Supporting Information

Synthesis and structure-activity relationships of inhibitors that target the C-terminal MEEVD on heat shock protein 90

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Supporting Information

^1^H-^{13}C HMBC NMR of 1.............................................................................................................. 51
^1^H-^1^H COSY NMR of 1................................................................................................................. 52
LC/MS of 2........................................................................................................................................ 53
^1^H NMR of 2.................................................................................................................................... 54
^1^H-^{13}C HSQC NMR of 2............................................................................................................... 55
^1^H-^{13}C HMBC NMR of 2............................................................................................................... 56
^1^H-^1^H COSY NMR of 2............................................................................................................... 57
LC/MS of 3........................................................................................................................................ 58
^1^H NMR of 3.................................................................................................................................... 59
LC/MS of 4........................................................................................................................................ 60
^1^H NMR of 4.................................................................................................................................... 61
^1^H-^{13}C HSQC NMR of 4............................................................................................................... 62
^1^H-^{13}C HMBC NMR of 4............................................................................................................... 63
^1^H-^1^H COSY NMR of 4............................................................................................................... 64
LC/MS of 5........................................................................................................................................ 65
^1^H NMR of 5.................................................................................................................................... 66
^1^H-^{13}C HSQC NMR of 5............................................................................................................... 67
^1^H-^{13}C HMBC NMR of 5............................................................................................................... 68
^1^H-^1^H COSY NMR of 5............................................................................................................... 69
LC/MS of 6........................................................................................................................................ 70
^1^H NMR of 6.................................................................................................................................... 71
LC/MS of 7........................................................................................................................................ 72
^1^H NMR of 7.................................................................................................................................... 73
^1^H-^{13}C HSQC NMR of 7............................................................................................................... 74
^1^H-^{13}C HMBC NMR of 7............................................................................................................... 75
^1^H-^1^H COSY NMR of 7............................................................................................................... 76
LC/MS of 8........................................................................................................................................ 77
^1^H NMR of 8.................................................................................................................................... 78
^1^H-^{13}C HSQC NMR of 8............................................................................................................... 79
^1^H-^{13}C HMBC NMR of 8............................................................................................................... 80
^1^H-^1^H COSY NMR of 8............................................................................................................... 81
LC/MS of 9........................................................................................................................................ 82
^1^H NMR of 9.................................................................................................................................... 83
| Supporting Information                                      | Page |
|-------------------------------------------------------------|------|
| LC/MS of 10                                                 | 84   |
| $^1$H NMR of 10                                             | 85   |
| $^1$H-$^{13}$C HSQC NMR of 10                               | 86   |
| $^1$H-$^{13}$C HMBC NMR of 10                               | 87   |
| $^1$H-$^1$H COSY NMR of 10                                  | 88   |
| LC/MS of 11                                                 | 89   |
| $^1$H NMR of 11                                             | 90   |
| $^1$H-$^{13}$C HSQC NMR of 11                               | 91   |
| $^1$H-$^{13}$C HMBC NMR of 11                               | 92   |
| $^1$H-$^1$H COSY NMR of 11                                  | 93   |
| LC/MS of 12                                                 | 94   |
| $^1$H NMR of 12                                             | 95   |
| LC/MS of 13                                                 | 96   |
| $^1$H NMR of 13                                             | 97   |
| $^1$H-$^{13}$C HSQC NMR of 13                               | 98   |
| $^1$H-$^{13}$C HMBC NMR of 13                               | 99   |
| $^1$H-$^1$H COSY NMR of 13                                  | 100  |
| LC/MS of 14                                                 | 101  |
| $^1$H NMR of 14                                             | 102  |
| LC/MS of 15                                                 | 103  |
| $^1$H NMR of 15                                             | 104  |
| $^1$H-$^{13}$C HSQC NMR of 15                               | 105  |
| $^1$H-$^{13}$C HMBC NMR of 15                               | 106  |
| $^1$H-$^1$H COSY NMR of 15                                  | 107  |
| LC/MS of 16                                                 | 108  |
| $^1$H NMR of 16                                             | 109  |
| $^1$H-$^{13}$C HSQC NMR of 16                               | 110  |
| $^1$H-$^{13}$C HMBC NMR of 16                               | 111  |
| $^1$H-$^1$H COSY NMR of 16                                  | 112  |
| LC/MS of 17                                                 | 113  |
| $^1$H NMR of 17                                             | 114  |
| $^1$H-$^{13}$C HSQC NMR of 17                               | 115  |
| $^1$H-$^{13}$C HMBC NMR of 17                               | 116  |
Supporting Information

\(^1\)H\(^1\)H COSY NMR of 17.................................................................................................................. 117
LC/MS of 18................................................................................................................................. 118
\(^1\)H NMR of 18.......................................................................................................................... 119
\(^1\)H\(^{13}\)C HSQC NMR of 18......................................................................................................... 120
\(^1\)H\(^{13}\)C HMBC NMR of 18...................................................................................................... 121
\(^1\)H\(^1\)H COSY NMR of 18.......................................................................................................... 122
LC/MS of 19................................................................................................................................. 123
\(^1\)H NMR of 19.......................................................................................................................... 124
\(^1\)H\(^{13}\)C HSQC NMR of 19......................................................................................................... 125
\(^1\)H\(^{13}\)C HMBC NMR of 19...................................................................................................... 126
\(^1\)H\(^1\)H COSY NMR of 19.......................................................................................................... 127
Supplementary Figure 1 (Figure S1)

**Figure S1.** Impact of LB51 analogues on Hsp90β-Cyp40 binding. Graphs represent mean ± SEM. IC\textsubscript{50} values were calculated using GraphPad Prism software. All experiments were performed at least twice in triplicate.
Figure S2. Impact of all analogues on cell growth of HCT116 cells. Graphs represent mean ± SEM. All experiments were performed at least twice in triplicate.
General Remarks

All chemicals were purchased from commercial suppliers (Chem-Impex International and Sigma Aldrich) and used without further purification. All moisture sensitive reactions were performed using anhydrous solvents under nitrogen gas. Removal of solvent was carried out under reduced pressure using a Buchi R-210 rotary evaporator.

Thin Layer Chromatography (TLC) was performed on aluminium silica gel sheets (Merck TLC silica gel 60 F254). Spots were visualised under ultraviolet light (\(\lambda = 254 \text{ nm}\)) and developed by heating with ninhydrin solution.

LC/MS analyses were performed using a Phenomenex Aeris XB-C18 column (3.6 \(\mu\)m, 2.1 x 100 mm) on either a Shimadzu LCMS 2020, Shimadzu LCMS 8030 or LCQ Deca XP Plus (Thermo Finnigan). The mobile phase consisted of milli-Q water with 0.1% (v/v) formic acid (Mobile Phase A), and HPLC grade acetonitrile with 0.1% (v/v) formic acid (Mobile Phase B) at a flow rate of 0.2 mL/min, starting at 95% Mobile Phase A and 5% Mobile Phase B.

Semi-preparative HPLC for purification was performed using a GRACE VisionHT C18 column (5 \(\mu\)m, 22 x 150 mm) or a Phenomenex Aeris XB-C18 column (5 \(\mu\)m, 21.2 x 150 mm) on a Shimadzu Prominence system. The mobile phase consisted of milli-Q water with 0.1% (v/v) formic acid (Mobile Phase A), and HPLC grade acetonitrile with 0.1% (v/v) formic acid (Mobile Phase B) at a flow rate of 5 mL/min, starting at 95% Mobile Phase A and 5% Mobile Phase B.

\(^1\)H and \(^{13}\)C NMR spectra were obtained on Bruker Avance III 600 MHz. Multiplicity of NMR signals were represented by the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, dd = doublet of doublet. Assignment of resonances for each residue was accomplished using \(^1\)H, HSQC, HMBC and COSY spectra.

General Synthetic Procedures

Solid-Phase Peptide Synthesis

Stepwise SPPS was performed in a polypropylene solid-phase extraction cartridge fitted with a 20 \(\mu\)m polyethylene frit purchased from Applied Separations (Allentown, PA).

Resin Loading

The resin was weighed, transferred to the cartridge and swelled in CH\(_2\)Cl\(_2\) for 30 minutes prior to the resin loading reaction. The appropriate Fmoc-protected amino acid was dissolved in the minimum amount of 0.4M DIPEA in CH\(_2\)Cl\(_2\). The swelled resin was then drained and the dissolved amino acid was added and the suspension was agitated for 4 hours. The resin was then washed 3 times with CH\(_2\)Cl\(_2\), 3 times with DMF and 3 times with CH\(_2\)Cl\(_2\). The resin was then dried \textit{in vacuo} overnight. A ~ 5 mg sample of resin was used to determine the amino acid loading. 20% piperidine in DMF was added to the sample to cleave the Fmoc protecting group. The resin was filtered away and the remaining solution was diluted 1 in 20 and the UV absorbance measured at 301 nm using a Cary 50 Bio UV-Vis instrument. DMF was used as a blank and samples were measured in a 1 mL quartz cuvette. The resin loading was then determined using the following formula:

Resin loading

\[
\text{Resin loading} = \frac{(\text{Abs} \times \text{cleavage volume} \times \text{dilution factor})}{(\text{extinction coefficient} \times \text{cuvette width} \times \text{resin mass})}
\]

\[
= \frac{(\text{Abs} \times 1 \text{ mL} \times 20)}{(7800 \text{ mL mmol}^{-1} \text{ cm}^{-1} \times 1 \text{ cm} \times \text{resin mass in g})}
\]

\[
= \frac{(\text{Abs} \times 20 \text{ mL})}{(7800 \text{ mL mmol}^{-1} \times \text{resin mass in g})}
\]
**Coupling Reaction**

Couplings were performed in DMF at a concentration of 0.3 M. Fmoc-protected amino acid (2 equiv.) and HOBt (2 equiv.) were mixed with the resin. DIC (4 equiv.) was then added to activate the reaction. Coupling reaction was run for a minimum of 2 hours while shaking (Labquake tube shaker, Thermo Fisher Scientific) at room temperature. A negative ninhydrin test was used to confirm reaction completion. Once completed, the reaction mixture was drained and the resin was subjected to *Fmoc Removal*. (Note: For particularly hindered coupling reactions, HOBt was replaced with HOAt.

**Fmoc Removal**

The Fmoc protecting group was removed using the following washes: DMF (3 x 1 min), 20% piperidine in DMF (1 x 5 min), 20% piperidine in DMF (1 x 10 min), DMF (2 x 1 min), iPrOH (1 x 1 min), iPrOH (1 x 1 min) and DMF (3 x 1 min). The resin was then ready for the next coupling reaction.

**Resin Cleavage of Linear Peptide**

Once the desired peptide was generated, the final Fmoc protecting group was removed following *Fmoc Removal* procedure with the following additional washes: DMF (3 x 1 min), iPrOH (3 x 1 min) and MeOH (3 x 1 min). The resin-bound peptide was then dried in vacuo overnight. The resin was then cleaved from the linear peptide using TFE and CH$_2$Cl$_2$ (1:1 v/v) at a concentration of 10 mL/g resin. The reaction mixture was stirred at room temperature for 24 hours before filtering the resin. The filtrate was concentrated and washed at least 10 times with CH$_2$Cl$_2$ to remove residual entrapped TFE. The product was then dried in vacuo overnight to produce the linear peptide.

**Macrocyclisation**

Macrocyclisation of the linear peptide was achieved using a cocktail of 3 coupling reagents: HATU (1 eq.), TBTU (0.8 equiv.) and DMTMM (0.8 equiv.). The reaction was performed in dilute conditions using anhydrous solvents at concentration of 0.001 M. The linear peptide and coupling reagents were dissolved separately in CH$_2$Cl$_2$, where 20% of the final volume was used to dissolve the linear peptide and the other 80% dissolved the coupling reagents. DIPEA (4 equiv.) was added to each solution. The linear peptide solution was then added drop-wise to the coupling reagents solution via a syringe pump over approximately 2 hours. The reaction was stirred overnight and monitored via LC/MS. (Note: if the reaction failed to reach completion after stirring overnight, additional HATU (1 equiv.) was added and the reaction was monitored using LC/MS.) Upon completion, the reaction mixture was evaporated and the dry solid was redissolved in CH$_2$Cl$_2$ and extracted 3 times with milli-Q water. The aqueous layers were combined and extracted 3 times with fresh CH$_2$Cl$_2$. All organic layers were combined and dried over Na$_2$SO$_4$, filtered and evaporated under reduced pressure before the compound was dried in vacuo overnight.

**Side Chain Deprotection**

Amino acid side chain protecting groups were removed using TFA in CH$_2$Cl$_2$ (9:1 v/v) with anisole (2 equiv. per protecting group). Anisole was added to the peptide, whilst stirring, followed by the TFA solution at a concentration of 4 mL/g compound. The reaction was left stirring at room temperature for 4 hours. The reaction was monitored using LC/MS and once complete the reaction solution was dried under a stream of nitrogen before before redissolving in CH$_2$Cl$_2$ and evaporating multiple times to remove residual entrapped TFA. The product was triturated in diethyl ether, collected via centrifugation and lyophilised to produce the crude cyclic peptide.
Biology Methods

Protein binding assay
The binding assays were performed using a HSP90β (C-terminal) Inhibitor Screening Kit (cat. 50314) purchased from BPS Bioscience. The assay was performed according to the manufacturer's protocol and utilized AlphaLISA technology (PerkinElmer). The test compounds were dissolved in 100% DMSO and diluted with water to the desired concentration so that the final dilution was dissolved in 5% DMSO with water. 2 µL of the dilution was added to a 10 µL reaction so that the final concentration of DMSO was 1% in all reactions. The reactions were conducted at room temperature for 30 min in a 10 µL mixture containing assay buffer, 6 ng (24 nM) of a C-terminal HSP90β (Uniprot P08238, a.a. 527-724), 40 ng (100 nM) Cyp40, and the test compound. After the 30 min incubation, 10 µL of buffer containing 20 µg/mL glutathione acceptor beads (PerkinElmer) were added to the reaction mix and incubated for 30 min in the dark. 10 µL of 40 µg/mL streptavidin donor beads (PerkinElmer) were then added and the final 30 µL mixture was incubated for one hour in the dark. The AlphaLISA signal was measured using a Tecan F200 Pro multimode plate reader.

Cytotoxicity Assay
HCT116 cells were seeded into 96-well plates at 2000 cells per well and allowed to adhere for 24 hours by incubating at 37°C with 5% CO₂. The cells were treated with test compounds or DMSO (1%) for 72 hours. After 72 hours the media was removed and replaced with 100 µL of Dulbecco’s modified Eagle medium (DMEM) with 10 µL of Cell Counting Kit 8 reagent (Dojindo). The cells were then incubated 3 hours and then the absorbance was measured at 450 nm using a Chromate plate reader.
Experimental Procedures for 1

Resin-O-Phe-NH₂

The resin bound amino acid Resin-O-Phe-NH₂ was synthesized according to the Resin Loading procedure. A sample of 2-chlorotriyl chloride resin (1.0 g, 1.1 mmol/g loading, 1 equiv.) was placed in a reaction vessel and swelled with CH₂Cl₂ for 30 minutes then drained. To the resin was added 0.83 g Fmoc-Phe-OH (2.1 mmol, 3 equiv.) that was pre-dissolved in the minimum amount of DIPEA in CH₂Cl₂ (0.40 M). The reaction was shaken at room temperature for 4 hours. The reaction mixture was drained and washed according to the protocol to produce Resin-O-Phe-NHFmoc. A sample of resin was removed and the resin loading was determined to be 0.70 mmol/g. The Fmoc group was then removed following the Fmoc Removal procedure to produce Resin-O-Phe-NH₂.

Resin-O-Phe-Tyr(t-Bu)-NH₂

Resin-O-Phe-Tyr(t-Bu)-NH₂ was synthesized following the Coupling Reaction procedure, using 1.0 g Resin-O-Phe-NH₂ (0.70 mmol, 1 equiv.), 0.65 g Fmoc-Tyr(t-Bu)-OH (1.4 mmol, 2 equiv.), 3.2 mL HOAt (2.1 mmol, 3 equiv.), 0.66 mL DIC (4.3 mmol, 6 equiv.), and 1.4 mL of DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained and washed according to the protocol to produce Resin-O-Phe-Tyr(t-Bu)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to produce Resin-O-Phe-Tyr(t-Bu)-NH₂.

Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH₂

Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-Tyr(t-Bu)-NH₂ from the previous reaction, 0.54 g Fmoc-Ser(t-Bu)-OH (1.4 mmol, 2 equiv.), 3.2 mL HOAt (2.1 mmol, 3 equiv.), 0.66 mL DIC (4.3 mmol, 6 equiv.), and 1.4 mL of DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH₂.

Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Ala-NH₂

Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Ala-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH₂ from the previous reaction, 0.50 g Fmoc-Ala-OH (1.4 mmol, 2 equiv.), 3.2 mL HOAt (2.1 mmol, 3 equiv.), 0.66 mL DIC (4.3 mmol, 6 equiv.), and 1.4 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Ala-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Ala-NH₂.

Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Ala-Lys(Boc)-NH₂

Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Ala-Lys(Boc)-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Ala-NH₂ from the previous reaction, 0.67 g Fmoc-Lys(Boc)-OH (1.4 mmol, 2 equiv.), 3.2 mL HOAt (2.1 mmol, 3 equiv.), 0.66 mL DIC (4.3 mmol, 6 equiv.), and 1.4 mL DMF to generate a concentration of 0.3 M. The coupling
reaction was run overnight and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Ala-Lys(Boc)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Ala-Lys(Boc)-NH₂.

**HO-Phe-Tyr(t-Bu)-Ser(t-Bu)-Ala-Lys(Boc)-NH₂**

The protected linear pentapeptide HO-Phe-Tyr(t-Bu)-Ser(t-Bu)-Ala-Lys(Boc)-NH₂ was generated following the Resin Cleavage of Linear Peptide procedure. The linear peptide was cleaved from the resin using a mixed solution of 7.5 mL trifluoroethanol and 7.5 mL CH₂Cl₂. The resin containing solution was filtered and dried in vacuo to yield the protected linear pentapeptide as a pale yellow solid (884 mg, overall 79%).

**cyclo-Phe-Tyr(t-Bu)-Ser(t-Bu)-Ala-Lys(Boc)**

The protected cyclic peptide was synthesized following the Macrocyclisation procedure using 0.23 g linear peptide (0.3 mmol, 1 equiv.), 0.11 g HATU (0.3 mmol, 1 equiv.), 0.05 g TBTU (0.15 mmol, 0.5 equiv.), 0.04 g DMTMM (0.15 mmol, 0.5 equiv.), 0.42 mL DIPEA (1.21 mmol, 8.0 equiv.) in anhydrous CH₂Cl₂ (302 mL, 0.001 M). The reaction was then stirred for 4 hours and monitored via LC/MS. Upon completion, the reaction was worked up as described in the Macrocyclisation procedure and dried in vacuo to produce the crude, protected, cyclic peptide cyclo-Phe-Tyr(t-Bu)-Ser(t-Bu)-Ala-Lys(Boc).

**cyclo-Phe-Tyr-Ser-Ala-Lys (1)**

The deprotected cyclic peptide was synthesized following the Side Chain Deprotection procedure using 0.25 g crude cyclo-Phe-Tyr(t-Bu)-Ser(t-Bu)-Ala-Lys(Boc) (0.31 mmol, 1 equiv.), 900 µL of a mixed solution of TFA and CH₂Cl₂ (9:1 v/v) and 200 µL anisole (1.8 mmol, 8 equiv.) to generate the free side chains. The reaction mixture was stirred for 4 hours and monitored via LC/MS. Upon completion, the reaction mixture was worked up as described in the Side Chain Deprotection procedure and lyophilised to produce the crude cyclic peptide. The crude product was purified using HPLC to generate pure compound as a white solid (79%).

LC/MS (ESI) m/z: [M+H]+ calculated for C₃₀H₄₁N₆O₇⁺, 597.31; found 597.20.

¹H NMR (600 MHz, D₂O): δ 7.33-7.12 (m, 5H, Phe), 6.85-6.84 (d, J = 7.63 Hz, 2H, γH Tyr), 6.70-6.68 (d, J = 8.35 Hz, 2H, δH Tyr), 4.60-4.58 (t, J = 7.28 Hz, 1H, αH Phe), 4.53-4.51 (t, J = 6.17 Hz, 1H, αH Tyr), 4.43-4.41 (t, J = 6.69 Hz, 1H, αH Ser), 4.14-4.10 (m, 2H, αH Lys), 4.11-4.06 (m, 2H, αH Ala), 3.09-2.99 (m, 2H, βH Ser), 2.96-2.88 (m, 2H, βH Phe), 2.89-2.82 (m, 2H, βH Tyr), 2.81-2.69 (m, 2H, εH Lys), 1.60-1.48 (m, 2H, βH Lys), 1.27-1.18 (m, 2H, γH Lys), 1.15-1.10 (d, J = 7.56 Hz, 3H, βH Ala), 1.05-0.91 (m, 2H, δH Lys).

S11
Experimental Procedures for 2

Resin-O-Tyr(t-Bu)-NH₂

The resin bound amino acid Resin-O-Tyr(t-Bu)-NH₂ was synthesized according to the Resin Loading procedure. A sample of 2-chlorotriyl chloride resin (1.02 g, 1.1 mmol/g loading, 1 equiv.) was placed in a reaction vessel and swelled with CH₂Cl₂ for 30 minutes then drained. To the resin was added 1.66 g Fmoc-Tyr(t-Bu)-OH (3.3 mmol, 3 equiv.) that was pre-dissolved in the minimum amount of DIPEA in CH₂Cl₂ (0.40 M). The reaction was shaken at room temperature for 4 hours. The reaction mixture was drained and washed according to the protocol to produce Resin-O-Tyr(t-Bu)-NHFmoc. A sample of resin was removed and the resin loading was determined to be 0.69 mmol/g. The Fmoc group was then removed following the Fmoc Removal procedure to produce Resin-O-Tyr(t-Bu)-NH₂.

Resin-O-Tyr(t-Bu)-Ser(t-Bu)-NH₂

Resin-O-Tyr(t-Bu)-Ser(t-Bu)-NH₂ was synthesized following the Coupling Reaction procedure, using 1.0 g Resin-O-Tyr(t-Bu)-Ser(t-Bu)-NH₂ (0.69 mmol, 1 equiv.), 1.66 g Fmoc-Ser(t-Bu)-OH (2.07 mmol, 3 equiv.), 2 mL HOAt (1.20 mmol, 2 equiv.), 0.43 mL DIC (2.8 mmol, 4 equiv.), and 2 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run overnight and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Tyr(t-Bu)-Ser(t-Bu)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Tyr(t-Bu)-Ser(t-Bu)-NH₂.

Resin-O-Tyr(t-Bu)-Ser(t-Bu)-Lys(Boc)-NH₂

Resin-O-Tyr(t-Bu)-Ser(t-Bu)-Lys(Boc)-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Tyr(t-Bu)-Ser(t-Bu)-Lys(Boc)-NH₂ from the previous reaction, 0.97 g Fmoc-Lys(Boc)-OH (2.07 mmol, 3 equiv.), 2 mL HOAt (1.20 mmol, 2 equiv.), 0.43 mL DIC (2.8 mmol, 4 equiv.), and 2 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run overnight and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Tyr(t-Bu)-Ser(t-Bu)-Lys(Boc)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Tyr(t-Bu)-Ser(t-Bu)-Lys(Boc)-NH₂.

Resin-O-Tyr(t-Bu)-Ser(t-Bu)-Lys(Boc)-Lys(Boc)-NH₂

Resin-O-Tyr(t-Bu)-Ser(t-Bu)-Lys(Boc)-Lys(Boc)-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Tyr(t-Bu)-Ser(t-Bu)-Lys(Boc)-Lys(Boc)-NH₂ from the previous reaction, 0.65 g Fmoc-Lys(Boc)-OH (1.38 mmol, 3 equiv.), 3 mL HOAt (1.80 mmol, 3 equiv.), 0.43 mL DIC (2.8 mmol, 4 equiv.), and 2 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run overnight and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Tyr(t-Bu)-Ser(t-Bu)-Lys(Boc)-Lys(Boc)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Tyr(t-Bu)-Ser(t-Bu)-Lys(Boc)-Lys(Boc)-NH₂.

Resin-O-Tyr(t-Bu)-Ser(t-Bu)-Lys(Boc)-Lys(Boc)-Phe-NH₂

Resin-O-Tyr(t-Bu)-Ser(t-Bu)-Lys(Boc)-Lys(Boc)-Phe-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Tyr(t-Bu)-Ser(t-Bu)-Lys(Boc)-Lys(Boc)-NH₂ from the previous reaction, 0.53 g Fmoc-Phe-OH (1.38 mmol, 3 equiv.), 3 mL HOAt (1.80 mmol, 3 equiv.), 0.43 mL DIC (2.8 mmol, 4 equiv.), and 2 mL DMF to generate a concentration of 0.3 M.
Supporting Information

The coupling reaction was run overnight and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Tyr(t-Bu)-Ser(t-Bu)-Lys(Boc)-Lys(Boc)-Phe-NH-Fmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Tyr(t-Bu)-Ser(t-Bu)-Lys(Boc)-Lys(Boc)-Phe-NH₂.

HO-Tyr(t-Bu)-Ser(t-Bu)-Lys(Boc)-Lys(Boc)-Phe-NH₂

The protected linear pentapeptide HO-Tyr(t-Bu)-Ser(t-Bu)-Lys(Boc)-Lys(Boc)-Phe-NH₂ was generated following the Resin Cleavage of Linear Peptide procedure. The linear peptide was cleaved from the resin using a mixed solution of 7 mL trifluoroethanol and 7 mL CH₂Cl₂. The resin containing solution was filtered and dried in vacuo to yield the protected linear pentapeptide as a pale yellow solid (532 mg, overall 66%)

cyclo-Tyr(t-Bu)-Ser(t-Bu)-Lys(Boc)-Lys(Boc)-Phe

The protected cyclic peptide was synthesized following the Macrocyclisation procedure using 0.359 g linear peptide (0.31 mmol, 1 equiv.), 0.12 g HATU (0.31 mmol, 1 equiv.), 0.079 g TBTU (0.25 mmol, 0.8 equiv.), 0.068 g DMTMM (0.25 mmol, 0.8 equiv.), 0.43 mL DIPEA (0.057 mmol, 8.0 equiv.) in anhydrous CH₂Cl₂ (310 mL, 0.001 M). The reaction was then stirred for 4 hours and monitored via LC/MS. Upon completion, the reaction mixture was worked up as described in the Macrocyclisation procedure and dried in vacuo to produce the crude, protected, cyclic peptide cyclo-Tyr(t-Bu)-Ser(t-Bu)-Lys(Boc)-Lys(Boc)-Phe.

cyclo-Tyr-Ser-Lys-Lys-Lys-Phe (2)

The deprotected cyclic peptide was synthesized following the Side Chain Deprotection procedure using 0.091 g of crude cyclo-Tyr(t-Bu)-Ser(t-Bu)-Lys(Boc)-Lys(Boc)-Phe (0.079 mmol, 1 equiv.), 430 μL of a mixed solution of TFA and CH₂Cl₂ (9:1 v/v, 0.4 M) and anisole (8 equiv.) to generate the free side chains. The reaction mixture was stirred overnight and monitored via LC/MS. Upon completion, the reaction mixture was worked up as described in the Side Chain Deprotection procedure and lyophilised to produce the crude cyclic peptide. The crude product was purified using HPLC to generate pure compound as a white solid (41%).

LC/MS (ESI) m/z: [M+H]+ C₃₃H₄₈N₇O₇+ called for 654.36; found 654.00.

¹H NMR (600 MHz, D₂O) δ 7.49-7.09 (m, 5H, Phe), 7.02 (d, J = 8.50 Hz, 2H, δH Tyr), 6.82 (d, J = 8.41 Hz, 2H, εH Tyr), 4.61-4.51 (m, 1H, αH, Phe), 4.50-4.37 (m, 1H, αH, Tyr), 4.37-4.29 (m, 1H, αH, Ser), 4.29-4.19 (m, 1H, αH, Lys), 4.19-3.99 (m, 1H, δH, Lys), 3.97-3.62 (m, 2H βCH₂, Ser), 3.34-3.20 (m, 2H, βCH₂, Phe), 3.20-3.05 (m, 2H, βCH₂, Tyr), 3.05-2.79 (m, 2H, γCH₂, Lys), 3.05-2.79 (m, 2H, εCH₂, Lys), 2.07-1.83 (m, 2H, βCH₂, Lys), 2.07-1.83 & 1.83-1.57 (m, 2H, βCH₂, Lys), 1.83-1.57 (m, 2H, δCH₂, Lys), 1.83-1.57 (m, 2H, δCH₂, Lys), 1.83-1.57 & 1.57-1.16 (m, 2H, γCH₂, Lys), 1.57-1.16 (m, 2H, γCH₂, Lys).
**Experimental Procedures for 3**

**Resin-O-Phe-Tyr(t-Bu)-NH₂**

Resin-O-Phe-Tyr(t-Bu)-NH₂ was synthesized following the *Coupling Reaction* procedure, using 0.7 g Resin-O-Phe-NH₂ (0.35 mmol, 1 equiv.), 0.32 g Fmoc-Tyr(t-Bu)-OH (0.7 mmol, 2 equiv.), 0.14 g HOBt (1.05 mmol, 3 equiv.), 0.33 mL DIC (2.1 mmol, 6 equiv.), and 1.16 mL of DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-NHFmoc. The Fmoc group was then removed following the *Fmoc Removal* procedure to afford Resin-O-Phe-Tyr(t-Bu)-NH₂.

**Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH₂**

Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH₂ was synthesized following the *Coupling Reaction* procedure, using Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH₂ from the previous reaction, 0.54 g Fmoc-Ser(t-Bu)-OH (0.7 mmol, 2 equiv.), 0.14 g HOBt (1.05 mmol, 3 equiv.), 0.33 mL DIC (2.1 mmol, 6 equiv.), and 1.16 mL of DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-NHFmoc. The Fmoc group was then removed following the *Fmoc Removal* procedure to afford Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH₂.

**Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-d-Asn(Trt)-NH₂**

Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-d-Asn(Trt)-NH₂ was synthesized following the *Coupling Reaction* procedure, using Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-d-Asn(Trt)-NH₂ from the previous reaction, 0.42 g Fmoc-d-Asn(Trt)-OH (0.7 mmol, 2 equiv.), 0.14 g HOBt (1.05 mmol, 3 equiv.), 0.33 mL DIC (2.1 mmol, 6 equiv.), and 1.16 mL of DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-d-Asn(Trt)-NHFmoc. The Fmoc group was then removed following the *Fmoc Removal* procedure to afford Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-d-Asn(Trt)-NH₂.

**Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-d-Asn(Trt)-Lys(Boc)-NH₂**

Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-d-Asn(Trt)-Lys(Boc)-NH₂ was synthesized following the *Coupling Reaction* procedure, using Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-d-Asn(Trt)-NH₂ from the previous reaction, 0.32 g Fmoc-Lys(Boc)-OH (0.7 mmol, 2 equiv.), 0.14 g HOBt (1.05 mmol, 3 equiv.), 0.33 mL DIC (2.1 mmol, 6 equiv.), and 1.16 mL of DMF to generate a concentration of 0.3 M. The coupling reaction was run overnight and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-d-Asn(Trt)-Lys(Boc)-NHFmoc. The Fmoc group was then removed following the *Fmoc Removal* procedure to afford Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-d-Asn(Trt)-Lys(Boc)-NH₂.

**HO-Phe-Tyr(t-Bu)-Ser(t-Bu)-d-Asn(Trt)-Lys(Boc)-NH₂**

The protected linear pentapeptide HO-Phe-Tyr(t-Bu)-Ser(t-Bu)-d-Asn(Trt)-Lys(Boc)-NH₂ was generated following the *Resin Cleavage of Linear Peptide* procedure. The linear peptide was cleaved from the resin using a mixed solution of 4 mL trifluoroethanol and 4 mL CH₂Cl₂. The resin containing solution was filtered and dried *in vacuo* to yield the protected linear pentapeptide as a pale yellow solid (290 mg, overall 63%).
Supporting Information

cyclo-Phe-Tyr(t-Bu)-Ser(t-Bu)-d-Asn(Trt)-Lys(Boc)

The protected cyclic peptide was synthesized following the *Macrocyclisation* procedure using 0.2 g linear peptide (0.18 mmol, 1 equiv.), 0.068 g HATU (0.18 mmol, 1 equiv.), 0.03 g TBTU (0.09 mmol, 0.5 equiv.), 0.025 g DMTMM (0.09 mmol, 0.5 equiv.), 0.25 mL DIPEA (1 mmol, 8.0 equiv.) in anhydrous CH$_2$Cl$_2$ (180 mL, 0.001 M). The reaction was then stirred for 4 hours and monitored via LC/MS. Upon completion, the reaction was worked up as described in the *Macrocyclisation* procedure and dried *in vacuo* to produce the crude, protected, cyclic peptide cyclo-Phe-Tyr(t-Bu)-Ser(t-Bu)-d-Asn(Trt)-Lys(Boc).

cyclo-Phe-Tyr-Ser-d-Asn-Lys (3)

The deprotected cyclic peptide was synthesized following the *Side Chain Deprotection* procedure using 0.11 g crude cyclo-Phe-Tyr(t-Bu)-Ser(t-Bu)-d-Asn(Trt)-Lys(Boc) (0.10 mmol, 1 equiv.), 800 µL of a mixed solution of TFA and CH$_2$Cl$_2$ (9:1 v/v) and 87 µL anisole (0.8 mmol, 8 equiv.) to generate the free side chains. The reaction mixture was stirred for 4 hours and monitored via LC/MS. Upon completion, the reaction mixture was worked up as described in the *Side Chain Deprotection* procedure and lyophilised to produce the crude cyclic peptide. The crude product was purified using HPLC to generate pure compound as a white solid (73%).

LC/MS (ESI) $m/z$: [M+H]$^+$ calculated for C$_{31}$H$_{42}$N$_7$O$_8$$^+$, 640.30; found, 640.30.

$^1$H NMR (600 MHz, D$_2$O): δ 7.30-7.17 (m, 5H, Phe), 7.03-7.01 (d, $J = 8.59$ Hz, 2H, γH Tyr), 6.74-6.72 (d, $J = 8.37$Hz, 2H, δH Tyr), 4.42-4.41 (t, $J = 6.8$ Hz, 1H, αH Phe), 4.29-4.26(t, $J = 8.23$ Hz, 1H, αH Asn), 4.20-4.18 (t, $J = 5.55$ Hz, 1H, αH Ser), 4.16-4.13 (t, 1H, αH Lys), 3.59-3.58 (d, $J = 5.67$, 2H, βH Ser), 3.09-3.08 (d, $J = 8.17$, 2H, βH Asn), 3.03-2.84 (m, 4H, βH Phe, βH Tyr), 2.73-2.58 (m, 2H, βH Lys), 1.77-1.69 (m, 2H, εH Lys), 1.61-1.55 (m, 2H, γH Lys), 1.20-1.15 (m, 2H, δH Lys).
Supporting Information

Experimental Procedures for 4

Resin-O-Phe-NH₂

The resin bound amino acid Resin-O-Phe-NH₂ was synthesized according to the Resin Loading procedure. A sample of 2-chlorotrityl chloride resin (1.01 g, 1.1 mmol/g loading, 1 equiv.) was placed in a reaction vessel and swelled with CH₂Cl₂ for 30 minutes then drained. To the resin was added 1.28 g Fmoc-Phe-OH (3.3 mmol, 3 equiv.) that was pre-dissolved in the minimum amount of DIPEA in CH₂Cl₂ (0.40 M). The reaction was shaken at room temperature for 4 hours. The reaction mixture was drained and washed according to the protocol to produce Resin-O-Phe-NHFmoc. A sample of resin was removed and the resin loading was determined to be 0.60 mmol/g. The Fmoc group was then removed following the Fmoc Removal procedure to produce Resin-O-Phe-NH₂.

Resin-O-Phe-Tyr(t-Bu)-NH₂

Resin-O-Phe-Tyr(t-Bu)-NH₂ was synthesized following the Coupling Reaction procedure, using 1.0 g Resin-O-Phe-NH₂ (0.60 mmol, 1 equiv.), 0.55 g Fmoc-Tyr(t-Bu)-OH (1.2 mmol, 2 equiv.), 0.18 g hydrated HOBt (1.2 mmol, 2 equiv.), 0.56 mL DIC (3.6 mmol, 6 equiv.), and 2 mL of DMF to generate a concentration of 0.3 M. The coupling reaction was run for 4 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Tyr(t-Bu)-NH₂.

Resin-O-Phe-Tyr(t-Bu)-Ala-NH₂

Resin-O-Phe-Tyr(t-Bu)-Ala-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-Tyr(t-Bu)-NH₂ from the previous reaction, 0.37 g Fmoc-Ala-OH (1.2 mmol, 2 equiv.), 0.18 g hydrated HOBt (1.2 mmol, 2 equiv.), 0.56 mL DIC (3.6 mmol, 6 equiv.), and 2 mL of DMF to generate a concentration of 0.3 M. The coupling reaction was run for 4 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-Ala-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Tyr(t-Bu)-Ala-NH₂.

Resin-O-Phe-Tyr(t-Bu)-Ala-Asn(Trt)-NH₂

Resin-O-Phe-Tyr(t-Bu)-Ala-Asn(Trt)-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-Tyr(t-Bu)-Ala-NH₂ from the previous reaction, 0.72 g Fmoc-Asn(Trt)-OH (1.2 mmol, 2 equiv.), 0.18 g hydrated HOBt (1.2 mmol, 2 equiv.), 0.56 mL DIC (3.6 mmol, 6 equiv.), and 2 mL of DMF to generate a concentration of 0.3 M. The coupling reaction was run for 4 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-Ala-Asn(Trt)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Tyr(t-Bu)-Ala-Asn(Trt)-NH₂.

Resin-O-Phe-Tyr(t-Bu)-Ala-Asn(Trt)-Lys(Boc)-NH₂

Resin-O-Phe-Tyr(t-Bu)-Ala-Asn(Trt)-Lys(Boc)-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-Tyr(t-Bu)-Ala-Asn(Trt)-NH₂ from the previous reaction, 0.56 g Fmoc-Lys(Boc)-OH (1.2 mmol, 2 equiv.), 0.18 g hydrated HOBt (1.2 mmol, 2 equiv.), 0.56 mL DIC (3.6 mmol, 6 equiv.), and 2 mL of DMF to generate a concentration of 0.3 M. The coupling reaction was run overnight and a negative ninhydrin test was used to confirm reaction
Supporting Information

completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-Ala-Asn(Trt)-Lys(Boc)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Ala-Lys(Boc)-NH₂.

**HO-Phe-Tyr(t-Bu)-Ala-Asn(Trt)-Lys(Boc)-NH₂**

The protected linear pentapeptide HO-Phe-Tyr(t-Bu)-Ala-Asn(Trt)-Lys(Boc)-NH₂ was generated following the Resin Cleavage of Linear Peptide procedure. The linear peptide was cleaved from the resin using a mixed solution of 7 mL trifluoroethanol and 7 mL CH₂Cl₂. The resin containing solution was filtered and dried in vacuo to yield the protected linear pentapeptide as a pale yellow solid (475 mg, overall 76%)

cyclo-Phe-Tyr(t-Bu)-Ala-Asn(Trt)-Lys(Boc)

The protected cyclic peptide was synthesized following the Macrocyclisation procedure using 0.25 g linear peptide (0.24 mmol, 1 equiv.), 0.091 g HATU (0.24 mmol, 1 equiv.), 0.039 g TBTU (0.12 mmol, 0.5 equiv.), 0.034 g DMTMM (0.12 mmol, 0.5 equiv.), 0.33 mL DIPEA (1.92 mmol, 8.0 equiv.) in anhydrous CH₂Cl₂ (240 mL, 0.001 M). The reaction was then stirred overnight and monitored via LC/MS. Upon completion, the reaction mixture was worked up as described in the Macrocyclisation procedure and dried in vacuo to produce the crude, protected, cyclic peptide cyclo-Phe-Tyr(t-Bu)-Ala-Asn(Trt)-Lys(Boc).

cyclo-Phe-Tyr-Ala-Asn-Lys (4)

The deprotected cyclic peptide was synthesized following the Side Chain Deprotection procedure using 0.18 g crude cyclo-Phe-Tyr(t-Bu)-Ala-Asn(Trt)-Lys(Boc) (0.18 mmol, 1 equiv.), 720 µL of a mixed solution of TFA and CH₂Cl₂ (9:1 v/v, 0.4 M) and 115 µL anisole (1 mmol, 6 equiv.) to generate the free side chains. The reaction mixture was stirred for 4 hours and monitored via LC/MS. Upon completion, the reaction mixture was worked up as described in the Side Chain Deprotection procedure and lyophilised to produce the crude cyclic peptide. The crude product was purified using HPLC to generate pure compound as a white solid (5%).

LC/MS (ESI) m/z: [M+H]+ calculated for C₃₁H₄₂N₇O₇⁺, 624.32; found 624.60.

¹H NMR (600 MHz, D₂O) δ 7.39-7.24 (m, 5H, Phe), 6.94-6.93 (d, J = 8.51 Hz, 2H, εH Tyr), 6.79-6.77 (m, 2H, δH Tyr), 4.69-4.67 (t, J = 7.23 Hz, 1H, βH Tyr), 4.62-4.60 (t, J = 6.22 Hz, 1H, βH Phe), 4.53-4.50 (t, J = 7.67 Hz, 1H, βH Asn), 4.23-4.17 (m, 1H, αLys), 4.23-4.17 (m, 1H, αH Ala), 3.15-3.00 (m, 2H, εH Lys), 2.99-2.93 (m, 2H, βH Asn), 2.97-2.88 (m, 2H, βH Tyr), 2.92-2.83 (m, 2H, βH Phe), 1.66-1.61 (m, 2H, βH Lys), 1.31-1.11 (m, 4H, γH, δH Lys), 1.23-1.21 (d, J = 7.26 Hz, 3H, βH Ala).
Experimental Procedures for 5

Resin-O-Phe-Tyr(t-Bu)-NH₂

A sample of commercially available 2-chlorotrityl resin pre-loaded with Fmoc-Phe-OH (0.6 g, 0.67 mmol, 1 equiv.) was placed in a reaction vessel and swelled with DMF for 30 minutes then drained. To the resin was added 0.76 g Fmoc-Tyr(t-Bu)-OH (1.67 mmol, 2.5 equiv.), 3.3 mL HOAt (2 mmol, 3 equiv.), 0.62 mL DIC (4 mmol, 6 equiv.), and 1.5 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Tyr(t-Bu)-NH₂.

Resin-O-Phe-Tyr(t-Bu)-Lys(Boc)-NH₂

Resin-O-Phe-Tyr(t-Bu)-Lys(Boc)-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-Tyr(t-Bu)-NH₂ from the previous reaction, 0.78 g Fmoc-Lys(Boc)-OH (1.67 mmol, 2.5 equiv.), 3.3 mL HOAt (2 mmol, 3 equiv.), 0.62 mL DIC (4 mmol, 6 equiv.), and 1.5 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-Lys(Boc)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Tyr(t-Bu)-Lys(Boc)-NH₂.

Resin-O-Phe-Tyr(t-Bu)-Lys(Boc)-Asn(Trt)-NH₂

Resin-O-Phe-Tyr(t-Bu)-Lys(Boc)-Asn(Trt)-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-Tyr(t-Bu)-Lys(Boc)-NH₂ from the previous reaction, 0.99 g Fmoc-Asn(Trt)-OH (1.67 mmol, 2.5 equiv.), 3.3 mL HOAt (2 mmol, 3 equiv.), 0.62 mL DIC (4 mmol, 6 equiv.), and 1.5 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-Lys(Boc)-Asn(Trt)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Tyr(t-Bu)-Lys(Boc)-Asn(Trt)-NH₂.

Resin-O-Phe-Tyr(t-Bu)-Lys(Boc)-Asn(Trt)-Lys(Boc)-NH₂

Resin-O-Phe-Tyr(t-Bu)-Lys(Boc)-Asn(Trt)-Lys(Boc)-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-Tyr(t-Bu)-Lys(Boc)-Asn(Trt)-NH₂ from the previous reaction, 0.78 g Fmoc-Lys(Boc)-OH (1.67 mmol, 2.5 equiv.), 3.3 mL HOAt (2 mmol, 3 equiv.), 0.62 mL DIC (4 mmol, 6 equiv.), and 1.5 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-Lys(Boc)-Asn(Trt)-Lys(Boc)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Tyr(t-Bu)-Lys(Boc)-Asn(Trt)-Lys(Boc)-NH₂.

HO-Phe-Tyr(t-Bu)-Lys(Boc)-Asn(Trt)-Lys(Boc)-NH₂

The protected linear pentapeptide HO-Phe-Tyr(t-Bu)-Lys(Boc)-Asn(Trt)-Lys(Boc)-NH₂ was generated following the Resin Cleavage of Linear Peptide procedure. The linear peptide was cleaved from the resin using a mixed solution of 5 mL trifluoroethanol and 5 mL CH₂Cl₂. The
Supporting Information

A resin containing solution was filtered and dried \textit{in vacuo} to yield the protected linear pentapeptide as a pale yellow solid (510 mg, overall 64%)

\textbf{cyclo-Phe-Tyr(t-Bu)-Lys(Boc)-Asn(Trt)-Lys(Boc)}

The protected cyclic peptide was synthesized following the \textit{Macrocyclisation} procedure using 0.15 g linear peptide (0.12 mmol, 1 equiv.), 0.048 g HATU (0.12 mmol, 1 equiv.), 0.02 g TBTU (0.063 mmol, 0.5 equiv.), 0.017 g DMTMM (0.063 mmol, 0.5 equiv.), 0.13 mL DIPEA (0.96 mmol, 8.0 equiv.) in anhydrous CH$_2$Cl$_2$ (125 mL, 0.001 M). The reaction was then stirred for 4 hours and monitored \textit{via} LC/MS. Upon completion, the reaction mixture was worked up as described in the \textit{Macrocyclisation} procedure and dried \textit{in vacuo} to produce the crude, protected, cyclic peptide \textit{cyclo-Phe-Tyr(t-Bu)-Lys(Boc)-Asn(Trt)-Lys(Boc)}.

\textbf{cyclo-Phe-Tyr-Lys-Asn-Lys (5)}

The deprotected cyclic peptide was synthesized following the \textit{Side Chain Deprotection} procedure using 0.08 g crude \textit{cyclo-Phe-Tyr(t-Bu)-Lys(Boc)-Asn(Trt)-Lys(Boc)} (0.085 mmol, 1 equiv.), 240 µL of a mixed solution of TFA and CH$_2$Cl$_2$ (9:1 v/v) and 74 µL anisole (0.68 mmol, 8 equiv.) to generate the free side chains. The reaction mixture was stirred for 4 hours and monitored \textit{via} LC/MS. Upon completion, the reaction mixture was worked up as described in the \textit{Side Chain Deprotection} procedure and lyophilised to produce the crude cyclic peptide. The crude product was purified using HPLC to generate pure compound as a white solid (14%).

\textbf{LC/MS (ESI)} \textit{m/z}: [M+H]$^+$ calculated for C$_{34}$H$_{49}$N$_8$O$_7^+$, 681.37; found 681.40 and [M+2H]$^{2+}$ 341.00

$^1$H NMR (600 MHz, D$_2$O): δ 7.42-6.97 (m, 5H, Phe), 6.79-6.55 (m, 4H, γH, δH Tyr), 4.61-4.51 (m, 1H, αH Phe), 4.58-4.53 (m, 2H, αH Tyr, αH Asn), 4.49-4.33 (m, 2H, αH Lys), 4.15-3.98 (m, 2H, βH Ser), 2.93-2.81 (m, 2H, βH Phe), 2.75-2.65 (m, 2H, βH Tyr), 2.88-2.73 (m, 2H, βH Asn), 2.75-2.65 (m, 2H, βH Tyr), 1.67-1.43 (m, 4H, εH Lys), 1.61-1.40 (m, 4H, βH Lys), 1.28-1.19 (m, 4H, γH Lys), 1.12-1.05 (m, 4H, δH Lys).
Supporting Information

Experimental Procedures for 6

Resin-O-Phe-Tyr(t-Bu)-NH$_2$

Resin-O-Phe-Tyr(t-Bu)-NH$_2$ was synthesized following the Coupling Reaction procedure, using 1 g Resin-O-Phe-NH$_2$ (0.6 mmol, 1 equiv.), 0.55 g Fmoc-Tyr(t-Bu)-OH (1.2 mmol, 2 equiv.), 0.24 g HOBt (1.8 mmol, 3 equiv.), 0.56 mL DIC (3.6 mmol, 6 equiv.), and 2 mL of DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Tyr(t-Bu)-NH$_2$.

Resin-O-Phe-Tyr(t-Bu)-d-Ser(t-Bu)-NH$_2$

Resin-O-Phe-Tyr(t-Bu)-d-Ser(t-Bu)-NH$_2$ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-Tyr(t-Bu)-NH$_2$ from the previous reaction, 0.46 g Fmoc- D-Ser(t-Bu)-OH (1.2 mmol, 2 equiv.), 0.24 g HOBt (1.8 mmol, 3 equiv.), 0.56 mL DIC (3.6 mmol, 6 equiv.), and 2 mL of DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-d-Ser(t-Bu)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Tyr(t-Bu)-d-Ser(t-Bu)-NH$_2$.

Resin-O-Phe-Tyr(t-Bu)-d-Ser(t-Bu)-Asn(Trt)-NH$_2$

Resin-O-Phe-Tyr(t-Bu)-d-Ser(t-Bu)-Asn(Trt)-NH$_2$ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-Tyr(t-Bu)-d-Ser(t-Bu)-NH$_2$ from the previous reaction, 0.72 g Fmoc-Asn(Trt)-OH (1.2 mmol, 2 equiv.), 0.24 g HOBt (1.8 mmol, 3 equiv.), 0.56 mL DIC (3.6 mmol, 6 equiv.), and 2 mL of DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-d-Ser(t-Bu)-Asn(Trt)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Tyr(t-Bu)-d-Ser(t-Bu)-Asn(Trt)-NH$_2$.

Resin-O-Phe-Tyr(t-Bu)-d-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH$_2$

Resin-O-Phe-Tyr(t-Bu)-d-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH$_2$ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-Tyr(t-Bu)-d-Ser(t-Bu)-Asn(Trt)-NH$_2$ from the previous reaction, 0.56 g Fmoc-Lys(Boc)-OH (1.2 mmol, 2 equiv.), 0.24 g HOBt (1.8 mmol, 3 equiv.), 0.56 mL DIC (3.6 mmol, 6 equiv.), and 2 mL of DMF to generate a concentration of 0.3 M. The coupling reaction was run overnight and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-d-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Tyr(t-Bu)-d-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH$_2$.

HO-Phe-Tyr(t-Bu)-d-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH$_2$

The protected linear pentapeptide HO-Phe-Tyr(t-Bu)-d-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH$_2$ was generated following the Resin Cleavage of Linear Peptide procedure. The linear peptide was cleaved from the resin using a mixed solution of 8 mL trifluoroethanol and 8 mL CH$_2$Cl$_2$. The resin containing solution was filtered and dried in vacuo to yield the protected linear pentapeptide as a white solid (510 mg, overall 76%)
**Supporting Information**

**cyclo-Phe- Tyr(t-Bu)-d-Ser(t-Bu)-Asn(Trt)-Lys(Boc)**

The protected cyclic peptide was synthesized following the *Macrocyclisation* procedure using 0.2 g linear peptide (0.18 mmol, 1 equiv.), 0.068 g HATU (0.18 mmol, 1 equiv.), 0.03 g TBTU (0.09 mmol, 0.5 equiv.), 0.025 g DMTMM (0.09 mmol, 0.5 equiv.), 0.25 mL DIPEA (1 mmol, 8.0 equiv.) in anhydrous CH$_2$Cl$_2$ (180 mL, 0.001 M). The reaction was then stirred for 4 hours and monitored via LC/MS. Upon completion, the reaction was worked up as described in the *Macrocyclisation* procedure and dried *in vacuo* to produce the crude, protected, cyclic peptide cyclo-Phe-Tyr(t-Bu)-d-Ser(t-Bu)-Asn(Trt)-Lys(Boc).

**cyclo-Phe-Tyr-d-Ser-Asn-Lys (6)**

The deprotected cyclic peptide was synthesized following the *Side Chain Deprotection* procedure using 0.25 g crude cyclo-Phe-Tyr(t-Bu)-d-Ser(t-Bu)-Asn(Trt)-Lys(Boc) (0.23 mmol, 1 equiv.), 1800 µL of a mixed solution of TFA and CH$_2$Cl$_2$ (9:1 v/v) and 199 µL anisole (1.8 mmol, 8 equiv.) to generate the free side chains. The reaction mixture was stirred for 4 hours and monitored via LC/MS. Upon completion, the reaction mixture was worked up as described in the *Side Chain Deprotection* procedure and lyophilised to produce the crude cyclic peptide. The crude product was purified using HPLC to generate pure compound as a white solid (51%).

LC/MS (ESI) $m/z$: [M+H]$^+$ calculated for C$_{31}$H$_{42}$N$_7$O$_8^{+}$, 640.30; found, 640.30.

$^1$H NMR (600 MHz, D$_2$O): δ 7.34-7.16 (m, 5H, Phe), 6.89-6.88 (d, $J = 8.59$ Hz, 2H, γH Tyr), 6.72-6.71 (d, $J = 8.59$ Hz, 2H, δH Tyr), 4.55-4.49 (m, 2H, αH Phe, αH Tyr), 4.40-4.39 (t, $J = 8.50$ Hz, 1H, αH Asn), 4.21-4.19 (t, $J = 7.95$, 1H, αH Ser), 4.04-4.02 (t, $J = 7.60$, 1H, αH Lys), 3.67-3.62 (m, 2H, βH Ser), 2.99-2.72 (m, 6H, βH Phe, βH Tyr, βH Asn), 2.67-2.64 (m, 2H, βH Lys), 1.72-1.52 (m, 4H, εH Lys, γH Lys), 1.27-1.13 (m, 2H, δH Lys).
Supporting Information

Experimental Procedures for 7

Resin-O-Ala-NH₂

The resin bound amino acid Resin-O-Ala-NH₂ was synthesized according to the Resin Loading procedure. A sample of 2-chlorotiryl chloride resin (0.93 g, 1.02 mmol/g loading, 1 equiv.) was placed in a reaction vessel and swelled with CH₂Cl₂ for 30 minutes then drained. To the resin was added 0.99 g Fmoc-Ala-OH (3.19 mmol, 3 equiv.) that was pre-dissolved in the minimum amount of DIPEA in CH₂Cl₂ (0.40 M). The reaction was shaken at room temperature overnight. The reaction mixture was drained and washed according to the protocol to produce Resin-O-Ala-NH₂. A sample of resin was removed and the resin loading was determined to be 0.57 mmol/g. The Fmoc group was then removed following the Fmoc Removal procedure to produce Resin-O-Ala-NH₂.

Resin-O-Ala-Ser(t-Bu)-NH₂

Resin-O-Ala-Ser(t-Bu)-NH₂ was synthesized following the Coupling Reaction procedure, using 1.0 g Resin-O-Ala-NH₂ (0.57 mmol, 1 equiv.), 0.84 g Fmoc-Ser(t-Bu)-OH (2.18 mmol, 2 equiv.), 0.37 g hydrated HOBT (2.39 mmol, 2 equiv.), 1.02 mL DIC (6.59 mmol, 6 equiv.), and 1.9 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run for 48 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Ala-Ser(t-Bu)-NH₂. The Fmoc group was then removed following the Fmoc Removal procedure to produce Resin-O-Ala-Ser(t-Bu)-NH₂.

Resin-O-Ala-Ser(t-Bu)-Asn(Trt)-NH₂

Resin-O-Ala-Ser(t-Bu)-Asn(Trt)-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Ala-Ser(t-Bu)-NH₂ from the previous reaction, 0.67 g Fmoc-Asn(Trt)-OH (1.127 mmol, 2 equiv.), 0.18 g hydrated HOBT (1.16 mmol, 2 equiv.), 0.60 mL DIC (3.87 mmol, 6 equiv.), and 1.9 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run overnight and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Ala-Ser(t-Bu)-Asn(Trt)-NH₂. The Fmoc group was then removed following the Fmoc Removal procedure to produce Resin-O-Ala-Ser(t-Bu)-Asn(Trt)-NH₂.

Resin-O-Ala-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH₂

Resin-O-Ala-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Ala-Ser(t-Bu)-Asn(Trt)-NH₂ from the previous reaction, 0.53 g Fmoc-Lys(Boc)-OH (1.13 mmol, 2 equiv.), 0.17 g hydrated HOBT (1.08 mmol, 2 equiv.), 0.53 mL DIC (3.42 mmol, 6 equiv.), and 1.9 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run overnight and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Ala-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH₂. The Fmoc group was then removed following the Fmoc Removal procedure to produce Resin-O-Ala-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH₂.

Resin-O-Ala-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-Phe-NH₂

Resin-O-Ala-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-Phe-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Ala-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH₂ from the previous reaction, 0.49 g Fmoc-Phe-OH (1.26 mmol, 3 equiv.), 0.17 g hydrated HOBT (1.13 mmol, 2 equiv.), 0.84 g Fmoc-Ser(t-Bu)-OH (2.18 mmol, 2 equiv.), 0.37 g hydrated HOBT (2.39 mmol, 2 equiv.), 1.02 mL DIC (6.59 mmol, 6 equiv.), and 1.9 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run overnight and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Ala-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-Phe-NH₂. The Fmoc group was then removed following the Fmoc Removal procedure to produce Resin-O-Ala-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-Phe-NH₂.
Supporting Information

equiv.), 0.60 mL DIC (3.87 mmol, 6 equiv.), and 1.9 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run overnight and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Ala-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-Phe-NH\textsubscript{2}. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Ala-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-Phe-NH\textsubscript{2}.

**HO-Ala-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-Phe-NH\textsubscript{2}**

The protected linear pentapeptide HO-Ala-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-Phe-NH\textsubscript{2} was generated following the Resin Cleavage of Linear Peptide procedure. The linear peptide was cleaved from the resin using a mixed solution of 6.6 mL trifluoroethanol and 6.6 mL CH\textsubscript{2}Cl\textsubscript{2}. The resin containing solution was filtered and dried in vacuo to yield the protected linear pentapeptide as a pale yellow solid (353 mg, overall 63%).

cyclo-Ala-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-Phe

The protected cyclic peptide was synthesized following the Macrocyclisation procedure using 0.25 g linear peptide (0.27 mmol, 1 equiv.), 0.10 g HATU (0.27 mmol, 1 equiv.), 0.044 g TBTU (0.14 mmol, 0.5 equiv.), 0.037 g DMTMM (0.13 mmol, 0.5 equiv.), 0.38 mL DIPEA (2.2 mmol, 8.0 equiv.) in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (271 mL, 0.001 M). The reaction was then stirred overnight and monitored via LC/MS. Upon completion, the reaction mixture was worked up as described in the Macrocyclisation procedure and dried in vacuo to produce the crude, protected, cyclic peptide cyclo-Ala-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-Phe.

cyclo-Ala-Ser-Asn-Lys-Phe (7)

The deprotected cyclic peptide was synthesized following the Side Chain Deprotection procedure using 0.04 g of crude cyclo-Ala-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-Phe (0.042 mmol, 1 equiv.), 100 \textmu L of a mixed solution of TFA and CH\textsubscript{2}Cl\textsubscript{2} (9:1 v/v, 0.4 M) and anisole (8 equiv.) to generate the free side chains. The reaction mixture was stirred overnight and monitored via LC/MS. Upon completion, the reaction mixture was worked up as described in the Side Chain Deprotection procedure and lyophilised to produce the crude cyclic peptide. The crude product was purified using HPLC to generate pure compound as a white solid (1%).

LC/MS (ESI) m/z: [M+H]\textsuperscript{+} calculated for C\textsubscript{25}H\textsubscript{38}N\textsubscript{7}O\textsubscript{7}, 548.29; found 548.57.

\textsuperscript{1}H NMR (600 MHz, D\textsubscript{2}O) δ 7.42-7.25 (m, 5H, Phe), 4.62 (m, 1H, αH Phe), 4.46-4.42 (m, 2H, αH Ser & Asn), 4.37 (m, 1H, αH Lys), 4.33 (m, 1H, αH Ala), 3.82 (m, 2H, βCH\textsubscript{2} Ser), 3.00 (m, 4H, βCH\textsubscript{2} Phe, εCH\textsubscript{2} Lys), 2.79-2.66 (m, 2H, βCH\textsubscript{2} Asn), 1.82 (m, 2H, βCH\textsubscript{2} Lys), 1.71 (m, 2H, δCH\textsubscript{2} Lys), 1.40 (m, 2H, γCH\textsubscript{2} Lys), 1.30 (m, 3H, CH\textsubscript{3} Ala).

S23
Experimental Procedures for 8

Resin-O-Phe-Lys(Boc)-NH₂

A sample of commercially available 2-chlorotrityl resin pre-loaded with Fmoc-Phe-OH (0.64 g, 0.64 mmol, 1 equiv.) was placed in a reaction vessel and swelled with DMF for 30 minutes then drained. To the resin was added 0.75 g Fmoc-Lys(Boc)-OH (1.67 mmol, 2.5 equiv.), 3.2 mL HOAt (1.9 mmol, 3 equiv.), 0.6 mL DIC (3.8 mmol, 6 equiv.), and 1.3 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Lys(Boc)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Lys(Boc)-NH₂.

Resin-O-Phe-Lys(Boc)-Ser(t-Bu)-NH₂

Resin-O-Phe-Lys(Boc)-Ser(t-Bu)-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-Lys(Boc)-NH₂ from the previous reaction, 0.61 g Fmoc-Ser(t-Bu)-OH (1.67 mmol, 2.5 equiv.), 3.2 mL HOAt (2 mmol, 3 equiv.), 0.6 mL DIC (3.8 mmol, 6 equiv.), and 1.3 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Lys(Boc)-Ser(t-Bu)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Lys(Boc)-Ser(t-Bu)-NH₂.

Resin-O-Phe-Lys(Boc)-Ser(t-Bu)-Asn(Trt)-NH₂

Resin-O-Phe-Lys(Boc)-Ser(t-Bu)-Asn(Trt)-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-Lys(Boc)-Ser(t-Bu)-NH₂ from the previous reaction, 0.96 g Fmoc-Asn(Trt)-OH (1.67 mmol, 2.5 equiv.), 3.2 mL HOAt (2 mmol, 3 equiv.), 0.6 mL DIC (3.8 mmol, 6 equiv.), and 1.3 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Lys(Boc)-Ser(t-Bu)-Asn(Trt)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Lys(Boc)-Ser(t-Bu)-Asn(Trt)-NH₂.

Resin-O-Phe-Lys(Boc)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH₂

Resin-O-Phe-Lys(Boc)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-Lys(Boc)-Ser(t-Bu)-Asn(Trt)-NH₂ from the previous reaction, 0.75 g Fmoc-Lys(Boc)-OH (1.67 mmol, 2.5 equiv.), 3.2 mL HOAt (2 mmol, 3 equiv.), 0.6 mL DIC (3.8 mmol, 6 equiv.), and 1.3 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run overnight and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Lys(Boc)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Lys(Boc)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH₂.

HO-Phe-Lys(Boc)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH₂

The protected linear pentapeptide HO-Phe-Lys(Boc)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH₂ was generated following the Resin Cleavage of Linear Peptide procedure. The linear peptide was cleaved from the resin using a mixed solution of 5 mL trifluoroethanol and 5 mL CH₂Cl₂. The
resin containing solution was filtered and dried in vacuo to yield the protected linear pentapeptide as a pale yellow solid (490 mg, overall 68%)

**cyclo-Phe-Lys(Boc)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)**

The protected cyclic peptide was synthesized following the *Macrocyclisation* procedure using 0.15 g linear peptide (0.13 mmol, 1 equiv.), 0.05 g HATU (0.13 mmol, 1 equiv.), 0.02 g TBTU (0.066 mmol, 0.5 equiv.), 0.019 g DMTMM (0.066 mmol, 0.5 equiv.), 0.13 mL DIPEA (0.1 mmol, 8.0 equiv.) in anhydrous CH₂Cl₂ (134 mL, 0.001 M). The reaction was then stirred for 4 hours and monitored via LC/MS. Upon completion, the reaction mixture was worked up as described in the *Macrocyclisation* procedure and dried in vacuo to produce the crude, protected, cyclic peptide *cyclo*-Phe-Lys(Boc)-Ser(t-Bu)-Asn(Trt)-Lys(Boc).

**cyclo-Phe-Lys-Ser-Asn-Lys (8)**

The deprotected cyclic peptide was synthesized following the *Side Chain Deprotection* procedure using 0.077 g crude *cyclo*-Phe-Lys(Boc)-Ser(t-Bu)-Asn(Trt)-Lys(Boc) (0.09 mmol, 1 equiv.), 360 µL of a mixed solution of TFA and CH₂Cl₂ (9:1 v/v) and 79 µL anisole (0.73 mmol, 8 equiv.) to generate the free side chains. The reaction mixture was stirred for 4 hours and monitored via LC/MS. Upon completion, the reaction mixture was worked up as described in the *Side Chain Deprotection* procedure and lyophilised to produce the crude cyclic peptide. The crude product was purified using HPLC to generate pure compound 6 as a white solid (18%).

LC/MS (ESI) m/z: [M+H]⁺ calculated for C₂₈H₄₅N₈O₇⁺, 605.34; found 605.65 and [M+2H]²⁺ 303.00

¹H NMR (600 MHz, D₂O): δ 7.34-7.17 (m, 5H, Phe), 4.70-4.65 (m, 1H, αH Phe), 4.60-4.55 (m, 1H, αH Ser), 4.35-4.28 (m, 1H, αH Asn), 4.20-4.08 (m, 2H, αH Lys), 3.92-3.76 (m, 2H, βH Ser), 3.20-3.08 (m, 2H, βH Phe), 2.95-2.79 (m, 2H, βH Asn), 2.88-2.80 (m, 4H, εH Lys), 1.61-1.40 (m, 4H, βH Lys), 1.66-1.45 (m, 4H, γH Lys), 1.42-1.09 (m, 4H, δH Lys).
Experimental Procedures for 9

Resin-O-Phe-d-Tyr(t-Bu)-NH₂

Resin-O-Phe-d-Tyr(t-Bu)-NH₂ was synthesized following the Coupling Reaction procedure, using 1.4 g Resin-O-Phe-NH₂ (0.88 mmol, 1 equiv.), 0.81 g Fmoc-d-Tyr(t-Bu)-OH (1.8 mmol, 2 equiv.), 0.36 g HOBT (2.65 mmol, 3 equiv.), 0.82 mL DIC (5.3 mmol, 6 equiv.), and 2.94 mL of DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-d-Tyr(t-Bu)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-d-Tyr(t-Bu)-NH₂.

Resin-O-Phe-d-Tyr(t-Bu)-Ser(t-Bu)-NH₂

Resin-O-Phe-d-Tyr(t-Bu)-Ser(t-Bu)-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-d-Tyr(t-Bu)-Ser(t-Bu)-NH₂ from the previous reaction, 0.68 g Fmoc-Ser(t-Bu)-OH (1.8 mmol, 2 equiv.), 0.36 g HOBT (2.65 mmol, 3 equiv.), 0.82 mL DIC (5.3 mmol, 6 equiv.), and 2.94 mL of DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-d-Tyr(t-Bu)-Ser(t-Bu)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-d-Tyr(t-Bu)-Ser(t-Bu)-NH₂.

Resin-O-Phe-d-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-NH₂

Resin-O-Phe-d-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-d-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-NH₂ from the previous reaction, 1.05 g Fmoc-Asn(Trt)-OH (1.8 mmol, 2 equiv.), 0.36 g HOBT (2.65 mmol, 3 equiv.), 0.82 mL DIC (5.3 mmol, 6 equiv.), and 2.94 mL of DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-d-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-d-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-NH₂.

Resin-O-Phe-d-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH₂

Resin-O-Phe-d-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-d-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH₂ from the previous reaction, 0.83 g Fmoc-Lys(Boc)-OH (1.8 mmol, 2 equiv.), 0.36 g HOBT (2.65 mmol, 3 equiv.), 0.82 mL DIC (5.3 mmol, 6 equiv.), and 2.94 mL of DMF to generate a concentration of 0.3 M. The coupling reaction was run overnight and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-d-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-d-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH₂.

HO-Phe-d-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH₂

The protected linear pentapeptide HO-Phe-d-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH₂ was generated following the Resin Cleavage of Linear Peptide procedure. The linear peptide was cleaved from the resin using a mixed solution of 7 mL trifluoroethanol and 7 mL CH₂Cl₂. The resin containing solution was filtered and dried in vacuo to yield the protected linear pentapeptide as a white solid (746 mg, overall 86%)
Supporting Information

cyclo-Phe-ð-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)

The protected cyclic peptide was synthesized following the Macrocyclisation procedure using 0.2 g linear peptide (0.18 mmol, 1 equiv.), 0.068 g HATU (0.18 mmol, 1 equiv.), 0.03 g TBTU (0.09 mmol, 0.5 equiv.), 0.025 g DMTMM (0.09 mmol, 0.5 equiv.), 0.25 mL DIPEA (1 mmol, 8.0 equiv.) in anhydrous CH₂Cl₂ (180 mL, 0.001 M). The reaction was then stirred for 4 hours and monitored via LC/MS. Upon completion, the reaction was worked up as described in the Macrocyclisation procedure and dried in vacuo to produce the crude, protected, cyclic peptide cyclo-Phe-ð-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc).

cyclo-Phe-ð-Tyr-Ser-Asn-Lys (9)

The deprotected cyclic peptide was synthesized following the Side Chain Deprotection procedure using 0.12 g crude cyclo-Phe-ð-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc) (0.11 mmol, 1 equiv.), 900 µL of a mixed solution of TFA and CH₂Cl₂ (9:1 v/v) and 95 µL anisole (0.8 mmol, 8 equiv.) to generate the free side chains. The reaction mixture was stirred for 4 hours and monitored via LC/MS. Upon completion, the reaction mixture was worked up as described in the Side Chain Deprotection procedure and lyophilised to produce the crude cyclic peptide. The crude product was purified using HPLC to generate pure compound as a white solid (61%).

LC/MS (ESI) m/z: [M+H]⁺ calculated for C₃₁H₄₂N₇O₈⁺, 640.30; found, 640.30.

¹H NMR (600 MHz, D₂O): δ 7.25-7.97 (m, 5H, Phe), 6.93-6.92 (d, J = 8.53 Hz, 2H, γH Tyr), 6.64-6.63 (d, J = 8.51 Hz, 2H, δH Tyr), 4.51-4.22 (m, 4H, αH Phe, αH Tyr, αH Ser, αH Asn), 3.76-3.67 (m, 2H, βH Ser), 2.94-2.71 (m, 8H, βH Phe, βH Tyr, βH Asn, βH Lys), 1.73-1.42 (m, 4H, εH Lys, γH Lys), 1.28-1.18 (m, 2H, δH Lys).
Experimental Procedures for 10

Resin-O-Ala-NH₂

The resin bound amino acid Resin-O-Ala-NH₂ was synthesized according to the Resin Loading procedure. A sample of 2-chlorotrtiy chloride resin (1.0 g, 1.1 mmol/g loading, 1 equiv.) was placed in a reaction vessel and swelled with CH₂Cl₂ for 30 minutes then drained. To the resin was added 1.03 g Fmoc-Ala-OH (3.3 mmol, 3 equiv.) that was pre-dissolved in the minimum amount of DIPEA in CH₂Cl₂ (0.40 M). The reaction was shaken at room temperature for 4 hours. The reaction mixture was drained and washed according to the protocol to produce Resin-O-Ala-NH₂. A sample of resin was removed and the resin loading was determined to be 0.79 mmol/g. The Fmoc group was then removed following the Fmoc Removal procedure to produce Resin-O-Ala-NH₂.

Resin-O-Ala-Tyr(t-Bu)-NH₂

Resin-O-Ala-Tyr(t-Bu)-NH₂ was synthesized following the Coupling Reaction procedure, using 1.0 g Resin-O-Ala-NH₂ (0.79 mmol, 1 equiv.), 0.34 g Fmoc-Tyr(t-Bu)-OH (1.58 mmol, 2 equiv.), 2.6 mL HOAt (1.58 mmol, 2 equiv.), 0.68 mL DIC (4.74 mmol, 6 equiv.), and 2.6 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run overnight and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Ala-Ser(t-Bu)-NH₂. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Ala-Tyr(t-Bu)-NH₂.

Resin-O-Ala-Tyr(t-Bu)-Ser(t-Bu)-NH₂

Resin-O-Ala-Tyr(t-Bu)-Ser(t-Bu)-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Ala-Tyr(t-Bu)-NH₂ from the previous reaction, 0.9 g Fmoc-Ser(t-Bu)-OH (1.58 mmol, 2 equiv.), 2.6 mL HOAt (1.58 mmol, 2 equiv.), 0.68 mL DIC (4.74 mmol, 6 equiv.), and 2.6 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run for 4 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Ala-Tyr(t-Bu)-Ser(t-Bu)-NH₂. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Ala-Tyr(t-Bu)-Ser(t-Bu)-NH₂.

Resin-O-Ala-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-NH₂

Resin-O-Ala-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Ala-Tyr(t-Bu)-Ser(t-Bu)-NH₂ from the previous reaction, 0.94 g Fmoc-Asn(Trt)-OH (1.58 mmol, 2 equiv.), 2.6 mL HOAt (1.58 mmol, 2 equiv.), 0.68 mL DIC (4.74 mmol, 6 equiv.), and 2.6 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run for 4 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Ala-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-NH₂. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Ala-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-NH₂.

Resin-O-Ala-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH₂

Resin-O-Ala-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Ala-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-NH₂ from the previous reaction, 0.70 g Fmoc-Lys(Boc)-OH (1.58 mmol, 2 equiv.), 2.6 mL HOAt (1.58 mmol, 2 equiv.), 0.68 mL DIC (4.74 mmol, 6 equiv.), and 2.6 mL DMF to generate a concentration of 0.3 M. The
Supporting Information

coupling reaction was run for 4 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Ala-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Ala-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH₂.

**HO-Ala-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH₂**

The protected linear pentapeptide HO-Ala-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH₂ was generated following the Resin Cleavage of Linear Peptide procedure. The linear peptide was cleaved from the resin using a mixed solution of 8.5 mL trifluoroethanol and 8.5 mL CH₂Cl₂. The resin containing solution was filtered and dried in vacuo to yield the protected linear pentapeptide as a pale yellow solid (690 mg, overall 72%).

**cyclo-Ala-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)**

The protected cyclic peptide was synthesized following the Macrocyclisation procedure using 0.3 g linear peptide (0.25 mmol, 1 equiv.), 0.09 g HATU (0.25 mmol, 1 equiv.), 0.06 g TBTU (0.2 mmol, 0.8 equiv.), 0.05 g DMTMM (0.2 mmol, 0.8 equiv.), 0.34 mL DIPEA (2.2 mmol, 8.0 equiv.) in anhydrous CH₂Cl₂ (245 mL, 0.001 M). The reaction was then stirred overnight and monitored via LC/MS. Upon completion, the reaction mixture was worked up as described in the Macrocyclisation procedure and dried in vacuo to produce the crude, protected, cyclic peptide cyclo-Ala-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc).

**cyclo-Ala-Tyr-Ser-Asn-Lys (10)**

The deprotected cyclic peptide was synthesized following the Side Chain Deprotection procedure using 0.238 g of crude cyclo-Ala-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc) (0.20 mmol, 1 equiv.), 1.52 mL of a mixed solution of TFA and CH₂Cl₂ (1:1 v/v) and 170 µL anisole (1.58 mmol, 8 equiv.) to generate the free side chains. The reaction mixture was stirred overnight and monitored via LC/MS. Upon completion, the reaction mixture was worked up as described in the Side Chain Deprotection procedure and lyophilised to produce the crude cyclic peptide. The crude product was purified using HPLC to generate pure compound as a white solid (29%).

LC/MS (ESI) m/z: [M+H]+ calculated for C₂₅H₃₈N₇O₈⁺, 564.28; found 564.70.

¹H NMR (600 MHz, D₂O) δ 7.13-7.04 (m, 2H, δH Tyr), 6.82-6.68 (m, 2H, εH Tyr), 4.65-4.56 (t, J = 6.74 Hz, 1H, αH Asn), 4.54-4.37 (m, 1H, εH Tyr), 4.35-4.21 (m, 2H, δH Ser), 4.21-3.97 (m, 2H, δH Lys & εH Lys & δH Ala), 3.77-3.59 (m, 2H, βCH₂ Ser), 3.15-2.56 (m, 6H, βCH₂ Asn & βCH₂ Tyr & εCH₂ Lys), 1.83-1.53 (m, 4H, βCH₂ Lys & δCH₂ Lys), 1.46- 0.98 (m, 5H, γH Lys & CH₃ Ala)
Experimental Procedures for 11

Resin-O-Lys(Boc)-NH₂

The resin bound amino acid Resin-O-Lys(Boc)-NH₂ was synthesized according to the Resin Loading procedure. A sample of 2-chlorotrityl chloride resin (1.0 g, 1.1 mmol/g loading, 1 equiv.) was placed in a reaction vessel and swelled with CH₂Cl₂ for 30 minutes then drained. To the resin was added 1.06 g Fmoc-Lys(Boc)-OH (3.3 mmol, 3 equiv.) that was pre-dissolved in the minimum amount of DIPEA in CH₂Cl₂ (0.40 M). The reaction was shaken at room temperature for 4 hours. The reaction mixture was drained and washed according to the protocol to produce Resin-O-Lys(Boc)-NHFmoc. A sample of resin was removed and the resin loading was determined to be 0.75 mmol/g. The Fmoc group was then removed following the Fmoc Removal procedure to produce Resin-O-Lys(Boc)-NH₂.

Resin-O-Lys(Boc)-Tyr(t-Bu)-NH₂

Resin-O-Lys(Boc)-Tyr(t-Bu)-NH₂ was synthesized following the Coupling Reaction procedure, using 1.0 g Resin-O-Lys(Boc)-NH₂ (0.79 mmol, 1 equiv.), 0.69 g Fmoc-Tyr(t-Bu)-OH (1.51 mmol, 2 equiv.), 3.8 mL HOAt (2.3 mmol, 3 equiv.), 0.7 mL DIC (4.5 mmol, 6 equiv.), and 1.6 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Lys(Boc)-Tyr(t-Bu)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Lys(Boc)-Tyr(t-Bu)-NH₂.

Resin-O-Lys(Boc)-Tyr(t-Bu)-Ser(t-Bu)-NH₂

Resin-O-Lys(Boc)-Tyr(t-Bu)-Ser(t-Bu)-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Lys(Boc)-Tyr(t-Bu)-NH₂ from the previous reaction, 0.58 g Fmoc-Ser(t-Bu)-OH (1.51 mmol, 2 equiv.), 3.8 mL HOAt (2.3 mmol, 3 equiv.), 0.7 mL DIC (4.5 mmol, 6 equiv.), and 1.6 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Lys(Boc)-Tyr(t-Bu)-Ser(t-Bu)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Lys(Boc)-Tyr(t-Bu)-Ser(t-Bu)-NH₂.

Resin-O-Lys(Boc)-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-NH₂

Resin-O-Lys(Boc)-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Lys(Boc)-Tyr(t-Bu)-Ser(t-Bu)-NH₂ from the previous reaction, 0.90 g Fmoc-Asn(Trt)-OH (1.51 mmol, 2 equiv.), 3.8 mL HOAt (2.3 mmol, 3 equiv.), 0.7 mL DIC (4.5 mmol, 6 equiv.), and 1.6 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Lys(Boc)-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Lys(Boc)-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-NH₂.

Resin-O-Lys(Boc)-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH₂

Resin-O-Lys(Boc)-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Lys(Boc)-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-NH₂ from the previous reaction, 0.70 g Fmoc-Lys(Boc)-OH (1.51 mmol, 2 equiv.), 3.8 mL HOAt (2.3 mmol, 3 equiv.), 0.7 mL DIC (4.5 mmol, 6 equiv.), and 1.6 mL DMF to generate a concentration
of 0.3 M. The coupling reaction was run for 4 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Lys(Boc)-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH\textsubscript{2}Fmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Lys(Boc)-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH\textsubscript{2}.

**HO-Lys(Boc)-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH\textsubscript{2}**

The protected linear pentapeptide HO-Lys(Boc)-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH\textsubscript{2} was generated following the Resin Cleavage of Linear Peptide procedure. The linear peptide was cleaved from the resin using a mixed solution of 5 mL trifluoroethanol and 5 mL CH\textsubscript{2}Cl\textsubscript{2}. The resin containing solution was filtered and dried in vacuo to yield the protected linear pentapeptide as a pale yellow solid (430 mg, overall 48%)

**cyclo-Lys(Boc)-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)**

The protected cyclic peptide was synthesized following the Macrocyclisation procedure using 0.15 g linear peptide (0.12 mmol, 1 equiv.), 0.05 g HATU (0.12 mmol, 1 equiv.), 0.02 g TBTU (0.063 mmol, 0.5 equiv.), 0.017 g DMTMM (0.063 mmol, 0.5 equiv.), 0.09 mL DIPEA (0.96 mmol, 8.0 equiv.) in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (126 mL, 0.001 M). The reaction was then stirred for 4 hours and monitored via LC/MS. Upon completion, the reaction mixture was worked up as described in the Macrocyclisation procedure and dried in vacuo to produce the crude, protected, cyclic peptide cyclo-Lys(Boc)-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc).

**cyclo-Lys-Tyr-Ser-Asn-Lys (11)**

The deprotected cyclic peptide was synthesized following the Side Chain Deprotection procedure using 0.088 g of crude cyclo-Lys(Boc)-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc) (0.08 mmol, 1 equiv.), 720 µL of a mixed solution of TFA and CH\textsubscript{2}Cl\textsubscript{2} (1:1 v/v) and 74 µL anisole (0.68 mmol, 8.0 equiv.) to generate the free side chains. The reaction mixture was stirred overnight and monitored via LC/MS. Upon completion, the reaction mixture was worked up as described in the Side Chain Deprotection procedure and lyophilised to produce the crude cyclic peptide. The crude product was purified using HPLC to generate pure compound as a white solid (31%).

LC/MS (ESI) m/z: [M+H]\textsuperscript{+} calculated for C\textsubscript{28}H\textsubscript{45}N\textsubscript{8}O\textsubscript{8}\textsuperscript{+}, 621.34; found 621.50 and [M+2H]\textsuperscript{2+} 311.00

\[1^1\text{H NMR (600 MHz, D}_2\text{O): } \delta 7.07-6.99 (m, 2H, } \delta \text{H Tyr), 6.80-6.70 (m, 2H, } \gamma \text{H Tyr), 4.66-4.57 (m, 1H, } \alpha \text{H Phe), 4.52-4.44 (m, 1H, } \alpha \text{H Ser), 4.38-4.30 (m, 1H, } \alpha \text{H Asn), 4.24-4.10 (m, 2H, } \alpha \text{H Lys), 3.76-3.65 (m, 2H, } \beta \text{H Ser), 3.00-2.85 (m, 2H, } \beta \text{H Phe), 2.96-2.82 (m, 2H, } \beta \text{H Asn), 2.80-2.61 (m, 4H, } \varepsilon \text{H Lys), 1.80-1.55 (m, 4H, } \beta \text{H Lys), 1.67-1.45 (m, 4H, } \gamma \text{H Lys), 1.44-1.20 (m, 4H, } \delta \text{H Lys).} \]
Experimental Procedures for 12

Resin-O-D-Phe-Tyr(t-Bu)-NH$_2$

Resin-O-D-Phe-Tyr(t-Bu)-NH$_2$ was synthesized following the Coupling Reaction procedure, using 1.1 g Resin-O-D-Phe-NH$_2$ (0.66 mmol, 1 equiv.), 0.60 g Fmoc-Tyr(t-Bu)-OH (1.3 mmol, 2 equiv.), 0.27 g HOBt (1.97 mmol, 3 equiv.), 0.61 mL DIC (3.9 mmol, 6 equiv.), and 2.19 mL of DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-D-Phe-Tyr(t-Bu)-NH$_2$. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-D-Phe-Tyr(t-Bu)-NH$_2$.

Resin-O-D-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH$_2$

Resin-O-D-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH$_2$ was synthesized following the Coupling Reaction procedure, using Resin-O-D-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH$_2$ from the previous reaction, 0.50 g Fmoc-Ser(t-Bu)-OH (1.3 mmol, 2 equiv.), 0.27 g HOBt (1.97 mmol, 3 equiv.), 0.61 mL DIC (3.9 mmol, 6 equiv.), and 2.19 mL of DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-D-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH$_2$. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-D-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH$_2$.

Resin-O-D-Phe-Tyr(t-Bu)-Asn(Trt)-NH$_2$

Resin-O-D-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-NH$_2$ was synthesized following the Coupling Reaction procedure, using Resin-O-D-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-NH$_2$ from the previous reaction, 0.78 g Fmoc-Asn(Trt)-OH (1.3 mmol, 2 equiv.), 0.27 g HOBt (1.97 mmol, 3 equiv.), 0.61 mL DIC (3.9 mmol, 6 equiv.), and 2.19 mL of DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-D-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-NH$_2$. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-D-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-NH$_2$.

Resin-O-D-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH$_2$

Resin-O-D-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH$_2$ was synthesized following the Coupling Reaction procedure, using Resin-O-D-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH$_2$ from the previous reaction, 0.61 g Fmoc-Lys(Boc)-OH (1.3 mmol, 2 equiv.), 0.27 g HOBt (1.97 mmol, 3 equiv.), 0.61 mL DIC (3.9 mmol, 6 equiv.), and 2.19 mL of DMF to generate a concentration of 0.3 M. The coupling reaction was run overnight and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-D-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH$_2$. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-D-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH$_2$.

HO-D-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH$_2$

The protected linear pentapeptide HO-D-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)-NH$_2$ was generated following the Resin Cleavage of Linear Peptide procedure. The linear peptide was cleaved from the resin using a mixed solution of 5 mL trifluoroethanol and 5 mL CH$_2$Cl$_2$. The resin containing solution was filtered and dried in vacuo to yield the protected linear pentapeptide as a white solid (510 mg, overall 70%).
Supporting Information

**cyclo-d-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc)**

The protected cyclic peptide was synthesized following the *Macrocyclisation* procedure using 0.2 g linear peptide (0.18 mmol, 1 equiv.), 0.068 g HATU (0.18 mmol, 1 equiv.), 0.03 g TBTU (0.09 mmol, 0.5 equiv.), 0.025 g DMTMM (0.09 mmol, 0.5 equiv.), 0.25 mL DIPEA (1 mmol, 8.0 equiv.) in anhydrous CH$_2$Cl$_2$ (180 mL, 0.001 M). The reaction was then stirred for 4 hours and monitored via LC/MS. Upon completion, the reaction was worked up as described in the *Macrocyclisation* procedure and dried *in vacuo* to produce the crude, protected, cyclic peptide cyclo-d-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc).

**cyclo-o-Phe-Tyr-Ser-Asn-Lys (12)**

The deprotected cyclic peptide was synthesized following the *Side Chain Deprotection* procedure using 0.12 g crude cyclo-d-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-Lys(Boc) (0.11 mmol, 1 equiv.), 900 µL of a mixed solution of TFA and CH$_2$Cl$_2$ (9:1 v/v) and 95 µL anisole (0.8 mmol, 8 equiv.) to generate the free side chains. The reaction mixture was stirred for 4 hours and monitored via LC/MS. Upon completion, the reaction mixture was worked up as described in the *Side Chain Deprotection* procedure and lyophilised to produce the crude cyclic peptide. The crude product was purified using HPLC to generate pure compound as a white solid (77%).

**LC/MS (ESI)** $m/z$: [M+H]$^+$ calculated for C$_{31}$H$_{42}$N$_7$O$_8$, 640.30; found, 640.30.

$^1$H NMR (600 MHz, D$_2$O): δ 7.30-7.13 (m, 5H, Phe), 7.04-7.03 (d, $J$ = 8.58 Hz, 2H, γH Tyr), 6.78-6.77 (d, $J$ = 8.56 Hz, 2H, δH Tyr), 4.79-4.77 (m, 1H, αH Phe), 4.51-4.48 (t, $J$ = 7.39 Hz, 1H, αH Tyr), 4.31-4.28 (m, 1H, αH Ser), 4.02-4.00 (t, $J$ = 5.60, 1H, αH Asn), 3.92-3.90 (m, 1H, αH Lys), 3.83-3.80 (m, 2H, βH Ser), 2.90-2.77 (m, 6H, βH Phe, βH Tyr, βH Asn), 2.74-2.64 (m, 2H, βH Lys), 1.68-1.33 (m, 4H, εH Lys, γH Lys), 0.84-0.79 (m, 2H, δH Lys).
Supporting Information

Experimental Procedures for 13

Resin-O-Phe-NH$_2$

The resin bound amino acid Resin-O-Phe-NH$_2$ was synthesized according to the Resin Loading procedure. A sample of 2-chlorotrityl chloride resin (0.7 g, 1.1 mmol/g loading, 1 equiv.) was placed in a reaction vessel and swelled with CH$_2$Cl$_2$ for 30 minutes then drained. To the resin was added 0.89 g Fmoc-Phe-OH (3.3 mmol, 3 equiv.) that was pre-dissolved in the minimum amount of DIPEA in CH$_2$Cl$_2$ (0.40 M). The reaction was shaken at room temperature for 7 hours. The reaction mixture was drained and washed according to the protocol to produce Resin-O-Phe-NHFmoc. A sample of resin was removed and the resin loading was determined to be 0.72 mmol/g. The Fmoc group was then removed following the Fmoc Removal procedure to produce Resin-O-Phe-NH$_2$.

Resin-O-Phe-Tyr(t-Bu)-NH$_2$

Resin-O-Phe-Tyr(t-Bu)-NH$_2$ was synthesized following the Coupling Reaction procedure, using 0.7 g Resin-O-Phe-NH$_2$ (0.5 mmol, 1 equiv.), 0.46 g Fmoc-Tyr(t-Bu)-OH (1.0 mmol, 2 equiv.), 1.7 mL HOAt (1.0 mmol, 2 equiv.), 0.3 mL DIC (2.0 mmol, 4 equiv.), and 1.7 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run overnight and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Tyr(t-Bu)-NH$_2$.

Resin-O-Phe-Tyr(t-Bu)-Ser(Trt)-NH$_2$

Resin-O-Phe-Tyr(t-Bu)-Ser(Trt)-NH$_2$ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-Tyr(t-Bu)-NH$_2$ from the previous reaction, 0.57 g Fmoc-Ser(Trt)-OH (1.0 mmol, 2 equiv.), 1.7 mL HOAt (1.0 mmol, 2 equiv.), 0.3 mL DIC (2.0 mmol, 4 equiv.), and 1.7 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-Ser(Trt)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Tyr(t-Bu)-Ser(Trt)-NH$_2$.

Resin-O-Phe-Tyr(t-Bu)-Ser(Trt)-Asn(Trt)-NH$_2$

Resin-O-Phe-Tyr(t-Bu)-Ser(Trt)-Asn(Trt)-NH$_2$ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-Tyr(t-Bu)-Ser(Trt)-NH$_2$ from the previous reaction, 0.60 g Fmoc-Asn(Trt)-OH (1.0 mmol, 2 equiv.), 1.7 mL HOAt (1.0 mmol, 2 equiv.), 0.3 mL DIC (2.0 mmol, 4 equiv.), and 1.7 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-Ser(Trt)-Asn(Trt)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Tyr(t-Bu)-Ser(Trt)-Asn(Trt)-NH$_2$.

Resin-O-Phe-Tyr(t-Bu)-Ser(Trt)-Asn(Trt)-Ala-NH$_2$

Resin-O-Phe-Tyr(t-Bu)-Ser(Trt)-Asn(Trt)-Ala-NH$_2$ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-Tyr(t-Bu)-Ser(Trt)-Asn(Trt)-NH$_2$ from the previous reaction, 0.31 g Fmoc-Ala-OH (1.0 mmol, 2 equiv.), 1.7 mL HOAt (1.0 mmol, 2 equiv.), 0.3 mL DIC (2.0 mmol, 4 equiv.), and 1.7 mL DMF to generate a concentration of 0.3 M. The coupling
reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-Ser(Trt)-Asn(Trt)-Ala-NHxFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Tyr(t-Bu)-Ser(Trt)-Asn(Trt)-Ala-NH₂.

**HO-Phe-Tyr(t-Bu)-Ser(Trt)-Asn(Trt)-Ala-NH₂**

The protected linear pentapeptide HO-Phe-Tyr(t-Bu)-Ser(Trt)-Asn(Trt)-Ala-NH₂ was generated following the Resin Cleavage of Linear Peptide procedure. The linear peptide was cleaved from the resin using a mixed solution of 5.7 mL trifluoroethanol and 5.7 mL CH₂Cl₂. The resin containing solution was filtered and dried in vacuo to yield the protected linear pentapeptide as a pale yellow solid (652 mg, overall 87%)

**cyclo-Phe-Tyr(t-Bu)-Ser(Trt)-Asn(Trt)-Ala**

The protected cyclic peptide was synthesized following a modified version of the Macrocyclisation procedure using 0.25 g linear peptide (0.22 mmol, 1 equiv.), 0.083 g HATU (0.22 mmol, 1 equiv.), 0.056 g TBTU (0.18 mmol, 0.8 equiv.), 0.049 g DMTMM (0.18 mmol, 0.8 equiv.), 0.31 mL DIPEA (1.8 mmol, 8.0 equiv.) in anhydrous CH₂Cl₂ (219 mL, 0.001 M). The procedure was modified so that 20% of the total volume of CH₂Cl₂ was added to the coupling reagents and the remaining 80% was added to the linear peptide. The reaction was then stirred overnight and monitored via LC/MS. Upon completion, the reaction mixture was worked up as described in the Macrocyclisation procedure and dried in vacuo to produce the crude, protected, cyclic peptide cyclo-Phe-Tyr(t-Bu)-Ser(Trt)-Asn(Trt)-Ala.

**cyclo-Phe-Tyr-Ser-Asn-Ala (13)**

The deprotected cyclic peptide was synthesized following the Side Chain Deprotection procedure using 0.289 g of crude cyclo-Phe-Tyr(t-Bu)-Ser(Trt)-Asn(Trt)-Ala (0.30 mmol, 1 equiv.). 1.15 mL of a mixed solution of TFA and CH₂Cl₂ (1:1 v/v) and 134 µL anisole (1.23 mmol, 8 equiv.) to generate the free side chains. The reaction mixture was stirred overnight and monitored via LC/MS. Upon completion, the reaction mixture was worked up as described in the Side Chain Deprotection procedure and lyophilised to produce the crude cyclic peptide. The crude product was purified using HPLC to generate pure compound as a white solid (45%).

LC/MS (ESI) m/z: [M+H]⁺ calculated for C₂₈H₃₅N₆O₈⁺, 583.25; found 583.30.

¹H NMR (600 MHz, D₂O) δ 7.39-7.20 (m, 3H, εH Phe & ẓH Phe), 7.20-7.07 (d, J = 7.08 Hz, 2H, δH Phe), 7.04-6.82 (d, J = 8.45 Hz, 2H, δH Tyr), 6.82-6.58 (d, J = 8.45 Hz, 2H, εH Tyr), 4.60-4.53 (t, J = 6.83 Hz, 1H, αH Asn), 4.49-4.39 (m, 1H, αH Ser), 4.32-4.23 (t, J = 5.97 Hz, 1H, εH Tyr), 4.20-4.08 (m, 1H, αH Phe), 4.07-3.98 (q, J = 7.19 Hz, 1H, αH Ala), 3.78-3.67 (d, J = 6.14 Hz, 2H, βCH₂ Ser), 3.32-2.43 (m, 6H, βCH₂ Asn & βCH₂ Tyr & βCH₂ Phe), 1.47-1.16 (d, J = 7.20 Hz, 3H, CH₃ Ala)
Experimental Procedures for 14

Resin-O-Phe-Tyr(t-Bu)-NH$_2$

Resin-O-Phe-Tyr(t-Bu)-NH$_2$ was synthesized following the Coupling Reaction procedure, using 0.7 g Resin-O-Phe-NH$_2$ (0.35 mmol, 1 equiv.), 0.32 g Fmoc-Tyr(t-Bu)-OH (0.7 mmol, 2 equiv.), 0.14 g HOBr (1.05 mmol, 3 equiv.), 0.33 mL DIC (2.1 mmol, 6 equiv.), and 1.16 mL of DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Tyr(t-Bu)-NH$_2$.

Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH$_2$

Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH$_2$ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-Tyr(t-Bu)-NH$_2$ from the previous reaction, 0.54 g Fmoc-Ser(t-Bu)-OH (0.7 mmol, 2 equiv.), 0.14 g HOBr (1.05 mmol, 3 equiv.), 0.33 mL DIC (2.1 mmol, 6 equiv.), and 1.16 mL of DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH$_2$.

Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-NH$_2$

Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-NH$_2$ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH$_2$ from the previous reaction, 0.42 g Fmoc-Asn(Trt)-OH (0.7 mmol, 2 equiv.), 0.14 g HOBr (1.05 mmol, 3 equiv.), 0.33 mL DIC (2.1 mmol, 6 equiv.), and 1.16 mL of DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-NH$_2$.

Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-d-Lys(Boc)-NH$_2$

Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-d-Lys(Boc)-NH$_2$ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-NH$_2$ from the previous reaction, 0.32 g Fmoc-d-Lys(Boc)-OH (0.7 mmol, 2 equiv.), 0.14 g HOBr (1.05 mmol, 3 equiv.), 0.33 mL DIC (2.1 mmol, 6 equiv.), and 1.16 mL of DMF to generate a concentration of 0.3 M. The coupling reaction was run overnight and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-d-Lys(Boc)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-d-Lys(Boc)-NH$_2$.

HO-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-d-Lys(Boc)-NH$_2$

The protected linear pentapeptide HO-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-d-Lys(Boc)-NH$_2$ was generated following the Resin Cleavage of Linear Peptide procedure. The linear peptide was cleaved from the resin using a mixed solution of 4 mL trifluoroethanol and 4 mL CH$_2$Cl$_2$. The resin containing solution was filtered and dried in vacuo to yield the protected linear pentapeptide as a pale yellow solid (302 mg, overall 67%).
Supporting Information

cyclo-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-d-Lys(Boc)

The protected cyclic peptide was synthesized following the *Macrocyclisation* procedure using 0.2 g linear peptide (0.18 mmol, 1 equiv.), 0.068 g HATU (0.18 mmol, 1 equiv.), 0.03 g TBTU (0.09 mmol, 0.5 equiv.), 0.025 g DMTMM (0.09 mmol, 0.5 equiv.), 0.25 mL DIPEA (1 mmol, 8.0 equiv.) in anhydrous CH$_2$Cl$_2$ (180 mL, 0.001 M). The reaction was then stirred for 4 hours and monitored via LC/MS. Upon completion, the reaction was worked up as described in the *Macrocyclisation* procedure and dried in vacuo to produce the crude, protected, cyclic peptide cyclo-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-d-Lys(Boc).

cyclo-Phe-Tyr-Ser-Asn-d-Lys (14)

The deprotected cyclic peptide was synthesized following the *Side Chain Deprotection* procedure using 0.12 g crude cyclo-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asn(Trt)-d-Lys(Boc) (0.11 mmol, 1 equiv.), 850 µL of a mixed solution of TFA and CH$_2$Cl$_2$ (9:1 v/v) and 110 µL anisole (0.8 mmol, 8 equiv.) to generate the free side chains. The reaction mixture was stirred for 4 hours and monitored via LC/MS. Upon completion, the reaction mixture was worked up as described in the *Side Chain Deprotection* procedure and lyophilised to produce the crude cyclic peptide. The crude product was purified using HPLC to generate pure compound as a white solid (67%).

LC/MS (ESI) m/z: [M+H]$^+$ calculated for C$_{31}$H$_{42}$N$_7$O$_8$$^+$, 640.30; found, 640.30.

$^1$H NMR (600 MHz, D$_2$O): δ 7.33-7.17 (m, 5H, Phe), 6.93-6.92 (d, J = 8.48 Hz, 2H, γH Tyr), 6.74-6.72 (d, J = 8.46 Hz, 2H, δH Tyr), 4.64-4.61 (m, 1H, αH Phe), 4.56-4.53 (t, J = 8.05 Hz, 1H, αH Tyr), 4.45-4.43 (m, 1H, αH Ser), 4.07-4.04 (t, J = 8.02, 1H, αH Asn), 3.99-3.97 (t, J = 7.69, 1H, αH Lys), 3.80-3.78 (d, J = 7.49, 2H, βH Ser), 2.99-2.78 (m, 6H, βH Phe, βH Tyr, βH Asn), 2.72-2.68 (m, 2H, βH Lys), 2.16-1.47 (m, 4H, εH Lys, γH Lys), 1.28-1.05 (m, 2H, δH Lys).
**Experimental Procedures for 15**

**Resin-O-Leu-NH₂**

The resin bound amino acid Resin-O-Leu-NH₂ was synthesized according to the Resin Loading procedure. A sample of 2-chlorotrityl chloride resin (1.00 g, 1.1 mmol/g loading, 1 equiv.) was placed in a reaction vessel and swelled with CH₂Cl₂ for 30 minutes then drained. To the resin was added 1.17 g Fmoc-Leu-OH (3.3 mmol, 3 equiv.) that was pre-dissolved in the minimum amount of DIPEA in CH₂Cl₂ (0.40 M). The reaction was shaken at room temperature for 4 hours. The reaction mixture was drained and washed according to the protocol to produce Resin-O-Leu-NH₂. A negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Leu-NH₂.

**Resin-O-Leu-Lys(Boc)-NH₂**

Resin-O-Leu-Lys(Boc)-NH₂ was synthesized following the Coupling Reaction procedure, using 1.0 g Resin-O-Leu-NH₂ (0.72 mmol, 1 equiv.), 0.67 g Fmoc-Lys(Boc)-OH (1.43 mmol, 2 equiv.), 0.22 g hydrated HOBT (1.43 mmol, 2 equiv.), 0.44 mL DIC (2.8 mmol, 4 equiv.), and 2.4 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run overnight and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Leu-Lys(Boc)-NH₂.

**Resin-O-Leu-Lys(Boc)-Phe-NH₂**

Resin-O-Leu-Lys(Boc)-Phe-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Leu-Lys(Boc)-NH₂ from the previous reaction, 0.56 g Fmoc-Phe-OH (1.43 mmol, 2 equiv.), 0.22 g hydrated HOBT (1.43 mmol, 2 equiv.), 0.44 mL DIC (2.8 mmol, 4 equiv.), and 2.4 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run overnight and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Leu-Lys(Boc)-Phe-NH₂.

**Resin-O-Leu-Lys(Boc)-Phe-Tyr(t-Bu)-NH₂**

Resin-O-Leu-Lys(Boc)-Phe-Tyr(t-Bu)-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Leu-Lys(Boc)-Phe-NH₂ from the previous reaction, 0.66 g Fmoc-Tyr(t-Bu)-OH (1.43 mmol, 2 equiv.), 0.22 g hydrated HOBT (1.43 mmol, 2 equiv.), 0.44 mL DIC (2.8 mmol, 4 equiv.), and 2.4 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Leu-Lys(Boc)-Phe-Tyr(t-Bu)-NH₂.

**Resin-O-Leu-Lys(Boc)-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH₂**

Resin-O-Leu-Lys(Boc)-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Leu-Lys(Boc)-Phe-Tyr(t-Bu)-NH₂ from the previous reaction, 0.55 g Fmoc-Ser(t-Bu)-OH (1.43 mmol, 2 equiv.), 0.22 g hydrated HOBT (1.43 mmol, 2 equiv.), 0.44 mL DIC (2.8 mmol, 4 equiv.), and 2.4 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run overnight and a negative ninhydrin test was used to confirm reaction completion.
Supporting Information

The reaction mixture was drained to afford Resin-O-Leu-Lys(Boc)-Phe-Tyr(t-Bu)-Ser(t-Bu)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Leu-Lys(Boc)-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH₂.

**HO-Leu-Lys(Boc)-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH₂**

The protected linear pentapeptide HO-Leu-Lys(Boc)-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH₂ was generated following the Resin Cleavage of Linear Peptide procedure. The linear peptide was cleaved from the resin using a mixed solution of 7 mL trifluoroethanol and 7 mL CH₂Cl₂. The resin containing solution was filtered and dried in vacuo to yield the protected linear pentapeptide as a pale yellow solid (241 mg, overall 39%).

**Cyclo-Leu-Lys(Boc)-Phe-Tyr(t-Bu)-Ser(t-Bu)**

The protected cyclic peptide was synthesized following the Macrocyclisation procedure using 0.126 g linear peptide (0.14 mmol, 1 equiv.), 0.054 g HATU (0.14 mmol, 1 equiv.), 0.045 g TBTU (0.115 mmol, 0.8 equiv.), 0.04 g DMTMM (0.115 mmol, 0.8 equiv.), 0.20 mL DIPEA (0.057 mmol, 8.0 equiv.) in anhydrous CH₂Cl₂ (122 mL, 0.001 M). The reaction was then stirred for 4 hours and monitored via LC/MS. Upon completion, the reaction mixture was worked up as described in the Macrocyclisation procedure and dried in vacuo to produce the crude, protected, cyclic peptide cyclo-Leu-Lys(Boc)-Phe-Tyr(t-Bu)-Ser(t-Bu).

**Cyclo-Leu-Lys-Phe-Tyr-Ser (15)**

The deprotected cyclic peptide was synthesized following the Side Chain Deprotection procedure using 0.138 g of crude cyclo-Leu-Lys(Boc)-Phe-Tyr(t-Bu)-Ser(t-Bu) (0.162 mmol, 1 equiv.) and TBTU (0.14 mmol, 8.0 equiv.), 0.04 g DMTMM (0.14 mmol, 8.0 equiv.) in anhydrous CH₂Cl₂ (122 mL, 0.001 M) to generate the free side chains. The reaction mixture was stirred overnight and monitored via LC/MS. Upon completion, the reaction mixture was worked up as described in the Side Chain Deprotection procedure and lyophilised to produce the crude cyclic peptide. The crude product was purified using HPLC to generate pure compound as a white solid (14%).

LC/MS (ESI) m/z: [M+H]+ calculated for C_{33}H_{47}N_{6}O_{7}^+, 639.35; found 639.40.

\(^1\)H NMR (600 MHz, D₂O) δ 7.45-7.29 (m, 5H, Phe), 7.0 (d, J = 8.35 Hz, 2H, δH Tyr), 6.81 (d, J = 8.42 Hz, 2H, εH Tyr), 4.56 (dd, J = 6.56, 9.44 Hz, 1H, αH Phe), 4.34-4.27 (m, 1H, αH Tyr), 4.34-4.27 (m, 1H, αH Leu), 4.34-4.27 (m, 1H, βCH₂ Phe), 3.76 (tr, J = 4.60 Hz, 1H, βCH₂ Ser), 3.69-3.64 (m, 1H, βCH₂ Ser), 3.22 (m, J = 6.56 Hz, 13.97, 1H, βCH₂ Phe), 3.13 (m, J = 9.60 Hz, 13.85, 1H, βCH₂ Phe), 3.03-2.93 (m, 2H, βCH₂ Lys), 3.03-2.93 (m, 2H, βCH₂ Leu), 1.94-1.82 (m, 1H, εCH₂ Lys), 1.94-1.82 (m, 1H, εCH₂ Leu), 1.74-1.60 (m, 1H, γCH₂ Leu), 1.74-1.60 (m, 1H, βCH₂ Lys), 1.74-1.60 (m, 1H, δCH Lys), 1.39-1.25 (m, 2H, γCH₂ Lys), 0.98 (d, J = 6.18 Hz, 3H, δCH₃ Leu), 0.92 (d, J = 6.12 Hz, 3H, δCH₃ Leu).
Experimental Procedures for 16

Resin-O-Phe-NH$_2$

The resin bound amino acid Resin-O-Phe-NH$_2$ was synthesized according to the Resin Loading procedure. A sample of 2-chlorotrityl chloride resin (1.00 g, 1.1 mmol/g loading, 1 equiv.) was placed in a reaction vessel and swelled with CH$_2$Cl$_2$ for 30 minutes then drained. To the resin was added 1.28 g Fmoc-Phe-OH (3.3 mmol, 3 equiv.) that was pre-dissolved in the minimum amount of DIPEA in CH$_2$Cl$_2$ (0.40 M). The reaction was shaken at room temperature for 4 hours. The reaction mixture was drained and washed according to the protocol to produce Resin-O-Phe-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to produce Resin-O-Phe-NH$_2$.

Resin-O-Phe-Lys(Boc)-NH$_2$

Resin-O-Phe-Lys(Boc)-NH$_2$ was synthesized following the Coupling Reaction procedure, using 1.0 g Resin-O-Phe-NH$_2$ (1.1 mmol, 1 equiv.), 1.04 g Fmoc-Lys(Boc)-OH (2.2 mmol, 2 equiv.), 0.34 g hydrated HOBt (2.2 mmol, 2 equiv.), 0.7 mL DIC (4.4 mmol, 4 equiv.), and 3.7 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run overnight and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained and washed according to the protocol to afford Resin-O-Phe-Lys(Boc)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Lys(Boc)-NH$_2$.

Resin-O-Phe-Lys(Boc)-Phe-NH$_2$

Resin-O-Phe-Lys(Boc)-Phe-NH$_2$ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-Lys(Boc)-NH$_2$ from the previous reaction, 0.86 g Fmoc-Phe-OH (2.2 mmol, 2 equiv.), 0.34 g hydrated HOBt (2.2 mmol, 2 equiv.), 0.7 mL DIC (4.4 mmol, 4 equiv.), and 3.7 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run overnight and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained and washed according to the protocol to afford Resin-O-Phe-Lys(Boc)-Phe-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Lys(Boc)-Phe-NH$_2$.

Resin-O-Phe-Lys(Boc)-Phe-Tyr(t-Bu)-NH$_2$

Resin-O-Phe-Lys(Boc)-Phe-Tyr(t-Bu)-NH$_2$ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-Lys(Boc)-Phe-NH$_2$ from the previous reaction, 1.02 g Fmoc-Tyr(t-Bu)-OH (2.2 mmol, 2 equiv.), 0.34 g hydrated HOBt (2.2 mmol, 2 equiv.), 0.7 mL DIC (4.4 mmol, 4 equiv.), and 3.7 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained and washed according to the protocol to afford Resin-O-Phe-Lys(Boc)-Phe-Tyr(t-Bu)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Lys(Boc)-Phe-Tyr(t-Bu)-NH$_2$.

Resin-O-Phe-Lys(Boc)-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH$_2$

Resin-O-Phe-Lys(Boc)-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH$_2$ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-Lys(Boc)-Phe-Tyr(t-Bu)-NH$_2$ from the previous reaction, 0.85 g Fmoc-Ser(t-Bu)-OH (2.2 mmol, 2 equiv.), 0.34 g hydrated HOBt (2.2 mmol, 2 equiv.), 0.7 mL DIC (4.4 mmol, 4 equiv.), and 3.7 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run overnight and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained and washed according to the protocol to afford Resin-O-Phe-Lys(Boc)-Phe-
Supporting Information

Tyr(t-Bu)-Ser(t-Bu)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Lys(Boc)-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH₂.

**HO-Phe-Lys(Boc)-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH₂**

The protected linear pentapeptide HO-Phe-Lys(Boc)-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH₂ was generated following the Resin Cleavage of Linear Peptide procedure. The linear peptide was cleaved from the resin using a mixed solution of 7 mL trifluoroethanol and 7 mL CH₂Cl₂. The resin containing solution was filtered and dried in vacuo to yield the protected linear pentapeptide as a pale yellow solid (303 mg, overall 31%).

**cyclo-Phe-Lys(Boc)-Phe-Tyr(t-Bu)-Ser(t-Bu)**

The protected cyclic peptide was synthesized following the Macrocyclisation procedure using 0.129 g linear peptide (0.14 mmol, 1 equiv.), 0.054 g HATU (0.13 mmol, 1 equiv.), 0.035 g TBTU (0.11 mmol, 0.8 equiv.), 0.033 g DMTMM (0.11 mmol, 0.8 equiv.), 0.20 mL DIPEA (1.12 mmol, 8.0 equiv.) in anhydrous CH₂Cl₂ (139 mL, 0.001 M). The reaction was then stirred for 4 hours and monitored via LC/MS. Upon completion, the reaction mixture was worked up as described in the Macrocyclisation procedure and dried in vacuo to produce the crude, protected, cyclic peptide cyclo-Phe-Lys(Boc)-Phe-Tyr(t-Bu)-Ser(t-Bu).

**cyclo-Phe-Lys-Phe-Tyr-Ser (16)**

The deprotected cyclic peptide was synthesized following the Side Chain Deprotection procedure using 0.186 g of crude cyclo-Phe-Lys(Boc)-Phe-Tyr(t-Bu)-Ser(t-Bu) (0.162 mmol, 1 equiv.), 2.6 mL of a mixed solution of TFA and CH₂Cl₂ (9:1 v/v) and anisole (6 equiv.) to generate the free side chains. The reaction mixture was stirred overnight and monitored via LC/MS. Upon completion, the reaction mixture was worked up as described in the Side Chain Deprotection procedure and lyophilised to produce the crude cyclic peptide. The crude product was purified using HPLC to generate pure compound as a white solid (23%).

**LC/MS (ESI) m/z:** [M+H]⁺ C₃₆H₄₅N₆O₇⁺ called for 673.34; found 673.35

**¹H NMR (600 MHz D₂O)** δ 7.44 − 7.21 (m, 10H, Phe), 7.06 (d, J = 8.85 Hz, 2H, δH Tyr), 6.83 (d, J = 8.48 Hz, 2H, εH Tyr), 4.55 (dd, J = 5.12, 10.93 Hz, αH Phe, 1H), 4.50 (dd, J = 6.72 Hz, 9.34, 1H, αH Phe), 4.37 (dd, J = 6.73, 8.75 Hz, 1H, αH Tyr), 4.28 (t, J = 5.84 Hz, 1H, αH Ser), 3.96 − 3.91 (m, 1H, αH Lys), 3.84 (d, J = 5.78 Hz, 2H, βCH₂ Ser), 3.37 − 3.30 (m, 1H, βCH₂ Phe), 3.24 − 3.10 (m, 3H, βCH₂ Phe), 3.02 − 2.91 (m, 2H, βCH₂ Tyr), 2.91 − 2.85 (t, J = 7.80 Hz, 2H, εCH₂ Lys), 1.72 − 1.63 and 1.63 − 1.51 (m, 2H, εCH₂ Lys), 1.63 − 1.51 (m, 2H, δCH₂ Lys), 1.19 − 1.09 and 1.07 − 0.98 (m, 2H, γCH₂ Lys).
Supporting Information

Experimental Procedures for 17

Resin-O-Phe-Tyr(t-Bu)-NH₂

A sample of commercially available pre-loaded 2-chlorotrityl resin (0.5 g, 0.25 mmol, 1 equiv.) was placed in a reaction vessel and swelled with DMF for 30 minutes then drained. To the resin was added 0.30 g Fmoc-Tyr(t-Bu)-OH (0.66 mmol, 2 equiv.), 1.1 mL HOAt (0.66 mmol, 2 equiv.), 0.2 mL DIC (1.32 mmol, 4 equiv.), and 0.55 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run for 4 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Tyr(t-Bu)-NH₂.

Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH₂

Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-Tyr(t-Bu)-NH₂ from the previous reaction, 0.25 g Fmoc-Ser(t-Bu)-OH (0.66 mmol, 2 equiv.), 1.1 mL HOAt (0.66 mmol, 2 equiv.), 0.2 mL DIC (1.32 mmol, 4 equiv.), and 0.55 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run overnight and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH₂.

Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asp(t-Bu)-NH₂

Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asp(t-Bu)-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH₂ from the previous reaction, 0.27 g Fmoc-Asp(t-Bu)-OH (0.66 mmol, 2 equiv.), 1.1 mL HOAt (0.66 mmol, 2 equiv.), 0.2 mL DIC (1.32 mmol, 4 equiv.), and 0.55 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run overnight and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asp(t-Bu)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asp(t-Bu)-NH₂.

Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asp(t-Bu)-Lys(Boc)-NH₂

Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asp(t-Bu)-Lys(Boc)-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asp(t-Bu)-NH₂ from the previous reaction, 0.31 g Fmoc-Lys(Boc)-OH (0.66 mmol, 2 equiv.), 1.1 mL HOAt (0.66 mmol, 2 equiv.), 0.2 mL DIC (1.32 mmol, 4 equiv.), and 0.55 mL DMF to generate a concentration of 0.3 M. The coupling reaction was run overnight and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asp(t-Bu)-Lys(Boc)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asp(t-Bu)-Lys(Boc)-NH₂.

HO-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asp(t-Bu)-Lys(Boc)-NH₂

The protected linear pentapeptide HO-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asp(t-Bu)-Lys(Boc)-NH₂ was generated following the Resin Cleavage of Linear Peptide procedure. The linear peptide was cleaved from the resin using a mixed solution of 8 mL trifluoroethanol and 8 mL CH₂Cl₂. The
resin containing solution was filtered and dried \textit{in vacuo} to yield the protected linear pentapeptide as a pale yellow solid (119 mg, overall 40\%)

\textbf{cyclo-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asp(t-Bu)-Lys(Boc)}

The protected cyclic peptide was synthesized following the \textit{Macrocyclisation} procedure using 0.10 g linear peptide (0.11 mmol, 1 equiv.), 0.041 g HATU (0.11 mmol, 1 equiv.), 0.028 g TBTU (0.86 mmol, 0.8 equiv.), 0.024 g DMTMM (0.88 mmol, 0.8 equiv.), 0.15 mL DIPEA (0.86 mmol, 8 equiv.) in anhydrous CH$_2$Cl$_2$ (110 mL, 0.001 M). The reaction was then stirred for 4 hours and monitored \textit{via} LC/MS. Upon completion, the reaction mixture was worked up as described in the \textit{Macrocyclisation} procedure and dried \textit{in vacuo} to produce the crude, protected, cyclic peptide cyclo-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asp(t-Bu)-Lys(Boc).

\textbf{cyclo-Phe-Tyr-Ser-Asp-Lys (17)}

The deprotected cyclic peptide was synthesized following the \textit{Side Chain Deprotection} procedure using 0.05 g of crude cyclo-Phe-Tyr(t-Bu)-Ser(t-Bu)-Asp(t-Bu)-Lys(Boc) (0.054 mmol, 1 equiv.), 180 µL of a mixed solution of TFA and CH$_2$Cl$_2$ (9:1 v/v) and 35 µL anisole (0.32 mmol, 6 equiv.) to generate the free side chains. The reaction mixture was stirred overnight and monitored \textit{via} LC/MS. Upon completion, the reaction mixture was worked up as described in the \textit{Side Chain Deprotection} procedure and lyophilised to produce the crude cyclic peptide. The crude product was purified using HPLC to generate pure compound as a white solid (14\%).

LC/MS (ESI) $m/z$: [M+H]$^+$ calculated for C$_{31}$H$_{41}$N$_6$O$_9$$^+$ , 641.30; found 641.25.

$^1$H NMR (600 MHz, D$_2$O): 5 7.41-7.21 (m, 5H, Phe), 7.08-7.04 (m, 2H, δH Tyr), 6.90-6.74 (m, 2H, εH Tyr), 4.56-4.53 (m, 1H, αH Phe), 4.51-4.48(m, 1H, αH Tyr), 4.35-4.32 (m, 1H, αCH Asp), 4.32-4.34 (t, J = 5.62 Hz, 1H, αCH Ser), 4.17-4.06 (m, 1H, αCH Lys), 3.80-3.76 (m, 2H, βCH$_2$ Ser), 3.19-3.05 (m, 2H, βCH$_2$ Phe), 3.01-2.93 (m, 2H, εCH$_2$ Lys), 2.89-2.80 (m, 2H, βCH$_2$ Tyr), 2.88-2.86 (m, 2H, βCH$_2$ Asn), 1.88-1.83 (m, 2H, γCH$_2$ Lys), 1.68-1.62 (m, 2H, βCH$_2$ Lys), 1.35-1.24 (m, 2H, δCH$_2$ Lys).
Experimental Procedures for 18

Resin-O-\(d\)-Ala-NH\(_2\)

The resin bound amino acid Resin-O-\(d\)-Ala-NH\(_2\) was synthesized according to the Resin Loading procedure. A sample of 2-chlorotrityl chloride resin (1.00 g, 1.1 mmol/g loading, 1 equiv.) was placed in a reaction vessel and swelled with CH\(_2\)Cl\(_2\) for 30 minutes then drained. To the resin was added 1.03 g Fmoc-\(d\)-Ala-OH (3.3 mmol, 3 equiv.) that was pre-dissolved in the minimum amount of DIPEA in CH\(_2\)Cl\(_2\) (0.40 M). The reaction was shaken at room temperature overnight. The reaction mixture was drained and washed according to the protocol to produce Resin-O-\(d\)-Ala-NHFmoc. A sample of resin was removed and the resin loading was determined to be 0.71 mmol/g. The Fmoc group was then removed following the Fmoc Removal procedure to produce Resin-O-\(d\)-Ala-NH\(_2\).

Resin-O-\(d\)-Ala-Lys(Boc)-NH\(_2\)

Resin-O-\(d\)-Ala-Lys(Boc)-NH\(_2\) was synthesized following the Coupling Reaction procedure, using 1.0 g Resin-O-\(d\)-Ala-NH\(_2\) (0.72 mmol, 1 equiv.), 0.66 g Fmoc-Lys(Boc)-OH (1.41 mmol, 2 equiv.), 0.19 g hydrated HOBt (1.41 mmol, 2 equiv.), 0.44 mL DIC (2.83 mmol, 4 equiv.), and 4 mL DMF to generate a concentration of 0.2 M. The coupling reaction was run overnight and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained and washed according to the protocol to produce Resin-O-\(d\)-Ala-Lys(Boc)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-\(d\)-Ala-Lys(Boc)-NH\(_2\).

Resin-O-\(d\)-Ala-Lys(Boc)-Phe-NH\(_2\)

Resin-O-\(d\)-Ala-Lys(Boc)-Phe-NH\(_2\) was synthesized following the Coupling Reaction procedure, using Resin-O-\(d\)-Ala-Lys(Boc)-NH\(_2\) from the previous reaction, 0.55 g Fmoc-Phe-OH (1.41 mmol, 2 equiv.), 0.19 g hydrated HOBt (1.41 mmol, 2 equiv.), 0.44 mL DIC (2.83 mmol, 4 equiv.), and 4 mL DMF to generate a concentration of 0.2 M. The coupling reaction was run overnight and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-\(d\)-Ala-Lys(Boc)-Phe-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-\(d\)-Ala-Lys(Boc)-Phe-NH\(_2\).

Resin-O-\(d\)-Ala-Lys(Boc)-Phe-Tyr(t-Bu)-NH\(_2\)

Resin-O-\(d\)-Ala-Lys(Boc)-Phe-Tyr(t-Bu)-NH\(_2\) was synthesized following the Coupling Reaction procedure, using Resin-O-\(d\)-Ala-Lys(Boc)-Phe-NH\(_2\) from the previous reaction, 0.65 g Fmoc-Tyr(t-Bu)-OH (1.41 mmol, 2 equiv.), 0.19 g hydrated HOBt (1.41 mmol, 2 equiv.), 0.44 mL DIC (2.83 mmol, 4 equiv.), and 4 mL DMF to generate a concentration of 0.2 M. The coupling reaction was run overnight and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-\(d\)-Ala-Lys(Boc)-Phe-Tyr(t-Bu)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-\(d\)-Ala-Lys(Boc)-Phe-Tyr(t-Bu)-NH\(_2\).

Resin-O-\(d\)-Ala-Lys(Boc)-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH\(_2\)

Resin-O-\(d\)-Ala-Lys(Boc)-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH\(_2\) was synthesized following the Coupling Reaction procedure, using Resin-O-\(d\)-Ala-Lys(Boc)-Phe-Tyr(t-Bu)-NH\(_2\) from the previous reaction, 0.54 g Fmoc-Ser(t-Bu)-OH (1.41 mmol, 2 equiv.), 0.19 g hydrated HOBt (1.41 mmol, 2 equiv.), 0.44 mL DIC (2.83 mmol, 4 equiv.), and 4 mL DMF to generate a concentration of 0.2 M. The coupling reaction was run overnight and a negative ninhydrin test was used to confirm
reaction completion. The reaction mixture was drained to afford Resin-O-d-Ala-Lys(Boc)-Phe-Tyr(t-Bu)-Ser(t-Bu)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-d-Ala-Lys(Boc)-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH₂.

**HO-d-Ala-Lys(Boc)-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH₂**

The protected linear pentapeptide HO-d-Ala-Lys(Boc)-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH₂ was generated following the Resin Cleavage of Linear Peptide procedure. The linear peptide was cleaved from the resin using a mixed solution of 5 mL trifluoroethanol and 5 mL CH₂Cl₂. The resin containing solution was filtered and dried in vacuo to yield the protected linear pentapeptide as a pale yellow solid (314 mg, overall 54%).

**cyclo-d-Ala-Lys(Boc)-Phe-Tyr(t-Bu)-Ser(t-Bu)**

The protected cyclic peptide was synthesized following the Macrocyclisation procedure using 0.160 g linear peptide (0.19 mmol, 1 equiv.), 0.072 g HATU (0.19 mmol, 1 equiv.), 0.049 g TBTU (0.15 mmol, 0.8 equiv.), 0.039 g DMTMM (0.13 mmol, 0.8 equiv.), 0.26 mL DIPEA (1.52 mmol, 8.0 equiv.) in anhydrous CH₂Cl₂ (190 mL, 0.001 M). The reaction was then stirred for 4 hours and monitored via LC/MS. Upon completion, the reaction mixture was worked up as described in the Macrocyclisation procedure and dried in vacuo to produce the crude, protected, cyclic peptide cyclo-d-Ala-Lys(Boc)-Phe-Tyr(t-Bu)-Ser(t-Bu).

**cyclo-d-Ala-Lys-Phe-Tyr-Ser (18)**

The deprotected cyclic peptide was synthesized following the Side Chain Deprotection procedure using 0.208 g of crude cyclo-d-Ala-Lys(Boc)-Phe-Tyr(t-Bu)-Ser(t-Bu) (0.258 mmol, 1 equiv.), 1.97 mL of a mixed solution of TFA and CH₂Cl₂ (9:1 v/v) and anisole (6 equiv.) to generate the free side chains. The reaction mixture was stirred overnight and monitored via LC/MS. Upon completion, the reaction mixture was worked up as described in the Side Chain Deprotection procedure and lyophilised to produce the crude cyclic peptide. The crude product was purified using HPLC to generate pure compound as a white solid (11%).

**LC/MS (ESI)** m/z: [M+H]+ C₃₀H₄₁N₈O₇+ called for 597.31; found 597.30.

\(^{1}\)H NMR (600 MHz, D₂O) δ 7.45 – 7.30 (m, 3H, Phe), 7.23 (d, J = 7.83 Hz, 2H, Phe) 7.15 (d, J = 8.53 Hz, 2H, δH Tyr), 6.86 (d, J = 8.53 Hz, 2H, εH Tyr), 4.58 (dd, J = 7.0, 9.01 Hz, 1H, αH Phe), 4.46 (q, J = 6.82 Hz, 1H, αH Ala), 4.41 (dd, J = 7.62, 8.66 Hz, 1H, αH Tyr), 4.30 (tr, J = 5.90 Hz, 1H, βCH₂ Serine), 3.90 (dd, J = 5.32, 9.71 Hz, 1H, αH Lys), 3.79 – 3.72 (m, 2H, βCH₂ Serine), 3.12 – 2.96 (m, 2H, βCH₂, Phe), 3.12 – 2.96 (m, 2H, βCH₂, Tyr), 2.92 (tr, J = 7.89 Hz, 2H, εCH₂ Lys), 1.73-1.65 & 1.60-1.50 (m, 2H, δCH₂, Lys), 1.60-1.50 (m, 2H, βCH₂, Lys), 1.28 (d, J = 6.83 Hz, 3H, Ala), 1.13 – 1.04 (m, 2H, γCH₂ Lys).
Supporting Information

Experimental Procedures for 19

Resin-O-Phe-NH₂

The resin bound amino acid Resin-O-Phe-NH₂ was synthesized according to the Resin Loading procedure. A sample of 2-chlorotrityl chloride resin (0.5 g, 1.1 mmol/g loading, 1 equiv.) was placed in a reaction vessel and swelled with CH₂Cl₂ for 30 minutes then drained. To the resin was added 0.65 g Fmoc-Phe-OH (3.3 mmol, 3 equiv.) that was pre-dissolved in the minimum amount of DIPEA in CH₂Cl₂ (0.40 M). The reaction was shaken at room temperature for 4 hours. The reaction mixture was drained and washed according to the protocol to produce Resin-O-Phe-NHFmoc. A sample of resin was removed and the resin loading was determined to be 0.57 mmol/g. The Fmoc group was then removed following the Fmoc Removal procedure to produce Resin-O-Phe-NH₂.

Resin-O-Phe-Tyr(t-Bu)-NH₂

Resin-O-Phe-Tyr(t-Bu)-NH₂ was synthesized following the Coupling Reaction procedure, using 0.53 g Resin-O-Phe-NH₂ (0.29 mmol, 1 equiv.), 0.27 g Fmoc-Tyr(t-Bu)-OH (0.58 mmol, 2 equiv.), 1.9 mL HOAt (2.1 mmol, 3 equiv.), 0.36 mL DIC (1.15 mmol, 6 equiv.), and 1.9 mL of DMF to generate a concentration of 0.3 M. The coupling reaction was run for 3 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-NH₂. The Fmoc group was then removed following the Fmoc Removal procedure to produce Resin-O-Phe-Tyr(t-Bu)-NH₂.

Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH₂

Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-Tyr(t-Bu)-NH₂ from the previous reaction, 0.22 g Fmoc-Ser(t-Bu)-OH (0.58 mmol, 2 equiv.), 1.9 mL HOAt (2.1 mmol, 3 equiv.), 0.36 mL DIC (1.15 mmol, 6 equiv.), and 1.9 mL of DMF to generate a concentration of 0.3 M. The coupling reaction was run for 48 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH₂. The Fmoc group was then removed following the Fmoc Removal procedure to produce Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH₂.

Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Ala-NH₂

Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Ala-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-NH₂ from the previous reaction, 0.18 g Fmoc-Ala-OH (0.58 mmol, 2 equiv.), 1.9 mL HOAt (2.1 mmol, 3 equiv.), 0.36 mL DIC (1.15 mmol, 6 equiv.), and 1.9 mL of DMF to generate a concentration of 0.3 M. The coupling reaction was run for 2 hours and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Ala-NH₂. The Fmoc group was then removed following the Fmoc Removal procedure to produce Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Ala-NH₂.

Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Ala-d-Lys(Boc)-NH₂

Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Ala-d-Lys(Boc)-NH₂ was synthesized following the Coupling Reaction procedure, using Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Ala-NH₂ from the previous reaction, 0.27 g Fmoc-d-Lys(Boc)-OH (0.58 mmol, 2 equiv.), 1.9 mL HOAt (2.1 mmol, 3 equiv.), 0.36 mL DIC (1.15 mmol, 6 equiv.), and 1.9 mL of DMF to generate a concentration of 0.3 M. The
coupling reaction was run overnight and a negative ninhydrin test was used to confirm reaction completion. The reaction mixture was drained to afford Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Ala-d-Lys(Boc)-NHFmoc. The Fmoc group was then removed following the Fmoc Removal procedure to afford Resin-O-Phe-Tyr(t-Bu)-Ser(t-Bu)-Ala-d-Lys(Boc)-NH2.

**HO-Phe-Tyr(t-Bu)-Ser(t-Bu)-Ala-d-Lys(Boc)-NH2**

The protected linear pentapeptide HO-Phe-Tyr(t-Bu)-Ser(t-Bu)-Ala-d-Lys(Boc)-NH2 was generated following the Resin Cleavage of Linear Peptide procedure. The linear peptide was cleaved from the resin using a mixed solution of 2.9 mL trifluoroethanol and 2.9 mL CH2Cl2. The resin containing solution was filtered and dried in vacuo to yield the protected linear pentapeptide as a pale yellow solid (174 mg, overall 73%).

**cyclo-Phe-Tyr(t-Bu)-Ser(t-Bu)-Ala-d-Lys(Boc)**

The protected cyclic peptide was synthesized following the Macrocyclisation procedure using 0.108 g linear peptide (0.13 mmol, 1 equiv.), 0.049 g HATU (0.13 mmol, 1 equiv.), 0.033 g TBTU (0.10 mmol, 0.8 equiv.), 0.028 g DMTMM (0.10 mmol, 0.8 equiv.), 0.18 mL DIPEA (1.04 mmol, 8.0 equiv.) in anhydrous CH2Cl2 (130 mL, 0.001 M). The reaction was then stirred for 4 hours and monitored via LC/MS. Upon completion, the reaction mixture was worked up as described in the Macrocyclisation procedure and dried in vacuo to produce the crude, protected, cyclic peptide cyclo-Phe-Tyr(t-Bu)-Ser(t-Bu)-Ala-d-Lys(Boc).

**cyclo-Phe-Tyr-Ser-Ala-D-Lys (19)**

The deprotected cyclic peptide was synthesized following the Side Chain Deprotection procedure using 0.064 g crude cyclo-Phe-Tyr(t-Bu)-Ser(t-Bu)-Ala-D-Lys(Boc) (0.079 mmol, 1 equiv.), 567 µL of a mixed solution of TFA and CH2Cl2 (9:1 v/v) and 101 µL anisole (0.47 mmol, 6 equiv.) to generate the free side chains. The reaction mixture was stirred for 5 hours and monitored via LC/MS. Upon completion, the reaction mixture was worked up as described in the Side Chain Deprotection procedure and lyophilised to produce the crude cyclic peptide. The crude product was purified using HPLC to generate pure compound as a white solid (12%).

LC/MS (ESI) m/z: [M+H]+ calculated for C30H41N6O7+, 597.31; found, 597.30.

1H NMR (600 MHz, D2O) δ 7.41-7.25 (m, 5H, Phe), 7.02-7.00 (m, 2H, δH Tyr), 6.82-6.80 (m, 2H, εH Tyr), 4.63-4.60 (t, J = 7.79 Hz, 1H, αH Phe), 4.53-4.50 (m, 1H, αH Tyr), 4.30-4.26 (dd, J = 7.34, 14.72 Hz, 1H, εH Ala), 4.14-4.11 (t, J = 7.86 Hz, 1H, αH Ser), 4.08-4.05 (t, J = 7.67 Hz, 1H, δH Lys), 3.88-3.82 (m, 2H, βCH2 Ser), 3.07-2.97 (m, 2H, βCH2 Tyr), 3.07-2.97 (m, 2H, βCH2 Phe), 2.95-2.92 (m, 2H, εCH2 Lys), 1.70-1.54 (m, 2H, δCH2 Lys), 1.70-1.54 (m, 2H, βCH2 Lys), 1.43-1.41 (d, J = 7.42 Hz, 3H, βCH3 Ala), 1.25-1.12 (m, 2H, γCH2 Lys).
Supporting Information

LC/MS of 1

Chemical Formula: C_{30}H_{40}N_{6}O_{7}
Exact Mass: 596.30
$^{1}H^{-13}C$ HSQC NMR of 1
$^{1}\text{H} - ^{13}\text{C}$ HMBC NMR of 1
$^{1}H-^{1}H$ COSY NMR of 1
Supporting Information

LC/MS of 2

Chemical Formula: C_{33}H_{47}N_{7}O_{7}
Exact Mass: 653.35
1H NMR of 170324-RK-Final Compound
600 MHz D2O 1H.pr

Supporting Information

1H NMR of 2

H NMR of DMSO

H2O

Current Data Parameters
NAME  170324-RK-Final Compound
RFPRO  2
FROCEO  1
F2 - Acquisition Parameters
Date  2017-03-14
Time  16:35 h
INSTRUM spect
PROG  E128744_2003
POLPROG  zgmppep
TD  55356
SOLVENT D2O
NS  16
DS  0
SNR  6002.401 Hz
FIDRES  0.183379 Hz
AQ  5.409189 sec
NS  80.39
DW  83.300 usec
DE  39.23 usec
TE  298.2 K
D1  5.0000000000 sec
D12  0.0000000000 sec
D14  0.0000000000 sec
TD0  1
GFP1  600.1628216 MHz
N01  18
F1  8.00 usec
PL1  3.81009994 W
PL2  0.00001215 W
GPM(11)  smpq10.100
GFP1  99.99 %
F16  1000.00 usec
F2 - Processing parameters
SI  111072
SF  600.1599469 MHz
WDR  EM
SUB  0
LB  0.30 Hz
GB  0
PC  1.00
Supporting Information

$^1$H-$^{13}$C HSQC NMR of 2
R.K. Final Compound
600 D2O 1H-13C HMBC

Supporting Information

1H-13C HMBC NMR of 2
Supporting Information

LC/MS of 3

Chemical Formula: C_{31}H_{41}N_{7}O_{8}
Exact Mass: 639.30

Sample Name: LB69
Data Filename: LB69_A.lcd
Batch Filename: 17-03-27.lcb
Injection Volume: 15 uL
Date Acquired: 27/03/2017 10:58:20 PM
Acquired by: System Administrator

PDA Multi 1 254nm,4nm

TIC(+881)

MS Spectrum
R.Time: 1.350 (Scan #: 82)
MassPeaks: 1938
Segment 1 - Event 1
Intensity

MS Spectrum
R.Time: 7.533 (Scan #: 453)
MassPeaks: 1878
Segment 1 - Event 1
Intensity
Supporting Information

H NMR of Formate

Current Data Parameters
NAME        170328-nri-LB69_C
EXPNO       2
PROCNO      1

F2 - Acquisition Parameters
Date_       20170328
Time_       23:02 h
INSTRUM_    spect
PROBHD_     2128744_0003 (PM1)
PULPROG_    zgcpuppr
TD_         65536
SOLVENT_    D2O
NS_         32
DS_         0
SWH_        6002.113 Hz
FIDRES_     0.201480 Hz
AQ_         4.9632597 sec
RG_         4.15
DW_         75,733 ussec
DE_         33.08 ussec
TE_         296.0 K
D1_         5.0000000000 sec
D12_        0.0000000000 sec
D16_        0.0000000000 sec
TD0_        1
GPO1_       600.168216 MHz
NUC1_       1H
F1_         8.00 ussec
PLW1_       3.81068994 W
PLW9_       0.00090123 W
GPOAM[1]_   SMSQ10.100
GPO1_       50.00 %
P16_        1000.00 ussec

F2 - Processing parameters
SI_         131072
SF_         600.16000000 MHz
NDW_        EM
SDB_        0
SB_         0.30 Hz
PC_         1.00
Supporting Information

LC/MS of 4

Chemical Formula: C_{31}H_{41}N_{7}O_{7}
Exact Mass: 623.31
$^1$H NMR of Formate and H$_2$O
Supporting Information

$^{1}$H-$^{13}$C HSQC NMR of 4
Supporting Information

$^1$H-$^1^3$C HMBC NMR of 4
$^{1}H$-$^{1}H$ COSY NMR of 4
Supporting Information

LC/MS of 5

Chemical Formula: C_{34}H_{48}N_{8}O_{7}
Exact Mass: 680.36
Supporting Information

$^1{H}-^1{C}$ HSQC NMR of 5
Supporting Information

LC/MS of 6

Chemical Formula: C_{31}H_{41}N_{7}O_{8}
Exact Mass: 639.30

Sample Name: LB73
Data File Name: LB73_A2.lcd
Batch File Name: 17-03-27.lcb
Injection Volume: 15 uL
Date Acquired: 27/03/2017 11:39:26 PM
Acquired by: System Administrator
Supporting Information

LC/MS of 7

Chemical Formula: C_{25}H_{37}N_{7}O_{7}
Exact Mass: 547.28
$^{1}H$ NMR of Formate
$^1$H-$^{13}$C HSQC NMR of 7
Supporting Information

H-13C HMBC NMR of 7

1H-13C HMBC NMR of 7

64 scans
Supporting Information

LC/MS of 8

Chemical Formula: C_{28}H_{44}N_{8}O_{7}
Exact Mass: 604.33

<Chromatogram>

PDA Multi 1 200mm.4nm

TIC(+)-Q1

R Time: 1.267 (Scan: 77)
Mass Peaks: 1949
Segment 1 - Event 1
Supervisor McAlpine
LB75
D20_HSQC
Supporting Information

$^1$H-$^{13}$C HMBC NMR of 8
Supporting Information

LC/MS of 9

Sample Name: LB72
Data Filename: LB72_B.lcd
Batch Filename: 17-03-27.lcb
Injection Volume: 15 uL
Date Acquired: 27/03/2017 11:18:53 PM
Acquired by: System Administrator

[Graph of PDA Multi 1 254nm,4nm]

[Graph of TIC(+)@1]

[MS Spectrum R.Time: 1.367 (Scan #: 83)]
Mass Peaks: 1931
Segment 1 - Event 1
Intensity

[MS Spectrum R.Time: 7.533 (Scan #: 453)]
Mass Peaks: 1963
Segment 1 - Event 1
Intensity

S82
Supporting Information

H NMR of 9

Current Data Parameters
NAME: 170316-LB72_P4amE
EXPNO: 3
PROCND: 1

F2 - Acquisition Parameters
Date: 20170316
Time: 16:26 h
INSTRUM: spect
PROCNO: 2128744_0003
FREQUENCY: zqopuppr
TD: 65536
SOLVENT: D2O
NS: 32
DS: 0
SNR: 6965,932 Hz
FIDRES: 0,193988 Hz
AQ: 5,1524965 sec
RG: 80,39
DN: 78,667 usec
DE: 35,01 usec
TE: 298,0 K
D1: 5,00000000 sec
D12: 0,00020000 sec
D16: 0,00020000 sec
TD0: 1
SFO1: 600,1288214 MHz
MUC1: 1H
P1: 8,00 usec
PLW1: 3,01089994 W
PLW9: 0,00000245 W
GPNAM[1]: 3MSQ10,100
GP21: 0,00 %
P16: 1000,00 usec

F2 - Processing parameters
SI: 131072
SF: 600,1600000 MHz
NDW: EM
SSB: 0
LS: 0,30 Hz
GB: 0
PC: 1.00

1H NMR of 9
Supporting Information

Chemical formula: C_{25}H_{37}N_{7}O_{8}

Exact Mass: 563.27
Formate

$\text{H}_2\text{O}$

$^{1}H$ NMR of 10

Current Data Parameters
NAME 160219-10b
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160219
Time 12.36h
INSTRUM spect
PROBBD Z114608_0002
FIDPROG 90CG
TD 65536
SOLVENT D2O
NS 32
DS 0
SWH 6002.401 Hz
FIDRES 0.183179 Hz
AQ 5.4591489 sec
BW 45.2
DN 83.350 usec
DE 7.94 usec
TE 298.0 K
D1 5.0000000 sec
TD0 1
SF01 600.1330000 MHz
NUC1 1H
P1 12.40 usec
PLW1 16.5968067 M

F2 - Processing parameters
SI 131072
SF 600.1330000 MHz
NOW EM
SSB 0
LB 0.30 Hz
GB 0
FC 1.00
$^{1}H-^{13}C$ HSQC NMR of 10
Supporting Information

$^1$H$^{-13}$C HMBC NMR of 10

LB63 purified
D2O 32 scans

Bruker

Current Data Parameters
NAME  100219-136
EXPNR  6
FREQUENCY

P2 - Acquisition Parameters

Data  20191212
INSTR  DRX400
PROBE  D114108_2000
POLIPRM  broadband
POLAR  F2R2
PULPROG  broadband
Selection
NS  512
DS  6000
TE  2.50 sec
T1  257.9 sec
T2  125.000000
T2SE  8.000000
DG  0.0000005 sec
D3  0.000000 sec
DS  0.000000 sec
DP1  0.000000 sec
DP2  0.000000 sec
MP1  11.00 sec
MP2  2000.00 sec
MP3  2000.00 sec
MP4  125.000000
GATE  125.000000
HETCOR  125.000000

F1 - Acquisition parameters
ND  128
SPPR  150.9679 MHz
F1FREQ  60.0000 MHz
F1FREQ  60.0000 MHz
F2FREQ  60.0000 MHz
F2FREQ  60.0000 MHz
F2FREQ  60.0000 MHz

F1 - Processing parameters
DG  1.2875 sec
NDW  128
SHAPE  4
DC  8 kHz
CH  4-40
PC  4-40

F2 - Processing parameters
DG  400.0000 sec
NDW  256
SHAPE  4-40
DC  8 kHz
CH  4-40
PC  4-40

UNITS  Hz

S87
Supporting Information

$^{1}H$-$^{1}H$ COSY NMR of LB63 purified D2O 32 scans
Supporting Information

LC/MS of 11

Chemical Formula: C_{28}H_{44}N_{8}O_{8}
Exact Mass: 620.33

<Chromatogram>

PDA Multi 1 200nm,4nm

(TIC(+))@1

R.Time:0.350(Scan#22)
MassPeaks:1931
Segment 1 - Event 1
$^1\text{H}-^{13}\text{C}$ HSQC NMR of 11
Supporting Information

1H-1H COSY NMR of 11
Supporting Information

LC/MS of 12

Chemical Formula: C_{31}H_{41}N_{7}O_{8}
Exact Mass: 639.30

Sample Name: LB71
Data File Name: LB71_C.lcd
Batch File Name: 17-03-27.lcb
Injection Volume: 15 μL
Date Acquired: 28/03/2017 1:01:43 AM
Acquired by: System Administrator

mAU

PDA Multi 1 254nm,4nm

(TIC(+)@B1)

R.Time: 1.383 (Scan#: 84)
Mass Peaks: 1937
Segment 1 - Event 1
Intensity

6000000
5000000
4000000
3000000
2000000
1000000

640.30
960.50
1279.55

R.Time: 2.530 (Scan#: 442)
Mass Peaks: 1861
Segment 1 - Event 1
Intensity

2000000
1000000

640.30
H NMR of Formate DMSO
Supporting Information

LC/MS of 13

Chemical Formula: C_{28}H_{34}N_{6}O_{8}
Exact Mass: 582.24

PDA Multi 1 254nm,4nm

MS Spectrum

R.Time:8.383(Scann:504)
MassPeaks:1904
Segment 1 - Event 1
Supporting Information

1H NMR of 13

LB60 5mg D2O
\textsuperscript{1}H-\textsuperscript{13}C HSQC NMR of 13
S100

H-1H COSY NMR of 13C
Supporting Information

LC/MS of 14

Chemical Formula: C_{31}H_{41}N_{7}O_{8}
Exact Mass: 639.30

![Chemical Structure](image)

**PDA Multi 254nm,4nm**

| min | 0.0 | 2.5 | 5.0 | 7.5 | 10.0 | 12.5 | 15.0 | 17.5 | 20.0 |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| mAU| 0.0 | 2.5 | 5.0 | 7.5 | 10.0 | 12.5 | 15.0 | 17.5 | 20.0 |

**TIC+(HB1)**

| min | 0.0 | 2.5 | 5.0 | 7.5 | 10.0 | 12.5 | 15.0 | 17.5 | 20.0 |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| (x10,000,000)| 1.77 | 1.50 | 0.0 | 2.5 | 5.0 | 7.5 | 10.0 | 12.5 | 15.0 |

**MS Spectrum**

R.Time: 1.367 (Scan# 83)
Mass Peaks: 1947
Segment 1 - Event 1

| m/z | Intensity |
|-----|-----------|
| 640.30 | 960.50 | 1279.60 |

**MS Spectrum**

R.Time: 7.333 (Scan# 441)
Mass Peaks: 1864
Segment 1 - Event 1

| m/z | Intensity |
|-----|-----------|
| 560.50 | 960.50 | 1279.60 |

Sample Name: LB70
Data File Name: LB70_A.lcd
Batch File Name: 17-03-27.lcb
Injection Volume: 15 μL
Date Acquired: 28/03/2017 12:41:09 AM
Acquired by: System Administrator
Supporting Information

LC/MS of 15

Chemical Formula: C_{33}H_{46}N_{6}O_{7}
Exact Mass: 638.34
1H NMR of 15

Supporting Information

170324-OL-Final Compound
600 MHz D2O 1H.pr

Formate

H2O

DMSO

Current Data Parameters
NAME 170324-OL-Final Compound
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20170324
Time 16:21 h
INSTRM spect
PROBNO 2128744_0003
FDLPDPG rppp2
TD 0.7516
SOLVENT D2O
NS 16
DS 10
SWM 6002.401 Hz
FIDRES 0.183179 Hz
DG 5.4591485 sec
DS 80.39
DW 83.306 usec
DE 38.21 usec
TE 298.2 K
D1 5.000000000 sec
D12 0.000000000 sec
D16 0.000000000 sec
DG 1
SF01 400.1628218 MHz
NSC1 16
P1 8.00 usec
PLW1 3.81069996 W
PLW9 0.000000000245 W
GPMAN(1) DMOQ10.100
GPS1 50.00 %
P16 1000.00 usec

F2 - Processing parameters
SI 131071
SF 600.1599470 MHz
MDW EM
LB 0
NB 0.30 Hz
PB 1.00
$^1$H-$^{13}$C HSQC NMR of 15
O.L. Final Compound
600 D2O 1H-13C HMBC
LC/MS of 16

Chemical Formula: C_{36}H_{44}N_{6}O_{7}
Exact Mass: 672.33
Supporting Information

$S_{109}$

$^1H$ NMR of 16

Formate
$^1$H-$^{13}$C HSQC NMR of 16
1H-1H COSY NMR of 16

Current Data Parameters
NAME  17031023-VC-Final Compound
EXPMN  4
PROCNO  1
F2 - Acquisition Parameters
Date_  20170323
Time  23:05 h
FIDSC  1
F2HNMR  1228744_0003
FIDPROG  cox1pige
TD  500
SOLVENT  0100
NS  16
D2  16
SNH  5760.36 Hz
FTRES  1.225560 Hz
AQ  0.3777866 sec
RS  134.76
DN  84.895 usec
dx  30.00 usec
dE  236.2 Hz
DO  0.00001661 sec
D1  0.00004600 sec
D13  0.00006800 sec
D16  0.00009000 sec
D18  0.00017661 sec
PPM  1
SPFO  500.1628220 MHz
NPP1  18
P1  8.00 usec
P2  16.00 usec

F1 - Acquisition parameters
TD  122
SPFO  500.1628 MHz
FIDRES  0.000764 Hz
SN  9.98 ppm
FUNCOE  States=6

F2 - Processing parameters
SI  2048
SP  500.1620000 MHz
MCW  QININE
SB  0
IA  0 Hz
GC  0
PC  1.40

F1 - Processing parameters
SI  2048
MC  States=6
SP  500.1620000 MHz
MCW  QININE
SB  0
IA  0 Hz
GC  0
Chemical Formula: C₃₁H₄₀N₆O₉
Exact Mass: 640.29
Supporting Information

1H NMR of 17

Current Data Parameters
NAME  170313-jkh
EXPMO  13
PROCNO  1

F2 - Acquisition Parameters
Date_  20170313
Time  16.57 h
INSTRUM  spect
PROCMD  E128744_0003 (spect
PULPROG  zgcpppr
TD  48076
SOLVENT  D2O
NS  16
DS  3
SNH  7211.539 Hz
FTRES  0.300806 Hz
AQ  3.3332694 sec
RG  80.39
DW  69.333 usec
DE  37.26 usec
TE  298.0 K
D1  5.00000000 sec
D12  0.00000000 sec
D16  0.00000000 sec
TDR  1
SPOL  600.1620214 MHz
MRCI  1H
P1  8.00 usec
PLM  3.8106999 W
PLMB  0.00000123 W
GPRAM[1]  SNSQ10.100
GPS  50.00 %
P16  1000.00 usec

F2 - Processing parameters
SI  131972
SF  600.1599530 MHz
WDM  0
SSB  0
LB  0.30 Hz
CB  0
PC  1.00
$^1$H-$^{13}$C HSQC NMR of 17

Supporting Information

Current Data Parameters

NAME         170306-jkh
EXPNO                 4
PROCNO                1

F2 - Acquisition Parameters
Date_          20170306
Time              11.08 h
INSTRUM           spect
PROBHD   Z128744_0003 (
PULPROG  hsqcedetgpsisp2.4
TD                 2048
SOLVENT             D2O
NS                   10
DS                  128
SWH            7352.941 Hz
FIDRES         7.180607 Hz
AQ            0.1392640 sec
RG               202.23
DW               68.000 usec
DE                30.00 usec
TE                298.0 K
CNST2       145.0000000
CNST17       -0.5000000
D0           0.00000300 sec
D1           1.00000000 sec
D2           0.00344828 sec
D4           0.00172414 sec
D11          0.03000000 sec
D16          0.00020000 sec
D21          0.00344828 sec
D24          0.00086207 sec
IN0          0.00001790 sec
L0       0
TD0                   2
TDav                  1
SFO1        600.1635259 MHz
NUC1                 1H
P1                 8.00 usec
P2                16.00 usec
P28      0 usec
PLW1         3.81069994 W
SFO2        150.9231794 MHz
NUC2                13C
CPDPRG[2 bi_p5m4sp_4sp.2
P3                11.50 usec
P14              500.00 usec
P24             2000.00 usec
P31             1730.00 usec
P63             1500.00 usec
PLW0     0 W
PLW2        89.94999695 W
PLW12        3.30439997 W
SPNAM[3] Crp60,0.5,20.1
SPOAL3            0.500
SPOFFS3  0 Hz
SPW3        18.17600060 W
SPNAM[7]    Crp60comp.4
SPOAL7            0.500
SPOFFS7  0 Hz
SPW7        18.17600060 W
SPNAM[14 Crp42,1.5,20.2
SPOAL14           0.500
SPOFFS14 0 Hz
SPW14       10.17800045 W
SPNAM[18  Crp60_xfilt.2
SPOAL18           0.500
SPOFFS18 0 Hz
SPW18        5.25309992 W
SPNAM[31 Crp42,1.5,20.2
SPOAL31           0.500
SPOFFS31 0 Hz
SPW31        2.54460001 W
GPNAM[1]     SMSQ10.100
GPZ1              80.00 %
GPNAM[2]     SMSQ10.100
GPZ2              20.10 %
GPNAM[3]     SMSQ10.100
GPZ3              11.00 %
GPNAM[4]     SMSQ10.100
GPZ4              -5.00 %
P16             1000.00 usec
P19              600.00 usec

F1 - Acquisition parameters
TD                  258
SFO1           150.9232 MHz
FIDRES       216.534576 Hz
SW              185.081 ppm
FnMODE    Echo-Antiecho

F2 - Processing parameters
SI                 1024
SF          600.1599534 MHz
WDW               QSINE
SSB                   2
LB       0 Hz
GB       0
PC                 1.40

F1 - Processing parameters
SI                 1024
MC2       echo-antiecho
SF          150.9103520 MHz
WDW               QSINE
SSB                   2
LB       0 Hz
GB       0
Supporting Information

\[ ^{1}H\text{-}^{13}C \text{ HMBC NMR of 17} \]

Current Data Parameters

- NAME: 170302-jkh
- EXPNO: 12
- PROCNO: 1

F2 - Acquisition Parameters

- Date: 20170302
- Time: 22.42 h
- INSTRUM: spect
- PROBHD: Z128744_0003
- PULPROG: hmbcetgpl3nd
- TD: 2048
- SOLVENT: D2O
- NS: 40
- DS: 16
- SWH: 7352.941 Hz
- FIDRES: 7.180607 Hz
- AQ: 0.1392640 sec
- RG: 202.23
- DW: 68.000 usec
- DE: 30.00 usec
- TE: 298.0 K
- CNST6: 125.0000000
- CNST7: 165.0000000
- CNST13: 8.0000000
- D0: 0.00000300 sec
- D1: 1.00000000 sec
- D6: 0.06250000 sec
- D16: 0.00020000 sec
- IN0: 0.00001380 sec
- TDav: 1
- SFO1: 600.1635259 MHz
- NUC1: 1H
- P1: 8.00 usec
- P2: 16.00 usec
- PLW1: 3.81069994 W
- SFO2: 150.9277 MHz
- NUC2: 13C
- P3: 11.50 usec
- P24: 2000.00 usec
- PLW2: 89.94999695 W
- SPNAM[7]: Crp60comp.4
- SPOAL7: 0.500
- SPOFFS7: 0 Hz
- SPW7: 18.17600060 W
- GPNAM[1]: SMSQ10.100
- GPZ1: 80.00 %
- GPNAM[3]: SMSQ10.100
- GPZ3: 14.00 %
- GPNAM[4]: SMSQ10.100
- GPZ4: -8.00 %
- GPNAM[5]: SMSQ10.100
- GPZ5: -4.00 %
- GPNAM[6]: SMSQ10.100
- GPZ6: -2.00 %
- P16: 1000.00 usec

F1 - Acquisition parameters

- TD: 128
- SFO1: 150.9277 MHz
- FIDRES: 566.123169 Hz
- SW: 240.061 ppm
- FnMODE: Echo-Antiecho

F2 - Processing parameters

- SI: 4096
- SF: 600.1599551 MHz
- WDW: SINE
- SSB: 4
- LB: 0 Hz
- GB: 0
- PC: 1.40

F1 - Processing parameters

- SI: 2048
- MC2: echo-antiecho
- SF: 150.9103520 MHz
- WDW: SINE
- SSB: 2
- LB: 0 Hz
- GB: 0

Current Data Parameters

- NAME: 170302-jkh
- EXPNO: 12
- PROCNO: 1
$^1$H-$^1$H COSY NMR of Lb104 - D2O - COSYwg

Current Data Parameters
NAME 170325-JK
EXPNO 4
PROCNO 1

F2 - Acquisition Parameters
Date 20170324
Time 1.56 h
INSTRUM spect
FREQRS 516580 Hz
AQ 0.1796779 sec
RG 202.23
DW 87.733 usec
DE 30.00 usec
TE 298.1 K
D0 0.00007751 sec
D1 2.50000000 sec
D11 0.03000000 sec
D12 0.00002000 sec
D13 0.00000400 sec
D16 0.00020000 sec
D19 0.00013868 sec
IN0 0.00017540 sec
TDav 1
SFO1 600.1628214 MHz
NUC1 1H
P0 8.00 usec
P1 8.00 usec
P2 8.00 usec
PLW1 3.81069994 W
GPNAM[1] SINE.100
GPZ1 30.00 %
P16 1000.00 usec

F1 - Acquisition parameters
TD 128
SFO1 600.1628 MHz
FIDNRS 49.0815100 Hz
SW 9.500 ppm
FIDMODE States-TPPI

F1 - Processing parameters
SI 2048
SF 600.1595545 MHz
VAM SINE
SSB 0
GB 0
PO 1.40

F2 - Processing parameters
SI 2048
MC2 States-TPPI
SP 600.1595625 MHz
VAM SINE
SSB 0
LB 0
GB 0
Supporting Information

LC/MS of 18

Chemical Formula: C_{30}H_{40}N_{6}O_{7}
Exact Mass: 596.30

![Chromatogram and MS Spectrum Graphs](image-url)
1H NMR of 18

Supporting Information

Formate

Current Data Parameters
NAME  170110-AG-Pure product A
EXPRO  3
PROCINO  1

F2 - Acquisition Parameters
Date_  20170119
Time_  13.31 b
INSTCMM  spec
c
PROMETH  1114744_0003 (c)
PULPROG  zpgoppwr
SD  69536
SOVENT  D2O
NS  16
DS
SSS  6345.178 Hz
FIDRES  0.193639 Hz
AQ  5.1642370 sec
BG  80.15
DW  78.800 usec
DE  44.72 usec
TE  298.0 K
D1  5.00000000 sec
D12  0.00000000 sec
D16  0.00000000 sec
TDQ  1
SFC1  600.1628217 MHz
MDC1  1.0
FP  1.00 usec
PLN  3.81069999 W
PLW  0.00000122 W
UFW[1]  0.00012200
UPF[1]  0.000000%
P16  1000.0000 usec

F2 - Processing parameters
J1  10.075
SF  600.1599470 MHz
SWX  15.000
SSB  0
SL  0.30 Hz
GB  0
PC  1.00
$^{1}H$-$^{13}C$ HSQC NMR of 18
$^{1}$H-$^{13}$C HMBC NMR of 18
Supporting Information

1H-1H COSY NMR of 18
LC/MS of 19

Chemical Formula: C_{30}H_{40}N_{6}O_{7}
Exact Mass: 596.30
Current Data Parameters
NAME          170313-jkh
EXPNO          17
PROCNO          1

F2 - Acquisition Parameters
Date            20170313
Time             17.26 h
INSTTRM         spect
PROBHD   2128744_0003
PULPROG        zgcpgppr
TD              48076
SOLVENT        D2O
NS                 3
DS                  5
SW                  7211.539 Hz
NSRES          600.1628214 MHz
AQ                3.3332694 sec
DG             80.35
DM                69.333 usec
DE                37.26 usec
TE                 298.0 K
D1           5.00000000 sec
D12          0.00020000 sec
D16          0.00020000 sec
T1D          600.1628214 MHz
F1C            19
P1                8.00 usec

F2 - Processing parameters
SF           600.1599525 MHz
DSM         0.1599525 MHz
IMM             8
LS                0 sec
GB               0
PC                1
SMG10.100
P16            1000.00 usec

Formate
Supporting Information

$^{1}$H–$^{13}$C HSQC NMR of 19
Supporting Information

$^1$H-$^{13}$C HMBC NMR of 19

Current Data Parameters
NAME: 170302-jkh
EXPNO: 20
PROCNO: 1

F2 - Acquisition Parameters
Date: 20170303
Time: 5.29 h
INSTRUM: spect
PROBHD: Z128744_0003
PULPROG: hmbcetgpl3nd
TD: 2048
SOLVENT: D2O
NS: 40
DS: 16
SWH: 7352.941 Hz
FIDRES: 7.180607 Hz
AQ: 0.1392640 sec
RG: 202.23
DW: 68.000 usec
DE: 30.00 usec
TE: 298.0 K
CNST6: 125.0000000
CNST7: 165.0000000
CNST13: 8.0000000
D0: 0.0000300 sec
D1: 1.00000000 sec
D6: 0.06250000 sec
D16: 0.00020000 sec
IN0: 0.001380 sec
IN1: 400.1435259 MHz
IN2: 16.00 usec
FW1: 3.81069994 W
FW2: 150.9277 MHz
F1: 1.00 usec
F2: 11.40 usec
GZ1: 80.00 %
GZ2: 14.00 %
GZ3: -8.00 %
GZ4: -4.00 %
GZ5: -2.00 %
P16: 1000.00 usec

F1 - Acquisition parameters
TD: 128
SFO1: 150.9277 MHz
FIDRES: 566.123169 Hz
SW: 240.061 ppm
FnMODE: Echo-Antiecho

F2 - Processing parameters
SI: 4096
SF: 600.1599492 MHz
WDW: SINE
SSB: 4
LB: 0 Hz
GB: 0
PC: 1.40

F1 - Processing parameters
SI: 2048
MC2: echo-antiecho
SF: 150.9103520 MHz
WDW: SINE
PC: 1.40

LB: 0 Hz
GS: 0
Supporting Information

$^1$H-$^1$H COSY NMR of LB108 - D2O - COSY

Current Data Parameters
NAME: 170324-jkh

EXPNO: 3
PROCNO: 1

F2 - Acquisition Parameters
Date: 20170324
Time: 17.36 h
INSTRUM: spect
PROBHD: Z128744_0003 (PULPROG: cosygpmfph)
TD: 2048
SOLVENT: D2O
NS: 16
DS: 16
SWH: 5699.088 Hz
FIDRES: 5.565516 Hz
AQ: 0.1796779 sec
RG: 202.23
DW: 87.733 usec
DE: 30.00 usec
DE: 238.0 K
D2: 0.00003781 sec
D1: 1.00000000 sec
D13: 0.00000000 sec
D16: 0.00013600 sec
T1ev: 600.1628214 MHz

F1 - Acquisition parameters
TD: 128
SFO1: 600.1628 MHz
FIDRES: 114.889709 Hz
SW: 12.252 ppm
FnMODE: States-TPPI

F2 - Processing parameters
SI: 2048
SF: 600.1599436 MHz
WDW: QSINE
SSB: 2
LB: 0 Hz
PC: 1.40

F1 - Processing parameters
SI: 2048
SF: 600.1599463 MHz
WW: QST10
LS: 0 Hz
CR: 0

F1 - Processing parameters
SI: 2048
SF: States-TPPI
WW: 600.1599456 MHz
LS: 0 Hz
CR: 0