ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Synthesis of Substituted Urea Derivatives Encompassing Naphtho[2,1-B]Furan and Evaluation of Their Antimicrobial Activity

Vaidya VP [1]*, Shruthi E[1], Yamuna AJ [1]

[1]Department of Chemistry, Kuvempu University, Shankaraghatta-577451, Shimoga District, Karnataka, India.

ABSTRACT

Ethyl 3-nitronaphtho[2,1-b]furan-2-carboxylate **1** has been synthesized and converted into 3-nitronaphtho[2,1-b]furan-2-carbohydrazide **2** by refluxing with hydrazine hydrate. The hydrazide **2** on diazotization with nitrous acid at 0^0C produced 3-nitronaphtho[2,1-b]furan-2-carbonylazide **3** which on subsequent reaction with ethanol underwent Curitus rearrangement to give ethyl 3-nitronaphtho[2,1-b]furan-2-carbamate **4**. The carbamate in turn, on condensation with hydrazine hydrate gave 3-nitronaphtho[2,1-b]furan-2-semicarbohydrazide **5**, which on reaction with different aromatic aldehydes produced corresponding 3-nitronaphtho[2,1-b]furan-2-semicarbazones **6(a-h)**. The newly synthesized compounds were characterized by analytical and spectral studies and evaluated for antimicrobial activity.

Keywords: Naphtho[2,1-b]furan, antimicrobial activity, Curitus rearrangement, urea derivatives, semicarbazones.

***Corresponding author**
Email: vaidyavijaya@hotmail.com

ISSN: 0975-8585

INTRODUCTION

The derivatives of naphtho[2,1-b]furan possess various biological and pharmacological activities, such as antimicrobial, anti-inflammatory, analgesic, antihelmintic and anticancer [1-6]. Carbamates and semicarbazones are of considerable interest due to their application towards biological and therapeutic activities such as antimicrobial, antineoplastic, anti-convulsant and anti-viral [7-14].

Encouraged by these findings and in continuation of our search for new biological active naphtho[2,1-b]furan derivatives [15-17], we report in this paper synthesis of carbamates and semicarbazones encompassing naphtho[2,1-b]furan moiety and evaluation of their antimicrobial activities.

MATERIALS AND METHODS

Melting points were recorded on open capillary tube method and are uncorrected. The progress of reaction and purity of the compounds were monitored by thin layer chromatography and spots were visualized by exposure to iodine vapours or under UV light and separation were carried out by column chromatography by using silica gel (60-120 mesh). IR spectra (in cm^{-1}) were recorded on Perkin-Elmer FT-IR Spectrophotometer using KBr optics. ^1H NMR spectra were recorded at 300 MHz on Bruker spectrometer and their chemical shift values are expressed in δ ppm with respect to TMS as an internal standard, the solvent used was $CDCl_3$ or DMSO. Mass spectra were recorded on 70ev EIMS. Elemental analyses were performed for C, H, O, N and were within ± 2% of theoretical values.

EXPIREMENTAL

Synthesis of ethyl 3-nitronaphtho[2,1-b]furan-2-carboxylate (1)

Ethyl naphtho[2,1-b]furan-2-carboxylate(3 g, 0.01 mol) in acetic acid (20 ml) was stirred at below 0^0C and nitrating mixture was added drop wise for 30 min [conc.H_2SO_4 (7.2 ml) and conc.HNO_3 (3.6 ml)] ,the stirring was continued for 2 hrs. The reaction mixture was poured into crushed ice, the product obtained as yellow solid was filtered and recrystallized using aqueous DMF.

IR spectra (in cm^{-1}) recorded in KBr on Perkin-Elmer FT-IR Spectrometer: 1715 (C=O), 1518 – 1355 (NO_2 str), 1282 (C-O-C str) and 2991- 3081 (C-H str aromatic). ^1H NMR (300MHz, $CDCl_3$): δ 1.5(3H, t, CH_3), δ 4.5(2H, q, CH_2) and δ 7.2-8.6(6H, m, Ar-H). EIMS, m/z: 285.9(M^+).

Synthesis of 3-nitronaphtho[2,1-b]furan-2-carbohydrazide (2)

Hydrazine hydrate (2.5 ml, 0.05 mol, 99%) was added to a solution of ethyl 3-nitronaphtho[2,1-b]furan-2-carboxylate (3 g, 0.01 mol) in ethanol (20 ml). The reaction mixture

was heated under reflux for 2 hrs and cooled to room temperature. The product that separated was collected and recrystallised using ethanol.

IR spectra (in cm^{-1}) recorded in KBr on Perkin-Elmer FT-IR Spectrometer: 1654.37 (C=O), 3337.35-3249.23 (NH_2 str), 3078.48 (N-H str), 1518.96 (NO_2 symmetric str), 1337.10(NO_2 asymmetric str) and 2923.74-2853.17(C-H str aromatic).^{1}H NMR(300MHz, $CDCl_3$): δ 4.7(2H, d, NH_2),δ 7.6-8.5(6H, m, Ar-H), and δ 10.3(1H, s, NH). EIMS, m/z: 272.1(M^+)**.**

Synthesis of 3-nitronaphtho[2,1-b]furan-2-carbonylazide (3)

The solution of sodium nitrite (0.2 g, 0.002 mol) in water (2 ml) was added drop wise with stirring at 0^0C to the mixture of 3-nitronaphtho[2,1-b]furan-2-carboxyhydrazide (0.28 g, 0.001 mol) in 1,4-dioxane (4 ml) and concentrated HCl (1 ml). The stirring was continued for 1 hr. The pale yellow solid separated was filtered washed with water and then with 1, 4-dioxane and dried under desiccator. It was used further without purification.

IR spectra (in cm^{-1}) recorded in KBr on Perkin-Elmer FT-IR Spectrometer: 1701.05(C=O), 1545.05 – 1358.78 (NO_2 str), 2199.92 (N_3 str) and 3125.09-2971.68(C-H str aromatic)

Synthesis of ethyl (3-nitronaphtho[2,1-b]furan-2-yl)carbamate (4)

A mixture of 3-nitronaphtho[2,1-b]furan-2-carboxyazide (0.3 g, 0.001 mol) and ethanol (10 ml) was heated under reflux for 3 hrs. The reaction mixture was cooled filtered to remove any insoluble substances present. After the evaporation of the solvent, the product obtained was washed with per-ether.

IR spectra (in cm^{-1}) recorded in KBr on Perkin-Elmer FT-IR Spectrometer: 1728.65 (C=O), 3445.90 - 3420.89 (N-H str free and associated),1531.52 - 1338.60 (NO_2 str), 3329.24 – 3088.85(C-H str aromatic) and 2966.53 – 2852.94(C-H str alkyl).^{1}H NMR(300MHz, $CDCl_3$): δ 1.3(3H, t, CH_3), δ 4.2(2H, q, CH_2), δ 7.2-8.6(6H, m, Ar-H) and δ 11.6(1H, s, NH). EIMS,m/z: 301.1(M^+).

Synthesis 3-nitronaphtho[2,1-b]furan-2-semicarbohydrazide(5)

Hydrazine hydrate (0.17 ml, 0.003 mol, 99%) was added to a solution of ethyl (3-nitronaphtho[2,1-b]furan-2-yl)carbamate (0.35 gm, 0.001 mol) in methanol (20 ml). The reaction mixture was heated under reflux for 2 hrs and cooled to room temperature. The product separated was collected used as it is for further reaction.

IR spectra (in cm^{-1}) recorded in KBr on Perkin-Elmer FT-IR Spectrometer: 1653.51(C=O), 3336.19-3238.18(NH_2 str),3086.55(N-H str), 1509.19–1320.79(NO_2 str) and 2924.65 (C-H str aromatic).^{1}H NMR (300MHz, $CDCl_3$): δ 4.7(2H, s, NH_2, D_2O exchangeable),δ 7.7-8.7(6H, m, Ar-H) and δ 10.3(1H, s, NH, D_2O exchangeable).

ISSN: 0975-8585

Synthesis of 3-nitronaphtho[2,1-b]furan-2- semicarbazones (6a-h)

Benzaldehyde (0.23 ml, 0.002 mol) was added to a solution of 3-nitronaphtho[2,1-b]furan-2-semicarbohydrazide (0.3 gm, 0.001 mol) in DMF (6 ml). The reaction mixture was refluxed for 5 hrs and quenched to crushed ice. The product **6a** that separated as solid was filtered and dried. Similarly remaining semicarbazones **6a-h** were synthesized by using appropriate aromatic aldehydes

Spectral data of benzaldehyde-N-3-nitronaphtho[2,1-b]furan-2-semicarbazones (6a)

IR spectra (in cm^{-1}) recorded in KBr on Perkin-Elmer FT-IR Spectrometer: 1673 (C=O), 3291-3421 (N-H str), 1611 (N-H bend), 1516 –1301 (NO_2 str) and 2921 (C-H str alkyl). ^{1}H NMR (300MHz, DMSO): δ 7.4-8.7 (11H, m, Ar-H),δ 8.4 (1H, s, CH), and δ 12.4 (1H, s, NH, D_2O exchangeable).

Spectral data of 4-methoxybenzaldehyde-N-3-nitronaphtho[2,1-b]furan-2-semicarbazones (6b)

IR spectra (in cm^{-1}) recorded in KBr on Perkin-Elmer FT-IR Spectrometer: 1652 (C=O), 3427 (N-H str), 1601 (N-H bend), 1513 –1313 (NO_2 str) and 2923 (C-H str alkyl).^{1}HNMR (300MHz, DMSO): δ 3.8 (3H,t, CH_3),δ 7.0-8.7 (10H, m, Ar-H), δ 8.4 (1H,s,CH) and δ 12.3 (1H, s, NH, D_2O exchangeable).

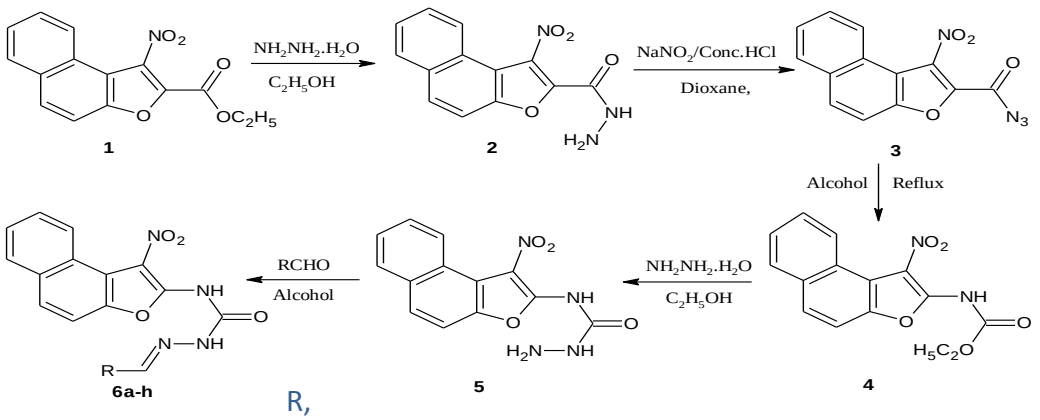
Spectral data of furan-2- carbaldehyde-N-3-nitronaphtho[2,1-b]furan-3-semicarbazones (6c)

IR spectra (in cm^{-1}) recorded in KBr on Perkin-Elmer FT-IR Spectrometer: 1613 (C=O), 3521 (N-H str), 1570 (N-H bend), 1511 –1329 (NO_2 str), 1280 (C-O-C str) and 2923 (C-H str alkyl).

^{1}H NMR (300MHz, DMSO): δ 3.8(3H,t, CH_3),δ 7.0-8.7 (10H, m, Ar-H), δ 8.4 (1H,s,CH) and δ 12.3 (1H, s, NH, D_2O exchangeable).

The sequence of reactions is shown in the scheme

ISSN: 0975-8585



a. $-C_6H_5$
b. $4-OCH_3-C_6H_4$
c. $-C_4H_3O$
d. $-CH=CH-C_6H_5$
e. $3-NO_2-C_6H_4$
f. $4-Cl-C_6H_4$
g. $2-OH-C_6H_4$
h. $2-Cl-C_6H_4$

The characterization of Physical and analytical data of the newly synthesized compounds is given in Table 1.

Table 1 –Physical and analytical data of synthesized compounds

Compound	Molecular formula	Molecular weight	Melting point (0^0C)	Yield %	Elemental analysis Found (Calculated %)			
					C	**H**	**O**	**N**
1	$C_{15}H_{11}NO_5$	285.25	93-95	76	63.15 (63.18)	3.87 (3.88)	28.00 (28.02)	4.90 (4.91)
2	$C_{13}H_9N_3O_4$	271.22	217-220	85	57.56 (57.57)	3.30 (3.34)	23.57 (23.58)	15.45 (15.49)
3	$C_{13}H_6N_4O_4$	282.21	110-112	90	55.31 (55.32)	2.12 (2.13)	22.69 (22.68)	19.85 (19.85)
4	$C_{15}H_{12}N_2O_5$	300.26	209-211	83	60.00 (60.02)	4.02 (4.02)	26.64 (26.64)	9.31 (9.32)
5	$C_{13}H_{10}N_4O_4$	286.24	220-223	63	54.55 (54.56)	3.51 (3.52)	22.33 (22.35)	19.57 (19.57)
6a	$C_{20}H_{14}N_4O_4$	374.35	224-225	82	64.15 (64.16)	3.75 (3.77)	17.09 (17.08)	14.96 (14.97)
6b	$C_{21}H_{16}N_4O_5$	404.37	221-222	80	62.36 (62.37)	3.97 (3.99)	19.78 (19.78)	13.85 (13.86)
6c	$C_{18}H_{12}N_4O_5$	364.31	196-200	79	59.33 (59.34)	3.30 (3.32)	21.95 (21.96)	15.37 (15.38)
6d	$C_{22}H_{16}N_4O_4$	400.38	228-230	70	65.98 (66.00)	4.01 (4.02)	15.97 (15.98)	13.99 (14.00)
6e	$C_{20}H_{13}N_5O_6$	419.34	235-237	72	57.25 (57.28)	3.10 (3.12)	22.88 (22.89)	16.70 (16.71)
6f	$C_{20}H_{13}N_4O_4Cl$	408.79	180-184	78	58.72 (58.76)	3.23 (3.21)	15.65 (15.66)	13.69 (13.71)
6g	$C_{20}H_{14}N_4O_5$	390.34	285-288	69	61.51 (61.54)	3.61 (3.62)	20.48 (20.49)	14.33 (14.35)
6h	$C_{20}H_{13}N_4O_4Cl$	408.79	236-240	68	58.69 (58.70)	3.17 (3.18)	15.71 (15.69)	13.67 (13.69)

Antimicrobial activity

ISSN: 0975-8585

In vitro antibacterial activity was determined by agar well diffusion method against 24 hrs old culture of pathogenic bacteria such as *Staphylococcus aureus* ATCC 11632 (Gram +ve), *Escherichia coli* ATCC 10536, *Xanthomonas campestris* and *Pseudomonas aeruginosa* ATCC 10145 **(**Gram –ve) using Ampicillin as standard a standard drug. The standard and test compounds were prepared in DMSO at different concentrations. The zone of inhibition was compared with standard drug after 24 hrs incubation at 37^0C. The results of antibacterial activity are presented in Table 2.

Similarly antifungal activity was performed against *Aspergillus niger, Aspergillus flavus* (moulds) using Fuconazole as standard. The standard and test compounds were prepared in DMSO at different concentrations. The zone of inhibition was compared with standard drug after 48 hrs at 25^0C. The results of antifungal activity are presented in Table .

Table 2 - Antibacterial activity of the synthesized compounds.

Compound	Zone of inhibition in mm											
	S. aureus			*E. coli*			*P. aeruginosa*			*X. campestris*		
	5mg	1.25 mg	0.625 mg	5mg	1.25 mg	0.625 mg	5mg	1.25 mg	0.625 mg	5mg	1.25 mg	0.625 mg
Standard	14	13	12	24	21	19	15	14	11	24	20	17
Control	0	0	0	0	0	0	0	0	0	0	0	0
4	8	9	11	15	10	9	15	11	10	14	13	11
5	6	5	5	11	8	9	12	8	7	7	3	2
6a	7	10	12	14	10	8	11	7	6	12	6	5
6b	8	11	5	7	5	3	4	3	3	6	4	3
6c	11	7	7	8	4	3	9	10	4	4	5	5
6d	12	14	6	11	11	7	8	6	4	14	11	11
6e	9	6	11	10	8	7	8	5	4	11	11	5
6f	11	11	10	12	8	7	5	5	3	7	6	5
6g	-	2	6	-	-	-	4	4	3	5	4	3
6h	5	5	6	10	8	7	4	4	3	11	11	5

Staphylococcus aureus , Escherichia coli, Xanthomonas campestris, Pseudomonas aeruginosa
Standard: Ampicillin

Table 3 - Antifungal activity of the synthesized compounds.

	Zone of inhibition in mm

ISSN: 0975-8585

	A.niger			*A.flavus*		
	5mg	1.25mg	0.625mg	5mg	1.25mg	0.625mg
Standard	20	18	16	15	14	13
Control	0	0	0	0	0	0
4	20	10	14	13	7	6
5	13	10	9	13	9	7
6a	15	13	10	10	10	8
6b	13	11	10	13	11	8
6c	11	10	7	10	7	6
6d	11	10	14	7	6	6
6e	14	9	8	7	6	6
6f	7	6	6	12	11	9
6g	5	4	5	8	6	6
6h	15	12	12	6	11	10

Aspergillus niger, Aspergillus flavus

Standard: Fuconazole

RESULTS AND DISCUSSION

The required starting material ethyl 3-nitronaphtho[2,1-b]furan-2-carboxylate 1 was synthesized according to the procedure reported in the literature [18] and it was confirmed by ^{1}H NMR spectrum in which multiplet at δ 7.2-8.6 due to aromatic protons, quartet at δ 4.5 due to CH_2 and triplet at δ 1.5 due to CH_3. Ethyl 3-nitronaphtho[2,1-b]furan-2-carboxylate 1 was converted into 3-nitronaphtho[2,1-b]furan-2-carbohydrazide 2 by refluxing with hydrazine hydrate(99%). The hydrazide 2 on diazotization with nitrous acid at 0^0C produced 3-nitronaphtho[2,1-b]furan-2-carbonylazide 3 which on subsequent reaction with ethanol underwent Curitus rearrangement to give ethyl 3-nitronaphtho[2,1-b]furan-2-carbamate 4. The IR spectrum of 4 exhibited ester C=O absorption peak at 1728.65, N-Hstr. at 3445.90-3420.89(free and associated) and NO_2 at 1531.52. ^{1}HNMR spectra showed characteristic peaks at δ 1.3 triplet for CH_3, δ 4.2 quartet for CH_2, δ 11.6 singlet for NH and δ 7.2-8.6 for aromatic protons. The mass spectrum showed m/z: 301.1(M^+) as an supporting data for the structure. The carbamate 4 in turn, on condensation with hydrazine hydrate gave 3-nitronaphtho[2,1-b]furan-2-semicarbohydrazide 5, which on reaction with different aromatic aldehydes produced corresponding 3-nitronaphtho[2,1-b]furan-2-semicarbazones 6a-h . The compound 6a was confirmed by ^{1}H NMR spectral studies shows the characteristic signals at δ 7.4-8.7 due to aromatic eleven protons, δ 8.4 due to CH proton and δ 12.4 due to NH proton on D_2O exchange missing of NH proton was absorbed .

In vitro antibacterial activity of selected compounds was carried out by agar well diffusion method against 24 hrs old culture of *Staphylococcus aureus, Escherichia coli, Xanthomonas campestris* and *Pseudomonas aeruginosa.* The compounds 4, 5, 6a, 6b, 6c, and 6f showed significant activity against all the bacteria. Enhanced activity was observed as in case of 6d by increasing in conjugation. Antifungal activity was performed on *Aspergillus niger* and *Aspergillus flavus*. The compounds 4, 5, 6a, 6b, 6c, 6d, 6f and 6h showed moderate activity

against both the fungus. The compounds 4 and 6d were more active among screened compounds.

CONCLUSION

In conclusion, the reaction profile explained in the present work is very efficient to synthesize semicarbazones. The prepared compounds showed potent antimicrobial activities and these are promising compounds for further pharmacological studies.

ACKNOWLEDGEMENT

The authors are thankful to the Principal, S J M College of Pharmacy, Chitradurga for providing spectral analysis and Chairman Department of Chemistry, Kuvempu University for providing laboratory facilities and we extend our thanks to Chairman Department of Biochemistry and Microbiology, Kuvempu University for assisting in carrying out antimicrobial activity.

REFERENCES

[1] Vanita GK, Ramaiah M, Shashikaladevi K, Veena K and Vaidya VP. J Chem Pharm Res 2010; 2(6): 258-264.
[2] Chaitanya MS, Nagendrappa G and Vaidya VP. J Chem Pharm Res 2010; 2(3): 206-213.
[3] Pandeya SN, Raja AS and Nath G. Indian J Chem 2006; 45B: 494-499.
[4] Vagdevi HM and Vaidya V P. I J Heterocyclic Chem 2001; 10:253-260.
[5] Srivastava V, Negi AS, Kumar JK, Faridi U, Sisodia BS, Darokar MP, Luqman S and Khanuja SP. Bio Org Med Chem Lett 2006; 16(4): 911-4.
[6] Salmon RJ, Buisson JP, Aussepe L, Royer R. Carcinogenesis 1985; 6: 109-11.
[7] Krishna Verma, Pandeya SN, Singh UK, Gupta S, Prashant P, Anurag, Gautam Bhardwaj. Int J Pharm Sci Nanotech 2009; 1(4): 357-362.
[8] Vijaya Laxmi S and Rajitha B. Med Chem Res 2010; DOI 10.1007/s00044-010-9502-3.
[9] Pandeya SN, Raja AS and James P Stables. J Pharm Sci 2002; 5(3): 266-271.
[10] Nardi D, Massarani E, Tajana A, Degen L, Magistretti MJ. J Med Chem 1967; 10: 530-533.
[11] Aggarwal Navneet and Mishra Pradeep. J Zhejiang University Science 2005; 6B (7): 617-621.
[12] Dimmock JR, Puthcode RN, Jennifer M Smith, Mark I Ietherington, Quail JW, Uma Pugazhenthi, Terry Lechler and James P Stables. J Med Chem 1996; 39: 3984-3997.
[13] Kasuga NC, Sekino K, Ishikawa M, Honda A, Yokoyama M, Nakano S, Shimada N, Koumo C, Nomiya K. J Inorganic Biochem 2003; 1: 96(2-3): 298-310.
[14] Jairo Paz, Carlos Perez-Balado, Beatriz Lglesias and Luis Munoz. Org Letters 2011; 13(7): 1800-1803.
[15] Shashikaladevi K, Ramaiah M, Roopa DL and Vaidya VP. E-J Chem 2010; 7(S1)
[16] Shashikaladevi K, Ramaiah M,. Vanita GK, Veena K and Vaidya VP. J Chem Pharm Res 2011; 3(1):445-451.

ISSN: 0975-8585

[17] Nagashree AS, Lohith Kumar PJ, Kusuma K and Vaidya VP. Res J Pharm Bio Chem Sci 2011; 2(2): 855.
[18] Rajashekhara H, Ramesh D, Chandrashekhar C, Mahadevan KM and Vaidya VP. I J Hetero Chem 2007; 16, 153.