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SYNTHESIS OF SOME NEW THIADIAZOLE DERIVATIVES ENDOWED WITH ANALGESIC AND ANTI-INFLAMMATORY ACTIVITIES

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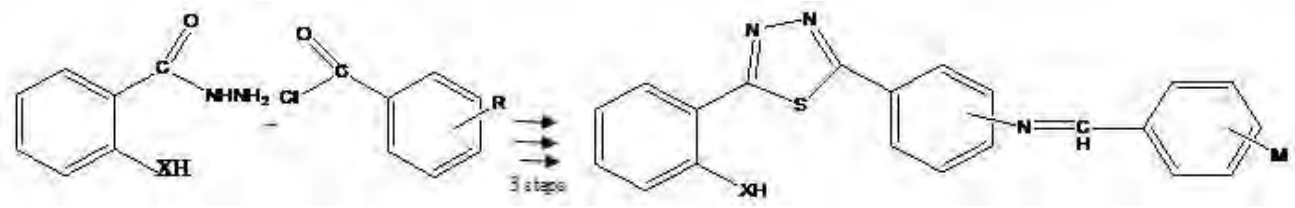
ABSTRACT In the present study, some new Schiff bases of 2,5-disubstituted-1,3,4-thiadiazole were synthesized. The chemical structures were confirmed by IR, ^{1}H NMR and elemental analysis. All the new compounds were tested *in vivo* for their analgesic and anti-inflammatory activities. Among them in particular compound 5-(2-Mercaptophenyl)-2-{N-(4-methoxybenzylidene)-4-aminophenyl}-1,3,4-thiadiazole **(7f)** was found to have a superior analgesic and anti-inflammatory profile with low gastric ulceration incidence.



KEYWORDS Analgesic, Anti-inflammatory, Schiff bases, Thiadiazole.

INTRODUCTION

The identification of compounds able to treat both acute and chronic pain is challenging in pharmaceutical research.[1] Pain is in fact a very important problem present in 90% of diseases, from the simple back pain to pain associated with different forms of cancer. The classical therapies for pain treatment are mainly the non-steroidal anti-inflammatory drugs (NSAIDs) and opiates, whose lead compounds, acetylsalicylic acid and morphine, respectively, were isolated in 19th century.[2]

NSAIDs show side effects such as gastrointestinal irritation and lesions, renal toxicity and inhibition of platelet aggregation, while the use of opoids is limited to severe pain because of adverse secondary reactions as respiratory depression, dependence, sedation, and constipation.[3,4] Molecular biology techniques and development of selective ligands for the different receptors classes involved in pain led a further insight in the research of the nociceptive transmission. At the moment it is known that 10-15 neurotransmitters or neuromodulators are involved in the pain processing pathway;[1] so it is potentially possible to develop novel analgesic classes of compounds apart from NSAIDs and opoids, preferably devoid of severe side effects.

During recent years there has been a large investigation on different classes of thiadiazole compounds, many of which were found to possess an extensive spectrum of pharmacological activities. Moreover, many reports indicate that acylthiosemicarbazides and their corresponding cyclized

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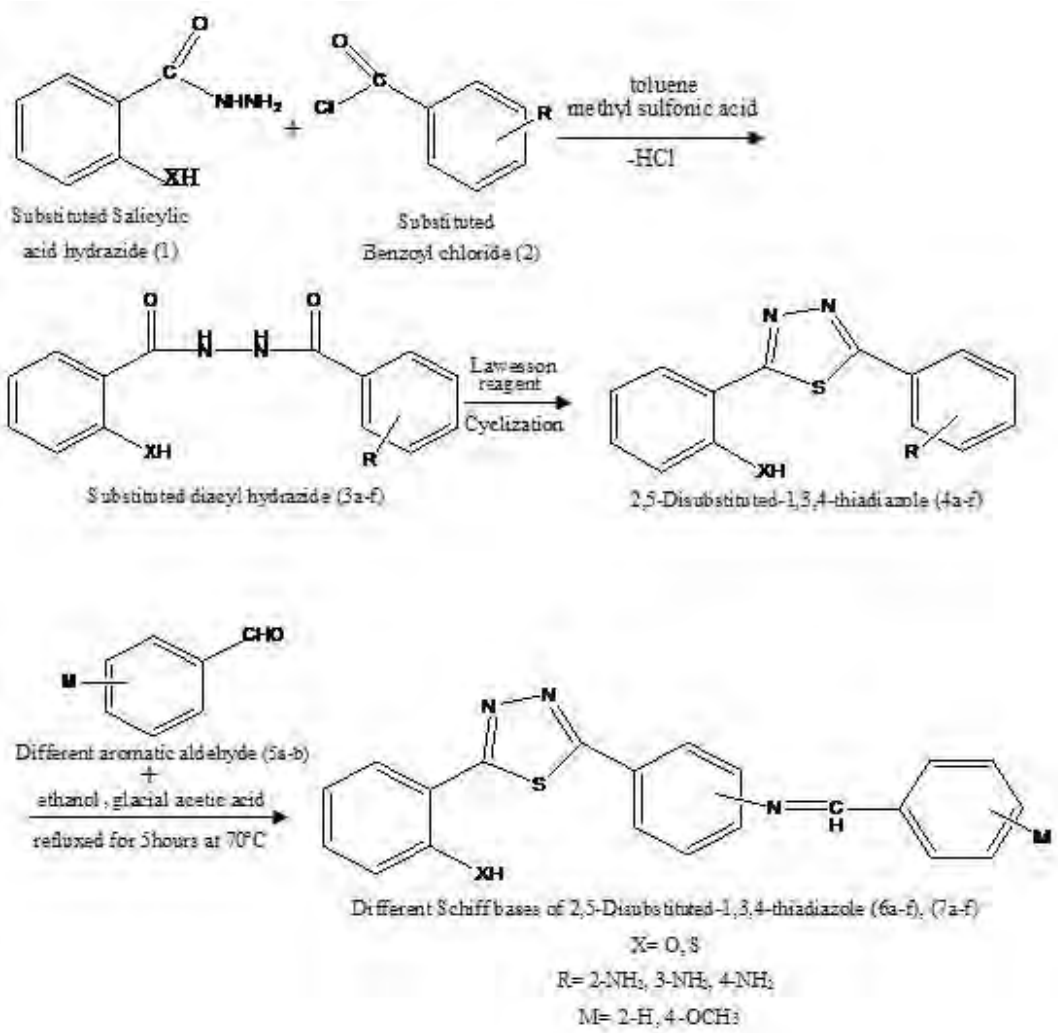
1,3,4-thiadiazole derivatives possess anti-inflammatory[5-8] and analgesic[9] activities. Being involved in a research program on non-steroidal anti-inflammatory and anti-pains agents, we focused our attention on the 1,3,4-thiadiazole ring.

The varied biological activities of 1,3,4-thiadiazoles and their analogs have been known from the beginning of the 20th century.[10,11] Literature survey revealed that slight modification in the structure can result in qualitative as well as quantitative changes in the activity.[10,12,13] This prompted us to undertake the synthesis of various novel Schiff bases derived from 2,5-disubstituted-1,3,4-thiadiazole and characterized using IR, ^{1}H NMR and Elemental analysis with the aim of having improved activity. The synthesized compounds were tested for their analgesic and anti-inflammatory activity.

RESULTS AND DISCUSSION

Synthesis

The synthesis involves reaction of substituted salicylic acid hydrazide **1** with substituted benzoyl chloride **2** which resulted in the formation of substituted diacylhydrazines **(3a-f)**. Cyclization of substituted diacylhydrazine was carried out using Lawesson reagent, which resulted in formation of 2,5-disubstituted-1,3,4-thiadiazoles **(4a-f)**. 2,5-disubstituted-1,3,4-thiadiazoles underwent reaction with different aromatic aldehyde to form different Schiff bases. The compounds were purified by repeated recrystallization from ethanol and then dried under vacuum.[14,15] The synthetic scheme illustrates the way used for the synthesis of target compounds **(Scheme 1)**. The structures of compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR spectral data and elemental analysis.



Scheme 1

Biological Investigation

Non- steroidal anti-inflammatory drugs (NSAIDs) are commonly used as analgesic, anti-inflammatory and antipyretic agents. The effects of NSAIDs are attributed to the inhibition of cyclooxygenase (COX) 1 and 2 enzymes, and eventual suppression of prostaglandins biosynthesis. Nevertheless, NSAIDs therapy is also accompanied with adverse effects like gastric irritation and ulceration.[16] Interestingly, 1,3,4-thiadiazole bioactive core showed selectivity towards COX 2 and therefore, devoid of any gastrointestinal adverse effects.[17] In this background, we have performed the screening for analgesic and anti-inflammatory activities of the newly synthesized 1,3,4-thiadiazole derivatives in the present study. The extremely important sites for molecular modification are the 2-position and 5-position, which play a dominant role in determining the pharmacological activities of 1,3,4-thiadiazole derivatives. The tested derivatives showed analgesic activity ranging from 46% to 56%, whereas standard drug acetylsalicylic acid showed 60% inhibition in acetic acid induced writhing reflex method **(Table 1)**. All the synthesized compounds and reference NSAID were screened for anti-inflammatory activities by carrageenan induced paw edema test. The obtained pharmacological results **(Table 2)** indicate that some of the synthesized compounds possess notable anti-inflammatory properties. Derivatives showed anti-inflammatory activity ranging from 35% to 44%, whereas standard drug indomethacin showed 56% inhibition in carrageenan-induced paw edema method **(Table 2)**. **7f** exhibit more potent analgesic and anti-inflammatory effect as compare to other derivatives. According to the results of the *in vivo* experiments, it is difficult to extract a definite structure activity relationship between the compounds and anti-inflammatory properties.

Table 1: Effects of 1,3,4-thiadiazole derivatives and acetylsalicylic acid on acetic acid-induced writhing reflex.

Treatment group[a]	Total number of writhes[b] (mean ± SEM)	% Inhibition[c]
Control	73.46 ± 1.92	—-
Acetylsalicylic acid	29.14 ± 1.23	60.33
6a	39.45 ± 1.05	46.29
6b	38.96 ± 1.49	46.96
6c	38.34 ± 1.08	47.80
6d	36.14 ± 1.23	50.80
6e	34.63 ± 1.41	52.85
6f	33.23 ± 1.52	54.76
7a	38.24 ± 1.47	47.94
7b	38.96 ± 1.21	46.96
7c	36.65 ± 1.15	50.10
7d	34.96 ± 1.17	52.40
7e	33.54 ± 1.13	54.34
7f	32.28 ± 1.45.	56.05

The results are given as mean of % inhibition of writhing. The data were analyzed by one way analysis of variance (ANOVA) followed by post hoc Dunnett's test. *$p < 0.001$ vs control.

[a]Different treatment groups.

[b]Total numbers of acetic acid induced writhes observed.

[c]Percentage inhibition of writhing reflex.

Table 2: Effects of 1,3,4-thiadiazole derivatives and indomethacin on carrageenan-induced paw edema.

Treatment group[a]	Paw volume[b] (ml) after 3 h (mean + SEM)	% Inhibition[c]
Control	3.76 ± 0.05	——
Indomethacin	1.64 ± 0.04	56.38
6a	2.43 ± 0.06	35.37
6b	2.42 ± 0.08	35.63
6c	2.39 ± 0.06	36.43
6d	2.32 ± 0.07	38.29
6e	2.13 ± 0.05	43.35
6f	2.14 ± 0.07	43.08
7a	2.41 ± 0.05	35.90
7b	2.42 ± 0.04	35.63
7c	2.37 ± 0.07	36.96
7d	2.35 ± 0.05	37.5
7e	2.13 ± 0.08	43.35
7f	2.07 ± 0.09	44.94

The results are given as mean of % inhibition of paw edema. The data were analyzed by one way analysis of variance (ANOVA) followed by post hoc Dunnett's test. *$p < 0.001$ vs control.

[a]Different treatment groups.

[b]Paw volume observed after 3 hours..

[c]Percentage inhibition in paw volume.

EXPERIMENTAL SECTION

Measurements

The melting points were taken in an open capillary tube and uncorrected. The IR spectra of the compounds were recorded on FT-IR spectrometer with KBr pellets. ^{1}H spectra was recorded using NMR spectrometer operating at 400.13 MHz. Microanalyses were obtained with an Elemental analysis. The purity of compounds was checked by TLC on pre-coated SiO_2 gel (HF254, 200mesh) aluminium plates (E Merk) and visualized in UV chamber. IR, ^{1}H NMR and elemental analysis were consistent with the assigned structures.

Synthesis

General Procedure for synthesis of Substituted diacyl hydrazine (3a-f)

To a stirred suspension of substituted salicylic acid hydrazide (1 mol) in 15 ml toluene, 0.96 g of methylsulfonic acid was added. The mixture was stirred for 10 min., afterwards 1 mol of substituted benzoyl chloride was added. The mixture was allowed to stir for 3 h, cooled, and poured into crushed ice. The separated solid product was filtered, washed and dried.

N-1-(2-Aminobenzoyl)-N-2-(2-hydroxybenzoyl)hydrazine (3a)

Yield 89%, m.p. 125-126°C; IR (KBr) cm^{-1}:3630($\nu_{O-H)}$,3200(ν_{N-H}), 3100(ν_{C-H}), 1710($\nu_{C=O}$), 1570($\nu_{C=C}$), 1310(ν_{C-N}), 755(o-disubstituted benzene). ^{1}H NMR (DMF-d_6) δ ppm 10.87 (s, 1H, ar-OH), 7.85 (d, 1H, ar-H), 7.58 (t, 1H, ar-H), 7.49 (d, 1H, ar-H), 7.46 (t, 1H, ar-H), 7.29 (t, 1H, ar-H), 7.28 (d, 1H, ar-H), 7.03 (t, 1H, ar-H), 6.88 (d, 1H, ar-H), 4.85 (s, 2H, ar-NH_2), 4.58 (d, 1H, NH), 4.58 (d, 1H, NH). ^{13}C NMR (DMF-d_6) δ ppm: 163.01, 163.01, 158.74, 146.49, 131.85, 130.81, 128.15, 128.09, 125.07, 121.98, 120.36, 118.92, 117.26, 115.66. Anal. Found (calc.) for $C_{14}H_{13}N_3O_3$ (%): C, 61.89, H, 4.86, N, 15.43, O, 17.61.

N-1-(2-Aminobenzoyl)-N-2-(2-mercapto-benzoyl)hydrazine (3b)

Yield 76%, m.p. 129-130°C; IR (KBr) cm^{-1}: 3190(ν_{N-H}), 3095(ν_{C-H}), 1712($\nu_{C=O}$), 1560($\nu_{C=C}$), 1350(ν_{C-N}), 760(o-

disubstituted benzene). ^{1}H NMR (DMF-d_6) δ ppm: 7.87 (d, 1H, ar-H), 7.67 (t, 1H, ar-H), 7.59 (t, 1H, ar-H), 7.58 (t, 1H, ar-H), 7.48 (d, 1H, ar-H), 7.40 (d, 1H, ar-H), 7.28 (t, 1H, ar-H), 6.87 (d, 1H, ar-H), 4.75 (s, 2H, ar-NH_2), 4.58 (d, 1H, NH), 4.58 (d, 1H, NH), 2.76 (s, 1H, ar-SH). ^{13}C NMR (DMF-d_6) δ ppm: 163.011, 163.011, 146.496, 138.7, 132.39, 131.21, 130.81, 130.55, 130.3, 128.09, 128.0, 125.07, 120.36, 115.66. Anal. Found (calc.) for $C_{14}H_{13}N_3O_2S$ (%): C, 58.46, H, 4.63, N, 14.51, O, 11.19, S, 11.21.

N-1-(3-Aminobenzoyl)-N-2-(2-hydroxy-benzoyl)hydrazine (3c)

Yield 87%, m.p. 161-162°C; IR (KBr) cm^{-1}: 3620($\nu_{O-H)}$, 3195(ν_{N-H}), 3065(ν_{C-H}), 1723($\nu_{C=O}$), 1530($\nu_{C=C}$), 1190(ν_{C-N}), 760(o-disubstituted benzene), 705,795(m-disubstituted benzene). ^{1}H NMR (DMF-d_6) δ ppm: 10.78 (s, 1H, ar-OH), 7.98 (s, 1H, ar-H), 7.84 (d, 1H, ar-H), 7.46 (t, 1H, ar-H), 7.45 (d, 1H, ar-H), 7.42 (t, 1H, ar-H), 7.29 (t, 1H, ar-H), 7.26 (d, 1H, ar-H), 7.03 (d, 1H, ar-H), 4.72 (s, 2H, ar-NH_2), 4.58 (d, 1H, NH), 4.58 (d, 1H, NH). ^{13}C NMR (DMF-d_6) δ ppm: 164.35, 163.011, 158.73, 146.73, 134.57, 131.85, 128.15, 127.52, 127.14, 121.98, 118.917, 117.26, 116.35, 115.48. Anal. Found (calc.) for $C_{14}H_{13}N_3O_3$ (%): C, 61.85, H, 4.72, N, 15.46, O, 17.48.

N-1-(3-Aminobenzoyl)-N-2-(2-mercapto-benzoyl)hydrazine (3d)

Yield 75%, m.p. 168-169°C; IR (KBr) cm^{-1}: 3192(ν_{N-H}), 3026(ν_{C-H}), 1718($\nu_{C=O}$), 1567($\nu_{C=C}$), 1250(ν_{C-N}), 763(o-disubstituted benzene), 702,798(m-disubstituted benzene). ^{1}H NMR (DMF-d_6) δ ppm: 7.98 (s, 1H, ar-H), 7.87 (d, 1H, ar-H), 7.67 (d, 1H, ar-H), 7.62 (d, 1H, ar-H), 7.59 (t, 1H, ar-H), 7.42 (t, 1H, ar-H), 7.40 (t, 1H, ar-H), 7.26 (d, 1H, ar-H), 4.82 (s, 2H, ar-NH_2), 4.57 (d, 1H, NH), 4.57 (d, 1H, NH), 2.18 (s, 1H, ar-SH). ^{13}C NMR (DMF-d_6) δ ppm: 164.35, 163.01, 146.73, 138.7, 134.57, 132.39, 131.21, 130.55, 130.3, 128.0, 127.52, 127.14, 116.35, 115.48. Anal. Found (calc.) for $C_{14}H_{13}N_3O_2S$ (%): C, 58.48, H, 4.59, N, 14.75, O, 11.18, S, 11.19.

N-1-(4-Aminobenzoyl)-N-2-(2-hydroxy-benzoyl)hydrazine (3e)

Yield 91%, m.p. 192-193°C; IR (KBr) cm^{-1}: 3642($\nu_{O-H)}$, 3200(ν_{N-H}), 3029(ν_{C-H}), 1698($\nu_{C=O}$), 1577($\nu_{C=C}$), 1286(ν_{C-N}), 753(o-disubstituted benzene), 821(p-disubstituted benzene). ^{1}H NMR (DMF-d_6) δ ppm: 10.68 (s, 1H, ar-OH), 7.78 (d, 1H, ar-H), 7.66 (d, 1H, ar-H), 7.66 (d, 1H, ar-H), 7.46 (t, 1H, ar-H), 7.29 (t, 1H, ar-H), 7.03 (d, 1H, ar-H), 6.87 (d, 1H, ar-H), 6.87 (d, 1H, ar-H), 4.87 (s, 2H, ar-NH_2), 4.57 (d, 1H, NH), 4.57 (d, 1H, NH). ^{13}C NMR (DMF-d_6) δ ppm: 164.35, 163.01, 158.73, 149.06, 133.82, 131.85, 128.69, 128.15, 121.98, 118.91, 117.26, 113.23, 113.23. Anal. Found (calc.) for $C_{14}H_{13}N_3O_3$ (%): C, 61.91, H, 4.79, N, 15.42, O, 17.52.

N-1-(4-Aminobenzoyl)-N-2-(2-mercapto-benzoyl)hydrazine (3f)

Yield 72%, m.p. 198-199°C; IR (KBr) cm^{-1}: 3187(ν_{N-H}), 3056(ν_{C-H}), 1727($\nu_{C=O}$), 1582($\nu_{C=C}$), 1328(ν_{C-N}), 742(o-disubstituted benzene), 810(p-disubstituted benzene). ^{1}H NMR (DMF-d_6) δ ppm: 7.87 (d, 1H, ar-H), 7.67 (d, 1H, ar-H), 7.66 (d, 1H, ar-H), 7.66 (d, 1H, ar-H), 7.58 (t, 1H, ar-H), 7.40 (t, 1H, ar-H), 6.87 (d, 1H, ar-H), 6.57 (d, 1H, ar-H), 4.87 (s, 2H, ar-NH_2), 4.57 (d, 1H, NH), 4.57 (d, 1H, NH), 2.39 (s, 1H, ar-SH). ^{13}C NMR (DMF-d_6) δ ppm: 164.35, 163.01, 149.06, 138.7, 133.82, 132.39, 131.21, 130.55, 130.3, 128.69, 128.69, 128.0, 113.23, 113.23. Anal. Found (calc.) for $C_{14}H_{13}N_3O_2S$ (%): C, 58.46, H, 4.52, N, 14.79, O, 11.12, S, 11.19.

General Procedure for synthesis of 2,5-Disubstituted-1,3,4-thiadiazole derivatives (4a-f)

2,5-Disubstituted-1,3,4-thiadiazoles were prepared from the reaction of diacylhydrazines (0.1mol) with sulphur source (Lawesson's reagent). The reaction involves thionation of the carbonyl group followed by cyclization with loss of H_2S. The use of Lawesson's reagent gave higher yield and cleaner reaction. The mixture was refluxed for 3 h, cooled, poured into crushed ice. The separated solid product was filtered, washed and dried.

2-(2-Aminophenyl)-5-(2-hydroxyphenyl)-1,3,4-thiadiazole (4a)

Yield 86%, m.p. 121-122°C; IR (KBr) cm^{-1}: 3631($\nu_{O-H)}$, 3300(ν_{N-H}), 3012(ν_{C-H}), 1572($\nu_{C=C}$), 1610($\nu_{C=N}$), 757(o-disubstituted benzene). ^{1}H NMR (DMF-d_6) δ ppm: 10.95 (s, 1H, ar-OH), 7.89 (d, 1H, ar-H), 7.84 (d, 1H, ar-H), 7.58 (t, 1H, ar-H), 7.54 (t, 1H, ar-H), 7.49 (t, 1H, ar-H), 7.39 (t, 1H, ar-H), 7.18 (d, 1H, ar-H), 6.75 (d, 1H, ar-H), 4.87 (s, 2H, ar-NH_2). ^{13}C NMR (DMF-d_6) δ ppm: 163.87, 163.87, 157.89, 147.38, 131.85, 130.81, 130.66, 128.3, 127.82, 127.58, 119.4, 117.8, 116.7, 115.08. Anal. Found (calc.) for $C_{14}H_{11}N_3OS$ (%): C, 62.35, H, 4.16, N, 15.54, O, 5.85, S, 11.92.

2-(2-Aminophenyl)-5-(2-mercaptophenyl)-1,3,4-thiadiazole (4b)

Yield 74%, m.p. 128-129°C; IR (KBr) cm^{-1}: 3190(ν_{N-H}), 3095(ν_{C-H}), 1560($\nu_{C=C}$), 1650($\nu_{C=N}$), 762(o-disubstituted benzene). ^{1}H NMR (DMF-d_6) δ ppm: 7.87 (d, 1H, ar-H), 7.82 (d, 1H, ar-H), 7.78 (d, 1H, ar-H), 7.58 (t, 1H, ar-H), 7.57 (t, 1H, ar-H), 7.53 (t, 1H, ar-H), 7.40 (t, 1H, ar-H), 6.75 (d, 1H, ar-H), 4.76 (s, 2H, ar-NH_2), 2.15 (s, 1H, ar-SH). ^{13}C NMR (DMF-d_6) δ ppm: 163.87, 163.87, 147.38, 131.32, 131.21, 130.80, 130.66, 130.66, 130.55, 127.82, 127.82, 127.58, 127.58, 115.08. Anal. Found (calc.) for $C_{14}H_{11}N_3S_2$ (%): C, 58.85, H, 3.82, N, 14.76, S, 22.32.

2-(3-Aminophenyl)-5-(2-hydroxyphenyl)-1,3,4-thiadiazole (4c)

Yield 89%, m.p. 149-150°C; IR (KBr) cm^{-1}: 3623(ν_{O-H}), 3395(ν_{N-H}), 3069(ν_{C-H}), 1537($\nu_{C=C}$), 1632($\nu_{C=N}$), 763(o-disubstituted benzene), 707, 798(m-disubstituted benzene). ^{1}H NMR (DMF-d_6) δ ppm: 10.88 (s, 1H, ar-OH), 8.05 (d, 1H, ar-H), 7.58 (t, 1H, ar-H), 7.49 (d, 1H, ar-H), 7.46 (s, 1H, ar-H), 7.39 (t, 1H, ar-H), 7.38 (t, 1H, ar-H), 7.19 (d, 1H, ar-H), 6.61 (d, 1H, ar-H), 4.82 (s, 2H, ar-NH_2). ^{13}C NMR (DMF-d_6) δ ppm: 163.87, 163.87, 157.89, 146.73, 131.85, 131.01, 128.3, 127.14, 126.92, 119.21, 117.8, 116.7, 116.35, 115.48. Anal. Found (calc.) for $C_{14}H_{11}N_3OS$ (%): C, 62.39, H, 4.16, N, 15.54, O, 5.84, S, 11.95.

2-(3-Aminophenyl)-5-(2-mercaptophenyl)-1,3,4-thiadiazole (4d)

Yield 78%, m.p.152-153°C; IR (KBr) cm^{-1}: 3390(ν_{N-H}), 3073(ν_{C-H}), 1585($\nu_{C=C}$), 1646($\nu_{C=N}$), 738(o-disubstituted benzene), 697,758(m-disubstituted benzene). ^{1}H NMR (DMF-d_6) δ ppm: 8.03 (d, 1H, ar-H), 7.84 (d, 1H, ar-H), 7.67 (s, 1H, ar-H), 7.55 (t, 1H, ar-H), 7.52 (d, 1H, ar-H), 7.48 (t, 1H, ar-H), 7.27 (t, 1H, ar-H), 6.64 (d, 1H, ar-H), 4.86 (s, 2H, ar-NH_2), 2.28 (s, 1H, ar-SH). ^{13}C NMR (DMF-d_6) δ ppm: 163.87, 163.87, 146.73, 131.32, 131.21, 131.01, 130.66, 130.55, 127.82, 127.58, 127.14, 126.92, 116.35, 115.48. Anal. Found (calc.) for $C_{14}H_{11}N_3S_2$ (%): C, 58.85, H, 3.74, N, 14.76, S, 22.42.

2-(4-Aminophenyl)-5-(2-hydroxyphenyl)-1,3,4-thiadiazole (4e)

Yield 83%, m.p. 192-193°C; IR (KBr) cm^{-1}: 3628(ν_{O-H}), 3345(ν_{N-H}), 3054(ν_{C-H}), 1523($\nu_{C=C}$), 1649($\nu_{C=N}$), 742(o-disubstituted benzene), 832(p-disubstituted benzene). ^{1}H NMR (DMF-d_6) δ ppm: 10.76 (s, 1H, ar-OH), 7.88 (d, 1H, ar-H), 7.63 (d, 1H, ar-H), 7.63 (d, 1H, ar-H), 7.58 (t, 1H, ar-H), 7.49 (t, 1H, ar-H), 7.18 (d, 1H, ar-H), 6.72 (d, 1H, ar-H), 6.72 (d, 1H, ar-H), 4.85 (s, 2H, ar-NH_2). ^{13}C NMR (DMF-d_6) δ ppm: 163.87, 163.87, 157.89, 149.06, 131.85, 131.01, 128.55, 128.55, 128.3, 119.4, 117.8, 116.7, 113.7, 113.7. Anal. Found (calc.) for $C_{14}H_{11}N_3OS$ (%): C, 62.39, H, 4.19, N, 15.56, O, 5.86, S, 11.95.

2-(4-Aminophenyl)-5-(2-mercaptophenyl)-1,3,4-thiadiazole (4f)

Yield 81%, m.p. 201-202°C; IR (KBr) cm^{-1}: 3445(ν_{N-H}), 3053(ν_{C-H}), 1526($\nu_{C=C}$), 1619($\nu_{C=N}$), 754(o-disubstituted benzene), 826(p-disubstituted benzene). ^{1}H NMR (DMF-d_6) δ ppm: 7.82 (d, 1H, ar-H), 7.77 (d, 1H, ar-H), 7.66 (d, 1H, ar-H), 7.66 (d, 1H, ar-H), 7.58 (t, 1H, ar-H), 7.53 (t, 1H, ar-H), 6.73 (d, 1H, ar-H), 6.73 (d, 1H, ar-H), 4.83 (s, 2H, ar-NH_2), 2.18 (s, 1H, ar-SH). ^{13}C NMR (DMF-d_6) δ ppm: 163.87, 163.87, 149.06, 131.32, 131.27, 131.01, 130.66, 130.55, 128.55, 128.55, 127.82, 127.58, 113.7, 113.7. Anal. Found (calc.) for $C_{14}H_{11}N_3S_2$ (%): C, 58.84, H, 3.76, N, 14.65, S, 22.42.

General procedure for synthesis of different Schiff base of 1,3,4-thiadiazole derivatives (6a-7f)

0.01mol of 2,5-Disubstituted-1,3,4-thiadiazole derivative (4a-f) was dissolved in 30 ml of ethanol containing few drops of glacial acetic acid. The appropriate aromatic aldehyde (5a-b) was added, and reaction mixture was refluxed for 5h at 70 °C. The reaction mixture was cooled, filtered, washed, dried and recrystalized with ethanol.

5-(2-Hydroxyphenyl)-2-(N-benzylidene-2-aminophenyl)-1,3,4-thiadiazole (6a)

Yield: 85%, m.p. 130-131°C; IR (KBr) cm^{-1}: 3627(ν_{O-H}), 3018(ν_{C-H}), 1531($\nu_{C=C}$), 1618($\nu_{C=N}$), 739(o-disubstituted benzene). ^{1}H NMR (DMF-d_6) δ ppm: 10.83 (s, 1H, ar-H), 8.65 (s, 1H, =CH), 8.25 (d, 1H, ar-H), 8.14 (d, 1H, ar-H), 8.06 (d, 1H, ar-H), 8.06 (d, 1H, ar-H), 7.77 (d, 1H, ar-H), 7.73 (t, 1H, ar-H), 7.68 (t, 1H, ar-H), 7.63 (t, 1H, ar-H), 7.58 (t, 1H, ar-H), 7.53 (t, 1H, ar-H), 7.50 (t, 1H, ar-H), 7.50 (t, 1H, ar-H), 7.23 (d, 1H, ar-H). ^{13}C NMR (DMF-d_6) δ ppm: 163.87, 163.87, 159.39, 157.89, 144.54, 136.01, 133.05, 131.85, 130.66, 128.92, 128.87, 128.87, 128.73, 128.73, 128.3, 127.82, 127.58, 125.08, 119.4, 117.8, 116.7. Anal. Found (calc.) for $C_{21}H_{15}N_3OS$ (%): C, 70.46, H, 4.35, N, 11.72, O, 4.41, S, 8.87.

5-(2-Mercaptophenyl)-2-(N-benzylidene-2-aminophenyl)-1,3,4-thiadiazole (6b)

Yield: 75%, m.p. 142-143°C; IR (KBr) cm^{-1}: 3052(ν_{C-H}), 1532($\nu_{C=C}$), 1638($\nu_{C=N}$), 744(o-disubstituted benzene). ^{1}H NMR (DMF-d_6) δ ppm: 8.66 (s, 1H, ar-CH), 8.18 (d, 1H, ar-H), 8.17 (d, 1H, ar-H), 8.07 (d, 1H, ar-H), 8.07 (d, 1H, ar-H), 7.76 (d, 1H, ar-H), 7.69 (d, 1H, ar-H), 7.68 (t, 1H, ar-H), 7.64 (t, H, ar-H), 7.62 (t, 1H, ar-H), 7.60 (t, 1H, ar-H), 7.54 (t, 1H, ar-H), 7.45 (t, 1H, ar-H), 7.45 (t, 1H, ar-H), 2.67 (s, 1H, ar-SH). ^{13}C NMR (DMF-d_6) δ ppm: 163.87, 163.87, 159.39, 144.54, 136.00, 133.05, 131.32, 131.21, 130.66, 130.66, 130.55, 128.92, 128.87, 128.87, 128.73, 128.73, 127.82, 127.82, 127.58, 127.58, 125.08. Anal. Found (calc.) for $C_{21}H_{15}N_3S_2$ (%): C, 67.47, H, 4.05, N, 11.31, S, 17.23.

5-(2-Hydroxyphenyl)-2-(N-benzylidene-3-aminophenyl)-1,3,4-thiadiazole (6c)

Yield: 87%, m.p. 156-157°C; IR (KBr) cm^{-1}: 3621(ν_{O-H}), 3029(ν_{C-H}), 1564($\nu_{C=C}$), 1649($\nu_{C=N}$), 693,785(m-disubstituted benzene). ^{1}H NMR (DMF-d_6) δ ppm: 10.88 (s, 1H, ar-OH), 8.82 (s, 1H, =CH), 8.15 (d, 1H, ar-H), 8.07 (s, 1H, ar-H), 7.91 (d, 1H, ar-H), 7.81 (d, 1H, ar-H), 7.86 (d, 1H, ar-H), 7.71 (t, 1H, ar-H), 7.61 (d, 1H, ar-H), 7.56 (t, 1H, ar-H), 7.56 (t, 1H, ar-H), 7.48 (t, 1H, ar-H), 7.48 (t, 1H, ar-H), 7.45 (t, 1H, ar-H), 7.14 (d, 1H, ar-H). ^{13}C NMR (DMF-d_6) δ ppm: 163.87, 163.87, 159.55, 157.89, 143.70, 136.60, 131.85, 131.01, 128.92, 128.87,

128.87, 128.73, 128.73, 128.3, 127.14, 126.92, 121.25, 119.4, 117.8, 116.7, 116.35. Anal. Found (calc.) for $C_{21}H_{15}N_3OS$ (%): C, 70.49, H, 4.34, N, 11.72, O, 4.41, S, 8.92.

5-(2-Mercaptophenyl)-2-(N-benzylidene-3-aminophenyl)-1,3,4-thiadiazole (6d)

Yield: 72%, m.p. 172-173°C; IR (KBr) cm^{-1}: 3078(ν_{C-H}), 1537($\nu_{C=C}$), 1654($\nu_{C=N}$), 702,792(m-disubstituted benzene). ^{1}H NMR (DMF-d_6) δ ppm: 8.82 (s, 1H, ar-CH), 8.09 (s, 1H, ar-H), 8.05 (d, 1H, ar-H), 7.94 (d, 1H, ar-H), 7.86 (d, 1H, ar-H), 7.86 (d, 1H, ar-H), 7.82 (d, 1H, ar-H), 7.67 (t, 1H, ar-H), 7.60 (t, 1H, ar-H), 7.57 (t, 1H, ar-H), 7.49 (t, 1H, ar-H), 7.48 (t, 1H, ar-H), 7.48 (t, 1H, ar-H), 2.22 (s, 1H, ar-SH). ^{13}C NMR (DMF-d_6) δ ppm: 163.87, 163.87, 159.55, 143.70, 136.00, 131.32, 131.21, 131.01, 130.66, 130.55, 128.92, 128.87, 128.87, 128.73, 128.73, 127.82, 127.58, 127.14, 126.92, 121.25, 116.35. Anal. Found (calc.) for $C_{21}H_{15}N_3S_2$ (%): C, 67.47, H, 4.11, N, 11.34, S, 17.12.

5-(2-Hydroxyphenyl)-2-(N-benzylidene-4-aminophenyl)-1,3,4-thiadiazole (6e)

Yield: 82%, m.p. 185-186°C; IR (KBr) cm^{-1}: 3632(ν_{O-H}), 3065(ν_{C-H}), 1584($\nu_{C=C}$), 1651($\nu_{C=N}$), 812(p-disubstituted benzene). ^{1}H NMR (DMF-d_6) δ ppm: 10.77 (s, 1H, ar-OH), 8.92 (s, 1H, =CH), 8.14 (d, 1H, ar-H), 8.06 (d, 1H, ar-H), 8.06 (d, 1H, ar-H), 7.92 (d, 1H, ar-H), 7.92 (d, 1H, ar-H), 7.78 (d, 1H, ar-H), 7.78 (d, 1H, ar-H), 7.68 (t, 1H, ar-H), 7.58 (t, 1H, ar-H), 7.53 (t, 1H, ar-H), 7.50 (t, 1H, ar-H), 7.50 (t, 1H, ar-H), 7.16 (d, 1H, ar-H). ^{13}C NMR (DMF-d_6) δ ppm: 163.87, 163.87, 159.55, 157.89, 149.62, 136.00, 131.85, 131.01, 128.92, 128.87, 128.87, 128.73, 128.73, 128.55, 128.55, 128.3, 123.52, 123.52, 119.4, 117.8, 116.7. Anal. Found (calc.) for $C_{21}H_{15}N_3OS$ (%): C, 70.48, H, 4.27, N, 11.69, O, 4.42, S, 8.97.

5-(2-Mercaptophenyl)-2-(N-benzylidene-4-aminophenyl)-1,3,4-thiadiazole (6f)

Yield: 71%, m.p. 204-205°C; IR (KBr) cm^{-1}: 3084(ν_{C-H}), 1552($\nu_{C=C}$), 1617($\nu_{C=N}$), 823(p-disubstituted benzene). ^{1}H NMR (DMF-d_6) δ ppm: 8.94 (s, 1H, ar-CH), 8.181 (d, 1H, ar-H), 8.065 (d, 1H, ar-H), 8.065 (d, 1H, ar-H), 7.991(d, 1H, ar-H), 7.991(d, 1H, ar-H), 7.838 (d, 1H, ar-H), 7.745 (d, 1H, ar-H), 7.745 (d, 1H, ar-H), 7.619 (t, 1H, ar-H), 7.6 (t, 1H, ar-H), 7.544 (t, 1H, ar-H), 7.445 (t, 1H, ar-H), 2.183 (s, 1H, ar-SH). ^{13}C NMR (DMF-d_6) δ ppm: 163.87, 163.87, 159.55, 149.62, 136.00, 131.32, 131.21, 131.02, 130.66, 130.55, 128.92, 128.87, 128.87, 128.73, 128.73, 128.55, 128.55, 127.82, 127.58, 123.52, 123.52. Anal. Found (calc.) for $C_{21}H_{15}N_3S_2$ (%): C, 67.46, H, 4.01, N, 11.29, S, 17.11.

5-(2-Hydroxyphenyl)-2-{N-(4-methoxybenzylidene)-2-aminophenyl}-1,3,4-thiadiazole (7a)

Yield: 81%, m.p. 131-132°C; IR (KBr) cm^{-1}: 3618(ν_{O-H}), 3032(ν_{C-H}), 1569($\nu_{C=C}$), 1648($\nu_{C=N}$), 1230(ν_{C-O}), 747(o-disubstituted benzene), 821(p-disubstituted benzene). ^{1}H NMR (DMF-d_6) δ ppm: 10.65 (s, 1H, ar-OH), 8.61 (s, 1H, ar-CH), 8.01 (d, 1H, ar-H), 7.89 (d, 1H, ar-H), 7.71 (d, 1H, ar-H), 7.71 (d, 1H, ar-H), 7.69 (t, 1H, ar-H), 7.65 (t, 1H, ar-H), 7.59 (d, 1H, ar-H), 7.54 (t, 1H, ar-H), 7.38 (t, 1H, ar-H), 7.19 (d, 1H, ar-H), 7.13 (d, 1H, ar-H), 7.13 (d, 1H, ar-H), 3.91 (s, 3H, CH_3). ^{13}C NMR (DMF-d_6) δ ppm: 163.87, 163.87, 160.41, 159.39, 157.89, 144.54, 133.05, 131.85, 131.76, 131.76, 130.66, 129.27, 128.3, 127.82, 127.58, 125.08, 119.4, 117.8, 116.7, 114.53, 114.53, 55.46. Anal. Found (calc.) for $C_{22}H_{17}N_3O_2S$ (%): C, 68.20, H, 4.36, N, 10.91, O, 8.22, S, 8.29.

5-(2-Hydroxyphenyl)-2-{N-(4-methoxybenzylidene)-2-aminophenyl}-1,3,4-thiadiazole (7b)

Yield: 72%, m.p. 145-146°C; IR (KBr) cm^{-1}: 3067(ν_{C-H}), 1526($\nu_{C=C}$), 1624($\nu_{C=N}$), 1265(ν_{C-O}), 754(o-disubstituted benzene), 816(p-disubstituted benzene). ^{1}H NMR (DMF-d_6) δ ppm: 8.619 (s, 1H, ar-CH), 8.147 (d, 1H, ar-H), 7.909 (d, 1H, ar-H), 7.764 (d, 1H, ar-H), 7.718 (d, 1H, ar-H), 7.718 (d, 1H, ar-H), 7.684 (t, 1H, ar-H), 7.591 (t, 1H, ar-H), 7.589 (d, 1H, ar-H), 7.578 (t, 1H, ar-H), 7.399 (t, 1H, ar-H), 7.143 (d, 1H, ar-H), 7.143 (d, 1H, ar-H), 3.909 (s, 3H, CH_3), 2.726 (s, 1H, ar-H). ^{13}C NMR (DMF-d_6) δ ppm: 163.87, 163.87, 160.41, 159.39, 144.54, 133.05, 131.76, 131.76, 131.32, 131.21, 130.66, 130.66, 130.55, 129.27, 127.82, 127.82, 127.58, 127.58, 125.08, 114.53, 114.53, 55.46. Anal. Found (calc.) for $C_{22}H_{17}N_3OS_2$ (%): C, 65.48, H, 4.25, N, 10.41, O, 3.96, S, 15.89.

5-(2-Hydroxyphenyl)-2-{N-(4-methoxybenzylidene)-3-aminophenyl}-1,3,4-thiadiazole (7c)

Yield: 79%, m.p. 146-147°C; IR (KBr) cm^{-1}: 3624(ν_{O-H}), 3069(ν_{C-H}), 1575($\nu_{C=C}$), 1641($\nu_{C=N}$), 1163(ν_{C-O}), 753(o-disubstituted benzene),708, 769(m-disubstituted benzene), 834(p-disubstituted benzene). ^{1}H NMR (DMF-d_6) δ ppm: 10.77 (s, 1H, ar-OH), 8.73 (s, 1H, ar-CH), 7.92 (s, 1H, ar-H), 7.74 (d, 1H, ar-H), 7.69 (d, 1H, ar-H), 7.65 (t, 1H, ar-H), 7.53 (t, 1H, ar-H), 7.51 (d, 1H, ar-H), 7.51 (d, 1H, ar-H), 7.51 (d, 1H, ar-H), 7.51 (t, 1H, ar-H), 7.11 (d, 1H, ar-H), 7.11 (d, 1H, ar-H), 7.11 (d, 1H, ar-H), 3.86 (s, 3H, CH_3). ^{13}C NMR (DMF-d_6) δ ppm: 163.87, 163.87, 160.41, 159.55, 157.89, 143.70, 131.85, 131.76, 131.76, 131.01, 129.27, 128.3, 127.14, 126.92, 121.25, 119.40, 117.80, 116.70, 116.35, 114.53, 114.53, 55.46. Anal. Found (calc.) for $C_{22}H_{17}N_3O_2S$ (%): C, 68.20, H, 4.42, N, 10.85, O, 8.26, S, 8.28.

5-(2-Mercaptophenyl)-2-{N-(4-methoxybenzylidene)-3-aminophenyl}-1,3,4-thiadiazole (7d)

Yield: 68%, m.p. 186-187°C; IR (KBr) cm^{-1}: 3074(ν_{C-H}), 1564($\nu_{C=C}$), 1642($\nu_{C=N}$), 1287(ν_{C-O}), 762(o-disubstituted benzene), 695, 782(m-disubstituted benzene), 836(p-disubstituted benzene). ^{1}H NMR (DMF-d_6) δ ppm: 8.705 (s, 1H, ar-CH), 7.951 (s, 1H, ar-H), 7.766 (d, 1H, ar-H), 7.757 (d, 1H, ar-H), 7.741 (d, 1H, ar-H), 7.567 (t, 1H, ar-H), 7.545 (d, 1H, ar-H), 7.542 (t, 1H, ar-H), 7.510 (d, 1H, ar-H), 7.510 (d, 1H, ar-H), 7.508 (t, 1H, ar-H), 7.121 (d, 1H, ar-H), 7.121 (d, 1H, ar-H), 3.858 (s, 3H, CH_3), 2.128 (s, 1H, ar-SH). ^{13}C NMR (DMF-d_6) δ ppm: 163.87, 163.87, 160.41, 159.55,

143.70, 131.76, 131.76, 131.32, 131.21, 131.01, 130.66, 130.55, 129.27, 127.82, 127.58, 127.14, 126.92, 121.25, 116.35, 114.53, 114.53, 55.46. Anal. Found (calc.) for $C_{22}H_{17}N_3OS_2$ (%): C, 65.42, H, 4.31, N, 10.38, O, 3.91, S, 15.85.

5-(2-Hydroxyphenyl)-2-{N-(4-methoxybenzylidene)-4-aminophenyl}-1,3,4-thiadiazole (7e)

Yield: 82%, m.p. 192-193°C; IR (KBr) cm^{-1}: 3641(ν_{O-H}), 3094(ν_{C-H}), 1545($\nu_{C=C}$), 1636($\nu_{C=N}$), 1289(ν_{C-O}), 764(o-disubstituted benzene), 812(p-disubstituted benzene). ^{1}H NMR (DMF-d_6) δ ppm: 10.68 (s, 1H, ar-OH), 8.85 (s, 1H, ar-CH), 7.94 (d, 1H, ar-H), 7.94 (d, 1H, ar-H), 7.89 (d, 1H, ar-H), 7.65 (t, 1H, ar-H), 7.61 (d, 1H, ar-H), 7.61 (d, 1H, ar-H), 7.60 (d, 1H, ar-H), 7.60 (d, 1H, ar-H), 7.19 (d, 1H, ar-H), 7.13 (d, 1H, ar-H), 7.13 (d, 1H, ar-H), 3.91 (s, 3H, CH_3). ^{13}C NMR (DMF-d_6) δ ppm: 163.87, 163.87, 160.41, 159.55, 157.89, 149.62, 131.85, 131.76, 131.76, 131.01, 129.27, 128.55, 128.55, 128.3, 123.52, 123.52, 119.40, 117.80, 116.70, 114.53, 114.53, 55.46. Anal. Found (calc.) for $C_{22}H_{17}N_3O_2S$ (%): C, 68.16, H, 4.38, N, 10.81, O, 8.32, S, 8.24.

5-(2-Mercaptophenyl)-2-{N-(4-methoxybenzylidene)-4-aminophenyl}-1,3,4-thiadiazole (7f)

Yield: 68%. m.p. 202-203°C; IR (KBr) cm^{-1}: 3089(ν_{C-H}), 1575($\nu_{C=C}$), 1648($\nu_{C=N}$), 1236(ν_{C-O}), 738(o-disubstituted benzene), 825(p-disubstituted benzene). ^{1}H NMR (DMF-d_6) δ ppm: 8.859 (s, 1H, ar-CH), 7.992 (d, 1H, ar-H), 7.992 (d, 1H, ar-H), 7.909 (d, 1H, ar-H), 7.764 (d, 1H, ar-H), 7.716 (d, 1H, ar-H), 7.716 (d, 1H, ar-H), 7.591 (t, 1H, ar-H), 7.589 (d, 1H, ar-H), 7.589 (d, 1H, ar-H), 7.578 (t, 1H, ar-H), 7.141 (d, 1H, ar-H), 7.141 (d, 1H, ar-H), 3.909 (s, 3H, CH_3), 2.318 (s, 1H, ar-SH). ^{13}C NMR (DMF-d_6) δ ppm: 163.87, 163.87, 160.41, 159.55, 149.62, 131.76, 131.76, 131.32, 131.21, 131.01, 130.66, 130.55, 129.27, 128.55, 128.55, 127.82, 127.58, 123.52, 123.52, 114.53, 114.53, 55.46. Anal. Found (calc.) for $C_{22}H_{17}N_3OS_2$ (%): C, 68.18, H, 4.38, N, 10.81, O, 8.29, S, 8.22.

Biological Investigation

In the present study, all 1,3,4- thiadiazole derivatives were administered via oral route in the overnight fasted animals. The maximum tolerated dose of 1,3,4-thiadiazole derivatives was found to be 1500 mg/kg approximately. According to OECD guidelines,[18] two to four fold descending dose level of maximum tolerated dose should be selected to examine the activity of the compound. Therefore, we have carried out dose response studies of the 1,3,4-thiadiazole derivatives using significantly lower dose. Based on the results of dose dependent studies, we choose 150 mg/kg dose of 1,3,4-thiadiazole derivatives to evaluate their analgesic and anti-inflammatory activities. All protocols of animal experiments were approved by the Institutional Animal Ethics Committee (IAEC).

Analgesic Activity

The test was performed according to the method given by Husain *et al*.[19] Adult male Swiss albino rats were used to evaluate the analgesic activity of 1,3,4-thiadiazole derivatives using acetic acid induced writhing reflex method. Animals were randomly divided into three groups: A. Control [acetic acid treated (n= 6)], B. 1,3,4-thiadiazole derivatives + acetic acid treated (n=6), C. Acetyl salicylic acid + acetic acid treated (n=6). As a positive control, a standard analgesic drug, acetylsalicylic acid (25 mg/kg) was taken for the comparison. The thiadiazole derivatives were given at the dose of 150 mg/kg. All derivatives were administered to overnight fasted animals via oral route 1 h prior to 0.7% glacial acetic acid (10ml/kg, intraperitoneal route). The numbers of writhes were recorded in each mouse for a period of 30 min. The inhibition of writhing by newly synthesized derivatives was compared against the inhibition of writhing by acetyl salicylic acid using a formula % inhibition = 100 – test/control x 100.

Anti-inflammatory activity

The test was performed according to the method given by Amir *et. al*..[20] Adult male rats (~250 g) were used to evaluate anti-inflammatory activity of 1,3,4-thiadiazole derivatives using carrageenan induced paw edema model. Animals were randomly divided into three groups: A. Control [carrageenan treated (n=6)], B. 1,3,4-thiadiazole derivatives + carrageenan treated (n=6), C. Indomethacin + carrageenan treated (n=6). As a positive control, a standard anti-inflammatory drug, indomethacin (10 mg/kg) was taken for the comparison. The thiadiazole derivatives were given at the dose of 150 mg/kg. All compounds were administered to overnight fasted animals via oral route 1 h prior to carrageenan challenge. Carrageenan suspension (1%) was prepared in saline. Foot paw edema was induced by injection 0.05 ml of carrageenan suspension into the planter tissue of left hind paw. In control animals, the equal volume of saline was injected. Mercury displacement method using plethysmograph was used to measure the paw volume of rats.

CONCLUSION

In conclusion, a new series of compounds showing analgesic and anti-inflammatory properties were synthesized. Among them in particular compound **7f** was found to have a superior analgesic and anti-inflammatory profile with low gastric ulceration incidence.

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AUTHORS DISCLOSURE STATEMENT

No competing financial interests exist.

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