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

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ABSTRACT
A new series of substituted 1,3,4-oxadiazole derivatives **(3a-j)** have been synthesized by reacting benzhydrazide **(1)** and substituted aromatic aldehydes **(2)** in the presence of ferric chloride as a catalyst in methanol medium and the structures of these compounds were characterized by FT-IR, ^{1}H-NMR and Mass spectral data. All the title compounds were evaluated for *In- vitro* antioxidant activity. Among the compounds tested **3f** displayed potent activity when comparison to ascorbic acid as standard.

KEYWORDS: 1,3,4-oxadiazoles, $FeCl_3$, Benzhydrazide, Antioxidant activity, DPPH.

INTRODUCTION
1,3,4-Oxadiazoles belongs to oxygen and nitrogen containing 5-membered heterocyclic compounds. It is a well established fact in the literature these molecules are essentially used in the prevention and treatment of various kinds of bacterial infection and fungal infections [I]. Compounds which are composed of nitrogen atom have showed good results in the treatment of various diseases [II].
Substituted 1,3,4-oxadiazole derivatives have showed their prominence in pharmaceutical and agrochemical fields. These compounds were reported to possess CNS depressant[III], anticonvulsant[IV], antitubercular[V], herbicidal[VI], anti-inflammatory[VII], virucidal[VIII] etc. A number of drugs are available in the market which are composed of 1,3,4-oxadiazole ring structure such as Tiodazosin, Nesapidil, Furamizole. Recently two more drugs are made available in the market are Raltegravir an antiretroviral drug and Zibotentan, is used as an anticancer agent.
1,3,4-Oxadiazoles are usually synthesized using carbohydrazides, schiff bases, diacylhydrazines. Many oxidizing agents/cyclizing agents are available for their synthesis viz, phosphorus oxy chloride[IX], iodo benzene diacetate[X], $FeCl_3$[XI], cerric ammonium nitrate[XII], chloramine–T[XIII], mercuric oxide/iodine[XIV] etc. Because of these observations, it was thought of worthwhile to synthesize a novel series of 1, 3, 4-oxadiazoles using ferric chloride as a catalyst.

EXPERIMENTAL

MATERIALS AND METHODS

Melting points were determined using Thiels's apparatus and are uncorrected. The homogeneity of the compounds was checked by using silica gel-G plates. IR spectra was recorded using Alpha Bruker IR spectrometer instrument in KBr discs. The ^{1}H-NMR spectra were recorded in $CDCl_3$ on Bruker-400 MHz NMR spectrometer. The mass spectra were recorded using

General procedure for the synthesis of 1,3,4-oxadiazoles (3a-j) [XV]

Benzhydrazide **(1)** and substituted aromatic aldehydes **(2)** was dissolved in 25ml of methanol. A pinch of ferric chloride is added to the reaction mixture and refluxed for 6-8 hrs and cooled to room temperature The precipitated compound was filtered, washed with water and recrystallized from alcohol to give the title compounds **(3a-j)** (Table-1).

2,5-diphenyl-1,3,4-oxadiazole (3b): IR (KBr): 3053 (C-H), 1599(C=N), 1548(C=C), 1018 (C-O-C). ^{1}H-NMR ($CDCl_3$) **:** δ 7.42-8.61 (10H, m, Ar-H). Mass m/z: 222 (M^+)

2-(4-methoxyphenyl)-5-phenyl-1,3,4-oxadiazole (3e): IR(KBr): 3060(C-H), 1600 (C=N), 1510 (C=C), 1052 (C-O-C). ^{1}H-NMR ($CDCl_3$)**:** δ 3.93 (s, OCH_3, 3H), 6.94-8.63 (9H, m, Ar-H).

2-(4-chlorophenyl)-5-phenyl-1,3,4-oxadiazole (3j): IR(KBr): 3058(C-H), 1626 (C=N), 1502 (C=C), 1150 (C-O-C). 708 (C-Cl). ^{1}H-NMR ($CDCl_3$)**:** δ 7.14-8.62 (9H, m, Ar-H). Mass m/z: 252 (M^+)

4-(5-phenyl-1,3,4-oxadiazol-2-yl)phenol (3g): IR(KBr): 3239 (OH), 3097 (C-H), 1615 (C=N), 1564 (C=C), 1081 (C-O-C). ^{1}H-NMR ($CDCl_3$)**:** δ 6.91-8.71 (9H, m, Ar-H), 11.29 (s, OH, 1H).

Antioxidant activity

α, α-Diphenyl-β -picrylhydrazyl radical scavenging (DPPH) assay[XV]

100µl of DPPH (0.2Mm in methanol) solution was added to different concentrations of test compounds (10 -50µg/ml). The test samples were incubated at 37^{0}C for 30 minutes and absorbance was measured at 517nm using Elisa plate reader. Ascorbic acid was used as the standard material. The IC_{50} values by DPPH radical scavenging are given in Table-2. The percentage of inhibition is calculated by using the formula

Inhibition (%) = $(A_0 – A_1 / A_0) \times 100$

Where, A_0 is the absorbance of the control, and A_1 is the absorbance of the test.

Nitric oxide scavenging radical assay[XV]

To 1ml of the test samples (10-50µg/ml) in phosphate buffer (pH 7.4) sodium nitroprusside (1ml of 10mM) is added. The test samples were incubated at 25°C for 2 hours 30 minutes. 1ml of Griess's reagent (1% sulphanilamide, 2% o-phosphoric acid and 0.1% naphthylethylenediaminedihydrochloride) is added to the incubated solution and absorbance was recorded at 546nm using Elisa plate reader and the results were calculated using the formula mentioned earlier. Ascorbic acid was used as standard drug material. The IC_{50} values by nitric oxide radical scavenging are given in Table-2.

RESULTS AND DISCUSSION

The designed target compounds were synthesized according to the following synthetic **Scheme-01.** Benzhydrazide was made to react with aromatic aldehydes in the presence of small amounts of ferric chloride, and all the reactions were monitored by TLC at each step (Table-1). The structures of the new compounds were elucidated on the basis of spectroscopic data which is discussed in the experimental section.

Scheme-01

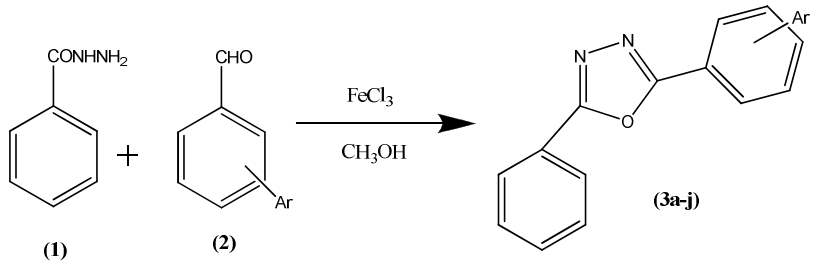

Table -1: Physical data of 1,3,4-Oxadiazole derivatives (3a-j)

Comp	Ar-CHO	Mol. Formula	Mol. Wt	Yield (%)	MP (˚C)
3a	4- $N(CH_3)_2$	$C_{16}H_{15}N_3O$	265.31	72	259-61
3b	C_6H_5	$C_{14}H_{10}N_2O$	222.24	69	194-96
3c	3, 4- $(OCH_3)_2$	$C_{16}H_{14}N_2O_3$	282.29	74	285-87
3d	3-NO_2	$C_{14}H_9N_3O_3$	267.24	73	177-79
3e	4-OCH_3	$C_{15}H_{12}N_2O_2$	252.27	77	223-25
3f	3-Cl	$C_{14}H_9ClN_2O$	256.69	73	256-58
3g	4-OH	$C_{14}H_{10}N_2O_2$	238.24	71	202-04
3h	4-F	$C_{14}H_9FN_2O$	240.23	66	210-12
3i	2-Cl	$C_{14}H_9ClN_2O$	256.69	67	218-20
3j	4-Cl	$C_{14}H_9ClN_2O$	256.69	65	235-37

Table-2: IC_{50} values of 1,3,4-oxadiazole derivatives (3a-j)

Comp	DPPH	Nitric oxide
Std (Ascorbic acid)	**15.58**	**16.63**
3a	27.97	19.40
3b	32.27	24.43
3c	6.129	28.97
3d	25.84	26.54
3e	29.30	23.06
3f	13.37	17.84
3g	25.87	29.10
3h	29.38	29.17
3i	16.00	28.60
3j	23.53	22.75

The IR spectrum of the compound clearly showed the absence of the carbonyl peak of the benzhydrazide in the region of 1640-1680 cm^{-1}. In the ^{1}H-NMR spectra, the aromatic protons were resonated as multiplets in the region of δ 6.94-8.71.The mass spectra of the compounds showed the prominent molecular ion peak, which is in consistent with the assigned molecular formula.

The newly synthesized compounds were evaluated for In-vitro antioxidant activity by DPPH and nitric oxide assay. All the compounds were tested at a concentration of 10-50 µgm/ml. In the DPPH method, compounds **3f, 3i** showed potent activity when compared to standard ascorbic acid. The other compounds **3d, 3g, 3j** showed moderate activity. In the nitric oxide radical scavenging activity, compounds **3a, 3f** showed potent activity and other compounds **3b, 3e, 3j** showed moderate activity.

CONCLUSION

In conclusion, a new series of 1,3,4-oxadiazoles were synthesized by using ferric chloride as a catalyst in methanol as the solvent medium. The final products were yielded in good yields. The use of ferric chloride has several advantages viz; requirement of less quantity, reaction time is less, non-hazardous, easy to handle, non-toxic. Some of the tested compounds showed good antioxidant activity.

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