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REGULAR ARTICLE

Synthesis and antibacterial activity of benzothiazole and benzoxazole-appended substituted 1,2,3-triazoles

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Abstract. A series of benzothiazole and benzoxazole linked 1,4-disubstituted 1,2,3-triazoles was synthesized through copper(I) catalyzed azide-alkyne cycloaddition reaction. FTIR, ^{1}H, ^{13}C-NMR and HRMS techniques were used to examine the structure of synthesized derivatives. Further, these triazole derivatives were screened for *in vitro* antibacterial activities against two Gram-positive bacteria *S. aureus, B. subtilis;* two Gram-negative bacteria *E. coli* and *K. pneumoniae* by serial dilution technique, reflecting moderate to good activity. Compound **7s** exhibited promising antibacterial activity among all the synthesized triazoles.

Keywords. 1,4-disubstituted 1,2,3-triazoles; antibacterial activity; benzothiazole; benzoxazole.

Abbreviations

MIC	Minimum Inhibitory Concentration
MTCC	Microbial Type Culture Concentration
NCDC	National Collection of Dairy Culture

1. Introduction

Heterocycles are an important class that is pervasive in vital bioactive molecules. Among various heterocycles, benzothiazole and benzoxazole compounds have been explored in past and are still in practice for a variety of therapeutic applications which makes this scaffold an interesting moiety for designing new broad-spectrum pharmacophore. Benzothiazole and benzoxazole and their derivatives have depicted various admirable biological properties in form of antioxidant,[1] anticancer,[2,3] anti-inflammatory,[4] analgesic[5] and acetylcholinesterase inhibitory[6] agents. Some of the important marketed drugs having benzothiazole and benzoxazole ring in their structures are Riluzole, Pramipexole, flunoxaprofen, benoxaprofen (Figures 1, 2, 3, 4), etc.

Molecules having triazole nucleus leads to diversified applications in medicine, agriculture, etc. The triazole derivatives have been found to possess immense biological importance like antitubercular,[7] anti-cancer,[8–13] antiparasitic,[14] antimicrobial,[15–22] antileishmanial,[23] antioxidant,[24,25] anti-inflammatory,[26–29] and anti-malarial,[30] α-glycosidase inhibitory,[31] antiviral,[32] antidepressant,[33] acetylcholinesterase inhibitory[34,35] activities have been identified. Triazole nucleus enjoys its importance as the core structure of blockbuster drugs such as fluconazole, Rufinamide, Cefatrizine, etc. In recent years, the chemistry of triazoles and its heterocyclic derivatives led to the development of lead compounds in medicinal chemistry. Owing to this, here click reaction has been used for the formation (synthesis) of 1,4-disubstituted 1,2,3-triazoles from azides and terminal alkynes. "Click" chemistry approach has been formulated to insert a link between triazole nucleus and benzothiazole and benzoxazole moiety with a thought to explore the synergic effect of these two scaffolds. The synthesized 1,2,3-triazoles containing benzothiazole and benzoxazole have also been explored for antibacterial activity against *Staphylococcus aureus, Bacillus subtilis, Klebsiella pneumoniae* and *Escherichia coli.*

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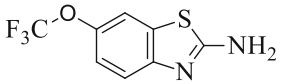


Figure 1. Riluzole.

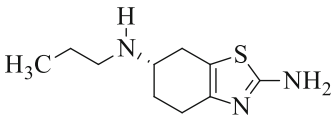


Figure 2. Pramipexole.

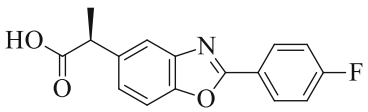


Figure 3. Flunoxaprofen.

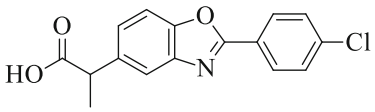


Figure 4. Benoxaprofen.

2. Experimental

2.1 *Chemistry*

The starting materials were purchased from Sigma-Aldrich, Alfa-Aesar, Hi-Media and used without any further purification. Melting points (°C) were determined by an open capillaries method and uncorrected. To monitor the progress of the reaction and to check the purity of compounds, thin-layer chromatography (TLC) was performed using silica gel plates (SIL G/UV254, ALUGRAM). The IR spectra were taken on SHIMAZDU IR AFFINITY-I FTIR spectrometer using potassium bromide (KBr) powder and values are given in cm^{-1}. Nuclear magnetic resonance (NMR) spectra were recorded on BRUKER AVANCE II apparatus operating at 400 MHz (^{1}H) and 100 MHz (^{13}C), in DMSO, and chemical shifts (δ) are given in parts per million downfield from the internal standard trimethylsilane (TMS). Coupling constant (J) values were observed in Hertz (Hz). HRMS were observed on Bruker micro TOF Q-II spectrometer.

General procedure for the synthesis of terminal Alkyne[36,37] **(3a-3b):** The 2-(prop-2-yn-1-ylthio)benzo[d] oxazole(**3a**)/2-(prop-2-yn-1-ylthio)benzo[d]thiazole (**3b**) were synthesized by dropwise addition of propargyl bromide (**2**) (1.0 mmol) to the solution of 2-mercaptobenzoxazole (**1a**)/2-mercaptobenzothiazole (**1b**) (1.0 mmol) in N,N-dimethylformamide in presence of potassium carbonate as base at 0-10 °C for 3 h. After the completion of the reaction, the cooled reaction mixture was poured in ice-cold water and the precipitated products were filtered to get the desired alkynes (**3a-3b**).

General procedure for the synthesis of 4-(bromomethyl)-N-arylbenzamide derivatives (**6a-6j**): The aromatic amines (**5a-5j**) (1.0 mmol) were reacted with 4-(bromomethyl)benzoylbromide (**4**) (1.0 mmol) in dichloromethane and potassium carbonate as a base at 0-10 °C for 2-3 h. After the completion of the reaction as indicated by TLC, the product was extracted with dichloromethane and the organic layer was dried with anhydrous sodium sulphate and concentrated under reduced pressure to obtain 4-(bromomethyl)-N-arylbenzamide derivatives (**6a-6j**) with 80-90% yield.

General procedure for the synthesis of 1,4-disubstituted 1,2,3-triazole derivatives (7a-7t): The targeted 1,4-disubstituted 1,2,3-triazoles with amide and thioether functionality were synthesized by the reaction of 2-(prop-2-yn-1-ylthio)benzo[d]oxazole (**3a**)/2-(prop-2-yn-1-ylthio)-benzo[d]thiazole (**3b**) (1.0 mmol), 4-(bromomethyl)-N-arylbenzamide derivatives (**6a-6j**) (1.0 mmol) and sodium azide using dimethylformamide:water as a solvent in the presence of the catalytic amount of copper sulphate pentahydrate and sodium ascorbate with stirring for 6–10 h at ambient temperature. After the completion of the reaction, the reaction mixture was quenched with ice-cold water and ammonia solution, the precipitates were filtered and recrystallized from ethyl acetate to yield the pure 1,4-disubstituted 1,2,3-triazoles (**7a-7t**).

2.2 *Characterization of benzothiazole and benzoxazole linked 1,4-disubstituted 1,2,3-triazoles*

2.2a *4-((4-((benzo[d]oxazol-2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)methyl)-N-phenylbenzamide* ***(7a)***: Appearance: Brown solid; yield: 79%; M.p.: 152–156 °C; FTIR (KBr): ν_{max} = 3336 (N–H str.), 3143 (C–H str., triazole ring), 2881 (C–H str., aliphatic), 1653 (C=O sym. str., amide), 1500, 1442 (C=C str., aromatic ring), 692 (C–S str.) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.23 (s, 1H, -CONH), 8.24 (s, 1H, C-H triazole), 8.02 (d, J = 8.0 Hz, 1H, ArH), 7.91 (d, J = 8.0 Hz, 2H, ArH), 7.76 (d, J = 8.0 Hz, 1H, ArH), 7.48 (t, J = 8.0, 1H, ArH), 7.41-7.08 (m, 7H, ArH), 5.68 (s, 2H,-NCH_2), 4.71 (s, 2H, -SCH_2); ^{13}C NMR (100 MHz, DMSO) δ 165.56 (C=O), 151.81, 143.14 (C_4 triazole), 141.71, 139.76, 139.53, 135.25, 129.06, 128.55, 128.25, 125.12, 124.85, 124.62 (C_5 triazole), 124.17, 120.79, 118.85, 110.73, 52.90 (-SCH_2), 26.95 (-NCH_2); HRMS (*m/z*) calculated for $C_{24}H_{19}N_5O_2S$ $[M+H]^+$: 442.1293. Found: 442.1318.

2.2b *4-((4-((benzo[d]oxazol-2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)methyl)-N-(o-tolyl)benzamide* ***(7b)***: Appearance: White solid; yield: 81%; M.p.: 152–156 °C; FTIR (KBr): ν_{max} = 3257 (N–H str.), 3124

(C–H str., triazole ring), 2983 (C–H str., aliphatic), 1643 (C=O sym. str., amide), 1500, 1452 (C=C str., aromatic ring), cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.83 (s, 1H, -CONH), 8.22 (s, 1H, C-H triazole), 7.88 (d, J = 8.0 Hz, 2H), 7.625 (d, J = 4.0 Hz, 2H, ArH), 7.36 (d, J = 8.0 Hz, 2H, ArH), 7.32-7.26 (m, 3H, ArH), 7.23 (d, J = 8.0 Hz, 1H, ArH), 7.19-7.12 (m, 2H, ArH), 5.63 (s, 2H,-NCH_2), 4.65 (s, 2H, -SCH_2), 2.17 (s, 3H, -CH_3). ^{13}C NMR (100 MHz, DMSO) δ 165.36 (C=O), 151.85, 143.21(C_4 triazole), 141.75, 130.85, 130.85, 128.60, 128.39, 127.07, 126.55, 125.20, 124.93, 124.73 (C_5 triazole), 118.91, 110.82, 52.93 (-SCH_2), 26.96 (-NCH_2), 18.40; HRMS (*m/z*) calculated for $C_{25}H_{21}N_5O_2S$ $[M+H]^+$: 456. 1450. Found: 456.1493.

2.2c *4-((4-((benzo[d]oxazol-2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)methyl)-N-(m-tolyl)benzamide* (***7c***): Appearance: White solid; yield: 85%; M.p.: 152–156 °C; FTIR (KBr): ν_{max} = 3346 (N–H str.), 3115 (C–H str., triazole ring), 2918 (C–H str., aliphatic), 1653 (C=O sym. str., amide), 1527, 1440 (C=C str., aromatic ring), cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.14 (s, 1H, -CONH), 8.22 (s, 1H, C-H triazole), 7.85 (d, J = 8.0 Hz, 2H, ArH), 7.64-7.58 (m, 3H, ArH), 7.35 (d, J = 8.0 Hz, 2H, ArH), 7.30 (t, J = 8.0 Hz, 2H, ArH), 7.20 (s, 1H, ArH), 7.11 (d, J = 8.0 Hz, 2H), 5.63 (s, 2H,-NCH_2), 4.65 (s, 2H, -SCH_2), 2.23 (s, 3H, -CH_3). ^{13}C NMR (100 MHz, DMSO) δ 166.22 (C=O), 165.42, 153.09, 143.30 (C_4 triazole), 139.79, 137.06, 135.24, 133.19, 129.54, 128.56, 128.28, 126.92, 125.11, 124.80 (C_5 triazole), 122.38, 121.80, 120.84, 52.91 (-SCH_2), 27.94 (-NCH_2), 21.03; HRMS (*m/z*) calculated for $C_{25}H_{21}N_5O_2S$ $[M+H]^+$: 456. 1450. Found: 456.1506.

2.2d *4-((4-((benzo[d]oxazol-2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)methyl)-N-(p-tolyl)benzamide* (***7d***): Appearance: White solid; yield: 82%; M.p.: 152–156 °C; FTIR (KBr): ν_{max} = 3361 (N–H str.), 3109 (C–H str., triazole ring), 2951 (C–H str., aliphatic), 1643 (C=O sym. str., amide), 1517, 1423 (C=C str., aromatic ring), cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H, -CONH), 8.22 (s, 1H, C-H triazole), 7.84 (d, J = 8.0 Hz, 2H, ArH), 7.62 (d, J = 8.0 Hz, 2H), 7.55 (s, 1H, ArH), 7.50 (d, J = 8.0 Hz, 1H, ArH), 7.35 (d, J = 8.0 Hz, 2H, ArH), 7.30 (m, 2H, ArH), 7.18 (m, 1H, ArH), 6.88 (d, J = 8.0 Hz, 1H, ArH), 5.63 (s, 2H,-NCH_2), 4.65 (s, 2H, -SCH_2), 2.26 (s, 3H, -CH_3); ^{13}C NMR (100 MHz, DMSO) δ 165.66 (C=O), 151.92, 143.23 (C_4 triazole), 141.74, 139.83, 139.50, 138.30, 135.31, 129.00, 128.60, 128.32, 125.21, 124.93, 124.74 (C_5 triazole), 121.35, 118.91, 118.00, 110.82, 52.92 (-SCH_2), 26.96 (-NCH_2), 21.74; HRMS (*m/z*) calculated for $C_{25}H_{21}N_5O_2S$ $[M+H]^+$: 456. 1450. Found: 456.1503.

2.2e *4-((4-((benzo[d]oxazol-2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)methyl)-N-(4-methoxyphenyl)benzamide* (***7e***): Appearance: White solid; yield: 83%; M.p.: 152–156 °C; FTIR (KBr): ν_{max} = 3311 (N–H str.), 3115 (C–H str., triazole ring), 2954 (C–H str., aliphatic), 1645 (C=O sym. str., amide), 1508, 1409 (C=C str., aromatic ring), cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.22 (s, 1H, -CONH), 8.28 (s, 1H, C-H triazole), 7.93 (s, 1H, ArH), 7.67-7.42 (m, 10H, ArH), 6.92 (s, 1H, ArH), 5.67 (s, 2H,-NCH_2), 4.67 (s, 2H, -SCH_2), 3.24 (s, 3H, -OCH_3); ^{13}C NMR (100 MHz, DMSO) δ 165.14 (C=O), 156.03, 143.13 (C_4 triazole), 141.79, 139.61, 135.16, 132.62, 128.51, 128.20, 125.13, 124.86, 124.72 (C_5 triazole), 122.47, 118.84, 114.16, 110.75, 55.64, 52.87 (-SCH_2), 26.92 (-NCH_2); HRMS (*m/z*) calculated for $C_{25}H_{21}N_5O_3S$ $[M+H]^+$: 472. 1399. Found: 472.1446.

2.2f *4-((4-((benzo[d]oxazol-2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)methyl)-N-(4-nitrophenyl)benzamide* (***7f***): Appearance: White solid; yield: 78%; M.p.: 152–156 °C; FTIR (KBr): ν_{max} = 3354 (N–H str.), 3107 (C–H str., triazole ring), 2942 (C–H str., aliphatic), 1658 (C=O sym. str., amide), 1504, 1406 (C=C str., aromatic ring), cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.77 (s, 1H, -CONH), 8.29 (s, 1H, C-H triazole), 8.26 (m, 2H, ArH), 8.045 (d, J = 12.0 Hz, 2H, ArH), 7.93 (d, J = 8.0 Hz, 2H, ArH), 7.69– 7.62 (m, 2H, ArH), 7.43 (d, J = 8.0 Hz, 2H, ArH), 7.39–7.30 (m, 2H, ArH), 5.69 (s, 2H,-NCH_2), 4.69 (s, 2H, -SCH_2). ^{13}C NMR (100 MHz, DMSO) δ 166.31 (C=O), 151.81, 145.84, 143.00 (C_4 triazole), 141.71, 140.45, 134.48, 128.83, 128.36, 125.26, 125.12, 124.85, 124.66 (C_5 triazole), 120.31, 118.85, 110.73, 52.87 (-SCH_2), 26.95 (-NCH_2); HRMS (*m/z*) calculated for $C_{24}H_{18}N_6O_2S$ $[M+H]^+$: 487. 1144. Found: 487.1177.

2.2g *4-((4-((benzo[d]oxazol-2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)methyl)-N-(4-fluorophenyl)benzamide* (***7g***): Appearance: Brown solid; yield: 81%; M.p.: 152–156 °C; FTIR (KBr): ν_{max} = 3365 (N–H str.), 3128 (C–H str., triazole ring), 3078 (C–H str., aliphatic), 1660 (C=O sym. str., amide), 1508, 1450 (C=C str., aromatic ring), 685 (C–S str.) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H, -CONH), 8.25 (s, 1H, C-H triazole), 7.90 (d, J = 8.0 Hz, 2H, ArH), 7.77 (dd, J = 8.0, 4.0 Hz, 2H, ArH), 7.67-7.65 (m, 2H, ArH), 7.40 (d, J = 8.0 Hz, 2H, ArH),7.36-7.33 (m, 2H, ArH) 7.22-7.18 (m, 2H, ArH), 5.68 (s, 2H,-NCH_2), 4.69 (s, 2H, -SCH_2); ^{13}C NMR (100 MHz, DMSO) δ 165.48 (C=O), 163.96, 151.82, 143.15 (C_4 triazole), 141.72, 139.84, 135.92, 135.07, 128.53, 128.28, 125.13, 124.86, 124.63 (C_5 triazole), 122.66, 122.59, 118.86, 115.76, 115.54, 110.73, 52.89 (-SCH_2), 26.96 (-NCH_2); HRMS (*m/z*) calculated for $C_{24}H_{18}FN_5O_2S$ $[M+H]^+$: 460. 1199. Found: 460.1254.

2.2h *4-((4-((benzo[d]oxazol-2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)methyl)-N-(4-chlorophenyl)benzamide* (***7h***): Appearance: White solid; yield: 77%; M.p.: 152–156 °C; FTIR (KBr): ν_{max} = 3298 (N–H str.), 3132 (C–H str., triazole ring), 2848 (C–H str., aliphatic), 1654 (C=O sym. str., amide), 1498, 1454 (C=C str., aromatic ring), cm^{-1}; ^1H NMR (400 MHz,

DMSO-d_6) δ 10.40 (s, 1H, -CONH), 8.27 (s, 1H, C-H triazole), 8.04 (d, J = 8.0 Hz, 1H, ArH), 7.98 (d, J = 8.0 Hz, 2H, ArH), 7.87 (d, J = 8.0 Hz, 1H, ArH), 7.69–7.65 (m, 2H, ArH), 7.62-7.53 (m, 3H, ArH), 7.44 (d, J = 8.0 Hz, 1H, ArH), 7.37–7.33 (m, 2H, ArH), 5.71 (s, 2H,-NCH_2), 4.71 (s, 2H, -SCH_2). ^{13}C NMR (100 MHz, DMSO) δ 166.19 (C=O), 163.96, 151.82, 143.15 (C_4 triazole), 141.73, 139.87, 134.75, 134.23, 129.60, 128.71, 128.53, 128.34, 126.76, 126.53, 126.43, 125.99, 125.12, 124.85, 124.65 (C_5 triazole), 124.26, 123.74, 118.86, 110.73, 52.94 (-SCH_2), 26.98 (-NCH_2); HRMS (*m/z*) calculated for $C_{24}H_{18}ClN_5O_2S$ $[M+H]^+$: 476.0870, $[M+3]^+$: 478.0840. Found: 476.0934, $[M+3]^+$: 478.0898.

2.2i *4-((4-((benzo[d]oxazol-2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)methyl)-N-(4-bromophenyl)benzamide* ***(7i)***: Appearance: White solid; yield: 86%; M.p.: 152–156 °C; FTIR (KBr): ν_{max} = 3304 (N–H str.), 3120 (C–H str., triazole ring), 2945 (C–H str., aliphatic), 1651 (C=O sym. str., amide), 1527, 1452 (C=C str., aromatic ring), cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (s, 1H, -CONH), 8.25 (s, 1H, C-H triazole), 7.90 (d, J = 8.0 Hz, 2H, ArH), 7.755 (d, J = 12.0 Hz, 2H, ArH), 7.68–7.64 (m, 2H, ArH), 7.535 (d, J = 12.0 Hz, 2H, ArH), 7.40 (d, J = 8.0 Hz, 2H, ArH), 7.37–7.31 (m, 2H, ArH), 5.68 (s, 2H,-NCH_2), 4.69 (s, 2H, -SCH_2); ^{13}C NMR (100 MHz, DMSO) δ 165.66 (C=O), 163.94, 151.81, 143.14 (C_4 triazole), 141.71, 139.95, 138.96, 134.93, 131.89, 128.60, 128.27, 125.11, 124.84, 124.63 (C_5 triazole), 122.67, 118.85, 115.83, 110.73, 52.88 (-SCH_2), 26.96 (-NCH_2); HRMS (*m/z*) calculated for $C_{24}H_{18}BrN_5O_2S$ $[M+H]^+$: 520.0365, $[M+3]^+$: 522.0344. Found $[M+H]^+$: 520.0407, $[M+3]^+$: 522.0405.

2.2j *4-((4-((benzo[d]oxazol-2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)methyl)-N-(naphthalen-1-yl)benzamide* ***(7j)***: Appearance: White solid; yield: 76%; M.p.: 152–156 °C; FTIR (KBr): ν_{max} = 3296 (N–H str.), 3113 (C–H str., triazole ring), 2984 (C–H str., aliphatic), 1654 (C=O sym. str., amide), 1539, 1450 (C=C str., aromatic ring), cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (s, 1H, -CONH), 8.25 (s, 1H, C-H triazole), 7.90 (d, J = 8.0 Hz, 2H, ArH), 7.81 (d, J = 8.0 Hz, 2H, ArH), 7.67–7.64 (m, 2H, ArH), 7.44– 7.38 (m, 4H, ArH), 7.37–7.20 (m, 5H, ArH), 5.68 (s, 2H,-NCH_2), 4.69 (s, 2H, -SCH_2). ^{13}C NMR (100 MHz, DMSO) δ 165.66 (C=O), 163.94, 151.81, 143.14 (C_4 triazole), 141.71, 139.94, 138.54, 134.94, 128.98, 128.60, 128.28, 125.12, 124.85, 124.63 (C_5 triazole), 122.30, 118.85, 110.73, 52.88 (-SCH_2), 26.96 (-NCH_2); HRMS (*m/z*) calculated for $C_{28}H_{21}N_5O_2S$ $[M+H]^+$: 492. 1450. Found: 492.1486.

2.2k *4-((4-((benzo[d]thiazol-2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)methyl)-N-phenylbenzamide* ***(7k)***: Appearance: White solid; yield: 75%; M.p.: 152–156 °C; FTIR (KBr): ν_{max} = 3363 (N–H str.), 3140 (C–H str., triazole ring), 3062 (C–H str., aliphatic), 1653 (C=O sym. str., amide), 1506, 1440 (C=C str., aromatic ring), cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.23 (s, 1H, -CONH), 8.24 (s, 1H, C-H triazole), 8.02 (d, J = 8.0 Hz, 1H, ArH), 7.91 (d, J = 8.0 Hz, 2H, ArH), 7.76 (d, J = 8.0 Hz, 1H, ArH), 7.48 (t, J = 8.0, 1H, ArH), 7.41-7.08 (m, 8H, ArH), 5.68 (s, 2H,-NCH_2), 4.71 (s, 2H, -SCH_2); ^{13}C NMR (100 MHz, DMSO) δ 165.54 (C=O), 143.09 (C_4 triazole)135.21, 129.05, 128.56, 128.22, 126.84, 125.03, 124.70 (C_5 triazole), 122.29, 121.75, 120.81, 113.73, 52.88 (-SCH_2), 26.90 (-NCH_2); HRMS (*m/z*) calculated for $C_{24}H_{19}N_5OS_2$ $[M+H]^+$: 458. 1065. Found: 458.1098.

2.2l *4-((4-((benzo[d]thiazol-2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)methyl)-N-(o-tolyl)benzamide* ***(7l)***: Appearance: White solid; yield: 82%; M.p.: 152–156 °C; FTIR (KBr): ν_{max} = 3361 (N–H str.), 3109 (C–H str., triazole ring), 2951 (C–H str., aliphatic), 1643 (C=O sym. str., amide), 1517, 1423 (C=C str., aromatic ring), cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H, -CONH), 9.18 (s, 1H, C-H triazole), 8.47 (d, J = 8.0 Hz, 1H, ArH), 8.39 (d, J = 8.0 Hz, 1H, ArH), 8.15 (d, J = 8.0 Hz, 1H, ArH), 8.08-8.01 (m, 2H, ArH), 7.62–7.45 (m, 5H, ArH), 7.42–7.34 (t, J = 8.0 Hz, 2H, ArH), 5.67 (s, 2H, -NCH_2), 4.72 (s, 2H, -SCH_2), 2.67 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 165.36 (C=O), 151.85, 143.21 (C_4 triazole), 141.75, 130.85, 130.85, 128.60, 128.39, 127.07, 126.55, 125.20, 124.93, 124.73 (C_5 triazole), 118.91, 110.82, 52.93 (-SCH_2), 26.96 (-NCH_2), 18.40; HRMS (*m/z*) calculated for $C_{25}H_{21}N_5OS_2$ $[M+H]^+$: 472. 1221. Found: 472.1271.

2.2m *4-((4-((benzo[d]thiazol-2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)methyl)-N-(m-tolyl)benzamide* ***(7m)***: Appearance: White solid; yield: 79%; M.p.: 152–156 °C; FTIR (KBr): ν_{max} = 3361 (N–H str.), 3124 (C–H str., triazole ring), 2942 (C–H str., aliphatic), 1645 (C=O sym. str., amide), 1521, 1423 (C=C str., aromatic ring), cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.83 (s, 1H, -CONH), 8.22 (s, 1H, C-H triazole), 7.88 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 8.0 Hz, 2H, ArH), 7.36 (d, J = 8.0 Hz, 2H, ArH), 7.32-7.26 (m, 3H, ArH), 7.23 (d, J = 8.0 Hz, 1H, ArH), 7.19-7.12 (m, 2H, ArH), 5.63 (s, 2H,-NCH_2), 4.65 (s, 2H, -SCH_2), 2.17 (s, 3H, -CH_3). ^{13}C NMR (100 MHz, DMSO) δ 165.36 (C=O), 151.85, 143.21 (C_4 triazole), 141.75, 130.85, 130.85, 128.60, 128.39, 127.07, 126.55, 125.20, 124.93, 124.73 (C_5 triazole), 118.91, 110.82, 52.93 (-SCH_2), 26.96 (-NCH_2), 18.40; HRMS (*m/z*) calculated for $C_{25}H_{21}N_5OS_2$ $[M+H]^+$: 472. 1221. Found: 472.1271.

2.2n *4-((4-((benzo[d]thiazol-2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)methyl)-N-(p-tolyl)benzamide* ***(7n)***: Appearance: Brown solid; yield: 80%; M.p.: 152–156 °C; FTIR (KBr): ν_{max} = 3361 (N–H str.), 3120 (C–H str., triazole ring), 2956 (C–H str., aliphatic), 1651 (C=O sym. str., amide), 1508, 1408 (C=C str., aromatic ring), cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.14 (s, 1H,

-CONH), 8.22 (s, 1H, C-H triazole), 7.85 (d, *J* = 8.0 Hz, 2H, ArH), 7.64-7.58 (m, 3H, ArH), 7.35 (d, *J* = 8.0 Hz, 2H, ArH), 7.30 (t, *J* = 4.0 Hz, 2H, ArH), 7.20 (s, 1H, ArH), 7.11 (d, *J* = 8.0 Hz, 2H), 5.63 (s, 2H,-NCH_2), 4.65 (s, 2H, -SCH_2), 2.23 (s, 3H, -CH_3). ^{13}C NMR (100 MHz, DMSO) δ 165.41 (C=O), 164.03, 151.85, 143.20 (C_4 triazole), 141.74, 139.76, 137.07, 135.32, 133.18, 129.53, 128.58, 128.30, 125.20, 124.92, 124.73 (C_5 triazole), 120.85, 118.91, 110.82, 52.92 (-SCH_2), 26.96 (-NCH_2), 21.03; HRMS (*m/z*) calculated for $C_{25}H_{21}N_5OS_2$ $[M+H]^+$: 472. 1221. Found: 472.1271.

2.2o *4-((4-((benzo[d]thiazol-2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)methyl)-N-(4-methoxyphenyl)benzamide (**7o**)*: Appearance: Brown solid; yield: 83%; M.p.: 152–156 °C; FTIR (KBr): ν_{max} = 3361 (N–H str.), 3109 (C–H str., triazole ring), 2951 (C–H str., aliphatic), 1643 (C=O sym. str., amide), 1517, 1423 (C=C str., aromatic ring), cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.07 (s, 1H, -CONH), 8.20 (s, 1H, C-H triazole), 7.98 (d, *J* = 8.0 Hz, 1H, ArH), 7.84 (m, 3H, ArH), 7.61 (d, *J* = 8.0 Hz, 2H, ArH), 7.44 (t, *J* = 8.0 Hz, 2H, ArH), 7.36-7.32 (m, 2H, ArH), 6.88 (d, *J* = 8.0 Hz, 2H, ArH), 5.63 (s, 2H,-NCH_2), 4.67 (s, 2H, -SCH_2), 3.70 (s, 3H, -OCH_3). ^{13}C NMR (100 MHz, DMSO) δ 166.33 (C=O), 153.23, 144.97 (C_4 triazole), 139.71, 135.24, 132.79, 128.50, 128.28, 126.93, 125.11(C_5 triazole), 122.42, 121.80, 114.26, 55.68, 52.91(-SCH_2), 28.08 (-NCH_2); HRMS (*m/z*) calculated for $C_{25}H_{21}N_5OS_2$ $[M+H]^+$: 488.1170. Found: 488.1203.

2.2p *4-((4-((benzo[d]thiazol-2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)methyl)-N-(4-nitrophenyl)benzamide (**7p**)*: Appearance: White solid; yield: 72%; M.p.: 152–156 °C; FTIR (KBr): ν_{max} = 3356 (N–H str.), 3112 (C–H str., triazole ring), 2953 (C–H str., aliphatic), 1658 (C=O sym. str., amide), 1506, 1423 (C=C str., aromatic ring), cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.75 (s, 1H, -CONH), 8.26 – 8.20 (m, 3H, C-H triazole, ArH), 7.99 (t, *J* = 8.0 Hz, 3H, ArH), 7.86 (t, *J* = 8.0 Hz, 3H, ArH), 7.46 – 7.30 (m, 4H, ArH), 5.65 (s, 2H,-NCH_2), 4.67 (s, 2H, -SCH_2). ^{13}C NMR (100 MHz, DMSO) δ 166.30 (C=O), 164.16, 151.56, 143.52 (C_4 triazole), 128.91, 128.41, 126.92, 125.37, 125.11, 124.84 (C_5 triazole), 122.38, 121.80, 120.34, 52.88 (-SCH_2), 27.93 (-NCH_2); HRMS (*m/z*) calculated for $C_{24}H_{18}N_6O_3S_2$ $[M+H]^+$: 503. 0915. Found: 503.0951.

2.2q *4-((4-((benzo[d]thiazol-2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)methyl)-N-(4-fluorophenyl)benzamide (**7q**)*: Appearance: White solid; yield: 81%; M.p.: 152–156 °C; FTIR (KBr): ν_{max} = 3361 (N–H str.), 3107 (C–H str., triazole ring), 3062 (C–H str., aliphatic), 1651 (C=O sym. str., amide), 150, 1458 (C=C str., aromatic ring), cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H, -CONH), 8.23 (s, 1H, C-H triazole), 8.02 (d, *J* = 8.0 Hz, 1H, ArH), 7.89 (d, *J* = 8.0 Hz, 3H, ArH), 7.79-7.73 (m, 2H, ArH), 7.51-7.46 (m, 1H, ArH), 7.42- 7.35 (m, 3H, ArH), 7.23-7.16 (m, 2H, ArH), 5.68 (s, 2H,-NCH_2), 4.71 (s, 2H, -SCH_2). ^{13}C NMR (100 MHz, DMSO) δ 165.00 (C=O), 163.33, 152.16, 145.86 (C_4 triazole), 141.25, 139.92, 137.23, 135.10, 128.51, 128.25, 126.84, 125.03, 124.68 (C_5 triazole), 123.32, 122.65, 122.58, 122.28, 121.74, 116.21, 115.76, 115.54, 52.92 (-SCH_2), 27.96 (-NCH_2); HRMS (*m/z*) calculated for $C_{24}H_{18}FN_5OS_2$ $[M+H]^+$: 476. 0970. Found: 476.1016.

2.2r *4-((4-((benzo[d]thiazol-2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)methyl)-N-(4-chlorophenyl)benzamide (**7r**)*: Appearance: White solid; yield: 78%; M.p.: 152–156 °C; FTIR (KBr): ν_{max} = 3284 (N–H str.), 3115 (C–H str., triazole ring), 2939 (C–H str., aliphatic), 1656 (C=O sym. str., amide), 1539, 1419 (C=C str., aromatic ring), cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.35 (s, 1H, -CONH), 8.23 (s, 1H, C-H triazole), 8.02 (d, *J* = 8.0 Hz, 1H, ArH), 7.98–7.87 (m, 3H, ArH), 7.81 (d, *J* = 8.0 Hz, 2H, ArH), 7.56–7.44 (m, 1H, ArH), 7.45–7.35 (m, 5H, ArH), 5.68 (s, 2H,-NCH_2), 4.71 (s, 2H, -SCH_2). ^{13}C NMR (100 MHz, DMSO) δ 166.11 (C=O), 165.65, 153.06, 143.23 (C_4 triazole), 139.97, 138.54, 135.20, 134.93, 128.98, 128.59, 128.25, 127.77, 126.84, 125.03, 124.70 (C_5 triazole), 122.29, 121.74, 52.87, 40.67, 40.46, 40.25, 40.04, 39.83, 39.63, 39.42, 27.96; HRMS (*m/z*) calculated for $C_{24}H_{18}ClN_5OS_2$ $[M+H]^+$: 492.0641, $[M+3]^+$: 494.0612. Found: 492.0707, $[M+3]^+$: 494.0676.

2.2s *4-((4-((benzo[d]thiazol-2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)methyl)-N-(4-bromophenyl) benzamide (**7s**)*: Appearance: White solid; yield: 73%; M.p.: 152–156 °C; FTIR (KBr): ν_{max} = 3284 (N–H str.), 3111 (C–H str., triazole ring), 2946 (C–H str., aliphatic), 1654 (C=O sym. str., amide), 1527, 1425 (C=C str., aromatic ring), cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (s, 1H, -CONH), 8.23 (s, 1H, C-H triazole), 8.02 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 3H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.42-7.34 (m, 3H), 5.68 (s, 2H,-NCH_2), 4.71 (s, 2H, -SCH_2). ^{13}C NMR (100 MHz, DMSO) δ 165.68 (C=O), 153.06, 143.25 (C_4 triazole), 140.00, 138.96, 135.21, 131.92, 128.59, 128.27, 126.85, 125.04, 124.71 (C_5 triazole), 122.65, 122.30, 121.75, 52.87 (-SCH_2), 27.95 (-NCH_2); HRMS (*m/z*) calculated for $C_{24}H_{18}BrN_5OS_2$ $[M+H]^+$: 536.0136, $[M+3]^+$: 538.0116. Found: $[M+H]^+$: 536.0183, $[M+3]^+$: 538.0185.

2.2t *4-((4-((benzo[d]thiazol-2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)methyl)-N-(naphthalen-1-yl)benzamide (**7t**)*: Appearance: Brown solid; yield: 85%; M.p.: 152–156 °C; FTIR (KBr): ν_{max} = 3305 (N–H str.), 3115 (C–H str., triazole ring), 2954 (C–H str., aliphatic), 1647 (C=O sym. str., amide), 1529, 1429 (C=C str., aromatic ring), cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6)

δ 10.40 (s, 1H, -CONH), 8.26 (s, 1H, C-H triazole), 8.06-8.01 (m, 2H, ArH), 7.98 (t, J = 8.0 Hz, 2H, ArH), 7.89 (dd, J = 16.0, 8.0 Hz, 2H, ArH), 7.63–7.53 (m, 5H, ArH), 7.49 (t, J = 8.0 Hz, 1H, ArH), 7.44 (d, J = 8.0 Hz, 2H, ArH), 7.38 (t, J = 16.0 Hz, 1H, ArH), 5.71 (s, 2H,-NCH_2), 4.73 (s, 2H, -SCH_2). ^{13}C NMR (100 MHz, DMSO) δ 166.19 (C=O), 166.12, 153.07, 143.25 (C_4 triazole), 139.91, 135.22, 134.73, 134.23, 129.60, 128.70, 128.53, 128.32, 126.85, 126.76, 126.53, 126.43, 126.00, 125.04, 124.73 (C_5 triazole), 124.27, 123.74, 122.29, 121.76, 52.93 (-SCH_2), 27.98 (-NCH_2); HRMS (m/z) calculated for $C_{28}H_{21}N_5OS_2$ $[M+H]^+$: 508. 1221. Found: 508.1253.

2.3 *General procedure for in vitro antibacterial evaluation*

All the newly synthesized triazole derivatives were screened for *in vitro* antibacterial activity against *S. aureus* (MTCC 7443), *B. subtilis* (MTCC 441) as Gram-positive bacterial strains and *E. coli* (MTCC 1231), *K. pneumoniae* (NCDC 138) as Gram-negative bacterial strains, by standard serial dilution technique.[38] Stock solution of 200 µg/mL concentration was prepared by dissolving 2.0 mg of the synthesized compound in 10 mL of DMSO. The fresh nutrient broth was used as a culture media for bacterial strains. Firstly, 1 mL of nutrient broth was taken in each test tube. Then, 1 mL of stock solution was added in the first test tube to get the solution of 100 µg/mL concentration. From this solution, concentrations of 50–6.25 µg/mL were obtained in other test tubes through serial dilution technique. Then, 0.1 mL of respective microorganism in sterile saline was injected in each test tube and then incubated at 37 °C for 24 h. Results were recorded visually in terms of Minimum Inhibitory Concentration (MIC) in µmol/mL.

3. Results and Discussion

3.1 *Chemistry*

The synthetic pathways adopted for the synthesis of benzothiazole and benzoxazole containing triazoles (**7a-7t**) have been presented in Scheme 1. The terminal alkynes *viz.,* 2-(prop-2-yn-1-ylthio)benzooxazole(**3a**)/2-(prop-2-yn-1-ylthio)benzothiazole (**3b**) were obtained from the propargylation of 2-mercaptobenzoxazole (**1a**)/2-mercaptobenzothiazole (**1b**) in DMF with propargyl bromide (**2**) in the presence of potassium carbonate.

4-(Bromomethyl)-N-arylbenzamide (**6a-6j**) were synthesized by reaction of 4-(bromomethyl)benzoylbromide (**4**) and aromatic amines (**5a-5j**) by using potassium carbonate.

Finally, 4-(bromomethyl)-N-arylbenzamide derivatives (**6a-6j**) and 2-(prop-2-yn-1-ylthio)benzooxazole (**3a**)/2-(prop-2-yn-1-ylthio)benzothiazole (**3b**) were dissolved in DMF followed by addition of aqueous sodium azide, a catalytic amount of copper sulphate pentahydrate, sodium ascorbate and continued stirring for 6-10 h at 25-40 °C to obtain targeted 1,4-disubstituted 1,2,3-triazoles (**7a-7t**).

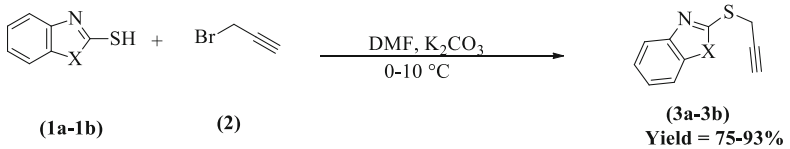
The structures of synthesized triazoles (**7a–7t**) were confirmed by FTIR, ^{1}H NMR, ^{13}C NMR spectroscopy and HRMS. In FTIR spectra of all the compounds characteristic absorption band due to C–H stretching of triazole ring observed at 3199–3107 cm^{-1}, N–H stretching of amide linkages at 3365–3257 cm^{-1} and 1660–1643 cm^{-1} were due to C=O stretching of amide bonds. The ^{1}H NMR spectra of all the compounds exhibited characteristic singlet due to N–H proton in the range of δ 10.07-10.77. A singlet in a range of δ 8.22-8.29 was assigned to triazolyl proton. Two singlets in the range of δ 4.65-4.71 and δ 5.63-5.71 in the ^{1}H-NMR spectra assigned to -SCH_2 and -NCH_2, respectively.

In ^{13}C-NMR spectral data, a characteristic signal of carbon of C=O of amide appeared in the range of δ 166.14-165.31. C–4 and C–5 signals corresponding to triazole ring appeared at δ 143.00–143.30 and δ 124.62–124.93, respectively. A signal in the range of δ 26.90-27.94 appeared due to carbon attached to sulphur and a signal in the range of δ 52.91-52.98 due to methylene carbon attached to nitrogen of triazole. The final confirmation was made by the HRMS analysis which showed the presence of $[M+H]^+$ ion peaks.

3.2 *Antibacterial activity*

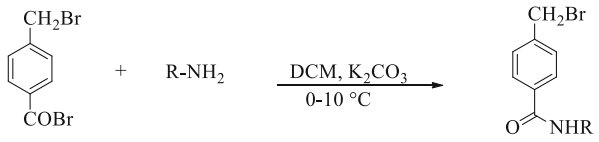
All the synthesized 1,2,3-triazoles were screened for antibacterial activities of against two Gram-positive bacteria *S. aureus, B. subtilis,* two Gram-negative bacteria *E. coli* and *K. pneumoniae via* serial dilution method. Ciprofloxacin was used as a standard against both Gram-positive and Gram-negative bacteria. The MIC values of synthesized compounds are presented in Table 1.

It has been observed that in most of the cases the presence of any substituent on benzene ring led to increased activity towards all the tested bacterial strain. Further, the presence of electron-withdrawing group showed an advantage over an electron-donating group on the benzene ring. The compounds **7f**, **7p** with a nitro group showed enhanced activity than its unsubstituted or alkyl-substituted analogs. 1,2,3-triazoles containing methyl group at *meta* position (**7c**, **7m**), showed better activity than its *ortho* or *para*



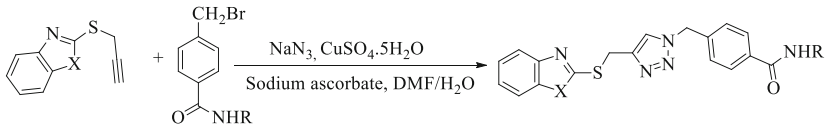
(1a-1b) **(2)** **(3a-3b)**
Yield = 75-93%

1a, 3a: X = O
1b. 3b: X = S



(4) **(5a-5j)** **(6a-6j)**
(Yield = 80-90%)

5a, 6a: R = C_6H_5 **5b, 6b**: R = 2-$CH_3C_6H_4$
5c, 6c: R = 3-$CH_3C_6H_4$ **5d, 6d**: R = 4-$CH_3C_6H_4$
5e, 6e: R = 4-$OCH_3C_6H_4$ **5f, 6f**: R = 4-$NO_2C_6H_4$
5g, 6g: R = 4-FC_6H_4 **5h, 6h**: R = 4-ClC_6H_4
5i, 6i: R = 4-BrC_6H_4 **5j, 6j**: R = α-naphthyl



(3a-3b) **(6a-6j)** **(7a-7t)**
Yield = 72-86%

Compounds	X	R	**Reaction time (h)**	Yield (%)
7a	O	C_6H_5	8	79
7b	O	2-$CH_3C_6H_4$	10	81
7c	O	3-$CH_3C_6H_4$	9	85
7d	O	4-$CH_3C_6H_4$	7	82
7e	O	4-$OCH_3C_6H_4$	9	83
7f	O	4-$NO_2C_6H_4$	6	78
7g	O	4-FC_6H_4	9	81
7h	O	4-ClC_6H_4	10	77
7i	O	4-BrC_6H_4	10	86
7j	O	α-naphthyl	10	76
7k	S	C_6H_5	6	75
7l	S	2-$CH_3C_6H_4$	10	82
7m	S	3-$CH_3C_6H_4$	9	79
7n	S	4-$CH_3C_6H_4$	7	80
7o	S	4-$OCH_3C_6H_4$	8	83
7p	S	4-$NO_2C_6H_4$	6	72
7q	S	4-FC_6H_4	8	81
7r	S	4-ClC_6H_4	9	78
7s	S	4-BrC_6H_4	9	73
7t	S	α-naphthyl	10	85

Scheme 1. Synthesis of benzothiazole and benzoxazole linked 1,4-disubstituted 1,2,3-triazoles.

Table 1. *In vitro* antibacterial activity of synthesized triazoles (**7a-7t**) (MIC in μmol/mL).

	Gram positive bacteria		Gram negative bacteria	
Compounds	*Staphylococcus aureus (MTCC 7443)*	*Bacillus subtilis (MTCC 441)*	*Klebsiella pneumoniae (NCDC 138)*	*Escherichia coli (MTCC1231)*
7a	0.113	0.056	0.056	0.113
7b	0.219	0.109	0.054	0.109
7c	0.054	0.054	0.054	0.054
7d	0.054	0.054	0.109	0.109
7e	0.212	0.106	0.212	0.106
7f	0.051	0.051	0.051	0.102
7g	0.108	0.054	0.054	0.108
7h	0.210	0.105	0.052	0.105
7i	0.024	0.024	0.024	0.048
7j	0.102	0.025	0.025	0.102
7k	0.081	0.054	0.054	0.054
7l	0.212	0.212	0.053	0.053
7m	0.053	0.053	0.053	0.053
7n	0.102	0.053	0.053	0.212
7o	0.205	0.051	0.051	0.102
7p	0.098	0.049	0.049	0.049
7q	0.053	0.105	0.105	0.105
7r	0.101	0.050	0.050	0.101
7s	0.023	0.023	0.023	0.046
7t	0.049	0.049	0.024	0.024
Ciprofloxacin	0.019	0.019	0.019	0.019

counterparts. Compounds **7i**, **7s** containing bromo group on benzene ring exhibited better activity in comparison with fluoro and chloro substituents. Compounds **7j** and **7t** with naphthyl ring displayed potential activity against all the tested bacterial strains. All the triazole derivatives containing benzothiazole ring exhibited better efficacy as compared to the benzoxazole ring.

4. Conclusions

In the present case, we have synthesized a new promising class of benzothiazole-triazole and benzoxazole-triazole hybrids (**7a-7t**) through click reaction in good yields by reacting 2-(prop-2-yn-1-ylthio)benzooxazole (**3a**)/2-(prop-2-yn-1-ylthio)benzothiazole (**3b**) with appropriate 4-(bromomethyl)-N-arylbenzamides (**6a-6j**) and sodium azide. The synthesized disubstituted-1,2,3-triazoles reflected encouraging antibacterial activity. However, compound **7s** exhibited promising antibacterial activity comparable with standard drug Ciprofloxacin.

Supplementary Information (SI)

^{1}H NMR, ^{13}C NMR and HRMS spectra of all the synthesized compounds are available at www.ias.ac.in/chemsci.

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Compliance with ethical standards

Conflicts of interest No potential conflict of interest was reported by the authors.

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