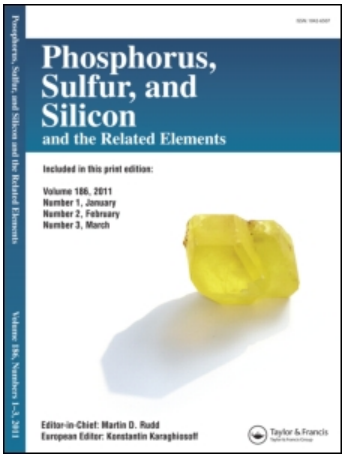


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis, Anti-HIV, and Antifungal Activity of New Benzensulfonamides Bearing the 2,5-Disubstituted-1,3,4-Oxadiazole Moiety

Muhammad Zareef[a]; Rashid Iqbal[a]; Najim A. Al-Masoudi[b]; Javid H. Zaidi[a]; Muhammad Arfan[a]; Sohail A. Shahzad[c]
[a] Department of Chemistry, Quaid-i-Azam University, Islamabad, Pakistan [b] Universitat Konstanz (Formerly Fachbereich Chemie), Postfach, Germany [c] International Centre for Chemical Sciences, HEJ Research Institute of Chemistry, University of Karachi, Karachi, Pakistan

To cite this Article Zareef, Muhammad , Iqbal, Rashid , Al-Masoudi, Najim A. , Zaidi, Javid H. , Arfan, Muhammad and Shahzad, Sohail A.(2007) 'Synthesis, Anti-HIV, and Antifungal Activity of New Benzensulfonamides Bearing the 2,5-Disubstituted-1,3,4-Oxadiazole Moiety', Phosphorus, Sulfur, and Silicon and the Related Elements, 182: 2, 281 — 298
To link to this Article: DOI: 10.1080/10426500600919074
URL: http://dx.doi.org/10.1080/10426500600919074

Phosphorus, Sulfur, and Silicon, 182:281–298, 2007

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500600919074

Taylor & Francis
Taylor & Francis Group

Synthesis, Anti–HIV, and Antifungal Activity of New Benzensulfonamides Bearing the 2,5-Disubstituted-1,3,4-Oxadiazole Moiety

Muhammad Zareef
Rashid Iqbal
Department of Chemistry, Quaid-i-Azam University, Islamabad, Pakistan

Najim A. Al-Masoudi
Universitat Konstanz (Formerly Fachbereich Chemie), Postfach, Germany

Javid H. Zaidi
Muhammad Arfan
Department of Chemistry, Quaid-i-Azam University, Islamabad, Pakistan

Sohail A. Shahzad
International Centre for Chemical Sciences, HEJ Research Institute of Chemistry, University of Karachi, Karachi, Pakistan

A series of novel chiral and achiral N-*[1-(1,3,4-oxadiazol-2ylthio)alkyl]-4-methyl / chloro / methoxybenzenesulfonamides* ***5a–l*** *were prepared by the reaction of 4-(4-methyl, chloro, methoxyphenylsulfonamido)alkyl carboxylic acid hydrazides* ***4a–l*** *with* CS_2 *and KOH. Another series of new secondary benzenesulfonamides* ***10a–j*** *and* bis-*benzenesulfonamides* ***11a–j*** *have been synthesized by a new approach using* Et_3N *and dimethylaminopyridine. All synthesized compounds were characterized by physical, microanalytical, and spectral data. Some of the synthesized compounds were screened in vitro for their anti–HIV and antifungal activities.*

Keywords Antifungal activity; anti–HIV activity; benezenesulfonamides chiral sulfonamides; 1,3,4-oxadiazole

The 1,3,4-oxadiazole family attracts significant attention due to their chemotherapeutic importance.[1–6] Such compounds showed high

Received February 26, 2006; accepted June 26, 2006.
Address correspondence to Muhammad Zareef, Quaid-i-Azam University, Department of Chemistry, Islamabad, 45320 Pakistan. E-mail: mkzareef@yahoo.com

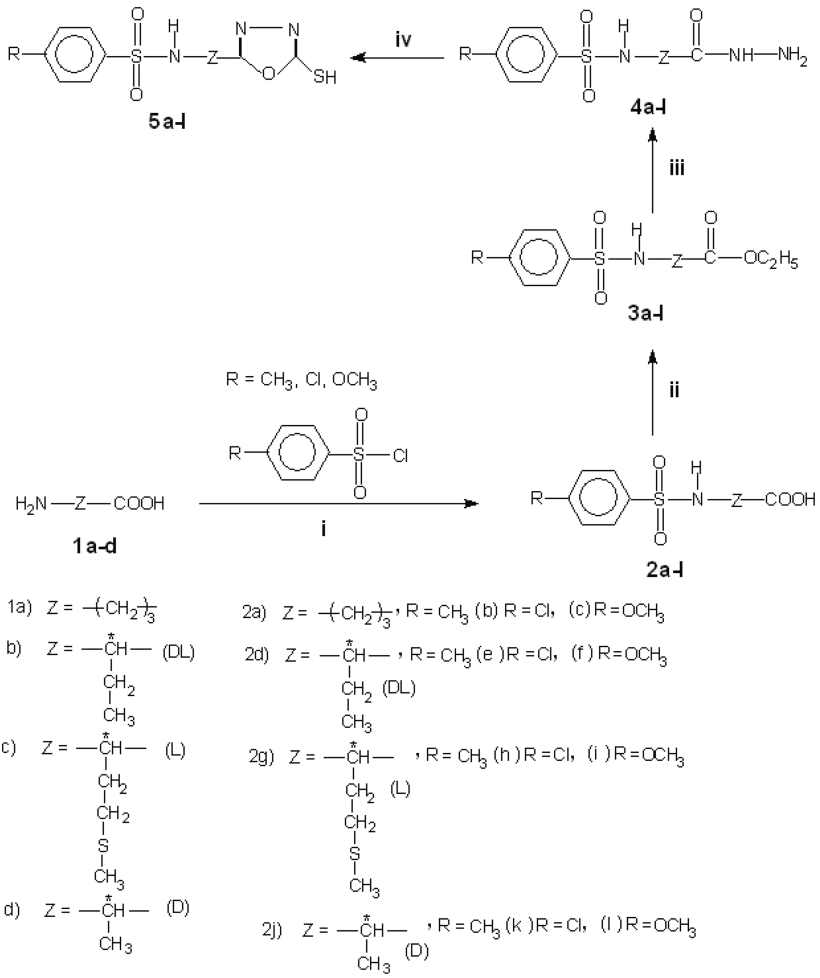
activity by carrying the potential sulfonamide and free thiol residues. The sulfonamide moiety is a crucial functionality because of its wide variety of pharmacological, activities, such as antimicrobial, anti–HIV,[7] insuline-releasing antidiabetic, carbonic anhydrase inhibitory,[8,9] high ceiling diuretic, and antithyroid and antitumor activities.[10–12] In addition, more recent articles have reported various sets of novel sulfonamide drugs, e.g., an inhibitor of membrane-bound human and bovine isozymes IV[13] and sildenafil citrate (Viagra®) as a drug for treating male erectile dysfunction (ED).[14] The second-generation antimitotic sulfonamide, ER-34410, is 2 to 3 times more potent than E7010 in a panel of various human tumor-cell lines in vitro and can be administered intravenously.[15]

Regarding the free thiol moiety (SH)/free mercaptoaryl group, it showed facil coordination with transition metal ions, such as Zn (ll), Cu (ll), and Fe (lll), giving products with highly physiological importance. A large number of metallo-enzymes incorporate Zn (ll) or Cu (ll) ions coordinated by one or several –SH groups belonging to Cys residues.[1,15,16] Furthermore, the free SH has a strong nucleophilic character and can easily be derivatized by many electrophiles (E^+), such as haloacetates, maleimides, and activated sulfonyl groups, which show different physicochemical properties.[16] The S-alkylation/arylation, S-acylation, or S-sulfonylation of the free SH is indeed of exceptional importance mainly for the design of novel chemotherapeutic agents.[1,15] These biological data prompted us to synthesize some novel chiral and achiral 1,3,4-oxadiazoles-bearing sulfonamides and thiol residues compounds and evaluate their anti–HIV-1 and antifungal activities.

RESULTS AND DISCUSSION

Although a number of methods are available for the synthesis of sulfonamides, they are usually prepared from carboxylic acids/hydrazides[17]and sulfonic acids/sulfonylchlorides[18] as starting compounds. We report herein a novel approach using different chiral and achiral amino acids as a starting material (Scheme 1), together with a series of new benzenesulfonamides with 2,5-disubstituted-1,3,4-oxadiazole moiety via a new alternative approach (Scheme 2). The advantages of these methods include the availability of the starting materials with high yields of products.

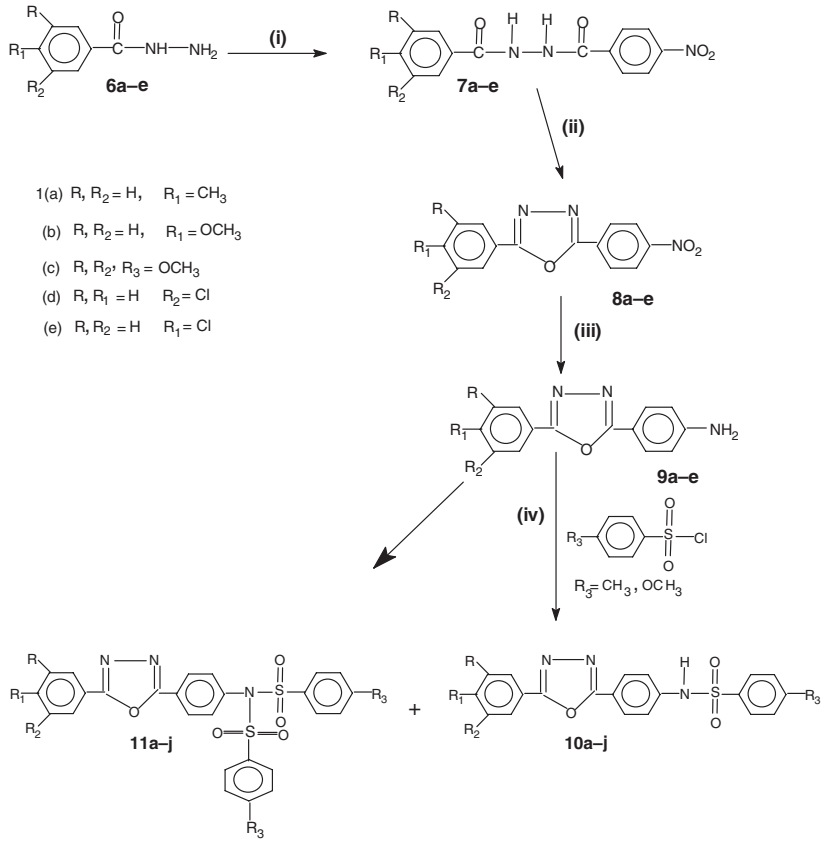
Four amino acids, **1a–d**, were converted into their corresponding sulfonamides **2a–l** by a reaction with 4-methylbenzenesulfonylchloride, 4-chlorobenzenesulfonylchloride, and 4-methoxybenzene-sulfonyl chloride in an alkaline medium (Scheme 1) using standard methods.[19a] Esterfication of **2a–l** with ethanol in an acidic medium afforded the



SCHEME 1 Reagents and conditions (i) aq. 5% NaOH, ether, 23°C, 6h; (ii) H_2SO_4/ethanol, reflux; (iii) NH_2-NH_2·H_2O/ethanol reflux, 9 h; (iv) CS_2/KOH, ethanol, reflux, 17 h.

esters **3a–d** following the literature method.[19b] Treatment of **3a–d**, with 80% hydrazine hydrate, furnished the corresponding hydrazides **4a–l** in good yields. The sulfonamides bearing a 2,5-disubstituted-1,3,4-oxadiazole moiety **5a–l** were then prepared by the reaction of hydrazides **4a–l** with CS_2 and KOH employing the literature method.[6,20]

The structures of the synthesized compounds were determined by the ^{1}H NMR, IR, and mass spectra, as well as the optical rotations (chiral



SCHEME 2 Conditions and reagents (i) *p*-NO_2-PhCOCl, CH_3CN, 23°C, 6 h; (ii) $SOCl_2$, reflux, 2 h; (iii) Pd/C (10%), ethanol, reflux, 9 h; (iv) Et_3N, DMAP, $CHCl_3$, 70°C, reflux 11 h.

compounds). Compound **5j** was selected for the spectroscopic analysis, since the analogues **5a–f** and **5k–l** showed a similar spectral pattern. The IR spectrum of **5j** revealed the presence of characteristic bands for -NH at 3282 cm^{-1}, 2551 cm^{-1} for -SH, 1589 cm^{-1} (C=N), and 1375 cm^{-1} and 1126 cm^{-1} for the $-SO_2$ functional group. The mass spectrum of **5j** showed a molecular ion peak at *m/z* 299 (M^+, 45). The ^1H NMR spectrum of **5j** showed a multiplet signal at δ 4.57–4.65, characteristic for the chiral *CH* (Z) center, whereas the other protons were fully analyzed. To the best of our knowledge, **5g–i** are not reported in the literature. Meanwhile, the new sulfonamides **5a–f, 5j–l**, and their corresponding intermediate compounds were prepared[21,22] recently in our laboratory (Scheme 1).

Alternatively, hydrazides **6a–e** were converted into the *N*,*N*-diacylhydrazines **7a–e** by treatment with 4-nitrobenzoylchloride in dry MeCN. Compounds **7a–e** were subjected to dehydrative cyclization in the presence of thionyl chloride to give **8a–e**.[23] The reduction of **8a–e** with Pd/C and hydrazine hydrate, following a reported method,[24] afforded the amino compounds **9a–e** in good yields. The treatment of **9a–e** with Et_3N and dimethylaminopyridine furnished, after purification, the corresponding sulfonamides **10a–e** and **11a–e** (Scheme 2).

Structures of the synthesized compounds were characterized by ^1H NMR, IR, and mass spectra. Compound **10a** was selected for the spectroscopic interpretation, whereas its analogs revealed similar spectral patterns. The IR spectrum of **10a** revealed the presence of characteristic bands for NH at 3266 cm^{-1}, 1589 cm^{-1} for C=N, and 1379 cm^{-1} and 1149 cm^{-1} for SO_2 functional groups. The mass spectrum of **10a** showed a molecular ion peak at m/z 405 (M^+). The ^1H NMR spectrum of **10a** demonstrated singlets at δ 2.44 and δ 2.84 that were attributed to CH_3-Ar, whereas the doublets at δ 7.26, 7.43, 7.49, 7.81, 8.06, and 8.20 ($J \sim 8.0$ Hz) belonged to aromatic protons. The NH signal appeared at δ 10.54, which exchanged with D_2O. The IR spectrum of *bis*-sulfonamide **11a** showed no signal for the NH group, whereas it showed a molecular ion peak at m/z 559 (M^+).

ANTI-HIV ACTIVITY

Compounds **4k, 5b, 5c, 5e, 5f, 5g, 9a, 9b, 10a**, and **10f** were tested for their anti–HIV-1 and HIV-2 activity in vitro using III_B and ROD strains, respectively, in human T-lymphocyte (MT-4) cells. The results are summarized in Table I in which the data have been included for comparison purposes. Compound-induced cytotoxicity was also measured in MT-4 cells parallel with antiviral activity. None of the oxadiazole derivatives (sulfonamides bearing a 2,5-disubstituted-1,3,4-oxadiazole moiety) were found to inhibit HIV-1 and HIV-2 replication in vitro at EC_{50} lower than the CC_{50} in comparison to the antiviral agent efavirenz (EFV)[24] and azidothymidine (AZT).[25] On the other hand, **5g** showed $IC_{50} > 18.3$ μg/mL and induced cytopathicity in human MT-4 lymphocyte cells at nontoxic concentrations, with no selectivity (SI = 3). Meanwhile, it showed an unusual result by the higher value of anti–HIV-2 activity in comparison to anti–HIV activity with maximum protection 62.

The cavity on gp41 of HIV plays an important role in the viral replication process, which could hold a small molecule inhibitor. Nonreverse transcriptase inhibitors that would fit this cavity have been

TABLE I In vitro anti–HIV-1[a] and HIV-2[b] of Some New Oxadiazole Derivatives

Compound	$IC_{50}(\mu g/mL)^c$ MT-4		$CC_{50}(\mu g/mL)^d$	SI[e]	Max. Prot.
4k	III_B	>113	=113	<1	1
	ROD	>125	=125	<1	2
5b	III_B	>70	=70	<1	4
	ROD	>74	=74	<1	5
5c	III_B	>110	=110	<1	17
	ROD	>125	=125	<1	32
5e	III_B	>122	=122	<1	2
	ROD	>125	=125	<1	5
5f	III_B	>125	=125	<1	1
	ROD	>125	=125	<1	24
5g	III_B	>71	=71	<1	8
	ROD	=18	=63	=3	62
9a	III_B	>22	=22	<1	6
	ROD	>35	=35	<1	13
9b	III_B	>98	=99	<1	1
	ROD	>116	=116	<1	5
10a	III_B	>89	=89	<1	1
	ROD	>119	=119	<1	2
10f	III_B	>94	=2.44	<1	1
	ROD	>103	=103	<1	3
EFV		40	0.003		
AZT		63	0.02		

[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 HIV-1 and 2 induced cytopathogenicity.

[e]SI: Selectivity index (IC_{50}/CC_{50}).

identified as active precursors[26] to inhibit virus replication. Accordingly, our synthetic strategy for the synthesis of new oxadiazole derivatives bearing mercapto (—SH) moieties depends on this hypothesis. In conclusion, compounds having an oxadiazole backbone carrying thio congeners offer more opportunity for further antiviral investigation than amino alkyl groups.

Antifungal Activity

Invasive aspergillosis is one of the most common fungal infections in immunocompromised patients and carries high mortality rates.[27]

TABLE II Antifungal Activity of Some New Oxadiazole Derivatives and Inhibition Zones (%)

Name of Fungi	Compound No.								Standard Drug
	5b	**5c**	**5e**	**5f**	**5g**	**5k**	**5l**	**8a**	
Trichphyton longifusus	90	50	0	0	0	50	0	0	Miconazole
Candida albicans	0	0	0	0	0	0	0	0	Miconazole
Aspergillus flavus	100	0	50	0	0	0	50	0	Amphotericin
Microsporum canis	0	0	0	0	0	0	0	0	Miconazole
Fusarium solani	0	0	30	50	0	0	0	50	Miconazole
Candida glabrata	50	0	0	0	0	0	0	0	Miconazole

Conc. of sample 200 μg/mL of DMSO at 27°C, incubation period 7 days.

Sulfonamides, especially sulfamethoxazole-trimethoprim, are antimicrobial agents frequently employed in AIDS patients to prevent bacterial and fungal infections.[28] Therefore, 16 selected representatives of newly synthesized sulfonamides and 1,3,4-oxadiazoles **5b, 5c, 5e–f, 5g, 5k–l, 8a, 8c, 8e, 10a–b, 10e, 11a–b**, and **11e** were screened in vitro for their antifungal activity against six species using the agar plate technique.[29] Linear growth of the fungus was obtained by measuring the diameter of the fungal colony after 7 days. The amount of growth inhibition in each case was calculated as percentage inhibition. The screening results are given in Tables II and III. It is worthwhile to note that compounds **5b, 8e**, and **10e** exhibited significant antifungal activities, which might be attributed to the presence of a free SH at position 5 of the oxadiazole ring, as well as the NO_2 and Cl substituents of the 1,3,4-oxadiazole ring.

TABLE III Antifungal Activity of Some Synthesized Compounds and Inhibition Zones (%)

Name of Fungi	Compound No.								Standard Drug
	8c	**8e**	**10a**	**10b**	**10e**	**11a**	**11b**	**11e**	
Trichphyton longifusus	35	0	50	0	90	0	0	0	Miconazole
Candida albicans	0	60	0	50	60	0	40	0	Miconazole
Aspergillus flavus	0	100	0	0	50	0	0	0	Amphotericin
Microsporum canis	40	90	0	60	40	0	0		Miconazole
Fusarium solani	40	0	0	40	0	50	0	40	Miconazole
Candida glabrata	0	0	0	0	0	0	0	0	Miconazole

Conc. of sample 200 μg/mL of DMSO at 27°C, incubation period 7 days.

EXPERIMENTAL

General Procedure

Melting points were determined on a Gallenkamp melting-point apparatus and were uncorrected. Optical rotation data were recorded on a Perkin-Elmer 241 polarimeter. IR spectra were recorded in KBr disc on an FTIR 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, using tetramethylsilane (TMS) as internal standard with δ values and coupling constants in Hz. Mass spectra were recorded on a MAT 312 and MAT 311A mass spectrometer. TLC was performed on precoated silica gel 60 F_{254} aluminum sheets (Merck, Darmstadt, Germany).

Preparation of the Sulfonamides 2a–l and the Corresponding Esters 3a–l

Compounds **2a–l** were prepared from the corresponding amino acids **1a–d** using 3 different sulfonyl chlorides, whereas the corresponding esters **3a–l** were prepared following the established procedure mentioned in the literature.[19a,b] Compound **2c** [m.p. 149°C (72%), lit.[19c] 149°C]. Compounds **2–8** were recrystallized from aq. Ethanol; meanwhile, compounds **10a–j** and **11a–j** were purified by TLC using ethyl acetate/pet. ether.

General Procedure for Preparation of Compounds 4a–l

A mixture of **3a** (10 mmol) and hydrazine monohydrate (80%) in absolute EtOH (50 mL) was heated under reflux for 9 h. The solution was concentrated, and the precipitate was filtered, washed with water, and recrystallized from 60% aqueous ethanol. Hydrazides **4b–l** were prepared in a similar fashion.

4a. Yield: 76%, m.p. 92–94°C. ν_{max} (cm^{-1}) 3316, 3286 (NH), 1651 (C=O), 1365 (SO_2), 1147 (SO_2). ^{1}H NMR (acetone-d_6) δ 1.65–1.72 (m, 2H, CH_2), 2.5 (t, 2H, $J = 7.4$ Hz, CH_2), 2.7 (t, 2H, $J = 6.6$ Hz, CH_2), 2.4 (s, 3H, CH_3), 7.35 (d, 2H, $J = 8.0$ Hz, ArH), 7.7 (d, 2H, $J = 8.0$ Hz, ArH), 9.3 (br s., 2H, NH_2), 10.5 (br s., 1H, NH). EI-MS: m/z 271 (M^+).

4b. Yield: 75%, m.p. 91–93°C. ν_{max} (cm^{-1}) 3377, 3285 (NH), 1671 (C=O), 1376, 1155 (SO_2). ^{1}H NMR (acetone-d_6) δ 1.66–1.75 (m, 2H, CH_2), 2.55 (t, 2H, $J = 7.4$ Hz, CH_2), 7.45 (d, 2H, $J = 8.0$ Hz, ArH), 7.89 (d, 2H, $J = 8.0$ Hz, ArH), 9.61 (br s., 2H, NH), 11.29 (br s., 1H, NH). EI-MS: m/z 291 (M^+).

4c. Yield: 62%, m.p. 110–112°C. ν_{max} (cm^{-1}) 3332, 3260 (NH), 1656 (C=O), 1372, 1161 (SO_2). ^1H NMR (acetone-d_6) δ 1.69–1.78 (m, 2H, CH_2), 2.84 (t, 2H, $J = 7.8$ Hz, CH_2), 2.78 (t, 2H, $J = 6.9$ Hz, CH_2), 7.25 (d, 2H, $J = 8.1$ Hz, ArH), 7.59 (d, 2H, $J = 8.2$ Hz, ArH), 9.57 (br s., 2H, NH_2), 10.75 (br s., 1H, NH). EI-MS: m/z 287 (M^+).

4d. Yield: 83%, m.p. 156–158°C. ν_{max} (cm^{-1}) 3342, 3285 (NH), 1653 (C=O), 1365 (SO_2), 1149 (SO_2). ^1H NMR (acetone-d_6) δ 0.93 (dd, 3H, $J = 7.4$ Hz, $J = 7.4$ Hz, CH_3), 1.83–1.89 (m, 2H, CH_2), 2.38 (s, 3H, CH_3), 4.40 (dd, 1H, $J = 7.5$ Hz, $J = 7.6$ Hz, CH), 7.32 (d, 2H, $J = 8.1$ Hz, ArH), 7.76 (d, 2H, $J = 8.0$ Hz, ArH), 9.50, 10.70 (2xbr s., 2H, 2xNH). EI-MS: m/z 271 (M^+).

4e. Yield: 85%, m.p. 161–163°C. ν_{max} (cm^{-1}) 3319, 3292 (NH), 1653 (C=O), 1365, 1149 (SO_2). ^1H NMR (acetone-d_6) δ 0.98 (dd, 3H, $J = 7.2$ Hz, CH_3), 1.82–1.92 (m, 2H, CH_2), 4.38 (t, 1H, $J = 7.5$ Hz, CH), 7.65 (d, 2H, $J = 8.0$ Hz, ArH), 8.01 (d, 2H, $J = 8.0$ Hz, ArH), 9.72 (br s., 2H, NH_2), 11.25 (br s., 1H, NH). EI-MS m/z: 291 (M^+).

4f. Yield: 65%, m.p. 165–167°C. ν_{max} (cm^{-1}) 3297, 3242 (NH), 1671 (C=O), 1375, 1166 (SO_2). ^1H NMR (acetone-d_6) δ 0.89 (t, 3H, $J = 7.4$ Hz, CH_3), 1.84–1.89 (m, 2H, CH_2), 3.91 (s, 3H, OCH_3), 4.37 (t, 3H, $J = 7.4$ Hz, CH_3), 7.12 (d, 2H, $J = 8.2$ Hz, ArH), 7.72 (d, 2H, $J = 8.2$ Hz, ArH), 9.75 (br s., 2H, NH_2), 10.75 (br s., 1H, NH). EI-MS: m/z 287 (M^+).

4g. Yield: 61%, m.p. 114–116°C. ν_{max} (cm^{-1}) 3365, 3282 (NH), 1675 (C=O), 1367, 1155 (SO_2). ^1H NMR (acetone-d_6) δ 2.03(s, 3H, CH_3S), 2.12–2.24 (m, 2H, CH_2), 2.52–2.59 (m, 2H, CH_2), 2.38 (s, 3H, CH_3), 4.68 (dd, 1H, $J = 8.0$ Hz, $J = 8.0$ Hz, CH), 7.35 (d, 2H, $J = 8.0$ Hz, ArH), 7.68 (d, 2H, $J = 8.0$ Hz, ArH), 9.30 (br s., 2H, NH_2), 10.51 (br s., 1H, NH). EI-MS: m/z 317 (M^+).

4h. Yield: 55%, m.p. 121–123°C. ν_{max} (cm^{-1}) 3342, 3271 (NH), 1672 (C=O), 1375, 1167 (SO_2). ^1H NMR (acetone-d_6) δ 2.11 (s, 3H, CH_3S), 2.15–2.27 (m, 2H, CH_2), 2.56–2.63 (m, 2H, CH_2), 4.65 (dd, 1H, $J = 8.2$ Hz, $J = 8.2$ Hz, CH), 7.57 (d, 2H, $J = 8.2$ Hz, ArH), 7.91 (d, 2H, $J = 8.2$ Hz, ArH), 9.57(br s., 2H, NH_2), 11.27 (br s., 1H, NH). EI-MS: m/z 337 (M^+).

4j. Yield: 81%, m.p. 151–153°C. ν_{max} (cm^{-1}) 3366, 3251 (NH), 1675 (C=O), 1378, 1165 (SO_2). EI-MS: m/z 257 (M^+).

4k. Yield: 89%, m.p. 155–157°C. ν_{max} (cm^{-1}) 3375, 3281 (NH), 1671 (C=O), 1369, 1165 (SO_2). ^1H NMR (acetone-d_6) δ 1.25 (d, 3H, $J = 7.0$ Hz, CH_3), 4.73–4.81 (m, 1H, *CH), 7.55 (d, 2H, $J = 8.0$ Hz, ArH), 7.80 (d, 2H, $J = 8.0$ Hz, ArH), 9.12 (br s., 2H, NH_2), 9.47, 10.38 (2xbr s., 2H, 2xNH). EI-MS: m/z 277 (M^+).

4l. Yield: 64%, m.p. 160–162°C. ν_{max} (cm^{-1}) 3388, 3282 (NH), 1672 (C=O), 1375, 1166 (SO_2). ^1H NMR (acetone-d_6) δ 1.35 (**d**, 3H, $J = 7.4$ Hz, CH_3), 3.91 (s, 3H, OCH_3), 4.55–4.63 (m, 1H, CH), 7.12 (d, 2H, $J = 8.0$ Hz,

ArH), 7.66 (d, 2H, $J = 8.0$ Hz, ArH), 9.45 (br s., 2H, NH_2), 10.92 (br s., 1H, NH). EI-MS: m/z 273 (M^+).

General Procedure for Preparation of Compounds 5a–l

To a solution of **4a** (5.5 mmol) in absolute EtOH (80 mL) was added CS_2 (6.6 mmol), followed by an addition of aq. solution of KOH (10 mL, 5.5 mmol). The reaction mixture was stirred for 15 min and then refluxed for 17 h. The solution was concentrated, diluted with water, and acidified with 4N HCl to pH 2–3. The solid obtained was filtered, washed with water, and recrystallized from 60% aqueous EtOH. Compounds **5b–l** were synthesized in a similar manner.

5a. Yield: 85%, m.p. 145–147°C. ν_{max} (cm^{-1}) 3206 (NH), 2564 (SH), 1589 (C=N), 1379 (SO_2 asym), 1179 (SO_2 sym). ^{1}H NMR (acetone-d_6) δ 1.89–1.96 (m, 2H, CH_2), 2.4 (s, 3H, CH_3), 2.8 (t, 2H, $J = 7.4$ Hz, CH_2), 3.04 (t, 2H, $J = 6.6$ Hz, CH_2), 7.38 (d, 2H, $J = 8.10$ Hz, ArH), 7.72 (d, 2H, $J = 8.2$ Hz, ArH), 12.8 (bs, 1H, NH). Anal. calcd. for $C_{12}H_{15}O_3N_3S_2$ (313.39): C, 45.99; H, 4.82; N, 13.41. Found: C, 45.71; H, 4.49; N, 13.22. EI-MS: m/z 313(M^+).

5b. Yield: 85%, m.p. 171–172°C. ν_{max} (cm^{-1}) 3287 (NH), 2545 (C=N), 1375, 1165 (SO_2). ^{1}H NMR (acetone-d_6) δ 1.92–1.98 (m, 2H, CH_2), 2.80 (t, 2H, $J = 7.5$ Hz, CH_2), 3.09 (t, 2H, $J = 6.7$ Hz, CH_2), 7.63 (d, 2H, $J = 8.1$ Hz, ArH), 7.87 (d, 2H, $J = 8.2$ Hz, ArH), 12.80 (br s.,1H, NH). Anal. calcd. for $C_{11}H_{12}O_3N_3S_2Cl$ (333.79): C, 39.58; H, 3.62; N, 12.59. Found: C, 39.68; H, 3.74; N, 12.77. EI-MS: m/z 335 (M^+).

5c. Yield: 87%, m.p. 159–161°C. ν_{max} (cm^{-1}) 3216 (NH), 2548 (SH), 1589 (C=N), 1369, 1179 (SO_2). ^{1}H NMR (acetone-d_6) δ 1.89–1.96 (m, 2H, CH_2), 2.79 (t, 2H, $J = 6.5$ Hz, CH_2), 3.00 (q, 2H, $J = 6.7$ Hz, CH_2), 3.88 (s, 3H, OCH_3), 7.07 (d, 2H, $J = 8.1$ Hz, ArH), 7.76 (d, 2H, $J = 8.2$ Hz, ArH) 12.92(br s., 1H, NH). Anal. calcd. for $C_{12}H_{15}O_4N_3S_2$ (329.39): C, 43.76; H, 4.60; N, 12.76. Found: C, 43.44; H, 4.56; N, 12.87. EI-MS: m/z 330 (M^+).

5d. Yield: 87%, m.p. 205–205°C, $[\alpha]_D = +44°$ (c = 1.05, acetone). ν_{max} (cm^{-1}) 3266 (NH), 2565 (SH), 1582 (C=N), 1356, 1145 (SO_2). ^{1}H NMR (acetone-d_6) δ 0.92 (t, 3H, $J = 7.4$ Hz, CH_3), 1.82–1.90 (m, 2H, CH_2), 2.38 (s, 3H, CH_3), 4.38 (dd, 1H, $J = 7.5$ Hz, $J = 7.6$ Hz, CH), 7.32 (d, 2H, $J = 8.1$ Hz, ArH), 7.66 (d, 2H, $J = 8.2$ Hz, ArH,), 12.7 (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, 45.81; H, 4.56; N, 13.26. EI-MS: m/z 313 (M^+).

5e. Yield: 81%, m.p. 191–192°C, $[\alpha]_D = +24°$ (c = 0.60, acetone). ν_{max} (cm^{-1}) 3233 (NH), 2545 (SH), 1589 (C=N), 1365, 1149 (SO_2). ^{1}H NMR (acetone-d_6) δ 0.94 (t, 3H, $J = 7.4$ Hz, CH_3), 1.84–1.90 (m, 2H, CH_2), 4.39 (dd, 1H, $J = 7.8$ Hz, $J = 7.5$ Hz, CH), 7.61 (d, 2H, $J = 8.0$ Hz, ArH), 7.85

(d, 2H, $J = 8.0$ Hz, ArH) 12.89 (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, 39.59; H, 3.65; N, 12.20. EI-MS: *m/z* 332/334 (M^+).

5f. Yield: 91%, m.p. 211–213°C, $[\alpha]_D = +43°$ (c = 1.04, acetone). ν_{max} (cm^{-1}) 3266 (NH), 2565 (SH), 1582 (C=N), 1356, 1145(-SO_2). ^1H NMR (acetone-d_6) δ 0.92 (t, 3H, $J = 7.5$ Hz, CH_3), 1.82–1.89 (m, 2H, CH_2), 3.86 (s, 3H, OCH_3), 4.36 (dd, 1H, $J = 7.6$ Hz, $J = 7.7$ Hz, CH), 7.01 (d, 2H, $J = 8.0$ Hz, ArH), 7.71 (d, 2H, $J = 8.2$ Hz, ArH). Anal. calcd. for $C_{12}H_{15}O_4N_3S_2$ (329.39): C, 43.76; H, 4.60; N, 12.76; Found: C, 43.56; H, 4.37; N, 12.78. EI-MS: *m/z* 330 (M^+).

5g. Yield: 61%, m.p. 163–165°C, $[\alpha]_D = +42°$ (c = 1.02, acetone). ν_{max} (cm^{-1}) 3275 (NH), 2550 (SH), 1589 (C=N), 1351, 1161 (SO_2). ^1H NMR (acetone-d_6) δ 2.01 (s, 3H, CH_3S), 2.08–2.15 (m, 2H, CH_2), 2.39 (s, 3H, CH_3-Ar), 2.50–2.59 (m, 2H, CH_2), 4.69 (dd, 1H, $J = 8.1$ Hz, $J = 8.0$ Hz, CH), 7.35 (d, 2H, $J = 8.0$ Hz, ArH), 7.67 (d, 2H, $J = 8.1$ Hz, ArH), 12.88 (br s., 1H, NH). Anal. calcd. for $C_{13}H_{17}O_3N_3S_3$ (359.35): C, 43.42; H, 4.77; N, 11.69. Found: C, 43.16; H, 4.85; N, 11.53. EI-MS: *m/z* 359 (M^+).

5h. Yield: 67%, m.p. 171–172°C, $[\alpha]_D = +45°$ (c = 1.07, acetone). ν_{max} (cm^{-1}) 3235 (NH), 1586 (C=N), 2553 (SH), 1379, 1167 (SO_2). ^1H NMR (acetone-d_6) δ 2.01 (s, 3H, CH_3S), 2.09–2.15 (m, 2H, CH_2), 2.48–2.57 (m, 2H, CH_2), 4.73 (dd, 1H, $J = 8.0$ Hz, $J = 8.0$ Hz, CH), 7.57 (d, 2H, $J = 8.1$ Hz. ArH), 7.83 (d, 2H, $J = 8.1$ Hz, ArH), 12.86 (br s., 1H, NH). Anal. calcd. for $C_{12}H_{14}O_3Cl\,N_3S_3$ (379.89): C, 37.94; H, 3.72; N, 11.06. Found: C, 37.65; H, 3.72; N, 11.14. EI-MS: *m/z* 378/380 (M^+).

5i. Yield: 65%, m.p. 158–160°C, $[\alpha]_D = +29°$ (c = 0.65, acetone). ν_{max} (cm^{-1}) 3271 (NH), 1585 (C=N), 1357, 1166 (SO_2). ^1H NMR (acetone-d_6) δ 2.02 (s, 3H, CH_3S), 2.07–2.14 (m, 2H, CH_2), 2.50–2.58 (m, 2H, CH_2), 3.88 (s, 3H, OCH_3), 4.37 (dd, 1H, $J = 8.0$ Hz, $J = 8.0$ Hz, CH), 7.01 (d, 2H, $J = 8.1$ Hz, ArH), 7.69 (d, 2H, $J = 8.2$ Hz, ArH), 12.89 (br s., 1H, NH). Anal. calcd. for $C_{13}H_{17}O_4N_3S_3$ (375.34): C, 41.57; H, 4.57; N, 11.21. Found: C, 41.75; H, 4.66; N, 11.36. EI-MS: *m/z* 375 (M^+).

5j. Yield: 83%, m.p. 205–207°C, $[\alpha]_D = +23°$ (c = 0.55, acetone). ν_{max} (cm^{-1}) 3282 (NH), 2551 (SH), 1589 (C=N), 1375, 1126 (SO_2). ^1H NMR (acetone-d_6) δ 1.46 (d, 3H, 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. EI-MS: *m/z* 299 (M^+).

5k. Yield: 90%, m.p. 172–174°C, $[\alpha]_D = +42°$ (c = 1.0, acetone). ν_{max} (cm^{-1}) 3285 (NH), 2550 (SH), 1611 (C=N), 1356 (SO_2 asym), 1149 (SO_2 sym). ^1H 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, $J = 8.0$ Hz, CH_2), 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. EI-MS: m/z 318/320 (M^+).

5l. Yield 79%, m.p. 177–179°C, $[\alpha]_D = +44°$ (c = 1.0, acetone). ν_{max} (cm^{-1}) 3266 (NH), 2550 (SH), 1586 (C=N), 1371, 1162 (SO_2). ^{1}H NMR (acetone-d_6) δ 1.53 (d, 3H, $J = 7.2$ Hz, CH_3), 3.89 (s, 3H, OCH_3), 4.74–4.65 (m, 1H, CH), 7.52(d, 2H, $J = 8.1$ Hz, ArH), 7.76 (d, 2H, $J = 8.1$ Hz, ArH), 12.85(br s., 1H, NH). Anal. calcd. for $C_{11}H_{13}O_4N_3S_2$ (315.36): C, 41.90; H, 4.21; N, 13.32. Found: C, 42.13; H, 4.20; N, 13.22. EI-MS: m/z 315 (M^+).

General Procedure for Preparation of *N,N′*-Diacylhydrazines 7a–e

To a suspension of **6a–e** (5.0 mmol) in dry acetonitrile (50 mL) was added, in portion, 4-nitrobenzoyl chloride (5.1 mmol), and the reaction mixture was stirred for 5–7 h at 23°C. The solution was concentrated, and the solid product was filtered and recrystallized from aqueous EtOH to afford **7a–e**. Compound **7a** (83%) had m.p. 241–243°C (lit.[2] 273–275°C, 67%).

7b. Yield: 91%, m.p. 231–233°C. ν_{max} (cm^{-1}) 3181 (NH), 3011 (ArH), 1655 (C=O).

7c. Yield: 82%, m.p. 180–182°C. ν_{max} (cm^{-1}) 3217 (NH), 3037 (ArH), 1649 (C=O).

7d. Yield: 79%, m.p. 216–218°C. ν_{max} (cm^{-1}) 3207 (NH), 3017 (ArH), 1647 (C=O).

7e. Yield: 90%, m.p. 277–279°C. ν_{max} (cm^{-1}) 3241 (NH), 3017 (ArH), 1643 (C=O).

General Procedure for Preparation of 2,5-Disubstituted 1,3,4-Oxadiazoles (8a–e)

A mixture of *N,N′*-diacylhydrazines **7a–e** (2.0 mmol) and thionyl chloride (10 mL) was heated under reflux for 2 h. After cooling, the resulting mixture was poured onto crushed ice and stirred vigorously. The solid product thus obtained was filtered off, washed with water, and recrystallized from aqueous ethanol to afford **8a–e**.

8a. Yield: 71%, m.p. 183–185°C. ν_{max} (cm^{-1}) 1601 (C=N), 1275 (Ar-NO_2). ^{1}H NMR (DMSO-d_6) δ 2.44 (s, 3H, CH_3-Ar), 7.27 (d, 2H, $J = 8.0$ Hz, ArH), 7.44 (d, 2H, $J = 8.0$ Hz, ArH), 8.32 (d, 2H, $J = 8.2$ Hz, ArH), 8.42 (d, 2H, $J = 8.2$ Hz, ArH). EI-MS: m/z 281 (M^+).

8b. Yield: 91%, m.p. 193–195°C. ν_{max} (cm^{-1}) 1603 (C=N), 1271 (Ar-NO_2). ^{1}H NMR (DMSO-d_6) δ 3.81 (s, 3H, OCH_3), 7.29–7.89 (m, 6H, ArH), 8.21 (d, 2H, $J = 7.2$ Hz, ArH). EI-MS: m/z 297 (M^+).

8c. Yield: 91%, m.p. 189–191°C. ν_{max} (cm^{-1}) 1621 (C=N), 1277(Ar-NO_2). ^1H NMR (DMSO-d_6) δ 3.79 (s, 9H, OCH_3), 6.95 (s, 2H, ArH), 7.96 (d, 2H, $J = 8.0$ Hz, ArH), 8.34 (d, 2H, $J = 8.0$, ArH). EI-MS: m/z 357 (M^+).

8d. Yield: 91%, m.p. 176–177°C. ν_{max} (cm^{-1}) 1621, (C=N), 1271 (Ar-NO_2). ^1H NMR (DMSO-d_6) δ 7.65–7.91 (m, 6H, ArH), 8.32 (d, 2H, $J = 8.0$ Hz, ArH). EI-MS: m/z 301 (M^+).

8e. Yield, 83%, m.p. 210–212°C. IR (ν, cm^{-1}): 1621 (C=N), 1271 (Ar-NO_2). ^1H NMR (DMSO-d_6) δ 7.66 (d, 2H, $J = 7.1$ Hz, ArH), 8.13–8.25 (m, 6H, ArH). EI-MS: m/z 301 (M^+).

General Procedure for Preparation of Compounds (9a–e)

To a suspension of **8a–e** (1.63 mmol) in EtOH (80 mL) containing 10% Pd/C (0.03 g) was added 10 mL of 80% hydrazine monohydrate dropwise at 85°C, followed by heating under reflux for 25 h. After cooling, the mixture was filtered, and the filtrate was evaporated to dryness. The crude product was recrystallized from EtOH to give **9a–e**.

9a. Yield: 81%, m.p. 191–193°C, ν_{max} (cm^{-1}) 3454, 3348 (NH), 1606, 1581 (C=N). ^1H NMR (DMSO-d_6) δ 2.38 (s, 3H, CH_3-Ar), 6.75 (d, 2H, $J = 8.1$ Hz, ArH), 7.26 (d, 2H, $J = 8.1$ Hz, ArH), 7.8 (d, 2H, $J = 8.1$ Hz, ArH), 7.96 (d, 2H, $J = 8.2$ Hz, ArH). EI-MS: m/z 251 (M^+).

9b. Yield: 89%, m.p. 205–207°C, ν_{max} (cm^{-1}) 3452, 3338 (NH), 1602, 1582 (C=N). ^1H NMR (DMSO-d_6) δ 3.89 (s, 3H, OCH_3), 6.72 (d, 2H, $J = 8.0$ Hz, ArH), 7.30 (d, 2H, $J = 8.0$ Hz, ArH), 7.73 (d, 2H, $J = 7.7$ Hz, ArH), 7.92 (d, 2H, $J = 7.8$ Hz, ArH). EI-MS: m/z 267 (M^+).

9c. Yield: 93%, m.p. 197–199°C. ν_{max} (cm^{-1}) 3399, 3348 (NH), 1586, 1561 (C=N). ^1H NMR (DMSO-d_6) δ 3.88 (s, 9H, OCH_3), 6.71 (d, 2H, $J = 8.5$ Hz, ArH), 7.25 (s, 2H, ArH), 7.86 (d, 2H, $J = 8.5$ Hz, ArH). EI-MS: m/z 327 (M^+).

9d. Yield: 73%, m.p. 181–183°C. ν_{max} (cm^{-1}) 3394, 3318 (NH), 1596, 1561 (C=N). ^1H NMR (DMSO-d_6) δ 6.80 (d, 2H, $J = 7.4$ Hz, ArH), 7.91–8.14 (m, 6H, ArH). EI-MS: m/z 271(M^+).

9e. Yield: 79%, m.p. 210–212°C. ν_{max} (cm^{-1}) 3424, 3338 (NH), 1606, 1582 (C=N). ^1H NMR (DMSO-d_6) δ 7.20 (d, 2H, $J = 8.0$ Hz, ArH), 7.76 (d, 2H, $J = 8.0$ Hz, ArH), 7.85 (d, 2H, $J = 8.1$ Hz, ArH). EI-MS: m/z 271 (M^+).

General Procedure for Preparation of Benzenesulfonamides Bearing 2,5-Disubstituted 1,3,4-Oxadiazoles (10a–j and 11a–j)

A mixture of **9a–e** (0.75 mmol), Et_3N (0.22 mmol), and a catalytic amount of DMAP (25 mg) was stirred in dry CH_3Cl (50 mL) for 15 min.

Sulfonyl chloride (1.5 mmol) was then added to the previously mentioned solution, and the mixture was refluxed for 5–9 h. The reaction mixture was washed with dilute HCl, brine solution, and water, and the organic layer was dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was recrystallized from aq. EtOH. The sulfonamides **10a–j** and **11a–j** were separated by preparative TLC, using ethyl acetate/pet. ether as an eluent.

10a. Yield, 61%, m.p. 193–195°C. ν_{max} (cm^{-1}) 3266 (NH), 1589 (C=N), 1379, 1149 (SO_2). ^{1}H NMR (acetone-d_6) δ 2.44 (s, 3H, CH_3-Ar), 2.84 (s, 3H, CH_3-Ar), 7.26 (d, 2H, $J = 8.1$ Hz, ArH), 7.43 (d, 2H, $J = 8.1$ Hz, ArH), 7.49 (d, 2H, $J = 8.1$ Hz, ArH), 7.81 (d, 2H, $J = 8.1$, Hz, ArH), 8.06 (d, 2H, $J = 7.9$ Hz, ArH), 8.20 (d, 2H, $J = 7.9$ Hz, ArH), 10.54 (br s., 1H, NH). Anal. calcd. for $C_{22}H_{19}O_3N_3S$ (405.47): C, 65.17; H, 4.72; N, 10.36. Found: C, 65.24; H, 4.71; N, 10.55. EI-MS: m/z 405 (M^+).

10b. Yield: 51%, m.p. 190–191°C. ν_{max} (cm^{-1}) 3281 (NH), 1595 (C=N), 1365, 1149 (SO_2). 1089 (br s, NH). ^{1}H NMR (acetone-d_6) δ 2.49 (s, 3H, CH_3-Ar), 3.89 (s, 3H, OCH_3), 7.1 (d, 2H, $J = 7.8$ Hz, ArH), 7.45 (d, 2H, $J = 7.9$ Hz, ArH), 7.49 (d, 2H, $J = 8.0$ Hz, ArH), 7.98 (d, 2H, $J = 8.1$ Hz, ArH), 8.06 (d, 2H, $J = 8.0$ Hz, ArH), 8.12 (d, 2H, $J = 8.1$ Hz, ArH). Anal. calcd. for $C_{22}H_{19}O_4N_3S$ (421.47): C, 62.71; H, 4.54; N, 9.97. Found: C, 62.85; H, 4.41; N, 9.66. EI-MS: m/z 421 (M^+).

10c. Yield: 54%, m.p. 197–199°C. ν_{max} (cm^{-1}) 3298 (NH), 1598 (C=N), 1377, 1164 (SO_2). ^{1}H NMR (acetone-d_6) δ 2.45(s, 3H, CH_3-Ar), 3.91 (s, 9H, OCH_3), 5.74(s, 1H, NH), 7.25 (d, 2H, $J = 8.0$ Hz, ArH), 7.41 (s, 2H, ArH), 7.50 (d, 2H,$J = 8.0$ Hz, ArH), 8.16 (d, 2H, $J = 8.1$ Hz, ArH), 8.22 (d, 2H, $J = 8.1$ Hz, ArH). 10.84 (br s., 1H, NH). Anal. calcd. for $C_{24}H_{23}O_6N_3S$ (481.28): C, 59.85; H, 4.82; N, 8.73. Found: C, 60.13; H, 4.62; N, 8.69. EI-MS: m/z 481 (M^+).

10d. Yield: 63%, m.p. 187–188°C. ν_{max} (cm^{-1}) 3258 (NH), 1581 (C=N), 1357, 1149 (SO_2). ^{1}H NMR (acetone-d_6) δ 2.45 (s, 3H, CH_3), 7.48 (d, 2H, $J = 8.1$ Hz, ArH), 7.59–8.08 (m, 9H, ArH) 8.14 (s, 1H, ArH). 10.88 (br s., 1H, NH). Anal. calcd. for $C_{21}H_{16}O_3ClN_3S$ (425.89): C, 59.22; H, 3.81; N, 9.87. Found: C, 59.39; H, 3.75; N, 9.66. EI-MS: m/z 424/426 (M^+).

10e. Yield: 53%, m.p. 183–185°C. ν_{max} (cm^{-1}) 3266 (NH), 1587 (C=N), 1351, 1161 (SO_2). ^{1}H NMR (acetone-d_6) δ 2.49 (s, 3H, CH_3-Ar), 7.17 (d, 2H, $J = 8.1$ Hz, ArH), 7.31 (d, 2H, $J = 8.1$ Hz, ArH), 7.51 (m, 4H, ArH), 7.78 (d, 2H, $J = 8.0$ Hz, ArH), 8.10 (d, 2H, $J = 8.0$ Hz, ArH). 10.91 (br s., 1H, NH). Anal. calcd. for $C_{21}H_{16}O_3ClN_3S$ (425.89): C, 59.22; H, 3.81; N, 9.91. Found: C, 59.25; H, 3.90; N, 10.11. EI-MS: m/z 424/426 (M^+).

10f. Yield: 61%, m.p. 194–195°C. ν_{max} (cm^{-1}) 3291 (NH), 1582 (C=N), 1372, 1166 (SO_2). ^{1}H NMR (acetone-d_6) δ 2.84 (s, 3H, CH_3-Ar), 3.88 (s, 3H, OCH_3), 6.92 (d, 2H, $J = 7.5$ Hz, ArH), 7.41 (d, 2H, $J = 8.0$ Hz, ArH),

7.49 (d, 2H, $J=8.0$ Hz, ArH), 7.78 (d, 2H, $J=8.1$ Hz, ArH), 7.97 (d, 2H, $J=8.1$ Hz, ArH), 8.06 (d, 2H, $J=8.0$ Hz, ArH). 10.74 (br s., 1H, NH). Anal. calcd. for $C_{22}H_{19}O_4N_3S$ (421.47): C, 62.71; H, 4.54; N, 9.97. Found: C, 62.33; H, 4.71; N, 10.33. EI-MS: *m/z* 421 (M^+).

10g. Yield: 57%, m.p. 177–179°C. ν_{max} (cm^{-1}) 3289 (NH), 1592 (C=N), 1379, 1159 (SO_2). ^1H NMR (acetone-d_6) δ 3.88 (s, 6H, OCH_3), 6.91 (d, 4H, $J=7.5$ Hz, ArH), 7.49 (d, 2H, $J=7.9$ Hz, ArH), 7.91–8.05 (m, 6H, ArH), 10.89 (br s.,1H, NH). Anal. calcd. for $C_{22}H_{19}O_5N_3S$ (435.47): C, 60.68; H, 4.41; N, 9.65. Found: C, 60.41; H, 4.63; N, 9.68. EI-MS. *m/z* 435 (M^+).

10h. Yield: 41%, m.p. 187–189°C. ν_{max} (cm^{-1}) 3295 (NH), 1581 (C=N), 1378, 1167 (SO_2). ^1H NMR (acetone-d_6) δ 3.89 (s, 12H, OCH_3), 6.91 (d, 2H, $J=7.6$ Hz, ArH), 7.12 (d, 2H, $J=7.6$ Hz, ArH), 7.26 (s, 1H, ArH), 7.91 (d, 2H, $J=8.1$ Hz, ArH), 7.98 (d, 2H, $J=8.1$ Hz, ArH). 11.54 (br s. 1H, NH). Anal. calcd. for $C_{24}H_{23}O_7N_3S_2$(497.52): C, 57.94; H, 4.66; N, 8.45. Found: C, 57.70; H, 4.65; N, 8.18. EI-MS: *m/z* 497 (M^+).

10i. Yield: 45%, m.p. 175–177°C. ν_{max} (cm^{-1}) 3266 (NH), 1592 (C=N), 1375, 1166 (SO_2). ^1H NMR (acetone-d_6) δ 3.86 (s, 3H, OCH_3), 7.02 (d, 2H, $J=8.1$ Hz, ArH), 7.48 (d, 2H, $J=8.0$ Hz, ArH), 7.76 (d, 2H, $J=8.1$ Hz, ArH), 7.61–7.90 (m, 5H, ArH), 8.13 (s, 1H, ArH). 11.14 (br s.,1H, NH). Anal. calcd. for $C_{21}H_{16}O_4ClN_3S$ (441.89): C, 57.10; H, 3.65; N, 9.51. Found: C, 57.19; H, 3.68; N, 9.51. EI-MS: *m/z* 440/442 (M^+).

10j. Yield: 48%, m.p. 195–196°C. ν_{max} (cm^{-1}) 3266 (NH), 1587 (C=N), 1351, 1161 (SO_2). ^1H NMR (acetone-d_6) δ 3.88 (s, 3H, OCH_3), 6.92 (d, 2H, $J=7.4$ Hz, ArH), 7.15 (d, 2H, $J=7.4$ Hz, ArH), 7.49 (d, 2H, $J=8.1$ Hz, ArH), 7.76 (d, 2H, $J=8.1$ Hz, ArH), 7.84 (d, 2H, $J=7.8$ Hz, ArH), 8.14 (d, 2H, $J=7.8$ Hz, ArH). 10.67 (br s., 1H, NH). Anal. calcd. for $C_{31}H_{29}O_{10}N_3S_3$ (441.89): C, 57.01; H, 3.65; N, 14.83. Found: C, 57.15; H, 3.67; N, 14.78. EI-MS: *m/z* 441 (M^+).

11a. Yield: 79%, m.p. 214–216°C. ν_{max} (cm^{-1}) 1592 (C=N), 1369, 1165 (SO_2). ^1H NMR (acetone-d_6) δ 2.49 (s, 6H, CH_3-Ar), 2.88 (s, 6H, $2CH_3$-Ar-oxa), 7.27 (d, 2H, $J=8.0$ Hz, ArH), 7.44 (d, 4H, $J=8.0$ Hz, ArH), 7.49 (d, 4H, $J=8.1$ Hz, ArH), 7.80 (d, 4H, $J=8.1$ Hz, ArH), 8.07 (d, 4H, $J=8.2$ Hz, ArH), 8.19 (d, 4H, $J=8.2$ Hz, ArH). Anal. calcd. for $C_{29}H_{25}O_5N_3S_2$ (559.65). C, 62.24; H, 4.50; N, 7.51. Found: C, 62.20; H, 4.23; N, 7.31. EI-MS: *m*/z 559 (M^+).

11b. Yield: 71%, m.p. 210–212°C. ν_{max} (cm^{-1}) 1586 (C=N), 1378, 1147 (SO_2). ^1H NMR (acetone-d_6) δ 2.48 (s, 6H, $2CH_3$), 3.88 (s, 3H, OCH_3), 6.98 (d, 2H, $J=7.9$ Hz, ArH), 7.35 (d, 2H, $J=7.9$ Hz, ArH), 7.48 (d, 2H, $J=8.0$ Hz, ArH), 7.89 (d, 2H, $J=8.1$ Hz, ArH), 7.95 (d, 2H, $J=8.1$ Hz, ArH), 8.05 (d, 2H, $J=8.0$ Hz, ArH). Anal. calcd. for $C_{29}H_{25}O_6N_3S_2$ (575.65): C, 60.51; H, 4.38; N, 7.30. Found: C, 60.77; H, 4.19; N, 7.39. EI-MS *m/z* 575 (M^+).

11c. Yield: 69%, m.p. 217–219°C. ν_{max} (cm^{-1}) 1595 (C=N), 1379, 1165 (SO_2).^{1}H NMR (acetone-d_6) δ 2.49 (s, 3H, CH_3-Ar), 3.90 (s, 9H, OCH_3), 7.23 (d, 2H, $J=8.4$ Hz, ArH), 7.40 (s, 2H, ArH), 7.49 (d, 2H, $J=8.4$ Hz, ArH), 8.14 (d, 2H, $J=8.2$ Hz, ArH), 8.21 (d, 2H, $J=8.2$ Hz, ArH). Anal. calcd. for $C_{31}H_{29}O_8N_3S_2$ (635.71): C, 58.57; H, 4.61; N, 6.61. Found: C, 58.28; H, 4.51; N, 6.40. EI-MS: m/z 635 (M^+).

11d. Yield: 62%, m.p. 221–223°C. ν_{max} (cm^{-1}) 1589 (C=N), 1371, 1166 (SO_2). ^{1}H NMR (acetone-d_6) δ 2.49 (s, 6H, CH_3), 7.51 (d, 4H, $J=8.1$ Hz, ArH), 7.60–7.98 (m, 11H, ArH), 8.13 (s, 1H, ArH). Anal. calcd. for $C_{28}H_{22}O_5ClN_3S_2$ (579.07): C, 58.08; H, 3.83; N, 7.26. Found: C, 58.34; H, 3.85; N, 7.50. EI-MS: m/z 578/580 (M^+).

11e. Yield: 63%, m.p. 214–215°C. ν_{max} (cm^{-1}) 1585 (C=N), 1353, 1159 (SO_2). ^{1}H NMR (acetone-d_6) δ 2.42 (s, 6H, CH_3-Ar), 7.16 (d, 2H, $J=8.0$ Hz, ArH), 7.30 (d, 4H, $J=7.9$ Hz, ArH), 7.50 (m, 4H, ArH), 7.77 (d, 2H, $J=7.7$ Hz, ArH), 8.08 (d, 2H, $J=7.9$ Hz, ArH). Anal. calcd. for $C_{28}H_{22}O_5ClN_3S_2$ (579.07): C, 58.77; H, 3.83; N, 7.31. Found: C, 58.56; H, 3.71; N, 7.29. EI-MS: m/z 578/580 (M^+).

11f. Yield: 65%, m.p. 219–222°C. ν_{max} (cm^{-1}) 1583 (C=N), 1377, 1165 (SO_2). ^{1}H NMR (acetone-d_6) δ 2.85 (s, 3H, CH_3-Ar), 3.89 (s, 6H, OCH_3), 6.93 (d, 4H, $J=8.0$ Hz, ArH), 7.15 (d, 2H, $J=8.1$ Hz, ArH), 7.46 (d, 2H, $J=8.0$ Hz, ArH), 7.93–7.98 (m, 8H, ArH). Anal. calcd. for $C_{29}H_{25}O_7N_3S_2$ (559. 59): C, 62.23; H, 4.50; N, 7.51. Found: C, 62.07; H, 4.51; N, 7.81. EI-MS: m/z 559 (M^+).

11g. Yield: 72%, m.p. 207–209°C. ν_{max} (cm^{-1}) 1579 (C=N), 1355, 1161 (SO_2). ^{1}H NMR (acetone-d_6) δ 3.89 (s, 6H, OCH_3), 6.93 (d, 6H, $J=7.2$ Hz, ArH), 7.47 (d, 2H, $J=7.5$ Hz, ArH), 7.93–7.98 (m, 8H, ArH). Anal. calcd. for $C_{29}H_{25}O_8N_3S_2$ (607.65): C, 57.32; H, 4.15; N, 6.92. Found: C, 57.52; H, 4.18; N, 7.23. EI-MS: m/z 607 (M^+).

11h. Yield: 69%, m.p. 219–220°C. ν_{max} (cm^{-1}) 1585 (C=N), 1375, 1165 (SO_2). ^{1}H NMR (acetone-d_6) δ 3.90(s, 15H, OCH_3), 6.93 (d, 4H, $J=7.8$ Hz, ArH), 7.13 (d, 2H $J=7.8$ Hz, ArH), 7.26 (s, 1H, ArH), 7.78 (d, 2H, $J=8.0$ Hz, ArH), 7.79 (d, 4H, $J=8.0$ Hz, ArH). Anal. calcd. for $C_{31}H_{29}O_{10}N_3S_3$ (699.77): C, 53.21; H, 4.21; N, 6.01. Found: C, 53.51; H, 4.29; N, 5.94. EI-MS: m/z 699 (M^+).

11i. Yield: 64%, m.p. 195–197°C. ν_{max} (cm^{-1}) 1582 (C=N), 1378, 1165 (SO_2). ^{1}H NMR (acetone-d_6) δ 3.89 (s, 6H, OCH_3), 6.92 (d, 4H, $J=8.0$ Hz, ArH), 7.12 (d, 2H, $J=8.0$ Hz, ArH), 7.75–7.95 (m, 10H, ArH). Anal. calcd. for $C_{28}H_{22}O_7ClN_3S_2$ (611.07): C, 55.04; H, 3.63; N, 6.80; S, 10.53 Found: C, 54.86; H, 3.57; N, 7.03. EI-MS: m/z 610/612 (M^+).

11j. Yield: 75%, m.p. 230–232°C. ν_{max} (cm^{-1}) 1569 (C=N), 1365, 1148 (SO_2). ^{1}H NMR (acetone-d_6) δ 3.89 (s, 6H, OCH_3), 6.91 (d, 4H, $J=7.0$ Hz, ArH), 7.48 (d, 2H, $J=7.1$ Hz, ArH), 7.76–7.89 (m, 8H, ArH), 8.12

(d, 2H, $J = 7.5$ Hz, ArH). Anal. calcd. for $C_{28}H_{22}O_7ClN_3S_2$ (611.07): C, 55.01; H, 3.62; N, 6.88. Found: C, 54.90; H, 3.61; N, 7.15. EI-MS: m/z 610/612 (M^+).

REFERENCES

[1] B. L. Valee and D. S. Auld, *Biochemistry*, **29,** 5447 (1990).
[2] X. J. Zou and J. G. Y. Zhang, *J. Chem. Res. (s)*, **5,** 228 (2002).
[3] K. Mogilaiah and G. R. Sudhakar, *Ind. J. Heterocycl. Chem*., **11,** 163 (2001).
[4] S. Cao, X. H. Qian, G. H. Song, and Q. C. Huang, *J. Fluorine Chem.*, **117,** 63 (2002).
[5] Y. Zhang, R. Z. Y. Qiao, P. F. Xu, Z. Y. Zhang, Q. Wang, L. M. Mao, and K. B. Yu, *J. Chin. Chem. Soc*., **49,** 369 (2002).
[6] R. Ahmad, R. Iqbal, H. Akhtar, Z. U. Haq, H. Duddeck, L. Stefaniak, and J. Sitkowski, *Nucleos., Nucleot., and Nucleic Acids*, **20,** 1671 (2001).
[7] R. C. Ogden and C. W. Flexner, Eds*., Protease Inhibitors in AIDS Therapy* (Marcel Dekker, New York, 2001).
[8] C. T. Supuran and A. Scozzafava, *Exp. Opin. Ther. Patents*, **10**, 575 (2000).
[9] C. T. Supuran and A. Scozzafava, *Curr. Med. Chem. Immunol. Endoc. Metab. Agents*, **1,** 61 (2001).
[10] M. A. Ilies, D. Vullo, J. Pastorek, A. Scozzafava, M. Ilies, M. T. Caproiu, S. Pastorokova, and C. T. Supuran, *J. Med. Chem.*, **46,** 2187 (2003).
[11] C. T. Supuran and A. Scozzafava, *J. Enzym Inhib.*, **15,** 597 (2000).
[12] S. Masereel, R. F. Abbate, A. Scozzafava, and C. T. Supuran, *J. Med. Chem.*, **45,** 312 (2002).
[13] A. Innocenti, M. A. Firnges, J. Antel, M. Wurl, A. Scozzafava, and C. T. Supuran, *Bioorg. Med. Chem. Lett.*, **15,** 1149 (2005).
[14] G. Xia, J. Li, A. Peng, S. Lai, S. Zhang, J. Shen, Z. Liu, X. Chen, and R. Ji, *Bioorg. Med. Chem. Lett.,* **15,** 2790 (2005).
[15] A. Casini, A. Scozzafava, A. Mastrolorenzo, and C. T. Supuran, *Curr. Cancer Drug Targets*, **2**, 55 (2002).
[16] A. Scozzafava, A. Mastrolorenzo, and C. T. Supuran, *Exp. Opin. Ther. Patents*, **11**, 785 (2001).
[17] K. Ladva, P. Patel, P. Upadhyay, and H. Parekh, *Ind. J. Chem*., **35B**, 1062 (1996).
[18] L. Y. Q. Lai, Y. Ferguson, and M. Jones, *Synth. Commun*., **33,** 3427 (2003).
[19] (a) B. S. Furniss, A. J. Hannaford, V. Rogers, P. W. G. Smith, and A. R. Tatchell, *Vogel Textbook of Practical Organic Chemistry*, p. 1135 (Longmann, London, 4th ed., 1978), (b) p. 505; (c) p. 1242.
[20] Y. Zhang, R. Z. Qiao, P. F. Xu, Z. Y. Zhang, Q. Wang, L. M. Mao, and K. B. Yu, *J. Chin. Chem. Soc*., **49,** 369 (2002).
[21] M. Zareef, A. Innocenti, R. Iqbal, J. H. Zaidi, M. Arfan, A. Scozzafava, and C. T. Supuran, *J. Enzyme Inhib. Med. Chem.,* **21,** 351 (2006).
[22] M. Zareef, R. Iqbal, N. G. Dominquez, J. Rodriques, J. H. Zaidi, M. Arfan, and C. T. Supuran, *J. Enzyme Inhib. Med. Chem.,* (2006) (accepted).
[23] X. Qian and R. Zhang, *J. Chem. Techol. Biotechnol*., **67,** 124 (1996).
[24] S. D. Young, S. F. Britcher, L. O. Tran, L. S. Payne, W. C. Lumma, T. A. Lyle, et al., *Antimicrob. Agents Chemother.*, **39,** 2602 (1995).
[25] H. Mitsuya, K. J. Weinhold, P. A. Furman, M. H. St. Clair, S. N. Lehrmann, R. C. Gallo, et al., *Proc. Natl. Acad. Sci. USA*, **82,** 7096 (1995).

[26] A. Asagarasu, T. Uchiyama, and K. Achiwa, *Pharm. Bull.*, **46,** 69 (1998).
[27] G. Bodey, B. Bueltmann, W. Duguid, D. Gibbs, H. Hanak, M. Hotchi, et al., *Eur. J. Clin. Microbiol. Infect. Dis.*, **11**, 99 (1992).
[28] J. Afeltra, J. F. Meis, J. W. Mouton, and P. E. Verweij, *AIDS*, **15**, 1067 (2001).
[29] J. G. Horsfall, *Bot. Rev.*, **11**, 419 (1945).