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Synthesis, Anticancer and Antibacterial Activity of Mannose-based bis-1,2,3-Triazole Derivatives

***Lamyaa Salih Mahdi*[1,2*]** ***Adnan Ibrahim Mohammed*[3*]**
***Majed Jari Mohammed*[1]**

[1]Department of Chemistry, Faculty of Science, University of Kufa, Kufa, Iraq
[2]Department of Pharmacognosy and Medicinal Plant, College of Pharmacy, University of Kerbala, Karbala, Iraq
[3]Department of Chemistry, College of Science, University of Kerbala, Karbala, Iraq
*Corresponding Author: adnan.i@uokerbala.edu.iq.
E-mail addresses: lamiaa.saleh@uokerbala.edu.iq, majed.jari@gmail.com

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Abstract:

In the current work, aromatic amines and alkyl halides have been converted to the corresponding azides **2a–d** and **4a-d** by the reaction with sodium nitrite and sodium azide respectively for amines and sodium azide for halides. Then, dipropargyl ether derivative of D-mannose **8** has been synthesized from diacetone mannose that has been obtained by the treatment of D-mannose (**5**) with dry acetone in the presence of sulfuric acid. Then, aldol condensation has been used to prepare diol **7** from the mannose diacetonide **6**. The reaction of compound **7** with propargyl bromide in alkaline media has been afforded dipropargyl derivative **8**. In a parallel step, both dialkyne with aromatic and aliphatic azide have been coupled to produce 1,2,3-triazole derivatives **9a–d** in the presence of Cu(I) salts. All synthesized compounds have been characterized by 1D and 2D NMR spectra alongside with HRMS data. The antibacterial activity against both gram-positive and gram-negative has been tested. Moreover, the anticancer activity has also been evaluated against AMJ13 cell line.

Keywords: Antibacterial activity, Anticancer activity, Bis-1,2,3-triazoles, Breast cancer, CuAAC, D-Mannose, Propargyl derivatives.

Introduction:

Cancer has life serious threats to global health that causes one out of six life losses in the world.[1] The triazoles derivatives revealed extensively anti-proliferative potency against human prostate,[2] breast,[3] liver,[4] lung,[5] bladder[6] and other cancer cells, in drug discovery. Mimicking glycosides, Nerella and co-workers[7] built new1,2,3-triazoles based on carbohydrate molecule that have notable anticancer activity against breast and prostate cancer cell lines. Recently, Oubella *et al*.[8] synthesized series of novel (R)-Carvone-based 1,4-disubistituted-1,2,3-triazoles via regioselective cupper (I)- catalyzed alkyne-azide click methodology. The hybrids Carvone triazoles in vitro evaluated the anticancer activity against breast adenocarcinoma (MCF-7 and MDA-MB-231), (HT-1080) and fibro sarcoma (A-549) lung carcinoma, cell line. On the other hand, Covid-19 is the most life-threatening disease to global health till now.[9] The widely fast spread and aggressive symptoms caused by the crown virus results in tremendous economic loss and mortality during the pandemic. The significant heterocyclic azole compounds have a potential role as antimicrobial[10,11] and enzyme inhibitors motivated many researchers to improve pharmaceutically active 1,2,3-triazoles scaffolds.[12] The recent *in silico* studies were confirmed by Holanda *et al*.,[13] that the phthalimide-based 1,2,3-triazoles derivatives were prepared via click are promising drug for COVID-19 treatment as the ability to disrupt virus spike, nucleocapsid or protease proteins. Also, many 1,2,3-triazole derivatives as FDA-approved drugs have exerted their pharmacological activities such as the antibacterial; tazobactam,[14] antibiotic; cefatrizine,[15] anticancer; Carboxyamido-triazole (CAI),[16] anti-HIV; TSAO,[17] and anti-Alzheimer; MTSMDL treatment.[18] 1,2,3-triazole employed superior antimicrobial,[19]

antifungal,[20] antioxidant[21] and cytotoxic activities.[22] Collections of glycoconjugated 1,2,3-triazoles derivatives from different sugars functionalized with alkyne or azide moieties have been synthesized *via* CuAA-click reaction and their antibacterial were evaluated.[23–25] Many factors improve the 1,2,3-triazoles biological value such as physical and chemical properties, high stability against oxidant agent, hydrolysis resistant in acid/base conditions, the hydrogen bonds forming and amide bioisoesters.[26] As a result of the special physicochemical properties, 1,2,3-triazole derivatives played a versatile role in the material sciences,[27] Anti-corrosions,[28] polymers,[29] dyes,[30] catalysts,[31] ligands,[32] surfactants,[33] chemo sensors for different species.[34] Click strategies is the concept introduced by Sharpless[35] and Meldal[36] in 2002 to design and synthesize wide scope of 1,2,3-triazoles scaffold molecules. The 1,3-dipolar cycloaddition reaction of terminal alkyne and azide catalyzed by Cu(I) CuAAC afforded regioselective1,4-disubstituted -1,2,3-triazoles in high yield, stereoselective, easily removable by-products, simplicity and green of click protocol.[37] In this work, novel bis-1,2,3-triazole derivatives have been synthesized starting from D-mannose and their structural properties were studied. They also have been examined against bacteria and breast cancer.

Material and Methods:

General Information

Chemicals were gained from Sigma-Aldrich and Alfa Aesar Chemicals. Infrared spectra were obtained using SHIMADZU 2001 FT-IR. NMR spectra were verified using 600 MHz, Bruker DPX spectrometers, NMR assignments of the synthesized compounds supported by COSY and HSQC. Orbit rap LTQ XL ion trap MS in positive ion mode using electrospray ionization (ESI) source was employed to assemble HRMS. Silica TLC plates were used with an aluminum backing (0.2 mm, 60 F_{254}). The reactions were monitored by TLC and envisioned by development of the TLC plates with an alkaline potassium permanganate solution dip. AMJ13 Cells have been provided by Iraqi Center for Genetics and Cancer Research ICGCR/ Mustansiriyah University -Baghdad / Iraq.

Synthesis of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (6)[38]

D-Mannose (**5**) (20 g, 0.11 mole) was added to the stirred mixture of anhydrous acetone (900 mL) and conc. sulfuric acid (14 mL) and the stirring continued for 4 hours. The light-yellow solution was neutralized with anhydrous sodium carbonate and filtered; the filtrate was evaporated under reduced pressure, to give a solid residue, which was recrystallized from (*n*-hexane / toluene; 6:1) to yield compound **6** as white crystals (22.5 g, 75 % yield). M.p. 120–122 °C (lit[39] 120–122 °C); $[\alpha]_D^{25}$ +16.1 (*c* 2.5, EtOH), R_f =0.65 (EtOAc). FT-IR(KBr) ν cm^{-1}: 3437, 2986, 2907, 1452, 1381, 1213, 1161, 1078. ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm: 5.37 (s, 1 H, H-1), 4.80 (dd, J = 5.8 Hz, J = 3.6 Hz, 1 H, H-3), 4.61 (d, J = 5.9 Hz, 1 H, H-2), 4.41–4.37 (m, 1 H, H-5), 4.18 (dd, J = 7.1 Hz, J = 3.7 Hz, 1 H, H-4), 4.08 (dd, J = 8.6 Hz, J = 6.3 Hz, 1 H, Ha-6), 4.04 (dd, J = 8.6 Hz, J = 4.7 Hz, 1 H, Hb-6), 1.46 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 112.8 (**C**(CH_3)), 109.2 (**C**(CH_3)), 101.4 (C-1), 85.6 (C-2), 80.4 (C4), 79.8 (C-3), 66.7 (C6), 27.0 (CH_3), 26.0 (CH_3), 25.3 (CH_3), 24.6 (CH_3). HRMS (ESI, +ve) $C_{12}H_{20}O_6Na^+$ $[M + Na]^+$ requires *m*/*z* 283.1152, found 283.1152.

Synthesis of 2-*C*-(Hydroxymethyl)-2,3:5,6-di-O-isopropylidene-D-mannofuranose (7)[38]

2,3:5,6-Di-O-isopropylidene-α-D-mannofuranose (**6**) (5 g, 18.5 mmol) was added to MeOH (25 mL) and the mixture was stirred for a while until diacetonide **2** was fully dissolved. Potassium carbonate (16 g, 115.7 mmol) was added and the mixture was stirred at 80 °C in an oil bath to give a milky suspension. Commercially available 37% formaldehyde (formalin, 17 mL) was introduced and the mixture was stirred at 90 °C (reflux began) for 15 min. Two portions of KOH (pellets, 0.52 g, 9.27 mmol) were over 15 minutes with continues stirring. Reflux and stirring was continued at 90 °C for 35 minutes and a third portion of KOH (0.52 g, 9.27 mmol) was added. The mixture was stirred/refluxed for another 35 minutes. After which, the heating bath was removed and cooled in an ice−water bath. All solids were filtered off and the filtrate was cooled in an ice−water bath and neutralized with aq. (10%) H_2SO_4 (10−15 mL). The MeOH in the filtrate was removed by rotary evaporation and the residue was extracted with CH_2Cl_2 (3 × 90 mL). The combined organic layers were washed with sat. NaCl solution (50 mL) and dried over anhydrous Na_2SO_4. The organic layers were concentrated under vacuum and the residue was purified by column chromatography (*n*-hexne / EtOAc; 2:1) on silica gel (mesh 60) to compound **7** as a *ca*. 2:1 mixture of two epimers colorless waxy which was solidified to white solid (4.2 g, 78%). M.p. 86−89 °C (lit[40] a colourless oil). $[\alpha]_D^{25}$ +10.7 (*c* 1.0, MeOH). R_f = 0.52 (EtOAc). FT-IR(KBr) cm^{-1}: 3451, 3312, 2988, 2943, 2891, 1458, 1414, 1377, 1240, 1067, 1032. ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm: 5.37 (1H, s, H-1A), 4.90 (1H, s, H-

1B), 4.66 (d, *J* = 3.0 Hz, 1H, H-3A), 4.65 (d, *J* = 3.0 Hz, 1H, H-3B), 4.40 (ddd, *J* = 7.6, 6.2, 4.6 Hz, 1H, H-5A), 4.37 (ddd, *J* = 8.4, 4.2, 2.2 Hz, 1H, H-5B), 4.15 (dd, *J* = 7.6, 2.9 Hz, 1H, H-4A), 4.11−4.01 (m, 4H, H-6A and H-6B), 3.98 (d, *J* = 12.0 Hz, 1H, H-2'aA), 3.85 (d, *J* = 12.0 Hz, 1H, H-2'bA), 3.79 (d, *J* = 11.9 Hz, 1H, H-2'aB), 3.76 (d, *J* = 11.8 Hz, 1H, H-2'bB), 3.51 (dd, *J* = 8.2, 2.9 Hz, 1H, H-4B), 1.56, 1.48, 1.46, 1.44, 1.43, 1.42, 1.37, 1.36 (s, 24H, 8 × CH_3 A and B). ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 114.3, 114.0, 109.5, 109.4 (4 × **C**(CH_3) A and B), 104.0 (C-1A), 97.7 (C-1B), 83.0 (C-3A), 82.0 (C-3B), 81.3 (C-4A), 76.5 (C-4B), 73.2 (C-5A), 73.0 (C-5B), 67.3 (C-6A), 66.8 (C-6B), 63.8 (C-2'A), 62.9 (C-2'B), 27.6, 27.5, 27.4, 27.2, 27.1, 27.0, 26.99, 25.3 (8 × **C**H_3-A and B). HRMS (ESI, +ve) $C_{13}H_{22}O_7Na^+$ [M + Na]$^+$ requires *m*/*z* 313.1258, found 313.1258

Synthesis of 2-*C*-(Hydroxymethyl)-2,3:5,6-di-O-isopropylidene-D-mannofuranose Dipropargyl Ether (8)[38,41]

Crushed NaOH (0.96 g, 24 mmol) was added to the solution of diol **7** (1.74 g, 6 mmol) in DMF (30 mL). The reaction flask was kept in ice-salt bath at −20 °C and the contents stirred for (10 minutes) before propargyl bromide (1.52 mL, 17.08 mmol) was added dropwise. The reaction mixture was then allowed to warm to r.t. and stirred for further 24 hours. The reaction mixture was quenched with distilled water (60 mL) and extracted with Et_2O (3 × 50 mL). The combined organic dried over Na_2SO_4, filtered and the solvent was evaporated to the dryness under reduced pressure to yield a pale-yellow oil. Flash chromatography on silica column (n-hexane / Et_2O, 8:1) yielded dialkyne **8** as a pale-yellow oil (1.32 g, 60 %). $[\alpha]_D^{25}$ +1.3 (*c* 0.02, MeOH). R_f = 0.72 (EtOAc). FT-IR (neat) cm^{-1} :3287, 2988, 2934, 2118, 1458, 1375, 1244, 1107, ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm: 5.13 (1H, s, H-1), 4.60 (d, *J* = 3.0 Hz, 1H, H-3), 4.41 (ddd, *J* = 8.3, 6.2, 4.2 Hz, 1H, H-5), 4.28 (dd, *J* = 15.8, 2.4 Hz, 1H, C**H**$_2$C≡CH), 4.21 (dd, *J* = 15.8, 2.2 Hz, 1H, C**H**$_2$C≡CH), 4.20 (d, *J* = 2.4 Hz, 2H, C**H**$_2$C≡CH), 4.11 (dd, *J* = 8.7, 6.2 Hz, 1H, H-6a), 4.04 (dd, *J* = 8.7, 4.2 Hz, 1H, H-b), 3.92 (dd, *J* = 8.3, 2.9 Hz, 1H, H-4), 3.83 (d, *J* = 10.9 Hz, 1H, H-2'a), 3.76 (d, *J* = 10.9 Hz, 1H, H-2'b), 2.42−2.415 (m, 2H, C≡C**H**), 1.47, 1.46, 1.44, 1.37 (s, 12H, 4 × CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 114.5 (**C**(CH_3)$_2$), 109.5 (**C**(CH_3)$_2$), 106.6 (C-1), 82.6 (C-3), 81.0 (C-4), 79.7 (CH_2**C**≡CH), 79.1 (CH_2**C**≡CH), 74.7 (CH_2C≡**C**H), 74.6 (CH_2C≡**C**H), 73.1 (C-5), 68.6 (C-2'), 67.1 (C-6), 59.1 (**C**H_2C≡CH), 54.8 (**C**H_2C≡CH), 27.8, 27.6, 27.1, 25.3 (4 × **C**H_3). HRMS (ESI, +ve) $C_{19}H_{26}O_7Na^+$ [M + Na]$^+$ requires *m*/*z* 389.1570, found 389.1570.

General Synthesis Procedure for *n*-alkyl Azide (2a and 2b)[24]

A solution of *n*-alkyl halide (48 mmol) in DMF (70 mL) was stirred with sodium azide (9.44 g, 145mmol) at 70 °C for (6 hours), then distilled water (100 mL) was added to the reaction mixture and extracted with Et_2O (3 × 100 mL), the organic layers were collected , washed with brine solution (2 × 100 mL), water (150 mL) dried with Na_2SO_4 and evaporated to gain *n*-alkyl azides (**2a** and 2**b**) as a colorless liquid.

***n*-Decyl azide (2a)** Colorless liquid (9.52 g, 89%) R*f* = 0.8 (EtOAc). FT-IR (neat): 2928, 2854, 2094, 1462, 1373, 1257, 1051, 895, 723 cm^{-1}. ^{1} H NMR (600 MHz, $CDCl_3$) δ ppm: 3.25 (t, *J* = 7.2 Hz, 2H, H1), 1.59 (quin, *J* = 7.2 Hz, 2H, H2), 1.38–1.29 (m, 14H, H3-9), 0.88 (t, *J* = 6.6 Hz 3H, H10). ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm: 51.6 (C1), 32.0 (C2), 29.6 (2 × C, C3, C4), 29.4 (C5), 29.3 (C6), 29.0 (C7), 26.9 (C8), 22.8 (C9), 14.2 (C10).

***n*-Dodecyl azide (2b)** Colorless liquid (8.62 g, 85%). Rf = 0.57 (EtOAc), FT- IR (neat): 2926, 2854, 2094, 1462, 1348, 1259, 1128, 895, 723, 557 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm: 3.25 (t, *J* = 7.2 Hz 2H, H1), 1.59 (quin, *J* = 7.8 Hz 2H, H2), 1.37–1.27 (m, 18H, H3-11), 0.86 (t, *J* = 7.2, 3H, H12). ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm: 51.6 (C1), 32.1 (C2), 29.8 (C3), 29.7 (C4), 29.6 (C5), 29.5 (C6), 29.3 (C7), 29.0 (C8), 228.9 (C9), 26.7 (C10), 22.8 (C11), 14.2 (C12).

General Synthesis Procedure for Aryl Azide 4a and 4b[42]

Aryl amine (2mmol) was added to a solution of *p*-TsOH.H_2O (3.24 g, 18.0 mmol) in H_2O (18.0 mL) and stirred for 1 minute. Anhydrous $NaNO_2$ (1.24 g, 18 mmol) was added portio-wise during 5 mim. After the reaction mixture stirring for 60 minutes, anhydrous NaN_3 (0.208 g, 3.2 mmol) was added. The solid aryl azide was filtered, washed with dist. water (100 mL) then dried to gain aryl azides **6c** as pale yellow solid 65–69 °C and **6d** as white solid 57–59 °C.

***p*-Azido nitrobenzene (4a):** Pale yellow solid (0.30 g, 92%), 65–69 °C. R_f = 0.79 (EtOAc), FT-IR (KBr): 3105, 3072, 2114, 1680, 1599, 1514, 1342, 1286, 1182, 1116, 852, 744, 690, 559, 434 cm^{-1}.

1-Azido-2, 4-dichloro benzene (4b): White solid (0.30 g, 92%), 60-64 °C, R_f = 0.80 (EtOAc), FT-IR

(KBr): 3057, 2115, 1575, 1475, 1435, 1301, 1145, 1097, 1049, 798, 759, 592, 565, 401 cm^{-1}. ^{1} H NMR (600 MHz, $CDCl_3$) δ ppm: 7.83–7.09 (3H, H-aromatic). ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm: 136.2, 130.7, 130.6, 128.2, 125.9, 120.5 (6C, C-aromatic).

General Synthesis Procedure for 2-*C*-(oxymethyl)-2,3:5,6-di-*O*-isopropylidene-D-mannofuranose bis-*O*-[(1-alkyl-1*H*-1,2,3-triazol-4-yl)methyl)]ether (9a–d)[43]

The dipropargyl ether 4 (0.366 g, 1 mmol) was dissolved in DMSO (3 mL) and added to a suspension of sodium ascorbate (0.0396 g, 0.2 mmol) and $CuSO_4.5H_2O$ (0.025g, 0.01 mmol) in DMSO (2 mL), then the reaction mixture was stirred for 2 minutes at room temperature. The azide (2.1 mmol) was added, and the mixture was heated to 60 °C for 48 hours, the reaction mixture was diluted with dist. water (10 mL), then extracted with EtOAc (3 × 25mL), the organic layers were collected, washed with brine solution (25mL), dried with Na_2SO4 and evaporated to afford compounds **9a** and **9b** as white waxy and compounds **9c** and **9d** as solid. All synthesized compounds were purified under column chromatography (silica gel, n-hexane / EtOAc; 2:1 → 1:2,) to yield the corresponding bis-1,2,3-triazole.

2-*C*-(Oxymethyl)-2,3:5,6-di-*O*-isopropylidene-D-mannofuranose bis-*O*-[(1-decyl-1H-1,2,3-triazol-4-yl) methyl)]ether (9a)

White solid (0.59 g, 80.5%); mp 50–53 °C, Rf = 0.59 (EtOAc), IR (KBr): 3136, 2926, 2858, 1460, 1373, 1219, 1145,1074, 889, 846, 786, 725, 511 cm^{-1} .**^{1}H NMR** (600 MHz, $CDCl_3$) δ ppm: 7.63 (s, 1H, H triazole), 7.57 (s, 1H, H triazole), 5.02 (s, 1H, H-1), 4.75 (d, *J* = 12.6 Hz, 1H, −O−C**H**$_2$−triazole), 4.70 (d, *J* = 12.3 Hz, 1H, −O−C**H**$_2$−triazole), 4.65 (d, *J* = 12.5 Hz, 1H, −O−C**H**$_2$−triazole), 4.64 (d, *J* = 12.6 Hz, 1H, −O−C**H**$_2$−triazole), 4.50 (d, *J* = 3.0 Hz, 1H, H-3), 4.39 (ddd, *J* = 8.1, 6.2, 4.2 Hz, 1H, H-5), 4.32 (broad q, *J* = 7.2 Hz, 4H, −C**H**$_2$−triazole), 4.10 (dd, *J* = 8.7, 6.4 Hz, 1H, H-6a), 3.98 (dd, *J* = 8.8, 4.3 Hz, 1H, H-6b), 3.89 (dd, *J* = 8.3, 3.1 Hz, 1H, H-4), 3.79 (d, *J* = 10.6 Hz, 1H, –C**H**$_2$O), 3.76 (d, *J* = 10.6 Hz, 1H, –C**H**$_2$O), 1.91–1.87 (m, 4H, –C**H**$_2$–alkyl), 1.44 (s, 3H, −C(C**H**$_3$)$_2$), 1.43 (s, 3H, −C(C**H**$_3$)$_2$), 1.40 (s, 3H, −C(C**H**$_3$)$_2$), 1.36 (s, 3H, −C(C**H**$_3$)$_2$), 1.31–1.24 (m, 28H, –C**H**$_2$–alkyl), 0.86 (t, *J* = 6.8 Hz, 6H, C**H**$_3$–alkyl). **^{13}C NMR** (150 MHz, $CDCl_3$) δ ppm: 145.0 (**C** triazole), 144.3 (**C** triazole), 122.8 (**C** triazole), 122.7 (**C** triazole), 114.4 (−**C**$(CH_3)_2$), 109.4 (−**C**$(CH_3)_2$), 106.7 (C-1), 94.5 (C-2), 82.7 (C-3), 80.6 (C-4), 73.0 (C-5), 69.8 (–**C**H_2O), 67.1 (C-6), 65.5 (−O−**C**H_2−triazole), 61.1 (−O−**C**H_2−triazole), 50.5 (**C** alkyl), 50.46 (**C** alkyl), 31.9 (**C** alkyl), 30.4 (**C** alkyl), 29.6 (**C** alkyl), 29.52 (**C** alkyl), 29.5 (**C** alkyl), 29.4 (**C** alkyl), 29.1 (**C** alkyl), 27.8, 27.7, 27.1, 26.7 (4 × (−C(**C**$H_3)_2$)), 26.6 (**C** alkyl), 25.3 (**C** alkyl), 22.8 (**C** alkyl), 14.2 (**C** alkyl). HRMS-ESI $[M + Na]^+$ calculated for $C_{39}H_{68}N_6O_7Na$: 755.5041; found: 755.5041.

2-*C*-(Oxymethyl)-2,3:5,6-di-*O*-isopropylidene-D-mannofuranose bis-*O*-[(1-dodecyl-1H-1,2,3-triazol-4-yl)methyl)]ether (9b)

White solid (0.68 g, 87%); mp 61–64°C, Rf = 0.56 (EtOAc), IR (KBr): 3136, 2926, 2854, 1462, 1375, 1217, 1136,1070, 848, 785, 723, 669, 511 cm^{-1} . **^{1}H NMR** (600 MHz, $CDCl_3$) δ ppm: 7.63 (s, 1H, H triazole), 7.57 (s, 1H, H triazole), 5.03 (s, 1H, H-1), 4.75 (d, *J* = 12.7 Hz, 1H, −O−C**H**$_2$−triazole), 4.70 (d, *J* = 12.2 Hz, 1H, −O−C**H**$_2$−triazole), 4.66 (d, *J* = 12.3 Hz, 1H, −O−C**H**$_2$−triazole), 4.65 (d, *J* = 12.7 Hz, 1H, −O−C**H**$_2$−triazole), 4.51 (d, *J* = 3.1 Hz, 1H, H-3), 4.39 (ddd, *J* = 8.1, 6.2, 4.2 Hz, 1H, H-5), 4.34–4.30 (m, 4H, −C**H**$_2$−triazole), 4.10 (dd, *J* = 8.7, 6.4 Hz, 1H, H-6a), 3.98 (dd, *J* = 8.8, 4.3 Hz, 1H, H-6b), 3.89 (dd, *J* = 8.3, 3.1 Hz, 1H, H-4), 3.79 (d, *J* = 10.6 Hz, 1H, –C**H**$_2$O), 3.76 (d, *J* = 10.6 Hz, 1H, –C**H**$_2$O), 1.92–1.85 (m, 4H, –C**H**$_2$–alkyl), 1.44 (s, 3H, −C(C**H**$_3$)$_2$), 1.43 (s, 3H, −C(C**H**$_3$)$_2$), 1.40 (s, 3H, −C(C**H**$_3$)$_2$), 1.36 (s, 3H, −C(C**H**$_3$)$_2$), 1.31–1.23 (m, 40H, –C**H**$_2$–alkyl), 0.86 (t, *J* = 6.9 Hz, 6H, C**H**$_3$–alkyl). **^{13}C NMR** (150 MHz, $CDCl_3$) δ ppm: 145.0 (**C** triazole), 144.3 (**C** triazole), 122.8 (**C** triazole), 122.7 (**C** triazole), 114.4 (−**C**$(CH_3)_2$), 109.4 (−**C**$(CH_3)_2$), 106.7 (C-1), 94.5 (C-2), 82.7 (C-3), 80.6 (C-4), 73.0 (C-5), 69.8 (–**C**H_2O), 67.1 (C-6), 65.5 (−O−**C**H_2−triazole), 61.1 (−O−**C**H_2−triazole), 50.5 (**C** alkyl), 50.45 (**C** alkyl), 32.0 (**C** alkyl), 30.4 (**C** alkyl), 29.7 (**C** alkyl), 29.65 (**C** alkyl), 29.5 (**C** alkyl), 29.4 (**C** alkyl), 29.1 (**C** alkyl), 27.8, 27.7, 27.1, 26.7 (4 × (−C(**C**$H_3)_2$)), 26.6 (**C** alkyl), 25.3 (**C** alkyl), 22.8 (**C** alkyl), 14.2 (**C** alkyl). HRMS-ESI $[M + Na]^+$ calculated for $C_{43}H_{76}N_6O_7Na$: 811.5667; found: 811.5661.

2-*C*-(Oxymethyl)-2,3:5,6-di-*O*-isopropylidene-D-mannofuranose bis-*O*-[(1-(*p*-nitro phenyl) -1H-1,2,3-triazol-4-yl)methyl)]ether (9c).

Yellow solid (0.43 g, 87%); mp 97–100°C, Rf = 0.65 (EtOAc), IR (KBr): 3138, 3093, 2987, 2931, 2874, 1600, 1527, 1458, 1375, 1344, 1234, 1111, 1022, 887, 845, 750, 686, 509 cm-1.**^{1}H NMR** (600 MHz, $CDCl_3$) δ ppm: 8.40 (d, *J* = 8.9 Hz, 2H, Ar−H), 8.39 (d, *J* = 8.9 Hz, 2H, Ar−H), 8.38 (s, 1H, H triazole), 8.30 (s, 1H, H triazole), 5.10 (s, 1H, H-1), 4.87 (d, *J* = 13.2 Hz, 1H, −O−C**H**$_2$−triazole), 4.85 (d, *J* = 12.7 Hz, 1H, −O−C**H**$_2$−triazole), 4.78 (d, *J* = 13.0 Hz, 1H, −O−C**H**$_2$−triazole), 4.75 (d, *J*

= 12.3 Hz, 1H, −O−C**H**$_2$−triazole), 4.51 (d, *J* = 3.1 Hz, 1H, H-3), 4.43 (ddd, *J* = 8.1, 6.1, 4.2 Hz, 1H, H-5), 4.13 (dd, *J* = 8.7, 6.3 Hz, 1H, H-6a), 4.03 (dd, *J* = 8.7, 4.3 Hz, 1H, H-6b), 3.96 (dd, *J* = 7.9, 3.0 Hz, 1H, H-4), 3.94 (d, *J* = 10.5 Hz, 1H, –C**H**$_2$O), 3.86 (d, *J* = 10.5 Hz, 1H, –C**H**$_2$O), 1.48 (s, 3H, −C(C**H**$_3$)$_2$), 1.44 (s, 3H, −C(C**H**$_3$)$_2$), 1.42 (s, 3H, −C(C**H**$_3$)$_2$), 1.37 (s, 3H, −C(C**H**$_3$)$_2$). **^{13}C NMR** (150 MHz, $CDCl_3$) *δ* ppm: 147.4 (Ar**C**), 147.3 (Ar**C**), 146.5 (**C** triazole), 146.0 (**C** triazole), 141.2 (Ar**C**), 141.16 (Ar**C**), 125.7 (Ar**C**), 125.7 (Ar**C**), 121.5 (**C** triazole), 121.4 (**C** triazole), 120.7 (Ar**C**), 120.6 (Ar**C**), 114.6 (−**C**(CH$_3$)$_2$), 109.5 (−**C**(CH$_3$)$_2$), 106.6 (C-1), 94.4 (C-2), 82.7 (C-3), 80.7 (C-4), 73.0 (C-5), 70.6 (–**C**H$_2$O), 67.0 (C-6), 65.1 (−O−**C**H$_2$−triazole), 60.6 (−O−**C**H$_2$−triazole), 27.9, 27.6, 27.1, 25.3 (4 × (−C(**C**H$_3$)$_2$)). HRMS-ESI [M + Na]$^+$ calculated for $C_{31}H_{34}N_8O_{11}Na$: 717.2239; found: 717.2239.

2-*C*-(Oxymethyl)-2,3:5,6-di-*O*-isopropylidene-D-mannofuranose bis-*O*-[(1-(2,4-dichloro phenyl)-1*H*-1,2,3-triazol-4-yl)methyl)]ether (9d).

White solid (0.43 g, 87%); mp 71–75°C, Rf = 0.56 (EtOAc), IR (KBr): 3142, 3091, 2987, 2935, 2877, 1564, 1498, 1456, 1375, 1242, 1107, 1031, 817, 648, 509, 401 cm-1. **^{1}H NMR** (600 MHz, $CDCl_3$) *δ* ppm: 8.05 (s, 1H, H triazole), 7.99 (s, 1H, H triazole), 7.56 (d, *J* = 8.5 Hz, 1H, Ar−H), 7.55 (t, *J* = 1.8 Hz, 2H, Ar−H), 7.51 (d, *J* = 8.6 Hz, 1H, Ar−H), 7.40 (dd, *J* = 8.6, 2.2 Hz, 2H, Ar−H), 5.10 (s, 1H, H-1), 4.86 (d, *J* = 12.8 Hz, 1H, −O−C**H**$_2$−triazole), 4.80 (d, *J* = 12.5 Hz, 1H, −O−C**H**$_2$−triazole), 4.76 (d, *J* = 12.3 Hz, 1H, −O−C**H**$_2$−triazole), 4.75 (d, *J* = 12.7 Hz, 1H, −O−C**H**$_2$−triazole), 4.55 (d, *J* = 3.1 Hz, 1H, H-3), 4.40 (ddd, *J* = 8.2, 6.2, 4.1 Hz, 1H, H-5), 4.10 (dd, *J* = 8.8, 6.4 Hz, 1H, H-6a), 3.99 (dd, *J* = 8.8, 4.2 Hz, 1H, H-6b), 3.93 (dd, *J* = 8.0, 3.0 Hz, 1H, H-4), 3.88 (d, *J* = 10.7 Hz, 1H, –C**H**$_2$O), 3.84 (d, *J* = 10.7 Hz, 1H, –C**H**$_2$O), 1.45 (s, 3H, −C(C**H**$_3$)$_2$), 1.42 (s, 3H, −C(C**H**$_3$)$_2$), 1.40 (s, 3H, −C(C**H**$_3$)$_2$), 1.35 (s, 3H, −C(C**H**$_3$)$_2$). **^{13}C NMR** (150 MHz, $CDCl_3$) *δ* ppm: 145.1 (**C** triazole), 144.5 (**C** triazole), 136.3 (Ar**C**), 133.6 (Ar**C**), 130.7 (Ar**C**), 130.6 (Ar**C**), 129.5 (Ar**C**), 129.4 (Ar**C**), 128.7 (Ar**C**), 128.5 (Ar**C**), 128.4 (Ar**C**), 128.35 (Ar**C**), 124.9 (**C** triazole), 124.8 (**C** triazole), 114.5 (−**C**(CH$_3$)$_2$), 109.4 (−**C**(CH$_3$)$_2$), 107.1 (C-1), 94.5 (C-2), 82.6 (C-3), 80.8 (C-4), 73.0 (C-5), 69.9 (–**C**H$_2$O), 67.1 (C-6), 65.3 (−O−**C**H$_2$−triazole), 60.9 (−O−**C**H$_2$−triazole), 27.8, 27.7, 27.0, 25.3 (4 × (−C(**C**H$_3$)$_2$)). HRMS-ESI [M + Na]$^+$ calculated for $C_{31}H_{32}Cl_4N_6O_7Na$: 765.0954; found: 765.0956.

Biological Activities:

Anticancer Activity

Maintenance of Cell Cultures

AMJ13 Cells were maintained in RPMI-1640 supplemented with 10% fetal bovine serum, 100 units/mL penicillin and 100µg/mL streptomycin. Cells were passaged using Trypsin-EDTA reseeded at 80% confluence twice a week, and incubated at 37 °C.[44]

Cytotoxicity Assays

To determine the cytotoxic effect of compounds **9a** and **9b**, the MTT assay was done using 96-well plates.[45] Cell line was seeded at 1 × 96 cells/well. After 24 hours or a confluent monolayer was achieved, cells were treated with compounds **9a** and **9b** different concentrations (6.25 µg/mL–400 µg/mL). Cell viability was measured after 24, 48, and 72 hours of treatment by removing the medium, adding 28 µL of 2 mg/mL solution of MTT and incubating the cells for 2.5 hours at 37 °C. After removing the MTT solution, the crystals remaining in the wells were solubilized by the addition of 130 µL of DMSO (Dimethyl Sulphoxide) followed by 37 °C incubation for 15 minutes with shaking .[46] The absorbency was determined on a micro plate reader at 492 nm; the assay was performed in triplicate. The inhibition rate of cell growth (the percentage of cytotoxicity) was calculated as the following equation: [47]

$$\text{The rate of Inhibition} = \frac{A-B}{A} \times 100$$

Where **A** is the optical density of control, and **B** is the optical density of the samples.[48]

To visualize the shape of the cells under an inverted microscope, the cells were seeded into 24-well micro-titration plates at a density of 1×105 cells mL^{-1} and incubated for 24 hours at 37 °C. Then, cells were exposed to **9a** and **9b** for 24 hours. After the exposure time, the plates were stained with crystal violet stain and incubated at 37 °C for 10–15 minutes. The stain was washed off gently with tap water until the dye was completely removed. The cells were observed under an inverted microscope at 100× magnification and the images were captured with a digital camera attached to the microscope.[49]

Statistical Analysis:

The obtained data were statically analyzed using an unpaired t-test with GraphPad Prism 6.[50] The values were presented as the mean ± SD of triplicate measurements.[51]

Antibacterial Activity

For assessing the antibacterial activity of the prepared compounds **9a–d,** bacterial suspension

was prepared by transferring 2-3 colonies with the same phenotypic characteristics growing on the Nutrient Agar medium to tubes containing the crystalline saline solution. The tubes were compared with a 0.5 McFarland standard, which gives an approximate number of cells to 1.5×10^8 colony /mL. The inhibitory efficacy of the prepared compounds with concentrations (50,100, 200, 400) µg/mL were tested against Gram positive bacteria *S. aureus* and Gram negative bacteria *E. coli* according to the agar gel diffusion method.[52] 0.1 mL of the bacterial suspension was added and spread to the Muller Hinton agar plates by cotton swab and leave the plates for drying at 37 ºC for 30 minutes followed by punching wells of 6 mm with the help of a sterile crock borer in appropriate diameter(6) mm under aseptic condition . DMSO and control DMSO 60 µL of each concentration were placed in the labeled wells respectively then incubated in the incubator at 37 ° C for 24 hours and the inhibition zone of bacteria (mm) was measured. The antibiogram sensitivity of these bacteria were tested using Levofloxacin, Amoxicillin clavulanic acid, Amikacin and Ciprofloxacin.

Result and Discussion:

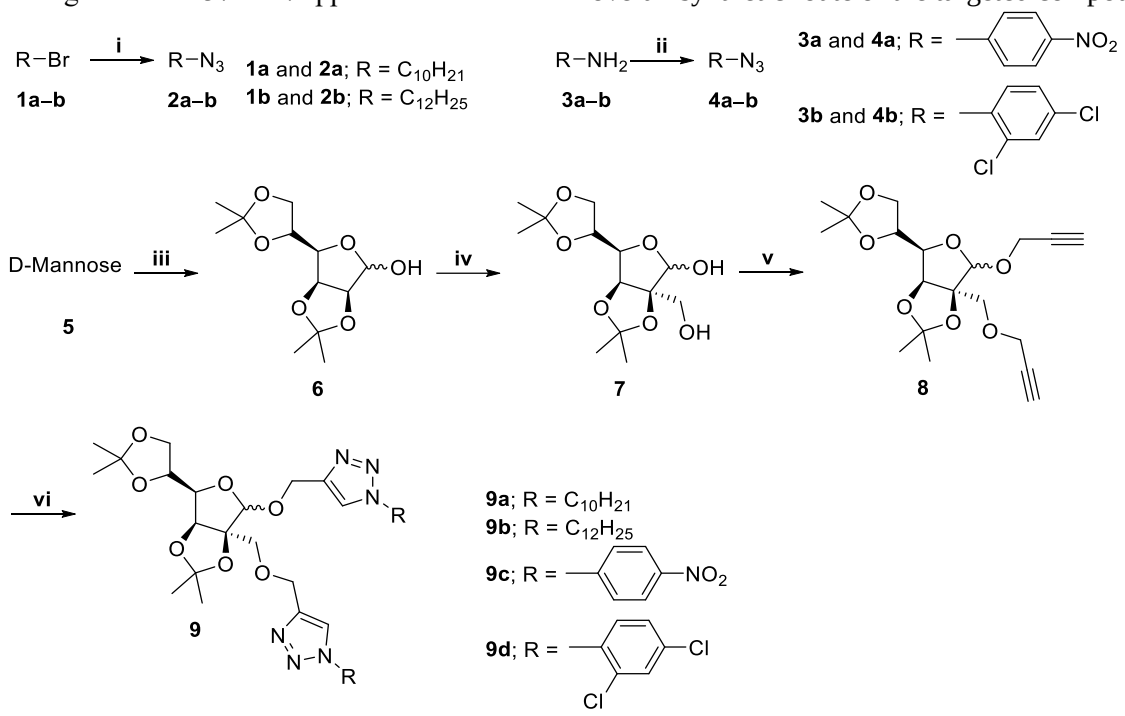
Synthesis and Characterization:

The general route of the synthesis is shown in Scheme (1). In the first step, D-mannose (**5**) was treated with dry acetone in the presence of concentrated sulfuric acid at room temperature for 4 hours to yield a mixture of α and β-isomers of 2,3:5,6-di-O-isopropylidene-D-mannofuranose (**6**) in a good yield 75%.70 .The significant stretching bands of FT-IR spectrum showed at ν 3437 cm^{-1} (O−H), 2985 cm^{-1} and 2906 cm^{-1} for aliphatic (C−H). ^{1}H NMR spectrum verified signals of *α* and **β** anomer and the ration of α anomer is the predominant. Four singlets appeared at 1.46 ppm, 1.45 ppm, 1.37 ppm and 1.32 ppm is a good proof of two isopropylidene group formation. ^{13}C NMR also afforded another evidence of the formation of compound **2** by the appearance of six signals at 112.8 ppm, 109.2 ppm, 27.0 ppm, 26.0 ppm, 25.3 ppm and 24.6 ppm corresponding to two isopropylidene protecting groups. Also, a base peak at *m*/*z* 283.1152 assigned to the suggested formula. Secondly, 2*C*-(hydroxyl methyl)-2,3:5,6-di-O-isopropylidene-D-manofuranose (**7**) was synthesized *via* aldol condensation of compound **6** with aq. formaldehyde in the presence of K_2CO_3 and excess of KOH to gain in approximately high yield 80 %. This protocol was developed by Tan et al., 2016 [71] who reported a new extension of work to gain the brunched sugar with quaternary center generating transformation and solved the mysterious retardation attributed to previous work introduced by Ho 1979[89], the formation of formic acid by a Cannizzaro reaction led to lower the basicity of this reaction. The excess amount of KOH was successfully accelerated the condensation and shorted the reaction time from 48 hours to 100 min in addition to consume the starting materials completely as well as the isolation / purification became easier. FT–IR spectrum of compound 7 afforded good evidence as two hydroxyl groups appeared at *ν* 3450 cm^{-1} and 3311 cm^{-1}. Two epimers A and B were detected in the 1H NMR spectrum in 2:1 ratio. The most important evidence of the formation of compound **6** is the appearance of four at δ 3.98 ppm, 3.85 ppm, 3.79 ppm and 3.76 ppm corresponding to (CH2OH) of two epimers A and B in addition to the disappearance of H-2 signal at 4.61 ppm. The formation of diol **7** is also approved by ^{13}C NMR when a signal appeared at 63.8 ppm and 62.9 ppm attributed to the extra branched carbon of two epimers. Subsequently, Williamson etherification of the sugar diols were carried to gain dipropargyl ether **8** by using propargyl bromide and NaOH as heterogeneous catalysts in DMF under S_N2 conditions to give compound **4** in a moderate yield 60%.[43] The formation of compound 4 was investigated by FT-IR as hydroxyl bands disappeared and both acetylenic proton and triple bond bands were assigned at 3286 cm^{-1} and 2117 cm^{-1} respectively. The attachment of the propargyl moieties to the sugar derivative was assigned by the appearance of two new doublet of doublet at 4.28 ppm and 4.21 ppm attributed to two protons of the methylene of the anomeric propargyl. However, the methylene group of the propargyl attached the position 2′ appeared as a doublet with J = 2.4 Hz. Furthermore, a multiplet centered at 2.41 ppm corresponding to two terminal alkyne protons was also observed in ^{1}H NMR spectrum (Fig. 1). The two propargyls were also assigned by the appearance of six new signals at 79.7 ppm, 79.1 ppm, 74.7 ppm, 74.6 ppm, 59.1 ppm, 54.8 ppm in ^{13}C NMR spectrum (Fig. 2). It is important to mention that only one anomer formed after the propargylation of the diol **7** as viewed by the NMR spectra of compound **8** (Figs. 1−4). The formation of compound **8** is confirmed by the appearance of a base peak at *m*/*z* 389.1570 corresponding to the formula $[M + Na]^+$ in HRMS.

In a parallel step, alkyl halides a and b were converted to the corresponding alkyl azides **2a** and **2b** under S_N2 nucleophilic substitution reaction while the aryl azides **4a** and **4b** were prepared through direct conversion of the corresponding aryl amines c and d to diazonium salt via one-put

diazotization with $NaNO_2$ and *p*-TsOH in aqueous solution that followed with sodium azide.

The high to excellent yields of the azides **2a** and **2b, 4a** and 4**b** about 90% was gained. The significant and strong azide bands of FT-IR spectrum showed around *v* 2100 cm^{-1} (N≡N) for alkyl and aryl azides, and the disappeared of both NH2 bands in aromatic amines. Proton NMR spectra of compounds **2a** and **2b** showed the multiplet signals at 1.37–1.27 ppm attributed to H10′ and H12′-H3′, in addition to signals at 3.3 ppm for H1′ and 1.6 ppm for H2′. ^{13}Carbon NMR spectra showed 12 and 10 signals for the corresponding compounds **2b** and **2a**. The compounds **4a** and **4b** showed a clear signal between 7 to 8 ppm which attributed to the H-aromatic of aryl azides. In addition, the six signals in ^{13}C NMR spectra for six C-aromatic provided excellent evidence for azides formation. The following scheme describes the overall synthetic route of the targeted compounds:



Reagents and conditions: i] NaN_3, DMF, 70 °C, 4h; ii] $NaNO_2$, *p*-TsOH•H_2O, NaN_3, r.t., 30 min.; iii] dry acetone, H_2SO_4, r.t., 4 h; iv] 37%aq. HCHO, MeOH, K_2CO_3, KOH, reflex, 2h; v] propargyl bromide, NaOH, 0 °C–r.t., 24 h; vi] **2a–b** or **4a–b,** $CuSO_4$•$5H_2O$, Na ascorbate, DMSO, 60 °C, 48 h.

Scheme 1. Synthesis of Mannose-based bis-1,2,3-triazoles

Finally, regioselective ligation between the sugar alkyne **8** as precursor of and the collection of azides 6a-d have been carried out via Cu-catalyzed Azide Alkyne- 1,3-dipolarcycloaddition Click reaction to afford the targeted bis-1,2,3-triazoles **9a**–**d** using Cu(I) as catalysts that was produced *in situ* by treating the $CuSO_4.5H_2O$ with the reducing agent Na ascorbate, Compounds **9a**–**d** were isolated in very good yields 80–87%. The constructions of these compounds were also confirmed by NMR spectroscopy furthermore to other techniques. Owing to facilitate the detection of NMR spectra, numbering of compounds 9b and c is shown below: Beside the sugar and aromatic azide signals, there was an important singlet at 7.63, 7.57ppm and 8.38, 8.30, 8.05 7.99 ppm which clearly referred to the 2H of triazoles for each compounds **9a,b**, and **9c,d** consequently. In the same way, ^{13}C NMR spectra supported the structures of bistriazoles. The signals at 144.3 and 122.7 ppm, for example, were attributed to the 2C of (CH=CN- triazole) of triazole heterocycle **9a**, respectively. All assignments of proton and carbon NMR were based on COSY and HSQC. The formation of compounds **9a**–**d** is confirmed by the appearance of a base peak at m/z 755.5041, 811.5660, 717.2230, 765.0956 corresponding to the formula $[M + Na]^+$ in HRMS.

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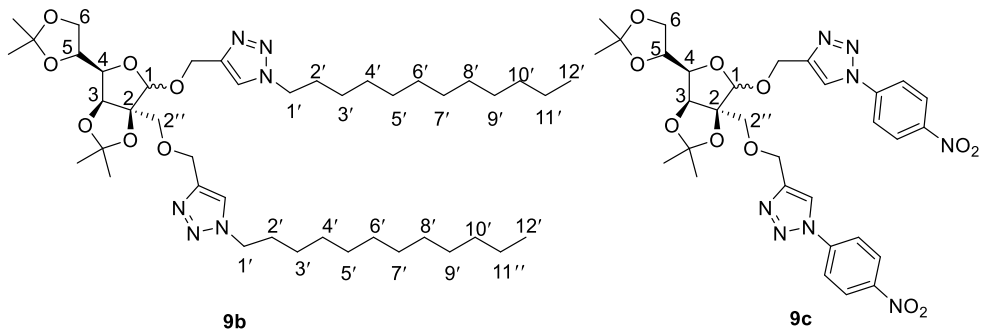


Figure 1. Numbering of compounds 9b and 9c

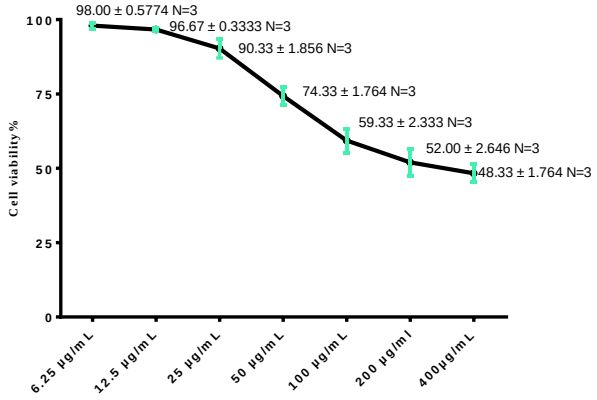
Biological Activities:

Anticancer Activity

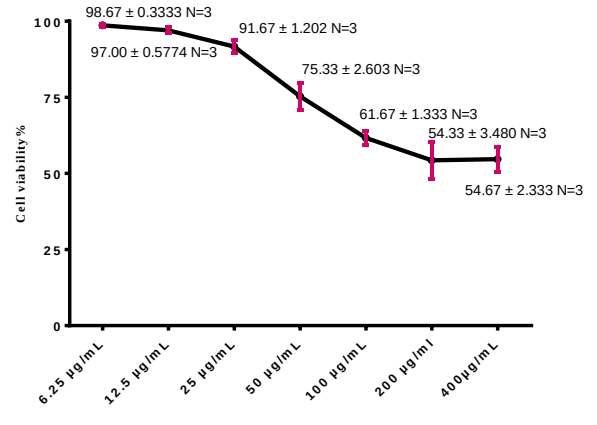
The cytotoxic effect of compounds **9a** and **9b** against AMJ13 cells was studied. The anti-proliferative activity of compounds **9a** and **9b** was tested by studying their ability to inhibit the proliferation of AMJ13 cell line. The results of this study showed there is cytotoxic activity of **9a** and **9b** compounds against the AMJ13 cell line and the results is concentration dependent manner as shown in Fig. 2 (a and b) as well as in Table 1.

Table 1. Cytotoxic activity of synthesized compounds 9a and 9b against AMJ13 cells

Concentration	Cell viability %	
µg / mL	Compound 9a	Compounds 9b
6.25	98.00	98.67
12.50	96.67	97.00
25.00	90.33	91.67
50.00	74.33	75.33
100.00	59.33	61.67
200.00	52.00	54.33
400.00	48.33	54.67
IC50	167.64 µg/mL	171.61 µg/mL

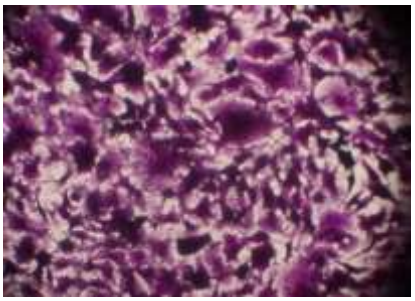


(a)

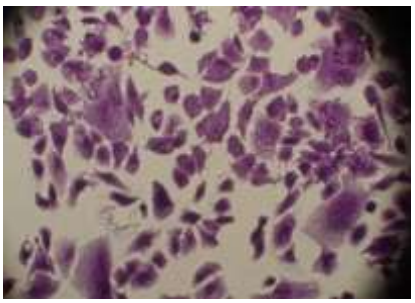


(b)

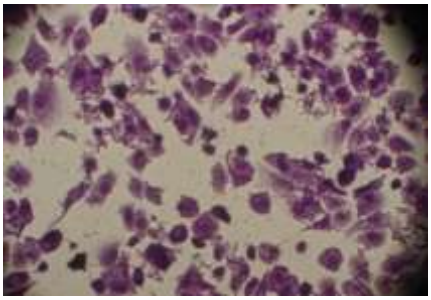
Figure 2. Cytotoxic effect against AMJ13 cells: (a) compound 9a (IC_{50}= 167.64 µg/mL); (b) compound 9b (IC_{50}= 171.61 µg/mL)



a



b



c

Figure 3. Morphology of AMJ13 cells (a) Control untreated; (b) treated with compound 9a; (c) treated with compound 9b

Antibacterial Activity:

The antibacterial activity of the prepared bistriazoles **9a–d** was verified against pathogenic Gram-positive bacteria *S. aureus* and Gram-negative bacteria *E. coli* via the agar well diffusion method. DMSO was used as control. As shown in Table 2, all compounds **9a–d** did not give any activity at against Gram positive bacteria *S. aureus*. In contrast, all the mentioned compounds exhibited moderate to good activity at the concentrations 50–400 µg /mL respectively. On the other hand, compound **9a** with C10 in the aliphatic chain and **9c** with substituted aryl exhibited maximum antibacterial activity compared to the other measured compounds. The antibacterial activity of bistriazoles **9a–d** can be recognized to their performance as glycoconjugate mimics[54] and biosurfactants analogs the asymmetrical structure of the whole molecule or the protein-binding properties. [55]

Table 2. Antibacterial activities of the synthesized compounds 9a–d

	Gram positive bacteria *S. aureus* Inhibition Zone in (mm)				**Gram negative bacteria *E. coli*** Inhibition Zone in (mm)			
	50 µg/mL	**100** µg/mL	**200** µg/mL	**400** µg/mL	**50** µg/mL	**100** µg/mL	**200** µg/mL	**400** µg/mL
DMSO	0	0	0	0	0	0	0	0
9a	0	0	0	0	17	16	14	15
9b	0	0	0	0	0	0	13	0
9c	0	0	0	0	14	13	13	13
9d	0	0	0	0	0	0	0	0
Ciprofloxacin	9				15			
Levofloxacin	23				25			
Amoxicillin	9				14			
Amikacin	18				14			

Conclusion:

Four bis-1,2,3-triazole derivatives **9a**–**9d** have been synthesized starting from the readily available monosaccharide (D-Mannose) using convenient reaction conditions particularly the azide-alkyne cycloaddition click reaction. The synthesized compounds were fully identified *via* modern spectroscopic techniques showing their high purity. These compounds were tested against pathogenic *G+* bacteria *S. aureus* and *G–* bacteria *E. coli*. All compounds demonstrated no activity against the mentioned types of bacteria. However, compound **9a** and **9c** demonstrated excellent inhibition zones ~16 mm and 13 mm respectively at concentrations of 50−400 µg/mL. On the other hand, triazole derivatives **9a** and **9b** were screened against breast cancer AMJ13 cells line and they exhibited remarkable activity IC_{50} of 167.64 µg/mL 171.61 µg/mL respectively.

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Authors' contributions statement:

L.S.M. contributed to implementation of the research project and writing the manuscript. A.I.M. and M.J.M. contributed to the suggestion of the project idea, interpretation of analytical data and proofreading of research.

Authors' declaration:

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are mine ours. Besides, the Figures and images, which are not mine ours, have been given the permission for re-publication attached with the manuscript.
- Ethical Clearance: The project was approved by the local ethical committee in University of Kufa.

References:

1. Rebecca L. Siegel MPH, Kimberly D. Miller MPH, Hannah E. Fuchs BS, Ahmedin Jemal DVM. Cancer Statistics, 2021. CA Cancer J Clin. 2021; 71:7–33. Available from: https://doi.org/10.3322/caac.21654.
2. Mandalapu D, Saini KS, Gupta S, Sharma V, Malik MY, Chaturvedi S, Bala V, Thakur S, Maikhuri JP, Wahajuddin M, Konwar R. Synthesis and biological evaluation of some novel triazole hybrids of curcumin mimics and their selective anticancer activity against breast and prostate cancer cell lines. Bioorg Med Chem Lett. 2016 ;26(17):4223-4232. Available from: https://www.sciencedirect.com/science/article/pii/S09

60894X16307818
3. Panda S, Pradhan N, Chatterjee S, Morla S, Saha A, Roy A, Kumar S, Bhattacharyya A, Manna D. 4, 5-Disubstituted 1, 2, 3-triazoles: effective inhibition of indoleamine 2, 3-dioxygenase 1 enzyme regulates T cell activity and mitigates tumor growth. Sci Rep. 2019; 9(1): 1-6. Available from: https://doi.org/10.1038/s41598-019-54963-9
4. Le TT, Le PT, Dam HT, Vo DD, Le TT. Anticancer Activity of New 1,2,3-Triazole-Amino Acid Conjugates. Molbank. 2021; 2021(2): M1204. Available from: https://doi.org/10.3390/M1204.
5. Carreiro EP, Sena AM, Puerta A, Padrón JM, Burke AJ. Synthesis of Novel 1,2,3-Triazole-Dihydropyrimidinone Hybrids Using Multicomponent 1,3-Dipolar Cycloaddition (Click)–Biginelli Reactions: Anticancer Activity. Synlett. 2020; 31(06): 615-621. Available from: https://doi.org/10.1055/s-0039-1690781.
6. Gomes AT, Fernandes R, Ribeiro CF, Tomé JP, Neves MG, Silva FD, Ferreira VF, Cavaleiro JA. Synthesis, characterization and photodynamic activity against bladder cancer cells of novel triazole-porphyrin derivatives. Molecules. 2020; 25(7): 1607. Available from: https://pubmed.ncbi.nlm.nih.gov/32244514.
7. Nerella S, Kankala S, Gavaji B. Synthesis of podophyllotoxin-glycosyl triazoles via click protocol mediated by silver (I)-N-heterocyclic carbenes and their anticancer evaluation as topoisomerase-II inhibitors. Nat Prod Res. 2021; 35(1): 9–16. Available from: https://doi.org/10.1080/14786419.2019.1610958.
8. Oubella A, Bimoussa A, N'ait Oussidi A, Fawzi M, Auhmani A, Morjani H, Riahi A, Esseffar MH, Parish C, Ait Itto MY. New 1, 2, 3-Triazoles from (*R*)-Carvone: Synthesis, DFT Mechanistic Study and In Vitro Cytotoxic Evaluation. Molecules. 2022; 27(3): 769. Available from: https://www.mdpi.com/1420-3049/27/3/769.
9. Zhou M, Kan M-Y. The varying impacts of COVID-19 and its related measures in the UK: A year in review. PLoS ONE. 2021; 16(9): e0257286. https://doi.org/10.1371/journal.pone.0257286.
10. Ali ZZ, Abdulla AM. Synthesis and Antimicrobial Schreening of New 4, 5, 6, 7-Tatra Hydro Benzo Thiophene Derivatives. Baghdad Sci J. 2019; 16(1): 68–77. Available from: http://dx.doi.org/10.21123/bsj.2019.16.1.0068.
11. AL-Joubory AK, Abdullah LW, Mohammed AJ. Synthesis, Characterization and Biological Activity Evaluation of Some Pyrazoles, Thiazoles and Oxazoles Derived from 2-Mercaptoaniline. Baghdad Sci J. 2021; 18(1 (Suppl.)):764–774. Available from: http://doi.org/10.21123/bsj.2021.18.1(Suppl.).0764.
12. Said MA, Khan DJ, Al-Blewi FF, Al-Kaff NS, Ali AA, Rezki N, et al. New 1, 2, 3-Triazole Scaffold Schiff Bases as Potential Anti-COVID-19: Design, Synthesis, DFT-Molecular Docking, and Cytotoxicity Aspects. Vaccines. 2021; 9(9): 1012. Available from: https://www.mdpi.com/2076-393X/9/9/1012.
13. Holanda VN, Lima EM, Silva WV, Maia RT, Medeiros RD, Ghosh A, Lima VL, Figueiredo RC. Identification of 1, 2, 3-triazole-phthalimide derivatives as potential drugs against COVID-19: a virtual screening, docking and molecular dynamic study. J Biomol Struct. 2021: 1-9. Available from: https://doi.org/10.1080/07391102.2020.1871073.
14. Higashitani F, Hyodo A, Ishida N, Inoue M, Mitsuhashi S. Inhibition of beta-lactamases by tazobactam and in-vitro antibacterial activity of tazobactam combined with piperacillin. J Antimicrob Chemother. 1990; 25(4): 567–574. Available from: https://doi.org/10.1093/jac/25.4.567.
15. Neu HC, Fu KP. Cefatrizine activity compared with that of other cephalosporins. Antimicrob Agents Chemother. 1979; 15(2): 209–212. Available from: https://doi.org/10.1128/AAC.15.2.209.
16. Soltis MJ, Yeh HJ, Cole KA, Whittaker N, Wersto RP, Kohn EC. Identification and characterization of human metabolites of CAI [5-amino-1-1(4'-chlorobenzoyl-3,5-dichlorobenzyl)-1,2,3-triazole- 4-carboxamide). Drug Metab Dispos. 1996; 24(7): 799–806. Available from: https://pubmed.ncbi.nlm.nih.gov/8818579/
17. Sheng C, Zhang W. New lead structures in antifungal drug discovery. Curr Med Chem. 2011; 18(5): 733–766. Available from: https://doi.org/10.2174/092986711794480113.
18. Perabo FG, Wirger A, Kamp S, Lindner H, Schmidt DH, Müller SC, Kohn EC. Carboxyamido-triazole (CAI), a signal transduction inhibitor induces growth inhibition and apoptosis in bladder cancer cells by modulation of Bcl-2. Anticancer Res. 2004; 24(5A): Available from: 2869-2878. https://pubmed.ncbi.nlm.nih.gov/15517890/
19. Yadav M, Lal K, Kumar A, Kumar A, Kumar D. Indole-chalcone linked 1,2,3-triazole hybrids: Facile synthesis, antimicrobial evaluation and docking studies as potential antimicrobial agents. J Mol Struct. 2022; 132867. Available from: https://www.sciencedirect.com/science/article/pii/S0022286022005397.
20. Marzi M, Farjam M, Kazeminejad Z, Shiroudi A, Kouhpayeh A, Zarenezhad E. A Recent Overview of 1,2,3-Triazole-Containing Hybrids as Novel Antifungal Agents: Focusing on Synthesis, Mechanism of Action, and Structure-Activity Relationship (SAR). Tiwari VK, editor. J Chem. 2022; 2022: 7884316. Available from: https://doi.org/10.1155/2022/7884316.
21. Kandula MK, Gundluru M, Nemallapudi BR, Gundala S, Kotha P, Zyryanov GV, Chadive S, Cirandur SR. Synthesis, antioxidant activity, and α-glucosidase enzyme inhibition of α-aminophosphonate derivatives bearing piperazine-1,2,3-triazole moiety. J Heterocycl Chem. 2021; 58(1): 172-181. Available from: https://doi.org/10.1002/jhet.4157.
22. Kuczynska K, Bończak B, Rárová L, Kvasnicová M, Strnad M, Pakulski Z, et al. Synthesis and cytotoxic activity of 1,2,3-triazoles derived from 2,3-seco-dihydrobetulin via a click chemistry approach. J Mol Struct. 2022;1250:131751. Available from:

https://www.sciencedirect.com/science/article/pii/S0022286021018767
23. Mohammed AI, Dawood AH, Ali KF, Al-mosawi M. Microwave assisted synthesis of new heterocyclic compounds: 1, 2, 3-Triazoles and Tetrazoles and study of their biological activity. Asian J Chem. 2012;24(12):5592–5596. Available from: https://asianjournalofchemistry.co.in/user/journal/viewarticle.aspx?ArticleID=24_12_47.
24. Mohammed AI, Jwad RS, Al-Radha NA. Copper (I) catalyzed synthesis and biological evaluation of tetrakis-1,2,3-triazoles based on D-iditol. Int J Chem Sc. 2013; 11(1): 1–11. Available from: https://www.tsijournals.com/articles/copper-i-catalyzed-synthesis-and-biologicalevaluation-of-tetrakis123triazoles-basedon-diditol.pdf.
25. Mohammed AI, Mansour NH, Mahdi LS. Synthesis and antibacterial activity of 1-N-(β-d-glucopyranosyl)-4-((1-substituted-1H-1,2,3-triazol-4-yl)ethoxymethyl)-1,2,3-triazoles. Arab J Chem . 2017; 10: S3508–S3514. Available from: https://www.sciencedirect.com/science/article/pii/S1878535214000513.
26. Grob NM, Schibli R, Béhé M, Valverde IE, Mindt TL. 1,5-Disubstituted 1,2,3-Triazoles as Amide Bond Isosteres Yield Novel Tumor-Targeting Minigastrin Analogs. ACS Med Chem Lett. 2021; 12(4): 585–592. Available from: https://doi.org/10.1021/acsmedchemlett.0c00636.
27. Mohamed HA, Abdel-Wahab BF, Fahmy HM. Thiazole Azodyes Containing Sulfonamide Moiety for UV Protection and Antimicrobial of Cotton Fabrics. Polycycl Aromat Compd. 2022; 42(1): 195–203. Available from: https://doi.org/10.1080/10406638.2020.1723655.
28. Raviprabha K, Bhat RS. Corrosion Inhibition Effect of Ethyl 1-(4-chlorophenyl)-5-methyl-1H-1,2,3-triazole-4-carboxylate on Aluminium Alloy in Hydrochloric Acid. Prot Met Phys Chem Surf. 2021; 57(1): 181–189. Available from: https://doi.org/10.1134/S2070205120060209.
29. Narea P, Hernández B, Cisterna J, Cárdenas A, Llanos J, Amo-Ochoa P, Zamora F, Priego JL, Cortijo M, Delgado GE, Brito I. Heterobimetallic three-dimensional 4d-4f coordination polymers based on 5-methyl-1-(pyridyn-4-ylmethyl)-1H-1,2,3-triazole-3, 4-dicarboxylate. J Solid State Chem. 2022; 310: 123027. Available from: https://www.sciencedirect.com/science/article/pii/S0022459622001517.
30. Jourdain A, Obadia M, Duchet-Rumeau J, Bernard J, Serghei A, Tournilhac F, et al. Comparison of poly(ethylene glycol)-based networks obtained by cationic ring opening polymerization of neutral and 1,2,3-triazolium diepoxy monomers. Polym Chem. 2020;11(11):1894-905.Available from: http://dx.doi.org/10.1039/C9PY01923E.
31. Xing Q, Zhou C, Jiang S, Chen S, Deng GJ. Acid-catalyzed three-component addition of carbonyl compounds with 1,2,3-triazoles and indoles. Org Biomol Chem. 2021; 19(36): 7838–7842. Available from: http://dx.doi.org/10.1039/D1OB01451J.
32. Xia M, Chen Y, Chen Z, Yu W, Cheng H, Feng C, et al. 1,2,3-Triazole lamellar liquid crystal and its non-covalent palladium complex dimer: structure, mesomorphism and self-assembly properties. Liq Cryst. 2022; 49(1): 72-84.Available from: https://doi.org/10.1080/02678292.2021.1944358.
33. Mohammed AI, Abboud ZH, Alghanimi AHO. Synthesis of D-mannitol substituted ether-linked bis-1,2,3-triazoles as models of gemini surfactants. Tetrahedron Lett. 2012; 53(38): 5081–5083. Available from: https://www.sciencedirect.com/science/article/pii/S004040391201180X.
34. Rani A, Saini P, Singh G, Singh H, Kaur G, Singh J. 'Quick CuAAC'Chemistry for Hg (II) and Mn (II) ion sensing via 9H-carbazole derivatives. Inorg Chim Acta. 2021; 527: 120560.Available from: https://www.sciencedirect.com/science/article/pii/S0020169321003169.
35. Rostovtsev V V, Green LG, Fokin V V, Sharpless KB. A Stepwise Huisgen Cycloaddition Process: Copper(I)-Catalyzed Regioselective "Ligation" of Azides and Terminal Alkynes. Angew Chemie Int Ed. 2002; 41(14): 2596–2599. Available from: https://doi.org/10.1002/1521-3773(20020715)41:14%3C2596::AID-ANIE2596%3E3.0.CO.
36. Tornøe CW, Christensen C, Meldal M. Peptidotriazoles on solid phase:[1,2,3]-triazoles by regiospecific copper (I)-catalyzed 1, 3-dipolar cycloadditions of terminal alkynes to azides. J Org Chem. 2002; 67(9): 3057–3064. Available from: https://doi.org/10.1021/jo011148j,
37. Jwad RS. Synthesis and variable temperature NMR study of glucose based 1,2,3-triazole. AIP Conf Proc. 2020;2290(1):30012. Available from: https://aip.scitation.org/doi/abs/10.1063/5.0027407
38. Mahdi LS, Mohammed AI, Mohammed MJ. Convenient synthesis of dipropargyl ether derivative of D-mannose. AIP Conf Proc. 2020; 2290(1): 30024. Available from: https://aip.scitation.org/doi/abs/10.1063/5.0027403.
39. Copeland C, Mcadam DP, Stick R V. The reaction of N-dichloromethylene-N,N-dialkylammonium chlorides with free sugars: an efficient synthesis of glycosyl chlorides. Aust J Chem. 1983; 36(6): 1239–1247. Available from: https://doi.org/10.1071/CH9831239.
40. Tan DX, You J, Xu MR, Wu Y. Greatly Accelerated Condensation of D-Mannose Diacetonide with Aqueous Formaldehyde (Formalin). J Org Chem. 2016; 81(15): 6792-67924. Available from: https://doi.org/10.1021/acs.joc.6b01000.
41. Jwad RS. Synthesis of 1-Nonyl-4-[(6-Deoxy-1,2:3,4-Di-*O*-Isopropylidene-α-D-Galactos-6-yl) oxymethyl] 1H-1,2,3-Triazole *Via* Click Chemistry. ANJS. 2011; 14(1): 1–10. Available from: https://doi.org/10.22401/JNUS.14.1.08.
42. Kutonova KV, Trusova ME, Postnikov PS, Filimonov VD, Parello J. A simple and effective synthesis of aryl azides via arenediazonium tosylates. Synthesis.

2013; 45(19): 2706–2710. Available from: https://doi.org/10.1055/s-0033-1339648.
43. Reddy LV, Reddy PV, Mishra NN, Shukla PK, Yadav G, Srivastava R, et al. Synthesis and biological evaluation of glycal-derived novel tetrahydrofuran 1,2,3-triazoles by 'click 'chemistry. Carbohydr Res. 2010;345(11):1515-1521. Available from: https://doi.org/10.1016/j.carres.2010.03.031.
44. Al-Ziaydi AG, Al-Shammari AM, Hamzah MI, Jabir MS. Hexokinase inhibition using D-Mannoheptulose enhances oncolytic newcastle disease virus-mediated killing of breast cancer cells. Cancer Cell Int. 2020; 20(1): 1-10. Available from: https://doi.org/10.1186/s12935-020-01514-2.
45. Al-Salman HNK, Ali ET, Jabir M, Sulaiman GM, Al-Jadaan SAS. 2-Benzhydrylsulfinyl-N-hydroxyacetamide-Na extracted from fig as a novel cytotoxic and apoptosis inducer in SKOV-3 and AMJ-13 cell lines via P53 and caspase-8 pathway. Eur Food Res Technol. 2020; 246(8): 1591–1608. Available from: Available from: https://doi.org/10.1007/s00217-020-03515-x.
46. Kareem SH, Naji AM, Taqi ZJ, Jabir MS. Polyvinylpyrrolidone loaded-MnZnFe2O4 magnetic nanocomposites induce apoptosis in cancer cells through mitochondrial damage and P53 pathway. J Inorg Organomet Polym Mater. 2020; 30(12): 5009–5023. Available from: https://doi.org/10.1007/s10904-020-01651-1.
47. Jabir MS, Hussien AA, Sulaiman GM, Yaseen NY, Dewir YH, Alwahibi MS, Soliman DA, Rizwana H. Green synthesis of silver nanoparticles from Eriobotrya japonica extract: a promising approach against cancer cells proliferation, inflammation, allergic disorders and phagocytosis induction. Artif Cells Nanomed Biotechnol. 2021; 49(1): 48–60. Available from: https://doi.org/10.1080/21691401.2020.1867152.
48. Khashan KS, Abdulameer FA, Jabir MS, Hadi AA, Sulaiman GM. Anticancer activity and toxicity of carbon nanoparticles produced by pulsed laser ablation of graphite in water. Adv Nat Sci Nanosci Nanotechnol. 2020; 11(3): 35010. Available from: https://doi.org/10.1088/2043-6254/aba1de.
49. Sameen AM, Jabir MS, Al-Ani MQ. Therapeutic combination of gold nanoparticles and LPS as cytotoxic and apoptosis inducer in breast cancer cells. AIP Conf Proc. 2020: 020215-1-6. Available from: https://doi.org/10.1063/5.0000161.
50. Bahjat HH, Ismail RA, Sulaiman GM, Jabir MS. Magnetic field-assisted laser ablation of titanium dioxide nanoparticles in water for anti-bacterial applications. J Inorg Organomet Polym Mater. 2021; 31(9): 3649–3656. Available from: https://doi.org/10.1007/s10904-021-01973-8.
51. Jihad MA, Noori F, Jabir MS, Albukhaty S, AlMalki FA, Alyamani AA. Polyethylene Glycol Functionalized Graphene Oxide Nanoparticles Loaded with Nigella sativa Extract: A Smart Antibacterial Therapeutic Drug Delivery System. Molecules. 2021; 26(11): 3067. Available from: https://doi.org/10.3390/molecules26113067.
52. Egorov NS. Antibiotics: A Scientific Approach. Moscow. Mir Publishers.1985; Print.
53. Ho P-T. Branched-chain sugars. Reaction of furanoses with formaldehyde: A simple synthesis of D-and L-apiose. Can J Chem. 1979; 57(4): 381–383. Available from: https://doi.org/10.1139/v79-063.
54. Reddy LV, Reddy PV, Mishra NN, Shukla PK, Yadav G, Srivastava R, Shaw AK. Synthesis and biological evaluation of glycal-derived novel tetrahydrofuran 1,2,3-triazoles by 'click'chemistry. Carbohydr Res. 2010; 345(11): 1515–1521. Available from: https://doi.org/10.1016/j.carres.2010.03.031.
55. Doiron JE, Le CA, Ody BK, Brace JB, Post SJ, Thacker NL, Hill HM, Breton GW, Mulder MJ, Chang S, Bridges TM. Evaluation of 1,2,3-Triazoles as Amide Bioisosteres In Cystic Fibrosis Transmembrane Conductance Regulator Modulators VX-770 and VX-809. Eur J Chem. 2019; 25(14): 3662–3674. Available from: https://doi.org/10.1002/chem.201805919.

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التحضير و الفعالية المضادة للسرطان و البكتريا لمشتقات ثنائي 3،2،1-تريازول مانوز

لمياء صالح مهدي*[1,2] **عدنان إبراهيم محمد[3]** **ماجد جاري محمد[1]**

[1]قسم الكيمياء، كلية العلوم، جامعة الكوفة، الكوفة، العراق
[2]قسم العقاقير والنباتات الطبية، كلية الصيدلة، جامعة كربلاء، كربلاء، العراق
[3]قسم الكيمياء، كلية العلوم، جامعة كربلاء، كربلاء، العراق

الخلاصة:

في العمل الحالي ، تم تحويل هاليدات الألكيل 1a–b و الأمينات الأروماتية 3a–b إلى الأزيدات المقابلة مرة عن مع أزيد الصوديوم في مذيب قطبي لا بروتوني لتعطي مشتقات الأزايد الأليفاتية 2a–b و أخرى عن طريق التفاعل مع نتريت الصوديوم ومن ثم أزيد الصوديوم لتنتج الأزايدات الأروماتية 4a–b. و في خطوة مقابلة حُضِر مشتق ثنائي بروبارجيل إيثر لسكر المانوز 8 بدءً من مشتق مانوز ثنائي الأسيتون (7) الذي تم الحصول عليه عن طريق معاملة سكر المانوز (5) مع الأسيتون الجاف بوجود حمض الكبريتيك. بعد ذلك ، تم إستخدام تفاعل تكاثف الألدول لتحضير مشتق ثنائي الكحول 6 بدءً من ثنائي أسيتونيد مانوز 5. و من ثم فوعل المركب 3 مع بروميد بروبارجيل في وسط قلوي لينتج مشتق ثنائي بروبارجيل 8. تضمنت الخطوة الأخيرة مفاعلة كل من مشتق ثنائي بروبارجيل 8 مع الأزيدات الأليفاتية 2a–b أو الأروماتية 4a–b للحصول على مشتقات ثنائي- 3،2،1-تريازول 9a–b وبوجود أملاح النحاس الأحادية كعامل مساعد. تم تشخيص جميع المركبات المحضرة النهائية و عدد من المركبات الأولية بتقنيات الرنين المغناطيسي النووي أحادي و ثنائي الأبعاد و كذلك بإستخدام طيف الكتلة عالي الدقة. تم تقييم فعالية المركبات المضادة للبكتيريا ضد كل من البكتيريا موجبة الجرام وسالبة الجرام و علاوة على ذلك تم تقييم الفعالية المضادة للمركبات المحضرة ضد سرطان الثدي (خط خلايا AMJ13) .

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