Synthesis, characterization, antimicrobial, and pharmacological evaluation of some 2, 5-disubstituted sulfonyl amino 1,3,4-oxadiazole and 2-amino-disubstituted 1,3,4-thiadiazole derivatives

ABSTRACT

The presence of heterocyclic structures in diverse types of compounds, this is strongly indicative of the profound effect like structure exerts on physiologic activity, and recognition of this is abundantly reflected in efforts to find useful synthetic drugs. The search for better pharmacological active drug and the importance of disubstituted 1,3,4-oxadiazole and 1,3,4-thiadiazole as active pharmacophores, prompted us to design, synthesize, characterize, and evaluate a series of differently substituted sulfonyl amino 1,3,4-oxadiazole and 1,3,4-thiadiazole for their potential antimicrobial, analgesic and antiinflammatory activity, respectively. New sulfonyl amino 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives were synthesized by intramolecular cyclization of thiosemicarbazole in alkaline medium. Reactions were carried out by the reaction between aromatic carbonyl halide and thiosemicarbazide.

Key words: 1,3,4-oxadiazole, 1,3,4-thiadiazole, thiosemicarbazole

INTRODUCTION

A fused aromatic ring consists of monocyclic rings that share their connecting bonds forming other aromatic compounds such as oxadiazoles and thiadiazoles with two nitrogen instead of one. These are the azoles with oxygen, or sulfur, and nitrogen separated by one carbon atom.[1] Oxadiazole and thiadiazole derivatives have been evaluated and proved for a wide range of pharmacological, biochemical, clinical uses and applications.[2] Phenyl 1,3,4-oxadiazole derivatives are known to have diverse biological activities like antifungal,[3] antibacterial,[4,5] anticonvulsant,[6-8] antiinflammatory,[9] etc., moreover, 1,3,4-thiadiazole derivatives also possess diverse chemical and pharmacological applications such as, antinflammatory,[10,11] analgesic,[12] anticonvulsant,[13] antimicrobial,[14] anticancer,[15] antifungal,[16] antiviral,[17] carbonic anhydrates inhibitor,[18] antidepressants,[19] and antioxidant.[20,21] properties. This property of 1,3,4-thiadiazole is particularly due to the presence of = N-C-S moiety.[22]

MATERIALS AND METHODS

All used chemicals and glass were supplied by (Merck and S.D. Fine Chemicals, Lucknow, Uttar Pradesh, India). Melting point was determined by open capillary tube method. Progress of each step was confirmed by teens learning control (TLC). Purification of compounds was checked by column chromatography and silica gel G (60-120 MESS) and silica gel GF 254 (4:1) for preparation of the TLC plates and spots were seen under iodine vapor and U.V. light chamber (Ramtech Laboratories Product, Chennai, India). Proton nuclear magnetic resonance (1HNMR) Spectra were recorded.
on a BRUKER DR × 300 MHz instrument) in DMSO-d$_6$ using (tetramethylsilane) as an internal standard. Chemical shifts (δ) were expressed in ppm. The mass spectra were recorded on water OPLC - TQDMS in positive mode electrospray Ionization mass spectrometry spectrophotometer.

**Experimental section**

**Synthesis**

**General method of synthesis of acid halides I (a-d)**

A mixture of substituted carboxylic acid (0.01 mole) and phosphorus pentachloride was taken in a renal blood flow connected with the condenser by means of the adapter. The mixture was heated gently to melt with vigorous shaking at around 50°C, after 30 min excess POCl$_3$ was distilled out, and the residue (I a-d) was dried well and used for the next reaction.

**Synthesis of compound (II a-d)**

Added semicarbazide to the respected acid chloride and reflux for 5 h. These programs of the reaction were monitoring by checking the TLC. The excess benzene was distilled out neutralizing with aq.NaHCO$_3$.

**Synthesis of compound (III a-d)**

Then hydrolyze it in the basic medium. Product was dried well and recrystallized from methanol.

**Synthesis of compound (IV a-d)**

The product was heated with 4-toluene-sulfonyl chloride in dry pyridine keeping the temperature 150°C-160°C for 3 h on a heating mantle to obtained respective oxadiazole. Progress of the reaction was checked by TLC using solvent system (a-c) chloroform: N-Hexane (2:3). Yield 72%, 77%, 70%, and solvent system for (d) was chloroform: Ethyl acetate: Petroleum ether: Methanol (2:1:3:2). Yield 70%.

**Synthesis of compound (V a-d)**

The mixture of thiosemicarbazide and aromatic substituted carbonyl chloride in the presence of benzene was refluxed for 3-4 h and added to crushed ice. Recrystallized with ethanol.

**Synthesis of compound (VI a-d)**

A mixture of 2-amino-5-phenyl-1,3,4-thiadiazole and aromatic substituted aldehyde was irradiated in a microwave oven for 20 min with 40% power and interval of 30s. After the completion of reaction, ice cold water was added to separate the solid, recrystallized with ethanol. Progress of the reaction was checked by TLC using the solvent system (a-d) ethyl acetate: Chloroform (3:8). Yield 72%, 74%, 78%, 70%.

**Antibacterial activity**

Antibacterial activity of all synthesized derivatives was determined by disc diffusion method (Kirby Baeur method) against two gram positive bacteria namely *Staphylococcus aureus* and *Bacillus subtilis* and two gram negative bacteria namely *Salmonella* sp. and *Pseudomonas* sp. minimum inhibitory concentration. Those compounds were determined which are showing activity in primary screening standard antibiotics namely ofloxacin was used for comparison.

**Pharmacological evaluations**

Antiinflammatory activity of 2-amino-disubstituted-1,3,4-thiadiazole compounds was done by carrageenan-induced rat paw edema method using diclofenac sodium-30 as a standard drug, and analgesic activity of 2-amino 5-disubstituted-1,3,4-thiadiazole derivatives was done by tail flick method using aspirin as a standard drug.

**Statistical analysis**

One-way ANOVA using Dunnett’s t-test was applied for statistical analysis; treatment groups were compared with the control group and the standard drug(s). $P < 0.05$
and $P < 0.001$ value was considered significant and highly significant, respectively.

**RESULTS AND DISCUSSION**

Physical data of the synthesized compounds are presented in Tables 1 and 2. The titled compounds 2, 5-disubstituted sulfonyl amino-1,3,4-oxadiazole (IV a-d) and 2-amino-disubstituted-1,3,4-thiadiazole derivatives were obtained in good yields (VI a-d). The structures were confirmed on the basis of spectral data.

**Spectral data**

- **Compound (IVA):** [2-(p-toluene sulfonyl amino-N-[5-(5-phenyl)-1,3,4-oxadiazole]
  Proton nuclear magnetic resonance (D$_2$O, δ, ppm): 2.1 (s, 3H, J = 2.385), 7.3 (s, 2H, J = 7.44), 7.6 (s, 3H, J = 7.699), 8.0 (s, 1H, J = 7.968), 8.5 (d, 1H, J = 8.688). MASS m/z (%): 424.2 (6), 372.1 (8), 380.9 (8), and 291.3 (10), 263.0 (14), 224.2 (16), 481.9 (30), 444.6 (32), 380.2 (34), 490.8 (48), 223.2 (100)

- **Compound (IVB):** [2-(p-toluene sulfonyl amino-N-[5-(2-chloro-phenyl)-1,3,4-oxadiazole]
  Proton nuclear magnetic resonance (D$_2$O, δ, ppm): 2.3 (s, 2H, J = 2.369), 7.28 (d, 2H, J = 7.375), 7.44 (s, 2H, J = 7.485), 7.61 (d, 1H, J = 7.675), 7.98 (s, 1H, J = 8.017), 8.54 (s, 1H, J = 8.567), 8.68 (d, 1H, J = 8.6465). MASS m/z (%): 80.1 (6), 228.6 (6), 468.7 (6), 473.3 (6), and 372.8 (12), 436.7 (16), 471.3 (16), 313.0 (24), 410.9 (26), 330.9 (44), 344.6 (46), 371.8 (46) 293.1 (54), 369.8 (72), 291.2 (100)

- **Compound (IVC):** [2-(p-toluene sulfonyl amino-N-[5-(4-phenyl)-1,3,4-oxadiazole]
  Proton nuclear magnetic resonance (D$_2$O, δ, ppm): 2.3 (s, 4H, J = 2.378), 7.3 (s, 4H, J = 7.344) 7.64 (d, 2H, J = 7.672), 8.0 (t, 2H, J = 8.062), 8.57 (t, 1H, J = 8.6106), 8.72 (d, 2H, J = 8.763), MASS m/z (%): 318.7 (8), 378.8 (10), 470.1 (10), 436.6 (14), 248.6 (15), 414.4 (18), 344.4 (21), 331.0 (24), 274.8 (26), 410.9 (26), 80.1 (28), 332.7 (34), 291.0 (100)

- **Compound (IVD):** [2-(p-toluene sulfonyl amino-N-[5-(3-nitro-phenyl)-1,3,4-oxadiazole]
  Proton nuclear magnetic resonance (D$_2$O, δ, ppm): 2.1 (s, 2H, J = 2.359), 7.23 (s, 2H, J = 7.322), 7.55 (s, 1H, J = 7.6704), 7.93 (s, 2H, J = 8.059), 8.52 (s, 2H, J = 8.587), 8.67 (s, 1H, J = 8.647). MASS m/z (%): 194.7 (6), 301.7 (6), 497.8 (7), 274.8 (8), 419.0 (8), and 387.8 (10), 348.6 (12), 378.8 (12), 448.5 (13), 248.5 (14), 332.6 (14), 306.6 (16), 468.3 (19), 410.9 (38), 80.1 (100)

- **Compound (IVA):** [2-aminobenzyl-5-phenyl-1,3,4-oxadiazole]
  Proton nuclear magnetic resonance (DMSO, δ, ppm): 0.42 (m, 1H, J = 7.5), 0.93 (m, 1H, J = 7.5), 1.0 (t, 1H, J = 7.4). Mass m/z (%): 166.1 (08), 179.2 (10), 237.5 (10), 338.0 (10), 279.0 (14), 501.0 (14), 610.9 (14), 561.0 (18), 586.4 (18), 661.2 (18), 453.1 (22), 378.8 (24), 569.1 (26), 712.6 (26), 178.2 (30), 428.1 (34), 523.0 (38), 685.4 (38), 664.3 (48), 452.1 (94), 663.3 (100)

- **Compound (VIB):** [2-amino-(2-chlorobenzyl)-5-(2-chlorobenzyl)-1,3,4-thiadiazole]
  Proton nuclear magnetic resonance (DMSO, δ, ppm): 0.02 (m, 1H, J = 7.5), 0.93 (m, 1H, J = 7.5). Mass m/z (%): 194.7 (6), 301.7 (6), 497.8 (7), 80.1 (100), 387.8 (10), 348.6 (12), 378.8 (12), 448.5 (13), 248.5 (14), 332.6 (14), 178.2 (20), 335.5 (22), 631.6 (24), 354.7 (100)

- **Compound (VLC):** [2-amino-(5-nitrobenzyl)-1,3,4-thiadiazole]
  Proton nuclear magnetic resonance (DMSO, δ, ppm): 1.0 (t, 1H, J = 7.8), 4.0 (m, 4H, J = 7.8). Mass m/z (%): 485.6 (10), 356.7 (14), 633.6 (14), 178.2 (20), 335.5 (22), 631.6 (24), 354.7 (100)

**Table 1:** Physical data of the synthesized compounds of 2,5-disubstituted sulfonyl amino-1,3,4-oxadiazole

| Compounds (IV) | R       | Yield % | M.P. (°C) | R' value | Molecular formula | Molecular weight |
|---------------|---------|---------|-----------|----------|------------------|------------------|
| a             | -C$_2$H$_5$ | 72      | 200-210   | 0.60     | C$_6$H$_{13}$N$_2$O$_5$S | 315.0 |
| b             | -2-CIC$_2$H$_4$ | 77      | 200-215   | 0.42     | C$_5$H$_{12}$N$_2$O$_3$S| 349.5 |
| c             | -3-CIC$_2$H$_4$ | 70      | 260-270   | 0.56     | C$_6$H$_{13}$N$_2$O$_3$S | 349.5 |
| d             | -3-NO$_2$C$_2$H$_4$ | 70      | 260-270   | 0.54     | C$_7$H$_{15}$N$_2$O$_5$S | 360.0 |

M.P.: Melting point

**Table 2:** Physical data of the synthesized compounds of 2-amino-disubstituted-1,3,4-thiadiazole

| Compounds (VI) | R       | Ar        | Yield (%) | M.P. (°C) | R' value | Molecular formula | Molecular weight |
|---------------|---------|-----------|-----------|-----------|----------|------------------|------------------|
| a             | -C$_2$H$_5$ | -C$_2$H$_5$ | 72        | 80-90     | 0.62     | C$_5$H$_{11}$N$_2$S | 265.2 |
| b             | -2-CIC$_2$H$_4$ | -2-CIC$_2$H$_4$ | 74      | 100-110   | 0.85     | C$_7$H$_{15}$N$_2$S| 334.1 |
| c             | -4-NO$_2$C$_2$H$_4$ | -4-NO$_2$C$_2$H$_4$ | 78      | 100-110   | 0.50     | C$_7$H$_{15}$N$_2$S| 355.1 |
| d             | -4-CIC$_2$H$_4$ | -4-CIC$_2$H$_4$ | 70      | 100-110   | 0.7      | C$_7$H$_{15}$N$_2$S| 334.1 |

M.P.: Melting point
1.83 (s, 1H, J = 10.112), 3.67 (d, 3H, J = 8.446), 3.95 (d, 3H, J = 8.172); mass m/z (%): 365.9 (10), 407.1 (10), 446.2 (10), 505.0 (10), 701.2 (12), 741.2 (12), 407.9 (14), 576.3 (14), 212.1 (16), 426.7 (20), 544.4 (22), 515.0 (24), 530.0 (34), 424.7 (70), 422.7 (100).

- Compound (VId): [2-amino- (4-chlorobenzyl)-5-(4-chlorophenyl)-1,3,4-thiadiazole]

Proton nuclear magnetic resonance (DMSO-d6, δ, ppm): 0.03 (s, 1H, J = 8.340), 0.18 (s, 1H, J = 9.873), 0.76 (m, 1H, J = 7.898), 1.00 (d, 1H, J = 7.710), 1.78 (m, 1H, J = 7.540); mass m/z (%): 458.6 (10), 356.7 (14), 633.6 (14), 178.2 (20), 335.5 (22), 631.6 (24), 354.7 (100).

**Evaluation of antibacterial activity**

Antibacterial activities of all synthesized compounds were determined by disc diffusion method. Results are exhibited in Table 3 and Figure 1. CompoundsIVA and IVB exhibited good activity, and IVC and IVD showed moderate activity as compared with standard drug Ofloxacin.

**Pharmacological evaluation**

Results are represented in Tables 4 and 5. Compounds VIb and VIc exhibited good antiinflammatory activity as compared with standard drug diclofenac-30, while VIc shows good analgesic activity as compared with standard drug aspirin.

**CONCLUSION**

A series of 2-amino-disubstituted-1,3,4-thiadiazoles ando2, 5-disubstituted-phenyl 1,3,4-oxadiazoles was synthesized with good yields, and their structures were elucidated by spectral data. All the compounds show good pharmacological activities. Compounds IVa and IVb exhibited good antimicrobial activity and IVc, IVd showed moderate microbial activity as compared with a standard drug ofloxacin. Compounds VIb and VIc exhibited good antiinflammatory activity as compared with standard drug diclofenac-30, while VIc shows good analgesic activity in comparison to aspirin used as standard drug.

![Graph showing zone of inhibition by different compounds against different bacteria](image)

**Figure 1:** Zone of inhibition by different compounds against different bacteria

**Table 3: Antibacterial activity of synthesized compounds (00A-00A-3)**

| Compounds            | IVa (00A) | IVb (00A-1) | IVc (00A-2) | IVd (00A-3) | Ofloxacin |
|----------------------|-----------|-------------|-------------|-------------|-----------|
| **Salmonella sp.**   | 19.6±1.1  | 19.4±1.1    | 18.6±1.1    | 17.5±1.1    | 29.0±1.1  |
| % inhibition         | 67.5      | 66.89       | 64.13       | 59.31       | 100       |
| **Pseudomonas sp.**  | 20.1±1.04 | 20.5±1.04   | 18.3±1.04   | 18.01±1.04  | 28.6±1.04 |
| % inhibition         | 70.27     | 71.67       | 63.98       | 62.97       | 100       |
| **Staphylococcus aureus** | 18.3±0.8  | 18.3±0.8    | 17.2±0.8    | 17.0±0.8    | 28.0±0.8  |
| % inhibition         | 65.35     | 65.35       | 61.42       | 60.71       | 100       |
| **Bacillus subtilis**| 18.8±0.9  | 19.1±0.9    | 18.1±0.9    | 18.2±0.9    | 28.6±0.9  |
| % inhibition         | 65.73     | 66.78       | 63.28       | 63.63       | 100       |

Data presented in mean±SD (n=3), concentration of derivatives=25 μg/dish, concentration of ofloxacin=25 μg/ml. In comparison to control, % inhibition by synthesized compound(s) is significant and potent, but not showing better activity than the standard drug (ofloxacin) used in this experiment. SD: Standard deviation.
Table 4: Antiinflammatory activity of the synthesized compound (2-amino-5-disubstituted-1,3,4-thiadiazole derivatives) by carrageen an induced rat paw edema method showing percentage of inhibition

| Treatment       | Time interval (h) | 0      | 1      | 2      | 3      | 6      | 24     |
|-----------------|-------------------|--------|--------|--------|--------|--------|--------|
| Control         |                   | 0.19±0.03 | 0.20±0.02 | 0.28±0.01 | 0.34±0.04 | 0.30±0.04 | 0.28±0.01 |
| Diclofenac-30   | (%) inhibition    | 0.07±0.01 (63) | 0.09±0.01* (55) | 0.11±0.07* (60) | 0.20±0.04** (41) | 0.12±0.02** (60) | 0.11±0.01** (60) |
| Vla (% inhibition) | 0.10±0.01 (47) | 0.14±0.02* (30) | 0.11±0.04 (60) | 0.21±0.01 (38) | 0.19±0.02* (36) | 0.15±0.01* (46) |
| Vlb (% inhibition) | 0.12±0.01*,# (36) | 0.14±0.02* (30) | 0.14±0.01 (50) | 0.25±0.04** (26) | 0.16±0.04 (46) | 0.12±0.01 (57) |
| Vlc (% inhibition) | 0.09±0.01* (52) | 0.11±0.01 (45) | 0.13±0.06* (53) | 0.23±0.04** (32) | 0.19±0.02* (37) | 0.12±0.01** (57) |
| Vld (% inhibition) | 0.11±0.02**,# (42) | 0.13±0.01* (35) | 0.16±0.01* (42) | 0.24±0.01 (29) | 0.19±0.02* (37) | 0.15±0.01* (46) |

Each data suggests mean±SEM (n=6), one-way ANOVA using Dunnett’s t-test is applied for statistical analysis. Treatment groups compared with the control group: *Significant at P<0.05, **Highly significant at P<0.01. Treatment groups compared with standard drug: #Significant at P<0.05. % inhibition, (1−Vt/Vc)×100, Vt = Increase in paw volume of test, Vc = Increase in paw volume of the control group of rats. SEM: Standard error of the mean.

Table 5: Analgesic activity of the synthesized compound (2-amino5-disubstituted-1,3,4-thiadiazole derivatives) by tail flick method (values obtained)

| Treatment       | Time interval (min) | 15     | 30     | 45     | 60     |
|-----------------|---------------------|--------|--------|--------|--------|
| Control         |                     | 2.90±0.21 | 3.10±0.19 | 2.80±0.15 | 3.07±0.06 |
| Aspirin         |                     | 4.17±0.30* | 5.50±0.40** | 6.93±0.72** | 8.25±0.13** |
| Vla (% inhibition) | 3.95±0.34 | 5.28±0.44 | 5.96±0.75 | 2.64±0.48* |
| Vlb (% inhibition) | 4.12±0.33 | 5.94±0.63 | 5.45±0.56 | 1.58±0.28* |
| Vlc (% inhibition) | 3.90±0.33* | 4.50±0.50* | 6.20±0.17** | 1.75±0.56** |
| Vld (% inhibition) | 3.84±0.40 | 4.11±0.40* | 6.12±0.24 | 1.46±0.17* |

Each datum suggests mean±SEM (n=6), one-way ANOVA using Dunnett’s t-test is applied for statistical analysis. Treatment groups compared with the control group: *Significant at P<0.05. **Moderate significant at P<0.01. Treatment groups compared with the standard drug: *Significant at P<0.05. SEM: Standard error of the mean.

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