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Synthesis and antimicrobial activity of new pyridines fused with naphtho[2,1-b]furan

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ABSTRACT

A series of 2-amino-4-(phenylsubstituted)-6-naphtho[2,1-b]furan-2-ylnicotinonitrile derivatives 4(a-g) have been prepared by the cyclocondensation of malononitrile, aromatic aldehyde and ammonium acetate with 2-acetylnaphtho[2,1-b]furan. The similar reaction of 4(a-g) with alcoholic KOH and phenylisothiocyanates resulted in the formation of various 2-amino-6-(1,2-dihydronaphtho[2,1-b]furan-2-yl)-4-phenylsubstitutedpyridine-3-carboxamides 5(a-g) and 6-{[-3-(phenylsubstituted)-1-(naphtho[2,1-b]furan-2-yl)but-2-en-1-ylidene]amino}-4-imino-3-phenyl-3,4-dihydro pyrimidine-2(1H)-thione derivatives 6(a-g) respectively. The structures of the newly synthesized compounds have been established on the basis of analytical and spectral data. The synthesized compounds have been screened for antimicrobial activity.

Keywords: 2-acetylnaphtho[2,1-b]furan, Pyridine, antimicrobial activity

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INTRODUCTION

The pyridine ring is one of the most well-known systems among the naturally occurring heterocycles[1]. Pyridine and fused pyridine moieties present in numerous natural products such as quinoline and isoquinoline alkaloids[2] and nicotine and its analogs.[3-5] 2-Aminopyridines are promising substituted pyridines which have been shown to be biologically active molecules.[6-10] Additionally because of their chelating abilities, 2-aminopyridines are commonly used as ligands in inorganic and organometallic chemistry.[11-12] In addition, Many of the condensed heterocycles and biheterocycles enclosing naphthofuran have been reported processes wide spectrum of activities.[13-18] In view of these reports we made an attempt to synthesize new series of pyridines fused with naphtho[2,1-*b*]furan and screened for antimicrobial activity.

Experimental

Melting points were determined in open capillary tubes and are uncorrected. Purity of the compounds were checked by TLC, FT-IR spectra were taken in a Perkin Elmer 157 infrared spectrophotometer. ^{1}H NMR spectra (300 MHz) were recorded on a Brucker supercon FT-NMR instrument using TMS as internal standard (chemical shifts in ppm).

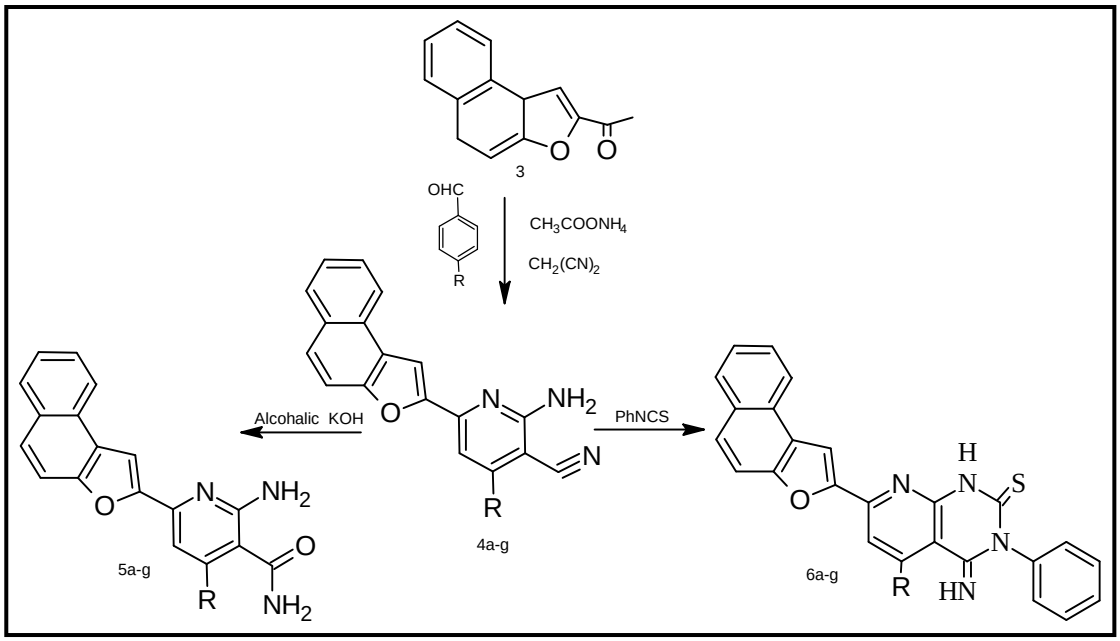
2-amino-6-(1,2-dihydronaphtho[2,1-*b*]furan-2yl)-4-(3-nitrophenyl)pyridine-3-carboxamides 5a

Compound **4**a (3.61 g, 0.04 mole) and KOH (6.53 g, 0.7 mole) in ethanol (50 ml) were refluxed for 7 hr. After cooling to room temperature, the reaction mixture was poured onto ice cold water and the product obtained as solid was filtered, washed with water and recrystallised from ethanol. The compounds **5**(b-g) were prepared from **4(**b-g) by similar method.

6-{[-3-(3-nitrophenyl)-1-(naphtho[2,1-b]furan-2-yl)but-2-en-1-ylidene] amino}-4-imino-3-phenyl-3,4-dihydropyrimidine-2(1*H*)-thiones 6a

Compound **4**a (4.06 g, 0.01 mole) and phenylisothiocyanate (1.35 ml, 0.01 mole) in ethanol (50 ml) were refluxed for 10 hr. The reaction mixture was poured on to ice cold water and the product obtained was filtered, washed with water and recrystallised from aqueous dimethylformamide. The compounds **6(b-g)** were prepared from **4(b-g)** by similar method.

SCHEME-1



R

a) *3-NO_2 C_6H_4* *e)* *3-OCH_3 C_6H_4*
b) *4-Cl C_6H_4* *f)* *4-$OCH_3C_6H_4$*
c) *C_6H_5* *g)* *4-OH 3-OCH_3 C_6H_3*
d) *4-OH C_6H_4*

Antibacterial activity

All the synthesized compounds were screened for their antibacterial activity against *Staphylococcus aureus, Escherichia coli, Psedomona auregenosa* and *Bacillus subtilis.* The activity was carried out using cup plate method.[19] The zone of inhibition was measured in mm. DMF was used as a vehicle and Ciproflaxacin as standard drug for comparison. The compounds were tested at 10 mg/mL concentration and each well was loaded with 50 µg/mL. All the synthesized compounds were found to exhibit moderate activity against all bacteria. The zones of inhibition are presented in Table -1

Table – 1

Compound	Diameter of zone of inhibition (mm*)			
	Staphylococcus aureus	*Escherichia coli*	*Psedomona auregenosa*	*Bacillus subtilis*
5a	00	09	00	08
5b	09	10	09	14
5c	10	12	00	12
5d	11	00	08	14
5e	09	11	10	09
5f	13	14	13	10
5g	11	13	15	12
6a	00	10	09	13
6b	00	08	00	14
6c	10	13	10	10
6d	12	00	10	12
6e	13	10	14	11
6f	09	10	10	10
6g	15	13	11	15
DMF	00	00	00	00
Ciproflaxacin	**25**	**40**	**43**	**44**

Antifungal activity

The synthesized compounds were evaluated invitro for antifungal activity by using standard agar disc diffusion method[19] against *Curvularia*, *Aspergillus niger* and *Candida albicans*. DMF was used as a vehicle. The compounds were tested at 10 mg/mL concentration and each well was loaded with 50 µg/mL of the sample. Clotrimazole was used standard drug. The zones of inhibition are presented in Table-2. All synthesized compounds were found to be febly active against fungi.

Table – 2

Compound	Diameter of zone of inhibition (mm*)		
	Curvularia	*Aspergillus niger*	*Candida albicans*
5a	08	09	08
5b	11	00	10
5c	13	11	13
5d	15	08	08
5e	09	13	12
5f	12	10	11
5g	11	12	09
6a	00	08	09
6b	08	10	10
6c	10	13	12
6d	10	12	14
6e	12	11	09
6f	11	09	11
6g	13	10	10
DMF	00	00	00
Clotrimazole	**48**	**38**	**27**

Table-3 Physical data of the compounds: 5**a-g**, and 6**a-g**

Compound	R	Mol. Formula	Yield (%)	M.P (°C)	Elemental Analyses Calcd (Found)%		
					C	H	N
5a	3-NO_2 C_6H_4	$C_{24}H_{16}N_4O_4$	49	245	67.87 (67.92)	3.70 (3.80)	13.10 (13.20)
5b	4-Cl C_6H_4	$C_{24}H_{16}ClN_3O_2$	55	227	69.00 (69.65)	3.80 (3.90)	10.00 (10.15)
5c	C_6H_5	$C_{24}H_{17}N_3O_2$	60	243	75.87 (75.97)	4.40 (4.52)	11.00 (11.08)
5d	4-OH C_6H_4	$C_{24}H_{17}N_3O_3$	55	237	72.85 (72.90)	4.29 (4.33)	10.59 (10.63)
5e	3- OCH_3 C_6H_4	$C_{25}H_{19}N_3O_3$	58	233	73.30 (73.34)	4.59 (4.68)	10.10 (10.26)
5f	4-OCH_3 C_6H_4	$C_{25}H_{19}N_3O_3$	58	239	73.29 (73.34)	4.50 (4.68)	10.00 (10.26)
5g	4-OH 3-OCH_3 C_6H_3	$C_{25}H_{19}N_3O_4$	55	225	70.46 (70.58)	4.44 (4.50)	9.80 (9.88)
6a	3-NO_2 C_6H_4	$C_{31}H_{19}N_5O_3S$	49	245	68.89 (68.93)	4.10 (4.16)	12.50 (12.56)
6b	4-Cl C_6H_4	$C_{31}H_{19}ClN_4OS$	55	227	70.20 (70.25)	4.20 (4.24)	10.21 (10.24)
6c	C_6H_5	$C_{31}H_{20}N_4OS$	60	243	74.90 (74.98)	4.69 (4.72)	11.90 (10.93)
6d	4-OH C_6H_4	$C_{31}H_{20}N_4O_2S$	55	237	72.68 (72.71)	4.55 (4.58)	10.55 (10.60)
6e	3- OCH_3 C_6H_4	$C_{32}H_{22}N_4O_2S$	58	233	73.00 (73.04)	4.79 (4.83)	10.30 (10.32)
6f	4-OCH_3 C_6H_4	$C_{32}H_{22}N_4O_2S$	58	239	73.00 (73.04)	4.78 (4.83)	10.28 (10.32)
6g	4-OH 3-OCH_3 C_6H_3	$C_{32}H_{22}N_4O_3S$	55	225	70.90 (70.95)	4.59 (4.69)	10.00 (10.03)

RESULTS AND DISCUSSION

The required starting material 2-acetylnaphtho[2,1-*b*]furan **3** was synthesised from 2-hydroxy-1-naphthaldehyde and chloroacetone in presence of anhydrous K_2CO_3 and dry acetone by well established method in our laboratory. The synthesis of key intermediate 2-amino-4-(substituted phenyl)-6-naphtho[2,1-*b*]furan-2-yl-nicotinonitriles **4**(a-g) was accomplished by reacting 2-acetylnaphtho[2,1-*b*]furan **3** with appropriate aromatic aldehydes, malanonitrile and ammonium acetate.

Compounds **4(**a-g) were treated with alcoholic KOH which resulted in the formation of various 2-amino-6-(1,2-dihydronaphtho[2,1-*b*]furan-2-yl)-4-phenylsubstitutedpyridine-3-carboxamides **5(**a-g). To substantiate the assigned structure, IR, ^{1}H NMR 2-amino-4-(3-hydroxy-4-methoxy phenyl)-6-naphtho[2,1-*b*]furan-2yl)pyridine-3-carboxamide **5g** is described. The IR spectrum exhibited a broad absorption band at 3448 cm^{-1} and 3050 cm^{-1} due to -OH and–NH_2 stretching frequencies respectively. The presence of –C=O was assigned by observing a strong stretching frequency at 1663 cm^{-1}.

The structure of the compound **5g** was supported by its ^{1}H NMR spectrum. A sharp singlet at δ 3.90 was attributed to three protons of –OCH_3, The presence of broad singlet at δ 6.9 indicated the two protons of -NH_2 (D_2O exchangeable), a multiplet between δ 7.5 to 8.5 were due to eleven aromatic protons and one proton of –OH group. The mass spectral data of **5g** showed molecular ion peak at m/z 426 corresponding to its molecular weight.

The compounds **6 (**a-g) were synthesized from **4 (**a-g) by reacting with phenylisothiocyanate. The IR spectrum compound **6**a exhibited the -C=S stretching frequency at 1588 cm^{-1} . The ^{1}H NMR spectrum was in good agreement with the assigned structure. A multiplet between δ 7.5 to 8.5 were due to seventeen aromatic protons and a proton due to -C=NH and a sharp singlet at δ 11.2 was attributed to a proton of –NH (D_2O exchangeable).

The molecular ion peak of **6a** was observed at m/z 543 corresponding to its molecular weight

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