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Synthesis of novel 3-deoxy-3-C-triazolylmethyl-allose derivatives and evaluation of their biological activity

Research Article

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Abstract: Recently, monosaccharide-triazole conjugates have proved to possess a large variety of useful biological activities. This paper describes synthesis of a new series of 3-deoxy-3-*C*-triazolylmethyl-allose derivatives. These new compounds are obtained from acetonide-protected 3-deoxy-3-azidomethyl allose and commercial alkynes via Cu(I) catalyzed 1,3-dipolar cycloaddition. The obtained molecular scaffolds differ from those described earlier by the presence of a methylene linker (-CH_2-) between the C(3) of allose and the triazole moiety. It was demonstrated that acetonide-protected monosaccharide, 3-deoxy-3-*C*-(4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose, inhibited α-L-fucosidase for 26% at 0.1 mM concentration, but a deprotected analog, 3-deoxy-3-*C*-(4-(4-*tert*-butylphenyl)-1*H*-1,2,3-triazol-1-yl)methyl-β-D-allofuranose, showed 15% inhibition of β-glucosidase at 1 mM concentration.

Keywords: *3-deoxy-3-C-triazolylmethyl-allose • Methylene linker • Triazolyl-monosaccharides • Click chemistry • Inhibitors of glycosidases*

1. Introduction

Nitrogen containing heterocycle-carbohydrate conjugates are widely represented in Nature in the form of DNA and RNA, and as elements in many biologically active compounds. 1,2,3-Triazoles became readily available after the discovery of Cu(I) catalyzed Huisgen cycloaddition [1] and a large array of compounds with different substituents were synthesized [2]. Some of them exhibited noticeable biological activity, such as antibacterial [3], antiviral [4], COX-2 inhibiting [5], and other activities [6].

The combination of both carbohydrate and 1,2,3-triazole structural motifs has led to the flourishing field of conjugates that have proved to possess various biological activities [7]. Thus, sugar-triazole conjugates were synthesized and tested for glycosidases [8], *trans*-sialidase [9], glycogen phosphorylase [10] inhibiting activities (Fig. 1), antitubercular activity [11], and as nucleoside mimetics [12].

Among the compounds tested, 4-substituted 1,2,3-triazolylglucosides **1** showed up to 90% inhibition of yeast α-glucosidase at 1 mM concentration [8], and rabbit muscle glycogen phosphorylase inhibition with K_i up to 26 μM [10], whereas galactose derivatives **2** and **3** showed moderate (up to 40%) to weak inhibition of *Trypanosoma cruzi trans*-sialidase at 0.5 – 1 mM level [9].

The field of triazolyl monosaccharides is dominated by compounds which contain the triazole moiety either at the glycosidic position or at the terminal exocyclic carbon, namely at C(5) for furanoses and C(6) for pyranoses. There are only a few reports dealing with 2- or 3-(1,2,3-triazol-1-yl)furanoses [13] and 2-, 3- or 4-(1,2,3-triazol-1-yl)pyranoses. Compounds that are easily derived from

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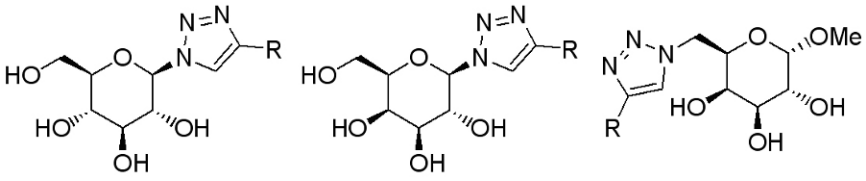
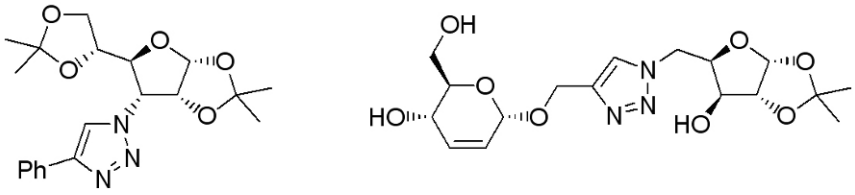


1 2 3

Figure 1. Sugar-triazole conjugates with glycosidases (**1**), glycogen phosphorylase (**1**) and *trans*-sialidase (**2, 3**) inhibiting activities.



4 5

Figure 2. Acetonide-protected carbohydrates as mediocre inhibitors of α-glucosidase.

e.g. glucosamine or 3-amino-3-deoxy-galactose fall into this last category [14]. In relation to this report, it is noteworthy that in the above mentioned molecules the triazole moiety is directly attached to the sugar ring at the 2-, 3-, or 4-position.

Most of the classically driven projects were focused on the synthesis and biological evaluation of fully deprotected sugar derivatives or those containing acyl groups that are easily cleaved by lipases within the cell.

However, a recent report showed acetonide-protected allose and xylose derivatives (**4** and **5**) as glucosidase inhibitors (Fig. 2) [15]. Specifically, diacetone-D-allose derivative **4** showed 73% inhibition of α-glucosidase at 0.5 mM concentration, while **5** appeared to be a weaker inhibitor of the same enzyme (26% inhibition at 0.1 mM). It was suggested, that compound **4** and its ribose analogs are mimicking acarbose in the active site of yeast maltase [15a]. Additionally, there have been successful examples of pharmaceutically active ingredients containing acetonide protecting groups. Topiramate, an anticonvulsant drug, is possibly one of the most prominent examples within the sugar series [16].

Hence, we decided to modify the structures reported by Ferreira and coworkers [15a] by introducing a methylene (-CH_2-) linker between the sugar core and triazole moiety. It has been shown on several occasions that incorporation of the latter has increased the biological activity more than 600-fold [17]. In terms of medicinal chemistry, variation of distance between the pharmacophores is a well-established practice for modification of the biological activity. Incorporation of a methylene linker also addresses issues of enzymatic lability connected with other linkers such as esters and amides [18].

As a result, we report here the synthesis and glycosidases inhibiting activity of novel triazole-3-deoxyallose conjugates, where triazoles are attached to the monosaccharide core via a CH_2 linker.

2. Experimental procedure

2.1. General

Reactions were carried out as described below using solvents and reagents dried according to standard procedures. Copper(II) sulfate pentahydrate, sodium ascorbate, 2,2 M *n*-butyl lithium, oxalyl chloride were purchased from Acros, mesyl chloride, methyltriphenyl phosphonium bromide and alkynes were purchased from Alfa Aesar and used without purification. Column chromatography was carried out using *Rocc* silica gel 40-60 μm. HPLC was performed on *Agilent Technologies 1200 Series* chromatograph with UV-Vis diode array detector; reverse phase C18, 2.6 μm, 4.6×100 mm, 0.8 mL min^{-1}; eluent A: 0.01 M KH_2PO_4 in water containing 6% MeOH; eluent B: MeOH; gradient: 10%→90% B in 4 min., 90% B 9 min, 90%→10% B in 2 min. Melting points are uncorrected. Specific rotation data was recorded on Perkin Elmer polarimeter. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded in $CDCl_3$, D_2O, or $DMSO_{d6}$ (with solvent residual signal as the internal standard).

2.2. General procedure for preparation of triazoles 12a-i

To a solution of azide **10** (0.1 g, 0.33 mmol) and alkyne (0.50 mmol) in THF (5 ml) copper(II) sulfate pentahydrate solution (7 mg, 0.03 mmol) in water (0.5 mL) and sodium ascorbate solution (10 mg,

0.05 mmol) in water (0.5 mL) were added. The resulting reaction mixture was stirred overnight at ambient temperature (12-24 h, monitored by TLC). Then it was concentrated under reduced pressure and the residue was dissolved in ethyl acetate (50 mL). The organic phase was washed with brine (3×10 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The product was purified by column chromatography (eluent hexanes/ethyl acetate 1:1) to yield triazoles **12a-i** (Table 1).

3-Deoxy-3-*C*-(4-phenyl-1*H*-1,2,3-triazol-1-yl) methyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (12a) Yield: 95%, white solid, m.p. 142 – 144°C. $[\alpha]_D$=+63 (c=1.00, CH_3OH). ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.37 (s, 3H), 1.46 (s, 3H), 1.58 (s, 3H), 2.68 (tt, *J*=10.2 Hz, *J*=4.2 Hz, 1H), 3.83 (dd, *J*=9.7 Hz, *J*=8.3 Hz, 1H), 3.98 (dd, *J*=8.2 Hz, *J*=4.8 Hz, 1H), 4.08 (m, 1H), 4.17 (dd, *J*=8.3 Hz, *J*=6.0 Hz, 1H), 4.53 (m, 2H), 4.96 (dd, *J*=13.5 Hz, *J*=4.2 Hz, 1H), 5.78 (d, *J*=3.6 Hz, 1H), 7.35 (d, *J*=7.2 Hz, 1H), 7.44 (t, *J*=7.8 Hz, 2H), 7.84 (d, *J*=8.2 Hz, 2H), 7.89 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1, 26.4, 26.7, 26.8, 46.3, 49.7, 68.0, 77.6, 79.8, 80.5, 105.0, 109.9, 112.5, 120.7, 125.7, 128.1, 128.8, 130.6, 154.3. IR (KBr) 3130, 2990, 2960, 2925, 2890, 1480, 1455, 1375, 1270, 1225, 1165, 1125, 1060, 1045, 1020. HRMS: Calculated for $C_{21}H_{28}N_3O_5$ m/z=402.2029. Found m/z=402.2025.

3-Deoxy-3-*C*-(4-(4-methylphenyl)-1*H*-1,2,3-triazol-1-yl)methyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (12b) Yield: 81%, white solid, m.p. 135°C. $[\alpha]_D$=+71 (c=1.26, CH_3OH) ^1H NMR (300 MHz, $CDCl_3$) (300 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.37 (s, 3H), 1.46 (s, 3H), 1.59 (s, 3H), 2.38 (s, 3H), 2.67 (tt, *J*=9.9 Hz, *J*=4.4 Hz, 1H), 3.83 (dd, *J*=9.8 Hz, *J*=8.1 Hz, 1H), 3.98 (dd, *J*=8.3 Hz, *J*=4.9 Hz, 1H), 4.07 (m, 1H), 4.16 (dd, *J*=8.3 Hz, *J*=6.0 Hz, 1H), 4.53 (m, 2H), 4.95 (dd, *J*=13.6 Hz, *J*=4.2 Hz, 1H), 5.77 (d, *J*=3.6 Hz, 1H), 7.24 (d, *J*=8.1 Hz, 2H), 7.73 (d, *J*=8.1 Hz, 2H,), 7.84 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 25.1, 26.4, 26.7, 26.8, 46.3, 49.7, 68.0, 77.6, 79.8, 80.5, 105.0, 109.9, 112.4, 120.4, 125.6, 127.8, 129.5, 138.0, 147.5. IR (KBr) 3135, 2990, 2940, 2890, 2865, 1385, 1375, 1265, 1240, 1220, 1205, 1170, 1125, 1020, 850. HRMS: Calculated for $C_{22}H_{30}N_3O_5$ m/z=416.2185. Found m/z=416.2208.

3-Deoxy-3-*C*-(4-(4-*tert*-butylphenyl)-1*H*-1,2,3-triazol-1-yl)methyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (12c) Yield: 93%, white solid, m.p. 140°C. $[\alpha]_D$=+71 (c=1.13, CH_3OH) ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.35 (s, 9H), 1.37 (s, 3H), 1.46 (s, 3H), 1.60 (s, 3H), 2.67 (tt, *J*=10.7 Hz, *J*=4.6 Hz, 1H), 3.83 (t, *J*=8.9 Hz, 1H), 3.98 (dd, *J*=8.2 Hz, *J*=4.8 Hz,, 1H), 4.07 (m, 1H), 4.16 (dd, *J*=8.1 Hz, *J*=6.0 Hz, 1H), 4.50 (m, 2H), 4.96 (dd, *J*=13.6 Hz, *J*=4.3 Hz, 1H), 5.77 (d, *J*=3.5 Hz, 1H), 7.46 (d, *J*=8.2 Hz, 2H), 7.78 (d, *J*=8.2 Hz, 2H), 7.85 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1, 26.4, 26.7, 26.8, 31.3, 34.7, 46.3, 49.7, 68.0, 77.6, 79.8, 80.5, 105.0, 109.9, 112.4, 120.5, 125.5, 125.8, 127.7, 147.4, 151.3. IR (KBr) 3150, 2975, 1460, 1370, 1265, 1215, 1065, 1020, 850. HRMS: Calculated for $C_{25}H_{36}N_3O_5$ m/z=458.2655. Found m/z=458.2617.

3-Deoxy-3-*C*-(4-cyclopropyl-1*H*-1,2,3-triazol-1-yl) methyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (12d) Yield: 92%, white solid, m.p. 95°C. $[\alpha]_D$=+85 (c=1.11, CH_3OH) ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (m, 2H), 0.97 (m, 2H), 1.32 (s, 3H), 1.35 (s, 3H), 1.43 (s, 3H), 1.57 (s, 3H), 1.97 (m, 1H), 2.59 (tt, *J*=10.8 Hz, *J*=4.4 Hz, 1H), 3.78 (dd, *J*=9.8 Hz, *J*=8.0 Hz, 1H), 4.00 (m, 2H), 4.12 (dd, *J*=8.2 Hz, *J*=5.9 Hz, 1H), 4.42 (m, 2H), 4.84 (dd, *J*=13.6 Hz, *J*=4.2 Hz, 1H), 5.75 (d, *J*=3.6 Hz, 1H), 7.36 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 6.6, 7.9, 25.0, 26.4, 26.7, 26.8, 46.2, 49.6, 68.0, 77.6, 79.8, 80.5, 105.0, 109.9, 112.4, 120.9, 149.8. IR (KBr) 3135, 2990, 2940, 2895, 1570, 1560, 1465, 1380, 1375, 1220, 1125, 1075, 1015, 880, 845. HRMS: Calculated for $C_{18}H_{28}N_3O_5$ m/z=366.2029. Found m/z=366.2048.

3-Deoxy-3-*C*-(4-(3-cyanoprop-1-yl)-1*H*-1,2,3-triazol-1-yl)methyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (12e) Yield: 92%, white solid, m.p. 91 – 92°C. $[\alpha]_D$=+73 (c=1.16, CH_3OH) ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (3H, s), 1.36 (3H, s), 1.44 (3H, s), 1.58 (3H, s), 2.09 (2H, quint, *J*=7.1 Hz), 2.43 (2H, t, *J*=6.9 Hz), 2.60 (1H, tt, *J*=10.0 Hz, *J*=4.3 Hz), 2.90 (2H, t, *J*=7.2 Hz), 3.79 (1H, dd, *J*=9.8 Hz, *J*=8.1 Hz), 3.97 (1H, dd, *J*=8.2 Hz, *J*=4.9 Hz), 4.04 (1H, m), 4.15 (1H, dd, *J*=8.2 Hz, *J*=5.8 Hz), 4.45 (2H, m), 4.90 (1H, dd, *J*=13.6 Hz, *J*=4.2 Hz), 5.76 (1H, d, *J*=3.6 Hz), 7.49 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 24.1, 24.8, 25.0, 26.4, 26.7, 26.8, 46.2, 49.7, 68.0, 77.6, 79.8, 80.5, 105.0, 109.9, 112.5, 119.3, 122.4, 145.1. IR (KBr) 3135, 2990, 2935, 2885, 2245, 1480, 1465, 1385, 1375, 1230, 1170, 1125, 1075, 1015, 985. HRMS: Calculated for $C_{19}H_{29}N_4O_5$ m/z=393.2138. Found m/z=393.2125.

3-Deoxy-3-*C*-(4-(but-1-yl)-1*H*-1,2,3-triazol-1-yl) methyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (12f) Yield 88%, white solid, m.p. 67 – 68°C. $[\alpha]_D$=+79 (c=1.40, CH_3OH) ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, J=7.3 Hz, 3H), 1.31 (s, 3H), 1.36 (m, 5H), 1.43 (s, 3H), 1.57 (s, 3H), 1.65 (quint, *J*=7.7 Hz, 2H), 2.60 (tt, *J*=9.9 Hz, *J*=4.3 Hz, 1H), 2.73 (t, *J*=7.5 Hz, 2H), 3.80 (dd, *J*=9.8 Hz, *J*=7.9 Hz, 1H), 4.01 (m, 2H), 4.14 (dd, *J*=8.1 Hz, *J*=5.8 Hz, 1H), 4.43 (m, 2H), 4.87 (dd, *J*=13.6 Hz, *J*=4.3 Hz, 1H), 5.75 (d, *J*=3.6 Hz, 1H), 7.39 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 22.2, 25.1, 25.3, 26.3, 26.7, 26.8, 31.6, 46.0, 49.8, 68.0, 77.6, 79.8, 80.6, 105.0, 109.8, 112.4, 121.8, 148.1. IR (KBr) 3130, 2995, 2950, 2935, 2875, 1460, 1385, 1375, 1225,

1165, 1125, 1075, 1015, 980, 850. HRMS: Calculated for $C_{19}H_{32}N_3O_5$ *m/z*=382.2342. Found *m/z*=382.2385.

3-Deoxy-3-*C*-(4-(hex-1-yl)-1*H*-1,2,3-triazol-1-yl) methyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (12g) Yield 92%, white solid, m.p. 71°C. $[\alpha]_D$=+75 (c=1.19, CH_3OH) ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, *J*=7.0 Hz, 3H), 1.31 (m, 9H), 1.35 (s, 3H), 1.43 (s, 3H), 1.57 (s, 3H), 1.65 (quint, *J*=7.5 Hz, 2H), 2.59 (tt, *J*=9.9 Hz, *J*=4.4 Hz, 1H), 2.71 (t, *J*=7.6 Hz, 2H), 3.79 (dd, *J*=9.8 Hz, *J*=8.0 Hz, 1H), 4.00 (m, 2H), 4.13 (dd, *J*=8.2 Hz, *J*=5.8 Hz, 1H), 4.43 (m, 2H), 4.87 (dd, *J*=13.6 Hz, *J*=4.3 Hz, 1H), 5.75 (d, *J*=3.6 Hz, 1H), 7.38 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 25.0, 25.6, 26.3, 26.7, 26.8, 28.9, 29.5, 31.6, 46.0, 49.8, 68.0, 77.6, 79.8, 80.6, 105.0, 109.8, 112.4, 121.7, 148.1. IR (KBr) 3130, 2995, 2935, 2860, 1455, 1385, 1375, 1225, 1165, 1125, 1065, 1015, 850. HRMS: Calculated for $C_{21}H_{36}N_3O_5$ m/z=410.2655. Found m/z=410.2644.

3-Deoxy-3-*C*-(4-(2-hydroxyprop-2-yl)-1*H*-1,2,3-triazol-1-yl)methyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (12h) Yield 92%, white solid, m.p. 94°C. $[\alpha]_D$=+77 (c=1.10, CH_3OH) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.36 (s, 3H), 1.44 (s, 3H), 1.57 (s, 3H), 1.64 (s, 6H), 2.42 (br s, 1H), 2.61 (m, 1H), 3.79 (dd, *J*=9.7 Hz, *J*=8.1 Hz, 1H), 4.00 (m, 2H), 4.14 (dd, *J*=8.2 Hz, *J*=5.9 Hz, 1H), 4.48 (m, 2H), 4.87 (dd, *J*=13.6 Hz, *J*=4.1 Hz, 1 H), 5.76 (d, *J*=3.5 Hz,1H), 7.56 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1, 26.4, 26.7, 26.8, 30.4, 30.6, 46.2, 49.6, 68.0, 68.5, 77.6, 79.7, 80.5, 105.0, 109.9, 112.4, 120.2, 155.2. IR (KBr) 3300, 3190, 2995, 2980, 2915, 1385, 1375, 1220, 1200, 1155, 1125, 1015, 850. HRMS: Calculated for $C_{18}H_{30}N_3O_6$ m/z=384.2135. Found m/z=384.2116.

3-Deoxy-3-*C*-(4-(3-aminophenyl)-1*H*-1,2,3-triazol-1-yl)methyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (12i) Yield: 90%, white solid, m.p. 133 – 134°C. $[\alpha]_D$=+73 (c=1.28, CH_3OH) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.36 (s, 3H), 1.45 (s, 3H), 1.59 (s, 3H), 2.66 (tt, *J*=10.0 Hz, *J*=4.3 Hz, 1H), 3.81 (dd, *J*=9.8 Hz, *J*=8.1 Hz, 1H), 3.86 (br s, 1H.), 3.97 (dd, *J*=8.3 Hz, *J*=4.9 Hz, 1H), 4.06 (m, 1H), 4.15 (dd, *J*=8.3 Hz, *J*=6.0 Hz, 1H), 4.50 (m, 2H), 4.94 (dd, *J*=13.6 Hz, *J*=4.3 Hz, 1H), 5.76 (d, *J*=3.6 Hz, 1H), 6.69 (d, *J*=7.6 Hz, 1H), 7.17 (m, 2H), 7.29 (s, 1H), 7.83 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1, 26.4, 26.7, 26.8, 46.3, 49.7, 68.0, 77.6, 79.8, 80.5, 105.0, 109.9, 112.4, 112.5, 115.1, 116.2, 120.8, 129.7, 131.6, 146.5, 147.5. IR (KBr) 3490, 3380, 3130, 2985, 2910, 1625, 1610, 1590, 1495, 1455, 1380, 1375, 1255, 1220, 1065. HRMS: Calculated for $C_{21}H_{29}N_4O_5$ m/z=417.2138. Found m/z=417.2143.

3-Deoxy-3-*C*-(4-(pent-1-yl)-1*H*-1,2,3-triazol-1-yl) methyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (12j) Yield 81%, white solid, m.p. 81 – 82°C. $[\alpha]_D$=+77 (c=1.26, CH_3OH) ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, *J*=6.9 Hz, 3H), 1.32 (m, 10H), 1.43 (s, 3H), 1.56 (s, 3H), 1.65 (m, 2H), 2.59 (tt, *J*=9.9 Hz, *J*=4.6 Hz, 1H), 2.71 (t, *J*=7.8 Hz, 2H), 3.79 (dd, *J*=9.8 Hz, *J*=8.0 Hz, 1H), 3.95 (dd, *J*=8.2 Hz, *J*=4.9 Hz, 1H), 4.01 (m, 1H), 4.13 (dd, *J*=8.2 Hz, *J*=5.9 Hz, 1H), 4.43 (m, 2H), 4.87 (dd, *J*=13.6 Hz, *J*=4.3 Hz, 1H), 5.74 (d, *J*=3.6 Hz, 1H), 7.39 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.4, 25.0, 25.5, 26.3, 26.7, 26.8, 29.1, 31.3, 46.0, 49.7, 68.0, 77.6, 79.8, 80.5, 105.0, 109.8, 112.4, 121.7, 148.0. IR (KBr) 3130, 2995, 2950, 2935, 2875, 1460, 1385, 1375, 1225, 1165, 1125, 1075, 1015, 980, 850. HRMS: Calculated for $C_{20}H_{34}N_3O_5$ m/z=396.2498. Found m/z=396.2470.

2.3. General procedure for synthesis of deprotected triazole-conjugates 13a-h.

Trifluoroacetic acid (0.5 mL) was added to a suspension of triazole **12** (50 mg) in water (2 mL). The resulting reaction mixture was stirred at ambient temperature until only the product was detected by HPLC (210 and 254 nm UV detection). Then the reaction mixture was evaporated to dryness followed by evaporation with water (4 x 2 mL). Freeze-drying of the water solution (1-2 mL) yielded an isomeric mixture of fully deprotected allose derivatives as white hygroscopic foam with the product **13** being the major component of this mixture.

3-Deoxy-3-*C*-(4-phenyl-1*H*-1,2,3-triazol-1-yl) methyl-β-D-allofuranose (13a). Product **13a** was obtained as a major component (Table 1) during acidic hydrolysis reaction of **12a**. Its structure was elucidated from spectra of the mixture of isomers. ^{1}H NMR (major isomer, 300 MHz, D_2O) δ 2.99 (tt, *J*=9.2 Hz, *J*=5.2 Hz, 1H), 3.63 (m, 2H), 3.78 (d, *J*=9.8 Hz, 1H), 3.95 (m, 2H), 4.69 (m, 2H), 5.25 (s, 1H), 7.45 (m, 3H), 7.74 (d, *J*=8.1 Hz, 2H), 8.28 (s, 1H). ^{13}C NMR (major isomer, 75 MHz, D_2O) δ 45.2, 47.5, 62.9, 74.8, 75.0, 80.2, 101.8, 122.7, 125.6, 128.9, 129.1, 129.2, 147.1. HRMS: Calculated for $C_{15}H_{20}N_3O_5$ m/z=322.13975. Found m/z=322.13904.

3-Deoxy-3-*C*-(4-(4-methylphenyl)-1*H*-1,2,3-triazol-1-yl)methyl-β-D-allofuranose (13b). Product **13b** was obtained as a major component (Table 1) during acidic hydrolysis reaction of **12b**. Its structure was elucidated from spectra of the mixture of isomers. ^{1}H NMR (major isomer, 300 MHz, D_2O) δ 3.06 (s, 3H), 3.71 (tt, *J*=9.2 Hz, *J*=5.1 Hz, 1H), 4.31 (dd, *J*=11.0 Hz, *J*=5.9 Hz, 1H), 4.42 (m, 2H), 4.73 (m, 2H), 5.36 (m, 1H), 5.48 (m, 1H), 5.96 (s, 1H), 8.05 (d, J=8.0 Hz, 2H), 8.39 (d, *J*=8.4 Hz, 2H), 8.97 (s, 1H). ^{13}C NMR (major isomer, 75 MHz, D_2O) δ 20.4, 45.2, 47.6, 63.0, 74.9, 75.0, 80.4, 101.9, 122.5, 125.7, 126.3, 129.8, 139.5, 147.2.

HRMS: Calculated for $C_{16}H_{22}N_3O_5$ m/z=336.15540. Found m/z=336.15485.

3-Deoxy-3-*C*-(4-(4-*tert*-butylphenyl)-1*H*-1,2,3-triazol-1-yl)methyl-β-D-allofuranose (13c). Product **13c** was obtained as a major component (Table 1) during acidic hydrolysis reaction of **12c**. Its structure was elucidated from spectra of the mixture of isomers. ^{1}H NMR (major isomer, 300 MHz, D_2O) δ 1.33 (s, 9H), 3.03 (tt, *J*=9.2 Hz, *J*=4.8 Hz, 1H), 3.64 (m, 2H), 3.80 (d, *J*=10.7 Hz, 1H), 3.99 (m, 2H), 4.85 (d, *J*=2.0 Hz, 1H), 4.92 (d, *J*=2.0 Hz, 1H), 5.27 (s, 1H), 7.62 (d, *J*=8.4 Hz, 2H), 7.77 (d, *J*=8.3 Hz, 2H), 8.35 (s, 1H). ^{13}C NMR δ (major isomer, 75 MHz, DMSO-d6) 31.7, 31.8, 35.1, 45.8, 47.7, 75.1, 75.8, 80.7, 102.2, 125.9, 126.5, 126.8, 128.1, 147.1, 151.8. HRMS: Calculated for $C_{19}H_{29}N_3O_5$ m/z=378.20235. Found m/z=378.20242.

3-Deoxy-3-*C*-(4-cyclopropyl-1*H*-1,2,3-triazol-1-yl)methyl-β-D-allofuranose (13d). Product **13d** was obtained as a major component (Table 1) during acidic hydrolysis reaction of **12d**. Its structure was elucidated from spectra of the mixture of isomers. ^{1}H NMR (major isomer, 300 MHz, DMSO-d6, 70°C) δ 0.71 (m, 2H, H-C(2'')), 0.89 (m, 2H, H-C(2'')), 1.93 (m, 2H, H-C(1'')), 2.70 (ddt, *J*=10.2 Hz, *J*=8.6 Hz, *J*=4.3 Hz, 1H, H-C(3)), 3.38 (dd, *J*=10.5 Hz, *J*=6.2 Hz, 1H, Ha-C(6)), 3.45 (dt, *J*=7.0 Hz, *J*=2.8 Hz, 1H, H-C(5)), 3.56 (dd, *J*=10.5 Hz, *J*=2.9, 1H, Hb-C(6)), 3.59 (d, *J*=4.4 Hz, 1H, H-C(2)), 3.68 (dd, *J*=8.8 Hz, *J*=7.7 Hz, 1H, H-C(4)), 4.44 (dd, *J*=13.0 Hz, *J*=10.6 Hz, 1H, H-C(3')), 4.52 (dd, *J*=13.0 Hz, *J*=3.0 Hz, 1H, H-C(3')), 4.98 (s, 1H, H-C(1)), 7.74 (s, 1H, triazole). ^{1}H NMR (major isomer, 300 MHz, D_2O) δ 0.86 (m, 2H), 1.15 (m, 2H), 2.06 (m, 1H), 2.98 (tt, *J*=8.8 Hz, *J*=5.2 Hz, 1H), 3.59 (m, 2H), 3.74 (d, *J*=9.4 Hz, 1H), 3.90 (t, *J*=7.9 Hz, 1H), 3.96 (d, *J*=4.7 Hz, 1H), 4.72 (m, 2H), 5.15 (s, 1H), 8.17 (s, 1H). ^{13}C NMR (major isomer, 75 MHz, D_2O) δ 4.0, 8.0 (2 carbons), 44.9, 49.9, 63.0, 74.7, 75.0, 79.9, 101.8, 125.3, 147.2. HRMS: Calculated for $C_{12}H_{20}N_3O_5$ m/z=286.13975. Found m/z=286.13962.

3-Deoxy-3-*C*-(4-(3-cyanoprop-1-yl)-1*H*-1,2,3-triazol-1-yl)methyl-β-D-allofuranose (13e). Product **13e** was obtained as a major component (Table 1) during acidic hydrolysis reaction of **12e**. Its structure was elucidated from spectra of the mixture of isomers. ^{1}H NMR (major isomer, 300 MHz, DMSO-d6+D_2O) δ 1.88 (quint, *J*=7.8 Hz, 2H), 2.71 (m, 3H), 3.38 (m, 2H), 3.55 (m, 3H), 3.68 (t, *J*=7.4 Hz, 2H), 4.49 (m, 2H), 4.97 (s, 1H), 7.81 (s, 1H). ^{13}C NMR (major isomer, 75 MHz, $DMSO_{d6}$+D_2O) δ 15.9, 24.0, 24.8, 45.6, 46.7, 63.4, 74.7, 75.3, 79.7, 102.0, 120.6, 122.6, 145.1. HRMS: Calculated for $C_{13}H_{21}N_4O_5$ m/z=313.15065. Found m/z=313.15063.

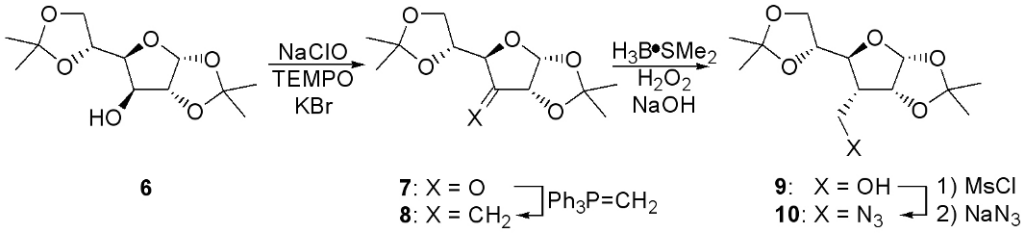
3-Deoxy-3-*C*-(4-(but-1-yl)-1*H*-1,2,3-triazol-1-yl)methyl-β-D-allofuranose (13f). Product **13f** was obtained as a major component (Table 1) during acidic hydrolysis reaction of **12f**. Its structure was elucidated from spectra of the mixture of isomers. ^{1}H NMR (major isomer, 300 MHz, D_2O) δ 0.86 (t, *J*=7.6 Hz, 3H), 1.29 (sextet, *J*=7.4 Hz, 2H), 1.61 (quint., *J*=7.5 Hz, 2H), 2.76 (t, *J*=7.4 Hz, 2H), 2.98 (tt, *J*=8.8 Hz, *J*=5.3 Hz, 1H), 3.61 (m, 2H), 3.76 (d, *J*=9.7 Hz, 1H), 3.94 (m, 2H), 4.73 (m, 2H), 5.24 (s, 1H), 8.07 (s, 1H). ^{13}C NMR (major isomer, 75 MHz, D_2O) δ 12.8, 21.2, 23.1, 30.1, 45.1, 48.6, 62.9, 74.7, 75.0, 80.0, 101.8, 125.3, 163.1. HRMS: Calculated for $C_{13}H_{24}N_3O_5$ m/z=302.17105. Found m/z=302.17087.

3-Deoxy-3-*C*-(4-(hex-1-yl)-1*H*-1,2,3-triazol-1-yl) methyl-β-D-allofuranose (13g). Product **13g** was obtained as a major component (Table 1) during acidic hydrolysis reaction of **12g**. Its structure was elucidated from spectra of the mixture of isomers. ^{1}H NMR (major isomer, 300 MHz, DMSO-d6, 70 °C) δ 0.88 (t, *J*=7.2 Hz, 3H, H-C(6'')), 1.33 (m, 6H, H-C(3'',4'',5'')), 1.62 (quint, *J*=7.2 Hz, 2H, H-C(2'')), 2.62 (t, *J*=7.8 Hz, 2H, H-C(1'')), 2.75 (ddt, *J*=8.4 Hz, *J*=7.5 Hz, *J*=4.7 Hz, 1H, H-C(3)), 3.43 (dd, *J*=10.3 Hz, *J*=5.4 Hz, 1H, Ha-C(6)), 3.52 (ddd, *J*=6.6 Hz, *J*=5.4 Hz, *J*=3.8 Hz, 1H, H-C(5)), 3.58 (dd, *J*=10.3 Hz, *J*=3.8, 1H, Hb-C(6)), 3.67 (d, *J*=4.7 Hz, 1H, H-C(2)), 3.77 (dd, *J*=8.4 Hz, *J*=6.6 Hz, 1H, H-C(4)), 4.53 (m, 2H, H-C(3')), 5.02 (s, 1H, H-C(1)), 7.71 (s, 1H, triazole). ^{1}H NMR (major isomer, 300 MHz, D_2O) δ 0.82 (m, 3H), 1.27 (m, 6H), 1.68 (m, 2H), 2.82 (t, *J*=7.5 Hz, 2H), 3.02 (tt, *J*=8.8 Hz, *J*=5.5 Hz, 1H), 3.63 (m, 2H), 3.77 (d, *J*=11.1 Hz, 1H), 3.96 (m, 2H), 4.84 (m, 2H), 5.25 (s, 1H), 8.26 (s, 1H). ^{13}C NMR (major isomer, 75 MHz, D_2O) δ 13.3, 21.8, 22.9, 27.5, 27.6, 30.5, 45.0, 49.8, 63.1, 74.9, 75.1, 80.1, 101.9, 126.6, 145.3. HRMS: Calculated for $C_{15}H_{28}N_3O_5$ m/z=330.20235. Found m/z=330.20203.

3-Deoxy-3-*C*-(4-(2-hydroxyprop-2-yl)-1*H*-1,2,3-triazol-1-yl)methyl-β-D-allofuranose (13h). Product **13h** was obtained as a major component (Table 1) during acidic hydrolysis reaction of **12h**. Its structure was elucidated from spectra of the mixture of isomers. ^{1}H NMR (major isomer, 300 MHz, D_2O) δ 1.60 (s, 6H), 2.96 (tt, *J*=8.8 Hz, *J*=5.6 Hz Hz, 1H), 3.59 (m, 2H), 3.7 (m, 1H), 3.93 (m, 2H), 4.68 (m, 2H), 5.24 (s, 1H), 8.04 (s, 1H). ^{13}C NMR (major isomer, 75 MHz, D_2O) δ 28.9 (2 carbons), 45.1, 47.8, 62.9, 68.1, 74.9, 74.9, 80.3, 101.8, 122.7, 154.2. HRMS: Calculated for $C_{12}H_{21}N_3O_5Na$ m/z=326.1328. Found m/z=326.1354.

2.4. Glycosidases inhibition assays

The experiments were performed essentially as previously described [19]. Briefly, the products were solubilized in 9:1 mixture of water/methanol. Tests



Scheme 1. Synthesis of the azidomethyl sugar **10**.

were performed at 1 mM (with 1.7% of MeOH, final concentration and a proportion of MeOH on the well) or 0.1 mM (with 0.17% of MeOH, final concentration and a proportion of MeOH on the well) concentration depending on solubility of the products. For the assays, 0.01–0.5 units/mL of enzyme and inhibitor were pre-incubated for 5 min at r.t., and the reaction started by addition of the substrate (*O*-*p*-nitrophenyl glycoside), buffered to the optimal pH of the enzyme. After 20 min of incubation at 37ºC, the reaction was stopped by addition of sodium borate buffer pH 9.8. The *p*-nitrophenolate formed was measured by visible absorption spectroscopy at 405 nm.

3. Results and discussion

The synthetic route involved modification of commercially available diacetone-D-glucose **6** in order to synthesize the necessary azide **10** via a previously reported sequence (Scheme 1) [20]. It started with oxidation of **6** to the corresponding ketone **7** [21] and continued with a Wittig reaction and hydroboration - oxidation. The intermediate 3-deoxy-3-hydroxymethylallose derivative **9** was mesylated and transformed into the target compound **10** upon treatment with NaN_3. The azide **10** was used in a 1,3-dipolar cycloaddition reaction with alkynes (Scheme 2).

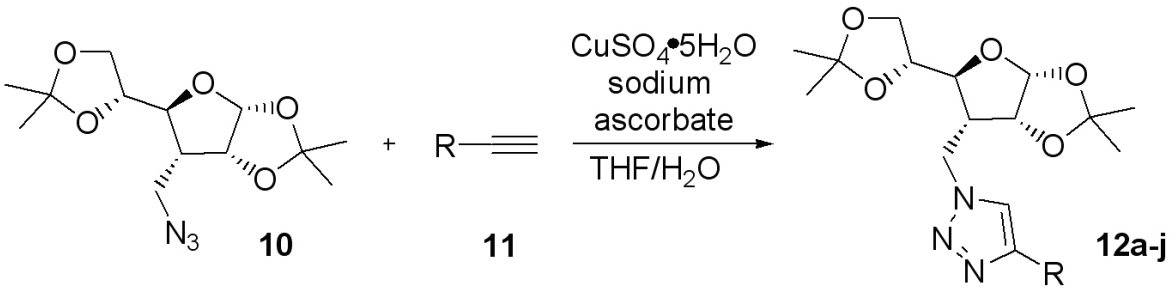
We chose ten structurally different terminal alkynes possessing aryl and alkyl substituents for use in the cycloaddition reactions. A convenient method, involving copper(II) sulfate pentahydrate as catalyst precursor with sodium ascorbate as the reducing agent, seemed very attractive due to its simplicity and robustness. Reactions were successfully carried out at ambient temperature in aqueous THF, and proceeded in 16 to 24 hours with excellent yields of products **12a-j** as summarized in Table 1.

In every case conversion was complete, and standard extractive work-up followed by silica gel column chromatography provided the aforementioned acetonide-protected products. All compounds were obtained as white solids and were stable during storage, except *m*-aminophenyl derivative **12i**, which showed signs of oxidation characteristic for aniline derivatives. All products were fully characterized by their ^{1}H-, ^{13}C-NMR spectra and HRMS analysis.

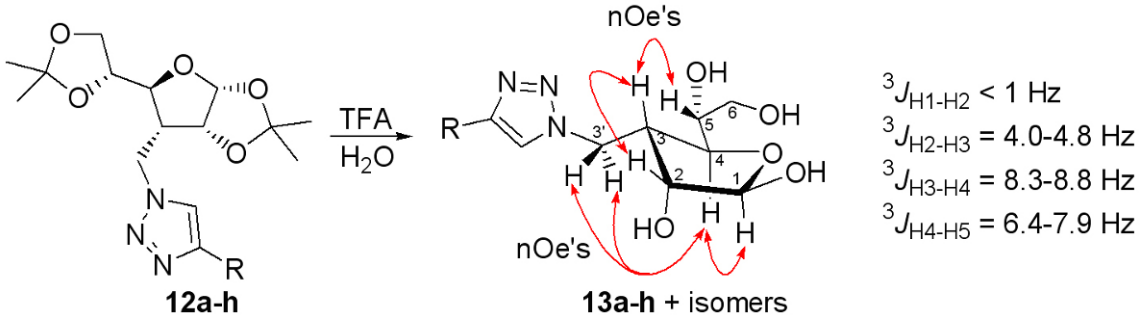
Selected compounds of acetonide-protected carbohydrate-triazole conjugates **12** were subjected to in vitro tests of glycosidase inhibiting activities [19]. The model compound **4** was also synthesized according to the reported method [15a] in order to compare its inhibitory activity with our triazolylmethyl derivatives **12**. In our hands the inhibitory activity of compound 4 could not be tested because of its insufficient solubility, whereas 3-deoxy-1,2:5,6-di-O-isopropylidene-D-allose-derivatives were soluble in water upon addition of a minimal amount of methanol (see experimental section). Compounds **12a,b,f,g,i** were tested at 0.1 mM level and compounds **12d,e** were tested at 1 mM level for inhibition of α-L-fucosidase (EC 3.2.1.51, bovine kidney), α-galactosidase (EC 3.2.1.22, coffee beans), β-galactosidases (EC 3.2.1.23, *Escherichia coli* and *Aspergillus oryzae*), α-glucosidases (EC 3.2.1.20, yeast and rice), β-glucosidase (EC 3.2.1.21, almonds), α-mannosidase (EC 3.2.1.24, jack beans), β-mannosidase (EC 3.2.1.25, snail), β-xylosidase (EC 3.2.1.37, *Aspergillus niger*), amyloglucosidase (EC 3.2.1.3, *Aspergillus niger*), and β-N-acetylglucosaminidase (EC 3.2.1.30, jack beans). However, only compound **12a** had 26% inhibitory activity towards α-L-fucosidase (EC 3.2.1.51, bovine kidney). Compound **12c** was not tested due to its insolubility in water/MeOH mixtures. On the other hand, the *n*-pentyl derivative **12j**, which was not tested either, is anticipated to have similar properties to those of **12f,g**.

We next turned to acetonide deprotection in order to obtain natural-like water soluble compounds of type **13** (Scheme 3, Table 1). Acidic hydrolysis reactions proceeded cleanly in water with trifluoroacetic acid giving isomeric mixtures of fully deprotected sugars in quantitative yields. It was found that 3-deoxy-3-

**We were not able to reproduce results reported by Ferreira et al. [15a]. Compound 4 was neither soluble in water, nor in 9:1 mixture water/methanol at 6 mM concentration. The compound was soluble at 1 mM concentration of 17:83 DMSO:H2O and the enzymatic assay revealed a 41% of inhibition of α-glucosidases from yeast (EC 3.2.1.20) at this concentration. However, the blank experiment using the same proportion of DMSO and without the inhibitor also showed a similar inhibition, which means that DMSO in this proportion is toxic for this enzyme.*

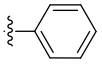
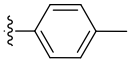
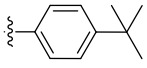
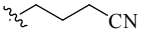
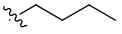
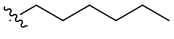
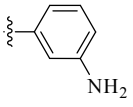
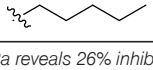


Scheme 2. Synthesis of carbohydrate-triazole conjugates **12a-j** (see Table 1).



Scheme 3. Deprotection of 3-deoxyallose-triazole conjugates **12a-h** (see Table 1).

Table 1. Synthesis of protected (**12a-j**) and deprotected (**13a-h**) 3-deoxyallose – triazole conjugates.

Entry	R	Compound 12, Yield, %	Compound 13, Total yield of process 12→13, (content of 13 in isomeric mixture, %)
1		12a,[a] 95	13a, quant., (76[b])
2		12b, 81	13b, quant., (70[b])
3		12c, 91	13c,[c] quant., (74[b]; 82[d])
4		12d, 92	13d, quant., (75[b]; 83[d])
5		12e, 92	13e, quant., (89[d])
6		12f, 88	13f, quant., (72[b])
7		12g, 92	13g, quant., (76[b]; 80[e])
8		12h, 92	13h, quant., (71[b])
9		12i, 90	-
10		12j, 81	-

[a] – *Compound 12a reveals 26% inhibition of α-L-fucosidase at 0.1 mM level.*
[b] – *Determined by ^{1}H-NMR (300 MHz, D_2O, 25°C).*
[c] – *Compound 13c reveals 15% inhibition of β-glucosidase at 1 mM level.*
[d] – *Determined by ^{1}H-NMR (300 MHz, DMSO-d6, 25°C).*
[e] – *Determined by ^{1}H-NMR (300 MHz, DMSO-d6, 70°C).*

C-triazolylmethyl-allose derivatives exist mainly (up to 89%) in their β-furanose form as reported for their deprotected 3-*C*-azidomethyl-3-deoxy-allose congener [20]. In every case the major components of compound series **13** revealed pronounced cross-peaks between H-C(3) and H-C(5) in their 2D-NOESY spectra. On some occasions also H-C(1) − H-C(4) cross-peaks were observed.

Deprotected carbohydrates **13a-h** were also subjected to the inhibition activity tests at 1 mM level with the aforementioned set of enzymes. Of the compounds tested, only **13c** had 15% β-glucosidase (EC 3.2.1.21, almonds) inhibiting activity at 1 mM concentration. In a parallel experiment diacetonide **4** was also deprotected and submitted to glycosidases inhibiting assays, but did not show any inhibitory activity. The latter product upon deprotection gave a mixture of all four possible isomers: α- and β-pyranose and α- and β-furanose forms in the ratio of 6:21:35:38 (^{1}H-NMR, D_2O). This ratio was changed to 3:16:55:26 in $DMSO_{d6}$. Due to the lack of glycosidases inhibiting activity the constitution of this isomeric mixture was not studied in detail.

4. Conclusions

We have described the synthesis of novel carbohydrate derivatives of 3-deoxy-D-allose with a 1,4-disubstituted 1,2,3-triazole moiety in the side chain. The title compounds differ from those reported previously by the presence of a methylene linker (-CH_2-) between C(3) of the monosaccharide and the triazole core. Several of these acetonide-protected allose-triazole conjugates **12** were subjected to glycosidases inhibiting activity tests, but only 4-phenyl-triazolyl derivative **12a** showed a moderate α-L-fucosidase inhibiting activity at 0.1 mM concentration (26%). Acetal protecting groups in the obtained compounds were cleaved by acidic hydrolysis in order to acquire the water soluble compounds. Products **13** were also tested for their ability to inhibit various glycosidases, but only the 4-(4-*t*-butylphenyl) triazole conjugate **13c** showed 15% β-glucosidase inhibiting activity at 1 mM level. Additionally, it was found that protecting group free derivatives of 3-deoxy-3-*C*-(1*H*-1,2,3-triazol-1-yl)methyl-D-allose exist mainly in β-D-furanose form. Despite of recent literature reports dealing with the use of isopropylidene-protected carbohydrate derivatives as glycosidases inhibitors, the present compounds do not show significant aforementioned biological activity. Our data clearly show the influence of CH_2 linker on the glycosidases inhibiting activity of the sugar-triazole conjugates.

Acknowledgements

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