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SYNTHESIS AND IN- VITRO ANTIOXIDANT ACTIVITY OF SOME NEW 2, 5-DISUBSTITUTED-1, 3, 4-OXADIAZOLES CONTAINING FURAN MOIETY

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ABSTRACT

A series of five membered heterocyclics was synthesized by the reaction between refluxing 2 - furoic acid with ethanol and conc. H_2SO_4. The obtained ester (2) with hydrazine hydrate and ethanol was refluxed to give hydrazides (3). Reaction of hydrazides (3) with different aromatic acids using phosphorousoxy trichloride ($POCl_3$) lead to the formation of 2-Aryl -5-furyl - 1, 3, 4-oxadiazoles [DM (1-6)], and was tested for their antioxidant activity. The synthesized compounds were characterized by IR, ^{1}HNMR and Mass Spectroscopy. All the compounds were screened for in vitro antioxidant activity by DPPH method and nitric oxide scavenging assay. Among the synthesized compounds DM-1, DM-2 and DM-4 were found to be promising compounds of the series substituted with electron donating groups like methoxy and hydroxyl showed higher antioxidant activity.

INTRODUCTION: From the past few decades the research on furoic acid derivative revealed that the derivative had wide range of therapeutic application [18] and 1, 3, 4- oxadiazoles are biologically active [15, 16], synthetically useful and important heterocyclic compounds.

For these reason the chemistry of 1, 3, 4- oxadiazoles has been the subject of many investigations. 1, 3, 4-oxadiazoles also have wide variety of uses as dyes, UV absorbing and fluorescent materials, heat resistant polymers and scintillation [17].

2, 5- Di-substituted - 1, 3, 4- oxadiazoles constitute a unique class of nitrogen and oxygen containing five membered heterocycles and are reported to possess antifungal [1], antibacterial [6, 7], anti-inflammatory [8, 11], antitubercular [12], analgesic [11] and antioxidant [5] activities. All the furoic acid derivatives were screened for in vitro antioxidant activity by DPPH method and nitric oxide scavenging assay.

MATERIALS AND METHODS: The chemicals used during synthesis were supplied by E. Merck (Germany) and S.D. Fine Chemicals (India). The products were purified by recrystallization using methanol as solvent. Melting points were determined in open capillary method and are uncorrected. The IR spectra were recorded on HITACHI 270-50 INFRA RED Spectrophotometer using a film supported on KBr pellets.

The ^{1}H NMR spectra were recorded on Bruker AC 300 F 300 MHZ NMR Spectrophotometer. All spectra were obtained in DMSO -d_6 and chemical shift values are reported as values in ppm relative to TMS (δ =0) as internal standard. The Mass spectra were recorded on a Jeol SX 102/DA-6000 mass spectrometer, m-nitro benzyl alcohol (NBA) used as the matrix and purity of compounds were checked by TLC on silica gel G plate.

Synthesis of furan-2- carboxylic acid ethyl ester (2) [18]: In a 500 ml round bottom flask, a mixture of furoic acid

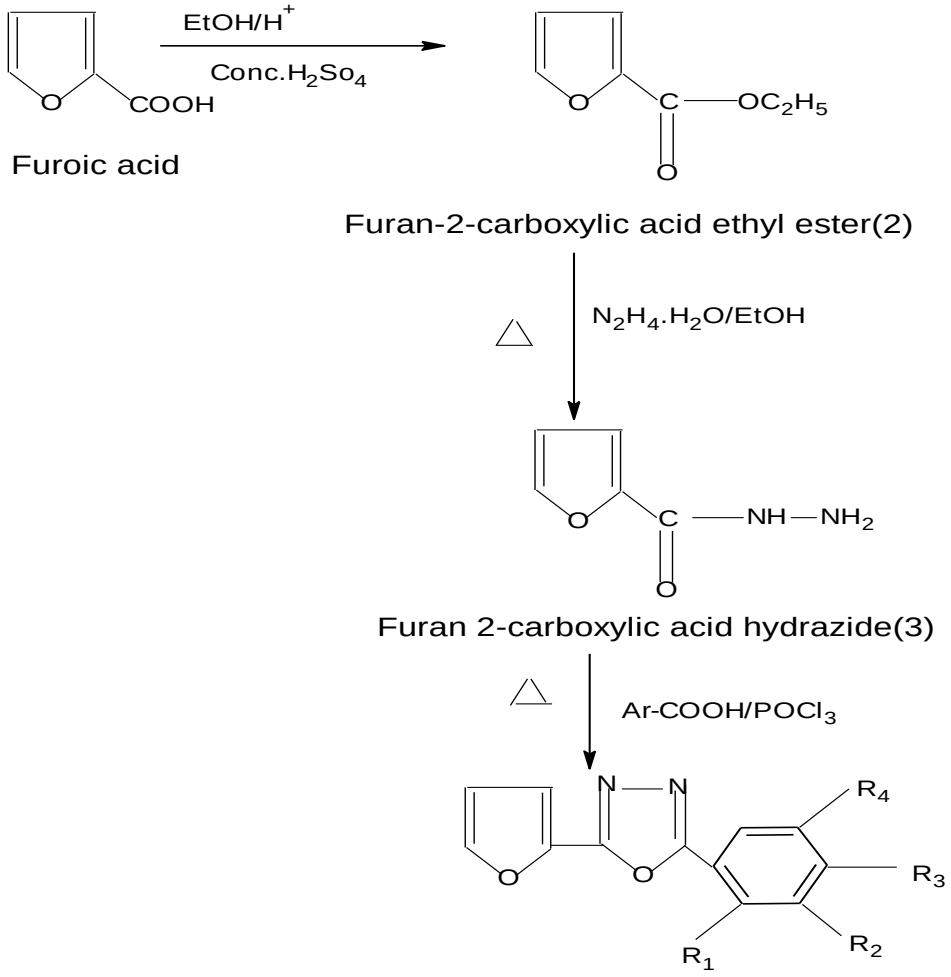
(11.2g, 0.1mol), ethanol (60 ml) and conc. H_2SO_4 (1.4 ml) were refluxed for 10 hours on a water bath. The solution was cooled and poured slowly with stirring on to 200 g of crushed ice. Sufficient ammonia solution was added to render the resulting solution alkaline, generally some ester separates as oil but most of it remains dissolved in the alkaline solution. The solution was extracted five times with ether (25 ml) the combined ethereal extract was dried with anhydrous $MgSO_4$. Ether was removed by evaporation on a water bath and the residue was collected. Physical data of ester was noted; yield 76%, b. pt.- 195^oC

Synthesis of furan-2- carboxylic acid hydrazide (3) [18]**:** A mixture of ester **(2)** and hydrazine hydrate in 1:1 portion and ethanol (30 ml) were taken in a round bottom flask and refluxed for 4-6 hrs. Excess of ethanol was removed by distillation. On cooling the product, acid hydrazide separates out. It was filtered and collected. Recrystallization was carried out with methanol and physical data was noted, yields 65%, m.p 71^oC.

Synthesis of 5-furyl-2-aryl-1, 3, 4-Oxadiazoles [DM (1-6)]: A mixture of acid hydrazide (3) (1.26g, 0.01 mol) and p-Cl benzoic acid (0.01mol) in $POCl_3$ (5ml) was refluxed on water bath for 5-6 hrs. The reaction mixture was cooled and poured onto crushed ice. It was neutralized with sodium bicarbonate solution and the resulting solid was filtered, dried and washed with water and recrystallized from methanol to give DM-1, yield 72%, m.p 110^oC.

Other compounds in the series were prepared similarly as given in **Scheme 1**.

Physical data of 5-furyl-2-aryl - 1, 3, 4 - oxadiazoles are given in **Table 1.** All the synthesized compounds have shown antioxidant activity to certain extent. Results of the screening studies are given in **Table 2 & 3.**



2,5- Disubstitutes -1,3,4- Oxadiazole [DM(1-6)]

SCHEME 1

TABLE 1: PHYSICAL DATA OF SYNTHESIZED COMPOUNDS [DM (1-6)]

Compound	R_1	R_2	R_3	R_4	Molecular Formula	M.P (^{0}C)	Yield (%)	Physical state
DM-1	H	H	CH_3	H	$C_{13}H_{10}N_2O_2$	110°C	72%	Yellow Crystals
DM-2	H	OCH_3	OH	H	$C_{13}H_{10}N_2O_3$	230°C	68%	White Crystals
DM-3	H	H	H	H	$C_{12}H_8N_2O_2$	147°C	74%	Yellow Crystals
DM-4	H	H	OH	H	$C_{12}H_8N_2O_3$	120°C	56%	White Crystals
DM-5	OH	H	H	H	$C_{12}H_8N_2O_3$	165°C	44%	Yellow Crystals
DM-6	H	OH	OH	OH	$C_{12}H_8N_2O_5$	151°C	62%	Orange crystals

TABLE 2: ANTIOXIDANT ACTIVITIES BY DPPH METHOD [DM (1-6)]

Compound	25µg/ml	50µg/ml	75µg/ml	100µg/ml	IC_{50}
DM-1	37.16±0.624	69.19±0.427	84.11±0.467	91.27±0.697	38
DM-2	18.24±0.137	33.06±0.425	47.84±0.401	63.31±0.471	84
DM-3	37.16±0.624	33.62±0.324	51.44±0.425	64.61±0.431	74
DM-4	17.50±0.494	65.15±0.629	75.21±0.529	83.11±0.721	44
DM-5	16.50±0.301	30.26±0.272	39.50±0.402	52.17±0.673	99
DM-6	19.40±0.325	36.35±0.467	43.23±0.451	59.31±0.568	89
BHT	21.48±0.610	25.69±0.610	58.71±0.403	97.31±0.503	48

TABLE 3: ANTIOXIDANT ACTIVITY BY NITRIC OXIDE RADICAL SCAVENGING METHOD [DM (1-6)]

Compound	25µg/ml	50µg/ml	75µg/ml	100µg/ml	IC_{50}
DM-1	37.16±0.29	62.27±0.24	75.41±0.21	87.59±0.21	42
DM-2	34.73±0.09	53.68±0.19	70.94±0.28	84.11±0.27	48
DM-3	11.21±0.31	17.74±0.29	26.83±0.31	43.11±0.03	>100
DM-4	30.51±0.13	56.67±0.25	76.47±0.23	85.20±0.34	42
DM-5	18.24±0.35	33.06±0.42	43.52±0.33	54.21±0.71	96
DM-6	22.81±0.24	33.16±0.42	44.11±0.46	55.01±0.21	94
BHT	13.30±0.04	27.69±0.17	59.61±0.31	96.97±0.60	49

The spectral data of the synthesized compounds:

5-furyl-2-tolyl-1, 3, 4-Oxadiazole (DM-1): IR: 3077 cm^{-1} (C-H str in furan); 1620cm^{-1} (C=N str); 1580 cm^{-1} (C=C str); 3056cm^{-1}(C-H Ar str), 2830-2950 cm^{-1}(C-H str in CH_3), 730-770 cm^{-1}(C-H bend). Mass: m/z 226, molecular ion peak, m/z 139; m/z 107, m/z 105, m/z 77 are other fragment peaks. ^{1}HNMR: 2.3 δ (3H CH_3 gp); 7.2-7.28 δ, 7.69 δ (protons of furan), 1.25δ (3H CH_3), 7.2-7.6δ (5H).

5- furyl- 2- [3- hydroxy- 4- methylphenyl]-1, 3, 4- Oxadiazole (DM-2): IR: 3077 cm^{-1} (C-H str in furan); 1620cm^{-1} (C=N str); 1580 cm^{-1} (C=C str); 3056cm^{-1}(C-H Ar str), 2835-2955 cm^{-1}(C-H str in CH_3), 730-770 cm^{-1}(C-H bend), 3600 cm^{-1}(O-H str), 1200 cm^{-1}(C-Ostr). Mass: m/z 242 molecular ion peak, m/z 134; m/z 107, m/z 105, m/z, 108, m/z 77 are other fragment peaks. ^{1}HNMR: 6.3δ (3H singlet OCH_3gp); 7.2-7.28 δ, 7.69 δ (protons of furan), 7.2-7.6δ (5H), 7.2-7.5δ (4H), 5.78δ (1H OH).

5- furyl- 2- phenyl-1, 3, 4- Oxadiazole (DM-3): IR: 3077 cm^{-1} (C-H str in furan); 1620cm^{-1} (C=N str); 1580 cm^{-1} (C=C str); 3056cm^{-1}(C-H Ar str), 730-770 cm^{-1}(C-H bend). Mass: m/z 212 molecular ion peak, m/z 145; m/z, m/z 78, m/z 51, m/z 39 are other fragment peaks. ^{1}HNMR: 7.2-7.28 δ, 7.69 δ (protons of furan), 7.5δ (5H).

5-furyl-2-[4-hydroxyrophenyl]-1, 3, 4-Oxadiazole (DM-4): IR: 3077 cm^{-1} (C-H str in furan); 1620cm^{-1} (C=N str); 1580 cm^{-1} (C=C str); 3056cm^{-1}(C-H Ar str), 730-770 cm^{-1}(C-H bend), 3600 cm^{-1}(O-H str), 1200 cm^{-1}(C-Ostr), 810 cm^{-1} (para gp.). Mass: m/z 228 molecular ion peak, m/z 130; m/z 107, m/z 65 are other fragment peaks. ^{1}HNMR: 7.2-7.25 δ, 7.63 δ (protons of furan), 7.2-7.6δ (5H), 5.78δ (1H OH).

5- furyl- 2- [2- hydroxyphenyl]-1, 3, 4- Oxadiazole (DM-5): IR: 3077 cm-^{1} (C-H str in furan); 1620cm-^{1} (C=N str); 1580 cm-^{1} (C=C str); 3056cm-^{1}(C-H Ar str), 730-770 cm-^{1}(C-H bend), 3600 cm-^{1}(O-H str), 1200 cm-^{1}(C-Ostr), 750 cm-^{1} (orto gp.) Mass: m/z 228 molecular ion peak, m/z 130; m/z 107, m/z 65 are other fragment peaks. ^{1}HNMR: 7.69 δ (protons of furan), 7.2-7.6δ (5H), 5.78δ (1H OH).

5-furyl-2-[3, 4, 5-trihydroxyphenyl]-1, 3, 4-Oxadiazole (DM-6): IR: 3077 cm^{-1} (C-H str in furan); 1620cm^{-1} (C=N str); 1580 cm^{-1} (C=C str); 3056cm^{-1}(C-H Ar str), 3600 cm^{-1}(O-H str),1200cm^{-1} (C-Ostr), 730-760cm^{-1} Mass: m/z 260 molecular ion isotope peak, m/z 134; m/z 107, m/z 126, m/z 108, m/z 77 are other fragment peaks. 1HNMR: 7.2-7.28 δ, 7.62 δ (protons of furan), 6.2-6.6 δ (2H), 5.18δ (3H OH).

Antioxidant Activity: In the present study DPPH scavenging and Nitric oxide scavenging assay are two in vitro methods used for screening the antioxidant activity. The antioxidant activity of the synthesized compounds expressed as IC_{50} values.

DPPH Assay method [2, 4]: Using the free radical, 2, 2-Diphenyl-1-picrylhydrazyl (DPPH), in its radical form. DPPH has an absorption band at 515 nm which disappears upon reduction by an antiradical compound. The antioxidant activity using the DPPH assay was assessed by the method of Tagas

Nitric Oxide Scavenging Activity Assay: Nitric oxide radical scavenging activity was determined according to the method reported[3]. Sodium nitroprusside in aqueous solution at physiological pH spontaneously generates nitric oxide, with interacts with oxygen to produce nitrite ions, 2ml of 10mM sodium nitroprusside in 0.5 ml phosphate buffer saline (pH 7.4) was mixed with 0.5 ml of test solution at various concentration and the mixture incubated at 25^{o}C for 150 min. From the incubated mixture 0.5 ml was taken out and added into 1.0 ml sulfanilic acid reagent (33% in 20% glacial acetic acid) and incubated at room temperature for 5 min. finally, 1.0 ml naphthylethylene diamine dihydrochloride (0.1% w/v) was mixed and incubated at room temperature for 30 min before measuring the absorbance at 540 nm was measured with a spectrophotometer. The nitric oxide radicals scavenging activity was calculated and data is given in Table 3.

RESULTS AND DISCUSSION: A series of 2-Aryl -5-furyl - 1, 3, 4-oxadiazoles [DM (1-6)] was synthesized. The synthesized compounds were characterized by IR, 1HNMR and Mass spectroscopy. All the synthesized compounds show characteristic absorption peaks in IR and NMR spectra. All the synthesized compounds were in good yield. The synthesized compounds were screened for their in vitro antioxidant activity by DPPH, Nitric oxide scavenging method shows good antioxidant activity, out of all the synthesized compounds 5- furyl -2-tolyl -1, 3, 4 - Oxadiazole (DM-1), 5-furyl-2- [3-hydroxy-4-methylphenyl]- 1, 3, 4-Oxadiazole (DM-2), 5-furyl-2-[4-hydroxyrophenyl]-1, 3, 4- Oxadiazole (DM-4) showed significant antioxidant activity, in these two methods (DPPH Assay method and Nitric oxide scavenging activity assay) remaining compounds possess comparable activity as that of standard drug when compared with butylated hydroxy toluene(BHT).

CONCLUSION: A series of 5-furyl-2-aryl-1, 3, and 4 – oxadiazoles [DM (1-6) derivatives were synthesized by reaction of furoic acid with acid hydrazide and various aromatic acids. The synthesized compounds were screened for in vitro antioxidant assay and out of all this synthesized compounds (DM-1), (DM-2) and (DM-4) showed significant antioxidant activity. The results revealed that the test compound is electron donor and could react with free radical chain reaction and further modifications may produce compounds of better activity with less toxic effects

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