Synthesis and Antiinflammatory Activity of 3-Aryl-5-Isopropyl-1,2,4-Oxadiazoles

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Abstract: Seven 4,5-dihydro-1,2,4-oxadiazoles **3a-g** have been synthesized from arylamidoximes **1a-g** and isobutyraldehyde **2** in the presence of an acid catalyst (IRP-64). Oxidation of **3a-g** either with MnO_2 or with nitric acid provided **4a-g**. Compounds **3b,c,f,g** and **4b,c,e-g** have not been reported in the literature. All seven oxadiazoles **4a-g** showed antiinflammatory activity.

Introduction

1,2,4-Oxadiazoles have been the subject of research for more than a century since the initial syntheses of oxadiazoles were achieved [1,2]. The subject has been reviewed twice by Clapp [3,4]. Search for newer and more efficient methods for the oxadiazole synthesis continues [5a-g]. A large number of 1,2,4-oxadiazole derivatives possess different pharmacological properties [3,4] including analgesic and antiinflammatory activities [6,7]. In this paper, we describe the synthesis of seven 4,5-dihydro-1,2,4-oxadiazoles and seven 1,2,4-oxadiazoles (Figure 1). The latter compounds have been examined for antiinflammatory activity and six of them, viz., **4a-c,e-g** showed reasonable activity.

Results and Discussion

Chemistry: The Synthesis of 4,5-dihydro-1,2,4-oxadiazoles **3a-g** was carried out following the literature procedure [8], but with modification. The modification involved the addition of Amberlite IRP-64 (carboxylic acid form). This acid catalyzed the reaction and reduced the reaction time from ten to three days. Although, it was assumed earlier that the reaction of an amidoxime with an aldehyde is acid-catalyzed [8], it's effect has been demonstrated experimentally in the present work. A literature search showed that two oxadiazolines **3d,e** have been synthesized by another method [9] while **3a** was prepared long ago [10]. The melting points, crystallization solvents and elemental analyses are given in Table 1. Tables 2 and 3 contain ^{1}H- and ^{13}C NMR chemical shifts [11].

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Table 1. Physical properties and elemental analyses of compounds **3a-g** and **4a-g**.

Compd.	mp (°C)	Yield (%)	Formula	Calcd. (%)			Found (%)		
				C	H	N	C	H	N
3a	96.0-96.7[a]	84	$C_{11}H_{14}N_2O$	69.45	7.42	14.72	69.22	7.50	14.73
3b	68.8-69.2[a]	68	$C_{12}H_{16}N_2O$	70.57	7.89	13.71	70.50	7.63	13.58
3c	81.4-81.8[a]	79	$C_{12}H_{16}N_2O$	70.57	7.89	13.71	70.66	7.96	13.72
3d	107.7-108.3[a]	83	$C_{12}H_{16}N_2O$	70.57	7.89	13.71	70.48	7.98	13.71
3e	124.5-124.9[a]	92	$C_{11}H_{13}N_2ClO$	58.79	5.83	12.46	58.61	5.64	12.41
3f	102.0-102.6[a]	90	$C_{11}H_{13}N_3O_3$	56.16	5.57	17.86	56.37	5.16	18.15
3g	113.6-113.9[a]	89	$C_{12}H_{16}N_2O_2$	65.43	7.32	12.72	65.42	6.95	13.18
4a	liquid[b,c]	84[d]	$C_{11}H_{12}N_2O$	70.20	6.42	14.88	70.22	6.62	14.52
4b	liquid[b]	78[d]	$C_{12}H_{14}N_2O$	71.26	6.98	13.85	71.45	6.99	13.87
4c	liquid[b]	76[d]	$C_{12}H_{14}N_2O$	71.26	6.98	13.85	71.28	7.18	14.06
4d	liquid[b]	76[d]	$C_{12}H_{14}N_2O$	71.26	6.98	13.85	71.34	7.21	13.63
4e	liquid[b]	95[d]	$C_{11}H_{11}N_2ClO$	59.32	4.98	12.57	60.03	5.11	12.39
4f	125.5-126.3[a]	81[d]	$C_{11}H_{11}N_3O_3$	56.65	4.75	18.02	56.88	4.73	18.06
4g	liquid[b]	93[d]	$C_{12}H_{14}N_2O_2$	66.04	6.47	12.84	66.42	6.58	12.61

[a] **3a-g** and **4f** were crystallized from chloroform-hexane. [b] The liquid was colorless and chromatographically pure. The combustion analyses were done after thorough drying of the samples. [c] The oxadiazole was prepared before (see ref. [10]). [d] The yields of oxadiazoles **4a-g** either by the MnO_2 or HNO_3 method are similar.

Next, we attempted to transform 4,5-dihydro-1,2,4-oxadiazoles **3a-g** to 1,2,4-oxadiazoles. We employed two methods: 1) using MnO_2 in CH_2Cl_2 [12a] and 2) employing concentrated HNO_3 in $CHCl_3$ at room temperature. Although both methods are mild and give excellent yields of **4a-g**, manganese dioxide has been claimed as a better reagent for the oxidation of 1,3,5-trisubstituted-2-pyrazolines to the corresponding pyrazoles [12b. The literature does not report the transformation of a 4,5-dihydro-1,2,4-oxadiazole to 1,2,4-oxadiazole using nitric acid. Although it has been reported [13] that nitric acid may contain other nitrogen oxides such as NO, N_2O_3, N_2O_4, and N_2O_5 as well as NO_2 and HNO_2. Some of these (NO, NO_2, etc.) are odd-electron species and hence initiate oxidation by abstracting a hydrogen atom either from N-4 or C-5 of a 4,5-dihydro-1,2,4-oxadiazole. The ^{1}H- and ^{13}C-NMR spectra of all these compounds agreed with their structures (Tables 2 and 3).

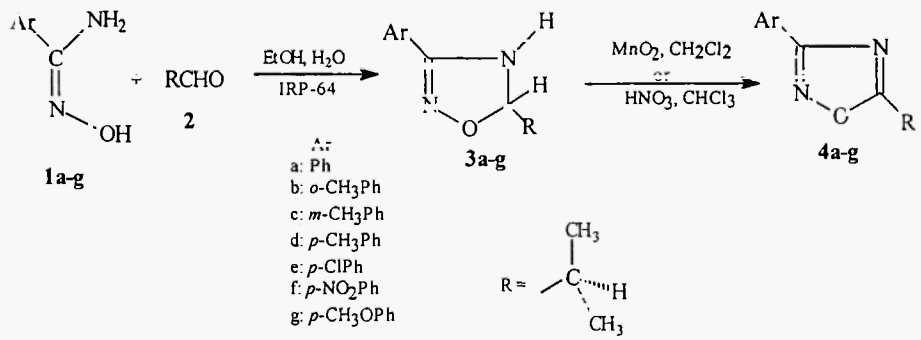


Figure 1. Reaction of arylamidoximes with isobutyraldehyde and oxidation of **3a-g** to **4a-g**.

Pharmacology: There has been a great interest for the last several years to discover new Non Steroidal Antiinflammatory Drugs (NSAIDs) which could specifically inhibit cyclooxygenase-2 (COX-2) responsible for producing prostaglandins which cause the symptoms associated with antiinflammatory process. A number of selective inhibitors of COX-2 have been reported and the search for new analogs continues [14]. Although, we have carried out

only preliminary tests against inflammation, our aim is to do *in vitro* tests to know with certainty the mode of action of these oxadiazoles, particularly **4c**, with an enzyme. Out of seven 1,2,4-oxadiazoles **4a-g** tested for antiinflammatory activity, three of them **4c,f,g** showed activities and were comparable with aspirin in terms of reducing inflammation. The other three, viz., **4a,b,e** were weaker than aspirin while **4d** didn't produce any significant antiinflammatory activity (Table 4).

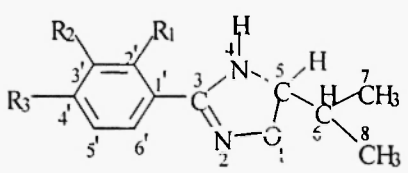
Table 2. Chemical shifts of the protons of compounds **3a-g** and **4a-g**

Compd.	$(CH_3)_2CH-$ [a]	$>CH$	$Ar-CH_3$	NH_2	$-\overset{1}{N}-CH-O-$	Ar
3a	1.00 1.01	1.94 m	–	4.72 b	5.45 t (J = 4.65 Hz)	7.36-7.45 m (3H) 7.36-7.70 m (2H)
3b	0.96 0.96	1.87 m	2.45 s	4.96 b	5.36 dd (J = 4.80 & 4.50 Hz)	7.12-7.31 m (3H) 7.43 dd (1H, J = 7.80 & 1.5 Hz)
3c	1.00 1.01	1.94 m	2.37 s	4.68 b	5.44 t (J = 4.8 Hz)	7.24-7.31 m (2H) 7.46-7.51 m (2H)
3d	0.99 1.00	1.93 m	2.38 s	4.74 b	5.43 dd (J = 4.50 & 4.20 Hz)	7.38[b] (AA'BB' system, J = 8.10 Hz)
3e	0.98 0.99	1.92 m	–	5.05 d (J = 3.6 Hz)	5.44 t (J = 4.8 Hz)	7.46[b] (AA'BB' system, J = 9.0 Hz)[c]
3f	1.02 1.03	1.98 m	–	4.65 d (J = 3.3 Hz)	5.54 t (J = 4.8 Hz)	8.10[b] (AA'BB' system, J = 9.0 Hz)[c]
3g[d]	1.00 1.01	1.93 m	–	4.61 d (J = 3.3 Hz)	5.41 t (J = 4.8 Hz)	7.27[b] (AA'BB' system, J = 9.0 Hz)[c]
4a	1.32 d[e]	3.27 sep.[f]	–	–	–	7.42-7.52 m (3H) 8.04-8.12 m (2H)
4b	1.46 d[e]	3.30 sep.[f]	2.62 s	–	–	7.25-7.42 m (3H) 7.95-8.02 m (1H)
4c	1.46 d[e]	3.29 sep.[f]	2.42 s	–	–	7.25-7.42 m (2H) 7.84-7.95 m (2H)
4d	1.46 d[e]	3.28 sep.[f]	2.41 s	–	–	7.62[b] (J = 8.45 Hz)
4e	1.46 d[e]	3.28 sep.[f]	–	–	–	7.74[b] (J = 8.70 Hz)
4f	1.49 d[e]	3.33 sep.[f]	–	–	–	8.31[b] (J = 9.0 Hz)
4g[g]	1.45 d[e]	3.27 sep.[f]	–	–	–	7.50[b] (J = 9.0 Hz)

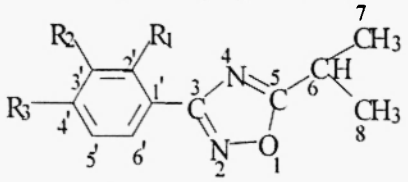
[a] The methyl groups are non-equivalent and gave doublet for each methyl group with J=6.90 Hz. [b] Mid-point chemical shift. [c] There are smaller signals present in the AA'BB' system which indicate that the splitting is of higher order. [d] The methoxy group signal absorbed at δ 3.84 ppm. [e] The methyl proton doublet has a J value of 6.90 Hz in all compounds. [f] Sep = septet. [g] The signal for the methoxy group appeared at δ 3.87 ppm.

Structure-Activity Relationships (SAR): To gain more insight about the antiinflammatory properties of this class of compounds, we tried to correlate the observed activities with some of their molecular properties. For the electronic structure calculations, we used the MOPAC 93 program [15] with the AM1 hamiltonian [16] and ChemSW Molecular Analysis Pro program [17] was used to calculate the lypophilic descriptors and for data treatment. All molecules had their geometry fully optimized and the final geometry was tested by gradients and vibrations to see whether or not the molecule is at a local energy minimum [18].

Table 3. ^{13}C NMR chemical shift assignments of 3-aryl-5-isopropyl-4,5-dihydro-1,2,4-oxadiazoles **3a-g** and **4a-g**.



3a-g



4a-g

a. $R_1=R_2=R_3=H$
b. $R_2=R_3=H$; $R_1=CH_3$
c. $R_1=R_3=H$; $R_2=CH_3$
d. $R_1=R_2=H$; $R_3=CH_3$
e. $R_1=R_2=H$; $R_3=Cl$
f. $R_1=R_2=H$; $R_3=NO_2$
g. $R_1=R_2=H$; $R_3=CH_3OPh$

Compd.	3	5	6	7 & 8	1'	2'	3'	4'	5'	6'	Ar–CH_3	CH_3O–
3a	156.5	97.9	34.4	17.1 & 17.0	126.3	127.1	129.3	131.4	129.3	127.1	–	–
3b	156.0	96.3	33.5	16.1	124.8	137.6	129.9	130.9	125.5	128.3	21.1	–
calcd.[a]					127.0	136.0	130.0	131.3	126.4	127.0		
3c	156.6	97.8	34.4	17.1 & 17.0	126.2	127.7	139.2	132.2	129.2	124.2	22.0	–
calcd.[a]					126.2	127.8	138.1	132.1	129.2	124.2		
3d	156.5	97.8	34.3	17.2 & 17.0	123.4	127.0	130.0	141.7	130.0	127.0	22.2	–
calcd.[a]					123.4	127.0	130.0	140.3	130.0	127.0		
3e	155.3	97.5	33.7	16.4 & 16.3	124.1	127.7	128.9	136.7	128.9	127.7	–	–
calcd.[a]					134.4	128.4	129.7	137.6	129.7	128.4		
3f	155.1	98.9	34.3	17.0 & 16.9	132.4	127.9	124.6	149.5	124.6	127.9	–	–
calcd.[a]					132.1	128.0	124.5	151.4	124.5	128.0		
3g	156.3	97.7	34.3	17.2 & 17.0	118.7	128.7	114.8	162.2	114.8	128.7	–	56.1
calcd.[a]					118.6	128.1	114.9	162.8	114.9	128.1		
4a	168.1	183.9	27.5	20.2	127.0	127.4	128.7	130.9	128.7	127.4	–	–
4b	168.7	182.7	27.4	20.2	129.5	138.1	130.0	130.4	125.9	131.3	22.0	–
calcd.[b]					127.7	136.3	129.4	130.8	125.8	127.3		
4c	168.2	183.8	27.5	20.2	126.9	127.9	138.5	131.8	128.7	124.5	21.3	–
calcd.[b]					126.9	128.1	137.6	131.6	128.6	124.5		
4d	168.1	183.7	27.5	20.2	124.2	127.3	129.5	141.2	129.5	247.3	21.5	–
calcd.[b]					124.1	127.3	129.4	139.8	129.4	247.3		
4e	167.4	184.1	27.5	20.2	125.5	128.7	129.1	137.1	129.1	128.7	–	–
calcd.[b]					125.1	128.7	129.1	137.1	129.1	128.7		
4f	166.6	184.8	27.4	20.1	133.0	128.3	124.0	149.3	124.0	128.3	–	–
calcd.[b]					132.8	128.1	123.9	150.9	123.9	128.1		
4g	167.8	183.6	27.5	20.2	119.5	129.0	114.1	161.7	114.1	129.0	–	55.3
calcd.[b]					119.3	128.4	114.3	162.3	114.3	128.4		

[a] The substituent chemical shifts' values have been taken from ref [11] and added to C-1', C-2', C-3', C-4', C-5' and C-6' of compound **3a**. The values thus obtained have been considered as calculated values. [b] Similarly, additions have been done in compound **4a** to get the calculated values.

Table 4. Biological tests results for the compounds **4a-g**.

Compound	Control	Aspirin	4[a]	4b	4c	4d	4e	4f	4g
Dose (mg/kg)	–	250	180	180	180	180	180	180	180
Average Paw Weight (g)	0.159	0.066[a]	0.130	0.136	0.098[a]	0.149	0.137	0.106[b]	0.109[b]
Inhibition (%)	–	58.49	18.24	14.47	38.37	6.29	13.84	33.34	31.45

[a] $P < 0.0001$; [b] $P < 0.001$

After an extensive search involving electronic and hydrophilic properties of the molecules, a set of molecular descriptors involving the charges on atoms C3, N4 and C5, the bond order between atoms O1 and C5, and the total dipole moment (μ) of the molecule was obtained, which provided a general equation with reasonable statistical values. The calculated values of these parameters are listed in Table 5. The multiple regression of these five descriptors using the observed biological (antiinflammatory) activity as the response parameter resulted in equation (1), with 96.78% of

the variance explained by the model (r^2) and 70% of probability that this model is not due to chance alone (prob. F). The values predicted from this equation are also listed in Table 5.

Table 5: Observed and predicted biological (antiinflammatory) activity of the compounds and the molecular descriptors chosen for SAR study.

Molecule	*Exp. BA*	*Calcd. BA*	*q (C3)*	*q (N4)*	*q (C5)*	*BO (O1-C5)*	*μ (D)*
4a	18.24	14.08	-0.04302	-0.15912	0.020882	1.045357	1.439
4b	14.47	14.72	-0.04677	-0.14964	0.015242	1.043271	1.910
4c	38.37	39.19	-0.04101	-0.16235	0.020315	1.046993	1.758
4d	6.29	7.70	-0.03935	-0.16295	0.020359	1.047546	1.417
4e	13.84	16.56	-0.04666	-0.15631	0.023036	1.04307	2.435
4f	33.34	32.91	-0.06454	-0.152	0.028584	1.040128	6.498
4g	31.45	30.82	-0.03505	-0.16067	0.020813	1.045165	2.893

$$BA = -8862.66\,q(C3) - 39283.1\,q(N4) - 35504.9\,q(C5) - 65164.1\,BO(O1\text{-}C5) + 8.00089\,\mu + 62231.7 \quad (1)$$
$$r^2 = 0.96782,\ F = 6.01444,\ Prob.\ F = 0.29968$$

Figure 2 plots the antiinflammatory activity values calculated *via* equation (1) *versus* the observed activity. The straight line in the figure is the linear fit of the values, resulting in equation (2).

$$BA_{Calcd.} = 0.71573 + 0.96777 \times BA_{obs.} \quad (2)$$
$$r = 0.98378,\ P < 0.0001$$

Both the correlation coefficient of the fit (r), and the angular coefficient of the equation approach unity. These values, combined with the low linear coefficient, show that the calculated values match well with the observed ones.

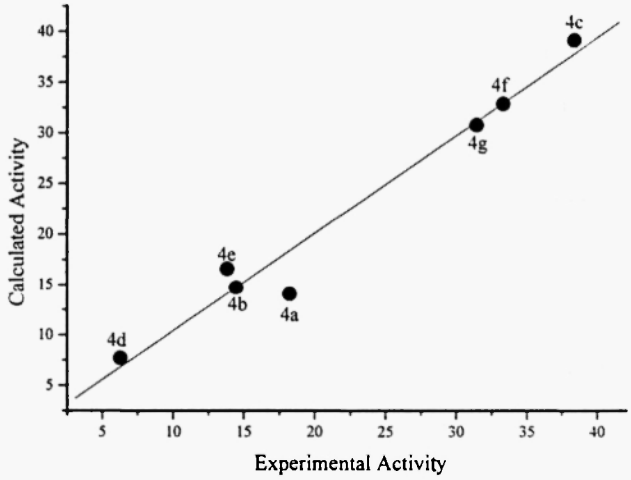


Figure 2. Predicted *versus* observed antiinflammatory activity

The results of our SAR study show a good correlation between the electronic properties and the antiinflammatory activity of 3-aryl-5-isopropyl-1,2,4-oxadiazoles, even though the statistical F values are somewhat low. Nevertheless, one should note that this is a preliminary study, and this model has been developed using only seven compounds, the addition of more experimentally tested molecules may give a better model and raise the F values significantly. A possible explanation is given below.

The biological activity of a drug involves an intricate path following administration, absorption, passage through a variety of hydrophilic and hydrophobic environments until it reaches its receptor (in case there is such interaction), binds to it and/or is metabolized and eventually excreted. A further complicating factor is whether or not the initial drug structure is the one that is ultimately responsible for its biological activity or one of its metabolites. We believe that a methyl group of the isopropyl function attached at C-5 of the 1,2,4-oxadiazole ring may oxidize *in vivo*. It is presumed that the oxidation would lead to a carboxylic acid. The literature does cite the conversion of the medium and long chain fatty acids to dicarboxylic acids (oxidation of the last carbon of the chain) [19]. This process, which is catalyzed by enzymes of the endoplasmic reticulum (microsomes), involves hydroxylation of a fatty acid's C_ω atom by

cytochrome P_{450}, a monooxygenase that utilizes the reduced form of Nicotinamide Adenine Dinucletotide Phosphate (NAPDH) and O_2. Once this oxidation of one of the methyl groups occurs, the compound will be antiinflammatory, because we already know that a carboxylic group in the side chain of C-5 of the oxadiazole is antiinflammatory [7].

Equation (1) provides us with a hint into what could be the type of interaction differentiating the biological activity of the molecules in Table 4. Such interaction could occur in any of the steps from administration of the drug until its excretion. We cannot know in which step is this interaction taking place or its details. Nevertheless, Equation (1) suggests that such interaction is perturbed in a way which increases the antiinflammatory activity if: (i) the slightly negative charge on C3 and the negative charge on N4 both become even more negative; (ii) the slightly positive charge in C5 becomes more neutral; (iii) the bond order between O1 and C5 is slightly weakened; (iv) the dipole moment of the molecule increases.

These five items which correspond to the five terms of Eq.(1) suggest that the step involved in the differentiation of the activities of seven molecules in Table 4, but not necessarily in the activity itself, is an environment with a positively charged region enveloping the 1,2,4-oxadiazole moiety of the molecules: their relative and differing abilities to deal with such an environment will determine how different their antiinflammatory activities will be. On the other side, the absence of a good correlation involving the hydrophobicity parameter used (ClogP) may be interpreted as an indication that this determining step may not be strictly dependant on it. For example, to reach their active site, the molecules may be transported by an active mechanism where the molecule is reversibly bound to a protein within the cell membrane (transporter) on one side, carrying the drug across the membrane and finally releasing the same on the other side [20].

Conclusion

We have been able to synthesize seven 4,5-dihydro-1,2,4-oxadiazoles **3a-g** and transformed them to 1,2,4-oxadiazoles **4a-g**. The latter showed antiinflammatory activity. One of them, **4c**, showed antiinflammatory potency comparable with aspirin's. The structure-activity relationships have been investigated and a good correlation has been found between the antiinflammatory activity and electronic properties of the heterocyclic ring.

Experimental

Melting points were determined with a digital Melting Point Apparatus, series 1A-9100, Electrothermal Engineering Ltd., England, and are uncorrected. Elemental analyses of all compounds were carried out by Mrs. Luzia Narimatsu, Instituto de Química, Universidade de São Paulo, SP. Infrared spectra were recorded on a Bruker spectrophotometer Model IFS66 and ^{1}H-NMR spectra were measured on a Varian Unity Plus Instrument, using $CDCl_3$ as solvent and TMS as an internal reference. Thin layer chromatography (tlc) was done on plates coated with silica gel g (Merck) having fluorescent indicator (F_{254}). The plates were developed with chloroform followed by the detection of the spots under uv light.

3-Aryl-5-isopropyl-4,5-dihydro-1,2,4-oxadiazoles 3a-g. General Method. To an appropriate amidoxime (3.67 mmol) in ethanol (3.0 to 6.0 ml) was added water dropwise until the solution turned slightly turbid, followed by the

addition of freshly distilled isobutyraldehyde (0.5 ml) and the catalyst Amberlitc IRP-64 (–COOH form). The contents were stirred for 24 h at room temperature and then another batch of aldehyde (0.5 ml) was added and stirring continued for an additional 48 h. During this period almost all amidoxime was consumed. Filtration followed by crystallization from chloroform-hexane provided analytically pure material (See Table 1).

3-Aryl-5-isopropyl-1,2,4-oxadiazoles 4a-g. General Method.

(i) Oxidation with Manganese dioxide. Manganese dioxide (5.75 mmol) was added to an appropriate 4,5-dihydro-1,2,4-oxadiazole (1 mmol) in dichloromethane (~25 ml) and stirred for 30 min at room temperature. The thin layer chromatography showed the disappearance of the starting material. The contents were stirred for additional 30 min., filtered through a layer of celite and washed with dichloromethane. Evaporation of the filtrate left a residue (generally liquid), which was purified by chromatography over silica gel. The properties of **4a-g** are given in Table 1.

(ii) Oxidation with concentrated nitric Acid (65%). An appropriate oxadiazoline (0.5 mmol) was dissolved in chloroform (10 mL) and nitric acid (4 drops) were added to it. The contents were stirred at room temperature for 2h, neutralized with solid sodium bicarbonate. Tlc plate showed the disappearance of the starting material. After solvent evaporation, the material was quickly chromatographed on a short column of silica gel using chloroform as eluent to remove impurities. The yields are given in Table 1. Oxadiazoles obtained by this method showed comparable infrared and nmr spectra with that obtained by the oxidation with manganese dioxide.

Procedure for evaluating antiinflammatory activity. Levy's method [21] was employed for determining antiinflammatory activity. We used male or female mice for the experiments and no difference was observed due to the animal's gender. Nine batches of five to ten animals have been used. The number of experiments were 3, one for testing new compounds having seven mice in each case and two for control experiments; 0.1 mL of a 1% solution of carraginine was injected on the left back paw of each mouse to produce inflammation. Among three groups of animals, the first one received 180 mg/kg (suspension in oil) of the animal's weight of the compound intraperitoneally, the second group was given 0.5 mL of 0.9% of aqueous saline solution and the third group was given 250 mg of aspirin intraperitoneally (the use of aspirin as standard for comparative studies was made because this medicine is widely used for pharmacological tests [22]). Four hours later, the animals were sacrificed, their paws were cut and weighed. The results were analyzed according to percentage reduction of inflammation and are given in Table 4. Three compounds, viz., **4c,f,g** showed antiinflammatory activity comparable to aspirin's.

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