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Synthesis and Anti-microbial Evaluation of Some Novel Bridged Benzofuran and 1,2,3-Triazole Based Analogues

Nagamani Modhumpuram[1], Jalapathi Pochampalli[1*], Kishore Kumar Angajala[1], Shanker Bhookya, Jayasree D[1]

[1]Department of Chemistry, University College of Science, Saifabad, Osmania University, Hyderabad, Telanagana, India

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ABSTRACT

A new series of substituted 1-(2-((1H-1,2,3-triazol-4-yl)methoxy)-5-((2-benzoyl-3-methylbenzofuran-5-yl)methyl)phenyl)ethanonederivatives were synthesized by copper(I) catalyzed azide-alkyne cyclo-addition (CuAAC) reaction. All the newly synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR and mass spectroscopy. The representative analogues were screened in vitro antibacterial and antifungal activity. The newly synthesized compounds were showed significant antibacterial activity and moderate antifungal activity compared to standard drugs ciprofloxacin and nystatin respectively.

Keywords: 1,2,3-Triazoles, Click reaction, Antibacterial activity, Antifungal activity

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INTRODUCTION

Benzofuran and its derivatives are important class heterocyclic compounds due to their excellent biological properties such as antibacterial [1], antimicrobial [2], antitumor [3] and the ability to control calcium level. Benzofurans have [4] been reported to exhibit antiproliferative activity via different mechanisms [5], such as inhibition of tubulin polymerization [6], inhibition of histone deacetylase enzymes [7], inhibition of angiogenesis [8] and induction of apoptosis [9], among others [10].

Triazoles and many other five membered heterocyclic compounds have been used very often in the pharmacological and medicinal applications. The 1,2,3-triazoles are most essential building blocks in chemistry and stable to moisture, oxygen, light and metabolism in the body. Moreover, these entities can be turned to form powerful pharmacophores and play an important role in bio-conjugation [11,12]. The"Click" protocol is a highly efficient process in bond formations among diverse building blocks for chemical synthesis [13,14], materials and surface science [15] and combinatorial chemistry [16]. In addition, several compounds containing 1,2,3-triazoles have shown a broad spectrum of biological activities such as antibacterial [17], fungicidal [18], antiallergic [19], anti-HIV [20], anti-inflammatory [21,22], analgesic [23], local anesthetic [24], anticonvulsant [25], antineoplastic [26], antimalarial [27] and anticancer activities [28].

MATERIALS AND METHODS

Thin layer chromatography (TLC) was performed on E. Merk AL silicagel 60 F254 plates and visualized under UV light. The NMR spectra were recorded on Varian EM-360 (400 MHz mercury plus) spectrometer in DMSO-d_6 or $CDCl_3$ and calibrated using solvent signals [7.25($CDCl_3$) and 2.50 (DMSO-d_6)]. All chemical shifts recorded in δ(ppm) using TMS as an internal standard. The mass spectra were recorded on Agilent ion trap MS. Spectrometer at energy of ionizing electron equal to 70 ev. All the reagents were purchased from Aldrich, Merck and Acros Organics and used without further purification.

Preparation of 5-chloromethyl-2-hydroxyacetophenone

Compound **2** was preparedby addition of17 g (0.125 mol) of 2-hydroxyacetophenone, in small portions with stirring, to 75 ml of concentrated hydrochloric acid containing 6.75 g (0.225 mol) of paraformaldehyde. This reaction mixture was maintained at room

temperature with stirring for 48 h until a precipitate formed. Then the solid product was collected by suction filtration, washed with an aqueous solution of sodium bicarbonate (0.5%), washed with water, dried, and recrystallized from a toluene–petroleum ether mixture.

Procedure for the synthesis of 1,1'-(Methylenebis(2-hydroxy-5,1-phenylene)) diethanone

A catalytic amount of conc. H_2SO_4 (0.1 mL) was slowly added to a solution of chloromethylated compound (2) (2.0 mmol) and the O-hydroxyacetophenone (2.0 mmol) in glacial acetic acid (5 mL) at room temperature, and the solution was stirred at 90°C during 2 h. The reaction mixture was then poured on ice cooled water (5 mL) and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$, dried over Na_2SO_4, filtered over silica gel and concentrated under reduced pressure to afford the pure products.
^{1}H-NMR (500 MHz, $CDCl_3$) 2.61 (d,6H), 3.97 (s, 2H), 6.94 (d, 2H), 7.36 (d, 2H), 7.61 (d, 2H), 12.20 (s,2H).(ES+) m/z=284.10.

Procedure for the synthesis of 1-(5-((2-benzoyl-3-methylbenzofuran-5-yl)methyl)-2-hydroxyphenyl)ethanone

The compound 1,1'-(Methylenebis(2-hydroxy-5,1-phenylene)) diethanone (1 mmol) was refluxed with 2-bromo-1-phenylethanone (0.5 mmol) in the presence of potassium carbonate in acetone for 3 h. The reaction was monitored by TLC. After the reaction is completed the solvent was removed by Rota evaporator the resulted crude was washed with water to obtain 1-(5-((2-benzoyl-3-methylbenzofuran-5-yl) methyl)-2-hydroxy phenyl) ethanone.
^{1}H-NMR (500 MHz, $CDCl_3$) 2.61 (d, 6H), 4.08 (s, 2H), 6.94 (d, 1H), 7.29-7.36 (m, 2H), 7.46-7.61 (m, 7H), 8.0 8(m, 2H), 12.1 (s, 1H). ^{13}C-NMR (500 MHz, $CDCl_3$) 156.14, 153.19, 143.41, 137.84, 136.07, 134.11, 133.84, 130.52, 129.69, 129.46, 128.25, 126.73, 122.49, 121.0, 63.97, 41.27, 32.27, 10.45. (ES+) *m/z*=384.14.

Procedure for the synthesis of 1-(5-((2-benzoyl-3-methylbenzofuran-5-yl)methyl)-2-(prop-2-yn-1-yloxy)phenyl)ethanone

The compound 1-(5-((2-benzoyl-3-methylbenzofuran-5-yl)methyl)-2-hydroxyphenyl)ethanone was taken in dry acetone (5 mL), anhydrous K_2CO_3 (1.01 equivalent) were refluxed with propargyl bromide (1 equivalent) for 8 h. Progress of the reaction was monitored by TLC, the reaction mixture was allowed to cool then solvent was removed *in vacuo*, then diluted with water (50 mL), extracted with ethyl acetate (3×50 mL). The organic layer was dried over anhydrous sodium sulphate filtered and concentrated *in vacuo*. The crude product was purified by column chromatography using 100-200 mesh silica gel, eluted at 5% ethyl acetate in pet ether to afford1-(5-((2-benzoyl-3-methylbenzofuran-5-yl)methyl)-2-(prop-2-yn-1-yloxy)phenyl)ethanone as light yellow solid.
^{1}H-NMR (500 MHz, $CDCl_3$) 2.61 (d, 6H), 2.54 (t, 1H), 4.07 (s, 2H), 4.78 (d, 2H), 7.00 (d, 1H), 7.3 (dd, 2H), 7.63-7.43 (m, 6H), 8.07 (d, 2H); ^{13}C-NMR (500 MHz, $CDCl_3$)199.8, 185.9, 156.0, 153.1, 143.4, 141.4, 137.8, 136.0, 134.1, 133.8, 130.5, 129.7, 128.7, 128.2, 126.7, 122.5, 121.0, 113.3, 112.3, 62.7, 50.2, 41.27, 32.2, 10.47. (ES+) *m/z*=422.15.

General procedure for the synthesis of 1-[5-(2-Benzoyl-3-methyl-benzofuran-5-ylmethyl)-2-(3-methyl-3H-[1,2,3] triazol-4-ylmethoxy)-phenyl]-ethanone

To a solution of alkyne substrate compound **7** (100 mg) dissolved in 5 mL DMF was added $CuSO_4.5H_2O$ (5 mol%) followed by sodium ascorbate (10%mol) and azide was added. The reaction mixture was stirred for 30 min at room temperature, monitored by TLC. After complete conversion of starting materials in to products, the reaction mixture was diluted with cold water (25 mL), extracted with ethyl acetate (3 × 25 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography using 100-200 mesh silica gel and ethyl acetate in petether to afford corresponding 1,4 disubstituted 1,2,3-triazole analogues.

1-(5-((2-benzoyl-3-methylbenzofuran-5-yl)methyl)-2-(1-butyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl)ethenone

Yield 73%, white solid. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.14-7.97 (m, 2H), 7.68-7.55 (m, 3H), 7.49 (*J*=22.09, 21.66, 11.32 Hz, 4H), 7.34-7.24 (m, 3H), 7.07 (d, *J*=8.53 Hz, 1H), 5.29 (s, 2H), 4.51-4.28 (m, 2H), 2.63-2.53 (m, 6H), 4.07 (s, 2H), 1.99-1.83 (m, 2H), 1.45-1.27 (m, 2H), 1.02-0.91 (m, 3H).^{13}C-NMR (500 MHz, $CDCl_3$): 199.8, 185.9, 156.0, 153.1, 148.6, 143.4, 141.4, 137.8, 136.0, 134.1, 133.8, 132.5, 130.5, 129.7, 129.5, 128.7, 128.2, 126.7, 122.5, 121.0, 113.3, 112.3, 62.7, 50.2, 40.7, 32.2, 31.9, 19.6, 13.4, 10.1; (ES+) *m/z*=522.23(M+H).

1-(5-((2-benzoyl-3-methylbenzofuran-5-yl)methyl)-2-(1-hexyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl)ethenone

Yield 82%, white solid. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.06 (dd, *J*=5.21, 3.26 Hz, 2H), 7.65-7.57 (m, 3H), 7.56-7.41 (m, 4H), 7.34-7.25 (m, 2H), 7.07 (d, *J*=8.54 Hz, 1H), 5.29 (s, 2H), 4.36 (t, *J*=7.25 Hz, 2H), 4.06 (s, 2H), 2.65-2.53 (m, 6H), 2.02-1.75 (m, 3H), 1.31-1.28 (m, 3H), 1.25 (s, 2H), 0.96-0.79 (m, 4H). ^{13}C-NMR (500 MHz, $CDCl_3$): 199.8, 185.9, 156.0, 153.1, 148.6, 143.4, 142.7, 142.2, 137.8, 136.0, 134.0, 133.8, 128.6, 128.2, 126.7, 122.4, 121.0, 113.27, 112.2, 62.6, 50.5, 40.7, 31.9, 31.0, 30.2, 29.6, 29.4, 29.3, 29.2, 29.0, 26.0, 22.3, 22.65, 13.9, 10.0; (ES+) *m/z*=549.26.

1-(5-((2-benzoyl-3-methylbenzofuran-5-yl)methyl)-2-(1-octyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl)ethanone

Yield 76%, white solid. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.07 (dd, *J*=10.77, 3.68 Hz, 2H), 7.66-7.56 (m, 3H), 7.55-7.41 (m, 4H), 7.29 (dd, *J*=8.49, 1.78 Hz, 2H), 7.07 (d, *J*=8.51 Hz, 1H), 5.29 (s, 2H), 4.36 (t, *J*=7.25 Hz, 2H), 4.07 (s, 2H), 0.92-2.67-2.47 (m, 6H), 1.91 (dd, *J*=13.93, 6.97 Hz, 2H), 1.35-1.27 (m, 9H), 0.79 (m, 4H).^{13}C-NMR (500 MHz, $CDCl_3$): 199.8, 185.8, 156.0, 153.1, 147.0, 141.8, 137.8, 136.0, 134.1, 133.8, 132.5, 130.5, 129.6, 128.6, 128.3, 126.7, 122.5, 121.0, 113.0, 112.2, 62.6, 40.7, 31.9, 31.6, 10.0; MS m/z: 577.29.

1-(5-((2-benzoyl-3-methylbenzofuran-5-yl)methyl)-2-(1-dodecyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl)ethenone

Yield 81%, white solid. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.14-7.99 (m, 2H), 7.66-7.56 (m, 3H), 7.56-7.40 (m, 4H), 7.29 (dd, *J*=14.19, 5.80 Hz, 2H), 7.08 (t, *J*=7.96 Hz, 1H), 5.29 (s, 2H), 4.36 (t, *J*=7.26 Hz, 2H), 4.06 (s, 2H), 2.69-2.49 (m, 6H), 1.90 (p, *J*=7.18 Hz, 2H), 1.38-1.20 (m, 18H), 0.87 (t, *J*=6.95 Hz, 3H).^{13}C-NMR(500 MHz, $CDCl_3$): 199.8, 185.8, 156.0, 153.1, 147.0, 141.8, 137.8, 136.0, 134.1, 133.8, 132.5, 130.5, 129.7, 129.4, 128.2, 122.4, 121.0, 117.0, 113.3, 112.2,52.4, 72.3, 50.5, 40.8, 31.9, 30.2, 29.3, 28.9,

26.4, 22.7, 14.1, 10.0; (ES+) *m/z*= 633.36.

1-(5-((2-benzoyl-3-methylbenzofuran-5-yl)methyl)-2-(1-pentadecyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl)ethenone

Yield 75%, white solid. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.22-7.91 (m, 2H), 7.73-7.37 (m, 7H), 7.29 (dd, *J*=8.51, 1.88 Hz, 2H), 7.07 (d, *J*=8.53 Hz, 1H), 5.29 (s, 2H), 4.36 (t, *J*=7.26 Hz, 2H), 4.07 (s, 2H), 2.75-2.38 (m, 6H), 1.91 (p, *J*=7.14 Hz, 2H), 1.62 (s, 3H), 1.33-1.20 (m, 21H), 0.87 (t, *J*=6.94 Hz, 3H).^{13}C-NMR(500 MHz, $CDCl_3$): 199.8, 185.8, 156.0, 153.1, 147.0, 141.8, 137.8, 136.0, 134.1, 133.8, 132.5, 130.5, 129.7, 129.4, 128.2, 122.4, 121.0, 113.3, 112.2, 50.5, 40.8, 31.9, 30.2, 28.9, 26.4, 22.7, 14.1, 10.0; (ES+) *m/z*=675.40.

1-(5-((2-benzoyl-3-methylbenzofuran-5-yl)methyl)-2-(1-phenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)ethenone

Yield 87%, white solid. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.13-7.96 (m, 5H),7.79-7.70 (m, 2H), 7.67-7.57 (m, 2H), 7.58-7.39 (m, 7H), 7.31 (dt, *J*=8.38, 2.01 Hz, 2H), 7.11 (d, *J*=8.53 Hz, 1H), 5.38 (s, 2H), 4.07 (s, 2H), 2.96 (s, 4H), 2.88 (s, 4H).^{13}C-NMR (500 MHz, $CDCl_3$): 199.7, 185.8, 155.8, 153.1, 148.6, 144.2, 137.8, 136.7, 136.0, 134.2, 133.8, 132.5, 130.5, 129.8, 129.6, 129.4, 129.0, 128.7, 128.2, 126.7, 121.0, 120.9, 120.5, 113.3, 112.2, 62.5, 40.7, 31.9, 10.0; (ES+) *m/z*=541.20.

1-(5-((2-benzoyl-3-methylbenzofuran-5-yl)methyl)-2-(1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)ethenone.

Yield 77%, pale yellow solid. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.62 (t, *J*=2.02 Hz, 1H), 8.32 (dd, *J*=8.25, 1.26 Hz, 1H), 8.24-8.14 (m, 2H), 8.06 (dd, *J*=6.51, 5.17 Hz, 2H), 7.76 (dd, *J*=13.65, 5.47 Hz, 1H), 7.60 (dd, *J*=7.14, 4.94 Hz, 2H), 7.51 (dd, *J*=15.79, 8.35 Hz, 4H), 7.47-7.42 (m, 1H), 7.36-7.28 (m, 2H), 7.10 (d, *J*=8.52 Hz, 1H), 5.40 (s, 2H), 4.08 (s, 2H), 2.61 (dd, *J*=14.86, 9.34, 5.19 Hz, 6H). ^{13}C-NMR (500 MHz, $CDCl_3$): 199.71, 185.8, 155.6, 153.1, 148.8, 137.7, 137.4, 135.9, 134.4, 133.8, 132.5, 131.0, 130.6, 129.6, 129.4, 128.8, 128.2, 126.7, 125.9, 123.4, 121.0, 120.8, 115.3, 113.2, 112.2, 62.3, 40.7, 31.8, 10.0; (ES+) *m/z*=586.19.

1-(5-((2-benzoyl-3-methylbenzofuran-5-yl)methyl)-2-((1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)ethanone

Yield 84%, white solid. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.21 (dd, *J*=11.94, 5.31 Hz, 2H), 8.09-8.03 (m, 2H), 7.66-7.56 (m, 3H), 7.54-7.37 (m, 6H), 7.34-7.21 (m, 3H), 7.05 (d, *J*=8.54 Hz, 1H), 5.65 (d, *J*=11.60 Hz, 2H), 5.29 (s, 2H), 4.06 (s, 2H), 2.55 (dd, *J*=30.75, 9.17 Hz, 6H).^{13}C-NMR (500 MHz, $CDCl_3$): 199.7, 185.8, 153.3, 153.0, 149.1, 148.6, 147.9, 145.2, 142.8, 141.6, 137.8, 136.7, 135.8, 134.1, 132.5, 129.9, 127.6, 126.7, 126.5, 124.2, 123.4, 120.9, 119.7, 112.2, 111.4, 68.2, 53.0, 41.7, 10.1; (ES+) *m/z*= 600.19

1-(5-((2-benzoyl-3-methylbenzofuran-5-yl)methyl)-2-(1-(2-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)ethenone

Yield 71%, white solid. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.07 (d, *J*=6.66 Hz, 3H), 7.70-7.56 (m, 4H), 7.48 (t sext., *J*=8.77, 5.56 Hz, 6H), 7.38-7.20 (m, 3H), 7.12 (d, *J*=8.50 Hz, 1H), 5.40 (d, *J*=7.45 Hz, 2H), 4.08 (s, 2H), 2.66-2.52 (m, 6H).^{13}C-NMR (500 MHz, $CDCl_3$): 199.6, 185.9, 155.9, 153.1, 148.6, 143.3, 137.8, 136.0, 134.6, 134.3, 133.9, 132.5, 130.9, 130.8, 130.6, 129.7, 129.4, 128.7, 128.5, 128.3, 128.0, 126.7, 124.9, 121.0, 113.3, 112.3, 62.5, 40.7, 31.9, 10.1; (ES+) *m/z*=575.16.

1-(5-((2-benzoyl-3-methylbenzofuran-5-yl)methyl)-2-(1-(o-tolyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)ethenone

Yield 76%, white solid. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.07 (d, *J*=7.37 Hz, 3H), 7.81 (s, 1H), 7.63-7.40 (m, 10H), 7.12 (d, *J*=8.50 Hz, 1H), 5.39 (d, *J*=7.37 Hz, 2H), 4.08 (s, 2H), 2.60 (d, *J*=6.96 Hz, 6H), 2.19 (s, 3H).^{13}C-NMR (500 MHz, $CDCl_3$): 199.6, 185.8, 155.9, 153.1, 148.6, 143.3, 137.8, 136.2, 136.0, 134.2, 133.8, 133.6, 132.5, 131.5, 130.5, 130.0, 129.9, 129.6, 129.4, 128.7, 128.2, 126.7, 126.9, 125.9, 124.3, 121.0, 113.3, 112.2, 62.6, 40,7, 31.8, 10.0; (ES+) *m/z*=555.22.

1-(5-((2-benzoyl-3-methylbenzofuran-5-yl)methyl)-2-(1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)ethenone

Yield 82%, white solid. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.20 (s, 1H), 8.14-7.97 (m, 2H), 7.81 (dd, *J*=7.88, 1.52 Hz, 1H), 7.61 (dd, *J*=10.15, 4.68 Hz, 2H), 7.57-7.37 (m, 5H), 7.38-7.24 (m, 4H), 7.22-7.02 (m, 3H), 5.38 (s, 2H), 4.08 (s, 2H), 3.87 (d, *J*=6.09 Hz, 3H), 2.67-2.53 (m, 6H).^{13}C-NMR (500 MHz, $CDCl_3$): 199.8, 185.6, 156.2, 153.2(2C), 150.9, 142.8, 136.1, 134.1, 133.9, 132.5, 130.6, 130.3, 129.9, 129.7, 129.5(2C), 128.6, 128.2, 127.7, 126.7, 126.0, 125.3, 125.0, 121.3, 121.0, 119.2, 113.3, 112.4, 112.2, 62.7, 55.9, 40.8, 32.0, 10.1; (ES+) *m/z*=571.21

1-(5-((2-benzoyl-3-methylbenzofuran-5-yl)methyl)-2-(1-(2-bromophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)ethenone

Yield 76%, pale red solid. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.21-7.94 (m, 3H),7.11 (d, *J*=8.48 Hz, 1H),7.76 (d, *J*=7.72 Hz, 1H),7.71-7.36 (m, 8H), 7.38-7.22 (m, 3H), 5.41 (s, 1H), 4.08 (s, 2H), 2.62 (t, *J*=8.45 Hz, 6H). ^{13}C-NMR (500 MHz, $CDCl_3$): 199.7, 185.98, 156.0, 153.2, 148.7, 143.2, 137.9, 136.4, 136.1, 134.3, 134.0 (2C), 132.6, 131.4, 130.7, 129.8, 129.5, 128.8, 128.6, 128.3 (2C), 126.8, 125.0, 121.1, 118.6, 113.4, 112.3, 62.6, 40.8, 32.0, 10.1; (ES+) *m/z*=619.11

1-(5-((2-benzoyl-3-methylbenzofuran-5-yl)methyl)-2-(1-(4-flourophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)ethenone

Yield 84%, white solid. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.21-7.94 (m, 3H), 7.76 (d, *J*=7.72 Hz, 1H),7.71-7.36 (m, 8H), 7.38-7.22 (m, 3H),7.11 (d, *J*=8.48 Hz, 1H), 5.41 (s, 2H), 4.08 (s, 2H), 2.62 (t, *J*=8.45 Hz, 6H). ^{13}C-NMR (500 MHz, $CDCl_3$): 200.45, 186.6, 164.2, 162.3, 156.5, 153.8, 149.4, 145.1, 138.5, 136.7, 135.0, 134.6, 133.2, 131.3, 130.4, 130.1, 129.53, 128.9, 127.4, 123.3 (2C), 121.7 (2C), 117.6, 117.4, 114.0, 113.0, 63.2, 41.5, 32.6, 10.78; (ES+) *m/z*= 559.19.

1-(5-((2-benzoyl-3-methylbenzofuran-5-yl)methyl)-2-(1-(2,4,6trifluorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)ethenone

Yield 83%, white solid. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.17-7.99 (m, 4H), 7.79-7.67 (m, 1H)7.62-7.43 (m, 6H), 7.32-7.29 (m, 1H), 7.24-7.15 (m, 1H), 7.10 (d, *J*=8.52 Hz, 1H), 4.07 (s, 2H), 2.57 (dd, *J*=17.35, 7.70 Hz, 6H).^{13}C-NMR (500 MHz, $CDCl_3$): 199.3, 185.5, 162.3, 155.5, 152.8, 148.3, 143.9, 137.5, 135.7, 134.0, 133.6, 132.2, 130.3, 129.3, 129.1, 128.4, 127.9, 126.4, 123.5, 120.7, 118.5, 118.4, 112.9(2C), 111.9, 61.9, 40.4, 36.2, 31.1, 13.8, 9.7; (ES+) *m/z*=595.17.

1-(5-((2-benzoyl-3-methylbenzofuran-5-yl)methyl)-2-(1-(4-trifluoromethoxy)phenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)ethenone

Yield 78%, white solid. ^{1}H-NMR(500 MHz, $CDCl_3$): 8.0(m,3H), 7.7(d, 2H), 7.6-7.4(m, 7H), 7.3-7.2(m, 3H), 7.0(d, 1H), 5.4(s, 2H), 4.07(s, 2H), 2.5(s, 6H).^{13}C-NMR(500 MHz, $CDCl_3$): 199.7, 185.9, 168.5, 155.7, 153.2, 137.8(2C), 136.0, 134.8, 134.9(2C), 134.4, 133.8, 132.5, 131.2, 130.6, 129.7, 129.4, 128.3, 118.4, 113.6(2C), 113.3, 112.3, 62.4, 40.7, 10.1; (ES+) *m/z*=625.18.

1-(5-((2-benzoyl-3-methylbenzofuran-5-yl)methyl)-2-(1-(2,4,6-trimethoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)ethenone

Yield 77%, white solid. ^{1}H-NMR(500 MHz, $CDCl_3$): 8.07(d, 2H), 8.0(s, 1H), 7.60(m, 2H), 7.53-7.43(m, 4H), 7.30(dt, 2H), 7.09(d, 1H), 6.93(s, 2H), 5.36(s, 2H), 4.07(s, 2H), 3.92(s, 6H), 3.88(s, 3H), 2.59(s, 6H).^{13}C-NMR(500 MHz, $CDCl_3$): 199.9, 185.8, 155.8, 153.9, 148.6, 144.1, 139.2, 138.5, 137.8, 135.9, 134.3, 133.8, 132.6, 132.5, 130.5, 129.7, 129.4, 128.8, 128.2, 126.7, 121.2, 121.0, 114.0, 113.3, 112.3, 98.6, 62.5, 61.0, 56.4, 40.7, 31.9, 10.1; (ES+) *m/z*=631.23.

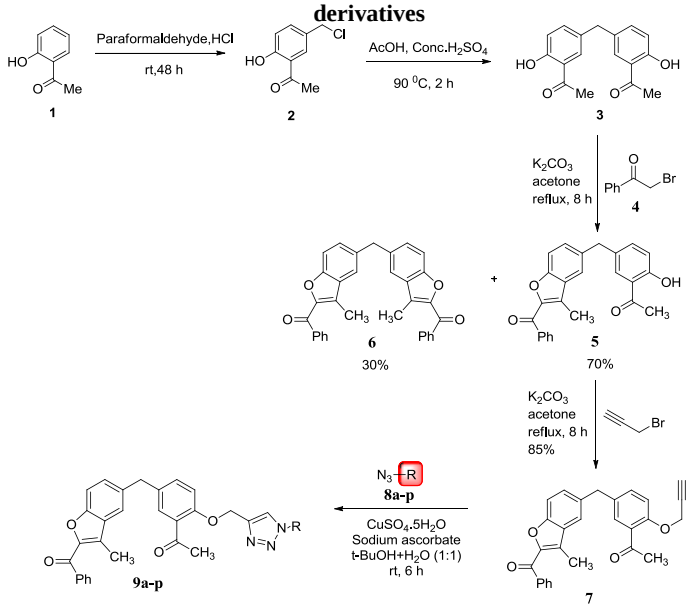
RESULTS AND DISCUSSION

In the present study substituted 1-(2-((1H-1,2,3-triazol-4-yl)methoxy)-5-((2-benzoyl-3-methylbenzofuran-5-yl)methyl)phenyl)ethanone derivatives (9a-p) were synthesized using 6 step protocol as shown in scheme 1. Chloromethylation of 2′-hydroxyacetophenone (1) was carried out in good yield in the presence of Conc. HCl and paraformaldehyde which produced 1-(5-(chloromethyl)-2-hydroxyphenyl)ethanone (2) at room temperature. Compound 2 was confirmed with reported data [29-31] which showed m.p. 100-102ºC.

Compound 2 was refluxed with *O*-hydroxyaceophenone (1) in the presence of acetic acid and catalytic amount of H_2SO_4 for 2 h at 90ºC. The structure of the compound 1,1'-(methylenebis(2-hydroxy-5,1-phenylene)diethanone (3) was confirmed by ^{1}H-NMR and Mass spectral data. In ^{1}H-NMR spectra of compound 3 the signal due to methylene bridge protons appeared at δ3.97 ppm as a singlet, this was also confirmed by MASS spectra which showed base peek at m/z: 384.14.

Compound 5 was synthesized by refluxing of 1,1'-(methylenebis(2-hydroxy-5,1-phenylene)diethanone (3) and 2-bromo-1-phenylethanone (4)in the presence of potassium carbonate and dry acetone to built-up new benzofuran ring, the major product is monomer rather than dimer. Compound 5 was refluxed with propargyl bromide in the presence of potassium carbonate and dry acetone for 8 h to yield 1-(5-((2-benzoyl-3-methylbenzofuran-5-yl)methyl)-2-(prop-2-yn-1-yloxy)phenyl)ethanone (7). This was confirmed by ^{1}H NMR and MASS spectral data. Appearance of peek at δ 4.78 ppm as doublet and δ 2.54 ppm as triplet indicates the compound 7, this was also confirmed by MASS spectra which showed base peek at m/z: 422.15.

Scheme 1: Synthesis of 1-(2-((1H-1,2,3-triazol-4-yl)methoxy)-5-((2-benzoyl-3-methylbenzofuran-5-yl)methyl)phenyl)ethenone derivatives



Different aliphatic and aromatic azides (8a-p) were synthesized by utilizing literature protocols. To prepare alkyl azides, corresponding alkyl halide was heated at 80-90 °C with NaN_3 in dimethylformamide (DMF). Aromatic azides were prepared from different substituted anilines using diazotization followed by treatment with NaN_3. According to Huisgen's [2+3] cycloaddition reaction, the targeted regioselective 1,4-disubstituted 1,2,3-triazole derivatives (9a-p) were synthesized by the cycloaddition reaction of 1-(5-((2-benzoyl-3-methylbenzofuran-5-yl)methyl)-2-(prop-2-yn-1-yloxy)phenyl)ethenone (7), with various aromatic and

aliphatic azides (8a-p). The chemical structures of all newly synthesized target compounds (Figure 1) were characterized by using NMR and mass spectral analytical techniques.

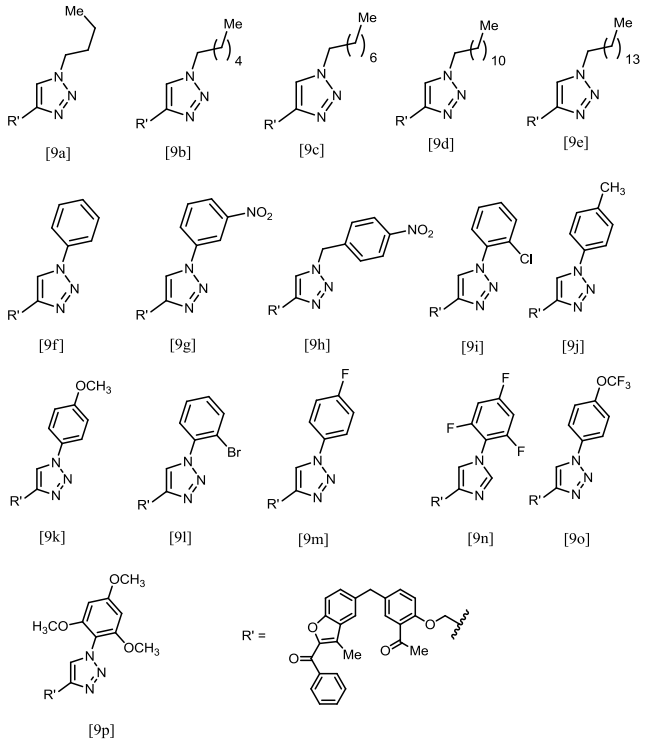


Figure 1: Derivatives of target compound (9a-p)

Antibacterial activity

The *in vitro* antibacterial activities of the newly synthesized derivatives 9a-p were assayed in two concentrations (600 and 900 µg/ml) against four representative bacteria viz *Corynebactereum glutamine, Bacillus subtilis, Staphylococcus, Staphylococcus aureus, Pseudomonous, Steptococci* using the Broth dilution method. The bacteria were grown overnight in nutrient both at 37 °C. The stock solutions of the total compounds were dissolved in $CHCl_3$ solvent and each stock solution was diluted with standard Broth method. The inhibition of microbial growth under standardized conditions was utilized to demonstrate anti-bacterial action of compounds.

The compound with nitro substitution at meta position of phenyl ring on triazole (9g) showed higher activity against *Staphylococcus* at both tested concentrations. The compound with nitro substitution at para position of benzyl ring on triazole (9h) showed better activity against *Corynebacterium glutamine, Bacillus subtilis, Staphylococcus aureus and Streptococci.* The molecules with nitro substitution (9h) and flouro (9m) substitution at para position of benzyl and phenyl ring on triazole showed good activity against all tested bacteria. It is attributed that these withdrawing groups are more responsible for activity. The analogs with longer chain like dodecyl (9d) and pentadecyl (9e) showed good activity against *Staphylococcus* and *Streptococci* respectively. The derivatives with 3-nitro (9g) and 2-chloro (9i) these strong electrons withdrawing groups showed better activity against *Pseudomonas.* The detailed numerical data listed in Table 1.

Table 1: Antibacterial activity of newly synthesized compounds

Compound	Conc. µg/ml	Zone of Inhibition					
		Corynebacterium glutamine	***Bacillus subtilis***	***StaphyloCocous***	***Staphylococcus aureus***	***Pseudomonas***	***Steptococci***
9a	600	NA	1	1.68	NA	NA	NA
	900	NA	1.35	2.52	NA	NA	NA
9b	600	NA	0.2	1.08	NA	NA	1.5
	900	NA	0.3	1.62	NA	NA	2.25
9c	600	NA	NA	NA	NA	NA	NA
	900	NA	NA	NA	NA	NA	NA
9d	600	NA	NA	2.58	NA	NA	NA
	900	NA	NA	4.17	NA	NA	NA
9e	600	0.6	NA	NA	NA	NA	1.14
	900	1	NA	NA	NA	NA	2.71
9f	600	NA	NA	0.8	NA	NA	1.52
	900	NA	NA	1.2	NA	NA	2.17
9g	600	NA	1,05	3	NA	1.8	NA
	900	NA	2.1	4.32	NA	2.7	NA

9h	600	1.8	1.8	1.17	1.44	0.56	2.7
	900	3.7	2.35	2.14	2.16	1.12	4.05
9i	600	0.72	0.3	NA	NA	1	NA
	900	1.08	0.45	NA	NA	1.35	NA
9j	600	NA	NA	NA	1.05	NA	NA
	900	NA	NA	NA	2.1	NA	NA
9k	600	0.64	NA	1.08	NA	NA	NA
	900	1.15	NA	1.62	NA	NA	NA
9l	600	0.15	0.1	NA	NA	NA	1.25
	900	0.35	0.23	NA	NA	NA	1.84
9m	600	1.08	0.7	0.57	0.95	NA	0.56
	900	1.62	1.42	1.14	1.9	NA	1.35
9n	600	NA	0.12	1.68	NA	NA	NA
	900	NA	0.22	2.52	NA	NA	NA
9o	600	0.64	NA	NA	NA	NA	NA
	900	1.15	1.62	NA	NA	NA	NA
9p	600	NA	0.1	NA	1.15	NA	NA
	900	NA	0.23	NA	0.35	NA	NA
Ciproflaxacin	600	1.68	1,08	1.5	1.5	NA	1.8
	900	2.52	1.62	2.25	2.25	NA	2.7

Anti-fungal activity

The antifungal activities of the N-substituted triazoles 9a-p were assayed against fungal organisms via *Aspergillus, Penicillium, Alternaria, Fusarium*. The test organisms were was grown for 48 h at 25 °C in YPD Broth (1% yeast extract, 2% peptone and 2% dextrose) harvested by centrifugation and then washed with sterile distilled water. All the newly synthesized compounds were tested in two concentrations 600 and 900 µg/ml.

The fungal activity was determined by using nystatin as standard, and all the prepared compounds were showed good to moderate activity in which 3-nitro (9 g)and 2,3,4-trifluoro (9n) substitution at benzyl and phenyl ring on triazole were showed better activity against all four strains, because it may be attributed with polar compounds (Table 2).

Table 2: Antifungal activity of newly synthesized compounds

Compound	Conc.	Zone of Inhibition			
	µg/ml	*Aspergillus*	*Pencillum*	*Alternesia*	*Fusarium*
9a	600	0.6	0.36	NA	NA
	900	0.9	0.54	NA	NA
9b	600	0.24	0.18	0.24	NA
	900	0.36	0.27	0.36	NA
9c	600	0.42	0.36	0.42	0.42
	900	0.63	0.54	0.63	0.63
9d	600	0.36	0.36	0.48	0.6
	900	0.54	0.54	0.72	0.9
9e	600	0.6	0.48	0.6	0.36
	900	0.9	0.72	0.9	0.54
9f	600	0.72	0.6	0.66	0.72
	900	1.08	0.9	0.99	1.08
9g	600	0.84	0.72	0.72	0.84
	900	1.26	1.08	1.08	1.26
9h	600	0.6	0.72	0.6	0.6
	900	0.9	1.08	0.9	0.9
9i	600	0.36	0.36	0.42	0.48
	900	0.54	0.54	0.63	0.72
9j	600	0.42	0.36	0.42	0.36
	900	0.63	0.54	0.63	0.54
9k	600	0.42	0.36	0.42	0.36
	900	0.63	0.54	0.63	0.54
9l	600	0.72	0.72	0.84	0.6
	900	1.08	1.08	1.26	0.9
9m	600	0.36	0.36	0.3	0.36
	900	0.54	0.54	0.45	0.54
9n	600	0.6	0.72	0.66	0.6
	900	0.9	1.08	0.99	0.9
9o	600	0.6	0.72	0.6	0.6
	900	0.9	1.08	0.9	0.9
9p	600	0.36	0.24	0.36	0.36
	900	0.54	0.36	0.54	0.54
Nystatine	600	0.9	0.96	0.9	0.9
	900	1.35	1.44	1.35	1.35

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