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ORIGINAL ARTICLE

A novel class of 1,4-disubstituted 1,2,3-triazoles: Regioselective synthesis, antimicrobial activity and molecular docking studies

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1,4-Disusbstituted-1,2,3-triazoles;
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Abstract A Novel class of 1,4-disubstituted 1,2,3-triazoles have been synthesized in good to excellent yields *via* Cu(I) accelerated azide-alkyne click chemistry reaction strategy. The newly synthesized compounds were assessed for their *in vitro* antimicrobial activity against five Gram-positive, seven Gram-negative bacteria and three fungi. Most of the synthesized compounds displayed significant activity against the tested Gram-positive and Gram-negative bacteria. Molecular docking study revealed that all docked compounds are bound efficiently with the active site of Topoisomerase IV (4EMV) receptor with the observed the free energy of binding from −7.79 to −9.44 kcal/mol. Interestingly, compound **13a** forms four hydrogen bonds and displayed high binding energy (−9.44 kcal/mol) with the Topoisomerase IV (4EMV) receptor which correlated with their *in vitro* antimicrobial assays.

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1. Introduction

The increasing emergence of drug resistance, intractable pathogenic microorganisms and newly rising pathogens have become a serious health threat for humanity worldwide. These circumstances stimulate an essential need to develop novel class of antimicrobial agents (Duraipandiyan et al., 2009), particularly, structurally diverse chiral small molecule with unique mechanism of action from currently available clinical antimicrobial drugs (Satish et al., 2020). In this context, the construction of chiral hybrid heterocycles is essential to explore new pharmaceutical agent and agrochemicals. Among the heterocyclic pharmacophores, 1,2,3-triazoles occupy protuberant place (Leiling et al., 2019) in drug discovery owing to their multifarious pharmaceutical activities. For instance, antifungal (Yi et al., 2020), anti-bacterial (Adnan et al., 2017), anti-HIV (Lin et al., 2020; Giffin et al., 2008), antitubercular (Patpi et al., 2012; Pravin et al., 2020; Abdul Aziz et al., 2017), anti-inflammatory (Hong-Jian et al., 2017) and antiproliferative activities (Zhi et al., 2019; Hupe et al., 1991). In addition, triazole comprising amino acids have been established for peptide drug conjugates, glycopeptides, peptide fluorescence labelling (Wei et al., 2018) and inhibitors of glycogen synthase kinase (Imran et al., 2016), antagonists of GABA receptors (Alessandro et al., 2018; Bascal et al., 1996). Tazobactam, Cephalosporin and Cefatrizine are clinically used efficient drug candidates for antibacterial infections, these drugs possesses 1,2,3-triazole as an active moiety.

In recent years 1,2,3-triazoles gains special attention in the drug discovery because their unique structural features in view of stability to metabolic degradation and are capable of hydrogen bonding, which is a favorable aspect for binding the biomolecular targets and can also improve the solubility (Era et al., 2020; Anlian et al., 2019). In addition, these structural motifs were synthesized easily through 1,3-dipolar cycloaddition Click chemistry approach (Leiling et al., 2020; Filip et al., 2020; Jie-Ping et al., 2016). The unique structural features of 1,2,3-triazole heterocycles including their biological importance prompted us towards their design, synthesis and antimicrobial activity of pure 1,4-disubsituted-1,2,3-triazole employing copper catalyzed azide-alkyne click chemistry reaction (Cu-AAC). Further, computational molecular docking study was also carried out to examine the binding interface template of the synthesized compounds to the amino acid residues combining active site of the respective receptor has been described in the manuscript.

2. Materials and methods

2.1. General experimental procedure to synthesize chloramine *2a* and *2b*

A 250 mL reaction flask was charged with *(1R,2S)*-phenylpropanolamine **1a** (150 g, 1.0 mol), chloroform (700 mL) and stirred for 10 min. to get a clear solution. Thionyl chloride (180 g, 1.5 mol) was very slowly added to the above solution at 30 to 50 °C for 4 h and continued the heating at 50 °C for 2 h. The excess $SOCl_2$ and chloroform were distilled off completely when the reaction was completed. Acetone (200 mL) was added to the solid mass and continued the distillation to remove traces of thionyl chloride. Later the solid mass was stirred with acetone (300 mL) at ambient temperature, filtered, washed with acetone (100 mL) and dried under vacuum at 60 °C to get the HCl salt of *(1S,2S)*-chloramine **2a.** The same procedure was repeated with *(1S,2R)*-phenylpropanolamine **1b** instead of **1a** to obtain the HCl salt of *(1R,2R)*-chloramine **2b.** Analytical data of **2a** and **2b** is presented below.

Compound **2a**: Yield 182 g (89%); mp 182–183 °C (lit 178–179 °C); SOR + 93.05° (c = 1.0%, methanol, 25 °C); IR (cm^{-1}): 3438, 2938, 2880, 2771, 1605, 1579, 1450, 1456, 1373, 1198, 713 and 700; ^{1}H NMR (400 MHz) δ_H: 0.99 (3H, d, J = 6.8 Hz), 4.42 (1H, m), 5.09 (1H, d, J = 3.9 Hz), 7.34–7.98 (5H, m) and 8.45 (3H, bs); ^{13}C NMR (100 MHz) δ_C: 17.87, 50.51, 66.40, 128.38, 128.80, 128.83 and 139.14; ESI-MS: m/z 170 and 172 in the ratio of 3:1.

Compound **2b**: Yield 19 2 g (94%), mp 179–180 °C [lit 168–170 °C; SOR −92.68° (c = 1.0%, methanol, 25 °C); IR (cm^{-1}): 3440, 2939, 2880, 2772, 1603, 1578, 1499, 1456, 1373, 1198, 712 and 619;^{1}H NMR (400 MHz, DMSO d_6) δ_H: 1.01 (2H, J = 6.8 Hz), 4.44 (1H, m), 5.12 (1H, d, J = 6.9 Hz)), 7.36 – 8.00 (5H, m) and 8.34 (3H, bs); ^{13}C NMR (100 MHz) δ_C: 17.90, 50.50.55, 66.42, 128.32, 128.82, 128.8 and 139.15; ESI-MS: m/z 170 and 172 in the ratio of 3:1.

2.2. General experimental procedure to synthesize N-Boc-chloramine *5a* and *5b*

Triethylamine (126 g, 1.24 mol) was slowly added at 0–5 °C to the HCl salt of *(1S,2S)*-chloramine **2a** (125 g, 0.61 mol) and chloroform (500 mL) for 2 h followed by addition of Boc anhydride (135 g, 0.62 mol) at the same temperature for 30 min for 6 h. After completion of the reaction (TLC), the solvent was removed and EtOAc (500 mL) was charged. Stirred for 10 min and separated the white crystalline HCl salt of triethylamine by filtration. The clear filtrate was collected and EtOAC was removed using a rota evaporator. The obtained solid was stirred with *n*-heptane (170 mL), filtered and dried at 60 °C for overnight to get *N*-Boc-*(1S,2S)*-chloramine **5a** (155 g). *N*-Boc-*(1R,2R)*-chloramine **5b** was obtained by following the same procedure with *(1R,2R)*-chloramine **2b** in place of **2a.** Analytical data of **5a** and **5b** is presented below.

Compound **5a**: White crystalline solid; Yield 155 g (95%); mp 94–96 °C; SOR +72.22° (c = 1.0%, methanol, 25 °C); IR (cm^{-1}): 3385, 3030, 2982, 2970, 2930, 1687, 1514, 1450, 1388, 1338, 1248, 1167, 1055, 748 and 706; ^{1}H NMR (400 MHz) δ_H: 1.20 (d, 3H, J = 6.7 Hz), 1.39 (9H, s), 4.18 (1H, bs), 4.63 (1H, m), 4.98 (1H, d, J = 4.3 Hz) and 7.26–7.38 (5H, m); ^{13}C NMR (100 MHz) δ_C: 18.28, 28.32, 51.85, 66.52, 79.62, 127.74, 128.34, 138.30 and 154.94. MS-ESI: m/z 270 and 272 in the ratio of 3:1.

Compound **5b**: White solid; Yield 152 g (93%); mp 95–96 °C; SOR −69.13° (c = 1.0%, methanol, 25 °C); IR (cm^{-1}): 3385, 3031, 2982, 2970, 2930, 1688, 1514, 1450, 1388, 1338, 1248, 1167, 1055, 748 and 706; ^{1}H NMR (400 MHz) δ_H: 1.21 (d, 3H, J = 6.7 Hz), 1.39 (s, 3H), 4.18 (1H, bs), 4.62 (1H, m), 4.97 (1H, d, J = 4.3 Hz) and 7.26–7.38 (5H, m); ^{13}C NMR (100 MHz) δ_C: 18.29, 28.32, 51.86, 66.52, 79.61, 127.74, 128.36, 138.32 and 154.95. MS-ESI: m/z 270 and 272 in the ratio of 3:1.

2.3. General experimental procedure for synthesis of N-Boc-azidamine **6a** and **6b**

(1S,2S)-N-Boc-chloramine **5a** (150 g, 0.56 mol), sodium azide (37 g, 0.57 mol) and dimethylsulfoxide (600 mL) were mixed and stirred at 25–30 °C for 10 h. About 2.0 L of water was added, the precipitate was filtered, washed with water and dried under vacuum over-night to get the *(1R,2S)-N*-Boc-azidamine **6a** as a white solid. The same experiment was repeated with *(1R,2R)-N*-Boc-chloramine **5b** instead of **5a** to obtain the *(1S,2R)-N*-Boc-azidamine **6b**. Analytical data *N*-Bocazidamines **6a** and **6b** is presented below.

Compound **6a**: Yield 132 g, (86%), mp 80–81 °C; SOR −19.36° (c = 1.0%, methanol, 25 °C); IR (cm^{-1}): 3375, 3032, 2980, 2104, 1684, 1528, 1454, 1321, 1263, 1165, 758, 743 and 704; ^{1}H NMR (400 MHz) δ_H: 0.99 (3H, d, J = 6.6 Hz), 1.46 (9H, s), 3.92 (1H, m), 4.68 (m, 1H), 4.90 (m, 1H), 7.26–7.40 (m, 5H, ArH); ^{13}C NMR (100 MHz) δ_C: 14.4, 28.4, 51.3, 69.4, 126.9, 128.0, 128.7, 137.1, 155.0; MS-ESI: m/z at 277 $[M+H]^+$; Anal. calcd for $C_{14}H_{20}N_4O_2$: C, 60.85; H, 7.30; N, 20.28. Found C, 61.12; H, 7.36; N, 20.31.

Compound **6b**: Yield 121 g (79%); mp 82–85 °C; SOR +20.42° (c = 1.0%, methanol, 25 °C); IR (cm^{-1}): 3375, 3032, 2980, 2104, 1684, 1526, 1454, 1321, 1163, 743 and 704; ^{1}H NMR (400 MHz) δ_H: 0.98 (3H, d, J = 6.6 Hz), 1.45 (9H, s), 3.91 (1H, m), 4.68(1H, m), 4.89 (1H, m), 7.25–7.39 (5H, m); ^{13}C NMR (100 MHz) δ_C: 14.4, 28.4, 51.3, 69.5, 126.9, 128.0, 128.7, 137.1, 155.0; MS-ESI: m/z at 277 $[M+H]^+$; Anal. calcd for $C_{14}H_{20}N_4O_2$: C, 60.85; H, 7.30; N, 20.28. Found C, 61.12; H, 7.36; N, 20.31.

2.4. General experimental procedure for the synthesis of triazole derivatives **9a-13a** and **9b-13b**

Terminal alkyne (**8a-e,** 36 mmol), *(1R,2S)-N*-Boc-azidamine (**6a** or **6b,** 10 g, 36 mmol), *N,N*-diisopropylethylamine (5.6 g, 43 mmol) and copper(I) iodide (0.68 g, 10 mol%) were mixed with 100 mL of solvent mixture (methanol/water/tetrahydro furan in equal volume) and stirred at 40–45 °C for 12–16 h to form the *N*-Boc protected triazole **7**. Progress of the reaction monitored by TLC, the obtained residue was filtered to remove the copper salts and the filtrate was concentrated in the rota evaporator to obtain a oily mass. The residue was diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (100 mL). The organic layer was washed well with water followed by drying over anhyd. $MgSO_4$. The dried organic layer was added with CF_3COOH (10 mL) at 20–25 °C and stirred for 2–4 h. The progress of reaction monitored by TLC (10% methanol in methylenedichloride). The reaction mass was reduced completely under vacuum at 50 °C using a rota evaporator. The residue was diluted with 100 mL of water and basified with sodium hydroxide to pH above 9.0. The obtained solid was filtered and recrystallized in isopropanol to get the novel 1,4-disubstituted 1,2,3-triazoles **9**–**13** as a white to off-white solids in 87 to 95% yield.

Compound **9a**: Prepared from *N*-Boc-azidamine **6a** and terminal alkyne **8a**. Yield 67%; mp 250–251 °C; SOR −35.5° (c = 1.0%, methanol, 25 °C); IR (cm^{-1}): 3375, 3122, 3030, 2926, 2852, 1606, 1514, 1493, 1454, 1227, 1165, 752 and 700; ^{1}H NMR (400 MHz) δ_H: 1.25 (3H, d, J = 6.4 Hz), 1.60 (2H, m), 1.63 (4H, m), 1.83 (4H, m), 4.92 (1H, m), 5.61 (1H, d, J = 9.4 Hz), 7.28–8.15 (6H, m); ^{13}C NMR (100 MHz) δ_C: 18.5, 22.2, 23.3, 25.7, 38.2, 38.3, 47.3, 68.2, 68.4, 121.2, 128.4, 128.6, 128.7, 138.0, 156.1, 168.7; MS-ESI: m/z at 283 $[M+H]^+$ as dehydrated one; Anal. calcd for $C_{17}H_{24}N_4O$: C, 67.97; H, 8.05; N, 18.65. Found C, 68.18; H, 8.10; N, 18.72.

Compound **9b**: Prepared from *N*-Boc-azidamine **6b** terminal alkyne **8a**.Yield 60%; mp 250–252 °C; SOR +30.1° (c = 1.0%, methanol, 25 °C); IR (cm^{-1}): 3371, 3297, 3030, 2936, 2855, 1493, 1452, 1379, 1157, 766 and 702; ^{1}H NMR (400 MHz) δ_H: 1.20 (3H, d, J = 6.4 Hz), 1.58 (2H, m), 1.60 (4H, m), 1.68 (2H, m), 1.70 (m, 2H), 4.38 (1H, m), 5.73 (m, 1H), 7.40–7.61 (6H, m), 8.41 (2H, brs); ^{13}C NMR (100 MHz) δc: 16.2, 22.3, 22.4, 25.9, 26.2, 49.3, 66.5, 74.5, 120.3, 124.5, 128.7, 129.5, 135.5, 148.9; MS-ESI: m/z at 283 $[M+]^+$ as dehydrated one; Anal. calcd for $C_{17}H_{24}N_4O$: C, 67.97; H, 8.05; N, 18.65. Found C, 68.15; H, 8.09; N, 18.61.

Compound **10a**: Prepared from *N*-Boc-azidamine **6a** terminal alkyne **8b**. Yield 87%; mp 86–87 °C, SOR: −22.8° (c = 1.0%, methanol, 25 °C); IR (cm^{-1}): 3366, 3280, 3061, 2966, 2924, 1551, 1456, 1375, 1138, 754 and 709; ^{1}H NMR (400 MHz) δ_H: 0.89 (3H, t, J = 7.3 Hz), 1.08 (3H, d, J = 5.9 Hz), 1.34 (2H, m), 1.62 (2H, m); 2.70 (2H, t, J = 7.7 Hz), 4.0 (1H, bs), 5.16 (1H, d, J = 7.6 Hz), 7.26–7.47 (6H, m); ^{13}C NMR (100 MHz) δ_C: 13.79, 22.33, 25.37, 31.47, 50.02, 71.91, 77.23, 120.49, 128.26, 128.75, 128.93, 136.60 and 148.16; MS-ESI: m/z at 259 $[M+H]^+$; Anal. calcd for $C_{15}H_{22}N_4$: C, 69.73; H, 8.58; N, 21.69. Found C, 69.54; H, 8.54; N, 21.80

Compound **10b**: Prepared from *N*-Boc-azidamine **6b** terminal alkyne **8b**. Yield 94%; mp 84–86 °C; SOR: +23.4° (c = 1.0%, methanol, 25 °C); IR (cm^{-1}) 3368, 3281, 3060, 2966, 2924, 1550, 1458, 1375, 1138, 754 and 707; ^{1}H NMR (400 MHz) δ_H: 0.89 (3H, t, J = 7.3 Hz), 1.09 (3H, d, J = 6.0 Hz), 1.34 (2H, m), 1.62 (2H, m); 2.67 (2H, t, J = 7.7 Hz), 4.02 (1H, bs), 5.18 (1H, d, J = 7.6 Hz), 7.28–7.48 (6H, m); ^{13}C NMR (100 MHz) δ_C: 13.82, 22.36, 25.38, 31.48, 50.01, 72.01, 77.22, 120.51, 128.30, 128.86, 128.96, 136.65 and 148.20; MS-ESI: m/z at 259 $[M+H]^+$; Anal. calcd for $C_{15}H_{22}N_4$: C, 69.73; H, 8.58; N, 21.69. Found C, 69.42; H, 8.63; N, 21.74.

Compound **11a***:* Prepared from *N*-Boc-azidamine **6a** terminal alkyne **8c**. Yield 87%; mp 117–118 °C; SOR: −10.1° (c = 1.0%, methanol, 25 °C); IR (cm^{-1}); 3364, 3285, 3071, 2965, 1715, 1589, 1493, 1456, 1279, 1194, 1105, 1053, 864, 767, 735 and 710; ^{1}H NMR (400 MHz) δ_H: 1.07 (d, 3H, J = 6.3 Hz), 2.37 (3H, s), 4.02 (1H, m), 5.19 (1H, d, J = 7.8 Hz), 5.43 (2H, s), and 7.26–7.83 (10*H*, m); ^{13}C NMR (100 MHz) δ_C: 20.8, 21.2, 50.1, 58.0, 72.2, 123.9, 126.9, 128.3, 129.0, 129.7, 130.3, 133.9, 136.1, 138.2, 142.7, 166.6; MS-ESI: m/z at 351 $[M+H]^+$; Anal. calcd for $C_{20}H_{22}N_4O_2$: C, 68.55; H, 6.33; N, 15.99. Found C, 68.69; H, 6.30; N, 16.00

Compound **11b***:* Prepared from *N*-Boc-azidamine **6b** terminal alkyne **8c**. Yield 76%; mp 118–120 °C; SOR: +9.7° (c = 1.0%, methanol, 25 °C); IR (cm^{-1}); 3364, 3069, 2965, 1715, 1684, 1528, 1456, 1279, 1192, 1105, 865, 739 and 708; ^{1}H NMR (400 MHz) δ_H: 1.13 (d, 3H, J = 6.3 Hz), 2.42 (3H, s), 4.08 (1H, m), 5.25 (1H, d, J = 7.8 Hz), 5.48 (2H, s), 7.31–7.89 (10*H*, m, ArH); ^{13}C NMR (100 MHz) δ_C: 19.9, 20.5, 49.4, 57.3, 71.5, 123.2, 126.2, 127.6, 128.2, 128.3, 129.5, 133.2, 135.3, 137.4, 141.9, 165.9; MS-ESI: m/z at 351 [M

$+H]^+$; Anal. calcd for $C_{20}H_{22}N_4O_2$: C, 68.55; H, 6.33; N, 15.99. Found C, 68.61; H, 6.39; N, 16.06.

Compound **12a***:* Prepared from *N*-Boc-azidamine **6a** terminal alkyne **8d**. Yield 95%; mp 110–113 °C; SOR: −12.4° (c = 1.0%, methanol, 25 °C); IR (cm^{-1}); 3372, 3136, 2967, 2905, 1711, 1609, 1454, 1275, 1115, 1097, 852, 779 and 704; ^1H NMR (400 MHz) δ_H: 1.07 (3H, d, J = 6.7 Hz), 1.32 (9H, s), 4.00 (1H, m), 5.18 (1H, d, J = 4.3 Hz), 5.22 (2H, s), 7.27–7.96 (10*H*, m) and 8.77 (2H, bs); ^{13}C NMR (100 MHz) δ_C: 20.77, 31.09, 35.09, 50.09, 57.94, 72.25, 123.88, 125.36, 126.97, 128.30, 128.95, 129.03, 129.64, 136.13, 142.81, 156.92 and 166.48; MS-ESI: m/z at 393 $[M+H]^+$; Anal. calcd for $C_{23}H_{28}N_4O_2$: C, 70.38; H, 7.19; N, 14.27. Found C, 70.51; H, 7.22; N, 14.30.

Compound **12b***:* Prepared from *N*-Boc-azidamine **6b** terminal alkyne **8d** Yield 90%; mp 114–115 °C; SOR: +12.9° (c = 1.0%, methanol, 25 °C); IR (cm^{-1}); 3372, 3136, 2967, 2905, 1711, 1609, 1454, 1276, 1115, 1098, 1049, 852, 779 and 704; ^1H NMR (400 MHz) δ_H: 1.07 (d, 3H, J = 6.7 Hz), 1.32 (s, 9H), 4.04 (1H, m), 5.18 (1H, d, J = 4.3 Hz), 5.43 (2H, s), 7.27–7.96 (10*H*, m) ^{13}C NMR (100 MHz) δ_C: 20.8, 31.0, 35.1, 50.1, 57.9, 72.3, 123.9, 125.4, 126.9, 128.3, 128.9, 129.0, 129.6, 136.1, 142.8, 156.9 and 166.5; MS-ESI: m/z at 393 $[M+H]^+$; Anal. calcd for $C_{23}H_{28}N_4O_2$: C, 70.38; H, 7.19; N, 14.27. Found C, 70.48; H, 7.25; N, 14.32.

Compound **13a***:* Prepared from *N*-Boc-azidamine **6a** terminal alkyne **8e.** Yield 95%; mp 193–195 °C, SOR: −20.6° (c = 1.0%, methanol, 25 °C); IR (cm^{-1}): 3383, 3134, 3076, 2980, 2932, 1686, 1528, 1450, 1365, 1277, 1163, 1061, 856, 768, 750 and 708; ^1H NMR (400 MHz) δ_H: 1.10 (d, 3H, J = 6.4 Hz), 3.85 (1H, m), 5.02 (1H, d, J = 7.8 Hz), 5.12 (2H, s) and 7.18–7.88 (10*H*, m) and 8.78 (2H, bs); ^{13}C NMR (100 MHz) δ_H: 19.12, 50.08, 54.88, 70.42, 124.45, 125.78, 127.56, 129.46, 130.17, 131.44, 132.36, 134.94, 138.78, 141.42 and 167.86; MS-ESI: m/z at 382 $[M+H]^+$; Anal. calcd for $C_{19}H_{19}N_5O_4$: C, 59.84; H, 5.02; N, 18.36. Found C, 59.96; H, 5.08; N, 18.42.

Compound **13b***:* Prepared from *N*-Boc-azidamine **6b** terminal alkyne **8e**. Yield 89%; mp 198–200 °C; SOR: +22.8° (c = 1.0%, methanol, 25 °C); IR (cm^{-1}): 3390, 3130, 3075, 2980, 2930, 1695, 1530, 1450, 1365, 1277, 1162, 1060, 858, 768, 750 and 710; ^1H NMR (400 MHz) δ_H: 1.11 (d, 3H, J = 6.4 Hz), 3.88 (1H, m), 5.03 (1H, d, J = 7.8 Hz), 5.10 (2H, s) and 7.16–7.87 (10*H*, m) and 8.65 (2H, bs); ^{13}C NMR (100 MHz) δ_H: 19.18, 50.12, 54.87, 70.46, 124.48, 125.77, 127.55, 129.48, 130.16, 131.42, 132.38, 134.95, 138.82, 141.40 and 167.78; MS-ESI: m/z at 382 $[M+H]^+$; Anal. calcd for $C_{19}H_{19}N_5O_4$: C, 59.84; H, 5.02; N, 18.36. Found C, 60.03; H, 5.06; N, 18.45.

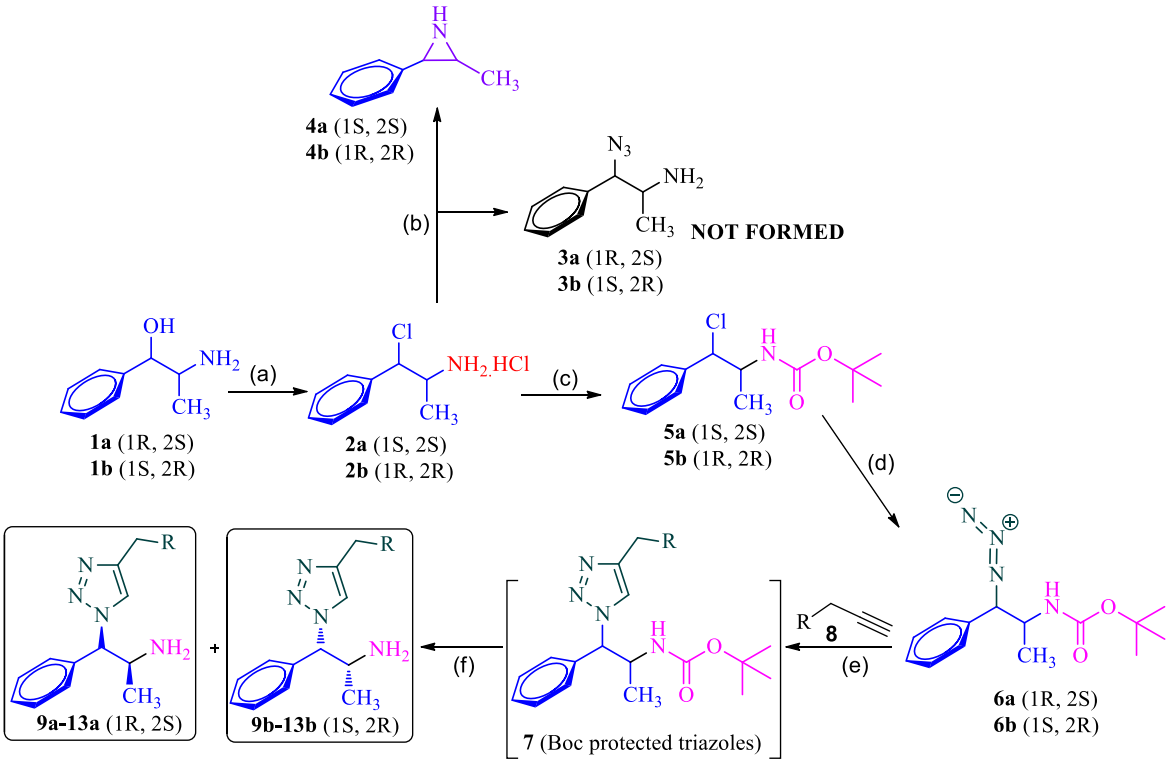
3. Results and discussion

3.1. Chemistry

Our synthetic work commenced with readily available chiral pure precursor *d*- and *l*- isomers of phenylpropanolamine (**1a** and **1b)** which was subjected to sequence of synthetic transformations as described in Scheme 1. Thus, phenylpropanolamine **1** was converted into its chloro derivative **2** by treatment with thionyl chloride. Nguyenet al., carried out the chlorination using PCl_5 with 78% yield. Angelina et al. and Raul et al. reported the chlorination of phenylpropanolamine **1** using thionyl chloride with 74% and 72% yield, respectively. Interestingly, we obtained **2a** in 89% and **2b** in 94% yield when the reaction was carried out at 50 °C against the literature method (0–30 °C). Noticed inversion configuration at benzylic carbon which was confirmed with their specific optical rotations which are having opposite sign from their precursors. The obtained values of **2a** and **2b** are equal in value and opposite in sign which indicates the formation of pseudo isomers **2a** with *(1S,2S)*- and **2b** with *(1R,2R)*-configuration (Table 1). The obtained specific optical rotation (SOR) values of **2a** and **2b** are matches with values reported in the literature (Nguyen et al., 2000) and the structure of **2b** was confirmed by XRD study (Angelina et al., 1998). The chloramines **2a** and **2b** were found to be enantiomers (pseudo) since they were prepared from their corresponding enantiomers **1a** and **1b** respectively.

Our next task was to convert the pseudo-chloramine **2** to azidamine **3.** The direct conversion of the chloro group to azide was attempted by azidation with sodium azide. But the reaction led to the formation of aziridine **4** which was confirmed by mass spectral analysis. The plausible reason for the formation of aziridine **4** was due to the lone pair of electrons on the nitrogen of the amine group of **2** attacks on **β**-carbon where chlorine is attached which leads to the formation of aziridien **4** by eliminating chlorine atom as described in Scheme 2. The formation of aziridine **4** was confirmed through LCMS analysis and shown molecular ion $[M+H]^+$ at m/z 149 instead of 177 of expected azide **3** and it further confirms the formation of aziridine **4** as evidenced by literature (Nguyen et al., 2000). Hence, a two-step sequence involving the protection of the amine group and subsequent azidation was adopted to obtain requisite azide **6**. The Boc protected amine **5** restricts the formation of azidridine **4** due to the non-availability of nitrogen lone pair due to keto-enol tautomerism as shown in Scheme 2. The Boc protected amino compound **5** was successfully executed in the subsequent azidation reaction without any difficulties. Thus, compound **5a** and **5b** were treated with sodium azide at room temperature to furnish the respective *N*-Boc-azidamines **6a** and **6b** respectively in excellent yield. Here observed one more inversion of configuration at benzylic carbon which was confirmed with their specific optical rotations (**6a** and **6b**) which are having opposite sign from their precursors **5a** and **5b** (Table 2). Hence overall retention of configuration at N-Boc-azidamine is expected with respect to phenylpropanolamine **1** (Scheme 1).

Having synthesized the N-Boc-azidamine **6** in excellent yield**,** one-pot click chemistry reaction was performed for the regioselective synthesis of 1,4-disubstituted-1,2,3-triazoles (Scheme 1). Thus, the *N*-Boc-azidamine **6** was treated with various terminal alkynes **8** to get *N*-Boc protected triazoles **7** as *in situ* and immediate hydrolysis in presence of trifluoroacetic acid to obtain the desired 1,4-disubstituted-1,2,3-triazoles **9**–**13** (Scheme 2) in good to excellent yields. The absolute configuration at the benzylic carbon of compounds **9**–**13** was expected to be retained with respect to starting material phenylpropanolamine **1**. Initially, optimization of the click chemistry reaction was investigated under various condition including different catalyst and temperature as described in Table 3. Among them, the reaction with $MeOH/H_2O/THF$ (1:1:1) in the presence of CuI at 35–40 °C afforded excellent yield with less reaction time (Table 3, entry 35). The structure



Reagent and conditions: (a) $SOCl_2$ (b) $Et_3N/CHCl_3$ at 0-5 °C, NaN_3/DMA (c) $(BOC)_2CO$, Et_3N (d) Dimethylacetamide, RT, 16-20 h, NaN_3, (e) CuI, DIPEA, $MeOH/H_2O/THF$, RT 16-20 h, (f) CF_3COOH, CH_2Cl_2, RT, 2 h

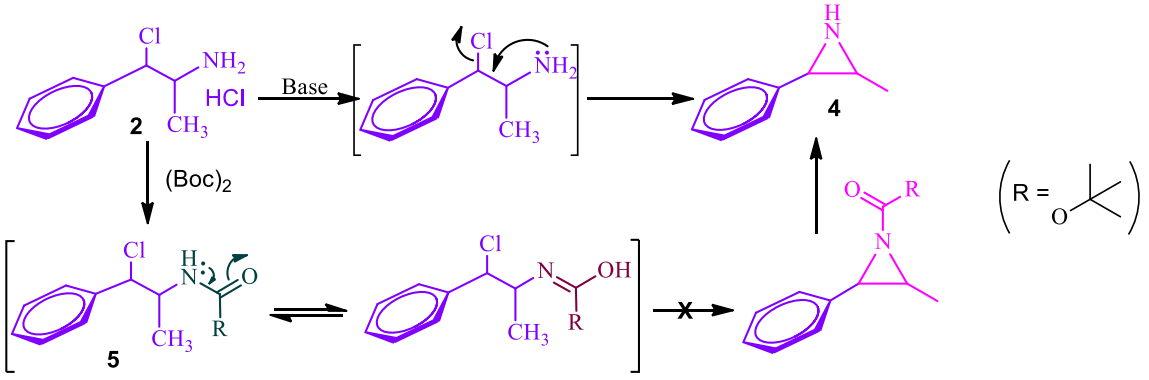
Scheme 1 Synthesis of novel 1,4-disubstituted 1,2,3-triazoles **9**–**13.**

Table 1 Specific optical rotations of HCl salts of chloramines **2.**

Compound	Specific optical rotation*
1a	−32°
1b	+32°
2a	+93.05° (+76°)[27a]
2b	−92.68° (−91°)[27a]

* c = 1.0% in methanol at 25 °C (as HCl salts).

of compounds **9**–**13** (Table 4) was elucidated by ^1H, ^{13}C and mass spectroscopic analysis as illustrated for a representative example **11a**. In the ^1H NMR spectrum of **11a,** a singlet at δ 2.37 ppm ascribable to methyl hydrogens of the phenyl ring. A doublet at δ 1.07 ppm assignable to the ester methylene hydrogens. The multiplet at δ 4.02 ppm belongs to methine hydrogen adjacent to the methyl group. A doublet at δ 5.19 ppm was assigned to methine hydrogen adjacent to the triazole ring. In the ^{13}C NMR spectrum, the ester carbonyl carbon displayed at 166.6 ppm. Finally, the structure of *N*-acetyl



Scheme 2 Azidation of chloramines **2** with and without the protection of amine group.

Table 2 Specific optical rotations of *N*-Boc-chloramines **5.**

Compound	Specific optical rotation*
5a	+72.22°
5b	−69.13°

* c = 1.0% in methanol, at 25 °C.

derivative of compound **9b** and its absolute stereo configuration have been unambiguously ascertained by X-ray diffraction analysis, which is shown in Fig. 1 (CCDC No.1443803). The molecular structure of **9b** was stabilized by intermolecular O-H. . ..N hydrogen bonding interaction. The detailed crystal data has been provided in supplementary file.

The feasible pathway for the formation of 1,2,3-triazole derivatives **9**–**13** is shown in Scheme 3. Initially, phenylpropanolamine **1** was reacted with thionyl chloride to form corresponding alkyl hydrochloride salt **2** with inversion of configuration at benzylic carbon. Compound **2** reacts with BOC anhydride in the presence of Et_3N to afford N-Boc product **5** in good yield. The *N*-Boc protected compound **5** was involved SN_2 reaction with sodium azide furnished azide **6** with one more inversion of configuration at benzylic carbon (overall retention of configuration). Simultaneously, the copper (I) generated *in situ* π-complex with terminal alkyne **8** in the presence of a base, the terminal hydrogen of the alkyne is deprotonated and consequently initiation of the reaction to form copper (I) acetylide **14** and then the azide **6** coordinates to copper acetylide to form copper complex **15** followed

Table 3 Optimization of reaction conditions of triazoles.

Entry	Cat.	mol%	Base	mol%	Solvent	Temp (°C)	Time (h)	TLC[a]	Yield[b] (%)
1	CuCl	10	DIPEA	200	S1	40–45	48	R1	–
2	CuCl	20	DIPEA	200	S3	40–45	48	R1	–
3	CuCl	50	DIPEA	200	S4	40–45	48	R1	–
4	CuCl	100	DIPEA	200	S5	40–45	48	R1	–
5	CuCl	100	DIPEA	200	S1	70–80	48	R1	–
6	CuCl	100	TEA	200	S1	70–80	48	R1	–
7	CuCl	100	DIPEA	300	S1	100–110	48	R1	–
8	CuCl	100	DIPEA	200	S2	70–80	48	R1	–
9	CuCl	100	DIPEA	200	S5	70–80	48	R1	–
10	CuBr	10	DIPEA	200	S1	40–45	48	R1	–
11	CuBr	50	DIPEA	200	S1	40–45	48	R2	–
12	CuBr	100	DIPEA	200	S2	40–45	48	R2	–
13	CuBr	100	DIPEA	200	S1	70–80	48	R2	–
14	CuBr	100	TEA	200	S5	70–80	48	R1	
15	CuBr	100	DIPEA	200	S2	70–80	48	R2	
16	CuBr	100	DIPEA	200	S3	70–80	48	R2	
17	CuBr	100	DIPEA	200	S4	70–80	48	R2	
18	CuBr	100	DIPEA	200	S5	70–80	48	R2	
19	CuI	5	DIPEA	200	S1	70–80	48	R2	–
20	CuI	5	DIPEA	200	S2	70–80	48	R2	–
21	CuI	5	DIPEA	200	S3	70–80	48	R2	–
22	CuI	5	DIPEA	200	S4	70–80	48	R2	–
23	CuI	5	DIPEA	200	S5	70–80	48	R2	–
24	CuI	5	DIPEA	200	S6	60–65	48	R2	–
25	CuI	10	DIPEA	200	S1	70–80	24	R3	72
26	CuI	10	DIPEA	200	S2	70–80	48	R2	–
27	CuI	10	DIPEA	200	S3	70–80	48	R2	–
28	CuI	10	DIPEA	200	S4	70–80	24	R3	75
29	CuI	10	DIPEA	200	S5	70–80	12	R3	79
30	CuI	10	DIPEA	200	S6	60–65	48	R2	–
31	CuI	20	DIPEA	200	S1	70–80	20	R3	81
32	CuI	20	DIPEA	200	S4	70–80	12	R3	72
33	CuI	20	DIPEA	200	S5	70–80	12	R3	88
34	CuI	20	TEA	200	S1	70–80	48	R1	–
35	CuI	20	TEA	200	S4	70–80	48	R1	–
36	CuI	20	TEA	200	S5	70–80	48	R1	–
37	CuI	20	NBA	200	S5	70–80	48	R1	–
38	CuI	10	DIPEA	200	S5	20–25	24	R3	82
39	CuI	10	DIPEA	200	S5	35–40	12	R3	95
40	CuI	10	DIPEA	200	S5	55–60	12	R3	83
41	$CuSO_4$	20	DIPEA	200	S5	70–80	48	R2	–
42	$CuSO_4$	50	TEA	200	S5	70–80	48	R2	–

S1: n-BuOH/water (1:1); **S2**: n-BuOH; **S3**: THF; **S4**: Methanol/water (1:1); **S5**:Methanol/water/THF (1:1:1); **S6**:MeOH; **R1**: No reaction; **R2**: Reaction proceeded but not completed; **R3**: Reaction completed; [a]TLC, mobile phase 10% methanol in dichlormetrhane, [b]Yield of **7a** after hydrolysis; DIPEA: *N*,*N*-Diisopropylethylamine; TEA:Triethylamine; NBA:*n*-Butyl alcohol.

Table 4 1,4-disubstituted 1,2,3-triazoles **9–13.**

Entry	Terminal alkyne	1,2,3-Triazole	1,2,3-Triazole	SOR	Yield
1	**8a**	**9a**	**9b**	−35.5°(**9a**)/ +30.1° (**9b**)	67% (**9a**)/ 60% (**9b**)
2	**8b**	**10a**	**10b**	−22.8°(**10a**)/ +23.4°(**10b**)	87% (**10a**)/ 94% (**10b**)
3	**8c**	**11a**	**11b**	−10.1°(**11a**)/ +9.7°(**11b**)	87% (**11a**)/ 76% (**11b**)
4	**8d**	**12a**	**12b**	−12.4(**12a**)/ +12.9(**12a**)	95% (**12a**)/ 90% (**12a**)
5	**8e**	**13a**	**13b**	−20.6°(**13a**)/ +22.8°(**13b**)	95% (**13a**)/ 89% (**13a**)

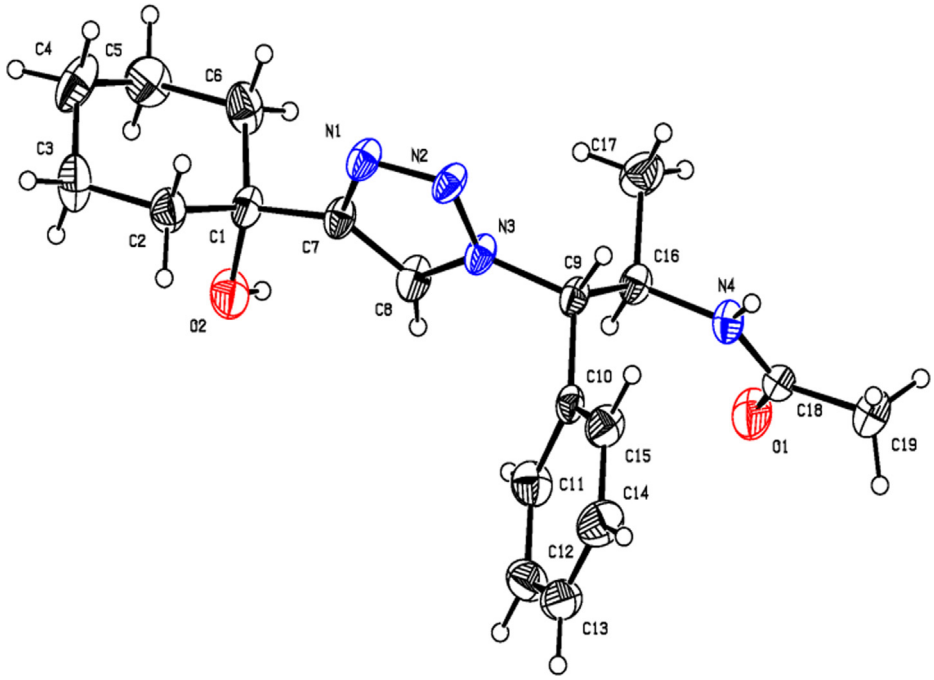
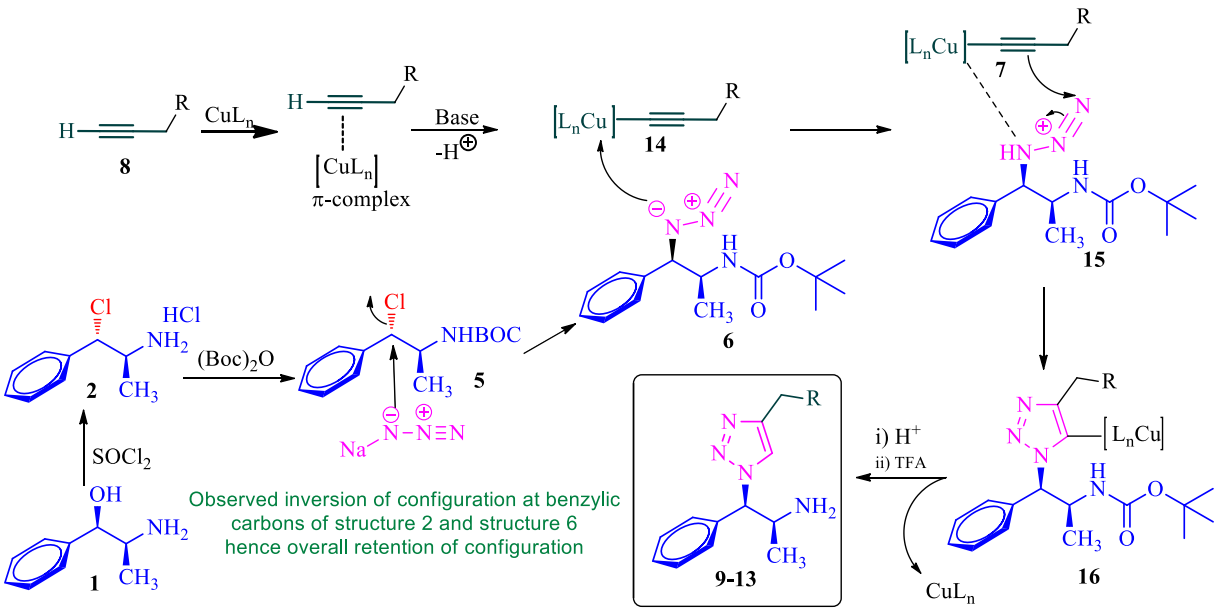


Fig. 1 ORTEP diagram of *N*-acetyl derivative of **9b.**

by the formation of regioselective 5-cuprated triazole **16**. Finally, acid hydrolysis furnishes the desired triazole product **9**–**13** along with the regeneration of the active catalyst.

3.2. Antimicrobial activity

All the newly synthesized compounds **9a-13a** and **9b-13b** were assessed for their antimicrobial activities against five Gram-positive and seven Gram-negative bacteria and three fungi using *in vitro* disk diffusion method (Balachandran et al. 2012). The bacterial strains were obtained from Institute of Microbial Technology (IMTECH), Chandigarh, India-160 036 and fungal strains were obtained from the Department of Microbiology, Christian Medical College, Vellore, Tamil Nadu, India. As shown in Table 5, compounds **9a**, **9b**, **10a**, **10b**, **11a**, **11b**, **13a** and **13b** exhibited promising antibacterial



Scheme 3 The feasible mechanism for the formation of 1,2,3-triazoles.

Table 5 Antibacterial and antifungal activity of novel 1,4-disubstituted 1,2,3-triazoles **9a-13a** and **9b-13a** busing disc diffusion method. (Zone of inhibition in mm-1 mg/disk).

S. No	Name of the microorganism	9a	9b	10a	10b	11a	11b	12a	12b	13a	13b	C
Gram positive Bacteria												
1	*B. subtilis*	20	22	18	15	25	16	15	22	22	16	22
2	*M. luteus*	26	25	22	15	17	25	16	17	14	13	26
3	*S. aureus*	19	23	20	17	15	20	NA	NA	14	12	14
4	*S. epidermidis*	24	26	22	19	20	23	14	15	19	15	25
5	*S. aureus* MRSA	20	22	21	18	NA	18	NA	NA	18	12	30
Gram negative Bacteria												
1	*E. aerogenes*	22	20	19	18	18	22	NA	NA	15	14	22
2	*S. typhimurium*	22	24	20	18	17	15	NA	NA	20	11	24
3	*K. pneumoniae*	20	22	19	NA	15	22	NA	NA	NA	NA	20
4	*P. vulgaris*	20	22	19	17	18	14	NA	NA	17	12	30
5	*S. paratyphi*-B	22	20	19	17	18	17	NA	16	19	12	18
6	*S. flexneri*	22	21	18	NA	17	20	15	NA	20	15	30
7	*P. aeruginosa*	24	16	19	17	25	19	19	16	14	23	30
Fungi												
1	*C. albicans*	14	12	NA	NA	14	12	NA	NA	12	12	28
2	*M. pachydermatis*	13	10	10	NA	NA	NA	NA	NA	14	14	26
3	*A. flavus*	**15**	NA	NA	NA	**17**	NA	**16**	**19**	NA	NA	24

NA- no activity, C-Streptomycin (standard antibacterial agent) C-Ketoconazole (standard antifungal agent)

activity against tested Gram-positive and Gram-negative bacteria at 1 mg/disk when compared with standard antimicrobial drug streptomycin (for bacteria). However, compounds **9a-13a** and **9b-13b** showed moderate activity against fungi. The minimum inhibitory concentration (MIC) of active compounds such as **9a**, **9b**, **10a**, **10b**, **11a**, **11b**, **13a** and **13b** were performed according to the standard reference methods (Balachandran et al., 2012; CLSI, 2008; NCCLS/CLSI, 2002) for Gram-positive and Gram-negative bacteria. The MIC values of all active compounds **9a**, **9b**, **10a**, **10b**, **11a**, **11b**, **13a** and **13b** showed potential activity against Gram-positive and Gram-negative bacteria with a range of 31.25 to 62.5 μg/mL are given in Table 6**.** Particularly, compounds **9a**, **9b**, **10a**, **11a** and **11b** were showed significant MIC values against tested Gram-positive and Gram-negative bacteria when compared to control. At the same time antimicrobial activity of the synthesized compounds was correlated against their substitutions, it was understood that aliphatic chain/ring substitution attached to triazole ring (**9a**, **9b** and **10a**) and substitutions in aryl ring such as *p*-nitro (**13a** and **13b**), *p*-methyl (**11b**) and *p*-*tert*-butyl (**12a**) enhanced the activity to the maximum. Only moderate activities were observed for the triazoles **10b**, **11a** and **12b** of other isomers displayed moderate to good activity.

Table 6 Minimum inhibitory concentration values of actives compounds against **Gram-positive** and **Gram-negative bacteria**.

S. No.	Name of the microorganism	9a	9b	10a	10b	11a	11b	13a	13b	C
Gram positive Bacteria										
1	*B. subtilis*	125	500	250	250	62.5	125	500	500	25
2	*M. luteus*	31.25	31.25	31.25	125	62.5	31.25	250	500	6.25
3	*S. aureus*	62.5	31.25	62.5	125	125	62.5	250	500	6.25
4	*S. epidermidis*	31.25	31.25	31.25	62.5	62.5	31.25	62.5	250	25
5	*S. aureus* MRSA	62.5	31.25	31.25	125	NA	125	62.5	500	6.25
Gram negative Bacteria										
1	*E. aerogenes*	31.25	62.5	62.5	125	62.5	31.25	250	250	25
2	*S. typhimurium*	31.25	31.25	62.5	125	125	250	62.5	500	6.25
3	*K. pneumoniae*	62.5	31.25	62.5	NA	250	31.25	NA	NA	25
4	*P. vulgaris*	62.5	31.25	62.5	125	62.5	250	62.5	500	6.25
5	*S. paratyphi*-B	31.25	62.5	62.5	125	62.5	125	62.5	500	30
6	*S. flexneri*	31.25	31.25	125	NA	125	62.5	62.5	250	6.25
7	*P. aeruginosa*	125	125	125	500	250	125	250	250	25

NA-no activity, C-Streptomycin (standard antibacterial agent).

Table 7 Free energy of binding (FEB) of 1,2,3-triazole compounds.

Compound	Binding energy (kcal/mol)[a]
	DNA Topoisomerase IV (4EMV)
9a	−9.23
9b	−8.98
10a	−8.25
10b	−8.50
11a	−8.51
11b	−8.93
12a	−7.79
12b	−7.84
13a	−9.44
13b	−9.38
Crystallized ligand	−9.80

[a] Calculated by Autodock.

3.3. Molecular docking studies

Docking simulation of the compounds **9**–**13** was performed on Topoisomerase IV (4EMV) (Takei et al., 2002) using AutoDock4 (Morris et al., 2009). The binding free energy was estimated and the docking scores are summarized in Table 7. Molecular docking results of all novel triazoles **9**–**13** with 4EMV receptor show that all the docked compounds bind efficiently with the receptor and exhibits free energy of binding value from −7.79 to −9.44 kcal/mol. Interestingly, among all the compounds docked, compound **13a** exhibited very high binding with 4EMV receptor and forms four hydrogen bonds resulting in a binding energy of −9.44 kcal/mol.

The compound **13a**, NH_2 interacts with the ASP-78 and forms two hydrogen bonds with bond lengths of 1.8 and 2.3 Å. Also, NO_2 interacts with the ARG-140 and forms two hydrogen bonds with bond lengths of 1.9 and 2.0 Å. In addition to the hydrogen bonds, C═O forms a polar interaction with the GLU-55 and triazole nitrogen forms a polar interaction with the ASN-51. Binding interaction of **13a** with the active site residues of the 4EMV receptor is shown in Fig. 4.

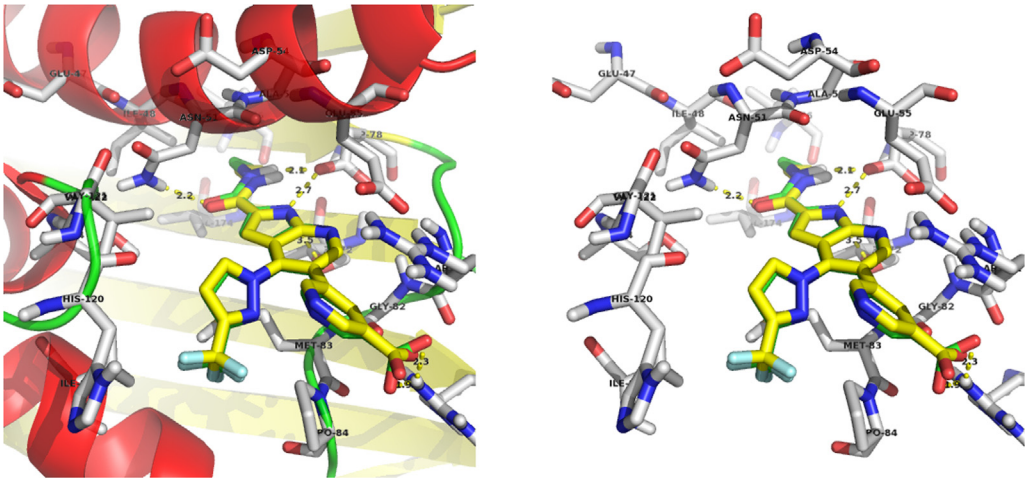


Fig. 2 Method validation using crystallised and docked ligand with 4EMV receptor.

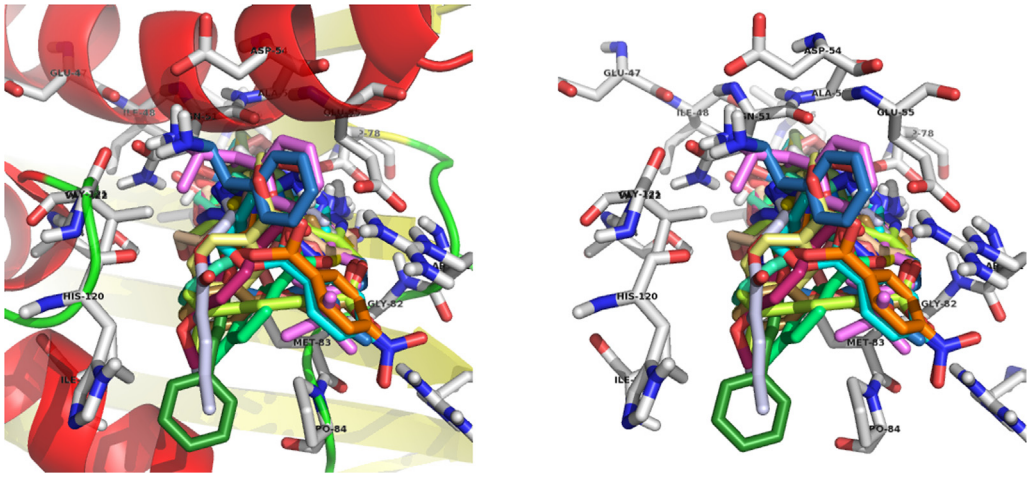


Fig. 3 Docking mode of all synthesized triazoles in the active site.

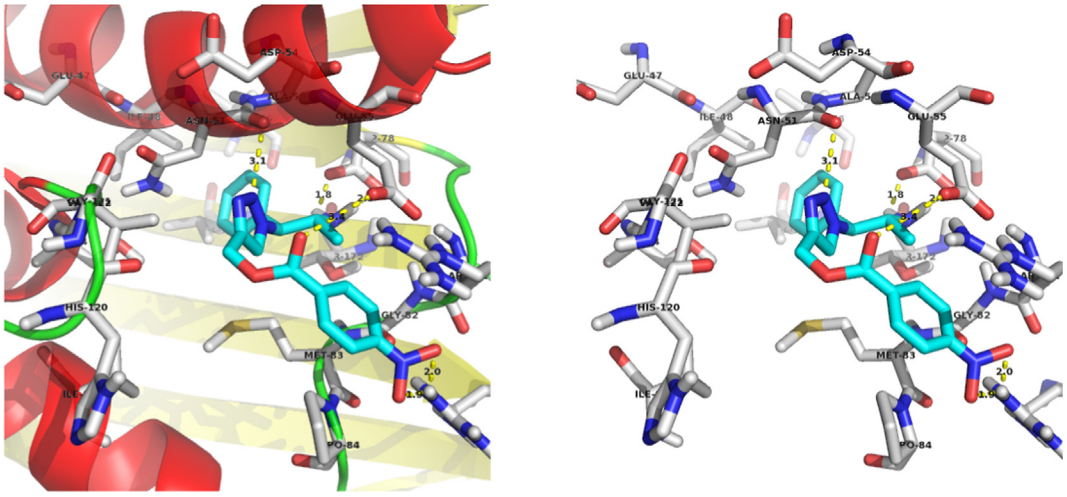


Fig. 4 Docking mode of the most binding energy compound **13a.**

Docking diagram of method validation using crystallized and docked ligand with 4EMV receptor and docking mode of all synthesized triazoles in the active site of the receptor are shown in Figs. 2 and 3. From the docking results, compound **13a** displayed higher binding energy (−9.44 kcal/mol). These docking results strongly correlate with *in vitro* antimicrobial activity.

4. Conclusion

A series of hitherto unexplored novel class of 1,2,3-triazoles were synthesized in good to excellent yields employing copper supported azide-alkyne 1,3-dipolar cycloaddition reaction. Most of the synthesized triazole compounds were displayed potent antibacterial activities against tested Gram-positive and Gram-negative bacteria. Particularly the compounds with aliphatic groups present in ester moiety showed significant antimicrobial activities when compared with others. Furthermore, all the synthesized 1,2,3-triazoles were also investigated for their docking simulation with Topoisomerase IV (4EMV) receptor and the result disclose that all compounds were binding efficiently with the receptor with binding free energy from −7.79 to −9.44 kcal/mol. Interestingly, compound **13a** forms four hydrogen bonds with high binding energy (−9.44 kcal/-mol) which strongly correlated to the *in vitro* findings due to presence of nitro function.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.arabjc.2020.10.026.

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