Synthesis of symmetrical and unsymmetrical 1,3,4-oxadiazoles and their interconversion to 1,3,4-thiadiazoles and 1,2,4-triazoles

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Abstract
A new class of symmetrical and unsymmetrical 1,3,4-oxadiazoles was prepared. Interconversion of oxadiazoles to thiadiazoles and triazoles was effected in the presence of appropriate nucleophiles.

Keywords: 1,3,4-Oxadiazoles, 1,3,4-thiadiazoles, 1,2,4-triazoles, cyclocondensation

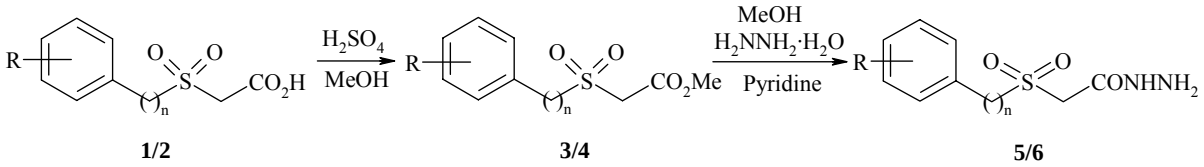
Introduction

Amongst five membered aromatic heterocycles oxadiazoles, thiadiazoles and triazoles have attracted significant interest in medicinal and pesticide chemistry and polymer and material science. Symmetrical and unsymmetrical 1,3,4-oxadiazoles are biologically versatile compounds displaying a variety of biological effects which include anti-inflammatory,[1] antifungal,[2] antiparasitic,[3] and antimicrobial activities.[4] The widespread use of 1,3,4-oxadiazoles as a scaffold in medicinal chemistry established this moiety as a member of the privileged structures class. One of the popular methods for the synthesis of 1,3,4-oxadiazoles involves cyclization of diacylhydrazines prepared from the reaction of acyl chlorides and hydrazine. Several cyclodehydrating agents such as $Et_2O{\cdot}BF_3$,[5] 1,1,1,3,3,3-hexamethyldisilazane,[6] triflic anhydride,[7] phosphorus pentoxide,[8] polyphosphoric acid,[9] thionyl chloride,[10] phosphorus oxychloride[11] and sulfuric acid[12] have been used. One-pot synthesis of 1,3,4-oxadiazoles from hydrazine with carboxylic acids have also been reported.[13] 2,5-Disubstituted 1,3,4-thiadiazoles possess various biological properties such as antitumor,[14] anticonvulsant,[15] antibacterial,[15] antifungal,[16] anti-inflammatory,[17] antihypertensive,[18] anaesthetic[19] and cardiotonic activities.[20] Most frequently used methods for the synthesis of thiadiazoles include the reaction of acylthiosemicarbazides with acidic reagents such as concentrated sulfuric acid,[21] acetic acid,[22] methanesulfonic acid,[23] 85% phosphoric acid.[24] In addition, triazoles have found wide use in medicinal chemistry as

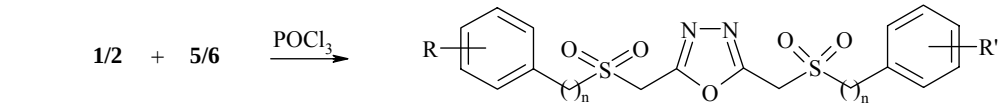
common structural motifs acting as peptidomimetic moieties and as hydrogen bond acceptors.[25] They possess important pharmacological activities such as antifungal and antiviral. Examples of antifungal drugs are fluconazole,[26] itraconazole,[27] ravuconazole,[28] voriconazole,[29] and posaconazole.[30] One of the synthetic methods for the preparation of triazoles involves the use of *N*,*N*-dimethyl formamide dimethyl acetals.[31] The present communication deals with the synthesis of hitherto unknown symmetrical and unsymmetrical 1,3,4-oxadiazoles and their interconversion into thiadiazoles and triazoles in the presence of appropriate reagents.

Results and Discussion

In order to synthesize the target molecules, we have used the acid hydrazides of arylsulfonylacetic acid **5** and arylmethanesulfonylacetic acid **6** as synthetic intermediates. The **5** and **6** were prepared from the corresponding acids on esterification followed by treatment with hydrazine hydrate. The symmetrical 1,3,4-oxadiazoles, 2,5-bis(arylsulfonylmethyl)-1,3,4-oxadiazoles **7** were prepared by the cyclocondensation of arylsulfonylacetic acid **1** with **5** in the presence of phosphorus oxychloride. Similarly, 2,5-bis(benzylsulfonylmethyl)-1,3,4-oxadiazoles **8** were obtained by the reaction of benzylsulfonylacetic acid (**2**) with **6** in the presence of phosphorus oxychloride (see Scheme 1 and Mechanism 1). The ^{1}H NMR spectrum of **7a** displayed a singlet at 4.18 ppm which was assigned to methylene protons. The ^{13}C NMR spectrum of **7a** exhibited a signal at 55.1 ppm for methylene carbon apart from signals due to aromatic carbons. However, **8a** showed two singlets at 4.07 and 4.59 ppm for the methylene protons flanked between sulfonyl and heterocyclic ring and benzylic protons. The ^{13}C NMR spectrum of **8a** displayed two signals at 55.4 and 57.8 ppm due to methylene carbons. The signal which appears in the downfield region was assigned to the benzylic carbon. Thus, the highly symmetric nature of the compounds **7** and **8** was confirmed by ^{1}H and ^{13}C NMR spectra. On the other hand, 2-(benzylsulfonylmethyl)-5-(arylsulfonylmethyl)-1,3,4-oxadiazoles **9** were obtained by the reaction of **1** with **6** (Method A) or **2** with **5** (Method B) in the presence of phosphorus oxychloride. The identity of compound **9** prepared in two methods was confirmed by TLC and ^{1}H NMR spectra. The ^{1}H NMR spectrum of **9a** displayed three singlets at 3.94, 4.18, 4.46 ppm which were assigned to the methylene protons present between the sulfonyl and the heterocyclic, the aryl and the sulfonyl and the arylsulfonyl and the heterocyclic moieties. The ^{13}C NMR spectrum of **9a** showed three signals at 57.7, 53.5 and 58.9 due to the benzylic carbon and the methylene carbons present between the sulfonyl group and the heterocyclic ring, and the arylsulfonyl group and the heterocyclic ring, respectively apart from signals due to aromatic carbons.

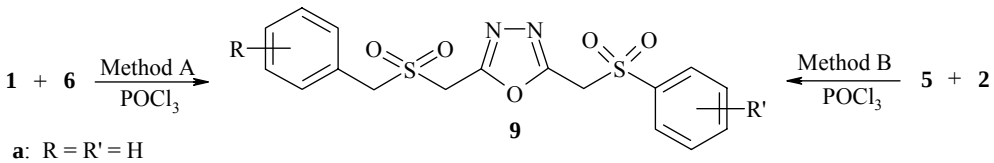


1/2 **3/4** **5/6**



1,**3**,**5**,**7** n = 0
2,**4**,**6**,**8** n = 1

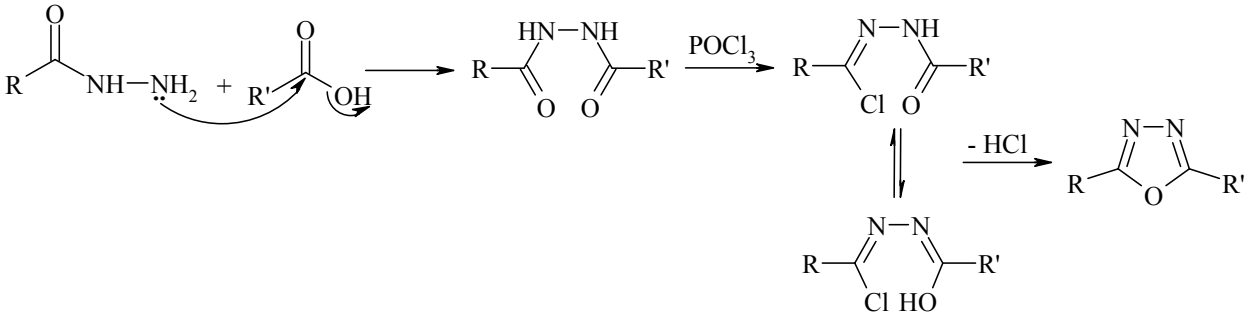
7/8



9

a: R = R' = H
b: R = R' = 4-Me
c: R = R' = 4-Cl

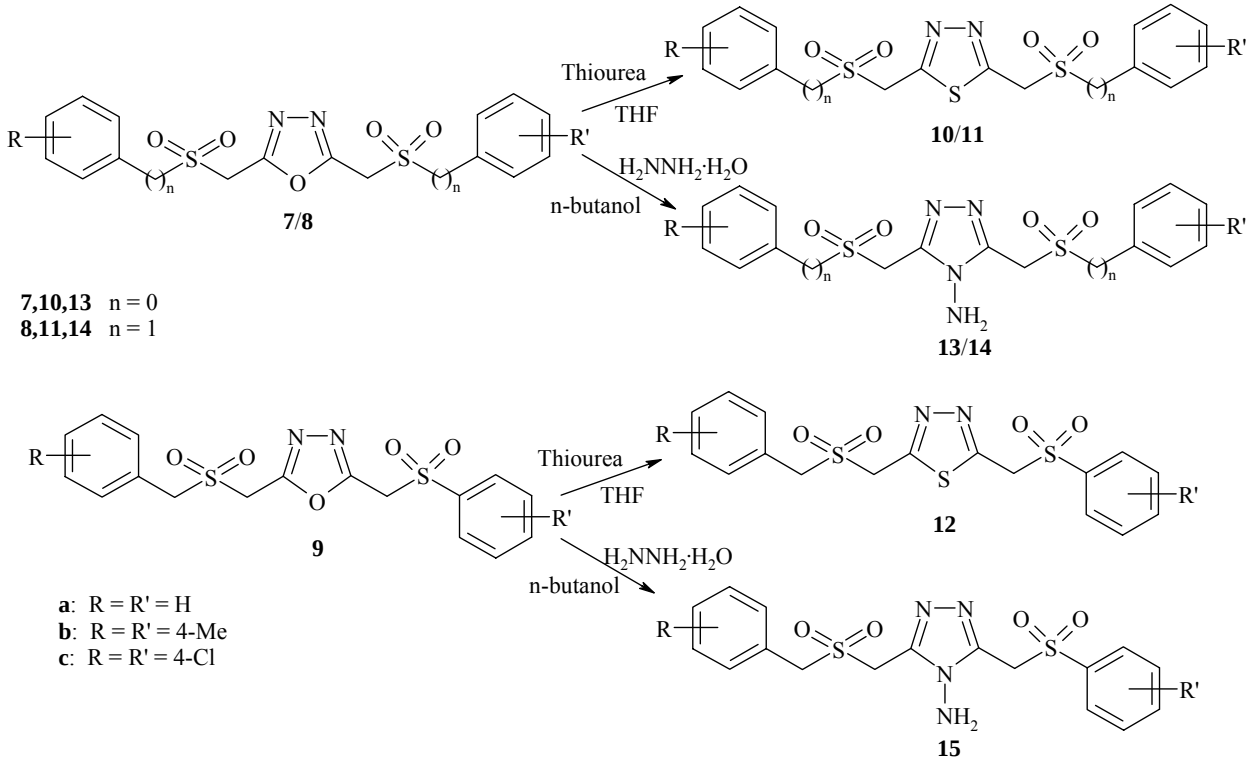
Scheme 1



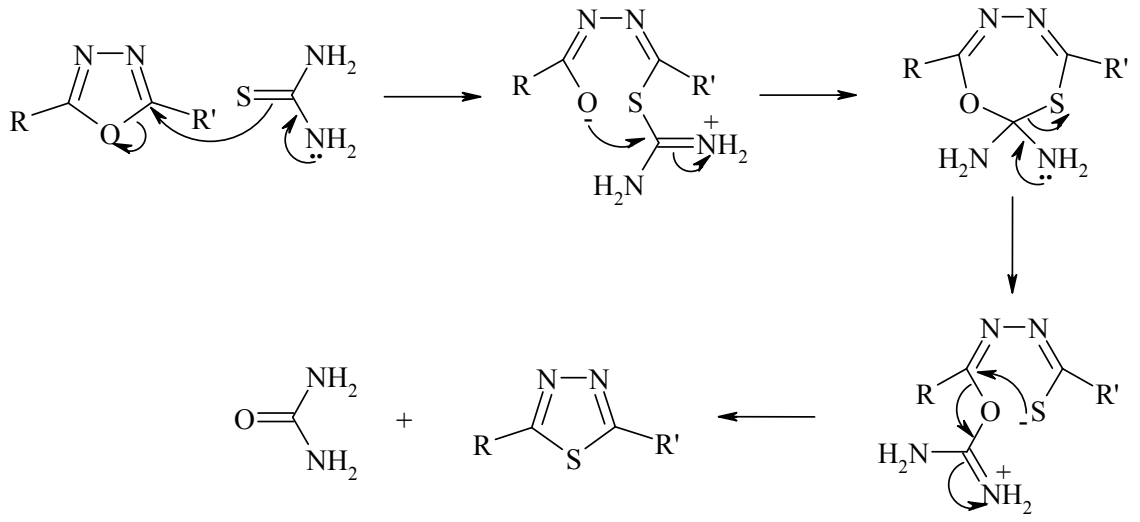
Mechanism 1

Replacement of –O– by –S– or –NH– in heterocycles was reported *viz.*, Bordners[32] preparation of pyrroles from furan and the transformation of epoxides to episulfides by the action of thiocyanates or thiourea.[33] The compounds **7**, **8** and **9** were treated with two fold excess thiourea in tetrahydrofuran. The reaction mixture after workup gave a solid which was identified as 2,5-bis(arylsulfonylmethyl)-1,3,4-thiadiazole **10**, 2,5-bis(benzylsulfonylmethyl)-1,3,4-thiadiazole **11** and 2-(benzylsulfonylmethyl)-5-(arylsulfonylmethyl)-1,3,4-thiadiazole **12**, respectively. The probable mechanism involves the formation of thiouronium salt which undergoes rearrangement to form mesomeric oxouronium salt *via* oxathiadiazepine derivative. Further, ring closure of oxouronium salt led to thiadiazole by the elimination of urea (see

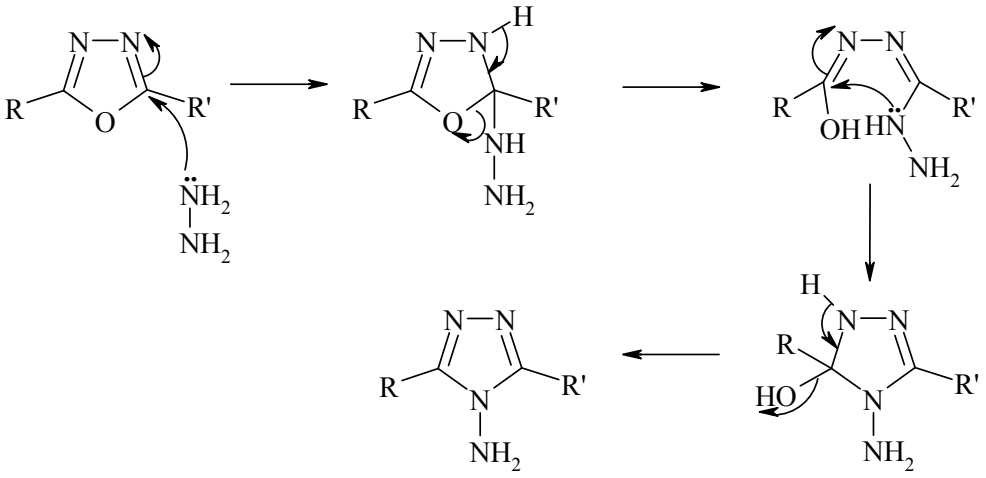
Scheme 2 and Mechanism 2). On the other hand, treatment of **7**, **8** and **9** with excess hydrazine hydrate gave 3,5-bis(arylsulfonylmethyl)-4-amino-1,2,4-triazole **13**, 3,5-bis(benzylsulfonylmethyl)-4-amino-1,2,4-triazole **14** and 3-(benzylsulfonylmethyl)-5-(arylsulfonylmethyl)-4-amino-1,2,4-triazole **15**, respectively. The reaction may proceed by the nucleophilic attack of hydrazine on α-carbon atom of oxadiazole ring followed by dehydration (see Mechanism 3). The ^{1}H NMR spectra of **10a**, **11a**, **13a** and **14a** exhibited a singlet at 4.21, 4.12, 4.22 and 4.14 ppm for methylene protons present between sulfonyl and heterocyclic moieties. Apart from this, compound **11a** and **14a** displayed another singlet at 4.65 and 4.64 ppm for benzylic protons. On the other hand, three singlets at 3.93, 4.25 and 4.52 ppm were observed in **12a** while at 3.92, 4.21 and 4.50 in **15a** due to methylene protons present between sulfonyl and heterocyclic ring, aryl and sulfonyl and arylsulfonyl and heterocyclic ring. The structure of these compounds was further confirmed by ^{13}C NMR spectra.



Scheme 2



Mechanism 2



Mechanism 3

Conclusions

A new class of symmetrical and unsymmetrical 1,3,4-oxadiazoles was prepared adopting simple and versatile methodology. Interconversion of oxadiazoles to thiadiazoles and triazoles was effected in the presence of appropriate nucleophiles.

Experimental Section

General Procedures. 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, ethyl acetate/hexane, 1:3). The IR spectra were recorded on a Thermo Nicolet IR 200 FT-IR spectrometer as KBr pellets and the wave numbers were given in cm^{-1}. The ^1H NMR spectra were recorded in $CDCl_3$ / DMSO-d_6 on a Varian EM-360 spectrometer (300 MHz). The ^{13}C NMR spectra were recorded in $CDCl_3$ / DMSO-d_6 on a Varian VXR spectrometer operating at 75.5 MHz. All chemical shifts are reported in δ (ppm) using TMS as an internal standard. The microanalyses were performed on a Perkin-Elmer 240C elemental analyzer. The starting compounds arylsulfonylacetic acid (**1**) arylmethanesulfonylacetic acid (**2**), arylsulfonylacetic acid hydrazide (**5**) and arylmethanesulfonylacetic acid hydrazide (**6**) were prepared by the literature procedure.[34]

2,5-Bis(phenylsulfonylmethyl)-1,3,4-oxadiazole (7a). Typical procedure
A mixture of **5a** (2.14 g, 10 mmol), **1a** (2.00 g, 10 mmol) and $POCl_3$ (7 mL) was heated under reflux for 5-6 h. The excess $POCl_3$ 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 to get **7a**. Yield 2.83 g (75%); white solid; m. p. 119-121 °C; ^1H NMR (300 MHz, DMSO-d_6): δ = 4.18 (s, 4H, CH_2), 7.18-7.49 (m, 10H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 55.1 (CH_2), 162.3 (C-2 & C-5), 126.4, 128.9, 129.7, 134.3 (aromatic carbons); IR (KBr): ν = 1636 (C=N), 1328, 1125 (SO_2); Anal. Calcd. for $C_{16}H_{14}N_2O_5S_2$ (378.42): C, 50.78; H, 3.73; N, 7.40. Found: C, 50.85; H, 3.71; N, 7.48.
2,5-Bis(4-methylphenylsulfonylmethyl)-1,3,4-oxadiazole (7b). Yield 3.08 g (76%); white solid; m. p. 145-147 °C; ^1H NMR (300 MHz, DMSO-d_6): δ = 2.25 (s, 6H, Ar-CH_3), 4.14 (s, 4H, CH_2), 7.24-7.52 (m, 8H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 21.2 (Ar-CH_3), 54.4 (CH_2), 162.7 (C-2 & C-5), 127.1, 127.6, 133.2, 134.4 (aromatic carbons); IR (KBr): ν = 1625 (C=N), 1323, 1132 (SO_2); Anal. Calcd. for $C_{18}H_{18}N_2O_5S_2$ (406.48): C, 53.19; H, 4.46; N, 6.89. Found: C, 53.24; H, 4.48; N, 6.82.
2,5-Bis(4-chlorophenylsulfonylmethyl)-1,3,4-oxadiazole (7c). Yield 3.57 g (80%); white crystals; m. p. 162-164 °C; ^1H NMR (300 MHz, DMSO-d_6): δ = 4.16 (s, 4H, CH_2), 7.42-7.78 (m, 8H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 54.9 (CH_2), 163.0 (C-2 & C-5), 126.7, 129.3, 134.7, 136.6 (aromatic carbons); IR (KBr): ν = 1628 (C=N), 1332, 1120 (SO_2); Anal. Calcd. for $C_{16}H_{12}Cl_2N_2O_5S_2$ (447.31): C, 42.96; H, 2.70; N, 6.26. Found: C, 42.90; H, 2.75; N, 6.32.

2,5-Bis(benzylsulfonylmethyl)-1,3,4-oxadiazole (8a). Typical procedure
A mixture of **6a** (2.28 g, 10 mmol), **2a** (2.14 g, 10 mmol) and $POCl_3$ (7 mL) was heated under reflux for 4-5 h. The excess $POCl_3$ 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 to get **8a**. Yield 3.21 g (79%); white solid; m. p. 195-197 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.07 (s, 4H, CH_2), 4.59 (s, 4H, Ar-CH_2), 7.28-7.36 (m, 10H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 55.4 (CH_2), 57.8 (Ar-CH_2), 160.8 (C-2 & C-5), 125.4, 127.3, 131.7, 134.2 (aromatic carbons); IR (KBr): ν = 1629 (C=N), 1334, 1137 (SO_2); Anal. Calcd. for $C_{18}H_{18}N_2O_5S_2$ (406.48): C, 53.19; H, 4.46; N, 6.89. Found: C, 53.26; H, 4.44; N, 6.93.

2,5-Bis(4-methylbenzylsulfonylmethyl)-1,3,4-oxadiazole (8b). Yield 3.56 g (82%); white crystals; m. p. 222-224 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.24 (s, 6H, Ar-CH_3), 4.12 (s, 4H, CH_2), 4.62 (s, 4H, Ar-CH_2), 7.30-7.39 (m, 8H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 21.7 (Ar-CH_3), 55.1(CH_2), 58.0 (Ar-CH_2), 161.3 (C-2 & C-5), 125.1, 129.4, 131.8, 134.1 (aromatic carbons); IR (KBr): ν = 1626 (C=N), 1336, 1134 (SO_2); Anal. Calcd. for $C_{20}H_{22}N_2O_5S_2$ (434.53): C, 55.28; H, 5.10; N, 6.45. Found: C, 55.32; H, 5.13; N, 6.49.

2,5-Bis(4-chlorobenzylsulfonylmethyl)-1,3,4-oxadiazole (8c). Yield 3.99 g (84%); white solid; m. p. 230-232 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.10 (s, 4H, CH_2), 4.64 (s, 4H, Ar-CH_2), 7.40-7.45 (m, 8H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 55.6 (CH_2), 58.4 (Ar-CH_2), 160.2 (C-2 & C-5), 127.2, 129.1, 133.5, 134.0 (aromatic carbons); IR (KBr): ν = 1622 (C=N), 1342, 1127 (SO_2); Anal. Calcd. for $C_{18}H_{16}Cl_2N_2O_5S_2$ (475.37): C, 45.48; H, 3.39; N, 5.89. Found: C, 45.43; H, 3.37; N, 5.94.

2-(Benzylsulfonylmethyl)-5-(phenylsulfonylmethyl)-1,3,4-oxadiazole (9a). Typical procedure

Method A. A mixture of **1a** (2.00 g, 10 mmol), **6a** (2.28 g, 10 mmol) and $POCl_3$ (7 mL) was heated under reflux for 5-6 h. The excess $POCl_3$ 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 to get **9a** as a white solid. Yield 3.06 g (78%).

Method B. A mixture of **2a** (2.00 g, 10 mmol), **5a** (2.14 g, 10 mmol) and $POCl_3$ (7 mL) was heated under reflux for 4-5 h. The excess $POCl_3$ 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 to get **9a**. Yield 2.74 g (70%); white solid; m. p. 148-150 °C; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ = 3.94 (s, 2H, SO_2-CH_2), 4.18 (s, 2H, Ar-CH_2), 4.46 (s, 2H, $ArSO_2$-CH_2), 7.23-7.41 (m, 10H, Ar-H); ^{13}C NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ = 53.5 (SO_2-CH_2), 57.7 (Ar-CH_2), 58.9 ($ArSO_2$-CH_2), 157.3 (C-2), 159.1 (C-5), 127.3, 127.4, 127.5, 128.2, 128.7, 131.7, 133.3, 135.7 (aromatic carbons); IR (KBr): ν = 1630 (C=N), 1320, 1135 (SO_2); Anal. Calcd. for $C_{17}H_{16}N_2O_5S_2$ (392.45): C, 52.03; H, 4.11; N, 7.14. Found: C, 52.11; H, 4.14; N, 7.18.

2-(4-Methylbenzylsulfonylmethyl)-5-(4-methylphenylsulfonylmethyl)-1,3,4-oxadiazole (9b). Yield 3.19 g (76%); white solid; m. p. 167-169 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.21 & 2.27 (s, 6H, Ar-CH_3), 3.93 (s, 2H, SO_2-CH_2), 4.22 (s, 2H, Ar-CH_2), 4.48 (s, 2H, $ArSO_2$-CH_2), 7.26-7.34 (m, 8H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 21.5 & 21.9 (Ar-CH_3), 53.2

(SO_2-CH_2), 57.4 (Ar-CH_2), 59.1 ($ArSO_2$-CH_2), 156.9 (C-2), 159.5 (C-5), 125.4, 126.4, 128.1, 129.5, 130.7, 132.1, 133.7, 136.2 (aromatic carbons); IR (KBr): ν = 1637 (C=N), 1334, 1140 (SO_2); Anal. Calcd. for $C_{19}H_{20}N_2O_5S_2$ (420.50): C, 54.27; H, 4.79; N, 6.66. Found: C, 54.22; H, 4.76; N, 6.60.

2-(4-Chlorobenzylsulfonylmethyl)-5-(4-chlorophenylsulfonylmethyl)-1,3,4-oxadiazole (9c). Yield 3.31 g (72%); white crystals; m. p. 184-186 °C;. ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ = 3.91 (s, 2H, SO_2-CH_2), 4.20 (s, 2H, Ar-CH_2), 4.51 (s, 2H, $ArSO_2$-CH_2), 7.34-7.66 (m, 8H, Ar-H); ^{13}C NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ = 53.8 (SO_2-CH_2), 57.9 (Ar-CH_2), 59.4 ($ArSO_2$-CH_2), 157.8 (C-2), 158.7 (C-5), 125.7, 127.8, 128.3, 128.4, 132.0, 133.4, 134.4, 138.4 (aromatic carbons); IR (KBr): ν = 1625 (C=N), 1345, 1144 (SO_2); Anal. Calcd. for $C_{17}H_{14}Cl_2N_2O_5S_2$ (461.34): C, 44.26; H, 3.06; N, 6.07. Found: C, 44.32; H, 3.00; N, 6.14.

2,5-Bis(phenylsulfonylmethyl)-1,3,4-thiadiazole (10a). Typical procedure

In a sealed test tube, a mixture of **7a** (1.89 g, 5 mmol), thiourea (1.52 g, 20 mmol) dissolved in tertahydrofuran (5 mL) was taken. The contents were heated at 120-150°C in an oil bath for 24-30 h. After the reaction was completed, it was extracted with dichloromethane. The organic layer was washed with water, brine solution and dried over anhydrous Na_2SO_4. The resultant solid was recrystallized from methanol to get **10a**. Yield 1.42 g (72%); white solid; m. p. 134-136 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.21 (s, 4H, CH_2), 7.23-7.56 (m, 10H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 55.4 (CH_2), 161.1 (C-2 & C-5), 125.9, 128.6, 129.2, 133.4 (aromatic carbons); IR (KBr): ν = 1631 (C=N), 1345, 1128 (SO_2); Anal. Calcd. for $C_{16}H_{14}N_2O_4S_3$ (394.49): C, 48.71; H, 3.58; N, 7.10. Found: C, 48.77; H, 3.62; N, 7.07.

2,5-Bis(4-methylphenylsulfonylmethyl)-1,3,4-thiadiazole (10b). Yield 1.44 g (68%); white solid; m. p. 156-158 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.27 (s, 6H, Ar-CH_3), 4.18 (s, 4H, CH_2), 7.25-7.59 (m, 8H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 21.9 (Ar-CH_3), 54.7 (CH_2), 161.5 (C-2 & C-5), 127.4, 128.9, 131.3, 134.6 (aromatic carbons); IR (KBr): ν = 1632 (C=N), 1342, 1145 (SO_2); Anal. Calcd. for $C_{18}H_{18}N_2O_4S_3$ (422.54): C, 51.16; H, 4.29; N, 6.63. Found: C, 51.12; H, 4.25; N, 6.67.

2,5-Bis(4-chlorophenylsulfonylmethyl)-1,3,4-thiadiazole (10c). Yield 1.73 g (75%); white solid; m. p. 173-175 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.24 (s, 4H, CH_2), 7.38-7.81 (m, 8H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 55.6 (CH_2), 160.8 (C-2 & C-5), 126.4, 129.1, 132.8, 136.5 (aromatic carbons); IR (KBr): ν = 1627 (C=N), 1348, 1136 (SO_2); Anal. Calcd. for $C_{16}H_{12}Cl_2N_2O_4S_3$ (463.38): C, 41.47; H, 2.61; N, 6.05. Found: C, 41.52; H, 2.62; N, 6.11.

2,5-Bis(benzylsulfonylmethyl)-1,3,4-thiadiazole (11a). Typical procedure

In a sealed test tube, a mixture of **8a** (2.03 g, 5 mmol), thiourea (1.52 g, 20 mmol) dissolved in tetrahydrofuran (5 mL) was taken. The contents were heated at 120-150°C in an oil bath for 20-22 h. After the reaction was completed, it was extracted with dichloromethane. The organic layer was washed with water, brine solution and dried over anhydrous Na_2SO_4. The resultant solid was recrystallized from methanol to get **11a**. Yield 1.52 g (72%); white solid; m. p. 210-212 °C; ^{1}H

NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ = 4.12 (s, 4H, CH_2), 4.65 (s, 4H, Ar-CH_2), 7.23-7.41 (m, 10H, Ar-H); ^{13}C NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ = 56.1 (CH_2), 58.0 (Ar-CH_2), 161.8 (C-2 & C-5), 126.1, 129.3, 132.8, 134.4 (aromatic carbons); IR (KBr): ν = 1633 (C=N), 1332, 1125 (SO_2); Anal. Calcd. for $C_{18}H_{18}N_2O_4S_3$ (422.54): C, 51.16; H, 4.29; N, 6.63. Found: C, 51.18; H, 4.33; N, 6.67.

2,5-Bis(4-methylbenzylsulfonylmethyl)-1,3,4-thiadiazole (11b). Yield 1.55 g (69%); white crystals; m. p. 238-240 °C; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ = 2.25 (s, 6H, Ar-CH_3), 4.09 (s, 4H, CH_2), 4.64 (s, 4H, Ar-CH_2), 7.16-7.44 (m, 8H, Ar-H); ^{13}C NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ = 21.4 (Ar-CH_3), 55.9 (CH_2), 58.2 (Ar-CH_2), 162.4 (C-2 & C-5), 126.4, 129.3, 131.3, 133.6 (aromatic carbons); IR (KBr): ν = 1625 (C=N), 1338, 1143 (SO_2); Anal. Calcd. for $C_{20}H_{22}N_2O_4S_3$ (450.59): C, 53.31; H, 4.92; N, 6.22. Found: C, 53.37; H, 4.96; N, 6.18.

2,5-Bis(4-chlorobenzylsulfonylmethyl)-1,3,4-thiadiazole (11c). Yield 1.89 g (77%); white solid; m. p. 253-255 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.14 (s, 4H, CH_2), 4.69 (s, 4H, Ar-CH_2), 7.34-7.62 (m, 8H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 56.3 (CH_2), 57.9 (Ar-CH_2), 162.4 (C-2 & C-5), 126.6, 129.5, 133.9, 137.5 (aromatic carbons); IR (KBr): ν = 1628 (C=N), 1334, 1138 (SO_2); Anal. Calcd. for $C_{18}H_{16}Cl_2N_2O_4S_3$ (491.43): C, 43.99; H, 3.28; N, 5.70. Found: C, 43.92; H, 3.25; N, 5.66.

2-(Benzylsulfonylmethyl)-5-(phenylsulfonylmethyl)-1,3,4-thiadiazole (12a). Typical procedure

In a sealed test tube, a mixture of **9a** (1.96 g, 5 mmol), thiourea (1.52 g, 20 mmol) dissolved in tetrahydrofuran (5 mL) was taken. The contents were heated at 120-150°C in an oil bath for 22-26 h. After the reaction was completed, it was extracted with dichloromethane. The organic layer was washed with water, brine solution and dried over anhydrous Na_2SO_4. The resultant solid was recrystallized from methanol to get **12a**. Yield 1.49 g (73%); white solid; m. p. 160-162 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.93 (s, 2H, SO_2-CH_2), 4.25 (s, 2H, Ar-CH_2), 4.52 (s, 2H, $ArSO_2$-CH_2), 7.28-7.62 (m, 10H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 52.9 (SO_2-CH_2), 57.3 (Ar-CH_2), 59.0 ($ArSO_2$-CH_2), 156.8 (C-2), 159.2 (C-5), 125.2, 126.4, 127.3, 129.5, 131.8, 131.9, 133.5, 135.3 (aromatic carbons); IR (KBr): ν = 1621 (C=N), 1320, 1144 (SO_2); Anal. Calcd. for $C_{17}H_{16}N_2O_4S_3$ (408.51): C, 49.98; H, 3.95; N, 6.86. Found: C, 50.05; H, 3.98; N, 6.90.

2-(4-Methylbenzylsulfonylmethyl)-5-(4-methylphenylsulfonylmethyl)-1,3,4-thiadiazole (12b). Yield 1.70 g (78%); white solid; m. p. 182-184 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.22 & 2.26 (s, 6H, Ar-CH_3), 3.91 (s, 2H, SO_2-CH_2), 4.22 (s, 2H, Ar-CH_2), 4.49 (s, 2H, $ArSO_2$-CH_2), 7.22-7.58 (m, 8H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 21.2 & 21.6 (Ar-CH_3), 53.4 (SO_2-CH_2), 57.8 (Ar-CH_2), 59.3 ($ArSO_2$-CH_2), 157.0 (C-2), 158.8 (C-5), 126.3, 127.5, 128.7, 129.4, 129.9, 131.8, 134.2, 135.7 (aromatic carbons); IR (KBr): ν = 1636 (C=N), 1322, 1140 (SO_2); Anal. Calcd. for $C_{19}H_{20}N_2O_4S_3$ (436.57): C, 52.27; H, 4.62; N, 6.42. Found: C, 52.24; H, 4.60; N, 6.45.

2-(4-Chlorobenzylsulfonylmethyl)-5-(4-chlorophenylsulfonylmethyl)-1,3,4-thiadiazole (12c). Yield 1.79 g (75%); white crystals; m. p. 201-203 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.94

(s, 2H, SO_2-CH_2), 4.20 (s, 2H, Ar-CH_2), 4.54 (s, 2H, $ArSO_2$-CH_2), 7.37-7.68 (m, 8H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 53.1 (SO_2-CH_2), 57.5 (Ar-CH_2), 58.8 ($ArSO_2$-CH_2), 157.4 (C-2), 160.2 (C-5), 125.2, 126.4, 127.3, 129.5, 131.8, 131.9, 133.5, 138.3 (aromatic carbons); IR (KBr): ν = 1630 (C=N), 1335, 1138 (SO_2); Anal. Calcd. for $C_{17}H_{14}Cl_2N_2O_4S_3$ (477.41): C, 42.77; H, 2.96; N, 5.87. Found: C, 42.82; H, 2.99; N, 5.83.

3,5-Bis(phenylsulfonylmethyl)-4-amino-1,2,4-triazoles (13a). Typical procedure

To a solution of **7a** (1.89 g, 5 mmol) in *n*-butanol (25 mL), hydrazine hydrate (0.75 g, 15 mmol) was added and refluxed for 3-4 h. Then, KOH (0.56 g, 10 mmol) was added to the reaction media and the precipitate formed was filtered. The solid obtained was acidified with conc. HCl to pH ≈ 3 and washed with water. The resultant solid was recrystallized from ethanol to get **13a**. Yield 1.39 g (71%); yellow solid; m. p. 139-141 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.22 (s, 4H, CH_2), 5.57 (bs, 2H, NH_2), 7.16-7.57 (m, 10H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 55.6 (CH_2), 161.7 (C-3 & C-5), 126.4, 129.5, 132.1, 133.7 (aromatic carbons); IR (KBr): ν = 3257, 3238 (NH_2), 1630 (C=N), 1338, 1135 (SO_2); Anal. Calcd. for $C_{16}H_{16}N_4O_4S_2$ (392.45): C, 48.97; H, 4.11; N, 14.28. Found: C, 49.05; H, 4.14; N, 14.35.

3,5-Bis(4-methylphenylsulfonylmethyl)-4-amino-1,2,4-triazoles (13b). Yield 1.59 g (76%); yellow solid; m. p. 162-164 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.23 (s, 6H, Ar-CH_3), 4.19 (s, 4H, CH_2), 5.63 (bs, 2H, NH_2), 7.18-7.62 (m, 8H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 21.5 (Ar-CH_3), 54.6 (CH_2), 161.8 (C-3 & C-5), 125.3, 127.5, 129.1, 132.4 (aromatic carbons); IR (KBr): ν = 3253, 3232 (NH_2), 1638 (C=N), 1330, 1132 (SO_2); Anal. Calcd. for $C_{18}H_{20}N_4O_4S_2$ (420.51): C, 51.41; H, 4.79; N, 13.32. Found: C, 51.47; H, 4.75; N, 13.38.

3,5-Bis(4-chlorophenylsulfonylmethyl)-4-amino-1,2,4-triazoles (13c). Yield: 1.68 g (73%); yellow solid; m. p. 171-173 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.16 (s, 4H, CH_2), 5.58 (bs, 2H, NH_2), 7.34-7.78 (m, 8H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 55.3 (CH_2), 162.5 (C-3 & C-5), 125.9, 130.7, 133.2, 136.8 (aromatic carbons); IR (KBr): ν = 3250, 3236 (NH_2), 1634 (C=N), 1336, 1128 (SO_2); Anal. Calcd. for $C_{16}H_{14}Cl_2N_4O_4S_2$ (461.34): C, 41.65; H, 3.06; N, 12.14. Found: C, 41.61; H, 3.08; N, 12.18.

3,5-Bis(benzylsulfonylmethyl)-4-amino-1,2,4-triazoles (14a). Typical procedure

To a solution of **8a** (2.03 g, 5 mmol) in 25 mL *n*-butanol, hydrazine hydrate (0.75 g, 15 mmol) was added and refluxed for 5-6 h. Then KOH (0.56 g, 10 mmol) was added to the reaction media and the precipitate formed was filtered. The solid obtained was acidified with conc. HCl to pH ≈ 3 and washed with water. The resultant solid was recrystallized from ethanol to get **14a**. Yield 1.40 g (67%); yellow solid; m. p. 215-217 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.14 (s, 4H, CH_2), 4.64 (s, 4H, Ar-CH_2), 5.66 (bs, 2H, NH_2), 7.27-7.45 (m, 10H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 55.7 (CH_2), 58.7 (Ar-CH_2), 163.2 (C-3 & C-5), 128.9, 129.6, 131.3, 133.5 (aromatic carbons); IR (KBr): ν = 3251, 3242 (NH_2), 1623 (C=N), 1334, 1128 (SO_2); Anal. Calcd. for $C_{18}H_{20}N_4O_4S_2$ (420.51): C, 51.41; H, 4.79; N, 13.32. Found: C, 51.45; H, 4.76; N, 13.35.

3,5-Bis(4-methylbenzylsulfonylmethyl)-4-amino-1,2,4-triazoles (14b). Yield 1.65 g (74%); yellow solid; m. p. 235-237 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.11 (s, 4H, CH_2), 4.59 (s, 4H, Ar-CH_2), 5.62 (bs, 2H, NH_2), 7.16-7.42 (m, 8H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 21.8 (Ar-CH_3), 55.4 (CH_2), 58.4 (Ar-CH_2), 162.8 (C-3 & C-5), 126.1, 128.7, 131.7, 134.2 (aromatic carbons); IR (KBr): v = 3258, 3244 (NH_2), 1632 (C=N), 1330, 1132 (SO_2); Anal. Calcd. for $C_{20}H_{24}N_4O_4S_2$ (448.56): C, 53.55; H, 5.39; N, 12.49. Found: C, 53.50; H, 5.43; N, 12.55.

3,5-Bis(4-chlorobenzylsulfonylmethyl)-4-amino-1,2,4-triazoles (14c). Yield 1.76 g (72%); yellow crystals; m. p. 258-260 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.17 (s, 4H, CH_2), 4.62 (s, 4H, Ar-CH_2), 5.68 (bs, 2H, NH_2), 7.31-7.65 (m, 8H, Ar-H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 54.9 (CH_2), 56.7 (Ar-CH_2), 163.2 (C-3 & C-5), 126.4, 129.5, 131.3, 135.5 (aromatic carbons); IR (KBr): v = 3262, 3249 (NH_2), 1628 (C=N), 1325, 1141 (SO_2); Anal. Calcd. for $C_{18}H_{18}Cl_2N_4O_4S_2$ (489.40): C, 44.18; H, 3.71; N, 11.45. Found: C, 44.42; H, 3.70; N, 11.50.

3-(Benzylsulfonylmethyl)-5-(phenylsulfonylmethyl)-4-amino-1,2,4-triazoles (15a). Typical procedure

To a solution of **9a** (1.96 g, 5 mmol) in *n*-butanol (25 mL), hydrazine hydrate (0.75 g, 15 mmol) was added and refluxed for 4-5 h. To this KOH (0.56 g, 10 mmol) was added and the precipitate formed was filtered. The solid obtained was acidified with conc. HCl to pH ≈ 3 and washed with water. The resultant solid was recrystallized from ethanol to get **15a**. Yield 1.38 g (68%); yellow solid; m. p. 166-168 °C; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ = 3.92 (s, 2H, SO_2-CH_2), 4.21 (s, 2H, Ar-CH_2), 4.50 (s, 2H, $ArSO_2$-CH_2), 5.60 (bs, 2H, NH_2), 7.29-7.47 (m, 10H, Ar-H); ^{13}C NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ = 53.2 (SO_2-CH_2), 56.9 (Ar-CH_2), 59.1 ($ArSO_2$-CH_2), 159.9 (C-3), 161.4 (C-5), 125.3, 125.9, 126.7, 127.4, 129.1, 131.3, 132.8, 134.3 (aromatic carbons); IR (KBr): v = 3259, 3241 (NH_2), 1633 (C=N), 1344, 1136 (SO_2); Anal. Calcd. for $C_{17}H_{18}N_4O_4S_2$ (406.48): C, 50.23; H, 4.46; N, 13.78. Found: C, 50.27; H, 4.42; N, 13.85.

3-(4-Methylbenzylsulfonylmethyl)-5-(4-methylphenylsulfonylmethyl)-4-amino-1,2,4-triazoles (15b). Yield 1.67 g (77%); yellow solid; m. p. 178-180 °C; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ = 2.21 & 2.25 (s, 6H, Ar-CH_3), 3.90 (s, 2H, SO_2-CH_2), 4.18 (s, 2H, Ar-CH_2), 4.48 (s, 2H, $ArSO_2$-CH_2), 5.58 (bs, 2H, NH_2), 7.26-7.52 (m, 8H, Ar-H); ^{13}C NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ = 21.2 & 21.7 (Ar-CH_3), 53.7 (SO_2-CH_2), 57.5 (Ar-CH_2), 59.4 ($ArSO_2$-CH_2), 158.7 (C-3), 161.7 (C-5), 122.1, 125.5, 127.1, 129.5, 131.4, 132.4, 133.0, 135.8 (aromatic carbons); IR (KBr): v = 3256, 3234 (NH_2), 1625 (C=N), 1343, 1142 (SO_2); Anal. Calcd. for $C_{19}H_{22}N_4O_4S_2$ (434.53): C, 52.52; H, 5.10; N, 12.89. Found: C, 52.60; H, 5.13; N, 12.93.

3-(4-Chlorobenzylsulfonylmethyl)-5-(4-chlorophenylsulfonylmethyl)-4-amino-1,2,4-triazoles (15c). Yield 1.66 g (70%); yellow solid; m. p. 207-209 °C; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ = 3.94 (s, 2H, SO_2-CH_2), 4.23 (s, 2H, Ar-CH_2), 4.53 (s, 2H, $ArSO_2$-CH_2), 5.64 (bs, 2H, NH_2), 7.37-7.70 (m, 8H, Ar-H); ^{13}C NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ = 53.5 (SO_2-CH_2), 57.3 (Ar-CH_2), 58.7 ($ArSO_2$-CH_2), 159.3 (C-3), 161.3 (C-5), 126.9, 127.0, 127.7,

129.3, 131.3, 132.8, 135.4, 137.9 (aromatic carbons); IR (KBr): ν = 3260, 3245 (NH_2), 1629 (C=N), 1352, 1139 (SO_2); Anal. Calcd. for $C_{17}H_{16}Cl_2N_4O_4S_2$ (475.37): C, 42.95; H, 3.39; N, 11.79. Found: C, 43.01; H, 3.40; N, 11.73.

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