Electronic Supplementary Information for

Copper (II)-mediated C-H sulphenylation or selenylation of tryptophan enabling macrocyclization of peptides

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Contents

General Information

Materials.

All reagents and solvents were obtained from Peptide Institute, Inc. (Osaka, Japan), FUJIFILM Wako Pure Chemical Corporation (Osaka, Japan), Tokyo Chemical Industry Co., Ltd (Tokyo, Japan), Nacalai Tesque, Inc. (Kyoto, Japan), Watanabe Chemical Industries, Ltd (Hiroshima, Japan), Merck KGaA (Darmstadt, Germany), Combi-Blocks Inc. (San Diego, USA), Sigma-Aldrich Co. LLC (St Louis, MO), and CEM Corporation (North Carolina, USA).

NMR.

NMR spectra were recorded using a Bruker AV400N at 400 MHz or Bruker AV500 at 500 MHz frequency for ^{1}H, and Bruker AV400N at 100 MHz or Bruker AV500 at 125 MHz frequency for ^{13}C in the stated solvents. Chemical shifts were reported in parts per million (ppm) on the δ scale from an internal standard (NMR descriptions: s, singlet; d, doublet; t, triplet; dd, double doublet; m, multiplet; br, broad). Coupling constants, *J*, are reported Hertz.

Circular dichroism (CD) spectroscopy.

All CD spectra were obtained with 2 mm path length quartz cuvette on JASCO J-1500 CD spectrometer at 25 °C. Sample preparation for CD: Peptide **2** or **22** (0.80 mg each) was dissolved in 1.0 mL of MeOH. Measurements were taken over 200–320 nm (0.2 nm steps).

HPLC, MS.

Each peptide was characterized by MS analysis as described below. Mass spectra were recorded on a Waters MICROMASS®LCT PREMIERTM (ESI-TOF) or a LC-MS (Shimadzu, Japan, Prominence-I LC-2030, LCMS-2020) and a Cosmosil 5C_{18}-AR-II analytical column (Nacalai Tesque, Japan, 4.6 × 250 mm, flow rate 1 mL min^{-1}) were used, and eluting products were detected by UV at 220 nm and MS. For HPLC analysis and separation, HPLC was carried out on HITACHI L-7150 with an L-2400 detector or Waters Alliance 2695 Separations Module with ELS 2420 System using a Cosmosil 5C_{18}-AR-II analytical column (Nacalai Tesque, 4.6 × 250 mm, flow rate 1.0 mL min^{-1}), a Cosmosil 5C_{18}-AR-II semipreparative column (Nacalai Tesque, 10 × 250 mm, flow rate 3.0 mL min^{-1}), or a Cosmosil 5C_{18}- AR-II preparative column (Nacalai Tesque, 20 × 250 mm, flow rate 10 mL min^{-1}) eluting with a linear gradient system (solvent A: 0.1% TFA in H_2O, solvent B: 0.1% TFA in MeCN), and eluting products were detected by UV at 220 nm.

Solid-phase peptide synthesis (SPPS) of peptides used in this research.

Manual SPPS

Peptide acids (**1**, **3**, **9**, and **20**) used in this work were synthesised on Fmoc-Gly-Cl-Trt resin (1.02 mmol g^{-1}). Peptide amides (**10a**, **11a**, **12a**, **13a**, **14a**, **15a**. **16a**, **17a,** and **S1**) used in this work were synthesised on Rink Amide AM resin (0.67 mmol g^{-1}). Manual Fmoc SPPS was performed according to the following protocol. 1) Removal of Fmoc groups was carried out using 20% piperidine in DMF for 10 min at room temperature (rt). 2) The resin was washed with DMF (× 5). 3) Fmoc-protected

amino acid (4.0 equiv.) was coupled with the aid of *N*,*N*-diisopropylcarbodiimide (DIPCI) (4.0 equiv.) and 1-hydroxybenzotriazole monohydrate (HOBt·H_2O) (4.0 equiv.) in DMF for 1.5 h at rt. Completion of the coupling reaction was checked by the Kaiser ninhydrin test. The coupling reaction was repeated until the Kaiser test became negative. 4) The resin was washed with DMF (× 3). A cycle of steps 1 to 4 was repeated. Deprotection of acid-labile protecting groups with concomitant release of peptides from the resin was achieved using a cocktail of TFA–triisopropylsilane (TIS)–H_2O (90:5:5, (*v*/*v*)) (50 μL/1 mg resin) at rt for 1.5–2 h. After the resin was filtered off, cooled diethyl ether (Et_2O) was added to the filtrate and the precipitate was collected by centrifugation. The obtained precipitate was dissolved in 0.1% TFA-containing H_2O–MeCN. For the incorporation of the N-terminal 1,3-thiazolidine-4-carbonyl (Thz) or 1,3-selenazolidine-4-carbonyl (Sez) residue, Boc-Thz-OH or Boc-Sez-OH[S1] was used. For the side chain protection of Fmoc amino acids, following side-chain protections were employed: 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl (Pbf) for Arg; Trt for Cys, His, Asn, and Gln; *t*Bu for Ser, Thr, and Tyr; Boc for Lys.

Microwave-assisted SPPS.

Peptide amides **18a** and **S2** were synthesised on Rink Amide ProTide® resin (0.56 mmol g^{-1}) using Liberty Blue® peptide synthesiser (CEM, USA). Microwave-assisted Fmoc SPPS was performed according to the following protocol. 1) Removal of Fmoc groups was carried out using 20% piperidine in DMF for 50 seconds at 90 °C with microwave irradiation. 2) The resin was washed with DMF (× 4). 3) Fmoc-protected amino acid (5.0 equiv.) was coupled with the aid of *N*,*N*-diisopropylcarbodiimide (DIPCI) (10.0 equiv.) and Oxyma Pure® (5.0 equiv.) in DMF for 110 seconds at 90 °C or 480 seconds at 50 °C with microwave irradiation. In the case of coupling of Fmoc-Arg(Pbf)-OH, this step was repeated twice. A cycle of steps 1 to 3 was repeated. Procedures identical to those employed in manual SPPS were used for the following steps. The N-terminal Thz residue was manually incorporated on resins using Boc Thz-OH.

Characterization of synthetic substrate peptides excepts for peptides 18a and S2.

*H-Thz-**NPI**-Trp-**GIG**-OH* (**1**) (7.83 mg, 7.95 μmol, 8% isolated yield). Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min (Column was heated to 60 °C), Retention time (RT) = 16.3 min. Preparative HPLC conditions: linear gradient of solvent B in solvent A, 30% to 40% over 30 min, RT = 8.3 min. LRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{40}H_{58}N_{10}O_{10}S$ 871.4, found 871.4.

*H-Cys-**NPI**-Trp-**GIG**-OH* (**3**) (6.68 mg, 6.87 μmol, 7% isolated yield.) Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min, RT = 16.1 min. Preparative HPLC conditions: linear gradient of solvent B in solvent A, 24% to 34% over 30 min, RT = 9.9 min. LRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{39}H_{58}N_{10}O_{10}S$ 859.4, found 859.3.

*Ac-Cys-**NPI**-Trp-**GIG**-OH* (**9**) (4.83 mg, 5.37 μmol, 5% isolated yield.) Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min, RT = 18.3 min. Preparative HPLC conditions: linear gradient of solvent B in solvent A, 28% to 38% over 30 min, RT = 12.1 min. LRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{41}H_{60}N_{10}O_{11}S$ 901.5, found 901.4.

*H-Thz-**GA**-Trp-**R**-NH_2* (**10a**) (9.59 mg, 11.55 μmol, 51% isolated yield.) Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min, RT = 10.5 min. Preparative HPLC conditions: linear gradient of solvent B in solvent A, 10% to 20% over 30 min, RT = 13.6 min. LRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{26}H_{38}N_{10}O_5S$ 603.3, found 603.3.

*H-Thz-**GALRA**-Trp-**R**-NH_2* (**11a**) (6.69 mg, 5.21 μmol, 31% isolated yield.) Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min, RT = 12.9 min. Preparative HPLC conditions: linear gradient of solvent B in solvent A, 14% to 24% over 30 min, RT = 12.7 min. LRMS (ESI-TOF) *m/z*: $[M+2H]^+$ calcd for $C_{41}H_{66}N_{16}O_8S$ 472.3, found 472.2.

*H-Thz-**GAL**-Trp-**R**-NH_2* (**S1**) (11.80 mg, 14.24 μmol, 21% isolated yield.) Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 45% over 30 min, RT = 17.6 min. Preparative HPLC conditions: linear gradient of solvent B in solvent A, 12% to 22% over 30 min, RT = 12.1 min. LRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{32}H_{49}N_{11}O_6S$ 716.4, found 716.3.

*H-Thz-**GFL**-Trp-**R**-NH_2* (**12a**) (20.47 mg, 20.07 μmol, 59% isolated yield.) Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min, RT = 15.9 min. Preparative HPLC conditions: linear gradient of solvent B in solvent A, 22% to 32% over 30 min, RT = 9.9 min. LRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{38}H_{53}N_{11}O_6S$ 792.4, found 792.0.

*H-Thz-**GKL**-Trp-**R**-NH_2* (**13a**) (19.06 mg, 17.09 μmol, 50% isolated yield.) Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min, RT = 11.4 min. Preparative HPLC conditions: linear gradient of solvent B in solvent A, 13% to 23% over 30 min, RT = 11.4 min. LRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{35}H_{56}N_{12}O_6S$ 773.4, found 773.0.

*H-Thz-**GHL**-Trp-**R**-NH_2* (**14a**) (21.82 mg, 19.41 μmol, 57% isolated yield.) Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min, RT = 11.5 min.

Preparative HPLC conditions: linear gradient of solvent B in solvent A, 13% to 23% over 30 min, RT = 11.5 min. LRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{35}H_{51}N_{13}O_6S$ 782.4, found 782.0.

*H-Thz-**GML**-Trp-**R**-NH₂* (**15a**) (21.01 mg, 20.93 μmol, 62% isolated yield.) Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min, RT = 14.2 min. Preparative HPLC conditions: linear gradient of solvent B in solvent A, 17% to 27% over 30 min, RT = 12.0 min. LRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{34}H_{53}N_{11}O_6S_2$ 776.4, found 775.9.

*H-Thz-**GSL**-Trp-**R**-NH₂* (**16a**) (15.41 mg, 16.05 μmol, 47% isolated yield.) Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min, RT = 12.5 min. Preparative HPLC conditions: linear gradient of solvent B in solvent A, 15% to 25% over 30 min, RT = 11.6 min. LRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{32}H_{49}N_{11}O_7S$ 732.4, found 732.0.

*H-Thz-**GYL**-Trp-**R**-NH₂* (**17a**) (19.77 mg, 19.08 μmol, 56% isolated yield.) Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min, RT = 14.0 min. Preparative HPLC conditions: linear gradient of solvent B in solvent A, 18% to 28% over 30 min, RT = 10.6 min. LRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{38}H_{53}N_{11}O_7S$ 808.4, found 808.0.

*H-Sez-**NPI**-Trp-**GIG**-OH* (**20**) (19.08 mg, 18.49 μmol, 18% isolated yield.) Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min (Column was heated to 60 °C), RT = 17.2 min. Preparative HPLC conditions: linear gradient of solvent B in solvent A, 24% to 34% over 30 min, RT = 11.9 min. LRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{40}H_{58}N_{10}O_{10}Se$ 919.4, found 918.9.

Optimization of copper-mediated Cys-Trp-linking reaction

Examination of Cys-Trp-linking reaction in aqueous buffers containing 6 M Gn·HCl (Table 1, entries 1 and 2)

Substrate peptide **1** (0.10 μmol) was dissolved in aqueous buffer containing 6 M Gn·HCl (100 μL). To the mixture was added 800 mM $CuCl_2 \cdot 2H_2O$ or $CuSO_4 \cdot 5H_2O$ in H_2O (5.0 μL, 4.0 μmol each), and then the solution was stirred at 37 °C for 45 min under aerobic conditions. The resulting mixture was diluted fivefold with 100 mM EDTA aq. and analyzed with HPLC.

Peptide **4**: Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min (Column was heated to 60 °C), RT = 17.0 min. LRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{39}H_{56}N_{10}O_{10}S$ 857.4, found 857.3.

By-product **A**: Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min (Column was heated to 60 °C), RT = 16.4 min. LRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{39}H_{56}N_{10}O_{12}S$ 889.4, found 889.2.

By-product **B**: Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min (Column was heated to 60 °C), RT = 15.7 min. LRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{39}H_{58}N_{10}O_{13}S$ 907.4, found 907.4.

Examination of Cys-Trp-linking reaction in HFIP or EtOH–aqueous buffer containing Gn·HCl (Table 1, entries 3 and 4)

Substrate peptide **1** (0.10 μmol) was dissolved in HFIP or EtOH (80 μL), and then 6 M Gn·HCl–0.1 M Tris·HCl aq. (20 μL) was added to the solution. After vigorous mixing, 800 mM $CuCl_2 \cdot 2H_2O$ in H_2O (5.0 μL) was added to the solution with additional stirring at 37 °C for 45 min under aerobic conditions. The reaction was diluted fivefold with 100 mM EDTA aq. and analyzed with HPLC.

By-product **C**: Analytical HPLC condition: linear gradient of solvent B in solvent A, 5% to 65% over 30 min (Column was heated to 60 °C), RT = 19.2 min. LRMS (ESI-TOF) *m/z*: $[M+2H]^+$ calcd for $C_{78}H_{114}N_{20}O_{20}S_2$ 858.4, found 858.5.

Examination of Cys-Trp-linking reaction in HFIP–ethylene glycol–aqueous buffer (Table 1, entry 5)

Substrate peptide **1** (0.10 μmol) was dissolved in HFIP (80 μL); then, 1 M Tris·HCl aq./ethylene glycol (1/1) (10 μL) was added to the solution.. After vigorous mixing, 400 mM $CuCl_2 \cdot 2H_2O$ in H_2O/ethylene glycol (1/1) (10 μL) was added to the mixture with additional stirring at 37 °C for 2 h under aerobic conditions. The reaction was diluted fivefold with 100 mM EDTA aq. and analyzed with HPLC.

By-product **D**: Analytical HPLC condition: linear gradient of solvent B in solvent A, 5% to 65% over 30 min (Column was heated to 60 °C), RT = 17.5-20.0 min (multi peak). LRMS (ESI-TOF) *m/z*: $[M+2H]^+$ calcd for $C_{78}H_{114}N_{20}O_{21}S_2$ 866.4, found 866.5.

By-product **E**: Analytical HPLC condition: linear gradient of solvent B in solvent A, 5% to 65% over 30 min (Column was heated to 60 °C), RT = 17.5-20.0 min (multi peak). LRMS (ESI-TOF) *m/z*: $[M+2H]^+$ calcd for $C_{78}H_{114}N_{20}O_{22}S_2$ 874.4, found 874.6.

Examination of Cys-Trp-linking reaction in HFIP–ethylene glycol–H_2O containing 20 mM $FeSO_4$ (Table 1, entries 6 and 7)

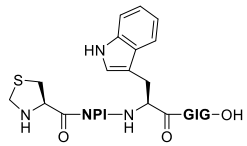
Substrate peptide **1** or **3** (0.10 μmol) was dissolved in HFIP (80 μL). To the solution was then added 1 M Tris·HCl–200 mM $FeSO_4 \cdot 7H_2O$ in H_2O/ethylene glycol (1/1) (10 μL), which afforded a white suspension. After vigorous mixing for a few seconds, 400 mM $CuCl_2 \cdot 2H_2O$ in H_2O/ethylene glycol (1/1) (10 μL) was added to the mixture with additional stirring at 37 °C for 2 h under aerobic conditions. The reaction was diluted fivefold with 100 mM EDTA aq. analyzed with HPLC.

Isolation of Cys-Trp-linked peptide 4

Substrate peptide **1** (3.91 mg, 3.97 μmol) was dissolved in HFIP (3.18 mL); then, 1 M Tris·HCl–200 mM $FeSO_4 \cdot 7H_2O$ solution in H_2O/ethylene glycol (1/1) (397 μL) was added to the solution, which afforded a white suspension. After vigorous mixing for a few seconds, 400 mM $CuCl_2 \cdot 2H_2O$ solution in H_2O/ethylene glycol (1/1) (397 μL) was added to the mixture with additional stirring at 37 °C for 2 h under aerobic conditions. The quenching of reaction with 100 mM EDTA aq. (3.97 mL) and the HPLC-purification afforded Cys-Trp-linked peptide **4** (1.88 mg, 49% isolated yield).

Preparative HPLC conditions of peptide **4**: linear gradient of solvent B in solvent A, 27% to 37% over 30 min (Column was heated to 60 °C), RT = 9.0 min. LRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{39}H_{56}N_{10}O_{10}S$ 857.4, found 857.3.

HPLC trace of the reactions listed in Table 1



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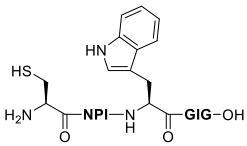

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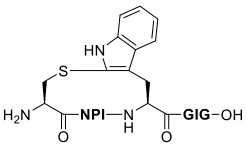

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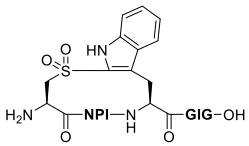
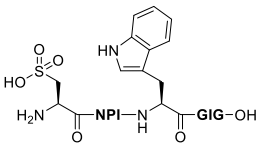


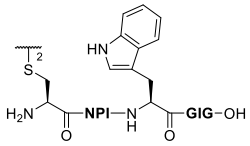
A

LRMS: $[M+H]^+$ calcd 889.4, found 889.2



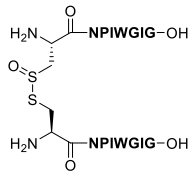
B

LRMS: $[M+H]^+$ calcd 907.4, found 907.4



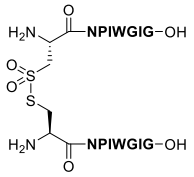
C

LRMS: $[M+H]^+$ calcd 858.4, found 858.5



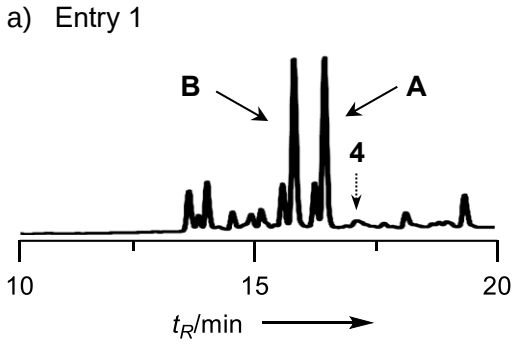
D

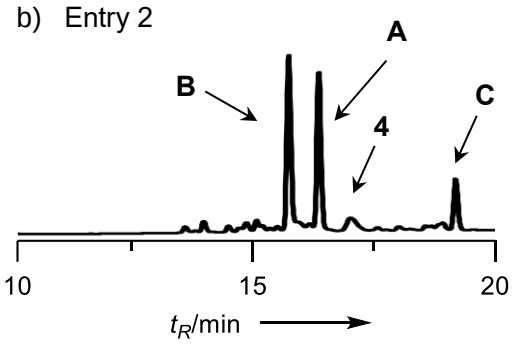
LRMS: $[M+H]^+$ calcd 866.4, found 866.5

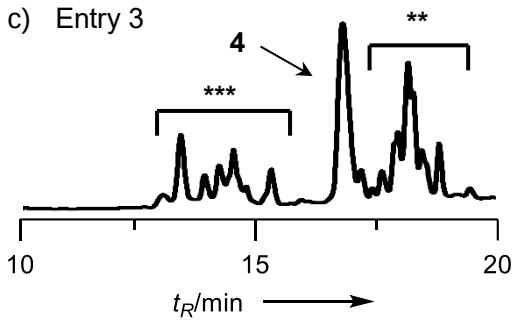


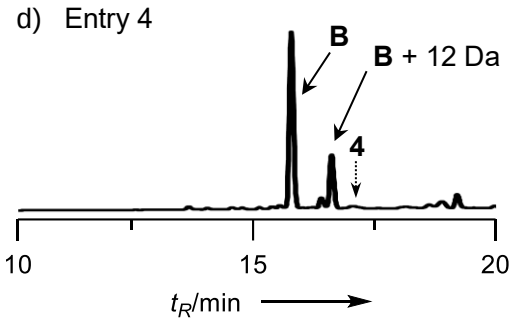
E

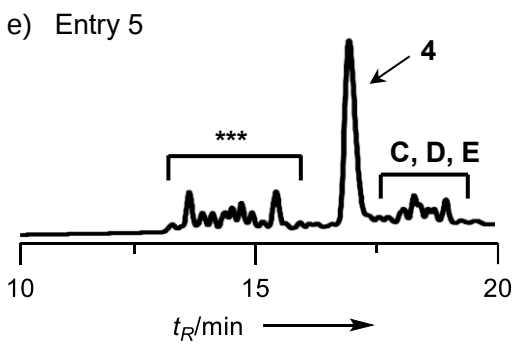
LRMS: $[M+H]^+$ calcd 874.4, found 874.6











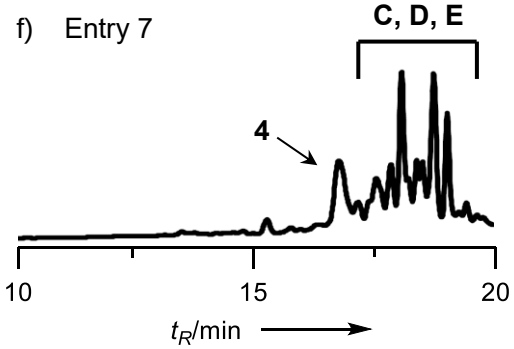


Figure S1. Analytical HPLC charts of crude reaction mixture. Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min. (Column was heated to 60 °C)
Peptides possessing molecular weight smaller than that of **3. ***Complex mixture of by-products containing **4** - 179.5 Da and **B** + 28 Da. Dotted arrowed line (in Figs. S1(a and d) indicated the expected elution point of the desired peptide **4**.

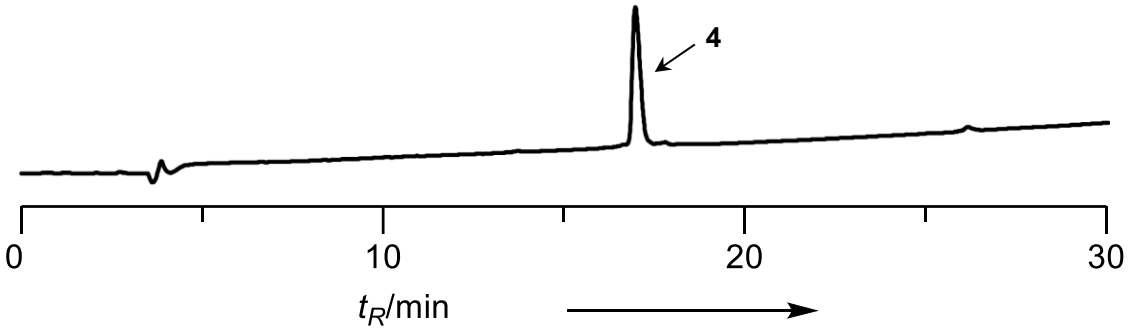
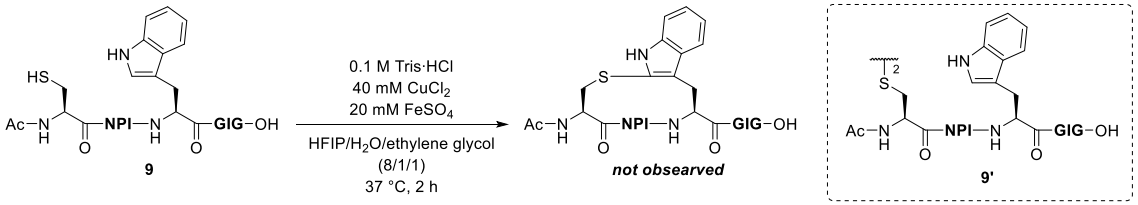


Figure S2. Analytical HPLC charts of purified Cys-Trp-linked peptide **4**. Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min (Column was heated to 60 °C).

The examination of Cys-Trp-linking reaction using N- acetyl Cys peptide (9)

Scheme S1. The reaction overview.



Substrate peptide **9** (0.10 μmol) was dissolved in HFIP (80 μL), and then 1 M Tris·HCl–200 mM $FeSO_4 \cdot 7H_2O$ solution in H_2O/ethylene glycol (1/1) (10 μL) was added to the solution, which afforded a white suspension. After vigorous mixing for a few seconds, 400 mM $CuCl_2 \cdot 2H_2O$ solution in H_2O/ethylene glycol (1/1) (10 μL) was added to the mixture with additional stirring at 37 °C for 2 h under aerobic conditions. The reaction was diluted fivefold with 100 mM EDTA aq. and analyzed with HPLC.

Disulphide peptide **9'**: Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min (Column was heated to 60 °C), RT = 21.8 min. LRMS (ESI-TOF) *m/z*: $[M+2H]^+$ calcd for $C_{82}H_{118}N_{20}O_{22}S_2$ 900.4, found 900.4.

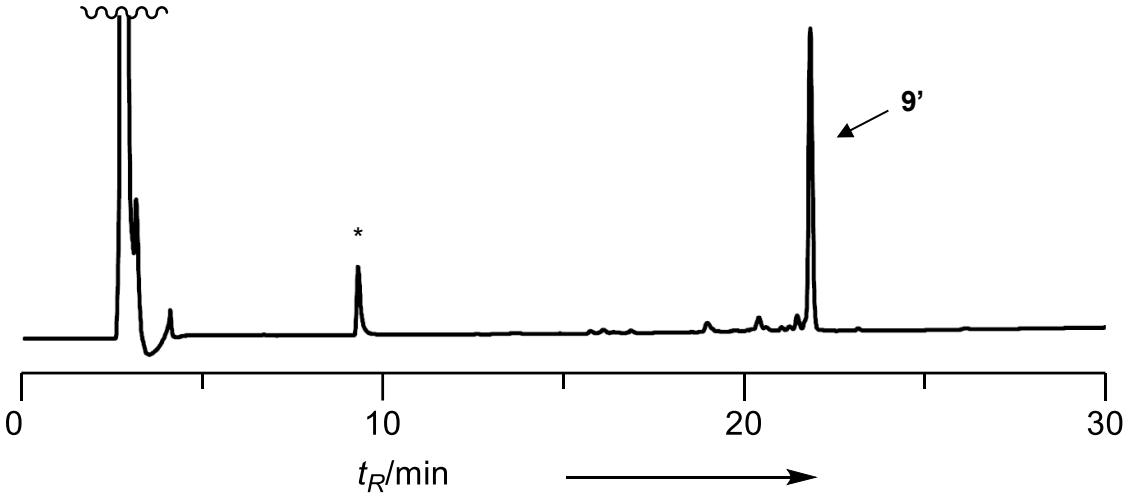
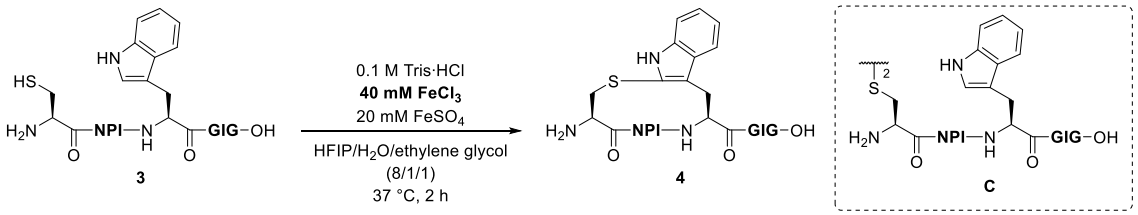


Figure S3. Analytical HPLC charts of crude reaction mixture. Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min (Column was heated to 60 °C). *non-peptidyl compounds.

The examination of $FeCl_3$-mediated Cys-Trp-linking reaction using N-terminal Cys peptide (3)

Scheme S2. The reaction overview.



Substrate peptide **3** (0.10 μmol) was dissolved in HFIP (80 μL), and then 1 M Tris·HCl–200 mM $FeSO_4 \cdot 7H_2O$in H_2O/ethylene glycol (1/1) (10 μL) was added to the solution, which afforded a white suspension. After vigorous mixing for a few seconds, 400 mM $FeCl_3$ solution in H_2O/ethylene glycol (1/1) (10 μL) was added to the mixture with additional stirring at 37 °C for 2 h under aerobic conditions. The reaction was diluted fivefold with 100 mM EDTA aq. analyzed by HPLC.

Disulphide-formed peptide **C**: Analytical HPLC condition: linear gradient of solvent B in solvent A, 5% to 65% over 30 min (Column was heated to 60 °C), RT = 19.2 min. LRMS (ESI-TOF) *m/z*: $[M+2H]^+$ calcd for $C_{78}H_{114}N_{20}O_{20}S_2$ 858.4, found 858.5.

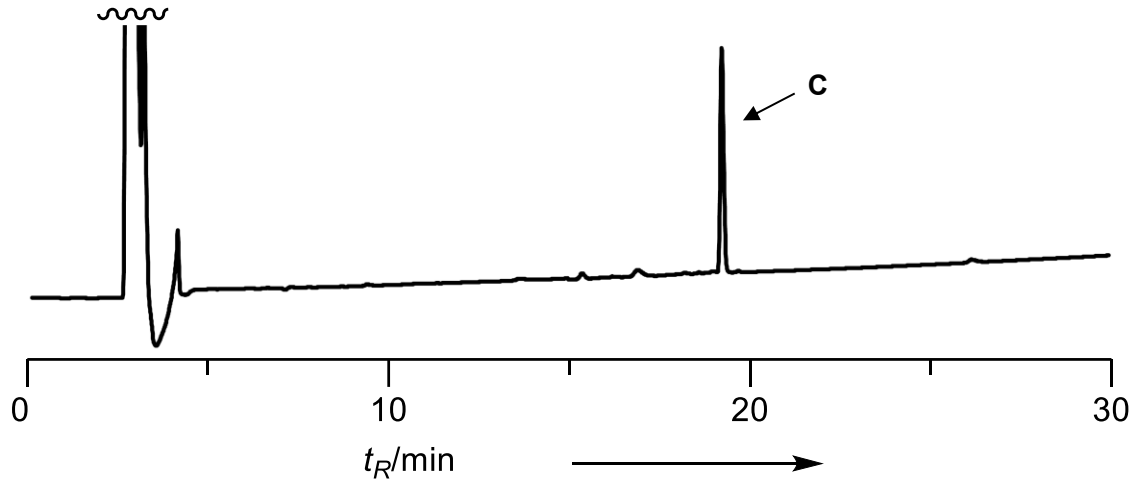


Figure S4. Analytical HPLC charts of crude reaction material. Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min (Column was heated to 60 °C).

Synthesis of Pro2-Ile3-S-deoxo amaninamide (2)

Synthesis of Pro2-Ile3-S-deoxo amaninamide (2) from the monocyclized peptide 4

Peptide **4** (1.88 mg, 1.94 μmol) was dissolved in NMP containing 20 mM PyBOP and 20 mM DIEA (388 μL), and the reaction was continued at rt for 2 h. After filtering, the purification of the resulting solution with HPLC afforded Pro2-Ile3-S-deoxo amaninamide (**2**) (1.16 mg, 1.38 μmol, 71% isolated yield).

Pro2-Ile3-S-deoxo amaninamide (**22**): Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min (Column was heated to 60 °C), RT = 19.7 min. Preparative HPLC conditions: linear gradient of solvent B in solvent A, 29% to 39% over 30 min, RT = 15.2 min. LRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{39}H_{54}N_{10}O_9S$ 839.4, found 839.3.

Verification of the structure of Pro2-Ile3-S-deoxo amaninamide (2) by comparison with standard sample of 2 synthesised by using Cys(MBzl)(O)[S2]

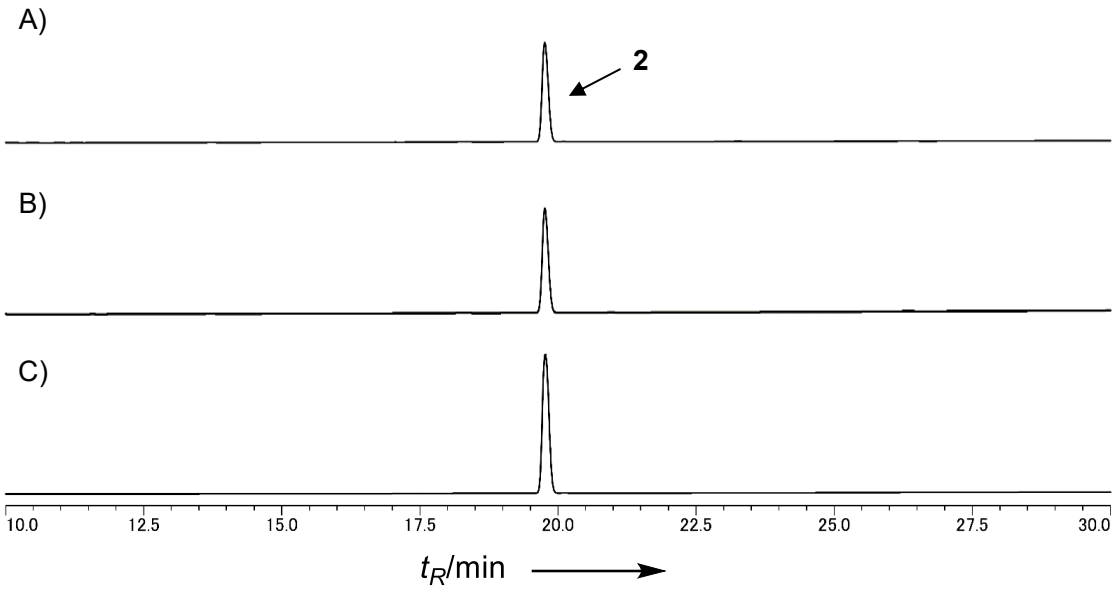


Figure S5. Analytical HPLC charts of Pro2-Ile3-S-deoxo amaninamide (**2**). A) Peptide **2** synthesised by using Cu^{2+} and Fe^{2+} (This work). B) Peptide **2** synthesised by using Cys(MBzl)(O) (Previous work)[S2]. C) Co-injection of the samples described above.

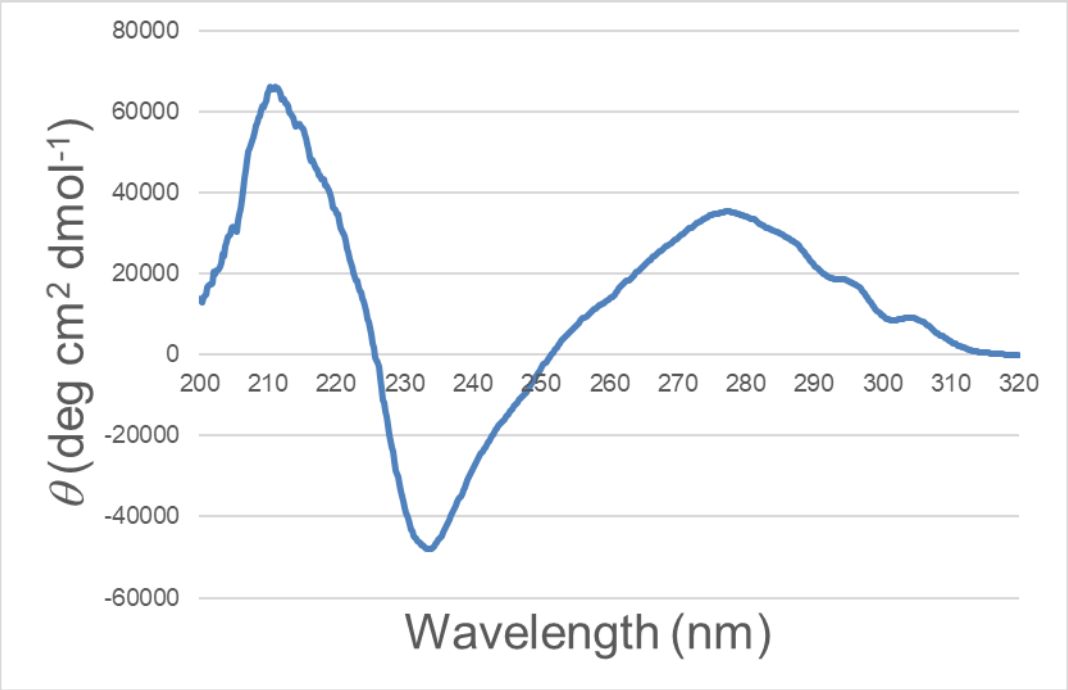


Figure S6. The CD spectrum of Pro2-Ile3-S-deoxo amaninamide (**2**).

Synthesis of Cys-Trp-linked peptides listed in Table 2.

Each substrate peptides (**10a**, **11a**, **12a**, **13a**, **14a**, **15a**, **16a** or **17a**) was dissolved in HFIP (peptide concentration: 1.25 mM). To the solution was then added 1 M Tris·HCl–200 mM $FeSO_4 \cdot 7H_2O$ dissolved in H_2O/ethylene glycol (1/1) (one-eighth volume of HFIP), which afford a white suspension. After vigorous mixing for a few seconds, 400 mM $CuCl_2$ dissolved in H_2O/ethylene glycol (1/1) (one-eighth volume of with HFIP) was added to the suspension with additional stirring at 37 °C for 2 h under aerobic conditions. The quenching of the reaction with twofold volume of 100 mM EDTA aq. and HPLC-purification of the resulting mixture afforded Cys-Trp linked peptides (**10b**, **11b**, **12b**, **13b**, **14b**, **15b**, **16b** or **17b**).

*Cys-Trp linked H-**CGAWR**-NH_2* (**10b**): (1.22 mg from 2.00 mg of **10a**, 62% isolated yield). Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min, RT = 10.3 min. Preparative HPLC conditions: isocratic elution with solvent A only over 15 min, RT = 11.5-13.2 min (multi peak). LRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{25}H_{36}N_{10}O_5S$ 589.3, found 589.3.

*Cys-Trp linked H-**CGALRAWR**-NH_2* (**11b**): (2.33 mg from 3.69 mg of **11a**, 63% isolated yield). Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min, RT = 13.5 min. Preparative HPLC conditions: linear gradient of solvent B in solvent A, 16% to 26% over 30 min, RT = 8.1 min. LRMS (ESI-TOF) *m/z*: $[M+2H]^+$ calcd for $C_{40}H_{64}N_{16}O_8S$ 465.3, found 465.4.

Phe-containing Cys-Trp-linked peptide (**12b**): (1.85 mg from 3.00 mg of **12a**, 63% isolated yield). Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min, RT = 16.6 min. Preparative HPLC conditions: linear gradient of solvent B in solvent A, 22% to 32% over 30 min, RT = 9.1 min. LRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{37}H_{51}N_{11}O_6S$ 778.4, found 778.1.

Lys-containing Cys-Trp-linked peptide (**13b**): (2.35 mg from 3.00 mg of **13a**, 79% isolated yield). Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min, RT = 11.8 min. Preparative HPLC conditions: linear gradient of solvent B in solvent A, 11% to 21% over 30 min, RT = 8.1 min. LRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{34}H_{54}N_{12}O_6S$ 759.4, found 759.1.

His-containing Cys-Trp-linked peptide (**14b**): (1.85 mg from 3.00 mg of **14a**, 62% isolated yield). Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min, RT = 11.5 min. Preparative HPLC conditions: linear gradient of solvent B in solvent A, 11% to 21% over 30 min, RT = 8.0 min. LRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{34}H_{49}N_{13}O_6S$ 768.4, found 768.1.

Met-containing Cys-Trp-linked peptide (**15b**): (1.14 mg from 3.00 mg of **15a**, 39% isolated yield). Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min, RT = 15.1 min. Preparative HPLC conditions: linear gradient of solvent B in solvent A, 18% to 28% over 30 min, RT = 9.2 min. LRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{33}H_{51}N_{11}O_6S_2$ 762.4, found 762.0.

Ser-containing Cys-Trp-linked peptide (**16b**): (1.46 mg from 2.67 mg of **16a**, 56% isolated yield). Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min, RT =

12.1 min. Preparative HPLC conditions: linear gradient of solvent B in solvent A, 14% to 24% over 30 min, RT = 8.0 min. LRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{31}H_{47}N_{11}O_7S$ 718.4, found 718.3.

Tyr-containing Cys-Trp-linked peptide (**17b**): (1.52 mg from 3.00 mg of **17a**, 51% isolated yield). Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min, RT = 14.4 min. Preparative HPLC conditions: linear gradient of solvent B in solvent A, 18% to 28% over 30 min, RT = 8.1 min. LRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{37}H_{51}N_{11}O_7S$ 794.4, found 794.0.

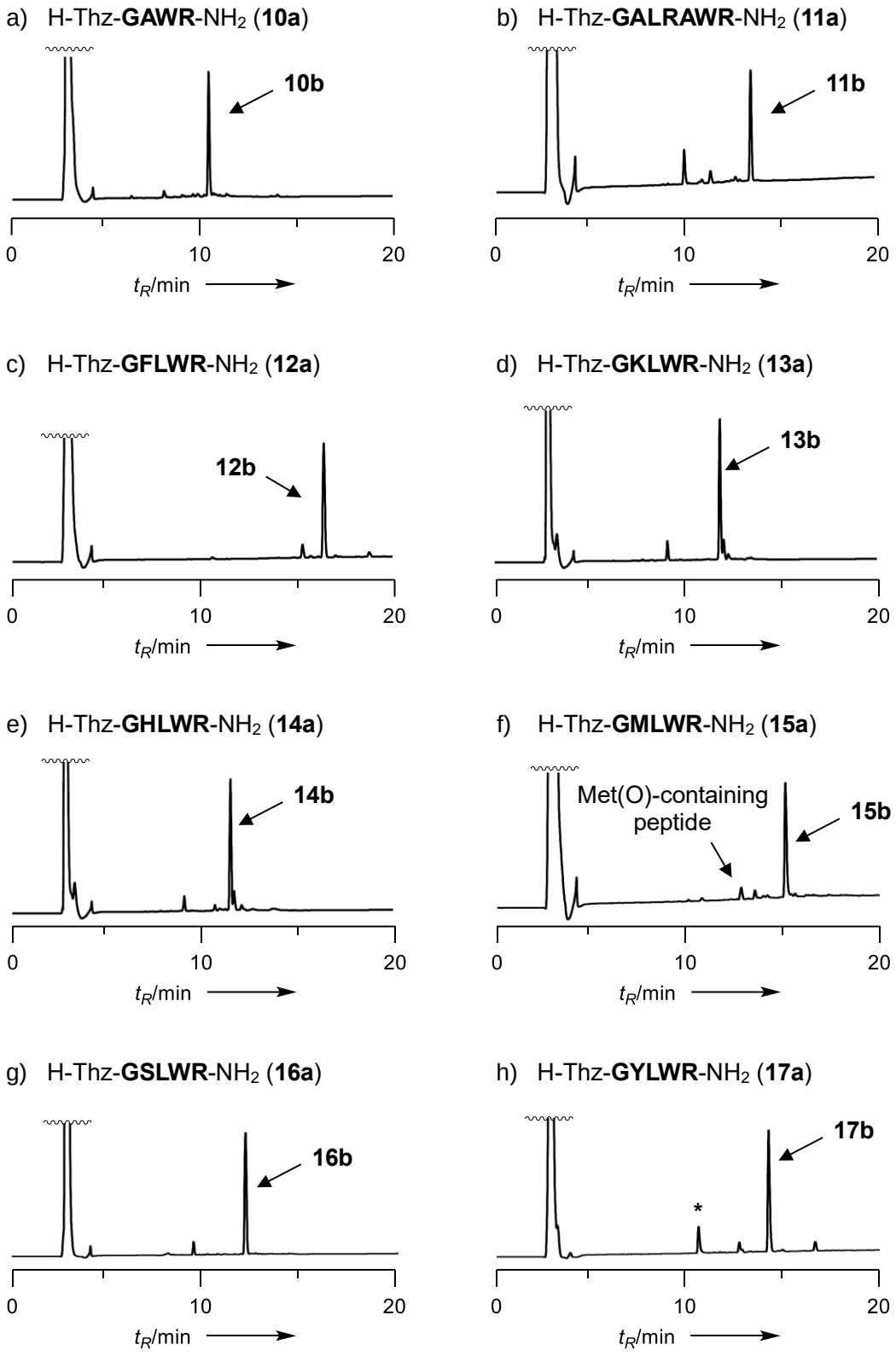


Figure S7. Analytical HPLC charts of crude reaction material. Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min. *nonpeptidyl compounds.

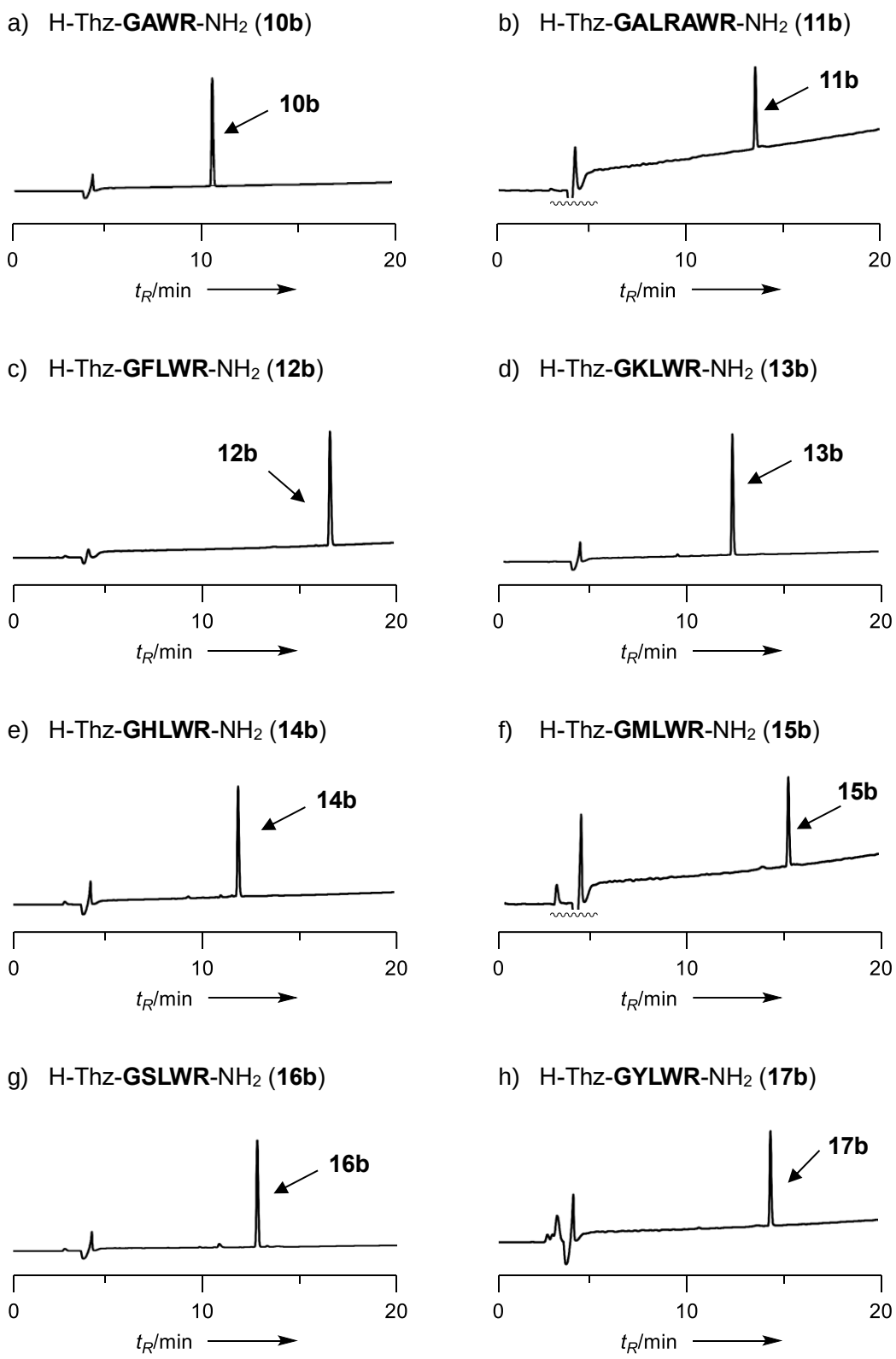


Figure S8. Analytical HPLC charts of purified Cys-Trp-linked peptides. Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min.

Synthesis of Cys-Trp-linked Vasopressin analogue (18b)

Synthesis of Vasopressin analogue precursor (18a)

*H-Thz-**YFQN**-Trp-**PRG**-NH₂* (**18a**): (3.65 mg, 2.82 μmol, 5% isolated yield). Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min, RT = 14.5 min. Preparative HPLC conditions of **18a**: linear gradient of solvent B in solvent A, 27% to 37% over 30 min, RT = 8.3 min. LRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{55}H_{72}N_{16}O_{12}S$ 1181.5, found 1181.0.

Cys-Trp-linking reaction affording Cys-Trp-linked Vasopressin analogue (18b)

Substrate peptide **18a** (3.00 mg, 2.32. μmol) was dissolved in HFIP (1.86 mL); then, 1 M Tris·HCl–200 mM $FeSO_4 \cdot 7H_2O$ in H_2O/ethylene glycol (1/1) (232 μL) was added to the solution, which afford a white suspension. After vigorous mixing for a few seconds, 400 mM $CuCl_2 \cdot 2H_2O$ in H_2O/ethylene glycol (1/1) (232 μL) was added to the mixture with additional stirring at 37 °C for 2 h under aerobic conditions. The quenching of the reaction with 100 mM EDTA aq. (2.32 mL) and the HPLC-purification of the resulting mixture afforded Cys-Trp linked peptide **4** (2.46 mg, 76% isolated yield). Cys-Trp-linked Vasopressin analogue: Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min, RT = 14.1 min. Preparative HPLC conditions of **18b**: linear gradient of solvent B in solvent A, 18% to 28% over 30 min, RT = 7.9 min. LRMS (ESI-TOF) *m/z*: $[M+2H]^+$ calcd for $C_{54}H_{70}N_{16}O_{12}S$ 584.3, found 584.2.

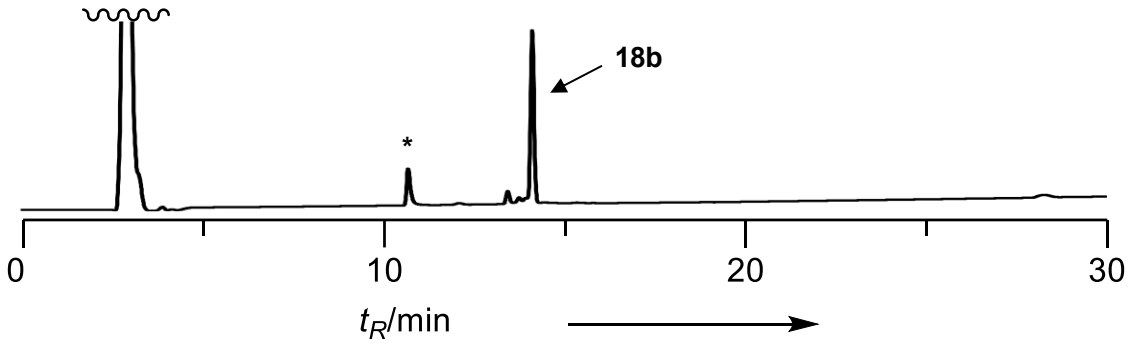


Figure S9. Analytical HPLC charts of crude reaction material. Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min. *non-peptidyl compounds.

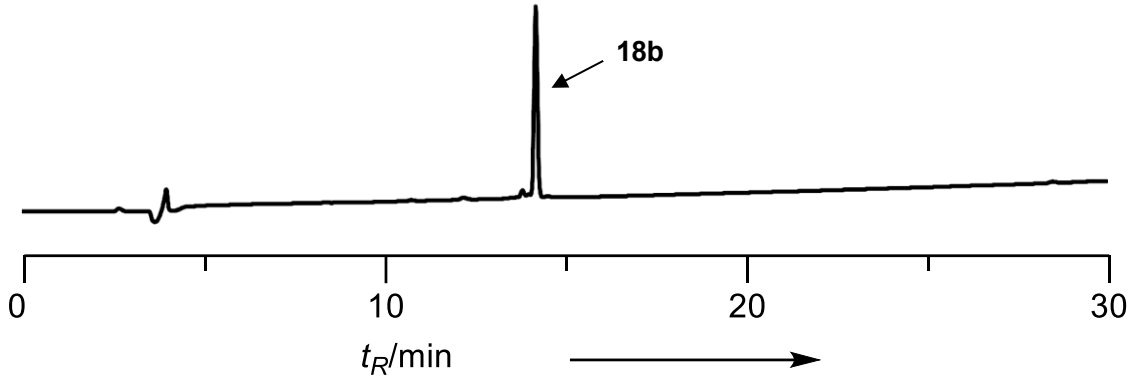


Figure S10. Analytical HPLC charts of purified Cys-Trp-linked peptide **18b**. Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min.

Synthesis of Cys-Trp-linked Apamin analogue (19b)

Synthesis of Cys-Trp-linked Apamin analogue precursor (S2)

*H-Thz-**N**-Cys-**KAPETL**-Trp-**AR**-Cys-**QQH**-NH₂* (**S2**): (5.03 mg, 2.25 μmol, 4% isolated yield). Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 40% over 30 min, RT = 19.9 min. Preparative HPLC conditions: linear gradient of solvent B in solvent A, 18% to 28% over 30 min, RT = 9.3 min. LRMS (ESI-TOF) *m/z*: $[M+2H]^+$ calcd for $C_{79}H_{123}N_{27}O_{22}S_3$ 949.9, found 950.1.

Disulphide formation of Apamin analogue precursor (S2)

Apamin analogue precursor (**S2**) (3.65 mg, 1.63 μmol) was dissolved in 6 M Gn·HCl–0.1 M HEPPS aq. (3.26 mL, pH 7.7), and then the mixture was stirred at 37 °C for 24 h under aerobic conditions. Dilution of the reaction mixture with 0.1% TFA aq. to twofold amount, followed by HPLC-purification, afforded disulphide-formed peptide **19a** (2.33 mg, 64% isolated yield).

Disulphide-formed peptide **19a**: Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 40% over 30 min, RT = 19.5 min. Preparative HPLC conditions: linear gradient of solvent B in solvent A, 16% to 26% over 30 min, RT = 11.9 min. LRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{79}H_{121}N_{27}O_{22}S_3$ 948.9, found 948.7.

Cys-Trp-linking reaction affording Cys-Trp-linked Apamin analogue precursor (19b)

Substrate peptide **19a** (2.33 mg, 1.04 μmol) was dissolved in HFIP (831 μL). To the solution was then added 1 M Tris·HCl–200 mM $FeSO_4 \cdot 7H_2O$ in H_2O/ethylene glycol (1/1) (104 μL), which afford a white suspension. After vigorous mixing for a few seconds, 400 mM $CuCl_2 \cdot 2H_2O$ solution in H_2O/ethylene glycol (1/1) (104 μL) was added to the mixture with additional stirring at 37 °C for 2 h under aerobic conditions. The quenching of reaction with 100 mM EDTA aq. (1.04 mL), and the HPLC-purification of the resulting mixture afforded Cys-Trp linked peptide **19b** (1.02 mg, 42% isolated yield).

Cys-Trp-linked Apamin analogue precursor (**19b**): Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 40% over 30 min, RT = 16.8 min. Preparative HPLC conditions of **19b**: linear gradient of solvent B in solvent A, 10% to 20% over 30 min, RT = 15.1 min. LRMS (ESI-TOF) *m/z*: $[M+2H]^+$ calcd for $C_{78}H_{119}N_{27}O_{22}S_3$ 941.9, found 942.3.

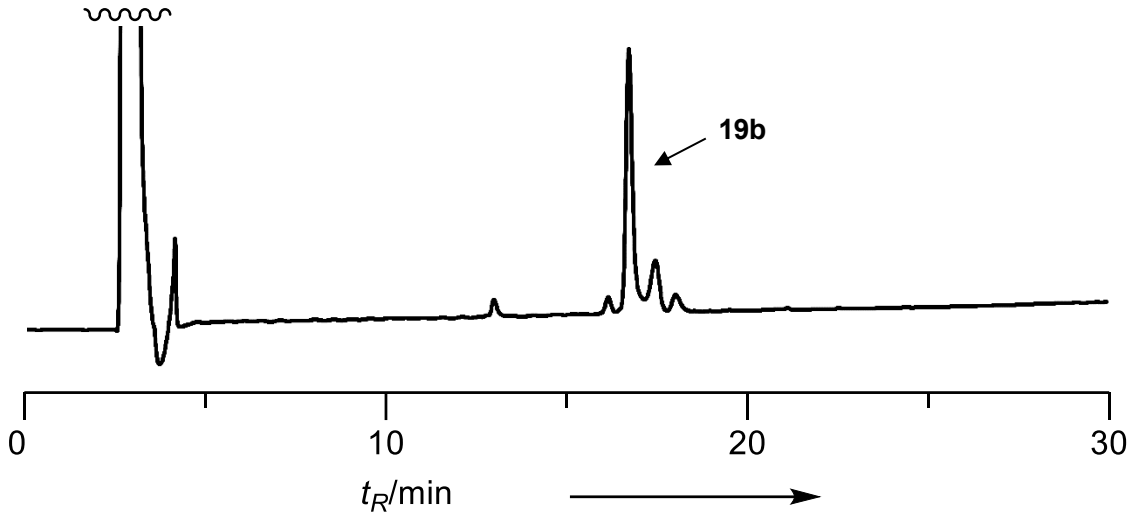


Figure S11. Analytical HPLC charts of crude reaction material. Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 40% over 30 min.

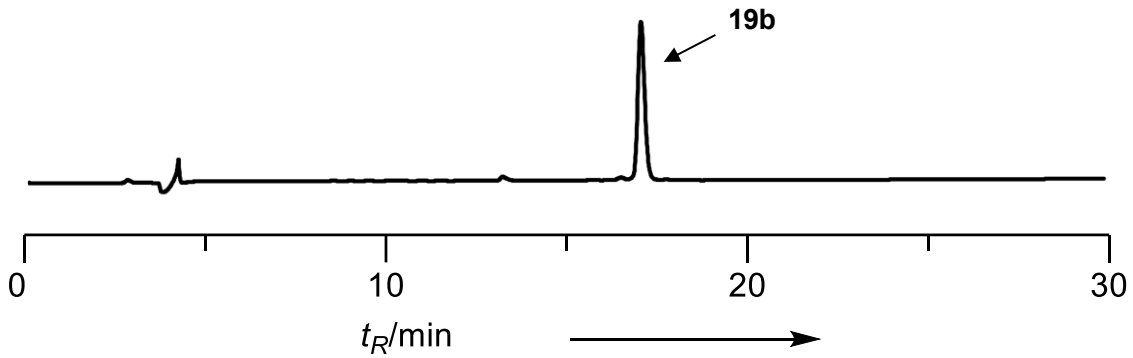


Figure S12. Analytical HPLC charts of purified Cys-Trp-linked peptide **19b**. Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 40% over 30 min.

Synthesis of Selenoamaninamide derivative (22)

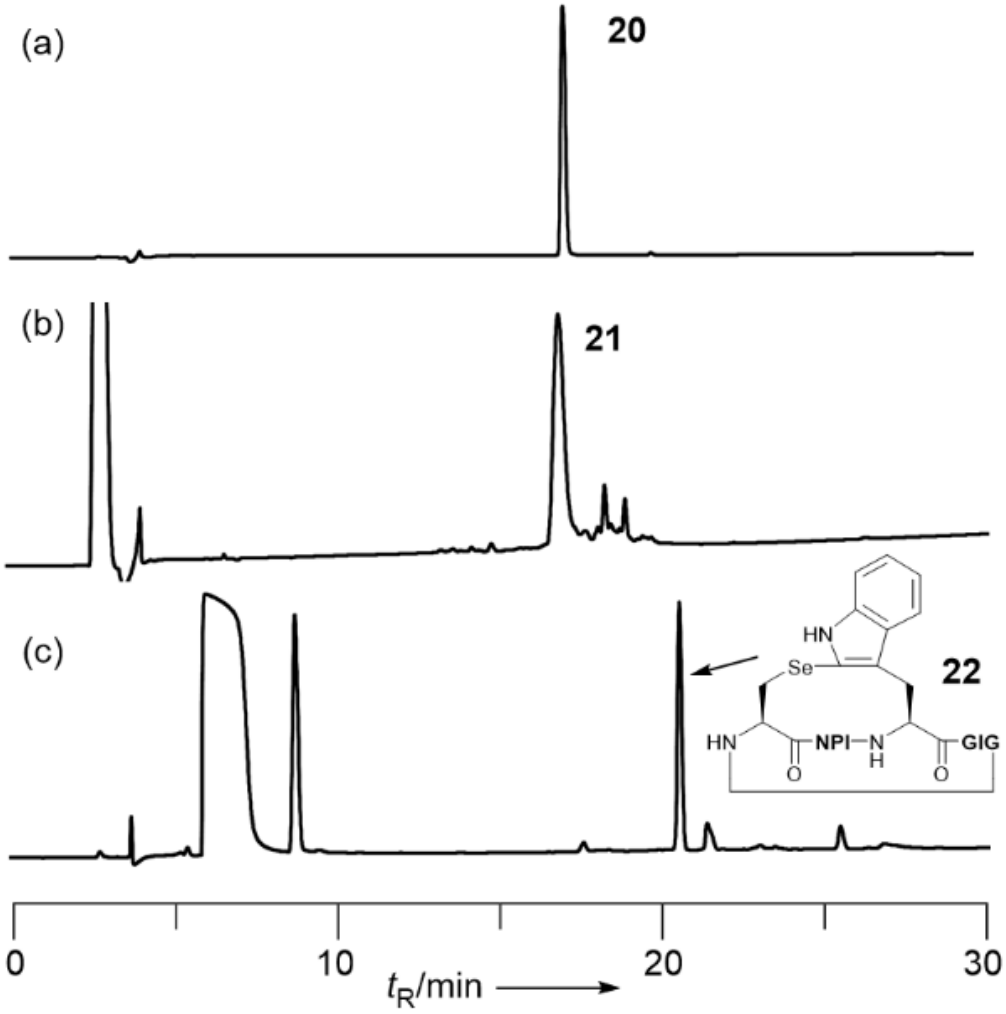


Figure S13. HPLC of the C-H selenylation of the Trp in **20** followed by lactam formation. (a) Purified Sez-containing substrate **20**. (b) C-H Selenylation. (c) Lactam formation. Analytical HPLC conditions: linear gradient of 0.1% TFA/CH_3CN in 0.1% TFA/H_2O, 5% to 65% over 30 min; detection at 220 nm; Column temperature 60 °C.

Sec-Trp-linking reaction using the optimum condition

Substrate peptide **20** (3.10 mg, 3.00 μmol) was dissolved in HFIP (2.4 mL). To the solution was then added 1 M Tris·HCl–200 mM $FeSO_4 \cdot 7H_2O$ in H_2O/ethylene glycol (1/1) (300 μL), which afford a white suspension. After vigorous mixing for a few seconds, 400 mM $CuCl_2 \cdot 2H_2O$ solution in H_2O/ethylene glycol (1/1) (300 μL) was added to the mixture with additional stirring at 37 °C for 2 h under aerobic conditions. The quenching of the reaction with 100 mM EDTA aq. (3.0 mL), and the HPLC-purification of the resulting mixture afforded Cys-Trp linked peptide **21** (1.69 mg, 1.66 μmol, 55% isolated yield).

Sec-Trp-linked peptide **21**: Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min (Column was heated to 60 °C), RT = 16.9 min. Semi preparative HPLC conditions: linear gradient of solvent B in solvent A, 25% to 35% over 30 min (Column was heated to 60 °C), RT = 25.1 min. LRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{39}H_{56}N_{10}O_{10}Se$ 905.3, found 904.8.

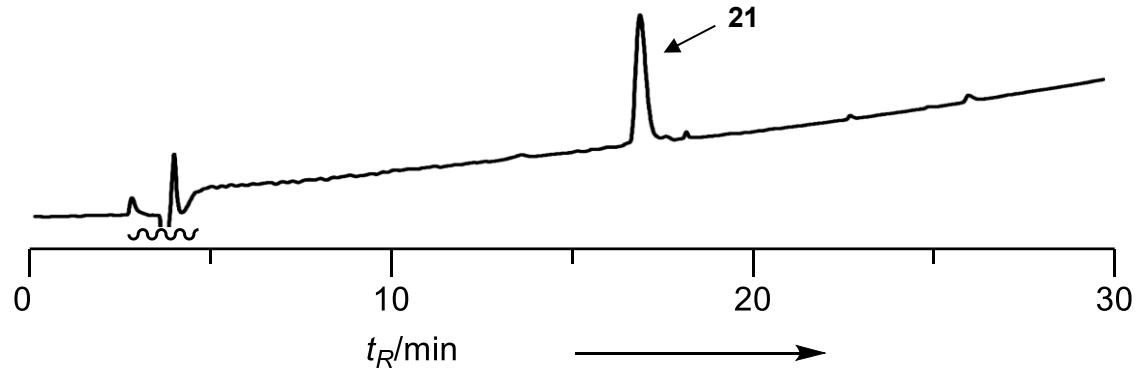


Figure S14. Analytical HPLC charts of purified Sec-Trp-linked peptide **21**. Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min (Column was heated to 60 °C).

Synthesis of Selenoamaninamide derivative (22) from the monocyclized peptide 21

Peptide **22** (1.69 mg, 1.66 μmol) was dissolved in NMP containing 20 mM PyBOP and 20 mM DIEA (332 μL), and the reaction was continued at rt for 2 h. After filtering, the purification of the resulting solution by HPLC afforded Selenoamaninamide derivative (**22**) (1.07 mg, 1.21 μmol, 73% isolated yield).

Pro2-Ile3-S-deoxo amaninamide (**22**): Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min (Column was heated to 60 °C), RT = 19.8 min. Preparative HPLC conditions: linear gradient of solvent B in solvent A, 29% to 29% over 30 min, RT = 15.5 min. LRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{39}H_{54}N_{10}O_9Se$ 887.3, found 887.0.

^{1}H-NMR (500 MHz, DMSO-d_6): δ=11.20 (s, 1H; NH^{indole}), 8.82 (t, J = 6.6 Hz, 1H; $CONH^{Gly}$), 8.49 (d, J = 2.5, 1H; $CONH^{Asn}$), 8.45 (d, J = 3.3 Hz, 1H; $CONH^{Ile}$), 8.22 (brs, 1H; NH_2^{Asn}), 8.14–7.90 (m,

4H; $CONH^{Gly,Ile,Trp,Sec}$), 7.60 (d, J = 7.9 Hz, 1H; ArH^{indole}), 7.51 (brs, 1H; NH_2^{Asn}), 7.25 (d, J = 7.9 Hz, 1H; ArH^{indole}), 7.08 (t, J = 7.9 Hz, 1H; ArH^{indole}), 6.99 (t, J = 7.9 Hz, 1H; ArH^{indole}), 4.98-4.85 (m, 1H; $CH^{Trp\alpha}$), 4.78-4.69 (m, 1H; $CH^{Asn\alpha}$), 4.56-4.45 (m, 1H; $CH^{Sec\alpha}$), 4.26 (dd, J = 18.3, 9.0 Hz, 1H; $CH^{Gly\alpha}$), 4.21–4.11 (m, 2H; $CH^{Pro\alpha,Ile\alpha}$), 3.97–3.89 (m, 1H; $CH^{Pro\delta}$), 3.86 (dd, J = 17.2, 6.6 Hz, 1H; $CH^{Gly\alpha}$), 3.74–3.47 (m, 2H; $CH^{Pro\delta,Ile\alpha}$), 3.45–3.38 (m, 1H; $CH^{Gly\alpha}$), 3.37–3.20 (m, 3H; $CH^{Asn\beta,Gly\alpha,Trp\beta}$), 3.14–3.06 (m, 1H; $CH^{Trp\beta}$), 3.04–2.92 (m, 2H; $CH^{Asn\beta,Sec\beta}$), 2.75 (dd, J = 10.0, 3.2 Hz, 1H; $CH^{Sec\beta}$), 2.37–2.26 (m, 1H; $CH^{Pro\beta}$), 2.03–1.95 (m, 1H; $CH^{Pro\gamma}$), 1.95–1.88 (m, 1H; $CH^{Ile\beta}$), 1.88–1.78 (m, 1H; $CH^{Pro\gamma}$), 1.76–1.63 (m, 1H; $CH^{Pro\beta}$), 1.60–1.02 (m, 5H; $CH_2^{Ile\gamma}$, $CH^{Ile\beta}$), 0.88 (d, J = 6.3 Hz, 3H; $CH_3^{Ile\gamma}$), 0.85–0.74 ppm (m, 9H; $CH_3^{Ile\gamma,Ile\delta}$).

^{13}C-NMR (125 MHz, DMSO-d_6): δ=172.5 ($CONH_2^{Asn}$), 171.8 (CO^{Asn}), 170.8 (CO^{Pro}), 170.5 (CO^{Trp}), 170.5 (CO^{Ile}), 170.0 (CO^{Ile}), 169.8 (CO^{Sec}), 168.2 (CO^{Gly}), 168.0 (CO^{Gly}), 137.3 (C^{indole}), 126.9 (C^{indole}), 121.9 (CH^{indole}), 120.2 (CH^{indole}), 119.2 (C^{indole}), 118.5 (CH^{indole}), 116.5 (C^{indole}), 111.0 (CH^{indole}), 63.3 ($CH^{Trp\alpha}$), 59.0 ($CH^{Pro\alpha}$), 58.0 ($CH^{Ile\alpha}$), 53.5 ($CH^{Sec\alpha}$), 52.9 ($CH^{Ile\alpha}$), 50.7 ($CH^{Asn\alpha}$), 47.4 ($CH_2^{Pro\delta}$), 42.4 ($2CH_2^{Gly\alpha}$), 35.6 ($CH^{Ile\beta}$), 34.6 ($CH^{Ile\beta}$), 33.9 ($CH_2^{Asn\beta}$), 31.0 ($CH_2^{Trp\beta}$), 30.3 ($CH_2^{Sec\beta}$), 29.9 ($CH_2^{Pro\beta}$), 25.0, 24.9 ($2CH_2^{Ile\gamma}$, $CH_2^{Pro\gamma}$), 15.8 ($CH_3^{Ile\gamma}$), 14.8 ($CH_3^{Ile\gamma}$), 10.7 ppm ($2CH_3^{Ile\delta}$)

HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{39}H_{54}N_{10}O_9Se$ 909.3138, found 909.3134.

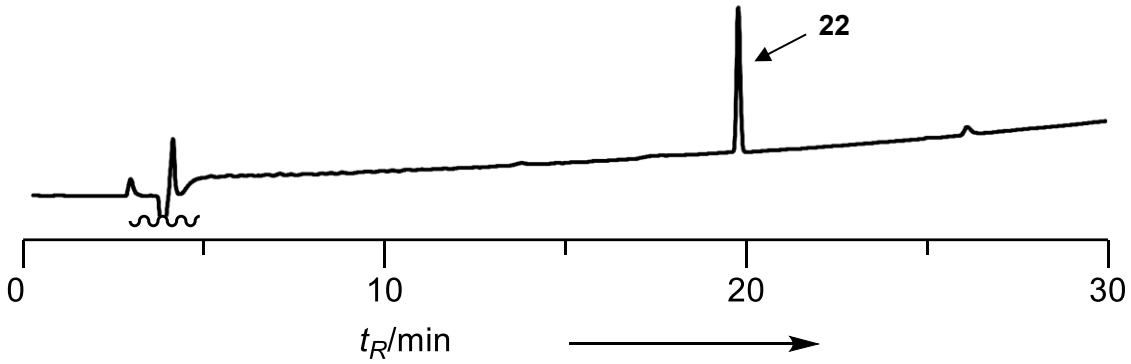


Figure S15. Analytical HPLC charts of purified Sec-Trp-linked peptide **21**. Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min (Column was heated to 60 °C).

Spectra of Selenoamaninamide derivative (22)

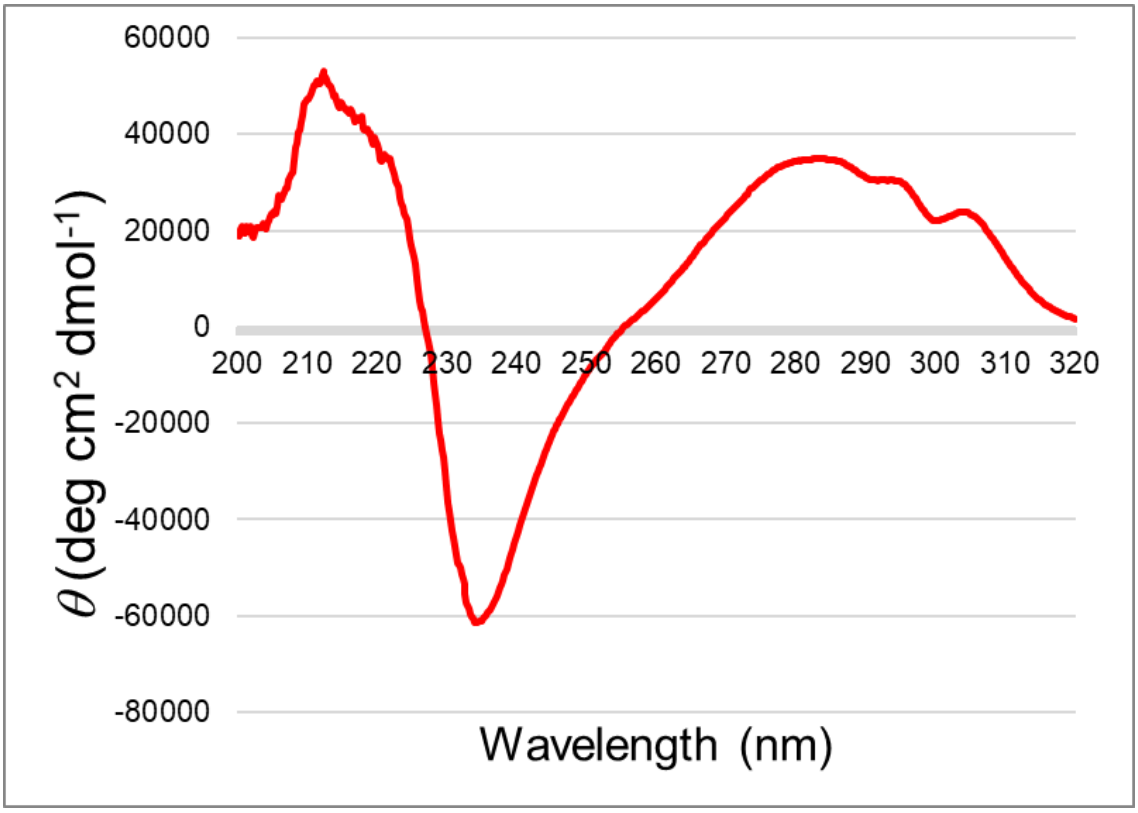
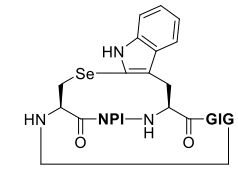
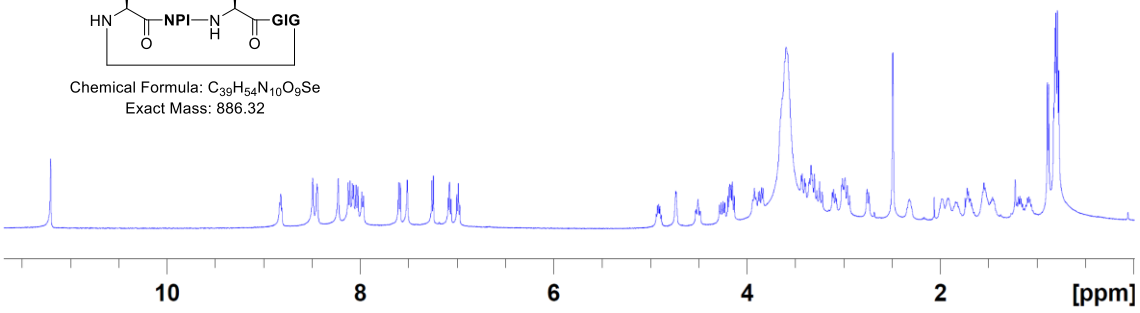


Figure S16. The CD spectrum of Selenoamaninamide derivative (**22**).

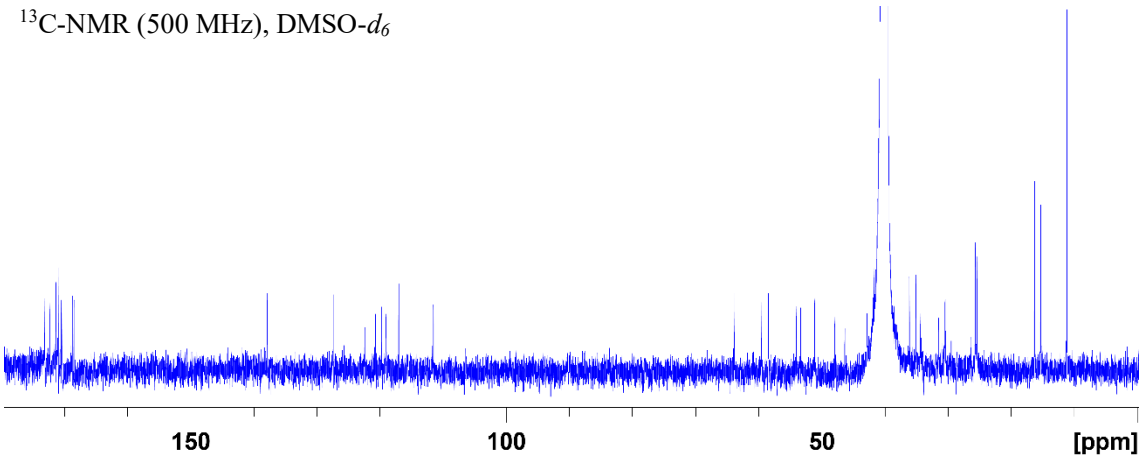
^{1}H-NMR (500 MHz), DMSO-*d*$_6$



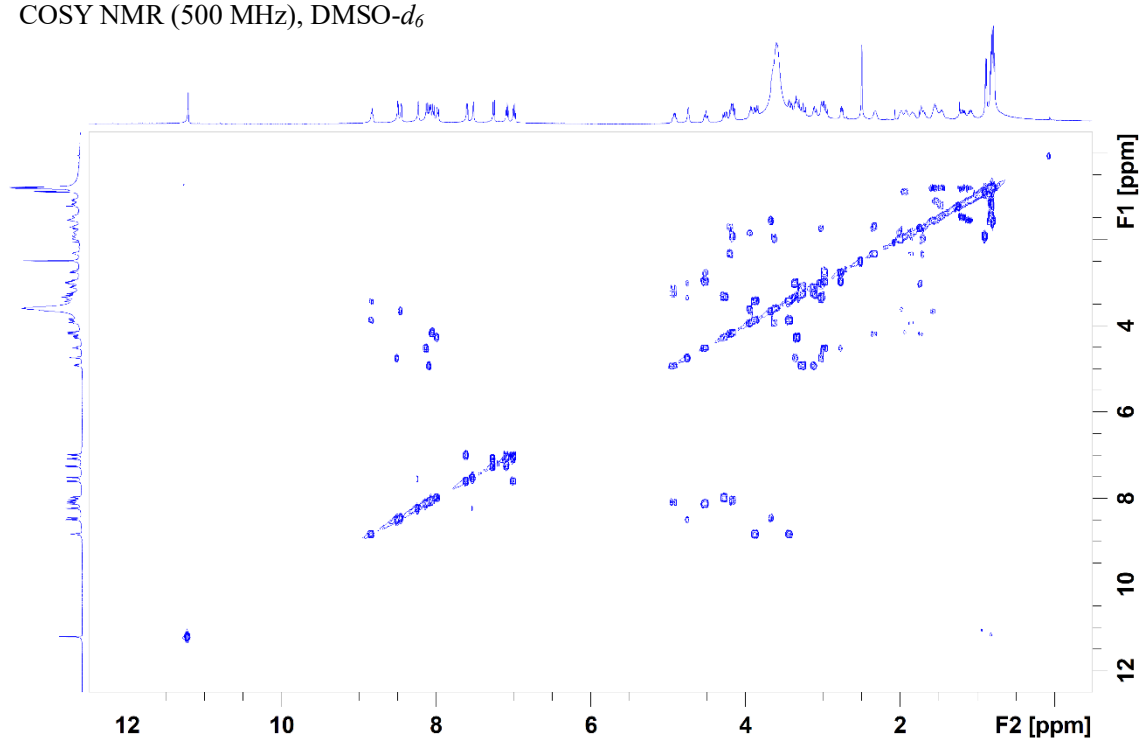
Chemical Formula: $C_{39}H_{54}N_{10}O_9Se$
Exact Mass: 886.32



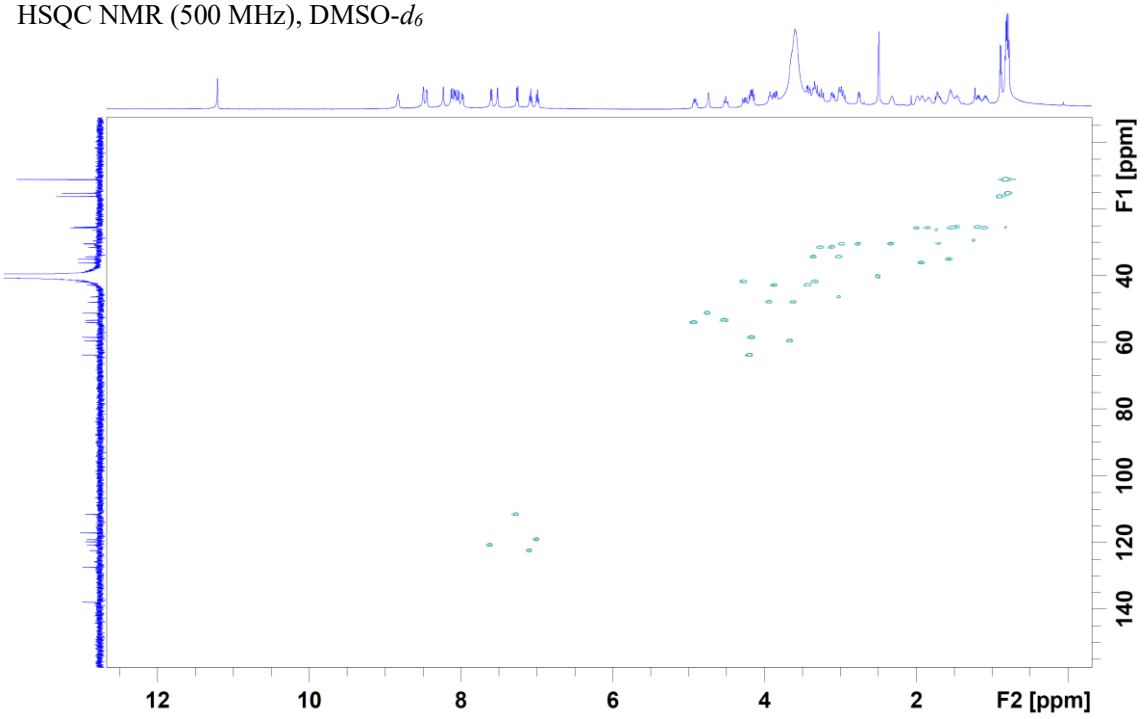
^{13}C-NMR (500 MHz), DMSO-*d*$_6$



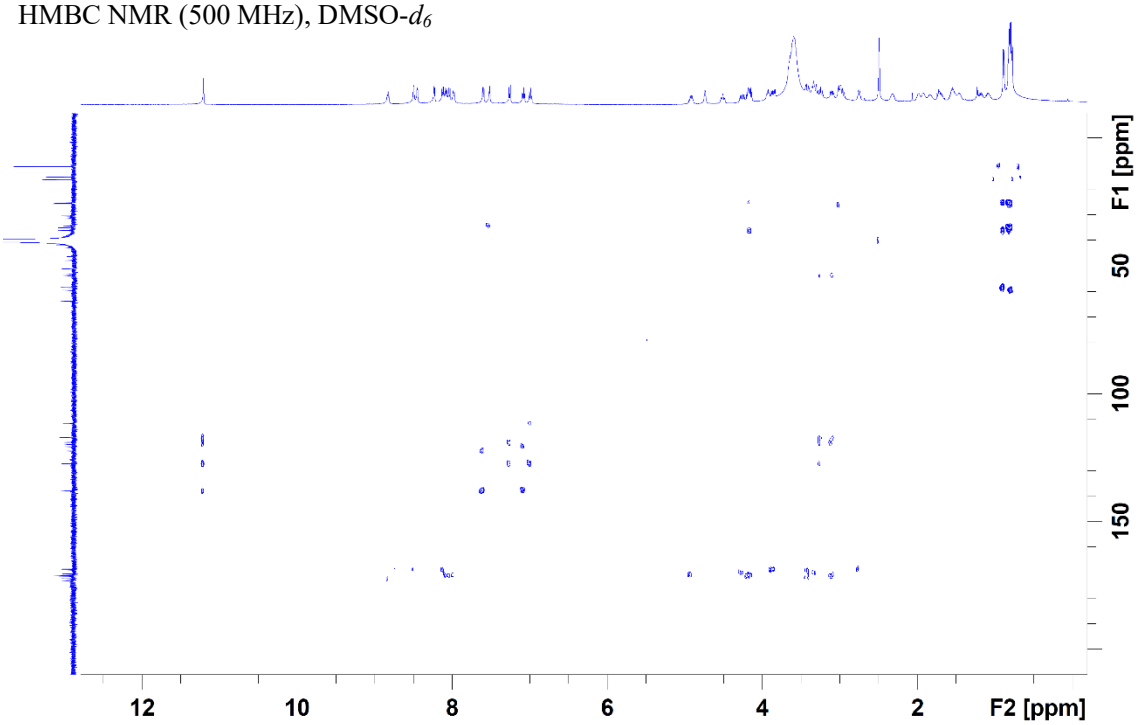
COSY NMR (500 MHz), DMSO-*d*$_6$



HSQC NMR (500 MHz), DMSO-d_6



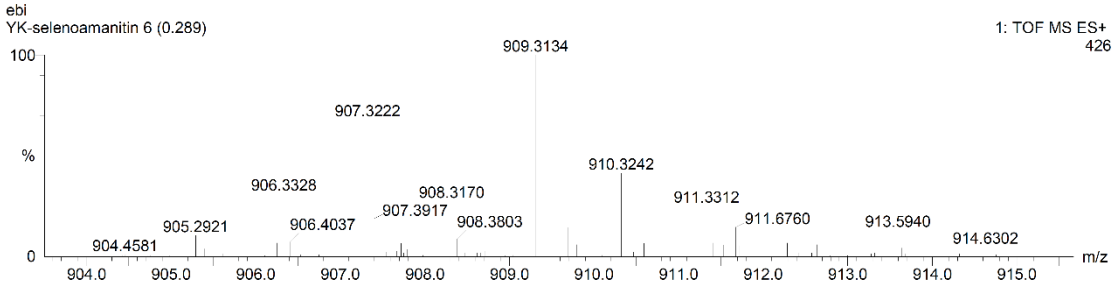
HMBC NMR (500 MHz), DMSO-d_6



Multiple Mass Analysis: 2 mass(es) processed
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
1 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 39-39 H: 54-54 N: 10-10 O: 9-9 Na: 1-1 Se: 1-1

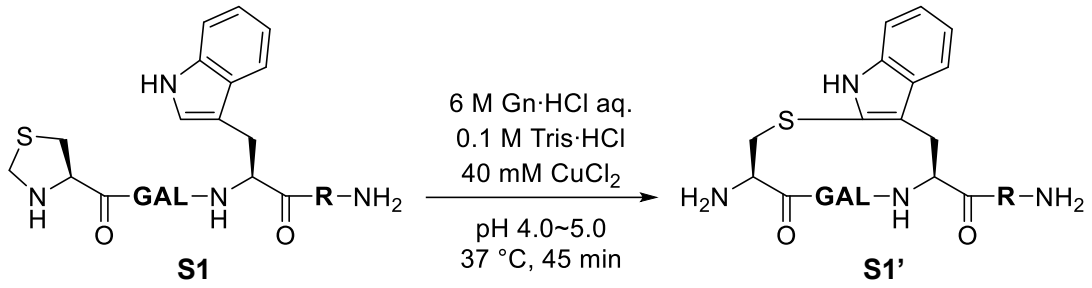
ebi
YK-selenoamanitin 6 (0.289)



Minimum:	50.00				-1.5		
Maximum:	100.00		1000.0	5.0	50.0		
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
907.3222	67.73	---					
909.3134	100.00	909.3138	-0.4	-0.4	18.5	85696.6	C39 H54 N10 O9 Na Se

Cys-Trp-linking reaction using peptide S1

Scheme S3. The reaction overview.



Substrate peptide **S1** (0.10 μmol) was dissolved in 6 M GnHCl–0.1 M Tris·HCl aq. (100 μL). To the mixture was added 800 mM $CuCl_2 \cdot 2H_2O$ (5.0 μL, 4.0 μmol), and then the solution was stirred at 37 °C for 45 min under aerobic conditions. The reaction was diluted to fivefold amount with 100 mM EDTA aq. and the resulting mixture was analyzed with HPLC.

Peptide **S1'**: Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min, RT = 13.6 min. LRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{31}H_{47}N_{11}O_6S$ 702.4, found 701.7.

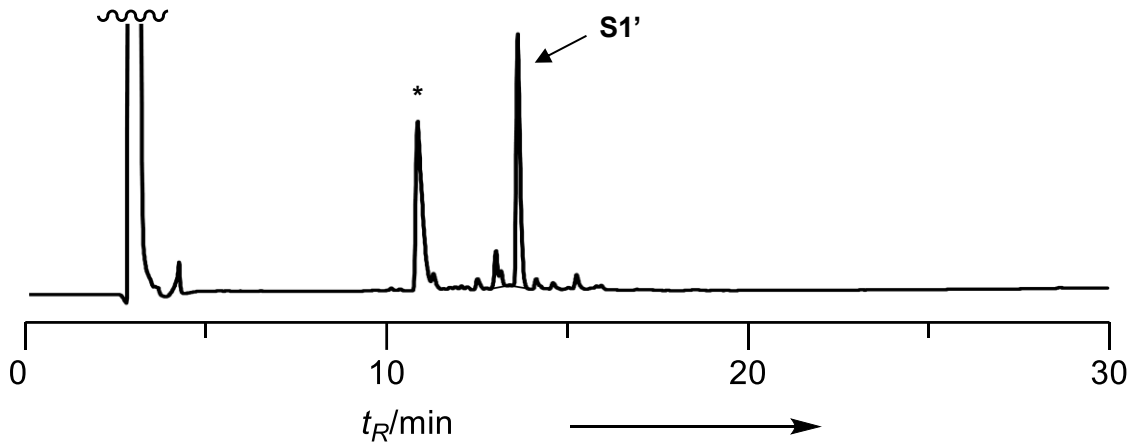
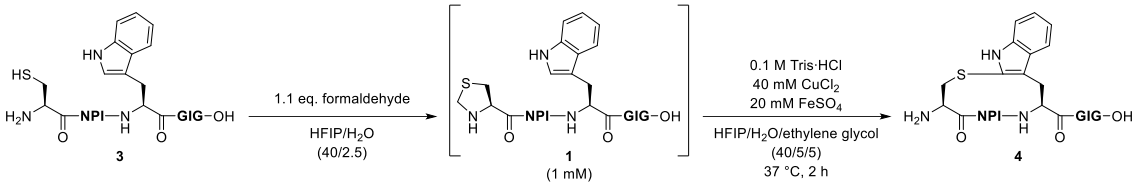


Figure S17. Analytical HPLC charts of crude reaction material. Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min. *non-peptidyl compounds.

The reaction using peptide **1** hardly affords Cys-Trp-linked peptide **4** in this condition (see Figure S1, entry 2).

Cys-Trp-linking reaction using HCHO-pretreated peptide 3

Scheme S4. The reaction overview.



To the solution of substrate peptide **3** (0.05 μmol) in HFIP (40 μL) was added 22 mM formaldehyde solution in H_2O (2.5 μL, 0.055 μmol). Without any stirring, 1 M Tris·HCl–200 mM $FeSO_4 \cdot 7H_2O$ solution in H_2O/ethylene glycol (1/1) (5.0 μL) was added to the mixture, which afford a white suspension. After vigorous mixing for a few seconds, 800 mM $CuCl_2 \cdot 2H_2O$ solution in ethylene glycol (2.5 μL) was added to the mixture, and then the resulting solution was stirred at 37 °C for 2 h under aerobic conditions. The reaction was diluted fivefold with 100 mM EDTA aq. and the mixture was analyzed by HPLC.

Peptide **4**: Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min (Column was heated to 60 °C), RT = 17.0 min. LRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{39}H_{56}N_{10}O_{10}S$ 857.4, found 857.3.

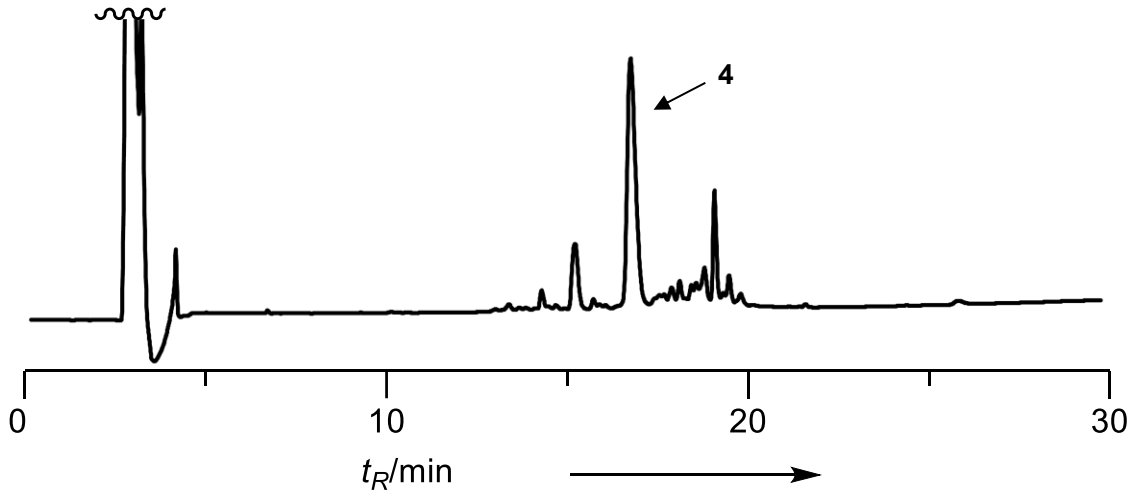


Figure S18. Analytical HPLC charts of crude reaction material. Analytical HPLC conditions: linear gradient of solvent B in solvent A, 5% to 65% over 30 min. *non-peptidyl compounds.

Reference

S1. (a) P. S. Reddy, S. Dery, N. Metanis, *Angew*. *Chem*., *Int*. *Ed*. **2016**, *55*, 992–995. (b) S. D. Whedon, N. Markandeya, A. S. J. B. Rana, N. A. Senger, C. E. Weller, F. Turecek, E. R. Strieter, C. Chatterjee, *J*. *Am*. *Chem*. *Soc*. **2016**, *138*, 13774–13777.

S2. D. Kobayashi, Y. Kohmura, T. Sugiki, E. Kuraoka, M. Denda, T. Fujiwara, A. Otaka, *Chem*. *Eur*. *J*. in press. (doi: 10.1002/chem.202102420)