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Synthesis, characterization and antimicrobial activity of some 2,5-disubstituted-3-acetyl-[1,3,4]-oxadiazoles carrying 2-(aryloxymethyl) phenyl moiety

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ABSRACT

A series of 3-acetyl-2-aryl-5-[2-(aryloxymethyl)phenyl]-2,3-dihydro-[1,3,4]-oxadiazoles ***(4a-p)*** *have been synthesized and evaluated for their antimicrobial activity. Initially, the acid hydrazides* ***(2a-d)*** *derived from 2-(aryloxymethyl) benzoic acids* ***(1a-d)*** *were reacted with various aromatic aldehydes to yield hydrazones* ***(3a-p)****. Further reaction of these hydrazones with acetic anhydride afforded the title compounds. All structures of the new compounds were established on the basis of their elemental analyses, IR,* ^{1}H *NMR,* ^{13}C *NMR and mass spectral data. The newly synthesized compounds were evaluated for their antimicrobial activities. Preliminary results indicated that some of them exhibit promising activities and they deserve more consideration as potential antimicrobial agents.*

Key words: 1,3,4-Oxadaiazoles; Antibacterial activity; Antifungal activity; 2-(Aryloxy-methyl)phenyl moiety; dehydrative cyclization.

INTRODUCTION

[1,3,4]-Oxadiazole derivatives are gaining importance in the heterocyclic family because of their broad-spectrum of biological activities in both agrochemicals and pharmaceuticals such as insecticidal[1], herbicidal[2], antibacterial [3], antifungal [4,5,6], analgesic[7], anti-inflammatory [8,9,10] antimalarial [11], antiviral [12], anti-HBV [13], antianexiety [14], anticancer, anti-HIV, antitubercular, antimicrobial, antimycobacterial and anticonvulsant[15,16,17]. As a continuation of our research work to explore potent bioactive oxadiazole derivatives containing 2-(aryloxymethyl)phenyl moiety[18], sixteen new 3-acetyl-2-aryl-5-[2-(aryloxymethyl)- phenyl]-2,3-dihydro-[1,3,4]-oxadiazoles **(4)** were prepared from the corresponding hydrazones **(3)** by dehydrative cyclization using acetic anhdride (Fig. 1).

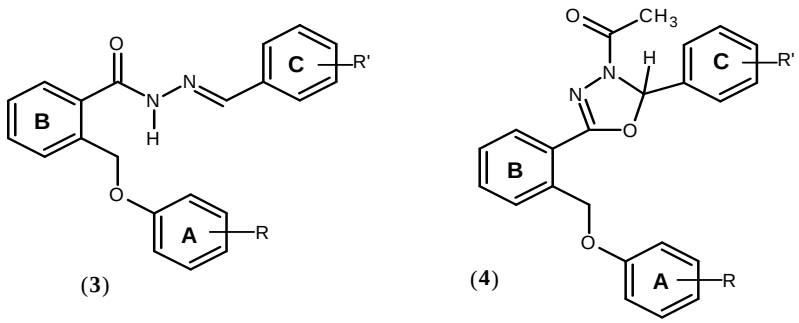
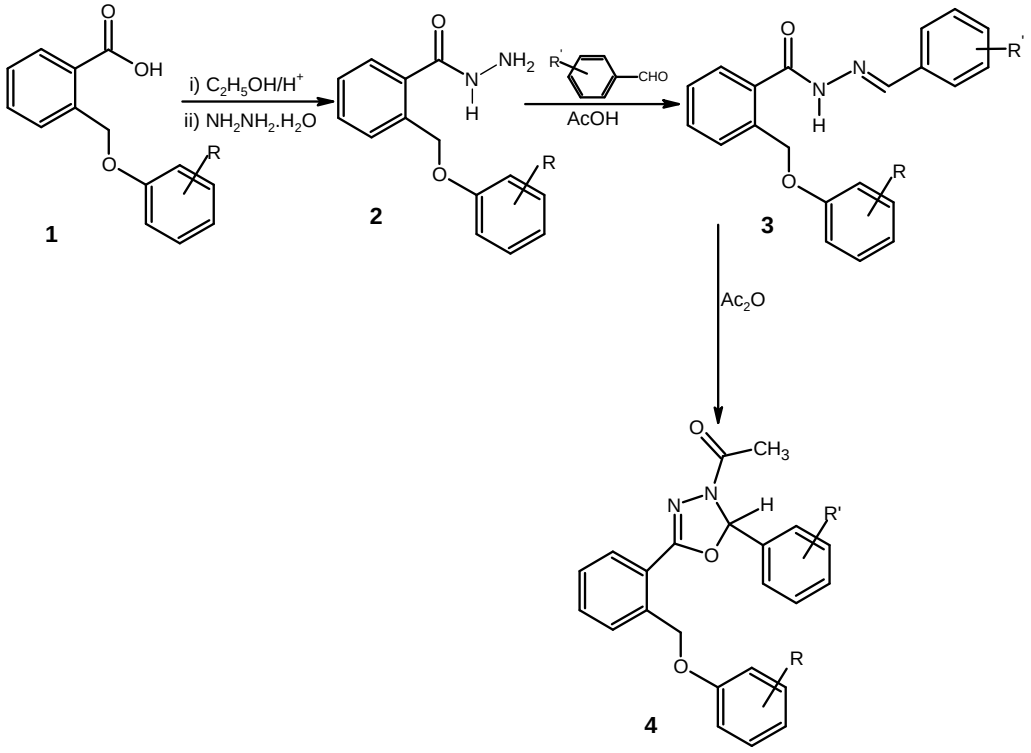


Fig. 1. General structures of hydrazones and substituted-[1,3,4]-oxadiazoles

MATERIALS AND METHODS

Melting points were determined by the open capillary method and are uncorrected. The IR spectra (in KBr pellets) were recorded on a Shimadzu FT-IR 4100 type A spectrophotometer. ^{1}H NMR and ^{13}C spectra were recorded on a Varian 400 MHz NMR spectrometer/Perkin-Elmer EM300 MHz spectrometer using TMS as an internal standard. The FAB mass spectra were recorded on a JEOL SX 102/DA-6000 spectrophotometer/Data system using Argon/Xenon (6KV, 10mA) FAB gas, at 70 eV. Mass spectra were recorded on LC–MS-Aglilent 1100 series with MSD (Ion trap) using 0.1% aqueous TFA in acetonitrile system on C18-BDS column for 10 min duration and in MDSSCIEX, API4000-Electron spray ionization. Elemental analysis was carried out using Flash EA 1112 Series, CHNSO Analyzer (Thermo). The progress of the reactionwas monitored by thin layer chromatography (TLC) on pre-coated silica gel G plates. Solvents and reagents were purchased from the commercial venders in the appropriate grade and were used without purification.



R= 2-CH_3; 3-CH_3; 4-CH_3; 4-Cl

R′ = 6-OCH_3-2-naphthyl; 4-biphenyl; 2,3,5-Cl_3-C_6H_2; 2-Br-6-NO_2 -C_6H_3.

Scheme 1. Synthesis of 2,5-disubstituted-3- acetyl [1,3,4]-oxadiazoles carrying 2-(Aryloxy- methyl)phenyl moiety.

All the reagents and solvents are from spectrochem and Aldrich and they were used as received without further purification.

Table 1. Characterization data of compounds 4(a-p)

No.	R	R'	Mol. Formula	Mol. Mass	Yield (%)	M.P °C	Elemental Analysis % found (cal) C	H	N
4a	2-CH_3	6-OCH_3-2-naphthyl	$C_{29}H_{26}N_2O_4$	466.5	65	98-100	74.62 (74.66)	5.58 (5.61)	6.04 (6.00)
4b	3-CH_3	6-OCH_3-2-naphthyl	$C_{29}H_{26}N_2O_4$	466.5	65	90-92	74.58 (74.66)	5.52 (5.62)	6.01 (6.00)
4c	4-CH_3	6-OCH_3-2-naphthyl	$C_{29}H_{26}N_2O_4$	466.5	65	94-96	74.60 (74.66)	5.64 (5.62)	6.07 (6.00)
4d	4-Cl	6-OCH_3-2-naphthyl	$C_{28}H_{23}ClN_2O_4$	486.9	64	88-90	69.02 (69.06)	4.68 (4.76)	5.71 (5.75)
4e	2-CH_3	4-biphenyl	$C_{30}H_{26}N_2O_3$	462.5	66	118-120	77.86 (77.90)	5.65 (5.67)	6.02 (6.06)
4f	3-CH_3	4-biphenyl	$C_{30}H_{26}N_2O_3$	462.5	66	114-116	77.84 (77.90)	5.60 (5.67)	5.96 (6.06)
4g	4-CH_3	4-biphenyl	$C_{30}H_{26}N_2O_3$	462.5	66	108-110	77.80 (77.90)	5.66 (5.67)	6.05 (6.06)
4h	4-Cl	4-biphenyl	$C_{29}H_{23}ClN_2O_3$	482.9	66	142-145	72.08 (72.12)	4.82 (4.80)	5.77 (5.80)
4i	2-CH_3	2,3,5-Cl_3-C_6H_2	$C_{24}H_{19}Cl_3N_2O_3$	489.7	67	142-145	58.81 (58.85)	3.88 (3.91)	5.70 (5.72)
4j	3-CH_3	2,3,5- Cl_3-C_6H_2	$C_{24}H_{19}Cl_3N_2O_3$	489.7	67	136-138	58.78 (58.85)	3.84 (3.91)	5.64 (5.72)
4k	4-CH_3	2,3,5- Cl_3-C_6H_2	$C_{24}H_{19}Cl_3N_2O_3$	489.7	67	124-125	58.80 (58.85)	3.90 (3.91)	5.65 (5.72)
4l	4-Cl	2,3,5- Cl_3-C_6H_2	$C_{23}H_{16}Cl_4N_2O_3$	510.2	67	152-154	54.10(54.15)	3.12 (3.16)	5.44 (5.49)
4m	2-CH_3	2-Br-6-NO_2-C_6H_3	$C_{24}H_{20}BrN_3O_5$	510.3	63	134-136	56.42 (56.48)	3.95 (3.95)	8.21 (8.23)
4n	3-CH_3	2-Br 6-NO_2-C_6H_3	$C_{24}H_{20}BrN_3O_5$	510.3	63	137-140	56.40 (56.48)	3.82 (3.95)	8.18 (8.23)
4o	4-CH_3	2-Br 6-NO_2-C_6H_3	$C_{24}H_{20}BrN_3O_5$	510.3	63	122-125	56.46 (56.48)	3.90 (3.95)	8.20 (8.23)
4p	4-Cl	2-Br 6-NO_2-C_6H_3	$C_{23}H_{17}BrClN_3O_5$	530.7	65	142-144	52.01 (52.05)	3.20 (3.23)	7.90 (7.92)

Experimental methods

Compound 2-(Substituted phenoxymethyl) benzoylhydrazide **(3a-d)** were prepared from 2-(substituted phenoxymethyl) benzoic acid ethyl ester by treating with hydrazine hydrate in methanol[18].

Preparation of aromatic aldehyde hydrazones (3a-p). To a solution of 2-(aryloxymethyl) benzohydrazides (**2a-d**) (5 mmol) in absolute ethanol (30 mL) was added aromatic aldehyde (5.5 mmol) and 0.1 mL of glacial acetic acid. The reaction mixture was stirred and refluxed for about 3.5 h and the end of the reaction was detected by TLC. The reaction mixture was concentrated. The precipitate was filtered off and crystallized from ethanol to afford hydrazones **3a-p** ethanol in 65-75% yield (**Table 1**).

2-[(3-Methylphenoxy)-methyl]-*N*'-[(2-methoxy6-naphthyl)-methylene]benzohydrazide (3b). IR (KBr, $\gamma_{max,}$ cm^{-1}): 3296 (N-H), 2962 (ArC-H), 1674 (C=O), 1610(C=N), 1245(C-O-C); ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 2.24 (s, 3H, Ring A-CH_3), 3.88(s, 3H, Ring C-OCH_3), 5.20 (s, 2H, -OCH_2), 6.68-7.06 (m, 4H, Ring A-H), 7.18 (s, 1H, =N-CH), 7.31-7.58 (m, 5H, Ring C-H), 7.62 (d, 1H, Ring B-H, J = 7.8 Hz), 7.94-8.14 (t, 1H, Ring B-H, J = 7.6 Hz), 8.22 (t, 1H, Ring B-H, J = 7.6 Hz), 8.40 (d, 1H, Ring B-H, J=7.8 Hz), 9.92 (s, 1H, NH); MS (VG, 70 eV): m/z 425 (M^+) consistent with the molecular formula, $C_{27}H_{24}N_2O_3$.

2-[(4-Methylphenoxy)-methyl]-*N*'-[(2-methoxy6-naphthyl)methylene]benzohydrazide (3c). IR (KBr, $\gamma_{max,}$ cm^{-1}): 3294 (N-H), 2965 (ArC-H), 1677 (C=O), 1614(C=N), 1246(C-O-C); MS (VG, 70 eV): m/z 425 (M^+, 6%) consistent with the molecular formula, $C_{27}H_{24}N_2O_3$.

2-[(4-Chlorophenoxy)-methyl]-*N*'-[(2-methoxy6-naphthyl)methylene]benzohydrazide (3d). IR (KBr, $\gamma_{max,}$ cm^{-1}): 3292 (N-H), 2960 (ArC-H), 1670 (C=O), 1613(C=N), 1244 (C-O-C), 748 (C-Cl); ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 3.92(s, 3H, Ring C-OCH_3), 5.63 (s, 2H, -OCH_2), 7.00 (d, 2H, Ring A-H, J = 7.2 Hz), 7.26 (d, 2H, Ring A-H, J = 7.2 Hz), 7.33 (s, 1H, =N-CH), 7.51-7.64 (m, 5H, Ring C-H), 7.85 (d, 1H, Ring B-H, J = 7.8 Hz), 8.09 (t, 1H, Ring B-H, J = 7.5 Hz), 8.12 (t, 1H, Ring B-H, J = 7.5 Hz), 8.18 (d, 1H, Ring B-H, J = 7.2 Hz), 9.96

(s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 67.82, 111.13, 120.247, 120.478, 123.26, 126.32, 126.52, 127.23, 127.26, 128.21, 128.68, 130.26, 131.23, 131.39, 137.53and 156.18; DEPT: 111.62, 120.73, 127.02, 127.75, 128.70, 129.17, 130.76, 131.72, 131.89; CH_2 δ = 68.23; Mass (m/z): 47476 (M^++1, 5%, consistent with the molecular formula, $C_{26}H_{21}ClN_2O_3$).

2-[(2-Methylphenoxy)-methyl]-*N*'-[(4-biphenyl)-methylene]benzohydrazide (3e). IR (KBr, $\gamma_{max,}$ cm^{-1}): 3292 (N-H), 2958 (ArC-H), 1677 (C=O), 1612(C=N), 1240(C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) : 2.30 (s, 3H, Ring A-CH_3), 5.62 (s, 2H, -OCH_2), 6.88-7.16 (m, 4H, Ring A-H), 7.26-7.42 (m, 9H, Ring C-H), 7.48 (t, 1H, Ring B-H, *J* = 7.5 Hz), 7.57 (t, 1H, Ring B-H, *J* = 7.5 Hz), 7.86 (d, 1H, Ring B-H, *J*=7.8 Hz), 8.16 (d, 1H, Ring B-H, *J*=7.8 Hz), 10.24 (s, 1H, NH); Mass (m/z):420 (M^+, 6%, consistent with the molecular formula, $C_{28}H_{24}N_2O_2$).

2-[(4-Chlorophenoxy)-methyl]-*N*'-[(4-biphenyl)-methylene]benzohydrazide (3h). IR (KBr, $\gamma_{max,}$ cm^{-1}): 3288 (N-H), 2958 (ArC-H), 1678 (C=O), 1613(C=N), 1244 (C-O-C).

2-[(2-Methylphenoxy)methyl]-*N*'-[(2,3,5trichlorophenyl) methylene] benzo hydrazide (3i). IR (KBr, $\gamma_{max,}$ cm^{-1}): 3296 (N-H), 2960 (ArC-H), 1672 (C=O), 1610 (C=N), 1240 (C-O-C).

2-[(3-Methylphenoxy)methyl]-*N*'-[(2,3,5trichlorophenyl) methylene] benzo hydrazide (3j). IR (KBr, $\gamma_{max,}$ cm^{-1}): 3298 (N-H), 2966 (ArC-H), 1672 (C=O), 1614(C=N), 1243(C-O-C), 748 (C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) :1.43 (s, 3H, Ring A-CH_3), 5.42 (s, 2H, -OCH_2), 6.84 (s, 2H, Ring C-H), 6.94 (s, 1H, =N-CH), 7.15-7.18 (m, 4H, Ring A-H), 7.35 (t, 1H, Ring B-H, *J*=7.3 Hz), 7.38 (t, 1H, Ring B-H, *J*=7.3 Hz), 7.46 (d, 1H, Ring B-H, *J*=7.6 Hz), 8.02 (d, 1H, Ring B-H, *J*=7.6 Hz), 9.92 (s, 1H, NH); Mass (m/z): 448 (M^++1, 5%, consistent with the molecular formula, $C_{22}H_{17}Cl_3N_2O_2$).

2-[(4-Methylphenoxy)methyl]-*N*'-[(2,3,5trichlorophenyl) methylene] benzo hydrazide (3k). IR (KBr, $\gamma_{max,}$ cm^{-1}): 3290 (N-H), 2968 (ArC-H), 1670 (C=O), 1614 (C=N), 1241(C-O-C), 745 (C-Cl).

2-[(4-Chlorophenoxy)methyl]-*N*'-[(2,3,5trichlorophenyl) methylene] benzo hydrazide (3l). IR (KBr, $\gamma_{max,}$ cm^{-1}): 3296 (N-H), 2960 (ArC-H), 1672 (C=O), 1612(C=N), 1240(C-O-C), 748 (C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 5.62 (s, 2H, -OCH_2), 6.94 (s, 1H, =N-CH), 7.02 (s, 2H, Ring C-H), 7.25-7.28 (m, 47H, Ring A-H), 7.42-8.16 (m, 47H, Ring B-H), 9.97 (s, 1H, NH); Mass (m/z): 468 (M^+) consistent with the molecular formula, $C_{21}H_{14}Cl_4N_2O_2$.

2-[(2-Methylphenoxy)methyl]-*N*'-[(2-bromo-6-nitrophenyl) methylene] benzo hydrazide (3m). IR (KBr, $\gamma_{max,}$ cm^{-1}): 3288 (N-H), 2960 (ArC-H), 1670 (C=O), 1614 (C=N), 1249(C-O-C), 607 (C-Br); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) : 2.33 (s, 3H, Ring A-CH_3), 5.65 (s, 2H, -OCH_2), 6.92 (s, 1H, =N-CH), 6.95-7.08 (m, 3H, Ring C-H,), 7.15-7.26 (m, 3H, Ring A-H), 7.28-7.33 (m, 1H, Ring A-H), 7.47-7.64 (m, 1H, Ring B-H), 7.95 (d, 1H, Ring B-H, *J*=7.7 Hz), 8.10-8.18 (m, 2H, Ring B-H), 10.23 (s, 1H, NH); Mass (m/z): 468 (M^++1) consistent with the molecular formula, $C_{22}H_{18}BrN_3O_4$.

2-[(3-Methylphenoxy)methyl]-*N*'-[(2-bromo-6-nitrophenyl) methylene] benzo hydrazide (3n). IR (KBr, $\gamma_{max,}$ cm^{-1}): 3296 (N-H), 2962 (ArC-H), 1674 (C=O), 1611(C=N), 1249(C-O-C), 607 (C-Br); Mass (m/z): 468 (M^++1) consistent with the molecular formula, $C_{22}H_{18}BrN_3O_4$.

2-[(4-Methylphenoxy)methyl]-*N*'-[(2-bromo-6-nitrophenyl) methylene] benzo hydrazide (3o). IR (KBr, $\gamma_{max,}$ cm^{-1}): 3286 (N-H), 2968 (ArC-H), 1677 (C=O), 1614(C=N), 1246 (C-O-C), 607 (C-Br); Mass (m/z): 468 (M^++1) consistent with the molecular formula, $C_{22}H_{18}BrN_3O_4$.

2-[(4-Chlorophenoxy)methyl]-*N*'-[(2-bromo-6-nitrophenyl) methylene] benzo hydrazide, (3p). IR (KBr, $\gamma_{max,}$ cm^{-1}): 3290 (N-H), 2965 (ArC-H), 1670 (C=O), 1615(C=N), 1240(C-O-C), 786 (C-Cl), 612 (C-Br); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) : 5.68 (s, 2H, -OCH_2), 6.80-6.92 (m, 2H, Ring C-H), 6.96 (s, 1H, =N-CH), 7.18-7.19 (m, 1H, Ring C-H), 7.40 (d, 2H, Ring A-H, *J* = 7.6 Hz), 7.66 (d, 2H, Ring A-H, *J* = 7.6 Hz), 8.14 (t, 2H, Ring B-H, *J* = 7.5 Hz), 8.19 (d, 2H, Ring B-H, *J* = 7.8 Hz), 10.23 (s, 1H, NH); Mass (m/z): 488 (M^+) consistent with the molecular formula, $C_{21}H_{15}BrClN_3O_4$.

General procedure for the preparation of 2-aryl-3-acetyl-5-[aryloxymethyl]-4,5-dihydro-[1,3,4]-oxadiazoles 4 (a-p)

A mixture of aromatic aldehyde hydrazones (**3a-p**) (2 mmol) and acetic anhydride (10 mL) was refluxed for 1 h. After cooling, the reaction mixture was poured into crushed ice and stirred vigorously until the oil become solid, which was them filtered off and recrystallized from ethanol.

2-(2-Methoxy-6-naphthyl)-3-acetyl-5-[2-[(3-methylphenoxy)methyl]phenyl]-4,5-dihydro-[1,3,4]-oxadiazole (4b). IR (KBr, $\gamma_{max,}$ cm^{-1}): 3024 (ArC-H), 2872 (C-H), 1680 (C=O), 1612 (C=N), 1250 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.28 (s, 3H, Ring A-CH_3), 2.32 (s, 3H, -$COCH_3$), 3.92 (s, 3H, -OCH_3), 5.36 (s, 2H, -OCH_2), 6.78-6.86 (m, 2H, Ring A-H), 7.08-7.12 (m, 2H, Ring A-H), 7.26 (s, 1H, CH), 7.32-7.50 (m, 6H, Ring C-H), 7.82-7.94 (m, 2H, Ring B-H), 8.02 (d, 1H, Ring B-H, *J* = 7.8 Hz), 8.14 (d, 1H, Ring B-H, *J* = 7.8 Hz).

2-(2-Methoxy-6-naphthyl)-3-acetyl-5-[2-[(4-methylphenoxy)methyl]phenyl]-4,5-dihydro-[1,3,4]-oxadiazole (4c). IR (KBr, $\gamma_{max,}$ cm^{-1}): 3026 (ArC-H), 2878 (C-H), 1687 (C=O), 1613 (C=N), 1255 (C-O-C); Mass (m/z): 468 (M^+ +1, 100%).

2-(2-methoxy-6-naphthyl)-3-acetyl-5-[2-[4-chlorophenoxy)methyl]phenyl]-4,5-dihydro-[1,3,4]-oxadiazole (4d). IR (KBr, $\gamma_{max,}$ cm^{-1}): 3032 (ArC-H), 2877 (C-H), 1681 (C=O), 1611 (C=N), 1250 (C-O-C), 748 (C-Cl); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.38 (s, 3H, -$COCH_3$), 3.92 (s, 3H, Ring C-OCH_3), 5.63 (s, 2H, -OCH_2), 6.96 (d, 2H, Ring A-H, *J* = 7.2 Hz), 7.16 (d, 2H, Ring A-H, *J* = 7.2 Hz), 7.22 (s, 1H, CH of oxadiazole), 7.36-7.547 (m, 6H, Ring C-H), 7.82 (d, 1H, Ring B-H, *J* = 7.8 Hz), 8.047 (t, 1H, Ring B-H, *J* = 7.5 Hz), 8.14 (t, 1H, Ring B-H, *J* = 7.5 Hz), 8.20 (d, 1H, Ring B-H, *J* = 7.2 Hz).

2-(4-Biphenyl)-3-acetyl-5-[2-[(2-methylphenoxy)methyl]phenyl]-4,5-dihydro-[1,3,4]-oxadiazole (4e). IR (KBr, $\gamma_{max,}$ cm^{-1}): 3028 (ArC-H), 28747 (C-H), 1680 (C=O), 1616 (C=N), 1256 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31 (s, 3H, Ar-CH_3), 2.35 (s, 3H, -$COCH_3$), 5.53 (s, 2H, -OCH_2), 6.84-6.92 (m, 1H, Ring A-H), 7.10-7.21 (m, 3H, Ring A-H), 7.26 (s, 1H, CH of oxadiazole), 7.34-7.46 (m, 4H, Ring B-H), 7.52-7.96 (m, 9H, Ring C-H); ^{13}C NMR (100 MHz, CDCl3, δ ppm): 16.51(RingA-CH_3), 21.46 ($COCH_3$), 68.20 (OCH_2) and peaks at 91.22 (C_5 of oxadiazole), 111.04 (C_6 of Ring A), 120.68 (C_2 of Ring C) ,121.40 (C_5 of Ring A), 126.88 (C_4 of Ring A), 127.25 (C_3 of Ring C), 127.54 (C_5 of Ring C),127.65 (C_2 of Ring B) , 128.84 (C_3 of Ring A), 128.90 (C_2 of Ring A),130.84 (C_4&C_5 of Ring B), 131.60 (C_2&C_6 of Ring B),

135.14 & 137.99 (C_1&C_4 of Ring C), 140.46(C_6 of Ring B), 142.97(C_1 of Ring B), 154.91 (C_2 of oxadiazole), 156.78 (C_1 of Ring A) and 167.91 (C=O) respectively. DEPT: CH and CH_3 ∂:16.52, 21.47, 91.22, 111.04, 120.68, 122.66, 126.88, 127.00, 127.25, 127.47,127.54, 127.65,128.84, 128.90, 130.84, 131.60; Mass (m/z): 464 (M^+ 100%).

2-(4-Biphenyl)-3-acetyl-5-[2-[(3-methylphenoxy)methyl]phenyl]-4,5-dihydro-[1,3,4]-oxadiazole (4f). IR (KBr, $\gamma_{max,}$ cm^{-1}): 3023 (ArC-H), 2872 (C-H), 1684 (C=O), 1614 (C=N), 1242 (C-O-C).

2-(4-Biphenyl)-3-acetyl-5-[2-[(4-methylphenoxy)methyl]phenyl]-4,5-dihydro-[1,3,4]-oxadiazole (4g). IR (KBr, $\gamma_{max,}$ cm^{-1}): 3036 (ArC-H), 2875 (C-H), 1680 (C=O), 1621 (C=N), 1550 (C=N), 1250 (C-O-C); LCMS : m/z 464 (M^+ 100%).

2-(4-Biphenyl)-3-acetyl-5-[2-[(4-chlorophenoxy)methyl]phenyl]-4,5-dihydro-[1,3,4]-oxadiazole (4h). IR (KBr, $\gamma_{max,}$ cm^{-1}): 3024 (ArC-H), 2873 (C-H), 1687 (C=O), 1613 (C=N), 1246 (C-O-C), 746 (C-Cl); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.31 (s, 3H, -$COCH_3$), 3.90 (s, 3H, Ring C-OCH_3), 5.48 (s, 2H, -OCH_2), 6.81 (d, 2H, Ring A-H, *J* = 7.2 Hz), 6.96 (d, 2H, Ring A-H, *J* = 7.2 Hz), 7.05 (s, 1H, CH of oxadiazole), 7.24-7.45 (m, 9H, Ring C-H), 7.62 (d, 1H, Ring B-H, *J* = 7.8 Hz), 7.86 (t, 1H, Ring B-H, *J* = 7.5 Hz), 8.02 (t, 1H, Ring B-H, *J* = 7.5 Hz), 8.14 (d, 1H, Ring B-H, *J* = 7.2 Hz).

2-(2,3,5-Trichlorophenyl)-3-acetyl-5-[2-[(2-methylphenoxy)methyl]phenyl]-4,5-dihydro-[1,3,4]-oxadiazole (4i). IR (KBr, $\gamma_{max,}$ cm^{-1}): 3031 (ArC-H), 2876 (C-H), 1680 (C=O), 1619 (C=N), 1239 (C-O-C), 751 (C-Cl); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.56 (s, 3H, -$COCH_3$), 2.27 (s, 3H, RingA-CH_3), 5.36 (s, 2H, -OCH_2), 6.82 (d, 1H, Ring C-H), 6.84 (d, 1H, Ring C-H), 7.16 (s, 1H, Ring C-H), 7.21-7.25 (m, 3H, Ring A-H), 7.37-7.41 (t, 1H, Ring A-H), 7.46-7.53 (m, 2H, Ring B-H), 7.64 (d, 1H, Ring B-H, *J* = 7.8 Hz), 7.85 (t, 1H, Ring B-H, *J* = 7.5 Hz); ^{13}C NMR (100 MHz, CDCl3, δ ppm): 16.58(CH_3), 21.25 (RingA-CH_3), 68.65 (OCH_2) and peaks at 89.10 (C_5 of oxadiazole), 115.76 (C_6 of Ring A), 121.60 (C_2 of Ring A) ,126.00 (C_4 of Ring C), 126.51 (C_1 of Ring C), 128.14 (C_6 of Ring C),128.59 (C_3 of Ring A), 129.34 & 129.45 (C_5 & C_4 of Ring A),130.51 (C_5 of Ring C) , 131.63 (C_2 &C_3 of Ring B), 131.88 (C_4 &C_5 of Ring B),133.41 (C_3 of Ring C), 134.98 (C_2 of Ring C), 135.85 & 136.75 (C_1&C_6 of Ring B), 154.90 (C_5 of oxadiazole), 157.22(C_1 of Ring A) 168.14 (C=O) respectively. Mass (m/z): 448 (M^+ 100%).

2-(2,3,5-Trichlorophenyl)-3-acetyl-5-[2-[(3-methylphenoxy)methyl]phenyl]-4,5-dihydro-[1,3,4]-oxadiazole (4j). IR (KBr, $\gamma_{max,}$ cm^{-1}): 3028 (ArC-H), 2881 (C-H), 1680 (C=O), 1613 (C=N), 1230 (C-O), 748 (C-Cl).

2-(2,3,5-Trichlorophenyl)-3-acetyl-5-[2-[(4-methylphenoxy)methyl]phenyl]-4,5-dihydro-[1,3,4]-oxadiazole (4k). IR (KBr, $\gamma_{max,}$ cm^{-1}): 3026 (ArC-H), 2870 (C-H), 1684 (C=O), 1610 (C=N), 1240 (C-O-C), 747 (C-Cl); Mass (m/z): 490 (M^+) consistent with the molecular formula, $C_{24}H_{19}Cl_3N_2O_3$.

2-(2,3,5-Trichlorophenyl)-3-acetyl-5-[2-[(4-chlorophenoxy)methyl]phenyl]-4,5-dihydro-[1,3,4]-oxadiazoles (4l). IR (KBr, $\gamma_{max,}$ cm^{-1}): 3029 (ArC-H), 2970 (C-H), 1550 (C=N), 1246 (C-O), 746 (C-Cl); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.21 (s, 3H, -$COCH_3$), 5.56 (s, 2H, -OCH_2), 6.86 (d, 2H, Ring A-H, *J* = 7.2 Hz), 6.98 (d, 2H, Ring A-H, *J* = 7.2 Hz), 7.12 (s, 1H,

CH of oxadiazole), 7.18-7.34 (m, 2H, Ring C-H), 7.51 (d, 1H, Ring B-H, *J* = 7.8 Hz), 7.64 (t, 1H, Ring B-H, *J* = 7.5 Hz), 7.94 (t, 1H, Ring B-H, *J* = 7.5 Hz), 8.03 (d, 1H, Ring B-H, *J* = 7.2 Hz).

2-(2-Bromo-6-nitrophenyl)-3-acetyl-5-[2-[(2-methylphenoxy)methyl]phenyl]-4,5-dihydro-[1,3,4]-oxadiazoles (4m). IR (KBr, $\gamma_{max,}$ cm^{-1}): 3028 (ArC-H), 2871 (C-H), 1684 (C=O), 1614 (C=N), 1256 (C-O-C), 612 (C-Br); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.31 (s, 3H, Ring A-CH_3), 2.30 (s, 3H, -$COCH_3$), 5.52 (s, 2H, -OCH_2), 6.80-6.92 (m, 3H, Ring A-H), 7.02-7.13 (m, 1H, Ring A-H), 7.31 (s, 1H, CH), 7.54-7.66 (m, 3H, Ring C-H), 7.74-7.95 (m, 4H, Ring B-H). LCMS: m/z 511 (M^++1, 100%).

2-(2-Bromo-6-nitrophenyl)-3-acetyl-5-[2-[(3-methylphenoxy)methyl]phenyl]-4,5-dihydro-[1,3,4]-oxadiazoles (4n). IR (KBr, $\gamma_{max,}$ cm^{-1}): 3026 (ArC-H), 2874 (C-H), 1680 (C=O), 1613 (C=N), 1248 (C-O-C), 612 (C-Br); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.35 (s, 3H, Ring A-CH_3), 2.38 (s, 3H, -$COCH_3$), 5.58 (s, 2H, -OCH_2), 6.88-6.96 (m, 3H, Ring A-H), 7.07-7.12 (m, 1H, Ring A-H), 7.26 (s, 1H, CH), 7.46-7.62 (m, 3H, Ring C-H), 7.40-7.86 (m, 4H, Ring B-H).

2-(2-Bromo-6-nitrophenyl)-3-acetyl-5-[2-[(4-methylphenoxy)methyl]phenyl]-4,5-dihydro-[1,3,4]-oxadiazoles (4º). IR (KBr, $\gamma_{max,}$ cm^{-1}): 3020 (ArC-H), 2871 (C-H), 1682 (C=O), 1621 (C=N), 1248 (C-O-C), 612 (C-Br); Mass (m/z):511 (M^++1, 100%).

2-(2-Bromo-6-nitrophenyl)-3-acetyl-5-[2-[(4-chlorophenoxy)methyl]phenyl]-4,5-dihydro-[1,3,4]-oxadiazoles (4p). IR (KBr, $\gamma_{max,}$ cm^{-1}): 3026 (ArC-H), 2872 (C-H), 1680 (C=O), 1614 (C=N), 1245 (C-O-C), 754 (C-Cl), 612 (C-Br); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm):): 2.28 (s, 3H, -$COCH_3$), 5.32 (s, 2H, -OCH_2), 6.95 (d, 1H, Ring C-H, *J* = 7.6 Hz), 6.96 (d, 2H, Ring A-H, *J* = 7.2 Hz), 7.02 (t, 1H, Ring C-H, *J* = 7.4 Hz), 7.08 (d, 1H, Ring C-H, *J* = 7.6 Hz), 7.16 (d, 2H, Ring A-H, *J* = 7.2 Hz), 7.22 (s, 1H, CH of oxadiazole), 7.62 (d, 1H, Ring B-H, *J* = 7.8 Hz), 7.84 (t, 1H, Ring B-H, *J* = 7.5 Hz), 8.04 (t, 1H, Ring B-H, *J* = 7.5 Hz), 8.16 (d, 1H, Ring B-H, *J* = 7.2 Hz).

RESULTS AND DISCUSSION

A synthetic approach to the title compounds is outlined in **Scheme 1**. Acid hydrazides (**2a-d)** derived from 2-(aryloxymethyl)benzoic acids (**1a-d)** were condensed with aromatic aldehydes to afford the corresponding hydrazones (**3a-p**). The carbonylamino and imino groups of **3a-p** underwent cyclization with acetic anhydride to give oxadiazoles **(4a-p)** in good yield. The new compounds and intermediates have been characterized by analytical and spectroscopic (IR, ^{1}H NMR, ^{13}C NMR and Mass) data. 2-(Aryloxymethyl) benzoic acids were prepared from Phthalide and substituted phenols according to the literature procedures [19].

The formation of 2-(4-chlorophenylmethyl) benzoic acid hydrazide **(2d)** was confirmed by its elemental analyses and spectral data. IR spectrum of it showed absorption bands at 3291, 3224, 3070, 2990, 1688 and 1244 cm^{-1} due to –NH_2, -NH, Ar-H, C-H, >C=O and C-O-C groups respectively, while ^{1}H NMR showed sharp singlets at δ 4.07 and δ 5.22, which correspond to -NH_2 and –OCH_2 protons respectively. Two doublets observed at δ 6.92 (*J* = 7.2 Hz) and δ 6.25 (*J* = 7.2 Hz) are accounted for the four aromatic protons of ring A. The ring B protons appeared as a multiplet in the region δ 7.48-7.58 integrating for four protons. The spectrum also showed a broad singlet at δ 7.40 for its NH protons. The formation of hydrazone was confirmed by ^{1}H NMR, ^{13}C NMR and Mass data. The ^{1}H NMR spectrum of hydrazone **3a,** showed sharp singlet

at δ 2.3& δ 3.93 for its CH_3 & OCH_3 protons while peaks due to -OCH_2 protons appeared at δ 5.26. The CH proton appears at δ 6.96 and six aromatic protons of naphthyl ring appear as complex multliplet in the region δ 7.0-7.26. The 3,4-aromatic protons ring B appeared as two distinct triplets at *δ* 7.49 (*J*=7.05 Hz) and *δ* 7.52 (*J*= 7.60 Hz), where as 2,5-aromatic protons resonated as two doublets at *δ* 7.55 (*J*=7.05 Hz) and *δ* 7.59 (*J*=7.60 Hz). Similarly, the 3,6-aromatic protons of ring A resonated as two distinct doublets at *δ* 7.63 and *δ* 7.73 with *J*=7.3 Hz and *J*=8.1 Hz respectively. The 4,5-protons resonated as a multiplet in the region, *δ* 7.78-7.83. The remaining NH protons appeared as a broad singlet at δ 9.8. Further, FAB MS spectrum showed the molecular ion peak at m/z 426 which corresponds to its molecular formula, $C_{27}H_{24}N_2O_3$.

Hydrazones on cyclization reaction with acetic anhydride yielded 3-acetyl-2,5-disubstituted-[1,3,4]-oxadiazoles (**4a-p)** (**Scheme 1**). [1,3,4]-oxadiazoles showed C=N stretching at around 1655 cm^{-1} and C-O-C stretching at around 1270 cm^{-1} and 1040 cm^{-1} in their IR spectra. The ^1H NMR spectrum of compound **5i,** showed sharp singlet at δ 1.56 and δ 2.27 for its $COCH_3$ and ring-A CH_3 protons. The two hydrogen atoms of the phenoxymethyl group were appeared as a singlet at *δ* 5.36. The two singlets at δ 6.82 and δ 6.84 corresponding to 4 and 6 aromatic protons of ring-C. The C-5 aromatic proton of oxadiazole appear as singlet δ 7.16. The four aromatic protons ring A appeared as multiplet at *δ* 7.21-7.41 where as 3,4-aromatic protons of ring-B resonated as multiplet at *δ* 7.46-7.53. Similarly the 2,5-aromatic protons of ring B resonated as two distinct doublets at *δ* 7.64 and *δ* 7.85 with *J*=7.3 Hz and *J*=8.1 Hz respectively. Further, ^{13}C NMR spectrum of (**5i)** showed signals at δ 16.23, 21.25, 68.65 and 89.10 due to -CH_3, ring A-CH_3, OCH_2 and CH of oxadiazole carbon atoms respectively. The other peaks seen in the spectrum are at δ 115.76 and 121.63 (C_6 and C_2 of ring A), 126.00 and 126.51 (C_4 and C_1 of ring C), 128.14 (C_6 of ring C), 128.59 (C_3 of ring A), 129.34 and 129.45 (C_5 and C_4 of ring A), 130.51(C_4 of ring C), 131.63 and 131.88(C_2,C_3 and C_4,$C_5$of ring B), 133.41 (C_3 of ring C), 134.98 (C_2 of ring C), 135.85 (C_1 of ring B), 136.75 (C_6 of ring B), 154.90 (C_5 of oxadiazole),157.22(C_1 of ring A), and 168.14 (C=O) respectively. The peaks due to quaternary carbon atoms of the compound disappeared on DEPT experimentation. Further, FAB MS spectrum showed the molecular ion peak at m/z 490 which corresponds to its molecular formula, $C_{22}H_{17}Cl_3N_2O_3$.

Antibacterial Activity Studies

The newly synthesized compounds were screened for their antibacterial activity against *Escherichia coli* (ATTC-25922), *Staphylococcus aureus* (ATTC-25923), *Pseudomonas aeruginosa* (ATTC-27853) and *Klebsiella pneumoniae (*recultured) bacterial stains by serial plate dilution method [20, 21]. Serial dilutions of the drug in Muller Hinton broth were taken in tubes and their pH was adjusted to 5.0 using phosphate buffer. A standardized suspension of the test bacterium was inoculated and incubated for 16-18 h at 37 ^oC. The minimum inhibitory concentration (MIC) was noted by seeing the lowest concentration of the drug at which there was no visible growth.

A number of antibacterial discs were placed on the agar for the sole purpose of producing zones of inhibition in the bacterial lawn. Twenty milliliters of agar media was poured into each Petri dish. Excess of suspension was decanted and plates were dried by placing in an incubator at 37 ^oC for an hour. Using a punch, wells were made on these seeds agar plates and minimum inhibitory concentrations of the test compounds in dimethyl sulfoxide (DMSO) were added into each labeled well. A control was also prepared for the plates in the same way using DMSO as a solvent. The Petri dishes were prepared in triplicate and maintained a 37 ^oC for 3-4 days.

Antibacterial activity was determined by measuring the diameter of inhibition zone. Activity of each compound was pcompared with ciprofloxacin as standard [22]. Zone of inhibition was determined for **4a-p** and results are summarized in **Table 2**.

Table 2. Antibacterial Activity of the Compounds 4(a-p)

Compd.	MIC [$\mu g\ mL^{-1}$] and Zone of Inhibition (mm) in Parentheses			
	S. aureus	***E. coli***	***P. aeruginosa***	***K. pneumoniae***
4a	12.5(11-15)	12.5(1 1-15)	12.5(11-15)	12.5(11-15)
4b	12.5(11-15)	12.5(11-15)	12.5(11-15)	12.5(11-15)
4c	6.25(16-20)	6.25(18-22)	6.25(16-20)	6.25(16-20)
4d	6.25(16-20)	6.25(18-22)	6.25(16-20)	6.25(16-20)
4e	25(<10)	25(<10)	25(<10)	25(<10)
4f	25(<10)	25(<10)	25(<10)	25(<10)
4g	25(<10)	25(<10)	25(<10)	25(<10)
4h	12.5(11-15)	12.5(11-15)	12.5(11-15)	12.5(11-15)
4i	6.25(16-20)	6.25(18-22)	6.25(16-20)	6.25(16-20)
4j	6.25(16-20)	6.25(18-22)	6.25(16-20)	6.25(16-20)
4k	6.25(16-20)	6.25(18-22)	6.25(16-20)	6.25(16-20)
4l	6.25(16-20)	6.25(18-22)	6.25(16-20)	6.25(16-20)
4m	25(<10)	25(<10)	25(<10)	25(<10)
4n	25(<10)	25(<10)	25(<10)	25(<10)
4o	25(<10)	25(<10)	25(<10)	25(<10)
4p	12.5(11-15)	12.5(11-15)	12.5(11-15)	12.5(11-15)
Standard (Ciprofloxacin)	1.56(22-30)	6.25(30-40)	6.25(25-33)	6.25(23-27)

Table 3. Antifungal Activity of the Compounds 4(a-p)

Compound	MIC [$\mu g\ mL^{-1}$] and zone of inhibition (mm) in parentheses			
	P. marneffei	***T. mentagrophytes***	***A. flavus***	***A. fumigatus***
4a	12.5(11-15)	12.5(11-15)	12.5(11-15)	12.5(11-15)
4b	25(<10)	25(<10)	25(<10)	25(<10)
4c	25(<10)	25(<10)	25(<10)	25(<10)
4d	6.25(18-21)	6.25(18-22)	6.25(18-21)	6.25(18-21)
4e	12.5(11-15)	12.5(11-15)	12.5(11-15)	12.5(11-15)
4f	25(<10)	25(<10)	25(<10)	25(<10)
4g	25(<10)	25(<10)	25(<10)	25(<10)
4h	6.25(16-20)	6.25(18-22)	6.25(16-20)	6.25(16-20)
4i	12.5(11-15)	12.5(11-15)	12.5(11-15)	12.5(11-15)
4j	12.5(11-15)	12.5(11-15)	12.5(11-15)	12.5(11-15)
4k	12.5(11-15)	12.5(11-15)	12.5(11-15)	12.5(11-15)
4l	6.25(18-21)	6.25(18-22)	6.25(18-21)	6.25(18-21)
4m	25(<10)	25(<10)	25(<10)	25(<10)
4n	25(<10)	25(<10)	25(<10)	25(<10)
4o	12.5(11-15)	12.5(11-15)	12.5(11-15)	12.5(11-15)
4p	12.5(11-15)	12.5(11-15)	12.5(11-15)	12.5(11-15)
Standard (Cyclopiroxolamine)	1.56(22-30)	6.25(30-40)	6.25(25-33)	6.25(23-27)

Antifungal Activity Studies

Newly prepared compounds were also screened for their antifungal activity against *Aspergilus flavus* (NCIM No. 524), *Aspergilus fumigatus* (NCIM No. 902), *Penicillium marneffei* (recultured) and *Trichophyton mentagrophytes* (recultured) in DMSO by serial plate dilution method [23, 24]. Sabourands agar media was prepared by dissolving peptone (1 g), D glucose (4g) and agar (2g) in distilled water (100 mL) and adjusting the pH to 5.7. Normal saline was used to make a suspension of sore of fungal strains for lawning. A loopful of particular fungal strain was transferred to 3 mL saline to get a suspension of corresponding species. Twenty milliliters of agar media was poured +into each Petri dish. Excess of suspension was decanted and plated were dried by placing in an incubator at 37 ^{o}C for 1h. Using a punch wells were made on these seeded agar plates. Minimum inhibitory concentrations of the test compounds in DMSO

were added into each labeled well. A control was also prepared for the plates in the same way using solvent DMSO. The Petri dishes were prepared in triplicate and maintained at 37 ^{o}C for 3-4 days. Antifungal activity was determined by measuring the diameter of inhibition zone. Activity of each compound was compared with cyclopiroxolamine as standard. Zones of inhibition were determined for **4a-p** and results are summarized in **Table 3.**

The investigation of antibacterial and antifungal screening data revealed that all the tested compounds **4a-p** showed moderate to good inhibition at 1.55 - 25 µg/mL in DMSO. The compounds **4c**, **4d**, **4i**, **4j**, **4k** and **4l** showed comparatively good activity against all the bacterial strains. The good activity is attributed to the presence of pharmacologically active 6-methoxy naphthyl group and 2,3,5-trichloro phenyl moiety attached to oxadiazole moiety. The compounds **4a**, **4b**, **4h** and **4p** exhibited moderate antibacterial activity.

The compounds **4d**, **4h** and **4l** showed comparatively good activity against all the fungal strains. The structure of these compounds contains biologically active Cl attached to the phenyl rings at position 4 and 6-methoxy naphthyl group and 2,3,5-trichloro phenyl moiety attached to oxadiazole moiety.The compounds **4a**, **4e**, **4i**, **4j**, **4k**, **4o** and **4p** showed moderate activity.

Two of the sixteen compounds namely **4d** and **4l** were found to be very active against all the tested bacterial and fungal strains which may be due to the presence of Cl at para positions of the phenyl ring and 6-methoxy naphthyl group and 2,3,5-trichloro phenyl moiety attached to oxadiazole moiety. Biphenyl ring attached to oxadiazole ring showed less activity when compared with the halosubstituted phenyl rings.

CONCLUSION

Several 3-acetyl-2,5-disubstituted-[1,3,4]-oxadaiazoles derived from 2-(aryloxymethyl)benzoic acids have been successfully synthesized in 60-70% yields and are characterized by ^{1}H NMR, ^{13}C NMR, Mass spectrometry and IR studies. All the newly synthesized compounds were screened for antibacterial and antifungal properties. The compounds **4c**, **4d**, **4i**, **4j**, **4k** and **4l** showed comparatively good activity against all the bacterial strains. The good activity is attributed to the presence of 6-methoxynaphthyl group and 2,3,5-trichlorophenyl moiety attached to oxadiazole moiety. The compounds **4d**, **4h** and **4l** showed comparatively good activity against all the fungal strains. The structure of these compounds contains 4-chlorophenoxymethyl group at position 4 and 6-methoxy-2-naphthyl/ 2,3,5-trichlorophenyl moiety at position 5 of oxadiazole ring.

The screening data showed that the newly prepared compounds have shown promising antibacterial and antifungal activities against the tested organisms. More extensive study is also warranted to determine additional physicochemical and biological parameters to have a deeper insight into structure-activity relationship and to optimize the effectiveness of this series of molecules.

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