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Research Article

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Studies on novel 1,3,4-oxadiazole derivatives

Darshan Raol and G. D. Acharya

Department of Chemistry, R. R. Mehta College of Science, Palanpur, Gujarat, India

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ABSTRACT

Ethyl naphtho[2,1-b]furan-2-carboxylate (1) react with hydrazine hydrate gives naphtho[2,1-b]furan-2-carbohydrazide (2),Which on reaction with CS_2/KOH gives 5-(naphtho[2,1-b] furan-2-yl)-1,3,4-oxadiazole-2(3H)-thione (3). The compound (3) on mannich reaction followed by reaction with phenyl hydrazine gives different 1-((dialkyamino) methyl)-3-(naphtha [2,1-b]furan-2-yl)-4-(phenylamino)-1H-1,2,4-triazole-5(4H)-thione(4a-e). The structures of these compounds were established on basis of analytical and spectral data. The newly synthesized compounds were evaluated for their antibacterial and antifungal activities.

Keywords: naphtho[2,1-b]furan, Oxadiazine, Mannich reaction, Spectral studies, antibacterial and antifungal activities.

INTRODUCTION

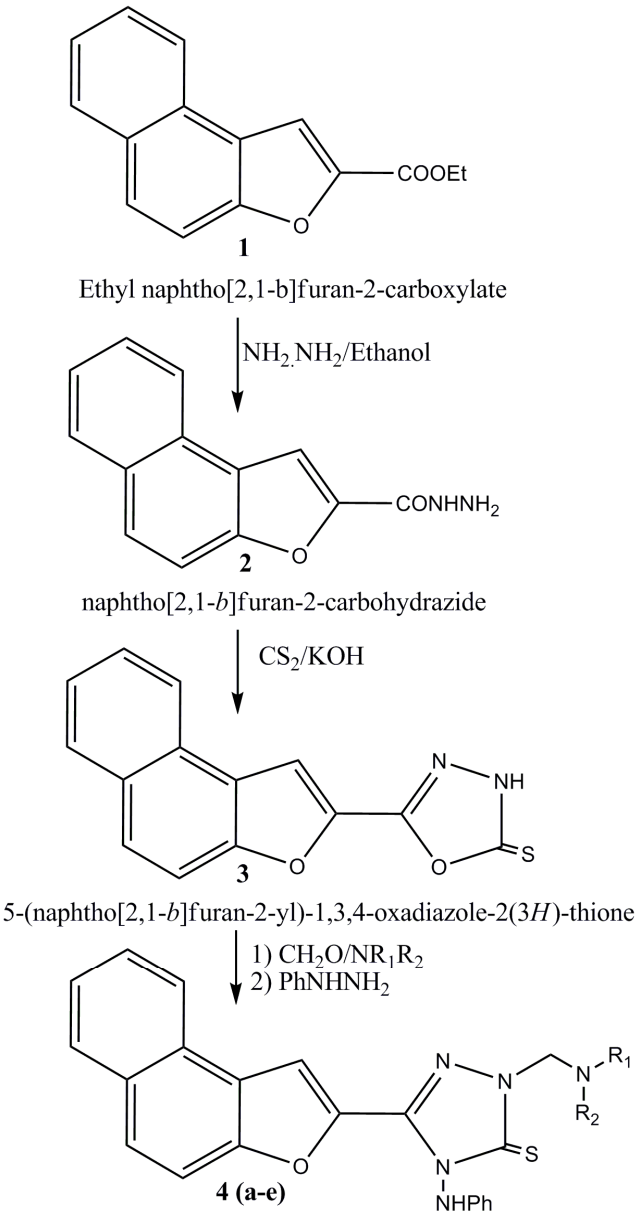
The Biheterocyclic compounds like oxadiazole, thiadiazole, pyrazole, imidazole and triazole are known to possess various biological applications [1-7]. Among them one of the interesting compounds, oxadiazoles and their condensed products shows number of biological activities such as antibacterial, antifungal, anti-inflammatory, analgesic and anticancer activity[8-13]. Naphthofuran derivatives were reported to possess various biological activities such as, antimicrobial agents, antimicrobial, anti-inflammatory activity and anthelmintic activities etc [14-18]. Hence, it was thought of interest to merge both of naphtho[2,1-b]furan and oxadiazole moieties which may enhance the drug activity of compounds to some extent, or they might possess some of the above mentioned biological activities. From this point of view, the objective of the present work is to prepare new derivatives of oxadiazole containing naphtho[2,1-b]furan moiety. Hence the current communication covers the study of 3-((dialkylamino)methyl)-5-((2-((dimethylamino)methyl)-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2(3H)-thione. The synthetic approach is shown in scheme-1.

EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes and were uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer and ^{1}H NMR spectra were recorded in DMSO with TMS as internal standard on a Bruker spectrometer at 400 MHz and 100 MHz, respectively.

Preparation of naphtho[2,1-b]furan-2-carbohydrazide (2):– The compound Ethyl naphtha [2,1-b]furan-2-carboxylate **1** (0.1mol) with hydrazine hydrate (99%), (0.1mol) under acidic condition in absolute ethanol (30 ml) were refluxed for 2-3 hrs. After the completion of reaction as evidenced by TLC, the reaction mixture was poured onto crushed ice; the solid mass thus separated out was filtered, washed with water and dried to gave the desired

compounds **3** in 82% yields.m.p.99°C. IR cm^{-1}: 3127(NH),3200(NH_2),3020-3080(C-H,of Ar.),1685(CONH). ^1H NMR : 7.31–8.63(m, 7H,Ar-H), 8.37 (s,1H,NH), 3.6(s,2H,NH_2). *Anal.* Calcd for $C_{13}H_{10}N_2O_2$(226): C, 69.03; H, 4.42; N, 12.39. Found: C, 69.01; H, 4.39; N, 12.37.



SCHEME – 1

Preparation of 5-(naphtho[2,1-b]furan-2-yl)-1,3,4-oxadiazole-2(3H)-thione (3):-

To a cold stirred solution of naphtho[2,1-b]furan-2-carbohydrazide (2) (0.01 mol) in ethanol (50 mL) containing potassium hydroxide (0.01 mol), carbon disulphide (0.05 mol)was added gradually. The reaction mixture was heated under reflux on a steam-bath until hydrogen sulphide evolution ceased. Ethanol was removed by distillation under reduced pressure and the residue was stirred with water, filtered and the filtrate was neutralized with dilute hydrochloric acid. The product was filtered, washed with water and recrystallized from ethanol to get the compound 5-(naphtho[2,1-b]furan-2-yl)-1,3,4-oxadiazole-2(3H)-thione(3),which were obtained in 65% yield. IR cm^{-1}: 1632-

1646(C=N), 3020-3080 cm^{-1}(C-H, of Ar.), 1185 (C=S),765(C-O-C ring).^{1}H NMR : 7.31–8.63 (m,7H,Ar-H), 9.40 (s,1H, NH). *Anal*. Calcd for $C_{14}H_8N_2O_2S$(268): C,62.67; H, 3.01; N,10.44; S,11.95. Found: C,62.65; H, 3.00; N,10.42; S,11.92.

Preparation of 1-((dialkylamino)methyl)-3-(naphtho[2,1-b]furan-2-yl)-4-(phenylamino)-1H-1,2,4-triazole-5(4H)-thione (4a-e):-

The mixture of 5-(naphtho[2,1-b]furan-2-yl)-1,3,4-oxadiazole-2(3H)-thione (3) (0.1mol) in ethyl alcohol (10ml), formaldehyde (0.1mole) and secondary amine **(a-e)** in ethyl alcohol (10ml) (0.12mol) and the reaction mixture was stirred for 20 hrs. The product that separated as solid was filtered and wash with ethyl alcohol. It was then refluxed with hydrazine hydrate (0.02 mloe) in ethyl alcohol (40 ml) on water bath for 9 hrs. The resultant mixture was poured into cold water, acidified with glacial CH_3COOH and recrystallization from R-sprit gave 3-((dialkylamino)methyl)-5-((2-((dimethyl amino) methyl)-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2(3H)-thione(4a-e), which was obtained in 58-76% yield. The yields, melting points and other characterization data of these compounds are given in Table-1.

Table:-1 Analytical Data and Elemental Analysis of Compounds (4a-e)

Compd.	R_1	R_2	Yield	M.P. ^{0}C	Elemental Analysis							
					%C		% H		%N		%S	
					Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
4a	CH_3	CH_3	70	207	66.46	66.48	5.07	5.09	16.83	16.85	7.70	7.72
4b	CH_3	Et	76	196	67.09	67.11	5.38	5.40	16.28	16.30	7.45	7.47
4c	Et	Et	73	192	67.68	67.69	5.65	5.68	15.76	15.79	7.21	7.23
4d	Et	C_6H_5	62	188	70.83	70.85	5.12	5.13	14.22	14.25	6.51	6.52
4e	C_6H_5	C_6H_5	58	186	73.42	73.45	4.65	4.67	12.96	12.98	5.93	5.94

***** *Uncorrected*

BIOLOGICAL SCREENING

Antibacterial activities

The antibacterial activities of all the compounds were studied against gram-positive bacteria and gram-negative bacteria at a concentration of 50µg/ml by agar cup plate method. A methanol system was used as control in this method. Similar conditions using tetracycline as a control was used standard for comparison. The area of inhibition of zone measured in cm. Compounds 4e was found more toxic for microbes. Other compounds found to be less or moderate active than tetracycline Tables -2.

Table:-3 Antibacterial Activity of Compounds (4a-e)

Compounds	Gram +Ve		Gram -Ve	
	Bacillus subtilis	***Staphylococcus aureus***	***Klebsiella Promioe***	***E.Coli***
4a	57	52	68	63
4b	58	56	67	66
4c	57	52	62	68
4d	65	57	73	73
4e	66	59	74	72
Tetracycline	68	60	77	80

Antifungal Activities

The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro. Plant pathogenic organisms used were *Nigrospora Sp, Aspergillus niger, Botrydepla diathiobromine, and Rhizopus nigricum***,** *Fusarium oxyporium*. The antifungal activities of all the compounds (4a-e) were measured on each of these plant pathogenic strains on a potato dextrose agar (PDA) medium. Such a PDA medium contained potato 200g, dextrose 20g, agar 20g and water 1c. Five days old cultures were employed. The compounds to be tested were suspended (1000ppm) in a PDA medium and autoclaved at 120^o C for 15 min. at 15atm. pressure. These media were poured into sterile Petri plates and the organisms were inoculated after cooling the Petri plates. The percentage inhibition for fungi was calculated after five days using the formula given below:

Percentage of inhibition = 100(X-Y) / X

Where, X = Area of colony in control plate

Y = Area of colony in test plate

The fungicidal activity displayed by various compounds (4a-e) is shown in Tables-4.

Table:-4 Antifungal Activity of Compounds (4a-e)

Zone of Inhibition at 1000 ppm (%)			
Compounds	***Rhizopus Nigricum***	***Nigrospora Sp.***	***Aspergillus Niger***
4a	60	66	67
4b	59	67	65
4c	64	64	64
4d	68	74	70
4e	73	73	72

RESULTS AND DISCUSSION

It was observed that naphtho[2,1-b]furan-2-carbohydrazide (2) react with carbon disulphide to afford the corresponding 5-(naphtho[2,1-b]furan-2-yl)-1,3,4-oxadiazole-2(3H)-thione**(3)**. The structures of (3) were confirmed by elemental analysis and IR spectra showing an absorption band at 3225(N-H),1612-1642(C=N), 3025-3080 cm^{-1}(C-H, of Ar.), 1168 (C=S),775(C-O-C ring).^{1}H NMR : 7.62–8.68(m, 8H,Ar-H and NH).

The structures assigned to 1-((dialkyamino)methyl)-3-(naphtho[2,1-b]furan-2-yl)-4-(phenylamino)-1H-1,2,4-triazole-5(4H)-thione(4a-e) were supported by the elemental analysis and IR spectra showing an absorption bands at 3225(N-H), 1612-1642(C=N), 3025-3080 cm^{-1}(C-H of Ar.), 1168(C=S), 775(C-O-C ring), 2950, 1370 cm^{-1} (-CH_3). ^{1}H NMR: 7.02–8.69(m, 12H, Ar-H), 4.56(s, 2H, CH_2), 3.98(s, 1H, NH), 4a; 2.15(s, 6H, CH_3), 4b; 2.27(s, 3H,CH_3), 1.12(t,3H,CH_3),2.66(q, 2H, CH_2), 4c; 1.11(t, 6H, CH_3), 2.67(q, 4H, CH_2), 4d; 1.11(t, 3H, CH_3), 2.66 (q, 2H, CH_2), 6.81–7.22(m,5H,Ar-H),4e; 6.81–7.23(m,10H,Ar-H).The C, H, N, S analysis data of all compounds are presented in Table-1.

The examination of elemental analytical data reveals that the elemental contents are consistence with the predicted structure shown in Scheme-1. The IR data also direct for assignment of the predicted structure.The Compound 4e shows good antibacterial and antifungal activity.

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