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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, characterization and antimicrobial activity of 4-((1-benzyl/phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)benzaldehyde analogues

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Abstract A diverse series of 4-((1-benzyl/phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)benzaldehyde analogues has been synthesized in good yield by the click reaction between 4-*O*-propargylated benzaldehyde and various organic bromides/azides. All the synthesized compounds were tested in vitro for their antimicrobial activity against Gram-positive bacteria (*Staphylococcus epidermidis* and *Bacillus subtilis*), Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) and fungi (*Candida albicans* and *Aspergillus niger*). Most of the compounds exhibited good-to-excellent antimicrobial activity. Compound **7b** was found to be more potent than ciprofloxacin against *B. subtilis*, whereas it showed activity comparable to ciprofloxacin against *E. coli*. Compounds **4h** and **4i** showed activity comparable to fluconazole against *A. niger*. Further, the binding mode of compound **7b** into the active site of *E. coli* topoisomerase II DNA gyrase B has also been investigated.

Keywords 1,4-Disubstituted 1,2,3-triazoles · Click chemistry · Antimicrobial activity · Docking studies

Introduction

Nitrogen-containing heterocycles play an important role in medicinal chemistry because of their presence in a vast number of natural and synthetic therapeutically important compounds. In particular, 1,2,3-triazoles are among the most studied five-membered heterocyclic compounds (El-Sagheer and Brown, 2010; Schulzeab and Schubert, 2014; Pola *et al.*, 2014). The copper-catalyzed variant (Tornoe *et al.*, 2002; Rostovtsev *et al.*, 2002) of Huisgen azide–alkyne cycloaddition (Huisgen, 1984) for the synthesis of 1,4-disubstituted 1,2,3-triazoles has attracted scientific community all over the world. The diverse libraries of molecules can be achieved by installing azide and alkyne functionalities to different molecules using various routes (Millward *et al.*, 2013, Thirumurugan *et al.*, 2013). The 1,4-disubstituted 1,2,3-triazoles are surrogate for the peptide bond (Bock *et al.*, 2007) and show chemical as well as biological stability (Agalave *et al.*, 2011). The triazole ring can act as a hydrogen bond acceptor and donor, simultaneously (Whiting *et al.*, 2006), thereby offering various types of binding to the target enzyme. Additionally, 1,2,3-triazoles are also associated with a broad range of pharmacological activities including anticancer (Kumbhare *et al.*, 2014; Ma *et al.*, 2014; Zhou *et al.*, 2014), antitubercular (Gonzaga *et al.*, 2013; Mir *et al.*, 2014), antimalarial (Kumar *et al.*, 2014) and antimicrobial activity (Genin *et al.*, 2000, Kaushik *et al.*, 2014). On the basis of above facts and in continuation of our studies on 1,2,3-triazoles (Lal *et al.*, 2012, 2014; Kaushik *et al.*, 2014), we report herein the synthesis and antimicrobial evaluation of a diverse series of 4-((1-benzyl/phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)benzaldehyde analogues.

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Materials and methods

Chemistry

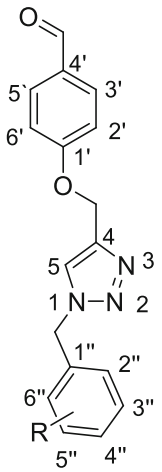
The melting points (°C) were observed in open capillaries and are uncorrected. The IR spectra were recorded on SHIMAZDU IR AFFINITY-I FTIR spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance III 400 nano bay spectrometer at 400 and 100 MHz, respectively. Tetramethylsilane (TMS) was used as an internal standard (chemical shift δ, in ppm, coupling constant J in Hertz (Hz)). The high-resolution mass spectra (HRMS) were obtained on Micromass QTOF micro-mass spectrometer. The thin-layer chromatography (TLC) was run on readymade silica gel plates (SIL G/UV254, ALUGRAM) and visualized under ultraviolet lamp. Azide precursors (**5a**–**5e**) were prepared via reported procedure (Xu *et al.*, 2013). The spectral data of compounds **7a**–**7e** were in accordance with the reported data (Kumar *et al.*, 2013).

Synthesis of alkyne (2)

To a solution of 4-hydroxy benzaldehyde (1.0 mmol) in 20 mL acetone, anhydrous potassium carbonate (1.5 mmol) was added, and the resulting suspension was refluxed for 30 min. Propargyl bromide (80 % in toluene, 1.5 mmol) was added to it slowly, and the reaction mixture was refluxed for 8 h. After completion of the reaction as monitored by TLC, the solvent was evaporated and the resulting solid residue was washed with ice-cold water and recrystallized from chloroform/hexane (8:2).

*General procedure for the synthesis of 1,4-disubstituted 1,2,3-triazoles (**4a**–**4o**)* To a mixture of substituted benzyl bromide **3a**–**3o** (1.0 mmol), sodium azide (3.0 mmol), alkyne **2** (1.0 mmol) in DMF/water (8:2), copper sulfate pentahydrate (10 mol%) and sodium ascorbate (20 mol%) were added. The reaction mixture was stirred for 4–16 h at room temperature, and the progress of the reaction was monitored by TLC. After completion of the reaction, ice-cold water (30 mL) was added to the reaction mixture. The residue thus obtained was filtered, washed with aqueous ammonium chloride/ammonia (9:1) solution and water and recrystallized with chloroform/hexane (8:2) to get 1,4-disubstituted 1,2,3-triazoles (**4a**–**4o**).

*General procedure for the synthesis of 1,4-disubtituted 1,2,3-triazoles (**7a**–**7e**)* A mixture of substituted phenyl azide **6a**–**6e** (1.0 mmol), alkyne **2** (1.0 mmol) in DMF/water (8:2), copper sulfate pentahydrate (10 mol%) and sodium ascorbate (20 mol%) was stirred for 4–10 h at room temperature. After the reaction was complete as monitored by TLC, ice-cold water (30 mL) was added to the reaction mixture. The resulting solid residue was filtered, washed with aqueous ammonium chloride/ammonia (9:1) solution and water and recrystallized with chloroform/hexane (8:2) to get 1,4-disubstituted 1,2,3-triazoles (**7a**–**7e**).



*4-(1-Benzyl-1H-[1,2,3]triazol-4-ylmethoxy)-benzaldehyde (**4a**)* White solid, 86 % yield, mp: 85–87 °C. IR (KBr, ν_{max}/cm^{-1}): 3132 (C–H str, triazole), 3066, 2843, 2760 (C–H str, CHO), 1682 (C=O str), 1604, 1578, 1506, 1456, 1431, 1254 (C–O str), 1169, 1113 (C–O str), 997, 869, 835, 752, 721, 696, 611, 515. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.27 (s, 2H, NCH_2), 5.56 (s, 2H, O-CH_2), 7.09 (d, J = 8.8 Hz, 2H, 2′-H, 6′-H), 7.28–7.31 (m, 2H, 2″-H, 6″-H), 7.38–7.39 (m, 3H, 3″-H, 4-H″, 5″-H), 7.58 (s, 1H, triazolyl-H), 7.84 (d, J = 8.8 Hz, 2H, 3′-H, 5′-H), 9.89 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.81 (CHO), 163.13 (Ar–C), 143.61 (C-4), 134.34 (Ar–C), 132.01 (Ar–C), 130.32 (Ar–C), 129.22 (Ar–C), 128.93 (Ar–C), 122.88 (C-5), 115.09 (Ar–C), 62.18 (OCH_2), 54.34 (NCH_2). HRMS: m/z (M^+) Cacld. for $C_{17}H_{15}N_3O_2$: 293.1164, found: 294.1229 $(M + H)^+$.

*4-[1-(2-Methyl-benzyl)-1H-[1,2,3]triazol-4-ylmethoxy]-benzaldehyde (**4b**)* Off-white solid, 89 % yield, mp: 88–90 °C. IR (KBr, ν_{max}/cm^{-1}): 3151 (C–H str, triazole), 2878, 2752 (C–H str, CHO), 1682 (C=O str), 1604, 1576, 1512, 1429, 1255 (C–O str), 1166, 1119 (C–O str), 1001, 835. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.37 (s, 1H, CH_3), 5.26 (s, 2H, NCH_2), 5.51 (s, 2H, OCH_2), 7.09 (d, J = 8.8 Hz, 2H, 2-H, 6′-H), 7.2 (s, 4H, 2″-H, 3″-H, 4″-H, 5″-H, 4H), 7.56 (s, 1H, triazolyl-H), 7.84 (d, J = 8.8 Hz, 2H, 3′-H, 5′-H), 9.89 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.82 (CHO), 163.15 (Ar–C), 143.52 (C-4), 138.91 (Ar–C), 132.01 (Ar–C), 131.27 (Ar–C), 130.32 (Ar–C), 129.87 (Ar–C), 128.24 (Ar–C), 122.75 (C-5), 115.08 (Ar–C), 62.19 (OCH_2), 54.15 (NCH_2), 21.19 (CH_3).

HRMS: *m/z* (M^+) Cacld. for $C_{18}H_{17}N_3O_2$: 307.1321, found: 308.1411 (M + H) $^+$.

*4-[1-(3-Methyl-benzyl)-1H-[1,2,3]triazol-4-ylmethoxy]-benzaldehyde (**4c**)* White solid, 83 % yield, mp: 60–62 °C. IR (KBr, ν_{max}/cm^{-1}): 3144 (C–H str, triazole), 3088, 2920, 2839, 2754, (C–H str, CHO), 1682 (C=O str), 1603, 1575, 1508, 1431, 1309, 1257 (C–O str), 1219, 1110 (C–O str), 1026, 835, 775. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.35 (s, 3H, CH_3), 5.27 (s, 2H, NCH_2), 5.51 (s, 2H, OCH_2), 7.08–7.11 (m, 4H, 2′-H, 6′-H, 4″-H, 6″-H), 7.19 (m, 1H, 2″-H), 7.26–7.30 (m, 1H, 6″-H), 7.58 (s, 1H, triazolyl-H), 7.82–7.85 (d, 2H, 3′-H, 5′-H), 9.88 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.82 (CHO), 163.15 (Ar–C), 143.55 (C-4), 139.08 (Ar–C), 134.22 (Ar–C), 132.00 (Ar–C), 130.32 (Ar–C), 129.66 (Ar–C), 129.08 (Ar–C), 128.89 (Ar–C), 125.24 (Ar–C), 122.89 (C-5), 115.09 (Ar–C), 62.18 (OCH_2), 54.34 (NCH_2), 21.34 (CH_3). HRMS: *m/z* (M^+) Cacld. for $C_{18}H_{17}N_3O_2$: 307.1321, found: 308.1420 (M + H) $^+$.

*4-[1-(4-Methyl-benzyl)-1H-[1,2,3]triazol-4-ylmethoxy]-benzaldehyde (**4d**)* White solid, 86 % yield, mp: 68–70 °C. IR (KBr, ν_{max}/cm^{-1}): 3155 (C–H str, triazole), 3072, 2868, 2758 (C–H str, CHO), 1689 (C=O str), 1603, 1574, 1508, 1466, 1431, 1256 (C–O str), 1225, 1165, 1118 (C–O str), 1005, 870, 839, 756, 609. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.28 (s, 1H, CH_3), 5.25 (s, 2H, NCH_2), 5.56 (s, 2H, OCH_2), 7.08 (d, J = 8.8 Hz, 2H, 2′-H, 6′-H), 7.16–7.31 (m, 4H, 2″-H, 3″-H, 5″-H, 6″H), 7.47 (s, 1H, triazolyl-H), 7.82 (d, J = 8.8 Hz, 2H, 3′-H, 5′-H), 9.87 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.81 (CHO), 163.13 (Ar–C), 143.37 (C-4), 136.97 (Ar–C), 132.24 (Ar–C), 131.98 (Ar–C), 131.48 (Ar–C), 131.12 (Ar–C), 130.31 (Ar–C), 129.50 (Ar–C), 129.30 (Ar–C), 126.73 (Ar–C), 122.76 (C-5), 115.09 (Ar–C), 62.16 (OCH_2), 52.50 (NCH_2), 18.99 (CH_3). HRMS: *m/z* (M^+) Cacld. for $C_{18}H_{17}N_3O_2$: 307.1321, found: 308.1417 (M + H) $^+$.

*4-[1-(2-Nitro-benzyl)-1H-[1,2,3]triazol-4-ylmethoxy]-benzaldehyde (**4e**)* Off-white solid, 92 % yield, mp: 90–92 °C. IR (KBr, ν_{max}/cm^{-1}): 3149 (C–H str, triazole), 3088, 2939, 2850, 2750 (C–H str, CHO), 1668 (C=O str), 1602, 1577, 1531 (N=O, str), 1514, 1429, 1350 (N=O, str), 1259 (C–O str), 1221, 1163, 1105 (C–O str), 1008, 866, 831, 727, 675. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.29 (s, 2H, NCH_2), 5.69 (s, 2H, OCH_2), 7.08 (d, J = 8.8 Hz, 2H, 2′-H, 6′-H), 7.58–7.64 (m, 2H, 4″-H, 6″-H), 7.74 (s, 1H, triazolyl-H), 7.82 (d, J = 8.4 Hz, 2H, 3′-H, 5′-H), 8.21 (d, J = 8.0 Hz, 1H, 3″-H), 8.16 (bs, 1H, 5″-H), 9.87 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.83 (CHO), 163.02 (Ar–C), 148.53 (Ar–C), 144.12 (C-4), 136.51 (Ar–C), 134.02 (Ar–C), 132.01 (Ar–C), 130.39 (Ar–C), 123.87 (Ar–C), 123.18 (Ar–C), 122.92 (C-5), 115.06 (Ar–C), 62.07 (OCH_2), 53.24 (NCH_2). HRMS: *m/z* (M^+) Cacld. for $C_{17}H_{14}N_4O_4$: 338.1015, found: 339.1093 (M + H) $^+$.

*4-[1-(3-Nitro-benzyl)-1H-[1,2,3]triazol-4-ylmethoxy]-benzaldehyde (**4f**)* White solid, 84 % yield, mp: 130–132 °C. IR (KBr, ν_{max}/cm^{-1}): 3146 (C–H str, triazole), 3086, 2922, 2837, 2753 (C–H str, CHO), 1695 (C=O str), 1604, 1579, 1517 (N=O str), 1344 (N=O str), 1255 (C–O str), 1219, 1161, 1108 (C–O str), 1039, 864, 731. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.33 (s, 2H, NCH_2), 5.97 (s, 2H, OCH_2), 7.12 (d, 2H, J = 8.8 Hz, 2′-H, 6′-H), 7.19 (d, J = 7.8 Hz, 1H, 5″-H), 7.57 (dt, J = 8.0 Hz, 1.6 Hz, 6″-H), 7.65 (dt, J = 7.8 Hz, 1.6 Hz, 4″-H), 7.84–7.88 (m, 3H, 3′-H, 5′-H, triazolyl-H), 8.17 (dd, 1H, 2″-H, J = 8.0 Hz, 1.2 Hz), 9.91 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.80 (CHO), 163.07 (Ar–C), 143.75 (C-4), 134.46 (Ar–C), 130.80 (Ar–C), 132.03 (Ar–C), 130.42 (Ar–C), 129.94 (Ar–C), 125.49 (Ar–C), 124.03 (C-5), 115.11 (Ar–C), 62.11 (OCH_2), 50.99 (NCH_2). HRMS: *m/z* (M^+) Cacld. for $C_{17}H_{14}N_4O_4$: 338.1015, found: 339.1089 (M + H) $^+$.

*4-[1-(4-Nitro-benzyl)-1H-[1,2,3]triazol-4-ylmethoxy]-benzaldehyde (**4g**)* White solid, 88 % yield, mp: 118-120 °C. IR (KBr, ν_{max}/cm^{-1}): 3133 (C–H str, triazole), 2850, 2754 (C–H str, CHO), 1687 (C=O str), 1604, 1516 (N=O, str), 1348 (N=O, str), 1251 (C–O str), 1077 (C–O str), 1002, 806. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.31 (s, 2H, NCH_2), 5.69 (s, 2H, OCH_2), 7.09–7.12 (d, J = 8.8 Hz, 2H, 2′-H, 6′-H), 7.44 (d, J = 8.8 Hz, 2H, 2″-H, 6″-H), 7.69 (s, 1H, triazolyl-H), 7.85 (d, J = 9.2 Hz, 2H, 3′-H, 5′-H), 8.25 (d, J = 8.4 Hz, 2H, 3″-H, 5″-H), 9.90 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.77 (CHO), 162.99 (Ar–C), 144.24 (C-4), 141.35 (Ar–C), 132.03 (Ar–C), 130.46 (Ar–C), 128.69 (Ar–C), 124.39 (Ar–C), 123.10 (C-5), 115.04 (Ar–C), 62.09 (OCH_2), 53.27 (NCH_2). HRMS: *m/z* (M^+) Cacld. for $C_{17}H_{14}N_4O_4$: 338.1015, found: 339.1083 (M + H) $^+$.

*4-[1-(2-Bromo-benzyl)-1H-[1,2,3]triazol-4-ylmethoxy]-benzaldehyde (**4h**)* White solid, 90 % yield, mp: 78–80 °C. IR (KBr, ν_{max}/cm^{-1}): 3130 (C–H str, triazole), 3093, 3070, 2935, 2883, 2835, 2756 (C–H str, CHO), 1901, 1687 (C=O str), 1602, 1575, 1510, 1433, 1305, 1246 (C–O str), 1226, 1168, 1109 (C–O str), 1037, 1003, 869, 821, 750, 648, 516. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.26 (s, 2H, NCH_2), 5.65 (s, 2H, OCH_2), 7.08 (d, J = 8.0 Hz, 2H, 2′-H, 6′-H), 7.16–7.32 (m, 3H, 4″-H, 5″-H, 6″-H), 7.6 (d, J = 7.6 Hz, 1H, 3″-H), 7.72 (s, 1H, triazolyl-H), 7.81 (d, J = 8.0 Hz, 2H, 3′-H, 5′-H), 9.86 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.81 (CHO), 163.12 (Ar–C), 143.42 (C-4), 133.89 (Ar–C), 133.28 (Ar–C), 131.99 (Ar–C), 130.59 (Ar–C), 130.50 (Ar–C), 130.30 (Ar–C), 128.30 (Ar–C), 123.57 (Ar–C), 123.39 (C-5), 115.10 (Ar–C),

62.11 (OCH_2), 53.96 (NCH_2). HRMS: *m/z* (M^+) Cacld. for $C_{17}H_{14}BrN_3O_2$: 371.0269, found: 372.0349 $(M + H)^+$.

4-[1-(3-Bromo-benzyl)-1H-[1,2,3]triazol-4-ylmethoxy]-benzaldehyde ***(4i)*** White solid, 94 % yield, mp: 81–83 °C. IR (KBr, ν_{max}/cm^{-1}): 3155 (C–H str, triazole), 3071, 2922, 2843, 2753 (C–H str, CHO), 1681 (C=O str), 1590, 1508, 1463, 1317, 1213 (C–O str), 1157, 1109 (C–O str), 1031, 825, 771, 634. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.26 (s, 2H, NCH_2), 5.51 (s, 2H, OCH_2), 7.07 (d, $J = 8.4$ Hz, 2H, 2′-H, 6′-H), 7.24 (m, 4H, 2″-H, 4″-H, 5″-H, 6″-H), 7.65 (s, 1H, triazolyl-H), 7.81 (d, $J = 8.8$ Hz, 2H, 3′-H, 5′-H), 9.86 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.82 (CHO), 163.08 (Ar–C), 143.79 (C-4), 136.59 (Ar–C), 132.02 (Ar–C), 132.01 (Ar–C), 131.04 (Ar–C), 130.76 (Ar–C), 126.68 (Ar–C), 123.10 (C-5), 115.08 (Ar–C), 62.10 (OCH_2), 53.48 (NCH_2). HRMS: *m/z* (M^+) Cacld. for $C_{17}H_{14}BrN_3O_2$: 371.0269, found: 372.0343 $(M + H)^+$.

4-[1-(4-Bromo-benzyl)-1H-[1,2,3]triazol-4-ylmethoxy]-benzaldehyde ***(4j)*** Off-white solid, 88 % yield, mp: 70–72 °C. IR (KBr, ν_{max}/cm^{-1}): 3149 (C–H str, triazole), 3070, 2939, 2885, 2752 (C–H str, CHO), 1674 (C=O str), 1602, 1575, 1500, 1429, 1400, 1307, 1251 (C–O str), 1226, 1165, 1114 (C–O str), 1043, 1006, 831, 777, 644, 611, 516, 487. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.27 (s, 2H, NCH_2), 5.51 (s, 2H, OCH_2), 7.09 (d, $J = 8.8$ Hz, 2H, 2″-H, 6″-H), 7.17 (d, $J = 8.4$ Hz, 2H, 2′-H, 6′-H), 7.51 (d, $J = 8.4$ Hz, 2H, 3″-H, 5″-H), 7.6 (s, 1H, triazolyl-H), 7.83 (d, $J = 8.4$ Hz, 2H, 3′-H, 5′-H), 9.88 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.80 (CHO), 163.08 (Ar–C), 143.82 (C-4), 133.36 (Ar–C), 132.38 (Ar–C), 132.01 (Ar–C), 130.37 (Ar–C), 129.77 (Ar–C), 123.10 (Ar–C), 122.86 (C-5), 115.07 (Ar–C), 62.12 (OCH_2), 53.63 (NCH_2). HRMS: *m/z* (M^+) Cacld. for $C_{17}H_{14}BrN_3O_2$: 371.0269, found: 372.0340 $(M + H)^+$.

4-[1-(2-Fluoro-benzyl)-1H-[1,2,3]triazol-4-ylmethoxy]-benzaldehyde ***(4k)*** Pale yellow solid, 92 % yield, mp: 89–91 °C. IR (KBr, ν_{max}/cm^{-1}): 3134 (C–H str, triazole), 3062, 2920, 2845, 2756 (C–H str, CHO), 1685 (C=O str), 1602, 1500, 1456, 1303, 1251 (C–O str), 1165, 1109 (C–O str), 1002, 869, 837, 756, 642, 513. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.26 (s, 2H, NCH_2), 5.65 (s, 2H, OCH_2), 7.09–7.17 (m, 4H, 3″-H, 4″-H, 5″-H, 6″-H), 7.29–7.40 (m, 2H, 2′-H, 6′-H), 7.69 (s, 1H, triazolyl-H), 7.83 (d, $J = 8.8$ Hz, 2H, 3′-H, 5′-H), 9.86 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.82 (CHO), 163.13 (Ar–C), 159.35 (Ar–C), 143.58 (C-4), 132.00 (Ar–C), 131.17 (Ar–C), 131.09 (Ar–C), 130.73 (Ar–C), 130.70 (Ar–C), 130.33 (Ar–C), 124.94 (Ar–C), 124.91 (Ar–C), 123.13 (Ar–C), 123.12 (C-5), 121.72 (Ar–C), 121.58 (Ar–C), 116.02 (Ar–C), 115.81 (Ar–C), 115.08 (Ar–C), 62.12 (OCH_2), 47.90 (NCH_2). HRMS: *m/z* (M^+) Cacld. for $C_{17}H_{14}FN_3O_2$: 311.1070, found: 312.1144 $(M + H)^+$.

4-[1-(3-Fluoro-benzyl)-1H-[1,2,3]triazol-4-ylmethoxy]-benzaldehyde ***(4l)*** Off-white solid, 96 % yield, mp: 60–62 °C. IR (KBr, ν_{max}/cm^{-1}): 3149 (C–H str, triazole), 3070, 2930, 2848, 2760 (C–H str, CHO), 1680 (C=O str), 1604, 1512, 1481, 1309, 1261 (C–O str), 1224, 1116 (C–O str), 1041, 947, 893. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.28 (s, 2H, NCH_2), 5.55 (s, 2H, OCH_2), 6.96 (d, $J = 1.6$ Hz, 1H, 5″-H), 6.98–7.10 (m, 3H, 2″-H, 4″-H, 6″-H), 7.33–7.37 (m, 2H, 2′-H, 6′-H), 7.63 (s, 1H, triazolyl-H), 7.82 (d, 2H, $J = 9.4$ Hz, 3′-H, 5′-H), 9.88 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.81, 164.23 (Ar–C), 163.08 (Ar–C), 161.76 (Ar–C), 143.81 (C-4), 136.69 (Ar–C), 132.01 (Ar–C), 130.92 (Ar–C), 130.83 (Ar–C), 130.36 (Ar–C), 123.65 (Ar–C), 123.00 (C-5), 115.83 (Ar–C), 114.95 (Ar–C), 62.12 (OCH_2), 53.64 (NCH_2). HRMS: *m/z* (M^+) Cacld. for $C_{17}H_{14}FN_3O_2$: 311.1070, found: 312.1148 $(M + H)^+$.

4-[1-(4-Fluoro-benzyl)-1H-[1,2,3]triazol-4-ylmethoxy]-benzaldehyde ***(4m)*** White solid, 94 % yield, mp: 69–71 °C. IR (KBr, ν_{max}/cm^{-1}): 3149 (C–H str, triazole), 3070, 3039, 2943, 2841, 2760 (C–H str, CHO), 1674 (C=O str), 1604, 1512, 1417, 1301, 1259 (C–O str), 1222, 1161, 1105 (C–O str), 866, 829, 648, 611, 520. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.29 (s, 2H, NCH_2), 5.54 (s, 2H, OCH_2), 7.06–7.12 (m, 4H, 2′-H, 6′-H, 2″-H, 6″-H), 7.29–7.32 (m, 2H, 3′-H, 5′-H), 7.58 (s, 1H, triazolyl-H), 7.85 (dt, 2H, $J = 8.8$ Hz, $J = 2.4$ Hz, 3″-H, 5″-H), 9.90 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.82 (CHO), 163.09 (Ar–C), 143.78 (C-4), 132.03 (Ar–C), 130.38 (Ar–C), 130.12 (Ar–C), 130.04 (Ar–C), 122.70 (C-5), 116.36 (Ar–C), 116.15 (Ar–C), 115.07 (Ar–C), 62.16 (OCH_2), 53.61 (NCH_2). HRMS: *m/z* (M^+) Cacld. for $C_{17}H_{14}FN_3O_2$: 311.1070, found: 312.1154 $(M + H)^+$.

4-(1-Pyridin-4-ylmethyl-1H-[1,2,3]triazol-4-ylmethoxy)-benzaldehyde ***(4n)*** Yellow colored liquid, 79 % yield. IR (KBr, ν_{max}/cm^{-1}): 3140 (C–H str, triazole), 3062, 2922, 2846, 2746 (C–H str, CHO), 1687 (C=O str), 1600, 1575, 1508, 1417, 1309, 1253 (C–O str), 1220, 1103 (C–O str), 1001, 833. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.30 (s, 2H, NCH_2), 5.59 (s, 2H, OCH_2), 7.69 (s, 1H, triazolyl-H), 7.84 (d, $J = 8.8$ Hz, 2′-H, 6′-H), 7.99 (bs, 2H, 3′-H, 5′-H), 8.60 (d, $J = 5.6$ Hz, 4H, 2″-H, 3″-H, 5″-H, 6″-H), 9.88 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.85 (CHO), 163.01 (Ar–C), 162.63 (Ar–C), 150.45 (Ar–C), 150.00 (Ar–C), 144.70 (Ar–C), 144.11 (Ar–C), 143.48 (C-4), 132.04 (Ar–C), 130.40 (Ar–C), 123.33 (Ar–C), 122.47 (C-5), 122.22 (Ar–C), 115.05 (Ar–C), 62.05 (OCH_2), 53.23 (NCH_2). HRMS: *m/z* (M^+) Cacld. for $C_{16}H_{14}N_4O_2$: 294.1117, found: 295.1204 $(M + H)^+$.

*4-[1-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-1H-[1,2,3] triazol-4-ylmethoxy]-benzaldehyde (**4o**)* White solid, 87 % yield, mp: 160–162 °C. IR (KBr, ν_{max}/cm^{-1}): 3145 (C–H str, triazole), 3062, 2922, 2852, 2746 (C–H str, CHO), 1710 (C=O str), 1601, 1510, 1462, 1311, 1250 (C–O str), 1163, 1106 (C–O str), 1005, 835. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.25 (s, 2H, NCH_2), 5.80 (s, 2H, OCH_2), 7.33–7.37 (m, 2H, 2′-H, 6′-H), 7.72 (s, 1H, triazolyl-H), 7.84–7.99 (m, 4H, 3′-H, 5′-H, 2″-H, 5″-H, 3″-H 4″-H), 9.80 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.89 (CHO), 168.28 (C=O), 163.09 (Ar–C), 144.27 (C-4), 134.34 (Ar–C), 132.66 (Ar–C), 130.38 (Ar–C), 123.62 (C-5), 115.07 (Ar–C), 114.96 (Ar–C), 114.77 (Ar–C), 60.30 (OCH_2), 53.45 (NCH_2). HRMS: *m/z* (M^+) Cacld. for $C_{19}H_{14}N_4O_4$: 362.1015, found: 363.1083 $(M + H)^+$.

Pharmacology

The procedure reported by Kaushik *et al.* (2014) was used for the evaluation of antimicrobial activities of the synthesized compounds.

Computational details

The docking studies were carried out by using Auto Dock Vina 1.1.2 (Kaushik *et al.*, 2014). Grid center was placed on the active site. The center and size of grid box were center_x = 19.0577118729, center_y = 29.6584661732 and center_z = 36.0719212982, and size_x = 25.0, size_y = 25.0 and size_z = 25.0 for DNA gyrase (PDB: 1 KZN), respectively.

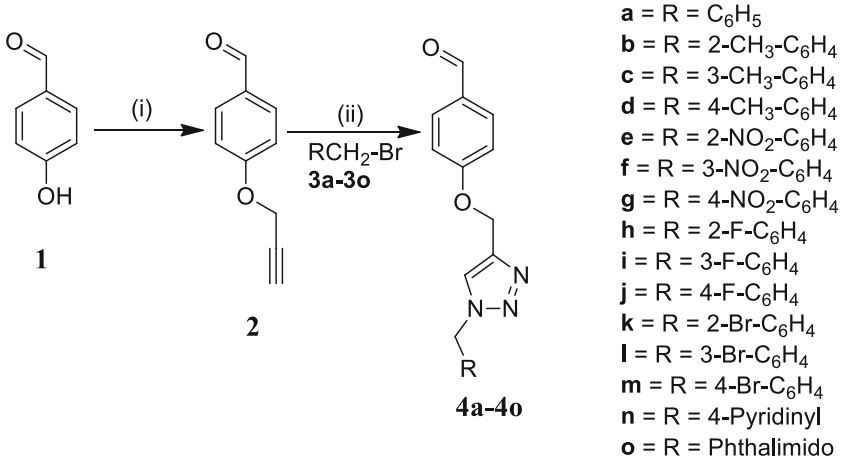
Results and discussion

Chemistry

The synthetic route for the desired 1,2,3-triazoles is outlined in Schemes 1 and 2. The first step involves the *O*-propargylation of commercially available 4-hydroxy benzaldehyde (**1**) by propargyl bromide in the presence of anhydrous K_2CO_3 in dry acetone under reflux. The 4-*O*-propargylated benzaldehyde (**2**) was subjected to one-pot multicomponent click reaction with various organic bromides (**3a**–**3o**) in the presence of catalytic amount of copper sulfate pentahydrate and sodium ascorbate in aqueous DMF to furnish desired 1,2,3-triazoles (**4a**–**4o**) in good-to-excellent yield.

The organic azides (**6a**–**6e**) were synthesized from various aniline derivatives (**5a**–**5e**) by classical diazotization–azidation process adapted from the literature (Xu *et al.*, 2013). Without further purification, organic azides (**6a**–**6e**) were treated with 4-*O*-propargylated benzaldehyde (**2**) using copper sulfate pentahydrate as catalyst and sodium ascorbate in DMF/water system to produce 1,2,3-triazoles (**7a**–**7e**) in better yield as compared to the yield reported earlier (Kumar *et al.*, 2013).

The structure of all the products was established on the basis of their FTIR, ^{1}H NMR, ^{13}C NMR and HRMS data. The FTIR spectra of all compounds (**4a**–**4o**) demonstrated a characteristic peak due to =C–H stretching of triazole ring in the region 3155–3130 cm^{-1}. The C–H stretching bands of aldehyde group were observed at 2850–2835 and 2760–2746 cm^{-1}. The C=O stretching bands appeared in the region of 1687–1668 cm^{-1}. The bands in the region 1261–1246 and 1119–1103 cm^{-1} showed the presence of ether linkage (C–O stretching). The ^{1}H NMR spectra of all



Scheme 1 Synthesis of 1,4-disubstituted 1,2,3-triazoles (**4a**–**4o**) by one-pot reaction. Reagents and conditions (i) propargyl bromide, K_2CO_3, acetone, reflux; 8 h (ii) NaN_3, sodium ascorbate, $CuSO_4{\cdot}5H_2O$, DMF/H_2O, RT

Scheme 2 Synthesis of 1,4-disubstituted 1,2,3-triazoles (**7a–7e**). Reagents and conditions: (i) HCl, $NaNO_2$, NaN_3; (ii) sodium ascorbate, $CuSO_4{\cdot}5H_2O$, DMF/H_2O, RT

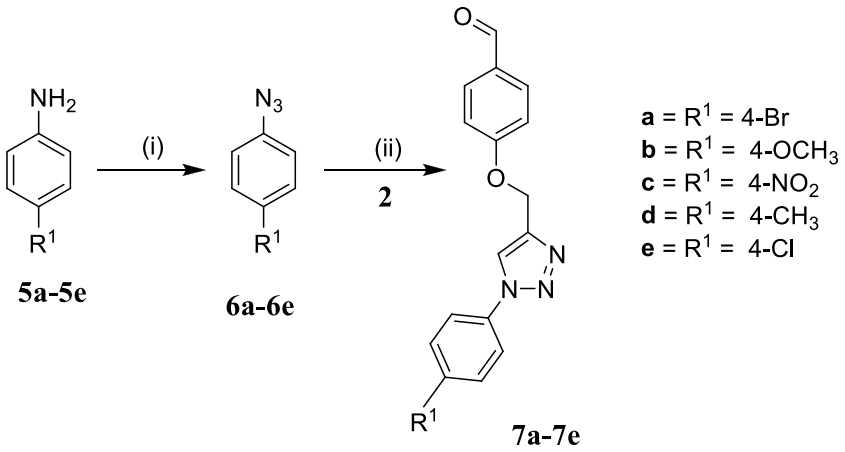


Table 1 In vitro antibacterial activity of compounds **4a–4o**; **7a–7e** (MIC in μM/mL)

Entry	Compounds	R/R^1	*S. epidermidis*	*B. subtilis*	*E. coli*	*P. aeruginosa*
1	**4a**	$-C_6H_5$	0.0054	0.0213	0.0213	0.0213
2	**4b**	2-CH_3-C_6H_4	0.0101	0.0407	0.0407	0.0203
3	**4c**	3-CH_3-C_6H_4	0.0203	0.0203	0.0407	0.0203
4	**4d**	4-CH_3-C_6H_4	0.0203	0.0407	0.0407	0.0203
5	**4e**	2-NO_2-C_6H_4	0.0369	0.0369	0.0369	0.0738
6	**4f**	3-NO_2-C_6H_4	0.0185	0.0093	0.0369	0.0185
7	**4g**	4-NO_2-C_6H_4	0.0185	0.0369	0.0185	0.0185
8	**4h**	2-Br-C_6H_4	0.0336	0.0336	0.0336	0.0336
9	**4i**	3-Br-C_6H_4	0.0168	0.0168	0.0336	0.0168
10	**4j**	4-Br-C_6H_4	0.0168	0.0168	0.0336	0.0168
11	**4k**	2-F-C_6H_4	0.0201	0.0201	0.0201	0.0402
12	**4l**	3-F-C_6H_4	0.0201	0.0201	0.0402	0.0402
13	**4m**	4-F-C_6H_4	0.0402	0.0402	0.0402	0.0201
14	**4n**	4-Pyridinyl	0.0849	0.0212	0.0424	0.0849
15	**4o**	Phthalimido	0.0172	0.0172	0.0172	0.0344
16	**7a**	4-Br	0.0349	0.0174	0.0174	0.0349
17	**7b**	4-OCH_3	0.0202	0.0027	0.0054	0.0202
18	**7c**	4-NO_2	0.0771	0.0193	0.0385	0.0193
19	**7d**	4-CH_3	0.0426	0.0213	0.0426	0.0213
20	**7e**	4-Cl	0.0199	0.0398	0.0199	0.0199
21	**Ciprofloxacin**	–	0.0047	0.0047	0.0047	0.0047

the compounds (**4a–4o**) exhibited a characteristics singlet due to triazolyl proton in the range of δ 7.47–7.74 and aldehydic proton appeared at δ 9.86–9.90. In the ^{13}C NMR spectra of all the compounds, peaks in the region δ 143.37–144.27 and δ 122.47–123.62 were assigned to the C-4 and C-5 carbon atoms of the triazole ring. A peak in the region δ 190.77–190.95 showed the presence of aldehydic carbon atom. Further, HRMS data of all the compounds confirmed their assigned structure.

Pharmacology

Antibacterial activity

The in vitro antibacterial activity of all the synthesized compounds was tested in vitro on two Gram-positive bacteria (*Staphylococcus epidermidis* MTCC 6880 and *Bacillus subtilis* MTCC 441) and two Gram-negative bacteria (*Escherichia coli* MTCC 16521 and *Pseudomonas*

Table 2 In vitro antifungal activity of compounds **4a–4o**; **7a–7e** (MIC in μM/mL)

Entry	Compounds	R/R′	*A. niger*	*C. albicans*
1	**4a**	$-C_6H_5$	0.0426	0.0107
2	**4b**	2-CH_3-C_6H_4	0.0203	0.0102
3	**4c**	3-CH_3-C_6H_4	0.0204	0.0102
4	**4d**	4-CH_3-C_6H_4	0.0407	0.0102
5	**4e**	2-NO_2-C_6H_4	0.0185	0.0185
6	**4f**	3-NO_2-C_6H_4	0.0369	0.0185
7	**4g**	4-NO_2-C_6H_4	0.0185	0.0093
8	**4h**	2-Br-C_6H_4	0.0084	0.0084
9	**4i**	3-Br-C_6H_4	0.0084	0.0084
10	**4j**	4-Br-C_6H_4	0.0336	0.0084
11	**4k**	2-F-C_6H_4	0.0201	0.0201
12	**4l**	3-F-C_6H_4	0.0100	0.0100
13	**4m**	4-F-C_6H_4	0.0100	0.0200
14	**4n**	4-Pyridinyl	0.0106	0.0106
15	**4o**	Phthalimido	0.0172	0.0344
16	**7a**	4-Br	0.0174	0.0087
17	**7b**	4-OCH_3	0.0202	0.0404
18	**7c**	4-NO_2	0.0193	0.0097
19	**7d**	4-CH_3	0.0213	0.0213
20	**7e**	4-Cl	0.0398	0.0199
21	**Fluconazole**	–	0.0102	0.0051

aeruginosa MTCC 424) by standard serial dilution method (Cappucino and Sherman, 1999). Ciprofloxacin was used as standard drug, and the minimum inhibitory concentrations (MIC) were recorded in μM/mL and are listed in Table 1.

From the antibacterial screening, it was observed that most of the compounds exhibited good-to-high activity. Compound **7b** with 4-methoxy group displayed very good activity against *E. coli* with MIC value of 0.0054 μM/mL and was found to be comparable to reference drug ciprofloxacin (MIC, 0.0047 μM/mL). Moreover, compound **7b** (MIC, 0.0027 μM/mL) also exhibited excellent potency against *B. subtilis* and was found to be almost two times more active than standard used. It was also observed that compounds with electron withdrawing group (**4e–4m**) on benzene ring exhibited better activity than the compounds containing electron releasing group (**4b–4d**).

In case of *B. subtilis*, compounds **4f** and **7b** exhibited high activity among all the compounds under study with MIC values of 0.0093 and 0.0027 μM/mL, respectively. In case of *S. epidermidis*, compounds **4a** and **4b** were found to be more active than others with MIC values of 0.0054 and 0.0101 μM/mL, respectively. It was also observed that the presence of methyl and nitro groups on benzyl increased the activity as compared to that present on benzene ring. Further, compound **4a** with benzyl group was found to be more potent than pyridinyl derivative **4n** against all bacterial strains except *B. subtilis.*

Antifungal activity

All the synthesized triazoles were also screened for antifungal activity against two fungal strains viz. *Aspergillus niger* (MTCC 8189) and *Candida albicans* (MTCC 227) by standard serial dilution method (Cappucino and Sherman, 1999). Fluconazole was used as standard drug and minimum inhibitory concentrations (MIC in μM/mL) were recorded and are depicted in Table 2. The activity data revealed good-to-high antifungal activity of most of the compounds. Compounds **4h** and **4i** showed better potency with MIC value of 0.0084 μM/mL than fluconazole (MIC = 0.0102 μM/mL) against *A. niger*. Similarly, **4l**, **4m** and **4n** showed activity comparable to the standard against *A. niger*. In case of *C. albicans*, the compounds with bromo group (**4h**, **4i**, **4j** and **7a**) exhibited better activity than all other triazoles with MIC values in the range 0.0084–0.0087 μM/mL.

Docking studies

From the antibacterial screening, compound **7b** was found to be the most promising molecule. Therefore, in

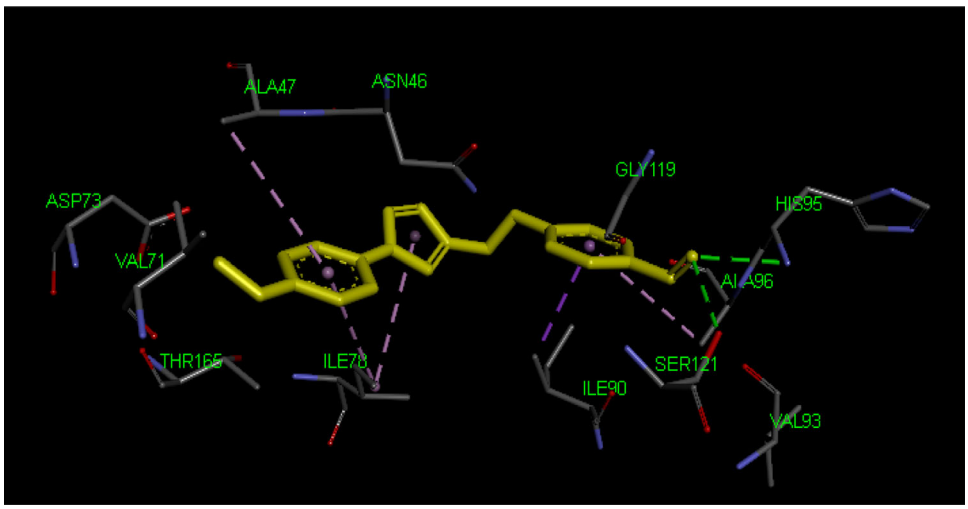


Fig. 1 Binding mode of compound **7b** in the active site of topoisomerase II DNA gyrase showing various types of interactions (*dotted lines*), i.e., hydrogen bond (*green*), pi-alkyl (*pink*), pi-sigma (*purple*) (Color figure online)

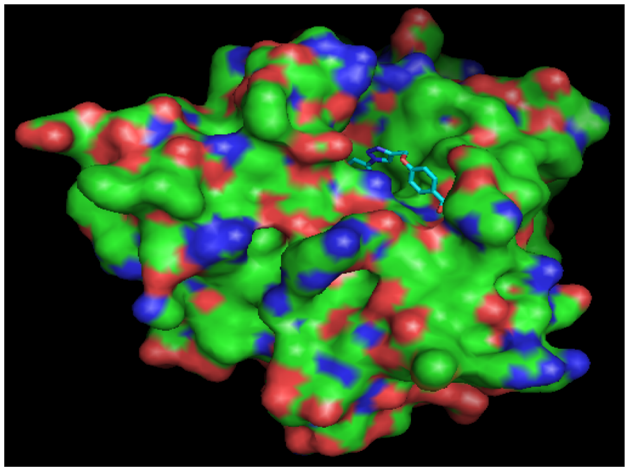


Fig. 2 Surface diagram of topoisomerase II DNA gyrase docked with compound **7b**

order to investigate a possible mechanism of action of **7b**, docking simulations into the active site of *E. coli* topoisomerase II DNA gyrase B were performed (Kaushik *et al.*, 2014). The binding mode of **7b** into active site of topoisomerase II DNA gyrase B and its surface diagram are shown in Figs. 1 and 2, respectively. It can be observed that the oxygen atom of carbonyl group is engaged in hydrogen bonding with Ser121 and His95 residues. Triazole ring and phenyl ring directly attached to triazole are involved in pi-alkyl interactions with Ile78, while same phenyl ring also demonstrate pi-alkyl interactions with Ala47. Another phenyl ring exhibits pi-alkyl interactions with Ala96 and pi-sigma interactions with Ile90. Therefore, it can be said that the compounds under study may inhibit DNA topoisomerase successfully via these interactions.

Conclusion

In conclusion, we have synthesized twenty 4-((1-benzyl/phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)benzaldehyde analogues from 4-O-propargylated benzaldehyde and various organic bromides/azides in good-to-excellent yield by using the click reaction. The antimicrobial evaluation of these compounds revealed good-to-high activities of most of the compounds against all the bacterial and fungal strains under study. Compound **7b** exhibited excellent and better potency than ciprofloxacin against *B. subtilis*. Compounds **4h** and **4i** showed activity comparable to fluconazole against *A. niger*. *In silico* docking studies of most promising compound **7b** with *E. coli* topoisomerase II DNA gyrase B showed various types of interactions with the active residues of the enzyme. The results of the present work can be used for further design and development of novel molecules against microbial infections.

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