Research & Reviews: Journal of Chemistry

e-ISSN:2319-9849
p-ISSN:2322-00

# Synthesis, Characterization and Biological Studies of Novel 1,3,4-Oxadiazole Derivatives

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## Research Article

Received date: 08/10/2017
Accepted date: 12/10/2017
Published date: 20/10/2018

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**Keywords:** Naphtho[2,1-b]furan, Oxadiazine, Mannich reaction, Spectral studies, Antibacterial and Antifungal activities

**ABSTRACT**

Naphtho[2,1-b]furan-2-carbohydrazide (2) prepared from reaction between ethyl naphtho[2,1-b]furan-2-carboxylate (1) and hydrazine hydrate, then compound (2) on reaction with CS2/KOH gives 5-(naphtho[2,1-b] furan-2-yl)-1,3,4-oxadiazole-2(3H)-thione (3), Which on mannich reaction followed by reaction with benzoic hydrazine gives different N-(1-((dialkylamino)methyl)-3-(naphtho[2,1-b]furan-2-yl)-5-thioxo$^{-1}$H$^{-1}$,2,4-triazol-4(5H)-yl)benzamide (4a-e). With the help of analytical and spectral data, the structure of these compounds were detected. Antibacterial and antifungal activities of the synthesized compounds were studied

## INTRODUCTION

Extensive biological activities as well as pharmaceutical activities like, antimicrobial agents, antimicrobial, anti-inflammatory activity and anthelmintic activities etc had been shown by Naphthofurans derivatives [1-5]. Recently, Napthofurans containing other heterocyclic systems were also reported to possess useful biological activities [6-10]. Number of biological activities such as antibacterial, antifungal and anti-inflammatory activity were shown by the compounds integrated with oxadiazole, thiadiazoles and triazoles nucleus [11-15]. Hence, it was interested to link naphtho[2,1-b]furan and oxadiazole moieties which may increase the drug activity of compounds to some limit, or they might show some of the above described biological activities. In continuation of our previous work [16], the aim of the present work is to prepare new derivatives of oxadiazole containing naphtho[2,1-b]furan moiety. Hence in this research paper study of N-(1-((dialkylamino)methyl)-3-(naphtho[2,1-b]furan-2-yl)-5-thioxo$^{-1}$H$^{-1}$,2,4-triazol-4(5H)-yl) benzamide was carried out. The synthetic scheme is shown in **Scheme 1.**

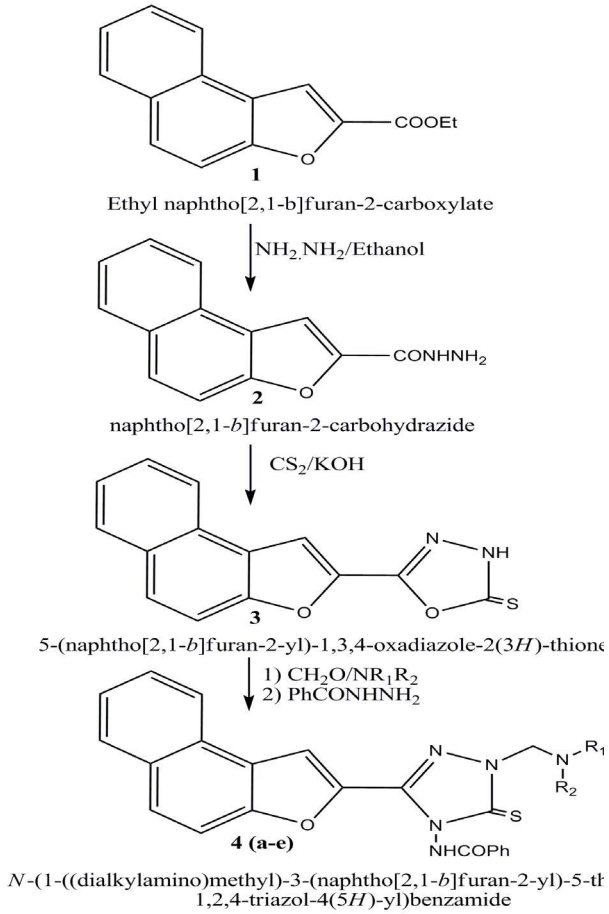
## EXPERIMENTAL

In open capillary tube method was used for melting points determination. With the help of KBr pellets on a Nicolet 400D spectrometer, the IR spectra were recorded and $^1$H NMR spectra were recorded using DMSO with TMS as internal standard on a Bruker spectrometer at 400 MHz and 100 MHz, respectively.

**Preparation of Naphtho[2,1-b]furan-2-carbohydrazide (2)**

Ethyl naphtho[2,1-b]furan-2-carboxylate 1 (0.1 mol) and hydrazine hydrate(0.1 mol) in absolute ethyl alcohol (30 ml) were refluxed for 2-3 hrs, under acidic condition. After the reaction was completed checked by TLC, the reaction mixture had been poured onto crushed ice; the solid compound was separated out, which was filtered, washed using water and dried to give the compound-3 of the above given scheme. The yield of the reaction was 82%. M.P. 99°C. IR cm$^{-1}$: 3127 (NH), 3200 ($NH_2$), 3020-3080 (C-H, of Ar.), 1685 (CONH). 1H NMR: 7.31–8.63 (m, 7H, Ar-H), 8.37 (s, 1H, NH), 3.6 (s, 2H, $NH_2$). Anal. Calcd for $C_{13}H_{10}N_2O_2$ (226): C, 69.03; H, 4.42; N, 12.39. Found: C, 69.01; H, 4.39; N, 12.37.

e-ISSN:2319-9849
p-ISSN:2322-00




**Scheme 1.** N-(1-((dialkylamino)methyl)-3-(naphtho[2,1-b]furan-2-yl)-5-thioxo-$^{1}H^{-1}$,2,4-triazol-4(5H)-yl) benzamide.

**Preparation of 5-(Naphtho[2,1-b]furan-2-yl)-$^{1}$,3,4-oxadiazole-2(3H)-thione (3)**

The reaction mixture of cold solution of naphtho[2,1-b]furan-2-carbohydrazide **(2)** (0.01 mol) in ethyl alcohol (50 mL) containing KOH (0.01 mol), $CS_2$ (0.05 mol) was reflux on a steam-bath until $H_2S$ evolution stopped. With the help of distillation, ethyl alcohol was removed. The solid compound was stirred with water, filtered. Using dilute HCl the filtrate was neutralized. The product was again filtered, washed using water. The recrystallized was carried out using alcohol to get the final compound 5-(naphtho[2,1-b]furan-2-yl)-$^{1}$,3,4-oxadiazole-2(3H)-thione **(3)**. Yield of the reaction was 65%. **IR cm$^{-1}$**: 1632$^{-1}$ 648 (C=N), 3020-3080 cm$^{-1}$ (C-H, of Ar.), 1190 (C=S), 760 (C-O-C ring). **$^{1}$H NMR**: 7.31–8.63 (m,7H, Ar-H), 9.40 (s,1H, NH). **Anal**. **Calcd** for $C_{14}H_8N_2O_2S$ (268): C, 62.67; H, 3.01; N, 10.44; S, 11.95. **Found:** C, 62.65; H, 3.00; N, 10.42; S, 11.92.

**Preparation of N-(1-((dialkylamino)methyl)-3-(naphtho[2,1-b]furan-2-yl)-5-thioxo-$^{1}H^{-1}$,2,4-triazol-4(5H)-yl)benzamide (4a-e)**

The mixture of 5-(naphtho[2,1-b]furan-2-yl)-1,3,4-oxadiazole-2(3H)-thione **(3)** (0.1 mol) in ethanol (10 ml), methanal (0.1 mol) and secondary amine **(a-e)** in ethanol (10 ml) (0.12 mol) and the reaction mixture was continuously stirred for about 20-21 hrs. The product was separated out as solid mass, which was filtered and washed using ethanol. The solid mass was refluxed with benzoic hydrazine (0.02 mol) in ethanol (40 ml) on water bath for 10 hrs. The final reaction mixture was poured into cold water, acidified using glacial acid. With the help of rectified spirit, recrystallization was carried out, which gave N-(1-((dialkylamino) methyl)-3-(naphtho[2,1-b]furan-2-yl)-5-thioxo-1H-1,2,4-triazol-4(5H)-yl)benzamide **(4a-e)**. yield of the reaction was 63-75%. The characterization data of these compounds are given in **Table 1**.

**Table 1.** Analytical Data and Elemental Analysis of Compounds (4a-e).

| Compd. | $R_1$ | $R_2$ | Yield | M.P. °C | Elemental Analysis | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | % C | | % H | | % N | | % S | |
| | | | | | Found | Calc. | Found | Calc. | Found | Calc. | Found | Calc. |
| **4a** | $CH_3$ | $CH_3$ | 75 | 222 | 64.97 | 64.99 | 4.75 | 4.77 | 15.78 | 15.79 | 7.21 | 7.23 |
| **4b** | $CH_3$ | Et | 72 | 204 | 65.62 | 65.63 | 5.06 | 5.07 | 15.30 | 15.31 | 6.99 | 7.01 |
| **4c** | Et | Et | 70 | 215 | 66.20 | 66.22 | 5.32 | 5.34 | 14.83 | 14.85 | 6.78 | 6.80 |
| **4d** | Et | $C_6H_5$ | 66 | 208 | 69.33 | 69.34 | 4.83 | 4.85 | 13.46 | 13.48 | 6.15 | 6.17 |
| **4e** | $C_6H_5$ | $C_6H_5$ | 62 | 205 | 71.92 | 71.94 | 4.42 | 4.44 | 12.32 | 12.34 | 5.64 | 5.65 |

*Uncorrected

e-ISSN:2319-9849
p-ISSN:2322-00

## BIOLOGICAL SCREENING

### Antibacterial Activities

With the help of the agar cup plate method, studie of the antibacterial activities of all the above mentioned compounds has been studied against gram-positive(+ve) bacteria and gram-negative(-ve) bacteria at a concentration of 50 µg/ml using agar. A methyl alcohol system had been used as control in this process. For the standard comparison, similar condition using tetracycline as control was done. The area of inhibition of zone measured in cm. it was noted that compound **4e** was more against micro-organism. Other compounds show less or moderate effectiveness against micro-organism than tetracycline **Table 2**.

**Table 2.** Antibacterial Activity of Compounds (4a-e).

| Compounds | Gram +Ve | | Gram –Ve | |
|---|---|---|---|---|
| | *Bacillus subtilis* | *Staphylococcus aureus* | *Klebsiella promioe* | *E. coli* |
| **4a** | 55 | 50 | 65 | 59 |
| **4b** | 56 | 54 | 64 | 62 |
| **4c** | 55 | 50 | 59 | 64 |
| **4d** | 63 | 55 | 70 | 69 |
| **4e** | 64 | 57 | 71 | 68 |
| **Tetracycline** | 68 | 60 | 77 | 80 |

### Antifungal Activities

The fungicidal activity of all the above compounds had been studied at 1000 ppm conc. in vitro. *Nigrospora Sp, Aspergillus niger, Botrydepladia thiobromine, and Rhizopus nigricum, Fusarium oxyporium* were used for the study of antifungal activities. The antifungal activities of all above mentioned compounds **(4a-e)** had been measured on each of these plant pathogenic strains on a potato dextrose agar (PDA) medium. This type of PDA medium contained potato 200 g, dextrose 20 g, agar 20 g and water 1 cc. Five days old cultures were used. The compounds which were liked to be tested were suspended (1000 ppm) in a PDA medium. Then it was heated in autoclave at 125°C for 15-20 min. at 15 atm. pressure. These media were poured into sterile Petri plates and the microbes were introduced after cooling the Petri plates. Using the formula given below, the percentage inhibition for fungi was calculated after five days:

**Percentage of inhibition=100(X-Y)/X**

Where, X=Area of colony in control plate; Y=Area of colony in test plate.

The fungicidal activity of various compounds **(4a-e)** is shown in **Table 3**.

**Table 3.** Antifungal Activity of Compounds (4a-e).

| Zone of Inhibition at 1000 ppm (%) | | | |
|---|---|---|---|
| **Compounds** | ***Rhizopus nigricum*** | ***Nigrospora Sp.*** | ***Aspergillus niger*** |
| **4a** | 58 | 64 | 64 |
| **4b** | 57 | 65 | 62 |
| **4c** | 62 | 62 | 61 |
| **4d** | 66 | 72 | 67 |
| **4e** | 71 | 70 | 69 |

## RESULTS AND DISCUSSION

It was found that naphtho[2,1-b]furan-2-carbohydrazide **(2)** react with $CS_2$ to give the above said 5-(naphtho[2,1-b]furan-2-yl)$^{-1}$,3,4-oxadiazole-2(3H)-thione **(3)**. The structures of **(3)** were confirmed by elemental analysis and IR spectra showing an absorption band at 3225 (N-H), 1613$^{-1}$643 (C=N), 3030-3080 cm$^{-1}$ (C-H, of Ar.), 1168 (C=S), 775 (C-O-C ring). $^1$H NMR: 7.62-8.68 (m, 8H, Ar-H and NH).

The structures given to N-(1-((dialkylamino)methyl)-3-(naphtho[2,1-b]furan-2-yl)-5-thioxo$^{-1}$H$^{-1}$,2,4-triazol-4(5H)-yl)benzamide **(4a-e)** were proved by the elemental analysis and IR spectra giving an absorption bands at 3225 (N-H), 1612$^{-1}$ 642 (C=N), 3025-3080 cm$^{-1}$ (C-H of Ar.), 1765 cm$^{-1}$ (C=O) 1169 (C=S), 775 (C-O-C ring), 2950, 1370 cm$^{-1}$ (-$CH_3$). **$^1$H NMR:** 7.02-8.69 (m, 12H, Ar-H), 4.56 (s, 2H, $CH_2$), 4.08 (s, 1H, NH), 4a; 2.15 (s, 6H, $CH_3$), 4b; 2.27 (s, 3H, $CH_3$), 1.12 (t, 3H, $CH_3$), 2.66 (q, 2H, $CH_2$), 4c; 1.11 (t, 6H, $CH_3$), 2.67 (q, 4H, $CH_2$), 4d; 1.11 (t, 3H, $CH_3$), 2.66 (q, 2H, $CH_2$), 6.81-7.22 (m, 5H, Ar-H), 4e; 6.81-7.23 (m, 10H, Ar-H). The C, H, N, S analysis data of all compounds are given in **Table 1**.

e-ISSN:2319-9849
p-ISSN:2322-00

The study of elemental analytical data unveil that the elemental contents are consistence with the forecasted structure given in **Scheme 1**. The IR data also support. the forecasted structure. The Compound **4e** is more effective against bacteria and fungi.

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