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Synthesis and characterization of some novel 1,3,4-oxadiazole for anti-inflammatory activity

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Abstract
A series of five-membered heterocyclic rings were synthesized by the reaction between 2[(4-chlorophenyl) acetyl] benzoic acid and and $SOCl_2$ produced acid chloride and the acid chloride on reaction with substituted aromatic acid to form (3a-3d) compounds and was tested for their anti-inflammatory activity determined by rat-paw-oedema method. All the synthesis compounds have been characterized by ^{1}HNMR, IR and Mass spectral data. The compounds were purified by column chromatography. All synthesized derivatives were determined by the carrageenan-induced rat-paw-oedema model for anti-inflammatory activity. The entire compound gives good response for the anti-inflammatory activity: **2**-(4'-Chloro-phenyl)-1-[2-(5"-phenyl-[1, 3, 4] oxadiazol-2-yl) phenyl]-ethanone (3b), and (2-(4'-Chloro-phenyl)-1-{2-[5"-(4-nitrophenyl)-[1, 3, 4] oxadiazol-2-yl]-phenyl}-ethanone) (3c). For this activity, indometacin was used as a standard drug and compared to new synthesized drugs. Some new synthesized drugs have shown better activities for the anti-inflammation.

Keywords: 1, 3, 4-Oxadiazoles, Anti-inflammatory, Indometacin, Paw-oedema

Introduction
1, 3, 4-oxadiazole derivatives are heterocyclic compounds containing one oxygen and two nitrogen atoms in a five-membered-ring. 1,3,4-oxadiazole derivatives have played a major role in the pharmaceutical chemistry. The number of so many synthetic compounds with oxadiazole nucleus used for antibacterial [1-5], antifungal [6-9], analgesic and anti-inflammatory activities [10-13]. Derivatives of 1,3,4-oxadiazole with suitable substitution at 2,5-position have already been reported to have possible biological activities. 1,3,4-oxadiazole derivatives act as anticonvulsant and diuretics [14]. These observations and our interest in the pharmaceutical chemistry of heterocyclic compounds promoted us to have synthesized different derivatives of 1,3,4-oxadiazole with different substituent at 2 and 5-positions. These derivatives have been also screened for their anti-inflammatory activity. Mostly, five-membered-ring aromatic systems having three heteroatoms at symmetrical position have been studied because of their physiological properties [15-16]. It is also well established that various derivatives of 1,3,4-oxadiazole exhibit broad spectrum of pharmacological properties such as antibacterial and antifungal activities [17-18]. 1,3,4-oxadiazole showed antibacterial properties similar to those of well known sulphonamide drugs [19].

Experimental
All melting points were determined using open capillaries in a liquid paraffin bath and were uncorrected. The completion of reaction was monitored frequently by thin layer chromatography (TLC) using silica gel-G as absorbent and Toluene: Ethyl acetate (75:25) was employed as mobile phase. The visualization of TLC was accomplished by UV light and Iodine. IR spectra (KBr pallet) were recorded on FT-IR, Perkin Elmer RX1 spectrophotometer and NMR spectra on BRUKER AVANCE II (400 MHz) using TMS as internal standard (chemical shifts in δ ppm). The mass spectrums of compounds were recorded on Waters, Q-TOF, Micro mass LC-MS spectrophotometer.

Materials and Methods

Synthesis Procedure

Synthesis of 2-[2-(4'-Chloro-phenyl)-acetyl]-benzoic acid hydrazide (2):

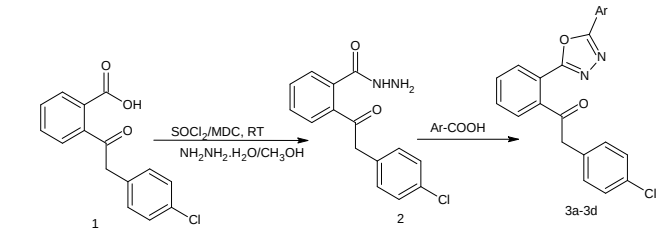
Compound **1** (2.37 g, 0.01 mol) and SOCl2 (2.17g 0.03 mol), MDC in 100 mL round bottom flask were stirred for 30 mins at room temperature to obtained acid chloride of compound **1**. Excess of reagent and solvents were distilled off. Acid chloride and excess of hydrazine hydrate in dry methanol were transferred in 100 mL round bottom flask and subjected for Microwave irradiation for 4-5 mins. After completion of the reaction (monitored by TLC), the reaction mixture was cooled, poured on crushed ice, on neutralization of the contents with sodium bicarbonate solution (20%) a solid mass separated out, which was filtered, washed with water, dried and recrystallized from methanol to get **2.** Yield 75 %, m.p. 224-226℃

Synthesis of 2-(4'-Chloro-phenyl)-1-{2-[5"-(substituted-phenyl)-[1, 3, 4] oxadiazol-2-yl]-phenyl} - ethanone (3 a-d):

Compound **2** (14.425g, 0.01 mol) was dissolved in phosphorous oxychloride (50mL) and to it was added substituted aromatic acid (0.05 mol). The reaction mixture, after refluxing for 6 hrs, was cooled to room temperature and poured onto crushed ice. The product was isolated in a similar manner as described above to obtain the desired product.
Under similar conditions 3a-d were prepared.

Current working scheme

Molecular formula	Elemental analysis					
	Calculate			Found		
	C	H	N	C	H	N
$C_{23}H_{17}O_2N_2Cl$	71.04	4.38	7.21	71.46	4.56	7.96



1 2-[(4-chlorophenyl)acetyl]benzoic acid

2 2-[(4-chlorophenyl)acetyl]benzohydrazide

Ar:
3a: Phenyl; 3b: 4-methylphenyl; 3c: 4-nitrophenyl; 3d: 4-hydroxyphenyl

Anti-inflammatory activity screening [20]

The anti-inflammatory activity was assessed as suggested by Winter *et al*. 26 by using carrageenan as edematogenic agent on adult albino rats of either sex weighing between 125-150g. The selected albino rats were housed in groups of six each in acrylic cages under laboratory conditions. The test compounds were administered intraperitoneally in the form of suspension with tween-40 and normal saline at a dose of 50mg/kg b.w. The Diclofenac sodium 10mg/kg was used as reference standard and administered in a similar manner. The control group received the solvent (tween-40 + normal saline) at 2ml/kg b.w. in a similar manner. All the test samples were administered 30mins before injection of carrageenan (0.1ml of 1% w/v in normal saline) into the sub-plantar region of left hind paw of each rat.

The contra-lateral paw was injected with an equal volume of saline. The increase in paw swelling (volume) was determined by plethysmometer by calculating the difference between the volumes of the mercury displaced by the two paws in ml. The increase in paw volume was measured at 1, 2 & 3 hrs after the administration of the test compounds. The percentage protection of edema was calculated at the end of 3 hrs as per the following formula.

$$\%\ of\ protection = \frac{P_c - P_t}{P_c} \times 100$$

Where P_c = Increase in paw volume at time't' of solvent control & P_t = Increase in paw volume at time't' of test.

Result and Discussion

Physicochemical properties

Table 1: Physical data of 2-(4'-Chloro-phenyl)-1-{2-[5"-(substitutedphenyl)-[1, 3, 4] oxadiazol-2-yl]-phenyl}- ethanone

Compound	Ar	Mf	MW	MP	% yield
3a	Phenyl	C22H15O2N2Cl	374.5	190	58
3b	4-methylphenyl	C23H17O2N2C	388.5	138	63
3c	4-nitrophenyl	C22H15O3N3Cl	419.5	180	62
3d	4-hydroxyphenyl	C22H15O3N2Cl	390.5	300	63

Compound 3a 2-(4'-Chloro-phenyl)-1-[2-(5"-phenyl-[1, 3, 4] oxadiazol-2-yl) phenyl]-ethanone

White compound obtained was found to have the molecular composition $C_{22}H_{15}O_2N_2Cl$ showed the following results on elemental analysis.

Elemental analysis of the compound (3a)

Molecular formula	Elemental analysis					
	Calculate			Found		
	C	H	N	C	H	N
$C_{22}H_{15}O_2N_2Cl$	70.49	4.01	7.48	70.65	4.23	7.96

IR (cm^{-1}): 3040(CH), 2984, 1675 (C=O), 1238 (N-N=C), 1095 (C-O-C)
^{1}H NMR interpretation ((δ ppm)): 4.70 (s, 2H, CH_2); 7.24-8.3 (m, 13H, Ar-H)
^{13}C NMR (δ ppm): 50.2 (CH_2); 122-139 (ArC); 156 C=N), 158 (C=N), 195.4(C=O)
Mass interpretation: m/e: M^+ 374.9
Compound 3b (2-(4'-Chloro-phenyl)-1-[2-(5"-p-tolyl-[1, 3, 4] oxadiazol-2-yl)-phenyl]-ethanone)
White compound obtained was found to have the molecular composition $C_{23}H_{17}O_2N_2Cl$ showed the following results on elemental analysis.

Elemental analysis of the compound (3b)

IR (cm^{-1}): 1690 (C=O), 1665 (C=O), 1245 (N-N=C), 1090 (C-O).
^{1}H NMR (δ ppm): 2.35 (s, 3H, CH_3), 4.78 (s, 2H, CH_2), 7.34-8.40 (m, 12H, ArH)
^{13}C NMR (δ ppm): 20.9 (CH3), 54.2 (CH2), 120.6-140.5 (ArC), 155.3(C=N),
158.5(C=N), 196.6 (C=O)
Mass: m/e: M+ 388.5
Compound 3c (2-(4'-Chloro-phenyl)-1-{2-[5"-(4-nitrophenyl)-[1, 3, 4] oxadiazol-2-yl]-phenyl}-ethanone)
Yellow compound obtained was found to have the molecular

composition $C_{22}H_{14}O_4N_3Cl$ showed the following results on elemental analysis.

Elemental analysis of the compound (3c)

Molecular formula	Elemental analysis					
	Calculate			Found		
	C	H	N	C	H	N
$C_{22}H_{14}O_4N_3Cl$	63.08	3.58	13.38	63.56	4.95	13.99

IR (cm^{-1}):1680 (C=O), 1560-1340 (NO_2), 1230 (N-N=C), 1085 (C-O).
^{1}H NMR (δ ppm): 4.79 (s, 2H, CH_2), 7.54- 8.65 (m, 12H, ArH)
^{13}C NMR (δ ppm): 50.2 (CH_2), 127.3-145.5 (ArC), 156.2 (C=N), 159.2 (C=N),
195.4 (C=O)
Mass: m/e: M+ 419.5
Compound 3d (1-{2-[5"-(4'-Hydroxy-phenyl)-[1, 3, 4] oxadiazol-2-yl]-phenyl}-2-phenyl-ethanone

White compound obtained was found to have the molecular composition C22H15O3N2Cl showed the following results on elemental analysis.

Elemental analysis of the compound (3c)

Molecular formula	Elemental analysis					
	Calculate			Found		
	C	H	N	C	H	N
C22H15O3N2Cl	67.61	3.84	7.17	67.98	3.94	7.65

IR (cm^{-1}): 3310 (OH), 3010 (CH); 1670 (C=O), 1242 (N-N=C), 1090(C-O)
^{1}H NMR (δ ppm): 4.81 (s, 2H, CH_2), 5.45 (s, 1H, OH), 7.50-8.56 (m, 12H, ArH);
^{13}C NMR (δ ppm): 50.2 (CH_2); 128.2-149.6 (ArC), 156.3(C=N), 159.5 (C=N), 195.4(C=O)
Mass: m/e: m/e: M+ 390.5

Anti-inflammatory activity

Table 2: Anti-inflammatory activity of 1,3,4-oxadiazole derivatives (3a, 3b, 3c and 3d) In Rats by Carrageenan induced hind paw edema model

Sl. No.	Compound	Increase in paw vol (ml)			% protection at 3h
		1h	2h	3h	
1	Solvent	0.48±0.02	0.73±0.03	0.78±0.01	
2	Diclofenac	0.38±0.02**	.0.33±0.04***	0.28±0.03***	64.10
3	**3a**	0.24±0.03***	0.29±0.01***	0.27±0.03***	65.38
4	**3b**	0.36±0.03**	0.49±0.06**	0.47±0.02***	39.74
5	**3c**	0.27±0.03***	0.34±0.05***	0.31±0.05***	60.25
6	**3d**	0.29±0.02***	0.40±0.01***	0.39±0.05***	50.00

Values expressed as Mean ± SEM, n=6, *p<0.05, **p<0.01, ***p<0.001, Dose of the test compound: 50 mg/kg.

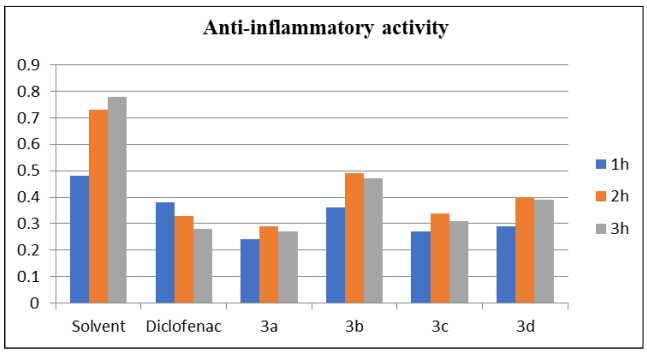


Fig 1

Discussion
Four novel 1, 3, 4-oxadiazole derivatives were synthesized by taking 2[4-chloriophenyl)acetyl] benzoic acid. All synthesized compound were analyzed for their phycochemical characteristics and spectral analysis like IR, H NMR, C NMR and Mass spectroscopy.
The anti-inflammatory activity of present synthesized compounds was evaluated by carrageenan induced acute inflammatory method in rats on comparison with standard diclofenac sodium. The result revealed that the all synthesized compounds shown anti-inflammatory activity (*p<0.05, **p<0.01, ***p<0.001) when compare to control and positive control group. These showed the percentage protection of edema ranges between 39.74 and 65.38 at the end of 3 hrs; where as the standard drug Diclofenac sodium registered 64.10% (Table – 2). It has been observed that the maximum anti-inflammatory activity was recorded by the compound **3a** having 65.38% percentage protection of edema followed by compound **3c** (60.25 %), **7d** (50 %) & **7b** (39.74%) anti-inflammatory potential. The compound **32a** showed more percentage protection of edema than that of standard drug Diclofenac sodium. It has been found that the extent of increase in paw volume reduces significantly up to 3 hrs when compared with solvent control.

Conclusion
The present study concluded the beneficial effect of synthesized novel 1, 3, 4-Oxadiazole derivatives in the Carrageenan induced acute inflammation in rats.
This study confirms the rational basis for its use in synthesized 1, 3, 4-Oxadiazole and its derivatives for the treatment of inflammation in patients. Further pharmacological investigations are under way to characterize active novel 1, 3, 4-Oxadiazole and to establish exact mechanism of inflammation action, which may have fewer side effects. This work, we believe, will be useful for further inflammation research works.

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