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SYNTHESIS AND BIOLOGICAL STUDIES OF NOVEL THIAZOLIDINONES

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ABSTRACT
3-hydroxybenzofuran-2-carbohydrazide (2) undergoes facile condensation with aromatic aldehydes to afford the corresponding N-arylidene-3-hydroxybenzofuran-2-carbohydrazide (3a-d) in good yields. Cyclocondensation of compounds (3a-d) with thioglycolic acid yields 3-hydroxy-N-(4-oxo-2-arylthiazolidin-3-yl)-benzofuran-2-carboxamide (4a-d). 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.
Keywords: 3-hydroxybenzofuran-2-carbohydrazide, thiazolidine, antibacterial activity.

INTRODUCTION

Hydrazide and their heterocyclised products display diverse biological activities including antibacterial, antifungicidal, analgesic, anti-inflammatory properties.[1-15] 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.[16-18] 4-Thiazolidinones and its arylidene compounds give good pharmacological properties.[19-23] 4-thiazolidinones are also known to exhibit antitubercular[24], antibacterial[25], antifungal[26] and anticonvulsant activities. 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 benzofuran-acetohydrazide containing thiazolidinone moiety. Benzofuran is one of the most important heterocyclic compounds, which are widely distributed in nature amongst the plant kingdom. These compounds are containing biological as well as pharmacological activities.[27-30] Hence the present communication comprises the synthesis of 3-hydroxy-N-(4-oxo-2-arylthiazolidin-3-yl)-benzofuran-2-carboxamide. The synthetic approach is shown in scheme-1.

EXPERIMENTAL

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 and ^{13}C NMR spectra were recorded in DMSO with TMS as internal standard on a Bruker spectrometer at 400 MHz and 100 MHz, respectively. LC-MS of selected samples taken on LC-MSD-Trap-SL_01046.

Materials

All the chemicals were laboratory grade and purchased from local market. 3-hydroxybenzofuran-2-carbohydrazide was prepared by reported metod.[31]

Preparation of N-arylidene-3-hydroxybenzofuran-2-carbohydrazide (3a-d)

General procedure

A mixture of 3-hydroxybenzofuran-2-carbohydrazide (2) (0.2mole) and the aromatic aldehydes (a-d) (0.2mole) in ethanol (15ml) was refluxed on a water bath for 1-2 hrs. The solid separated was

collected by filtration, dried and recrystallized from Ethanol: H_2O (1:1). The yields, melting points and other characterization data of these compounds are given in Table -1.

Preparation 3-hydroxy-N-(4-oxo-2-arylthiazolidin-3-yl)-benzofuran-2-carboxamide (4a-d)

General procedure

An equimolar mixture N-arylidene-3-hydroxybenzofuran-2-carbohydrazide (3a-d) in THF (30ml) and thioglycolic acid with a pinch of anhydrous $ZnCl_2$ was refluxed for 8 hrs. The solvent was then removed to get a residue, which was dissolved in benzene and passed through a column of silica gel using p-xylene: chloroform (6:4) mixture as eluent. The eluate was concentrated and the product crystallized from alcohol to give 3-hydroxy-N-(4-oxo-2-arylthiazolidin-3-yl)-benzofuran-2-carboxamide (4a-d), which were obtained in 62-65% yield. The yields, melting points and other characterization data of these compounds are given in Table -2.

Biological Screening

Antibacterial activities

The antibacterial activities of all the compounds were studied against gram-positive bacteria (*Staphylococcus aureus and Bacillus subtilis*) and gram-negative bacteria (*E.coli, and klebsiella promioe*) 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 5c and 5d were found more toxic for microbes. Other compounds found to be less or moderate active than tetracycline Tables -3.

Antifungal Activities

The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro. Plant pathogenic organisms used were *Nigrospora Sp, Aspergillus niger, Botrydepladia thiobromine, and Rhizopus nigricum***,** *Fusarium oxyporium*. The antifungal activities of all the compounds (5a-d) 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 15 atm. 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:

$$\text{Percentage of inhibition} = 100(X-Y) / X$$

Where, X = Area of colony in control plate

Y = Area of colony in test plate

The fungicidal activity displayed by various compounds (5a-d) is shown in Tables-4.

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

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	$C_{16}H_{12}N_2O_3$ (280)	296	80	208-211	68.5	68.56	4.3	4.32	9.9	9.99
3b	$C_{17}H_{14}N_2O_3$ (294)	309	78	212-214	69.3	69.38	4.7	4.79	9.5	9.52
3c	$C_{16}H_{12}N_2O_4$ (296)	432	75	211-213	64.8	64.86	4.0	4.08	9.4	9.46
3d	$C_{17}H_{14}N_2O_4$ (310)	328	76	216-218	65.7	65.80	4.5	4.55	9.0	9.03

*Uncorrected

RESULTS AND DISCUSSION

It was observed that 3-hydroxybenzofuran-2-carbohydrazide (2), on condensation with aromatic aldehydes, yields N-arylidene-3-hydroxybenzofuran-2-carbohydrazide (3a-d). The structures of (3a-d) were confirmed by elemental analysis and IR spectra showing an absorption band at 3385(-OH), 1240-

1260 (C-O-C), 3030-3080 cm^{-1} (C-H, of Ar.), 1720-1750 cm^{-1} (-CO), 2815-2850 cm^{-1} (-OCH_3), 2950, 1370 cm^{-1} (-CH_3). ^{1}H NMR: 7.34 –7.94 (4H, m) (Ar - H), 5.38 (1H,s) (-OH), 11.8-11.9 (1H, s) (-CONH), 8.43-8.8 (1H, s) (-N=CH), 4b; 3.9 (3H, s) (-OCH_3). ^{13}C NMR:111.9-156.8 (Ar-8C), 163.5-163.8 (-CONH), 146.9-150.4 (-CH); (4b): 55.5-56.7(-OCH_3). The C, H, N analysis data of all compounds are presented in Table -1.

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

Compd.	Molecular formula (Mol.wt.)	LC-MS Data	Yield	M.P.* ^{0}C	Elemental Analysis							
					%C		%H		%N		%S	
4a	$C_{18}H_{14}N_2O_4S$ (354)	368	69	217-219	60.9	61.01	3.9	3.98	7.8	7.90	9.0	9.05
4b	$C_{19}H_{16}N_2O_4S$ (368)	381	66	215-217	61.9	61.94	4.3	4.38	7.5	7.60	8.6	8.70
4c	$C_{18}H_{14}N_2O_5S$ (370)	386	62	222-225	58.3	58.37	3.7	3.81	7.5	7.56	8.6	8.66
4d	$C_{19}H_{16}N_2O_5S$ (384)	402	65	214-216	59.3	59.37	4.1	4.20	7.2	7.29	8.3	8.34

* Uncorrected

Table- 3: Antibacterial Activities of Compounds (5a-d)

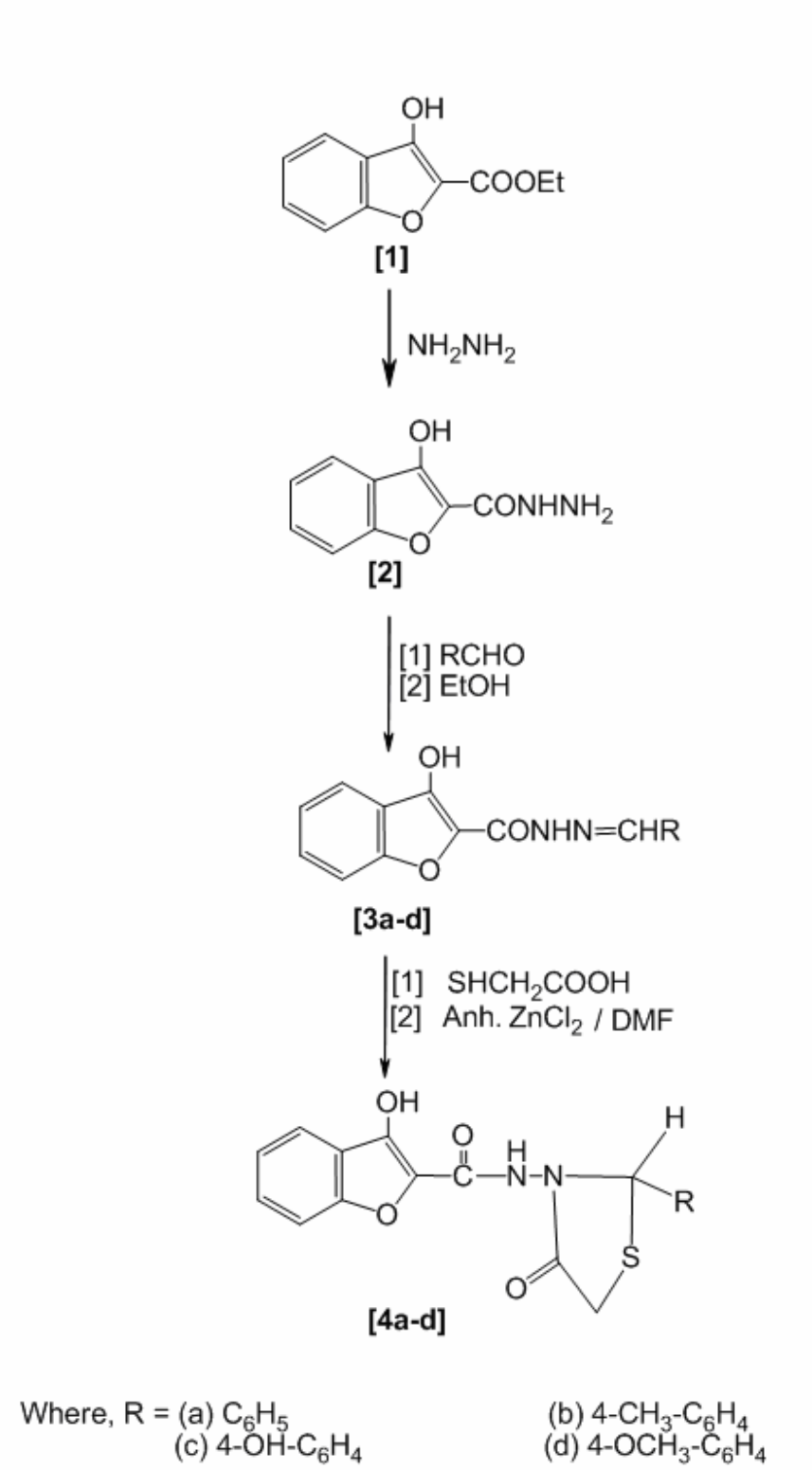
Compounds	Gram +Ve		Gram -Ve	
	Staphylococcus aureus	Bacillus subtilis	E.coli	Klebsiella promioe
5a	53	54	62	49
5b	58	56	55	57
5c	64	59	58	66
5d	69	68	79	48
Tetracycline	57	76	74	84

Table-4: Antifungal Activities of Compounds (5a-d)

Zone of Inhibition at 1000 ppm (%)					
Compounds	Nigrospora Sp.	Aspergillus Niger	Botrydepladia Thiobromine	Rhizopus Nigricum	Fusarium oxyporium
5a	69	69	65	57	71
5b	62	53	63	66	65
5c	73	69	75	63	78
5d	68	67	68	74	62

The structures assigned to 3-hydroxy-N-(4-oxo-2-arylthiazolidin-3-yl)-benzofuran-2-carboxamide (4a-d) were supported by the elemental analysis and IR spectra showing an absorption bands at 1690cm^{-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.), 3450-3550 cm^{-1} (-OH), 1660-1670 cm^{-1} (-CONH) for (5a) compound.

^{1}H NMR: 3.85-3.95 (2H, s) (-CH_2 of the ring), 5.950-5.959 (1H, s) (-CH), 7.34-7.94 (4H, m) (Ar-H), 5.38 (1H, s) (-OH), 8.20-8.22 (1H, s) (-CONH), 11.200-11.209 (1H, s) (-OH), 5b; 3.91 (3H, s) (-OCH_3). ^{13}C NMR:112-157.2 (Ar-8C), 38.9-39.5 (–CH_2 of the ring), 67.8-68.3 (–CH), 164.8-165.9 (-CONH), 168.9-169.9 (-CO of the ring), (5b): 56.0-56.4 (-OCH_3). The C, H, N, S analysis data of all compounds are presented in Table-2.



Scheme-1

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 and 2.

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REFERENCES

1. M. R. Shiradkar, K. K. Murahari, H. R. Gangadasu, T. Suresh, C. C. Kalyan, D. Panchal, R. Kaur, P. Burange, J.Ghogare, V.Mokale, M.Raut, *Bioorg.Med. Chem.,* **15**, 3997(2007).
2. Y. Janin, *Bioorg. Med. Chem.,* **15**, 2479(2007).
3. E. Gursoy, N. Guzeldemirci-Ulusoy, *Eur. J. Med. Chem.*,**42**,320(2007).
4. M. R. Rao, K. Hart, N. Devanna and K. B. Chandrasekhar, *Asian J. Chem.*,**20**, 1402(2008).
5. K. B. Kaymakcıoglu, E. E. Oruc, S. Unsalan, F. Kandemirli, N. Shvets, S. Rollas, D. Anatholy, *Eur. J. Med. Chem.,* **41**, 1253(2006).
6. R. Kalsi, M. Shrimali, T. N. Bhalla, J. P. Barthwal, *Indian J. Pharm. Sci.*,**41**, 353 (2006).
7. S. Gemma, G. Kukreja, C. Fattorusso, M. Persico, M. Romano, M. Altarelli,L. Savini, G. Campiani, E. Fattorusso, N. Basilico, *Bioorg. Med. Chem. Lett.*,**16**, 5384 (2006).
8. D. Sriram, P. Yogeeswari, K. Madhu, *Bioorg. Med. Chem. Lett.*,**15**, 4502(2006).
9. A. Nayyar, R. Jain, *Curr. Med. Chem.*, 12, 1873(2006).
10. R. M. Fikry, N. A. Ismael, A. A. El-Bahnasawy, A. A. Sayed El-Ahl., *Phosphorus Sulfur and Silicon*,**179**,1227(2006).
11. A. Walcourt, M. Loyevsky, D. B. Lovejoy, V. R. Gordeuk, D. R. Richardson, *Int. J. Biochem. Cell Biol.*,**36**,401(2004).
12. M. G. Mamolo, V. Falagiani, D. Zampieri, L. Vio, E. Banfi , G. Scialino,*Farmaco,*,***58,*** 631(2003).
13. N. Terzioglu, A. Gursoy, *Eur. J. Med. Chem.*, **38**,781(2003).
14. S. G. Kucukguzel, E. E. Oruc, S. Rollas, F. Sahin, A. Ozbek, *Eur. J. Med. Chem.***,37**,197(2002).
15. S. Rollas, N. Gulerman, H. Erdeniz, *Farmaco*,**57**,171(2002).
16. Al- Mawsawi LQ, R. Dayam, L. Taheri, M. Witvrouw, Z. Debyser, N. Neamati, *Bioorg. Med. Chem. Lett.*,**17(23),**6472(2002).
17. C. Plasencia, R. Daym, Q. Wang, J. Pinski, T. R. Jr. Burke, D. I. Quinn, and N. Neamati, *Mol. Cancer Ther.*, **4(7)**,1105(2005).
18. H. Zhao, N. Neamati, S. Sunder, H. Hong, S. wang; G. W. Milne, Y. Pommier,T. R. Jr. Burke, *J. Med. Chem.*,**40(6)**, 937(1997).
19. K.C. Asati, S K srivastava and S. D. Srivastava,*Ind.J.Chem.*,**45(B)**,526(2006).
20. A. Bishnoi, K Srivastava and C. K. M. Tripathi, *Ind.J.Chem.*,**45(B)**,2136(2006).
21. N. P. Shetgiri and A. D. Chitre, *Ind .J .Chem.*, **45(B)**,1308(2006).
22. R. Jadav, S. Srivastava and S. D. Srivastava, *Chemistry, An Indian Journal*,**1**,95 (2006).
23. S. Srivastava, A. Jain, and S. Srivastava, *J. Indian Chem. Soc.*,**83**,1118(2006).
24. K. M. Mistry and K. R. Desai, *E- Journal of Chem.*, **1(4)**, 189(2004).
25. H. S. Patel, H. J. Mistry, *Phosphorous, Sulfur and Silicon*, **179**, 1085(2004).
26. J. J. Bhatt, B. R. Shah and N. C. Desai, *Ind .J. Chem.*, **33B, 189**(1994).
27. M. Koca, S. Servi, C. Kirilmis, M. Ahmedzade, C. Kazaz, *Eur. J. Med. Chem.*, **40**,1351(2005).
28. S. Alper-Hayta, M. Arisoy, O. Temiz-Arpaci, I .Yildiz, E. Aki , *Eur. J. Med.Chem.*,**xx**,1(2008).
29. C. Kirilmis, M. Ahmedzade, S. Servi, M. Koca, A. Kizirgil, *Eur. J. Med. Chem.*, **43**,300(2008).
30. B.F.A. Wahab, H.A.A. Aziz, E.M. Ahmed, *Eur. J. Med. Chem*., **XXX**,1(2008)
31. V.P. Vaidya and Y.S. Agasimundin, *Indian J Chem*., **22(B)**, 432(1983).

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