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Microwave-Assisted Synthesis and Anti-HIV Activity of New Benzenesulfonamides Bearing 2,5-Disubstituted-1,3,4-oxadiazole Moiety

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ABSTRACT: *New benzenesulfonamides, most of which are chiral, incorporating 1,3,4-oxadiazole, and selected amino acid entities have been synthesized, using the microwave irradiation method. Most of the synthesized compounds were tested against HIV activity.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:425–431, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20316

INTRODUCTION

The increasing environmental consciousness throughout the world has put a pressing need to develop an alternate synthetic approach for biologically and synthetically important compounds. However, the short reaction time offered by microwave-assisted organic synthesis fulfills the increased demands in industry [1–3] as well as is suited to meet the above-mentioned challenges.

On the other hand, various pharmacological importances of 2,5-disubstituted-1,3,4-oxadiazoles and sulfonamides [4–8] have been extensively documented for their wide variety of pharmacological activities such as antimicrobial, insulin-releasing antidiabetic, carbonic anhydrase inhibitory, anti-HIV, high-ceiling diuretic, antithyroid, and antitumor [9–11]. Furthermore, the benzenesulfonamides having free SH/mercaptoaryl group showed remarkable potency by optimizing the antiviral and anticarbonic anhydrase enhancement activity, because the thiol compounds can bind the zinc in the active site of enzymes [12,13]. Regarding the anti-HIV activity, update, numerous classes of nonnucleoside reverse transcriptase inhibitors (NNRTIs), carrying heterocycle backbones, have been approved for the treatment of HIV infection, such as nevirapine [14], delaviridine [15], and efavirenz (EFV) [16]. However, the mutation associated with the therapeutic treatment led many laboratories to develop continuously new type of NNRTIs compound. De Clercq has reviewed [17] recently the new development in anti-HIV chemotherapy.

In respect with such mutation in the life cycle of HIV-1 and the carried attempts to inhibit the reverse transcriptase (RT), the enzyme responsible for HIV, we have synthesized new derivatives of benzenesulfonamides bearing 2,5-disubstituted-1,3,4-oxadiazole moiety, using the microwave irradiation method, and evaluated in vitro their HIV-1 and HIV-2 activity by using III_B and ROD strains.

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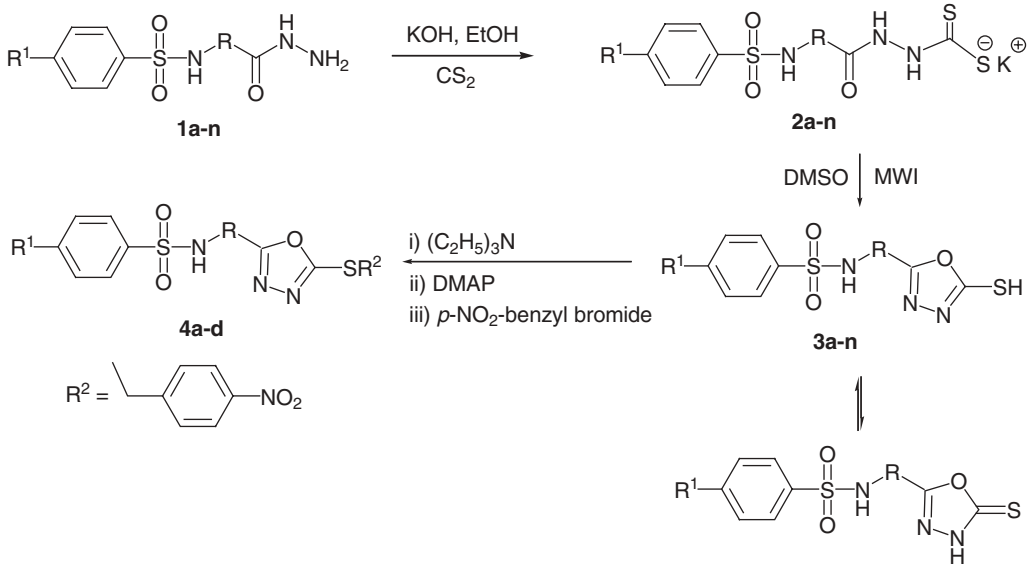

	R		R^1		R		R^1
a	iPr*CH	(L)	CH_3	**h**	$MeS(CH_2)_2$*CH	(D)	CH_3
b	iPr*CH	(L)	Cl	**i**	2-MePr*CH	(L)	CH_3
c	Et*CH	(L)	CH_3	**j**	2-MePr*CH	(L)	Cl
d	Et*CH	(L)	Cl	**k**	*$CH(CH_2)_4NHSO_2C_6H_4$ (4R)	(L)	CH_3
e	Me*CH	(D)	CH_3	**l**	*$CH(CH_2)_4NHSO_2C_6H_4$ (4R)	(L)	Cl
f	Me*CH	(D)	Cl	**m**	*o*-C_6H_4		CH_3
g	$MeS(CH_2)_2$*CH	(L)	OCH_3	**n**	*o*-C_6H_4		Cl

SCHEME 1

RESULTS AND DISCUSSION

Chemistry

A number of methods have been reported in the literature for the synthesis of benzenesulfonamides, e.g., using carboxylic acids/hydrazides [18] and sulfonic acids/sulfonylchlorides [19] as starting compounds. Therefore, in continuation of our research [20] on benzenesulfonamides, we report here the microwave irradiation method for the synthesis of some new chiral and achiral benzenesulfonamides. New optically active benzenesulfonamides bearing 2-substituted-5-mercapto-1,3,4-oxadiazole moiety **3a–l** (**3m** and **3n** are achiral) have been synthesized under microwave irradiation, using DMSO as a solvent (Scheme 1).

Microwave irradiation gave significant reduction in reaction time with comparative good yields. By using the microwave irradiation of the potassium salt of dithiocarbazinate derivatives **2a–n** in DMSO, the required reaction time was 2.5–3.0 min to give **3a–n** in 77–89% yield. In comparison, the conversion of **1a–n** to **3a–n** by the conventional method in EtOH under reflux, it required 16–17 h. Therefore, it is worthwhile to note that the reaction time has been reduced from ~17 h to ~3.0 min (Table 1) under microwave irradiation and gives an advantage for the synthesis of various sulfonamides derivatives by this method for more pharmacological applications.

The potassium salts of 3-[2-(4-methyl/chloro or methoxyphenylsulfonamido)]alkyl dithiocarbazinates **2** were prepared by reaction of the hydrazides **1** with CS_2 in alcoholic KOH [21].

The structures of all the synthesized compounds were confirmed by elemental analysis, IR, ^{1}H NMR, mass spectra, and optical rotation. The synthesis of compounds **3a–l** by the conventional method has been reported earlier by our group [20,22].

TABLE 1 Reaction Time, Yield and Melting Point of New Benzenesulfonamides

	Time		*Yield (%)*		*mp (°C)*	
	MWI (*min*)	*Thermal* (*h*)	*MWI*	*Thermal*	*MWI*	*Thermal*
3a	2.5	16	93	87	192	191
3b	3.0	17	91	89	195	196
3c	3.0	17	85	89	181	184
3d	3.0	17	88	91	192	193
3e	2.5	16	89	81	205	207
3f	3.0	16	79	78	161	160
3g	3.0	17	86	87	158	159
3h	3.0	16	87	93	162	163
3i	3.0	16	85	80	171	172
3j	3.0	17	91	73	185	186
3k	2.5	16	91	89	147	149
3l	3.0	17	87	81	153	155
3m	3.0	17	81	65	191	193
3n	3.0	17	87	69	211	213

CONCLUSION

Microwave irradiation procedure showed an advantage in comparison to the alternative conventional method and those previously reported by our group [20,22], in terms of simplicity and shorter reaction times. In addition, the availability of starting material, high yields of the final products (sulfonamides), free mercapto group at position 5 of the oxadiazole ring, and incorporation of chiral center of these compounds for the possible stereoselectivity in various applications (e.g., anti-HIV agents), all these requirements gave more advantages for our present work.

In Vitro Anti-HIV ASSAY

Compounds **3a, 3d, 3f, 3g–i, 3k, 3m, 4a**, and **4d** were tested for their anti-HIV-1 (strain III_B) and HIV-2 (strain ROD) activity in human T-lymphocyte (MT-4) cells, and the results are reported in Table 2, in which the data for efavirenz [16] and capravirine [23] were included for comparison purposes.

The gp41 subunit of the human immunodeficiency virus type-1 (HIV-1) envelope glycoprotein plays an important role in HIV-1 entry and serves as an attractive target for the development of HIV-1 entry inhibitors, a new class of anti-HIV drugs [24]. Triggered by gp120 binding to CD4 and a coreceptor, gp41 undergoes a conformation shift from a native prefusogenic state to a fusogenic state, in which the N-terminal heptad repeat (NHR) and C-terminal heptad repeat (CHR) associate to form a six-helix bundle, representing the fusion-active gp41 core. Any compound that disrupts the gp41 sixhelix bundle formation may inhibit the gp41-mediated membrane fusion, thereby blocking HIV-1 entry into target cells [25].

TABLE 2 In Vitro Anti-HIV-1[a] and HIV-2[b] of Some Benzenesulfonamides

	Virus Strain	*IC_{50} (μg/mL)[c]*	*CC_{50} (μg/mL)[d]*	*SI[e]*
3a	III_B	>66.3	66.3	≤1
	ROD	>56.3	56.3	≤1
3d	III_B	>125	>125	≤1
	ROD	>125	>125	≤1
3f	III_B	>125	>110	<1
	ROD	>125	125	≤1
3g	III_B	19.5	55.8	3
	ROD	>14.2	75.3	18
3h	III_B	>125	>125	≤1
	ROD	>125	>125	≤1
3i	III_B	>125	>125	≤1
	ROD	>125	>125	≤1
3k	III_B	>125	>125	≤1
	ROD	>125	>125	≤1
3m	III_B	>25.4	25.4	≤1
	ROD	>33.2	33.2	≤1
4a	III_B	>125	>125	≤1
	ROD	>125	>125	≤1
4d	III_B	>14	14	≤1
	ROD	>14.5	14.5	≤1
Efavirenz	III_B	0.003	40	13,333
Capravirine	III_B	0.0014	11	7,857

[a]Anti-HIV-1 activity measured with strain III_B.
[b]Anti-HIV-2 activity measured with strain ROD.
[c]Compound concentration required to reduce the viability of mock-infected MT-4 cells by 50%.
[d]Compound concentration required to achieve 50% protection of MT-4 cells from the HIV-1 and 2 induced cytopathogenicity.
[e]SI: Selectivity index (IC_{50}/CC_{50}).

Our target was the disruption of the gp41 sixhelix bundle formation by the newly synthesized amino acids, leading to inhibition of HIV. Compound **3g** was found to be the only compound from the series inhibiting HIV-1 and HIV-2 replication in cell culture, which showed an IC_{50} of 19.5 μg/mL and a CC_{50} of 55.8 μg/mL against HIV-1, resulting in a selectivity index of 3, meanwhile it showed an IC_{50} of 14.2 μg/mL and a CC_{50} of 75.3 μg/mL against HIV-1, resulting in a selectivity index of 18. This result encouraged us to modify such molecules with another potential group might fulfill the need of our target.

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Optical rotation data were recorded on a Perkin-Elmer 241 polarimeter. IR spectra were recorded in KBr disk on an FT-IR model FTS 3000 MX spectrometer. Elemental analysis was performed on a Carlo

Erba 1106 elemental analyzer. ^{1}H NMR (400 and 500 MHz) spectra were recorded on a Bruker NMR spectrophotometer, with TMS as internal standard and on the δ scale in ppm. EI–MS spectra were recorded on MAT 312 and MAT 311A mass spectrometers.

*Potassium 3-[2-[4-Methyl/chloro/methoxyphenylsulfonamido)alkynoyldithiocarbazinates (**2**)*

These compounds were prepared by using the reported procedure [21] from hydrazides **1**.

*General Procedure for Preparation of 4-Methyl/chloro-N-(1-(5-mercapto-1,3,4-oxadiazol-2-yl)-phenyl)benzenesulfonamide (**3a–n**)*

A suspension of the salt **2** (1.50 mmol) in DMSO (2 mL) was irradiated in microwave for 2.5–3.0 min. The reaction mixture was diluted with water and acidified with 4 N HCl. The solid obtained was filtered, washed with water, dried, and recrystallized from aq. EtOH. The melting points and comparative yields of the compounds obtained are given in Table 1. Compounds **3a–n** were prepared previously by the conventional method [22].

*4-Methyl-N-(1-(5-mercapto-1,3,4-oxadiazol-2-yl)-2-methylpropyl)benzenesulfonamide (**3a**).* Yield: 0.46 g (93%), mp 191–192°C, $[\alpha]_D^{20} = +39°$ ($C = 1.09$, acetone). IR (KBr) ν_{max} (cm^{-1}): 3285 (NH), 1591 (C=N), 1351, 1161 (SO_2), 1283 (C=S). ^{1}H NMR (acetone-d_6): δ 0.89 (d, 3H, $J = 6.7$ Hz, CH_3); 1.02 (d, 3H, $J = 6.7$ Hz, CH_3); 2.14–2.11 (m, 1H, CH); 2.37 (s, 3H, CH_3); 4.20 (dd, 1H, $J = 8.5$ Hz, $J = 9.0$ Hz, CH); 7.24 (d, 1H, $J = 9.0$ Hz, NH); 7.31 (d, 2H, $J = 8.2$ Hz, ArH); 7.63 (d, 2H, $J = 8.2$ Hz, ArH); 12.85 (br s, 2H, NH, SH). Anal. Calcd for $C_{13}H_{17}O_3N_3S_2$ (327.41): C, 47.69; H, 5.23; N, 12.83. Found: C, 47.39; H, 4.98; N, 13.02. MS: *m/z* (EI) 327 (M^+).

*4-Chloro-N-(1-(5-mercapto-1,3,4-oxadiazol-2-yl)-2-methylpropyl)benzenesulfonamide (**3b**).* Yield: 0.47 g (91%), mp 195–196°C, $[\alpha]_D^{20} = +29°$ ($C = 0.70$, acetone). IR (KBr) ν_{max}(cm^{-1}): 3287 (NH), 2550 (SH), 1598 (C=N), 1371, 1166 (SO_2). ^{1}H NMR (acetone-d_6): δ 0.92 (d, 3H, $J = 7.4$ Hz, CH_3); 1.08 (d, 3H, $J = 7.4$ Hz, CH_3); 2.25–2.27 (m, 1H, CH); 4.29 (dd, 1H, $J = 8.4$ Hz, $J = 9.0$ Hz, CH); 7.68 (d, 2H, $J = 8.0$ Hz, ArH); 7.91 (d, 2H, $J = 8.0$ Hz, ArH); 13.35 (br s, 1H, NH) MS: *m/z* (EI) 347 (M^+); $C_{12}H_{14}O_3N_3S_2Cl$ (347.8463), HRMS: (347.8412).

*4-Methyl-N-(1-(5-mercapto-1,3,4-oxadiazol-2yl)-propyl)benzenesulfonamide (**3c**).* Yield: 0.41 g (87%), mp 181–182°C, $[\alpha]_D^{20} = +36°$ ($C = 1.01$, acetone). IR (KBr) ν_{max} (cm^{-1}): 3286 (NH), 1587 (C=N), 1356, 1145 (SO_2), 1285(C=S). ^{1}H NMR (acetone-d_6): δ 0.94 (t, 3H, $J = 7.4$ Hz, CH_3); 1.82–1.89 (m, 2H, CH_2); 2.37 (s, 3H, CH_3); 4.38 (dd, 1H, $J = 7.8$ Hz, $J = 7.7$ Hz, CH); 7.33 (d, 2H, $J = 8.0$ Hz, ArH); 7.69 (d, 2H, $J = 8.0$ Hz, ArH); 12.79 (br s, 1H, NH). Anal. Calcd for $C_{12}H_{15}O_3N_3O_3S_2$ (313.39): C, 45.99; H, 4.82; N, 13.41. Found: C, 45.87; H, 4.66; N, 13.33. MS: *m/z* (EI) 313 (M^+).

*4-Chloro-N-(1-(5-mercapto-1,3,4-oxadiazol-2-yl)-propyl)benzenesulfonamide (**3d**).* Yield: 0.44 (88%), mp 192–193°C, $[\alpha]_D^{20} = +39°$ ($C = 1.08$, acetone). IR (KBr) ν_{max} (cm^{-1}): 3283 (NH), 2545 (SH), 1589 (C=N), 1365, 1149 (SO_2). ^{1}H NMR (acetone-d_6): δ 0.95 (t, 3H, $J = 7.4$ Hz, CH_3); 1.86–1.92 (m, 2H, CH_2); 4.42 (dd, 1H, $J = 7.6$ Hz, $J = 7.5$ Hz, CH); 7.62 (d, 2H, $J = 8.0$ Hz, ArH); 7.88 (d, 2H, $J = 8.0$ Hz, ArH); 12.96 (br s, 1H, NH). Anal. Calcd for $C_{11}H_{12}O_3ClN_3S_2$ (333.79): C, 39.58; H, 3.62; N, 12.59. Found: C, 39.49; H, 3.69; N, 12.44. MS: *m/z* (EI) 332/334 (M^+).

*4-Methyl-N-(1-(5-mercapto-1,3,4-oxadiazol-2-yl)-ethyl)benzenesulfonamide (**3e**).* Yield: 0.37 g (83%), mp 205–207°C, $[\alpha]_D^{20} = +29°$ ($c = 0.89$, acetone). IR (KBr) ν_{max} (cm^{-1}): 3282 (NH), 2551 (SH), 1589 (C=N), 1375, 1126 (SO_2). ^{1}H NMR (acetone-d_6): δ 1.46 (d, 3H, $J = 6.5$ Hz, CH_3); 2.40 (s, 3H, CH_3); 4.57–4.65 (m, 1H, CH); 7.34 (d, 2H, $J = 8.2$ Hz, ArH); 7.68 (d, 2H, $J = 8.2$ Hz, ArH); 12.85 (br s, 1H, NH). Anal. Calcd for $C_{11}H_{13}O_3N_3S_2$ (299.36): C, 44.13; H, 4.38; N, 14.04; Found: C, 44.07; H, 4.43; N, 14.31. MS: *m/z* (EI) 299 (M^+).

*4-Chloro-N-(1-(5-mercapto-1,3,4-oxadiazol-2-yl)-ethyl)benzenesulfonamide (**3f**).* Yield: 0.44 g (91%), mp 172–174°C, $[\alpha]_D^{20} = +43°$ ($C = 1.04$ acetone). IR (KBr) ν_{max} (cm^{-1}): 3285 (NH), 2550 (SH), 1611 (C=N), 1356 (SO_2 asym), 1149 (SO_2 sym). ^{1}H NMR (acetone-d_6): δ 1.51 (d, 3H, $J = 7.0$ Hz, CH_3); 4.73–4.65 (m, 1H, CH); 7.58 (d, 2H, $J = 8$ Hz, ArH); 7.83 (d, 2H, $J = 8$ Hz, ArH); 12.86 (br s, 1H, NH). Anal. Calcd for $C_{10}H_{10}O_3ClN_3S_2$ (319.78): C, 37.56; H, 3,15; N, 13.14. Found: C, 37.74; H, 2.88; N, 13.10. MS: *m/z* (EI) 318/320 (M^+).

*4-Methoxy-N-[1-(5-mercapto-1,3,4-oxadiazol-2yl)-4-(methylthio)propyl]benzenesulfonamide (**3g**).* Yield: 0.37 g (65%), mp 158–160°C, $[\alpha]_D^{20} = +31°$ ($C = 0.62$, acetone). λ_{max} (MeOH): 277, 234 nm, IR (KBr) ν_{max} (cm^{-1}): 3271 (NH), 1585 (C=N), 1357, 1166 (SO_2). ^{1}H NMR (400 MHz, acetone-d_6): δ 2.02 (s, 3H, SCH_3); 2.07–2.14 (m, 2H, CH_2CH_2SMe);

2.50–2.58 (m, 2H, CH_2CH_2SMe); 3.88 (s, 3H, OCH3); 4.37 (dd, 1H, $J = 7.5$ Hz, $J = 9.0$ Hz, NCH); 7.21 (br s, 1H, NH); 7.01 (d, 2H,$J = 8.1$ Hz, ArH); 7.69 (d, 2H, $J = 8.2$ Hz, ArH); 12.89 (br s, 1H, NH).^{13}C NMR (63.2 MHz, $CDCl_3$): δ 178.2 (C=S); 162.1 (C=N), 144.8, 136.1, 130.4, 127.8 (Ar), 56.2 (OMe); 52.2 (*C*HN); 38.6 (CH_2CH_2SMe); 31.1 (CH_2CH_2SMe); 20.2 (SMe). Anal. Calcd for $C_{13}H_{17}N_3O_4S_3$ (375.49): C, 41.58; H, 4.56; N, 11.19. Found: C, 41.27; H, 4.49; N, 10.95. MS; *m/z* (EI) 376 $(M + H)^+$.

*4-Methyl-N-[1-(5-mercapto-1,3,4-oxadiazol-2yl]-4-(methylthio)propyl]benzenesulfonamide (***3h***).* Yield: 0.47 g (87%), mp 160–162°C, $[\alpha]_D^{20} = -32°$ ($C = 1.0$, acetone). IR (KBr) ν_{max} (cm^{-1}): 3286 (NH), 1599 (C=N), 1351, 1161 (SO_2), 1285 (C=S). ^{1}H NMR (400 MHz, acetone-d_6): δ 2.02 (s, 3H, SCH_3); 2.05–2.16 (m, 2H, CH_2CH_2SMe); 2.51–2.57 (m, 2H, CH_2CH_2SMe); 4.65 (dd, 1H, $J = 7.5$ Hz, $J = 9.0$ Hz, NCH); 2.37 (s, 3H, CH_3–Ar); 7.22 (br s, 1H, NH); 7.33 (d, 2H, $J = 8.0$ Hz, ArH); 7.68 (d, 2H, $J = 8.0$ Hz, ArH); 12.78 (br s, 1H, NH).^{13}C NMR (75.0 MHz, acetone-d_6): δ 178.2 (C=S), 162.1 (C=N), 143.4, 132.2, 128.7, 115.6 (Ar); 55.9 (*C*HN); 30.4 (CH_2CH_2SMe); 22.0, (CH_2CH_2SMe); 21.0 (*Me*-Ar), 20.7 (SMe). Anal. Calcd for $C_{13}H_{17}O_3N_3S_3$ (359.3467): C, 43.42; H, 4.77; N, 11.69. Found: C, 43.16; H, 4.85; N, 11.53.

*4-Methyl-N-[1-(5-mercapto-1,3,4-oxadiazol-2-yl)-2-methylbutane]benzenesulfonamide (***3i***).* Yield: 0.43 g (85%), mp 171–173°C, $[\alpha]_D^{20} = +43°$ ($C = 1.0$, acetone). λ_{max} (MeOH): 265, 234 nm, IR (KBr) ν_{max} (cm^{-1}): 3309 (NH), 1593 (C=N), 1375, 1157 (SO_2). ^{1}H NMR (400 MHz, acetone-d_6): δ 0.82, 0.86 (m, 6H, CH*Me*CH_2*Me*); 1.63–1.66 (m, 2H, CHMe*C*H_2Me); 2.37 (s, 3H, Ar-CH_3); 2.29 (m, 1H, *CH*$MeCH_2CH_3$); 4.33 (dd, 1H, $J = 7.0$ Hz, 9.0 Hz, NCH); 7.33 (d, 2H, $J =$ 8.0 Hz, ArH); 7.66 (d, 2H, $J = 8.0$ Hz, ArH); 11.79 (br s, 1H, NH).^{13}C NMR (63.2 MHz, $CDCl_3$): δ 178.2 (C=S); 162.4 (C=N); 144.7, 136.8, 131.0, 127.8 (Ar); 54.0 (*C*HN); 38.4 (*CH*$MeCH_2Me$); 25.0 (CHMe*C*H_2Me); 21.6 (*Me*-Ar); 15.5 (CH*Me*CH_2Me), 10.9 ($CHMeCH_2$*Me*). MS; *m/z* (EI) 341 (M^+); $C_{14}H_{19}O_3N_3S_2$ (341.4553), HRMS: (341.4678).

*4-Chloro-N-[1-(5-mercapto-1,3,4-oxadiazol-2-yl)-2-methylbutane]benzenesulfonamide (***3j***).* Yield: 0.49 g (91%), mp 185–187°C, $[\alpha]_D^{20} = +30°$ ($C = 0.72$, acetone). λ_{max} (MeOH): 279, 236 nm, IR (KBr) ν_{max} (cm^{-1}): 3295 (NH), 1599 (C=N), 1376, 1148 (SO_2). ^{1}H NMR (400 MHz, acetone-d_6): δ 0.88, 0.93 (m, 6H, CH*Me*CH_2*Me*); 1.79–1.86 (m, 2H, CHMe*C*H_2CH_3); 2.31 (m, 1H, *CH*$MeCH_2CH_3$); 4.38 (dd, 1H, $J = 7.6$ Hz, $J = 9.1$ Hz, NCH); 7.65 (d, 2H, $J = 8.1$ Hz, ArH); 7.81 (d, 2H, $J = 8.1$ Hz, ArH). ^{13}C NMR (63.2 MHz, $CDCl_3$): δ 178.4 (C=S), 162.7 (C=N), 145.2, 136.8, 132.5, 128.4 (Ar); 55.2 (*C*HN), 38.5 (*CH*$MeCH_2Me$); 24.9 (CHMe*C*H_2Me); 15.6 15.5 (CH*Me*CH_2CH_3); 11.2 ($CHMeCH_2$*Me*). MS; *m/z* (EI) 361(M^+); $C_{13}H_{16}O_3N_3S_2Cl$ (361.8731), HRMS: (361.8620).

*2-[1,5-Bis(4-methylphenylsulfonamido)]-pentyl-5-mercapto-1,3,4-oxadiazole (***3k***).* Yield: 0.68 g (89%), mp 147–149°**C**. IR (KBr) ν_{max} (cm^{-1}): 3299 (NH), 1597 (C=N), 1321, 1161 (SO_2).^{1}H NMR (400 MHz, acetone-d_6): δ 1.37–1.48 (m, 4H, 2 × CH_2); 1.78 (m, 2H, CH_2); 2.37 (s, 3H, CH_3); 2.79 (m, 2H, CH_2); 4.38 (dd, 1H, $J = 6.5$ Hz, 9.0 Hz, NCH); 7.21 (br s, 1H, NH); 7.32 (m, 3H, ArH); 7.37 (d, 2H, $J = 7.9$ Hz, ArH); 7.65 (d, 2H, $J = 8.0$ Hz, ArH); 7.74 (d, 2H, $J = 8.0$ Hz, ArH); 12.85 (br s, 2H, NH, SH). Anal. Calcd for $C_{21}H_{26}O_5N_4S_3$: (510.66): C, 49.39; H, 5.13; N, 10.97. Found: C, 49.28; H, 5.13; N, 11.27.

*2-[1,5-Bis(4-chlorophenylsulfonamido)]-pentyl-5-mercapto-1,3,4-oxadiazole (***3l***).* Yield: 0.67 g (81%), mp 153–155°C. IR (KBr) ν_{max} (cm^{-1}): 3286 (NH), 2555 (SH), 1607 (C=N), 1327, 1165 (SO_2).^{1}H NMR (400 MHz, acetone-d_6): δ 1.39–1.53 (m, 4H, 2 × CH_2); 1.75 (m, 2H, CH_2); 2.79 (m, 2H, CH_2); 4.39 (dd, 1H, $J = 6.5$ Hz, 9.1 Hz, NCH); 7.21 (br s, 2H, NH); 7.52 (m, 3H, ArH); 7.57 (d, 2H, $J = 7.9$ Hz, ArH); 7.79 (d, 2H, $J = 8.0$ Hz, ArH); 7.82 (d, 2H, $J = 8.0$ Hz, ArH); 12.91 (br s 2H, NH, SH). Anal. Calcd for $C_{19}H_{20}O_5N_4S_3Cl2$ (551.48): C, 41.38; H, 3.66; N, 10.16. Found: C, 41.18; H, 3.69; N, 10.47.

*4-Methyl-N-(1-(5-mercapto-1,3,4-oxadiazol-2-yl)-phenyl)benzenesulfonamide (***3m***).* Yield: 0.34 g (65%), mp 191–192°C. IR (KBr) ν_{max} (cm^{-1}): 3295 (NH), 2565 (SH), 1581 (C=N), 1281 (C=S), 1375,1141 (SO_2). ^{1}H NMR (acetone-d_6): δ 2.38 (s, 3H, CH3); 7.33 (d, 2H, ArH, $J = 8.2$ Hz); 7.41–7.64 (m, 4H, ArH); 7.78 (d, 2H, ArH, $J = 8.0$ Hz); 10.35 (br s, 1H, NH); 12.89 (br s, 1H, NH). Anal. Calcd for $C_{15}H_{13}N_3O_3S_2$ (347.41): C, 51.86; H, 3.77; N, 12.10. Found: C, 51.58; H, 3.68; N, 11.95. MS: *m/z* (EI) 347 (M^+).

*4-Chloro-N-(1-(5-mercapto-1,3,4-oxadiazol-2-yl)-phenyl)benzenesulfonamide (***3n***).* Yield: 69%, mp 210-211°C. IR (KBr) ν_{max} (cm^{-1}): 3316 (NH), 1562 (C=N), 1281 (C=S), 1361, 1155 (SO_2), 679 (C—S) cm^{-1}. ^{1}H NMR (acetone-d_6): δ 7.42-7.58 (m, 4H, ArH); 7.79 (d, 2H, ArH, $J = 8.5$ Hz); 7.89 (d, 2H,

ArH, $J =$ 8.4 Hz); 10.23 (br s, 1H, NH); 12.89 (br s, 1H, NH). Anal. Calcd for $C_{14}H_{10}ClN_3O_3S_2$ (367.83): C, 45.71; H, 2.74; N, 11.42. Found: C, 45.39; H, 2.67; N, 11.17. MS: *m/z* (FAB) 367/369 (M + H^+).

*General Procedure for Preparation of Alkylsulfanyl Derivatives (**4a–d**)*

A solution of **3a–d** (0.75 mmol) in $CHCl_3$ (25 mL) containing Et_3N (0.30 mL), 0.22 mmol) and catalytic amount of DMAP [4-(*N*, *N*-dimethylamino)pyridine] (25 mg) was stirred at 23°C for 15 min. To this solution, *p*-nitrobenzyl bromide (0.17 g, 0.80 mmol) was added and the mixture was stirred for 5 h at 30–70°C. The reaction mixture was washed with dil. HCl, brine sol., water and the organic layer was dried (Na_2SO_4). The solvent was evaporated to dryness, and the residue was recrystallized from aq. EtOH to give the desired product.

*N-(1-(5-(4-Nitrobenzylthio)-1,3,4-oxadiazol-2-yl)-methylpropyl)-4-methylbenzenesulfonamide (**4a**).* Yield: 0.29 g (85%), mp 123–125°C, $[\alpha]_D^{20} = +27°$ ($c = 0.57$, acetone). IR (KBr) ν_{max} (cm^{-1}): 3286 (NH), 1612 (C=N), 1375, 1155 (SO_2) 697 (C—S). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.27 (d, 2H, $J = 8.0$ Hz, ArH); 7.69 (d, 2H, $J = 8.4$ Hz, ArH), 7.56 (d, 2H, $J = 8.4$ Hz, ArH); 7.34 (d, 2H, $J = 8.2$ Hz, ArH); 7.28 (br s, 1H, NH); 4.30 (s, 2H, CH_2Ar); 4.27 (dd, 1H, $J = 8.0$ Hz, $J = 9.2$ Hz, NCH); 2.21–2.29 (m, 1H, CHMe$_2$); 2.41 (s, 3H, Ar-CH_3); 1.06, 0.94 (2 × d, 6H, $J = 6.7$ Hz, CHMe_2). Anal. Calcd. for $C_{20}H_{22}N_4O_5S_2$ (462.54): C, 51.93; H, 4.79; N, 12.11. Found: C, 51.69; H, 4.71; N, 11.92. MS: *m/z* (FAB) 485 (M + Na^+).

*N-(1-(5-(4-Nitrobenzylthio)-1,3,4-oxadiazol-2-yl)-methylpropyl)-4-chlorobenzenesulfonamide (**4b**).* Yield: 0.26 g (70%), mp 165–167°C, $[\alpha]_D^{20} = +20°$ ($c = 0.63$, acetone). IR (KBr) ν_{max} (cm^{-1}): 3266 (NH), 1588 (C=N), 1375, 1173 (SO_2) 692 (C—S). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.20 (d, 2H, $J = 8.4$ Hz, ArH); 7.89 (d, 2H, $J = 8.0$ Hz, ArH), 7.72 (d, 2H, $J = 8.0$ Hz, ArH); 7.58 (d, 2H, $J = 7.8$ Hz, ArH); 7.27 (br s, 1H, NH), 4.62 (dd, 1H, $J =$ 7.2 Hz, $J = 9.2$ Hz, NCH); 4.46 (s, 2H, CH_2Ar), 1.97–2.03 (m, H, CHMe$_2$); 0.98, 0.91 (d, 3H, $J = 6.8$ Hz, CHMe_2). Anal. Calcd for $C_{19}H_{19}ClN_4O_5S_2$ (482.96): C, 47.25; H, 3.97; N, 11.60. Found: C, 47.01; H, 3.83; N, 11.24. MS: *m/z* (FAB) 504/506 (M + Na^+).

*N-(1-(5-(4-Nitrobenzylthio)-1,3,4-oxadiazol-2-yl)-propyl)-4-methylbenzenesulfonamide (**4c**).* Yield: 0.22 g (64%), mp 113–115°C, $[\alpha]_D^{20} = +31°$ ($c = 0.76$, acetone). IR (KBr) ν_{max} (cm^{-1}): 3295 (NH), 1585 (C=N), 1375, 1162 (SO_2), 679 (C—S).^{1}H NMR (400 MHz, acetone-d_6): δ 8.25 (d, 2H, $J = 8.4$ Hz, ArH); 7.78 (d, 2H, $J = 8.2$ Hz, ArH); 7.65 (d, 2H, $J = 8.4$ Hz, ArH); 7.33 (d, 2H, $J = 8.1$ Hz, ArH); 7.20 (br s, 1H, NH); 4.51 (dd, 1H, $J = 7.0$ Hz, $J = 9.2$ Hz, NCH); 4.42 (s, 2H, CH_2Ar); 2.38 (s, 3H, Ar-CH_3); 1.75–1.80 (m, 2H, CH_2CH_3); 0.87 (t, 3H, $J = 7.4$ Hz, CH_2CH_3). Anal. Calcd for $C_{19}H_{20}N_4O_5S_2$ (448.52): C, 50.88; H, 4.49; N, 12.49. Found: C, 50.69; H, 4.39; N, 12.18. MS *m/z* (FAB) 449 (M + $H)^+$.

*N-(1-(5-(4-Nitrobenzylthio)-1,3,4-oxadiazol-2-yl)-propyl)-4-chlorobenzenesulfonamide (**4d**).* Yield: 0.29 g (83%), mp 121–122°C, $[\alpha]_D^{20} = +22°$ ($c =$ 0.63, acetone). IR (KBr) ν_{max} (cm^{-1}): 3286 (NH), 1597 (C=N), 1375, 1166 (SO_2), 679 (C—S). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.17 (d, 2H, $J = 8.0$ Hz, ArH); 7.69 (d, 2H, $J = 8.4$ Hz, ArH); 7.57 (d, 2H, $J = 8.4$ Hz, ArH); 7.33 (d, 2H, $J = 8.2$ Hz, ArH); 7.22 (br s, 1H, NH); 4.64–4.72 (m, 1H, NCH); 4.36 (s, 2H, CH_2CH_3); 1.49 (d, 3H, $J = 7.0$ Hz, CH_2CH_3). Anal. Calcd for $C_{18}H_{17}ClN_4O_5S_2$ (468.93): C, 46.10; H, 3.65; N, 11.95. Found: C, 45.88; H, 3.49; N, 11.69. MS: *m/z* (FAB) 468/470 (M + $H)^+$.

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