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Synthesis and Antibacterial Activity of Some {6-[(1*H*-1,2,3-Triazol-4-yl)methoxy]-3-methylbenzofuran-2-yl}(4-bromophenyl)methanone Derivatives[1]

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Abstract—A series of novel benzofuran−1,2,3-triazole hybrid heterocyclic molecules were synthesized using a click chemistry approach. The structure of the synthesized compounds was assessed by IR and NMR spectroscopy and mass spectrometry. The products showed moderate to high activity against gram-positive and gram-negative bacteria.

Keywords: benzofuran, 1,2,3-triazoles, click chemistry, antibacterial activity

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INTRODUCTION

Benzofurans belong to one of the most studied structural units in both synthetic and medicinal chemistry. They are known to be present in many natural products and have found application as agrochemicals [1], hypnotics [2], cosmetics [3], and pharmaceuticals [4–6]. Benzofuran derivatives possess diverse pharmacological and biological activities, including antibacterial [7], antifungal [8], anti-inflammatory [9], anti-HIV [10], antitubercular [11], antidiabetic [12], antidepressant, anticonvulsant [13], and analgesic effects. Benzofuran is a promising pharmacophore for drug discovery, and a large number of synthetic methodologies for its derivatives have been developed.

In recent years, the chemistry of triazoles has received considerable attention due to their synthetic and biological importance. The triazole nucleus is incorporated into a wide range of therapeutically interesting antibacterial [14], antifungal [15], anti-inflammatory [14], antiviral [16], antitubercular [17], anticancer [18], and cytotoxic [19] drug candidates. 1,4-Disubstituted 1,2,3-triazoles have been recently employed as amide mimics [20, 21], with a higher binding affinity to receptors. 1,2,3-Triazoles possess a remarkable metabolic stability, and they were used as amide surrogates in various bioactive compounds [22].

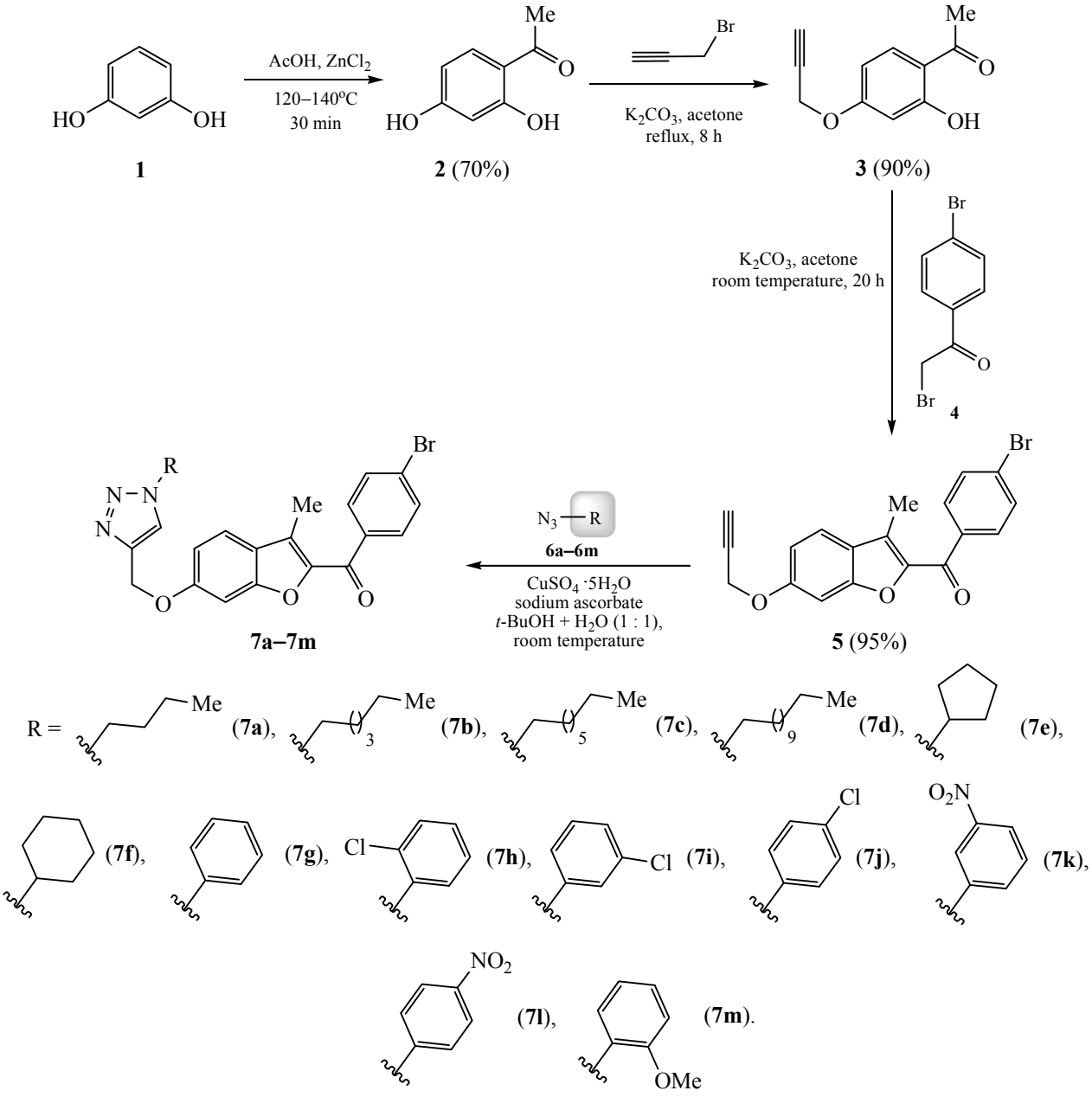
In a continuation of our previous work [7], we synthesized a series of novel hybrid molecules which contain a benzofuran and a 1,2,3-triazole moieties. The purpose of this study was to explore the antibacterial activity of benzofuran-1,2,3-triazole hybrids **7a–7m**, with the aim to develop novel potent antimicrobial agents.

RESULTS AND DISCUSSION

(4-Bromophenyl){3-methyl-6-[1*H*-1,2,3-triazol-4-yl)methoxy]benzofuran-2-yl}me-thanones **7a–7m** were synthesized by a 4-step protocol using known procedures [7]. Resorcinol (**1**) was reacted with acetic acid in the presence of freshly fused $ZnCl_2$ to obtain 1-(2,4-dihydroxyphenyl)ethanone (**2**) in a 70% yield. The selective *O*-alkylation of compound **2** with propargyl bromide in the presence of K_2CO_3 in dry acetone under N_2 for 8 h under reflux gave 1-(2-hydroxy-4-(prop-2-yn-1-yloxy)phenyl)ethanone (**3**) in a 90% yield. The structureof the product was confirmed by the ^{1}H NMR spectrum, which showed a characteristic singlet at δ 12.6 ppm and two doublets at δ 4.71 and 2.53 ppm assignable to a chelated phenolic

[1] The text was submitted by the authors in English.

Scheme 1.



hydrogen of the *o*-OH group, O–CH_2–, and ≡CH, respectively. (4-Bromophenyl)[3-methyl-6-(prop-2-yn-1-yloxy)benzofuran-2-yl]methanone (**5**) was easily prepared by the base-mediated reaction of compound **3** with 2-bromo-1-(4-bromophenyl)ethanone (**4**) for 20 h. The structure of compound **5** was confirmed by the ^{1}H NMR spectrum, which showed a three-proton singlet at δ 2.63 ppm suggesting the presence of the methyl group and a two-proton doublet at δ 4.78 and a one-proton triplet at δ 2.57 ppm assignable for the O–CH_2 and ≡CH groups. In the ^{13}C NMR spectrum of compound **5**, the carbonyl, O-CH_2, –C≡, and ≡CH carbons appeared at δ_C 184.0, 56.2, 76.2, and 77.9 ppm, respectively. The presence of the ν(C=O) band at 1664 cm^{-1} and the absence of the ν(OH) band at 3422 cm^{-1} provides evidence for the formation of compound **5**. Aliphatic and aromatic azide intermediates **6a–6m** were synthesized by published protocol [23]. The target benzofuran–1,2,3-triazole hybrid heterocycles **7a–7m** (see Scheme 1) were synthesized by the cycloaddition of compound **5** to azides **6a–6m** and characterized by means of IR and

Antibacterial activity of compounds **7a–7m**

Comp. no.	Concentration, μg/mL	Zone of inhibition, mm							
		gram-positive bacteria				gram-negative bacteria			
		Micrococcus luteus	Methcillin-resistant *Staphylococcus aureus*	*Bacillus subtilis*	*Bacillus cereus*	*Pseudomonas aeruginosa*	*Klebsiella pneumonia*	*Escherichia coli*	*Proteus vulgaris*
7a	75	18	19	18	20	16	18	21	18
	100	21	21	20	23	18	20	23	21
7b	75	16	17	14	18	14	16	19	16
	100	10	19	17	21	17	19	22	19
7c	75	10	09	10	10	11	09	10	10
	100	12	12	13	13	14	11	13	12
7d	75	9	8	9	8	8	7	7	8
	100	12	11	11	10	11	9	9	10
7e	75	19	20	17	21	17	19	22	19
	100	21	22	19	24	19	21	24	20
7f	75	12	10	11	12	13	10	9	9
	100	15	13	13	15	15	13	11	11
7g	75	8	No activity	No activity	**7**	7	6	No activity	9
	100	11	No activity	No activity	9	10	9	No activity	9
7h	75	27	28	28	29	27	26	30	27
	100	31	32	32	32	30	29	33	30
7i	75	25	28	27	28	25	24	29	26
	100	27	30	29	30	27	26	30	28
7j	75	26	28	28	29	26	25	29	27
	100	27	31	30	31	29	28	31	30
7k	75	24	26	26	28	24	23	28	25
	100	26	28	29	31	26	26	30	27
7l	75	20	21	19	22	18	20	22	19
	100	22	23	21	24	20	22	25	21
7m	75	29	31	31	30	20	28	31	29
	100	32	34	33	33	35	32	34	32
Gentamycin	75	27	31	30	31	28	27	31	29
	100	30	33	33	34	31	30	33	31

NMR spectroscopy and mass spectrometry. The presence of a 1,2,3-triazole fragment in the synthesized compounds is confirmed by the observation of a singlet signal between δ 7.59–7.65 ppm in their ^{1}H NMR spectra.

The synthesized benzofuran-based 1,4-disubstituted 1,2,3-triazoles **7a–7m** were tested for their antibacterial activity in two concentrations (75 and 100 μg/mL) against four gram-positive bacteria (*Micrococcus luteus*, Methcillin-resistant *Staphylococcus aureus*,

Bacillus subtilis, and *Bacillus cereus*) and four gram-negative bacteria (*Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli* and *Proteus vulgaris*) using Gentamycin sulfate as standard drug. The test compounds all displayed potent to moderate inhibitory effects on the growth of the test bacterial strains (see table). Compounds **7h**–**7m** showed the highest activity. It was interesting to note that the compounds with strong electron-donor (MeO), weak electron-acceptor (Cl), and strong electron electron-acceptor (NO_2) groups in the phenyl substituent in the triazole ring proved to be more potent antibacterial agents compared with the compounds with aliphatic substituents in the triazole ring.

EXPERIMENTAL

The melting points were measured in open capillaries and are uncorrected. The IR spectra were recorded on a Perkin–Elmer 337 grating IR spectrophotometer for solid samples pelleted in KBr. The NMR spectra were obtained on Bruker AV-400 and AV-300 NMR spectrometers for $CDCl_3$ solutions. The chemical shifts were measured in ppm against internal TMS. CHN analysis was obtained on Perkin Elmer Model 2400 CHNS elemental analyzer. Electron Spray Ionization (ESI) mass spectra were recorded on a QSTARXL hybrid MS system (Applied Bio Systems) under electro spray ionization. Thin layer chromatography was carried out on Merck TLC silica gel 60 F254 plates. The spots were visualized in UV light at 254 nm or, alternatively, by staining with aqueous basic potassium permanganate. Column chromatography was performed on a Merck silica gel 60A (100–200 mesh). Commercially available reagents were used as supplied, and all solvents were distilled before use. All reactions were performed in an oven-dried glassware.

Synthesis of 1-(2,4-dihydroxyphenyl)ethanone (2). Acetic acid (3 g, 0.05 mol) was added to anhydrous $ZnCl_2$ (6.8 g, 0.05 mol), the mixture was heated at 120°C for 30 min and then resorcinol (5.5 g, 0.05 mol) was added. The reaction mixture was heated at 140°C for 30 min with TLC monitoring of the degree of conversion. After completion of the reaction, the reaction mixture was allowed to warm up to room temperature, poured into an ice-cold water (100 mL), and extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with 20% HCl (50 mL) and saturated $NaHCO_3$ (25 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography, eluent 10% ethyl acetate in ether. Yield 70%, reddish brown needles, mp 142–144°C [7].

Synthesis of 1-[2-hydroxy-4-(prop-2-yn-1-yloxy)-phenyl]ethanone (3). A solution of propargyl bromide (2.34 g, 0.019 mol) in toluene was added dropwise to a well-stirred mixture of a 25 mL solution of 1-(2,4-dihydroxyphenyl)ethanone (**2**) (3 g, 0.019 mol) in dry acetone and K_2CO_3 (2.72 g, 0.019 mol), and the reaction mixture was refluxed for about 8 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled down to room temperature, and excess acetone was evaporated under reduced pressure. The residue was diluted with water (50 mL) and extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine (2×25 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography, eluent 5% ethyl acetate in petroleum ether. Yield 92%, white solid, mp 196–198°C. IR spectrum, ν, cm^{-1}: 3411, 2357, 1640. ^1H NMR spectrum (300 MHz, δ, ppm: 12.6 s (1H), 7.63 d.d (J = 7.05 and 2.3 Hz, 1H), 6.46–6.43 m (2H), 4.71 d (J = 2.3 Hz, 2H), 2.55 s (3H), 2.53 d (J = 2.28 Hz, 1H). ESI+ mass spectrum: *m/z* 191.1 $[M + 1]^+$.

Synthesis of (4-bromophenyl)[3-methyl-6-(prop-2-yn-1-yloxy)benzofuran-2-yl]methanone (5). A mixture of 1-[2-hydroxy-4-(prop-2-yn-1-yloxy)phenyl]-ethanone (**3**) (2 g, 0.010 mol), 2-bromo-1-(4-bromophenyl)ethanone (**4**) (2.89 g, 0.010) (Sigma-Aldrich, 98%), and K_2CO_3 (2.90 g, 0.021 mol) was stirred in acetone (20 mL) at room temperature for 20 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the precipitate that formed was filtered off and washed with acetone (2 × 15 mL), and washings were combined. The solution was concentrated, and the residue was purified by column chromatography, eluent 10% ethyl acetate in petroleum ether. Yield 95%, white solid, mp 178–180°C. IR spectrum, ν, cm^{-1}: 1665 (C=O). ^1H NMR spectrum (300 MHz), δ, ppm: 7.99–7.94 m (2H), 7.69–7.65 m (2H), 7.62–7.58 m (1H), 7.12 d (J = 2.16 Hz, 1H), 7.04 d.d (J = 8.68 and 2.22 Hz, 1H), 4.78 d (J = 2.41 Hz, 2H), 2.63 s (3H), 2.57 t (J = 2.39 Hz, 1H). ^{13}C NMR spectrum, δ_C, ppm: 184.0, 159.0, 155.3, 148.0, 136.7, 131.5, 131.2, 128.2, 127.4, 123.3, 122.1, 114.2, 96.8, 77.9, 76.2, 56.2, 10.2. ESI+ mass spectrum: *m/z* 369 $[M + H]^+$.

Synthesis of (4-bromophenyl){3-methyl-6-[1*H*-1,2,3-triazol-4-yl)methoxy]benzofuran-2-yl}methanone derivatives *(general procedure)*. (4-Bromophenyl)[3-methyl-6-(prop-2-yn-1-yloxy)benzofuran-2-yl]methanone (**5**) (100 mg, 0.271 mmol) was dissolved in 5 mL of 50% aqueous *t*-BuOH, and $CuSO_4 \cdot 5H_2O$ (5 mol %), sodium ascorbate (10 mol %), and azide (0.45 mmol) were added to the solution. The reaction mixture was stirred for 1 h at room temperature. After complete conversion of starting materials into products, as indicated by TLC, the reaction mixture was diluted with water (25 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with brine (2 × 25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (eluent ethyl acetate–petroleum ether, 30-50%) to afford the corresponding (4-bromophenyl){3-methyl-6-[1*H*-1,2,3-triazol-4-yl)methoxy]benzofuran-2-yl}-methanone derivative.

(4-Bromophenyl){6-[1-butyl-1*H*-1,2,3-triazol-4-yl)methoxy]-3-methyl-benzofuran-2-yl}methanone (7a). Yield 85%, white solid, mp 192–194°C. IR spectrum, ν, cm^{-1}: 1661 (C=O). ^{1}H NMR spectrum (400 MHz), δ, ppm: 7.98–7.94 m (2H), 7.76–7.64 m (3H), 7.62–7.57 m (1H), 7.13 d (*J* = 2.15 Hz, 1H), 7.05 d.d (*J* = 8.69, 2.23 Hz, 1H), 5.25 s (2H), 4.36 d (*J* = 8.43 Hz, 2H), 2.64 s (3H), 1.97–1.88 m (2H), 1.38–1.28 m (2H), 0.96-0.88 m (3H). ^{13}C NMR spectrum, δ_C, ppm: 185.3, 159.7, 155.6, 148.4, 143.6, 138.1, 132.4, 129.7, 128.4, 127.5, 123.2, 122.7, 122.0, 114.2, 97.1, 62.7, 50.4, 30.1, 22.2, 13.7, 10.1. ESI+ mass spectrum: *m/z* 468 $[M + H]^+$. Calculated, %. C 58.98; H 4.73; N 8.97. $C_{23}H_{22}BrN_3O_3$. Found, %. C 58.28; H 4.28; N 8.47.

(4-Bromophenyl){6-[1-hexyl-1*H*-1,2,3-triazol-4-yl)methoxy]-3-methyl-benzofuran-2-yl}methanone (7b). Yield 96%, white solid, mp 201–203°C. IR spectrum, ν, cm^{-1}: 1666 (C=O). ^{1}H NMR spectrum (400 MHz), δ, ppm: 8.01–7.96 m (2H), 7.78–7.65 m (3H), 7.65–7.56 m (1H), 7.15 d (*J* = 2.17 Hz, 1H), 7.06 d.d (*J* = 8.68, 2.22 Hz, 1H), 5.27 s (2H), 4.39 t (*J* = 6.51 Hz, 2H), 2.66 s (3H), 2.08–1.99 m (2H), 1.40–1.27 m (4H), 0.98-0.87 m (5H). ^{13}C NMR spectrum, δ_C, ppm: 185.0, 159.6, 155.8, 149.0, 144.0, 137.9, 132.5, 129.8, 128.3, 127.4, 123.5, 122.8, 122.1, 113.0, 97.4, 62.9, 51.5, 32.0, 30.2, 26.5, 22.4, 13.5, 10.2. ESI+ mass spectrum: *m/z* 496 $[M + H]^+$. Calculated, %. C 60.49; H 5.28; N 8.47. $C_{25}H_{26}BrN_3O_3$. Found, %. C 60.01; H 5.03; N 8.15.

(4-Bromophenyl){3-methyl-6-[1-octyl-1*H*-1,2,3-triazol-4-yl)methoxy]benzofuran-2-yl}(4-bromophenyl)methanone (7c). Yield 95%, white solid, mp 210–212°C. IR spectrum, ν, cm^{-1}: 1664 (C=O). ^{1}H NMR spectrum (400 MHz), δ, ppm: 8.02–7.95 m (2H), 7.79–7.64 m (3H), 7.66–7.54 m (1H), 7.15 d (*J* = 2.17 Hz, 1H), 7.07 d.d (*J* = 8.67, 2.23 Hz, 1H), 5.25 s (2H), 4.36 t (*J* = 6.46 Hz, 2H), 2.65 s (3H), 2.01–1.82 m (2H), 1.37–1.16 m (10H), 0.98-0.77 m (3H). ^{13}C NMR spectrum, δ_C, ppm: 185.0, 159.6, 155.8, 149.0, 144.0, 137.9, 132.5, 129.8, 128.3, 127.4, 123.5, 122.8, 122.1, 113.0, 97.4, 62.6, 50.7, 31.8, 30.4, 29.3, 28.7, 26.5, 22.8, 14.3, 10.1. ESI+ mass spectrum: *m/z* 524 $[M + H]^+$. Calculated, %. C 61.83; H 5.77; N 8.01. $C_{27}H_{30}BrN_3O_3$. Found, %. C 61.30; H 5.29; N 7.81.

(4-Bromophenyl){6-[1-dodecyl-1*H*-1,2,3-triazol-4-yl)methoxy]-3-methyl-benzofuran-2-yl}methanone (7d). Yield 90%, white solid, mp 225–227°C. IR spectrum, ν, cm^{-1}: 1667 (C=O). ^{1}H NMR spectrum (400 MHz), δ, ppm: 8.12–8.04 m (2H), 7.62–7.47 m (4H), 7.17 s (1H), 7.05 d (*J* = 8.67 Hz, 1H), 5.28 s (2H), 4.36 t (*J* = 7.18 Hz, 2H), 2.64 s (3H), 2.05–1.83 m (2H), 1.39–1.26 m (18H), 0.99-0.86 m (3H). ^{13}C NMR spectrum, δ_C, ppm: 185.1, 159.8, 155.7, 147.9, 144.0, 137.9, 132.5, 129.6, 128.4, 126.0, 122.9, 122.5, 122.0, 114.1, 96.7, 62.6, 51.3, 33.8, 31.9, 30.4, 29.0, 27.0, 26.6, 24.6, 22.6, 20.2, 17.3, 14.0, 10.0. ESI+ mass spectrum: *m/z* 580 $[M + H]^+$. Calculated, %. C 64.13; H 6.60; N 7.24. $C_{31}H_{38}BrN_3O_3$. Found, %. C 63.81; H 6.47; N 7.06.

(4-Bromophenyl){6-[1-cyclopentyl-1*H*-1,2,3-triazol-4-yl)methoxy]-3-methyl-benzofuran-2-yl}methanone (7e). Yield 88%, white solid, mp 188–190°C. IR spectrum, ν, cm^{-1}: 1668 (C=O). ^{1}H NMR spectrum (400 MHz), δ, ppm: 8.08 d (*J* = 7.27 Hz, 2H), 7.71 s (1H), 7.67–7.49 m (3H), 7.17 s (1H), 7.06 d.d (*J* = 8.66, 1.73 Hz, 1H), 5.28 s (2H), 5.03–4.90 m (1H), 2.65 s (3H), 2.34-2.22 m (2H), 2.15-2.02 m (2H), 1.99–1.88 m (2H), 1.84–1.72 m (2H). ^{13}C NMR spectrum, δ_C, ppm: 185.6, 160.1, 156.0, 148.7, 143.5, 138.1, 132.3, 130.1, 128.0, 127.7, 122.9, 122.0, 121.4, 114.1, 96.8, 62.5, 62.1, 33.4, 24.1, 10.3. ESI+ mass spectrum: *m/z* 480 $[M + H]^+$. Calculated, %. C 60.01; H 4.62; N 8.75. $C_{24}H_{22}BrN_3O_3$. Found, %. C 59.82; H 4.55; N 8.70.

(4-Bromophenyl){6-[1-cyclohexyl-1*H*-1,2,3-triazol-4-yl)methoxy]-3-methyl-benzofuran-2-yl}methanone (7f). Yield 94%, white solid, mp 204-206°C. IR spectrum, ν, cm^{-1}: 1659 (C=O). ^{1}H NMR spectrum (400 MHz), δ, ppm: 8.09–8.00 d (*J* = 6.44 Hz, 2H), 7.67 s (1H), 7.63–7.43 m (3H), 7.15 s (1H), 7.03 d

(*J* = 7.70 Hz, 1H), 5.25 s (2H), 4.44 s (1H), 2.59 s (3H), 2.23 d (*J* = 9.66 Hz, 2H), 1.93–1.87 m (2H), 1.76–1.70 m (3H), 1.46–1.42 m (2H), 1.27–1.23 m (1H). ^{13}C NMR spectrum, δ_C, ppm: 185.7, 160.1, 155.8, 148.4, 143.3, 137.9, 132.6, 130.1, 128.5, 127.8, 123.3, 122.1, 120.8, 114.2, 96.6, 62.7, 60.4, 33.4, 25.3, 25.2, 10.3. ESI+ mass spectrum: *m/z* 494 $[M + H]^+$. Calculated, %. C 60.74; H 4.89; N 8.50. $C_{25}H_{24}BrN_3O_3$. Found, %. C 60.58; H 4.81; N 8.12.

(4-Bromophenyl){3-methyl-6-[1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy]benzofuran-2-yl}(4-bromophenyl)methanone (7g). Yield 88%, white solid, mp 177–179°C. IR spectrum, ν, cm^{-1}: 1669 (C=O). ^{1}H NMR spectrum (400 MHz), δ, ppm: 8.14–8.09 m (3H), 7.80–7.75 m (2H), 7.64–7.60 m (2H), 7.54–7.53 m (3H), 7.49–7.46 m (1H), 7.21 d (*J* = 2.13 Hz, 1H), 7.09 d.d (*J* = 8.68, 2.21 Hz, 1H), 5.40 s (2H), 2.65 s (3H). ^{13}C NMR spectrum, δ_C, ppm: 185.4, 159.7, 155.6, 148.4, 144.4, 138.1, 137.0, 132.4, 130.1, 129.7, 129.1, 128.4, 127.6, 123.4, 122.1, 121.3, 120.8, 114.1, 97.0, 62.7, 10.3. ESI+ mass spectrum: *m/z* 488 $[M + H]^+$. Calculated, %. C 61.49; H 3.72; N 8.60. $C_{25}H_{18}BrN_3O_3$. Found, %. C 61.26; H 3.66; N 8.54.

(4-Bromophenyl)(6-{1-(2-chlorophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}-3-methylbenzofuran-2-yl)-methanone (7h). Yield 82%, white solid, mp 217–219°C. IR spectrum, ν, cm^{-1}: 1656 (C=O). ^{1}H NMR spectrum (400 MHz), δ, ppm: 8.10 s (1H), 8.06 d (*J* = 7.17 Hz, 2H), 7.68–7.44 m (7H), 7.21 d (*J* = 2.10 Hz, 1H), 7.09 d.d (*J* = 8.70, 2.10 Hz, 1H), 5.37 s (2H), 2.62 s (3H). ^{13}C NMR spectrum, δ_C, ppm: 185.5, 159.8, 155.6, 148.2, 143.5, 138.1, 134.6, 132.4, 131.3, 131.0, 129.8, 128.7, 128.4, 128.1, 128.1, 127.6, 124.9, 123.5, 121.8, 113.9, 97.0, 62.5, 10.3. ESI+ mass spectrum: *m/z* 522 $[M + H]^+$. Calculated, %. C 57.44; H 3.28; N 8.04. $C_{25}H_{17}BrClN_3O_3$. Found, %. C 57.34; H 3.20; N 7.96.

(4-Bromophenyl)(6-{1-(3-chlorophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}-3-methylbenzofuran-2-yl)-methanone (7i). Yield 80%, white solid, mp 230–232°C. IR spectrum, ν, cm^{-1}: 1668 (C=O). ^{1}H NMR spectrum (400 MHz), δ, ppm: 8.13–7.97 m (3H), 7.79 s (1H), 7.71–7.38 m (6H), 7.15 s (1H), 7.04 d (*J* = 8.29 Hz, 1H), 5.34 s (2H), 2.60 s (3H). ^{13}C NMR spectrum, δ_C, ppm: 185.5, 160.1, 155.6, 148.4, 138.1, 137.9, 135.8, 132.5, 131.0, 129.7, 129.6, 129.1, 128.3, 127.5, 123.4, 122.1, 121.3, 120.7, 118.5, 114.1, 96.8, 62.4, 10.3. ESI+ mass spectrum: *m/z* 522 $[M + H]^+$. Calculated, %. C 57.44; H 3.28; N 8.04. $C_{25}H_{17}BrClN_3O_3$. Found, %. C 57.34; H 3.21; N 7.94.

(4-Bromophenyl)(6-{1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}-3-methylbenzofuran-2-yl)-methanone (7j). Yield 88%, white solid, mp 235–237°C. IR spectrum, ν, cm^{-1}: 1669 (C=O). ^{1}H NMR spectrum (400 MHz), δ, ppm: 8.15–8.03 m (3H), 7.71 d (*J* = 8.83 Hz, 2H), 7.66–7.58 m (2H), 7.58–7.47 m (4H), 7.19 d (*J* = 2.00 Hz, 1H), 7.09–7.05 m (1H), 5.39 s (2H), 2.63 s (3H). ^{13}C NMR spectrum, δ_C, ppm 185.4, 159.6, 155.7, 148.4, 144.7, 138.1, 135.5, 135.0, 132.5, 130.2, 129.8, 128.5, 127.7, 123.4, 122.1, 121.8, 121.1, 114.1, 96.7, 62.5, 10.1. ESI+ mass spectrum: *m/z* 522 $[M + H]^+$. Calculated, %. C 57.44; H 3.28; N 8.04. $C_{25}H_{17}BrClN_3O_3$. Found, %. C 57.34; H 3.20; N 7.95.

(4-Bromophenyl)(3-methyl-6-{[1-(3-nitrophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}benzofuran-2-yl)-methanone (7k). Yield 84%, white solid, mp 245–247°C. IR spectrum, ν, cm^{-1}: 1655 (C=O). ^{1}H NMR spectrum (400 MHz), δ, ppm: 8.61 s (1H), 8.34–8.25 m (2H), 8.24–8.15 m (1H), 8.06 d (*J* = 7.45 Hz, 2H), 7.77 t (*J* = 8.17 Hz, 1H), 7.63–7.42 m (4H), 7.15 s (1H), 7.05 d (*J* = 8.3 Hz, 1H), 5.34 s (2H), 2.56 s (3H). ^{13}C NMR spectrum, δ_C, ppm: 185.5, 160.1, 155.6, 148.9, 148.5, 149.0, 138.1, 137.6, 132.5, 131.2, 129.7, 128.2, 127.5, 126.0, 123.4, 123.4, 122.3, 121.2, 115.3, 114.0, 96.8, 62.4, 10.3. ESI+ mass spectrum: *m/z* 533 $[M + H]^+$. Calculated, %. C 56.30; H 3.21; N 10.51. $C_{25}H_{17}BrN_4O_5$. Found, %. C 56.10; H 3.21; N 10.44.

(4-Bromophenyl)(3-methyl-6-{[1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}benzofuran-2-yl)-methanone (7l). Yield 90%, white solid, mp 261–263°C. IR spectrum, ν, cm^{-1}: 1660 (C=O). ^{1}H NMR spectrum (400 MHz, δ, ppm: 8.43 d (*J* = 8.88 Hz, 2H), 8.24 s (1H), 8.10–7.94 m (3H), 7.66–7.58 m (2H), 7.57–7.50 m (2H), 7.19 s (1H), 7.09 d (*J* = 8.55 Hz, 1H), 5.39 s (2H), 2.61 s (3H). ^{13}C NMR spectrum, δ_C, ppm: 185.5, 159.8, 155.7, 148.9, 147.4, 145.5, 141.1, 138.1, 132.5, 130.1, 128.4, 127.7, 125.7, 123.7, 122.4, 121.0, 120.4, 113.9, 96.9, 62.3, 10.2. ESI+ mass spectrum: *m/z* 533 $[M + H]^+$. Calculated, %. C 56.30; H 3.21; N 10.51. $C_{25}H_{17}BrN_4O_5$. Found, %. C 56.12; H 3.21; N 10.42.

(4-Bromophenyl)(6-{[1-(2-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}-3-methylbenzofuran-2-yl)methanone (7m). Yield 85%, white solid, mp 230–232°C. IR spectrum, ν, cm^{-1}: 1664 (C=O). ^{1}H NMR spectrum (400 MHz), δ, ppm: 8.27 s (1H), 8.14–8.07 m (2H), 7.81 d.d (*J* = 7.77, 1.61 Hz, 1H), 7.66–7.50 m (3H), 7.49–7.41 m (1H), 7.22 d (*J* = 2.10 Hz, 1H), 7.17–7.07 m (3H), 5.38 s (2H), 3.89 s (3H), 2.63 s (3H). ^{13}C NMR spectrum, δ_C, ppm: 185.3, 160.1, 155.6, 151.2, 148.5, 143.0, 138.2, 132.5, 130.8, 130.1, 128.5,

127.8, 126.3, 125.6, 124.9, 123.7, 122.1, 121.4, 114.4, 112.7, 97.1, 62.8, 56.1, 10.3. ESI+ mass spectrum: *m/z* 518 $[M + H]^+$. Calculated, %. C 60.24; H 3.89; N 8.11. $C_{26}H_{20}BrN_3O_4$. Found, %. C 60.96; H 3.68; N 8.02.

Antibacterial activity testing. *Bacterial Strains.* The gram-positive strains *Micrococcus luteus* (ATCC 10240), methicillin-resistant *Staphylococcus aureus* (MRSA, NCTC 13616), *Bacillus subtilis* (ATCC 6633), and *Bacillus cereus* (ATCC 14579) and the gram-negative strains *Pseudomonas aeruginosa* (ATCC 27853), *Klebsiella pneumoniae* (ATCC 43816), *Escherichia coli* (ATCC 8739) and *Proteus vulgaris* (ATCC 13315) were purchased from the American Type Culture Collection. Methicillin-resistant *Staphylococcus aureus* was purchased from the Public Health England Culture Collections. All bacterial strains stored at –80°C were streaked on Luria–Bertani (LB) agar plates (Hi-media Laboratories, Mumbai, India) and incubated at 37°C for 20–24 h. A few isolated colonies were selected from each plate and suspended in 5 mL of LB broth in a sterile culture vessel. The vessel was plugged with cotton and incubated with gentle shaking (140 rpm) at 37°C for 20 h.

Preparation of inocula. Following the protocol of the Kirby–Bauer disk diffusion assay [24], four to five well-isolated colonies of the same morphological type were picked with an inoculating loop, transferred into 5 mL of nutrient broth, and incubated at 37°C for 24 h until a slight visible turbidity appeared. The turbidity of the actively growing broth cultures was then adjusted with broth to a density equivalent to that of a 0.5 McFarland standard, and the resulting suspensions were used as the initial inocula in the assay.

*Antibacterial assay***.** The initial inocula of the test organisms, 100 μL, were swabbed over the surface of the agar media (20 mL) in Petri dishes and let to be absorbed for 15 min. Wells, 8 mm in diameter, were made with a sterile cork borer in the seeded agar plates. Solutions of the test compounds in DMSO (100 μL; *c* 75 and 100 mg/mL) were then loaded into the wells and incubated in air at 37°C for 24 h. The inhibition zone diameter was measured with a zone reader (HiAntibiotic Zone Scale). The positive control was the standard drug Gentamycin.

CONCLUSIONS

A series of novel (4-bromophenyl){3-methyl-6-[1*H*-1,2,3-triazol-4-yl)methoxy]benzofuran-2-yl}methanones **7a–7m** were synthesized in good yields using a click chemistry approach and characterized by different spectroscopic techniques. The synthesized molecules all showed an excellent antibacterial activity. The highest activities were found in compounds **7m**, **7h**–**7l**. These results positively encouraged us for further developing novel bioactive agents.

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