ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Synthesis and antimicrobial activity of 2-substituted -4h-naphtho [2, 1-b] furo-m-oxazin-4-one

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ABSTRACT

The desired oxazinones were prepared by using 2-hydroxy-1-naphthaldehyde **1,** which was synthesized by using the 2-naphthol, chloroform and sodium hydroxide through Reimer-Tiemann reaction. The aldehyde **1** was converted into its oxime **2** by reaction with hydroxylamine hydrochloride, which on dehydration with acetic anhydride gave 2-hydroxy-1-naphthonitrile **3**. The compound **3** on reaction with ethyl chloroacetate in presence of weak base underwent both condensation and cyclisation simultaneously and resulted in the formation of ethyl 3-amiononaphtho[2,1-b]furan-2-carboxylatye **4**, in good yield. The amino ester **4** was treated with various acid chlorides/anhydrides to obtain corresponding acyl derivatives **5a-f**, which were then hydrolyzed to obtain respective acids **6a-f**. The title compounds i.e. 2-substituted -4H-naphtho[2,1-b]furo-m-oxazin-4-one **7a-f,** were obtained by cyclodehydration of acids **6a-f** by using acetic anhydride. The structures of the newly synthesized compounds were established by analytical and spectral studies. Evaluation of antibacterial and antifungal activity of the synthesized compounds was carried out by agar well diffusion method and encouraging results were obtained.

Key words: Naphthofuran, oxazinones, naphthofurooxazinones, antibacterial activity, antifungal activity.

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ISSN: 0975-8585

INTRODUCTION

The various naphtho[2,1-b]furan derivatives, synthesized in our laboratory have shown wide spectrum of biological and pharmacological activities[1-9]. Oxazolidin-2-ones and oxazin-2-ones are important class of nitrogen heterocyclic compounds containing five and six membered rings respectively [10]. The novel derivatives of benzoxazinones have been found to posses promising antibacterial activity [11-12]. Oxazinones have been reported to exhibit antitumor activity [13]. Many of the derivatives of oxazinones have been patented as antibacterial agents [14]. Some compounds involving bicyclic oxazinones have been synthesized and evaluated as chiral glycines [15].

MATERIALS AND METHODS

Melting points were determined by open capillary method and are uncorrected. IR spectra (cm^{-1}) were recorded on Perkin Elmer and Nicolet spectrometers. NMR spectra were recorded on AMX and Brucker 400 MHz and standard chemical shifts are expressed in δ ppm values. The compounds were checked for their purity by TLC on silica gel pates and spots were visualized in iodine vapour.

Synthesis of ethyl-3-acylaminonaphtho[2,1-b]furan-2-carboxylates (5a-c)

Ethyl 3-aminonaphtho[2,1-b]furan-carboxylate **4** (2.55 g, 0.01 mol) was treated with acetic anhydride(4 ml) and then warmed on water bath for 30 min. The reaction mixture on decomposition with ice water gave the compound **5a** as a colorless solid. It was recrystallised from ethanol. The dry material (53.44% yield) melted at 93^{o}C.

Similarly compounds **5 b-c** were synthesized using propionic anhydride and succinic anhydride.

Synthesis of ethyl 3-benzamidonaphtho[2,1-b]furan – 2-carboxylate (5 d-f).

Ethyl 3-aminonaphtho[2,1-b]furan-carboxylate **4** (2.55 g, 0.01 mol) was suspended in aqueous sodium hydroxide (2N, 25 ml) and then treated with benzoyl chloride (7.5 ml) in portions while vigorously shaking. After shaking for 30 minutes the reaction mixture was poured to ice cold water. The product 5d thus obtained as solid was filtered, washed with water and recrystallised from ethanol.

Similarly compounds **5e-f** were synthesized using appropriately substituted acid chlorides.

ISSN: 0975-8585

Synthesis of 3- substituted aminonaphtho[2,1-b]furan - 2-carboxylic acid (6a-f).

The compounds **5a** (2.97g 0.01mol) was dissolved in ethanol (10 ml) by warming and then treated with a solution of ethanolic potash (1.25 g, in 12 ml ethanol). The reaction mixture was boiled just for 2 min, diluted with water and cooled in ice. Acidification with dilute hydrochloric acid liberated the carboxylic acid **6a** as colorless solid. This was filtered, washed with water and dried.

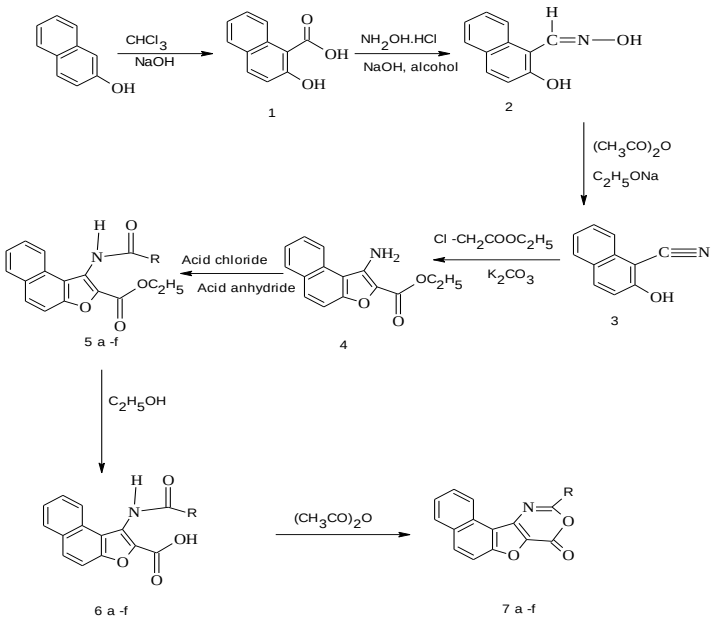
Similarly the esters **5b-f** were hydrolyzed to obtain corresponding carboxylic acids **6b-f.** The acids **6a-f** were recrystallised from suitable solvents.

Synthesis of 2-substituted -4-H-naphtho[2,1-b]furo-m-oxazin-4-ones (7 a-f).

The compound **6a** (2.69g, 0.01 mol) was heated under reflux in acetic anhydride (8 ml) for about 1 hour. Excess of acetic anhydride was distilled off under reduced pressure. The residual product was treated with petroleum ether and crystalline solid thus obtained was collected and recrystallized from suitable solvent. The dry material (38.12% yield) melted at 102^{o}C.

Similarly the compounds **7b-f** were synthesized from the compounds **6b-f**.

The sequence of the reactions is depicted in the scheme.



R,

a = CH_3 **d = C_6H_5**
b = C_2H_5 **e = 4-$NO_2C_6H_4$**
c = CH_2CH_2COOH **f = 4-ClC_6H_4**

Analytical data of the all the synthesized compounds has been summarized in the Table 1.

Table 1 – Physical characterization data of synthesized compounds

Compound	Molecular formula	m.p ^{o}C	% Yeild	m/z
5a	$C_{17}H_{15}O_4N$	93	53.44	297.17
5b	$C_{18}H_{17}O_4N$	101	54.09	311.17
5c	$C_{20}H_{17}O_6N$	162	53.62	355.17
5d	$C_{22}H_{17}O_4N$	110	54.26	359.17
5e	$C_{22}H_{16}O_6N_2$	166	53.16	404.17
5f	$C_{22}H_{16}O_4NCl$	172	53.24	393.52
6a	$C_{15}H_{11}O_4N$	116	72.22	269.17
6b	$C_{16}H_{13}O_4N$	132	73.49	283.17
6c	$C_{17}H_{13}O_6N$	140	73.19	327.17
6d	$C_{20}H_{13}O_4N$	95	73.91	331.17
6e	$C_{20}H_{12}O_6N_2$	189	71.66	376.17
6f	$C_{20}H_{12}O_4NCl$	236	71.13	365.5
7a	$C_{15}H_7O_3N$	102	46.13	251.17
7b	$C_{16}H_{11}O_3N$	152	46.79	265.17
7c	$C_{17}H_{11}O_5N$	164	45.13	315.17
7d	$C_{20}H_{11}O_3N$	123	44.25	320.17
7e	$C_{20}H_{10}O_5N_2$	242	46.6	358.17
7f	$C_{20}H_{10}O_3NCl$	203	45.03	347.5

Antimicrobial activity

In vitro antibacterial activity was determined by agar well diffusion method, against 24 hr old cultures of *Escherichia coli, Salmonella paratyphi, Bacillus subtilis* using 0.01 g/ml and 0.005 g/ml of Streptomycin as standard. The compounds were tested at the concentration of 0.01 g/ml and 0.005 g/ml in dimethyl sulfoxide for all the organisms. The zone of inhibition was compared with the standard drug after 24 hr incubation at 37^{0}C. The results of antibacterial activity are presented in Table 2.

Similarly antifungal activity was carried out by agar well diffusion method against *Aspergillus niger, Micropporsum gupseum, Candida albicans* using 0.01 g/ml and 0.005g/ml of Fluconazole as standard. The compounds were tested at the concentration of 0.01g/ml and 0.005 g/ml in dimethyl sulfoxide for all the organisms. The zone of inhibition was compared with the standard drug after 48 hr incubation at 25 ^{0}C. The results of antifungal activity are presented in Table 3.

ISSN: 0975-8585

Table 2- Antibacterial activity of the synthesized compounds.

	Zone of inhibition in mm					
Compounds	*E. c*		*B .s*		*S. p*	
	0.01 g/ml	0.005 g/ml	0.01 g/ml	0.005 g/ml	0.01 g/ml	0.005 g/ml
Standard	16	10	20	12	15	11
Distilled water	Nil	Nil	Nil	Nil	Nil	Nil
DMSO	Nil	Nil	Nil	Nil	Nil	Nil
5a	11	06	10	07	12	08
5b	05	03	10	06	07	04
5c	07	05	09	06	12	09
5d	08	06	15	09	11	04
5e	10	07	12	08	10	06
5f	06	03	12	08	09	06
6a	08	05	11	07	11	08
6b	12	08	10	06	12	09
6c	11	07	10	05	11	08
6d	12	07	17	12	08	08
6e	13	08	16	10	07	07
6f	12	08	15	09	07	06
7a	10	06	11	08	07	05
7b	08	05	12	08	08	06
7c	11	07	10	05	08	07
7d	14	09	17	11	08	07
7e	13	08	16	10	13	09
7f	14	08	16	10	13	08

E.c : Escherichia coli, B.s : Bacillus subtilis, S.p : Salmonella paratyphi

Table 3- Antifungal activity of the synthesized compounds.

	Zone of inhibition in mm					
Compounds	*A.n*		*M. g*		*C .a*	
	0.01 g/ml	0.005 g/ml	0.01 g/ml	0.005 g/ml	0.01 g/ml	0.005 g/ml
Standard	13	11	15	13	22	19
Distilled water	Nil	Nil	Nil	Nil	Nil	Nil
DMSO	Nil	Nil	Nil	Nil	Nil	Nil
5a	09	08	11	07	15	13
5b	08	07	11	08	14	12
5c	06	05	10	08	14	13
5d	10	09	11	07	16	14
5e	11	08	09	08	18	16
5f	12	09	13	11	18	16
6a	10	07	10	06	14	12
6b	11	07	09	06	13	11
6c	08	06	08	06	13	11
6d	12	09	13	10	18	16
6e	10	08	11	08	17	13
6f	11	10	12	10	16	13

ISSN: 0975-8585

7a	08	06	08	06	13	09
7b	17	06	09	06	14	10
7c	11	07	08	06	14	10
7d	12	09	09	07	17	12
7e	11	08	11	09	18	15
7f	11	09	12	11	19	18

A.n: Aspergillus niger, M.g: Micropporsum gupseum, C.a: Candida albicans

RESULTS AND DISCUSSION

Ethyl 3-amino naphtho[2,1-b]furan-2-carboxylate **4** was synthesized by well established procedure in our laboratory[16-17]. It involved the conversion of 2-naphthol into 2-hydroxy-1-naphthaldehyde through Reimer-Tiemann reaction employing chloroform and sodium hydroxide in presence of ethanol. The aldehyde **1** on treatment with hydroxylamine hydrochloride in ethanol produced oxime **2**, which on subsequent dehydration using acetic anhydride yielded 2-hydroxy-1-naphthnitrile **3** in good yield. The compound **3** on reaction with ethyl chloroacetate under basic condition underwent condensation and Thorpe-Zeigler cylisation in one step resulting in the formation of ethyl 3- aminonaphtho[2,1-b]furan-2-carboxylate **4**. The structure of compounds **1, 2, 3** and **4** were established by comparison of IR and ^{1}H NMR spectra with authentic sample. The mixed melting points of these compounds with known sample showed no depression.

The amino ester **4** was converted into ethyl-3-acylaminonaphtho[2,1-b]furan-2-carboxylates **(5 a-c)** by treating it with acetic anhydride, propionic anhydride and succinic anhydride respectively. The structure of **5a** i.e. ethyl 3-acetamidonaphtho[2,1-b]furan-2-carboxylate was established by its spectral data. It exhibited strong absorption band at 1705 cm^{-1} and 1685 cm^{-1} due to ester carbonyl group and amide carbonyl groups. ^{1}H NMR spectrum showed a quartet and triplet at δ 3.3 and at δ 2.5 due to –CH_2 and –CH_3 protons , a singlet at δ 2.4 due to –CH_3 protons, a multiplet at δ 7.2-8.1 due to aromatic protons and D_2O exchangeable singlet at δ 12.1 due to –NH proton.

Similarly ethyl 3-benzamidonaphtho[2,1-b]furan-2-carboxylate **(5d-f**) were synthesized by Schotten-Baumann reaction between amino ester **4** and appropriately substituted benzoyl chlorides in presence of aqueous sodium hydroxide. The structure of **5d** i.e. ethyl 3-benzamidonaphtho[2,1-b]furan-2-carboxylate was established by its spectral data. It exhibited strong absorption band at 1737cm^{-1} and 1681 cm^{-1} due to ester carbonyl group and amide carbonyl groups in its IR spectrum. ^{1}H NMR spectrum showed a quartet and triplet at δ 2.8 and at δ 1.2 due to –CH_2 and –CH_3 protons, a multiplet at δ 7.6-8.4 due to aromatic protons and D_2O exchangeable singlet at δ 12.1 due to –NH proton.

The 3-substituted esters **(5a-f)** were subjected to hydrolysis with ethanolic potassium hydroxide to obtain corresponding acids i.e. 3-substituted naphtho[2,1-b]furan-2-carboxylic acid **(6 a-f).** The IR spectrum of **6a** exhibited two absorption bands at 1669 and 1625 cm^{-1} corresponding to acid and amide carbonyl groups respectively. The ^{1}H NMR spectrum was

ISSN: 0975-8585

conspicuous by the absence of quartet and triplet due to ester $-CH_2-CH_3$ protons confirming the hydrolysis.

The conversion of acids **(6 a-f)** into 2-substituted-4-H-naphtho[2,1-b]furo-m-oxazin-4-ones **(7 a-f)** was accomplished by treating the acids **(6 a-f)** with acetic anhydride where in cyclodehydration occurred very smoothly. The formation of **7d** was supported by its IR spectrum which showed carbonyl absorption band at 1685 cm^{-1} characteristic C=O of oxazinones.

In vitro antibacterial activity of the compounds was carried out by agar well diffusion method using 24 hour old culture of gram +ve bacteria *Bacillus subtilis* and gram -ve bacteria *Escherichia coli and Salmonella paratyphi* by agar well diffusion method using Streptomycin as a standard. The compounds **7d** and **7f** exhibited zone of inhibition of 14 cm at the concentration of 0.01g/ml as compared with standard Streptomycin with zone of inhibition of 16 cm of against *Escherichia coli*. The compounds **6d, 6e, 7d,** and **7f** exhibited comparable activity against *Bacillus subtilis*, where as compound **7e** and **7f** showed considerable activity against *Salmonella paratyphi.*

In vitro antifungal activity of the compounds was carried out by agar well diffusion method against *Aspergillus niger, Micropporsum gupseum, Candida albicaus* using Fluconazole as a standard. The compounds **6e, 6f, 7f** were found to be active against all the organism.
The results indicate that presence of halogen in aromatic ring enhanced activity to considerable extent.

ACKNOWLEDGEMENT

The authors are thankful to the Director, Indian Institute of Science, Bangalore for spectral analysis and Chairman Department of Chemistry, Kuvempu University for providing laboratory facilities and Chairman Department of Biohemistry, Kuvempu University for assisting us in carrying out antimicrobial activity.

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