Synthesis of glycoconjugates containing a 1,2,3-triazole unit

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Abstract:

The preparation of several alkynyl esters, derived from amino acids, coumarins and an alkynyl derivative of acetylated D-glucose is described. Eight new glycoconjugates containing the 1,2,3-triazole unit were obtained, by a click approach from the above referred alkynyl derivatives with tetracetyl-β-D-glucosylazide, prepared *in situ* from α-acetobromoglucose.

Keywords: glycoconjugates, click chemistry, triazole, alkynyl esters

Introduction

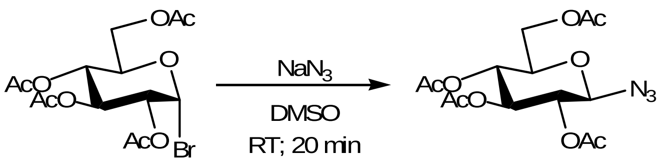
The glycoconjugates have an enormous potential in drug design[1]. Between them, glycopeptides are particularly important as they combine the structural features of amino acids and carbohydrates in the same molecule. Glycoconjugates containing the 1,2,3-triazole unit find application in medicinal chemistry, particularly in those cases where this unit acts as a bridge between an amino acid/peptide and the sugar moiety.[2]

In this work the synthesis of several glycoconjugates containing the 1,2,3-triazole unit as a bridge between a sugar (D-glucose) moiety and an amino acid or heteroaromatic unit is described. The 1,2,3-triazole unit was formed by an azide-alkyne 1,3-dipolar cycloaddition, catalysed by a Cu(I) species, a chemical process usually known as click chemistry.[3,4] The azido component was prepared *in situ* from α-acetobromoglucose.[4,5]

Results and Discussion

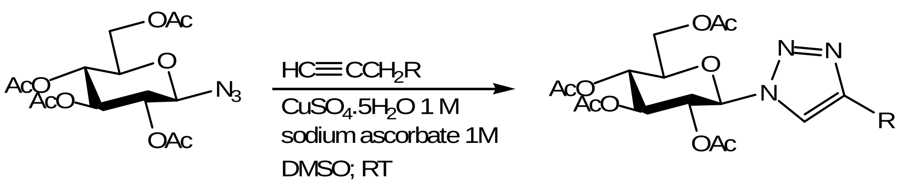
The starting alkynyl esters **1**-**5** (figure 1) were prepared by reaction between *N*-protected glycine, tyrosine and phenylalanine, 7-hydroxycoumarin and 7-hydroxy-4-methylcoumarin and propargyl bromide with high yields. All these compounds showed in the proton NMR spectra the coupling patterns for the alkynyl function, for instance for compound **1** a triplet (*J*=2.4 Hz) at 3.58 and a doublet (*J*=2.4 Hz) at 4.73 ppm for ≡CH and CH_2C≡, respectively.

The formation of the 1,2,3-triazole unit occurred by reaction between an azide component and acetylenic compounds. The azido component was prepared *in situ* from α-acetobromoglucose, by a known method[4], as shown in scheme 1**.**



Scheme 1. Preparation of glucosylazide

Compounds **1**-**5** and also three commercial alcohols, prop-2-yn-1-ol (propargyl), *rac*-but-3-yn-1-ol and but-3-yn-2-ol, were used as acetylenic components. The final compounds **6**-**12** (figure 1), containing the 1,2,3-triazole unit, were obtained following the conditions described in scheme 2.

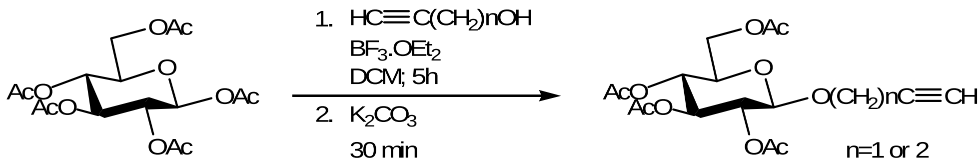


Scheme 2. General method for click reactions.

Compounds **6**, **7** and **8** **10** were obtained in low yields (47, 24 and 14, respectively), and compounds **9**, **10**, **11** and **12** in good yields (74, 64, 71 and 74%).

All the final compounds showed the NMR spectra consistent with the proposed structure, namely the signal for the proton of the triazole ring (a singlet 8.13-8.59 ppm).

Compounds **13** and **14** were prepared using as starting material the acetylenic derivative of glucose and but-3-yn-1-ol and propargyl alcohol, respectively (scheme 3). These compounds were isolated in 60-69% yields and were fully characterized. The NMR confirms their structures, it can be observed besides the typical glucosyl moiety signals the protons for the alkynyl function [2.48 (1H, t, *J* 2.4 Hz, H-1; 4.37 (2H, d, *J* 2.1 Hz, H-3)] for **14**.



Scheme 3. Synthesis of acetylenic derivatives of D-Glucose.

Compound **15** was synthesised, under the conditions of click reaction, using glycosylazide and compound **13** as the acetylenic component in 80% yield. The NMR showed the triazole proton at 8.09 ppm, along with the signals expected for the two glucosyl moieties.

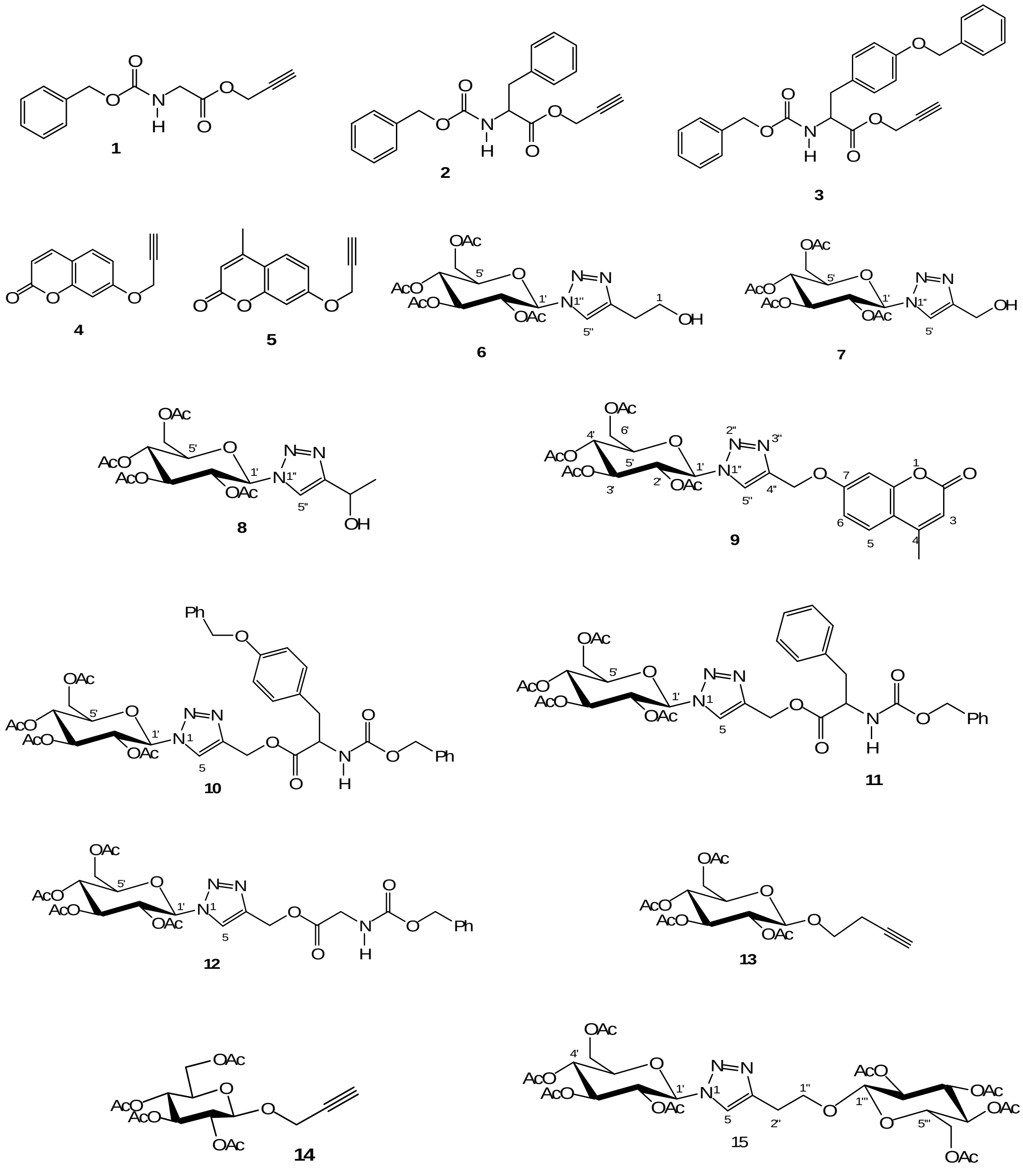


Figure 1. Structures and numbering of the compounds prepared.

Conclusions

Glyconjugates containing the 1,2,3-triazole unit were obtained by an azide-alkyne 1,3-dipolar cycloaddition, catalysed by Cu(I). The azide component, glycosylazide, was obtained *in situ* from α-acetobromoglucose and the alkyne components were prepared by reaction of propargyl bromide with *N*-protected glycine, tyrosine and phenylalanine, 7-hydroxycoumarin and 7-hydroxy-4-methylcoumarin with high yields. The final glyconjugates were isolated with a wide range of yields, varying from low, 14% to as high as 80%.

Experimental

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 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; ap states for apparent and Cq for quaternary carbon. 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 (ESI-TOF) 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 60 F254. Column chromatography was performed on silica gel (70-230 or 230-400 mesh). Light petroleum refers to the fraction boiling in the range 40-60ºC.

General method for the preparation of alkynyl esters- method A

To a solution of appropriated substrate in DMSO (5 mL) anhydrous K_2CO_3 (1.01 equiv.) and propargyl bromide (1 equiv.) were added and the reaction mixture was stirred at room temperature for 4 hours. Water was added, and the mixture extracted with ethyl acetate and the organic extracts were combined, dried ($MgSO_4$) and evaporated to dryness.

General method for the cycloaddition reaction by click chemistry-method B

To a solution of α-acetobromoglucose in dry DMSO dry NaN_3 (1.2 equiv.) was added and the mixture stirred at room temperature for 20 mins, forming the glycosylazide *in situ*. The acetylenic substrate (1.5 equiv. for the but-3-yn-1-ol, but-3-yn-2-ol and propargyl alcohol; 1.05 equiv. for the others), sodium L-ascorbate (1M aqueous solution, 2.5 mL/mmol azide) and $CuSO_4.5H_2O$ (1M aqueous solution, 2.5 mL/mmol azide) were then added to the reaction mixture, that which was stirred at room temperature for the time indicated. After filtration water was added to the filtrate, and the mixture extracted with ethyl acetate and the organic extracts were combined, dried ($MgSO_4$) and evaporated to dryness.

Synthesis of Z-Gly-OCH$_2$C≡CH (1)

The general procedure A, starting from Z-GlyOH, gave the ester **1** as a greenish solid (89%), m.p. 84.2-85.6ºC. ν_{max}(Nujol) 1732 and 1749 (C=O), 2125 (C≡C), 2854 and 2924 (CH), 3158 (NH), 3243 (≡CH) cm^{-1}.

^{1}H (300 MHz, DMSO-d$_6$) δ : 3.58 (1H, t, *J* 2.4 Hz, ≡CH); 3.81 (2H, d, *J* 6.0 Hz, CH_2N); 4.73 (2H, t, *J* 2.4 Hz, CH_2C≡); 5.04 (2H, s, OCH_2Ar); 7.30-7.37 (5H, m, Ar); 7.73 (1H, t, *J* 6.3 Hz, NH). ^{13}C (75.4 MHz, DMSO-d$_6$) δ: 42.05 (CH_2N); 52.17 (CH_2C≡); 65.62 (CH_2Ar); 77.98 (C≡); 78.19 (≡CH); 127.73, 127.88, 128.39 (5 x CHAr); 136.91 (CqAr); 156.52 (CONH); 166.91 (C=O). Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63,15; H, 5,30; N,5.67. Found: C, 62,78; H, 5.36; N, 5.56.

Synthesis of Z-Phe-OCH$_2$C≡CH (2)

Following the general method A, and starting from Z-PheOH, compound **2** was isolated as a pure brown solid (88%), m.p. 64.2-65.4ºC.

^{1}H (300 MHz, DMSO-d$_6$) δ: 2.87 (1H, dd, *J* 13.8 and 10.2 Hz, Ha-βCH_2); 3.04 (1H, dd, *J* 14.1 and 5.1 Hz, Hb-βCH_2); 3.59 (1H, t, *J* 2.4 Hz, ≡CH); 4.25-4.33 (1H, m, α-CH); 4.73 (2H, t, *J* 2.4 Hz, CH_2C≡); 4.97 (2H, s, OCH_2Ar); 7.23-7.34 (10H, m, 2x Ar); 7.87 (1H, d, *J* 8.4 Hz, NH).

Synthesis of Z-Tyr(OBn)-OCH$_2$C≡CH (3)

Following the general method A, and starting from Z-Tyr(OBn)OH, compound **3** was isolated as a pure brown solid (68%), m.p. 67.3-68.4ºC. Recrystallization from a mixture of ethyl acetate, ethyl ether and light petroleum yielded a white solid.

^{1}H (300 MHz, DMSO-d$_6$) δ: 2.81 (1H, dd, *J* 13.8 and 9.9 Hz, Ha-βCH_2 -Tyr); 2.98 (1H, dd, *J* 13.8 and 4.8 Hz, Hb-βCH_2 -Tyr); 3.58 (1H, t, *J* 2.4 Hz, ≡CH); 4.54 (1H, m, α-CH); 4.73 (2H, t, *J* 2.4 Hz, CH_2C≡); 4.98 (2H, s, OCH_2Ar(Z) or (Bn)); 5.05 (2H, s, OCH_2Ar(Z) or (Bn)); 6.91 (2H, d, *J* 8.4 Hz, H*o*-Tyr); 7.16 (2H, d, *J* 8.7 Hz, H*m*-Tyr); 7.32-7.42 (10H, m, 2 x Ar); 7.84 (1H, d, *J* 7.8 Hz, NH). ^{13}C (75.4 MHz, DMSO-d$_6$) δ: 35.47 (CH_2-Tyr); 52.37 (CH_2C≡); 55.67 (α-CH) 65.41 (CH_2Z or Bn)); 69.14 (CH_2Z or Bn)); 78.20 (C≡); 78.50 (≡CH); 114.53 (2x C*o*-Tyr); 127.53 (Ar), 127.66 (Ar), 127.76 (Ar), 127.79 (Ar), 128.32 (Ar), 128.42 (Ar), 129.25 (Cq-Tyr), 130.20 (CH*m*-Tyr);136.88 ((Cq-Z (or Bz));

137.16 (Cq-Z (or Bn)), 155.95(Cq*p*-Tyr); 157.12 (C=O Z), 171.22 (C=O Tyr). Anal. Calcd for $C_{27}H_{25}NO_5$: C, 73.12; H, 5.68; N, 3.16. Found: C, 72.65; H, 5.69; N, 3.34.

7-propargyloxycoumarin (4)

The titled compound was prepared by the general method A, starting from the 7-hydroxycoumarin, and was isolated as a pure brownish solid, 99%, m.p. 118.1-119.2ºC. ν_{max}(Nujol) 1735 (C=O), 2133 (C≡C), 2854 and 2923 (CH), 3320 (≡CH) cm^{-1}. ^{1}H (300 MHz, DMSO-d_6) δ: 3.64 (1H, br s, ≡CH); 4.92 (2H, d, *J* 1.8 Hz, CH_2C≡); 6.32 (1H, d, *J* 9.6 Hz, H-3); 6.97 (1H, d, *J* 2.1 Hz, H-8); 7.00 (1H, dd, *J* 8.7 and 2.1 Hz, H-6); 7.65 (1H, d, *J* 8.7 Hz, H-5); 7.99 (1H, d, *J* 9.8 Hz, H-4). Anal. Calcd for $C_{12}H_8O_3$: C, 72.00; H, 4.06. Found: C, 72.13; H, 4.06. m/z (ESI) 201.17 (M+1, 100%).

4-Methyl-7-propargyloxycoumarin (5)

General method A, starting from 7-hydroxy-4-methylcoumarin, yielded compound **5** as a pure white solid (99%), m.p. 133-2-134.6ºC. ν_{max}(Nujol) 1604 (C=C Ar), 1700 (C=O), 2854 and 2924 (CH) cm^{-1}.

^{1}H (400 MHz, DMSO-d_6) δ: 2.41 (3H, d, *J* 1.2 Hz, CH_3); 2.58 (1H, t, *J* 2.4 Hz, ≡CH); 4.77 (2H, d, *J* 2.4 Hz, CH_2C≡); 6.17 (1H, dd, *J* 2.4 and 1.2 Hz, H-8); 6.95 (1H, br s, H-3); 6.94 (1H, dd, *J* 9.2 and 2.4 Hz, H-6); 7.53 (1H, dd, *J* 8.0 and 1.2 Hz, H-5). Anal. Calcd for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 72.70; H, 4.73. m/z (ESI) 216.08 (M+1, 100%).

2- [1’’-(2’,3’,4’,6’-tetra-*O*-acetyl-β-D-glucopyranosyl)-(1*H*-1’’,2’’,3’’-triazol-4’’-yl)]ethanol (6)

Following the general method B and using but-3-yn-1-ol as the acetylenic substrate and a reaction time of 60 min. Compound **6** was obtained as a greenish solid (47%) after recrystallization from a mixture of dichloromethane-ethyl acetate-light petroleum, m.p. 162.6-163.4ºC. $[\alpha]_D^{25.5}$ -14.4 (0.02, $CHCl_3$). ν_{max}(Nujol) 1750 (C=O), 2133 (C≡C), 2854 and 2924 (CH), 3390 (OH) cm^{-1}.

^{1}H (300 MHz, DMSO-d_6) δ: 1.78 (3H, s, CH_3CO-2’); 1.95 (3H, s, CH_3CO-3’); 1.99 (3H, s, CH_3CO-6’); 2.02 (3H, s, CH_3CO-4’); 2.75 (2H, t, *J* 6.6 Hz, $\underline{CH_2}CH_2OH$); 3.60 (2H, ap q, *J* 6.3 Hz, $CH_2\underline{CH_2}OH$); 4.04 (1H, dd, *J* 12.6 and 2.1 Hz, Ha-6’); 4.12 (1H, dd, *J* 12.3 and 5.1 Hz, Hb-6’); 4.34 (1H, ddd, *J* 9.6, 5.1 and 2.1 Hz, H-5’); 4.71 (1H, t, *J* 5.4 Hz, OH); 5.15 (1H, t, *J* 9.6 Hz, H-4’); 5.53 (1H, t, *J* 9.3 Hz, H-3’); 5.61 (1H, ap t, *J* 9.6/8.7 Hz, H-2’); 6.28 (1H, d, *J* 8.7 Hz, H-1’); 8.13 (1H, s, H-5´´). ^{13}C (75.4 MHz, DMSO-d_6) δ: 19.84 (CH_3-2’); 20.18 (CH_3-3’); 20.31 (CH_3-6’); 20.44 (CH_3-4’); 28.92 ($\underline{CH_2}CH_2OH$); 60.05 ($\underline{CH_2}OH$); 61.76 (C-6’); 67.49 (C-4’); 70.02 (C-2’); 72.15 (C-3’); 73.13 (C-5’);

83.63 (C-1'); 121.64 (C-5''); 144.88 (C-4''); 168.41 (CO-2'); 169.30 (CO-4'); 169.50 (CO-3'); 169.98 (CO-6´). m/z (ESI) 466.42 (M+Na, 100%).

1- [1''-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyl)-(1*H*-1'',2'',3''-triazol-4''-yl)]methanol (7)

Prepared as compound **6** with propargyl alcohol as the acetylenic substrate. An oil was obtained which after recrystallization from a mixture of dichloromethane-ethyl acetate-light petroleum yielded a white solid (24%), m.p. 157.0-157.8ºC [Lit.[4] oil, 85%]. $[\alpha]_D^{25.5}$ -20.4 (0.02, $CHCl_3$). ν_{max}(Nujol) 1720 (C=O), 2854 and 2924 (CH), 3520 (OH) cm^{-1}.

^{1}H (300 MHz, DMSO-d_6) δ: 1.79 (3H, s, CH_3CO-2'); 1.95, 1.99, 2.02 (9H, 3s, CH_3CO-3', CH_3CO-4', CH_3CO-6'); 4.05 (1H, dd, *J* 12.3 and 2.4 Hz, Ha-6'); 4.12 (1H, dd, *J* 12.6 and 5.4 Hz, Hb-6'); 4.35 (1H, ddd, *J* 9.9, 5.1 and 2.4 Hz, H-5'); 4.50 (2H, d, *J* 5.7 Hz, $\underline{CH_2}$OH); 5.17 (1H, t, *J* 9.7 Hz, H-4'); 5.26 (1H, t, *J* 5.7 Hz, OH); 5.54 (1H, t, *J* 9.4 Hz, H-3'); 5.66 (1H, t, *J* 9.3 Hz, H-2'); 6.31 (1H, d, *J* 9.0 Hz, H-1'); 8.25 (1H, s, H-5''). m/z (ESI) 452.33 (M+Na, 100%). Anal. Calcd for $C_{17}H_{23}N_3O_{10}$: C, 47.55; H, 5.40; N, 9.79. Found: C, 47.65; H, 5.38; N, 9.53.

1-[1''-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyl)-(1*H*-1'',2'',3''-triazol-4''-yl)]ethanol (8)

Prepared as compound **6** with *rac*-but-3-yn-2-ol as the acetylenic substrate. An oil was obtained which after recrystallization from a mixture of dichloromethane-ethyl acetate-light petroleum yielded a white solid (14%), as a mixture of the two diastereoisomers (1.5:1), m.p. 177.9-178.6ºC. $[\alpha]_D^{27}$-20.9 (0.02, $CHCl_3$). ν_{max}(Nujol) 1751 (C=O), 2854, 2925 and 2952 (CH), 3330 (≡CH) cm^{-1}.

^{1}H (300 MHz, DMSO-d_6) δ: 1.36 (1.8H, d, *J* 6.6 Hz, CH_3); 1.38 (1.2H, d, *J* 6.2 Hz, CH_3); 1.78 (1.8H, s, CH_3CO-2'); 1.79 (1.2H, s, CH_3CO-2'); 1.96, 1.99, 2.02 (9H, 3s, CH_3CO-3', CH_3CO-4', CH_3CO-6'); 4.05 (1H, dd, *J* 12.3 and 2.4 Hz, Ha-6'); 4.12 (1H, dd, *J* 12.3 and 5.4 Hz, Hb-6'); 4.34 (1H, ddd, *J* 12.6, 5.4 and 2.4 Hz, H-5'); 4.75-4.84 (1H, m, CH); 5.16 (1H, t, *J* 9.7 Hz, H-4'); 5.31 (0.6H, t, *J* 5.1 Hz, OH); 5.32 (0.4H, t, *J* 5.1 Hz, OH); 5.53 (1H, t, *J* 9.4 Hz, H-3'); 5.66 (1H, t, *J* 9.3 Hz, H-2'); 6.29 (0.6H, d, *J* 9.3 Hz, H-1'); 6.30 (0.4H, d, *J* 9.3 Hz, H-1'); 8.18 (0.6H, s, H-5'');); 8.20 (0.4H, s, H-5'').

7- {[1''-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1'',2'',3''-triazol-4-yl)]methoxy}-4-methylcoumarin (9)

Following method B, with the acetylenic substrate **5**, and stirring the reaction mixture for 60 min., a white solid was obtained after recristalization from dichloromethane-ethyl acetate-light petroleum (74%, m.p. 194.1-195.9ºC). $[\alpha]_D^{27}$ -22.0 (0.02, $CHCl_3$). ν_{max} (Nujol) 1721 and 1740 (C=O), 2854, 2923 (CH), 3096 (≡CH) cm^{-1}.

^{1}H (300 MHz, DMSO-d_6) δ: 1.75 (3H, s, CH_3CO-2'); 1.95, 1.99, 2.02 (9H, 3s, CH_3CO-3', CH_3CO-4', CH_3CO-6'); 2.39 (3H, d, *J* 0.9 Hz, CH_3); 4.06 (1H, dd, *J* 12.3 and 2.4 Hz, Ha-6'); 4.13 (1H, dd, *J* 12.6 and 5.4 Hz, Hb-6'); 4.37 (1H, ddd, *J* 9.9, 4.8 and 2.4 Hz, H-5'); 5.17 (1H, ap t, *J* 9.9/9.3 Hz, H-4'); 5.29 (2H, s, CH_2O); 5.55 (1H, ap t, *J* 9.3/9.4 Hz, H-3'); 5.67 (1H, t, *J* 9.3 Hz, H-2'); 6.21 (1H, d, *J* 0.9 Hz, H-3); 6.38 (1H, d, *J* 9.0 Hz, H-1'); 7.02 (1H, dd, *J* 8.7 and 2.4 Hz, H-6); 7.11 (1H, d, *J* 2.4 Hz, H-8); 7.68 (1H, d, *J* 9.0 Hz, H-5); 8.59 (1H, s, H-5''). ^{13}C (75.4MHz, DMSO-d_6) δ: 18.12 (CH_3-4''); 19.83 (CH_3-2'); 20.23 (CH_3-3'); 20.38 (CH_3-4'); 20.49 (CH_3-6'); 61.49 (CH_2O); 61.77 (C-6'); 67.49 (C-4'); 70.11 (C-2'); 72.11 (C-3'); 73.26 (C-5'); 83.87 (C-1'); 101.65 (C-8); 111.36 (C-3); 112.67 (C-6); 113.45 (C-4); 123.91 (C-5''); 126.50 (C-5); 142.81 (C-4); 153.38 (C-4a); 154.64 (C-2); 160.11 (C-8a); 160.86 (C-7); 168.46 (CH_3CO-2'); 169.37 (CH_3CO-4'); 169.56 (CH_3CO-3'); 170,02 (CH_3CO-6') ppm.

1-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl)methyl-O(OBn)TyrZ (10)

Prepared by method B, with the acetylenic substrate **3**, and stirring the reaction mixture for 90 min., a white solid was obtained after recrystallization from ethyl acetate-light petroleum (64%, m.p. 144.7-146.6ºC). ν_{max}(Nujol) 1690 and 1720 (C=O), 2855, 2925 (CH), 3241 (NH) cm^{-1}.

^{1}H (300MHz, DMSO-d_6) δ: 1.77 (3H, s, CH_3CO-2'); 1.95 (3H, s, CH_3CO-4'); 1.97 (3H, s, CH_3CO-6'); 2.02 (3H, s, CH_3CO-3'); 2.77 (1H, dd, *J* 13.8 and 10.5 Hz, βCH_a Tyr); 2.95 (1H, dd, *J* 13.8 and 4.8 Hz, βCH_b Tyr); 4.06 (1H, dd, *J* 12.3 and 2.4 Hz, Ha-6'); 4.14 (1H, dd, *J* 12.6 and 5.1 Hz, Hb-6'); 4.17-4.25 (1H, m, α-CH); 4.37 (1H, ddd, *J* 10.0, 5.1 and 2.4 Hz, H-5'); 4.96 (2H, s, CH_2-Z); 5.04 (2H, s, OCH_2Ph); 5.13-5.24 (3H, m, CH_2, and H-3'); 5.56 (1H, ap t, *J* 9.0/9.9 Hz, H-4'); 5.67 (1H, ap t, *J* 9.3/ 9.6 Hz, H-2'); 6.38 (1H, d, *J* 9.0 Hz, H-1'); 6.88 (2H, d, *J* 8.7 Hz, Tyr); 7.12 (2H, d, *J* 8.4 Hz, Tyr); 7.24-7.44 (10H, m, 2×C_6H_5); 7.81 (1H, d, *J* 8.1 Hz, NH); 8.45 (1H, s, H-5) ppm. ^{13}C (75.4MHz, DMSO-d_6) δ: 19.90 ($\underline{C}H_3$CO-2'); 20.26 ($\underline{C}H_3$CO-3'); 20.34 ($\underline{C}H_3$CO-4'; 20.40 ($\underline{C}H_3$CO-6'); 35.48 ($\underline{C}H_2$Phe); 55.79 (α-CH); 57.58 (CH_2-1); 61.76 (C-6'); 65.41 (Z-CH_2 ou CH_2Ph); 67.49 (C-3'); 69.12 (CH_2-Z ou CH_2Ph); 70.09 (C-2'); 72.13 (C-4'); 73.31 (C-5'); 83.86 (C-1'); 114.51 (2×C Tyr); 123.96 (C-5); 127.57 (Ar); 127.67 (Ar); 127.79 (Ar); 128.33 (Ar); 128.43 (Ar); 129.37 (CH_2-$\underline{C}$Ar); 130.15 (2×C Tyr); 136.83 and 137.25 (Cq Z and CH_2Ph); 142.42 (C-4''); 155.99 (C=O (Z)); 157.08 ($\underline{C}$Ar-OCH_2Ph); 168.51 (C=O (2')); 169.39 (C=O (3')); 169.59 (C=O (4')); 170.04 (C=O (6')); 171.61 (C=O) ppm. Anal. Calcd for $C_{41}H_{44}N_4O_{14}$.1½H_2O: C, 58.36; H, 5.61; N, 6.64. Found: C, 58.42; H, 6.26; N, 6.29.

1-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl)methyl-OPheZ (11)

Following method B, with the acetylenic substrate **2**, and stirring the reaction mixture for 60 min., a greenish solid was obtained after recrystallization from ethyl acetate and light petroleum (71%, m.p. 110.1-114.4ºC). $[\alpha]_D^{27}$ -8.0 (0.02, $CHCl_3$).

^{1}H (300MHz, DMSO-d_6) δ: 1.77 (3H, s, CH_3CO-2'); 1.95 (3H, s, CH_3CO-4'); 1.97 (3H, s, CH_3CO-6'); 2.02 (3H, s, CH_3CO-3'); 2.85 (1H, dd, *J* 13.8 and 10.5 Hz, βCHPhe); 3.01 (1H, dd, *J* 13.8 and 4.8 Hz, βCHPhe); 4.07 (1H, d, *J* 12.0 Hz, Ha-6'); 4.14 (1H, dd, *J* 12.6 and 5.1 Hz, Hb-6'); 4.23-4.31 (1H, m, α-CH); 4.37 (1H, ddd, *J* 10.0, 5.1 and 2.1 Hz, H-5'); 4.96 (2H, s, Z-CH_2); 5.14-5.24 (3H, m, CH_2 and H-3'); 5.56 (1H, ap t, *J* 9.6/9.3 Hz, H-4'); 5.66 (1H, ap t, *J* 9.0/9.3 Hz, H-2'); 6.37 (1H, d, *J* 8.7 Hz, H-1'); 7.16-7.33 (10H, m, 2×C_6H_5); 7,86 (1H, d, *J* 8.4 Hz, NH); 8.42 (1H, s, H-5) ppm. ^{13}C (75.4MHz, DMSO-d_6) δ: 19.88 (CH_3CO-2'); 20.24 (CH_3CO-3'); 20.38 (CH_3CO-4'); 20.48 (CH_3CO-6'); 36.31 (CH_2Phe); 55.55 (α-CHPhe); 57.54 (CH_2-1); 61.77 (C-6'); 65.41 (Z-CH_2); 67.47 (C-3'); 70.08 (C-2'); 72.11 (C-4'); 73.28 (C-5'); 83.84 (C-1'); 123.92 (C-5); 126.51 (Ar); 127.55 (Ar); 127.78 (Ar), 128,21 (Ar), 128.33 (Ar), 129,07 (Ar), 136.83 e 137.25 (Cq Z and CH_2Ph), 142.37 (C-4''); 155.96 (C=O (Z)); 168.50 (C=O (2')); 169.38 (C=O (3')); 169.57 (C=O (4')); 170.03 (C=O (6')); 171.53 (C=O (Phe)) ppm.

1-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl)methyl-OGlyZ (12)

Prepared by method B, with the acetylenic substrate **1**, and stirring the reaction mixture for 60 min., an off-white solid was obtained after recrystallization from ethyl acetate-light petroleum (74%, m.p. 145.9-147.4ºC). ν_{max}(Nujol) 1714 and 1720 (C=O), 2855, 2925 (CH), 3242 (NH) cm^{-1}.

^{1}H (300MHz, DMSO-d_6) δ: 1.79 (3H, s, CH_3CO-2'); 1.96 (3H, s, CH_3CO-4'); 1.99 (3H, s, CH_3CO-6'); 2.02 (3H, s, CH_3CO-3'); 3.79 (2H, d, *J* 6.3 Hz, CH_2Gly); 4.05 (1H, dd, *J* 12.3 and 2.4 Hz, Ha-6'); 4.13 (1H, dd, *J* 12.6 and 5.4 Hz, Hb-6'); 4.60 (1H, ddd, *J* 10.2, 5.4 and 2.4 Hz, H-5'); 5.03 (2H, s, Z-CH_2); 5.16 (1H, ap t, *J* 9.9/9.6 Hz, H-4'); 5.18 (2H, s, CH_2O); 5.55 (1H, ap t, *J* 9.0/9.6 Hz, H-3'); 5.64 (1H, ap t, *J* 9.6/9.0 Hz, H-4'); 6.36 (1H, d, *J* 9.3 Hz, H-1'); 7.27-7.39 (5H, m, C_6H_5); 7.72 (1H, t, *J* 6.0 Hz, NH); 8.48 (1H, s, H-5) ppm. ^{13}C (75.4MHz, DMSO-d_6) δ: 19.92 (CH_3CO-2'); 20.27 (CH_3CO-3'); 20.40 (CH_3CO-4'); 20.53 (CH_3CO-6'); 42.14 (CH_2Gly); 57.36 (CH_2-O); 61.80 (C-6'); 65.62 (Z-CH_2); 67.51 (C-3'); 70.12 (C-2'); 72.17 (C-4'); 73.33 (C-5'); 83.87 (C-1'); 124.08 (C-5); 127.75 (2xC-Ar); 127.89 (Ar); 128.41 (Ar); 136.85(Cq-Z); 137.16 (Cq-Ph); 142,36 (C-4''); 152.54 (C=O (Z)); 168.56 (C=O (2')); 169.41 (C=O (3')); 169.62 (C=O (4')); 169.96

(C=O (6’)); 170.08 (C=O (Ph)) ppm. Anal. Calcd for $C_{27}H_{32}N_4O_{13}$: C, 52.26; H, 5.20; N, 9.03. Found: C, 52.10; H, 5.21; N, 8.64.

4-(2’,3’,4’,6’-tetra-*O*-acetyl-β-D-glucopyranosyloxy)but-1-yne (13)

But-3-yn-1-ol (0.45 mL, 6.0 mmol) and $BF_3(Et)_2O$ (0.95 mL, 7.5 mmol) were added to a solution of commercial D-glucose β-pentaacetate (1.95 g, 5.0 mmol) in dichloromethane (40 mL). The mixture was stirred at room temperature for 5 hours and for further 30 mins after addition of K_2CO_3 (0.152 g, 1.1. mmol). The solid was filtered off and the filtrate washed with water (2x30 mL) and the aqueous phase extracted with dichloromethane (2x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to a solid product which was crystallized from dichloromethane-light petroleum yielding compound **13** (69%, m.p. 134.2-135.4ºC). ν_{max}(Nujol) 1171 (C-O-C sym.), 1223 and 1259 (C-O-C asym.), 1737 (C=O), 2120 (C≡C), 2855 and 2925 (CH) cm^{-1}.

^1H (400MHz, $CDCl_3$) δ: 1.97 (1H, t, *J* 2.7 Hz, H-1); 2.00 (3H, s, CH_3CO-3’); 2.02 (3H, s, CH_3CO-4’); 2.05 (3H, s, CH_3CO-2’); 2.08 (3H, s, CH_3CO-6’); 2.47 (2H, dt, *J* 2.7 and 7.0 Hz, H-3); 3.63-3.72 (2H, m, H-5’ and H-4); 3.94 (1H, dt, *J* 10.0 and 6.8 Hz, H-4); 4.13 (1H, dd, *J* 12.4 and 2.4 Hz, Ha-6’); 4.26 (1H, dd, *J* 12.4 and 4.8 Hz, Hb-6’); 4.57 (1H, d, *J* 8.1 Hz, H-1’); 4.99 (1H, dd, *J* 9.6 and 7.6 Hz, H-2’); 5.08 (1H, t, *J* 9.6 Hz, H-4’); 5.20 (1H, ap t, *J* 9.2/9.6 Hz, H-3’) ppm. ^{13}C (100.62MHz, $CDCl_3$) δ: 19.80 (C-3); 20.54 (CH_3CO-3’); 20.56 (CH_3CO-4’); 20.64 (CH_3CO-2’); 20.68 (CH_3CO-6’); 61.86 (C-6’); 67.88 (C-4); 68.34 (C-4’); 69.49 (C-1); 71.08 (C-2’); 71.81 (C-5’); 72.69 (C-3’); 80.52 (C-2); 100.78 (C-1’); 169.30 (C=O (2’)); 169.35 (C=O (4’)); 170.23 (C=O (3’)); 170.62 (C=O (6’)) ppm. Anal. Calcd for $C_{18}H_{24}O_{10}$: C, 53.87; H, 6.07. Found: C, 54.00; H, 6.04.

3-(2’,3’,4’,6’-tetra-*O*-acetyl-β-D-glucopyranosyloxy)prop-1-yne (14)

This compound was prepared as **13**, with propargyl alcohol, and isolated as a white solid (60.2%, m.p. 127.7-128.5ºC). ν_{max} (Nujol) 1159 and 1125 (C-O-C sym.), 1212 and 1236 (C-O-C asym.), 1757 and 1734 (C=O), 2119 (C≡C), 2855 and 2924 (CH) cm^{-1}.

^1H (300MHz, $CDCl_3$) δ: 2.01 (3H, s, CH_3CO-2’); 2.03 (3H, s, CH_3CO-4’);. 2.06 (3H, s, CH_3CO-3’); 2.09 (3H, s, CH_3CO-6’); 2.48 (1H, t, *J* 2.4 Hz, H-1); 3.73 (1H, ddd, *J* 10.0,4.5 and 2.4 Hz, H-5’); 4.14 (1H, dd, *J* 12.3 and 2.4 Hz, Ha-6’); 4.28 (1H, dd, *J* 12.3 and 4.5 Hz, Hb-6’); 4.37 (2H, d, *J* 2.1 Hz, H-3); 4.78 (1H, d, *J* 7.8 Hz, H-1’); 5.01 (1H, dd, *J* 9.3 and 7.8 Hz, H-2’); 5.10 (1H, t, *J* 9.6 Hz, H-4’); 5.24 (1H, ap t, *J* 9.9/9.3 Hz, H-3’) ppm. ^{13}C (100.62MHz, $CDCl_3$) δ: 20.56, 20.58, 20.66 and 20.70 (4xCH_3CO); 55.90 (C-3); 61.70 (C-6’); 68.22 (C-4’); 70.89 (C-2’); 71.87 (C-5’); 72.70 (C-3’); 75.47 (C-1); 78.05 (C-2); 98.06 (C-1’); 169.38 (C=O (4’)); 169.43 (C=O (2’)); 170.24 (C=O (3’));

170.25 (C=O (6')) ppm. Anal. Calcd for $C_{17}H_{22}O_{10}$: C, 53.02; H, 5.72. Found: C, 52.85; H, 5.74.

1-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyl)-4-[1''-(2''',3''',4''',6'''-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-ethyl]-1*H*-1,2,3-triazole (15)

Following method B, with the acetylenic substrate **13**, and stirring the reaction mixture for 2 h 45 min., a greenish solid was obtained after recrystallization from ethyl acetate-light petroleum (80%, m.p. 106.4-108.6ºC). ν_{max}(Nujol) 1122 and 1041 (C-O-C sym.), 1225 (C-O-C asym.), 1747 (C=O), 2855 and 2925 (CH) cm^{-1}.

^{1}H (300MHz, $CDCl_3$) δ: 1.78, 1.89, 1.91, 1.95, 1.96, 1.98, 2.00, 2.01 (24H, 8 s, 8x CH_3CO); 2.86 (2H, ap t, *J* 6.9/6.3 Hz, H-2''); 3.70-3.78 (1H, m, H.5'''); 3-92-4.18 (5H, m, H-6' and H-6''); 4.35 (1H, ddd, *J* 9.9, 5.4 and 2.4 Hz, H-5'); 4.69-4.91 (3H, m, H-2''', H-4''', H-1'''); 5.13 (1H, ap t, *J* 9.3/9.9 Hz, H-4'); 5.19-5.26 (1H, m, H-3'''); 5.50-5.61 (2Hm, H-2' and H-3'); 6.28 (1H, d, *J* 9.0 Hz, H-1') ppm; 8.09 (1H, s, H-5). Anal. Calcd for $C_{32}H_{43}N_3O_{19}.0.35CuSO_4$: C, 46.33; H, 5.24; N, 5.07. Found: C, 46.36; H, 5.15; N, 5.07.

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