Synthesis and antimicrobial activity of some derivatives of acylhydrazine including novel benzenediazasulfonamides

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Abstract

Some novel derivatives of acylhydrazine such as; 5-substituted-2-mercapto-1,3,4-oxadiazoles **2a-g** their corresponding S-esters **3a-g,** amides **4a-g** and benzenediazasulfonamides **6a-d** have been prepared. Twenty four synthesized compounds were screened *in vitro* for their antibacterial and some for their antifungal activities. Minimum Inhibitory Concentration (MIC) values of all the twenty four synthesized compounds were also determined. Some of the synthesized compounds exhibited significant antimicrobial activity.

Keywords: Acylhydrazine derivatives, benzenediazasulfonamides, 1, 3, 4- oxadiazole, acyloxyborohydride, antimicrobial activity

Introduction

Acylhydrazine derivatives are of significant interest due to their chemotherapeutic history.[1-5] Secondly, the sulfonamides constitute an important class of drugs, with several types of pharmacological agents possessing antibacterial, antifungal, diuretic, anticarbonic anhydrase, antithyroid, hypoglycemic and antitumour activity[6-10] among others. In continuation of our research in the chemistry of sulfonamides[11] and acylhydrazine derivatives,[12] we report herein the synthesis of novel acylhydrazine derivatives including benzenediazasulfonamides (Scheme 1)**.** This is a simple and efficient approach of synthesis of novel acylhydrazine derivatives and benzenediazasulfonamides.

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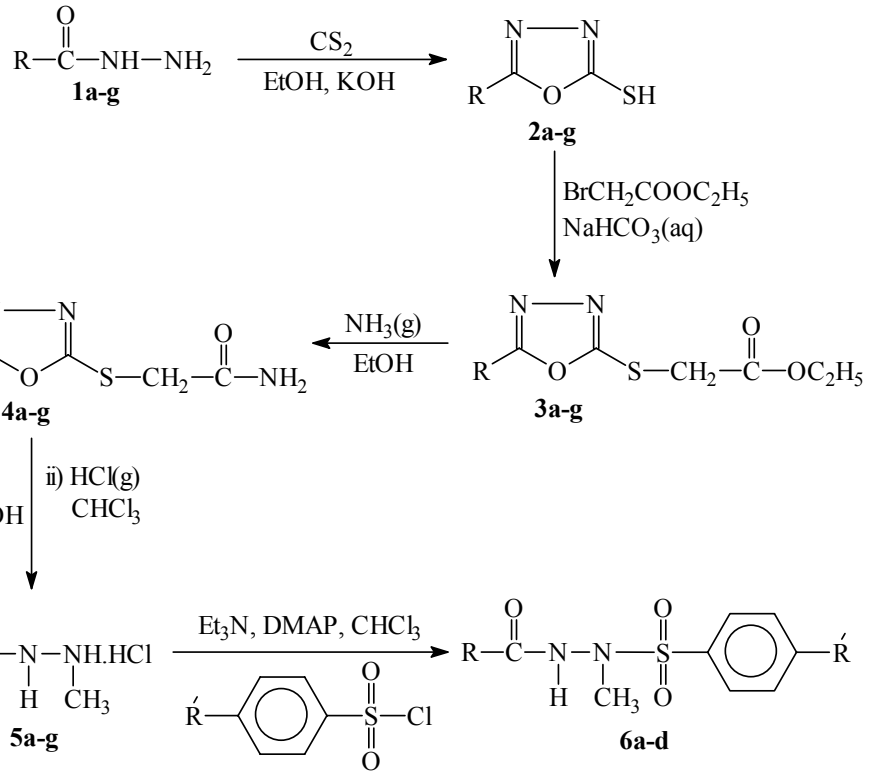
Results and Discussion

Novel derivatives of acylhydrazine such as; 5-substituted-2-mercapto-1,3,4-oxadiazoles **2a-g** their corresponding S-esters **3a-g**, amides **4a-g** and benzenediazasulfonamides **6a-d** have been prepared using reported and convenient methods (Scheme 1).



1-5	R
a	$-C_6H_5$
b	$-C_6H_4CH_3(3)$
c	$-C_6H_4OCH_3(3)$
d	$-C_6H_4Cl(2)$
e	$-C_6H_4Cl(3)$
f	$-C_6H_4Cl(4)$
g	$-C_5H_4N(3)$

6	R	R’
a	$-C_6H_5$	$-CH_3$
b	$-C_6H_5$	-Cl
c	$-C_6H_4Cl(3)$	$-CH_3$
d	$-C_6H_4Cl(3)$	-Cl

Scheme 1. Synthetic pathway for the preparation of derivatives of acylhydrazine **(2-6)**.

5-Substituted-2-mercapto-1,3,4-oxadiazoles **2a-g** were synthesized by the reported method.[13] Ester derivatives **3a-g** were synthesized by the reaction of ethylbromoacetate with 5-substituted-2-mercapto-1,3,4-oxadiazoles **2a-g** in saturated aqueous sodium hydrogencarbonate solution in excellent yields (81-83%).[14] The amide derivatives **4a-g** were synthesized by passing dry ammonia gas in ethanolic solution of their respective ester.[15] In an attempt to reduce the synthesized amide derivatives **4a-g** of substituted-1,3,4-oxadiazoles with acyloxyborohydride[16] in 1,4-dioxane, the oxadiazole ring was cleaved and the resulting product was isolated as acylhydrazine hydrochloride **5a-g**. It was, therefore, concluded that the oxadiazole ring is not stable to reduction in presence of acyloxyborohydride (sodium borohydride + acetic acid) under reflux conditions. The resulting acylhydrazine hydrochlorides **5a-g** were reacted directly with various sulfonylchlorides in presence of triethylamine and DMAP, to get novel benzenediazasulfonamides **6a-d.** The purity of the synthesized compounds was established by TLC in two different solvent systems (petroleum ether: ethyl acetate 2:1; chloroform: methanol 3:1). All the synthesized compounds were characterized by elemental, IR, ^{1}H NMR, ^{13}C NMR and mass spectral data.

The IR spectra of compounds **2a-g** displayed SH weak absorption at 2610–2540 cm^{-1} beside the C=S absorption at 1300–1124 cm^{-1}. In the ^{1}H NMR spectra, the NH and SH protons derived from tautomeric equilibrium, resonated between 13.90–8.75 ppm as a broad singlet integrating for one proton. In each case the absence of C=O absorption (1690–1670 cm^{-1}) of the corresponding substituted-1,3,4-oxadiazole indicated that the dehydrative cyclization reaction had occurred. In the IR spectra of compounds **3a-g**, the absence of absorption bands due to SH stretching frequencies of parent compounds **2a-g** and appearance of C=O strong absorption at 1745–1703 cm^{-1} clearly indicated the formation of the respective esters. The ^{1}H NMR of compounds **3a-g** showed disappearance of broad singlet of (SH + NH) and corresponding appearance of a triplet (1.35-1.17 ppm) and a quartet (4.11-1.35 ppm) integrating for three and two protons of the methyl and methylene groups respectively. The singlet at 4.35-4.15 ppm integrating for two protons was due to SCH_2 group. In the IR spectra, the characteristic absorption was found at 3393-3187 cm^{-1} for NH of primary amides **4a-g**. A shift was noted for the C=O absorption from esters ($\simeq$1750) to 1693-1672 cm^{-1} for amides. In ^{1}H NMR, two broad singlet, integrating for one proton in each case in the region 7.77-6.67 ppm for NH_2 group, the characteristic singlet integrating for two protons at 4.27-4.02 ppm attributed to SCH_2. The aromatic protons appeared at their usual values. These observations established the formation of synthesized primary amides **4a-g**. Mass spectral data of these compounds, described in the experimental protocol, further supported the structures of all the synthesized compounds.

The structures of the resulting novel benzenediazasulfonamides (*N*-substitutedbenzoyl-*N*′-methyl-*N*′-(4-substitutedbenzenesulfonyl)hydrazines) **6a-d** (Scheme 1), were established by spectral data. The IR spectra of compounds **6a-d**, displayed the NH absorption at 3317-3245 cm^{-1}, characteristic absorption of C=O at 1682–1672 cm^{-1} besides the SO_2 absorption in the usual range (1376-1141 cm^{-1}). In ^{1}H NMR spectra, the NH protons resonated between 9.67-9.54 ppm as a broad singlet integrating for one proton. Moreover, the proton signals due to NCH_3

group of these compounds were resonated in the region 3.31–3.02 ppm as a singlet integrating for the three protons. The different aromatic protons were found in their usual range. In the ^{13}C NMR of these compounds, the characteristic signal belonging to carbonyl carbon appeared between 177–171 ppm. Complete ^{13}C NMR data is given in the experimental protocol. Molecular ion peaks along with the base peaks in mass spectra, and elemental analysis/HRMS values, in the acceptable range, provided an additional evidence to establish the structures of the synthesized compounds. It is worth noting that crystals of compound **6a** were analyzed by X-ray single crystallography to assign the exact structural geometry, and reported earlier by our research group.[17]

Twenty four newly synthesized compounds were screened *in vitro* for their antibacterial and some for their antifungal activities.

Antimicrobial activity

Twenty four newly synthesized compounds have been tested *in vitro* for their antibacterial activity against *Staphylococcus aureus* (ATCC-25923), *Bacillus subtilis* (recultured), Escherichia *coli* (ATCC-25922), *Pseudomonas picketti* (recultured) and *Micrococcus luteus* (recultured) bacteria by agar well diffusion method.[18] DMSO was used as a control solvent, Roxythromycin and Cefixime as a standard drug. After 24 hrs of incubation at 37 °C, the zone of inhibition was measured in mm. The investigation results are listed in Table 1**.** The results showed that all compounds were active against *Escherichia coli* except **4f** and **6d**. It is worth noting here that compounds **6c** and **6d** showed moderate (15 mm) to significant activity (18 mm) against *Staphylococcus aureus,* respectively. The other compounds showed none to low activity as displayed in Table 1.

The investigation on the structure-activity relationship (SAR), shows that, in general, free SH at position 2 of the oxadiazole ring, presence of the chloro group at the phenyl substituent and 3-pyridyl of the oxadiazole ring enhanced the antibacterial action of the synthesized compounds. Minimum Inhibitory Concentration (MIC) values of all the twenty four synthesized compounds were determined by agar well diffusion method[18] and the results are displayed in Table 1. Five selected representatives of newly synthesized compounds **2e, 3d, 4e, 6c** and **6d** were screened *in vitro* for their antifungal activity against six species using agar plate technique.[19] The linear growth of the fungus was obtained by measuring the diameter of the fungal colony after seven days. The amount of growth inhibition in each case was calculated as percentage inhibition. The screening results are given in Table 2, indicated that compounds **3d** and **6c** exhibit moderate activity (60%) against *Aspergillus flavus and Trichphyton longifusus respectivly*, whereas, compound **6d** showed significant activity (90%) against *Candida albicans*. It is worthwhile to note that compound **6d** exhibits significant (maximum) antibacterial and antifungal activities, possibly due to the presence of chloro group on both sides of the phenyl substituent of the oxadiazole ring, and the sulfonamido moiety. Whereas, in case of compounds **3** and **4** the substitution at free SH (ester and amide derivatives) diminished the antimicrobial activity as given in Table 1 and 2.

Table 1. Antibacterial activity and minimum inhibitory concentrations (MIC) of the synthesized compounds **2b-g, 3a-g, 4a-g, 6a-d**

Comp No.	*Escherichia coli* (MIC)	*Pseudomonas picketti* (MIC)	*Bacillus subtilis* (MIC)	*Staphylococcus aureus* (MIC)	*Micrococcus luteus* (MIC)
2b	11.60 (0.4)	-	-	-	-
2c	11.16 (0.2)	-	-	-	-
2d	12.86 (0.5)	-	-	10.95 (0.8)	-
2e	13.42 (0.2)	-	-	-	-
2f	12.47 (0.6)	-	10.10 (1.0)	-	-
2g	12.20 (0.5)	-	-	-	-
3a	11.35 (0.8)	-	-	11.85 (0.6)	-
3b	11.90 (0.6)	-	-	-	-
3c	11.37 (0.8)	10.32 (0.8)	-	-	-
3d	10.18 (0.8)	10.62 (0.8)	-	-	-
3e	14.65 (0.8)	11.42 (0.6)	-	-	10.20 (1.0)
3f	10.85 (0.8)	-	-	-	-
3g	10.30 (0.6)	10.35 (0.8)	-	-	-
4a	10.37 (0.8)	-	-	-	-
4b	11.12 (0.8)	-	-	-	-
4c	10.32 (0.8)	-	-	-	-
4d	10.97 (0.8)	10.10 (1.0)	-	-	-
4e	10.47 (0.8)	-	2.85 (1.0)	-	10.60 (0.8)
4f	-	10.95 (0.8)	-	-	-
4g	11.22 (0.8)	-	-	13.10 (0.5)	-
6a	10.75 (0.8)	9.70 (1.0)	-	-	-
6b	11.37 (0.6)	9.85 (1.0)	-	-	-
6c	10.15 (1.0)	10.05 (1.0)	2.90 (1.0)	15.05 (0.2)	-
6d	-	10.42 (0.8)	-	18.25 (0.08)	-
Roxythromy-cin (Standard)	15.00	30.60	11.80	26.45	13.20
Cefixime (Standard)	29.90	15.02	29.90	36.10	34.80

Zone diameter of growth inhibition (mm) after 24 hours, < 10 mm (-), concentration 1 mg/mL in DMSO.

- () Minimum Inhibitory Concentrations (MIC) in mg/mL
- The data represents the mean values of two replicates

Table 2. Antifungal activity of the synthesized compounds **2e, 3d, 4e, 6c, 6d**

Name of Fungi	Compd. Nos. and Inhibition Zones (%)					Standard drug (%)
	2e	**3d**	**4e**	**6c**	**6d**	
Trichphyton longifusus	35	40	30	60	0	Miconazole (100)
Candida albicans	0	0	40	0	90	Miconazole (90)
Aspergillus flavus	50	60	0	0	0	Amphotericin (90)
Microsporum Canis	40	0	0	0	0	Miconazole (90)
Fusarium Solani	40	0	0	50	60	Miconazole (90)
Candida glabrata	0	0	0	0	0	Miconazole (100)

Conc. of Sample 200μg/mL of DMSO at 27°C, Incubation period 07 days, Inhibition Zones (%).

Experimental Section

General Procedures. Melting points were determined on a Gallenkamp digital melting point apparatus and are uncorrected. IR spectra were recorded in KBr disc on a FT-IR model FTS 3000 MX spectrometer. NMR spectra were recorded in Acetone-d_6, DMSO-d_6 or $CDCl_3$ on a Bruker (300, 400 and 500 MHz; ^{13}C, 75 MHz) spectrophotometer. The chemical shifts of proton signals are in parts per million (ppm) downfield from tetramethylsilane (TMS) as an internal standard. EI-MS spectra were recorded on MAT 311A mass spectrometer (EI at 70 eV). Elemental analysis was performed on a Carlo Erba 1106 elemental analyzer. Thin layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} aluminum sheets (Merck).

General procedure for the preparation of 5-substituted-2-mercapto-1,3,4-oxadiazoles (44a-w)

These compounds were prepared according to the procedure reported in the literature[13] (Scheme 1).To a solution of appropriate carboxylic acid hydrazide **1 (**50 mmol) in ethanol (150-200 mL), carbon disulfide (55 mmol) was added. This was followed by the addition of potassium hydroxide (50 mmol) dissolved in 25 mL of water. The reaction mixture was stirred and subjected to reflux. The progress of the reaction was monitored by TLC in each case using pet.ether: ethyl acetate (2:1). After reaction completion, excess ethanol was distilled off. The crude solid obtained was dissolved in excess water and acidified with 4N HCl to pH 2-3 (Congo

red). The separated product was filtered, washed with water and recrystallized from aqueous ethanol (20-30%).

2-Mercapto-5-phenyl-1,3,4-oxadiazole (2a). Reaction time 20.5 hours, yield = 87%, m.p. = 216-217 °C (lit. m.p. = 218 °C, yield = 72%).[20]

2-Mercapto-5-(3-methylphenyl)-1,3,4-oxadiazole (2b). Reaction time 18 hours, yield = 82%, m.p. = 201-203 °C (lit. m.p. = 205 °C, yield = 80%).[20]

2-Mercapto-5-(3-methoxyphenyl)-1,3,4-oxadiazole (2c). Reaction time 19 hours, yield = 89%, m.p. = 188-189 °C. IR (ν_{max}, KBr, cm^{-1}): 3043 (Ar−H), 2551 (SH), 1592 (C=N), 1259 (C=S). ^{1}H NMR (Acetone-d_6, 400 MHz) δ(ppm): 3.88 (s, 3H, OCH_3), 7.13 (d, J = 5.1 Hz, 1H, ArH), 7.57-7.54 (m, 2H, ArH), 7.85 (s, 1H, ArH, J = 5.0 Hz), 13.13 (s(br), NH+SH). EI-MS; m/z (rel. int. %): 208 (M^+, 73), 176 (8), 167 (2), 148 (36), 136 (3), 135 (28), 133 (78), 119 (4), 107 (7), 105 (22), 104 (4), 77 (22), 69 (40), 57 (100), 55 (56). Analysis calculated for $C_9H_8N_2O_2S$ (208.235): C, 51.91; H, 3.87; N, 13.45; S, 15.39. Found: C, 51.52; H, 3.55; N, 13.57; S, 15.61.

5-(2-Chlorophenyl)-2-mercapto-1,3,4-oxadiazole (2d). Reaction time 20 hours, yield = 85%, m.p. = 171-172 °C (lit. m.p. = 170 °C, yield = 80%).[20]

5-(3-Chlorophenyl)-2-mercapto-1,3,4-oxadiazole (2e). Reaction time 21 hours, yield = 91%, m.p. = 167-169 °C. IR (ν_{max}, KBr, cm^{-1}): 3056 (Ar-CH), 1682 (C=N), 1265 (C=S). ^{1}H NMR (Acetone-d_6, 300 MHz) δ(ppm): 7.68 (d, 1H, ArH, J = 6.0 Hz), 7.78 (bs, 1H, ArH), 7.92 (s, 1H, ArH), 7.94-7.96 (m, 1H, ArH), 12.91 (s(br), 1H, NH+SH). EI-MS (%): 212 (M^+, 90), 155 (8), 139 (100), 111 (95), 76 (15), 75 (47). HRMS for $C_8H_5N_2OSCl$ (212.654). Found: (212.653).

5-(4-Chlorophenyl)-2-mercapto-1,3,4-oxadiazole (2f). Reaction time 22 hours, yield = 79%, m.p. = 175-177 °C (lit. m.p. = 175 °C, yield = 76%).[20]

2-Mercapto-5-(3-pyridyl)-1,3,4-oxadiazole (2g). Reaction time required 21 hours, yield = 86 %, m.p. = 235 °C (lit. m.p. = 233°C, yield = 83%).[20b]

General procedure for the synthesis of [5-(Aryl)-1,3,4-oxadiazol-2-ylthio]esters (3a-g)

These esters were prepared according to the procedure reported in the literature[14] (Scheme 1). The reaction was comprised of two steps; the first step is the salt formation by reacting corresponding 5-substituted-2-mercapto-1,3,4-oxadiazole with aqueous sodium bicarbonate solution, and in the second step the salt was treated with ethylbromoacetate to produce the respective ester. Corresponding 2-mercapto-1,3,4-oxadiazole (20 mmol) was dissolved in saturated aqueous sodium bicarbonate solution by magnetic stirring. The required ethylbromoacetate (20 mmol) in absolute ethanol (10 mL) was added to the reaction mixture with continuous stirring. The progress of the reaction was monitored by TLC (silica, ethylacetate : pet.ether 1:2) in each case. After reaction completion, the resulting solid was filtered off, washed with water and recrystallized from aqueous ethanol (60%).

Ethyl-(5-phenyl-1,3,4-oxadiazol-2-ylthio)acetate (3a). Reaction time 4 hours, yield = 83 %, m.p. = 71-72 °C. IR (ν_{max}, KBr, cm^{-1}): 3037 (Ar−CH), 1741 (C=O), 1586 (C=N), 702 (C−S). ^{1}H NMR (Acetone-d_6, 400 MHz) δ(ppm): 1.24 (t, 3H, J = 7.2 Hz, CH_3), 4.15 (q, 2H, J = 7.2 Hz,

CH_2−O), 4.23 (s, 2H, CH_2−S), 7.25-7.44 (m, 5H, ArH). EI-MS; m/z (rel. int., %): 264 (M^+, 11), 190 (2), 117 (7), 105 (100), 77 (19).

Ethyl-[5-(3-methylphenyl)-1,3,4-oxadiazol-2-ylthio]acetate (3b). Reaction time 4 hours, yield = 80%, m.p. = 77-78 °C. IR (ν_{max}, KBr, cm^{-1}): 3051 (Ar−CH), 1731 (C=O), 1593 (C=N), 695 (C−S). ^{1}H NMR (Acetone-d_6, 400 MHz) δ(ppm): 1.21 (t, 3H, J = 7.1 Hz, CH_3), 2.38 (s, 3H, CH_3−Ar), 4.12 (q, 2H, J = 7.0 Hz, CH_2−O), 4.21 (s, 2H, CH_2−S), 7.22 (d, 1H, J = 8.1 Hz, ArH), 7.47-7.51 (m, 2H, ArH), 7.78 (s, J = 9 Hz, 1H, ArHz), EI-MS; m/z (rel. int., %): 278 (M^+, 78), 205 (3). 192 (2), 135 (12), 117 (25), 91 (36), 76 (5), 65 (7).

Ethyl-[5-(3-methoxyphenyl)-1,3,4-oxadiazol-2-ylthio]acetate (3c). Reaction time 6 hours, yield = 79 %, m.p. = 80-82 °C. IR (ν_{max}, KBr, cm^{-1}): 3041 (Ar−CH), 1729 (C=O), 1607 (C=N), 702 (C−S). ^{1}H NMR (Acetone-d_6, 400 MHz) δ(ppm): 1.19 (t, 3H, J = 7.0 Hz, CH_3), 3.87 (s, 3H, OCH_3), 4.11 (q, 2H, J = 7.0 Hz, CH_2−O), 4.22 (s, 2H, CH_2−S), 7.12 (d, 2H, J = 8.0 Hz, ArH), 7.44-7.47 (m, 2H, ArH), 7.72 (s, J = 9 Hz, 1H, ArHz), EI-MS; m/z (rel. int., %): 294 (M^+, 75), 275 (37), 221 (3), 208 (4), 135 (100), 133 (21), 92 (11), 77 (4).

Ethyl-[5-(2-chlorophenyl)-1,3,4-oxadiazol)-2-ylthio]acetate (3d). Reaction time 5 hours, yield = 89%, m.p. = 81-83 °C. 279. IR (ν_{max}, KBr, cm^{-1}): 3061 (CH−Ar), 1733 (C=O), 1595 (C=N), 705 (C−S). ^{1}H NMR (Acetone-d_6, 500 MHz) δ(ppm): 1.25 (t, J = 7.0 Hz, 3H), 4.16 (q, J = 7.2 Hz, 2H), 7.81-7.89 (m, 2H, ArH), 7.93 (d, 1H, J = 7.5 Hz, ArH), 7.99 (d, 1H, J = 7.4 Hz, ArH). EI-MS; m/z (rel. int. %): 298 (M^+, 68), 253 (6), 225 (6), 212 (8), 179 (100), 155 (37), 139 (66), 111(17),73 (5).

Ethyl-[5-(3-chlorophenyl)-1,3,4-oxadiazol)-2-ylthio]acetate (3e). Reaction time 5 hours, yield = 91%, m.p. = 79-80 °C. 275. IR (ν_{max}, KBr, cm^{-1}): 3055 (CH−Ar), 1727 (C=O), 1582 (C=N), 695 (C−S). ^{1}H NMR (Acetone-d_6, 500 MHz) δ(ppm): 1.22 (t, 3H, J = 7.0 Hz, CH_3), 4.23 (bs, 2H, CH_2), 4.18 (q, 2H, J = 7.0 Hz, CH_2O), 7.59-7.65 (m, 1H, ArH), 7.72 (d, 1H, J = 8.0 Hz, ArH), 7.91 (s, 1H, ArH), 7.95 (d, 1H, J = 8.0 Hz, ArH). EI-MS; m/z (rel. int., %): 298 (M^+, 61), 253 (5), 225 (3), 212 (9), 179 (100), 155 (31), 139 (67), 111 (12), 75 (4).

Ethyl-[5-(4-chlorophenyl)-1,3,4-oxadiazol)-2-ylthio]acetate (3f). Reaction time 6 hours, yield = 86%, m.p. = 83-85 °C. 277. IR (ν_{max}, KBr, cm^{-1}): 3057 (CH−Ar), 1741 (C=O), 1586 (C=N), 696 (C−S). ^{1}H NMR (Acetone-d_6, 400 MHz) δ(ppm): 1.23 (t, 3H, J = 7.1 Hz, CH_3), 4.19 (q, 2H, J = 7.1 Hz, CH_2O), 4.24 (s, 2H, CH_2−S), 7.62 (d, 2H, J = 8.5 Hz, ArH), 8.01 (d, 2H, J = 8.6 Hz, ArH). EI-MS; m/z (rel. int. %): 298 (M^+, 93), 253 (7), 225 (9), 212 (6), 179 (100), 155 (39), 139 (94), 137 (47), 111 (51), 75 (19).

Ethyl-[5-(3-pyridyl)-1,3,4-oxadiazol)-2-ylthio]acetate (3g). Reaction time 5 hours, yield = 75%, m.p. = 71-73 °C.: 274. IR (ν_{max}, KBr, cm^{-1}): 3051 (CH−Ar), 1741 (C=O), 1601 (C=N), 707 (C−S). ^{1}H NMR (Acetone-d_6, 400 MHz) δ(ppm): 1.24 (t, 3H, J = 7.2 Hz, CH_3), 4.20 (q, 2H, J = 7.4 Hz, CH_2O), 4.27 (bs, 2H, CH_2−S), 7.59 (dd, 1H, J = 4.5 Hz, J = 4.6 Hz, ArH), 8.31-8.34 (m, 1H, ArH), 8.76 (dd, 1H, J = 6.61 Hz, J = 3.3, ArH), 9.16 (d, 1H, J = 2.0 Hz, ArH). EI-MS; m/z (rel. int., %): 265 (M^+, 14), 192 (2), 160 (7), 146 (35), 119 (5), 106 (71), 78 (99), 51 (100).

General procedure for synthesis of [5-(substitutedaryl)-1,3,4-oxadiazol-2-ylthio]amides (4a-g)

These amides were prepared following the standard procedure reported in the literature[15] with slight modification (Scheme 1). Respective [5-(aryl)-1,3,4-oxadiazol-2-ylthio]ester (10 mmol) was dissolved in dry ethanol (60 mL). Dry ammonia gas was bubbled through the ester solution, with continuous stirring, for 4-7 hours. The progress of the reaction was monitored by TLC (silica; methanol: chloroform; 1:2). The excess solvent was distilled off under reduced pressure. The crude product was washed with cold water and recrystallized from aqueous ethanol (30%).

[5-Phenyl-1,3,4-oxadiazol-2-ylthio]acetamide (4a). Reaction time 5 hours, yield = 87%, m.p. = 178-180 ^{o}C. IR (ν_{max}, KBr, cm^{-1}): 3286 (NH), 3055 (CH–Ar), 1675 (C=O), 1582 (C=N), 695 (C–S). ^{1}H NMR (Acetone – *d*$_6$, 400 MHz) δ(ppm): 4.15 (s, 2H, CH_2), 6.68 (s (br),, 1H, NH, exchangeable with D_2O), 7.26 (bs, 1H, NH, exchangeable with D_2O), 7.55-7.61 (m, 3H, ArH), 8.01 (dd, 2H, *J* = 7.9 Hz, *J* = 1.6 Hz, ArH). EI–MS; m/z (rel. int. %): 235 (M^+, 20), 192 (32), 145 (54), 118 (3), 117 (2), 105 (69), 90 (7), 77 (100), 89 (4), 78 (79).

[5-(3-Methylphenyl-1,3,4-oxadiazol-2-ylthio)]acetamide (4b). Reaction time 4 hours, yield = 80%, m.p. = 184-186 ^{o}C. IR (ν_{max}, KBr, cm^{-1}): 3310 (NH), 3066 (CH–Ar), 1681 (C=O), 1597 (C=N), 702 (C–S). ^{1}H NMR (Acetone – d_6, 400 MHz) δ(ppm): 2.37 (s, 3H, CH3–Ar), 4.10 (s, 2H, CH2), 7.34 (s(br),, 1H, exchangeable with D_2O), 7.36 (d, 1H, *J* = 7.9 Hz, ArH), 7.47-7.52 (m, 2H, ArH), 7.75 (bs, 1H, NH, exchangeable with D_2O), 7.83 (d, 1H, *J* = 8.0 Hz, ArH). EI–MS; m/z (rel. int. %): 235 (M^+, 63), 206 (49), 177 (2), 159 (100), 131 (15), 119 (92), 118 (14), 177 (44), 91 (69), 77 (7), 65 (18).

[5-(3-Methoxyphenyl)-1,3,4-oxadiazol-2-ylthio]acetamide(4c). Reaction time 5 hours, yield = 87%, m.p. = 213-215 ^{o}C. IR (ν_{max}, KBr, cm^{-1}): 3315 (NH), 3051 (CH–Ar), 1672 (C=O), 1586 (C=N), 702 (C–S). ^{1}H NMR (Acetone – *d*$_6$, 400 MHz) δ(ppm): 3.86 (s, 3H, OCH_3), 4.12 (s, 2H, CH_2), 7.21 (dd, 1H, *J* = 7.5 Hz, 7.6Hz, ArH), 7.26 (s(br),, 1H, NH exchangeable with D_2O), 7.37 (bs, 1H, NH), 7.40-7.45 (m, 2H, ArH), EI–MS; m/z (rel. int. %): 235 (M^+, 49), 207 (11), 176 (5), 167 (2), 148 (35), 136 (12), 135 (100), 133 (57), 107 (9), 105 (19), 77 (81).

[5-(2-Chlorophenyl)-1,3,4-oxadiazol-2-ylthio]acetamide(4d). Reaction time 5 hours, yield = 79 %, m.p. = 185-187 ^{o}C. IR (ν_{max}, KBr, cm^{-1}): 3310 (NH), 3056 (CH–Ar), 1675 (C=O), 1597 (C=N), 702 (C–S). ^{1}H NMR (DMSO – *d*$_6$, 400 MHz) δ(ppm): 4.13 (s, 2H, CH_2), 7.35 (s(br), 1H, NH, exchangeable with D_2O), 7.54 (s(br),, 1H, NH, exchangeable with D_2O), 7.67 (d, 1H, *J* = 7.0 Hz, ArH), 7.79 (m, 1H, ArH), 7.91-7.97 (m, 2H, ArH). EI–MS; m/z (rel. int. %): 269 (M^+, 7), 253 (4), 211 (51), 155 (9), 139 (100), 111 (81), 75 (29).

[5-(3-Chlorophenyl)-1,3,4-oxadiazed-2-ylthio]acetamide (4e). Reaction time 6 hours, yield = 85%, m.p. = 198-199 ^{o}C. IR (ν_{max}, KBr, cm^{-1}): 3295 (NH), 3051 (CH–Ar), 1672 (C=O), 1595 (C=N), 695 (C–S). ^{1}H NMR (DMSO – *d*$_6$, 300 MHz) δ(ppm): 4.11 (s, 2H, CH_2), 7.38 (s(br), 1H, NH, exchangeable with D_2O), 7.59-7.72 (m, 2H, ArH), 7.78 (s(br),, 1H, NH, exchangeable with D_2O), 7.91 (s, 1H, ArH), 7.95 (d, 1H, *J* = 7.5 Hz, ArH). EI–MS; m/z (rel. int. %): 269 (28), 228 (20), 226 (20), 226 (57), 179 (56), 141 (29), 139 (100), 137 (22), 113 (30), 111 (94), 89 (18), (76) (15), 75(46).

[5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-ylthio]acetamide(4f). Reaction time 4 hours, yield = 83%, m.p. = 202-204 ^{o}C. IR (ν_{max}, KBr, cm^{-1}): 3306 (NH), 3041 (CH–Ar), 1680 (C=O), 1597 (C=N), 702 (C–S). ^{1}H NMR (Acetone – d_6, 400 MHz) δ(ppm): 4.16 (s, 2H, CH_2), 6.67 (s(br), 1H, exchangeable with D_2O), 7.26 (s(br),, 1H, NH, exchangeable with D_2O), 7.62 (d, 2H, J = 8.5 Hz, ArH), 8.01 (d, 2H, J = 8.6 Hz, ArH). EI–MS; m/z (rel. int. %): 269 (M^+, 72), 228 (52), 226 (73), 181 (61), 180 (25), 179 (87), 155 (33), 151 (39), 141 (66), 140 (40), 139 (100), 123 (19), 113 (52), 102 (37), 76 (37), 75(70).

[5-(3-Pyridyl)-1,3,4-oxadiazol-2-ylhtio]acetamide (4g). Reaction time 6.5 hours, yield = 74%, m.p. = 191-193 ^{o}C. IR (ν_{max}, KBr, cm^{-1}): 3317 (NH), 3051 (CH–Ar), 1687 (C=O), 1594 (C=N), 703 (C–S). ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm): 4.11 (s, 2H, CH_2), 7.24 (s, 1H, NH) 7.47 (m, 1H, ArH), 8.31 (d, 1H, J = 6.7 Hz, ArH), 8.75 (d, 1H, J = 5.0 Hz, ArH), 9.21 (m, 1H, ArH). EI–MS; m/z (rel. int. %): 236 (M^+, 9), 193 (100), 146 (11), 106 (39), 90 (3), 89 (4), 78 (79).

General procedure for the synthesis of benzenediazasulfonamides [N-substituted-benzoyl-N′-methyl-N′-(4-substitutedbenzenesulfonyl)-hydrazines] 6a-d

These benzenediazasulfonamides were obtained during an attempt to reduce [5-substituted-1,3,4-oxadiazol-2-ylthio]acetamides **4** to their corresponding amines, for the preparation of their corresponding sulfonamides (Scheme 1). The procedure adopted was reported by Umino et al.[16] To a stirred suspension of sodium borohydride (50 mmol) and corresponding amide (10 mmol) in 1,4-dioxane (25 mL) was added acetic acid (50 mmol) in dioxane (10 mL) over a period of 10 minutes at 10^{o}C, and the resulting mixture was stirred under reflux for 1.5-2.5 hours. The progress of the reaction was monitored by TLC (silica; pet. ether: ethylacetate; 2:1). After completion of reaction, the solvent was distilled off and the excess reagent was decomposed with water and extracted with chloroform (3 x 50 mL). The extract was washed with water and dried over anhydrous sodium sulfate. The resulting chloroform layer was treated with dry hydrogen chloride, evaporated in vacuo, and the residue was crystallized from methanol-ether to corresponding acylhydrazine hydrochloride **5**. The resulting acylhydrazine hydrochlorides were used, without further purification, in the next step, for the synthesis of corresponding benzenediazasulfonamides **6a-d**. Appropriate acylhydrazine hydrochloride **5** (2 mmol), triethylamine (4 mmol) and DMAP (25 mg) in anhydrous chloroform were stirred at room temperature for fifteen minutes. An appropriate sulfonyl chloride (2.2 mmol), dissolved in anhydrous chloroform, was then added to the reaction mixture in portions, with the help of dropping funnel. The reaction mixture was stirred at room temperature for 23-25 hours. The progress of the reaction was monitored by TLC (silica; methanol: chloroform; 1:2). After reaction completion, the reaction mixture was washed with saturated solution of sodium bicarbonate, brine and water followed by an extraction with chloroform (2 x 25 mL). Combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The isolated product was purified by recrystallization from aqueous ethanol (30%).

***N*-Benzoyl-*N*′-methyl-*N*′-(4-methylbenzenesulfonyl)hydrazine (6a).** Reaction time 25 hours, yield = 81%, m.p. = 190-191 ^{o}C. IR (ν_{max}, KBr, cm^{-1}): 3254 (NH), 3053 (CH-Ar), 1672 (C=O),

1354, 1157 (SO_2). ^{1}H NMR (Acetone-d_6, 500 MHz) δ(ppm): 2.43 (s, 3H, CH_3−Ar), 3.19 (s, 3H, NCH_3), 7.41 (d, 2H, *J* = 8.0 Hz, ArH), 7.44-7.56 (m, 5H, ArH), 7.79 (d, 2H, *J* = 7.8 Hz, ArH), 9.55 (s(br), 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ(ppm): 21.1, 41.5, 127.5, 127.8, 128.2, 128.5, 129.5, 137.3, 139.1, 139.2, 177.7. EI-MS, m/z (rel. int. %): 305 (M^++1, 2), 304 (M^+, 6), 160 (7), 258 (5), 256 (6), 212 (7), 198 (4), 183 (3), 156 (4), 155 (9), 150 (17), 149 (100), 139 (8), 119 (12), 106 (46), 105 (100), 103 (2), 91 (35), 77 (92), 76 (3), 65 (10). Anal. calcd. for $C_{15}H_{16}N_2O_3S$ (304.3646): C, 59.19; H, 5.31; N, 9.20; S, 10.53. Found: C, 59.42; H, 5.10; N, 9.31; S, 10.25.

***N*-Benzoyl-*N′*-methyl-*N′*-(4-chlorobenzenesulfonyl)hydrazine (6b).** Reaction time 24 hours, yield = 75%, m.p. = 195-197 °C. IR (ν_{max}, KBr, cm^{-1}): 3245 (NH), 3041 (CH-Ar), 1678 (C=O), 1375, 1166 (SO_2).^{1}H NMR (Acetone-d_6, 500 MHz) δ(ppm): 3.25 (s, 3H, NCH_3), 7.41-7.57 (m, 3H, ArH), 7.64 (d, 2H, *J* = 8.6 Hz, ArH), 7.79 (d, 2H, *J* = 8.5 Hz, ArH), 7.92 (d, 2H, *J* = 8.6 Hz, ArH), 9.72 (bs, 1H, NH). ^{13}C NMR (Acetone-d_6, 75 MHz) δ(ppm): 42.2, 125.3, 128.2, 130.1, 132.1, 132.6, 136.5, 138.9, 146.8, 171. 5. EI-MS, m/z (rel. int. %): 324 (2), 279 (2), 232 (3), 177 (3), 175 (7), 150 (9), 149 (95), 106 (23), 105 (100), 177 (44), 76 (3), 75 (4). Anal. calcd. for $C_{14}H_{13}N_2O_3S$ (324.7826): C, 51.77; H, 4.03; N, 8.63; S, 9.87. Found: C, 51.45; H, 4.32; N, 8.82; S, 9.73.

***N*-(3-Chlorobenzoyl)-*N′*-methyl-*N′*-(4-methylbenzenesulfonyl)hydrazine (6c).** Reaction time 23 hours; yield = 85%, m.p. = 185-187 °C. IR (ν_{max}, KBr, cm^{-1}): 3235 (NH), 3031 (CH-Ar), 1675 (C=O), 1356, 1158 (SO_2). ^{1}H NMR (Acetone-d_6, 400 MHz) δ(ppm): 2.37 (s, 3H, CH_3−Ar), 3.29 (s(br), 3H, NCH_3), 7.28 (d, 2H, *J* = 7.9 Hz, ArH), 7.40 (d, 1H, *J* = 8.0 Hz, ArH), 7.49 (d, 1H, *J* = 7.8 Hz, ArH), 7.54-7.58 (m, 1H, ArH), 7.72 (d, 2H, *J* = 8.1 Hz, ArH), 7.81 (d, 1H, *J* = 7.6 Hz, ArH), 7.95 (s(br), 1H, ArH), 9.62 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ(ppm): 21.2, 40.7 (NCH_3), 125.9, 127.7, 128.3, 128.7, 130.2, 131.2, 133.6, 138.3, 145.9, 172.1 (C=O). EI-MS; m/z (rel. int. %): 339 (M^+, 2), 246 (6), 212 (5), 186 (2), 185 (17), 184 (12), 183 (51), 172 (37), 156 (4), 155 (21), 142 (5), 141 (61), 140 (16), 139 (100), 111 (27), 91 (53), 75 (6), 65 (12). Anal. calcd. for $C_{15}H_{15}N_2O_3SCl$ (338.8096): C, 53.18; H, 4.46; N, 14.17; S, 9.46. Found: C, 53.31; H, 4.27; N, 14.48; S, 9.27.

***N*-(3-Chlorobenzoyl)-*N′*-methyl-*N′*-(4-chlorobenzenesulfonyl)hydrazine (6d).** Reaction time 24 hours; yield = 78%, m.p. = 193-195 °C. IR (ν_{max}, KBr, cm^{-1}): 3317 (NH), 3065 (CH-Ar), 1682 (C=O), 1375, 1166 (SO_2). ^{1}H NMR (Acetone-d_6, 500 MHz) δ(ppm): 3.31 (NCH_3), 7.51 (d, 1H, *J* = 8.0 Hz, ArH), 7.58-7.62 (m, 1H, ArH), 7.68 (d, 1H, *J* = 8.0 Hz, ArH), 7.78 (d, 2H, *J* = 8.5 Hz, ArH), 7.99 (bs, 1H, ArH), 7.97 (d, 2H, *J* = 8.5 Hz, ArH), 9.67 (s(br), 1H, NH). EI-MS; m/z (rel. int. %): 359 (M^+, 2), 295 (3), 246 (2), 212 (17), 185 (2), 184 (5), 183 (50), 172 (27), 156 (4), 155 (61), 140 (21), 139 (100), 111 (37), 75 (5), 65 (12). Anal. calcd. for $C_{14}H_{12}N_2O_3SCl_2$ (359.2276): C, 46.81; H, 3.37; N, 7.81; S, 8.92. Found: C, 46.50; H, 3.12; N, 7.75; S, 9.20.

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