Synthesis A. Shamim et al. Paper

Synthesis of Glycosyl Azides and Their Applications Using CuAAC Click Chemistry to Generate Bis- and Tris(triazolyl)glycosyl Derivatives

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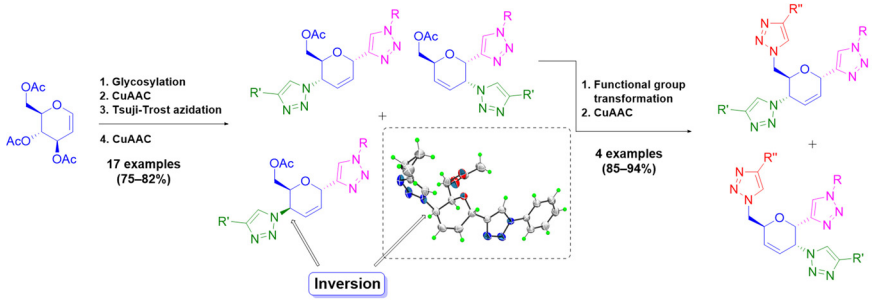

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Abstract 2,3-Unsaturated *C*-(triazolyl)glycosyl acetates have been synthesized from 3,4,6-tri-*O*-acetyl-D-glucal using *C*-glycosylation and click chemistry and were then used in a palladium-catalyzed Tsuji–Trost type allylic azidation reaction to afford the corresponding regioisomeric glucal-azide derivatives. Copper-catalyzed azide-alkyne cycloaddition (CuAAC) reactions with these glucal-based allylic azides using CuI as the catalyst, led to the corresponding glucal-based bis(triazole) derivatives. Performing further functional group modification and another click (CuAAC) reaction with each of these bis(triazolyl) glycosyl derivatives afforded tris(triazolyl)glycosyl derivatives. Two libraries of regioisomeric bis(triazole) derivatives and a small library of regioisomeric tris(triazole) derivatives of glucal were then synthesized using different alkynes.

Key words D-glucal, azide, click chemistry, bis(triazole), tris(triazole)

Glucal-derived triazoles are important in carbohydrate-based biochemistry and organic synthesis. They have been found to have antibacterial,[1] anticancer[2] and antidiabetic[3] properties. A few examples of biologically important glucal derived triazoles include an α-glucosidase inhibitor (compound **A**),[4a] an antibacterial (compound **B**),[4b] and two anti-inflammatory compounds (compounds **C** and **D**)[4c,d] (Figure 1). Due to the biological importance of glucal-derived triazoles, many research groups have designed syntheses of glucal-derived triazoles using different glucal precursors and applying the azide-alkyne cyclization reaction[5] (click reaction), as well as other syntheses.[6]

The remarkable property of the copper-catalyzed azide-alkyne cycloaddition (CuAAC), the main 'click' reaction to link a wide variety of potential compounds via formation of a triazole ring, is well known and has been investigated by many research groups.[7] This process of linking two species via CuAAC reaction has been used extensively for the synthesis of important drugs, bioactive compounds, and various other industrially and photophysically important compounds.[8] Being a type of click chemistry reaction, the CuAAC reaction is fast, efficient, mild, and an easy process to connect an azide-containing moiety with a terminal alkyne in the presence of a copper catalyst to generate a 1,4-substituted 1,2,3-triazole compound. The bioisosteric potential of the triazole ring makes it a key moiety for potential exploration as a drug, as a linker of a drug with another biocompatible moiety, or to enhance the effect of a drug.[9] The applications of triazole ring compounds in polymer chemistry and nanochemistry are also numerous and are continuing to gain importance.[10]

Based on these potential applications and the inspiring properties of triazoles and especially glycosyl triazole derivatives, we report herein various methods to synthesize libraries of bis- and tris(triazolyl)glycosyl derivatives starting from 3,4,6-tri-*O*-acetyl-D-glucal (**1**). We look forward to investigating and reporting the biological properties of these libraries of glycosyl triazoles in future work.

In connection with our recently reported work on the synthesis of glucal-based triazoles, 2-alkynyl D-glucal derivatives and other glycosyl derivatives,[11] here we first synthesized bis(triazole) derivatives of D-glucal starting from 3,4,6-tri-*O*-acetyl-D-glucal (**1**). This was followed by the synthesis of tris(triazolyl)glycoside derivatives using functional group modifications and the click (CuAAC) reaction. The synthesis of the glucal-based bis(triazole) derivatives involved a Ferrier rearrangement to obtain glucal alkynes **2**,

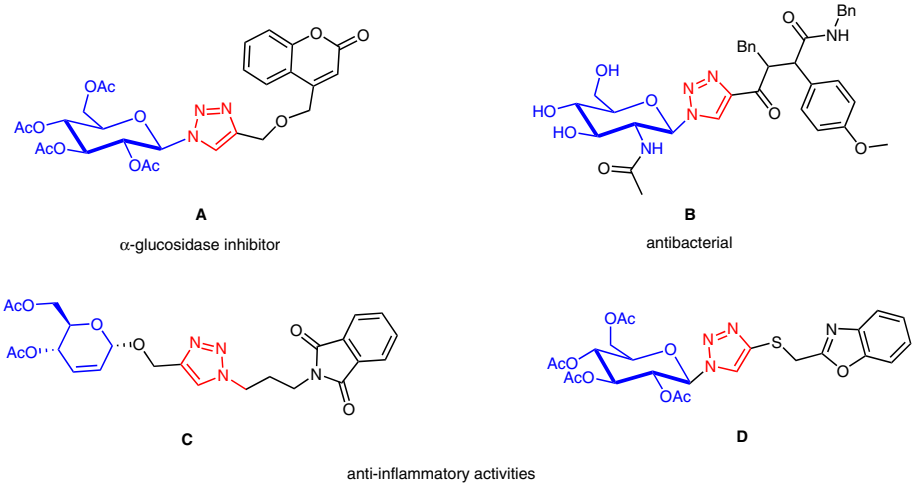
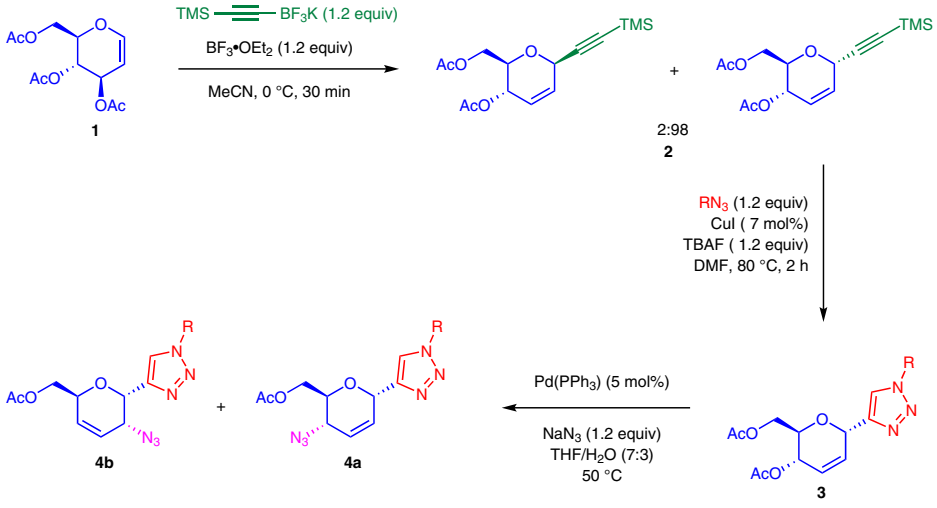


Figure 1 Selected biologically active glucal-based triazole compounds

and a click reaction to obtain the glycosyl-triazoles **3**, as previously reported.[12] These glycosyl triazoles **3**, bearing allylic acetate functionality, were then subjected to palladium-catalyzed Tsuji–Trost type allylic azidation to obtain regioisomeric glucal-based allylic azides **4a** and **4b** (Scheme 1).

Three *C*-(triazolyl)glycosyl derivatives **3a–c** were synthesized using the reaction conditions summarized in Table 1. To optimize the amount of catalyst (CuI), some experiments were performed using different amounts of CuI (Table 1, entries 1–3). It was observed that the use of 7 mol% of CuI resulted in higher yields, rather than less than 7 mol%, which resulted in lower yields; however, using higher concentrations of CuI did not increase in the yields (entry 3). Thus, 7 mol% of CuI was used in the rest of CuAAC reactions in this work.

Use of flash column chromatography to separate the two regioisomeric azides **4a** and **4b** was unsuccessful; furthermore, the use of gas chromatography to determine the regioisomeric ratio of the two regioisomeric azides **4a** and **4b** was also unsuccessful. Therefore, both of the regioisomeric azides were used in the next synthetic step, that is, the copper-catalyzed azide-alkyne cycloaddition reaction. The resultant pair of regioisomeric bis(triazolyl)glycosyl derivatives were, however, separable via flash column chromatography. Thus, a library of bis(triazolyl)glycosyl derivatives was synthesized; the products were purified using flash column chromatography and were analyzed using NMR, IR, and HRMS data (Table 2). A range of terminal alkynes including alkyl, cycloalkyl, and aryl alkynes were used with different substituted glycosyl azides in the pres-

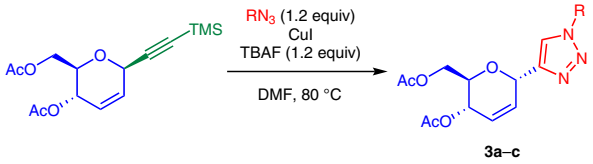


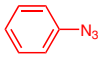
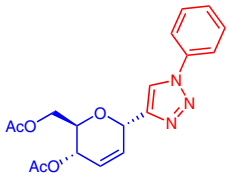
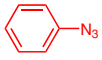
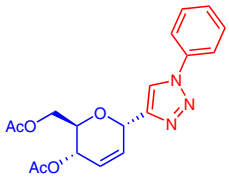
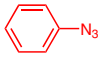
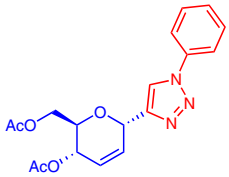
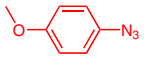
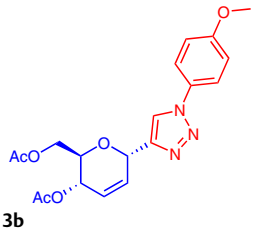
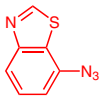
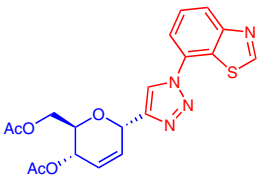
Scheme 1 Synthesis of glucal-based allylic azide regioisomers from 3,4,6-tri-*O*-acetyl-D-glucal

ence of CuI in DMF at 60 °C with the reaction time ranging from 2 to 4 hours to obtain a library of glycosyl bis(triazole) derivatives (Table 2).

The stereoselectivity of the palladium-catalyzed allylic substitution reaction has been discussed in the literature and it has been found to be influenced by the palladium catalyst used, the solvent system, substituents on the allylic system, the nature of the leaving group (LG), the nature and concentration of nucleophile (Nu), and temperature.[12] Under normal reaction conditions, the commonly observed

Table 1 Synthesis of *C*-Glycosyl Triazole Derivatives **3a–c** Using CuAAC Reaction

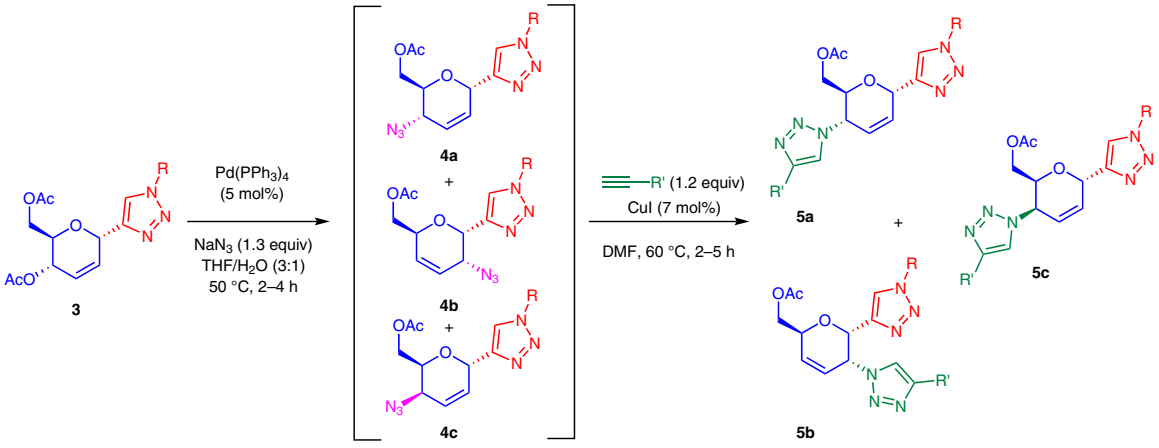


Entry	CuI (mol%)	Azide (R–N_3)	Product	Time (h)	Yield (%)[a]
1	5		 **3a**	3	90
2	7		 **3a**	2	95
3	10		 **3a**	2	95
4	7		 **3b**	2	91
5	7		 **3c**	3	89

[a] Isolated yields.

product is the allylic regioisomer that has the new nucleophile added to the same position from where the leaving group departed. In most cases in this work, we also observed retention of configuration at C-4 in the bis(triazolyl)glycosyl products (Table 2, entries 1–6). However, in one case (entry 8) where higher temperatures and larger amounts of sodium azide (2.5 equiv) were used, it was observed that the products also included a regioisomer with inversion of configuration at C-4, as confirmed by single-crystal X-ray diffraction (Figure 2). It is important to mention here that as we could not isolate the azide products, so our observations for the stereochemistry of the Tsuji–Trost azidation reaction are based on the bis(triazolyl) products.

Table 2 Synthesis of Bis(triazole) Glycosyl Derivatives via Click Reaction with Glucal Azides



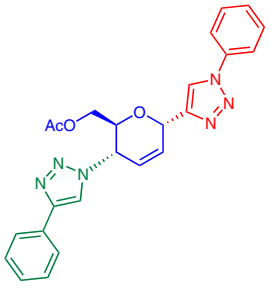
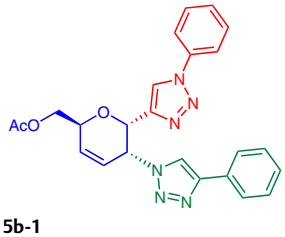
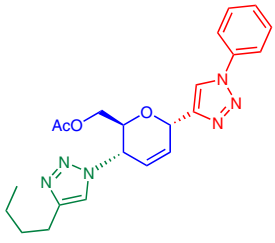
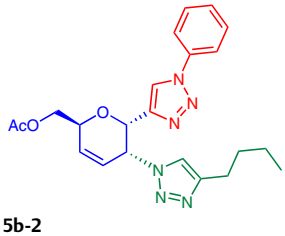
Entry	Glucal azide (R)	Alkyne	Product a:b:c	Yield (%)[a]
1			 **5a-1** 60:40  **5b-1**	79
2			 **5a-2** 60:40  **5b-2**	77

Table 2 (continued)

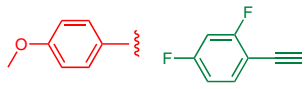
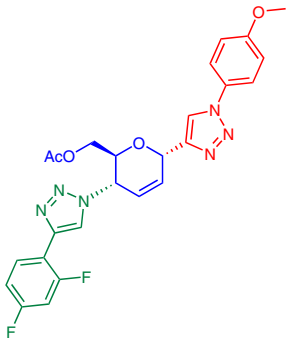
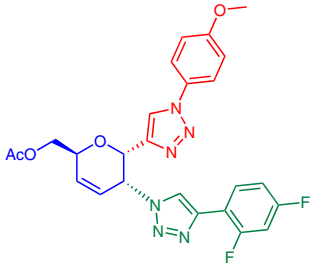
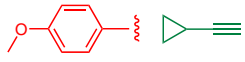
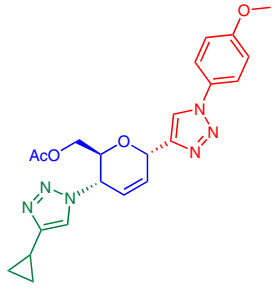
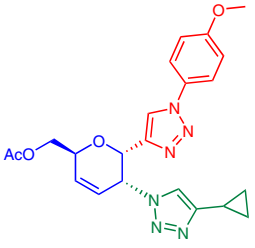
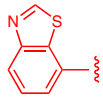
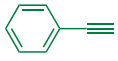
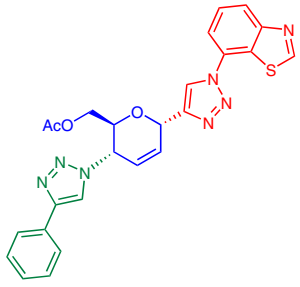
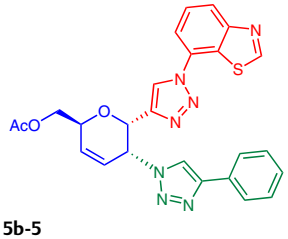
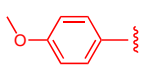
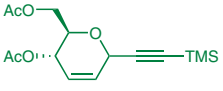
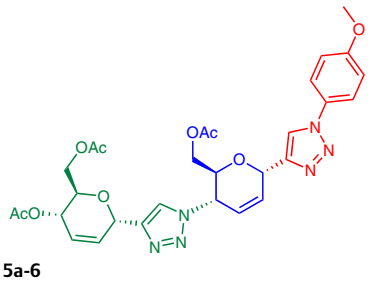
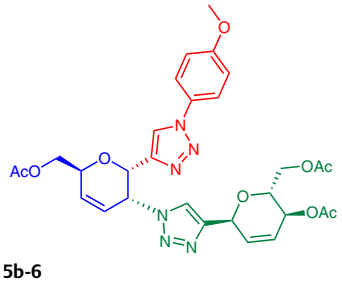
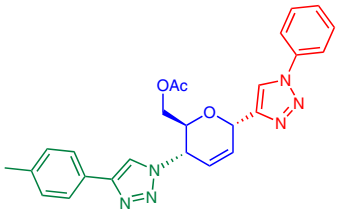
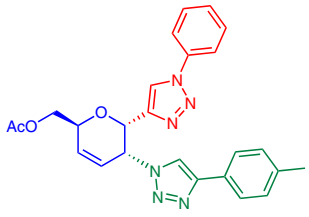
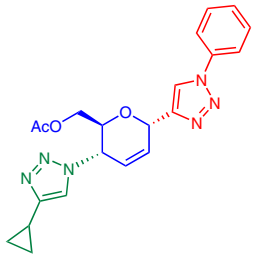
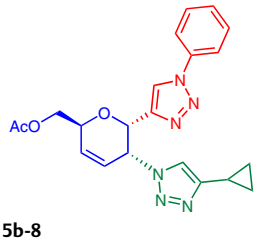
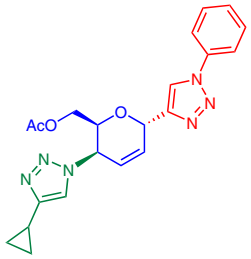
Entry	Glucal azide (R)	Alkyne	Product a:b:c	Yield (%)[a]
3			 **5a-3** 69:31	81
			 **5b-3**	
4			 **5a-4** 58:42	78
			 **5b-4**	
5			 **5a-5** 70:30	76
			 **5b-5**	
6[b]			 **5a-6** 68:32	75
			 **5b-6**	

Table 2 (continued)

Entry	Glucal azide (R)	Alkyne	Product a:b:c	Yield (%)[a]
7			 **5a-7** 61:39	 **5b-7**	82
8			 **5a-8** 24:42:34	 **5b-8**	 **5c-8**	80[c]

[a] Isolated combined yield (for the two steps) of the regioisomers.
[b] Tetrabutylammonium fluoride (TBAF, 1.3 equiv) was used in the cycloaddition step to remove the trimethylsilyl group.
[c] Reflux conditions (in the azidation step) and a larger amount (2 to 2.5 equiv) of NaN_3 were used.

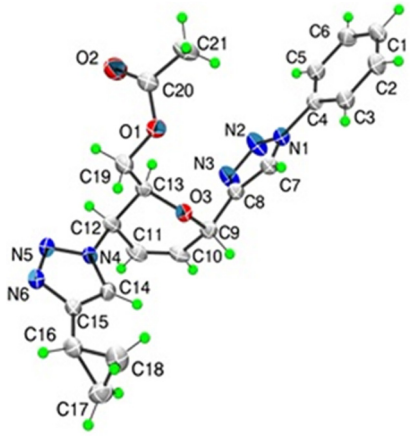
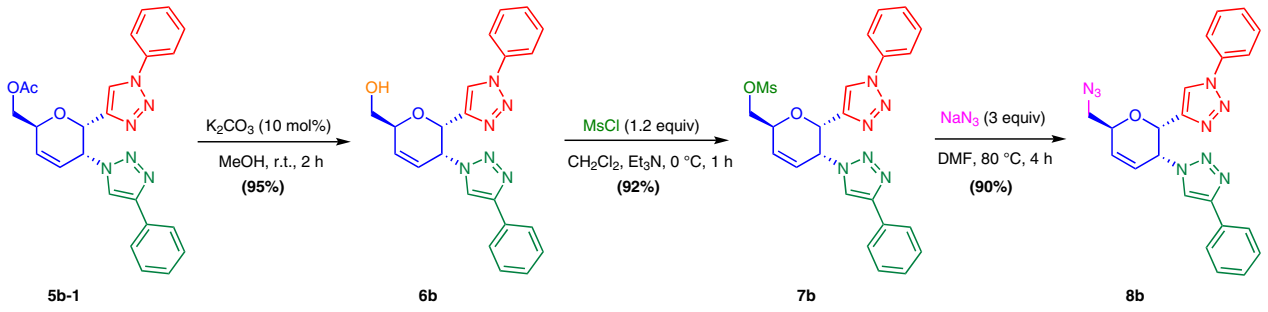


Figure 2 The crystal structure of compound **5c-8**

The compound **5c-8** (Table 2, entry 8) is an epimer of **5a-8** with the opposite (inversion of) configuration at C-4 of the glycosyl ring. The changed reaction conditions suppressed the formation of the epimer **5a-8**. To avoid this complication, the temperature was kept at 50 °C in the azidation reaction and 60 °C in the CuAAC reaction, comparatively lesser quantities of sodium azide (1.2 equiv) were used, and the reaction was quenched as soon as the starting material disappeared (TLC monitoring). On the other hand, this feature of the reactions could be used as an opportunity to make the epimers of such compounds by varying the temperature and/or concentration.

Based on the isolated yields of the bis(triazolyl)glycosyl products, the ratio of regioisomer **a** to **b** was roughly 3:2 and was in accordance with literature precedent.[13] As we were interested in both of the regioisomers of the bis(triazolyl)glycosyl compound, we did not explore other palladium catalysts or attempted to use ligands to improve the regioselectivity as reported by several groups.[14] The structure of each bis(triazolyl)glycoside was confirmed by the COSY NMR analysis of both or one of the regioisomers of each pair (SI) and with the XRD analysis of **5c-8**, and in some cases with the coupling constants.

The synthetic scope of these bis(triazolyl)glycosyl derivatives was explored using **5a-1** and **5b-1** as representative compounds to synthesize tris(triazolyl)glycosyl compounds **9**. This process consisted of functional group modification including base-catalyzed transesterification, mesylation, and nucleophilic azidation. In the first step, methoxide-catalyzed transesterification of the acetate group of **5a-1** and **5b-1** was used to synthesize the corresponding hydroxyl derivatives **6a** and **6b** respectively. Mesylation of the hydroxy group of each of the two products **6a** and **6b** was then performed, generating the corresponding mesylate de-



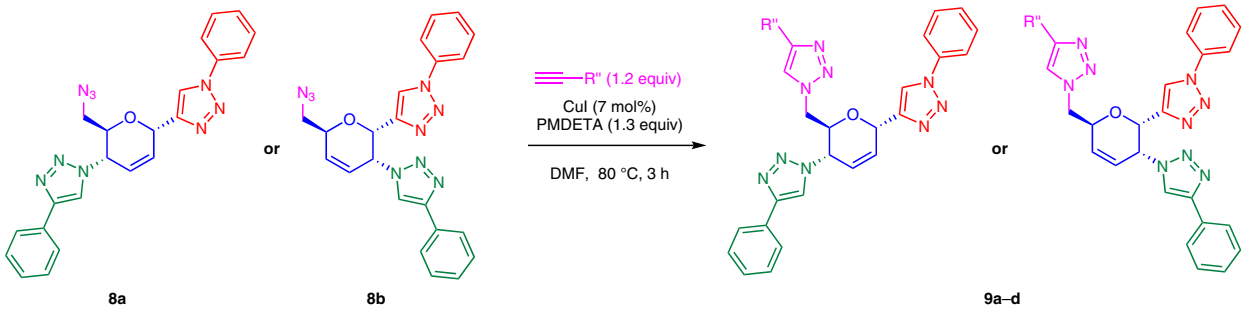
Note: The same steps were performed for compound **5a-1** to obtain the corresponding products **6a**, **7a** and **8a** respectively.

Scheme 2 Synthesis of glycosyl azides from the corresponding glucal acetates via functional group transformations

rivatives **7a** and **7b**, respectively, followed by azidation of the mesyl group in each case to afford the azide products **8a** and **8b** (Scheme 2). For simplicity, in Scheme 2 these steps have been represented with only the **5b-1** but the same was performed for **5a-1**. The yields of these reactions were excellent and the products in most of the cases did not need purification via flash column chromatography.

Once the two glycosyl azides **8a** and **8b** were synthesized, they were used in another CuAAC reaction using the same above-mentioned reaction conditions but with different alkynes to synthesize a small library of tris(triazolyl)glycosyl derivatives **9a–d**. It appeared that the presence of triazole rings in compounds **8a** and **8b** did not inhibit the catalysis by CuI in the CuAAC reaction as indicated by the yields of the tris(triazolyl)glycoside products **9a–d** (Table 3).

Table 3 Synthesis of Tris(triazolyl)glycosyl Derivatives Using CuAAC Reactions[a]



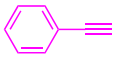
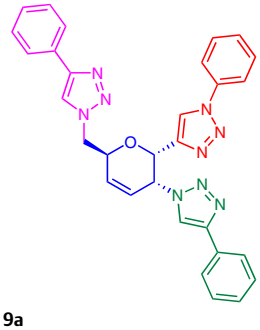
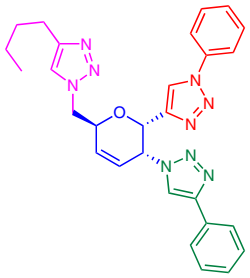
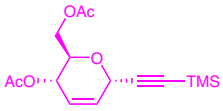
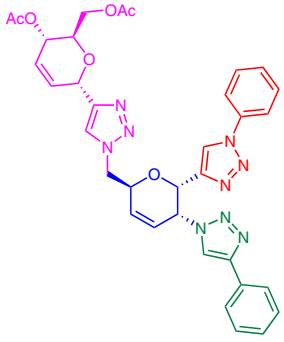
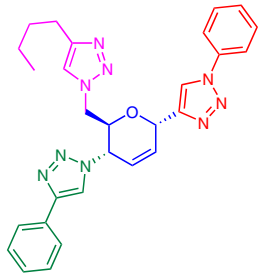
Entry	Azide	Alkyne	Product	Yield (%)[b]
1	**8b**		 **9a**	85

Table 3 (continued)

Entry	Azide	Alkyne	Product	Yield (%)[b]
2	**8b**		 **9b**	94
3	**8b**[c]		 **9c**	92
4	**8a**		 **9d**	89

[a] PMDETA: Pentamethyldiethylenetriamine.
[b] Isolated yield.
[c] TBAF (1.2 equiv) was used to deprotect the TMS group.

In conclusion, libraries of regioisomeric bis(triazolyl)glycosyl derivatives have been synthesized starting from 3,4,6-tri-*O*-acetyl-D-glucal and using a click (CuAAC) reaction, Tsuji–Trost type azidation, and functional group transformations. The reactions tolerated the presence of aryl, hetero-aryl, alkyl, and cycloalkyl groups. Further synthetic evaluations of these bis(triazolyl)glycosyl derivatives were done by performing functional groups transformations and another click (CuAAC) reaction to obtain a small library of tris(triazolyl)glycosyl derivatives in very good to excellent yields. It was also observed that in some products more glucal units can be installed to generate polymeric structures that may have applications in future studies.

Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained at 300 MHz. Spectra were recorded in chloroform-*d* solutions, some of them in DMSO-*d6*. Chemical shifts are reported in ppm, referenced to the solvent peak of chloroform-*d* or tetramethylsilane (TMS) as the external reference. Data are reported as follows: chemical shift (δ), multiplicity, coupling constant (*J*) in Hertz and integrated intensity. Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 75 MHz. Spectra were recorded in chloroform-*d* solutions, some of them in DMSO-*d6*. Chemical shifts are reported in ppm, ref-

erenced to the solvent peak of chloroform-*d* or DMSO-*d6*. Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sex (sextet) and m (multiplet). Column chromatography was performed using silica gel (230–400 mesh). High resolution mass spectra were obtained using a high-resolution ESI-TOF mass spectrometer Shimadzu LCMS-IT-TOF using methanol as solvent, analysis was done in ESI+ and ESI–, with 50% solution of acetonitrile\H_2O and 0.1% formic acid. Thin layer chromatography (TLC) was performed using silica gel UV_{254}, 0.20 mm thickness. For visualization, TLC plates were either placed under ultraviolet light, or stained with iodine or acidic vanillin solution. Tetrahydrofuran was dried from sodium with a benzophenone indicator and purified by distillation. All other solvents were ACS or HPLC grade unless otherwise noted. Air- and moisture-sensitive reactions were conducted in flame-dried or oven-dried glassware equipped with tightly fitted rubber septa and under a positive atmosphere of dry nitrogen. Reagents and solvents were handled using standard syringe techniques.

The glycosyl-triazoles **3** were prepared as previously reported.[12]

Bis- and Tris(triazolyl)glycosyl Derivatives 5a, 5b, and 9a–d; General Procedure

A single-necked round-bottom flask equipped with a magnetic stirrer bar and a reflux condenser was charged with $Pd(PPh_3)_4$ (5 mol%) and allylic acetate **3** (0.5 mmol), THF/H_2O (7:3), and NaN_3 (1.1 equiv). The reaction mixture was then heated at 50 °C for 1–2 h with magnetically mediated stirring. The color of the mixture changed from yellow to brown as the reaction progressed to completion and TLC was used to monitor the reaction. When the reaction was complete, sat. aq NH_4Cl (25 mL) was added followed by extraction with EtOAc (3 × 20 mL). The organic phases were combined, dried ($MgSO_4$), filtered, and the solvent was removed by rotary evaporation. The mixture of the two products was passed through a flash chromatographic column (hexane/EtOAc 1:1) to remove any residual ligands and side products. A two-necked round-bottom flask equipped with a magnetic stirrer bar and a reflux condenser was charged with the mixture of azides **4**, the terminal alkyne (1.2 equiv), CuI (7 mol%), and DMF (5 mL). For the preparation of **9**, PMDETA (1.3 equiv) was added. The reaction mixture was then heated at 60 °C for 2–5 h (80 °C for 3 h for **9**) with magnetically mediated stirring. When the reaction was complete, sat. aq NH_4Cl (25 mL) was added followed by extraction with EtOAc (3 × 20 mL). The organic phases were combined, dried ($MgSO_4$), filtered, and the solvent was removed by rotary evaporation. The products were purified by flash column chromatography using hexane and EtOAc as eluents (50–80% EtOAc/hexane) (Tables 2, 3).

[(2*S*,3*S*,6*S*)-3-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)-6-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-3,6-dihydro-2*H*-pyran-2-yl]methyl Acetate (5a-1)

Yield: 105 mg (47%); white solid; mp 59–61 °C.

IR (film): 1737, 1600, 1505, 1367, 1229, 1045, 910, 761, 728, 693 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.16 (s, 1 H), 8.11 (s, 1 H), 7.83 (d, *J* = 8.8 Hz, 2 H), 7.75 (d, *J* = 9.1 Hz, 2 H), 7.53 (t, *J* = 7.5 Hz, 2 H), 7.48–7.37 (m, 3 H), 7.31 (t, *J* = 7.5 Hz, 1 H), 6.50 (d, *J* = 10.2 Hz, 1 H), 6.15 (d, *J* = 10.3 Hz, 1 H), 5.73 (s, 1 H), 5.45 (d, *J* = 7.6 Hz, 1 H), 4.32 (dt, *J* = 7.8, 4.4 Hz, 1 H), 4.21 (d, *J* = 4.4 Hz, 2 H), 2.04 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.53, 148.08, 146.11, 136.78, 130.92, 130.32, 129.88, 129.86, 129.08, 128.84 (2 C), 128.27, 125.73 (2 C), 124.00, 121.06, 120.59, 120.54, 119.15, 71.27, 67.09, 62.80, 54.67. 20.74.

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{23}N_6O_3$ [M + H]$^+$: 443.1832; found: 443.1795.

[(2*S*,5*R*,6*S*)-5-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)-6-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-5,6-dihydro-2*H*-pyran-2-yl]methyl Acetate (5b-1)

Yield: 70 mg (32%); yellow solid; mp 63–65 °C.

IR (film): 1737, 1601, 1505, 1439, 1367, 1231, 1078, 1046, 909, 728, 703, 693 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.12 (s, 1 H), 8.08 (s, 1 H), 7.81 (d, *J* = 7.8 Hz, 2 H), 7.71 (d, *J* = 8.7 Hz, 2 H), 7.55–7.27 (m, 6 H), 6.32 (d, *J* = 10.5 Hz, 1 H), 6.15 (d, *J* = 10.4 Hz, 1 H), 5.98 (s, 1 H), 5.46 (d, *J* = 4.1 Hz, 1 H), 4.59 (dd, *J* = 11.8, 5.8 Hz, 1 H), 4.49 (dd, *J* = 5.7, 2.9 Hz, 1 H), 4.22 (dd, *J* = 11.8, 3.2 Hz, 1 H), 2.11 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.70, 147.59, 143.98, 136.71, 130.55, 130.35, 129.80 (2 C), 129.06, 128.81 (2 C), 128.17, 125.71 (2 C), 124.75, 121.74, 120.59 (2 C), 119.93, 69.74 (2 C), 64.41, 55.22, 20.94.

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{23}N_6O_3$ [M + H]$^+$: 443.1832; found: 443.1792.

[(2*S*,3*S*,6*S*)-3-(4-Butyl-1*H*-1,2,3-triazol-1-yl)-6-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-3,6-dihydro-2*H*-pyran-2-yl]methyl Acetate (5a-2)

Yield: 98 mg (47%); colorless oil.

IR (film): 3134, 3077, 2933, 2959, 1739, 1601, 1506, 1374, 1235, 1048, 763, 735 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.11 (s, 1 H), 7.76 (d, *J* = 8.1 Hz, 2 H), 7.59–7.45 (m, 4 H), 6.46 (dt, *J* = 10.2, 2.8 Hz, 1 H), 6.10 (dt, *J* = 10.2, 2.5 Hz, 1 H), 5.71 (d, *J* = 2.7 Hz, 1 H), 5.36 (dt, *J* = 7.8, 2.5 Hz, 1 H), 4.24 (dt, *J* = 8.0, 4.2 Hz, 1 H), 4.15 (d, *J* = 5.4 Hz, 2 H), 2.71 (t, *J* = 7.8 Hz, 3 H), 2.06 (s, 3 H), 1.65 (pent, *J* = 7.6 Hz, 3 H), 1.38 (hept, *J* = 7.3 Hz, 3 H), 0.92 (t, *J* = 7.3 Hz, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.57, 148.91, 146.21, 136.83, 130.42, 129.89 (2 C), 129.10, 124.41, 120.92, 120.60 (2 C), 119.90, 71.13, 67.18, 62.82, 54.39, 31.51, 25.42, 22.36, 20.77, 13.80.

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{23}N_6O_3$ [M + H]$^+$: 423.2145; found: 423.2105.

[(2*S*,5*R*,6*S*)-5-(4-Butyl-1*H*-1,2,3-triazol-1-yl)-6-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-5,6-dihydro-2*H*-pyran-2-yl]methyl Acetate (5b-2)

Yield: 65 mg (31%); light yellow oil.

IR (film): 3146, 2952, 2935, 2874, 1737, 1601, 1506, 1378, 1235, 1086, 1046, 763, 735, 694 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.04 (s, 1 H), 7.72 (d, *J* = 7.8 Hz, 2 H), 7.60–7.41 (m, 4 H), 6.28 (dd, *J* = 8.5, 1.7 Hz, 1 H), 6.12 (d, *J* = 10.4 Hz, 1 H), 5.86 (s, 1 H), 5.37 (d, *J* = 4.2 Hz, 1 H), 4.57 (dd, *J* = 11.6, 6.0 Hz, 1 H), 4.49 (s, 1 H), 4.20 (dd, *J* = 11.7, 2.8 Hz, 1 H), 2.69 (t, *J* = 7.6 Hz, 2 H), 2.12 (s, 3 H), 1.63 (pent, *J* = 7.6 Hz, 2 H), 1.34 (hept, *J* = 7.2 Hz, 3 H), 0.90 (t, *J* = 7.4 Hz, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.68, 148.21, 144.14, 136.74, 129.91, 129.82 (2 C), 129.08, 125.05, 121.59, 120.77, 120.60 (2 C), 69.84, 69.68, 64.41, 55.12, 31.52, 25.42, 22.29, 20.90, 13.78.

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{23}N_6O_3$ [M + H]$^+$: 423.2145; found: 423.2098.

{(2*S*,3*S*,6*S*)-3-[4-(2,4-Difluorophenyl)-1*H*-1,2,3-triazol-1-yl]-6-[1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]-3,6-dihydro-2*H*-pyran-2-yl}methyl Acetate (5a-3)

Yield: 142 mg (56%); pale yellow oil.

IR (film): 3153, 3082, 2963, 1743, 1628, 1601, 1521, 1493, 1257, 1235, 1041, 808, 737 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.16 (dd, *J* = 15.2, 8.4 Hz, 1 H), 7.90 (d, *J* = 3.5 Hz, 1 H), 7.39 (d, *J* = 8.8 Hz, 2 H), 7.16 (s, 1 H), 7.07–6.80 (m, 4 H), 6.49–6.36 (m, 1 H), 6.32 (d, *J* = 10.3 Hz, 1 H), 5.71 (s, 1 H), 5.56 (s, 1 H), 4.91 (d, *J* = 2.9 Hz, 1 H), 4.54 (dd, *J* = 12.0, 7.1 Hz, 1 H), 4.30 (dd, *J* = 12.1, 3.2 Hz, 1 H), 3.81 (s, 3 H), 2.12 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.35, 170.72, 159.86, 131.12, 130.19, 128.81, 124.38, 122.32, 120.14, 114.64, 112.14, 112.07, 111.84, 111.80, 104.43, 104.08, 103.75, 72.43, 68.55, 63.57, 55.72, 55.58, 20.88.

HRMS (ESI): *m*/*z* calcd for $C_{25}H_{23}F_2N_6O_4$ $[M + H]^+$: 509.1749; found: 509.1697.

{(2*S*,5*R*,6*S*)-5-[4-(2,4-Difluorophenyl)-1*H*-1,2,3-triazol-1-yl]-6-[1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]-5,6-dihydro-2*H*-pyran-2-yl}methyl Acetate (5b-3)

Yield: 64 mg (25%); light brown oil.

IR (film): 3144, 2956, 1739, 1601, 1562, 1520, 1493, 1229, 1039, 834, 734 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.36–8.18 (m, 1 H), 8.12 (s, 1 H), 8.02 (s, 1 H), 7.65 (d, *J* = 8.6 Hz, 2 H), 7.04 (d, *J* = 7.7 Hz, 3 H), 6.89 (t, *J* = 9.0 Hz, 1 H), 6.52 (d, *J* = 9.9 Hz, 1 H), 6.16 (d, *J* = 10.2 Hz, 1 H), 5.74 (s, 1 H), 5.45 (dd, *J* = 4.8, 2.2 Hz, 1 H), 4.32 (d, *J* = 4.1 Hz, 1 H), 4.22 (d, *J* = 3.6 Hz, 2 H), 3.88 (s, 3 H), 2.07 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.52, 160.06, 145.94, 140.87, 132.69, 131.25, 130.27, 128.83, 123.66, 122.99, 122.29, 121.71, 121.55, 120.89, 120.71, 114.90, 114.86, 112.19, 112.15, 111.91, 111.86, 104.48, 104.14, 103.80, 71.31, 67.29, 62.73, 55.66, 54.71, 20.73.

HRMS (ESI): *m*/*z* calcd for $C_{25}H_{23}F_2N_6O_4$ $[M + H]^+$: 509,1749; found: 509.1708.

{(2*S*,3*S*,6*S*)-3-(4-Cyclopropyl-1*H*-1,2,3-triazol-1-yl)-6-[1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]-3,6-dihydro-2*H*-pyran-2-yl}methyl Acetate (5a-4)

Yield: 99 mg (45%); pale yellow oil.

IR (film): 3144, 3088, 2959, 1739, 1520, 1443, 1255, 1231, 1041, 836, 732 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.96 (s, 1 H), 7.61 (d, *J* = 8.6 Hz, 2 H), 7.53 (s, 1 H), 7.01 (d, *J* = 8.5 Hz, 2 H), 6.25 (d, *J* = 10.1 Hz, 1 H), 6.10 (d, *J* = 10.4 Hz, 1 H), 5.82 (s, 1 H), 5.35 (d, *J* = 2.8 Hz, 1 H), 4.54 (dd, *J* = 11.5, 5.8 Hz, 1 H), 4.46 (s, 1 H), 4.21 (d, *J* = 11.5 Hz, 1 H), 3.86 (s, 3 H), 2.13 (s, 3 H), 2.01–1.84 (m, 1 H), 0.92 (d, *J* = 8.2 Hz, 2 H), 0.82 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.62, 160.05, 143.89, 130.18, 130.14, 124.83, 122.23 (3 C), 121.65, 119.91, 114.83 (2 C), 69.84, 69.57, 64.50, 55.64, 55.02, 20.87, 7.63, 7.57, 6.72.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{25}N_6O_4$ $[M + H]^+$: 437.1937; found: 437.1687.

{(2*S*,5*R*,6*S*)-5-(4-Cyclopropyl-1*H*-1,2,3-triazol-1-yl)-6-[1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]-5,6-dihydro-2*H*-pyran-2-yl}methyl Acetate (5b-4)

Yield: 71 mg (33%); colorless oil.

IR (film): 3138, 3088, 2941, 1739, 1520, 1441, 1253, 1229, 1082, 1039, 836, 728 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.94 (s, 1 H), 7.57 (d, *J* = 9.0 Hz, 2 H), 7.42 (s, 1 H), 6.96 (d, *J* = 9.0 Hz, 2 H), 6.44–6.29 (m, 1 H), 5.99 (dd, *J* = 10.2, 2.2 Hz, 1 H), 5.60 (d, *J* = 2.3 Hz, 1 H), 5.25 (dd, *J* = 7.7, 2.4 Hz, 1 H), 4.17–4.10 (m, 1 H), 4.10–4.02 (m, 2 H), 3.80 (s, 3 H), 1.97 (s, 3 H), 1.92–1.76 (m, 1 H), 0.92–0.81 (m, 2 H), 0.84–0.61 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.50, 160.07, 145.97, 132.09, 130.53, 130.25, 124.27, 122.23, 121.04, 114.90, 71.05, 67.18, 62.85, 55.65, 54.46, 20.71, 7.76, 7.72, 6.73.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{25}N_6O_4$ $[M + H]^+$: 437.1937; found: 437.1693.

{(2*S*,3*S*,6*S*)-6-[1-(Benzo[*d*]thiazol-7-yl)-1*H*-1,2,3-triazol-4-yl]-3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-3,6-dihydro-2*H*-pyran-2-yl}methyl Acetate (5a-5)

Yield: 133 mg (53%); white solid; mp 189–191 °C.

IR (film): 3136, 3080, 2954, 1739, 1609, 1486, 1369, 1233, 1046, 816, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.08 (s, 1 H), 8.36 (s, 1 H), 8.23 (dd, *J* = 16.4, 8.8 Hz, 2 H), 8.09 (s, 1 H), 7.89–7.76 (m, 3 H), 7.42–7.28 (m, 3 H), 6.40–6.27 (m, 1 H), 6.21–6.11 (m, 1 H), 5.99 (s, 1 H), 5.49 (d, *J* = 4.1 Hz, 1 H), 4.61 (dd, *J* = 11.7, 5.9 Hz, 1 H), 4.53 (s, 1 H), 4.23 (d, *J* = 11.1 Hz, 1 H), 2.10 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.37, 161.30, 157.88, 152.11, 149.02, 139.82, 139.04, 135.60, 135.34, 133.60 (3 C), 132.93, 130.39 (2 C), 129.20, 129.07, 127.26, 124.78, 124.03, 119.01, 74.70, 74.26, 69.26, 60.08, 25.66.

HRMS (ESI): *m*/*z* calcd for $C_{25}H_{22}N_7O_3S$ $[M + H]^+$: 500.1505; found: 500.1453.

{(2*S*,5*R*,6*S*)-6-[1-(Benzo[*d*]thiazol-7-yl)-1*H*-1,2,3-triazol-4-yl]-5-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-5,6-dihydro-2*H*-pyran-2-yl}ethyl Acetate (5b-5)

Yield: 57 mg (23%); pale yellow gummy solid.

IR (film): 3136, 3069, 2965, 1739, 1480, 1439, 1372, 1233, 1046, 767, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.37 (s, 1 H), 8.20 (d, *J* = 8.8 Hz, 1 H), 8.09 (s, 1 H), 7.91 (s, 1 H), 7.80 (dd, *J* = 11.5, 4.3 Hz, 3 H), 7.41–7.17 (m, 4 H), 6.62 (dd, *J* = 10.0, 3.1 Hz, 1 H), 6.36–6.21 (m, 1 H), 5.79 (s, 1 H), 5.29 (d, *J* = 3.6 Hz, 1 H), 4.59 (dd, *J* = 11.7, 5.9 Hz, 1 H), 4.50 (s, 1 H), 4.22 (dd, *J* = 11.7, 2.7 Hz, 1 H), 1.87 (s, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.18, 155.98, 147.90, 146.14, 134.34, 132.31, 130.50, 128.83 (2 C), 128.23, 125.75 (2 C), 124.76, 123.45, 121.02, 119.61, 119.19, 114.32, 69.18, 68.33, 62.71, 53.65, 20.64.

HRMS (ESI): *m*/*z* calcd for $C_{25}H_{22}N_7O_3S$ $[M + H]^+$: 500.1505; found: 500.1461.

[(2*R*,3*S*,6*S*)-3-Acetoxy-6-(1-{(2*S*,3*S*,6*S*)-2-(acetoxymethyl)-6-[1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]-3,6-dihydro-2*H*-pyran-3-yl}-1*H*-1,2,3-triazol-4-yl)-3,6-dihydro-2*H*-pyran-2-yl]methyl Acetate (5a-6)

Yield: 147 mg (51%); light yellow gummy solid.

IR (film): 3140, 3115, 2957, 1739, 1600, 1503, 1372, 1231, 1045, 762, 690 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (s, 1 H), 7.76 (s, 1 H), 7.64 (d, *J* = 8.0 Hz, 2 H), 7.05 (d, *J* = 8.8 Hz, 2 H), 6.67 (dd, *J* = 10.0, 3.4 Hz, 1 H), 6.42–6.21 (m, 2 H), 5.99 (d, *J* = 8.6 Hz, 1 H), 5.78 (s, 1 H), 5.53 (s, 1 H), 5.34 (d, *J* = 4.2 Hz, 2 H), 4.43 (s, 1 H), 4.31–4.05 (m, 4 H), 3.95–3.80 (m, 4 H), 2.09 (s, 6 H), 1.97 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.78, 170.34, 170.06, 160.15, 146.33, 145.47, 132.56, 130.20, 129.52, 125.85, 123.12, 122.24 (2 C), 122.01, 120.61, 114.92 (2 C), 69.64, 69.01, 68.33, 67.69, 64.97, 63.06, 62.55, 55.65, 53.63, 21.02, 20.72, 20.62.

HRMS (ESI): *m*/*z* calcd for $C_{28}H_{31}N_6O_8$ [M + H]$^+$: 579.2203; found: 579.2181.

[(2*R*,3*S*,6*S*)-3-Acetoxy-6-(1-{(2*S*,3*R*,6*S*)-6-(acetoxymethyl)-2-[1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl]-3,6-dihydro-2*H*-pyran-3-yl}-1*H*-1,2,3-triazol-4-yl)-3,6-dihydro-2*H*-pyran-2-yl]methyl Acetate (5b-6)

Yield: 69 mg (24%); light yellow oil.

IR (film): 3142, 3118, 1745, 1600, 1503, 1372, 1231, 1046, 765, 693 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (s, 1 H), 7.77 (s, 1 H), 7.54 (d, *J* = 9.0 Hz, 2 H), 6.95 (d, *J* = 8.9 Hz, 2 H), 6.28–5.98 (m, 3 H), 5.95–5.79 (m, 2 H), 5.41 (s, 1 H), 5.30 (d, *J* = 3.7 Hz, 1 H), 5.28–5.17 (m, 1 H), 4.51–4.35 (m, 2 H), 4.10 (ddd, *J* = 14.8, 10.9, 2.7 Hz, 3 H), 3.89–3.72 (m, 4 H), 2.05 (s, 3 H), 1.99 (d, *J* = 3.6 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.72, 170.65, 170.31, 160.10, 145.96, 143.68, 132.13, 132.00, 130.70, 130.12, 129.71, 128.56, 128.40, 125.54, 124.36, 122.35, 122.20 (2 C), 121.64, 114.87 (2 C), 69.96, 69.69, 69.59, 67.51, 64.84, 64.40, 62.86, 55.64, 55.25, 20.96, 20.87, 20.74.

HRMS (ESI): *m*/*z* calcd for $C_{28}H_{31}N_6O_8$ [M + H]$^+$: 579.2203; found: 579.2187.

{(2*S*,3*S*,6*S*)-6-(1-Phenyl-1*H*-1,2,3-triazol-4-yl)-3-[4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl]-3,6-dihydro-2*H*-pyran-2-yl}methyl Acetate (5a-7)

Yield: 114 mg (50%); white solid; mp 182–183 °C.

IR (film): 3140, 2924, 1737, 1600, 1501, 1229, 1045, 761, 732, 693 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 (s, 1 H), 8.01 (s, 1 H), 7.70 (t, *J* = 6.4 Hz, 4 H), 7.57–7.42 (m, 3 H), 7.20 (d, *J* = 7.8 Hz, 2 H), 6.32 (d, *J* = 8.9 Hz, 1 H), 6.15 (d, *J* = 10.3 Hz, 1 H), 5.95 (s, 1 H), 5.45 (d, *J* = 4.1 Hz, 1 H), 4.60 (dd, *J* = 11.7, 5.9 Hz, 1 H), 4.50 (s, 1 H), 4.22 (dd, *J* = 11.8, 3.0 Hz, 1 H), 2.36 (s, 3 H), 2.11 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.78, 170.34, 170.06, 160.15, 146.33, 145.47, 132.56, 130.20, 129.52, 125.85, 123.12, 122.24 (2 C), 122.01, 120.61, 114.92 (2 C), 69.64, 69.01, 67.69, 64.97, 63.06, 62.55, 55.65, 53.63, 21.02, 20.72, 20.62.

HRMS (ESI): *m*/*z* calcd for $C_{25}H_{25}N_6O_3$ [M + H]$^+$: 457.1988; found: 457.2019.

{(2*S*,5*R*,6*S*)-6-(1-Phenyl-1*H*-1,2,3-triazol-4-yl)-5-[4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl]-5,6-dihydro-2*H*-pyran-2-yl}methyl Acetate (5b-7)

Yield: 73 mg (32%); white solid; mp 183–185 °C.

IR (film): 3140, 2926, 1737, 1600, 1501, 1229, 1045, 909, 728, 693 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 (s, 1 H), 7.94 (s, 1 H), 7.73 (t, *J* = 9.0 Hz, 4 H), 7.61–7.41 (m, 3 H), 7.22 (t, *J* = 6.9 Hz, 2 H), 6.68 (dd, *J* = 10.0, 2.9 Hz, 1 H), 6.32 (dd, *J* = 9.8, 5.6 Hz, 1 H), 5.83 (s, 1 H), 5.33 (d, *J* = 3.2 Hz, 1 H), 4.43 (s, 1 H), 4.31 (dd, *J* = 7.3, 4.3 Hz, 1 H), 4.21 (d, *J* = 4.2 Hz, 1 H), 2.37 (s, 3 H), 1.93 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.16, 147.95, 145.85, 138.03, 136.84, 132.36, 129.88 (2 C), 129.51 (2 C), 129.11, 129.07, 127.72, 125.66 (2 C), 123.36, 120.62, 120.58 (2 C), 119.25, 69.17, 68.36, 62.79, 53.64, 21.26.

HRMS (ESI): *m*/*z* calcd for $C_{25}H_{25}N_6O_3$ [M + H]$^+$: 457.1988; found: 457.2011.

[(2*S*,3*S*,6*S*)-3-(4-Cyclopropyl-1*H*-1,2,3-triazol-1-yl)-6-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-3,6-dihydro-2*H*-pyran-2-yl]methyl Acetate (5a-8)

Yield: 39 mg (19%); white solid; mp 182–184 °C.

IR (film): 3144, 3006, 2956, 1739, 1600, 1505, 1233, 1043, 763, 693 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.04 (s, 1 H), 7.72 (d, *J* = 8.1 Hz, 2 H), 7.53 (t, *J* = 7.5 Hz, 3 H), 7.49–7.37 (m, 1 H), 6.25 (d, *J* = 10.3 Hz, 1 H), 6.11 (d, *J* = 10.4 Hz, 1 H), 5.84 (s, 1 H), 5.37 (d, *J* = 3.9 Hz, 1 H), 4.55 (dd, *J* = 11.7, 5.9 Hz, 1 H), 4.47 (s, 1 H), 4.21 (dd, *J* = 11.6, 2.8 Hz, 1 H), 2.13 (s, 3 H), 1.97–1.86 (m, 1 H), 0.92 (d, *J* = 8.3 Hz, 2 H), 0.88–0.72 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.16, 150.33, 145.94, 136.85, 132.01, 129.88 (2 C), 129.11, 123.46, 120.58 (2 C), 120.45, 119.57, 69.21, 68.30, 62.80, 53.40, 20.63, 7.77, 7.72, 6.79.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{23}N_6O_3$ [M + H]$^+$: 407.1832; found: 407.1801.

[(2*S*,5*R*,6*S*)-5-(4-Cyclopropyl-1*H*-1,2,3-triazol-1-yl)-6-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-5,6-dihydro-2*H*-pyran-2-yl]methyl Acetate (5b-8)

Yield: 68 mg (34%); light yellow gummy solid.

IR (film): 3142, 3118, 1743, 1600, 1503, 1372, 1231, 1046, 763, 692 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03 (s, 1 H), 7.76 (d, *J* = 7.7 Hz, 2 H), 7.63–7.36 (m, 4 H), 6.63 (dd, *J* = 10.0, 2.6 Hz, 1 H), 6.37–6.18 (m, 1 H), 5.78 (s, 1 H), 5.25 (d, *J* = 2.9 Hz, 1 H), 4.37 (dd, *J* = 9.9, 4.5 Hz, 1 H), 4.28–4.11 (m, 2 H), 2.01–1.86 (m, 4 H), 1.07–0.80 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.59, 149.90, 144.12, 136.76, 130.13, 129.79 (2 C), 129.03, 124.82, 121.55, 120.58 (2 C), 119.89, 69.81, 69.59, 64.46, 55.00, 20.86, 7.63, 7.57, 6.72.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{23}N_6O_3$ [M + H]$^+$: 407.1832; found: 407.1811.

[(2*S*,3*R*,6*S*)-3-(4-Cyclopropyl-1*H*-1,2,3-triazol-1-yl)-6-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-3,6-dihydro-2*H*-pyran-2-yl]methyl Acetate (5c-8)

Yield: 52 mg (27%); white solid; mp 187–189 °C.

IR (film): 3142, 3118, 1739, 1600, 1503, 1372, 1231, 1046, 765, 693 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.04 (s, 1 H), 7.75 (d, *J* = 7.4 Hz, 2 H), 7.60–7.44 (m, 4 H), 6.63 (dd, *J* = 10.1, 3.5 Hz, 1 H), 6.27 (ddd, *J* = 9.9, 5.7, 1.9 Hz, 1 H), 5.79 (s, 1 H), 5.32–5.20 (m, 1 H), 4.45–4.31 (m, 1 H), 3.83 (dd, *J* = 11.8, 5.4 Hz, 1 H), 3.70 (dd, *J* = 11.8, 6.8 Hz, 1 H), 2.05–1.90 (m, 4 H), 1.02–0.92 (m, 2 H), 0.92–0.84 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.16, 150.33, 145.94, 136.85, 132.01, 129.88 (2 C), 129.11, 123.46, 120.58 (2 C), 120.45, 119.57, 69.21, 68.30, 62.80, 53.40, 20.63, 7.77, 7.72, 6.79.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{23}N_6O_3$ [M + H]$^+$: 407.1832; found: 407.1803.

[(2*S*,3*S*,6*S*)-3-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)-6-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-3,6-dihydro-2*H*-pyran-2-yl]methanol (6a)

Yield: 180 mg (90%); yellow solid; mp 200–202 °C.

IR (film): 3342, 3118, 2975, 1600, 1503, 1372, 1231, 1046, 765, 693 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (s, 1 H), 7.94 (s, 1 H), 7.86 (d, *J* = 6.9 Hz, 2 H), 7.75 (d, *J* = 7.2 Hz, 2 H), 7.61–7.29 (m, 6 H), 6.74 (d, *J* = 9.9 Hz, 1 H), 6.47–6.26 (m, 1 H), 5.81 (s, 1 H), 5.35 (s, 1 H), 4.29 (d, *J* = 6.3 Hz, 1 H), 3.24 (d, *J* = 17.4 Hz, 2 H), 2.65 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.83, 133.28, 130.40, 129.85, 129.11, 128.87, 128.31, 125.76, 122.76, 120.69, 120.61, 119.90, 71.36, 68.25, 61.29, 53.34.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{21}N_6O_2$ [M + H]$^+$: 401.1726; found: 401.1731.

[(2*S*,5*R*,6*S*)-5-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)-6-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-5,6-dihydro-2*H*-pyran-2-yl]methanol (6b)

Yield: 190 mg (95%); yellow solid; mp 194–196 °C.

IR (film): 3340, 3118, 2970, 1603, 1505, 1372, 1231, 1045, 765, 693 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (s, 1 H), 8.08 (s, 1 H), 7.85 (d, *J* = 7.8 Hz, 2 H), 7.74 (d, *J* = 8.0 Hz, 2 H), 7.62–7.30 (m, 6 H), 6.35 (d, *J* = 10.6 Hz, 1 H), 6.23 (d, *J* = 10.2 Hz, 1 H), 5.94 (s, 1 H), 5.49 (s, 1 H), 4.36 (s, 1 H), 3.94 (s, 2 H), 2.36 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.83, 133.28, 130.40, 129.85 (2 C), 129.11, 128.87 (2 C), 128.31, 125.76 (2 C), 122.76, 120.69 (2 C), 120.61, 119.90, 71.36, 68.25, 61.29, 53.34.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{21}N_6O_2$ [M + H]$^+$: 401.1726; found: 401.1743.

[(2*S*,3*S*,6*S*)-3-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)-6-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-3,6-dihydro-2*H*-pyran-2-yl]methyl Methanesulfonate (7a)

Yield: 162 mg (85%); light yellow solid; mp 128–130 °C.

IR (film): 3130, 3118, 2970, 1601, 1503, 1372, 1231, 1045, 763, 692 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.18 (s, 1 H), 8.05–7.73 (m, 5 H), 7.66–7.31 (m, 6 H), 6.84 (dd, *J* = 10.1, 3.6 Hz, 1 H), 6.34 (ddd, *J* = 10.0, 5.8, 2.1 Hz, 1 H), 5.88 (d, *J* = 2.2 Hz, 1 H), 5.34 (d, *J* = 5.5 Hz, 1 H), 4.56–4.39 (m, 1 H), 4.28–4.05 (m, 1 H), 3.75 (dd, *J* = 11.4, 7.7 Hz, 1 H), 2.96 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.08, 145.59, 133.21, 130.25, 129.84 (2 C), 129.04, 128.90 (2 C), 128.82, 128.42, 125.79 (2 C), 122.33, 120.60 (3 C), 119.67, 69.87, 68.90, 68.81, 53.28, 37.84.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{23}N_6O_4S$ [M + H]$^+$: 479.1501; found: 479.1491.

[(2*S*,5*R*,6*S*)-5-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)-6-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-5,6-dihydro-2*H*-pyran-2-yl]methyl Methanesulfonate (7b)

Yield: 176 mg (92%); light yellow solid; mp 224–226 °C.

IR (film): 3130, 3118, 2970, 1601, 1503, 1372, 1231, 1045, 763, 692 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-*d6*): δ = 8.98 (s, 1 H), 8.54 (s, 1H), 8.00–7.80 (m, 4 H), 7.61 (t, *J* = 7.6 Hz, 2 H), 7.56–7.39 (m, 3 H), 7.34 (t, *J* = 7.1 Hz, 1 H), 6.42–6.21 (m, 2 H), 5.84 (s, 1 H), 5.44 (d, *J* = 3.7 Hz, 1 H), 4.69–4.56 (m, 2 H), 4.51 (d, *J* = 9.3 Hz, 1 H), 3.26 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-*d6*): δ = 146.89, 144.61, 136.96, 131.03, 130.58, 130.39 (2 C), 129.34 (3 C), 128.44, 125.66 (2 C), 124.98, 122.89, 120.89, 120.64 (2 C), 70.60, 69.95, 69.64, 55.79, 37.35.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{23}N_6O_4S$ [M + H]$^+$: 409.1501; found: 409.1483.

4-[(2*S*,5*S*,6*R*)-6-(Azidomethyl)-5-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-5,6-dihydro-2*H*-pyran-2-yl]-1-phenyl-1*H*-1,2,3-triazole (8a)

Yield: 102 mg (80%); light yellow gummy solid.

IR (film): 3132, 3099, 2924, 2121, 1600, 1506, 1233, 1046, 763, 694 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (s, 1 H), 7.78 (d, *J* = 8.1 Hz, 2 H), 7.43 (ddd, *J* = 19.8, 16.6, 9.2 Hz, 9 H), 6.55 (dd, *J* = 10.3, 1.9 Hz, 1 H), 6.10 (dd, *J* = 10.3, 2.2 Hz, 1 H), 5.65 (d, *J* = 2.2 Hz, 1 H), 4.87–4.68 (m, 2 H), 4.25 (td, *J* = 7.6, 3.9 Hz, 1 H), 3.91 (dd, *J* = 5.0, 2.4 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.31, 147.10, 136.80, 131.26 (2 C), 130.04, 129.62 (2 C), 128.97 (2 C), 128.64 (2 C), 125.92 (2 C), 123.12, 120.37 (2 C), 119.46, 72.18, 67.99, 55.82, 54.83.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{20}N_9O$ [M + H]$^+$: 426.1791; found: 426.1734.

1-[(2*S*,3*R*,6*S*)-6-(Azidomethyl)-2-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-3,6-dihydro-2*H*-pyran-3-yl]-4-phenyl-1*H*-1,2,3-triazole (8b)

Yield: 115 mg (90%); light yellow gummy solid.

IR (film): 3132, 3099, 2924, 2099, 1600, 1506, 1233, 1046, 763, 694 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16 (s, 1 H), 8.08 (s, 1 H), 7.84 (d, *J* = 7.1 Hz, 2 H), 7.72 (d, *J* = 7.2 Hz, 2 H), 7.58–7.28 (m, 6 H), 6.41–6.29 (m, 1 H), 6.16 (d, *J* = 10.3 Hz, 1 H), 5.97 (d, *J* = 1.3 Hz, 1 H), 5.46 (d, *J* = 2.8 Hz, 1 H), 4.42 (s, 1 H), 3.68–3.54 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.77, 143.94, 136.73, 131.48, 130.61, 129.85 (2 C), 129.15, 128.83 (2 C), 128.15, 125.74 (2 C), 124.30, 121.44, 120.65 (2 C), 119.79, 70.37, 69.86, 54.89, 53.58.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{20}N_9O$ [M + H]$^+$: 426.1791; found: 426.1751.

1-Phenyl-4-{(2*S*,3*R*,6*S*)-3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-6-[(4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl]-3,6-dihydro-2*H*-pyran-2-yl}-1*H*-1,2,3-triazole (9a)

Yield: 112 mg (85%); light yellow gummy solid.

IR (film): 3130, 2957, 2931, 1600, 1505, 1462, 1231, 1076, 1046, 765, 694 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-*d6*): δ = 8.98 (s, 1 H), 8.63 (s, 1 H), 8.04 (s, 1 H), 7.87 (dd, *J* = 15.7, 7.4 Hz, 4 H), 7.75 (d, *J* = 6.9 Hz, 2 H), 7.61 (t, *J* = 7.5 Hz, 2 H), 7.43 (ddd, *J* = 24.3, 15.4, 7.1 Hz, 7 H), 6.47 (d, *J* = 10.2 Hz, 1 H), 6.29 (d, *J* = 9.1 Hz, 1 H), 5.82 (s, 1 H), 5.50 (d, *J* = 3.6 Hz, 1 H), 4.92 (ddd, *J* = 17.2, 14.4, 5.0 Hz, 2 H), 4.72 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-*d6*): δ = 146.38, 146.24, 144.01, 136.43, 131.24, 130.58, 130.31, 129.90 (3 C), 128.85 (3 C), 128.76 (2 C), 127.86, 127.83, 125.12 (3 C), 123.96, 122.54, 122.49, 120.15 (2 C), 119.86, 69.54, 69.29, 55.14, 51.42.

HRMS (ESI): *m*/*z* calcd for $C_{30}H_{26}N_9O$ [M + H]$^+$: 528.2260; found: 528.2234.

4-Butyl-1-{[(2*S*,5*R*,6*S*)-5-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-6-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-5,6-dihydro-2*H*-pyran-2-yl]methyl}-1*H*-1,2,3-triazole (9b)

Yield: 127 mg (94%); light yellow gummy solid.

IR (film): 3136, 2957, 2931, 1601, 1505, 1462, 1231, 1076, 1046, 765, 696 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 (s, 1 H), 7.82 (d, *J* = 7.1 Hz, 2 H), 7.73 (d, *J* = 7.2 Hz, 2 H), 7.59–7.38 (m, 5 H), 7.35 (d, *J* = 5.3 Hz, 3 H), 6.43–6.24 (m, 2 H), 5.83 (d, *J* = 1.4 Hz, 1 H), 5.47 (d, *J* = 2.7 Hz, 1 H), 4.72 (dd, *J* = 14.9, 5.9 Hz, 1 H), 4.65–4.56 (m, 2 H), 2.65–2.40 (m, 2 H), 1.50 (tq, *J* = 13.1, 6.4 Hz, 2 H), 1.22 (dq, *J* = 14.8, 7.3 Hz, 2 H), 0.81 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.69, 147.57, 143.77, 136.69, 131.80, 130.37 (2 C), 129.86, 129.20, 128.80 (2 C), 128.22, 125.84 (2 C), 123.74, 122.52, 121.35, 120.67 (2 C), 119.36, 70.71, 69.06, 54.54, 52.22, 31.29, 25.26, 22.25, 13.67.

HRMS (ESI): *m*/*z* calcd for $C_{28}H_{30}N_9O$ [M + H]$^+$: 508.2573; found: 528.2554.

[(2*R*,3*S*,6*S*)-3-Acetoxy-6-(1-{[(2*S*,5*R*,6*S*)-5-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-6-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-5,6-dihydro-2*H*-pyran-2-yl]methyl}-1*H*-1,2,3-triazol-4-yl)-3,6-dihydro-2*H*-pyran-2-yl]methyl Acetate (9c)

Yield: 152 mg (92%); light yellow solid; mp 119–121 °C.

IR (film): 1657, 1236, 1052, 1026, 1002, 763, 665 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-*d6*): δ = 8.93 (s, 1 H), 8.26 (s, 1 H), 8.14 (s, 1 H), 7.88 (t, *J* = 6.8 Hz, 4 H), 7.62 (t, *J* = 7.6 Hz, 2 H), 7.56–7.42 (m, 3 H), 7.36 (t, *J* = 7.3 Hz, 1 H), 6.40 (d, *J* = 10.4 Hz, 1 H), 6.28 (d, *J* = 10.5 Hz, 1 H), 6.10 (d, *J* = 10.3 Hz, 1 H), 5.79 (d, *J* = 10.4 Hz, 2 H), 5.52 (d, *J* = 4.9 Hz, 1 H), 5.39 (s, 1 H), 5.15 (d, *J* = 7.9 Hz, 1 H), 4.97 (dd, *J* = 14.3, 7.5 Hz, 1 H), 4.90 – 4.78 (m, 1 H), 4.74 (s, 1 H), 4.09 (dd, *J* = 12.0, 5.4 Hz, 1 H), 4.04–3.94 (m, 1 H), 3.78 (dd, *J* = 5.0, 2.3 Hz, 1 H), 1.98 (s, 3 H), 1.93 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-*d6*): δ = 170.02, 169.85, 146.38, 144.94, 144.24, 136.42, 130.58, 130.47, 130.22, 129.89 (3 C), 128.84 (2 C), 127.96, 125.23 (2 C), 124.78, 124.53, 122.33, 120.29, 120.09 (3 C), 70.25, 68.68, 68.60, 66.72, 64.31, 62.44, 55.61, 51.00, 20.64, 20.39.

HRMS (ESI): *m*/*z* calcd for $C_{34}H_{34}N_9O_6$ [M + H]$^+$: 664.2632; found: 664.2601.

4-Butyl-1-{[(2*R*,3*S*,6*S*)-3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-6-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-3,6-dihydro-2*H*-pyran-2-yl]methyl}-1*H*-1,2,3-triazole (9d)

Yield: 113 mg (89%); yellowish green gummy solid.

IR (film): 3136, 2957, 2931, 1601, 1505, 1462, 1231, 1076, 1046, 765, 696 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (s, 1 H), 7.76–7.68 (m, 2 H), 7.64 (s, 1 H), 7.58–7.48 (m, 3 H), 7.42–7.32 (m, 6 H), 6.62 (dd, *J* = 10.3, 2.9 Hz, 1 H), 6.10 (dd, *J* = 12.4, 2.1 Hz, 1 H), 5.73 (d, *J* = 2.0 Hz, 1 H), 5.44 (dd, *J* = 7.9, 2.3 Hz, 1 H), 4.72 (dd, *J* = 14.2, 8.3 Hz, 1 H), 4.58 (dd, *J* = 14.2, 3.0 Hz, 1 H), 4.50 (td, *J* = 8.1, 3.0 Hz, 1 H), 2.72 (t, 2 H), 1.66 (dt, *J* = 15.4, 7.5 Hz, 2 H), 1.38 (dq, *J* = 14.5, 7.3 Hz, 2 H), 0.92 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.04, 148.17, 146.51, 136.68, 131.18, 130.97, 129.94, 129.67 (2 C), 128.94 (2 C), 128.77, 128.63, 125.83, 123.83 (2 C), 120.33 (2 C), 120.08, 119.85, 72.13, 67.70, 55.47, 55.39, 31.40, 25.44, 22.34, 13.78.

HRMS (ESI): *m*/*z* calcd for $C_{28}H_{30}N_9O$ [M + H]$^+$: 508.2573; found: 508.2601.

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Supporting Information

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