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Research Article

SYNTHESIS, ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES OF SOME NOVEL 1, 3, 4-OXADIAZOLE ANALOGUES

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ABSTRACT

5-(5'-fluoro-2'-methoxybiphenyl-3-yl)-1,3,4-oxadiazol-2-amine and its sulfonamide derivatives have been synthesized by multi step organic synthesis. The synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, IR, LCMS and elemental spectroscopic analysis. They were screened for their antibacterial activity against the Gram-positive (*Staphylococcus aureus*, *Bascillus subtilis*), Gram-negative (*Eschericia coli*, *Pseudomonas aeruginosa*) bacteria and antifungal activity against *Aspegillus niger* and *Candida albicans* by cup-plate method. Compound **3g** with promising activity has been identified.

Keywords: Oxadiazole Analogues

INTRODUCTION

The need of new antimicrobial agents is justified because more microorganisms are being resistance to the currently available antibacterial drugs and this is bringing alarming threat to public health and causing growing concern among people across the globe. At the same time as the old antibiotics are losing their effectiveness, the supply of new effective biologically active chemical entities is drying up. Worldwide researchers are trying to synthesize new drugs with better pharmacokinetic and dynamic properties with less adverse effects.

Derivatives of 1,3,4-oxadiazoles have been reported to have a large spectrum of pharmacological activities such as anti-inflammatory[1], anticonvulsant[2], antifungal[3], antibacterial[4-6], anticancer[7], anthelmintic[8] and analgesic[9]. The sulfonamide drugs were the first effective chemotherapeutic agents to be employed systemically for the prevention and cure of bacterial infection in human beings. Due to this reason, sulfonamides occupy a unique position in the drug industry. The sulfonyl group plays a very important role as key constituent of a number of biologically active molecules[10, 11]. Prompted by these observations and in continuation to our ongoing efforts directed toward the synthesis of novel heterocyclic compounds with anticipated biological activities[12-14], we report herein the synthesis of novel 5-(5'-fluoro-2'-methoxybiphenyl-3-yl)-1,3,4-oxadiazol-2-amine, its sulfonamide derivatives and their antibacterial and antifungal activities.

MATERIALS AND METHODS

The synthesis of title compounds is given in scheme-1. TLC on silica gel plates (Merck, Silica gel 60 F254) was used to reach the completion of the reaction and purity of the compounds synthesized. Melting points were recorded in open capillaries with electrical melting point apparatus and were uncorrected. IR spectra were obtained in KBr disc on a Shimadzu-8400 FTIR spectrophotometer. ^{1}H NMR spectra were recorded on Brucker spectrometer (400 MHz) using DMSO-d_6/$CDCl_3$ as a solvent. ^{13}C NMR spectra were recorded on Brucker spectrometer (100 MHz) in DMSO-d_6/$CDCl_3$. ^{19}F NMR spectra were recorded on 376 MHz in $CDCl_3$ as solvent. Mass spectra were recorded on Agilent 6320 Ion Trap. CHN analysis was carried out on Elementar Vario-EL III model analyzer. The synthetic procedure involved following steps.

Compound **1** was synthesized by earlier reported procedure[10].

Synthesis of 5-(5'-fluoro-2'-methoxybiphenyl-3-yl)-1,3,4-oxadiazol-2-amine (2)

To a solution of compound **1** (3.84 mmol) in 1,4-dioxane (10 mL) cyanogen bromide (3.84 mmol) was added, followed by solution of sodium bicarbonate (3.84 mmol) in water (10 mL). The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was taken in ethyl acetate (100 mL), washed with water (20 mL) followed by saturated sodium chloride solution (20 mL) and dried over sodium sulphate. The resulting solution was concentrated and purified by column chromatography [30-40% ethyl acetate in petroleum ether] to afford compound **2** as white solid. Yield: 82%; M.P.: 223-226^{0}C; IR (KBr): 1067 (-C-O-C), 1618 (C=N), 3118, 3314 (NH_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 3.77 (s, 3H, -OCH_3), 5.88 (bs, 2H, NH_2), 7.12-7.18 (m, 3H, Ar-H), 7.56-7.58 (m, 2H, Ar-H), 7.76-7.81 (m, 2H, Ar-H); ^{13}C NMR (DMSO-d_6) δ: 56.6, 113.6, 115.7, 117.3, 121.4, 124.7, 126.2, 129.6, 130.4, 131.6, 138.2, 152.9, 155.7 (d, *J* = 228.4 Hz), 158.1, 164.3; ^{19}F NMR ($CDCl_3$) δ: -128.2 (1F); LCMS: 286.1 (M+1); Anal. Calcd. for $C_{15}H_{12}FN_3O_2$: C, 63.15; H, 4.24; N, 14.73. Found: C, 63.21; H, 4.22; N, 14.75.

General method for syntheis of Sulfanamide derivatives of 5-(5'-fluoro-2'-methoxybiphenyl-3-yl)-1,3,4-oxadiazol-2-amine (3a-h)

To a solution of compound **2** (0.70 mmol) in dichloromethane (2 mL), triethylamine (0.70 mmol) and sulfonyl chloride (0.70 mmol) were added and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was extracted with dichloromethane (20 mL), washed with water (10 mL) followed by saturated sodium chloride solution (10 mL) and dried over sodium sulphate. The resulting solution was concentrated and purified by column chromatography [5-10% ethyl acetate in petroleum ether].

3a: White solid; yield: 79%; M.P.: 189-191^{0}C; IR (KBr): 1112 (-C-O-C), 1609 (C=N), 1378, 1150 cm^{-1} (SO_2); ^{1}H NMR (DMSO-d_6): δ 3.05 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 6.84-7.13 (m, 4H, Ar-H), 7.88-8.16 (m, 2H, Ar-H), 8.23 (s, 1H, Ar-H), 10.46 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 41.6, 55.2, 112.3, 115.1, 120.3, 121.3, 124.6, 126.7, 127.2, 129.7, 130.1, 131.8, 148.1, 154.1 (d, *J* = 228.4 Hz), 158.1, 161.3; ^{19}F NMR ($CDCl_3$) δ: -125.2 (1F); LCMS: 364.1 (M+1)); Anal. Calcd. for $C_{16}H_{14}FN_3O_4S$: C, 52.89; H, 3.88; N, 11.56. Found: C, 52.86; H, 3.89; N, 11.58.

3b: Off white solid; yield: 83%; M.P.: 176-179^{0}C; IR (KBr): 1108 (-C-O-C), 1611 (C=N), 1384, 1152 cm^{-1} (SO_2); ^{1}H NMR (DMSO-d_6) δ: 3.77 (s, 3H, OCH_3), 6.80-7.08 (m, 3H, Ar-H), 7.29-7.46 (m, 4H, Ar-H), 7.54-7.83 (m, 5H, Ar-H), 9.46 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 55.1, 112.1, 115.3, 120.2, 121.4, 124.1, 125.2, 126.1, 128.1, 128.8, 129.3, 129.8, 130.2, 137.5, 138.4, 152.1, 153.1 (d, *J* = 228.4 Hz), 159.2, 161.2; ^{19}F NMR ($CDCl_3$) δ: -128.2 (1F); LCMS: 426.2 (M+1); Anal. Calcd. for $C_{21}H_{16}FN_3O_4S$: C, 59.29; H, 3.79; N, 9.88. Found: C, 59.25; H, 3.81; N, 9.85.

3c: White solid; yield: 85%; M.P.: 183-185^{0}C; IR (KBr): 1089 (-C-O-C), 1618 (C=N), 1380, 1158 cm^{-1} (SO_2); ^{1}H NMR (DMSO-d_6) δ: 3.75 (s, 3H, OCH_3), 6.80-7.08 (m, 3H, Ar-H), 7.29-7.44 (m, 4H, Ar-H), 7.71-8.16 (m, 3H, Ar-H), 9.46 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 55.6, 112.1, 116.3, 120.2, 122.4, 124.1, 125.5, 126.1, 128.1, 129.1, 129.8, 130.2, 131.3, 134.5, 136.5, 137.5, 138.4, 152.1, 153.1 (d, *J* = 228.4 Hz), 159.2, 161.2; ^{19}F NMR ($CDCl_3$) δ: -127.2 (1F); LCMS: 495.2 (M+1); Anal. Calcd. for $C_{21}H_{14}Cl_2FN_3O_4S$: C, 51.02; H, 2.85; N, 8.50. Found: C, 51.06; H, 2.81; N, 8.53.

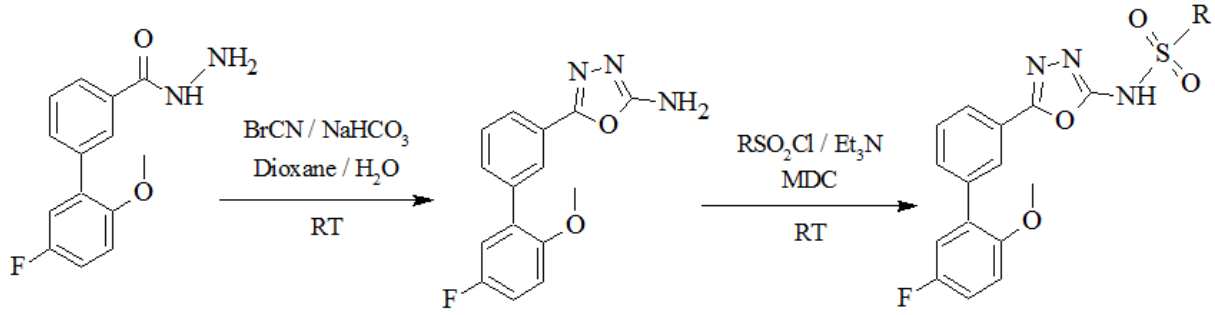
3d: Pale yellow solid; yield: 78%; M.P.: 163-165^{0}C; IR (KBr): 1098 (-C-O-C), 1604 (C=N), 1381, 1158 cm^{-1} (SO_2); ^{1}H NMR (DMSO-d_6) δ: 3.77 (s, 3H, OCH_3), 6.80-7.08 (m, 3H, Ar-H), 7.27-7.66 (m, 4H, Ar-H), 7.88-8.06 (m, 4H, Ar-H), 9.46 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 55.1, 111.8, 115.5, 120.2, 121.6, 124.1, 125.2, 126.7, 128.1, 129.3, 129.8, 130.2, 130.8, 131.3, 134.5, 137.5, 138.4, 152.1, 153.1 (d, *J* = 228.4 Hz), 159.2, 161.2; ^{19}F NMR ($CDCl_3$) δ: -129.5 (1F); LCMS: 460.9 (M+1); Anal. Calcd. for $C_{21}H_{15}ClFN_3O_4S$: C, 54.85; H, 3.29; N, 7.71. Found: C, 54.81; H, 3.31; N, 7.75.

3e: White solid; yield: 75%; M.P.: 153-155^{0}C; IR (KBr): 1106 (-C-O-C), 1611 (C=N), 1384, 1145 cm^{-1} (SO_2); ^{1}H NMR (DMSO-d_6) δ: 3.76 (s, 3H, OCH_3), 6.80-7.08 (m, 3H, Ar-H), 7.19-7.66 (m, 5H, Ar-H), 7.88-8.16 (m, 2H, Ar-H), 9.46 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 55.5, 112.1, 115.3, 120.2, 121.4, 124.1, 124.8, 125.2, 126.1, 128.1, 129.3, 129.8, 130.2, 131.3, 137.5, 138.4, 152.1, 153.1 (d, *J* = 228.4 Hz), 157.3 (d, *J* = 195.4 Hz), 159.2, 161.2; ^{19}F NMR ($CDCl_3$) δ: -127.4 (1F), -122.1 (1F); LCMS: 478.9 (M+1); Anal. Calcd. for $C_{21}H_{14}ClF_2N_3O_4S$: C, 52.78; H, 2.95; N, 8.79. Found: C, 52.81; H, 2.92; N, 8.75.

3f: White solid; yield: 80%; M.P.: 145-147^{0}C; IR (KBr): 1113 (-C-O-C), 1621 (C=N), 1379, 1152 cm^{-1} (SO_2); ^{1}H NMR (DMSO-d_6) δ: 3.71 (s, 3H, OCH_3), 6.80-7.08 (m, 3H, Ar-H), 7.01-7.66 (m, 5H, Ar-H), 7.78-8.16 (m, 3H, Ar-H), 9.46 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 55.3, 113.1, 116.3, 118.7, 120.7, 121.4, 124.1, 124.5, 125.2, 127.1, 128.5, 129.3, 130.2, 131.3, 137.5, 138.4, 152.1, 153.1 (d, *J* = 228.4 Hz), 157.3 (d, *J* = 195.4 Hz), 159.2, 161.2; ^{19}F NMR ($CDCl_3$) δ: -129.5 (1F), -123.1 (1F); LCMS: 444.2 (M+1); Anal. Calcd. for $C_{21}H_{15}F_2N_3O_4S$: C, 56.88; H, 3.41; N, 9.48. Found: C, 56.81; H, 3.42; N, 9.45.

3g: Yellow solid; yield: 82%; M.P.: 180-182^{0}C; IR (KBr): 1099 (-C-O-C), 1608 (C=N), 1384, 1147 cm^{-1} (SO_2); ^{1}H NMR (DMSO-d_6) δ: 3.77 (s, 3H, OCH_3), 6.80-7.08 (m, 3H, Ar-H), 7.21-7.66 (m, 5H, Ar-H), 7.78-7.96 (m, 2H, Ar-H), 9.46 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 55.1, 113.1, 115.8, 120.6, 121.4, 124.1, 125.2, 125.8, 126.1, 127.9, 129.3, 130.5, 131.3, 137.5, 138.4, 149.4 (d, *J* = 190.3 Hz), 152.1, 153.1 (d, *J* = 228.4 Hz), 157.3 (d, *J* = 195.4 Hz), 159.2, 161.2; ^{19}F NMR ($CDCl_3$) δ: -130.5 (1F), -122.1 (1F), -119.5 (1F); LCMS: 462.4 (M+1); Anal. Calcd. for $C_{21}H_{14}F_3N_3O_4S$: C, 54.66; H, 3.06; N, 9.11. Found: C, 56.68; H, 3.09; N, 9.14.

3h: Yellow solid; yield: 80%; M.P.: 210-212^{0}C; IR (KBr): 1099 (-C-O-C), 1608 (C=N), 1384, 1147 cm^{-1} (SO_2); ^{1}H NMR (DMSO-d_6) δ: 3.75 (s, 3H, OCH_3), 6.80-7.08 (m, 3H, Ar-H), 7.28-7.56 (m, 4H, Ar-H), 7.71-8.27 (m, 4H, Ar-H), 9.46 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6) δ: 55.1, 112.1, 115.3, 120.2, 121.4, 124.1, 124.8, 125.2, 126.1, 128.1, 129.3, 130.2, 131.1, 131.8, 137.5, 138.4, 142.3, 152.1, 153.1 (d, *J* = 228.4 Hz), 159.2, 161.2; ^{19}F NMR ($CDCl_3$) δ: -122.1 (1F); LCMS: 471.4 (M+1); Anal. Calcd. for $C_{21}H_{15}FN_4O_6S$: C, 53.62; H, 3.21; N, 11.91. Found: C, 53.68; H, 3.25; N, 11.96.



1 **2** **3a-h**

	R		R
3a	CH_3	**3e**	3-Cl,4-FC_6H_3
3b	C_6H_5	**3f**	3-FC_6H_4
3c	3,4-ClC_6H_3	**3g**	3,4-FC_6H_3
3d	3-ClC_6H_4	**3h**	2-$NO_2C_6H_4$

Scheme 1: Scheme for synthesis of target compounds

Antibacterial activity

The newly synthesized compounds were screened for their antibacterial activity against four bacterial strains namely *Staphylococcus aureus, Pseudomonas aeruginosa, Eschericia coli* and *Bascillus subtilis* by cup-plate method. The sterilized nutrient agar medium was distributed 100 mL each in two 250 mL conical flasks and allowed to cool to room temperature. To these media, 18-24 h grown bacterial sub-cultures were added and shaken thoroughly to ensure uniform distribution of organism's throughout the medium. Then, this agar medium was distributed in equal portions, in sterilized petridishes, ensuring that each petridish contains about 45-50 mL of the medium. The medium was then allowed for solidification. Then, cups were made with the help of a sterile cork borer (6 mm diameter) punching into the set of agar media.

The solutions of required concentrations (50, 100 µg/mL) of test compounds were prepared by dissolving the compounds in DMF were filled into the cups with 1mL of respective solution. Then, the petridishes were kept for incubation in an inverted position for 24-

48 h at 37^{0}C in an incubator. When growth inhibition zones were developed surrounding each cup, their diameter in mm was measured and compared with that of the standard drugs Streptomycin, Procaine penicillin.

Antifungal activity

The newly synthesized compounds were screened for their antifungal activity against two fungi *Aspegillus niger* and *Candida albicans* at the concentration levels of 50 µg/mL and 100 µg/mL by cup-plate method, using Griseofulvin as the standard. To the sterilized potato dextrose agar medium incubated for 72 h, subculture of fungus were added and shaken thoroughly to ensure uniform distribution. Then, this was poured into previously sterilized and labeled petridishes and allowed to solidify. Then, with the help of a borer four cups were made in each plate. Two cups were filled with 0.1 mL of two test dilutions and the other two cups with respective concentrations of standard dilutions. Then, the plates were left as it is for 2-3 h for diffusion and then they were kept for incubation at 37^{0}C for 24 h. Then the diameter of the zones of growth inhibition was measured and compared with that of standard.

RESULTS AND DISCUSSION

As described in Scheme 1, treatment of hydrazide **1** with cyanogen bromide under alkaline conditions gave 5-(5'-fluoro-2'-methoxybiphenyl-3-yl)-1,3,4-oxadiazol-2-amine **2**, which on treatment with various sulfonyl chlorides gave compounds **3a-h** in good yield. The structures of the newly synthesized compounds have been established on the basis of elemental analysis, IR, ^{1}H, ^{13}C, ^{19}F NMR and mass spectral studies. In the IR spectra of compounds **2** and **3a-h**, the C-O-C and C=N absorption bands of oxadiazole ring were observed in the region of 1067-1113 cm^{-1} and 1608-1621 cm^{-1} respectively. Further, in compound **2** two NH absorption bands were observed at 3118, 3314 cm^{-1}. In compounds **3a-h** the SO_2 absorption bands were seen at 1378-1384cm^{-1} and 1145-1158 cm^{-1}. In the ^{1}H NMR spectra of compound **2**, broad singlet at 5.88 ppm integrating for two protons is attributed to NH_2 of oxadiazole. Similarly in compounds **3a-h** NH peak was observed in the region of 9.46-10.46 ppm. Further in the ^{13}C NMR of compounds **2** and **3a-h** the C2 and C5 carbon of oxadiazole were observed in the region of 158.1-159.5 ppm and 161.3-164.6 ppm respectively.

The considerable antibacterial and antifungal activities were shown by all the synthesized compounds compared to standard drugs. The antibacterial activity results are summarized in Table 1. The results indicated that sulfonamide derivatives (**3a-h**) showed better activity than its precursor compound **2** and the modification of functional group in the sulfonamide derivatives varies the activity. Compound **3g** showed excellent activity against all the four bacterial strains. This may be due to the presence of difluoro substitution in the phenyl ring of sulfonamide. Compounds **3e** and **3f** showed moderate activities. Compounds **3c** and **3d** having the chloro substitution showed moderate activity against gram positive bacteria and showed good activity against gram negative bacteria. Accordingly, in antifungal activity compounds **3b** and **3g** were found to have good activity against *Aspegillus niger* while compounds **3a**, **3g** and **3f** were found to have good activity against *Candida albicans* fungi. The antifungal activity results are summarized in Table 2.

Table 1: Antibacterial activity of the synthesized compounds (2 and 3a-h): zone of inhibition in mm

Compound No.	Gram–positive bacteria				Gram–negative bacteria			
	S.aureus		*B.subtilis*		*E.coli*		*P.aeruginosa*	
	50 (µg/mL)	100 (µg/mL)	50 (µg/mL)	100 (µg/mL)	50 (µg/mL)	100 (µg/mL)	50 (µg/mL)	100 (µg/mL)
2	08	11	11	13	08	13	10	14
3a	09	12	13	15	09	14	11	15
3b	10	12	14	15	11	13	10	16
3c	11	11	14	15	16	18	14	18
3d	10	16	13	14	17	18	13	19
3e	14	16	15	16	15	16	14	15
3f	15	17	15	19	12	16	13	14
3g	19	24	20	23	18	21	17	19
3h	10	12	10	14	12	13	11	13
Streptomycin	-	-	-	-	21	25	21	25
Procaine penicillin	22	27	24	28	-	-	-	-

Table 2: Antifungal activity of the synthesized compounds (2 and 3a-h): zone of inhibition in mm

Compound No.	*A. niger*		*C.albicans*	
	50 ((µg/mL)	100 (µg/mL)	50 (µg/mL)	100 (µg/mL)
2	11	21	11	20
3a	13	17	16	29
3b	16	25	10	16
3c	10	16	10	14
3d	14	17	11	20
3e	09	16	12	19
3f	10	14	17	31
3g	17	29	16	28
3h	09	16	07	15
Griseofulvin	20	35	22	37

CONCLUSION

In summary, we have synthesized 5-(5'-fluoro-2'-methoxybiphenyl-3-yl)-1,3,4-oxadiazol-2-amine, its sulfonamide derivatives in good yield and screened for their antibacterial and antifungal activities. Compound **3g** showed promising antibacterial and antifungal activity.

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