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Synthesis, characterization and antimicrobial activity of novel benzo[b]furan derivatives bearing phenylcarbamate moiety

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ABSTRACT

Benzo[b]furan ring systems bearing various substituent's at the C-2 position are broadly distributed in nature and have been reported to have antifungal, antiviral, antioxidant activities. Many, 2-arylbenzofuran derivatives are well known to reveal a wide range of biological activities, including calcium blockers, phytoestrogens, antioxidative, anticancer, insecticidal, antiproliferative, antiviral, antifungal, antiplatelet, anti-inflammatory, immunosuppressive, antifeedant, and cancer preventative activity. The present paper the synthesis, characterization and antibacterial activity of ten new benzo[b]furan derivatives bearing sulphonamide and phenylcarbamate moieties from commercially available 4-methyl-2-nitrophenol as starting material. The newly synthesized benzo[b]furan derivatives ***6a-6j*** *compounds were screened to evaluate their antibacterial activity against Gram-positive (Staphylococcus aureus and Staphylococcus pyogenes) and two Gram-negative strains (Escherichia coli and Pseudomonas aeruginosa). Most of the compounds were found to display good to moderate antibacterial activity against all the above tested strains of bacteria.*

Key words: Antibacterial activity, 2-arylbenzo[b]furan, phenylcarbamate, benzofuran synthesis

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INTRODUCTION

Benzo[*b*]furan nucleus is widespread in various synthetic pharmaceuticals [1] and is also prevalent in biologically active natural and unnatural compounds [2]. Especially, benzo[*b*]furan ring systems bearing various substituent's at the C-2 position are broadly distributed in nature and have been reported to have antifungal, antiviral, antioxidant and activities [3, 4]. Many, 2-arylbenzofuran derivatives are well known to reveal a wide range of biological activities, including calcium blockers [5], phytoestrogens [6], antioxidative [7], anticancer [8], insecticidal [9], antiproliferative [10], antiviral [11], antifungal [12], antiplatelet [13], anti-inflammatory [14], immunosuppressive [15], antifeedant [16], and cancer preventative activity [17].

As pathogenic bacteria incessantly develop mechanisms of resistance to currently used antibacterials, so the discovery of novel and potent antibacterial drugs is the finest way to overcome bacterial resistance and build up effective therapies [18]. In spite of the many antibiotics and chemotherapeutics available, the materialization of old and new antibiotic-resistant bacterial strains in the last decades constitute a substantial need for new classes of anti-bacterial agents [19].

Encouraged by the biological activities associated with the benzo[b]furan ring system and in continuation to our work reported earlier [20], we report here in the present paper the synthesis, characterization and antibacterial activity of ten new benzo[b]furan derivatives (**6a- 6j**) bearing sulphonamide and phenylcarbamate moieties.

MATERIALS AND METHODS

Chemical and solvents used were purchased either from Fluka or Merck. All the reagents were of analytical grade. 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 ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian EM-360 spectrometer (400MHz). The ^{13}C NMR spectra recorded in $CDCl_3$ on a Varian EM-360 spectrometer operating at 100MHz. All the chemical shifts were reported in δ (ppm) using TMS as an internal standard. The mass spectra were recorded on Agilent ion trap MS. All the reactions were carried out under argon atmosphere.

Synthesis of 2-iodo-4-methyl-6-nitrophenol 2:
To the stirred mixture of compound 1 (5 g, 32.67 mmol) in 10% aq; NaOH solution (50 mL) heated to 80 ^{o}C was added iodine (8.3 g, 32.67 mmol) in small portions for 1h and refluxed for 10 h. The reaction mixture was cooled to rt , acidified with 1N HCl and then extracted with diethyl-ether (50 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; 8 g, 88 %; m.p. 97-99 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.20 (s, 1H), 7.98 (s, 2H), 2.30 (s, 3 H). 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** (4 g, 14.33 mmol), 10% Pd/C (0.6 g), Triphenylphosphine (0.45 g, 1.72 mmol), CuI (0.16 g, 0.85 mmol) and piperidine (43 mmol) in water (20 mL) was stirred at room temperature for 1 h under nitrogen. Prop-2-yn-1-ol (43 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 cellite bed. The filtrate was collected, washed with water (2 x 50mL), dried over sodium sulphate, filtered and concentrated to afford compound **3**. Yield: 2 g, 62 %, m.p. 72- 73^{o}C. ^{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). EI-MS: m/z (rel.abund.%) 207.2 (M+, 100).

Synthesis of (5-methyl-7-nitrobenzofuran-2-yl)methyl phenylcarbamate 4:
A solution of compound **3** (0.5 g, 2.41 mmol) containing phenylisocyanate (0.31 g, 2.65 mmol) and catalytic amount of pyridine in 2-MeTHF was stirred at 80 ^{o}C for 1 h under nitrogen. The reaction mixture was poured into saturated sodium bicarbonate and extracted with ethylacetate (5 x10 mL).The combined extracts were washed with water followed by brine solution, dried over sodium sulphate and concentrated to obtain compound **4**. Yellow solid, Yield: 76 %, m.p.123-125 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.68 (s, 1H), 7.40-7.22 (m, 4H), 7.08 (t, *J* = 6.8 Hz, 1H), 6.88 (s, 1H), 6.72 (br.s, 1H), 5.40 (s, 2H), 2.48 (s, 3 H).

Synthesis of (7-amino-5-methylbenzofuran-2-yl)methyl phenylcarbamate 5:
A mixture of compound **5** (0.5 g, 1.53 mmol), Hydrazine hydrate (1.84 mmol) and 10% Pd/C (0.15g) in methanol was heated to reflux for 3 h. The reaction mixture was poured into cold water and extracted with ethylacetate (20 mL).The combined extracts were washed withwater followed by brine solution, dried over sodium sulphate and concentrated to obtain compound **5**. Yellow solid, Yield: 66%; m.p. 98-99 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 - 7.28 (m, 4H), 7.08 (t, *J* = 6.8 Hz, 1H), 6.78 (s, 1H), 6.68 (br.s, 1H), 6.50 (s, 1H), 5.20 (s, 2H), 3.96 (br.s, 2H), 2.40 (s, 3 H). EI-MS: m/z (rel.abund.%) 295.4 (M+, 100).

General experimental procedure for the preparation of 6a-6h
A mixture of compound **5** (0.1 g, 0.322 mmol), sulphonyl chlorides (0.322 mmol) in pyridine (1.0 mL) was stirred to room temperature for 2.0h –16.0h The reaction mixture was concentrated in *vacuo* and the residue diluted with H_2O and extracted with ethyl acetate to obtain crude compounds. The crude compounds were purified by column chromatography using silica gel (60-120 mesh). Yields of the products varied between 80 to 90%.

Synthesis of {5-methyl-7-[(methylsulfonyl)amino]-1-benzofuran-2-yl}methyl phenylcarbamate (6a):
Yellow solid, Yield: 86%; m.p. 100-102 ^{o}C; IR (KBr): ν_{max} 3294, 3242, 2937, 1740, 1701, 1601, 1544, 1448, 1377, 1331, 1244, 1150, 1067, 1031, 979, 936, 903, 875, 850, 814, 781, 753, 694, 654 cm $^{-1}$; ^{1} H NMR (400 MHz,

$CDCl_3$): δ 7.39-7.29 (m, 4H), 7.24 (s, 1H), 7.16 (s, 1H), 7.08 (t, *J* = 7.2 Hz, 1H), 6.77 (s, 2H), 6.71 (s, 1H), 5.28 (s, 2H), 3.08 (s, 3H), 2.42 (s, 3H); ESI-MS: m/z, 372.9 (M-1).

Synthesis of {5-ethyl-7-[(ethylsulfonyl)amino]-1-benzofuran-2-yl}methyl phenylcarbamate (6b):
Pale yellow solid, Yield: 90%; m.p. 100-102 ^oC IR (KBr): ν_{max} 3350, 3236, 2948, 1734, 1604, 1546, 1501, 1479, 1442, 1380, 1314, 1216, 1148, 1128, 1082, 1054, 994, 952, 927, 899, 872, 840, 785, 744, 690, 649 cm^{-1}; ^{1} H NMR (400 MHz, $CDCl_3$): δ 7.39-7.29 (m, 5H), 7.14-7.06 (m, 2H), 6.76-6.73 (m, 3H), 5.28 (s, 2H), 3.15 (q, *J* = 7.2 Hz, 2H), 2.41 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H); ESI-MS: m/z, 387.0 (M-1).

Synthesis of {5-methyl-7-[(propyllsulfonyl)amino]-1-benzofuran-2-yl}methyl phenylcarbamate (6c):
Yellow solid, Yield: 86%; m.p. 97-98 ^oC IR (KBr): ν_{max} 3306, 3183, 2967, 1740, 1709, 1605, 1544, 1500, 1445, 1379, 1312, 1286, 1229, 1206, 1128, 1085, 1053, 1029, 978, 940, 902, 849, 790, 750, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.29 (m, 5H), 7.13-7.06 (m, 2H), 6.76 (s, 3H), 5.28 (s, 2H), 3.18-3.09 (m, 2H), 2.42 (s, 3H), 1.94-1.88 (m, 2H), 0.99 (t, *J* = 7.2 Hz, 1H); ESI-MS: m/z, 401.0 (M-1).

Synthesis of {5-methyl-7-[(phenylsulfonyl)amino]-1-benzofuran-2-yl}methyl phenylcarbamate (6d):
Off-white solid, Yield: 81%; m.p. 121-122 ^oC IR (KBr): ν_{max} 3385, 3247, 1727, 1601, 1529, 1442, 1381, 1325,1214, 1170, 1085, 1038, 931, 890, 832, 754, 694, 629 cm^{-1}; ^{1} H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 7.2 Hz, 2H), 7.46 (d, *J* = 7.2 Hz, 1H), 7.38-7.30 (m, 6H), 7.25 (s, 1H), 7.10 (s, 2H), 6.92 (s, 1H), 6.64 (s, 2H), 5.12 (s, 2H), 2.40 (s, 3H); ESI-MS: m/z, 435.0 (M-1).

Synthesis of {5-methyl-7-[(4-methylphenylsulfonyl)amino]-1-benzofuran-2-yl}methyl pheylcarbamate (6e):
Yellow solid, Yield: 86%; m.p. 100-102 ^oC; IR (KBr): ν_{max} 3297, 3239, 3130, 3052, 2919, 1698, 1601, 1532, 1441, 1384, 1324, 1234, 1161, 1066, 968, 935, 883, 839, 750, 666 cm^{-1}; ^{1} H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.40-7.30 (m, 4H), 7.24 (s, 1H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.10-7.05 (m, 2H), 6.94 (s, 1H), 6.65 (s, 2H), 5.14 (s, 2H), 2.38 (s, 3H), 2.32 (s, 3H); ESI-MS: m/z, 449.1 (M-1).

Synthesis of {5-methyl-7-[(4-chlorophenylsulfonyl)amino]-1-benzofuran-2-yl}methyl pheylcarbamate (6f):
Yellow solid, Yield: 90%; m.p. 114-115 ^oC; IR (KBr): ν_{max} 3297, 3235, 3030, 2885, 2774, 1739, 1699, 1600, 1536, 1483, 1441, 1381, 1333, 1234, 1169, 1084, 979, 935, 884, 833, 754, 698, 643 cm^{-1} ; ^{1} H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 9.2 Hz, 2H), 7.42-7.30 (m, 6H), 7.25 (s, 1H), 7.12 (s, 2H), 6.89 (s, 1H), 6.68 (s, 2H), 5.12 (s, 2H), 2.40 (s, 3H); ESI-MS: m/z, 469.2 (M-1).

Synthesis of {5-methyl-7-[(benzylsulfonyl)amino]-1-benzofuran-2-yl}methyl pheylcarbamate (6g):
Yellow solid, Yield: 88%; m.p. 82-83 ^oC; IR (KBr): ν_{max} 3298, 3186, 2881, 2778, 1741, 1698, 1602, 1537, 1451, 1377, 1312, 1237, 1126, 1071, 980, 928, 851, 755, 698 cm^{-1};^{1} H NMR (400 MHz, $CDCl_3$): δ 7.44-7.28 (m, 7H), 7.24-7.05 (m, 4H), 6.77 (s, 1H), 6.67 (s, 1H), 6.60 (s, 1H), 5.25 (s, 2H), 4.41 (s, 2H), 2.40 (s, 3H); ESI-MS: m/z, 449.1 (M-1).

Synthesis of {5-methyl-7-[(thiophene-2ylsulfonyl)amino]-1-benzofuran-2-yl}methyl phenylcarbamate (6h):
Yellow solid, Yield: 84%; m.p. 130-132 ^oC; IR (KBr): ν_{max} 3381, 3244, 2970, 1729, 1601, 1527, 1441, 1381, 1320, 1215, 1157, 1127, 1077, 1045, 1026, 931, 890, 837, 753, 716, 674, 631cm $^{-1}$; ^{1} H NMR (400 MHz, $CDCl_3$): δ 7.50 (dd, *J* = 1.6, 4.0 Hz, 1H), 7.44-7.30 (m, 6H), 7.12-7.03 (m, 3H), 6.92 (t, *J* = 5.2 Hz, 1H), 6.68 (s, 2H), 5.16 (s, 2H), 2.40 (s, 3H); ESI-MS: m/z, 441.0 (M-1).

Synthesis of {5-methyl-7-[(5-chlorothiophene-2ylsulfonyl)amino]-1-benzofuran-2-yl}methyl phenyl cararbamate (6i):
Paleyellow solid, Yield: 82%; m.p. 127-128 ^oC IR (KBr): ν_{max} 3297, 3240, 2922, 2857, 1735, 1703, 1603, 1534, 1485, 1443, 1379, 1341, 1231, 1158, 1069, 993, 937, 883, 838, 801, 751, 685, 628 cm^{-1}; ^{1} H NMR (400 MHz, $CDCl_3$): δ 7.40-7.25 (m, 6H), 7.15 (s, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.02 (br.s, 1H), 6.75 (d, *J* = 4.0 Hz, 1H), 6.70 (s, 1H), 6.68 (s, 1H), 5.18 (s, 2H), 2.43 (s, 3H); ESI-MS: m/z, 474.9 (M-1).

Synthesis of {5-methyl-7-[(5-bromothiophene-2ylsulfonyl)amino]-1-benzofuran-2-yl}methyl phenylcarbamate (6j):
Yellow solid, Yield: 89%; m.p. 119-120 ^oC IR (KBr): ν_{max} 3233, 1740, 1699, 1601, 1537, 1480, 1442, 1396, 1343, 1314, 1234, 1160, 1130, 1082, 1059, 1024, 969, 935, 880, 837, 751, 717, 688, 619 cm^{-1}; ^{1} H NMR (400 MHz,

$CDCl_3$): δ 7.39-7.29 (m, 6H), 7.15 (s, 1H), 7.09 (t, *J* = 7.2 Hz, 1H), 7.01 (s, 1H), 6.90 (d, *J* = 4.0 Hz, 1H), 6.71 (s, 1H), 6.68 (s, 1H), 5.18 (s, 2H), 2.42 (s, 3H); ESI-MS: m/z, 521.0 (M-1).

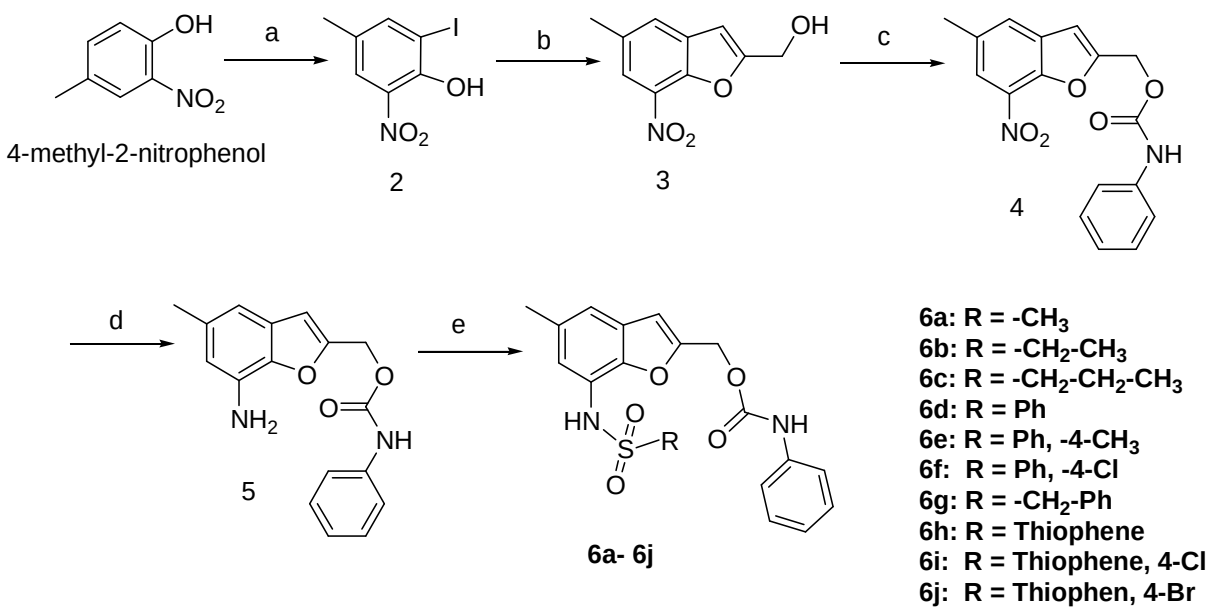
Antimicrobial Activity

The antimicrobial activity was determined using disc diffusion method by measuring zone of inhibition in mm. All the compounds, **6a-6j** were screened *in-vitro* at a concentration of 100 µg/mL for antibacterial activity against two Gram-positive (*Staphylococcus aureus* and *Staphylococcus pyogenes*) and two Gram-negative strains (*Escherichia coli* and *Pseudomonas aeruginosa*). Standard antibacterial drug ciprofloxacin (100 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**.

RESULTS AND DISCUSSION

Scheme 1 depicts the synthetic strategy of novel Benzo[b]furan derivatives **6a-6j.** 4-methyl-2-nitrophenol was iodinated using I_2 in presence of aq.10% NaOH at 80 ^oC for 10 h to generate iodide compound **2**. Benzo[b]furan ring **3** formation was accomplished using the protocol reported earlier [21] with slight modification to produce alcohol **3**, we have used piperidine as a base which is inexpensive when compared to s-prollinol. Reaction of benzyl alcohol **3** with benzyl isocyanate in 2-MeTHF in presence of catalytic quantity of pyridine at reflux for 1h resulted in the formation of carbamate derivative **4**. Compound **4** was reduced to corresponding amine derivative **5** in presence of hydrazine hydrate in methanol at reflux for 3 h. Reaction of amine **5** with various sulphonyl chloride in presence of triethylamine in 2-MeTHF at room temperature for 6 hours resulted in the formation of novel benzo[b] furan sulphonyl derivatives **6a – 6j**. During the course of the synthesis of **6a – 6j,** 2-Methyl tetrahydrofuran (2-MeTHF) was used as a choice of solvent, since it is derived from renewable resources such as corncobs and bagasse and offers both economical and environmentally friendly advantages over acetonitrile, dimethyl formamide and tetrahydrofuran [22]. The newly synthesized benzo[b]furan derivatives bearing sulphonamide and phenylcabamate moiety **6a- 6j** were screened to evaluate their antibacterial activity against Gram-positive (*Staphylococcus aureus* and *Staphylococcus pyogenes*) and two Gram-negative strains (*Escherichia coli* and *Pseudomonas aeruginosa*). Most of the compounds were found to display good to moderate antibacterial activity against all the tested bacterial strains. It is evident from the **Table 1,** that among all the compounds tested, sulphonyl derivatives **6e, 6g, 6h, 6i and 6j** showed good to excellent activity, while the remaining derivatives **6a, 6b, 6c** and **6d** showed moderate activity against all the tested bacterial strains.

Scheme 1



Experimental conditions: a) I_2, 10% NaOH, water, 80 ^oC, 10 h; b) propargyl alcohol, piperidine, 5% Pd-C, CuI, TPP, water, reflux, 6 h; c) Phenyl socyanate, pyridine, acetonitrile, 70 ^oC, 4 h; d) $SnCl_4.2H_2O$, ethanol, r.t., 2h; e) RSO_2Cl, TEA, THF, r.t, 6h.

Table 1: Results of Antibacterial Bioassay of Compounds 6a-6j

Compound no.	R	*Gram negative bacteria*		*Gram positive bacteria*	
		E. coli MTCC 443	***P. aeruginosa MTCC 424***	***S.aureus MTCC 96***	***S.poygenes MTCC 442***
6a	CH_3	16	13	14	11
6b	CH_2-CH_3	16	14	13	12
6c	CH_2-CH_2-CH_3	14	13	14	15
6d	Ph	15	13	12	11
6e	Ph, 4-CH_3	23	23	20	19
6f	Ph,4-Cl	--	--	--	--
6g	CH_2-Ph	23	24	20	21
6h	Thiophene	24	22	19	19
6i	Thiophene, 5-Cl	26	25	20	18
6j	Thiophene, 5-Br	25	24	19	18
Standard drug Ciprofloxacin (Conc. 100 µg /mL)		28	26	21	22

CONCLUSION

The newly synthesized benzo[b]furan derivatives bearing sulphonamide and phenylcabamate moiety **6a- 6j** were screened to evaluate their antibacterial activity against Gram-positive (*Staphylococcus aureus* and *Staphylococcus pyogenes*) and two Gram-negative strains (*Escherichia coli* and *Pseudomonas aeruginosa*). Most of the compounds were found to display good to moderate antibacterial activity against all the above tested strains of bacteria. Among all the compounds tested, sulphonyl derivatives **6e, 6g, 6h, 6i** and **6j** showed good to excellent activity, while the remaining derivatives **6a, 6b, 6c** and **6d** showed moderate activity against all the tested bacterial strains.

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