Synthesis of One New Sugar Imine Molecule

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Summary: In this research, the molecule N'-((E)-5-methoxy-2-((1-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)-4,5-dihydro-1H-1,2,3-triazol-4-yl)methoxy) benzylidene)-4-methyl-1,2,3-thiadiazole-5-carbohydrazide were synthesized and characterized by several conventional analysis methods. Its physical properties and thermal stability was studied. The synthesis was conducted based on D-glucose using concept of click chemistry reaction mechanism. Some of the reaction was conducted using microwave irradiation. The synthesis steps initiated by adding propargyl bromide to 2-hydroxy-5-methoxy benzaldehyde under vigorous measure of moister isolated environment to produce propargyl ether(5-methoxy-2-(prop-2-yn-1-yloxy)benzaldehyde) 3 in which has terminal triple bond. In parallel a glycocyl azide was prepared by applying glycocyl acetate (acetate for protection) via bromination and then substituted by treatment with sodium azide to produce glycocyl azide in which actively reacted with terminated triple bond by click reaction in the present of Cu(II) catalyst. The coupling reaction of terminal alkyle group in compound 3 with azide group of (2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-azidotetrahydro-2H-pyran-3,4,5-triyl triacetate) has given high yield of triazole. The produced triazole molecule is triazole(2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-(4-((2-formyl-4-methoxy)methyl)-1H-1,2,3-triazole-1-yl)tetrahydro-2H-pyran-3,4,5,-triyacetate) **7** undergoes further reaction to substitute carbonyl of the aromatic with hydrazide by applying 4-methyl-1,2,3-thiadiazole-5-carbohydrazide reagent. The glycocyl acetate was de-esterifide by sodium methoxide to remove the acetate protection. The structure of all these synthesized molecules was confirmed by FTIR, H^1NMR, C^{13}NMR.

Keywords: Triazole derivatives of sugar, Schiff-bases, Cu (II)-catalyst, Propargyl ethers.

Introduction

The derivatives of triazoles as heterocyclic chemicals bring an attention of researchers in the field of organic synthesis due to its biological activities [1]. Triazole compounds are containing three nitrogen atoms in the five-membered of aromatic azole ring. They are readily able to bind with a variety of enzymes and receptors in biological system via diverse non-covalent interactions [2]. A large number of triazole compounds used as clinical drugs or candidates have been frequently employed for the treatment of various types of diseases such as antineoplasic where they have some cytotoxic potential effects that can be utilized as therapeutic option by affecting the cell membrane permeability [1], antibacterial by modulating and attacking bacterial cell wall and many biological membranes and enzymes [3], antitubercular especially resistant strains [4]. It has been reported that triazoles shows a good yield on base of carbohydrate derivative using Cu (II) catalyst [1] for a coupling of fast reactions. The fast reaction and easy synthesis of these compounds in which recently called as click chemistry concept which is encouraged a glycol-scientist to synthesis a numerous number of very useful compounds using a simple and modules chemical tools [5, 6]. One of the effective tool is to use reaction of propargyl bromide with moiety of aromatic substituted aldehyde to produce propargyl ether contains a terminal alkyne group. This kind of chemical intermediates bring attention of researchers to perform a fast reaction [7]. These intermediates are leading for further synthesis. The appending of carbohydrate namely "D-Glucose" with propargyl ether shows a great potential to produce a form of new drugs in which offers a less toxicity with higher solubility [8].

The synthesis of these compounds become more available after reporting the activity of Cu(II) catalyst on coupling a diverse range of azide with alkynes and aldehydes bearing alkyl, halogenated, silyl, aryl, and heteroaryl groups [9]. The azide alkyne of 1,3-cycloaddition reaction to produce glucose triazoide is a typically consider as click chemistry kind of reaction [10]. The reaction is dominated by triazole glycoside [11, 12], where the 1,2,3-triazole and 1,2,4-triazole were successfully synthesized in this work. The 1,3-dipolar cycloaddition of azides and alkynes become a milestone for a series of synthesis *via* high activities of Cu(II) catalyst [13–15]. The coupling of N′,N′-diaryl acylhydrazines was developed and reported by Ji-Quan Zhang *et al* [16] as achieved by such catalyst. They have shown the coupling reaction using Cu(II) catalyst

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exhibited high functional selectivity. The click reaction is a powerful method to produce 1,2,3-trizole and 1,2,4-trizole moiety with good selectivity. These stable molecules are used to design a series of further molecular synthesis specially of those biologically active [17]. A combination of 1,2,3-trizole and 1,2,4-trizole with glucose and Schiff-base was successfully synthesized in this work. The protected glucose was de-esterified in the final step of synthesis process to produce sugar-imine derivative. The molecular structure is proven via spectroscopic analysis.

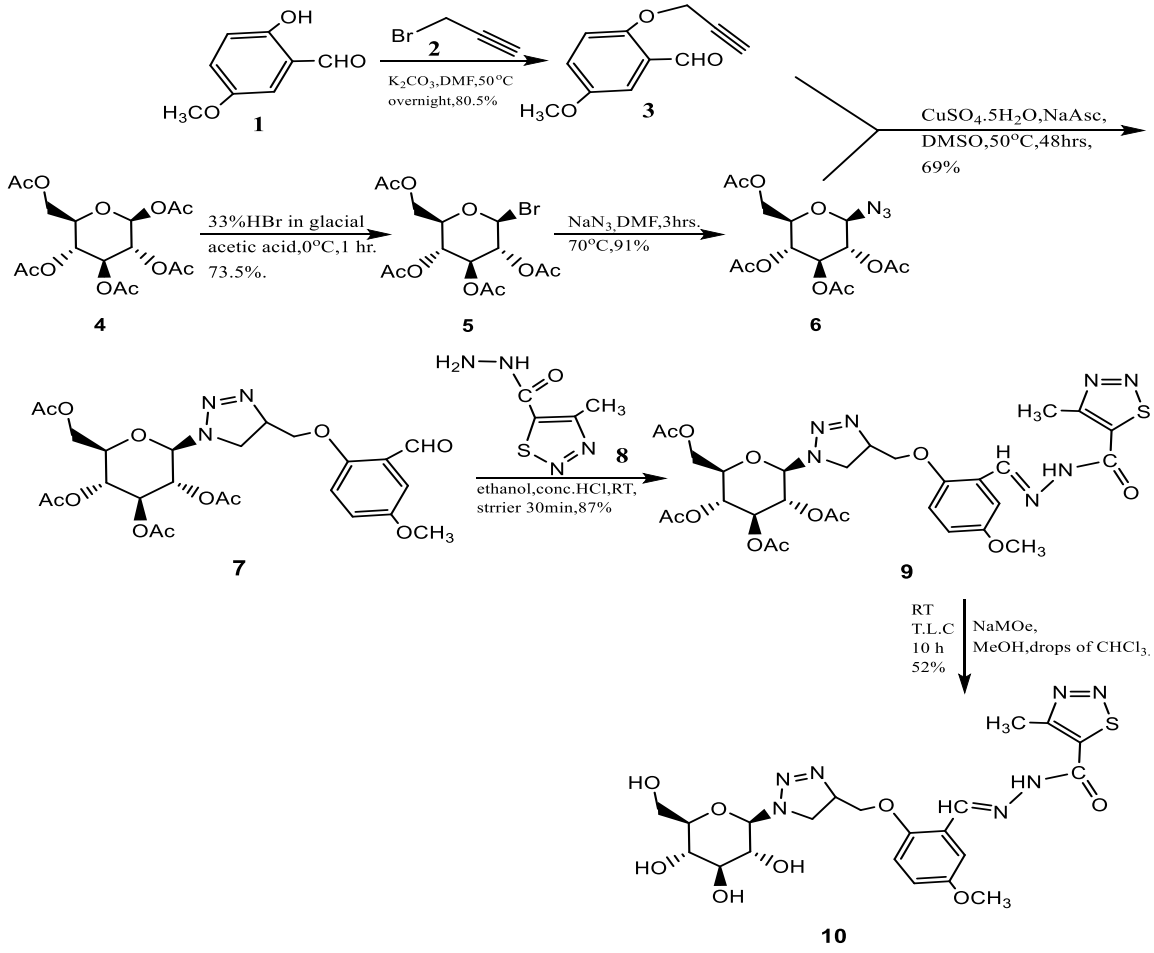
Experimental

Chemicals and Instrumentation

All chemicals were purchased from Sigma Aldrich. Most of chemicals were used without further purification. The reactions sensitive to atmosphere were conducted under nitrogen environment. The reaction progress was followed by thin layer chromatography visualized by UV light and Iodine. Analysis of all these organic compounds was done by conventional way using, Fourier Transform Nuclear Magnetic Resonance H^1NMR, Bruker/ Avance III HD 400 MHz for hydrogen determination and C^{13}NMR. Thermal scientific and Nicolet 6700- FTIR scanning for bond formation detection and functional group determination. Melting points were determined using Melting Point Meter M 5000, KRÜSS – Germany.

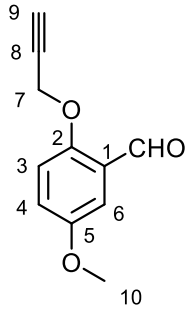
Synthesis

The synthesis steps were started with preparing a terminal alkyne by using propargyl bromide to combine with the hydroxyl of 2-hydroxy-5mothoxybenzeldehyde by proton elimination to produce molecule 3. In parallel to this a fully esterified glucose was brominated, molecule 5, and converted to azide using sodium azide by bromine substitution, molecule 6. The coupling step between molecule 3 and 6 was performed by using $CuSO_4$ as catalyst in DMSO solvent to produce molecule 7. Further reaction steps for molecule 10 synthesis steps are presented in scheme 1.



Scheme-1: Synthesis of Sugar-imine derivative, **10.**

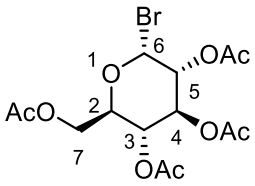
5-methoxy-2-(prop-2-yn-1-yloxy)benzaldehyde **3**



Molecule **3**

To the solution of 2-hydroxy-5-methoxy benzaldehyde **1** (5.2 ml, 0.04 mole) in dry DMF (50 ml) anhydrous potassium carbonate (5.6g, 0.04mole) anhydrous potassium carbonate was added and stirred for a 20 minutes. Propargyl bromide **2** (4 ml, 0.04 mole) was added to the reaction mixture and stirred for overnight at room temperature. The reaction was quenched with water (100 ml). The crude product (4.65g) was re-crystallized from hexane to give a golden yellow crystals **3** (4.19g, 80.5%), mp 62.7 °C, R_f o.75 (hexane: ethyl acetate; 9:1), FTIR (cm^{-1}): 3221, 3002, 2975, 2944, 2865, 2125, 1681, 1668, 1613; =^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 10.43 (s, 1H, C<u>H</u>O), 7.33 (d, *J*= 3.2 Hz, 1H, H6), 7.13 (dd, *J*= 9.1, 3.2 Hz, 1H, H4), 7.06 (d, *J*= 9.1 Hz, 1H, H3), 4.77 (d, *J*= 2.4 Hz, 2H, H7), 3.78 (s, 3H, H10), 2.54 (t, *J* =2.4 Hz, 1H, H9). ^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm: 189.5 (<u>C</u>HO), 154.6 (d, *J* =1.2 Hz, C1), 126.3 (C5), 123.3 (C4), 115.8 (C3), 110.5 (C6), 78.1 (C8), 76.5 (C9), 57.5 (C7), 55.9 (C10).

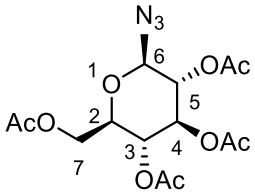
(2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-bromotetraydro-2H-pyran-3,4,5-triyl triacetate **5**



Molecule **5**

(2R,3R,4S,5R,6R)-6-(actoxymethyl)tetrahydro-2*H*-pyrn-2,3,4-tetrayl tetra acetate **4** (10g , 0.025 mole) added in the form of batches to a stirred solution of HBr 33% in glacial acetic acid (50 ml) at 0°C. After all the sugar has been added, the mixture stirring at the same temperature for half an hour, after that the reaction quenched with cold water. A white crystal was precipitated and filtered directly. The product is dried to afford compound **5** (7.3g ,73.5%), **mp** 60.3°C, **R_f** 0.37 (dichloromethane, methanol; 8:2), **FTIR** (cm^{-1}): 2963, 1742; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ ppm: 6.58 (d, *J*= 4.0 Hz, 1H, H6), 5.52 (t, *J*= 9.7 Hz, 1H, H4), 5.13 (t, *J*= 9.8 Hz, 1H, H3), 4.81 (dd, *J*= 10.0, 4.0 Hz, 1H, H5), 4.30 (m, 1H, H7a), 4.27 (m, 1H, H2), 4.10 (m, 1H, H7b), 2.07, 2.06, 2.02, 2.00 (s, 12H, C<u>H</u>$_3$). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ ppm: 170.6, 169.9, 169.8, 169.5 (4C=O acetate), 86.6 (C6), 72.2 (C2), 70.7 (C5), 70.3 (C4), 67.3 (C3), 61.05 (C7), 20.72, 20.7, 20.67, 20.61 (4C, CH_3 acetate).

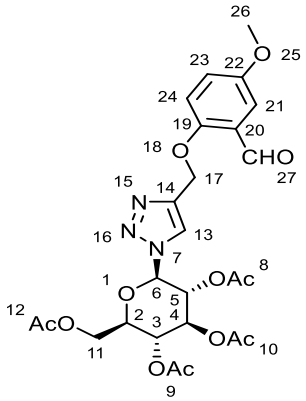
(2R,3R,4S,5R,6R)-2-(aceoxymethyl)-6-azidotetrahydro-2H-pyran-3,4,5-triyl triacetate **6**



Molecule **6**

Sodium azide (2.9g, 0.04 mole) was added to the stirred solution of **5** (6g, 0.014 mole) in DMF (100 ml). The mixture was heated to 70°C for 3 hours. The mixture of the reaction was poured on 100 ml of water immediately. A white crystal was precipitated, filtered, washed with water. The product is dried to afford compound **6** (5.5g, 91%), mp 128.1°C, R_f 0.54 (hexane:ethylacetate;8:2), FTIR (cm^{-1}): 2969, 2909, 2119, 1754, 1732; ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 5.19 (dt, *J*= 9.5, 1.8 Hz, 1H, H4), 5.07 (dt, *J*= 9.8, 1.6 Hz, 1H, H3), 4.92 (dt, *J*= 9.2, 2.2 Hz, 1H, H5), 4.62 (dd, *J*=10.0, 1.0 Hz, 1H, H6), 4.24 (ddd, *J*= 12.5, 4.8, 1.9 Hz, 1H, H7a), 4.14 (ddd, *J*= 12.5, 4.2, 2.0 Hz, 1H, H7b), 3.77 (dddd, *J* =10.0, 4.7, 2.2, 1.0 Hz, 1H, H2), 2.07 (d, *J*= 2.2 Hz, 3H, C<u>H</u>$_3$), 2.04 (d, *J*= 2.2 Hz, 3H, C<u>H</u>$_3$), 2.00 (d, *J*= 2.1 Hz, 3H, C<u>H</u>$_3$), 1.97 (d, *J*= 2.2 Hz, 3H, C<u>H</u>$_3$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm: 170.6, 170.2, 169.4, 169.3 (4C=O acetate), 87.9 (C6), 74.1 (C2), 72.7 (C4), 70.7 (C5), 68.0 (C3), 61.7 (C7), 20.7, 20.6 (4C, CH_3 acetate).

(2R,3R, 4S, 5R,6R)-2-(acetoxymethyl)-6-(-((2-formyl-4-methoxyphenoxy)methyl)-1H-1,2,3-triazole-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate **7**

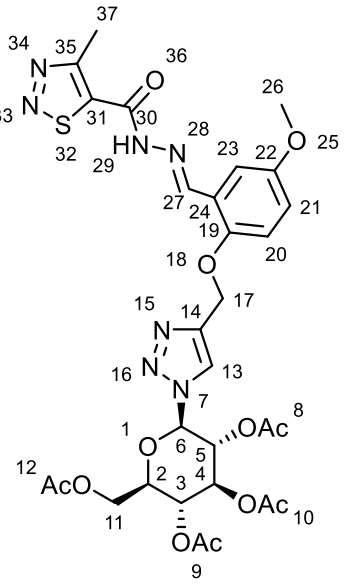


Molecule **7**

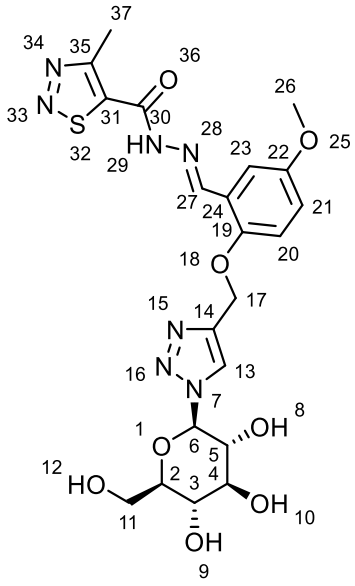
A solution of propargyl ether **3** (1.9g ,0.01 mole) in DMSO (10 ml) was added dropwise to the suspension of sodium ascorbate (0.18g, 0.0009 mole) and $CuSO_4.5H_2O$ (0.11g, 0.0004 mole) in DMSO (10 ml). The mixture was stirred for 10 minutes and to this was added glycosyl azide **6** (3.73g, 0.01 mole) then stirred at 50°C for 48 hours. The reaction mixture is poured on water (100 ml), after a few minutes a yellow pale crude residuum appeared. The crude was crystallizes from (hexane: ethanol; 8:2), R_f 0.84 (hexane: ethyl acetate; 1:1), to afford **7** (3.9g, 69 %) as a white crystalline solid , mp 122.5°C, FTIR (cm^{-1}): 3142, 2976, 1758, 1746, 1686;^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 10.39 (s, 1H, H27), 7.88 (s, 1H, H13), 7.31 (d, *J*= 3.0 Hz, 1H, H21), 7.11 (dd, *J*= 9.0, 3.1 Hz, 1H, H23), 7.06 (d, *J*= 9.1 Hz, 1H, H24), 5.88 (dd, *J*= 6.6, 2.6 Hz, 1H, H6), 5.41 (m, 2H, H4, H5), 5.27 (s, 1H, H17), 5.23 (m, 1H, H3), 4.29 (ddd, *J*= 12.6, 5.0 Hz, 1H, H11a), 4.14 (ddd, *J*= 12.6, 1.9 Hz, 1H, H11b), 4.0 (ddd, *J*= 10.1, 4.8, 2.0 Hz, 1H, H2), 3.78 (s, 3H, H26), 2.06, 2.05, 2.00 (s, 12 H, H12, H10, H9, H8). ^{13}C-NMR (100 MHz, $CDCl_3$) δ ppm: 189.4 (C27), 170.6, 170.0, 169.4, 168.9 (4C=O acetate), 155.1 (C14), 154.3 (C20), 125.8 (C22), 123.4 (C23), 121.6 (C13), 115.3 (C24), 110.7 (C21), 85.9 (C6), 75.4 (C2), 72.6 (C4), 70.5 (C5), 67.8 (C3), 63.2 (C17), 61.6 (C11), 55.9 (C26), 20.8, 20.61, 20.6, 20.1 (4C, C12, C10, C9, C8).

To a solution of sugar-triazole derivative **7** (1.126g, 0.002 mole) in ethanol (30 ml), aromatic amine **8** (0.316g, 0.002 mole) was slowly added. The mixture of the reaction was stirred to dissolve. A slow addition of drops of conc. HCl was added. Forty minutes later, a white precipitate was produced. T.L.C analysis (dichloromethane; methanol;9:1), R_f 0.82, indicated to complete the formation of **9**. Re-crystallization of ethanol has given the yellow crystalline solid (0.98g, 87%), mp 203.8°C, FTIR(cm^{-1}): 3054, 2942, 1754, 1652, 1595; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 12.30 (s, 1H, H29), 8.52 (s, 1H, H13), 8.49 (broad s, 1H, H27), 7.43 (broad s, 1H, H23), 7.24 (broad s, 1H, H20), 7.06 (broad s, 1H, H21), 6.38 (d, *J*= 9.1 Hz, 1H, H6), 5.66 (d, *J*= 9.3 Hz, 1H, H4), 5.56 (d, *J*= 9.4 Hz, 1H, H5), 5.23 (s, 1H, H17), 5.18 (d, *J*= 9.8 Hz, 1H, H3), 4.38 (broad m, 1H, H2), 4.15 (dd, *J* =12.6, 5.2 Hz, 1H, H11a), 4.08 (broad d, *J* =12.2 Hz, 1H, H11b), 3.82 (s, 3H, H26), 2.95 (s, 3H, H37), 2.03, 1.99, 1.96, 1.76 (s, 12 H, H12, H10, H9, H8). ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 170.0, 169.5, 169.3, 168.5 (4C=O acetate), 163.3 (C27), 159.7 (C14), 153.7 (C22), 151.2 (C19), 143.3, 141.3 (C35, C31), 135.2 (C30), 123.7 (C13), 122.7 (C20), 118.1 (C24), 115.5 (C23), 109.9 (C21), 83.8 (C6), 73.3 (C2), 72.2 (C4), 70.1 (C5), 67.5 (C3), 62.3 (C17), 61.7 (C11), 55.4 (C26), 20.5, 20.4, 20.2, 19.8 (4C, C12, C10, C9, C8), 15.0 (C37).

(2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-(4-((4-methoxy-2-((E)-(2-(4-methyl-1,2,3-thiadiazole-5-carbonyl)hydrazono)methyl)phenoxy)methyl)-4,5-dihydro-1H-1,2,3-triazol-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate **9**



N'-((E)-5-methoxy-2-((1-((2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl) tetrahydro-2H-pyran-2-yl)-4,5-dihydro-1H-1,2,3-triazol-4-yl)methoxy)benzylidene)-4-methyl-1,2,3-thiadiazole-5-carbohydrazide **10**



Molecule **10**

A solution of glucose-triazole-imine derivative **9** (0.5g, 0.00071 mole) was dissolved in methanol (10 ml), a drop of chloroform was added in order to dissolve **9**. A drops of methanolic NaOMe(0.5 M) was added to solution of the reaction until the pH is 10-11. The reaction was kept at (40-50°C) and stirred for 10 hours to complete the reaction. T.L.C run (dichloromethane: methanol; 9:1) shows the retention time of the compound **10** is Rf 0.32 in referring to compound **9** indicating the removal of acetyl protecting groups. Amberlite IR 120 (H^+) was added and the mixture stirred for 5 minutes and then neutralized. The solution of the mixture reaction filtered. The filtrate was concentrated in vacuum to afford **10** (0.26g, 52%), mp 140.4°C, FTIR (cm^{-1}): 3364, 2930, 1660; ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 8.53 (s, 1H, H13), 8.45 (broad s, 1H, H27), 7.46 (d, *J* =3.0 Hz, 1H, H23), 7.32 (d, *J*= 9.0 Hz, 1H, H20), 7.09 (dd, *J*= 9.1, 3.1 Hz, 1H, H21), 5.56 (d, *J*= 9.3 Hz, 1H, H6), 5.21 (s, 1H, H17), 3.84 (s, 3H, H26), 3.80 (t, *J*= 9.2 Hz, 1H, H5), 3.70 (dd, *J* =14.9, 5.1 Hz, 1H, H11a), 3.46–3.39 (m, 3H, H2, H4, H11b), 3.24 (t, *J* =8.8 Hz, 1H, H3), 2.96 (s, 3H, H37). ^{13}C-NMR (100 MHz, DMSO-d_6) δ ppm: 163.2 (C27), 160.0 (C14), 153.6 (C22), 151.5 (C19), 142.5, 141.2 (C35, C31), 135.4 (C30), 123.9 (C13), 122.6 (C20), 118.0 (C24), 115.2 (C23), 110.0 (C21), 87.6 (C6), 80.1 (C2), 77.0 (C4), 72.1 (C5), 69.6 (C3), 62.4 (C17), 60.8 (C11), 55.5 (C26), 15.1 (C37).

Results and Discussion

Sugar imine molecule (Molecule 10) is successfully synthesized. The key reaction start is to form terminal alkyne group by using 3-bromopropyne a three carbon building block, in which has good stereoselective of propargylation reaction with α- alkyl aldehyde of 2-hydroxy-methoxybenzeldehyde **1** with the yield of more than 80%. The synthesized propargyl ether **3**, was well purified and subjected to further reaction. In parallel a β-D-glucose pentaacetate **4** was brominated using 33% HBr in glacial acetic acid. The reaction is well isolated from any moisture to produce glycosyl bromide **5** with a yield 73.5%. Molecule **5** was converted to glycosyl azide **6**, by using sodium azide in DMF with a yield 91%. The coupling reaction between Propargyl ether **3** and glycosyl azide **6** was performed by using Cu(II) catalyst to produce the derivatives of triazole with moiety of benzaldehyde, molecule **7**. The carbonyl group of aldehyde was substituted by 4-amino-5-methyl-4H-1,2,4-triazole-3-thiol **8**, to produce a glucose-triazole-imine **9**. The protection groups of glucose in compound **9**, was de-esterified by very sensitive environment reaction toward pH. The best pH of this reaction is 9-10. The molecule of compound **9**, is so sensitive to acidic medium and also humidity. The molecule 9, will undergoes a decomposition if the de-esterification pH reaction below 7. We have notice also the molecule 9 is not so stable and sensitive to daylight. Synthesis of this molecule was conducted in reduce laboratory light. Under the light, the group of triazole will spilt from the bulk of the molecule. A great care was taken to run the de-esterification under nitrogen and well controlled pH. The final product is glucose-imine derivative molecule **10**. This molecule is quite stable and its structure is well proven by spectroscopic analysis. Samples for any further investigation are available.

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