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Synthesis, Characterization and Anti-Bacterial Evaluation of Novel Benzo[b] Furan Analogs

N. J. P. Subhashini[1]*, P. Janaki[1], B. Bhadraiah[1], Shivaraj[2]

1. Department of Chemistry, University College of Technology, Osmania University, Hyderabad -500 007, **INDIA**
2. Department of Chemistry, University College of Science, Osmania University, Hyderabad -500 007, **INDIA**

Email: njsubhashini@yahoo.co.in

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ABSTRACT

*A series of novel benzofuran derivatives have been synthesized by interesting biological activities associated with Benzo[b]furan derivatives. These compounds have been characterized by IR, ^{1}HNMR, ^{13}C NMR, and mass spectral data. So we report here the synthesis, characterization and antibacterial evaluation of the newly synthesized benzo[b]furan derivatives. The newly prepared benzo[b]furan derivatives **7a-7o** were screened in-vitro at a concentration of 10 $\mu g\ mL^{-1}$ for antibacterial activity against bacterial strains viz., Staphylococcus aureus and Bacillus Subtilis (Gram positive bacteria), Escherichia coli and Klebsialla pneumonia (Gram negative bacteria). Among all the compounds, the benzo[b]furan derivatives **7h** exhibited excellent activity, compounds **7g** and **7m** displayed good activity, compounds **7e** and **7f** showed moderate activity compared with standard drug Gentamycin. When tested against all the tested bacterial strains.*

Keywords: Antibacterial activity, Benzo[b]furan derivatives, Gentamycin, Synthesis.

INTRODUCTION

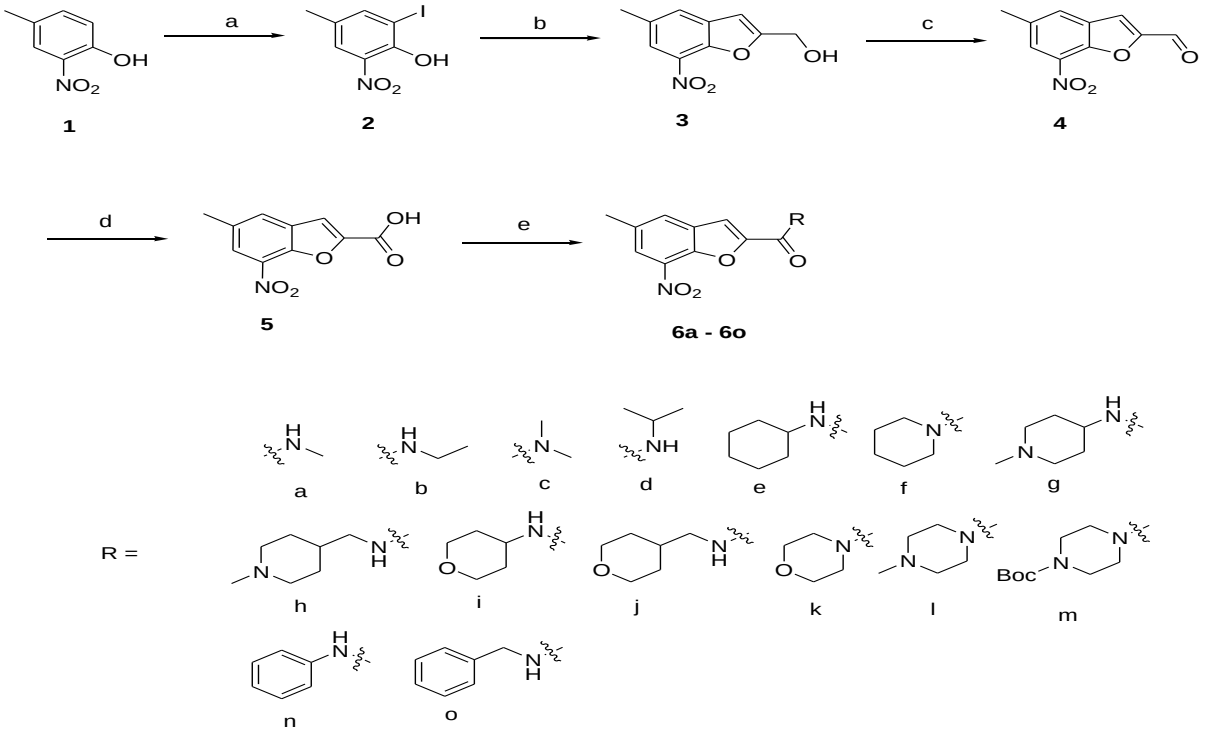
Benzo[b]furan derivatives are found in abundance in nature and are well recognized to have various biological activities [1–5]. Members of this class of compounds have shown biological activities ranging from anti-tumor, antifungal, anti-viral, anti-inflammatory, anti-arrhythmic, hemostatic, anti-oxidant activities and antimicrobial, and angiotensin II, antagonists for the H3 receptor [6-22]. Benzo[b]-furan-based molecules have been also disclosed as promising drugs against Parkinson's [23] and Alzheimer's disease, the inhibitors of b-amyloid (Ab) aggregation[24-25] and cyclooxygenase-2 (COX-2) [26]. 5-Nitro-benzofurans possess antibacterial and anti-cancer activities and recently have been used as a synthetical precursor of the new antiarrhythmic agent, dronedarone [27].

In spite of a large number of antibiotics and chemotherapeutics available for medical use [28, 29], the antimicrobial resistance has created a substantial need for design of new class of antimicrobials and this field will always remain an area of immense significance. Enthused by the vast importance of a variety of biological activity of benzo[b]furan derivatives, we report herein the synthesis, characterization and antibacterial evaluation of fifteen new benzo[b]furan derivatives **7a-7o**.

MATERIALS AND METHODS

The ^{1}H-NMR spectra were recorded in DMSO on a Varian EM-360 spectrometer (400 MHz). The ^{13} C NMR spectra recorded in DMSO on a Varian EM-360 spectrometer operating at 400 MHz. Thin-layer chromatography (TLC) was performed on E.Merck AL silica gel 60 F254 plates and visualized under UV light. The IR spectra were recorded on a Perkin Elmer FT-IR spectrometer. The mass spectra were recorded on Agilent ion trap MS. All the reactions were carried out under argon atmosphere. Chemical and solvents used were purchased either from Fluka or Merck. All the reagents were of analytical grade. The starting material and all the amines used for the preparation of of compounds **6a-6o** were purchased from commercial sources.

Experimental Conditions: a) I_2, $NaHCO_3$, Water, 95^{o}C, 2.5 h; b) Propargyl alcohol, TPP, CuI, Morpholine, Water, 10% Pd/C, 50 min, 115^{o}C; c) MnO_2, DCM, r.t., 6 h; d) NaH_2PO_4, $NaClO_2$, 30% H_2O_2, ACN:H_2O, r.t., 90 min; e) EDC.HCl, HOBT, DIPEA, **amines 6a-6o**, DCM, r.t., 4h



Scheme 1: Synthesis of novel Benzo[b]furan derivatives **7a – 7o**

Synthesis of 2-iodo-4-methyl-6-nitrophenol 2: To the stirred mixture of compound **1** (10 g, 65.40 mmol) in water (100 mL) was added sodium bicarbonate (523 mmol) followed by iodine (16.6 g, 65.40 mmol) in small portions for 1h and heated to 80^{o}C for 2.5 h. The reaction mixture was cooled to rt, acidified with 1N HCl and then extracted with diethyl-ether (3x50 mL). The organic layer was separated and washed with water, brine solution and dried over sodium sulphate, filtered and evaporated to obtain compound **2**. Yellow solid, Yield: 88 % (8 g). Mp: 97-99^{o}C. IR (KBr): υ_{max} 3079, 3025, 2971, 1740, 1613, 1537, 1450, 1407, 1371, 1320, 1300, 1260, 1212, 1149, 1087, 1046, 1014, 937, 871, 842, 781, 759, 723, 683 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.20 (s, 1H), 7.98 (s, 2H), 2.30 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 151.9, 148.0, 132.6, 131.6, 125.0, 86.6, 19.9. EI-MS: m/z (rel.abund. %) 154.2 (M+, 100).

Synthesis of (5-methyl-7-nitrobenzofuran-2-yl)methanol 3: A mixture of compound **2** (2 g, 7.16 mmol), 10% Pd/C (0.3 g), Triphenylphosphine (0.23 g, 0.86 mmol), CuI (80 mg, 0.43 mmol) and morpholine (23 mmol) in water (10 mL) was stirred at room temperature for 1 h under nitrogen. Prop-2-yn-1-ol (23 mmol) was added to the above reaction mixture and heated to reflux for 6 h. The reaction mixture was cooled to room temperature, diluted with ethylacetate (100 mL) and filtered through celite bed. The filtrate was collected, washed with water (2 x 50mL), dried over sodium sulphate, filtered and concentrated to afford compound **3**. Yield: 62 % (1 g). Mp: 153-154^{o}C. IR (KBr): υ_{max} 3200, 3083, 2925, 2854, 1741, 1632, 1585, 1516, 1449, 1427, 1361, 1325, 1278, 1222, 1188, 1152, 1129, 1019, 968, 922, 876, 834, 781, 751, 672, 639 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.62 (s, 1H), 6.68 (s, 1H), 4.85 (d, *J* = 6.8 Hz), 2.58 (s, 3 H), 2.10 (t, *J* = 6.6 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.5, 145.4, 133.0, 132.2, 128.1, 121.4, 133.1, 103.7, 57.8, 21.0. EI-MS: m/z (rel.abund.%) 207.2 (M+, 100).

Synthesis of 5-methyl-7-nitrobenzofuran-2-carbaldehyde 4: A mixture of compound **3** (2g, 9.66 mmol), MnO_2 (67.7 mmol) in dichloromethane (40 mL) was stirred at room temperature for 6 h. The reaction mixture was filtered through celite pad and the organic layer was evaporated to obtain pale yellow solid. Yield: 78 % (1.54 g). Mp: 179-180^{o}C; IR (KBr): υ_{max} 3083, 2970, 2871, 1740, 1671, 1636, 1565, 1514, 1469, 1420, 1364, 1331, 1307, 1284, 1213, 1120, 1039, 997, 932, 882, 752, 738, 662 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.94 (s,1H), 8.28 (s,1H), 8.17 (s,1H), 2.51 (s, 3H); EI-MS: m/z (rel.abund.%) 206.1 (M+, 100).

Synthesis of 5-methyl-7-nitrobenzofuran-2-carboxylic acid 5: To a stirred solution of aldehyde (5g 24.40 m.mol), NaH_2PO_4 (6.20 m.mol) and 35% H_2O_2 (21.70 mmol) in 120 mL of ACN: H_2O (5:1, v/v) was added a solution of $NaClO_2$ (3.27 g, 28.92 mmol) in water (30 mL) at 10^{o}C. The reaction mixture was stirred at room temperature for 90 min. $Na_2S_2O_3$ (20 mmol) was added and the mixture was stirred for a further 5 min to decompose the excess of H_2O_2. The mixture was diluted with aq.NaCl and extracted with EtOAC (3 x 30 mL). The organic extracts were separated, washed with aq.NaCl and extracted with aq.$NaHCO_3$. The alkaline extracts were separated, acidified with Conc.HCl and extracted with EtOAC. The organic layer was further washed with water followed by brine solution to obtain compound **5** as a pale yellow solid. Yield: 80 % (4.3 g). Mp: 248-249^{o}C. IR (KBr): υ_{max} 2970, 2610, 2528, 1702, 1632, 1576, 1524, 1475, 1422, 1362, 1317, 1291, 1253, 1205, 1138, 1112, 1039, 1002, 941, 906, 876, 829, 783, 752, 674 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.0 (br s,1H), 8.17 (s, 1H), 8.03 (s, 1H), 7.77 (s, 1H), 2.50 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.6, 132.4, 132.2, 127.6, 120.5, 102.9, 102.8, 56.7, 20.6. EI-MS: m/z (rel.abund. %) 222.1 (M+, 100).

General Experimental Procedure for the Synthesis of benzo[b]furan derivatives (7a-7o): To a dichloromethane solution containing carboxylicacid **5** (300 mg, 1.35 mmol) was added di-isopropyl ethyl amine (2.02 mmol) followed by EDCI. HCl (1.35 mmol), HOBT (2.02 mmol) and the contents were stirred at room temperatures for 4-8 h. The reaction mixture was diluted with water and extracted with ethylacetate. The organic layer was washed with water followed by brine solution, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure, to obtain the pure compounds **7a – 7o**. Yields of the products varied between 80 and 95%.

Synthesis of N,5-dimethyl-7-nitrobenzofuran-2-carboxamide 7a: Yield: 82%. Mp: 227-228^{o}C. IR (KBr): υ_{max} 3314, 3124, 3094, 2923, 2852, 1646, 1583, 1531, 1461, 1416, 1359, 1325, 1299, 1263, 1217, 1153, 1015, 940, 871, 834, 781, 753, 731, 656 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.08 (s, 1H), 7.79 (s, 1H), 7.50 (s, 1H), 6.84 (br s, 1H), 3.05 (d, *J* = 5.2 Hz, 3H,), 2.54 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 157.7, 151.2, 144.3, 133.8, 132.9, 131.0, 129.9 (2C), 123.2, 108.7, 25.8(1C), 22.2. ESI-MS: m/z (rel.abund. %) 235.1 (M+, 100)

N-ethyl-5-methyl-7-nitrobenzofuran-2-carboxamide 7b: Yield: 80%. Mp: 151-152^{o}C. IR (KBr): υ_{max} 3328, 3110, 2941, 2876, 1740, 1655, 1573, 1524, 1447, 1359, 1324, 1296, 1254, 1216, 1144, 1089, 1040,

1002, 945, 902, 872, 851, 780, 752, 663 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.08 (s, 1H), 7.78 (s, 1H), 7.49 (s, 1H), 6.81 (br s, 1H), 3.59-3.52 (m, 3H), 2.54 (s, 3H), 1.31 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 157.1, 151.3, 144.3, 133.8, 132.9, 131.0, 130.0, 123.3, 108.7, 33.8, 20.3, 14.6. ESI-MS: m/z (rel.abund. %) 249.1 (M+, 100).

N,N-dimethyl-7-nitrobenzofuran-2-carboxamide 7c: Yield: 85%. Mp: 147-148°C. IR (KBr): υ_{max} 3311, 2933, 2855, 1740, 1643, 1601, 1519, 1453, 1425, 1357, 1324, 1286, 1255, 1200, 1134, 1076, 1049, 998, 974, 946, 911, 891, 871, 844, 778, 752, 727, 646 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.07 (s, 1H), 7.77 (s, 1H), 7.46 (s, 1H), 3.48 (s, 3H), 3.17 (s, 3H), 2.54 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 158.9, 150.8, 144.1, 133.8, 132.8, 130.7, 129.8, 123.1, 110.4, 37.9, 35.7, 20.3 20.3. ESI-MS: m/z (rel.abund. %) 249.2 (M+, 100).

N-isopropyl-7-nitrobenzofuran-2-carboxamide 7d: Yield: 90%; Mp: 167-168°C. IR (KBr): υ_{max} 3430, 3140, 2972, 2955, 2875, 1664, 1603, 1514, 1464, 1391, 1362, 1325, 1269, 1237, 1195, 1169, 1131, 1104, 1047, 1003, 946, 919, 880, 860, 831, 780, 751, 673 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.07 (s, 1H), 7.78 (s, 1H), 7.49 (s, 1H), 6.60 (br s, 1H), 4.35-4.30 (m, 1H), 2.54 (s, 3H), 1.34 (d, *J* = 6.8 Hz, 3H), 1.26 (d, *J* = 6.84, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 156.5, 151.3, 144.3, 133.7, 132.9, 131.0, 129.9, 123.2, 108.6, 41.0, 22.0, 20.2. ESI-MS: m/z (rel.abund. %) 263.2 (M+, 100).

N-cyclohexyl-7-nitrobenzofuran-2-carboxamide 7e: Yield: 88%. Mp: 148-149°C; IR (KBr): υ_{max} 3311, 2933, 2855, 1740, 1643, 1601, 1519, 1453, 1425, 1357, 1324, 1286, 1255, 1200, 1134, 1076, 1049, 998, 974, 946, 911, 891, 871, 844, 778, 752, 727, 646 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.07 (s, 1H), 7.77 (s, 1H), 7.48 (s, 1H), 6.65 (br s, 1H), 4.03-4.0 (m, 1H), 2.54 (s, 3H), 2.06-2.03 (m, 2H), 1.82-1.77 (m, 2H), 1.69-1.65 (m, 1H), 1.47-140 (m, 5H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 156.4, 151.2, 144.3, 133.7, 132.9, 131.0, 129.9 (2C), 123.2, 108.7, 48.2, 32.1(2C), 25.1, 24.8, 20.2. ESI-MS: m/z (rel.abund. %) 303.2 (M+, 100).

(7-nitrobenzofuran-2-yl)(piperidin-1-yl)methanone 7f: Yield: 88% . Mp: 135-136°C. IR (KBr): υ_{max} 3102, 2993, 2860, 1740, 1618, 1579, 1526, 1473, 1427, 1358, 1324, 1276, 1247, 1201, 1157, 1128, 1108, 1074, 1032, 1004, 943, 915, 878, 860, 832, 814, 780, 751, 685 cm^{-1}. ^1H NMR (CDCl3, 400 MHz): δ 8.12 (s, 1H), 7.99 (s, 1H), 7.49 (s, 1H), 3.60 (br s, 4H), 2.50 (s, 3H), 1.67-1.60 (m, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 157.7, 150.8, 144.0, 133.7, 132.8, 130.7, 129.6, 122.9, 109.8, 47.4, 43.20, 26.2, 25.3, 23.9, 20.3. ESI-MS: m/z (rel.abund. %) 289.1 (M+, 100).

N-(1-methylpiperidin-4-yl)-7-nitrobenzofuran-2-carboxamide 7g: Yield: 84% . Mp: 111-112°C. IR (KBr): υ_{max} 3133, 3082, 2954, 1720, 1630, 1584 1524, 1432, 1363, 1328, 1293, 1248, 1201, 1132, 1094, 1033, 1002, 973, 948, 911, 879, 836, 783, 750, 674 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 8.76 (d, *J* = 6.8 Hz, 1H), 8.12 (s, 1H), 8.11 (s, 1H), 7.82 (s, 1H), 3.94-3.91 (m, 1H), 3.18-3.02 (m, 2 H), 2.58-2.44 (m, 2H), 2.48 (s, 3H), 2.40 (s, 3H), 1.90-1.80 (m, 4H). ESI-MS: m/z (rel.abund. %) 318.2 (M+, 100).

Synthesis of N-((1-methylpiperidin-4-yl)methyl)-7-nitrobenzofuran-2-carboxamide 7h: Yield: 80% . Mp: 179-180°C. IR (KBr): υ_{max} 3406, 2929, 1740, 1688, 1599, 1523, 1440, 1361, 1326, 1291, 1199, 1134, 1075, 1048, 951, 921, 876, 845, 829, 776, 746, 672, 642 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ 8.8 (t, *J* = 8.0 Hz, 1H), 8.13 (s, 1H), 8.05 (s, 1H), 7.33 (s, 1H), 3.20 (t, *J* = 10.4 Hz, 2H), 3.14-3.05 (m, 3H), 2.50 (s, 3H), 2.45 (s, 3H), 2.40-2.37 (m, 2H), 1.77-1.67 (m, 3H) 1.39-1.33 (m, 1H). ESI-MS: m/z (rel.abund. %) 332.2 (M+, 100).

Synthesis of N-(tetrahydro-2H-pyran-4-yl)-7-nitrobenzofuran-2-carboxamide 7i: Yield: 80% Mp: 169-170°C. IR (KBr): υ_{max} 3645, 3075, 2882, 1739, 1683, 1656, 1604, 1574, 1524, 1472, 1450, 1427, 1389, 1357, 1323, 1297, 1239, 1206, 1141, 1082, 1011,987, 945, 828, 781, 750, 673, 631 cm^{-1}. ^1H NMR DMSO-d_6, 400 MHz): δ 8.63 (d, *J* = 8.0 Hz, 1H), 8.13 (s, 1H), 8.05 (s, 1H), 7.73 (s, 1H), 4.05-4.01 (m,

1H), 3.91-3.87 (m, 2 H), 3.40 (t, *J* = 10.4, 2H), 3.34 (s, 3H), 1.79-1.75 (m, 2H), 1.68-1.59 (m, 2H). ESI-MS: m/z (rel.abund. %) 305.1 (M+, 100).

N-((tetrahydro-2H-pyran-4-yl) methyl)-7-nitrobenzofuran-2-carboxamide 7j: Yield: 80%. Mp: 137-138^{o}C. IR (KBr): υ_{max} 3396, 3125, 2929, 2852, 1718, 1663, 1630, 1598, 1468, 1436, 1364, 1329, 1284, 1245, 1198, 1134, 1091, 1047, 1010, 984, 9568, 922, 881, 858, 781, 751, 673, 637 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz): 8.75 (t, 1H), 8.12 (s, 1H), 8.04 (s, 1H),7.60 (s, 1H), 3.86-3.83 (m, 2H), 3.38-3.20 (m, 2H), 3.10-2.98 (m, 1H), 2.56 (s, 3H), 2.18-2.16 (m, 1H), 1.95-1.80 (m, 1H), 1.68-1.60 (m,2H), 1.32-1.20 (m, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 157.5, 151.1, 144.0, 133.8, 133.0, 131.0, 130.0, 123.3, 108.8, 66.7, 44.5, 37.2, 34.8, 34.0, 30.4, 27.2, 20.3. ESI-MS: m/z (rel.abund. %) 319.0 (M+, 100).

Morpholino (7-nitrobenzofuran-2-yl) methanone 7k: Yield: 89%. Mp: 146-147^{o}C. IR (KBr): υ_{max} 3078, 2969, 2865, 1738, 1621, 1574, 1520, 1423, 1362, 1324, 1281, 1245, 1200, 1143, 1115, 1069, 1017, 949, 872, 840, 820, 780, 742, 681 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.08 (s, 1H), 7.78 (s, 1H), 7.48 (s, 1H), 4.11-4.10 (br m, 2H), 3.84 (m, 6H), 2.54 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 157.8, 150.1, 144.1, 133.8, 132.8, 130.6, 129.7, 123.1, 110.7, 66.1, 46.9, 42.7, 28.9, 20.3. ESI-MS: m/z (rel.abund. %) 291.2 (M+, 100).

(4-methylpiperazin-1-yl)(7-nitrobenzofuran-2-yl)methanone 7l: Yield: 90%. Mp: 150-151^{o}C. IR (KBr): υ_{max} 3387, 2952, 2854, 1737, 1656, 1602, 1528, 1468, 1425, 1359, 1326, 1246, 1202, 1137, 1100, 1059, 944, 879, 837, 775, 750, 672 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.13 (s, 1H), 7.80 (s, 1H), 7.58 (s, 1H), 4.01 (s, 3H), 2.55 (s, 3H), 1.30-1.26 (m, 4H), 0.88-0.83 (m, 4H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 158.4, 146.9, 145.0, 134.2, 133.0, 130.4 (2C), 124.6, 113.8, 52.5 (2C), 20.2 (2C). ESI-MS: m/z (rel.abund. %) 304.1 (M+, 100).

(4-N-Boc-piperazin-1-yl)(7-nitrobenzofuran-2-yl)methanone 7m: Yield: 94% . Mp: 143-144^{o}C; IR (KBr): υ_{max} 3090, 2972, 2952, 2858, 1742, 1691, 1624, 1577, 1523, 1478, 1419, 1362, 1325, 1283, 1244, 1197, 1146, 1114, 1072, 1010, 940, 866, 828, 782, 762, 744, 683 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.08 (s, 1H), 7.78 (s, 1H), 7.47 (s, 1H), 4.02 (br m, 2H), 3.80 (br m, 2H), 3.60 (br m, 4H), 2.55 (s, 3H), 1.48 (s, 9H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 158.0, 153.7, 150.2, 144.1, 133.9, 132.8, 130.6, 129.8, 123.2, 110.7, 79.23, 46.2, 42.1, 27.9 (4C), 20.3. ESI-MS: m/z (rel.abund. %) 390.2 (M+, 100).

7-nitro-N-phenylbenzofuran-2-carboxamide 7n: Yield: 90%. Mp: 169-170^{o}C. IR (KBr): υ_{max} 3415, 3347, 3095, 2970, 2925, 1740, 1672, 1600, 1523, 1428, 1361, 1326, 1277, 1201, 1131, 1077, 1051, 996, 945, 919, 877, 834, 782, 750, 732, 693, 649 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.47 (br s, 1H), 8.12 (s, 1H), 7.82 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.62 (s, 1H), 7.42 (t, *J* = 8.0 Hz, 2H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.25 (br s, 1H), 2.56 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 155.9, 150.6, 144.6, 138.1, 134.0, 133.0, 130.9, 130.2, 128.7 (4C), 124.2, 123.7, 120.5, 109.8. ESI-MS: m/z (rel.abund. %) 297.1 (M+, 100).

N-benzyl-7-nitrobenzofuran-2-carboxamide 7o: Yield: 86%. Mp: 139-140^{o}C. IR (KBr): υ_{max} 3415, 3095, 3024, 2928, 1740, 1671, 1599, 1523, 1451, 1426, 1360, 1326, 1280, 1252, 1202, 1131, 1051, 996, 947, 920, 880, 836, 781, 751, 731, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01 (s, 1H), 7.80 (s, 1H), 7.54 (s, 1H), 7.38-7.33 (m, 5H), 7.14 (br m, 1H), 4.70 (d, *J* = 6.0 Hz, 1H), 2.54 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 157.4, 151.0, 144.4, 139.0, 133.8, 133.0, 131.0, 130.0 (2C), 128.3, (2C), 127.4, 126.9, 123.4, 109.2, 42.3, 20.3. ESI-MS: m/z (rel.abund. %) 311.2 (M+, 100).

Antimicrobial Bioassay: The antimicrobial activity was determined using disc diffusion method by measuring zone of inhibition in mm [30- 31]. The newly prepared benzo[b]furan derivatives **7a-7o** were screened *in-vitro* at a concentration of 10 µg/mL for antibacterial activity against bacterial strains viz., *Staphylococcus aureus and Bacillus Subtilis* (Gram positive bacteria), *Escherichia coli* and *Klebsialla pneumonia* (Gram negative bacteria). Standard antibacterial drug gentamycin (10 µg/disc) was also tested

under similar conditions against these organisms. Each experiment was done in triplicate and the average reading was taken. The results of antibacterial activity are expressed in terms of zone of inhibition and presented in **Table 1**. Growth inhibition was calculated with reference to positive control. Benzo[b]furan derivatives (**7a – 7o**) were dissolved in dimethyl sulphoxide at 10 µg/mL concentration. The inhibition zones were measured in millimeters at the end of an incubation period of 48 hours at (35±2) °C. DMSO alone showed no inhibition. The composition of nutrient agar medium was Bactotryptone (10 g), yeast extract (5 g), NaCl (10 g), final pH 7.4.

RESULTS AND DISCUSSION

Chemistry: Scheme 1 depicts the synthetic strategy of novel Benzo[b]furan derivatives **7a-7j.** 4-methyl-2-nitrophenol was iodinated using I_2 in presence of aq.$NaHCO_3$ gave iodide compound **2**. Benzo[b]furan ring **3** formation was accomplished using the protocol reported earlier [32] with slight modification to produce alcohol **3.** Oxidation of alcohol **3** in presence of MnO_2 in DCM produced aldehyde **4**, further oxidation of aldehyde **4** to carboxylic acid **5** was achieved utilizing NaClO2, 30% H_2O_2 in presence of NaH_2PO_4 in acetonitrile : water [33]. Benzo[b]furan carboxylic acid **5** was reacted with various amines 6a – 6o in presence of EDC.HCl, HOBT, and DIPEA in DCM to obtain novel benzo [b] furan derivatives **7a – 7o**. All the newly synthesized benzo[b]derivatives **7a-7o** was characterized by ^{1}H NMR, ^{13}C NMR, IR and Mass spectral data. The mass spectra of compounds showed (M+1) peaks, is in agreement with their molecular formula.

Antibacterial evaluation : The outcome of the antibacterial results indicated that the benzo[b]furan derivatives **7h** exhibited excellent activity, compounds **7g** and **7m** displayed good activity, compounds **7e** and **7f** showed moderate activity when tested against all the tested bacterial strains. The benzo[b]furan derivatives such as **7a, 7b, 7c, 7d, 7i** and **7j** showed weak activity and the remaining compounds in the series showed no activity. In general, it is observed that, among the tested benzo[b]furan derivatives, compounds having N-methyl piperidine (**7g, 7h**) and N-Boc piperazine ring system in the scaffold structure exhibited good to excellent antibacterial activity. As some of the tested compounds are found to be active against all the tested microorganisms, it is essential that this particular basic moiety can be an encouraging scaffold for anti bacterial drugs. It may be recommended that the benzo[b]furan derivative with a appropriate R group may lead to a good antibacterial agent for all the tested bacterial strains viz., *Staphylococcus aureus and* Bacillus Subtilis (Gram positive bacteria), *Escherichia coli* and Klebsialla pneumonia (Gram negative bacteria). This is a very potential preliminary study and further assessment is required to use them for clinical use.

Table-1 Results of Antibacterial Activity of Compounds **7a-7o**
(Concentration Used 10 µg mL^{-1} of DMSO [a]).

Compound No.	*Gram negative*		*Gram positive*	
	E.Coli ***MTCC 443***	*K. Pneumoniae* ***MTCC 109***	*S.Aureus* ***MTCC 96***	*B. Subtilis* ***MTCC 441***
	Zones of Inhibition of compounds 7a –7o in mm [c]			
7a	7	7	7	6
7b	6	8	6	8
7c	8	7	8	6
7d	7	8	8	7
7e	11	15	10	11
7f	11	16	11	12
7g	14	21	16	19
7h	17	23	17	25

7i	8	9	8	6
7j	9	8	7	7
7k	-	-	-	-
7l	-	-	-	-
7m	14	19	13	18
7n	-	-	-	-
7o	-	-	-	-
Standard Drug	15	22	15	20

a: DMSO alone showed no inhibition; **b**: no activity; **c**: mean ± SD of three independent experiments

APPLICATIONS

In the present study, we have synthesized novel benzo[b]furan derivatives **7a-7o** and were evaluated for their potential antibacterial activity, the results revealed that these derivatives emerged as promising active pharmacophore. Further studies are undergoing to discover the extent of a variety of biological activities.

CONCLUSIONS

In conclusion, we have synthesized and characterized fifteen new benzo[b]furan derivatives **7a-7o** and tested for their potential antibacterial activities at the concentrations 10 μg mL^{-1} with reference to the standard antibacterial drug Gentamycin. The benzo[b]furan derivatives **7h** exhibited excellent activity, compounds **7g** and **7m** displayed good activity, compounds **7e** and **7f** showed moderate activity when tested against all the tested bacterial strains. The benzo[b]furan derivatives such as **7a, 7b, 7c, 7d, 7i** and **7j** showed weak activity and the remaining compounds in the series showed no activity. In general, it is observed that, among the tested benzo[b]furan derivatives, compounds having N-methyl piperidine (**7g, 7h**) and N-Boc piperazine ring system in the scaffold structure exhibited good to excellent antibacterial activity.

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