EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 3
Issue: 8
314-318
Year: 2016

SYNTHESIS AND STUDY OF NEW PYRROLE DERIVATIVES CONTAINING BENZOFURAN MOIETY AND THEIR ANTIMICROBIAL ACTIVITY

Nidhi Patel[1*], Arun Singh[2] and D.K. Gupta[3]

[1]Department of Chemistry, Govt. MVM, Bhopal, India.
[2]Department of Chemistry, Govt. college, Jeerapur, India.
[3]Department of Chemistry, Govt. Institute for excellence in higher education, Bhopal, India

Corresponding Author: Nidhi Patel
Department of Chemistry, Govt. MVM, Bhopal, India.

Article Received on 02/06/2016 **Article Revised on 23/06/2016** **Article Accepted on 14/07/2016**

ABSTRACT
3-hydroxybenzofuran-2-carbohydrazide undergoes facile condensation with aromatic aldehydes to afford the corresponding N-arylidene-3-hydroxybenzofuran-2-carbohydrazide (3a-e) in good yields. On heterocyclization reactions of compounds (3a-e) with maleic anhydride gave the desired products 1-(3-hydroxybenzofuran-2-carboxyamido)-5-oxo-2-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylic acid (6a-e). The structures of these compounds were established on the basis of analytical and spectral data. All the newly synthesized compounds were evaluated for there antibacterial and antifungal activities.

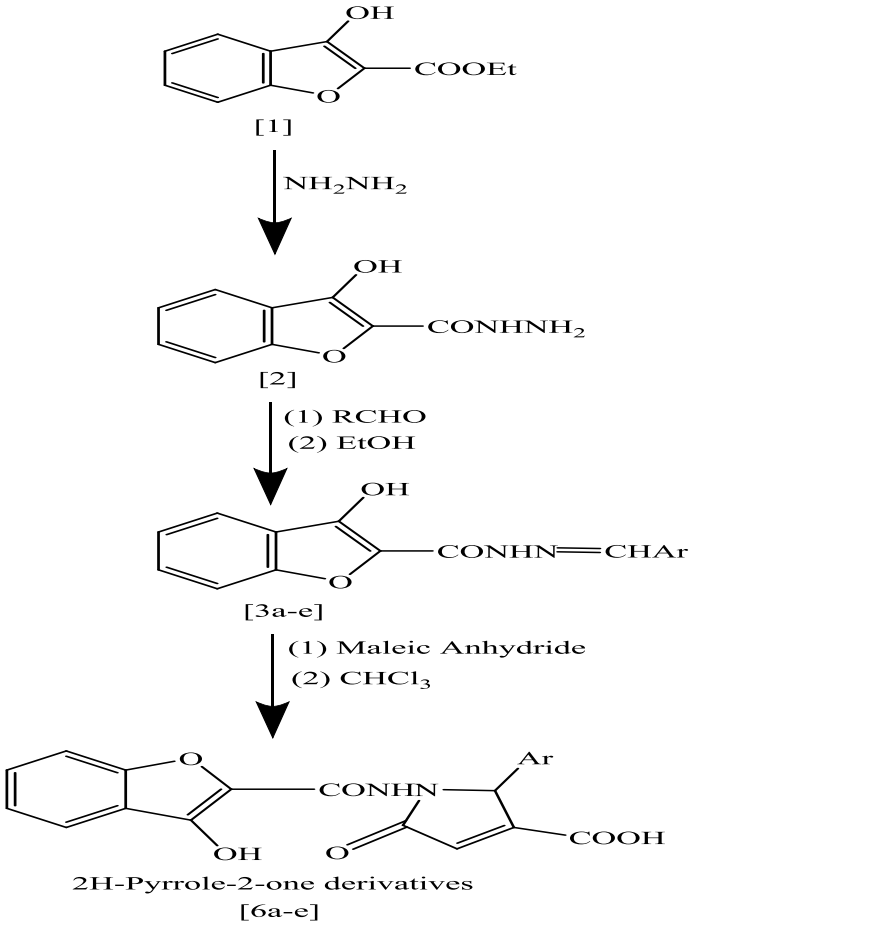
KEYWORDS: antibacterial activity; antifungal activity; 3-hydroxybenzofuran-2-carbohydrazide; pyrrole.

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. 2H-Pyrrole can be used as pesticides[16] and herbicides.[16,20,22[. They are also known to exhibit antiviral[17], antibacterial[18], anticancer[19], antidiabetic, anti-inflammatory and antitumor[21] activities and can also used as memory enhancing drug.[23] Hence, it was thought of interest to merge both of pyrrole and hydrazide of benzofuran 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 2H-Pyrrole-2-ones, containing benzofuran 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.[24-27] Hence the present communication comprises the synthesis of 1-(3-hydroxybenzofuran-2-carboxyamido)-5-oxo-2-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylic acid. 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 ate taken on LC-MSD-Trap-SL_01046.

MATERIALS
All the chemicals were laboratory grade and are purchased from local-market, 3-hydroxybenzofuran-2-cabohydrazide was prepared by reported method.[28]

Synthesis of *N-arylidene-3hydroxy benzofuran-2-carbohydrazide (3a-e)*
General Procedure
A mixture of 3-hydroxybenzofuran-2-carbohydrazide (0.2mole) and the aromatic aldehydes (2a-e) in ethanol (15ml) was refluxed on a water bath for 1-2 hrs. The solid separated was collected by filteration, 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.



Scheme 1

Synthesis of *1-(3-hydroxybenzofuran-2-carboxyamido)-5-oxo-2-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylic acid (6a-e)*

General procedure

The equimolar mixture of Maleic anhydride (0.1mole) and an imine (3a-e) (0.1mole) were heated at reflux in chloroform (30ml) for about 5 hours with TLC monitoring. After the mixture was allowed to stand for 2 days, the solid was filtered. The product thus formed was re-crystallized from ethanol to give pure 1-(3-hydroxybenzofuran-2-carboxyamido]-5-oxo-2-phenyl-2,5-dihydro-*1H*-pyrrole-3-carboxylic acid (6a-e) in good 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-e)

Compd	Molecular formula (Mol.wt.)	Yield %	M.P.* ^{0}C	Elemental Analysis					
				%C		% H		%N	
				Found	Calcd	Found	Calcd	Found	Calcd
3a	$C_{16}H_{12}N_2O_4$ (296)	75	211-213	64.8	64.86	4.0	4.08	9.4	9.46
3b	$C_{17}H_{14}N_2O_4$ (310)	76	216-218	65.7	65.80	4.5	4.55	9.0	9.03
3c	$C_{17}H_{14}N_2O_3$ (294)	78	212-214	69.3	69.38	4.7	4.79	9.5	9.52
3d	$C_{17}H_{14}N_2O_5$ (326)	70	217-221	62.5	62.57	4.3	4.32	8.4	8.59
3e	$C_{20}H_{20}N_2O_5$ (368)	71	220-222	65.1	65.21	5.3	5.47	7.5	7.60

** Uncorrected*

Table: 2 Analytical Data and Elemental Analysis of Compounds (6a-e)

Compd	Molecular formula (Mol.wt.)	Yield %	M.P.* ^{0}C	Elemental Analysis					
				%C		%H		%N	
				Found	Calcd	Found	Calcd	Found	Calcd
6a	$C_{20}H_{14}N_2O_7$ (394)	72	256-258	60.9	60.92	3.5	3.58	7.0	7.10
6b	$C_{20}H_{14}N_2O_7$ (394)	70	256-257	60.9	60.92	3.5	3.58	7.0	7.10
6c	$C_{21}H_{16}N_2O_6$ (392)	74	251-253	64.2	64.28	4.1	4.11	7.1	7.14
6d	$C_{21}H_{16}N_2O_8$ (424)	66	244-245	59.4	59.44	3.8	3.80	6.5	6.50
6e	$C_{24}H_{22}N_2O_8$ (466)	62	243-246	61.7	61.80	4.7	4.75	5.9	6.01

** Uncorrected*

RESULTS AND DISCUSSION

It was observed that 3-hydroxybenzofuran-2-carbohydrazide, on condensation with aromatic aldehydes, yields N-arylidene-3-hydroxybenzofuran-2-carbohydrazide (3a-e). The structures of (3a-e) were confirmed by elemental analysis and IR spectra showing an absorption band at 3361(-OH), 1090 cm^{-1} (C-O-C), 3030-3080 cm^{-1} (C-H, of Ar.), 1655 cm^{-1} (-CO), 3450 cm^{-1} (sec.amide); 3c: 2950, 1370 cm^{-1} (-CH_3); 3d: 2950, 1370 cm^{-1} (-CH_3). ^{1}H NMR: 7.34 –7.94 (4H, m) (Ar - H), 10.43 (1H,s) (-OH), 11.8-11.9 (1H, s) (-CONH), 8.43-8.8 (1H, s) (-N=CH); 3c: 2.5 (3H,s) (-CH_3); 3d: 3.36 (3H,s) (-OCH_3); 3e: 4.0 (4H,q) (2CH_2), 1.33 (6H,t) (2CH_3). ^{13}C NMR: 136-152 (benzofuran), 152 (–CHN), 163.5-163.8 (-CONH), 146.9-150.4 (-CH); 3c: 21 (-CH_3); 3d: 55.5-56.7 (-OCH_3); 3e: 65 (-CH_2). The C, H, N analysis data of all compounds are presented in Table -1.

The structures assigned to 1-(3-hydroxybenzofuran-2-carboxyamido)-5-oxo-2-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylic acid (6a-e) were supported by the elemental analysis and IR spectra showing an absorption bands at 1717 cm^{-1} (C=O of Pyrrole-2-one), 750 cm^{-1} (C-O-C of Pyrrole-2-one), 3054 cm^{-1}, 1600 cm^{-1} and 1532 cm^{-1} (C-H, of Ar.), 3390 cm^{-1} (-OH), 1667 cm^{-1} (C=O of -COOH), 1660-1670 cm^{-1} (-CONH) for (6a) compound.

^{1}H NMR: 10.67 (1H, s) (-OH), 4.7 (1H, s) (-C_5H), 5.15 (1H, s) (-C_3H), 12.92 (1H, s) (-COOH); 6c: 2.3 (3H,s) (-CH_3); 6d: 3.8 (3H,s) (-OCH_3); 6e: 2.1 (6H, t) (2CH_3), 2.9 (4H, q, 2CH_3).

^{13}C NMR: 110-131 (Benzene), 133-150 (Benzofuran), 158 (C of -COOH), 167 (C of -CO), 60 (-CH); 6c: 21 (-CH_3); 6d: 52 (-OCH_3); 6e: 38 (-CH_2). The C, H, N, S analysis data of all compounds are presented in Table-2.

The examination of elemental analytical data of compounds 3a-e and 6a-e, 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.

BIOLOGICAL SCREENING

To evaluate the biological potential of these compounds, laboratory experiments have been conducted. The following techniques have been used for antimicrobial activities of these compounds.

Antibacterial activities

The antibacterial activities of 6a-e 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 and a methanol system was used as control in this method. At similar conditions, tetracycline standard was used as a control for comparison. The area of inhibition of zone measured in mm.

Table: 3 Antibacterial Activities of Compounds (6a-e)

Compounds	*Gram +Ve*		*Gram –Ve*	
	Staphylococcus aureus	*Bacillus subtillis*	*E.coli*	*Klebsiella promioe*
6a	64	59	58	66
6b	69	68	79	48
6c	68	66	69	69
6d	79	75	77	72
6e	78	76	75	70
Tetracyline	76	57	74	84

Antifungal Activities

The antifungal activity of 6a-e 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*. Their antifungal activities 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 1cc. Five days old cultures were employed. The compounds to be tested were suspended (1000 ppm) 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:

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 (6a-e) is shown in Tables-4.

Table: 4 Antifungal Activities of Compounds (6a-e)

Zone of Inhibition at 1000 ppm (%)					
Compounds	**Nigrospora Sp.**	**Aspergillus Niger**	**Botrydepladia Thiobromine**	**Rhizopus Nigricum**	**Fusarium oxyporium**
6a	78	72	65	64	60
6b	77	70	68	62	65
6c	75	73	60	60	67
6d	64	72	60	56	64
6e	67	78	68	66	54

The examination of antimicrobial activity of various pyrrole compounds reveals that compounds 6d and 6e were found to be more toxic for microbes. Other compounds found to be less or moderate active than tetracycline (Table-3). Whereas compounds 6a, 6b and 6c were found to be more active against antifungal activity (Table-4) and the other compounds are moderately more or less active against various organisms.

ACKNOWLEDGEMENT

The authors greatfully thanks to the Principal of Govt.MVM, Bhopal and Head of the Department of Chemistry, for providing laboratory facilities.

REFERENCES

1. Shiradkar, M. R.; Murahari, K. K.; Gangadasu, H. R.; Suresh, T.; Kalyan, C. C.; Panchal, D.; Kaur, R.; Burange, P.; Ghogare, J.; Mokale, V.; Raut, M., Bioorg. Med. Chem., 2007; 15: 3997.
2. Janin, Y.; Bioorg. Med. Chem., 2007; 15: 2479.
3. Gursoy, E.; Guzeldemirci-Ulusoy, N., Eur. J. Med. Chem., 2007; 42: 320.
4. Rao, M. R.; Hart, K.; Devanna, N.; and Chandrasekhar, K. B., Asian J. Chem., 2008; 20: 1402.
5. Kaymakcıoglu, K. B.; Oruc, E. E.; Unsalan, S.; Kandemirli, F.; Shvets, N.; Rollas, S.; Anatholy, D., Eur. J. Med. Chem., 2006; 41: 1253.
6. Kalsi, R.; Shrimali, M.; Bhalla, T. N.; Barthwal, J. P., Indian J. Pharm. Sci., 2006; 41: 353.
7. Gemma, S.; Kukreja, G.; Fattorusso, C.; Persico, M.; Romano, M.; Altarelli, M.; Savini, L.; Campiani, G.; Fattorusso, E.; Basilico, N., Bioorg. Med. Chem. Lett., 2006; 16: 5384.
8. Sriram, D.; Yogeeswari, P.; Madhu, K., Bioorg. Med. Chem. Lett., 2006; 15: 4502.
9. Nayyar, A.; Jain, R., Curr. Med. Chem., 2006; 12: 1873.
10. Fikry, R. M.; Ismael, N. A.; El-Bahnasawy, A. A.; Sayed El-Ahl, A. A., Phosphorus Sulfur and Silicon, 2006; 179: 1227.
11. Walcourt, A.; Loyevsky, M.; Lovejoy, D. B.; Gordeuk, V. R.; Richardson, D. R., Int.J. Biochem. Cell Biol., 2004; 36: 401.
12. Mamolo, M. G.; Falagiani, V.; Zampieri, D.; Vio, L.; Banfi, E.; Scialino G., Farmaco, 2003; 58: 631.
13. Terzioglu, N.; Gursoy, A., Eur. J. Med. Chem., 2003; 38: 781.
14. Kucukguzel, S. G.; Oruc, E. E.; Rollas, S.; Sahin, F.; Ozbek, A., Eur. J. Med. Chem., 2002, vol. 37, pp. 197.
15. Rollas, S.; Gulerman, N.; Erdeniz, H., Farmaco, 2002; 57: 171.
16. Folker, L., Hermann, H., Pat., Dec 6, 1995; 19,545,467, C.A., 126, 74741j, 1997.
17. Gein, V.L.; Shumilovskikh, E.V.; Andreichikov, Y.S.; Saraeva, R.F.; Korobchenko, L.V.; Vladyko, V.G.; Boreko, E.I., Khim-Farm. Zn., 1991; 25: 37.
18. El-Kousy, S.M.; El-Torgoman, A.M.; El-Basiouny, A.A.; Hashem, A.J.; Pharmazie, 1988; 43: 80.
19. Nagashima, N.; Irinoda, K.; Motsuda, H.; Katori, T., Jap. Pat. 01, 143, 853 06 June (1989); C.A., 111, 232567d (1990).
20. Kummer, R.; Fischer, R., U.Vegt, Ger. Pat. DE 3,630,613 17, March; C.A., 1988; 109: 73344u (1989).
21. Antony, M.; Gupta, K.P.; Janardann, K.K.; Mehrotra, N.K., Cancer Lett., 1991; 61: 21.
22. Moriyashu, K.; Suzuki, H.; Suzzuki, M.; Matso, S.; Aoki, H.; Mihashi, T.; Fukai, S., Jap. Pat. 97,124,596 13, May 1997; C.A., 1997; 127: 50536r.

23. Toja, E.; Gorini, C.; Berzaghi, F.; Galliando, G., Eur. Pat. EP-300, 850 25 january 1989); C.A., 1990; 111: 7219x).
24. Koca, M.; Servi, S.; Kirilmis, C.; Ahmedzade, M.; Kazaz, C., Eur. J. Med. Chem., 2005; 40: 135.
25. Alper-Hayta, S.; Arisoy, M., Temiz-Arpaci, O.; Yildiz, I., Aki, E., Eur. J. Med. Chem., 2008; 1.
26. Kirilmis, C.; Ahmedzade, M.; Servi, S.; Koca, M.; Kizirgil, A., Eur. J. Med. Chem., 2008; 43: 300.
27. Wahab, BFA; Aziz, HAA; Ahmed, EM., Eur. J. Med. Chem., 2008; 1.
28. Vaidya, V.P. and agasimundin, Y.S., Indian J Chem., 1983; 22(B): 432.