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Research Article

EFFICIENT AND SCALABLE SYNTHESIS OF *N*-(4-OXO-3-SUBSTITUTED-2-SULFANYLIDENE IMIDAZOLIDIN-1-YL)-8-NITRONAPHTHO [2,1-*B*]FURAN-2-CARBOXAMIDE DERIVATIVES AND THEIR ANTIMICROBIAL ACTIVITIES

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ABSTRACT

The various substituted aromatic isothiocyanates in glacial acetic acid on treatment with 8-nitronaphtho[2,1-*b*]furan-2-carbohydrazide **4** afforded 2-(8-nitronaphtho[2,1-*b*]furan-2-carbonyl)-N-substituted)hydrazine-1-carbothioamides **5a-e.** These on refluxing with chloroacetylchloride in DMF as a solvent yields *N*-(4-oxo-3-substituted-2-sulfanylideneimidazolidin-1-yl)8-nitronaphtho[2,1-*b*]furan-2-carboxamides **6 a-e. The** structures of **5a-e** and **6a-e** have been established by spectral studies and they have been screened for antimicrobial activities.

Keywords: 8-nitronaphtho[2,1-b]furan-2-carbohydrazide and antimicrobial activities.

INTRODUCTION

A heterocyclic Imidazolidines are important building blocks in biologically active compounds containing highly conserved five- member ring which formed of nitrogen-containing pharmacophores acts as a structure blocks in biologically active compounds because it carriers of pharmacologically active carbonyl compounds, its derivatives found to have application in the field of medicinal chemistry. Imidazolidines and their fused derivatives are keys in many bioactive compounds and they showed goodbiological activities[1-2]likeanticonvulsant, antihypertensive activity[3-4], anti-proliferative[5], antihyperglycemic[6], anticancer[7].These derivatives were also showed good results towards anti-inflammatory, antinociceptiveactivities[8], antibacterial and antifungal[9]activities.In particular, the derivatives of Naphtho[2,1-*b*]furanhasvarious pharmacological activities[10-12]and biological activities[13-14].The application of these compounds in pharmaceutical field prompted us to synthesize some new nitro substituted naphtho[2,1-*b*]furan with imidazolidines. Encouraged by the wide spectrum of biological activities associated with naphtho[2,1-*b*]furan and different heterocyclic bearing compounds and in continuation of our earlier work[15-22], we reported in this paper the synthesis of title compounds by different routes and investigation of their biological activity. Further, the efficiency of the synthesized molecules was confirmed by their 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

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

To a mixture of 2-hydroxy-1-naphthaldehyde**1**(5.46 g) and anhydrous potassium carbonate (13.5 g) in dry N, N-dimethylformamide (30 ml), chloroethylacetate (3.86 g) was added and reaction mixture was refluxed on water bath for an about 24 hours. The reaction mixture was then poured into crushed ice, to obtain crude product, which was collected by filtration, dried and recrystallised using ethanol.

Synthesis of ethyl 8-nitronaphtho[2,1-*b*]furan-2-carboxylate 3

The solution containing Ethyl naphtho[2,1-*b*]furan-2-carboxylate**2**(2 g, 0.01 mol) in acetic acid (20 ml) at below 0^0C, a cooled nitrating mixture of conc. HNO_3 and conc. H_2SO_4 (1:2, 20 mL) was added drop wise for 30 min, the stirring was continued for 3 hours. The reaction mixture was poured into crushed ice, the product obtained as yellow solid was filtered and recrystallised using ethanol.

Synthesis of 8-nitronaphtho[2,1-*b*]furan-2-carbohydrazide 4

Hydrazine hydrate (3.5 ml, 0.05 mol, 99%) was added to a solution of ethyl 8-nitronaphtho[2,1-*b*]furan-2-carboxylate **3** (3.5 g, 0.05 mol) in ethanol (20 ml). The reaction mixture was heated under reflux for 4 hours and cooled to room temperature. The solid thus separated was filtered, washed with ethanol and recrystallised from ethanol to obtain the product.

Synthesis of 2-(8-nitronaphtho[2,1-*b*]furan-2-carbonyl)-*N*-substitutedhydrazine-1-carbothio amides 5a-e

8-nitronaphtho[2,1-*b*]furan-2-carbohydrazide **4**(1.5g) was dissolved in glacial acetic acid (50 ml). To this substituted phenylisothiocyanates (0.85 g) were added. The reaction mixture was stirred at room temperature for 6 hours and 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.Similarly the compounds **5b-e**were synthesized by using the procedure which was used to synthesise**5a** from different substituted aromatic isothiocynates.

Synthesis of *N*-(4-oxo-3-arylsubstituted-2-sulfanylideneimidazolidin-1-yl)-8-Nitronaphtho[2,1-*b*]furan-2-carboxamides 6a-e

The chloroacetyl chloride (1.1 g). was added to 2-(Naphtho[2,1-*b*]furan-2-carbonyl)-*N*-phenylhydrazine-1-carbothioamide(2 g)**5a**was dissolved in DMF (15ml.) This reaction mixture was refluxed on water bath for 5 hours. Then reaction mixture was poured into ice cold water to get *N*-(4-oxo-3-phenyl-2-sulfanyli deneimidazolidin-1-yl)-8-nitronaphtho [2,1-*b*]furan-2-carboxamide **6a**.

The same procedure was followed to obtained compounds **6b-e**from **5b-e**. The IR and ^{1}H NMR and other spectral data of these compounds were recorded in **Table I**. 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, and Imidazolidinesare known to exhibit wide spectrum of biological activities. Hence, it was contemplated to evaluate newly synthesized compounds for antimicrobial activities by adopting literature procedure.

Antimicrobial activity

The newly synthesized compounds **6a-e** were screened for their *in vitro* antibacterial activity against *P.aeruginosa* and *S.aureus* and antifungal activity against *A.niger* and *C.lunata* according to cup plate method 28 at a concentration of 0.001 mol/ml in DMF against all the organisms. Chloramphenicol and Fluconazole were used as standards for antibacterial and antifungal activity respectively. The zone of inhibition was compared with the standard drug after 24 hours of incubation at 25^0 C for antibacterial activity and after 48 hours at 30^0 C for antifungal activity.

RESULT AND DISCUSSION

In this synthetic protocol, starting compound obtained by refluxing 2-hydroxy-1-naphthaldehyde**1**with anhydrous potassium carbonate and chloroacetyl chloride in DMF medium gave ethyl naphtho[2,1-*b*]furan-2-carboxylate **2**. The ester **2** which on

nitrationgave ethyl 8-nitronaphtho[2,1-*b*]furan-2-carboxylate **3** intermediate . The intermediate obtained is on condensed with hydrazine hydrate in alcohol gave 8-nitronaphtho[2,1-*b*]furan-2-carbohydrazide **4**. Further this was treatedwith various substituted aromatic isothiocyanates in glacial acetic acid results 2-(8-nitronaphtho[2,1-*b*]furan-2-carbonyl)-N-(substituted)hydrazine-1-carbothioamides**5 a-e**. Then the obtained productson condensation with chloroacetyl chloride in DMF produces *N*-(4-oxo-3-substituted-2-sulfanylidene imidazolidin-1-yl)-8-nitronaphtho[2,1-*b*]furan-2-carboxamides in high yield**6 a-e.** Further, the synthesized compound**6a** confirmed by the^{1}H NMR (CDCl3): δ 3.9 (s, 2H, CH_2), 7.1– 8.4 (m, 11H, ArH) and δ 9.7 (s, 1NH). IR (KBr): 1752 cm-1 (C = O), 1691 cm-1 & 3063 cm-1 (CONH). MS; 447 (M+1).Remaining IR and ^{1}H NMR spectral data of compounds **6b-e** is summarized in **Table 1**. The newlysynthesized molecules were screened for various antimicrobialactivities.The zone of inhibition was measured in mm and results are presented in **Table 3**. The compounds **6a-c** showed significant antibacterial activity against both organisms. Remaining compounds displayed substantial activity against both the organisms. It was observed that electron withdrawing groups resulted in enhancement of activity. The compounds **6a-c** 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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Scheme 1

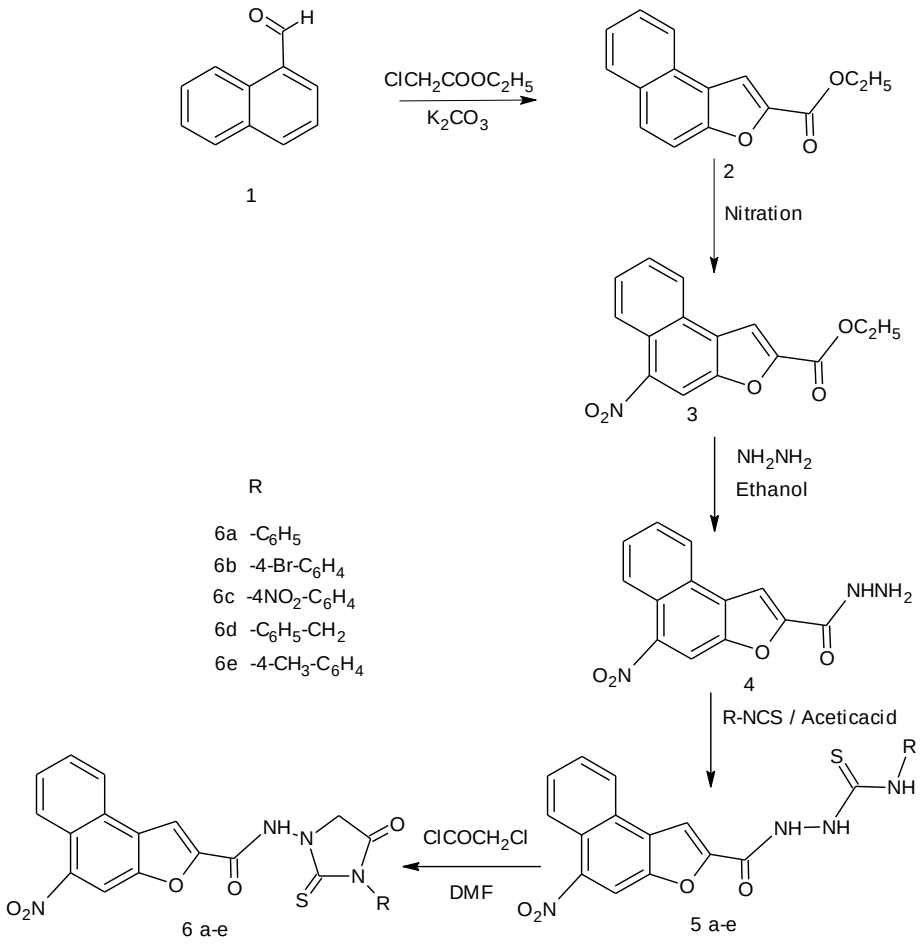

Table 1: Spectral data of *N*-(4-oxo-3-substituted-2-Sulfanylidene Imidazolidin-1-yl)-8-Nitronaphtho[2,1-*b*]Furan-2-Carboxamide6b-6e

Comp	R	IR cm^{-1} C=O, CO, -NH	NMR in δ ppm and m/z
6b	4-Br-C_6H_4	1751 1695 3063	δ4.2 (s, 2H CH_2), δ 11.6(s,1H, NH), δ 7.1-8.4(m,10H, ArH) Mass Spectral analysis m/z 524.96(M+1),
6c	4-NO_2-C_6H_4	1753 1689 3063	δ 4.3 (s, 2H CH_2), δ 11.7 (s,1H, NH), δ 6.8-8.4(m, 10H, ArH) Mass Spectral analysis m/z 492.96 (M+1)
6d	C_6H_5-CH_2	1749 1686 3063	δ 4.6 (s, 2H CH_2), δ 3.1 (s, 2H CH2), δ 10.1(s,1H, NH), δ 7.1-7.9(m, 11H, ArH) Mass Spectral analysis m/z 461.1 (M+1),
6e	4-CH_3-C_6H_4	1752 1686 3061	δ 2.3 (s, 3H CH_3), δ 3.9 (s, 2H CH_2), δ 9.6(s,1H, NH), δ 6.9-7.9(m, 10H, ArH) Mass Spectral analysis m/z 461.49 (M+1)

Table 2: Physical data of newly synthesised compounds

Comp	R	M.P ^0C	Yield %	Mol.Formula	Found (calculated) %		
					C	H	N
6a	C_6H_5	R	81.3	$C_{22}H_{14}N_4O_5S$	59.19 (59.09)	3.16 (3.11)	12.55 (12.49)
6b	4-Br-C_6H_4	172	82.2	$C_{22}H_{13}N_4O_5SBr$	50.30 (50.19)	2.49 (2.43)	10.67 (10.62)
6c	4-NO_2-C_6H_4	168	84.7	$C_{22}H_{13}N_5O_7S$	53.775 (3.71)	2.67 (2.61)	14.25 (14.22)
6d	C_6H_5-CH_2	166	79.5	$C_{23}H_{16}N_4O_5S$	59.99 (59.93)	3.50 (3.48)	12.17 (12.12)
6e	4-CH_3-C_6H_4	175	80.6	$C_{23}H_{16}N_4O_5S$	59.995 (9.93)	3.50 (3.48)	12.17 (12.12)

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

Compound	Comp.zone of inhibition in mm			
	Antibacterial activity		Antifungal activity	
	P.aeruginosa	*S.aureus*	*A.niger*	*C.lunata*
6a	19	19	18	17
6b	20	19	19	17
6c	18	18	19	18
6d	17	17	17	18
6e	16	16	17	16
Std	**24**	**24**	**24**	**26**
DMF	NIL	NIL	NIL	NIL

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