Efficient solid-phase based synthesis of jasplakinolide analogs by intramolecular azide/alkyne cycloaddition

Tai-Shan Hu, René Tannert, Hans-Dieter Arndt, Herbert Waldmann*

Universität Dortmund, Fachbereich Chemie, Otto-Hahn-Str. 6, D-44227 Dortmund, Germany, and Max-Plank-Institut für Molekulare Physiologie, Otto-Hahn-Str. 11, D-44227 Dortmund, Germany

herbert.waldmann@mpi-dortmund.mg.de

Supplementary Information

Table of contents

Table of contents S1
General methods S2-S3
General procedures S4-S6
Analytical data for compounds 5b, 7j, 3a-3d, 3h, 10a-10c, 4a-4d, 4h-4l and 2a-2l S7-S30
$^1$H-NMR spectra for compounds 3a-3d, 3h, 10a-10c, 4a-4d, 4h-4l and 2a-2l S31-S59
General methods

All solvents, when not purchased in suitable purity or dryness, were distilled using standard methods\(^1\). Deionized water was used for all experiments. Thin Layer Chromatography (TLC) was carried out on Merck precoated silica gel plates (60F-254) using ultraviolet light irradiation at 254 nm or KMnO\(_4\) solution as staining reagent (1 g KMnO\(_4\), 6.6 K\(_2\)CO\(_3\), 1.7 mL 5% NaOH solution, 100 mL H\(_2\)O). Silica gel chromatography was performed using silica gel from J. T. Baker or Merck (particle size 40-60 µm) under approximately 0.5 bar pressure.

\(^1\)H- and \(^1\)C-NMR spectra were recorded on Bruker DRX 500 (500 MHz (\(^1\)H) and 125.7 MHz (\(^1\)C)), Bruker DRX 400 (400 MHz (\(^1\)H) and 100.5 MHz (\(^1\)C)) and Varian Mercury 400 (400 MHz (\(^1\)H) and 100.6 MHz (\(^1\)C)) spectrometers. Chemical shifts are expressed in parts per million (ppm) and the spectra are calibrated to residual solvent signals of CDCl\(_3\) (7.26 ppm (\(^1\)H) and 77.0 ppm (\(^1\)C)) and DMSO (2.50 ppm (\(^1\)H) and 39.43 ppm (\(^1\)C)), respectively. Coupling constants are given in Hertz (Hz) and the following notations indicate the multiplicity of the signals: s (singlet), d (doublet), t (triplet), q (quartet), m (multiple), br (broad signal).

Optical rotations were measured in a Schmidt + Haensch Polartronic HH8 polarimeter at 589 nm, with concentrations given in g/100mL.

Fourier transform infrared spectroscopy (FT-IR) spectra were obtained with a Bruker Tensor 27 spectrometer (ATR, neat). Wavenumbers \(\nu\) are given in cm\(^{-1}\).

Preparative HPLC was performed on a Waters machine using a Macherey Nagel C18 gravity 5 µm Reversed Phase column. The separations were started at 10% MeCN (with 0.1% TFA) in H\(_2\)O (with 0.1% TFA), and the MeCN proportion was linearly increased to 100% over 20 min with a flow of 20 mL·min\(^{-1}\).

High Resolution Mass Spectra were recorded on a Jeol SX 102 A (FAB; matrix m-nitrobenzylalcohol) or Thermo Electron LTQ Orbitrap (ESI; source voltage 3.8 kV) spectrometer.

Melting points were determined with a Büchi Melting Point B-540 apparatus (uncorrected).

---

All reagents were purchased from commercial suppliers (Acros, Aldrich, Novabiochem, Fluka) and used without purification. The following building blocks were prepared according to known procedures: homopropargylic alcohol \(9k\) as well as the azido building blocks \(7a\) and \(7b\).

\[9k\] \hspace{1cm} \[7a\] \hspace{1cm} \[7b\]

General Procedures

A general procedure for the synthesis of acid 3 (procedure 1)\(^5\)

To a suspension of 2-Cl-trityl chloride resin (280 mg) in DCM (3 mL) were added Fmoc-\(\beta\)-AlaOH (5, \(R^1 = H, 0.225\) g, 0.72 mmol), Diisopropylethylamine (DIPEA, 0.48 mL, 2.89 mmol). After shaken for 1h, the resin was filtered, and the residue resin sites were capped with a mixture of DCM/MeOH/DIPEA (17:2:1, 3 \(\times\) 3 mL, 3 min for each time). After filtration, the resin was washed with DCM (3 \(\times\) 4 mL), and dried in vacuo. The loading was determined by quantitative Fmoc analysis to be 0.98 mmol/g.

The resin was subjected to Fmoc-peptide synthesis using the following conditions:

1. Fmoc deprotection: 20% piperidine in DMF (8 mL) for 30 min, followed by washing with DMF (4 \(\times\) 4 mL) and DCM (4 \(\times\) 4 mL).
2. Coupling conditions: (a) Fmoc-D-TrpOH (0.358 g, 0.84 mmol), HOBt (0.129 g, 0.84 mmol), and DIC (0.13 mL, 0.84 mmol) in DMF (8 mL), 1.5 h. (b) Fmoc-L-AlaOH (0.261 g, 0.84 mmol), HOBt (0.129 g, 0.84 mmol), and DIC (0.13 mL, 0.84 mmol) in DMF (8 mL), 1.5 h. (c) azido acid, 7 (3 equiv), HOBt (0.129 g, 0.84 mmol), and DIC (0.13 mL, 0.84 mmol) in DMF (8 mL), 1.5 h. Following all the couplings, the resin was filtered and washed with DMF (6 \(\times\) 4 mL) and DCM (6 \(\times\) 4 mL).

The above procedure gave polymer-bound peptide 8.

On-resin 1,3-dipolar cycloaddition reaction: polymer-bound peptide 8 (0.14 mmol, 1 equiv) was treated with alkyne 9 (5 equiv), DIPEA (10 equiv) and CuI (0.1 equiv) in degassed THF (4 mL) for 16 h at rt. Resin was filtered and washed with THF (4 \(\times\) 4 mL) and DCM (4 \(\times\) 4 mL).

Acidic Cleavage: Resin (0.14 mmol) was treated with a mixture of acetic acid, trifluoroethanol and DCM (1:1:8, 2 \(\times\) 4 mL, each 1h). After filtration, the combined filters were condensed under reduced pressure to give acid 3 (>68% overall yield).

A typical procedure for the macrolactonization of 3 (procedure 2)

To a solution of seco acid 3d (42 mg, 0.08 mmol) in DCM/DMF (40 mL/2 mL) at room temperature was added DIPEA (0.16 mL, 0.93 mmol), DMAP (117 mg, 0.96 mmol) and 2,4,6-trichlorobenzoyl chloride (75 μL, 0.48 mmol). The resulting mixture was stirred for 26 h, and sat. aq. NH₄Cl solution (8 mL) was added. The aqueous phase was extracted with DCM (2 × 10 mL), and the combined organic layers were washed with brine and dried with MgSO₄. After filtration, the solvent was removed under reduced pressure and the residue was purified by preparative HPLC to give 24 mg (59%) of cyclic peptide 2d as a white solid. In cases of seco acids 3e-3g, the crude products from macrolactonization were treated with TBAF (2 eq.) in THF at 0 °C for 2h. Removal of the solvent gave a residue, which was purified by preparative HPLC to give 2e-2g, respectively.

A general procedure for the preparation of azido acid 10 (procedure 3)
The polymer-bound peptide 8 (0.14 mmol), prepared according to Fmoc-peptide synthesis described in procedure 1, was treated with a mixture of acetic acid, trifluoroethanol and DCM for 2 h. (1:1:8, 2 × 4 mL, each 1h). After filtration, the combined filters were condensed under reduced pressure to give azido acid 10.

A typical procedure for the preparation of azido alkyne 4 by esterification (procedure 4)
To a solution of azido acid 10a (R₁ = H, n = 1, 0.291 g, 0.66 mmol) in DCM/DMF (16 mL/2.5 mL) propargyl alcohol (0.15 mL, 2.57 mmol), EDC (0.253 g, 1.32 mmol), DMAP (0.161 g, 1.32 mmol) and DIPEA (0.22 mL, 1.32 mmol) were added. The reaction mixture was stirred at room temperature for 8 h, and quenched with sat. aq. NH₄Cl (5 mL) solution. The aqueous phase was extracted with DCM (8 mL × 2), the combined organic layers were washed with brine and dried with MgSO₄. After filtration and removal of the solvent, the residue was purified by silica gel chromatography (cyclohexane/EA 1:1 to DCM/MeOH 25:1 to DCM/MeOH 20:1) to give 0.220 g (70%) of 4a as a white solid.

A typical procedure for the preparation of azido alkyne 4 by amide bond formation (procedure 5)
To a solution of azido acid 10b ($R_1 = H$, $R_2 = H$, $n = 2$, 0.150 g, 0.33 mmol) in DCM/DMF (7 mL/1.4 mL) propargyl amine (0.085 mL, 1.32 mmol), EDC (0.126 g, 0.66 mmol) and DIPEA (0.11 mL, 0.66 mmol) were added. The reaction mixture was stirred overnight at room temperature for 8 h, and the precipitate was collected to give 0.130 g (80%) of 4l as a white solid.

A typical procedure for the Cu(I)-catalyzed intramolecular 1,3-dipolar cycloaddition reaction of azido alkyne 4 (procedure 6)

4a (100 mg, 0.21 mmol) was dissolved in a small amount of DMSO (ca 0.2 mL) and diluted with CH$_3$CN/THF (160 mL/40 mL). Argon was bubbled through the resulting solution for 30 min. DIPEA (0.11 mL, 0.64 mmol), 2,6-lutidine (47 μL, 0.40 mmol) and CuI (14 mg, 0.07 mmol) were added. After stirring at room temperature for 14 h the reaction mixture was filtered and the volatiles were removed. (In case of 4i, the resulting residue was treated with 1.1 equiv of TBAF in THF at 0 °C for 15 min, and then THF was removed under reduced pressure) The residue was purified by preparative HPLC to give 87 mg (87%) of cyclic peptide 2a as a white solid.
Analytical Data

Synthesis of (R)-N-Fmoc-O-TBS-β-tyrosine 5b

n-Butyllithium (2.5 M solution in hexane, 5.4 mL, 13.7 mmol, 1.5 equiv) was added dropwise to a stirred solution of (S)-N-benzyl-N-α-methylbenzylamine (2.9 mL, 13.7 mmol, 1.6 equiv) in anhydrous THF (60 mL) at -78 °C under Argon. After 30 min, a solution of benzyl (E)-3-(4-tert-butyldimethylsilyloxyphenyl)prop-2-enoate (3.320 g, 9.0 mmol) in anhydrous THF (20 mL) was added dropwise. The mixture was stirred at -78 °C for 2 h before addition of sat. aq. NH₄Cl (20 mL). The aqueous phase was extracted with Ethyl acetate (EA, 3 × 10 mL). The combined organic phases were washed with brine and dried over MgSO₄. After filtration and concentration, the residue was purified by column chromatography on silica gel (cyclohexane/EA, 20:1 then 10:1) to give benzyl (R)-3-(benzyl((S)-1-phenylethyl)amino)-3-(4-tert-butyldimethylsilyloxyphenyl)propanoate (3.215 g, 62%) as a yellow syrup. \([\alpha]_D^{\circ} -0.64\) (c 0.9, CHCl₃); ¹H-NMR (500 MHz, CDCl₃) ppm 7.40 (d, 2H, \(J = 7.4\) Hz), 7.34-7.27 (m, 5H), 7.25-7.15 (m, 8H), 7.13 (dd, 2H, \(J = 7.0, 2.5\) Hz), 6.79 (d, 2H, \(J = 8.5\) Hz), 4.92 (d, 1H, \(J = 12.4\) Hz), 4.89 (d, 1H, \(J = 12.4\) Hz), 4.41 (dd, 1H, \(J = 9.6, 5.4\) Hz), 3.99 (q, 1H, \(J = 6.8\) Hz), 3.69 (d, 1H, \(J = 15.0\) Hz), 3.65 (d, 1H, \(J = 15.0\) Hz), 2.68 (dd, 1H, \(J = 14.7, 5.4\) Hz), 2.60 (dd, 1H, \(J = 14.7, 9.6\) Hz), 1.21 (d, 3H, \(J = 6.8\) Hz), 0.99 (s, 9H), 0.19 (s, 6H). ¹³C NMR (100 MHz, CDCl₃) 171.7, 154.7, 144.2, 141.5, 135.8, 134.2, 129.1, 128.4, 128.09, (two more carbons are overlapped in this region) 128.06, 128.01, 127.8, 126.5, 119.7, 66.0, 58.8, 56.8,

---

Pd(OH)$_2$ on Carbon (0.917 g) was added to a solution of benzyl (R)-3-(benzyl((S)-1-phenylethyl)amino)-3-(4-tert-butyldimethylsilyloxyphenyl)propanoate (3.670 g, 6.3 mmol) in EtOH (50 mL). The mixture was stirred under 6 bar H$_2$ for 20 h at rt, and 6 mL of AcOH was added to dissolve the precipitate. After filtration through Celite® and wash with EtOH, the filtrate was concentrated under reduced pressure and the residue was triturated with EtOH (5 mL) to give, after filtration, (R)-3-amino-3-(4-tert-butyldimethylsilyloxyphenyl)propanoic acid (1.480 g, 79%) as a white solid. [$\alpha$]$_D$ +8.0 (c 0.92, MeOH), $^1$H NMR (400 MHz, CD$_3$OD) 7.35 (d, 2H, $J = 8.5$ Hz), 6.90 (d, 2H, $J = 8.5$ Hz), 4.47 (dd, 1H, $J = 9.7, 4.5$ Hz), 2.76 (dd, 1H, $J = 16.7, 9.7$ Hz), 2.64 (dd, 1H, $J = 4.5, 16.7$ Hz), 1.00 (s, 9H), 0.20 (s, 6H); $^{13}$C-NMR (100 MHz, CD$_3$OD) 177.3, 157.7, 131.4, 129.6, 121.8, 53.93, 41.3, 26.2, 19.1, -4.3; IR (neat) 2930, 2857, 1628, 1610, 1554, 1538, 1511, 1298, 1262, 919, 836, 783; HRMS (FAB) Calcd. for C$_{15}$H$_{26}$NO$_3$Si (M+H$^+$) 296.1682; Found 296.1667

To as suspension of (R)-3-amino-3-(4-tert-butyldimethylsilyloxyphenyl)propanoic acid (1.020 g, 3.45 mmol) in a mixture of dioxane and water (1:1, 34 mL) at 0 °C were added NaHCO$_3$ (1.259 g, 13.79 mmol) and FmocOSu (1.397 g, 4.14 mmol). The mixture was stirred at 0 °C for 1 h, then allowed to stir at rt for 4 h, acidified to pH = 2 with 6 N HCl, and extracted with EA (2 × 30 mL). The combined organic phases were washed with brine, and dried over MgSO$_4$. After filtration and concentration, the residue was purified by column chromatography on silica gel (DCM then DCM/MeOH 20:1) to give (R)-N-Fmoc-O-TBS-β-tyrosine 5b (1.706 g, 95%) as a white foam-like solid. [$\alpha$]$_D$ +21.4 (c 1.2, CHCl$_3$); $^1$H-NMR (500 MHz, CD$_3$OD) 7.78 (d, 2H, $J = 7.5$ Hz), 7.62 (d, 2H, $J = 7.3$ Hz), 7.36 (m, 2H), 7.27 (m, 2H), 7.21 (d, 2H, $J = 8.2$ Hz), 6.79 (d, 2H, $J = 8.4$ Hz), 5.05 (t, 1H, $J = 6.9$ Hz), 4.32 (m, 2H), 4.19 (t, 1H, $J = 6.7$ Hz), 2.79 (dd, 1H, $J = 15.5, 8.6$ Hz), 2.71 (dd, 1H, $J = 15.5, 6.3$ Hz), 0.99 (s, 9H), 0.19 (s, 6H); $^{13}$C-NMR (100 MHz, CD$_3$OD) 174.3, 158.0, 156.2, 145.2, 142.5, 136.3, 128.7, 128.6, 128.1, 126.2, 121.1, 120.9, 67.7, 52.8, 48.4, 42.1, 26.2, 19.0, -4.2; IR (neat) 2953, 2930, 2857, 1708, 1608, 1252, 912, 838, 738; HRMS (FAB) Calcd. for C$_{36}$H$_{35}$NO$_5$Si 517.2284; Found 517.2294
(S)-3-azido-2-methylpropanoic acid, 7j

\[
\begin{align*}
\text{N}_3 \quad \text{CO} \quad \text{OMe} & \quad \xrightarrow{\text{LiOH}} \\
\text{N}_3 \quad \text{CO} \quad \text{OH} & 
\end{align*}
\]

At 0 °C 0.14 g (2.1 mmol) of LiOH·H₂O was added to a solution of 0.30 g (2.1 mmol) (S)-methyl-3-azido-2-methylpropanoate in THF/H₂O (2:1) and stirred for 4 h at rt followed by treatment with diethyl ether. The aqueous layer was separated, acidified to pH 2 with 4 N aqueous HCl and extracted with three times with diethyl ether. The combined organic layers were washed with brine, dried with MgSO₄ and concentrated under reduced pressure to give 0.17 g (1.3 mmol; 63 %) of 7j as a colorless oil. [α]$_D$ +11.9 (c 3.7, CHCl₃). ¹H-NMR (400 MHz, CDCl₃) 10.7 (br s, 1H), 3.57 (dd, 1H, $J = 12.2, 7.2$ Hz), 3.43 (dd, 1H, $J = 12.2, 5.7$ Hz), 2.73 (m, 1H), 1.27 (d, 3H, $J = 7.2$ Hz). ¹³C-NMR (100 MHz, CDCl₃) 180.4, 53.5, 39.7, 14.7.

Seco Acid 3a

\[
\begin{align*}
\text{OH} \quad \text{N} \quad \text{O} \quad \text{O} \quad \text{NH} \quad \text{O} \quad \text{NH} \quad \text{O} \\
\text{HN} \quad \text{HN} \quad \text{HN} \quad \text{HN} \quad \text{HN} \quad \text{HN} \quad \text{HN} \quad \text{HN} 
\end{align*}
\]

Prepared according to procedure 1. The following 5 building blocks were used sequentially, Fmoc-β-AlaOH, Fmoc-D-TrpOH, Fmoc-L-AlaOH, 3-azidopropanoic acid, and prop-2-yn-1-ol. Polymer-bound peptide 8a (0.20 mmol), after on-resin cycloaddition, gave 83 mg (0.17 mmol, 84 % overall yield) of 3a as a slightly yellow solid.

$^1$H-NMR (500 MHz, DMSO-$d^6$) 10.80 (s, 1H), 8.21 (d, 1H, $J = 7.0$ Hz), 8.18 (d, 1H, $J = 8.3$ Hz), 8.02 (t, 1H, $J = 5.4$ Hz), 7.86 (s, 1H), 7.58 (s, 1H, $J = 8.0$ Hz), 7.31 (d, 1H, $J = 8.0$ Hz), 7.09 (s, 1H), 7.04 (t, 1H, $J = 7.5$ Hz), 6.96 (t, 1H, $J = 7.4$ Hz), 4.58-4.46 (m, 2H), 4.48 (s, 2H), 4.45-4.38 (m, 1H), 4.28-4.18 (m, 1H), 3.33-3.22 (m, 2H), 3.14 (dd, 1H, $J = 4.2$, 14.5 Hz), 2.90 (d, 1H, $J = 9.4$, 14.5 Hz), 2.80-2.64 (m, 2H), 2.34 (t, 2H, $J = 6.6$ Hz), 0.95 (d, 3H, $J = 7.0$ Hz). $^{13}$C-NMR (125 MHz, DMSO-$d^6$) 171.8, 171.1, 168.9, 147.7, 135.9, 127.2, 123.5, 122.7, 120.7, 118.3, 118.0, 111.1, 110.1, 54.9, 53.3, 48.3, 45.4, 35.2, 35.1, 34.1, 27.6, 17.8. IR 3292(br), 1717, 1643, 1538, 1178, 746 cm$^{-1}$. HRMS (ESI) Calcd. for C$_{23}$H$_{30}$N$_7$O$_6$ (MH$^+$) 500.2252; Found 500.2246.

**Seco Acid 3b**

Prepared according to procedure 1. The following 5 building blocks were used sequentially, Fmoc-$\beta$-AlaOH, Fmoc-D-TrpOH, Fmoc-L-AlaOH, 4-azidobutanoic acid, and prop-2-yn-1-ol. Polymer-bound peptide 8b (0.19 mmol), after on-resin cycloaddition, gave 70 mg (0.14 mmol, 74 % overall yield) of 3b as a slightly yellow solid.

$^1$H-NMR (400 MHz, DMSO-$d^6$+D$_2$O 35:1) 7.95 (br s, 1H), 7.56 (d, 1H, $J = 7.3$ Hz), 7.30 (d, 1H, $J = 8.0$ Hz), 7.08 (s, 1H), 7.04 (t, 1H, $J = 7.4$ Hz), 6.95 (t, 1H, $J = 7.3$ Hz), 4.48 (s, 2H), 4.39 (m, 1H), 4.30 (m, 2H), 4.18 (m, 1H), 3.25 (m, 2H), 3.20-3.07 (m, 1H), 2.95-2.82 (m, 1H), 2.48-2.25 (m, 2H), 2.15-2.05 (m, 2H), 2.05-1.92 (m, 2H), 0.97 (d, 3H, $J = 6.8$ Hz). HRMS (ESI) Calcd. for C$_{24}$H$_{32}$N$_7$O$_6$ (MH$^+$) 514.2409; Found 514.2402.

**Seco Acid 3c**
Prepared according procedure 1. The following 5 building blocks were used sequentially, Fmoc-β-AlaOH, Fmoc-D-TrpOH, Fmoc-L-AlaOH, 3-azidopropanoic acid, and but-3-yn-1-ol. Polymer-bound peptide 8a (0.17 mmol), after on-resin cycloaddition, gave 83 mg (0.16 mmol, 95 % overall yield) of 3c as a slightly yellow solid.

$^1$H-NMR (400 MHz, DMSO-d$_6$+D$_2$O 35:1) 7.75 (br s, 1H), 7.56 (d, 1H, $J = 7.8$ Hz), 7.30 (d, 1H, $J = 7.8$ Hz), 7.08 (s, 1H), 7.04 (t, 1H, $J = 7.7$ Hz), 6.95 (t, 1H, $J = 7.3$ Hz), 4.47 (m, 2H), 4.39 (m, 1H), 4.18 (m, 1H), 3.60 (m, 2H), 3.25 (m, 2H), 3.14 (m, 1H), 2.88 (m, 1H), 2.80-2.60 (m, 4H), 2.48-2.25 (m, 2H), 0.93 (d, 3H, $J = 6.8$ Hz). HRMS (ESI) Calcd. for C$_{24}$H$_{32}$N$_7$O$_6$ (MH$^+$) 514.2409; Found 514.2402.

**Seco Acid 3d**

Prepared according to procedure 1. The following 5 building blocks were used sequentially, Fmoc-β-AlaOH, Fmoc-D-TrpOH, Fmoc-L-AlaOH, 4-azidobutanoic acid, and but-3-yn-1-ol. Polymer-bound peptide 8b (0.19 mmol), after on-resin cycloaddition, gave 102 mg (0.19 mmol, quant.) of 3d as a slightly yellow solid.

$^1$H-NMR (400 MHz, DMSO-d$_6$+D$_2$O 35:1) 7.80 (br s, 1H), 7.54 (d, 1H, $J = 8.0$ Hz), 7.30 (d, 1H, $J = 8.0$ Hz), 7.08 (s, 1H), 7.04 (t, 1H, $J = 7.5$ Hz), 6.95 (t, 1H, $J = 7.5$ Hz), 4.37 (m, 1H), 4.24 (m, 2H), 4.13 (q, 1H, $J = 6.8$ Hz), 3.60 (m, 2H), 3.23 (m, 2H), 3.14 (dd, 1H, $J = 4.1$, 14.6 Hz), 2.87 (dd, 1H, $J = 9.8$, 14.6 Hz), 2.80-2.65 (m, 2H), 2.48-2.25 (m,
2H), 2.15-2.05 (m, 2H), 2.05-1.87 (m, 2H), 0.96 (d, 3H, J = 6.8 Hz). HRMS (ESI) Calcd. for C_{25}H_{34}N_{7}O_{6} (MH^+) 528.2565; Found 528.2562.

ω-Amino Acid 3h

Prepared according to procedure 1. The following 5 building blocks were used sequentially, Fmoc-β-AlaOH, Fmoc-D-TrpOH, Fmoc-L-AlaOH, 3-azidopropanoic acid, and propargyl amine. 0.375 g of the trityl resin (0.375 mmol), after peptide synthesis, gave Polymer-bound peptide 8a (0.20 mmol), after on-resin cycloaddition, gave 89 mg (0.18 mmol, 89 % overall yield) of 3h as a slightly yellow solid. 

$[\alpha]_D$ -4.5 (c 0.31, DMSO). 1H-NMR (500 MHz, DMSO-d_{6}) 10.84 (s, 1H), 8.28 (d, 2H, J = 6.3 Hz), 8.03-7.95 (m, 2H), 7.57 (d, 1H, J = 7.9 Hz), 7.30 (d, 1H, J = 8.1 Hz), 7.09 (s, 1H), 7.03 (t, 1H, J = 7.2 Hz), 6.95 (t, 1H, J = 7.4 Hz), 4.54 (t, 2H, J = 6.3 Hz), 4.43-4.35 (m, 1H), 4.26-4.17 (m, 1H), 3.29-3.20 (m, 2H), 3.18 (dd, 1H, J = 4.0, 5.0 Hz), 2.89 (dd, 1H, J = 9.8, 14.6 Hz), 2.7 (t, 2H, J = 6.4 Hz), 2.28-2.18 (m, 2H), 0.94 (d, 3H, J = 7.0 Hz). IR 3403, 3284, 1661, 1634, 1544, 1183, 1130, 745, 722 cm^{-1}. HRMS (ESI) Calcd. for C_{23}H_{31}N_{8}O_{5} (MH^+) 499.2412; Found 499.2405.

Azido Acid 10a
Prepared according to procedure 3. The following 4 building blocks were used sequentially, Fmoc-β-AlaOH, Fmoc-D-TrpOH, Fmoc-L-AlaOH, and 3-azidopropanoic acid. 0.375 g (0.375 mmol) of the trityl resin, after peptide synthesis, gave 0.156 g (94%) of 10a as a slightly yellow solid.

\[ \text{mp} = 171^\circ \text{C (dec.)} \quad [\alpha]_D -5.5 \quad (c \, 0.7, \text{MeOH}). \]

\[ ^1\text{H-NMR (500 MHz, CD}_3\text{OD)} \]

\[
\begin{align*}
7.58 \, (d, \, 1H, \, J = 8.0 \, Hz), \quad 7.31 \, (d, \, 1H, \, J = 8.0 \, Hz), \quad 7.10-7.05 \, (m, \, 3H), \quad 7.00 \, (t, \, 1H, \, J = 8.0 \, Hz), \quad 4.59 \, (dd, \, 1H, \, J = 5.4, \, 8.6 \, Hz), \quad 4.20 \, (q, \, 1H, \, J = 7.2 \, Hz), \quad 3.58-3.52 \, (m, \, 1H), \quad 3.50-3.44 \, (m, \, 1H), \\
3.42-3.36(\, m, \, 2H), \quad 3.33 \, (dd, \, 1H, \, J = 5.5, \, 14.7 \, Hz), \quad 2.45-2.37 \, (m, \, 4H), \quad 1.12 \, (d, \, 3H, \, J = 7.2 \, Hz). \\
\end{align*}
\]

\[ ^{13}\text{C-NMR (100 MHz, DMSO-d}_6) \]

\[
172.8, \quad 171.9, \quad 171.3, \quad 169.4, \quad 169.36, \quad 127.2, \quad 123.5, \quad 120.8, \quad 118.4, \quad 118.1, \quad 111.2, \quad 110.1, \quad 53.3, \quad 48.4, \quad 46.8, \quad 34.9, \quad 34.2, \quad 33.6, \quad 27.7, \quad 17.9; \quad \text{IR 3402,} \\
3288, \quad 2982, \quad 2127, \quad 1697, \quad 1661, \quad 1641, \quad 1542, \quad 1437, \quad 744 \, \text{cm}^{-1}; \quad \text{HRMS (FAB) Calcd. for} \\
C_{20}H_{26}N_7O_5 \, (\text{MH}^+) \quad 444.1995; \quad \text{Found 444.1984.}
\]

Azido Acid 10b

Prepared according to procedure 3. The following 4 building blocks were used sequentially, Fmoc-β-AlaOH, Fmoc-D-TrpOH, Fmoc-L-AlaOH, and 4-azidobutanoic acid. 0.625 g (0.625 mmol) of the trityl resin, after peptide synthesis, gave 0.223 g (78%) of 10b as a slightly yellow solid.

\[ \text{mp} = 144^\circ \text{C (dec.)} \quad [\alpha]_D -35 \quad (c \, 0.89, \text{MeOH}). \]

\[ ^1\text{H-NMR (400 MHz, DMSO-d}_6) \]

\[
\begin{align*}
12.23 \, (s, \, 1H), \quad 10.80 \, (s, \, 1H), \quad 8.13 \, (d, \, 1H, \, J = 8.3 \, Hz), \quad 8.08 \, (d, \, 1H, \, J = 6.8 \, Hz), \quad 8.02 \, (t, \, 1H, \, J = 5.4 \, Hz), \\
7.58 \, (d, \, 1H, \, J = 7.8 \, Hz), \quad 7.31 \, (d, \, 1H, \, J = 8.0 \, Hz), \quad 7.08 \, (d, \, 1H, \, J = 1.9 \, Hz), \quad 7.04 \, (t, \\
1H, \, J = 7.5 \, Hz), \quad 6.96 \, (t, \, 1H, \, J = 7.3 \, Hz), \quad 4.41 \, (dt, \, 1H, \, J = 4.5, \, 9.0 \, Hz), \quad 4.27-4.14 \, (m, \\
1H), \quad 3.33-3.20 \, (m, \, 4H), \quad 3.15 \, (dd, \, 1H, \, J = 4.3, \, 14.6 \, Hz), \quad 2.89 \, (dd, \, 1H, \, J = 9.6, \, 14.6 \, Hz), \\
2.37 \, (t, \, 2H, \, J = 7.2 \, Hz), \quad 2.17 \, (t, \, 2H, \, J = 7.3 \, Hz), \quad 1.77-1.66 \, (m, \, 2H), \quad 0.98 \, (d, \, 3H, \, J =
\end{align*}
\]
7.04 Hz). IR 3402, 3303, 2103, 1725, 1539, 1248, 743 cm⁻¹; HRMS (FAB) Calcd. for C₂₁H₂₈N₇O₅ (MH⁺) 458.2152; Found 458.2153.

**Azido Acid 10j**

![Azido Acid 10j](image)

Prepared according to procedure 3. The following 4 building blocks were used sequentially, Fmoc-β-AlaOH, Fmoc-D-TrpOH, Fmoc-L-AlaOH, and (S)-3-azido-2-methylpropanoic acid. 0.500 g (0.5 mmol) of the trityl resin, after peptide synthesis, gave 0.160 g (70%) of 10j as a slightly yellow solid. [α]D +5.0 (c 1.9, DMSO). ¹H-NMR (500 MHz, DMSO-d⁶) 10.78 (s, 1H), 8.15 (d, 1H, J = 7.1 Hz), 8.07 (d, 1H, J = 8.4 Hz), 8.01 (t, 1H, J = 5.5 Hz), 7.58 (d, 1H, J = 7.9 Hz), 7.31 (d, 1H, J = 8.1 Hz), 7.08 (d, 1H, J = 2.1 Hz), 7.04 (t, 1H, J = 8.0 Hz), 6.96 (t, 1H, J = 7.4 Hz), 4.44 (dt, 1H, J = 4.9, 8.9 Hz), 4.31-4.17 (m, 1H), 3.43 (dd, 1H, J = 8.1, 12.0 Hz), 3.30-3.20 (m, 3H), 3.13 (dd, 1H, J = 4.7, 14.6 Hz), 2.88 (dd, 1H, J = 9.3, 14.6 Hz), 2.65-2.54 (m, 2H), 2.35 (t, 2H, J = 7.2 Hz), 1.02-0.98 (m, 6H). ¹³C-NMR (125 MHz, DMSO-d⁶) 175.0, 174.6, 173.7, 173.1, 137.9, 129.2, 125.4, 122.7, 120.3, 120.0, 113.1, 112.0, 55.4, 55.2, 50.3, 41.2, 36.8, 35.5, 29.7, 19.7, 17.1. HRMS (FAB) Calcd. for C₂₁H₂₇N₇O₅ (M⁺) 457.2053; Found 457.2073.

**Azido Alkyne 4a**

![Azido Alkyne 4a](image)
Following procedure 4, 291 mg (0.66 mmol) of azido acid 10a were subjected to esterification reaction conditions to give 220 mg (0.46 mmol, 70 %) of 4a as a slightly yellow solid.

mp = 197°C (dec.). [α]D –3.7 (c 0.6, MeOH). 1H-NMR (400 MHz, DMSO-d6) 10.80 (s, 1H), 8.19 (d, 2H, J = 6.9 Hz), 8.06 (t, 1H, J = 5.4 Hz), 7.58 (d, 1H, J = 7.8 Hz), 7.31 (d, 1H, J = 8.0 Hz), 7.09 (d, 1H, J = 1.9 Hz), 7.05 (t, 1H, J = 7.5 Hz), 6.97 (t, 1H, J = 7.3 Hz), 4.69 (d, 2H, J = 2.4 Hz), 4.42 (dt, 1H, J = 4.8, 8.9 Hz), 4.34-4.18 (m, 1H), 3.54 (t, 1H, J = 2.4 Hz), 3.53-3.40 (m, 2H), 3.35-3.21 (m, 2H), 3.14 (dd, 1H, J = 4.5, 14.5 Hz), 2.97-2.81 (m, 1H), 2.48 (t, 2H, J = 7.1 Hz), 2.39 (m, 2H), 0.99 (d, 3H, J = 7.0 Hz). 13C-NMR (100 MHz, DMSO-d6) 171.9, 171.3, 170.4, 169.4, 135.9, 127.1, 123.5, 120.7, 118.3, 118.1, 111.1, 110.0, 78.3, 77.6, 53.2, 51.7, 48.3, 46.8, 34.6, 34.1, 33.1, 27.6, 17.8. IR 3402, 3294, 2108, 1743, 1639, 1539, 1169, 743 cm⁻¹. HRMS (ESI) Calcd. for C23H28N7O5 (MH⁺) 482.2146; Found 482.2142.

Azido Alkyne 4b

Following procedure 4, 209 mg (0.46 mmol) of azido acid 10b were subjected to esterification reaction conditions to give 187 mg (0.39 mmol, 82 %) of 4b as a white solid.

mp = 198°C (dec.). [α]D +0.56 (c 1.5, DMSO). 1H-NMR (400 MHz, DMSO-d6) 10.80 (s, 1H), 8.15 (d, 1H, J = 8.3 Hz), 8.13-7.99 (m, 2H), 7.57 (d, 1H, J = 7.8 Hz), 7.31 (d, 1H, J = 8.0 Hz), 7.09 (d, 1H, J = 1.9 Hz), 7.05 (t, 1H, J = 7.2 Hz), 6.96 (t, 1H, J = 7.1 Hz), 4.69 (d, 2H, J = 2.4 Hz), 4.40 (dt, 1H, J = 4.7, 9.0 Hz), 4.32-4.13 (m, 1H), 3.55 (t, 1H, J = 2.4 Hz), 3.37-3.20 (m, 4H), 3.20-3.05 (m, 1H), 2.89 (dd, 1H, J = 9.5, 14.6 Hz), 2.47 (t, 2H, J = 7.0 Hz), 2.17 (t, 2H, J = 7.3 Hz), 1.86-1.60 (m, 2H), 0.99 (d, 3H, J = 7.0 Hz). 13C-NMR (100 MHz, DMSO-d6) 172.1, 171.35, 171.33, 170.4, 135.9, 127.1, 123.4,
120.7, 118.3, 118.1, 110.0, 78.3, 77.6, 53.3, 51.7, 50.1, 48.3, 34.6, 33.1, 31.7, 27.5, 24.3, 17.6; IR 3402, 3305, 2103, 1734, 1660, 1638, 1536, 1179, 744 cm⁻¹. HRMS (ESI) Calcd. for C₂₄H₃₀N₇O₅ (MH⁺) 496.2303; Found 496.2299.

**Azido Alkyne 4c**

Following procedure 4, 134 mg (0.30 mmol) of azido acid 10a were subjected to esterification reaction conditions to give 80 mg (0.16 mmol, 53 %) of 4c as a white solid.

mp = 240°C (dec.). [α]D -38.0 (c 0.51, MeOH). ¹H-NMR (400 MHz, DMSO-d₆) 10.80 (s, 1H), 8.19 (d, 2H, J = 7.3 Hz), 8.04 (t, 1H, J = 5.5 Hz), 7.58 (d, 1H, J = 7.8 Hz), 7.31 (d, 1H, J = 8.0 Hz), 7.09 (d, 1H, J = 1.8 Hz), 7.05 (t, 1H, J = 7.4 Hz), 6.96 (t, 1H, J = 7.3 Hz), 4.41 (dt, 1H, J = 4.7, 9.0 Hz), 4.33-4.19 (m, 1H), 4.15-4.02 (m, 2H), 3.57-3.39 (m, 2H), 3.34-3.21 (m, 2H), 3.13 (dd, 1H, J = 4.5, 14.6 Hz), 2.94-2.83 (m, 2H), 2.48-2.28 (m, 4H), 0.99 (d, 3H, J = 7.01 Hz). ¹³C-NMR (100 MHz, DMSO-d₆) 171.9, 171.3, 170.9, 169.4, 135.9, 127.1, 123.5, 120.7, 118.3, 118.0, 111.1, 110.0, 80.7, 72.4, 61.7, 53.2, 48.3, 46.8, 34.7, 34.1, 33.4, 27.6, 18.2, 17.8. IR 3404, 3302, 2108, 1727, 1660, 1640, 1542, 1179, 744 cm⁻¹. HRMS (ESI) Calcd. for C₂₄H₃₀N₇O₅ (MH⁺) 496.2303; Found 496.2298.

**Azido Alkyne 4d**

Supplementary Material (ESI) for Chemical Communications
This journal is (c) The Royal Society of Chemistry 2007

S16
Following procedure 4, 209 mg (0.46 mmol) of azido acid 10b were subjected to esterification reaction conditions to give 166 mg (0.33 mmol, 71%) of 4d as a white solid.

\[ mp = 186^\circ C \ (\text{dec.}) \] 
\[ [\alpha]_D -4.1 \ (c \ 0.58, \text{MeOH}) \]

\[^1\text{H}-\text{NMR} \ (400 \text{ MHz, DMSO-d}^6) \]
\[ 10.80 \ (s, 1H), \]
\[ 8.15 \ (d, 1H, J = 8.3 \text{ Hz}), \]
\[ 8.08 \ (d, 1H, J = 6.8 \text{ Hz}), \]
\[ 8.03 \ (t, 1H, J = 5.5 \text{ Hz}), \]
\[ 7.57 \ (d, 1H, J = 7.8 \text{ Hz}), \]
\[ 7.31 \ (d, 1H, J = 8.0 \text{ Hz}), \]
\[ 7.09 \ (d, 1H, J = 1.9 \text{ Hz}), \]
\[ 7.05 \ (t, 1H, J = 7.2 \text{ Hz}), \]
\[ 6.96 \ (t, 1H, J = 7.2 \text{ Hz}), \]
\[ 4.40 \ (dt, 1H, J = 4.6, 9.0 \text{ Hz}), \]
\[ 4.30-4.14 \ (m, 1H), \]
\[ 4.09 \ (t, 2H, J = 6.7 \text{ Hz}), \]
\[ 3.35-3.19 \ (m, 4H), \]
\[ 3.15 \ (dd, 1H, J = 4.4, 14.6 \text{ Hz}), \]
\[ 3.00-2.79 \ (m, 2H), \]
\[ 2.45 \ (t, 2H, J = 7.1 \text{ Hz}), \]
\[ 2.17 \ (t, 2H, J = 7.3 \text{ Hz}), \]
\[ 1.83-1.61 \ (m, 2H), \]
\[ 0.99 \ (d, 3H, J = 7.04 \text{ Hz}). \]

\[^{13}\text{C}-\text{NMR} \ (100 \text{ MHz, DMSO-d}^6) \]
\[ 172.2, \]
\[ 171.4, \]
\[ 171.3, \]
\[ 170.9, \]
\[ 136.0, \]
\[ 127.2, \]
\[ 123.5, \]
\[ 120.767, \]
\[ 118.3, \]
\[ 118.1, \]
\[ 111.8, \]
\[ 110.1, \]
\[ 80.7, \]
\[ 72.5, \]
\[ 61.8, \]
\[ 53.3, \]
\[ 50.2, \]
\[ 48.4, \]
\[ 34.8, \]
\[ 33.4, \]
\[ 31.7, \]
\[ 27.5, \]
\[ 24.4, \]
\[ 18.2, \]
\[ 17.6. \]

IR \[ 3403, \]
\[ 3301, \]
\[ 2101, \]
\[ 1725, \]
\[ 1659, \]
\[ 1639, \]
\[ 1537, \]
\[ 1181, \]
\[ 744 \text{ cm}^{-1}. \]

HRMS (FAB) Calcd. for \( \text{C}_{25}\text{H}_{32}\text{N}_7\text{O}_5 \) (MH\(^+\)) 510.2465; Found 510.2437.

Azido Alkyne 4i

Following procedure 4, 209 mg (0.31 mmol) of azido acid 10i were subjected to esterification reaction conditions to give 187 mg (0.27 mmol, 82%) of 4i as a white solid.

\[ [\alpha]_D +11.4 \ (c \ 0.33, \text{DMSO}) \]

\[^1\text{H}-\text{NMR} \ (400 \text{ MHz, DMSO-d}^6) \]
\[ 10.80 \ (s, 1H), \]
\[ 8.35 \ (d, 1H, J = 8.5 \text{ Hz}), \]
\[ 8.28 \ (d, 1H, J = 8.1 \text{ Hz}), \]
\[ 8.18 \ (d, 1H, J = 6.1 \text{ Hz}), \]
\[ 7.54 \ (d, 1H, J = 7.9 \text{ Hz}), \]
\[ 7.31 \ (d, 1H, J = 8.1 \text{ Hz}), \]
\[ 7.10 \ (d, 2H, J = 8.5 \text{ Hz}), \]
\[ 7.07 \ (d, 1H, J = 2.0 \text{ Hz}), \]
\[ 7.04 \ (t, 1H, J = 7.2 \text{ Hz}), \]
\[ 6.95 \ (t, 1H, J = 7.3 \text{ Hz}), \]
\[ 6.72 \ (d, 2H, J = 8.5 \text{ Hz}), \]
\[ 5.20 \ (q, 1H, J = 7.9 \text{ Hz}), \]
\[ 4.66 \ (d, 2H, J = 2.4 \text{ Hz}), \]
\[ 4.40 \ (ddd, 1H, J = 4.3, 8.4, 9.4 \text{ Hz}), \]
\[ 4.24-4.15 \ (m, 1H), \]
\[ 3.53 \ (t,
Following procedure 4, 100 mg (0.22 mmol) of azido acid 10j were subjected to esterification reaction conditions to give 69 mg (0.14 mmol, 62%) of 4j as a white solid. 

[α]D +6.6 (c 1.9, DMSO). 1H-NMR (500 MHz, DMSO-d6) δ 10.79 (d, 1H, J = 1.2 Hz), 8.16 (d, 1H, J = 7.1 Hz), 8.09 (d, 1H, J = 8.4 Hz), 8.02 (t, 1H, J = 5.6 Hz), 7.57 (d, 1H, J = 7.9 Hz), 7.31 (d, 1H, J = 8.1 Hz), 7.09 (d, 1H, J = 1.9 Hz), 7.05 (t, 1H, J = 7.2 Hz), 6.97 (t, 1H, J = 7.1 Hz), 4.44 (dt, 1H, J = 5.0, 8.8 Hz), 4.30-4.20 (m, 1H), 4.09 (t, 2H, J = 6.6 Hz), 3.43 (dd, 1H, J = 8.1, 12.0 Hz), 3.33-3.22 (m, 3H), 3.13 (dd, 1H, J = 4.8, 14.6 Hz), 2.89 (dd, 1H, J = 9.6, 14.7 Hz), 2.85 (t, 1H, J = 2.7 Hz), 2.64-2.56 (m, 1H), 2.52-2.48 (m, 2H), 2.43 (t, 2H, J = 7.1 Hz), 1.01 (d, 3H, J = 8.3 Hz), 1.00 (d, 3H, J = 7.07 Hz). 13C-NMR (125 MHz, DMSO-d6) δ 172.9, 171.7, 171.1, 170.8, 135.9, 127.1, 123.4, 120.6, 118.2, 118.0, 110.9, 80.6, 72.3, 61.7, 53.4, 53.2, 48.2, 39.1, 34.6, 33.3, 27.6, 18.1, 17.7, 15.1. IR 3280, 3083, 2930, 2104, 1729, 1631, 1546, 1176, 741, 658 cm⁻¹. HRMS (FAB) Calcd. for C23H32N7O5 (MH⁺) 510.2465; Found 510.2467.

Azido Alkyne 4k
Following procedure 4, 100 mg (0.22 mmol) of azido acid 10j were subjected to esterification reaction conditions to give 74 mg (0.14 mmol, 65 %) of 4k as a white solid. 

\[ \alpha \]D –1.1 (c 2.7, DMSO). 1H-NMR (400 MHz, DMSO-d6) 10.78 (d, 1H, \( J = 1.5 \) Hz), 8.15 (d, 1H, \( J = 7.1 \) Hz), 8.07 (d, 1H, \( J = 8.3 \) Hz), 8.00 (t, 1H, \( J = 5.6 \) Hz), 7.57 (d, 1H, \( J = 7.8 \) Hz), 7.31 (d, 1H, \( J = 8.0 \) Hz), 7.09 (d, 1H, \( J = 2.0 \) Hz), 7.05 (t, 1H, \( J = 7.0 \) Hz), 6.97 (t, 1H, \( J = 7.0 \) Hz), 4.93-4.82 (m, 1H), 4.44 (dt, 1H, \( J = 4.9, 8.6 \) Hz), 4.30-4.18 (m, 1H), 3.43 (dd, 1H, \( J = 8.1, 12.0 \) Hz), 3.35-3.20 (m, 3H), 3.14 (dd, 1H, \( J = 4.7, 14.5 \) Hz), 2.89 (dd, 1H, \( J = 9.6, 14.9 \) Hz), 2.85 (t, 1H, \( J = 2.6 \) Hz), 2.66-2.54 (m, 1H), 2.46 (td, 2H, \( J = 2.6, 5.5 \) Hz), 2.40 (t, 2H, \( J = 7.1 \) Hz), 1.24 (d, 3H, \( J = 6.3 \) Hz), 1.02 (d, 3H, \( J = 7.5 \) Hz), 1.00 (d, 3H, \( J = 7.0 \) Hz). 13C-NMR (100 MHz, DMSO-d6)173.0, 171.8, 171.2, 170.4, 135.9, 127.1, 123.4, 120.7, 118.3, 118.0, 111.1, 109.9, 80.1, 72.9, 68.2, 53.4, 53.2, 48.3, 39.2, 34.7, 33.7, 27.7, 24.7, 18.7, 17.7, 15.1. IR 3284, 3079, 2930, 2105, 1724, 1633, 1543, 1156, 1059, 740, 654 cm\(^{-1}\). HRMS (FAB) Calcd. for C\(_{26}H_34N_7O_5\) (MH\(^+\)) 524.2622; Found 524.2646.

**Azido Alkyne 4h**

Following procedure 5, 90 mg (0.20 mmol) of azido acid 10a gave 74 mg (0.15 mmol, 74 %) of 4h as a white solid.
mp = 240°C (dec.). \([\alpha]_D^{+} 150 (\text{c} 0.54, \text{DMSO/MeOH 1:1}). \) \(^1\)H-NMR (500 MHz, DMSO-d\(^6\)) 10.78 (s, 1H), 8.31 (t, 1H, \(J = 5.5 \text{ Hz}, \text{NH}\)), 8.18-8.11 (m, 2H, NH), 8.02 (t, 1H, \(J = 5.5 \text{ Hz}\)), 7.58 (d, 1H, \(J = 7.7 \text{ Hz}\)), 7.31 (d, 1H, \(J = 7.7 \text{ Hz}\)), 7.08 (s, 1H), 7.04 (t, 1H, \(J = 7.6 \text{ Hz}\)), 6.96 (t, 1H, \(J = 7.4 \text{ Hz}\)), 4.45-4.37 (m, 1H), 4.29-4.22 (m, 1H), 3.88-3.82 (m, 2H), 3.57-3.48 (m, 1H), 3.48-3.41 (m, 1H), 3.29-3.19 (m, 2H), 3.12 (dd, 1H, \(J = 4.4, 14.6 \text{ Hz}\)), 3.09 (t, 1H, \(J = 2.5 \text{ Hz}\)), 2.88 (dd, 1H, \(J = 9.6, 14.6 \text{ Hz}\)), 2.46-2.34 (m, 2H), 2.32-2.22 (m, 2H), 0.97 (d, 3H, \(J = 7.0 \text{ Hz}\)). \(^{13}\)C-NMR (125 MHz, DMSO-d\(^6\)) 171.8, 171.2, 169.9, 169.3, 135.9, 127.2, 123.5, 120.7, 118.3, 118.0, 111.1, 110.0, 81.1, 72.8, 53.2, 48.3, 46.8, 35.3, 34.8, 34.2, 34.1, 27.7, 17.9. IR 3403, 3290, 2107, 1668, 1638, 1538, 744 cm\(^{-1}\). HRMS (FAB) Calcd. for C\(_{23}\)H\(_{29}\)N\(_8\)O\(_4\) (MH\(^+\)) 481.2312; Found 481.2298.

Azido Alkyne 4l

Following procedure 5, 150 mg (0.33 mmol) of azido acid 10b gave 130 mg (0.26 mmol, 80 %) of 4l as a white solid.

mp = 239°C (dec.). \([\alpha]_D^{-} 21.0 (\text{c} 0.55, \text{DMSO}). \) \(^1\)H-NMR (500 MHz, DMSO-d\(^6\)) 10.78 (s, 1H), 8.30 (t, 1H, \(J = 5.3 \text{ Hz}\)), 8.09 (d, 1H, \(J = 8.4 \text{ Hz}\)), 8.05 (d, 1H, \(J = 6.9 \text{ Hz}\)), 8.00 (t, 1H, \(J = 5.6 \text{ Hz}\)), 7.58 (d, 1H, \(J = 7.9 \text{ Hz}\)), 7.31 (d, 1H, \(J = 8.1 \text{ Hz}\)), 7.08 (d, 1H, \(J = 1.7 \text{ Hz}\)), 7.05 (t, 1H, \(J = 8.7 \text{ Hz}\)), 6.96 (t, 1H, \(J = 7.29 \text{ Hz}\)), 4.42 (dt, 1H, \(J = 4.5, 9.0 \text{ Hz}\)), 4.27-4.15 (m, 1H), 3.85 (dd, 2H, \(J = 2.4, 5.3 \text{ Hz}\)), 3.34-3.19 (m, 4H), 3.14 (dd, 1H, \(J = 4.3, 14.6 \text{ Hz}\)), 3.08 (t, 1H, \(J = 2.40 \text{ Hz}\)), 2.89 (dd, 1H, \(J = 9.5, 14.6 \text{ Hz}\)), 2.33-2.22 (m, 2H), 2.17 (t, 2H, \(J = 7.3 \text{ Hz}\)), 1.76-1.68 (m, 2H), 0.98 (d, 3H, \(J = 7.05 \text{ Hz}\)). \(^{13}\)C-NMR (125 MHz, DMSO-d\(^6\)) 172.0, 171.2, 171.1, 169.8, 135.9, 127.1, 123.4, 120.7, 118.3, 118.0, 111.1, 110.0, 81.0, 72.8, 53.2, 50.1, 48.3, 35.2, 34.8, 31.7, 27.6, 27.6, 24.3, 17.6. HRMS (ESI) Calcd. for C\(_{24}\)H\(_{31}\)N\(_8\)O\(_4\) (MH\(^+\)) 495.2463; Found 495.2458.
Cyclic Peptide 2a

76 mg (0.15 mmol) of seco acid 3a were subjected to macrolactonization conditions as described in procedure 2 to give 26 mg (0.054 mmol, 37 %) of 2a as a white solid.

When 100 mg (0.21 mmol) of azido alkyne 4a were subjected to intramolecular cycloaddition reaction conditions as described in procedure 6, 87 mg (0.18 mmol, 87 %) of the same product (2a) were obtained.

mp = 140°C (dec.). \([\alpha]_D^{11.6}\) (c 0.6, DMSO). \(^1\)H-NMR (400 MHz, DMSO-d\(^6\)) 10.80 (s, 1H), 8.20 (d, 1H, J = 4.3 Hz), 8.18 (d, 1H, J = 4.9 Hz), 7.96 (t, 1H, J = 5.4 Hz), 7.78 (s, 1H), 7.59 (d, 1H, J = 7.8 Hz), 7.30 (d, 1H, J = 8.0 Hz), 7.13 (d, 1H, J = 1.5 Hz), 7.04 (t, 1H, J = 7.3 Hz), 6.96 (t, 1H, J = 7.3 Hz), 5.08 (q, 2H, J = 12.9 Hz), 4.70-4.59 (m, 2H), 4.58-4.49 (m, 2H), 4.47-4.38 (m, 2H), 4.38-4.27 (m, 2H), 3.48-3.34 (m, 1H), 3.25-3.14 (m, 1H), 3.08 (d, 1H, J = 4.1, 14.5 Hz), 2.81-2.68 (m, 1H), 2.68-2.57 (m, 1H), 0.86 (d, 3H, J = 7.0 Hz). \(^{13}\)C-NMR (100 MHz, DMSO-d\(^6\)) 171.9, 171.6, 171.5, 168.9, 141.8, 136.0, 127.1, 124.3, 123.7, 120.8, 118.4, 118.1, 111.2, 110.1, 57.6, 53.2, 47.6, 46.1, 35.4, 34.9, 33.6, 27.4, 18.0. IR 3292, 1734, 1644, 1531, 1167, 745 cm\(^{-1}\). HRMS (FAB) Calcd. for C\(_{23}\)H\(_{28}\)N\(_7\)O\(_5\) (MH\(^+\)) 482.2152; Found 482.2138.

Cyclic Peptide 2b
51 mg (0.10 mmol) of seco acid 3b were subjected to macrolactonization conditions as described in procedure 2 to give 14 mg (0.028 mmol, 28 %) of 2b as a white solid.

When 98 mg (0.20 mmol) of azido alkyne 4b were subjected to intramolecular cycloaddition reaction conditions as described in procedure 6, 64 mg (0.13 mmol, 65 %) of the same product (2b) were obtained.

mp = 63°C (dec.). [α]D –19.0 (c 0.8, DMSO). 1H-NMR (400 MHz, DMSO-d6) 10.80 (s, 1H), 8.14 (dd, 1H, J = 4.4, 6.1 Hz), 8.07 (d, 1H, J = 7.5 Hz), 8.03 (d, 1H, J = 8.3 Hz), 7.63-7.56 (m, 2H), 7.30 (d, 1H, J = 8.0 Hz), 7.12 (d, 1H, J = 1.8 Hz), 7.04 (t, 1H, J = 7.4 Hz), 6.96 (t, 1H, J = 7.3 Hz), 5.22 (d, 1H, J = 13.1 Hz), 5.09 (d, 1H, J = 13.1 Hz), 4.50-4.41 (m, 2H), 4.33-4.23 (m, 2H), 3.18-3.07 (m, 2H), 2.93 (dd, 1H, J = 9.8, 14.5 Hz), 2.66-2.53 (m, 1H), 2.16-2.04 (m, 1H), 2.03-1.89 (m, 3H), 2.46 (t, 2H, J = 5.6 Hz), 0.94 (d, 3H, J = 7.1 Hz). 13C-NMR (125 MHz, DMSO-d6) 172.0, 171.4, 171.2, 170.9, 142.5, 135.9, 127.1, 124.1, 123.6, 120.7, 118.3, 118.0, 111.1, 109.9, 58.0, 53.1, 47.9, 47.6, 34.8, 33.9, 31.1, 27.6, 25.3, 17.0. IR 3284, 1734, 1646, 1534, 1166, 746 cm−1. HRMS (FAB) Calcd. for C24H30N7O5 (MH+) 496.2308; Found 496.2283.

**Cyclic Peptide 2c**

57 mg (0.11 mmol) of seco acid 3c were subjected to macrolactonization conditions as described in procedure 2 to give 25 mg (0.050 mmol, 45 %) of 2c as a white solid.

When 60 mg (0.12 mmol) of azido alkyne 4c were subjected to intramolecular cycloaddition reaction conditions as described in procedure 6, 55 mg (0.11 mmol, 92 %) of the same product (2c) was obtained.
mp = 115 °C (dec.). \([\alpha]_D +1.9 \) (c 0.8, DMSO). \(^1\)H-NMR (400 MHz, DMSO-d\(^6\)) 10.80 (s, 1H), 8.29 (d, 1H, \(J = 8.6 \) Hz), 8.26 (d, 1H, \(J = 6.5 \) Hz) 8.01 (t, 1H, \(J = 5.6 \) Hz), 7.68 (s, 1H), 7.60 (d, 1H, \(J = 7.8 \) Hz), 7.30 (d, 1H, \(J = 8.0 \) Hz), 7.09 (s, 1H), 7.13 (d, 1H, \(J = 1.8 \) Hz), 7.04 (t, 1H, \(J = 7.3 \) Hz), 7.00 (t, 1H, \(J = 7.3 \) Hz), 4.62-4.47 (m, 2H), 4.43-4.32 (m, 2H), 4.20-4.12 (m, 1H), 4.10-4.03 (m, 1H), 3.47-3.38 (m, 1H), 3.20-3.10 (m, 2H), 2.97-2.83 (m, 3H), 2.66-2.59 (m, 2H), 2.46 (t, 2H, \(J = 5.6 \) Hz), 0.92 (d, 3H, \(J = 7.1 \) Hz). \(^{13}\)C-NMR (100 MHz, DMSO-d\(^6\)) 172.1, 171.6, 171.3, 169.7, 143.6, 135.9, 127.1, 123.5, 123.0, 120.7, 118.3, 118.0, 111.1, 110.3, 63.0, 53.5, 48.5, 45.8, 35.0, 34.8, 33.9, 26.8, 24.9, 17.1. IR 3274, 1730, 1651, 1542, 1176, 746 cm\(^{-1}\). HRMS (FAB) Calcd. for C\(_{24}\)H\(_{30}\)N\(_7\)O\(_5\) (MH\(^+\)) 496.2308; Found 496.2297.

Cyclic Peptide 2d

42 mg (0.080 mmol) of seco acid 3d were subjected to macrolactonization conditions as described in procedure 2 to give 24 mg (0.047 mmol, 59 %) of 2d as a white solid.

When 100 mg (0.20 mmol) of azido alkyne 4d were subjected to intramolecular cycloaddition reaction conditions as described in procedure 6, 82 mg (0.16 mmol, 82 %) of the same product (2d) was obtained.

mp = 64 °C (dec.). \([\alpha]_D -9.0 \) (c 0.6, DMSO). \(^1\)H NMR (500 MHz, DMSO-d\(^6\)) 10.80 (s, 1H), 8.28 (d, 1H, \(J = 8.2 \) Hz), 8.26 (d, 1H, \(J = 6.4 \) Hz), 7.93 (t, 1H, \(J = 5.7 \) Hz), 7.81 (s, 1H), 7.56 (d, 1H, \(J = 7.9 \) Hz), 7.31 (d, 1H, \(J = 8.1 \) Hz), 7.13 (d, 1H, \(J = 2.1 \) Hz), 7.05 (ddd, 1H, \(J = 0.9, 7.5, 8.0 \) Hz), 6.97 (ddd, 1H, \(J = 0.8, 7.2, 7.9 \) Hz), 4.36-4.29 (m, 3H), 4.27-4.21 (m, 2H), 4.19-4.14 (m, 1H), 3.31-3.24 (m, 1H), 3.24-3.18 (m, 2H), 2.95 (t, 2H, \(J = 5.5 \) Hz), 2.90 (dd, 1H, \(J = 10.0, 14.8 \) Hz), 2.42 (td, 1H, \(J = 7.3, 14.8 \) Hz), 2.32 (td, 1H, \(J = 6.5, 13.6 \) Hz), 2.14-2.08 (m, 1H), 2.07-2.00 (m, 1H), 1.98-1.92 (m, 1H), 1.90-1.84
(m, 1H), 1.00 (d, 3H, J = 7.1 Hz). $^{13}$C NMR (125 MHz, DMSO-d$_6$) 172.4, 171.7, 171.3, 170.8, 143.4, 135.9, 127.1, 123.3, 123.1, 120.7, 118.2, 118.1, 111.2, 110.3, 62.5, 53.8, 48.5, 48.1, 34.6, 33.6, 31.4, 26.8, 26.2, 24.6, 16.4. IR 3292, 1732, 1646, 1540, 1174, 746 cm$^{-1}$. HRMS (FAB) Calcd. for C$_{25}$H$_{31}$N$_7$O$_5$ 509.2387; Found 509.2402

Cyclic Peptide 2e

87 mg (0.15 mmol) of seco acid 3e were subjected to macrolactonization conditions as described in procedure 2 to give 11 mg (0.019 mmol, 15%) of 2e as a white solid.

mp = 231°C (dec.). [α]$_D$ –24.6 (c 0.47, DMSO). $^1$H NMR (400 MHz, DMSO-d$_6$) 10.76 (d, 1H, J = 1.7 Hz), 9.29 (s, 1H), 8.68 (d, 1H, J = 8.5 Hz), 8.26 (d, 1H, J = 8.2 Hz), 8.20 (d, 1H, J = 8.0 Hz), 7.75 (s, 1H), 7.59 (d, 1H, J = 7.9 Hz), 7.30 (d, 1H, J = 8.1 Hz), 7.13-6.99 (m, 4H), 6.94 (t, 1H, J = 7.4 Hz), 6.68 (d, 2H, J = 8.5 Hz), 5.23 (ddd, 1H, J = 3.3, 8.5, 11.9 Hz), 5.06 (dd, 2H, J = 12.8, 33.3 Hz), 4.73-4.52 (m, 2H), 4.52-4.29 (m, 2H), 3.02 (dd, 1H, J = 5.0, 14.7 Hz), 2.93-2.78 (m, 2H), 2.68 (dd, 1H, J = 4.6, 16.1 Hz), 2.66-2.52 (m, 2H), 0.97 (d, 3H, J = 7.1 Hz). $^{13}$C NMR (100 MHz, DMSO-d$_6$) 171.8, 170.1, 169.9, 169.2, 156.0, 141.7, 135.8, 132.5, 127.2, 126.9 (2x), 124.3, 123.6, 120.6, 118.4, 117.9, 114.9 (2x), 111.0, 109.6, 58.2, 53.0, 48.2, 47.6, 46.2, 41.5, 35.4, 27.5, 17.0. IR 1731, 1651, 1516, 1174, 746 cm$^{-1}$. HRMS (ESI) Calcd. for C$_{29}$H$_{32}$N$_7$O$_6$ (MH$^+$) 574.2409; Found 574.2407.

Cyclic Peptide 2f
87 mg (0.14 mmol) of seco acid 3f were subjected to macrolactonization conditions as described in procedure 2 to give 23 mg (0.039 mmol, 32%) of 2f as a white solid.

mp = 146°C (dec.). [α]D +6.1 (c 1.1, DMSO). 1H-NMR (400 MHz, DMSO-d6) 10.76 (d, 1H, J = 1.5 Hz), 9.33 (s, 1H), 8.50 (d, 1H, J = 9.0 Hz), 8.19 (t, 2H, J = 8.3 Hz), 7.60 (d, 1H, J = 7.9 Hz), 7.56 (s, 1H), 7.30 (d, 1H, J = 8.0 Hz), 7.11 (d, 2H, J = 8.5 Hz), 7.08 (d, 1H, J = 1.9 Hz), 7.03 (t, 1H, J = 7.6 Hz), 6.94 (t, 1H, J = 7.5 Hz), 6.69 (d, 2H, J = 8.5 Hz), 5.28-5.19 (m, 1H), 4.64-4.54 (m, 2H), 4.56-4.46 (m, 1H), 4.35-4.25 (m, 1H), 4.22-4.07 (m, 2H), 3.08 (dd, 1H, J = 4.1, 14.8 Hz), 2.97-2.81 (m, 2H), 2.78 (dd, 1H, J = 4.7, 15.0 Hz), 2.72-2.52 (m, 4H), 0.87 (d, 3H, J = 7.0 Hz). 13C-NMR (100 MHz, DMSO-d6) 171.6, 170.6, 170.2, 169.2, 156.1, 142.9, 135.9, 132.1, 127.0 (3x), 123.7, 122.5, 120.6, 118.3, 117.9, 114.9 (2x), 111.0, 109.8, 63.0, 53.1, 48.8, 47.6, 46.2, 41.3, 36.0, 27.6, 24.7, 18.0; IR 3293, 1732, 1654, 1516, 1173, 747 cm⁻¹. HRMS (ESI) Calcd. for C30H34N7O6 (MH⁺) 588.2565; Found 588.2563.

Cyclic Peptide 2g
95 mg (0.15 mmol) of seco acid 3g were subjected to macrolactonization conditions followed by TBS deprotection as described in procedure 2 to give 20 mg (0.033 mmol, 26 %) of 2g as a white solid.

mp = 127°C (dec.). [α]D −0.73 (c 0.69, DMSO). 1H-NMR (400 MHz, DMSO-d6) 10.77 (d, 1H, J = 1.9 Hz), 8.53 (d, 1H, J = 8.6 Hz), 8.08 (d, 1H, J = 7.4 Hz), 7.98 (d, 1H, J = 8.3 Hz), 7.65 (s, 1H), 7.55 (d, 1H, J = 7.9 Hz), 7.30 (d, 1H, J = 8.6 Hz), 7.08-6.98 (m, 4H), 6.94 (t, 1H, J = 7.4 Hz), 6.67 (d, 2H, J = 8.4 Hz), 5.12 (q, 1H, J = 8.1 Hz), 4.57-4.44 (m, 1H), 4.37-4.28 (m, 1H), 4.29-4.13 (m, 4H), 3.06 (dd, 1H, J = 1.9 Hz), 2.96-2.78 (m, 2H), 2.75 (dd, 1H, J = 6.3, 15.3 Hz), 2.66 (dd, 1H, J = 8.9, 15.3 Hz), 2.18-2.02 (m, 2H), 2.04-1.83 (m, 2H), 0.98 (d, 3H, J = 15.3 Hz). 13C-NMR (100 MHz, DMSO-d6) 171.7, 170.9, 170.5, 169.8, 156.2, 142.8, 135.9, 131.8, 127.3 (2x), 127.1, 123.5, 123.3, 120.6, 118.3, 118.0, 114.9 (2x), 111.1, 109.7, 62.5, 53.0, 48.8, 48.1, 47.4, 41.1, 31.2, 27.5, 25.3, 24.7, 16.8. IR 3292, 1732, 1650, 1517, 1174, 747 cm−1. HRMS (ESI) Calcd. for C31H36N7O6 (MH+) 602.2722; Found 602.2719.

**Cyclic Peptide 2h**

30 mg (0.062 mmol) of azido alkyne 4h were subjected to intramolecular cycloaddition reaction conditions as described in procedure 6 to give 21 mg (0.044 mmol, 70 %) of 2h as a white solid.

mp = 158°C (dec.). [α]D −4.1 (c 0.4, MeOH). 1H NMR (400 MHz, DMSO-d6) 10.80 (s, 1H), 8.19 (d, 2H, J = 6.9 Hz), 8.06 (t, 1H, J = 5.4 Hz), 7.58 (d, 1H, J = 7.8 Hz), 7.31 (d, 1H, J = 8.0 Hz), 7.09 (d, 1H, J = 1.9 Hz), 7.05 (t, 1H, J = 7.2 Hz), 6.97 (t, 1H, J = 7.3 Hz), 4.69 (d, 2H, J = 2.4 Hz), 4.42 (dt, 1H, J = 4.8, 8.9 Hz), 4.32-4.22 (m, 1H), 3.54 (t, 1H, J = 2.44 Hz), 3.53-3.40 (m, 2H), 3.34-3.21 (m, 2H), 3.14 (dd, 1H, J = 4.5, 14.5 Hz), 2.89 (dd, 1H, J = 9.5, 14.6 Hz), 2.47 (d, 1H, J = 7.1 Hz), 2.45-2.33 (m, 2H), 0.99 (d, 3H,
$J = 7.0$ Hz). $^{13}$C NMR (100 MHz, DMSO-$d_6$) 171.9, 171.4, 170.7, 169.1, 145.0, 136.0, 127.1, 123.6, 122.6, 120.7, 118.3, 118.1, 111.1, 110.1, 53.4, 47.6, 46.0, 35.8, 35.0, 34.5, 34.4, 27.4, 18.2. IR 3278, 1641, 1538, 1200, 744. HRMS (FAB) Calcd. for $C_{23}H_{29}N_8O_4$ (MH$^+$) 481.2312; Found 481.2344.

**Cyclic Peptide 2i**

![Cyclic Peptide 2i](image)

68 mg (0.097 mmol) of azido alkyne 4i were subjected to intramolecular cycloaddition reaction conditions followed by TBS deprotection as described in procedure 6 to give 36 mg (0.061 mmol, 63%) of 2i as a white solid.

mp = 158°C (dec.). $[\alpha]_D$ –21.5 (c 0.6, DMSO). $^1$H-NMR (400 MHz, DMSO-$d_6$) 10.77 (d, 1H, $J = 2.2$ Hz), 9.35 (br s, 1H), 8.84 (d, 1H, $J = 9.1$ Hz), 8.16 (d, 1H, $J = 8.2$ Hz), 8.01 (d, 1H, $J = 8.9$ Hz), 7.65 (d, 1H, $J = 8.1$ Hz), 7.53 (s, 1H), 7.30 (dd, 1H, $J = 0.6, 8.0$ Hz), 7.12 (d, 2H, $J = 8.6$ Hz), 7.08 (d, 1H, $J = 2.1$ Hz), 7.04 (t, 1H, $J = 7.5$ Hz), 6.96 (t, 1H, $J = 7.5$ Hz), 6.70 (d, 2H, $J = 8.6$ Hz), 5.28 (ddd, 1H, $J = 3.2, 9.1, 12.5$ Hz), 5.15 (dd, 2H, $J = 12.7, 27.4$ Hz), 4.55-4.45 (m, 3H), 4.29-4.18 (m, 1H), 2.96 (dd, 1H, $J = 3.8, 14.5$ Hz), 2.88-2.80 (m, 2H), 2.68 (dd, 1H, $J = 12.1, 15.6$ Hz), 2.12-1.94 (m, 3H), 1.84-1.72 (m, 1H), 0.92 (d, 3H, $J = 7.1$ Hz). $^{13}$C-NMR (100 MHz, DMSO-$d_6$) 172.0, 170.7, 170.4, 169.9, 156.2, 141.9, 135.8, 132.6, 127.0, 126.9 (2x), 125.3, 123.9, 120.6, 118.5, 118.0, 115.0 (2x), 111.0, 109.6, 58.3, 53.2, 48.5, 47.2, 47.1, 41.6, 30.2, 27.9, 25.0, 17.7. IR 3291, 1732, 1649, 1516, 1162, 746 cm$^{-1}$. HRMS (FAB) Calcd. for $C_{30}H_{34}N_7O_6$ (MH$^+$) 588.2565; Found 588.2562.

**Cyclic Peptide 2j**
60 mg (0.12 mmol) of azido alkyne 4j were subjected to intramolecular cycloaddition reaction conditions as described in procedure 6 to give 45 mg (0.088 mmol, 75%) of 2j as a white solid.

mp = 126°C (dec.). [α]D +4.3 (c 2.3, DMSO). 1H-NMR (500 MHz, DMSO-d6) 10.79 (s, 1H), 8.30-8.17 (m, 2H), 8.03 (t, 1H, J = 5.7 Hz), 7.65-7.54 (m, 2H), 7.31 (d, 1H, J = 8.1 Hz), 7.14 (d, 1H, J = 1.8 Hz, 1H), 7.04 (t, 1H, J = 7.5 Hz), 6.96 (t, 1H, J = 7.4 Hz), 4.52-4.34 (m, 4H), 4.25-4.14 (m, 1H), 4.09-3.98 (m, 1H), 3.48-3.36 (m, 1H), 3.32-3.21 (m, 1H), 3.16 (dd, 1H, J = 4.3, 14.6 Hz), 2.97-2.91 (m, 1H), 2.92-2.82 (m, 2H), 2.82-2.76 (m, 1H), 2.50-2.39 (m, 2H), 1.04 (d, 3H, J = 7.0 Hz), 0.92 (d, 3H, J = 7.1 Hz). 13C-NMR (125 MHz, DMSO-d6) 173.0, 172.0, 171.5, 171.3, 143.7, 135.9, 127.1, 123.5, 122.9, 120.7, 118.3, 118.0, 111.1, 110.2, 63.0, 53.4, 52.1, 48.3, 40.0, 34.7, 33.9, 27.0, 25.0, 17.4, 15.3. IR 3294, 1730, 1650, 1536, 1172, 745 cm⁻¹. HRMS (FAB) Calcd. for C25H31N7O5 (M⁺) 509.2387; Found 509.2374.

Cyclic Peptide 2k

60 mg (0.11 mmol) of azido alkyne 4k were subjected to intramolecular cycloaddition reaction conditions as described in procedure 6 to give 41 mg (0.078 mmol, 70%) of 2k as a white solid.
mp = 127°C (dec.). $[\alpha]_D$ –6.8 (c 2.1, DMSO). $^1$H-NMR (500 MHz, DMSO-d$_6$) 10.80 (s, 1H), 8.26 (d, 2H, $J = 7.6$ Hz), 7.85 (t, 1H, $J = 5.6$ Hz), 7.69 (s, 1H), 7.55 (d, 1H, $J = 7.9$ Hz), 7.31 (d, 1H, $J = 8.1$ Hz), 7.11 (d, 1H, $J = 1.9$ Hz), 7.05 (t, 1H, $J = 7.5$ Hz), 6.96 (t, 1H, $J = 7.4$ Hz), 5.08-4.96 (m, 1H), 4.54-4.34 (m, 3H), 4.20-4.08 (m, 1H), 3.46-3.35 (m, 1H), 3.35-3.25 (m, 1H), 3.21 (dd, 1H, $J = 4.7$, 14.7 Hz), 2.99-2.90 (m, 2H), 2.89-2.84 (m, 1H), 2.81 (dd, 1H, $J = 7.3$, 15.1 Hz), 2.44 (t, 2H, $J = 5.5$ Hz), 1.22 (d, 3H, $J = 6.3$ Hz), 1.04 (d, 3H, $J = 7.0$ Hz), 0.99 (d, 3H, $J = 7.2$ Hz). $^{13}$C-NMR (125 MHz, DMSO-d$_6$) 173.2, 172.0, 171.2, 170.7, 142.6, 135.9, 127.1, 123.6, 123.3, 120.7, 118.1, 118.1, 111.1, 110.2, 69.7, 53.9, 52.1, 48.6, 40.0, 34.8, 34.2, 31.2, 26.7, 19.4, 17.1, 15.1. IR 3292, 2980, 1727, 1651, 1537, 1177, 745 cm$^{-1}$. HRMS (ESI) Calcd. for C$_{26}$H$_{34}$N$_7$O$_5$ (MH$^+$) 524.2616; Found 524.2609.

**Cyclic Peptide 2l**

70 mg (0.14 mmol) of azido alkyne 4l were subjected to intramolecular cycloaddition reaction conditions as described in procedure 6 to give 40 mg (0.081 mmol, 57 %) of 2l as a white solid.

mp = 236°C (dec.). $[\alpha]_D$ –22.9 (c 0.28, DMSO). $^1$H-NMR (400 MHz, DMSO-d$_6$) 10.78 (s, 1H), 8.32 (t, 1H, $J = 5.7$ Hz), 8.18 (t, 1H, $J = 5.5$ Hz), 8.09 (d, 1H, $J = 7.4$ Hz), 7.99 (d, 1H, $J = 8.5$ Hz), 7.62 (d, 1H, $J = 7.8$ Hz), 7.41 (s, 1H), 7.29 (d, 1H, $J = 8.0$ Hz), 7.13 (s, 1H), 7.03 (t, 1H, $J = 7.3$ Hz), 6.95 (t, 1H, $J = 7.4$ Hz), 4.69-4.36 (m, 3H), 4.36-4.16 (m, 2H), 4.13 (dd, 1H, $J = 4.4$, 15.6 Hz), 3.61-3.39 (m, 1H), 3.33-3.13 (m, 1H), 3.13 (dd, 1H, $J = 4.0$, 14.5 Hz), 2.94 (dd, 1H, $J = 9.9$, 14.5 Hz), 2.48-2.33 (m, 1H), 2.27 (dd, 1H, $J = 6.7$, 13.8 Hz), 2.21-1.76 (m, 4H), 0.92 (d, 3H, $J = 7.1$ Hz). $^{13}$C-NMR (100 MHz, DMSO-d$_6$) 172.0, 171.5, 171.2, 170.6, 145.7, 135.9, 127.1, 123.6, 122.6, 120.6, 118.4, 117.9, 111.0, 109.9, 52.9, 47.9, 47.2, 35.4, 35.2, 34.6, 31.3, 27.7, 25.8, 16.8; IR 3292,
1634, 1543, 1236, 1053, 744 cm\(^{-1}\). HRMS (ESI) Calcd. for C\(_{24}\)H\(_{31}\)N\(_8\)O\(_4\) (MH\(^+\)) 496.2463; Found 496.2457.

\(^1\)H-NMR spectra
3a
500 MHz; DMSO-d6
$3b$

400 MHz, DMSO-d6 + D2O (35:1)
$3c$

400 MHz; DMSO-d$_6$ + D$_2$O (35:1)
3d
400 MHz; DMSO-d6 + D2O (35:1)
10b
400 MHz, DMSO-d6
Supplementary Material (ESI) for Chemical Communications

This journal is (c) The Royal Society of Chemistry 2007
4a
400 MHz; DMSO-d6
$4\text{b}$

$400 \text{ MHz; DMSO-d}_6$
Supplementary Material (ESI) for Chemical Communications

This journal is (c) The Royal Society of Chemistry 2007

4c

400 MHz; DMSO-d6

ppm

10.0

5.0

0.0

0.0
Supplementary Material (ESI) for Chemical Communications
This journal is (c) The Royal Society of Chemistry 2007

4d
400 MHz; DMSO-d6
**Supplementary Material (ESI) for Chemical Communications**

This journal is (c) The Royal Society of Chemistry 2007

**4i**

400 MHz; DMSO-d6
$4\text{k}$

$400 \text{ MHz; DMSC-d6}$
500 MHz; DMSO-d6
Supplementary Material (ESI) for Chemical Communications
This journal is (c) The Royal Society of Chemistry 2007

2a
400 MHz: DMSO-d6
2b
500 MHz; DMSO-d6
$^{1}H$ NMR spectrum of compound 2c at 500 MHz in DMSO-$d_6$.
Supplementary Material (ESI) for Chemical Communications

This journal is (c) The Royal Society of Chemistry 2007

2e
400 MHz; DMSO-d6
2f
400 MHz; DMSO-d6
2h
400 MHz; DMSO-d6
$^{2}J$
400 MHz; DMSO-d6
Supplementary Material (ESI) for Chemical Communications

This journal is (c) The Royal Society of Chemistry 2007

2I
400 MHz; DMSO-d6

ppm

10.0

5.0

0.0