



COPPER (I) CATALYZED SYNTHESIS AND BIOLOGICAL EVALUATION OF TETRAKIS-1,2,3-TRIAZOLES BASED ON D-IDITOL

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ABSTRACT

This work describes the synthesis of D-iditol based tetrakis-1,2,3-triazoles. In the first approach, in which the heterocyclic portions were built from the click 1,3-dipolar cycloaddition of *n*-octyl azide, *n*-nonyl azide and *n*-decyl azide, respectively with propargyl alcohol. Alkynyl triazoles **4 a-c** were readily prepared in very good yields under biphasic conditions from the corresponding triazolyl alcohols **3 a-c** and propargyl bromide in the presence of NaOH pellets in DMF. 3,4-Diazido-3,4-dideoxy-1,2 : 5,6-di-O-isopropylidene-D-iditol **7** was prepared in three subsequent steps from D-mannitol. The reaction of **7** with propargyl ethers **4 a-c** under Cu (I)-catalyzed Huisgen-Meldal 1,3-dipolar cycloaddition conditions gave the desired tetrakis-1,2,3-triazole derivatives **8 a-c** in very good yields. Removal of the acetal groups of **8 a-c** using Amberlite IR 120 H⁺ in EtOH afforded the deprotected tetrakis triazoles **9 a-c** in excellent yields. The synthesized compounds have characterized by TLC, FTIR, CHN and most of them by NMR. The biological activities of the synthesized compounds **8** and **9** were measured *in vitro* against different types of bacteria, some of the prepared compounds showed activity against the microorganism.

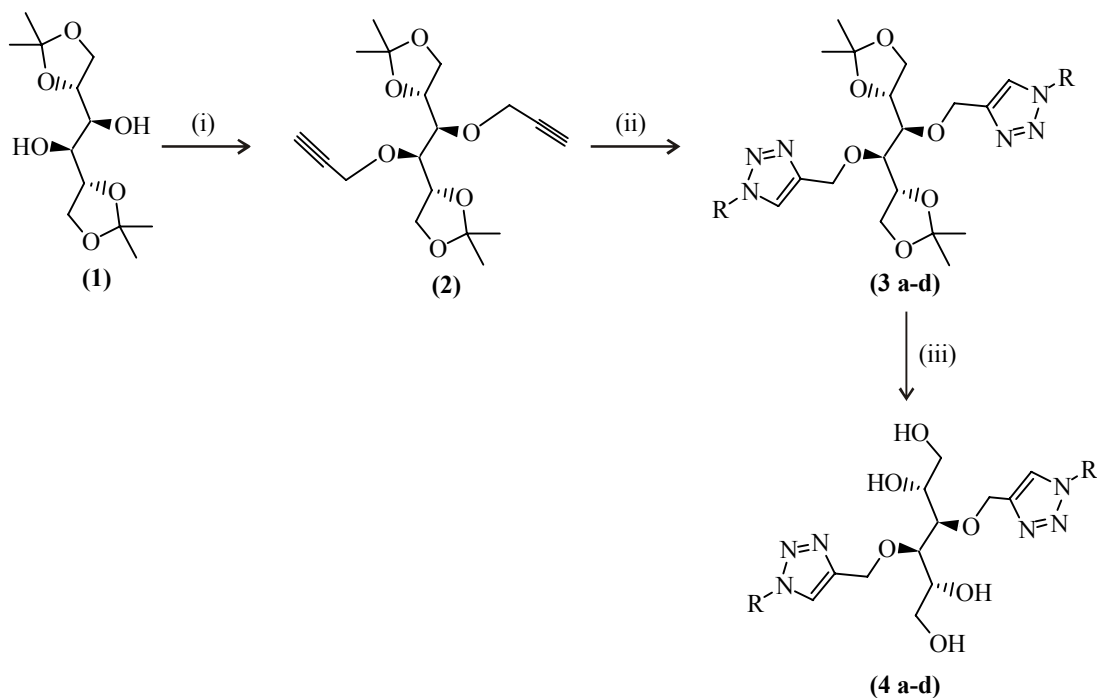
Key words: Tetrakis-1,2,3-triazoles, D-iditol, Click chemistry, 1,3-dipolar cycloaddition, Biological activity.

INTRODUCTION

1,2,3-Triazoles verified to be one of the important heterocyclic compounds because of their wide range of biological uses^{1,2}. These heterocycles have displayed various biological activities such as anti-HIV activity³, antitubercular agents⁴, antifungal⁵, antibacterial⁶, antibiotic⁷, and anticancer⁸. Introduction of carbohydrate moiety to the triazole core increasing the hydrophilicity of the whole molecule, which helps in the

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biological studies. D-mannose based 1, 2, 3-triazoles have been synthesized⁹, Jwad *et al.*^{10,11} prepared a number of 1, 2, 3-triazoles built from phenacyl azide derivatives as well as 1-nonyl-4-[(6-deoxy-1, 2 : 3, 4-di-*O*-isopropylidene- α -D-galactos-6-yl) oxymethyl] 1*H*-1, 2, 3-triazole *via* click chemistry. Mohammed *et al.*¹² synthesized novel D-mannitol substituted ether-linked bis-1, 2, 3-triazoles as models of gemini surfactants (Scheme 1).



Reagents and conditions: (i) Propargyl bromide, NaOH, DMF, -20°C-rt, 24 h; (ii) R-N₃, Na ascorbate, CuSO₄·5H₂O, DMSO, 50°C, 36 h; (iii) Amberlite IR 120 H⁺, EtOH/reflux 30 h, R = C₇H₁₅, C₈H₁₇, C₁₀H₂₁ and C₁₂H₂₅

Scheme 1: Synthesis of D-mannitol bistrizoles

Also in a separated work we have synthesized sugar-substituted ether-linked bis-1,2,3-triazoles¹³. In this work, we prepared a novel molecules containing multiple (four) 1,2,3-triazole rings and measured their effect on inhibition of two types of bacteria; *G*⁺ *Staphylococcus* and *G*⁻ *Escherichia coli* *in vitro*.

EXPERIMENTAL

Chemical were obtained from Ajax and Sigma-Aldrich Chemical. Infrared spectra were recorded using AVATAR 320 FT-IR. ¹H and ¹³C NMR spectra were recorded using

300 MHz, Bruker DPX spectrometers. Microelemental analysis was performed with Elemental Analyzer EA-300 Eurovector. Silica TLC plates were used with an aluminum backing (0.2 mm, 60 F₂₅₄). The reactions were monitored by TLC and visualized by development of the TLC plates with an alkaline potassium permanganate dip.

Synthesis of triazolyl alcohols

Triazolyl alcohols **3 a-c** were synthesized according to the previous work¹⁴ starting from corresponding alkyl azides.

Synthesis of alkynyl triazoles **4 a-c**

Triazolyl alcohol (1.7 mmol) was dissolved in DMF (10 mL) and NaOH pellets (0.25 g, 6.3 mmol) were added. The mixture was cooled to -20°C stirred vigorously for 10 min in an ice bath under N₂, then propargyl bromide (0.20 mL of 80% solution in toluene, 0.214 g, 1.8 mmol) was added dropwise and the heterogeneous reaction mixture was stirred vigorously for 24 h, slowly warming to r.t. The mixture was filtered and H₂O (30 mL) was added and the product was extracted with EtOAc (4 × 50 mL). The organic phases were combined and washed sequentially with 5% HCl (2 × 30 mL) and H₂O (30 mL). The organic phase was dried over Na₂SO₄ and evaporated to dryness under reduced pressure. The resulting yellow liquid was flash chromatographed over silica gel (Et₂O/hexane, 1 : 1) to generate alkynyl triazoles.

1-n-Octyl-4-((prop-2-ynoxy)methyl)-1H-1,2,3-triazole **4 a**

Pale yellow oil (0.34 g, 80%) (Found: C, 67.45; H, 9.33; N, 16.84% for C₁₄H₂₃N₃O requires C, 67.43; H, 9.30; N, 16.85%), IR (neat): 3288, 3137, 2926, 2856, 2111, 1465, 1358, 1336, 1221, 1141, 1083, 1050, 1023 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ: 0.84 (t, J 6.4 Hz, 3H, CH₃), 1.27 (m, 10H, (CH₂)₅CH₃), 1.87 (m, 2H, N1CH₂CH₂), 2.45 (t, J 2.4 Hz, 1H, OCH₂CCH), 4.20 (d, J 2.4 Hz, 2H, OCH₂CCH), 4.32 (t, J 7.2 Hz, 2H, N1CH₂CH₂), 4.71 (s, 2H, 4-CH₂O), 7.54 (s, 1H, H5). ¹³C NMR (75 MHz) δ: 14.0 (CH₃), 22.5 (CH₂CH₃), 26.4 (CH₂), 28.9 (CH₂), 29.0 (CH₂), 30.2 (CH₂), 31.6 (N1CH₂CH₂), 50.4 (N1CH₂CH₂), 57.4 (4-CH₂O), 63.0 (OCH₂CCH), 74.9 (OCH₂CCH), 79.3 (OCH₂CCH), 122.6 (C5-H), 144.2 (C4).

1-n-Nonyl-4-((prop-2-ynoxy)methyl)-1H-1,2,3-triazole **4 b**

White needles (0.36 g, 81 %) (Found: C, 68.38; H, 9.58; N, 15.91% for C₁₅H₂₅N₃O requires C, 68.40; H, 9.57; N, 15.95%), m.p. 77-79°C. IR (neat, cm⁻¹): 3289, 3136, 2926, 2856, 2114, 1464, 1358, 1336, 1262, 1221, 1141, 1082, 1050, 1023, 941, 890, 818, 783. ¹H NMR (300 MHz, CDCl₃) δ: 0.86 (t, J 6.9 Hz, 3H, CH₂CH₃), 1.24 (m, 8H, (CH₂)₄), 1.30 (m, 4H, (CH₂)₂), 1.89 (m, 2H, N1CH₂CH₂), 2.46 (t, J 2.4 Hz, 1H, OCH₂CCH), 4.22 (d, J 2.4 Hz,

2H, OCH₂CCH), 4.34 (t, J 7.2 Hz, 2H, N1CH₂CH₂), 4.74 (d, J 0.5 Hz, 2H, 4-CH₂O), 7.56 (s, 1H, H5). ¹³C NMR (75 MHz, CDCl₃) δ: 14.0 (CH₃), 22.6 (CH₂CH₃), 26.4 (CH₂), 28.9 (CH₂), 29.1 (CH₂), 29.3 (CH₂), 30.2 (CH₂), 31.7 (N1CH₂CH₂), 50.5 (N1CH₂CH₂), 57.5 (4-CH₂O), 62.9 (OCH₂CCH), 74.9 (OCH₂CCH), 79.2 (OCH₂CCH), 122.6 (C5-H), 144.1 (C4).

1-n-Decyl-4-((prop-2-ynyloxy)methyl)-1H-1,2,3-triazole 4 c

White needles (0.36 g, 81 %) (Found: C, 69.25; H, 9.78; N, 15.12 % for C₁₆H₂₇N₃O requires C, 69.27; H, 9.81; N, 15.15%), m.p. 86-88 °C. IR (neat, cm⁻¹): 3288, 3137, 2927, 2856, 2114, 1464, 1357, 1335, 1262, 1221, 1140, 1082, 1052, 1023, 941, 891, 818, 783. ¹H NMR (300 MHz, CDCl₃) δ: 0.87(t, J 6.9 Hz, 3H, CH₂CH₃), 1.25 (m, 8H, (CH₂)₄), 1.31 (m, 4H, (CH₂)₂), 1.88 (m, 2H, N1CH₂CH₂), 2.46 (t, J 2.3Hz, 1H, OCH₂CCH), 4.22 (d, J 2.3 Hz, 2H, OCH₂CCH), 4.34 (t, J 7.2 Hz, 2H, N1CH₂CH₂), 4.73 (d, J 0.5 Hz, 2H, 4-CH₂O), 7.56 (s, 1H, H5). ¹³C NMR (75 MHz, CDCl₃) δ: 14.0 (CH₃), 22.6 (CH₂CH₃), 26.2 (CH₂), 26.3 (CH₂), 28.9 (CH₂), 29.1 (CH₂), 29.3 (CH₂), 30.1 (CH₂), 31.8 (N1CH₂CH₂), 50.6 (N1CH₂CH₂), 57.5 (4-CH₂O), 62.9 (OCH₂CCH), 74.9 (OCH₂CCH), 79.2(OCH₂CCH), 122.5 (C5-H), 144.2 (C4).

Synthesis of 1,2:5,6-di-O-isopropylidene-d-mannitol 5

Compound **5** was synthesized according to the modified procedure¹⁵.

Synthesis of 1,2 : 5,6-di-O-isopropylidene-3,4-di-O-methanesulfonyl-d-mannitol 6

Methanesulfonylchloride (13.4 g, 0.12 mmol) was added dropwise for 15 min. under argon at 0°C to the solution of compound **5** (16 g, 47 mmol) in dry DCM (200 mL) and triethylamine (16 g, 0.15 mmol). The mixture was allowed to warm to rt and further stirred for 45 min. After which time it was washed with ice water (3 x 250 mL), the organic layer was separated, dried over Na₂SO₄ and then evaporated under reduced pressure to a white solid. The resulting crude solid was recrystallized from MeOH: H₂O 1:1 (150 mL) to give compound **6** (18 g, 91%) as white needles, mp 142-144°C; [α]_D-5.4 (c1.0 in CHCl₃). Microelemental analysis; found C, 40.15; H, 6.24 % for C₁₄H₂₆O₁₀S₂ calculated: C, 40.18; H, 6.26. IR (KBr, cm⁻¹): 2991, 2922, 1416, 1384, 1284, 1212, 1072, 1013, 951, 902.

Synthesis diazido-3,4-dideoxy1,2:5,6-di-O-isopropylidene-D-iditol 7

Sodium azide (4.6 g, 70 mmol) was added to the stirred solution of compound **6** (8.36 g, 20 mmol) in dry DMF (50 mL), the mixture was heated to 50°C for 20 h, the reaction was quenched with water (100 mL) and extracted with ether (3 x 100 mL), the combined organic layers were washed with brine (50 mL), dried over dried over Na₂SO₄ and evaporated under reduced pressure to give a yellow syrup. The residue was flash chromatographed (silica gel, *n*-hexane, EtOAc 3 : 1) to afford the azide **7** (4.5 g, 72%) as a

yellow syrup. $[\alpha]_D + 131.1$ ($c 1.0$ in CHCl_3). Microelemental analysis; found C, 45.17; H, 6.42; N, 26.88 % for $\text{C}_{12}\text{H}_{20}\text{N}_6\text{O}_4$ calculated: C, 46.15; H, 6.45; N, 26.91. IR (neat, cm^{-1}): 2989, 22936, 2103, 1455, 1383, 1286, 1256, 1212, 1070, 1007, 1052, 1023, 916, 862.

General procedure for synthesis of tetrakis-1,2,3-triazoles 8 a-c

Alkynyl triazoles **4** (2 mmol) and diazido compound **7** (1 mmol) were added to a suspension of sodium ascorbate (0.18 mmol) and $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (0.09 mmol) in DMSO (10 mL). The mixture was heated to 70°C and stirred for 48 h. It was then diluted with H_2O (30 mL), extracted with EtOAc (3 x 30 mL), and the combined organic layers washed with brine (2 x 20 mL), dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was flash chromatographed (silica gel, EtOAc/hexane 1 : 1) to yield the desired compounds.

3,4-Bis-[4-(((1-n-octyl-1H-1,2,3-triazol-4-yl) methoxy) methyl)-1H-1,2,3-triazol-1-yl] 3,4-dideoxy-1,2:5,6-di-O-isopropylidene-D-Iditol **8a**

White solid (0.71 g, 88%) (Found: C, 59.21; H, 8.18; N, 20.69% for $\text{C}_{40}\text{H}_{66}\text{N}_{12}\text{O}_6$ requires C, 59.24; H, 8.20; N, 20.72%), mp $115\text{-}116^\circ\text{C}$, $R_f = 0.38$ (n-hexane: EtOAc, 1 : 2), $[\alpha]_D - 23.6$ ($c 1.0/\text{DCM}$). IR (KBr, cm^{-1}): 3090, 2925, 2857, 1464, 1357, 1336, 1222, 1141, 1084, 1050, 1023, 999, 920, 807, 666 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ : 0.87 (t, J 6.5 Hz, 6H, 2 x CH_3), 1.26 (m, 20H, 2 x $(\text{CH}_2)_5\text{CH}_3$), 1.28 and 1.39 (s, 12H, CH_3 isopropylidene), 1.86 (m, 4H, 2 x $\text{N}1\text{CH}_2\text{CH}_2$), 3.80 (d, J 5.5 Hz, 2H, 2 x $\text{H}3'$), 3.89 (dd, J 8.3, 6.4 Hz, 2H, 2 x $\text{Ha}1'$), 3.99 (dd, J 8.3, 6.2 Hz, 2H, 2 x $\text{Hb}1'$), 4.23 (q, J 6.2 Hz, 2H, 2 x $\text{H}2'$), 4.29 (t, J 7.2 Hz, 4H, 2 x $\text{H}1'$), 4.81 (s, 4H, 2 x $-\text{CH}_2\text{-a}$), 4.82 (s, 4H, 2 x $-\text{CH}_2\text{-b}$), 7.57 (s, 2H, 2 x $\text{H}5\text{a}$), 7.75 (s, 2H, 2 x $\text{H}5\text{b}$).

3,4-Bis-[4-(((1-n-nonyl-1H-1,2,3-triazol-4-yl) methoxy) methyl)-1H-1,2,3-triazol-1-yl] 3,4-Dideoxy-1,2:5,6-di-O-isopropylidene-D-Iditol **8b**

White solid (0.70 g, 83%) (Found: C, 60.10; H, 8.40; N, 20.00% for $\text{C}_{42}\text{H}_{70}\text{N}_{12}\text{O}_6$ requires C, 60.12; H, 8.41; N, 20.03%), mp $116\text{-}117^\circ\text{C}$, $R_f = 0.36$ (n-hexane: EtOAc, 1 : 2), $[\alpha]_D - 25.5$ ($c 1.0/\text{DCM}$). IR (KBr, cm^{-1}): 3092, 2926, 2858, 1465, 1357, 1337, 1221, 1141, 1083, 1052, 1021, 996, 922, 807, 666, 512 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ : 0.86 (t, J 6.5 Hz, 6H, 2 x CH_3), 1.27 (m, 24H, 2 x $(\text{CH}_2)_6\text{CH}_3$), 1.27 and 1.38 (s, 12H, CH_3 isopropylidene), 1.87 (m, 4H, $\text{N}1\text{CH}_2\text{CH}_2$), 3.81 (d, J 5.6 Hz, 2H, 2 x $\text{H}3'$), 3.88 (dd, J 8.4, 6.3 Hz, 2H, 2 x $\text{Ha}1'$), 3.98 (dd, J 8.4, 6.3 Hz, 2H, 2 x $\text{Hb}1'$), 4.22 (q, J 6.3 Hz, 2H, 2 x $\text{H}2'$), 4.29 (t, J 7.3 Hz, 4H, 2 x $\text{H}1'$), 4.82 (s, 4H, 2 x $-\text{CH}_2\text{-a}$), 4.83 (s, 4H, 2 x $-\text{CH}_2\text{-b}$), 7.57 (s, 2H, 2 x $\text{H}5\text{a}$), 7.74 (s, 2H, 2 x $\text{H}5\text{b}$).

3,4-Bis-[4-(((1-n-decyl-1H-1,2,3-triazol-4-yl) methoxy) methyl)-1H-1,2,3-triazol-1-yl] 3,4-Dideoxy-1,2:5,6-di-O-isopropylidene-D-Iditol 8c

White solid (0.71 g, 88%) (Found: C, 60.92; H, 8.60; N, 19.36% for $C_{44}H_{74}N_{12}O_6$ requires C, 60.94; H, 8.60; N, 19.38%;), mp 122-24°C, $R_f = 0.38$ (n-hexane: EtOAc, 1 : 2), $[\alpha]_D -17.1$ (c1.0/DCM). IR (KBr, cm^{-1}): 3090, 2925, 2857, 1466, 1356, 1337, 1221, 1141, 1083, 1052, 1021, 997, 921, 810, 665, 511 cm^{-1} . 1H NMR (300 MHz, $CDCl_3$) δ : 0.87 (t, J 6.4 Hz, 6H, 2 x CH_3), 1.28 (m, 28H, 2 x $(CH_2)_7CH_3$), 1.28 and 1.38 (s, 12H, CH_3 isopropylidene), 1.88 (m, 4H, $N1CH_2CH_2$), 3.80 (d, J 5.5 Hz, 2H, 2 x $H3'$), 3.88 (dd, J 8.3, 6.4 Hz, 2H, 2 x $Ha1'$), 3.99 (dd, J 8.3, 6.4 Hz, 2H, 2 x $Hb1'$), 4.22 (q, J 6.4 Hz, 2H, 2 x $H2'$), 4.29 (t, J 7.2 Hz, 4H, 2 x $H1'$), 4.81 (s, 4H, 2 x $-CH_2-a$), 4.83 (s, 4H, 2 x $-CH_2-b$), 7.56 (s, 2H, 2 x $H5a$), 7.75 (s, 2H, 2 x $H5b$).

General procedure synthesis of compounds 9 a-c

Compound 8 (1.0 mmol) was dissolved in EtOH/ H_2O (10 mL), to this was added Amberlite IR 120 H^+ (1.0 g, 1 $g \cdot mol^{-1}$) and the mixture was stirred at reflux for 48 h. The resin was filtered off and washed with EtOH (3×5 mL), the solvent was evaporated to yield the deprotected tetrakis triazoles.

3,4-Bis-[4-(((1-n-octyl-1H-1,2,3-triazol-4-yl) methoxy) methyl)-1H-1,2,3-triazol-1-yl] 3,4-dideoxy-D-iditol 9a

White solid (0.70 g, 96 %) (Found: C, 55.89; H, 8.01; N, 22.98% for $C_{34}H_{58}N_{12}O_6$ requires C, 55.87; H, 8.00; N, 23.00%), mp 166-168°C, $R_f = 0.36$ (DCM/MeOH, 15 : 2), $[\alpha]_D + 22.1$ (c 0.5/MeOH). IR (KBr) cm^{-1} : 3560, 3410, 2926, 2863, 1641, 1548, 1511, 1460, 1221, 1062, 675. 1H NMR (300 MHz, MeOH- d_4) δ ppm: 0.88 (t, J 6.6 Hz, 6H, 2 x CH_3), 1.29 (m, 20H, 2 x $(CH_2)_5CH_3$), 1.87 (broad m, 4H, 2 x $N1CH_2CH_2$), 3.67 (dd, J 11.2, 5.1 Hz, 2H, 2 x $Ha1'$), 3.80 and 3.84 [m, 4H, 2 x ($Hb1'$ and $H2'$)], 3.93 (d, J 8.1 Hz, 2H, 2 x $H3'$), 4.35 (t, J 7.3 Hz, 4H, 2 x $N1CH_2CH_2$), 4.81 (s, 4H, 2 x $-CH_2-a$), 4.82 (s, 4H, 2 x $-CH_2-b$), 7.97 (s, 2H, 2 x $H5a$), 8.01 (s, 2H, 2 x $H5b$).

3,4-Bis-[4-(((1-n-nonyl-1H-1,2,3-triazol-4-yl) methoxy) methyl)-1H-1,2,3-triazol-1-yl] 3,4-dideoxy-D-iditol 9b

White solid (0.71 g, 94 %) (Found: C, 56.95; H, 8.22; N, 22.11% for $C_{36}H_{62}N_{12}O_6$ requires C, 56.97; H, 8.23; N, 22.15%), mp 170-171°C, $R_f = 0.37$ (DCM/MeOH, 15 : 2), $[\alpha]_D + 31.8$ (c0.5/MeOH). IR (KBr) cm^{-1} : 3565, 3411, 2927, 2862, 1644, 1545, 1510, 1460, 1221, 1062, 675, 553. 1H NMR (300 MHz, MeOH- d_4) δ ppm: 0.87 (t, J 6.5 Hz, 6H, 2 x CH_3), 1.28 (m, 24H, 2 x $(CH_2)_6CH_3$), 1.88 (broad m, 4H, 2 x $N1CH_2CH_2$), 3.66 (dd,

J 11.3, 5.2 Hz, 2H, 2 × Ha1'), 3.81 and 3.83 [m, 4H, 2 × (Hb1' and H2')], 3.93 (d, J 8.2 Hz, 2H, 2 × H3'), 4.36 (t, J 7.2 Hz, 4H, 2 × N1CH₂CH₂), 4.82 (s, 4H, 2 × -CH₂-a), 4.83 (s, 4H, 2 × -CH₂-b), 7.98 (s, 2H, 2 × H5a), 8.01 (s, 2H, 2 × H5b).

3,4-Bis-[4-(((1-n-decyl-1H-1,2,3-triazol-4-yl) methoxy) methyl)-1H-1,2,3-triazol-1-yl] 3,4-dideoxy-D-iditol 9c

White solid (0.70 g, 96 %) (Found: C, 55.98; H, 8.43; N, 21.35% for C₃₈H₆₆N₁₂O₆ requires C, 57.99; H, 8.45; N, 21.36%), mp 166-168°C, R_f = 0.37 (DCM/MeOH, 15 : 2), [α]_D + 28.4 (c 0.5/MeOH). IR (KBr) cm⁻¹: 3560, 3411, 2927, 2862, 1545, 1510, 1462, 1222, 1062, 674. ¹H NMR (300 MHz, MeOH-d₄) δ ppm: 0.87 (t, J 6.6 Hz, 6H, 2 × CH₃), 1.29 (m, 28H, 2 × (CH₂)₇CH₃), 1.88 (broad m, 4H, 2 × N1CH₂CH₂), 3.66 (dd, J 11.2, 5.2 Hz, 2H, 2 × Ha1'), 3.81 and 3.84 [m, 4H, 2 × (Hb1' and H2')], 3.94 (d, J 8.2 Hz, 2H, 2 × H3'), 4.35 (t, J 7.3 Hz, 4H, 2 × N1CH₂CH₂), 4.81 (s, 4H, 2 × -CH₂-a), 4.82 (s, 4H, 2 × -CH₂-b), 7.97 (s, 2H, 2 × H5a), 8.01 (s, 2H, 2 × H5b).

Biological activity¹⁶

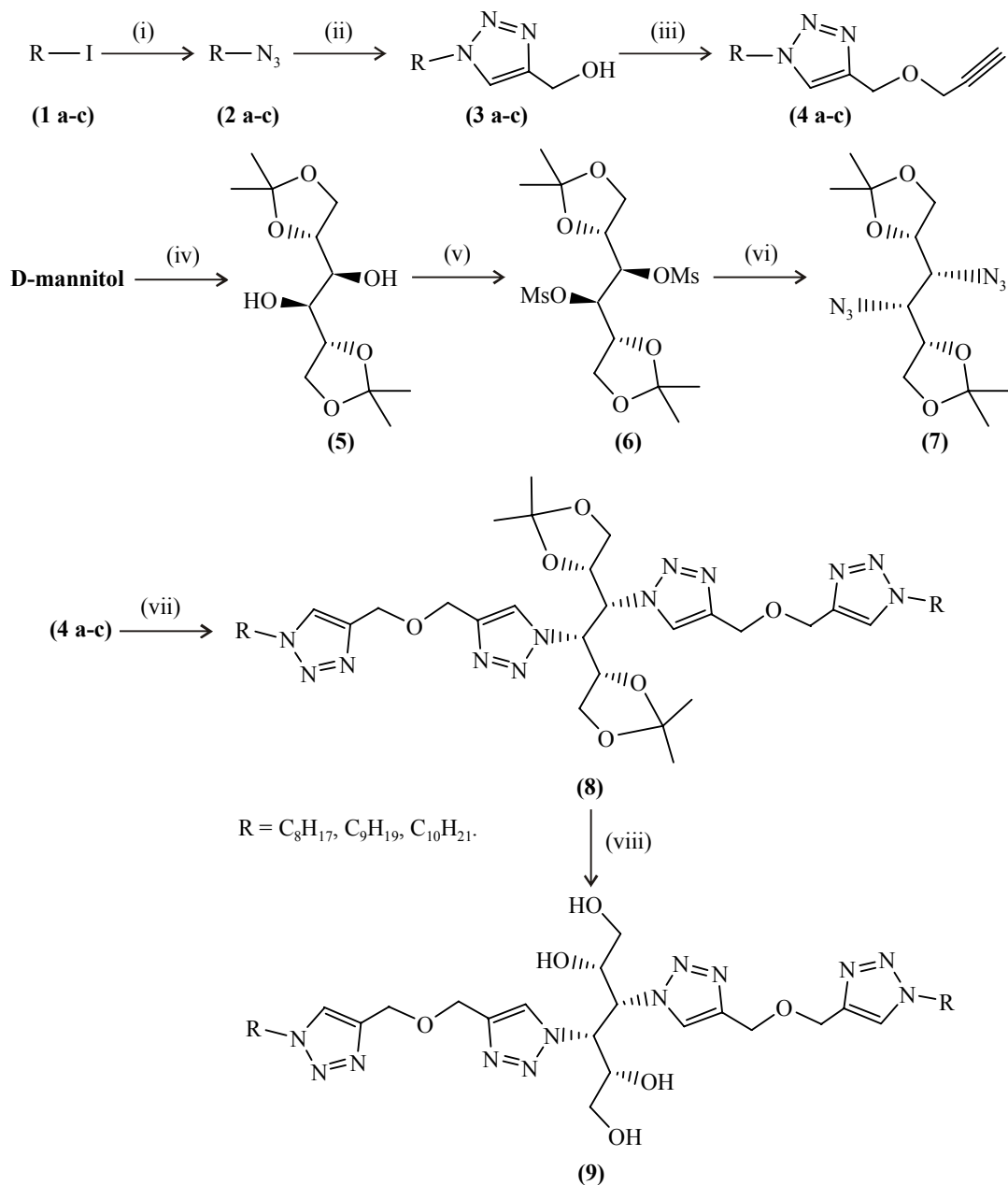
The antibacterial efficacy of the synthesized compounds was tested against Gram positive bacteria *Staphylococcus aureus* and Gram negative bacteria *Escherichia coli* by agar well diffusion method.

Twenty four old Muller-Hinton broth cultures of test bacteria were swabbed on sterile Muller-Hinton agar plates using sterile cotton swab followed by punching wells of 6 mm with the help of sterile cork borer. (20 mg/mL in 10% DMSO) and control (10% DMSO) were added to respectively labeled wells. The plates are allowed to stand for 30 minutes and were incubated at 37°C for 24 h in upright position and the zone of inhibition was recorded.

RESULTS AND DISCUSSION

In the first approach the conversion of triazolyl alcohols **3** to the triazolyl alkynes **4** was investigated by FTIR and NMR. The stretching bands around 3288 cm⁻¹ which belong to the (C-H acetylenic) in addition to the stretching bands around 2114 cm⁻¹ of (C≡C) also ¹H NMR spectra enhance the formation of alkyne; the triplet signals around 2.45 ppm are excellent evidence of the formation of alkynes **4**.

The following scheme describes the overall synthetic route of the targeted compounds:



Reagents and conditions: (i) NaN_3 , DMF, 70°C , 4 h; (ii) HCCCH_2OH , Na ascorbate, $\text{CuSO}_4 \cdot \text{H}_2\text{O}$, DMSO, 50°C , 36 h; (iii) HCCCH_2Br , NaOH, DMF, -20°C -rt, 24 h; (iv) Acetone, ZnCl_2 , rt, 20 h; (v) MsCl, TEA, DCM, 0°C -rt, 1 h; (vi) NaN_3 , dry DMF, 50°C , 20 h; (vii) Compound 7, Na ascorbate, $\text{CuSO}_4 \cdot \text{H}_2\text{O}$, DMSO, 70°C , 48 h; (viii) Amberlite IR 120 H^+ , EtOH/reflux, 48 h.

Scheme 2: The synthetic route of tetrakis-1,2,3-triazoles

The diazide **7** was prepared in two subsequent steps starting from D-mannitol the first one is a condensation reaction to form the di-OMs compound while the second is an S_N2 reaction, the formation of the diazide **7** was followed by FTIR technique because there are essential changes in functional groups; the disappearance of (O-H) stretching band is a good proof of formation of the di-OMs **6** while the presence of the ($-N_3$) stretching band at 2103 cm^{-1} is an excellent evidence of the preparation of the diazide **7**. Cu (I) catalyzed 1,3-dipolarcycloaddition reaction of the terminal alkynes **4** with the diazido sugar **7** afforded the tetrakis-1,2,3-triazoles **8**. The formation of compounds **8** was monitored by FTIR and ^1H NMR. The vanishing of the alkynes stretching bands around 3288 cm^{-1} and 2114 cm^{-1} as well as the azide stretching band at 2103 cm^{-1} is a significant indication of the success of the click reaction. ^1H NMR spectra gave the more important proofs of the formation of the tetrakis-triazoles; the singlet signals around 7.57 ppm and 7.75 ppm and their integration which go to the aromatic triazoles protons at H-5 for both rings in addition to the two singlet signals belong to ($-\text{CH}_2\text{-a}$) and ($-\text{CH}_2\text{-b}$) around 4.81 and 4.83 , respectively. We numbered the compounds **8** as follows in order to explain the NMR signals:

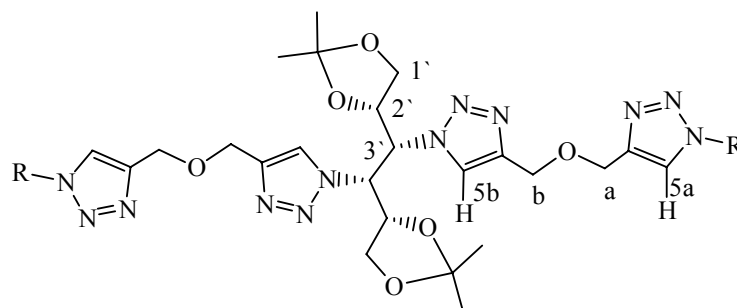


Fig. 1: Numbering of compounds 8

The removal of isopropylidene protecting groups was carried out under acidic conditions. The same scenario was used for the investigation of the deprotection process. In FTIR spectra, the appearance of broad (O-H) stretching bands around 3560 and 3410 cm^{-1} is a very good indication for the diacetone removal while the most important proof came from ^1H NMR spectra; the disappearance of isopropylidene signals around 1.27 and 1.38 ppm as well as the presence of the signals near 4.81 (s, 4H, $2 \times -\text{CH}_2\text{-a}$), 4.82 (s, 4H, $2 \times -\text{CH}_2\text{-b}$), 7.97 (s, 2H, $2 \times \text{H5a}$) and 8.01 (s, 2H, $2 \times \text{H5b}$) is an excellent proof for the non-cleavage of the triazolyl compounds **8** during the deprotection process and formation of compounds **9**.

Biological activity

The antibacterial activity of the synthesized compounds was tested against Gram positive bacteria *Staphylococcus aureus* and Gram negative bacteria *Escherichia coli* by agar well diffusion method. DMSO was used as control while Kenamycin was used as standard.

Table 1: Antibacterial activity of the synthesized compounds

Compound	Zone of inhibition in (mm), concentration ($\mu\text{g/mL}$)					
	<i>G</i> ⁺ <i>Staphylococcus</i>			<i>G</i> ⁻ <i>Escherichia coli</i>		
	5	10	20	5	10	20
DMSO	-	-	-	-	-	-
Kenamycin	27	28	28	28	27	28
8a	-	08	13	-	05	09
8b	-	07	11	-	06	10
8c	-	10	12	-	09	13
9a	-	11	17	-	10	14
9b	-	10	15	-	09	14
9c	-	09	15	-	09	13

CONCLUSION

In conclusion, we have developed a first-time, convenient strategy for the synthesis of novel, biologically important tetrakis-1,2,3-triazoles starting from D-mannitol employing the copper catalyzed ‘click’ protocol. The products thus obtained were found to be effective antibacterial agents in different concentrations.

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REFERENCES

1. K. Pericherla, P. Khedar, B. M. Khungar and A. Kumar, *Tetrahedron Lett.*, **53**, 6761 (2012).
2. K. Slamova, P. Marhol, K. Bezouška, L. Lindkvist, S. Hansen, V. Kren and H. Jensen, *Bioorg. Med. Chem. Lett.*, **20**, 4263 (2010).
3. M. Klein, K. Krainz, I. Redwan, P. Dinér and M. Grötli, *Molecules*, **14**, 5124 (2009).
4. S. Kim, S. Cho, T. Ohc and P. Kim, *Bioorg. Med. Chem. Lett.*, **22**, 6844 (2012).
5. M. Mao, Y. Li, Y. Zhou, W. Chen, T. Liu, S. Yu, S. Wang and Z. Li, *Chem. Biol. Drug. Des.*, **78**, 695 (2011).
6. A. Mohammed, A. Dawood, K. Ali and M. Al-Mosawi, *Asian J. Chem.*, **24**, 5592 (2012).
7. K. Rathwell, J. Sperry and M. Brimble, *Tetrahedron*, **66**, 4002 (2010).
8. Q. Wan, J. Chen, G. Chen and S. Danishefsky, *J. Org. Chem.*, **71**, 8244 (2006).
9. Y. Ali, A. Mohammed and R. Jwad, *Proceeding of 3rd Scientific Conference of the College of Science, (University of Baghdad, Baghdad, Iraq), 26-28 March, 1370 (2009).*
10. R. Jwad, A. Mohammed and M. Shihab, *Iraqi J. Science* (2012).
11. R. Jwad, *J. AL-Nahrain Univ.*, **14**, 44 (2011).
12. A. Mohammed, Z. Abboud and A. Alghanimi, *Tetrahedron Lett.*, **53**, 5081 (2012).
13. A. Mohammed, *Asian J. Chem.*, **24**, 5585 (2012).
14. D. Francis, D. Miles, A. Mohammed, R. Read and X. Wang, *J. Fluorine Chem.*, **132**, 898 (2011).
15. B. Furniss, A. Hannaford, P. Smith and A. Tatchell, *Vogel's Text Book of Practical Organic Chemistry, 5th Ed.*, Longman Ltd., Harlow, UK, 654 (1989).
16. N. Jayanna, H. Vagdevi, J. Dharshan and T. Prashith Kekuda, *Int. J. Chem. Sci.*, **10**, 1529 (2012).

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