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Synthesis and antimicrobial activity of novel benzo[b]furan derivatives

T. Venkateshwarlu*[1], A. Ravinder Nath[1], K. Prasad Chennapragada[2]

[1]*University College of Technology, Osmania University, Hyderabad-500 007, India*
[2]*Department of Chemistry, JNTU, Kakinada, Andhrapradesh-533003, India*

ABSTRACT

Many 2-arylbenzofuran derivatives are well known to exhibit a broad range of biological activities, including anticancer, antiproliferative, antiviral, antifungal, immunosuppressive, anti-platelet, anti-oxidative, insecticidal, anti-inflammatory, anti-feedant, and cancer preventative activity. The present paper describes the synthesis and antibacterial activity of some novel benzo[b]furan derivatives ***6a -6h*** *(****Scheme 1****) from commercially available 4-methyl-2-nitrophenol as starting material. The newly synthesized benzo[b]furan derivatives* ***6a- 6h*** *compounds were screened to evaluate their antibacterial activity. Most of the compounds were found to display good to moderate antibacterial activity against different strains of bacteria, it was observed that among all the compounds tested, sulphonyl derivatives* ***6b****,* ***6d****,* ***6e****,* ***6f****,* ***6g*** *and* ***6h*** *showed good to excellent activity, while the carbonyl derivatives* ***6a*** *and* ***6c*** *showed least activity against all the tested bacterial strains.*

Keywords: Benzo[b]furan, 2-MeTHF, antibacterial activity, Gram-positive bacteria, Ciprofloxacin

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INTRODUCTION

Infectious diseases have been serious and growing threatens to human health during the past few decades [1,2]. As pathogenic bacteria continuously evolve mechanisms of resistance to currently used antibacterials, so the discovery of novel and potent antibacterial drugs is the bestway to overcome bacterial resistance and develop effective therapies [3]. Despite the many antibiotics and chemotherapeutics available, the emergence of old and new antibiotic-resistant bacterial strains in the last decades constitutes a substantial need for new classes of anti-bacterial agents [4].

The benzo[*b*]furan nucleus is widespread in a variety of biologically active natural and unnatural compounds [5], and used in cosmetics [6] and as synthetic pharmaceuticals [7,8]. Moreover, benzo[b]furans build blocks for fluorescent sensors [9] and are used as optical brighteners. Especially, benzo[*b*]furan ring systems bearing various substituents at the C-2 position are widely distributed in nature and have been reported to have antiviral, antioxidant and antifungal activities [10, 11]. Many 2-arylbenzofuran derivatives are well known to exhibit a broad range of biological activities, including anticancer [12], antiproliferative [13], antiviral [14], antifungal [15], immunosuppressive [16], antiplatelet [17], antioxidative [18], insecticidal [19], anti-inflammatory [20], antifeedant [21], and cancer preventative activity [22]. These compounds are also important calcium blockers [23] and phytoestrogens [24].

These observations have encouraged us to synthesize some new products containing the benzo[b] furan moiety hoping to obtain new compounds with potential biological activity. In addition all the newly synthesized benzo[b] furan derivatives (**Scheme 1**) were screened for their *in vitro* antimicrobial activity.

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.

*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).

*(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).

*(5-methyl-7-nitrobenzofuran-2-yl)methyl benzylcarbamate (**4**)*
A solution of compound **3** (0.5 g, 2.41 mmol) containing benzyl isocyanate (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: 0.55g, 70 %, m.p.103-105 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.0 (s, 1H), 7.68 (s, 1H), 7.42-7.22 (m, 5 H), 6.82 (s, 1H), 5.24 (s, 2H), 5.10 (br.s, 1H), 4.38 (d, *J* = 6.8 Hz), 2.56 (s, 3 H); EI-MS: m/z (rel.abund.%) 339.2 (M+, 100).

*(7-amino-5-methylbenzofuran-2-yl)methyl benzylcarbamate (**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: 50%; m.p. 65-67 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.22 (m, 5 H), 6.78 (s, 1H), 6.62 (s, 1H), 6.42 (s, 1H), 5.22 (s, 2H), 5.10 (br.s, 1H), 4.38 (d, *J* = 6.8 Hz, 2H), 3.85 (br.s, 2H), 2.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 24.7, 45.6, 57.1, 105.0, 110.3, 111.9, 126.8, 127.0 (2C), 128.6 (2C), 129.9, 130.2, 132.4, 138.9, 141.7, 152.5, 156.3; EI-MS: m/z (rel.abund.%) 310.2 (M+, 100).

General experimental procedure for the preparation of 6a-6h
A mixture of compound **5** (0.1 g, 0.322 mmol), acid chlorides or 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 66 and 85%.

*{5-methyl-7-[(acetyl)amino]-1-benzofuran-2-yl}methyl benzylcarbamate (**6a**)*
Yellow solid, Yield: 66%; m.p. 105-106 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.0 (s, 1H), 7.65 (br.s, 1H), 7.40-7.20 (m, 5H), 7.0 (s, 1H), 6.65 (s, 1H), 5.22 (s, 2H), 5.18 (br.s, 1H), 4.40 (d, *J* = 6.8 Hz, 2H), 3.85 (br.s, 2H), 2.56 (s, 3H), 2.25 (s, 3H); EI-MS: m/z (rel.abund.%) 353.0 (M+, 100).

*{5-methyl-7-[(methylsulfonyl)amino]-1-benzofuran-2-yl}methyl benzylcarbamate (**6b**)*
Yellow solid, Yield: 66%; m.p. 90-92 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.20 (m, 6H), 7.20 (s, 1H), 6.82 (br.s, 1H), 6.60 (s, 1H), 5.22 (s, 2H), 5.18 (br.s, 1H), 4.40 (d, *J* = 6.8 Hz, 2H), 3.10 (s, 3H), 2.56 (s, 3H), 2.40 (s, 3H); EI-MS: m/z (rel.abund.%) 389.1 (M+, 100).

*{5-methyl-7-[(phenylcarbonyl)amino]-1-benzofuran-2-yl}methyl benzylcarbamate (**6c**)*
Yellow solid, Yield: 77%; m.p. 114-116 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.0 Hz, 2H), 7.90-7.20 (m, 8H), 7.37 (d, *J* = 7.2 Hz, 2 H), 6.50 (s, 1H), 5.02 (s, 2H), 4.24 (d, *J* = 8.0 Hz, 2 H); EI-MS: m/z (rel.abund.%) 415.1 (M+, 100).

*{5-methyl-7-[(phenylsulfonyl)amino]-1-benzofuran-2-yl}methyl benzylcarbamate (**6d**)*
Yellow solid, Yield: 84%; m.p. 122-124 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.0 Hz, 2H), 7.50-7.20 (m, 8H), 7.02 (d, *J* = 7.2 Hz, 2 H), 6.50 (s, 1H), 5.02 (s, 2H), 4.24 (d, *J* = 8.0 Hz, 2 H); EI-MS: m/z (rel.abund.%) 451.0 (M+, 100).

*{5-methyl-7-[(4-methylphenylsulfonyl)amino]-1-benzofuran-2-yl}methyl benzylcarbamate (**6e**)*
Yellow solid, Yield: 79%; m.p. 118-119 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.28 (s, 1H), 7.88 (t, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 10.6 Hz, 2 H), 7.38-7.20 (m, 8H), 6.82 (d, *J* = 7.2 Hz, 2 H), 5.02 (s, 2H), 4.24 (d, *J* = 8.0 Hz, 2 H), 2.34 (s, 3H), 2.28 (s, 3H); EI-MS: m/z (rel.abund.%) 465.3 (M+, 100).

*{5-methyl-7-[(4-methoxyphenylsulfonyl)amino]-1-benzofuran-2-yl}methyl benzylcarbamate (**6f**)*
Yellow solid, Yield: 85%; m.p. 111-112 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (t, *J* = 8.0 Hz, 1H), 7.64 (d, J = 10.4 Hz, 2 H), 7.40-7.18 (m, 6H), 7.0 – 7.02 (d, *J* = 7.2 Hz, 2 H), 6.82 (d, *J* = 10.2 Hz, 2 H), 5.04 (s, 2H), 4.22 (d, *J* = 8.0 Hz, 2 H), 3.80 (s, 3H), 2.25 (s, 3H); EI-MS: m/z (rel.abund.%) 481.0 (M+, 100).

*{5-methyl-7-[(4-chlorophenylsulfonyl)amino]-1-benzofuran-2-yl}methyl benzylcarbamate (**6g**)*
Yellow solid, Yield: 72%; m.p. 122-124 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (t, *J* = 8.0 Hz, 1H), 7.66 (d, J = 10.4 Hz, 2 H), 7.40-7.18 (m, 6H), 7.0 – 7.02 (d, *J* = 7.2 Hz, 2 H), 6.82 (d, *J* = 10.2 Hz, 2 H), 5.04 (s, 2H), 4.22 (d, *J* = 8.0 Hz, 2 H), 3.80 (s, 3H), 2.25 (s, 3H); EI-MS: m/z (rel.abund.%) 451.2 (M+, 100).

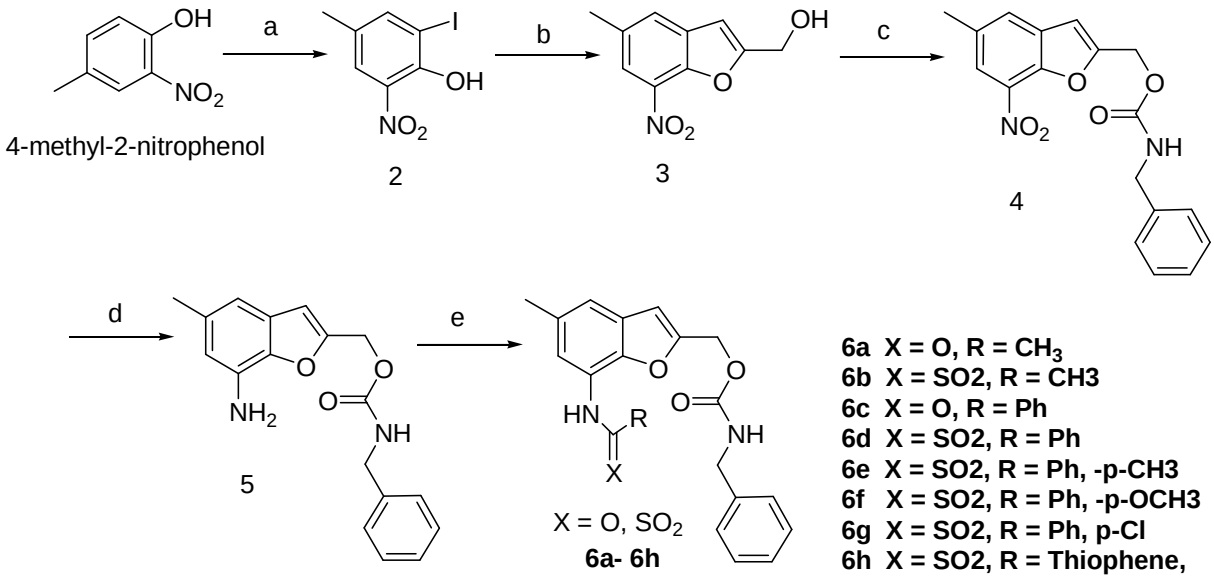
*{5-methyl-7-[(thiophene-2ylsulfonyl)amino]-1-benzofuran-2-yl}methyl benzylcarbamate (**6h**)*
Orange solid, Yield: 75%; m.p. 91-92 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.50 (s, 1H), 7.92-7.84 (m, 4H), 7.50 (dd, *J* = 3.2, 6.6 Hz, 1H), 7.36-7.26 (m, 5H), 7.06 (t, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 10.6 Hz, 2 H), 5.05 (s, 2H), 4.25 (d, *J* = 6.24 Hz, 2 H), 2.30 (s, 3H); EI-MS: m/z (rel.abund.%) 457.0 (M+, 100).

Antimicrobial Activity
The antimicrobial activity was determined using disc diffusion method by measuring zone of inhibition in mm [25]. All the compounds, **6a-6h** 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

Synthesis of novel Benzo[b]furan derivatives **6a-6h** is outline in **Scheme-1**. Iodination of 4-methyl-2-nitrophenol was carried out in presence of aq.10% NaOH at 80 ^{o}C for 10 h to generate iodide compound **2**. Benzo[b]furan ring **3** formation was accomplished using the protocol reported earlier [26] with slight modification to produce alcohol **3**, we have used piperidine as a base which is inexpensive when compared to s-prollinol. Alcohol **3** was reacted with

benzyl isocyanate in presence of catalytic quantity of pyridine in 2-MeTHF at reflux for 1h to obtain carbamate derivative **4**. Reduction of carbamate **4** was done in presence of hydrazine hydrate in methanol at reflux for 3 h to afford key intermediate amino compound **5**. Reaction of amine **5** with corresponding acid chloride/sulphonyl chloride in presence of triethylamine in 2-MeTHF at room temperature for 6 hours resulted in the formation of novel benzo[b] furan derivatives **6a – 6h**. During the course of the synthesis of **6a – 6h,** 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 [27]. The newly synthesized benzo[b]furan derivatives **6a- 6h** compounds were screened to evaluate their antibacterial activity. Most of the compounds were found to display good to moderate antibacterial activity against different strains of bacteria. From the **Table 1,** it was observed that among all the compounds tested, sulphonyl derivatives **6b**, **6d**, **6e**, **6f**, **6g** and **6h** showed good to excellent activity, while the carbonyl derivatives **6a** and **6c** showed least activity against all the tested bacterial strains.



Scheme 1; Reagents and Conditions: a) I_2, aq. 10% NaOH, 80 ^oC, 10 h; b) propargyl alcohol, piperidine, 5% Pd-C, CuI, TPP, water, reflux, 6 h; c) Benzyl isocyanate, pyridine, 2-MeTHF, reflux, 1 h; d) NH2.NH2, methanol, reflux, 3 h; e) i. RCOCl, TEA,2-Me-THF, r.t, 6 h; ii. RSO_2Cl, TEA, 2-MeTHF, r.t, 6h.

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

Compound no.	X	R	*Gram negative bacteria*		*Gram positive bacteria*	
			E. coli MTCC 443	*P. aeruginosa MTCC 424*	*S.aureus MTCC 96*	*S.poygenes MTCC 442*
6a	O	$-CH_3$	15	12	14	11
6b	SO_2	$-CH_3$	28	22	20	19
6c	O	Ph	14	11	10	10
6d	SO_2	Ph	24	22	19	20
6e	SO_2	Ph, 4-CH_3	25	23	19	19
6f	SO_2	Ph, 4-OMe	28	27	21	20
6g	SO_2	Ph,4-Cl	23	24	17	21
6h	SO_2	Thiophene	26	24	19	20
Standard drug Ciprofloxacin (Conc. 100 µg /mL)	Standard drug Ciprofloxacin		28	26	21	22

CONCLUSION

Novel benzo[b]furan analogs **6a – 6h** were prepared from 4-methyl-2-nitrophenol as starting material and tested for Gram positive and Gram Negative bacterial cultures. The newly synthesized benzo[b]furan derivatives **6a- 6h** compounds were screened to evaluate their antibacterial activity. Most of the compounds were found to display

good to moderate antibacterial activity against different strains of bacteria; it was observed that among all the compounds tested, sulphonyl derivatives **6b**, **6d**, **6e**, **6f**, **6g** and **6h** showed good to excellent activity, while the carbonyl derivatives **6a** and **6c** showed least activity against all the tested bacterial strains.

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