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Research Article

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Synthesis and biological activity of carbamates derived from ethyl 1-[(phenylcarbonyl)amino]naphtho[2,1-b]furan-2-carboxylate

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ABSTRACT

Ethyl 3-aminonaphtho[2,1-b]furan-2-carboxylate ***(1)*** *on benzoylation, produced ethyl1- [(phenylcarbonyl)amino] naphtho[2,1-b]furan-2-carboxylate* ***(2)****. Treatment of ester* ***(2)*** *with hydrazine hydrate gave N-[2-(hydrazilylcarbonyl)naphtho[2,1-b]furan-1-yl]benzamide* ***(3)****, which on diazotization resulted in the formation of 1-[(phenylcarbonyl)amino] naphtho [2,1-b]furan-2-carbonyl azide* ***(4)****. The azide* ***(4)*** *on Curtius rearrangement with alcohols and phenols afforded the corresponding carbamates,****(5a-g).*** *The structures of newly synthesized carbamates were confirmed by spectral and analytical data and were screened for their antimicrobial activity by agar diffusion method. Some of the carbamates were found to possess better antibacterial activity against bacteria V. cholerae and E. coli.*

Keywords: Naphthofurans, carbamates, antimicrobial, agar diffusion method.

INTRODUCTION

Continuous evolution of new microbes that are resistant to antimicrobial agents that are currently available possess a serious threat to the survival of the mankind and presents a challenge for the development of newer such agents with a broadened spectrum of activity and improved pharmacological properties. In search of such kind of drugs, many heterocyclic ring systems and compounds involving a naphtho[2,1-b]furan ring has been synthesized and screened for their antimicrobial [1-7], anticancer[8-11], anti-inflammatory[12-15] anti hypertensive [16], antipyretic[17], antiviral[18],analgesic[19,20] activities and also as CNS depressants[21].

Carbamates are important intermediates in the synthesis of compounds in pharmaceutical, medical, agrochemical and polymer chemistry, which possess biologically potent properties such as inhibitors of HIV, anticancer, anticonvulsants, antibacterials, antiepileptics and enzyme inhibitors [22-27]. A number of organic carbamates have emerged in the recent past as potential antibacterial and antiviral agents. The carbamate residue present in such molecules either contributes as a core component or towards improvement of their pharmacological and pharmacokinetic properties. The presence of aroyl functionality at β-lactum ring of penicillin, is well known to contribute to its antibiotic activity. Hence, it was thought of to benzoylate amino group at C-3 of naphtho[2,1-b]furan moiety and then synthesize corresponding carbamates (Scheme 1) with a goal to obtain more potent compounds with enhanced biological profile.

EXPERIMENTAL SECTION

General procedures: All the reagents were obtained commercially and used with further purification. The melting points were determined in open capillary and are uncorrected. IR spectra were recorded on FT-IR Perkin -Elmer spectrum GX spectrometer (υ in cm^{-1}), ^{1}HNMR and ^{13}CNMR were recorded on Bruker spectrometer operating at 400MHz using DMSO or $CDCl_3$ as solvent and TMS as an internal standard(chemical shifts in δ) mass spectral analysis was carried out with GCMS Shimadzu QP 5050 mass spectrometer.

Ethyl-[(phenylcarbonyl)amino]naphtho[2,1-b]furan-2-carboxylate (2)
To a mixture of ethyl 3-aminonaphtho[2,1-b]furan-2-carboxylate **(1)** (2.55 g, 0.01mole) and aqueous sodium hydroxide (5%, 15 ml), benzoyl chloride(1.5 ml, 0.01mole) was added drop wise, along with stirring in an ice bath. The stirring was continued until the odour of the benzoyl chloride disappeared. The solid formed was filtered, washed with water and recrystallised from ethanol to get the product as light brown crystalline solid.

N-[2-(hydraziylcarbonyl)naphtho[2,1-b]furan-1-yl]benzamide (3)
An aqueous solution of hydrazine hydrate(15 ml, 99%) was added to the solution of ethyl [(phenyl carbonyl)amino]naphtho[2,1-b]furan-2-carboxylate **(2) (**3.59 g, 0.01mole) in ethanol(20 ml). The reaction mixture was heated under reflux for 5hr, cooled to room temperature and poured to the crushed ice, the solid that separated was filtered, and recrystallised from ethanol.

1-[(Penylcarbonyl)amino]naphtho[2,1-b]furan-2-carbonyl azide (4)
The solution of sodium nitrite(0.7 g) in water (4 ml) was added drop wise with stirring at 0^0C to a mixture of N-[2-(hydraziylcarbonyl)naphtho[2,1-b]furan-1-yl]benzamide **(3)** (3.45 g, 0.01 mole) in dioxan (12 ml) and acetic acid(3.5 ml). The stirring was continued for 30 min. The pale yellow solid that separated was filtered washed with ice cold water and then with dioxin (10 ml) and dried over anhydrous $CaCl_2$. Used for further reactions without any purification.

Isopropyl{1-[(phenylcarbonyl)amino]naphtho[2,1-b]furan-2-yl}carbamate (5c)
A suspension of azide (**4)** (0.356 g, 0.001 mole) in isopropyl alcohol(5ml) was refluxed on a water bath for 3 hr. The reaction mixture was concentrated and diluted with water. The product separated was collected and recrystallized from ethanol to get brown needles of **5c**.

Similarly azide **(4)** was refluxed with other alcohols like methanol, ethanol and n-butanol to get their corresponding derivatives (**5a-b** and **d**).

Phenyl{1-[(phenylcarbonyl)amino]naphtho[2,1-b]furan-2-yl}carbamate(5e).
To a solution of azide 4 (0.356 g, 0.01 mole) in dry dioxin (5 ml), phenol (0.9ml, 0.01 mole) was added .The reaction mixture was heated at reflux for 5 hrs and the solvent was removed under reduced pressure. The residue was worked up with chloroform to obtain solid, the product as solid, which was collected by filtration and recrystallised from ethanol to get (**5e).**

Similarly azide **(4**) was refluxed with appropriate phenols like 4-chlorophenol and 2-methyl phenol to get their corresponding derivatives **5f** and **5g**.

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

The sequence of reactions is presented in Scheme 1.

RESULTS AND DISCUSSION

The starting material ethyl 3-aminonaphtho[2,1-b] furan-2-carboxylate (**1)** was synthesized by well established method[28] in good yield. Benzoylation of (**1),** yielded **e**thyl [(phenylcarbonyl)amino]naphtho[2,1-b]furan-2-carboxylate**(2)**. Its IR spectrum showed the absence of two absorption bands at 3426 cm^{-1} and 3339 cm^{-1} of NH_2 groups which were present in its precursor. It also exhibited broad band at 3061 cm^{-1} due to NH group of amide. Appearance of sharp band at 1678 cm^{-1} due to ester carbonyl, a shoulder band at 1640 cm^{-1} due to carbonyl groups supported the assigned structure.^{1}H NMR spectrum of (**2)** showed a peak (D_2O exchangeable) at δ 9.1 indicating the presence of NH proton and multiplet at δ 7.5-8.1 due to eleven aromatic protons. Treatment of (**2)** with hydrazine hydrate, yielded N-[2-(hydraziylcarbonyl)naphtho[2,1-b]furan-1-yl]benzamide **(3)**. The structure of (**3)** was confirmed by its IR spectrum, showing broad band at 3141 cm^{-1} due to NH group, two sharp bands at 3284 cm^{-1} and 3365 cm^{-1} due to NH_2 group, a sharp band at 1668 cm^{-1} due to ester carbonyl, and a shoulder band at 1626cm^{-1} due to amide carbonyl group. ^{1}H NMR spectrum of **3** showed two broad singlets at δ 9.8 and δ 8.7 due to presence of two NH (D_2O exchangeable) protons, a multiplet at δ7.4-8.1 due to eleven aromatic protons and D_2O exchangeable singlet at δ 3.8 due to NH_2 protons.

N-[2-(Hydraziylcarbonyl)naphtho[2,1-b]furan-1- yl]benzamide **(3)** , on reaction with acetic acid and sodium nitrite in dioxan at 0^0C, produced 1-[(phenylcarbonyl) amino] naphtho[2,1-b]furan-2-carbonyl azide**(4),** the IR spectrum of which exhibited the bands at 2140 cm^{-1} and 1676 cm^{-1} accounting for absorption due to $N=N^+=N$ and C=O groups respectively. The azide (**4)** underwent Curtius rearrangement, on refluxing with methyl alcohol, ethyl alcohol,

isopropyl alcohol, n-butanol, phenol, 4-chlorophenol and 2-methylphenol and furnished the expected carbamates **5a-g.** The structure of methyl{1-[(phenylcarbonyl) amino] naphtho[2,1-b]furan-2-yl}carbamate **(5a)** was confirmed by its ^{1}H NMR spectrum which exhibited a singlet at δ 1.8 integrating for three protons of CH_3 group, multiplet at δ 7.3-8.5 integrating for eleven aromatic protons and two D_2O exchangeable singlets at δ 8.6 and δ 9.1 integrating for one proton each of NH and NH groups.

The structure of isopropyl{1-[(phenylcarbonyl) amino] naphtho[2,1-b]furan-2-yl}carbamate **(5c)** was confirmed by its spectral data. The ^{1}HNMR of **5c** showed a septet at δ5.0 due –CH proton attached to two equivalent methyl groups, multiplet at δ7.3-8.6 due to aromatic protons. To provide further evidence for the proposed structure, ^{13}C NMR was recorded, which exhibited the peak at δ70.44 due to ester carbonyl carbon, peak at δ166.35 due to amide carbonyl carbon , peak at δ14.09 due to terminal $–CH_3$ group, two peaks at δ 22.6 and δ 21.9 due to two $–CH_2$ carbons. The peaks at δ166, 153, 147, 143, 140, 133, 132.9, 132.2, 130.7, 130.3, 128.8, 127.5, 126.3, 125.3, 124.5, 123.7, and 122.9 were attributed to the seventeen ring carbon atoms. Final proof for the structure was obtained by recording its mass spectrum, which exhibited the molecular ion peak at m/z 388 corresponding to its molecular weight.

The IR spectra of the compounds **5a-g** exhibited absorption bands around 1718 cm^{-1}, 1654 cm^{-1} 3278 cm^{-1} and 3058 cm^{-1} due to ester and amide carbonyl groups and due to two –NH groups respectively.

Scheme 1

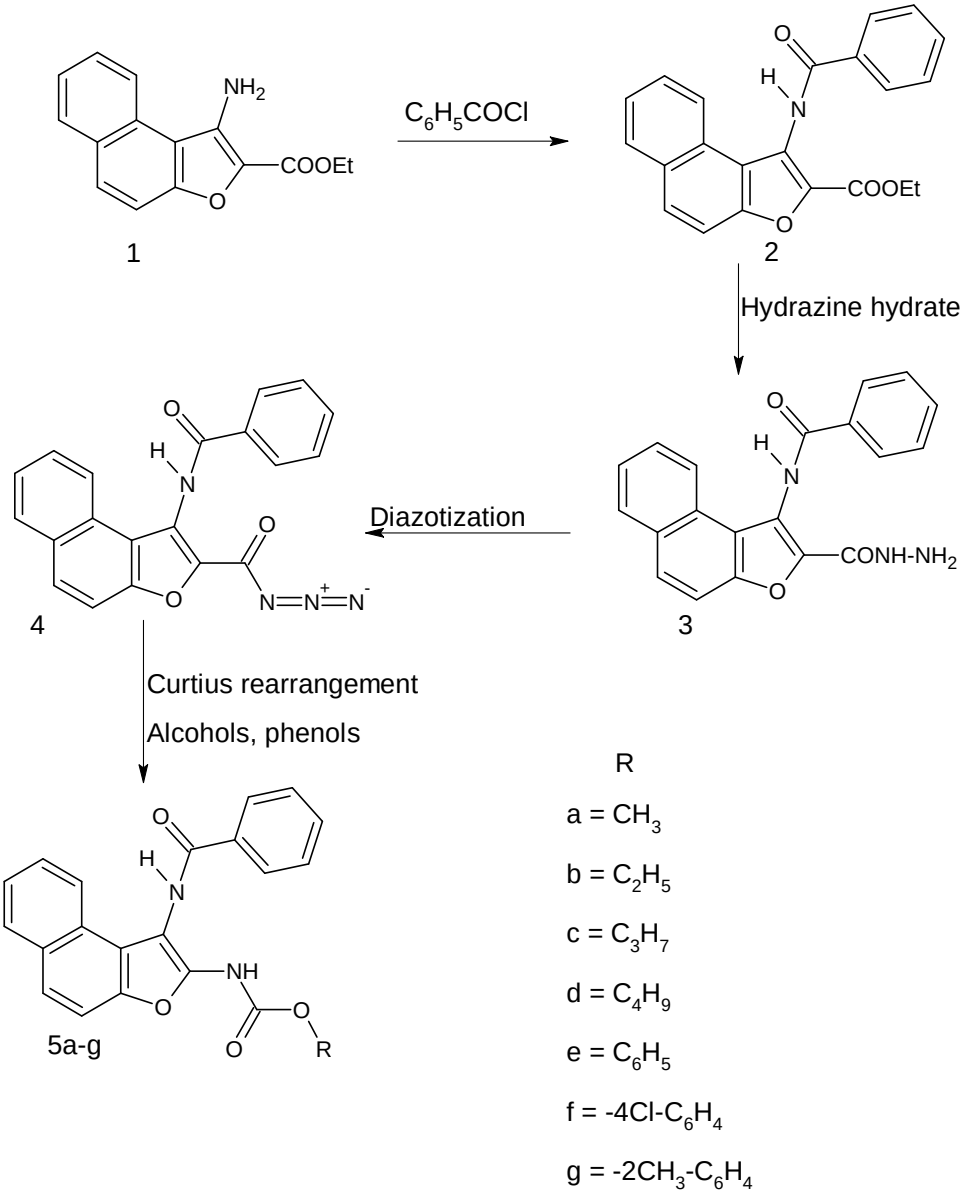

Table 1. The physical and analytical data of the synthesized compounds

Compounds	R	Molecular formula	MP (^{0}C)	Yield (%)	Found(Calcd) %		
					C	H	N
1	-	$C_{15}H_{13}O_3N$	118	82	70.56 (70.58)	5.03 (5.09)	5.36 (5.49)
2	-	$C_{22}H_{17}O_4N$	142	79	73.50 (73.53)	4.67 (4.73)	3.72 (3.89)
3	-	$C_{20}H_{15}O_3N_3$	85	67	69.39 (69.56)	4.27 (4.34)	12.09 (12.17)
4	-	$C_{20}H_{12}O_3N_4$	79	72	67.32 (67.41)	3.29 (3.37)	15.66 (15.73)
5a	CH_3	$C_{21}H_{16}O_4N_2$	132	85	69.96 (70.00)	4.38 (4.44)	7.70 (7.77)
5b	C_2H_5	$C_{22}H_{18}O_4N_2$	108	76	70.51 (70.58)	4.76 (4.81)	7.41 (7.48)
5c	C_3H_7	$C_{23}H_{20}O_4N_2$	98	86	71.06 (71.13)	5.09 (5.15)	7.17 (7.21)
5d	C_4H_9	$C_{24}H_{22}O_4N_2$	124	71	71.58 (71.64)	5.39 (5.47)	6.89 (6.96)
5e	C_6H_5	$C_{26}H_{18}O_4N_2$	77	80	73.86 (73.93)	4.19 (4.26)	6.57 (6.63)
5f	4-Cl-C_6H_4	$C_{26}H_{17}O_4N_2Cl$	171	78	68.37 (68.42)	3.58 (3.72)	6.06 (6.14)
5g	2-CH_3-C_6 H_4	$C_{27}H_{20}O_4N_2$	68	65	74.26 (74.31)	4.51 (4.58)	6.36 (6.42)

BIOLOGICAL ACTIVITY

Antibacterial activity:

The antimicrobial activity of synthesized compounds was determined by agar diffusion method [29,30] . The *in vitro*, antibacterial activity was carried out against 18 hr old cultures of two gram positive bacteria *Staphylococcus aureus* , *Bacillus subtilis* and two gram negative bacteria *Escherichia coli*, and *Vibrio cholera*. The compounds were screened at different concentrations 0.0625, 0.125, 0.25, 0.5, 1.0 and 2.0 mg using DMSO as a solvent against all organisms. The zone of inhibition was measured after 24 hrs incubation at 37^{0}C and compared with the standard drug Gentamycin at the concentrations of 25, 50, 100, 200, 400, 800µg.

Antifungal activity:

Similarly the *in vitro* antifungal activity was carried out against 48 hr old cultures of *Aspergillus niger* and *Cladosporium oxysporum*. The concentrations of compounds screened were 0.0625, 0.125, 0.25, 0.5, 1.0 and 2.0mg dissolved in DMSO. The zone of inhibition was measured after 48 hrs of incubation at 27^{0}C and compared with the standard drug Amphotericin at the concentrations of 25, 50, 100, 200, 400 and 800µg.

The results of antibacterial and antifungal activities are given in **Table 2** and are represented in minimum inhibitory concentration (MIC), where MIC is the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism after overnight incubation.

Table 2: Antimicrobial activity of the compounds 5a-g

Compounds	Antibacterial activity MIC in mg				Antifungal activity MIC in mg	
	S.aureus	***B.subtilis***	***E.coli***	***V.cholerae.***	***C.oxysporum***	***A.niger***
5a	2	NF	2	2	NF	NF
5b	0.5	NF	0.125	0.125	2	1
5c	NF	NF	0.5	0.5	NF	NF
5d	NF	NF	0.5	0.5	NF	2
5e	NF	2	0.125	0.125	NF	2
5f	0.5	2	0.5	0.25	NF	0.125
5g	1	1	0.125	0.0625	1	0.5
DMSO	0	0	0	0	0	0
Gentamycin	0.025	0.025	0.025	0.025	-	-
Amphotericin	-	-	-	-	0.05	0.1

CONCLUSION

The new series of carbamates encompassing naphtho[2,1-b]furan ring system **5a-g** were synthesized by utilizing a simple and efficient method in good yields. The structures assigned have been supported by adequate analytical and

spectral data. The results of antimicrobial activity revealed that of the compounds exhibited prominent activity against the bacteria *E .coli* and *V. cholerae* compared to other bacteria and fungi.

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