Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2012, 4(5):2643-2648

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis of 3-methoxy-2-(1,3,4-oxadiazolyl,1,3,4-thiadiazolyl and 1,2,4-triazolyl)naphtho[2,1-b]furans of biological interest

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ABSTRACT

*The naphthofuran nucleus [**3**b] was constructed by refluxingmethyl-2-hydroxy-1-naphthoate [**2**] and diethyl bromomalonate in presence of dry potassium carbonate. The tautomer product [**3**a] was ethylated to get a stable 3-methoxy derivative [**4**]. The compound [**4**] was converted into 3-methoxynaphtho[2,1-b]furan-2-carbohydrazide[**5**] by refluxing with 95% hydrazine hydrate in absolute ethanol. The hydrazide [**5**] was condensed with various isothiocyanates(a-e) to form respective 3-methoxynaphtho[2,1-b]furan-2-carbo(-arylamino)thiosemicarbazides using iodine in potassium iodide, NaOH and H_3PO_4 gave the title compounds. Newly synthesized compounds were screened for their antibacterial and antifungal activity. Some of them gave encouraging activity.*

Key words: naphthofuran, thiadiazole, oxadiazole triazole, antimicrobial, antifungal.

INTRODUCTION

Naphthofuran derivatives were reported to possess various biological activities. Naphtho[2,1-b]furopyrozolyl, isoxalyl and pyridyl derivatives were reported[1] as potential antimicrobial agents. Some of the 2, 9-disubstituted naphtha[2, 1-b]furans were known to possess antimicrobial and anthelmintic activities[2]. Napthofurans coupled with another heterocyclic system were also reported to possess useful biological activities[3,4]. The importance of 1, 3, 4-oxadiazoles, 1, 3, 4-thiodiazoles and 1, 2, 4-triazoles is also been reported. Compounds incorporated with oxadiazole nucleus were reported to possess varied biological activities[5,6] 1,3,4-Thiadiazoles were also reported to be biologically active[7]. 1, 3, 4-Triazoles were known for their wide spectrum of biological potency[8,9]. In view of their wide range of biological properties, an effort has been made from our laboratory to couple these biologically potent 1, 3, 4-oxadiazole, 1, 3, 4-thiadiazoles and 1, 2, 4-triazoles with another biologically potent oxygen heterocycle benzofuran. Such biheterocycles reported earlier from our laboratory were known to possess antimicrobial and anti-inflammatory activity[10,11]. In view of the varied biological activities and in continuation of our search for biologically active oxygen containing biheterocycles, we have undertaken the synthesis and antimicrobial screening of naphthofuran biheterocycles coupled with 1, 3, 4-oxadiazole, 1, 3, 4-thiadiazoles and 1, 2, 4-triazoles.

Theoretical

Among the various methods available for the construction of naphthofuran molecule we opted to construct it using methyl 2-hedroxy-1-naphthoate **[2]** and diethyl bromomalonate. The synthetic route is depicted in the scheme-1. The scheme-2 shows the synthesis of title compounds.

Commercially available 2-hydroxy-1-naphthoic acid **[1]** was subjected to esterification using HCl saturated methanol. The resulting ester **[2]** was refluxed with diethylbromomalonate in presence of dry potassium carbonate to give a 3-oxo compound **[3a]**. This tautomeric compound **[3a]** methylated using dimethyl sulphate to get a stable compound ethyl-3-methoxy naphtha[2, 1-b]furan-2-carboxylate [**4].** The formation of ethyl ester **[4]** was well supported by its IR and ^{1}H NMR spectral data. The IR spectrum of compound **[4]** has shown a sharp absorption band at 1700 cm^{-1} due to ester carbonyl. The ^{1}H NMR spectra has shown four main signals at δ 1.5 (3H, t, CH_3), δ 4.5(2H, q, -CH_2-), δ 4.2 (3H, s, -OCH_3) and δ 7.5-8.6 (6H, m, Ar-H).

The ethyl ester [**4**] was treated with 95% hydrazine hydrate in refluxing ethanol to get anticipated 3-methoxynaphtho[2, 1-b]furan-2-carbohydrazide [**5**] in encouraging yields. The structure of compound [**5**] was well established by spectral data. The IR spectrum of carbohydrazide [**5**] has shown an absorption band at 1690 cm^{-1} due to C=O and two absorption bands, one for symmetric and another for asymmetric stretching of –NH_2 at 3300 cm^{-1}. Yet another band at 3200 cm^{-1} due to –NH- group. ^{1}H NMR spectrum of this compound [**5**] has showed four main signals at δ δ 4.1 (3H, s, -OCH_3), δ 6.3 (2H, s, -NH_2), δ 7.1-8.0 (6H, m, Ar-H) and δ 9.1(1H, s, -NH-).

The reaction of hydrazide **[5]** with different isothiocyanates in benzene was straight forward and furnished the anticipated 3-methoxynaphtho[2, 1-b]furan-2-carbo(arylamino)thiosemicarbazide **[6a-e**] in good yields. The structure assigned to these thiosemicarbazides was well supported by the IR and ^{1}H NMR spectral data. The IR spectrum of compounds **[6a-e]** contained absorption bands in the region of 3360-3200 (-NH), 1680 (C=O) and 1150 (C=S) cm^{-1} were particularly diagnostic. ^{1}H NMR spectra of a representative compound (6a) has displayed signals at δ 4.8 (3, S, -OCH_3), d 7.0-7.8 (10H, m, Ar-H), d 9.5 (2H, s, NH-NH) and d 10.3 (1H, s, -NH).

Cyclization of these thiosemicarbazides using Iodine in KI, NaOH and H_3PO_4 yielded the title compounds. The oxidative cyclization of thiosemicarbazides **[6a-e]** using saturated solution of Iodine in KI yielded 3-methoxy-2-(5`arylamino,1`,3`,4`-oxadiazol-2`-yl)naphtha[2,1-b]furans [**7**a-e] in good yields. Structure of these compounds **[7a-e]** were well supported by their IR, ^{1}H NMR and mass spectral data. The disappearance of C=S stretching band around 1150 cm^{-1} in IR spectra of all five analogous compounds was particularly diagnostic. Absorption bands around 1650 cm^{-1} and 3200 cm^{-1} due to C=N and –NH respectively were added support towards the assigned structure. The ^{1}H NMR spectra of a representative compound **[7a]** exhibited signals at d 4.2 (3H, S, -OCH_3), d 10.1 (1H, s, Ar-NH), d 7.0-8.1 (11H, m, Ar-H). The mass spectrum of compound [**7a]** showed molecular ion peak at m/z 357.

The cyclodehydration of **[6a-e]** with orthophosphoric acid furnished corresponding 3-methoxy-2-(5`-arylamino-1`,3`,4`-thiadiazol-2`-yl)naphtha[2,1-b]furans **[8a-e]**. The structures assigned to these thidiazoles were well supported by their IR ^{1}H NMR and mass spectral data. The IR spectra of compound **[8a-e]** have showed absorption bands at 1620 cm^{-1} and 3200 cm^{-1} due to C=N and NH respectively. The ^{1}H NMR spectral data of a representative compound 8a displayed signals at d 4.2 (3H, s, -OCH_3), d 10.1 (1H, s, -NH) and d 7.0-8.1 (11H, m, Ar-H). the mass spectrum of **[8a]** has shown molecular ion peak at m/z 373 which is in agreement with the assigned structure.

Reaction of thiosemicarbazides **[6a-e]** with alkali NaOH yielded the cyclised product 3-methoxy-2-(4`-aryl-3`-mercapto-1`,2`,4`-triazol-5`-yl)naphtha[2,1-b]furans **[9a-e]** in good yields. The absence of carbonyl absorption band and appearance of new band around 1620 cm^{-1} due to C=N stretching frequency in IR spectra of **[9a-e]** were particularly diagnostic. The ^{1}H NMR spectral data of a representative compound **[9a]** has shown three main signals at d 4.2 (3H, s, -OCH_3), d 7.0-7.9 (11H, m, Ar-H) and d 10.6 (1H, s, -NH). The mass spectra of **[9a]** has displayed molecular ion peak at m/z 373.

EXPERIMENTAL SECTION

Methyl 2-hydroxy-1-naphthoate [2].

An equimolar mixture of 2-hydroxy-1-naphthoic acid (0.1 mol) and anhydrous methanol saturated with dry HCl was refluxed on a water bath for 4 hours. The reaction mixture was cooled to the room temperature and the methanol was evaporated. The solid thus obtained was collected and purified by recrystallization from aqueous ethanol. Yield was 85% and M P recorded was 54^{o}C.

2-Carbethoxy-3-(2H)naphthofuranone [3a].
A mixture of compound [**2**], diethylbromomalonate (1:1 mol) and anhydrous potassium carbonate in dry acetone was heated under reflux for 12 hours. It was filtered and potassium salt was washed with anhydrous ether. The dry salt was suspended in water and cooled thoroughly. Acidifying the cooled suspension with dilute HCl yielded the product. Purified b recrystallization with aqueous ethanol and M.P recorded was 88^{o}C.

Ethyl 3-methoxynaphtho[2,1-b]furan-2-carboxylate [4].
The mixture of compound [**3**] and dimethylsulphate (1:1 mol) was refluxed in acetone on a water bath for 6 hours. The reaction mixture was filtered and filtrate on removal of solvent under reduced pressure furnished viscous oil which solidified on cooling. The solid was recrystallized from ethanol and M.P recorded was 120^{o}C.

3-Methoxynaphtho[2,1-b]furan-2-carboydrazide [5].
The equimolar mixture of compound **[4]** and 95% hydrazine hydrate in dry ethanol was heated under reflux for 4 hours. The reaction mixture was diluted with ice cold water to get the product as solid. It was filtered, dried and recrystallized from ethanol. M.P recorded was 185^{o}C.

3-Methoxynaphtho[2,1-b]furan-2-carbo(e-arylamino)thiosemicarbazide [6a-e].
A suspention of hydrazide [**5]** in benzene was treated with appropriate aryl isothiocyanate (1:1 mol) and heated under reflux for 2-4 hours on a water bath. The solid separated on cooling was collected and recrystallized from suitable solvent. The physical constant, solvent for recrystallization, analytical data and percentage yield of these compounds is given in the table-1 (data table for compounds **6a-e**).

3-Methoxy-2-(5`-arylamino-1`,3`,4`-oxadiazol-2`-yl)naphtha[2,1-b]furans [7a-e].
To the stirred suspension of appropriate thiosemicarbazide **[6a-e]** (0.001 mol) in ethanol (30 ml) aqueous sodium hydroxide (0.4ml 4N) was added. A saturated solution of iodine in potassium iodide (5% aqueous) was then introduced slowly till the color persists. The reaction mixture was refluxed on steam bath for one hour, cooled and diluted with cold water. The compound thus precipitated was collected after thorough washing with water. The solvent for recrystallization and physical constant are given in the data table-2

3-Methoxy-2-(5`-arylamino-1`,3`,4`-thiadiazol-2`-yl)naphtha[2,1-b]furans [8a-e].
The appropriate thiosemicarbazide **[6a-e]** (0.002mol) was added in small portions to anhydrous orthophosphoric acid (10 ml) during half an hour while stirring. The reaction mixture was heated at 110-120^{o}C for half an hour. It was cooled and treated with ice cold water. The resulting solid was collected and recrystallized from suitable solvent. The solvent for recrystallization and M.P are given in the table-3

3-Methoxy-2-(4`-aryl-3`-mercato-1`,2`,4`-triazol-5`-yl)naphtha[2,1-b]furans [9a-e].
Appropriate thiosemicarbazide **[6a-e]** (0.002mol) was suspended in aqueous sodium hydroxide (30 ml 4%) and heated under gentle reflux for 2-6 hours. The solution was treated with decolourizing carbon and filtered. The filtrate was cooled and acidified carefully with dilute acetic acid (10%). The products thus obtained were washed with water and they were purified by recrystallization using suitable solvents. Physical constant, solvent for crystallization are given in the table-4.

Antimicrobial Activity
Antibacterial Activity
The antibacterial activity of newly synthesized compounds was studied comparatively using Gentamycin and Ciprofloxacin as standard drugs at a concentration of 100 mg/ml. the microorganisms used in the present study were *E.coli, P.aeruginosa, S. aureus and B. subtilis* by cup-plate method.

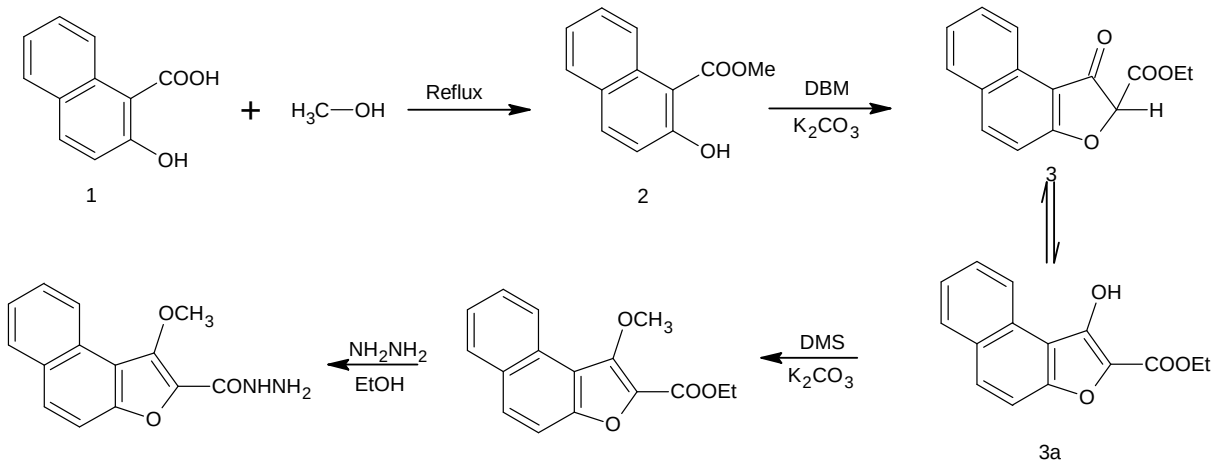
Among the compounds tested p-bromophenyl derivative **9d** has shown good activity against gram negative organisms. The chloro derivative 9e is moderately active against all the organisms. Compounds 6d and 6e are most active against *P.aeruginosa and B. subtilis* respectively. The remaining compounds have moderate to poor activity against the organisms used.

Antifungal Activity

The title compounds were subjected to the antifungal activity at a concentration of 100mg/ml against the fungi *A. niger and C. albicans.* The screening study was a comparative study of test compounds compared with standards viz.. Griseofulvin and Flucanazole.

The results of this study revealed that compounds **9c, 9e, 8a, 8d** and **6d** are highly active against the organisms used. The remaining compounds are either moderately active or poorly active against the said organisms.

SCHEME-1



Comp	Substituent 'R'
a	C_6H_5
b	$C_6H_5.CH_3(p)$
c	$C_6H_5.OCH_3(p)$
d	$C_6H_5.Br(p)$
e	$C_6H_5.Cl(p)$

SCHEME-2

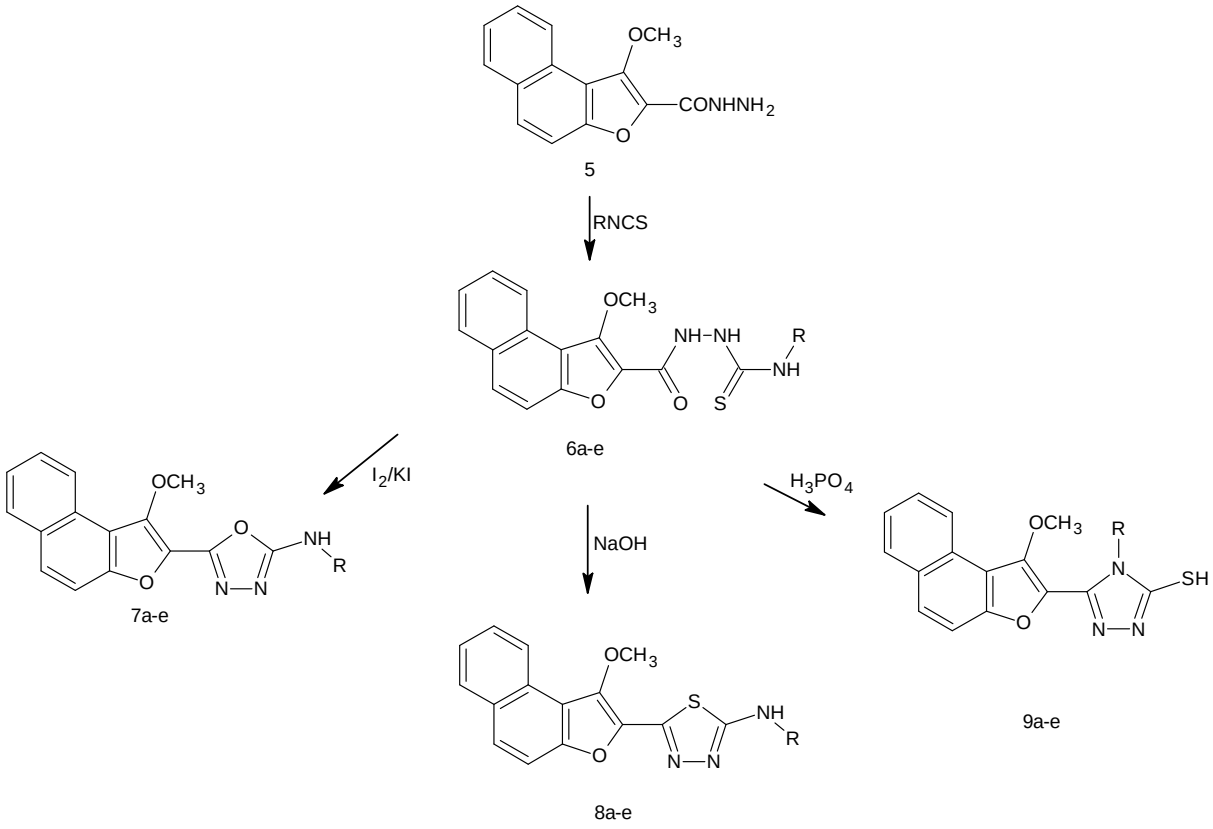


Table-1

Comp	Substituent 'R'	M.P In ^{0}C	Yield (%)	Solvent	Mol. Formula	Found(calculated) %		
						C	H	N
6a	C_6H_5	258	70	Methanol	$C_{21}H_{17}N_3O_3S$	64.41 (64.43)	04.36 (04.38)	10.71 (10.73)
6b	$C_6H_5.CH_3$(p)	186	74	Methanol	$C_{22}H_{19}N_3O_3S$	65.15 (65.17)	04.71 (04.72)	10.35 (10.36)
6c	$C_6H_5.OCH_3$(p)	209	62	Ethanol	$C_{22}H_{19}N_3O_4S$	62.68 (62.69)	04.52 (04.54)	09.96 (09.97)
6d	C_6H_5.Br(p)	229	68	Ethanol	$C_{21}H_{16}N_3O_3SBr$	53.62 (53.63)	03.42 (03.43)	08.91 (08.93)
6e	C_6H_5.Cl(p)	198	70	Methanol	$C_{21}H_{16}N_3O_3SCl$	59.21 (59.22)	03.77 (03.79)	09.85 (09.87)

Table-2 (4.2) (7a-e)

Comp	Substituent 'R'	M.P In ^{0}C	Yield (%)	Solvent	Mol. Formula	Found(calculated) %		
						C	H	N
7a	C_6H_5	267	65	Ethanol	$C_{21}H_{15}N_3O_3$	70.56 (70.58)	04.21 (04.23)	11.75 (11.76)
7b	$C_6H_5.CH_3$(p)	221	63	Ethanol	$C_{22}H_{19}N_3O_3$	71.13 (71.15)	04.61 (04.61)	11.30 (11.32)
7c	$C_6H_5.OCH_3$(p)	243	70	Ethanol	$C_{22}H_{17}N_3O_4$	68.20 (68.21)	04.41 (04.42)	10.84 (10.85)
7d	C_6H_5.Br(p)	179	75	Methanol	$C_{21}H_{14}N_3O_3Br$	57.81 (57.82)	03.22 (03.23)	09.61 (09.63)
7e	C_6H_5.Cl(p)	212	76	1,4-dioxane	$C_{21}H_{14}N_3O_3Cl$	64.35 (64.37)	03.59 (03.60)	10.71 (10.72)

Table-3 (4.3) (8a-e)

Comp	Substituent 'R'	M.P In ^{0}C	Yield (%)	Solvent	Mol. Formula	Found(calculated) %		
						C	H	N
8a	C_6H_5	254	75	1,4-dioxane	$C_{21}H_{15}N_3O_2S$	67.52 (67.54)	04.04 (04.05)	11.24 (11.25)
8b	$C_6H_5.CH_3$(p)	177	77	1,4-dioxane	$C_{22}H_{17}N_3O_2S$	68.19 (68.20)	04.41 (04.42)	10.84 (10.85)
8c	$C_6H_5.OCH_3$(p)	200	80	1,4-dioxane	$C_{22}H_{17}N_3O_3S$	65.48 (65.49)	04.23 (04.25)	10.41 (10.42)
8d	C_6H_5.Br(p)	226	68	Methanol	$C_{21}H_{14}N_3O_2SBr$	55.74 (55.76)	03.11 (03.12)	09.27 (09.29)
8e	C_6H_5.Cl(p)	196	74	Methanol	$C_{21}H_{14}N_3O_2SCl$	61.83 (61.84)	03.44 (03.46)	10.28 (10.30)

Table-4 (4.4) (9a-e)

Comp	Substituent 'R'	M.P In ^{0}C	Yield (%)	Solvent	Mol. Formula	Found(calculated) %		
						C	H	N
9a	C_6H_5	175	64	1,4-dioxane	$C_{21}H_{15}N_3O_2S$	67.53 (67.54)	04.03 (04.05)	11.22 (11.25)
9b	$C_6H_5.CH_3$(p)	203	70	Ethanol	$C_{22}H_{17}N_3O_2S$	68.19 (68.20)	04.40 (04.42)	10.84 (10.85)
9c	$C_6H_5.OCH_3$(p)	258	71	1,4-dioxane	$C_{22}H_{17}N_3O_3S$	65.47 (65.49)	04.23 (04.25)	10.41 (10.42)
9d	C_6H_5.Br(p)	214	68	1,4-dioxane	$C_{21}H_{14}N_3O_2SBr$	55.75 (55.76)	03.10 (03.12)	09.27 (09.29)
9e	C_6H_5.Cl(p)	284	75	Ethanol	$C_{21}H_{14}N_3O_2SCl$	61.83 (61.84)	03.45 (03.46)	10.29 (10.30)

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