Research Article

New Approach for the Synthesis of *N*-(4-oxo-3-substituted-2-Sulfanylidene Imidazolidin-1-yl)Naphtho[2,1-*b*]Furan-2-Carboxamide Derivatives and Their Antimicrobial Activity

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ABSTRACT

The reaction of naphtho[2,1-*b*]furan-2-carbohydrazide **4** on treatment with various aromatic phenyl isothiocyanates in glacial acetic acid affords 2-(naphtho[2,1-*b*]furan-2-carbonyl)-N-(substitued)hydrazine-1-carbothioamides **5a-f.** This on heating with chloroacetyl chloride in DMF produces *N*-(4-oxo-3-substituted-2-sulfanylidene imidazolidin-1-yl)naphtho[2,1-*b*]furan-2-carboxamides **6a–f**. The structures of **6a-f** have been established by spectral studies. In addition they have been screened for antimicrobial activities.

Key words: naphtho[2,1-*b*]furan-2-carbohydrazide and antimicrobial activities.

INTRODUCTION

Imidazolidenes are important heterocycles found in many biologically active compounds. Imidazolidines are biologically active pharmacophores and synthetic intermediates in medicinal chemistry. Imidazolidenes exhibit high range of biological activities[1-2] including anti-inflammatory, antinociceptive activities[3], anticonvulsant[4] anti-proliferative[5], antihyperglycemic[6], antihypertensive[7], anticancer[8] and antiulcer[9] activities. Naphtho[2,1-*b*]furan derivatives were known to show various biological[10-14] and pharmacological activities. Naphtho[2,1-*b*]furan derivatives with imidazolidene ring is not synthesised so far. Hence it was thought to synthesize new derivatives of naphtho[2,1-*b*]furan derivatives with imidazolidene ring by simple method and screened them for antimicrobial activities.

MATERIALS AND METHODS

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

EXPERIMENTAL

2-Naphthol is subjected to Reimar-Tiemann reaction to get 2-hydroxy-1- naphthaldehyde **2**. This on reaction with ethyl chloroacetate gives ethyl naptho[2,1-*b*] furan-2-carboxylate **3**. The ester **3** on condensation with hydrazine hydrate in ethanol gave naphtho[2,1-*b*]furan-2-carbohydrazide **4**. This on treatment with various isothiocyanates yielded 2-(naphtho[2,1-*b*]furan-2-carbonyl)-*N*-(substituted)hydrazine-1-carbothioamide. These compounds on condensation with chloroacetyl chloride in DMF gave the title compounds *N*-(4-oxo-3-substituted-2-sulfanylideneimidazolidin-1-yl)naphtho[2,1-*b*]furan-2-carboxamide derivatives **6a–f.**

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

A mixture of 2-hydroxy-1-naphthaldehyde **2** (5.16 g), chloroethylacetate (3.66 g) and anhydrous potassium carbonate (12.8 g) in DMF (25 ml) was refluxed on water bath for 24 hours. The crude product obtained was recrystallised using ethanol.

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

Ethyl napththo[2,1-*b*]furan-2-carboxylate **3** was refluxed with hydrazine hydrate in ethanol in presence of catalytic amount of Conc. HCl for 2 hours and then cooled and poured into ice cold water to get a grey white colored naphtho[2,1-*b*]furan-2-carbohydrazide **4**. The crude product so obtained was purified using ethanol.

Synthesis of 2-(naphtho[2,1-*b*]furan-2-carbonyl)-*N*-substitutedhydrazine-1-carbothio amides 5a-f

Naphtho[2,1-*b*]furan-2-carbohydrazide **4** (1g) was dissolved in glacial acetic acid (80 ml). To this phenylisothiocyanate (0.6 g) was added. The reaction mixture was stirred at room temperature until the completion of reaction, then poured into ice cold water to get 2-(Naphtho[2,1-*b*]furan-2-carbonyl)-*N*-phenylhydrazine-1-carbothioamide **5a.** It was purified using ethanol.

The compounds *N*-(4-fluorophenyl)-2-(naphtho[2,1-*b*]furan-2-carbonyl)hydrazine-1-carbothioamide **5b**, *N*-(3-chlorophenyl)-2-(naphtho[2,1-*b*]furan-2-carbonyl)hydrazine-1-carbothioamide **5c**, 2-(naphtho[2,1-*b*]furan-2-carbonyl)-*N*-(4-nitrophenyl)hydrazine-1-carbothioamide **5d**, *N*-benzyl-2-(naphtho[2,1-*b*]furan-2-carbonyl)hydrazine-1-carbothioamide **5e** and *N*-(4-methyl phenyl)-2-(naphtho[2,1-*b*]furan-2-carbonyl)hydrazine-1-carbothioamide **5f** were synthesized by using the procedure which was followed for the synthesis of 2-(Naphtho[2,1-*b*]furan-2-carbonyl)-*N*-phenylhydrazine-1-carbothioamide.

Synthesis of *N*-(4-oxo-3-arylsubstituted-2-sulfanylideneimidazolidin-1-yl) naphtho[2,1-*b*]furan-2-carboxamides (6a-f)

2-(Naphtho[2,1-*b*]furan-2-carbonyl)-*N*-phenylhydrazine-1-carbothioamide **5a** was dissolved in DMF (5ml.) To this chloroacetyl chloride was added. The reaction mixture was refluxed for 1 hour. Then poured into ice cold water to get *N*-(4-oxo-3-phenyl-2-sulfanylideneimidazolidin-1-yl)naphtho[2,1-*b*]furan-2-carboxamide **6a**.

The obtained product was filtered, washed with water and purified using DMF. (74.29 %); m.p. 128 ^{o}C. ^{1}H NMR ($CDCl_3$): δ 3.9 (s, 2H, CH_2), 7.0 - 7.9 (m, 12H, 12ArH) and δ 9.7 (s, 1NH). IR (KBr): 1751 cm^{-1} (C = O), 1692 cm^{-1} & 3061 cm^{-1} (CONH). MS; 402 (M+1). Same method was employed to get compounds **6b-f** from **5b-f**. The IR and ^{1}H NMR spectral data of these compounds are summarized in Table 1. Physical data of these newly synthesized compounds were reported in Table-2. The synthetic route was showed 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[15]. 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 3.

RESULT AND DISCUSSION

The key starting material ethyl naphtho[2,1-*b*]furan-2-carboxylate **3** was synthesised by the reaction of 2-hydroxy-1-naphthaldehyde with chloroethyl acetate in presence of potassium carbonate. Ethyl naphtho[2,1-*b*]furan-2-carboxylate on condensation with hydrazine hydrate gives naphtho[2,1-*b*]furan-2-carbohydrazide **4.** The reaction of **4** on treatment with various aromatic phenyl isothiocyanates in glacial acetic acid affords 2-(naphtho[2,1-*b*]furan-2-carbonyl)-N-(substitued)hydrazine-1-carbothioamides **5a-f**. This on heating with chloroacetyl chloride in DMF produces *N*-(4-oxo-3-substituted-2-sulfanylidene imidazolidin-1-yl)naphtho[2,1-*b*]furan-2-carboxamides **6a–f**. The selection of aromatic aldehydes was based upon presence of electron withdrawing and electron donating groups which could enable to study structure activity. The newly synthesized compounds were evaluated for antimicrobial

activity. The zone of inhibition was measured in mm and results are presented in Table 3. The compounds **6a-d** exihibited significant antibacterial activity against both organisms. Rest of the compounds exhibited substantial activity against both the organisms. It was observed that electron withdrawing groups resulted in enhancement of activity. The compounds 6a-d showed promising antifungal activity, whereas remaining compounds were found to be considerably active. In this case also electron withdrawing groups have much more pronounced effect on antifungal activity.

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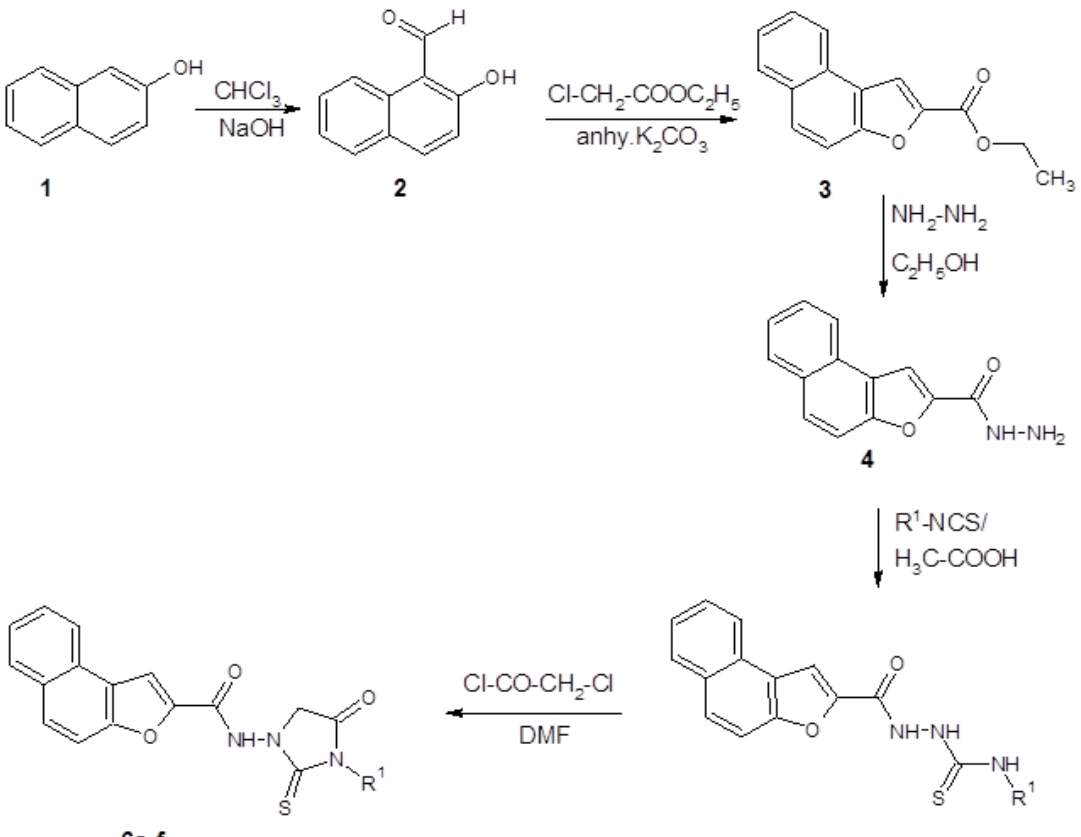

1 2 3 4 5a-f 6a-f

R^1

6a $-C_6H_5$,
6b $4\text{-F-}C_6H_4$,
6c $3\text{-Cl-}C_6H_4$,
6d $4\text{-}NO_2\text{-}C_6H_4$,
6e $C_6H_5\text{-}CH_2$-,
6f $4\text{-}CH_3\text{-}C_6H_4$,

SCHEME 1

Table 1: *N*-[3-(substituted)-4-oxo-2-sulfanylideneimidazolidin-1-yl] naphtho[2,1-*b*]furan-2-carboxamides 6b-f

Comp.	R	IR cm^{-1} C=O, CO, -NH	NMR δ in ppm and m/z
6b	4-F-C_6H_4	1751 1692 3063	δ 4.2 (s,2H,CH_2), δ 11.6 (s,1H, NH), δ 6.8–8.4 (m, 11H, ArH). Mass Spectral analysis m/z 419.96 (M+1),
6c	3-Cl-C_6H_4	1754 1695 3058	δ 4.2(s,2H,CH_2), δ 5.9 (s,1H, NH), δ 6.8–8.4 (m, 11H, ArH), δ 11.7 (s, 1NH). Mass Spectral analysis m/z 435.94(M+1)
6d	4-NO_2-C_6H_4	1753 1689 3063	δ 4.3(s,2H,CH_2), δ 11.7 (s,1H, NH), δ 7.1–8.4 (m, 11H, ArH). Mass Spectral analysis m/z 446.96 (M+1),
6e	C_6H_5-CH_2-	1749 1686 3063	δ 4.6(s,2H,CH_2), δ 3.1 (s,2H, CH_2), δ 7.1–7.9 (m, 12H ArH), δ 10.1 (s, 1NH). Mass Spectral analysis m/z 416.1 (M+1),
6f	4-CH_3-C_6H_4	1752 1686 3061	δ 2.3(s,3H,CH_3), δ 3.9 (s,2H, CH_2), δ 6.9–7.9 (m, 11H ArH), δ 9.6 (s, 1NH). Mass Spectral analysis m/z 415.99 (M+1)

Table 2: Physical data of newly synthesized compounds

Comp.	R	M.P ^{0}C.	Yield	Mol. Formula	Found (calculated)%		
					C	H	N
6a	C_6H_5	128	74.3	$C_{22}H_{15}N_3O_3S$	65.82	3.77	10.47
6b	4-F-C_6H_4	120	87.3	$C_{22}H_{14}N_3O_3SF$	63.00	3.36	10.02
6c	3-Cl-C_6H_4	130	80.0	$C_{22}H_{14}N_3O_3SCl$	60.62	3.24	9.64
6d	4-NO_2-C_6H_4	140	85.0	$C_{22}H_{14}N_4O_5S$	59.19	3.16	12.55
6e	C_6H_5-CH_2-	110	85.7	$C_{23}H_{17}N_3O_3S$	66.49	4.12	10.11
6f	4-CH_3-C_6H_4	150	89.0	$C_{23}H_{17}N_3O_3S$	66.49	4.12	10.11

Table 3: Antimicrobial activity data of the compounds 6a-f

Compd.	Comp. Zone of Inhibition in mm			
	Antibacterial activity		Antifungal activity	
	P. aerugenosa	*S. aureus*	*A. niger*	*C. lunata*
6a	19	19	18	17
6b	20	19	19	17
6c	18	17	18	18
6d	18	18	19	18
6e	17	17	17	18
6f	16	16	17	16
Std.	24	24	24	26
DMF	NIL	NIL	NIL	NIL

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