International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.6, No.7, pp 2015-2021, November 2014

Synthesis, Antibacterial and Antifungal Activity of 2,5-Disubstituted-1,3,4-oxadiazole Derivatives

Ajmer Singh Grewal[1], Sonika Redhu[2]*

[1]Department of Pharmaceutical Chemistry, JCDM College of Pharmacy, Sirsa, Haryana - 125055, India
[2]Department of Pharmaceutical Chemistry, Shekhawati College of Pharmacy, Jhunjhunu, Rajasthan - 333702, India

***Corres.author: sonika285@yahoo.co.in, Mobile: +91 9549991855**

Abstract : In the present article synthesis and evaluation for antibacterial and antifungal activity of a new series of 2,5-disubstituted-1,3,4-oxadiazole derivatives is described. 2,5-disubstituted-1,3,4-oxadiazole derivatives were synthesized by the reaction of quinolinyl hydrazone derivatives with dichloromethane. The compounds (6a-h) were characterized by IR, NMR, and mass spectroscopy. All the synthesized compounds were screened for their antimicrobial activity. The antimicrobial results reveal that among the synthesized compounds 6b and 6f showed excellent antibacterial and antifungal activity. The compounds 6c, 6d and 6e did not show antifungal activity against the *Colletotrichum capsici*.
Keywords: Antibacterial activity; Antifungal activity; Oxadiazoles; 2,5-disubstituted-1,3,4-oxadiazole.

Introduction

Oxadiazole is a heterocyclic aromatic compound containing one oxygen and two nitrogen atoms in a five membered ring. It occurs in various isomeric forms like 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole and 1,3,4-oxadiazole. However, 1,3,4-oxadiazole and 1,2,4-oxadiazole are better known, and more widely studied by researchers because of their many important chemical and biological properties.[1] Oxadiazole derivatives had been reported to exhibit several biological activities like antibacterial[2], anti-HIV[3], antifungal[3], genotoxic[3], anti-tubercular[4], virucidal[5], antimalarial[6], insecticidal[7], herbicidal[8], analgesic[9], anti-inflammatory[10,11], muscle relaxants[12], anticonvulsant[13], sedative, hypnotic[14], anticancer[15,16] and lipid peroxidation inhibitor[17]. They have also attracted interest in medicinal chemistry as bioisosteres for carboxylic acids, esters and carboxamides.[18]

In recent past it has been observed and reported that considerable antibacterial and antifungal activity had been exhibited by the 1,3,4-oxadiazole derivatives suitably substituted at 2 and 5 positions.[2-8] Some of the previous studies have reported the synthesis of 1,3,4-oxadiazole derivatives using Vilsmeier-Haack reaction and evaluated for antibacterial and antifungal activity.[16,19] Prompted by the above observations, as a part of our work on development of novel antibacterial and antifungal agents, we have attempted to explore the possibility of generation of antibacterial and antifungal activity in 2,5-disustituted-1,3,4-oxadiazoles by the reaction of quinolinyl hydrazone derivatives with dichloromethane.

Experimental

All chemicals used were obtained from commercial sources and were used without further purification. Melting points were determined on heated liquid bath (Thiele apparatus) in open capillaries and are uncorrected. IR spectra of compounds were recorded on a Thermo Scientific U.S.A, Model No. Nicolet 380 FT-

IR spectrometer using KBr pellets and the wave numbers were given in cm^{-1}. ^1H NMR (300 and 400 MHz) spectra of synthesized compounds were recorded on a Bruker NMR spectrometer using $CDCl_3$/DMSO-d_6 as a solvents and chemical shift values are expressed in parts per million (δ, ppm) downfield from tetramethylsilane (TMS) as an internal standard. NMR data are given as multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet) and number of protons.

General procedure for synthesis of 2,5-disubstituted-1,3,4-oxadiazoles (6a-h):

Synthesis of acetanilides (1a-b):

A solution of appropriate aromatic aniline (0.1 mol) in water (5 ml) and 6N hydrochloride acid was added until the solution become homogeneous (pH = 1.5). The resulting homogenous solution was cooled in an ice bath. Acetic anhydride was added (1 mmol) to the above homogenous solution followed by 300 mg solid sodium bicarbonate until no further effervescence occurs or pH of the mixture becomes 5.5. The precipitated product was filtered, washed with water, dried and recrystallized from ethanol. The purity of compounds was checked by thin layer chromatography (TLC) using toluene-ethyl acetate-formic acid (5:4:1) as mobile phase.

Synthesis of 2-chloro-3-formylquinolines (2a-b):

6 mol of phosphorus oxychloride was added drop wise to a solution of acetanilide derivatives (1a-b) in 1.5 mol of dimethylformamide (DMF) at 0-5˚C by stirring. The addition was done using the pressure equalizing funnel over a period of 30 min and the mixture was further stirred at 80-90˚C for 18 hrs. The cooled reaction mixture was poured into ice water (300 ml) and stirred for an hour at 0-10˚C. The precipitated 2-chloroquinoline-3-carbaldehyde was filtered off, washed with water (100 ml), dried and recrystallization from ethyl acetate to give the final product. The purity of compound was checked by TLC using ethyl acetate-hexane (1:9) as mobile phase.

Synthesis of acid hydrazides (4a-e):

0.011 mol of Hydrazine hydrate, 0.01 mol of synthesized ethyl ester of acid derivatives was taken in a 100 ml of round bottomed flask. A minimum amount of ethyl alcohol was added to make the reaction-mixture a clear solution. The contents were refluxed for 8-12 hrs. The progress of the reaction was monitored by thin layer chromatography plate using toluene-ethyl acetate-formic acid (5:4:1) as mobile phase. After completion of the reaction, the ethanol was distilled off under reduced pressure to give the product. The hydrazide was recrystallized using alcohol.

Synthesis of quinolinyl hydrazones (5a-h):

0.01 mol of acid hydrazide which were designated 4a-f, 0.01 mol of synthesized aromatic aldehyde and 0.01 mol of p-toluene sulphonic acid were taken individually in a mortar the mixture was grounded with pestle for about 5 min at room temperature. The completion of reaction was monitored by TLC using ethyl acetate-hexane (4: 6) as mobile phase. Ice cold water was added once the reaction was completed. The resulting solid product was filtered, washed with water, dried and recrystallized from DMF.

Synthesis of 2,5-disubstituted-1,3,4-oxadiazoles (6a-h):

0.1 mol of quinolinyl hydrazones (5a-h), 0.12 mol of bis(trifluoroacetoxy)iodobenzene and 5 ml of dichloromethane were taken in 100 ml of round bottomed flask, then mixture was stirred at room temperature with magnetic stirrer. The progress of reaction was monitored by TLC using ethyl acetate-hexane (4:6) as mobile phase. After the completion of the reaction, the mixture was cooled. The solid thus obtained was filtered, washed with water (4-5 times) and then with hexane. The product was dried and recrystallized from DMF.

Physicochemical and Spectral data of 2,5-disubstituted-1,3,4-oxadiazoles (6a-h):

The physiochemical properties of the synthesized compounds (**6a-6h**) are collected and presented in Table 1.

2-Chloro-3-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)quinoline (6a): R_f value 0.44; % yield 67; mp 236-238˚C**;** IR (KBr $\upsilon_{max}cm^1$): 3182.75 (aromatic C-H), 2921.23 (aliphatic C-H), 1585.02 (C=C str.), 1654.48 (C=N str.),

1486.95(C-N), 1155.96 (C-O-C), 841.32 (C-Cl); ^{1}H-NMR, δppm (DMSO-d_6): 9.07 (s, 1H, H-4), 8.17-8.10 (m, 2H, H-5 & 8), 8.08-8.06 (d, 2H, H-2' & 6'), 7.94-7.74 (m, 2H, H-6 & H-7), 7.62-7.60 (d, 2H, H-3' & 5').

2-Chloro-3-(5-(2,4-dichlorophenyl)-1,3,4-oxadiazol-2-yl)quinoline (6b): R_f value 0.91; % yield 60; mp 252-254˚C; IR (KBr $\upsilon_{max}cm^1$): 3068.33 (aromatic C-H), 1593.19 (C=C str), 1621.79 (C=N str), 1470.60 (C-N), 1147.79 (C-O-C), 747.33 (C-Cl); ^{1}H-NMR, δppm (DMSO-d_6): 9.24 (s, 1H, H-4), 8.28-8.25 (d, 1H, H-8), 8.19-8.16 (d, 1H, H-5), 8.01-7.96 (m, 2H, H-3',7), 7.74-7.71 (d, 1H, H-5'), 8.08-8.05 (d, 1H, H-6'), 7.81-7.76 (t, 1H, H-6).

2-Chloro-3-(5-phenyl-1,3,4-oxadiazol-2-yl)quinoline (6c): R_f value 0.34; %yield 65; mp 180-182˚C; IR (KBr $\upsilon_{max}cm^1$): 3419.61 (aromatic C-H), 1576.79 (C=C str.), 1609.48 (C=N str), 1482.81 (C-N), 1135.49 (C-O-C), 775.92 (C-Cl); ^{1}H-NMR, δppm (DMSO-d_6): 9.33 (s, 1H, H-4), 8.29-8.27 (d, 1H, H-8), 8.03-7.98 (t, 1H, H-7), 7.84-7.79 (t, 1H, H-6), 8.10-8.08 (d, 1H, H-5), 7.70-7.67 (m, 3H, H-3'4'5'), 8.19-8.17 (m, 2H, H-2',6').

2-Chloro-3-(5-p-tolyl-1,3,4-oxadiazol-2-yl)quinoline (6d): R_f value 0.76; % yield 66; mp 208-210˚C ; IR (KBr $\upsilon_{max}cm^1$): 3039.61 (aromatic C-H), 2917.03 (aliphatic C-H), 1589.05 (C=C str.), 1613.57 (C=N str.), 1495.07 (C-N), 1188.61 (C-O-C), 755.49 (C-Cl); ^{1}H-NMR, δppm (DMSO-d_6): 2.50 (s, 3H, CH_3), 9.31 (s, 1H, H-4), 8.26-8.293(d, 1H, H-8), 7.47-8.07 (m, aromatic proton).

2-Chloro-3-(5-methoxyphenyl-1,3,4-oxadiazol-2-yl)quinoline (6e): R_f value 0.76; % yield 64; mp 192-194˚C IR (KBr $\upsilon_{max}cm^1$): 3047.78 (aromatic C-H), 2839.39 (aliphatic C-H), 1560.45 (C=C str.), 1613.57 (C=N str.), 1425.61 (C-N), 1176.36 (C-O-C), 747.32 (C-Cl), 1253.99 (OCH_3); ^{1}H-NMR, δppm (DMSO-d_6): 9.30 (s, 1H, H-4), 8.28-8.26 (d, 2H, H-5), 8.02-7.97 (t, 1H, H-7), 7.83-7.78 (t, 1H, H-6), 8.12-8.07 (m, 3H, H-8,2' and 6'),7.22-7.20 (d, 2H,H-3' & H-5'),3.88 (s, 3H, OCH_3); ^{13}C-NMR,δppm(DMSO-d_6): 165.12 (C_2'), 162.86 (C_2'), 161.19 (C_4'') 147.75 (C_2), 142.09 (C_4), 146.30 (C_{10}), 56.07 (OCH_3), 146.30, 133.63, 129.47, 128.94, 128.29, 126.39, 117.70, ,115.48, 115.74; M^+: 338.1 (M^+; 100%), 340.1 (M^++2, 38.7%).

2-Chloro-3-(5-pyridin-4-yl)-1,3,4-oxadiazol-2-yl)quinoline (6f): R_f value 0.45; % yield 69; mp 234-236˚C IR (KBr $\upsilon_{max}cm^1$): 3043.81 (aromatic C-H), 2925.31 (aliphatic C-H), 1542.39 (C=C str.), 1618.08 (C=N str.), 1491.06 (C-N), 1145.90 (C-O-C), 701.02 (C-Cl); ^{1}H-NMR, δppm (DMSO-d_6): 9.34 (s, 1H ,H-4), 8.90-8.91 (d, 2H, pyridyl 3' and 5'), 8.26-8.29 (d, 1H, H-8), 8.08-8.11 (m, 3H, H-5, pyridyl 2',6'), 7.99-8.03 (t, 1H, H-6), 7.79-7.84 (t, 1H, H-7).

2-Chloro-6-methoxy-3-(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)quinoline (6g): R_f value 0.73; % yield 64; mp 208-210˚C IR (KBr $\upsilon_{max}cm^1$): 3435.96 (aromatic C-H), 2912.94 (aliphatic C-H), 1576.79 (C=C str), 1613.57 (C=N str), 1490.98 (C-N), 1172.27 (C-O-C), 743.23 (C-Cl), 1253.99 (OCH_3); ^{1}H-NMR, δppm (DMSO-d_6): 9.13 (s, 1H, H-4), 8.10-8.07 (d, 2H, H-2' & 6') , 7.99-7.93 (d, 1H, H-8), 7.58 - 7.66 (m, 2H, H-5 & H-7), 7.21-7.18 (d, 2H, H- 3'&H5'), 3.93 (s, 3H, OCH_3, C-6), 3.86 (s, 3H, OCH_3, C-4').

2-Chloro-6-methoxy-3-(5-phenyl)-1,3,4-oxadiazol-2-yl)quinoline (6h): R_f value 0.73; % yield 69; mp 218-220˚C IR (KBr $\upsilon_{max}cm^1$): 3047.90 (aromatic C-H), 2888.54 (aliphatic C-H), 1580.93 (C=C str.), 1617.71 (C=N str.), 1491.03 (C-N), 1160.05 (C-O-C), 702.38 (C-Cl), 1225.43 (OCH_3); ^{1}H-NMR, δppm (DMSO-d_6): 9.15 (s, 1H, H-4), 3.92 (s, 3H, -OCH_3), 7.67-7.59 (m, 5H, aromatic protons, H-5,7,3',4',5'), 7.98-7.95 (d, 1H, H-8), 8.16-8.14 (m, 2H, H-2' & 6').

Antibacterial activity:

The antibacterial activity of the synthesized compounds was determined using Disc-diffusion method (20), against *Escherichia coli* (Gram negative bacteria). Stock solutions of different test compounds (100 µg per ml) were made in DMSO. Standard inoculums were introduced on to the surface of sterilized agar plates and a sterilized glass spreader was used for even distribution of inoculum. The inoculum was allowed to dry for 5 minutes with lid in placed. Sterile discs of 6 mm diameter (Hi Media Laboratories Ltd., Mumbai, India) were used. Test compounds (100 µg per ml) were incorporated in to the sterile disc using micropipette. Precautions were taken to prevent the flow of the solution from the disc to outer surface. The disc was applied under aseptic technique. The plates were inverted and incubated for 24 hours at 37˚C. Carbenicillin was used as a standard drug (100 µg per disc). The diameters of the zones were measured to the nearest millimeter using Zone scales PW096. In all the determinations test were performed in triplicate and the results were taken as a mean of at three determinations. The results are presented in Table 2.

Antifungal activity:

The antifungal activity of the synthesized compounds was determined using Poison Food technique (21). This technique involves the cultivation of test organism on a growth medium containing the test chemical and then measuring its growth. For the work efficacy of the test compounds was determined against three strains; namely *Penicillium marneffei, Aspergilus niger, Colletotrichum capsici.* 25 ml of water blanks were prepared separately in conical flask using distilled water and sterilized these water blanks at 121°C in an autoclave for 15 minutes. The water blanks were cooled at 45-47˚C and then test compounds (each 5 mg) were dissolved into the minimum quantity of acetone and finally made up the volume to 25 ml with sterilized water to get 200 µg per ml (double strength). Potato dextrose agar (PDA) medium was mixed with the test compounds aseptically to get the final concentrations of 100 µg per ml. The medium containing the test compounds was poured into the sterile petri-dishes of 9 cm diameter in quantities of approximately 16 ml and allowed to solidify. 5 mm mycelial disc were prepared by cutting from 7 days old fungus grown on PDA medium seeded with the microorganism (10^6 cfu per ml). These discs were placed in the center of the petri-dishes containing 50 ml poisoned PDA medium. The petri-dishes were incubated at 25˚C for 7 days. Three replicates were used for each test compounds together with three petri-dishes containing the solvents (control) and Griseofulvin (as standard drug). The % inhibition of growth was calculated from mean differences between treatments and control by using following formula:

% inhibition = (C – T)/C x 100
Where, C = mycelial growth in control; and T = mycelial growth in treated dish
The results of the antifungal activity studies are presented in Table 3.

Results and Discussion

A new series of 2,5-disubstituted-1,3,4-oxadiazole derivatives was synthesized by the condensation of quinolinylhydrazone derivatives with dichloromethane (**Scheme 1**). The physiochemical data of the synthesized compounds (**6a-6h**) was collected and presented in **Table 1**. The percentage yield of all the synthesized compounds (**6a-6h**) was found to be in the range of 60-70%. The purity of the synthesized compounds was studied by TLC. The synthesized compounds were confirmed structurally by means of their FT-IR, ^{1}H-NMR, ^{13}C-NMR and mass spectra (MS). The spectral (IR, 1H NMR and MS) and analytical data are in good agreement with their structures. All the synthesized compounds were evaluated for antibacterial and antifungal activity.

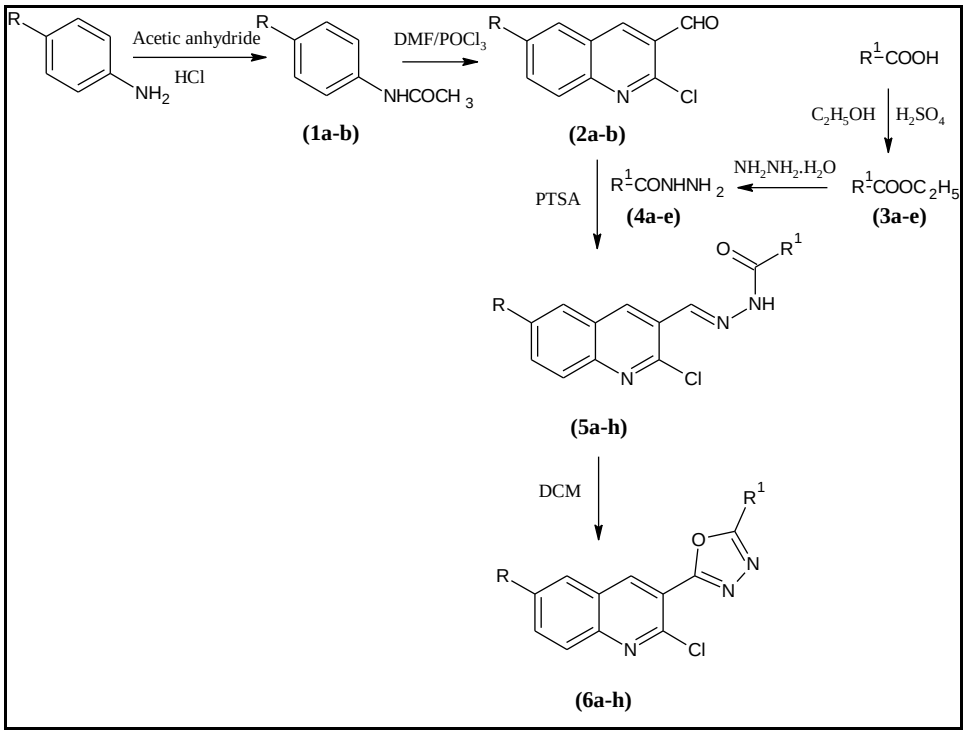
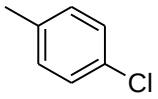
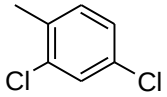
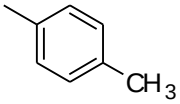
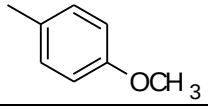
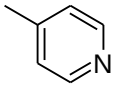
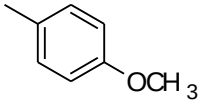


Figure 1. Synthesis of 2,5-disubstituted-1,3,4-oxadiazoles (6a-h).

Table 1. Physicochemical data of the synthesized compounds (6a-6h)

Compound	R	R_1	R_f value	% yield	Melting point (°C)
6a	- H		0.44	67.29	236-238
6b	-H		0.91	60.25	252-254
6c	-H	C_6H_5-	0.34	65.38	180-182
6d	-H		0.76	66.28	208-210
6e	-H		0.76	64.30	192-194
6f	-H		0.45	69.00	234-236
6g	-OCH_3		0.73	64.20	208-210
6h	-OCH_3	C_6H_5-	0.73	69.10	218-220

The antibacterial activity study of the synthesized compounds against *Escherichia coli* reveals that the zone of inhibition (diameter) for the synthesized compounds was in the range 15-24 mm of *Escherichia coli* stain (antibacterial activity data of the synthesized compounds is presented in Table **2**). Among the synthesized compounds evaluated for antibacterial activity, compound **6f** was found to be the most active compound with zone of inhibition of 24 mm when compared with the standard drug Carbenicillin (zone of inhibition 25 mm). Other most active compound was **6b** with zone of inhibition of 23 mm when compared with standard. The other synthesized compounds showed moderate antibacterial activity against *Escherichia coli.*

Table 2. Antibacterial activity data of synthesized compound (6a-6h)

Compound	Zone of Inhibition (mm) against *Escherichia coli*
6a	22
6b	23
6c	15
6d	18
6e	19
6f	24
6g	21
6h	17
Control	6
Carbenicillin (Standard)	25

The synthesized compounds were evaluated for antifungal activity against *Penicillium marneffei*, *Aspergilus niger*, *Colletotrichum capsici* (antifungal activity data of synthesized compounds is presented in Table **3**). Among the synthesized compounds evaluated for antifungal activity, compound **6f** was found to be the most active compound against *Aspergilus niger* and *Penicillium marneffei*. Other active compound was **6b** against *Aspergilus niger* and *Penicillium marneffei*. The compounds **6c**, **6d** and **6e** did not show antifungal

activity against the *Colletotrichum capsici*. In general, The activity of **6f** compound may be attributed to the presence of the pyridine ring along with two other rings 1,3,4-oxadiazole and quinoline. Other active compound which shows activity is **6b,** due to the two electron withdrawing (chlorine group) substituent present at 2nd and 4th position of the phenyl ring linked with quinoline and 1,3,4-oxadiazole.

Table 3. Antifungal activity data of synthesized compounds (6a-6h)

Compound	Zone of inhibition (mm)			Percent inhibition of growth (%)		
	Aspergilus niger	***Penicillium marneffei***	***Colletotrichum capsici***	***Aspergilus niger***	***Penicillium marneffei***	***Colletotrichum capsici***
6a	19	12	30	77.7	86.6	66.6
6b	20	11	28	78.8	87.7	68.8
6c	30	21	-	66.6	76.6	-
6d	26	19	-	70.0	78.8	-
6e	27	16	-	71.1	82.2	-
6f	15	10	30	83.3	88.8	66.6
6g	23	15	10	74.4	83.3	88.8
6h	29	20	20	67.7	77.7	77.7
Control	90	90	90	0	0	0
Griseofulvin (Standard)	7	6	8	92.2	93.3	91.1

Conclusion

A new series of 2,5-disubstituted-1,3,4-oxadiazole derivatives was synthesized and evaluated for the antibacterial and antifungal activity by disc diffusion method and poison food technique respectively. Among the synthesized compounds evaluated for antibacterial studies against *Escherichia coli*, and antifungal studies against *Aspergilus niger*, *Penicillium marneffei* and *Colletotrichum capsici*, compound **6f** was found to be the most active compound. The compounds **6c**, **6d** and **6e** did not show antifungal activity against the *Colletotrichum capsici.*

Conflict of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Sharma S, Sharma PK, Kumar N, Dudhe R. A review: Oxadiazole their chemistry and pharmacological potentials. Der Pharma Chemica, 2010, 2: 253-263.
2. El-Emam AA, Al-Deeb OA, Al-Omar M. Synthesis, antibacterial and anti-HIV activity of certain 5-(1-adamantyl)-2-substituted thio-1,3,4-oxadiazoles and 5-(1-adamantyl)-3-substituted aminomethyl-1,3,4-oxadiazolin-2-thiones. Bioorg Med Chem., 2004, 12: 5107-5113.
3. Maslat AO, Abussaud M, Tashtoush H, Al-Talib M. Synthesis, antibacterial, antifungal and genotoxic activity of bis-1,3,4-oxadiazole derivatives. Pol J Pharmacol., 2002, 54: 55-59.
4. Kucukguzel SG, Oruc EE, Rollas S, Sahin F, Ozbek A. Synthesis, characterization and biological activity of novel 4-thiazolidinones, 1,3,4-oxadiazoles and some related compounds. Eur J Med Chem., 2002, 37: 197-206.
5. Chauhan D, Chauhan JS, Singh J, Bajpai SK, Joshi MN. Synthesis and bioevaluation of some novel nucleosides as antiherptic agents. Indian J Chem., 2003, 42B: 215-218.
6. Kagthara PR, Shah NS, Doshi RK, Parekh HH. Synthesis of 2,5-disubstituted-1,3,4-oxadiazoles as biologically active heterocycles. Indian J Chem., 1999, 38B: 572-576.
7. Mohan TP, Vishalakshi B, Bhat KS, Kendappa GN. Synthesis and insecticidal activity of some 1,3,4-oxadiazole derivatives containing phenoxyfluorophenyl group. Indian J Chem., 2004, 43B: 1798-1801.
8. Kennedy DA, Summers LA. Chemical constitution and activity of bipyridinium herbicides. Part XIV. Reduction potential and herbicidal activity of 4,4′-(1,3,4-thiadiazole-2,5-diyl)- and 4,4′-(1,3,4-oxadiazole-2,5-diyl)bis(1-methylpyridinium) diiodides. J Heterocycl Chem., 1981, 18: 401-410.

9. Santagati M, Modica M, Santagati A, Russo F, Caruso A, Cutuli V, et al. Synthesis and pharmacological properties of benzothiazole, 1,3,4-oxadiazole and 1,2,4-thiadiazole derivatives. Pharmazie, 1994, 49: 880-884.
10. Mullican MD, Wilsonj MW, Connor DT, Kostlan CR, Schrier DJ, Dyer RD. Design of 5-(3,5-Di-ter-butyl-4-hydroxyphenyl)-1,3,4-thiadiazol-1-yl-1,3,4-oxadiazoles and 1,2,4-triazoles as orally active, nonulcerogenic anti-inflammatory agents. J Med Chem., 1993, 36: 1090-1099.
11. Nagalakshmi G. Synthesis, Antimicrobial and antiinflammatory activity of 2,5-disubstituted-1,3,4-oxadiazoles. Indian J Pharm Sci., 2008, 70: 49-55.
12. Khalilullah H, Ahsan MJ, Hedaitullah M, Khan S, Ahmed B. 1,3,4-oxadiazole: a biologically active scaffold. Mini Rev Med Chem., 2012, 12: 789-801.
13. Yar MS, Akhter MW. Synthesis and anticonvulsant activity of substituted oxadiazole and thiadiazole derivatives. Acta Pol Pharm., 2009, 66: 393-397.
14. Kashaw SK, Gupta V, Kashaw V, Mishra P, Stables JP, Jain NK. Anticonvulsant and sedative-hypnotic activity of some novel 3-[5-(4-substituted) phenyl-1,3,4-oxadiazole-2yl]-2-styrylquinazoline-4(3H)-ones. Med Chem Res., 2010, 19: 250-261.
15. Jessen KA, English NM, Wang JY, Maliartenou SK, Archer SP, Qiu L, et al. The discovery and mechanism of action of novel tumour-selective and apoptosis-inducing 3,5-diaryl-1,2,4-oxadiazole series using a chemical genetics approach. Mol Cancer Ther., 2005, 4: 761-771.
16. Abu-Zaied MA, El-Telbani EM, Elgemeie GH, Nawwar GA. Synthesis and in vitro anti-tumor activity of new oxadiazole thioglycosides. Eur J Med Chem., 2011, 46: 229-235.
17. Farghaly AA, Bekhit AA, Park JY. Design and synthesis of some oxadiazolyl, thiazolidinyl and thiazolyl derivatives of 1H-pyrazole as anti-inflammatory and antimicrobial agents. Arch Pharm (Weinheim), 2000, 333: 53-57.
18. de Oliveira CS, Lira BF, Barbosa-Filho JM, Lorenzo JG, de Athayde-Filho PF. Synthetic approaches and pharmacological activity of 1,3,4-oxadiazoles: a review of the literature from 2000-2012. Molecules, 2012, 17: 10192-10231.
19. Rajput AP, Girase PD. Review Article on Vilsmeier-Haack Reaction. Int J Pharm Chem Biol Sci., 2012, 3: 25-43.
20. Zaidan MRS, Rain AN, Badrul AR, Adlin A, Norazah A, Zakiah I. In vitro screening of five local medicinal plants for antibacterial activity using disc diffusion method. Trop Biomed., 2005, 22: 165-170.
21. Sridhar SR, Rajagopal RV, Rajavel R, Masilamani S, Narasimhan S. Antifungal Activity of Some Essential Oils. J Agric Food Chem., 2003, 51: 7596-7599.

*****