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Synthesis, Characterization and Antibacterial Activity of Surfactants Containing Alkyl-Sugar 1,4-Disubstituted Triazoles

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Abstract

Two surfactants containing alkyl-sugar 1,4-disubstituted triazoles glycoconjugates were synthesized via Cu(I) catalyzed click conditions between azido alkane(C7,C8) and D-mannose based bis –*O*- propynyl ether. The latter was prepared via Williamson etherification between propargyl bromide and the2C-branched-D-mannose diacetonide which was synthesized in a previous work by aldol condensation between formaldehyde and the protected sugar in MeOH. The two surfactants have been examined in vitro by inhibition of bacteria growth (*Escherichia coli* and *staphylococcus aureus*) and showed a moderate activity. The two prepared surfactants were purified by column chromatography and identified by TLC, FTIR, ^{1}HNMR , ^{13}CNMR, 2D-NMR correlation COSY and HSQC.

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تحضير, تشخيص وفحص الفعالية المضادة للبكتريا لمنشطات السطح المتضمنة الكيل - سكر -1,4- ترايازول ثنائي التعويض

لمياء صالح مهدي

تم تحضير اثنين من المواد الخافضة للتوتر السطحي التي تحتوي على ألكيل-سكر 1،4- ترياز ولات جليكوكونجاتس عبر ظروف تفاعلات النقرة المحفزة بالنحاس (I) بين أزيدو ألكان (C7)، (C8) وإيثر بروبينيل ثنائي -O-المانوز. تم تحضير الأخير عن طريق تفاعل ويليامسون لتحضير الايثر بين بروميد البروبارجيل وثنائي أسيتونيد المانوز المتفرع 2 C والذي تم تحضيره في عمل سابق عن طريق تكثيف الألدول بين الفورمالديهايد والسكر المحمي فيMeOH . .تم فحص المادتين الخافضة للتوتر السطحي في المختبر عن طريق تثبيط نمو البكتيريا ((*Escherichia coli* and *staphylococcus aureus*)**) وأظهرتا نشاطاً معتدلاً. تمت تنقية المواد الخافضة للتوتر السطحي المحضرة بواسطة كروماتوجرافيا العمود وتم تشخيصها بواسطةTLC ، FTIR، ^{1}HNMR، ^{13}CNMR،و 2D-NMR (COZY , HSQC)**

1. Introduction

Surfactant substances have two groups contrary in nature, one of them is hydrophilic and soluble in the aqueous solution but the other is hydrophobic and soluble in the organic solution.(J., Agrawal and Sahariah, 2024) These Surface active molecules known as surfactants allow the gas, liquid and solid materials to suspended or spread freely, such as emulsions in water or other liquids, by lowering surface and interfacial tension at their interfaces. (Banjare and Banjare, 2024)Surface molecules also have an amphibious arrangement that provides attractiveness for both oil and water. Researchers have been studying surfactants for a long time because of their potential uses in medicine, biology, industry, and chemistry.(Morales, Peters and Williams, 2011),(Ismail, Shahruddin and Othman, 2022),(da Silva and Sarubbo, 2022)(Begum, Saha and Mandal, 2023),(Aguirre-Ramírez *et al.*, 2021) A variety of biological properties, including antibacterial (Soliman, 2023) and anti-inflammatory effects are associated with surfactants, (Lu, 2020), (Willson, 2015), antioxidant (Ng *et al.*, 2020)antiviral (Isasi-Campillo *et al.*, 2023) anti-cancer , in addition Pain relieving procedures.(Wei *et al.*, 2024). The heterocyclic ring 1,2,3-Triazole play a specific ligation tool to link two portions , sugar with alkyl chain *via* CUAA cycloaddition reaction. The sugar portion is hydrophilic and soluble in aqueous or polar solution. While the other portion is hydrophobic, that is soluble in the oily or non-polar mediums but insoluble in the polar solution.(Ng, Mazlee and Heidelberg, 2021) The amphipathic resultant sugar based molecule called as 1,2,3-glycocongugates has a surfactant features thus it plays a potential role in the manufacturing and designing the industrial and many important products such as cosmetics, paints, paper produces, detergents and paints .(Mohammed, Abboud and Alghanimi, 2012),(Piispanen *et al.*, 2004), (Piispanen, 2002). Since many FDA approved chemotherapeutic drugs consist of the 1,2,3-triazole nucleus have been incorporated into many compounds as antibacterial drugs; tazobactam (Higashitani *et al.*, 1990), anticancer;(Govindarajan, 2018) Carboxyamido-triazole (CAI), anti-Alzheimer; MTSMDL therapy, anti-HIV; TSAO treatment, antibiotic; cefatrizine.(Neu and Fu, 1979) Also the 1,2,3-triazole derivatives play superior rule as antibacterial, antiviral, antimalarial, and antifungal agent, (Deshmukh *et al.*, 2021)so they became known to be an interesting scaffold in Drug design.(Begum, Saha and Mandal, 2023) Click chemistry is a powerful, modular and green approach that a warded two noble prizes for their inventors *B.Sharpless, M.Meldal* in 2001 and the developer *C.Bertozzi* and *M.Meldal* in 2022.(Kiessling, 2023) Mohammed *et al*. (Mohammed, Mansour and Mahdi, 2017), (MOHAMMED *et al.*, 2013)synthesized and biological evaluated of group of glycocongugated 1,2,3-triazoles scaffold on variety of sugars bounded to terminal alkyne or azide fraction catalyzed by Copper (I) Azide/Alkyne-click CUAA cycloaddition reaction. In the current work, new surfactants bis -1,2,3-triazole derivatives based on D-mannose were prepared *via* a green protocol click strategies and their structural conformation was confirmed. Also, the biological properties against bacteria (*Escherichia coli*, *Staphylococcus aureus*) were verified.

2. Material and Method

2.1. Preparation of The Chemical Compounds

The chemical compounds were bought from Alpha –Aesar and Sigma –Aldrich. SHIMADZU 2001 FT-IR was employed to obtain the infrared spectra. Bruker DPX 600MHz spectrometer was using to verify NMR spectra which assigned the target molecules assisted by ^{1}H, ^{1}H- COSY and $^{1}H,^{13}C$-HSQC. HRMS were verified *via* (Orbit rap LTQ-

XL) Ion trap in positive ion mode utilizing electrospray ionization source (ESI) . All reactions were observed using silica plates TLC with aluminum backing of (0.2 mm, 60 F254) and the TLC sheets were visualized by development with alkaline potassium permanganate solution dip.

2.1.1. Synthesis procedure of 2*C*- (methylenoxy) -2, 3: 5, 6-di –*O*- isopropylidene – D- mannofuranosyl bis-*O*-[(1- alkyl- 1*H*- 1, 2, 3- triazolyl - 4-yl) methyl)] ether (Mohammed, Abboud and Alghanimi, 2012)**.**

Solution of the dipropargyl ether (2*C* (methylenoxy)- 2,3 : 5, 6- di-O- isopropylidene D-mannofuranosyl bis propargyl ether **2** that was prepared according to a previous work,(Mahdi, Mohammed and Mohammed, 2020) (0.732 g, 2mmol.) in dimethyl sulphixide added dropwise to solution of $CuSO_4.5H_2O$ (0.05, 0.02 mmoles) and sodium ascorbate (0.0792 g, 0.4 mmol) , the resultant mixture stirred for 2 min. at room tempriture . Prepared azides **a** and **b** (2.1mmole) added wisely to the reaction mixture then the mixture heated to 65 ˚C for 48 hours. The reaction mixture diluted with dist.water 50 ml , then shaked three times with Ethyl acetate (100mL).The organic three layers were combined, washed with the brine solution (100mL), dried with the sodium sulphate anhydrous , then finally the solvent was evaporated to give the product 3a and 3b as a pale yellow oily compounds. The products **2a** and **2b** were purified by column chromatography (silica gel; n-Hexane :Ethyl acetate),(2:1 to 1: 2) to produce the target molecules.

2.1.2. 2*C* - (methylenoxy) -2, 3: 5, 6- di-*O*-isopropyledine- D- mannofuranos yl- bis –*O*- [(1- heptyl- 1*H*- 1, 2, 3 – triazole – 4 –yl) methyl)] Ether 2a

Solid white (1.15 g, 87 %) : mp. (45- 47 ˚C), R*f* = 0.65 (ethyl acetate). FT-IR (KBr) : 3136, 2924, 2855, 1464, 1375, 1247, 1219, 1148, 1076, 891, 835, 785, 723, 515cm-1, 1HNMR (600 MH, CDCl3) δ ppm : [7.5 (s, 1 H; ***H***- Ar – triazole), 7.26 (s,1 H ; ***H***- Ar- triazole), 5.08 (s, 1 H; ***H*** – 1), 4.82 (d , J = 12.6 Hz , 2 H; - O- *C****H***$_2$- triazole) , 4.69 (d, J = 12.6 Hz, 2 H; -O- C***H***$_2$- triazole) , 4.60 (d, J= 2.4 Hz ; 1 H , ***H*** - 3) , 4.4(ddd, J = 7.2 ; 1 H, **H** – 5) , 4.34 (broad q, J = 7.2 Hz , 4 H; C***H***$_2$N-Ar-triazole-1`), 4.11 (dd, J= 6.6 Hz , 1 H; ***H*** – 6a) , 4.00 (dd, J= 7.2 , 6.0 Hz , 1 H; ***H***- 6b) , 3.98 (dd, J= 12..0 Hz , 3.0 , 1 H; ***H*** – 4), 3.90 (dd, J = 12 Hz , 1 H; C***H***$_2$–O–; 2``), 3.84 ( d, J= 12.0Hz , 1 H , C***H***$_2$–O–; 2``), 1.90 , 1.88 (m , 4 H; C***H***$_2$ –alkyl-2`), 1.45 , 1.43, 1.40, 1.35 (s,12 H; 4× (–C(C***H***$_3$)), 1.32-1.25 (m, 16 H; 8 × ( C***H***2 – alkyl-3`-6`), 0.87 (t, *J* = 4.8 Hz, 6 H, 2× ( -C***H***3- alkyl -7`)]. ^{13}CNMR (150 MHz , CDCl3) ; δ ppm : [144.1 (2× ***C***- Ar – triazole) , 122.8 (2 × ***C***-Ar-triazole), 114.0 (- ***C*** (CH3)$_2$), 109.4 (-***C*** (CH3)$_2$), 108.1(***C*** – 1) , 94.3 (***C*** – 2) , 82.7 (***C*** – 3) , 81.4 (***C*** – 4) , 73.1 (***C*** – 5) , 67.0 (– ***C***H2-O- ; ***C***-2``) , 66.9 (***C*** – 6), 63.5 , 61.2 (2 ×C ; (O - ***C***H$_2$ - Ar- triazole) , 50.6 , 50.5 (2 × C ; ***C*** - 1`) , 31.8, 30.4 , 29.2, 29.1 , 29.0 , 28.7, ( 6× C; ***C***H$_2$ – ( 2`- 4`) , 27.6, 27.5, 26.6 , 26.1 (4× (–C(**C**H$_3$)$_2$ ), 25.3, 22.6 ( 4× C ; ( ***C***H2 – (5`- 6`) , 14.1 ( 2 × C; ( ***C***H2 –7`) . HRMS – ESI ; [M+ Na+] = 671.4103 theoretical value for $C_{33}H_{56}N_6O_7Na$ and 671.4098 experimentally found .

2.1.3. 2*C* - (methylenoxy) -2, 3 : 5, 6 - di-*O*-isopropyledine –D - mannofuranos yl- bis –*O*- [(1- Octyl - 1*H*- 1,2, 3- triazole- 4-yl) methyl)] ether 2b

Solid white (1.15g, 85%); mp : (46 – 48 ˚C) , R*F* = 0.63 (Ethyl acetate) , FT – IR ; (KBr) 3122,3086, 2928, 2860, 1458, 1375, 1223, 1105, 1039, 945, 846, 704, 604, 569 cm-1 , ^{1}HNMR (600 MH, CDCl3) δ ppm : [7.45 (s, 1H ; ***H*** – Ar- triazole) , 7.62 (s, 1 H ; ***H*** – Ar-triazole) 5.10 (s, 1 H ; ***H*** – 1) , 4.82 (d, J = 12.6 Hz , 2 H ; - O- C***H***$_2$- triazole) , 4.68 (d, J = 4.68 (d, *J* = 12.6 Hz , 2 H ; - O- C***H***$_2$- triazole) , 4.6 (d, J = 3.0 Hz , 1 H ; ***H*** – 3) , 4.4 (ddd,

J = 6.6, 3.0, 1.8 Hz , 1 H ; ***H*** – 5) , 4.33 (broud q , J = 7.2 Hz , 4 H ; C***H***$_2$ – N- Ar-triazole-1`) , triazole), 4.11 ( dd , J = 6.6, 2.4 Hz , 1 H ; ***H*** – 6a ) , 4.0 ( dd, J = 6.6, 3 Hz , 1 H ; ***H*** – 6b ) , 3.90 (dd, J = 12.0, 2.4 `Hz 1 H ; ***H*** – 4) , 3.78 (d, J = 12.0 Hz , 2 H ; (d, *J* = 12 Hz, 2H ; (C***H***$_2$–O–; 2``)) , 1.89 , 1.87 (m, 4 H ; C***H***2 – alkyl- 2`) , 1.44 , 1.43 , 1.40, 1.36 (s,12H, 4×(–C(***C***H$_3$)), 1.30 -1.24 ( m , 20 H, 10 × ( ***C***H$_2$ – alkyl- 3` – 7` ) , 0.87 ( t , J = 6.6 Hz , 6 H ; 2× ( C***H***$_3$ –alkyl – 8`) . ^{13}CNMR (150 MHz , CDCl3) ; δ ppm : [144.9 (***C*** – Ar-triazole), 144.3 (***C*** – Ar-triazole) , 122.8 (***C*** – Ar-triazole) , 122.7 (C – Ar-triazole) , 114.5 (- ***C*** (CH3)$_2$) , 109.4 (- ***C*** (CH$_3$)$_2$) , 106.8 (***C*** – 1) , 94.5 (C – 2) , 82.7 (C – 3) , 80.6 (C – 4) , 73.1 (C – 5) , 69.8 (- ***C***H2 -O- ; 2``) , 67.1 (***C*** – 6) , 65.4 , 61.2 (2× C ; -O- ***C***H2- Ar-triazole), 50.6 , 50.5 (2× C(***C*** - 1`) Alkyl ) , 31.8 , 30.4 , 29.2 , 29.1 ( 4C ; ***C*** – 2` , 3` ) , 27.8 , 27.6 , 72.5 , 27.4 ( 4 × C ; - C (***C***H$_3$)$_2$) , 27.1 – 22.7 ( 4 C ; ***C***H$_2$ –alkyl (4` - 7`)) , 14.2 ( 2 × C ; ***C***H$_2$- alkyl-8`) . HR MS – ESI ; [M+ Na] + =699.4416 theoretical value for $C_{35}H_{60}N_6O_7Na$ and 699.4417 experimentally found.

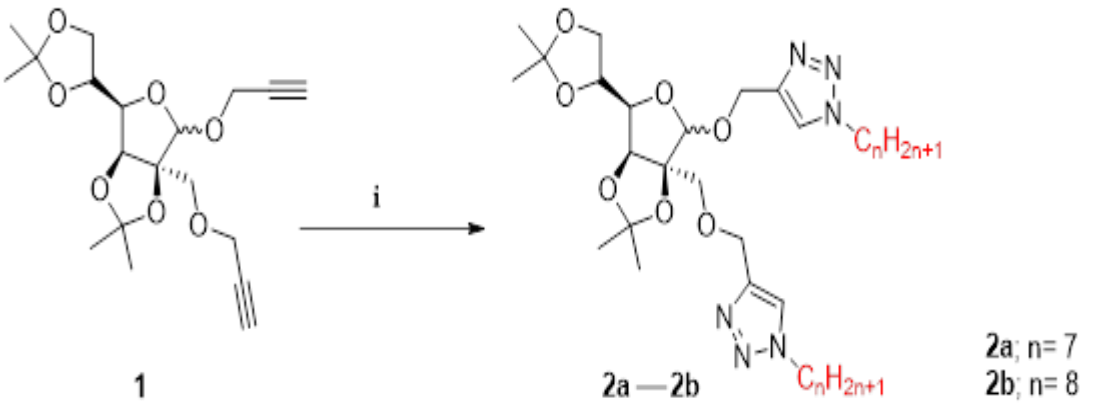
2.2. Antibacterial Activity

The antibacterial activity has been confirmed for the prepared **2a** and **2b**. To preparing bacterial suspension, two to three similar phenotypic characteristics colonies of Gram-positive bacteria like *Staphylococcus aureus* and Grame negative bacteria like *Escherichia coli* growing on Blood Agar medium have been transferred to tubes coated with crystalline saline solution. The bacterial suspension turbidity was adjusted by using VITEK DENSY CHECK from (bioMérieux) was used to adjusted the bacterial suspension turbidity to match (0.5) MacFarland standard. Antibacterial activities of surfactants **2a-2b** was tested in four concentrations of 50, 100 , 200, 400 μg/mL. Next spreading (0.1) ml of bacterial suspension on the Muller Hinton Agar medium by using cotton swab, then leave it for drying at 37ºC for half an hour. Then, a sterile crock borer used to make wells of (6 mm) in diameter under septic conditions. Followed by adding 60 μL of the tested compounds and incubated at 37ºC for 24 hours. DMSO and antibiotics discs such as (Levofloxacin and Amikacin) were used as a control in this study. The inhibitions zones were measured and the interpretation of the results were done according to CLSI.

3. Results and Discussions

Glycosides mimics' compounds similar to surfactants have two moieties as dipole entity that serve particular role in drug design and discovery of pharmaceuticals and medications. D-mannose Synthesis of **2*C* – (methylenoxy)- 2, 3 : 5, 6 – di – *O*- isopropyledine – D- mannofuranosyl bis – *O*- [(1- alkyl – 1 H 1, 2, 3, - triazole – 4 – yl)methyl] ether** was verified via click reaction. The reaction route is shown in Fig.1. The starting material terminal bisalkyne was firstly prepared from previous work that introduced by L.Mahdi *et.al.* 2020.(Mahdi, Mohammed and Mohammed, 2023) The sugar mannose protected with two isopropyledine groups from acetone using conc.H_2SO_4 as catalyst at 24 ˚C and stirred for 4 h. to produce the 2, 3: 5, 6- di- *O*- isopropyledine – D- mannose in two isomers α and β mixture. Then the protected sugar was reacted with aq.HCOH in a basic solution of KOH and K_2CO_3 *via* aldol reaction to yield the brunched sugar 2*C* - (methylenoxy)- 2, 3: 5, 6 -di – *O* - D -mannofuranos with second quaternary carbon center.(Tan *et al.*, 2016) The last diole brunched sugar was reacted with propargyl bromide and catalyzed with sodium hydroxide heterogeneously in DMF solution by Williamson etherification to give the precursor 2*C* - (methylenoxy)- 2, 3 : 5, 6 - di – O-isopropyledine – D - mannofuranosyl propargyl ether **1**.(Mahdi, Mohammed and Mohammed, 2020) The other precursors also prepared from S_N2 nucleophilic substitution reaction of n-heptyl

and n-octyl bromide with sodium azide to produce the corresponding n-heptyl and n-octyl azide (a and b) from a previous work.(Francis *et al.*, 2011) Finally, regioselective surfactants 2*C* - (methylenoxy)- 2, 3 : 5, 6 - di – *O* - isopropyledine – D- mannofuranosyl bis [(1 - alkyl –1 *H*- 1, 2, 3 – triazole – 4-yl) methyl)] Ether **2a** and **2b** were achieved by cupper (I) catalyzed Azide/ Alkyne - 1,3- dipolarcycloaddition reactions between the mannose based- bis alkyne **1** and the alkyle azides **a** and **b** catalyzed in situ with hydrated copper sulphate and sodium ascorbate to afford the target molecules D-mannose based bis – 1, 2, 3- triazole **2a** and **2b** in very good yields 85% and 87%. The structures of these surfactants were studied and detected by FTIR, ^{1}HNMR, ^{13}CNMR, 2 D –NMR and HR MS - ESI. The surfactants 2a and 2b is numbering as shown below to facilitate verifying of NMR spectra. The important ^{1}H NMR signals was the singlet at 7.5, 7.26 and 7.45, 7.26 ppm which definitely owed to 2H-Triazole ring for **2a** and **2b** prospectively, (Fig.2, Fig.3 and Fig.8). Spectra of ^{13}C-NMR also confirmed the structural skeletal formula of the surfactants bistriazoles. Signals at 144.1, 122.8 as well as 144.3, 122.8 ppm were referred to 2C of (**C**H=**C**N-) of bistriazole rings of the compounds **2a** and **2b** consequently, (Fig.4 and Fig.9). The interpretations of ^{1}H NMR, ^{13}C NMR were established to the 2D NMR, COSY and HSQC, (Fig.5, Fig.6, Fig.10 and Fig.11). HRMS-ESI base peaks according to the formula $[M^{+}Na]^{+}$ were appeared at m/z 671.4098 and 699.4417 in HRMS assigned to compounds **2a** and **2b** consequently as presented in Fig.8.



Reagents and conditions: i] a;$C_7H_{15}N_3$ and b; $C_8H_{17}N_3$, CuSO4.5H2O, Na ascorbate, DMSO, 70 °C, 48h

Figure 1: Synthesis of the surfactants D – mannofuranosyl bis – 1, 2, 3- triazole **2a – 2b**

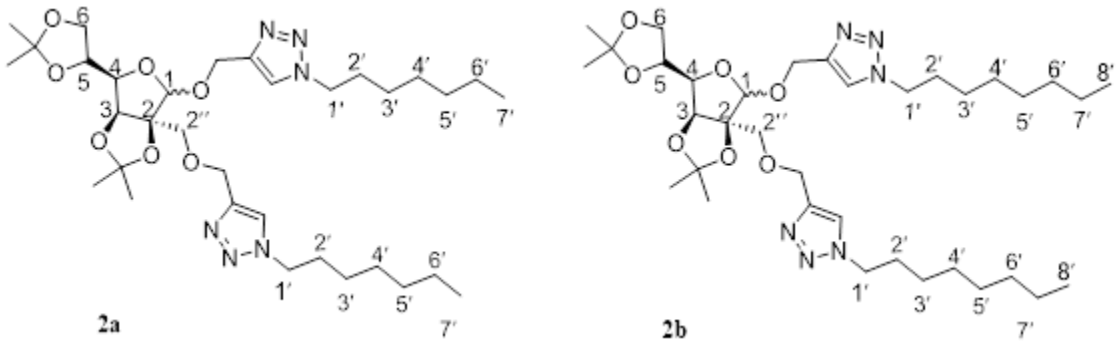


Figure 2: Labeling of surfactants 2**a** and **2b**

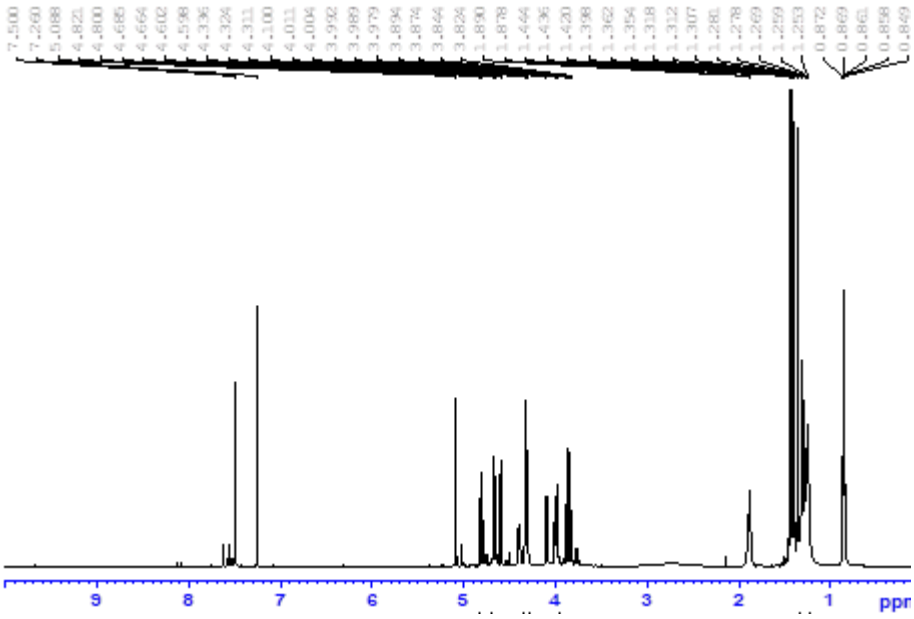


Figure 3: ^{1}H NMR spectrum (CDCl3, 600 MHz) of **2a**

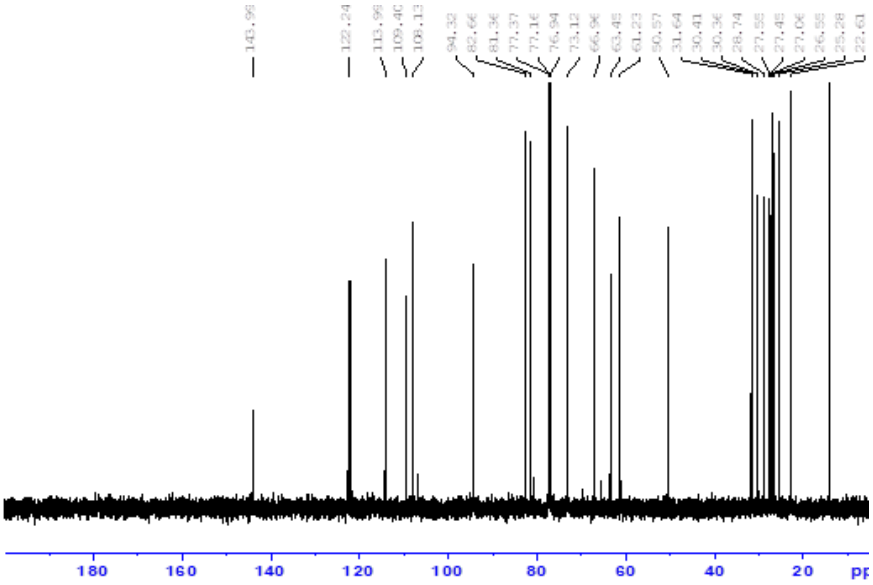


Figure 4: ^{13}C-NMR spectrum (150 MHz, CDCl3) for **2a**

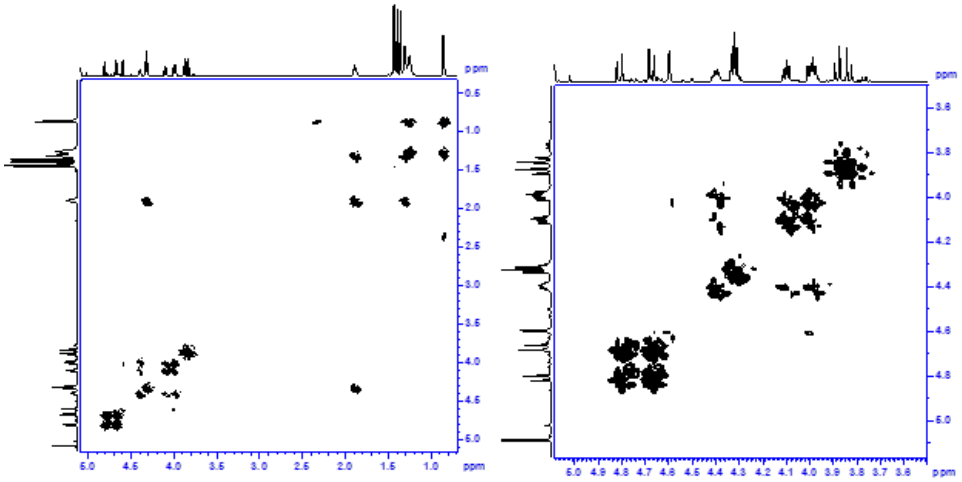


Figure 5: ^{1}H, ^{1}H Cosy and the expansion of ^{1}H, ^{1}H Cosy of **2a**

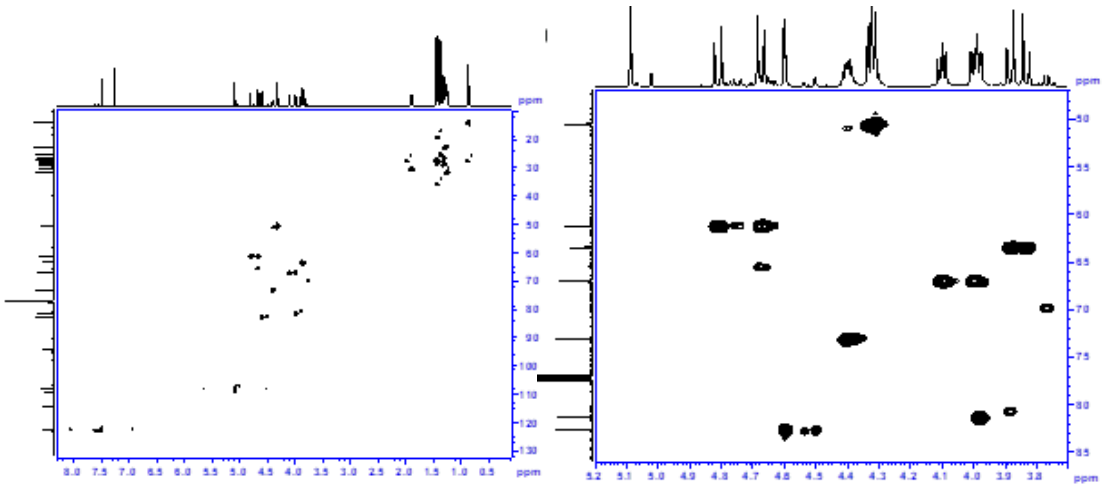


Figure 6: ^{1}H, ^{13}C HSQC and the expansion ^{1}H, ^{13}C HSQC of **2a**

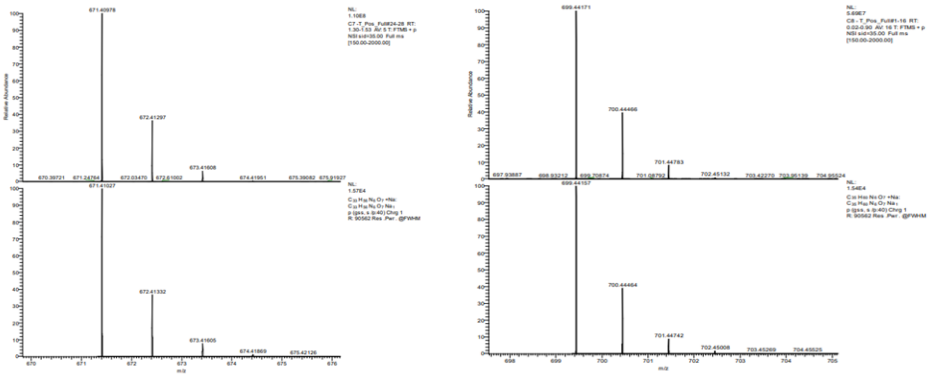


Figure 7: HRMS-ESI of **2a** and **2b**

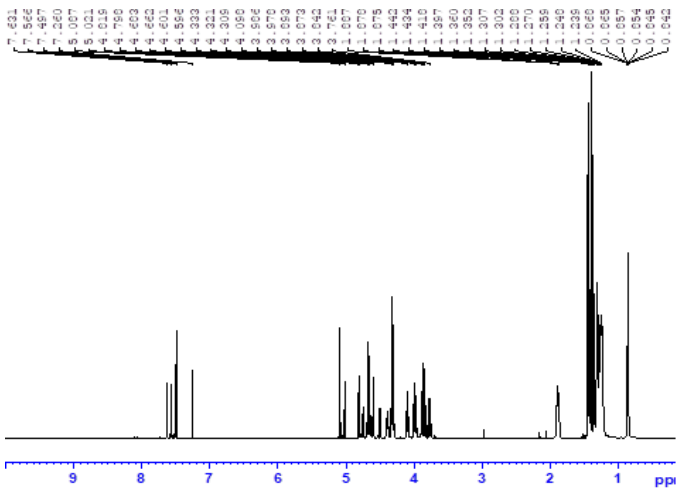


Figure 8: [1]H NMR spectrum (CDCl3, 600 MHz) of **2b**

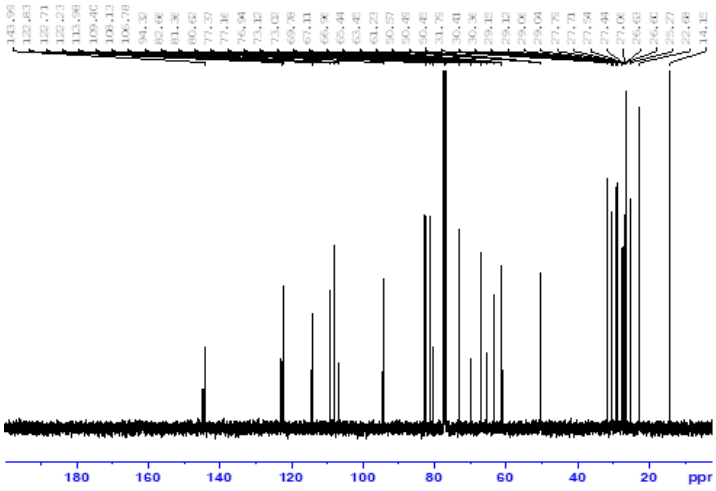


Figure 9: [13]CNMR - spectrum (150 MHz, CDCl3) of **2b**

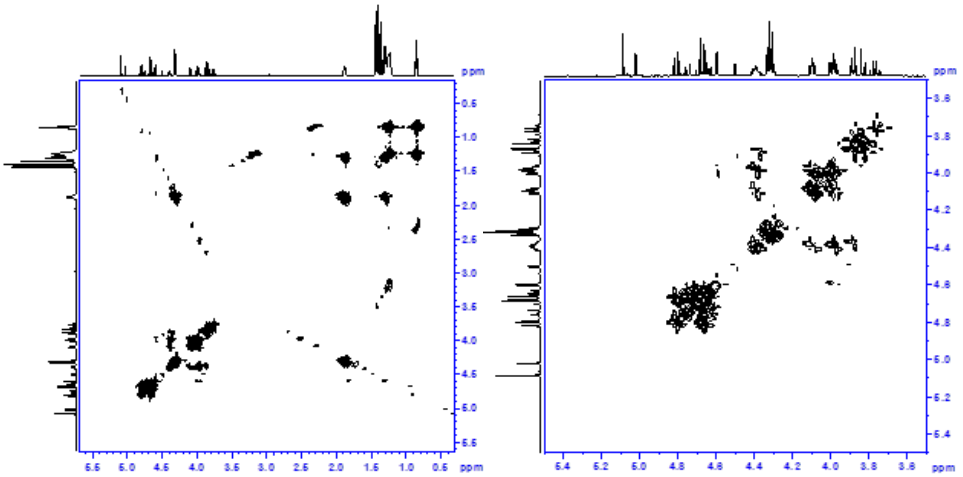


Figure 10: ^{1}H, ^{1}H Cosy and the expansion of ^{1}H, ^{1}H Cosy of **2b**

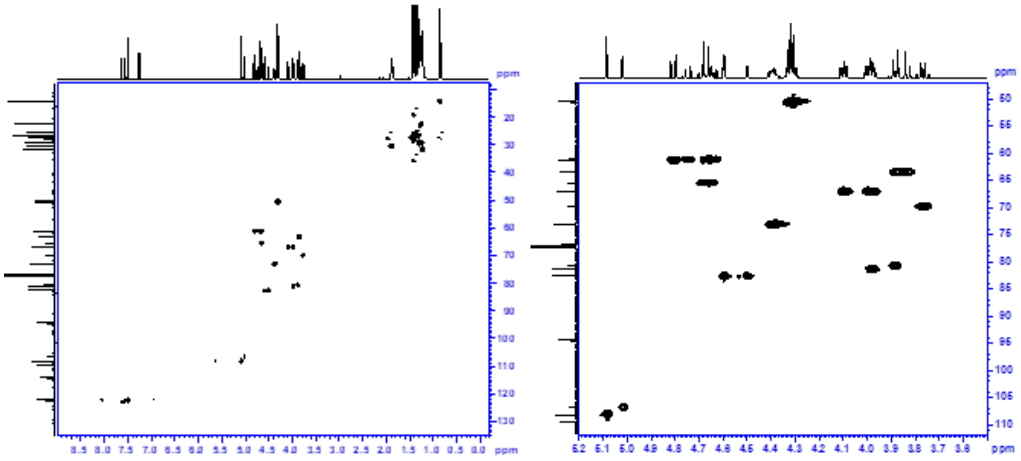


Figure 11: ^{1}H, ^{13}C HSQC and the expansion ^{1}H, ^{13}C HSQC of **2b**

Antibacterial Activities

The targets surfactants **2a** and **2b** were tested against bacteria gram – positive *S.aureus* and gram- negative *E. coli* by using Agar - diffusion well method , Table 1. The compound **2a** and **2b** exhibit good to very good inhibition activities toward gram-negative bacteria like E.*coli* at concentration 50 µg /mL . There was no inhibition activities noticed against gram - positive bacteria like S.*aureus* . these synthesized compounds are a model of non-ionic Gemini surfactants sugar derivative type.(Lu, 2020) The suggested antimicrobial mechanism of the Gemini surfactants depends on the molecular affinity of the cell membrane which consists mainly of phospholipid as referred in the Table1. These compounds may be changed the bacteria cell membrane permeability so forming ion channels through the pores causing nutrients and gas exchange disorder then cell death. (Wei *et al.*, 2024).

Table 1: Antibacterial Potency of The Compounds 2a and 2b

Gram – positive *S. aureus* bacteria Inhibition zone (mm)					Gram - negative E. *coli* bacteria Inhibition zone (mm)			
Concentration µg / ml	50	100	200	400	50	100	200	400
DMSO	0	0	0	0	0	0	0	0
2a	0	0	0	0	15	14	14	14
2b	0	0	0	0	18	16	14	15
Levofloxacine	23				25			
Amikacine	18				14			

4. Conclusion

Surfactants D-mannose based-1,2,3-bis triazoles deravatives (**2a** and **2b**) have been synthesized via click strategies between D-manofuranosyl bis alkyne and alkyl azides which catalyzed with $CuSO_4$. $5H_2O$ and Na- ascorbate that using particularly CUAA cycloaddition reaction conditions. The two surfactants completely characterized by advanced spectroscopic techniques. The surfactants **2a – 2b** examined toward gram – positive like S. *aureus* as well as gram – negative like *E. coli*. The targets **2a- 2b** showed very good activities 15 and 18 mm inhibition zone respectively of (50 µg /mL) concentration , toward gram –negative while have not potency toward gram - posetive bacteria *S. aureus.*

5. Acknowledgment

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