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Research Article

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Synthesis of novel antimicrobial agents encompassing naphthofuran, pyrimidine and thiadiazole moieties

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ABSTRACT

*Ethyl 3-aminonaphtho [2,1-b] furan-2-carboxylate **1**, which was obtained by Thorpe-Zeigler cyclization reaction between 2-hydroxy-1-naphthonitrile and ethylchloroacetate in presence of weak base-on treatment with formamide produced 3,4-dihydro-4-oxo-naphtho[2,1-b]furo[3,2-d] pyrimidine **2**. The oxopyrimidine**2** was converted into 4-chloronaphtho[2,1-b]furo[3,2-d] pyrimidine **3** by refluxing it with phosphorous oxychloride. Various 3- amino-5-aryl-1, 3, 4-thiadiazoles **4a-f** were synthesized by reaction between appropriately substituted aromatic acids with thiosemicarbazide. The thiazoles**4a-f** on treatment with 4-chloronaphtho[2, 1-b]furo[3,2-d] pyrimidine **3** using triethylamine as a catalyst in DMF, resulted in the formation of desired products. 4-substituted-naphtho[2,1-b]furo[3,2-d]pyrimidine-2-amino-5-aryl-1,3,4-thiadiazoles. **5a-f.**The newly synthesized compounds have been characterized by analytical and spectra studies. Evaluation of the synthesized compounds for antibacterial activity against Staphylococcus aureus, Bacillus subtillis, Bacillus polymixa, Vibrio cholera and Salmonella typhi using Gentamycin as a standard by agar diffusion method, indicated that some of the compounds possessed moderate antibacterial activity.*

Key words: Naphthofuran, pyrimidines, thiadiazoles, thiosemicarbazide, bacterial activity**.**

INTRODUCTION

Fused pyrimidines are interesting class of heterocyclic compounds not for their important biological and pharmacological properties but also for rich and varied chemistry [1-7].Particularly the compounds encompassing pyrimidine and furan ring systems are associated with wide spectrum of biological activities such as antimicrobial [8,9], antitumor [10], antiviral [11], anti-infammatory [12], anti-HIV [13]. Association of pyrimidine with benzo[b]furan and naphtho[2,1-b]furan has been shown to yield a series of benzofuropyrimidines [14] and naphthofuropyrimidines [15,16]with enhanced biological activities. In fact the derivatives of naphtho[2,1-b]furan synthesized in our laboratory have been reported to possess wide spectrum of biological and pharmacological activities [17-23].

1,3,4-Thiadiazole is yet another important class of five membered heterocyclic ring system. The derivatives of 1,3,4-thiadiazole and thiazole exhibit many biological activities, that has been attributed to the presence of the =N-C-S [24,25]. The heterocyclic compounds composed of 1,3,4-thiadiazole either in fused form or coupled form are known to possess diverse biological activities such as antibacterial, antifungal, antitubercular and anticonvulsant [26,27].

Hence in continuation of research programme of synthesis of novel heterocycles encompassing naphtho[2,1-b]furan nucleus, we report in this paper, synthesis of new class of compounds containing naphtho[2,1-b]furopyrimidine and 1,3,4-triazole moiety in a single molecular framework.

EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes and are uncorrected. IR spectra [in cm^{-1}] were recorded in KBr on FT-IR research spectro photometer series and Perkin-Elimer FT-IR [spectrum 1000] NMR spectra on Jeol GSX 270 FINMR Spectrometer using DMSO-d_6 or $CDCl_3$ as solvent and TMS as an internal standard [Chemical shifts are given in δppm] values. Compounds were checked for their purity by TLC Silica Gel G plates using Methanol-carbon tetra chloride [v/v] by varying polarity and the spots located by iodine vapours.

Synthesis of ethyl 3-aminonaphtho[2,1-b]furan-2-carboxylate[28] **1**
2-Hydroxy-1-naphthaldoxime (0.93g, 0.05 mol), ethyl chloroacetate(6.13 g, 0.05 mol) and anhydrous potassium carbonate (4.9 g, 0.05 mol) were mixed well and heated under reflux in anhydrous dimethyl formamide(60 ml) for 12 hours. The reaction mixture was cooled, potassium salts were filtered off and the filtrate was poured into crushed ice to obtain the product as light brown coloured solid. It was collected by filtration and recrystallized from aqueous ethanol (Yield 0.95 g, 75%).

Synthesis of 4-oxo-naphtho[2,1-b furo[3,2-d]pyrimidine 2
Ethyl 3-aminonaphto[2,1-b]furan-2-carboxylate **1 (**0.255 g, 0.001 mol) was refluxed with formamide (15 ml) at 160^0 C for 8 hours in an oil bath and cooled to room temperature. The solid thus separated was filtered, washed with water, dried and recrystalized from aqueous dimethyl formamide (Yield 0.118 g, 80%).

Synthesis of 5-chloronaphtho[2,1-b]furo[3,2-d]pyrimidine 3
4-Oxo-naphtho[2,1-b]furo[3,2-d]pyrimidine **2 (**0.236 g, 0.001 mol) was refluxed with little excess of phosphorous oxychloride (15 ml) for 2 hours in an oil bath. The excess of phosphorous oxychloride was distilled off under reduced pressure and the resulting suspension was poured into ice cold water and neutralized with 10% sodium hydroxide solution. The solid thus obtained was filtered, washed with water and recrystallized from aqueous dimehtylformamide (Yield 0.193 g, 76%).

Synthesis of 2-amino-5-aryl-thiadiazoles.4 a-f
Benzoic acid (1.22 g,0.01 mol) was mixed with thiosemicarbzide (0.8 g, 0.01 mol) and concentrated sulphuric acid (12 ml) was added slowly with stirring, while cooling to 0^o C. The reaction mixture was left at room temperature for 2 hours and poured onto crushed ice. The product **4a** that separated as solid was collected by filtration and recrystallized from aqueous ethano. (Yield 1.8 g, 86%).

Similarly the compounds **4b-f** were synthesized by using appropriately substituted benzoic acids.

Synthesis of 4-substituted naphtho[2-1-b]furo[3,2-d]pyrimidine-2-amino-5-aryl-1,3,4-thiadiazoles.5a-f.
Mixture of 2-amino-5-aryl-1,3,4-thiadiazoles**4a** (0.001 mol) and 4-chloronaphtho[2,1-b]furo [3,2-d]pyrimidine **3** (0.254g, 0.001 mol) was refluxed in dimehtylformamide (20 ml) which contained catalytic amount triethyl amine. Upon completion of the reaction, which was monitored by TLC, the reaction mixture was poured onto crushed ice with stirring. The solid obtained was filtered, washed thoroughly with water, dried and crystallized to get the compound **5a**.

Similarly the compounds **5b – f**were prepared by using 2-amino-5-aryl-thiadiazoles **4b-f.**

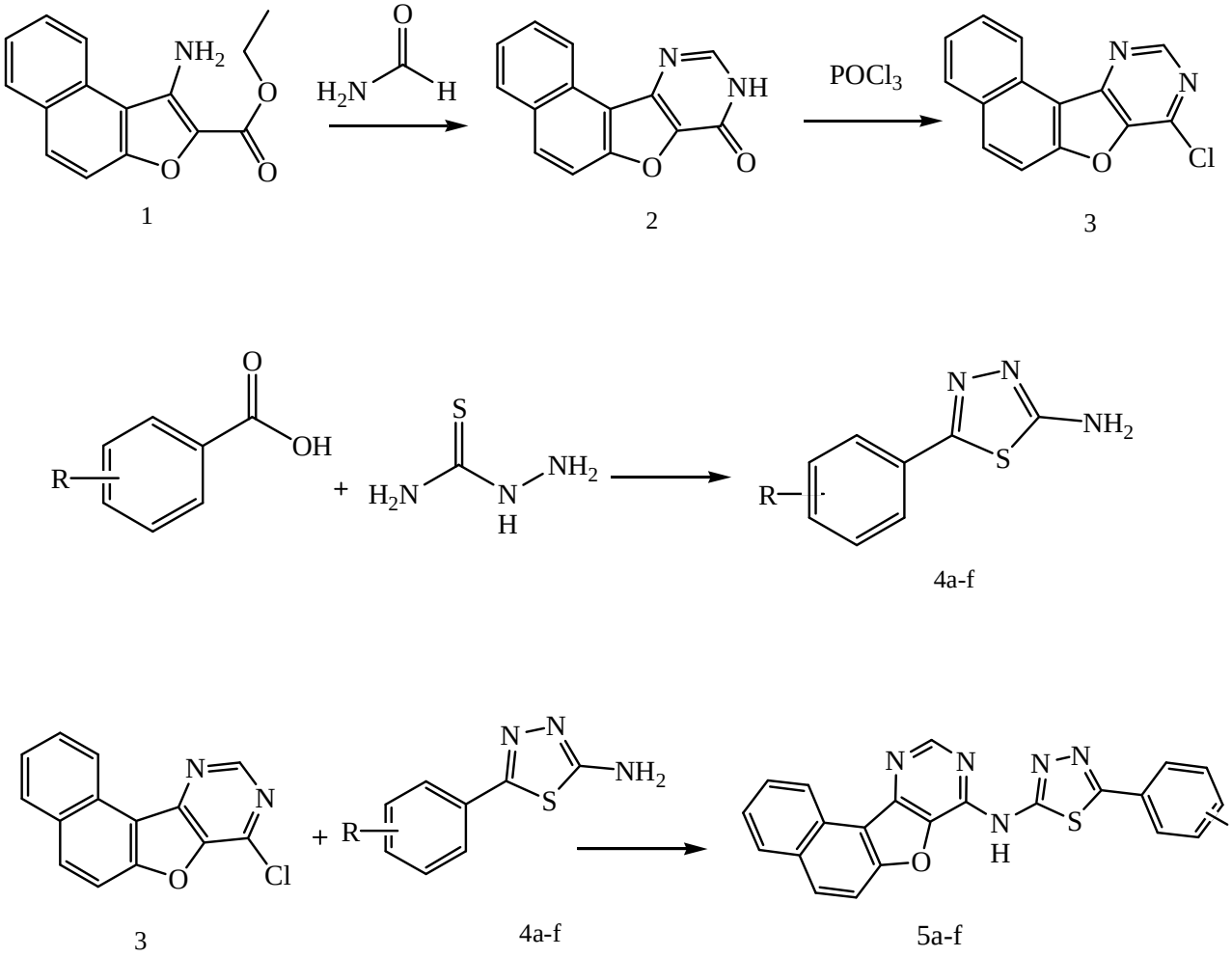
The physical and analytical data of the compounds is presented in table 1.

^{1}H NMR spectral data of compounds:

5b :δ 11.9 (s, 1H, NH, D_2O exchangeable), δ 7.2-8.5(m, 11H, ArH)
5c : δ 12.1 (s, 1H, OH, D_2O exchangeable), δ 11.9 (s, 1H, NH, D_2O exchangeable), δ 7.1-8.4 (m. 11H, ArH).
5d : δ 11.8 (s, 1H, NH, D_2O exchangeable), δ 7.2-8.6 (m, 11H, ArH)
5e : δ 12.0 (s, 1H, NH, D_2O exchangeable), δ 7.35-8.65 (m, 10H, ArH)
5f : δ 11.8 (s, 1H, NH, D_2O exchangeable), δ 7.21-8.59 (m, 11H, ArH), δ 4.5 (s, 3H, OCH_3)

The physical and analytical data of the compounds is presented in table-1

SCHEME



R
a; H
b; 4-Cl,
c; 2-OH,
d; 2-Cl,
e; 3,5-$(NO_2)_2$,
f; 4-OMe

Table-1: Physical and Analytical data of the newly synthesized compounds 5a-f

Compd.	R	Molecular Formula	m.p.^{0}C	% Yield	Found % (Calculated)			
					C	H	N	S
5a	H	$C_{22}H_{13}N_5SO$	121-124	58.7	66.68 (66.83)	3.20 (3.29)	17.62 (17.72)	8.00 (8.10)
5b	4-Cl	$C_{22}H_{12}N_5SOCl$	125-130	61.3	61.01 (61.47)	2.65 (2.79)	16.11 (16.30)	7.39 (7.45)
5c	2-OH	$C_{22}H_{13}N_5SO_2$	138-141	57.4	63.98 (64.23)	3.10 (3.16)	16.86 (17.03)	7.49 (7.78)
5d	2-Cl	$C_{22}H_{12}N_5SOCl$	135-138	62.3	61.09 (61.47)	2.63 (2.79)	16.18 (16.30)	7.35 (7.45)
5e	3,5-$(NO_2)_2$	$C_{22}H_{12}N_7SO_5$	130-135	58.9	54.12 (54.43)	2.15 (2.27)	20.10 (20.20)	6.37 (6.59)
5f	4-OCH_3	$C_{23}H_{15}N_5SO_2$	135-140	60.4	64.19 (64.60)	3.38 (3.56)	16.33 (16.63)	7.34 (7.60)

Antibacterial activity:

Antibacterialactivity of the compounds has been evaluated by agar diffusion technique using Gram positive bacteria viz., *Staphylococcus aureus, Bacillus subtilis, Bacillus polymyxa*and Gram negative bacteria viz., *Vibrio cholerae, Salmonella typhi.* Gentamycin was used as a standard for the comparison of activity. The activity was measured at the concentration of 1.0 mg and 2.0 mg using dimehtylsulphoxideas a solvent. The results of antibacterial activity are presented in table 2 and table 3.

Table 2: Antibacterial activity against gram positive bacteria for the compounds 5a-f

Samples	***Staphylococcusaureus***			***Bacillussubtillis***			***Bacilluspolymyxa***		
	1.0 mg	2.0 mg	MIC mg	1.0 mg	2.0 mg	MIC mg	1.0 mg	2.0 mg	MIC mg
	Zone of Inhibition in mm								
5a	0	0.4	2	0	1	2	0	0	>2
5b	0	0.5	2	0	0	>2	0	0	>2
5c	0	0	>2	0	0.4	2	0	0.2	2
5d	0.3	1.3	1	0.4	0.8	1	0	0	.>2
5e	0	0.2	2	0	0.5	2	0	0	>2
5f	0	0.7	2	0.6	1	1	0	0	>2
	400 µg	800µg	MICµg	400 µg	800µg	MICµg	400 µg	800µg	MICµg
Gentamycin	2.7	3.4	25	2.2	2.5	25	3.1	3.3	25

Table -3 :Antibacterial activity againstgram negative bacteria for the compounds 5a-f.

Samples	***Vibrio cholera***			***Salmonellatyphi***		
	1.0 mg	2.0 mg	MIC mg	1.0 mg	2.0 mg	MIC mg
	Zone of Inhibition in mm					
5a	0	0.6	2	0	0.3	2
5b	0.2	0.7	1	0.3	1.4	1
5c	0	0.2	2	0	0.2	2
5d	0	0	>2	0	0.2	2
5e	0	0.7	2	0	0.2	2
5f	0	0.6	2	0	1.1	2
	400 µg	800µg	MICµg	400 µg	800µg	MICµg
Gentamycin	2.3	2.7	25	2.5	2.7	25

The compounds **5a, 5b, 5e** and **5f** are found to have antibacterial activity on the bacteria *S.aureus* at 2 mgMIC. The compound **5c** and **5d** have antibacterial activity on the same bacteria at >2 mgMIC and at 1 mgMIC respectively. Similarly the compounds **5a, 5c** and **5e** have antibacterial activity on the bacteria *Bacillus subtillis* at 2 mgMIC. **5b i**s found to be active on the same bacteria at >2 mgMIC. **5d** and **5f** are active on the same bacteria at 1 mgMIC.

RESULTS AND DISCUSSION

The starting material ethyl 3-aminonaphtho[2,1-b]furan-2-carboxylate **1** was obtained by the base catalyzed reaction between 2-hydroxy-1-naphthonitrile, where in both condensation and Thorpe -Zeigler cyclization occurred in a single step[24]. The ester **1** on reaction with formamide underwent cyclization and produced 4-oxo-naphtho[2,1-b]furo[3,2-d]pyrimdine**2** in good yield. The IR spectrum of compound **2** showed absorption band at 1700 cm^{-1} due to ring carbonyl stretch frequency. The ^1H NMR spectrum was conspicuous by the absence of triplet and quartet due to $–CH_2-CH_3$ protons of ester group which were present in its precursor ester **1.** The compound **2** on refluxing with phosphorous oxychloride resulted in the formation of 4-chloronaphtho[2,1-b]furo[3,2-d]pyrimidine **3.** The absence of absorption band at 1700 cm^{-1} in its IR spectrum confirmed the structure of **3.** Its ^1H NMR spectrum exhibited a multiplet ð 6.9-8.3 due to aromatic protons and no peak was observed due to –NH protons.

The various 1,2-amino-5-aryl-1,3,4-triazoles **4a-f** were obtained by well established experimental protocol which involved the reaction between thiosemicarbazide and suitably substituted aromatic acids. These triazoles**4a-f** were condensed with 4-chloronaphtho[2,1-f]furo[3,2-d]pyridimine**3** using dimethyl formamideas a solvent and triethylamine as catalyst to obtain 4-substitutednaphtho[2-1-b]furo[3,2-d] pyrimidine 2-amino-5aryl-1,3,4-thiadiazoles **5a-f**.

The IR spectra of all these compounds exhibited absorption band at 1680-1690 cm^{-1} due – C=N stretching frequency. The ^1H NMR spectrum of compound **5a** showed D_2O exchangeable singlet at δ11.8 due to – NH proton as well as aromatic protons recorded atδ7.0-8.4 as a multiplet.

The newly synthesized compounds **5a-f**were evaluated for antibacterial activity against *Staphylococcus aureus,Bacillus subtillis, Bacillus polymixa, Vibrio cholera* and *Salmonella typhi*by agar diffusion technique. For the

comparison of antibacterial activity, using Gentamycin as a standard compound, minimum inhibitory concentration of these compounds was determined by serial dilution method.

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