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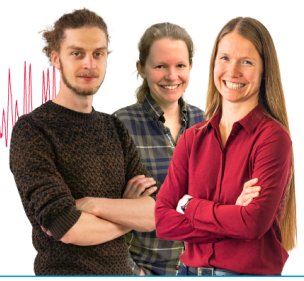

Synthesis and Study Biological Activity of New Heterocyclic Compounds Based on Sugar

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Abstract. Gluco-triazole derivatives were prepared CuCl catalyzed click reactions between 4,4'-diazido-3,3'-dimethyl-1,1'-biphenyl and Synthesis of 2-Propynyl (2,3,4,6-tetra-O-acetyl-α-D-gluco pyranoside). Whereas gluco-tetrazole compound prepared employing NH4Cl catalyzed cycloaddition reaction between acetylated glucosyl azide and 3,3'-dimethyl-[1,1'-biphenyl]-4,4'-dicarbonitrile. Finally elimination of the protection groups via methanol with Potassium carbonate afforded end products. All prepared heterocyclic derivatives were evaluated toward inhibition of bacterial growth (Escherichia coli, Staphylococcus aureus). Slight growth inhibition compared to standard drug is Azithromycin was showed at a highest concentration of 25 μg/mL, while no growth inhibition was showed at the lowest concentration (10 μg/mL).

Keywords: Click reaction, Gluco-triazole, 1,2,3-Triazole, Tetrazole and Antibacterial activity.

INTRODUCTION

Carbohydrates are important organic compounds and they have unique in the complexity of their structures and configurations.[1] They are a particularly various class that are contain monosaccharide units in their structure as building blocks with a change of stereo chemical bonds, branching in addition to chain lengths between them. These carbohydrates be existent in different forms in the human body, for example as glycopeptides, polysaccharides, glycoaminoglycans, glycolipids, or other glycoconjugates.[2-5] Heterocyclic compounds conceder one of the biggest group of cyclic organic compounds.[6,7] Numerous heterocyclic derivatives are utilized since of their high activity in the treatment of various infectious diseases. [8-10] There are many organic compounds contain hetero atoms that have been prepared for the increase of significant pharmacological materials, for example tetrazole and 1,2,3-triazole.[11,12] In this study, a number derivatives contain tetrazole and 1,2,3-triazole ring based on glucopyranosyl were prepared. Conceptually, the search will lead to products with important properties for pharmaceutics due to an rise of water solubility. The end products were screened their activity against Escherichia Coli and Staphylococcus aureus bacteria with using Azithromycin as positive control.

EXPERIMENTAL

Starting materials, reagents and organic solvents were achieved from many companies are Merck, Thomas baker, Sigma Aldrich, Fluke chemicals and commercial. TLC plates were achieved on a silica gel (Merck) SG-40 and developed with organic solvents declared, spots of products were visualized with Iodine vapor. Infrared spectra were analyzed by utilize Fourier transformation infrared, Bruker ALPHA, Faculty of Science, University of Kufa. NMR spectrum were analyzed on Bruker 300 MHz, 1HNMR and 75MHz, 13CNMR, Mashhad University.

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Synthesis methods

Synthesis 3,3'-dimethyl-[1,1'-biphenyl]-4,4'-dicarbonitrile (m1) [13]

To a mixture of water (10 mL) and concentrated HCl (37% , 3 mL) cooled to 0 °C, 0.008 mol of 3,3'-dimethylbiphenyl-4,4'-diamine (O-Tolidine) was added slowly in portions over 20 min while keeping a temperature between -2 and 0 °C. To the solution which formed, equivalent number of moles 0.016 mol of $NaNO_2$ solution was dissolved in water 7 mL, added at same temperature. The resulting colored solution which formed and then stirred at 0 °C for 30 min, before it was added dropwise over 15 min to a solution of 0.016 mol NaCN was dissolved in water 10 mL then stirred at 0 °C for 50 min. The separated nitrile derivatives product is filtered, washed with water many times and recrystallized with ethanol. It was synthesized as a light yellow solid powder, Chemical formula: $C_{16}H_{12}N_2$, reaction yield: 84%; m p: 193-195 ºC; FTIR , 3087 cm^{-1} due to aromatic CH, 2217 cm^{-1} due to nitrile group, 1602 cm^{-1} due to C=C, ^{1}H NMR (DMSO-*d6*, 300 MHz) δ ppm: 7.68 (d, *J* = 8.0 Hz, 2H), 7.49 (s, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 2.61 (s, 6H).

Synthesis 4,4'-diazido-3,3'-dimethyl-1,1'-biphenyl (m2) [13]

The method described for the synthesis of azide derivatives were used O-Tolidine 0.008 mol in 2mL of concentrated hydrochloric acid and 10 mL of distilled water at 0-5 ºC. Then a equivalent moles 0.016 mol of sodium nitrite was added to prepare diazonium salt and then added 0.016 mol of sodium azide at 0-5 ºC. It was synthesized as a brawn solid powder, Chemical formula: $C_{14}H_{12}N_6$, reaction yield: 85%; m.p: 132-134 ºC; FTIR, 3026 cm^{-1} due to aromatic CH stretching, 2920, 2864 cm^{-1} due to aliphatic CH stretching, 2117 cm^{-1} due to azide group stretching, 1600 cm^{-1} due to C=C stretching, ^{1}H NMR (DMSO-*d6*,300 MHz) δ ppm: 7.53-7.31(m, Ar-H, 6H), 2.47 (s, CH_3,6H).

Synthesis of 2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl bromide [14]

Glucose pentacetate 2g (0.00534mol) was dissolved into 100 ml CH2Cl2 and to this 25ml HBr (33%) in (HOAC) was added. The reaction was stirred for 3 hours. TLC indicated the completion of the reaction. The reaction was quenched by washing with NaHCO3 (aq., sat., 2X50 mL), solution three times until no bubbling. Then the product was washed with water and brine. Dried over MgSO4 filtered and solvent was removed.

It was synthesized as a white crystalline solid, Chemical formula: C14H19BrO9 , reaction yield: 90%: m p 88–90 oC, FTIR, 2937, 2878 cm−1 due to aliphatic CH stretching, 1754 cm−1 due to carbonyl group; 1H NMR (Chloroform-d, 300 MHz) δ ppm 6.65 (d, J = 4.0 Hz, 1H, H1), 5.57 (t, J= 9.8 Hz, 1H,H3), 5.18 (tt, J = 10.1, 1.6 Hz, 1H,H4), 4.85 (dd, J = 10.1, 4.1 Hz, 1H,H2), 4.42 (dd, J=13.5, 3.6 Hz, 1H, H6-b), 4.31 (m,1H,H5), 4.17 (ddd, J = 13.9, 3.6, 1.5 Hz, 1H,H6-a), 2.07,2.06,2.04,2.03,2.01 (s,12H, 4CH3acetate).

Synthesis of 2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl azide (g1) [14]

(0.237 g, 0.0036 mol) Sodium azide was added into the stirred mixture of (glycosyl bromide 1.5 g, 0.0036mol) in DMF:THF (1:3, 30 mL), the solution reaction was heated for 4 hours to 65 oC, the reaction was stopped with (50 mL) of water and separated with diethyl ether (3 x 40 mL), the organic layers was treated with (50 mL) saturated NaCl, then with (50 mL)water, dried by added Na2SO4, finally the solvent was evaporated.

It was synthesized as a white solid, Chemical formula: C14H19N3O9, reaction yield: 84%, m p 126-128 oC, FTIR, ν 2971, 2866 cm−1 due to aliphatic CH stretching, 2115 cm−1 due to azide group, 1745 cm−1 due to carbonyl group, 1H NMR (300 MHz, Chloroform-d): δ ppm 5.23 (t, J = 9.4 Hz, 1H,H3), 5.08 (t, J = 9.9 Hz, 1H, H4), 4.91 (t, J = 9.4 Hz, 1H,H2), 4.67 (d, J = 8.8 Hz, 1H,H1), 4.28 (dd, J = 12.5, 4.5 Hz, 1H,H6-b), 4.15 (dd, J = 12.5, 2.4 Hz, 1H,H6-a), 3.81 (ddd, J = 9.8, 4.8, 2.3 Hz, 1H,H5), 2.09,2.07,2.03,2.00(s, 12H, 4CH3acetate).

Synthesis of 2-Propynyl (2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside) (g2) [14]

A solution of (1.5 g, 0.004 mol, 1,2,3,4,6-penta-O-acetyl-β-D-glucopyranose) in dry DCM (40 mL) was cooled in ice bath to (0 oC). (Stannic chloride 5 mL, 0.005mol) was added slowly, the solution was stirred vigorously for (20 min) at 0 oC, then (propargyl alcohol 5.05 mmol) was added dropwise, the reaction solution was let it warm to room temperature and the stirring was continued for (3hours). Then the solution was diluted with (75 mL) DCM and poured on cooled water (75 mL), the organic solvent was separated and washed with a solution of NaHCO3 (3x50 mL, aq., sat.) then with water, dried with Na2SO4 and concentrated by evaporated solvent.

It was synthesized as a white solid, Chemical formula: C17H22O10, reaction yield: 74%, m p 114-116 oC, FTIR, 3288 cm−1due to acetylic protons,2955, 2860 cm−1 due to aliphatic CH stretching, 2232due to triple bond of acetyline,1744cm−1 due to carbonyl group; 1H NMR (300 MHz, Chloroform-d): δ ppm 5.21 (t, J = 9.4 Hz, 1H,H3), 5.11 (t, J = 9.9 Hz, 1H,H4), 4.96 (dd, J = 9.4, 7.9 Hz, 1H,H2), 4.64 (d, J = 7.9 Hz, 1H,H1), 4.39 (d, J = 2.4 Hz, 2H), 4.24 (dd, J = 12.4, 4.5 Hz, 1H,H6-b), 4.18 (s, 2H,CH2), 4.07 (dd, J = 12.4, 2.4 Hz,1H,H6-a), 3.69 (ddd, J = 9.8, 4.8, 2.4 Hz,1H,H5),2.48(s,1H,C≡CH),2.07,2.04,200, 1.99 (s,12H, 4CH3acetate).

Synthesis of 1,2,3-triazole derivative (a1) [8,15]

1,2,3-Triazole derivatives were prepared according click chemistry condition. 0.001mol of alkyne compounds (g3) were dissolved in 15 mL of DM. CuCl 0.002 mol and Sodium ascorbate 0.004 mol were added to the solution. Then 0.001mol of 2-azido gemcitabine (m2) was added and stirred continues at 60-70 oC until completed the reaction. The progress of reaction was checked by TLC. The final product were separated with diethyl ether and DW three times. The organic phase dried over MgSO4.The solvent were evaporated to produce end 1,2,3-triazole derivatives.

1,3-bis(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl)oxy)methyl)-1H-1,2,3-triazol-1-yl) methyl)O-tolidine:

It was synthesized as semi solid, Chemical formula: $C_{46}H_{52}N_6O_{18}$, reaction yield (80%); FTIR, 3113 cm^{-1} assigned to aromatic C-H stretching, 2974 cm^{-1}, 2865 cm^{-1} assigned to C-H aliphatic stretching, 1741 cm^{-1} due to (C=O) group stretching, 1611 cm^{-1}, 1575 cm^{-1} assigned to C=N and double bond (C=C) stretching, ^{1}H NMR (DMSO- *d6*),300 MHz) δ ppm: 8.23 (s, 2H, H triazole ring), 7.64-7.42(m, Ar-H, 6H), 6.27 (d, *J* =8.9 Hz, 2H, H-1), 5.62 (t, *J* =8.8 Hz, 2H, H-4), 5.53(t, *J* =8.8 Hz, 2H, H-3), 5.14 (t, *J* =8.7 Hz, 2H, H-2), 4.67 (q, *J* =7.8 Hz, 4H, H-6), 4.34 (ddd, *J* =7.9 Hz, *J* =4.2 Hz, *J* =2.1 Hz, 2H, H-5), 4.13(m, 2H, H-1), 2.46 (s, 6H, CH_3), 2.07,2.04,2.01,1.98(s, 24H, CH_3 acetate).

Synthesis tetrazole derivative (a2) [14]

A mixture 0.003 mol of phenyl cyanide derivatives (m1), 0.006 mol and ammonium chloride 6mmol in DMF (80 mL) was heated to 90 ºC for completed of the reaction. The progress of reaction was followed by TLC. After cooling the reaction mixture and was extracted with water. The organic solvent layer was washed with a saturated of NaCl solution and then with water, and dried it over anhydrous sodium sulfate (Na_2SO_4).The solvent were removed to yield compound (a2).

1,3-bis((1-((2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl)oxy)-1H-tetrazol-5-yl)methyl) O-toluidine:

It was synthesized as a solid product, Chemical formula: $C_{44}H_{50}N_8O_{18}$, reaction yield (81%); (m p: 141-143 ºC), FTIR, 3087 cm^{-1} assigned to aromatic C-H stretching, 2978 cm^{-1}, 2870 cm^{-1} assigned to aliphatic C-H stretching, 1745 cm^{-1} due to carbonyl group(C=O) stretching, 1621 cm^{-1}, 1579 cm^{-1} assigned to C=N and C =C stretching. ^{1}H NMR (DMSO- ***d6*),**300 MHz) δ ppm: 7.71-7.46 (m, Ar-H, 6H), 6.29 (d, J =8.8 Hz, 2H, H-1), 5.65 (t, J =8.8 Hz, 2H, H-4), 5.56(t, J =8.9 Hz, 2H, H-3), 5.17 (t, J =8.7 Hz, 2H, H-2), 4.65 (q, J =7.8 Hz, 4H, H-6), 4.31(ddd, J =7.8 Hz, J =4.2 Hz, J =2.0 Hz, 2H, H-5), 4.13(m, 2H, H-1), 2.47 (s, 6H, CH3),2.07,2.03,2.01,1.99 (s, 24H, CH_3 acetate).

Removal of protective groups Synthesis of (b1, b2) [14]

(0.3 mmol) of end compounds were dissolved in (5 mL) methanol, then (4.1 mg, 0.03 mmol) was Potassium carbonate was added thereto. The reaction mixture was stirred slowly for 6 hours at (25 °C) until the starting material disappearance and concentrated. Then it was separation by extracted with 40 mL three times of diethyl ether and then

the organic phase was wished three times with 100 mL of water. Subsequently, the organic phase was treated with anhydrous (Na_2SO_4) to dried and then filtered. Finally the organic solvent (diethyl ether) was evaporated.

1,3-bis(1-((α-D-glucopyranosyl)oxy)methyl)-1H-1,2,3-triazol-1-yl)methyl))O-tolidine

It was synthesized as semi solid, Chemical formula: $C_{30}H_{36}N_6O_{10}$, reaction yield (80%); FTIR, 3411 cm^{-1}, 3321 cm^{-1} assigned to OH stretching, 3087 cm^{-1} assigned to aromatic C-H stretching, 2979 cm^{-1}, 2845 cm^{-1} assigned to aliphatic C-H stretching, 1585 cm^{-1} assigned to C=C stretching, ^{1}H NMR (DMSO- ***d6***),300 MHz) δ 8.29 ppm (s, 1H triazole ring), 7.68 ppm (d, *J* = 7.7 Hz, 1H,1H-6, HC=N proton pyrimidine ring)), 6.48 ppm (s, 1H-1), 5.86 ppm (m, 1H-3), 5.83 ppm (d, *J* = 7.5 Hz, 1H-5, HC=N proton pyrimidine ring), 4.79 ppm (s, 2H, -CH_2-Cl), 4.51 ppm (dt, *J* = 4.6, 5.5 Hz, 1H-4), 3.79-3.56 ppm (m, 1H-5a,1H-5b). ^{13}C NMR (DMSO- ***d6***),75 MHz) δ 164.86 ppm, 158.57 ppm, 147.87 ppm,143.44 ppm,122.91 ppm, 115.29 ppm, 95.98 ppm, 95.01 ppm, 82.72 ppm, 72.11 ppm, 61.76 ppm, 55.79 ppm.

1,3-bis((1-((α-D-glucopyranosyl)-1H-tetrazol-5-yl)O-tolidine:

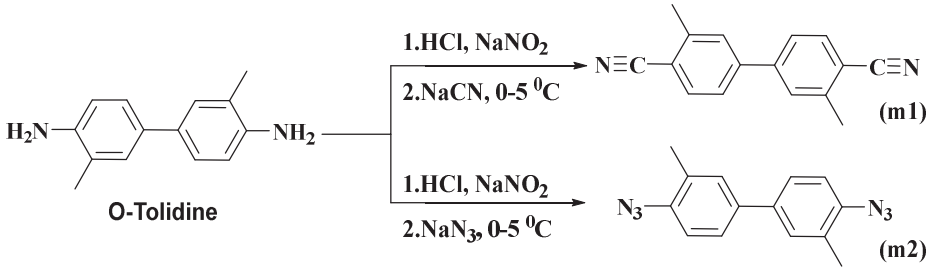
It was synthesized as a solid product, Chemical formula: $C_{28}H_{34}N_8O_{10}$, reaction yield (81%); (m p: 102-104 ºC); FTIR, 3435 cm^{-1}, 3361 cm^{-1} assigned to OH stretching, 3071 cm^{-1} assigned to aromatic C-H stretching, 2964 cm^{-1}, 2834 cm^{-1} assigned to aliphatic C-H stretching, 1581 cm^{-1} assigned to C=C stretching. ^{1}H NMR (DMSO- ***d6***),300 MHz) δ 7.78–7.69 and 7.48– 7.42 (m, Ar-H), 7.59 ppm (d, *J* = 7.8 Hz, 1H, H-6,HC=N proton of pyrimidine ring), 6.83 ppm (s, 1H-1),5.99 ppm (m, 1H-3), 5.78 ppm (d, *J* = 7.6 Hz, 1H-5,HC=N proton of pyrimidine ring), 4.39 ppm (dt, *J* = 4.6, 5.7 Hz, 1H-4), 3.78-3.67 ppm (m, 1H-5a,1H-5b). ^{13}C NMR (DMSO- ***d6***),75 MHz) δ 165.14 ppm,164.48 ppm,154.89 ppm, 142.41 ppm, 134.78 ppm, 129.28 ppm, 128.57 ppm,126.07 ppm, 113.97 ppm, 94.79 ppm, 93.08 ppm, 82.98 ppm, 71.99 ppm, 62.86 ppm.

Antibacterial activity assay [16]

The end compounds were analyzed for antibacterial activity against two types of bacteria are Gram-negative (*Escherichia coli*) and Gram-positive bacteria (*Staphylococcus aureus*) in Muller Hinton agar by measuring the inhibition zone in (mm). Azithromycin (200 µg/ µL) was used as a positive control drug for antibacterial activity. The isolation bacteria was injected on to the Muller-Hinton Agar by plunging in to the suspension of tested compounds by used a cotton swab and streaking over the agar plates surface. four holes with (6 mm)were made in the solidified medium. The target compounds dissolved in 1mLof DMSO, and then take 0.5 mL of prepared solution to fill holes. The prepared plates were incubated for 24 hours at 37 ^{0}C and measured inhibition zone.

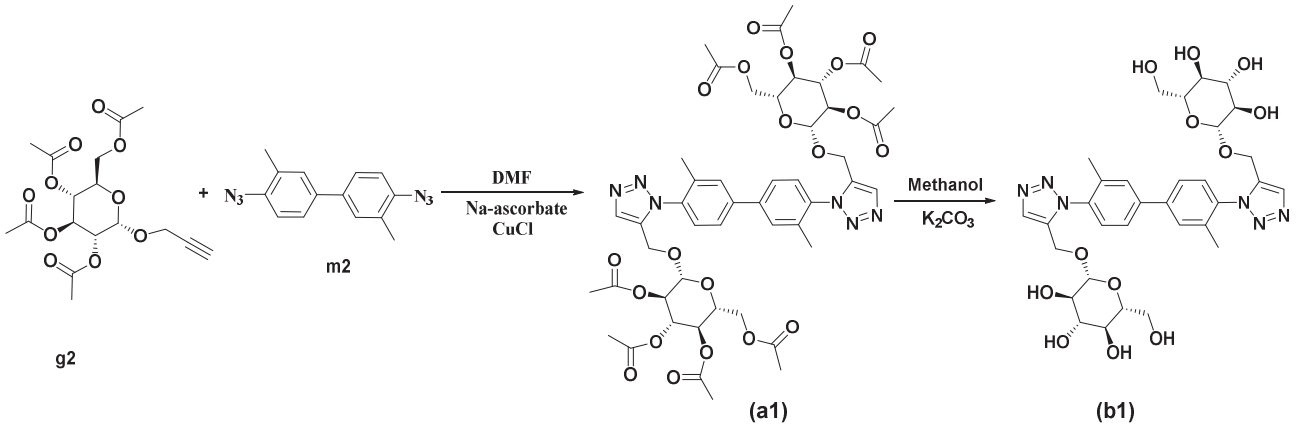
RESULTS AND DISCUSSION

According to the prepare rout explain in Scheme 1. All prepared azide and nitrile derivatives (m1,m2) were synthesized by nucleophilic substitution reaction of intermediate diazonium salt with sodium cyanide or with sodium azide.



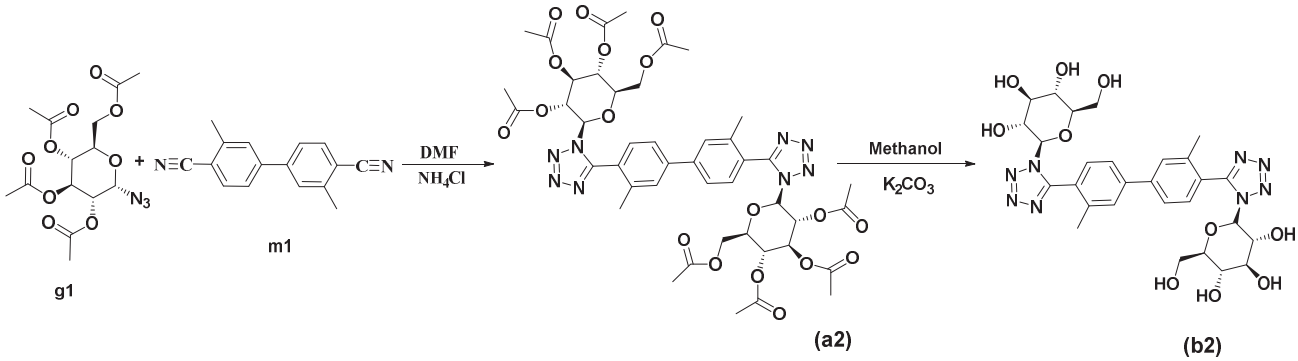
Scheme 1. Synthesis azide and nitrile derivatives

The prepare of 1,2,3-triazole derivatives included reaction azide derivative and 2-Propynyl (2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside) [14] under click reaction approach as shown in Scheme 2.



Scheme 2. Synthesis 1,2,3-triazole derivatives

The end step included preparation tetrazole derivatives by reaction nitrile compounds with 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl azide [14] in presence ammonium chloride as shown in Scheme 3. The acetal groups of end products tetrazole and triazole were removed under basic conditions to give the deprotected heterocyclic compounds.



Scheme 3. Synthesis tetrazole derivatives

The structures of all the prepared compounds were confirmed on the basis of their ^{1}H NMR, ^{13}C NMR and FTIR.

Characterization

FTIR spectra of 3,3'-dimethyl-[1,1'-biphenyl]-4,4'-dicarbonitrile(m1) a new peak appeared in the region 2217 cm^{-1} assigned to nitrile group. Whereas azide group in 4,4'-diazido-3,3'-dimethyl-1,1'-biphenyl (m2) appeared in the 2117 cm^{-1}. The presence bands in the region 3118-31137 cm^{-1} in the FTIR spectra of all the end products good indicator the formation of tetrazole and triazole rings, in addition to absence peaks of azide and nitrile in starting substances . On the other hand ^{1}HNMR spectrum of 1,2,3- triazole derivatives (a1) shows a new singlet signal at 8.23 ppm due to protons of 1,2,3-triazole ring and disappears peak at 2.5 ppm assigned to propargyl protons C≡CH, in addition to the singlet signal at the range of 4.67 ppm assigned as the CH_2 group of alkyne moiety. Whereas in ^{1}HNMR spectrum of 1,2,3-triazole and tetrazole compounds confirmed by singlet signals in the region 2.07-1.98 ppm were assigned to methyl protons CH_3 of acetate groups. After removal of protective groups on sugar molecules in (1b,2b) derivatives were disappearance singlet signals of methyl protons CH_3 of acetate groups in the region 2.07-1.98 ppm.^{13}C NMR spectrum, the new peaks of 1,2,3-triazole ring carbon atoms C-5 and C-4 were appeared in the region 143.44,147.87ppm and 123.42-122.77 ppm respectively. On the other hand the new peaks of C-4 carbon atom of tetrazole ring appeared in the region 164.48 ppm.

Antibacterial activities

All target tetrazole and triazole compounds were evaluated for antibacterial activity toward two types of bacteria are Gram-positive (*Staphylococcus aureus*) and Gram negative (*Escherichia coli*). Whereas used Azithromycin drug as positive control. The results listed in table 1. the results of antibacterial activity shows compound with tetrazole ring (b2) more active than other prepared compounds against *Escherichia coli* but compound with triazole ring (a2) have a high activity against *Staphylococcus aureus.*

Table 1. Antibacterial activity of the synthesized bis -1,2,3- triazoles and tetrazole

Compound	Zone of inhibition in (mm), concentration (µg/mL)			
	G^+ Staphylococcus aureus		G^- Escherichia coil	
	10	25	10	25
a1	04	09	05	12
a2	05	15	07	14
b1	10	11	03	11
b2	05	12	08	16
DMSO	-	-	-	-
Azithromycin	24	27	25	28

CONCLUSIONS

In conclusion, the synthesis and identification of new heterocyclic compounds with 1,2,3-triazole and tetrazole rings using click reaction approach. The prepared compounds exhibited good antibacterial activity against selected types of bacteria (*Staphylococcus aureus*) and Gram negative (*Escherichia coli*).

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