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A simple protocol for the synthesis of triazole-linked cyclic glycopeptidomimetics: a sequential Ugi-MCR and azide–alkyne cycloaddition approach

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ABSTRACT

Sequential combination of Ugi-MCR and click chemistry has been employed for the synthesis of triazole linked cyclic glycopeptidomimetics. The protocol employs Poc-amino alkyl isonitriles, sugar-1-amines, azido acids, and simple aldehydes as precursors. The dual nature of the propargyloxycarbonyl (Poc) group was explored for amine protection as well as cycloaddition with an azide. All the cyclic glycopeptidomimetics are isolated and characterized.

Affluence of cyclic glycopeptides[1] in natural sources and the knowledge about their biological and structural significance emphasize the importance of the development of synthetic methodologies for such molecules and related analogs. From the biochemist's perspective, glycopeptide cyclization is an interesting aspect of study that may lead to valuable architectural repertoire possessing structurally and pharmacologically useful properties.[2] Cyclic glycopeptides do not possess ionizable N- and C-terminals rendering them with improved membrane permeability and stability to in vivo enzymatic degradation.[3] However, cyclization is, in general, yield-limiting and synthetically a difficult step. This evokes to suitably design the sites for gluing the head to tail affording a ring structure in an efficient manner through the establishment of a native or non-native linkage.[4] On the other hand, substantial focus has been paved toward development of new protocols for the construction of glycopeptidomimetics[5] and peptidomimetcis.[6] In the former, the carbohydrate is linked to peptide backbone through a non-native linkage and in the latter class of molecules, one or more amide bonds in the backbone are replaced by artificial tethers.

Multi-component reactions such as Ugi-MCR[7] and Passerini-3CR[8] are being utilized for accessing complex molecules from simple substrates.[9] Isonitrile based MCRs, especially those involving isocyano esters have emerged as tools of choice to access peptide-like constructs.[10] It is useful to tag MCRs with another reaction(s) in a sequential manner so as to modify the Ugi-product to obtain desired products.[11] Till recently, isocyano esters, prepared by N-modification of amino acid esters were the isonitrile components generally used in the MCRs. Sureshbabu and co-workers described another class of amino acid derived isonitriles by modifying the C-terminus of N-protected amino acids and the resulted N-protected amino alkyl isonitriles have been employed as key substrates in a couple of MCRs to obtain a few peptidomimetics.[12] The Cu-catalyzed azide–alkyne cycloaddition ('click' chemistry)[13] is a robust chemical transformation in bridging two components. This reaction has accelerated the research in drug discovery due to the efficient and non-sensitive reaction conditions, thus ideal for the synthesis of a library of compounds. Triazole has been used as a surrogate to the native bond in the synthesis of cyclic peptidomimetic and glycopeptidomimetic scaffolds[14] involving multistep protocol. Our interest in the development of a useful strategy for accessing cyclic neoglyco-peptidomimetics led us to explore a sequential combination of Ugi-MCR and azide–alkyne cycloaddition as a tool to synthesize the title compounds.

The present study involves the design of suitable starting components for MCR that would yield a linear molecule which can be cyclized through click reaction. A combination of an isonitrile, amine, aldehyde, and a carboxy compound would lead to a linear peptidic derivative wherein the isonitrile and carboxy acid components flank at either terminus. This directed us to deposit the alkyne and azide groups required to operate post-MCR step, in the isonitrile and carboxy substrates before initiating the MCR. In this context, it is to note that both azide and alkyne groups are compatible to Ugi reaction conditions. The azido acid was an

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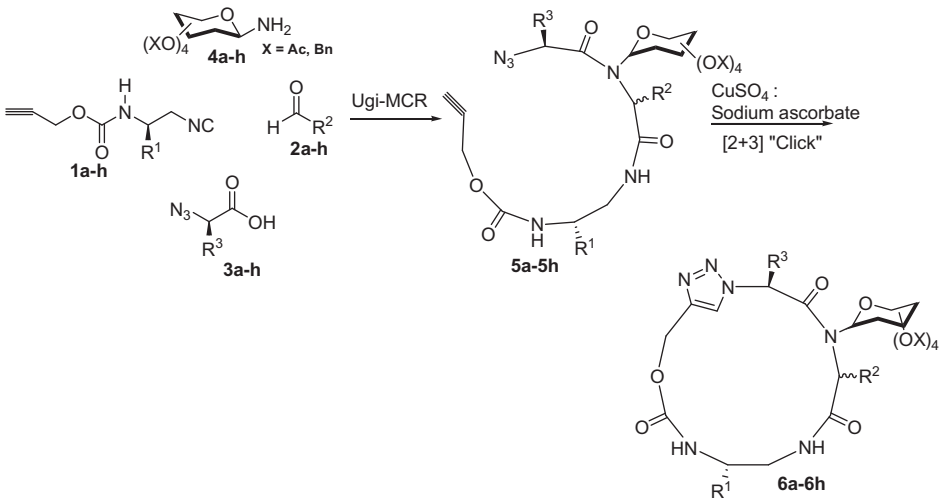
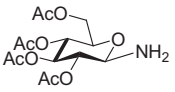
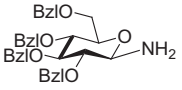
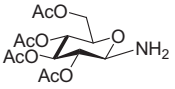
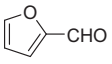
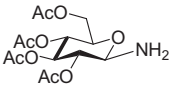
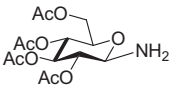
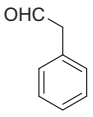
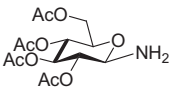
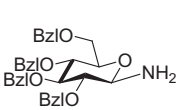
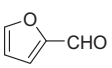
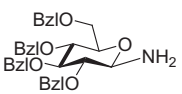
immediate choice as one of the components because it serves as amino acid precursor in peptide bond formation. Another key aspect is to obtain a linear peptidic unit possessing both isonitrile and alkyne groups as terminals. The dual utility of propargyloxycarbonyl (Poc) group can be explored for amino protection as well as a reactant for Huisgen's cycloaddition reaction.[15] Thus, Poc-protected amino alkyl isonitriles are chosen as suitable substrates in this protocol. The sugar component was selected as an amino component which can be prepared easily. The aldehydes were selected from the commercially available sources.

The preparation of the substrates was straightforward and simple. Briefly, azido acids were prepared by a reaction of amino acids with imidazole-1-sulfonyl azide as reported by Goddard-Borger.[16] For the preparation of 2,3,4,6-tetra-*O*-acetyl glucosyl-1-amine, glucose was reacted with acetyl chloride and the resulting 1,2,3,4,6-penta-*O*-acetyl-α,β-D-glucopyranose was reacted with HBr in AcOH to obtain 2,3,4,6-tetra-*O*-acetyl glycopyranosyl-1-bromide. Replacement of bromide with azide followed by catalytic hydrogenation of the azido group afforded 2,3,4,6-tetra *O*-acetyl glucopyranosyl-1-amine.[17] Poc-amino acids were prepared by



Scheme 1. Synthesis of triazole linked cyclic glycopeptidomimetics **6** via Ugi products **5**.

Table 1
List of Ugi products **5a–5h** and cyclic glycopeptidomimetics **6a–6h**

Entry	Poc-Xaa-ψ[CH_2NC] (**1**)	Aldehyde (**2**)	Azido acid (**3**)	Sugar amines (**4**)	Ugi-product (**5**) Yield (%)	Cyclic product (**6**) Yield (%)
1	Phe		Ala		75	64
2	Leu		Gly		71	61
3	Gly		Leu		69	65
4	Val		Leu		73	62
5	Leu		Gly		66	68
6	Ala		Phe		67	66
7	Isoleucine	HCHO	Val		72	59
8	Phe		Ala		65	60

treating amino acids with Poc-OPfp according to Chandrasekaran and co-workers[18] The carboxy terminus was modified into methylene isonitrile through a series of operations as described previously by us.[19]

The Ugi MCR was initiated by mixing equimolar quantities of the four reactants in MeOH. In a typical reaction, Poc-Val-ψ[CH_2NC] **1d**, azido-Leucine **3d** were added to a stirred solution of furfural **2d** and 2,3,4,6-tetra *O*-acetyl glucopyranosyl-1-amine **4d** in MeOH under nitrogen (Scheme 1). The course of the reaction was monitored through TLC. After 24 h, the crude reaction mixture was column chromatographed to obtain the desired linear peptidic product **5d** as solid in 73% yield. As expected, the product was a mixture of two diastereomers. The chiral HPLC analysis revealed that the two compounds were present in the ratio-95:5; however, the isomers were not separated any further. The same protocol was utilized to prepare a series of examples of Ugi adducts **5a–5h** (Table 1).[20] In the ultimate step, the head to tail cyclization of thus obtained linear molecule was undertaken.

During the cyclization reactions, dimerization and oligomerization are a concern.[21] This aspect is usually circumvented by taking millimolar concentration of the reaction mixture. However, the problem will not be so serious if the ring size is large so as to keep the strain at minimum.[22] In the present case, when the linear molecule **5d** was subjected to Cu catalyzed azide–alkyne cycloaddition, the designed triazole linked cyclic neoglycopeptide was formed as a major component along with only a small amount of dimer and meager quantities of other unidentified byproducts. It can be reasoned that the target molecule is a 15-membered ring and thus the ring strain is less due to which mono-cyclization is the major reaction.

In the initial experiment for the cyclization of **5d**, the catalytic system comprising $CuSO_4{\cdot}5H_2O$/sodium ascorbate in ^{t}BuOH/water was used. It led to **6d** in 62% yield in about 10 h at rt. In order to improve the yield as well as to reduce the duration of reaction, other catalysts CuI/DIPEA in acetonitrile and CuBr/1,8-Diazabicyclo[5.4.0] undec-7-ene (DBU) in toluene were explored. Both systems yielded only 40% and 46% of the cyclized product **6d**. In light of these results, the $CuSO_4$/sodium ascorbate was finally chosen and thus was utilized in the synthesis of **6a–6h**. In a typical reaction,[23] $CuSO_4$ (0.02 equiv, 0.64 mg), sodium ascorbate (0.3 equiv, 7.6 mg) were added to the solution of linear peptidic component **5d** (100 mg 0.128 mmol) in ^{t}BuOH/water (3:1; 120:40 mL). The resulting solution was allowed to stir for 10 h at rt. The reaction was monitored by RP-HPLC. A simple work-up afforded the target compound along with small amounts of dimer product. The desired cyclic glycopeptidomimetic **6d** was then isolated by column chromatography using *n*-hexane/EtOAc (40:60) in 62% yield (Table 1). The reaction worked well with other linear molecules as well. All the products **6a–6h** were characterized by mass and ^{1}H NMR spectroscopy.

In summary, an effective protocol has been designed to access cyclic glycopeptidomimetics by employing Ugi MCR and click reactions in a sequential manner. Poc-amino alkyl isonitrile is used for the first time in MCR reactions and the alkyne moiety of Poc group is made to participate in the intramolecular cycloaddition with an azide situated at the other terminus. The resulting cyclic neoglycopeptidomimetic was isolated in moderate yield and characterized. Click reaction is very efficient in bringing out the cyclization without considerable byproducts.

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20. General procedure for the preparation of Ugi products **5a–h**: To a stirred solution of aldehyde **2** (0.1 mmol) and glucose amine **4** (0.1 mmol) in methanol (5 mL) Poc-AA-ψ[CH_2NC] **1** (0.1 mmol) and azido acid **3** (0.1 mmol) were added under nitrogen atmosphere. The stirring was continued for 18 h. After completion of the reaction by TLC, the solvent was evaporated and the residual mass extracted into ethyl acetate. The organic layer was washed with water (2 × 15 mL) and brine (1 × 15 mL) and concentrated under reduced pressure to yield the crude product. The crude was then purified by column chromatography (35% AcOEt in *n*-hexane) to obtain the pure linear peptidic component **5** as a solid (yield 73%).
Characterization data for compound **5d**: Brown solid; mp = 76–78 °C; IR (KBr) υ_{max} = 1692, 1735, 2122, 3340 cm^{-1}; R_f = 0.21 (EtOAc: *n*-hexane, 40:60); RP-HPLC R_t = 16.8 (20–100% CH_3CN, 30 min); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.87 (d, 6H, *J* = 5.8 Hz), 0.93 (d, 6H, *J* = 6.4 Hz), 1.32 (m, 2H), 1.65 (m, 1H), 1.98 (s, 12H), 2.1 (t, 1H, *J* = 4.6 Hz), 2.31 (m, 1H), 2.48 (s, 1H), 3.46 (m, 2H), 4.10 (m, 1H), 4.24 (d, 2H, *J* = 7.2 Hz), 4.53 (s, 2H), 4.61 (m, 1H), 4.69 (m, 1H), 4.98 (m, 1H), 5.21 (m, 1H), 6.02 (s, 1H), 6.10-6.22 (m, 2H), 6.24 (d, 1H, *J* = 6.4 Hz), 6.89 (br, 2H), 7.18 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 17.6, 20.8, 21.8, 22.1, 22.5, 30.6, 41.2, 53.4, 56.4, 56.6, 58.3, 59.1, 69.1, 69.2, 69.8, 76.2, 76.3, 78.6, 79.1, 106.4, 110.2, 141.8, 152.8, 155.3, 169.1, 173.2; HRMS Calcd for

$C_{35}H_{48}N_6O_{14}$ *m*/z 799.3100 [M+Na]$^+$. Found 799.3101, 155.3, 169.1, 173.2; HRMS Calcd for $C_{35}H_{48}N_6O_{14}$ *m*/z 799.3100 [M+Na]$^+$. Found 799.3101.

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23. Typical procedure for the preparation of triazole linked cyclic neoglycopeptidomimetic **6d**: To a 250 mL round-bottomed flask charged with linear peptidic component **5d** (0.10 g, 0.128 mmol, 1 equiv) in ^{t}BuOH (120 mL) and H_2O (40 mL) were added sodium ascorbate (7.6 mg, 0.038 mmol, 0.3 equiv), $CuSO_4$, and·$5H_2O$ (0.64 mg, 0.0025 mmol, 0.02 equiv). The solution was then stirred at rt for about 10 h. Completion of the reaction was monitored by RP-HPLC. The reaction mixture was then filtered through a pad of celite to remove the salts and washed thoroughly with EtOAc (3 × 25 mL). Crude product was then isolated by giving water (1 × 30 mL) and brine (1 × 30 mL) wash. The product was purified via chromatography (60% EtOAc in hexane) to afford triazole linked cyclic neoglycopeptidomimetic **6d** (62 mg, 62% yield) as a solid.

Characterization data for compound **6d**: Brown solid; mp = 137–141 °C; IR (KBr) υ_{max} = 1692, 1735, 2122, 3340 cm^{-1}; R_f = 0.21 (EtOAc: *n*-hexane, 40:60); RP-HPLC R_t = 16.8 (20–100% CH_3CN, 30 min); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.93 (d, 6H, *J* = 6.8 Hz), 0.98 (d, 6H, *J* = 7.2 Hz), 1.20 (s, 12H), 1.73 (m, 1H), 1.89 (m, 2H), 2.32 (m, 1H), 3.48 (m, 2H), 4.16 (m, 1H), 4.26 (d, 2H, *J* = 5.8 Hz), 4.54 (t, 1H, *J* = 4.8 Hz), 4.63 (m, 1H), 4.66 (m, 1H), 4.96 (m, 1H), 5.23 (m, 1H), 5.28 (s, 2H), 6.06 (s, 1H), 6.12–6.21 (m, 2H), 6.24 (d, 1H, *J* = 6.2 Hz), 6.86 (br, 2H), 7.16 (s, 1H), 7.21 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 17.4, 20.9, 21.9, 22.2, 30.6, 40.4, 45.3, 56.4, 58.2, 58.3, 59.2, 64.3, 67.6, 69.5, 69.8, 76.3, 79.2, 106.4, 110.2, 120.6, 141.8, 142.1, 152.1, 157.4, 170.6, 171.2, 173.2; HRMS calcd for $C_{35}H_{48}N_6O_{14}$ *m*/z 799.3100 [M+Na]$^+$, found 799.3104.