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Synthesis of Triazole-Linked Glycoconjugates by Copper(I)-Catalyzed Regiospecific Cycloaddition of Alkynes and Azides

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Abstract: Several 1,2,3-triazole-linked glycoconjugates were efficiently synthesized via a Cu(I)-mediated 1,3-dipolar cycloaddition with high regiospecificity and yield ($\geq 85\%$), providing a simple and efficient route to synthesize protected and unprotected neoglycoconjugates. Introduction of a spacer between glycosyl moieties and other compounds reduces steric hindrance, promotes yield, and expands the varieties of glycoconjugates to satisfy various needs of biological events. The structures of all the synthesized glycoconjugates were clearly confirmed by infrared(IR), ^{1}H NMR, ^{13}C NMR, elemental analysis (EA), or MS.

Keywords: Click chemistry, 1,3-dipolar cycloaddition, glycoconjugates, 1,2,3-triazoles

Oligosaccharides and glycoconjugates have been shown to govern crucial life processes and disease states,[1,2] so a lot of effort has been made to attach sugars to scaffolds to construct neoglycoconjugates in rapid and convenient way.[3–6] Our research efforts have been aimed at synthesis of triazole-linked neoglycoconjugates via a mild, Cu(I)-catalyzed procedure for the [3 + 2] cycloaddition between organic azides

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and acetylenes, leading to a regioselective reaction toward 1,4-disubstituted 1,2,3-triazole in high yields ("click reactions"), developed independently by the Sharpless and Meldal groups.[7,8]

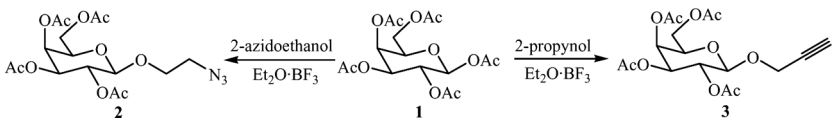
Click chemistry has been widely used in medicinal,[9] supramolecular, and material chemistry[10] such as in dendrimers[11–13] and liquid crystals.[14,15] Application of this protocol to oligosaccharides and glycoconjugates has recently begun, and most of the reports are concerned with the use of anomeric azides.[16–19] Because of steric hindrance, lots of compounds had low yields[13–16] which limited application of click chemistry to oligosaccharides and glycoconjugates. Therefore, an introduction of a spacer between the sugar moiety and lipids or peptides or other compounds is required.[23,24] This will also expand structural diversity of glycoconjugates and satisfy various needs of biological events. Based on these facts, we designed efficient procedures to synthesize 1,2,3-triazole-linked glycoconjugates with aromatic compounds, heterocyclic compounds, amino acids, sterol, and steroid saponin.

In our approach, to obtain 1,4-disubstituted-1,2,3-triazole-linked glycoconjugtes, galactose was chosen as a model of glycosyl moiety. 2-Azidoethyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (**2**) and 2-propynyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (**3**) used in Huisgen 1,3-dipolar cycloaddition reaction were obtained by reactions of peracetylated galactose with 2-azidoethanol or 2-propynol in the presence of $Et_2O \cdot BF_3$ (Scheme 1).[25,26]

Reaction of 2-azidoethyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (**2**) with *p*-methoxyphenyl acetylene (**4a**) or *p*-pentylphenyl acetylene (**4b**) in the presence of CuI in toluene afforded exclusively the 1,4-disubstituted 1,2,3-triazole-linked glycoconjugtes **5a** and **5b** in high yield, respectively (Table 1).

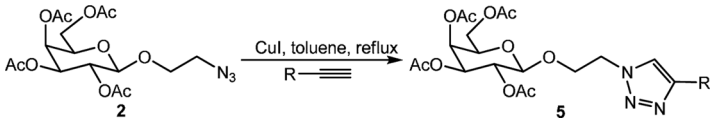
Our next endeavors were devoted toward performing the Huisgen 1,3-dipolar cycloaddition reaction with 2-propynyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (**3**). To this end, we have synthesized various azido moieties in three strategies as follows (Scheme 2).

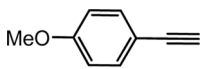
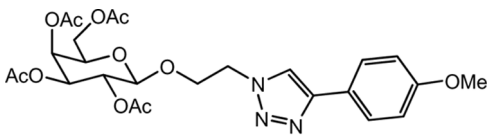
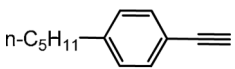
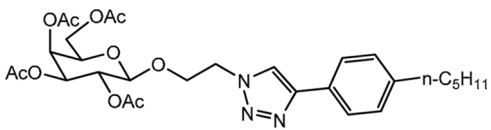
Subsequently, those azides were reacted with glycosyl alkyne (**3**) in the presence of CuI to produce various glycoconjugates (**9a**–**f**) as show in Table 2. Most reactions were highly regioselective and yielded more than 85% except the reaction between **3** and **6**, in which 1,4-disubstituted



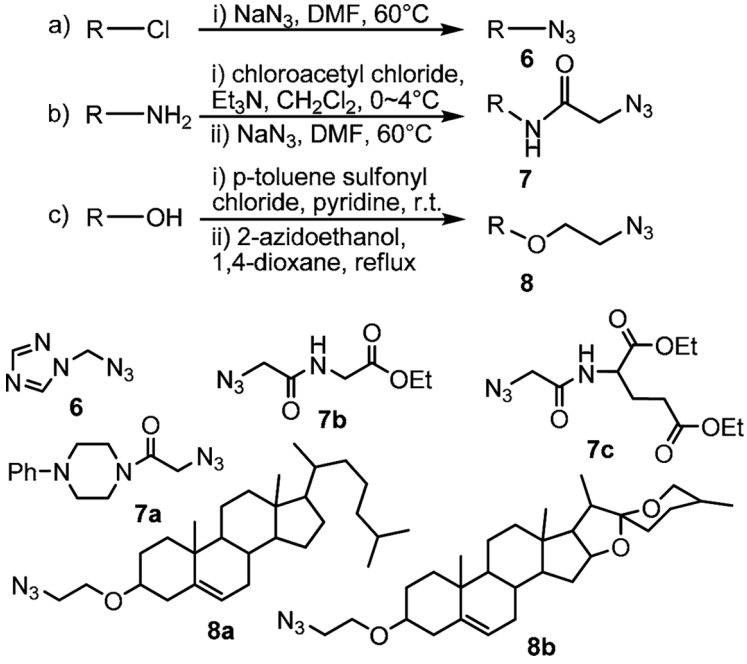
Scheme 1. Synthesis of azido and alkynyl glycoside.

Table 1. Synthesis of 1,2,3-triazole-linked glycoconjugtes with 2-azidoethyl 2,3,4,6-tetra-O-acetyl-β-D-galactopyranoside and aryl alkyne



Entry	R–≡	Product	Yield[a] (%)
1	 **4a**	 **5a**	93
2	 **4b**	 **5b**	92

[a]Isolated yield.



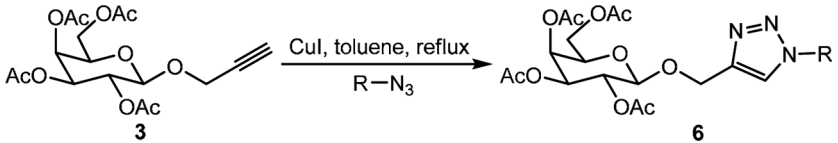
Scheme 2. Synthesis of azido moiety.

triazole was not exclusively obtained and an isomer (1,5-disubstituted triazole) was produced, judging from NMR. It was found that the isomer had been decreasing as the CuI increased because the ratio of integral area of ^{1}H NMR and the ratio of 1,4- and 1,5-disubstituted triazole was 47:53, 63:37, and 83:17 in the presence of 0.1 eq CuI, 0.2 eq CuI, and 0.5 eq CuI, respectively. Subsequently, the other method[24,25] was adopted in which **9a** was exclusively synthesized and yielded 88% using the catalyst of 2 eq CuI and 3 eq *N,N*-diisopropylethylamine (DIPEA) in dried toluene under room temperature for 24 h, possibly because of DIPEA promoting Cu(I) insertion into terminal alkynes.[27,28] All those target products were confirmed by ^{1}H NMR, ^{13}C NMR, IR, and EA or Ms.

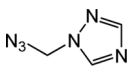
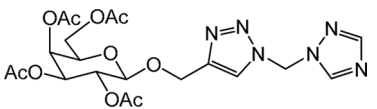
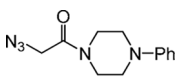
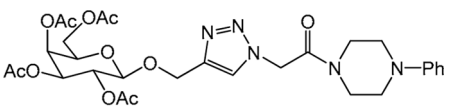
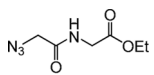
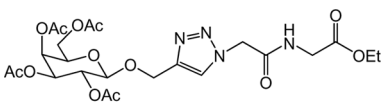
In addition, all products synthesized by us would be deprotected easily in alkaline solution[25,26] without a side reaction, which could satisfy some biological need for unprotected oligosaccharides or glycoconjugates. Therefore, our strategies could be comprehensively applied to synthesize a series of protected or unprotected neoglycoconjugates.

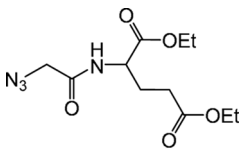
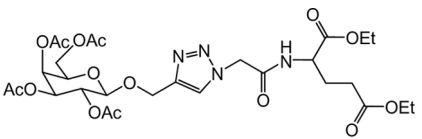
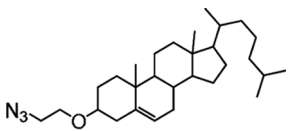
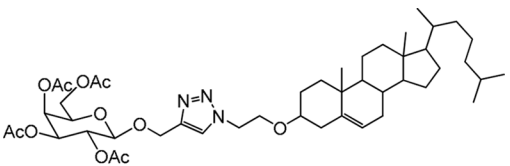
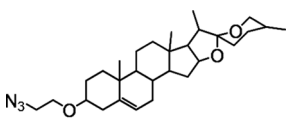
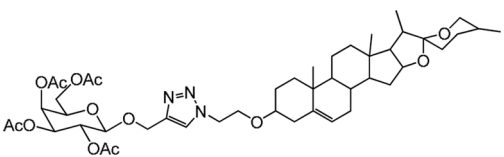
In conclusion, we have developed a practical strategy for the ligation of sugar to amino acids, lipids, and aryl and heterocyclic compounds under mild reaction conditions with high regioselectivity.

Table 2 Synthesis of 1,2,3-triazole-linked glycoconjugtes with 2-propynyl 2,3,4,6-tetra-O-acetyl-β-D-galactopyranoside and azides



3 **6**

Entry	R–N_3	Product	Yield[a] (%)
1	 **6**	 **9a**	88
2	 **7a**	 **9b**	92
3	 **7b**	 **9c**	95

4	 **7c**	 **9d**	93
5	 **8a**	 **9e**	89
6	 **8b**	 **9f**	85

[a]Isolated yield.

Through introduction of a spacer between the glycosyl moiety and other compounds, steric hindrance effect was reduced, and high yields were achieved. Therefore, this diversity-oriented synthesis opens a simple way to build a metabolically stable triazole linkage between carbohydrates and other biomolecules, which can be used as new strategies for the fast generation of small library of neoglycoconjugates.

EXPERIMENTAL

Compounds **1**,[29] **2**,[25] **3**,[26] 5-cholesten-3β-tosylate, and 5-spirosten-3β-tosylate[30,31] were obtained following the procedures described in literature.

Synthesis of 5a

CuI (0.038 g, 0.1 eq) was added to a solution of compound **2** (0.83 g, 2.0 mmol) and *p*-methoxyphenyl acetylene (0.27 g, 1 eq) in toluene (20 mL) and then refluxed for 2 h. At the end of the reaction as judged by thin-layer chromatographic (TLC) analysis, the reaction solution was concentrated, and the residue was again dissolved in ethyl acetate (50 mL), and washed with water (3×50 mL). The organic phase was dried over anhydrous sodium sulfate and subsequently filtered and concentrated. The crude product was purified by silica-gel column chromatography to afford **5a** as a slightly yellow, viscous product (1.02 g, 93%). IR (KBr): ν/cm^{-1} 3134, 2108, 1746; ^{1}H NMR ($CDCl_3$): δ/ppm 7.77 (s, 1 H), 7.75 (d, 2 H, $J = 9.0$ Hz), 6.91 (d, 2 H, $J = 9.0$ Hz), 5.34 (d, 1 H, $J = 3.0$ Hz), 5.16 (dd, 1 H, $J = 8.0$, 10.5 Hz), 4.94 (dd, 1 H, $J = 3.0$, 10.5 Hz), 4.52 (m, 1 H), 4.46 (m, 1 H), 4.41 (d, 1 H, $J = 8.0$ Hz), 4.22–4.24 (m, 1 H), 4.04–4.14 (m, 2 H), 3.83–3.91 (m, 2 H), 3.81 (s, 3 H), 2.11, 1.98, 1.90, 1.67 (4 s, 12 H); ^{13}C NMR ($CDCl_3$): δ/ppm 172.5, 170.6, 168.7, 165.9, 159.0, 147.2, 126.8, 123.0, 120.8, 113.9, 105.9, 70.1, 68.2, 67.3, 66.2, 61.0, 55.1, 50.1, 20.7. Anal. calcd. for $C_{25}H_{31}N_3O_{11}$: C, 54.64; H, 5.69; N, 7.65. Found: C, 54.59; H, 5.60; N, 5.74.

Synthesis of 5b

The compound **5b** was obtained according to general procedure of compound **5a** and isolated as a slightly yellow, viscous product (1.08 g, 92%). IR (KBr): ν/cm^{-1} 3134, 2109, 1761; ^{1}H NMR ($CDCl_3$): δ/ppm 7.29 (s, 1 H, $J = 3.0$ Hz), 7.23 (d, 2 H, $J = 9.0$ Hz), 7.19 (d, 2 H, $J = 9.0$ Hz), 5.34

(d, 1 H, $J = 3.0$ Hz), 5.15 (dd, 1 H, $J = 8.0$, 10.5 Hz), 4.93 (dd, 1 H, $J = 3.0$, 10.5 Hz), 4.59–4.65 (m, 1 H), 4.45–4.52 (m, 1 H), 4.42 (d, 1 H, $J = 8.0$ Hz), 4.21–4.23 (m, 1 H), 4.03–4.07 (m, 2 H), 3.82–3.91 (m, 2 H), 2.57 (t, 2 H, $J = 8.0$ Hz), 2.10, 1.98, 1.90, 1.68 (4 s, 12 H), 1.57 (quint, 2 H, $J = 7.0$ Hz), 1.23–1.62 (m, 4 H), 0.84 (t, 3 H, $J = 7.0$ Hz); ^{13}C NMR ($CDCl_3$): δ/ppm 172.5, 170.6, 168.8, 166.1, 147.6, 142.7, 128.7, 127.9, 125.4, 120.8, 104.6, 70.6, 68.2, 67.8, 66.9, 61.0, 49.9, 35.1, 31.2, 22.3, 20.2, 14.1. Anal. calcd. for $C_{29}H_{39}N_3O_{10}$: C, 59.07; H, 6.67; N, 7.13; Found: C, 59.10; H, 6.57; N, 7.21.

Synthesis of 6

1-(Chloromethyl)-1*H*-1,2,4-triazole (2.0 g, 17.1 mmol) was dissolved in *N,N*-dimethylformamide (DMF) (50 mL), followed by the addition of NaN_3 (7.8 g, 0.12 mol). The heterogeneous mixture was stirred vigorously at 60 °C for 16 h. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with water (3×100 mL). The organic phase was dried with anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography to finally obtain a slightly yellow product **6** (1.7 g, 80%). IR (KBr): ν/cm^{-1} 2105; ^{1}H NMR ($CDCl_3$): δ/ppm 8.20 (s, 1 H), 7.93 (s, 1 H), 5.39 (s, 2 H). Anal. calcd. for $C_3H_4N_6$: C, 29.03; H, 3.25; N, 67.72. Found: C, 29.28; H, 3.21; N, 67.68.

Synthesis of 7a

Chloroacetyl chloride (0.8 mL, 1 eq) dropwise at 0 °C. was added to a solution of 1-phenylpiperazine hydrochloride (2.0 g, 10 mmol) and triethylamine (2.8 mL, 2 eq) in anhydrous dichloromethane (50 mL). The reaction mixture was stirred at room temperature for 2 h and monitored by TLC. Then the mixture was diluted with dichloromethane (50 mL) and washed with water (2×100 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated to yield a solid, which was crystallized to obtain 2-chloroacetyl 4-phenylpiperazine (2.2 g, 92%). ^{1}H NMR ($CDCl_3$): δ/ppm ^{1}H NMR ($CDCl_3$): δ/ppm 7.26–7.29 (m, 2 H), 6.89–6.93 (m, 3 H), 4.10 (s, 2 H, $J = 7.0$ Hz), 3.78, 3.67, 3.22, 3.17 (4 t, 8 H, $J = 5.0$ Hz).

The compound **7a** was obtained according to general procedure of compound **6** with 2-chloroacetyl 4-phenylpiperazine, and isolated as a slightly brown solid (1.7 g, 81%). IR (KBr): ν/cm^{-1} 3010, 2105, 1644; ^{1}H NMR ($CDCl_3$): δ/ppm 7.28–7.33 (m, 2 H), 6.92–6.96 (m, 3 H), 4.02

(s, 2 H), 3.82, 3.56, 3.21 (3 t, 8 H,$J = 5.0$ Hz). Anal. calcd. for $C_{12}H_{15}N_5O$: C, 58.76; H, 6.16; N, 28.55. Found: C, 58.71; H, 6.13; N, 28.61.

Synthesis of 7b

The compound **7b** was obtained according to general procedure of compound **7a**. First, ethyl N-(2-chloroacetyl)-glycinate was synthesized and isolated as a white solid (2.3 g, 92%). ^{1}H NMR ($CDCl_3$): δ/ppm 4.29 (quart, 2 H, $J = 7.0$ Hz), 4.06–4.09 (m, 4 H), 1.30 (t, 3 H, $J = 7.0$ Hz).

Compound **7b** was obtained according to general procedure of compound **6** with ethyl N-(2-chloroacetyl)-glycinate and isolated as a white solid (1.5 g, 72%). IR (KBr): ν/cm^{-1} 3321, 2108, 1747, 1674; ^{1}H NMR ($CDCl_3$): δ/ppm 6.87 (s, 1 H), 4.23 (quart, 2 H, $J = 7.0$ Hz), 4.03–4.15 (m, 4 H), 1.30 (t, 3 H, $J = 7.0$ Hz). Anal. calcd. for $C_6H_{10}N_4O_3$: C, 38.71; H, 5.41; N, 30.09; Found: C, 38.66; H, 5.44; N, 30.11.

Synthesis of 7c

The compound **7c** was obtained according to general procedure of compound **7a**. First, diethyl N-(2-chloroacetyl)-*L*-glutamate was synthesized and isolated as a white solid (2.6 g, 91%). ^{1}H NMR ($CDCl_3$): δ/ppm 7.26 (d, 1 H, $J = 6.5$ Hz), 4.47–4.51 (m, 1 Hz), 4.10, 4.02 (2 quart, 4 H, $J = 7.0$ Hz), 3.97 (s, 2 H), 2.22–2.36 (m, 2 Hz), 2.10–2.17 (m, 1 Hz), 1.91–1.99 (m, 2 Hz), 1.18, 1.12 (2 t, 6 H, $J = 6.5$ Hz).

The compound **7c** was obtained according to general procedure of compound **6** with diethyl N-(2-chloroacetyl)-*L*-glutamate and isolated as a white solid (1.5 g, 73%). IR (KBr): ν/cm^{-1} 3334, 2104, 1733, 1693; ^{1}H NMR ($CDCl_3$): δ/ppm 7.02 (d, 1 H, $J = 7.5$ Hz), 4.58–4.63 (m, 1 Hz), 4.22, 4.19 (2 quart, 4 Hz), 4.00 (s, 2 H), 2.32–2.46 (m, 2 Hz), 2.18–2.27 (m, 1 Hz), 2.00–2.08 (m, 2 Hz), 1.29, 1.25 (2 t, 6 H, $J = 7.0$ Hz). Anal. calcd. for $C_{11}H_{18}N_4O_5$: C, 46.15; H, 6.34; N, 19.57. Found: C, 46.21; H, 6.36; N, 19.59.

Synthesis of 8a

A solution of 5-cholesten-3β-tosylate (2.0 g, 3.7 mmol) in freshly distilled dioxane (24 mL) was allowed to mix with 2-azidoethanol (3.9 g, 12 eq) and then refluxed for 24 h under an argon atmosphere. After the concentration of the reaction solution, the residue was again dissolved in ethyl acetate. The organic layer was washed with water, dried over anhydrous

sodium sulfate, and subsequently filtered and concentrated. The crude product was purified with column chromatography to finally obtain a white solid **8a** (1.0 g, 48%). IR (KBr): ν/cm^{-1} 2103; ^1H NMR ($CDCl_3$): δ/ppm 5.36 (d, 1 H, $J = 5.0$ Hz), 3.67 (t, 2 H, $J = 5.0$ Hz), 3.37 (t, 2 H, $J = 5.0$ Hz), 3.17–3.26 (m, 1 H), 1.00 (s, 3 H), 0.92 (d, 3 H, $J = 2.5$ Hz), 0.89 (d, 6 H, $J = 2.5$ Hz), 0.69 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ/ppm 140.6, 121.7, 79.7, 66.7, 56.7, 56.1, 51.0, 50.1, 42.3, 39.7, 39.5, 38.9, 37.1, 36.8, 36.2, 35.8, 31.9, 31.8, 28.3, 28.2, 28.0, 24.3, 23.8, 22.8, 22.5, 21.0, 19.3, 18.7, 11.8. Anal. calcd. for $C_{29}H_{49}N_3O$: C, 76.43; H, 10.84; N, 9.22. Found: C, 76.39; H, 10.90; N, 9.17.

Synthesis of 8b

The compound **8b** was obtained according to general procedure of compound **8a** with 5-spirosten-3β-tosylate and isolated as a slightly white solid (0.95 g, 57%). IR (KBr): ν/cm^{-1} 2103; ^1H NMR ($CDCl_3$): δ/ppm 5.33 (d, 1 H, $J = 5.0$ Hz), 4.39 (quart, 1 H,$J = 7.0$ Hz), 3.63–3.64 (m, 2 H), 3.43–3.44 (m, 1 H), 3.33–3.38 (m, 3 H), 3.12–3.22 (m, 1 H), 2.39 (dd, 1 H), 2.21 (t, 1 H); ^{13}C NMR ($CDCl_3$): δ/ppm 140.7, 121.5, 109.3, 80.8, 79.6, 66.9, 66.8, 62.0, 56.5, 51.0, 50.1, 41.6, 40.2, 39.8, 38.9, 37.1, 36.9, 32.1, 31.8, 30.3, 28.8, 28.3, 20.8, 19.4, 17.1, 16.3, 14.5. Anal. calcd. for $C_{29}H_{45}N_3O_3$: C, 72.01; H, 9.38; N, 8.69. Found: C, 71.97; H, 9.44; N, 8.70.

Synthesis of 9a

The compound **9a** was obtained by the reported method.[18,19] To a solution of 2-propynyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (**3**) (0.2 g, 1.6 mmol) and 1-(azidomethyl)-1*H*-1,2,4-triazole (**6**) (0.75 g, 1 eq) in 20 mL of anhydrous toluene, CuI (0.61 g, 2eq) and *N*,*N*-diisopropylethylamine (0.84 mL, 3 eq) were added at room temperature, and the mixture was stirred for 24 h. At the end of the reaction, as judged by TLC analysis, the reaction mixture was diluted using 50 mL of water, the aqueous layer was extracted with ethyl acetate (3×70 mL), and the combined organic layer was washed with brine solution, dried over anhydrous sodium sulfate, and concentrated in vacuo to obtain a crude residue that was purified to obtain the desired 1,4-disubstited 1,2,3-triazole as a slightly yellow, viscous product (0.72 g, 88%). IR (KBr): ν/cm^{-1} 2108, 1741; ^1H NMR ($CDCl_3$): δ/ppm 8.43 (s, 1 H), 7.86 (s, 1 H), 7.54 (s, 1 H), 6.63 (s, 2 H), 5.33 (d, 1 H, $J = 3.5$ Hz), 5.16 (dd, 1 H, $J = 7.5$, 10.5 Hz), 5.05 (d, 1 H, $J = 12.5$ Hz), 4.98 (dd, 1 H, $J = 3.5$, 10.5 Hz),

4.90 (d, 1 H, $J = 12.5$ Hz), 4.62 (d, 1 H, $J = 7.5$ Hz), 4.02–4.08 (m, 2 H), 3.92 (t, 2 H, $J = 6.5$ Hz), 2.08, 1.95, 1.93, 1.89 (4 s, 12 H); ^{13}C NMR ($CDCl_3$): δ/ppm 170.3, 170.1, 169.9, 169.5, 153.0, 134.3, 144.3, 133.2, 100.5, 72.4, 70.6, 68.5, 67.0, 61.3, 59.1, 58.4, 20.7, 20.6, 20.5. Anal. calcd. for $C_{20}H_{26}N_6O_{10}$: C, 47.06; H, 5.13; N, 16.46. Found: C, 47.01; H, 5.10; N, 16.52.

Synthesis of 9b

The compound **9b** was obtained according to general procedure of compound **5a**, and isolated as a slightly yellow, viscous product (1.16 g, 92%). IR (KBr): v/cm^{-1} 3147, 2108, 1746, 1668; ^{1}H NMR ($CDCl_3$): δ/ppm 8.43, 7.72 (s, 1 H), 7.27 (t, 2 H), 6.91 (t, 3 H), 5.37 (d, 1 H, $J = 3.5$ Hz), 5.26 (s, 2 H), 5.20 (dd, 1 H, $J = 8.0$, 10.5 Hz), 5.00 (dd, 1 H, $J = 3.5$, 10.5 Hz), 4.97 (d, 1 H, $J = 12.5$ Hz), 4.82 (d, 1 H, $J = 12.5$ Hz), 4.63 (d, 1 H, $J = 8.0$ Hz), 4.08–4.15 (m, 2 H), 3.91 (t, 2 H, $J = 6.5$ Hz), 3.76, 3.67, 3.21, 3.15 (4 t, 8 H, $J = 5.0$ Hz), 2.11, 2.02, 1.97, 1.95 (4 s, 12 H). ^{13}C NMR ($CDCl_3$): δ/ppm 170.4, 170.2, 170.0, 169.6, 163.3, 150.6, 144.2, 129.3, 124.7, 120.8, 116.7, 100.2, 70.8, 70.7, 68.7, 67.0, 62.7, 61.3, 50.8, 49.5, 49.1, 45.2, 42.2, 20.7, 20.6, 20.5. Anal. calcd. for $C_{29}H_{37}N_5O_{11}$: C, 55.14; H, 5.90; N, 11.09. Found: C, 55.06; H, 5.97; N, 11.03.

Synthesis of 9c

The compound **9c** was obtained according to general procedure of compound **5a** and isolated as a slightly yellow, viscous product (1.08 g, 95%). IR (KBr): v /cm^{-1} 3321, 1754, 1698; ^{1}H NMR ($CDCl_3$): δ/ppm 8.43, 7.72 (s, 1 H), 5.30 (d, 1 H, $J = 3.5$ Hz), 5.09–5.30 (m, 3 H), 4.95 (dd, 1 H, $J = 3.5$, 10.5 Hz), 4.86 (d, 1 H, $J = 12.5$ Hz), 4.72 (d, 1 H, $J = 12.5$ Hz), 4.58 (d, 1 H, $J = 8.0$ Hz), 4.03–4.11 (m, 4 H), 3.89–3.94 (m, 3 H), 2.05, 1.96, 1.90, 1.87 (4 s, 12 H), 1.17 (t, 3 H, $J = 7.0$ Hz); ^{13}C NMR ($CDCl_3$): δ/ppm 170.2, 170.0, 169.8, 169.4, 169.1, 165.4, 144.0, 124.7, 99.8, 70.7, 70.6, 68.5, 67.8, 62.3, 61.2, 52.4, 41.1, 20.7, 19.9, 19.8, 13.6. Anal. calcd. for $C_{23}H_{32}N4O_1$: C, 48.25; H, 5.63; N, 9.79. Found: C, 48.19; H, 5.87; N, 9.82.

Synthesis of 9d

The compound **9d** was obtained according to general procedure of compound **5a** and isolated as a slightly yellow, viscous product (1.24 g,

93%). IR (KBr): ν/cm^{-1} 3350, 2108, 1748, 1699; ^1H NMR ($CDCl_3$): δ/ppm 8.43, 7.70 (s, 1 H), 7.24 (s, 1 H), 5.33 (d, 1 H, $J = 3.0$ Hz), 5.13 (dd, 1 H, $J = 8.0$, 10.5 Hz), 5.03 (d, 2 H, $J = 12.0$ Hz), 4.96 (dd, 1 H, $J = 3.5$, 10.5 Hz), 4.92 (d, 1 H, $J = 12.5$ Hz), 4.77 (d, 1 H, $J = 12.5$ Hz), 4.60 (d, 1 H, $J = 8.0$ Hz), 4.52 (quart, 1 H, $J = 6.0$ Hz), 4.04–4.14 (m, 6 H), 3.91 (t, 1 H, $J = 6.5$ Hz), 2.25–2.38 (m, 2 H), 1.90–2.12 (m, 14 H), 1.17–1.22 (m, 6 H); ^{13}C NMR ($CDCl_3$): δ/ppm 172.5, 171.2, 170.3, 170.1, 169.9, 169.5, 165.2, 144.2, 124.8, 99.8, 70.7, 70.6, 68.7, 67.1, 62.3, 61.6, 61.3, 60,6, 52.2, 51.9, 30.1, 26.8, 20.8, 20.5, 20.3, 14.0, 13.9. Anal. calcd. for $C_{28}H_{40}N_4O_{15}$: C, 50.00; H, 5.99; N, 8.33. Found: C, 50.10; H, 5.97; N, 8.41.

Synthesis of 9e

The compound **9e** was obtained according to general procedure of compound **5a** and isolated as a white solid (1.50 g, 89%). IR (KBr): ν/cm^{-1} 1748; ^1H NMR ($CDCl_3$): δ/ppm 8.43, 7.70 (s, 1 H), 5.38 (d, 1 H, $J = 3.5$ Hz), 5.30–5.32 (m, 1 H), 5.21 (dd, 1 H, $J = 8.0$, 10.5 Hz), 4.98 (dd, 1 H, $J = 3.5$, 10.5 Hz), 4.95 (d, 1 H, $J = 12.5$ Hz), 4.80 (d, 1 H, $J = 12.5$ Hz), 4.64 (d, 1 H, $J = 8.0$ Hz), 4.45–4.54 (m, 2 H), 4.12–4.19 (m, 2 H), 3.94 (t, 1H, $J = 6.5$ Hz), 3.78–3.87 (m, 2 H), 3.08–3.15 (m, 1 H), 0.97 (s, 3 H), 0.89 (d, 3 H, $J = 3.0$ Hz), 0.85 (d, 3 H, $J = 2.0$ Hz), 0.83 (d, 3 H, $J = 2.0$ Hz), 0.65 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ/ppm 170.3, 170.2, 170.0, 169.4, 143.8, 122.0, 100.1, 79.7, 70.8, 70.7, 68.7, 67.0, 66.2, 62.7, 61,2, 56.7, 56.1, 50.8, 50.1, 42.2, 39.7, 39.4, 38.9, 37.0, 36.7, 36.1, 35.7, 31.8, 28.2, 27.9, 24.2, 23.8, 22.8, 22.6, 21.0, 20.7, 20.6, 20.6, 20.5, 19.3, 18.7, 11.2; ESI MS $[M + H]^+$m/e: calcd. for $C_{46}H_{68}N_3O_{13}$, 870.5, found 870.5.

Synthesis of 9f

The compound **9f** was obtained according to general procedure of compound **5a** and isolated as a white solid (1.48 g, 85%). IR (KBr): ν/cm^{-1} 1751; ^1H NMR ($CDCl_3$): δ/ppm 7.70 (s, 1 H), 5.42 (d, 1 H, $J = 3.0$ Hz),), 5.34 (d, 1 H, $J = 5.0$ Hz), 5.23 (dd, 1 H, $J = 8.0$, 10.5 Hz), 5.12 (dd, 1 H, $J = 3.5$, 10.5 Hz), 4.97 (d, 1 H, $J = 12.5$ Hz), 4.83 (d, 1 H, $J = 12.5$ Hz), 4.67 (d, 1 H, $J = 8.0$ Hz), 4.45–4.46 (m, 2 H), 4.30–4.40 (quart, 1 H, $J = 7.0$ Hz), 4.14–4.22 (m, 2 H), 3.96 (t, 1 H, $J = 6.5$ Hz), 3.81–3.91 (m, 2 H), 3.45–3.51 (m, 1 H), 3.38 (t, 1 H, $J = 7.5$ Hz), 3.10–3.18 (m, 1 H); ^{13}C NMR ($CDCl_3$): δ/ppm 170.2, 170.1, 169.9, 169.3, 143.7, 121.6, 109.1, 100.1, 80.8, 80.7, 70.8, 70.7, 68.7, 67.0, 66.7, 66.1, 62.7, 62.0,

61,2, 56.4, 50.7, 49.9, 41.5, 40.1, 39.6, 38.8, 36.9, 36.8, 31.9, 31.7, 31.3, 30.2, 28.7, 28.1, 20.7, 20.6, 20.5, 20.4, 19.2, 17.0, 16.1, 14.4; ESI MS $[M+H]^+$ m/e: calcd. for $C_{46}H_{72}N_3O_{11}$ 842.5; found 842.6.

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