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SYNTHESIS AND ANTI-ARTHRITIC ACTIVITY OF NOVEL 1,3,4-OXADIAZOLE DERIVATIVES

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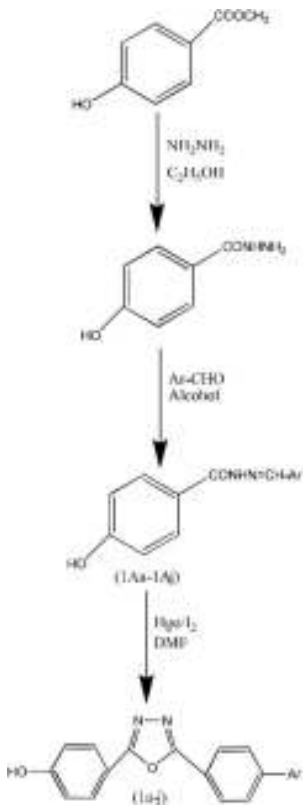
ABSTRACT
A novel series of 2,5-disubstituted-1,3,4-oxadiazoles **(2a-j)** were synthesized by the reaction of Schiff base **(1a-j)** and mercuric oxide/iodine in DMF medium. All the new compounds were assigned on the basis of ^{1}H-NMR, IR and Mass spectral data. The newly synthesized compounds were evaluated for *In-Vitro* anti-arthritic activity. Most of the synthesized compounds showed moderate anti-arthritic activity when compared to standard Diclofenac sodium.

INTRODUCTION
Azoles containing oxygen and nitrogen atom in its structure are important class of heterocyclic compounds resulted as new therapeutic molecules. 1,3,4-Oxadizoles, obtained from furan by substituting two nitrogen of pyridine type(-N=) in the place of two methane (-CH=) groups provides a wide range of pharmacological activities. Its derivatives have shown a noticeable interest in the development of novel compounds containing potent activity such as anticonvulsant[I], antioxidant[II], antifungal[III], ant-inflammatory[IV], antiallergic[V], antimycobacterial[VI], antihypertensive[VII], ulcerogenic[VIII] , herbicidal[IX], anti-HIV[X], analgesic[XI] etc.
So many drugs are available in the market which are composed of 1,3,4-oxadiazoles moiety. It includes Nesapidil, categorized as a class IV antiarrhythmic drug. Furamizole, a nitrofuran derivatives possess a strong antibacterial activity.[XII] . 1,3,4-oxadiazoles are usually synthesized using carbohydrazides, Schiff base, diacylhydrazines. Many oxidizing agents are available for their synthesis viz, phosphorus oxy chloride, iodo benzene diacetate etc.[XIII] . The direct reaction of benzoic acid derivatives with (N-isocyanimino) triphenylphosphorane results in a greater yield.[XIV]
Here we report the synthesis of 1,3,4-Oxadiazoles from methyl paraben carbohydrazide and intermediate Schiff base. The reaction is carried out in presence of oxidizing agent like mercuric oxide and Iodine in DMF medium.

Scheme-1



EXPERIMENTAL

All the reagents and the solvents that are used in the reactions were purchased from Loba Chemie Pvt.Ltd and were used without further purifications. The melting points of the compounds were recorded by open capillary method. IR spectra is recorded using FTIR and frequencies are expressed in cm^{-1}. ^{1}H-NMR spectra were recorded at 400MHZ Bruker Avance-II NMR Spectrometer obtained in $CDCl_3$ and DMSO solution. The chemical shift values were reported as values in ppm relative to TMS (δ=0) as internal standard. Mass Spectrum were recorded on GC-MS Perkin Elmer Clarus 680 Spectrometer obtained by electron impact ionization method. The purity of compound is checked by TLC using silica G plates.

Synthesis of Schiff's bases (1a-j)

Methyl paraben carbohydrazide [0.01mol] was dissolved in DMF solutions [20ml], and few drops of glacial acetic acid is added. Substituted aromatic aldehydes [0.01mol] is added to the above reaction mixture. The reaction mixture is refluxed for 10 hrs. After refluxing, the reaction mixture was poured into crushed ice (100ml) with stirring. The precipitated compound was filtered, washed with water & dried. The physical data of Schiff base **(1a-j)** is given in table-1.

General procedure for the synthesis of 1,3,4-oxadiazoles derivatives (2a-j)

Schiff base [0.01mol] **(1a-j)** is dissolved in 40ml of DMF. 3gm of yellow mercuric oxide and 1.5gm of iodine crystals is added. The reaction mixture is stirred for 24 hrs at room temperature. After 24 hrs, the solid particles are removed by filtration and the reaction mixture was poured into crushed ice (100ml) with stirring. Filtration of the precipitated

compound was done followed by washing with water, and recrystallization using alcohol. The physical data of the title compounds **(2a-j)** is given in the table-2.

Table-1: Physical data of Schiff base (1a-j)

Comp	Ar-CHO	Molecular Weight	MP (^{0} C)	Yield (%)
1a	2-Cl	274.70	200-02	83.09
1b	4-$N(CH_3)_2$	283.33	230-32	80.04
1c	C_6H_5	240.26	210-12	79.67
1d	3-OH	256.26	254-56	83.05
1e	4-OCH_3	270.28	243-45	80.56
1f	3-NO_2	281.31	238-40	81.76
1g	4-OH	256.26	264-66	83.23
1h	4-Cl	274.70	190-92	84.67
1i	3-Cl	274.70	183-85	82.07
1j	3,4-$(OCH_3)_2$	300.31	224-226	81.56

Table-2: Physical data of 1,3,4-oxadiazole derivatives (2a-j)

Comp	Ar-CHO	Molecular Weight	MP (^{0} C)	Yield (%)
2a	2-Cl	272.69	170-72	80.98
2b	4-$N(CH_3)_2$	281.31	178-80	78.90
2c	C_6H_5	238.24	184-86	76.78
2d	3-OH	254.24	196-98	80.09

2e	4-OCH_3	268.27	190-92	78.98
2f	3-NO_2	283.24	105-07	79.09
2g	4-OH	254.24	201-03	78.09
2h	4-Cl	272.69	237-39	79.89
2i	3-Cl	272.69	223-25	80.67
2j	3,4-$(OCH_3)_2$	298.29	210-12	79.87

2c: IR (KBr,cm^{-1}) ν_{max}: 1035 (C-O-C), 1489 (C=C), 1612(C=N), 3058 (C-H), 3359 (OH), ^{1}H-NMR (300 MH_Z, DMSO-d_6) (δ, ppm): 7.30-8.49(m, Ar-H, 9H), 10.10(s, 1H, OH). MS(m/z): 238.24 (M+).
2g: IR (KBr,cm^{-1}) ν_{max}: 1085 (C-O-C). 1528 (C=C), 1604(C=N), 3057 (C-H), 3357 (OH), 1035 (C-O-C). ^{1}H-NMR (300 MH_Z, DMSO-d_6) (δ, ppm)**:** 6.95-8.72 (m, Ar-H, 8H), 11.79 (s, 1H, OH), 11.89 (s, 1H, OH). MS(m/z): 254.24 (M+).
2h: IR (KBr,cm^{-1}) ν_{max}: 1033(C-O-C). 1512 (C=C), 1605(C=N), 3069 (C-H), 3247 (OH), 1035 (C-O-C). ^{1}H-NMR (300 MH_Z, DMSO-d_6) (δ, ppm)**:** 6.95-8.69 (m, Ar-H, 8H), 11.88 (s, 1H, OH), MS(m/z): 272.69 (M+).

General procedure *In vitro* anti-arthritic activity
Protein denaturation by bovine serum albumin method [xv]
Test solution (0.5ml) consists of 0.45ml of bovine serum albumin (5%w/v aqueous solution) and 0.05ml of test solution. Control solution (0.5ml) consists of 0.45ml of bovine serum albumin (5%w/v aqueous solution) and 0.05ml of distilled water. Product control (0.5ml) consists of 0.45ml of distilled water and 0.05ml of test solution. Standard solution (0.5ml) consists of 0.45ml of bovine serum albumin (5%w/v aqueous solution) and 0.05ml 0f Diclofenac sodium. All of the above solutions were adjusted to pH 6.3 using a small amount of 1N HCl. The samples were incubated at 37°C for 20 minutes and heated at 57°C for 3 minutes. After cooling, add 2.5ml of phosphate buffer to the above solutions. The absorbance of the solutions was measured using UV-Visible spectrophotometer at 416nm. (Table-3). The percentage inhibition of protein denaturation was calculated using the formula.
% inhibition = $100 \times [V\,t / V_C - 1]$
Where, Vt = absorbance of the test sample, Vc = absorbance of control
Protein denaturation by egg albumin method [xv]
The reaction mixture (5 mL) consisted of 0.2 mL of egg albumin (from fresh hen's egg), and 2 mL of varying concentrations (10-50 μg/mL) of synthesized 1,3,4-oxadiazole derivatives. A similar volume of double-distilled water served as the control. The mixtures were incubated at room temperature in a BOD incubator for 15minutes and then heated at 70°C for five minutes. The pH is adjusted to 6.4 by adding 2.8 ML of phosphate-buffered saline to each of the test tube. The absorbance was measured at 660 nm .

Diclofenac sodium was used as the reference drug. (Table-4).The percentage inhibition of protein denaturation was calculated by using the following formula.

% inhibition = $100 \times [V\ t / V_C - 1]$

Where, Vt = absorbance of the test sample, Vc = absorbance of control.

Table-3: Data of bovine serum albumin denaturation of 1,3,4-oxadiazoles derivatives (2a-j)

	Percentage inhibition										
Conc	**Std**	**2a**	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**	**2h**	**2i**	**2j**
10µg/ml	26.34	11.95	25.53	7.17	8.51	27.55	6.12	24.47	4.25	1.08	14.89
20µg/ml	34.33	15.21	26.59	11.60	17.02	30.61	15.30	30.85	7.44	5.43	28.72
30µg/ml	48.32	26.08	28.72	15.21	24.47	41.83	18.36	60.64	10.63	13.04	38.29
40µg/ml	60.23	35.86	37.23	29.34	31.91	53.06	20.40	71.27	23.40	14.13	50.01
50µg/ml	75.23	54.34	76.59	54.34	63.83	61.22	44.89	78.72	31.91	29.34	76.59
IC_{50}	**20.90**	**40.20**	**29.81**	**43.61**	**36.61**	**55.68**	**55.06**	**17.85**	**68.35**	**77.33**	**25.73**

Table-4: Data of egg albumin denaturation of 1,3,4-oxadiazoles derivatives (2a-j)

	Percentage inhibition										
Conc	**Std**	**2a**	**2b**	**2c**	**2d**	**2e**	**2f**		**2g**	**2h**	**2i**
10µg/ml	36.55	5.26	38.86	7.37	4.29	8.02	0.21	23.5	7.28	1.57	3.33
20µg/ml	47.81	6.32	44.43	21.16	15.57	24.33	1.89	49.67	9.01	6.01	17.83
30µg/ml	62.06	18.94	46.86	34.95	41.28	45.01	9.053	55.17	25.57	21.71	44.67
40µg/ml	74.71	24.21	48.02	44.42	51.71	63.33	25.05	58.33	29.71	32.01	65.01
50µg/ml	98.73	32.63	49.71	55.47	54.01	98.16	27.17	78.17	46.143	50.86	73.17
IC_{50}	**10.75**	**64.78**	**37.51**	**34.50**	**32.26**	**21.01**	**68.44**	**17.48**	**46.88**	**42.13**	**24.92**

RESULTS AND DISCUSSION

The main aim of this work was to synthesize 2,5-substituted 1,3,4-oxadiazole by using oxidizing reagent like mercuric oxide/iodine with Schiff bases.**(Scheme-1).** All the compounds were in conformity with the structure envisaged. The structures were proved on the basis of spectral data.

The IR spectrum of the compounds **(2a-j)** clearly showed the absence of carbonyl group and indicates the formation of oxadiazole ring. OH stretching band of 1,3,4-oxadiazole were observed at 3400-3200 cm^{-1} region. All the synthesized compounds showed absorption band at 1620-1600cm^{-1} and 1550-1450 cm^{-1} indicating for the presence of C=N and C=C in the molecules respectively. The ^{1}H-NMR spectrum of the compounds showed the appearance of multiplets in the region δ 6.95-8.72 integrating for the presence of aromatic protons. A sharp singlet observed at δ 10.00-12.00 integrating the presence of OH protons of 4-hydroxy benzhydrazide. In the mass spectrum, compound **2c,** showed the presence of molecular ion peak at 258 which is in consistent with the molecular formula $C_{14}H_{10}N_2O_2$. The other series are also in conformity with the molecular formula.

The synthesized compounds were subjected for their anti-arthritic activity. *In vitro* anti-arthritic activity was carried out by two different methods- bovine serum albumin denaturation assay and egg albumin denaturation assay. The newly synthesized compounds were tested at 10-50µg/ml by using diclofenac sodium as the standard for comparison purpose. The results revealed that, compounds **2b, 2d, 2j** showed moderate activity and also compound **2g** showed potent activity in bovine serum albumin method. Similarly compounds **2e, 2g** showed moderate activity in the egg albumin method. All the other tested compounds showed weak to moderate activity in both the methods. The presence of electron donating groups on the phenyl group is responsible for the anti-arthritic activity.

CONCLUSION

An efficient method of synthesis of 2,5-disubstituted-1,3,4-oxadiazole derivatives is demonstrated. The present methodology offers several advantages such as simple procedure, clean reaction, fast reaction with less time and good yields. The new compounds were synthesized for the first time via an easy, convenient and efficient synthetic route. Most of the tested compounds showed moderate anti-arthritic activity. The compounds with electron donating group showed moderate anti-arthritic activity. Here it can be concluded that 2,5-disubstituted-1,3,4-oxadiazole derivatives can be used as anti-arthritic agents. The study further requires structural modification of the compounds to get better pharmacological profile.

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