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Research Article

SYNTHESIS OF *N*'-(CHLOROACETYL)NAPHTHO[2,1-*B*]FURAN-2-CARBOHYDRAZIDE AND *N*'-(ARYLAMINOACETYL)NAPHTHO [2,1-*B*]FURAN-2-CARBOHYDRAZIDE DERIVATIVES AND THEIR ANTIMICROBIAL ACTIVITIES

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ABSTRACT

The reaction of naphtho[2,1-*b*]furan-2-carbohydrazide **4** on treatment with chloroacetyl chloride in acid media afforded *N*'-(chloroacetyl)naphtho[2,1-*b*]furan-2-carbohydrazide **5.** This on treatment with various aryl amines in DMF produced *N*'-(arylaminoacetyl)naphtho[2,1-*b*]furan-2-carbohydrazides **6a–f**. The structures of 5 and 6a-f have been established by spectral studies. In addition the synthesised compounds have been screened for antimicrobial activities.

Keywords: naphtho[2,1-*b*]furan, *N*'-(chloroacetyl)naphtho[2,1-*b*]furan-2-carbohydrazide.

INTRODUCTION

Naphtho[2,1-*b*]furan derivatives both natural and synthesised were known to show various biological[1-5] and pharmacological activities. Survey of literature revealed that, the parent and newly constructed nucleus were exhibited potent biological activities such as antimicrobial[6], analgesic[7] etc. Hence it was thought to synthesize new derivatives of naphtho[2,1-*b*]furan derivatives by simple method and screened them for antimicrobial activities.

2-Naphthol **1** is subjected to Reimer–Tiemann reaction to get 2–hydroxy–1–naphthaldehyde **2**. This on condensation with chloroethylacetate yielded ethyl naptho[2,1-*b*]furan-2-carboxylate **3.** The formed ester on condensation with hydrazine hydrate gave naphtho[2,1-*b*]furan-2-carbohydrazide **4**. This on treatment with chloroacetylchloride gave *N*'–(chloroacetyl)naphtho[2,1-*b*]furan-2-carbo hydrazide **5**, which on treatment with various aromatic primary amines produced a series of compounds **6a-f**.

MATERIALS AND METHODS

All the chemical used were of AR grade. Melting points were recorded in open capillaries and are uncorrected. IR spectra was recorded in Nicolet 5700 FT–IR instrument (Nicolet, Madison, WI, USA) as using KBr pellets. The ^{1}H NMR and ^{13}C NMR spectra are recorded on VNMRS-400 Agilent-NMR instrument using TMS as internal reference. Chemical shifts are reported in □ (ppm). Mass spectra were recorded using Water's SYNAPT G2 QTOF LCMS instrument. Purity of the compounds was checked by TLC.

EXPERIMENTAL

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

A mixture of 2-hydroxy-1- naphthaldehyde (5.16g), ethylchloroacetate (3.66 g) and anhydrous potassium carbonate (12.8 g) in DMF (25 ml) were refluxed on water bath for 24 hour. The crude product obtained was recrystallised using ethanol to get pure sample of **3**.

Synthesis of naphtho[2,1-*b*]furan-2-carbohydrazide 4

Ethyl naphtho[2,1-*b*]furan-2-carboxylate was refluxed with hydrazine hydrate in ethanol for 2 hour and then cooled, poured into ice cold water to get a grey white colored naphtho[2,1-*b*]furan-2-carbohydrazide. The crude product obtained was dissolved in ethanol to get pure crystals of **4.**

Synthesis of *N*'-(chloroacetyl)naphtho[2,1-*b*]furan-2carbohydrazide 5

Naphtho[2,1-*b*]furan-2-carbohydrazide **4** (1g) was dissolved in glacial acetic acid (80 ml), to this chloroacetylchloride (0.5g) was added. The reaction mixture was stirred at room temperature for 1 hour, then poured into ice cold water. A creamy white coloured crystals of *N*-(chloroacetyl)naphtho[2,1-*b*]furan-2-carbohydrazide was separated.

Synthesis of *N*-[(4-methoxyanilino)acetyl]naphtho[2,1-*b*]furan-2-carbohydrazide 6a

N-(Chloroacetyl)naphtho[2,1-*b*]furan-2-carbohydrazide **4** (0.3g) was dissolved in DMF (5 ml). To this, 4-methoxy aniline and KI crystals were added. The reaction mixture was stirred at room temperature for 8 hour then poured into ice cold water to get *N*'-[(4-methoxy anilino)acetyl]naphtho[2,1-*b*]furan-2-carbohydrazide **6a**. The product so obtained was filtered, washed with water and purified using ethanol.

The compounds *N'*-[(4-methyl anilino)acetyl]naphtho[2,1-*b*]furan-2-carbohydrazide **6b**, *N'*-(anilinoacetyl)naphtho[2,1-*b*]furan-2-carbohydrazide **6c** *N'*-[(4-bromoanilino) acetyl]naphtho[2,1-*b*]furan-2-carbohydrazide **6d**, *N'*-[(3-chloroanilino)acetyl] naphtho[2,1-*b*]furan-2-carbohydrazide **6e** and *N'*-[(4-fluoroanilino)acetyl]naphtho[2,1-*b*]furan-2-carbohydrazide **6f** were synthesized by following the same procedure. Physical data of newly synthesised compounds were reported in Table 1. The synthetic route is shown in Scheme 1.

Evaluation of biological activities

The compounds encompassing naphthofuran have been 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.

Antimicrobial activity

The *in vitro* antimicrobial activity was carried out against 24 hour old cultures of two bacteria and two fungi by cup–plate method[8]. The compounds **6a-f** have been investigated for their antibacterial activity against *Pseudomonas aeruginosa* and *Staphylococcus aureus* and antifungal activity against *Aspergillus niger* and *Curvularia lunata*. Chloramphenicol and fluconazole were used as standards for antibacterial and antifungal activity respectively. The compounds were tested at a concentration of 0.001 mol/ml in DMF against all organisms. The zone of inhibition was compared with the standard drug after 24 hour of incubation at 25 ^{0}C for antibacterial activity and 48 hour at 30^{0}C for antifungal activity. The results are presented in Table 2.

RESULT AND DISCUSSION

The starting material ethyl naphththo[2,1-b]furan-2-carboxylate **3** was synthesized by the reaction of 2-hydroxy-1-naphthaldehyde **2** with chloroethyl acetate in presence of potassium carbonate in DMF. The compound **3** on treatment with hydrazine hydrate in presence of catalytic amount of acid produced naphtho[2,1-*b*]furan-2-carbohydrazide **4**. The compound **4** on treatment with chlorocetyl chloride produces *N*'-(chloroacetyl)naphtho[2,1-*b*]furan-2-carbohydrazide **5.** The compound **5** was characterized by IR (KBr): 3420 & 3205 cm^{-1} (two NH), 3011, 2922 cm^{-1} (Ar H), 1693 (C=O), 1656 cm^{-1} (CONH), ^{1}H NMR (DMSO): δ 4.21 (s, 2H, CH_2), δ 7.56-8.37 (m, 7H, ArH, δ 10.44 and 10.81 (two, s, 2NH). MS m/z: 302 (M+), 304 (M+2). The selection of aromatic amines was based on electron withdrawing and electron donating groups/ which could enable to study structure activity relationship during the evaluation of pharmacological activities. The reaction of **5** with various amines in DMF in the presence of catalytic amount of KI produces **6a-f.** The compound **6a** characterized by IR (KBr): 3379 & 3333 (two NH); 3050 (Ar C-H), 1702 (C=O), 1665 (CONH). ^{1}H NMR (DMSO): δ 3.6 (s, 3H, OCH_3), δ 3.7 (s, 2H, CH_2), d 5.5 (s 1H, NH) δ 6.4–6.7 (m, 4H, ArH), δ 7.5–8.3 (m, 7H ArH), δ 10.0 and 10.6 (two s, 2NH). ^{13}C NMR (DMSO): δ 39.4-40.66, 46.7, 55.8, 110.3, 112.9, 114.0, 115.0, 122.8, 124.0, 125.8, 127.7, 127.9,

128.8, 129.3, 130.5, 142.9, 147.4, 151.7, 152.8, 157.7, 170.4 (21 carbon atoms). MS m/z; 390 (M+1)

Similar method was employed to get compounds **6b-f** from **5** with p-toluidine, aniline, 3-chloroaniline, 4-bromoaniline and 4-fluoroaniline. The IR and ^{1}H NMR spectral data of these compounds is summarized in Table 3. The newly synthesized compounds were evaluated for antimicrobial activity. The compound **5** and **6a-f were** displayed significant antibacterial activity against both the organisms. Rest of the compounds exhibited substantial activity against both the organisms. It is observed that electron withdrawing groups resulted in enhancement of activity. The compounds **5** and **6a-f** exhibited promising antifungal activity, whereas remaining compounds found to be considerably active. In this case also electron withdrawing groups have much more pronounced effect on antifungal activity.

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Table 1: Physical data of synthesized compounds 5 and 6a–f

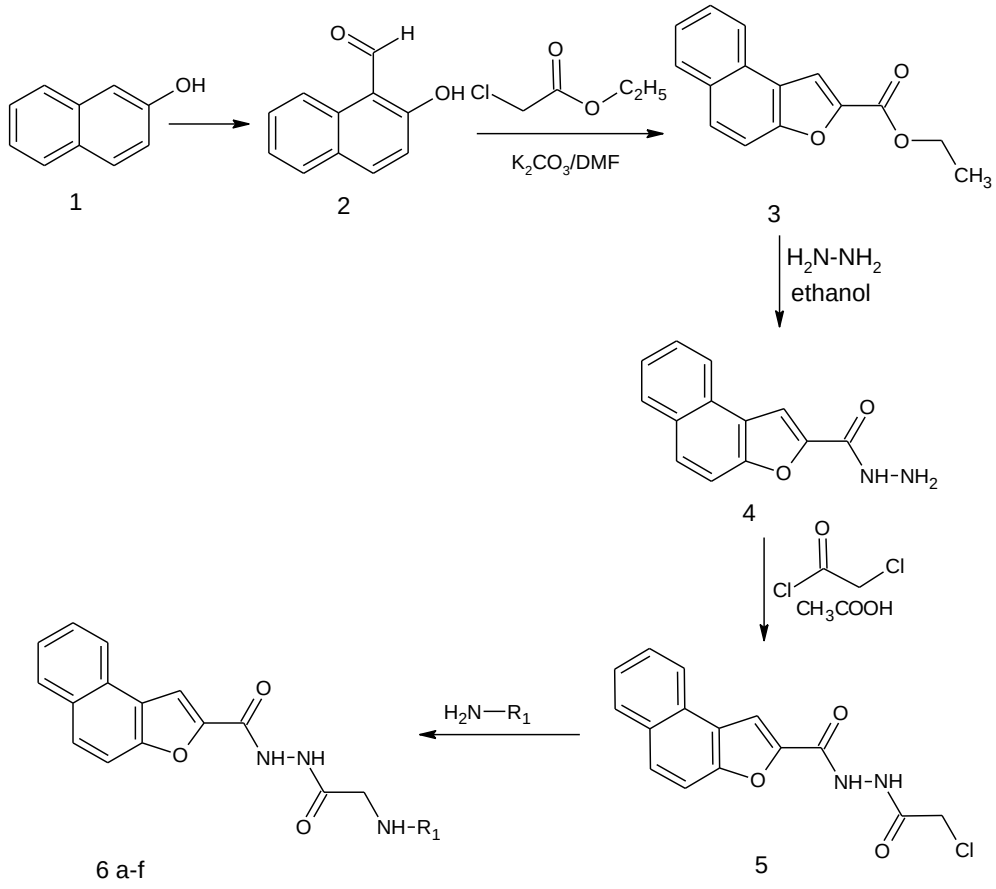
Comp.	R	M.P ^{0}C.	Yield	Mol. Formula	Found (calculated)%		
					C	H	N
5	-	196	85	$C_{15}H_{11}ClN_2O_3$	59.52 (59.11)	3.66 (3.52)	9.08 (9.25)
6a	4-$OCH_3C_6H_4$	224	81	$C_{21}H_{17}N_3O_4$	67.03 (67.19)	4.41 (4.56)	11.09 (11.19)
6b	4-$CH_3C_6H_4$	235	84	$C_{21}H_{17}N_3O_3$	70.10 (70.18)	4.65 (4.77)	11.58 (11.69)
6c	C_6H_5	234	86	$C_{20}H_{15}N_3O_3$	69.48 (69.56)	4.30 (4.38)	12.09 (12.17)
6d	4-Br-C_6H_4	236	87	$C_{20}H_{14}BrN_3O_3$	56.51 (56.62)	3.26 (3.33)	9.81 (9.90)
6e	3-Cl-C_6H_4	237	67	$C_{20}H_{14}ClN_3O_3$	63.16 (63.25)	3.61 (3.72)	10.98 (11.08)
6f	4-F-C_6H_4	190	70	$C_{20}H_{14}FN_3O_3$	66.05 (66.11)	3.80 (3.88)	11.56 (11.49)

Table 2: Antimicrobial activity data of the compounds 5 and 6a–f

Comp.	Zone of Inhibition in mm			
	Antibacterial activity		Antifungal activity	
	P. aerugenosa	*S. aureus*	*A. niger*	*C. lunata*
5	18	17	17	17
6a	19	19	18	17
6b	19	18	17	16
6c	17	17	18	16
6d	20	19	19	18
6e	20	19	17	19
6f	21	20	21	19
Standard	25	26	23	24
DMF	Nil	Nil	Nil	Nil

Table 3: IR and NMR Spectral data of compounds 6b–f

Comp.	R	IR cm^{-1} C = O, CONH	NMP δ ιν ππμ ανδ μ/ζ
6b	4-$CH_3C_6H_4$	1739, 1678, 3032.	δ 2.1 (σ,3H,XH_3), δ 3.7(σ,2H,XH_2), δ 5.7 (σ,1H, NH), δ 6.4–6.9 (μ, 4H, ΑρH), δ 7.5–8.3 (μ, 7H ΑρH), δ 10.0 ανδ 10.6 (τωο σ, 2NH). μ/ζ 374 (M+1),
6c	C_6H_5	1704, 1665, 3052.	δ 3.8 (σ, 2H, XH_2), δ 5.9 (σ,1H, NH), δ 6.5–7.5 (μ, 5H, ΑρH), δ 7.5–8.3 (μ, 7H Αρ H), δ 10.1 ανδ 10.6 (τωο σ, 2NH). μ/ζ 360 (M+1),
6d	4-Br-C_6H_4	1704, 1651, 3047.	δ 3.8(σ,2H,XH_2), δ 5.2 (σ,1H, NH), δ 6.5–6.5 (μ, 4H, ΑρH), δ 7.2–8.3 (μ, 7H Αρ H), δ 10.1 ανδ 10.6 (τωο σ, 2NH). μ/ζ 438 (M+1), 440 (M+2),
6e	3-Cl-C_6H_4	1727, 1698, 3055.	δ 3.8(σ,2H,XH_2), δ 5.3 (σ,1H, NH), δ 6.5–7.1 (μ, 4H, ΑρH), δ 7.5–8.3 (μ, 7HΑρH) , δ 10.1 ανδ 10.6 (τωο σ, 2NH). μ/ζ 393.9 (M+1), 395.9 (M+2),
6f	4-F-C_6H_4	1675, 1592, 3055.	δ 3.7 (σ,2H,XH_2), δ 5.9 (σ,1H, NH), δ 6.5–7.9 (μ, 4H, ΑρH), δ 7.5–8.3 (μ, 7HΑρH), δ 10.1 ανδ 10.6 (τωο σ, 2NH). μ/ζ 378 (M+1), 379 (M+2),



R_1

6a: 4-OCH_3-C_6H_4,

6b: 4-CH_3-C_6H_4,

6c:C_6H_5,

6d:3-Br-C_6H_4,

6e:3-Cl-C_6H_4,

6f:4-F-C_6H_4

SCHEME 1

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