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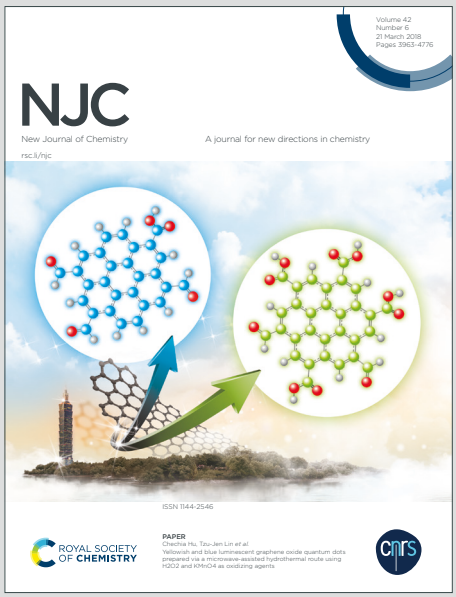

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COMMUNICATION

Click inspired Synthesis of Hexa and Octadecavalent Peripheral Galactosylated Glycodendrimer and their Possible Therapeutic Applications

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Cu(I)-Catalyzed azide-alkyne 1,3-dipolar cycloaddition reaction (CuAAC) has been utilized for the synthesis of novel glycodendrimers containing rigid hexapropargyloxy benzene centered core with 6- and 18-peripheral β-D-galactopyranosidic units. Structures of novel glycodendrimers and intermediates are well elucidated by NMR spectroscopy, MALDI-TOF MS, IR and SEC analysis. The therapeutic evaluations of developed glycodendrimers were investigated and found potentially good as anti-bacterial, anti-biofilm, and anti-tumour agent.

Introduction

Dendrimers are well-known to possess in general high monodispersity, good biocompatibility, multivalency, and high pharmacokinetics. Moreover, the synthesis of the exactly controllable size of dendrimers by only deciding the number of generation, charge, and dimension of the molecule as biological system can be possible with various easy synthetic methods.[1] These properties of dendrimers make them interesting for the further detailed investigation.[1-3] Carbohydrates are fundamental entities to sustain and nurture the living system. Since long back, carbohydrates and their derivatives have been widely explored in a different area of science ranging from chemical biology to catalysis and medicinal chemistry to material science.[4] Dendritic sugar architectures modulate a wide array of biological phenomena, which may be due to either specific recognition of functional motif(s) directly by the glycodendrimers or they self-assemble on the molecular scaffolds as and when needed.[5] This is evidenced by the fact that multivalent carbohydrate-protein interactions are pivotal in the majority of biological recognition and dissemination/ transduction processes, for instance, surface sensing and adhesion by the bacteria and virus, drug effectors modalities, immunological cascades, cellular interactions, cell cycle regulation and differentiation, and cancer cell aggregation as well as its metastatic spread.[6] Therefore, over the last few years, investigators across the globe have put their efforts to explore the potency of carbohydrates in drug discovery and development and also exploit the desired biological interactions by tuning the spatial arrangements of sugar residues on dendritic scaffolds for better mimics/decoys.[2,7] The outstanding interaction profiles of large dendritic glycoconjugates, due to their avidity, pave the path to use them as *drugs per se* in different therapeutic fields.[8-10] The development of newer moieties with potential therapeutic activity against drug-resistant pathogens with minimal toxicity was the main intent of the study. The most alluring solution seems to be the inhibition of initial bacterial attachment to target cells/ surfaces using anti-adhesive molecules. Bacterial biofilms are the noteworthy illustrations of adherence phenomena on inanimate as well as animate surfaces.[11] We are interested in the biocompatible neutral motifs of galactose because It has been reported that galactosylated or mannosylated dendrimers are more therapeutically active compared to other sugars.[12] Cu(I)-catalyzed azide-alkyne cycloaddition (Click chemistry)[13] nowadays is widely exploited in the field of carbohydrate chemistry for fostering regio-, chemoselective with a quantitative yield of glycoconjugates, such as glycopeptides, glycopolymers, polysaccharides, glycodendrimers, glycol-arrays, glyco-macrocylces, etc.[2a,14-16] Regioselective triazole generated from azide-alkyne stitching is the bioisostere of the amide functional group. Amide shows natural connector in the biological system and being the bioisostere of amide, triazole is also an important pharmacophore[17a] and therefore Click inspired triazoles has been widely used as a linker to adhere two distinct scaffolds.[17]

Considering the importance of glycodendrimer, herein we wish to report the Click inspired synthesis of novel glycodendrimers which were evaluated for their biological activities against multi-drug resistant bacterial isolates and human colorectal carcinoma cells (HCT116), and also their biocompatibility profiling.

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† **Electronic Supplementary Information (ESI) available**: Copies of ^{1}H and ^{13}C NMR of developed glycodendrimers and their precursors (**1-10**) has been provided. MaldI-TOF spectra, IR, SEC and DLS spectrum has also been given. See DOI: 10.1039/x0xx00000x

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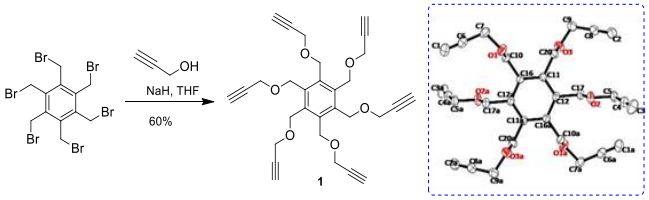
Results and discussion

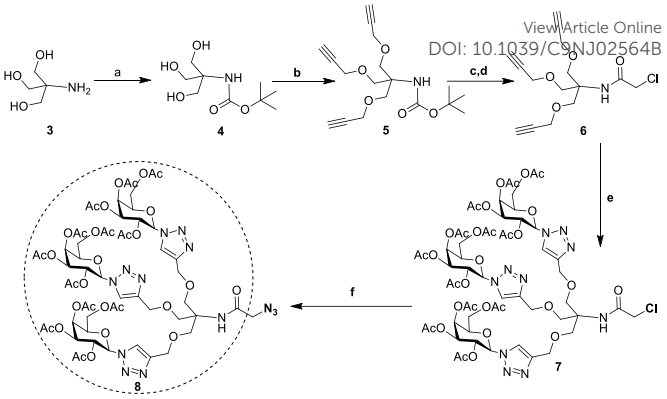
Our overall strategy for the formation of G(0) and G(1) type glycodendrimer involves the Cu(I)-catalyzed azide-alkyne 1,3-dipolar cycloaddition reaction (CuAAC) of hexakis(propargyloxymethyl) benzene core unit with galactosylated azide as well as multi functionalized dendritic azide **8** (**Scheme S1**).

We followed the convenient convergent method for the construction of glycodendrimers **9** and **10** and thus our strategy began with the synthesis of six arm hexakis(propargyloxymethyl) benzene core unit (**1**) which was obtained from commercially available hexakis (bromomethyl) benzene. When hexakis (bromom ethyl)benzene reacted with propargyl alcohol in presence of NaH in anhydrous THF at room temperature, propargyl group displaced the bromide and afforded the desired core **1** with a 60% yield (**Scheme 1**). The synthesized core was fully characterized by ^{1}H and ^{13}C NMR, MS and FT-IR spectrometry. The formation of the core was further confirmed by single crystal XRD, which exhibited the unequivocal formation of our desired core moiety **1.**

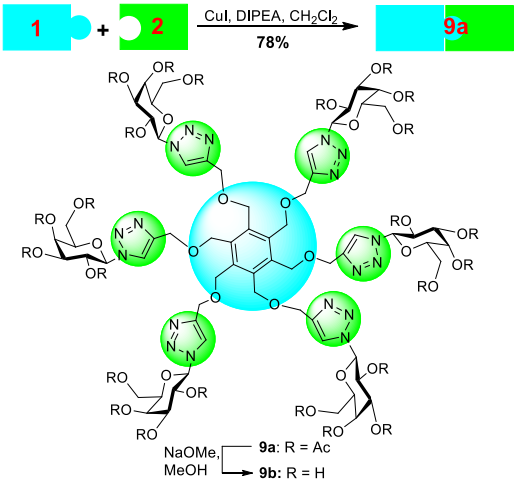


Scheme 1. Synthesis of hexakis((prop-2-yn-1-yloxy)methyl)benzene & ortep diagram of Crystal

After the successful synthesis of the core, we focused to synthesize other parts of glycodendrimers i.e. galactose azide **2** and Dendron **8.** For this purpose, we followed the well reported work for the synthesis of galactose azide **2** i.e. acetyl protection of D-galactose by acetic anhydride and I_2.[18] followed by treatment with HBr in acetic acid affording selective bromination at the **C-1** position and then azidation to produce desired galactose azide.[15] Whereas, for the synthesis of galactosylated dendritic wedge **8**, we started with *N*-BOC protection of tris-hydroxyaminomethane followed by propargylation using propargyl bromide in presence of KOH to furnish *N*-(tert-butyloxycarbonyl)tris[(propargyloxy)methyl] aminomethane **5** with 64% yield. The product was well characterized by NMR.[19] Deprotection of amine group of **5** by reaction with trifluoroacetic acid followed by treatment with chloroacetyl chloride in presence of DIPEA, produced 2-chloroacetamide-tris[(propargyloxy)methyl]aminomethane **6** (61%) (**Scheme 2**). At the end of the sequence, 2-chloroacetamide-tris[(propargyloxy) methyl]aminomethane (AB_3monomers) was clicked with galactosylated azide (end groups) to afford the multivalent galactosylated dendritic compound **7**. The Appearance of triazolyl peak at 7.83 ppm and disappearance of the alkenyl-H peak in NMR clearly confirmed the formation of compound **7.** Further, azide functionalized dendritic architecture **8** was prepared by reacting **7** with NaN_3 in DMF at r.t. for 24 h (88%) (**Scheme 2**). Furthermore, six armed core unit **1** was clicked with galactosylated azide (end group) to afford multivalent glycodendrimer **9a** with 78% yield after purification by flash column chromatography. Compound **9a** was characterized by ^{1}H and ^{13}C NMR, IR, MALDI-TOF MS and SEC analysis (**Scheme 3**).



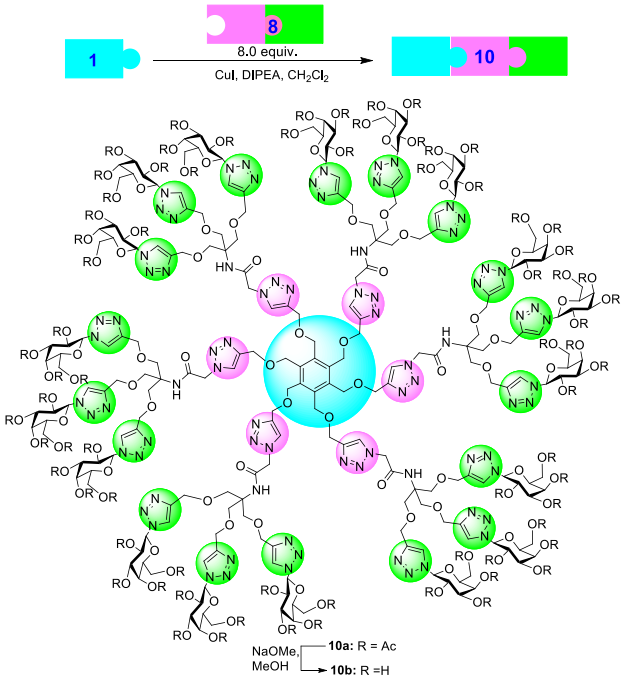
Scheme 2. Synthesis of galactosylated dendritic architecture: (a) di-tert-butyl dicarbonate, *t*-BuOH/MeOH, 18h, r.t.; (b) propargyl bromide, KOH, r.t.; (c) TFA, Dry DCM, 0˚C-rt; (d) Chloroacetylchloride, DIPEA, Dry DCM, 0˚C-rt; (e) Acetyl galactosylated azide **2**, CuI, DIPEA, anhydrous dichloromethane; (f) NaN_3, DMF, 24h, r.t.



Scheme 3. Synthesis of glycoconjugate cluster **9a** and **9b**

Complete vanishing of the alkenyl-H peak of core **1** in ^{1}H NMR and azide peak of compound **2** in IR spectrum demonstrated the purity of the desired product. The appearance of triazolyl peak at 7.87 and 145.3 ppm, in ^{1}H and ^{13}C NMR, respectively showed the formation of the triazole ring. Moreover, the ratio of the anomeric and triazolyl proton is 1:1, which confirms the formation of symmetric glycodendrimer with one triazole linker for each sugar moiety.

Glycodendrimer **10a** was synthesized by amalgamating two moieties through dipolar cycloaddition reaction of alkyne tethered core **1** with the azide functionalized dendritic wedge **8** in the presence of CuI and DIPEA which resulted in the final 18 peripheral galactosylated glycodendrimer **10a**. Compound **10a** was purified by column chromatography (SiO_2) and characterized by its NMR, IR, and MALDI-TOF MS. Absence of the azide peak in FT-IR of glycodendrimer **10a** showed the formation of first-generation glycodendrimer **10a**. Furthermore, SEC analysis shows the size progression from **9a** to **10a** and the low dispersity index (*Đ)* (1.03 to 1.01) reveals the monodispersity of the developed glycodendrimer.[20]



Scheme 4. Synthesis of 1st generation glycodendrimer **10a** and **10b**

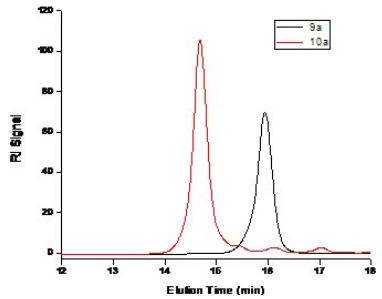


Figure 1: SEC chromatogram of glycodendriners **9a** and **10a**

To make the glycodendrimers water-soluble, compound **9a** and **10a** were quantitatively de-*O*-acetylated using NaOMe in MeOH by applying Zemplén reaction method to afford the water soluble dendrimers **9b** and **10b (Scheme 3 and 4**). Both the glycodendrimers **9b** and **10b** were characterized by using standard spectroscopic techniques such as, NMR, and IR analysis.

The biological data clearly reveal the potential antibacterial activity of the synthesized glycodendrimers **9a** and **10a** against both gram-negative and gram-positive pathogens irrespective of their susceptibility profile with other conventional drugs. The MIC ranged from 2 to 32 µg/mL (**Table 1**). For comparison, MIC indices of vancomycin (for gram-positive isolates) and meropenem (for gram-negative) were also evaluated. Of note dendrimer **9a** (relatively smaller dendrimer) showed mediocre activity against the tested isolates.

Biofilm, an important adaptation in bacteria wherein they remain enmeshed within self-produced exopolysaccharides, bestows them protection against antimicrobials and host immune responses.[11,21-23] We investigated bacterial viability in biofilms post treatment. A sharp reduction in CFUs was noted. Besides, we also observed biofilm biomass reduction in a dose dependent manner with increasing concentration of dendrimers **9a** and **10a (Figure 2)**.

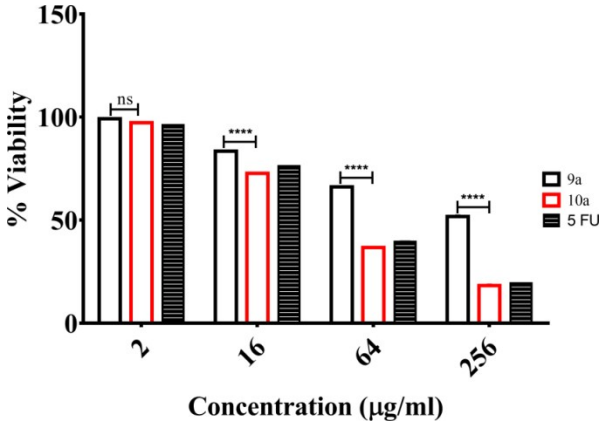


Figure 2: Comparative evaluation of cellular viability of HCT116 cell lines upon exposure to dendrimers **9a, 10a** and the drug 5-Fluoro Uracil.

Cell viability upon treatment with dendrimer **10a** decreased to 10.33, 6 and 1.667 $\log_{10}$ CFU/mL at concentrations 8, 16, and 32 µg/mL, respectively, whereas bacterial count reduced to zero when the concentration was escalated to 128 µg/mL compared to control where $\log_{10}$ CFU/mL was found to be 19.67. The minimum biofilm inhibitory concentration (MBIC) of **10a** was found to be 2 and 8 µg/mL against drug-resistant *S. aureus* and *E. coli* biofilms, respectively. The MBIC data is in consonance with the results of the biofilm disruption test. At the concentration 4 µg/mL, dendrimer **10a** was found to inhibit the biofilm formation by 54% but, no sooner, the concentration was increased to 64 µg/mL then, significant inhibition of 83.5%, was observed against MRSA (1028/2018), while at the same concentration complete inhibition was noted in *Staphylococcus aureus* (ATCC 25923). Interestingly, dendrimer **9a** was less effective against the biofilms of tested isolates at the said concentration where merely 12% and 68.8 % inhibition was realized (**Figure 3**). Remarkably, the inhibition was less pronounced in the case of gram-negative isolate.

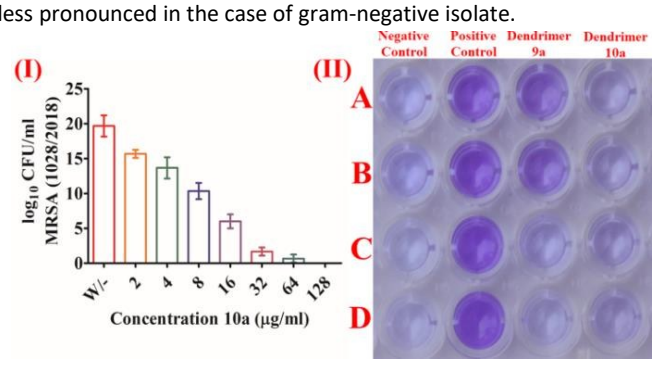


Figure 3: (I) Plot depicting reduction in colony forming units (CFUs) of *Staphylococcus aureus* MRSA (1028/2018) with escalating concentration of glycodendrimer **10a**. (II) Tissue culture plate assay for biofilm quantification exhibiting dose-dependent reduction in biomass in presence of dendrimers **9a** and **10a**. Well A, B, C, and D depict the effective concentration of 8, 16, 32, and 64 µg/mL respectively.

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Table 1: Minimum inhibitory concentration and minimum biofilm inhibitory concentration of glycodendrimers 9a and 10a

Drugs	MIC/MBIC (µg/ml) Staphylococcus aureus, MRSA(1672/2018)	MIC/MBIC (µg/ml) Staphylococcus aureus ATCC 29213	MIC/MBIC (µg/ml) Staphylococcus aureus USA300	MIC/MBIC (µg/ml) Escherichia coli, (2147/2018)	MIC/MBIC (µg/ml) Escherichia coli ATCC 25922
Vancomycin/ Meropenem	4/< 0.1953	> 0.25 / 0.114	2 / 0.125	1/ 0.03125	0.25 /0.125
9a	32/ 16	4/ 4	8/ 4	32/ 16	8/ 8
10a	16/ 4	4/ 2	2/ 1	32/ 8	8/ 4

Freshly grown bacteria were then challenged with the MIC concentration of the dendrimer **10a** (16 and 32 µg/mL for MRSA and *E. coli* respectively, data shown in micrograph) and **9a** (32 and 32 µg/mL for MRSA and *E. coli* respectively, not shown in micrograph) and the image has been taken after staining with the red fluorescent dye propidium iodide. After 6 hrs of drug exposure, the said bacteria produced an intense PI-staining, indicating the cell death (**Figure 4**). Fluorescent micrographs showed very intense uptake of PI post **10a** treatment, indicating compromised cell membrane permeability. Red signals veiled complete cellular obliteration. Thus, the above results indicated that dendrimers **9a** and **10a** fostered bacterial killing by disrupting their cell membranes.

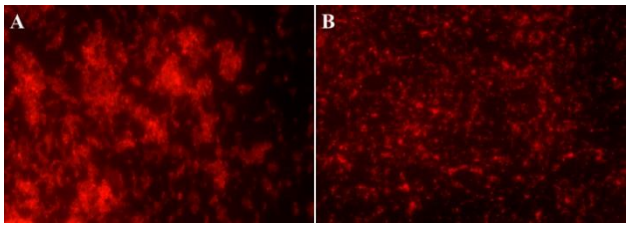

Figure 4: Fluorescent Micrographs of (A) *Staphylococcus aureus* and (B) *Escherichia coli*for the evaluation of anti-bacterial potential of compound **10a.** PI staining of *S. aureus* and *E. coli* after dendrimer 10a treatment reveals the substantial bacterial deaths by the presence of abundant red emission wavelength. At MIC concentration of dendrimer **10a**, the clear uptake of PI symbolizes membrane perturbations.

To ensure the anti-tumour potential of dendrimers **9a** and **10a**, the *in vitro* cellular viability was evaluated by SRB assay against HCT116 cells.[24] Incubation of HCT116 with compound **9a** did not influence cell viability in the tested range, which can easily be conjectured from the fact that upon exposure to 2 µg/mL of compound **9a**, cell viability was around 97% which remained 77% when exposed to 256 µg/mL (**Figure 5**). Unlike compound **9a**, the exposure to the compound **10a** had pronounced hostile consequences over the cell viability in a concentration-dependent manner. For instance, at 2 µg/mL concentration, around 96% cell viability was noted but as the concentration was escalated to 256 µg/mL; cell viability reduced to 53%. After exposure for 48 hrs, the GI_{50} and LC_{50} values for compounds **9a** and **10a** were estimated and for **10a** were 15.8 and 159.6 µg/mL, respectively, whereas for **9a**, were 10.7 and 123.2 µg/mL, respectively.[24,25] On consideration of the GI50 and LC50, we investigated the percentage of growth inhibition in identical cell cultures treated with 5 to 200 µg/mL of **9a** and **10a**. The results (**Figure 5**) indicated that the concentration of 20 µg/mL, **9a** inhibited the cell proliferation by ~88%, whereas **10a** resulted in virtually complete inhibition of proliferation that is, glycodendrimer **10a** was dramatically more effective than **9a**. At the 150 µg/mL concentrations of **10a** and 200 µg/mL of **9a**, were both highly anti-proliferative against HCT116, and therefore, no differences were observed in the effectiveness of **9a** and **10a** at these concentrations.

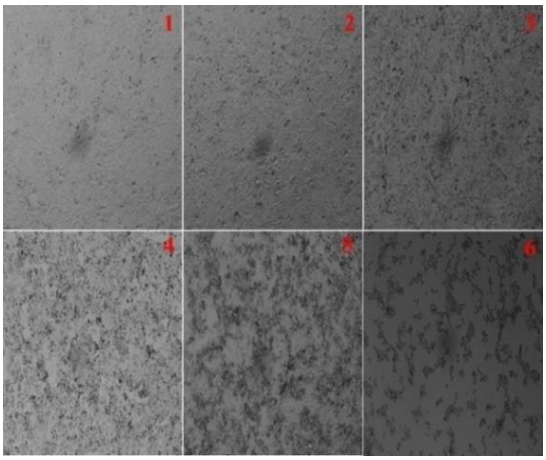

Figure 5: Dose dependent anti-tumour assay of glycodendrimer **10a** against HCT116. (1) Untreated, (Negative control), (2) Treated HCT116 cells with 2 µg/mL **10a,** (3) Treated HCT116 cells with 16 µg/mL **10a,** (4) Treated HCT116 cells with 64 µg/mL **10a,** (5) Treated HCT116 cells with 256 µg/mL **10a**; (6) Treated with 256 µg/mL with 5-fluoro uracil (Positive control)

The phase contrast microscopy was used to evaluate the morphological alterations if any. We noted the alterations in cellular morphology and adherences, which eventually resulted in the cellular deaths upon treatment with compound **10a** even at the concentration of 2 µg/mL compared to the control in the dose dependent manner. Thus, the outcome is in agreement with the results obtained after SRB assay.

Damage to the cell membrane is one of the hallmarks of the drug-toxicity.[23] To ensure whether the glycodendrimers **9a** and **10a** foster any cell membrane damage, we investigated the treated and

untreated cells using lactate dehydrogenase assay. LDH is a cytosolic enzyme and its presence in the cell soup indicates the membrane damage. Result demonstrates that the LDH activity (in terms of mean absorbance) in percentage after 48 hrs exposures of the SiHa cells to the glycodendrimers **9a** and **10a** (see, supporting Table S1). At any given time, SiHa cells incubated with dendrimers **9a** and **10a** at various concentrations (32, 64, 128, 256, 512, 1024 µg/mL) showed insignificant LDH activity than the group inoculated with amphotericin B in the same concentration range, signifying the biocompatibility of dendrimers **9a** and **10a.** At the concentration of 1024 µg/mL, around 67% cytotoxicity was noted in amphotericin B treated cells while on the same concentration, no significant leakage was noted in **9a** and **10a** treated cells. This indicates biocompatibility of compounds **9a** and **10a**. In addition, as evident from the differential light scattering experiment, the dendrimers exfoliate in the aqueous phase owing to its potential to open up in aqueous environments; we found its potential applicability in using as anti-adhesive. The two distant peaks depict agglomeration however; in the exploitation of therapeutic capacity this minimal aggregation exhibits minimal contrivances. The larger extent is showing the exfoliation which is prerequisite for being the anti-biofilm agent. The compounds are more soluble in DMSO than in aqueous phase therefore when this binary system is used for the DLS experiment two different peaks appeared depicting two different particle size distribution (See, Supporting information, **Figure S30)**. The smaller size shows exfoliation in the aqueous phase while the larger particle size shows aggregation.[26-28]

In conclusion, we successfully explored Click chemistry for the development of targeted glycodendrimers. The *in vitro* results obtained in the current study indicate its possible therapeutic potential with regard to antibacterial, anti-biofilm and anti-tumor activities.

Experimental

Synthesis of azide functionalized first generation dendron (8):

Compound **7** (0.3 g, 0.21 mmol) was dissolved in Dry DMF (3.0 mL) in an R.B., then NaN_3 (40 mg, 0.625 mmol) was added to the reaction mixture and stirred for 12 h at r.t., after completion of the reaction (monitored by TLC) solvent was evaporated in continuation to that ethyl acetate (30 mL) was added to the mixture and taken up in a separating funnel, washed with water (3 x 15 mL) followed by brine solution. Further, the organic layer was collected and dried over anhydrous sodium sulphate and reduced under high vacuum to obtain the crude compound which was further subjected to column chromatography to afford compound **8** as yellow solid. Yield (0.265 g, 88%); R_f = 0.5 (5% Methanol/DCM); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (s, 3H, Triazolyl-H), 6.62 (s, 1H, NH), 5.91 (d, *J* = 9.5 Hz, 3H, H_4), 5.61 (d, *J* = 9.5 Hz, 3H, H_2), 5.56 (d, *J* = 3.0 Hz, 3H, H_3), 5.30-5.27 (m, 3H, H_1), 4.67-4.61 (m, 6H, OCH_2CH=CH), 4.29-4.27 (m, 3H, H_{6a}), 4.19 (d, *J* = 7.0 Hz, 6H, $CqCH_2O$), 3.87-3.86 (m, 3H, H_{6b}), 3.84 (s, 2H, $ClCH_2$), 3.77 (d, *J* = 9.5 Hz, 3H, H_5), 2.22 (s, 9H, $COCH_3$), 2.05 (s, 9H, $COCH_3$), 2.01 (s, 9H, $COCH_3$), 1.83 (s, 9H, $COCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 170.0, 169.8, 169.0, 166.7, 145.3, 121.5, 86.0, 73.8, 70.7, 68.8, 67.8, 66.8, 64.5, 61.0, 59.8, 52.6, 20.6, 20.4 and 20.1 ppm. IR (KBr): ν_{max} 3395.50, 3145.80, 2928.33, 2111.58, 1755.66, 1674.53, 1529.27, 1459.94, 1432.22, and 1371.78 cm^{-1}.

Physical data of glycodendrimer 9a:

2,3,4,6-Tetra-*O*-acetyl-*β*-D-galactopyranosyl azide (184 mg, 0.493 mmol) was dissolved in dry DCM, synthesized core compound 1 (30 mg, 6.17x10^{-2} mmol) was added to the solution, CuI (0.21 mg, 0.111 mmol) and DIPEA (32.0µL, 0.185 mmol) were added to the reaction mixture and stirred under argon atmosphere for 12h. When the reaction shows the complete disappearance (monitored by TLC) of the compound **1**, the mixture was passed through cellite to remove the metal, 20 mL of DCM was added to the obtained the filtrate and taken in separating funnel, the organic layer was washed with water (2 x 20 mL). Organics were dried over anhydrous Na_2SO_4 and evaporated to afford crude product. Purification of the compound was done by flash column chromatography in (2% methanol/DCM) to obtain the compound **9a** as yellow solid. Yield (131 mg, 78%); R_f = 0.4 (5% methanol/DCM); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (s, 6H, Triazolyl-H), 5.85 (d, *J* = 9.5 Hz, 6H, H_4), 5.56-5.44 (m, 12H, H_2, H_3), 5.22-5.19 (m, 6H, H_1), 4.56-4.48 (m, 24H, H_{6a}, H_{6b}, OCH_2CH=CH), 4.28-4.2 0 (m, 6H, H_5), 4.04-3.99 (m, 12H, OCH_2Ar), 2.11 (s, 18H, 6 x $COCH_3$), 1.93-1.90 (m, 36H, 12 x $COCH_3$), 1.74 (s, 18H, 6 x $COCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 170.1, 169.8, 168.9, 145.3, 137.9, 122.2, 85.9, 73.7, 70.9, 67.9, 66.9, 63.7, 61.0, 60.3, 54.7, 42.9, 21.0, 20.6, 20.5 and 20.2 ppm. IR (KBr): ν_{max} 3479.91, 3146.72, 2934.72, 1755.54, 1639.17, 1434.53, 1371.90 cm^{-1}, MALDI-TOF MS: m/z $C_{114}H_{144}N_{18}O_{60}Na^+$, calculated = 2748.8696; found = 2748.9348 $(M+Na)^+$.

Synthesis of first generation glycodendrimer 10a:

Compound **1** (12 mg, 2.47x10^{-2} mmol) and compound 8 (0.266 mg, 0.185 mmol) were dissolved in DCM. CuI (9 mg, 4.73 x 10^2 mmol) and DIPEA (13 µL, 7.74 x 10^{-2} mmol) both were added to the solution and stirred at r.t. for 12 h, the disappearance of the core i.e. compound 1 (monitored by TLC) inferred the completion of the reaction. The reaction mixture was passed through cellite and obtained filtrates were taken in separating funnel, DCM (20 mL) was mixed and followed by washing with water (2x 30 mL). The organic layer was collected and dried over anhydrous sodium sulphate and evaporated to give residue **10a**, which was purified by flash column chromatography (2-9%, M-D). The product 10a was obtained as off white solid. Yield : (157 mg, 70%); R_f = 0.50 (10% methanol/DCM); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (br s, 18H, Peripheral triazolyl-H), 7.87 (br s, 6H, Inner triazolyl-H), 7.03 (br s, 6H, NH), 5.97-5.95 (m, 18H, H_4), 5.59-5.55 (m, 18H, H_2), 5.50 (br s, 18H, H_3), 5.30-5.25 (m, 18H, H_1), 4.55 (br s, 72H, H_{6a}, H_{6b}, OCH_2CH=CH), 4.29 (br s, 18H, H_5), 4.15-4.07 (m, 36H, CH_2C_q), 3.74-3.69 (m, 36H, CH_2CON, OCH_2Ar, OCH_2CH=CH), 2.15-2.12 (m, 54H, 18 x $COCH_3$), 1.96-1.95 (m, 108 H, 36 x $COCH_3$), 1.74 (s, 54H, 18 x $COCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 170.1, 169.9, 169.1, 165.3, 145.1, 139.3, 138.0, 125.7, 122.2, 114.0, 85.8, 73.7, 70.8, 68.7, 68.0, 67.0, 64.4, 61.1, 50.8, 40.5, 20.7, 20.6, 20.2 and 19.6 ppm. IR (KBr): ν_{max} 3454.46, 3144.32, 2925.33, 2854.91, 1755.21, 1636.08, 1552.67, 1463.37, 1432.7, 1371.64 cm^{-1}; MALDI-TOF MS:

m/z $C_{372}H_{484}N_{78}O_{192}Na_3^+$ calculated = 9187.0296; found = 9187.0693 $(M+3Na+4H)^+$.

"De-*O*-acetylation" (Zemplèn reaction) procedure for the synthesis of glycodendrimer **9b** and **10b:**

Glycoconjugate cluster **9a** or **10a** was dissolved in a mixture of anhydrous methanol: anhydrous THF: anhydrous DCM in the ratio of 3:0.5:0.5 by fixing the cluster molarity 2.5 x 10^{-3}M. A freshly prepared solution of NaOMe (1M, 30-40µL approx.) was added until the solution pH became 9-10. The reaction was stirred for 48 h at room temperature. After that, Milli-Q water was poured to solubilize the whole mixture and neutralized by ion exchange resin (Amberlite 120 H^+) till pH reaches in between 6-7, followed by filtration, and the solvent was evaporated under reduced pressure to afford the deprotected glycodendrimers **9b** and **10b**. The developed compound further characterized by the NMR, and MALDI-TOF MS and IR spectroscopy.

Physical data of glycodendrimer 9b:

White solid, yield (26 mg, 88%); ^{1}H NMR (500 MHz, D_2O): δ 8.21 (s, 6H, Triazolyl-H), 5.57 (d, *J* = 8.5 Hz, 6H, H_4), 4.40 (br s, 12H, OCH_2CH=CH), 4.30 (br s, 12H, H_2, H_3), 4.12-4.08 (m, 6H, H_1), 3.925-3.920 (m, 6H, H_{6a}), 3.83-3.80 (m, 6H, H_{6b}), 3.73-3.70 (m, 6H, H_5), 3.59-3.51(m, 12H, OCH_2Ar); ^{13}C NMR (125 MHz, D_2O): δ 146.7, 143.9, 137.7, 130.3, 125.7, 124.8, 88.1, 78.2, 73.0, 69.7, 68.5, 64.7, 62.7 and 60.7 ppm. IR (KBr): ν_{max} 3425.79, 2925.43, 2851.8, 1633.62, 1457.3, 1404.34, 1093.77 cm^{-1}; MALDI-TOF MS: for $C_{66}H_{100}N_{18}O_{37}^+$ Calculated = 1736.6492; found = 1736.1666 $(M+H_2O+2H)^+$.

Physical data of glycodendrimer 10b: White solid, yield (28 mg, 84%); ^{1}H NMR (500 MHz, D_2O): δ 8.06 (br s, 18H, Peripheral triazolyl-H), 7.88 (br s, 6H, Inner triazolyl-H), 5.51-5.49 (m, 18H, H_4), 5.02 (br s, 12H, CH_2CON), 4.45-4.36 (m, 54H, H_1, H_2, H_3), 3.90 (br s, 18H, H_{6a}), 3.80 (br s, 18H, H_{6b}), 3.69-3.67 (m, 24H, OCH_2CH=CH, OCH_2Ar), 3.62-3.50 (m, 90H, H_5, OCH_2CH=CH, CH_2C_q);^{13}C NMR (125 MHz, D_2O): δ 170.3, 147.6, 145.1, 133.2, 131.2, 130.1, 126.7, 126.6, 125.1, 109.5, 89.0, 79.2, 73.9, 70.6, 69.5, 68.5, 64.4, 61.7 and 61.2 ppm. IR (KBr): ν_{max} 3419.51, 2925.22, 1686.02, 1642.3, 1401.87, 1195.52, 1095.55 cm^{-1}.

Biological investigations of glycodendrimers:

Growth inhibition assays of glycodendrimers 9a and **10a**

We explored the effect(s) of glycodendrimers **9a** and **10a** over multi-drug resistant clinical isolates of *Escherichia coli* (Lab code: 2764/2018) and Methicillin resistant *Staphylococcus aureus* (MRSA, lab code: 1028/2018) as described earlier.[21,23,26] Further, effect against select control bacteria namely *Staphylococcus aureus* (ATCC 25923), *Escherichia coli* (ATCC 25922) was also investigated. In this study, multi-drug resistance was defined as resistance against at least 5 different classes of drugs. Antibiotic susceptibility testing was performed by modified Kirby–Bauer method in accordance with the Clinical and Laboratory Standards Institute guidelines 2018 using the following antibioticsm e.g. Ampicillin (10 µg), Amikacin (30 µg), Amoxicillin/clavulanate (20/10 µg), Ciprofloxacin (5 µg), Co-trimoxazole (23.75/1.25 µg), Ertapenem (10 µg), Gentamicin (120 µg), Imipenem (10 µg), Levofloxacin (5 µg), Meropenem (10 µg), and Piperacillin & tazobactum (100/10 µg).

Minimum Inhibitory Concentration (MIC) determination

MIC of the dendrimers **9a** and **10a** was determined by the broth micro dilution method as described earlier with minor modifications.[21,23] Methicillin resistant *Staphylococcus aureus* (MRSA, USA300, Lab code 1028/2018), Methicillin sensitive *Staphylococcus aureus* (MSSA, ATCC 25923), *Escherichia coli* (ATCC 25922, Lab code: 2764/2018) were used in the current study and bacteria were cultured in Brain Heart Infusion Broth (BHI) media (HiMedia laboratories, Mumbai). Initially the bacteria were streaked from −80°C glycerol stock onto Brain Heart Infusion Agar (BHIA) plate and single colony was inoculated into BHI broth (50% brain heart with 4% glucose) and incubated at 37°C for 24 hrs. From there, 10^6 CFU/mL bacterial cell suspensions were taken for all subsequent experiments. The freshly prepared stock solution of **9a** and **10a** (20 mg/mL in DMSO) were used for the study. The stock was diluted in a series of two-fold dilutions ranging from 0.5 to 64 µg/mL in sterile BHI broths in microtiter wells. Each well of 96-well microtiter plate was then inoculated with 200 µl of standardized cell suspension (10^6 CFU/mL) and incubated at 37°C for next 24 hrs along with the test compounds. The MIC of compounds **9a** and **10a** against the said bacterial isolates were delineated as their minimum concentration at which no perceivable bacterial growth was manifested as outlined by CLSI. Positive controls were devoid of compounds **9a** and **10a** while the sterile broth was used as negative control. Experiments were performed in triplicate.

Antibiofilm Activity Determination

Tissue Culture Plate Assay (TCP)

The antibiofilm assay was performed in 96-well tissue culture plate as described previously with minor modifications.[4,5] Briefly, the overnight cultures of MRSA (USA 300, Lab code: 1028/2018) and *E. coli* (ATCC 25922, Lab code: 2764/2018) were grown in Brain Heart Infusion broth. A volume of 180 µl of each diluted bacterial suspension (0.5 McFarland's, 10^8 CFU/mL) was dispensed into flat-bottom polystyrene 96-well tissue culture plate along with 20 µl of dendrimers **9a** and **10a** (50 µg/mL) at 37°C without shaking for 24 hrs. Wells without the said compounds were set as controls. As a positive control, we used *Staphylococcus epidermidis* (ATCC 35984), a known high biofilm former. After the respective incubations, biofilm was quantitated by crystal violet (CV) assay as described earlier.[22] The assays were performed in triplicate, and the results were expressed as mean OD570 ± the standard deviation of the mean (SD).

% Reduction = (Mean absorbance of the control-Mean absorbance of the test sample)/(Mean absorbance of the control) × 100

Fluorescent Microscopy for determination of anti-bacterial properties:

For fluorescent analysis of the effects of the said compounds, we grew MRSA isolate and *E. coli* clinical isolates in chambered slides (Nunc, Denmark). Briefly, the overnight grown isolates were diluted 1:100 in fresh BHI broth to adjust its absorbance to 0.2 at λ_{max} 600nm. Fifty-microliters of its diluted suspension was then dispensed into flat-bottom chambered slide containing 480 µl of BHI broth and incubated for 3 hrs. This was followed by the treatment with MIC dose of dendrimers **9a** and **10a** for next 3 hrs. Prior to staining,the residual broth was aspirated and washed thrice by phosphate buffer (pH 7.5). The 4% (v/v) paraformaldehyde was used for bacterial fixation for 30 mins. The PI stock solution (1mg/mL) was prepared in DMSO and stored frozen in aliquots of 100 µl. For use, stock solutions were diluted with PBS to the concentration of 10 µg/mL. Fifteen-microliters of these staining solutions were applied directly to the top of the biofilms. The Nikon Eclipse microscope was used to detect the red fluorescence from the stains. Propidium iodide was excited with the HeNe2 530nm laser and emission fluorescence was collected with the 620 nm filter.

Anti-tumor and Cytotoxicity Profiling:

Cell culture:

We cultured HCT116 and SiHa cells (Cancer cell lines) in Dulbecco's Modified Eagle's medium, which was supplemented with 10% fetal bovine serum (added with 100 U/mL penicillin and 100 mg/mL streptomycin) in a 5% CO_2 humidified atmosphere at 37°C in a CO_2 incubator. The cells were exposed to both the compounds **9a** and **10a** for 48 hours.

Anti-tumor assay:

We procured the Human colon carcinoma HCT116 cells from the National Centre for Cell Science (NCCS, Pune, India) and customized to proliferate in DMEM with added bovine serum (10%) and antibiotics. We seeded HCT116 cells in 96-well plates and incubated it overnight at 37°C to allow them to adhere to the substratum and resume exponential proliferation. Afterwards, the left overmedium and non-adhered cells were aspirated out with subsequent addition of 0.5 mL of the fresh medium containing various concentrations of dendrimers **9a** and **10a**. A 2 mg/mL stock solution of said compounds were prepared in DMSO and were stored as small aliquots at 4°C and diluted two folds in a different dose ranging from 2-256 µg/mL in Dulbecco's modified Eagle's medium. The final DMSO concentrations were adjusted such that it remained < 2 % (v/v). Negative control cultures had DMSO alone. However, for positive control drug 5-fluro uracil was used. For each drug concentration, we used four wells. Both the treated and untreated cells were incubated for next 48 hrs at 37°C. After the incubation is over, we fixed the cells *in situ* using trichloroacetic acid followed by sulforhodamine B staining.[29] The absorbance was read at 530 nm on Synergy H1 Hybrid Multi-Mode Reader (version 3.02.1, BioTek Instruments, Inc., Winooski, VT, USA). Each experiment was run in triplicates. GI50 (i.e., the drug concentration required to inhibit cell proliferation by 50%) and LC50 (i.e., the drug concentration required to kill 50% of the cultured cells) values were calculated as the mean of the three independent experiments.

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†Electronic Supplementary Information (ESI) available: Copies of ^{1}H and ^{13}C NMR of all the developed glycodendrimers and their precursors (**1-10b**) has been provided. MaldI-TOF spectra, an IR, SEC and DLS spectrum has also been given.

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Click inspired synthesis of hexa- and octadecavalent peripheral galactosylated Glycodendrimer and its possible therapeutic Applications

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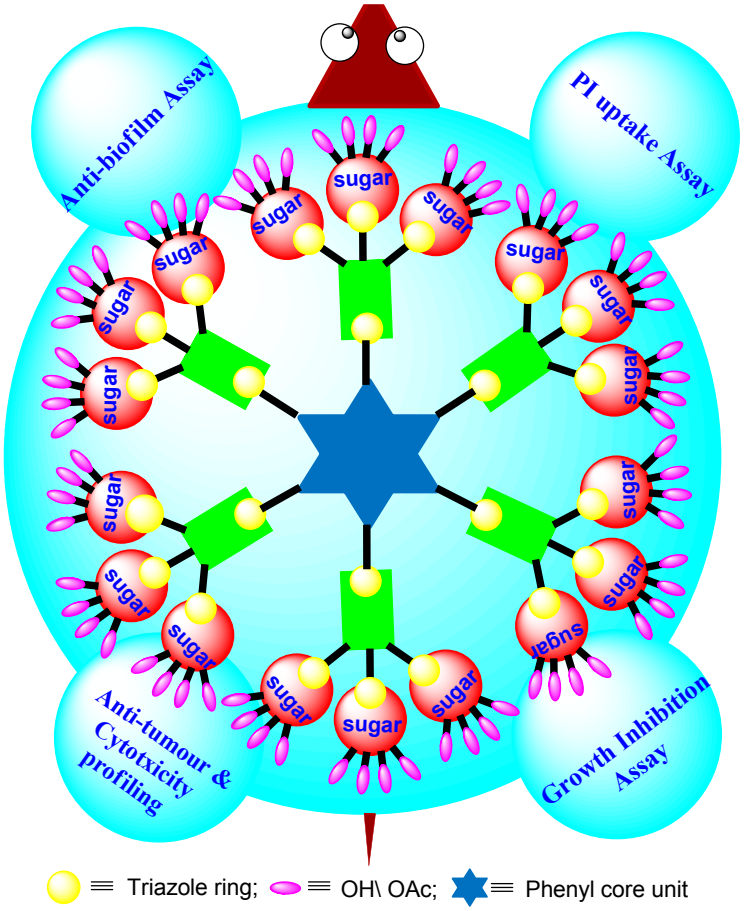
TOC:



Click inspired glycodendrimers comprising of rigid hexapropargyloxy benzene core peripheral β-D-galactopyranosidic units were developed and evaluated for their therapeutic potential.