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Original Article

Synthesis, Characterization and Anti-Inflammatory Activity of Some 1, 3,4 -Oxadiazole Derivatives

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Abstract

A series of five-membered heterocyclic rings were synthesized by the reaction between benzoyl chloride and various chlolro-nitro-benzoyl chlorides and semi carbazide to form (C_1-C_7) 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: [3-Chloro-*N*-[5-(3-Chloro-phenyl)-[1,3,4] oxadiazole-2yl] benzamide (C_4), and [4-Nitro-*N*-[5-(4-Nitro-phenyl)-[1,3,4] oxadiazole-2yl] benzamide (C_7). 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; Synthesis; Heterocyclic.

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 chemicals were supplied by (Merck and

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S.D fine chemicals Lucknow India). Melting point (m.p) was determined by open capillary tube method. Purification of compounds was checked by column chromatography and silica gel-G (60-120 mess) and silica gel GF_{254} (4:1) for preparation of TLC plates and also used the solvent system 5% ethyl acetate in pet. Ether and spots were seen under iodine vapours and UV light chamber. IR spectra were obtained on a Perkin-Elmer 1720 FT-IR-Spectrometer (KBr-sol^n/pellets). ^{1}HNMR spectra were noted in Brucker Ac-400 MHz spectrometer using TMS as internal standard in DMSO/$CDCl_3$ and mass spectra (m/z %) recorded by VG ZAB-HS (FAB) instrument.

Material and methods

General procedure for synthesis of compounds (C_1 to C_7):- (1:1 molar ratio) Aromatic, phosphorus pentachloride and benzene were taken in RBF, fitted with air condenser and calcium chloride guard tube. The mixture was heated gently to melt with vigorous shaking at around 50°C. After 30 min excess $POCl_3$ was distilled out. The residue was dried well and used for the next reaction. Then, semicarbazide was added to the respected acid chloride and reflux for 5 h. These programs of the reaction were monitored by checking the TLC. The excess benzene was distilled out, neutralizing with aq. $NaHCO_3$ and the compound was extracted with chloroform. The crude was obtained through distillation of chloroform under reduce pressure

Anti-inflammatory activity[20]

Anti-inflammatory activity of all synthesized derivatives was determined by the carrageenan-induced rat paw oedema model. Albino rats (100-200 g) were divided into 3 groups as control, test and standard (six animals per group). Overnight fasted animals were used and during that period only tap water was given. Generally, indomethacin was used as standard drug. Both test and standard drugs were suspended in 1% carboxymethyl cellulose (CMC) and administered orally through gastric gavage needle. One percent of CMC was administered in control group. After 1 h of administrating the compound, we induced the carrageenan (1%) by the sub planner surface of the right hind paws of animals. The initial paw volume and also the paw volume after 3 and 6 h of administrating carrageenan were measured. Percent paw oedema inhibition was calculated.

Results and Discussion

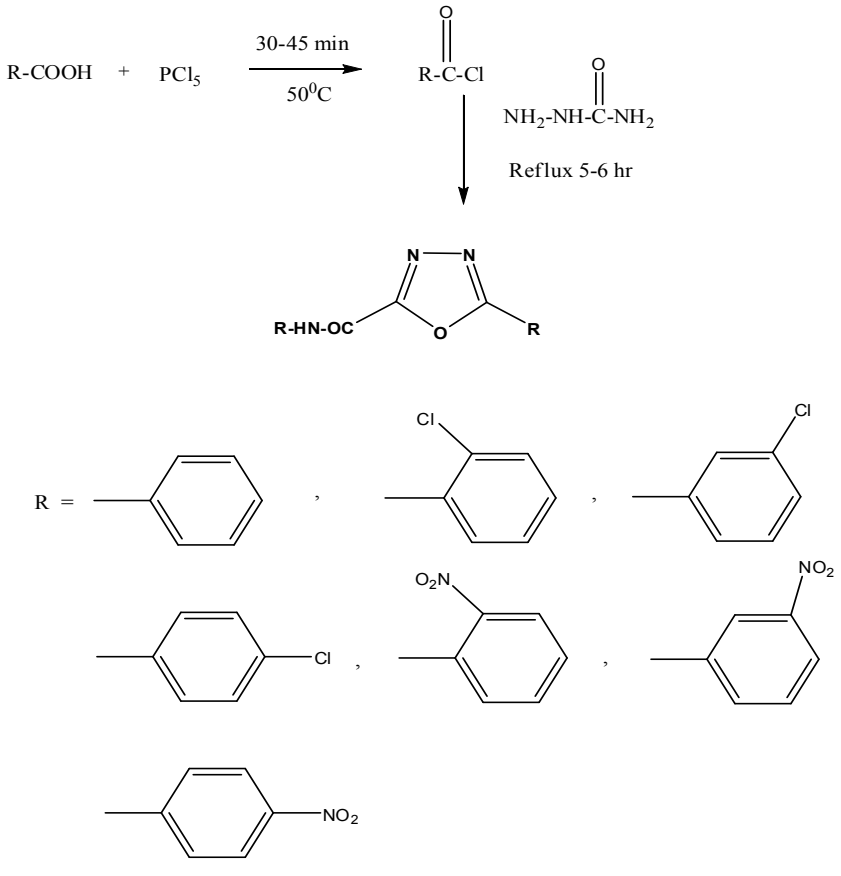
At the end of the experiment, it has been concluded that the compounds synthesized in the project have good yield value. The synthesized oxadiazole compounds were identified and characterized by IR, ^{1}H NMR and MASS spectra. Then, the pharmacological activity was done. The entire compound had a good response for Anti-inflammatory activity : [3-Chloro-N-[5-(3-Chloro-phenyl)-[1,3,4] oxadiazole-2yl] benzamide (C_4),and [4-Nitro-N-[5-(4-Nitro-phenyl)-[1,3,4] oxadiazole-2yl]benzamide (C_7). Substitution of 2-chloro-benzoic acid at 2,5-position anti-inflammatory activity greater (C_2) than 3-chloro substituted compound (C_3)and 4-cloro-benzoic acid compound (C_4) substituted at 2,5 position anti-inflammatory activity greater than 2-chloro-substituted compound ($C_{2)}$. While substitution of 4-nitro-compounds (C_7) at 2,5-position greater than other 2-nitro and 3-nitro substituted compounds (C_5 and C_6).

Compound 1: [N-(5-Phenyl-[1, 3, 4] oxadiazol-2-yl)-benzamide]

IR(KBr,cm-1) : 3214(NH) ,1664(C=O) , 1070(N-N) ,1232(C-O-C) ; ^{1}HNMR(DMSO-ds,400 M Hz), 8.72 (s, 1H, J = 7.6 Hz) , 7.72 (d, 3H, J = 7.9 Hz), 7.82 (d, 1H, J = 7.9 Hz), 7.62 (d, 1H, J = 7.6 Hz, MASS (ESI):m/z (%), 266 (23), 262 (14), 260 (100), 249 (17), 248 (100). analytical calculated for $C_{15}H_{11}N_3O_2$ c = 67.90, H = 4.23, N = 15.86, O = 12.12, found = C = 67.92, H = 4.15, N = 15.84, O = 12.07.

Compound 2: [2-Chloro-N-[5-(2-chloro-phenyl)-[1,3,4]oxadiazol-2-yl]benzamide]

IR(KBr,cm-1): 3270(NH),1670(C=O) ,1072(N-N)1240(C-O-C),776(C-Cl) ;1HNMR (DMSO-ds, 400 MHz) ,7.96 (d, 1H, J = 7.5) ,7.78 (d, 1H, J = 7.4) ,7.72 (d, 2H, J = 8.87), 7-7.8 (m, 3H, J = 8.2); MASS (CSM), m/z (%), analytical calculated for $C_{15}H_9N_3O_2Cl_2$; C = 49.60, H = 2.96, N = 23.48. found C = 49.62, H = 2’86, N = 23.44.



Compound 3: [4-Chloro-N-[5-(4-chloro-phenyl)-[1,3,4] oxadiazol-2-yl]-benzamide]

IR (KBr , cm-1) P: 3272 (NH) , 1668 (C=O), 1076 (N-N), 1242 (C-O-C), 778 (C-Cl); 1HNMR (DMSO-ds,400 MHz), 7.76 (d, 2H, J = 7.3 Hz), 7.68 (d, 1H, J = 7.2 Hz), 7.73 (d, 2H, J = 8.2 Hz),7.78 (m, 3H, J = 8.32 Hz); MASS (C-SI), m/z (%) analytical calculated for C15H9N3O2Cl2, C = 48.98, H = 2.83, N = 23.48, found, C = 47.96, H = 2.81, H = 23.32.

Compound 4: [3-Chloro-N-[5-(3-Chloro-phenyl)-[1,3,4] oxadiazole-2yl]benzamide

IR (KBr, cm-1): 3268 (NH), 1668 (C=O), 1072 (N-N), 1242 (C-O-C), 725 (C-Cl); 1HNMR (DMSO, ds, 400 MHz) ,7.72-7.75 (d, 2H, J = 8.4 Hz), 7.78 (m, 3H, J = 8.32 Hz). MASS (CSM); M\Z%-Anal calculator for C15H9N3O2Cl2, C = 48.41, H = 2.79, N = 23.25, Found C = 47.98, H = 2.76; N = 23.16.

Compound 5: [2-Nitro-N-[5-(2-Nitro-phenyl)-[1, 3, 4] oxadiazole-2yl] benzamide

IR (KBr cm-1) :- 3272 (NH), 1670 (C=O), 1078 (N-N), 1260 (C-O-C), 780 (C-Cl) H1NMR (DMS+ds400M H2):- 7.70 (d, 1H, J = 7.25 Hz), 7.78 (d, 1H, J = 7.4 Hz), 7.78 (d, 2H, J = 8.1 Hz), 7.25 (m, 3H, J = 8.21 Hz) Mass (CSM) (M/Z (%)-Anal calculator for C14H9N5O6, C = 48.97, H = 2-93, N = 30.48, formed C = 48.27, N = 2.90, N = 30.42.

Compound 6: [3-Nitro-N-[5-(3-Nitro-phenyl)-[1,3,4] oxadiazole-2yl]benzamide

IR (KBr Cm-1):- 3271(NH), 1668(C=O), 1070(N-H), 1265(C-O-C), 786(C-Cl) H1NMR (DMS+ds400M H2):- 7.71(d, 1H, J = 7.24 Hz), 7.77(d, 1H, J = 7.3 Hz), 7.73 (d, 1H, J = 8.3 Hz), 7.22 (m, 1H, J = 8.21 Hz), Mass,(CSM) M/Z (%)-Anal calculator for C14H9N5O6 C = 48.92, H = 2.44, N = 30.47, found C = 48.46, H = 2.90,

Table 1. Physical properties of compounds (C_1 to C_7).

Compounds	Yield (%)	Rf	MP(°C)	Mol. Formula	Mol. Wt.
C_1	72%	0.715	212	$C_{15}H_{11}N_3O_2$	265.2
C_2	66%	0.692	214	o-$C_{15}H_9N_3O_2Cl_2$	334.16
C_3	79%	0.678	213	m-$C_{15}H_9N_3O_2Cl_2$	334.16
C_4	82%	0.682	211	p-$C_{15}H_9N_3O_2Cl_2$	334.16
C_5	80%	0.721	273	o-$C_{15}H_9N_5O_6$	355.26
C_6	73%	0.761	266	m-$C_{15}H_9N_5O_6$	355.26
C_7	78%	0.672	271	p-$C_{15}H_9N_5O_6$	355.26

N = 30.45.

Compound 7: [4-Nitro-N-[5-(4-Nitro-phenyl)-[1, 3, 4] oxadiazole-2yl] benzamide

IR(KBr Cm-1) :- 3272(NH), 1665 (C=O), 1078 (N-N), 1260 (C-O-C), 783(C-Cl) H1NMR (DMS+ds400M H2):- 7.70(d, 1H, J = 7.23 H2), 7.2 (d, 1H, J = 7.2 H2), 7.74 (d, 1H, J = 8.4 H2), 7.26 (m, 1H, J = 8.20 H2), Mass, (CSM) M/Z(%)-Anal calculator for C14H9N5O6 C = 48.98, H = 292, H = 30.46, formed C = 48.92, H = 2.48, N = 30.36.

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Table 2. Anti-inflammatory activities of compounds C_1 to C_7).

Columns	Dose Mg/Kg	Inhibition of paw oedema after 3 h (%)1	Inhibition of paw oedema after 6 h (%)2
C-1	30	3.28 ± 0.28	58.24
C-2	30	2.48 ± 0.23	56.48
C-3	30	3.46 ± 0.22	51.16
C-4	30	1.62 ± 0.27	70.98
C-5	30	3.26 ± 0.241	59.48
C-6	30	3.22 ± 0.281	53.98
C-7	30	1.52 ± 0.271	69.54
Control	_	0 .36 ± 0.28	_
Indomethacine	40	1.78 ± 0.340	66.44

1: Dose for 1-7: 30 mg/Kg b.wt; 2: Dose for indomethacin 40 mg/Kg b.wt; mean ± SEM; n+6

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