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REGULAR ARTICLE

An expeditious and clean synthesis of novel benzotriazole-triazole conjugates *via* Copper-catalyzed Azide-Alkyne cycloaddition click protocol (CuAAC)

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Abstract. A simple, efficacious, and regioselective synthesis of hitherto unreported benzotriazole-triazole conjugates *via* copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction between benzotriazole alkynes and aryl azides has been described. The structure of the synthesized molecules has been explicitly confirmed by spectroscopic analysis (^{1}H NMR, ^{13}C NMR, and mass spectroscopy).

Keywords. Benzotriazole alkynes; aryl azides; benzotriazole-triazole conjugates; Copper-catalysed azide-alkyne cycloaddition.

1. Introduction

To fulfil the accrescent demand of novel effective drugs, synthetic chemists are continuously making efforts to discover drug molecules through the generation of novel series of bioactive compounds.[1] Benzo-fused analogue of triazole, also known as benzotriazole is gaining the conspicuous recognition as a potential therapeutic agent due to its rich array of functionalities and is being widely recognized as a useful building block for the synthesis of a broad and interesting range of biologically active heterocyclic compounds having anti-convulsant,[2] anti-microbial,[3–5] anti-fungal,[6,7] anti-inflammatory,[8] anti-bacterial,[9,10] anti-cancer,[11,12] anti-depressant,[13] anti-tubercular,[14,15] anti-viral[16,17] properties (Figure 1). On the other hand, triazole and its derivatives are also known to have significant importance because of their broad spectrum of applications in medicinal chemistry.[18,19] Triazoles play a powerful role in the area of drug discovery because of their medicinal virtues like antimicrobial,[20–22] analgesic,[23] anti-tubercular,[24,25] antiviral,[26,27] anticancer[28,29] activities (Figure 1). Additionally, they are also extensively used as an important constituent of herbicides,[30] optical brightening agents[31] and anti-corrosive agents.[32,33]

Moreover, it was evident from the literature[34–36] that the development of molecules that are synthesized by the conjugation of different pharmaceutical agents has led to an improvement in biological activity. Despite having several biological applicabilities, there are very few organic structures comprising both benzotriazole and triazole moieties.[37–39] In view of the pharmacological aspects of these two moieties and our inclination toward the development of new organic bioactive scaffolds, we envisioned synthesizing a new family of heterocycles containing both benzotriazole and triazole pharmacophores using the highly acclaimed copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction.

The CuAAC method, developed independently by Meldal and Sharpless, is potentially a useful route in the design and synthesis of a new array of compounds with excellent regiocontrol, favouring the synthesis of 1,4-disubstituted-1,2,3-triazoles in high yields.[40] Further, it was reported that the catalytic moiety involved in this protocol is Cu(I). Afterwards, several modified protocols were reported, however in all the cases, it was established that the reaction proceeded either with

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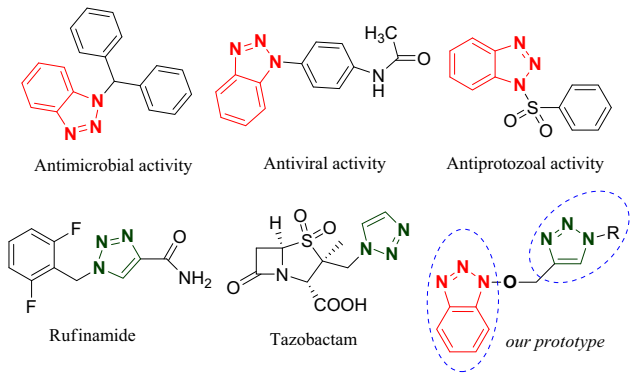


Figure 1. Biologically active benzotriazole and triazole containing heterocyclic compounds.

the direct use of the Cu(I) salts or *in situ* generation of Cu(I) species through the reduction/oxidation of Cu(II)/Cu(0) respectively.[41,42] In addition, the comproportionation of Cu(II) and Cu(0) can also be employed to execute CuAAC reaction.[43]

In view of the importance of benzotriazole and triazole pharmacophores, the effectiveness of CuAAC protocol, and our utmost interest in the synthesis of new heterocycles[44,45] especially benzotriazole,[46] herein, we report facile and expeditious access to a previously unknown family of benzotriazole-triazole analogs through copper-catalyzed azide-alkyne cycloaddition reaction between benzotriazole alkyne and aryl azides using copper acetate as a catalyst in methanol at room temperature in 34-98% yields.

2. Experimental

All the starting reactants and reagents were commercially available and were used without any further purification. The reaction was carried in an open glass round-bottom flask. Thin layer chromatography (TLC) technique using silica gel plates (60 F254) was carried out in an appropriate mixture of hexane and ethyl acetate to monitor the progress of the reaction. All the melting points were recorded on analab melting point apparatus in open glass capillaries. HRMS was recorded on XEVO G2-XS QTof mass spectrometer and Bruker impact HD mass spectrometer. ^{1}H NMR and ^{13}C NMR spectral studies of benzotriazole alkynes were carried in $CDCl_3$ on Bruker 400 and 100 MHz, respectively, whereas the ^{1}H NMR and ^{13}C NMR of the benzotriazole-triazole conjugates were recorded in DMSO-d6 on Bruker 400, 101 MHz spectrometer respectively. Coupling constants (J) are given in Hertz (Hz), whereas the chemical shifts (δ) are given in parts per million (ppm) and are relative to tetramethyl silane (Me_4Si) as internal standard.

2.1 *General procedure for the synthesis of hydroxybenzotriazole alkyne **3a-e***

To the stirred solution of 1.0 mmol of 1-hydroxybenzotriazole in 3.0 mL of acetone, 1.5 eq. of potassium carbonate was added followed by the gradual addition of 1.2 eq. of propargyl bromide. The reaction mixture was refluxed for 1-3 h until the disappearance of the reactant as indicated by TLC. The mixture was finally extracted with ethyl acetate (3×30 mL). The organic layer was collected and washed with water (30 mL) and brine (20 mL) and was dried using anhydrous Na_2SO_4. The solvent was then removed under reduced pressure, and the crude residue was further purified using column chromatography (silica 60-120, eluent: ethyl acetate-hexane), incurring the pure product in good to moderate 50-85% yields. ^{1}H NMR, ^{13}C NMR, and mass spectral studies were carried out to characterize the structures of the resultant compounds.

2.2 *Spectroscopic data of the synthesized compounds*

2.2a *1-(prop-2-yn-1-yloxy)-1H-benzo[d][1,2,3]triazole (**3a**)*: Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.59 (t, J= 2.3 Hz, 1 H), 5.19 (d, J= 2.4 Hz, 2 H,), 7.39 (t, J= 7.7 Hz,1 H), 7.52 (t, J= 7.6 Hz, 1H), 7.70 (d, J= 8.3 Hz, 1 H), 8.01 (d, J= 8.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.28, 75.45, 80.34, 107.06, 119.69, 121.36, 128.00, 145.11, 147.48 ppm.

2.2b *6-chloro-1-(prop-2-yn-1-yloxy)-1H-benzo[d][1,2,3]triazole (**3b**)*: White solid; M.p. 96-98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 (t, J= 2.4 Hz, 1H), 5.19 (d, J= 2.4 Hz, 2H), 7.36 (dd, J= 8.9, 1.7 Hz, 1H), 7.70 (d, J= 1.4 Hz, 1H), 7.94 (d, J= 8.9 Hz, 1H) ppm;^{13}C NMR (100 MHz, $CDCl_3$) δ 67.79, 75.83, 79.78, 109.30, 121.29, 126.24, 129.10, 134.91, 142.06 ppm; HRMS calc. for $C_9H_7ClN_3O$ $[M+H]^+$ 208.02, found 208.03.

2.2c *6-fluoro-1-(prop-2-yn-1-yloxy)-1H-benzo[d][1,2,3]triazole (**3c**)*: White solid; M.p. 48-50 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62 (t, J= 2.4 Hz, 1H), 5.21 (d, J= 2.4 Hz, 2H), 7.19 (td, J= 9.1, 2.3 Hz, 1H), 7.37 (dd, J= 7.4, 2.0 Hz, 1H), 8.01 (dd, J= 9.0, 4.4 Hz, 1H) ppm;^{13}C NMR (100 MHz, $CDCl_3$) δ 67.79, 75.83, 79.78, 109.30, 121.30, 126.24, 129.10, 134.91, 142.09 ppm; HRMS calc. for $C_9H_7FN_3O$ $[M+H]^+$ 192.05, found 192.06.

2.2d *5-chloro-1-(prop-2-yn-1-yloxy)-1H-benzo[d][1, 2,3]triazole (**3d**)*: Creamish white solid; M.p. 100-102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 (t, *J*= 2.4 Hz, 1H), 5.22 (d, *J*= 2.4 Hz, 2H), 7.51 (dd, *J*= 8.8, 1.7 Hz, 1H), 7.67 (d, *J*= 8.8 Hz, 1H), 8.03 (d, *J*= 1.1 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 67.85, 75.85, 79.75, 110.59, 119.60, 127.29, 129.35, 130.83, 143.98 ppm; HRMS calc. for $C_9H_7ClN_3O$ $[M+H]^+$ 208.02, found 208.03.

2.2e *6-nitro-1-(prop-2-yn-1-yloxy)-1H-benzo[d][1,2, 3]triazole (**3e**)*: White solid; M.p. 130-132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.65 (t, *J*= 2.4 Hz, 1H), 5.30 (d, *J*= 2.4 Hz, 2H), 8.19 (d, *J*= 9.1 Hz, 1H), 8.30 (dd, *J*= 9.1, 2.0 Hz, 1H), 8.70 (d, *J*= 1.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 67.50, 75.91, 77.09, 79.35, 109.39, 120.11, 124.83, 128.15, 128.30, 143.37 ppm; HRMS calc. for $C_9H_7N_4O_3$ $[M+H]^+$ 219.04, found 219.05.

2.3 *General procedure for the synthesis of (1H-1,2,3-triazol-4-yl)methoxy-1H-benzo[d][1,2,3]triazole*

To the stirred solution of aryl azide **4a-d** (1.0 mmol) and hydroxybenzotriazole alkyne **3a-e** (1.5 mmol) in methanol (1-2 mL), add copper acetate (1.0 mol%). The resultant reaction mixture was then stirred at ambient temperature for the appropriate time till the reaction is completed. The resultant solid product is then filtered and washed with methanol to get the pure compounds.

2.4 *Spectroscopic data of resultant compounds **5a-n***

2.4a *1-((1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-1H-benzo[d][1,2,3]triazole (**5a**)*: White solid; M.p. decomposed at 240 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 5.81 (s, 2H), 7.41 (t, *J*= 6.9 Hz, 1H), 7.54 (q, *J*= 8.5 Hz, 2H), 8.04 (d, *J*= 8.4 Hz, 1H), 8.16 (d, *J*= 8.9 Hz, 2H), 8.45 (d, *J*= 8.9 Hz, 2H), 9.22 (s, 1H) ppm; ^{13}C NMR (101 MHz, DMSO-d6) δ 72.49, 109.04, 119.72, 120.84, 124.93, 125.39, 125.66, 127.41, 128.45, 140.50, 141.56, 142.64, 146.97 ppm; HRMS calc. for $C_{15}H_{12}N_7O_3$ $[M+H]^+$ 338.09, found 338.10.

2.4b *1-((1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl) methoxy)-1H-benzo[d][1,2,3]triazole (**5b**)*: White solid; M.p. 157-159 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 5.77 (s, 2H), 7.41 (dd, *J*= 8.3, 4.0 Hz, 1H), 7.53 (d, *J*= 3.7 Hz, 2H), 7.80 (s, 4H), 8.04 (d, *J*= 8.4 Hz, 1H), 9.03 (s, 1H) ppm; ^{13}C NMR (101 MHz, DMSO-d6) δ 72.64, 109.05, 119.71, 121.75, 122.18, 124.92, 125.00, 127.46, 128.42, 132.91, 135.50, 141.12, 142.64 ppm; HRMS (TOF MS ES$^+$) calc. for $C_{15}H_{11}N_6OBrNa$ $[M+Na]^+$ 393.01, found 393.01.

2.4c *1-((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl) methoxy)-1H-benzo[d][1,2,3]triazole (**5c**)*: Brown solid; M.p. 140-142 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 3.83 (s, 1H), 5.76 (s, 2H), 7.13 (d, *J*= 9.0 Hz, 2H), 7.42 (ddd, *J*= 8.1, 5.6, 2.3 Hz, 1H), 7.53 (d, *J*= 5.5 Hz, 2H), 7.71 (d, *J*= 9.0 Hz, 2H), 8.05 (d, *J*= 8.4 Hz, 1H), 8.88 (s, 1H) ppm; ^{13}C NMR (101 MHz, DMSO-d6): δ 56.06, 73.23, 109.51, 115.40, 120.13, 122.39, 125.33, 127.96, 128.81, 130.13, 141.12, 143.07, 159.95 ppm; HRMS (TOF MS ES$^+$) calc. for $C_{16}H_{14}N_6O_2Na$ $[M+Na]^+$ 345.11, found 345.11.

2.4d *6-chloro-1-((1-(4-nitrophenyl)-1H-1,2,3-triazol -4-yl)methoxy)-1H-benzo[d][1,2,3]triazole (**5d**)*: Creamish white solid; M.p. 210-212 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 5.81 (s, 2H), 7.45 (dd, *J*= 8.9, 1.9 Hz, 1H), 7.77 (d, *J*= 8.9 Hz, 1H), 8.09 (d, *J*= 8.9 Hz, 1H), 8.18 (d, *J*= 9.1Hz, 2H), 8.47 (d, *J*= 9.1 Hz, 2H), 9.23 (s, 1H) ppm; ^{13}C NMR (101 MHz, DMSO-d6): δ 73.16, 109.37, 121.36, 121.86, 126.06, 126.11, 126.30, 128.51, 134.00, 140.93, 141.79, 141.88, 147.46 ppm; HRMS (TOF MS ES$^+$) calc. for $C_{15}H_{10}N_7O_3ClNa$ $[M + Na]^+$ 394.04, found 394.04.

2.4e *1-((1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl) methoxy)-6-chloro-1H-benzo[d][1,2,3]triazole (**5e**)*: White solid; M.p. 175-177 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 5.78(s, 2H), 7.45 (dd, *J*= 8.9, 1.6 Hz, 1H), 7.73 (s, 1H), 7.82 (s, 4H), 8.09 (d, *J*= 8.9 Hz), 9.06 (s, 1H) ppm; ^{13}C NMR (101 MHz, DMSO-d6) δ 72.92, 108.96, 121.45, 121.85, 122.30, 125.27, 125.86, 128.16, 132.96, 133.54, 135.53, 141.04, 141.37 ppm; HRMS (TOF MS ES$^+$) calc. for $C_{15}H_{10}N_6OBrClNa$ $[M+Na]^+$ 426.97, found 426.96.

2.4f *6-chloro-1-((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)-1H-benzo[d][1, 2, 3]triazole (**5f**)*: Creamish white solid; M.p. 120-122 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 3.83 (s, 3H), 5.77 (s, 2H), 7.15 (d, *J*= 9.0 Hz, 2H), 7.45 (dd, *J*= 8.9, 1.9 Hz, 1H), 7.71 (dd, *J*= 8.4, 5.13 Hz, 3H), 8.09 (d, *J*= 8.9 Hz, 1H), 8.92 (s, 1H) pp; ^{13}C NMR (101 MHz, DMSO-d6) δ 56.07, 73.49, 109.37, 115.40, 121.83, 125.57, 126.22,

128.62, 130.12, 133.90, 141.01, 141.76, 159.99 ppm; HRMS (TOF MS ES$^+$) calc. for $C_{16}H_{13}N_6O_2ClNa$ $[M+Na]^+$ 379.07, found 379.07.

*2.4.4a. d 6-fluoro-1-((1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-1H-benzo[d][1,2,3]triazole (**5g**)*

Creamish white solid; M.p. 242-244 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 5.18 (s, 2H), 7.34 (td, *J*= 9.4, 2.2 Hz, 1H), 7.53 (dd, *J*= 8.0, 2.0 Hz, 1H), 8.13 (dd, *J*= 9.1, 4.5 Hz, 1H), 8.19 (d, *J*= 9.0 Hz, 2H), 8.48 (d, *J*= 9.0 Hz, 2H), 9.25(s, 1H) ppm; ^{13}C NMR (101 MHz, DMSO-d6): δ 72.59, 95.11 (d, ^2J= 29.3 Hz), 114.99 (d, ^2J= 27.3 Hz), 120.90, 122.01 (d, ^3J= 11.0 Hz), 125.58, 125.73, 127.88 (d, ^3J= 15.1 Hz,), 139.70, 140.54, 141.48, 147.04, 161.98 (d, ^1J= 246.8 Hz) ppm; HRMS (TOF MS ES$^+$) calc. for $C_{15}H_{10}N_7O_3$-FNa $[M+Na]^+$ 378.07, found 378.07.

2.4g *1-((1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-6-fluoro-1H-benzo[d][1,2,3]triazole (**5h**)*: Creamish white solid; M.p. 174-176 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 5.77 (s, 2H), 7.33 (td, *J*= 9.3, 2.2 Hz, 1H), 7.48 (dd, *J*= 8.0, 2.1 Hz, 1H), 7.82 (s, 4H), 8.12 (dd, *J*= 9.1, 4.5 Hz, 1H), 9.06 (s, 1H) ppm; ^{13}C NMR (101 MHz, DMSO-d6) δ 77.91, 100.26 (d, ^2J= 29.3 Hz), 119.97, 120.24 (d, ^3J= 27.4 Hz), 127.17 (d, ^2J= 40.4 Hz), 133.09 (d, ^3J= 15.2 Hz), 138.12, 140.71, 144.85, 146.20, 167.13 (d, ^1J= 247.5 Hz) ppm; HRMS calc. for $C_{15}H_{11}N_6OBrF$ $[M+H]^+$ 390.18, found 391.01.

2.4h *5-chloro-1-((1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-1H-benzo[d][1,2,3]triazole (**5i**)*: Pale yellow solid; M.p. 140-142 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 5.83 (s, 2H), 7.61 (d, *J*= 10.6 Hz, 2H), 8.17 (d, *J*= 9.1 Hz, 2H), 8.24 (s, 1H), 8.47 (d, *J*= 9.1 Hz, 2H), 9.23 (s, 1H) ppm; ^{13}C NMR (101 MHz, DMSO-d6) δ 73.20, 111.30, 119.53, 125.96, 126.12, 126.85, 129.55, 140.93, 141.85, 143.65, 147.43 ppm; HRMS calc. for $C_{15}H_{11}N_7O_3Cl$ $[M+H]^+$ 372.74, found 372.06.

2.4i *1-((1-(4-bromophenyl)-5-chloro-1H-1,2,3-triazol-4-yl)methoxy)-1H-benzo[d][1,2,3]triazole (**5j**)*: Creamish White solid; M.p. 108-110 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 5.79 (s, 2H), 7.58 (s, 2H), 7.81 (s, 4H), 8.29 (s, 1H), 9.03(s. 1H) ppm; ^{13}C NMR (101 MHz, DMSO-d6) δ 73.35, 111.28, 119.50, 122.22, 122.65, 125.52, 126.90, 129.49, 129.94, 133.34, 135.93, 141.40, 143.64 ppm; HRMS (TOF MS ES$^+$) calc. for $C_{15}H_{10}N_6OBrClNa$ $[M+Na]^+$ 426.97, found 426.966.

2.4j *5-chloro-1-((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)-1H-benzo[d][1,2,3]triazole (**5k**)*: White solid; M.p. 185-187 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 3.83 (s, 3H), 5.78 (s, 2H), 7.14 (d, *J*= 9.0 Hz, 2H), 7.58 (d, *J*= 1.1 Hz, 2H), 7.72 (d, *J*= 9.0 Hz, 2H), 8.23 (s, 1H), 8.89 (s, 1H) ppm; ^{13}C NMR (101 MHz, DMSO-d6) δ 56.07, 73.51, 112.29, 115.40, 119.49, 122.42, 125.42, 126.95, 129.45, 129.92, 130.11, 140.96, 143.63, 159.97 ppm; HRMS calc. for $C_{16}H_{14}N_6O_2Cl$ $[M+H]^+$ 357.08, found 357.09.

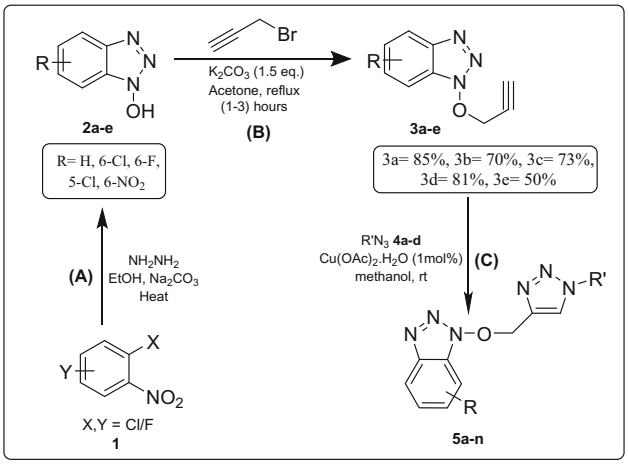
2.4k *1-((1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-6-nitro-1H-benzo[d][1,2,3]triazole (**5l**)*: Pale yellow solid; M.p. 172-175 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 5.78 (s, 2H), 7.45 (dd, *J*= 8.9,1.7 Hz, 1H), 7.73 (d, *J*= 1.2 Hz, 1H), 7.83 (s, 4H), 8.09 (d, *J*= 8.9 Hz, 1H), 9.06 (s, 1H) ppm; ^{13}C NMR (101 MHz, DMSO-d6) δ 72.90, 108.94, 121.43, 121.83, 122.28, 125.24, 125.83, 128.14, 132.94, 133.52, 135.52, 141.02, 141.35 ppm; HRMS calc. for $C_{15}H_{11}N_7O_3Br$ $[M+H]^+$ 416.00, found 416.01.

2.4l *6-chloro-1-((1-(3-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)-1H-benzo[d][1,2,3]triazole (**5m**)*: Pale yellow solid; M.p. 135-137 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 3.85 (s, 3H), 5.78 (s, 2H), 7.09 (d, *J*= 7.0 Hz, 1H), 7.55-7.33 (m, 5H), 7.72 (s, 1H), 8.09 (d, *J*= 8.6 Hz, 1H), 9.04 (s, 1H) ppm; ^{13}C NMR (101 MHz, DMSO-d6) δ 56.69, 72.99, 105.94, 108.96, 112.32, 114.87, 121.43, 125.31, 125.84, 128.19, 131.00, 133.52, 137.35, 140.79, 141.35, 160.23 ppm; HRMS (TOF MS ES$^+$) calc. for $C_{16}H_{13}N_6O_2ClNa$ $[M+Na]^+$ 379.07, found 379.07.

2.4m *1-((1-(3-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methoxy)-6-nitro-1H-benzo[d][1,2,3]triazole (**5n**)*: Pale yellow solid; M.p. 170-172 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 3.85 (s, 3H), 5.88 (s, 2H), 7.21–6.99 (m, 1H), 7.39 (d, *J*= 6.3 Hz, 2H), 7.50 (t, *J*= 8.4 Hz, 1H), 8.22 (dd, *J*= 9.1, 1.9 Hz, 1H), 8.34 (d, *J*= 9.1 Hz, 1H), 8.51 (d, *J*= 1.7 Hz, 1H), 9.09 (s, 1H) ppm; ^{13}C NMR (101 MHz, DMSO-d6) δ 56.07, 74.04, 106.28, 107.41, 112.67, 115.32, 120.11, 121.75, 125.64, 127.53, 131.39, 137.72, 141.13, 145.01, 147.44, 160.62 ppm; HRMS (TOF MS ES$^+$) calc. for $C_{16}H_{13}N_7O_4Na$ $[M+Na]^+$ 390.09, found 390.09.

3. Results and Discussion

At the very onset, 1-hydroxybenzotriazoles (HoBT) **2a-e** were synthesized using the previously reported protocol,[47] as depicted in Scheme 1(A). Next, the



Scheme 1. Synthesis of benzotriazole-triazole conjugates.

synthesis of benzotriazole alkyne **3**, a key partner for CuAAC was carried out by the propargylation of 1-hydroxybenzotriazole **2** using the well-known strategy shown in the Scheme 1 (B). The structure of these benzotriazole alkynes has been characterized by spectroscopic techniques (^{1}H NMR and ^{13}C NMR). In ^{1}H NMR, the characteristic acetylenic proton is observed at delta 2.5 ppm clearly indicating the formation of benzotriazole alkyne, which is further supported by the ^{13}C NMR and mass spectral studies. Similarly, a series of aryl azides **4a-d**, the second coupling partner in click reaction, was synthesized from arylamines using a method available in the literature.[48]

With these benzotriazole alkynes **3a-e** and azides **4a-d** in hand, we intended to synthesize the series of target benzotriazole-triazole conjugates using the azide-alkyne cycloaddition route described in Scheme 1 (C). In this context, the focus was set up on the optimization of the click reaction for the synthesis of benzotriazole-triazole conjugate **5a** from benzotriazole alkyne **3a** and 1-azido-4-nitrobenzene **4a** in acetonitrile at room temperature under catalyst-free conditions (Entry 1, Table 1).

It was found that no product formation was observed when copper (I) oxide was used as the sole catalyst (Entry 3, Table 1), but with copper (I) iodide, the desired product was observed in 51% yield (Entry 2, Table 1). The formation of the product is confirmed by physical data and spectroscopic techniques. In ^{1}H NMR, the characteristic singlet peaks displaying at delta 9.2 ppm and 5.81 ppm correspond to triazolyl proton and methylene protons, respectively (Figure 2), thereby confirming the formation of desired product, which ^{13}C NMR and HRMS further support.

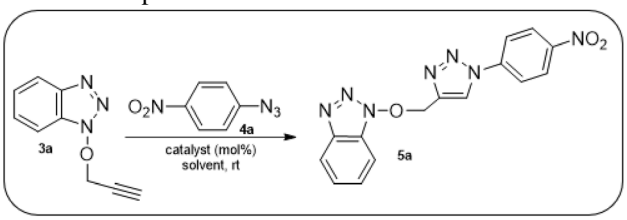
Next, the same reaction with copper (II) sulphate was attempted, which delivered the desired product in 57% yield (Entry 4, Table 1). However, a further increase in yield (60%) was observed with copper acetate as a catalyst (Entry 5, Table 1). Afterward, the reaction was investigated in methanol and water to probe the effect of these solvents. Surprisingly, 70% yield was observed in methanol (Entry 6, Table 1) compared to 51% in water (Entry 7, Table 1). Notably, the reaction gave maximum yield with copper acetate (1.0 mol%) in methanol without using any reducing agent.

It is pertinent to mention that CuAAC is the most common protocol for click reaction and generally uses Cu(II) in the presence of reducing agents such as sodium ascorbate[49] in order to reduce Cu(II) to Cu(I), which is an active catalytic entity involved. However, under the present protocol, no external reducing agent was used.

Further, to optimize the concentration of catalyst, we raised the concentration of catalyst to 5.0 mol%, but no improvement in product yield was observed (69%, Entry 8, Table 1), which indicated that 1.0 mol% of catalyst in methanol is the best condition for the envisaged protocol. With the systematic optimization of the reaction conditions, the devised protocol was employed on differently substituted benzotriazole alkynes and aryl azides, the results of which are shown in Table 2. The reaction proceeded efficiently in all the cases to deliver the desired product in yields ranging from 34-98%. In order to check the synthetic applicability of the developed protocol, the gram-scale reaction was performed. When the reaction was carried out with 6.0 mmol (1.04 gm) of alkyne **3a** and 4.0 mmol of aryl azide **4a** under standard conditions, 1.3 gm of **5a** was obtained in 62% yields.

Using the above-optimized conditions, various substituted aromatic azides (for the CuAAC reaction) with both electron-donating and withdrawing-groups present in ortho, para, and meta positions were used for the synthesis of a series of novel benzotriazole-triazole scaffolds. When either electron-donating or electron-withdrawing substituents (–Br, $–NO_2$, and $–OCH_3$) were present in the para position, the target products were formed in good to excellent yields. However, with aromatic azides having electron-donating or electron-withdrawing groups in the meta position, there was a slight decrease in the yield of the desired product, whereas the yield was insignificant with ortho-substituted azides. This decrease in the yield of the desired product may be attributed to electronic effects. But when the benzotriazole alkynes

Table 1. Optimization of the reaction conditions for CuAAC.



Entry No.	Catalyst (mol%)	Solvent	Time (min)	Yield %
1	No catalyst	CH_3CN	120	No reaction
2	CuI (1)	CH_3CN	120	51
3	Cu_2O (1)	CH_3CN	120	No reaction
4	$CuSO_4.5H_2O$ (1)	CH_3CN	120	57
5	$Cu(OAc)_2$ (1)	CH_3CN	120	60
6	$Cu(OAc)_2$ (1)	CH_3OH	120	70
7	$Cu(OAc)_2$ (1)	H_2O	120	51
8	$Cu(OAc)_2$(5)	CH_2OH	120	69

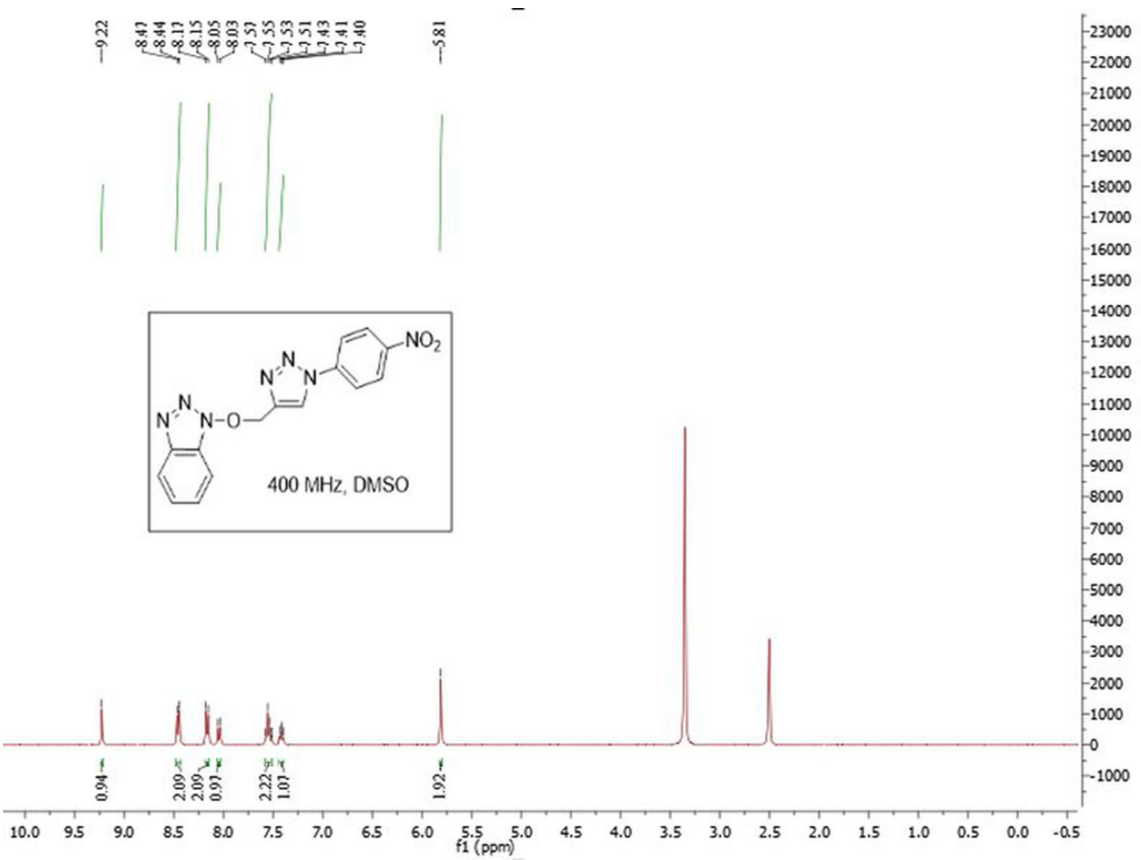
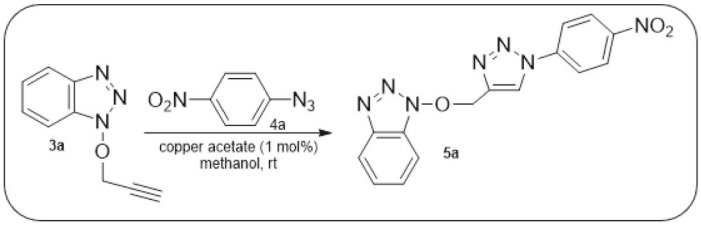


Figure 2. Representation of ^{1}H NMR spectrum of **5a**.

having electron-withdrawing and electron-donating groups were used (Table 2), no significant substituent effects were observed.

Further, the current protocol shows complete regioselectivity in favour of the 1,4-disubstituted product which is confirmed by the characteristic ^{13}C NMR peak at delta 119 ppm.[50] The formation of 1,4- vs 1,5-isomer has been very well studied by Creary *et al.* using ^{13}C NMR spectral data.[50] The studies established that the 1,4-isomer shows a

Table 2. Substrate scope of the copper-acetate catalysed CuAAC[a].



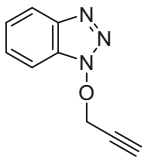
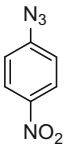
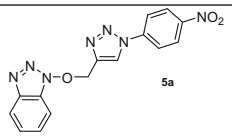
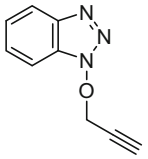
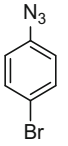
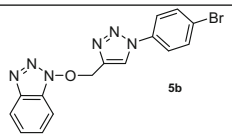
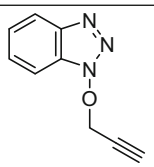
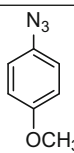
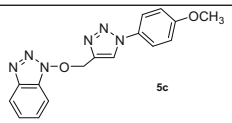
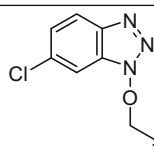
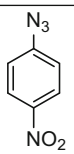
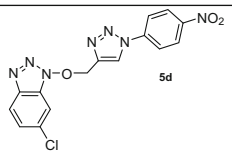
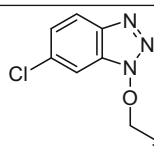
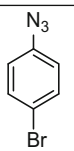
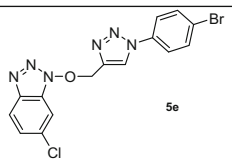
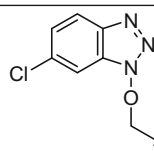
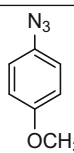
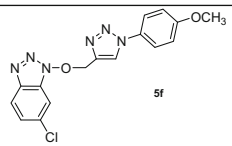
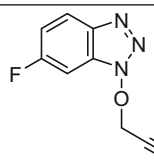
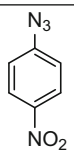
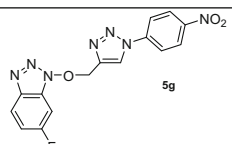
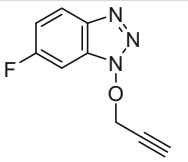
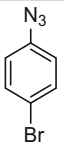
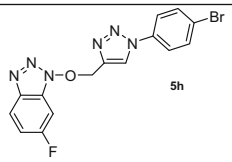
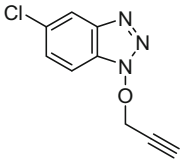
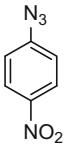
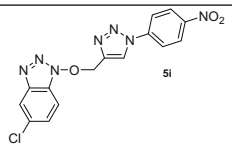
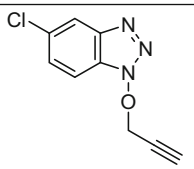
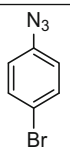
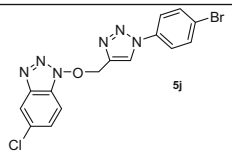
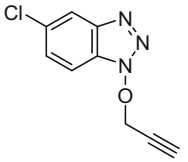
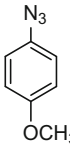
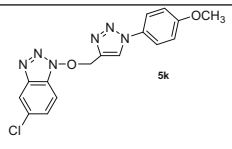
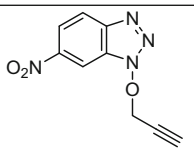
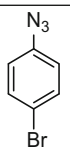
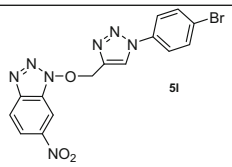
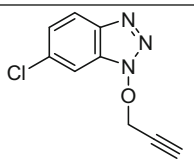
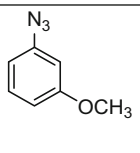
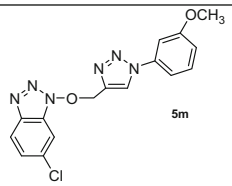
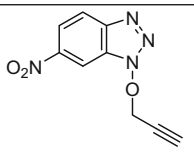
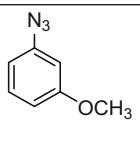
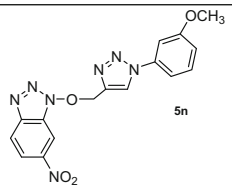
Entry	Starting material	Azide	Product	Time (minutes)	Yield[b] (%)
1				120	70
2				120	97
3				120	94
4				120	65
5				120	83
6				120	98
7				120	70

Table 2. continued

Entry	Starting material	Azide	Product	Time (minutes)	Yield[b] (%)
8			 **5h**	120	98
9			 **5i**	120	96
10			 **5j**	120	98
11			 **5k**	120	75
12			 **5l**	120	82
13			 **5m**	120	34
14			 **5n**	120	50

[a]Reaction conditions: Hydroxybenzotriazole alkyne (1.5 mmol), aryl azide (1 mmol), copper acetate (1 mol%), Methanol (1-2 mL).

[b]Yields of pure isolated product.

characteristic peak at δ 120±3 ppm (Figure 3-A) in ^{13}C NMR; however peak at δ 133±3 ppm is observed in the 1,5-isomer (Figure 3-B). However, in the current study, the presence of a consistent peak at 120±3 ppm in all the synthesized molecules **5a-n** fully supports the exclusive formation of 1,4-disubstituted-1,2,

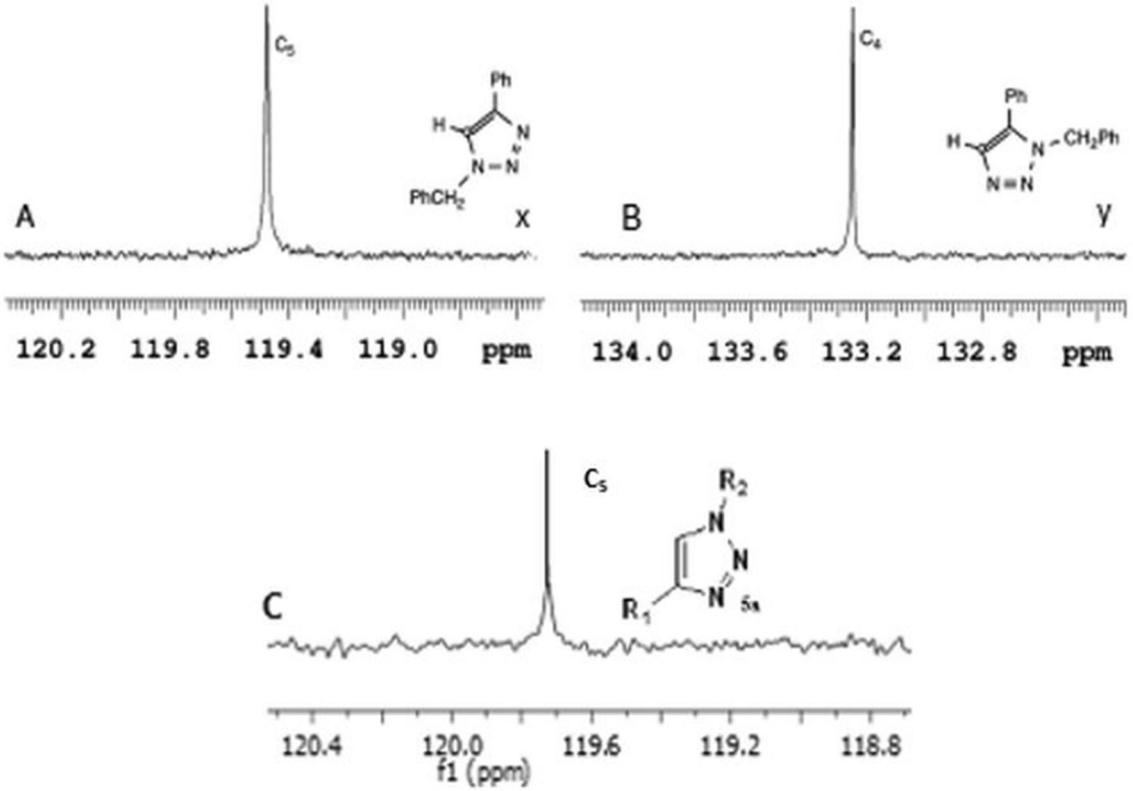


Figure 3. (**A**) Expanded ^{13}C NMR spectrum of **x**[50] (**B**) Expanded ^{13}C NMR spectrum of **y**[50] (**C**) Expanded ^{13}C NMR spectrum of **5a.**

3- triazoles (Figure 3-C). This is strictly in accordance with literature records where copper catalysed reactions exclusively delivered 1,4-disubstituted product[51] but ruthenium catalysed protocols were found to deliver 1,5-disubstituted product as a major product.[52] After completion of the reaction, the product was simply filtered followed by washing with methanol. The structure of the newly synthesized compounds **5a-n** was fully characterized by ^{1}H NMR, ^{13}C NMR, and mass spectroscopy.

4. Conclusions

To summarize, a novel series of benzotriazole-triazole conjugates have been synthesized from a wide range of benzotriazole alkynes and aryl azides using a copper-catalyzed azide-alkyne cycloaddition route. The current protocol avoids using any reducing agent, making this protocol a better route for synthesizing a variety of benzotriazole-linked triazole scaffolds. The notable features of this method include simplicity, cleaner reaction profiles, eliminating the use of reducing agents, and complete regioselectivity in favour of 1,4-disubstituted product. The isolation and purification of all the resultant compounds was carried out by filteration followed by washing without the use of column chromatography. Biological screening of the synthesized molecules is currently underway and will be disclosed in due course of time.

Supplementary Information (SI)

Figures S1-S58 and all additional data for the compound characterization (^{1}H NMR and ^{13}C NMR and mass) is available at www.ias.ac.in/chemsci.

Acknowledgments

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