



Research Article

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## Synthesis and antioxidant activity of disubstituted 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles

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### ABSTRACT

Some new disubstituted 1,3,4-oxadiazoles / thiadiazoles and 1,2,4-triazoles were synthesized by cyclocondensation of arylsulfonylethylsulfonylacetic acid methyl ester and benzylsulfonylethylsulfonylacetic acid methyl ester with different nucleophiles. All the new compounds were evaluated for antioxidant activity. The compound **8c** exhibited greater antioxidant activity.

**Key words:** arylsulfonylethylsulfonylacetic acid methyl ester, benzylsulfonyl-ethylsulfonylacetic acid methyl ester, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,2,4-triazole, cyclocondensation, antioxidant activity and ultrasonication.

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### INTRODUCTION

Amongst different five membered heterocyclic systems oxadiazole, thiadiazole, triazole and their derivatives have gained importance as they constitute the structural features of many bioactive compounds. Substituted 1,3,4-oxadiazoles have revealed antibacterial [1], antifungal [2], anti-inflammatory [3], analgesic [4,5] and anticonvulsant properties [6]. Compounds possessing oxadiazole moiety show anticancer [7] and tyrosinase inhibitory activity [8]. 2,5-Disubstituted 1,3,4-thiadiazoles possess various biological properties such as antitumor [9], anticonvulsant [10], antifungal [11], anti-inflammatory [12,13], antihypertensive [14] and anaesthetic activities [15]. Besides, 2-mercapto-5-methyl-1,3,4-thiadiazole is an intermediate for therapeutically useful antibiotic cefazolin [16]. Moreover, derivatives of 1,2,4-triazole are known to exhibit anti-inflammatory [17], antiviral [18], diuretic [19], antimicrobial [20,21], anticonvulsant [22] and antidepressant activities [23]. The most frequently used triazoles are fluconazole and itraconazole that display a broad spectrum of antifungal activity and reduced toxicity when compared with imidazole antifungals [24]. One of the popular methods for the synthesis of 1,3,4-oxadiazoles involves cyclization of diacylhydrazines prepared by the reaction of acyl chlorides and hydrazine. Several cyclodehydrating agents such as  $\text{Et}_2\text{O} \cdot \text{BF}_3$  [25], triflic anhydride [26], phosphorus pentoxide [27], polyphosphoric acid [28], thionyl chloride [29] and phosphorus oxychloride [30] have been used. One-pot synthesis of 1,3,4-oxadiazoles from hydrazine and carboxylic acids have also been reported [31]. Most frequently used methods for the synthesis of thiadiazoles include the reaction of acylthiosemicarbazides with acidic reagents such as trifluoroacetic acid [32], methanesulfonic acid [3]. One of the synthetic methods for the preparation of triazoles involves the use of *N,N'*-dimethyl formamide dimethyl acetals [33]. In fact, we have reported the synthesis of 1,3,4-oxadiazoles from acid hydrazides and carboxylic acids in the presence of  $\text{POCl}_3$  and their interconversion to thiadiazoles and triazoles in the presence of appropriate nucleophiles [34]. In continuation of our interest in the synthesis and bioassay of different heterocyclic compounds, we focused our attention to develop some new oxadiazoles, thiadiazoles and triazoles.

## EXPERIMENTAL SECTION

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The purity of the compounds was checked by TLC (silica gel H, BDH, hexane/ethyl acetate, 3:1). The IR spectra were recorded on a Thermo Nicolet IR 200 FT-IR spectrometer as KBr pellets and the wave numbers were given in  $\text{cm}^{-1}$ . The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were run in  $\text{CDCl}_3$  /  $\text{DMSO}-d_6$  on a Jeol JNM spectrometer operating at 400 and 100 MHz. All chemical shifts are reported in  $\delta$  (ppm) using TMS as an internal standard. The elemental analyses were determined on a Perkin-Elmer 240C elemental analyzer. Experiment under ultrasound irradiation was carried out in ultrasonic cleaner model CB2150, manufactured by Cyberlab, 22, SaloTerrace, Millbury, MA01527, USA having maximum power out put 200W / 46 KHz operating frequency. The arylsulfonylethylsulfonylacetic acid (**1**) and benzylsulfonylethyl-sulfonylacetic acid (**2**) were prepared by the literature procedure [35].

**Arylsulfonylethylsulfonylacetic acid methyl ester (3) / benzylsulfonylethyl-sulfonylacetic acid methyl ester (4).**

A mixture of **1/2** (100 mmol), conc. $\text{H}_2\text{SO}_4$  (2 ml) and methanol (20 ml) were taken in a 50 ml round bottomed flask and the contents were sonicated in ultrasound-bath for 12-16 min. at room temperature. The contents of the flask were cooled and poured onto crushed ice. The solid separated was filtered, dried and recrystallized from methanol

**Phenylsulfonylethylsulfonylacetic acid methyl ester (3a):** Yield 20.8 g (68 %). White solid, mp 121-123°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1143, 1335 ( $\text{SO}_2$ ), 1738 (CO).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 3.58 (t, 2H,  $\text{CH}_2\text{-SO}_2$ ,  $J = 4.0$  Hz), 3.68 (t, 2H,  $\text{SO}_2\text{-CH}_2$ ,  $J = 4.0$  Hz), 3.82 (s, 3H,  $\text{OCH}_3$ ), 4.05 (s, 2H,  $\text{CH}_2\text{-CO}$ ), 7.60-7.95 (m, 5H, Ar-H).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 46.9 ( $\text{CH}_2\text{-SO}_2$ ), 48.6 ( $\text{SO}_2\text{-CH}_2$ ), 53.3 ( $\text{OCH}_3$ ), 57.9 ( $\text{CH}_2\text{-CO}$ ), 162.8 (CO), 128.1, 129.5, 134.3, 138.2 (aromatic carbons). Found, %: C 43.08; H 4.60.  $\text{C}_{11}\text{H}_{14}\text{O}_6\text{S}_2$ . Calculated, %: C 43.13; H 4.61.

**4-Methylphenylsulfonylethylsulfonylacetic acid methyl ester (3b):** Yield 22.4 g (70 %). White solid, mp 142-144°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1142, 1328 ( $\text{SO}_2$ ), 1734 (CO).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 2.41 (s, 3H, Ar- $\text{CH}_3$ ), 3.49 (t, 2H,  $\text{CH}_2\text{-SO}_2$ ,  $J = 4.2$  Hz), 3.61 (t, 2H,  $\text{SO}_2\text{-CH}_2$ ,  $J = 4.2$  Hz), 3.79 (s, 3H,  $\text{OCH}_3$ ), 4.13 (s, 2H,  $\text{CH}_2\text{-CO}$ ), 7.66-8.01 (m, 4H, Ar-H).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 24.9 (Ar- $\text{CH}_3$ ), 45.4 ( $\text{CH}_2\text{-SO}_2$ ), 47.6 ( $\text{SO}_2\text{-CH}_2$ ), 54.1 ( $\text{OCH}_3$ ), 58.6 ( $\text{CH}_2\text{-CO}$ ), 164.7 (CO), 130.1, 132.0, 134.7, 139.5 (aromatic carbons). Found, %: C 45.06; H 5.06.  $\text{C}_{12}\text{H}_{16}\text{O}_6\text{S}_2$ . Calculated, %: C 44.99; H 5.03.

**4-Chlorophenylsulfonylethylsulfonylacetic acid methyl ester (3c):** Yield 24.5 g (72 %). White solid, mp 157-159°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1139, 1341 ( $\text{SO}_2$ ), 1743 (CO).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 3.50 (t, 2H,  $\text{CH}_2\text{-SO}_2$ ,  $J = 4.3$  Hz), 3.59 (t, 2H,  $\text{SO}_2\text{-CH}_2$ ,  $J = 4.3$  Hz), 3.80 (s, 3H,  $\text{OCH}_3$ ), 4.12 (s, 2H,  $\text{CH}_2\text{-CO}$ ), 7.58-8.01 (m, 4H, Ar-H).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 45.7 ( $\text{CH}_2\text{-SO}_2$ ), 47.9 ( $\text{SO}_2\text{-CH}_2$ ), 53.8 ( $\text{OCH}_3$ ), 56.4 ( $\text{CH}_2\text{-CO}$ ), 164.2 (CO), 129.2, 130.5, 134.7, 137.1 (aromatic carbons). Found, %: C 38.72; H 3.83.  $\text{C}_{11}\text{H}_{13}\text{ClO}_6\text{S}_2$ . Calculated, %: C 38.77; H 3.84.

**Benzylsulfonylethylsulfonylacetic acid methyl ester (4a):** Yield 21.4 g (67 %). White solid, mp 145-147°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1150, 1330 ( $\text{SO}_2$ ), 1740 (CO).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 3.65 (t, 2H,  $\text{CH}_2\text{-SO}_2$ ,  $J = 4.8$  Hz), 3.85 (s, 3H,  $\text{OCH}_3$ ), 3.90 (t, 2H,  $\text{SO}_2\text{-CH}_2$ ,  $J = 4.8$  Hz), 4.08 (s, 2H,  $\text{CH}_2\text{-CO}$ ), 4.76 (s, 2H, Ar- $\text{CH}_2$ ), 7.62-7.98 (m, 5H, Ar-H).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 47.1 ( $\text{CH}_2\text{-SO}_2$ ), 48.8 ( $\text{SO}_2\text{-CH}_2$ ), 54.2 ( $\text{OCH}_3$ ), 58.5 ( $\text{CH}_2\text{-CO}$ ), 61.2 (Ar- $\text{CH}_2$ ), 163.3 (CO), 128.7, 129.5, 134.8, 138.5 (aromatic carbons). Found, %: C 44.89; H 5.08.  $\text{C}_{12}\text{H}_{16}\text{O}_6\text{S}_2$ . Calculated, %: C 44.98; H 5.03.

**4-Methylbenzylsulfonylethylsulfonylacetic acid methyl ester (4b):** Yield 22.7 g (68 %). White solid, mp 162-164°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1142, 1320 ( $\text{SO}_2$ ), 1730 (CO).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 2.34 (s, 3H, Ar- $\text{CH}_3$ ), 3.62 (t, 2H,  $\text{CH}_2\text{-SO}_2$ ,  $J = 5.1$  Hz), 3.78 (s, 3H,  $\text{OCH}_3$ ), 3.88 (t, 2H,  $\text{SO}_2\text{-CH}_2$ ,  $J = 5.1$  Hz), 4.18 (s, 2H,  $\text{CH}_2\text{-CO}$ ), 4.74 (s, 2H, Ar- $\text{CH}_2$ ), 7.70-8.07 (m, 4H, Ar-H).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 24.9 (Ar- $\text{CH}_3$ ), 45.7 ( $\text{CH}_2\text{-SO}_2$ ), 47.9 ( $\text{SO}_2\text{-CH}_2$ ), 55.2 ( $\text{OCH}_3$ ), 58.9 ( $\text{CH}_2\text{-CO}$ ), 60.8 (Ar- $\text{CH}_2$ ), 162.8 (CO), 128.5, 129.3, 130.1, 131.5 (aromatic carbons). Found, %: C 46.77; H 5.34.  $\text{C}_{13}\text{H}_{18}\text{O}_6\text{S}_2$ . Calculated, %: C 46.69; H 5.42.

**4-Chlorobenzylsulfonylethylsulfonylacetic acid methyl ester (4c):** Yield 24.8 g (70 %). White solid, mp 175-177°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1138, 1310 ( $\text{SO}_2$ ), 1725 (CO).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 3.67 (t, 2H,  $\text{CH}_2\text{-SO}_2$ ,  $J = 4.9$  Hz), 3.85 (s, 3H,  $\text{OCH}_3$ ), 3.92 (t, 2H,  $\text{SO}_2\text{-CH}_2$ ,  $J = 4.9$  Hz), 4.24 (s, 2H,  $\text{CH}_2\text{-CO}$ ), 4.80 (s, 2H, Ar- $\text{CH}_2$ ), 7.59-8.12 (m, 4H, Ar-H).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 46.1 ( $\text{SO}_2\text{-CH}_2$ ), 48.6 ( $\text{CH}_2\text{-SO}_2$ ), 54.1, ( $\text{OCH}_3$ ), 56.8, ( $\text{CH}_2\text{-CO}$ ), 61.5 (Ar- $\text{CH}_2$ ), 163.5 (CO), 130.5, 132.4, 135.0, 136.4 (aromatic carbons). Found, %: C 40.67; H 4.23.  $\text{C}_{12}\text{H}_{15}\text{ClO}_6\text{S}_2$ . Calculated, %: C 40.61; H 4.26.

**Arylsulfonylethylsulfonylacetic acid hydrazide (5) / benzylsulfonylethyl-sulfonylacetic acid hydrazide (6)**

The compound **3/4** (10 mmol) in methanol (8 ml), hydrazine hydrate (20 mmol) and three drops of pyridine were taken in a 50ml round bottomed flask and the contents were sonicated in ultrasound-bath for 15-20 min. at room temperature. The reaction mixture was cooled and the solid separated was filtered, dried and recrystallized from methanol.

**Phenylsulfonylethylsulfonylacetic acid hydrazide (5a):** Yield 2.29 g (75 %). White solid, mp 120-122°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1155, 1336 ( $\text{SO}_2$ ), 1655 (CO), 3262 ( $\text{NH}_2$ ), 3331 (NH).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 3.68 (t, 2H,  $\text{CH}_2\text{-SO}_2$ ,  $J = 4.5$  Hz), 3.87 (t, 2H,  $\text{SO}_2\text{-CH}_2$ ,  $J = 4.5$  Hz), 3.99 (bs, 2H,  $\text{NH}_2$ ), 4.15 (s, 2H,  $\text{CH}_2\text{-CO}$ ), 7.09-7.35 (m, 5H, Ar-H), 7.95 (bs, 1H, NH).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 43.8 ( $\text{CH}_2\text{-SO}_2$ ), 47.2 ( $\text{SO}_2\text{-CH}_2$ ), 56.3 ( $\text{CH}_2\text{-CO}$ ), 164.6 (CO), 127.7, 129.8, 133.1, 133.9 (aromatic carbons). Found, %: C 39.28; H 4.62; N 9.18.  $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}_5\text{S}_2$ . Calculated, %: C 39.20; H 4.61; N 9.14.

**4-Methylphenylsulfonylethylsulfonylacetic acid hydrazide (5b):** Yield 2.56 g (80 %). White solid, mp 133-135°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1148, 1342 ( $\text{SO}_2$ ), 1661 (CO), 3258 ( $\text{NH}_2$ ), 3338 (NH).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 2.37 (s, 3H, Ar- $\text{CH}_3$ ), 3.62 (t, 2H,  $\text{CH}_2\text{-SO}_2$ ,  $J = 4.7$  Hz), 3.84 (t, 2H,  $\text{SO}_2\text{-CH}_2$ ,  $J = 4.7$  Hz), 3.95 (bs, 2H,  $\text{NH}_2$ ), 4.12 (s, 2H,  $\text{CH}_2\text{-CO}$ ), 7.03-7.27 (m, 4H, Ar-H), 7.89 (bs, 1H, NH).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 22.1 (Ar- $\text{CH}_3$ ), 43.5 ( $\text{CH}_2\text{-SO}_2$ ), 46.8 ( $\text{SO}_2\text{-CH}_2$ ), 55.9 ( $\text{CH}_2\text{-CO}$ ), 163.9 (CO), 123.9, 130.5, 133.7, 134.9 (aromatic carbons). Found, %: C 41.21; H 5.08; N 8.80.  $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_5\text{S}_2$ . Calculated, %: C 41.24; H 5.03; N 8.74.

**4-Chlorophenylsulfonylethylsulfonylacetic acid hydrazide (5c):** Yield 2.65 g (78 %). White solid, mp 150-152°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1162, 1332 ( $\text{SO}_2$ ), 1652 (CO), 3267 ( $\text{NH}_2$ ), 3329 (NH).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 3.66 (t, 2H,  $\text{CH}_2\text{-SO}_2$ ,  $J = 4.8$  Hz), 3.89 (t, 2H,  $\text{SO}_2\text{-CH}_2$ ,  $J = 4.8$  Hz), 4.01 (bs, 2H,  $\text{NH}_2$ ), 4.17 (s, 2H,  $\text{CH}_2\text{-CO}$ ), 7.20-7.47 (m, 4H, Ar-H), 7.97 (bs, 1H, NH).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 44.1 ( $\text{CH}_2\text{-SO}_2$ ), 47.5 ( $\text{SO}_2\text{-CH}_2$ ), 56.5 ( $\text{CH}_2\text{-CO}$ ), 164.9 (CO), 124.1, 129.9, 133.1, 134.9 (aromatic carbons). Found, %: C 35.29; H 3.82; N 8.30.  $\text{C}_{10}\text{H}_{13}\text{ClN}_2\text{O}_5\text{S}_2$ . Calculated, %: C 35.24; H 3.84; N 8.22.

**Benzylsulfonylethylsulfonylacetic acid hydrazide (6a):** Yield 2.33 g (73 %). White solid, mp 138-140°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1152, 1337 ( $\text{SO}_2$ ), 1657 (CO), 3264 ( $\text{NH}_2$ ), 3330 (NH).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 3.70 (t, 2H,  $\text{CH}_2\text{-SO}_2$ ,  $J = 5.0$  Hz), 3.92 (t, 2H,  $\text{SO}_2\text{-CH}_2$ ,  $J = 5.0$  Hz), 4.02 (bs, 2H,  $\text{NH}_2$ ), 4.18 (s, 2H,  $\text{CH}_2\text{-CO}$ ), 4.69 (s, 2H, Ar- $\text{CH}_2$ ), 7.18-7.39 (m, 5H, Ar-H), 8.03 (bs, 1H, NH).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 44.8 ( $\text{CH}_2\text{-SO}_2$ ), 47.4 ( $\text{SO}_2\text{-CH}_2$ ), 57.2 ( $\text{CH}_2\text{-CO}$ ), 58.5 (Ar- $\text{CH}_2$ ), 165.1 (C=O), 127.4, 129.2, 132.3, 133.6 (aromatic carbons). Found, %: C 41.20; H 5.02; N 8.79.  $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_5\text{S}_2$ . Calculated, %: C 41.24; H 5.03; N 8.74.

**4-Methylbenzylsulfonylethylsulfonylacetic acid hydrazide (6b):** Yield 2.60 g (78 %). White solid, mp 155-157°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1149, 1331 ( $\text{SO}_2$ ), 1651 (CO), 3259 ( $\text{NH}_2$ ), 3325 (NH).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 2.30 (s, 3H, Ar- $\text{CH}_3$ ), 3.67 (t, 2H,  $\text{CH}_2\text{-SO}_2$ ,  $J = 5.2$  Hz), 3.88 (t, 2H,  $\text{SO}_2\text{-CH}_2$ ,  $J = 5.2$  Hz), 3.97 (bs, 2H,  $\text{NH}_2$ ), 4.15 (s, 2H,  $\text{CH}_2\text{-CO}$ ), 4.65 (s, 2H, Ar- $\text{CH}_2$ ), 7.08-7.31 (m, 4H, Ar-H), 7.99 (bs, 1H, NH).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 21.8 (Ar- $\text{CH}_3$ ), 44.5 ( $\text{CH}_2\text{-SO}_2$ ), 46.9 ( $\text{SO}_2\text{-CH}_2$ ), 56.9 ( $\text{CH}_2\text{-CO}$ ), 57.6 (Ar- $\text{CH}_2$ ), 164.8 (C=O), 123.7, 130.2, 133.3, 134.7 (aromatic carbons). Found, %: C 43.16; H 5.45; N 8.35.  $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}_5\text{S}_2$ . Calculated, %: C 43.10; H 5.42; N 8.38.

**4-Chlorobenzylsulfonylethylsulfonylacetic acid hydrazide (6c):** Yield 2.73 g (77 %). White solid, mp 172-174°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1156, 1345 ( $\text{SO}_2$ ), 1665 (CO), 3271 ( $\text{NH}_2$ ), 3337 (NH).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 3.72 (t, 2H,  $\text{CH}_2\text{-SO}_2$ ,  $J = 5.1$  Hz), 3.95 (t, 2H,  $\text{SO}_2\text{-CH}_2$ ,  $J = 5.1$  Hz), 4.04 (bs, 2H,  $\text{NH}_2$ ), 4.20 (s, 2H,  $\text{CH}_2\text{-CO}$ ), 4.72 (s, 2H, Ar- $\text{CH}_2$ ), 7.24-7.51 (m, 4H, Ar-H), 8.05 (bs, 1H, NH).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 45.9 ( $\text{CH}_2\text{-SO}_2$ ), 47.6 ( $\text{SO}_2\text{-CH}_2$ ), 57.5 ( $\text{CH}_2\text{-CO}$ ), 58.7 (Ar- $\text{CH}_2$ ), 165.5 (C=O), 123.9, 129.6, 132.8, 135.5 (aromatic carbons). Found, %: C 37.26; H 4.26; N 7.95.  $\text{C}_{11}\text{H}_{15}\text{ClN}_2\text{O}_5\text{S}_2$ . Calculated, %: C 37.23; H 4.25; N 7.89.

**2-(Arylsulfonylethylsulfonylmethyl)-5-(2-chlorophenyl)-1,3,4-oxadiazole(7)/2-(benzyl-sulfonylethylsulfonyl methyl)-5-(2-chlorophenyl)-1,3,4-oxadiazole (8)**

An equimolar (10 mmol) mixture of **5/6** and 2-chlorobenzoic acid,  $\text{POCl}_3$  (7 ml) was added and heated under reflux for 5-8 h. The excess  $\text{POCl}_3$  was removed under reduced pressure and the residue was poured onto crushed ice. The resulting precipitate was filtered, washed with saturated sodium bicarbonate solution and then with water, dried and recrystallized from ethanol.

**2-(Phenylsulfonylethylsulfonylmethyl)-5-(2-chlorophenyl)-1,3,4-oxadiazole (7a):** Yield 3.28 g (77 %). White solid, mp 115-117°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1117, 1310 ( $\text{SO}_2$ ), 1575 ( $\text{C}=\text{N}$ ).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 3.75 (t, 2H,  $\text{CH}_2\text{-SO}_2$ ,  $J = 4.3$  Hz), 3.96 (t, 2H,  $\text{SO}_2\text{-CH}_2$ ,  $J = 4.3$  Hz), 4.60 (s, 2H,  $\text{CH}_2\text{-C}=\text{N}$ ), 7.02-7.43 (m, 9H, Ar-H).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 45.2 ( $\text{CH}_2\text{-SO}_2$ ), 46.7 ( $\text{SO}_2\text{-CH}_2$ ), 54.6 ( $\text{CH}_2\text{-C}=\text{N}$ ), 157.4 (C-2), 167.7 (C-5), 122.4, 128.5, 130.7, 131.2, 131.9, 132.5, 133.7, 134.1, 134.5, 138.4 (aromatic carbons). Found, %: C 47.90; H 3.56; N 6.62.  $\text{C}_{17}\text{H}_{15}\text{ClN}_2\text{O}_5\text{S}_2$ . Calculated, %: C 47.83; H 3.54; N 6.56.

**2-(4-Methylphenylsulfonylethylsulfonylmethyl)-5-(2-chlorophenyl)-1,3,4-oxadiazole (7b):** Yield 3.14 g (72 %). White solid, mp 126-128°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1126, 1323 ( $\text{SO}_2$ ), 1570 ( $\text{C}=\text{N}$ ).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 2.28 (s, 3H, Ar- $\text{CH}_3$ ), 3.73 (t, 2H,  $\text{CH}_2\text{-SO}_2$ ,  $J = 4.1$  Hz), 3.94 (t, 2H,  $\text{SO}_2\text{-CH}_2$ ,  $J = 4.1$  Hz), 4.57 (s, 2H,  $\text{CH}_2\text{-C}=\text{N}$ ), 6.95-7.38 (m, 8H, Ar-H).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 22.5 (Ar- $\text{CH}_3$ ), 44.9 ( $\text{CH}_2\text{-SO}_2$ ), 47.2 ( $\text{SO}_2\text{-CH}_2$ ), 54.3 ( $\text{CH}_2\text{-C}=\text{N}$ ), 157.2 (C-2), 166.5 (C-5), 123.1, 128.7, 130.4, 131.5, 131.9, 132.2, 133.7, 134.5, 135.7, 138.5 (aromatic carbons). Found, %: C 48.98; H 3.86; N 6.30.  $\text{C}_{18}\text{H}_{17}\text{ClN}_2\text{O}_5\text{S}_2$ . Calculated, %: C 49.03; H 3.89; N 6.35.

**2-(4-Chlorophenylsulfonylethylsulfonylmethyl)-5-(2-chlorophenyl)-1,3,4-oxadiazole (7c):** Yield 3.46 g (75 %). White solid, mp 132-134°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1122, 1317 ( $\text{SO}_2$ ), 1572 ( $\text{C}=\text{N}$ ).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 3.78 (t, 2H,  $\text{CH}_2\text{-SO}_2$ ,  $J = 4.4$  Hz), 3.98 (t, 2H,  $\text{SO}_2\text{-CH}_2$ ,  $J = 4.4$  Hz), 4.65 (s, 2H,  $\text{CH}_2\text{-C}=\text{N}$ ), 7.04-7.44 (m, 8H, Ar-H).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 45.5 ( $\text{CH}_2\text{-SO}_2$ ), 47.6 ( $\text{SO}_2\text{-CH}_2$ ), 54.8 ( $\text{CH}_2\text{-C}=\text{N}$ ), 157.7 (C-2), 166.9 (C-5), 123.7, 128.9, 130.8, 131.7, 132.1, 132.8, 133.8, 134.7, 135.4, 138.9 (aromatic carbons). Found, %: C 44.22; H 3.10; N 6.14.  $\text{C}_{17}\text{H}_{14}\text{Cl}_2\text{N}_2\text{O}_5\text{S}_2$ . Calculated, %: C 44.26; H 3.06; N 6.07.

**2-(Benzylsulfonylethylsulfonylmethyl)-5-(2-chlorophenyl)-1,3,4-oxadiazole (8a):** Yield 3.30 g (75 %). White solid, mp 95-97°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1127, 1329 ( $\text{SO}_2$ ), 1580 ( $\text{C}=\text{N}$ ).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 3.77 (t, 2H,  $\text{CH}_2\text{-SO}_2$ ,  $J = 4.9$  Hz), 3.97 (t, 2H,  $\text{SO}_2\text{-CH}_2$ ,  $J = 4.9$  Hz), 4.62 (s, 2H,  $\text{CH}_2\text{-C}=\text{N}$ ), 4.85 (s, 2H, Ar- $\text{CH}_2$ ), 7.08-7.49 (m, 9H, Ar-H).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 45.7 ( $\text{CH}_2\text{-SO}_2$ ), 47.8 ( $\text{SO}_2\text{-CH}_2$ ), 55.0 ( $\text{CH}_2\text{-C}=\text{N}$ ), 58.5 (Ar- $\text{CH}_2$ ), 158.6 (C-2), 168.5 (C-5), 124.5, 128.4, 130.1, 131.6, 132.3, 133.9, 134.9, 136.0, 137.3, 138.4 (aromatic carbons). Found, %: C 49.10; H 3.92; N 6.42.  $\text{C}_{18}\text{H}_{17}\text{ClN}_2\text{O}_5\text{S}_2$ . Calculated, %: C 49.03; H 3.88; N 6.35.

**2-(4-Methylbenzylsulfonylethylsulfonylmethyl)-5-(2-chlorophenyl)-1,3,4-oxadiazole (8b):** Yield 3.23 g (71 %). White solid, mp 107-109°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1131, 1332 ( $\text{SO}_2$ ), 1574 ( $\text{C}=\text{N}$ ).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 2.32 (s, 3H, Ar- $\text{CH}_3$ ), 3.74 (t, 2H,  $\text{CH}_2\text{-SO}_2$ ,  $J = 5.0$  Hz), 3.95 (t, 2H,  $\text{SO}_2\text{-CH}_2$ ,  $J = 5.0$  Hz), 4.59 (s, 2H,  $\text{CH}_2\text{-C}=\text{N}$ ), 4.83 (s, 2H, Ar- $\text{CH}_2$ ), 6.98-7.45 (m, 8H, Ar-H).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 22.6 (Ar- $\text{CH}_3$ ), 45.4 ( $\text{CH}_2\text{-SO}_2$ ), 47.5 ( $\text{SO}_2\text{-CH}_2$ ), 54.9 ( $\text{CH}_2\text{-C}=\text{N}$ ), 58.3 (Ar- $\text{CH}_2$ ), 158.3 (C-2), 168.3 (C-5), 125.0, 128.6, 130.5, 131.4, 132.1, 134.2, 134.6, 135.1, 136.3, 138.4 (aromatic carbons). Found, %: C 50.25; H 4.19; N 6.18.  $\text{C}_{19}\text{H}_{19}\text{ClN}_2\text{O}_5\text{S}_2$ . Calculated, %: C 50.16; H 4.20; N 6.15.

**2-(4-Chlorobenzylsulfonylethylsulfonylmethyl)-5-(2-chlorophenyl)-1,3,4-oxadiazole (8c):** Yield 3.51 g (74 %). White solid, mp 119-121°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1122, 1321 ( $\text{SO}_2$ ), 1585 ( $\text{C}=\text{N}$ ).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 3.80 (t, 2H,  $\text{CH}_2\text{-SO}_2$ ,  $J = 5.1$  Hz), 3.99 (t, 2H,  $\text{SO}_2\text{-CH}_2$ ,  $J = 5.1$  Hz), 4.64 (s, 2H,  $\text{CH}_2\text{-C}=\text{N}$ ), 4.86 (s, 2H, Ar- $\text{CH}_2$ ), 7.01-7.50 (m, 8H, Ar-H).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 45.9 ( $\text{CH}_2\text{-SO}_2$ ), 47.9 ( $\text{SO}_2\text{-CH}_2$ ), 55.2 ( $\text{CH}_2\text{-C}=\text{N}$ ), 58.7 (Ar- $\text{CH}_2$ ), 158.9 (C-2), 167.8 (C-5), 125.9, 129.2, 130.3, 131.7, 132.3, 132.7, 134.5, 135.6, 136.8, 137.5 (aromatic carbons). Found, %: C 45.54; H 3.41; N 5.95.  $\text{C}_{18}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}_5\text{S}_2$ . Calculated, %: C 45.48; H 3.39; N 5.88.

**2-(Arylsulfonylethylsulfonylmethyl)-5-(2-chlorophenyl)-1,3,4-thiadiazole (9) / 2-(benzyl-sulfonylethylsulfonylmethyl)-5-(2-chlorophenyl)-1,3,4-thiadiazole (10)**

In a sealed test tube, a mixture of **7/8** (2 mmol), thiourea (10 mmol) and tetrahydrofuran (3 ml) was taken and heated at 120-150°C in an oil bath for 20-25 h. After the reaction was completed, it was extracted with dichloromethane. The organic layer was washed with water, brine solution and dried (an.  $\text{Na}_2\text{SO}_4$ ). Removal of the solvent under reduced pressure resulted in a solid which was recrystallized from methanol.

**2-(Phenylsulfonylethylsulfonylmethyl)-5-(2-chlorophenyl)-1,3,4-thiadiazole (9a):** Yield 0.57 g (65 %). White solid, mp 206-208°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1126, 1315 ( $\text{SO}_2$ ), 1582 ( $\text{C}=\text{N}$ ).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 3.64 (t, 2H,  $\text{CH}_2\text{-SO}_2$ ,  $J = 4.3$  Hz), 3.88 (t, 2H,  $\text{SO}_2\text{-CH}_2$ ,  $J = 4.3$  Hz), 4.54 (s, 2H,  $\text{CH}_2\text{-C}=\text{N}$ ), 7.06-7.32 (m, 9H, Ar-H).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 44.3 ( $\text{CH}_2\text{-SO}_2$ ), 46.4 ( $\text{SO}_2\text{-CH}_2$ ), 53.6 ( $\text{CH}_2\text{-C}=\text{N}$ ), 155.3 (C-2), 164.7 (C-5), 124.4, 129.5, 131.2, 131.8, 132.9, 133.3, 134.1, 134.9, 135.7, 138.7 (aromatic carbons). Found, %: C 46.15; H 3.45; N 6.37.  $\text{C}_{17}\text{H}_{15}\text{ClN}_2\text{O}_4\text{S}_3$ . Calculated, %: C 46.09; H 3.41; N 6.32.

**2-(4-Methylphenylsulfonylethylsulfonylmethyl)-5-(2-chlorophenyl)-1,3,4-thiadiazole (9b):** Yield 0.62 g (68 %). White solid, mp 218-220°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1123, 1317 ( $\text{SO}_2$ ), 1585 ( $\text{C}=\text{N}$ ).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 2.21 (s, 3H, Ar- $\text{CH}_3$ ), 3.62 (t, 2H,  $\text{CH}_2\text{-SO}_2$ ,  $J = 4.4$  Hz), 3.86 (t, 2H,  $\text{SO}_2\text{-CH}_2$ ,  $J = 4.4$  Hz), 4.49 (s, 2H,  $\text{CH}_2\text{-C}=\text{N}$ ), 6.92-7.38 (m, 8H, Ar-H).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 21.9 (Ar- $\text{CH}_3$ ), 44.1 ( $\text{CH}_2\text{-SO}_2$ ), 46.3 ( $\text{SO}_2\text{-CH}_2$ ), 53.5 ( $\text{CH}_2\text{-C}=\text{N}$ ), 155.1 (C-2), 164.5 (C-5), 124.7, 129.5, 130.5, 131.2, 132.8, 133.5, 134.0, 135.1, 135.6, 138.8 (aromatic carbons). Found, %: C 47.36; H 3.72; N 6.10.  $\text{C}_{18}\text{H}_{17}\text{ClN}_2\text{O}_4\text{S}_3$ . Calculated, %: C 47.31; H 3.75; N 6.13.

**2-(4-Chlorophenylsulfonylethylsulfonylmethyl)-5-(2-chlorophenyl)-1,3,4-thiadiazole (9c):** Yield 0.66 g (70 %). White solid, mp 226-228°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1131, 1324 ( $\text{SO}_2$ ), 1590 ( $\text{C}=\text{N}$ ).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 3.69 (t, 2H,  $\text{CH}_2\text{-SO}_2$ ,  $J = 4.7$  Hz), 3.90 (t, 2H,  $\text{SO}_2\text{-CH}_2$ ,  $J = 4.7$  Hz), 4.52 (s, 2H,  $\text{CH}_2\text{-C}=\text{N}$ ), 7.05-7.53 (m, 8H, Ar-H).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 44.5 ( $\text{CH}_2\text{-SO}_2$ ), 46.6 ( $\text{SO}_2\text{-CH}_2$ ), 53.9 ( $\text{CH}_2\text{-C}=\text{N}$ ), 155.7 (C-2), 165.0 (C-5), 124.9, 129.8, 130.6, 131.1, 132.5, 133.2, 134.7, 135.2, 135.8, 139.1 (aromatic carbons). Found, %: C 42.72; H 2.97; N 5.92.  $\text{C}_{17}\text{H}_{14}\text{Cl}_2\text{N}_2\text{O}_4\text{S}_3$ . Calculated, %: C 42.77; H 2.96; N 5.87.

**2-(Benzylsulfonylethylsulfonylmethyl)-5-(2-chlorophenyl)-1,3,4-thiadiazole (10a):** Yield 0.56 g (62 %). White solid, mp 187-189°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1138, 1312 ( $\text{SO}_2$ ), 1595 ( $\text{C}=\text{N}$ ).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 3.67 (t, 2H,  $\text{CH}_2\text{-SO}_2$ ,  $J = 5.1$  Hz), 3.93 (t, 2H,  $\text{SO}_2\text{-CH}_2$ ,  $J = 5.1$  Hz), 4.55 (s, 2H,  $\text{CH}_2\text{-C}=\text{N}$ ), 4.76 (s, 2H, Ar- $\text{CH}_2$ ), 7.10-7.39 (m, 9H, Ar-H).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 44.7 ( $\text{CH}_2\text{-SO}_2$ ), 46.9 ( $\text{SO}_2\text{-CH}_2$ ), 54.0 ( $\text{CH}_2\text{-C}=\text{N}$ ), 57.6 (Ar- $\text{CH}_2$ ), 156.7 (C-2), 165.1 (C-5), 127.2, 128.6, 129.3, 130.8, 131.1, 132.6, 134.2, 134.7, 135.6, 137.8 (aromatic carbons). Found, %: C 46.36; H 3.76; N 6.17.  $\text{C}_{18}\text{H}_{17}\text{ClN}_2\text{O}_4\text{S}_3$ . Calculated, %: C 46.31; H 3.74; N 6.13.

**2-(4-Methylbenzylsulfonylethylsulfonylmethyl)-5-(2-chlorophenyl)-1,3,4-thiadiazole (10b):** Yield 0.62 g (66 %). White solid, mp 206-208°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1116, 1318 ( $\text{SO}_2$ ), 1589 ( $\text{C}=\text{N}$ ).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 2.25 (s, 3H, Ar- $\text{CH}_3$ ), 3.65 (t, 2H,  $\text{CH}_2\text{-SO}_2$ ,  $J = 5.2$  Hz), 3.89 (t, 2H,  $\text{SO}_2\text{-CH}_2$ ,  $J = 5.2$  Hz), 4.50 (s, 2H,  $\text{CH}_2\text{-C}=\text{N}$ ), 4.72 (s, 2H, Ar- $\text{CH}_2$ ), 6.95-7.40 (m, 8H, Ar-H).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 22.1 (Ar- $\text{CH}_3$ ), 43.9 ( $\text{CH}_2\text{-SO}_2$ ), 46.7 ( $\text{SO}_2\text{-CH}_2$ ), 53.7 ( $\text{CH}_2\text{-C}=\text{N}$ ), 57.2 (Ar- $\text{CH}_2$ ), 156.4 (C-2), 164.9 (C-5), 127.6, 130.3, 131.6, 132.9, 133.4, 134.5, 135.3, 135.9, 136.6, 138.0 (aromatic carbons). Found, %: C 48.40; H 4.03; N 6.02.  $\text{C}_{19}\text{H}_{19}\text{ClN}_2\text{O}_4\text{S}_3$ . Calculated, %: C 48.45; H 4.06; N 5.95.

**2-(4-Chlorobenzylsulfonylethylsulfonylmethyl)-5-(2-chlorophenyl)-1,3,4-thiadiazole (10c):** Yield 0.66 g (68 %). White solid, mp 217-219°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1135, 1325 ( $\text{SO}_2$ ), 1577 ( $\text{C}=\text{N}$ ).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 3.69 (t, 2H,  $\text{CH}_2\text{-SO}_2$ ,  $J = 5.4$  Hz), 3.95 (t, 2H,  $\text{SO}_2\text{-CH}_2$ ,  $J = 5.4$  Hz), 4.57 (s, 2H,  $\text{CH}_2\text{-C}=\text{N}$ ), 4.78 (s, 2H, Ar- $\text{CH}_2$ ), 7.02-7.46 (m, 8H, Ar-H).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 44.6 ( $\text{CH}_2\text{-SO}_2$ ), 47.4 ( $\text{SO}_2\text{-CH}_2$ ), 54.1 ( $\text{CH}_2\text{-C}=\text{N}$ ), 57.8 (Ar- $\text{CH}_2$ ), 156.9 (C-2), 165.3 (C-5), 128.2, 129.9, 130.7, 131.8, 132.4, 133.6, 134.8, 135.7, 136.4, 138.4 (aromatic carbons). Found, %: C 44.06; H 3.03; N 5.75.  $\text{C}_{18}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}_4\text{S}_3$ . Calculated, %: C 43.99; H 3.27; N 5.70.

**3-(Arylsulfonylethylsulfonylmethyl)-4-amino-5-(2-chlorophenyl)-1,2,4-triazole (11) / 3-(benzylsulfonylethylsulfonylmethyl)-4-amino-5-(2-chlorophenyl)-1,2,4-triazole (12)**

A solution of **7/8** (1 mmol) in *n*-butanol (13 ml) and hydrazine hydrate (3 mmol) was refluxed for 6-9 h. Then KOH (5 mmol) was added to the reaction media and the precipitate formed was filtered. The solid obtained was acidified with conc. HCl to  $\text{p}^{\text{H}} \approx 3$  and washed with water and dried. The resultant solid was recrystallized from ethanol.

**3-(Phenylsulfonylethylsulfonylmethyl)-4-amino-5-(2-chlorophenyl)-1,2,4-triazole (11a):** Yield 0.29 g (66 %). White solid, mp 171-173°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1122, 1312 ( $\text{SO}_2$ ), 1592 ( $\text{C}=\text{N}$ ), 3204 ( $\text{NH}_2$ ).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 3.57 (t, 2H,  $\text{CH}_2\text{-SO}_2$ ,  $J = 4.4$  Hz), 3.76 (t, 2H,  $\text{SO}_2\text{-CH}_2$ ,  $J = 4.4$  Hz), 5.43 (s, 2H,  $\text{CH}_2\text{-C}=\text{N}$ ), 5.56 (bs, 2H,  $\text{NH}_2$ ), 7.08-7.50 (m, 9H, Ar-H).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 43.5 ( $\text{CH}_2\text{-SO}_2$ ), 45.3 ( $\text{SO}_2\text{-CH}_2$ ), 51.6 ( $\text{CH}_2\text{-C}=\text{N}$ ), 147.7 (C-3), 164.4 (C-5), 123.8, 127.1, 127.6, 128.3, 128.6, 129.3, 129.7, 130.5, 131.8, 134.3 (aromatic carbons). Found, %: C 46.35; H 3.87; N 12.79.  $\text{C}_{17}\text{H}_{17}\text{ClN}_4\text{O}_4\text{S}_2$ . Calculated, %: C 46.31; H 3.89; N 12.71.

**3-(4-Methylphenylsulfonylethylsulfonylmethyl)-4-amino-5-(2-chlorophenyl) 1,2,4-triazole (11b):** Yield 0.31 g (69 %). White solid, mp 190-192°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1130, 1320 ( $\text{SO}_2$ ), 1580 ( $\text{C}=\text{N}$ ), 3218 ( $\text{NH}_2$ ).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 2.18 (s, 3H, Ar- $\text{CH}_3$ ), 3.55 (t, 2H,  $\text{CH}_2\text{-SO}_2$ ,  $J = 4.3$  Hz), 3.73 (t, 2H,  $\text{SO}_2\text{-CH}_2$ ,  $J = 4.3$  Hz), 4.41 (s, 2H,  $\text{CH}_2\text{-C}=\text{N}$ ), 5.39 (bs, 2H,  $\text{NH}_2$ ), 6.78-7.21 (m, 8H, Ar-H).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 21.2 (Ar- $\text{CH}_3$ ), 43.2 ( $\text{CH}_2\text{-SO}_2$ ), 45.1 ( $\text{SO}_2\text{-CH}_2$ ), 52.4 ( $\text{CH}_2\text{-C}=\text{N}$ ), 146.4 (C-3), 163.8 (C-5), 127.8, 128.6, 129.1, 130.2, 130.9, 131.2, 132.7, 133.5, 135.4, 138.2 (aromatic carbons). Found, %: C 47.57; H 4.25; N 12.37.  $\text{C}_{18}\text{H}_{19}\text{ClN}_4\text{O}_4\text{S}_2$ . Calculated, %: C 47.52; H 4.21; N 12.31.

**3-(4-Chlorophenylsulfonylethylsulfonylmethyl)-4-amino-5-(2-chlorophenyl)-1,2,4-triazole (11c):** Yield 0.32 g (71 %). White solid, mp 202-204°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1121, 1306 ( $\text{SO}_2$ ), 1587 ( $\text{C}=\text{N}$ ), 3227 ( $\text{NH}_2$ ).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 3.59 (t, 2H,  $\text{CH}_2\text{-SO}_2$ ,  $J = 4.3$  Hz), 3.78 (t, 2H,  $\text{SO}_2\text{-CH}_2$ ,  $J = 4.3$  Hz), 4.46 (s, 2H,  $\text{CH}_2\text{-C}=\text{N}$ ), 5.51 (bs, 2H,  $\text{NH}_2$ ), 7.07-7.46 (m, 8H, Ar-H).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 43.7 ( $\text{CH}_2\text{-SO}_2$ ), 45.6 ( $\text{SO}_2\text{-CH}_2$ ), 52.8 ( $\text{CH}_2\text{-C}=\text{N}$ ), 147.9 (C-3), 164.6 (C-5), 127.5, 128.3, 128.9, 130.5, 131.8, 132.6, 133.5, 134.1, 137.2, 138.1 (aromatic carbons). Found, %: C 43.00; H 3.38; N 11.83.  $\text{C}_{17}\text{H}_{16}\text{Cl}_2\text{N}_4\text{O}_4\text{S}_2$ . Calculated, %: C 42.95; H 3.39; N 11.79.

**3-(Benzylsulfonylethylsulfonylmethyl)-4-amino-5-(2-chlorophenyl)-1,2,4-triazole (12a):** Yield 0.29 g (64 %). White solid, mp 152-154°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1119, 1311 ( $\text{SO}_2$ ), 1575 ( $\text{C}=\text{N}$ ), 3235 ( $\text{NH}_2$ ).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 3.60 (t, 2H,  $\text{CH}_2\text{-SO}_2$ ,  $J = 5.3$  Hz), 3.81 (t, 2H,  $\text{SO}_2\text{-CH}_2$ ,  $J = 5.3$  Hz), 4.48 (s, 2H,  $\text{CH}_2\text{-C}=\text{N}$ ), 4.68 (s, 2H, Ar- $\text{CH}_2$ ), 5.63 (bs, 2H,  $\text{NH}_2$ ) 7.10-7.52 (m, 9H, Ar-H).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 43.9 ( $\text{CH}_2\text{-SO}_2$ ), 45.8 ( $\text{SO}_2\text{-CH}_2$ ), 53.1 ( $\text{CH}_2\text{-C}=\text{N}$ ), 56.2 (Ar- $\text{CH}_2$ ), 147.5 (C-3), 164.6 (C-5), 123.8, 127.1, 127.6, 128.3, 128.6, 129.3, 129.7, 130.5, 131.8, 134.3 (aromatic carbons). Found, %: C 47.58; H 4.22; N 12.40.  $\text{C}_{18}\text{H}_{19}\text{ClN}_4\text{O}_4\text{S}_2$ . Calculated, %: C 47.52; H 4.20; N 12.31.

**3-(4-Methylbenzylsulfonylethylsulfonylmethyl)-4-amino-5-(2-chlorophenyl)-1,2,4-triazole (12b):** Yield 0.31 g (67 %). White solid, mp 173-175°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1124, 1320 ( $\text{SO}_2$ ), 1573 ( $\text{C}=\text{N}$ ), 3231 ( $\text{NH}_2$ ).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 2.20 (s, 3H, Ar- $\text{CH}_3$ ), 3.54 (t, 2H,  $\text{CH}_2\text{-SO}_2$ ,  $J = 5.1$  Hz), 3.75 (t, 2H,  $\text{SO}_2\text{-CH}_2$ ,  $J = 5.1$  Hz), 4.47 (s, 2H,  $\text{CH}_2\text{-C}=\text{N}$ ), 4.64 (s, 2H, Ar- $\text{CH}_2$ ), 5.58 (bs, 2H,  $\text{NH}_2$ ), 6.89-7.38 (m, 8H, Ar-H).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 21.4 (Ar- $\text{CH}_3$ ), 43.8 ( $\text{CH}_2\text{-SO}_2$ ), 45.5 ( $\text{SO}_2\text{-CH}_2$ ), 52.8 ( $\text{CH}_2\text{-C}=\text{N}$ ), 55.9 (Ar- $\text{CH}_2$ ), 148.3 (C-3), 165.5 (C-5), 121.1, 126.3, 127.6, 128.3, 128.9, 129.2, 129.8, 131.2, 133.6, 135.4 (aromatic carbons). Found, %: C 48.71; H 4.52; N 12.03.  $\text{C}_{19}\text{H}_{21}\text{ClN}_4\text{O}_4\text{S}_2$ . Calculated, %: C 48.66; H 4.51; N 11.95.

**3-(4-Chlorobenzylsulfonylethylsulfonylmethyl)-4-amino-5-(2-chlorophenyl)-1,2,4-triazole (12c):** Yield 0.33 g (69 %). White solid, mp 186-188°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1115, 1307 ( $\text{SO}_2$ ), 1584 ( $\text{C}=\text{N}$ ), 3243 ( $\text{NH}_2$ ).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 3.63 (t, 2H,  $\text{CH}_2\text{-SO}_2$ ,  $J = 5.5$  Hz), 3.79 (t, 2H,  $\text{SO}_2\text{-CH}_2$ ,  $J = 5.5$  Hz), 4.50 (s, 2H,  $\text{CH}_2\text{-C}=\text{N}$ ), 4.70 (s, 2H, Ar- $\text{CH}_2$ ), 5.70 (bs, 2H,  $\text{NH}_2$ ), 7.02-7.40 (m, 8H, Ar-H).  $^{13}\text{C}$  NMR spectrum,  $\delta$ , ppm: 44.1 ( $\text{CH}_2\text{-SO}_2$ ), 46.0 ( $\text{SO}_2\text{-CH}_2$ ), 53.3 ( $\text{CH}_2\text{-C}=\text{N}$ ), 56.5 (Ar- $\text{CH}_2$ ), 148.9 (C-3), 165.9 (C-5), 121.3, 127.2, 128.1, 128.7, 129.2, 130.6, 131.5, 132.8, 133.4, 135.3 (aromatic carbons). Found, %: C 44.25; H 3.73; N 11.50.  $\text{C}_{18}\text{H}_{18}\text{Cl}_2\text{N}_4\text{O}_4\text{S}_2$ . Calculated, %: C 44.18; H 3.70; N 11.45.

### Biological assays

#### Antioxidant testing

The compounds **7-12** were tested for antioxidant property by nitric oxide [36, 37] and DPPH [38] methods.

#### Assay for Nitric Oxide (NO) scavenging activity

Sodium nitroprusside (5  $\mu\text{M}$ ) in phosphate buffer pH 7.4 was incubated with 100  $\mu\text{M}$  concentration of test compounds dissolved in a suitable solvent (dioxane/methanol) and tubes were incubated at 25 °C for 120 min. Control experiment was conducted with equal amount of solvent in an identical manner. At intervals, 0.5 ml of incubation solution was taken and diluted with 0.5 ml of Griess reagent (1% Sulfanilamide, 0.1% *N*-naphthylethylenediamine dihydrochloride and 2% *o*-phosphoric acid dissolved in distilled water). The absorbance of the chromophore formed during diazotization of nitrite with sulfanilamide and subsequent *N*-naphthylethylenediamine dihydrochloride was read at  $\lambda$  546 nm. The experiment was repeated in triplicate.

#### Reduction of 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical (DPPH method)

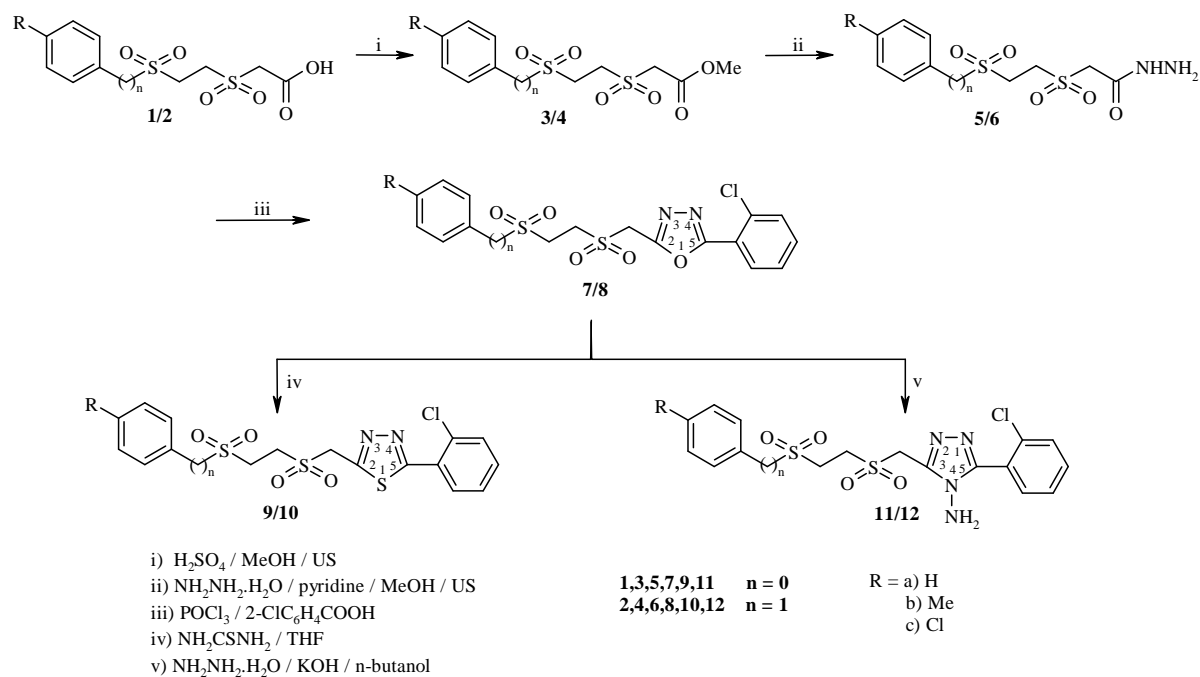
The nitrogen centered stable free radical 1,1-diphenyl-2-picrylhydrazyl (DPPH) has often been used to characterize antioxidants. It is reversibly reduced and the odd electron in the DPPH free radical gives a strong absorption maximum at  $\lambda$  517 nm, which is purple in color. This property makes it suitable for spectrophotometer studies. A radical scavenging antioxidant reacts with DPPH stable free radical and converts it into 1,1-diphenyl-2-picrylhydrazine. The resulting decolorization is stoichiometric with respect to the number of electrons captured. The change in the absorbance produced in this reaction has been used to measure antioxidant properties.

The solutions of test compounds (100  $\mu\text{M}$ ) were added to DPPH (100  $\mu\text{M}$ ) in dioxane/ethanol. The tubes were kept at an ambient temperature for 20 min and the absorbance was measured at  $\lambda$  517 nm. The inhibition percentage was

calculated by using the formula % inhibition =  $[(A_{\text{Control}} - A_{\text{Sample}}) / A_{\text{Control}}] \times 100$  where  $A_{\text{Control}}$  is the absorbance of the L-ascorbic acid and  $A_{\text{Sample}}$  is the absorbance of different compounds.

## RESULTS AND DISCUSSION

To achieve the desired heterocycles, arylsulfonylethylsulfonylacetic acid methyl ester (**3**) and benzylsulfonylethylsulfonylacetic acid methyl ester (**4**) were used as synthetic intermediates. The compounds **3** and **4** were prepared by esterification of arylsulfonylethylsulfonylacetic acid (**1**) and benzylsulfonylethylsulfonylacetic acid (**2**) with methanol in the presence of conc.  $\text{H}_2\text{SO}_4$  under ultrasound (**Scheme**). The IR spectra of **3** and **4** exhibited absorption bands in the region 1138-1150 & 1310-1341, 1725-1743  $\text{cm}^{-1}$  which were attributed to  $\text{SO}_2$  and CO, respectively. The  $^1\text{H}$  NMR spectra of **3a** and **4a** showed two singlets at  $\delta$  4.05, 4.08 ( $\text{CH}_2\text{-CO}$ ), 3.82, 3.85 ( $\text{OCH}_3$ ) and two triplets at 3.58, 3.65 ( $\text{CH}_2\text{-SO}_2$ ) and 3.68, 3.90 ppm ( $\text{SO}_2\text{-CH}_2$ ) apart from signals due to aromatic protons. In addition to these, **4a** displayed a singlet at 4.76 ppm for benzylic protons. The signals observed at  $\delta$  46.9, 48.6, 57.9, 162.8 in **3a** and at  $\delta$  47.1, 48.8, 58.5, 163.3 ppm in **4a** in the  $^{13}\text{C}$  NMR spectra were assigned to  $\text{CH}_2\text{SO}_2$ ,  $\text{SO}_2\text{CH}_2$ ,  $\text{CH}_2\text{CO}$  and CO. In addition, the compound **4a** displayed another signal at  $\delta$  61.2 ppm due to benzylic carbon. The arylsulfonylethylsulfonylacetic acid hydrazide (**5**) and benzylsulfonylethylsulfonylacetic acid hydrazide (**6**) were obtained by the reaction of **3/4** with hydrazine hydrate in the presence of pyridine under ultrasound (**Scheme**).



**Scheme**

Compounds **5** and **6** in their IR spectra showed absorption bands at 1148-1162 & 1331-1345 ( $\text{SO}_2$ ), 1651-1665 ( $\text{CO}$ ), 3258-3271 ( $\text{NH}_2$ ) and 3325-3338  $\text{cm}^{-1}$  ( $\text{NH}$ ). The absence of a singlet corresponding to carbomethoxy group and the presence of two broad singlets at  $\delta$  7.95, 8.03 and 3.99, 4.02 ppm due to CONH and  $\text{NH}_2$  in the  $^1\text{H}$  NMR spectra of **5a** and **6a** confirmed their formation. The cyclocondensation of **5/6** with 2-chlorobenzoyl chloride in the presence of phosphorus oxychloride at reflux temperature for 5-8 h yielded 2-(arylsulfonylethylsulfonylmethyl)-5-(2-chlorophenyl)-1,3,4-oxadiazole (**7**) and 2-(benzyl-sulfonylethylsulfonylmethyl)-5-(2-chlorophenyl)-1,3,4-oxadiazole (**8**) (**Scheme**). The IR spectra of **7** and **8** exhibited absorption bands at 1117-1131 & 1310-1332 ( $\text{SO}_2$ ), 1570-1585  $\text{cm}^{-1}$  ( $\text{C}=\text{N}$ ). The  $^1\text{H}$  NMR spectra of **7a** and **8a** displayed a singlet at  $\delta$  4.60, 4.62 ppm due to methylene protons flanked between sulfonyl and heterocyclic ring in addition to signals due to ethyl protons present between two sulfonyl groups and benzylic protons in **8a**. Interconversion of compounds **7** and **8** to 2-(arylsulfonylethylsulfonylmethyl)-5-(2-chlorophenyl)-1,3,4-thiazole (**9**) and 2-(benzyl-

sulfonylethylsulfonylmethyl)-5-(2-chlorophenyl)-1,3,4-thiadiazole (**10**) was affected by treating with thiourea in THF. On the other hand, 3-(arylsulfonylethyl-sulfonylmethyl)-4-amino-5-(2-chlorophenyl)-1,2,4-triazole (**11**) and 3-(benzylsulfonyl-ethylsulfonylmethyl)-4-amino-5-(2-chlorophenyl)-1,2,4-triazole (**12**) were prepared by the treatment of **7** and **8** with hydrazine hydrate (**Scheme**). The IR spectra of **9-12** showed absorption bands at 1115-1138 & 1306-1325 (SO<sub>2</sub>), 1573-1595 cm<sup>-1</sup> (CN), respectively. Moreover, **11** and **12** displayed an absorption band at 3204-3243 cm<sup>-1</sup> due to NH<sub>2</sub> group. The <sup>1</sup>H NMR spectra of **9-12** exhibited two triplets due to CH<sub>2</sub>-SO<sub>2</sub>, SO<sub>2</sub>-CH<sub>2</sub> and a singlet due to methylene protons flanked between sulfonyl and heterocyclic ring. Apart from these, **10** and **12** showed a singlet for benzylic protons. Furthermore, a broad singlet was also observed in **11** and **12** due to NH<sub>2</sub> which disappeared on deuteration. The structures of the compounds **5-12** were further confirmed by <sup>13</sup>C NMR spectra.

## Biological results

### Antioxidant testing

The compounds **7-12** are tested for antioxidant property by nitric oxide and DPPH methods. The results revealed that the compounds **7** and **8** with oxadiazole moiety showed high antioxidant property when compared with compounds having thiadiazole (**9**, **10**) and triazole (**11**, **12**) moieties in both nitric oxide and DPPH methods at a 100 μM concentration. Further, it was observed that the benzyl series, **8** exhibited greater antioxidant activity than aryl series, **7** (**Table I**).

**Table I - Antioxidant property of compounds 7-12**

Compound	NO scavenging (%)	DPPH scavenging (%)
<b>7a</b>	67.66	65.19
<b>7b</b>	58.21	57.94
<b>7c</b>	70.68	71.25
<b>8a</b>	75.35	74.28
<b>8b</b>	77.82	78.23
<b>8c</b>	89.94	88.62
<b>9a</b>	44.52	45.10
<b>9b</b>	40.34	39.72
<b>9c</b>	47.16	45.98
<b>10a</b>	49.06	48.25
<b>10b</b>	45.42	44.73
<b>10c</b>	50.77	51.47
<b>11a</b>	28.29	27.84
<b>11b</b>	26.45	25.76
<b>11c</b>	29.12	28.47
<b>12a</b>	35.71	36.62
<b>12b</b>	33.45	34.43
<b>12c</b>	39.98	40.51
Ascorbic acid	96.90	95.37

## CONCLUSION

Some new 2-(arylsulfonylethylsulfonylmethyl)-5-(2-chlorophenyl)-1,3,4-oxadiazoles / thiadiazoles / triazoles (**7,9,11**) and 2-(benzylsulfonylethylsulfonyl-methyl)-5-(2-chlorophenyl)-1,3,4-oxadiazole / thiadiazoles / triazoles (**8,10,12**) were prepared by exploiting carbomethoxy group in arylsulfonylethylsulfonylacetic acid methyl ester (**1**) and benzylsulfonylethylsulfonylacetic acid methyl ester (**2**) adopting simple and well versed methodologies. All the lead compounds were screened for antioxidant activity. The benzylsulfonylethylsulfonylmethyl substituted oxadiazoles displayed pronounced antioxidant activity.

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