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Research Article

SYNTHESIS OF 2-(NAPHTHO[2,1-B]FURAN-2-YL)-5-PHENYL-1,3,4-OXADIAZOLE DERIVATIVES AND THEIR ANTIMICROBIAL ACTIVITIES

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ABSTRACT

The reaction of ethyl naphtho[2,1-b]furo-2-carboxylate (2) with hydrazine hydrate in presence of catalytic amount conc. HCl in ethanol at reflux temperature afforded naphtho[2,1-b]furan-2-carbohydrazide (3) in good yield. The reaction of naphtho[2,1-b]furan-2-carbohydrazide with aromatic aldehydes (4a-f) in ethanol in the presence of acid catalyst produces N1-[substituted-phenylmethylidene]naphtho[2,1-b]furan-2-carbohydrazide (5a-f). These N1-[substituted-phenyl methylidene]naphtho[2,1-b]furan-2-carbohydrazide 5a-f on treatment with 1.2 equivalence of iodine and potassium carbonate in DMSO produces 2-(naphtho[2,1-b]furan-2-yl)-5-(substituted) phenyl 1,3,4-oxidiazole derivatives (6a-f). The structures of newly synthesized compounds have been established by elemental analysis and spectral studies. These compounds have been screened for antimicrobial activities.

Keywords: Ethyl naphtho[2,1-b]furo-2-carboxylate, naphtho[2,1-b]furan-2-carbohydrazide, aromatic aldehydes, 2-(naphtho[2,1-b]furan-2-yl)-5-phenyl-1,3,4-oxadiazole, antimicrobial activity

INTRODUCTION

The chemistry of the compounds containing the condensed oxadiaoles play significant role in pharmaceutical industry. Among various oxadiazoles, 1,3,4-oxadiazoles and its derivatives attracted attention due to their wide spectrum of biological and pharmacological activities such as antimicrobial, antifungal [1-4], anticonvulsant activity [5,6], anti-inflammatory, analgesic [7], antitumor [8,9] and other biological activities [10,11]. The derivatives of 1,3,4-oxadiazoles act as HIV reverse transcriptase inhibitors [12]. Several derivatives of naphtho[2,1-b]furan synthesized in our laboratory have been reported to possess many biological and pharmacological activities such as antimicrobial, analgesic, anti-inflammatory, diuretic, anthelmintic, antipyretic etc [13-15].

Survey of literature revealed that, similar type of work involving 1,3,4-oxadiazole and naphtho[2,1-b]furan either in condensed form or in coupled form has not been reported. Hence it is thought of interest to synthesize 2-(naphtho[2,1-b]furan-2-yl)-5-phenyl-1,3,4-oxadiazole derivatives and evaluate them for antibacterial and antifungal activities.

EXPERIMENTAL METHODS AND CHARACTERIZATION

Step 1: Synthesis of 2-hydroxy-1-naphthaldehyde (1)

2-Naphthol (0.04 mol) was dissolved in 15 ml ethanol to this NaOH (0.25 mol) of in 21 ml water was added and kept stirring. To this 4.2 ml of chloroform was added drop wise, after the completion of addition the reaction mixture kept for stirring for about 2 hours. The reaction mixture was poured to ice cold water and neutralized with dilute HCl solid separates filtered and dried. The product obtained was recrystallised from ethanol.

Step 2: Synthesis of ethyl naphtho[2,1-b]furan-2-carboxylate (2)

To a solution of 2-hydroxy-1-naphthaldehyde (1) (0.03 mol) in dry N, N-dimethylformamide (25 ml), ethyl chloro acetate (0.03 mol) and anhydrous potassium carbonate (0.9 mol) were added and the reaction mixture was refluxed on water bath for 24 hours. The reaction mixture was filtered and potassium carbonate was washed with DMF.

The filtrate was concentrated by distillation then poured into ice cold water, to obtain the product as solid which was collected by filtration, dried and recrystallised from ethanol (2).

The IR spectrum of (2) exhibited the absorption band at 1732 cm^{-1} due to C=O of ester group. In 1H NMR spectrum ($CDCl_3$) triplet at d 1.5 due to -CH_3 protons, a quartet at δ 4.5 due to –CH_2 protons and a multiplet at δ 7.6-8.2 integrating for 7 aromatic protons.

Step 3: Synthesis of naphtho[2,1-b]furan-2-carbohydrazide (3)

Ethyl naphtho[2,1-b]furo-2-carboxylate (2) (0.01 mol), catalytic amount of conc. hydrochloric acid and hydrazine hydrate (0.02 mol) were refluxed in absolute ethanol (25 ml) for 2 hrs on water bath. Then the reaction mixture was cooled to room temperature, the solid thus obtained was filtered and dried. The product obtained was recrystallised from ethanol (3).

The structure of (3) was well confirmed by elemental analysis and spectral studies. The IR spectrum of (3) exhibited broad absorption band at 3304-2969 cm^{-1} due to NH_2 and a sharp absorption band at 1657 cm^{-1} due to C=O group. 1H NMR spectrum of (3) shows a broad singlet at d 4.6, 1H, NH, (D_2O exchangeable), multiplet d 7.4-8.6, for 7 aromatic protons and a singlet at d 9.8 for 2 NH_2 protons.

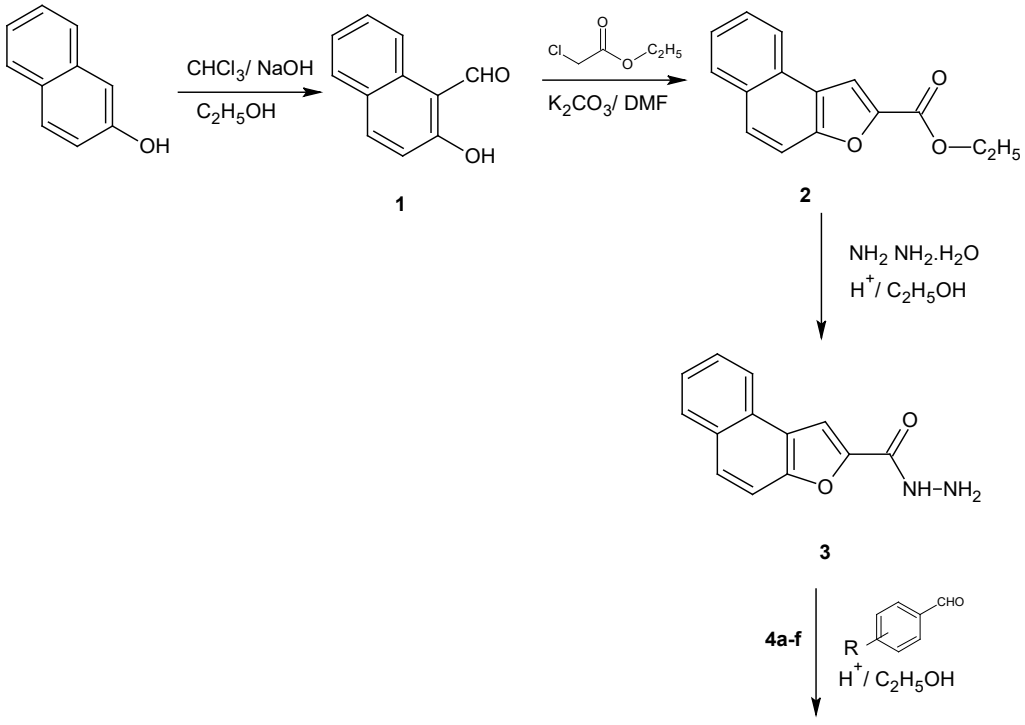
Step 4: Synthesis of N1-[substituted-phenylmethylidene]naphtho[2,1-b]furan-2-carbohydrazide (5a-f).

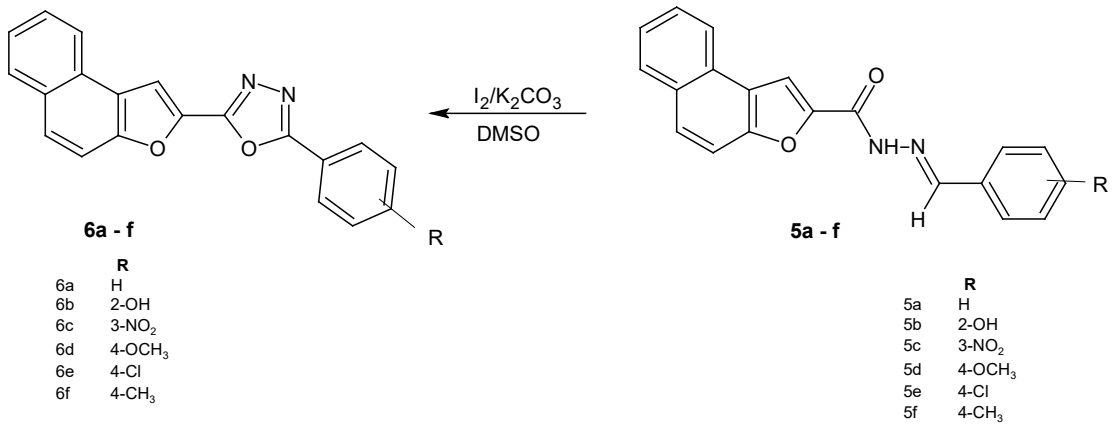
The reaction of naphtho[2,1-b]furan-2-carbohydrazide (0.452 gm 0.002 mol) with anisaldehyde (0.27 gm, 0.002mol) in ethanol (10 ml) at reflux temperature in presence of Conc. HCl undergo condensation and produces N'-[(4methoxyphenyl) methylidene]naphtho[2,1-b]furan-2-carbohydrazide (5d).

The structure of (5d) was well confirmed by spectral studies. The IR spectrum of (5d) exhibited broad absorption band at 3300-2970 cm^{-1} due to NH, a sharp absorption band at 1652 cm^{-1} due to C=O group and band at 1585 cm^{-1} due to C=N. In 1H NMR spectrum ($CDCl_3$) singlet at δ 3.9 integrating for 3-OCH_3 protons, singlet at d 4.4, for 1 NH proton and a multiplet at δ 7.6-8.6 integrating for 11 aromatic protons. The same method employed for the synthesis of (5a-c) and (5e-f).

Step 5: Synthesis of 2-(naphtho[2,1-b]furan-2-yl)-5-(substituted) phenyl 1,3,4-oxidiazole (6a-f)

The reaction of N1-[substituted-phenylmethylidene] naphtho[2,1-b]furan-2-carbohydrazide (0.344 gm 0.001 mol) with iodine (1.2 equivalent 0.30 gm) and potassium carbonate (0.69 gm 0.005 mol) in DMSO 10 ml refluxed for 8 hours produces 2-(4-methoxyphenyl)-5-(naphtho[2,1-b]furan-2-yl)-1,3,4-oxadiazole (6d). The same method was followed for the synthesis of compounds (6a-c) and (6e-f) from (5a-c) and (5e-f) (Figure 1).





R	
6a	H
6b	2-OH
6c	3-NO_2
6d	4-OCH_3
6e	4-Cl
6f	4-CH_3

R	
5a	H
5b	2-OH
5c	3-NO_2
5d	4-OCH_3
5e	4-Cl
5f	4-CH_3

Figure 1: Synthetic route-1

The structure of (6d) was well confirmed by elemental analysis and spectral studies. 1H NMR (DMSO-d_6) spectrum of (6d) shows a singlet at d 3.8, 3H, OCH_3 and a multiplet d 7.6-8.6, for 11 aromatic protons. The physical data of newly synthesized compounds were reported in (Table 1). The compounds encompassing naphthofuran and oxadiazole are known to exhibit wide spectrum of biological and pharmacological activities. Hence, it was intrigued to evaluate newly synthesized compounds for antimicrobial activities by adopting literature procedure [13,14]. The results were reported in (Table 2).

Table 1: Physical data of newly synthesized compounds

Comp.	R	M.p. 0 C	Yield (%)	Mol. formula	Clad (Found) %		
						H	N
1	-----	80	65	$C_{12}H_{10}O_2$	77.4	5.41	----
					77.28	5.29	
2	----	100	63	$C_{15}H_{12}O_3$	74.99	5.03	19.98
					74.86	4.89	19.81
3	----	270	67	$C_{13}H_{10}N_2O_2$	69.02	4.46	12.38
					68.85	4.32	12.25
5a	H	109	71	$C_{20}H_{14}N_2O_2$	76.42	4.49	8.91
					76372	4.37	8.82
5b	2-OH	134	67	$C_{20}H_{14}N_2O_3$	72.72	4.27	8.28
					72.61	4.18	8.16
5c	3-NO_2	141	68	$C_{20}H_{13}N_3O_4$	66.85	3.65	11.9
					66.76	3.54	11.81
5d	4-OCH_3	168	69	$C_{21}H_{16}N_2O_3$	73.24	4.68	8.13
					73.13	4.56	8.01
5e	4-Cl	153	71	$C_{20}H_{13}ClN_2O_2$	68.87	3.76	8.03
					68.77	3.65	7.91
5f	4-CH_3	127	71	$C_{21}H_{16}N_2O_2$	76.81	4.91	8.53
					76.7	4.82	8.42
6a	H	143	68	$C_{20}H_{12}N_2O_2$	76.91	3.87	8.97
					76.8	3.76	8.86
6b	2-OH	149	66	$C_{20}H_{12}N_2O_3$	73.16	3.68	8.53
					73.07	3.57	8.41
6c	3-NO_2	165	67	$C_{20}H_{11}N_3O_4$	67.23	3.1	11.76
					67.11	3	11.64
6d	4-OCH_3	189	69	$C_{21}H_{14}N_2O_3$	73.68	4.12	8.18
					73.53	4.02	8.05
6e	4-Cl	170	65	$C_{20}H_{11}ClN_2O_2$	69.27	3.2	8.08
					69.18	3.11	7.99
6f	4-CH_3	156	65	$C_{21}H_{14}N_2O_2$	77.29	4.32	8.58
					77.2	4.21	8.49

Table 2: The results of antimicrobial activities

Comp.	Antibacterial activity		Antifungal activity	
	P. aeruginosa	*S. aureus*	*A. niger*	*C. Lunata*
6a	20	20	19	19
6b	21	19	20	19
6c	19	18	19	19
6d	19	18	19	18
6e	18	18	18	18
6f	17	17	18	17
Standard	24	24	24	26
DMF	NIL	NIL	NIL	NIL

RESULTS AND DISCUSSION

With the literature survey, it was found that the derivatives of the 1,3,4-oxadiazole show action as the HIV reverse transcriptase inhibitors and several naphtho[2,1-b]furan derivatives show the analgesic, anti-inflammatory, antipyretic, antibacterial as well as the antifungal activities and therefore the derivatives of 2-(naphtho[2,1-b]furan-2-yl)-5-phenyl-1,3,4-oxadiazole were synthesized and evaluated for their mentioned properties. By reacting ethyl naphtho[2,1-b]furo-2-carboxylate (2) with hydrazine hydrate in the presence of concentrated HCl in an ethanol solution at the an optimum temperature, naphtho[2,1-b]furan-2-carbohydrazide (3) was formed. Further reactions of the naphtho[2,1-b]furan-2-carbohydrazide with aromatic aldehydes in the presence of acid catalyst in ethanol, N1-[substituted-phenylmethylidene] naphtho[2,1-b]furan-2-carbohydrazide (5a-f) was formed and these N1-[substituted-phenyl methylidene]naphtho[2,1-b]furan-2-carbohydrazide 5a-f when treated in the presence of DMSO with iodine and potassium carbonate, it produces 2-(naphtho[2,1-b]furan-2-yl)-5-(substituted) phenyl 1,3,4-oxidiazole derivatives (6a-f).

The compounds were synthesized and their several biological as well as the pharmacological activities were evaluated by applying or performing the elemental or structural analysis and the spectral studies. Firstly, the 2-hydroxy-1-naphthaldehyde was synthesized and then ethyl naphtho[2,1-b] furan-2-carboxylate (2) was synthesized, where by performing one of the spectral analysis i.e., IR spectroscopy, which has shown its absorption band at 1732 cm^{-1} due to the presence of the C=O of ester group. In ^1H NMR spectrum ($CDCl^3$) triplet at d 1.5 due to -CH_3 protons, a quartet at δ 4.5 due to –CH_2 protons and a multiplet at δ 7.6-8.2 integrating for 7 aromatic protons. Later on, the naphtho[2,1-b]furan-2-carbohydrazide (3) was synthesized and its IR spectrum of (3) exhibited broad absorption band at 3304-2969 cm^{-1} due to the presence of NH_2 and a sharp absorption band at 1657 cm^{-1} due to the presence of C=O group. While coming to the NMR studies, ^1H NMR spectrum of (3) has shown a broad singlet at d 4.6, ^1H, NH, (D_2O exchangeable), multiplet d 7.4-8.6, for 7 aromatic protons and a singlet at d 9.8 for 2 NH_2 protons.

The another compound that has been synthesized and analyzed was N1-[substituted-phenylmethylidene] naphtho[2,1-b]furan-2-carbohydrazide. After synthesizing the compound, the IR spctra of (5d) have been exhibited with the broad band as well as the sharp absorption band. The broad band was seen at 3300-2970 cm^{-1} due to the presence of NH. The sharp absorption band was seen at the 1652 cm^{-1} due to the presence of C=O group and another band at 1585 cm^{-1} due to the presence of C=N. In NMR studies, ^{1}HNMR spectrum has shown a singlet at δ 3.9 integrating for 3 -OCH_3 protons, another singlet at d 4.4, for one NH proton and a multiplet at δ 7.6-8.6 integrating for 11 aromatic protons. The same method employed for the synthesis of (5a-c) and (5e-f). After synthesizing 2-(naphtho[2,1-b]furan-2-yl)-5-(substituted) phenyl 1,3,4-oxidiazole (6a-f), the NMR studies i.e., ^1H NMR (DMSO-d6) spectrum of (6d) shown a singlet at d 3.8, 3H, OCH_3 and a multiplet d 7.6-8.6, for 11 aromatic protons.

The various compounds were synthesized and evaluated through the elemental as well as the spectral analysis. From the data obtained after analyzing, the newly synthesized compounds that are exhibiting the naphthofuran and oxadiazole are found to be shown with the wide spectrum of biological and pharmacological activities. Therefore, the newly synthesized compounds exhibit the antimicrobial activities so as the literature survey.

CONCLUSION

The newly synthesized compounds were evaluated for antimicrobial activity. All the compounds were displayed significant antibacterial activity against both the organisms. It is observed that electron withdrawing groups resulted in enhancement of activity.

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