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Synthesis of Some Novel Oxadiazole and Oxadiazoline Analogues for Their Antiinflammatory Activity

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The search for newer non-steroidal antiinflammatory drugs (NSAIDs) and the importance of oxadiazoles as antiinflammatory agents prompted us to undertake the synthesis of some novel oxadiazole and related analogues with unreported antiinflammatory activities. The antiinflammatory potential of the compounds was investigated using the carrageenan-induced rat paw edema method and cotton pellet-induced granuloma method. Some compounds demonstrated marked antiinflammatory activities. The antiinflammatory activity of oxadiazoles at doses of 100 mg/kg was shown by their ability to provide 28–55%, 21–36%, and 27–49% protection against carrageenan-induced rat paw edema, moist cotton pellet-induced, and dry cotton pellet-induced granuloma, respectively. On the other hand, the antiinflammatory properties of oxadiazolines at doses of 100 mg/kg was reflected by their ability to provide 15–47%, 22–39%, and 23–47 % protection against carrageenan-induced rat paw edema, moist cotton pellet-induced, and dry cotton pellet-induced granuloma, respectively. Structure-activity relationships among synthesized compounds were also studied.

Key words——oxadiazole; oxadiazoline; antiinflammatory activity

INTRODUCTION

Non-steroidal antiinflammatory drugs (NSAIDs) are widely used for the treatment of pain, fever, and inflammation. The pharmacologic activity of NSAIDs is related to the suppression of prostaglandin biosynthesis from arachidonic acid by inhibiting the enzyme cyclooxygenases (COX). With the chronic use of NSAIDs, one prominent side effect is the formation of gastric ulcers. This adverse effect may be attenuated in the presence of an inhibitor of 5-lipoxygenases (5-LOs). 1,3,4-Oxadiazoles have antiinflammatory properties by virtue of a dual mechanism, *i.e.*, inhibiting both COX and LOs to reduce gastric ulcer formation.[1,2]

Numerous studies have been performed with the aim of exploring the antiinflammatory properties of 1,3,4-oxadiazole analogues.[3–7] Those studies found that 1,3,4-oxadiazole analogues are equipotent with phenylbutazone, naproxen and other NSAIDs. With the aim of finding a COX/LO dual inhibitor, which may have improved efficacy and fewer side effects compared with existing NSAIDs, we considered it of interest to synthesize novel 1,3,4-oxadiazole analogues to investigate their antiinflammatory activities. Compounds with an oxadiazole and oxadiazolin nucleus with a naphthalene-1-yloxymethyl substitution at the 5 position and substituted phenyl group at the 2 position have not been reported. Moreover, the synthetic strategy employed in their preparation is novel because no oxadiazole and oxadiazoline analogues with a naphthalene-1-yloxymethyl substitution have been prepared using oxidative cyclization with bromination in the presence of acetic acid.

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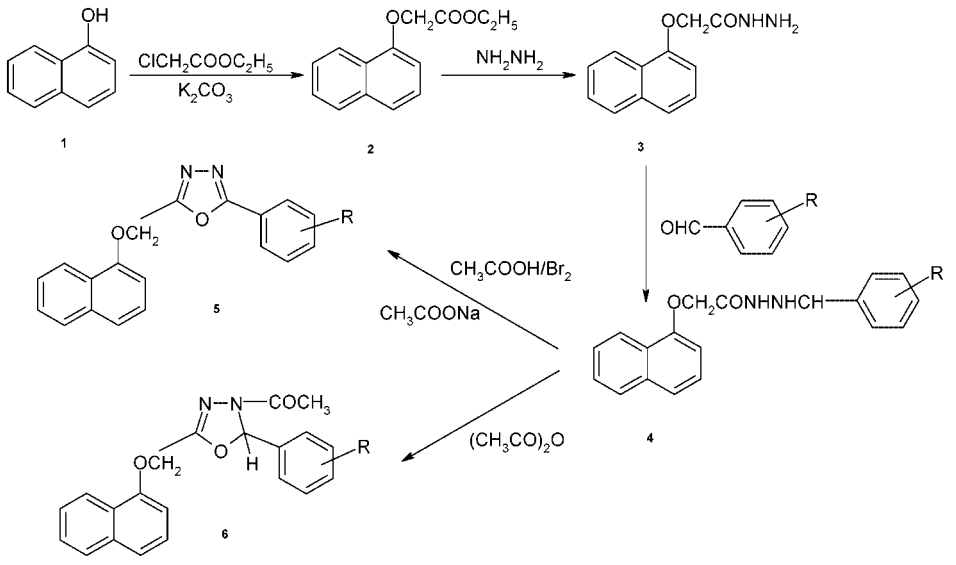
MATERIALS AND METHODS

Chemistry All the chemicals were from E-Merck, Aldrich, and Himedia. Melting points were determined using the open capillary method and are uncorrected. Nitrogen estimation was done using an elemental analyzer Heraeus Carlo Erba-1108, IR spectra were recorded on a Perkin Elmer IR spectrophotometer (KBr disc), ^{13}C–NMR spectra on a Bruker DRX-300 NMR spectrometer (DMSO-d_6, TMS), and the electrospray mass spectra on a Micromass Quattro II triple-quadrupole mass spectrometer (methanol). The title compounds were prepared using the scheme described in Fig. 1.

(Naphthalen-1-yloxy)-acetic acid ethyl ester (2) and (naphthalen-1-yloxy)-acetic acid hydrazide (3) were synthesized using the method reported earlier.[8,9]



5a: R = 4-Cl	**6a**: R = 4-Cl
5b: R = 4-CH_3O	**6b**: R = 4-CH_3O
5c: R = 4-NO_2	**6c**: R = 4-NO_2
5d: R = 4-CH_3	**6d**: R = 4-CH_3
5e: R = 4-OH	**6e**: R = 4-OH
5f: R = 3, 4-(CH_3O)	**6f**: R = 3, 4-(CH_3O)

Fig. 1. Scheme for Synthesis of Oxadiazole and Oxadiazoline Analogues

4-(Naphthalen-1-yloxy)-butyric acid-(4-substituted-benzylidene)-hydrazide (4a-f): A solution of **3** (0.01 mol) was prepared in 50 ml of absolute ethanol in a round-bottomed flask. The required aldehyde (0.01 mol) dissolved in 20 ml of absolute ethanol was added, dropwise to it, and the mixture was refluxed for 5–6 h. The solid mass, which separated out on cooling, was filtered and finally recrystallized from DMF/water.

Compound **4a**: yield 74%, mp 189–191℃, IR (KBr) 1695.1 (C=O Str), 3345.3 (N–H Str), 3072.6 (aromatic C–H str), 1602.5, 1496.6 (aromatic C–C Str).

2-(4-Substituted-phenyl)-5-(naphthalen-1-yloxy-methyl)-[1,3,4]oxadiazole (5a–f): A mixture of **4a–f** (0.01 mol), anhydrous sodium acetate (0.02 mol), and glacial acetic acid was placed in a round-bottomed flask equipped with a separating funnel for the addition of bromine. Bromine (0.8 ml in 5 ml of glacial acetic acid) was added slowly to it while stirring magnetically. After 1.5 h of stirring, the solution was poured on crushed ice, and the resulting solid was separated, dried, and recrystallized from aldehyde-free ethanol.

1-[2-(4-Substituted-phenyl)-5-(naphthalen-1-yloxy-methyl)-[1,3,4] oxadiazol-3-yl]ethanone (6a–f): A mixture of **4a–f** (0.01 mol) and acetic anhydride (30 ml) was refluxed for 1 h. Excess acetic acid (byproduct) and acetic anhydride were removed by distillation under reduced pressure, and the residue obtained was recrystallized from aldehyde-free ethanol.

Pharmacology The antiinflammatory activity of test compounds in acute and chronic inflammatory conditions was evaluated using the carrageenan-induced rat paw edema method and cotton pellet-induced granuloma method, respectively. The carrageenan-induced inflammation model is a COX-dependent reaction and is used to determine COX inhibition. The cotton pellet-induced granuloma method is widely used to evaluate the transudative and proliferative components of chronic inflammation.

For antiinflammatory evaluation, adult albino rats

of either sex weighing 150–175 g were divided in groups of 6. All test compounds and indomethacin (reference drug) were administered orally suspended in 1% carboxymethylcellulose (CMC). The acute oral toxicity test[10] was performed for all the synthesized compounds according to the Organization of Economic Cooperation and Development (OECD) guidelines. Statistical analyses were carried out with the single tailed *t*-test. A level of $P<0.001$ was adopted as the test of significance. The procedure employed for antiinflammatory evaluation was reviewed and approved by the University Animal Ethical Committee.

Acute oral toxicity was performed following the OECD-423 guidelines (acute toxic class method). Swiss albino mice ($n=3$) of either sex selected by random sampling were used for the study. The animals were fasted for 3–4 h with water *ad libitum*, after which the test compounds (suspended in CMC) were administered orally at the dose of 5 mg/kg and the mice observed for 3 days. If mortality was observed in 2 to 3 animals, the dose administered was assigned as the toxic dose. If mortality was observed in 1 animal, then the same dose was repeated to confirm the toxic dose. In the present study, mortality was not observed with the 5 mg/kg dose and the procedure was repeated for higher doses of 50, 250, 500, 1000 and 2000 mg /kg. All 3 mice survived at the 2000 mg/kg dose, indicating that the compounds are nontoxic to animals.

Carrageenan-induced Rat Paw Edema Test The antiinflammatory activity of the synthesized compounds was assessed using the rat paw edema assay[11] utilizing 0.1 ml of 1% carrageenan as a phlogistic agent. A mark was made on both hind paws just below the tibiotarsal junction so that the paw could be dipped in the mercury column of the plethysmograph up to the mark to ensure constant paw volume. To each group of 6 animals, with the exception of the control group, the test (100 mg/kg of body weight) compounds were administered orally. The control group received an equivalent amount of CMC used as solvent to dissolve the compounds. The standard drug indomethacin (10 mg/kg) was administered to one group. After 1 h, carrageenan (0.1 ml, 1% w/v solution in sterile saline) was injected into the subplantar tissue of the left paw of the control as well as the indomethacin group. The right paw served as the reference non-inflamed paw for comparison. The initial paw volume was measured using the plethysmograph within 30 sec after the injection. The relative increase in paw volume was measured in control, standard, and treated groups 1, 2, and 3 h after carrageenan injection. After 3 h, the final paw volume of each animal was measured. The percent reduction in paw volume was calculated by subtracting the difference between the right and left hind paw volumes in the treated group from the difference in the control group and dividing by the difference in the control group. The antiinflammatory activity of test compounds and the standard reference drug was determined using the formula % antiinflammatory activity $=(1\text{-}Vt/Vc)\times 100$, where Vt represents the mean increase in paw volume in rats treated with test compounds and Vc represents the mean increase in paw volume in the control group of rats.

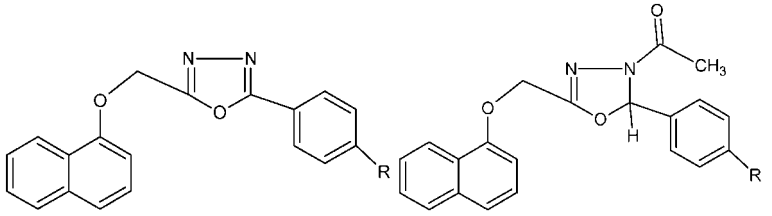
Cotton Pellets-induced Granuloma Method After shaving the fur, rats were anesthetized and 10 $\pm$ 1 mg of sterile cotton pellets were inserted, one each in axilla. The test compounds, indomethacin and control vehicle, were administered orally for 7 consecutive days from the day of cotton pellet implantation. On the 8th day, animals were anesthetized and the cotton pellets were removed surgically and freed from extraneous tissues. The moist cotton pellets were weighed and then dried at 60°C for 24 h, and then the dried cotton pellets were weighed again. The actual weight of the cotton pellets was subtracted from the weight of dried granuloma pellets. The increase in the weight of dried cotton pellets was taken as the measure of granuloma formation. The antiproliferative effects of test compounds were determined by comparing the results obtained in test groups with those in the control group.[12]

RESULTS AND DISCUSSION

The yield of the final compounds, their melting points, and percentage nitrogen found are given in Table 1. The structures of the compounds were elucidated on the basis of nitrogen analysis, IR, ^{13}C–NMR, and electrospray mass spectroscopy (ESMS).

The IR data of synthesized oxadiazole analogues clearly shows a C=N stretching band around 1640 cm^{-1} and C–O absorption band around 1090 cm^{-1}, which indicates ring closure of the 1,3,4-oxadiazole ring. All the final compounds have strong absorption around 3065 cm^{-1} which is evidence of the presence of aromatic C–H bonds. The presence of aromatic C–C bonds can be confirmed by observing absorption

Table 1. Physical Data of the Synthesized Oxadiazoles and Oxadiazolines



5a—f (Oxadiazoles) **6a—f (Oxadiazolines)**

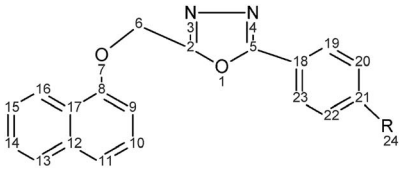
Compound	R	Mol. formula (mol. wt.)	mp (℃)	Yield (%)	Nitrogen estimation found (calculated)
5a	4-Cl	$C_{19}H_{13}N_2O_2Cl$ (336.77)	212	60	8.21 (8.32%)
5b	4-CH_3O	$C_{20}H_{16}N_2O_3$ (332.35)	189	55	8.37 (8.43%)
5c	4-NO_2	$C_{19}H_{13}N_3O_4$ (347.32)	197	68	12.35 (12.10%)
5d	4-CH_3	$C_{20}H_{16}N_2O_2$ (316.35)	176	52	8.96 (8.86%)
5e	4-OH	$C_{19}H_{14}N_2O_3$ (318.32)	205	65	8.62 (8.80%)
5f	3,4-(CH_3O)	$C_{21}H_{18}N_2O_4$ (362.37)	191	59	7.91 (7.73%)
6a	4-Cl	$C_{21}H_{17}N_2O_3Cl$ (380.82)	160	56	7.48 (7.36%)
6b	4-CH_3O	$C_{22}H_{20}N_2O_4$ (376.40)	157	58	7.53 (7.44%)
6c	4-NO_2	$C_{21}H_{17}N_3O_5$ (391.37)	171	65	10.86 (10.74%)
6d	4-CH_3	$C_{22}H_{20}N_2O_3$ (360.40)	146	65	7.54 (7.77%)
6e	4-OH	$C_{21}H_{18}N_2O_4$ (362.37)	152	62	7.81 (7.73%)
6f	3,4-(CH_3O)	$C_{23}H_{22}N_2O_5$ (406.43)	166	61	6.75 (6.89%)

bands around 1602 and 1501 cm^{-1}. The IR data also confirm the presence of specific functional groups present in the final synthesized compounds. In the ^{13}C–NMR spectra, C-2 and C-5 of the oxadiazole nucleus were seen around 165 and 172 ppm, respectively. All carbons and protons of the final compounds were also seen based on the expected chemical shift. The mass spectra of test compounds are in conformity with the assigned structures. The mass spectra of these compounds showed molecular ion peaks corresponding to their molecular formula (Tables 2 and 3).

The antiinflammatory activity of oxadiazoles, *i.e.*, **5a–f**, at doses of 100 mg/kg is indicated by their ability to provide 28–55%, 21–36% and 27–49% protection against carrageenan-induced rat paw edema, moist cotton pellet-induced granuloma and dry cotton pellet-induced granuloma, respectively. On the other hand, the antiinflammatory properties of oxadiazolines, *i.e.*, **6a–f**, at doses of 100 mg/kg is reflected by their ability to provide 15–47%, 22–39%, and 23–47% protection against carrageenan-induced rat paw edema, moist cotton pellet-induced granuloma, and dry cotton pellet-induced granuloma, respectively (Table 4). Among the synthesized oxadiazoles, the maximum antiinflammatory activity was exhibited by compound **5e** with 55.93%, 36.64%, and 49.33% protection against carrageenan-induced rat paw edema, moist cotton pellet-induced granuloma, and dry cotton pellet-induced granuloma, respectively. In the case of oxadiazolines, the maximum activity was shown by compound **6e** with 47.45%, 39.30%, and 47.79% protection against carrageenan-induced rat paw oedema, moist cotton pellet-induced granuloma, and dry cotton pellet-induced granuloma, respectively.

In correlating the biological activity of compounds with their structure, it was observed that the most potent antiinflammatory compounds **5e** and **6e** had a hydroxy group on the benzene ring attached to C-2 of the oxadiazole and oxadiazoline moiety, respectively. The significant antiinflammatory activity of compounds **5e** and **6e** may be attributed to the electronegativity of the hydroxy group, which can withdraw electron more strongly than chloro, nitro, or other groups of the compounds. On the other hand, among all compounds, **5d** and **6d** had the weakest antiinflammatory activity. Another notable point is that compounds with the methoxy group, *i.e.*, **5f** and **6f**, exhibited greater activity in comparison with compounds with the methyl group, *i.e.*, **5d** and

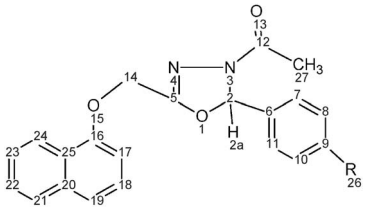
Table 2. Spectral Data of Synthesized Oxadiazoles



Compound Code	IR (cm^{-1}) (KBr)	^{13}C-NMRδ (ppm) (DMSO-d_6, TMS)	ESMS m/z molecularion
5a	3057.2 (aromatic C-H), 1089.5 (C-O of 1,3,4-oxadiazole nucleus), 1642.4 (C=N of 1,3,4-oxadiazole nucleus), 1603.5, 1501.8 (aromatic C-C), 1020.7 (Ar-O-C), 831.9 (C-H def disubstituted benzene).	165.8 (C-2 of oxadiazole ring), 172.9 (C-5 of oxadiazole ring), 62.6 (C-6), 155.3 (C-8), 103.8 (C-9), 125.7 (C-10), 120.5 (C-11), 134.8 (C-12), 127.2 (C-13), 126.4 (C-14), 125.1 (C-15), 121.9 (C-16), 124.6 (C-17), 134.2 (C-18), 127.3 (C-19 and C-23), 129.4 (C-20 and C-22), 133.7 (C-21).	337
5b	3057.9 (aromatic C-H str), 1088.3 (C-O of 1,3,4-oxadiazole nucleus), 1639.6 (C=N of 1,3,4-oxadiazole nucleus), 1601.2, 1502.7 (aromatic C-C str), 1022.5 (Ar-O-C), 1252.8 (C-O of OCH_3), 832.6 (C-H def disubstituted benzene).	166.0 (C-2 of oxadiazole ring), 173.7 (C-5 of oxadiazole ring), 62.4 (C-6), 155.2 (C-8), 103.7 (C-9), 125.8 (C-10), 120.3 (C-11), 134.7 (C-12), 127.1 (C-13), 126.2 (C-14), 125.0 (C-15), 121.8 (C-16), 124.7 (C-17), 130.1 (C-18), 127.3 (C-19 and C-23), 116.5 (C-20 and C-22), 163.8 (C-21), 56.2 (C-24).	333
5c	3059.3 (aromatic C-H str), 1093.2 (C-O of 1,3,4-oxadiazole nucleus), 1640.5 (C=N of 1,3,4-oxadiazole nucleus), 1601.1, 1503.5 (aromatic C-C str), 1020.8 (Ar-O-C), 1546.4, 1358.7 (N=O str in Ar NO_2 group), 831.2 (C-H def disubstituted benzene).	165.4 (C-2 of oxadiazole ring), 173.2 (C-5 of oxadiazole ring), 62.8 (C-6), 155.6 (C-8), 104.2 (C-9), 125.6 (C-10), 120.2 (C-11), 134.8 (C-12), 127.2 (C-13), 126.3 (C-14), 125.0 (C-15), 122.0 (C-16), 124.5 (C-17), 142.1 (C-18), 127.4 (C-19 and C-23), 124.4 (C-20 and C-22), 148.8 (C-21).	348
5d	3057.5 (aromatic C-H str), 1092.3 (C-O of 1,3,4-oxadiazole nucleus), 1641.3 (C=N of 1,3,4-oxadiazole nucleus), 1601.1, 1500.6 (aromatic C-C str), 1025.2 (Ar-O-C), 2934.9 (aliphatic C-H str), 1433.1 (aliphatic C-H def), 832.1 (C-H def disubstituted benzene).	165.2 (C-2 of oxadiazole ring), 173.3 (C-5 of oxadiazole ring), 62.5 (C-6), 155.7 (C-8), 104.1 (C-9), 125.8 (C-10), 120.4 (C-11), 134.4 (C-12), 127.2 (C-13), 126.3 (C-14), 124.9 (C-15), 121.9 (C-16), 124.6 (C-17), 134.2 (C-18), 127.2 (C-19 and C-23), 124.4 (C-20 and C-22), 137.5 (C-21), 20.8 (C-24).	317
5e	3058.4 (aromatic C-H str), 1090.8 (C-O of 1,3,4-oxadiazole nucleus), 1641.7 (C=N of 1,3,4-oxadiazole nucleus), 1599.4, 1501.9 (aromatic C-C str), 1019.6 (Ar-O-C), 3442.2 (O-H str of alcoholic group), 1154.7 (C-O str of alcoholic group), 832.8 (C-H def disubstituted benzene).	165.9 (C-2 of oxadiazole ring), 172.9 (C-5 of oxadiazole ring), 62.1 (C-6), 155.4 (C-8), 103.9 (C-9), 125.6 (C-10), 120.1 (C-11), 134.5 (C-12), 127.4 (C-13), 126.1 (C-14), 125.0 (C-15), 122.1 (C-16), 124.4 (C-17), 134.4 (C-18), 128.5 (C-19 and C-23), 115.5 (C-20 and C-22), 155.7 (C-21).	319
5f	3056.8 (aromatic C-H str), 1090.5 (C-O of 1,3,4-oxadiazole nucleus), 1642.8 (C=N of 1,3,4-oxadiazole nucleus), 1602.4, 1501.7 (aromatic C-C str), 1021.3 (Ar-O-C), 1250.6 (C-O of OCH_3), 831.3 (C-H def disubstituted benzene).	165.7 (C-2 of oxadiazole ring), 173.5 (C-5 of oxadiazole ring), 62.7 (C-6), 155.3 (C-8), 103.8 (C-9), 125.7 (C-10), 120.5 (C-11), 134.6 (C-12), 127.0 (C-13), 126.2 (C-14), 125.1 (C-15), 122.1 (C-16), 124.5 (C-17) 129.8 (C-18), 113.2 (C-19), 120.6 (C-23), 148.3 (C-20) 117.1 (C-22), 147.6 (C-21), 56.4 (C-24), 56.1 (C-25).	363

6d. This may be because the methoxy group supplies its electron more strongly than the methyl group, as the former group contains an electronegative oxygen atom. Replacement of the methyl group on the aryl moiety with other groups, *i.e.*, hydroxy, nitro, and chloro groups, resulted in a considerable increase in

Table 3. Spectral Data of Synthesized Oxadiazolines



Compound Code	IR (cm^{-1}) (KBr)	^{13}C-NMRδ (ppm) (DMSO-d_6, TMS)	ESMS m/z molecularion
6a	3065.2 (aromatic C-H), 1090.4 (C-O of 1,3,4-oxadiazoline nucleus), 1641.5 (C=N of 1,3,4-oxadiazoline nucleus), 1601.2, 1502.8 (aromatic C-C), 1021.6 (Ar-O-C), 832.5 (C-H def disubstituted benzene), 2825.1 (C-H str of $COCH_3$).	76.2 (C-2 of oxadiazoline ring), 153.5 (C-5 of oxadiazoline ring), 139.2 (C-6), 129.1 (C-7 and C-11), 128.5 (C-8 and C-10), 134.1 (C-9), 170.4 (C-12), 62.3 (C-14), 155.1 (C-16), 103.8 (C-17) 125.6 (C-18), 120.3 (C-19), 134.2 (C-20), 127.4 (C-21), 126.3 (C-22), 125.4 (C-23), 121.8 (C-24), 125.4 (C-25), 23.2 (C-27).	381
6b	3065.6 (aromatic C-H str), 1089.7 (C-O of 1,3,4-oxadiazoline nucleus), 1642.1 (C=N of 1,3,4-oxadiazoline nucleus), 1602.4, 1501.6 (aromatic C-C str), 1020.7 (Ar-O-C), 832.7 (C-H def disubstituted benzene), 2825.4 (C-H str of $COCH_3$).	76.4 (C-2 of oxadiazoline ring), 153.7 (C-5 of oxadiazoline ring), 133.6 (C-6), 127.4 (C-7 and C-11), 112.4 (C-8 and C-10), 159.6 (C-9), 170.6 (C-12), 62.4 (C-14), 155.0 (C-16), 103.9 (C-17), 125.9 (C-18), 120.5 (C-19), 134.5 (C-20), 127.3 (C-21), 126.5 (C-22), 125.2 (C-23), 121.9 (C-24), 125.2 (C-25), 23.4 (C-27), 56.8 (C-26).	377
6c	3064.8 (aromatic C-H), 1089.2 (C-O of 1,3,4-oxadiazoline nucleus), 1640.3 (C=N of 1,3,4-oxadiazoline nucleus), 1601.5, 1502.3 (aromatic C-C), 1021.6 (Ar-O-C), 831.8 (C-H def disubstituted benzene), 2826.3 (C-H str of $COCH_3$).	76.1 (C-2 of oxadiazoline ring), 153.2 (C-5 of oxadiazoline ring), 148.2 (C-6), 127.9 (C-7 and C-11), 123.2 (C-8 and C-10), 148.4 (C-9), 170.7 (C-12), 62.7 (C-14), 155.4 (C-16), 104.2 (C-17), 125.4 (C-18), 120.6 (C-19), 134.3 (C-20), 127.3 (C-21), 126.4 (C-22), 125.5 (C-23), 121.8 (C-24), 125.3 (C-25), 23.5 (C-27).	392
6d	3065.4 (aromatic C-H), 1090.6 (C-O of 1,3,4-oxadiazoline nucleus), 1639.7 (C=N of 1,3,4-oxadiazoline nucleus), 1601.6, 1502.5 (aromatic C-C), 1022.4 (Ar-O-C), 832.4 (C-H def disubstituted benzene), 2825.5 (C-H str of $COCH_3$).	76.3 (C-2 of oxadiazoline ring), 152.9 (C-5 of oxadiazoline ring), 139.9 (C-6), 126.6 (C-7 and C-11), 128.9 (C-8 and C-10), 135.5 (C-9), 170.5 (C-12), 62.8 (C-14), 155.3 (C-16), 104.5 (C-17), 125.7 (C-18), 120.4 (C-19), 134.5 (C-20), 127.5 (C-21), 126.2 (C-22), 125.2 (C-23), 121.7 (C-24), 125.4 (C-25), 20.9 (C-26), 23.5 (C-27).	361
6e	3065.0 (aromatic C-H), 1090.9 (C-O of 1,3,4-oxadiazoline nucleus), 1640.6 (C=N of 1,3,4-oxadiazoline nucleus), 1601.3, 1501.9 (aromatic C-C), 1020.9 (Ar-O-C), 3435.8 (O-H str of alcoholic group), 1156.3 (C-O str of alcoholic group), 832.7 (C-H def disubstituted benzene), 2826.8 (C-H str of $COCH_3$).	76.8 (C-2 of oxadiazoline ring), 153.4 (C-5 of oxadiazoline ring), 135.2 (C-6), 126.8 (C-7 and C-11), 115.3 (C-8 and C-10), 155.8 (C-9), 170.2 (C-12), 62.9 (C-14), 155.5 (C-16), 103.9 (C-17), 125.6 (C-18), 120.3 (C-19), 134.2 (C-20), 127.4 (C-21), 126.3 (C-22), 125.7 (C-23), 121.6 (C-24), 125.3 (C-25), 23.3 (C-27).	363
6f	3065.7 (aromatic C-H), 1090.3 (C-O of 1,3,4-oxadiazoline nucleus), 1641.4 (C=N of 1,3,4-oxadiazoline nucleus), 1599.6, 1500.2 (aromatic C-C), 1021.8 (Ar-O-C), 831.6 (C-H def disubstituted benzene), 2825.6 (C-H str of $COCH_3$).	76.5 (C-2 of oxadiazoline ring), 153.3 (C-5 of oxadiazoline ring), 135.2 (C-6), 120.2 (C-7), 113.9 (C-11), 115.3 (C-10), 147.2 (C-8), 145.4 (C-9), 170.1 (C-12), 62.1 (C-14), 155.4 (C-16), 104.2 (C-17), 125.5 (C-18), 120.5 (C-19), 134.5 (C-20), 127.2 (C-21), 126.5 (C-22), 125.3 (C-23), 121.9 (C-24), 125.4 (C-25), 56.7 (C-26, C-28), 23.4 (C-27).	407

Table 4. Antiinflammatory Activity‡ of the Synthesized Oxadiazoles and Oxadiazolines (100 mg/kg *p.o.*) Using Carrageenan Induced Rat Paw Edema Method and Cotton Pellets Induced Granuloma Method

Compound	Carrageenan-induced rat paw edema method		Cotton pellets-induced granuloma method			
	Mean increase in paw volume mL ± SEM§	% Protection	Weight of moist cotton pellet ± SEM** (mg)	% inhibition	Weight of dry cotton pellet ± SEM†† (mg)	% inhibition
5a	0.32 ± 0.007	45.76	146.94 ± 0.68	29.58	29.15 ± 0.38	37.09
5b	0.29 ± 0.005	50.84	149.48 ± 0.52	28.26	31.68 ± 0.47	31.63
5c	0.37 ± 0.008	37.28	141.11 ± 0.67	32.37	27.76 ± 0.36	40.09
5d	0.42 ± 0.004	28.81	164.37 ± 0.74	21.22	33.37 ± 0.21	27.28
5e	0.26 ± 0.004	55.93	132.21 ± 0.46	36.64	23.48 ± 0.41	49.33
5f	0.40 ± 0.01	32.20	136.71 ± 0.85	34.48	26.52 ± 0.33	42.61
6a	0.39 ± 0.006	33.89	143.71 ± 0.48	31.13	29.46 ± 0.26	36.42
6b	0.38 ± 0.006	35.59	148.14 ± 0.65	29.00	32.82 ± 0.48	29.17
6c	0.41 ± 0.009	30.50	138.44 ± 0.64	33.65	28.35 ± 0.76	38.82
6d	0.50 ± 0.008	15.25	160.69 ± 0.56	22.99	35.46 ± 0.65	23.47
6e	0.31 ± 0.006	47.45	126.65 ± 0.73	39.30	24.19 ± 0.52	47.79
6f	0.47 ± 0.006	20.33	130.69 ± 0.90	37.37	25.62 ± 0.57	44.71
Control	0.59 ± 0.003	—	208.11 ± 0.46	—	46.34 ± 0.32	—

‡ The results were statistically significant ($p<0.001$) during all observations. § The mean increase in paw volume in rats treated with indomethacin (10 mg/kg) observed in this experiment was 0.11 ± 0.004 ml with percentage protection of 81.35 ($p<0.0001$). ** The mean increase in the weight of moist cotton pellets in rats treated with indomethacin (10 mg/kg) observed in this experiment was 101.54 ± 0.31 mg with percentage protection of 51.28 ($p<0.0001$). †† The mean increase in the weight of dry cotton pellets in rats treated with indomethacin (10 mg/kg) observed in this experiment was 20.74 ± 0.26 mg with percentage protection of 55.24 ($p<0.0001$).

antiinflammatory activity. Structure-activity relationships among the synthesized oxadiazole and oxadiazolines analogues indicates that the hydroxy, nitro, or chloro group in the aromatic ring is responsible for imparting significant antiinflammatory activity to the oxadiazole and oxadiazoline nucleus.

In conclusion, two novel series of compounds, 1,3,4-oxadiazole and oxadiazoline analogues, were synthesized for their potential antiinflammatory activities, using the carrageenan-induced rat paw edema method and cotton pellet-induced granuloma method. Among both series, the most potent antiinflammatory compounds were **5e**, **5b**, **5a**, **6e**, and **6b**. In general, all the oxadiazoles have greater antiinflammatory activity than their corresponding oxadiazoline analogues. On the other hand, it can also be concluded that all the oxadiazole and related analogues exhibit greater antiinflammatory activity in the carrageenan-induced rat paw edema assay than in the cotton pellet-induced granuloma method, indicating that the studied compounds are more effective in acute inflammatory conditions than in chronic ones. In our laboratory, further research work is underway on optimization of the 1,3,4-oxadiazole lead to explore their antiinflammatory potential.

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