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Synthesis characterization and pharmacological activities of some novel napthofuryltriazolothiadiazoles

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ABSTRACT

Ethyl naphtho [2, 1-b] furan-2-carboxylate **2a** was synthesized from 2-hydroxy-1-naphthaldehyde by treating it with ethyl chloroacetate. This was subsequently brominated and nitrated under suitable reaction conditions to get compounds **2b and 2c.** The compounds **2a-c** were hydrolyzed to obtain corresponding 3-substituted naphtho [2, 1-b] furan-2 carboxylic acids **3a-c.** The title compounds i.e. 3-alkyl-6-(naphtho[2,1-b]furan-2yl)[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles **5a-i** were synthesized by reacting acids **3a-c** with 3-alkyl-3-amino-5-mercapto-1,2,4-triazoles **4a-c** in presence of phosphorus oxychloride. All the newly synthesized title compounds have been characterized and evaluated for antibacterial and antifungal activity.

Keywords: Naphtho [2, 1-b] furan**,** 1, 2, 4-triazoles, 1, 3, 4-thiadiazoles, naphthofuroic acids*,* antifungal and antibacterial activities.

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INTRODUCTION

1, 2, 4-Triazoles and 1, 3, 4- thiadiazoles represent one of the most biologically active classes of compounds, possessing a wide spectrum of activities [1-5]. Various substituted 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles are associated with diverse pharmacological activities such as antibacterial [6,7], antitubercular [8], anti-inflammatory [9,10], antifungal [11]. Moreover, triazoles fused with other heterocyclic rings have attracted particular attention due to their diverse applications such as antibacterial, antidepressant, antiviral, antitumor, anti-inflammatory, pesticide, herbicide, lubricant and analytical reagents [12,13]. A number of triazoles fused with thiadiazines and thiadiazoles are incorporated into a wide variety of therapeutically important compounds possessing a broad spectrum of biological activities [13-16].

Naphthofurans possess a wide range of biological activities that are constituents of important natural products [17-24]. Naphthofuran derivatives exhibit very potent antibacterial [25-27], genotoxic [28,29] and anticancer activities [30,31].

Prompted by these facts and in continuation of our research work on synthesis of biologically and pharmacologically important derivatives of naphtho [2, 1-b] furan, it was contemplated to synthesize various novel fused napthofuryltriazolothiadiazoles and to screen them for their antimicrobial activities.

MATERIALS AND METHODS

Melting points were determined in open capillaries and are found uncorrected. The purity of the compounds was checked by TLC. IR spectra were recorded in KBr on a Perkin Elmer Spectrometer. ^{1}H NMR spectra were recorded on Brucker 300 MHz instrument in DMSO-d_6 as solvent and TMS as an internal standard.

Synthesis of ethyl naphtho [2, 1-b] furan-2-carboxylate 2a

To a solution of 2-hydroxy-1-naphthaldehyde **1** (5.16 g, 0.03 mol) in dry N,N-dimethylformamide (25 ml), ethyl chloroacetate (3.66 g, 0.03 mol) and anhydrous potassium carbonate (12.4 g, 0.9 mol) were added and the reaction mixture was heated on water bath for 24 h. The reaction mixture was then poured into ice cold water, to obtain the product ethyl naphtho [2, 1- *b*] furan-2-carboxylate **2a** as solid, which was collected by filtration, dried and recrystallised from ethanol.

Synthesis of ethyl 3-bromonaphtho [2, 1-b] furan-2carboxylate 2b

To a solution of ethyl naphtho[2,1-b]furan- 2-carboxylate **2a** (0.1 mol) in glacial acetic acid(20 ml) was added a solution of bromine (0.1 mol) in acetic acid (20 ml) with stirring during 1h at 10-20^0 C and the stirring was continued for 3h. The reaction mixture was poured into ice-

cold water and the solid obtained was filtered out. It was washed with water, dried and the product was recrystallised from ethanol.

Synthesis of ethyl 3-nitronaphtho [2, 1-b] furan-2-carboxylate 2c

To a solution of ethyl naphtho[2,1-b]furan-2-carboxylate **2a** (0.1 mol) in glacial acetic acid (20 ml), nitrating mixture of concentrated sulphuric acid and concentrated nitric acid (1:1, 5 ml) was added with stirring during 1h at 10-20^0 C and the stirring was continued for 3h. The reaction mixture was poured into ice-cold water and the solid obtained was filtered out. It was washed with water, dried and the product was recrystallised from ethanol.

Synthesis of 3-substituted-naphtho [2, 1- *b*] furan-2-carboxylic acids (3a-c)

Ethyl naphtho [2, 1-b] furan 2-carboxylate **2a** (0.01 mol) was dissolved in methanol (25 ml) and mixed with aqueous sodium hydroxide solution (10%, 10 ml). The mixture was refluxed for 2h. After the completion of the hydrolysis (TLC), the reaction mixture was poured into ice cold water and acidified with hydrochloric acid. The compound 3a that separated as solid was collected by filtration and recrystallised from ethanol.

Similarly the carboxylic acids **3b-c** was synthesized by the hydrolysis of corresponding esters **2b-c.**

Synthesis of 3-Alkyl-6-(naphtho [2,1-b] furan-2-yl) [1,2,4]triazolo[3,4-b] [1,3,4]thiadiazoles(5a-i)

To an equimolecular mixture of suitable 3-alkyl-4-amino-5-mercapto-1, 2, 4-triazoles **4a-c** (10 mmol) and 3-substituted-naphtho [2, 1-b] furan-2-carboxylic acids **(3a-c)** (10 mmol) in dry toluene (15 ml), phosphorous oxychloride (2 ml, 20 mmol) was added. The resulting solution was refluxed for 2h on a water bath. The excess of $POCl_3$ and toluene were distilled off under reduced pressure and the residue was poured into crushed ice with stirring. The resultant solid was collected, washed with water and dilute sodium bicarbonate solution and was recrystallised from dimethylformamide to yield the title compounds. The characterization data of compounds **5a-i** are recorded in Table 1.

The sequence of the reaction is depicted in the Scheme-I.

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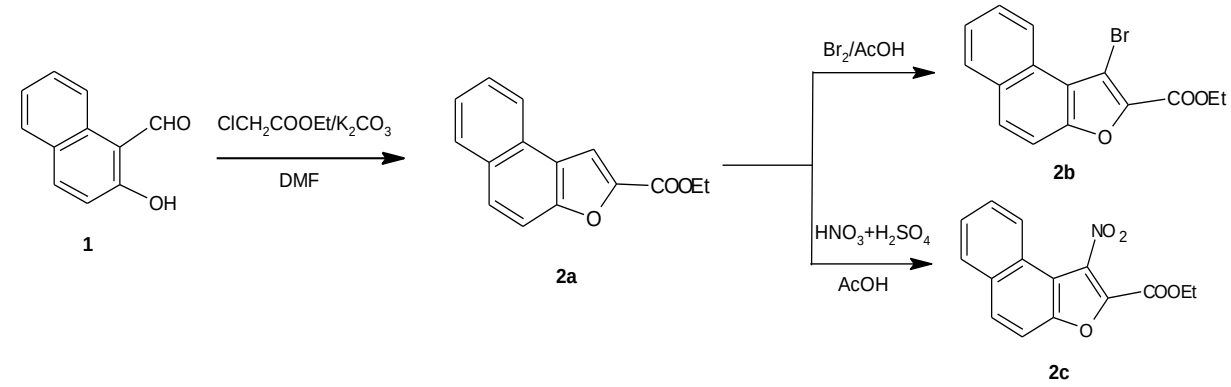

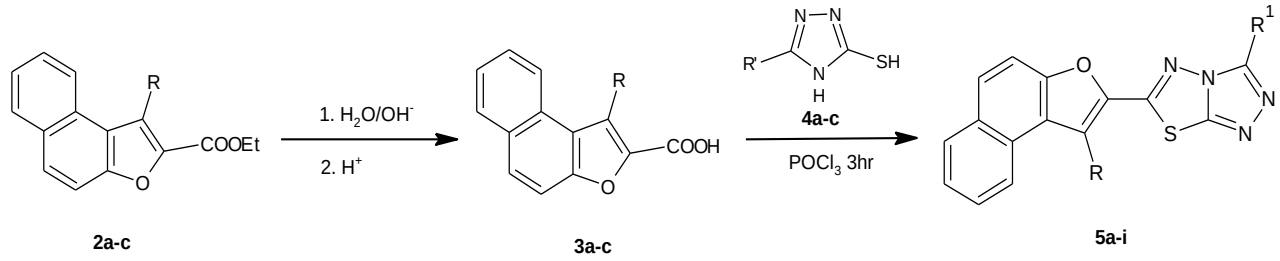

	R
2a	H
2b	Br
2c	NO_2

	R
3a	H
3b	Br
3c	NO_2

	R	R^1
5a	H	H
5b	H	CH_3
5c	H	C_2H_5
5d	Br	H
5e	Br	CH_3
5f	Br	C_2H_5
5g	NO_2	H
5h	NO_2	CH_3
5i	NO_2	C_2H_5

SCHEME-1

The physical and analytical data of all the compounds has been summarized in Table 1.

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Table 1- Physical and analytical data of synthesized compounds

Compd.	R	R^1	Molecular formula	m.p. ^0C	Yield (%)	Elemental Analysis (%) Calculated (Found)		
						C	H	N
3a	H	-	$C_{13}H_8O_3$	174	85	73.5(73.2)	3.0(2.98)	-
3b	Br	-	$C_{13}H_7BrO_3$	228	88	53.6(53.22)	2.4(2.33)	-
3c	NO_2	-	$C_{13}H_7NO_5$	>280	75	60.7(60.31)	2.7(2.53)	5.44(5.32)
5a	H	H	$C_{15}H_8N_4OS$	200	70	61.6(61.2)	2.7 (2.3)	19.1(18.9)
5b	H	CH_3	$C_{16}H_{10}N_4OS$	238	78	62.7(62.2)	3.26(3.11)	18.3(17.98)
5c	H	C_2H_5	$C_{17}H_{12}N_4OS$	232	83	63.75(63.20)	3.75(3.33)	17.18(16.96)
5d	Br	H	$C_{15}H_7BrN_4OS$	229	76	48.51(48.25)	1.88(1.76)	15.08(15.1)
5e	Br	CH_3	$C_{16}H_9BrN_4OS$	241	85	49.84(49.43)	2.33(2.21)	14.53(14.23)
5f	Br	C_2H_5	$C_{17}H_{11}BrN_4OS$	>290	79	51.10(51.13)	2.75(2.70)	14.02(13.97)
5g	NO_2	H	$C_{15}H_7N_5O_3S$	>295	82	53.36(53.11)	2.07(1.98)	20.75(20.36)
5h	NO_2	CH_3	$C_{16}H_9N_5O_3S$	300	81	54.64(54.15)	2.56(2.51)	19.92(19.42)
5i	NO_2	C_2H_5	$C_{17}H_{11}N_5O_3S$	>300	70	55.83(55.21)	3.01(2.95)	19.15(18.88)

Antimicrobial activity

The compounds **5a-i** was evaluated for antibacterial and antifungal activities by agar diffusion method.

Antibacterial activity

The compounds **5a-i** were screened for their *in vitro* antibacterial activity against Gram positive bacteria viz., *Staphyllococcus aureus* and Gram negative bacteria viz., *Escherichia coli*. Gentamycin was used as the standard drug for comparison of activity at concentrations of 2.0 mg. The zone of inhibition was measured after incubation at 37^0 C for 24 h.

Antifungal activity

The compounds **5a-i** was evaluated for antifungal activity by agar diffusion method against *Candida albicans* and *Aspergillus niger* Amphotericin was used as the standard drug for comparison of activity at concentration of 2.0 mg. The zone of inhibition was measured after incubation at 27^0 C for 48 h.

The results of preliminary screening are presented in Table-2.

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Table 2- Antimicrobial activity data at 2 mg concentration of 3-alkyl-6-(naphtho [2,1-b]furan-2-yl)[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles(5a-i)

Compd.	Zone of inhibition in cm			
	Antibacterial activity		Antifungal activity	
	S. aureus	*E. coli*	*A.niger*	*C.albicans*
5°	0.2	0.6	0.6	0.6
5b	0.0	0.2	0.5	0.4
5c	0.0	0.0	0.0	0.0
5d	0.0	0.2	0.4	0.2
5e	0.0	0.0	0.0	0.3
5f	0.2	0.6	0.6	0.3
5g	0.0	0.9	0.0	1.2
5h	0.0	0.8	0.0	1.5
5i	0.0	0.0	0.0	1.4

The screening data indicated that all the synthesized naphthofuryltriazolothiadiazoles did not show any appreciable antibacterial activity against *S. aureus*. The compounds **5a, 5f, 5g, 5h** were found to be active against *E. coli.* The compounds **5a, 5b, 5d,** and **5f,** were found to be active against *A. niger, where* as the compounds **5a, 5b, 5g, 5h** and **5i** were found to be considerable active against *C. albicans.*

Hence, the above compounds were selected for further evaluation to find out minimum inhibitory concentration (MIC) by similar method.

Tube dilution method used to obtain the solutions of different concentration. The solution of concentrations of 0.0625 mg, 0.125 mg, 0.25 mg, 0.5 mg, 1.0 mg and 2.0 mg were tested for activity. Gentamycin was used as the standard drug at concentrations of 25 µg, 50 µg, 100 µg, 200 µg, 400 µg and 800 µg for comparison of antibacterial activity and Amphotericin was used as the standard drug at concentrations of 25 µg, 50 µg, 100 µg, 200 µg, 400 µg and 800 µg for comparison of antifungal activity. The minimum inhibitory concentrations (MIC values) were determined.

The results are presented in Tables 3 to 5.

Table 3- Antibacterial **of the selected compounds with zone of inhibition >0.5 cm at different concentrations against. *E. coli.***

Compound	0.0625 mg	0.125 mg	0.25 mg	0.5 mg	1.0 mg	2.0 mg	MIC mg
5a	0	0	1.3	1.4	1.5	1.7	**0.25**
5f	0	0	0	0	0	0	**>2**
5g	0	0	0	0	0	0.6	**2**
5h	0	0	0.8	1	1.2	1.3	**0.25**
	25 µg	50 µg	100 µg	200 µg	400 µg	800 µg	**MIC µg**
Gentamycin	1.8	2	2.3	2.6	2.8	3.1	25

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Table-4: Antifungal activity of the selected compounds with zone of inhibition >0.5 cm at different concentrations against *A. niger*.

Compound	0.0625 mg	0.125 mg	0.25 mg	0.5 mg	1.0 mg	2.0 mg	MIC mg
5a	0	0	0	0	1	1.2	1
5b	0	0	0	0	0.6	1.1	1
5d	0	0	0	0	0	1.2	2
5f	0	0	0	0	0.6	0.8	1
	25 µg	**50 µg**	**100 µg**	**200 µg**	**400 µg**	**800 µg**	**MIC µg**
Amphotericin	0	0	0.2	0.3	0.5	0.7	100

Table 5- Antifungal **activity of the selected compounds with zone of inhibition >0.5 cm at different concentrations against *C. albicans.***

Compound	0.0625 mg	0.125 mg	0.25 mg	0.5 mg	1.0 mg	2.0 mg	MIC mg
5a	0	0	0	0	1.1	1.3	1
5b	0	0	0	0	0.8	1.2	1
5g	0	0	0	0	0.8	1.2	1
5h	0	0	0	0	1	1.4	1
5i	0	0.5	1	1.3	1.5	1.8	0.125
	25 µg	**50 µg**	**100 µg**	**200 µg**	**400 µg**	**800 µg**	**MIC µg**
Amphotericin	0	0.2	0.7	0.9	1.3	1.5	50

RESULTS AND DISCUSSION

Ethyl naphtho [2, 1-b] furan-2-carboxylate (**2a**) was synthesized by treating 2-hydroxy-1-naphthaldehyde (**1**) with ethyl chloroacetate in presence of potassium carbonate in dimethylformamide. The structure of this compound was authenticated by comparing IR and ^{1}H NMR spectra with that of an authentic sample. The ester (**2a**) was brominated by using bromine in acetic acid at low temperature to get ethyl naphtho [2, 1-b] furan -2-carboxylate (**2b**). Ethyl 3-nitronaphtho [2, 1-b] furan-2-carboxylate (**2c**) was obtained by nitration of ester **2a**. These esters **2a-c** were hydrolyzed in alkaline medium to obtain their respective carboxylic acids (**3a-c**). The structure of **3a** was supported by spectral data. Its IR spectrum showed bands at 813 cm^{-1}, 1700 cm^{-1}, 3490 cm^{-1}(broad) respectively corresponding to naphthalene ring, carbonyl group and hydroxyl group. The ^{1}H NMR (400 M Hz) spectrum exhibited a singlet at δ 12.0 (D_2O exchangeable) corresponding to the proton of –COOH group. The seven protons of naphthofuran moiety appeared at δ 8.45 as doublet, δ 8.38 as a singlet, δ 8.04 as doublet, δ 7.86 as doublet, δ 7.71 as doublet, δ 7.6 as a triplet and δ 7.59 as a triplet respectively. The mass spectrum showed a molecular ion peak at m/z 210 corresponding to its molecular weight confirmed structure.

The resulting carboxylic acids (**3a-c**) on refluxing with 3-alkyl-4-amino-5-mercapto-1,2,4-triazole (**4a-c**) employing phosphorus oxychloride resulted in the formation of 3-alkyl-6-

(naphtho[2,1-b]furan-2-yl)[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles (**5a-i**). The required 3-alkyl-4-amino-5-mercapto-1, 2, 4-triazole (**4a-c**) were prepared according the literature procedure [32]. The purity of these compounds was monitored by TLC.

The IR spectra of the title compounds did not show any characteristic bands corresponding to both carbonyl and OH stretching frequencies of carboxylic group thus confirmed the disappearance of carboxylic group in the cyclized products. The ^{1}H NMR (400 M Hz) spectrum of the compound (**5c**) showed a triplet at δ 1.42 and a quartet at δ 3.1 corresponding the ethyl group. The seven protons of naphthofuran moiety were seen at δ, 8.48 as doublet, δ 8.73 as a singlet, δ 7.96 as doublet, δ 7.74 as doublet, δ 7.9 as doublet, δ 8.12 as a triplet and δ 7.63 as a triplet. The mass spectrum of this showed a molecular ion peak at m/z 311 thus confirming the formation of the cyclized product.

CONCLUSION

The compounds **5a** and **5h** showed considerable activity against *E. coli* with MIC value of 0.25 mg, the compound **5i** exhibited noticeable activity against *C. albican* indicating that introduction of nitro group increased the activity.

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