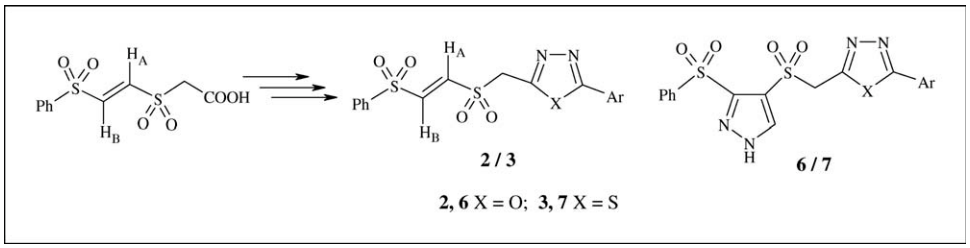
Venkatapuram Padmavathi,* Sanapalli Nagi Reddy, Guda Dinneswara Reddy, Bhumireddy Chinnachennaiahgari Venkatesh, and Adivireddy Padmaja

Department of Chemistry, Sri Venkateswara University, Tirupati 517 502, India
*E-mail: vkpuram2001@yahoo.com
Received April 13, 2010
DOI 10.1002/jhet.645
Published online 12 May 2011 in Wiley Online Library (wileyonlinelibrary.com).



A new class of bis heterocycles—sulfone linked pyrazolyl oxadiazoles thiadiazoles were prepared from *E*-phenylsulfonylethenesulfonylacetic acid and studied their antimicrobial activities.

J. Heterocyclic Chem., **48**, 1197 (2011).

INTRODUCTION

Pyrazole and its derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activities. During the past years, considerable evidence has been accumulated to demonstrate the efficacy of pyrazole derivatives including antibacterial [1], antifungal [2,3], herbicidal [4], insecticidal [5], and other biological activities [6,7]. Some commercial pesticides have been developed *viz*., fripronil (MB46030) [8], ET-751 [9] and pyrazolate (A-544) [10]. 1,3,4-Oxadiazole is associated with potent pharmacological activity due to the presence of toxophoric —N=C—O— linkage [11]. The 1,3,4-oxadiazole derivatives have been found to exhibit diverse biological activities such as antimicrobial [12], anti-HIV [12], antitubercular [13], antimalarial [14], analgesic [15], anti-inflammatory [16], anticonvulsant [17], and hypoglycemic [18]. 1,3,4-Thiadiazoles are known to possess antibacterial and antifungal properties similar to those of well-known sulphonamide drugs [19]. Thus, the 1,3,4-thiadiazoles exhibit a broad spectrum of biological activities possibly due to the presence of the toxophoric N=C—S moiety [20]. Prompted by these observations and in continuation of our search for bioactive molecules, we herein report the synthesis of novel bis heterocycles, emphasizing in particular on the strategy of combining two chemically different but pharmacologically compatible heterocycles in one frame to study their antibacterial and antifungal activities.

RESULTS AND DISCUSSION

The synthetic pathway followed for the preparation of the title compounds is as shown in Scheme 1. The multifunctional synthetic intermediate *E*-phenylsulfonyl ethenesulfonyl acetic acid (**1**) is prepared as per the literature procedure [21]. The compound **1** is treated with different aromatic acid hydrazides in the presence of phosphorus oxychloride to get 2-(((*E*)-2-(phenylsulfonyl)vinylsulfonyl)methyl)-5-aryl-1,3,4-oxadiazole (**2**). Intercoversion of **2** to 2-(((*E*)-2-(phenylsulfonyl)vinylsulfonyl) methyl)-5-aryl-1,3,4-thiadiazole (**3**) is effected by the reaction of **2** with thiourea. The ^{1}H-NMR spectra of **2a** and **3a** showed two doublets at δ 7.84, 8.04 and 7.81, 8.06 ppm for H_B and H_A. The coupling constant value J = 14.7 Hz indicates that they are in *trans* geometry. In addition, a singlet is observed at δ 5.43 in **2a** and at 5.52 ppm in **3a** for methylene protons. The olefin functionality in **2** and **3** is used to develop pyrazoline ring. Thus the 1,3-dipolar cycloaddition of etherial diazomethane to **2** and **3** in the presence of triethylamine gave 2-((4′,5′-dihydro-3′-(phenylsulfonyl)-1′*H*-pyrazol-4′-ylsulfonyl) methyl)-5-aryl-1,3,4-oxadiazole (**4**) and 2-((4′,5′-dihydro-3′-(phenylsulfonyl)-1′*H*-pyrazol-4′-ylsulfonyl)methyl)-5-aryl-1,3,4-thiadiazole (**5**), respectively (Tables 1 and 2). The ^{1}H-NMR spectra of **4a** and **5a** displayed AMX splitting pattern for pyrazoline ring protons. Thus three double doublets observed at δ 4.53, 4.10, 3.66 in **4a** and at 4.61, 4.22, 3.72 ppm in **5a** are assigned to H_A, H_M and H_X, respectively. The coupling constant values J_{AM} = 12.5, 12.8, J_{AX} = 5.8, 6.1, J_{MX} = 10.3, 10.7 Hz indicates that H_A, H_M are *cis*, H_A, H_X are *trans* and H_M, H_X are *geminal*. Apart from these, a singlet is observed at δ 4.52 in **4a** and at 4.55 ppm in **5a** due to methylene protons.

The compounds **4** and **5** are subjected to aromatization to get 2-((3′-(phenylsulfonyl)-1′*H*-pyrazol-4′-ylsulfonyl)methyl)-5-aryl-1,3,4-oxadiazole (**6**) and 2-

Scheme 1

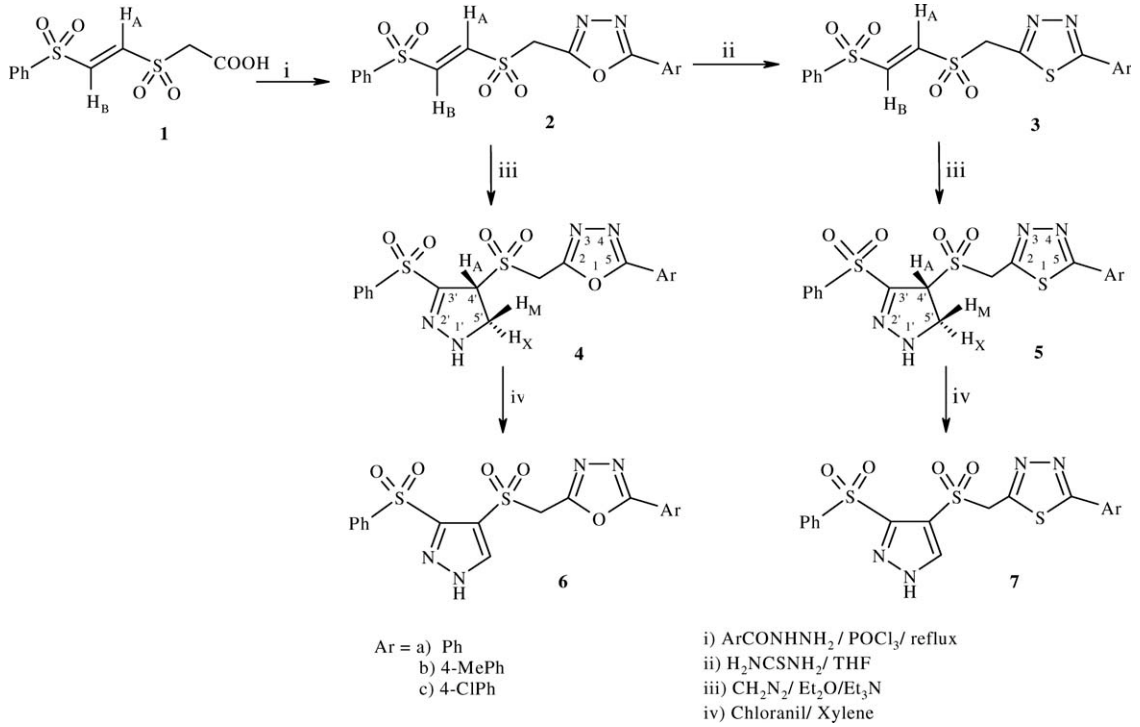


Table 1

Physical and analytical data of compounds **2–7**.

Compound	Mp (°C)	Yield (%)	Molecular formula	Analysis % calcd./found		
				C	H	N
2a	146–148	69	$C_{17}H_{14}N_2O_5S_2$	52.30	3.61	7.17
				52.38	3.65	7.25
2b	129–131	64	$C_{18}H_{16}N_2O_5S_2$	53.45	3.99	6.93
				53.37	3.94	7.02
2c	152–154	72	$C_{17}H_{13}ClN_2O_5S_2$	48.06	3.08	6.59
				48.15	3.13	6.64
3a	164–166	66	$C_{17}H_{14}N_2O_4S_3$	50.23	3.47	6.89
				50.16	3.51	6.79
3b	171–173	62	$C_{18}H_{16}N_2O_4S_3$	51.41	3.83	6.66
				51.49	3.86	6.74
3c	182–184	65	$C_{17}H_{13}ClN_2O_4S_3$	46.31	2.97	6.35
				46.25	3.01	6.28
4a	157–159	79	$C_{18}H_{16}N_4O_5S_2$	49.99	3.73	12.95
				49.87	3.68	12.84
4b	163–165	75	$C_{19}H_{18}N_4O_5S_2$	51.11	4.06	12.55
				51.02	4.00	12.66
4c	172–174	83	$C_{18}H_{15}ClN_4O_5S_2$	46.30	3.24	12.00
				46.39	3.28	12.14
5a	171–173	77	$C_{18}H_{16}N_4O_4S_3$	48.20	3.60	12.49
				48.31	3.65	12.35
5b	182–184	76	$C_{19}H_{18}N_4O_4S_3$	49.33	3.92	12.11
				49.42	3.98	12.21
5c	197–199	80	$C_{18}H_{15}ClN_4O_4S_3$	44.76	3.13	11.60
				44.66	3.08	11.71
6a	165–167	75	$C_{18}H_{14}N_4O_5S_2$	50.22	3.28	13.02
				50.13	3.22	13.15
6b	169–171	69	$C_{19}H_{16}N_4O_5S_2$	51.34	3.63	12.60
				51.45	3.57	12.70
6c	185–187	76	$C_{18}H_{13}ClN_4O_5S_2$	46.50	2.82	12.05
				46.61	2.86	12.14
7a	183–185	72	$C_{18}H_{14}N_4O_4S_3$	48.42	3.16	12.55
				48.51	3.20	12.43
7b	196–198	68	$C_{19}H_{16}N_4O_4S_3$	49.55	3.50	12.17
				49.62	3.56	12.08
7c	210–212	74	$C_{18}H_{13}ClN_4O_4S_3$	44.95	2.72	11.65
				45.04	2.65	11.74

Table 2
IR data of compounds **2–7**.

Compound	IR (KBr) cm^{-1}				
	SO_2		C=C	C=N	NH
2a	1136	1318	1630	1589	–
2b	1141	1321	1626	1594	
2c	1144	1325	1631	1608	
3a	1138	1317	1635	1583	–
3b	1143	1320	1632	1597	
3c	1146	1323	1623	1603	–
4a	1131	1336		1586	3345
4b	1143	1340		1594	3340
4c	1135	1338	–	1609	3336
5a	1140	1333	–	1585	3332
5b	1138	1335	–	1598	3348
5c	1145	1337	–	1606	3341
6a	1132	1332	–	1582	3325
6b	1137	1336	–	1595	3342
6c	1141	1339	–	1607	3346
7a	1134	1335	–	1585	3340
7b	1139	1332	–	1593	3343
7c	1143	1338	–	1605	3347

((3′-(phenylsulfonyl)-1′*H*-pyrazol-4′-ylsulfonyl)methyl)-5-aryl-1,3,4-thiadiazole (**7**). The ^{1}H-NMR spectra of **6a** and **7a** displayed two singlets at δ 7.21, 5.44 and 7.25, 5.47 ppm due to pyrazole ring and methylene protons. A broad singlet is observed at δ 6.52 in **6a** and at 6.55 ppm in **7a** due to NH which disappeared on deuteration. The structures of all the compounds **2–7** are further ascertained by ^{13}C-NMR spectra (Table 3).

ANTIMICROBIAL STUDIES

The bis heterocycles **6** and **7** are screened for their antibacterial and antifungal activity. For antibacterial studies, microorganisms employed are *Staphylococcus aureus*, *Bacillus subtilis*, (Gram-positive) and *Escherichia coli*, *Klebsiella pneumoniae* (Gram-negative). For antifungal, *Fusarium solani*, *Curvularia lunata*, and *Aspergillus niger* are used as microorganisms. Chloramphenicol and Ketoconazole are used as standard drugs for antibacterial and antifungal studies, respectively. The results of the compounds of preliminary antimicrobial testing are shown in Tables 4 and 5. Among the screened samples, the compounds **7a** and **7c** showed excellent antibacterial activity against Gram-positive bacteria (35–38 mm) and good activity against Gram-negative bacteria (26–32 mm). On the other hand, the compound **6** exhibited least activity against both bacteria. The compound having thiadiazole unit in combination with pyrazole with chloro substituent on the phenyl ring (**7c**) accounted for significant antimicrobial activity. The compounds **7a** and **7c** showed maximum antifungal activity. However the remaining compounds displayed significant antifungal activity.

CONCLUSION

A new class of pyrazolyl oxadiazoles and thiadiazoles are prepared adopting simple and well-versed methodologies. Preliminary antimicrobial studies of these compounds showed that the bis heterocycles, pyrazole in combination with thiadiazole exhibited excellent antimicrobial activity.

EXPERIMENTAL

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The purity of the compounds was checked by TLC (silica gel H, BDH, ethyl acetate/hexane, 1:3). The IR spectra were recorded on a Thermo Nicolet IR 200 FT-IR spectrometer as KBr pellets and the wave numbers were given in cm^{-1}. The ^{1}H-NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Bruker spectrospin operating at 400 MHz. The ^{13}C-NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Bruker spectrospin operating at 100 MHz. All chemical shifts are reported in δ (ppm) using TMS as an internal standard. The microanalyses were performed on a Perkin-Elmer 240C elemental analyzer. The starting compound *E*-phenylsulfonylethenesulfonylacetic acid (**1**) was prepared by the literature procedure [21].

2-(((*E*)-2-(Phenylsulfonyl)vinylsulfonyl)methyl)-5-aryl-1,3,4-oxadiazole (2): General procedure. To the compound *E*-phenylsulfonylethenesulfonylacetic acid (**1**) (5 mmol), benzoic acid hydrazide (5 mmol) and $POCl_3$ (4 mL) were added and heated under reflux for 5–6 h. The excess $POCl_3$ was removed under reduced pressure and the residue was poured onto crushed ice. The resulting precipitate was filtered, washed with saturated sodium bicarbonate solution and then with water, dried and recrystallized from ethanol.

2-(((*E*)-2-(Phenylsulfonyl)vinylsulfonyl)methyl-5-aryl-1,3,4-thiadiazole (3): General procedure. In a sealed test tube, the compound **2** (5 mmol), thiourea (20 mmol) dissolved in tetrahydrofuran (5 mL) was taken. The contents were heated at 120–150°C in an oil bath for 22–26 h. After the reaction was completed, it was extracted with dichloromethane. The organic layer was washed with water, brine solution and dried over anhydrous Na_2SO_4. The resultant solid was recrystallized from methanol.

2-((4′,5′-Dihydro-3′-(phenylsulfonyl)-1′*H*-pyrazol-4′-ylsulfonyl)methyl)-5-aryl-1,3,4-oxadiazole (4)/2-((4′,5′-Dihydro-3′-(phenylsulfonyl)-1′*H*-pyrazol-4′-ylsulfonyl)methyl)-5-aryl-1,3,4-thiadiazole (5): General procedure. To a cooled solution of **2/3** (2.5 mmol) in dichloromethane (10 mL), an ethereal solution of diazomethane (20 mL, 0.4 *M*) and triethylamine (0.06 g) were added. The reaction mixture was kept at −20 to −15°C for 40–48 h. The solvent was removed under reduced pressure. The resultant solid was purified by column chromatography (hexane-ethyl acetate, 4:1).

2-((3′-Phenylsulfonyl)-1′*H*-pyrazol-4′-ylsulfonyl)methyl)-5-aryl-1,3,4-oxadiazole (6)/2-((3′-Phenylsulfonyl)-1′*H*-pyrazol-4′-ylsulfonyl)methyl)-5-aryl-1,3,4-thiadiazole (7): General procedure. A solution of **4/5** (1 mmole) and chloranil (1 mmole) in xylene (10 mL) was refluxed for 24–32 h. Then,

Table 3

^{1}H and ^{13}C NMR data of compounds **2–7**.

Compound	^{1}H NMR (δ, ppm)	^{13}C NMR (δ, ppm)
2a	5.43 (s, 2H, SO_2—CH_2), 7.84 (d, 1H, H_B, J = 14.7 Hz), 8.04 (d, 1H, H_A, J = 14.7 Hz), 7.58–7.84 (m, 10H, Ar—H)	50.5 (SO_2—CH_2), 130.1 (*C*—H_B), 145.1 (*C*—H_A), 156.6 & 165.2 (C=N), 121.1, 126.2, 128.1, 129.0, 129.8, 130.2, 131.4, 139.1 (aromatic carbons)
2b	2.34 (s, 3H, Ar—CH_3), 5.40 (s, 2H, SO_2—CH_2), 7.87 (d, 1H, H_B, J = 14.6 Hz), 8.06 (d, 1H, H_A, J = 14.6 Hz), 7.67–8.16 (m, 9H, Ar—H)	21.6 (Ar—CH_3), 50.8 (SO_2—CH_2), 130.8 (*C*—H_B), 144.8 (*C*—H_A), 156.6 & 165.4 (C=N), 121.3, 126.1, 128.2, 129.2, 129.8, 130.6, 131.5, 138.7 (aromatic carbons)
2c	5.56 (s, 2H, SO_2—CH_2), 7.86 (d, 1H, H_B, J = 14.8 Hz), 8.08 (d, 1H, H_A, J = 14.8 Hz), 7.62–7.97 (m, 9H, Ar—H)	50.3 (SO_2—CH_2), 130.3 (*C*—H_B), 143.7 (*C*—H_A), 157.5 & 165.1 (C=N), 122.1, 128.7, 128.9, 130.2, 130.4, 135.5, 137.7, 139.4 (aromatic carbons)
3a	5.52 (s, 2H, SO_2—CH_2), 7.81 (d, 1H, H_B, J = 14.7 Hz), 8.06 (d, 1H, H_A, J = 14.7 Hz), 7.58–7.97 (m, 10H, Ar—H)	51.0 (SO_2—CH_2), 131.5 (*C*—H_B), 145.3 (*C*—H_A), 156.8 & 165.7 (C=N), 121.2, 126.1, 127.2, 129.3, 130.2, 130.4, 131.6, 138.2 (aromatic carbons)
3b	2.29 (s, 3H, Ar—CH_3), 5.46 (s, 2H, SO_2—CH_2), 7.84 (d, 1H, H_B, J = 14.5 Hz), 8.05 (d, 1H, H_A, J = 14.8 Hz), 7.59–7.98 (m, 9H, Ar—H)	21.8 (Ar—CH_3), 51.3 (SO_2—CH_2), 130.2 (*C*—H_B), 145.2 (*C*—H_A), 156.8 & 164.6 (C=N), 121.5, 126.3, 128.4, 129.5, 130.3, 130.4, 131.6, 138.5 (aromatic carbons)
3c	5.54 (s, 2H, SO_2—CH_2), 7.85 (d, 1H, H_B, J = 14.9 Hz), 8.09 (d, 1H, H_A, J = 14.9 Hz), 7.64–7.98 (m, 9H, Ar—H)	51.8 (SO_2—CH_2), 130.6 (*C*—H_B), 145.4 (*C*—H_A), 156.5 & 165.3 (C=N), 121.5, 126.3, 128.6, 129.5, 130.3, 130.7, 131.8, 138.6 (aromatic carbons)
4a	4.52 (s, 2H, SO_2—CH_2), 3.66 (dd, 1H, H_X, J_{AX} = 5.8 Hz, J_{MX} = 10.3 Hz), 4.10 (dd, 1H, H_M, J_{AM} = 12.5 Hz), 4.53 (dd, 1H, H_A), 7.22–7.95 (m, 10H, Ar—H), 8.85 (bs, 1H, NH)	51.4 (SO_2—CH_2), 48.5 (C-4′), 58.9 (C-5′), 149.3 (C-3′), 157.9 (C-5), 164.8 (C-2), 121.8, 127.5, 128.4, 129.8, 130.2, 137.1, 139.5, 140.2 (aromatic carbons)
4b	2.33 (s, 3H, Ar—CH_3), 4.49 (s, 2H, SO_2—CH_2), 3.59 (dd, 1H, H_X, J_{AX} = 5.5 Hz, J_{MX} = 10.5 Hz), 4.12 (dd, 1H, H_M, J_{AM} = 12.2 Hz), 4.51 (dd, 1H, H_A), 7.18–7.89 (m, 9H, Ar—H), 8.97 (bs, 1H, NH)	21.7 (Ar—CH_3), 53.2 (SO_2—CH_2), 47.9 (C-4′), 57.8 (C-5′), 151.3 (C-3′), 159.9 (C-5), 163.4 (C-2), 121.5, 127.3, 129.1, 131.1, 132.8, 139.1, 140.4, 141.3 (aromatic carbons)
4c	4.57 (s, 2H, SO_2—CH_2), 3.65 (dd, 1H, H_X, J_{AX} = 5.3 Hz, J_{MX} = 10.2 Hz), 4.14 (dd, 1H, H_M, J_{AM} = 12.4 Hz), 4.56 (dd, 1H, H_A), 7.24–7.98 (m, 9H, Ar—H), 9.13 (bs, 1H, NH)	52.8 (SO_2—CH_2), 47.4 (C-4′), 58.6 (C-5′), 148.6 (C-3′), 158.5 (C-5), 162.9 (C-2), 121.6, 128.3, 129.5, 131.2, 132.7, 138.6, 139.8, 140.7 (aromatic carbons)
5a	4.55 (s, 2H, SO_2—CH_2), 3.72 (dd, 1H, H_X, J_{AX} = 6.1 Hz, J_{MX} = 10.7 Hz), 4.22 (dd, 1H, H_M, J_{AM} = 12.8 Hz), 4.61 (dd, 1H, H_A), 7.26–7.93 (m, 10H, Ar—H), 8.85 (bs, 1H, NH)	51.8 (SO_2—CH_2), 48.9 (C-4′), 59.3 (C-5′), 147.4 (C-3′), 156.8 (C-5), 167.5 (C-2), 122.5, 128.6, 126.3, 131.5, 133.4, 137.2, 140.5, 141.4 (aromatic carbons)
5b	2.35 (s, 3H, Ar—CH_3), 4.53 (s, 2H, SO_2—CH_2), 3.64 (dd, 1H, H_X, J_{AX} = 6.3 Hz, J_{MX} = 10.6 Hz), 4.16 (dd, 1H, H_M, J_{AM} = 12.6 Hz), 4.55 (dd, 1H, H_A), 7.28–7.92 (m, 9H, Ar—H), 8.81 (bs, 1H, NH)	22.3 (Ar—CH_3), 53.6 (SO_2—CH_2), 46.4 (C-4′), 58.1 (C-5′), 149.5 (C-3′), 163.2 (C-5), 165.4 (C-2), 123.5, 127.6, 129.7, 130.6, 131.7, 138.7, 139.6, 140.8 (aromatic carbons)
5c	4.62 (s, 2H, SO_2—CH_2), 3.71 (dd, 1H, H_X, J_{AX} = 6.2 Hz, J_{MX} = 10.5 Hz), 4.18 (dd, 1H, H_M, J_{AM} = 12.7 Hz), 4.58 (dd, 1H, H_A), 7.24–7.98 (m, 9H, Ar—H), 8.92 (bs, 1H, NH)	51.3 (SO_2—CH_2), 48.3 (C-4′), 57.5 (C-5′), 149.7 (C-3′), 159.4 (C-5), 163.4 (C-2), 122.5, 129.2, 130.2, 131.6, 132.8, 137.9, 140.2, 141.5 (aromatic carbons)
6a	5.44 (s, 2H, SO_2—CH_2), 6.52 (bs, 1H, NH), 6.84–7.78 (m, 11H, $C_{5'}$—H, Ar—H)	51.5 (SO_2—CH_2), 48.9 (C-4′), 58.3 (C-5′), 148.2 (C-3′), 158.6 (C-5), 165.5 (C-2), 121.4, 127.6, 128.8, 129.9, 130.4, 137.6, 139.8, 140.6 (aromatic carbons)
6b	2.32 (s, 3H, Ar—CH_3), 5.52 (s 2H, SO_2—CH_2), 6.54 (bs, 1H, NH), 6.86–7.76 (m, 10H, $C_{5'}$—H, Ar—H)	21.9 (Ar—CH_3), 53.5 (SO_2—CH_2), 47.7 (C-4′), 57.6 (C-5′), 151.9 (C-3′), 160.3 (C-5), 163.6 (C-2), 121.8, 127.8, 129.6, 131.5, 132.5, 139.6, 140.6, 141.1 (aromatic carbons)
6c	5.56 (s, 2H, SO_2—CH_2), 6.72 (bs, 1H, NH), 6.87–7.78 (m, 10H, $C_{5'}$—H, Ar—H)	52.9 (SO_2—CH_2), 47.8 (C-4′), 58.9 (C-5′), 149.7 (C-3′), 159.8 (C-5), 162.5 (C-2), 121.2, 128.7, 129.9, 131.8, 132.5, 138.2, 139.6, 141.4 (aromatic Carbons)
7a	5.47 (s, 2H, SO_2—CH_2), 6.55 (bs, 1H, NH), 6.86–7.74 (m, 11H, $C_{5'}$—H, Ar—H)	51.2 (SO_2—CH_2), 48.3 (C-4′), 59.2 (C-5′), 147.5 (C-3′), 158.4 (C-5), 164.2 (C-2), 122.4, 128.3, 126.1, 131.2, 133.3, 137.8, 140.3, 141.1 (aromatic carbons)
7b	2.34 (s, 3H, Ar—CH_3), 5.43 (s, 2H, SO_2—CH_2), 6.57 (bs, 1H, NH), 6.87–7.76 (m, 10H, $C_{5'}$—H, Ar—H)	22.8 (Ar—CH_3), 53.9 (SO_2—CH_2), 47.7 (C-4′), 58.6 (C-5′), 150.7 (C-3′), 158.8 (C-5), 165.9 (C-2), 123.2, 127.4, 129.6, 130.3, 131.2, 138.5, 139.3, 140.7 (aromatic carbons)
7c	5.52 (s, 2H, SO_2—CH_2), 6.58 (bs, 1H, NH), 6.89–7.78 (m, 10H, $C_{5'}$—H, Ar—H)	51.9 (SO_2—CH_2), 48.2 (C-4′), 57.8 (C-5′), 149.7 (C-3′), 157.6 (C-5), 163.7 (C-2), 122.9, 129.6, 130.5, 131.4, 132.6, 137.3, 140.8, 141.7 (aromatic carbons)

Table 4

The *in vitro* antibacterial activity of **6–7**.

		Zone of inhibition (mm)			
		Gram (+)ve		Gram (−)ve	
Compound	Concentration (μg/mL)	*S. aureus*	*B. subtilis*	*E. coli*	*K. pneumoniae*
6a	100	14	16	09	–
	200	17	18	11	09
6b	100	12	11	–	–
	200	14	12	10	–
6c	100	16	14	10	11
	200	19	16	12	13
7a	100	32	33	25	24
	200	36	35	28	26
7b	100	25	26	19	17
	200	29	30	22	19
7c	100	35	33	29	27
	200	38	36	32	31
Chloramphenicol	100	35	38	40	42
	200	39	41	44	45

Table 5

The *in vitro* antifungal activity of **6–7**.

		Zone of inhibition (mm)		
Compound	Concentration (μg/mL)	*F. solani*	*C. lunata*	*A. niger*
6a	100	20	22	18
	200	23	24	20
6b	100	18	19	16
	200	20	20	18
6c	100	24	22	19
	200	26	25	21
7a	100	30	27	22
	200	33	29	25
7b	100	28	30	23
	200	33	31	25
7c	100	32	34	26
	200	35	37	29
Ketoconazole	100	38	41	36
	200	42	44	39

the reaction mixture was treated with a 5% NaOH solution. The organic layer was separated and repeatedly washed with water. It was dried over anhydrous Na_2SO_4, and the solvent was removed on a rotary evaporator. The resultant solid was purified by recrystallization from 2-propanol.

Acknowledgments. The authors are grateful to Council of Scientific and Industrial Research (CSIR), New Delhi, for financial assistance under major research project.

REFERENCES AND NOTES

[1] Patel, H. V.; Fernandez, P. S.; Vyas, K. A. Indian J Chem 1990, 29B, 135.

[2] Sasse, K.; Haensler, G.; Schmidt. Ger. Offen. DE 1987, 3, 527; Chem Abstr 1987, 106, 133794u.

[3] Pulido, M. L.; Fenyes, J. G.; Eur. Pat. Appl. EP 467,708; Chem Abstr 1992, 116, 146150j.

[4] Morimoto, K. M.; Makino, K.; Yamamoto, S.; Sakato, G. J. J Heterocycl Chem 1990, 27, 807.

[5] Naoto, M.; Kazue, N.; Tomotoshi, I.; Hiroaki, F.; Kenichi, M.; Hirotaka, T.; Yoriko, O.; Masahiro, T. Eur. Pat. Appl. EP 361,827 (1990), p 120.

[6] Pande, A.; Saxena, V. K. Indian J Chem 1987, 26B, 390.

[7] Kopp, M.; Lancelot, J. C.; Dallemagne, P.; Rault, S. J Heterocycl Chem 2001, 38, 1045.

[8] Colliot, F.; Kukorowski, K. A.; Hawkins, D. W.; Roberts, D. A. Brighton Crop Prot Conf Pests Dis 1992, 1, 29.

[9] Miura, Y.; Ohnishi, M.; Mabuchi, T.; Yanai, I. Brighton Crop Prot Conf Weeds 1993, 1, 35.

[10] Konotsune, T.; Kawakubo, K.; Honma, T. Jpn. Pat. 8,035,035 (1980); Chem Abstr 1980, 93, 20750.

[11] Rigo, B.; Couturier, D. J Heterocycl Chem 1985, 22, 287.

[12] El-Emam, A. A.; Al-Deeb, O. A.; Al-Omar, M.; Lehmann, J. Bioorg Med Chem 2004, 12, 5107.

[13] Kucukguzel, S. G.; Oruc, E. E.; Rollas, S.; Sahin, F.; Ozbek, A. Eur J Med Chem 2002, 37, 197.

[14] Kagthara, P. R.; Shah, N. S.; Doshi, R. K.; Parekh, H. H. Indian J Chem 1999, 38B, 572.

[15] Akhter, M.; Husain, A.; Azad, B.; Ajmal, M. Eur J Med Chem 2009, 44, 2372.

[16] Unangast, P. C.; Shrum, G. P.; Conner, D. T.; Dyer, C. D.; Schrier, D. J. J Med Chem 1992, 35, 3691.

[17] Khan, M. S. Y.; Khan, R. M.; Drabu, S. Indian J Heterocycl Chem 2001, 11, 119.

[18] O'Neal, J. B.; Rosen, H.; Russell, P. B.; Adams, A. C.; Blumenthal, A. J Med Chem 1962, 5, 617.

[19] Sandström, J. Adv Heterocycl Chem 1968, 9, 165.

[20] Mohsen, A.; Omar, M. E.; Wafa, A. J Heterocycl Chem 1986, 23, 1339.

[21] (a) Bhaskar Reddy, D.; Chandrasekhar Babu, N.; Padmavathi, V.; Sumathi, R. P. Synthesis 1999, 491; (b) Padmavathi, V.; Nagendra Mohan, A.V.; Triveni, P.; Shazia, A. Eur J Med Chem 2009, 44, 2313.