Click Chemistry Approach for the Synthesis of Water-Soluble Glycodendrimer with Triazole as Building Unit

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Abstract: A new family of chiral glycodendrimers scaffolds containing di-, tetra- and octavalent glucose residues as peripheral unit and with 1,2,3-triazole as building unit has been synthesized through Cu(I)-catalyzed click chemistry by convergent approach.

Key words: click chemistry, glycodendrimers, chiral (*S*)-BINOL, alkynes, azide, 1,2,3-triazole

Dendrimers are large regularly branched synthetic molecules, which continue to receive much attention due to their unique properties and applications in medicinal and material chemistry. The ability to tune the properties of dendrimers has allowed their development for use in diverse applications including light harvesting systems,[1] catalysis,[2] molecular encapsulation,[3] biomedical applications,[4] bioconjugate chemistry,[5] drug delivery,[6] biomedicine,[7] and material science.[8] Dendrimers with carbohydrate units are important in medical and biological fields in which multiple carbohydrate–protein interaction[9] are responsible at the molecular level, for several critical biology events such as cellular adhesion and recognition, physiological function regulation, and biological infections.

The application of click chemistry developed by Meldal[10]and Sharpless[11] involving the Cu(I)-catalyzed 1,3-dipolar cycloaddition of an azide to a terminal alkyne is a rapidly emerging field in biological, material and medicinal chemistry. Deguise[12] and co-workers reported the synthesis of homo- and hetero bifunctional glycodendrimers ending with up to 16 fucoside and/or galactoside residues through convergent approach. Chabre et al.[13] also have reported glycodendrimers scaffolds containing 12 and 18 peripheral α-D-mannopyranosidic units through click chemistry. We wish to report herein the synthesis of (*S*)-BINOL-based glycodendrimers **1**–**6** (Scheme 1) with 1,2,3-triazole as building unit through click chemistry by convergent approach. The core moiety of chiral bis(propargyloxy)(*S*)-BINOL (**7**) plays an important role in liquid crystals as well as in biology.[14] The glycodendrimers reported herein can be used to study protein binding and for biological evolution of multivalent glycomimetic inhibitors against bacterial adhesion. Exploiting Cu(I)-catalyzed reaction for the synthesis of dendrimers, we envisaged AB_2 monomer based on terminal alkynes and azide compounds through the synthesis of glycodendrimers by convergent method.[13,15]

The core unit bis(propargyloxy)(*S*)-BINOL (**7**) was obtained in 92% yield, by the reaction of (*S*)-BINOL with propargyl bromide in the presence of K_2CO_3 in DMF rather than the reported procedure using K_2CO_3 in acetone or NaH in THF[16] (Scheme 2).

Treatment of glucose with Ac_2O and $ZnCl_2$ gave the pentaacetate which on further treatment with 33% HBr in acetic acid followed by NaN_3 in acetone at 60 °C gave the glycoazide **8** in 45% yield. Reaction[17] of the bis(propargyloxy)(*S*)-BINOL (**7**) with two equivalents of acetylated glycoazide **8** in the presence of $CuSO_4$ and sodium ascorbate in water and *t*-BuOH mixture at room temperature gave G_0-dendrimer **1** in 97% yield (Scheme 2). In ^{1}H NMR spectrum compound **1** showed up as four singlets at δ = 1.70, 2.04, 2.06 and 2.09 ppm for the four different glycoacetoxy protons, and as a singlet at δ = 5.18 ppm for the methylene protons attached to (*S*)-BINOL in addition to aromatic protons. The ^{13}C NMR spectrum of compound **1** displayed the four different glycoacetoxy carbons at δ = 19.9, 20.6, 20.6 and 20.7 ppm, the triazole CH carbon at δ = 145.5 ppm and carbon attached to the oxygen of (*S*)-BINOL unit resonated at δ = 153.7 ppm. The appearance of molecular ion peak at *m*/*z* = 1108 also confirmed the structure of the glycodendrimer **1**.

In order to synthesize the first-generation dendron, the building unit 3,5-bis(propargyloxy)benzyl chloride (**9**) was obtained from methyl 3,5-dihydroxybenzoate and propargyl bromide in DMF in the presence of K_2CO_3, followed by treatment with $LiAlH_4$ and further with $SOCl_2$–py in CH_2Cl_2. Reaction of 3,5-bis(propargyloxy)benzyl chloride (**9**) with two equivalents of acetylated carbohydrate azide **8** under the Cu(I)-catalyzed Huisgen 'click reaction' condition gave the dendritic chloride **10** in 96% yield (AB_2-type). The use of NaN_3 in a mixture of acetone and water[18] at 60 °C allowed the transformation of the dendritic chloride **10** to the corresponding dendritic azide **11** in 98% yield.[19] Reaction of the bis(propargyloxy)(*S*)-BINOL core unit (**7**) with two equivalents of dendritic azide **11** in the presence of the Cu(I)-catalyzed Huisgen 'click reaction' generated the (AB_2-type) first generation dendrimer (G_1) **3** with triazole building block in 94% yield. The IR spectrum of dendrimer **3** showed carbonyl stretching at 1752 cm^{-1}. In the ^{1}H NMR spectrum compound **3** showed up as four singlets at δ = 1.70, 2.02, 2.04

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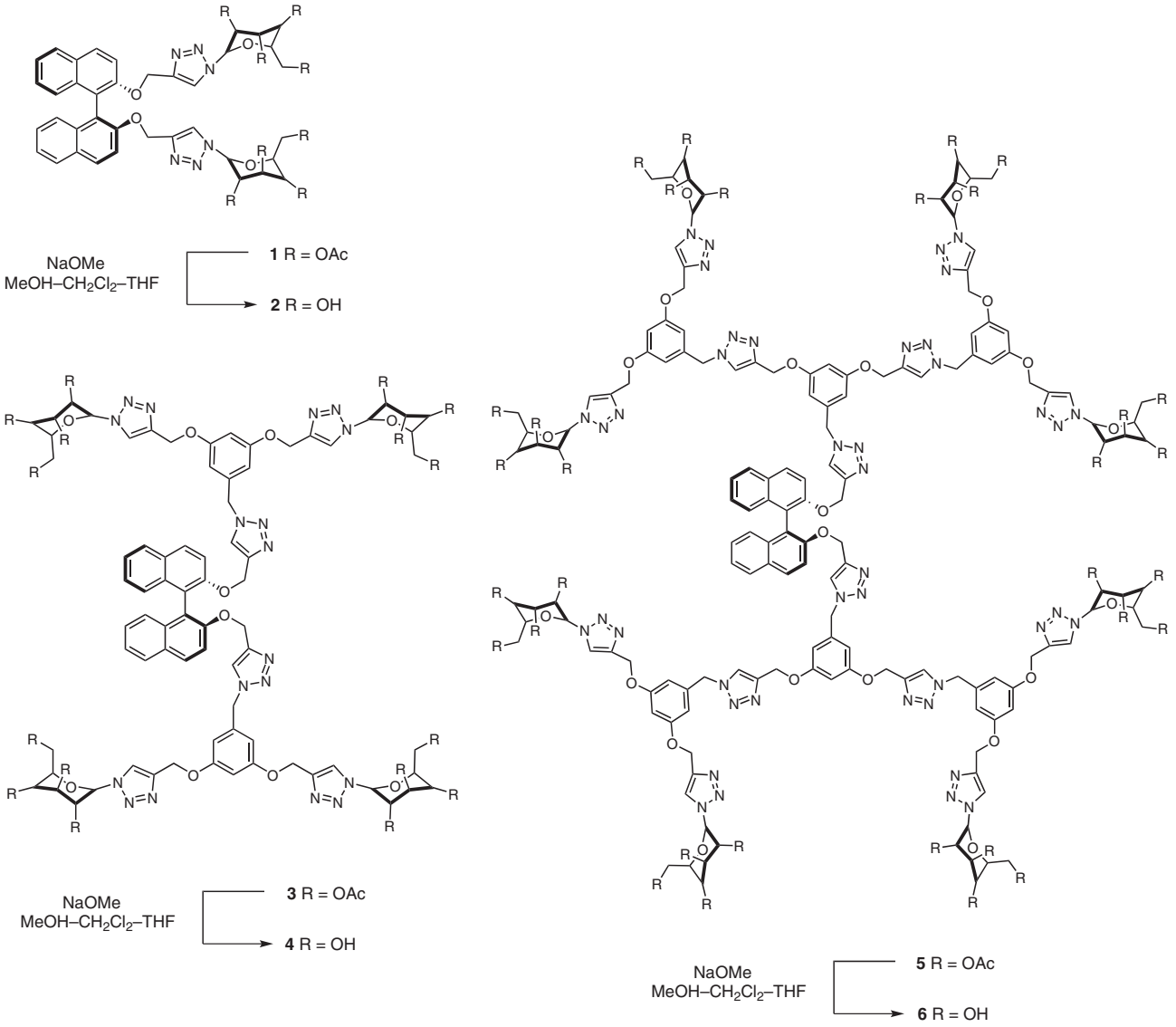
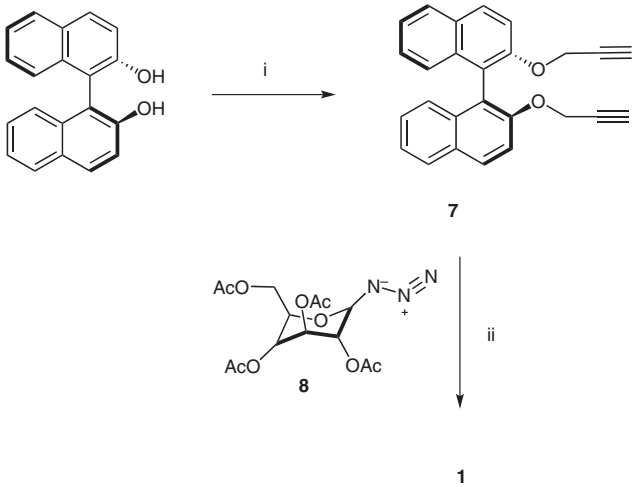


Scheme 1

and 2.07 ppm for the four different glycoacetoxy protons, two sharp singlets at δ = 5.11 and 5.13 ppm for OCH_2 and NCH_2 protons, and another sharp singlet for 4-H at δ = 8.04 ppm for triazole CH carbons. The ^{13}C NMR spectrum of **3** displayed four different glycoacetoxy carbons at δ = 20.1, 20.5, 20.5 and 20.6 ppm, the OCH_2 carbon of (*S*)-BINOL resonated at δ = 153.6 ppm, and the four different carbonyl carbon appeared at δ = 168.9, 169.4, 169.9 and 170.5 ppm. The appearance of molecular ion peak at *m*/*z* = 2337 also confirmed the structure of the first generation (G_1) glycodendrimer **3** (Scheme 3).

A similar synthetic strategy was adopted for the synthesis of second generation of dendron from the building block of 3,5-bis(propargyloxy)benzyl chloride (**9**). Reaction of the dendritic azide G_1-N_3 **11** with the chloride **9** in the presence of the Cu(I)-catalyzed Huisgen 'click reaction' condition gave the dendritic chloride **12** (AB_2-type) in 93% yield. The use of NaN_3 in a mixture of acetone and water at 60 °C allowed the transformation of the desired



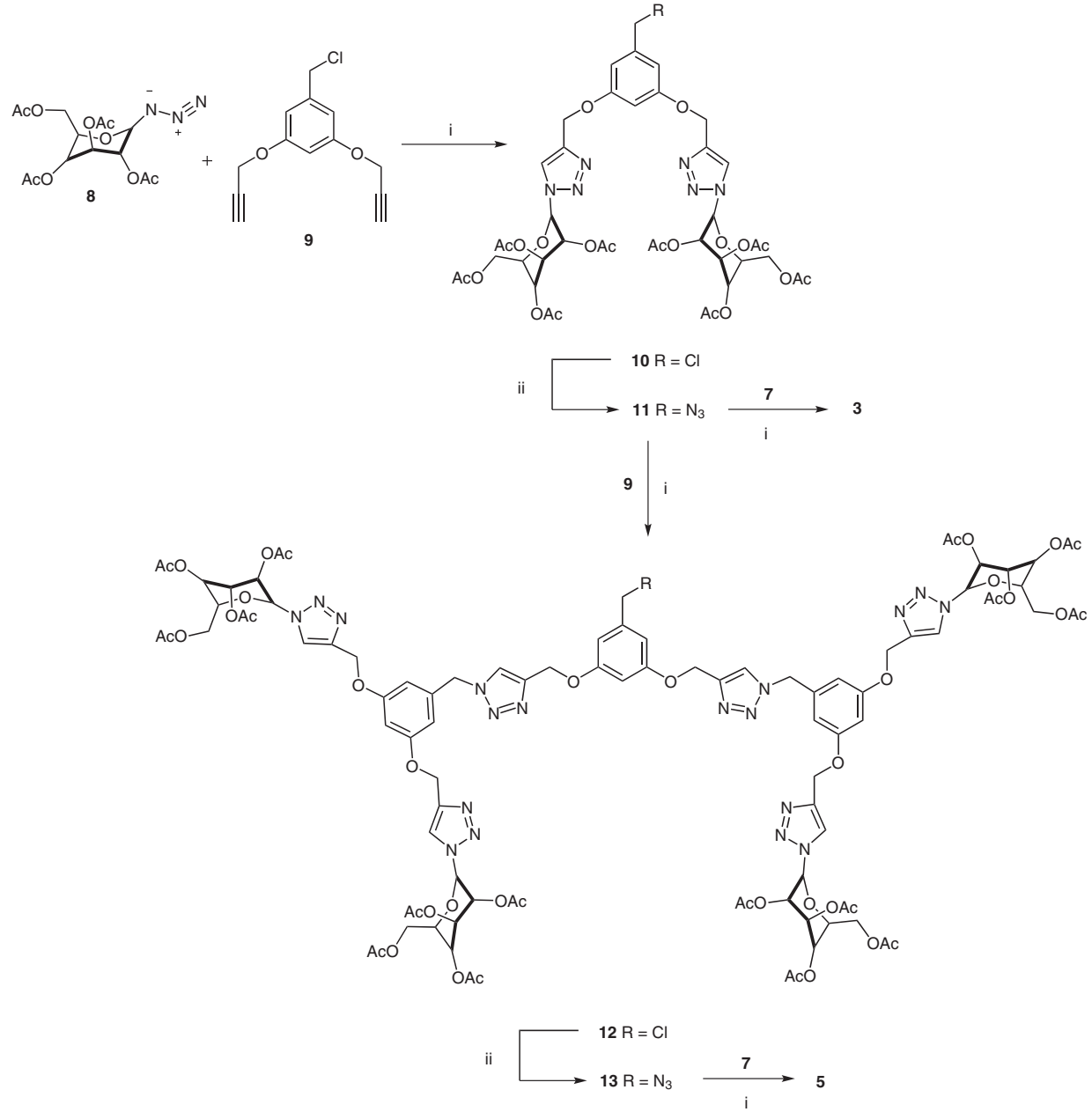
Scheme 2 *Reagents and conditions*: (i) propargyl bromide, K_2CO_3, DMF, r.t., 48 h; (ii) $CuSO_4$ (5 mol%), sodium ascorbate (10 mol%), H_2O–*t*-BuOH (1:1), r.t., 10 h.

dendritic chloride **12** to the corresponding dendritic azide **13** in 99% yield.[20] Reaction of the bis(propargyloxy)(*S*)-BINOL core unit (**7**) with two equivalents of dendritic azide **13** in the presence of the Cu(I)-catalyzed Huisgen 'click reaction' generated the second-generation dendrimer (G_2) **5** with triazole as building block (AB_2-type) in 98% yield. Second-generation glycodendrimer **5** was characterized from spectral and analytical data.

All the glycodendrimers **1**, **3** and **5** were de-O-acetylated under slightly modified Zemplen conditions[21] (NaOMe, MeOH–CH_2Cl_2–THF) to afford the di-, tetra-, octavalent glycodendrimers **2**, **4** and **6** in 95%, 92% and 92% yields, respectively. The structure of the glycodendrimers **2**,[22] **4**[23] and **6**[24] was completely characterized from spectral and analytical data. In conclusion, the chiral acetylated glycodendrimers **1**, **3** and **5** and the chiral deacetylated glycodendrimers **2**, **4** and **6** were obtained in good yields by the application of click chemistry.

Chiroptical and UV-Absorption Studies on Enantiopure Chiral Dendrimers 1–6

Molar specific rotation values were determined for glycodendrimers **1**–**6** in DMSO at 589 nm. Acetylated glycodendrimers **1**, **3** and **5** at 10^{-4} M concentration showed molar rotation as 530.0, 481.4 and 237.4, respectively. The chiral rotation values of all dendrimers are due to (*S*)-BINOL and the acetylated glucose units. (*S*)-BINOL unit has a molar rotation value of $[\alpha]_D^{25}$–36 and the glucose unit has a molar rotation value of $[\alpha]_D^{25}$ –29 at 10^{-4} M concentration and hence the observed values for dendrimer **1**



Scheme 3 *Reagents and conditions*: (i) $CuSO_4$ (5 mol%), sodium ascorbate (10 mol%), H_2O–*t*-BuOH (1:1), r.t., 10 h; (ii) NaN_3 (1.5 equiv), acetone–H_2O (4:1), 60 °C, 1–3 h.

is the cumulative result of both effects and hence **1** showed molar rotation as 530.0. However, on increasing the number of glucose units, the molar rotation values should be still more positive. But the molar rotation value decreases for dendrimers **3** and **5** which could be due to the increase in torsional angle at (*S*)-BINOL unit which could increase the negative rotational values and hence the overall effect is a decrease in the molar rotation values for dendrimers **3** and **5**. Further the torsional strain is more in dendrimer **5** due to the presence of highly branched dendritic arms and the dendritic wedges move farther apart and hence the observed effect. The deacetylated glycodendrimers **2**, **4** and **6** also exhibited similar behavior at 10^{-4} M concentration. Glycodendrimers **2**, **4** and **6** shows the molar rotation values as 343.5, 258.1 and 75.9, respectively. Molar rotation values were measured for dendrimers **2**, **4** and **6** at three different concentrations, namely 10^{-3}, 10^{-4} and 10^{-5} mol/L, in order to examine the possibility of association. Glycodendrimer **2** showed molar rotation values as 466.3, 343.5 and –3.1 at 10^{-3}, 10^{-4}, 10^{-5} mol/L, respectively, which indicates that at very low concentration there is no or very low degree of aggregation and hence the dendritic wedges widens the dihedral angle and at higher concentration (10^{-3} M) the presence of aggregation compresses the dihedral angle of (*S*)-BINOL unit and hence high positive values of molar rotation is observed. Similarly dendrimer **4** also exhibited molar rotation values as 4072.6, 258.1 and –15.0 which again indicates the aggregation in the glycodendrimer **4** at high concentration (10^{-3} M) and no or negligible aggregation at lower concentration (10^{-5} M). Similar trends in the rotation values were observed for dendrimer **6** also. In conclusion the dihedral angle of (*S*)-BINOL unit is controlled by the degree of aggregation as well as by branching of the dendritic wedges, which in turn is reflected in the molar rotation values. The results are given in Table 1.

Table 1 Variation of Molar Rotational Values by the Variation of Dentritic Wedges as well as Concentration

Dendrimer	Conc.	$[\alpha]_D^{25}$	Molecular wt.	Molar rotation
1	10^{-4}	+47.8	1108	+530.0
2	10^{-3}	+60.4	772	+466.3
2	10^{-4}	+44.5	772	+343.5
2	10^{-5}	–0.4	772	–3.1
3	10^{-4}	+20.6	2337	+481.4
4	10^{-3}	+244.6	1665	+4072.6
4	10^{-4}	+15.5	1665	+258.1
4	10^{-5}	–0.9	1665	–15.0
5	10^{-4}	+5.7	4796	+273.4
6	10^{-3}	+88.5	3451	+3054.1
6	10^{-4}	+2.2	3451	+75.9
6	10^{-5}	–0.8	3451	–105.3

Electronic absorption spectra of the acetylated glycodendrimers **1**, **3** and **5** were recorded at a concentration of 10^{-4} mol/L and are depicted in Figure 1. Two main bands were observed at 283 and 337 nm. The most intense band appears at λ_{max} = 283 nm. The intensity of the band at 283 nm increases from dendrimers **1**, **3** and **5** and the intensity of the band at 337 nm decreases, which probably shows a very low degree of aggregation. The deacetylated glycodendrimers **2**, **4** and **6** also exhibited λ_{max} at 283 nm and 337 nm at a concentration of 10^{-4} mol/L (Figure 2). However intensity of the peak at 283 nm was very high for **6** which probably indicates the presence of large degree of aggregation when compared with dendrimers **2** and **4**. Further all the dendrimers showed the 283 nm peak with high intensity and 373 nm peak with low intensity.

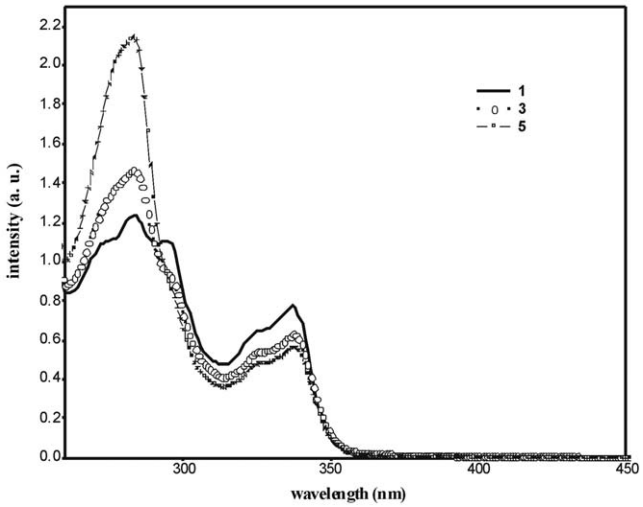


Figure 1 Absorption intensity spectrum of the dendrimers **1**, **3** and **5** at 10^{-4} M concentration in DMSO

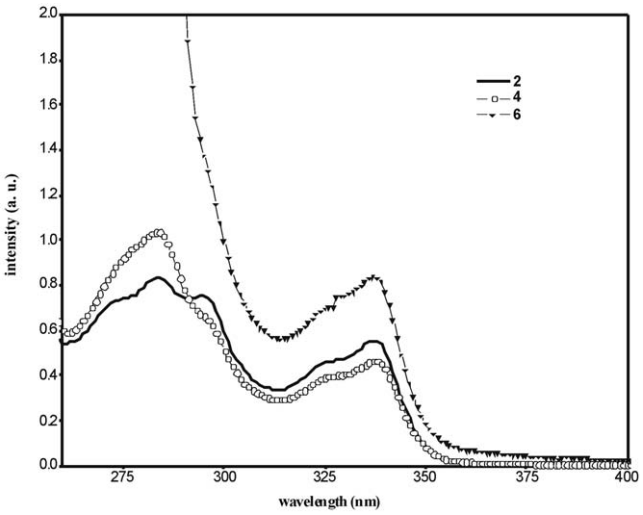


Figure 2 Absorption intensity spectrum of the dendrimers **2**, **4** and **6** at 10^{-4} M concentration in DMSO

Table 2 Indication the Variation for ψ_{max} for the Dendrimers **1–6**

Dendrimer	Conc.	ψ_{max}	
		283 nm	337 nm
1	10^{-4}	1.23	0.77
2	10^{-4}	0.84	0.56
2	10^{-5}	0.30	0.17
3	10^{-4}	1.47	0.64
4	10^{-4}	1.04	0.47
4	10^{-5}	0.34	0.15
5	10^{-4}	2.15	0.56
6	10^{-4}	–	0.84
6	10^{-5}	0.64	0.19

From the absorption spectra it can be gathered that the association is more in deacetylated glycodendrimer **6** at 10^{-4} mol/L when compared with all other dendrimers (Table 2).

Further studies are under way to unequivocally confirm the presence of aggregation in the deacetylated glycodendrimers. The presence of triazole building unit, chiral (*S*)-BINOL core unit and glucose peripheral unit might impart novel biological properties. Investigations of the antimicrobial and antioxidant properties of the synthesized dendrimers are under way.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(17) **General Procedure for the Cu-Catalyzed Huisgen 'Click Reaction'**: Acetylenic derivative (1.0 mmol) was mixed with acetylated carbohydrate azide (2.1 mmol, 2.1 equiv) in *t*-BuOH and H_2O mixture (1:1, 8 mL) solution. Sodium ascorbate (0.4 mmol, 0.4 equiv) was added as a solid, followed by the addition of $CuSO_4$ (0.2 mmol, 0.2 equiv). The reaction was stirred overnight at r.t. The solvent was evaporated under reduced pressure and the crude product was dissolved in EtOAc (100 mL), washed with NH_4Cl solution (50 mL), brine solution (50 mL) and H_2O (50 mL) and then dried over Na_2SO_4 and concentrated on a rotary evaporator. The residue was purified by column chromatography (SiO_2) with hexane–EtOAc as eluent to give the corresponding triazole compound.

(18) **General Procedure for the Conversion of Dendritic Chlorides to Azides**: Dendritic chloride (1.0 mmol) was dissolved in acetone and H_2O (4:1, 8 mL). NaN_3 (1.5 mmol, 1.5 equiv) was added, and the mixture was heated at 60 °C for 3 h. The reaction mixture was cooled to r.t., acetone was evaporated and the reaction mixture was diluted with H_2O (100 mL), and extracted with EtOAc (2 × 100 mL). The organic layer was washed with sat. NaCl (50 mL), dried over Na_2SO_4, and evaporated to give the dendritic azide.

(19) **First-Generation Dendritic Azide 11**: white solid; yield: 99%; R_f 0.6 (EtOAc–hexane, 1:1); mp 133 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.78, 1.96, 2.00 (3 × s, 24 H), 3.92–3.97 (m, 2 H), 4.04–4.11 (m, 2 H), 4.21–4.26 (m, 4 H), 5.13 (s, 4 H), 5.18–5.21 (m, 2 H), 5.32–5.43 (m, 4 H), 5.84 (d, *J* = 2.7 Hz, 2 H), 6.50 (d, *J* = 2.1 Hz, 2 H), 6.57 (d, *J* = 2.1 Hz, 1 H), 7.86 (s, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1, 19.5, 19.5, 19.6, 53.6, 60.6, 60.9, 66.8, 69.4, 71.7, 74.2, 84.8, 100.6, 106.8, 120.3, 137.0, 143.6, 158.6, 167.9, 168.4, 168.9, 169.5. MS (FAB): *m*/*z* = 987 [M$^+$]. Anal. Calcd for $C_{41}H_{49}N_9O_{20}$: C, 49.85; H, 5.00; N, 12.76. Found: C, 49.81; H, 4.96; N, 12.51.

(20) **Second-Generation Dendritic Azide 13**: white solid; yield: 99%; R_f 0.72 (EtOAc–hexane, 7:3); mp 159 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.82, 2.02, 2.05, 2.07 (4 × s, 48 H), 4.02–4.05 (m, 4 H), 4.11–4.17 (m, 4 H), 4.24 (d, *J* = 4.8 Hz, 2 H), 4.27–4.32 (m, 4 H), 5.14 (s, 8 H), 5.17 (s, 4 H), 5.27 (t, *J* = 9.6 Hz, 4 H), 5.39–5.50 (m, 12 H), 5.93 (d, *J* = 8.7 Hz, 4 H), 6.51 (s, 4 H), 6.59 (s, 2 H), 6.60 (s, 1 H), 6.64 (s, 2 H), 7.63 (s, 2 H), 7.96 (s, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.1, 20.5, 20.5, 20.6, 54.0, 54.6, 61.6, 61.8, 62.1, 67.7, 70.4, 72.6, 75.1, 85.8, 101.7, 107.9,107.7, 107.8, 121.6, 123.0, 137.0, 144.2, 144.3, 159.4, 159.7, 168.9, 169.4, 169.9, 170.5. MS (FAB): *m*/*z* = 2217 [M$^+$]. Anal. Calcd for $C_{95}H_{109}N_{21}O_{42}$: C, 51.46; H, 4.95; N, 13.27. Found: C, 51.41; H, 4.90; N, 13.14.

(21) **General Procedure for the De-O-acetylation (Zemplen Reaction)**: Acetylated dendrimers (1.0 mmol) was dissolved in a mixture of anhyd MeOH–anhyd THF–anhyd CH_2Cl_2 (16 mL, 6:1:1) and to this mixture was added a solution of sodium methoxide (1 M MeOH) until pH 9–10 was reached. The reaction was stirred at r.t. for 48 h. At the end, H_2O was added for entire solubilization of desired compound and the solution was neutralized by addition of ion-exchange resin (Amberlite IR 120 H$^+$) until pH 6–7 was attained. The solution was filtered and the solvent was removed in vacuo with rotary evaporator. The residue was then lyophilized to yield the fully deprotected glycodenrimer in a ca. 99% yield.

(22) **Glycodendrimer 2**: white solid; yield: 95%; $[\alpha]_D^{25}$ +44.5 (*c* = 1, DMSO). IR (KBr): 3404, 1372, 1230, 1042, 826 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.21 (d, *J* = 8.4 Hz, 4 H), 3.55–3.66 (m, 8 H), 5.18 (q, *J* = 3.6 Hz, 4 H), 5.43 (d, *J* = 9.0 Hz, 2 H), 6.88 (d, *J* = 8.4 Hz, 2 H), 7.22 (t, *J* = 7.4 Hz, 2 H), 7.33 (t, *J* = 7.5 Hz, 2 H), 7.75–7.78 (m, 4 H), 7.94 (d, *J* = 9.0 Hz, 2 H), 8.06 (d, *J* = 9.0 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 60.4, 62.2, 72.0, 76.4, 79.4, 87.2, 115.8, 119.3, 123.0, 123.9, 124.4, 126.5, 128.9, 129.5, 133.2, 143.2, 143.2, 153.4. MS (FAB): *m*/*z* = 772 [M$^+$]. Anal. Calcd for $C_{38}H_{40}N_6O_{12}$: C, 59.06; H, 5.22; N, 10.88. Found: C, 59.03; H, 5.20; N, 10.87.

(23) **Glycodendrimer 4**: white solid; yield: 92%; $[\alpha]_D^{25}$ +15.5 (*c* = 1, DMSO). IR (KBr): 3426, 1595, 1412, 1046, 834 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.00 (s, 8 H), 3.43–3.56 (m, 8 H), 4.85–4.94 (m, 12 H), 5.14 (s, 8 H), 5.31 (d, *J* = 9.0 Hz, 4 H), 5.54 (s, 4 H), 6.26 (s, 4 H), 6.53 (s, 2 H), 6.60 (d, *J* = 8.4 Hz, 2 H), 7.90 (t, *J* = 7.5 Hz, 2 H), 7.04 (t, *J* = 7.5 Hz, 2 H), 7.34 (s, 2 H), 7.45 (d, *J* = 9.0 Hz, 2 H), 7.65 (d, *J* = 9.0 Hz, 2 H), 7.76 (d, *J* = 9.0 Hz, 2 H), 8.20 (s, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.7, 60.5, 60.8, 62.3, 69.2, 72.0, 76.6, 79.4, 87.4, 100.8, 107.1, 115.8, 119.3, 123.8, 124.0, 124.3, 126.3, 128.0, 128.9, 129.4, 133.1, 137.7, 142.4, 143.5, 153.2, 159.3. MS (MALDI–TOF): *m*/*z* = 1665 [M$^+$]. Anal. Calcd for $C_{76}H_{84}N_{18}O_{26}$: C, 54.80; H, 5.08; N, 15.14. Found: C, 54.79; H, 5.08; N, 15.11.

(24) **Glycodendrimer 6**: white solid; yield: 92%; $[\alpha]_D^{25}$ +2.2 (*c* = 1, DMSO). IR (KBr): 3390, 1598, 1461, 1384, 1168, 1047, 828 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.24 (s, 16 H), 3.68–3.82 (m, 16 H), 5.07 (s, 8 H), 5.11 (s, 16 H), 5.18 (d, *J* = 4.8 Hz, 8 H), 5.32 (d, *J* = 3.6 Hz, 12 H), 5.44 (d, *J* = 9.0 Hz, 8 H), 5.54 (s, 8 H), 5.57 (s, 4 H), 6.45 (s, 4 H), 6.62 (s, 8 H), 6.71 (s, 2 H), 6.77 (s, 4 H), 6.81 (d, *J* = 8.4 Hz, 2 H), 7.10 (t, *J* = 7.8 Hz, 2 H), 7.24 (t, *J* = 6.6 Hz, 2 H), 7.52 (s, 2 H), 7.66 (d, *J* = 8.7 Hz, 2 H), 7.83 (d, *J* = 7.5 Hz, 2 H), 7.96 (d, *J* = 8.4 Hz, 2 H), 8.29 (s, 4 H), 8.32 (s, 8 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.8, 60.5, 60.8, 62.2, 69.2, 72.0, 76.6, 79.4, 87.3, 100.9, 107.1, 115.7, 119.3, 123.8, 124.0, 124.3, 124.8, 125.7, 126.3, 127.8, 127.9, 128.8, 129.2, 129.3, 133.0, 137.6, 138.0, 142.4, 142.7, 143.5, 153.2, 159.1, 159.2. MS (MALDI–TOF): *m*/*z* = 3451 [M$^+$]. Anal. Calcd for $C_{152}H_{172}N_{42}O_{54}$: C, 52.90; H, 5.02; N, 17.05. Found: C, 52.89; H, 5.02; N, 17.02.