Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Archives of Applied Science Research, 2011, 3 (2):558-567

(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-508X
CODEN (USA) AASRC9

Microwave assisted synthesis and pharmacological evaluation of some 1, 3, 4-oxadiazole derivatives

Sudhir Bhardwaj[1], Bharat Parashar[2], Narendra Parashar[3] and V. K. Sharma[4*]

[1] Shriram College of Pharmacy, Bamor, Gwalior (M.P.)
[2]Geetanjali instituted of Pharmacy, Dabok, Udaipur, (Rajasthan).
[3]Pacific college of Pharmacy, Udaipur (Rajasthan)
[4]Microwave Chemistry Laboratory, Department of Chemistry, M.L. Sukhadia University, Udaipur, (Rajasthan)

ABSTRACT

Reaction of isonicotinohydrazide with different aromatic aldehydes under the microwave irradiation gives Schiff's bases. These Schiff's bases were converted into 1, 3, 4-oxadiazole derivatives by treating with acetic anhydride under the microwave irradiation. The structures of the compounds were confirmed by elemental analysis, IR, [1]HNMR and Mass spectral data's .The synthesized compounds were screened for antimicrobial, analgesic and anti-inflammatory activities.

Keywords: Isonicotinohydrazide, microwave irradiation, Silica gel, antibacterial activity, antifungal activity, anti-inflammatory activity, analgesic activity.

INTRODUCTION

Oxadiazole nucleus is continuously drawing interest for development of newer drug moiety. Due to the interesting activity of substituted 1, 3, 4-oxadiazole as biological agent's considerable attention has been focused on this class. Oxadiazole types of heterocyclic compounds contain oxygen and two nitrogen atoms. As evident from the literature, these derivatives are synthesized by both conventional as well as microwave assisted methods. In recent years a significant portion of research work in heterocyclic chemistry has been devoted to 1, 3, 4-oxadiazole containing different aryl groups as substituent's

The pharmaceutical importance of these compounds lies in the fact that they can be effectively utilizing as antibacterial [1-6], anticancer[7], and chitin biosynthesis[8], anticonvulsant agents[9], Monoamineoxidase (MAO) inhibitors[10] , anti-inflammatory [11-14] ant-tubercular[15] , insecticidal agents [16] Analgesic [17-18] ,antiparkinsonian[19] Some of these compounds have also anti-HIV agent [20-21]

The solvent-free organic reactions assisted by microwaves in particular, have gained special attention in recent years [22]. The use of microwave irradiation in organic synthesis can increase the purity of the resulting products, enhance the chemical yield and shorten the reaction time. Solvent-free reaction leads to a clean, eco-friendly and economic technology. Reactions on solid support without using solvent usually with open vessel in domestic microwave ovens are currently in use for synthetic chemist to create eco-friendly atmosphere. [23, 24].

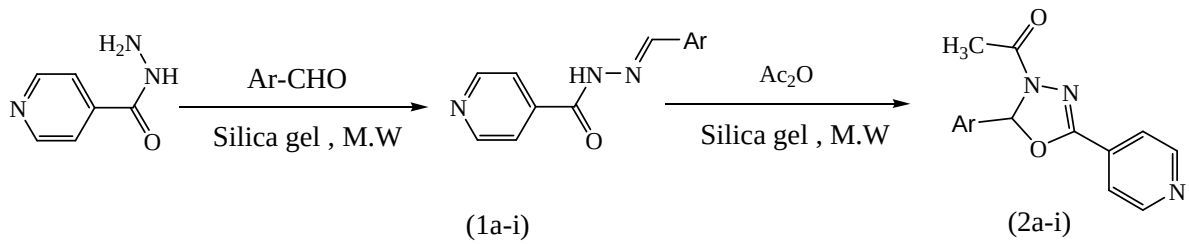
In view of these facts, and in continuation of the interest in the microwave-assisted organic synthesis of 1, 3, 4-oxadiazoles we present herein a rapid and efficient method for the synthesis of 1-(2-(-Substituted phenyl)-5-(pyridine- 4-yl)-1, 3, 4-oxadiazol-3(2H)-yl) ethanone in solvent-free conditions under microwave irradiation using silica gel as solid support.

MATERIALS AND METHODS

Chemicals were purchased from commercial suppliers and were used without any further purification. All the reactions were carried out in a Modified Microwave oven (Kenstar, model no: OM26.EGO). The progress of the reaction was monitored on percolated silica gel 60 F254 plates (Merck) using ethyl acetate: n-hexane (7:3) as an eluent and spot was detected by using iodine vapours. Melting points are determined by open capillary tube method and are uncorrected. The IR (KBr pellets) spectra were recorded on a Perkin Elimer-1800-spectrophotometer and H^1NMR spectra were recorded on BRUKER DRX-300MHz spectrophotometer, (TMS as a internal reference) and chemical shifts are expressed in δ. Mass spectra were recorded on Jeol D30 spectrophotometer. Elemental analyses for C, H and N were conducted using a Perkin -Elmer C, H, and N analyzer

General method for the synthesis of N'-(4-subsituted benzylidene) isonicotinohydrazide:
Isonicotinohydrazide, (0.01 mol), appropriate aromatic aldehyde (0.01mole), was dissolved in 10.00 ml of ethanol containing 1.0 mL of GAA. Silica gel (5 g) was added to the mixture. The reaction mixture was thoroughly mixed and adsorbed material was dried in air and irradiated in microwave oven at 400 W intermittently at 30 s intervals for 1to 2.30 min**.** The completion of the reaction was monitored by TLC using n-hexane: ethyl acetate (6:4) as mobile phase. The reaction mixture was cooled and the product was extracted with methanol. Dilution of methanol solution with ice-cold water gave the product, which was filtered, washed with water and recrystallization from methanol to give **1a-l.** The M.P. of the synthesised compound was checked by the given literatures[25-26].

General procedure for the synthesis of 1-(2-(substituted- phenyl)-5-(pyridin-4-yl)-1, 3, 4-oxadiazol-3(2h)-yl) ethanone: Silica gel (6 g) was added to the different isonicotinohydrazide (**1a-l**, 0.01 mol) and Ac_2O (10 mL) at room temperature. The reaction mixture was thoroughly mixed and adsorbed material was dried in air and irradiated in microwave oven at 400 W intermittently at 30 s intervals for the time indicated in **Table 1**. The completion of the reaction was monitored by TLC using n-hexane: ethyl acetate (6:4) as mobile phase. The reaction mixture was cooled and the product was extracted with methanol. Dilution of methanol solution with ice-cold water gave the crude product, which was filtered, washed with water and recrystallization from methanol to give **2a-l**.



(1a-i) (2a-i)

Ar.= (a) C_6H_5 (b) 4-FC_6H_4 (c) 4-ClC_6H_4 (d) 3-ClC_6H_4

(e) 4-NO_2 C_6H_4 (f) 3-NO_2 C_6H_4 (g) 2-NO_2 C_6H_4 (h) 4-OH C_6H_4

(i) 3-OH C_6H_4 (j) 4-OCH_3 C_6H_4 (k) 4-$N(CH_3)_2C_6H_4$ (l) C_4H_3O(2-furyl)

(2a).1-(2-phenyl-5-(pyridin-4-yl)-1, 3, 4-oxadiazol-3(2H)-yl) ethanone:
Mol. Formula; $C_{15}H_{13}N_3O_2$: Elemental analysis Calculated; C, 67.40; H, 4.90; N, 15.72 Found: C, 67.28.; H, 4.52; N, 15.52 : IR (KBr cm^{-1}): 3035 (CH-Ar str .of aromatic ring), 1665 (C=O str, of acetyl group), 1630 (C=N str. of 1,3,4 Oxadiazole), 1540 (C=N str. of pyridine), 1470 (. C-O-C str. of 1,3,4-oxadiazole) : ^{1}H NMR (400 MHz, DMSO-d_6) : 7.75- 8.64 (4H, m, Ar-H of pyridine); 7.12-7.36 (5H, m, Ar-H), 8.24 (s,1H,CH-oxadiazole), 1.89 (s, 3H, OCH_3) : MS (m/z+) [M^+] 267;

(2b). 1-(2-(4-fluorophenyl)-5-(pyridin-4-yl)-1, 3, 4-oxadiazol-3(2H)-yl) ethanone:
Mol. Formula; $C_{15}H_{12}FN_3O_2$: Elemental analysis Calculated; C, 63.15; H, 4.24; N, 14.73 Found: C, 63.36.; H, 4.40; N, 15.00 : IR (KBr cm^{-1}): 3105 (CH-Ar str .of aromatic ring), 1685 (C=O str, of acetyl group), 1650 (C=N str. of 1,3,4 Oxadiazole), 1560 (C=N str. of pyridine), 1464 (C-O-C str. of 1,3,4-oxadiazole) : ^{1}H NMR (400 MHz, DMSO-d_6) : 7.72- 8.54 (4H, m, Ar-H of pyridine); 7.08-7.40 (4H, m, Ar-H), 8.36 (s,1H,CH-oxadiazole), 1.94 (s, 3H, OCH_3) : MS (m/z+) [M^+] 285;

(2c).1-(2-(4-chlorophenyl)-5-(pyridin-4-yl)-1, 3, 4-oxadiazol-3(2H)-yl) ethanone:
Mol. Formula; $C_{15}H_{12}ClN_3O_2$:Elemental analysis Calculated; C, 59.71; H, 4.01; N, 13.93 Found: C, 59.46.; H, 4.22; N, 14.12 : IR (KBr cm^{-1}): 3080 (CH-Ar str .of aromatic ring), 1665 (C=O str, of acetyl group), 1662 (C=N str. of 1,3,4 Oxadiazole), 1543 (C=N str. of pyridine), 1442 (C-O-C str. of 1,3,4-oxadiazole) : ^{1}H NMR (400 MHz, DMSO-d_6) : 7.62- 8.64 (4H, m, Ar-H of pyridine); 7.02-7.46 (4H, m, Ar-H), 8.54 (s,1H,CH-oxadiazole) 1.98 (s, 3H, OCH_3) : MS (m/z+) [M^+] 301;

(2f). 1-(2-(3-nitrophenyl)-5-(pyridin-4-yl)-1, 3, 4-oxadiazol-3(2H)-yl) ethanone:
Mol. Formula; $C_{15}H_{12}N_4O_4$: Elemental analysis Calculated C, 57.69; H, 3.87; N, 17.94; Found: C, 57.38.; H, 4.00; N, 18.10 : IR (KBr cm^{-1}): 3120(CH-Ar str .of aromatic ring), 1645(C=O str, of acetyl group), 1632 (C=N str. of 1,3,4 Oxadiazole), 1523 (C=N str. of pyridine), 1422 (C-O-C str. of 1,3,4-oxadiazole) : ^{1}H NMR (400 MHz, DMSO-d_6) : 7.88- 8.84 (4H, m, Ar-H of pyridine); 7.40-8.04 (4H, m, Ar-H), 8.62 (s,1H, CH-oxadiazole), 2.02 (s, 3H, OCH_3) : MS (m/z+) [M^+] 312;

(2h). 1-(2-(4-hydroxyphenyl)-5-(pyridin-4-yl)-1, 3, 4-oxadiazol-3(2H)-yl) ethanone:
Mol. Formula; $C_{15}H_{13}N_3O_3$: Elemental analysis Calculated; C, 63.60 ; H, 4.63; N, 14.83; Found: C, 63.36.; H, 4.40; N, 14.62 : IR (KBr cm^{-1}): 3208 (O-H, str.) 3100 (CH-Ar str .of aromatic ring), 1640 (C=O str, of acetyl group), 1634 (C=N str. of 1,3,4 Oxadiazole), 1542

(C=N str. of pyridine), 1432 (C-O-C str. of 1,3,4-oxadiazole) : ^{1}H NMR (400 MHz, DMSO-d_6) : 9.58 (s,1H, O-H), 7.80- 8.88 (4H, m, Ar-H of pyridine); 6.62-7.04 (4H, m, Ar-H), 8.62 (s,1H,CH-oxadiazole), 2.04 (s, 3H, OCH_3) : MS (m/z+) [M^+] 283;

(2j).1-(2-(4-methoxyphenyl)-5-(pyridin-4-yl)-1, 3, 4-oxadiazol-3(2H)-yl) ethanone:
Mol. Formula; $C_{16}H_{15}N_3O_3$: Elemental analysis Calculated; C, 64.64 ; H, 5.09; N, 14.13; Found: C, 64.38.; H, 4.82; N, 14.34 : IR (KBr cm^{-1}): 3082(CH-Ar str .of aromatic ring), 1652 (C=O str, of acetyl group), 1665 (C=N str. of 1,3,4 Oxadiazole), 1552 (C=N str. of pyridine), 1448 (str. C-O-C str. of 1,3,4-oxadiazole) : ^{1}H NMR (400 MHz, DMSO-d_6) : 8.04- 8.82 (4H, m, Ar-H of pyridine); 6.72-7.10 (4H, m, Ar-H), 8.58 (s,1H,CH-oxadiazole), 3.38 (s, 3H, OCH_3,) 2.08 (s, 3H, OCH_3, 1,3,4-oxadiazole): MS (m/z+) [M^+] 297;

(2k). 1-(2-(3-(dimethylamino) phenyl)-5-(pyridin-4-yl)-1, 3, 4-oxadiazol-3(2H)-yl) ethanone:
Mol. Formula; $C_{17}H_{18}N_4O_2$: Elemental analysis Calculated; C, 65.79 ; H, 5.85; N, 18.05; Found: C, 66.02.; H, 5.62; N, 18.38 : IR (KBr cm^{-1}): 3070 (CH-Ar str .of aromatic ring), 1646 (C=O str, of acetyl group), 1652 (C=N str. of 1,3,4 Oxadiazole), 1538 (C=N str. of pyridine), 1442 (C-O-C str. of 1,3,4-oxadiazole) : ^{1}H NMR (400 MHz, DMSO-d_6) : 8.14- 8.86 (4H, m, Ar-H of pyridine); 6.52-7.08 (4H, m, Ar-H), 8.64 (s,1H,CH-oxadiazole), 1.57 (s, 6H, -N (CH_3)$_2$,) 1.86 (s, 3H, OCH_3, 1,3,4-oxadiazole) : MS (m/z+) [M^+] 310;

(2l).1-(2-(furan-2-yl)-5-(pyridin-4-yl)-1, 3, 4-oxadiazol-3(2H)-yl) ethanone:
Mol. Formula; $C_{13}H_{11}N_3O_3$: Elemental analysis Calculated; C, 60.70 ; H, 4.31; N, 16.33; Found: C, 60.54.; H, 4.62; N, 16.58: IR (KBr cm^{-1}): 3084 (CH-Ar str .of aromatic ring), 1642 (C=O str, of acetyl group), 1654 (C=N str. of 1,3,4 Oxadiazole), 1542 (C=N str. of pyridine), 1456 (str. C-O-C str. of 1,3,4-oxadiazole) : ^{1}H NMR (400 MHz, DMSO-d_6) 8.04- 8.82 (4H, m, Ar-H of pyridine); 6.32-7.30 (3H, m, furan-H), 8.68 (s,1H,CH-oxadiazole), 2.02 (s, 3H, OCH_3, 1,3,4-oxadiazole) : MS (m/z+) [M^+] 257;

Antibacterial activity: The antibacterial activity of all the synthesized compounds (2a-m) were examined against Gram-positive (S.*aureus)* and Gram-negative (*E.coli*) organisms by measuring zone of inhibition. The antibacterial activity was performed by Agar diffusion method [27,28] at the concentration level 200 ,100 .50 µg/mL ciprofloxcine was used as standard drug at concentration of 50 µg /ml. Nutrient agar was used as culture media and DMSO was used as solvent control. The zones of inhibition were measured with antibiotic zone scale in mm. The tests were carried out in duplicate the results of the antibacterial activity are shown in Table 2.

Antifungal activity : The antifungal activity of all the synthesized compounds (2a-l) were examined against *C.albicans* and *A.niger* by measuring zone of inhibition. The antifungal activity was performed by agar well diffusion method [29] at the concentration level of 200, 100, 50 µg /mL ketoconazole was used as standard drug at a concentration of 50 µg / mL. Sabouraud dextrose agar was used as culture media and DMF was used as solvent control. The zones of inhibition were measured with antibiotic zone scale in mm. The tests were carried out in duplicate .The results of the antifungal activity are shown in Table 2.

Anti-inflammatory activity : Swiss albino rats (100 - 120 g) of either sex were selected for the experiments. Animals were allowed to be acclimatise for a period of 2 weeks in our laboratory environment prior to the study. Animals were housed in polypropylene cages(4 animals per cage), maintained under standard laboratory conditions (i.e. 12:12 hour light and dark sequence; at an ambient temperature of 25 ± 2ºC; 35-60 % humidity); the animals

were fed with standard rat pellet diet (Hindustan Liver Ltd. Mumbai) and water *ad libitum.* The principles of Laboratory Animal Care were followed and instructions given by our institutional animal ethical committee were maintained throughout the experiment.

All the synthesized compounds were screened for *in vivo* anti-inflammatory activity by carrageenan induced paw edema test in rats [30,31]. Diclofenac sodium (50 mg/kg) was administered as standard drug for comparison. Rats were divided in to XIV groups each group containing four rats. Group I was treated with tween-80 (1%) suspension which served by vehicle control. Group II was administered with standard drug Diclofenac sodium. Group III to XIV were treated with the suspension of the test compounds in tween-80 at a dose of 50.0 mg/ kg. After 30 minutes, the animals were injected with 0.1 mL of Carrageenan (1%w/v), in the sub planter region of left hind paw of rats. The paw volume was measured every 60 min using the mercury displacement technique with the help of a plethysmometer after the induction of inflammation. The results were expressed as percentage reduction in oedema volume, which can be calculated by using the formula:

$$\% \text{ of inhibition} = \frac{(V_t - V_0)\ \text{control} - (V_t - V_0)\ \text{treated}}{(V_t - V_0)\ \text{control}} \times 100$$

V_t = The paw volume at 60, 120 and 180 min .

V_0 = The paw volume at 00 min.

The results are compiled in the Table 2:

Analgesic Activity: The compounds that exhibited good anti-inflammatory activity (> 45 %) were screened for analgesic activity. Analgesic activity was tested by the acetic acid induced writhing method [32]. The mice were divided into seven groups of twelve animals each. A 1 % aqueous acetic acid solution (i.p. injection, 0.1 mL) was used as a writhing inducing agent. Mice were kept individually in the test cage before acetic acid injection and habituated for 30 min. Screening of analgesic activity was performed after administration of test compounds and the standard drug (acetylsalicylic acid) at a dose of 50 mg/ kg. The control group was given orally 0.5 %(*V/V*) Tween 80 (0.5 mL) suspension. The compound and standard drug were administered orally to the animals, respectively. Twenty minutes after administration of the test compounds and a standard, all groups of mice were given the writhing agent, 1 % aqueous acetic acid solution (*i.p.* injection, 0.1 mL). The total number of writhing produced in these animals was counted visually for 15 minutes and the number of writhing produced by 3 to 9 groups was compared with that in the control group. The results given in Table- 4: are expressed as percentage protection.

Percentage Inhibition = [Wt (Control) - Wt (test group) / Wt (Control)] X 100
Wt = Mean number of writhing

RESULTS AND DISCUSSION

The starting compound, N'-(4-subsituted benzylidene) isonicotinohydrazide1 was prepared by the reaction of isonicotinohydrazide and appropriate aromatic aldehyde in the presence of glacial acetic acid by using silica gel as a solid support under microwave irradiation. The

hydrazide 1 on treatment with acetic anhydride under microwave irradiation using silicagel as solid support resulted in the formation of the desired compound **1-(2**-(substituted- phenyl)-5-(pyridin-4-yl)-1, 3, 4-oxadiazol-3(2h)-yl) ethanone. The cyclization reactions progressed efficiently to completion giving very good yields within a few minutes. The products were obtained with a high degree of purity by this procedure and no further purification was required. The experimental procedure is very simple. The process is environmentally benign.

The structures of these synthesized compounds were confirmed by their elemental and spectral analysis. In general, infrared spectral data (n, cm–^{1}) revealed bands at 3105-3055 (Aromatic CH-Ar str.), 1685-1640 (C=O, stretching acetyl), 1662-1630 (C=N stretching), 1560-1523 (C=N stretching of pyridine), 1470-1422 (C-O-C, stretching of 1, 3, 4-oxadiazole), 1258-1238 (O-CH_3 stretching). In the nuclear magnetic resonance spectra (^{1}H NMR, δ ppm), the signals of the respective protons at 8.24- 8.68 (s,1H, CH-oxadiazole), 1.89-2.08 (s, 3H, OCH_3, 1,3,4-oxadiazole) were verified on the basis of their chemical shifts. Multiple signals between δ 6.32-8.04 δ ppm confirmed the presence of aromatic protons. Other signals were observed at 7.72-8.86 indicated the presence of pyridine ring in the compound. Further, the molecular ion recorded MS (m/z+) [M^+] in the mass spectrum is also in agreement with the molecular mass of the compounds.

All the synthesized compounds **2a-l** were tested against two gram-positive bacterial strains *i.e. S. aureus* and *B. subtilis* and two Gram-negative bacterial strains *i.e. E. coli, P. aeruginosa* . The results were compared with standard drug Ciprofloxacin as depicted in Table-**2**. Compound (**2b) 1**-(2-(4-fluorophenyl)-5-(pyridin-4-yl)-1, 3, 4-oxadiazol-3(2H)-yl) ethanone is active on all the four bacterial strains i.e. *E.coli, P. aeruginosa, B .subtitis* and *S .aureus.* The most active antibacterial agent against *E.coli* and *P. aeruginosa* found to be compound **(2c)** 1-(2-(4-chlorophenyl)-5-(pyridin-4-yl)-1, 3, 4-oxadiazol-3(2H)-yl) ethanone. Similarly compound **(2h)** 1-(2-(4-hydroxyphenyl)-5-(pyridin-4-yl)-1, 3, 4-oxadiazol-3(2H)-yl) ethanone is highly active on *B .subtitis* and *S .aureus* bacterial strains.

Table 1: Physical data and Rf values of synthesized compounds

S.No.	Compo Und No.	Molecular formula	M. Wt	Microwave Method		M.P °C ±1	R_f
				Time (min)	Yield (%)		
1	2a	$C_{15}H_{13}N_3O_2$	267	**8.50**	92	232	0.65
2	2b	$C_{15}H_{12}FN_3O_2$	285	9.45	94	189	0.68
3	2c	$C_{15}H_{12}ClN_3O_2$	301	7.00	94	158	0.72
4	2d	$C_{15}H_{12}ClN_3O_2$	301	10.30	88	178	0.70
5	2e	$C_{15}H_{12}N_4O_4$	312	11.00	92	201	0.68
6	2f	$C_{15}H_{12}N_4O_4$	312	9.30	88	198	0.65
7	2g	$C_{15}H_{12}N_4O_4$	312	8.30	90	188	0.64
8	2h	$C_{15}H_{13}N_3O_3$	283	8.45	92	206	0.66
9	2i	$C_{15}H_{13}N_3O_3$	283	12.00	88	210	0.74
10	2j	$C_{16}H_{15}N_3O_3$	297	10.30	88	209	0.68
11	2k	$C_{17}H_{18}N_4O_2$	310	12.30	90	234	0.72
12	2l	$C_{13}H_{11}N_4O_2$	257	9.30	85	204	0.62

All the synthesized compounds **2a-l** were also tested against, *C.albicans, A. niger* and found that compounds showed varying degree of inhibition. The results were compared with the standard drug Ketoconazole as reported in Table-2. The compounds (2**e)** 1-(2-(4-nitrophenyl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2H)-yl)ethanone, **(2 i)** 1-(2-(3-hydroxyphenyl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2H)-yl)ethanone and **(l).** 1-(2-(3-(dimethylamino) phenyl)-5-(pyridin-4-yl)-1, 3, 4-

oxadiazol-3(2H)-yl) ethanone found to be active against both the fungal strains i.e. *C.albicans* and *A. niger*,. On the basis of biological activity results, it may be concluded that the introduction of F, Cl, OH and NO_2, groups to the heterocyclic frame work enhanced antibacterial and antifungal activities. On the basis of their excellent inhibition it may be concluded that these 1, 3, 4-oxadiazol derivatives may serve as lead compounds for drug designing against these bacterial and fungal strains.

Table No.2: Antimicrobial Activity of the compounds. (1a-f)

Compd.	Drug/ µg/mL	Antibacterial activity (zone of inhibition in mm)				Antifungal activity (zone of inhibition in mm)	
		E.coli	***P. aeruginosa***	***B .subtitis***	***S .aureus***	***C.albicans***	***A. niger***
2a	50	10	08	10	10	10	08
	100	15	12	12	12	12	10
	200	18	14	15	14	16	12
2b	50	12	12	10	12	10	08
	100	20	21	15	16	12	12
	200	26	26	24	23	16	16
2c	50	12	12	14	14	18	18
	100	20	20	16	16	20	20
	200	27	27	22	22	21	22
2d	50	12	12	14	14	14	14
	100	16	17	16	18	16	18
	200	18	20	20	20	21	21
2e	50	12	12	14	14	18	18
	100	17	18	18	18	22	22
	200	22	22	20	20	26	26
2f	50	12	14	13	10	12	13
	100	18	18	16	18	14	14
	200	20	20	20	20	22	22
2g	50	12	13	12	12	12	13
	100	16	16	14	16	19	18
	200	22	22	20	19	22	22
2h	50	14	15	17	16	13	13
	100	20	20	23	22	18	18
	200	22	22	26	26	20	20
2i	50	14	12	14	14	14	14
	100	16	16	20	18	20	21
	200	18	20	20	22	24	24
2j	50	10	08	10	10	10	08
	100	15	12	12	12	12	10
	200	18	14	15	14	16	12
2k	50	10	08	10	10	10	08
	100	15	12	12	12	12	10
	200	18	14	15	14	16	12
2l	50	10	08	10	10	17	17
	100	15	12	12	12	21	21
	200	18	14	15	14	24	24
Control		03	03	03	02	02	02
Stand.1	50	28	28	30	30	-	-
Stand.2	50	-	-	-	-	28	26

Stand.1 = Ciprofloxacin ; Stand.2 = Ketoconazole

Table No.3: Anti-inflammatory Activity of the synthesized compounds (1a-f).

S.No	Compd	Dose mg /kg	Paw volume (in mL) after min (Mean± S.E.M.)				Inhibition after(min) (Mean± S.E.M.)		
			00	60	120	180	60	120	180
1	Control	0.1% 3ml/kg	0.60 ±0.022	0.76 ± 0.036	0.85 ±0.14	0.96 ± 0.36	-	-	-
2	Diclofenace Sodium	50	0.58 ±0.024	0.67 ± 0.022	0.62 ± .024	0.64 ± 0.24	43.75	52.00	83.33
3	2a	50	0.58 ±0.026	0.69 ±0.22	0.73 ±0.24	0.78±0.20	31.25	40.00	44.45
4	2b	50	0.59 ±0.22	0.69 ±0.24	0.72 ±0.26	0.76 ±0.28	37.50	48.00	52.77
5	2c	50	0.56 ±0.16	0.67 ±0.14	0.70 ±0.12	0.72 ±0.16	31.25	44.00	55.56
6	2d	50	0.64 ±0.20	0.75 ± 0.24	0.77 ± 0.18	0.79 ±0.22	31.25	48.00	58.34
7	2e	50	0.63 ±0.02	0.73 ±0.06	0.76 ±0.04	0.78 ±0.06	37.50	48.00	58.34
8	2f	50	0.62 ±0.14	0.74 ±0.16	0.76 ±0.14	0.78 ±0.12	25.00	30.56	55.56
9	2g	50	0.65 ±0.20	0.76 ±0.18	0.80 ±0.16	0.78 ±0.20	31.25	40.00	58.34
10	2h	50	0.60 ±0.22	0.70±0.24	0.73±0.26	0.72 ±0.24	37.50	48.00	66.67
11	2i	50	0.62 ±0.24	0.72±0.20	0.76±0.22	0.75 ±0.24	37.50	44.00	63.89
12	2j	50	0.61 ±0.24	0.70 ±0.22	0.73 ±0.24	0.67 ±0.26	43.75	56.00	83.34
13	2k	50	0.60 ±0.20	0.69 ±0.22	0.72 ±0.20	0.69 ±0.26	43.75	52.00	75.00
14	2l	50	0.56 ±0.20	0.67 ±0.24	0.72 ±0.022	0.76±0.22	31.25	36.00	44.45

Table- 4: Analgesic activity of synthesized compounds (2b-k) .

Compound.	Dose mg/kg	Before Administration of drug (Mean± S.E.M.)	After Administration of drug (Mean± S.E.M.)	Protection %
Control	(0.1% 3ml / kg i.p.)	56.00 ± 0.3	-----	-----
Standard	50	60.20 ± 0.24	10.00 ± 0.26	83.92
2b	50	62.40 ± 0.64	29.40 ± 0.62	52.88
2c	50	61.40 ± 0.44	27.60 ± 0.40	55.04
2d	50	64.20 ± 0.48	27.40 ± 0.40	57.32
2e	50	57.60 ± 0.62	25.20 ± 0.68	56.25
2f	50	56.40 ± 0.40	23.60 ± 0.38	58.15
2g	50	56.40 ± 0.42	22.60 ± 0.38	59.92
2h	50	58.60 ± 0.64	20.60 ± 0.60	64.84
2i	50	61.60 ± 0.62	22.20 ± 0.68	63.64
2j	50	66.40 ± 0.40	11.80 ± 0.38	82.23
2k	50	64.60 ± 0.42	14.80 ± 0.38	77.08

CONCLUSION

Exhaustive pharmacological studies have been conducted with the 1, 3, 4-oxadiazole derivative. The 2 and 5-position are an extremely important site of molecular modification, which play a dominant role in determining the pharmacological activates of 1, 3, 4- oxadiazole derivatives. Synthesized compounds 2a-l exhibited good anti-inflammatory activity (44.45– 83.34 % protection) against carragenean induced paw edema, whereas the standard drug diclofenac sodium (Novartis Laboratories, India) showed 83 % inhibition under similar conditions. Among the compounds tested, compounds (**2j)** 1-(2-(4-methoxyphenyl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2H)-yl)ethanone exhibited highest (83.34 %) anti-inflammatory activity, while compound(**2k)** 1-(2-(4-(dimethylamino)phenyl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2H)-yl)ethanone and (**2h)** 1-(2-(4-hydroxyphenyl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2H)-yl)ethanone showed good (75, and 66 %) anti-inflammatory activity. Synthesized compounds **2b-l** exhibited good analgesic activity (52 to 82 %).

The presence of methoxy group at 2-position and pyridine group at 5-position shown highest analgesic activity of 1, 3, 4-oxadiazole derivative. . However, still need some more novel

approach towards the functional group at the SAR to explore the pharmacological activity.

Acknowledgements
The authors are thankful to Dr.Suman Jain, Director of shri ram college of Pharmacy, for providing laboratory facilities authors are also thankful to Director, CDRI Lucknow, India for providing spectral and analytical data. Special thanks to Dr. Ashok Kumar Sharma (A.D.) Regional Disease Diagnostic Center, Kota (Rajasthan) for antimicrobial screening.

REFERENCES

[1] C. S. Andotra, T. C. Langer, S. Dham, P. Kour, *Ind. J. Pharma. Scie.*, **1994,** 56, (1) 19-24
[2] H. Chen, Z. Li, Y. Han, *J. Agri. and Food Chem.*, **200**,48: 5312–5315.
[3] A.O. Maslat,**.** M Abussaud, **H.** Tashtoush, M**.** Al-Talib,.*Pol.J.Pharmacool*, **2002,** 54,(1) 55-9
[4] F. Macaev, G. Rusu, S. Pogrebnoi, A. Gudima, E. Stingaci, L. Vlad, N. Shvets, F. Kandemirli, A. Dimoglo, R. Reynolds, *Bioorg. and Medic. Chem.* , **2005** 13: 4842-4850
[5] V.V. Mulwad, Chaskar, C. Atul, *Ind. J. Chem*. **2006,** 45B(7) ,1710-15
[6] N. Anil, H. S. Mayekar, B. Yathirajan, B. K. Narayana, N. Sarojini, K. Suchetha, *Inte. J.Chem*.**2010**, l2 (1), 39-43
[7] A. S. Aboraia, H. M. Abdel-Rahman, . *Bioor. and Medi. Chem.*, **2006,** 14, 1236-1246.
[8] S. Ke, F. Liu, N. Wang, Q. Yang, X. Qian, *Bioorga. and Medic. Chem. Lette.*, **2009,** 19 (2): 332-335
[9] A. Zarghi, Z. Hajimahdi, S. Mohebbi, H. Rashidi, S. Mozaffari, M. Sarraf , S.A. Faizi , S. A. Tabatabaee, *Chem. and Pharma. Bull.*, 2008,56, (4), 509-512.
[10] S. Ke, Z. Li, X. Qian, *Bioorg. and Medic. Chemi.* **2008,** 16, (16):7565-7572
[11] A. Kumar, S. Singh, M. Verma, A.K. Saxena, K. Shanker, *Indi.J.Pharm. Sci*., **1987,** 49, (6), 201-204
[12] G. Nagalakshmi, *Indi. J. Pharma. Sci.*, **2008,** 70, 1 , 49-55
[13] B. Narayana, V.K. Raj , B. V. Ashalatha,. K.N. Suchetha, *Archive der Pharmazie – Chemistry in Life Sciences*, 2005, 338: 373-377.
[14] H. Rajak, M. D. Kharya, P. Mishra, *J. Phar. Soc. Japan*, **2007,** 127,(10), 1757-1764.
[15] D. Dewangan, A. Pandey, T. Sivakumar, T. Rajavel, R. D. Dubey,; Int. J. Chem.Tech Res., **2010** ,2(3) 1397-1403
[16] T. P. Mohan, B. Vishalakshi, K. S . Bhat , K. S . Rao, G. N. Kendappa, *India J Chem* **2004**, 43B, 1798-801.
[17] A. H., M. Ajmal, *Acta Pharm.***2009,** 59, 223–233
[18] S.Wagle, A.A. Vasudeva, N.K. Suchetha, Ind. *J. Chem.*, **2008;** 47B, 439-48.
[19] R. Betarbet, T. Sherer, G. MacKenzie, M. Garcia-Osuna, A. Panov, *Nature neuroscience* **,** , **3,** 1301-1306
[20] B.A. Johns, J.G. Weatherhead, S.H. Allen, J.B. Thompson, E.P. Garvey, S.A. Foster J.L.Jeffrey, W.H. Miller, *Bioorg . Med .Chem. Lett*. **2009,** 15, 19 (6): 1807-10
[21] W.A. El-Sayed, F.A. El-Essawy, O.M. Ali, B.S. Nasr,M.M. Abdalla, A.A. Abdel-Rahman, *Z Naturforsch C* . **2009** , 64 (11-12), 773-8
[22] N. N. Pesyan and A.H. Dabbagh, *Molecules* **2005**, *10*, 1364-1368
[23] A.H. Kategaonkar, S.A. Sadaphal, K.A. Shelke, B.B. Shingate,M.S. Shingare,, *Ukrainica Bioorganica Acta* ,**2009**,1,3-7
[24] E. Ramu, V. Kotra, N. Bansal, R. Varala and S. R. Adapa; *Rasyan j.chem*. **2008** , 1,1, 188-194
[25] D. Shriram, P. Yogeeswari, K. Mandu, *Bioorg.Med.Chem.Letters*, **2005,** 15, 15, (20), 4502-5
[26] A.G. Nerkar, A.K. Saxena, S.A. Ghone and A.K. Thaker, *E-Journal of Chemistry*,

2009, 6(S1), S97-S102
[27] R. Chuickshank, J.P. Dugid, D.P. Marmon and R.H.Swain, (Churchill-livingstone, Edinburgh, Londone) In Medical Microbiology, **1975**, 2.
[28] National Committee for Clinical Laboratory Standards (NCCLs). Standard methods for dilution antimicrobial susceptibility tests for bacteria, which grows aerobically, *Nat. Comm. Lab. Stands*. Villanova, 242, **1992**.
[29] C. Perez,M. Paul, and P. Bezique, *Alta. Biomed*. **1990,** 15, 113.
[30] C.A.Winter, E.A. Risley andg.w. Nuss, *Proc Soc Exp Bio. Med. N Y*, 111, **1962**, 544.
[31] R. A. Turner, . Screening Methods in Pharmacology; Academic Press: New York and London, **1965**; p 100.
[32] M.N. Ghose, Evolution of Analgesic agents, Fundamentals of experimental Pharmacology , 2nd ed. , Calcutta, Scientific Book Agency, **1984**