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Synthesis Characterization and Anti-Inflammatory Activities of Substituted Aniline Oxadiazolyl Derivatives

Bhupender Singh Rawat[1*], Shrawan Kumar Shukla[2], Nidhi Gangwar[3], Roopali Tandon[1] and S.C Mehra[1]

*[1]Department of Chemistry, Bareilly College, Bareilly, Uttar Pradesh, India
[2]Department of Plastic Technology, H.B.T.I., Kanpur, Uttar Pradesh, India
[3]Department of Chemistry, G.B.P.U.A &T Pantnagar, Uttarakhand, India

ABSTRACT

Oxadiazoles are an important class of bioactive and industrially important organic compounds with diverse pharmacological activities such as antibacterial, anthelmintic, antifungal, Anti-inflammatory etc. oxadiazole derivatives have been studied in the past few decades. It is a five membered heterocyclic structure and exist in four isomeric forms out of its four isomers 1, 3, 4- oxadiazole exhibited a wide range of biological activities . In the present work isomeric forms of ortho/meta/ para toluidine, is converted to 3- methyl-N-(5- substituted phenyl)-1, 3, 4 oxadiazol-2yl-methyl aniline. The synthesized compounds were investigated for anti-inflammatory activities.

Keywords: Oxadiazole, Antifungal, Antibacterial, Anti-Inflammatory Activity

I. INTRODUCTION

Oxadiazoles have antibacterial, anti-inflammatory, anticonvulsant, anticancer, ant tubercular, anti-diabetic, anthelmintic, and analgesic CNS depressant activities, among others. Due to their broad biological activity potentials, the synthesis of oxadiazole derivatives is of interest to medicinal chemists working in drug development. Oxadiazole moiety and its various derivatives studied frequently in the past few decades and found potent in various pharmacological and pathological conditions [1]. Literature reveals that 1, 3, 4-Oxadiazole is a highly privileged structure the derivatives of which exhibit a wide range of biological activities including antibacterial [2], antitubercular [3], vasodialatory [4], antifungal [5], cytotoxic [6], anti-inflammatory and analgesic [7,8], hypolipidemic [9], anticancer [10] and ulcerogenic [11] activities. Dhansay Dewangan *et al*, Synthesized some of the Novel 2, 5-disubstituted 1, 3, 4-Oxadiazoles and evaluated as analgesic and anti-inflammatory activities. All the synthesized compounds shown significant analgesic and anti-inflammatory activities [12]. Biju C R *et al*, worked on the Design and Microwave-assisted Synthesis of 1,3,4-Oxadiazole derivatives and screened for analgesic and anti-inflammatory activities. Almost all the compounds possess good activity against the standard [13]. Rajgopal H.Udupi *et al*, Synthesized a series of pyrimidine substituted 1,3,4-oxadiazole derivatives. The synthesized compounds were evaluated for their *in vitro* antimicrobial and anti-inflammatory activity. Some of the newly synthesized compounds showed good antimicrobial and anti- inflammatory activities [14] Bhat, *et al* worked on the Synthesis, characterization and biological activity studies of 1, 3, 4-oxadiazole analogs. The newly synthesized compounds were screened for antibacterial, Anti-fungal and anti-inflammatory activities. Some of the compounds showed remarkable antibacterial, antifungal and anti-inflammatory activities [15]. Kumar Singh A *et al*, worked on the Synthesis, Characterization and Anti-Inflammatory Activity of Some 1,3,4-Oxadiazole Derivatives. 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 [16]. Chandrakantha et al synthesized a new series of 1,3,4-oxadiazoles bearing 2- flouro-4-methoxy phenyl moiety and their antimicrobial studies were performed. Few of the compounds showed significant antimicrobial activity [17]. Shridhar et al synthesized a series of 2,5-disubstituted-1,3,4-oxadiazolines by the reaction of isonicotinic acid hydrazide with various substituted aromatic acids in the presence of $POCl_3$. Ten compounds from this series were screened for anti-

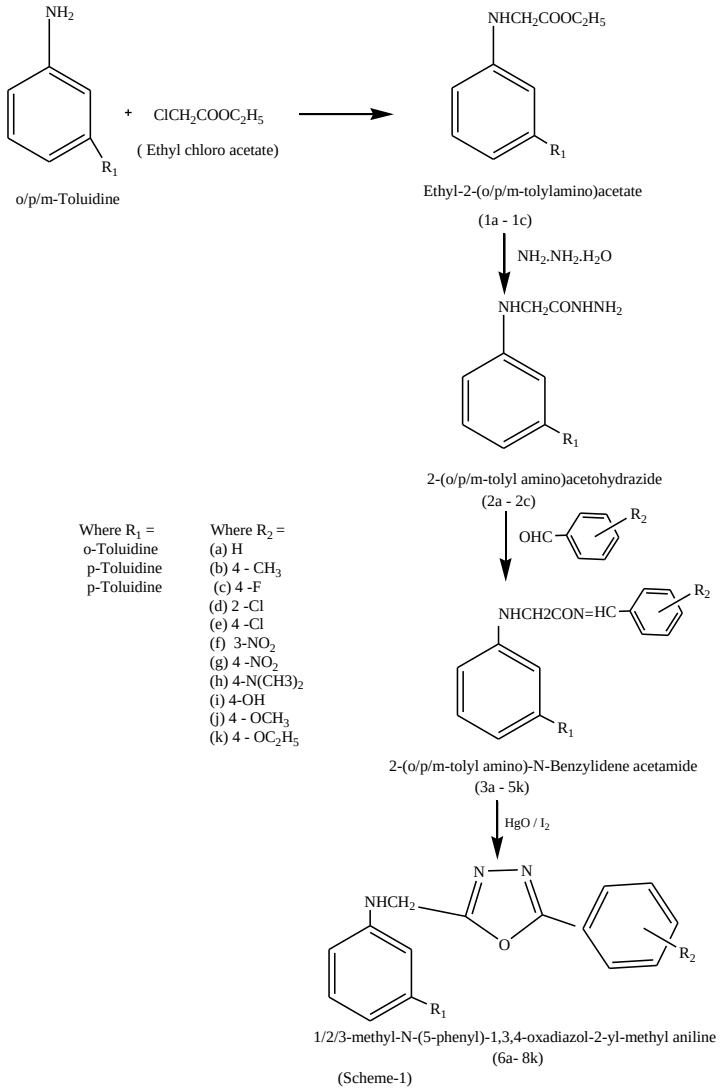
bacterial and anti-fungal activity. The synthesized compounds showed good anti-fungal with moderate anti-bacterial activity [18].

Bansal et al synthesized a novel series of 2-phenyl-5-(1,3-diphenyl-1H-pyrazol-4-yl)-1,3,4-oxadiazoles were designed and synthesized for selective COX- 2 inhibition with potent anti-inflammatory activity [19] Grewal et al synthesized a new series of 2,5-disubstituted-1,3,4-oxadiazole derivatives by the reaction of quinolinyl hydrazone derivatives with dichloromethane. All the synthesized compounds were screened for their antimicrobial and antifungal activity [20]. Dhumal et al synthesized some new 1,3,4 oxadiazoles bearing Pyridyl and Thiazolyl scaffolds and screened for anti-bacterial and anti-tuberculosis activities [21].

Lots of work has been done on thiazole, oxazole, thiadiazole and oxadiazole nucleus with potential biological activities like antifungal, antibacterial, anti-inflammatory, antiviral, antidiuretic, antiviral anticancer and antioxidant activities. The present work describes the synthesis characterization anti-inflammatory activities of substituted1,3,4 oxadiazole derivatives by reaction with ethyl chloroacetate to form substituted phenyl amino acetate which on subsequent reaction with hydrazine hydrate to give substituted phenyl amino hydrazide which on reaction with benzaldehyde gives substituted phenyl amino –N-(substituted Benzylidine) acetohydrazide, which in presence of mercuric oxide and iodine gives title compound according to scheme1.

II. METHODS AND MATERIAL

All the melting points were determined in open capillary tubes. IR spectra were recorded in solid state using KBr pellet method. The spectra were recorded on Perkin Elmer FT-IR spectrophotometer (model RX-1). The PMR spectra were recorded in DMSO-d6 solvent at room temperature using TMS as reference compound. The spectra were recorded on Perkin Elmer Model 32 NMR spectrometer at 300MHz at CDRI Lucknow. The reactions were monitored by TLC. The physical Data of compounds are given in Table 1.



Scheme 1

A. Preparation of Ethyl-2-(o/p/m-tolyl amino) acetate [1a-1k]

A mixture of m- toluidine (10.7 gm, 0.1 mol), ethylchloroacetate (12.25 ml, 0.1 mol) and anhydrous potassium carbonate (19.5 gm, 0.15 mol) in dry acetone was refluxed on a water bath for 24 hours at 75 °C. The resultant reaction mixture was cooled and filtered. Excess of acetone was removed by distillation and resultant solid was recrystallized from ethanol.
Yield: 72%, M.P 122-124°C.

IR (KBr): 3385-3370 cm^{-1} (due to -NH), 1720- 1680 cm^{-1} (due to C=O), 1600 -1590 cm^{-1} (due to C=C) , 2865-2850 cm^{-1} (due to –CH)

PMR: δ 2.25-2.35 (3H, m, due to methyl), δ 6.25 – 6.42 (4H, m, due to aromatic proton), δ 3.8-4.2 (1H,s, due to-

NH), δ 4.0 – 4.12 (2H, s, due to- CH_2), δ 4.12-4.15 (2H,s, due to –CH_2), δ 1.2 – 1.3 (3H,t, due to CH_3).
Similarly various Ethyl-2-(o/p-tolyl amino) acetate were synthesized by using similar reaction procedure.

B. Preparation of 2- (m- tolyl amino) acetohydrazide [2a-2k]

A mixture of (I) (9.05 gm, 0.05 mol) and hydrazine hydrate (2.4 ml, 99%, 0.75 mol) in ethanol (100 ml) was refluxed on a water bath for 8 hours. From the reaction mixture excess of solvent was removed by distillation. The resultant mixture was collected and recrystallized from ethanol.

Yield: 63%, M.P 139-141°C.
IR (KBr): 3385-3370 cm^{-1} (due to -NH), 1720- 1680 cm^{-1} (due to C=O), 1600 -1590 cm^{-1} (due to C=C), 2865-2850 cm^{-1} (due to –CH) , 2910 – 2900 (due to –CH)
PMR: δ 2.25-2.35 (3H, t, due to methyl), δ 6.25 – 6.92 (4H, m, due to aromatic proton), δ 2.0-2.2 (1H, d, due to-NH_2), δ 7.8 – 8.1 (1H, s, due to –NH), δ 3.8 – 4.1 (1H, s, due to –NH), δ 3.8 – 4.0 (2H, s, due to- CH_2),
Similarly various 2-(o/p- tolyl amino) acetohydrazide were synthesized by using similar reaction procedure.

C. Preparation of 2- (m- tolyl amino)-N-Benzylidene acetamide [3a-3k]

A mixture of (II) and different aromatic or substituted aromatic aldehyde (0.01 mol) in ethanol was refluxed in presence of acetic acid (2-3 drops) for 8 hours. The reaction mixture was cooled and washed with cooled water and recrystallized from ethanol.
Yield: 53%, M.P 163-165°C.

IR (KBr): 3385-3370 cm^{-1} (due to -NH), 1720- 1680 cm^{-1} (due to C=O), 1600 -1590 cm^{-1} (due to C=C), 2995-3010 cm^{-1} (due to –CH_2)

TABLE 1
PHYSICAL DATA OF SYNTHESIZED COMPOUNDS

Comp'd No.	Nature of R_1	Nature of R_2	Molecular Formula	MP°(C)	Yield (%)
1a	o-Toluidine	-----	$C_{11}H_{15}O_2N$	132 - 134	72
1b	p-Toluidine	-----	$C_{11}H_{15}O_2N$	149 - 151	65
1c	m-Toluidine	-----	$C_{11}H_{15}O_2N$	122 - 124	72
2a	o-Toluidine	-----	$C_9H_{14}N_3O$	139-141	69
2b	p-Toluidine	-----	$C_9H_{14}N_3O$	166-168	60
2c	m-Toluidine	-----	$C_9H_{14}N_3O$	139 - 141	63
3a	o-Toluidine	H	$C_{15}H_{14}N_2O$	142 - 144	62
3b	o-Toluidine	4-CH3	$C_{16}H_{16}N_2O$	133-139	58
3c	o-Toluidine	4- F	$C_{15}H_{13}N_2OF$	159-161	55
3d	o-Toluidine	2- Cl	$C_{15}H_{13}N_2OCl$	162-164	58
3e	o-Toluidine	4- Cl	$C_{15}H_{13}N_2OCl$	165-167	60
3f	o-Toluidine	3- NO2	$C_{15}H_{13}N_3O_3$	153-155	52
3g	o-Toluidine	4- NO2	$C_{15}H_{13}N_3O_3$	157-159	55
3h	o-Toluidine	4- N(CH3)2	$C_{17}H_{19}N_3O$	144-146	60
3i	o-Toluidine	4- OH	$C_{15}H_{14}N_2O_2$	134-136	61
3j	o-Toluidine	4- OCH3	$C_{16}H_{16}N_2O_2$	140-142	58
3k	o-Toluidine	4- OC2H5	$C_{17}H_{18}N_2O_2$	149-151	55
4a	p-Toluidine	H	$C_{15}H_{14}N_2O$	159- 161	62
4b	p-Toluidine	4-CH3	$C_{16}H_{16}N_2O$	157-159	55
4c	p-Toluidine	4- F	$C_{15}H_{13}N_2OF$	151-153	52
4d	p-Toluidine	2- Cl	$C_{15}H_{13}N_2OCl$	155-157	56
4e	p-Toluidine	4- Cl	$C_{15}H_{13}N_2OCl$	150-152	62
4f	p-Toluidine	3- NO2	$C_{15}H_{13}N_3O_3$	152-154	63
4g	p-Toluidine	4- NO2	$C_{15}H_{13}N_3O_3$	157-159	59
4h	p-Toluidine	4- N(CH3)2	$C_{17}H_{19}N_3O$	145-147	63
4i	p-Toluidine	4- OH	$C_{15}H_{14}N_2O_2$	149-151	55
4j	p-Toluidine	4- OCH3	$C_{16}H_{16}N_2O_2$	143-145	58
4k	p-Toluidine	4- OC2H5	$C_{17}H_{18}N_2O_2$	159-161	55

5a	m-Toluidine	H	$C_{15}H_{14}N_2O$	163-165	53
5b	m-Toluidine	4-CH3	$C_{16}H_{16}N_2O$	169-171	50
5c	m-Toluidine	4- F	$C_{15}H_{13}N_2OF$	173-175	47
5d	m-Toluidine	2- Cl	$C_{15}H_{13}N_2OCl$	176-178	50
5e	m-Toluidine	4- Cl	$C_{15}H_{13}N_2OCl$	171- 173	50
5f	m-Toluidine	3- NO2	$C_{15}H_{13}N_3O_3$	169-171	55
5g	m-Toluidine	4- NO2	$C_{15}H_{13}N_3O_3$	175-177	56
5h	m-Toluidine	4- N(CH3)2	$C_{17}H_{19}N_3O$	153-155	52
5i	m-Toluidine	4- OH	$C_{15}H_{14}N_2O_2$	169-171	49
5j	m-Toluidine	4- OCH3	$C_{16}H_{16}N_2O_2$	165-167	48
5k	m-Toluidine	4- OC2H5	$C_{17}H_{18}N_2O_2$	162-164	51
6a	o-Toluidine	H	$C_{16}H_{15}N_3O$	165- 167	39
6b	o-Toluidine	4-CH3	$C_{17}H_{17}N_3O$	169-171	37
6c	o-Toluidine	4- F	$C_{16}H_{14}N_3OF$	175-177	35
6d	o-Toluidine	2- Cl	$C_{16}H_{14}N_3OF$	181-183	31
6e	o-Toluidine	4- Cl	$C_{16}H_{14}N_3OF$	187-189	32
6f	o-Toluidine	3- NO2	$C_{16}H_{14}N_4O_3$	180-182	35
6g	o-Toluidine	4- NO2	$C_{16}H_{14}N_4O_3$	179-181	37
6h	o-Toluidine	4- N(CH3)2	$C_{18}H_{20}N_4O$	185-187	42
6i	o-Toluidine	4- OH	$C_{16}H_{15}N_3O_2$	190-192	38
6j	o-Toluidine	4- OCH3	$C_{17}H_{17}N_3O_2$	178-179	40
6k	o-Toluidine	4- OC2H5	$C_{18}H_{19}N_3O_2$	182-184	45
7a	p-Toluidine	H	$C_{16}H_{15}N_3O$	196-198	42
7b	p-Toluidine	4-CH3	$C_{17}H_{17}N_3O$	198-200	32
7c	p-Toluidine	4- F	$C_{16}H_{14}N_3OF$	192-194	49
7d	p-Toluidine	2- Cl	$C_{16}H_{14}N_3OF$	185-187	41
7e	p-Toluidine	4- Cl	$C_{16}H_{14}N_3OF$	183-186	43
7f	p-Toluidine	3- NO2	$C_{16}H_{14}N_4O_3$	189-191	40
7g	p-Toluidine	4- NO2	$C_{16}H_{14}N_4O_3$	192-194	39
7h	p-Toluidine	4- N(CH3)2	$C_{18}H_{20}N_4O$	197-199	42
7i	p-Toluidine	4- OH	$C_{16}H_{15}N_3O_2$	190-192	45
7j	p-Toluidine	4- OCH3	$C_{17}H_{17}N_3O_2$	186-188	48
7k	p-Toluidine	4- OC2H5	$C_{18}H_{19}N_3O_2$	191-193	47
8a	m-Toluidine	H	$C_{16}H_{15}N_3O$	179-181	45
8b	m-Toluidine	4-CH3	$C_{17}H_{17}N_3O$	185-187	40
8c	m-Toluidine	4- F	$C_{16}H_{14}N_3OF$	183-185	38
8d	m-Toluidine	2- Cl	$C_{16}H_{14}N_3OF$	172-174	47
8e	m-Toluidine	4- Cl	$C_{16}H_{14}N_3OF$	176-178	45
8f	m-Toluidine	3- NO2	$C_{16}H_{14}N_4O_3$	183-185	49
8g	m-Toluidine	4- NO2	$C_{16}H_{14}N_4O_3$	187-189	50
8h	m-Toluidine	4- N(CH3)2	$C_{18}H_{20}N_4O$	183-185	52
8i	m-Toluidine	4- OH	$C_{16}H_{15}N_3O_2$	187-189	50
8j	m-Toluidine	4- OCH3	$C_{17}H_{17}N_3O_2$	180-182	49
8k	m-Toluidine	4- OC2H5	$C_{18}H_{19}N_3O_2$	187-189	42

PMR: δ 2.25-2.35 (3H, t, due to methyl), δ 6.8 – 7.2 (9H, m, due to aromatic proton), δ 2.25 – 2.35 (1H, s, due to –NH), δ 3.8 – 4.0 (2H, s, due to- CH_2), 2865-2850 cm^{-1} (1H, s, due to –CH).

Similarly various 2-(o/p-tolyl amino)-N- substituted Benzylidene acetamide were synthesized by using similar reaction procedure.

D. Preparation of 3- methyl-N-(5-phenyl)-1, 3, 4 oxadiazol-2yl-methyl aniline [4a-4k]

A solution of (III), 0.01 mol in DMF (40 ml) was stirred in presence of yellow mercuric oxide (3gm) and iodine (1.5 gm) at room temperature for 48 hours under anhydrous conditions. The reaction mixture was filtered and poured in to crushed ice and stirred well. The solid thus separated out was washed with water and recrystallize from DMF: ethanol (1:1).

Yield: 45%, M.P 179- 181°C.

IR (KBr): 3385-3370 cm^{-1} (due to -NH), 1100 - 1140 cm^{-1} (due to C-O-C), 1615 -1590 cm^{-1} (due to C=N),1600-1590 cm^{-1} (due to C=C).
PMR: δ 2.25-2.35 (3H, t, due to methyl), δ 6.8 – 7.3 (9H, m, due to aromatic proton), δ 3.95 – 4.12 (1H, s, due to –NH), δ 3.0 – 3.2 (2H, s, due to- CH_2).

Similarly various 2/4- methyl-N-(5- substituted phenyl)-1, 3, 4 oxadiazol-2yl-methyl aniline were synthesized by using similar reaction procedure.

III. RESULTS AND DISCUSSION

Anti-inflammatory activity by Carrageenan- induced rat hind paw edema method [22]

Anti-inflammatory activity of few selected 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 hour of administrating the compound, we induced the carrageenan (1%) by the sub planner surface of the right hind paws of animals. The initial, after 3 h and 6 h paw volume of administrating carrageenan were measured. Percent paw oedema inhibition was calculated.

The percentage inhibition of edema volume was calculated as;

$$\% \text{ inhibition} = \left(1 - \frac{Vt}{Vc}\right) X\ 100$$

Where V_t and V_c are the relative change in the edema volume of paw after the administration of the test and control, respectively. Data of anti-inflammatory activity is summarized in Table 2.

All the values were expressed as mean ± SEM using one way ANOVA followed by Dunnet`s t test.

TABLE 2

Comp'd No	Dose mgm/kg	Inhibition of paw edema after 3 hrs (%) 1	Inhibition of paw edema after 6 hrs (%) 2
6a	20	3.58±0.25	57.55
6c	20	2.58±0.23	58.48
6e	20	2.28 ± 0.23	53.16
6g	20	3.21 ± 0.23	67.23
6i	20	1.41 ± 0.26	58.22
7a	20	3.26 ± 0.241	55.75
7c	20	3.22 ± 0.281	64.44
7e	20	1.52 ± 0.271	55.13
7g	20	0 .36 ± 0.28	57.11
7i	20	2.35 ± 0.23	51.16
8a	20	1.62 ± 0.27	59.33
8d	20	3.46 ± 0.22	**67.98**
8e	20	2.31 ± 0.241	53.21
8g	20	3.11 ± 0.281	**66.23**
8i	20	1.52 ± 0.271	59.48
Control	--	0 .35 ± 0.25	--
Indomethacin	30	1.52 ± 0.320	63.66

1: Dose for 1-7: 20 mg/Kg b.wt; 2: Dose for indomethacin 30 mg/Kg b.wt; mean ± SEM; n+6

IV. CONCLUSION

Although From the above Anti-inflammatory screening data the compounds it has been concluded that the synthesized compounds shows significant anti-inflammatory activity. Compound no 6g, 7c, 8a and 8g shows very good response against standard drug indomethacin. It can also be concluded that the introduction of nitro group & fluoro group in para positions significantly increases or shows very good response. All other rest compounds show average response with respect to standard drug.

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