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Synthesis, Characterization and Antimicrobial Activities of 1-((5-Bromobenzofuran-2yl)methyl)-4-substituted phenyl-1*H*-1,2,3-triazoles

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A synthesis of useful intermediate, 2-(azidomethyl)-5-bromobenzofuran starting from 5-bromobenzofuran-2-carboxylic acid is described. The reaction of 5-bromo-2-(iodomethyl)benzofuran with sodium azide affords 2-(azidomethyl)-5-bromobenzofuran. 5-Bromo-2-(iodomethyl)benzofuran was obtained from a combination of consecutive 5-bromobenzofuran-2-carboxylic acid reactions involving $NaBH_4$ reduction followed by the iodination of the resulting alcohol. The utility of 2-(azidomethyl)-5-bromobenzofuran has been demonstrated for the preparation of a novel series of 1-((5-bromobenzofuran-2-yl-)methyl)-4-substituted phenyl-1*H*-1,2,3-triazoles in excellent yields. The newly synthesized compounds have been characterized and evaluated for antimicrobial activities against Gram-negative and Gram-positive bacterial strains.

Keywords: 2-(Azidomethyl)-5-bromobenzofuran, Substituted benzofuran, Triazole, Antimicrobial activity, Antibacterial activity.

INTRODUCTION

Benzofuran derivatives are the scaffolds of many natural products and several complex structures. Benzofuran ring is a part of a range of synthetic as well as natural compounds which have diverse biological activities and are used as pharmacological agents [1]. Well-known natural compounds isolated from various plant species, *e.g. Krameria ramosissima*, *Machilus glaucescens*, *Ophryosporus lorentzii*, *Ophryosporus charua* and *Zanthoxylum ailanthoidol* contain benzofuran rings as part of their complex structure with different C-2 substitutes. The most commonly known benzofurans are amiodarone, ailanthoidol and bufuralol. Ailanthoidol is a neolignan isolated from *Zanthoxylum ailanthoides* containing a 2-arylbenzofuran skeleton. Neolignans and lignans display different forms of biological activity, such as immunosuppressive, anticancer, antiviral, antioxidant, antifeeding and antifungal activity [2]. 2-Substituted benzofurans have gained a greater attention due to their anti-HIV activity [3], anticancer and antimicrobial activity [4-7]. Keto benzofuran derivatives, such as amiodarone and benziodarone, are used in the treatment of cardiovascular disease pathological syndromes such as arrhythmia [8]. Some benzofurans have anticonvulsant and anti-inflammatory effects, while some of the amino-benzofurans display antiarrhythmic activity [9]. The most prominent benzofurans are amiodarone, angelicin, xanthotoxin, bergaptene, nodekenetin and usnic acid compound [1,10].

Human struggles with microbial agents are never-ending. Day after day, dangerous microbes are becoming resistant to the wide variety of chemotherapeutic antibacterial agents in use. This envisages the need to design and create new chemotherapeutic agents. Several benzofuran ring systems with various C-2 substituents are found to be extensive in nature. For example, 2-arylbenzofuran has been isolated from a Chinese herbal plant showing a wide range of biological activities [11]. Benzofuran ring carrying the other five-membered heterocyclic rings such as thiazole ring displayed interesting pharmacological activity [11]. It is therefore, worthwhile to synthesize new benzofruan compounds carrying rings such as tirazole, which display promising resistance and strong inhibitory action.

Keeping in view of all the above observations and in the continuation of our research interest [12-14] on various five-membered heterocyclic compounds, herein the benzofuran moiety was combined with the triazole ring to synthesize

5-bromobenzofuran substituted 1,2,3-triazoles and also screened for their antimicrobial activitives.

EXPERIMENTAL

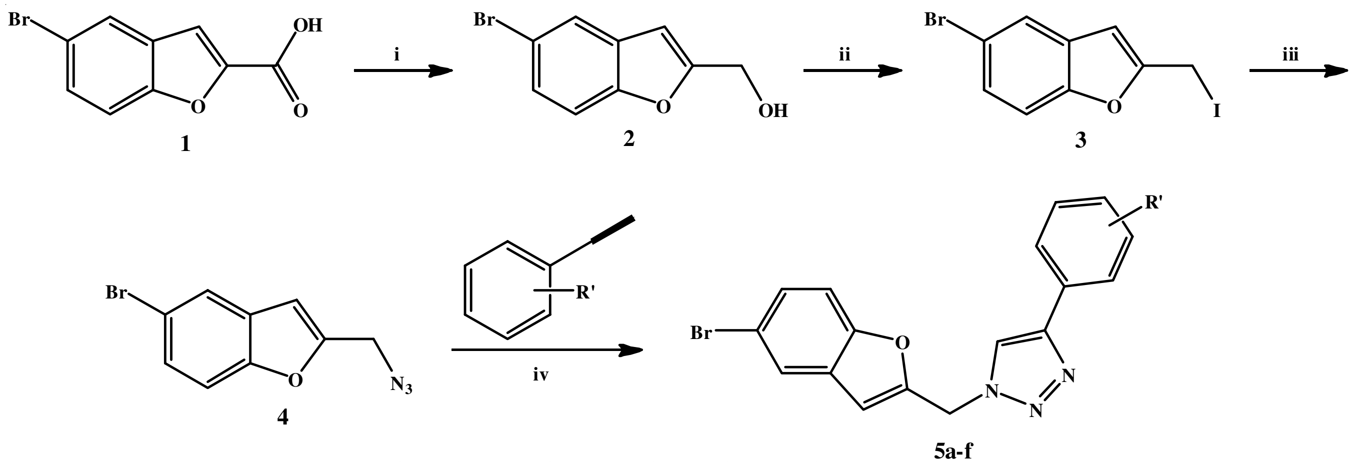
Miscellaneous chemicals were used as obtained and the solvents were purified in compliance with normal pre-use procedures. The melting points were determined in the open capillaries of the Mel-Temp apparatus and are uncorrected. For thin-layer chromatographic analysis, Merck pre-coated plates (60G F_{254} silica gel) were used with ethyl acetate-hexane, 3:5 as an eluting solvent. The IR spectra were recorded on a Perkin-Elmer FT-IR spectrometer as KBr pellets. The NMR spectra of the proton were recorded on the Bruker 400 MHz machine. The ^{13}C NMR spectra were recorded on the Bruker 100 MHz spectrometer in $CDCl_3$/DMSO-d_6. Chemical shifts in ppm were recorded using TMS as an internal standard. The mass spectra were obtained on the mass spectrometer VG 7070G. Microanalyses were performed on the Perkin-Elmer 240C elementary analyzer.

The starting compound, 5-bromo-benzofuran-2-carboxylic acid (**1**) was obtained from DENISCO Chemicals Pvt. Ltd., Hyderabad, India. 5-Bromobenzofuran-2-carboxylic acid (**1**) was converted to 2-(azidomethyl)-5-bromobenzofuran (**4**) in three steps by known method [15]. The steps involved in the synthesis of title compounds are shown in **Scheme-I**.

Synthesis of (5-bromobenzofuran-2-yl)methanol (2): 5-Bromobenzofuran-2-carboxylic acid (1 equiv.) (2.4 g, 0.01 mmol) in THF (10 mL) was stirred while cooling in a freezing mixture to maintain a temperature of -15 ºC for around 30 min. Then, triethylamine (1.2 equiv.) (1.68 mL, 0.01 mmol) and ethylchloroform (1.2 equiv.) (1.19 mL, 0.01 mmol) were added successively with a difference of 5 min and stirred for about another 10 min. The filtrate was cooled down to 0 ºC and treated with $NaBH_4$ (2 equiv.) (0.79 g, 0.02 mmol). Few drops of water were added and stirred for around 5-10 min. TLC monitored the progress of the reaction until the starting materials had vanished. The resulting solution was concentrated under reduced pressure and then dissolved in ethyl acetate followed by washing successively with 5% HCl, 5% Na_2CO_3 solution, water (2 × 30 mL) and brine solution. The ethyl acetate layer was collected, dried over anhydrous Na_2SO_4 and finally concentrated under reduced pressure. The separated solid mass was collected, dried and recrystallized from ethanol to obtain compound **2**. Yield 78%; m.p.: 115-116 ºC. IR (KBr, ν_{max}, cm^{-1}): 3425 (OH *str.* in alcohol), 3030 (arom. CH *str.*), 2930 (CH *str.* in aliphatics). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.821 (s, 1H, OH); 5.442 (s, 2H, CH_2) 7.131 (d, 1H, J = 9.2 Hz, H7); 7.660 (dd, 1H, J = 2.4, 6.4 Hz, H6); 8.076 (d, 1H, J = 2.4 Hz, H4); 8.942 (s, 1H, H3).

Synthesis of 5-bromo-2-(iodomethyl)benzofuran (3): A solution of imidazole (5 equiv.) (4.53 g, 0.06 mmol) in dry DCM (10 mL), PPh_3 (5 equiv.) (21.99 g, 0.06 mmol) was added and stirred at room temperature for around 20 min. The solution was brought to 0 ºC and I_2 (3 equiv.) (0.03 mmol) was added in portions for 30 min. The resulting mixture was vigorously stirred for 10 min and finally, (5-bromobenzofuran-2-yl)-methanol (**2**) (1 equiv.) (2.26 g) was added and kept in stirring overnight. Progress of the reaction was monitored by the TLC. The solution was concentrated under reduced pressure. The resultant mass was purified by column chromatography using 1:9 ethyl acetate and *n*-hexane. The solid mass separated out was collected and dried to obtain compound **3**. Yield 82%; m.p.: 122-123 ºC. IR (KBr, ν_{max}, cm^{-1}): 3060 (arom. CH *str.*), 2930 (CH *str.* in aliphatics). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 5.082 (s, 2H, CH_2) 7.131 (d, 1H, J = 9.2 Hz, H7), 7.662 (dd, 1H, J = 2.4, 6.4 Hz, H6), 8.078 (d, 1H, J = 2.4 Hz, H4), 8.943 (s, 1H, H3).

Synthesis of 2-(azidomethyl)-5-bromobenzofuran (4): Sodium azide (2 equiv.) (0.2 g, 0.003 mmol) was added to a 5-bromo-2-(iodomethyl)benzofuran solution (**3**) (1 equiv.) (0.33 g, 0.001 mmol) in DMF (3 mL) and stirred at room temperature for about 3 h. The progress of the reaction was monitored by TLC until the initial materials were disappeared. The solution was dissolved in DCM and water, stirring vigorously for around



R' = (a) -H, (b) 4-CH_3, (c) 4-OCH_3, (d) 4-Cl, (e) 4-NO_2, (f) 2-Cl

(i) TEA, ECF, THF, -15 °C, 30 min, $NaBH_4$, H_2O, 0 °C, 5 min
(ii) Imidazole, PPh_3, I_2, dry DCM, over night; (iii) DMF, NaN_3, room temp., 3 h
(iv) $CuSO_4$, sodium ascorbate, room temp., *t*-BuOH + H_2O (1:1) room temp.

Scheme-I: Synthesis of 1-((5-bromobenzofuran-2yl)methyl)-4-substituted phenyl-1*H*-1,2,3-triazoles

15 min. The DCM layer was collected and concentrated under reduced pressure to obtain 2-(azidomethyl)-5-bromobenzofuran (**4**), which was then converted to 1,2,3-triazoles by means of a literature procedure [16].

Synthesis of 1-((5-bromobenzofuran-2-yl)methyl)-4-phenyl-1*H*-1,2,3-triazoles (5a-f): To phenylacetylene (1 equiv.) (0.3 g, 0.002 mmol) taken in a 250 mL round-bottomed flask was added 2-(azidomethyl)-5-bromobenzofuran (**4**) (1.1 equiv.) (0.75 g, 0.003 mmol) in *t*-BuOH (120 mL), H_2O (40 mL), sodium ascorbate (10 mol) (0.05 g, 0.0002 mmol) and $CuSO_4{\cdot}5H_2O$ (5 mol) (0.02 g, 0.0001 mmol). The solution was stirred for about 30 min. The progress of the reaction was monitored by TLC. The reaction mixture was then filtered through a celite pad to remove the salts and washed thoroughly with ethyl acetate (3 × 25 mL). The isolated product was then isolated by washing water (1 × 30 mL) followed by brine water (1 × 30 mL). The product was purified by chromatography using 60% EtOAc in hexane) to yield traizole **5a**. Similarly, compounds **5b-f** were also synthesized with the appropriate alkyne in place of phenyl acetylene.

Spectral data

1-((5-Bromobenzofuran-2-yl)methyl)-4-phenyl-1*H*-1,2,3-triazole (5a): Yield 82%; m.p: 151-152 ºC. IR (KBr, ν_{max}, cm^{-1}): 3060 (arom. CH *str.*), 2960, 2820 (asym./sym. CH *str.* in aliphatics), 1582 (N=N *str.* in triazole ring). ^1H NMR (DMSO-d_6, 400 MHz): δ 5.60 (s, 2H, CH_2), 7.131 (d, 1H, *J* = 9.2 Hz, H7), 7.38-7.00 (m, 3H, phenyl ring), 7.52 (m, 2H, phenyl ring), 7.663 (dd, 1H, *J* = 2.4, 6.4 Hz, H6), 7.73 (s, 1H, triazole ring), 8.077 (d, 1H, *J* = 2.4 Hz, H4), 8.942 (s, 1H, H3). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 149.4, 148.2, 145.5, 144.1, 139.5, 131.5, 130.3, 130.3 (2C), 127.6, 125.9, 119.3, 112.9, 102.5, 101.5, 53.1. LCMS *m/z*: 354.03 [M+H], (353.02); Anal. calcd. (found) % for $C_{17}H_{12}N_3OBr$: C, 57.65 (56.51); H, 3.41 (3.35); N, 11.86 (11.74).

1-((5-Bromobenzofuran-2-yl)methyl)-4-*p*-tolyl-1*H*-1,2,3-triazole (5b): Yield 76%; m.p.: 139-140 ºC. IR (KBr, ν_{max}, cm^{-1}): 3064 (arom. CH *str.*), 2930 (CH *str.* in aliphatics), 1582 (N=N *str.* in triazole). ^1H NMR (DMSO-d_6, 400 MHz): δ 2.21 (s, 3H, CH_3), 5.58 (s, 2H, CH_2), 7.131 (d, 1H, *J* = 9.2 Hz, H7), 7.24 (dd, 2H, *J* = 7.4 Hz phenyl ring), 7.40 (s, 1H, triazole ring), 7.663 (dd, 1H, *J* = 2.4, 6.4 Hz, H6), 7.86 (dd, 2H, *J* = 7.2 Hz phenyl ring), 8.077 (d, 1H, *J* = 2.4 Hz, H4), 8.942 (s, 1H, H3). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 148.8, 146.8, 145.2, 144.3, 139.4, 130.2, 129.5, 127.5, 126.6, 124.5, 118.1, 112.1, 101.6, 101.2, 53.3 (CH_2), 21.2 (CH_3). LCMS *m/z*: 368.03 [M+H], (367.03); Anal. calcd. (found) % for $C_{18}H_{14}N_3OBr$: C, 58.71 (57.42); H, 3.83 (3.71); N, 11.41 (11.30).

1-((5-Bromobenzofuran-2-yl)methyl)-4-(4-methoxyphenyl)-1*H*-1,2,3-triazole (5c): Yield 77%; m.p.: 138-139 ºC. IR (KBr, ν_{max}, cm^{-1}): 3053 (arom. CH *str.*), 2925 (CH *str.* in aliphatics), 1586 (N=N *str.* in triazole). ^1H NMR (DMSO-d_6, 400 MHz): δ ^1H NMR (400 MHz, DMSO-d_6): δ 3.76 (s, 3H, OCH_3), 5.57 (s, 2H, CH_2), 6.96 (d, 2H, phenyl ring), 7.1315 (d, 1H, *J* = 9.2 Hz, H7), 7.42 (s, 1H, triazole ring), 7.663 (dd, 1H, *J* = 2.4, 6.4 Hz, H6), 7.74 (d, 2H, phenyl ring), 8.077 (d, 1H, *J* = 2.4 Hz, H4); 8.942 (s, 1H, H3). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 159.3, 149.4, 148.2, 144.8, 143.1, 139.5, 130.5, 127.6 (2C), 121.8, 118.9, 113.1(2C), 112.4, 101.9, 101.6, 53.4, 55.2. LCMS *m/z*: 384.13 [M+H], (383.03); Anal. calcd. (found) % for $C_{18}H_{14}N_3O_2Br$: C, 56.27 (55.68); H, 3.67 (3.56); N, 10.94 (10.82).

1-((5-Bromobenzofuran-2-yl)methyl)-4-(4-chlorophenyl)-1*H*-1,2,3-triazole (5d): Yield 75%; m.p.: 158-159 ºC. IR (KBr, ν_{max}, cm^{-1}): 3052 (arom. CH *str.*), 2924 (CH *str.* in aliphatics), 1582 (N=N *str.* in triazole). ^1H NMR (400 MHz, DMSO-d_6): δ 5.56 (s, 2H, CH_2), 7.131 (d, 1H, *J* = 9.2 Hz, H7), 7.62 (d, 2H, *J* = 7.6 Hz, phenyl ring), 7.663 (dd, 1H, *J* = 2.4, 6.4 Hz, H6), 7.70 (s, 1H, triazole ring), 7.79 (d, 2H, *J* = 7.6 Hz, phenyl ring), 8.077 (d, 1H, *J* = 2.4 Hz, H4), 8.942 (s, 1H, H3). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 149.6, 148.5, 144.5, 142.8, 139.6, 133.6, 131.0, 130.6, 130.2, 129.2, 120.2, 112.6, 101.8, 101.5, 53.8. LCMS *m/z*: 387.98 [M+H], (386.98); Anal. calcd. (found) % for $C_{17}H_{11}N_3OBrCl$: C, 52.54 (51.61); H, 2.85 (2.79); N, 10.81 (10.72).

1-((5-Bromobenzofuran-2-yl)methyl)-4-(4-nitrophenyl)-1*H*-1,2,3-triazole (5e): Yield 74%; m.p.: 186-187 ºC. IR (KBr, ν_{max}, cm^{-1}): 3056 (arom. CH *str.*), 2924 (CH *str.* in aliphatics), 1585 (N=N *str.* in triazole). ^1H NMR (400 MHz, DMSO-d_6): δ 5.54 (s, 2H, CH_2); 7.131 (d, 1H, *J* = 9.2 Hz, H7), 7.663 (dd, 1H, *J* = 2.4, 6.4, 2.4, H6), 7.68 (s, 1H, triazole ring), 7.92 (d, 2H, *J* = 8.0 Hz, phenyl ring), 8.077 (d, 1H, *J* = 2.4 Hz, H4); 8.23 (d, 2H, *J* = 8.0 Hz, phenyl ring), 8.942 (s, 1H, H3). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 149.5, 148.9, 147.9, 144.4, 143.2, 140.5, 134.4, 130.0, 127.3, 125.2, 119.5, 112.2, 101.3, 101.2, 54.2. LCMS *m/z*: 399.12 [M+H], (398.00); Anal. calcd. (found) % for $C_{17}H_{11}N_4O_3Br$: C, 51.15 (51.04); H, 2.78 (2.64); N, 14.03 (14.04).

1-((5-Bromobenzofuran-2-yl)methyl)-4-(2-chlorophenyl)-1*H*-1,2,3-triazole (5f): Yield 71%; m.p.: 229-230 ºC. IR (KBr, ν_{max}, cm^{-1}): 3052 (arom. CH *str.*), 2925 (CH *str.* in aliphatics), 1582 (N=N *str.* in triazole). ^1H NMR (400 MHz, DMSO-d_6): δ 5.52 (s, 2H, CH_2), 7.1315 (d, 1H, *J* = 9.2 Hz, H7), 7.30-7.52 (m, 5H; 4H of phenyl ring; 1H of triazole ring), 7.663 (dd, 1H, *J* = 2.4, 6.4 Hz, H6), 8.077 (d, 1H, *J* = 2.4 Hz, H4); 8.942 (s, 1H, H3). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 148.9, 148.1, 145.0, 144.2, 140.3, 132.4, 131.5, 130.5, 129.6, 128.9, 128.4, 127.2, 119.4, 112.6, 102.2, 101.4, 53.5. LCMS *m/z*: 387.98 [M+H], (386.98); Anal. calcd. (found) % for $C_{17}H_{11}N_3OBrCl$: C, 52.54 (51.52); H, 2.85 (2.75); N, 10.81 (10.68).

Biological assays: Triazole benzofuran derivatives **(5a-f)** were dissolved in dimethyl sulphate at 100 µg/mL concentration. The composition of nutrient agar medium was yeast extract (5 g), NaCl (10 g), bactotryptone (10 g), with a final pH of 7.4. Triazole benzofuran derivatives were tested against two Gram-negative strains *viz*. *Escherichia coli*, *Pseudomonas aeruginosa* and two Gram-positive strains *viz. Staphylococcus aureus*, *Streptococcus pyogenes* using the agar disc diffusion method [17,18]. After 18 h, the exponentially growing cultures of the four bacteria in nutrient broth at 37 ºC were diluted in sterile broth. From each of these diluted cultures, 1 mL was added to 100 mL sterilized and cooled nutrient agar media to give a final bacterial count of 1×10^6 cell/mL. The plates were set at room temperature and later dried at 37 ºC for 20 h. Paper discs (6 mm, punched from Whatman no 41 paper) were sterilized under UV irradiation and used for the assays. Discs were soaked in 100 μg/mL concentration of the test solution and placed on the inoculated agar media at regular intervals of 6-7 cm. The plates were incubated at 37 ºC in an inverted fashion. All the samples were tested thrice and the mean zone of inhibition were measured.

RESULTS AND DISCUSSION

The title compounds, 1-((5-bromobenzofuran-2yl)methyl)-4-substituted phenyl-1*H*-1,2,3-triazoles were synthesized and characterized successfully. A reactive intermediate (5-bromobenzofuran-2-yl)methanol **(2)** was synthesized by the reduction of 5-bromobenzofuran-2-carboxylic acid (**1**) with sodium borohydride in THF at -15 ºC in presence of triethylamine and ethyl chloroformate. The disappearance of signal for carboxylic proton in compound **1** and the appearance of signals at δ 2.82 and 5.44 ppm, respectively for OH and CH_2 protons along with the signals for four protons of benzofuran ring in ^{1}H NMR confirms the formation of compound **2**.

Iodination of compound **2** with iodine in the presence of imidazole and PPh_3 in dry DCM at 0 ºC at room temperature results in the formation of 5-bromo-2-(iodomethyl)benzofuran **(3)** at approximately 82% of the yield. The disappearance of the signal corresponding to the alcohol proton of OH in both the IR and ^{1}H NMR spectra of compound **3** confirms its formation. 2-(Azidomethyl)-5-bromobenzofuran (**4**) was obtained by the addition of NaN_3 to a solution of 5-bromo-2-(iodomethyl)benzofuran (**3**) in DMF at room temperature.

Finally, 1-(5-Bromobenzofuran-2-yl)methyl)-4-phenyl-1*H*-1,2,3-triazole (**5a**) was synthesized in a 1,3-dipolar cycloaddition reaction of azide and terminal alkyne in a Click reaction. The reaction of 2-(azidomethyl)-5-bromobenzofuran (**4**) with substituted phenylacetylene in the presence of $CuSO_4$ and the catalytic amount of sodium ascorbate in the solvent mixture of *t*-BuOH and H_2O at room temperature leads to the formation of 1-(5-bromobenzofuran-2-yl)methyl)-4-phenyl-1*H*-1,2,3-triazole (**5a**). In the same manner, compounds **5b-f** were synthesized by the reaction of azide **4** with appropriate substituted phenylacetylene. The formation of these compounds has been confirmed by the appearance of a single proton singlet in ^{1}H NMR at around δ 7.7 ppm corresponding to the triazole ring proton along with the signals for newly introduced aromatic ring protons. The IR, ^{1}H & ^{13}C NMR and mass spectral data aslo confirmed the successful formation of the synthesized compounds.

Antimicrobial activity: Compounds **5a-f** showed good antibacterial activity against the bacteria tested. Among the synthesized compounds **5d**, **5e** and **5f** were found to be more active than the other compounds. The results of the antimicrobial activity are shown in Table-1. Compounds with -Cl and $-NO_2$ substituents are found to be much more active than others.

Conclusion

A reactive intermediate 2-(azidomethyl)-5-bromobenzofuran had been successfully synthesized and employed for the synthesis of a new sequence of 1-(5-bromobenzofuran-2-yl)-methyl)-4-substituted phenyl-1*H*-1,2,3-triazoles in good yields. The structures of all the synthesized compounds have been established by IR, NMR and mass spectral analysis. All the compounds exhibited good antibacterial activity against both Gram-positive (*S. aureus* and *S. pyogenes*) and Gram-negative (*E. coli* and *P. aeruginosa*) bacterial strains and those with electron withdrawing groups like -Cl and $-NO_2$ being much more potent.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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TABLE-1
ANTIBACTERIAL SCREENING DATA OF THE 1-((5-BROMOBENZOFURAN-2-YL)METHYL)-4-SUBSTITUTED PHENYL-1*H*-1,2,3-TRIAZOLES (**5a-f**)

Compound No.	1-((5-Bromobenzofuran-2yl-)-methyl)-4-substituted phenyl-1*H*-1,2,3-triazoles	Zone of inhibition (mm)			
		Gram-negative bacteria		Gram-positive bacterial	
		E. coli	*P. aeruginosa*	*S. aureus*	*S. pyogenes*
5a	-H	16	16	15	16
5b	4'-CH_3	19	17	17	18
5c	4'-OCH_3	18	16	16	18
5d	4'-Cl	21	20	19	22
5e	4'-NO_2	23	21	20	23
5f	2'-Cl	22	20	21	20
Standard drug	Gentamicin (10 μg/mL of DMSO)	28	29	29	30

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