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# SYNTHESIS, SPECTRAL AND ANTIMICROBIAL STUDIES OF NEW 2-PYRROLIDINONES CONTAINING BENZOFURAN MOIETY

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**ABSTRACT**

3-hydroxybenzofuran-2-carbohydrazide undergoes facile condensation with aromatic aldehydes to afford the corresponding N-arylidene-3-hydroxybenzofuran-2-carbohydrazide (3a-f) in good yields. On heterocyclization reactions of compounds (3a-f) with succinic anhydride gave the desired products 1-(3-hydroxybenzofuran-2-carboxamido)-5-oxo-2-phenylpyrrolidine-3-carboxylic acid (4a-f). 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:** 3-hydroxybenzofuran-2-carbohydrazide, 2-pyrrolidinone, antimicrobial activity.



## INTRODUCTION

Hydrazide and their heterocyclised products show different biological activities like antibacterial, antifungicidal, analgesic, anti-inflammatory properties[1-15]. These heterocyclic compounds are widely used for medicine to cure various diseases, in agriculture as pesticides and herbicides and in industry. 2-Pyrrolidinone can be used as antiarrhythmic and antihypertensive[16], antiamnestic[17], as metabotropic glutamate receptor antagonists[18], Xa inhibitor[19], in diseases related to connective tissue degradation[20], transdermal and dermal enhancing activity[21], anticonvulsant[22] and can also used as antipsychotic and anti ischemic activity[23]. Hence, it was thought of interest to merge both of pyrrolidinone 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 2-Pyrrolidinones, 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-carboxamido)-5-oxo-2-phenylpyrrolidine-3-carboxylic acid (4a-f). 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 sample was 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-f)**

A mixture of 3-hydroxybenzofuran-2-carbohydrazide (0.2mole) and the aromatic aldehydes (a-f) 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.

**Synthesis of 1-(3-hydroxybenzofuran-2-carboxamido)-5-oxo-2-phenyl pyrrolidine-3-carboxylic acid (4a-f)**

The equimolar mixture of Succinic anhydride (0.1mole) and Schiff bases of benzofuran (3a-f) (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-carboxamido)-5-oxo-2-phenylpyrrolidine-3-carboxylic acid (4a-f) good yield. The yields, melting points and other characterization data of these compounds are given in Table -2.

**Biological Screening**

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

**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.

**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 (7a-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 (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:

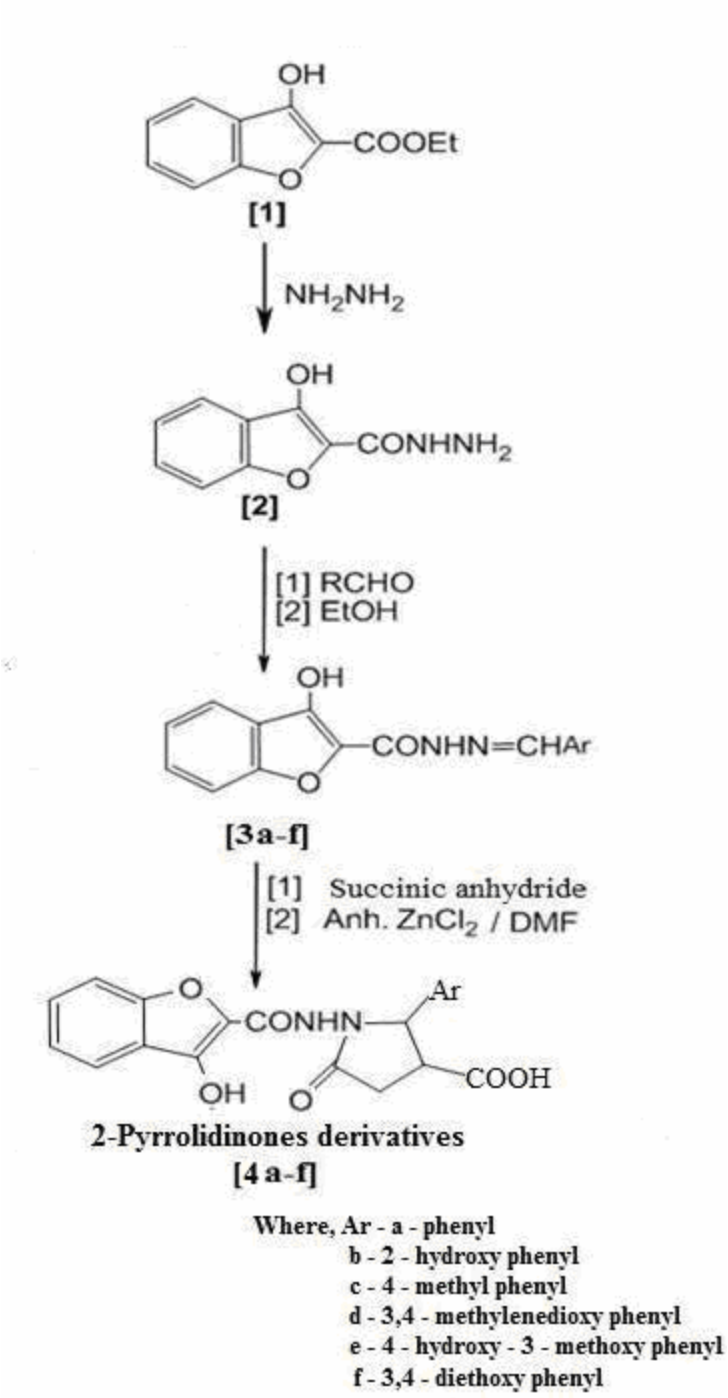
**Percentage of inhibition = 100(X-Y) / X**

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

The fungicidal activity displayed by various compounds (7a-f) is shown in Tables-4.

## RESULTS AND DISCUSSION

It was observed that 3-hydroxybenzofuran-2-carbohydrazide, on condensation with aromatic aldehydes, yields N-arylidene-3-hydroxybenzofuran-2-carbohydrazide (3a-f). The LC-MS of selected compound (3f) was 367. The structures of (3a-f) 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). $^{13}C$ NMR:111.9-156.8 (Ar-8C), 163.5-163.8 (-CONH), 146.9-150.4 (-CH). The C, H, N analysis data of all compounds are presented in Table-1.




Scheme-1

The structures assigned to 1-(3-hydroxybenzofuran-2-carboxamido)-5-oxo-2-phenylpyrrolidine-3-carboxylic acid (4a-f), were supported by the elemental analysis and IR spectra. The LC-MS of selected compound (4d) was 424.4 and the IR spectra shows an absorption bands at 1717 $cm^{-1}$ (C=O of Pyrrole-2-one), 748 $cm^{-1}$ (C-O-C linkage), 3055 $cm^{-1}$, 1600 $cm^{-1}$ and 1532 $cm^{-1}$ (C-H, of Ar.), 3380 $cm^{-1}$ (-OH), 1670 $cm^{-1}$ (C=O of -COOH) for (4a) compound. $^1$H NMR: 6.3-8.1 (9H, multiplet aromatic + NH of $–CONH_2$), 10.60 (1H, s) (-OH), 4.7, (H, s, $-C_5H$), 5.15 (H, s, $-C_3H$), 12.9 (H, s, -COOH).

$^{13}$C NMR: 110-131 (Benzene), 133-150 (Benzofuran), 159 (C of -COOH), 167 (C of -CO), 35(-$CH_2$), 52 (-CH), 4c; 24 (-$CH_3$). The C, H, N, S analysis data of all compounds are presented in Table-2.
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.

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

| Compd | Molecular formula (Mol.wt.) | Yield % | M.P.* $^0$C | Elemental Analysis | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | %C | | % H | | %N | |
| | | | | Found | Calcd. | Found | Calcd. | Found | Calcd. |
| 3a | $C_{16}H_{12}N_2O_3$ (280) | 80 | 208-211 | 68.5 | 68.56 | 4.3 | 4.32 | 9.9 | 9.99 |
| 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 | $C_{17}H_{12}N_2O_5$ (324) | 68 | 212-215 | 62.8 | 62.96 | 3.6 | 3.73 | 8.5 | 8.64 |
| 3e | $C_{17}H_{14}N_2O_5$ (326) | 70 | 217-221 | 62.4 | 62.57 | 4.3 | 4.32 | 8.4 | 8.59 |
| 3f | $C_{20}H_{20}N_2O_5$ (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 (4a-f)

| Compd | Molecular formula (Mol.wt.) | Yield % | M.P.* $^0$C | Elemental Analysis | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | %C | | %H | | %N | |
| | | | | Found | Calcd. | Found | Calcd. | Found | Calcd. |
| 4a | $C_{20}H_{16}N_2O_6$ (380) | 68 | 240-242 | 63.1 | 63.16 | 4.2 | 4.24 | 7.2 | 7.37 |
| 4b | $C_{20}H_{16}N_2O_7$ (396) | 66 | 230-234 | 60.5 | 60.61 | 4.0 | 4.07 | 6.9 | 7.07 |
| 4c | $C_{21}H_{18}N_2O_6$ (394) | 72 | 235-238 | 63.8 | 63.96 | 4.5 | 4.60 | 7.0 | 7.10 |
| 4d | $C_{21}H_{16}N_2O_8$ (424) | 68 | 225-229 | 59.3 | 59.44 | 3.7 | 3.80 | 6.5 | 6.60 |
| 4e | $C_{21}H_{18}N_2O_8$ (426) | 67 | 223-225 | 59.1 | 59.16 | 4.2 | 4.26 | 6.4 | 6.57 |
| 4f | $C_{24}H_{24}N_2O_8$ (468) | 61 | 220-223 | 61.3 | 61.53 | 5.0 | 5.16 | 5.9 | 5.98 |

* Uncorrected

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

| Compounds | Gram +Ve | | Gram –Ve | |
|---|---|---|---|---|
| | Staphylococcus aureus | Bacillus subtillis | E.coli | Klebsiella promioe |
| 4a | 74 | 70 | 78 | 72 |
| 4b | 58 | 56 | 58 | 59 |
| 4c | 56 | 58 | 54 | 58 |
| 4d | 55 | 54 | 57 | 52 |

| | | | | |
|---|---|---|---|---|
| 4e | 72 | 70 | 76 | 69 |
| 4f | 74 | 72 | 75 | 77 |
| Tetracyline | 76 | 57 | 74 | 84 |

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

| Zone of Inhibition at 1000 ppm (%) | | | | | |
|---|---|---|---|---|---|
| Compounds | Nigrospora Sp. | Aspergillus Niger | Botrydepladia Thiobromine | Rhizopus Nigricum | Fusarium oxyporium |
| 4a | 64 | 76 | 68 | 64 | 68 |
| 4b | 66 | 78 | 65 | 65 | 70 |
| 4c | 68 | 75 | 67 | 67 | 73 |
| 4d | 68 | 76 | 70 | 66 | 75 |
| 4e | 70 | 67 | 60 | 65 | 60 |
| 4f | 68 | 70 | 63 | 66 | 60 |

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 structures are confirmed by LC-MS. And the examination of antimicrobial activity of various pyrrolidinone compounds reveals that compounds 4a, 4e and 4f were found more toxic for microbes. Other compounds found to be less or moderate active than tetracycline (Table-3 & 4). Whereas compounds 4b, 4c and 4d were found to be more active against antifungal activity and the other compounds are moderately more or less active against various organisms.

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