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Synthesis, Antiinflammatory and Antiimicrobial Activity of Some 2,5-Disubstituted-1,3,4-oxadiazoles

RINA DAS* and DINESH KUMAR MEHTA
Sri Sai College of Pharmacy, Badhani, Pathankot-145 001, India
E-mail-rinadas30@indiatimes.com; dimpusa@rediffmail.com

Oxadiazoles are five-membered heterocyclic compounds with two nitrogen atoms and one oxygen atom. A series of 2-aryl-5-furyl-1,3,4-oxadiazoles were synthesized by refluxing 2-furoic acid with ethanol and conc. H_2SO_4. The obtained ester (**2**) was refluxed with hydrazine hydrate and ethanol to give hydrazides (**3**). Reaction of hydrazides (**3**) with different aromatic acids using phosphorousoxy trichloride lead to the formation of 2-aryl-5-furyl-1,3,4-oxadiazoles [**RD(1-9)**]. All the newly synthesized compounds were characterized by analytical and FT-IR, ^{1}H NMR and mass spectra studies. All the newly synthesized compounds were screened for their antibacterial, antifungal and antiinflammatory activities. Some of them have shown significant activity.

Key Words: Antibacterial, Antifungal and Antiinflammatory activity, Furoic acid, Hydrazides, Oxadiazoles.

INTRODUCTION

1,3,4-Oxadiazoles are biologically active[1,2], 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[3].

2,5-Disubstituted-1,3,4-oxadiazoles constitute a unique class of nitrogen and oxygen containing 5 membered heterocycles and are reported to possess antifungal[4], antibacterial[5,6], antiinflammatory[7-10], antitubercular[11], analgesic[10], anticonvulsant activities, *etc*. Similarly a number of furan derivatives are known for their biological activities like antibacterial, antifungal, antihypertensive, diuretic and useful in renal biliary cholic and stomach disorders. In view of the above observations, an attempt was made towards the incorporation of 1,3,4-oxadiazoles with furan moiety to investigate how this combination could influence the antimicrobial and antiinflammatory activity. The newly synthesized compounds were screened for their antibacterial, antifungal and antiinflammatory activity.

EXPERIMENTAL

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 infrared. Spectrophotometer using a film supported on KBr pellets. The ^{1}H NMR spectra were recorded on Bruker AC300 F300 MHz NMR spectrophotometer. All spectra were obtained in DMSO-d_6 and chemical shift values are reported as values in ppm relative to TMS ($\delta = 0$) as internal standard. 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): In a 500 mL round bottom flask, a mixture of furoic acid (11.2 g, 0.1 mol), 60 mL of ethanol and 1.4 mL of conc. H_2SO_4 were refluxed for 10 h on a water bath. The solution was cooled and poured slowly with stirring on to 200 g of crushed ice. Added sufficient ammonia solution 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 5 times with 25 mL ether, 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.p 195 ºC.

Synthesis of furan-2-carboxylic acid hydrazide (3): 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 h. 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.

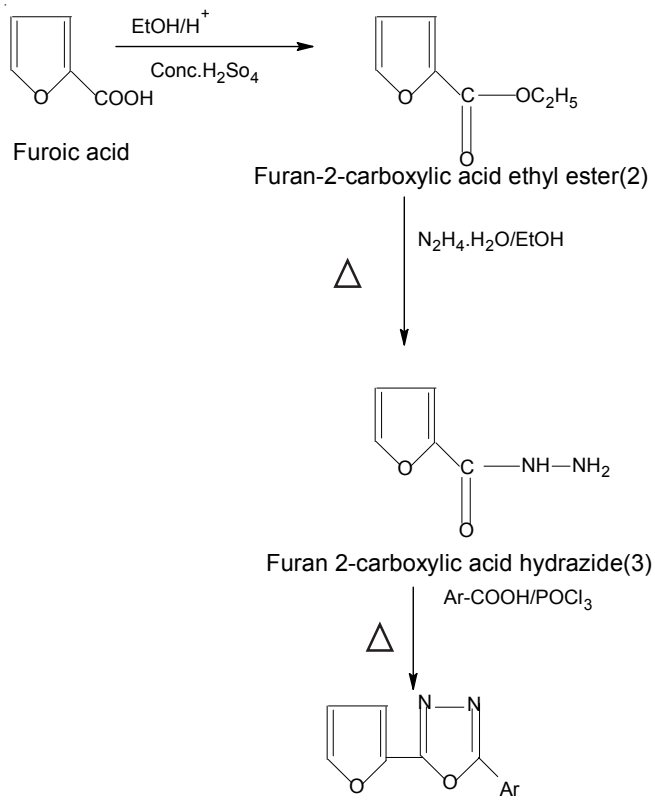
Synthesis of 5-furyl-2-aryl-1,3,4-oxadiazoles [RD (1-9)]: A mixture of acid hydrazide (1.26 g, 0.01 mol) (**3**) and *p*-chloro benzoic acid (0.01mol) in $POCl_3$ (5 mL) was refluxed on water bath for 5-6 h. The reaction mixture was cooled and poured onto crushed ice. It was neutralized with sodium bicarbonate solution and the resulting solid was filtered, dried and washed with water and recrystallized from methanol to give **RD-1**, yield 72 %, m.p. 110 ºC. Other compounds in the series were prepared similarly (**Scheme-I**).

RESULTS AND DISCUSSION

All the synthesized compounds have shown antibacterial activity, antifungal activity and antiinflammatory activity to certain extent. Sensitivity testing was carried out on all the synthesized compounds. Physical characteristic data of the synthesized compounds [**RD(1-9)**] are given in Table-1.

Spectral data

RD-1: [IR: 3077 cm^{-1} (C-H *str.* in furan); 1620 cm^{-1} (C=N *str.*); 1580 cm^{-1} (C=C *str.*); 739 cm^{-1} (C-Cl bend). Mass: m/z 246, 248 molecular ion isotope peak, m/z 139; m/z 107, m/z 105, m/z 154 are other fragment peaks. ^{1}H NMR: 8.0. 8.1 δ (*ortho*-protons of Cl-benzene); 7.54 δ,7.51 δ (*meta*-protons of Cl-benzene); 7.2-7.28 δ,7.69 δ (protons of furan).



2,5-Disubstituted-1,3,7-oxadiazoles [**RD(1-9)**]

RD-1: Ar = *p*-Cl phenyl
RD-2: Ar = *p*-Nitro phenyl
RD-3: Ar = 3,5-Dinitro phenyl
RD-4: Ar = *p*-OH phenyl
RD-5: Ar = *o*-Amino phenyl
RD-6: Ar = Phenyl
RD-7: Ar = *o*-Hydroxy phenyl
RD-8: Ar = 3,4,5-Trihydroxy phenyl
RD-9: Ar = Benzyl

Scheme-I

TABLE-1
PHYSICAL DATA OF SYNTHESIZED COMPOUNDS [**RD (1-9)**]

Compd.	Ar	m.f.	m.p. (ºC)	Yield (%)	Physical state
RD-1	*p*-Cl phenyl	$C_{12}H_7N_2O_2Cl$	110	72	White crystals
RD-2	*p*-Nitro phenyl	$C_{12}H_7N_3O_4$	230	78	Yellow crystals
RD-3	3,5-Dinitro phenyl	$C_{12}H_6N_4O_6$	147	74	Yellow crystals
RD-4	*p*-OH phenyl	$C_{12}H_8N_2O_3$	120	46	White crystals
RD-5	*o*-Amino phenyl	$C_{12}H_9N_3O_2$	107	60	Yellow crystals
RD-6	Phenyl	$C_{12}H_8N_2O_2$	95	68	Yellow crystals
RD-7	*o*-Hydroxy phenyl	$C_{12}H_8N_2O_3$	120	56	Yellow crystals
RD-8	3,4,5-Trihydroxy phenyl	$C_{12}H_8N_2O_5$	165	44	Orange crystals
RD-9	Benzyl	$C_{13}H_{10}N_2O_2$	151	62	Creamy crystals

RD-2: [IR: 3003 cm^{-1}(C-H *str.* in furan); 1623 cm^{-1} (C=N-Ar *str.*); 1514 cm^{-1} (asymmetric), 1348 cm^{-1} (symmetric), N =O *str*. Mass: m/z 257 molecular ion peak, m/z 150, m/z 105, m/z 135, m/z 164 are other fragment peaks. ^{1}H NMR: 8.4 δ (*o*-protons of nitro benzene); 8.35 δ (*meta*-protons of nitro benzene); 6.8, 7.2, 7.78 δ (protons of furan).

RD-3: [IR: 3074 cm^{-1} (C-H *str.* in furan); 1599.66 cm^{-1} (C=N *str.*); 1517 cm^{-1} (C=C *str.*); 1540 cm^{-1} (asymmetric) and 1347 cm^{-1} (symmetric) -N=O *str*. Mass: m/z 302 molecular ion peak; m/z 107, m/z 105, m/z 135 are other fragment peaks ^{1}H NMR: 8.1 δ and 8.0 δ (*ortho* and *para* protons of dinitrobenzene); 6.7-7.7 δ (protons of furan).

Biological activity studies

Antimicrobial activity: All the newly synthesized compounds were screened for their antibacterial activity against some gram positive (*Bacillus subtilis, Staphylococcus aureus*) and gram negative (*Esherichia coli, Pseudomonas aeruginosa*) using ampicillin as standard while the antifungal activity was done against *Candida albicans* and *Aspergilus niger* using griseofulvin as standard drug. Agar diffusion (Cup Plate) method[13] was used with DMF (dimethyl formamide) as the solvent.

Compounds **RD-1**, **RD-2** and **RD-3** are found to be highly active against *E. coli, B. subtilis, P. aeruginosa*. Whereas **RD-4**, **RD-5** and **RD-7** compounds showed moderate activity against *E. coli, P. aeruginosa* and *B. substilis*. All the compounds were found to be mildly active against *S. aureus* compared to the standard drug as shown in Table-2.

The compounds **RD-1**, **RD-2** and **RD-3** are found to be highly active against *C. albicans* and *A. niger* compared to the standard drug. The compounds **RD-4**, **RD-5** and **RD-7** are moderately active against *C. albicans* and *A. niger*. Rest of the compounds exhibited mild activity as shown in Table-3.

TABLE-2
ANTIBACTERIAL DATA OF SYNTHESIZED COMPOUNDS [RD (1-9)]

Compound	Diameter of zone of inhibition (mm)			
	E. coli	*P. aeruginosa*	*S. aureus*	*B. subtilis*
RD-1	18	19	12	18
RD-2	19	18	11	18
RD-3	20	19	12	20
RD-4	15	16	10	15
RD-5	16	15	8	16
RD-6	13	13	9	13
RD-7	16	17	8	16
RD-8	13	14	10	14
RD-9	12	13	9	14
Standard	20	19	22	20
DMF (control)	–	–	–	–

18-20 mm highly active, 15-17 mm moderately active, less than 15 mildly active, 20 mm standard

TABLE-3
ANTIFUNGAL DATA OF SYNTHESIZED COMPOUNDS RD (1-9)

Compound	Diameter of zone of inhibition (mm)	
	C. albicans	*A. niger*
RD-1	18	16
RD-2	19	17
RD-3	19	16
RD-4	16	14
RD-5	17	15
RD-6	13	12
RD-7	16	15
RD-8	14	13
RD-9	12	10
Standard	20	18
DMF (control)	–	–

18-20 mm highly active, 15-17 mm moderately active, less than 15 mm mildly active, 20 mm standard.

Antiinflammatory activity: Carrageenen induced paw edema method was used for evaluation of antiinflammatory activity of the given compounds. The activity was carried out on female albino Wistar rats weighing between 100-140 g using carrageenan (1 % w/v) on the plantar surface of the hind paw of the above stated animals. The test compounds and the standard drug (indomethacin, 20 mg/kg) were administered.

Antiinflammatory test revealed that among the tested compounds **RD-1**, **RD-2, RD-3**, **RD-4** and **RD-5** showed good activity. Whereas compounds **RD-6**, **RD-7**, **RD-8** and **RD-9** were found to have moderate activity in comparison to the reference drug indomethacin as shown in Table-4.

TABLE-4
ANTIINFLAMMATORY DATA OF THE SYNTHESIZED COMPOUNDS

Compound	Increase in paw volume (mL + SE)	% Inhibition in oedema at a dose of 20 mg/kg p.o.
RD-1	0.43±0.014	55.50
RD-2	0.45±0.006	53.72
RD-3	0.40±0.009	58.72
RD-4	0.47±0.011	51.42
RD-5	0.48±0.013	50.34
RD-6	0.56±0.014	42.60
RD-7	0.55±0.012	43.70
RD-8	0.52±0.080	46.27
RD-9	0.54±0.014	44.20
Indomethacin (std.)	0.36±0.014	62.25
Control	0.98±0.027	–

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