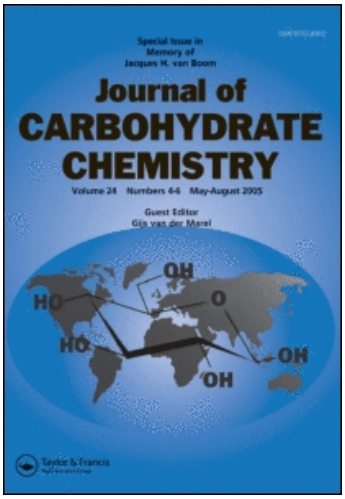

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Synthesis of Some Novel Glucosyl Triazoles from 2,3,4,6-Tetra-O-pivaloyl-D-glucopyranosyl Azide

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In the present study, we have synthesized a series of novel glucosyl triazoles for the first time. The glucosyl triazoles **4a–e** were synthesized by reaction of some azidoglycosides with various terminal alkynes via a copper-catalyzed [3+2] cycloaddition ("click chemistry") and were deprotected to afford the corresponding glucosyl triazoles **5a–e** in good yields. The structures of the new compounds were determined by IR, NMR spectroscopy, and mass spectrometry. The antitumor (human cervical cancer cell) activity was evaluated for the target compounds.

Keywords Click chemistry; Glucosyl triazoles; Azidoglycosides

INTRODUCTION

Organic compounds bearing triazoles of different pharmacodynamic nuclei were found to possess various biological activity. Glucosyl triazoles and their derivatives also have received considerable attention because of their bioactivity and many applications in organic and medicinal chemistry.[1] For example, Poulsen's group has reported that a series of glucosyl triazole benzene sulfonamide derivatives are a novel class of carbonic anhydrase inhibitors.[2] The classical method for the preparation of 1,2,3-triazoles is the Huisgen reaction.[3] This powerful and reliable Cu-catalyzed 1,3-dipolar cycloaddition has

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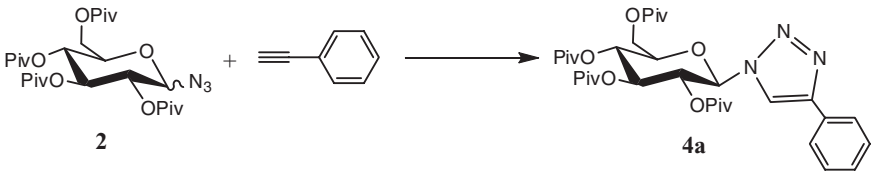
found widespread applications in combinatorial chemistry for drug discovery,[4] material science,[5] and bioconjugation.[6] Since that time triazole-linked glycoconjugates have become increasingly useful and important in glycobiology.[7] Glycoconjugates exert important effects on many complex biological processes,[8] including the cellular recognition in the processes of immune response,[9] inflammation,[10] tumor metastasis,[11] and viral infections. In addition, glycosylation of proteins and lipids are key factors in modulating their structures and functions. Therefore, the preparation of these compounds has become increasingly important. Herein, we report a convenient method for the synthesis of novel glucosyl triazole derivatives from D-glucose by means of a three-step sequence involving stereospecific displacement with azide anion, copper-catalyzed [3+2] cycloaddition, and deprotection of the pivaloyl group.

RESULTS AND DISCUSSION

During our previous research,[12] we developed a novel route for the synthesis of thiazol-2(3*H*)-imine-linked glycoconjugates, which were screened for their antitumor activities against Hela, HCT-8, and Bel-7402. Some of the compounds showed moderate cytotoxicity against HCT-8. That study forms part of our research program to evolve new methodologies for the construction of novel glycoconjugates and to discover new lead molecules with antitumor activities. Further synthesis and biological investigation of new glucosyl triazoles containing different active sugar moieties for antitumor activity are reported here.

The glucosyl triazole **4a** was used as a model to study the rate of triazole formation.[13] Using a procedure adapted from the literature,[14,15] the 2,3,4,6-tetra-*O*-pivaloyl-D-glucopyranosyl azide **2** is available from compound **1** by means of stereospecific displacement with azide anion. Then reaction of phenylacetylene with the azide **2** in the presence of a $CuSO_4$/ascorbate mixture affords exclusively the glucosyl triazole **4a** with complete retention of anomeric stereochemistry and in high yield. The effects of various solvents were studied for the preparation of **4a** and comparative results are presented in Table 1. As a result, the reaction of azide **2** proceeded smoothly in *tert*-butanol within a short period at room temperature to afford the desired products in very high yield (Table 1, entry 8). In other cases, the yields varied 75% to 91%. These results encouraged further studies with various other alkynes such as 2-ethynylpyridine, 4-bromophenylacetylene, 4-fluorophenyla-cetylene, and 4-methylphenylacetylene. These alkynes readily reacted with glucosyl azides under identical conditions to produce triazole-linked glycosides in high yields (Table 2, entries 2–4). The structure of all new compounds was confirmed by ^{1}H NMR, ^{13}C NMR, IR, and elemental analysis. The *O*-pivaloyl group of glucosyl triazoles **4a–e** was subsequently removed to obtain the fully deprotected sugar analog **5a–e** in quantitative or near-quantitative yields (Scheme 1).

Table 1: Study of formation of glucosyl triazole **4a**[a]



Entry	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	CH_3CN	40	2.0	83
2	CH_2Cl_2	40	2.0	80
3	Toluene	40	2.0	75
4	THF	40	2.0	78
5	Methanol	40	2.0	88
6	Isopropanol	40	2.0	91
7	*tert*-Butanol	40	2.0	95
8	*tert*-Butanol	25	2.5	95

[a]All reactions were carried out using **2** (0.5 M), phenylacetylene (0.5 M), 20 mol% $CuSO_4$, 40 mol% sodium ascorbate (relative to substrate).
[b]Isolated yield after chromatography.

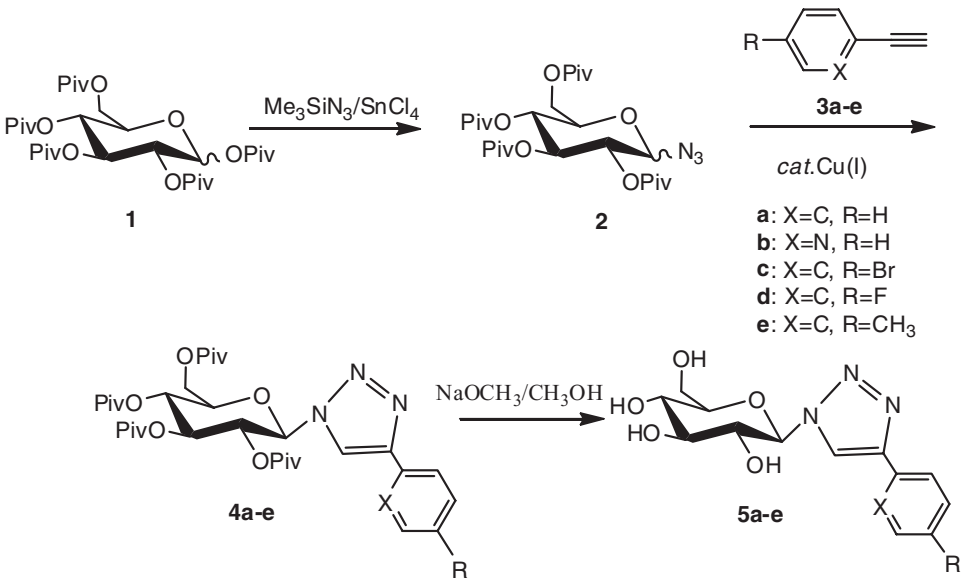
Next, some of the newly synthesized glucosyl triazoles **5a–e** were screened for their antitumor activity against Hela (cervical carcinoma), HCT-8 (colon carcinoma), and Bel-7402 (liver carcinoma). The cytotoxicity was evaluated by MTT assay.[16] However, all the compounds showed very weak cytotoxicity against Bel-7402, Hela, and HCT-8.

In conclusion, we have synthesized a series of triazole derivatives bearing sugar moieties, providing a convenient method for constructing such glucosyl triazole derivatives under very mild conditions. The preliminary biological

Table 2: Synthesis of different D-glucose-derived 1,2,3-triazoles[a]

Entry	Ar	Product	Time (h)	Yield (%)[b]	Mp (°C)
1	Ph	4a	2.5	92	230–231
2	*p*-Br-C_6H_4	4b	2.5	88	218–220
3	*p*-F-C_6H_4	4c	2.5	92	208–210
3	*p*-CH_3-C_6H_4	4d	2.5	95	215–217
4	C_5H_4N	4e	2.5	96	214–216

[a]All reactions were carried out using **2** (0.5 M), alkynes (0.5 M), 20 mol% $CuSO_4$, 40 mol% sodium ascorbate (relative to substrate).
[b]Isolated yield after chromatography.



Scheme 1: A general glucosyl triazoles synthesis.

evaluation of compounds **5a–e** showed no antitumor activities. Further syntheses and biological studies of new triazoles containing different active sugar moieties for biological activity are continued by our group.

EXPERIMENTAL

General Methods

1,2,3,4,6-Penta-*O*-pivaloyl-D-glucopyranose (**1**) was prepared according to our previous reports.[12] Other chemicals and solvents were either purchased or purified by standard techniques. Analytical TLC was performed on a Merck precoated TLC (silica gel 60 F254) plate. Melting points were recorded on an X_4-Data microscopic melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet 380 FT-IR spectrophotometer using KBr discs. Optical rotation values were measured on a Perkin Elmer P241 polarimeter. ESI-MS were acquired on a Bruker Esquire 3000 plus spectrometer. ^1H and ^{13}C NMR spectra of samples in $CDCl_3$ or CD_3OD were recorded on a Bruker Avance 400 spectrometer using TMS as internal standard. Elemental analyses were performed on Carlo-Erba 1106.

General procedure for the synthesis of glucosyl triazoles via click chemistry

To a mixture of the corresponding 2,3,4,6-tetra-*O*-pivaloyl-D-gluco pyranosyl azide **2** (541 mg, 1.0 mmol) and alkyne (1.0 mmol) in *tert*-butyl alcohol (1 mL), 0.5 mL of an aqueous solution of $CuSO_4$ (50 mg, 0.2 mmol) and 0.5 mL of an aqueous solution of sodium ascorbate (79.2 mg, 0.4 mmol) were added. The reaction mixture was stirred vigorously for 24 h. The suspended product was filtered and washed with water. The crude product was purified by column chromatography on silica gel, eluting with hexane/ethyl acetate mixtures of increasing polarity to afford the triazole products.

4-Phenyl-1-(2,3,4,6-tetra-*O*-pivaloyl-1-D-glucopyranosyl)-1,2,3-triazole (4a)

Yellow solid; yield: 92%; mp 216–220°C; $[\alpha]_D^{20} = -18.0$ (*c* 0.1, CH_3OH); ^1H NMR (400 MHz, $DCCl_3$): δ 8.05 (s, 1H), 7.85 (d, $J = 8.6$ Hz, 2H), 7.46 (t, 2H), 7.38 (t,1H), 5.87 (d, $J = 8.0$ Hz, 1H), 5.65 (t, $J = 9.6$ Hz, 2H), 5.60 (d, $J = 3.8$ Hz, 1H), 5.36 (d, $J = 3.3$ Hz, 1H), 4.74 (m, 1H), 4.31 (m, 1H), 4.04 (m, 1H), 0.92–1.25 (m, 36H, Piv-CH_3); ^{13}C NMR (100 MHz, $DCCl_3$): δ 177.78, 176.52, 147.43, 144.60, 129.00, 127.95, 127.58, 125.01, 85.12, 74.64, 71.14, 69.15, 66.18, 60.42, 37.76, 25.79–26.12; IR (KBr, cm^{-1}) υ: 2970, 2077, 1744, 1637, 1481, 1400, 1368, 1280, 1140, 1037.

4-Pyridyl-1-(2,3,4,6-tetra-*O*-pivaloyl-1-D-glucopyranosyl)-1,2,3-triazole (4b)

Yellow solid; yield: 95%; mp 179–181°C; $[\alpha]_D^{20} = -43.2$ (*c* 0.1, CH_3OH); ^1H NMR (400 MHz, $DCCl_3$): δ 8.60 (s, 1H), 8.37 (d, $J = 3.6$ Hz, 1H), 8.11 (t, 1H), 7.78 (t, 1H), 7.76 (d, $J = 12.2$ Hz, 1H), 5.97 (d, $J = 9.2$ Hz, 1H), 5.55 (m, 2H), 5.32 (m, 1H), 4.21 (m, 2H), 4.05 (d, $J = 2.4$ Hz, 1H), 1.89 (m, 1H), 0.94–1.21 (m, 36H, Piv-CH_3); ^{13}C NMR (100 MHz, $DCCl_3$): δ 177.71, 177.12, 177.10, 155.3, 149.20, 137.21, 131.41, 129.52, 123.64, 97.62, 78.21, 73.69, 69.15, 69.82, 62.42, 36.76, 25.79–26.12; IR (KBr, cm^{-1}) υ: 3431, 2974, 1742, 1601, 1479, 1400, 1281, 1141, 1034. Anal. Calcd for $C_{33}H_{48}N_4O_9$: C, 61.55; H, 7.82; N, 8.78. Found: C, 61.58; H, 7.80; N, 8.75.

4-(4-Bromophenyl)-1-(2,3,4,6-tetra-*O*-pivaloyl-1-D-glucopyranosyl)-1,2,3-triazole (4c)

Yellow solid; yield: 88.1%; mp 220–222°C; $[\alpha]_D^{20} = -38.2$ (*c* 0.1, CH_3OH); ^1H NMR (400 MHz, $DCCl_3$): δ 7.97 (s, 1H), 7.70 (d, $J = 5.6$ Hz, 2H), 7.56 (t, 2H), 5.99 (d, $J = 9.6$ Hz, 1H), 5.55 (m, 2H), 5.36 (d, $J = 4.2$ Hz, 1H), 4.21 (m, 2H), 4.06 (m, 1H), 0.92–1.25 (m, 36H, Piv-CH_3); ^{13}C NMR (100 MHz, $DCCl_3$): δ

177.71, 176.74,131.9, 129.72, 127.24, 122.36, 85.94, 77.18, 71.84, 69.96, 66.94, 61.14, 38.76, 25.53–26.92; IR (KBr, cm^{-1}) υ: 3422, 2974, 1742, 1637, 1481, 1403, 1368, 1140, 1040. Anal. Calcd for $C_{34}H_{48}BrN_3O_9$: C, 56.62; H, 6.73; N, 5.93. Found: C, 56.65; H, 6.70; N, 5.91.

4-(4-Fluorophenyl)-1-(2,3,4,6-tetra-*O*-pivaloyl-1-D-glucopyranosyl)-1,2,3-triazole (4d)

White solid; yield: 89.1%; mp 190–192°C; $[\alpha]_D^{20} = -21.6$ (c 0.1, CH_3OH); ^1H NMR (400 MHz, $DCCl_3$): δ 8.02 (s, 1H), 7.82 (d, 2H), 7.82 (t, 2H), 5.96 (d, $J = 9.6$ Hz, 1H), 5.58 (m, 2H), 5.38 (d, $J = 2.4$ Hz, 1H), 4.20 (m, 2H), 4.11 (d, $J = 12.4$ Hz, 1H), 0.95–1.26 (m, 36H, Piv-CH_3); ^{13}C NMR (100 MHz, $DCCl_3$): δ 178.71, 176.99, 132.1, 128.72, 127.24, 122.36, 85.94, 77.20, 71.86, 69.98, 66.90, 61.20, 38.73, 25.53–26.92; IR (KBr, cm^{-1}) υ: 3436, 2976, 1740, 1641, 1485, 1406, 1360, 1141, 1039. Anal. Calcd for $C_{34}H_{48}FN_3O_9$: C, 61.76; H, 7.22; N, 6.43. Found: C, 61.73; H, 7.20; N, 6.45.

4-(4-Methylphenyl)-1-(2,3,4,6-tetra-*O*-pivaloyl-1-D-glucopyranosyl)-1,2,3-triazole (4e)

White solid; yield: 92.6%; mp 208–210°C; $[\alpha]_D^{20} = +3.2$ (c 0.1, CH_3OH); ^1H NMR (400 MHz, $DCCl_3$): δ 8.00 (s, 1H), 7.74 (d, $J = 5.6$ Hz, 2H), 7.25 (t, 2H), 5.86 (d, $J = 11.6$ Hz, 1H), 5.55 (d, $J = 4.2$ Hz, 1H), 5.34 (m, 1H), 4.71 (m, 2H), 4.45 (d, $J = 2.2$ Hz, 1H), 4.30 (d, $J = 6.2$ Hz, 1H), 2.39 (s, 1H), 0.92–1.25 (m, 36H, Piv-CH_3); ^{13}C NMR (100 MHz, $DCCl_3$): δ 177.46, 8176.18, 176.18, 144.29, 137.99, 129.11, 126.46, 126.24, 115.86, 86.16, 76.82, 76.19, 66.02, 65.94, 60.03, 38.38, 29.19–26.47; IR (KBr, cm^{-1}) υ: 3443, 2352, 2118, 1746, 1649, 1540, 1398, 1280, 1146. Anal. Calcd for $C_{35}H_{51}N_3O_9$: C, 63.86; H, 7.74; N, 6.50; Found: C, 63.86; H, 7.74; N, 6.50.

Representative procedure for the depivaloylation of glucosyl triazoles

The corresponding glucosyl triazole (1 mmol) was dissolved in 10 mL of methanol. Freshly prepared sodium methoxide was then added portion-wise and the reaction was monitored by TLC. Upon completion, Amberlite resin (H^+ form) was added until the solution was at neutral pH, and the solution was filtered and concentrated in vacuo. The crude product was taken up in hot water and treated with activated charcoal. The product was recrystallized from water to give a white solid. 4-Phenyl-1-D-glucopyranosyl-1,2,3-triazole (**5a**) was reported by Basu et al.[16]

4-Pyridyl-1-D-glucopyranosyl-1,2,3-triazole (5b)

Yellow solid; yield: 97%; mp 198–200°C; $[\alpha]_D^{20} = -11.2$ (*c* 0.055, CH_3OH); ^1H NMR (400 MHz, CD_3OD): δ 8.53 (s, 1H), 8.37 (d, $J = 10.2$ Hz, 1H), 8.13 (t, 1H), 7.81 (t, 1H), 7.73 (d, $J = 6.4$ Hz, 1H), 5.72 (d, $J = 9.6$ Hz, 1H), 4.26 (t, 1H), 4.03 (d, $J = 8.2$ Hz, 1H), 3.78–3.71 (m, 4H); ^{13}C NMR (100 MHz, CD_3OD): δ 177.69, 177.10, 177.08, 155.30, 149.20, 137.21, 131.43, 129.49, 123.64, 95.62, 76.09, 71.26, 69.15, 62.42; Anal. Calcd for $C_{13}H_{16}N_4O_5$: C, 50.68; H, 5.96; N, 18.02. Found: C, 50.70; H, 5.93; N, 18.16.

4-(4-Bromophenyl)-1-D-glucopyranosyl-1,2,3-triazole (5c)

Yellow solid; yield: 96%; mp 215–217°C; $[\alpha]_D^{20} = -7.8$ (*c* 0.062, $CHCl_3$); ^1H NMR (400 MHz, CD_3OD): δ 8.01 (s, 1H), 7.81 (d, $J = 11.2$ Hz, 2H), 7.72 (d, $J = 4.6$ Hz, 2H), 5.81 (d, $J = 9.2$ Hz, 1H), 4.41 (t, 1H), 4.21 (d, $J = 8.2$ Hz, 1H), 3.65–3.70 (m, 4H); ^{13}C NMR (100 MHz, CD_3OD): δ 177.66, 176.45, 131.9, 129.72, 127.24, 122.36, 85.94, 77.08, 71.76, 69.77, 66.80, 61.19; Anal. Calcd for $C_{14}H_{16}BrN_3O_5$: C, 43.89; H, 4.02; N, 10.56. Found: C, 43.86; H, 4.10; N, 10.52.

4-(4-Fluorophenyl) -1-D-glucopyranosyl -1,2,3-triazole (5d)

White solid; yield: 95%; mp 182–185°C; $[\alpha]_D^{20} = -15.8$ (*c* 0.068, $CHCl_3$); ^1H NMR (400 MHz, CD_3OD): δ 8.12 (s, 1H), 7.86 (d, $J = 6.2$ Hz, 2H), 7.73 (d, $J = 3.2$ Hz, 2H), 5.79 (d, $J = 9.8$ Hz, 1H), 4.66 (t, 1H), 4.21 (d, $J = 3.6$ Hz, 1H), 3.69–3.72 (m, 4H); ^{13} C NMR (100 MHz, CD_3OD): δ 177.53, 176.31, 131.09, 129.14, 127.12, 122.28, 85.44, 77.11, 72.03, 69.66, 66.52, 61.28; Anal. Calcd for $C_{14}H_{16}FN_3O_5$: C, 51.56; H, 4.81; N, 12.23. Found: C, 51.52; H, 4.78; N, 12.19.

4-(4-Methylphenyl)-1-D-glucopyranosyl -1,2,3-triazole (5e)

White solid; yield: 95%; mp 216–219°C; $[\alpha]_D^{20} = -22.1$ (*c* 0.075, $CHCl_3$); ^1H NMR (400 MHz, CD_3OD): δ 8.03 (s, 1H), 7.56 (d, $J = 5.6$ Hz, 2H), 7.31 (d, $J = 5.6$ Hz, 2H), 5.66 (d, $J = 9.4$Hz, 1H), 4.70 (t, 1H), 4.18 (d, $J = 2.6$ Hz, 1H), 3.68–3.72 (m, 4H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 177.21, 176.22, 175.58, 144.28, 138.20, 128.02, 126.24, 126.11, 115.75, 86.25, 76.74, 76.09, 66.12, 65.34, 60.23, 38.14. Anal. Calcd for $C_{15}H_{19}N_3O_5$: C, 56.26; H, 5.82; N, 13.11. Found: C, 56.30; H, 5.81; N, 13.14.

Biological activity assays

Cell culture

Three different human carcinoma cell lines were used for cytotoxicity determination: Hela (cervical carcinoma), HCT-8 (colon carcinoma), and Bel-7402

(liver carcinoma). They were obtained from the American Type Culture Collection (ATCC) and cultured in RPMI-1640 medium supplemented with 10% FBS, 100 units/mL of penicillin, and 100 μg/mL of streptomycin. Cells were maintained at 37°C in a humidified atmosphere of 5% CO_2 in air.

Cytotoxicity Analysis

Briefly, cells were plated in 96-well culture plates (10^4 cells per well) and incubated overnight at 37°C in a 5% CO_2 incubator. Then, compounds were added to the wells to achieve final concentrations ranging from 10^{-7} to 10^{-4} M. Control wells were prepared by addition of culture medium. Wells containing culture medium without cells were used as blanks. The plates were incubated at 37°C in a 5% CO_2 incubator for 44 h. Upon completion of the incubation, MTT dye solution (20 μL, 5 mg/mL) was added to each well. After 4 h of incubation, 2-propanol (100 μL) was added to solubilize the MTT formazan. The OD was measured at a wavelength of 570 nm by a microplate spectrophotometer. The IC_{50} value was determined from plots of% viability against the dose of complexes added.

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