Copper (I) Catalyzed Synthesis and Antibacterial activity of 1,2,3-Triazoles Based on D-Fructose

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Abstract
Four *n*-alkyl azides; *n*-heptyl azide, *n*-octyl azide, *n*-decyl azide and *n*-dodecyl azide (1a-d) were prepared via S_N2 reaction of alkyl halides and sodium azide. In different step, D-fructose was converted to 2,3:4,5-di-O-isopropylidene-D-fructopyranose (3) using acetone and sulfuric acid as catalyst. The reaction of compound (3) with propargyl bromide in DMF afforded the terminal acetylene (4) in very good yield. The derivative (4) was reacted with synthesized *n*-alkyl azides (1a-d) *via* cycloaddition reaction using Cu(I) as catalyst afforded D-fructose based 1,2,3-triazoles (5a-d). The acetal groups of triazoles (5a-d) were removed under acidic conditions to give the deprotected triazoles (6a-d). All synthesized compound were identified by TLC, FTIR and most of them were characterized by 1H NMR, 13C NMR, COSY, HSQC and HRMS. The synthesized compounds showed antibacterial activity *in vitro* against two kinds of bacteria: *Escherichia coli (-)* and *Staphylococcus aureus (+).*

تحضير 3,2,1-ترايزولات باستخدام النحاس (I) كعامل مساعد بدءاً من سكر د- فركتوز وفحص الفعالية المضادة للبكتريا للمركبات المحضرة

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الكلمات المفتاحية: د-فركتوز, كيمياء Click , 3,2,1-ترايزولات, الفعالية المضادة للبكتريا, الحلقات غير المتجانسة السكرية.

الخلاصة
تضمنت هذه الدراسة تحضير وتشخيص مجموعة جديدة من مشتقات 3,2,1-ترايزولات باستخدام النحاس (I) لتحفيز تفاعل الإضافة الحلقيه 3,1-الكاين-أزايد بدءاً من سكر د- فركتوز. حضرت أربعة أزايدات ألكيل مستقيمة **(1a-d)** عن طريق تفاعل التعويض الباحث عن النواة الثنائي الجزيء لمركبات هاليدات الألكيل الاولية المقابلة مع أزيد الصوديوم في خطوات مختلفة. وفي خطوة منفصلة تم تحضير المشتق 5,4:3,2-ثنائي-*O*-ايزوبروبايلدين- D- فركتوبايرانوز **(3)** بتفاعل د- فركتوز مع الأسيتون بوجود حامض الكبريتيك كعامل مساعد. أجري تفاعل وليمسون لتكوين الإيثر للمركب **(3)** مع بروميد البروبرجيل في وسط قاعدي مع ثنائي

مثيل فورمأمايد لينتج المركب **(4)**. تفاعل الإضافة الحلقية [3+2] لمشتق الألكاين الطرفي **(4)** مع أزيدات الألكيل الاولية المحضرة **(1a-d)** بوجود النحاس الأحادي كعامل مساعد أنتج مشتقات 3,2,1-ترايازول د-فركتوز**(5a-d)**. تم ازالة مجاميع الأسيتال لمشتقات الترايازول **(5a-d)** في ظروف حامضية ليعطي الترايازولات السكرية **(6a-d)** بمنتوج جيد. تم تشخيص كل المركبات المحضرة بواسطة كروموتوغرافيا الطبقة الرقيقة, مطيافية الأشعة تحت الحمراء و معظمها بإستخدام مطيافية الرنين النووي المغناطيسي البروتوني والكاربوني, وتقنيات الرنين النووي المغناطيسي ثنائية الأبعادCOSY, HSQC, HMQC ; و مطيافية الكتلة عالية الدقة HRMS. كذلك تم فحص الفعالية البيولوجية ضد البكتريا السالبة الغرام (*Escherichia coli*) والبكتريا الموجبة الغرام (*Staphylococcus aureus*) للمركبات المحضرة وبتراكيز مختلفة.

1.Introduction

Click reaction is the conversion of organic azides and terminal acetylenes completely into the corresponding 1,4-disubstituted 1,2,3-triazoles. Since the innovation of the click reaction, this method has found use in varied areas of chemistry such as dendrimers and polymers [1], drug [2], materials [3], bioconjugation [4], antibiotic [5], anticancer [6] and HIV protease inhibitors [7]. The pharmaceutical importance of triazoles has prompted the design and synthesis of various triazolo nucleosides. Recently, A. Mohammed [8] *etal.* synthesized new sugar based triazoles and bistriazoles starting from D-mannitol. D. Francis [9] *etal.* synthesized a number of hydrophilic fluorous surfactants based on bistriazoles. 1-Nonyl-4-[(6-deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactos-6-yl)oxymethyl]-1*H*1,2,3-triazole was prepared via click chemistry starting from D-galactose [10]. Ali *et al.* [11] prepared high yield water soluble 1,2,3-trizole starting from D-mannose using Cu(I) as a catalyst.

Small libraries of fluorous molecules with one and two heterocyclic core elements, 1,2,3-triazoles and tetrazoles were developed [12].

A number of 1,2,3-triazoles have been synthesized *via* click conditions using microwave irradiation and the biological activity of the prepared compounds was monitored against different type of microorganisms [13]. Recently, biologically important tetrakis-1,2,3-triazoles starting from D-mannitol employing the copper catalyzed ‘click’ protocol were synthesized [14].

In this work we prepared eight new 1,2,3-triazole derivatives starting from D-fructose and the antibacterial activities of these derivatives were measured *in vitro* against two kinds of bacteria: *Escherichia coli (-)* and *Staphylococcus aureus (+).*

2. Experimental Section

2.1. General experimental information

All chemicals and solvents were obtained from commercial sources and were used without further purification. Optical rotations were determined at the sodium D line at 25^{o}C. Infrared spectra were recorded using SHIMADZU 2001 FT-IR and Bruker FTIR spectrophotometer. Routine ^{1}H and ^{13}C NMR spectra were obtained on Bruker Avance III 400 spectrometer (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR, respectively). Chemical shifts were recorded in parts per million (ppm) relative to solvent nuclei as an internal reference. HRMS spectra were recorded on Thermo LTQ FT mass spectrometer. Purification of the crude products by column chromatography was performed on silica gel 60 (230–400 mesh, 0.040–0.063 mm). Silica TLC plates were used with an aluminum backing (0.2 mm, 60 F254). The reactions were monitored by TLC and visualized by development of the TLC plates with an alkaline potassium permanganate dip. The antibacterial activity was determined using agar well diffusion method.

2.2. Synthesis

2.2.1. Synthesis of 1-azidoheptane (1a)

Sodium azide (3.0 g, 45 mmol) was added to the stirred solution of 1-bromoheptane (2.4 mL , 15 mmol) in DMF (50 mL), the suspension was stirred at 70^{o}C for 24h, and then the reaction mixture was diluted with distilled water (100 mL), extracted with Et_2O (3×60 mL). The combined organic layer was washed with saturated solution of NaCl (2 ×40 mL), water (50 mL), dried over Na_2SO_4 and evaporated to dryness under reduced pressure to give 1-azidoheptane **1a** as a colorless liquid (2.0 g, 70%)

2.2.2. Synthesis of *n*-alkyl azides (1b-d)

Sodium azide (3.0 g, 45 mmol) was added to the stirred solution of *n*-alkyl iodide (15 mmol) in DMF (50 mL); the suspension was stirred at 70^{o}C for 4h, the reaction mixture was poured in distilled water (50 mL) and extracted with Et_2O (3 × 60 mL), the combined organic layer was washed with saturated solution of NaCl (2 × 40 mL), water (100 mL), dried over Na_2SO_4 and evaporated under reduced pressure to give *n*-alkyl azides **1b-d** as colorless liquids **1b** (80%), **1c** (77%) and **1d** (72%)

2.2.3. Synthesis of 2,3:4,5-di-O-isopropylidene-D-fructopyranose (3) [15]

D-Fructose (18 g, 100 mmol) was added to the clear solution of anhydrous acetone (350 mL) and conc. H_2SO_4 (17.5 ml). The resulting suspension stirred vigorously for

2 h at room temperature until all of the sugar had dissolved. The mixture was neutralized by a solution of NaOH (55 g) in H_2O (250 mL) was gradually added with stirring and cooling in an ice bath. The solution was freed of acetone by evaporation under diminished pressure and the resulting aqueous suspension was extracted with DCM (3 × 100 mL). The extracts were combined washed with H_2O (2 × 50 mL), dried over Na_2SO_4 and evaporated under reduced pressure to a crystalline solid. Recrystallization from Et_2O:*n*-hexane 1:1 (75 mL) to give compound **(3**) as white crystals (8.5 g, 70%), R_f=0.179 (*n*-hexane : Et_2O, 1:2), m.p. 118-120˚C.

2.2.4. 1-O-propargyl-2,3,4,5-Di-*O*-isopropylidene-beta-D-fructopyranose (4)

2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose **(3)** (20 mmol, 5.2 g) was dissolved in DMF (60 mL) in a dry flask and treated with crushed NaOH (3.2 g). The flask was cooled in an ice salt bath at -20^{o}C and the contents stirred for 15 min before propargyl bromide (2 mL) was added dropwise. The mixture was then allowed to stir for a further 24 h, while gradually warming to rt. The mixture was quenched with H_2O (120 mL) and extracted with ether (3 × 70 mL). The combined organic layers were washed with 10% aqueous HCl (2 × 50 mL), dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure to yield compound **(4)** (5 g, 84%) as pale yellow oil. R_f = 0.48 (n-hexane: EtOAc, 2:1).

2.2.5. Synthesis of 1-Alkyl-4-[(2,3,4,5-di-*O*-isopropylidene-β-D-fructopyranos-O-yl)methyl]1*H*-1,2,3-triazole (5a-d)

A suspension of sodium ascorbate (0.0954 g) and CuSO4.5H_2O (0.0583 g) in DMSO (2 mL) was added to a solution of terminal alkyne **(4)** (5.3 mmol, 1.58 g) in DMSO (6 mL) and the mixture stirred for 10 min. Next, *n*-alkyle azide was added and the mixture heated at 65^{o}C with stirring for 48 h. The mixture was diluted with H_2O (80 mL), extracted with EtOAc (3 × 60 mL), the combined organic layers washed with satd NaCl (2 × 40 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The residue was flash chromatographed (silica gel, 3:1 to 1:3, n-hexane:EtOAc) to yield compounds **(5a-d)** as yellow syrup.

2.2.6. Deprotection of compounds (5a-d). Synthesis of compounds (6a-d)

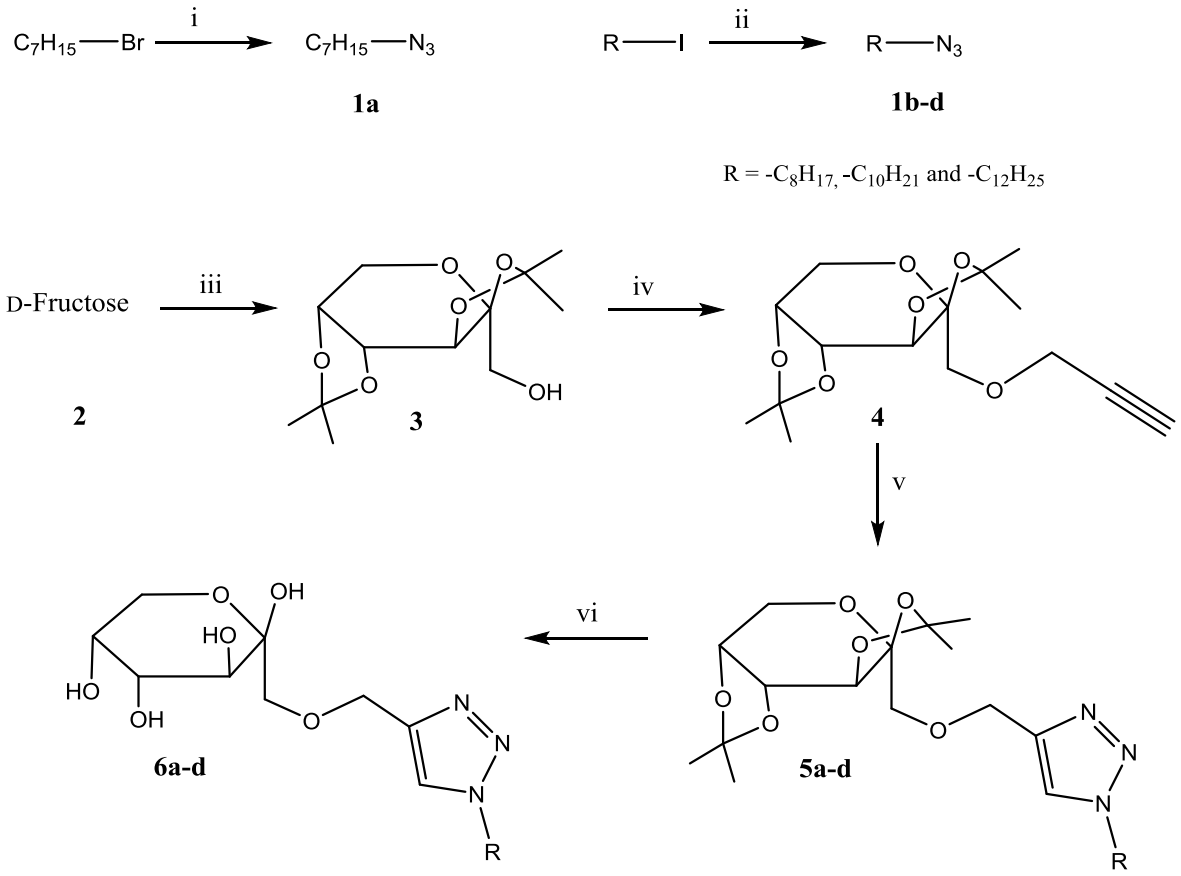
Triazole derivative (1 mmol) was dissolved in MeOH/H_2O (9:1) (10 mL). To this solution was added Amberlite IR 120 H^+ (0.5 g) and the mixture stirred at 60^{o}C form 48 h. The resin was filtered and washed with MeOH (3 × 5 mL). The filtrate was evaporated to yield compounds **(6a-d)** as yellow oil.

2.3. Antibacterial assay [16]

All the microbial cultures were sourced from the Microbial Type Culture Collection (MTCC, Queensland/Australia). The microbial isolates representing Gram-negative *(Escherichia coli*) and Gram-positive bacteria *(Staphylococcus aureus)* were sub-cultured on nutrient agar. The screening of eight compounds **(5a–d)** and **(6a-d)** was done *in vitro* using the agar well diffusion method. the stock solutions (5 mg/mL) of the test compounds were prepared by dissolving 5 mg of test compound in DMSO 1 mL. All samples were sterilized through a 0.2 mm membrane filter and stored at 5°C until further use. Microbial inoculums were prepared from 24 h-old cultures by inoculating 100 μL of each test bacterial culture in 20 mL of warm, melted, autoclaved Mueller Hinton agar, seed layers were prepared (separate flasks were used for each bacterial culture). After mixing, these were poured into sterilized labeled Petri plates (150 mm × 20 mm). The 8 mm wells were punched in the solidified Petri plates with the help of a sterile cork borer. Using a micropipette, 100 mL of each test compound (stock 5, 10 and 20 mg/mL) was added aseptically to the individual wells. The loaded plates were incubated in an upright position at 37°C ± 1°C for 24 h. The diameter of the zone of growth inhibition around each well after incubation was measured in millimeters using a zone reader (HiAntibiotic zone scale). Kanamycin 5, 10 and 20 mg/mL was used as the standard antibiotic, with DMSO as a negative control under similar conditions for comparison. This procedure was performed in two replicate plates for each organism.

3. Results and Discussion

First of all, n-heptyl azide 1a, n-octyl azide 1b, n-decyl azide 1c and n-dodecyl azide 1d were prepared in very good yields in two pathways starting from suitable n-alkyl halide and sodium azide in traditional S_N2 reaction. FTIR spectra of alkyl azides showed the significant ($-N_3$) band around 2095 cm^{-1} as a very good indicator of formation of the mentioned azides. The overall synthetic route of D-fructose based triazoles is shown in scheme 1:



Reagents and coditions: i] NaN_3 , DMF, 70°C, 24 h; ii] NaN_3 , DMF, 70°C, 4 h; iii] Acetone, H_2SO_4, rt, 2 h; iv] propargyl bromide, NaOH, DMF, -20°C - rt, 24 h; v] n-alkyl azide, Na ascorbate, $CuSO_4.5H_2O$, DMSO, 65°C, 48h; vi] Amberlite IR 120 H^+, MeOH/H_2O, 60°C, 48 h.

Scheme 1: Outline for the synthesis of D-fructose based 1,2,3-triazoles

2,3:4,5-Di-O-isopropylidene-D-fructopyranose **(3)** was prepared form the acetonation of D-fructose in the presence of H_2SO_4 as a catalyst. FTIR spectrum of compound (3) figure (1) showed the following significant bands: 3279 cm^{-1} (υ, -OH), 2984, 2937 and 2897 cm^{-1} (υ, -CH, $-CH_2-$, $-CH_3$), 1242, 1104 and 1063 cm^{-1} (υ, C-O).

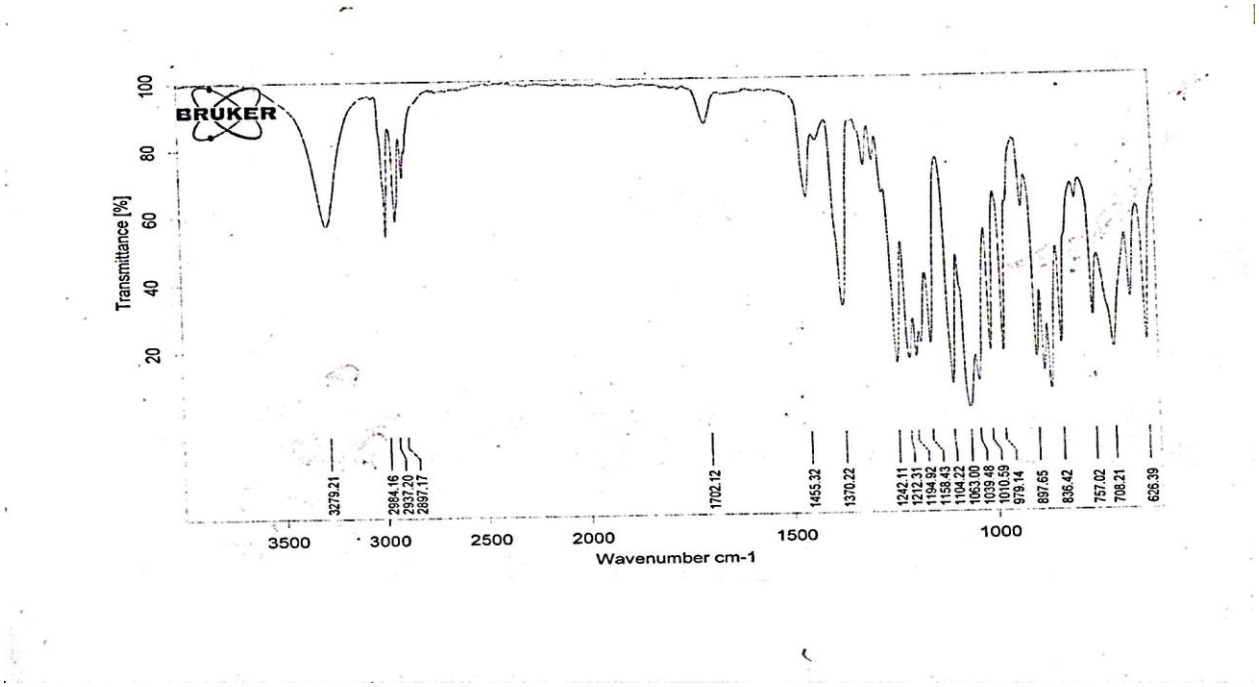


Figure 1: FTIR spectrum of compound **3**

Propargylation of compound (3) was occurred under basic conditions using propargyl bromide to afford compound (4) in very good yield. The bands at 3268 cm^{-1} (C-H acetylenic) and 2117 cm^{-1} (C≡C) in FTIR spectrum figure (2) gave a very good proof for the formation of compound (4).

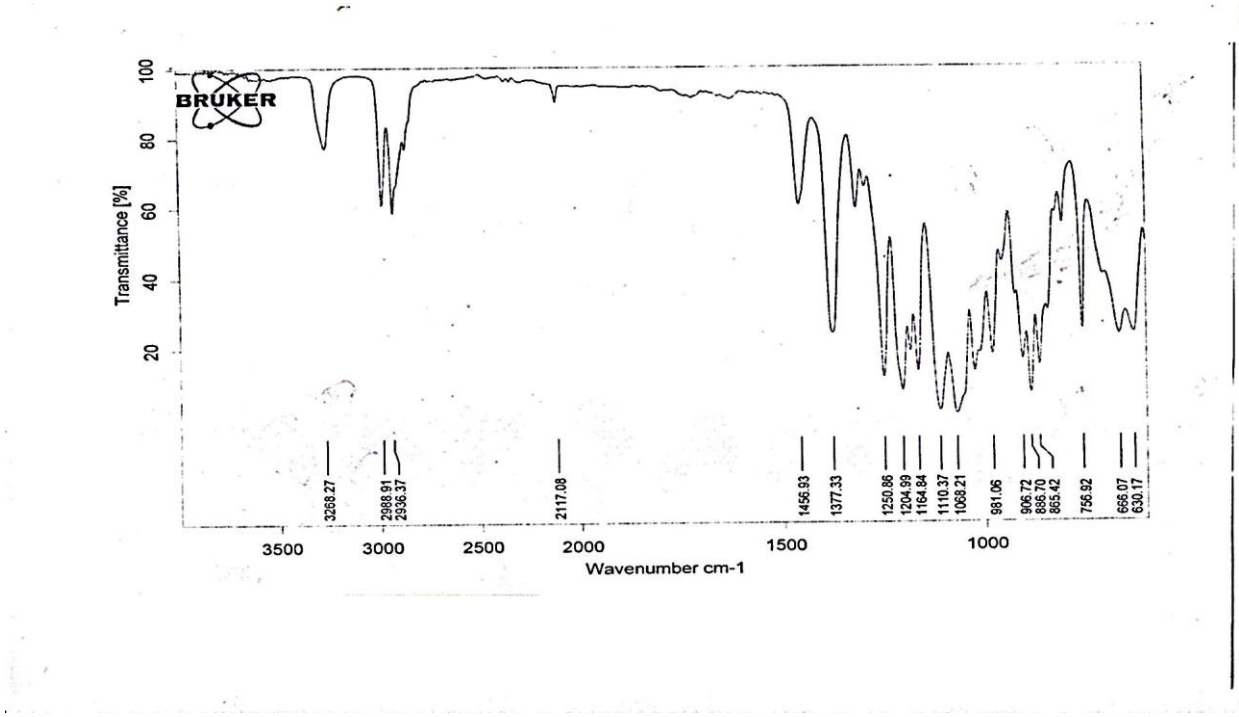


Figure 2: FTIR spectrum of compound **4**

^{1}H NMR spectrum figure (3) (400 MHz, $CDCl_3$) δ ppm: 1.31, 1.39, 1.45, 1.51 (s, 12H, -C***H*****$_3$**, isopropylidene), 2.40 (t, *J* 2.4 Hz, 1H, H3`), 3.64 (s, 2H, H1), 3.69 (dd, *J*

12.9, 0.6 Hz, 1H, Ha6), 3.86 (dd, *J* 12.9, 1.8 Hz, 1H, Hb6), 4.20 (dd, *J* 7.8, 1.0 Hz, 2H, H5), 4.21 (dd, *J* 7.9, 2.4 Hz, 2H, Ha1`), 4.24 (dd, *J* 15.7, 2.4 Hz, 2H, Hb1`), 4.34 (d, *J* 2.6 Hz, 1H, H3), 4.56 (dd, *J* 7.9, 2.6 Hz, 1H, H4).

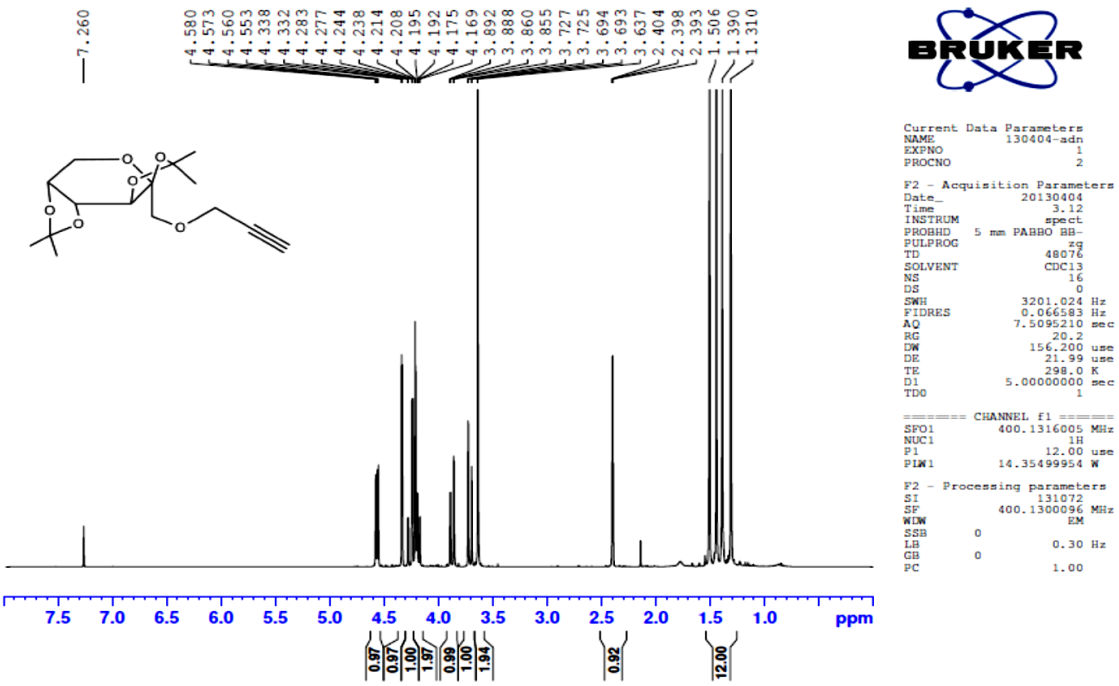


Figure 3: ^{1}H NMR spectrum of compound **4**

^{13}C NMR spectrum figure (4) (100 MHz, $CDCl_3$) δ ppm: 24.1, 25.3, 25.9, 26.6 (4C, -***C***H_3, isopropylidene), 59.1 (C1`), 61.1 (C6), 70.2 (C4), 70.3 (C3), 71.0 (C5), 71.2 (C1), 74.7 (C3`), 79.4 (C2`), 102.6 (C2), 108.6, 109.0 [2C, ***C***$(CH_3)_2$, isopropylidene] ; HRMS (ESI) figure (5). Calculated for $C_{15}H_{22}N_3O_6Na$ 321.1309 $[M+Na]^+$, found 321.1304. All the assignments are based on COSY figure (6) and HSQC figure (7).

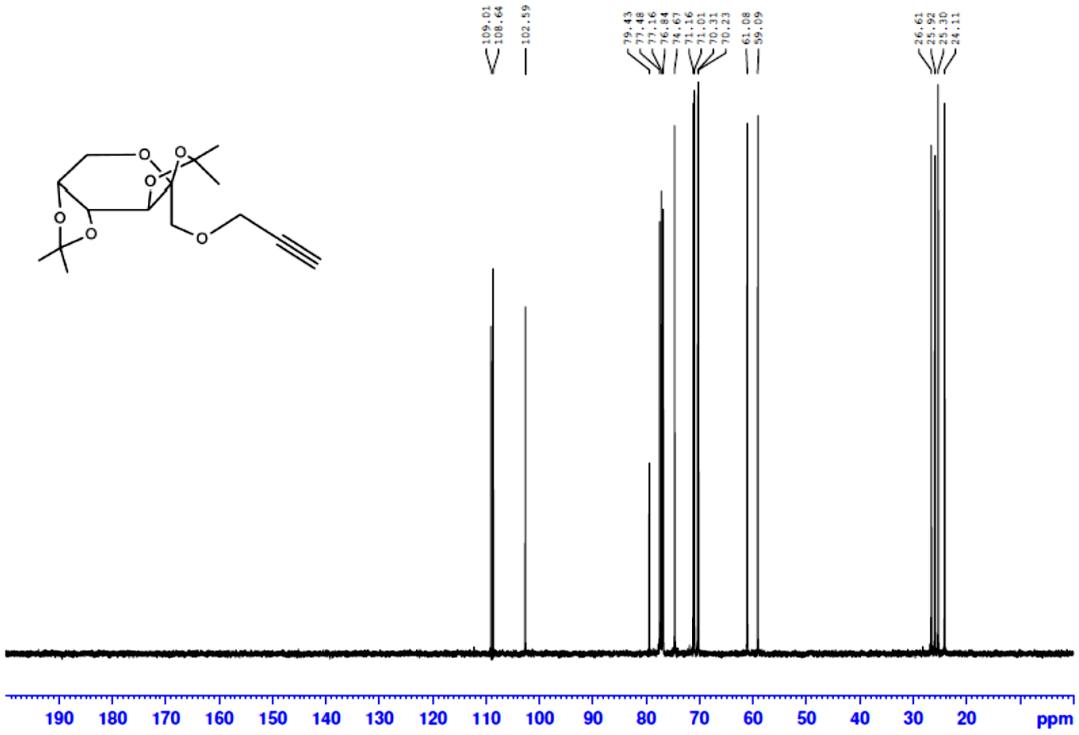


Figure 4: ^{13}C NMR spectrum of compound **4**

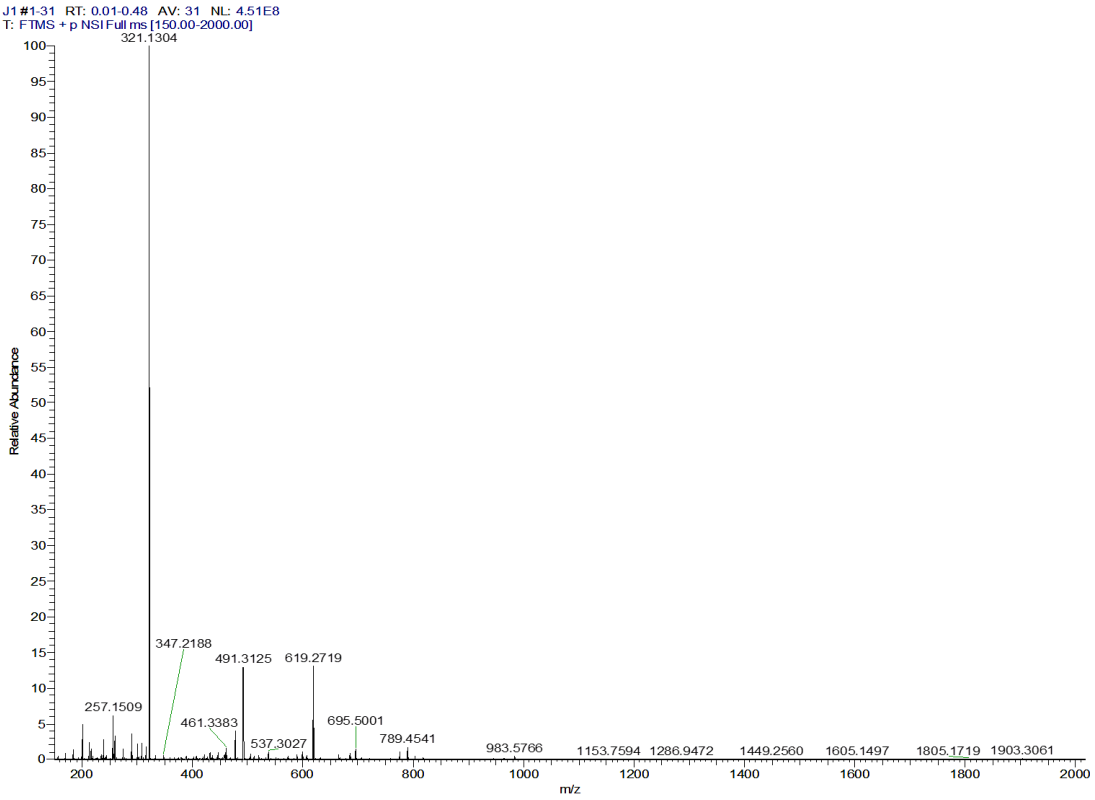


Figure 5: High resolution mass spectrum HRMS of compound **4**

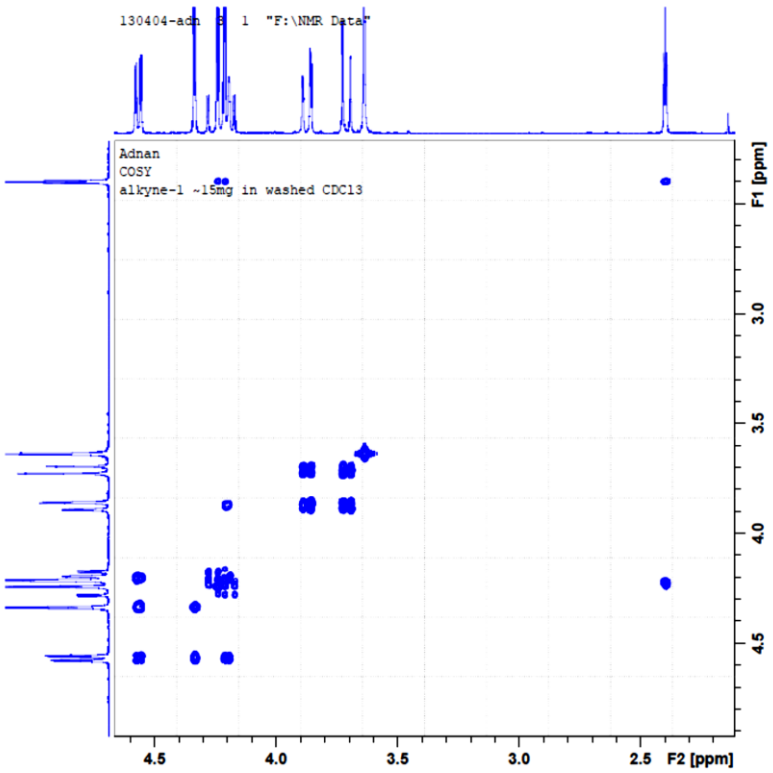


Figure 6: $^{1}H,^{1}H$ COSY of compound **4**

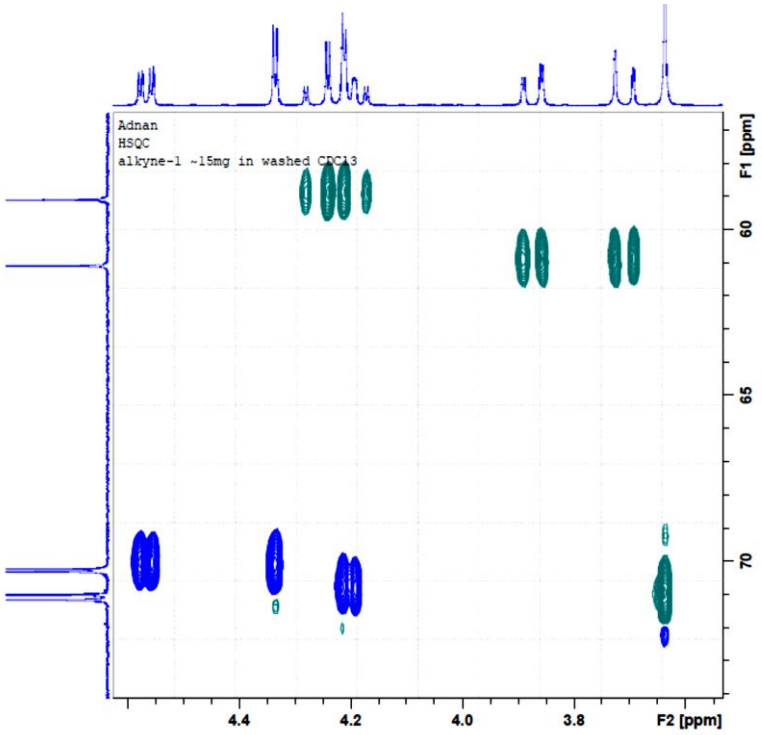
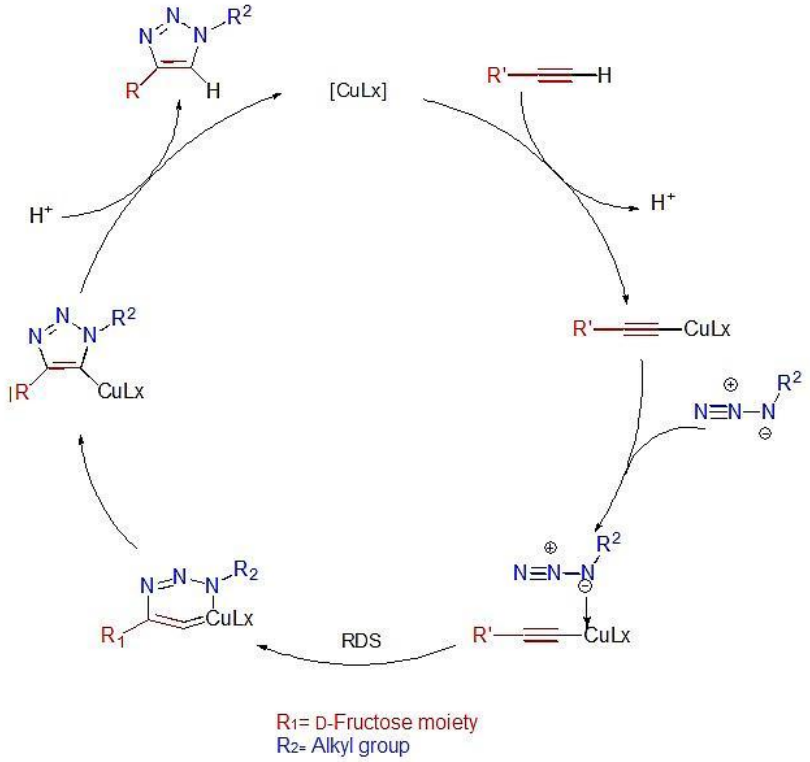


Figure 7: $^{1}H,^{13}C$ HSQC of compound **4**

Copper catalyzed cycloaddition reaction of compound **(4)** with alkyl azides **1a-d** yielded the D-fructose based 1,2,3-triazoles 5a-d followed the mechanism in scheme 2

[17]. Let us discuss the formation of compound 5a in details and the other derivatives are same with a simple difference in alkyl group.



Scheme 2: The mechanism of formation of 1,2,3-triazoles [17]

FTIR spectrum figure (8) of compound 5a showed the following significant bands: 3078 cm^{-1} (υ, C-H aromatic), 2955, 2924 and 2854 cm^{-1} (υ, C-H aliphatic) and 1649 (C=C aromatic).

^{1}H NMR spectrum figure (9) (400 MHz, $CDCl_3$) δ ppm: of 0.84 (t, *J* 6.7 z 3H, H7`), 1.23 (m, 8H, H3`-H6`), 1.29, 1.35, 1.39, 1.50 (s, 12H, -C***H*****$_3$**, isopropylidene), 1.85 (quin, *J* 7.4 Hz, 2H, H2`), 3.63 (dd, *J* 18.0, 10.7 Hz, 2H, H1``), 3.71 (d, *J* 13.0 Hz, 1H, Ha6``), 3.85 (dd, *J* 13.0, 1.8 Hz, 1H, Hb6``), 4.20 (dd, *J* 7.9, 1.0 Hz, 1H, H5``), 4.29 (t, *J* 7.2 Hz, 2H, H1`), 4.33 (d, *J* 2.6 Hz, 1H, H3``), 4.56 (dd, *J* 7.9, 2.6 Hz, 1H, H4``), 4.75 (dd, *J* 31.6, 12.5 Hz, 2H, C4-C***H*****$_2$**-O), 7.50 (s, 1H, H5) . ^{13}C NMR spectrum figure (10) (100 MHz, $CDCl_3$) δ ppm: 14.1 (C7`), 22.6 (C6`), 24.1, 25.4, 25.9, 26.6, (4C, -***C***H_3, isopropylidene), 26.5 (C5`or C4` or C3`), 28.7(C5`or C4` or C3`), 30.3 (C2`), 31.6 (C5`or C4` or C3`), 50.4 (C1`), 61.1 (C6``), 65.6 (C4-***C***$H_2$-O), 70.18 (C4``), 70.2 (C3``), 71.0 (C5``), 71.1 (C1``), 102.6 (C2``), 108.6, 109.0 [2C, ***C***$(CH_3)_2$, isopropylidene], 122.2 (C5), 145.0 (C4); HRMS (ESI) figure (11).

Calculated for $C_{25}H_{37}N_3O_6Na$ 462.2575 $[M+Na]^+$, found 462.2568. All the assignments are based on COSY figure (13) and HSQC figure (14).

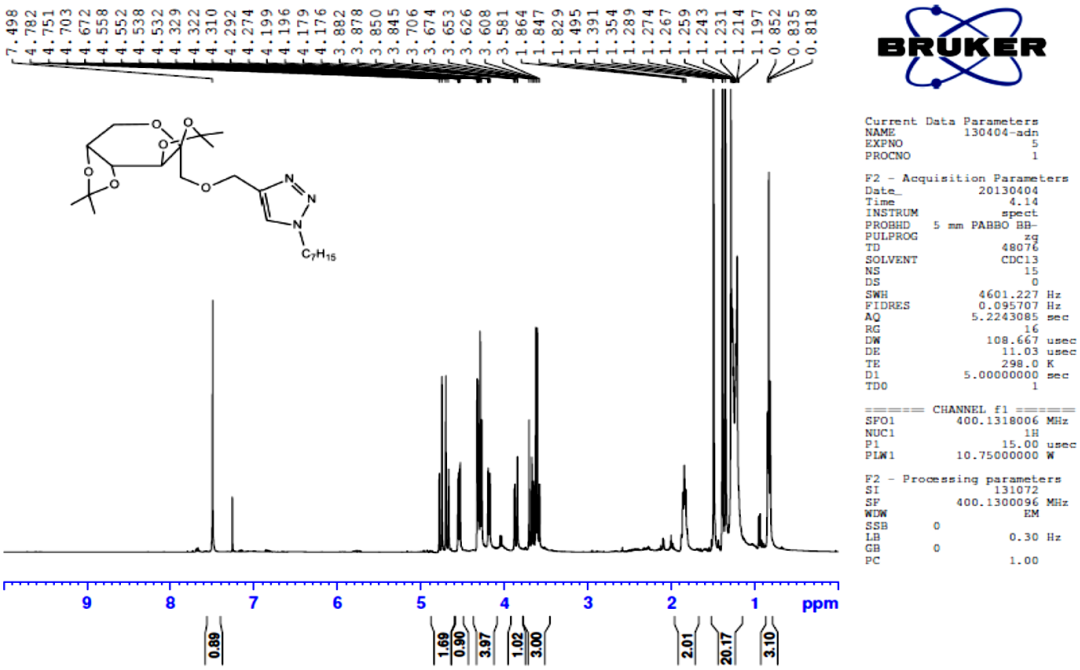


Figure 8: ^{1}H NMR spectrum of compound **5a**

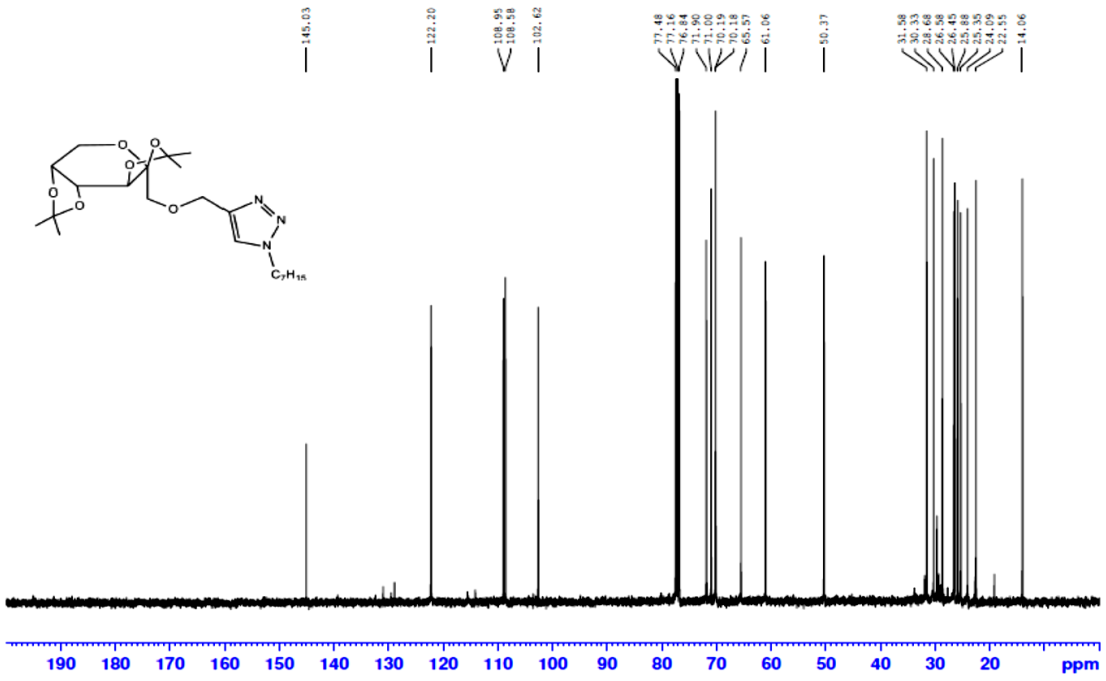


Figure 9: ^{13}C NMR spectrum of compound **5a**

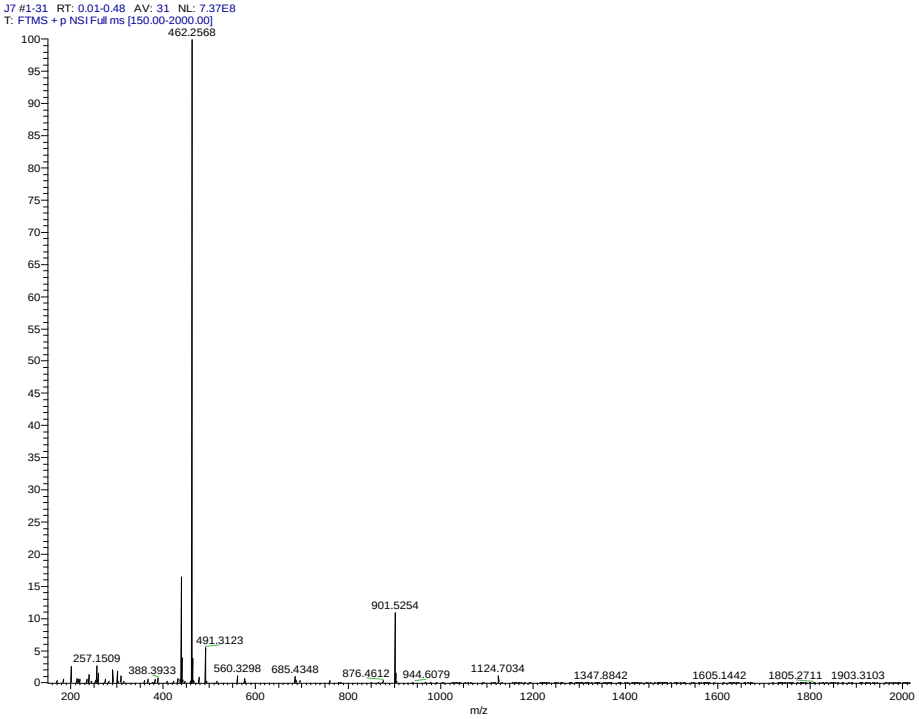


Figure 10: High resolution mass spectrum HRMS of compound **5a**

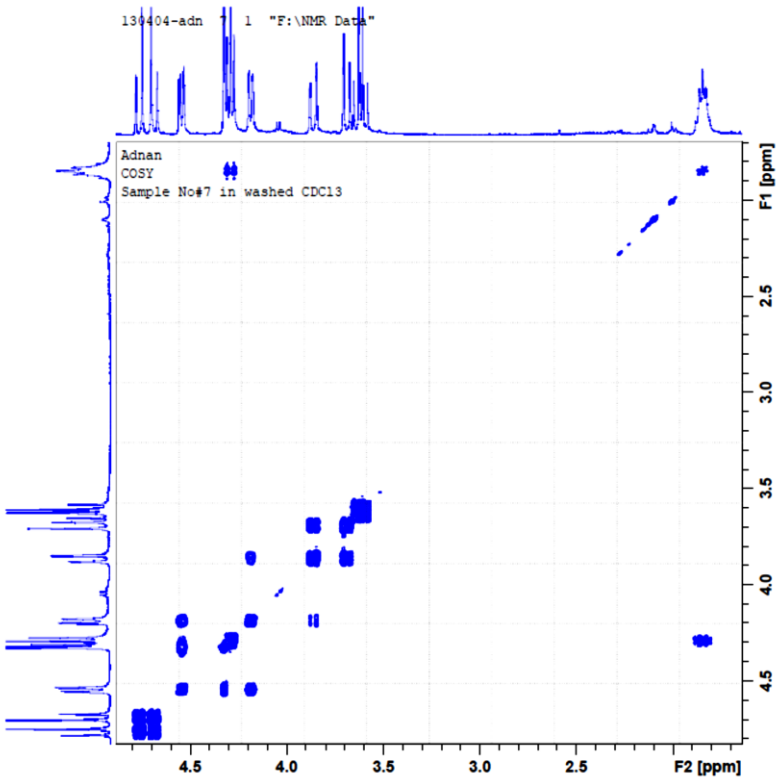


Figure 11: $^{1}H,^{1}H$ COSY of compound **5a**

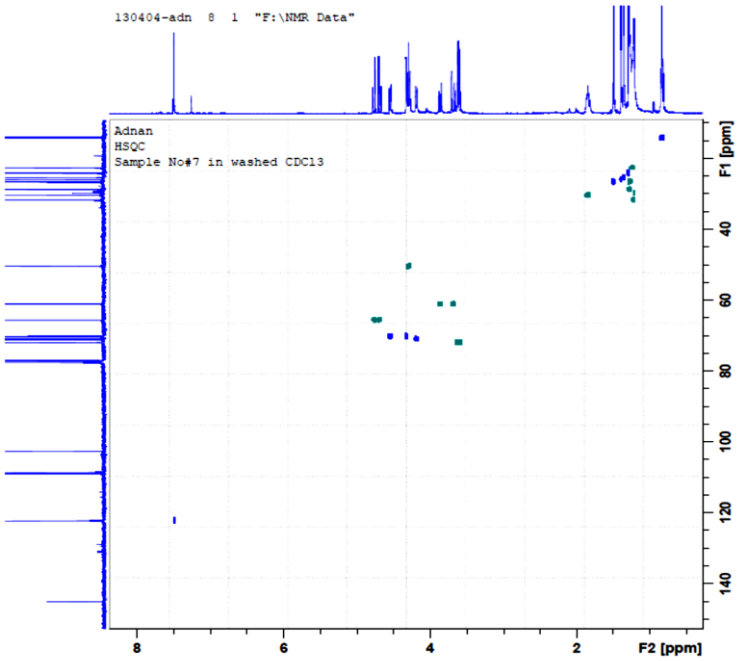


Figure 12: $^{1}H,^{13}C$ HSQC of compound **5a**

Table 1 summarize the important FTIR bands for the compounds 5a-d

Table 1 Important FTIR bands for compounds 5a-d

Compound	υ, C-H aromatic cm^{-1}	υ, C-H aliphatic cm^{-1}	υ, C=C aromatic cm^{-1}	υ, C-O cm^{-1}	C-H oop cm^{-1}
5a	3078	2955, 2924	1649	1211, 1072	893, 760, 675
5b	3140	2983, 2929	1656	1211, 1072	891, 758, 671
5c	3119	2953, 2922	1645	1211, 1070	889
5d	3140	2927, 2855	1595	1211, 1072	889, 758, 671

Table 2 showed the chemical formula, calculated and found molecular masses for compounds 5a-d.

Table 2 Chemical formula, calculated and found molecular masses for compounds 5a-d.

Compound	Mw+Na^+	Calculated Molecular Mass	Found Molecular Mass
5a	$C_{22}H_{37}N_3O_6Na$	462.2575	462.2568
5b	$C_{23}H_{39}N_3O_6Na$	476.2731	476.2725
5c	$C_{25}H_{43}N_3O_6Na$	504.3044	504.3038
5d	$C_{27}H_{47}N_3O_6Na$	532.3357	532.3350

Isopropylidene groups of compounds 5a-d were deprotected under acidic conditions using Amberlite IR 120 H^+ as catalyst in aqueous methanol. The broad band around 3400 cm^{-1} which attributed to the hydrogen bonded O-H stretching is a very good evidence of the deprotection. Table 3 illustrates the important FTIR bands for the compounds 6a-d

Table 3 Significant FTIR bands for compounds 6a-d

Compound	υ, O-H aromatic cm^{-1}	υ, C-H aliphatic cm^{-1}	υ, C=C aromatic cm^{-1}	υ, C-O cm^{-1}	C-H oop cm^{-1}
6a	3400	2943, 2873	1618	1219, 1072	869, 781, 609
6b	3390	2931, 2856	1622	1220, 1089	866, 779, 613
6c	3387	2926, 2856	1629	1217, 1076	829, 779, 617
6d	3404	2926, 2856	1629	1213, 1074	893, 779, 619

Table 4 Antibacterial activity of compounds 5a-d and 6a-d

Compound	Zone of inhibition in (mm), concentration (µg/mL)					
	G^+ *Staphylococcus*			G^- *Escherichia coli*		
	5	10	20	5	10	20
DMSO	-	-	-	-	-	-
Kanamycin	27	28	28	28	27	28

5a	-	02	04	-	02	05
5b	-	04	06	-	02	03
5c	-	04	07	-	03	05
5d	-	04	05	-	02	04
6a	-	03	05	-	03	03
6b	-	03	04	-	03	04
6c	-	04	06	-	05	10
6d	-	05	07	-	04	05

The antibacterial activity can be attributed on one hand to the triazole moiety which active in different biological field, on the other hand, the chirality of sugar moiety is an important reason for the inhibition as well as the overall synthesized molecules are mimics to the glycolipids because they contains both hydrophilic and lipophilic parts.

Table 5 Names and some properties of synthesized triazoles

Symbol	Name of compound	% Yield	R_f	$[\alpha]_D$
5a	1-Heptyl-4-[(2,3,4,5-di-*O*-isopropylidene-β-D-fructopyranos-O-yl)methyl]1*H*-1,2,3-triazole	76	0.22	+13.1
5b	1-Octyl-4-[(2,3,4,5-di-*O*-isopropylidene-β-D-fructopyranos-O-yl)methyl]1*H*-1,2,3-triazole	80	0.24	+9.8
5c	1-Decyl-4-[(2,3,4,5-di-*O*-isopropylidene-β-D-fructopyranos-O-yl)methyl]1*H*-1,2,3-triazole	81	0.28	+16.9
5d	1-Dodecyl-4-[(2,3,4,5-di-*O*-isopropylidene-β-D-fructopyranos-O-yl)methyl]1*H*-1,2,3-triazole	78	0.32	+22.7
6a	1-Heptyl-4-[(β -D-fructopyranos-O-yl)methyl]1H-1,2,3-triazole	88	0.09	+35.8
6b	1-Octyl-4-[(β -D-fructopyranos-O-yl)methyl]1H-1,2,3-triazole	85	0.15	+44.7
6c	1-Decyl-4-[(β -D-fructopyranos-O-yl)methyl]1H-1,2,3-triazole	81	0.20	+16.1
6d	1-Dodecyl-4-[(β -D-fructopyranos-O-yl)methyl]1H-1,2,3-triazole	86	0.24	+28.5

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