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Design and Synthesis of a Novel *N*-(1*H*-tetrazol-5-yl)methyl Cyclic Peptoid Using Nosyl-protected *N*-(1-trityl-1*H*-tetrazol-5-yl)methyl Substituted Glycine

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Abstract A solid phase synthesis of a cyclic peptoid bearing (1*H*-tetrazol-5-yl)methyl as N-substituent has been developed employing the monomer approach. The requisite monomeric Nosyl-protected *N*-(1-trityl-1*H*-tetrazol-5-yl) methyl substituted glycine was accessed by a convenient synthesis involving Click reaction of Nosyl-protected *N*-(cyanomethyl)glycine methyl ester and sodium azide as a key step. This building block was then employed in the solid phase synthesis of a tetramer peptoid. The linear tetramer was subjected to macrocyclization using PyBOP to obtain a cyclic peptoid with (1*H*-tetrazol-5-yl)methyl pendants in good yield.

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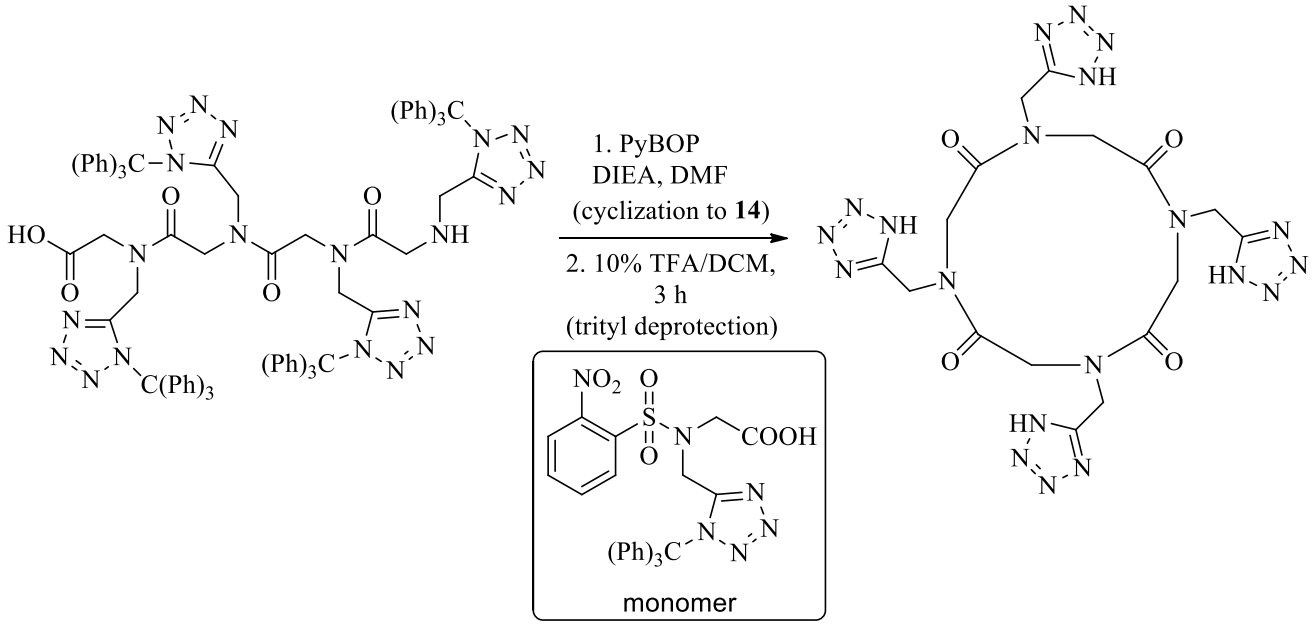
Graphical Abstract



Keywords Cyclic peptoid · Nosyl-protected N-(1-trityl-1H-tetrazol-5-yl)methyl substituted glycine · Click chemistry · Macrocyclization

Introduction

Peptoids, (poly-*N*-substituted glycines) (Simon et al. 1992; Culf and Ouellette 2010) represent a class of α-peptide mimics where in the backbone side chains attached to α-carbon are "moved" to the backbone amide nitrogen atom. In addition to *N*-substituted versions of the proteinogenic side chains, various primary amines can be directly incorporated as their N-substituents (Miller et al. 1994; Timothy et al. 2003). They can be generated using a straight forward, modular synthesis and offer great promise for biological applications because of the incorporation of a wide variety of functionalities. The enhanced proteolytic stability (Udugamasooriya et al. 2008; Wender et al. 2000; and; Kwon and Kodadek 2007) and increased cellular permeability (Zukermann et al. 1992a, b; Yu et al. 2005) relative to α-peptides are the important attributes that hold potential for their use as tools to study biomolecular interactions and for therapeutic applications (Hara et al. 2006; Xiao et al. 2007; and; Patch and Barron 2002; Patch et al. 2004). A number of short oligomeric peptoids (<8-mers) have been found to bind therapeutically relevant proteins, act as antagonists, inhibitors or activators (Goodson et al. 1999; Ng et al. 1999; Zuckermann et al. 1992a, b; Heizmann et al. 1999; Marti´nez et al. 2002; Thompson et al. 2003). Similar to peptides, cyclization of peptoids has been an efficient strategy to enhance conformational order resulting in improved biostability, biological activity and unique supramolecular architectures (Shin et al. 2007; Shah et al. 2008; Maulucci et al. 2008; Huang et al. 2013). Cyclic peptoids have also found applications in metal binding (Izzo et al. 2013; Cola et al. 2014), phase transfer catalysis (Schettini et al. 2014) and cation transport (Cola et al. 2009).

On the other hand, heterocycles play vital role in drug discovery as underscored by their structural rigidity, complexity and diversity of the library of heterocycle containing small molecule drugs (Abell 2002; El-Dahshan et al. 2011; Cerminara et al. 2012; Yu et al. 2002). Moreover, heterocycles can increase the aqueous solubility of oligomers when compared to all carbon units (Combs and Lokey 2007; Aquino et al. 2012). The insertion of heterocycles in to peptoids is of significant interest which is expected to favor the conformational constraints in the peptoid oligomer (Aditya and Kodadek 2012). The heterocyclic motives may confer stabilized three-dimensional structure on the resulting hybrid molecules leading to improvements in ligand binding or inhibition, there by improved pharmacokinetic properties (Aditya and Kodadek 2012). The side chain heterocyclic nitrogen atoms are significant by their ability to chelate metals and exhibit unique spectroscopic properties. In line with this strategy, heterocycles such as oxazole, thiazole, pyridazine have been incorporated into peptoid backbone (Aditya and Kodadek 2012). Also the incorporation of a 1,5-disubstituted-1,2,3-triazole (Pokorski et al. 2007) or a 1,3,5-triazine (Lee et al. 2010) unit into the peptoid has resulted in improved conformational

stability of those peptoids. In addition, several nitrogen containing heterocycles such as imidazoles, quinolines, indoles, pyridines and pyrazines have been incorporated as N-side chains in peptoids (Burkoth et al. 2003).

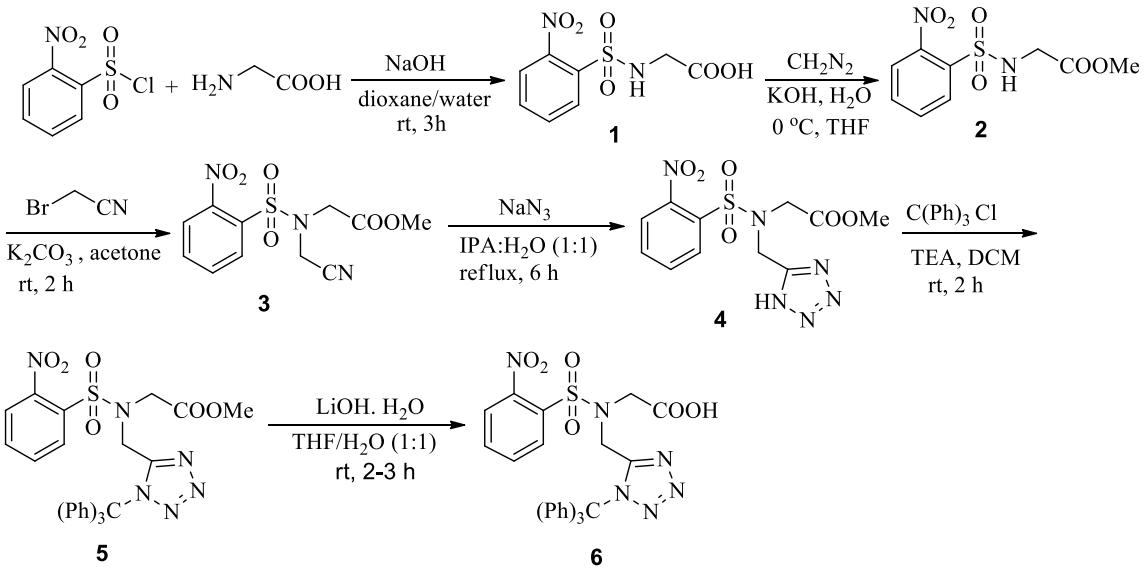
Tetrazoles are an important class of heterocycles with wide range of applications as drugs in pharmaceuticals and as carboxylic acid surrogates for biological studies (Singh et al. 1980; Myznikov et al. 2007; Meanwell 2011; and; Biot et al. 2004). They are also known as cis amide bond surrogates with increased resistance towards metabolic degradation pathways (Zabrocki et al. 1988, 1992). Click chemistry {[3 + 2] cycloaddition between azide and alkyne/nitrile} based triazole or tetrazole formation is often employed to bridge two molecular fragments to increase the conformational order and to improve the bioactivity (Holub and Kirshenbaum 2010, 2007, 2006; Jang et al. 2005; Sidonie et al. 2012). Tetrazole-containing analogues of amino acids and peptides exhibit biological activity including antibacterial (Stone et al. 2004), antiviral (Johansson et al. 2003), antiarrhythmic activity (Wu et al. 2006) and also serves as inhibitors of nitric oxide biosynthesis (Penke et al. 2006). It is also well documented in the literature that the derivatives of tetrazoles are useful as stimulators of growth hormone release and are explored as metallo-protease inhibitors (Popova and Trifonov 2015). In this report, we present a design for the synthesis of a (1*H*-tetrazol-5-yl)methyl tethered cyclic peptoid tetramer by a solution phase head to tail macrocyclization approach. The requisite tetramer was accessed via solid phase monomer approach using Nosyl-protected *N*-(1-trityl-1*H*-tetrazol-5-yl)methyl substituted glycine. The building block can be obtained by a convenient synthesis involving Click reaction of Nosyl-protected *N*-(cyanomethyl)glycine methyl ester and sodium azide as a key step.

Results and Discussion

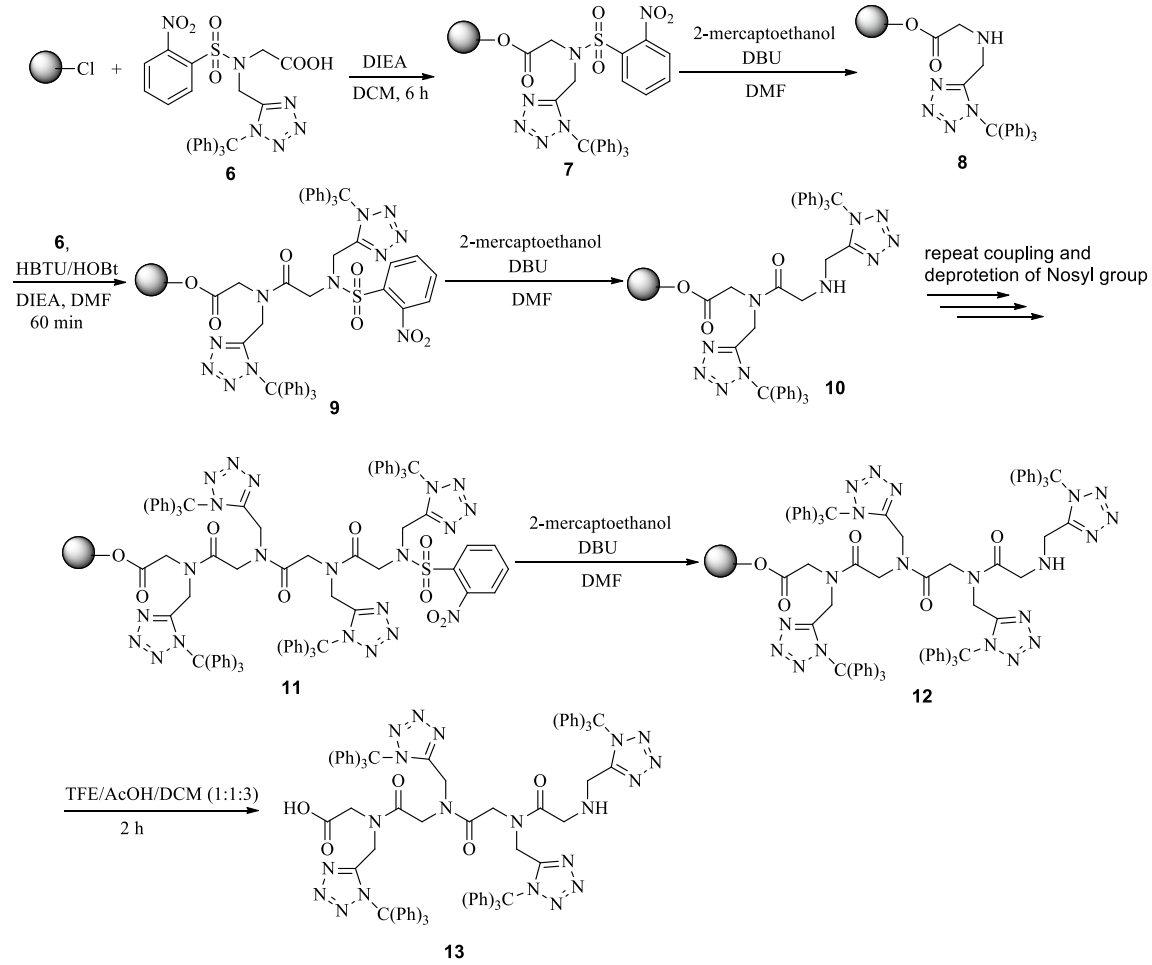
We started with the preparation of monomeric Nosyl-protected *N*-(1-trityl-1*H*-tetrazol-5-yl)methyl substituted glycine (Nosyl = *o*-nitrobenzenesulfonyl) (Scheme 1). Firstly, the alkylation of Nosyl-protected glycine methyl ester with bromoacetonitrile was carried out. Various bases such as NaH, K_2CO_3, Cs_2CO_3 and Na_2CO_3 were screened in different solvents including DMF, THF, acetone and CH_3CN. The K_2CO_3as a base in acetone solvent at room temperature was found to be an optimized condition for the N-alkylation on Nosyl protected glycine methyl ester with 95% yield.

Thus obtained alkylated compound was subjected to Click chemistry employing NaN_3 in DMF under reflux condition for 6 h (Scheme 1). After completion of the reaction (as monitored by TLC), the reaction mixture was cooled and treated with water and ethyl acetate (EtOAc). A simple work up provided the desired Nosyl-protected *N*-(1*H*-tetrazol-5-yl)methyl substituted glycine methyl ester. In the next step, the acidic tetrazole-NH is protected with trityl group to avoid any undesired side reactions during solid phase peptide synthesis (SPPS). The ester hydrolysis resulted in the desired monomer Nosyl-protected *N*-(1-trityl-1*H*-tetrazol-5-yl)methyl substituted glycine (80%) **6** to be employed in SPPS of target *N*-(1*H*-tetrazol-5-yl)methyl peptoid.

With the monomeric building block in hand, SPPS of (1-trityl-1*H*-tetrazol-5-yl)methyl peptoid tetramer was undertaken (Scheme 2). The 2-chlorotrityl resin was



Scheme 1 Preparation of Nosyl-protected *N*-(1-trityl-1*H*-tetrazol-5-yl)methyl substituted glycine monomer



Scheme 2 Solid phase synthesis of (1-trityl-1*H*-tetrazol-5-yl)methyl peptoid tetramer

chosen as the support. The chlorotrityl resin was treated with the *N*-(1-trityl-1*H*-tetrazol-5-yl)methyl substituted glycine monomer in the presence of diisopropylethylamine (DIEA)/DCM for 6 h to establish an ester linkage. The first attachment was confirmed by weight gain experiments.

After the successful attachment of first monomer, the Nosyl group was deprotected using 2-mercaptoethanol and 1,8-diazabicyclo[5.4.0]undec-7-ene(DBU) in DMF solvent. Thus, 2-mercaptoethanol (10 equiv.) and DBU (5 equiv.) in DMF were added to the resin and the mixture was allowed to swirl for 20 min. The same process was repeated again to avail the complete Nosyl deprotection. Next, the resin attached monomer was then coupled with the monomer **6** using*O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate (HBTU; 4 equiv.)/1-hydroxybenzotriazole (HOBt; 4 equiv.)/DIEA (6 equiv.) in DMF for 60 min. The formation of dimer was confirmed by the cleavage of small portion of resin for mass analysis. In the next stage, deprotection of nosyl group and the subsequent coupling with peptoid monomer **6** was repeated to achieve the desired peptoid tetramer **11**. After deprotection of Nosyl group, the (1-trityl-1*H*-tetrazol-5-yl)methyl tethered peptoid tetramer was released from 2-chlorotrityl resin. The resin cleavage was performed with trifluoroethanol (TFE)/AcOH/DCM (1:1:3) solution for 2 h at room temperature. The resin was filtered and washed with the DCM thoroughly. The combined filtrate was evaporated to dryness at reduced pressure to afford the free peptoid tetramer as a solid in 81% yield. The product was purified by semi-Prep RP-HPLC chromatography and characterized by MALDI-TOF mass spectrometry (see supporting information).

Cyclic peptides and cyclic peptidomimetics are of great interest in drug discovery and chemical biology. Relative to their linear counterparts, they have desirable features such as protein binding property (Roxin and Zheng 2012). In the next part of the study, the cyclization of thus obtained (1-trityl-1*H*-tetrazol-5-yl)methyl tethered peptoid tetramer was carried out. Various coupling reagents were examined for the effective cyclization of (1-trityl-1*H*-tetrazol-5-yl)methyl tethered peptoid tetramer to obtain the 18 membered cyclic

peptoid (Table 1). In general, macrocyclization is a yield limiting step which has to be performed under high dilution conditions. A suitable coupling reagent can render an efficient cyclization. Thus, to affect the head to tail cyclization of the linear peptoid several coupling reagents such as benzotriazole-1-yloxytris(pyrrolidino)-phosphonium hexafluorophosphate (PyBOP), bromotris(pyrrolidino)phosphonium hexafluorophosphate (PyBrOP), 2-(6-chloro-1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethylaminium hexafluorophosphate (HCTU), HBTU and *N,N*'-diisopropylcarbodiimide (DIC) were examined (Table 1).

All the coupling reagents (Table 1, entries b–e) could generate the desired cyclic product albeit with low yield and significant by products. However, cyclization using PyBOP (Table 1; entry a) resulted in a better yield (60%) of the cyclic peptoid tetramer as compared to other reagents. In a typical cyclization, the linear peptoid (100 mg) was dissolved in DMF (140 ml). PyBOP (40.48 mg, 1.2 eq), DIEA (33.87 µl, 3 eq) was added to the reaction mixture and allowed to stir for 6–8 h at room temperature (Scheme 3). The formation of undesired products may be due to the ring strain has been reported previously for cyclization of tetramer and pentamer peptoids (Davies 2003). It can be noted that, PyBOP is especially useful for the cyclization of hindered amino acids and has been successfully employed in some of the previously reported macrocyclizations (Shin et al. 2007; Shah et al. 2008).

After completion of the peptoid cyclization, the trityl groups were deprotected using 10% TFA in DCM for 3 h. The reaction mixture was filtered and washed with DCM. Evaporation of TFA followed by lyophilization provided the desired cyclic peptoid derivative as a gummy solid in 60% yield. HRMS analysis of the crude product confirmed the formation of the cyclic peptoid. The RP-HPLC analysis of crude reaction mixture had two peaks with retention times at 13.67 (corresponding to the cyclic peptoid **15)** and at 18.60 (unprotected linear N-methyltetrazole peptoid tetramer **13)**. The crude cyclic peptoid was then dissolved in acetonitrile : water (1 : 1) and purified by semi-Prep RP-HPLC chromatography (conditions: 10–80% ACN in 90 min, 232 nm, 10 ml flow). The pure product **15** was obtained about 52% yield and characterized by HRMS analysis.

Table 1 Optimization of macrocyclization using coupling reagents

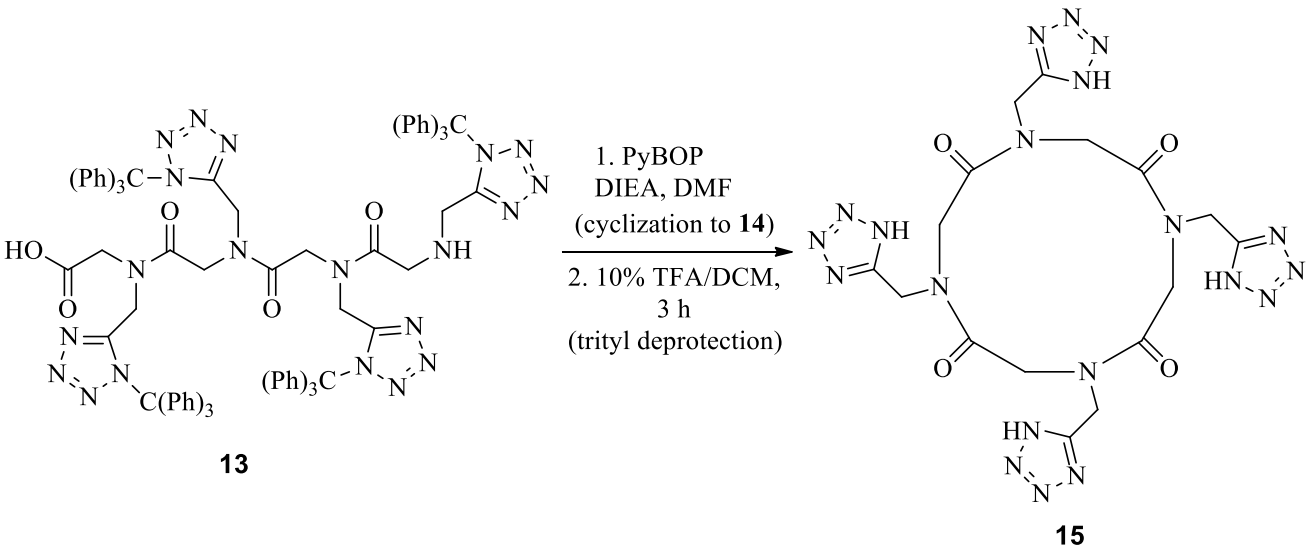
Entry	Condition	Yield (%)[a]
a	PyBOP/DIEA/DMF	60
b	PyBrOP/DIEA/DMF	18
c	HCTU/DIEA/DMF	25
d	HBTU/DIEA/DMF	15
e	DIC/DIEA/DMF	12

[a]Yield of the crude product

Experimental

Materials and Methods

All solvents, reagents and glycine were purchased from sigma aldrich company and were used as received. All reaction mixtures were stirred magnetically and were monitored by thin-layer chromatography (TLC) using precoated silica gel 60F-254 (0.25) plates. Spots were visualized with UV light and ninhydrin. Solvents were evaporated under



Scheme 3 Head to tail macrocyclization of (1-trityl-1*H*-tetrazol-5-yl)methyl tethered peptoid tetramer using PyBOP and detritylation

reduced pressure at 40 °C. Column chromatography was carried out using silica gel (100–200 mesh). ^{1}H NMR spectra were recorded on a Bruker AMX 300 MHz with $CDCl_3$ as an internal standard. Mass spectra were recorded using high resolution mass spectrometer (HRMS) and electron spray ionization mass spectrometry (ESI–MS) of mass spectrometer. The splitting patterns of proton are s (singlet), d (doublet), t (triplet) m (multiplet) and br s (broad singlet). The synthetic purity was determined by using analytical RP-HPLC, column: Agilent eclipse XDB-C-18, pore size −5 µm, diameter × length = 4.6 × 150 mm (method: Water-MeCN; MeCN 30% −100% in 30 min; gradient 0.1% TFA; λ = 254 nm, flow: 0.5 ml/min).

General Procedure for the Preparation of Methyl 2-(N-(cyanomethyl)-2-nitrophenylsulfonamido)Acetate (3)

To a solution of nosyl protected glycine methyl ester (1.0 equiv.) in acetone was added K_2CO_3 (2.2 equiv.) and 2-bromoacetonitrile (1.1 equiv.). The reaction mixture was allowed to stir at room temperature till completion (as monitored by TLC). Solvent was evaporated in vacuo and the residue was dissolved in EtOAc (3 × 10 ml). The organic layer was washed with 5% HCl (20 ml), water (20 ml), brine solution (10 ml) and dried over anhydrous Na_2SO_4 and the organic layer was evaporated to obtain the product.

General Procedure for the Preparation of Methyl 2-(N-((1*H*-tetrazol-5-yl) methyl)-2-nitrophenylsulfonamido)Acetate (4)

To a solution of methyl 2-(N-(cyanomethyl)-2-nitrophenylsulfonamido) acetate (1.0 equiv.) in IPA: H_2O (1:1), sodium azide (2.5 equiv.), sodium ascarbonate (0.1 equiv.) and copper sulphate (0.76 equiv.) were added. The reaction mixture was stirred at 80 °C for 6 h (as monitored by TLC). The reaction mixture was then diluted with water (3 × 10 ml) and ethyl acetate (3 × 15 ml). The organic layer was separated and washed with 5% HCl (20 ml), water (15 ml) brine solution (10 ml) and dried over anhydrous Na_2SO_4, followed by concentration to obtain the product.

General Procedure for the Preparation of Methyl 2-(2-nitro-N-((1-trityl-1*H*-tetrazol-5-yl)methyl) phenylsulfonamido)Acetate (5)

Methyl 2-(N-((1*H*-tetrazol-5-yl)methyl)-2-nitrophenylsulfonamido)acetate (1.0 equiv.) was dissolved in DCM, Et_3N (1.2 equiv.) and trityl chloride (1.5 equiv.) were added at 0 °C. The reaction mixture was stirred at rt about 2 h. Solvent was evaporated in vacuo and the residue was dissolved in EtOAc (3 × 10 ml). The organic layer was washed with water (20 ml), brine solution (10 ml) and dried over anhydrous Na_2SO_4 and the organic layer was evaporated to obtain the product about 80% yield.

Synthesis of Peptoid: The Tetramer Sequence was Carried Out by Following this General Procedure:

Nosyl Deprotection

β-Mercaptoethanol (10 equiv.) and DBU (5.0 equiv.) in DMF were added to the resin bound monomer (1.0 equiv.) and the mixture was allowed to swirl for 20 min. The same process was repeated again to ensure the complete deprotection of nosyl group.

Step 1: The chlorotrityl resin bound halogen was added to the solution of tetrazole substituted glycine monomer (1.0 equiv.), DIEA (5.0 equiv.) in dry DCM. Agitate the mixture with a shaker for 5 min, then add 1.5 equiv. of respective to the monomer and DIPEA. Agitate the mixture vigorously for 45 min, washed with DMF (5 × 2.0 mL).

Step 2: To the resin bound tetrazole substituted glycine amine was added to the solution of tetrazole substituted glycine monomer, HBTU (4.0 equiv)/HOBt (4.0 equiv)/DIEA (6.0 equiv) in DMF, and this was allowed to react for 60 min. After completion, the resin was drained and washed with DMF (6 × 2.0 ml).

The monomer coupling cycle was repeated until the desired tetramer length was achieved.

Cleavage Protocol

The peptoid product was cleaved from the resin by employing TFE/AcOH/DCM (1:1:3) solution for 2 h at room temperature with gentle stirring. The cleavage solution was filtered to remove the resin beads, and the filtrate was evaporated under a stream of nitrogen, resuspende in 1:1 acetonitrile/water and then lyophilized twice. The crude percent yield was calculated on the basis of the weight of the lyophilized product plus the appropriate counter ions.

General Procedure for Head to Tail Cyclization and Trityl Group Deprotection (15)

A solution of (1-trityl-1*H*-tetrazol-5-yl)methyl tethered peptoid tetramer (1.0 equiv.) in DMF and PyBOP (1.2 equiv.) was added DIEA (3.0 equiv.) to the reaction mixture and allowed to stir for 6–8 h at room temperature. The reaction vessel was flushed with nitrogen and sealed to exclude air. After completion of the reaction, 10% TFA in DCM was added and stirred for 3 h. The reaction mixture was diluted with 50% ACN in H_2O to quench the reaction. The diluted sample was analyzed by HPLC.

Characterization Data

Methyl 2-(N-(cyanomethyl)-2-nitrophenylsulfonamido) Acetate [3]

Yield: (86%), ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.59 (s, 3H), 4.24 (s, 2H), 4.54 (s, 2H), 8.17 (t, $J = 5.7$ Hz, 2H), 8.41 (d, $J = 5.4$ Hz, 2H) ppm; ESI-MS: m/z $[M+Na]^+$calcd for $C_{11}H_{11}N_3NaO_6S$: 313.04; found: 337.13.

Methyl 2-(N-((1H-tetrazol-5-yl) methyl)-2-nitrophenylsulfonamido)acetate [4]

Yield: (82%), ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.58 (s, 3H), 4.19 (s, 2H), 4.93 (s, 2H), 7.79–8.11 (m, 4H) ppm; ESI-MS: m/z $[M+Na]^+$calcd for $C_{11}H_{12}N_6NaO_6S$: 356.05; found: 380.11.

2-(2-Nitro-N-((1-trityl-1H-tetrazol-5-yl)methyl) phenylsulfonamido)Acetic Acid [6]

Yield: (75%), ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.15 (s, 2H), 4.28 (s, 2H), 7.21–7.80 (m, 19H), 8.50 (br s, 1H) ppm.

Conclusion

We have developed an efficient strategy for the synthesis of peptoid monomer Nosyl-protected *N*-(1*H*-tetrazol-5-yl) methyl substituted glycine. Furthermore, a convenient solid phase synthesis of novel (1-trityl-1*H*-tetrazol-5-yl)methyl peptoid tetramer and its cyclization in solution phase to the corresponding cyclomer has been achieved. The peptoid tetramer was synthesized using solid phase monomer strategy and the coupling reagent PyBOP could achieve the head to tail cyclization of linear tetramer into the cyclic peptoid in moderate yield. The formation of the linear and cyclic peptoid tetramer was confirmed by HRMS analysis. The pure cyclic (1*H*-tetrazol-5-yl)methyl peptoid molecule was isolated after semi-prep RP-HPLC purification.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and Animal Participants This article does not contain any studies with human or animal subjects performed by the any of the authors.

Informed Consent Authors declare that there is no informed consent in the article.

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