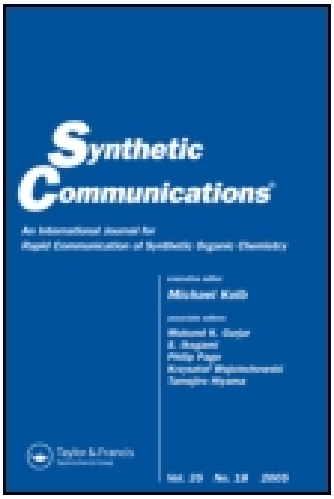

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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF PYRAZOLYL 1,3,4-OXADIAZOLES

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The pyrazolyl oxadiazoles are synthesized from arylsulfonylacetic acid methyl ester and benzylsulfonylacetic acid methyl ester. Preliminary antimicrobial screening of the compounds showed that bis heterocycles with a chloro-substituted benzyl moiety exhibited high activity.

Keywords: Antimicrobial activity; 1,3-dipolar cycloaddition; 1,3,4-oxadiazoles; pyrazolines

INTRODUCTION

The development of simple, facile, and efficient methodologies for the synthesis of five-membered heterocycles is one of the major challenges in the field of synthetic organic chemistry. Among five-membered heterocycles, oxadiazoles and pyrazoles represent a class of compounds of great importance. Symmetrical and unsymmetrical 1,3,4-oxadiazoles are biologically versatile compounds possessing anti-inflammatory,[1] antifungal,[2–4] antiparasitic,[5] antimicrobial,[6,7] and antiviral activities.[8–10] The widespread use of 1,3,4-oxadiazoles as a scaffold in medicinal chemistry established this moiety as a member of the privileged structures class. In addition, pyrazolines have gained importance because of their chemotherapeutic properties. Celecoxib, a pyrazole derivative, is now widely used in the market as an anti-inflammatory drug.[11] Different methods have been reported for the synthesis of 1,3,4-oxadiazoles involving cyclization of diacylhydrazines prepared from acyl chlorides and hydrazine. Several cyclodehydrating agents such as $Et_2O \cdot BF_3$,[12] 1,1,1,3,3,3-hexamethyldisilazane,[13] triflic anhydride,[14] phosphorus pentoxide,[15] polyphosphoric acid,[16] thionyl chloride,[17,18] phosphorus oxychloride,[19] and sulfuric acid[20] have been used. Similarly, 1,3-dipolar cycloaddition of 1,3-dipole onto an alkene in a $[3+2]$ manner is a facile route for the synthesis of pyrazolines.[21,22] Among the ylides, diazomethane and nitrile imines have been used extensively as reactive intermediates. The present communication deals with the synthesis and antimicrobial activity of hitherto unknown bis heterocycles having oxadiazole and pyrazoline moieties by a simple, facile, and elegant synthetic methodology.

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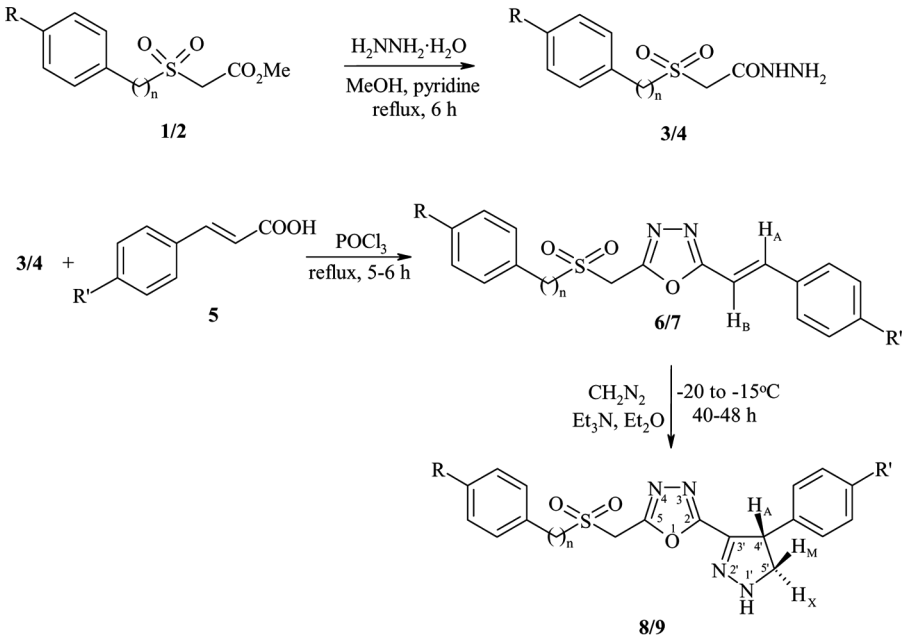
RESULTS AND DISCUSSION

To synthesize the desired bis heterocycles, the acid hydrazides of arylsulfonylacetic acid methyl ester (**1**) and arylmethanesulfonylacetic acid methyl ester (**2**) are used as synthetic intermediates. The arylsulfonylacetic acid hydrazide (**3**) and arylmethanesulfonylacetic acid hydrazide (**4**) are prepared by the condensation of the previous compounds with hydrazine hydrate in the presence of pyridine. The cyclocondensation of **3**/**4** with cinnamic acid **5** in the presence of phosphorus oxychloride led to 2-(styryl)-5-(arylsulfonylmethyl)-1,3,4-oxadiazole (**6**) and 2-(styryl)-5-(arylmethanesulfonylmethyl)-1,3,4-oxadiazole (**7**) (Scheme 1). The ^{1}H NMR spectra of **6a** and **7a** displayed a singlet at δ 4.60, 4.76 for methylene protons flanked between heterocyclic and sulfonyl moieties. Two doublets are observed at δ 7.68, 7.42 in **6a** and at δ 7.55, 7.34 in **7a** that are due to olefin protons, H_A and H_B. The coupling constant value $J_{AB} = 15.7$ in **6a** and 15.1 Hz in **7a** indicates that they possess *E*-configuration. Apart from these, **7a** showed a singlet at δ 5.05 for benzylic protons. The olefin moiety present in **6** and **7** is used to build the pyrazoline ring by 1,3-dipolar cycloaddition of diazomethane. Thus, treatment of **6**/**7** with diazomethane at −20 to 15°C for 48 h in the presence of Et_3N resulted in 5-(arylsulfonylmethyl)-2-(4′,5′-dihydro-4′-phenyl-1′*H*-pyrazol-3′-yl)-1,3,4-oxadiazole (**8**) and 5-(arylmethanesulfonylmethyl)-2-(4′,5′-dihydro-4′-phenyl-1′*H*-pyrazol-3′-yl)-1,3,4-oxadiazole (**9**), respectively. The ^{1}H NMR spectra of **8a** and **9a** displayed three double doublets at δ 4.64, 4.60 (H_A); 4.04, 4.01 (H_M); and 3.72, 3.66 (H_X), respectively. The coupling constant values $J_{AX} = 4.2$, 4.6; $J_{MX} = 8.7$, 8.6; and $J_{AM} = 12.0$, 12.6 indicate that H_A, H_M are *cis*; H_A, H_X are *trans*, and H_M, H_X are



Scheme 1. (a) R = H, R^1 = H; (b) R = H, R^1 = Cl; (c) R = Me, R^1 = H; (d) R = Cl, R^1 = H; and (e) R = Cl, R^1 = Cl; n = 0 (1,3,6,8); n = 1 (2,4,7,9).

geminal. Besides, **8a** and **9a** showed a singlet at δ 4.37 and 4.34 for methylene protons present between sulfonyl and the oxadiazole ring. However, **9a** displayed an additional singlet at δ 5.02 for benzylic protons. The structures of **6**–**9** are further established by ^{13}C NMR spectra.

Antimicrobial Testing

The compounds **8** and **9** were tested for in vitro antimicrobial activity against the Gram-positive bacteria *Staphylococcus aureus and Bacillus subtilis*, the Gram-negative bacteria *Klebsiella pneumoniae* and *Proteus vulgaris*, and fungi *Fusarium solani*, *Curvularia lunata*, and *Aspergillus niger*. The primary screen was carried out by the agar disc-diffusion method[23] using nutrient agar medium. The minimum inhibitory concentration for the most active compounds **9b**, **9d**, and **9e** against the same microorganisms used in the preliminary screening was carried out using the microdilution susceptibility method.[24] Chloramphenicol and ketoconazole were used as control drugs.

Biological Results

The results of preliminary antibacterial testing for the compounds **8** and **9** are shown in Table 1. The results revealed that 5-(benzylsulfonylmethyl)-2-[4′,

Table 1. In vitro antibacterial activity of **8** and **9**

		Zone of inhibition (mm)			
		Gram-positive bacteria		Gram-negative bacteria	
Compound	Concentration (μg/disc)	*Staphylococcus aureus*	*Bacillus subtilis*	*Klebsiella pneumoniae*	*Proteus vulgaris*
8a	100	15	15	14	12
	200	18	17	16	15
8b	100	20	23	19	16
	200	25	27	21	19
8c	100	12	11	16	14
	200	15	13	18	17
8d	100	20	22	14	18
	200	24	25	18	21
8e	100	22	23	16	15
	200	27	26	19	20
9a	100	17	19	14	15
	200	22	25	19	18
9b	100	28	29	26	26
	200	32	35	28	30
9c	100	16	14	15	16
	200	18	17	18	18
9d	100	27	30	25	24
	200	30	33	29	27
9e	100	32	34	31	29
	200	36	37	35	33
Chloramphenicol	100	35	38	37	42
	200	41	44	42	45

5′-dihydro-4′-(*p*-chlorophenyl)-1′*H*-pyrazol-3′-yl]-1,3,4-oxadiazole (**9b**) and 5-(*p*-chlorobenzylsulfonylmethyl)-2-[4′,5′-dihydro-4′-(*p*-chlorophenyl)-1′*H*-pyrazol-3′-yl]-1,3,4-oxadiazole (**9e**) exhibited pronounced activity on both Gram (+ve) (32–36 mm) and Gram (−ve) (28–32 mm) bacteria. The compounds **8b**, **8d**, **8e**, **9a**, and **9d** showed moderate to high activity toward Gram (+ve) bacteria (22–27 mm) and moderate activity toward Gram (−ve) bacteria (18–21 mm). On the other hand, **8a**, **8c**, and **9c** displayed the least activity against both bacteria.

All the test compounds inhibited the spore germination of tested fungi *Aspergillus niger*, *Fusarium solani*, and *Curvularia lunata*. Results of the investigation presented in Table 2 revealed that all the compounds except **8a** and **8c** showed relatively more inhibitory effect on *Fusarium solani* and *Curvularia lunata* than on *Aspergillus niger*. Further, the compounds 5-benzylsulfonylmethyl-2-[4′,5′-dihydro-4′-(*p*-chlorophenyl)-1′*H*-pyrazol-3′-yl]-1,3,4-oxadiazole (**9b**), 5-(*p*-chlorobenzylsulfonylmethyl)-2-(4′,5′-dihydro-4′-phenyl-1′*H*-pyrazol-3′-yl)-1,3,4-oxadiazole (**9d**), and 5-(*p*-chlorobenzylsulfonylmethyl)-2-[4′,5′-dihydro-4′-(*p*-chlorophenyl)-1′*H*-pyrazol-3′-yl]-1,3,4-oxadiazole (**9e**) displayed greater activity.

The minimum inhibitory concentration (MIC) values were determined as the lowest concentration that completely inhibited visible growth of the microorganisms (Table 3). The structure–antimicrobial activity relationship of the synthesized compounds revealed that the compounds having an aryl moiety exhibited the least activity when compared with compounds having a benzyl group. Besides, the

Table 2. In vitro antifungal activity of **8** and **9**

		Zone of inhibition (mm)		
Compound	Concentration (μg/mL)	*Fusarium solani*	*Curvularia lunata*	*Aspergillus niger*
8a	100	17	19	16
	200	21	23	19
8b	100	24	23	17
	200	27	25	20
8c	100	15	15	14
	200	18	19	17
8d	100	22	20	19
	200	25	24	22
8e	100	28	25	20
	200	31	27	23
9a	100	20	20	17
	200	25	23	21
9b	100	28	28	22
	200	33	32	26
9c	100	22	18	18
	200	26	23	21
9d	100	27	26	22
	200	32	30	28
9e	100	31	34	28
	200	37	39	32
Ketoconazole	100	38	41	36
	200	42	44	39

Table 3. Minimum inhibitory concentration (MIC, μg/mL) of **9b**, **9d**, and **9e**

Compound	*S. aureus*	*B. subtilis*	*K. pneumoniae*	*P. vulgaris*	*F. solani*	*C. lunata*	*A. niger*
9b	50	100	100	100	100	100	100
9d	50	100	100	200	100	100	100
9e	25	25	50	50	100	50	50
Chloramphenicol	6.25	6.25	6.25	12.5	—	—	—
Ketoconazole	—	—	—	—	12.5	6.25	6.25

compounds with a chloro substituent at the 4-position of the aryl ring were the most active. The maximum activity was observed with compounds **9b**, **9d**, and **9e** (Table 3).

CONCLUSIONS

A new class of bis heterocycles, pyrazolyl oxadiazoles, are prepared from arylsulfonylacetic acid methyl ester and benzylsulfonylacetic acid methyl ester with a simple, facile, and well-versed methodology. The compounds having benzyl groups showed greater antimicrobial activity. Further, the presence of a chloro substituent enhances the 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 thin-layer chromatography (TLC; silica gel H, BDH, ethyl acetate/hexane, 1:3). The infrared (IR) spectra were recorded on a Thermo Nicolet IR 200 Fourier transfrom (FT)–IR spectrometer as KBr pellets, and the wave numbers were given in centimeters^{-1}. The ^{1}H NMR spectra were recorded in $CDCl_3$/ dimethylsulfoxide (DMSO-d_6) on a Varian EM-360 spectrometer (300 MHz). The ^{13}C NMR spectra were recorded in $CDCl_3$/ DMSO-d_6 on a Varian VXR spectrometer operating at 75.5 MHz. All chemical shifts are reported in δ (ppm) using tetramethylsilane (TMS) as an internal standard. The microanalyses were performed on a Perkin-Elmer 240C elemental analyzer. The starting compounds arylsulfonylacetic acid methyl ester (**1**), arylmethanesulfonylacetic acid methyl ester (**2**), arylsulfonylacetic acid hydrazide (**3**), and arylmethanesulfonylacetic acid hydrazide (**4**) were prepared by the literature procedure.[25–27]

General Procedure of Synthesis of 2-(Styryl)-5-(arylsulfonylmethyl)-1,3,4-oxadiazole (6a–e)

$POCl_3$ (4 mL) was added to compounds **3** (5 mmol) and **5** (5 mmol) 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 to get **6**.

Selected Data

2-(Styryl)-5-(phenylsulfonylmethyl)-1,3,4-oxadiazole (6a). Yellow solid; yield 1.06 g (65%); mp 91–93°C; ^{1}H NMR (DMSO-d_6) δ (ppm): 4.60 (s, 2H, SO_2-CH_2), 7.42 (d, 1H, H_B, $J = 15.7$ Hz), 7.68 (d, 1H, H_A, $J = 15.7$ Hz), 7.15–7.48 (m, 10H, Ar-H); ^{13}C NMR (DMSO-d_6) δ (ppm): 53.4 (CH_2), 137.8 (CN-*C*H), 143.8 (Ar-*C*H), 157.5 (C-5), 165.8 (C-2), 126.8, 127.2, 128.3, 128.6, 129.2, 130.4, 132.2, 133.6 (aromatic carbons); IR (KBr, cm^{-1}): 1569 (C=N), 1536 (C=C), 1345, 1144 (SO_2): Anal. calcd. for $C_{17}H_{14}N_2O_3S$ (326.37): C, 62.56; H, 4.32; N 8.58. Found: C, 62.44; H, 4.35; N, 8.64.

2-(*p*-Chlorostyryl)-5-(phenylsulfonylmethyl)-1,3,4-oxadiazole (6b). Yellow solid; yield 1.26 g (70%); mp 102–104°C; ^{1}H NMR (DMSO-d_6) δ (ppm): 4.57 (s, 2H, SO_2-CH_2), 7.38 (d, 1H, H_B, $J = 15.3$ Hz), 7.61 (d, 1H, H_A, $J = 15.3$ Hz), 7.26–7.52 (m, 9H, Ar-H); ^{13}C NMR (DMSO-d_6) δ (ppm): 53.8 (CH_2), 137.2 (CN-*C*H), 143.3 (Ar-*C*H), 157.6 (C-5), 166.3 (C-2), 126.8, 127.6, 128.1, 128.7, 129.2, 129.6, 134.5, 136.8 (aromatic carbons); IR (KBr, cm^{-1}): 1573 (C=N), 1541 (C=C), 1333, 1137 (SO_2). Anal. calcd. for $C_{17}H_{13}ClN_2O_3S$ (360.81): C, 56.59; H, 3.63; N, 7.76. Found: C, 56.50; H, 3.65; N, 7.80.

2-(Styryl)-5-(*p*-methylphenylsulfonylmethyl)-1,3,4-oxadiazole (6c). Yellow solid; yield 1.07 g (63%); mp 96–98°C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.28 (s, 3H, Ar-CH_3), 4.53 (s, 2H, SO_2-CH_2), 7.46 (d, 1H, H_B, $J = 15.9$ Hz), 7.59 (d, 1H, H_A, $J = 15.9$ Hz), 7.20–7.51 (m, 9H, Ar-H); ^{13}C NMR (DMSO-d_6) δ (ppm): 23.4 (Ar-CH_3), 54.1 (CH_2), 138.1 (CN-*C*H), 144.2 (Ar-*C*H), 156.4 (C-5), 165.5 (C-2), 125.4, 126.1, 127.3, 128.7, 129.8, 131.7, 134.2, 135.1 (aromatic carbons); IR (KBr, cm^{-1}): 1570 (C=N), 1537 (C=C), 1338, 1131 (SO_2). Anal. calcd. for $C_{18}H_{16}N_2O_3S$ (340.40): C, 63.51; H, 4.74; N, 8.23. Found: C, 63.42; H, 4.70; N, 8.26.

2-(Styryl)-5-(*p*-chlorophenylsulfonylmethyl)-1,3,4-oxadiazole (6d). Yellow crystals; yield 1.19 g (66%); mp 103–105°C; ^{1}H NMR (DMSO-d_6) δ (ppm): 4.59 (s, 2H, SO_2-CH_2), 7.41 (d, 1H, H_B, $J = 15.5$ Hz), 7.64 (d, 1H, H_A, $J = 15.5$ Hz), 7.28–7.72 (m, 9H, Ar-H); ^{13}C NMR (DMSO-d_6) δ (ppm): 56.8 (CH_2), 138.7 (CN-*C*H), 141.8 (Ar-*C*H), 156.8 (C-5), 167.2 (C-2), 126.5, 128.9, 129.2, 129.6, 130.5, 133.7, 134.3, 136.5 (aromatic carbons); IR (KBr, cm^{-1}): 1572 (C=N), 1532 (C=C), 1335, 1135 (SO_2); Anal. calcd. for $C_{17}H_{13}ClN_2O_3S$ (360.81): C, 56. 59; H, 3.63; N, 7.76. Found: C, 56.49; H, 3.60; N, 7.78.

2-(*p*-Chlorostyryl)-5-(*p*-chlorophenylsulfonylmethyl)-1,3,4-oxadiazole (6e). Yellow solid; yield 1.42 g (72%); mp 115–117°C; ^{1}H NMR (DMSO-d_6) δ (ppm): 4.51 (s, 2H, SO_2-CH_2), 7.35 (d, 1H, H_B, $J = 15.2$ Hz), 7.57 (d, 1H, H_A, $J = 15.2$ Hz), 7.32–7.87 (m, 8H, Ar-H); ^{13}C NMR (DMSO-d_6) δ (ppm): 57.2 (CH_2), 137.6 (CN-*C*H), 142.3 (Ar-*C*H), 157.3 (C-5), 168.4 (C-2), 125.5, 126.4, 127.8, 129.5, 131.3, 133.7, 134.5, 137.2 (aromatic carbons); IR (KBr, cm^{-1}): 1567 (C=N), 1539 (C=C), 1342, 1129 (SO_2); Anal. Calcd. for $C_{17}H_{12}Cl_2N_2O_3S$ (395.26): C, 51.66; H, 3.06; N, 7.09. Found: C, 51.76; H, 3.09; N, 7.05.

General Procedure of Synthesis of 2-styryl-5-(arylmethanesulfonylmethyl)-1,3,4-oxadiazole (7a–e)

A mixture of **4** (5 mmol), **5** (5 mmol), and $POCl_3$ (4 mL) was heated under reflux for 5–6 h. The excess $POCl_3$ was removed under reduced pressure, and the residue was poured onto crushed ice. The resulting precipitate was filtered, washed with saturated sodium bicarbonate solution followed by water, dried, and recrystallized from ethanol to get **7**.

Selected Data

2-(Styryl)-5-(benzylsulfonylmethyl)-1,3,4-oxadiazole (7a). Yellow solid; yield 1.25 g (74%); mp 101–103°C; ^{1}H NMR (DMSO-d_6) δ (ppm): 4.76 (s, 2H, SO_2-CH_2), 5.05 (s, 2H, Ar-CH_2), 7.34 (d, 1H, H_B, $J = 15.1$ Hz), 7.55 (d, 1H, H_A, $J = 15.1$ Hz), 7.20–7.57 (m, 10H, Ar-H); ^{13}C NMR (DMSO-d_6) δ (ppm): 48.4 (SO_2-CH_2), 58.9 (Ar-*C*H_2), 138.1 (CN-*C*H), 145.2 (Ar-*C*H), 157.4 (C-5), 165.2 (C-2), 127.6, 128.3, 128.9, 129.6, 131.5, 132.6, 133.4, 134.8 (aromatic carbons); IR (KBr, cm^{-1}): 1571 (C=N), 1533 (C=C), 1333, 1141 (SO_2). Anal. calcd. for $C_{18}H_{16}N_2O_3S$ (340.40): C, 63.51; H, 4.74; N, 8.23. Found: C, 63.58; H, 4.78; N, 8.27.

2-(*p*-Chlorostyryl)-5-(benzylsulfonylmethyl)-1,3,4-oxadiazole (7b). Yellow solid; yield 1.34 g (72%); mp 105–107°C; ^{1}H NMR (DMSO-d_6) δ (ppm): 4.72 (s, 2H, SO_2-CH_2), 5.07 (s, 2H, Ar-CH_2), 7.38 (d, 1H, H_B, $J = 15.7$ Hz), 7.59 (d, 1H, H_A, $J = 15.7$ Hz), 7.26–7.64 (m, 9H, Ar-H); ^{13}C NMR (DMSO-d_6) δ (ppm): 48.7 (SO_2-CH_2), 58.2 (Ar-*C*H_2), 138.8 (CN-*C*H), 145.6 (Ar-*C*H), 157.8 (C-5), 164.6 (C-2), 127.9, 128.7, 129.7, 130.4, 131.8, 133.1, 134.3, 136.6 (aromatic carbons); IR (KBr, cm^{-1}): 1575 (C=N), 1546 (C=C), 1339, 1136 (SO_2). Anal. calcd. for $C_{18}H_{15}ClN_2O_3S$ (374.84): C, 57.68; H, 4.03; N, 7.47. Found: C, 57.60; H, 4.01; N, 7.44.

2-(Styryl)-5-(*p*-methylbenzylsulfonylmethyl)-1,3,4-oxadiazole (7c). Yellow solid; yield 1.22 g (69%); mp 98–100°C; ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ (ppm): 2.27 (s, 3H, Ar-CH_3), 4.68 (s, 2H, SO_2-CH_2), 5.11 (s, 2H, Ar-CH_2), 7.31 (d, 1H, H_B, $J = 15.9$ Hz), 7.57 (d, 1H, H_A, $J = 15.9$ Hz), 7.18–7.62 (m, 9H, Ar-H); ^{13}C NMR ($CDCl_3$+DMSO-d_6) δ (ppm): 23.1 (Ar-CH_3), 49.3 (SO_2-CH_2), 57.9 (Ar-*C*H_2), 138.5 (CN-*C*H), 146.1 (Ar-*C*H), 157.2 (C-5), 164.7 (C-2), 125.5, 127.2, 129.5, 131.3, 132.4, 133.0, 133.3, 135.8 (aromatic carbons); IR (KBr, cm^{-1}): 1570 (C=N), 1540 (C=C), 1331, 1134 (SO_2). Anal. calcd. for $C_{19}H_{18}N_2O_3S$ (354.42): C, 64.39; H, 5.12; N, 7.90. Found: C, 64.47; H, 5.09; N, 7.93.

2-(Styryl)-5-(*p*-chlorobenzylsulfonylmethyl)-1,3,4-oxadiazole (7d). Yellow solid; yield 1.40 g (75%) mp 108–110°C; ^{1}H NMR (DMSO-d_6) δ (ppm): 4.75 (s, 2H, SO_2-CH_2), 5.02 (s, 2H, Ar-CH_2), 7.36 (d, 1H, H_B, $J = 15.2$ Hz), 7.60 (d, 1H, H_A, $J = 15.2$ Hz), 7.36–7.78 (m, 9H, Ar-H); ^{13}C NMR (DMSO-d_6) δ (ppm): 48.8 (SO_2-CH_2), 58.1 (Ar-*C*H_2), 138.7 (CN-*C*H), 147.3 (Ar-*C*H), 157.9 (C-5), 164.5 (C-2), 125.4, 126.4, 128.1, 129.5, 130.7, 132.1, 135.7, 136.2 (aromatic carbons); IR (KBr, cm^{-1}): 1578 (C=N), 1543 (C=C), 1338, 1146 (SO_2). Anal. calcd. for $C_{18}H_{15}ClN_2O_3S$ (374.84): C, 57.68; H, 4.03; N, 7.47. Found: C, 57.75; H, 4.07; N, 7.52.

2-(*p*-Chlorostyryl)-5-(*p*-chlorobenzylsulfonylmethyl)-1,3,4-oxadiazole (7e). Yellow crystals; yield 1.59 g (78%); mp 112–114°C; ^{1}H NMR (DMSO-d_6) δ (ppm): 4.70 (s, 2H, SO_2-CH_2), 5.09 (s, 2H, Ar-CH_2), 7.33 (d, 1H, H_B, $J = 15.4$ Hz), 7.62 (d, 1H, H_A, $J = 15.4$ Hz), 7.32–7.80 (m, 8H, Ar-H); ^{13}C NMR (DMSO-d_6) δ (ppm): 51.0 (SO_2-CH_2), 58.4 (Ar-CH_2), 139.1 (CN-*C*H), 146.7 (Ar-*C*H), 158.4 (C-5), 167.5 (C-2), 128.6, 129.2, 129.8, 130.2, 132.4, 133.1, 134.6, 137.9 (aromatic carbons); IR (KBr, cm^{-1}): 1565 (C=N), 1534 (C=C), 1333, 1130 (SO_2). Anal. calcd. for $C_{18}H_{14}Cl_2N_2O_3S$ (409.29): C, 52.82; H, 3.45; N, 6.84. Found: C, 52.76; H, 3.47; N, 6.88.

General Procedure of Synthesis of 5-(arylsulfonylmethyl)-2-(4′,5′-dihydro-4′-phenyl-1′*H*-pyrazol-3′-yl)-1,3,4-oxadiazole (8a–e)

An ethereal solution of diazomethane (20 mL, 0.4 M) and triethylamine (0.06 g) was added to a cooled solution of **6** (2.5 mmol) in DCM (10 mL). 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).

Selected Data

5-(Phenylsulfonylmethyl)-2-[4′,5′-dihydro-4′-phenyl-1′*H*-pyrazol-3′-yl]-1,3,4-oxadiazole (8a). Yellow solid; yield 0.77 g (84%); mp 127–129°C; ^{1}H NMR (DMSO-d_6) δ (ppm): 3.72 (dd, 1H, H_X, $J_{AX} = 4.2$ Hz, $J_{MX} = 8.7$ Hz), 4.04 (dd, 1H, H_M, $J_{AM} = 12.0$ Hz), 4.37 (s, 2H, SO_2-CH_2), 4.64 (dd, 1H, H_A), 7.26–7.73 (m, 10H, Ar-H), 10.49 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 50.9 (SO_2-CH_2), 52.4 (C-5′), 65.8 (C-4′), 151.9 (C-3′), 152.6 (C-5), 163.4 (C-2), 128.6, 129.2, 129.8, 130.2, 132.4, 133.1, 134.6, 134.9 (aromatic carbons); IR (KBr, cm^{-1}): 3345 (NH), 1563 (C=N), 1337, 1138 (SO_2). Anal. calcd. for $C_{18}H_{16}N_4O_3S$ (368.41): C, 58.68; H, 4.38; N, 15.21. Found: C, 58.60; H, 4.40; N, 15.27.

5-(Phenylsulfonylmethyl)-2-[4′,5′-dihydro-4′-(*p*-chlorophenyl)-1′*H*-pyrazol-3′-yl]-1,3,4-oxadiazole (8b). Yellow crystals; yield 0.80 g (80%); mp 132–134°C; ^{1}H NMR (DMSO-d_6) δ (ppm): 3.66 (dd, 1H, H_X, $J_{AX} = 4.6$ Hz, $J_{MX} = 10.1$ Hz), 3.98 (dd, 1H, H_M, $J_{AM} = 12.5$ Hz), 4.32 (s, 2H, SO_2-CH_2), 4.59 (dd, 1H, H_A), 7.19–7.75 (m, 9H, Ar-H), 10.51 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 50.3 (SO_2-CH_2), 51.9 (C-5′), 65.9 (C-4′), 150.2 (C-3′), 153.3 (C-5), 163.1 (C-2), 127.2, 128.8, 129.2, 130.8, 131.3, 132.2, 134.8, 135.5 (aromatic carbons); IR (KBr, cm^{-1}): 3340 (NH), 1565 (C=N), 1335, 1130 (SO_2). Anal. calcd. for $C_{18}H_{15}ClN_4O_3S$ (402.85): C, 53.67; H, 3.75; N, 13.91. Found: C, 53.74; H, 3.72; N, 13.99.

5-(*p*-Methylphenylsulfonylmethyl)-2-(4′,5′-dihydro-4′-phenyl-1′*H*-pyrazol-3′-yl)-1,3,4-oxadiazole (8c). Yellow solid; yield 0.81 g (85%); mp 139–141°C; ^{1}H NMR (CDCl$_3$+DMSO-d_6) δ (ppm): 2.25 (s, 3H, Ar-CH_3), 3.62 (dd, 1H, H_X, $J_{AX} = 5.1$ Hz, $J_{MX} = 9.8$ Hz), 4.01 (dd, 1H, H_M, $J_{AM} = 12.3$ Hz), 4.35 (s, 2H, SO_2-CH_2), 4.62 (dd, 1H, H_A), 7.15–7.64 (m, 9H, Ar-H), 10.54 (bs, 1H, NH); ^{13}C NMR (CDCl$_3$+DMSO-d_6) δ (ppm): 22.9 (Ar-CH_3), 50.7 (SO_2-CH_2), 52.6 (C-5′), 65.6 (C-4′), 151.5 (C-3′), 153.9 (C-5), 161.6 (C-2), 127.9, 128.7, 129.7, 130.4, 131.8,

132.6, 133.5, 134.3 (aromatic carbons); IR (KBr, cm^{-1}): 3336 (NH), 1566 (C=N), 1342, 1148 (SO_2). Anal. calcd. for $C_{19}H_{18}N_4O_3S$ (382.44): C, 59.67; H, 4.74; N, 14.65. Found: C, 59.75; H, 4.72; N, 14.71.

5-(*p*-Chlorophenylsulfonylmethyl)-2-(4′,5′-dihydro-4′-phenyl-1′*H*-pyrazol-3′-yl)-1,3,4-oxadiazole (8d). Yellow crystals; yield 0.82 g (82%); mp 147–149°C; ^{1}H NMR (DMSO-d_6) δ (ppm): 3.70 (dd, 1H, H_X, $J_{AX} = 5.5$ Hz, $J_{MX} = 10.3$ Hz), 4.06 (dd, 1H, H_M, $J_{AM} = 12.5$ Hz), 4.30 (s, 2H, SO_2-CH_2), 4.58 (dd, 1H, H_A), 7.20–7.70 (m, 9H, Ar-H), 10.49 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 51.7 (SO_2-CH_2), 52.1 (C-5′), 66.5 (C-4′), 152.8 (C-3′), 155.6 (C-5), 165.8 (C-2), 126.5, 127.1, 127.9, 129.2, 130.5, 132.5, 135.8, 136.3 (aromatic carbons); IR (KBr, cm^{-1}): 3328 (NH), 1564 (C=N), 1330, 1140 (SO_2). Anal. calcd. for $C_{18}H_{15}ClN_4O_3S$ (402.85): C, 53.67; H, 3.75; N, 13.91. Found: C, 53.60; H, 3.79; N, 13.82.

5-(*p*-Chlorophenylsulfonylmethyl)-2-[4′,5′-dihydro-4′-(*p*-chlorophenyl)-1′*H*-pyrazol-3′-yl]-1,3,4-oxadiazole (8e). Yellow crystals; yield 0.95 g (87%); mp 154–156°C; ^{1}H NMR (DMSO-d_6) δ (ppm): 3.74 (dd, 1H, H_X, $J_{AX} = 5.2$ Hz, $J_{MX} = 10.0$ Hz), 4.00 (dd, 1H, H_M, $J_{AM} = 12.1$ Hz), 4.37 (s, 2H, SO_2-CH_2), 4.59 (dd, 1H, H_A), 7.23–7.81 (m, 8H, Ar-H), 10.52 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 51.3 (SO_2-CH_2), 52.3 (C-5′), 65.9 (C-4′), 154.2 (C-3′), 157.5 (C-5), 168.2 (C-2), 125.1, 125.7, 126.6, 127.4, 128.3, 131.7, 133.8, 138.4 (aromatic carbons); IR (KBr, cm^{-1}): 3324 (NH), 1568 (C=N), 1338, 1146 (SO_2). Anal. calcd. for $C_{18}H_{14}Cl_2N_4O_3S$ (437.30): C, 49.44; H, 3.23; N, 12.81. Found: C, 49.40; H, 3.20; N, 12.74.

General Procedure of Synthesis of 5-(Arylmethanesulfonylmethyl)-2-(4′,5′-dihydro-4′-phenyl-1′*H*-pyrazol-3′-yl)-1,3,4-oxadiazole (9a–e)

An ethereal solution of diazomethane (20 mL, 0.4 M) and triethylamine (0.06 g) were added to a cooled solution of **7** (2.5 mmol) in DCM (10 mL). The reaction mixture was kept at −20 to −15°C for 40–46 h. The solvent was removed under reduced pressure. The resultant solid was purified by column chromatography (hexane–ethyl acetate, 4:1).

Selected Data

5-(Benzylsulfonylmethyl)-2-[4′,5′-dihydro-4′-phenyl-1′*H*-pyrazol-3′-yl]-1,3,4-oxadiazole (9a). Yellow solid; yield 0.75 g (79%); mp 117–119°C; ^{1}H NMR (DMSO-d_6) δ (ppm): 3.66 (dd, 1H, H_X, $J_{AX} = 4.6$ Hz, $J_{MX} = 8.6$ Hz), 4.01 (dd, 1H, H_M, $J_{AM} = 12.6$ Hz), 4.34 (s, 2H, SO_2-CH_2), 4.60 (dd, 1H, H_A), 5.02 (s, 2H, Ar-CH_2), 7.25–7.59 (m, 10H, Ar-H), 10.57 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 48.6 (SO_2-CH_2), 51.7 (C-5′), 57.4 (Ar-*C*H_2), 66.2 (C-4′), 152.5 (C-3′), 157.8 (C-5), 166.6 (C-2), 126.4, 126.9, 127.2, 129.3, 130.4, 131.3, 133.6, 134.2 (aromatic carbons); IR (KBr, cm^{-1}): 3330 (NH), 1582 (C=N), 1336, 1126 (SO_2). Anal. calcd. for $C_{19}H_{18}N_4O_3S$ (382.44): C, 59.67; H, 4.74; N, 14.65. Found: C, 59.62; H, 4.70; N, 14.72.

5-(Benzylsulfonylmethyl)-2-[4′,5′-dihydro-4′-(*p*-chlorophenyl)-1′*H*-pyrazol-3′-yl]-1,3,4-oxadiazole (9b). Yellow crystals; yield 0.83 g (80%); mp 146–148°C; ^{1}H NMR (DMSO-d_6) δ (ppm): 3.75 (dd, 1H, H_X, $J_{AX} = 4.2$ Hz, $J_{MX} = 8.2$ Hz), 4.03 (dd, 1H, H_M, $J_{AM} = 12.3$ Hz), 4.41 (s, 2H, SO_2-CH_2), 4.68 (dd, 1H, H_A), 5.07 (s, 2H, Ar-CH_2), 7.28–7.73 (dd, 9H, Ar-H), 10.54 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 49.3 (SO_2-CH_2), 52.3 (C-5′), 57.6 (Ar-CH_2), 66.5 (C-4′), 152.8 (C-3′), 158.5 (C-5), 167.5 (C-2), 125.3, 127.1, 128.6, 129.5, 131.7, 133.9, 135.2, 137.5 (aromatic carbons); IR (KBr, cm^{-1}): 3328 (NH), 1577 (C=N), 1330, 1142 (SO_2). Anal. calcd. for $C_{19}H_{17}ClN_4O_3S$ (416.88): C, 54.74; H, 4.11; N, 13.44. Found: C, 54.70; H, 4.13; N, 13.50.

5-(*p*-Methylbenzylsulfonylmethyl)-2-(4′,5′-dihydro-4′-phenyl-1′*H*-pyrazol-3′-yl)-1,3,4-oxadiazole (9c). Yellow solid; yield 0.82 g (83%); mp 133–135°C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.25 (s, 3H, Ar-CH_3), 3.70 (dd, 1H, H_X, $J_{AX} = 4.6$ Hz, $J_{MX} = 8.7$ Hz), 4.05 (dd, 1H, H_M, $J_{AM} = 12.7$ Hz), 4.46 (s, 2H, SO_2-CH_2), 4.66 (dd, 1H, H_A), 5.01 (s, 2H, Ar-CH_2), 7.14–7.68 (m, 9H, Ar-H), 10.51 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 23.6 (Ar-CH_3), 48.7 (SO_2-CH_2), 51.1 (C-5′), 56.4 (Ar-CH_2), 65.6 (C-4′), 151.7 (C-3′), 156.9 (C-5), 167.8 (C-2), 127.9, 128.7, 129.7, 131.8, 132.6, 133.1, 134.3, 135.6 (aromatic carbons); IR (KBr, cm^{-1}): 3335 (NH), 1585 (C=N), 1324, 1136 (SO_2). Anal. calcd. for $C_{20}H_{20}N_4O_3S$ (396.46): C, 60.59; H, 5.08; N, 14.13. Found: C, 60.65; H, 5.12; N, 14.17.

5-(*p*-Chlorobenzylsulfonylmethyl)-2-(4′,5′-dihydro-4′-phenyl-1′*H*-pyrazol-3′-yl)-1,3,4-oxadiazole (9d). Yellow crystals; yield 0.81 g (78%); mp 159–161°C; ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ (ppm): 3.69 (dd, 1H, H_X, $J_{AX} = 4.8$ Hz, $J_{MX} = 8.5$ Hz), 4.00 (dd, 1H, H_M, $J_{AM} = 12.2$ Hz), 4.36 (s, 2H, SO_2-CH_2), 4.65 (dd, 1H, H_A), 5.05 (s, 2H, Ar-CH_2), 7.19–7.68 (m, 9H, Ar-H), 10.44 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$+DMSO-d_6) δ (ppm): 49.5 (SO_2-CH_2), 51.8 (C-5′), 57.0 (Ar-CH_2), 65.8 (C-4′), 152.2 (C-3′), 157.4 (C-5), 166.5 (C-2), 128.6, 129.2, 129.8, 130.2, 132.7, 133.1, 134.6, 136.4 (aromatic carbons); IR (KBr, cm^{-1}): 3327 (NH), 1579 (C=N), 1333, 1145 (SO_2). Anal. calcd. for $C_{19}H_{17}ClN_4O_3S$ (416.88): C, 54.74; H, 4.11; N, 13.44. Found: C, 54.77; H, 4.07; N, 13.48.

5-(*p*-Chlorobenzylsulfonylmethyl)-2-[4′,5′-dihydro-4′-(*p*-chlorophenyl)-1′*H*-pyrazol-3′-yl]-1,3,4-oxadiazole (9e). Yellow solid; yield 0.95 g (85%); mp 166–168°C; ^{1}H NMR (DMSO-d_6) δ (ppm): 3.72 (dd, 1H, H_X, $J_{AX} = 4.3$ Hz, $J_{MX} = 8.9$ Hz), 4.03 (dd, 1H, H_M, $J_{AM} = 12.5$ Hz), 4.37 (s, 2H, SO_2-CH_2), 4.68 (dd, 1H, H_A), 5.10 (s, 2H, Ar-CH_2), 7.24–7.72 (m, 8H, Ar-H), 10.49 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 49.1 (SO_2-CH_2), 51.4 (C-5′), 56.8 (Ar-CH_2), 65.5 (C-4′), 152.7 (C-3′), 158.2 (C-5), 167.0 (C-2), 124.9, 128.8, 129.3, 130.8, 131.1, 133.4, 134.6, 137.2 (aromatic carbons); IR (KBr, cm^{-1}): 3334 (NH), 1580 (C=N), 1330, 1125 (SO_2). Anal. calcd. for $C_{19}H_{16}Cl_2N_4O_3S$ (451.33): C, 50.56; H, 3.57; N, 12.41. Found: C, 50.60; H, 3.59, N, 12.37.

Antimicrobial Testing

The compounds **8** and **9** were dissolved in DMSO at concentrations of 100, 200, and 800 μg/mL.

Antibacterial and Antifungal Assays

Preliminary antimicrobial activities of these compounds were tested by the agar disc-diffusion method. Sterile filter-paper discs (6 mm diameter) moistened with the test compound solution in DMSO of specific concentrations of 100 μg and 200 μg/disc were carefully placed on the agar culture plates that had been previously inoculated separately with the microorganisms. The plates were incubated at 37°C, and the diameter of the growth-inhibition zones were measured after 24 h in the case of bacteria and after 48 h in the case of fungi.

The MICs of the compounds assays were carried out using the microdilution susceptibility method. Chloramphenicol was used as the reference antibacterial agent. Ketoconazole was used as the reference antifungal agent. The test compounds, chloramphenicol and ketoconazole, were dissolved in DMSO at a concentration of 800 μg/mL. Twofold dilutions of the solution were prepared (400, 200, 100, 50, 25, 12.5, 6.25 μg/mL). The microorganism suspensions were inoculated to the corresponding wells. The plates were incubated at 36°C for 24 and 48 h for bacteria and fungi, respectively. The MICs of the compounds were recorded as the lowest concentration of each chemical compounds in the tubes with no turbidity (i.e., no growth) of inoculated bacteria/fungi.

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