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Synthesis of esters derived from 2,3,4,6-tetra-*O*-acetyl-1-[4-(2-hydroxyethyl)-1*H*-1,2,3-triazol-1-yl]-*β*-D-glucopyranose

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ABSTRACT

2,3,4,6-Tetra-*o*-acetyl-1-[4-(2-hydroxyethyl)-1*H*-1,2,3-triazol-1-yl]-*β*-D-glucopyranose was prepared and reacted with several acids, either commercially available or prepared. These included, aliphatic or aromatic acids (phenylacetic acid derivatives, benzoic derivatives), palmitic acid and the protected amino acids *N*-(benzyloxycarbonyl)glycine and *N*-(*tert*-butyloxycarbonyl)-phenylalanine. Two other acids, 2-(3-bromopropoxy)benzoic acid and 2-(5-bromopentoxy)benzoic acid (analogues of salicylic acid were synthesized), whose preparation is also described in this work. The esterification was performed either with *N*,*N*′-dicyclohexylcarbodiimide (DCC)/4-dimethylaminopyridine (DMAP) or by reacting the acyl chlorides with the alcohol in the presence of triethylamine. The products were isolated in fair yields and fully characterized by the usual analytical techniques.

1. Introduction

Salicylic acid derivatives are widely known either as natural products or as synthetic derivatives and they are often used for their biological properties, such as antibacterial [1], antioxidant and cytotoxic [2], analgesic and antifungal [3]. Polymeric systems containing those derivatives may be used as potential drug carriers [4,5], e.g. for colon [6] or as implants [7] for localized salicylic acid release on bone.

Benzoic acid and 6-benzoyl-D-glucose are reported to have antimicrobial activity [8]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly used agents for the treatment of pain and inflammation. The prototype of NSAIDs is aspirin, which displays anti-inflammatory and analgesic properties, and also antithrombotic effects, thus protecting against ischemic vascular disorders [9].

Biocompatible non-ionic surfactants can be obtained by linking a hydrophobic alkyl chain to a polyhydroxylated system, usually a carbohydrate molecule, through ester linkages. The surface-active behavior of these esters depends on the length of the lipophilic chain, the temperature, and the position of the ester group in the hydrophilic head of the sugar. Surfactants are molecules which exert a wide range of biological activity [10].

Glycoconjugates, namely glycopeptides, have great potential in drug design, since they mimic fragments of glycoproteins but they are smaller and simpler [11-16]. The sugar moiety influences the drug molecules behavior and enhances the transport through cell membranes [17-20]. In a similar way to that observed in nature, chemists have been using carbohydrate scaffolds, to obtain libraries of compounds for screening in drug research [21].

It is thus anticipated that the ester derivatives presented in this work, combining the 1,2,3-triazole unit and the acid components, may have interesting biological properties. Two examples of a similar type, in the literature, are the assessment as potential glycosidase inhibitors [22] of a set of β-D-glucopyranosyl triazoles, and the preparation of esters derivatives of 1,2,3-triazole glycosides showing cell growth inhibition against two cell strains: NCI-H292 (Lung carcinoma) and HEp-2 (larynx carcinoma) [23].

Recently, we became interested in the use of click chemistry [24,25] to form a triazole bridge to carbohydrates [26]. The 1,2,3-triazole unit can mimic the length and bond angles of the amide bond, displaying resistance to hydrolysis [27]. The pharmaceutical applications of 1,2,3-triazole based drugs may be related to reduced toxicity and increased activity [28].

In this work, it was decided to explore the concept of "*click-chemistry*" to synthesize ester derivatives of sugars. Copper(I) 1,3-dipolar azide-alkyne cycloaddition (*click reaction*) proved to be an useful synthetic process to obtain 1,4-dissubstituted 1,2,3-triazole glycosides and it was used to prepare the starting alcohol **1** for esterification (Figure 1). The acid components included amino acids, palmitic acid, phenyl acetic acid and benzoic acid derivatives, and analogues of salicylic acid containing bromine as a reactive site for further modifications.

2. Experimental

2.1. Instrumentation

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.4 MHz) spectra were recorded on a Varian Unity

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Plus Spectrometer at 298 K or on a Bruker Avance III 400 spectrometer (400 MHz for ^{1}H and 100.6 MHz for ^{13}C). Chemical shifts are reported in ppm relative to solvent peak or TMS; coupling constants (*J*) are given in Hz. Double resonance, HMQC (heteronuclear multiple quantum coherence) and HMBC (heteronuclear multiple bond correlation) experiments were carried out for complete assignment of ^{1}H and ^{13}C signals in the NMR spectra. High-resolution mass spectra were obtained on a Bruker FTMS APEXIII spectrometer. Elemental analyses were obtained on a Leco CHNS-932 instrument. TLC was carried out on plates coated with silica gel 60F_{254}. Column chromatography was performed on silica gel (70-230 or 230-400 mesh). Light petroleum refers to the fraction boiling in the range 40-60 °C. Specific optical rotations were calculated from measurements carried out with an Optical Activity-AA-1000 Polarimeter (sodium D line); concentration c of the test solutions is expressed in % weight of the sample with respect to the volume of the solution.

2.2. Synthesis

2.2.1. Synthesis of precursors

2,3,4,6-Tetra-O-acetyl-1-[4-(2-hydroxyethyl)-1H-1,2,3-triazol-1-yl]-β-D-glucopyranose (**1**): To a solution of α-ABG (1.244 g, 3 mmol) in DMSO (15 mL) dry NaN_3 (0.236 g, 3.6 mmol) was added. The reaction mixture was stirred at room temperature for 20 minutes followed by addition of but-3-yn-1-ol (0.34 mL, 4.5 mmol), sodium L-ascorbate 1 M solution (7.5 mL) and $CuSO_4.5H_2O$ 1 M solution (7.5 mL). The mixture was stirred at room temperature for further 60 mins and a solid was filtered off, and water (60 mL) was added to the filtrate. The mixture was extracted with ethyl acetate (4x50 mL), the combined extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure giving an oily product. The compound was purified by crystallization (DCM-ethyl acetate-light petroleum) giving a light green solid (0.62 g, 47%) (Figure 1). M.p.: 162.6-163.4 °C. $[\alpha]_D^{25.5}$: -14.4 (c 0.02, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.78 (s, 3H, Me-C-2), 1.95 (s, 3H, Me-C-3), 1.99 (s, 3H, Me-C-6), 2.02 (s, 3H, Me-C-4), 2.75 (t, *J* = 6.6 Hz, 2H, CH_2), 3.60 (q, *J* = 6.3 Hz, 2H, CH_2O), 4.04 (dd, *J* = 12.6, 2.1 Hz, 1H, H-6a), 4.12 (dd, *J* = 12.3, 5.1 Hz, 1H, H-6b), 4.34 (ddd, *J* = 9.6, 5.1, 2.1 Hz, 1H, H-5), 4.71 (t, *J* = 5.4 Hz, 1H, OH), 5.15 (t, *J* = 9.6 Hz, 1H, H-4), 5.53 (t, *J* = 9.3 Hz, 1H, H-3), 5.61 (apt, *J* = 9.6/8.7 Hz, 1H, H-2), 6.28 (d, *J* = 8.7 Hz, 1H, H-1), 8.13 (s, 1H, H-5´). ^{13}C NMR (75.4 MHz, DMSO-d_6, δ, ppm): 19.8 (Me-C-2), 20.2 (Me-C-3), 20.3 (Me-C-6), 20.4 (Me-C-4), 28.9 (CH_2), 60.1 (CH_2O), 61.8 (C-6), 67.5 (C-4), 70.0 (C-2), 72.2 (C-3), 73.1 (C-5), 83.6 (C-1), 121.6 (C-5'), 144.9 (C-4'), 168.4 (CO-C-2), 169.3 (CO-C-4), 169.5 (CO-C-3), 170.0 (CO-C-6). ESI-MS (*m/z*): calcd. for $C_{18}H_{25}N_3O_{10}$: 443.15; found: 466.42 $(M+Na)^+$.

2-(5-Bromopentoxy)benzoic acid (**2**): To a solution of salicylaldehyde (2.00 g, 16.3 mmol) in acetonitrile (100 mL), 1,5-dibromopentane (4.5 g, 19.6 mmol) and K_2CO_3 (4.52 g, 32.6 mmol) were added and the reaction mixture was stirred at room temperature for 40 h. Then, dichloromethane and water were added and the organic layer was washed with water, dried (Na_2SO_4) and the solvent was evaporated giving a brown-orange oil. Purification by column chromatography (elution with mixtures of light petroleum and ethyl acetate of increasing polarity) gave the 2-(5-bromopentoxy)benzaldehyde as a yellow oil (1.00 g, 22.6%).

The above derivative was dissolved in acetonitrile (10 mL) and cooled to 0 °C. A 0.1 M aqueous solution of $KMnO_4$ (55.4 mL, 5.5 mmol) was added dropwise and the mixture was left stirring for 36 hrs. The solid was filtered and washed with acetonitrile. The solvent was evaporated and the residue acidified to pH = 2 (with 2 M HCl) and extracted with ethyl acetate (3 x 30 mL). The organic extract was dried (Na_2SO_4) and the solvent was evaporated giving compound **2** as a brown oil (0.72 g, 67%) (Figure 1). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 1.55-1.70 (m, 2H, CH_2-C-3'), 1.77-1.88 (m, 2H, CH_2-C-4' or CH_2-C-2'), 1.88-2.00 (m, 2H,CH_2-C-2' or CH_2-C-4'), 3.45 (t, *J* = 6.6 Hz, 2H, CH_2-Br), 4.37 (t, *J* = 6.3 Hz, 2H, CH_2-O), 6.89 (t, *J* = 7.1 Hz, 1H, H-5), 6.99 (d, *J* = 7.1 Hz, 1H, H-3), 7.46 (dt, *J* = 7.2, 1.5 Hz, 1H, H-4), 7.85 (dd, *J* = 7.8, 1.8 Hz, 1H, H-6). ^{13}C NMR (75.4 MHz, $CDCl_3$, δ, ppm): 24.6 (CH_2-C-3'), 27.7 (CH_2-C-2'), 32.2 (CH_2-C-4'), 33.3 (CH_2-Br), 64.9 (CH_2-O), 112.4 (C-1), 117.5 (C-3), 119.1 (C-5), 129.8 (C-6), 135.6 (C-4), 161.6 (C-2), 170.1 (C=O). ESI-HRMS: calcd. for $C_{12}H_{16}BrO_3$ 287.02773; found 287.02769.

2.2.2. Typical procedure for the synthesis by DCC/DMAP - Method A

A solution of the alcohol **1** (0.325 mmol, 2,3,4,6-tetra-*O*-acetyl-1-[4-(2-hydroxy-ethyl)-1*H*-1,2,3-triazol-1-yl]-β-D-gluco pyranose), DCC (0.358 mmol), the acid (0.325 mmol) and DMAP (0.325 mmol) in dichloromethane (8 mL) was stirred at room temperature for 5 h. The *N*,*N'*-dicyclohexylurea was filtered off and the filtrate was washed with water (3 x 20 mL), 5% acetic acid solution (2 x 20 mL), again with water (3 x 20 mL) and then dried (Na_2SO_4). After evaporation the residue was purified either by crystallization and/or chromatography.

2,3,4,6-Tetra-O-acetyl-1-[(4-phenylacetoxyethyl)-1H-1,2,3-triazol-1-yl]-β-D-glucopyranose (**3**): The compound was prepared from phenyl acetic acid (1.15 mmol), and purified by recrystallization (ethyl acetate and light petroleum) followed by PLC (ethyl acetate: light petroleum; 1:1) and recrystallized again. A white solid (0.26 g) was obtained in 40% yield (Figure 1). M.p.: 122.4-123.9 °C. $[\alpha]_D^{25.5}$: -15.4 (c 0.02, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.77, 1.96, 1.98, 2.02 (4s, 12H, 4xMe-CO), 2.96 (t, *J* = 6.3 Hz, 2H, CH_2), 3.65 (s, 2H, CH_2Ar), 4.07 (dd, *J* = 12.6, 2.4 Hz, 1H, H-6a), 4.14 (dd, *J* = 12.6, 5.1 Hz, 1H, H-6b), 4.25 (t, *J* = 6.3 Hz, 2H, CH_2O), 4.33-4.41 (m, 1H, H-5), 5.17 (t, *J* = 9.6 Hz, 1H, H-4), 5.51-5.65 (m, 2H, H-3 and H-2), 6.30 (d, *J* = 9.0 Hz, 1H, H-1), 7.20-7.37 (m, 5H, Ar-H), 8.13 (s, 1H, H-5'). ^{13}C NMR (75.4 MHz, DMSO-d_6, δ, ppm): 19.9, 20.3, 20.4, 20.5 (4xMe-(CO)), 24.8 (CH_2), 40.3 (CH_2Ar), 61.8 (C-6), 63.0 (CH_2), 67.6 (C-4), 70.1 (C-2), 72.2 (C-3), 73.2 (C-5), 83.7 (C-1), 121.7 (C-5'), 126.5, 126.8 (C-Ar), 128.2, 128.3 (C-Ar), 129.4 (C-Ar), 134.3, 143.9 (C-4'), 168.5, 169.4, 169.6, 170.0, 171.1 (C=O). ESI-MS (*m/z*): calcd. for $C_{26}H_{31}N_3O_{11}$: 561.54; found: 562.08 $(M+H)^+$. Anal. Calcd. for $C_{26}H_{31}N_3O_{11}$: C, 55.61; H, 5.56; N, 7.48. Found: C, 55.81; H, 5.44; N 7.47%.

2,3,4,6-Tetra-O-acetyl-1-[(4-p-nitrophenylacetoxyethyl)-1H-1,2,3-triazol-1-yl]-β-D-glucopyranose (**4**): The compound was prepared from 4-nitrophenyl acetic acid (1.13 mmol), and purified by column chromatography (mixtures of light petroleum and ethyl acetate of increasing polarity) giving a thick oil which yielded, on standing, a white solid (0.52 g, 76%) (Figure 1). M.p.: 97.6-99.1 °C. $[\alpha]_D^{25.5}$: -17.6 (c 0.02, $CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.77, 1.96, 1.97, 2.02 (4s, 12H, 4xMe-CO), 2.97 (t, *J* = 6.6 Hz, 2H, CH_2), 3.86 (s, 2H, Ar-CH_2), 4.07 (dd, *J* = 12.4, 2.4 Hz, 1H, H-6a), 4.13 (dd, *J* = 12.4, 5.2 Hz, 1H, H-6b), 4.28 (t, *J* = 6.4 Hz, 2H, CH_2O), 4.34-4.40 (m, 1H, H-5), 5.17 (t, *J* = 9.6 Hz, 1H, H-4), 5.55 (t, *J* = 9.6 Hz, 1H, H-2), 5.62 (t, *J* = 9.2 Hz, 1H, H-3), 6.30 (d, *J* = 9.2 Hz, 1H, H-1), 7.53 (d, *J* = 8.8 Hz, 2H, H-2" and H-6"), 8.17 (d, *J* = 8.8 Hz, 2H, H-3" and H-5"), 8.22 (s, 1H, H-5'). ^{13}C NMR (100.6 MHz, DMSO-d_6, δ, ppm): 19.9, 20.2, 20.4, 20.5 (4xMe-(CO)), 24.7 (CH_2), 39.7 (CH_2Ar), 61.8 (C-6), 63.3 (CH_2), 67.6 (C-4), 70.1 (C-3), 72.2 (C-2), 73.2 (C-5), 83.8 (C-1), 121.8 (C-5'), 123.3 (C-2" and C-6"), 130.9 (C-3" and C-5"), 142.3 (C-1"), 143.9 (C-4'), 146.5 (C-4"), 168.5, 169.4, 169.6, 170.02, 170.2 (C=O). ESI-MS (*m/z*): calcd. for $C_{26}H_{30}N_4O_{13}$: 606.54; found: 629.42 $(M+Na)^+$. Anal. Calcd. for $C_{26}H_{30}N_4O_{13}$: C, 51.49; H, 4.99; N, 9.24. Found: C, 51.62; H, 4.93; N 9.00%.

2,3,4,6-Tetra-O-acetyl-1-[(4-diphenylacetoxyethyl)-1H-1,2,3-triazol-1-yl]-β-D-glucopyranose (**6**): The compound was prepared from diphenyl acetic acid (0.25 mmol), filtered and recrystallized from ethyl acetate and light petroleum. A beige solid was obtained (0.1 g, 64%) (Figure 1). M.p.: 91.3-92.9 °C. $[\alpha]_D^{25.5}$: -17.3 (c 0.02, $CHCl_3$).

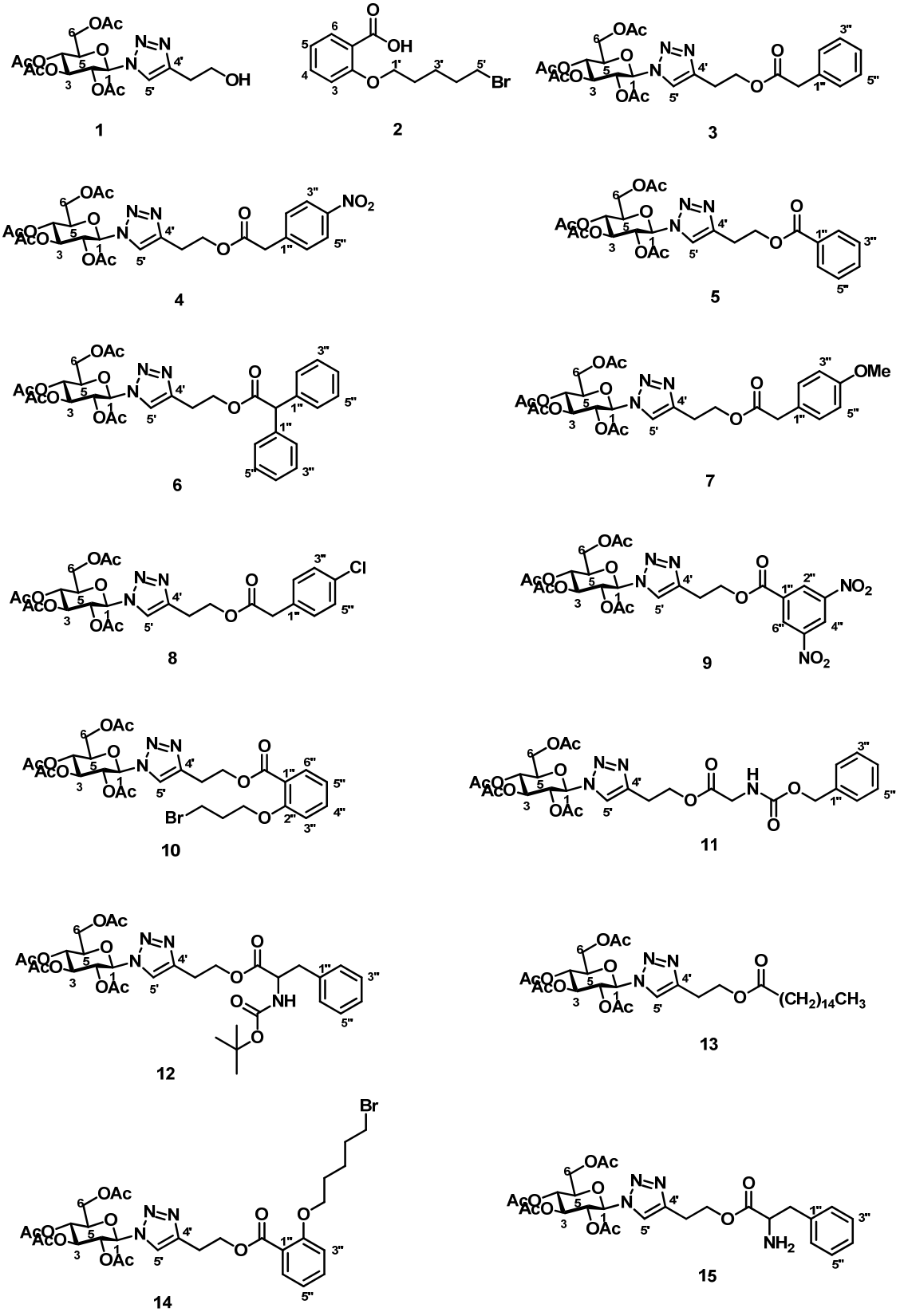

Figure 1. Structures and atom numbering of compounds prepared.

^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.73 (s, 3H, Me-CO), 1.95-2.02 (m, 6H, 2xMe-CO), 2.03 (s, 3H, Me-CO), 2.94 (t, *J* = 6.5 Hz, 2H, CH_2), 4.06 (dd, *J* = 12.3, 2.1 Hz, 1H, H-6a), 4.15 (dd, *J* = 12.3, 5.4 Hz, 1H, H-6b), 4.32 (t, *J* = 6.6 Hz, 2H, CH_2O), 4.24-4.40 (m, 1H, H-5), 5.16 (t, *J* = 9.6 Hz, 1H, H-4), 5.17 (s, 1H, CH-Ar), 5.46-5.60 (m, 2H, H-2 and H-3), 6.28 (d, *J* = 8.7 Hz, 1H, H-1), 7.20-7.38 (m, 10H, Ar-H), 7.94 (s, 1H, H-5'). ^{13}C NMR (75.4 MHz, DMSO-d_6, δ, ppm): 19.9, 20.3, 20.4, 20.5 (4xMe-CO), 24.7 (CH_2), 55.8 (CH), 61.9 (C-6), 63.5 (CH_2), 67.5 (C-4), 70.1 (C-3), 72.1 (C-2), 73.2 (C-5), 83.7 (C-1), 121.6 (C-5'), 127.1, 128.5, 128.5, 128.6 (CH-Ar), 138.4 (2x Cq-Ar), 143.8 (C-4'), 168.5 169.4, 169.6, 170.1, 171.9 (C=O). ESI-MS (*m/z*): calcd. for $C_{32}H_{35}N_3O_{11}$: 637.63; found: 660.50 (M+Na). Anal. Calcd. for $C_{32}H_{35}N_3O_{11}$: C, 60.28; H, 5.53; N, 6.59. Found: C, 60.07; H, 5.66; N, 6.59%.

2,3,4,6-Tetra-O-acetyl-1-[(4-p-methoxy-phenylacetoxyethyl)-1H-1,2,3-triazol-1-yl]-β-D-glucopyranose (**7**): The compound was prepared from 4-methoxyphenyl acetic acid (0.45 mmol), filtered and recrystallized from ethyl acetate and light petroleum. A light brown solid was obtained (0.149 g, 56%) (Figure 1). M.p.: 101.6-103.2 °C. $[\alpha]_D^{25.5}$: -13.5 (c 0.02, $CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.76, 1.96, 1.98, 2.02 (4s, 12H, 4xMe-CO), 2.94 (t, *J* = 6.4 Hz, 2H, CH_2), 3.56 (s, 2H, CH_2Ar), 3.72 (s, 3H, OMe), 4.07 (dd, *J* = 12.4, 2.4 Hz, 1H, H-6a), 4.14 (dd, *J* = 12.4, 5.6 Hz, 1H, H-6b), 4.23 (t, *J* = 6.4 Hz, 2H, CH_2O), 4.33-4.40 (m, 1H, H-5), 5.18 (t, *J* = 9.6 Hz, 1H, H-4), 5.55 (t, *J* = 9.2 Hz, 1H, H-2), 5.60 (t, *J* = 9.6 Hz, 1H, H-3), 6.30 (d, *J* = 8.8 Hz, 1H, H-1), 6.86 (d, *J* = 8.8 Hz, 2H, H-3" and H-5"), 7.14 (d, *J* = 8.8 Hz, 2H, H-2" and H-6"), 8.13 (s, 1H, H-5'). ^{13}C NMR (100.6 MHz, DMSO-d_6, δ, ppm): 19.9, 20.2, 20.4, 20.5 (4xMe-CO), 24.8 (CH_2), 39.3 (CH_2Ar), 55.0 (OMe), 61.8 (C-6), 62.9 (CH_2), 67.6 (C-4), 70.1 (C-3), 72.2 (C-2), 73.2 (C-5), 83.8 (C-1), 113.7 (C-2" and C-6"), 121.7 (C-5'), 126.2 (C-1"), 130.4 (C-3" and C-5"), 143.9 (C-4'), 158.1 (C-4"), 168.5, 169.4, 169.6, 170.0, 171.4 (C=O). ESI-MS (*m/z*): calcd. for $C_{27}H_{33}N_3O_{12}$: 591.56; found: 592.08 $(M+H)^+$. Anal. Calcd. for $C_{27}H_{33}N_3O_{12}$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.92; H, 5.62; N, 7.12%.

2,3,4,6-Tetra-O-acetyl-1-[(4-p-chlorophenylacetoxyethyl)-1H-1,2,3-triazol-1-yl]-β-D-glucopyranose (**8**): The titled compound was prepared from 4-chlorophenyl acetic acid (0.45 mmol) and purified by column chromatography (mixtures of light petroleum and ethyl acetate of increasing polarity) followed by recrystallization from ethyl acetate and light petroleum (0.174 g, 65%) (Figure 1). M.p.: 131.6-133.4 °C. $[\alpha]_D^{28.5}$: -17.2 (c 0.02, $CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.76, 1.95, 1.98, 2.02 (4s, 12H, 4xMe-CO), 2.96 (t, *J* = 6.4 Hz, 2H, CH_2), 3.67 (s, 2H, ArCH_2), 4.07 (dd, *J* = 12.4, 2.4 Hz, 1H, H-6a)), 4.14 (dd, *J* = 12.4, 5.2 Hz, 1H, H-6b), 4.25 (t, *J* = 7.0 Hz, 2H, CH_2O), 4.33-4.40 (m, 1H, H-5), 5.17 (t, *J* = 9.6 Hz, 1H, H-4), 5.55 (t, *J* = 9.6 Hz, 1H, H-2), 5.62 (t, *J* = 9.6 Hz, 1H, H-3), 6.30 (d, *J* = 8.8 Hz, 1H, H-1), 7.25 (d, *J* = 8.5 Hz, 2H, H-3" and H-5"), 7.35 (d, *J* = 8.5 Hz, 2H, H-2" and H-6"), 8.19 (s, 1H, H-5'). ^{13}C NMR (100.6 MHz, DMSO-d_6, δ, ppm): 19.9, 20.2, 20.4, 20.5 (4x Me-CO), 24.7 (CH_2), 39.3 (CH_2Ar), 61.8 (C-6), 63.1 (CH_2), 67.6 (C-4), 70.1 (C-3), 72.2 (C-2), 73.2 (C-5), 83.8 (C-1), 121.7 (C-5'), 128.2 (C-2" and C-6"), 131.3 (C-3" and C-5"), 131.5 (C-1"), 133.3 (C-4"), 143.9 (C-4'), 168.5, 169.4, 169.6, 170.0, 170.8 (C=O). ESI-MS (*m/z*): calcd. for $C_{26}H_{30}ClN_3O_{11}$: 595.98; found: 618.42 $(M+Na)^+$. Anal. Calcd. for $C_{26}H_{30}ClN_3O_{11}$: C, 52.40; H, 5.07; N, 7.05. Found: C, 52.38; H, 5.03; N 7.06%.

2,3,4,6-Tetra-O-acetyl-1-[4-(2-bromopropoxybenzoyloxy ethyl)-1H-1,2,3-triazol-1-yl]-β-D-glucopyranose (**10**): The titled compound was from 2-(5-bromopropoxy)benzoic acid (0.40 mmol) and alcohol **1**. The amounts of other reagents and solvents were adjusted accordingly. The oil obtained was crystallized from ethyl acetate-light petroleum affording a white solid (0.246 g, 90%) (Figure 1). M.p.: 122.3-123.4 °C. $[\alpha]_D^{21}$: -23.8 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.71, 1.95, 1.97, 2.01 (4s, 12H, 4xMe-CO), 2.19 (t, *J* = 6.0 Hz, 2H, CH_2), 3.07 (t, *J* = 6.6 Hz, 2H, CH_2), 3.69 (t, *J* = 6.3 Hz, 2H, CH_2), 4.00-4.18 (m, 4H, H-6 and CH_2O), 4.30-4.40 (m, 1H, H-5), 4.44 (t, *J* = 6.3 Hz, 2H, CH_2), 5.14 (t, *J* = 9.3 Hz, 1H, H-4), 5.53 (t, *J* = 9.3 Hz, 1H, H-2 or H-3), 5.60 (t, *J* = 9.3 Hz, 1H, H-2 or H-3), 6.30 (d, *J* = 9.0 Hz, 1H, H-1), 6.99 (t, *J* = 7.5 Hz, 1H, H-5"), 7.14 (d, *J* = 8.1 Hz, 1H, H-3"), 7.51 (td, *J* = 7.8, 1.8 Hz, 1H, H-4"), 7.61 (dd, *J* = 2.1, 7.8 Hz, 1H, H-6"), 8.26 (s, 1H, H-5'). ^{13}C NMR (75.4 MHz, DMSO-d_6, δ, ppm): 19.8, 20.3, 20.4, 20.5 (4x Me-CO), 24.9 (CH_2), 31.4 (CH_2), 31.8 (CH_2), 61.9 (C-6), 63.2 (CH_2), 65.9 (CH_2), 67.6 (C-4), 70.1 (C-2 or C-3), 72.2 (C-2 or C-3), 73.3 (C-5), 83.8 (C-1), 113.6 (C-3"), 120.0 (C-1"), 120.3 (C-4" or C-5"), 121.8 (C-5'), 131.0 (C-6"), 133.8 (C-4" or C-5"), 144.1 (C-4'), 157.6 (C-2"), 165.4, 168.5, 169.4, 169.6, 170.1 (C=O). ESI-HRMS: Calcd. for $C_{28}H_{35}BrN_3O_{12}$: 684.13986 $[M+H]^+$; found 684.13987. Anal. Calcd. for $C_{29}H_{36}BrN_3O_{12}$: C, 49.86; H, 5.19; N, 6.02. Found: C, 49.43; H, 5.18; N, 6.16%.

2,3,4,6-Tetra-O-acetyl-1-[4-(benzyloxycarbonylamino acetoxyethyl)-1H-1,2,3-triazol-1-yl]-β-D-glucopyranose (**11**): The compound was prepared from *N*-(benzyloxycarbonyl)-L-glycine (0.56 mmol). All other reagents and solvents were used in appropriate amounts. Purification by column chromatography (chloroform-methanol 16:1) gave a white solid (0.227 g, 64%) (Figure 1). M.p.: 94.0-95.9 °C. $[\alpha]_D^{21}$: -7.4 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.78, 1.94, 1.98, 2.01 (4s, 12H, 4xMe-CO), 2.96 (t, *J* = 6.0 Hz, 2H, CH_2), 3.76 (d, *J* = 5.7 Hz, 2H, CH_2Gly), 4.06 (br d, *J* = 11.4 Hz, 1H, H-6a), 4.13 (dd, *J* = 12.6, 5.4 Hz, 1H, H-6b), 4.26 (t, *J* = 6.0 Hz, 2H, CH_2O), 4.30-4.40 (m, 1H, H-5), 5.04 (s, 2H, ZCH_2), 5.15 (t, *J* = 9.6 Hz, 1H, H-4), 5.54 (t, *J* = 9.6 Hz, 1H, H-3), 5.62 (t, *J* = 9.3 Hz, 1H, H-2), 6.30 (d, *J* = 8.7 Hz, 1H, H-1), 7.22-7.50 (m, 5H, Ar-H), 7.67 (t, *J* = 6.0 Hz, 1H, NH), 8.23 (s, 1H, H-5'). ^{13}C NMR (75.4 MHz, DMSO-d_6, δ, ppm): 19.9, 20.2, 20.4, 20.5 (4x Me-CO), 24.7 (CH_2), 42.1 (CH_2Gly), 61.8 (C-6), 63.1 (CH_2), 65.6 (CH_2Z), 67.5 (C-4), 70.1 (C-2), 72.1 (C-3), 73.2 (C-5), 83.7 (C-1), 121.8 (C-5'), 127.8 (C-2" and C-6"), 127.9 (C-4"), 128.4 (C-3" and C-5"), 136.9 (C-1"), 143.8 (C-4'), 156.5 (CO-Z), 168.5 (CO-C-2), 169.4 (CO-C-4), 169.6 (CO-C-3), 170.0 (CO-C-6), 170.2 (CO-(Gly)). ESI-HRMS: Calcd. for $C_{28}H_{35}N_4O_{13}$, 635.21951 $[M+H]^+$; found 635.21936.

2,3,4,6-Tetra-O-acetyl-1-[4-(2-tert-butyloxycarbonylamino-3-phenyl-propanoyloxyethyl)-1H-1,2,3-triazol-1-yl]-β-D-glucopyranose (**12**): The compound was prepared from *N*-(*tert*-butoxycarbonyl)-L-phenylalanine (0.56 mmol). All other reagents and solvents were used in appropriate amounts. A greenish oily solid was obtained which was recrystallized twice from ethyl acetate-diethyl ether-light petroleum affording a beige solid (0.193 g, 50%) (Figure 1). M.p.: 140-142.5 °C. $[\alpha]_D^{21}$: -8.34 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.32 (s, 9H, 3xMe), 1.76, 1.95, 1.95, 2.01 (4s, 12H, 4xMe-CO), 2.75 – 3.00 (m, 4H, CH_2 and β-CH_2), 4.00 – 4.30 (m, 5H, H-6, α-CH and CH_2O), 4.30 – 4.40 (m, 1H, H-5), 5.14 (t, *J* = 9.6 Hz, 1H, H-4), 5.50-5.64 (m, 2H, H-2 and H-3), 6.30 (d, *J* = 8.4 Hz, 1H, H-1), 7.18-7.28 (m, 6H, Ar-H and NH), 8.22 (s, 1H, H-5'). D_2O exchange showed simplification on the multiplet at 2.75 – 3.00 ppm. ^{13}C NMR (75.4 MHz, DMSO-d_6, δ, ppm): 19.8, 20.2, 20.3, 20.4 (4xMe-CO), 24.7 (CH_2), 27.7, 28.1 (3xMe-Boc), 36.2 (β-CH_2), 55.2 (α-CH), 61.7 (C-6), 63.0 (CH_2), 67.5 (C-4), 70.1 (C-3), 72.1 (C-2), 73.1 (C-5), 78.2 (C-Boc), 83.7 (C-1), 121.7 (C-5'), 126.4, 128.1, 129.0 (Ar-H), 137.5 (Cq, Ar), 143.7 (C-4'), 155.4 (CO-Boc), 168.4, 169.3, 169.5, 169.9 (4xCO-Me), 172.0 (CO-Phe). ESI-HRMS: Calcd. for $C_{32}H_{43}N_4O_{13}$, 691.28211 $[M+H]^+$; found 691.28201.

2,3,4,6-Tetra-O-acetyl-1-[4-palmitoyloxyethyl)-1H-1,2,3-triazol-1-yl]-β-D-glucopyranose (**13**): The compound was prepared in 0.6 mmol scale, using palmitic acid and the alcohol **1** as the starting materials. A greenish solid was obtained (0.139 g, 34%) (Figure 1). M.p.: 120-124 °C. $[\alpha]_D^{21}$: -12.2 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 0.84 (t, *J* = 7.2 Hz, 3H, Me), 1.16-1.30 (m, 26H, 13xCH_2), 1.40-1.52 (m, 2H, CH_2), 1.77, 1.95, 1.99, 2.02 (4s, 12H, 4xMe-CO), 2.25 (t, *J* = 7.2 Hz, 2H, CH_2-CO), 2.94 (t, *J* = 6.6 Hz, 2H, CH_2), 4.00 – 4.20 (m, 2H, H-6), 4.22 (t, *J* = 6.6 Hz, 2H, CH_2O), 4.03- 4.04 (m, 1H, H-5), 5.15 (t, *J* = 9.0 Hz, 1H, H-4), 5.50-5.65 (m, 2H, H-2 and H-3), 6.29 (d, *J* = 9.6 Hz, 1H, H-1), 8.20 (s, 1H, H-5'). ^{13}C NMR (75.4 MHz, DMSO-d_6, δ, ppm): 13.9 (Me), 19.9, 20.2, 20.4, 20.5 (4xMe-CO), 22.1 (CH_2),

24.3 (CH_2), 24.8 (CH_2), 28.4 (CH_2), 28.6 (CH_2), 28.7 (CH_2), 28.8 (CH_2), 28.9 (CH_2), 29.0 (2xCH_2), 31.3 (CH_2), 33.3 (CH_2), 61.8 (C-6), 62.4 (OCH_2), 67.5 (C-4), 70.1 (C-3), 72.1 (C-2), 73.2 (C-5), 83.7 (C-1), 121.6 (C-5'), 143.9 (C-4'), 168.4, 169.4, 169.5, 170.0, 172.9 (C=O). Anal. Calcd. for $C_{34}H_{55}N_3O_{12}$: C, 59.89; H, 8.13; N, 6.16. Found: C, 59.45; H, 7.91; N, 6.27%.

2,3,4,6-Tetra-O-acetyl-1-[4-(2-bromopentoxybenzoyloxy ethyl)-1H-1,2,3-triazol-1-yl]-β-D-glucopyranose (**14**): The titled compound was prepared from 2-(5-bromopentyloxy)benzoic acid (1.72 mmol) and alcohol **1**. The amounts of other reagents and solvents were adjusted accordingly. The compound was purified by chromatography with ethyl acetate-petroleum ether 3:2, yielding a white solid (0.723 g, 59%) (Figure 1). M.p.: 70.4-71.2 °C. $[\alpha]_D^{21}$: -19.4 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.48-1.60 (m, 2H, CH_2), 1.64-1.74 (m, 2H, CH_2), 1.72 (s, 3H, Me-CO), 1.78-1.90 (m, 2H, CH_2), 1.95, 1.97, 2.01 (3s, 9H, 3xMe-CO), 3.07 (t, *J* = 6.6 Hz, 2H, CH_2), 3.53 (t, *J* = 6.6 Hz, 2H, CH_2), 3.96-4.16 (m, 4H, H-6 and CH_2O), 4.30-4.39 (m, 1H, H-5), 4.43 (t, *J* = 6.6 Hz, 2H, CH_2OCO), 5.15 (t, *J* = 9.3 Hz, 1H, H-4), 5.53 (t, *J* = 9.3 Hz, 1H, H-2), 5.60 (t, *J* = 9.6 Hz, 1H, H-3), 6.30 (d, *J* = 9.0 Hz, 1 H, H-1), 6.96 (t, *J* = 7.8 Hz, 1 H, H-5"), 7.10 (d, *J* = 8.1 Hz, 1H, H-3"), 7.49 (td, *J* = 7.5, 1.8 Hz, 1H, H-4"), 7.57 (dd, *J* = 1.8, 7.8 Hz, 1H, H-6"), 8.25 (s, 1H, H-5'). ^{13}C NMR (75.4 MHz, DMSO-d_6, δ, ppm): 19.8, 20.3, 20.4, 20.5 (4xMe-CO), 24.3 (CH_2), 24.9 (CH_2), 27.7 (CH_2), 31.9 (CH_2), 35.1 (CH_2), 61.8 (C-6 or CH_2O), 63.1 (CH_2OCO), 67.6 (C-4), 68.0 (C-6 or CH_2O), 70.1 (C-3), 72.2 (C-2), 73.2 (C-5), 83.7 (C-1), 113.5 (C-3"), 120.0 (C-5"), 120.2 (C-1"), 121.7 (C-5'), 130.7 (C-6"), 133.5 (C-4"), 144.0 (C-4'), 157.7 (C-2"), 165.7, 168.4, 169.4, 169.6, 170.0 (C=O). Anal. Calcd. for $C_{30}H_{38}BrN_3O_{12}$: C, 50.57; H, 5.38; N, 5.90. Found: C, 50.90; H, 5.44; N, 6.05%.

2.2.3. Typical procedure for the synthesis by acyl chloride/Et$_3$N - Method B

To a solution of compound **1** (0.37 mmol) in ethyl acetate (10 mL) at 0 °C, acyl chloride (0.44 mmol) and triethylamine (0.44 mmol) were added. The reaction mixture was stirred at room temperature for 1-3 h (TLC controlled). The solid triethylamine hydrochloride was filtered off and water (50 mL) was added to the filtrate. The mixture was extracted with ethyl acetate (4 x 50 mL), the combined extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The resulting product was purified either by column chromatography or/and recrystallization.

2,3,4,6-Tetra-O-acetyl-1-[(4-benzoyloxyethyl)-1H-1,2,3-triazol-1-yl]-β-D-glucopyranose (**5**): This compound was prepared from benzoyl chloride (0.86 mmol). The organic extract obtained was an oil that after treatment with ethyl ether gave a white solid (0.282 g, 60%) (Figure 1). M.p.: 166.0-167.8 °C. $[\alpha]_D^{25.5}$: -19.6 (c 0.02, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.69, 1.95, 1.97, 2.02 (4s, 12H, 4xMe-CO), 3.11 (t, *J* = 6.5 Hz, 2H, CH_2), 4.00-4.16 (m, 2H, H-6), 4.30-4.38 (m, 1H, H-5), 4.49 (t, *J* = 6.5 Hz, 1H, CH_2O), 5.15 (t, *J* = 9.6 Hz, 1H, H-4), 5.53 (t, *J* = 9.3 Hz, 1H, H-2), 5.62 (t, *J* = 9.3 Hz, 1H, H-3), 6.31 (d, *J* = 9.0 Hz, 1H, H-1), 7.49 (t, *J* = 7.7 Hz, 2H, H-3" and H-5"), 7.64 (t, *J* = 7.7 Hz, 1H, H-4"), 7.89 (d, *J* = 7.6 Hz, 2H, H-2" and H-6"), 8.31 (s, 1H, H-5'). ^{13}C NMR (75.4 MHz, DMSO-d_6, δ, ppm): 19.8, 20.3, 20.4, 20.5 (4xMe-CO), 24.9 (CH_2), 61.8 (C-6), 63.5 (CH_2), 67.6 (C-4), 70.1 (C-3), 72.2 (C-2), 73.2 (C-5), 83.7 (C-1), 121.8 (C-5'), 128.7 (C-3" and C-5"), 129.2 (C-2" and C-6"), 129.7 (C-1"), 133.3 (C-4"), 144.1 (C-4'), 165.7, 168.4, 169.4, 169.6, 170.0 (C=O). ESI-MS (*m/z*): calcd. for $C_{25}H_{29}N_3O_{11}$: 547.51; found: 570.42 $(M+Na)^+$. Anal. calcd. for $C_{25}H_{29}N_3O_{11}$: C, 54.84; H, 5.34; N, 7.67. Found: C, 54.81; H, 5.26; N, 7.73%.

2,3,4,6-Tetra-O-acetyl-1-[4-(3,5-dinitrobenzoyloxyethyl)-1H-1,2,3-triazol-1-yl]-β-D-glucopyranose (**9**): The compound was prepared from 3,5-dinitrobenzoyl chloride (0.40 mmol) and a reaction time of 4 hours. An oily product was obtained which was purified by column chromatography (silica, solvent of increasing polarity of mixtures of petroleum ether and ethyl acetate). The obtained solid was recrystallized from ethyl acetate and light petroleum yielding a white powder (0.140 g, 55%) (Figure 1). M.p.: 166.1-167.8 °C. $[\alpha]_D^{28.5}$: -15.9 (c 0.02, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.67, 1.93, 1.97, 2.01 (4s, 12H, 4xMe-CO), 3.19 (t, *J* = 6.6 Hz, 2H, CH_2), 4.04 (dd, *J* = 12.3, 2.4 Hz, 1H, H-6a), 4.11 (dd, *J* = 12.3, 6.4 Hz, 1H, H-6b), 4.25-4.40 (m, 1H, H-5), 4.63 (t, *J* = 6.6 Hz, 2H, CH_2O), 5.13 (t, *J* = 9.6 Hz, 1H, H-4), 5.43-5.60 (m, 2H, H-3 and H-2), 6.30 (d, *J* = 9.0 Hz, 1H, H-1), 8.32 (s, 1H, H-5'), 8.89 (d, *J* = 2.1 Hz, 2H, H-2" and H-6"), 9.04 (t, *J* = 2.1, 1H, H-4"). ^{13}C NMR (75.4 MHz, DMSO-d_6, δ, ppm): 19.8, 20.3, 20.4, 20.5 (4xMe-CO), 24.6 (CH_2), 61.8 (C-6), 65.0 (CH_2), 67.6 (C-4), 70.2 (C-2 or C-3), 72.1 (C-3 or C-2), 73.2 (C-5), 83.8 (C-1), 121.8 (C-5'), 122.6 (C-4"), 128.9 (C-2" and C-6"), 132.7 (C-1"), 143.9 (C-4'), 148.4 (C-3" and C-5"), 162.5, 168.4, 169.4, 169.6, 170.1 (C=O). ESI-HRMS: Calcd. for $C_{25}H_{28}N_5O_{15}$: 638.1574 $[M+H]^+$; found 638.1576.

2.2.4. Deprotection of compound 12

2,3,4,6-Tetra-O-acetyl-1-[4-(2-amino-3-phenylpropanoyloxy ethyl)-1H-1,2,3-triazol-1-yl]-β-D-glucopyranose (**15**): Compound **12** (0.16 mmol) was treated at 0 °C with a mixture of TFA (10 mL) and DCM (10 mL) and set aside for 3.5 hrs at room temperature. Solvents were removed and the residue was purified by column chromatography (mixtures of light petroleum and ethyl acetate of increasing polarity) and obtained as an oil (12 mg, 13%) (Figure 1). ^{1}H NMR (400 MHz, MeOD, δ, ppm): 1.85, 2.02, 2.06, 2.07 (4s, 12H, 4xMe-CO), 2.93 (t, *J* = 6.6 Hz, 2H, CH_2), 3.04 (dd, *J* = 6.8, 13.6 Hz, 1H, β-CH_2), 3.14 (dd, *J* = 6.0, 13.6 Hz, 1H, β-CH_2), 3.82 (t, *J* = 7.2 Hz, 2H, CH_2O), 3.90-3.95 (m, 1H, α-CH), 4.19 (dd, *J* = 12.0, 2.0 Hz, 1H, H-6a), 4.21-4.28 (m, 1H, H-5), 4.33 (dd, *J* = 12.4, 4.8 Hz, 1H, H-6b), 5.28 (t, *J* = 9.6 Hz, 1H, H-4), 5.54 (t, *J* = 9.2 Hz, 1H, H-2 or H-3), 5.62 (t, *J* = 9.2 Hz, 1H, H-3 or H-2), 6.12 (d, *J* = 9.2 Hz, 1H, H-1), 7.20-7.35 (m, >5 H, Ar-H), 8.07 (s, 1H, H-5'). The sample was contaminated with the precursor; the aromatic region integrates for more than 5 protons. The NH_2 was not assigned; we believe that the signal is hidden under the acetyl groups. ^{13}C NMR (100.6 MHz, MeOD, δ, ppm): 20.1, 20.5, 20.6 (4xMe-CO), 29.8 (CH_2), 40.4 (β-CH_2), 56.2 (α-CH), 61.9 (CH_2O), 63.0 (C-6), 69.2 (C-4), 71.9 (C-3 or C-2), 74.2 (C-2 or C-3), 75.9 (C-5), 86.5 (C-1), 123.7 (C-5'), 137.4 (Cq-Ar), 147.0 (C-4'), 170.4, 171.2, 171.5, 172.2, 174.5 (C=O). ESI-HRMS: calcd. for $C_{27}H_{35}N_4O_{11}$, 591.22968 $[M+H]^+$; found 591.22975.

3. Results and discussion

The reaction of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide (prepared *in situ* from α-acetobromoglucose (α-ABG) upon reaction with NaN_3 in DMSO) [29] with but-3-yn-1-ol alcohol under click chemistry conditions [29,30] afforded the alcohol (**1**) with an overall yield of 47%. The presence of a singlet at 8.13 ppm for the H-5 of the triazole ring, as well as the expected signals for CH_2CH_2OH confirms the structure of the alcohol.

For the synthesis of the esters, commercial reagents such as benzoic acid, 3,5-dinitrobenzoic acid, phenyl acetic acid, *p*-nitrophenyl acetic acid, *p*-methoxyphenyl acetic acid, *p*-chlorophenyl acetic acid, diphenylacetic acid, palmitic acid, *N*-(benzyloxycarbonyl)glycine and *N*-(*tert*-butyloxycarbonyl)-phenylalanine were used as acid components. Two other acids were synthesized, 2-(3-bromopropoxy)benzoic acid [31,32] and 2-(5-bromopentoxy)benzoic acid (**2**) described in this work. The latter was prepared by alkylation of salicylaldehyde with 1,5-dibromopentane followed by $KMnO_4$ oxidation in a global yield of 15%.

The esterification was achieved either with DCC/DMAP (method A) or by reacting the acyl chlorides with the alcohol in the presence of triethylamine (method B). The yields obtained ranged between 34 and 90% by DCC/DMAP method. The dinitrobenzoic acid derivative (**9**) was prepared in 55% yield

via acyl chloride. The ester (**10**) was obtained in quantitative yield by method A and in low yield, 19%, by method B.

The ^{1}H-NMR data were used to confirm the structure of the esters. In the phenyl acetic derivatives (esters **3**, **4**, **6**, **7** and **8**) the singlet for the CH_2Ar appears at, for example, 3.65 ppm for compound **3**, 3.86 ppm for compound **4**. The ^{1}H-NMR for the amino acid containing derivatives shows the singlet for three CH_3 groups at 1.32 ppm for compound **12**, and a doublet (J= 5.7) at 3.76 ppm for the glycine CH_2, **11**. For the ester **13** the significant signals for the terminal protons of the alkyl chain at 0.84 (t, CH_3) and at 4.22 (t, CH_2O) were observed. On the ^{13}C-NMR spectra the expected signals were observed namely CH_2O at 24.8 and C-4' and C-5' of triazole ring at around 143.9 and 121.7 ppm, respectively. Ester **15** was prepared by the removal of the Boc (protective group of compound **12**) and in the ^{1}H-NMR it was possible to confirm the structure by the disappearance of the singlet of the Boc-CH_3.

4. Conclusion

A series of esters derived from 2,3,4,6-tetra-*O*-acetyl-1-[4-(2-hydroxyethyl)-1*H*-1,2,3-triazol-1-yl]-β-D-glucopyranose and carboxylic acids, either aliphatic or aromatic and amino acids were prepared. The methods used (DCC/DMAP or acyl chloride) were appropriate affording the final compounds in fair yields.

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