Int J Pharm Bio Sci 2013 Apr; 4(2): (B) 1046 - 1055

Research Article **Microbiology**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

SYNTHESIS OF NEW 2-(2,4-DIMETHOXYPHENYL) -1,3,4-OXADIAZOLES AND THEIR ANTIMICROBIAL ACTIVITY

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ABSTRACT

A series of new 2-(2,4-dimethoxyphenyl)-1,3,4-oxadiazole derivatives, 4(a-m) were synthesized by using 2,4-dimethoxybenzoic acid (1) as starting material. Different spectral data were used to characterize the newly synthesized compounds. All the compounds were screened for their *in vitro* antimicrobial activity. The results indicated that some of the compounds showed potential activity and comparable to those of commercial antibiotics. Few compounds showed good antimicrobial activity against tested strains.

KEYWORDS: Oxadiazoles, 2,4-Dimethoxybenzoic acid, Antibacterial activity, Antifungal activity.

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INTRODUCTION

Diseases caused by microbial infection are a serious menace to the health of mankind and often have connection to some the other diseases, whenever the body system gets debilitated. Developing antimicrobial drugs and maintaining their potency, in opposition to resistance by different classes of microorganisms as well as a broad spectrum of antibacterial activity are some of the major concern of research in this area. In recent years, considerable interest has been devoted in finding a new methodology for the synthesis of oxadiazole building blocks. A large number of oxadiazole derivatives have been prepared and many of these compounds have shown a wide spectrum antimicrobial activity[1-4]. The observation that some oxadiazoles with different substituent's at different location on the heterocyclic ring resulted in fungicidal [5,6] and antibacterial agents[7-9] of various potencies. Since they discovered during the 20th century, antimicrobial agents have substantially reduced the threat posed by infectious diseases. 1,3,4-Oxadiazoles are an important class of heterocyclic compound with broad spectrum biological activities such as anti-inflammatory[10], anticonvulsant[11], anticancer[12] and antimalarial activity[13]. Keeping in view of these and in continuation of our research on biologically active molecules, the present paper reporting on the synthesis of some new 2-(2,4-dimethoxyphenyl)-1,3,4-oxadiazoles 4(a-m) and evaluate them for antimicrobial activity.

MATERIALS AND METHODS

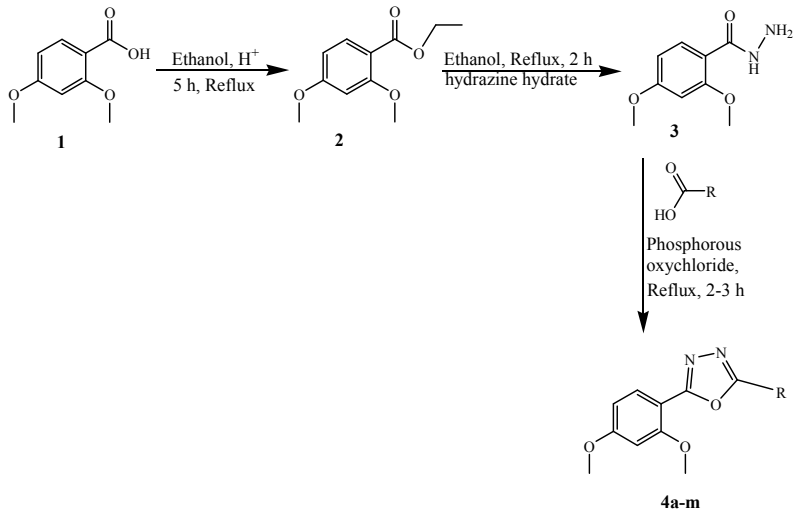
All solvents and reagents were purchased from Sigma Aldrich Chemicals Pvt Ltd. Melting range was determined by Veego Melting Point VMP III apparatus. Elemental analyses were recorded on VarioMICRO superuser V1.3.2 Elementar. ^{1}H NMR and ^{13}C-NMR spectra were recorded on Bruker DRX -500 spectrometer at 400 MHz using d_6-DMSO as solvent and TMS as an internal standard. Mass spectral data were obtained by LC/MSD Trap XCT. Silica gel column chromatography was performed using Merck 7734 silica gel (60–120 mesh) and Merck-made TLC plates.

Synthesis of ethyl-2,4-dimethoxybenzoate (2)

Compound 2 was synthesized as per the reported procedure[14,15]. The mixture of 2,4-dimethoxybenzoic acid (1, 15 g, 0.0823 mol) was taken in ethanol (150 mL), conc. sulphuric acid (1.0 mL) was added and refluxed for 5 h. The reaction mixture was concentrated to syrup stage. Syrup was taken in ethyl acetate (150 mL) and organic layer was washed with water (1x100 mL) followed by brine (1x100 mL). The ethyl acetate layer was concentrated to one volume (20 ml) stage and hexane was added. Stirred at 25-30 °C for 30 minutes, solid formed was filtered, dried to give 2 (ethyl-2,4-dimethoxybenzoate) as a white solid (15 g, 86 %). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.29 (t, J = 4.40 Hz, 3H), 3.60 (s, 3H), 3.81 (s, 3H), 4.28 (q, J = 3.48 Hz, 2H), 6.75 (dd, J = 2.32, 8.66 Hz, 1H, aromatic), 6.80 (d, J = 2.24 Hz, 1H, aromatic), 7.92 (d, J = 8.64 Hz, 1H, aromatic).

Synthesis of 2,4-dimethoxybenzohydrazide (3)

Compound 3 was synthesized as per the reported procedure[16,17]. To a mixture of ethyl 2,4-dimethoxybenzoate (15.0 g, 0.07135 mol) and ethanol (120 mL) at 0-5 °C, hydrazine hydrate (6.95 mL, 0.1427 mol) was added. The reaction mass was heated to reflux for 2.0 h. The reaction completion was monitored by TLC. The reaction mixture was cooled to 0-5 °C stirred for 30 minutes. The solid formed was filtered and dried to get compound **3** as off white solid (11.2 g, 80 %). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.12 (d, J = 8.00 Hz, 2H), 3.64 (s, 3H), 3.83 (s, 3H), 6.75 (dd, J = 2.32, 8.66 Hz, 1H, aromatic), 6.80 (d, J = 2.24 Hz, 1H, aromatic), 7.92 (d, J = 8.72 Hz, 1H, aromatic), 8.02 (br, s, 1H).



Scheme 1
Scheme for synthesis of the new oxadiazoles

General procedure for preparation of 2-(2,4-dimethoxyphenyl)-5-substituted-1,3,4-oxadiazoles 4(a-m)

An equimolar mixture of acid hydrazide (**3**, 1 g, 0.0050 mol) with different aromatic carboxylic acid (0.0050 mol) was refluxed with phosphorous oxychloride (10 vol). The mixture was refluxed at 100 °C for 2-3 h. Reaction completion was monitored by TLC. Reaction mixture was concentrated though rotavapour, the residue was quenched with ice water and the solid precipitated were filtered, washed with water and further crystallized using ethanol to afford 5-substituted 1,3,4- oxadiazole bearing 3,4-dimethoxy moiety as white solid.

Synthesis 2-(2,4-dimethoxyphenyl)-5-phenyl-1,3,4-oxadiazole (4a)

Obtained as white solid (1.14 g, 79 %). FT-IR (KBr, cm^{-1}): 1692 (C=O), 1651 (C=N), 1093 (C-O). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.79 (s, 3H), 3.95 (s, 3H), 6.74 (dd, J = 2.10, 9.86 Hz, 1H, aromatic), 6.80 (d, J = 2.24 Hz, 1H, aromatic), 7.61-7.62 (m, 3H, aromatic), 7.92 (d, J = 8.64 Hz, 1H, aromatic), 8.05-8.07 (m, 2H, aromatic). ^{13}C-NMR (400 MHz, DMSO-d_6): δ 56.1, 56.4, 99.5, 105.5, 106.6, 115.2, 127.2, 128.6, 129.5, 131.6, 162.3, 162.8, 163.7. MS (ESI) *m/z*: 283.1 (M^++1). Anal. Calcd. for $C_{16}H_{14}N_2O_3$ (in %): C, 68.07; H, 5.00; N, 9.92. Found: C, 68.10; H, 5.03; N, 9.84.

Synthesis of 2-(4-bromo-3-fluorophenyl)-5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazole (4b)

Obtained as white solid (1.54 g, 80 %). FT-IR (KBr, cm^{-1}): 1694 (C=O), 1655 (C=N), 1096 (C-O), 691(C-Cl), 527 (C-Br). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.82 (s, 3H), 3.94 (s, 3H), 6.74 (dd, J = 2.00, 8.40 Hz, 1H), 6.79 (d, J = 2.00 Hz, 1H), 7.64 (d, J = 8.40 Hz, 1H), 7.95 (d, J = 8.40 Hz, 1H), 8.09-8.11 (m, 1H), 8.33 (dd, J = 2.00, 6.40 Hz, 1H). ^{13}C-NMR (400 MHz, DMSO-d_6): δ 56.1, 56.6, 99.5, 105.0, 106.7, 118.3, 118.6, 122.3, 128.7, 128.8, 131.9, 159.6, 161.8, 163.5, 164.1. MS (ESI) *m/z*: 378.0 (M^+), 380.0 (M^++2). Anal. Calcd. for $C_{16}H_{12}BrFN_2O_3$ (in %): C, 50.68; H, 3.19; N, 7.39. Found: C, 50.71; H, 3.12; N, 7.41.

Synthesis of 2-(2,4-dimethoxyphenyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (4c)

Obtained as white solid (1.27 g, 80 %). FT-IR (KBr, cm^{-1}): 1696 (C=O), 1656 (C=N), 1094 (C-O). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.83 (s, 6H), 3.91 (s, 3H), 6.70 (d, J = 8.64 Hz, 2H), 7.12 (d, J = 8.70 Hz, 2H), 7.85 (d, J = 8.61 Hz, 1H), 7.96 (d, J = 8.67 Hz, 2H). ^{13}C-NMR (400 MHz, DMSO-d_6): δ 55.9, 56.0, 56.5, 99.5, 105.5, 106.6, 115.2, 116.4, 128.6, 131.6, 159.4, 162.3, 162.8, 163.7. MS (ESI) *m/z*: 313.1 (M^++1). Anal. Calcd. for $C_{17}H_{16}N_2O_4$ (in %): C, 65.38; H, 5.16; N, 8.97. Found: C, 65.41; H, 5.12; N, 8.87.

Synthesis of 2-(2,4-dimethoxyphenyl)-5-(4-fluorophenyl)-1,3,4-oxadiazole (4d)

Obtained as white solid (1.22 g, 80 %). FT-IR (KBr, cm^{-1}): 1692 (C=O), 1651 (C=N), 1224 (C-F), 1093 (C-O). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.85 (s, 3H), 3.89 (s, 3H), 6.70 (dd, J = 2.37, 4.77 Hz, 1H), 6.77 (d, J = 5.10 Hz, 1H), 7.39-7.44 (m, 2H), 7.89 (d, J = 8.64 Hz, 1H), 8.07-8.10 (m, 2H). ^{13}C-NMR (400 MHz, DMSO-d_6): δ 56.1, 56.5, 99.6, 105.5, 106.4, 115.3, 116.4, 128.7, 130.6, 158.4, 161.3, 162.9, 163.8. MS (ESI) *m/z*: 301.0 (M^++1). Anal. Calcd. for $C_{16}H_{13}FN_2O_3$ (in %): C, 64.00; H, 4.36; N, 9.33. Found: C, 64.06; H, 4.32; N, 9.41.

Synthesis of 2-(2,3-dimethoxyphenyl)-5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazole (4e)

Obtained as white solid (1.39 g, 80 %). FT-IR (KBr, cm^{-1}): 1694 (C=O), 1655 (C=N), 1095 (C-O). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.90 (s, 12H), 6.71-6.74 (m, 2H), 7.23-7.25 (m, 2H), 7.46 (d, J = 6.24 Hz, 1H), 7.86 (d, J = 8.52 Hz, 1H). ^{13}C-NMR (400 MHz, DMSO-d_6): δ 55.9, 56.1, 56.2, 56.5, 99.4, 105.1, 106.6, 118.2, 118.6, 123.0, 128.5, 128.8, 131.9, 158.6, 161.8, 163.5, 164.1. MS (ESI) *m/z*: 343.4 (M^++1). Anal. Calcd. for $C_{18}H_{18}N_2O_5$ (in %): C, 63.15; H, 5.30; N, 8.18. Found: C, 63.19; H, 5.38; N, 8.21.

Synthesis of 2-(2,4-dimethoxyphenyl)-5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazole (4f)

Obtained as white solid (1.39 g, 80 %). FT-IR (KBr, cm^{-1}): 1889 (C=O), 1663 (C=N), 1083 (C-O). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.85 (s, 6H), 3.89 (s, 6H), 6.70 (dd, J = 2.28, 8.64 Hz, 2H), 6.75 (d, J = 2.19 Hz, 2H), 7.80 (d, J = 8.58 Hz, 2H). ^{13}C-NMR (400 MHz, DMSO-d_6): δ 56.1, 56.5, 99.6, 105.2, 107.3, 128.9, 159.4, 162.6, 163.9. MS (ESI) *m/z*: 343.4 (M^++1). Anal. Calcd. for $C_{18}H_{18}N_2O_5$ (in %): C, 63.15; H, 5.30; N, 8.18. Found: C, 63.11; H, 5.37; N, 8.20.

Synthesis of 2-(2-bromophenyl)-5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazole (4g)

Obtained as white solid (1.50 g, 80 %). FT-IR (KBr, cm^{-1}): 1696 (C=O), 1654 (C=N), 1096 (C-O), 536 (C-Br). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.89 (s, 6H), 6.57 (dd, J = 2.78, 8.54 Hz, 1H), 6.72 (d, J = 6.20 Hz, 1H), 7.61 (t, J = 7.64 Hz, 1H), 7.61 (t, J = 7.56 Hz, 1H), 7.89 (d, J = 8.24 Hz, 1H), 7.91 (d, J = 6.91 Hz, 1H), 8.05 (d, J = 7.46 Hz, 1H). ^{13}C-NMR (400 MHz, DMSO-d_6): δ 56.0, 56.3, 99.8, 105.0, 106.7, 118.3, 118.6, 120.2, 122.3, 128.2, 128.9, 131.9, 159.6, 161.4, 163.5. MS (ESI) *m/z*: 360.0 (M^+), 362.0 (M^++2). Anal. Calcd. for $C_{16}H_{13}BrN_2O_3$ (in %): C, 53.21; H, 3.63; N, 7.76. Found: C, 53.19; H, 3.59; N, 7.71.

Synthesis of 2-(2-chlorophenyl)-5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazole (4h)

Obtained as white solid (1.29 g, 80%). FT-IR (KBr, cm^{-1}): 1696 (C=O), 1654 (C=N), 1097 (C-O), 685 (C-Cl). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.87 (s, 6H), 6.56 (dd, J = 2.68, 8.54 Hz, 1H), 6.74 (d, J = 6.20 Hz, 1H), 7.58 (t, J = 7.64 Hz, 1H), 7.66 (t, J = 7.56 Hz, 1H), 7.88 (d, J = 8.24 Hz, 1H), 7.90 (d, J = 6.84 Hz, 1H), 8.05 (d, J = 7.36 Hz, 1H). ^{13}C-NMR (400 MHz, DMSO-d_6): δ 56.1, 56.3, 99.5, 105.3, 106.9, 118.3, 118.9, 122.3, 128.2, 128.8, 130.4, 131.9, 159.6, 161.3, 163.2. MS (ESI) *m/z*: 316.1 (M^+), 317.0 (M^++1), 318.1 (M^++2). Anal. Calcd. for $C_{16}H_{13}ClN_2O_3$ (in %): C, 60.67; H, 4.14; N, 8.84. Found: C, 60.70; H, 4.09; N, 8.81.

Synthesis of 2-(4-chlorophenyl)-5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazole (4i)

Obtained as white solid (1.32 g, 82 %). FT-IR (KBr, cm^{-1}): 1694 (C=O), 1662 (C=N), 1098 (C-O), 688 (C-Cl). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.82 (s, 3H), 3.84 (s, 3H), 6.72 (dd, J = 2.37, 4.77 Hz, 1H), 6.77 (d, J = 5.10 Hz, 1H), 7.38-7.44 (m, 2H), 7.89 (d, J = 8.64 Hz, 1H), 7.90-8.11 (m, 2H). ^{13}C-NMR (400 MHz, DMSO-d_6): δ 56.4, 56.6, 99.8, 105.6, 106.7, 122.9, 129.9, 130.3, 131.5, 136.8, 159.6, 163.5, 166.5. MS (ESI) *m/z*: 316.0 (M^+), 317.1 (M^++1), 318.0 (M^++2). Anal. Calcd. for $C_{16}H_{13}ClN_2O_3$ (in %): C, 60.67; H, 4.14; N, 8.84. Found: C, 60.71; H, 4.11; N, 8.82.

Synthesis of 2-(2,4-dimethoxyphenyl)-5-(2-fluorophenyl)-1,3,4-oxadiazole (4j)

Obtained as white solid (1.32 g, 82 %). FT-IR (KBr, cm^{-1}): 1695 (C=O), 1652 (C=N), 1236 (C-

F), 1095 (C-O). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.82 (s, 6H), 6.56 (dd, J = 2.68, 8.54 Hz, 1H), 6.74 (d, J = 6.20 Hz, 1H), 7.58 (t, J = 7.64 Hz, 1H), 7.64-7.66 (m, 1H), 7.89 (d, J = 8.24 Hz, 1H), 7.90 (d, J = 6.84 Hz, 1H), 8.10 (d, J = 7.36 Hz, 1H). ^{13}C-NMR (400 MHz, DMSO-d_6): δ 55.9, 56.3, 99.6, 105.3, 106.8, 118.4, 122.3, 128.2, 128.8, 130.4, 131.9, 157.3, 159.6, 161.3, 163.2. MS (ESI) *m/z*: 301.3 (M^++1). Anal. Calcd. for $C_{16}H_{13}FN_2O_3$ (in %): C, 64.00; H, 4.36; N, 9.33. Found: C, 64.04; H, 4.32; N, 9.37.

Synthesis of 2-(2,4-dimethoxyphenyl)-5-(4-ethoxyphenyl)-1,3,4-oxadiazole (4k)

Obtained as white solid (1.33 g, 80 %). FT-IR (KBr, cm^{-1}): 1698 (C=O), 1659 (C=N), 1098 (C-O). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.14 (t, J = 6.0 Hz, 3H), δ 3.83 (s, 6H), 4.26 (q, J = 3.47 Hz, 2H), 6.70 (d, J = 8.64 Hz, 2H), 7.12 (d, J = 8.70 Hz, 2H), 7.86 (d, J = 8.61 Hz, 1H), 7.92 (d, J = 8.67 Hz, 2H). ^{13}C-NMR (400 MHz, DMSO-d_6): δ 14.8, 55.9, 56.2, 64.1, 99.5, 105.6, 106.7, 115.3, 116.5, 128.6, 131.6, 159.4, 162.3, 162.8, 163.7. MS (ESI) *m/z*: 327.1 (M^++1). Anal. Calcd. for $C_{18}H_{18}N_2O_4$ (in %): C, 66.25; H, 5.56; N, 8.58. Found: C, 66.21; H, 5.52; N, 8.57.

Synthesis of 2-(2,4-dimethoxyphenyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole (4l)

Obtained as white solid (1.33 g, 80 %). FT-IR (KBr, cm^{-1}): 1692 (C=O), 1651 (C=N), 1093 (C-O). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.86 (s, 3H), 3.89 (s, 3H), 6.73 (dd, J = 2.38, 4.80 Hz, 1H), 6.77 (d, J = 5.10 Hz, 1H), 7.38-7.45 (m, 2H), 7.90 (d, J = 8.65 Hz, 1H), 7.88-7.98 (m, 2H). ^{13}C-NMR (400 MHz, DMSO-d_6): δ 56.3, 56.5, 99.6, 106.2, 108.7, 122.9, 128.3, 130.0, 131.5, 148.3, 159.5, 163.5, 166.5. MS (ESI) *m/z*: 328.2 (M^++1). Anal. Calcd. for $C_{16}H_{13}N_3O_5$ (in %): C, 58.72; H, 4.00; N, 12.84. Found: C, 58.69; H, 4.03; N, 12.89.

Synthesis of 2-(4-bromophenyl)-5-(2,4-dimethoxyphenyl)-1,3,4-oxadiazole (4m)

Obtained as white solid (1.5 g, 80 %). FT-IR (KBr, cm^{-1}): 1697 (C=O), 1655 (C=N), 1097 (C-O), 549 (C-Br). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.77 (s, 3H), 3.89 (s, 3H), 6.72 (dd, J = 2.22, 8.67 Hz, 1H), 6.77 (d, J = 2.10 Hz, 1H), 7.55 (d, J = 8.55 Hz, 1H), 7.67 (d, J = 8.58 Hz, 2H), 7.91 (dd, J = 2.60, 8.52 Hz, 2H), 8.05 (d, J = 8.55 Hz, 2H). ^{13}C-NMR (400 MHz, DMSO-d_6): δ 56.1, 56.6, 99.5, 105.2, 106.7, 122.9, 129.1, 130.0, 131.5, 136.8, 159.5, 163.5, 166.9. MS (ESI) *m/z*: 360.0 (M^+), 362.0 (M^++2). Anal. Calcd. For $C_{16}H_{13}BrN_2O_3$ (in %): C, 53.21; H, 3.63; N, 7.76. Found: C, 53.18; H, 3.61; N, 7.81.

Antibacterial activity

Antibacterial activity of the synthesized compounds was determined against Gram-positive bacteria (*Bacillus subtilis* MTCC 121, *Staphylococcus aureus* MTCC 7443) and Gram-negative bacteria (*Xanthomonas campestris* MTCC 7908 and *Escherichia coli* MTCC 7410) in DMF by disc diffusion method on nutrient agar medium[18]. 15 ml of nutrient agar sterile medium was uniformly smeared with cultures of Gram positive and Gram negative bacteria in each of the three petri-plates. 10 mm diameter sterile discs (Hi-Media) was placed in the petriplates, to which 50 µl (1 mg/ml i.e., 50 µg/disc) of the different synthesized compounds were added. The treatments also included 50 µl of DMF as negative, bacteriomycin and gentamycin as positive control for comparison. For each treatment, three replicates were maintained. The plates were incubated at 37 ± 2 ºC for 24 h and the zone of inhibition was determined.

Antifungal activity

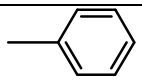
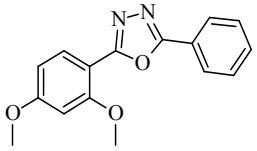
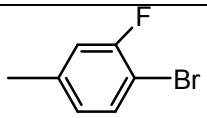
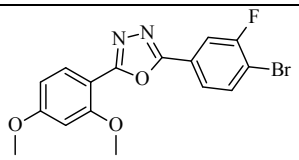
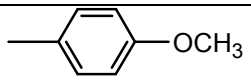
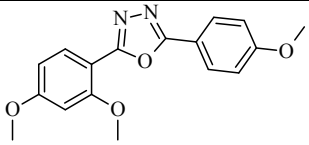
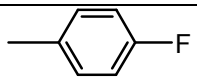
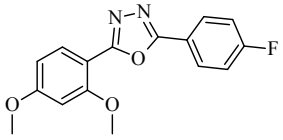
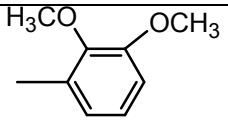
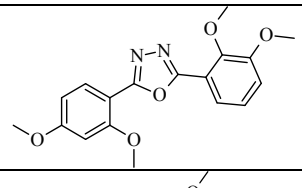
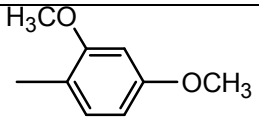
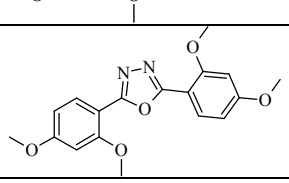
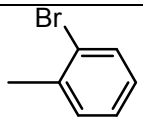
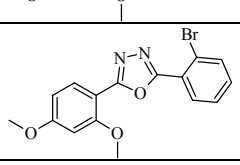
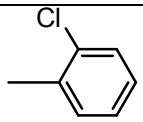
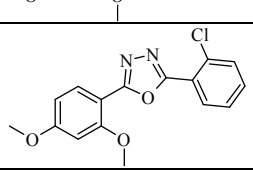
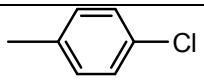
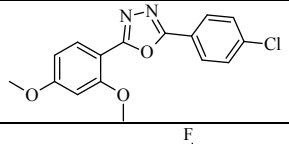
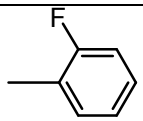
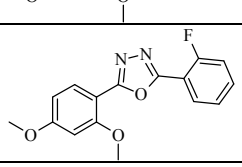
The synthesized compounds were screened for their antifungal activity against *Fusarium oxysporum* MTCC 2480 in DMF by poisoned food technique[19]. 15 ml of Potato Dextrose Agar (PDA) media was prepared and taken in each of the three petriplates, and allowed to solidify. 5 mm disc of seven days old culture of the test fungi was placed at the center of the petriplates and incubated at 26 °C for 7 days. Then percentage inhibition was measured for all the three replicates. Nystatin was used as standard. All the synthesized compounds were tested (at the dosage of 500 µl of the new

compounds/petriplate, where concentration was 0.1 mg/ml) by poisoned food technique.

RESULTS AND DISCUSSION

The new 2-(2,4-dimethoxyphenyl)-1,3,4-oxadiazoles 4(a-m) were synthesized according to Scheme 1. Readily available starting materials and simple synthesizing procedures make this method very attractive and convenient for the synthesis of various oxadiazoles. Formation of 2-(2,4-dimethoxyphenyl)-1,3,4-oxadiazoles was confirmed by recording their elemental analyses, ^{1}H NMR and mass spectra. The ^{1}H NMR spectrum of 4b and 4d showed multiplet in the region of δ, 8.09 - 8.11 and 8.07 - 8.10, respectively. Similarly a singlet appeared at δ, 8.35 - 3.89 are due to the three protons of the methoxy groups. The ^{13}C NMR spectra present the correct number of carbon atoms at the appropriate chemical shift values. The mass spectra of 4b showed molecular ion peaks at m/z 378, 380 (1:1) which is in agreement with the molecular formula $C_{16}H_{12}BrFN_2O_3$. The elemental analyses data showed good agreement between the experimentally determined values and the theoretically calculated values within ± 0.4 %.The investigation of antibacterial screening data revealed that all the tested compounds showed antibacterial activity against four pathogenic bacterial strains. Among the series 4(a-m), compound 4b exhibited an elevated antibacterial activity against Gram positive (zone of inhibition 29 - 34 mm) and Gram negative (zone of inhibition 32 - 33 mm) bacteria. Compounds 4d, 4h, 4i, 4j and 4m showed good antibacterial activity against all the tested organisms. Compounds 4a, 4c, 4e, 4f, 4g, 4k and 4l also showed moderate inhibitory activity. The results were compared with standard drugs bacteriomycin and gentamycin as depicted in Table 2.The *in vitro* antifungal activity of the synthesized compounds 4(a-m) was studied against *Fusarium oxysporum*. The results were compared with the standard drug nystatin as in Table 2. Compound 4b showed significant antifungal activity with 98.4 % inhibition when compared with other compounds in the series against *F. oxysporum*. The good inhibition by the compound 4b could be attributed to the presence of an electron withdrawing halogen groups. Compounds 4d, 4h, 4i, 4j and 4m showed good antifungal activity against *F. oxysporum.* Compounds 4a, 4c, 4e, 4f, 4g, 4k and 4l were found to be moderately active against tested fungal strain.In the present study, different electron withdrawing and electron donating groups attached to oxadizoles ring as substituent were linkage to benzene ring. The close survey of antimicrobial efficacy indicated that the inhibition values of all the compounds exhibited a varied range (15 – 34 mm and 64.5 % - 98.4 %) of antibacterial and antifungal activities against all the tested microbial strains. The electron withdrawing bromine and fluorine atoms in 4b produces enhanced antimicrobial activity. The fluorine atom in 4j produces enhanced activity probably by *m*-effect compared to the *p*-position in 4d. The electron withdrawing chlorine atom in 4h produces good activity probably by *m*-effect compared to the *p*-position in 4i. The electron donating ethoxy group in 4k showed good antimicrobial activity against tested microbial strains. The above studies reveal that, the nature of the linkage (substituent on aromatic ring) influences the antimicrobial activity. The compounds having unsubstituted phenyl ring in 4a revealed relatively moderate antimicrobial activity.

Table 1
Chemical structure and melting range of 2-(2,4-dimethoxyphenyl) -1,3,4-oxadiazoles 4(a-m).

Compound	R	Structure	mp (°C)
4a			95-96
4b			155-158
4c			95-98
4d			105-110
4e			101-104
4f			134-136
4g			106-108
4h			110-112
4i			112-114
4j			120-124

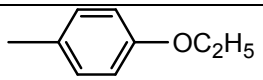
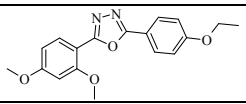
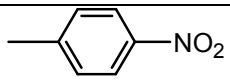
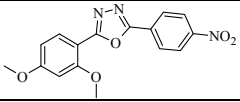
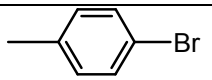
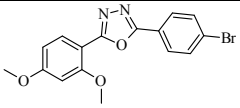
4k			96-99
4l			130-134
4m			138-140

Table 2
In vitro antimicrobial activity of 2-(2,4-dimethoxyphenyl) -1,3,4-oxadiazoles 4(a-m).

Compound	Zone of inhibition in diameter (mm)				% Inhibition
	B. subtilis	*S. aureus*	*X. campestris*	*E. coli*	*F. oxysporum*
4a	18	17	16	15	64.5
4b	34	29	32	33	98.4
4c	20	19	18	19	72.1
4d	31	26	30	30	88.1
4e	22	21	21	20	75.2
4f	21	20	21	20	75.7
4g	24	22	23	22	77.3
4h	28	26	29	29	81.7
4i	27	24	28	28	80.8
4j	32	27	30	31	88.4
4k	21	20	20	19	74.4
4l	25	23	26	24	79.6
4m	26	23	26	28	80.8
Bacteriomycin	-	-	34	-	-
Gentamycin	35	30	-	35	-
Nystatin	-	-	-	-	100

CONCLUSION

In conclusion, a series of new 2-(2,4-dimethoxyphenyl)-1,3,4-oxadiazoles, 4(a-m) were synthesized in good yield, characterized by different spectral studies and their antimicrobial activity have been evaluated. Compounds 4b, 4d, 4j and 4h produced significant changes in activity against tested microbial strain. Therefore, this work presents a new class of potent, wide-spectrum antimicrobial activity of the compounds. The nature of functional linkage and substituents (electron withdrawing and electron donating groups) on benzene ring are crucial for antimicrobial activities.

ACKNOWLEDGEMENTS

Authors thank Dr. S. Satish, Department of Microbiology, University of Mysore, Mysore India to carryout antimicrobial studies.

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