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Synthesis, Characterization and Antimicrobial Activity of Hydrazone Derivatives of 2-(2,3-dihydrobenzofuran-5yl)acetic acid

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ABSTRACT

*Hydrazone derivatives are molecules containing highly reactive azomethine group (CO-NH-N=CH) and are found to possess various biological activities such as anti-inflammatory, anti-convulsant etc., The present paper describes the synthesis, characterization and antibacterial activity of novel hydrazones (**4a – 4j**) from 2-(2,3-dihydrobenzofuran-5-yl)acetohydrazide coupled with various aromatic aldehydes (a - j). The synthesized hydrazide-hydrazone derivatives **4a-4j** was characterized by ^{1}H NMR, Mass and IR spectral data. The antibacterial activity results revealed that hydrazone derivatives **4e** (4-NO_2), **4g** (4-F) and **4i** (4-OCF_3) exhibited good antibacterial activity, while the compounds **4b** (4-OMe) and **4h** (4-CF_3) displayed moderate antibacterial activity against all the tested bacterial strains.*

Keywords: Antibacterial Activity, Atovaquone, Gram-positive bacteria, Hydrazones, Synthesis.

INTRODUCTION

Despite the fact that a wide variety of drugs are being used in dealing of bacterial infections still there is an explore for a safe and potent antibacterial agent. Since these antibacterial agents are supposed to be taken for more than three days to complete their doses, thus there is a genuine need in a safer drug for the treatment of antibacterial infections. Most of the present diseases are due to the incursion by the pathogenic organisms like bacteria, fungi and virus. Many potent and broad spectrum antibiotics were discovered eg: ampicillin, amoxicillin, Carbenicillin, Oflaxacin, Tetracyclines etc, to treat these diseases. The treatment of bacterial and fungal infectious diseases remains a challenging problem because of the increasing number of multi-drug microbial pathogens [1, 2]. Hydrazone derivatives are molecules containing highly reactive azomethine group (CO-NH-N=CH) and thus useful in new drug development [3]. In recent times a lot of biologically important hydrazone derivatives with a number of functional groups have been synthesized from aromatic and aliphatic compounds [4]. Also, these are found to possess anti-tumoral [5-7], anti-mycobacterial [8], anti-inflammatory [9,10], anti-convulsant [11], analgesic [12], anti-platelet [13], anti-tubercular [14-16] and anti-microbial [17-19] activities.

Based on the bio-reactivity of hydrazones, we have synthesized novel hydrazones (**4a – 4j**) from 2-(2,3-dihydrobenzofuran-5-yl)acetohydrazide coupled with various aromatic aldehydes (a - j). The anti-bacterial studies were effectively done for newly synthesized hydrazones by standard disc diffusion method [20].

MATERIALS AND METHODS

Solvents and reagents were obtained from commercial source and used without purification. The IR spectra (ϑ_{max}, cm^{-1}) were recorded in solid state KBr dispersion using Perkin Elmer FT-IR spectrometer. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker-Avance 300 MHz spectrometer. The chemical shifts were reported in δ/ ppm relative to TMS. The mass spectra were recorded on API 2000 Perkin Elmer PE-Sciex mass spectrometer. The reactions were monitored by Thin–layer chromatography (TLC). Melting points were determined on plowman melting point apparatus (Model No MP96) by open capillary method and are uncorrected. All the reactions were carried out under nitrogen atmosphere. The 2-(2,3-dihydrobenzofuran-5yl)acetic acid and all the benzaldehydes used for the preparation of **4a-4j** were purchased from commercial sources.

Synthesis of Ethyl 2-(2, 3-dihydrobenzofuran-yl)acetate 2: To a solution of compound **1 (**10 g, 56.12 mmol) in ethanol (100 mL) was added sulphuric acid (1.66 mL) and refluxed for 12 h. After completion of reaction, ethanol was evaporated under reduced pressure and the obtained residue was taken in ethyl acetate (250 mL)and washed with 10% aq; $NaHCO_3$ solution (2 x35 mL) followed by water wash and brine solution. The organic layer was separated, dried over Na_2SO_4, filtered and evaporated to afford compound **2.** Dark brown color liquid, Yield: 9 g, 85%; b.p: 220-223°C

Synthesis of 2-(2,3-dihydrobenzofuran-yl)acetohydrazide 3: To a solution of compound **2 (**6 g**,** 31.21 mmol) in methanol (90.0 mL) was added hydrazine hydrate (6.24 g, 124.86 mmol) and heated to 50°C for 5h. after completion of the reaction , methanol was concentrated under reduced pressure to obtain crude compound **3 .** The crude compound was dissolved in ethanol (20 mL) at 45°C to get clear solution and cooled to 10°C, filtered at high vacuum pump and dried to obtain compound **3.** Offwhite solid, Yield :5 g,83%; m.p.: 112-113 ^{o}C

General Experimental Procedure for the Synthesis of Hydrazones derivatives (4a-4j): To a stirred solution of compound **3** (500 mg, 2.60 mmol) in ethanol(15 mL) was added corresponding benzaldehydes (1.03 mmol) and heated to 45°C for 1h. After completion of reaction cooled to 10°C, filtered and washed with cooled ethanol and fallowed by n-Hexane to obtain the pure compound. Yields of the product varied between 65 and 90%

(E)-N'-benzylidene-2-(2,3-dihydrobenzofuran-5-yl)acetohydrazide (4a): White solid; Yield: 85%; m.p: 107-108 ^{o}C; IR (KBr): υ_{max} 3247, 3215, 3073, 2983, 2955, 2896, 1668, 1616, 1601, 1572, 1550, 1494, 1446, 1366, 1344, 1314, 1291, 1259, 1233, 1196, 1176, 1137, 1105, 1083, 1065, 985, 967, 938, 912, 899, 863, 806, 776, 740, 692 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.60 (* 11.40, s, 1H), 8.20 (* 8.0, s, 1H), 7.74-7.72 (m, 2H), 7.60-7.58 (m, 3H), 7.20-7.18 (m, 1H), 7.4-7.0 (m, 1H), 6.70-6.62 (m, 1H), 4.60-4.58 (m, 2H), 3.88 (*3.44,s, 2H), 3.20-3.10 (m, 2H); ESI-MS: m/z, 281.1 (M^{+1}).

(E)-N'-(4-methoxybenzylidene)-2-(2,3-dihydrobenzofuran-5-yl)acetohydrazide(4b): Pale yellow solid; Yield: 90%; m.p: 98-100 ^{o}C; IR (KBr): υ_{max} 3869, 3732, 3239, 3070, 2983, 2956, 2896, 1666, 1615, 1600, 1572, 1551, 1492, 1444, 1401, 1365, 1343, 1315, 1298, 1259, 1231, 1195, 1175, 1136, 1128, 1103, 1091, 1071, 985, 968, 939, 913, 898, 866, 829, 806, 776, 717 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.40 (*11.20, s, 1H), 8.10 (* 7.9, s, 1H), 7.64-7.60 (m, 2H), 7.20 (d, *J* = 7.2 Hz, 1H), 6.98-6.92 (m, 1H), 6.62-6.60 (m, 1H), 4.70-4.64 (m, 2H), 3.88 (*3.46, s, 2H), 3.80 (s, 3H), 3.16-3.12 (m, 2H); ESI-MS: m/z, 311.0 (M^{+1}).

(E)-N'-(2-chlorobenzylidene)-2-(2,3-dihydrobenzofuran-5-yl)acetohydrazide (4c): Yellow solid; Yield: 88%; m.p: 108-109 ^{o}C; IR (KBr): υ_{max} 3732, 3182, 3070, 2965, 2899, 1668, 1598, 1561, 1491, 1471, 1434, 1387, 1354, 1316, 1286, 1275, 1244, 1219, 1195, 115,3 1119, 1105, 1050, 1033, 982, 953,

939, 917, 887, 820, 806, 761, 754, 710 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.75 (*11.56, s, 1H), 8.60 (* 8.38, s, 1H), 8.01 (*8.0, d, *J* = 3.6 Hz, 1H), 7.52 (d, *J* = 5.2 Hz, 2H,), 7.42 (d, *J* = 5.2 Hz, 2H,), 7.14 (d, *J* = 8.8 Hz, 1H), 7.02 (t, *J* = 6.4 Hz, 1H,), 6.70-6.63 (m, 1H), 4.48 (t, *J* = 6.8 Hz, 2H,), 3.89 (*3.44, s, 1H), 3.15 (t, *J* = 6.6 Hz, 2H); ESI-MS: m/z, 315.0 (M^{+1}).

(E)-N'-(4-chlorobenzylidene)-2-(2,3-dihydrobenzofuran-5-yl)acetohydrazide (4d): Pale yellow solid; Yield: 90%; m.p: 112-114 ^oC; IR (KBr): υ_{max} 3246, 3214, 3078, 3018, 2995, 2967, 2935, 2897, 2862, 2838, 2, 1664, 1607, 1572, 1552, 1512, 1493, 1464, 1444, 1412, 1374, 1344, 1305, 1260, 1216, 1196, 1171, 1136, 1104, 1066, 1027, 985, 964, 941, 911, 890, 870, 836, 807, 784, 743, 703 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.60 (*11.40, s, 1H), 8.20 (*8.0, s, 1H), 7.82-7.84 (m, 2H), 7.54-7.50 (m, 2H), 7.20 (d, *J* = 5.4 Hz, 1H,), 6.98 (d, *J* = 5.6 Hz, 1H,), 6.56-6.52 (m, 1H), 4.46-4.42 (m, 1H), 3.88 (*3.40, s, 2H), 3.16-3.10 (m, 2H); ESI-MS: m/z, 315.0 (M^{+1}).

(E)-N'-(4-nitrobenzylidene)-2-(2,3-dihydrobenzofuran-5-yl)acetohydrazide (4e): Yellow solid; Yield: 92%; m.p: 88-89 ^oC; IR (KBr): υ_{max} 3650, 3188, 3079, 2969, 2910, 2872, 2444, 1674, 1611, 1596, 1583, 1518, 1493, 1440, 1403, 1391, 1344, 1300, 1267, 1247, 1218, 1200, 1175, 1150, 1107, 1011, 981, 935, 901, 851, 838, 816, 803, 772, 749, 720, 689 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.82 (*11.61, s, 1H), 8.32 (*8.0, s, 1H), 8.28 (d, *J* = 7.4 Hz, 2H,), 7.94 (d, *J* = 7.2 Hz, 2H), 7.15 (d, *J* = 4.8 Hz, 1H), 7.02 (d, *J* = 4.6 Hz, 1H), 6.68 (d, *J* = 6.8 Hz, 1H), 4.46 (t, *J* = 6.8 Hz, 2H), 3.92 (*3.48, s, 1H), 3.15 (t, *J* = 6.6 Hz, 2H); ESI-MS: m/z, 326.10 (M+1).

(E)-N'-(4-bromobenzylidene)-2-(2,3-dihydrobenzofuran-5-yl)acetohydrazide (4f): Pale yellow solid; Yield: 88%; m.p: 119-120 ^oC; IR (KBr): υ_{max} 3422, 3211, 3069, 2983, 2955, 2896, 1906, 2862, 1666, 1614, 1601, 1597, 1552, 1493, 1444, 1412, 1398, 1364, 1343, 1315, 1298, 1259, 1230, 1195, 1176, 1136, 1127, 1104, 1070, 1010, 985, 940, 913, 898, 865, 828, 806, 774, 729 cm^{-1};^1H NMR (400 MHz, DMSO-d_6): δ 11.58 (*11.37, s, 1H), 8.18 (* 7.95, s, 1H), 7.62 (d, *J* = 6.8 Hz, 4H), 7.14 (d, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 4.8 Hz, 1H), 6.68 (dd, *J* = 6.4, 10.0 Hz, 1H), 4.48 (t, *J* = 6.4 Hz, 2H), 4.45 (*3.38, s, 2H), 3.14 (t, *J* = 6.4 Hz, 2H); ESI-MS: m/z, 359.03 (M+1).

(E)-N'-(4-fluorobenzylidene)-2-(2,3-dihydrobenzofuran-5-yl)acetohydrazide (4g): Pale yellow solid; Yield: 86%; m.p: 108-109 ^oC; IR (KBr): υ_{max} 3426, 3242, 3206, 3063, 2962, 2921, 2893, 2857, 2597, 1894, 1787, 1682, 1662, 1614, 1599, 1556, 1508, 1494, 1439, 1415, 1364, 1371, 1330, 1296, 1244, 1228, 1208, 1182, 1156, 1129, 1105, 1097, 1067, 1012, 985, 958, 937, 916, 895, 869, 849, 806, 795, 773, 741, 714, 679 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.52 (*11.31, s, 1H), 8.21 (*7.98, s, 1H), 7.76 (t, *J* = 4.4 Hz, 2H), 7.74 (t, *J* = 4.2 Hz, 2H), 7.28 (d, *J* = 8.8 Hz, 1H), 7.00 (d, *J* = 4.8 Hz, 1H), 6.68 (dd, *J* = 6.4, 10.0 Hz, 1H), 4.50 (t, *J* = 6.8 Hz, 2H), 3.88 (*3.42, s, 2H), 3.16 (t, *J* = 6.4 Hz, 2H); ESI-MS: m/z, 299.12 (M^{+1}).

(E)-N'-(4-(trifluoromethyl)benzylidene)-2-(2,3-dihydrobenzofuran-5-yl)acetohydrazide (4h): Yellow solid; Yield: 82%; m.p: 90-92 ^oC; IR (KBr): υ_{max} 3813, 3685, 3331, 3240, 3217, 3081, 3063, 3016, 2985, 2956, 2933, 2897, 2862, 2752, 2297, 2136, 1668, 1886, 1824, 1614, 1555, 1515, 1494, 1444, 1412, 1367, 1328, 1260, 1232, 1196, 1177, 1160, 1130, 1107, 1069, 1017, 991, 985, 971, 949, 912, 899, 871, 8501, 836, 779, 764. 746, 734, 717, 670 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.67 (*11.46, s, 1H), 8.24 (* 8.01, s, 1H), 7.86 (t, *J* = 7.2 Hz, 2H), 7.74 (t, *J* = 7.2 Hz, 2H), 7.11 (d, *J* = 7.2 Hz, 1H), 6.96 (d, *J* = 4.8 Hz, 1H), 6.64 (dd, *J* = 6.4, 10.0 Hz, 1H), 4.45 (t, *J* = 6.8 Hz, 2H), 3.86 (*3.42, s, 2H), 3.08 (t, *J* = 6.8 Hz, 2H); ESI-MS: m/z, 349.11 (M^{+1}).

(E)-N'-(4-(trifluoromethoxy)benzylidene)-2-(2,3-dihydrobenzofuran-5-yl)acetohydrazide (4i): Yellow solid; Yield: 86%; m.p: 101-102 ^oC; IR (KBr): υ_{max} 3837, 3746, 3688, 3671, 3547, 3627, 3615, 3586, 3565, 3544, 3524, 3329, 3246, 3216, 3077, 2984, 2955, 2897, 2728, 2625, 2354, 1885, 1667, 1606, 1582, 1552, 1507, 1494, 1444, 1413, 1367, 1344, 1306, 1259, 1228, 1195, 1161, 1103, 1070, 1016, 985, 973,

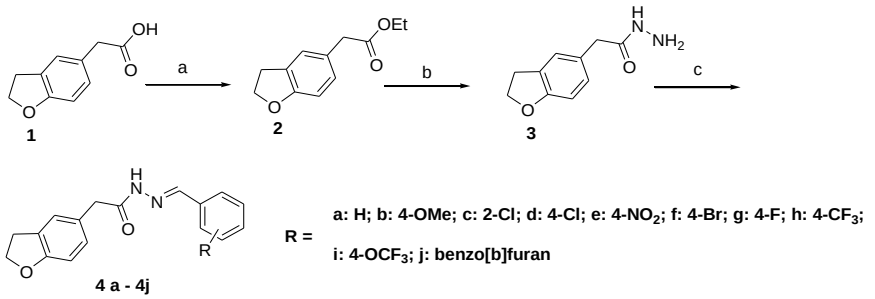
922, 912, 899, 869, 870, 830, 806, 796, 774, 743, 713 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.60 (*11.40, s, 1H), 8.24 (* 8.00, s, 1H), 7.82 (t, *J* = 4.0 Hz, 2H), 7.42 (t, *J* = 4.0 Hz, 2H), 7.14 (d, *J* = 6.8 Hz, 1H), 7.00 (d, *J* = 6.4 Hz, 1H), 6.60 (dd, *J* = 7.6, 10.0 Hz, 1H), 4.50 (t, *J* = 6.8 Hz, 2H), 3.88 (*3.42, s, 2H), 3.16 (t, *J* = 6.8 Hz, 2H); ESI-MS: m/z, 365.11 (M^{+1}).

(E)-N'-((benzofuran-2-yl)methylene)-2-(2,3-dihydrobenzofuran-5-yl)acetohydrazide (4j): Yellow solid; Yield: 86%; m.p: 88-89 ^oC; IR (KBr): υ_{max} 3837, 3647, 3565, 3171, 3111, 3064, 3035, 2921, 2889, 2836, 2355, 2319, 2260, 2041, 1735, 1667, 1652, 1615, 1598, 1553, 1508, 1488, 1471, 1448, 1394, 1350, 1330, 1317, 1291, 1276, 1255, 1239, 1219, 1201, 1192, 1159, 1144, 1123, 1104, 1059, 1006, 982, 963, 943, 930, 892, 882, 809, 743, 720, 690, 668, 657 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.68 (*11.51, s, 1H), 8.24 (* 8.0, s, 1H), 7.70 (s, 1H), 7.68-7.61 (m, 1H), 7.38 (t, *J* = 5.6 Hz, 1H), 7.30 (t, *J* = 5.6 Hz, 2H), 7.20 (d, *J* = 4.4 Hz, 1H), 7.00 (d, *J* = 5.6 Hz, 1H), 6.70 (dd, *J* = 6.4, 10.0 Hz, 1H), 4.52 (t, *J* = 6.8 Hz, 2H), 3.88 (*3.46, s, 2H), 3.16 (t, *J* = 6.4 Hz, 2H); ESI-MS: m/z, 321.12 (M^{+1}).

Antibacterial Bioassay: Hydrazone derivatives (**4a – 4j**) were dissolved in dimethyl sulphoxide at 250 µg/mL concentration. The composition of nutrient agar medium was Bactotryptone (10 g), yeast extract (5 g), NaCl (10 g), final pH 7.4. After 18 h the exponentially growing cultures of the six bacteria in nutrient broth at 37 ^oC were diluted in sterile broth. From each of these diluted cultures, 1mL was added to 100 mL sterilized and cooled nutrient agar media to give a final bacterial count of 1 x 10^6 cell mL^{-1}. The plates were set at room temperature and later dried at 37 ^oC for 20h. Paper discs (6mm, punched from Whatman no 41 paper) were ultraviolet sterilized and used for the assays. Discs were soaked in different concentration of the test solution and placed on the inoculated agar media at regular intervals of 6-7 cm, care was taken to ensure that excess solution was not on the discs. All the samples were taken in triplicates. The plates were incubated at 37 ^oC in an inverted fashion. Activity was determined by zones showing complete inhibition (mm). Growth inhibition was calculated with reference to positive control.

RESULTS AND DISCUSSION

The synthesis of ten new hydrazone derivatives **4a-4j** is presented in **scheme 1.** The starting material 2-(2,3-dihydrobenzofuran-5yl)acetic acid **1** is used as one of the key intermediate for the preparation of the well known drug Darifenacin [21]. The starting material **1** was converted to corresponding ethyl 2-(2,3-dihydrobenzofuran-yl)acetate **2** in presence of con H_2SO_4 (catalytic amount) in ethanol. The ethyl 2-(2,3-dihydrobenzofuran-yl)acetate derivative **2** was treated with hydrazine hydrate in methanol to afford the key intermediate hydrazide-hydrazone derivative **4a-4j** . The synthesized hydrazide-hydrazone derivatives **4a-4j** was characterized by ^1H NMR, Mass and IR spectral data. The mass spectra of compounds showed (M^{+1}) peaks, in agreement with their molecular formula.



Experimental Conditions**:** a) EtOH, Conc; H_2SO_4, 12 h; b) $NH_2NH_2.H_2O$, methanol, reflux, 50°C, 5 h; c) benzaldehydes **a-j,** ethanol, 45-50°C, 1 h.

Scheme 1: Synthesis of novel hydrazone derivatives **4a – 4j**

As a representative example, the ^{1}H NMR spectra of the compound **4d** is elucidated as follows, the broad singlets at 11.60 (* 11.40 ppm) and 8.20 ppm (* 8.0 ppm) corresponds to the protons representing to -N=C*H*- and -N*H*-N=C- groups respectively. The doublets appearing at 7.80 and 7.43 ppm represents to the para substituted protons attached to the phenyl ring bearing methoxy substituent. All the other aliphatic protons were observed at expected regions. All the synthesized hydrazones derivatives **4a-4j** compounds were found to exist as a mixture of two rotameric forms in solution [22] e.g. antiperiplanar (*ap*) and synperiplanar (*sp*) as indicated by their ^{1}H NMR spectra.

The antibacterial activity of the synthesized compounds **4a-4j** was evaluated against two Gram negative strains viz., i) *Escherichia coli*, *(ii) Pseudomonas aeruginosa*, and two Gram positive strains *viz. iii). Streptococcus pyogenes and ivi) Staphylococcus aureus* using agar well diffusion method following the literature procedure [20, 22]. The antibacterial activity of the hydrazone derivatives **4a – 4j** (250 μg mL^{-1} concentration) was compared with standard drug Ampicillin and the results of investigation have been presented in table **1.** From the table 1, it is observed that hydrazone derivatives **4e** (4-NO_2), **4g** (4-F) and **4i** (4-OCF_3) exhibited good antibacterial activity, while the compounds **4b** (4-OMe) and **4h** (4-CF_3) displayed moderate antibacterial activity against all the tested bacterial strains and the remaining compounds in the series did not show any bacterial activity.

Table 1: Results of Antibacterial Bioassay of Compounds **4a-4j** (concentration used 250 μg/mL of DMSO)

Compound no.	**Name of the Bacteria**				
	R	***E.coli***	***P. aeruginosa***	***S.aureus***	***S.pyogenes***
		Zones of inhibition in mm			
4a	H	--	--	--	--
4b	4-OMe	16	12	16	13
4c	2-Cl	--	--	--	--
4d	4-Cl	--	--	--	--
4e	4-NO_2	18	17	18	17
4f	4-Br	--	--	--	--
4g	4-F	17	16	14	15
4h	4-CF_3	15	16	17	13
4i	4-OCF_3	22	21	19	19
4j	Benzo[b]furan	20	20	19	21
Standard drug	Ampicillin **(250 μg/mL)**	20	20	19	18

APPLICATIONS

The novel hydrazones derivatives **4a-4j** synthesized in the present study were evaluated for antibacterial activity and are found to be as active pharmacophore.

CONCLUSIONS

In conclusion, the present paper describes the synthesis, characterizations and antibacterial activity of novel hydrazone derivatives **4a-4j** derived from the starting material 2-(2,3-dihydrobenzofuran-5yl)acetic acid **1** that is used as one of the key intermediate for the preparation of the well known drug Darifenacin.
The structures of the synthesized compounds were confirmed by ^{1}H NMR, Mass and IR spectral data. Among the newly synthesized hydrazone derivatives 4a-4j, **4e** (4-NO_2), **4g** (4-F) and **4i** (4-OCF_3) exhibited good antibacterial activity, while the compounds **4b** (4-OMe) and **4h** (4-CF_3) displayed moderate antibacterial activity against all the tested bacterial strains.

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