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Synthesis of N^{α}-Z protected amino alkyl triazole acids and their application to neo-glycopeptides synthesis

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The synthesis of triazole linked glycopeptides employing 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) mediated coupling of Z-protected triazole acids with glycosyl amines and amino acid esters is described. The coupling proceeded smoothly at room temperature and the products are obtained in good yields. Z-Protected triazole acids have been synthesized *via* click chemistry protocol through the cycloaddition of Z-protected alkyl azides with propiolic acid.

Keywords: Triazole, CDMT, neoglycopeptides, click reaction

A regio controlled variation of Huisgen 1,3-dipolar cycloaddition between azides and alkynes has emerged as a stitching maneuver to connect different structural units endowed with unparalled chemical and biological stability[1]. Copper catalyzed synthesis of 3,5-disubstituted 1,2,3-triazoles[2] show particular promise as *cis* peptide isosters and it features a combination of hydrogen bond donor and acceptor sites capable of mimicking the hydrogen bonding acidity and basicity of a peptide bond[3]. Hence, triazole chemistry has lead to broad application in both peptides and carbohydrate synthesis[4]. In the realm of rapidly growing protein chemistry, glycosylation of peptides/proteins are also key factors in modulating structure and function. Glycopeptides are involved in different biological processes[5], including cell signaling[6], cell adhesion and cell growth regulation[7]. In a recent investigation, it has been found that natural glycosylated amino acids/peptides are resistant to chemical and enzymatic degradation and do not undergo hydrogen bonding at the former anomeric position[8]. Therefore, a class of modified glycopeptides called neoglycopeptides has emerged[8,9]. Among the several modifications, triazole linked glycopeptides are found to be robust to chemical and enzymatic degradation. They have potential as probes for studying biological activity and as drug candidates for diseases associated with carbohydrate based metabolic disorders.

In the context of triazole linked glycoconjugates, two major forms of triazole linkages have generally been found. C-Linked glycoconjugates[10] synthesized by the cycloaddition of carbohydrate moiety bearing alkyne group at the anomeric center with *N*-protected amino/peptide containing azido moiety (especially in the side chain). And, *N*-linked glycocojugates[11] formed by reversing the orientation of the two functional groups on both the substrates *via* click approach. These two protocols have a wide scope due to substrate availability. Indeed, several kinds of amino acid tethered propargylic units have also been recognized as click substrates to make neoglycopeptides for biological screening. The resulting triazole linked glycopeptides were then coupled with either serine or cystine residues of a peptide[12]. Some of the known neoglycoconjugates are depicted in **Figure 1** (Ref 13). However, the ligation made through click approach was usually of long duration and the preparation of starting materials seemed to be difficult.

In spite of significant progress made towards the synthesis of triazole linked glycopeptides, still there is a need for new type of glycoconjugates as biological targets. Hence herein we report the synthesis of triazole linked glycol peptides through the preparation of amino acid derived triazole acid which is then coupled with amine via appropriate coupling agents. Click ligation of amino acid/peptide with carbohydrate in the main chain provided new entry for glycopeptide chemistry. Our group has synthesized a series of amino alkyl triazole acids using Fmoc chemistry. Further, they have been employed as building blocks for the synthesis of triazole linked peptides[14]. In this present study, Z group was selected in view of its practical utility in solution phase peptide synthesis and thus circumventing the

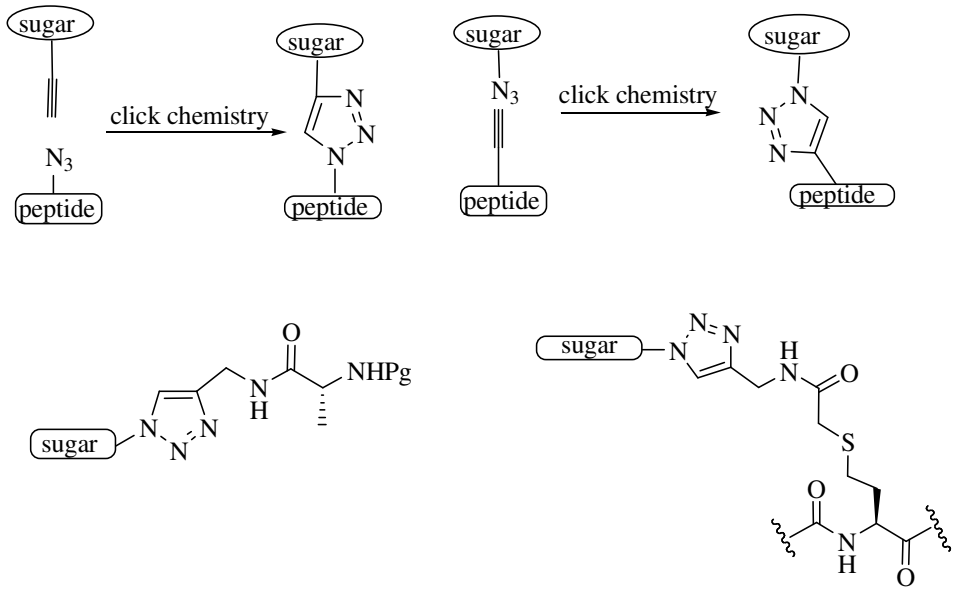
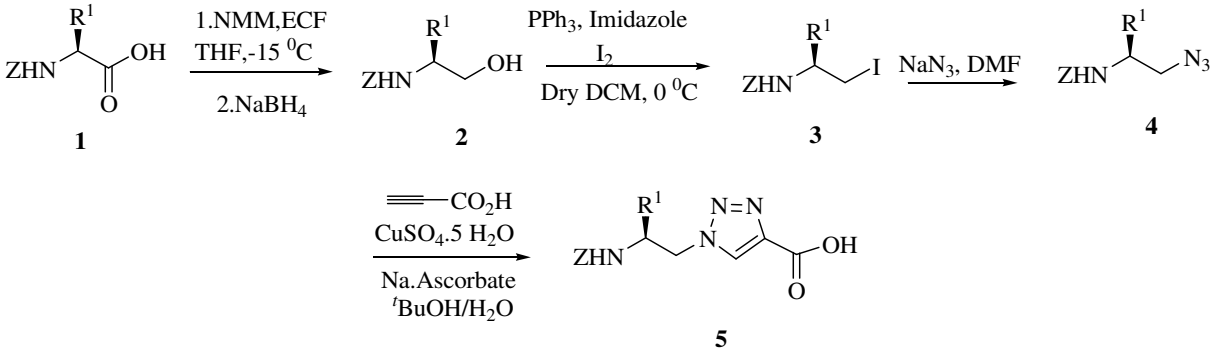


Figure 1 — Various triazole linked neoglycopeptides reported in literature



Scheme I — Synthesis of *N*-Z-amino alkyl triazole acids **5**

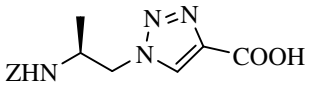
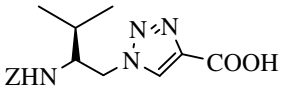
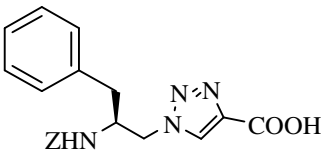
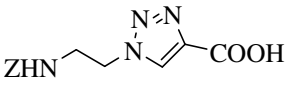
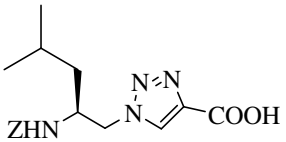
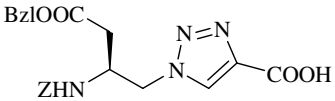
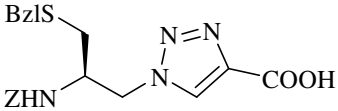
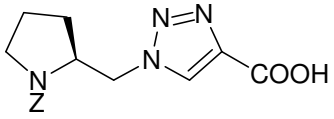
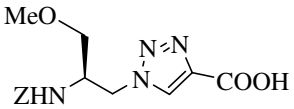
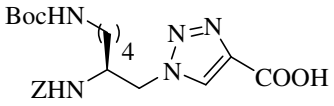
solubility problems associated with Fmoc group. Herein we describe the synthesis of Z-protected amino alkyl triazole acids *via* copper catalyzed azide-alkyne cycloaddition. The resulting products were used as monomers for the synthesis neoglycopeptides and triazole linked peptides. The condensation of carboxylic group next to triazole ring with glycosylamines and amino acid esters proceeded efficiently with 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) as coupling reagent.

Results and Discussion

To execute proposed strategy, *N*-Z-protected aminoalkyl azides were synthesized by employing reported protocol[15]. Initially, *N*-Z-protected amino acids **1** were reduced to corresponding alcohols **2** *via* $NaBH_4$ reduction of corresponding mixed anhydride of the acid. The resulting alcohols were then converted to iodides **3** by treatment with I_2 under Mitsunobu conditions. Latter upon reaction with NaN_3 in DMF afforded azides **4** as white solids in good yields. With the required azides in hand, we then carried out cycloaddition reaction with propiolic acid. In a typical procedure, **4a** was treated with propiolic acid in standard click condition ($CuSO_4.5H_2O$, sodium ascorbate in ^tBuOH/ H_2O, RT). After completion of the reaction, the pure triazole acid **5a** was isolated by the simple acidification of the crude product (**Scheme I**).

Employing the above protocol, a series of Z-amino alkyl triazole acids were synthesized including sterically hindered and bifunctional amino acids such as Pro, Lys(Boc), Ser(O^{t}Bu), Cys(Bzl), and Asp(Bzl) (**Table I**). In all the cases no significant loss of yield

Table I — List of *N*-Z-protected triazole acids

Entry	Triazole acid **5**	Yield (%)	m.p. (°C)
a		88	169-70
b		81	167-68
c		91	173-74
d		86	186-87
e		78	153-54
f		72	140-41
g		74	142-43
h		71	88-89
i		69	130-32
j		67	119-21

and purity were observed. These unnatural amino acids were obtained as solids and can be stored for several days at normal room temperature.

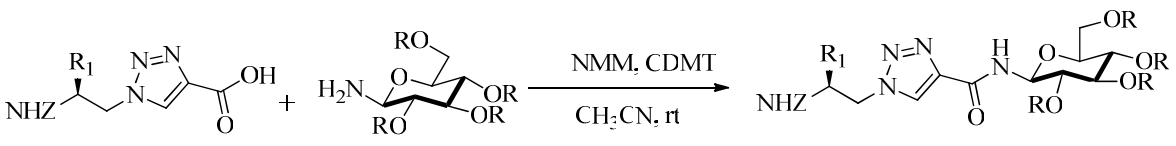
In the next part of the study, we investigated the synthesis of triazole functionalized glycopeptides. A number of coupling reagents were screened in this step by taking **5a** and **6a** (Ref 16) as model substrates (**Scheme II**). Among the reagents utilized (**Table II**), the use of DCC has provided good yield of the product **7a**, however, due to the formation of insoluble byproduct (*N*,*N*-dicyclohexylurea) purification became tedious. Other related carbodimide based reagents EDC and DIC showed less coupling efficiency, consequently less yield of **7a** was recorded after column purification. In the next set of experiments, **5a** and **6a** were coupled using carbonyldiimidazole (CDI) which lead to 67% of **7a**. Nevertheless, long reaction time does not benefit for the general applicability. Finally we employed CDMT as coupling reagent for the synthesis of **7a**.

CDMT was developed over several years ago and has been widely employed for amide bond formation and peptide synthesis[17]. Additionally, the resulting side products can be completely removed by washing with dilute acids which circumvents the need for chromatographic purification of the product. These results encouraged us to use CDMT for the formation of **7a**. Interestingly, the use of CDMT leads to complete consumption of **5a** and **6a.** It was found that the reaction was completed in 3 hr at RT. Simple work-up of the

Table II — Optimization of the coupling reagents and conditions for the synthesis of **7a**

Entry	Coupling conditions[a]	Reaction time (hr)	Yield (%)[b]
1	DCC, HOBt, DMF	6	78
2	EDC, HOBt, CH_2Cl_2	8	66
3	DIC, HOBt, DMF	8	59
4	CDI, TEA, THF	12	67
5	CDMT, NMM, CH_3CN	3	86

[a]All reactions were carried out at rt.
[b]Isolated yields after column chromatography



5 **6** **6a= R= Ac** **6b= R= Bz** **7a-e**

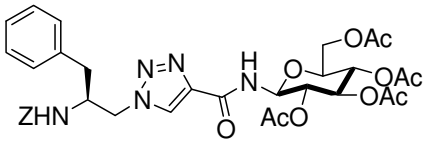
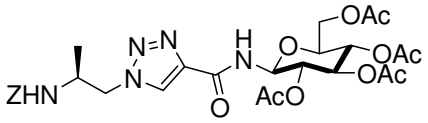
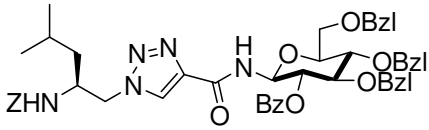
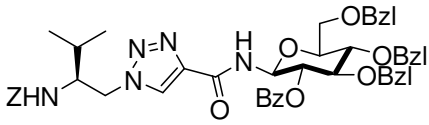
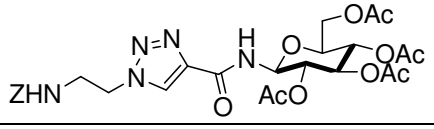
Scheme II — Synthesis of triazole linked glycosyl peptides

crude product using acid and base wash affords **7a** in 86% yield. Thus, the optimized reaction conditions were then used i.e., 1.1 equiv of CDMT (relative to **5**), 1.2 equiv of NMM at rt in CH_3CN for 3 hr.

Then, the optimized reaction conditions were extended to obtain a series of Z-protected triazole acids with glycosyl amines to afford the corresponding triazole linked glycopeptides. All the compounds **7a-e** were obtained in good yields (**Table III**).

Finally, the 1,2,3-triazole based unnatural amino acid **5** was inserted into peptide to afford new class of peptidomimetics. A reaction of **5** with amino acid ester under normal CDMT coupling reaction conditions, the reaction was completed in 4 hr. The resulting dipeptide **8** in good yields (**Scheme III**).

Table III — List of *N*-Z-protected triazole linked glycosylated amino acids

Entry	Compounds (**7a-e**)	Yield (%)
7a		83
7b		85
7c		69
7d		71
7e		75

Experimental Section

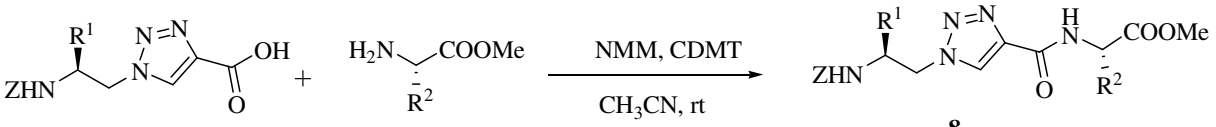
All solvents were freshly distilled before use. Amino acids were used as received from Sigma-Aldrich. Thin-layer chromatographic (TLC) analysis was carried out using the pre coated silica-gel G254 plates. The crude product was purified by column chromatography over silica gel (100-200 mesh). Melting points were determined on a Buchi model 150 melting point apparatus in open capillaries and are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 400 and 75 MHz respectively, with tetramethyl silane (TMS), $CDCl_3$ and DMSO-d_6 as internal standards. Mass spectra were recorded on HRMS.

General procedure for the preparation of *N*-aminoalkyl 1,2,3-triazol acids, 5a-j

To a solution of *N*-Z-aminoalkyl azide **4** (5 mmol) in tert-butanol and water mixture (3:2, 10 mL), propiolic acid (5.1 mmol) was added at RT followed by $CuSO_4.5H_2O$ (0.5 mmol) and sodium ascorbate (0.05 mmol), the reaction was monitored by TLC. After completion of the reaction (4-5 hr), the reaction mixture was acidified with 10% HCl and the precipitated solid was filtered. Washed with water and dried.

General procedure for the preparation of *N*-triazole linked glyco peptides, 7a-e

To a stirred solution of **5** (3 mmol) in ACN, CDMT (3.6 mmol) at 0°C was added NMM (3.3 mmol) dropwise. Subsequently sugar amine (3.3 mmol) was added, after complete conversion of starting components (by TLC analysis), ACN was evaporated and residue was extracted in to EtOAc, and the organic layer was washed with 10% HCl, 5% Na_2CO_3, water and brine. The organic phase was dried over anhydrous Na_2SO_4 and evaporated to afford crude product **7,** which was then subjected to silica gel column chromatography to obtain the pure product.



5 + H_2N–CH(R^2)–COOMe —NMM, CDMT; CH_3CN, rt→ **8**

8a: $R^1 = CH_3$; $R^2 = CH_2CH(CH_3)_2$ (83%)
8b: $R^1 = CH(CH_3)_2$; $R^2 = CH_2C_6H_5$ (89%)
8c: $R^1 = CH_2CH(CH_3)_2$; $R^2 = C_6H_5$ (78%)
8d: $R^1 = CH_2C_6H_5$; $R^2 = CH(CH_3)CH_2CH_3$ (86%)

Scheme III — Synthesis of triazole linked peptidomimetics **8**

General procedure for the preparation of *N*-triazole linked dipeptidomimetics, 8

To a stirred solution of **5** (3 mmol) in ACN, CDMT (3.6 mol) at 0°C was added NMM (3.3 mmol) dropwise. Subsequently amino acid methyl ester (3.3 mmol) was added, after complete conversion of starting components (by TLC analysis) solvent was evaporated and residue was extracted in to EtOAc, and washed with 10% HCl, 5% Na_2CO_3, water and brine. The organic phase was dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to afford product 8 in good yields

Spectral data

Compound 5a: White solid, m.p. 168-70°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.98 (s, 1H), 8.14 (s, 1H), 7.16-7.12 (m, 5H), 6.9 (br, 1H), 4.89 (s, 2H), 4.29 (d, 2H, *J* = 7.1 Hz), 3.9 (m, 1H), 1.06 (d, 3H, *J* = 6.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 166.3, 155.9, 141.3, 139.6, 129.3, 127.6, 127.0, 125.4, 66.5, 60.4, 42.1, 17.6; HRMS: Calcd *m/z* $C_{14}H_{16}N_4O_4$ 304.1172. Found: *m/z* 327.1058 $[M+Na]^+$.

Compound 5b: White solid. m.p. 166-68°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.2 (s, 1H), 8.13 (s, 1H), 7.33-7.05 (m, 5H), 6.59 (br, 1H), 4.96 (s, 2H), 4.21 (d, 2H, *J* = 4.5 Hz), 3.74 (m, 1H), 2.3 (m, 1H), 0.91 (d, 6H, *J* = 3.9 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.1, 156.5, 141.8, 140.6, 129.9, 128.1, 127.4 124.3, 67.3, 57.4, 52.1, 33.6,18.1; HRMS: Calcd *m/z* $C_{16}H_{20}N_4O_4$ 332.1485. Found: *m/z* 355.1386 $[M+Na]^+$.

Compound 5c: White solid. m.p. 172-74°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.56 (s, 1H), 8.2 (s, 1H), 7.33-6.99 (m, 10H), 7.1 (br, 1H), 4.83 (s, 2H), 4.11 (d, 2H, *J* = 5.2 Hz), 4.0 (m, 1H), 2.71 (t, 2H, *J* = 3.6 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.6, 157.9, 141.1, 140.2, 139.0, 128.9, 128.7, 128.4, 127.2, 126.5, 125.1, 66.7, 59.4, 49.1, 39.5; HRMS: Calcd *m/z* $C_{20}H_{20}N_4O_4$ 380.1485. Found: *m/z* 403.1378 $[M+Na]^+$.

Compound 5d: White solid. m.p. 186-88°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.58 (s, 1H), 8.19 (s, 1H), 7.4 (br, 1H), 7.24-7.04 (m, 5H), 4.92 (s, 2H), 4.45 (t, 2H, *J* = 3.5 Hz), 3.42 (t, 2H, *J* = 3.7 Hz), ; ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.9, 156.7, 140.5, 140.0, 128.7, 127.3, 127.0, 126.1, 67.2, 53.1, 39.5; HRMS: Calcd *m/z* $C_{13}H_{14}N_4O_4$ 290.1015. Found: *m/z* 313.1015 $[M+Na]^+$.

Compound 5e: White solid. m.p. 152-54°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.6 (s, 1H), 8.3 (s, 1H), 7.26-7.05 (m, 5H), 7.2 (br, 1H), 4.67 (s, 2H), 4.12 (d, 2H, *J* = 6.8 Hz), 3.76 (m, 1H), 1.96 (m,1H), 1.45 (m, 2H),1.04 (d, 6H, *J* = 6.5 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.1, 156.9, 141.8, 140.5, 129.1, 128.6, 127.5, 126.2, 68.1, 60.9, 44.3, 42.6, 24.1, 22.6; HRMS: Calcd *m/z* $C_{17}H_{22}N_4O_4$ 346.1641. Found: *m/z* 369.1547 $[M+Na]^+$.

Compound 5f: White solid. m.p. 139-41°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.93 (s, 1H), 8.26 (s, 1H), 7.26-7.12 (m, 10H), 7.1 (br, 1H), 5.15 (s, 2H), 4.75 (s, 2H), 4.3 (m, 1H), 4.09 (d, 2H, *J* = 7.1 Hz), 2.7 (d, 2H, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 177.9,166.7, 156.1,141.3, 140.7, 140.1,129.6, 128.7, 128.3 127.7, 127.5,127.1, 125.4, 69.3, 66.1, 59.4, 42.9, 40.1; HRMS: Calcd *m/z* $C_{22}H_{22}N_4O_6$ 438.1539. Found *m/z* 461.1442 $[M+Na]^+$.

Compound 5g: White solid. m.p. 141-43°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.86 (s, 1H), 8.17 (s, 1H), 7.23-7.09 (m, 10H), 6.92 (br, 1H), 5.27 (s, 2H), 4.89 (s, 2H), 3.96 (d, 2H, *J* = 6.8 Hz), 3.76 (m, 1H), 2.82 (d, 2H, *J* = 6.3 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 178.3,167.2, 156.8,141.5, 141.1, 140.7,128.9, 128.3, 128.0 127.8, 127.3,127.0, 126.1, 68.4, 67.5, 58.1, 45.8, 32.3; HRMS: Calcd *m/z* $C_{21}H_{22}N_4O_4S$ 426.1362. Found: *m/z* 449.1253 $[M+Na]^+$.

Compound 5h: White solid. m.p. 88-90°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.2 (s, 1H), 8.16 (s, 1H), 7.38-7.26(m, 5H), 5.18 (s, 2H), 4.52 (d, 2H, *J* = 6.8 Hz), 3.4 (t, 2H, *J* = 4.9 Hz), 3.26 (m, 1H), 1.96(m, 2H), 1.78 (m,2H) ; ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.3, 156.9, 141.5, 140.8, 128.9, 128.1, 127.5, 125.4, 68.2, 55.7, 51.6, 49.6, 31.1, 30.5; HRMS: Calcd *m/z* $C_{16}H_{18}N_4O_4$ 330.1328. Found: *m/z* 353.1218 $[M+Na]^+$.

Compound 5i: White solid. m.p. 130-32°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.8 (s, 1H), 8.43 (s, 1H), 7.5 (br, 1H), 7.13 (s, 5H), 5.17 (s, 2H), 3.18 (s, 3H), 4.01 (m, 1H), 3.81 (d, 2H, *J* = 5.8 Hz),3.63 (d, 2H, *J* = 5.4 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 166.7, 156.1, 141.3, 140.8, 129.5, 127.3, 126.9, 125.6, 73.1, 66.3, 60.4, 55.1, 46.3; HRMS: Calcd *m/z* $C_{15}H_{18}N_4O_5$ 334.1277. Found: *m/z* 357.1163 $[M+Na]^+$.

Compound 5j: White solid. m.p. 119-21°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.89 (s, 1H), 8.25 (s, 1H), 7.43 (br, 1H), 7.3 (br, 1H), 7.15 (s, 5H), 5.25 (s, 2H), 3.72 (d, 2H, *J* = 6.1 Hz), 3.52 (m, 1H), 3.11 (t, 2H, *J* = 3.2 Hz), 1.50-1.53 (m, 4H), 1.35 (s, 9H), 1.23 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.9, 156.8, 155.7, 141.2, 140.8, 129.3, 128.1, 127.4, 124.9, 80.1, 66.3, 57.5, 45.9, 42.1, 32.3, 29.7, 28.8, 20.9; HRMS: Calcd *m/z* $C_{22}H_{31}N_5O_6$ 461.2274. Found: *m/z* 484.2163 $[M+Na]^+$.

Compound 7a: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35 (s, 1H), 7.91 (br, 2H), 7.13-7.25 (m, 10 H), 6.38

(m, 1H), 5.42 (s, 2H), 5.37 (m, 1H), 5.25 (m, 1H), 4.7 (m, 2H), 4.12 (d, 2H, *J* = 4.9 Hz), 3.97 (m, 1H), 3.72 (d, 2H, *J* = 5.6 Hz), 2.13 (d, 2H, *J* = 6.1 Hz), 1.95 (s, 12H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 171.4, 159.6, 155.3, 142.9, 142.0, 139.1,133.2, 129.2, 128.8, 127.8, 127.1, 126.5, 125.8, 79.3, 76.1, 73.7, 69.6, 68.5, 67.3, 58.9, 57.3, 47.4, 39.2, 21.4, 20.3; HRMS: Calcd *m/z* $C_{34}H_{39}N_5O_{12}$ 709.2595. Found: *m/z* 732.251 $[M+Na]^+$.

Compound 7b: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.12 (s, 1H), 7.62 (br, 2H), 7.21 (s, 5H), 6.15 (m, 1H), 5.41 (s, 2H), 5.27 (m, 1H), 5.18 (m, 1H), 4.5 (m, 1H), 4.32 (m, 1H), 4.21 (m, 1H), 3.92 (d, 2H), 3.71 (m, 1H), 2.1 (s, 12H), 1.25 (d, 3H, *J* = 4.5 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.5, 161.2, 155.4, 143.2, 141.8, 132.3, 128.9, 127.3, 126.8, 79.5, 76.1, 73.4, 68.7, 67.1, 66.3, 60.4, 59.3, 42.3, 20.8, 17.3; HRMS: Calcd *m/z* $C_{26}H_{35}N_5O_{12}$ 633.2282. Found: *m/z* 656.223 $[M+Na]^+$.

Compound 7c: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.42 (s, 1H), 7.5 (br, 2H), 7.35-7.43 (m, 20H), 7.15 (s, 5H), 6.13 (m, 1H), 5.43 (s, 2H), 5.27 (m, 2H), 4.81 (m, 1H), 4.7 (m, 1H), 4.21 (d, 2H), 3.91 (d, 2H), 3.43 (m, 1H), 1.74 (m, 1H), 1.43 (m, 2H), 1.14 (d, 6H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.9, 161.2, 156.2, 133.7, 132.3, 130.1, 129.3, 128.9, 128.7, 127.5, 126.9, 77.3, 76.7, 71.0, 67.4, 66.3, 64.7, 58.3, 57.9, 43.1, 42.3, 22.6, 21.3; HRMS: Calcd *m/z* $C_{51}H_{49}N_5O_{12}$ 923.3378. Found: *m/z* 946.3271 $[M+Na]^+$.

Compound 7d: ^{1}H NMR (400 MHz, DMSO-d_6): *δ* 8.5 (s, 1H), 7.91 (br, 2H), 7.2-7.43 (m, 20H), 7.123 (s, 5H), 5.25 (m, 2H), 4.8 (m, 1H), 4.51 (m, 1H), 4.32 (d, 2H, *J* = 6.2 Hz), 3.9 (d, 2H, *J* = 5.6 Hz), 3.32 (m, 2H), 2.49 (m, 1H), 1.2 (d, 6H, *J* = 4.8 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.9, 159.3, 155.5, 143.9, 141.5, 133.7, 131.3, 130.0, 129.7, 129.2, 128.3, 127.1, 126.3, 79.0, 75.3, 72.9, 67.2, 66.4, 63.4, 60.1, 56.3, 53.4, 30.3, 16.9; HRMS: Calcd *m/z* $C_{50}H_{47}N_5O_{12}$ 909.3221. Found: *m/z* 932.32$[M+Na]^+$.

Compound 7e: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.34 (s, 1H), 7.4 (br, 2H), 7.2 (s, 5H), 6.3 (m, 1H), 5.41 (s, 2H), 5.23 (m, 1H), 5.15 (m, 1H), 4.68 (m, 1H), 4.53 (m, 1H), 4.21 (d, 2H), 3.8 (d, 2H), 3.41 (m, 2H), 2.05 (s, 12H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.3, 161.2, 156.2, 143.4, 141.3, 132.0, 128.7, 127.3, 126.8, 79.6, 76.1, 73.3, 49.8, 36.3, 21.1; HRMS: Calcd *m/z* $C_{27}H_{33}N_5O_{12}$ 619.2126. Found: *m/z* 642.2011$[M+Na]^+$.

Compound 8a: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H), 7.27 (br, 1H), 7.2 (s, 5H), 6.53 (br, 1H), 5.21 (s, 2H), 4.5 (t, 1H, *J* = 5.2 Hz), 3.9 (d, 2H. *J* = 6.8 Hz), 3.71 (m, 1H), 3.53 (s, 3H), 1.82 (m, 2H), 1.75 (m, 1H), 1.23 (d, 3H, *J* = 7.2 Hz), 1.08 (d, 6H, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8, 161.0, 156.4, 143.1, 140.7, 131.2, 128.4, 127.2, 126.3, 63.1, 61.3, 50.1, 48.3, 42.7, 41.2, 22.7, 21.3, 17.6; HRMS: Calcd *m/z* $C_{21}H_{29}N_5O_5$ 431.2169. Found *m/z* 454.2052$[M+Na]^+$.

Compound 8b: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (s, 1H), 7.3 (br, 1H), 7.15-7.21 (m, 10H), 5.27 (s, 2H), 4.53 (t, 1H, *J* = 5.0 Hz), 3.54 (s, 3H), 3.41-3.48 (m, 5H), 2.32 (m, 1H), 1.03 (d, 6H, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.1, 159.4, 156.1, 142.7, 141.5, 130.3, 129.4, 128.3, 127.9, 127.4, 126.3, 125.8, 66.1, 54.4, 53.1, 52.3, 52.0, 36.1, 30.7, 17.5; HRMS: Calcd *m/z* $C_{26}H_{31}N_5O_5$ 493.2325. Found: *m/z* 516.2231$[M+Na]^+$.

Compound 8c: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (s, 1H), 7.25 (br, 1H), 7.12-7.2 (m, 10H), 6.34 (br, 1H), 5.62 (s, 2H), 5.25 (s, 2H), 3.73 (m, 2H), 3.57 (s, 3H), 1.74 (m, 2H), 1.31 (m, 1H), 1.08 (d, 6H, *J* = 7.2 Hz); ^{13}CNMR (75 MHz, $CDCl_3$): δ 170.8, 161.3, 156.7, 142.1, 141.7, 134.3, 132.5, 129.9, 129.4, 129.0, 128.1, 127.8, 127.1, 66.1, 56.9, 54.8, 52.3, 42.6, 40.3, 22.7, 21.5; HRMS: Calcd *m/z* $C_{26}H_{31}N_5O_5$ 493.2325. Found: *m/z* 516.2229$[M+Na]^+$.

Compound 8d: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (s, 1H), 7.45 (br, 1H), 7.14-7.23 (m, 10H), 6.3 (br, 1H), 5.21 (s, 2H), 4.34 (d, 1H, *J* = 6.2 Hz), 4.12 (m, 2H), 3.57 (s, 3H), 2.83 (m, 3H), 1.23 (m, 2H), 1.1 (d, 3H, *J* = 6.8 Hz), 0.95 (t, 3H, *J* = 5.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 161.3, 156.7, 142.9, 141.5, 137.4, 130.8, 129.4, 128.8, 128.1, 127.4, 127.0, 126.4, 64.8, 57.9, 51.1, 50.3, 47.1, 41.8, 34.7, 24.2, 15.6, 11.7; HRMS: Calcd *m/z* $C_{27}H_{33}N_5O_5$ 507.2482. Found: *m/z* 530.2381$[M+Na]^+$.

Conclusion

In conclusion, Z-protected triazole amino acids were synthesized employing click chemistry. These unnatural amino acids were used as building blocks to functionalize the dipeptides and glycopeptide bond with triazole tethered unit. The use of CDMT as coupling reagent affords glycosylated amino acids in excellent yield and purity.

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