Exploiting the Interplay of Quantum Interference and Backbone Rigidity on Electronic Transport in Peptides: A Step Towards Bio-Inspired Quantum Interferometers

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1. General Information

Chemicals

Fmoc-Aib-OH, Boc-Aib-OH, Fmoc-Lys(Boc)-OH, Boc-Lys(Cbz)-OH, Boc-Glu(OBzl)-OH, H-Leu-OMe, H-Ala-OMe, 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide HCl (EDC·HCl), Fmoc-OSu, 2-chlorotrityl chloride polystyrene resin, 1-hydroxy-7-azabenzotrizole (HOAt) and 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uranium hexafluorophosphate methanaminium (HATU) were purchased from GL Biochem (Shanghai) Ltd, China. Dichloromethane (DCM), diethyl ether (Et_2O), ethyl acetate (EtOAc), methanol and ethanol were purchased from Ajax Finechem Pty Ltd (Australia). Piperidine, acetonitrile, propan-2-ol, potassium carbonate, and *N*,*N*-dimethylformamide (DMF) were purchased from Merck, Australia. Anhydrous *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), tetrahydrafuran (THF), dioxane, 2,2,2-trifluoroethanol (TFE), trifluoroacetic acid (TFA), 4 M HCl/dioxane solution, cysteamine, methyl iodide, Pd/C and diisopropylethylamine (DIPEA) were purchased from Sigma-Aldrich, Australia. $SOCl_2$, CH_3COOH and NaOH were purchased from Chem Supply, Australia. Single-walled carbon nanotubes (P2-SWCNTs), were purchased from Carbon Solutions Inc., USA. Ferrocenylmethylamine[1, 2] was prepared as published. All solvents and reagents were used without purification unless noted.

High-Performance Liquid Chromatography

The synthetic peptides were analyzed and purified by reverse phase HPLC, using an HP 1100 LC system equipped with a Phenomenex C18 column (250x4.6 mm) for analytical traces and a Phenomenex C18 column (250 x 21.2 mm) for purification, a photodiode array detector, and a Sedex evaporative light scattering detector. Water/TFA (100/0.1 by v/v) and ACN/TFA (100/0.08 by v/v) solutions were used as aqueous and organic buffers.

NMR Spectroscopy.

^1H NMR spectra were recorded in DMSO-d_6 or $CDCl_3$-d solutions using a Varian Gemini-300 NMR. ^{13}C NMR and two-dimensional NMR experiments utilized COSY, ROESY, HSQC and HMBC were obtained on a Varian Inova 600 MHz spectrometer. Chemical shifts are reported in ppm (δ) using TMS (0.00 ppm) as the internal standard. Signals are reported as s (singlet), d (doublet), t (triplet) or m (multiplet).

Mass Spectroscopy

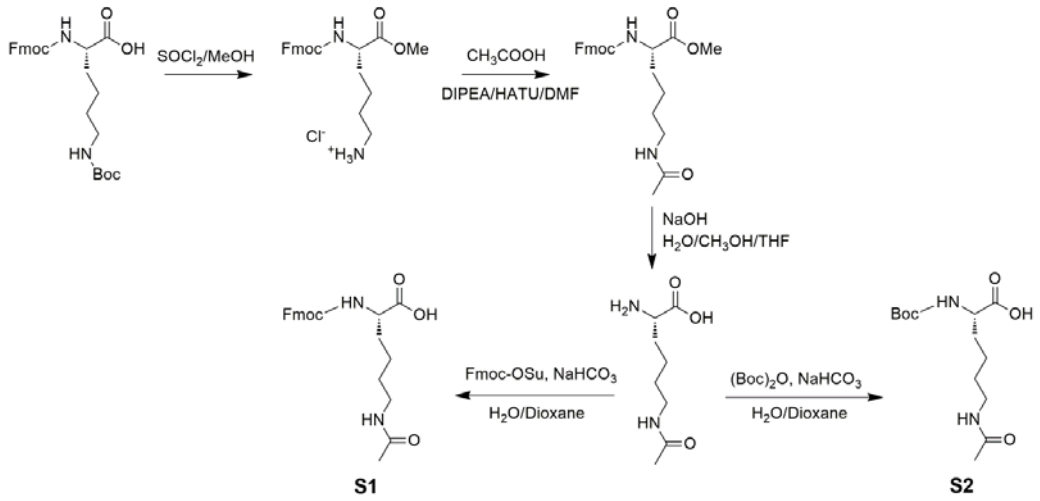
Low resolution mass spectral data were analyzed using a Finnigan MAT LCQ spectrometer with MS/MS and ESI probe, utilizing XCalibur software. High resolution mass spectral data were analyzed using an Ultimate 3000 RSL HPLC (Thermo Fisher Scientific Inc., MA) and an LTQ Orbitrap XL ETD using a flow injection method, with a flow rate of 5 µL/min. The HPLC flow is interfaced with the mass spectrometer using the Electrospray source (Thermo Fisher Scientific Inc., MA). Mass spectra were obtained over a range of $100 < m/z < 1000$. Data was analyzed using XCalibur software (Version 2.0.7, Thermo Fisher Scientific).

FTIR Spectroscopy

Infrared spectra were collected on a Perkin Elmer Spectrum 100 FT-IR spectrometer, with attenuated total reflectance (ATR) imaging capabilities, fitted with a ZnSe crystal, with an average reading taken from 4 scans at 4 cm^{-1} resolution.

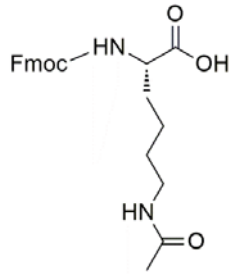
2. Synthesis of peptides

Scheme S1. The synthetic steps for building blocks S1 and S2.



Fmoc-Lys(Boc)-OH (4.19 g, 8.9 mmol) was dissolved in 40 mL dry methanol (over molecular sieves) and cooled to 0 ^{o}C. Thionyl chloride (2.5 mL) was added dropwise to the methanolic solution over 5 min. The mixture was stirred at 0 ^{o}C for 30 min, then warmed to room temperature and further stirred overnight. The volatiles were removed to yield the intermediate Fmoc-Lys-OMe, an off-white solid (3.80 g, quant). The resulting residue and CH_3COOH (2.0 mL) were dissolved in anhydrous DMF (15 mL) and stirred at rt under an N_2 atmosphere. HATU (6.50 g, 17.1mmol) and DIPEA (6.0 mL) were added, and the mixture stirred for 48 h. The solvent was removed and the residue taken up in EtOAc (200 mL) and H_2O (200 mL). The organic layer was separated and washed with $NaHCO_3$ (200 mL), brine (200 mL) and dried over Na_2SO_4. The volatiles were removed *in vacuo* to reveal a white solid (3.91 g, quant). The resulting residue was dissolved in the mixture of THF (23.0 mL) and methanol (16.0 mL). 9.0 mL of NaOH solution (1.6 M, aqueous) was added to the mixture, and the reaction stirred at rt for 18 h. The solvent was removed *in vacuo* and the residue redissolved in H_2O (200mL), washed with Et_2O (200 mL). The aqueous layer was separated and dried over $MgSO_4$. The solvent was removed *in vacuo* to yield the amphoteric intermediate, an off-white solid (1.85 g, quant).

Compound **S1**



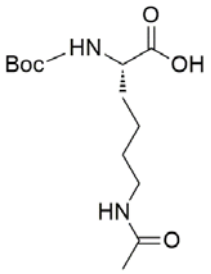
The amphoteric residue (1.85 g, 8.0 mmol) was dissolved in para-dioxane (20.0mL). A solution of $NaHCO_3$ (2.20 g in 20.0 mL H_2O, 16.0mmol, 2equiv) was added followed by Fmoc-OSu (2.90 g, 8.0mmol, 1 equiv). The reaction mixture was stirred overnight at rt after which the volatiles

were removed under reduced pressure. The residue was dissolved in 2.5% $NaHCO_3$ and washed with Et_2O (3x20 mL). The aqueous layer was then acidified to pH 4 by dropwise addition of 6 M aqueous HCl and extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and the solvent removed under reduced pressure to give the product as a white solid (2.51 g, 76%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.88 (d, 2H, arom*H*), 7.81 (t, 1H, N*H*CH$_2$), 7.41 (t, 2H, arom*H*), 7.72 (d, 2H, arom*H*), 7.62 (d, 1H, N*H*CH), 7.46-7.28 (m, 4H, arom*H*), 4.32-4.16 (d, 3H, C*H*& CH_2in Fmoc), 3.90 (m, 1H, NHC*H*), 3.06-2.96 (m, 2H, NHCH_2), 1.78 (s, 3H, CH_3), 1.64 (m, 2H, CH_2), 1.36 (m, 4H, 2xCH_2) .

MS: $[M+H]^+_{calcd}$=411.2, $[M+H]^+_{found}$=411.2.

Compound **S2**

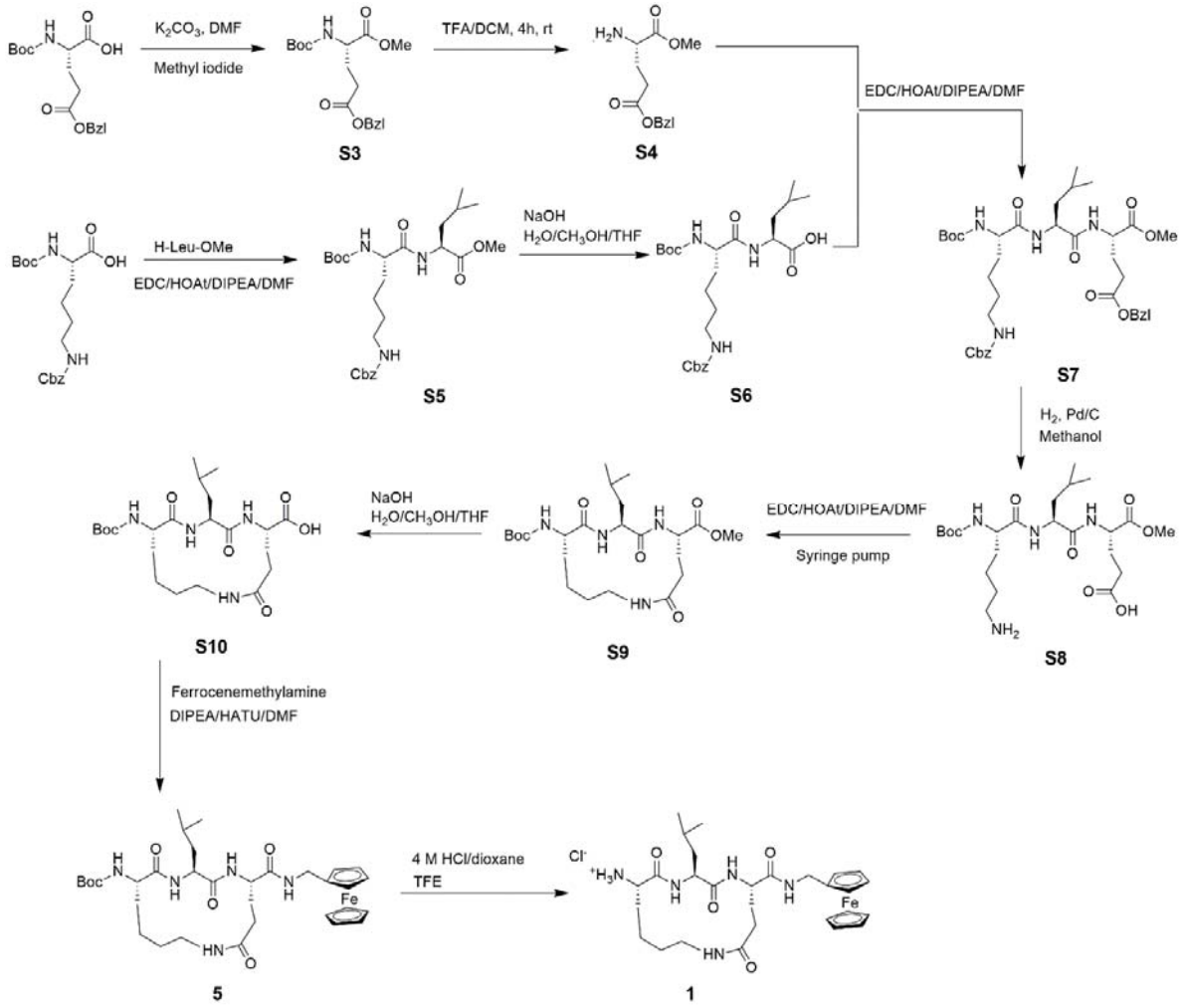


The amphoteric residue (3.93 g, 17.0mmol) and $NaHCO_3$ (2.86 g, 34.0 mmol) were dissolved in water (60.0 mL). A solution of $(Boc)_2O$ (5.60 g in 60.0 mL para-dioxane) was added. The reaction mixture was stirred overnight at rt after which the volatiles were removed under reduced pressure. The residue was redissolved in 200 mL of water, washed with EtOAc (200 mL). The aqueous layer was then acidified to pH 3 by dropwise addition of 6 M aqueous HCl and extracted with EtOAc (3x100 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and the solvent removed under reduced pressure to give the product as a white solid (4.40 g, 89%).

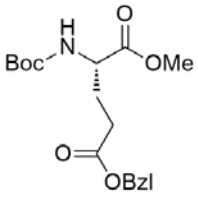
^{1}H NMR (300 MHz, DMSO-d_6): δ 7.78(t, 1H, N*H*CH$_2$), 7.05 (d, 1H, N*H*CH), 3.80 (m, 1H, NHC*H*), 3.06-2.92 (m, 2H, NHCH_2), 1.76 (s, 3H, CH_3), 1.58 (m, 2H, CH_2), 1.40-1.20 (m, 13H, Boc & 2xCH_2).

MS: $[M+H]^+_{calcd}$=289.2, $[M+H]^+_{found}$=289.2.

Scheme S2. The final synthetic steps for lactam-bridged β-strand peptides



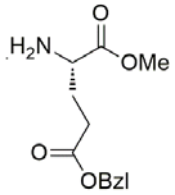
Compound **S3**



K_2CO_3 (982 mg, 7.11 mmol) was suspended in anhydrous DMF (20 mL). Boc-Glu(OBzl)-OH (2.0 g, 5.93 mmol) was added, followed by MeI (1.01 g, 7.11 mmol, 443µL). The reaction was stirred at rt under an N_2 atmosphere for 18 h. The solvent was removed and the residue taken up in EtOAC (200 mL) and H_2O (200 mL). The pH was adjusted to pH 3-4 and the organic layer separated and washed with brine (200 mL) and dried over $NaSO_4$. The solvent was removed *in vacuo* to reveal golden oil (1.80 g, 86%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.40-7.30 (m, 6H, benzene, N*H*), δ 5.09 (s, 2H, OCH_2), δ 4.06-3.98 (m, 1H, Cα*H*), δ 3.61 (s, 3H, OCH_3), δ 2.45 (dd, 2H, CH_2, *J*=9.8, 5.8 Hz), δ 2.01-1.74 (m, 2H, CH_2), δ 1.37 (s, 9H, Boc).

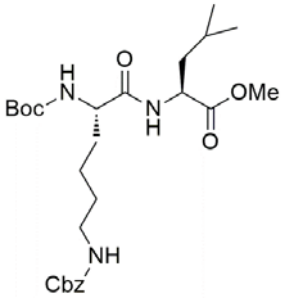
Compound **S4**



Compound **S3** (877 mg, 2.50 mmol) was dissolved in DCM (5 mL). TFA (5 mL) was added dropwise and the reaction stirred at rt for 3 h. The solvent was removed *in vacuo* to reveal golden oil (1.21 g, quant).

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.44 (br s, 3H, N*H*), 7.37 (m, 5H, benzene), 5.11 (s, 2H, OCH_2), 4.10 (br s, 1H, Cα*H*), 3.72 (s, 3H, OCH_3), 2.56 (m, 2H, CH_2), 2.04 (m, 2H, CH_2).

Compound **S5**

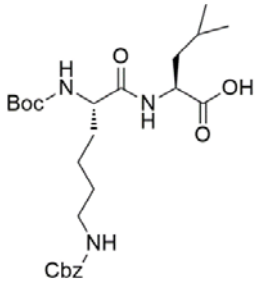


Boc-Lys(Z)-OH (1.00 g, 2.63 mmol) and HCl·H_2N-Leu-OMe (572 mg, 3.16 mmol) were dissolved in anhydrous DCM (20 mL) and stirred at rt under an N_2 atmosphere. Anhydrous DIPEA (1.6 mL), EDC·HCl (552 mg, 2.89 mmol) and HOAt (393 mg, 2.89 mmol) were added and the solution stirred for 36 h. DCM (30 mL) and H_2O (50 mL) were added and the pH adjusted to pH 2-3. The organic layer was separated and washed with brine (50 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to yield clear oil (1.07 g, 81%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.11 (d, 1H, N*H*, *J*=7.6 Hz), 7.40-7.30 (m, 5H, benzene), 7.23 (t, 1H, N*H*, *J*=10.5 Hz), 6.79 (d, 1H, N*H*, *J*=8.1 Hz), 5.00 (s, 2H, OCH_2), 4.33-4.26 (m, 1H, Cα*H*), 3.90 (d, 1H, Cα*H*, *J*=5.4 Hz), 3.60 (s, 3H, OCH_3), 2.97 (d, 2H, CH_2NH, *J*=5.9 Hz), 1.70-1.22 (m, 9H, 4xCH_2, C*H*), 1.37 (s, 9H, Boc), 0.90-0.82 (m, 6H, 2xCH_3 Leu).

MS: $[M+Na]^+_{calcd}$=530.2, $[M+Na]^+_{found}$=530.2.

Compound **S6**

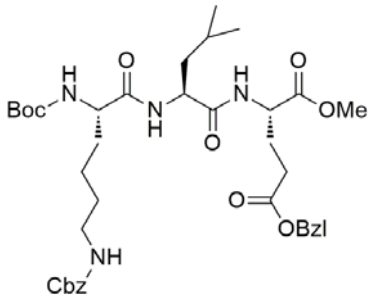


Compound **S5** (1.06 g, 2.10 mmol) was dissolved in THF (8.37 mL) and methanol (2.13 mL). NaOH (125 mg, 3.14 mmol) was dissolved in H_2O (2.13 mL) and added to the solution and stirred at rt for 24 h. The THF was removed *in vacuo* and EtOAC (50 mL) and H_2O (50 mL) added. The pH was adjusted to pH 2-3, the organic layer separated and washed with brine (50 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to yield a clear solid (904 mg, 87%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.93 (d, 1H, N*H*, *J*=7.7 Hz), 7.40-7.30 (m, 5H, benzene), 7.23 (t, 1H, N*H*, *J*=10.2 Hz), 6.79 (d, 1H, N*H*, *J*=8.3 Hz), 5.00 (s, 2H, OCH_2), 4.22 (dd, 1H, Cα*H*, *J*=14.2, 8.5 Hz), 3.89 (d, 1H, Cα*H*, *J*=4.8 Hz), 2.96 (d, 2H, CH_2NH, *J*=5.6 Hz), 1.70-1.22 (m, 9H, 4xCH_2, C*H*), 1.37 (s, 9H, Boc), 0.90-0.82 (m, 6H, 2xCH_3 Leu).

MS: $[M+Na]^+_{calcd}$=516.2, $[M+Na]^+_{found}$=516.2.

Compound **S7**

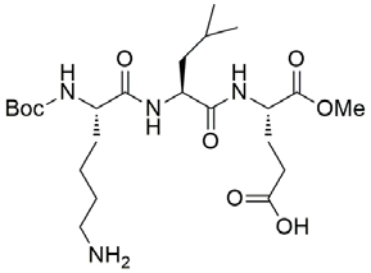


Compound **S4** (627 mg, 2.50 mmol) and compound **S6** (1.12 g, 2.27 mmol) were dissolved in anhydrous DCM (42 mL) and stirred at rt under an N_2 atmosphere. Anhydrous DIPEA (1.58 mL), HATU (949 mg, 2.50 mmol) and HOAt (308 mg, 2.27 mmol) were added and the solution stirred for 42 h. DCM (60 mL) and H_2O (100 mL) were added and the pH adjusted to pH 3. The organic layer was separated and washed with brine (100 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to reveal a white solid, which was purified by column chromatography on silica gel (70/30 EtOAC/PE), yielding (785 mg, 48%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.31 (d, 1H, N*H*, *J*=7.2 Hz), 7.77 (d, 1H, N*H*, *J*=7.9 Hz), 7.40-7.30 (m, 10H, 2x benzene), 7.23 (t, 1H, N*H*, *J*=9.0 Hz), 6.87 (d, 1H, N*H*, *J*=8.0 Hz), 5.09 (s, 2H, OCH_2), 4.99 (s, 2H, OCH_2), 4.30 (dd, 2H, 2x Cα*H*, *J*=13.5, 6.2 Hz), 3.89-3.82 (m, 1H, Cα*H*), 3.59 (s, 3H, OCH_3), 2.99-2.91 (m, 2H, CH_2NH), 2.43 (t, 2H, CH_2, *J*=7.5 Hz), 2.07-1.22 (m, 11H, 5x CH_2, C*H*), 1.36 (s, 9H, Boc), 0.89-0.82 (m, 6H, (CH_3)$_2$ Leu).

MS: $[M+Na]^+_{calcd}$=749.3, $[M+Na]^+_{found}$=749.3.

Compound **S8**

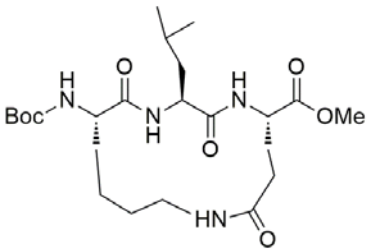


Compound **S7** (464 mg, 0.639 mmol) was dissolved in (methanol over molecular sieves, 10 mL) and stirred at rt under an N_2 atmosphere for 10 min. Pd/C (15% w/w, 70 mg) was added. A H_2 balloon was fitted under vacuum and the solution stirred at rt for a further 24 h. The solution was filtered through celite and washed with methanol (3x 20 mL), and the solvent removed *in vacuo* to yield a white solid (232 mg, 72%).

^{1}H NMR (600 MHz, DMSO-d_6): δ 8.89 (d, 1H, N*H*, *J*=6.5 Hz), 8.02 (d, 1H, N*H*, *J*=8.5 Hz), 6.78 (d, 1H, N*H*, *J*=8.0 Hz), 4.33 (dd, 1H, Cα*H*, *J*=14.4, 9.0 Hz), 4.23 (t, 1H, Cα*H*, *J*=9.8 Hz), 3.95 (dd, 1H, Cα*H*, *J*=14.0, 7.4 Hz), 3.58 (s, 3H, OCH_3), 2.03-1.26 (m, 15H, 7x CH_2, C*H*), 1.36 (s, 9H, Boc), 0.87-0.81 (m, 6H, 2xCH_3 Leu).

MS: $[M+Na]^+_{calcd}$=525.3, $[M+Na]^+_{found}$=525.3.

Compound **S9**



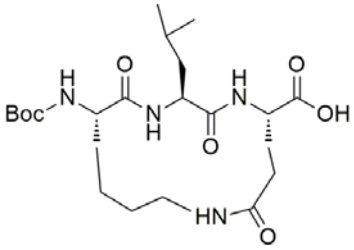
Compound **S8** (127 mg, 0.253 mmol) was suspended in anhydrous DMF (26 mL) and anhydrous THF (20 mL) and sonicated. EDC·HCl (238 mg, 1.25 mmol), HOAt (170 mg, 1.25 mmol) and DIPEA (435 µL) were dissolved in anhydrous DMF (15 mL) and anhydrous THF (8 mL) and the solution stirred at rt under an N_2 atmosphere. The compound **S8** mixture was placed into a syringe pump and added to the coupling reagents at the rate of 30 µL/min, and stirred for 48 h. The crude product was purified using reverse phase HPLC to yield a white solid (39 mg, 31%).

^{1}H NMR (600 MHz, DMSO-d_6): δ 8.25 (d, 1H, N*H*, *J*=7.4 Hz), 8.06 (d, 1H, N*H*, *J*=8.2 Hz), 7.42 (m, 1H, N*H*), 6.43 (d, 1H, N*H*, *J*=7.3 Hz), 4.43 (m, 1H, Cα*H*), 4.34 (m, 1H, Cα*H*), 4.05 (m, 1H, Cα*H*), 3.60 (s, 3H, OCH_3), 3.32 (m, 1H, C*H*HNH), 2.71 (m, 1H, CH*H*NH), 2.28-1.04 (m, 13H, 6x CH_2, C*H*), 1.36 (s, 9H, Boc), 0.90-0.84 (m, 6H, 2xCH_3 Leu).

^{13}C NMR (150 MHz, DMSO-d_6):δ 172.4, 172.1, 171.4, 170.7, 158.0, 154.5, 77.8, 53.2, 51.7, 50.8, 50.4, 48.5, 41.0, 36.9, 31.4, 28.4, 28.1, 27.9, 25.5, 24.6, 23.9, 23.8, 21.7.

MS: $[M+Na]^+_{calcd}$=507.2, $[M+Na]^+_{found}$=507.2.

Compound **S10**

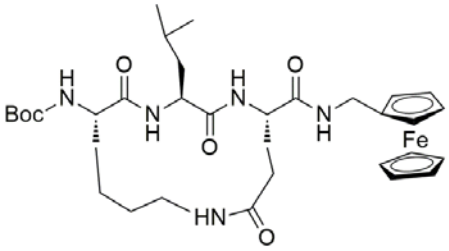


Compound **S9** (125 mg, 0.258 mmol) was dissolved in THF (2.6 mL) and methanol (750 µL). NaOH (15 mg, 0.387 mmol) was dissolved in H_2O (250 µL) and added to the acid, and the reaction stirred at rt for 17 h. The solvent was removed *in vacuo* and the residue redissolved in EtOAc (25 mL) and H_2O (25 mL). The pH was adjusted to pH 2 and the organic layer separated and washed with brine (25 mL), and dried over $MgSO_4$. The solvent was removed *in vacuo* to reveal a white solid (95 mg, 78%).

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.15-8.01 (m, 2H, 2x N*H*), 7.37 (br s, 1H, N*H*), 6.43 (d, 1H, N*H*, *J*=7.2 Hz), 4.37-4.29 (m, 2H, 2x Cα*H*), 4.06 (dd, 1H, Cα*H*, *J*=14.1, 7.0 Hz), 3.30 (m, 1H, C*H*HNH), 2.73 (m, 1H, CH*H*NH), 2.28-1.06 (m, 13H, 6x CH_2, C*H*), 1.36 (s, 9H, Boc), 0.89-0.83 (m, 6H, 2xCH_3 Leu).

MS: $[M+Na]^+_{calcd}$=493.2, $[M+Na]^+_{found}$=493.2.

Peptide **5**



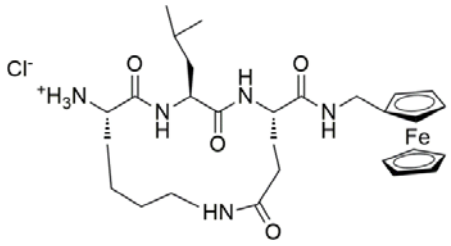
Compound **S10** (95 mg, 0.202 mmol) and ferrocenylmethylamine were dissolved in anhydrous DMF (4 mL) and stirred at rt under an N_2 atmosphere. HATU (84 mg, 0.222 mmol), HOBt (27 mg, 0.202 mmol) and DIPEA (140 µL) were added, and the mixture stirred for 48 h. The solvent was removed and the residue taken up in EtOAc (25 mL) and H_2O (25 mL). The pH was adjusted to pH 3 and the organic layer separated and washed with $NaHCO_3$ (25 mL), brine (25 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* to yield a brown solid (98 mg, 73%).

^{1}H NMR (600 MHz, DMSO-d_6): δ 8.24-8.19 (m, 2H, 2x N*H*), 7.63 (t, 1H, N*H*, *J*=5.8 Hz), 7.49 (br s, 1H, N*H*), 6.37 (d, 1H, N*H*, *J*=7.4 Hz), 4.32 (m, 1H, Cα*H*), 4.20 (m, 1H, Cα*H*), 4.18-4.05 (m, 9H, Cp), 4.09 (m, 1H, Cα*H*), 3.98 (d, 2H, CH_2Fc, *J*=5.7 Hz), 3.32 (m, 1H, C*H*HNH), 2.75 (m, 1H, CH*H*NH), 2.28-1.01 (m, 13H, 6xCH_2, C*H*), 1.36 (s, 9H, Boc), 0.89-0.83 (m, 6H, 2xCH_3 Leu).

^{13}C NMR (150 MHz, DMSO-d_6):δ 172.8, 172.3, 172.0, 170.9, 155.0, 86.3, 78.3, 73.4, 70.7, 69.8, 69.3, 69.2, 68.8, 68.7, 67.98, 67.93, 67.6, 67.5, 60.1, 53.5, 52.4, 52.2, 46.3, 40.9, 38.0, 31.5, 30.7, 28.5, 26.3, 24.4, 23.3, 22.2.

MS: $[M+Na]^+_{calcd}$=690.3, $[M+Na]^+_{found}$=690.3.

Peptide **1**



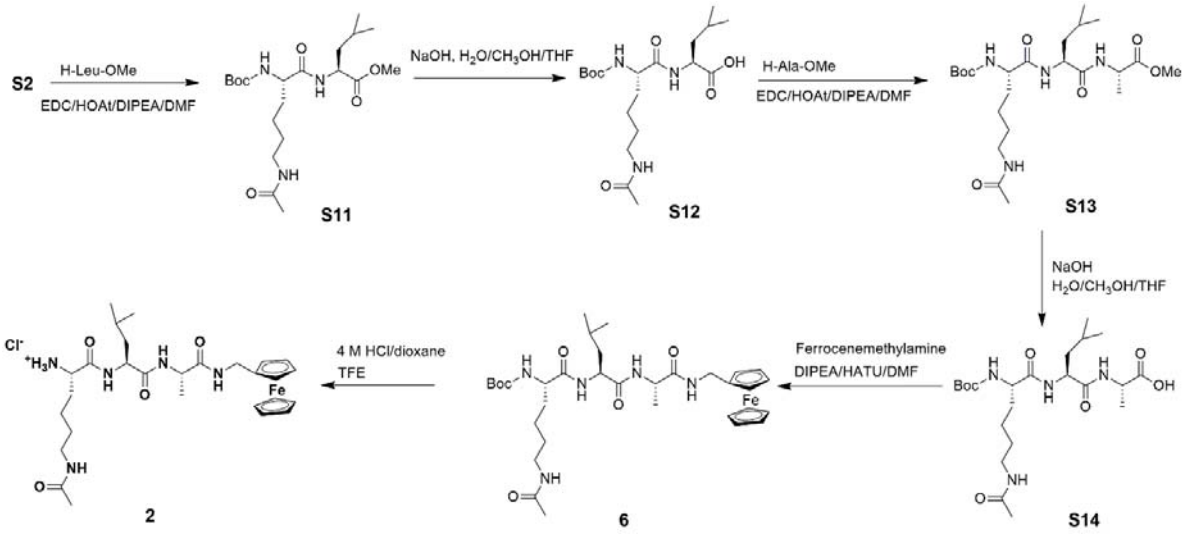
Peptide **5** (86 mg, 0.129 mmol) was dissolved in TFE (2 mL) and 4M HCl in dioxane (1 mL) added dropwise. The reaction was stirred at rt for 25 min. The solvent was removed *in vacuo* to reveal a brown solid. The crude product was purified using reverse phase HPLC to yield a sandy brown solid (15 mg, 21%).

^{1}H NMR (600 MHz, DMSO-d_6): δ 8.54 (d, 1H, N*H*, *J*=7.9 Hz), 8.36 (d, 1H, N*H*, *J*=7.6 Hz), 8.07 (br s, 3H, N*H*), 7.79 (br s, 1H, N*H*), 7.55 (m, 1H, N*H*), 4.41-4.34 (m, 2H, 2 x Cα*H*), 4.19-3.93 (m, 9H, Cp), 4.07 (br s, 2H, CH_2Fc), 3.88 (br s, 1H, Cα*H*), 3.28 (m, 1H, C*H*HNH), 2.79 (m, 1H, CH*H*NH), 2.32-1.05 (m, 13H, 6 x CH_2, C*H*), 0.90-0.87 (dd, 6H, (CH_3)$_2$ Leu, *J*=9.3, 6.6 Hz).

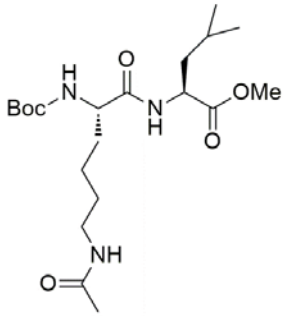
^{13}C NMR (150 MHz, DMSO-d_6): δ 171.63, 171.29, 170.68, 168.36, 157.88, 70.92, 69.38, 68.92, 68.37, 67.33, 67.14, 51.81, 51.77, 51.58, 45.45, 41.49, 40.04, 37.45, 36.69, 30.19, 28.76, 25.20, 24.26, 23.98, 22.99, 22.63, 21.86, 19.50.

HRMS (*m/z*): $[M+H]^+_{calcd}$=568.2586, $_{found}$=568.2582.

Scheme S3. The final synthetic steps for linear β-strand peptides



Compound **S11**

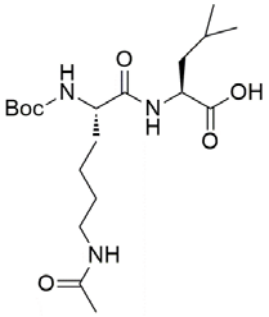


Compound **S2** (367 mg, 1.27 mmol) was dissolved in anhydrous DCM (10 mL). H-Leu-OMe (275 mg, 1.52 mmol) was added and stirred at rt under an N_2 atmosphere. Anhydrous DIPEA (883 µL) was added, followed by EDC·HCl (267 mg, 1.40 mmol) and HOAt (173 mg, 1.27 mmol), and the reaction mixture stirred for 24 h. DCM (20 mL) and H_20 (30 mL) were added and the pH adjusted to pH 2-3. The organic layer was collected, washed with brine (30 mL), and dried over $MgSO_4$. The solvent was removed *in vacuo* to yield pale golden oil (373 mg, 71%).

^{1}H NMR (300 MHz, d-DMSO) δ 8.12 (d, 1H, N*H*, *J*=7.6 Hz), δ 7.79 (br s, 1H, N*H*), δ 6.80 (d, 1H, N*H*, *J*=8.2 Hz), δ 4.29 (m, 1H, Cα*H*), δ 3.89 (m, 1H, Cα*H*), δ 3.60 (s, 3H, OCH_3), δ 3.02-2.85 (m, 2H, CH_2NH), δ 1.78 (s, 3H, CH_3), δ 1.66-1.23 (m, 9H, 4xCH_2, C*H*), δ 1.37 (s, 9H, Boc), δ 0.90-0.81 (m, 6H, (CH_3)$_2$Leu).

MS: $[M+Na]^+_{calcd}$=438.2, $[M+Na]^+_{found}$=438.2.

Compound **S12**

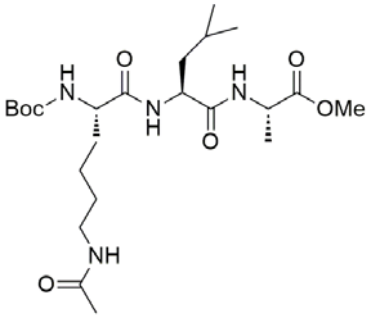


Compound **S11** (357 mg, 0.86 mmol) was dissolved in THF (2.5 mL) and methanol (714 µL) and the mixture stirred. NaOH (52 mg, 1.29 mmol) was dissolved in H_2O (714 µL) and this solution was added to the acid and stirred at rt for 31 h. The THF was removed *in vacuo* and the residue dissolved in EtOAC (25 mL) and H_2O (25 mL). The pH was adjusted to pH 2-3 and the organic layer collected and washed with brine (25 mL), and dried over $MgSO_4$. The solvent was removed *in vacuo* to reveal a clear solid (294 mg, 85%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.94 (d, 1H, N*H*, *J*=7.8 Hz), 7.77 (t, 1H, N*H*, *J*=9.0 Hz), 6.79 (d, 1H, N*H*, *J*=8.2 Hz), 4.22 (dd, 1H, Cα*H*, *J*=13.9, 8.5 Hz), 3.88 (d, 1H, Cα*H*, *J*=4.8 Hz), 3.00-2.85 (m, 2H, CH_2NH), 1.77 (s, 3H, CH_3), 1.70-1.23 (m, 9H, 4xCH_2, C*H*), 1.36 (s, 9H, Boc), 0.89-0.81 (m, 6H, 2xCH_3Leu).

MS: $[M+Na]^+_{calcd}$=400.2, $[M+Na]^+_{found}$=400.2.

Compound **S13**

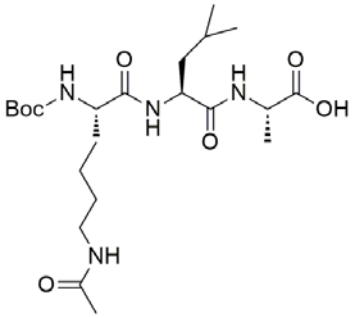


Compound **S12** (275 mg, 0.69 mmol) and HCl·H_2N-Ala-OMe (105 mg, 0.754 mmol) were dissolved in anhydrous DMF (11.5 mL) and stirred at rt under an N_2 atmosphere. Anhydrous DIPEA (477 µL), HATU (287 mg, 0.754 mmol) and HOAt (93 mg, 0.686 mmol) were added and the reaction stirred for 25 h. The solvent was removed and the residue dissolved in EtOAC (50 mL) and H_2O (50 mL). The pH was adjusted to pH 3 and the organic layer washed with $NaHCO_3$ (50 mL) and brine (50 mL), before being dried over $MgSO_4$. The solvent was removed *in vacuo* to yield a pale golden oil (265 mg, 79%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.36 (d, 1H, N*H*, *J*=6.8 Hz), 7.77 (t, 1H, N*H*, *J*=9.0 Hz), 7.72 (d, 1H, N*H*, *J*=8.2 Hz), 6.87 (d, 1H, N*H*, *J*=8.1 Hz), 4.35 (d, 1H, Cα*H*, *J*=7.6 Hz), 4.23 (m, 1H, Cα*H*), 3.87 (m, 1H, Cα*H*), 3.60 (s, 3H, OCH_3), 3.03-2.90 (m, 2H, CH_2NH), 1.77 (s, 3H, CH_3), 1.70-1.34 (m, 9H, 4xCH_2, C*H*), 1.37 (s, 9H, Boc), 1.27 (d, 3H, CH_3, Ala, *J*=7.3 Hz), 0.89-0.81 (m, 6H, 2xCH_3Leu).

MS: $[M+Na]^+_{calcd}$=509.3, $[M+Na]^+_{found}$=509.3.

Compound **S14**

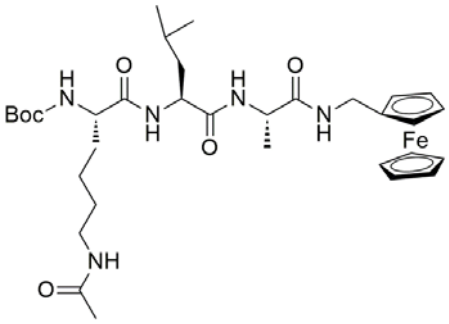


Compound **S13** (246 mg, 0.51 mmol) was dissolved in THF (1.72 mL) and methanol (492 µL), and the mixture stirred. NaOH (30 mg, 0.75 mmol) was dissolved in H_2O (492 µL) and this solution was added to the acid and stirred at rt for 27 h. The THF was removed *in vacuo* and the residue dissolved in EtOAC (35 mL) and H_2O (35 mL). The pH was adjusted to pH 2 and the organic layer collected and washed with brine (35 mL), and dried over $MgSO_4$. The solvent was removed *in vacuo* to reveal clear oil (189 mg, 79%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.19 (d, 1H, N*H*, *J*=7.0 Hz), 7.78 (t, 1H, N*H*, *J*=9.9 Hz), 7.72 (d, 1H, N*H*, *J*=8.3 Hz), 6.88 (d, 1H, N*H*, *J*=8.1 Hz), 4.35 (dd, 1H, Cα*H*, *J*=15.5, 7.7 Hz), 4.16 (m, 1H, Cα*H*), 3.86 (d, 1H, Cα*H*, *J*=4.7 Hz), 3.03-2.83 (m, 2H, CH_2NH), 1.77 (s, 3H, CH_3), 1.70-1.34 (m, 9H, 4xCH_2, C*H*), 1.37 (s, 9H, Boc), 1.25 (d, 3H, CH_3Ala, *J*=7.3 Hz), 0.89-0.82 (m, 6H, 2xCH_3 Leu).

MS: $[M+Na]^+_{calcd}$=495.2, $[M+Na]^+_{found}$=495.2.

Peptide **6**



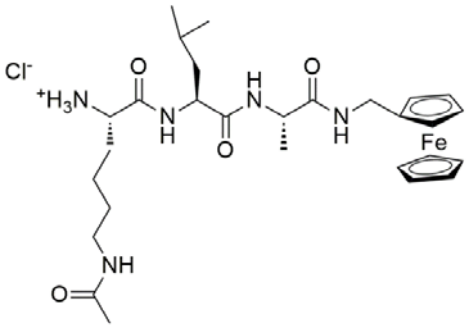
Compound **S14** (164 mg, 0.347 mmol) and ferrocenylmethylamine (82 mg, 0.382 mmol) were dissolved in anhydrous DMF (5.8 mL) and stirred at rt under an N_2 atmosphere. Anhydrous DIPEA (242 µL), HATU (145 mg, 0.382 mmol) and HOAt (47 mg, 0.347 mmol) were added and the reaction stirred for 66 h. The solvent was removed and the residue dissolved in EtOAC (35 mL) and H_2O (35 mL). The pH was adjusted to pH 2 and the organic layer washed with $NaHCO_3$ (35 mL) and brine (35 mL), before being dried over $MgSO_4$. The solvent was removed *in vacuo* to yield a brown solid (192 mg, 83%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.05-7.95 (m, 2H, 2xN*H*), 7.86-7.76 (m, 2H, 2xN*H*), 6.93 (d, 1H, N*H*, *J*=7.5 Hz), 4.35-3.82 (m, 14H, CH_2Fc, Cp, 3xCα*H*), 3.02-2.92 (m, 2H, CH_2NH), 1.77 (s, 3H, CH_3), 1. 70-1.34 (m, 9H, 4xCH_2, C*H*), 1.37 (s, 9H, Boc), 1.22 (d, 3H, CH_3 Ala, *J*= 8.1 Hz), 0.89-0.82 (m, 6H, (CH_3)$_2$ Leu).

^{13}C NMR (150 MHz, DMSO-d_6): 172.1, 171.5, 171.4, 168.5, 155.3, 123.1, 122.6, 115.5, 86.0, 78.0, 77.3, 68.9, 68.35, 68.30, 67.5, 67.3, 54.4, 50.7, 48.0, 40.8, 38.6, 37.4, 31.5, 31.3, 30.6, 28.8, 28.2, 28.1, 23.9, 23.1, 22.6, 21.4.

MS: $[M+Na]^+_{calcd}$=692.3, $[M+Na]^+_{found}$=692.3.

Peptide **2**



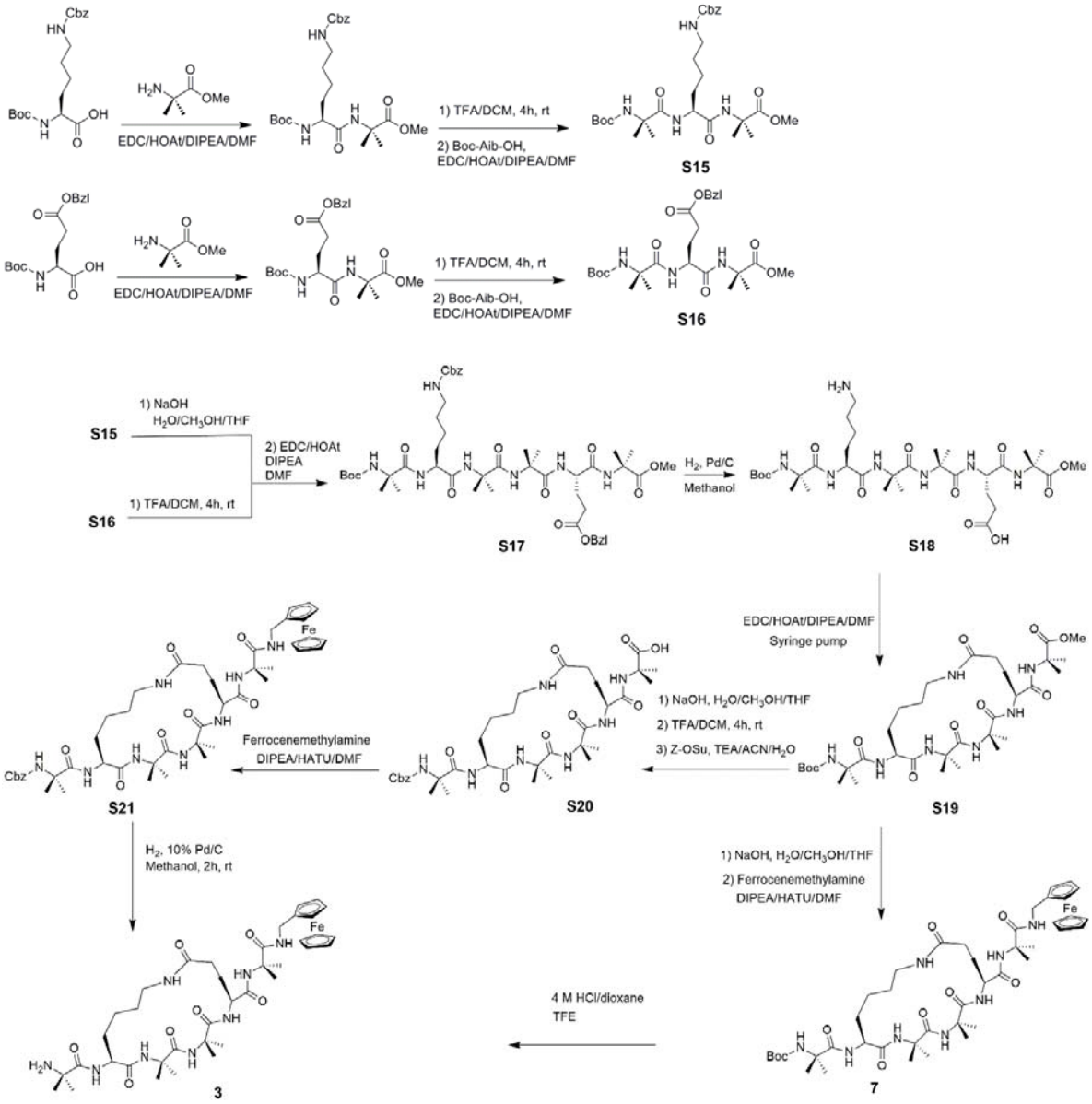
Peptide **6** (120 mg, 0.179 mmol) was dissolved in TFE (4 mL) and 4M HCl in dioxane (3 mL) added dropwise. The solution was stirred for 25 min., the solvent removed *in vacuo* and the residue washed with MeOH (2x10 mL). The crude product was purified using reverse phase HPLC to yield a sandy brown solid (25 mg, 25%).

^{1}H NMR (600 MHz, DMSO-d_6): δ 8.48 (d, 1H, N*H*, *J*=8.1 Hz), 8.16 (d, 1H, N*H*, *J*=7.3 Hz), 8.07 (d, 3H, N*H*, *J*=4.0 Hz), 8.01 (br s, 1H, N*H*), 7.77 (t, 1H, N*H*, *J*=5.4 Hz), 4.39 (dd, 1H, Cα*H*, *J*=14.1, 8.8 Hz), 4.31 (m, 1H, Cα*H*), δ 4.20-3.94 (m, 11H, Cp, CH_2Fc), 3.76 (dd, 1H, Cα*H*, *J*=11.2, 5.7 Hz), 2.99 (dd, 2H, CH_2NH, *J*=13.1, 6.8 Hz), 1.78 (s, 3H, CH_3), 1.71-1.61 (m, 3H, CH_2, C*H*), 1.49-1.45 (m, 2H, CH_2), 1.39-1.35 (dd, 2H, CH_2, *J*=14.3, 7.1 Hz), 1.32-1.26 (dt, 2H, CH_2, *J*=14.9, 7.2 Hz), 1.22 (d, 3H, CH_3, *J*=6.3 Hz), 0.90-0.86 (dd, 6H, (CH_3)$_2$ Leu, *J*=15.2, 6.6 Hz).

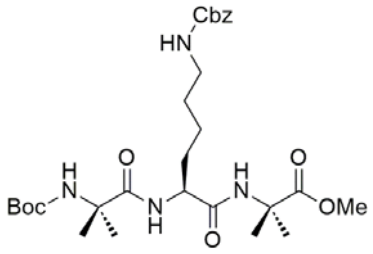
^{13}C NMR (150 MHz, DMSO-d_6)**:** δ 171.8, 171.5, 169.3, 168.8, 158.3, 71.3, 69.8, 69.3, 68.8, 67.8, 67.5, 52.4, 51.5, 48.5, 41.2, 38.6, 37.8, 31.3, 24.4, 23.5, 23.0, 21.9, 18.8.

HRMS (*m/z*): $[M+H]^+_{calcd}$=570.2737; $_{found}$=570.2743.

Scheme S4. The final synthetic steps for lactam-bridged 3_{10}-helical peptides.



Compound **S15**



Boc-Lys(Cbz)-OH (1.68 g, 4.4 mmol) and HCl·H_2N-Aib-OMe (880 mg, 4.4 mmol) were dissolved in anhydrous DMF (28 mL) and stirred at rt under an N_2 atmosphere. HOAt (780 mg, 5.7 mmol), EDC·HCl (1.09 g, 5.7 mmol) and DIPEA (3.50 mL, 20 mmol) were added, and the

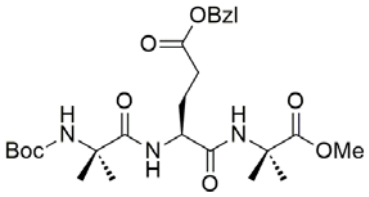
mixture stirred for 26 h. The solvent was removed and the residue taken up in EtOAc (200 mL) and H_2O (200 mL). The organic layer separated and washed with $NaHCO_3$ (200 mL), brine (200 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (EtOAc: Petroleum ether 50:50 by v/v) to reveal the dipeptide Boc-Lys(Cbz)-Aib-OMe, a white solid (1.70 g, 81%).

The resulting was dissolved in DCM (10 mL) and TFA (10 mL) added dropwise. The reaction was stirred at rt for 3 h. The solvent was removed *in vacuo* to reveal brown oil. The oil and Boc-Aib-OH (880 mg, 4.4 mmol) were dissolved in anhydrous DMF (25 mL) and stirred at rt under an N_2 atmosphere. HOAt (884 mg, 6.5 mmol), EDC·HCl (1.24 g, 6.5 mmol) and DIPEA (3.5 mL, 20 mmol) were added, and the mixture stirred for 40 h. The solvent was removed and the residue taken up in EtOAc (200 mL) and H_2O (200 mL). The organic layer separated and washed with $NaHCO_3$ (200 mL), brine (200 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (EtOAc: Petroleum ether 70:30 by v/v) to yield the product, a white solid (1.98 g, 80%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.04 (s, 1H, N*H*), 7.35-7.25 (m, 6H, N*H*, benzene), 7.16 (t, 1H, N*H*CH$_2$), 7.08 (br s, 1H, N*H*), 4.96 (s, 2H, OC*H*$_2$), 4.09 (m, 1H, Cα*H*), 3.51 (s, 3H, OC*H*$_3$), 2.92 (m, 2H, NHC*H*$_2$), 1.76 (s, 3H, COC*H*$_3$), 1.65-1.45 (m, 2H, C*H*$_2$), 1.40-1.10 (m, 25H, 2xC*H*$_2$, Boc, 4xC*H*$_3$).

MS: $[M+H]^+_{calcd}$=565.3, $[M+H]^+_{found}$=565.3.

Compound **S16**



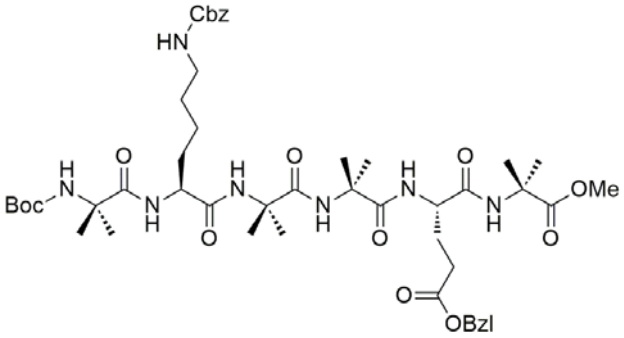
Boc-Glu(OBzl)-OH (1.68 g, 5 mmol) and HCl·H$_2$N-Aib-OMe (1.00 g, 5 mmol) were dissolved in anhydrous DMF (28 mL) and stirred at rt under an N_2 atmosphere. HOAt (884 mg, 6.50 mmol), EDC·HCl (1.24 g, 6.50 mmol) and DIPEA (3.50 mL, 20 mmol) were added, and the mixture stirred for 26 h. The solvent was removed and the residue taken up in EtOAc (200 mL) and H_2O (200 mL). The organic layer separated and washed with $NaHCO_3$ (200 mL), brine (200 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (EtOAc: Petroleum ether 50:50 by v/v) to reveal the dipeptide Boc-Glu(OBzl)-Aib-OMe, a white solid (1.98 g, 92%).

Boc-Glu(OBzl)-Aib-OMe (453 mg, 1.04 mmol) was dissolved in DCM (5 mL) and TFA (5 mL) added dropwise. The reaction was stirred at rt for 3 h. The solvent was removed *in vacuo* to reveal brown oil. The resulting oil and Boc-Aib-OH (210 mg, 1.04 mmol) were dissolved in anhydrous DMF (2 mL) and stirred at rt under an N_2 atmosphere. HOBt (207 mg, 1.35 mmol), EDC·HCl (260 mg, 1.35 mmol) and DIPEA (0.75 mL, 4.16 mmol) were added, and the mixture stirred for 40 h. The solvent was removed and the residue taken up in EtOAc (50 mL) and H_2O (50 mL). The organic layer separated and washed with $NaHCO_3$ (50 mL), brine (50 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (EtOAc: Petroleum ether 70:30 by v/v) to yield the product, a white solid (430 mg, 80%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.15 (s, 1H, N*H*), 7.50 (d, 1H, N*H*, *J*=6.0 Hz), 7.42-7.25 (m, 5H, benzene), 7.16 (s, 1H, N*H*), 5.08 (s, 2H, OCH_2), 4.17 (m, 1H, Cα*H*), 3.52 (s, 3H, OCH_3), 2.35 (t, 2H, CH_2), 1.98 (m, 1H, C*H*H), 1.83 (m, 1H, CH*H*), 1.45-1.20 (m, 12H, 4xCH_3).

MS: $[M+H]^+_{calcd}$=522.3, $[M+H]^+_{found}$=522.3.

Compound **S17**



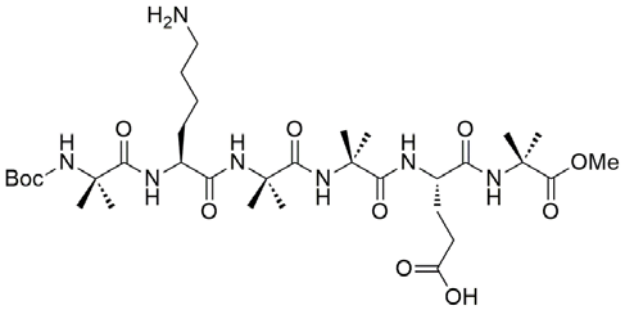
Compound **S15** (2.23 g, 4.0 mmol) was dissolved in THF (12.0 mL) and methanol (8.0 mL). 4.0 mL of NaOH solution (1.6 M, aqueous) was added to the mixture, and the reaction stirred at rt for 18 h. The solvent was removed *in vacuo* and the residue redissolved in EtOAc (200 mL) and H_2O (200mL). The pH was adjusted to pH 3 and the organic layer separated and washed with brine (200 mL), and dried over $MgSO_4$. The solvent was removed *in vacuo* to reveal a white solid (2.29 g).

Compound **S16** (2.08 g, 4.0 mmol) was dissolved in DCM (5 mL) and TFA (5 mL) added dropwise. The reaction was stirred at rt for 3 h. The solvent was removed *in vacuo* to reveal brown oil. The resulting oil and the above hydrolysed compound **S15** (2.29 g) were dissolved in anhydrous DMF (28 mL) and stirred at rt under an N_2 atmosphere. HOAt (707 mg, 5.2 mmol), EDC·HCl (1.0 g, 5.2 mmol) and DIPEA (2.8 mL, 16 mmol) were added, and the mixture stirred for 40 h. The solvent was removed and the residue taken up in EtOAc (200 mL) and H_2O (200 mL). The organic layer separated and washed with $NaHCO_3$ (200 mL), brine (200 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (EtOAc: Petroleum ether 90:10 by v/v) to yield the title product, a white solid (2.10 g, 55%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.32-8.06 (m, 2H, 2xN*H*), 7.93-7.14 (m, 15H, 5xN*H*, 2x benzene), 5.06 (s, 2H, OCH_2), 4.98 (s, 2H, OCH_2), 4.05 (m, 1H, Cα*H*), 3.94-3.67 (m, 1H, Cα*H*), 3.53 (s, 3H, OCH_3), 2.95 (m, 2H, CH_2NH), 2.44 (m, 2H, CH_2), 2.14-1.22 (m, 41H, 4xCH_2, 8xCH_3, Boc).

MS: $[M+H]^+_{calcd}$=954.5, $[M+H]^+_{found}$=954.5.

Compound **S18**

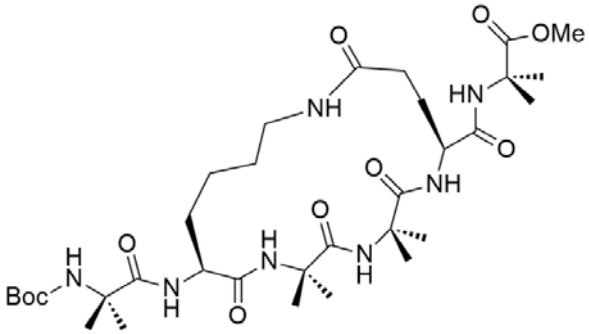


Compound **S17** (1.73 g, 1.81 mmol) was dissolved in (methanol over molecular sieves, 20 mL). Pd/C (15% w/w, 260 mg) was added and the mixture stirred. A H_2 balloon was fitted under vacuum and the solution stirred at rt for a further 18 h. The solution was filtered through celite and washed with methanol (3x 20 mL), and the solvent removed *in vacuo* to yield a white solid (1.26 g, 95%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.60 (br s, 1H, N*H*), 8.29 (br s, 1H, N*H*), 8.19 (br s, 1H, N*H*), 7.65 (br s, 1H, N*H*), 7.56 (br s, 1H, N*H*), 7.47 (br s, 1H, N*H*), 3.90 (m, 1H, Cα*H*), 3.74 (m, 1H, Cα*H*), 3.55 (s, 3H, OCH_3), 2.75-1.52 (m, 12H, 6xCH_2), 1.41-1.30 (m, 24H, 8xCH_3), 1.34 (s, 9H, Boc).

MS: $[M+H]^+_{calcd}$=730.4, $[M+H]^+_{found}$=730.4.

Compound **S19**



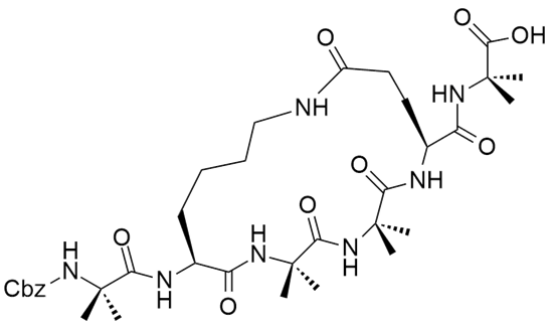
EDC·HCl (815 mg, 4.27 mmol), HOBt (576 mg, 4.27 mmol) and DIPEA (1.5 mL) were dissolved in anhydrous DMF (255 mL), and the solution stirred at rt under an N_2 atmosphere. Compound **S18** (622 mg, 0.853 mmol) was dissolved in anhydrous DMF (25 mL), placed into a syringe and pumped into the solution containing the coupling agents at the rate of 20 µL/min, and stirred for 68 h. The solvent was removed and the residue taken up in EtOAc (100 mL) and H_2O (100 mL). The pH was adjusted to pH 3, the organic layer separated and washed with $NaHCO_3$ (100 mL), brine (100 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* to give the crude product, which was purified using reverse phase HPLC, to yield a white solid (90 mg, 15%).

^{1}H NMR (600 MHz, DMSO-d_6): δ 8.33 (br s, 1H, N*H*), 8.04 (br s, 1H, N*H*), 7.79-7.70 (m, 2H, 2x N*H*), 7.63 (m, 1H, N*H*), 7.53 (s, 1H, N*H*), 7.45 (d, 1H, N*H*, *J*=8.0 Hz), 3.80-3.73 (m, 2H, 2x Cα*H*), 3.54 (s, 3H, OCH_3), 3.07 (m, 1H, C*H*HNH), 2.90 (m, 1H, CH*H*NH), 2.15-1.22 (m, 10 H, 5x CH_2), 1.41-1.27 (m, 24H, (CH_3)$_8$), 1.34 (s, 9H, Boc).

^{13}C NMR (150 MHz, DMSO-d_6):δ 175.6, 174.8, 174.7, 174.6, 172.9, 171.6, 171.5, 158.7, 158.5, 79.3, 79.2, 56.7, 56.6, 56.2, 55.3, 55.2, 52.1, 40.3, 28.6, 26.0, 25.2, 25.1.

MS: $[M+H]^+_{calcd}$=712.4, $[M+H]^+_{found}$=712.4.

Compound **S20**



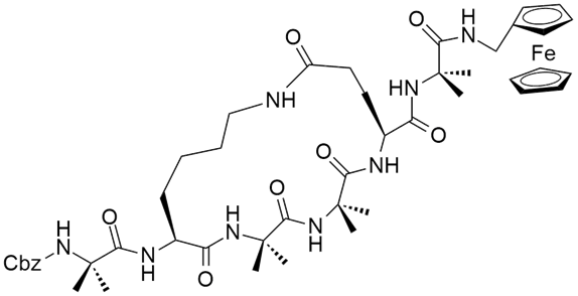
Compound **S19** (380 mg, 0.53mmol) was dissolved in THF (3.80 mL) and H_2O (3.80 mL). NaOH (85 mg) solid was added and the reaction stirred at rt for 2 h. The reaction was quenched by 1M HCl (2 mL) aqueous solution. The solvent was removed *in vacuo* to reveal a white solid (514 mg). The resulting intermediate (190 mg, 0.27 mmol) was dissolved in DCM (5 mL) and TFA (2 mL) added dropwise. The reaction was stirred at rt overnight. The solvent was removed *in vacuo* to reveal a brown oil (350 mg).

The resulting oil and triethylamine (150 µL) were dissolved in a solvent mixture of water (5 mL) and acetonitrile (3 mL). A solution of Z-OSu (82 mg in 2 mL acetonitrile) was added. The reaction mixture was stirred overnight at rt, after which the volatiles were removed under reduced pressure. The residue was redissolved in MeOH (5 mL), and purified using reverse phase HPLC to yield a white solid (120 mg).

^{1}H NMR (600 MHz, DMSO-d_6): δ 8.01 (d, 1H, N*H*), 7.79 (s, 1H, N*H*), 7.77 (m, 1H, N*H*), 7.71 (t, 1H, N*H*), 7.61 (d, 1H, N*H*), 7.58 (s, 1H, N*H*), 7.40 (s, 1H, N*H*). 7.38-7.26 (m, 5H, arom*H*), 5.05 (dd, 2H, Cbz CH_2), 4.12 (m, 1H, Cα*H*), 3.72 (m, 1H, Cα*H*), 3.06 (m, 2H, CH_2NH), 2.04 (m, 1H, CH*H*CO), 1.92 (m, 1H, CH*H*CO), 1.85 (m, 1H, CH*H*CO), 1.54 (m, 1H, CH*H*CO), 1.48-1.09 (m, 26H, CH_2, 8x CH_3), 1.22 (m, 2H, CH_2).

MS: $[M+H]^+_{calcd}$=732.4, $[M+H]^+_{found}$=732.4.

Compound **S21**



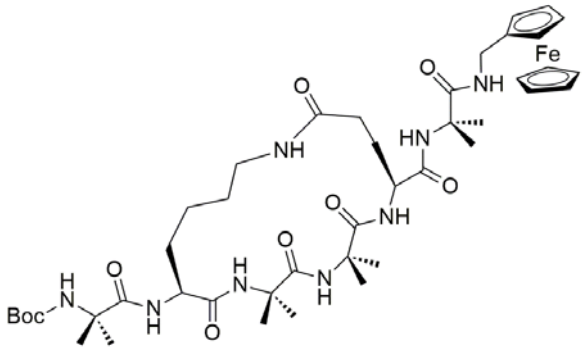
Compound **S20** (120 mg, 0.16mmol) and ferrocenylmethylamine (60 mg, 0.27mmol) were dissolved in anhydrous DMF (2 mL) and stirred at rt under an N_2 atmosphere. EDC·HCl (67 mg),

HOAt (50 mg) and DIPEA (200 µL) were added, and the mixture stirred for 36 h. The solvent was removed and the residue redissolved in MeOH (15 mL), and purified using reverse phase HPLC to yield a sandy brown solid (90 mg).

^{1}H NMR (600 MHz, DMSO-d_6): δ 8.05 (d, 1H, N*H*), 7.84 (d, 1H, N*H*), 7.82 (s, 1H, N*H*), 7.78 (s, 1H, N*H*), 7.74 (s, 1H, N*H*), 7.72 (t, 1H, N*H*), 7.44 (s, 1H, N*H*), 7.39-7.28 (m, 5H, arom*H*), 7.26 (t, 1H, N*H*), 5.06(dd, 2H, CH_2), 4.25-3.90 (m, 12H, Cp, CH_2Fc, Cα*H*), 3.70 (m, 1H, Cα*H*), 3.18 (m, 2H, CH_2CH_2NH), 1.99 (m, 2H, CH*H*CO), 1.85 (m, 1H, CH*H*CO), 1.54 (m, 1H, CH*H*CO), 1.48-1.19 (m, 28H, 2x CH_2, 8x CH_3).

MS: $[M+H]^+_{calcd}$=929.9, $[M+H]^+_{found}$=929.9.

Peptide **7**



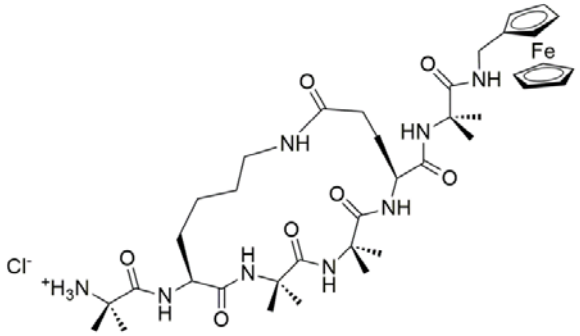
Compound **S19** (125 mg, 0.176 mmol) was dissolved in THF (1.25 mL) and H_2O (1.5 mL). NaOH aqueous solution (1.6 M, 352 µL) was added and the reaction stirred at rt for 2 h. The solvent was removed *in vacuo* to reveal a white solid (157 mg, quant). The resulting intermediate (122 mg, 0.176 mmol) and ferrocenylmethylamine (75 mg, 0.352 mmol) were dissolved in anhydrous DMF (3.4 mL) and stirred at rt under an N_2 atmosphere. EDC·HCl (37 mg, 0.194 mmol), HOAt (24 mg, 0.176 mmol) and DIPEA (122 µL) were added, and the mixture stirred for 36 h. The solvent was removed *in vacuo* and the residue redissolved in MeOH (15 mL), and purified using reverse phase HPLC to yield a sandy brown solid (40 mg, 29%).

^{1}H NMR (600 MHz, DMSO-d_6): δ 8.16 (br s, 1H, N*H*), 7.96 (s, 1H, N*H*), 7.86 (d, 1H, N*H*, *J*=3.9 Hz), 7.82 (s, 1H, N*H*), 7.70 (t, 1H, N*H*, *J*=12.0 Hz), 7.46 (s, 1H, N*H*), 7.35 (s, 1H, N*H*), 7.27 (br s, 1H, N*H*), 4.25-4.02 (m, 9H, Cp), 3.99-3.90 (m, 3H, CH_2Fc, Cα*H*), 3.71 (m, 1H, Cα*H*), 3.18 (m, 1H, C*H*HNH), 2.96 (m, 1H, CH*H*NH), 2.15-1.37 (m, 10H, 5xCH_2), 1.44-1.29 (m, 24H, 8 xCH_3), 1.34 (s, 9H, Boc).

^{13}C NMR (150 MHz, DMSO-d_6):175.83, 175.37, 174.89, 173.61, 171.07, 170.75, 155.31, 86.55, 78.79, 68.66, 68.34, 66.99, 66.97, 66.92, 56.35, 56.29, 56.02, 55.70, 53.63, 38.12, 37.82, 33.63, 31.26, 31.02, 29.40, 28.97, 28.86, 28.66, 28.50, 28.19, 25.48, 24.55, 24.26, 22.96, 22.06.

HRMS: $[M]^+_{calcd}$=894.4302, $[M]^+_{found}$=894.4303.

Peptide **3**



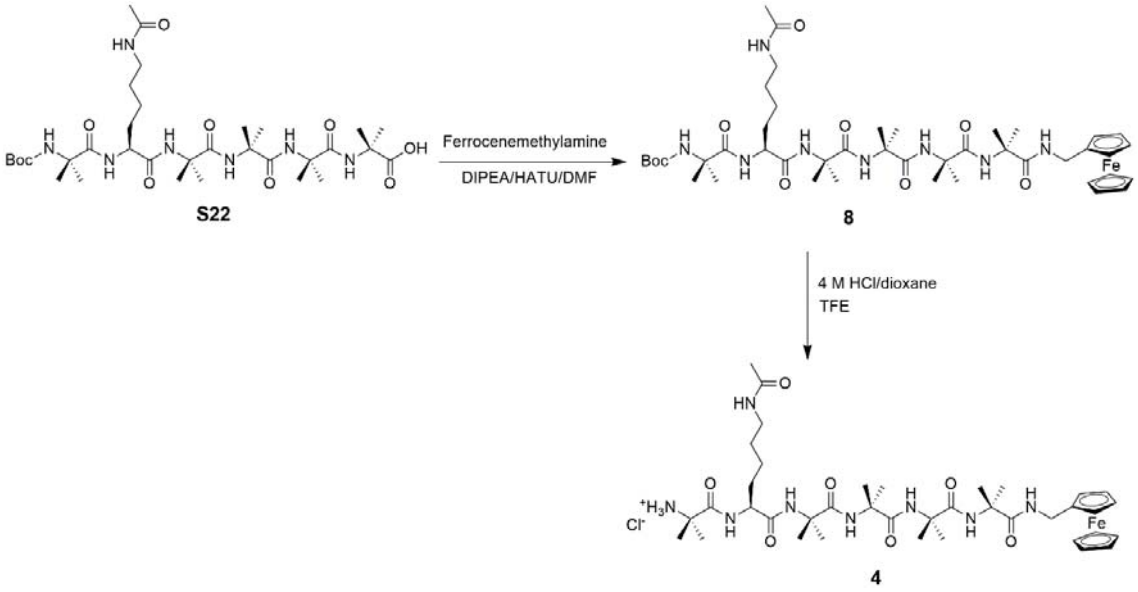
Peptide **7** (5 mg, 0.006 mmol) was dissolved in TFE (600 µL) and 4M HCl in dioxane (200 µL) added. The reaction was stirred at rt for 25 min. The solvent was removed *in vacuo* to reveal a light brown solid (quant). The crude product was purified using reverse phase HPLC to yield a sandy brown solid (2 mg, 45%).

^{1}H NMR (600 MHz, DMSO-d_6): δ 8.30 (s, 1H, N*H*), 8.08 (s, 1H, N*H*), 7.75 (d, 1H, N*H*), 7.72 (m, 1H, N*H*), 7.54 (s, 1H, N*H*), 7.49 (m, 1H, N*H*), 7.33 (s, 1H, N*H*), 7.18 (t, 1H, N*H*), 4.25-3.90 (m, 12H, Cp, CH_2Fc, Cα*H*), 3.85 (m, 1H, Cα*H*), 3.04-2.90 (m, 2H, CH_2NH), 2.30-1.80 (m, 4H, 4 x CH*H*), 1.80-1.10 (m, 28H, 8 x CH_3, 2 x CH_2).

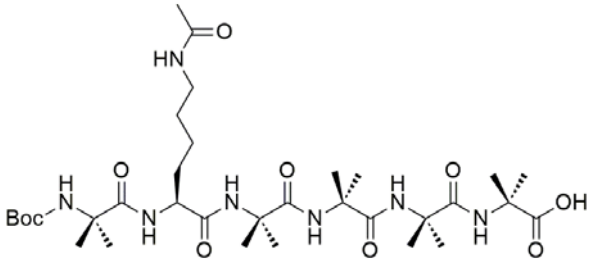
^{13}C NMR (150 MHz, DMSO-d_6): 173.66, 172.51, 172.26, 171.96, 169.20, 166.27, 149.91,144.91, 105.60, 100.89, 85.08, 84.44, 78.30, 77.34, 68.80, 67.45, 68.34, 66.99, 66.97, 66.92, 56.38, 56.02, 55.70, 53.68, 44.99, 43.47, 38.72, 31.50, 29.46, 28.95, 28.53, 24.89.

HRMS (*m/z*): $[M]^+_{calcd}$=794.3778, $_{found}$=794.3778.

Scheme S5. The final synthetic steps for linear 3_{10}-helical peptides.



Compound **S22**

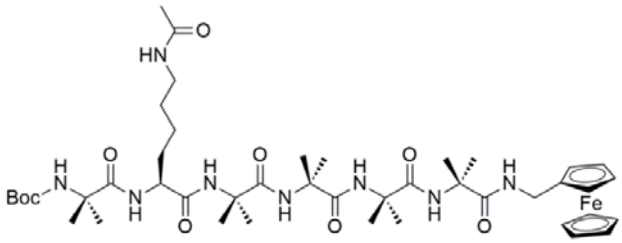


Fmoc-Aib-OH loaded 2-chlorotrityl chloride resin [3] (2.00 g, typically 0.5 mmol/g of resin) was transferred into a sintered funnel fitted with a Teflon stopcock, and then rinsed with DCM (2x20 mL). After air drying, the Fmoc group was removed by reaction with a solution of 25% piperidine in DMF (20 mL) for 30 min followed by washing successively with DCM (3x20 mL), DMF (3 x 20 mL), and DCM (3 x 20 mL). To a solution of Fmoc-Aib-OH (1.00 g, 2 equiv) in DMF (4 mL) was added a 0.5 M solution of HATU in DMF (2 mL) followed by DIPEA (1.2 mL, 4-fold excess) and the resulting solution was added to the deprotected resin. The mixture was left for 2 h, with occasional stirring. The resin was isolated by filtration and rinsed successively with DCM (3 x 50 mL), DMF (3 x 50 mL), and DCM (3 x 50 mL). The sequence was repeated twice to ensure complete coupling. Using this protocol, the tetrapeptide (Aib_4) was produced by additions of Fmoc-Aib-OH. The peptide was then coupled with the building block **S1** to yield the appropriate pentapeptide. In the last cycle, Boc-Aib-OH was capped to the pentapeptide. The resulting hexapeptide was cleaved from the resin with 2% TFA / DCM (v/v). The crude products were purified by HPLC.

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.22 (s, 1H, N*H*), 8.08 (s, 1H, N*H*), 7.78 (t, 1H, N*H*CH_2), 7.56 (s, 1H, N*H*), 7.32-7.20 (m, 3H, 3xN*H*), 3.85 (m, 1H, NHC*H*), 2.95 (m, 2H, NHCH_2), 1.75 (s, 3H, COCH_3), 1.68 (m, 2H, CH_2), 1.50-1.20 (m, 23H, 2xCH_2, Boc, 10xCH_3).

MS: $[M+H]^+_{calcd}$=714.4, $[M+H]^+_{found}$=714.4.

Peptide **8**



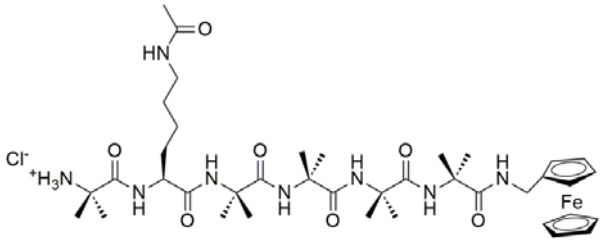
Peptide **S22** (410 mg, 0.57mmol) and ferrocenylmethylamine (140 mg, 0.65mmol) were dissolved in anhydrous DMF (8 mL). DIPEA (400µL, 4 equiv), HOAt (160 mg, 2 equiv) and HATU (430 mg, 2equiv) were added. Reaction mixture was stirred overnight under an N_2 atmosphere at rt. The solvent was removed *in vacuo* and the peptide purified using reverse phase HPLC.

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.21 (s, 1H, N*H*), 7.99 (s, 1H, N*H*), 7.73 (t, 1H, N*H*CH$_2$), 7.61 (s, 1H, N*H*), 7.57 (s, 1H, N*H*), 7.47 (br s, 1H, N*H*), 7.28 (s, 1H, N*H*), 7.20 (s, 1H, N*H*), 4.31-3.40 (m, 12H, Cp, Cα*H*, C*H*$_2$Fc), 2.95 (m, 2H, NHC*H*$_2$), 1.76 (s, 3H, COC*H*$_3$), 1.68 (m, 2H, C*H*$_2$), 1.45-1.20 (m, 43H, 2xC*H*$_2$, Boc, 10xC*H*$_3$).

^{13}C NMR (150 MHz, DMSO-d_6): 175.59, 175.09, 175.08, 174.98, 174.82, 174.41, 173.73, 173.41, 172.80, 168.93, 158.29, 154.93, 78.59, 68.33, 66.94, 56.14, 56.03, 56.02, 55.63, 54.25, 42.69, 42.66, 42.62, 40.04, 38.24, 37.73, 35.12, 29.66, 28.91, 28.14, 25.39, 24.91, 24.70, 22.64, 22.57. .

MS: $[M+H]^+_{calcd}$=911.5, $[M+H]^+_{found}$=911.5.

Peptide **4**



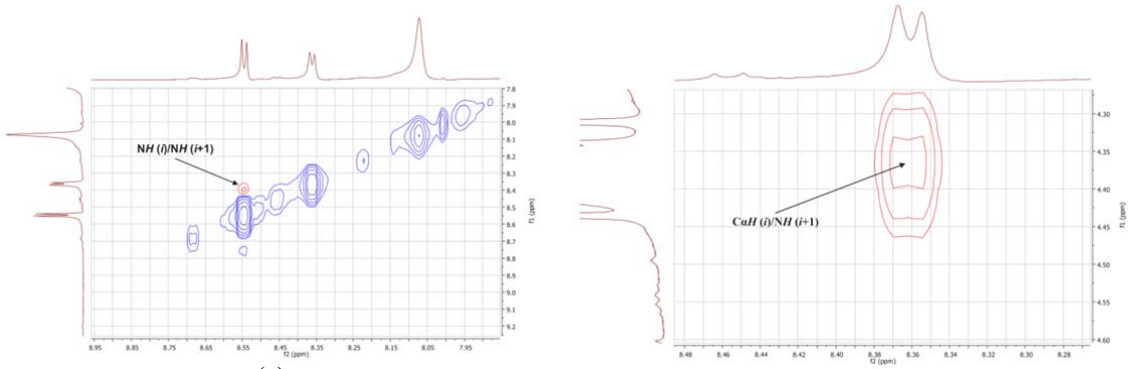
Peptide **8** (10 mg, 0.012 mmol) was dissolved in TFE (600 µL) and 4M HCl in dioxane (200 µL) added. The reaction was stirred at rt for 25 min. The solvent was removed *in vacuo* to reveal a light brown solid (quant). The crude product was purified using reverse phase HPLC to yield a sandy brown solid (4 mg, 45%).

^{1}H NMR (600 MHz, DMSO-d_6): δ 8.51 (s, 1H, N*H*), 8.13 (s, 1H, N*H*), 8.10 (s, 3H, N*H*$_3$), 7.84 (t, 1H, N*H*CH$_2$), 7.68 (s, 1H, N*H*), 7.63 (s, 1H, N*H*), 7.43 (m, 1H, N*H*), 7.34 (br s, 1H, N*H*), 4.55-3.50 (m, 12H, Cp, Cα*H*, C*H*$_2$), 3.02 (m, 2H, NHC*H*$_2$), 1.76 (s, 3H, COC*H*$_3$), 1.68 (m, 2H, C*H*$_2$), 1.45-1.20 (m, 34H, 2 x C*H*$_2$, 10 x C*H*$_3$).

^{13}C NMR (150 MHz, DMSO-d_6): δ 174.81, 174.35, 173.74, 173.47, 172.21, 171.81, 169.00, 128.89, 127.25, 121.35, 119.99, 109.72, 68.41, 66.90, 56.31, 56.10, 56.01, 55.93, 55.79, 53.26, 40.03, 38.30, 37.69, 30.45, 29.14, 28.87, 26.00, 25.38, 25.10, 24.97, 24.50, 24.20, 23.50, 23.37, 23.24, 22.60.

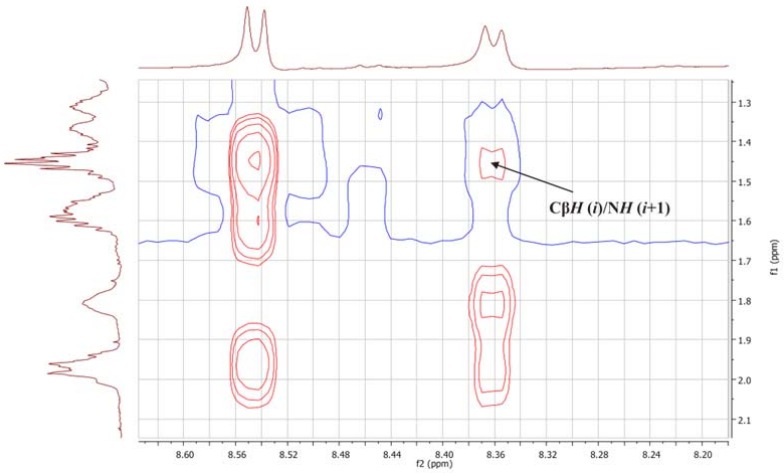
HRMS (*m/z*): $[M]^+_{calcd}$=811.4164, $_{found}$=811.4162.

3. ROESY spectra for peptides **1**-**4** and **5**-**7**



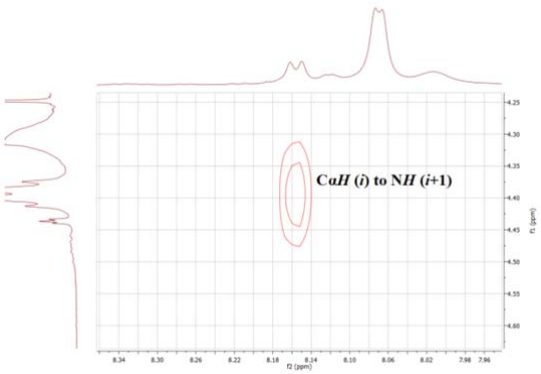
(a)

(b)

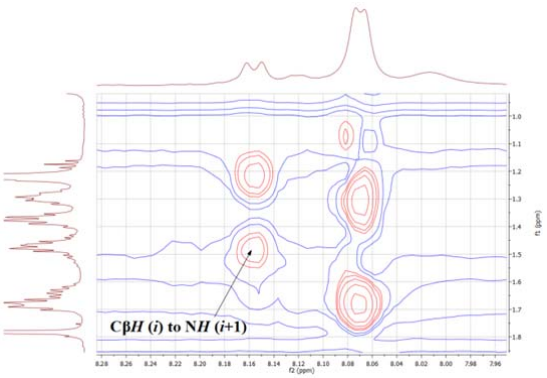


(c)

Figure S1. ROESY spectra of peptide **1**, showing (a) N*H* (*i*) to N*H* (*i*+1), (b) Cα*H* (*i*) to N*H* (*i*+1) and (c) Cβ*H* (*i*) to N*H* (*i*+1) correlations.



(a)



(b)

Figure S2. ROESY spectra of peptide **2**, showing (a) Cα*H* (*i*) to N*H* (*i*+1) and (b) Cβ*H* (*i*) to N*H* (*i*+1) correlations.

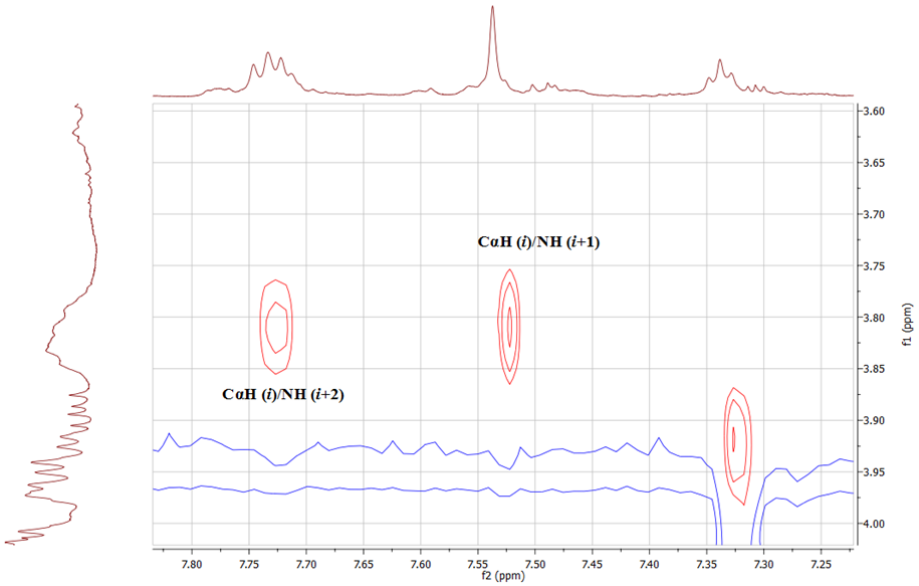


Figure S3. ROESY spectrum of peptide **3**, showing Cα*H* (*i*) to N*H* (*i*+1), and Cα*H* (*i*) to N*H* (*i*+2) correlations.

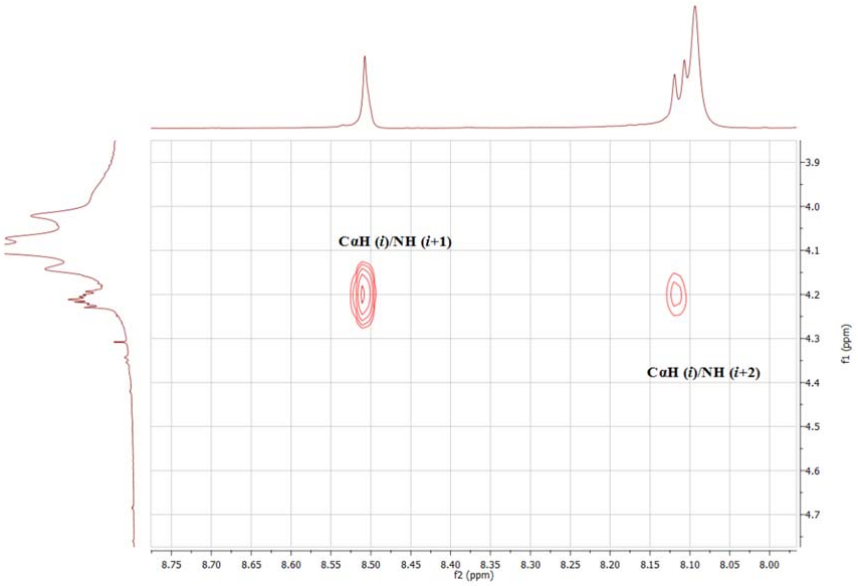
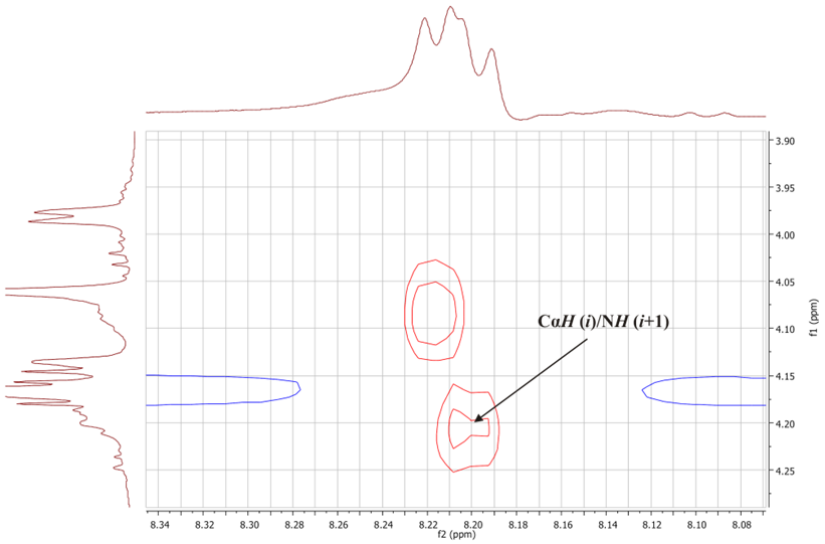
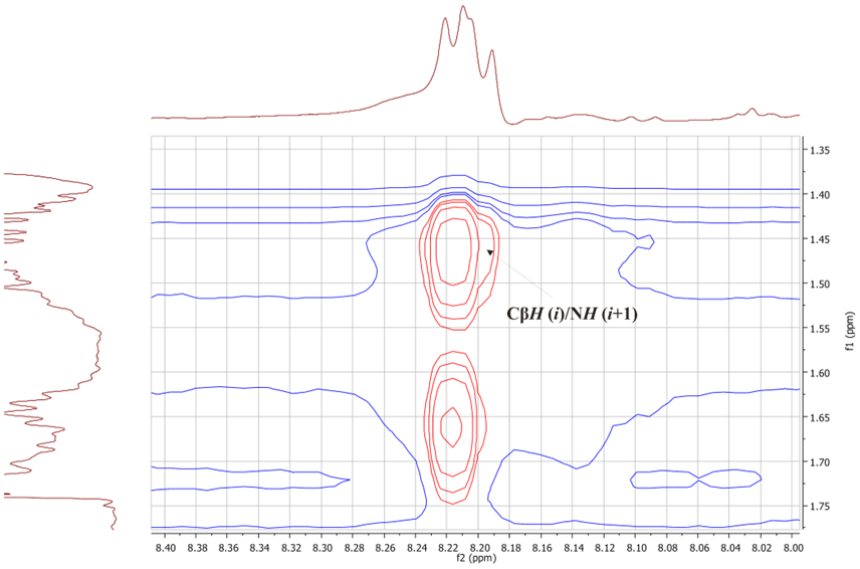


Figure S4. ROESY spectrum of peptide **4**, showing Cα*H* (*i*) to N*H* (*i*+1), and Cα*H* (*i*) to N*H* (*i*+2) correlations.



(a)



(b)

Figure S5. ROESY spectra of peptide **5**, showing (a) Cα*H* (*i*) to N*H* (*i*+1) and (b) Cβ*H* (*i*) to N*H* (*i*+1) correlations.

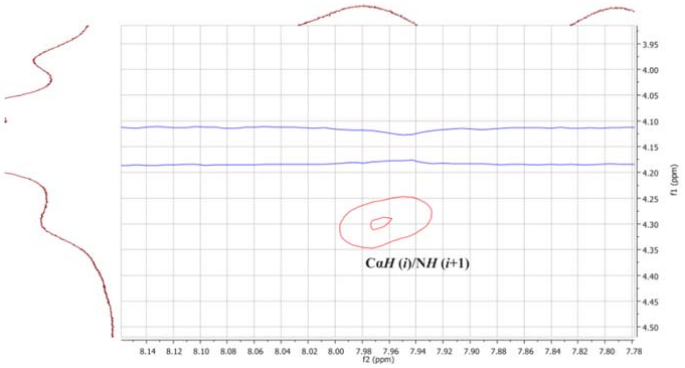


Figure S6. ROESY spectrum of peptide **6**, showing Cα*H* (*i*) to N*H* (*i*+1) correlation.

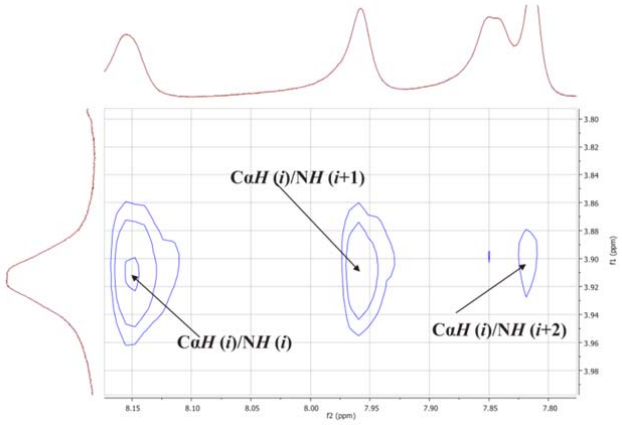


Figure S7. ROESY spectrum of peptide **7**, showing Cα*H* (*i*) to N*H* (*i*+1) and medium range Cα*H* (*i*) to N*H* (*i*+2) correlations.

4. IR spectrum for peptide **7**

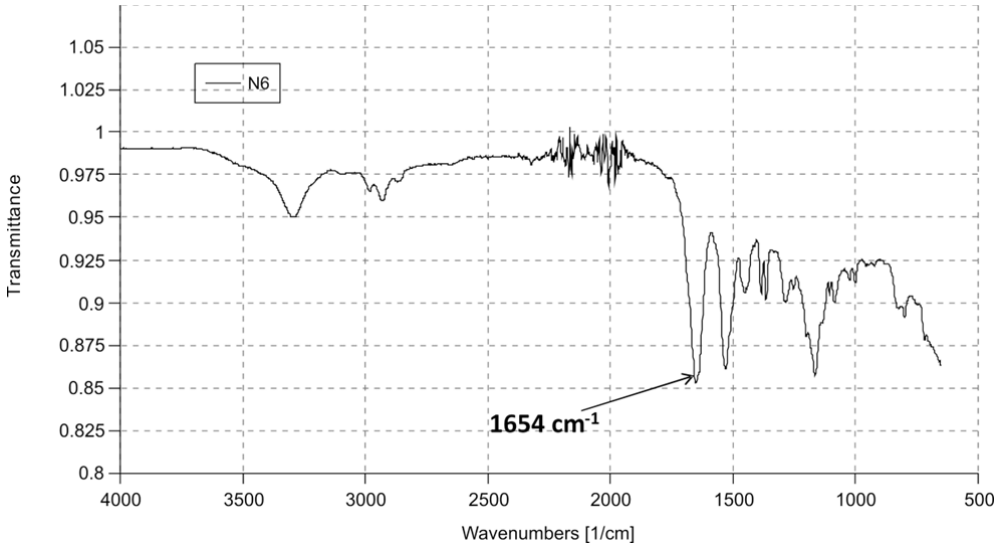


Figure S8. IR spectrum for peptide **7**.

5. Analysis of computational models for peptides **5**, **6** and **7, 8**

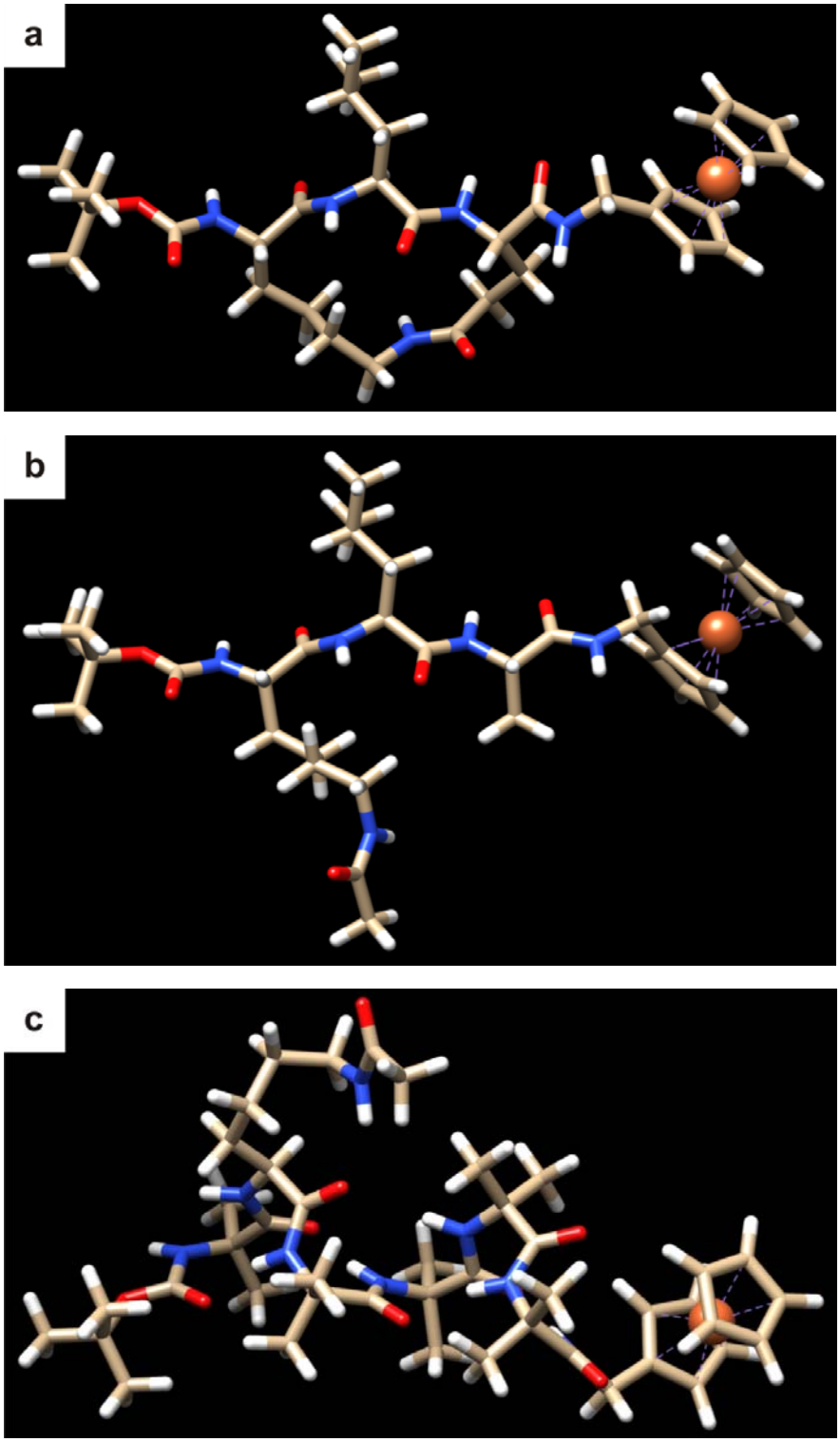


Figure S9. The lowest energy conformer for (a) peptide **5**, (b) peptide **6**, and (c) peptide **8**, optimized by the hybrid B3LYP method with 6-31G** basis set for all C, H, N, O atoms, and Lanl2dz basis set for Fe atom.

5.1 Characteristics of *N*-protected β-strand peptides **5** and **6**.

Table S1. N*H* to N*H* distances and total lengths for peptides **5** and **6**.

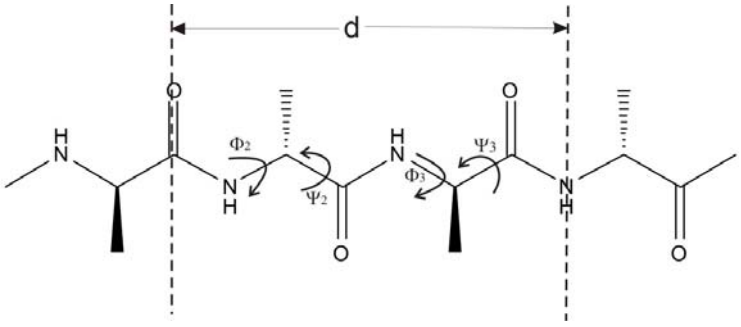
N*H* to N*H* distance (Å)	peptide **5**	peptide **6**
1-2	4.207	4.311
2-3	4.316	4.374
3-4	4.357	4.271
Distance from first to last carbonyl carbon (Å)	10.205	10.627

Table S2. Dihedral angles for all residues in the lowest energy conformers for peptides **5** and **6**.

	peptide **5**		peptide **6**	
	Φ	ψ	Φ	ψ
Residue 1	-150.366	122.799	-157.060	146.222
Residue 2	-126.024	158.039	-129.267	162.041
Residue 3	-118.162	151.364	-157.670	163.394

Table S3. Important characteristic correlations for peptides **5** and **6**, with comparison to optimal β-strand values. (all distances in Å)

	peptide **5**	peptide **6**	optimal β-strand conformation
Length (first to last carbonyl)	10.205	10.627	
Distance (d)*	8.0	8.2	8.0[4]
N-Leu to CO-Leu	2.4	2.4	2.5[5]
NH to NH (Average)	4.3	4.3	4.3[5]
αH to NH+1	2.5	2.5	2.2[5]
βH_2 to NH+1	3.5	3.6	3.2 to 4.5[5]



Note: * This distance (d) is defined between the *C* atom (*i*) and *N* atom (*i*+3). This is indicative of an optimal extended β-strand, as shown above.

5.2 Characteristics of *N*-protected helical peptides **7** and **8**.

Table S4. Hydrogen bond lengths, N*H* to N*H* distances and total peptide length for peptide **7**.

Residue	Hydrogen bond lengths (Å)	Distance (N*H* to N*H*) (Å)
1	2.074	2.996
2	2.184	2.817
3	2.061	2.837
4	2.157	2.779
5	2.198	2.680
6		2.602
Average	2.13	2.78
• Distance from first to last carbonyl carbon 11.989 Å.		

Table S5. Hydrogen bond lengths, N*H* to N*H* distances and total peptide length for peptide **8**.

Residue	Hydrogen bond lengths (Å)	Distance (N*H* to N*H*) (Å)
1	2.123	2.987
2	2.073	2.790
3	2.535	2.743
4	2.140	2.832
5	2.066	2.804
6		2.680
Average	2.18	2.80
• Distance from first to last carbonyl carbon 11.816 Å.		

Table S6. Distances between dαN, dβN and dNN, characteristic of a 3_{10}-helix.

Distance	peptide **7**	peptide **8**	Ideal 3_{10} helix[5]
dαN (Å)	3.5	3.5	3.4
dβN (Å)	3.0-4.1	3.0-4.1	2.9-4.4
Averaged NN (Å)	2.7	2.8	2.6

Table S7. Dihedral angles for all residues in the lowest energy conformers for peptides **7** and **8**.

	peptide **7**		peptide **8**	
	Φ	ψ	Φ	ψ
Residue 1	-64.156	-28.640	-64.329	-28.300
Residue 2	-55.638	-27.008	-56.464	-28.097
Residue 3	-52.532	-31.510	-59.037	-23.420
Residue 4	-55.092	-29.286	-55.844	-28.940
Residue 5	-70.469	-10.385	-53.315	-31.545
Residue 6	-66.630	-24.062	-66.533	-20.283
Average	-60.75	-25.14	-59.25	-26.76
Differs from ideal 3_{10} helix	3.75°	4.86°	2.25°	3.24°

6. Electrochemical measurements

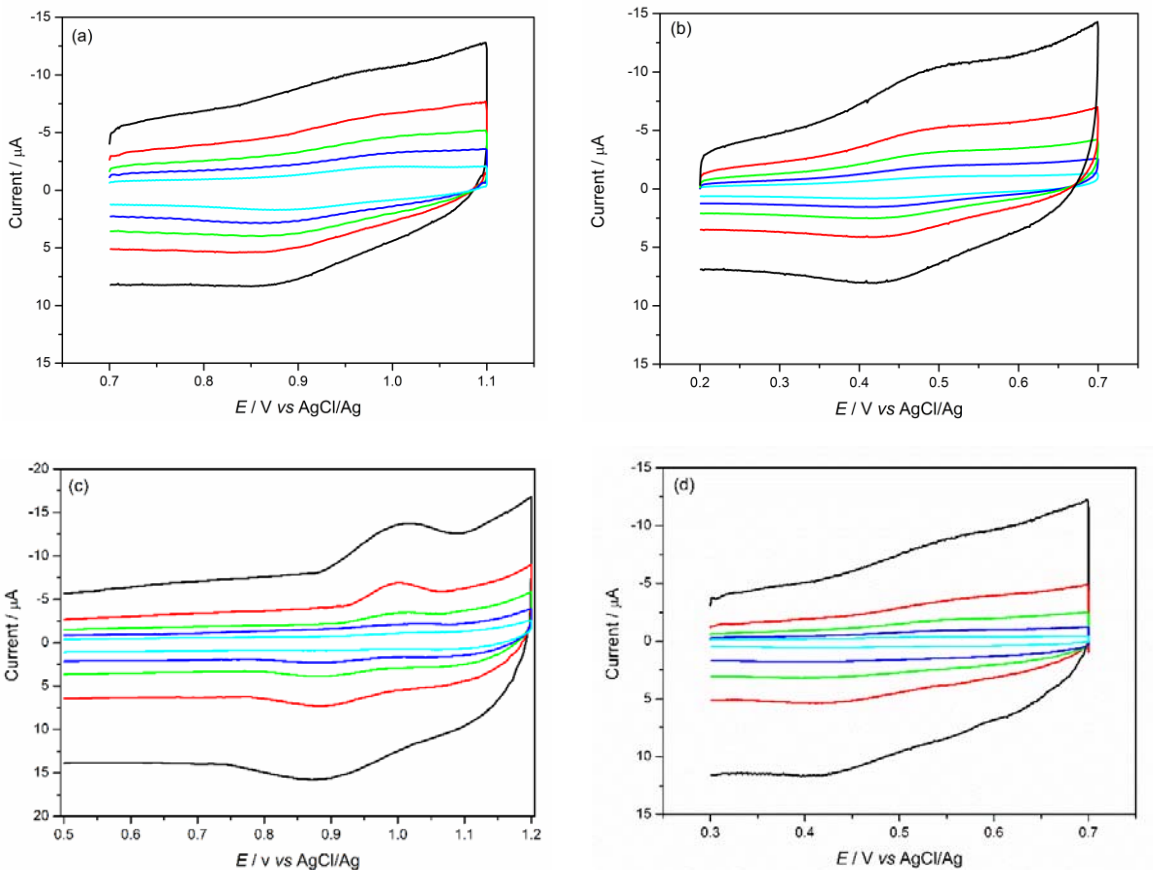


Figure S10. Cyclic voltammograms for (a) peptide **1** (b) peptide **2** (c) peptide **3** and (d) peptide **4** immobilized on SWCNTs/Au electrodes taken at 5, 2, 1, 0.5 and 0.2 V s^{-1} (from top to centre).

7. Electronic transport simulations

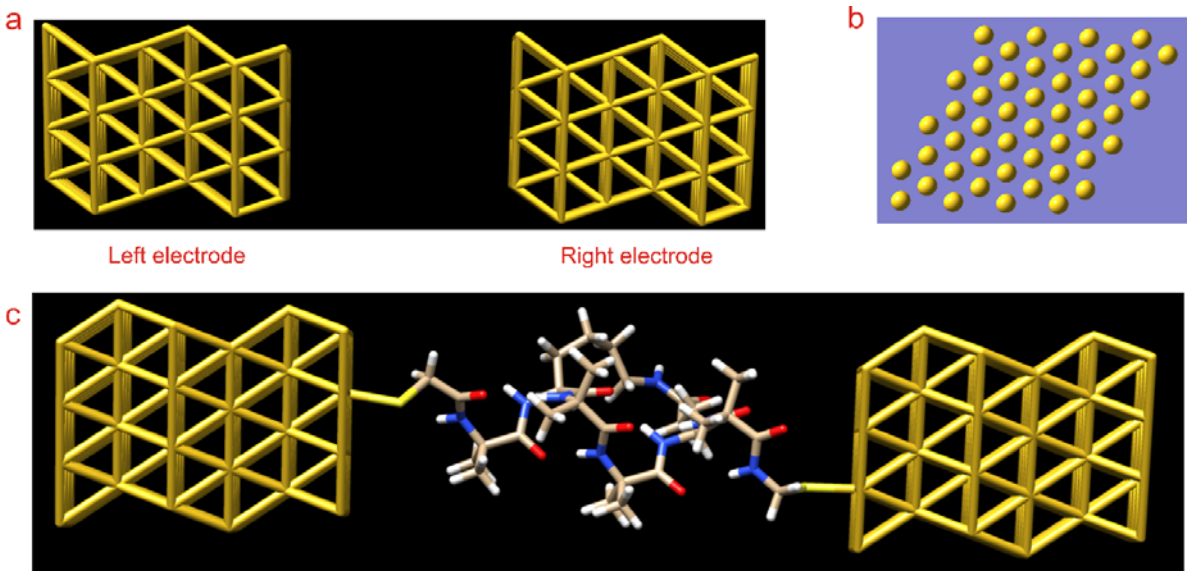


Figure S11. Scheme of the gold leads used for building the extended molecule, with (a) side view and (b) top view of 4 x 4 x 6 gold layers for each lead. The face of the leads corresponds to a (111) surface.
(c) A typical Au-peptide-Au setup for electronic transport simulation, with peptide **11** incorporated here.

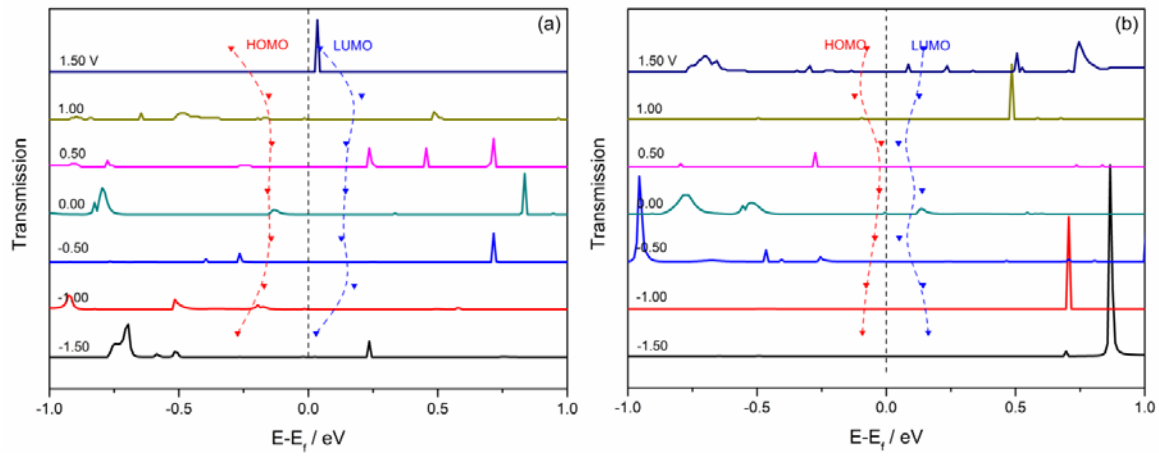


Figure S12. Transmission spectra of (a) the constrained **9** and (b) linear peptide **10** at different bias voltages, indicating the molecular orbital energy levels in proximity to the Au Fermi level (E_f) .

Sample input for TranSIESTA calculation:
0V calculation for Au-peptide 11-Au

```
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SystemLabel cyclic_0d00V

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=====================================================
# SPECIES AND BASIS

# Chemical species
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 1          79          Au
 2          16          S                 # Species index, atomic number, species label
 3          1           H                 # Species index, atomic number, species label
 4          8           O                 # Species index, atomic number, species label
 5          6           C                 # Species index, atomic number, species label
 6          7           N                 # Species index, atomic number, species label
%endblock ChemicalSpeciesLabel

# Basis set variables
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PAO.BasisSize                 DZP
PAO.EnergyShift               0.05 Ry
PAO.SplitNorm                 0.17888
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xc.authors                    PBE
SpinPolarized                 .false.      # Exchange-correlation version
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SolutionMethod                  transiesta
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DM.Tolerance                    1.d-5       # Tolerance in maximum difference
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DM.NumberPulay                   6
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MD.NumCGsteps                    000
MD.UseSaveXV                     .true.
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SaveHS                          .false.
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SaveTotalPotential              .true.
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WriteMDXmol                     .false.
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WriteEigenvalues                .false.
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TS.ComplexContour.NLine          10
TS.biasContour.NumPoints        15

# BIAS OPTIONS
TS.Voltage                      0.000000 eV

# TBT OPTIONS
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TS.TBT.Emax                      +5.00 eV
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TS.TBT.NEigen                   3
TS.TBT.Eta                      0.000001 Ry

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TS.SaveLead                     .false.

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TS.ReplicateA2Left              1
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TS.BufferAtomsLeft              0

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TS.ReplicateA2Right             1
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1.57794989	4.03506976	45.25013000	1	290	Au

%endblock AtomicCoordinatesAndAtomicSpecies

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8. Geometric similarity of peptide backbones in molecular junctions

8.1 Geometric similarity of β-strand peptide backbones (**9** and **10**).

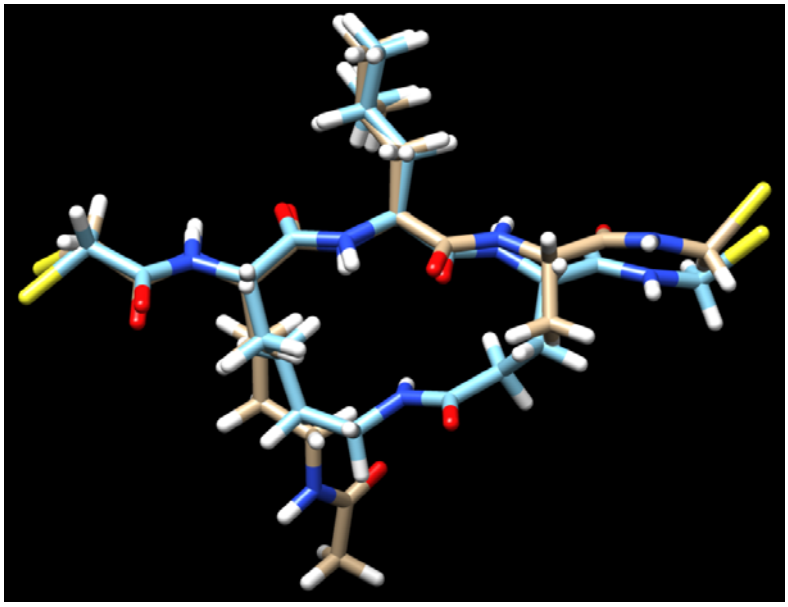


Figure S13. The superposition of the two β-strand peptides, **9** and **10**. (The light blue strand denotes the constrained peptide **9**, while the grey strand represents the linear peptide **10**).

8.2 Geometric similarity of helical peptide backbones (**11** and **12**).

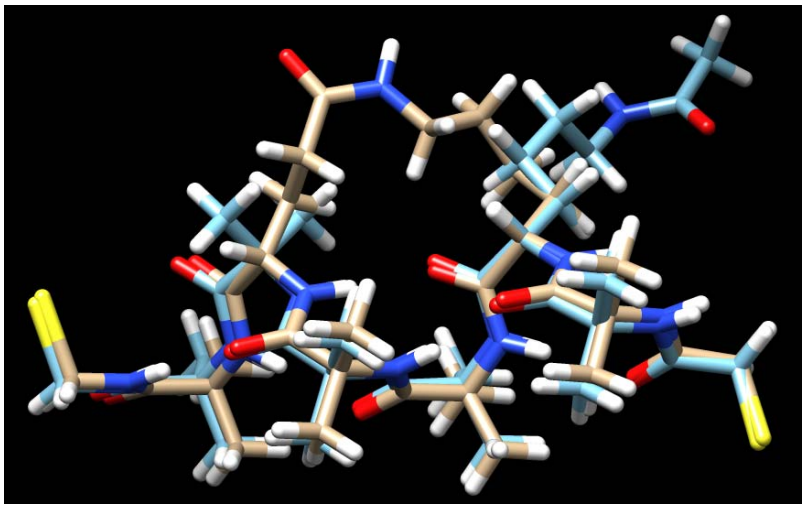
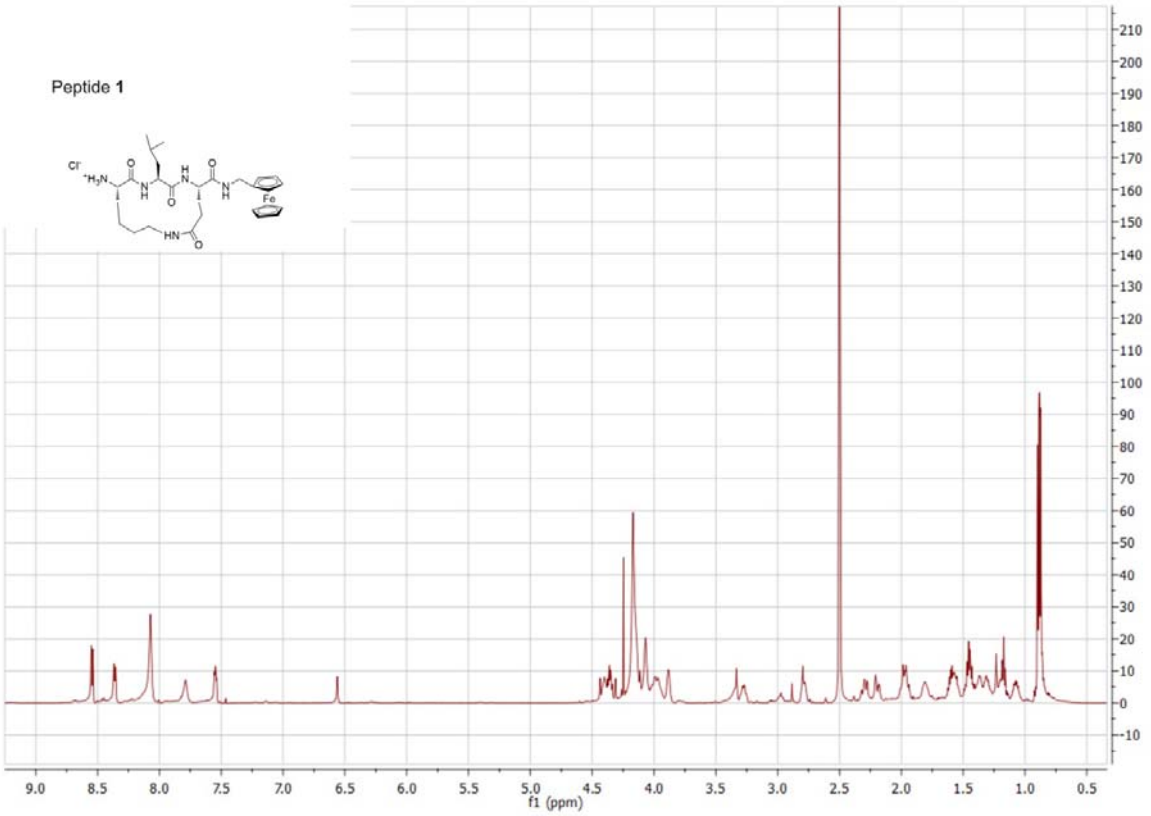


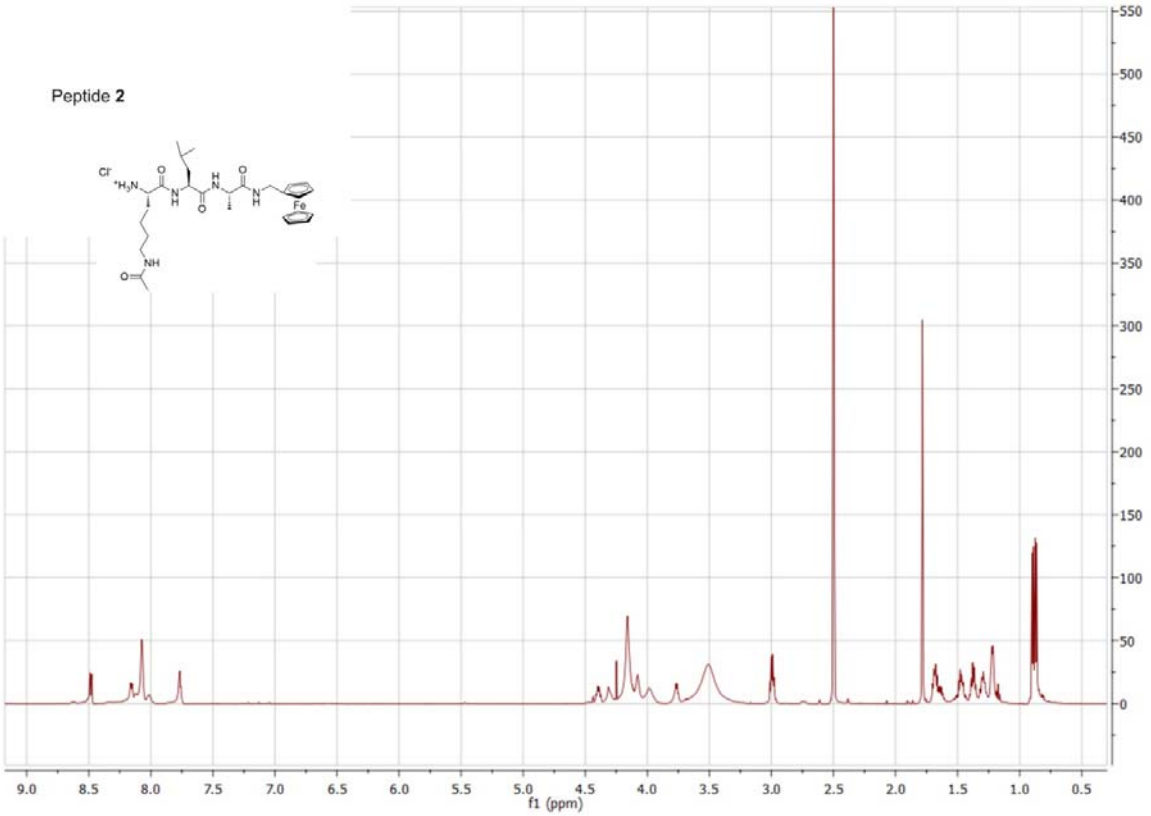
Figure S14. The superposition of the two helical peptides, **11** and **12**. (The grey strand denotes the constrained peptide **11**, while the light blue strand represents the linear peptide **12**).

Table S8. Distances between S-S atoms in molecular junctions containing peptides **9**-**12**.

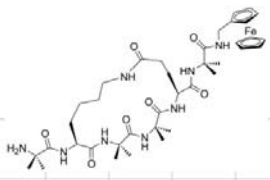
Peptide	Secondary structure	Linear or constrained	S-S distance (Å)
9	β-strand	Constrained	18.13
10	β-strand	Linear	18.02
11	3_{10}-helical	Constrained	17.36
12	3_{10}-helical	Linear	17.38

9. ^{1}H NMR spectra for target peptides and key intermediates

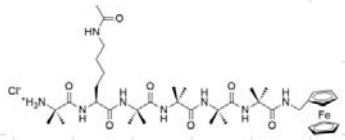




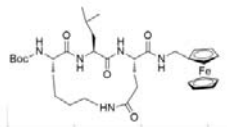
Peptide **3**



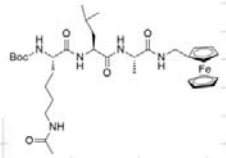
Peptide **4**



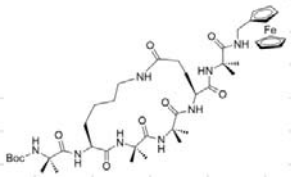
Peptide **5**



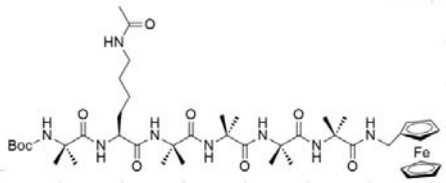
Peptide **6**



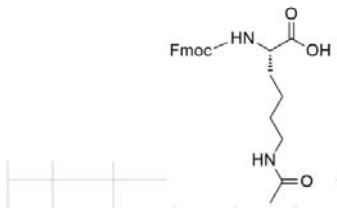
Peptide **7**



Peptide **8**



Compound **S1**



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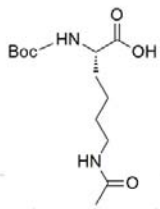

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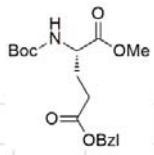

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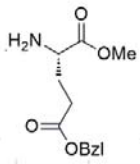

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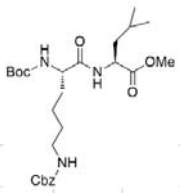

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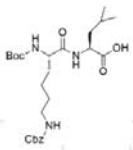

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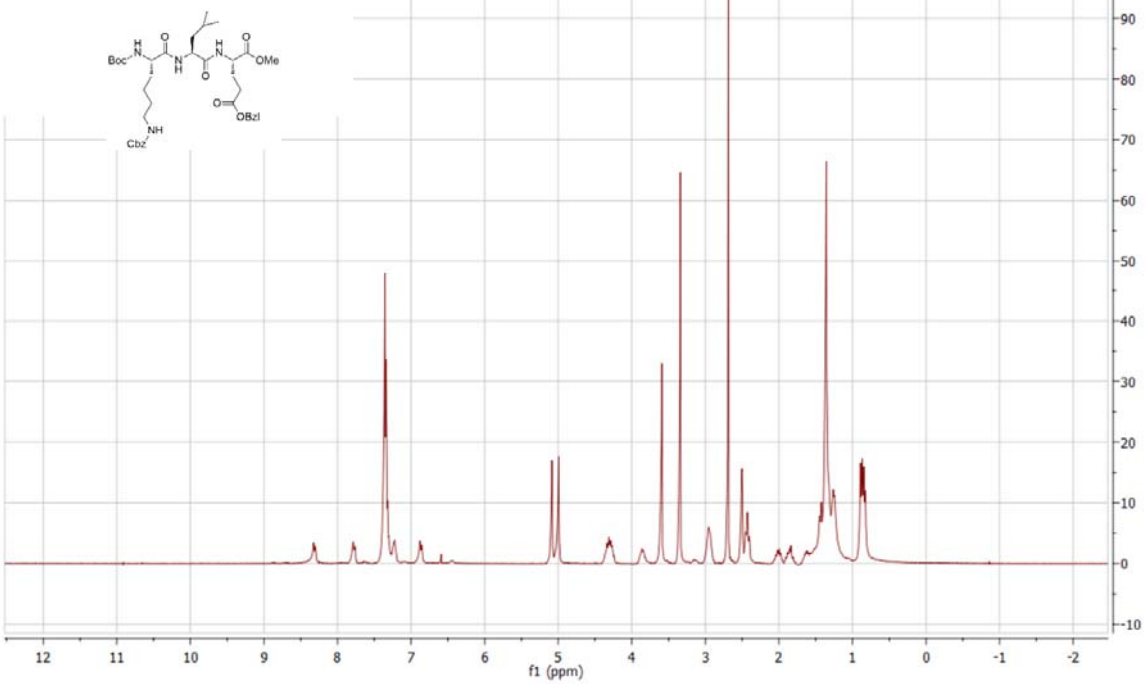

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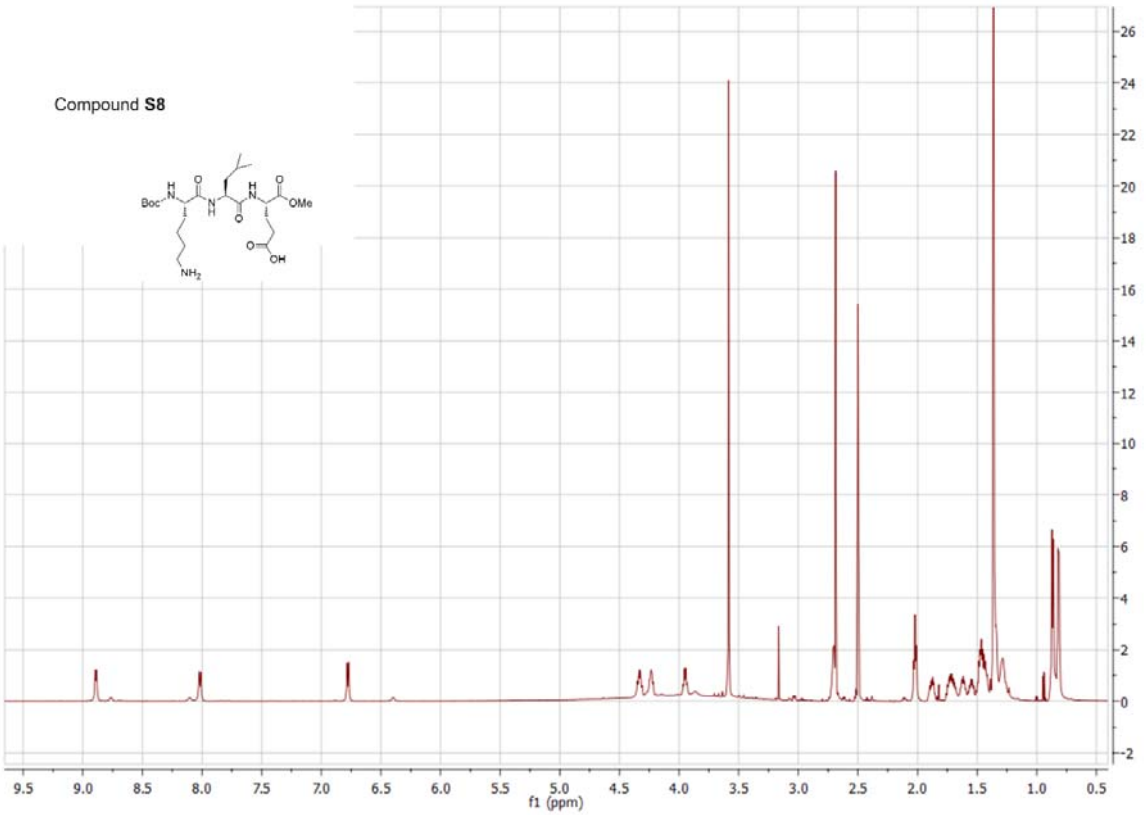

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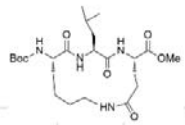

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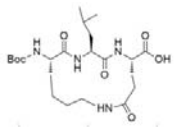

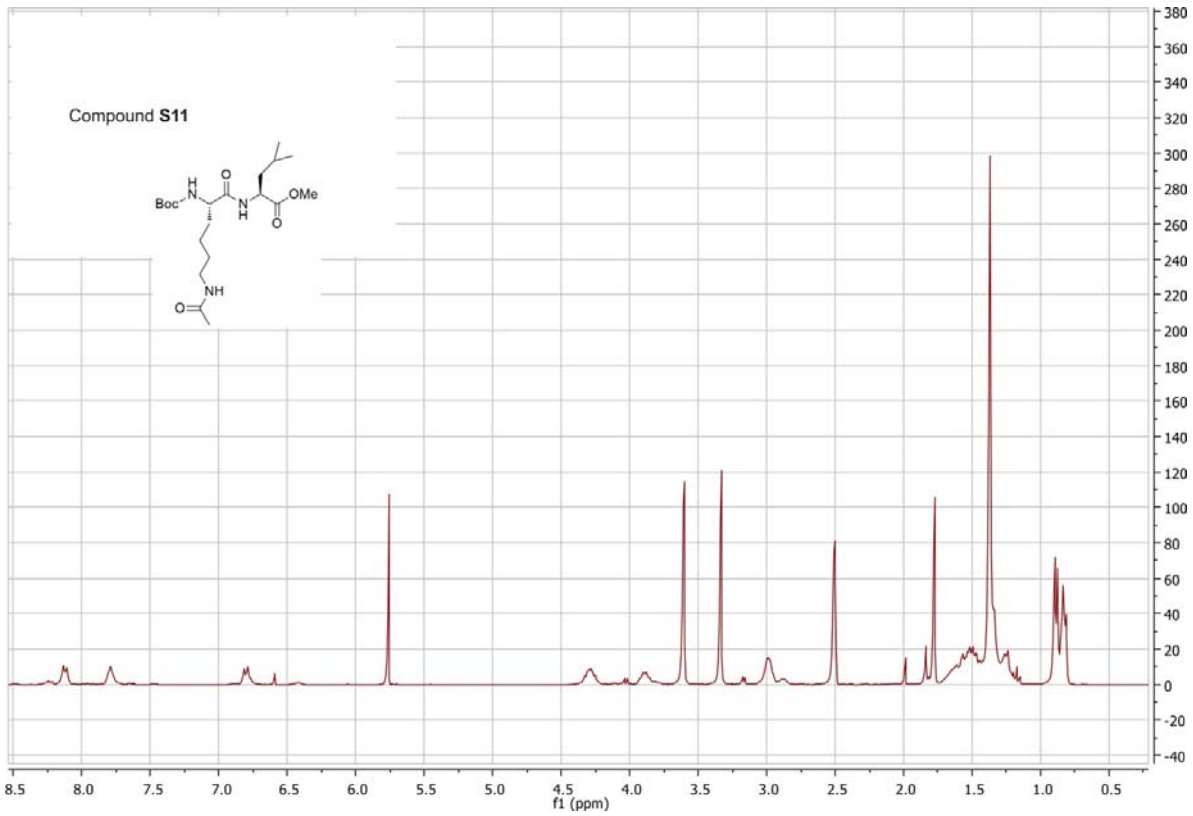
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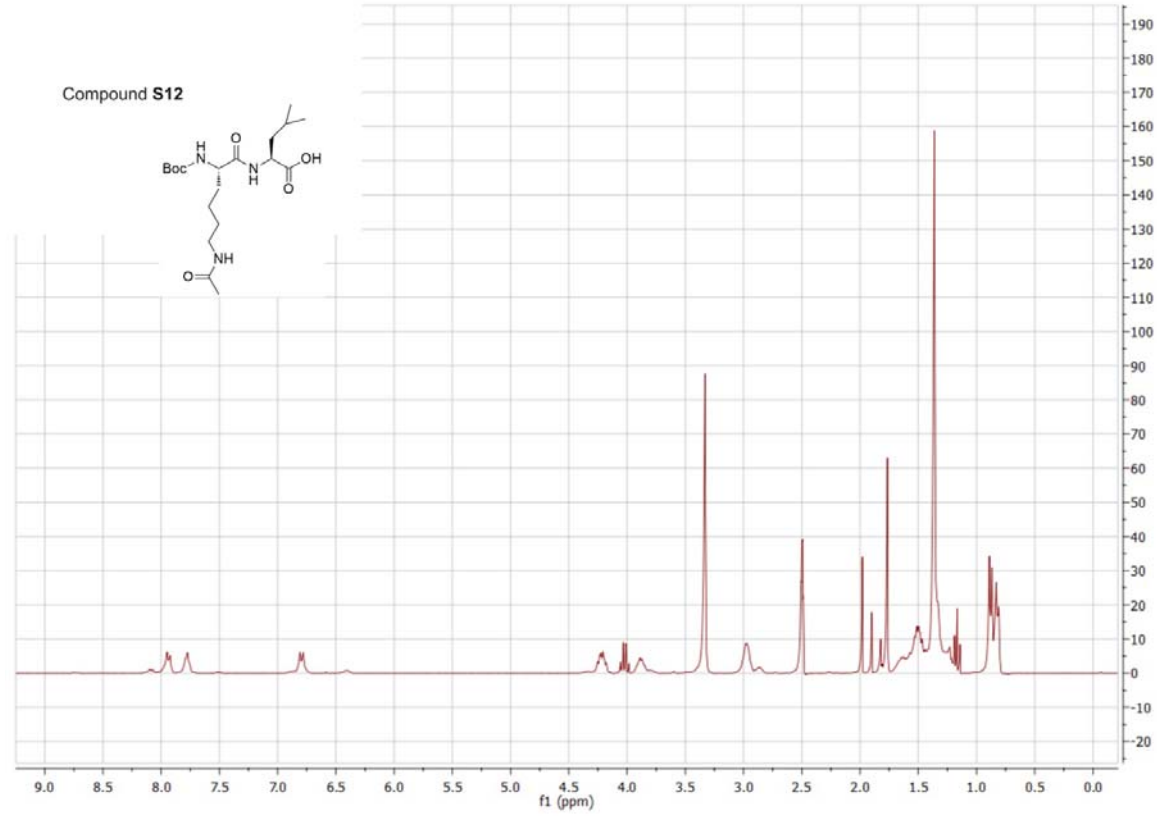
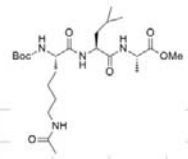
OMe
NH
f1 (ppm)


Compound **S12**
Boc
OH
NH
f1 (ppm)

Compound **S13**



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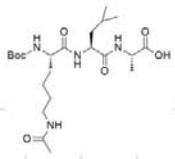

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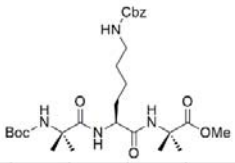

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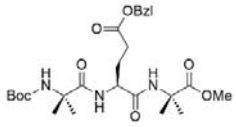

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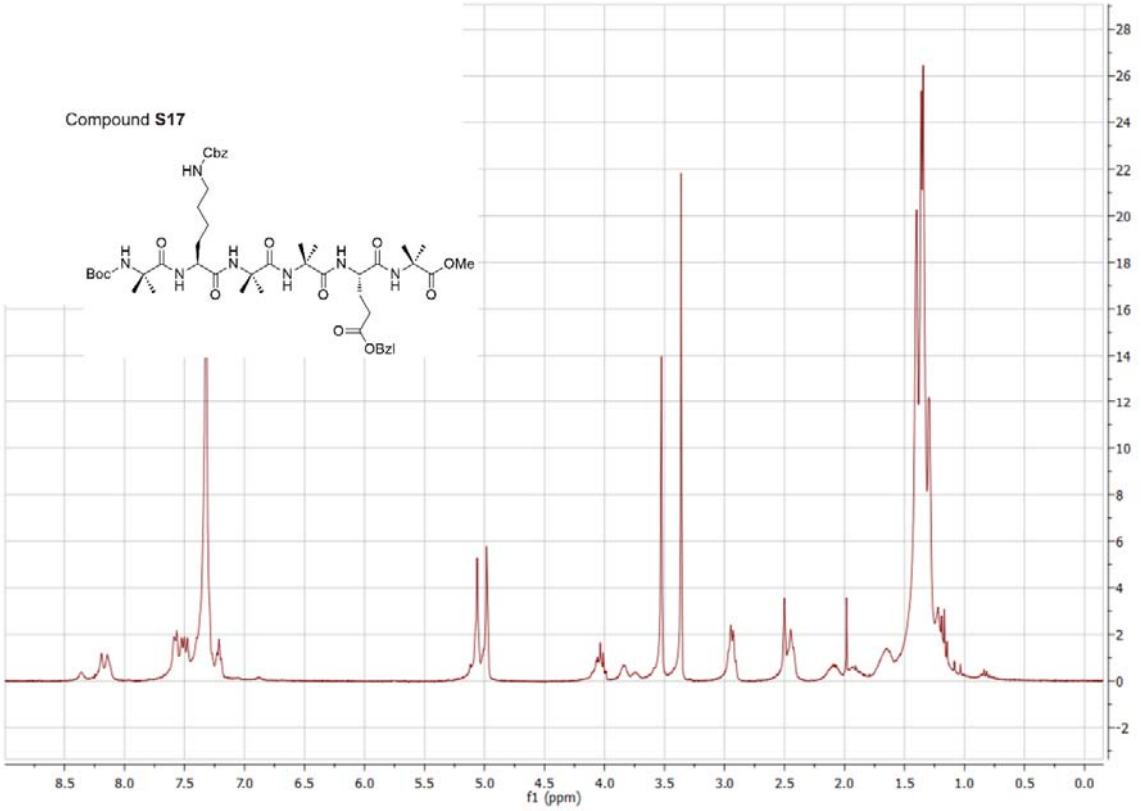

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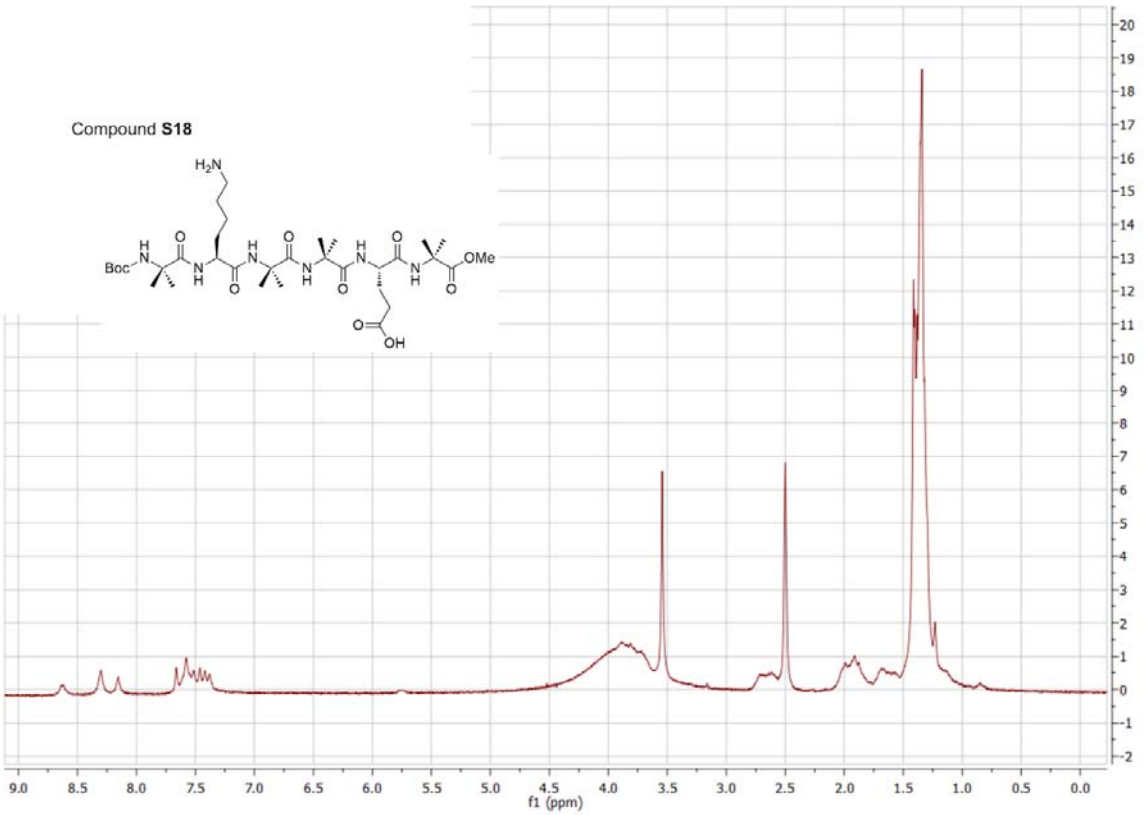

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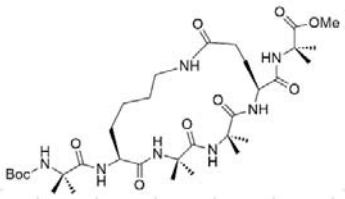

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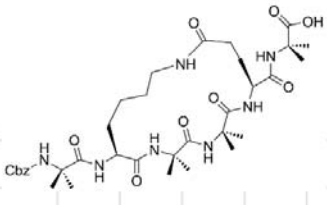

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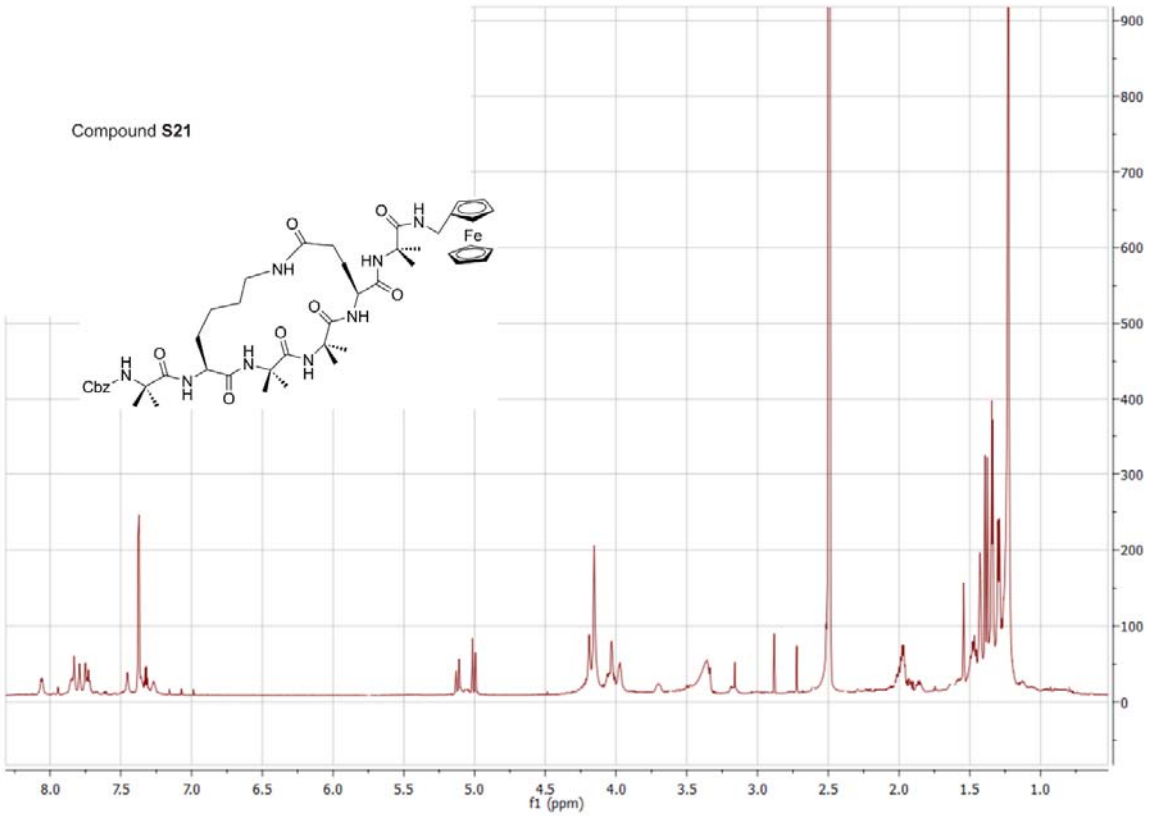

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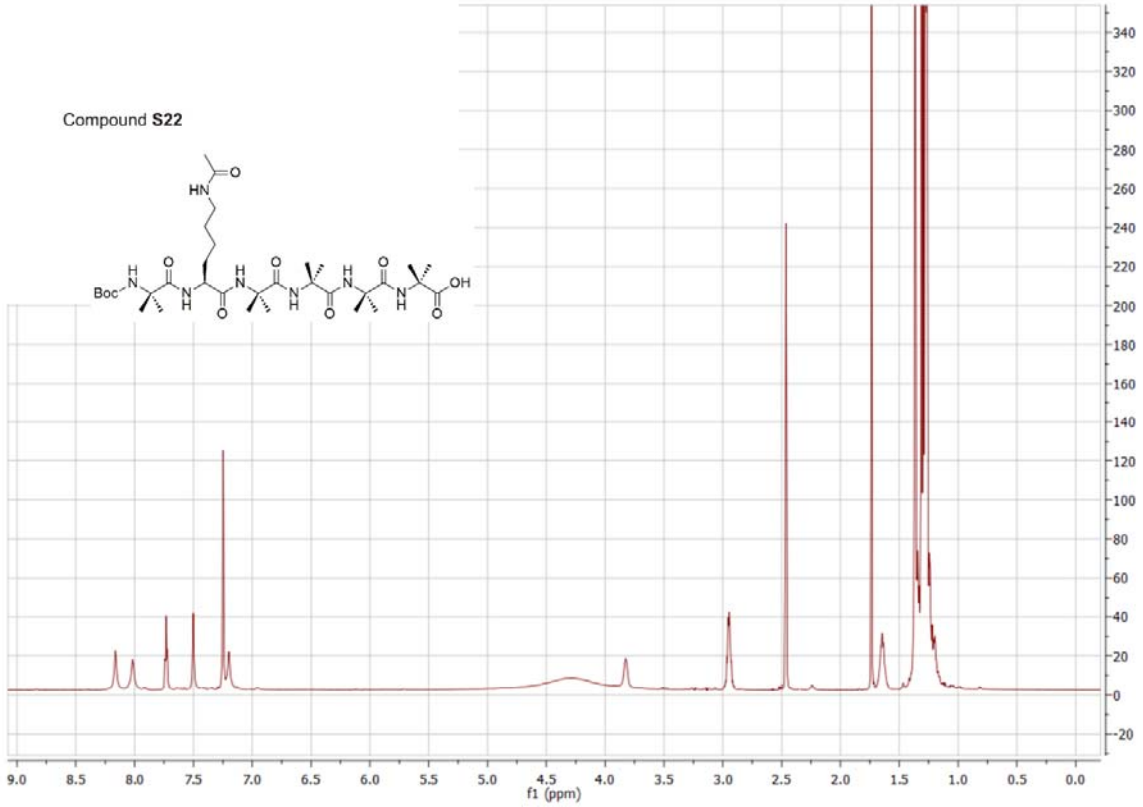

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