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Der Pharma Chemica, 2015, 7(8):25-29
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Synthesis and biological evaluation of some new heterocyclic derivatives incorporating napthofuran moiety

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ABSTRACT

Naphtho[2,1-b]furan-2-carbohydrazide (1) undergoes facile condensation with aromatic aldehydes to afford the corresponding N-arylidenenaphtho[2,1-b]furan-2-carbohydrazide(3a-h) in good yields. Cyclocondensation of compounds (3a-h) with thioglycolic acid yields N-(4-oxo-2-arylthiazolidin-3-yl) naphtho[2,1-b]furan-2-carboxamide (4a-h). The structures of these compounds were established on the basis of analytical and spectral data. All the newly synthesized compounds were evaluated for their antibacterial and antifungal activities.

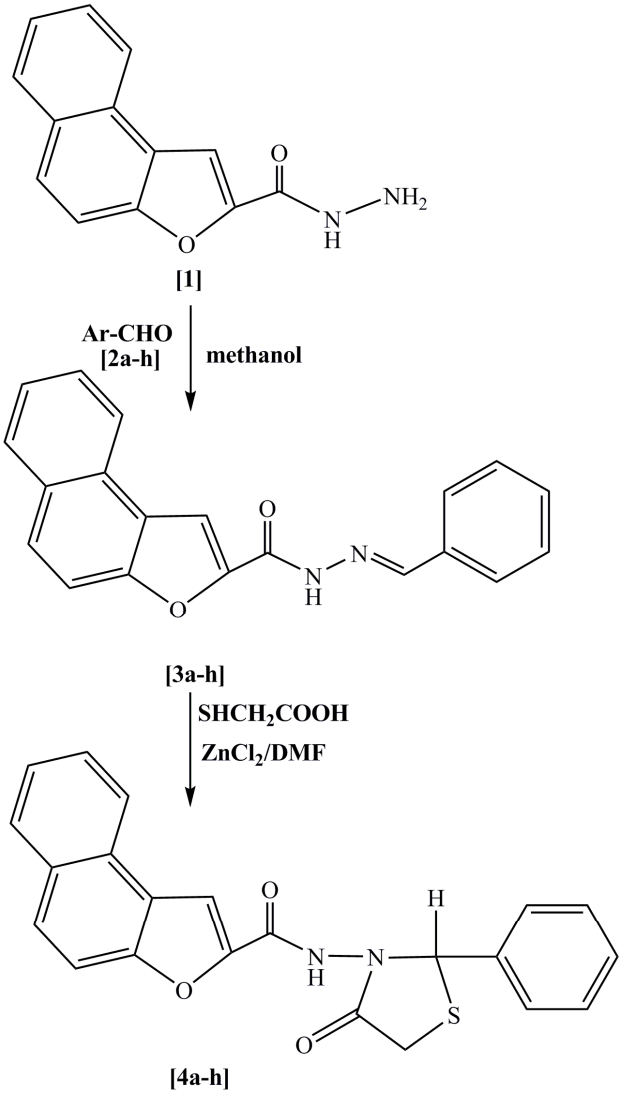
Key words: Naphtho[2,1-b]furan-2-carbohydrazide, Thiazolidine, Arylidine compounds, Antibacterial activity, Antifungal activity.

INTRODUCTION

Nitrogen containing biheterocyclic compounds, such as Thiazolidinones, are known to possess a wide range of activities biological as well as good pharmacological properties [1-3]. 4-thiazolidinones are exhibit antitubercular [4], antibacterial [5], antifungal [6], anticancer [7], anti-inflammatory [8], and anticonvulsant activities [9]. Naphthofuran derivatives have been isolated from various natural sources like Fusariumoxysporum, Gossypiumbarbadense, etc. [10,11]. Naphthofuran are well known for various biological activities like antitumor, antifertility, mutagenic, growth inhibitory and estrogenic [12-14]. Many of the condensed heterocycles and biheterocycles enclosing naphthofuran have been reported processes wide spectrum of activities [15,16].

Hydrazide and their heterocyclised products display diverse biological activities including antibacterial, antifungicidal, analgesic, anti-inflammatory properties [17-21]. These heterocyclic systems find wide use in medicine, agriculture and industry. One of the hydrazides, 2-hydroxy benzoic acid hydrazide (i.e. salicylhydrazide) and their condensed products play a vital role in medicinal chemistry [22].

Hence, it was thought of interest to merge both of thiazolidinone and hydrazide moieties which may enhance the drug activity of compounds to some extent, or they might possess some of the above mentioned biological activities. From this point of view, the objective of the present work is to prepare new derivatives of naphthofuran containing thiazolidinone moiety. Hence the present communication comprises the synthesis of N-(4-oxo-2-arylthiazolidin-3-yl)naphtho[2,1-b]furan-2-carboxamide. The synthetic approach is shown in **Scheme-1**.



Where Ar= (a) C_6H_5 (b) 2-CH_3-C_6H_4
(c) 4-CH_3-C_6H_4 (d) 2-OH-C_6H_4
(e) 4-OH-C_6H_4 (f) 2-OCH_3-C_6H_4
(g) 4-OCH_3-C_6H_4 (h) 2-ClC_6H_4

Scheme-1

MATERIALS AND METHODS

Melting points were determined in open capillary tubes and were uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer and ^{1}H NMR spectra were recorded in DMSO with TMS as internal standard on a Bruker spectrometer at 400 MHz. LC-MS of selected samples taken on LC-MSD-Trap-SL-01046.

All the chemicals were laboratory grade and purchased from local market. naphtho[2,1-b]furan-2-carbohydrazide was prepared by reported method [23].

Preparation of N-arylidene-naphtho[2,1-b]furan-2-carbohydrazide (3a-h)

General procedure: – A mixture of naphtho[2,1-b]furan-2-carbohydrazide (1) (0.2mole) and various aromatic aldehydes (2a-h) (0.2mole) in ethanol (20ml) was refluxed on a water bath for 3.5 hrs. The solid separated was

collected by filtration, dried and recrystallized from aqueous DMF. The yields, melting points and other characterization data of these compounds are given in **Table -1**.

Preparation N-(4-oxo-2-arylthiazolidin-3-yl)naphtho[2,1-b]furan-2-carboxamide (4a-h)

General procedure: The reaction mixture N-arylidene-naphtho[2,1-b]furan-2-carbohydrazide (3a-h) in THF (25ml) and thioglycolic acid with a pinch of anhydrous $ZnCl_2$ was refluxed for 11-12 hrs. The solvent was then removed to get a residue, which was dissolved in benzene and passed through a column of silica gel using ethyl acetate: hexane mixture as eluent. The eluate was concentrated and the product crystallized from alcohol to give N-(4-oxo-2-arylthiazolidin-3-yl)naphtho[2,1-b]furan-2-carboxamide(4a-h), which were obtained in 67-72% yield. The yields, melting points and other characterization data of these compounds are given in **Table -2**.

Table: 1 Analytical Data and Elemental Analysis of Compounds (3a-h)

Compd.	Molecular formula (Mol.wt.)	LC-MS Data	Yield	M.P.* ^{0}C	Elemental Analysis					
					%C		% H		%N	
					Found	Calcd.	Found	Calcd.	Found	Calcd.
3a	$C_{20}H_{14}N_2O_2$ (314)	315	66	178-180	76.40	76.42	4.47	4.49	8.89	8.91
3b	$C_{21}H_{16}N_2O_2$ (328)	324	64	175-176	76.79	76.81	4.90	4.91	8.51	8.53
3c	$C_{21}H_{16}N_2O_2$ (328)	327	63	181-183	76.80	76.81	4.88	4.91	8.51	8.53
3d	$C_{20}H_{14}N_2O_3$ (330)	333	65	176-178	72.69	72.72	4.25	4.27	8.46	8.48
3e	$C_{20}H_{14}N_2O_3$ (330)	336	67	182-184	72.71	72.72	4.26	4.27	8.47	8.48
3f	$C_{21}H_{16}N_2O_3$ (344)	341	65	167-168	73.22	73.24	4.66	4.68	8.10	8.13
3g	$C_{21}H_{16}N_2O_3$ (344)	348	63	173-174	73.22	73.24	4.67	4.68	8.12	8.13
3h	$C_{20}H_{13}N_2O_2Cl$ (348.5)	353	63	180-182	68.86	68.87	3.74	3.76	8.01	8.03

** Uncorrected*

Table: 2 Analytical Data and Elemental Analysis of Compounds (4a-h)

Compd.	Molecular formula (Mol.wt.)	LC-MS Data	Yield	M.P.* ^{0}C	Elemental Analysis							
					%C		%H		%N		%S	
					Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
4a	$C_{22}H_{16}N_2O_3S$ (388)	390	69	232-234	68.00	68.02	4.13	4.15	7.19	7.21	8.23	8.25
4b	$C_{23}H_{18}N_2O_3S$ (402)	400	66	216-217	68.61	68.64	4.50	4.51	6.95	6.96	7.96	7.97
4c	$C_{23}H_{18}N_2O_3S$ (402)	403	64	208-210	68.62	68.64	4.49	4.51	6.94	6.96	7.96	7.97
4d	$C_{22}H_{16}N_2O_4S$ (404)	408	66	218-219	65.32	65.33	3.97	3.99	6.92	6.93	7.92	7.93
4e	$C_{22}H_{16}N_2O_4S$ (404)	405	60	213-215	65.31	65.33	3.98	3.99	6.91	6.93	7.91	7.93
4f	$C_{23}H_{18}N_2O_4S$ (418)	415	63	209-211	66.00	66.01	4.32	4.34	6.67	6.69	7.64	7.66
4g	$C_{23}H_{18}N_2O_4S$ (418)	416	64	203-205	65.99	66.01	4.33	4.34	6.68	6.69	7.65	7.66
4h	$C_{22}H_{15}N_2O_3SCl$ (422)	425	62	217-219	62.46	62.48	3.57	3.58	6.60	6.62	7.57	7.58

****** Uncorrected*

BIOLOGICAL SCREENING

Antibacterial activities

The antibacterial activities of all the compounds were studied against gram-positive bacteria and gram-negative bacteria at a concentration of 50µg/ML by agar cup plate method. A methanol system was used as control in this method. Similar conditions using tetracycline as a control was used standard for comparison. The area of inhibition of zone measured in mm. Compounds 4h and 4g were found more toxic for microbes. Other compounds found to be less or moderate active than tetracycline **Table -3**.

Table: 3 Antibacterial Activities of Compounds (4a-h)

Compounds	Gram +Ve		Gram -Ve	
	Staphylococcus aureus	*Bacillus subtilis*	*E.coli*	*Klebsiellapromioe*
4a	40	50	61	70
4b	46	54	60	69
4c	44	58	65	72
4d	43	56	63	74
4e	40	55	68	71
4f	45	60	65	74
4g	49	65	69	76
4h	51	69	71	80
Tetracycline	57	76	74	84

Antifungal Activities

The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro. Plant pathogenic organisms used were*Botrydepladiathiobromine*, *NigrosporaSp*, *Aspergillusniger and Rhizopusnigricum*. The antifungal activities of all the compounds (4a-h) were measured on each of these plant pathogenic strains on a potato dextrose agar (PDA) medium. Such a PDA medium contained potato 200g, dextrose 20g, agar 20g and water 1c. Five days old cultures were employed. The compounds to be tested were suspended (1000ppm) in a PDA medium and autoclaved at 120^{o} C for 15 min. at 15atm. pressure. These media were poured into sterile Petri plates and the organisms were inoculated after cooling the Petri plates. The percentage inhibition for fungi was calculated after five days using the formula given below:

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 displayed by various compounds (4a-h) is shown in **Table-4**.

Table: 4 Antifungal Activities of Compounds (4a-h)

Zone of Inhibition at 1000 ppm (%)				
Compounds	***Nigrospora Sp.***	***Aspergillus niger***	***Botrydepladia thiobromine***	***Rhizopus nigricum***
4a	70	65	64	55
4b	64	60	62	58
4c	70	65	64	61
4d	63	57	63	63
4e	71	66	65	64
4f	66	62	63	60
4g	73	66	68	61
4h	72	68	66	68

RESULTS AND DISCUSSION

It was observed that naphtho[2,1-b]furan-2-carbohydrazide (1), on condensation with aromatic aldehydes, yields N-arylidene-naphtho[2,1-b]furan-2-carbohydrazide (3a-h). The structures of (3a-h) were confirmed by elemental analysis and IR spectra showing an absorption band at 3435 cm^{-1} (N-H), 1240 cm^{-1} (C-O), 3030-3080cm^{-1} (C-H of Ar.), 1690cm^{-1}(CONH), 2815-2850cm^{-1}(-OCH_3), 2950,1370cm^{-1}(-CH_3). **^{1}H NMR:** 7.53 –8.56(12H,m,Ar-H), 11.6-11.9(1H,s,CONH), 8.4-8.6(1H,s,N=CH), 3b; 2.28(3H,s,CH_3), 3c; 2.32(3H,s,CH_3), 3d; 5.10(1H,s,-OH), 3e; 5.23(1H,s,-OH), 3f; 3.84(3H,s,-OCH_3), 3g; 3.85(3H,s,-OCH_3). The C, H, N analysis data of all compounds are presented in **Table -1**.

The structures assigned to N-(4-oxo-2-arylthiazolidin-3-yl)naphtho[2,1-b]furan-2-carboxamide (4a-h) were supported by the elemental analysis and IR spectra showing an absorption bands at1690cm^{-1} (C=O of thiazolidinone ring), 718cm^{-1} (C-S-C of thiazolidinone ring), 3075-3095cm^{-1} (CH_2 of thiazolidinone ring), 3030-3080 cm^{-1} (C-H, of Ar.), 1725,1675 cm^{-1} (-CO,CONH), 3410-3425(N-H), 1240-1250 (C-O), 3030-3080 cm^{-1} (C-H of Ar.), 2815-2850 cm^{-1} (-OCH_3), 2950,1370 cm^{-1} (-CH_3) for (4a-h) compound.

[1]H NMR: 3.82-3.98 (2H, s,-CH_2 of the ring), 5.86-5.89 (1H, s,-CH), 7.32 –8.62 (12H, m,Ar - H), 11.2-11.4 (1H, s,-CONH), 4b; 2.27 (3H,s,-CH_3), 4c; 2.32(3H,s,CH_3), 4d; 5.13(1H,s,-OH), 4e; 5.22(1H,s,-OH), 4f; 3.84(3H,s,-OCH_3), 4g; 3.86(3H,s,-OCH_3).The C, H, N, S analysis data of all compounds are presented in **Table-2**.

CONCLUSION

The examination of elemental analytical data reveals that the elemental contents are consistence with the predicted structure shown in **Scheme-1**. The IR data also direct for assignment of the predicted structure. The final structure of all compounds is confirmed by LC-MS. LC-MS data of all compounds are presented in **Tables-1, 2**. The antibacterial activity data suggest that all the compound shown good to moderate activity compare to standard tetracycline, while primary evaluation of all compounds shows good to moderate activity against employed strains.

REFERENCES

[1]. K. M. Iqbal, A.Y. Khan, M. B. Kalashetti, N. S. Belavagi, Y. D. Gong, I. A. M.Khazi, *Eur. J. Med. Chem.*, **2012**, 53, 308.
[2]. D. Pareek, M. Chaudhary, P. K. Pareek, R. Kant, K. G. Ojha, A. Pareek, *Der ChemicaSinica.*, **2010**, 1, 22.
[3]. D. Pareek, M. Chaudhary, P. K. Pareek, R. Kant, K. G. Ojha, A. Pareek, *Der Pharmacia Sinica.*, **2011**, 2, 170.
[4]. D. Havrylyuk, N. Kovach, B. Zimenkovsky, O. Vasylenko, R. Lesyk, *Arch. Pharm.*, **2011**,344, 514.
[5]. H. S. Patel, H. J. Mistry, *Phosphorous, Sulfur and Silicon.*, **2004**, 179, 1085.
[6]. T. Singh, D. S. Khobragade, *Unique J. Pharm. Bio. Sci.*, **2014**, 2, 13.
[7]. G. Cihan-Ustundag, D. Şatana, G. Ozhan, G. Çapan, *J. Enzyme Inhib. Med. Chem.*, **2015**, 1-12.
[8]. M. F. Mahdi, A. M. R. Raauf, F. A.H. Kadhim, J. Nat. Sci. Res., **2015**, 5, 21.
[9]. B. Nusrat, Ruhi Ali, N. Siddiqui, A. Habib, Bull. Pharm. Res., **2014**, 4, 21.
[10]. K. S. V. Murthy, B. Rajitha, M. K. Rao, T. R. Komuraiah, S. M. Reddy, *Heterocycl. Commun.*,**2002**, 8, 179.
[11]. R. D. Stipanovic, A. A. Bell, C. R. Howell, *Phytochem.*,**1975**, 14,1809.
[12]. H. Hagiwara, K. Sato, T. Suzuki, M. Ando, *Heterocycles*, **1999**, 51,497.
[13]. S. S. Maigali, M. El-Hussieny, F. M. Soliman, J. Heterocyclic Chem., **2015**, 52, 15.
[14].C. H. Chandrashekhar, K. P. Latha, H. M. Vagdevi, V. P. Vaidya,*Der Pharma Chemica.*, **2011**, 3, 365.
[15]. H. M. Vagdevi, V. P. Vaidya, *Ind. J. Heterocyclic Chem.*, **2001**, 10,193.
[16]. V. P. Vaidya, H. M. Vagdevi, K. M. Mahadevan, C. S. Shreedhara, *Ind. J. Chem.*, **2004**, 43B,1537.
[17]. E. Gursoy, N. Guzeldemirci-Ulusoy, *Eur. J. Med. Chem.*,**2007**, 42, 320.
[18]. P. J. Shah, H. S. Patel, B. P. Patel, *J. Saudi Chem. Soc.*, **2013**, 17, 307.
[19]. R. Kalsi, M. Shrimali, T. N. Bhalla, J. P. Barthwal, *Ind. J. Pharm. Sci.***2006**, 41, 353.
[20]. R. Y. Morjan, A. M. Mkadmh, I. Beadham, A. A. Elmanama, M. R. Mattar, J. Raftery, R. G. Pritchard, A. M. Awadallah, J. M. Gardiner, Bioorg. Med. Chem. Lett., **2014**, 24, 5796.
[21]. P. J. Shah, H. S. Patel, B. P. Patel, *Bulgarian Chem. Comm.*, **2010**, 42, 474.
[22]. L. Q. Al- Mawsawi, R. Dayam, L. Taheri, M. Witvrouw, Z. Debyser, N. Neamati, *Bioorg. Med. Chem. Lett.*,**2007**, 17, 6472.
[23]. K. C. Ravindra, H. M. Vagdevi, V. P. Vaidya, B. Padmashi, *Ind. J. Chem.*, **2006**, 45B, 2506.