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Synthesis of novel multidentate carbohydrate-triazole ligands

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Abstract

Cu(I)-catalyzed 1,3-dipolar cycloaddition (click reaction) of 1 mol equiv of *N*,*N*′-di-prop-2-ynyl-phthalamide (**1a**), *N*,*N*′-di-prop-2-ynyl-isophthalamide (**1b**), and pyridine-2,6-dicarboxylic acid bis-prop-2-ynylamide (**1c**), respectively with 2 mol equiv of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide (**2a**), 2-azidoethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**2b**), and 2-azidoethyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (**2c**), respectively, afforded the corresponding bis-cycloadducts **3**–**5**, containing two 1,2,3-triazole moieties each, in 38–76% yield. Reaction of 1 mol equiv of **2c** with 1 mol equiv of **1c** under otherwise identical conditions gave the mono-cycloadduct **6**, containing one 1,2,3-triazole and one 2-propynylamide moiety, in 77% yield. Reaction of **6** with **2a** afforded **7**, containing two different sugar moieties, in 67% yield.

Multivalent carbohydrate–protein interactions play fundamental roles in many biological processes like infection mechanisms, immunological processes, inflammation, signal transduction and cell differentiation. The majority of biogenic proteins is also glycosylated, and the glycosyl part of these proteins influences their biological activity. However, the molecular basis for such processes is still unclear.[1,2] This is especially true for carbohydrates and complex saccharides where cluster effects and the topographic arrangement of the sugar moieties are crucial factors, which reign over the magnitude of the binding of a sugar to a receptor or the specific interaction of saccharides with proteins. Often, carbohydrate–metal complexes are also involved in the specific binding of sugars to proteins.[3] Therefore, synthetic carbohydrate ligands are useful tools to study their complex interactions with proteins on a molecular level. Especially, carbohydrate–metal complexes had been recently shown to provide for deeper insight into carbohydrate–protein interactions[4–8] or for analytical tools valuable for studying such interactions in greater detail.[9,10]

Here, we describe a flexible and straightforward synthesis of novel multidentate carbohydrate ligands via Cu(I)-catalyzed 1,3-dipolar cycloaddition[11–23] of glycosyl azides and azidoethyl glycosides with bivalent 2-propynyl derivatives. Thus we obtained 1,2,3-triazole-linked multidentate carbohydrate ligands that are aimed at further studying the topography of their complexes with metal ions which, in turn, is thought to tune the binding properties of the sugar moieties to proteins (i.e., switchable carbohydrate recognition). We chose the 2-propynyl diamides **1a**–**c** as the alkynyl components for the 1,3-dipolar cycloaddition of glycosyl azides and 2-azidoethyl glycosides. They were prepared from the corresponding acid dichlorides and 2-propynyl amine (THF, 0–20 °C, 3 h) in 50–84% yield.[24] Scheme 1 and Table 1 summarize the 1,3-dipolar cycloadditions of **1a**–**c** with 2 mol equiv each of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide (**2a**),[25] 2-azidoethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**2b**),[17] and 2-azidoethyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (**2c**),[26], respectively.

Under catalysis with $(EtO)_3PCuI$,[27] all double click-reactions proceed smoothly at rt without the need of ultrasound irradiation. Careful inspection of the TLCs drawn in the course of the reactions revealed that the two cycloaddition steps proceed at different velocities. The first addition

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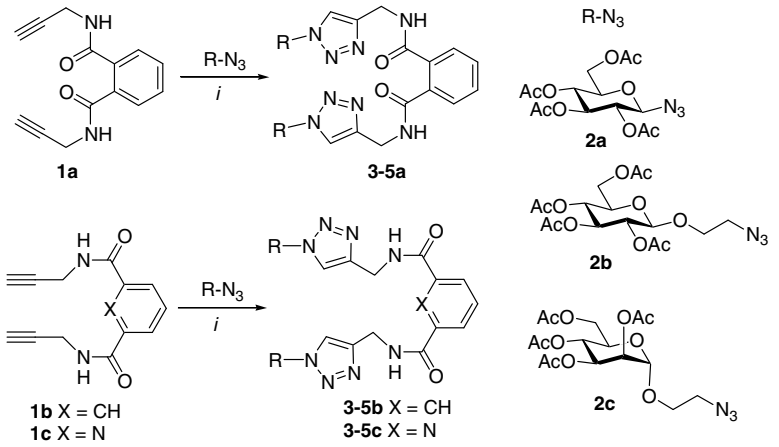


Scheme 1. Reagents and conditions: (i): 0.1 equiv $(EtO)_3PCuI$, 3 equiv DIPEA, DME, 1–18 h rt, 38–79%.[28]

Table 1
Click reaction of bis-2-propynyl derivatives **1** with azides **2**[28]

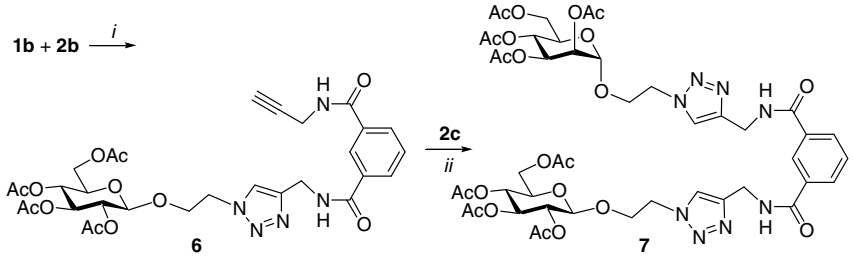
1	$R–N_3$	Conditions	3–5	Yield (%)
1a	**2a**	18 h, 20 °C	**3a**	68
1b	**2a**	18 h, 20 °C	**3b**	72
1c	**2a**	18 h, 20 °C	**3c**	38
1a	**2b**	12 h, 20 °C	**4a**	79
1b	**2b**	14 h, 20 °C	**4b**	76
1c	**2b**	1 h, 20 °C	**4c**	76
1a	**2c**	15 h, 20 °C	**5a**	69
1b	**2c**	15 h, 20 °C	**5b**	71
1c	**2c**	2 h, 20 °C	**5c**	76

of 1 mol equiv azide **2** to **1** proceeds faster while the addition of the 2 mol equiv azide **2** proceeds significantly slower.

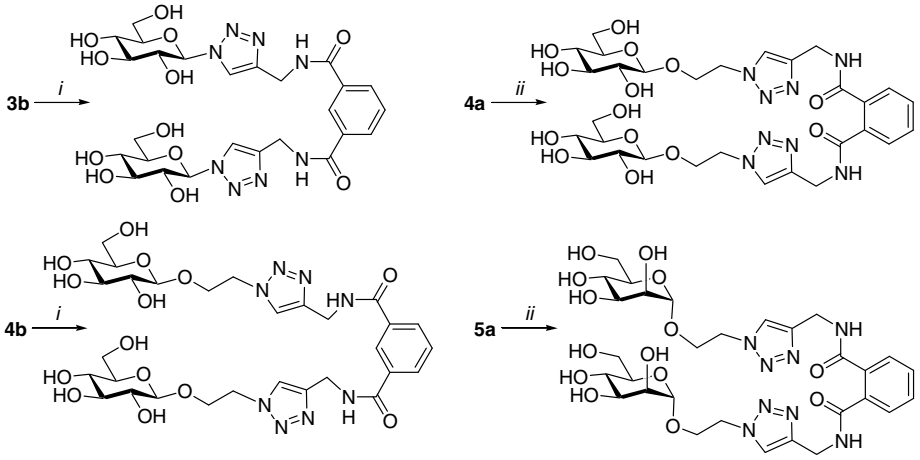
The different velocities of the two cycloaddition steps also allow for the preparation of ligands bearing two different sugar moieties. When dipolarophile **1b** is reacted with only 1 mol equiv of glucoside **2b**, the mono adduct **6** is obtained in 77% yield. Next, crude **6** was treated with mannoside **2c** to afford the mixed ligand **7** in 67% yield (Scheme 2).

All ligands **3**–**5**, and **7** can easily be deacetylated by treatment of a methanolic solution of the ligands with ammonia in MeOH for 16 h at rt, or by a classical Zemplén deacetylation with a catalytic amount of NaOMe in MeOH for 30 min at rt, followed by concentration under reduced pressure, filtration through a short layer of silica gel, and drying in vacuo as exemplified for ligands **3b**, **4a**,**b**, and **5a** in Scheme 3.[29]

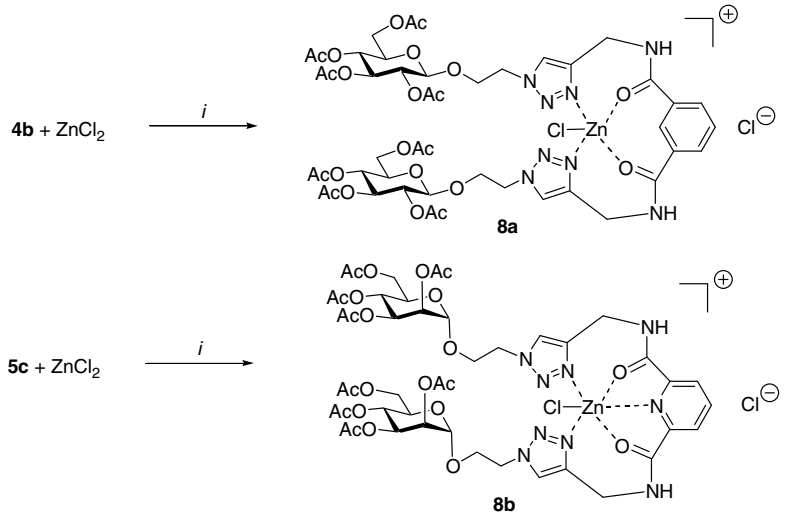
Preliminary results for the complexation of the ligands **3**–**5**, and **7** with $ZnCl_2$ show that complex formation does take place at the amide carbonyl group and N-3 of the triazole groups. Similar coordination complexes, where N-3 of a triazole moiety of the ligand is involved, have been reported recently.[30,31] For example, treatment of a solution of **4b** in acetone–methanol (1:1) with 1 mol equiv of $ZnCl_2$ for 72 h, followed by slow evaporation of the solvents furnishes an amorphous white solid, the spectral properties of which are in accordance with structure **8a** (Scheme 4).[32] Most significantly, the specific rotation decreases from −13.4 for **4b** to −15.1° for **8a**, and the proton NMR signals for the NH group and the CH group of the triazole moiety are shifted downfield upon complexation. Similarly, the carbon NMR signals for the carbonyl group of the isophthalamide moiety, the NCH_2 group, and C-4 of the 1,2,3-triazole moiety show an upfield shift of 1.1–2.5 ppm while the methylene groups of the sugar and the triazole moieties are downfield shifted by 1.1 and 1.9 ppm, respectively. Furthermore, MS data[32] and NMR titration experiments show that a 1:1 complex between **4b** and $ZnCl_2$ is formed. Similar observations were made for the $ZnCl_2$ complex **8b** obtained from ligand **5c**. However, no crystals suitable for X-ray could be obtained from any of the complexes so far. Thus, structures **8a** and **8b** are preliminary.



Scheme 2. Reagents and conditions: (i): 1 equiv **1b**, 1 equiv **2b**, 0.1 equiv $(EtO)_3PCuI$, 3 equiv DIPEA, DME, 1 h, 0 °C, 12 h, rt, 77% **6**; (ii): 1 equiv **6**, 1 equiv **2c**, 0.1 equiv $(EtO)_3PCuI$, 3 equiv DIPEA, DME, 12 h, rt, 67% **7**.



Scheme 3. Reagents and conditions: (i): 7 M NH_3 in MeOH, 16 h, rt, 99% from **3b**, 72% from **4b**; (ii): cat. NaOMe in MeOH, 30 min, rt, 96% from **4a**, 98% from **5a**.



Scheme 4. Reagents and conditions: (i): 1 mol equiv **4b** or **5c**, 2 mol equiv $ZnCl_2$, acetone–MeOH 1:3, 72 h, rt, 100% **8a**,**b**.

Further investigations for the complex-forming properties of the multidentate ligands **3**–**5** and **7** are underway.

Acknowledgments

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24. Compound **1a**: 84% yield, mp 177 °C (EtOH), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.45 (m, 4H, H^{Ph}), 6.92 (br s, 2H, NH), 4.17 (dd, 4H, CH_2), 2.25 (t, 2H, CH); Compound **1b**: 80% yield, mp 131–132 °C (EtOH), ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.05 (t, 2H, NH), 8.33 (s, 1H, H^{Ph}), 7.98 (dd, 2H, H^{Ph}), 7.57 (t, 1H, H^{Ph}), 4.07 (dd, 4H, CH_2), 3.14 (t, 2H, CH). Compound **1c**: 50% yield, mp 192 °C (EtOH), ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.73 (t, 2H, NH), 8.19 (m, 3H, H^{Ph}), 4.19 (dd, 4H, CH_2), 3.20 (t, 2H, CH); all compounds gave satisfactory elemental analyses.
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28. In a typical example, **1b** (288 mg, 1.2 mmol) and **2b** (1008 mg, 2.4 mmol) are dissolved in DME (10 mL), DIPEA (1.24 mL, 7.2 mmol) is added, and the clear solution is stirred at rt $(EtO)_3PCuI$ (ca. 0.1 mmol) is added and stirring at rt is continued until TLC (toluene/acetone 1:3) indicates complete disappearance of the educts (14 h). The mixture is concentrated and the residue is chromatographed on silica gel (toluene/acetone 1:3) to give **4b**, (980 mg, 76%). $[\alpha]_D^{20}$ −13.4 (*c* 1.0, $CHCl_3$), EI-MS: 1075.3 $[MH]^+$, ^{1}H NMR (significant signals, 400 MHz, acetone-d_6) δ 8.33 (t, 2H, NH), 7.86 (s, 2H, $H^{triazole}$), 4.80 (d, 2H, H-1, $J = 8.1$ Hz); ^{13}C NMR (significant signals, 100 MHz, acetone-d_6) δ 169.7 (CONH), 135.7 ($C_q^{triazole}$), 124.2 ($CH^{triazole}$), 101.0 (C-1), 73.3 (C-3), 72.5 (C-5), 71.9 (C-2), 69.3 (OCH_2), 68.4 (C-4), 62.6 (C-6), 50.5 (OCH_2CH_2), 36.1 (NCH_2). Similarly prepared are: Compound **3a**: $[\alpha]_D^{20}$ −32.6 (*c* 1.0, DMSO), EI-MS: 987.3 $[MH]^+$, ^{1}H NMR (significant signals, 400 MHz, DMSO-d_6) δ 8.33 (t, 2H, NH), 8.33 (s, 2H, $H^{triazole}$), 6.34 (d, 2H, H-1, $J = 9.1$ Hz); ^{13}C NMR (significant signals, 100 MHz, DMSO-d_6) δ 168.2 (CONH), 136.0 ($C_q^{triazole}$), 122.1 ($CH^{triazole}$), 83.7 (C-1), 73.2 (C-5), 72.2 (C-2), 70.1 (C-3), 67.5 (C-4), 61.8 (C-6), 34.7 (NCH_2). Compound **3b**: $[\alpha]_D^{20}$ −44.1 (*c* 1.0, DMSO), EI-MS: 987.3 $[MH]^+$, ^{1}H NMR (significant signals, 400 MHz, DMSO-d_6) δ 9.17 (t, 2H, NH), 8.28 (s, 2H, $H^{triazole}$), 6.32 (d, 2H, H-1, $J = 9.4$ Hz); ^{13}C NMR (significant signals, 100 MHz, DMSO-d_6) δ 165.7 (CONH), 134.3 ($C_q^{triazole}$), 122.0 ($CH^{triazole}$), 83.8 (C-1), 73.3 (C-5), 72.3 (C-2), 70.1 (C-3), 67.5 (C-4), 61.9 (C-6), 34.8 (NCH_2). Compound **3c**: $[\alpha]_D^{20}$ −41.4 (*c* 1.0, DMSO), EI-MS: 988.3 $[MH]^+$, ^{1}H NMR (significant signals, 400 MHz, DMSO-d_6) δ 9.29 (t, 2H, NH), 8.18 (s, 2H, $H^{triazole}$), 6.22 (d, 2H, H-1, $J = 9.1$ Hz); ^{13}C NMR (significant signals, 100 MHz, DMSO-d_6) δ 164.0 (CONH), 146.0 ($C_q^{triazole}$), 122.5 ($CH^{triazole}$), 85.6 (C-1), 75.1 (C-5), 73.2 (C-2), 71.1 (C-3), 68.5 (C-4), 62.5 (C-6), 35.1 (NCH_2). Compound **4a**: $[\alpha]_D^{20}$ −14.0 (*c* 1.0, $CHCl_3$), EI-MS: 1075.3 $[MH]^+$, ^{1}H NMR (significant signals, 400 MHz, acetone-d_6) δ 8.18 (t, 2H, NH), 7.94 (s, 2H, $H^{triazole}$), 4.79 (d, 2H, H-1, $J = 8.1$ Hz); ^{13}C NMR (significant signals, 100 MHz, acetone-d_6) δ 169.4 (CONH), 136.7 ($C_q^{triazole}$), 124.1 ($CH^{triazole}$), 101.1 (C-1), 73.3 (C-3), 72.4 (C-5), 71.8 (C-2), 69.3 (OCH_2), 68.7 (C-4), 62.6 (C-6), 50.4 (OCH_2CH_2), 36.3 (NCH_2). Compound **4c**: $[\alpha]_D^{20}$ −14.2 (*c* 1.0, $CHCl_3$), EI-MS: 1076.2 $[MH]^+$, ^{1}H NMR (significant signals, 400 MHz, acetone-d_6) δ 9.26 (t, 2H, NH), 7.81 (s, 2H, $H^{triazole}$), 4.77 (d, 2H, H-1, $J = 8.1$ Hz); ^{13}C NMR (significant signals, 100 MHz, acetone-d_6) δ 164.0 (CONH), 145.6 ($C_q^{triazole}$), 124.1 ($CH^{triazole}$), 101.1 (C-1), 73.2 (C-3), 72.4 (C-5), 71.8 (C-2), 69.3 (OCH_2), 68.7 (C-4), 62.6 (C-6), 50.5 (OCH_2CH_2), 35.4 (NCH_2). Compound **5a**: $[\alpha]_D^{20}$ +25.5 (*c* 1.0, $CHCl_3$), EI-MS: 1075.3 $[MH]^+$, ^{1}H NMR (significant signals, 400 MHz, acetone-d_6) δ 8.09 (t, 2H, NH), 8.05 (s, 2H, $H^{triazole}$), 4.88 (s, 2H, H-1); ^{13}C NMR (significant signals, 100 MHz, acetone-d_6) δ 169.5 (CONH), 146.1 ($C_q^{triazole}$), 124.2 ($CH^{triazole}$), 98.1 (C-1), 69.9 (2C, C-3, C-5), 69.5 (C-2), 67.0 (OCH_2), 66.4 (C-4), 62.9 (C-6), 50.2 (OCH_2CH_2), 36.3 (NCH_2). Compound **5b**: $[\alpha]_D^{20}$ +31.5 (*c* 1.0, $CHCl_3$), EI-MS: 1075.2 $[MH]^+$, ^{1}H NMR (significant signals, 400 MHz, acetone-d_6) δ 8.34 (t, 2H, NH), 7.98 (s, 2H, $H^{triazole}$), 4.87 (s, 2H, H-1); ^{13}C NMR (significant signals, 100 MHz, acetone-d_6) δ 166.7 (CONH), 135.6 ($C_q^{triazole}$), 124.2 ($CH^{triazole}$), 97.9 (C-1), 69.9 (2C, C-3, C-5), 69.5 (C-2), 67.0 (OCH_2), 66.4 (C-4), 62.8 (C-6), 50.1 (OCH_2CH_2), 36.0 (NCH_2). Compound **5c**: $[\alpha]_D^{20}$ +27.9 (*c* 1.0, $CHCl_3$), EI-MS: 1076.2 $[MH]^+$, 1H NMR (significant signals, 400 MHz, acetone-d_6) δ 9.29 (t, 2H, NH), 7.96 (s, 2H, $H^{triazole}$), 4.89 (s, 2H, H-1); ^{13}C NMR (significant signals, 100 MHz, acetone-d_6) δ 164.1 (CONH), 146.0 ($C_q^{triazole}$), 124.2 ($CH^{triazole}$), 98.0 (C-1), 69.9 (C-3), 69.8 (C-5), 69.6 (C-2), 66.9 (OCH_2), 66.4 (C-4), 62.9 (C-6), 50.2 (OCH_2CH_2), 35.4 (NCH_2).
29. In a typical example, **4b** (540 mg, 0.5 mmol) was dissolved in 7 M methanolic NH_3 solution (10 mL), and the mixture was stirred at rt for 16 h, whereupon a light blue solution was formed. The solution was concentrated, and the residue was filtered with $CHCl_3$/MeOH (1:3) through a short column packed with silica gel to furnish deacetylated **4b** (270 mg, 72%). EI-MS: 739.2 $[MH]^+$.
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32. A solution of **4b** (100 mg, 93 μmol) and $ZnCl_2$ (12.7 mg, 93 μmol) in acetone–MeOH (1:3, 5 mL) was stirred at rt for 72 h. Slow removal of the solvent in a weak vacuum afforded **8a** (110 mg, 100%) as a white amorphous solid. $[\alpha]_D^{20}$ −15.1 (*c* 1.0, $CHCl_3$), EI-MS: 1175.2 $[M-Cl]^+$, ^{1}H NMR (significant signals, 400 MHz, acetone-d_6) δ 8.69 (s, 2H, NH), 8.20 (s, 2H, $H^{triazole}$), 4.81 (d, 2H, H-1, $J = 8.0$ Hz); ^{13}C NMR (significant signals, 100 MHz, acetone-d_6) δ 167.2 (CONH), 134.6 ($C_q^{triazole}$), 126.1 ($CH^{triazole}$), 100.7 (C-1), 72.9 (C-3), 72.1 (C-5), 71.5 (C-2), 68.9 (OCH_2), 67.4 (C-4), 62.2 (C-6), 51.6 (OCH_2CH_2), 34.8 (NCH_2).