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Microwave assisted synthesis of 2,5-distyryl-1,3,4-oxadiazole derivatives as anti microbial agents

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ABSTRACT

A new series of 2,5-distyryl-1,3,4-oxadiazoles derivatives have been synthesized from cinnamic hydrazide on reaction with various cinnamic acid derivatives. The structures of synthesized compounds have been elucidated by spectral studies like IR, ^{1}HNMR, Mass and also Elemental Analysis. Furthermore, all synthesized compounds were screened for in vitro anti microbial activity against the gram positive (*Staphylococcus aureus*, *Pseudomonas aeruginosa*) and gram negative (*Escherichia coli*) bacterial strain. In which some the compounds show potential inhibition against the test organisms.

***Keywords*:** Substituted cinnamic acid; Substituted 1,3,4-oxadiazoles; antimicrobial activity

1. INTRODUCTION

Oxadiazole exists in different isomeric form such as 1,2,4; 1,2,3; 1,2,5 and 1,3,4. Particularly 1,3,4-oxadiazole ring was thermally stable and have played an important role in medicinal chemistry. They are building blocks for the synthesis of biologically active scaffold. Various remarkable biological activity of 1,3,4-oxadiazoles derivative were reported in literature such as antimicrobial [1-3], antifungal [4,5], anticonvulsant [6], Monoamine oxidase inhibitor [7] and anti-proliferative [8], Hypoglycemic [9] and also they are very good bio isosteres of esters and amides, which can contribute significantly in increasing pharmacological activity by in hydrogen bonding interaction with the receptors [10]. B. Narayana and et al have reported synthesis via modified Fischer Indole method and the anti-inflammatory activity [11]. The synthetic adaptability of 1,3,4-oxadiazole has led to the wide-ranging use of this compound in organic synthesis and have attracted the researcher to work on this type of scaffold and study their biological application.

On the other hand, derivatives of cinnamic acid are important intermediate in organic synthesis and also posses wide range of activity such as antimicrobial [12], anti allergic [13], antitubulin [14], anticancer [15], antioxidant [16,17]. Using the cinnamic hydrazide and

triethyl orthoester, microwave assisted synthesis of styryl-1,3,4-oxadiazoles have been reported by Kudelko and Zieliski [18-24].

Therefore, considering that the cinnamic acid derivatives and 1,3,4-oxadiazole are important building blocks for the development of new series of heterocycles for pharmacological interest, we have embarked upon development of various new 1,3,4-oxadiazole derivatives which have been described in following sections.

2. EXPERIMENTAL

Melting points of the synthesized compounds were taken in open capillaries tubes. The purity of the compounds was checked by thin layer chromatography (TLC). The IR spectra were recorded on a Perkin-Elmer 1800 FTIR spectrometer in KBr pellets. The ^{1}HNMR spectra were recorded in DMSO-d_6 solutions on a Bruker Avance Ultra shielded 400 MHz NMR spectrometer using TMS as the internal standard. The mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX. Elemental analysis of the all the synthesized compounds were carried out in Euro EA 3000 Elemental Analyzer and the results are in agreements with the structures assigned. The necessary chemicals were purchased from Spectrochem, Sisco, Loba Chemie, and Sigma Aldrich.

Substituted aromatic aldehyde (10 m mol), malonic acid (15 m mol), piperidine (4 m mol) and pyridine as solvent were taken in 100 ml two necked round bottom flask and refluxed for 6 hours. After the completion the reaction, the reaction mixture was allowed to cool ambient temperature and it was poured on to the mixture of 1:1 HCl: cold water. The separated product was filtered and washes with diluted HCl and crystallized from methanol. The product was enough pure and taken for next step without further purification. Yield 75 % to 88 %.

Cinnamic acid (0.1 mol) was taken in dried 250 ml RBF and cooled it to 0-5 °C then thionyle chloride (12 ml) was added drop wise with the time period of 40 minute and stirred for 1 hour. Excess thionyle chloride was distilled off under reduced pressure and then added hydrazine hydrate (0.1 mol). After the addition of hydrazine hydrate, reaction mixture was stirred at ambient temperature for 2 hour. The progress and the completion of the reaction were checked by thin layer chromatography. After completion of reaction, reaction mass was poured on to the crushed ice, filtered separated product and washed with cold water. Product was crystallized from glacial CH_3COOH. M.P. 116-118 °C, Yield was 89 %.

2. 1. General procedure for the synthesis of 2-((E)-substituted styryl)-5-((E)-styryl-1,3, 4-oxadiazole: (5a-5o).

In dried 100 ml round bottom flask, compound 4a (cinnamohydrazide 10 mmol), substituted cinnamic acid (10 mmol) and $POCl_3$ (15 mmol) were taken and subjected to irradiated under microwave (600 watts) for 5 to 10 minutes under the inert condition. The reaction mixture was cooled to ambient temperature and then poured on to crush ice, stirred for 30 minutes at room temperature and filtered. The obtained solids were further neutralized with 50 ml 10 % sodium bicarbonate solution and wash with 50 ml demineralized water. The resulting compound was purified by column chromatography by silica gel 230-400 mesh using ethyl acetate: hexane (4: 6 v/v) as eluent. Yield: 75-89 %. Physical constants of newly synthesized 2-((E)-substituted styryl)-5-((E)-styryl-1,3,4-oxadiazole derivatives 5a-5o are recorded in Table 1.

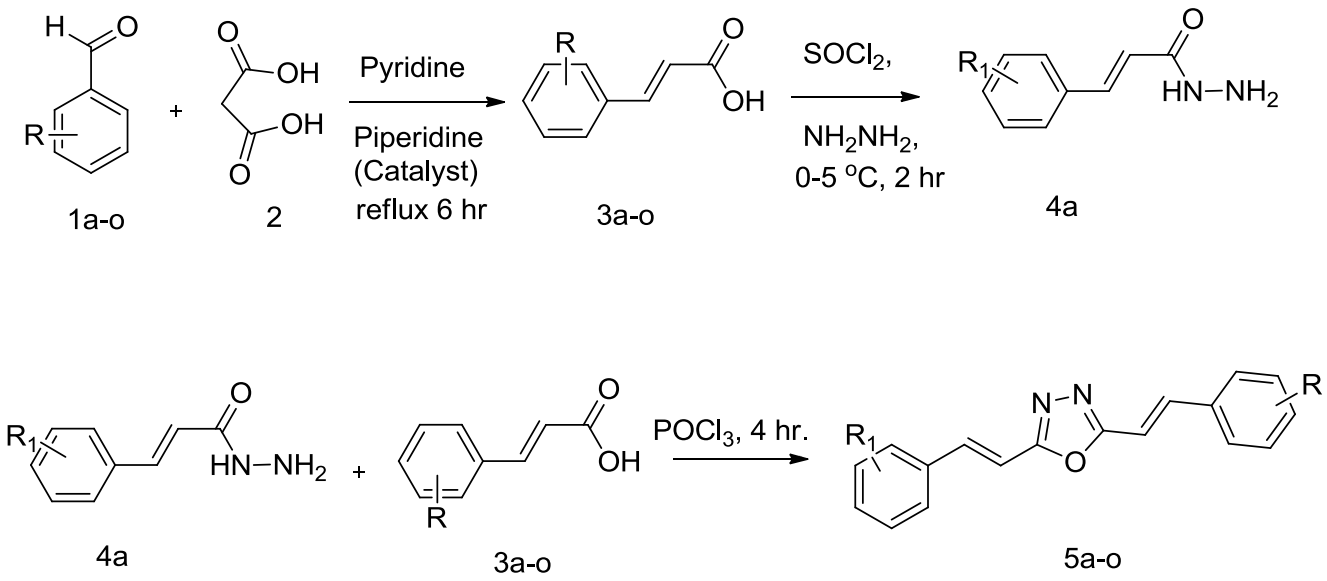

Table 1. Physical data of compounds (5a-5o).

Code	Substitution		Microwave Method		M.P. °C
	R	R_1	Time (min)	Yield %	
5a	H	H	4	87	162-164
5b	2,4-OCH_3	H	6	79	158-160
5c	4-NO_2	H	7	89	240-242
5d	4-OC_2H_5	H	9	80	152-154
5e	4-OC_8H_{15}	H	7	78	132-130
5f	4-F	H	8	84	166-168
5g	4-OH	H	10	75	198-200
5h	4-Cl	H	6	85	162-164
5i	2,5-OCH_3	H	6	78	156-158
5j	2-NO_2	H	6	82	258-260
5k	4-OC_4H_9	H	7	83	142-144
5l	4-CH_3	H	12	85	158-160
5m	3,4,5-OCH_3	H	11	76	146-148
5n	3-OCH_3, 4-OH	H	9	89	168-170
5o	2-F	H	8	87	176-178

2. 2. Analytical data

2, 5-di((E)-styryl)-1,3,4-oxadiazole (5a)

MP: 162-164 °C; IR (cm^{-1}): 3045 (Ar–H stretch), 1680 (C=N stretch of 1,3,4-oxadiazole ring), 2145 (C=C stretching), 1250 (C–O–C stretch of 1,3,4-oxadiazole ring); MS: m/z = 274; ^{1}H NMR ($CDCl_3$) δ ppm: 7.05 (2H, d, *J* = 15.5 Hz), 7.12 (2H, d, *J* = 15.5 Hz), 7.41-7.52 (10H, m); Elemental Analysis: Calculated for $C_{18}H_{14}N_2O$; C, 78.81; H, 5.14; N, 10.21; O, 5.83 Found: C, 76.36; H, 6.20; N, 9.17; O, 7.48.

2-((E)-2, 4-dimethoxystyryl)-5-((E)-styryl)-1,3,4-oxadiazole (5b)

MP: 158-160 °C; IR (cm^{-1}): 3052 (Ar–H stretch), 2965(C-H stretch) 1678 (C=N stretch of 1,3,4-oxadiazole ring), 2148 (C=C stretching), 1254 (C–O–C stretch of 1,3,4-oxadiazole ring), 1075 (C–O stretch); MS: m/z = 334; ^{1}H NMR ($CDCl_3$) δ ppm: 3.75 (6H,s), 6.98 (1H, d, *J* = 15.4 Hz), 6.70 (1H, d, *J* = 15.4 Hz), 6.46 (1H, d, *J* = 15.8 Hz), 7.17 (1H, d, *J* = 15.8 Hz), 7.52-7.68 (9H, m); Elemental Analysis: Calculated for $C_{20}H_{18}N_2O_3$; C, 71.84; H, 5.43; N, 8.38; O, 14.35 Found: C, 70.64; H, 5.33; N, 7.95; O, 16.35.

2-((E)-4-nitrostyryl)-5-((E)-styryl)-1,3,4-oxadiazole) (5c)

MP: 240-242 °C; IR (cm^{-1}): 3052 (Ar–H stretch), 1685 (C=N stretch of 1,3,4-oxadiazole ring), 2156 (C=C stretching), 1255 (C–O–C stretch of 1,3,4-oxadiazole ring), 1366 (Assymetric N–O stretch of C–NO_2); MS: m/z = 319; ^{1}H NMR ($CDCl_3$) δ ppm: 6.98 (1H, d, *J* = 15.3 Hz), 6.72 (1H, d, *J* = 15.3 Hz), 6.92 (1H,d, *J* = 15.6 Hz), 7.13 (1H, d, *J* = 15.6 Hz), 7.39-7.47 (5H, m), 7.59-7.67 (4H, d); Elemental Analysis: Calculated for $C_{18}H_{13}N_3O_3$; C, 67.71; H, 4.10; N, 13.16; O, 15.03 Found: - C, 67.80; H, 4.25; N, 12.96; O, 15.12.

2-((E)-4-ethoxystyryl)-5-((E)-styryl)-1,3,4-oxadiazole (5d)

MP: 152-154 °C; IR (cm^{-1}): 3042 (Ar–H stretch), 2981 (C-H stretch), 1679 (C=N stretch of 1,3,4-oxadiazole ring), 2145 (C=C stretching), 1260 (C–O–C stretch of 1,3,4-oxadiazole ring), 1082 (C–O stretch); MS: m/z = 318; ^{1}H NMR ($CDCl_3$) δ ppm: 1.30 (3H, t), 3.89 (2H, q), 6.99 (1H, d, *J* = 15.1 Hz), 6.71 (1H, d, *J* = 15.1 Hz), 6.65 (1H, d, *J* = 15.4 Hz), 7.01 (1H,d, *J* = 15.4 Hz), 7.95-8.12 (9H, m); Elemental Analysis: Calculated for $C_{20}H_{18}N_2O_2$; C, 75.45; H, 5.70; N, 8.80; O, 10.05 Found: C, 75.80; H, 4.96; N, 9.00; O, 11.05.

2-((E)-4-(n-octyloxy)styryl)-5-((E)-styryl)-1,3,4-oxadiazole (5e)

MP: 132-130 °C; IR (cm^{-1}): 3062 (Ar–H stretch), 2975 (C-H stretch), 1675 (C=N stretch of 1,3,4-oxadiazole ring), 2150 (C=C stretching), 1250 (C–O–C stretch of 1,3,4-oxadiazole ring), 1080 (C–O stretch); MS: m/z = 400; ^{1}H NMR ($CDCl_3$) δ ppm: 1.12 (3H, t), 2.54 (2H, t), 2.60-2.82 (7H, m), 4.22 (2H, d), 7.21 (1H, d, *J* = 15.2 Hz), 6.98 (1H, d, *J* = 15.2 Hz), 7.01 (1H, d, *J* = 15.9 Hz), 7.25 (1H, d, *J* = 15.9 Hz), 7.35-7.48 (9H, m); Elemental Analysis: Calculated for $C_{26}H_{28}N_2O_2$; C, 77.97; H, 7.05; N, 6.99; O, 7.99 Found: C, 76.07; H, 6.12; N, 7.09; O, 8.02.

2-((E)-4-fluorostyryl)-5-((E)-styryl)-1,3,4-oxadiazole (5f)

MP: 166-168 °C; IR (cm^{-1}): 3060 (Ar–H stretch), 1684 (C=N stretch of 1,3,4-oxadiazole ring), 2164 (C=C stretching), 1258 (C–O–C stretch of 1,3,4-oxadiazole ring), 1088 (C–O stretch) 740,1352 (C-Fstretch); MS: m/z = 292; ^{1}H NMR ($CDCl_3$) δ ppm: 7.0 (1H, d, *J* = 15.5

Hz), 6.71 (1H, d, *J* = 15.5 Hz), 6.66 (1H, d, *J* = 15.1 Hz), 7.14 (1H, d, *J* = 15.1 Hz), 7.54-7.68 (9H, m); Elemental Analysis: Calculated for $C_{18}H_{13}FN_2O$; C, 73.96; H, 4.48; F, 6.50; N, 9.58; O, 5.47 Found: C, 73.62; H, 5.09; F, 6.25; N, 9.40; O, 6.10.

4-((E)-2-(5-((E)-styryl)-1,3,4-oxadiazol-2-yl)vinyl)phenol (5g)

MP: 198-200 °C; IR (cm^{-1}): 3454 (O-H stretch) 3058 (Ar–H stretch), 1684 (C=N stretch of 1,3,4-oxadiazole ring), 2145 (C=C stretching), 1248 (C–O–C stretch of 1,3,4-oxadiazole ring); MS: m/z = 290; ^{1}H NMR ($CDCl_3$) δ ppm: 6.02 (1H, d, *J* = 15.3 Hz), 7.04 (1H, d, *J* = 15.3 Hz), 6.70 (1H, d, *J* = 15.8 Hz), 6.65 (1H, d, *J* = 15.7 Hz), 7.06 (1H, d, *J* = 15.7 Hz), 7.64-7.92 (9H, m); Elemental Analysis: Calculated for $C_{18}H_{14}N_2O_2$; C, 74.47; H, 4.86; N, 9.65; O, 11.02 Found: C, 74.11; H, 5.96; N, 9.86; O, 12.08.

2-((E)-4-chlorostyryl)-5-((E)-styryl)-1,3,4-oxadiazole (5h)

MP: 162-164 °C; IR (cm^{-1}): 3056 (Ar–H stretch), 1685 (C=N stretch of 1,3,4-oxadiazole ring), 2148 (C=C stretching), 1256 (C–O–C stretch of 1,3,4-oxadiazole ring), 552,890 (C-Cl stretch); MS: m/z = 308; ^{1}H NMR ($CDCl_3$) δ ppm: 6.07 (1H, d, *J* = 15.5 Hz), 7.12 (1H, d, *J* = 15.5 Hz), 6.75 (1H, d, *J* = 15.9 Hz), 6.70 (1H, d, *J* = 15.8 Hz), 7.06 (1H, d, *J* = 15.7 Hz), 7.74-7.95 (8H, m); Elemental Analysis: Calculated for $C_{18}H_{13}ClN_2O$; C, 70.02; H, 4.24; Cl, 11.48; N, 9.07; O, 5.18 Found: C, 71.00; H, 4.24; Cl, 11.48; N, 9.07; O, 5.18.

2-((E)-2,5-dimethoxystyryl)-5-((E)-styryl)-1,3,4-oxadiazole (5i)

MP: 156-158 °C; IR (cm^{-1}): 3052 (Ar–H stretch), 2860 (C-H stretch), 1682 (C=N stretch of 1,3,4-oxadiazole ring), 2162 (C=C stretching), 1260 (C–O–C stretch of 1,3,4-oxadiazole ring), 1086 (C–O stretch); MS: m/z = 334; ^{1}H NMR ($CDCl_3$) δ ppm: 3.76 (6H,s), 7.02(1H, d, *J* = 15.4 Hz), 6.71(1H, d, *J* = 15.4 Hz), 6.51 (1H, d, *J* = 15.7 Hz), 7.19 (1H, d, *J* = 15.7 Hz), 7.25 (2H, m), 7.56-7.89 (6H, m); Elemental Analysis: Calculated for $C_{20}H_{18}N_2O_3$; C, 71.84; H, 5.43; N, 8.38; O, 14.35 Found: C, 71.65; H, 4.83; N, 8.58; O, 15.20

2-((E)-2-nitrostyryl)-5-((E)-styryl)-1,3,4-oxadiazole (5j)

MP: 258-260 °C; IR (cm^{-1}): 3110 (Ar–H stretch), 1678 (C=N stretch of 1,3,4-oxadiazole ring),2175 (C=C stretching), 1282 (C–O–C stretch of 1,3,4-oxadiazole ring), 1421 (Assymetric N–O stretch of C–NO_2); MS: m/z = 319; ^{1}H NMR ($CDCl_3$) δ ppm: 7.00 (1H, d, *J* = 15.4 Hz), 6.07 (1H, d, *J* = 15.4 Hz), 6.62 (1H, d, *J* = 15.9 Hz), 7.54 (1H, d, *J* = 15.9 Hz), 7.40-7.51 (5H, m), 7.59-7.62 (4H, d); Elemental Analysis: Calculated for $C_{18}H_{13}N_3O_3$; C, 67.71; H, 4.10; N, 13.16; O, 15.03 Found: C, 67.92; H, 4.86; N, 12.56; O, 15.88.

2-((E)-4-butoxystyryl)-5-((E)-styryl)-1,3,4-oxadiazole (5k)

MP: 142-144 °C; IR (cm^{-1}): 3083 (Ar–H stretch), 2946 (C-H stretch), 1688 (C=N stretch of 1,3,4-oxadiazole ring), 2182 (C=C stretching), 1274 (C–O–C stretch of 1,3,4-oxadiazole ring), 1132 (C–O stretch); MS: m/z = 346; ^{1}H NMR ($CDCl_3$) δ ppm: 1.12 (3H, t), 1.48 (2H, q), 1.78 (2H, q), 4.51 (2H, t), 7.00 (1H, d, *J* = 15.2 Hz), 6.71 (1H, d, *J* = 15.2 Hz), 6.64 (1H, d, *J* = 15.9 Hz), 6.99 (1H, d, *J* = 15.9 Hz), 6.97-7.72 (9H, m); Elemental Analysis: Calculated for $C_{22}H_{22}N_2O_2$; C, 76.28; H, 6.40; N, 8.09; O, 9.24 Found: C, 76.37; H, 6.90; N, 8.51; O, 10.16.

2-((E)-4-methylstyryl)-5-((E)-styryl)-1,3,4-oxadiazole (5l)

MP: 158-160 °C; IR (cm^{-1}): 3060 (Ar–H stretch), 2889 (C-H stretch) 1658 (C=N stretch of 1,3,4-oxadiazole ring), 2158 (C=C stretching), 1260 (C–O–C stretch of 1,3,4-oxadiazole ring); MS: m/z = 288; ^{1}H NMR ($CDCl_3$) δ ppm: 2.10 (3H, s), 7.01 (1H, d, *J* = 15.1 Hz), 6.72 (1H, d, *J* = 15.1 Hz), 6.67 (1H, d, *J* = 15.6 Hz), 7.02(1H, d, *J* = 15.6 Hz), 7.48-7.56 (9H, m); Elemental Analysis: Calculated for $C_{19}H_{16}N_2O$; C, 79.14; H, 5.59; N, 9.72; O, 5.55 Found: C, 79.82; H, 4.49; N, 8.71; O, 7.12.

2-((E)-styryl)-5-((E)-3,4,5-trimethoxystyryl)-1,3,4-oxadiazole (5m)

MP: 146-148 °C; IR (cm^{-1}): 3124 (Ar–H stretch), 2966 (C-H stretch) 1645 (C=N stretch of 1,3,4-oxadiazole ring), 2171 (C=C stretching), 1264 (C–O–C stretch of 1,3,4-oxadiazole ring), 1085 (C–O stretch); MS: m/z = 364; ^{1}H NMR ($CDCl_3$) δ ppm: 4.12 (9H, s), 7.04 (1H, d, *J* = 15.3 Hz), 6.72 (1H, d, *J* = 15.3 Hz), 6.71 (1H, d, *J* = 15.8 Hz), 7.06 (1H, d, *J* = 15.8 Hz), 7.64-7.78 (7H, m); Elemental Analysis: Calculated for $C_{21}H_{20}N_2O_4$; C, 69.22; H, 5.53; N, 7.69; O, 17.56 Found: C, 69.32; H, 5.64; N, 6.29; O, 18.55

2-methoxy-4-((E)-2-(5-((E)-styryl)-1,3,4-oxadiazol-2-yl)vinyl)phenol (5n)

MP: 168-170 °C; IR (cm^{-1}): 3458 (O-H stretch), 3072 (Ar–H stretch), 2935 (C-H stretch) 1670 (C=N stretch of 1,3,4-oxadiazole ring), 2164 (C=C stretching), 1310 (C–O–C stretch of 1,3,4-oxadiazole ring), 1108 (C–O stretch); MS: m/z = 320; ^{1}H NMR ($CDCl_3$) δ ppm: 3.71 (3H, s), 6.998 (1H, d, *J* = 15.2 Hz), 6.69 (1H, d, *J* = 15.2 Hz), 6.65 (1H, d, *J* = 15.9 Hz), 7.00 (1H, d, *J* = 15.9 Hz), 7.43-7.78 (8H, m); Elemental Analysis: Calculated for $C_{19}H_{16}N_2O_3$; C, 71.24; H, 5.03; N, 8.74; O, 14.98 Found: C, 72.24; H, 6.05; N, 7.71; O, 13.99.

2-((E)-2-fluorostyryl)-5-((E)-styryl)-1,3,4-oxadiazole (5o)

MP: 176-178 °C; IR (cm^{-1}): 3076 (Ar–H stretch), 1675 (C=N stretch of 1,3,4-oxadiazole ring), 2168 (C=C stretching), 1275 (C–O–C stretch of 1,3,4-oxadiazole ring), 752,1386 (C-Fstretch); MS: m/z = 292; ^{1}H NMR ($CDCl_3$) δ ppm: 6.97 (1H, d, *J* = 15.4 Hz), 6.71 (1H, d, *J* = 15.4 Hz), 6.57 (1H, d, *J* = 15.8 Hz), 7.20 (1H, d, *J* = 15.8 Hz), 7.40-7.68 (9H, m); Elemental Analysis: Calculated for $C_{18}H_{13}FN_2O$; C, 73.96; H, 4.48; F, 6.50; N, 9.58; O, 5.47 Found: C, 74.76; H, 5.98; F, 5.80; N, 9.71; O, 6.4

3. ANTIMICROBIAL ACTIVITY

The all synthesized compounds (5a-o) were screened for in vitro antimicrobial activity against the gram negative bacteria (*Escherichia coli*) and the gram positive bacteria (*Staphylococcus aurous and Bacillus subtitles*), expressed plate agar diffusion method.

Comparisons of inhibition zone in bacterial culture by the synthesized compounds were studied by using ofloxacin as a standard drug, at 100 μg/ml concentration. Dimethyl sulphoxide (DMSO) was used to prepare stock and standard solution of compounds (5a-o) and ofloxacin. Bacterial cultures of *Bacillus subtilis*, *Staphylococcus aureus*, and *Escherichia coli* were prepared in the nutrient agar medium. Discs of whatman filter paper (9 cm diameter) were moistened with 100 μg/ml solution of the compounds and discs were carefully placed on bacterial culture plates that had been previously inoculated separately with the microorganism. The bacterial cultures were incubated at 37 °C for 24 hours. The radius of

zone of inhibition (in mm) was observed around the cup after respective incubation was secure and measured in triplicate sets by using a scale.

Table 2. Antimicrobial activity of 2,5-distyryl-1,3,4-oxadiazole derivatives (5a-5o).

Compound code	Zone of inhibition (mm)		
	Gram Positive		Gram Negative
	Staphylococcus aureus	Pseudomonas aeruginosa	Escherichia coli
5a	09	08	09
5b	10	13	11
5c	14	11	10
5d	11	14	12
5e	13	16	13
5f	15	12	15
5g	18	10	14
5h	20	12	16
5i	10	14	12
5j	13	11	11
5k	13	15	12
5l	12	12	09
5m	12	14	10
5n	18	11	14
5o	15	12	16
Ofloxacin Standard	41	38	37

4. CONCLUSION

In present report , we have developed an efficient, simple, rapid and eco-friendly microwave- indused method for preparation of asymmetric 2,5-disyryl-1,3,4-oxadiazole derivatives which give the higher yield and also redused the reaction time. From the result of biological data, compound 5g, 5h, 5n, showed excellent activity against *Staphylococcus aureus*, while compound 5e and 5k showed maximum bacterial activity against *Pseudomonas*

aeruginosa and compound 5o, 5h maximum activity against *Escherichia coli*. Antibacterial activity was compared with ofloxacin as a standard drug. All the compounds were less potent than the standard drugs ofloxacin. The compound having the halogen group shows greater antimicrobial activity.

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