 223–225 °C; IR (υ cm^{-1}, KBr): 3335 (NH), 1681 (CONH), 1579 (C═N), 1313 (C–F), 1296, 1222 (C–S–C); ^{1}H NMR (300 MHz, DMSO0-d_6): δ 7.32–7.65 (m, 9H, ArH), 7.84 (s, 1H, pyrazole-CH), 8.83 (bs, 1H, CONH), 13.74 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 118.13, 123.37, 127.86, 128.93, 129.41, 130.23, 132.39, 133.10, 133.53, 134.38, 151.35, 161.23, 165.49, 176.73; (ESI−MS) *m*/*z*: 366 $[M+H]^+$. *Anal*. Calcd. for $C_{18}H_{12}FN_5OS$: C, 59.17; H, 3.31; N, 19.17. Found: C, 59.15; H, 3.33; N, 19.15.

*4.13. 4-(4-Iodophenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-1H-pyrazole-3-carboxamide (**3e**)*

Yield: 95 %; mp 185–187 °C; IR (υ cm^{-1}, KBr): 3320 (NH), 1667 (CONH), 1564 (C═N), 1293, 1176 (C–S–C), 556 (C–I); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.29–7.76 (m, 9H, ArH), 7.92 (s, 1H, pyrazole-CH), 8.88 (bs, 1H, CONH), 13.72 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 93.13, 123.28, 127.80, 128.91, 129.36, 130.25, 132.34, 133.47, 134.30, 136.51, 137.32, 151.27, 165.50, 176.69; (ESI−MS) *m*/*z*: 473 $[M+H]^+$. *Anal*. Calcd. for $C_{18}H_{12}IN_5OS$: C, 45.68; H, 2.56; N, 14.80. Found: C, 45.71; H, 2.59; N, 14.83.

*4.14. 4-(4-Chlorophenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-1H-pyrazole-3-carboxamide (**3f**)*

Yield: 91 %; mp 217–219 °C; IR (υ cm^{-1}, KBr): 3330 (NH), 1671 (CONH), 1580 (C═N), 1276, 1195 (C–S–C), 710 (C–Cl); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.28–7.60 (m, 9H, ArH), 7.87 (s, 1H, pyrazole-CH), 8.80 (bs, 1H, CONH), 13.71 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 26.82, 30.48, 54.50, 68.19, 123.74, 125.16, 126.40, 127.51, 127.58, 128.62, 130.13, 134.75, 146.82, 151.42, 153.72, 155.51, 157.29; (ESI−MS) *m*/*z*: 382 $[M+H]^+$. *Anal*. Calcd. for $C_{18}H_{12}ClN_5OS$: C, 56.62; H, 3.17; N, 18.34. Found: C, 56.60; H, 3.19; N, 18.37.

*4.15. General procedure for the synthesis of 4-(4-substitutedphenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-1H-pyrrole-3-carboxamide derivatives (**4a–f**)*

A mixture of TosMIC (1 mmol) and **2** (1 mmol) in Et_2O/DMSO (2:1) was added dropwise to a stirred mixture of NaH (0.05 g) in dry Et_2O (10 ml) at room temperature and stirring was continued for 12–14 h. Then the reaction mixture was diluted with water and extracted with ether. The ethereal layer was dried (an.Na_2SO_4) and the solvent was removed under reduced pressure. The resultant solid was purified by passing through a column of silica gel (60–120 mesh) using ethyl acetate-hexane 1:2 as eluent.

*4.16. 4-Phenyl-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-1H-pyrrole-3-carboxamide (**4a**)*

Yield: 90 %; mp 233–234 °C; IR (υ cm^{-1}, KBr): 3286 (NH), 1681 (CONH), 1577 (C═N), 1273, 1185 (C–S–C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.70 (s, 1H, pyrrole-CH), 6.76 (s, 1H, pyrrole-CH), 7.18–7.69 (m, 10H, ArH), 8.08 (bs, 1H, CONH), 10.64 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 109.21, 115.40, 121.82, 127.78, 128.29, 128.68, 130.02, 134.32, 137.11, 151.29, 167.53, 176.68; (ESI−MS) *m*/*z*: 347 $[M+H]^+$. *Anal*. Calcd. for $C_{19}H_{14}N_4OS$: C, 65.88; H, 4.07; N, 16.07. Found: C, 65.91; H, 1.04; N, 16.01.

*4.17. 4-(4-Bromophenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-1H-pyrrole-3-carboxamide (**4b**)*

Yield: 93 %; mp 209–210 °C; IR (υ cm^{-1}, KBr): 3292 (NH), 1693 (CONH), 1573 (C═N), 1283, 1195 (C–S–C), 613 (C–Br); ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.73 (s, 1H, pyrrole-CH), 6.79 (s, 1H, pyrrole-CH), 7.20–7.74 (m, 9H, ArH), 8.24 (bs, 1H, CONH), 10.68 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 109.27, 115.42, 121.80, 125.03, 127.81, 128.37, 128.92, 130.19, 130.53, 133.37, 134.35, 136.93, 151.36, 167.61, 176.71; (ESI−MS) *m*/*z*: 426 $[M+2H]^+$. *Anal*. Calcd. For $C_{19}H_{13}BrN_4OS$: C, 53.66; H, 3.08; N, 13.17. Found: C, 53.62; H, 3.05; N, 13.21.

*4.18. 4-(4-Nitrophenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-1H-pyrrole-3-carboxamide (**4c**)*

Yield: 88 %; mp 199–201 °C; IR (υ cm^{-1}, KBr): 3297 (NH), 1695 (CONH), 1581 (C═N), 1283, 1195 (C–S–C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.77 (s, 1H, pyrrole-CH), 6.83 (s, 1H, pyrrole-CH), 7.25–8.31 (m, 9H, ArH), 8.33 (bs, 1H, CONH), 10.72 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 109.66, 115.91, 119.28, 121.73, 127.86, 128.59, 128.97, 129.62, 130.21, 134.43, 144.57, 149.18, 151.43, 167.80, 176.75; (ESI−MS) *m*/*z*: 392 $[M+H]^+$. *Anal*. Calcd. for $C_{19}H_{13}N_5O_3S$: C, 58.30; H, 3.35; N, 17.89. Found: C, 58.33; H, 3.30; N, 17.93.

*4.19. 4-(4-Fluorophenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-1H-pyrrole-3-carboxamide (**4d**)*

Yield: 92 %; mp 220–221 °C; IR (υ cm^{-1}, KBr): 3294 (NH), 1690 (CONH), 1576 (C═N), 1320 (C–F), 1268, 1205 (C–S–C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.74 (s, 1H, pyrrole-CH), 6.81 (s, 1H, pyrrole-CH), 7.28–7.76 (m, 9H, ArH), 8.18 (bs, 1H, CONH), 10.73 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 109.31, 115.47, 118.08, 121.83, 127.84, 128.39, 128.93, 129.38, 130.21, 133.06, 134.40, 151.37, 161.14, 167.66, 176.72; (ESI−MS) *m*/*z*: 365 $[M+H]^+$. *Anal*. Calcd. for $C_{19}H_{13}FN_4OS$: C, 62.63; H, 3.60; N, 15.38. Found: C, 62.66; H, 3.63; N, 15.41.

*4.20. 4-(4-Iodophenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-1H-pyrrole-3-carboxamide (**4e**)*

Yield: 89 %; mp 189–191 °C; IR (υ cm^{-1}, KBr): 3289 (NH), 1692 (CONH), 1574 (C═N), 1264, 1195 (C–S–C), 552 (C–I); ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.74 (s, 1H, pyrrole-CH), 6.78 (s, 1H, pyrrole-CH), 7.26–7.80 (m, 9H, ArH), 8.35 (bs, 1H, CONH), 10.65 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 93.01, 109.18, 115.39, 121.79, 127.80, 128.36, 128.90, 129.35, 130.24, 134.30, 136.47, 137.29, 151.28, 167.58, 176.69; (ESI−MS) *m*/*z*: 472 $[M+H]^+$. *Anal*. Calcd. for

$C_{19}H_{13}IN_4OS$: C, 48.32; H, 2.77; N, 11.86. Found: C, 48.30; H, 2.81; N, 11.83.

*4.21. 4-(4-Chlorophenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-1H-pyrrole-3-carboxamide (**4f**)*

Yield: 94 %; mp 215–217 °C; IR (υ cm^{-1}, KBr): 3288 (NH), 1690 (CONH), 1575 (C═N), 1267, 1205 (C–S−C), 713 (C–Cr); ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.73 (s, 1H, pyrrole-CH), 6.79 (s, 1H, pyrrole-CH), 7.22–7.71 (m, 9H, ArH), 8.16 (bs, 1H, CONH), 10.70 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 109.30, 115.45, 121.81, 127.82, 128.40, 128.78, 129.12, 129.84, 130.33, 134.38, 135.10, 135.52, 151.36, 167.58, 176.74; (ESI−MS) m/z: 381 $[M+H]^+$. *Anal.* Calcd. for $C_{19}H_{13}ClN_4OS$: C, 59.92; H, 3.44; N, 14.71. Found: C, 59.95; H, 3.40; N, 14.67.

5. Conclusion

In conclusion, we have described an efficient and benign synthesis of 1,3,4-thiadiazole systems containing pyrazoles and pyrroles with good yields. 1,3,4-Thiadiazol-2-yl-acrylamide is the key intermediate in the formation of these heterocyclic compounds. All the synthesized compounds have been investigated for their anti-inflammatory activity. With our newly synthesized compounds, it is evident that **3c, 3d, 4c, 3f, 4d, 3b** and **3e** have shown excellent anti-inflammatory activity. Accordingly, this novel class of new 1,3,4-thiadiazole derivatives reported from our laboratory, emerge as a valuable lead series with great potential to be used as anti-inflammatory agents, and as promising candidates for further efficacious evaluation.

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