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Clickable Glycopeptoids for Synthesis of Glycopeptide Mimic

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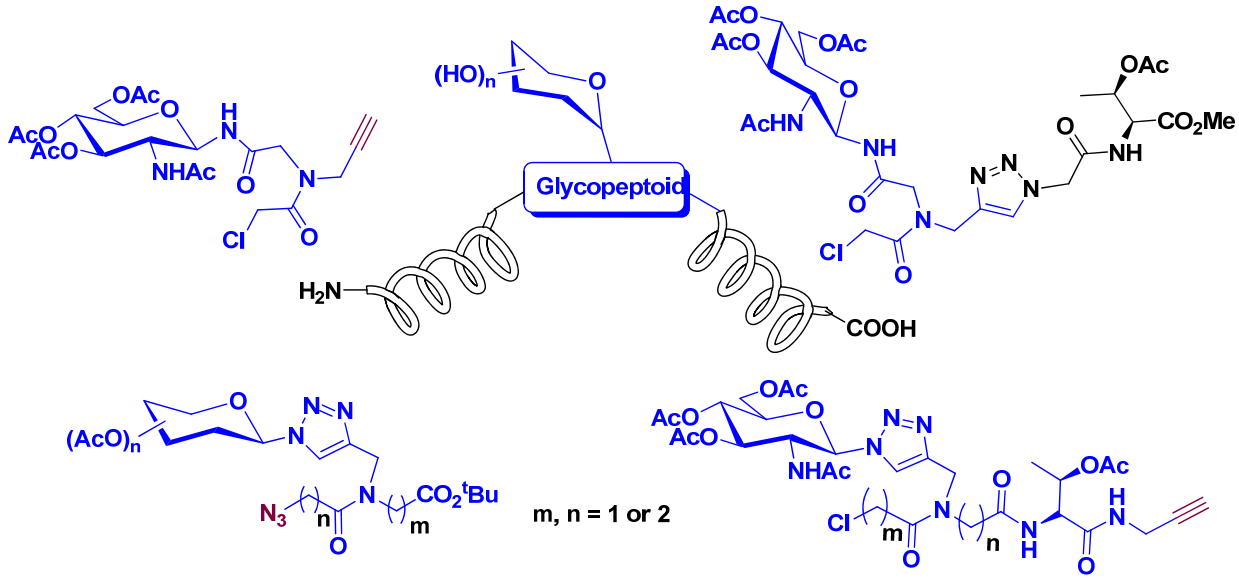
[ł] Deceased on 9th February, 2013



Abstract

Structurally diverse novel glycopeptoids were synthesized which can be attached to biologically important peptides by *click reaction* to improve their potential to be used in medicinal chemistry. Triazole linked αβ-hydrid glycopeptoids were synthesized which mimic the conserved linkage region of *N*-linked glycoproteins in eukaryotes. The amide bonds were replaced with triazole rings and αβ-hybrid peptoids were introduced as the backbone modification in peptidomimetic. In addition to their facile synthesis, these modifications has the possibility to introduce otherwise impossible conformations in the peptide backbone.

Introduction

Diversely functionalized bio-molecules with higher conformational flexibility for the synthesis of bio-inspired synthetic polymers and macromolecules have developed as a useful tool in chemical biology. Glycosylation is the most significant post-translational modification of proteins, playing vital roles in cell-cell recognition, cell growth regulation, cell differentiation, immunological response, metastasis, and bacterial and viral infections. Being secondary gene products and due to their template independent bio-synthesis, glycoproteins are micro-heterogeneous in nature. The glycan part of *N*-linked glycoptroteins controls not only the biological function of the proteins but also their physical attributes e.g. solubility, conformation and folding.[1-5] To understand the structure activity relation of *N*-linked glycoprotein and to utilize it for bio-medical application is a challenging problem in glycobiology. It is difficult to extract glycopeptides from natural sources with significant quantity and sufficient purity for practical applications. In addition to that, their low bioavailability and poor proteolytic stability have hindered the potential application of these bio-molecules in medicinal chemistry. Synthesis of glycopeptide mimics is an alternative approach in this regard. In the last couple of decades, peptoids have emerged as a major class of backbone modified peptide mimic[6-10] and also have been used in the area of glycopeptide mimetics.[11-19] These bio-inspired synthetic compounds are basically oligo(*N*-substituted glycines), with almost limitless structural diversity and relatively easy synthesis. The enhanced proteolytic stability, increased cellular permeability and higher conformational flexibility compared to natural peptides make this class of molecules potentially useful for medical application. Unlike natural peptides which mainly exist in trans amide conformation, these peptoid molecules are facilitated with free rotation around the amide bonds.[20] In case of β-peptoid, the addition of extra methylene group introduces additional torsion angle (θ) in the peptoid backbone[21] (Figure 1).

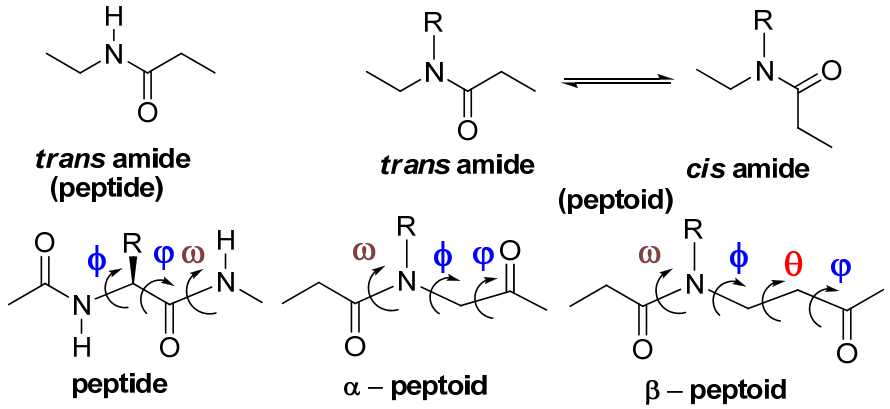


Figure 1 Comparative conformation of peptide, α-peptoid and β peptoid

In the literature of synthetic peptides and glycopeptide mimetic, triazole rings are frequently used as the replacement of the trans amide bonds not only because of their facile synthesis by *click* reaction but also their similarity in structure, polarity and the ability to compensate the hydrogen bonding of amide bonds to some extent.[22-25] Selective and systematic substitution of natural amide bonds with triazole rings in synthetic *N*-linked glycopeptoids will introduce not only structural diversity but also improve their proteolytic stability for bio-medical application. In this present work, a series of triazole linked **αβ**-hybrid glycopeptoids were synthesized with systematic variation of the peptoid and the glycan part (Figure 2). These peptoid building blocks (**1a-4c**) can be used for synthesis of larger peptides or incorporated in natural peptides.

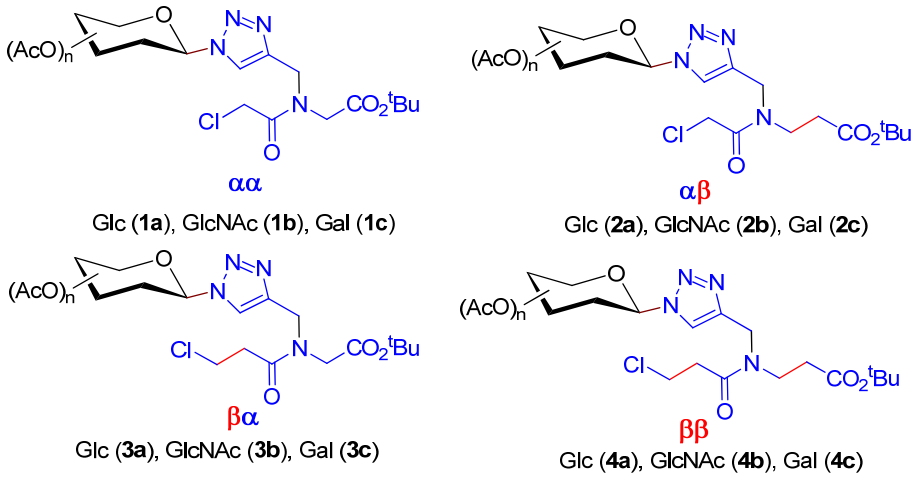
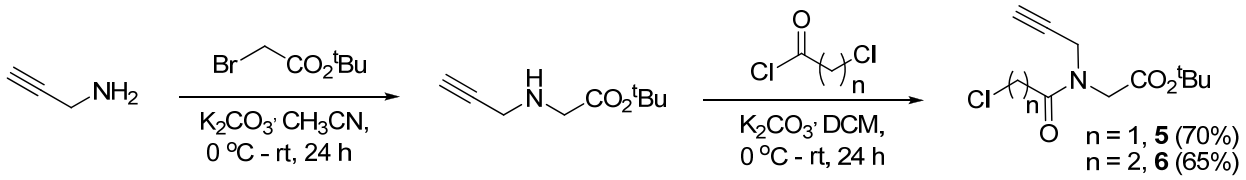


Figure 2 Triazole linked hybrid glycopeptoid building blocks

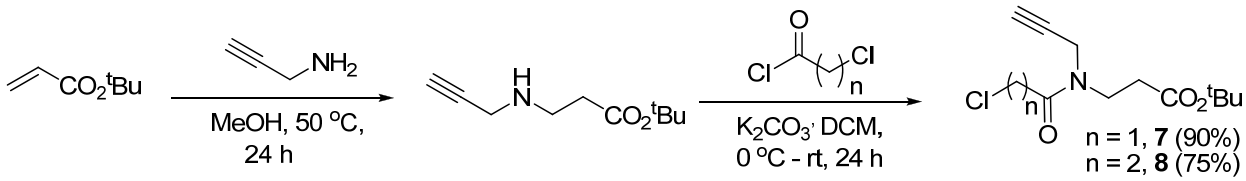
Results and discussion

For the synthesis of triazole linked αβ-hybrid glycopeptoids (Figure 2), we started with the synthesis of *N*-propargylated peptoid based starting materials (**5-8**). Propargyl amine was alkylated using *tert*-butyl bromoacetate (1 equiv.) in presence of K_2CO_3 (2 equiv.) as the base. The resulting mixture of mono and dialkylated amines were reacted with chloroacetyl chloride (1.2 equiv.) using K_2CO_3 (2 equiv.) as the base (Scheme 1). Column purification of the crude reaction mixture gave the desired product *N*-propargylated αα-peptoid building block (**5**) in 70% overall yield in two steps.



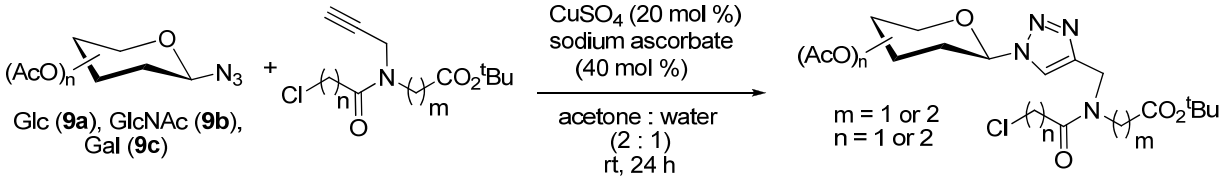
Scheme 1 Synthesis of *N*-propargylated αα- and βα-peptoid building block

N-propargylated βα-peptoid building block (**6**) was synthesized in 65% yield (in 2 steps) using the same methodology as that of **5**, except for using 2-chloropropionyl chloride (1.2 equiv.) in place of chloroacetyl chloride. *N*-propargylated αβ-peptoid building block (**7**) was synthesized in 90% overall yield by Michael addition of propargyl amine (1.5 equiv.) to *tert*-butyl acrylate (1 equiv.) followed by reaction of the resulting secondary amine with chloroacetyl chloride (1.1 equiv.) in presence of K_2CO_3 (2 equiv.) as the base (Scheme 2). Replacing chloroacetyl chloride with 2-chloropropionyl chloride (1.1 equiv.) resulted in the formation of *N*-propargylated ββ-peptoid building block (**8**) in 75% overall yield in two steps.



Scheme 2 Synthesis *N*-propargylated αβ- and ββ-peptoid building block

All the *N*-propargylated αβ-hybrid building blocks (**5**-**8**) exist as mixture of *cis* and *trans* isomers in 1: 1 ratio as calculated from the integration of the protons in ^{1}H NMR spectra. For the synthesis of triazole-linked glycopeptoids, per-*O*-acetylated glycopyranosyl azides[26] derived from D-glucose (**9a**), 2-acetamido-2-deoxy-D-glucose (**9b**) and D-galactose (**9c**) were used for *click* reaction with *N*-propargylated hybrid peptoid building blocks (**5**-**8**). Per-*O*-acetylated β-D-glucopyranosyl azide (**9a**) was reacted with *N*-propargylated αα-peptoid building block (**5**) in presence of Cu(I) as the catalyst which was generated *in situ* by the reaction of copper sulfate (20 mol%) and sodium ascorbate (40 mol%) (Scheme 3). Triazole-linked αα-glycopeptoid (**1a**) was obtained in 80% yield after column purification. In the ^{1}H NMR spectrum of compound **1a,** all the peaks corresponding to each protons appeared as two peaks or broad peaks due to presence of rotamers resulting from the rotation of *N*-alkylated amide bonds. The trizole proton appeared as two singlets at 7.87 and 7.86 ppm with integral ratio of 1: 1.4 in 400 MHz ^{1}H NMR spectrum recorded in $CDCl_3$ at 298K. The C4 carbon of the triazole ring appeared as two signals at 143.8 and 143.7 ppm and the C5 carbon at 122.2 and 121.1 ppm in 100 MHz ^{13}C NMR which confirmed the formation of the 1,4-triazole ring. The formation of the desired compound was further confirmed from the presence of molecular ion peak at 619.2037 in the ESI-MS HRMS spectrum.

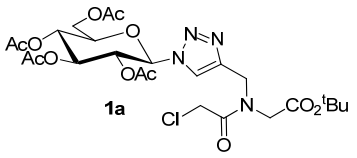
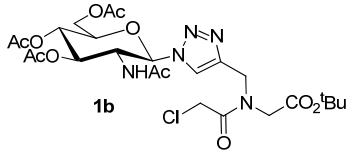
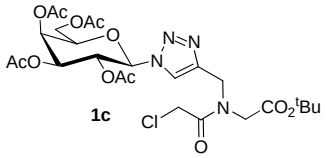
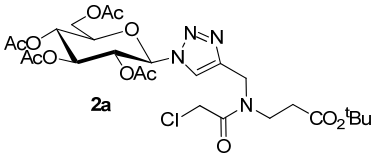
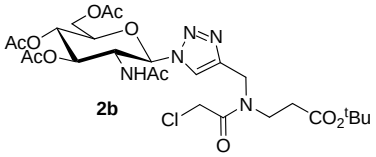
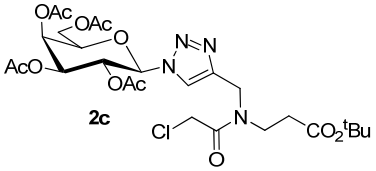
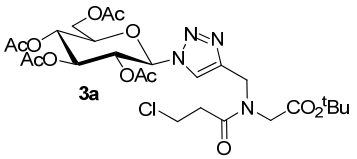
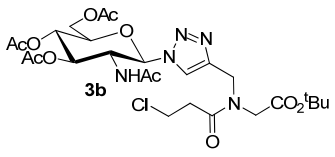


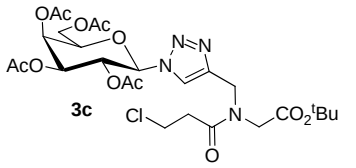
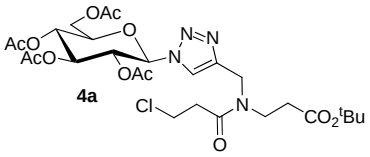
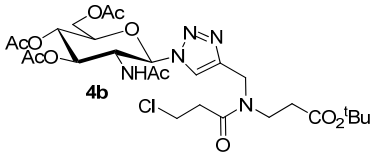
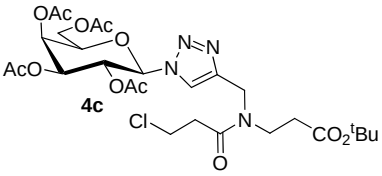
Scheme 3 Synthesis triazole linked αβ-hybrid glycopeptoid building blocks

With systematic variation in the glycan part and the aglycan part a series of triazole linked glycopeptoids (Table 1) were synthesized by Cu(I) catalyzed *click* reaction of per-*O*-acetylated β-D-glycopyranosyl azides (**9a**, **9b** and **9c**) and *N*-propargylated hybrid building blocks (**5**-**8**). For the αα-glycopeptoid derived from D-GlcNAc the triazole proton appeared as a singlet at 7.94 ppm in the 400

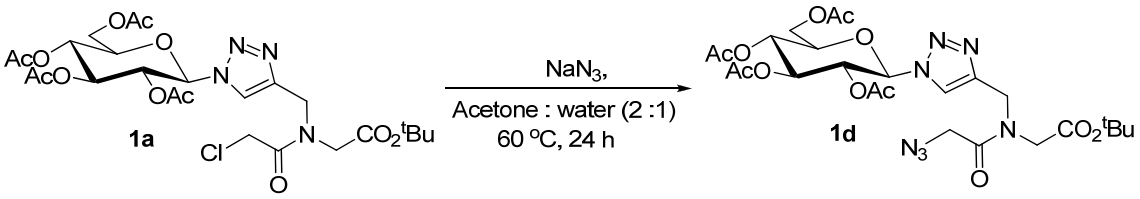
MHz ^{1}H NMR spectrum recorded in $CDCl_3$ at 298K. The C4 carbon of the triazole ring appeared as two signals at 143.4 and 143.2 ppm in 100 MHz ^{13}C NMR spectrum. Two signals at 122.9 and 121.8 ppm in the ^{13}C NMR spectrum of the same compound were assigned as peaks corresponding to the C5 carbon of the triazole ring. In case of D-galactose derived αα-glycopeptoid (**1c)** the triazole proton appeared as two singlets at 7.90 and 7.88 ppm with integral ratio of 3:2.

Table 1 Synthesis of triazole linked αβ-hybrid glycopeptoid

Sl. No.	Azide	Alkyne	Product	Yield (%)
1.	**9a**	**5**	 **1a**	80
2.	**9b**	**5**	 **1b**	90
3.	**9c**	**5**	 **1c**	82
4.	**9a**	**7**	 **2a**	94
5.	**9b**	**7**	 **2b**	95
6.	**9c**	**7**	 **2c**	95
7.	**9a**	**6**	 **3a**	95
8.	**9b**	**6**	 **3b**	85

9.	**9c**	**6**	 **3c**	90
10.	**9a**	**8**	 **4a**	98
11.	**9b**	**8**	 **4b**	90
12.	**9c**	**8**	 **4c**	95

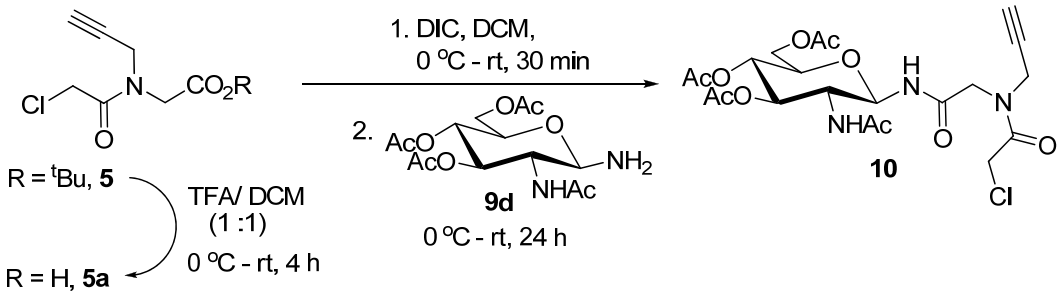
The triazole protons appeared as two signals in the ^{1}H NMR spectra and the C5 and C4 carbon of the triazole rings gave two signals each in the ^{13}C NMR spectrum except in case of peptoid derived from D-GlcNAc **1b**. The variation in the ratio of integrals of the two peaks corresponding to the triazole protons in the glycopeptoids (**1a-4c**) reflects the conformational heterogeneity in the molecules with variation in both the glycan and aglycan parts. The chloroacetamide derivative **1a** was converted to azidoacetamide (**1d**) by reaction with sodium azide in a mixture of acetone and water (2: 1) at 60 °C (scheme 4).



Scheme 4 Synthesis of azide functionalized triazole linked αα-glycopeptoid

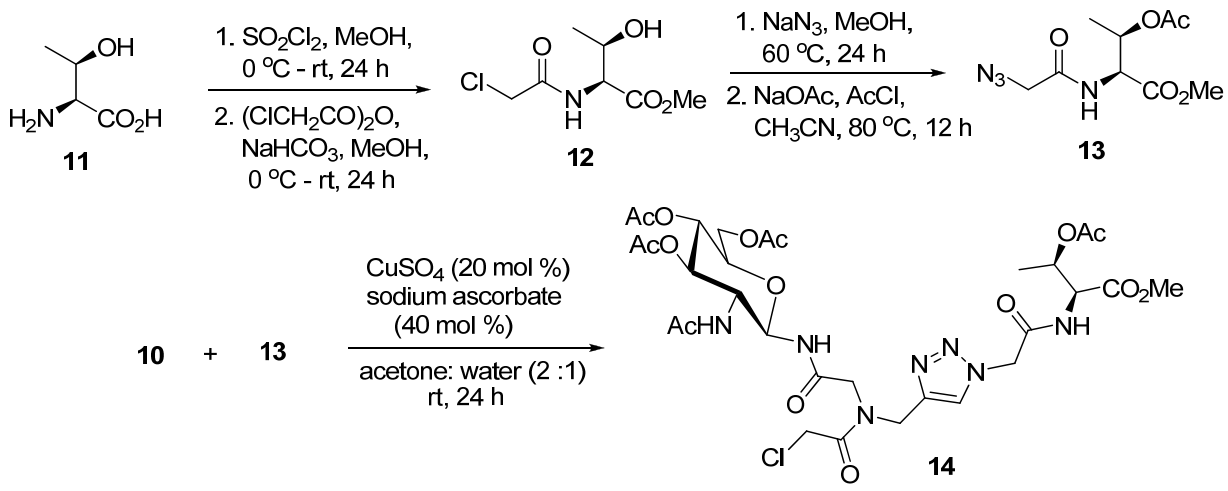
The linkage region of *N*-linked glycoproteins is conserved as **-(D-GlcNAc)-Asn-Xaa-Ser/Thr-** (Xaa = any amino acid other than proline) in all the eukaryotic cells. After synthesis of the triazole linked hybrid glycopeptoids, amide linked *N*-propargylated glycopeptoid (**10**) was synthesized as a mimic of the GlcNAc-Asn linkage region which can be used for the synthesis of triazole linked large

glycopeptide mimic. The synthesis started with selective deprotection of the *tert*-butyl ester of compound **5,** followed by activation of the resultant free acid group using diisopropylcarbodiimide (DIC). The DIC activated acid (**5a**) was reacted with per-*O*-acetylated 2-acetamido-2-deoxy-β-D-glucopyranosyl amine which was obtained by catalytic hydrogenation of the corresponding azide using Pd/C in H_2 atmosphere (Scheme 5).[26] Compound **10** was obtained in 70% yield after purification using column chromatography. The alkyne protons of the *N*-propargyl group appeared as two singlets at 2.45 and 2.35 ppm with integral ratio of 4 : 1 in 400 MHz ^{1}H NMR, attributed to presence of rotamers in the compound.



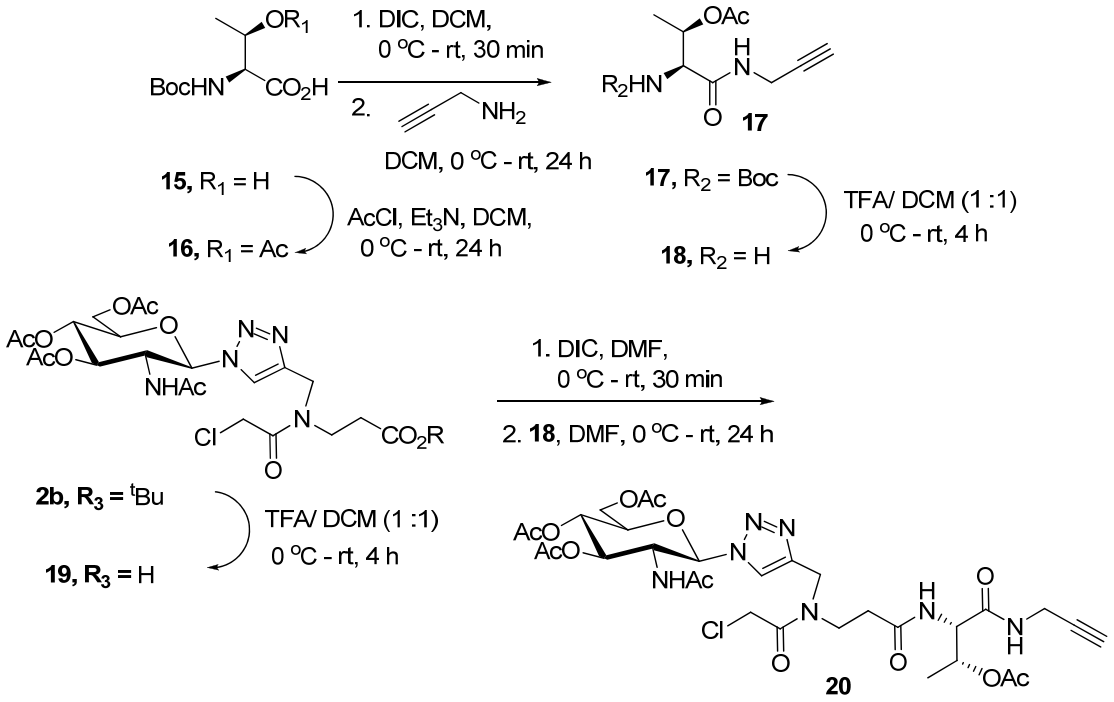
Scheme 5 Synthesis *N*-propargylated **GlcNAc-Asn** mimic

To extend the peptoid chain by click reaction *N*-azidoacetamide functionalized L-threonine derivative (**13**) was synthesized by protecting the the acid group of L-threonine (**11**) as methyl ester followed by selective chloroacylation of the amine using chloroacetic anhydride. The free hydroxyl group of compound **12** was protected as acetate following the conversion of the chloroacetamide to azidoacetamide (Scheme 6). Compound **13** was obtained in 50% overall yield starting from L-threonine (**11**). The azidoacetamide **13** was reacted with *N*-propargylated glycopeptoid **10** in presence of Cu(I) as catalyst (Scheme 6). The desired glycotripeptoid **14** was obtained in 80% yield after column purification.



Scheme 6 Synthesis of triazole linked glycotripeptide mimic

To extend the use of glycopeptoid for the synthesis of glycopeptide mimic with unlimited size, alkyne functionalized mimic (**20**) of the conserved linkage region in *N*-linked glycotripeptide (**-GlcNAc-β-Asn-Xaa-Ser/Thr-**) was synthesized starting from **αβ**-glycopeptoid **2b**. Alkyne functionalized L-threonine derivative **17** was synthesized starting from commercially available *N*-Boc protected L-threonine (**15**) by acetylation of the secondary hydroxyl group followed by reaction of the free acid with propargyl amine after activation using DIC (Scheme 7). Compound **17** was obtained in 70% overall yield in two steps after purification using column chromatography. The *N*-Boc protection of compound **17** and the *tert*-butyl ester protection of compound **2b** were removed using mixture of TFA and DCM (1:1). The acid group of compound **19** was activated using DIC and reacted with the amine **18** to give the desired peptoid **20** in 65% yield after column purification (Scheme 7).



Scheme 7 Synthesis of alkyne functionalized glycotripeptide mimic

In conclusion, a series of glycopeptoids were synthesized with systematic variation in the glycan and aglycan parts. The NMR spectra of all the compounds showed conformational heterogeneity in solution as observed from the presence of two peaks or broad peaks for each protons and carbons in their ^{1}H and ^{13}C NMR which can be attributed to the presence of rotamers due to rotation around the *N*-alkylated amide bonds. Alkyne functionalized glycopeptoid **10** was synthesized which was used for the synthesis of peptoid based mimic (**17**) of the conserved glycotripeptide linkage region of all eukaryotes. As a representative example for the application of triazole linked **αβ**-hybrid glycopeptoids (**1a-4c**), alkyne functionalized glycotripeptoid **20** was synthesized from glycopeptoid **1b**. The alkyne functionalized glycopeptoids **10** and glycotripeptoid **20** are *just a click away* from the synthesis of glycopeptide mimic with unlimited size by *click* reaction with azide functionalized peptide. The incorporation of these glycopeptoid in natural peptides will introduce higher flexibility with unnatural conformational, improved proteolytic stability and greater scope for therapeutic application.

Experimental Section

General Information: All the solvents were used after distillation and dry solvents were prepared using standard methods. All reagents purchased from commercial sources were used without any purification. ^{1}H and ^{13}C NMR spectra were recorded on 400 MHz NMR spectrometer. The assignment of ^{1}H NMR spectra was done with the help of ^{1}H-^{1}H COSY spectra. All mass spectra were recorded in Q-TOF electrospray ionization spectrometer. Column chromatography was performed over 100-200 mesh silica with ethyl acetate and hexane as the eluent.

1. Synthesis of *N*-propargylated αα-peptoid building block (5)

Propargyl amine (0.2 mL, 3.1 mmol) was added to a suspension of K_2CO_3 (850 mg, 6.2 mmol) in dry acetonitrile (5 mL) at 0 °C. To this mixture *tert*-butyl bromoacetate (0.5 mL, 3.3 mmol) was added drop by drop at 0 °C. Stirring was continued for 24 h allowing the mixture to come to room temperature. Excess reagents and solvents were removed by applying vacuum. The reaction mixture was dissolved in dry dichloromethane (10 mL) and cooled to 0 °C. Then chloroacetyl chloride (0.3 mL, 3.7 mmol) was added drop by drop and the reaction mixture was stirred for 24 h allowing it to come to room temperature. After completion of the reaction, the reaction mixture was filtered and washed with dichloromethane (10 mL x 2). The combined filtrate was concentrated to dryness and the crude reaction mixture, thus obtained, was purified by column chromatography to give the title compound as syrup.

Yield 70% (540 mg), ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.32 (d, 1H, J = 2.4 Hz, -C$\underline{H}_2$-), 4.24 (d, 1H, J = 2.4 Hz, -C$\underline{H}_2$-), 4.21 (s, 1H, -C$\underline{H}_2$-), 4.17 (s, 1H, -C$\underline{H}_2$-), 4.13 (s, 1H, -C$\underline{H}_2$-), 4.05 (s, 1H, -C$\underline{H}_2$-), 2.42 (t, 0.5H, J = 2.4 Hz, C$\underline{H}$), 2.31 (t, 0.5H, J = 2.4 Hz, C$\underline{H}$), 1.49, 1.46 (2s, 9H, -C(C$\underline{H}_3$)$_3$) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 167.5, 166.5, 166.4 , 83.0, 82.3, 74.0, 73.5, 48.9, 47.7, 40.9, 40.8, 38.5, 36.1, 28.0, 27.9 ppm; ESI-MS HRMS Calculated for $C_{11}H_{17}NO_3Cl$ ($[M+H]^+$): 246.0897; found 246.0900.

2. Synthesis of *N*-propargylated βα-peptoid building block (6)

Following the same procedure as for *N*-propargylated αα-peptoid building block except for using 2-chloropropionyl chloride in place of chloroacetyl chloride.

Yield 65% (520 mg), ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.31 (d, 1H, J = 2.0 Hz, C$\underline{H}_2$), 4.15 (d, 1H, J = 2.0 Hz, C$\underline{H}_2$), 4.12 (s, 1H, C$\underline{H}_2$), 4.09 (s, 1H, C$\underline{H}_2$), 3.82 (q, 2H, C$\underline{H}_2$), 2.95 (t, 1H, J = 5.6 Hz, C$\underline{H}_2$), 2.73 (t, 1H, J = 5.6 Hz, C$\underline{H}_2$), 2.37 (t, 0.5H, J = 2.0 Hz, C$\underline{H}$), 2.27 (t, 0.5H, J = 2.0 Hz, C$\underline{H}$), 1.49, 1.46 (2 x s, 9 H, -C(C$\underline{H}_3$)$_3$) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 169.9, 168.2, 167.8, 83.1, 82.3, 78.2, 77.5, 73.6, 73.1, 48.9, 47.5, 39.5, 39.4, 38.2, 36.3, 36.2, 35.6, 28.2, 28.1 ppm; ESI-MS HRMS Calculated for $C_{12}H_{19}NO_3Cl$ ($[M+H]^+$): 260.1053; found 260.1041.

3. Synthesis of *N*-propargylated αβ-peptoid building block (7)

Propargyl amine (0.3 mL, 4.6 mmol) was added to a solution of *tert*-butyl acrylate (0.5 mL, 3.4 mmol) in dry methanol (10 mL) at room temperature. The mixture was stirred at 50 °C for 24 h. Then excess reagents and solvents were removed by applying vacuum. The reaction mixture was dissolved in dry dichloromethane (10 mL) and added to K_2CO_3 (940 mg, 6.8 mmol) at 0 °C. To this reaction mixture at 0 °C chloroacetyl chloride (0.3 mL, 3.7 mmol) was added drop by drop. The reaction mixture was stirred for 24 h allowing it to come to room temperature. After completion of the reaction, the reaction mixture was filtered and washed with dichloromethane (10 mL x 2). The combined filtrate was concentrated to dryness and the crude reaction mixture thus obtained was purified by column chromatography to give the title compound as syrup.

Yield 90% (790 mg), ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.25 (s, 1H, C$\underline{H}_2$), 4.23, 422 (2s, 2H, -C$\underline{H}_2$-), 4.16 (s, 1H, C$\underline{H}_2$), 3.77 (t, 1H, J = 6.8 Hz, -C$\underline{H}_2$-), 3.68 (t, 1H, J = 6.8 Hz, -C$\underline{H}_2$-), 2.64–2.57 (m, 2H, -C$\underline{H}_2$-), 2.36 (bs, 0.5H, C$\underline{H}$), 2.26 (bs, 0.5H, C$\underline{H}$), 1.44 (s, 9 H, -C(C$\underline{H}_3$)$_3$) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 171.1, 170.3, 166.5, 81.7, 81.0, 78.1, 77.4, 73.5, 72.7, 43.7, 43.3, 41.3, 41.2, 38.8, 34.6, 34.2, 33.7, 28.2 ppm; ESI-MS HRMS**:** Calculted for $C_{12}H_{19}NO_3Cl$ ($[M+H]^+$): 260.1053; found 260.1041.

4. Synthesis of *N*-propargylated ββ-peptoid building block (8)

Following the same procedure as for *N*-propargylated αβ-peptoid building block except for using 2-chloropropionyl chloride in place of chloroacetyl chloride.

Syrup, yield 75% (750 mg), ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.24 (d, 1H, J = 2.4 Hz, C$\underline{H}_2$), 4.13 (d, 1H, J = 2.4 Hz, -C$\underline{H}_2$-), 3.85–3.80 (m, 2H, -C$\underline{H}_2$-), 3.72 (t, 1H, J = 7.2 Hz, -C$\underline{H}_2$-), 3.67 (t, 1H, J = 6.8 Hz, -C$\underline{H}_2$-), 2.90 (q, 2H, -C$\underline{H}_2$-), 2.58 (q, 2H, -C$\underline{H}_2$-), 2.33 (t, 0.5H, J = 2.4 Hz, C$\underline{H}$), 2.23 (t, 0.5H, J = 2.4 Hz, C$\underline{H}$), 1.45, 1.44 (2 x s, 9 H, -C(C$\underline{H}_3$)$_3$) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 171.2, 170.2, 169.8, 169.5, 81.6, 80.9, 78.7, 78.4, 73.0, 72.2, 43.3, 42.8, 39.7 (x2), 38.5, 36.4, 36.2, 34.5, 34.2, 34.1, 28.1 ppm; ESI-MS HRMS Calculated for $C_{13}H_{20}NO_3NaCl$ ($[M+Na]^+$): 296.1029; found 296.1042.

5. Synthesis of triazole-linked *N*-glycopeptoids (1a-4c)

N-propargylated peptoid building block (1 mmol) and per-*O*-acetylated glycopyranosyl azide (1 mmol) were dissolved in acetone (12 mL). To the stirred reaction mixture, a solution of copper sulfate (50 mg, 0.2 mmol) in water (3 mL), was added followed by the addition of aqueous solution (3 mL) of sodium ascorbate (80 mg, 0.4 mmol). The reaction mixture was allowed to stir at room temperature for 24 h. After completion of the reaction as monitored by TLC, acetone was removed by applying vacuum. The reaction mixture was extracted with ethyl acetate (80 mL) and washed with water (20 mL) followed by brine solution (20 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to dryness. The crude product was purified by column chromatography by eluting with ethyl acetate and hexane.

Glycopeptoid **1a**: Yield 80% (495 mg), m.p. 114-116 $^{\circ}$C, $[\alpha]_D$ -26.3° (c = 0.1, $CHCl_3$), ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.87 , 7.86 (2s, 1H, triazole $\underline{H}$), 5.89-5.82 (m, 1H, H-1), 5.45-5.37 (m, 2H, H-2 & H-3), 5.27-5.22 (m, 1H, H-4), 4.74-4.63 (m, 2H, -C$\underline{H}_2$-Cl), 4.34-4.27 (m, 2H, H-6a, N-C$\underline{H}_2$-CO), 4.18-4.00 (m, 5H, H-6b, H-5, N-C$\underline{H}_2$-CO, N-C$\underline{H}_2$-C=), 2.09, 2.07, 2.06, 2.03 (x 2), 1.88, 1.87 (7s, 12H,

4 x –$COCH_3$), 1.46, 1.45 (2s, 9H, -C($C\underline{H}_3$)$_3$) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 170.6, 170.5, 170.0, 169.9, 169.4, 169.3, 169.0, 168.7, 167.7, 167.1, 167.0, 143.8, 143.7, 122.2, 121.1, 85.9, 85.8 (C-1), 83.1, 82.3, 75.3, 75.2, 72.7, 72.4, 70.5, 70.4, 67.7, 67.6, 61.5, 50.3, 48.3, 44.4, 42.6, 41.1, 28.1, 28.0, 20.7, 20.6, 20.2 ppm; ESI-MS HRMS Calculated for $C_{25}H_{36}N_4O_{12}Cl$ ($[M+H]^+$): 619.2018; found 619.2037.

Glycopeptoid **1b**: Yield 90% (570 mg), m.p. 80-81 °C, $[\alpha]_D$ -20.8° (c = 0.2, $CHCl_3$), ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.94 (s, 1H, triazole $\underline{H}$), 6.49-6.42 (m, 1H, -NH-), 6.08, 6.02 (2d, 1H, J = 9.6 Hz, H-1), 5.56-5.44 (m, 1H, H-3), 5.30-5.21 (m, 1H, H-4), 4.75-4.66 (m, 2H, -C$\underline{H}_2$-Cl), 4.34-4.27 (m, 2H, H-6a, N-C$\underline{H}_2$-CO), 4.18-4.00 (m, 5H, H-6b, H-5, N-C$\underline{H}_2$-CO, N-C$\underline{H}_2$-C=), 2.08, 2.07, 2.06, 2.05, 1.76, 1.75 (6s, 12H, 4 x –$COCH_3$), 1.46, 1.45 (2s, 9H, -C($C\underline{H}_3$)$_3$) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 170.9, 170.8, 170.7, 170.6 (x 2), 169.4, 167.8, 167.7, 167.2 (x 2), 143.4, 143.2, 122.9, 121.8, 86.4, 85.8, 83.1, 82.3, 75.0 (x 2), 72.3, 72.2, 68.2, 68.1, 61.9, 61.8, 53.9, 53.6, 50.4, 48.4, 44.3, 42.7, 41.3, 41.2, 28.1, 28.0, 22.9, 22.8, 20.8 ppm; ESI-MS HRMS Calculated for $C_{25}H_{36}N_5O_{11}NaCl$ ($[M+Na]^+$): 640.1998; found 640.2015.

Glycopeptoid **1c**: Yield 82% (500 mg), m.p. 58-61 °C, $[\alpha]_D$ -1.6° (c = 0.5, $CHCl_3$), ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.90, 7.88 (2s, 1H, triazole $\underline{H}$), 5.82-5.77 (m, 1H, H-1), 5.56-5.43 (m, 2H, H-2 & H-3), 5.27-5.21 (m, 1H, H-4), 4.79-4.59 (m, 2H, -CH_2-), 4.32-4.02 (m, 7H, H-5, H-6a, H-6b, -N-$\underline{CH_2}$-CO-,-N-$\underline{CH_2}$-C=) , 2.24, 2.05, 2.04, 2.01, 2.00, 1.89, 1.88 (7s, 12H, 4 x -CO$C\underline{H}_3$), 1.46, 1.45 (2s, 9H, C($C\underline{H}_3$)$_3$) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 170.4, 170.2, 169.9, 169.2, 168.9, 167.7, 167.0, 143.9, 143.8, 122.3, 121.1, 86.5, 86.4, 83.1, 82.3, 74.3, 74.2, 70.9, 70.6, 68.2, 68.1, 66.9, 61.3, 61.2, 50.3, 48.4, 44.6, 42.7, 41.2, 28.2, 28.1, 20.8, 20.7, 20.6, 20.3 ppm; ESI-MS HRMS Calculated for $C_{25}H_{36}N_4O_{12}Cl$ ($[M+H]^+$): 619.2018; found 619.2031.

Glycopeptoid **2a**: Yield 94% (600 mg), m.p. 72-74 °C, $[\alpha]_D$ -22.4° (c = 0.5, $CHCl_3$), ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.87, 7.79 (2s, 1H, triazole H), 5.87-5.79 (m, 1H, H-1), 5.43-5.36 (m, 2H, H-2, H-3), 5.26-5.21 (m, 1H, H-4), 4.72-4.54 (m, 2H, CO-CH_2-Cl), 4.32-4.26 (m, 3H, H-6a, N-CH_2-C=), 4.17-4.13 (m, 1H, H-6b), 4.00-3.97 (m, 1H, H-5), 3.70-3.56 (m, 2H, -N-CH_2-CH_2-), 2.64-2.55 (m, 2H, -N-CH_2-CH_2-), 2.10, 2.07, 2.06, 2.03, 2.02, 1.87, 1.86 (7s, 12H, 4 x –CO-CH_3), 1.44, 1.42 (2s, 9H, C(CH_3)$_3$) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 170.7, 170.3, 170.1, 169.4, 168.7, 166.9, 144.3, 122.5, 120.6, 85.9, 81.7, 77.4, 75.4, 75.3, 72.6, 72.4, 70.6, 67.7, 61.5, 44.2, 43.0, 41.7, 41.4, 41.1, 34.3, 33.6, 28.2, 28.1, 20.8, 20.6, 20.2 ppm; ESI-MS HRMS Calculated for $C_{26}H_{38}N_4O_{12}Cl$ ($[M+H]^+$): 633.2175; found 633.2193.

Glycopeptoid **2b**: Yield 95% (620 mg), m.p. 55-56 °C, $[\alpha]_D$ -11.8° (c = 0.1, $CHCl_3$), ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.94, 7.91 (2s, 1H, triazole H), 6.47-6.38 (m 1H, NH), 6.05-6.00 (m, 1H, H-1), 5.53-5.44 (m, 1H, H-3), 5.23 (t, 1H, J = 9.6 Hz, H-4), 4.72-4.46 (m, 3H, H-2, -CO-CH_2-Cl), 4.33-4.25 (m, 3H, H-6a, N-CH_2-C=), 4.16-4.13 (m, 1H, H-6b), 4.07-4.04 (m, 1H, H-5), 3.70-3.58 (m, 2H, N-CH_2-CH_2-), 2.64-2.58 (m, 2H, N-CH_2-CH_2-), 2.09, 2.07, 2.06, 2.05, 1.75, 1.73 (6s, 12H, 4 x –CO-CH_3), 1.44, 1.42 (2s, 9H, C(CH_3)$_3$) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 171.4, 170.9, 170.8, 170.7, 170.6, 170.5, 170.4, 169.4, 167.2, 167.1, 143.9, 143.8, 123.0, 121.4, 86.4, 86.0, 81.7, 81.1, 77.4, 75.1, 75.0, 72.3, 72.2, 68.2, 68.1, 61.8, 53.9, 53.5, 44.1, 43.2, 41.8, 41.5, 41.1, 34.4, 33.6, 28.2, 28.1, 22.9, 22.8, 20.8 ppm; ESI-MS HRMS Calculated for $C_{26}H_{38}N_5O_{11}NaCl$ ($[M+Na]^+$): 654.2154; found 654.2147.

Glycopeptoid **2c**: Yield 95% (600 mg), m.p. 68-70 °C, $[\alpha]_D$ -6.8° (c = 1, $CHCl_3$), ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.93, 7.82 (2s, 1H, triazole H), 5.83-5.77 (m, 1H, H-1), 5.56-5.54 (m, 1H, H-2), 5.50-5.44 (m, 1H, H-3), 5.27-5.22 (m, 1H, H-4), 4.73, 4.62 (2s, 2H, CO-CH_2-Cl), 4.31-4.11 (m, 5H, H-6a, H-6b, H-5, N-CH_2-C=), 3.73-3.58 (m, 2H, N-CH_2-CH_2-), 2.69-2.59 (m, 2H, N-CH_2-CH_2-), 2.25, 2.05, 2.04, 2.01, 2.00, 1.88, 1.87 (7s, 12H, 4 x –CO-CH_3), 1.45, 1.42 (2s, 9H, C(CH_3)$_3$) ppm; ^{13}C-NMR ($CDCl_3$, 100

MHz): δ 171.4, 170.4, 170.3, 170.2, 170.0, 169.9, 169.8, 169.2, 168.9, 167.1, 166.9, 144.4, 144.3, 122.5, 120.6, 86.5, 81.6, 81.1, 74.3, 74.2, 70.8, 70.6, 68.2, 66.9, 61.3, 44.3, 44.2, 43.1, 41.7, 41.5, 41.1, 34.3, 33.6, 28.2, 28.1, 20.8, 20.7, 20.5, 20.2 ppm; ESI-MS HRMS Calculated for $C_{26}H_{38}N_4O_{12}Cl$ ($[M+H]^+$): 633.2175; found 633.2161.

Glycopeptoid **3a**: Yield 95% (620 mg), m.p. 48-49 $^\circ$C, $[\alpha]_D$ -20.5° (c = 0.5, $CHCl_3$), ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.84, 7.83 (2s, 1H, triazole H), 5.87-5.81 (m, 1H, H-1), 5.44-5.39 (m, 2H, H-2 & H-3), 5.26-5.22 (t, 1H, H-4), 4.68 (s, 2H, N-CH_2-CO), 4.33-4.27 (m, 1H, H-6a), 4.17-4.13 (m, 1H, H-6b), 4.10-3.96 (m, 2H, H-5 & N-CH_2-C=), 3.87-3.81 (m, 2H, CO-CH_2-CH_2-Cl), 2.98, 2.70 (2t, 2H, J = 6.8 Hz, CO-CH_2-CH_2-Cl), 2.09, 2.07, 2.06, 2.04, 2.03, 1.88, 1.87 (7s, 12H, 4 x –CO-CH_3), 1.46, 1.45 (2s, 9H, C(CH_3)$_3$) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 170.6, 170.4, 170.3, 170.1, 169.9, 168.8, 168.2, 167.9, 144.4, 122.0, 120.8, 86.0, 85.6, 82.9, 75.3, 75.2, 72.7, 72.4, 70.5, 70.4, 67.7, 61.5, 50.2, 48.3, 44.2, 42.1, 39.7, 36.2, 36.1, 31.7, 28.1, 28.0 22.7, 20.8 ppm; ESI-MS HRMS Calculated for $C_{26}H_{37}N_4O_{12}NaCl$ ($[M+Na]^+$): 655.1994; found 655.1999.

Glycopeptoid **3b**: Yield 85% (555 mg), m.p. 107-108 $^\circ$C, $[\alpha]_D$ -29.5° (c = 0.7, $CHCl_3$), ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.93, 7.92 (2s, 1H, triazole H), 6.70-6.63 (m, 1H, NHAc), 6.12-6.03 (m, 1H, H-1), 5.58-5.30 (m, 1H, H-3), 5.25-5.20 (m, 1H, H-4), 4.76-4.46 (m, 3H, H-2 & N-CH_2-CO), 4.32-4.28 (m, 1H, H-6a), 4.16-3.98 (m, 4H, H-6b, H-5, N-CH_2-C=), 3.87-3.71 (m, 2H, CO-CH_2-CH_2-Cl), 3.02, 2.74 (2t, 2H, J = 6.8 Hz, CO-CH_2-CH_2-Cl), 2.08, 2.07, 2.06, 2.05 (x2), 1.76, 1.75 (6s, 12H, 4 x –CO-CH_3), 1.45 (s, 9H, C(CH_3)$_3$) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 170.8, 170.7, 170.6, 170.5, 170.4, 169.4, 167.9, 143.9, 143.8, 122.6, 121.5, 86.3, 85.7, 83.0, 82.1, 74.9, 74.8, 72.2, 72.1, 68.2, 68.1, 61.9, 61.8, 53.8, 53.4, 50.2, 48.3, 44.0, 42.1, 39.7, 36.2, 31.6, 28.1, 28.0, 22.9, 22.8, 22.7, 20.8, 20.7, 20.6 ppm; ESI-MS HRMS Calculated for $C_{26}H_{38}N_5O_{11}NaCl$ ($[M+Na]^+$): 654.2154; found 654.2125.

Glycopeptoid **3c**: Yield 90% (570 mg), m.p. 68-70 °C, $[\alpha]_D$ -0.6° (c = 0.4, $CHCl_3$), ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.89, 7.88 (2s, 1H, triazole H), 5.80-5.78 (m, 1H, H-1), 5.56-5.53 (m, 2H, H2 & H-3), 5.27-5.21 (m, 1H, H-4), 4.77-4.61 (m, 2H, N-CH_2-CO), 4.24-3.98 (m, 5H, H-5, H-6a, H-6b & N-CH_2-C=), 3.88-3.82 (m, 2H, CO-CH_2-CH_2-Cl), 2.99, 2.71 (2t, 2H, J = 6.8 Hz, CO-CH_2-CH_2-Cl), 2.24, 2.23, 2.05, 2.01, 2.00, 1.90, 1.88 (7s, 12H, 4 x –CO-CH_3), 1.46, 1.45 (2s, 9H, C(CH_3)$_3$) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 170.4 (x2), 170.2, 170.0, 169.9 (x2), 169.2, 168.9, 168.2, 167.9, 144.4, 144.3, 122.1, 120.8, 86.5, 86.3, 82.9, 82.2, 74.2, 74.1, 70.8, 70.6, 68.2, 68.0, 66.8, 61.3, 50.2, 48.4, 44.3, 42.1, 39.8, 39.7, 36.1, 28.2, 28.1, 28.0 (x2), 22.7, 20.8 ppm; ESI-MS HRMS Calculated for $C_{26}H_{38}N_4O_{12}Cl$ ($[M+H]^+$): 633.2175; found 633.2156.

Glycopeptoid **4a**: Yield 98% (650 mg), m.p. 53-55 °C, $[\alpha]_D$ -17.6° (c = 0.4, $CHCl_3$), ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.84, 7.75 (2s, 1H, triazole H), 5.87-5.80 (m, 1H, H-1), 5.43-5.34 (m, 2H, H-2 & H-3), 5.26-5.20 (m, 1H, H-4), 4.72-4.52 (m, 2H, N-CH_2-C=), 4.32-4.27 (m, 1H, H-6a), 4.17-4.13 (m, 1H, H-6b), 4.00-3.96 (m, 1H, H-5), 3.86-3.82 (m, 2H, CO-CH_2-CH_2-Cl), 3.67-3.59 (m, 2H, N-CH_2-CH_2-CO), 2.95-2.86 (m, 2H, CO-CH_2-CH_2-Cl), 2.57-2.47 (m, 2H, N-CH_2-CH_2-CO), 2.09, 2.07, 2.06, 2.03, 2.02, 1.87, 1.86 (7s, 12H, 4 x –CO-CH_3), 1.44, 1.43 (2s, 9H, C(CH_3)$_3$) ppm; ^{13}C-NMR($CDCl_3$, 100 MHz) δ 171.4, 170.7, 170.6, 170.2, 170.0, 169.9, 169.4, 169.0, 168.7, 145.0, 122.2, 120.3, 86.0, 85.9, 81.5, 75.3, 75.2, 72.6, 72.4, 70.6, 70.5, 67.7, 61.5, 44.0, 43.9, 42.9, 40.9, 40.0, 36.4, 35.9, 34.7, 34.1, 31.7, 28.1, 20.8 ppm; ESI-MS HRMS Calculated for $C_{27}H_{39}N_4O_{12}NaCl$ ($[M+Na]^+$): 669.2151; found 669.2159.

Glycopeptoid **4b**: Yield 90% (580 mg), m.p. 130-132 °C, $[\alpha]_D$ -19.44° (c = 0.9, $CHCl_3$), ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.89, 7.86 (2s, 1H, triazole H), 6.49-6.34 (m, 1H, -NHAc), 6.06-6.01 (m, 1H, H-1), 5.54-5.45 (m, 1H, H-3), 5.25-5.20 (m, 1H, H-4), 4.76-4.44 (m, 3H, H-2 & N-CH_2-C=), 4.32-4.27 (m, 1H, H-6a), 4.16-4.13 (m, 1H, H-6b), 4.07-4.05 (m, 1H, H-5), 3.87-3.83 (m, 2H, CO-CH_2-CH_2-Cl), 3.69-3.58 (m, 2H, N-CH_2-CH_2-CO), 2.97-2.89 (m, 2H, CO-CH_2-CH_2-Cl), 2.57-2.54 (m, 2H, N-CH_2-CH_2-

CO), 2.09, 2.06, 2.03, 1.75, 1.74 (4s, 12H, 4 x –CO-C$\underline{H}_3$), 1.43 (s, 9H, C(C$\underline{H}_3$)$_3$) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 171.4, 170.9, 170.8, 170.7, 170.4, 170.3, 170.0, 169.4, 144.6, 144.4, 122.7, 121.1, 86.3, 85.9, 81.5, 81.0, 74.9, 72.3, 72.2, 68.1, 61.8, 53.9, 53.5, 44.0, 43.7, 42.9, 40.8, 40.0, 36.4, 36.0, 34.7, 34.1, 28.1, 22.9, 20.8 (x 2) ppm; ESI-MS HRMS Calculated for $C_{27}H_{41}N_5O_{11}Cl$ ($[M+H]^+$): 646.2491; found 646.2514.

Glycopeptoid **4c**: Yield 95% (610 mg), m.p. 48-50 °C, $[\alpha]_D$ -3.2° (c = 0.5, $CHCl_3$), ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.90, 7.80 (2s, 1H, triazole $\underline{H}$), 5.86-5.80 (m, 1H, H-1), 5.56-5.54 (m, 1H, H-4), 5.49-5.44 (m, 1H, H-2), 5.29-5.23 (m, 1H, H-3), 4.71-4.56 (m, 2H, N-C$\underline{H}_2$-C=), 4.27-4.12 (m, 3H, H-5, H-6a & H-6b), 3.87-3.84 (m, 2H, CO-CH$_2$-C$\underline{H}_2$-Cl), 3.68-3.62 (m, 2H, N-C$\underline{H}_2$-CH$_2$-CO), 2.96-2.88 (m, 2H, CO-C$\underline{H}_2$-CH$_2$-Cl), 2.58-2.53 (m, 2H, N-CH$_2$-C$\underline{H}_2$-CO), 2.24, 2.05, 2.04, 2.01, 2.00, 1.88, 1.87 (7s, 12H, 4 x –CO-C$\underline{H}_3$), 1.44 (s, 9H, C(C$\underline{H}_3$)$_3$) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 171.3, 170.3, 170.2, 170.1 (x 2), 170.0, 169.9, 169.8, 169.7, 169.0, 168.8, 144.8, 122.1, 120.3, 86.4, 86.3, 81.4, 80.8, 74.1, 74.0, 70.7, 70.5, 68.1 (x 2), 66.8, 61.2, 44.1, 43.7, 42.9, 40.8, 40.0, 36.2, 35.8, 34.6, 34.0, 28.1, 28.0 (x 2), 20.7 ppm; ESI-MS HRMS Calculated for $C_{27}H_{40}N_4O_{12}Cl$ ($[M+H]^+$): 647.2331; found 647.2355.

6. Synthesis of azide functionalized triazole linked *N*-glycopeptoids (1d)

Glycopeptoid **1a** (320 mg, 0.5 mmol) was dissolved in acetone (14 mL) and aqueous solution (7 mL) of sodium azide (160 mg, 2.5 mmol) was added to it. The reaction mixture was stirred at 60 °C for 24 h. After completion of the reaction, acetone was removed by applying vacuum. The reaction mixture was extracted with ethyl acetate (50 mL) and washed with water (20 mL) followed by brine solution (20 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to dryness to give the desired compound (**1d**) as white solid.

Glycopeptoid **1d**: Yield 95% (310 mg), m.p. 52-53 °C, $[\alpha]_D$ -12.6° (c = 0.2, $CHCl_3$), ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.87 , 7.84 (2s, 1H, triazole $\underline{H}$), 5.87-5.81 (m, 1H, H-1), 5.47-5.32 (m, 2H, H-2 & H-3),

5.27-5.22 (m, 1H, H-4), 4.75-4.59 (m, 2H, -C$\underline{H}_2$-), 4.34-4.27 (m, 1H, H-6a), 4.17-3.85 (m, 6H, H-6b, H-5, N-C$\underline{H}_2$-CO, N-C$\underline{H}_2$-C= & N-C$\underline{H}_2$-CO), 2.09, 2.07, 2.06, 2.03 (x 2), 1.88, 1.87 (7s, 12H, 4 x –COCH_3), 1.46, 1.45 (2s, 9H, -C(C$\underline{H}_3$)$_3$) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 170.6, 170.5, 170.1, 169.9, 169.4, 169.3, 169.0, 168.8, 168.0, 167.9, 167.5, 143.9, 143.8, 122.3, 120.9, 86.0, 85.8, 83.2, 82.4, 75.4, 75.2, 72.7, 72.3, 70.6, 70.5, 67.7, 61.5, 50.7, 50.5, 49.7, 48.3, 43.6, 42.5, 28.1, 28.0, 20.8, 20.6, 20.3, 20.2 (x2) ppm; ESI-MS HRMS Calculated for $C_{25}H_{36}N_7O_{12}$ ($[M+H]^+$): 626.2422; found 626.2439.

7. Synthesis of alkyne functionalized *N*-glycopeptoid (10)

Peptoid building block **5** (250 mg, 1 mmol) was added to a mixture of trifluoroacetic acid and DCM (1:1, 4 mL) at 0 °C. The mixture was stirred for 4 h allowing it to come to room temperature. After completion of the reaction, as monitored by TLC, the reaction mixture was dried by applying vacuum. To the crude product in dry dichloromethane, diisopropylcarbodiimide (130 mg, 1 mmol) was added under nitrogen atmosphere at 0 °C. After stirring the mixture for 30 min at 0 °C, solution of sugar amine **9d**[26] in dry dichloromethane was added. After stirring the reaction mixture for 24 h at room temperature, it was diluted with dichloromethane (20 mL) and filtered. The filtrate was concentrated by applying vacuum and purified by column chromatography to give the title compound **10** in 70% overall yield.

Glycopeptoid **10**: Yield 70% (360 mg), m.p. 172-174 °C, $[\alpha]_D$ +17.3° (c = 0.2, $CHCl_3$), ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.61 (d, 1H, J = 7.5 Hz, N$\underline{H}$-COCH_2), 6.59-6.56 (m, 1H, N$\underline{H}$Ac), 5.33-5.05 (m, 3H, H-1, H-3, H-4), 4.43-4.37 (m, 2H, CO-C$\underline{H}_2$-N), 4.34-3.98 (m, 7H, H-2, H-6a, H-6b, N-C$\underline{H}_2$-CO & COC$\underline{H}_2$-Cl), 3.90-3.82 (m, 1H, H-5), 2.45, 2.35 (2s, 1H, C-$\underline{H}$), 2.09, 2.05, 2.03, 1.99 (4s, 12H, COC$\underline{H}_3$) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 173.4, 171.6, 170.8, 169.5, 169.1, 167.3, 80.6, 77.4, 76.7, 74.8, 73.2, 72.5, 68.2, 61.9, 53.1, 50.5, 41.9, 39.3, 23.2, 20.9, 20.8, 20.7 ppm; ESI-MS Calculated for $C_{21}H_{29}N_3O_{10}Cl$ ($[M+H]^+$): 518.1541; found 518.1528.

8. Synthesis of azidoacetamide of L-threonine (13)

To a suspension of L-threonine (250 mg, 2 mmol) in dry methanol (10 mL) at 0 °C, thionyl chloride (0.3 mL, 4 mmol) was added. The mixture was stirred for 24 h allowing it to come to room temperature. After completion of the reaction, the reaction mixture was dried applying vacuum. The residue was dissolved in methanol (15 mL) and sodium bicarbonate (600 mg, 7 mmol) was added. To the stirring solution at 0 °C, chloroacetic anhydride (500 mg, 3 mmol) was added. After stirring the mixture for 24 h at room temperature it was concentrated to dryness. The residue was filtered after diluting it with ethyl acetate (30 mL). The filtrate was concentrated to dryness. The crude product (**12**) thus obtained was dissolved in methanol and stirred at 60 °C for 24 h with sodium azide (650 mg, 10 mmol). After completion of the reaction, methanol was removed by applying vacuum and the residue was mixed with anhydrous sodium acetate (330 mg, 4 mmol) in dry acetonitrile (10 mL). To the stirring reaction mixture at room temperature, acetyl chloride (3 mmol) was added drop by drop. The reaction mixture was stirred at 80 °C for 12 h. Then the reaction mixture was allowed to come to room temperature and diluted with 80 mL ethyl acetate and washed with water (20 mL) and brine solution (20 mL) successively. The organic layer was dried over anhydrous sodium sulfate and concentrated to dryness to give compound **13** as syrup.

Yield 50% (280 mg), $[\alpha]_D$ -62.1° (c = 1, $CHCl_3$), ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 6.98 (d, 1H, J = 9.2 Hz, N<u>H</u>), 5.45-5.43 (m, 61 (d, 1H, J = 7.6 Hz, N<u>H</u>-$COCH_2$), 4.79-4.76 (m, 1H, NH-C<u>H</u>-CH), 4.09-4.05 (m, 2H, CO-C<u>H_2</u>-N_3), 3.75 (s, 3H, O-C<u>H_3</u>), 2.04 (s, 3H, COC<u>H_3</u>), 1.28-1.21 (m, 3H, CHC<u>H_3</u>) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 169.7, 167.3, 70.0, 55.3, 52.8, 52.3, 20.8, 17.0 ppm; ESI-MS HRMS Calculated for $C_9H_{14}N_4O_5Na$ ($[M+Na]^+$): 281.0862; found 281.0871.

9. Synthesis of glycopeptoid 14 by *click* reaction

Alkyne functionalized glycopeptoid **10** (255 mg, 0.5 mmol) and azidoacetamide of L-threonine **13** (150 mg, 0.5 mmol) were dissolved in acetone (12 mL). To the stirring reaction mixture, a solution of copper

sulfate (25 mg, 0.1 mmol) in water (3 mL) was added followed by the addition of aqueous solution (3 mL) of sodium ascorbate (40 mg, 0.2 mmol). The reaction mixture was allowed to stir at room temperature for 24 h. After completion of the reaction as monitored by TLC, the solvents were removed by applying vacuum. The crude reaction mixture was purified by column chromatography to give the title compound as a solid.

Yield 80% (310 mg), m.p. 115-118 $^{\circ}$C, $[\alpha]_D$ +68.2° (c = 0.2, MeOH), ESI-MS HRMS Calculated for $C_{30}H_{42}N_7O_{15}NaCl$ ($[M+Na]^+$): 798.2325; found 798.2311. [^{1}H and ^{13}C NMR in figure **S41** and **S42** respectively]

10. Synthesis of alkyne functionalized L-threonine (17)

N-Boc L-threonine (**15**, 440 mg, 2 mmol) was dissolved in dry DCM (10 mL) and triethyl amine (0.6 mL, 4 mmol) was added to it. The reaction mixture was stirred for 24 h after adding acetyl chloride (0.2 mL, 2.8 mmol). The reaction mixture was dried by applying vacuum. The crude reaction mixture was dissolved in dry DCM (10 mL) and diisopropylcarbodiimide (0.4 mL, 2.5 mmol) was added to it at 0 $^{\circ}$C. After stirring the reaction mixture at the same temperature for 30 min, propargyl amine (0.2 mL, 3 mmol) was added to it. After stirring the reaction mixture for 24 h at room temperature, the reaction mixture was concentrated in rotaevaporator. The product was purified by column chromatography to give the desired compound **17** as syrup.

Yield 70% (400 mg); $[\alpha]_D$ +37.1° (c = 0.7, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 6.86 (bs, 1H, N<u>H</u>CH_2), 5.44-5.36 (m, 2H, N<u>H</u>CO & C<u>H</u>), 4.32-4.31 (m, 1H, C<u>H</u>), 4.04 (bs, 2H, NH-C<u>H</u>$_2$), 2.24-2.23 (m, 1H, C<u>H</u>), 2.04 (bs, 3H, OCOC<u>H</u>$_3$), 1.46 (s, 9H, OCOC(C<u>H</u>$_3$)$_3$), 1.27 (d, 3H, J = 4.8, CHC<u>H</u>$_3$) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 169.9, 169.1, 155.9, 80.6, 79.2, 71.7, 70.3, 57.8, 29.2, 28.3, 21.1, 16.6 ppm; ESI-MS HRMS Calculated for $C_{14}H_{23}N_2O_5$ ($[M+H]^+$): 299.1607; found 299.1605.

11. Synthesis of alkyne functionalized glycotripeptoid (20)

The *tert*-butyl ester of peptoid building block **2b** (300 mg, 0.4 mmol) was removed by stirring it in a mixture of trifluoroacetic acid and DCM (5 mL, 1 : 1) for 24 h. The reaction mixture was dried applying vacuum to give compound **19**. The *N*-Boc protection of compound **17** (150 mg, 0.5 mmol) was removed by stirring it in a mixture of trifluoroacetic acid and DCM (5 mL, 1: 1) for 24 h. Excess reagent and solvent were removed by applying vacuum to give compound **18**. To the crude product **19** in dry DMF (5 mL) diisopropylcarbodiimide (0.1 mL, 0.5 mmol) was added under nitrogen atmosphere at 0 $^{\circ}$C. After stirring the mixture for 30 min at 0 $^{\circ}$C, the solution of amine **18** (0.5 mmol) in dry DMF (5 mL), was added. The reaction mixture was stirred for 24 h at room temperature. After completion of the reaction, monitored by TLC, the reaction mixture was concentrated by applying vacuum the product was purified by column chromatography to give the title compound as a white solid.

Yield 65% (150 mg); m.p. 158-160 $^{\circ}$C; $[\alpha]_D$ +39.8° (c = 0.3, MeOH); ESI-MS HRMS Calculated for $C_{31}H_{42}N_7O_{13}NaCl$ ($[M+Na]^+$): 778.2427; found 778.2420. [^{1}H and ^{13}C NMR in figure **S43** and **S44** respectively]

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Supporting Information Available: Spectral data (^{1}H and ^{13}C NMR) of selected compounds. This material is available free of charge via the internet at http://pubs.acs.org.

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