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ORIGINAL ARTICLE

A facile one-pot synthesis of novel 2,5-disubstituted-1,3,4-oxadiazoles under conventional and microwave conditions and evaluation of their *in vitro* antimicrobial activities

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KEYWORDS

2,5-Disubstituted-1,3,4-oxadiazoles;
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Spectral data;
Antimicrobial activities

Abstract A rapid and efficient solvent-free synthesis of 2,5-disubstituted-1,3,4-oxadiazoles (**3a–l**) from fatty acid hydrazides (**1a–f**) under microwave irradiation is described. The structural elucidation of these compounds is based on their spectral data (IR, ^{1}H NMR, ^{13}C NMR and MS). All the newly synthesized compounds have been screened for their antibacterial and antifungal activities. The compounds **3f**, **3j** and **3l** were found to be most potent anti-microbial agents.

1. Introduction

1,3,4-Oxadiazole is apparently among the most significant heterocyclic cores. The 1,3,4-oxadiazole derivatives may act as ester and amide bioisosteres and hence are of interest in pharmaceutical and agrochemical fields (Zarudnitskii et al., 2008). The wide range of biological activities associated with 1,3,4-oxadiazoles include anti-viral (Tan et al., 2006), antimicrobial (Mayekar, 2010), antineoplastic (Aboraia et al., 2006), fungicidal (Li et al., 2006), inhibition of tyrosinase (Khan et al., 2005) and cathepsin K (Palmer et al., 2006). Also, much attention has been focused on the oxadiazole core Π-systems as electron-transporting and hole-blocking materials in the area of organic light-emitting diodes (OLEDs) (He et al., 2008). Further 1,3,4-oxadiazole heterocycles can contribute substantially in increasing the pharmacological activity by participating in hydrogen bonding interactions with the receptors (Guimaraes et al., 2005).

Several methods have been reported in the literature for the synthesis of 1,3,4-oxadiazoles (Coppo et al., 2004; Brain and Brunton, 2001). Most of these protocols are multi-step in nature and generally involve the cyclization of acid hydrazides with a variety of reagents, such as, phosphorus oxy chloride,

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sulfuric acid and thionyl chloride, usually under harsh conditions. Recently a few efficient examples have been reported for the synthesis of 1,3,4-oxadiazoles, especially from readily available carboxylic acids and acid hydrazides. However, these protocols use expensive catalysts and require longer times for the completion of the reaction (Dolman et al., 2006; Jakopin et al., 2007). Consequently, the development of effective methods for the rapid and concise synthesis and modification of oxadiazole motif need to be developed.

The application of microwave irradiation in organic synthesis for conducting reactions at highly accelerated rates is an emerging technique (Loupy, 2004). In fact, in recent years, the use of microwaves have become popular among synthetic organic chemists both to improve classical organic reactions (shortening reaction times and/or improving yields) as well as to promote new reactions.

The substantial reduction in the reaction times under microwave irradiation and the pharmacological importance of 1,3,4-oxadiazole ring systems prompted us to synthesize the 2,5-disubstituted-1,3,4-oxadiazoles bearing an alkanyl/alkenyl/hydroxyalkenyl chain substituent and evaluate them for their antimicrobial activity. To the best of our awareness this contribution reports for the first time the simple and straightforward synthesis of 1,3,4-oxadiazoles under microwave condition having a long chain substituent.

2. Experimental

2.1. Chemistry

Undec-10-enoic (purity 98%), (9Z)-octadec-9-enoic (97%), benzoic acid and chlorobenzoic acids were purchased from Fluka chemicals (Bucks, Switzerland). (9Z,12R)-12-Hydroxyoctadec-9-enoic (ricinoleic) and (9R,12Z)-9-hydroxyoctadec-12-enoic (isoricinoleic) acids were isolated from the natural sources, i.e. from Ricinus communis and Wrightia tinctoria seed oils, respectively. The concentrate of pure hydroxy acids were obtained by Gunstone's partitioning (Gunstone, 1954) of freshly prepared acids and further purified by column chromatography. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker DRX-400 instrument. The chemical shifts (d) were measured relative to TMS as an internal standard. Coupling constants (J) are expressed in Hz. Mass spectra were obtained on a Jeol SX-102 (FAB) spectrometer. IR spectra were obtained on Shimadzu 8201 PC FTIR using KBr pellet with absorption given in cm^{-1}. The microwave irradiations were carried out using a modified domestic microwave oven (LG, 2.45 GHz, 850 W). Briefly, the modified microwave oven consists of a perforation on the top to accommodate a reflux condenser and a 10-cm stainless steel cylinder to avoid leakage of microwave energy. In addition to this the turnable was replaced with the magnetic stirrer and a temperature detector was added.

2.1.1. General procedure for the synthesis of fatty acid hydrazides (**1a**–**d**)

The hydrazides of long chain alkenoic acids (**1a**–**d**) used as the starting material were prepared by previously reported method (Rauf et al., 2007). The synthesized hydrazides were characterized by their melting points.

2.1.2. General procedure for the conventional synthesis of 2,5-disubstituted-1,3,4-oxadiazoles(**3a**–**l**)

Phosphorus oxy chloride (5 ml) was added to a mixture of substituted carboxylic acid (0.01 mol) and fatty acid hydrazide (0.01 mol) in abs. ethanol. The reaction mixture was refluxed for 8–14 h on a water bath. After the completion of the reaction, the contents were cooled at room temperature and poured into crushed ice. The precipitated crude product was washed with 10% solution of $NaHCO_3$ and further recrystallized from 95% ethanol (Table 1).

2.1.3. General procedure for the synthesis of 2,5-disubstituted-1,3,4-oxadiazoles (**3a**–**l**) under solvent-free microwave conditions

A mixture of fatty acid hydrazide (0.01 mol), carboxylic acid (0.01 mol) and alumina (1.50 g) was mixed and ground in a mortar and pestle until a fine homogenous powder was obtained (5 min). Phosphorus oxy chloride (5 ml) was added. The mixture was irradiated under microwave irradiation for the required time (Table 3). After the completion of the reaction (TLC analysis), ice cold water (10 ml) was added to the reaction mixture and the precipitated crude product was filtered. The crude 1,3,4-oxadiazole was washed with 10% solution of $NaHCO_3$ and further purified by column chromatography over silica gel using petroleum ether-diethyl ether mixture as eluent.

The synthesized 2,5-disubstituted-1,3,4-oxadiazoles (**3a**–**l**) were characterized from their spectral data (IR, ^{1}H NMR, ^{13}C NMR and mass spectra).

2.1.4. 2-(Dec-9′-enyl)-5-(furan-2-yl)-1,3,4-oxadiazole (**3a**)

IR (KBr, cm^{-1}): 1668 (C═C), 1568 (C═N), 1240 (C–O–C). ^{1}H NMR ($CDCl_3$, δ_H): 7.64 (m, 1H, furan 5″-H), 7.32 (m, 1H, furan 2″-H), 6.55 (m, 1H, furan 4″-H), 5.82 (tdd, 1H, $J_{H-^9CH_2}$ = 6.6 Hz, J_{H-H_Z} = 10.2 Hz, J_{H-H_E} = 17.0 Hz, CH_2-═CH─), 5.01 (dd, 1H, J_{H_Z-H} = 11.8 Hz, $J_{H_Z-H_E}$ = 1.9 Hz, H_ZC═CH), 4.94 (dd, 1H, J_{H_E-H} = 16.7 Hz, $J_{H_E-H_Z}$ = 2.2 Hz, H_EC═CH─), 2.36 (t, 2H, J = 7.4 Hz, CH_2 α to ring), 2.02 (m, 2H, CH_2═CH–CH_2), 1.64 (m, 2H, CH_2 β to ring), 1.40-1.25 (br, s, 10H, $(CH_2)_5$). ^{13}C NMR ($CDCl_3$, δ_C): 172.4, 168.2, 142.7, 139.4, 139.0, 114.7, 111.6, 40.2, 39.8, 38.3, 37.9, 31.3, 29.7, 28.4, 26.8. ESI-MS: found $[M+Na]^+$ 297.08; requires 297.12.

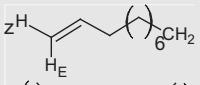
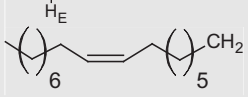
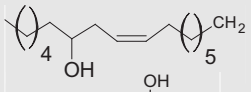
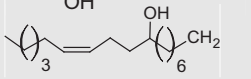
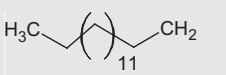
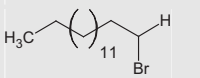
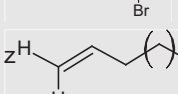
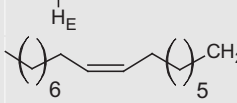
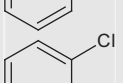
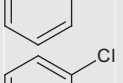
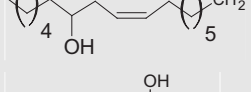
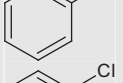
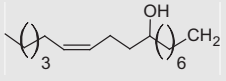
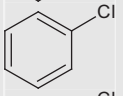
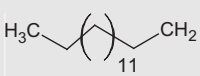
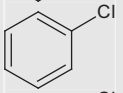
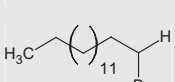
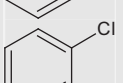
2.1.5. 2-[(8′Z)-Heptadecenyl]-5-(furan-2-yl)-1,3,4-oxadiazole (**3b**)

IR (KBr, cm^{-1}): 1666 (C═C), 1561 (C═N), 1245 (C–O–C). ^{1}H NMR ($CDCl_3$, δ_H): 7.68 (m, 1H, furan 5″-H), 7.35 (m, 1H, furan 2″-H), 6.51 (m, 1H, furan 4″-H), 5.36 (m, 2H, CH_2─CH═CH─CH_2), 2.31 (t, 2H, J = 7.4 Hz, CH_2 α to ring), 2.05 (m, 4H, CH_2-CH═CH─CH_2), 1.66 (m, 2H, CH_2 β to ring), 1.28 (br, s, 20H, $(CH_2)_{10}$), 0.85 (dist. t, 3H, terminus CH_3). ^{13}C NMR ($CDCl_3$, δ_C): 172.4, 168.3, 142.6, 131.6, 125.3, 111.7, 40.9, 40.5, 38.6, 38.3, 33.6, 32.7, 31.8, 30.5, 29.8, 28.7, 28.4, 21.9, 20.6, 20.3, 14.0. ESI-MS: found $[M+Na]^+$ 395.11; requires 395.19.

2.1.6. (8′Z,11′R)-2-(11′-Hydroxy-octadec-8′-enyl)-5-(furan-2-yl)-1,3,4-oxadiazole (**3c**)

IR (KBr, cm^{-1}): 3358 (OH), 1668 (C═C), 1554 (C═N), 1247 (C–O–C). ^{1}H NMR ($CDCl_3$, δ_H): 7.61 (m, 1H, furan 5″-H),

Table 1 2,5-Disubstituted-1,3,4-oxadiazoles **3a**–**l**.

Entry	R	R_1	Product	Time (h.)	Yield (%)
1			**3a**	10	82
2			**3b**	11	84
3			**3c**	14	78
4			**3d**	14	79
5			**3e**	8	86
6			**3f**	8	85
7			**3g**	11	80
8			**3h**	12	82
9			**3i**	13	75
10			**3j**	14	78
11			**3k**	9	85
12			**3l**	9	83
					

7.28 (m, 1H, furan 2″-H), 6.53 (m, 1H, furan 4″-H), 5.37 (m, 2H, CH_2─CH═CH─CH_2), 3.69 (m, 1H, CH–OH), 2.38 (t, 2H, J = 7.5 Hz, CH_2 α to ring), 2.10 (m, 1H, CH–O*H*), 1.96 (m, 4H, CH_2─CH═CH─CH_2), 1.58 (m, 2H, CH_2 β to ring), 1.28 (br, s, 18H, $(CH_2)_9$), 0.86 (dist. t, 3H, terminus CH_3). ^{13}C NMR ($CDCl_3$, δ_C): 172.3, 168.6, 142.8, 131.1, 124.9, 111.8, 70.5, 40.3, 38.9, 38.6, 31.5, 31.3, 29.0, 28.9, 28.3, 27.9, 27.3, 26.4, 26.1, 22.6, 14.2. ESI-MS: found $[M+Na]^+$ 411.17; requires 411.18.

*2.1.7. (8′R,11′Z)-2-(8′-Hydroxy-octadec-11′-enyl)-5-(furan-2-yl)-1,3,4-oxadiazole (**3d**)*

IR (KBr, cm^{-1}): 3353 (OH), 1669 (C═C), 1557 (C═N), 1251 (C–O–C). ^{1}H NMR ($CDCl_3$, δ_H): 7.63 (m, 1H, furan 5″-H), 7.30 (m, 1H, furan 2″-H), 6.55 (m, 1H, furan 4″-H), 5.36 (m, 2H, CH_2─CH═CH─CH_2), 3.65 (m, 1H, CH–OH), 2.36 (t, 2H, J = 7.5 Hz, CH_2 α to ring), 2.08 (m, 1H, CH–O*H*), 1.98 (m, 4H, CH_2─CH═CH─CH_2), 1.54 (m, 2H, CH_2 β to ring), 1.30 (br, s, 18H, $(CH_2)_9$), 0.88 (dist. t, 3H, terminus CH_3). ^{13}C NMR ($CDCl_3$, δ_C): 172.5, 168.1, 142.7, 131.9, 125.1, 111.1, 70.6, 40.3, 38.7, 38.3, 31.7, 31.6, 29.5, 28.7, 28.4, 27.6, 27.4, 26.8, 26.3, 22.5, 14.1. ESI-MS: found $[M+Na]^+$ 411.17; requires 411.18.

*2.1.8. 2-Pentadec-5-(furan-2-yl)-1,3,4-oxadiazole (**3e**)*

IR (KBr, cm^{-1}): 1667 (C═C), 1571 (C═N), 1249 (C–O–C). ^{1}H NMR ($CDCl_3$, δ_H): 7.63 (m, 1H, furan 5″-H), 7.32 (m, 1H, furan 2″-H), 6.54 (m, 1H, furan 4″-H), 2.36 (t, 2H, J = 7.4 Hz, CH_2 α to ring), 1.69 (m, 2H, CH_2 β to ring), 1.25 (br, s, 24H, $(CH_2)_{12}$), 0.87 (dist. t, 3H, terminus CH_3). ^{13}C NMR ($CDCl_3$, δ_C): 172.1, 168.2, 142.2, 111.7, 40.6, 40.4, 40.2, 40.0, 39.8, 39.6, 33.9, 33.7, 29.2, 28.9, 28.7, 26.4, 25.4, 25.1, 14.0. ESI-MS: found $[M+Na]^+$ 369.15; requires 369.17.

*2.1.9. 2-[1-Bromopentadec]-5-(furan-2-yl)-1,3,4-oxadiazole (**3f**)*

IR (KBr, cm^{-1}): 1665 (C═C), 1569 (C═N), 1248 (C–O–C), 558 (C–Br). ^{1}H NMR ($CDCl_3$, δ_H): 7.65 (m, 1H, furan 5″-H), 7.33 (m, 1H, furan 2″-H), 6.56 (m, 1H, furan 4″-H), 2.38 (t, 2H, J = 7.4 Hz, CH_2 α to ring), 1.65 (m, 2H, CH_2 β to ring), 1.29 (br, s, 24H, $(CH_2)_{12}$), 0.87 (dist. t, 3H, terminus CH_3). ^{13}C NMR ($CDCl_3$, δ_C): 172.5, 168.5, 143.0, 111.6,

52.1, 40.7, 40.5, 40.1, 39.2, 38.9, 34.0, 33.3, 29.0, 28.7, 28.1, 26.3, 24.9, 25.5, 14.1. ESI-MS: found $[M+Na]^+$ 448.04; requires 448.07.

2.1.10. 2-(Dec-9′-enyl)-5-(chlorobenzene-2-yl)-1,3,4-oxadiazole (**3g**)

IR (KBr, cm^{-1}): 1665 (C═C), 1563 (C═N), 1242 (C–O–C), 748 (C–Cl). ^1H NMR ($CDCl_3$, δ_H): 7.99 (m, 1H, Ar-H-3″), 7.47 (m, 2H, Ar-H-4″/5″), 7.34 (m, 1H, Ar-H-6″), 5.80 (tdd, 1H, $J_{H-^9CH_2}$ = 6.6 Hz, J_{H-H_Z} = 10.2 Hz, J_{H-H_E} = 16.9 Hz, CH_2═CH─), 4.98 (dd, 1H, J_{H_Z-H} = 11.8 Hz, $J_{H_Z-H_E}$ = 1.9 Hz, H_ZC═CH), 4.93 (dd, 1H, J_{H_E-H} = 16.7 Hz, $J_{H_E-H_Z}$ = 2.2 Hz, H_EC═CH─), 2.35 (t, 2H, J = 7.4 Hz, CH_2 α to ring), 2.02 (m, 2H, CH_2═CH─CH_2), 1.63 (m, 2H, CH_2 β to ring), 1.29-1.40 (br, s, 10H, $(CH_2)_5$). ^{13}C NMR ($CDCl_3$, δ_C): 172.9, 168.4, 139.6, 131.4, 128.7, 128.3, 125.8, 122.6, 114.3, 40.1, 39.7, 38.6, 37.4, 32.0, 29.5, 28.6, 26.6. ESI-MS: found $[M+Na]^+$ 341.5; requires 341.6.

2.1.11. 2-[(8′Z)-Heptadecenyl]-5-(chlorobenzene-2-yl)-1,3,4-oxadiazole (**3h**)

IR (KBr, cm^{-1}): 1667 (C═C), 1562 (C═N), 1248 (C–O–C), 743 (C–Cl). ^1H NMR ($CDCl_3$, δ_H): 7.98 (m, 1H, Ar-H-3″), 7.46 (m, 2H, Ar-H-4″/5″), 7.33 (m, 1H, Ar-H-6″), 5.34 (m, 2H, CH_2─CH═CH─CH_2), 2.33 (t, 2H, J = 7.4 Hz, CH_2 α to ring), 2.03 (m, 4H, CH_2─CH═CH─CH_2), 1.62 (m, 2H, CH_2 β to ring), 1.26 (br, s, 20H, $(CH_2)_{10}$), 0.87 (dist. t, 3H, terminus CH_3). ^{13}C NMR ($CDCl_3$, δ_C): 172.4, 168.3, 131.6, 131.4, 128.9, 128.6, 125.7, 125.3, 122.2, 40.9, 40.5, 38.6, 38.3, 33.6, 32.7, 31.8, 30.5, 29.8, 28.7, 21.9, 20.6, 20.3, 14.0. ESI-MS: found $[M+Na]^+$ 439.65; requires 439.67.

2.1.12. (8′Z,11′R)-2-(11′-Hydroxy-octadec-8′-enyl)-5-(chlorobenzene-2-yl)-1,3,4-oxadiazole (**3i**)

IR (KBr, cm^{-1}): 3352 (OH), 1665 (C═C), 1569 (C═N), 1243 (C–O–C), 745 (C–Cl). ^1H NMR ($CDCl_3$, δ_H): 7.90 (m, 1H, Ar-H-3″), 7.42 (m, 2H, Ar-H-4″/5″), 7.29 (m, 1H, Ar-H-6″), 5.27 (m, 2H, CH_2─CH═CH─CH_2), 3.58 (m, 1H, CH–OH), 2.34 (t, 2H, J = 7.4 Hz, CH_2 α to ring), 2.09 (m, 1H, CH–O*H*), 1.98 (m, 4H, CH_2─CH═CH─CH_2), 1.56 (m, 2H, CH_2 β to ring), 1.25 (br, s, 18H, $(CH_2)_9$), 0.81 (dist. t, 3H, terminus CH_3). ^{13}C NMR ($CDCl_3$, δ_C): 172.4, 168.3, 131.6, 131.1, 128.6, 128.5, 125.9, 125.2, 122.6, 70.1, 40.2, 38.5, 37.9, 31.8, 31.1, 29.3, 28.7, 27.4, 27.0, 26.3, 26.0, 22.5, 14.1. ESI-MS: found $[M+Na]^+$ 455.62; requires 455.66.

2.1.13. (8′R,11′Z)-2-(8′-Hydroxy-octadec-11′-enyl)-5-(chlorobenzene-2-yl)-1,3,4-oxadiazole (**3j**)

IR (KBr, cm^{-1}): 3353 (O–H), 1667 (C═C), 1565 (C═N), 1244 (C–O–C), 741 (C–Cl). ^1H NMR ($CDCl_3$, δ_H): 7.91 (m, 1H, Ar-H-3″), 7.40 (m, 2H, Ar-H-4″/5″), 7.27 (m, 1H, Ar-H-6″), 5.29 (m, 2H, CH_2─CH═CH─CH_2), 3.56 (m, 1H, CH–OH), 2.30 (t, 2H, J = 7.4 Hz, CH_2 α to ring), 2.11 (m, 1H, CH–O*H*), 1.95 (m, 4H, CH_2─CH═CH─CH_2), 1.57 (m, 2H, CH_2 β to ring), 1.22 (br, s, 18H, $(CH_2)_9$), 0.81 (dist. t, 3H, terminus CH_3). ^{13}C NMR ($CDCl_3$, δ_C): 172.6, 168.7, 131.9, 131.1, 128.6, 128.3, 125.5, 125.2, 122.1, 70.1, 40.6, 38.5, 37.5, 31.8, 31.0, 29.3, 28.1, 27.4, 27.0, 26.9, 26.5, 22.5, 14.1. ESI-MS: found $[M+Na]^+$ 455.62; requires 455.66.

2.1.14. 2-Pentadec-5-(chlorobenzene-2-yl)-1,3,4-oxadiazole (**3k**)

IR (KBr, cm^{-1}): 1663 (C═C), 1565 (C═N), 1244 (C–O–C), 743 (C–Cl). ^1H NMR ($CDCl_3$, δ_H): 8.00 (m, 1H, Ar-H-3″), 7.47 (m, 2H, Ar-H-4″/5″), 7.34 (m, 1H, Ar-H-6″), 2.35 (t, 2H, J = 7.4 Hz, CH_2 α to ring), 1.64 (m, 2H, CH_2 β to ring), 1.27 (br, s, 24H, $(CH_2)_{12}$), 0.87 (dist. t, 3H, terminus CH_3). ^{13}C NMR ($CDCl_3$, δ_C): 172.2, 168.1, 131.3, 128.7, 128.5, 125.9, 122.3, 40.3, 40.1, 40.0, 39.6, 39.3, 33.5, 33.0, 29.1, 28.3, 26.9, 25.1, 25.0, 14.0. ESI-MS: found $[M+Na]^+$ 413.64; requires 413.65.

2.1.15. 2-[1-Bromopentadec]-5-(chlorobenzene-2-yl)-1,3,4-oxadiazole (**3l**)

IR (KBr, cm^{-1}): 1668 (C═C), 1569 (C═N), 1249 (C–O–C), 748 (C–Cl), 552 (C–Br). ^1H NMR ($CDCl_3$, δ_H): 8.00 (m, 1H, Ar-H-3″), 7.47 (m, 2H, Ar-H-4″/5″), 7.35 (m, 1H, Ar-H-6″), 2.37 (t, 2H, J = 7.4 Hz, CH_2 α to ring), 1.66 (m, 2H, CH_2 β to ring), 1.26 (br, s, 24H, $(CH_2)_{12}$), 0.88 (dist. t, 3H, terminus CH_3). ^{13}C NMR ($CDCl_3$, δ_C): 172.5, 168.3, 131.5, 128.6, 128.3, 125.6, 122.7, 52.4, 40.6, 40.4, 39.9, 39.2, 37.9, 34.6, 33.1, 29.6, 28.7, 28.0, 26.4, 24.6, 25.1, 14.0. ESI-MS: found $[M+Na]^+$ 492.53; requires 492.55.

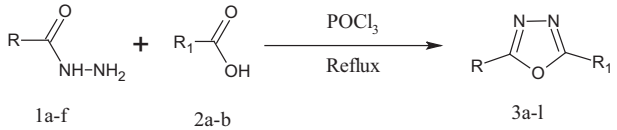
2.2. Determination of antibacterial activity

The newly prepared compounds were screened for their antibacterial activity against *Escherichia coli* (ATCC-25922), Methicillin resistant *Staphylococcus aureus* (MRSA +Ve), *Pseudomonas aeruginosa* (ATCC-27853), *Streptococcus pyogenes* and *Klebsiella pneumoniae* (Clinical isolate) bacterial strains by disc diffusion method (Cruickshank et al., 1975; Collins, 1976). Ciprofloxacin (30 μg) was used as positive control. While the disk immersed in DMSO was used as negative control. The susceptibility was assessed on the basis of the diameter of zone of inhibition against Gram-positive and Gram-negative strains of bacteria. Inhibition zones were measured and compared with the controls. The bacterial zones of inhibition values are given in Table 4.

Minimum inhibitory concentrations (MICs) were determined by broth dilution technique. The lowest concentration (highest dilution) required to arrest the growth of bacteria was regarded as minimum inhibitory concentration (MIC). MBC was defined as the lowest drug concentration at which 99.9% of the inoculums were killed. The minimum inhibitory concentrations and minimum bactericidal concentrations are given in Table 5.

2.3. Determination of antifungal activity

Antifungal activity was also determined by disk diffusion method. For assaying antifungal activity *Candida albicans*,



Scheme 1 Conventional synthesis of 2,5-disubstituted-1,3,4-oxadiazoles **3a**–**l**.

Aspergillus fumigatus, *Penicillium marneffei and Trichophyton mentagrophytes* (recultured) in DMSO were tested by agar diffusion method (Khan, 1997; Varma, 1998). The fungal activity of each compound was compared with Greseofulvin as standard drug. Inhibition zones were measured and compared with the controls. The fungal zones of inhibition values are given in Table 6. The lowest concentration (highest dilution) required to arrest the growth of fungus was regarded as minimum inhibitory concentration (MIC). MFC was defined as the lowest drug concentration at which 99.9% of the inoculums were killed. The minimum inhibitory concentrations and minimum fungicidal concentrations are given in Table 7.

3. Results and discussion

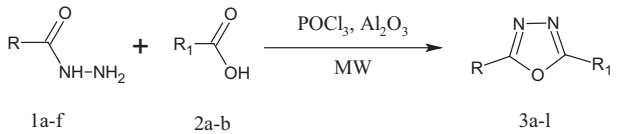
3.1. Chemistry

Due to the beneficial pharmacological properties of certain molecules containing 1,3,4-oxadiazole moiety the synthesis of new 1,3,4-oxadiazole derivatives using procedures in which some aspect of green chemistry could be met is desirable. Our main strategy in this work was to synthesize new 1,3,4-oxadiazole derivatives with potential biological activities, using microwave-induced organic reaction enhancement methodology, which is extremely fast, cleaner than conventional reactions and lead to a higher atom economy (less chemical waste).

The conventional synthesis of the target 2,5-disubstituted-1,3,4-oxadiazoles (**3a**–**l**) was achieved by refluxing a mixture of fatty acid hydrazide (**1a**–**f**) and appropriate carboxylic acid (**2a**–**b**) in presence of phosphorus oxy chloride (Scheme 1). The product yields and the reaction times required for the completion of the reaction under reflux conditions are given in Table 1. As, can be seen from Table 1, the reaction time ranged within 8–14 h.

Further to explore the probability of getting the pharmacophoric important moiety in higher yields and in shorter reaction times, our attention turned toward employing the microwave irradiation. The application of microwave energy to organic compounds for conducting synthetic reactions at highly accelerated rates is an emerging technique. In fact, in recent years, microwave has become popular among synthetic organic chemists both to improve classical organic reactions, shortening reaction times and/or improving yields, as well as to promote new reactions. Under microwave conditions, the reactions were carried out by irradiating a mixture of fatty acid hydrazide (**1a**–**f**) with the appropriate carboxylic acid (**2a**–**b**), supported on neutral alumina, using phosphorus oxy chloride as the cyclizing agent (Scheme 2).

At first, the condensation reaction of hydrazide of undec-10-enoic acid (**1a**) with 2-furoic acid (**2a**) was chosen as a model to optimize the conditions for the preparation of compounds **3a**–**l** (Table 2). In order to determine the optimum conditions



Scheme 2 Synthesis of 2,5-disubstituted-1,3,4-oxadiazoles (**3a**–**l**) under microwave irradiation.

for the synthesis of oxadiazoles, variations in molar ratios of reagents, the microwave irradiation time and the power level of microwave setup were investigated.

After some experimentation, we found a set of conditions that generally provided the products in good yields. The optimum conditions were set up and the target 2,5-disubstituted-1,3,4-oxadiazoles (**3a**–**l**) were synthesized in appreciable yields (Table 3).

As per our requirement, the strategy successfully worked out. All the reactions proceeded in shorter reaction time and an appreciable increment in the product yield was observed as compared to conventional reaction conditions. The generality and ability of this methodology in the synthesis of 2,5-disubstituted-1,3,4-oxadiazoles were demonstrated by using a variety of structurally divergent fatty acid hydrazides and carboxylic acids. The scope of the reaction using saturated, olefin (internal and terminal) and hydroxy fatty acid hydrazides was found to be good. Moreover, the nature of hydrazide and the carboxylic acid did not show strongly obvious effects in terms of yields. The synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis.

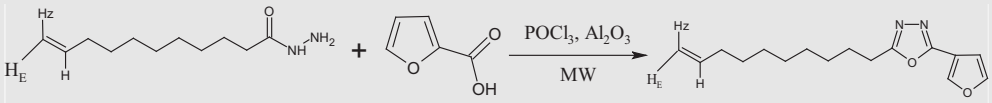
The spectra of compound **3a** showed IR absorption bands at 1668, 1568, 1240 cm^{-1} due to C=C, C=N and C–O–C functions. The ^{1}H NMR was more informative in assigning the structure. Diagnostic peaks at δ 7.64, 7.32 and 6.55 were observed for the furan ring system. A triplet at δ 2.36 was observed for the methylene protons α to the oxadiazole ring. The methine proton of C-9 showed a signal at 5.82. The C-10 methylene protons designated as H_E and H_Z displayed two distinct δ values when coupled with adjacent C-9 methine protons. Thus, the ^{1}H NMR showed two doublet of doublet at δ 5.01 and 4.94 for H_Z and H_E protons, respectively. In the ^{13}C NMR peaks at δ 172.4 and 168.2 were observed for the ring carbon atoms. The mass spectrum was also consistent with the assigned molecular formula.

Similarly, the spectra of compound **3g** showed the IR absorption bands at 1665, 1563, 1242 cm^{-1} due to C=C, C=N and C–O–C functions. A characteristic IR band at 748 cm^{-1} was also observed for the aromatic ring system. The ^{1}H NMR was more informative in assigning the structure. Diagnostic peaks at δ 7.98, 7.46 and 7.33 were observed for the aromatic ring system. A triplet at 2.35 was observed for the methylene protons α to the oxadiazole ring. The methine proton of C-9 showed a signal at 5.80. The C-10 methylene protons designated as H_E and H_Z displayed two distinct δ values when coupled with adjacent C-9 methine protons. Thus, the ^{1}H NMR showed two doublet of doublet at δ 4.98 and 4.93 for H_Z and H_E protons, respectively. The ^{13}C NMR showed characteristic peaks at δ 172.9 and 168.4 for the oxadiazole ring carbon atoms. The mass spectrum was also consistent with the assigned molecular formula Detailed spectral data of the titled compounds are given in the experimental section.

3.2. Antibacterial studies

The newly prepared compounds were screened for their antibacterial activity against *E. coli* (ATCC-25922), Methicillin resistant *S. aureus* (MRSA +Ve), *P. aeruginosa* (ATCC-27853), *S. pyogenes* and *K. pneumoniae* (Clinical isolate) bacterial strains by disc diffusion method (Mayekar, 2010; Palmer et al., 2006). Ciprofloxacin (30 μg) was used as positive

Table 2 Optimization of the microwave-assisted condensation of **1a** and **2a** on neutral alumina.



1a **2a** **3a**

Entry	Support	Molar ratio (1a/2a)	Time (min.)	Power (%)	Yield (%)
1	Neutral alumina	0.2/0.5	5	30	45
2	Neutral alumina	0.5/0.8	7	40	52
3	Neutral alumina	0.8/1.0	12	50	71
4	Neutral alumina	1.0/1.0	16	60	90

Table 3 2,5-Disubstituted-1,3,4-oxadiazoles (**3a–l**) under microwave conditions.

Entry	1	2	1/2[a]	Power (%)[b]	Time (h.)[c]	Product	Yield (%)[d]
1	1a	2a	1/1	60	16	**3a**	90
2	1b	2a	1/1	60	16	**3b**	90
3	1c	2a	1/1	60	17	**3c**	85
4	1d	2a	1/1	60	17	**3d**	87
5	1e	2a	1/1	60	15	**3e**	92
6	1f	2a	1/1	60	15	**3f**	93
7	1a	2b	1/1	60	19	**3g**	89
8	1b	2b	1/1	60	19	**3h**	90
9	1c	2b	1/1	60	20	**3i**	86
10	1d	2b	1/1	60	20	**3j**	88
11	1e	2b	1/1	60	18	**3k**	91
12	1f	2b	1/1	60	17	**3l**	91

[a] All reactions were carried out using fatty acid hydrazides (1 eq) with respect to carboxylic acids and POCl3 under microwave irradiation.
[b] Microwave equipment multimode was used.
[c] Monitored by TLC.
[d] All yields refer to isolated products and the products were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis.

Table 4 Antibacterial activity of 2,5-disubstituted-1,3,4-oxadiazoles **3a–l**.

Compounds	Diameter of zone of inhibition (mm)				
	Gram positive bacteria		Gram negative bacteria		
	S. pyogenes	*MRSA*[c]	*P. aeruginosa*	*K. pneumoniae*	*E. coli*
3a	11.4 ± 0.4	11.1 ± 0.3	13.2 ± 0.2	11.5 ± 0.3	12.1 ± 0.4
3b	21.3 ± 0.4	20.8 ± 0.3	23.4 ± 0.2	19.4 ± 0.5	20.9 ± 0.4
3c	19.1 ± 0.5	18.3 ± 0.4	21.1 ± 0.4	17.1 ± 0.5	18.5 ± 0.3
3d	13.4 ± 0.4	13.2 ± 0.4	16.1 ± 0.6	13.6 ± 0.2	14.3 ± 0.2
3e	16.2 ± 0.4	15.5 ± 0.2	13.2 ± 0.3	15.5 ± 0.4	16.5 ± 0.3
3f	22.5 ± 0.2	21.6 ± 0.4	27.3 ± 0.6	22.5 ± 0.2	23.4 ± 0.5
3g	14.5 ± 0.4	14.4 ± 0.4	16.1 ± 0.6	13.6 ± 0.2	14.3 ± 0.2
3h	17.1 ± 0.2	16.6 ± 0.3	14.1 ± 0.4	15.5 ± 0.4	16.5 ± 0.3
3i	20.1 ± 0.3	19.5 ± 0.2	22.2 ± 0.3	18.2 ± 0.3	19.6 ± 0.2
3j	20.2 ± 0.4	19.7 ± 0. 3	22.3 ± 0. 2	18.3 ± 0.5	19.8 ± 0.4
3k	12.4 ± 0.5	12.1 ± 0.5	14.2 ± 0.4	11.7 ± 0.5	12.1 ± 0.5
3l	21.4 ± 0.3	20.5 ± 0.4	26.2 ± 0.4	21.4 ± 0.4	22.3 ± 0.4
Standard	23.0 ± 0.2	22.0 ± 0.2	32.0 ± 0.3	19.0 ± 0.2	27.0 ± 0.2
DMSO	–	–	–	–	–

[a]Positive control (standard) Ciprofloxacin and negative control (DMSO), [b]Measured by the Halo Zone Test (Unit, mm), [c]Methicillin resistant *Staphylococcus aureus* (MRSA +Ve).

Table 5 MIC and MBC results of 2,5-disubstituted-1,3,4-oxadiazoles **3a**–**l**.

Compounds	Gram positive bacteria				Gram negative bacteria					
	S. pyogenes		*MRSA*[d]		*P. aeruginosa*		*K. pneumoniae*		*E.coli*	
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
3a	50	100	50	> 100	50	> 100	100	> 100	100 >	100
3b	25	50	12.5	50	12.5	50	50	100	25	100
3c	25	100	25	50	25	100	50	50	25	100
3d	50	100	50	100	50	100	50	100	50	> 100
3e	25	100	50	100	25	100	25	100	50	100
3f	12.5	25	12.5	50	12.5	50	12.5	50	12.5	50
3g	50	100	50	100	50	100	25	100	50	> 100
3h	25	100	25	50	25	100	25	100	50	100
3i	25	100	25	50	12.5	100	25	50	25	100
3j	25	50	12.5	25	12.5	50	25	100	25	100
3k	50	100	50	> 100	100	> 100	100	> 100	100	> 100
3l	12.5	25	12.5	25	12.5	25	12.5	50	12.5	50
Standard	12.5	12.5	6.25	12.5	12.5	25	6.25	25	6.25	12.5

[a]Positive control Ciprofloxacin. [b]MIC (μg/ml) = minimum inhibitory concentration, i.e., the lowes concentration of the compound to inhibit the growth of bacteria completely; [c]MBC (μg/ml) = minimum bacterial concentration, i.e., the lowest concentration of the compound for killing the bacteria completely. [d]Methicillin resistant *Staphylococcus aureus* (MRSA + Ve).

Table 6 Antifungal activity of 2,5-disubstituted-1,3,4-oxadiazoles **3a**–**l**.

Compounds	Diameter of zone of inhibition (mm)			
	CA	AF	TM	PM
3a	19.9 ± 0.3	18.5 ± 0.5	16.4 ± 0.2	11.9 ± 0.3
3b	26.1 ± 0.3	21.1 ± 0.2	18.3 ± 0.3	13.7 ± 0.2
3c	23.1 ± 0.3	20.2 ± 0.5	16.7 ± 0.4	13.1 ± 0.4
3d	21.1 ± 0.3	18.5 ± 0.4	14.7 ± 0.5	13.2 ± 0.4
3e	22.8 ± 0.5	19.6 ± 0.6	17.1 ± 0.3	13.3 ± 0.6
3f	26.2 ± 0.4	21.6 ± 0.5	18.2 ± 0.4	14.1 ± 0.3
3g	22.2 ± 0.4	19.7 ± 0.3	15.8 ± 0.9	14.3 ± 0.2
3h	23.9 ± 0.6	20.7 ± 0.2	18.1 ± 0.2	14.3 ± 0.6
3i	24.1 ± 0.5	21.3 ± 0.3	17.8 ± 0.5	14.2 ± 0.9
3j	27.2 ± 0.4	22.1 ± 0.2	19.4 ± 1.2	14.8 ± 0.3
3k	21.3 ± 0.3	19.6 ± 0.4	16.4 ± 0.2	12.9 ± 0.3
3l	27.1 ± 0.3	22.7 ± 1.2	19.3 ± 0.7	15.1 ± 0.2
Standard	30.0 ± 0.2	27.0 ± 0.2	24.0 ± 0.3	20.0 ± 0.5
DMSO	–	–	–	–

[a]Positive control (Greseofulvin) and negative control (DMSO), [b]Measured by the Halo Zone Test (Unit, mm). [c]CA = *Candida albicans*, [d]AF = *Aspergillus fumigatus*, [e]TM = *Trichophyton mentagrophytes*, [f]PM = *Penicillium marneffei*.

control. While the disk immersed in DMSO was used as negative control. The susceptibility was assessed on the basis of the diameter of zone of inhibition against Gram-positive and Gram-negative strains of bacteria. Inhibition zones were measured and compared with the controls. The bacterial zones of inhibition values are given in Table 4.

Minimum inhibitory concentrations (MICs) were determined by broth dilution technique. The lowest concentration (highest dilution) required to arrest the growth of bacteria was regarded as minimum inhibitory concentration (MIC). MBC was defined as the lowest drug concentration at which 99.9% of the inoculums were killed. The minimum inhibitory concentrations and minimum bactericidal concentrations are given in Table 5.

The investigation of antibacterial screening data revealed that all the tested compounds showed moderate to good bacterial inhibition. Good inhibitory results were obtained against *S. pyogenes*, *S. aureus and E. coli* species. The structure activity data showed that various substituted 1,3,4-oxadiazoles **3a**–**l** have varying degree of microbial inhibition. The antibacterial activity seemed to be dependent on both substituents. The presence of chlorobenzyl substituents at C-5 of the oxadiazole ring system in compounds **3a**–**l** was found to enhance the bacterial inhibition effects. Further, a marked enhancement in the antibacterial activity was observed for the compounds bearing a bromo or a hydroxy group in the long chain substituent at C-2 of the oxadiazole moiety. The compounds **3c**, **3d**, **3f**, **3i**, **3j** and **3l** showed good inhibition against *S. pyogenes*, *S. aureus and E. coli* species. The oxadiazoles **3f**, **3j** and **3l** showed activity nearly equivalent to that of Ciprofloxacin ranging from 21.6 ± 0.4 to 27.3 ± 0.6 for **3f**, 18.3 ± 0.5 to 22.3 ± 0.2 for **3j** and 20.5 ± 0.4 to 26.2 ± 0.4 for **3l**. The MICs and MBCs also revealed good antibacterial activity. The MBC in most of the compounds was two or three or four fold higher than the corresponding MIC results.

3.3. Antifungal studies

Antifungal activity was also done by disk diffusion method. For assaying the antifungal activity *C. albicans*, *A. fumigatus*, *P. marneffei and T. mentagrophytes* (recultured) in DMSO were tested by agar diffusion method (Rauf et al., 2007; Tan et al., 2006). The fungal activity of each compound was compared with Greseofulvin as standard drug. Inhibition zones were measured and compared with the controls. The fungal zones of inhibition values are given in Table 6. The lowest concentration (highest dilution) required to arrest the growth of fungus was regarded as minimum inhibitory concentration (MIC). MFC was defined as the lowest drug concentration at which 99.9% of the inoculums were killed. The minimum inhibitory concentrations and minimum fungicidal concentrations are given in Table 7.

Table 7 MIC and MFC of 2,5-disubstituted-1,3,4-oxadiazoles **3a–l**.

Compounds	CA		AF		TM		PM	
	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC
3a	50	100	50	> 100	50	100	50	> 100
3b	12.5	25	25	50	25	50	25	100
3c	12.5	100	25	50	25	50	25	100
3d	25	100	50	100	25	> 100	25	100
3e	25	100	25	100	25	100	25	100
3f	6.25	12.5	25	12.5	25	100	25	50
3g	25	100	50	100	25	100	25	100
3h	25	50	25	50	25	100	25	100
3i	12.5	50	25	50	25	50	25	100
3j	12.5	25	25	50	25	50	12.5	100
3k	50	100	50	100	50	100	50	100
3l	6.25	12.5	6.25	12.5	12.5	25	12.5	25
Standard	6.25	25	12.5	12.5	6.25	25	12.5	25

[a]CA = *Candida albicans*, [b]AF = *Aspergillus fumigatus*, [c]TM = *Trichophyton mentagrophytes*, [d]PM = *Penicillium marneffei*. [e]MIC (μg/ml) = minimum inhibitory concentration, i.e the lowest concentration of the compound to inhibit the growth of fungus completely; [f]MFC (μg/ml) = minimum fungicidal concentration, i.e., the lowest concentration of the compound for killing the fungus completely.

The antifungal screening data showed moderate to good activity. The 2,5-disubstituted-1,3,4-oxadiazoles **3a–l** showed same antifungal activity trends as for the bacterial strains. Good inhibition results were obtained against *C. albicans*, *A. fumigatus* and *P. marneffei* fungal strains. Moderate activity was obtained in case of *T. mentagrophytes* fungal strains. The compounds **3f**, **3j** and **3l** were found to be the most potent antifungal agents with the diameter of zone of inhibition ranging from 14.1 ± 0.3 to 26.2 ± 0.4 for **3f**, 14.8 ± 0.3 to 27.2 ± 0.4 for **3j** and 15.1 ± 0.2 to 27.1 ± 0.3 for **3l**. The MFC of the synthesized compounds was two or three or four fold higher than the corresponding MIC results, suggesting that the newly synthesized compounds possess moderate to good antifungal activity.

4. Conclusion

In conclusion we have developed a simple and efficient method for the synthesis of 2,5-disubstituted-1,3,4-oxadiazole bearing an alkanyl/alkenyl/hydroxyalkenyl chain substituent. This protocol leads to a considerable reduction in reaction time and is energetically profitable. Some of the newly synthesized compounds showed significant anti-bacterial and anti-fungal activities. The diameter of zone of inhibition of synthesized compounds ranged from 11.1 ± 0.3 to 26.2 ± 0.4 for various bacterial strains and from 11.9 ± 0.3 to 27.2 ± 0.4 for fungal strains. The MBC/MFC of the synthesized compounds was two or three or four fold higher than the corresponding MIC results. Further, it was found that the nature of substituent has a strong influence on the extent of antibacterial and antifungal activities. The data analysis revealed that all the compounds have produced a marked enhancement in the potency of these analogues as antibacterial and antifungal agents.

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