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Synthesis of Glycopeptoid Sulfonamides Diversifying *N*-glycopeptide Linkage Region Mimic

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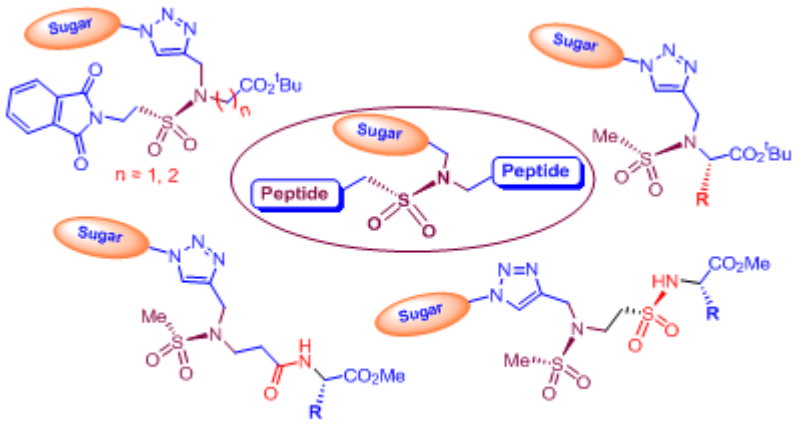
Graphical Abstract



Replacing planar carboxamides with tetrahedral sulfonamides, glycopeptoid sulfonamides were synthesized with diverse conformations and ability to participate in non-covalent interactions.

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Abstract

Replacing the planar carboxamides with tetrahedral sulfonamides in the glycopeptoid backbone, glycopeptoid sulfonamides were synthesized as *N*-glycopeptide mimic with diverse structures using β-peptoid, chiral amino acids and β-amide or β-sulfonamide linked amino acids with different functional groups. The sulfonamide group exists in different conformations and participates in C-H…O interactions.

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Glycosylation of proteins acts as a decisive factor in a range of biological processes including cell-cell recognition, cell growth regulation, cell differentiation, immunological response, metastasis and bacterial and viral infection.[1] As the natural glycoproteins suffer from poor proteolytic stability, low bioavailability and microheterogeneity, glycopeptide mimics were developed for targeted medical applications. Glycopeptoids are recent inclusion to this list.[2] Including synthesis of *clickable* glycopeptoid reported from our group[3] in recent literature, there are several reports on synthesis of glycopeptoids with diverse linkages and modifications in the peptoid backbone with rapidly growing interest in this area of research.[4] Sulfonamides are known as transition state analogs for the hydrolysis of amide bonds in peptide. Considering their importance in medicinal chemistry,[5] sulfonamides are used as replacement of carboxamides in peptidomimetics.[6] The present work includes synthesis of glycopeptoid sulfonamide building blocks by replacing the carboxamide group with sulfonamide in the peptoid backbone. The tetrahedral geometry of the sulfonamide group compared to planar carboxamides and the relatively low energy for the rotation around S-N bond may introduce unnatural conformations in the peptide backbone useful for their specific biological activities (Figure 1).

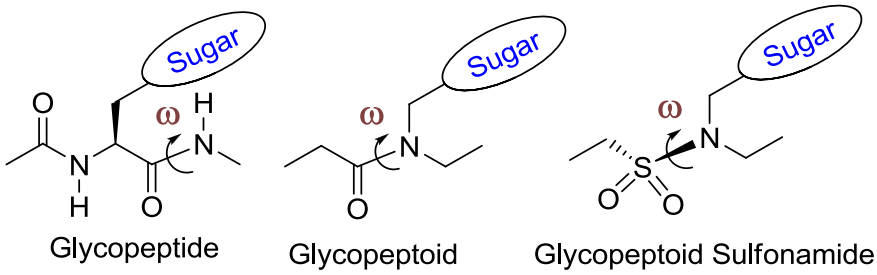

Figure 1 Comparative conformation of glycopeptide, glycopeptoid and glycopeptoid sulfonamide

Due to the absence of NH protons, amide groups in peptoid cannot participate as hydrogen bond donor but they can act as hydrogen bond acceptor. Compared to amides, sulfonamides having two oxygen atoms have better probability to act as hydrogen bond acceptor. Thus, this present work was initiated with the objective to diversify the conformation of peptoid backbone using more flexible sulfonamides

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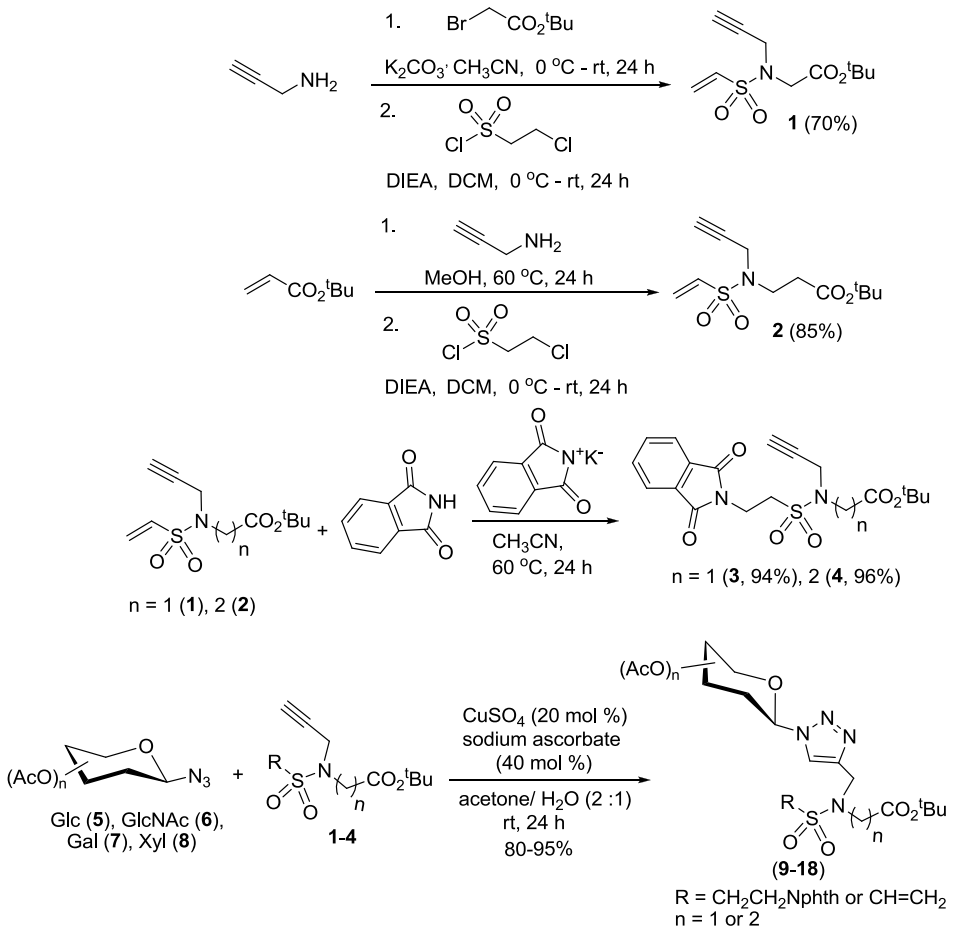
with enhanced ability to participate in non-covalent interactions with other biomolecules for biomedical applications.

Propargyl amine was alkylated with *tert*-butyl bromoacetate (1 equiv.) in presence of K_2CO_3 (2 equiv.) as the base followed by reaction of the secondary amine synthesized with 2-chloroethanesulfonyl chloride (1.2 equiv.) in presence of diisopropylethylamine (2 equiv.) as the base (Scheme 1) to give *N*-propargylated vinylsulfonamide (**1**). The synthesis of other isomer of *N*-propargylated vinylsulfonamide (**2**) was done by Michael addition of propargyl amine on *tert*-butyl acrylate followed by reaction with 2-chloroethanesulfonyl chloride (1.2 equiv.) in presence of diisopropylethylamine (2 equiv.) as the base (Scheme 1).



Scheme 1 Synthesis of glycopeptoid sulfonamides (**9-18**)

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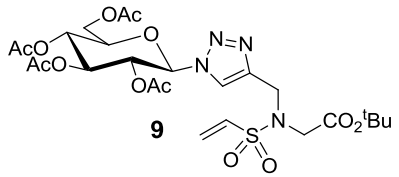
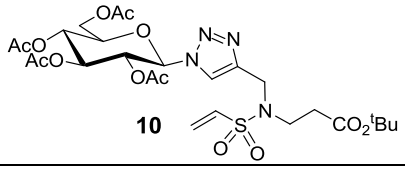
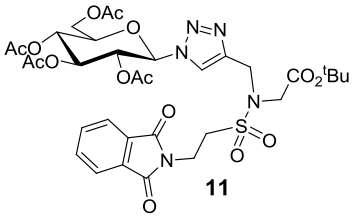
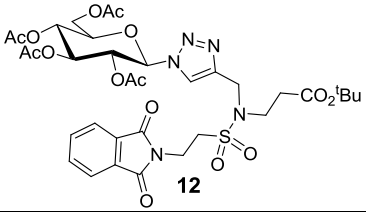
Compound **1** and **2** were converted to the *N*-phthalimide protected derivatives **3** and **4** respectively by Michael addition of phthalimide (1 equiv.) in presence of potassium phthalimide (20 mol%) as the base (Scheme 1). The *N*-propargylated sulfonamides (**1-4**) were reacted with per-*O*-acetylated β-D-glycopyranosyl azides[7] derived from D-glucose (**5**), 2-acetamido-2-deoxy-D-glucose (**6**), D-galactose (**7**) and D-xylose (**8**) in presence of Cu(I) as the catalyst[8] (Scheme 1) which was generated *in situ* by reaction of copper sulfate (20 mol%) and sodium ascorbate (40 mol%) to give a series of triazole-linked glycopeptoid sulfonamides with systematic variation in the glycan and the peptoid part (Table 1). Analytically pure sample of all the compounds were obtained in excellent yields after column purification.

Table 1 Synthesis of glycopeptoid sulfonamides (**9-18**)

Sl. No.	Azide	Alkyne	Product	Yield (%)
1	**5**	**1**	 **9**	90
2	**5**	**2**	 **10**	92
3	**5**	**3**	 **11**	95
4	**5**	**4**	 **12**	92

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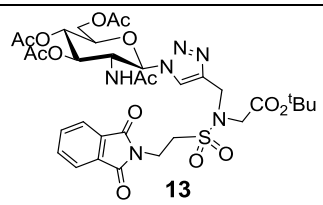
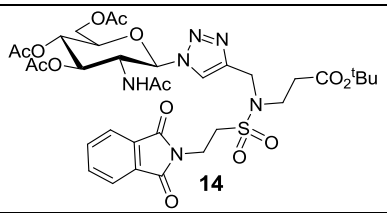
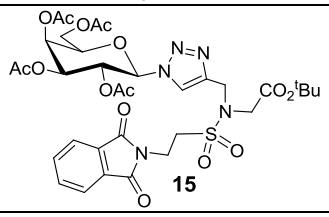
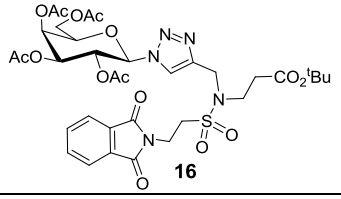
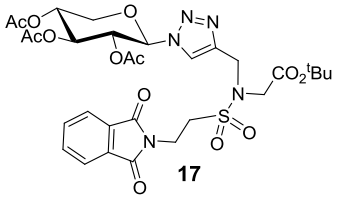
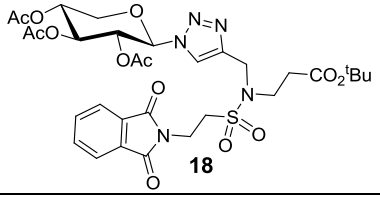
5	**6**	**3**	 **13**	85
6	**6**	**4**	 **14**	80
7	**7**	**3**	 **15**	94
8	**7**	**4**	 **16**	92
9	**8**	**3**	 **17**	87
10	**8**	**4**	 **18**	90

The structural diversity was further explored with synthesis of triazole-linked glycopeptoid sulfonamides (**31**-**34**) with chiral amino acids such as L-valine (**19**), L-pheylalanine (**20**), D-pheylalanine (**21**) and L-isoleucine (**22**). The acid group of the amino acids (**19**-**22**) was protected as methyl ester by reaction with methanol and thionyl chloride (2 equiv.) followed by conversion of the amine to methane sulfonamide by reaction with methanesulfonyl chloride (1.2 equiv.) in presence of diisopropylethylamine (2 equiv.) as the base (Scheme 2). *N*-alkylation of methane sulfonamides of

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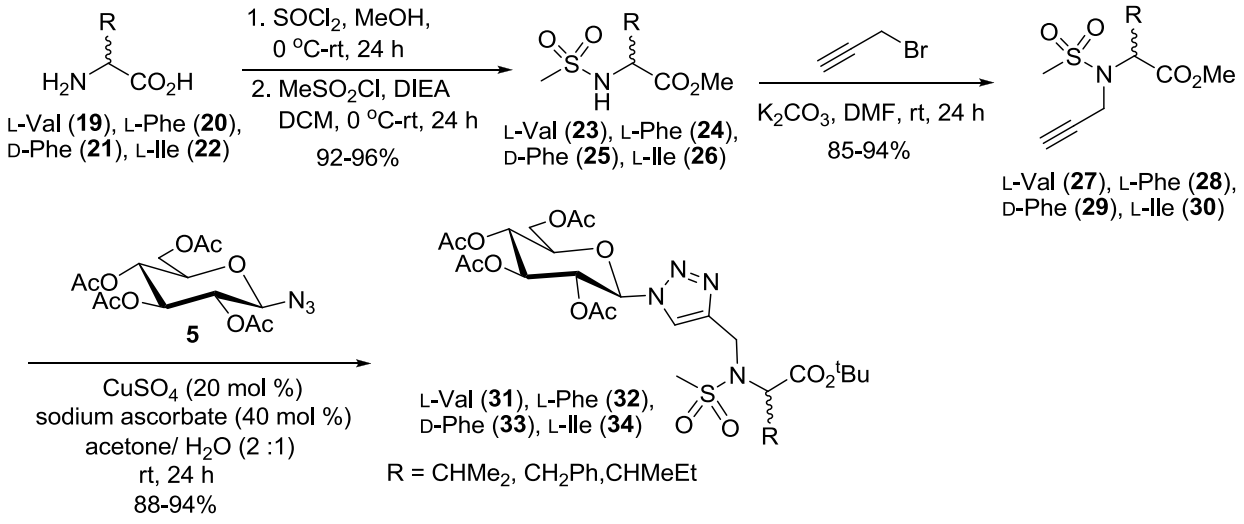
amino acids (**23**-**26**) using propargyl bromide (1.2 equiv.) in presence of potassium carbonate (2 equiv.) as the base gave the *N*-propargylated sulfonamides of amino acids (**27**-**30**). These alkyne functionalized peptoid sulfonamides derived from amino acids (**27**-**30**) were reacted with 2,3,4,6-tetra-*O*-acetylated-β-D-glucopyranosyl azide (**5**) in prsence of Cu(I) as the catalyst to give triazole-linked *N*-glycopeptoid sulfonamides (**31**-**34**) in excellent yields after column purification (Scheme 2).



Scheme 2 Synthesis of triazole-linked *N*-glycopeptoid sulfonamides with chiral amino acids (**31**-**34**)

The versatility of this methodology was further extended to synthesis of glycopeptoid sulfonamides with β-amide (**37**) and β-sulfonamide (**40**) linked L-valine (Scheme 3).

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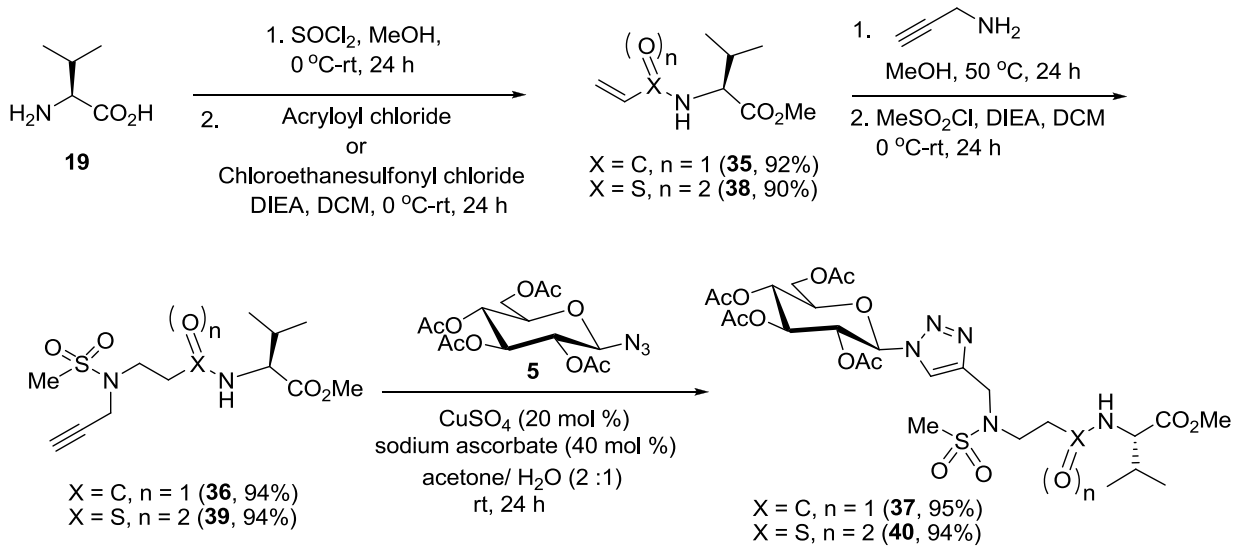

Scheme 3 Synthesis of glycopeptoid sulfonamides with β-amide and β-sulfonamide linked L-valine (**37** & **40**)

The amino group of the methyl ester protected amino acid was converted to either acrylamide (**35**) or vinyl sulphonamide (**38**) by reaction with acryloyl chloride or 2-chloroethanesulfonyl chloride respectively (Scheme 3). Michael addition of propargyl amine to acrylamide (**35**) or vinyl sulfonamide (**38**) followed by reaction with methalesulfonyl chloride (1.2 equiv.) in presence of diisopropylethylamine (2 equiv.) as the base gave compound **36** and **39** respectively. Cu(I) catalyzed *click* reaction of *N*-propargylated sulfonamides (**36** and **39**) with per-*O*-acetylated glucopyranosyl azide (**5**) gave triazole-linked glycopeptoid sulfonamides with β-amide (**37**) and β-sulfonamide (**40**) linked L-valine (Scheme 3).

X-ray structural study of *N*-propargylated sulfoamides (**3**, **4**, **28** and **29**) showed in all the molecules the nitrogen atom of sulfonamide has almost planner geometry and the sulfur atom has tetrahedral geometry (Figure 2).

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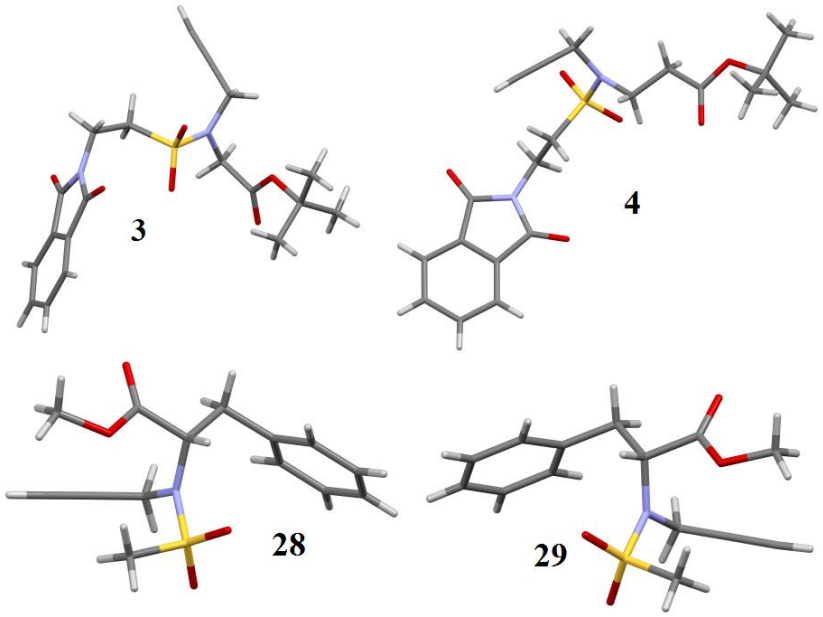

Figure 2 Crystal structures of *N*-propargylated sulfonamides (**3**, **4**, **28** and **29**)

The torsion angle (ω) of the sulfonamide backbone have values -103.60˚, 75.25˚, 89.85˚ and -90.23˚ respectively for compound **3**, **4**, **28** and **29** (Figure 3). The presence of an extra methylene group in compound **4** introduces extra torsion angle (N2-C14-C15-C16) with the value of -177.34˚. For sulfonamides derived from chiral amino acids (**28** and **29**), the side chain of the amino acid (benzyl group) and the propargyl substituent on sulfonamide nitrogen has torsion angle -65.15˚ and 64.80˚ respectively for compound **28** and **29**. In addition to their diversity in conformation, these molecules differ in their ability to participate in non-covalent interactions. Due to absence of NH proton the sulfonamide group cannot participate in regular hydrogen bonds but the oxygen atoms of the sulfonamide participate in C-H…O interactions. In compound **3** one oxygen atom of sulfonamide participate in C-H…O interaction with aromatic C-H proton of *N*-phthalimide group whereas the other oxygen participate in two C-H…O interactions with two C-H protons of *tert*-butyl groups. One of the sulfonamide oxygens in compound **4** participates in C-H…O interaction with alkyne proton of the propargyl group. In the crystal structure of compound **28** and **29**, one oxygen of the sulfonamide

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participates in C-H…O interaction with the alkyne proton of the propargyl group whereas the other oxygen participates in C-H…O interaction with one of the methylene protons of the propargyl group (Figure 3).

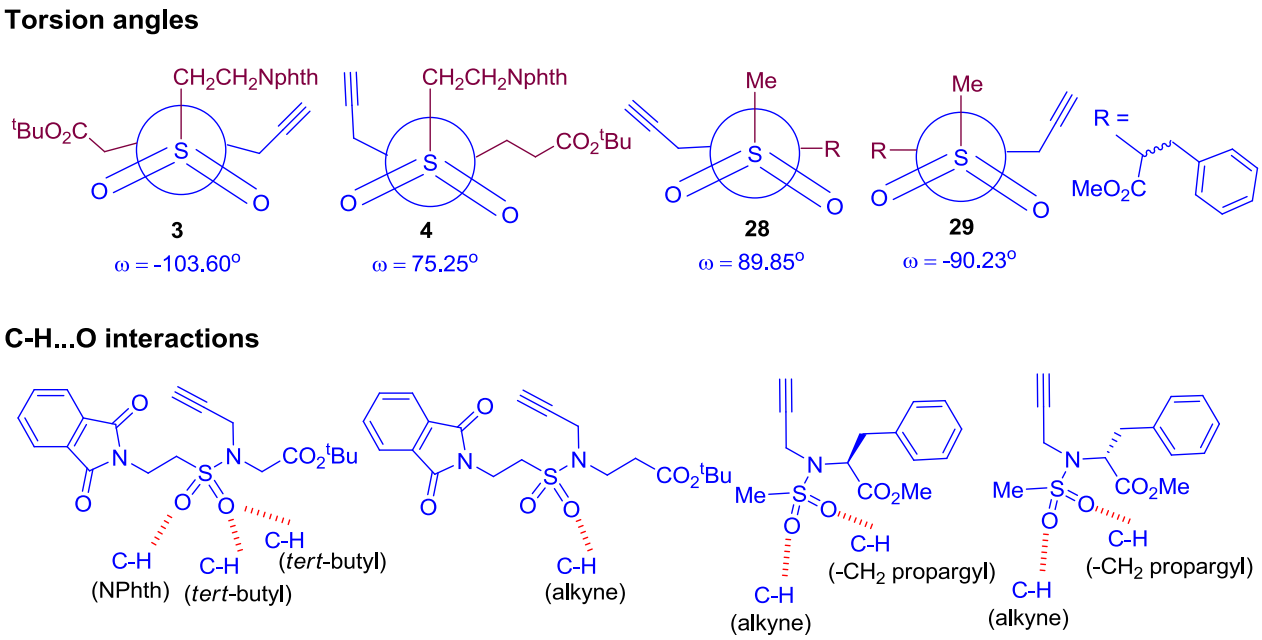

Figure 3 Comparative torsion angles and C-H…O interactions in the crystal structures of *N*-propargylated sulfonamides (**3**, **4**, **28** and **29**)

To summarize, a series of triazole-linked glycopeptoid sulfonamides were synthesized with diverse structures involving simple synthetic methodology using Cu(I) catalyzed *click* reaction with high yield. Unlike carboxamide based peptoids, the ^{1}H and ^{13}C NMR spectra of these sulfonamide containing peptoids did not show the existence of *cis-trans* isomers. The triazole protons in all the compounds appeared as singlet in ^{1}H NMR spectrum. The X-ray structural study of *N*-propargylated sulfonamides (**3, 4, 28** and **29**) showed variation of torsion angles with small modifications in the structure which proves the conformational flexibility of peptoid sulfonamide backbone. The oxygen atoms of the sulfonamide group participated in C-H…O interactions which vary significantly with changes in the structure. In addition to that the triazole rings which are in close proximity of sulfonamides in triazole-

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linked glycopeptoid sulfonamides, may also participate in non-covalent interactions (H-bonds and C-H...O interactions). The ability to participate in these types of interactions will help the molecules to interact with target biomolecules for bio-medical applications. The *tert*-butyl ester and phthalimide protected glycopeptoid sulfonamides (**11**-**18**) can be used for synthesis of large peptides following selective deprotection of the ester or *N*-phthalimide groups. These methodologies can be further extended for the synthesis of larger glycopeptoid sulfonamides which may introduce unusual conformation in the peptide backbone and improve their pharmacokinetic properties. Thus in conclusion, it can be said that a plethora of sequence space using glycopeptoid sulfonamides with myriad structures, varied conformations and huge potential to be used for medical application are yet to be explored in the area of peptidomimetics.

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Notes and references

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Electronic Supplementary Information (ESI) available: [Experimental procedure, spectral data (^{1}H and ^{13}C NMR), X-ray data and CIF files of selected compounds; CCDC deposition numbers CCDC 968919, CCDC 968920, CCDC 969104 and CCDC 969105]. See DOI: 10.1039/c000000x/

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